

Dott. Orlandini Francesco  
Direttore Sanitario ASL 4  
Regione Liguria

# **9º Corso Incontri Pratici Di Ematologia**

**Anticoagulanti dopo emorragia:  
quale farmaco, come e quando**

**SAVONA**  
9-10-11 novembre 2017  
Hotel NH Darsena  
Via Chiodo 9

**Responsabile scientifico del progetto**

Dott. Rodolfo TASSARA  
S.C. Medicina Interna, Savona



***Il sottoscritto Orlandini Francesco***

*ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,*

dichiara

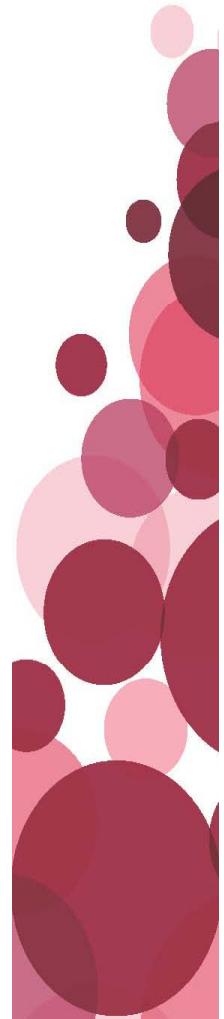
*che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*

*che negli ultimi due anni non ha avuto rapporti diretti di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario*



# Agenda

- Tipi di emorragia e gestione in acuto
- Timing della ripresa della terapia anticoagulante
- Come riprendere la terapia anticoagulante ?
- Con quale farmaco?
- Conclusioni e take home messages



# Classificazione degli eventi emorragici

## A) EMORRAGIE MAGGIORI

- a) fatali
- b) tutte le emorragie nelle seguenti sedi:  
intracranica (con conferma TAC e/o RMN),  
oculare (con riduzione del visus),  
nelle articolazioni maggiori,  
retroperitoneale;
- c) se necessaria chirurgia o manovre invasive;
- d) se riduzione di Hb  $\geq$  2 g/dl, o trasfusione di  $\geq$  2 unità sangue;



# Classificazione degli eventi emorragici

B) EMORRAGIE MINORI: tutti le altre

N.B. Non considerate = piccole ecchimosi,  
epistassi saltuarie (se non necessario tamponamento  
sanguinamento emorroidario occasionale.



## *L'ENTITA' DEL PROBLEMA*

Emorragia maggiore: 2.4- 8% pz/anno (Fitzmaurice DA, Br Med J 2002)

### SEDE DEL SANGUINAMENTO

40-50% emorragie gastrointestinali

20% emorragie cutanee e dei tessuti molli

10% emorragie del tratto genito-urinario

10% emorragie intracraniche



# Incidenza, presentazione e mortalità degli eventi emorragici dopo

- Incidenza annuale anticoagulanti

Emorragia maggiore: 2%-5%

Emorragia fatale: 0,5% - 1%

- Presentazione abituale

emorragie tratto gastrointestinale (GIB) 5-15% dei casi

emorragie intracraniche (ICH) 1 su 250 anticoagulati; 15 volte più frequente



# La gestione in acuto

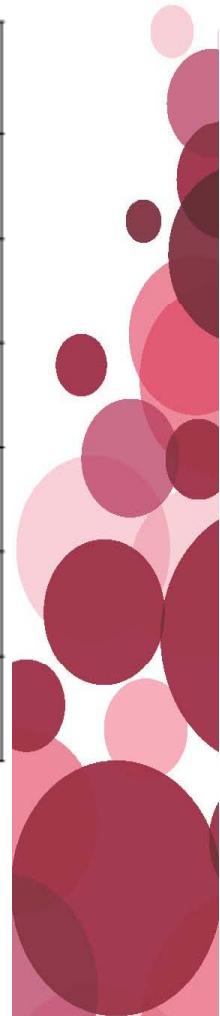
Più luci che ombre



## REVERSIBILITA' DELL'EFFETTO ANTICOAGULANTE

AZIONE	EFFETTO
Sospensione TAO	3-7 gg
Vit.K x os	24 ore
Vit.K ev	10-12 ore
Plasma Fresco congelato	3-6 ore
Fattore VIIa ricombinante	10 minuti
Complessi protrombinici	5 minuti

FCSA 2010



## *CONCENTRATI DEL COMPLESSO PROTROMBINICO (CCP)*

Due prodotti disponibili in Italia non contengono Fattore VII : Uman Complex, Protromplex TIM 3 (FII, FIX, FX + PC e PS)

Due prodotti contengono anche il FVII (Confidex e Pronativ)

L'effetto è immediato. Volume di infusione modesto (media 120 ml).

L'infusione può essere rapida (8 ml/ min) (Thromb Haemost 2007)

La dose individualizzata in base a INR e peso corporeo è più efficace della dose fissa (van Aarte Lonneke, Thromb Res 2005)



## *CCP vs PFC*

- Non studi di comparazione su hard endpoints
- CCP più rapida (15-30 min) e completa reversione di INR rispetto a PFC
- Non rischio di sovraccarico di volume
- CCP da considerare prima scelta per reversione rapida INR (es. emorragia intracranica)



## Un protocollo condiviso in tutte le indicazioni di emergenza

### **PROCEDURA DI REVERSE RAPIDO CON CONCENTRATO DEL COMPLESSO PROTROMBINICO A QUATTRO FATTORI (CONFIDEX) O TRE FATTORI (UMAN COMPLEX ,PROTROMPLEX TIM3)\***

- Infusione di Concentrati del Complesso Protrombinico (CCP) ( 15-20 Minuti)**

INR 1.5 -2	:	20	UI/Kg
INR 2.1 – 3.9	:	30	UI/Kg
INR 4 - 5.9	:	40	UI/Kg
INR > 6	:	50	UI/Kg

- Controllo INR dopo 5 minuti dalla fine della infusione (invio in laboratorio)**
- Infondere Vitamina K (Konakion) 10 mg in Sol.Fis. 100 ml in 30 min.**
- Valutazione del risultato dell'INR**

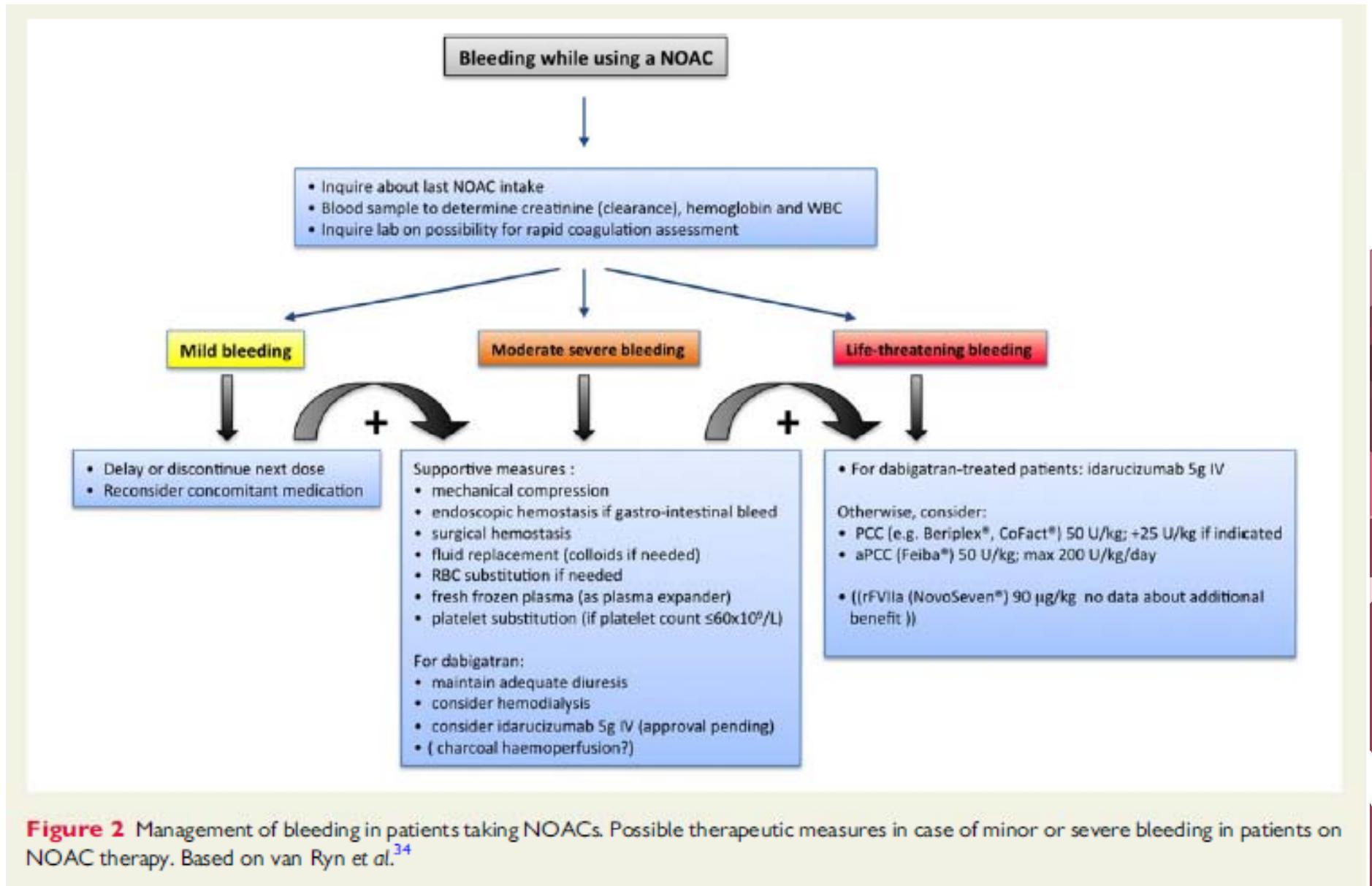


**INR > 1.5 Infusione di CCP (dose correlata INR residuo )  
Dose totale: max 100 UI/kg**

- Non associare Plasma**
- \*Pronativ (®) : riferirsi alla scheda tecnica per il dosaggio**

**FCSA-SIMEU**

# DOACs



# La ripresa della terapia anticoagulante



**Boh ??**  
Alto rischio trombotico  
Alto rischio emorragico

• **Si**

Basso rischio emorragico

Alto rischio trombotico

Alto rischio emorragico

• **No**

Basso rischio trombotico

• **Ni**

Rischio trombotico ed  
emorragico intermedio

# Problemi



Alcuni eventi tromboembolici come EP o stroke correlato a FA, si verificano più frequentemente nelle prime settimane dopo la sospensione dell'anticoagulante, sia esso warfarin o Doacs

## **Factors influencing the decision to resume anticoagulation after a bleeding event**

### **Arguing for resuming anticoagulation**

Strong or near-absolute indication for anticoagulation

- Mechanical mitral valve
- Hypercoagulable state
- CHADS<sub>2</sub> score > 5 (see TABLE 2)
- CHA<sub>2</sub>DS<sub>2</sub>-VASc score > 6 (see TABLE 2)

Anticipated low risk of rebleeding with successful source control and international normalized ratio target control

### **Arguing against resuming anticoagulation**

No absolute indication for ongoing anticoagulation

Near completion of planned anticoagulation course

High risk of rebleeding or presence of additional risk factors for bleeding

Anticipated high risk of morbidity or death if rebleeding occurs



TABLE 2

**Thromboembolic risk by anticoagulation indication**

Risk stratum	Mechanical heart valve <sup>a</sup>	Atrial fibrillation	Venous thromboembolism
<b>High<sup>b</sup></b>	Any mitral valve prosthesis Any caged-ball or tilting-disc aortic valve prosthesis Stroke or transient ischemic attack within past 6 months	CHADS <sub>2</sub> score of 5 or 6 CHA <sub>2</sub> DS <sub>2</sub> -VASC score of 6 to 9 (suggesting adjusted stroke rate $\geq$ 9% per year) Stroke or transient ischemic attack within past 3 months Rheumatic valvular heart disease	Venous thromboembolism within past 2 months Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
<b>Moderate<sup>c</sup></b>	Bileaflet aortic valve prosthesis and one or more of the following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age $>$ 75	CHADS <sub>2</sub> score of 3 or 4 CHA <sub>2</sub> DS <sub>2</sub> -VASC score of 5 (suggesting adjusted stroke rate of 5%–9% per year)	Venous thromboembolism within the past 6 months Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) Recurrent venous thromboembolism Active cancer (treated within 6 months or palliated)
<b>Low</b>	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	CHADS <sub>2</sub> score of 0 to 2 CHA <sub>2</sub> DS <sub>2</sub> -VASC score of 0 to 4 (suggesting adjusted stroke rate $<$ 5% per year and assuming no prior stroke or transient ischemic attack)	Venous thromboembolism more than 6 months previously and no other risk factors

# Emorragia gastrointestinale

- Fra le più frequenti ....la meno pericolose, anche se...

## Gastrointestinal tract bleeding

Gastrointestinal tract bleeding complicates long-term anticoagulation therapy in 5% to 15% of patients<sup>5</sup> and is probably the most commonly occurring major bleeding complication in patients receiving anticoagulation therapy.<sup>1</sup> Gastrointestinal tract bleeding is rarely acutely fatal but often initiates a cascade of events that contributes to the aforementioned high-case fatality rates associated with major bleeding.<sup>3</sup>





## What to do after the bleed: resuming anticoagulation after major bleeding

Daniel M. Witt

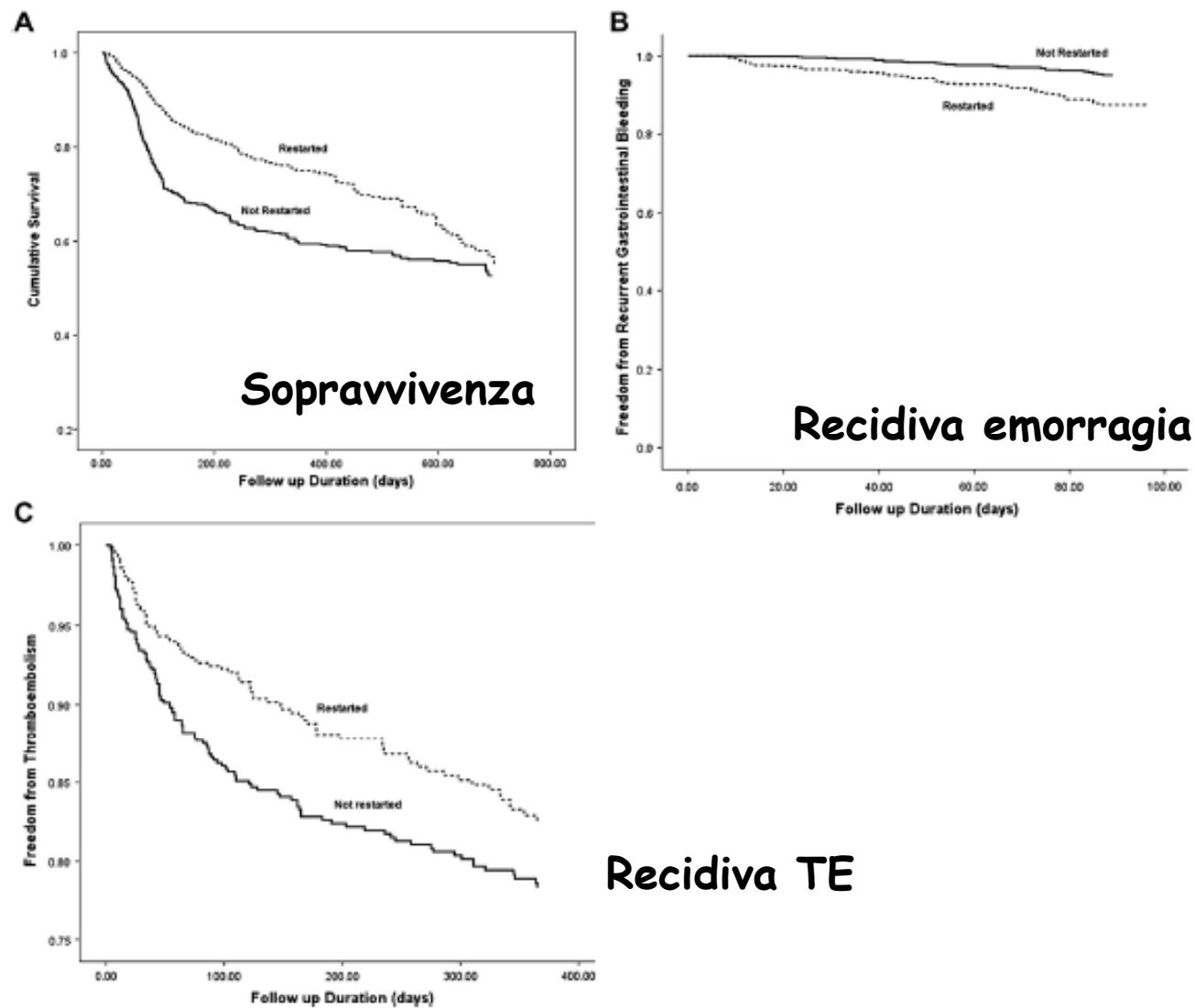
Table 1. Outcomes after anticoagulation-related gastrointestinal tract bleeding in patients who do and do not resume anticoagulation th

Study	Indication for anticoagulation	Anticoagulant	Follow-up period	Adjusted HR-TE (95% CI)	Adjusted HR-recurrent GIB (95% CI)	Adjusted HR all-cau mortality (95%
Witt 2012, N = 442 <sup>6</sup>	AF, VTE, MVR, Other	Warfarin	90 d	0.05 (0.01-0.58)	1.32 (0.50-3.57)	0.31 (0.15-0.47)
Qureshi 2014, N = 1329 <sup>5</sup>	AF	Warfarin	1-y (TE) 90-d (GIB) 2-y (ACM)	0.71 (0.54-0.93)	1.18 (0.94-1.10)	0.67 (0.56-0.78)
Staerk 2015, N = 3409 <sup>7</sup>	AF	Single OAC* Single antiplatelet† OAC + antiplatelet* Dual antiplatelet‡	5-y	0.41 (0.31-0.54) 0.76 (0.61-0.95) 0.54 (0.36-0.82) 0.79 (0.34-1.84)	1.22 (0.84-1.77) 1.19 (0.82-1.74) 1.34 (0.79-2.28) 0.58 (0.08-4.30)	0.39 (0.34-0.44) 0.76 (0.68-0.84) 0.41 (0.32-0.52) 0.88 (0.57-1.19)
Sengupta 2015, N = 197 <sup>8</sup>	Various	Warfarin	90 d	0.12 (0.006-0.81)	2.17 (0.86-6.67)	0.63 (0.22-0.84)

These results strongly suggest that most patients with anticoagulation-related GIB should probably resume anticoagulation therapy once the acute event has been managed.

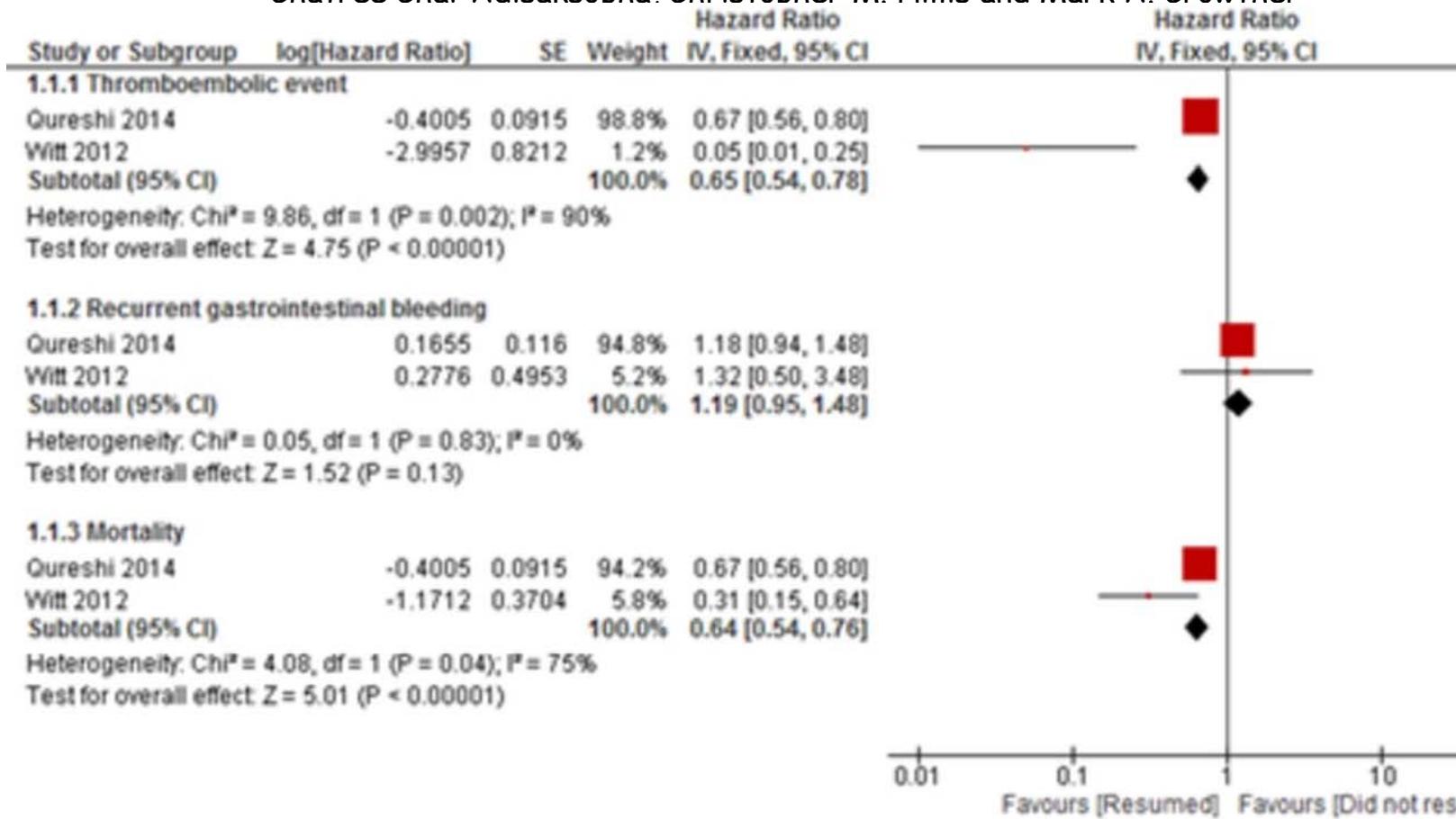
# Restarting Anticoagulation and Outcomes After Major Gastrointestinal Bleeding in Atrial Fibrillation

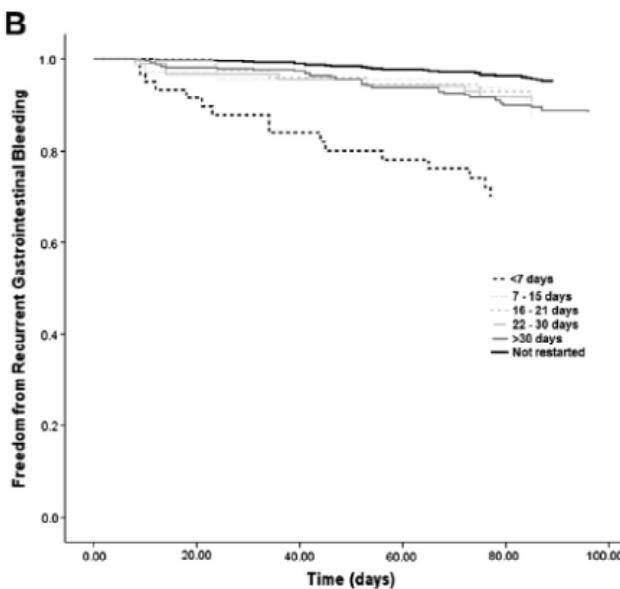
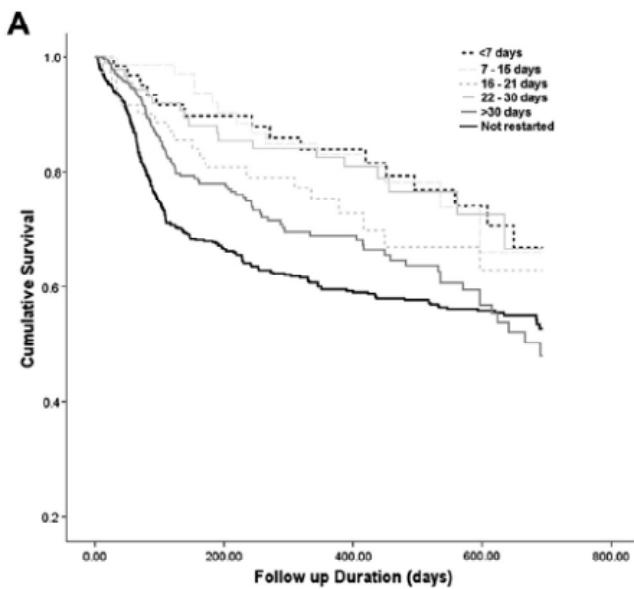
Waqas Qureshi, MD<sup>a,\*</sup>, Chetan Mittal, MD<sup>b</sup>, Iani Patsias, MD<sup>b</sup>, Kiran Garikapati, MD<sup>b</sup>,  
Aishwarya Kuchipudi, MD<sup>b</sup>, Gagandeep Cheema, MD<sup>b</sup>, Mohammad Elbatta, MD<sup>b</sup>, Zaid Alirhayim, MD<sup>b</sup>,  
and Fatima Khalid, MD<sup>c</sup>



# Thromboembolic Events, Recurrent Gastrointestinal Bleeding and Mortality after Resuming Anticoagulant Following Gastrointestinal Bleeding: A Systematic Review and Meta-Analysis

Chatree Chai-Adisaksopha, Christopher M. Hillis and Mark A. Crowther





When the outcomes were stratified by duration of warfarin interruption, restarting warfarin after 7 days was not associated with increased risk of GIB but was associated with decreased risk of mortality and thromboembolism compared with resuming after 30 days of interruption. Decision to restart warfarin after an episode of major GIB is associated with improved survival and decreased thromboembolism without increased risk of GIB after 7 days of interruption. © 2014 Elsevier Inc. All rights reserved. (Am J Cardiol 2014;113:662–668)

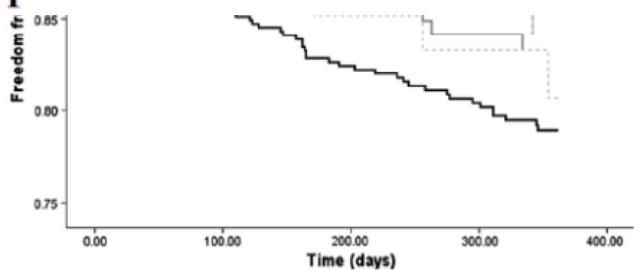


Figure 2. (A) Kaplan-Meier survival analysis showing 1-year mortality stratified by duration of interruption of warfarin. (B) Time-to-event analysis showing 90-day cumulative incidence of recurrent GIB stratified by duration of interruption of warfarin. (C) Time-to-event analysis showing 1-year cumulative incidence of thromboembolism stratified by duration of interruption of warfarin.



# Meglio warfarin o Doacs ?

## THROMBOSIS AND HEMOSTASIS

### The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis

Chatree Chai-Adisaksoha,<sup>1,2</sup> Mark Crowther,<sup>1</sup> Tetsuya Isayama,<sup>3</sup> and Wendy Lim<sup>1</sup>

<sup>1</sup>Department of Medicine, McMaster University, Hamilton, ON, Canada; <sup>2</sup>Department of Medicine, Chiang Mai University, Chiang Mai, Thailand; and

<sup>3</sup>Sunnybrook Health Sciences Center, University of Toronto, Toronto, ON, Canada

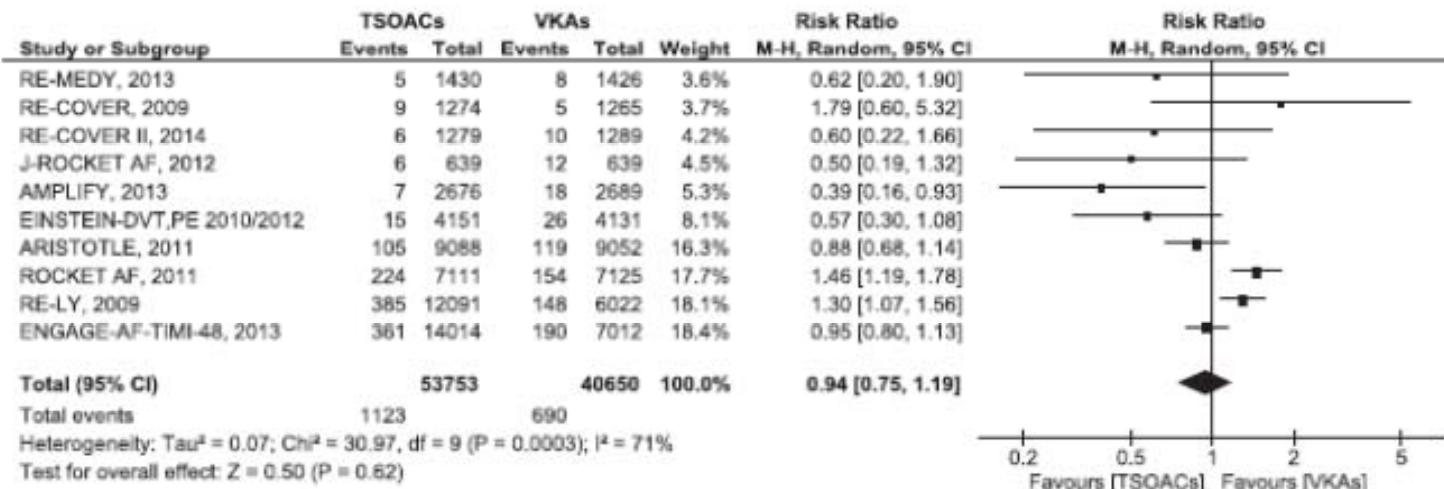


Figure 6. Major GI bleeding events comparing TSOACs with VKAs.

In conclusion, when compared with VKAs administered to a target INR of 2.0 to 3.0, TSOACs are associated with less major bleeding, fatal bleeding, intracranial bleeding, clinically relevant nonmajor bleeding, and total bleeding. Additionally, TSOACs do not appear to increase the risk of GI hemorrhage.

# Gastrointestinal hemorrhage and re-initiation of Doacs

Data from an open cohort study (upper GI bleed 21,641) gave an age-standardized incidence rate (per 1000 person-years) for upper GI tract bleeding of

- 5.8 in those prescribed warfarin
- 2.7 in those prescribed DOACs.

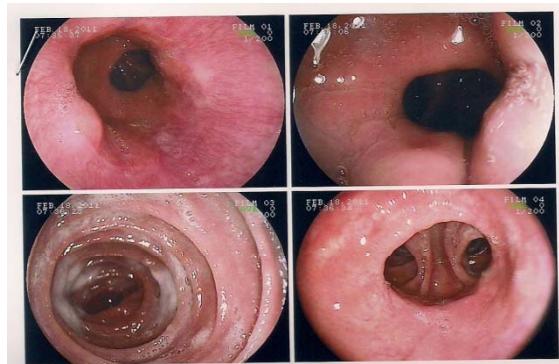
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A meta-analysis of data from 11 phase 3 randomized controlled trials reported no significant difference in the overall incidence of major GI bleeding between DOACs and VKAs (relative risk 0.94; P = .62).

There is evidence, some of it prospective, that restarting OAC therapy after GI hemorrhage is beneficial.



# Situazioni particolari



For MHV patients at highest thrombotic risk (mitral MHV, multiple MHVs, MHV with prior stroke or AF, and MVH implanted within 6 months) a potential role for heparin bridge therapy starting 72 h after endoscopy may be advocated, provided that the haemostasis is established and the risk of rebleeding is low.

Another issue is the timing of anticoagulant resumption in patients with clinically significant GI haemorrhage and no source of bleeding identified at endoscopy. In these patients, the timing should be decided based on estimates of the individual risks of rebleeding and thrombosis.

Lastly, in patients for whom the endoscopist is not fully confident in the achievement of haemostasis, no clear-cut recommendations on anticoagulant therapy resumption can be made. In such cases, a “second look” endoscopy might be indicated, although its role should be better evaluated.

# Quindi riassumendo

Dopo una emorragia gastrointestinale



**Se CHA2DS2 Vasc score >=2 : re-iniziare la terapia anticoagulante**

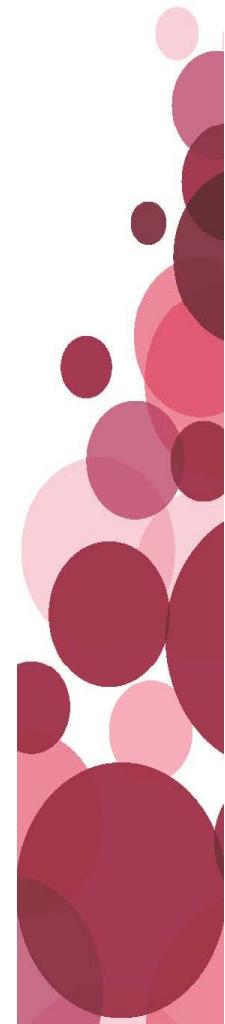
**Quando?** Nel momento in cui la emorragia è cessata, (circa 7 giorni) Evitare di procrastinare per oltre 14 giorni

**Come?** Per os; non necessario in genere ricorrere a EBPM

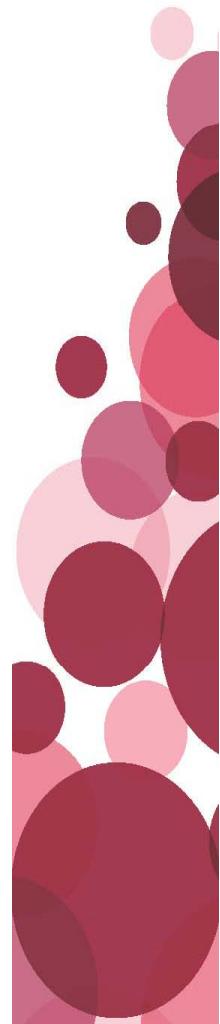
**Quale farmaco?** Alcuni Doacs sono a maggior rischio di emorragia gastrointestinale (comprese MICI e diverticoliti) rispetto al warfarin ( dabigatran e rivaroxaban) e secondo alcuni andrebbero evitati

# Emorragia cerebrale

POLITICALLY CORRECT



# Ripresa terapia anticoagulante



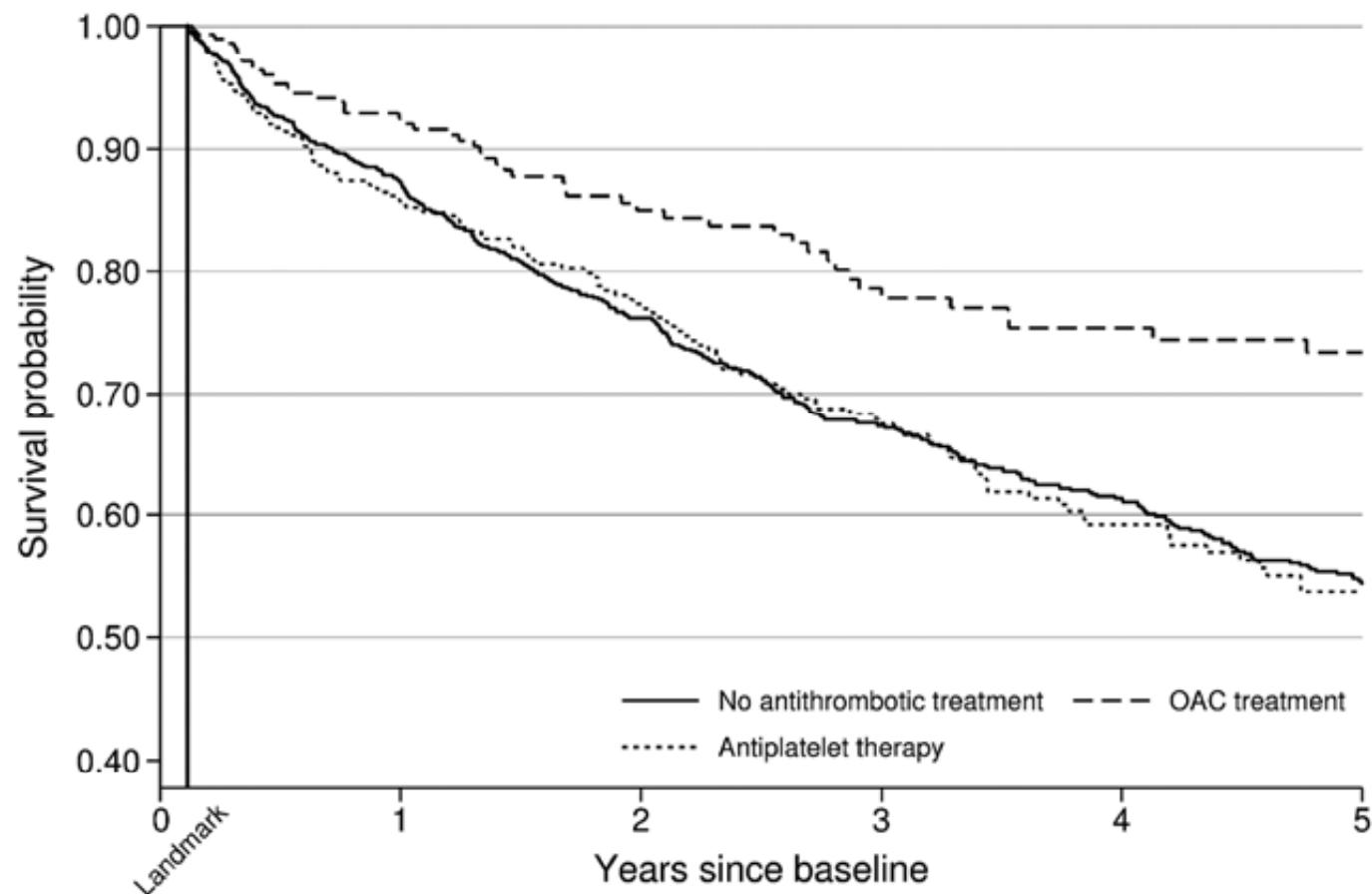
# Pochi studi recenti con conclusioni simili

Table 2. Outcomes after anticoagulation-related intracranial bleeding in patients who do and do not resume anticoagulation therapy

Study	Indication for anticoagulation	Anticoagulant	Follow-up period	HR-TE (95% CI)	HR-recurrent ICH (95% CI)	HR all-cause mortality (95% CI)
Kuramatsu 2015, N = 719 <sup>17</sup>	AF, VTE, MVR, Other	VKA	<b>31 giorni</b>	1-y NR* ↓	NR†	0.26 (0.13-0.53)‡
Witt 2015, N = 160 <sup>18</sup>	AF, VTE, MVR, Other	Warfarin	<b>14 giorni</b>	1-y 0.28 (0.06-1.27)§ ↓	0.47 (0.10-2.30)§ ↓	0.76 (0.30-1.89)¶ ↓
Nielsen 2015, N = 1752 <sup>19</sup>	AF	VKA, DOAC Antiplatelet therapy	<b>34 giorni</b>	1-y 0.59 (0.33-1.03)¶ ↓ 0.98 (0.65-1.49)¶ ↓	0.91 (0.56-1.49)¶ ↓ 0.60 (0.37- 1.03)¶ ↓	0.55 (0.37-0.82)¶ ↓ 0.90 (0.67-1.21)¶ ↓

Primi due studi : la sede di emorragia (lobare o profonda) era simile fra i pazienti che riprendevano e quelli che non riprendevano TAO

# Restarting anticoagulant treatment after intracranial hemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality, and bleeding: a nationwide cohort study



Five-year Kaplan-Meier survival curve for restarting OAC treatment, for receiving antiplatelet therapy, and for not receiving anti-thrombotic treatment with the use of a landmark at 6 weeks (relative to discharge from hospital) for treatment regimens stratification

# Reinitiation of anticoagulation after warfarin-associated intracranial hemorrhage and mortality risk :

The Best Practice for Reinitiating Anticoagulation Therapy After Intracranial Bleeding (BRAIN) study.  
Unadjusted outcomes

	Warfarin restarted (n = 91)	Warfarin not restarted (n = 193)	P value
Death			
In-hospital	30 (33.0)	98 (50.8)	0.005
1 month	29 (31.9)	105 (54.4)	<0.001
6 months	38 (41.8)	114 (59.1)	0.006
1 year	44 (48)	118 (61)	0.04
ICH expansion or recurrence	14 (15.4)	29 (15.0)	0.94
Death or intracranial bleeding			
1 month	32 (35.2)	106 (54.9)	0.002
1 year	46 (50.5)	118 (61.1)	0.09
Death, bleeding, or thrombotic complication at 1 year	47 (51.6)	119 (61.7)	0.11
Neurologic worsening in-hospital	39 (42.9)	101 (52.3)	0.14
Modified Rankin score < 3 at discharge	17 (18.7)	22 (11.4)	0.10
Discharge to home/retirement home	18 (19.8)	26 (13.5)	0.17

# INTRACRANIAL HEMORRHAGE AND RE-INITIATION OF OACS

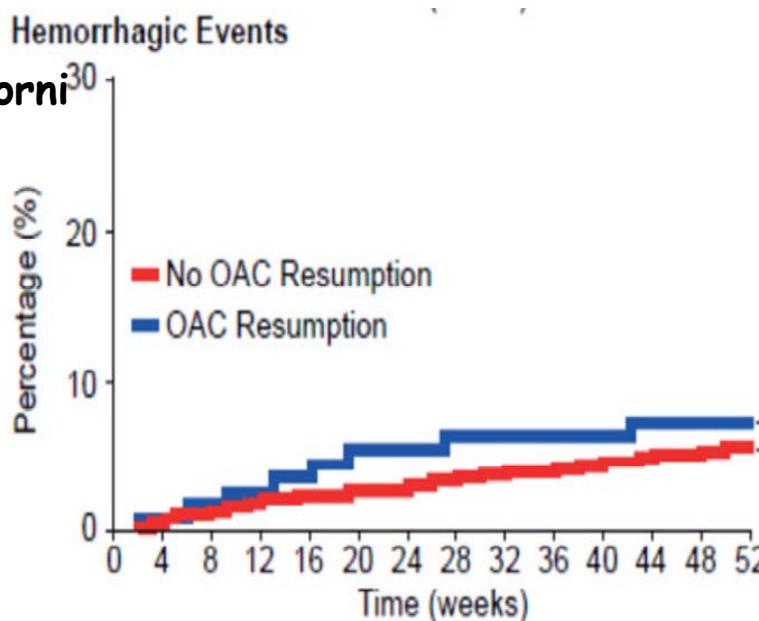
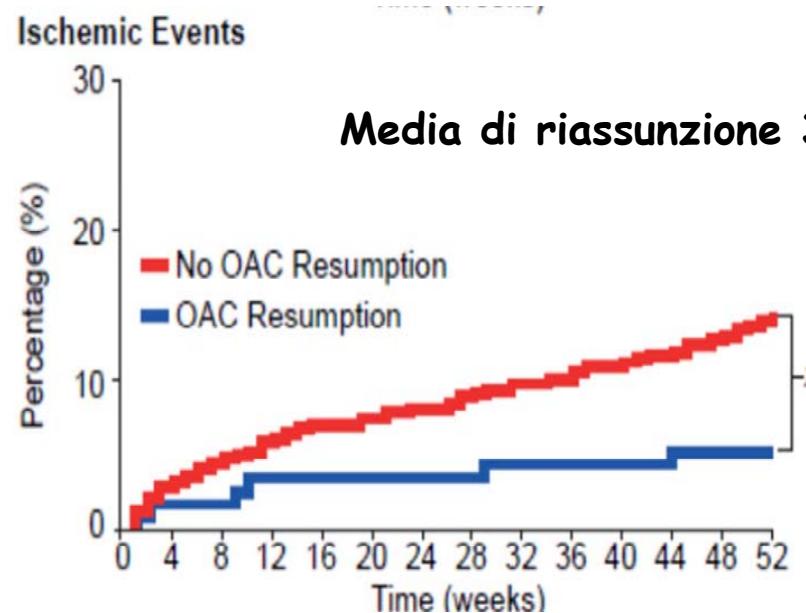
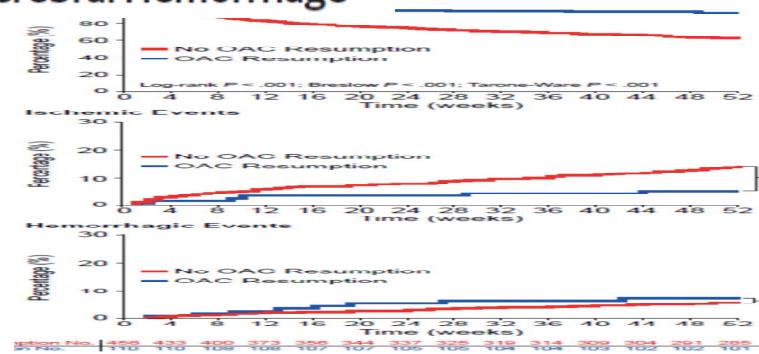
... A Canadian registry study of 284 spontaneous warfarin related ICH (intracerebral or subarachnoid hemorrhage) cases, in which warfarin was restarted in 91 (32%) patients, reported that there was no increase in 30-day mortality in patients who restarted warfarin (adjusted odds ratio 0.49; 95% CI, 0.26-0.93; P = .03).

This trend continued at 1 year but was  
Re-Initiation of Dabigatran and Direct Factor Xa Antagonists After a Major Bleed. The American Journal of Medicine (2016)

# Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage

*Unmatched survival and event rates  
atrial fibrillation patients with and without  
OAC resumption from index-intracranial  
hemorrhage until 1-year follow-up.*

The crude incidence of bleeding events was not significantly different among AF patients with and without OAC resumption



# Non tutti sono d'accordo



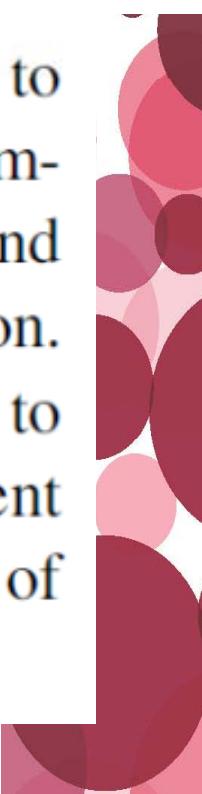
Recurrence of ICH after resumption of anticoagulation with VK antagonists  
CHIRONE Study

**Conclusions:** Our results show that patients with a history of ICH carry a significant risk of recurrent ICH when treated with VKA anticoagulation. The risk is also present, though to a lower degree, in patients with previous posttraumatic events. All patients with a history of ICH require a careful evaluation of their thromboembolic risk to estimate the net clinical benefit of (re)starting anticoagulation with VKAs. *Neurology® 2014;82:1020-1026*

## Restarting oral anticoagulants after intracerebral hemorrhage: cons

Silvia Ricci · Francesca Pistoia · Antonio Carolei ·  
Simona Sacco

In conclusion, we want to underscore that the chance to have an ICH and to require anticoagulants for cardioembolism is an extremely difficult situation for the patient and for the physician who has to take a troublesome decision. At the moment, while hoping for new clinical evidence to emerge, we suggest to avoid the prescription of a treatment that may contribute to worsening of the natural history of our patients.





Riskier or  
Stop  
Antithrombotics  
Randomised  
Trial

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Our target is to recruit **720** participants by 31 May 2018. So far, we have recruited: **453**

### What is RESTART?

**RESTART** is a randomised controlled trial for adults surviving spontaneous intracerebral haemorrhage who had taken an antithrombotic drug (i.e. anticoagulant or antiplatelet medication) for the prevention of vaso-occlusive disease before the ICH.

**RESTART** is testing whether a policy of starting antiplatelet drugs (one or more of aspirin, clopidogrel, or dipyridamole, chosen at investigator's discretion) results in a beneficial net reduction of all serious vascular events over two years compared with a policy of avoiding antiplatelet drugs.

**RESTART** began recruitment in the United Kingdom in May 2013.

### Who is running RESTART?

**RESTART** is run by a team from the University of Edinburgh, in collaboration with researchers at the University of Dundee, the University of Newcastle-upon-Tyne, and University College London.

**RESTART** is overseen by a Steering Committee led by an independent chairperson, with representation from the British Heart Foundation.

**RESTART** accumulating data is overseen by a completely independent Data Monitoring Committee.

Sponsors:



Registered

ISRCTN71907627:



Funder:



## When should you restart anticoagulation in patients who suffer an intracranial bleed who also have a prosthetic valve?

Dinesh Chandra, Anubhav Gupta\*, Vijay Grover and Vijay Kumar Gupta

Table 1: Best evidence papers

S. no.	Author, date, journal and country Study type	Patient group Prosthesis ICH location	Management	Outcomes	Key results	Comments
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Table 1: (Continued)

S. no.	Author, date, journal and country	Patient group Prosthesis	Management	Outcomes	Key results	Comments
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We conclude that anticoagulants, either heparin or OAC, can safely be withheld for a short period of up to 7–14 days in a patient with ICH on OAC with a very low probability of thromboembolic phenomenon and can safely be reinstated as early as 3 days for heparin and 7 days for OAC without major concerns of rebleeding. At the same time, there is a definite role for the rapid reversal of coagulopathy in acute settings using vitamin K, fresh frozen plasma or prothrombin concentrate.

Neurosurgery, USA [7]

Retrospective  
(level III)

7 Claassen *et al.* (2008),  
Arch Neurol, USA [8]

Retrospective  
(level III)

ICH

Mitral: 16

Aortic: 20

Double: 3

SDH: 20

SAH: 4

Ganglionic: 2

Lobar: 10

Cerebellar: 3

with FFP, and some of them given vitamin K.  
All patient started on OAC on median of 8 days (2 days to 3 months) with 5 patients received heparin

months with 14 deaths of which 13 were due to acute event and 1 after 3 years following haemorrhage

stopped and safely OAC started without any valve-related complication and 5 patients were also given heparin

anticoagulant for a brief period, i.e. 2–90 days with a median of 8 days

OAC: oral anticoagulant; ICH: intracranial haemorrhage; CCF: congestive cardiac failure, LMWH: low molecular weight heparin, FFP: fresh frozen plasma; PCC: prothrombin concentration.

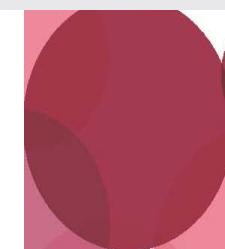
Reversal treatment strategy not reported, 12 patients started on OAC on median of 10 days (7–28 days)

Followed up for 43 months with two deaths in patients where OAC not restarted, one CCF and other comorbidity and one myocardial infarction

All patients' OAC stopped and safely OAC started in 10 without any valve-related complication, excluding 2 deaths which were not related to valve or ICH

OAC can be safely withheld in patients with ICH for a short duration like 7–28 days but reinstitution of OAC definite advantage of preventing unnecessarily thromboembolic complication

Continued

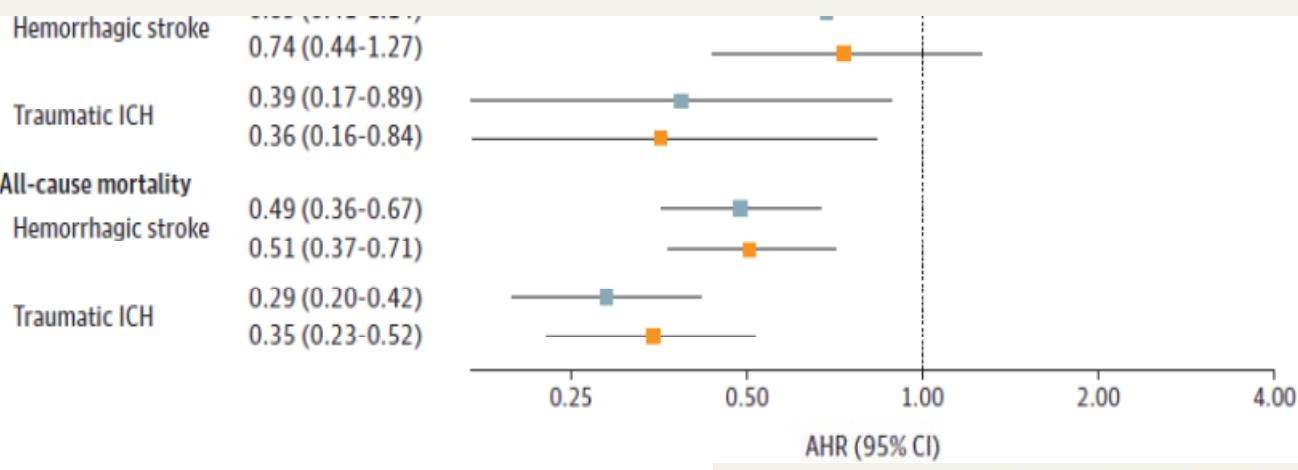


## Outcomes Associated With Resuming Warfarin Treatment After Hemorrhagic Stroke or Traumatic Intracranial Hemorrhage in Patients With Atrial Fibrillation

Figure 2. Forest Plots of Study Outcomes Associated With Resuming Warfarin Treatment



**CONCLUSIONS AND RELEVANCE** Resumption of warfarin therapy after spontaneous hemorrhagic stroke in patients with AF was associated with a lower rate of ischemic events and a higher rate of recurrent ICH. Among patients with a traumatic ICH, a similar lower rate of ischemic events was found; however, a lower relative risk for recurrent ICH despite resuming warfarin treatment was also revealed.

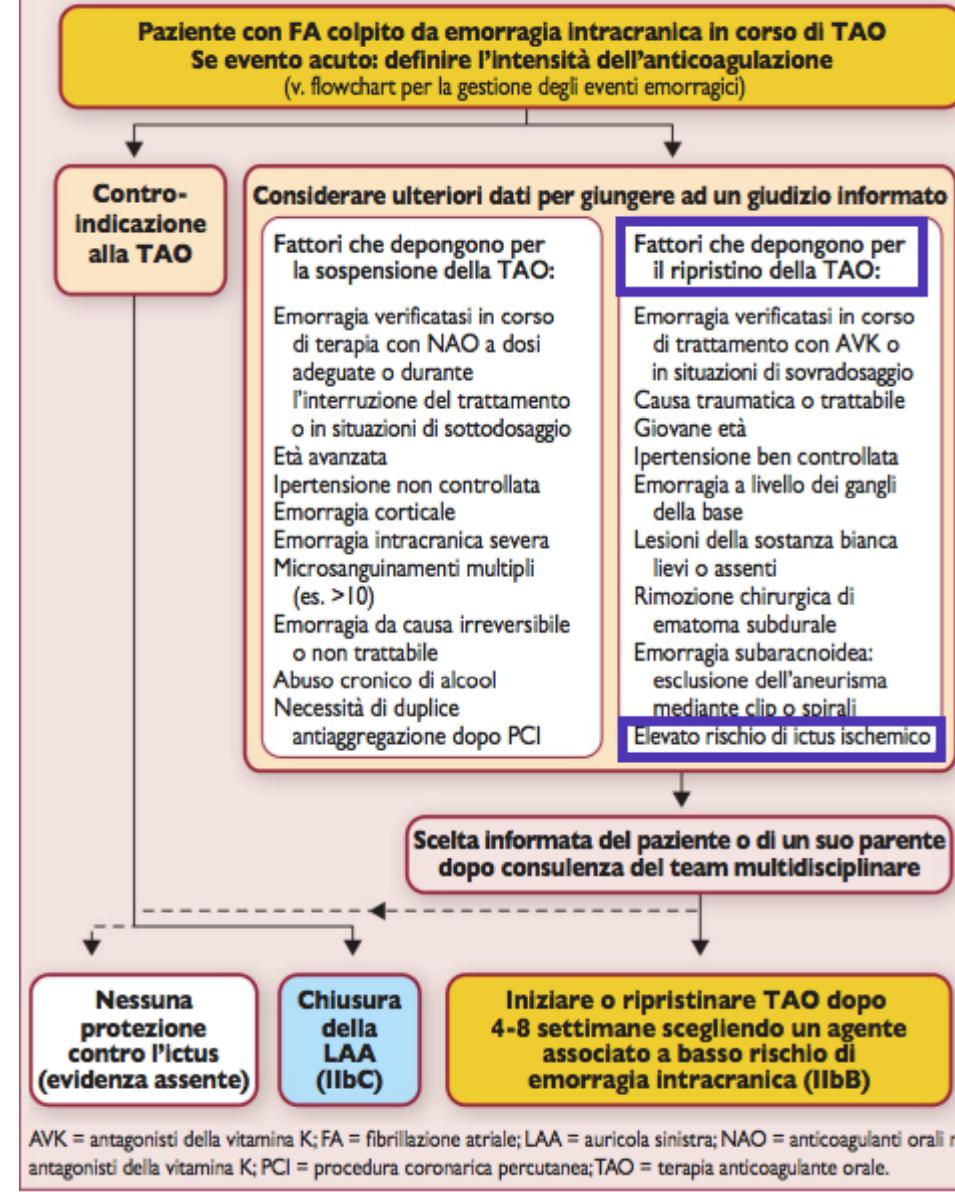


No resumption was the reference condition. The analyses were stratified by index ICH event. Crude analyses are depicted by lines with blue boxes; lines with orange boxes for adjusted analyses. AHR indicates adjusted hazard ratio; ICH, intracranial hemorrhage; and SE, systemic embolism.

# Linee guida....

Guideline and Citation	Recommendation
European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage, 2014 <sup>50</sup>	<p><i>Recommendation 18:</i> Unable to make firm recommendations about whether and when to resume antithrombotic drugs after ICH in the absence of RCTs to address treatment dilemmas</p> <p><i>Additional information:</i> Suggested timings for restarting these drugs range from not earlier than 14 days up to 30 weeks (data from observational studies)<sup>30,31</sup></p>
Guidelines for the management of spontaneous intracerebral hemorrhage (American Heart Association/American Stroke Association), 2015 <sup>51</sup>	<p><i>Prevention of Recurrent ICH, Recommendation 6:</i> Optimal timing to resume OAC after OAC-related ICH is uncertain. Avoidance of OAC for at least 4 weeks, in patients without mechanical heart valves, might decrease the risk of ICH recurrence. If indicated, aspirin monotherapy can probably be restarted in the days after ICH, although the optimal timing is uncertain</p> <p><i>Recommendation 4.3:</i> In patients with a history of a symptomatic primary ICH, we suggest against the long-term use of antithrombotic therapy for the prevention of ischemic stroke</p> <p><i>Remarks:</i> Patients with a history of ICH who might benefit from antithrombotic therapy are those at relatively low risk of recurrent ICH (eg, with deep hemorrhages) and relatively high risk (&gt;7% per year) of cardiac thromboembolic events (eg, with mechanical heart valves or CHADS<sub>2</sub>* score of ≥4 points)</p>
Antithrombotic and thrombolytic therapy for ischemic stroke, (Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians), 2012 <sup>52</sup>	<p>ICH = intracranial hemorrhage; OAC = oral anticoagulant; RCT = randomized controlled trial.</p> <p>* CHADS<sub>2</sub>, (score for atrial fibrillation stroke risk) congestive heart failure history, hypertension history, age ≥75 years, diabetes mellitus history, stroke or transient ischemic attack previously (see also Table 2).</p>

**Figura 6 Inizio o ripristino della terapia anticoagulante nei pazienti con FA colpiti da emorragia intracranica.** Questo approccio si basa su opinioni di consenso e su dati retrospettivi. Prima di iniziare il trattamento, il paziente deve essere valutato da un team multidisciplinare (medico/neurologo esperto nella gestione dell'ictus, cardiologo, neuroradiologo e neurochirurgo).



# Doacs or Warfarin?

## Review

Re-initiation of dabigatran and direct factor Xa antagonists after a major bleed 

- Currently, there are few data on how DOACs might change the risk-benefit analysis of when to restart therapy after a major bleed event, particularly in ICH.
- However, the available data are reassuring in that practitioners would expect approximately 50% fewer of these events vs VKA-treated patients

# Quindi riassumendo

Dopo una emorragia cerebrale



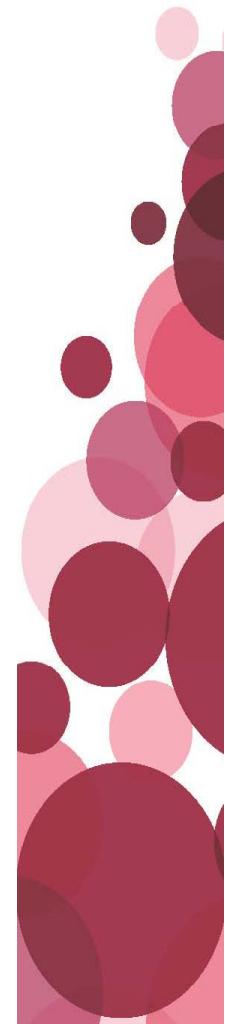
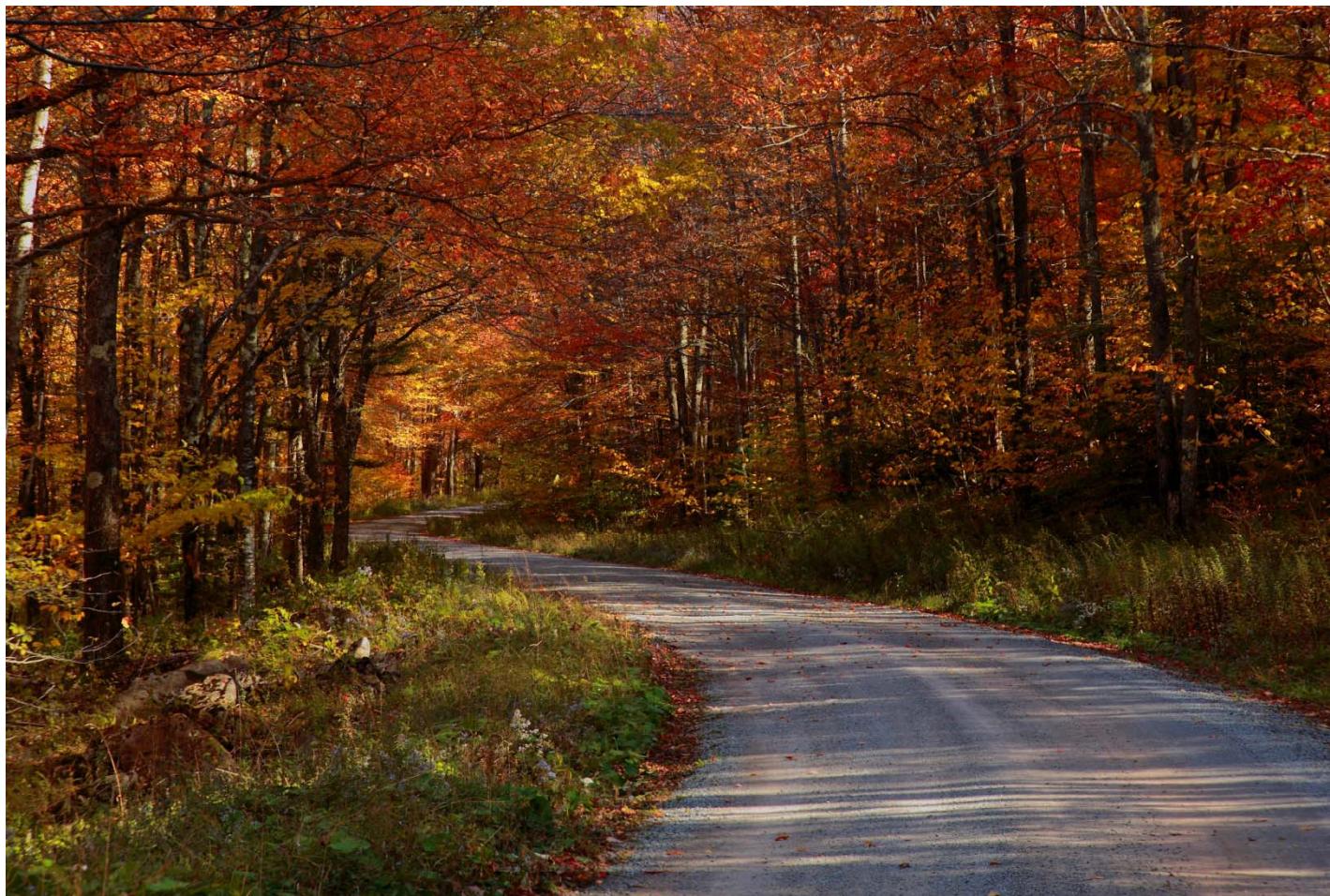
**Calcolare adeguatamente il rischio tromboembolico dal momento che quello emorragico è alto**

**Quando riprendere? In media 1 mese (alcuni casi 6 mesi)**

**Come? Per os; opportuno ricorrere a EBPM a dosi ridotte in caso di valvole protesiche o alto rischio tromboembolico**

**Quale farmaco? I Doacs mostrano un profilo di rischio migliore rispetto al warfarin**

# Altre sedi di sanguinamento



# Altre sedi di sanguinamento

Riprendere la anticoagulazione se necessaria  
risolta la causa del sanguinamento

Table 3. Clinical characteristics arguing for or against resuming anticoagulation after major bleeding

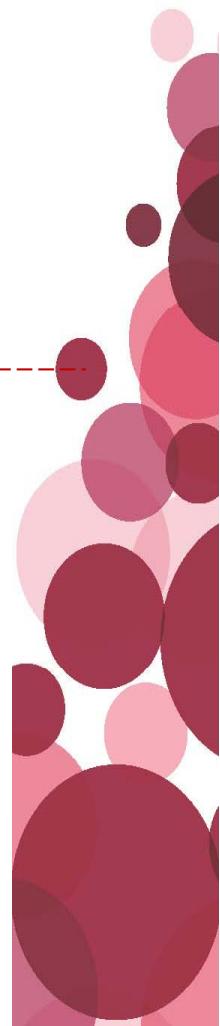
Clinical characteristic	For	Against
<b>Bleed-related characteristics</b>		
Known, correctable source	+++	
Known, uncorrectable source	+	
Unknown source		+

## Per esempio

Finding and controlling the source of bleeding is important.<sup>26,37</sup> For example, a patient with gross hematuria who is found on cystoscopy to have a urothelial papilloma is unlikely to have rebleeding if the tumor is successfully resected and serial follow-up shows no regrowth. In contrast, consider a patient with a major gastrointestinal hemorrhage, the source of which remains elusive after upper, lower, and capsule endoscopy or, alternatively, is suspected to be from one of multiple angiodyplastic lesions. Without definitive source management, this patient faces a high risk of rebleeding.

SI

???



# Ripresa dell'anticoagulazione dopo emorragia dei tessuti molli

- Rappresentano circa il 20% delle emorragie correlate alla terapia anticoagulante
- Le emorragie retroperitoneali sono associate ad alta morbidità e mortalità; 20% di esse sono associate a neuropatia femorale
- Quando: 4 giorni dopo l'evento (ragionevole)

# Ci sono differenze fra i Doacs ?



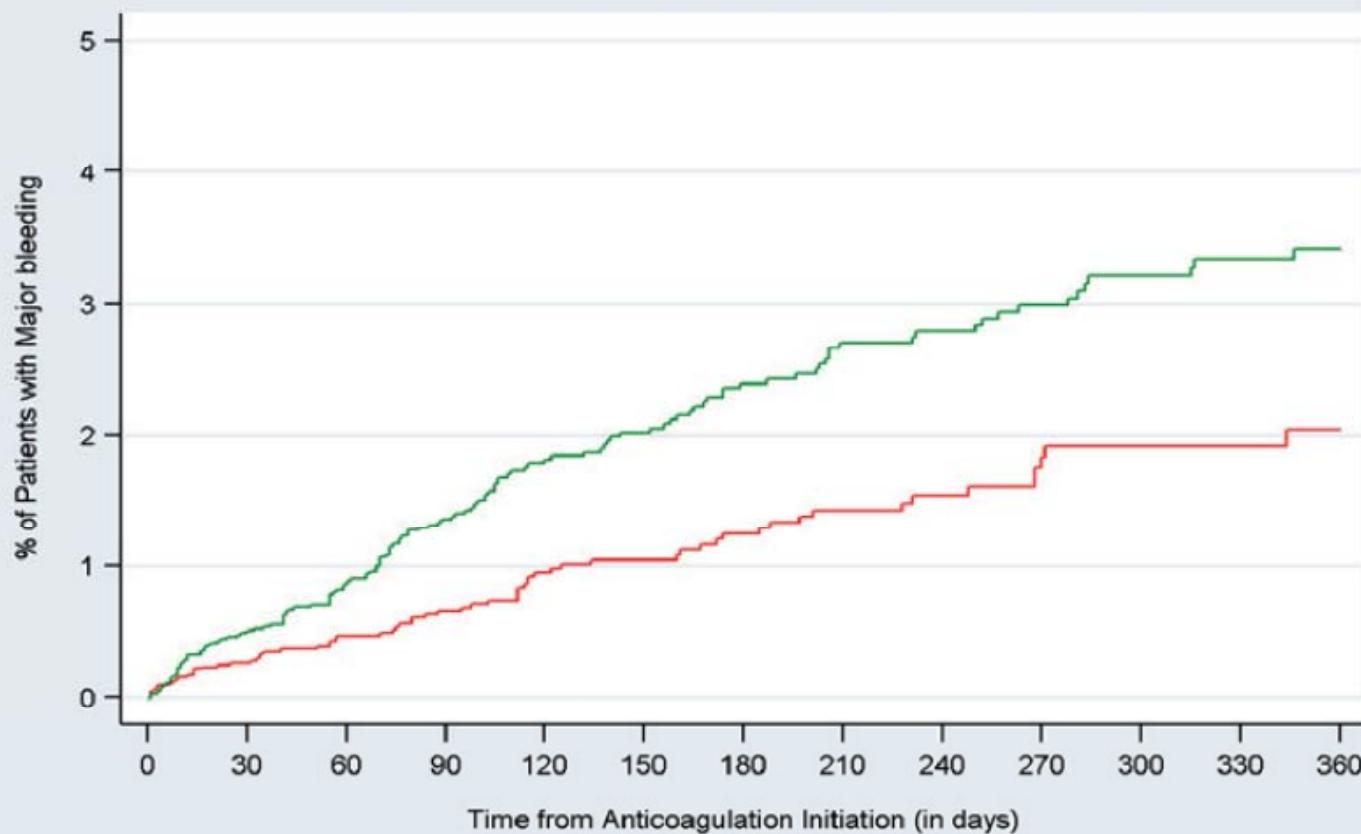
# **Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin**

**A propensity score matched analysis**

## **What does this paper add?**

- Using propensity score matching (PSM), the risk of major bleeding among NVAF patients newly prescribed warfarin, dabigatran, apixaban, or rivaroxaban was compared.
- Compared to warfarin initiation, dabigatran and apixaban initiation demonstrated significantly lower risk of major bleeding. There was no significant difference in risk of major bleeding when matched rivaroxaban and warfarin patients were compared.
- When NOACs were compared, matched rivaroxaban patients had a significantly higher risk of major bleeding compared to patients newly initiated on apixaban. There was no statistically significant difference in risk of major bleeding between apixaban or rivaroxaban initiators matched to dabigatran initiators.
- This is one of the first PSM comparative safety studies assessing the risk of major bleeding among newly-initiated warfarin, dabigatran, rivaroxaban, and apixaban US-based patients.

### Cumulative Incidence of Major Bleeding after Matching



Number of people at risk

Apixaban	7399	6612	4835	4041	3189	2710	2272	1912	1575	1293	1048	856	666
Rivaroxaban	7399	6696	5010	4343	3586	3140	2751	2395	2119	1849	1602	1371	1151

— Apixaban — Rivaroxaban

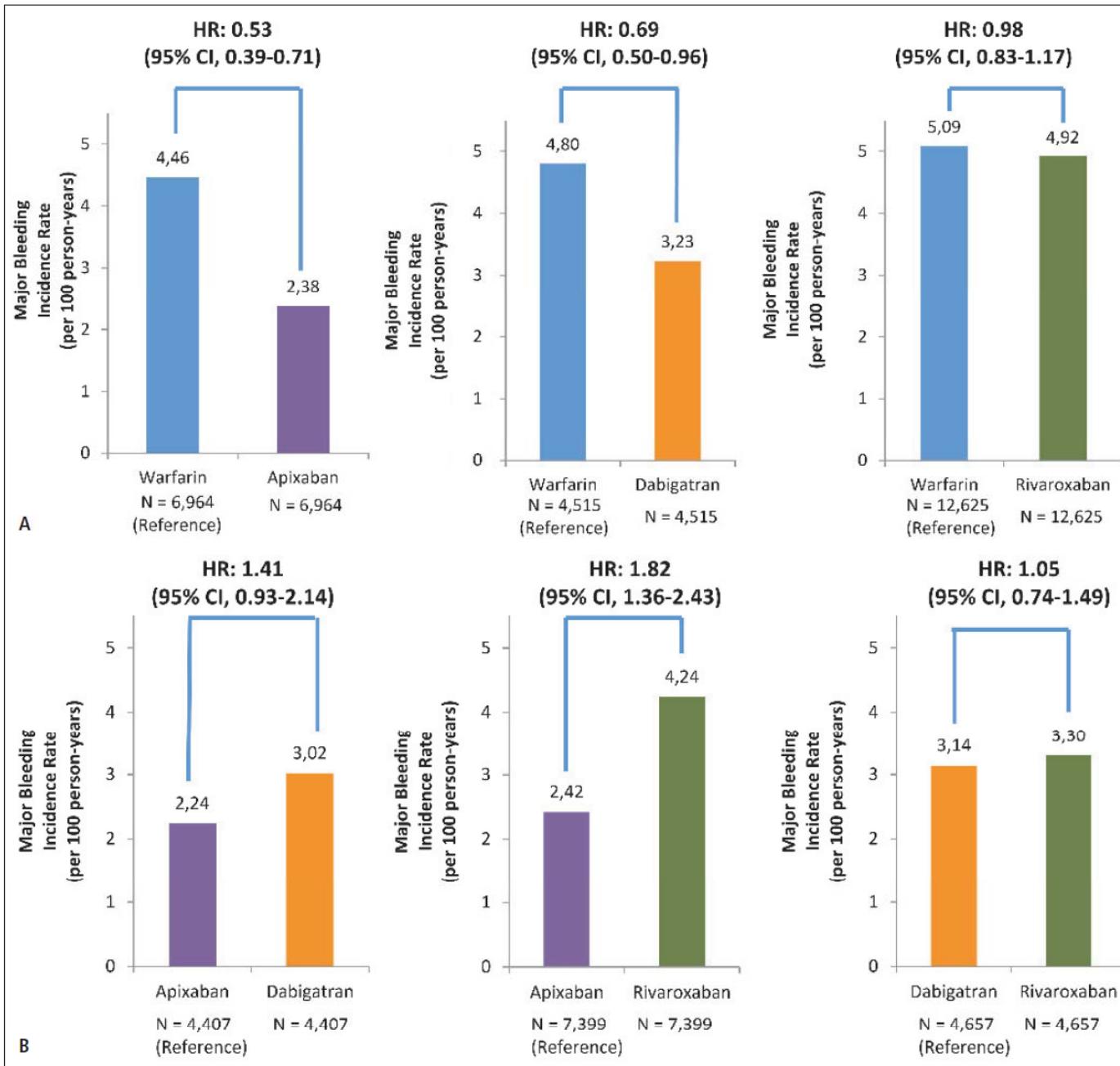


Figure 3: Major bleeding incidence rates and hazard ratios in warfarin-NOAC propensity score matched cohorts (A) and in NOAC-NOAC propensity score matched cohorts (B). CI: confidence interval; HR: hazard ratio.

# Conclusioni



# Conclusioni

**Table 3. Clinical characteristics arguing for or against resuming anticoagulation after major bleeding**

Clinical characteristic	For	Against
<b>Bleed-related characteristics</b>		
Known, correctable source	+++	
Known, uncorrectable source	+	
Unknown source		+
Deep ICH location, blood pressure-controlled	++	
Lobar ICH location, MRI evidence of microbleeding		+
<b>Indication for anticoagulation</b>		
Mechanical heart valve	+++	
Idiopathic or recurrent VTE	+++	
Provoked VTE, completed 3 mo of therapy		+++
VTE + protein C/S or antithrombin deficiency or APLA syndrome	++	
Atrial fibrillation, prior history of stroke or higher CHADS <sub>2</sub> or CHA <sub>2</sub> DS <sub>2</sub> -VASc score	+++	
Atrial fibrillation, lower CHADS <sub>2</sub> , or CHA <sub>2</sub> DS <sub>2</sub> -VASc score	+	
Atrial fibrillation, no additional stroke risk factors		+++
<b>Other characteristics</b>		
History of anticoagulation therapy nonadherence	+	
Previously unstable INR control despite adequate adherence	+	
Renal failure	+	
Poor prognosis, limited life expectancy	+	



## Managing Anticoagulation Patients After a Bleed

### Quando

Interrompere TAO aumenta il rischio tromboembolico e la morte

Dopo emorragia GI riprendere TAO dopo 7 giorni

Dopo emorragia cerebrale riprendere dopo un mese ma anche dopo 10 settimane

large bleed, brainstem or cerebellar ICH).<sup>42</sup>

- Direct oral anticoagulants (DOACs) may be used more often than warfarin in patients with A Fib or VTE due to lower risk of intracranial hemorrhage (e.g., apixaban, dabigatran).<sup>43</sup>
- Involve appropriate specialists in this decision (e.g., cardiologist, gastroenterologist, neurologist, urologist).

## Managing Anticoagulation Patients After a Bleed

### Quale

Doacs hanno un minor rischio di emorragia cerebrale

Warfarin ha un minor rischio di emorragia GI rispetto a dabigatran e rivaroxaban

- |  |  |
|--|--|
|  | <p>bleed compared to treatment with warfarin.<sup>30,31</sup></p> <ul style="list-style-type: none"><li>• Use particular caution with dabigatran or rivaroxaban in patients with inflammatory bowel disease, intestinal angiodyplasia, or diverticulitis.<sup>38</sup></li></ul> |
|--|--|

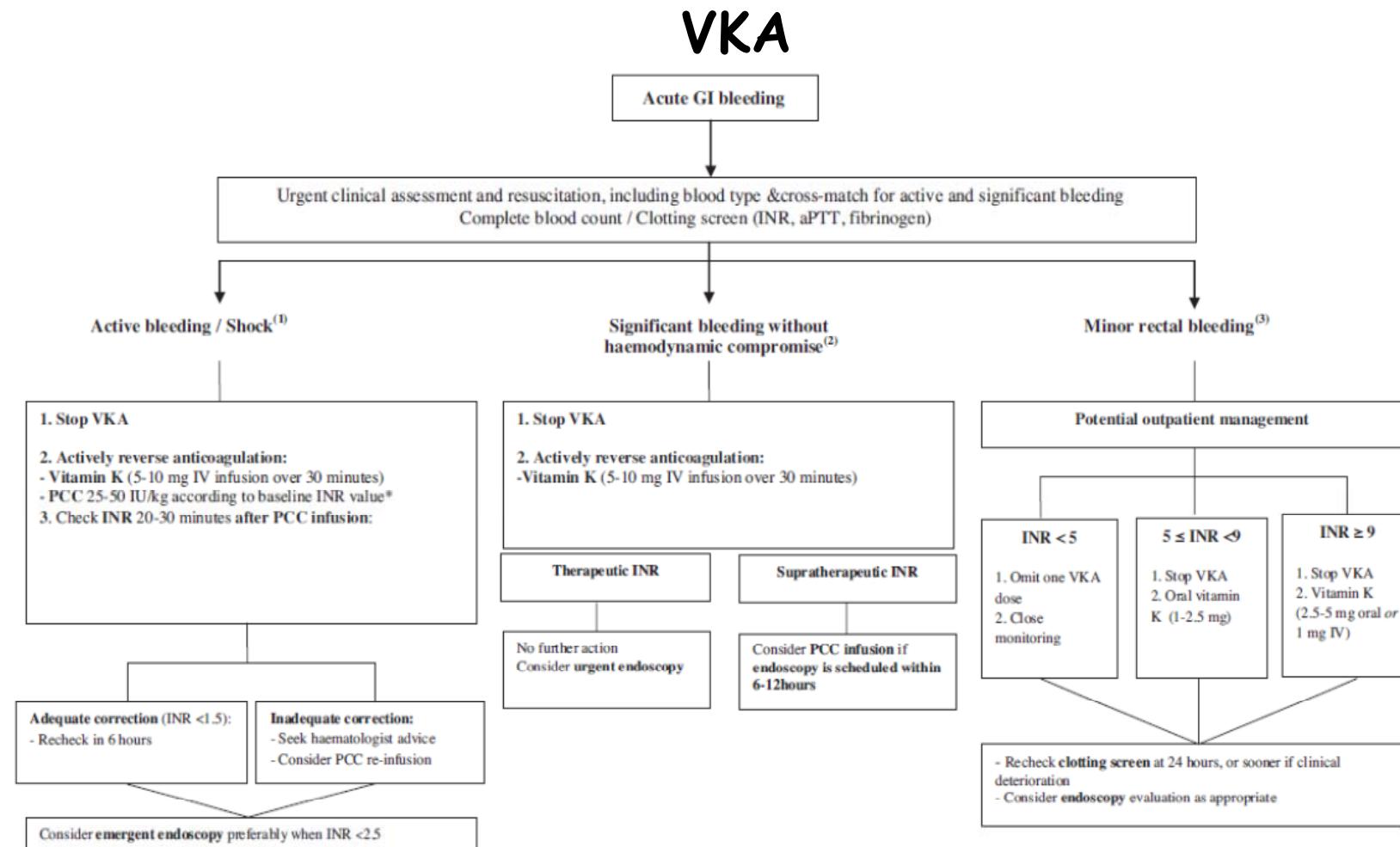




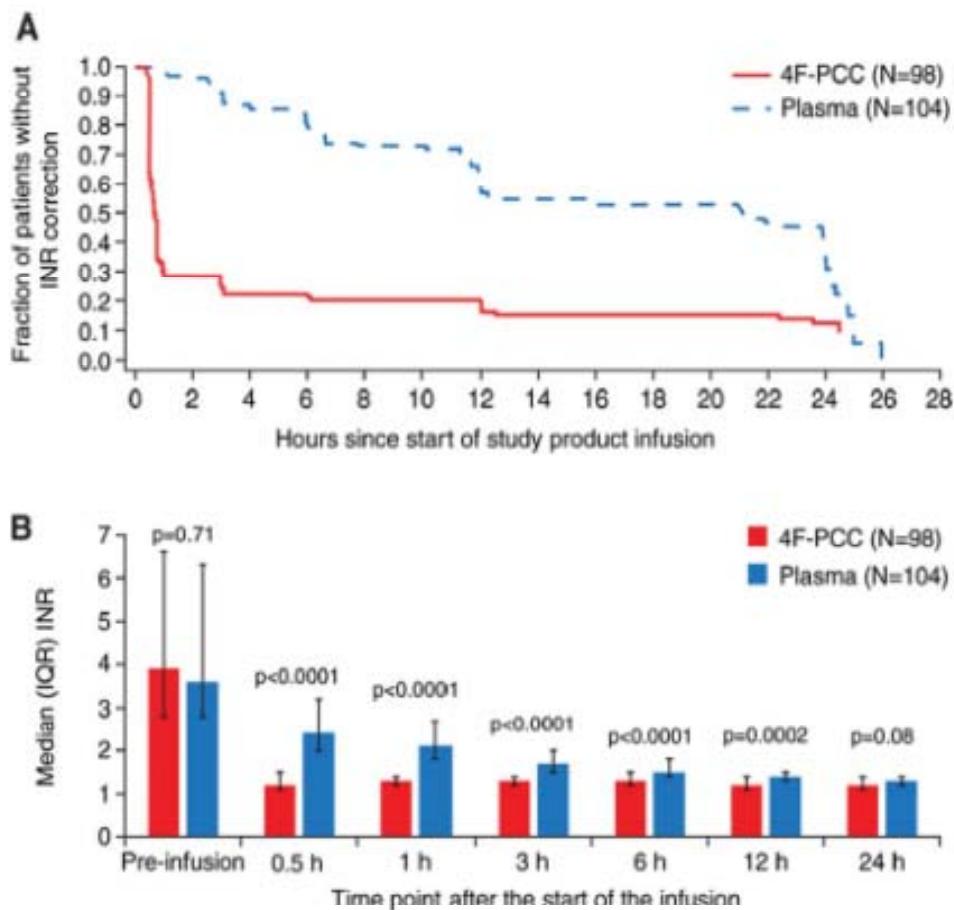
# Management of anticoagulation in patients with acute gastrointestinal bleeding



Franco Radaelli <sup>a,\*</sup>, Francesco Dentali <sup>b</sup>, Alessandro Repici <sup>c</sup>, Arnaldo Amato <sup>a</sup>, Silvia Paggi <sup>a</sup>, Emanuele Rondonotti <sup>a</sup>, Jean Marc Dumonceau <sup>d</sup>



# *CCP vs PFC*



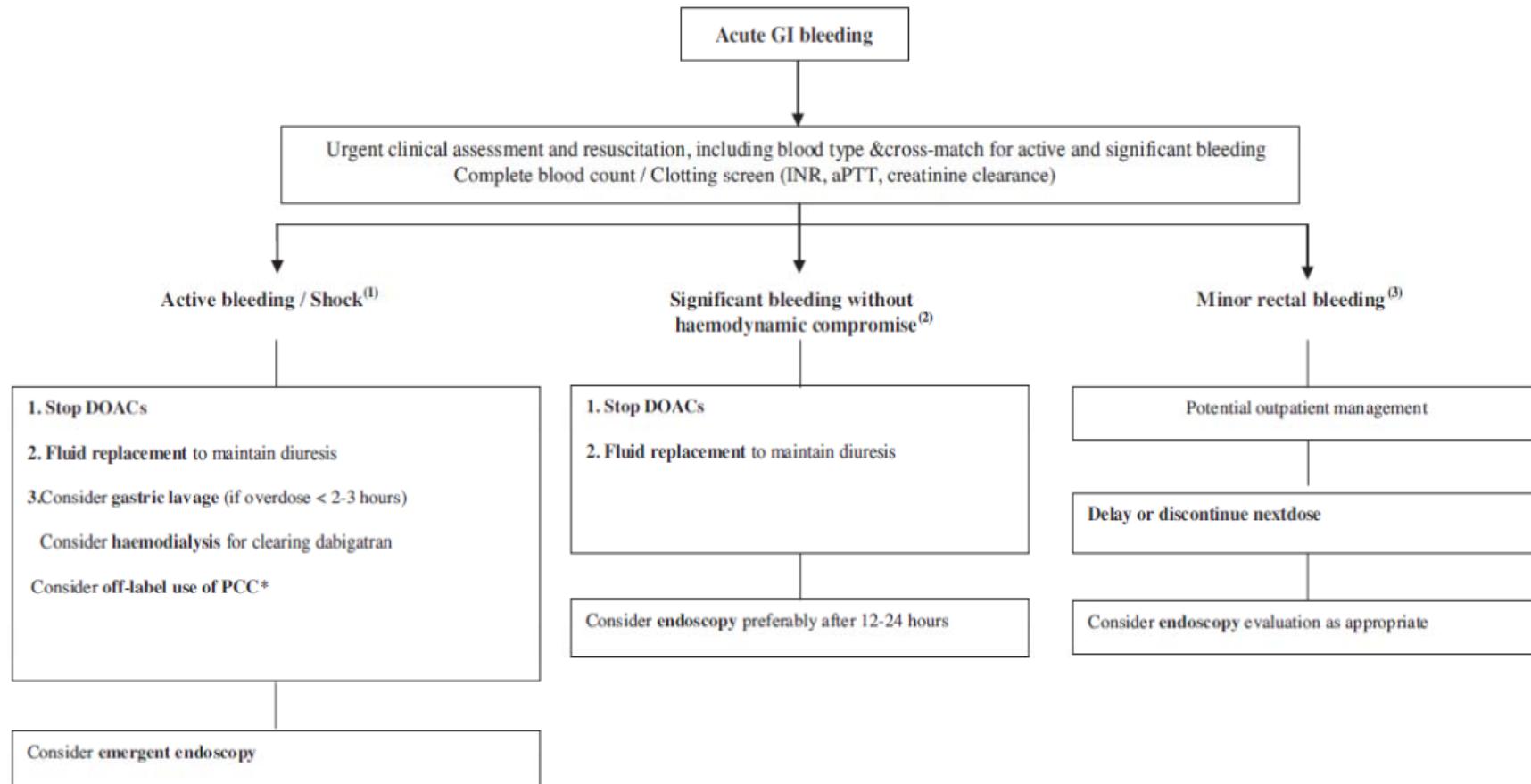
Sarode R et al. Circulation. 2013;128:1234-1243

# Management of anticoagulation in patients with acute gastrointestinal bleeding



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## DOACs



# Categorie di emorragie

- Maggiori

- Minori

Emorragie gastrointestinali

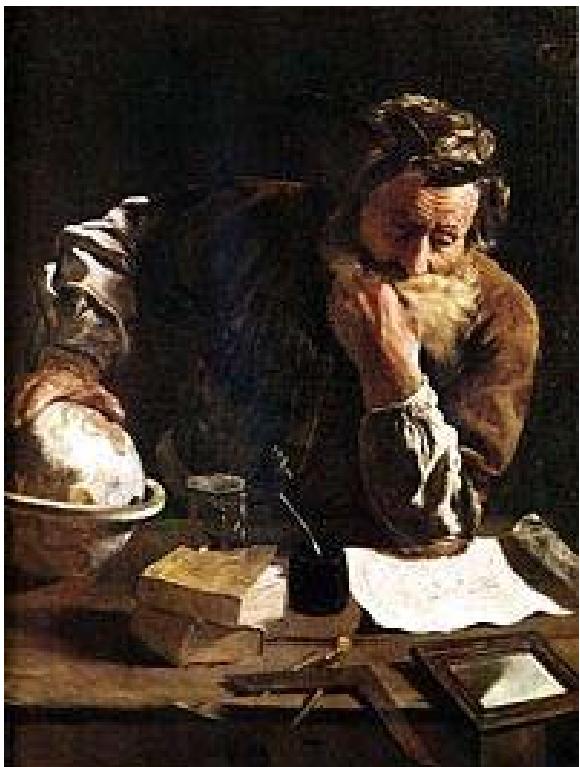
Emorragie intracraniche

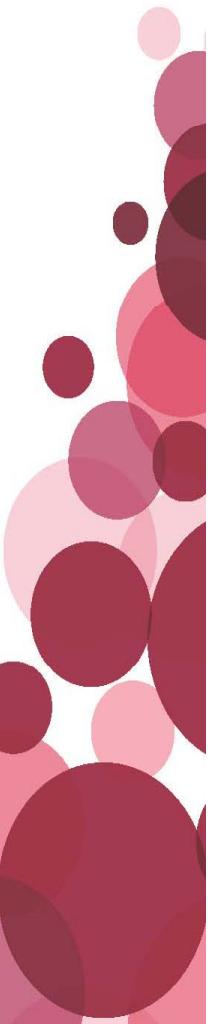
Epistassi

Ematuria

Emorragia tessuti molli

Emorragie retroperitoneali





There is evidence, some of it prospective, that restarting OAC therapy after GI hemorrhage is beneficial.

Restarting OAC therapy at hospital discharge was associated with a lower risk of major thrombotic episodes within 90 days (HR 0.121 95% CI, 0.006-0.812; P = .03), and no significant difference in mortality was observed (at 90 days, HR 0.632; 95% CI, 0.216- 1.89; P = .40).

Furthermore, restarting OAC was not significantly associated with an increased risk of recurrent GI bleeding at 90 days (HR 2.17; 95% CI, 0.861-6.67; P = .10).





