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LA GESTIONE DELLE PROBLEMATICHE PERI-OPERATORIE DEL PAZIENTE IN TERAPIA ANTICOAGULANTE

Sophie Testa, Domenico Prisco

TERAPIE ANTICOAGULANTI

- In Italia si stimano oltre 1.500.000 persone in trattamento anticoagulante cronico (~2% della popolazione generale; ~6% popolazione sopra i 65 anni), di cui circa 750.000 in terapia con DOACs (Osmed 2018)
- **Chirurgia/manovre invasive sono sempre piu' frequenti…**

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GESTIONE PERI-OPERATORIA

1. Chirugia d'urgenza o Chirurgia in Elezione
2. Il rischio emorragico della Chirurgia
3. Il rischio tromboembolico ed emorragico del paziente
4. I tipi di anestesia
5. Il tipo di anticoagulante
6. *Residual anticoagulant level before surgery?*

AVK

- Gestione clinica del paziente condotta in base al controllo dei livelli di anticoagulazione
- Il controllo e' espressione dell'entita' dell'anticoagulazione e guida le necessita' posologiche relative alla correzione emostatica
- Reverse efficace e sicuro con CCP+vit K
- Possibilita' di intervenire con livelli di anticoagulazione PT INR < 1.5 (cut off di intervento)

Chest 2012, LG FCSA 2019

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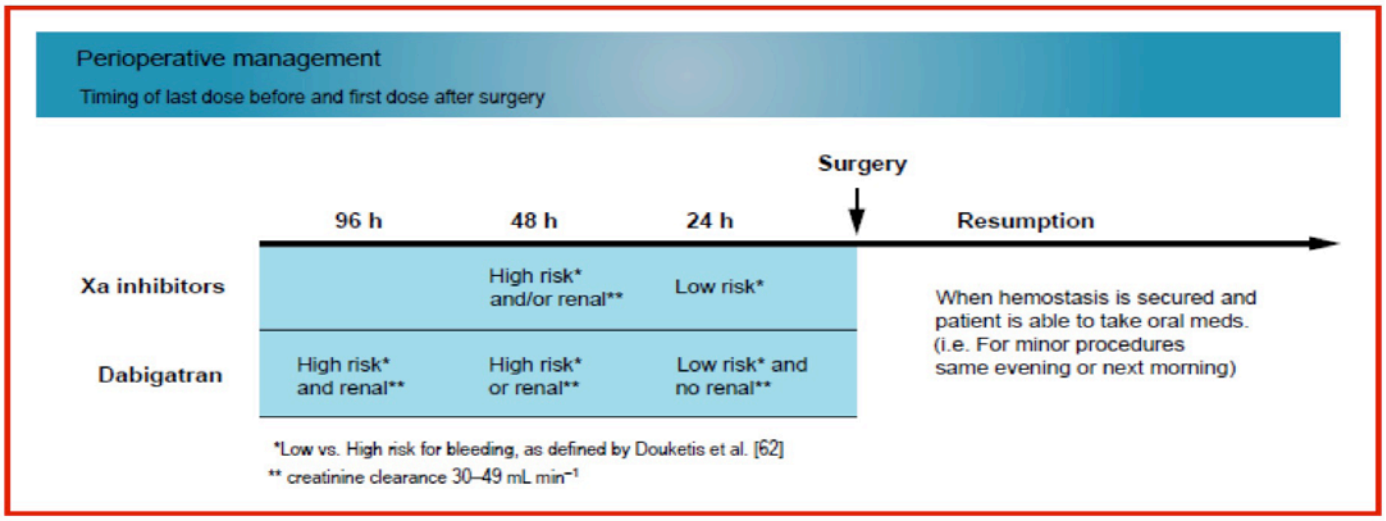
E I PAZIENTI IN DOAC?

DOAC CHARACTERISTICS

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct, reversible inhibitor of free and clot-bound thrombin	Direct, reversible inhibitors of free and prothrombinase bound factor Xa		
Bioavailability	3–7%	80–100%	50%	62%
Protein binding	35%	92–95%	87%	55%
Primary clearance	80% renal	67% renal	56% faecal	50% renal
Tmax	1.5–3 h	2–3 h	3–4 h	1–2 h
Half-life[a]	12–14 h	5–13 h	12 h	10–14 h

Gosselin R et al, Thromb Haemost 2018

PERIOPERATIVE MANAGEMENT: THE GUIDELINES



Schulman S. J Intern Med 2014;275:1-11

ESC European Society of Cardiology
European Heart Journal (2018) 39, 1330–1393
doi:10.1093/eurheartj/ehy136

SPECIAL ARTICLE

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Jan Steffel[1]*, Peter Verhamme[2], Tatjana S. Potpara[3], Pierre Albaladejo[4], Matthias Antz[5], Lien Desteghe[6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[2], Ronan Collins[12], A. John Camm[13], and Hein Heidbüchel[6,14]

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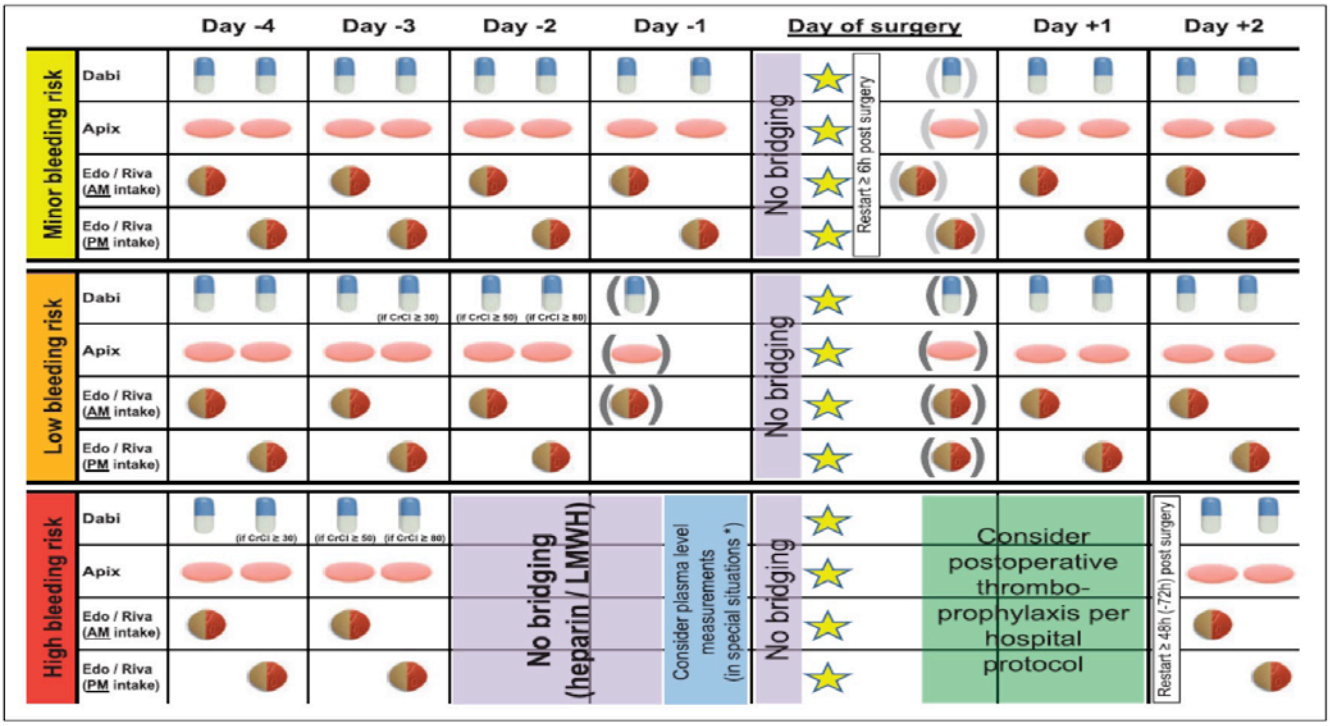
Table 11 **Timing of last non-vitamin K antagonist oral anticoagulant intake before start of an elective intervention**

	Dabigatran		Apixaban – Edoxaban – Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. 12 h or 24 h after last intake)			
	Low risk	**High risk**	**Low risk**	**High risk**
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–79 mL/min	≥36 h	≥72 h	≥24 h	≥48 h
CrCl 30–49 mL/min	≥48 h	≥96 h	≥24 h	≥48 h
CrCl 15–29 mL/min	Not indicated	Not indicated	≥36 h	≥48 h
CrCl <15 mL/min	No official indication for use			
No bridging with LMWH/UFH				
Resume full dose of NOAC ≥24 h post-low bleeding risk interventions and 48 (–72) h post-high-bleeding risk interventions (see also *Figure 8*)				
Patients undergoing a planned intervention should receive a written note indicating the anticipated date and time of their intervention, and the date and time of the last intake of their NOAC (and any other medication)				

Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk: with a high frequency of bleeding and/or important clinical impact. See also *Table 12*.
CrCl, creatinine clearance; LMWH, low molecular weight heparin; UFH, unfractionated heparin.



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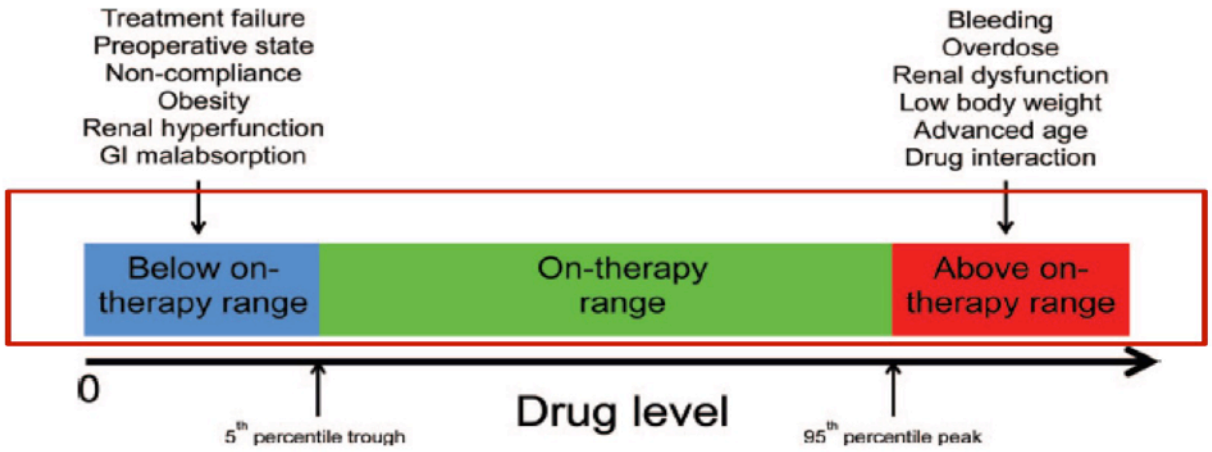
BASED ON PK MODELS, "A PRIORI" DOAC PLASMA LEVELS ARE SUPPOSED AS FOLLOW



Therapeutic ranges for the DOACs have not been established. The "on-therapy" range is defined as the interval from the 5th to 95th percentile of DOAC concentration. Drug levels below this range may be regarded as "below on-therapy", those exceeding this range as "above on-therapy".

Cuker A, Siegal D, Haematology 2015

EXPECTED PEAK AND TROUGH DOAC LEVELS IN NVAF AND VTE PATIENTS ENROLLED IN PHASE II-III CLINICAL STUDIES

	Dabigatran		Rivaroxaban		Apixaban		Edoxaban	
Indication	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE
Dose	150 mg bid	150 mg bid	20 mg qd	20 mg qd	5 mg bid	5 mg bid	60 mg qd	60 mg qd
Peak concentration, ng/mL	175[a] (117–275)	175[a] (117–275)	249[b] (184–343)	270[b] (189–419)	171[c] (91–321)	132[c] (59–302)	170[d] (125–245)	234[e] (149–317)
Trough concentration, ng/mL	91[a] (61–143)	60[a] (39–95)	44[b] (12–137)	26[b] (6–87)	103[c] (41–230)	63[c] (22–177)	36[e] (19–62)	19[e] (10–39)

aMean (25th–75th percentile); bMean (5th–95th percentile); cMedian (5th–95th percentile); dMedian (1.5 x IQR); eMedian (IQR).

Gosselin R et al, Thromb Haemost 2018

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PERIPROCEDURAL MANAGEMENT OF DOAC SHOULD BE GUIDED BY ACCURATE LABORATORY TESTS

Interruption of DOAC should not be based only on their respective half-life but also on the residual drug concentration

- Poor correlation between renal function and plasma concentration of apixaban and rivaroxaban was found except dabigatran measured at trough (Testa S et al, TR 2016)
- Mass spectrometry measured dabigatran level greater than 20ng/ml in nearly 16% of patients undergoing high bleeding risk procedures (Douketis JD et al JT&H 2016)

Douxfils J et al, Reg Anesthesia and Pain Medicine, Sept 2016

WHAT ARE WE DOING IN THE "REAL WORLD"?

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Bleeding Complications After Use of Novel Oral Anticoagulants in Patients Undergoing

Background. The study was performed to analyze the results of open-heart surgery and bleeding complications after administration of novel oral anticoagulants (NOAC).

Methods. We investigated 81 consecutive patients (median age 74 years, interquartile range [IQR]: 68 to 78) who underwent open-heart operations at our institution between July 2014 and June 2016. All patients presented for surgery while on NOAC therapy: 37 received rivaroxaban (45.7%), 35 apixaban (43.2%), and 9 dabigatran (11.1%). The calculated risk using the European System for Cardiac Operative Risk Evaluation II was 3.5% (IQR: 2.0% to 8.1%).

Results. Surgery was performed at a median 4 days (IQR: 3 to 6) after NOAC withdrawal. Reduced renal function was predictive for length of intensive care unit stay and administration of red blood cells ($p < 0.0001$ and $p = 0.0291$, respectively). The NOAC withdrawal interval significantly influenced postoperative drainage volume ($p = 0.0056$). Five patients needed rethoracotomy because of relevant bleeding (6.2%), 4 after apixaban (11.4%) and 1 after rivaroxaban therapy (2.7%). Apixaban showed a borderline influence on prolonged intensive care unit stay ($p = 0.0736$). Prolonged cardiopulmonary bypass time was predictive for thrombocyte administration ($p = 0.0249$). Intensive care unit stay was 2 days after NOAC withdrawal of 10 days, compared with 4.2 days without termination. Thirty-day mortality was 3.7%.

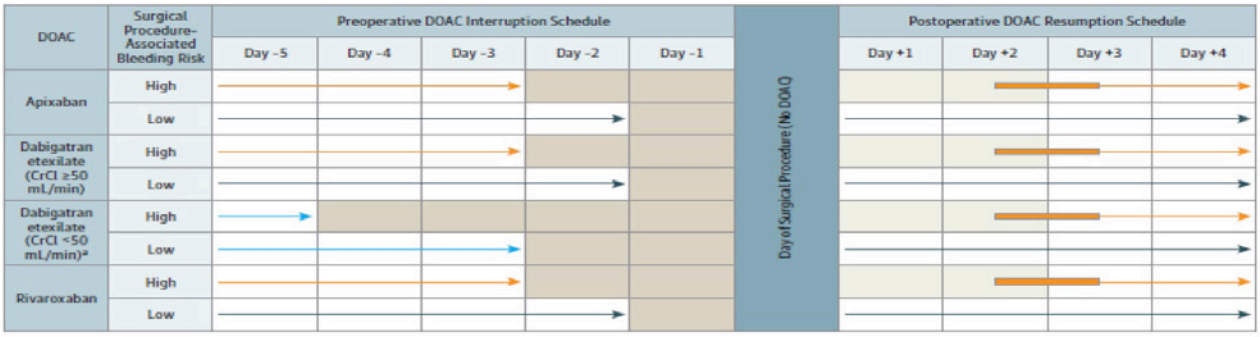
Conclusions. A lengthy NOAC withdrawal period, particularly for patients with reduced renal function, is essential for safe open-heart surgery. We conclude that despite official recommendations, patients should whenever possible not be considered for elective cardiac surgery within 10 days of terminating NOAC treatment.

?

(Ann Thorac Surg 2018;105:702–8)
© 2018 by The Society of Thoracic Surgeons

Hassan K et al, Ann Thorac Surg, 2018

Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant



CONCLUSIONS AND RELEVANCE In this study, patients with AF who had DOAC therapy interruption for elective surgery or procedure, a perioperative management strategy without heparin bridging or coagulation function testing was associated with low rates of major bleeding and arterial thromboembolism.

Douketis J et al, Jama Intern Med 2019

COMMENTS on JAMA

- Altogether the study showed **3.43% of major and clinically relevant**, plus 5% of minor bleeding complications
- The adopted management algorithm was based on the DOACs pharmacokinetics, CrCl and the procedure-associate bleeding risk.
- However, DOACs plasma levels have a high inter-individual variability; furthermore, the drug elimination rate may not be constant in all patients
- **Our question is: may we be really confident that a standardized model, which never takes into consideration the high drug level variability** or the high risk of bleeding both from individual patients or from anesthesiology procedures**, may be the best strategy to be adopted in all patients?**

Testa S , Paoletti O, Palareti G Comment on JAMA 2019

NECESSITA' SANITARIE DEL PAZIENTE ANTICOAGULATO:

-Riconoscimento e Gestione idonea del trattamento anticoagulante

-Chirurgia in Elezione: massima riduzione dei rischi emorragici perioperatori, massima riduzione dei rischi tromboembolici associati alla sospensione dei trattamenti anticoagulanti

-Chirurgia in Emergenza: normalizzazione dell'emostasi ?

NECESSITA' DEI MEDICI (ANESTESISTI, CHIRURGHI..)

-Chirurgia in Elezione: necessità di operare in massima sicurezza emostatica

-Chirurgia in Emergenza: necessità di operare riducendo il rischio associato al "potenziale emorragico" indotto dal trattamento

Abbiamo necessità di dati oggettivi rispetto al bilancio emostatico individuale?

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I QUESITI

1. Le problematiche chirurgiche (chirurgia maggiore, minore, in elezione, d'urgenza) SIOT, ACEMC, SIMEU
2. I rischi relativi delle procedure anestesiologiche (anestesia generale, loco regionale, etc) SIAARTI , ESRA
3. La valutazione individuale dei rischi emorragici e tromboembolici del paziente FCSA, SISET
4. Le evidenze scientifiche sono sufficienti per agire in sicurezza? Tutti
5. Quali mezzi diagnostici a disposizione per controllare la capacità emostatica FCSA SISET

Discussione

Proposte e conclusioni

CHIRURGIA: CLASSIFICAZIONE

Interventions with minor bleeding risk
Dental interventions
Extraction of 1–3 teeth
Paradontal surgery
Incision of abscess
Implant positioning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g. abscess incision; small dermatologic excisions; . . .)
Interventions with low bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation (except complex procedures, see below)
Non-coronary angiography (for coronary angiography and ACS: see Patients undergoing a planned invasive procedure, surgery or ablation section)
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)

Interventions with high bleeding risk (i.e. frequent and/or with high impact)
Complex endoscopy (e.g. polypectomy, ERCP with sphincterotomy etc.)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)
Interventions with high bleeding risk AND increased thromboembolic risk
Complex left-sided ablation (pulmonary vein isolation; some VT ablations)

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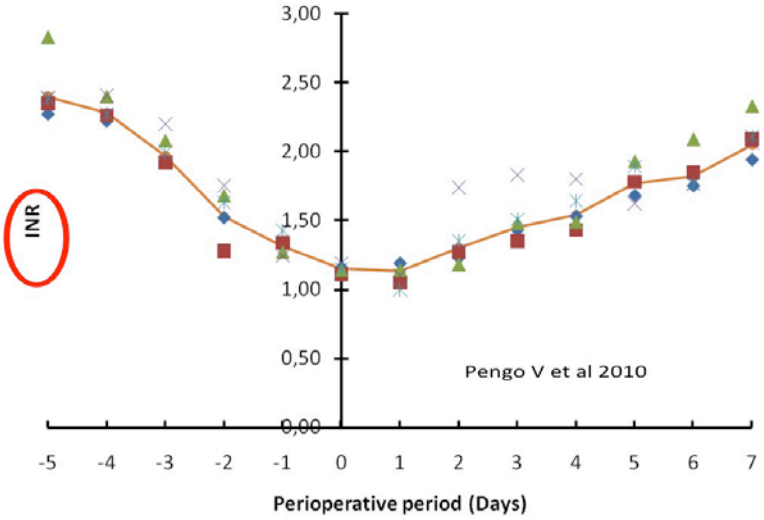
FEDERAZIONE CENTRI PER LA DIAGNOSI DELLA TROMBOSI E LA SORVEGLIANZA DELLE TERAPIE ANTITROMBOTICHE (FCSA)

Anti-Vitamin K antagonists

AVK measurement useful to assess anticoagulant level, as measured with PT INR



Risk of major bleeding in cardiosurgical pts increases if PT INR> 1.46 (Tinker et al, JAMA 1978)

Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin

Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial

	D110 (N=1487) % (n)	D150 (N=1546) % (n)
Bleeding events		
Minor bleed	8.1 (120)	9.0 (139)
Major bleed	3.8 (57)	5.1 (78)
Fatal bleed	0.2 (3)	0.1 (2)
Requiring reoperation	0.6 (9)	1.4 (22)
Requiring RBC transfusion	3.3 (49)	3.5 (54)

	D110 % (n/N)	D150 % (n/N)
Urgent surgery	17.8 (19/107)	17.7 (25/141)
Elective surgery	2.8 (38/1380)	3.8 (53/1405)
Major surgery	6.1 (29/473)	6.5 (33/511)
Minor surgery	1.9 (8/424)	3.2 (14/435)

Healey JS et al, Circulation 2012