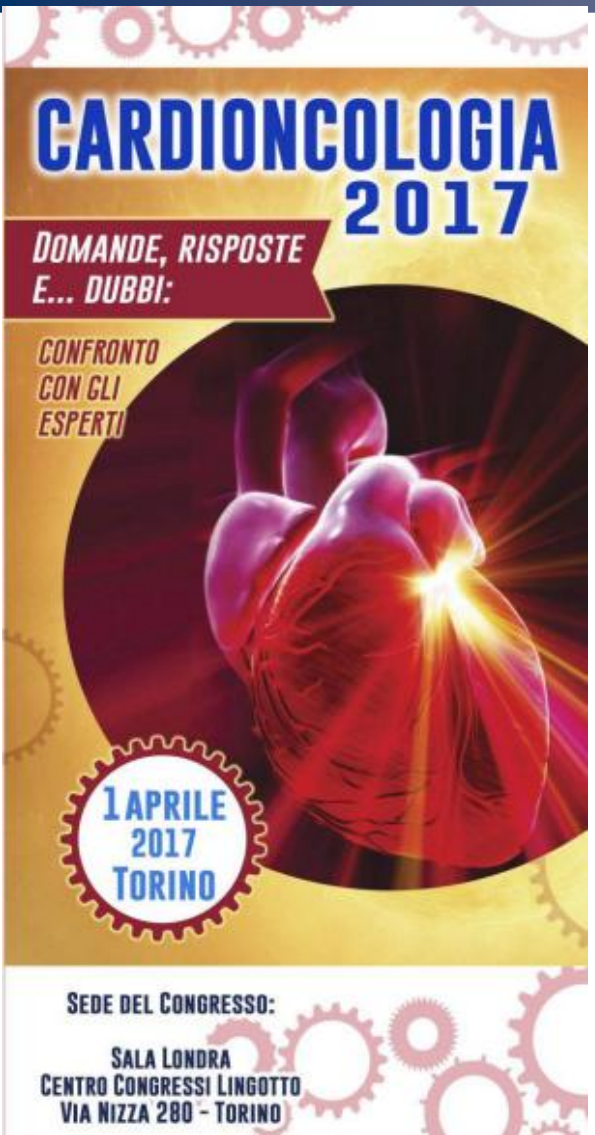
Cardiotossicità e terapia anticoagulante



Il parere del cardiologo:
Quale spazio per i DOAC?

Paola Lusardi

MD, Specialista in Cardiologia

rete oncologica
PIEMONTE | VALLE D'AOSTA
si prende cura di te

Problematiche

- FA di nuova insorgenza nel paziente oncologico in trattamento : che fare?
- Diagnosi di neoplasia nel paziente che assume DOACS: che fare?
- Come stratificare il rischio emorragico e trombotico?
- Quale anticoagulante?
- Quali interferenze farmacologiche?
- Ci aiutano le linee guida?

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Fibrillazione atriale e cancro

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

Farmakis D et al, J Am Coll Cardiol. 2014 Mar 18;63(10):945-53.

Drug Saf 2015;38:129–152.

European Heart Journal Advance Access published August 26, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

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.

Problematiche

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DOACS e cancro di nuova diagnosi

1. Tipo di neoplasia e rischio di sanguinamento (tratto gastro-enterico, fegato, polmone, prostata, vescica, testa-collo)

2. Qual è il programma terapeutico del paziente (mielosoppressione, nefrotossicità, epatotossicità,…)

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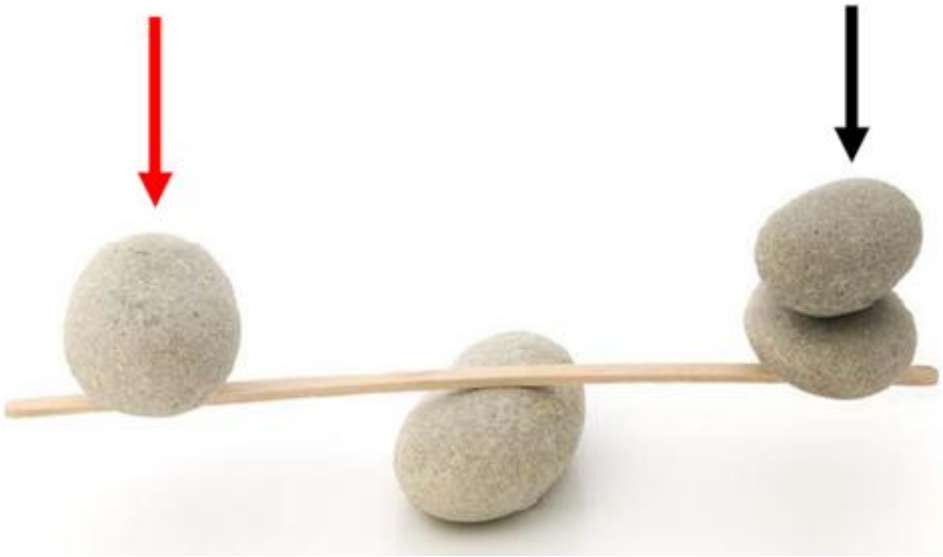
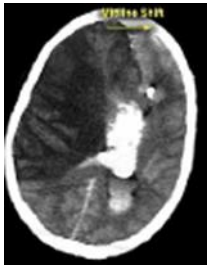
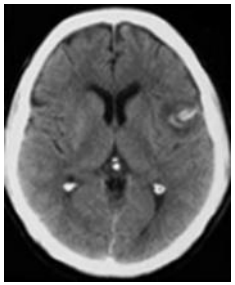
IL PAZIENTE ONCOLOGIGO





SANGUINAMENTO

TROMBOSI



IL PAZIENTE ONCOLOGICO

Trombosi

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

Rischio emorragico

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

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

- i pazienti possono sviluppare una TVP nonostante la corretta anticoagulazione

- I pazienti hanno un rischio di sanguinamento di 2-6 volte più elevato, pur in assenza di anticoagulazione

Oltre il Khorana Score?

KHORANA Risk Score

Patient Characteristics	Risk Score*
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥ 350,000/mm³	1
Hemoglobin level < 100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count > 11,000/mm³	1
Body mass index ≥ 35 kg/m²	1

*High-risk score ≥ 3; intermediate-risk score = 1–2; low-risk score = 0.
Adapted from Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:3786–4907, with permission.

Medscape Source: J Natl Compr Canc Netw © 2011 JNCCN

- No risk population (score 0): **36.8%** (139/378)
- Intermediate Risk Population (score 1-2): **52.1%** (197/378)
- High risk population (score ≥ 3): **11.1%** (42/378)

33.3% (5/15) of the TEs was in the high risk population

PROTECHT Risk Score

- Site of cancer
  - Stomach, Pancreas **2 points**
  - Lung, gynaecologic, testicular **1 point**
- Pre-chemotherapy platelet count 350 x 10^9L or more **1 point**
- Hemoglobin level less than 100 g/L **1 point**
- Pre-chemotherapy **Leukocyte>11000/mm3** nore **1 point**
- BMI 35 Kg/sqm or more **1 point**
- Chemotherapy regimen containing
  - Cisplatin or carboplatin or gemcitabine **1 point**
  - Platinum compound plus gemcitabine **2 points**

- No risk population (score 0): **30.2%** (114/378)
- Intermediate Risk Population (score 1-2): **37%** (140/378)
- High risk population (score ≥ 3): **32.8%** (124/378)

66.7% (10/15) of the TEs was in the high risk population

Barni S et al. MASCC 2011

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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
- Ipoalbuminemia
- Anoressia, nausea, vomito
- In caso di basso peso corporeo

J Gen Intern Med 2007;22: 997–1002

Considerare che:

- La funzione renale si può modificare rapidamente in caso di vomito, diarrea, disidratazione e con alcuni trattamenti chemioterapici

- La possibilità di 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

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Table 3 Summary of pharmacological properties of novel oral anticoagulants

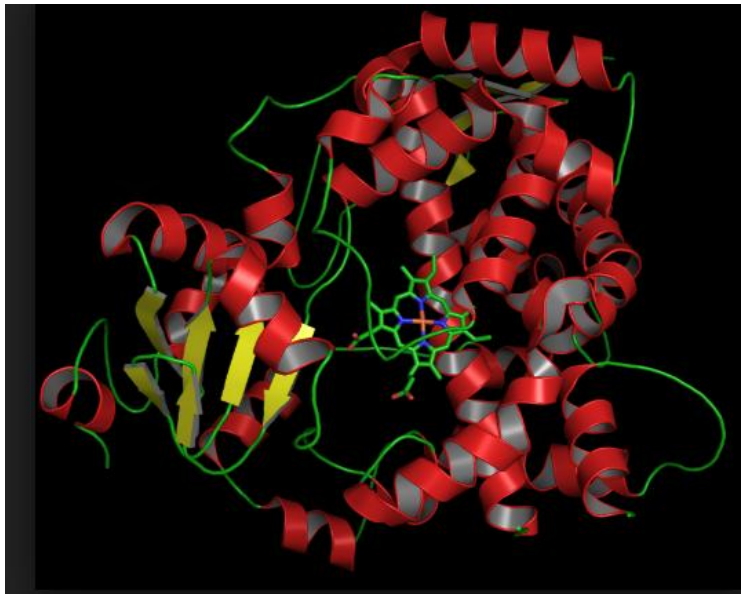
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mode of action	Direct thrombin inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor
Approved for VTE treatment in Europe and the US?	Yes	Yes	Yes	Yes
VTE treatment regimen	Parenteral anticoagulant for 5–10 days, then 150 mg 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.[4,14,22–26]
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

CYP3A4

- E’ responsabile del metabolismo ossidativo di rivaroxaban ed apixaban.
- Gli induttori di CYP3A4 assunti contemporaneamente a DOACS ne riducono l’effetto
- Gli inibitori di CYP3A4 assunti contemporaneamente a DOACS ne aumentano la tossicità.

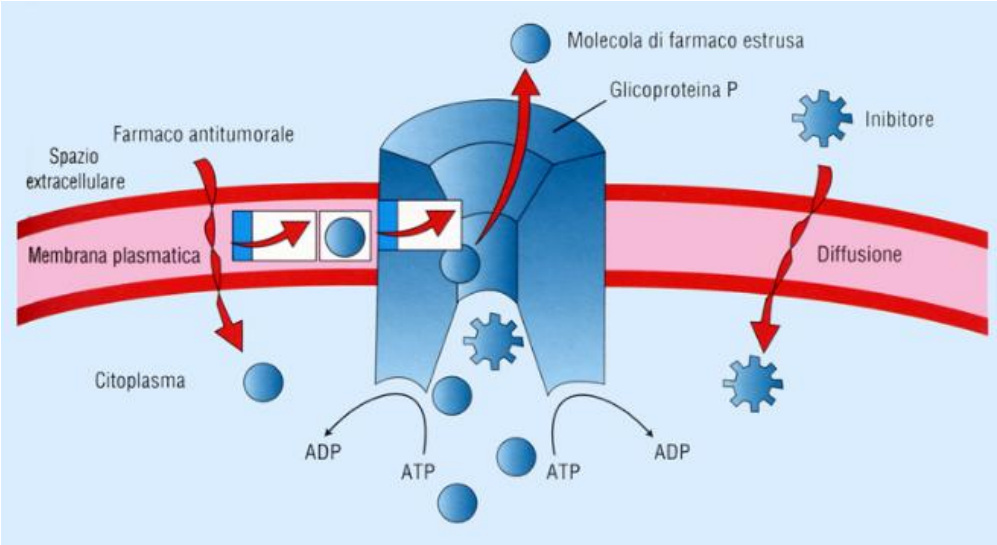


Glicoproteina P

- Trasportatore ATP-dipendente, che media l'assorbimento e l'escrezione dei farmaci.

- Nella membrana luminale degli enterociti e nella membrana apicale degli enterociti e delle cellule tubulari renali

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



Glicoproteina P

Nell'intestino: escrezione delle sostanze assorbite nel lume intestinale, riducendone l'assorbimento netto

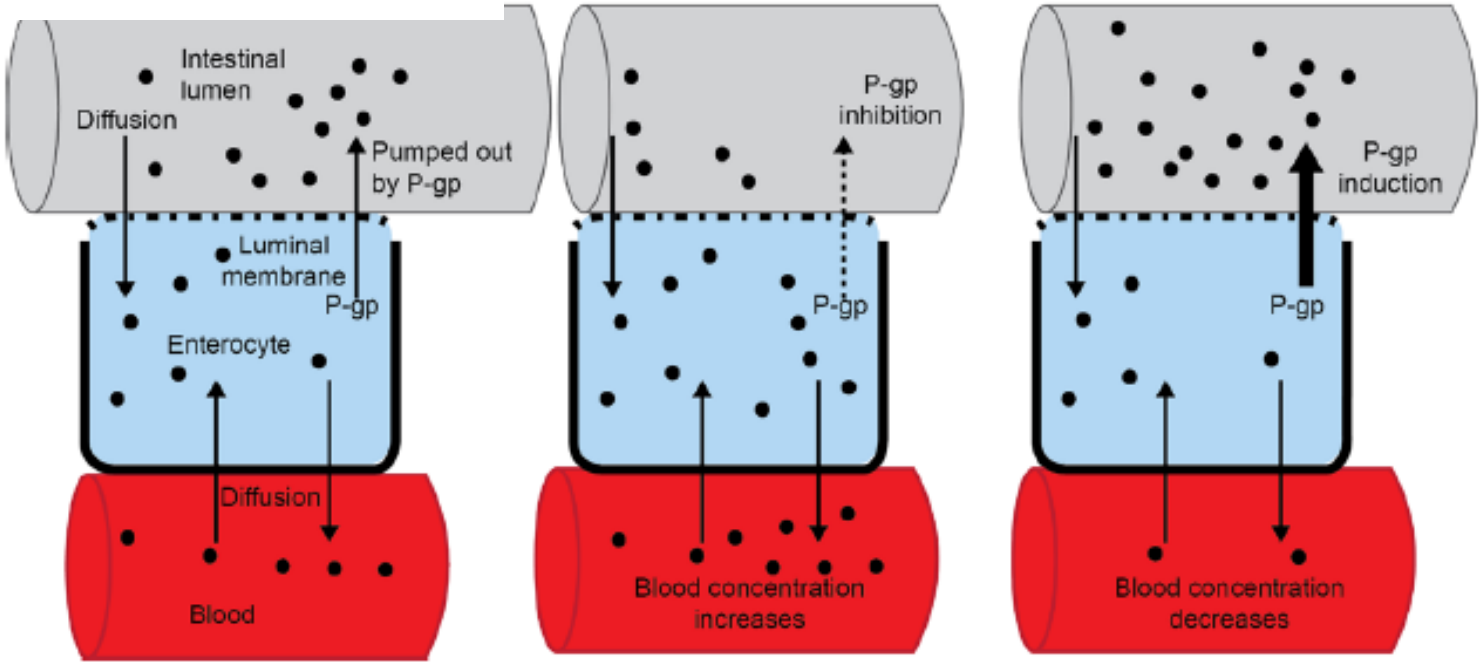
Nei canalicoli biliari e nei tubuli renali: escrezione dei farmaci, riducendone l'assorbimento netto attraverso l'eliminazione con bile ed urine

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.



Interazioni DOACS 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]

Interazioni farmacologiche e DOACS

	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]

Interazioni farmacologiche e DOACS

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

NICHOLAS J. SHORT,[a] JEAN M. CONNORS[b,c]

[a]Department of Medicine and [b]Hematology Division, Brigham and Women's Hospital, Boston, Massachusetts, USA; [c]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

TheOncologist 2014;19:82–93

	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	+++		+	●		

	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**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
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

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Non sono state studiate le polichemioterapie

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European Heart Journal Advance Access published August 26, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

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The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Cosa utilizzare?

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

European Heart Journal Advance Access published August 26, 2016

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

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 eventuale 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. 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

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

Criteria for NOAC use in cancer patients requiring anticoagulation

TheOncologist 2014;19:82–93

1. SANGUINAMENTO
2. PIASTRINE
3. COAGULAZIONE
4. FUNZIONE EPATICA
5. FUNZIONE RENALE
6. FARMACI

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 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

Grazie dell’attenzione