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# 9º Corso Incontri Pratici Di Ematologia

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 Marcello Brignone***

*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 ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:*

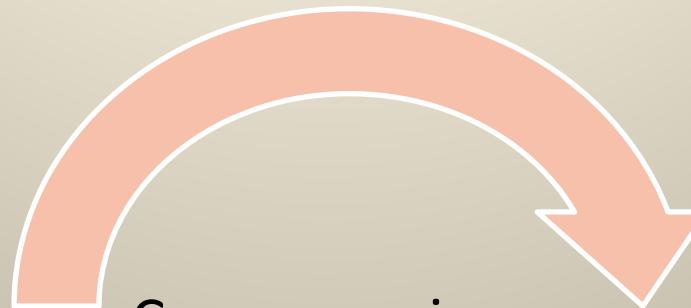
# Gestione anticoagulazione periprocedurale



INTERNISTA  
EMATOLOGO



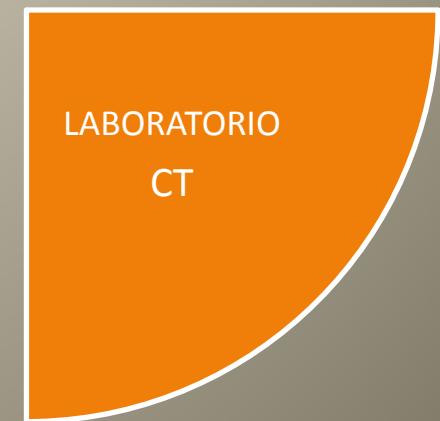
CHIRURGO  
ANESTESISTA



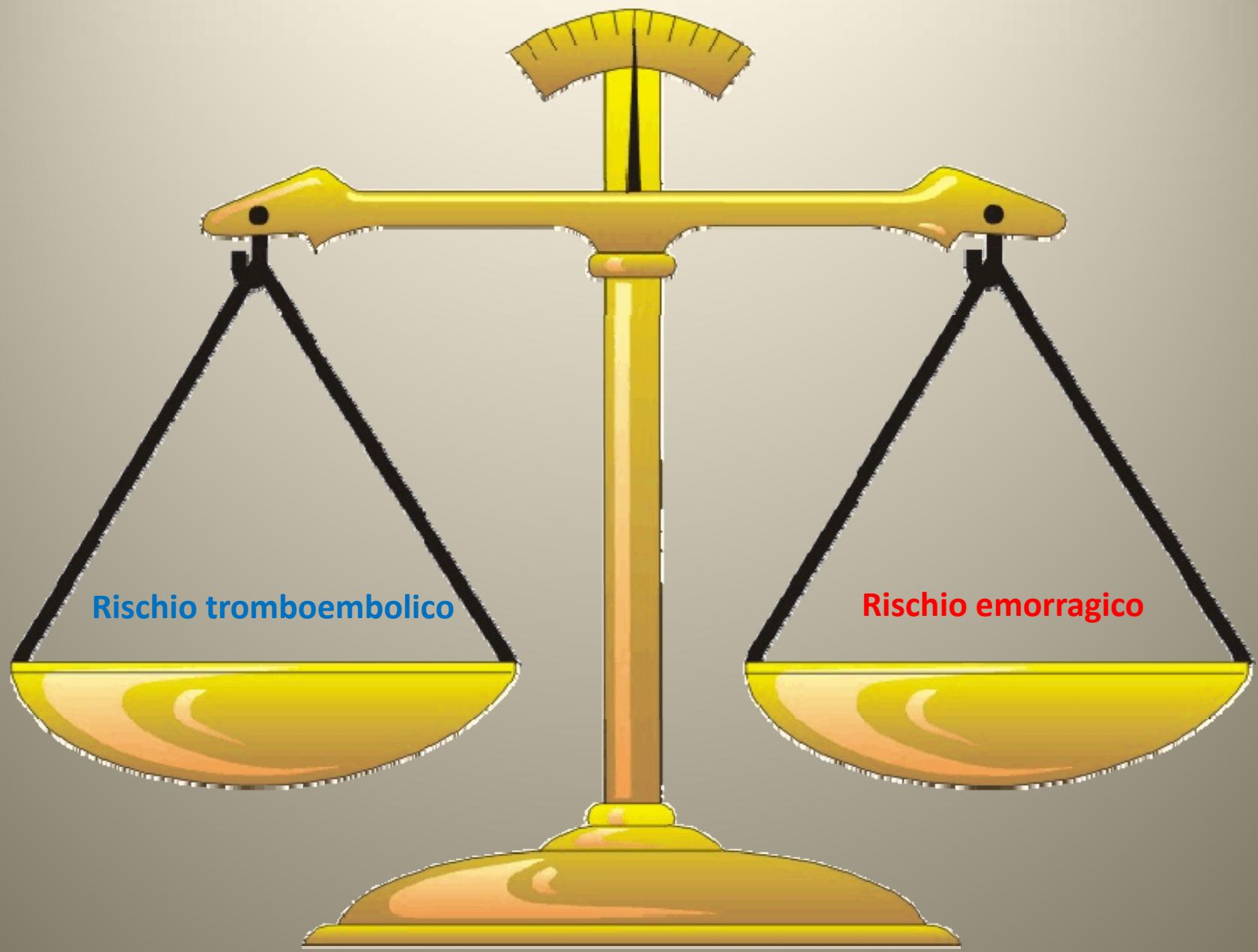
Comune enigma  
clinico che  
coinvolge un  
**team  
multidisciplinare**



CARDIOLOGO  
NEFROLOGO



LABORATORIO  
CT



## **2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation**

A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force

Periprocedural Management of Anticoagulation Writing Committee, John U. Doherty, Ty J. Gluckman, William J. Hucker, James L. Januzzi Jr., Thomas L. Ortel, Sherry J. Saxonhouse and Sarah A. Spinler

J Am Coll Cardiol. 2017 Feb 21;69(7):871-898. doi: 10.1016/j.jacc.2016.11.024. Epub 2017 Jan 9

## **Management of Patients on Non–Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting: A Scientific Statement From the American Heart Association**

Amish N. Raval, Joaquin E. Cigarroa, Mina K. Chung, Larry J. Diaz-Sandoval, Deborah Diercks, Jonathan P. Piccini, Hee Soo Jung, Jeffrey B. Washam, Babu G. Welch, Allyson R. Zazulia, Sean P. Collins,

Circulation. 2017;135:e604-e633

## APPROCCIO DECISIONALE

- Stima del rischio tromboembolico
- Stima del rischio emorragico
- Determinare il timing dello stop dell'anticoagulante
- Determinare se è necessario bridging

# Stima del rischio tromboembolico

- Fibrillazione atriale
- Valvole cardiache protesiche
- Recente TVE

# Stima del rischio emorragico

Dipende dal tipo di intervento o procedura  
e dalle comorbidità del paziente

Alto rischio: sanguinamento maggiore a  
48 ore 2-4%

by-pass coronarico, biopsia renale, procedure più lunghe di 45 min

Basso rischio: sanguinamento maggiore  
a 48 ore 0-2%

colecistectomia, tunnel carpale, isterectomia, procedure odontoiatriche

# **Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients**

## **MAJOR BLEEDING**

### **1. Fatal bleeding**

and/or

### **2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome,**

and/or

### **3. Bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.**

# Classificazione del rischio TE ed emorragico

## Rischio tromboembolico

## Rischio emorragico

A	ALTO -tromboembolia venosa o arteriosa recente (<3mesi) -FA con recente complicanza embolica -Protesi valvolari cardiache	1	ALTO Nch, chirurgia midollo spinale, chirurgia orbitaria, biopsie trans-bronchiali o a cielo coperto, chirurgia prostatica e vescicale, chirurgia addominale maggiore
B	BASSO -FA (CHADS2-Vasc <2) -Pregresso TEV	2	MODERATO-BASSO Chirurgia generale, ortopedica,plastica, biopsie, endoscopia, cateterismo vasi

# Fattori legati al paziente

- ✓ Insufficienza epatica
- ✓ Citopenie
- ✓ Fragilità
- ✓ Farmaci
- ✓ Insufficienza renale

	Via	Dabigatran	Apixaban	Edoxaban <sup>a</sup>	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18% <sup>29</sup>	No data yet	No effect <sup>30</sup>	No effect <sup>27,31</sup>
Digoxin	P-gp competition	No effect <sup>32</sup>	No data yet	No effect <sup>30</sup>	No effect <sup>27,33</sup>
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180% <sup>24</sup> (reduce dose and take simultaneously)	No data yet	+53% (SR) <sup>30</sup> (reduce dose by 50%) <sup>a</sup>	Minor effect (use with caution if CrCl 15–50 mL/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect <sup>24</sup>	+40% <sup>SmPC</sup>	No data yet	Minor effect (use with caution if CrCl 15–50 mL/min)
Quinidine	P-gp competition	+50%	No data yet	+80% <sup>30</sup> (reduce dose by 50%) <sup>b</sup>	+50%
Amiodarone	P-gp competition	+12–60% <sup>24</sup>	No data yet	No effect <sup>30</sup>	Minor effect (use with caution if CrCl 15–50 mL/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70–100% (US: 2 × 75 mg)	No data yet	+85% (reduce dose by 50%) <sup>3</sup>	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 × 75 mg)	+100% <sup>SmPC</sup>	No data yet	Up to +160% <sup>27</sup>
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered) <sup>27</sup>
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% <sup>26,27</sup>
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase <sup>SmPC</sup>	No data yet	Up to +153% <sup>27</sup>
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	-66% <sup>34</sup>	-54% <sup>SmPC</sup>	-35%	Up to -50%

**Red**, contraindicated/not recommended.

**Orange**, reduce dose (from 150 mg bid to 110 mg bid for dabigatran; from 20 mg to 15 mg qd for rivaroxaban; from 5 mg bid to 2.5 mg bid for apixaban).

**Yellow**, consider dose reduction if another 'yellow' factor is present.

**Hatching**, no data available; recommendation based on pharmacokinetic considerations.

## Stima del rischio emorragico in procedure particolari

- Anestesia spinale
- Endoscopia digestiva
- Angioplastica percutanea
- Procedure oftalmologiche

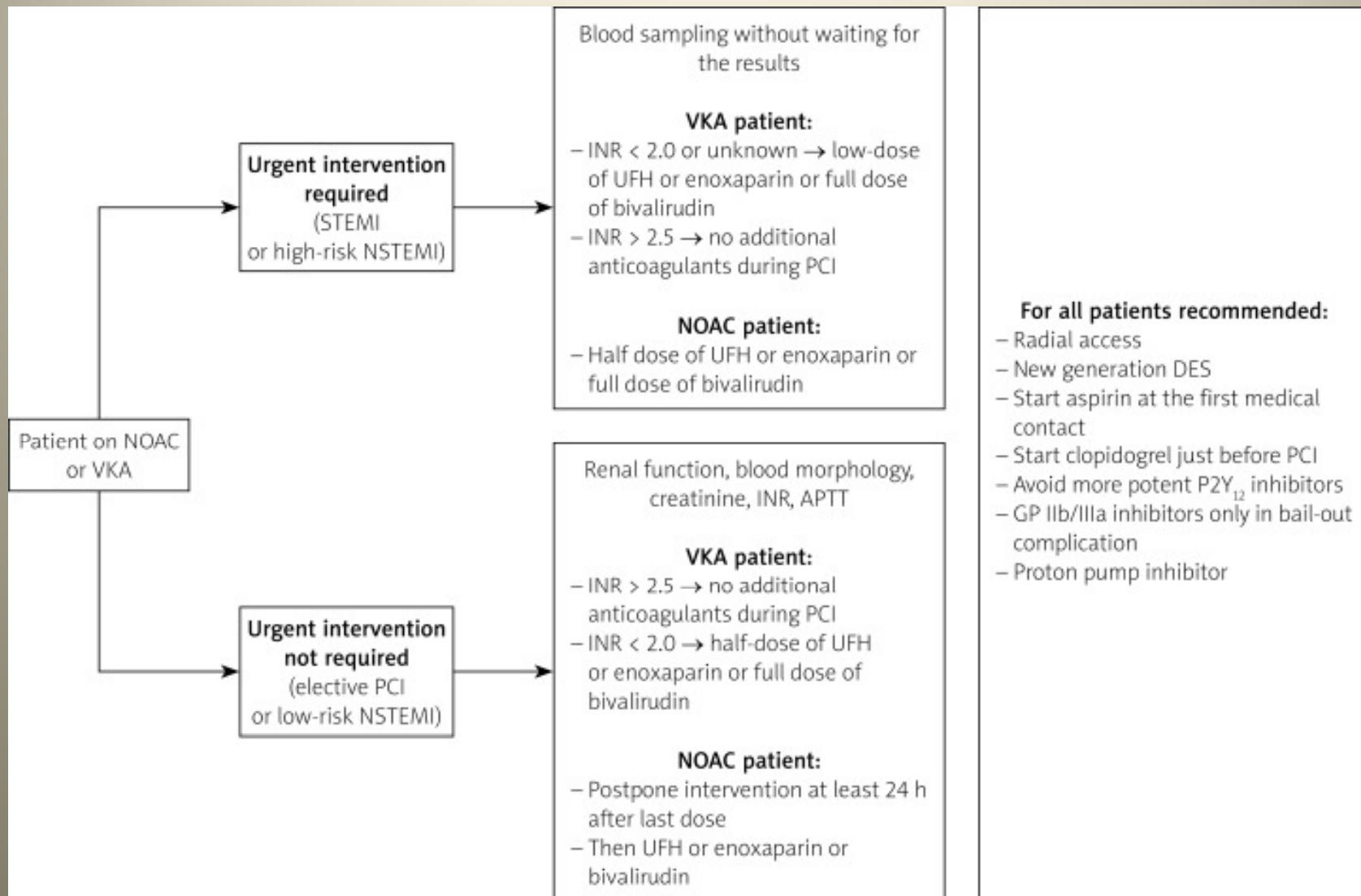
# Procedure endoscopiche e rischio di sanguinamento

Higher-risk procedures	Low-risk procedures
Polypectomy	Diagnostic (EGD, colonoscopy, flexible sigmoidoscopy) including mucosal biopsy
Biliary or pancreatic sphincterotomy	ERCP with stent (biliary or pancreatic) placement or papillary balloon dilation without sphincterotomy
Treatment of varices	
PEG placement*	Push enteroscopy and diagnostic balloon-assisted enteroscopy
Therapeutic balloon-assisted enteroscopy	Capsule endoscopy
EUS with FNA‡	Enteral stent deployment (Controversial)
Endoscopic hemostasis	EUS without FNA
Tumor ablation	Argon plasma coagulation
Cystgastrostomy	Barrett's ablation
Ampullary resection	
Endoscopic submucosal dissection	
Pneumatic dilation	
PEJ, Percutaneous endoscopic jejunostomy	

## **Antithrombotic management in patients with percutaneous coronary intervention requiring oral anticoagulation**

Regardless of the type of chronic anticoagulation therapy, in patients on OAC,

- radial access should be the default to minimize the risk of access-related bleeding,
- new generation DES or bare metal stents (BMS) are recommended if triple therapy is planned,
- routine use of ticagrelor or prasugrel is discouraged because of their unknown safety profile in association with VKA or NOAC
- GP IIb/IIIa inhibitors should be avoided unless for bail-out situations.



## Ongoing clinical trials regarding optimal combination of anticoagulation with NOAC versus VKA with antiplatelet agents in AF patients after PCI with stenting

Trial acronym/status	N	Trial aim/hypothesis	Study arms
RE-DUAL PCI/recruiting	2800	To study non-inferiority of each dose of <b>dabigatran</b> arm when compared to warfarin in terms of safety determined by major bleeding and clinically relevant non-major bleeding events according to the modified ISTH classification	<ul style="list-style-type: none"> <li>• 110 mg dabigatran BID plus clopidogrel or ticagrelor</li> <li>• 150 mg dabigatran BID plus clopidogrel or ticagrelor</li> <li>• A triple antithrombotic therapy of warfarin plus clopidogrel or ticagrelor plus low-dose aspirin (&lt; 100 mg OD)</li> </ul>
PIONEER AF PCI/study completed	2129	To evaluate the safety of three different treatment strategies ( <b>Rivaroxaban</b> ) Safety in this trial is determined by significant bleeding as a composite of TIMI major bleeding, minor bleeding, and bleeding requiring medical attention	<ul style="list-style-type: none"> <li>• 15 mg rivaroxaban OD or 10 mg for subjects with moderate renal impairment plus clopidogrel, prasugrel or ticagrelor</li> <li>• 2.5 mg rivaroxaban BID plus low-dose of aspirin and clopidogrel, prasugrel or ticagrelor followed by 15 mg rivaroxaban OD plus low-dose aspirin</li> <li>• VKA treatment strategy (target INR 2.0–3.0) plus low-dose aspirin and clopidogrel, prasugrel or ticagrelor followed by VKA plus low-dose aspirin for 12 months</li> </ul>
AUGUSTUS/recruiting	4600	To determine whether <b>apixaban</b> is safer than VKA given for 6 months in terms of bleeding in AF patients with ACS or PCI with stent implantation within the prior 14 days. The primary outcome measure is time to first occurrence of major or clinically relevant non-major bleeding according to the ISTH classification	Randomization in a 2 × 2 factorial design to receive apixaban 5 mg OD or 2.5 mg BID, with or without aspirin, versus a VKA, with or without aspirin. All patients are receiving P2Y <sub>12</sub> inhibitors
EVOLVE AF PCI/accepted by institutional board to start recruitment	Not determined yet	Treatment strategies with <b>edoxaban</b> are planned	

**Table 3 Interpretation of coagulation assays in patients treated with different NOACs**

	<b>Dabigatran</b>	<b>Apixaban</b>	<b>Edoxaban<sup>a</sup></b>	<b>Rivaroxaban</b>
Plasma peak level	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2–4 h after ingestion
Plasma trough level	12–24 h after ingestion	12–24 h after ingestion	12–24 h after ingestion <sup>9</sup>	16–24 h after ingestion
PT	Cannot be used	Cannot be used	Prolonged but no known relation with bleeding risk <sup>5,9</sup>	Prolonged: may indicate excess bleeding risk but local calibration required
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	At trough: >2x ULN suggests excess bleeding risk	Cannot be used	Prolonged but no known relation with bleeding risk <sup>9</sup>	Cannot be used
dTT	At trough: >200 ng/ml or >65 s: excess bleeding risk	Cannot be used	Cannot be used <sup>10</sup>	Cannot be used
Anti-FXa chromogenic assays	Not applicable	No data yet	Quantitative; <sup>10</sup> no data on threshold values for bleeding or thrombosis	Quantitative; no data on threshold values for bleeding or thrombosis
ECT	At trough: $\geq 3 \times$ ULN: excess bleeding risk	Not affected	Not affected	Not affected

# Decidere se e quando interrompere l'anticoagulazione

Meglio continuare anticoagulazione

- Procedure odontoiatriche, cutanee
- Impianto di devices cardiaci
- Intervento per cataratta

**DURATA DI SOSPENSIONE RACCOMANDATA DEI NAO , BASATA SUL RISCHIO DI  
SANGUINAMENTO PROCEDURALE E SULLA CrCl STIMATA NEI CASI IN CUI NON VI  
SIANO AUMENTATI FATTORI DI RISCHIO EMORRAGICI LEGATI AL PAZIENTE**

dabigatran

apixaban, edoxaban, rivaroxaban

ClCr ml/min	>80	50-79	30-49	<15	>30	15-29	<15
Emivita stimata, h	13	15	18	30	6-15	Apix 17 Edox 17 Rivarox 9	Apix 17 Edox 17 Rivarox 13
Rischio emorragico procedurale							
basso	≥24 h	≥36	≥48	No data	≥24	≥36	No data
Incerto, intermedio, alto	≥48 h	≥72	≥96	No data	≥48	No data	No data

modificato da Doherty et al 2017  
periprocedural anticoag. pathway. ACC

# Procedure urgenti/emergenti reversal

- Dabigatran → idarucizumab (Praxbind)  
5 mg ev
- Inibitori del fattore X → complesso protrombinico concentrato (in attesa di farmaco specifico andexanet  $\alpha$  - AndexXa<sup>®</sup> )

N Engl J Med 2016; 375:1131-1141. September 22, 2016

# Bridging

- In generale gli anticoagulanti orali diretti NON necessitano di bridging con EBPM
- Può essere necessario in pazienti selezionati in cui coesiste alto rischio TE con impossibilità ad assumere terapia orale

# Gestione anticoagulazione periprocedurale

