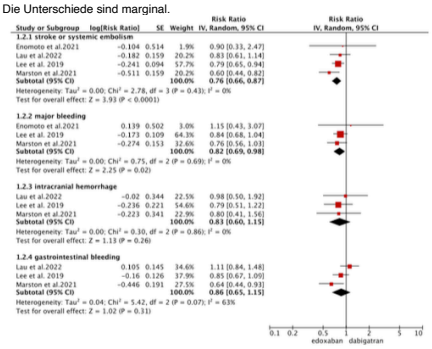
Androgen Receptor Pathway Inhibitors and Oral Antikoagulants: Drug-Drug Interactions
Stand: 10. und 11.2.2025

Fragen an Dr. K. Selleng	Antwort von Dr. K. Selleng
Wir hätten gern Ihre Empfehlung zur Anpassung der Dosis von Dabigatran bei nicht-valvulärem Vorhofflimmern, wenn wir den P-gp-Inhibitor Enzalutamid zur Therapie hinzunehmen. CHA2DS2 = 5, HASBLED = 3, revised by Grok: 2 (1 stroke, 1 elderly) Kreatinin-Clearance (CrCl) nach **Cockcroft-Gault** (Cockcroft-Gault - Alternative) Kreatinin-Clearance (CrCl in ml/min) = (140 – Alter) x Körpergewicht (kg) / 72 x Kreatinin im Serum (mg/dL) (für Männer) Grok: If you're using the Cockcroft-Gault formula for clinical practice or drug dosing, use the serum creatinine value as reported by your lab (likely IDMS-standardized) without conversion. Datum / Alter (a) | Serum Kreatinin | Körpergewicht (kg) | CrCl (ml/min) 16.04.2024 / 83 | 83 umol/L (*) (= 0.94 mg/dL#) | 68 | 57.3 (57.9) (**) 06.08.2024 / 83 | 90 umol/L (*) (= 1.02 mg/dL) | 68 | 52.9 (52.8) (**) 14.01.2025 / **83** | 0.86 mg/dL | **68** | 62.6 14.01.2025 / **84** | 0.86 mg/dL | 68 | 61.5 14.01.2025 / 83 | 0.86 mg/dL | **67** | 61.7 20.02.2025 / 83 | 79 umol/L (*) (= 0.89 mg/dL) | 68 | 60.2 (60.5) (**) 20.02.2025 / 84 | 79 umol/L (*) (= 0.89 mg/dL) | 68 | 59.2 (59.4) (**) 11.03.2025 / 84 | 88 umol/L | 68 | 53.1 05.05.2025 / 84 | 86 umol/L (= 0.97 mg/dL) | 64 | 51.2 12.05.2025 / 84 | 84 umol/L (= 0.95 mg/dL) | 64 | 52.4 25.06.2025 / 84 | 77 umol/L | 64 | 57.1 17.07.2025 / 84 | 78 umol/L | 65 | 57.3 (*) umol = mikromol (**) Wert in Klammern aus Kreatinin-Wert in Klammern berechnet. #) mit 1 mmol Kreatinin / L = 11.31 mg Kreatinin / dL = 113.1 mg Kreatinin / L oder 1 mol Kreatinin = 113.12 g (online Rechner benutzt 113.36 g) Kreatinin (mg/dL) = Kreatinin (umol/L) / 88.42 (umol/L/mg/dL)	Ich habe einen guten Übersichtsartikel zu Ihrer angefragten Problematik gefunden. *Joseph J. Shatzel, Molly M. Daughety, Sven R. Olson, Tomasz M. Beer, and Thomas G. DeLoughery* Management of Anticoagulation in Patients With Prostate Cancer Receiving Enzalutamide *Journal of Oncology Practice Volume 13 / Issue 11 / November 2017, 720 - 728* Dabigatran ist geeignet. Bei gleichzeitiger Einnahme mit Enzalutamide kann es bei niereninsuffizienten Patienten zu einer Wirkspiegelsteigerung/Blutungsneigung kommen: - Ab einer Kreatinin-Clearance <50ml/min wird die Dosisreduktion empfohlen. - Ab Kreatinin-Clearance <30 ml/min sollte Dabigatran abgesetzt werden. Dann können nur Vitamin K Antagonisten zur oralen Antikoagulation verwendet werden. Bewegt sich die Kreatinin-Clearance zwischen 50-95ml/min, wäre auch Edoxaban eine Option, ohne dass die Dosierung reduziert werden muss.
Geben Sie bei der Auswahl zwischen Dabigatran und Edoxaban einem den Vorzug? Wir haben Dabigatran ausgewählt, weil es zweimal pro Tag eingenommen wird und sein Plasmaspiegel daher zeitlich weniger variiert.	Ihre Überlegungen zur 2 x täglichen vs. 1 x tgl. Einnahme teile ich. Allerdings sind die klinischen Studiendaten für Edoxaban, was das Schlaganfall-Risiko beim Vorhofflimmern angeht, auch mit einer einmal täglichen Einnahme sehr gut. Ich fand eine Metaanalyse aus 17 Studien (mehr als 60.000 Patienten) *Zhang B, Cheng W, Kaisaier W, Gu Z, Zhu W, Jiang Q.* Effect of edoxaban compared with other oral anticoagulants for stroke prevention in patients with atrial fibrillation: A meta-analysis. *Heliyon. 2023 Nov 3;9(11):e21740.* *doi: 10.1016/j.heliyon.2023.e21740.* *PMID: 38027839; PMCID: PMC10665752* die herausfand, dass Edoxaban im Vergleich zu Dabigatran - ein niedrigeres Schlaganfall- UND niedrigeres Risiko für schwere Blutungen, - allerdings keinen ganz überzeugenden Vorteil für Hirnblutungen oder Magen-Darm-Blutungen hatte. Die Unterschiede sind marginal.  Fig. 2. Effectiveness and safety data of edoxaban compared with dabigatran in atrial fibrillation patients. Auch mit Dabigatran sind Sie auf der sicheren Seite.

Stand unserer PubMed/PMC-Recherche vor dem 10.2.2025

Cancers 2024, 16(19), 3336; https://doi.org/10.3390/cancers16193336

Drug Interactions between Androgen Receptor Axis-Targeted Therapies and Antithrombotic Therapies in Prostate Cancer: Delphi Consensus

Kori Leblanc (Department of Pharmacy, University Health Network, Toronto, ON M5G 2C4, Canada) et al.

ATTs: \ ARATs:	Abiraterone	Apalutamide	Darolutamide	Enzalutamide
Apixaban	Moderate	Major/Catastrophic	Moderate	Major/Catastrophic
	Avoid this pair	Avoid this pair	Avoid this pair	Avoid this pair
Dabigatran	Negligible/Minor	Major/Catastrophic	Negligible/Minor	Moderate
	Modify dose and/or monitoring	Avoid this pair	No action needed	Modify dose and/or monitoring
Edoxaban	Moderate	Moderate	Negligible/Minor	Moderate
	Modify dose and/or monitoring	Avoid this pair	No action needed	Modify dose and/or monitoring
Rivaroxaban	Moderate	Major/Catastrophic	Moderate	Major/Catastrophic
	Avoid this pair	Avoid this pair	Avoid this pair	Avoid this pair
Warfarin	Moderate	Major/Catastrophic	Negligible/Minor	Major/Catastrophic
	Modify dose and/or monitoring	Modify dose and/or monitoring	Modify dose and/or monitoring	Modify dose and/or monitoring
Clopidogrel	No consensus (70% Moderate, 30% Major)	No consensus (70% Major, 30% Moderate)	Negligible/Minor	Moderate
	-	-	No action needed	Avoid this pair

This figure displays the results of the e-Delphi consensus process. The top row of each drug pair box (black font) indicates the consensus obtained with regard to the consequences of using the drug pair, while the bottom row (white font) indicates the consensus obtained for the suggested action to manage the drug pair; the results of the final round of voting are shown if no consensus was obtained. "Avoid this pair" (red boxes) indicates that one member of the drug pair should be changed, if possible. "Modify dose and/or monitoring" (orange boxes) indicates that the dose should be adjusted to another regulatory-approved dose and/or changes made to monitoring, as appropriate. "No action needed" (green boxes) indicates the drug pair can be used as planned with no additional actions taken. It should be noted that obtaining a specialist consult is an option in all cases. ARAT, androgen receptor axis-targeted therapy; ATT, antithrombotic therapy.

ESMO Open Volume 9, Issue 11103736 November 2024

Androgen receptor pathway inhibitors and drug–drug interactions in prostate cancer

H. Bolek et al.

"Potential drug interactions between ARPIs and medications commonly prescribed for older individuals were thoroughly evaluated through Lexicomp® Drug Interactions provided by UpToDate® (Wolters Kluwer Health, Alphen aan den Rijn, The Netherlands)."

8 https://doi.org/10.1016/j.esmoop.2024.103736 Volume 9 ■ Issue 11 ■ 2024

Table 2. Continued

	Abiraterone acetate		Enzalutamide		Apalutamide		Darolutamide	
	Risk Level	Mechanism-Result	Risk Level	Mechanism-Result	Risk Level	Mechanism-Result	Risk Level	Mechanism-Result
Oral Antidiabetics								
Metformin	A	—	A	—	A	—	A	—
Gliclazide	A	—	C	CYP2C9/CYP3A4 Gliclazide ↓	A	—	A	—
Glyburide	A	—	C	CYP2C9/CYP3A4 Glyburide ↓	A	—	C	OATP1B1-1B3 Glyburide↑
Pioglitazone	C	? Hypoglycemia	A	—	A	—	A	—
Sitagliptin	A	—	A	—	A	—	A	—
Linagliptin	A	—	D	CYP3A4 Linagliptin ↓	D	CYP3A4/P-gp Linagliptin ↓	A	—
Saxagliptin	A	—	C	CYP3A4 Saxagliptin ↓	C	CYP3A4/P-gp Saxagliptin ↓	A	—
Empagliflozin	A	—	A	—	A	—	A	—
Dapagliflozin	A	—	A	—	A	—	A	—
Canagliflozin	A	—	A	—	A	—	A	—
Drugs for coronary artery disease and heart failure								
Furosemide	A	—	A	—	A	—	A	—
Spironolactone	D	AR activity Abiraterone↓	A	—	A	—	A	—
Nitroglycerin	A	—	A	—	A	—	A	—
Digoxin	A	—	D	P-gp Digoxin↑	C	P-gp Digoxin↓	A	—
Acetylsalicylic Acid	A	—	A	—	A	—	A	—
Clopidogrel	A	—	C	CYP2C8 Enzalutamide↑	D	CYP2C19/CYP3A4 Clopidogrel ↓	A	—
Prasugrel	A	—	B	CYP3A4 Prasugrel ↑	B	CYP3A4 Prasugrel ↑	A	—
Ticagrelor	A	—	X	CYP3A4 Ticagrelor ↓	X	CYP3A4 Ticagrelor ↓	A	—
Oral anticoagulants								
Rivaroxaban	A	—	D	CYP3A4 Rivaroxaban ↓	X	CYP3A4/P-gp Rivaroxaban ↓	A	—
Apixaban	A	—	D	CYP3A4 Apixaban ↓	X	CYP3A4/P-gp Apixaban ↓	A	—
Edoxaban	A	—	C	P-gp Edoxaban↑	D	P-gp Edoxaban ↓	A	—
Dabigatran	A	—	C	P-gp Dabigatran↑	X	P-gp Dabigatran ↓	A	—
Warfarin	A	—	D	CYP2C9/CYP3A4 Warfarin ↓	C	CYP2C9 Warfarin ↓	A	—

größeres Bild

by the way:

Table 2. Actual and predicted drug–drug interactions between androgen receptor pathway inhibitors and commonly used drugs[a]

	Abiraterone acetate		Enzalutamide		Apalutamide		Darolutamide	
	Risk Level	Mechanism-Result	Risk Level	Mechanism-Result	Risk Level	Mechanism-Result	Risk Level	Mechanism-Result
Lipid-lowering drugs								
Rosuvastatin	C	OATP1B1 Myopathic effect↑	A	—	C	BCRP/OATP1B1 Rosuvastatin↓	D	BCRP/ OATP1B1-1B3 Rosuvastatin↑
Atorvastatin	C	OATP1B1 Myopathic effect↑	C	CYP3A4 Atorvastatin↓	C	CYP3A4 Atorvastatin↓	C	OATP1B1-1B3 Atorvastatin↑

A = no known interaction, B = no action needed, C = monitor therapy, D = consider therapy modification, X (red) = avoid pair

Grok:

Switching from atorvastatin to rosuvastatin, while maintaining an equivalent dose (e.g., 40 mg atorvastatin to 20 mg rosuvastatin for similar LDL cholesterol reduction), could potentially improve or maintain statin efficacy in your case due to differences in how enzalutamide interacts with each drug.

- Enzalutamide is a strong inducer of CYP3A4, which can decrease atorvastatin plasma levels and reduce its effectiveness in lowering cholesterol. (PMC)
- In contrast, clinical studies in patients with metastatic castration-resistant prostate cancer (similar to your regimen with enzalutamide and leuprorelin) have shown no significant pharmacokinetic interaction between enzalutamide and rosuvastatin, meaning rosuvastatin levels and effects are unlikely to be reduced (PMC, PubMed). This could lead to more consistent cholesterol management without needing dose adjustments for the statin.

Unsere Erfahrungen mit dem Paar Rivaroxaban / Apalutamid

2021 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Ganzes Papier ist hilfreich. Die folgenden Bilder sind Erinnerung an Wichtigstes

10 of 46 matches Contains ACS

NOAC indications and dosing for stroke prevention in atrial fibrillation (SPAF)

Stroke prevention in Atrial Fibrillation (SPAF)		
	Standard dose	**Comments / dose reduction**
Apixaban	5 mg BID	2.5 mg BID if 2 out of 3: • Weight ≤60 kg • Age ≥80 yrs • serum Creatinine ≥133 µmol/l (1.5 mg/dl) or single criterion: if CrCl 15-29 ml/min
Dabigatran	150 mg BID /or 110 mg BID	No pre-specified dose-reduction criteria in phase III trial *SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding*
Edoxaban	60 mg QD	30 mg QD if: • Weight ≤60 kg • CrCl 15-49 ml/min • concomitant therapy with strong P-Gp inhibitor
Rivaroxaban	20 mg QD	15 mg QD if CrCl ≤15-49 ml/min

NOAC dosing in AF patients post ACS / PCI*		
	Standard dose	**Comments / dose reduction**
Apixaban	5 mg BID	Dose reduction as for SPAF
Dabigatran	150 mg BID or 110 mg BID	110mg as for SPAF
Edoxaban	60 mg QD	Dose reduction as for SPAF
Rivaroxaban	15 mg QD	Dose reduction to 10 mg QD if CrCl 30-49 ml/min

*in addition to single / dual antiplatelet therapy, where applicable. See page 49 for details.

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Enzalutamide is not considered a strong P-gp inhibitor (Boujonnier, 2024, weiter unten)

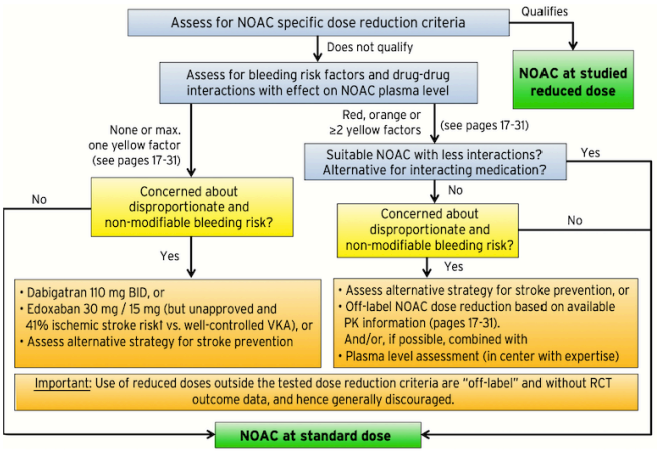
NOAC = new oral anticoagulant, ACS = acute coronary syndrome, PCI = percutaneous coronary intervention, SmPC = summary of product characteristics

phase III trial

Important pointers:

- Identify best NOAC and correct dose to individualize treatment.
- Dose reduction primarily recommended according to the published dose reduction criteria.
- Whenever possible, the tested standard dose of NOACs should be used.
- Consider patient age, weight, renal function, co-medications and other comorbidities
- Consider interactions
- **The use of plasma level monitoring for NOAC dose-adjustment is discouraged for the vast majority of patients due to the lack of outcome data**.
  - Only to be used in very rare cases (see page 5) and in centres with extensive experience.
- An elevated HAS-BLED score in itself should not automatically result in decision not to anticoagulate.
- Minimize modifiable risk factors for bleeding

Choosing a NOAC based on drug-drug interactions and / or risk of bleeding



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Other factors with potential impact on NOAC plasma levels / anticoagulant effect

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Age ≥80 years	Potential for increased plasma levels	110mg BID (per SmPC)			
Age ≥75 years	Potential for increased plasma levels				
Weight ≤60 kg (see page 56)	Potential for increased plasma levels			Dose reduction according to label	
Weight ≥120 kg (see page 56)	Potential for decreased plasma levels				
Chronic kidney disease	Potential for increased plasma levels				
Other factors with potentially increased bleeding risk		E.g.,: • Concomitant antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants • Severe Frailty / falls risk • H/o bleeding or predisposition (anemia, thrombocytopenia)			

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Bedeutung der Farben

Interactions of commonly used anticancer drugs (6)

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Hormonal agents					
Abiraterone	Moderate CYP3A4 inhibition, strong P-gp inhibition; CYP3A4/P-gp competition				
Enzalutamide	Strong CYP3A4 induction, strong P-gp inhibition; CYP3A4/P-gp competition				
Bicalutamide	Moderate CYP3A4 inhibition				
Tamoxifen	Strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4 competition				
Anastrozole	Mild CYP3A4 inhibition				
Flutamide	CYP3A4 competition; no relevant interaction anticipated				
Letrozole, Fulvestrant	CYP3A4 competition; no relevant interaction anticipated				
Raloxifene, Leuprolide, Mitotane	No relevant interaction anticipated				

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Farben und Schraffur

Vergleich mit Fig.1 von
Management of Anticoagulation in Patients With Prostate Cancer Receiving Enzalutamide, Shatzel et al, 2017

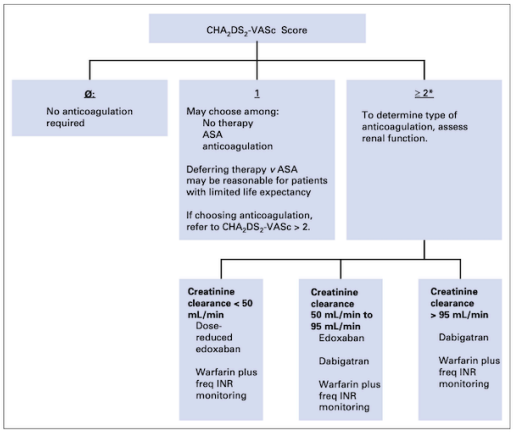
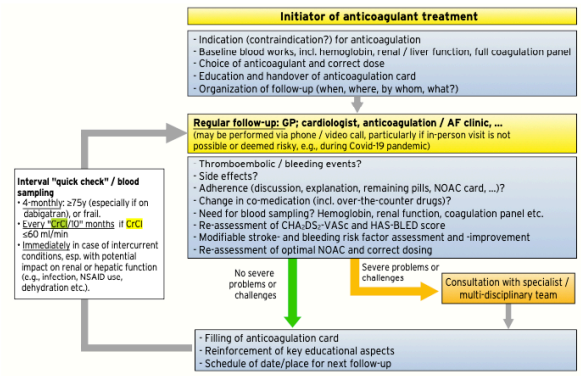


Fig 1. Anticoagulation for atrial fibrillation in a patient receiving enzalutamide. ASA, acetylsalicylic acid; CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes, prior stroke or transient ischemic attack (2 points), vascular disease, age 65 to 74 years, and sex category (female); freq, frequent; INR, international normalized ratio. (*)Patients with a high CHADS-VASc score but very limited life expectancy may not benefit from anticoagulation.

creatinine clearance nach Cockcroft-Gault

Structured Follow-up for NOAC treated patients



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GP = general practitioner (Hausarzt), NSAID = non steroidal anti-inflammatory drug, NOAC = new oral anti-coagulant

Checklist during follow-up contacts of AF patients on anticoagulation

	Interval	Comments
1. Adherence	Each visit	• Instruct patient to bring NOAC card and complete list of medication: make note and assess adherence. • Re-educate on importance of strict intake schedule. • Inform about adherence aids (special boxes; smartphone applications; ...). Consider specific adherence-measuring interventions (see page 6) • Inform about minor bleeding (gum, epistaxis, small ecchymosis) and instruct not to skip any dose • Assess cognitive function
2.Thromboembolism	Each visit	• Systemic circulation (TIA, stroke, peripheral). • Deep vein thrombosis, pulmonary embolism
3. Bleeding	Each visit	• For every bleeding: Look for reason. Cancer? Ulcer? Other causes, lesions etc.? Treatment or prevention possible? • "Nuisance" bleeding: Reason? Treatment / prevention (see above)? • Assess impact on quality of life.
4. Other side effects	Each visit	• Carefully assess relation with NOAC: decide for continuation (and motivate) or change NOAC.
5. Co-medications	Each visit	• Prescription drugs; over-the-counter drugs. • Careful interval history (also temporary use, e.g., NSAIDs)
6. Blood sampling (incl. Hb, renal / liver function)	Yearly	In all patients except those below
	4-monthly	≥75 yrs (especially if on dabigatran), or frail.
	Variable	If renal function CrCl ≤60 ml/min: CrCl / 10 = minimum recheck interval [in months]
	If needed	In case of intercurrent conditions, especially with potential impact on renal or hepatic function (e.g., infection, NSAID use, dehydration etc.)

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Checklist during follow-up contacts of AF patients on anticoagulation (continued)

	Interval	Comments
7. Re-assess stroke risk	Each visit	CHA_2DS_2-VASc score, as recommended by current guidelines
8. Assessing and minimizing modifiable risk factors for bleeding	Each visit	As recommended by current guidelines
		Particularly: • Uncontrolled hypertension (systolic >160 mmHg) • Medication predisposing for bleeding (e.g., aspirin, NSAIDs) • Labile INR (if on VKA) • Excessive alcohol intake • Falls
9. Assessing for optimal NOAC and correct dosing	Each visit	Especially based on the above, re-assess whether - The chosen NOAC is the best for the patient - The chosen dose is correct

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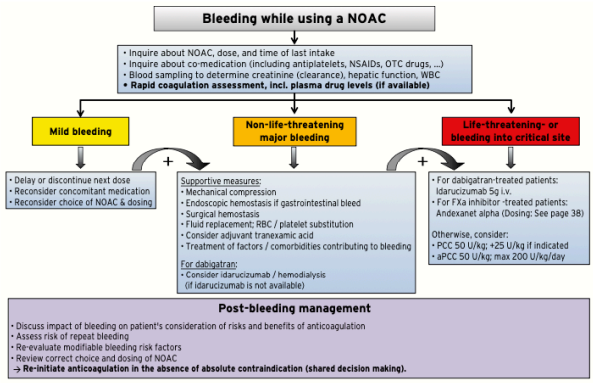
6. Management of bleeding under NOAC therapy



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PRADAXA-Boehringer-Ingelheim
Dabigatran-Dosis-Reduktion

2.2 Recommended PRADAXA Capsules Dosage for Adults

Indication	Dosage	
Reduction in Risk of Stroke and Systemic Embolism in Non-valvular AF	CrCl > 30 mL/min:	150 mg twice daily
	CrCl 15 to 30 mL/min:	75 mg twice daily
	CrCl < 15 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl 30 to 50 mL/min with concomitant use of P-gp inhibitors:	Reduce dosage to 75 mg twice daily if given with P-gp inhibitors dronedarone or systemic ketoconazole.
	CrCl < 30 mL/min with concomitant use of P-gp inhibitors:	Avoid coadministration

AF = atrial fibrillation

SAVAYSA (edoxaban) tablets
Edoxaban-Dosis-Reduction

DOSAGE AND ADMINISTRATION

- Treatment of NVAF:
  Assess CrCL before initiating therapy (2.1)
  The recommended dose is 60 mg once daily in patients with CrCL >50 to ≤ 95 mL/min. Do not use SAVAYSA in patients with CrCL > 95 mL/min (2.1)
  Reduce dose to 30 mg once daily in patients with creatinine clearance 15 to 50 mL/min (2.1)

- Treatment of DVT and PE:
  The recommended dose is 60 mg once daily (2.2)
  The recommended dose is 30 mg once daily for patients with CrCL 15 to 50 mL/min or body weight less than or equal to 60 kg or who use certain P-gp inhibitors (2.2)

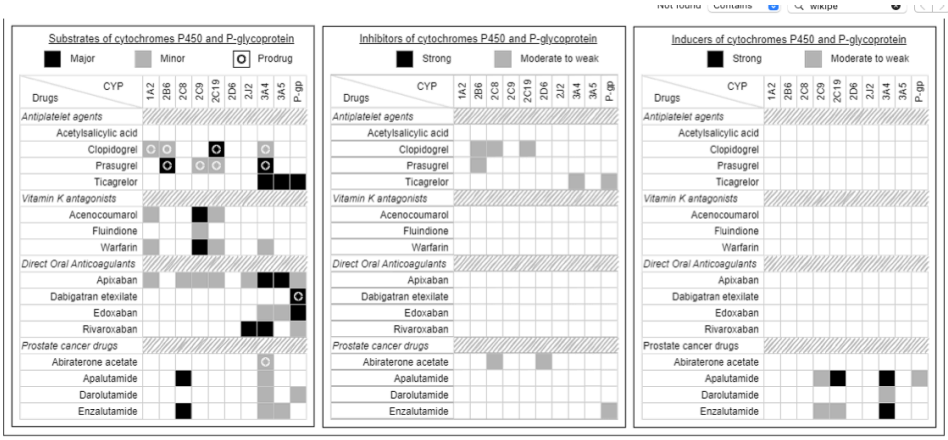
NVAF = non-valvular atrial fibrillation, DVT = deep vein thrombosis, PE = pulmonary embolism

7.3 P-gp Inhibitors
Treatment of NVAF
Based on clinical experience from the ENGAGE AF-TIMI 48 study, dose reduction in patients concomitantly receiving P-gp inhibitors resulted in edoxaban blood levels that were lower than in patients who were given the full dose. Consequently, **no dose reduction is recommended for concomitant P-gp inhibitor use** [see Dosage and Administration (2.1), Clinical Pharmacology (12.3) and Clinical Studies (14.1)].

Cardiovasc. Drugs Ther. 2024 Aug;38(4):757-767. doi: 10.1007/s10557-023-07453-0. Epub 2023 May 1.

Pharmacokinetic Interactions Between Abiraterone, Apalutamide, Darolutamide or Enzalutamide and Antithrombotic Drugs: Prediction of Clinical Events and Review of Pharmacological Information

François Boujonnier , Florian Lemaitre, Lucie-Marie Scailteux



Grok on how to use this schematic for the pairs enzalutamide-dabigatran and enzalutamide-edoxaban (link)

This Figure 1 of Boujonnier et al, 2023 provides a detailed schematic of the pharmacokinetic interactions between enzalutamide and antithrombotic drugs, including edoxaban and dabigatran, focusing on
- their **metabolism** by cytochrome P450 (CYP) enzymes and
- P-glycoprotein (P-gp) **transport**.

Below, I summarize the relevant information from Figure 1 and the article regarding
- the metabolism of edoxaban and dabigatran by CYP450 enzymes and P-gp, and
- whether their elimination pathways are independent of these mechanisms,

integrating insights from Shatzel et al. (2017), Zhang et al. (2023), and the provided web results where applicable.

Metabolism by CYP450 Enzymes and P-gp

Figure 1 in Boujonnier et al. (2023) illustrates the metabolic and transport pathways of enzalutamide and antithrombotic drugs, highlighting their interactions with CYP450 enzymes and P-gp. The key points for edoxaban and dabigatran are:

1. **Edoxaban**:
   - **CYP450 Metabolism**: Edoxaban is a minor substrate of CYP3A4, with approximately 15% of its metabolism mediated by this enzyme (Boujonnier et al., 2023; Shatzel et al., 2017). The majority of its metabolism occurs via
     - hydrolysis (primarily by carboxylesterase 1) and
     - conjugation (e.g., glucuronidation), which are non-CYP450 pathways (Boujonnier et al., 2023).
   - **P-gp Transport**: Edoxaban is a substrate of P-gp, an **efflux transporter** in the gut, liver, and kidneys. P-gp reduces edoxaban's bioavailability by pumping it out of enterocytes and facilitates its renal excretion (approximately 50% of edoxaban is cleared renally).
     - Enzalutamide's
       - potential P-gp inhibition may increase edoxaban's plasma concentrations by reducing its efflux, while its
       - CYP3A4 induction may slightly decrease plasma levels by enhancing the minor CYP3A4-mediated metabolism (Boujonnier et al., 2023).
   - **Interaction with Enzalutamide**: Figure 1 shows that enzalutamide, a strong CYP3A4 inducer and potential P-gp inhibitor, creates a complex interaction.
     - The CYP3A4 induction may reduce edoxaban's plasma levels, but this effect is minimal due to the small contribution of CYP3A4. Conversely,
     - P-gp inhibition may increase edoxaban's bioavailability and reduce [by reduing] its renal clearance, potentially offsetting the CYP3A4 effect and leading to a net neutral or slightly increased plasma concentration.
2. **Dabigatran**:
   - **CYP450 Metabolism**: Dabigatran is not metabolized by CYP450 enzymes. Its primary metabolic pathway involves glucuronidation, forming active acyl-glucuronide metabolites that retain anticoagulant activity (Boujonnier et al., 2023; Shatzel et al., 2017). This lack of CYP450 involvement means enzalutamide's CYP3A4 induction does not affect dabigatran's metabolism.
   - **P-gp Transport**: Dabigatran etexilate, the prodrug, is a P-gp substrate.
     - P-gp [mediated] efflux in the gut limits its absorption, and
     - P-gp in the kidneys contributes to its high renal clearance (80%).
     - Enzalutamide's potential P-gp inhibition increases dabigatran's bioavailability and reduces its renal excretion, leading to higher plasma concentrations and an increased bleeding risk (Boujonnier et al., 2023).
   - **Interaction with Enzalutamide**: Figure 1 indicates that enzalutamide's P-gp inhibition significantly affects dabigatran by increasing its systemic exposure, without any counteracting CYP3A4 effect, as dabigatran bypasses CYP450 metabolism entirely.

Are Elimination Pathways Independent of Listed Metabolisms?

The article and Figure 1 clarify the elimination pathways for edoxaban and dabigatran, addressing whether these pathways are independent of CYP450 and P-gp mechanisms:

1. **Edoxaban**:
   - **Elimination Pathways**: Edoxaban is eliminated through multiple pathways:

        - **Renal Clearance**: Approximately 50% of edoxaban is excreted unchanged in the urine, mediated partly by P-gp in the kidneys (Boujonnier et al., 2023).
        - **Non-Renal Clearance**: The remaining 50% is cleared via metabolism (hydrolysis by carboxylesterase 1, conjugation via glucuronidation, and minor CYP3A4 metabolism) and biliary excretion. Hydrolysis and glucuronidation are independent of CYP450 and P-gp, occurring primarily in hepatocytes via carboxylesterase 1 and UDP-glucuronosyltransferases (UGTs), respectively.
    - **Independence**: Edoxaban's elimination is partially independent of CYP450 and P-gp due to significant contributions from hydrolysis and glucuronidation. However, renal clearance (50%) is influenced by P-gp, and a minor portion (~15%) of metabolism involves CYP3A4, making its elimination not fully independent of these pathways. Enzalutamide's P-gp inhibition may reduce renal clearance, while its CYP3A4 induction may enhance the minor CYP3A4-mediated clearance, but non-CYP450/P-gp pathways (hydrolysis, glucuronidation) provide a buffer against significant pharmacokinetic changes.
2. **Dabigatran**:
    - **Elimination Pathways**: Dabigatran is predominantly eliminated via renal excretion (80% unchanged in urine), with the remainder undergoing glucuronidation to form active metabolites that are also renally excreted (Boujonnier et al., 2023; Shatzel et al., 2017). P-gp plays a significant role in renal excretion by facilitating dabigatran's transport into the urine.
    - **Independence**: Dabigatran's elimination is independent of CYP450 metabolism, as it is not a CYP450 substrate. However, it is heavily dependent on P-gp for both intestinal absorption (of the prodrug) and renal clearance. Enzalutamide's P-gp inhibition significantly reduces renal excretion, increasing plasma concentrations and bleeding risk, indicating that dabigatran's elimination is not independent of P-gp-mediated pathways.

Impact on Edoxaban's Marginal Advantage

The information from Figure 1 and Boujonnier et al. (2023) reinforces and refines the marginal advantage of edoxaban over dabigatran in patients with CrCl 52 mL/min receiving enzalutamide, as discussed previously:

- **Edoxaban's Advantage**: Edoxaban's lower renal clearance (50% vs. 80%) and partial reliance on non-CYP450/non-P-gp pathways (hydrolysis, glucuronidation) reduce the impact of enzalutamide's P-gp inhibition compared to dabigatran. The minor CYP3A4 metabolism (~15%) may be enhanced by enzalutamide's CYP3A4 induction, slightly reducing plasma levels, but this is counterbalanced by P-gp inhibition, resulting in a net neutral or slightly increased plasma concentration (Boujonnier et al., 2023). This balance minimizes the risk of excessive accumulation and bleeding compared to dabigatran. Zhang et al. (2023) support edoxaban's favorable bleeding profile (HR: 0.80, 95% CI: 0.71–0.91 vs. warfarin), which is likely preserved due to these diverse elimination pathways.
- **Dabigatran's Disadvantage**: Dabigatran's high renal clearance (80%) and dependence on P-gp for absorption and excretion make it more susceptible to enzalutamide's P-gp inhibition, leading to significant increases in plasma concentrations and bleeding risk (Boujonnier et al., 2023). Its lack of CYP450 metabolism means no counteracting effect from enzalutamide's CYP3A4 induction, amplifying the P-gp-mediated interaction.
- **Mechanistic Reinforcement**: Figure 1 highlights that edoxaban's mixed elimination pathways (renal, hydrolysis, glucuronidation, minor CYP3A4) provide a buffer against enzalutamide's dual effects (CYP3A4 induction and P-gp inhibition), whereas dabigatran's reliance on P-gp and renal clearance heightens its vulnerability to P-gp inhibition. This supports edoxaban's marginal advantage, as its pharmacokinetics are less disrupted by enzalutamide, particularly at CrCl 52 mL/min, where renal function is relatively stable.

Conclusion

According to Figure 1 in Boujonnier et al. (2023):

- **Edoxaban**: Metabolized minimally by CYP3A4 (~15%) and significantly by P-gp (gut and renal transport). Elimination is partially independent of CYP450 and P-gp due to hydrolysis (carboxylesterase 1) and glucuronidation (UGTs), with 50% renal clearance influenced by P-gp. Enzalutamide's CYP3A4 induction slightly reduces plasma levels, but P-gp inhibition counteracts this, maintaining efficacy and safety.
- **Dabigatran**: Not metabolized by CYP450, but a P-gp substrate. Elimination is heavily P-gp-dependent (80% renal clearance), with glucuronidation as a minor pathway. Enzalutamide's P-gp inhibition significantly increases plasma levels, elevating bleeding risk.
- **Edoxaban's Advantage**: Edoxaban's diverse elimination pathways (including non-CYP450/non-P-gp routes) and lower renal clearance reduce the impact of enzalutamide's P-gp inhibition compared to dabigatran, preserving its marginal advantage in safety and pharmacokinetic stability at CrCl 52 mL/min. The recommended dose remains 60 mg once daily, with regular CrCl monitoring. Clinicians should consider warfarin or LMWH in high-risk patients, as suggested by Shatzel et al. (2017).

reminder (eliminate when cleaning up):
cytochromes P450 and P-glycoprotein activity influences the efflux of the substrates.
By down-regulating the expression of P450/P-gp, inhibitors of P450 and P-gp reduce the efflux,
by up-regulating the expression of P450 and P-gp inducers increase the efflux.
In the case of Dabigatran etexilate (the Prodrug which is converted to Dabigatran in the gastrointestinal tract and then enters into the plasma):
reducing its efflux means reducing the prodrug's efflux into the gastrointestinal lumen, so more prodrug is available for conversion to Dabigatran, thus increasing the plasma concentration of Dabigatran

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Enzalutamide

... Following oral administration of enzalutamide at 160 mg in patients with metastatic CRPC, the median time to reach maximum plasma enzalutamide concentrations is 1 hour (range 0.5 to 3 hours).
The enzalutamide mean terminal elimination half-fife (T1/2), in patients with metastatic CRPC, following a single oral dose is 5.8 days (range 2.8 to 10.2 days).
With daily dosing regimen, enzalutamide steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose.
Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25).

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