The 44th Annual International Congress of the
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Drug-Drug Interactions of Non-Vitamin K Antagonist Oral Anticoagulants (NOACs): How to Manage?

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Outline

- History and large scale clinical trials of NOACs
- Advantages and clinical challenges of NOACs
- Drug-Drug Interactions of NOACs and their management
- Evidence of clinical significance of Drug-Drug Interactions of NAOCs

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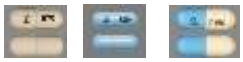
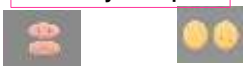
Non-Vitamin K Antagonist Oral Anticoagulants (NOAC)

2010 **Dabigatran** (Direct thrombin inhibitor) **Pradaxa®** — Boehringer Ingelheim



2011 **Rivaroxaban** (Factor Xa inhibitor) **Xarelto®** — Bayer

2012 **Apixaban** (Factor Xa inhibitor) **Eliquis®** — Bristol Myers-Squibb



2015 **Edoxaban** (Factor Xa inhibitor) **Savaysa®, Lixiana®** — Daiichi-Sankyo

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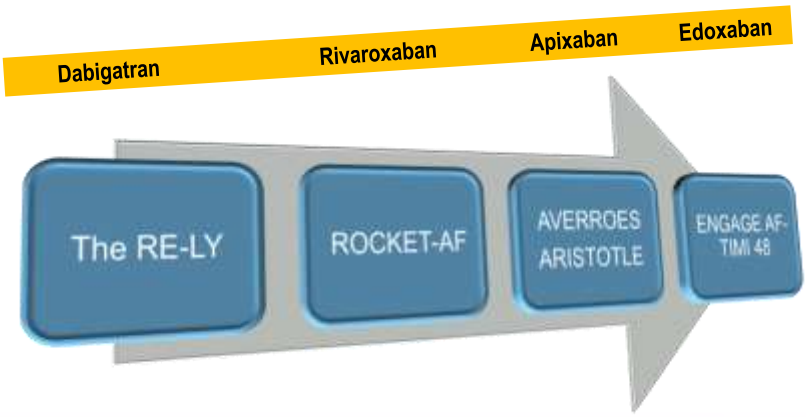
Four Randomised Controlled Trials



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Advantages of NOACs

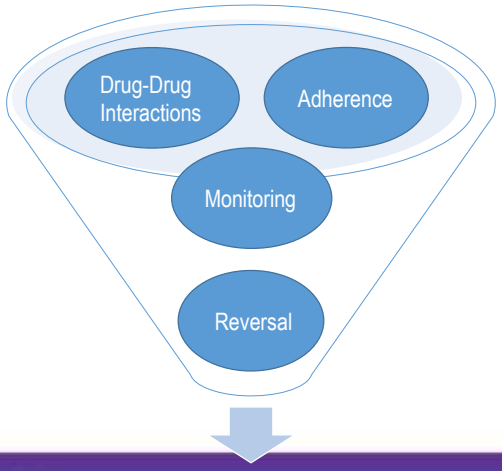
- Lack for monitoring
- Fixed-dose regimens
- Predictable pharmacokinetic profile
- Short Half lives and quicker onset of action
- Fewer food and drug interactions

Kocabas U. et al. IJCAC; 2016. 2(4): 167-173

Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)

Vitamin K antagonists (VKA)

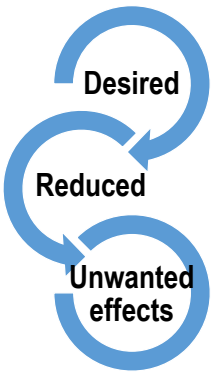
Clinical Challenges of New Oral Anticoagulants



Drug-Interactions

- Drug-Drug Interactions
- Drug-Nutrient Interactions
- Drug-Dietary Supplement Interactions

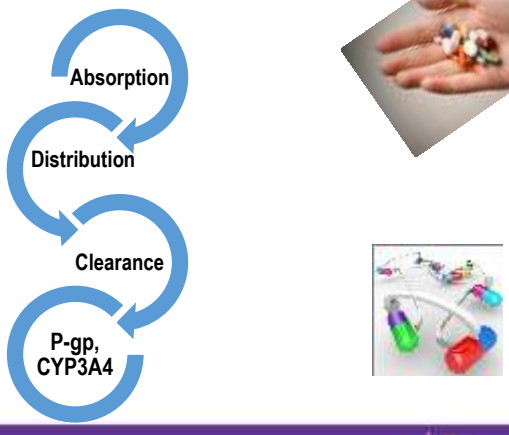
Drug-Drug interactions



Types of Drug-Drug interactions

Pharmacokinetic Interactions	• One **drug** affects the other's absorption, distribution, metabolism, or excretion
Pharmacodynamic Interactions	• Interactions in which drugs influence each other's effects directly

Pharmacokinetic Drug-Drug Interactions of NOACs



Main Pharmacokinetic Interactions of New Oral Anticoagulants

P-gp

All NOACs

One of the drug transporters that determine the uptake and efflux of a range of drugs

In the gut, P-glycoprotein pumps drugs back into the lumen, decreasing their absorption

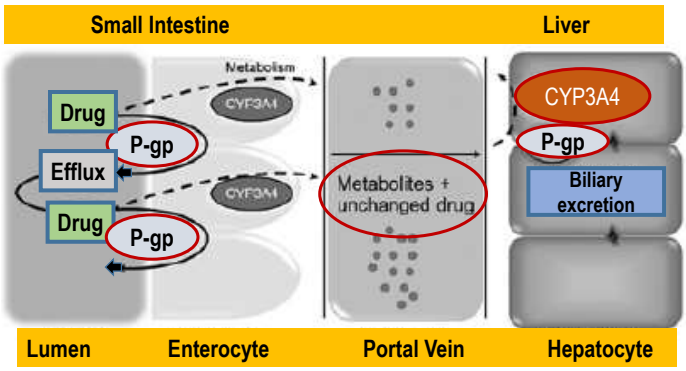
CYP3A4

Many, but not all, of the drugs which are transported by P-glycoprotein are also metabolised by CYP3A4

Inducers and inhibitors can affect serum drug concentrations

All NOACs except Dabigatran

Main Pharmacokinetic Interactions of New Oral Anticoagulants



Ann Pharmacother. 2013;47(11):1478-87

Dabigatran Etexilate

- It is a prodrug which becomes active via hydrolysis following oral absorption
- **Elimination**
- Primarily renally eliminated (80%)
- Half life=12-17 hrs
- **Metabolism**
- It is a substrate of the p-glycoprotein transport system (P-gp)

Drug-Drug Interactions of Dabigatran

Renal

Gastric PH

P-gp

\+ **Pharmacodynamic**

Antiplatelet , NSAIDs and antithrombotic effects can increase bleeding risk

Connolly SJ. et al. N Engl J Med. 2009;361:1139-1151

StangierJ. ClinPharmacokinet 2008; 47:285-95
Pradaxa prescribing information. Boehringer-Ingelheim, 2016

Strong P-glycoprotein Inhibitors			Strong P-glycoprotein Inducers
Alfentanil	Indinavir	Quinidine *	Barbiturates
Amiodarone *	Itraconazole	Ritonavir	Carbamazepine
Bepridil	Ketoconazole **	Saquinavir	Dexamethasone
Carvedilol	Lapatinib	Tacrolimus	Phenytoin
Clarithromycin *	Lovastatin	Tamoxifen	Rifampin *
Conivaptan	Mefloquine	Telaprevir	St John's Wort
Cyclosporine	Mifepristone	Telithromycin	
Diltiazem *	Nelfinavir	Testosterone	
Dronedarone **	Nicardipine	Ticagrelor	
Duloxetine	Posaconazole	Verapamil *	
Fenofibrate	Propafenone		

*= Adjust dose CrCl =30-50 ml/min

*= Avoid use at CrCl =15-30 ml/min

*= Avoid use

U.S. Food and Drug Administration, Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers

Rivaroxaban

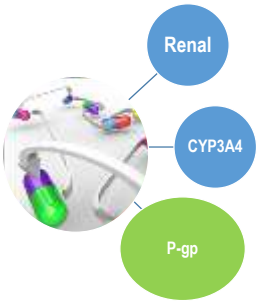
- **Elimination**

- one-third is eliminated via the kidneys unchanged (66%)
- The remaining as inactive metabolites after hepatic transformation
- Half life=5-9 hrs ((9–13 h in the elderly)

- **Metabolism**

- Cytochrome P-450 system (CYP) and includes both the 3A4 and 2J2 families of enzymes
- P-glycoprotein, adenosine triphosphate–binding cassette G2 (ABCG2) efflux transporter protein, which is expressed in the liver and kidneys

Drug-drug interactions of Rivaroxaban



+ Pharmacodynamic

Antiplatelet, NSAIDs and antithrombotic effects can increase bleeding risk

Patel MR. et al. N Engl J Med. 2011;365:883-891
Oldgren J. et al. Eur Heart J. 2013;34:1670-1680

Xarelto prescribing information. Janssen, 2015

CYP3A4 Inhibitors					CYP3A4 Inducers	
amiodarone	cyclosporine	fluvoxamine	nelfinavir	voriconazole	aminoglutethimide	nafcillin
amprenavir	dalfopristin	fosamprenavir	posaconazole	zafirlukast	armodafinil	nevirapine
aprepitant	danazol	imatinib	propoxyphene		artemether	phenobarbital
atazanavir	darunavir	indinavir	quinupristin		barbiturates	phenytoin
basiliximab	dasatinib	isoniazid	ritonavir		bexarotene	primidone
boceprevir	delavirdine	itraconazole	saquinavir		bosentan	rifabutin
chloramphenicol	diltiazem	ketoconazole	tamoxifen		carbamazepine	rifampin
ciprofloxacin	dronedarone	lapatinib	telaprevir		dexamethasone	rifapentine
clarithomycin	erythromycin	miconazole	telithromycin		efavirenz	St John's wort
conivaptan	ethinyl estradiol	mifepristone	troleandomycin		etravirine	vemurafenib
crizotinib	fluconazole	nefazodone	verapamil		modafinil	

U.S. Food and Drug Administration, Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers

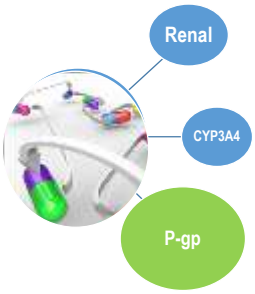
Combined Strong P-glycoprotein AND CYP3A4 Inhibitors		Combined Strong P-glycoprotein AND CYP3A4 Inducers
amiodarone	nelfinavir	barbiturates
clarithromycin	posaconazole	carbamazepine
conivaptan	ritonavir	dexamethasone
cyclosporine	saquinavir	phenytoin
indinavir	tamoxifen	rifampin
itraconazole	telaprevir	St John's wort
ketoconazole	telithromycin	
mifepristone		

U.S. Food and Drug Administration, Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers

Apixaban

- **Elimination**
- Less renal excretion than rivaroxaban (27%)
- Half life=10-14 hrs
- **Metabolism**
- - Substrate for CYP3A4, P-glycoprotein ABCG2 transporter proteins

Drug-drug interactions of Apixaban



+ **Pharmacodynamic**

Antiplatelet, NSAIDs and antithrombotic effects can increase bleeding risk

Alexander JH. Et al. N Engl J Med. 2011;365:699-708
Oldgren J. et al. Eur Heart J. 2013;34:1670-1680

Eliquis prescribing information. Bristol-Myers Squibb, Pfizer 2016

Combined Strong P-glycoprotein AND CYP3A4 Inhibitors		Combined Strong P-glycoprotein AND CYP3A4 Inducers
amiodarone	nelfinavir	barbiturates
clarithromycin	posaconazole	carbamazepine
conivaptan	ritonavir	dexamethasone
cyclosporine	saquinavir	phenytoin
indinavir	tamoxifen	rifampin
itraconazole	telaprevir	St John's wort
ketoconazole	telithromycin	
mifepristone		

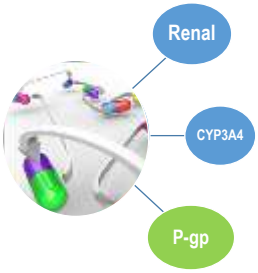
2.5 mg twice daily

U.S. Food and Drug Administration, Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers

Edoxaban

- **Elimination**
- Renal excretion (50%)
- Do not use edoxaban in patients with CrCl >95 ml/min in the US
- Half life=9-11 hrs
- **Metabolism**
- Substrate for both CYP3A4 and P-glycoprotein

Drug-Drug interactions of Edoxaban



+ Pharmacodynamic

Antiplatelet, NSAIDs and antithrombotic effects can increase bleeding risk

Mendell J. et al. Cardiovasc Pharmacol. 2013;62:212-221
Oldgren J. et al. Eur Heart J. 2013;34:1670-1680

Savaysa prescribing information. Daiichi-Sankyo, 2015

Drug-Drug Interactions of Edoxaban

Dual P-gp/CYP3A4 inhibitors	Dual P-gp/CYP3A4 inducers
↓	↓
No dose adjustment or use 30 mg once daily	Avoid concomitant use of rifampin

Drug Absorption: Food

Dabigatran	Rivaroxiban	Apixaban	Edoxaban
Take with or without food	10 mg, take with or without food 15 mg, 20 mg with food (Enhances bioavailability)	Take with or without food	Take with or without food

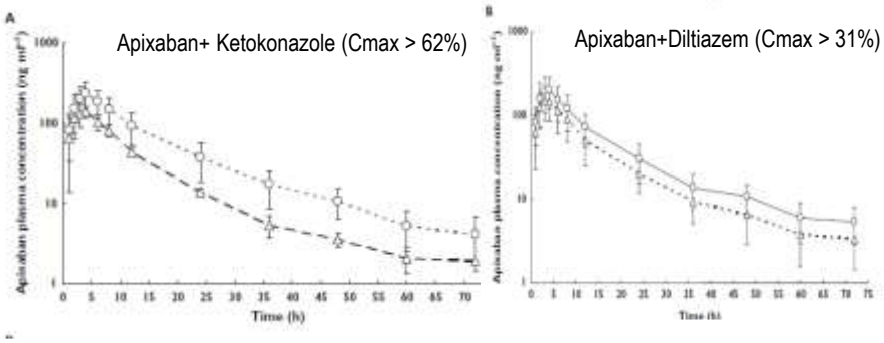
Drug-Drug Interactions of NOACs

Drug	Dual P-gp/CYP3A4 inhibitors	Dual P-gp/CYP3A4 inducers
Dabigatran	Reduce 75 mg b.i.d. dose for patients with moderate renal impairment (CrCl 30–50 ml/min) with ketoconazole, dronedarone No dose adjustment required for clarithromycin, amiodarone, quinidine, verapamil, ticagrelor	Avoid coadministration with rifampin
Rivaroxaban	Avoid use with P-gp and strong CYP3A4 inhibitors (ketoconazole, itraconazole, lopinavir, ritonavir, indinavir, conivaptan)	Avoid strong dual inducers of P-gp and CYP3A4 carbamazepine, phenytoin, rifampin, St. John's wort
Apixaban	A 50% dose reduction is recommended for patients receiving a dose >2.5 mg b.i.d. when coadministered with strong dual inhibitors of CYP3A4 and P-gp (ketoconazole, itraconazole, ritonavir, or clarithromycin); avoid use of these drugs when dosage is 2.5 mg, b.i.d.	Avoid strong dual inducers of P-gp and CYP3A4 carbamazepine, phenytoin, rifampin, St. John's wort
Edoxaban	No dose reduction	Avoid concomitant use of rifampin

Trikha R et al. Cardiology 2017;136:115–124

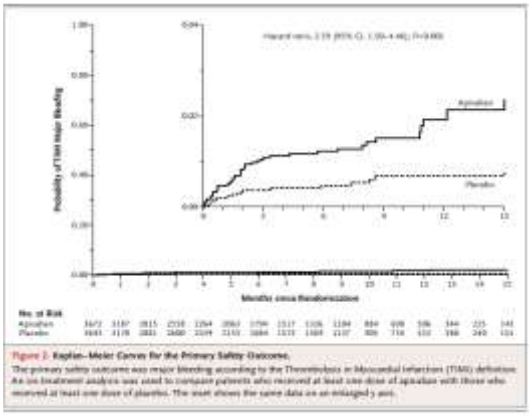
• **Clinical Significance of New Oral anticoagulants Drug-drug Interactions**

Effect of Ketoconazole and Diltiazem on the Pharmacokinetics of Apixaban,



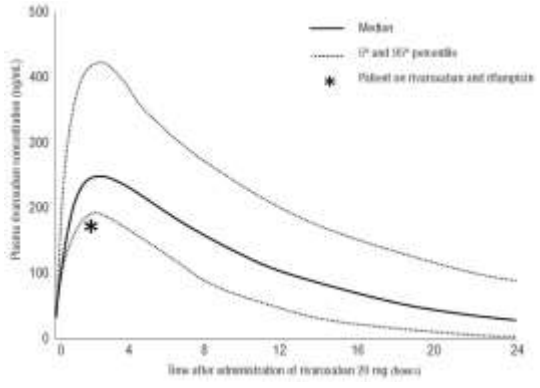
Frost CE et al., BJCP. 2014

Apixaban with Antiplatelet Therapy After ACS



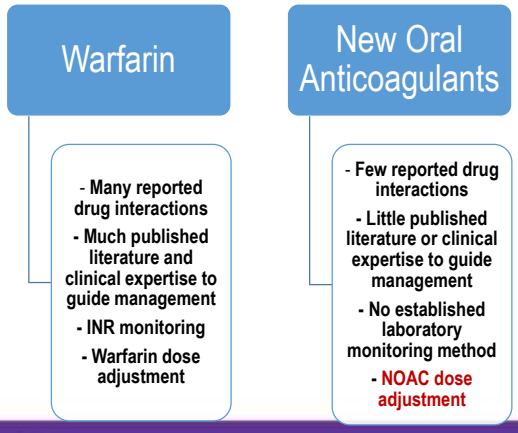
Alexander JH. Et al. N Engl J Med. 2011;365:699-708

A case of fatal pulmonary embolism may be related to sub-therapeutic levels of rivaroxaban, through the interaction of rifampicin with rivaroxaban



Mueck W. et al. Clin Pharmacokinet., 2011

Drug Interaction Management of Warfarin Versus New Oral Anticoagulants



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Conclusion

- **Pharmacokinetic drug-drug interactions that may occur in association with the new oral anticoagulants are largely mediated by the P-gp efflux transporter protein alone (dabigatran etexilate) or in combination with CYP3A4 enzymes**
- **In addition to managing pharmacokinetic-based interactions, clinicians should avoid unnecessary pharmacodynamics interactions between the newer oral Anticoagulants and antiplatelet agents (eg, ASA, clopidogrel) and NSAIDs (eg, naproxen)**
- **Drug-drug interactions of NOACs are more significant in patients with renal impairment**

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Conclusion

- **Praxbind (IDARUCIZUMAB) is humanized monoclonal antibody fragment (Fab) which is an antidote for dabigatran and there are ongoing clinical trials of antidotes for direct factor Xa inhibitors**
- **Real-world data investigating the clinical significance of drug-drug interactions of NOACs is needed**
- **Importance of anticoagulation specialist/ clinical pharmacist involvement in patient education and follow-up**

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- Drug Interactions of New Oral Anticoagulants Exist…How do we manage them?