Interazioni farmacologiche e vita di qualità nel paziente nmCRPC

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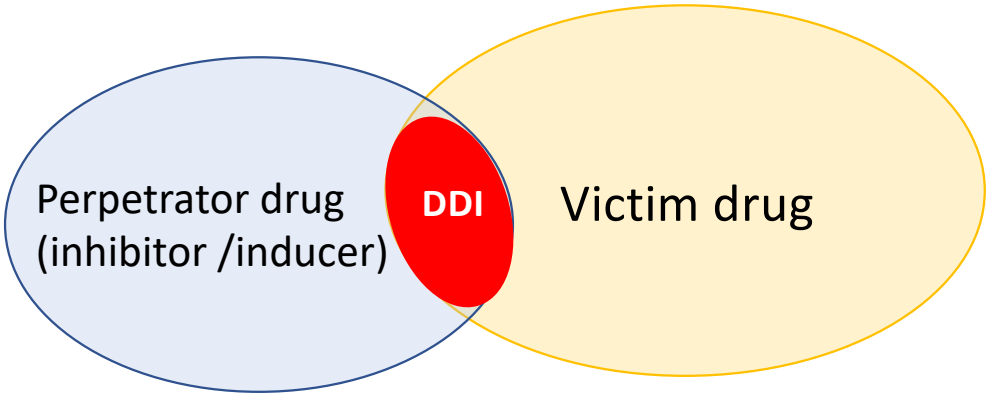
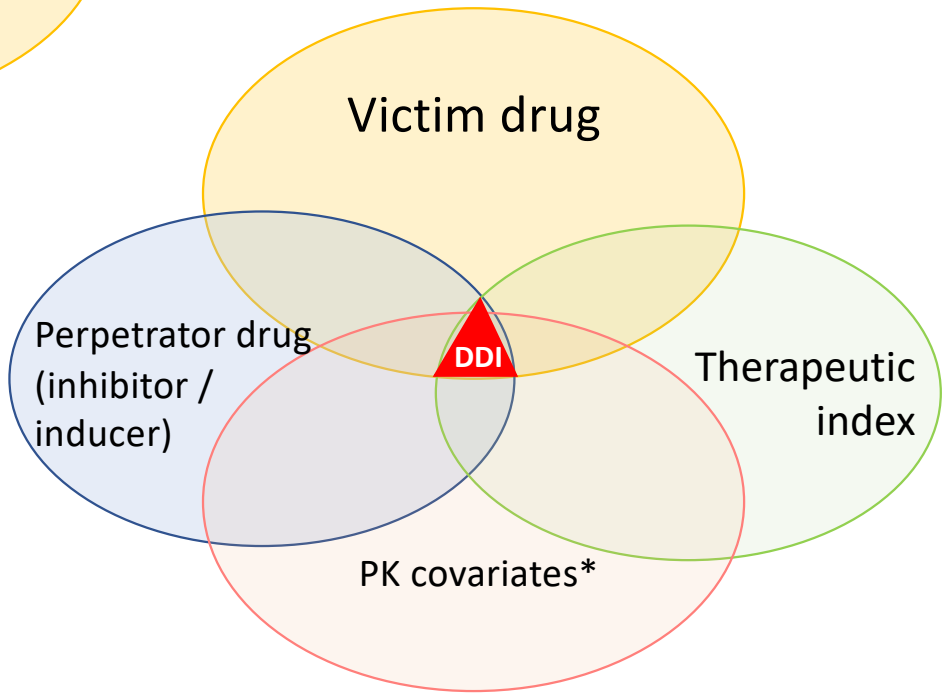
The drug metabolism vs. multifactorial model of DDI



Common covariates

1. Weight, fat free mass
2. Liver/Renal function
3. Age, Race, Gender
4. Clinical chemistry values e.g. bilirubin etc
5. Hematologic values e.g. WBC count, hematocrit
6. Protein Binding
7. Genotype
8. Disease stage

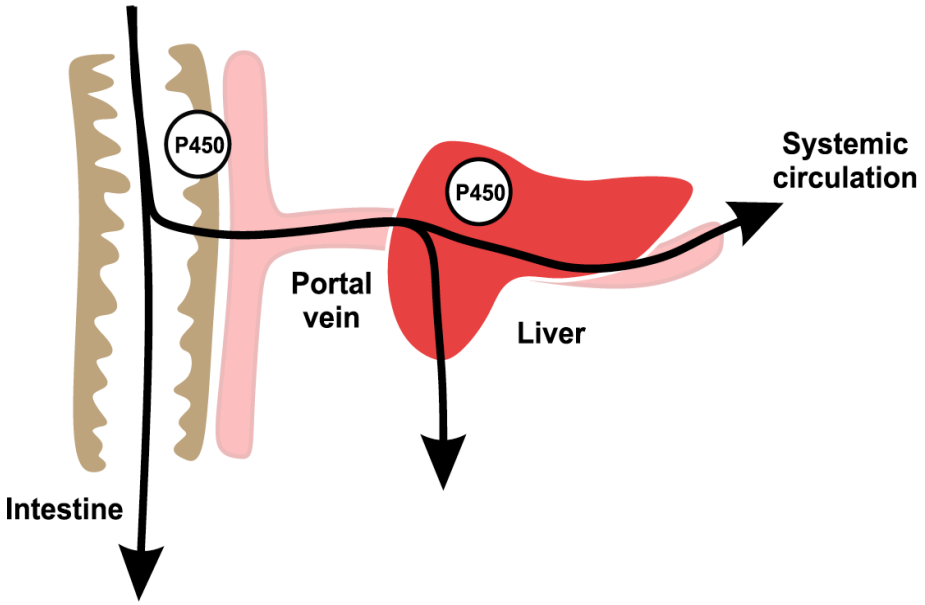
What is the most reliable?



A clinical case

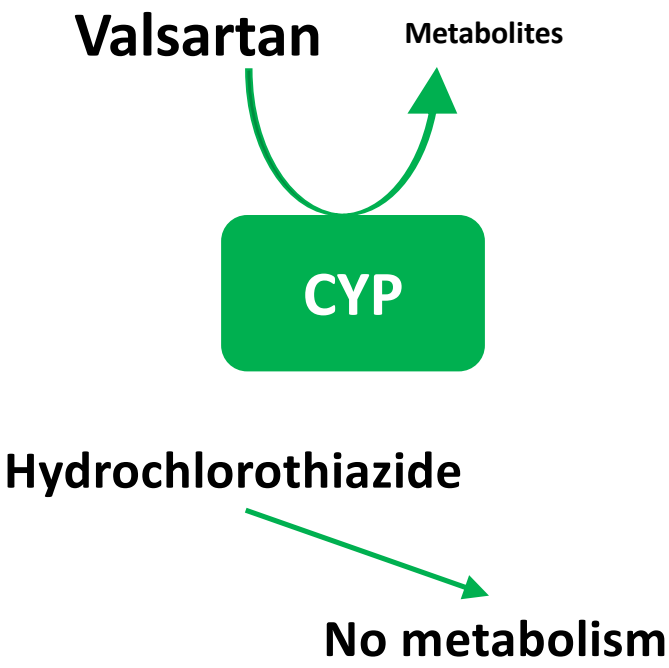
The patient is currently on:

- Valsartan and hydrochlorothiazide
- ASA
- Gliclazide
- Simvastatin
- Rivaroxaban
- Omeprazole



Valsartan and hydrochlorothiazide pharmacologic profiles

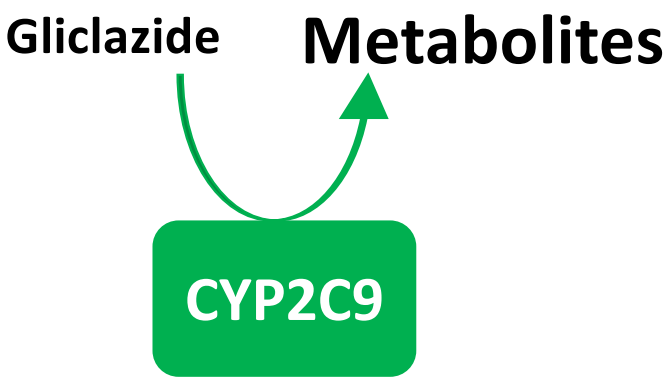
- Valsartan undergoes minimal liver metabolism.
- Hydrochlorothiazide is not metabolized and is eliminated by renal route as unchanged drug.



Black HR et al. Drugs. 2009;69(17):2393-414

Gliclazide pharmacologic profile

- The drug is extensively metabolized in the liver by CYP2C9.
- Metabolites include oxidized and hydroxylated derivates, as well as glucuronic acid conjugates.

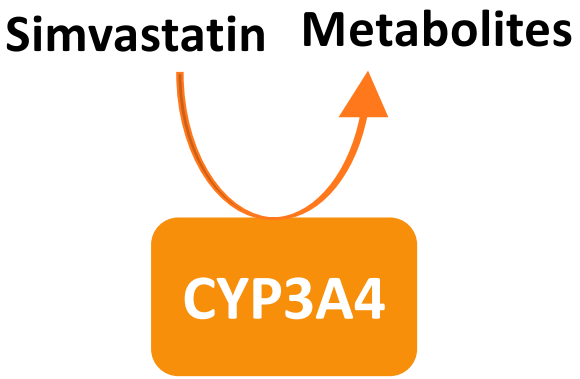


Yifan Zhang et al. Br J Clin Pharmacol 2007; 64(1): 67–74

Simvastatin pharmacologic profiles

- Simvastatin is metabolised in the liver by CYP3A4 and CYP3A5.

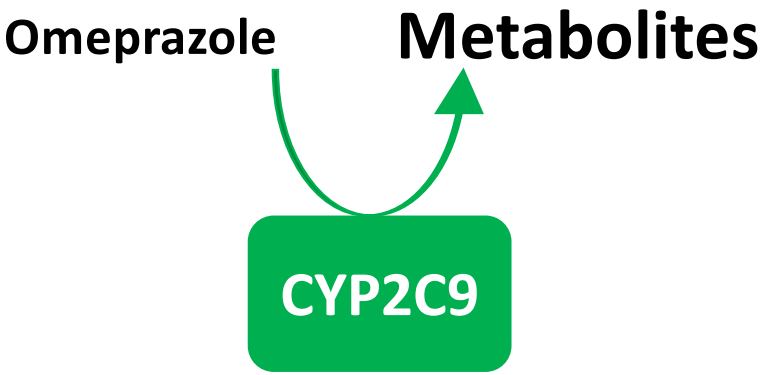
- Concomitant use of potent inducers of CYP3A4 can lead to a reduced cholesterol-lowering efficacy of simvastatin.



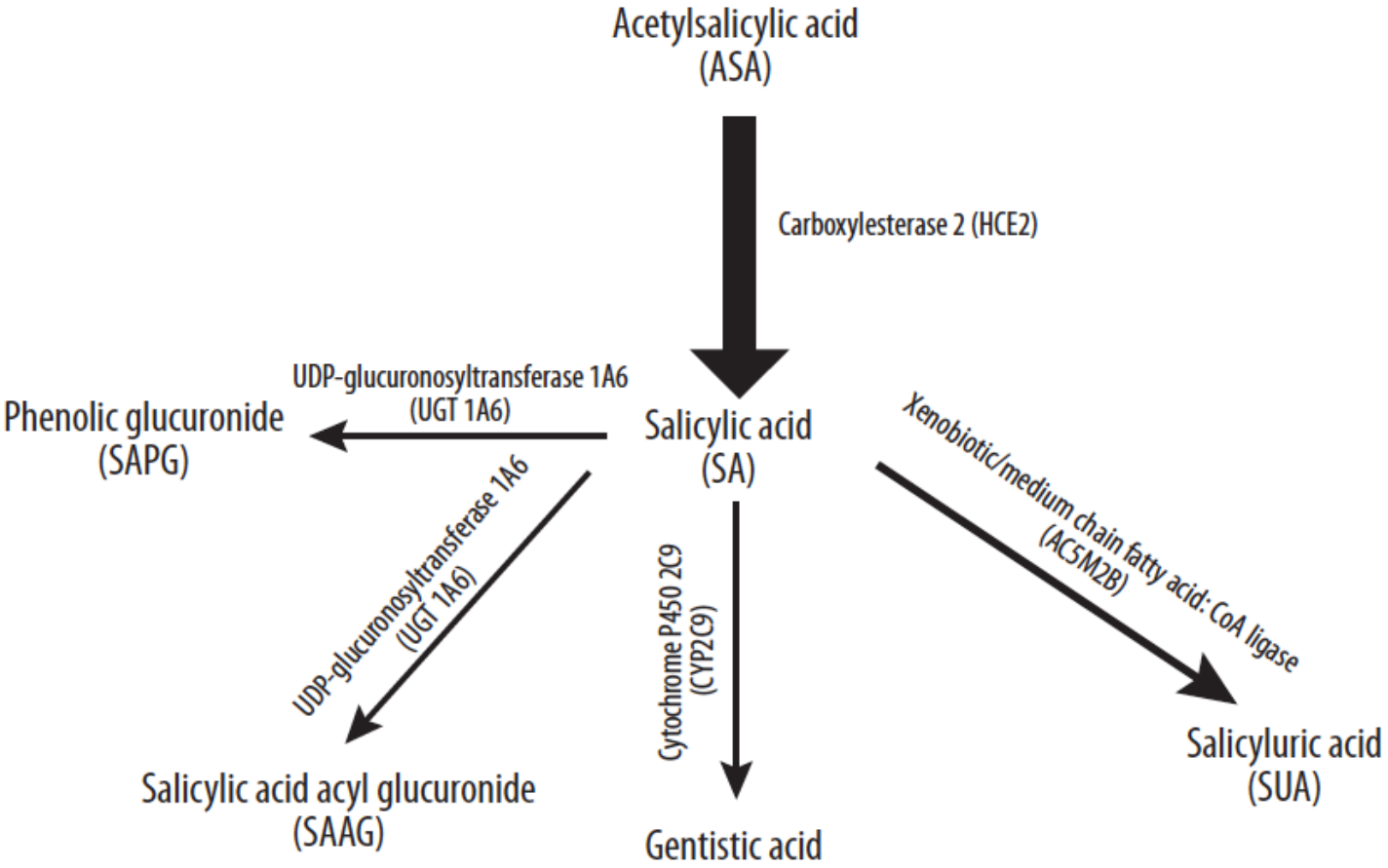
Kyrklund C et al. Clin Pharmacol Ther 2000;68(6):592-7
Tubic-Grozdanis M, et al. Pharm Res. 2008 Jul;25(7):1591-600
Kosoglou T, et al. Clin Pharmacokinet 2005;44(5):467-94

Omeprazole pharmacologic profile

- Omeprazole is metabolised in the liver by CYP2C19 and CYP3A4.
- Omeprazole is an ihibitor of CYP3A4 and CYP2C19.
- Omeprazole reduces the absorption of acid-soluble drugs



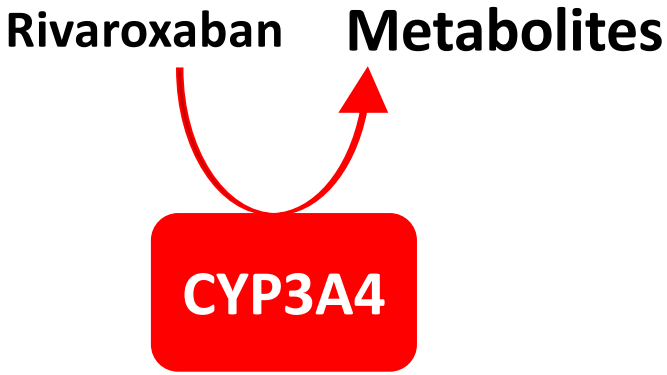
ASA pharmacologic profile



Rivaroxaban pharmacologic profile

- Approximately two-thirds of the dose is metabolized by CYP3A4 and CYP3A5.

- Avoid concomitant administration of strong inhibitors/inducers of CYP3A4 and rivaroxaban or apixaban, because both are substrates of CYP3A4.



Shatzel JJ et al. J Oncol Pract 13:720-727, 2017

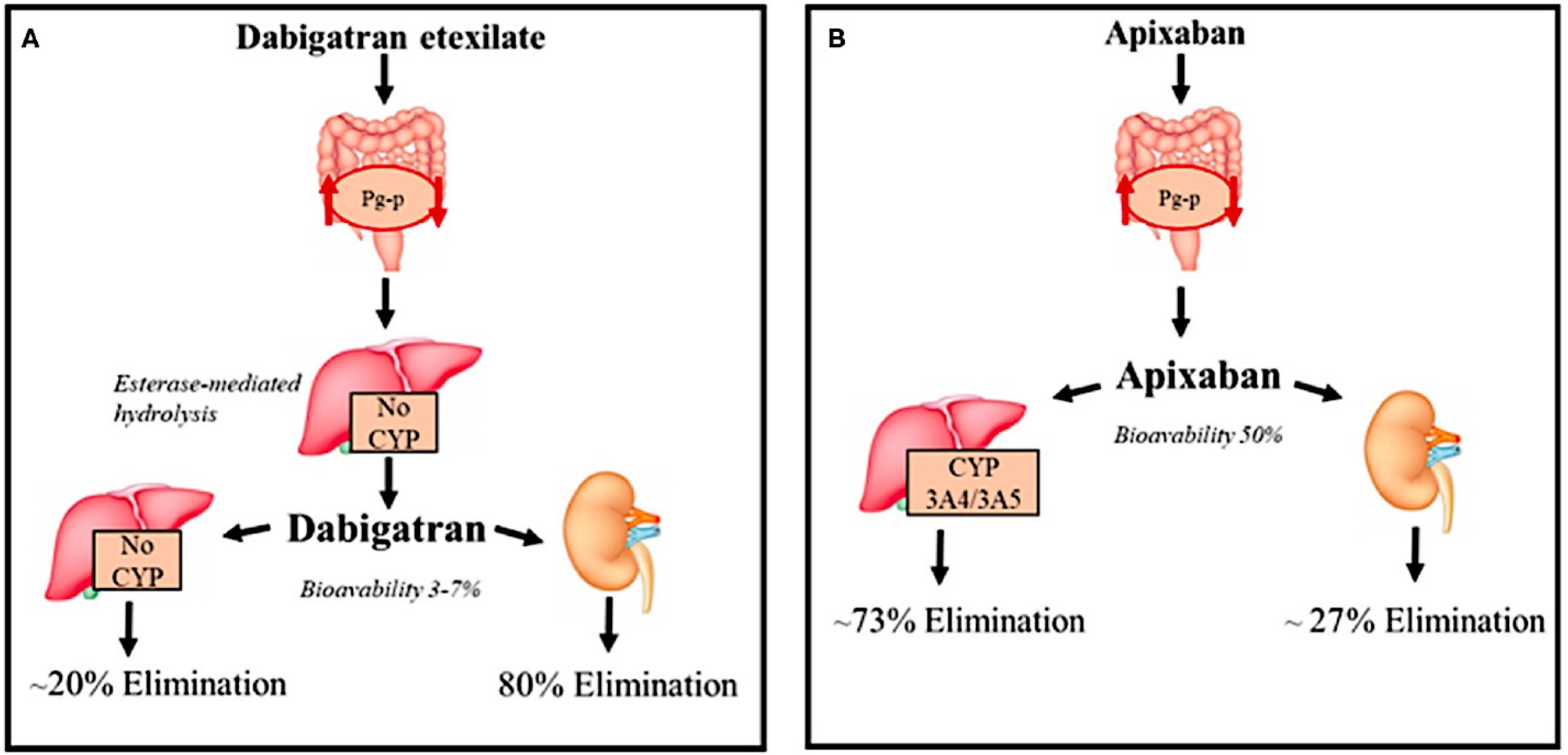
DDI: how to manage them?

Abiraterone	Enzalutamide	Apalutamide	Darolutamide	Docetaxel
Inhibits liver CYP2C8 and CYP2D6	Induces CYP3A4, 2C9 and 2C19	Induces CYP3A4 2C9 and 2C19	No effect on CYPs Inhibits BCRP and OATP1B1/3	Docetaxel has limited effect on CYP

Metabolic DDI

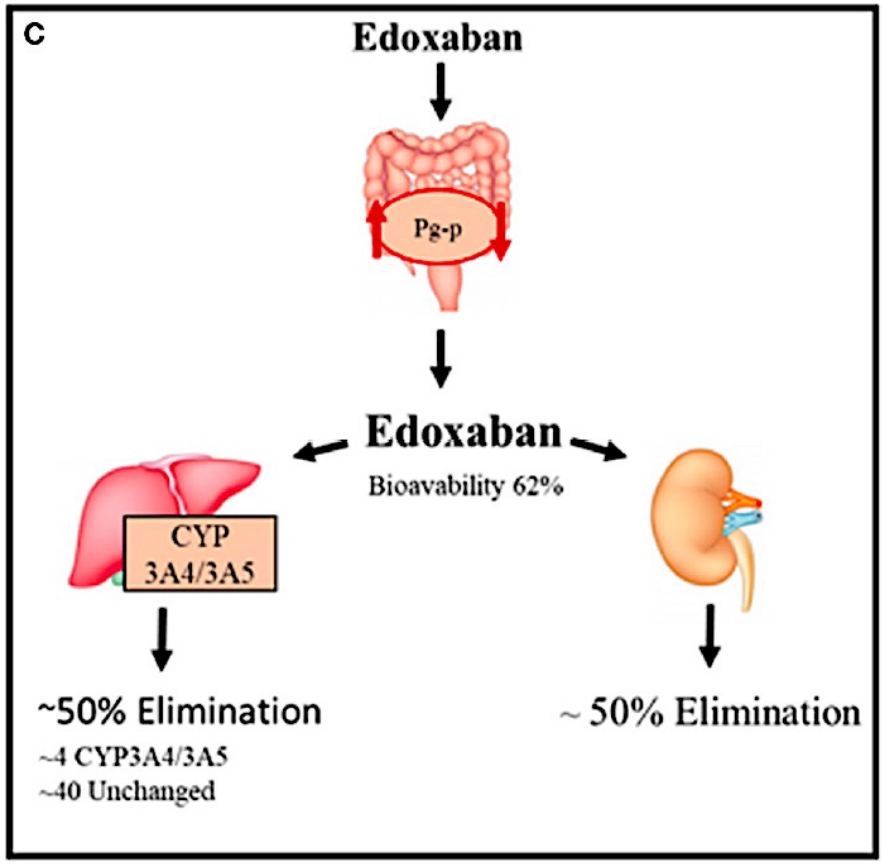
	Enzalutamide	Abiraterone	Apalutamide	Darolutamide	Docetaxel
Valsartan and hydrochlorothiazide					
Gliclazide					
Simvastatin					
Omeprazole					
ASA					
Rivaroxaban					

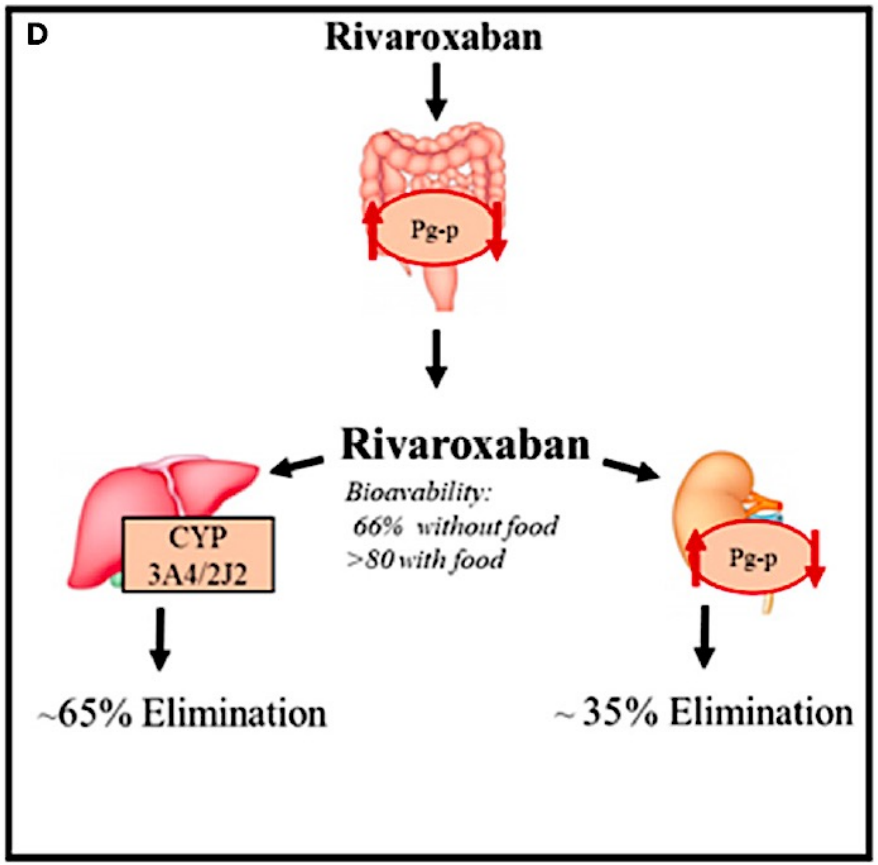
DOACs pharmacokinetic characteristics



Galgani A et al. Front. Neurol. 9:1067. doi: 10.3389/fneur.2018.01067

DOACs pharmacokinetic characteristics





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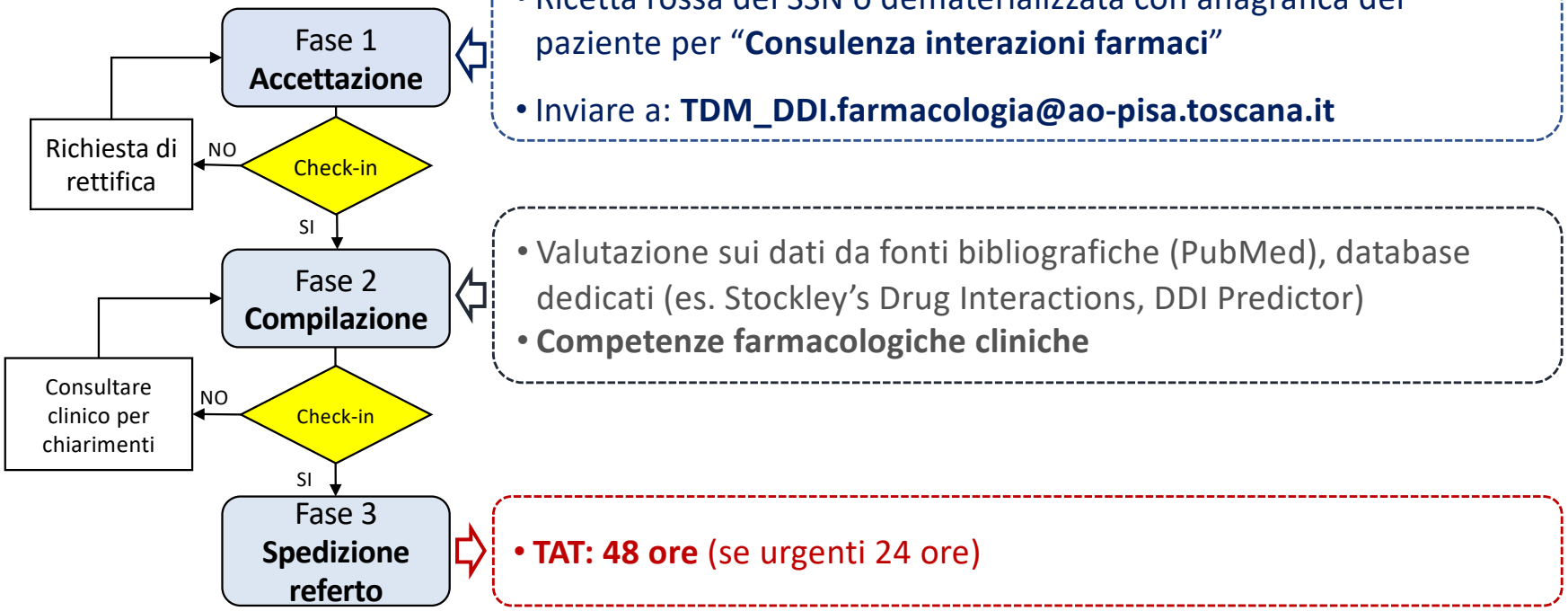
Ambulatorio DDI presso Azienda Ospedaliero-Universitaria Pisana

Azienda Ospedaliero-Universitaria Pisana
U.O. Farmacologia clinica e Farmacogenetica

Referente:
Prof. Stefano Fogli, MD, PharmD, PhD



- Ricetta rossa del SSN o dematerializzata con anagrafica del paziente per "**Consulenza interazioni farmaci**"
- Inviare a: **TDM_DDI.farmacologia@ao-pisa.toscana.it**

- Valutazione sui dati da fonti bibliografiche (PubMed), database dedicati (es. Stockley's Drug Interactions, DDI Predictor)
- **Competenze farmacologiche cliniche**

- **TAT: 48 ore** (se urgenti 24 ore)

Quale strategia utilizzata nella valutazione delle DDI?

- Scegliere il farmaco oncologico più appropriato per la paziente
- Revisione, se necessaria, della terapia non oncologica che il paziente sta assumendo
- Valutare anamnestica di pregressi episodi di reazioni avverse a farmaci assunti singolarmente o in combinazione
- Suddivisione dei farmaci «vittima» non solo sulla base del potenziale di interazione metabolico con il farmaco «perpetrator» ma anche - almeno con la stessa importanza – sulla base dell'indice terapeutico che, se ampio, riduce a entità subclinica la DDI di tipo metabolico.