I DOACS e il paziente cardioncologico: matrimonio possibile? Il punto di vista del cardiologo

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Problematiche

- FA di nuova insorgenza nel paziente oncologico in trattamento : che fare?
- Diagnosi di neoplasia nel paziente che assume DOACS: che fare?
- Ci aiutano le linee guida?

Fibrillazione atriale e cancro

La FA è l'aritmia più comune che può insorgere durante o dopo chemioterapia e radioterapia

- Comorbidità
- Effetti diretti del tumore
- Disfunzione ventricolare
- Tossicità
- Disordini elettrolitici (vomito, diarrea)

Drug Saf 2015;38:129–152.

J Am Coll Cardiol 2014;63:945–953.

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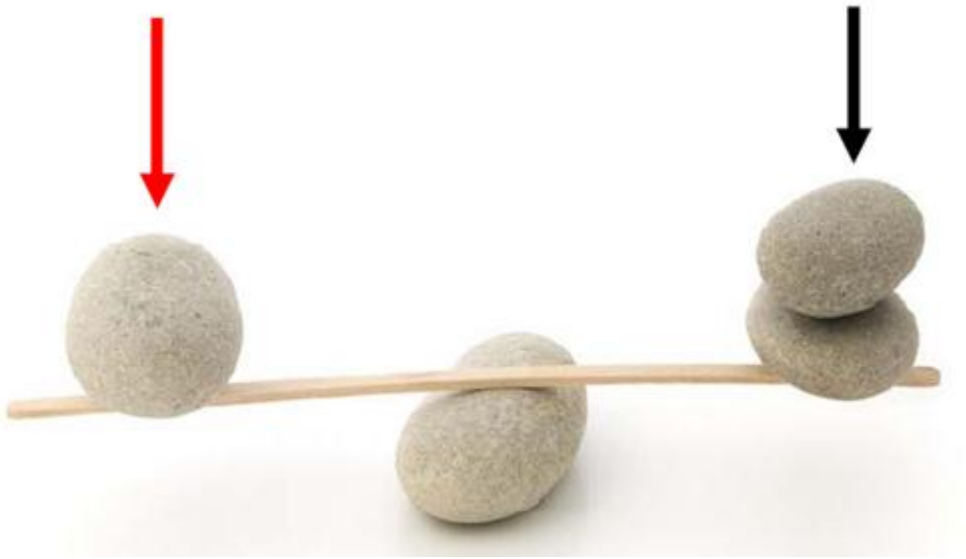
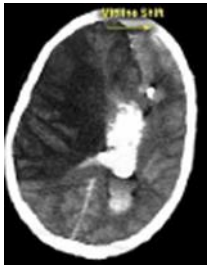
Table 8 Cancer drug agents associated with cardiac arrhythmias

Type of arrhythmia	Causative drug
Bradycardia	Arsenic trioxide, bortezomib, capecitabine, cisplatin, cyclophosphamide, doxorubicine, epirubicine, 5-FU, ifosfamide, IL-2, methotrexate, mitoxantrone, paclitaxel, rituximab, thalidomide.
Sinus tachycardia	Anthracyclines, carmustine.
Atrioventricular block	Anthracyclines, arsenic trioxide, bortezomib, cyclophosphamide, 5-FU, mitoxantrone, rituximab, taxanes, thalidomide.
Conduction disturbances	Anthracyclines, cisplatin, 5-FU, imatinib, taxanes.
Atrial fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), anthracyclines, antimetabolites (capecitabine, 5-FU, gemcitabine), IL-2, interferons, rituximab, romidepsin, small molecule TKIs (ponatinib, sorafenib, sunitinib, ibrutinib), topoisomerase II inhibitors (amsacrine, etoposide), taxanes, vinca alkaloids.
Supraventricular tachycardias	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), amsacrine, anthracyclines, antimetabolites (capecitabine, 5-FU, methotrexate), bortezomib, doxorubicin, IL-2, interferons, paclitaxel, ponatinib, romidepsin.
Ventricular tachycardia/fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide), amsacrine, antimetabolites (capecitabine, 5-FU, gemcitabine), arsenic trioxide, doxorubicin, interferons, IL-2, methothrexate, paclitaxel, proteasome inhibitors (bortezomib, carfilzomib), rituximab, romidepsin.
Sudden cardiac death	Anthracyclines (reported as very rare), arsenic trioxide (secondary to torsade de pointes), 5-FU (probably related to ischaemia and coronary spasm), interferons, nilotinib, romidepsin.

5-FU = 5-fluorouracil; IL-2 = interleukin 2; TKI = tyrosine kinase inhibitor.

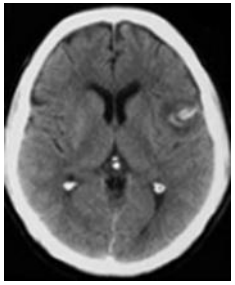
IL PAZIENTE ONCOLOGIGO





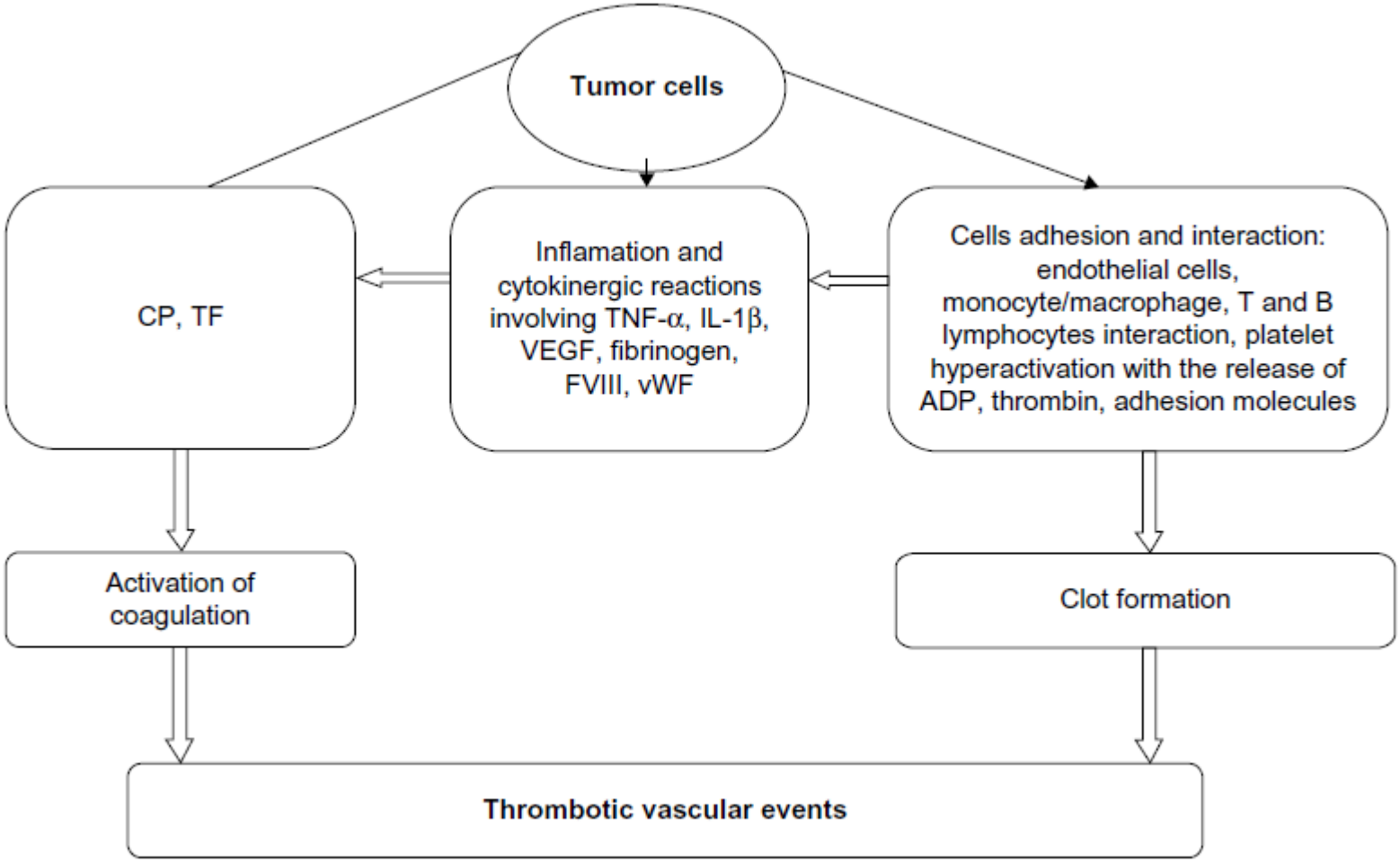
SANGUINAMENTO

TROMBOSI



CHADS2Vasc Score e HASBLED non sono validati nella popolazione oncologica !!!

Trombosi e cancro



The Open Cardiovascular Medicine Journal 2010;4:78–82.
doi:10.2174/1874192401004020078.

Fattori di rischio di trombosi nel paziente oncologico

PATIENT CHARACTERISTICS	TUMOR -RELATED FACTORS	TREATMENT-RELATED FACTORS	BIOMARKERS
Female gender	Anatomical site of tumor	Major surgery	High TF expression by tumor cells[31]
Older age	Tumour histology	Hospitalization	Pre-chemotherapy platelet count >350,000/mm[38,35]
Race (black ethnicity)	Advanced stage of cancer	Cancer therapy	Pre-chemotherapy leukocyte count >11,000/mm[38]
Common comorbidities: DM, Obesity, Previous VTE, atherosclerosis, inflammation, others	Initial period after diagnosis of cancer	Erythropoiesis-stimulating agents	Elevated D-dimer[34,35]
Inherited prothrombotic mutations	–	Central venous catheters	High level of[35] - TF plasma levels - soluble P-selectin - C-reactive protein

Korana AA, American Society of Clinical Oncology; ASCO Educational Book; 2008:240–8.

Khorana Score

Table 3. Predictive model for chemotherapy-associated VTE.[8,77]

PATIENT CHARACTERISTICS	VTE RISK SCORE
Site of cancer	
Very high risk (primary brain, stomach or pancreas)	2
High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate or multiple myeloma)	1
Low risk (breast, colorectal or head and neck)	0
Other characteristics	
Platelet count $\geq 350 \times 10^9$/l	1
Hemoglobin <100 g/l or use of red blood cell growth factors	1
Leukocyte count $>11 \times 10^9$/l	1
BMI ≥ 35 kg/m^2	1
sP-selectin ≥ 53.1 ng/ml	1
D-dimer ≥ 1.44 µg/ml	1

Notes: 0 score, Low risk. 1 or 2 score, Intermediate risk. 3 or higher, High risk.

Ann Oncol. 2009;20(10):1619–30.

Blood. 2010;116:5377–82

Rischio emorragico e cancro

- I pazienti con cancro attivo in terapia anticoagulante: rischio di 2-6 volte più elevato di eventi emorragici

  (J Clin Oncol 2000;18:3078–3083; Blood 2002;100:3484–3488)

- I pazienti con maggior rischio tromboembolico sono anche quelli a maggior rischio di sanguinamento

  (Agnelli et. Al N Engl J Med 2012;366:601–609)

TROMBOSI E RISCHIO EMORRAGICO NEI PAZIENTI ONCOLOGICI

- Localizzazione tumore
- Trombocitosi
- Leucocitosi
- BMI > 35
- EPO
- CVC

- Chirurgia
- Danno da radiazioni
- Tumori polmonari, gastrointestinali e vescicali
- Trombocitopenia da terapia mielosoppressiva
- Futtuazioni delle funzioni epatica e renale
- Età >75

LG ASCO

Recommendation 4.6: Use of NOACs for Prevention or Treatment of VTE in Patients with Cancer is NOT Recommended

Concerns:

- Few patients with active malignancy enrolled in RCTS
- Unpredictable absorption
- Higher risk of GI bleeding or other GI complications
- Altered metabolism in those with liver or renal impairment
- Drug interaction with hormonal and chemotherapeutic agents
- Inability to measure the AC activity using standard assays
- Lack of an antidote

American Society of Clinical Oncology

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

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

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

15. Non-vitamin K antagonist anticoagulants vs. vitamin K antagonists in atrial fibrillation patients with a malignancy

Suggerimenti pratici

1. I pazienti oncologici con FA necessitano una valutazione multidisciplinare per pianificare la strategia antitrombotica

2. La neoplasia nel paziente fibrillante aumenta il rischio di stroke: se il paziente è già in NOACS, è possibile che continui dopo aver valutato l'eventuale terapia mielosoppressiva e le interazioni farmacologiche

3. Nel pz naive sono di prima scelta i VKA e le eparine (esperienza clinica, possibilità di monitoraggio ed ev. reversal)

Suggerimenti pratici

4. Basandosi sui dati relativi alla TVP la posologia dei NOACS utilizzata per la FA protegge nei confronti della TVP. Pertanto non bisogna aggiungere altri farmaci (LMWH)

5. Nei pazienti oncologici che assumono NOACS che devono sottoporsi a chirurgia valgono le stesse raccomandazioni della chirurgia elettiva

6. I pazienti in NOACS che devono sottoporsi a radioterapia o chemioterapia non marcatamente mielosoppressiva possono continuare, eventualmente adattando il dosaggio in caso di alterazioni delle funzioni epatica e renale

Suggerimenti pratici

7. In caso di radioterapia o chemioterapia mielosoppressiva è necessario un team multidisciplinare che discuta la riduzione posologica o la momentanea sospensione del NOACS

8. Considerare la gastroprotezione con IPP o anti-H2

9. Addestrare i pazienti a monitorare attentamente i segni di sanguinamento (petecchie, emottisi, feci picee) e contattare i medici di riferimento

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Cosa utilizzare?

- LMWH per terapia a breve-medio termine
- VKA se INR stabile ed in assenza di malattia metastatica o rischio emorragico elevato
- NOAC

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- Nei pz con CHA2DS2VASc Score ≥ 2 e PTL > 50000/mm2: VKA mantenendo TTR > 70%, in stretta collaborazione con ematologo/oncologo
- Nei pz con CHA2DS2VASc Score < 2 può essere comunque indicata la scoagulazione se il paziente è a rischio di VTE
- Valutare accuratamente il paziente: ecocardiogramma, comorbidità, rischio di sanguinamento, preferenze

VKA e cancro

Ridotta efficacia per difficoltà a mantenere INR stabile:

- Numerosi farmaci (tra cui i chemioterapici) ed alimenti utilizzano gli stessi isoenzimi di CYP450 utilizzati da VKA
- Elevato legame con le proteine plasmatiche di VKA, che può essere spiazzato da altri farmaci
- Anoressia, nausea, vomito
- Basso peso corporeo
- Ipoalbuminemia

J Gen Intern Med 2007;22: 997–1002

EHRA 2015

Table 5 Absorption and metabolism of the different NOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3 to 7%	50%	62%[51]	66% without food. Almost 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose (if normal renal function; see also 'Patients with chronic kidney disease' section)[a]	20%/80%	73%/27%[52–55]	50%/50%[36,51,56]	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination, moderate contribution)[57]	Minimal (<4% of elimination)	Yes (elimination, moderate contribution)
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure[58]	+39% more[59]
Intake with food recommended?	No	No	No	Mandatory
Absorption with H2B/PPI	−12 to 30% (not clinically relevant)[60–62]	No effect[63]	No effect	No effect[59,64]
Asian ethnicity	+25%[62]	No effect	No effect[58]	No effect
GI tolerability	Dyspepsia 5 to 10%	No problem	No problem	No problem
Elimination half-life	12 to 17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)

H2B, H2-blocker; PPI, proton pump inhibitor; GI, Gastrointestinal.

[a]For clarity, data are presented as single values, which are the mid-point of ranges as determined in different studies.

Farmacocinetica e farmacodinamica

	Dabigatran[1]	Rivaroxaban[2,3]	Apixaban[4]	Edoxaban[5–8]
Target	IIa (thrombin)	Xa	Xa	Xa
Biodisponibilità, %	3–7	100 con il cibo	50	62
Tempo per raggiungere la C_{max}	1–3	2–4	3–4	1–2
Emivita, h	12–17	5–13	12	10-14
Eliminazione renale, %	80	33	27	35-50*
Trasportatori	P-gp	P-gp	P-gp	P-gp
Metabolismo epatico (CYP), %	No	Si (moderato)	Si (moderato)	Minimo (<4%)
Legame alle proteine, %	35	92–95	87	40–59
Regime di dosaggio	BID	OD/BID	BID	OD

Considerare:

- Possibile riduzione della funzione renale, anche rapida in caso di vomito, diarrea e disidratazione
- Concomitante chemioterapia che può causare alterazione dei parametri ritentivi renali
- Possibile insufficienza epatica (NOAC consentiti solo per Child Pugh A) con conseguente coagulopatia ed accumulo di farmaco

Vantaggi e svantaggi

	VKA	LMWH	NOAC
Advantages	Oral agent Extensive clinical experience Reliable laboratory measure of anticoagulant activity (i.e., INR) Efficacious reversal agents (e.g., vitamin K, FFP, PCC) Safe in renal insufficiency	Rapid onset and offset Few drug-drug interactions Extensive clinical experience Reliable laboratory measure of anticoagulant activity (i.e., anti-Xa) Laboratory monitoring not routinely needed	Oral agent Rapid onset and offset Few drug-drug interactions Laboratory monitoring not needed
Disadvantages	Delayed onset and offset Many drug-drug and drug-food interactions Unpredictable dose requirements Narrow therapeutic window Requires frequent laboratory monitoring	Parenteral agent Lack of reliable reversal agent[a] Caution advised in renal insufficiency Need for high level of adherence	Limited clinical experience Lack of validated laboratory testing of anticoagulant effect Lack of reversal agent Caution advised in renal insufficiency Need for high level of adherence

NOACS ed interazioni farmacologiche CYP3A4

- CYP3A4 fa parte del sistema enzimatico epatico P450
- E’ responsabile del metabolismo ossidativo di rivaroxaban ed apixaban.
- Gli induttori di CYP3A4 assunti contemporaneamente a NOACS possono ridurne l’effetto
- Gli inibitori di CYP3A4 assunti contemporaneamente a NOACS possono aumentarne la tossicità.

NOACS ed interazioni farmacologiche Glicoproteina P

- La glicoproteina P è un trasportatore ATP-dipendente, che media l'assorbimento e l'escrezione dei farmaci.

- Rappresenta uno dei meccanismi di resistenza ai chemioterapici: la sua attività riduce l'uptake di alcuni chemioterapici in alcune cellule tumorali

- Presente soprattutto nella membrana luminale degli enterociti e nella membrana apicale degli enterociti e delle cellule tubulari renali.

P-gp

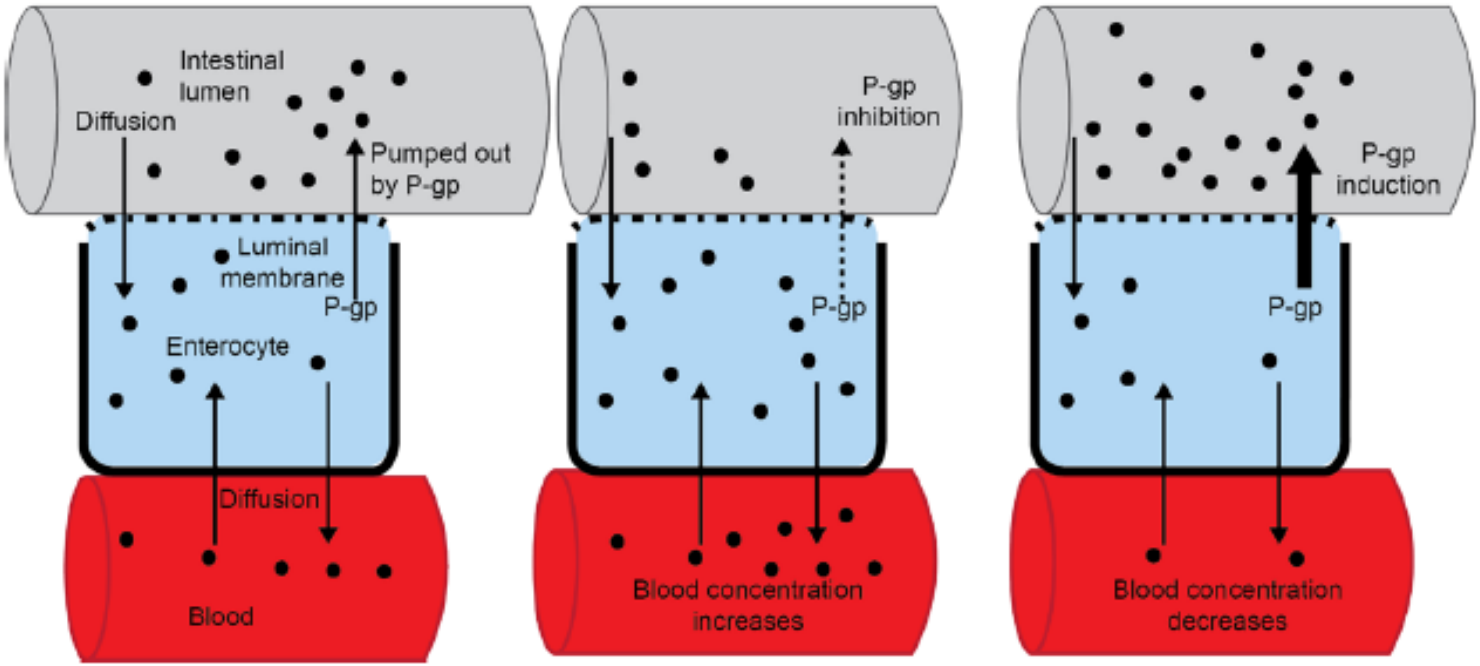
Drug diffuses from intestinal lumen through luminal membrane into enterocyte. P-gp pumps drup out of cell back into intestinal lumen.

P-gp Inhibition

P-gp activity reduced; less drug pumped back into intestine, greater systemic exposure.

P-gp Induction

P-gp activity increased; more drug pumped back into intestine, less systemic exposure.



NOACS ed interazioni farmacologiche Glicoproteina P

- Nell'intestino: escrezione delle sostanze assorbite nel lume intestinale, riducendone l'assorbimento netto
- Nei canalicoli biliari e nei tubuli renali: escrezione dei farmaci, riducendone l'assorbimento netto attraverso l'eliminazione con bile ed urine

Gli inibitori della GP aumentano i livelli ematici dei suoi substrati, mentre gli induttori li riducono

I DOACS sono substrati di GP e sono perciò suscettibili di forte inibizione o induzione di questo trasportatore.

APIXABAN

- Dimezzamento dose o sospensione in pazienti che assumono un forte duplice inibitore di CYP3A4 e GP

- Utilizzo non raccomandato in pazienti che assumono un forte induttore di CYP3A4 e GP

Eliquis (Apixaban) Prescribing Information. Princeton, NJ: Bristol-Myers Squibb Company, 2013. Available at http://packageinserts.bms.com/pi/pi_eliquis.pdf. Accessed June 14, 2013.

Dabigatran

- Riduzione della dose in pazienti con moderata insufficienza renale che assumono un forte inibitore di GP
- Utilizzo non raccomandato in pazienti con severa insufficienza renale che assumono un forte inibitore di GP
- Utilizzo concomitante a forte induttore di GP non raccomandato

Pradaxa (Dabigatran Etexilate Mesylate) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, 2013. Available at http://bidocs.boehringer Ingelheim.com/BIWebAccess/ViewServlet.ser?docBase5renetnt&folderPath5/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf. Accessed June 14, 2013.

Rivaroxaban

- Cautela nei pazienti con CrCl 15-50 ml/min che assumono un debole o moderato duplice inibitore di CYP3A4 e GP

- Utilizzo con forte duplice inibitore o induttore di CYP3A4 e GP non raccomandato.

Xarelto (Rivaroxaban) Prescribing Information.Titusville, NJ: Janssen Pharmaceuticals, 2013.Available at http://www.janssenmedicalinformation.

com/assets/pdf/products/files/Xarelto/pi/ENC-010330-11.pdf.Accessed June 14, 2013

Table 3 Summary of pharmacological properties of novel oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mode of action	Direct thrombin inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor
Approved for VTE treatment in Europe and the US?	Yes	Yes	Yes	Yes
VTE treatment regimen	Parenteral anticoagulant for 5–10 days, then 150 mg bid	15 mg bid for 21 days, then 20 mg od	10 mg bid for 7 days, then 5 mg bid	Parenteral anticoagulant, then 60 mg od
Dose adjustments for VTE treatment	None tested	None mandated[a]	None tested	30 mg od tested in patients who were expected to have an increased bleeding risk[b]
Food	Take with or without food	VTE treatment doses to be taken with food	Take with or without food	Take with or without food
Time to maximum concentration/anticoagulant effect (hours)	0.5–2	2–4	3–4	1–2
Half-life in healthy individuals (hours)	12–14	5–13	~12	8–10
Proportion of drug subject to renal clearance[c] (%)	85	33[d]	27	35
Co-medications contraindicated/ not recommended	Strong P-gp inhibitors and inducers	Strong CYP3A4 and P-gp inhibitors	Strong CYP3A4 and P-gp inhibitors	Strong P-gp inhibitors

Notes: [a]A reduced dose of rivaroxaban 15 mg od after the initial period of 15 mg bid dosing (ie, after 21 days) may be considered based on individual patient benefit–risk analysis (Europe only, not tested in Phase III treatment studies); [b]creatinine clearance 30 mL/min –50 mL/min, body weight ≤60 kg, taking co-medications that are potent P-gp inhibitors; [c]unchanged drug; [d]33% of the dose also undergoes renal excretion as inactive metabolites. Data from previous studies.[4,14,22–24]
Abbreviations: bid, twice daily; CYP3A4, cytochrome P450 3A4; od, once daily; P-gp, P-glycoprotein; VTE, venous thromboembolism.

Vascular Health and Risk Management 2016:12 23–34

Induttori ed inibitori di Gp e CYP

Inhibitors

Azole antifungals

- Ketoconazole
- Itraconazole
- Voriconazole
- Posaconazole
- Fluconazole

Protease inhibitors

- Ritonavir
- Lopinavir/ritonavir
- Indinavir/ritonavir

Immunosuppressive drugs[a]

- Cyclosporine
- Tacrolimus

Other

- Clarithromycin
- Conivaptan

Inducers

Anti-epileptic drugs

- Phenytoin
- Carbamazepine

Other

- Rifampin
- St. John's wort

Interazioni NOACS e farmaci CV

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12-60%[58]	No PK data[$]	+40%[63, 64, 244]	Minor effect[$] (use with caution if CrCl <50 ml/min)
Digoxin	P-gp competition	No effect[245]	No data yet	No effect	No effect[246, 247]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[58]	+40%[60]	No data yet	Minor effect[*] (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp competition and CYP3A4 inhibition	+70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min)	No PK or PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect[*] but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%[248 & SMPC]	No data yet	+77%[240, 249, 250] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[58] (reduce NOAC dose and take simultaneously)	No PK data.	+53% (SR)[64, 249] (No dose reduction required by label)	Minor effect[**] (use with caution if CrCl 15-50 ml/min)
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[251]	No data yet	No effect	No effect[252]

Dabigatran

- **75 mg bid in CrCl 30-50 mL/min**
  →Dronedarone, ketoconazole
- **Avoid concurrent use**
  → Rifampin

Rivaroxaban

- **Avoid concurrent use**
  → Ketoconazole, Itraconazole, ritonavir, rifampin

Thrombosis. 2012;2012:108983.

Table 6 Common P-glycoprotein inhibitors and inducers

P-glycoprotein inhibitors ↑ The substrates absorption ↑ serum concentration of p-gp substrates	Amiodarone[a]
	Ceftriaxone
	Clarithromycin, erythromycin
	Cyclosporine
	Diltiazem[a]
	Dipyridamole
	Hydrocortisone
	Ketoconazole, itraconazole[b]
	Nicardipine, nifedipine
	Propranolol
	Quinine
	Quinidine[a]
	Ritonavir, saquinavir, nelfinavir[b]
	Tamoxifen
	Tacrolimus
	Verapamil
P-glycoprotein inducers ↓ the serum concentration of p-gp substrates	Rifampin[c]
	Clotrimazole
	Phenytoin
	Phenobarbital
	St. John's wort

Interazioni NOACS ed antibiotici

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[247]
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100%[60]	+87-95%[64] (reduce NOAC dose by 50%)	Up to +160%[247]
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	No data yet	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%[254]	No effect (but pharmacodynamically increased bleeding time)	No data yet
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%[45, 53, 58]	No effect[55]	No effect	No effect[241, 242]
Others					
Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[SmPC]	minus 35%	Up to minus 50%
Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15-20%	No data yet	+90%[64] (reduce NOAC dose by 50%)	+30-54%[42, 247]
Rifampicin***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[238]	avoid if possible: minus 35%, but with compensatory increase of active metabolites[243]	Up to minus 50%
Antiviral drugs					
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%[247]

Novel oral anticoagulants (NOACs)

NOAC INTERACTIONS WITH ANTICANCER THERAPIES BASED ON KNOWN METABOLIC PATHWAYS

Interaction effect*	Dabigatran P-glycoprotein	Rivaroxaban P-glycoprotein CYP3A4	Apixaban P-glycoprotein CYP3A4
Increases NOAC plasma levels†	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib
Reduces NOAC plasma levels‡	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine

Novel oral anticoagulants may not be suitable for use in some cancer patients because they share metabolic pathways. Further research is needed to find out more about the impact of the interaction

† Inhibitors of pgp transport and CYP34A pathway; ‡ Inducers – lower NOAC levels

The Oncologist®

New Drug Development and Clinical Pharmacology

New Oral Anticoagulants and the Cancer Patient

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	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Antimitotic agents						
Vinca alkaloids						
Vinblastine	+++		+	●	●	
Vincristine	+++		+	●		
Vinorelbine	+++		+			
Taxanes						
Docetaxel	+++		+	●		
Paclitaxel	**+++**	**++**		●		
Topoisomerase inhibitors						
Topotecan						
Irinotecan	+++			●		
Etoposide	+++		+	●		

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Antimetabolites						
Antifolates						
Methotrexate				●		
Pemetrexed						
Purine analogs						
Mercaptopurine						
Thioguanine						
Pentostatin						
Cladribine						
Clofarabine						
Fludarabine						
Pyrimidine analogs						
Fluorouracil						
Capecitabine						
Cytarabine						
Gemcitabine						
Azacitadine						
Decitabine						

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Anthracyclines/ anthracenediones						
Doxorubicin	+++		+	●	●	
Daunorubicin				●		
Idarubicin			+	●		
Mitoxantrone						
Alkylating agents						
Cyclophosphamide	+		+			
Ifosfamide	+++		+			
Chlorambucil						
Melphalan						
Bendamustine				●		
Carmustine						
Lomustine			+			
Busulfan	+++					
Procarbazine						
Dacarbazine						
Temozolomide						

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Platinum-based agents						
Cisplatin						
Carboplatin						
Oxaliplatin						
Intercalating agents						
Bleomycin						
Mitomycin C				●		
Dactinomycin						
Tyrosine kinase inhibitors						
Imatinib	+++		++	●		●
Dasatinib	+++		+			
Nilotinib	+++		+	●		●
Erlotinib	+++					
Gefitinib	+++					
Lapatinib	+++		+	●		●
Sunitinib	+++					●
Sorafenib	+					
Crizotinib	+++		++	●		●
Vemurafenib	+	++		●		
Vandetanib	+++					●

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Monoclonal antibodies						
Rituximab						
Brentuximab	+++					
Alemtuzumab						
Cetuximab						
Trastuzumab						
Bevacizumab						
Hormonal agents						
Tamoxifen	+++		+			●
Raloxifene						
Anastrozole			+			
Letrozole	+					
Fulvestrant	+					
Leuprolide						
Flutamide	+++					
Bicalutamide			++			
Enzalutamide	+++	+++				●
Abiraterone	+++		++			●
Mitotane						

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Immune-modulating agents						
Cyclosporine	+++		++	●		●
Sirolimus	+++		+	●		
Everolimus	+++			●		
Temsirolimus	+++		+	●		
Tacrolimus	+++		+	●		●
Dexamethasone	+++	+++		●	●	●
Prednisone	+	++				
Miscellaneous						
Lenalidomide				●		
Bortezomib	+++		+			
Bexarotene	+	++				

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Supportive care						
Prochlorperazine						
Ondansetron	+++			●		
Palonosetron	+					
Metoclopramide						
Aprepitant	+++	++	++			
Fosaprepitant	+++	++	++			
Oxycodone	+++					
Hydromorphone						
Morphine						
Fentanyl	+++		+			
Methadone	+++		+			
Acetaminophen	+		+			
Lorazepam						
Clonazepam	+++					
Filgrastim						
Epoetin alfa						
Darbepoetin alfa						

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling

Criteria for NOAC use in cancer patients requiring anticoagulation

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Patient assessment
Risk factors for bleeding No major bleeding events in the past 2 months Absence of intracranial or visceral tumor at high risk for major bleeding
Platelets Platelet count >50,000 per μL No anticipated decrease due to disease or chemotherapy
Coagulation studies Normal PT, PTT, and fibrinogen
Liver function tests No significant hepatic impairment (e.g., Child-Pugh B or C, cirrhosis)
Renal function CrCl >30 mL/min (rivaroxaban) CrCl >15 mL/min (dabigatran and apixaban) No anticipated fluctuations due to nephrotoxic chemotherapy or other drugs
Medications No concomitant use of drugs with strong effect on CYP3A4 and/or P-glycoprotein Fig. 1 lists strong CYP3A4 and/or P-glycoprotein inhibitors and inducers Table 4 lists chemotherapy drugs that modulate CYP3A4 and/or P-glycoprotein Good medication compliance

Rivaroxaban

"Avoid concomitant use of rivaroxaban with combined P-gp and strong CYP 3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, and conivaptan)."

"Avoid concomitant use of rivaroxaban with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St John's wort)."

Apixaban

"The dose of apixaban should be decreased to 2.5 mg twice daily when it is co-administered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin)."

"Avoid concomitant use of apixaban with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St John's wort) because such drugs will decrease exposure to apixaban."

Xarelto prescribing information. Janssen, 2012.
Eliquis prescribing information. Bristol-Myers Squibb, 2012.