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Drug-drug interactions

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466-BE-2200052 - 10/22

Conflicts of interest

Relevant to this session:

- Bayer
- BMS/Pfizer
- Daiichi Sankyo

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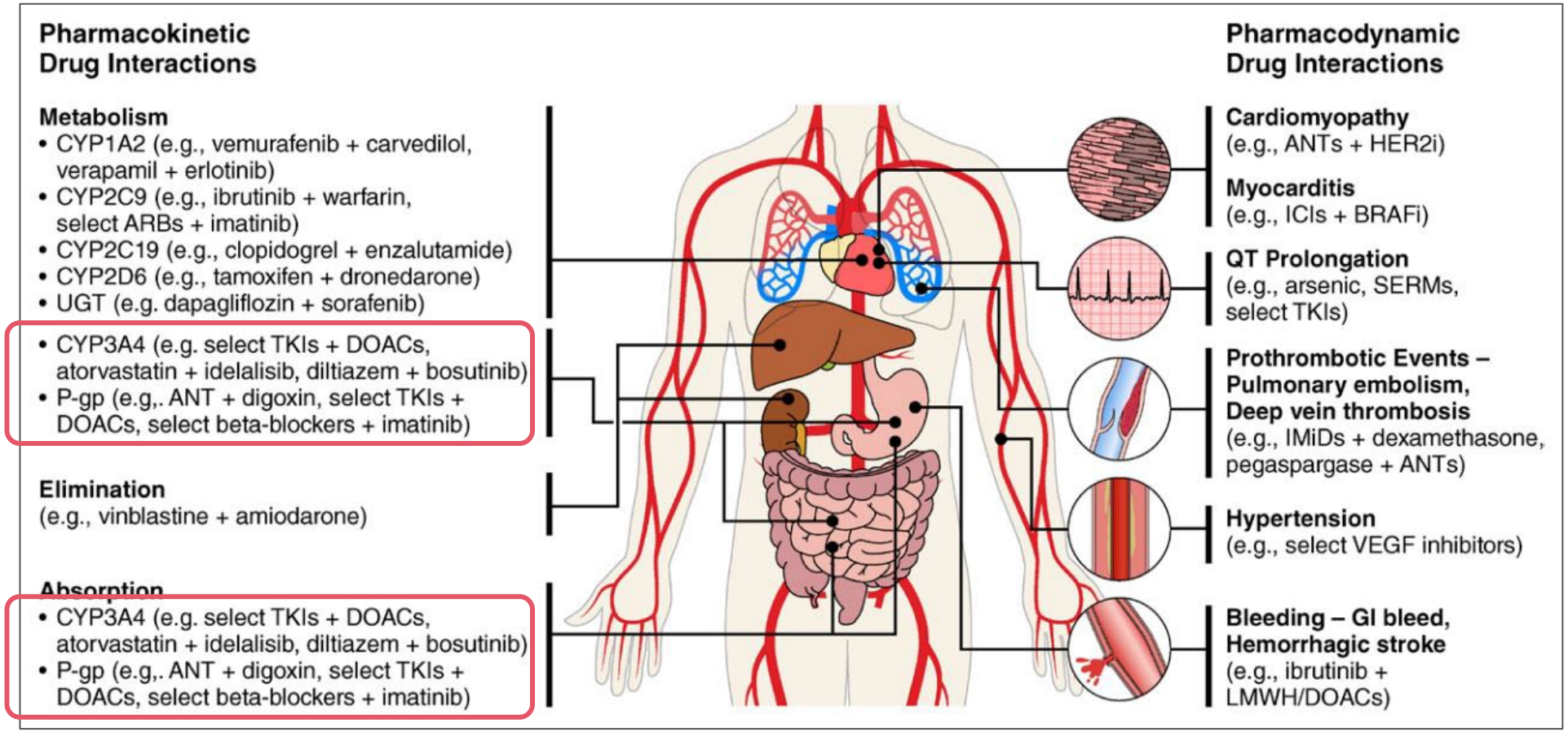
Drug-drug interactions are **common** in oncology

AHA SCIENTIFIC STATEMENT

Cardio-Oncology Drug Interactions: A Scientific Statement From the American Heart Association

Craig J. Beavers, PharmD, FAHA, Chair; Jo E. Rodgers, PharmD, Vice Chair; Aaron J. Bagnola, PharmD; Theresa M. Beckie, PhD, FAHA; Umberto Campia, MD, MSc, FAHA; Katherine E. Di Palo, PharmD, FAHA; Tochi M. Okwuosa, MD, FAHA; Eugene R. Przespolewski, PharmD; Susan Dent, MD; on behalf of the American Heart Association Clinical Pharmacology Committee and Cardio-Oncology Committee of the Council on Clinical Cardiology and Council on Genomic and Precision Medicine; and the Council on Peripheral Vascular Disease

Cardio-oncology PK and PD drug interactions



ANT, anthracycline; BRAFi, BRAF inhibitor; CYP, cytochrome P450; DOAC, direct acting oral anticoagulant; GI, gastrointestinal; HER2i, human epidermal growth factor receptor 2 inhibitor; ICI, immune checkpoint inhibitor; IMiD, immunomodulatory agent; LMWH, low-molecular weight heparin; PD, pharmacodynamic; P-gp, P-glycoprotein; PK, pharmacokinetics; SERM, selective estrogen receptor modulator; TKI, tyrosine kinase inhibitor; UGT, uridine 5′-diphosphoglucuronosyltransferase; VEGF, vascular endothelial growth factor.

Please refer to Product SmPC of above-mentioned products for further information

Beavers CJ et al. *Circulation*. 2022;145(15):e811-e838.

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NOACs in **CAT**

Recommendations for the management of VTE in patients receiving anticancer treatment

Recommendations	COR	LOE
Apixaban, edoxaban, or rivaroxaban care recommended for the treatment of symptomatic or incidental VTE in patients with cancer without contraindications[a]	I	A

[a]High risk of GI or GU bleeding, GI absorption concerns, significant drug-drug interactions, severe renal dysfunction (CrCl <15mL/min), significant liver disease (alanine aminotransferase/aspartate aminotransferase >2×ULN), or significant thrombocytopaenia (platelet count <50000/μL). In addition, patients with primary brain tumours or brain metastases and acute leukaemia were excluded from the seminal apixaban trial.

Lyon AR et al. *Eur Heart J*. 2022;ehac244.

Anticoagulation for atrial fibrillation in patients with cancer

ESC 2022

[a]**Very high bleeding risk**: active or recent major bleeding (<1 month); recent/evolving intracranial lesions; platelet count <25 000/μL. According to the International Society on Thrombosis and Haemostasis,[529] major bleeding is defined as: fall in haemoglobin level ≥ 2 g/dL, transfusion of ≥2 units of red blood cells, fatal bleeding, or bleeding in a critical area (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal). [b]**Conditions favouring LMWH**: unoperated GI/GU cancer; GI comorbidities or toxicity; severe renal dysfunction (CrCl < 15 mL/min); NOAC major drug–drug interactions, platelet count < 50 000/μL.

Lyon AR et al. *Eur Heart J*. 2022;ehac244.

Anticoagulation for atrial fibrillation in patients with cancer

ASH 2021

suggests using a DOAC (apixaban or rivaroxaban) or LMWH for initial treatment for patients with cancer and VTE. The period of initial treatment may range from 5 to 10 days, covering the early period of care starting from the time of diagnosis of VTE. The choice of treatment must be based on the specific clinical setting to minimize risk, after careful consideration of bleeding risk, drug-drug interactions, patient preference, and the availability of treatment options, including cost considerations. DOACs should be used carefully for patients with GI cancers because of the higher risk of GI bleeding and for patients with prior upper GI resections.[303]

Lyman GH et al. *Blood Adv*. 2021;5(4):927-974.

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We need to **care** about DDIs with NOACs

Package label information

	APIXABAN	RIVAROXABAN	EDOXABAN
Dose adjustments (AF, VTE) owing to concomitant treatments	None	None	Use 30mg instead of 60mg in the case of concomitant treatment with cyclosporin, dronedarone, erythromycin or oral ketoconazole.
Contra-indicated drug combinations (mainly based on SPC)	Other anticoagulants	Other anticoagulants	Other anticoagulants
To be avoided, use not recommended (mainly based on SPC)	Chronic use of NSAIDs	Chronic use of NSAIDs	Chronic use of NSAIDs
	Inducers such as rifampicin, phenytoin, fenobarbital, St John's wort, carbamazepine, unless the patient can be monitored closely. Strong combined inhibitors of CYP3A4 and P-GP: oral ketoconazole, itraconazole, voriconazole, posaconazole, HIV-protease inhibitors (e.g., ritonavir)	Inducers such as rifampicin, phenytoin, fenobarbital, St John's wort, carbamazepine if the patient is receiving apixaban for management of acute VTE (DVT/PE). Strong combined inhibitors of CYP3A4 and P-GP: oral ketoconazole, itraconazole, voriconazole, posaconazole, HIV-protease inhibitors (e.g., ritonavir)	Strong P-GP-inhibitors, other than cyclosporin, dronedarone, erythromycin or ketoconazole (not investigated)
Should be used with caution (mainly based on SPC)	Antiplatelet agents (on indication), NSAIDs, systemic steroids, SSRI/SNRI	Antiplatelet agents (on indication), NSAIDs, systemic steroids, SSRI/SNRI	Antiplatelet agents (on indication), NSAIDs, systemic steroids, SSRI/SNRI
		Inducers such as rifampicin, phenytoin, fenobarbital, St John's wort, carbamazepine in other indications than acute VTE treatment	Inducers such as rifampicin, phenytoin, fenobarbital, St John's wort, carbamazepine

Please refer to Product SmPC of apixaban, rivaroxaban and edoxaban for further information

Courtesy of prof. dr. apr. Van der Linden

Pharmacodynamic DDI

	APIXABAN	RIVAROXABAN	EDOXABAN
Dose adjustments (AF, VTE) owing to concomitant treatments	None	None	Use 30mg instead of 60mg in the case of concomitant treatment with cyclosporin, dronedarone, erythromycin or oral ketoconazole.
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Pharmacokinetic DDI

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ADME

ADME of NOAC: short summary

	APIXABAN	EDOXABAN	RIVAROXABAN
Target	Xa	Xa	Xa
T_{max}	3-4h	1-2h	2-4h
$T_{1/2}$	~12h	~8-10h	5-9h; older adults: 11-13h Summarized: 5-13 h
F (%)	~50%	~62%	90-100% (food)
Protein binding	87%	40-59%	92-95%
Dialyzable	No	No	No
Renal elimination	27%	50%	33%

Steffel J et al. *Eur Heart J*. 2018;39(16):1330-1393.

ADME of NOAC: short summary

	APIXABAN	EDOXABAN	RIVAROXABAN	
Target	Xa	Xa	Xa	Direct acting
T_{max}	3-4h	1-2h	2-4h	Fast
$T_{1/2}$	~12h	~8-10h	5-9h; older adults: 11-13h Summarized: 5-13 h	Short
F (%)	~50%	~62%	90-100% (food)	Orally active
Protein binding	87%	40-59%	92-95%	
Dialyzable	No	No	No	
Renal elimination	27%	50%	33%	Renally eliminated

Steffel J et al. *Eur Heart J*. 2018;39(16):1330-1393.

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Lower DDI potential compared to VKA

≠zero

Common mechanisms of drug-drug interactions

Mechanism	Description	Interaction of DOACs with CYP450 enzymes and transporters		
		Apixaban	Edoxaban	Rivaroxaban
CYP450 enzymes	• Key enzymes involved in the metabolism of select drugs • CYP450 enzymes commonly involved in drug-drug interactions: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5	20%-25% metabolized by CYP3A4	<4% metabolized by CYP3A4	50% metabolized by CYP3A4
P-gp	• Member of the multidrug resistance protein 1 (MDR1) family encoded by the ATP-binding cassette subfamily B (ABCB1) • An efflux pump that minimizes tissue exposure of potentially harmful substrates and promotes their removal	Substrate	Substrate	Substrate
BCRP	• An efflux transporter involved indrug metabolism and uptake,whose main purpose is to limitintestinal absorption of lowpermeability substrate drugs, andlimit organ exposure ofsubstrates	Substrate	No activity	Substrate
OATP	• Influx transporters belonging to the superfamily SLCO, of which, the SLC22A superfamily consists of the organic anion transporters (OATs) and the organic cation transporters (OCTs) • Although more than 300 members of the OATP (SLCO) transporter superfamily have been identified, only 11 are known to be expressed in humans	No activity	Weak inhibitory effects on OATP1B1 and OATP1B3. Minimal effect on OAT1, OAT3 and OCT2	Substrate of OAT3

Wiggins BS et al. *J Am Coll Cardiol*. 2020;75(11):1341-1350.

Pretty much straightforward

Apixaban

- Strong inducers => exposure ↓
- Strong dual CYP3A4/PGP inhibitors => exposure ↑

Rivaroxaban

- Strong inducers => exposure ↓
- Strong dual CYP3A4/PGP inhibitors => exposure ↑

Edoxaban

- Strong inducers => exposure ↓
- Strong PGP inhibitor => exposure ↑

Please refer to Product SmPC of apixaban, rivaroxaban and edoxaban for further information

Pharmacokinetic DDI

	APIXABAN	RIVAROXABAN	EDOXABAN
Dose adjustments (AF, VTE) owing to concomitant treatments	None	None	Use 30mg instead of 60mg in the case of concomitant treatment with **CYCLOSPORIN, DRONEDARONE, ERYTHROMYCIN OR ORAL KETOCONAZOLE**.
Contra-indicated drug combinations (mainly based on SPC)	Other anticoagulants	Other anticoagulants	Other anticoagulants
To be avoided, use not recommended (mainly based on SPC)	Chronic use of NSAIDs	Chronic use of NSAIDs	Chronic use of NSAIDs
	INDUCERS such as rifampicin, phenytoin, fenobarbital, St John's wort, carbamazepine, unless the patient can be monitored closely. **STRONG COMBINED INHIBITORS OF CYP3A4 AND P-GP**: oral ketoconazole, itraconazole, voriconazole, posaconazole, HIV-protease inhibitors (e.g., ritonavir)	**INDUCERS** such as rifampicin, phenytoin, fenobarbital, St John's wort, carbamazepine if the patient is receiving apixaban for management of acute VTE (DVT/PE). **STRONG COMBINED INHIBITORS OF CYP3A4 AND P-GP**: oral ketoconazole, itraconazole, voriconazole, posaconazole, HIV-protease inhibitors (e.g., ritonavir)	**STRONG P-GP-INHIBITORS**, other than cyclosporin, dronedarone, erythromycin or ketoconazole (not investigated)
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			INDUCERS such as rifampicin, phenytoin, fenobarbital, St John's wort, carbamazepine

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How to **interpret** this information?

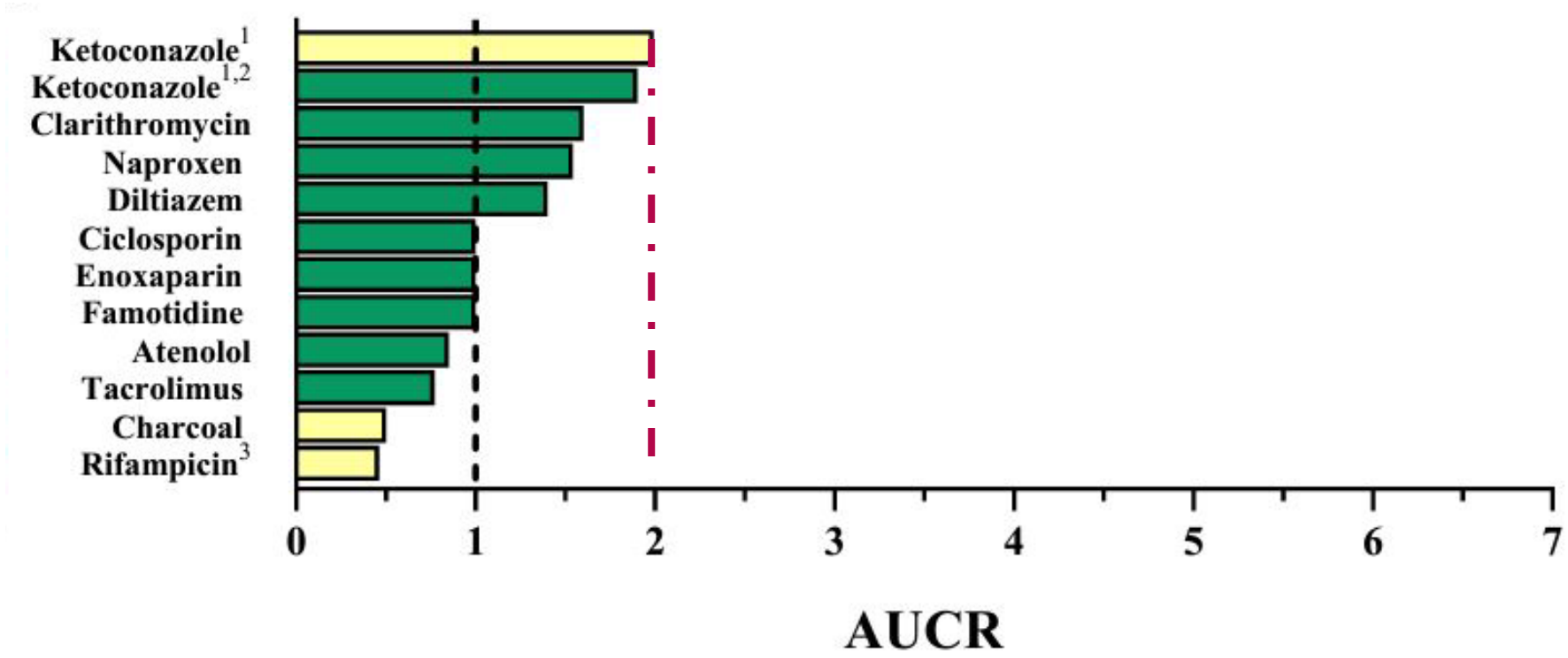
FDA & EMA guidance for industry

DDI from inhibition or induction which results in:

- ≥5-fold AUC change: **strong**
- 2- to 5-fold AUC change: **moderate**
- 1.25- to 2-fold AUC change: **weak**

Yu J et al. *Drug Metab Dispos*. 2019;47(2):135-144; Clinical Drug Interaction Studies: Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry - U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Investigation of drug interactions - EMA.

Drug-drug interactions with apixaban



Foerster KI et al. *Clin Pharmacokinet*. 2020;59(8):967-980.

AUCx2 or AUC/2
= actionable

Pharmacokinetic DDI

	APIXABAN	RIVAROXABAN	EDOXABAN
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What does all of this mean in the **cancer** setting?

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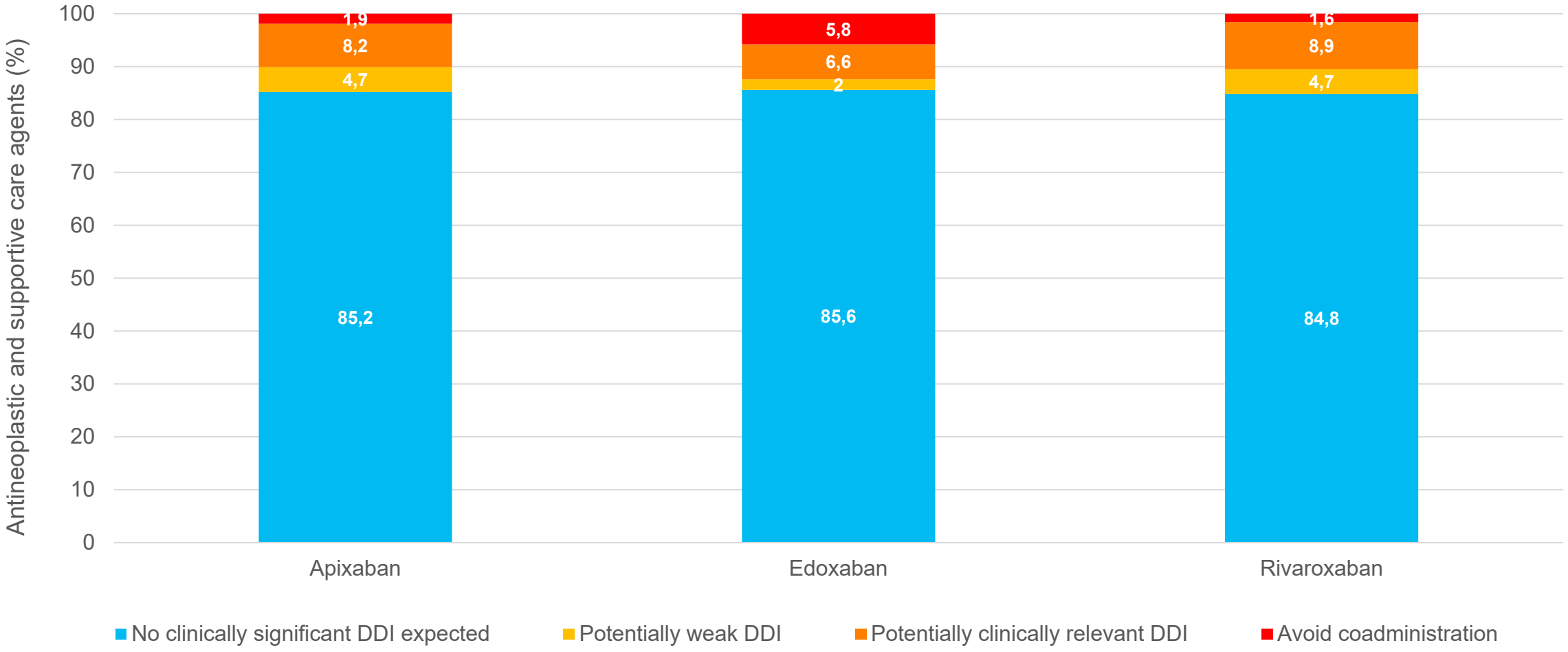
First the **good** news

DDI between antineoplastic agents and NOACs



Peixoto de Miranda ÉJF et al. *Clin Appl Thromb Hemost*. 2020;26:1076029620936325.

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Then the **practical** news

- NOAC in CAT: **apixaban, rivaroxaban, edoxaban**
- Rule of thumb: **AUCx2 or AUC/2 = actionable**
- **SmPC**: no relevant information on cancer therapies
- Other data?

SELECT-D (rivaroxaban) & **CARAVAGGIO** (apixaban):

- Overall, mostly in line with SmPC
- **No guidance on oncology therapies in trial protocol**

HOKUSAI VTE CANCER (edoxaban):

- Overall, mostly in line with SmPC
- **Guidance on oncology therapies in trial protocol**
  - Following P-GP inhibitors require a **reduction** in the edoxaban dose to 30 mg QD:
    - Tyrosine kinase inhibitors: imatinib, nilotinib, lapatinib, sunitinib, criozitinib, vandetanib
    - Hormonal agents: tamoxifen, enzalutamide, abiraterone,
    - Immuno-modulating agents: cyclosporine, tacrolimus, dexamethasone
- Once treatment with these P-gp inhibitors is complete, the full 60 mg edoxaban dosesshould be resumed.
- Note: Other agents in these classes may be administered concurrently without reducing the edoxaban dose.

Young AM et al. *J Clin Oncol*. 2018;36(20):2017-2023 and Study Protocol; Agnelli G et al. *N Engl J Med*. 2020;382(17):1599-1607 and Study Protocol; Raskob GE et al. *N Engl J Med*. 2018;378(7):615-624 and Study Protocol.

SELECT-D (rivaroxaban) & **CARAVAGGIO** (apixaban):

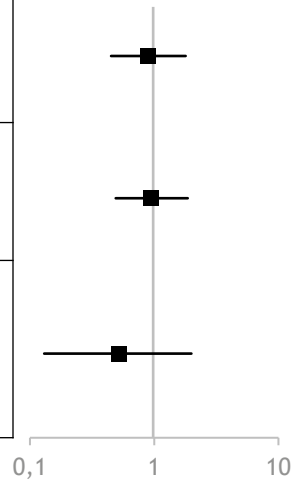
- Overall, mostly in line with SmPC
- **No guidance on oncology therapies in trial protocol**

Concomitant use of strong inhibitors or inducers of both cytochrome P-450 3A4 and P-gp was not allowed in the study, but none of the anticancer agents were included in the list of excluded drugs

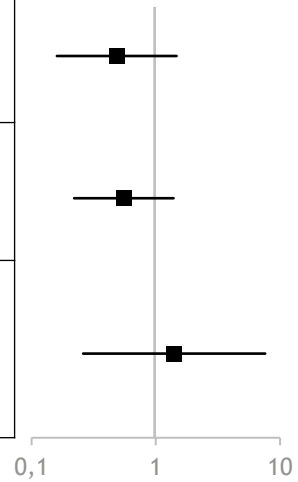
Young AM et al. *J Clin Oncol*. 2018;36(20):2017-2023 and Study Protocol; Agnelli G et al. *N Engl J Med*. 2020;382(17):1599-1607 and Study Protocol; Raskob GE et al. *N Engl J Med*. 2018;378(7):615-624 and Study Protocol; Verso M et al. *Eur J Cancer*. 2021;148:371-381.

Clinical outcomes based on potential interactions between anticoagulants and anticancer agents by P-gp and/or CYP3A4 pathways

	Recurrent VTE		
	Apixaban n/N (%)	Dalteparin n/N (%)	HR (95% CI)
CYP3A4/P-gp inducers	16/181 (8.8)	16/167 (9.6)	0.90 (0.45-1.79)
CYP3A4/P-gp inhibitors or competitors	17/250 (6.8)	17/243 (7.0)	0.95 (0.49-1.86)
No CYP3A4/P-gp inducers or inhibition or competition	3/82 (3.7)	7/85 (8.2)	0.52 (0.13-1.99)



	Major bleeding		
	Apixaban n/N (%)	Dalteparin n/N (%)	HR (95% CI)
CYP3A4/P-gp inducers	6/181 (3.3)	10/167 (6.0)	0.49 (0.16-1.47)
CYP3A4/P-gp inhibitors or competitors	8/250 (3.2)	13/243 (5.3)	0.56 (0.22-1.39)
No CYP3A4/P-gp inducers or inhibition or competition	4/82 (4.9)	3/85 (2.4)	1.41 (0.26-7.61)



CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism; DOAC, direct oral anticoagulant; P-gp, permeability glycoprotein.

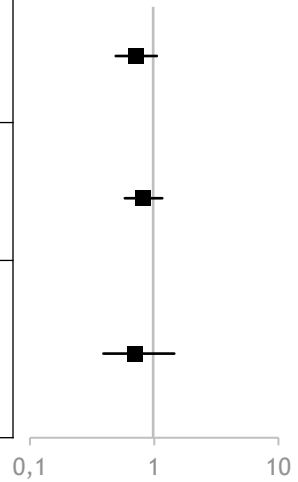
List of systemic anticancer agents determining CYP3A4 or P-gp induction: taxanes (paclitaxel, docetaxel), hormonal therapy (enzalutamide), vinca alkaloids (vinblastine, vincristine, vinorelbine), kinase inhibitors (vemurafenib, vandetanib, sunitinib), immunomodulating agents (dexamethasone, prednisone).

List of systemic anticancer agents determining CYP3A4 or P-gp inhibition or competition: antimetabolites (methotrexate), monoclonal antibodies (nivolumab, pembrolizumab, ipilimumab, atezolizumab, avelumab, brentuximab), antiangiogenic drugs (sorafenib, sunitinib, pazopanib, regorafenib, axitinib, cabozantinib, lenvatinib, nintedanib, fruquintinib, apatinib and anlotinib), taxanes (paclitaxel), hormonal therapy (abiraterone, bicalutamide, tamoxifen, anastrozole, enzalutamide, flutamide, letrozole, exemestane, fulvestrant), topoisomerase inhibitors (etoposide, irinotecan), alkylating agents (ifosfamide, cyclophosphamide, lomustine, bendamustine, busulfan), anthracyclines (doxorubicin, idarubicin, daunorubicin), vinca alkaloids (vinblastine, docetaxel, vincristine, vinorelbine), kinase inhibitors (imatinib, crizotinib, nilotinib, lapatinib, dasatinib, vemurafenib, vandetanib, erlotinib, gefitinib, sorafenib, sunitinib, pazopanib, regorafenib, axitinib, cabozantinib).

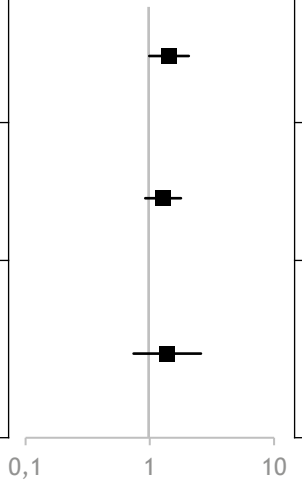
Verso M et al. *Eur J Cancer*. 2021;148:371-381.

Clinical outcomes based on potential interactions between anticoagulants and anticancer agents by P-gp and/or CYP3A4 pathways

	Death from any cause		
	Apixaban n/N (%)	Dalteparin n/N (%)	HR (95% CI)
CYP3A4/P-gp inducers	49/181 (27.1)	56/167 (33.5)	0.71 (0.49-1.05)
CYP3A4/P-gp inhibitors or competitors	61/250 (24.4)	67/243 (27.6)	0.82 (0.58-1.16)
No CYP3A4/P-gp inducers or inhibition or competition	12/82 (14.6)	19/85 (22.4)	0.70 (0.39-1.45)



	Event-free survival		
	Apixaban n/N (%)	Dalteparin n/N (%)	HR (95% CI)
CYP3A4/P-gp inducers	128/181 (70.7)	104/167 (62.3)	1.42 (0.99-2.06)
CYP3A4/P-gp inhibitors or competitors	185/250 (74.0)	167/243 (68.7)	1.28 (0.92-1.78)
No CYP3A4/P-gp inducers or inhibition or competition	65/82 (79.3)	61/85 (71.8)	1.38 (0.74-2.58)



CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism; DOAC, direct oral anticoagulant; P-gp, permeability glycoprotein.

List of systemic anticancer agents determining CYP3A4 or P-gp induction: taxanes (paclitaxel, docetaxel), hormonal therapy (enzalutamide), vinca alkaloids (vinblastine, vincristine, vinorelbine), kinase inhibitors (vemurafenib, vandetanib, sunitinib), immunomodulating agents (dexamethasone, prednisone).

List of systemic anticancer agents determining CYP3A4 or P-gp inhibition or competition: antimetabolites (methotrexate), monoclonal antibodies (nivolumab, pembrolizumab, ipilimumab, atezolizumab, avelumab, brentuximab), antiangiogenic drugs (sorafenib, sunitinib, pazopanib, regorafenib, axitinib, cabozantinib, lenvatinib, nintedanib, fruquintinib, apatinib and anlotinib), taxanes (paclitaxel), hormonal therapy (abiraterone, bicalutamide, tamoxifen, anastrozole, enzalutamide, flutamide, letrozole, exemestane, fulvestrant), topoisomerase inhibitors (etoposide, irinotecan), alkylating agents (ifosfamide, cyclophosphamide, lomustine, bendamustine, busulfan), anthracyclines (doxorubicin, idarubicin, daunorubicin), vinca alkaloids (vinblastine, docetaxel, vincristine, vinorelbine), kinase inhibitors (imatinib, crizotinib, nilotinib, lapatinib, dasatinib, vemurafenib, vandetanib, erlotinib, gefitinib, sorafenib, sunitinib, pazopanib, regorafenib, axitinib, cabozantinib).

Verso M et al. *Eur J Cancer*. 2021;148:371-381.

- NOAC in CAT: apixaban, rivaroxaban, edoxaban
- Rule of thumb: AUCx2 or AUC/2 = actionable
- SmPC: no relevant information on cancer therapies
- Other data? **Reassuring**

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- **CPOE (= prescriber software) / online database / papers**

ESC Cardio-Oncology: DDI table

CV drug	Interacting drug	Clinical consequences
Apixaban	Acalabrutinib, bemurafenib, dasatinib, ibritumomab, ibrutinib, nintedanib, obinutuzumab, pazopanib, ribociclib, vemurafenib	Additive effect: ↑risk of bleeding. Monitor platelet counts and haemorrhagic episodes
	Abiraterone, crizotinib, doxorubicin, enzalutamide, idelasilib, imatinib, nilotinib, sunitinib, vandetanib, vinblastine	Potent inhibitors of CYP3A4 and/or P-gp:↑apixaban exposure. Avoid the combination
	Bicalutamide, cyclophosphamide, cyclosporine, dasatinib, docetaxel, encorafenib, etoposide, idarubicin, ifosfamide, lomustine, paclitaxel, ribociclib, rucaparib, sirolimus, tacrolimus, tamoxifen, temsirolimus, repotinib, vemurafenib, vincaalkaloids	Mild CYP3A4 and/or P-gp inducers or inhibitors. Caution is needed in case of polypharmacy or in the presence of ≥2 bleeding risk factors
Edoxaban	Acalubrutinib, bemurafenib, dasatinib, ibritumomab, ibrutinib, nintedanib, obinutuzumab, pazopanib, ribociclib, vemurafenib	Additive effect: ↑risk of bleeding. Monitor platelet counts and haemorrhagic episodes
	Abiraterone, crizotinib, doxorubicin, enzalutamide, erdafitinib, idelasilib, imatinib, lapatinib, nilotinib, sunitinib, tamoxifen, tacrolimus, vandetanib, vinblastine	Potent inhibitors of CYP3A4and/or P-gp. Avoid the combination
Rivaroxaban	Bemurafenib, dasatinib, ibritumomab, ibrutinib, nintedanib, obinutuzumab, pazopanib, ribociclib, vemurafenib, zanobrutinib	Additive effect: ↑risk of bleeding. Monitor platelet counts and haemorrhagic episodes
	Abiraterone, doxorubicin, idelasilib, imatinib, nilotinib, sunitinib, vandetanib	Potent inhibitors of CYP3A4 and/or P-gp. Avoid the combination
	Acalabrutinib, bicalutamide, crizotinib, cyclophosphamide, cyclosporine, dasatinib, docetaxel, enzalutiamide, etoposide, idarubicin, ifosfamide, lapatinib, paclitaxel, sirolimus, tacrolimus, tamoxifen, temsirolimus, vincaalkaloids	Mild inhibitors of CYP3A4 and/or P-gp, ↑risk of bleeding. Caution is needed in case of polypharmacy or in the presence of ≥2 bleeding risk factors
	Apalutamide, lorlatinib	↓rivaroxaban exposure. Avoid the coadministration

Lyon AR et al. *Eur Heart J*. 2022;ehac244 (supplementary data).

apixaban	apalutamide	Explanation:	Action:
systemic	systemic	Apalutamide is predicted to decrease the exposure to apixaban, and therefore also decreases its anticoagulant effects.	Consider a non-interacting drug. If this is not possible, consider switching to an alternative anticoagulant for which monitoring is available to ensure adequate anticoagulation is maintained.

Severity: Moderate **Action**: Adjust **Evidence**: Theoretical

For full information, see Stockley's Drug Interactions

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- SmPC: no relevant information on cancer therapies
- Rule of thumb: AUCx2 or AUC/2 = actionable
- Other data? Reassuring
- **CPOE/online database**
  - Many PK interactions will **not** be **actionable**
  - Increased **awareness** is frequently recommended

- NOAC in CAT: apixaban, rivaroxaban, edoxaban
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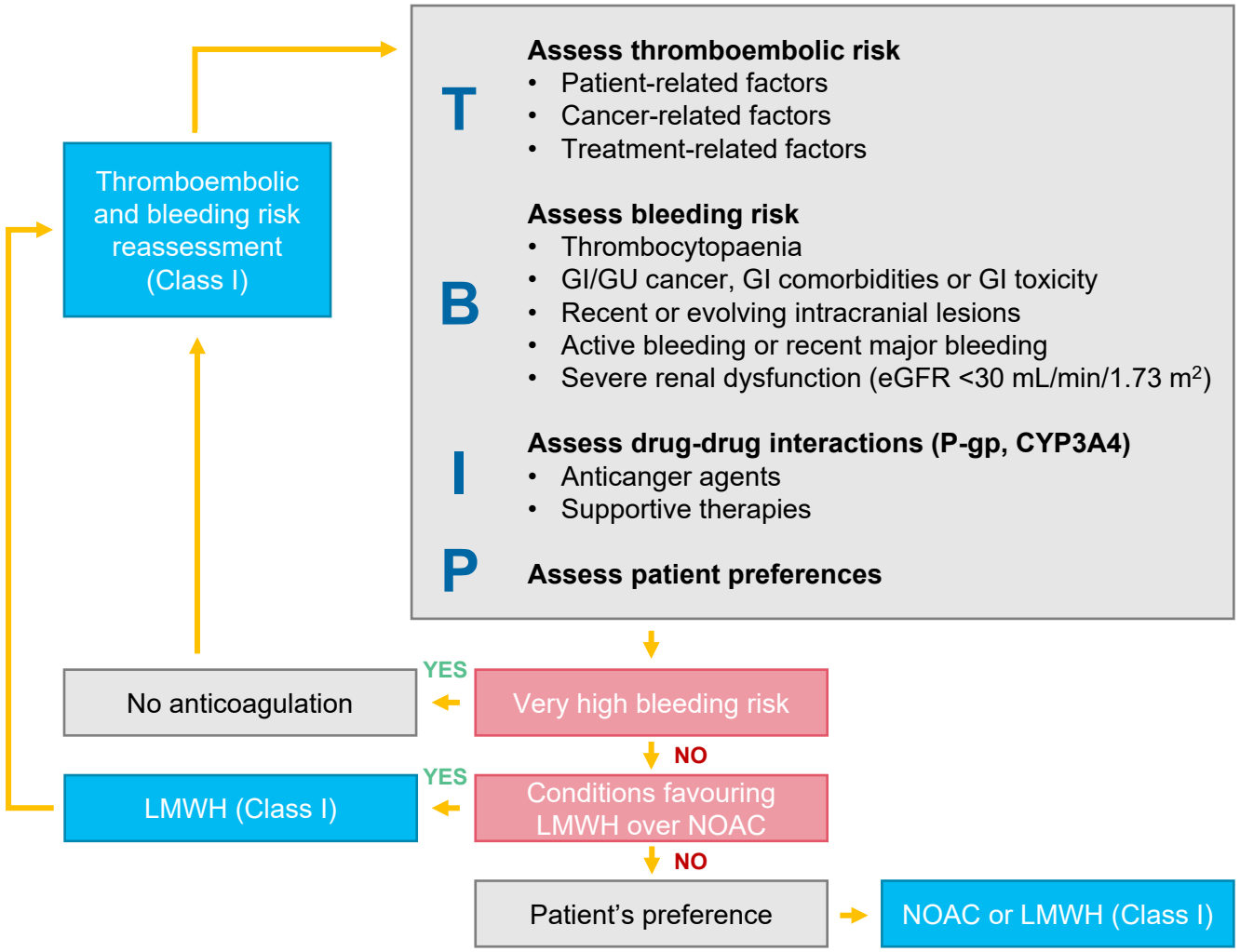
- Other data? Reassuring
- CPOE/online database
- **Plasma monitoring?**

Potential limitations and solutions in measurement of plasma levels

Limitations		Potential solutions
Patient selection	Most patients do not have an indication for plasma monitoring	Limit the assessment to patients with a high pretest risk of falling outside the observed on-therapy ranges and/or to exclude residual anticoagulant activity in (semi)urgent situations
Sampling	NOACs have a short $t_{1/2}$ compared to VKA; timing of sampling is hence more important. It is difficult to estimate the C_{max} (given the substantial variability inT_{max}). Beware of clinical decisions based on incorrectly timed sampling	Trough levels are theoretically more 'stable' in chronic NOAC use. If information needed about absorption (e.g., short bowel) is important, peak levels may be considered
Analysis	Availability of laboratory tests	Technical analytical aspects are not really a limitation anymore. Most laboratories will be able to estimate plasma concentration using available tests. Easy to measure, good reference values, functional assay-based tests correlate extremely well with direct concentration measurements (LC-MS/MS)
Clinical consequences	The clinical effect of adapting a dose based on plasma levels has not been studied.There is no certainty that administering an altered dose will result in improved efficacy and/or safety	The greatest caution should be made in adapting clinical doses based on PK measurements
Retesting frequency	Several studies have shown considerable between person and within-person variability between serial measurements, with values changing from within range to out-of-range values between measurements in otherwise stable patients	

Van der Linden L et al. *Eur Heart J Suppl*. 2022;24(Suppl A):A32-A41.



DDI for NOAC:

1. Are all therapies still **used** & **indicated**?
2. If both therapies are needed: assess the **impact** of the DDI
    1. Use an **online database or <u>CPOE</u>** (*if* fed by an up-to-date database)
3. Remember:
    1. Use the correct tested dose as much as possible (age, weight, renal function)
    2. Most DDIs concern **PD** or **PK (inhibitors)**
    3. AUC change
        1. **<2-fold**
            1. Most likely not relevant, particularly in case of inhibitors
        2. **≥ 2- fold = actionable**
            1. Choose alternative
4. Consult with **expert** (and/or measure exposure)

Lyon AR et al. *Eur Heart J*. 2022;ehac244.

Open poll question

How would you approach the combined use of **apixaban** and **enzalutamide** in a cancer patient with a first VTE?

Enzalutamide is a potent CYP inducer (multiple CYP iso-enzymes) and mild PGP inhibitor; apixaban is both a CYP and a PGP substrate

1. Cautiously combine
2. Combine & measure (chromogenic FXa assay)
3. Choose another NOAC
4. Switch to LMWH

Please refer to Product SmPC of apixaban and enzalutamide for further information.