

# Comment prédire les interactions médicamenteuses in vivo ?

M. TOD

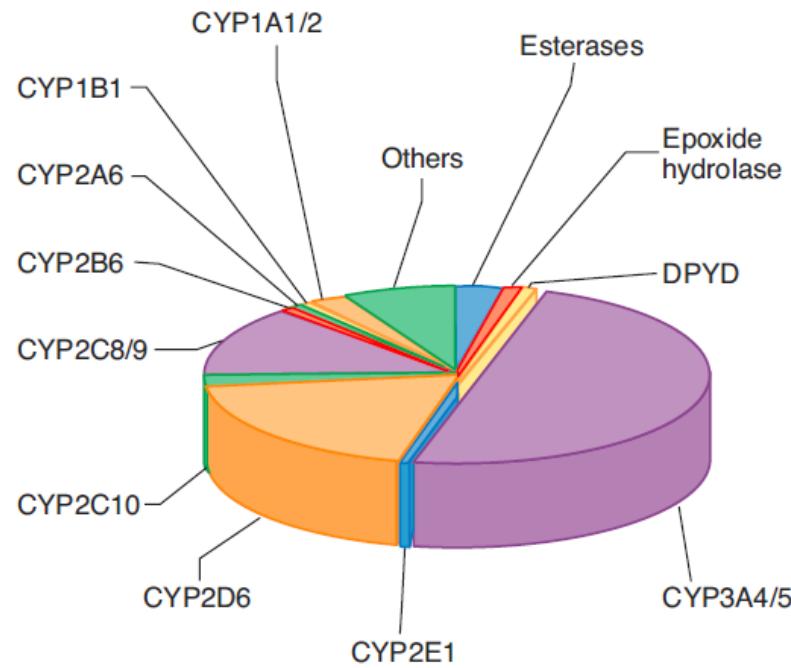
# Evénements Indésirables Médicamenteux

- Prévalence des EIM était de 19% chez les patients hospitalisés <sup>1</sup>
- 9,2% des EIM provoqués par une interaction médicamenteuse <sup>2</sup>
- Exemple: saignement chez les patients traités par antithrombotique pour une fibrillation atriale <sup>3</sup>:
  - 4.9 % en l'absence d'interaction
  - 8.6 % en cas d'interaction PK
  - 9.2 % en cas d'interaction PD
  - 26.3 % en cas d'interaction PK et PD

*<sup>1</sup> Laatikainen 2017, <sup>2</sup> Santos 2020, <sup>3</sup> Momo 2019*

# Notions de base (1)

- Le métabolisme se produit essentiellement au niveau de l'intestin et du foie.
- Les enzymes les plus souvent impliquées dans les interactions sont CYP3A4, 2D6, 2C9, 2C19 et 1A2.
- Les interactions surviennent par induction ou inhibition des CYP.



## Notions de base (2)

- Le paramètre caractérisant l'interaction est :

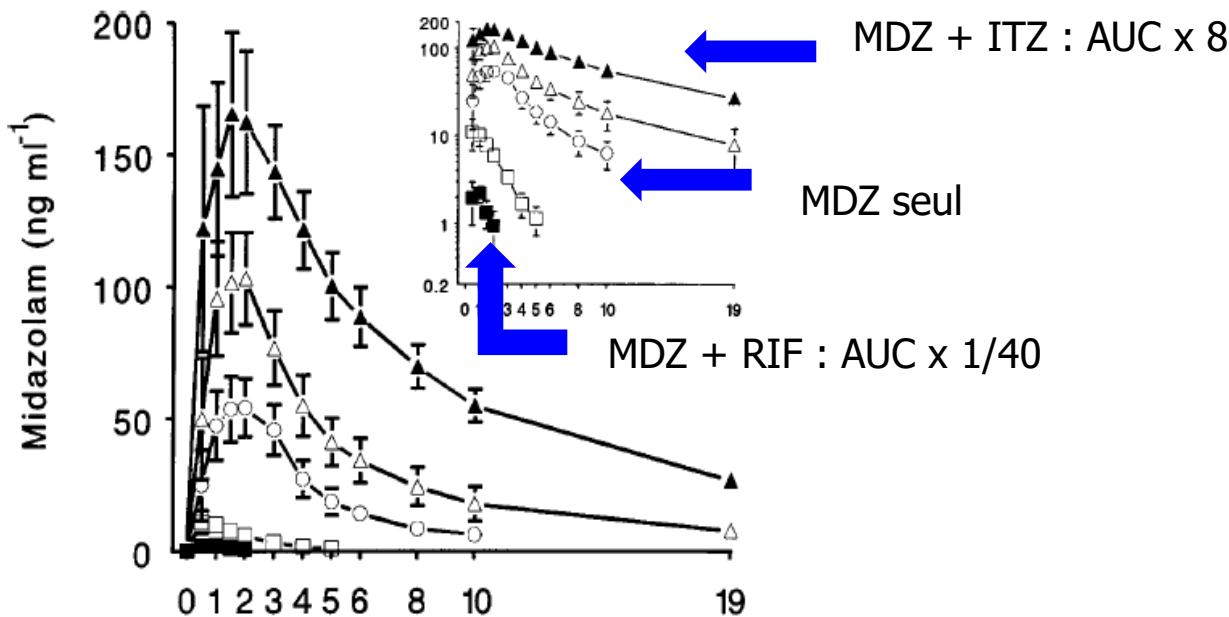
$R_{AUC} = \text{AUC en présence interacteur} / \text{AUC en absence interacteur}$

- $R_{AUC} < 1$  si induction,  $> 1$  si inhibition

# Variabilité de la clairance due aux interactions

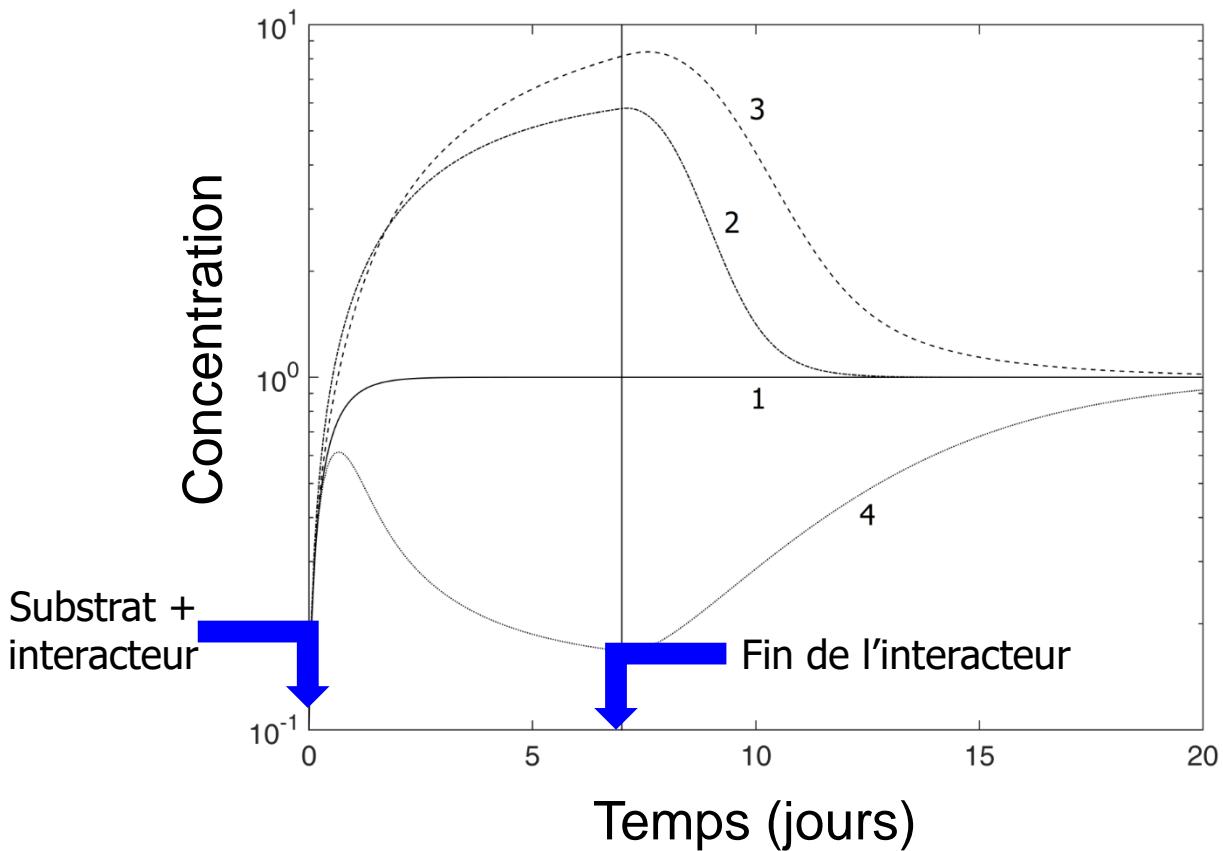
**Clairance du midazolam, per os, associé à :**

- itraconazole 200 mg/j (inhibiteur) ou
- rifampicine 600 mg/j (inducteur).



# Cinétique d'une interaction métabolique

## Profil de la concentration moyenne du substrat



1: substrat seul

2: substrat + inhib. compét.

3: substrat + inhib. suicide

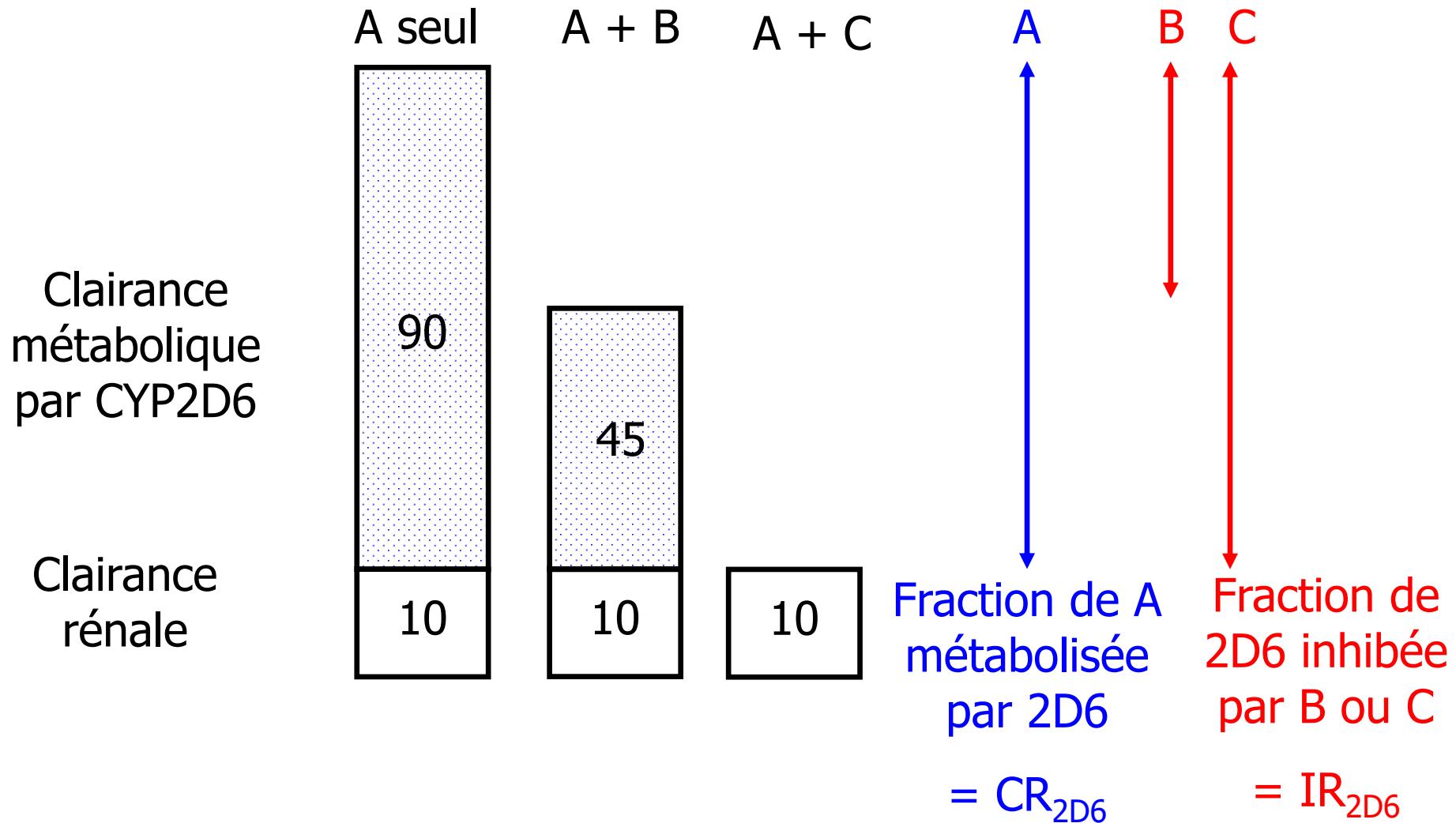
4: substrat + inducteur

# **Principe de la prédition du rapport d'AUC**

# Paramètres caractéristiques de l'interaction

	A seul	A + B	A + C
Clairance métabolique par CYP2D6	90	Blocage du CYP à 50%	Blocage du CYP à 100%
Clairance rénale	10	45	10
Clairance totale de A	100	55	10
Rapport d'AUC	-	100/55	100/10

# Paramètres caractéristiques de l'interaction



# Modèle de prédition

- Prédiction de l'impact de l'interaction :

$$R_{AUC} = \frac{1}{1 + CR_{3A4} \cdot IR_{3A4}}$$

$$R_{AUC} = \frac{1}{1 + CR_{3A4} \cdot IC_{3A4}}$$

- IR compris entre 0 et -1, IC compris entre 0 et  $+\infty$
- Calcul de la posologie du substrat, en présence d'une interaction:

Posologie ajustée = Posologie actuelle /  $R_{AUC}$

# **Estimation de CR**

## basée sur des données cliniques

- à partir d'une étude clinique d'interaction:

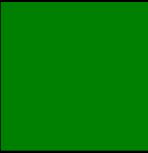
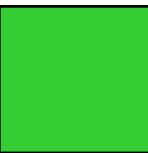
$$CR = \frac{R_{AUC} - 1}{R_{AUC}.IR}$$

- à partir d'une étude pharmacogénétique chez des métaboliseurs nuls:

$$CR = \frac{R_{AUC} - 1}{R_{AUC}}$$

# The 3-step approach:

## learning, confirming, predicting

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	
Inh. 1	Dark Green	White	Light Green	White	Light Green	
Inh. 2	White	Light Green	White	White	Dark Green	
Inh. 3	Light Green	White	Dark Green	Dark Green	White	
Inh. 4	White	Dark Green	White	Light Green	White	

Learning data

Validation data

Unknown data,  
to be predicted

# Estimer les paramètres *in vivo* versus *in vitro* : quel intérêt ?

Supprime les problèmes liés à l'extrapolation vitro-vivo :

- métabolites, énantiomères non pris en compte in vitro
- voies d'élimination non prises en compte in vitro
- incertitude sur les  $K_i$ ,  $I_{h,u}$ ,  $k_{inact}$ , etc
- PBPK: scaling factors !!

**[www.ddi-predictor.org](http://www.ddi-predictor.org)**

Site dédié à la prédiction quantitative de l'impact des:

- interactions médicamenteuses
- polymorphismes génétiques

médiés par les cytochromes P450 (CYP),

pour des médicaments administrés par voie orale,

chez des patients d'âge quelconque, cirrhotiques ou non.

**[www.ddi-predictor.org](http://www.ddi-predictor.org)**

- N'est pas une base de données classique
- Fait des prédictions même pour des cas *non documentés* dans la littérature

# Etendue de la base DDI-Predictor

Substrats	Inhibiteurs	Inducteurs
270	130	35

soit environ 40 000 combinaisons

CYPs:

3A4, 2D6, 2C9, 2C19, 1A2

Genotypes:

5 genotypes ou groupes de genotypes  
pour CYP 2D6, 2C9, 2C19

# Page d'accueil de DDI-predictor

DDI-Predictor is a website dedicated to quantitative prediction of the impact on drug exposure of drug-drug interactions mediated by cytochromes P450 3A4, 2D6, 2C9, 2C19 and 1A2, as well as genetic polymorphism of these cytochromes, the combined effect of drug interaction and cytochrome polymorphism, cirrhosis, and drug-drug interactions in cirrhotic patients.

DDI

Polymorphism

DDI-Polymorphism

Cirrhosis

DDI-Cirrhosis

## DISTINCTIVE FEATURE

DDI-Predictor is NOT a database in the usual sense. DDI-Predictor is able to make quantitative predictions of drug exposure e.g. in case of drug-drug interaction even if this interaction has not been studied. This is the distinctive feature of DDI-Predictor. The predictions are made using static equations of physiologically-based pharmacokinetic models.

## ADJUSTING DRUG DOSE

The predictions are made under the form of AUC ratios.

**Estimating the dose to be given is very simple in most cases:**

Adjusted dose = (Current or usual dose) / (AUC ratio)

## DDPRED API

DDI-Predictor's database and prediction engines are now accessible via an API, which makes it more convenient for anyone wishing to take advantage of DDI-Predictor's predicting capabilities in their own applications.

Access is per request only, and each project will be evaluated before any access is granted.

In the meantime, anyone can [checkout the documentation](#)

For more information, or any inquiry:

Contact us

## LATEST NEWS

### A new publication in July 2022

Tod M, Rodier T, Auffret M. Quantitative Prediction of Adverse Event Probability Due to Pharmacokinetic Interactions. Drug Saf. 2022 Jul;45(7):755-764. PMID: 35737292.

### Award in May 2022

The DDI-Predictor team, represented by M. Tod, has received the Michael Maler Price from the Fondation pour la Recherche en Pharmacie Hospitalière for his work.

Subscribe to the DDI-PREDICTOR newsletter

Your e-mail

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## CHANGELOG

### 11/2022 - Updates

**12 new substrates:** acalabrutinib, dapoxetine, dexamethasone, elexacaftor, fenerenone, lemborexant, pemigatinib, selpercatinib, selumetinib, tezacaftor, upadacitinib, tucatinib.

**7 new interactors:** berotralstat, cenobamate, dapoxetine, tecovirimat, tucatinib.

**18 new references** in the database.

### 02/2022 - Updates

**11 new substrates:** avapritinib, fedratinib, fostemsaviv, ionafarnib, nirmatrelvir/r, perampanel, pexidartinib, quizartinib, rimegepant, ubrogepant, voclosporin.

**5 new interactors:** fedratinib, ionafarnib, pexidartinib, viloxazine, voclosporin.

**WARNING 5 updates of parameter values:** ruxolitinib, cimetidine,

# Fonctionnalités

D·PREDICTOR

## DDI

IMPACT OF DRUG-DRUG INTERACTIONS ON DRUG EXPOSURE

## POLYMORPHISM

IMPACT OF CYP POLYMORPHISM ON DRUG EXPOSURE

## DDI & POLYMORPHISM

COMBINED IMPACT OF DRUG-DRUG INTERACTION AND CYP POLYMORPHISM

## CIRRHOsis

IMPACT OF CIRRHOsis ON DRUG EXPOSURE

## DDI & CIRRHOsis

COMBINED IMPACT OF DRUG-DRUG INTERACTION AND CIRRHOsis

# Choisir un substrat

**DDI**  
IMPACT OF DRUG-DRUG INTERACTIONS ON DRUG EXPOSURE

**AGE OF PATIENT**

Age >= 2 years  
 Age < 2 years

**SUBSTRATE**  
Start typing the name of a drug or scroll down the list to choose one

Choose...  
ome|  
Omeprazole

**INTERACTOR**  
Start typing the name of a drug or scroll down the list to choose one

Choose...

Compute

# Choisir un inhibiteur

## SUBSTRATE

Start typing the name of a drug or scroll down the list to choose one

Omeprazole

## INTERACTOR

Start typing the name of a drug or scroll down the list to choose one

Choose...

fluv



Fluvastatin 40-80 mg/d

Fluvooxamine 50-200 mg/d

Compute

# Lire le résultat

www.ddi-predictor.org/predictor/ddi

D-PREDICTOR

## DDI IMPACT OF DRUG-DRUG INTERACTIONS ON DRUG EXPOSURE

SUBSTRATE	Fraction metabolized by each CYP				
	3A4	2D6	2C9	2C19	1A2
OMEPRAZOLE	0.11	0	0	0.84	0

0 signifie "zéro" OU "pas d'information"

INHIBITOR	Inhibition potency with respect to each CYP				
	3A4	2D6	2C9	2C19	1A2
FLUVOXAMINE 50-200 MG/D	-0.3	0	0	-0.98	-0.99

AUC\*/AUC      6.95

# Cas clinique

Monsieur D, 74 ans, est traité habituellement par:

Fluindione PREVISCAN 15 mg/j

L'INR est à 2.5

Hospitalisé pour une aspergillose, Monsieur D se voit prescrire:

Lansoprazole OGASTORO 15 mg/j

Voriconazole VFEND 600mg/j per os

Quel est le risque encouru par le patient ?

Quelles mesures prendre pour diminuer le risque ?

# Fluindione + voriconazole

SUBSTRATE <b>FLUINDIONE</b>	Fraction metabolized by each CYP				
	cyp3A4	cyp2D6	cyp2C9	cyp2C19	cyp1A2
	0.00	0.00	0.74	0.00	0.00

## WARNING!

This drug has a low safety margin. An AUC ratio lower than 0.5 or greater than 2 may require a dosing adaptation or another intervention.

The elimination half-life of this drug or its active metabolite is greater than 48h in the absence of drug-drug interaction. Hence, the predicted AUC ratio may take several days to be reached. Consider a gradual dosing adaptation. Impact of a long term coadministration on AUC ratio may be underrated.

INHIBITOR <b>VORICONAZOLE 400-800 MG/D</b>	Inhibition potency with respect to each CYP				
	cyp3A4	cyp2D6	cyp2C9	cyp2C19	cyp1A2
	-0.98	0.00	-0.66	-0.64	0.00

AUC RATIO	AUC <sup>EM*</sup> /AUC <sup>EM</sup>	1.95	1.25 3.05

Show AUC ratios' interindividual distribution (5th to 95th percentiles)

# Réponses

Lansoprazole (inhibiteur CYP2C19) augmente la concentration du voriconazole.

Voriconazole (inhibiteur CYP2C9) augmente la concentration de la fluindione.

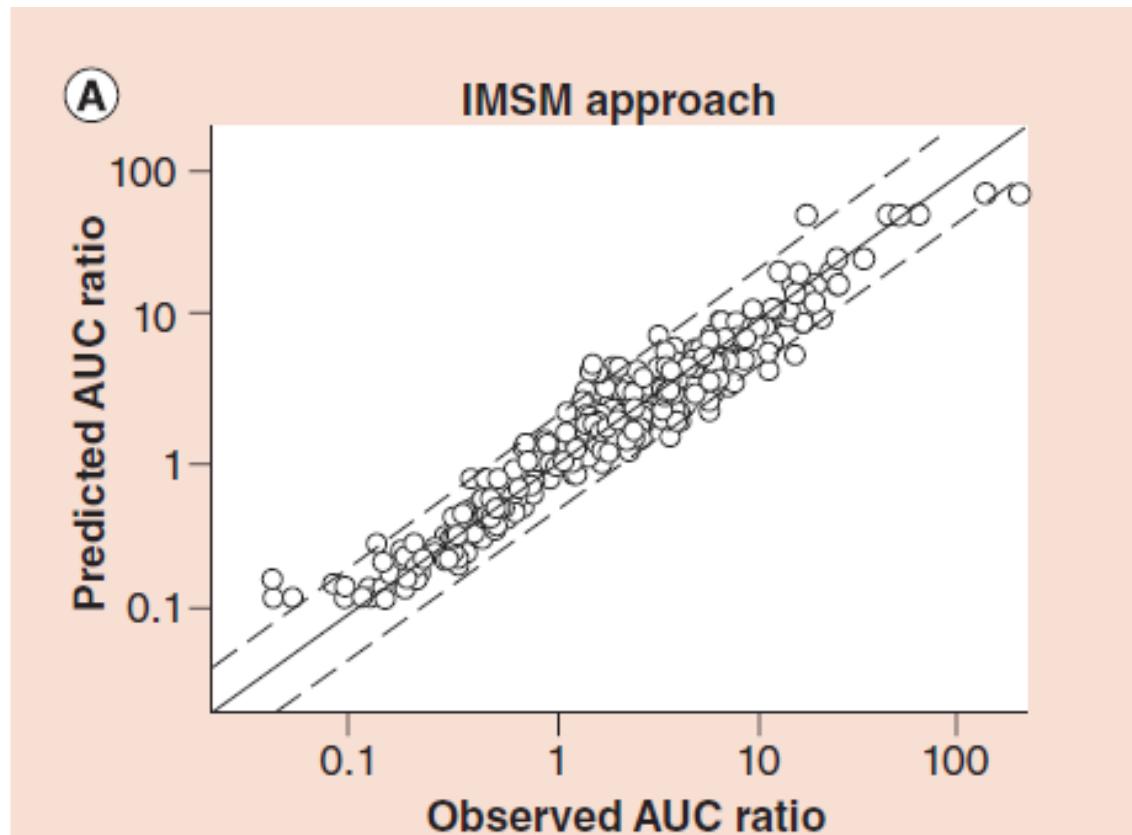
L'INR risque d'augmenter fortement: risque de saignement.

Utiliser la famotidine (pas d'action sur les CYP).

Baisser la posologie de PREVISCAN d'un facteur 2.

Contrôler l'INR tous les deux jours jusqu'à stabilisation.

# Validation externe sur 628 exemples



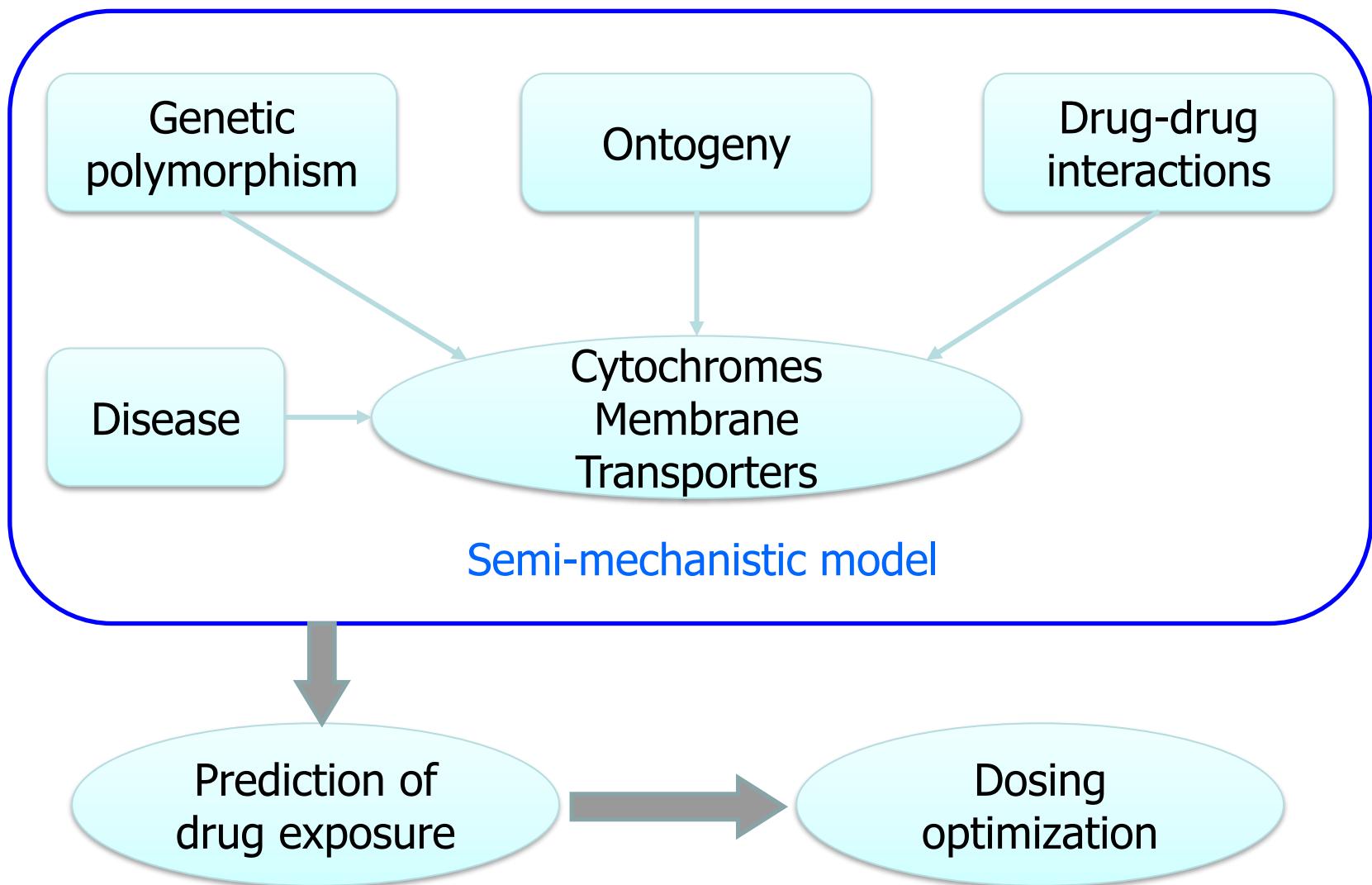
Tod M, Int J Pharmacokin 2016

The line is the  $y = x$  line. The dashed lines represent the 50–200% interval. Values above  $x = 1$  represent DDIs by inhibition. Values below  $x = 1$  represents DDIs by induction

# Limites de ddi-predictor

- Limité à CYP3A4, 2D6, 2C9, 2C19, 1A2 | Provisoire
- La cinétique doit être linéaire (ex: phénytoïne)
- Pb des mécanismes multiples (ex ciclosporine / statines)
- Ne distingue pas intestin / foie
- Pb des CR et IR proches de 1
- Pb des interactions sur la LP (phénytoïne / valproate)
- Pb des interactions entre plusieurs médicaments

# Genophar Working Group (2010 - )



# **Back-up**

# References (1)

23. Tuloup V, et al. Evaluation of Renal Impairment Influence on Metabolic Drug Clearance using a Modelling Approach. *Clin Pharmacokinet*. 2023 Feb;62(2):307-319.
22. Tod M, Rodier T, Auffret M. Quantitative Prediction of Adverse Event Probability Due to Pharmacokinetic Interactions. *Drug Saf*. 2022 Jul;45(7):755-764.
21. Tuloup V et al. Model-Based Comparative Analysis of Rifampicin and Rifabutin Drug-Drug Interaction Profile. *Antimicrob Agents Chemother*. 2021 Aug 17;65(9):e0104321.
20. Moreau F et al. Does DDI-Predictor Help Pharmacists to Detect Drug-Drug Interactions and Resolve Medication Issues More Effectively? *Metabolites*. 2021 Mar 17;11(3):173.
19. Le Corvaisier C, et al. Drug interactions between emergency contraceptive drugs and cytochrome inducers: literature review and quantitative prediction. *Fundam Clin Pharmacol*. 2021 Apr;35(2):208-216.
18. Tod M et al. Quantitative Prediction of Interactions Mediated by Transporters and Cytochromes: Application to Organic Anion Transporting Polypeptides, Breast Cancer Resistance Protein and Cytochrome 2C8. *Clin Pharmacokinet*. 2020 Jun;59(6):757-770.

## References (2)

17. Tod M et al. A Generic Model for Quantitative Prediction of Interactions Mediated by Efflux Transporters and Cytochromes: Application to P-Glycoprotein and Cytochrome 3A4. *Clin Pharmacokinet*. 2018 Sep 8.
16. Fermier N et al. Identification of CYP450-Mediated DDIs at Risk in Cases of Gene Polymorphisms by Using a Quantitative Prediction Model. *Clin Pharmacokinet*. 2018 Dec;57(12):1581-1591.
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14. Tod M et al. Quantitative Prediction of DDIs Involving Inhibitory Metabolites by Physiologically Based Pharmacokinetic Models: Is it Worth ? *CPT Pharmacometrics Syst Pharmacol*. 2017 Apr;6(4):226.
13. Tod M et al. A model for predicting the interindividual variability of drug-drug interactions. *AAPS J*. 2017 Mar;19(2):497-509.

## References (3)

12. Tod M et al. Comparison of the static *in vivo* approach to a PBPK approach for metabolic drug–drug interactions prediction. *Int J Pharmacokin* 2016; 1(1):25-34 <http://www.future-science.com/toc/ipk/1/1>
11. Gabriel L et al. Quantitative Prediction of Drug Interactions Caused by CYP1A2 Inhibitors and Inducers. *Clin Pharmacokinet*. 2016;55(8):977-90.
10. Steelandt J et al. A Prediction Model of Drug Exposure in Cirrhotic Patients According to Child-Pugh Classification. *Clin Pharmacokinet*. 2015;54(12):1245-58.
9. Goutelle S, Tod M. Quantitative methods for prediction of the effect of cytochrome P450 gene polymorphisms on substrate drug exposure. *Clin Pharmacokinet*. 2015;54(3):319-20.
8. Loue C, Tod M. Reliability and extension of quantitative prediction of CYP3A4-mediated drug interactions based on clinical data. *AAPS J*. 2014;16(6):1309-20.
7. Tod M et al. Impact of genetic polymorphism on drug-drug interactions mediated by cytochromes: a general approach. *AAPS J*. 2013;15(4):1242-52.

## References (4)

6. Castellan AC et al. Quantitative prediction of the impact of drug interactions and genetic polymorphisms on cytochrome P450 2C9 substrate exposure. *Clin Pharmacokinet.* 2013;52(3):199-209.
5. Goutelle S et al. In vivo quantitative prediction of the effect of gene polymorphisms and drug interactions on drug exposure for CYP2C19 substrates. *AAPS J.* 2013;15(2):415-26.
4. Tod M et al. Genotype-based quantitative prediction of drug exposure for drugs metabolized by CYP2D6. *Clin Pharmacol Ther.* 2011;90(4):582-7.
3. Tod M et al. Quantitative prediction of cytochrome P450 (CYP) 2D6-mediated drug interactions. *Clin Pharmacokinet.* 2011;50(8):519-30.
2. Ohno Y et al. General framework for the prediction of oral drug interactions caused by CYP3A4 induction from in vivo information. *Clin Pharmacokinet.* 2008;47(10):669-80.
1. Ohno Y et al. General framework for the quantitative prediction of CYP3A4-mediated oral drug interactions based on the AUC increase by coadministration of standard drugs. *Clin Pharmacokinet.* 2007;46(8):681-96.

# Principe de ddi-predictor

## Modèle mécanistique statique FDA-EMA

The "mechanistic static model" of the FDA and EMA for the AUC ratio of a DDI, assuming  $F_g = 1$ , is:

$$\frac{AUC^*}{AUC} = \cdot \frac{1}{A_h \cdot B_h \cdot C_h \cdot fm + (1 - fm)}$$

where

$$A_h = \frac{1}{1 + \frac{I_{h,u}}{K_i}} \quad B_h = C_h = 1$$

for competitive or non-competitive inhibition

# Principe de ddi-predictor

## Puissance inhibitrice IR

$I_{h,u} / Ki$       remplacé par      Puissance inhibitrice IR  
(déterminé *in vitro*)       $\xrightarrow{}$       (déterminée *in vivo*)

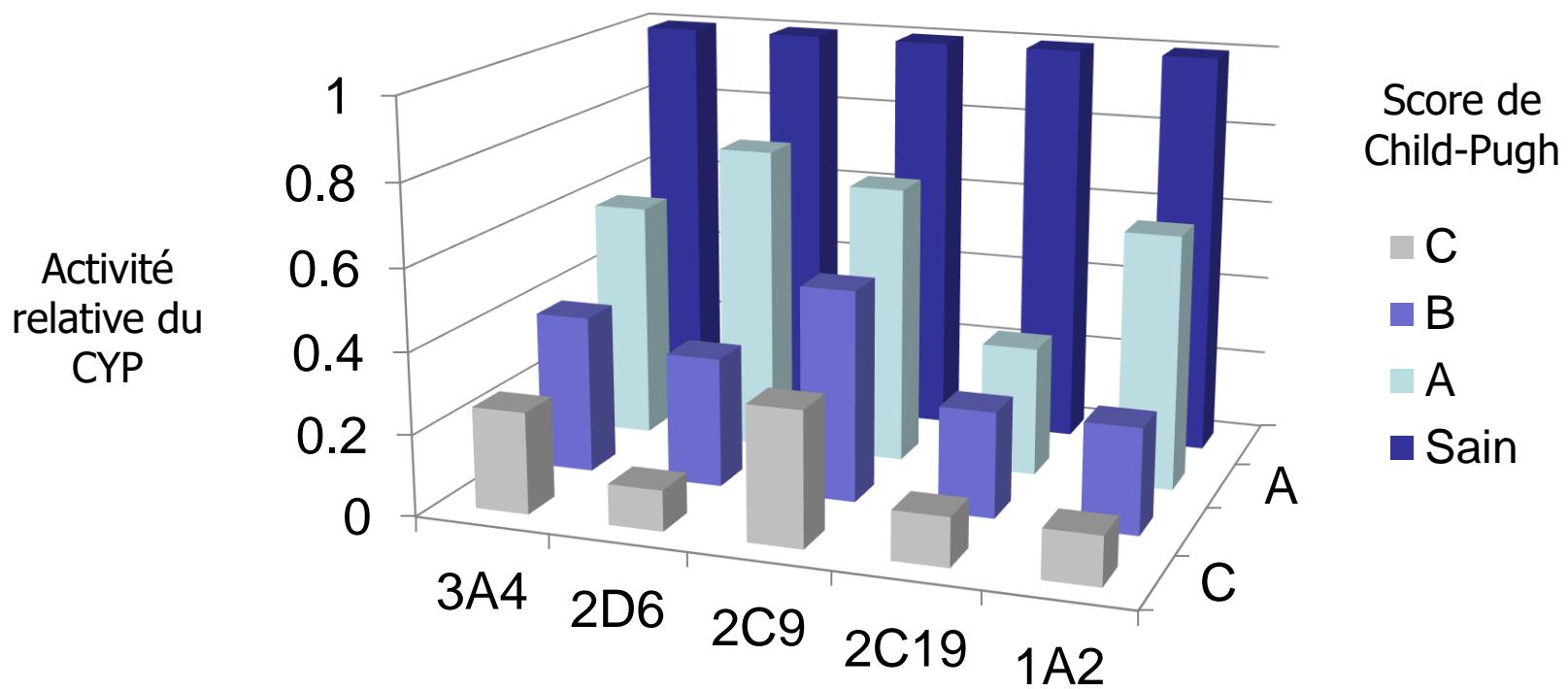
$$IR = \frac{(AUC^*/AUC) - 1}{(AUC^*/AUC).CR}$$

- On peut démontrer que :

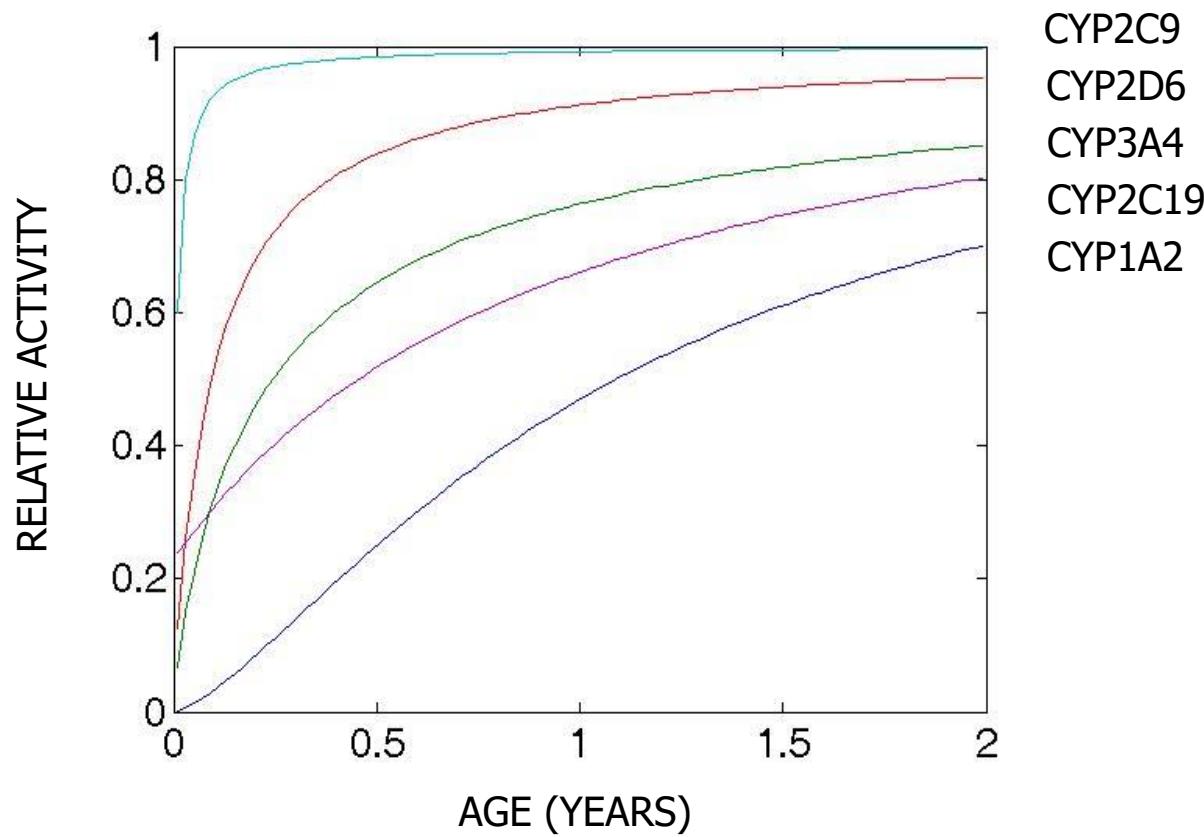
$$IR = \frac{I_{h,u} / Ki}{1 + (I_{h,u} / Ki)}$$

- IR est compris entre 0 et 1

# Activité des cytochromes selon la sévérité de la cirrhose



# Age : activité relative des CYP chez l'enfant



Derived from  
Johnson TN,  
CPK 2006

# **Insuffisance des recommandations officielles**

# Etude Pharmacie GHN HCL 2017

**Extraction de DDI Predictor:** 278 IAM impliquant 47 substrats et 29 inhibiteurs, ratios d'AUC prédicts compris entre 5 et 50

## Thésaurus de l'ANSM :

- 180 IAM identifiées (65%)
- 8 % de façon précise (DCI des 2 médicaments).

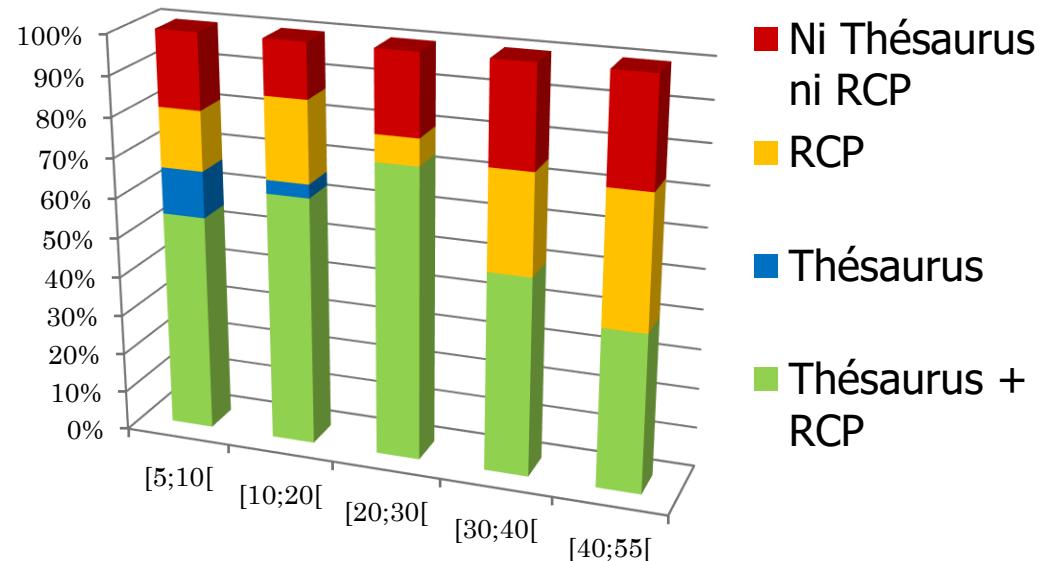
## RCP des substrats:

- 204 IAM (73%)

## Ni l'un ni l'autre:

- 47 IAM (17%) citées ni dans RCP ni dans Thésaurus.

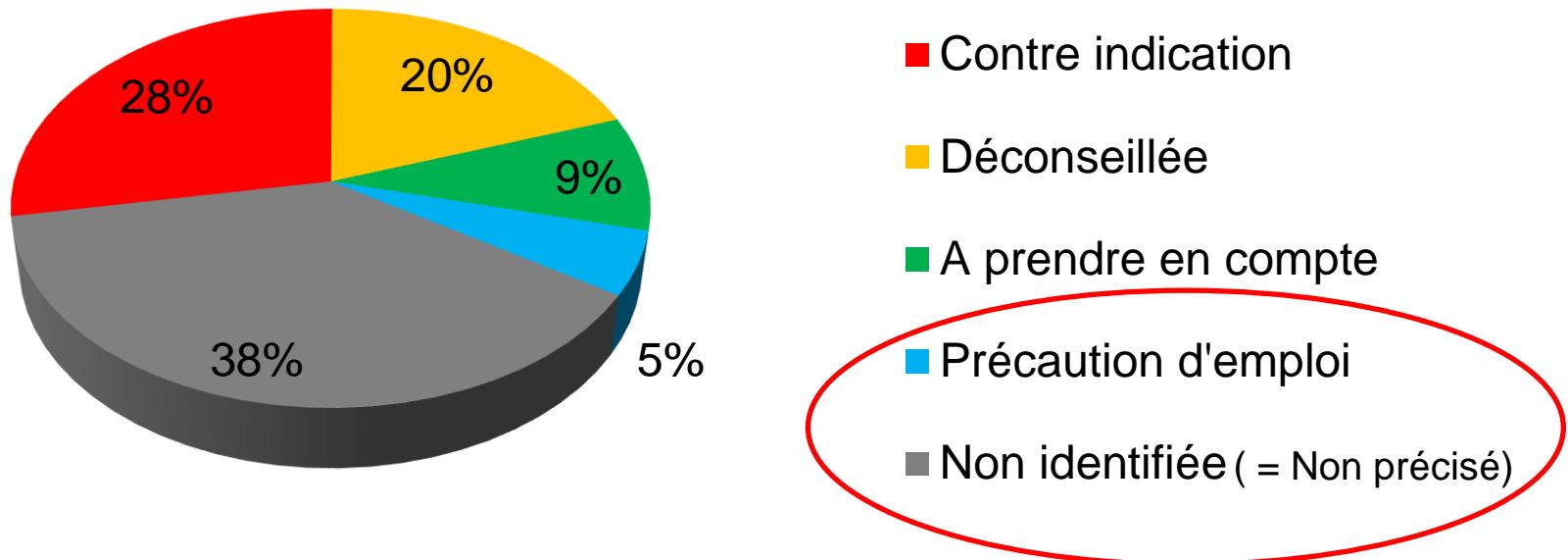
## Identification des interactions par ratio d'AUC



# Etude Pharmacie GHN HCL 2017

Quel niveau de précaution est affecté par le Thésaurus aux interactions avec un ratio d'AUC  $\geq 10$  ?

(97 IAM avec un ratio d'AUC  $\geq 10$  d'après DDI-predictor, retrouvées dans le Thésaurus)



# **Prédiction de la fréquence des effets indésirables lors d'une interaction PK**

# Predicting the impact of DDIs on Adverse Events frequency (2)

Under the assumption of a logistic model :

$$\text{OR(AE)}_{\text{combo predicted}} = [1 + (\text{OR}_{\text{drug A}} - 1) \cdot \text{Rauc}] \cdot \text{OR}_{\text{drug B}}$$

AUC ratio  
DDI-Predictor

ROR of AE	Parameter to estimate	Calibration	Validation
Drug A vs control	$\text{OR}_{\text{drug A}}$	RCT or FAERS	-
Drug B vs control	$\text{OR}_{\text{drug B}}$	RCT or FAERS	-
Combo A+B vs control	$\text{OR}_{\text{combo predicted}}$	-	$\text{OR}_{\text{combo observed}}$ FAERS

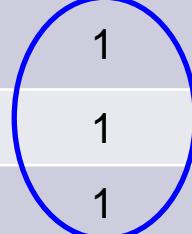
RCT: Randomized Controlled Trial

FAERS : FDA pharmacovigilance database

# Results

## Some examples

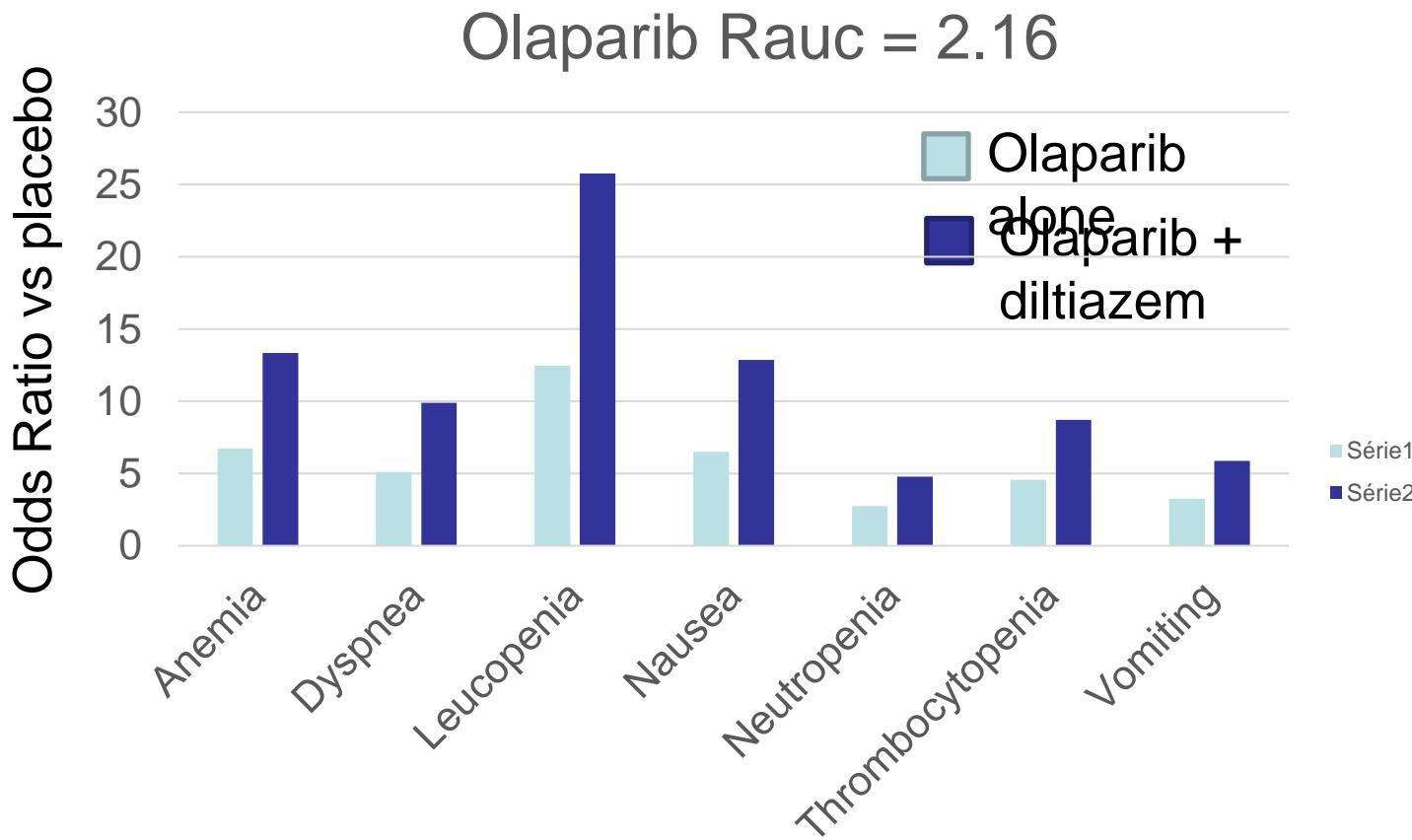
Substrate	Interactor	AUC ratio	Adverse event	ORcombo_obs	ORcombo_pred
Metoprolol	Paroxetine	3.37	Bradycardia	1.64	1.25
Metoprolol	Bupropion	2.94	Bradycardia	1.4	2.65
Metoprolol	Ritonavir	1.55	Bradycardia	1.19	1.37
Digoxin	Clarithromycin	1.7	Bradycardia	5.74	3.99
Digoxin	Diltiazem	1.5	Bradycardia	2.37	4.75
Digoxin	Verapamil	1.6	Bradycardia	2.41	6.40
Clonidine	Metoprolol	1	Bradycardia	1.42	2.26
Clonidine	Diltiazem	1	Bradycardia	2.26	3.19
Clonidine	Verapamil	1	Bradycardia	2.69	4.16



PD interactions

# OR predictions based on RCT

## Interaction with diltiazem



# **Impact des polymorphismes génétiques sur les interactions métaboliques**

# Practical application: an example

Imagine a patient treated by fluoxetine (antidepressant). He suffers from mycosis. His doctor prescribes terbinafine (antifungal). Is there a risk of drug-drug interaction ?

SUBSTRATE	Fraction metabolized by each CYP				
	cyp3A4	cyp2D6	cyp2C9	cyp2C19	cyp1A2
FLUOXETINE	0.00	0.40	0.00	0.59	0.00

INHIBITOR	Inhibition potency with respect to each CYP				
	cyp3A4	cyp2D6	cyp2C9	cyp2C19	cyp1A2
TERBINAFINE 150-250 MG/D	0.00	-0.92	0.00	0.00	-0.23

Answer : Yes, on CYP2D6, but the AUC ratio is expected to be low (1.59)

## Practical application: an example, ctd.

Fluoxetine is metabolized mainly by CYP2C19. Is the interaction with terbinafine different in CYP2C19 poor metabolizers ?

AUC RATIOS			
Phenotype	EM	IM	PM
Genotype	cyp2c19*1*1	cyp2c19*1*2-3	cyp2c19*2-3*2-3
AUC <sup>XM*</sup> /AUC <sup>XM</sup>	1.59	2.68	10.25

Answer : the interaction is weak in extensive metabolizers, but much stronger in poor metabolizers.