A unified *in vivo* modeling approach for quantitative prediction of the impact of gene polymorphism and drug interactions on drug exposure

Sylvain Goutelle , Michel Tod,
Laurent Bourguignon, Nathalie Bleyzac , Johanna Berry,
Fannie Clavel-Grabit, and the Genophar II working group

University Hospitals of Lyon; UMR CNRS 5558, University of Lyon 1; Department of Pharmacology, School of Pharmacy, University of Lyon 1, Lyon, France

Population Approach Group in Europe, 21st annual meeting, Venice, 5-8 June 2012

Drug Interactions and Gene Polymorphism

▸ Cytochrome P450 (CYP) are key enzymes in drug metabolism

▸ CYP-mediated drug interactions (DDI) and CYP gene polymorphism are major determinants of variability in drug exposure in patients

▸ For a substrate drug of a polymorphic CYP, it is desirable:

  ▸ To predict the magnitude of DDI (induction or inhibition)

  ▸ To predict the change in drug exposure in poor (**PM**) and ultra-rapid (**UM**) metabolizers with respect to extensive metabolizers (**EM**)

▸ For DDI, mechanistic and PBPK models based on *in vitro* data have been proposed but are rather complex (Fahmi, 2009)

▸ *Fahmi et al. Drug Metab Dispos 2009,37:1658*

Drug Interactions and Gene Polymorphism

▶ Alteration in drug exposure caused by DDI or gene polymorphism is essentially the same matter:

    " the difference in drug exposure between EM and PM subgroups would generally represent the most extreme change that could be caused by a strong inhibitor of that pathway "

    " for example, an individual who is a CYP2D6 EM may be converted de facto CYP2D6 PM by concomitant administration of a strong CYP2D6 inhibitor"

    FDA Guidance, Clinical Pharmacogenomics, Feb 2011

▶ The objective of this study is to propose a general framework for *in vivo* quantitative prediction of the impact of gene polymorphism and DDI on CYP substrate drug exposure

▶ An application to drugs metabolized by CYP2C19 is presented

▶

Methods: Pharmacological Basis

▸ In 2007, Ohno et al. proposed the following model for inhibition:

$$R_{AUC} = \frac{AUC^*}{AUC} = \frac{1}{1 - CR_{CYP} \cdot IR}$$ Equation 1

R_AUC, AUC increase of the CYP substrate drug

IR, **the inhibition ratio** is a measure of inhibitor potency based (range, 0-1)

CR, the **contribution ratio**, is the *in vivo* equivalent of the fraction metabolized by a given cytochrome (range, 0-1)

▸ In 2011, we proposed a similar model for CYP gene polymorphism :

$$R_{AUC} = \frac{AUC^{XM}}{AUC^{EM}} = \frac{1}{1 - CR_{CYP} \cdot (1 - FA)}$$ Equation 2

FA, **the fraction of activity** characterizes the relative activity of the CYP

FA = 1 in **EM**, FA < 1 in **PM**, FA > 1 in **UM** subjects

▸ *Ohno et al. Clin Pharmacokinet 2007, 46:681*
Tod et al. Clin Pharmacol Ther 2011, 90:582

Methods: Data and Analysis

‣ A three-step approach: learning, confirming, predicting

	CYP2C19 substrates				
	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5
*1*2		Validation			Learning
*2*2	Validation		Learning	Learning	
*17*17		Learning		Validation	
*1*17			Learning	Validation	

■ Learning data

■ Validation data

☐ Unknown data, to be predicted

Methods: Data and Analysis

▸ For **drug interaction** data

  ▸ Similar three-step approach based of PK interaction studies

  ▸ **CR values fixed** at their point estimates from the previous analysis

▸ Goodness-of-fit and predictive performance

  ▸ Proportion of predicted AUC ratio out of 50-200% range of observed value ≤ 10%

  ▸ Mean error and mean absolute error of prediction of AUC ratio

▸ Model extrapolation

  ▸ Predicted AUC ratios for unpublished CYP2C19 substrate/genotype and substrate/inhibitor pairs

▸

Methods: Bayesian Modeling

‣ For each substrate/genotype pair, each variable (AUC ratio, CR, FA) was considered as a random variable

$$R_{AUC(i,j)} = \frac{1}{1 - CR_{CYP2C19(i)} \cdot (1 - FA_j)}$$

$R_{AUC} \sim N (\mu_{AUC}, tau_{AUC})$ $\quad$ Logit(CR) $\sim N (\mu_{CR}, tau_{CR})$ $\quad$ Logit(FA) $\sim N (\mu_{FA}, tau_{FA})$

‣ The initial estimates of CRs and FAs and the mean observed AUC ratios were used as means of the prior distributions μ

‣ Moderatly informative prior gamma distributions were set for the precisions tau

‣ Posterior distributions of R_{AUC}, CRs and FAs were calculated by MCMC in Winbugs 1.4

‣ Convergence and shape of posterior distributions were examined

‣ For **DDI**, same approach, except **fixed CRs**

Results: CYP2C19 Gene Polymorphism

▸ 99 AUC ratios were available from 42 studies:

▸ 25 CYP2C19 oral substrate drugs

▸ 5 genotypes: *1*2 (IM) , *2*2 (PM), *17*17 (UM), *1*17, *2*17

▸ Reference genotype: *1*1 (EM)

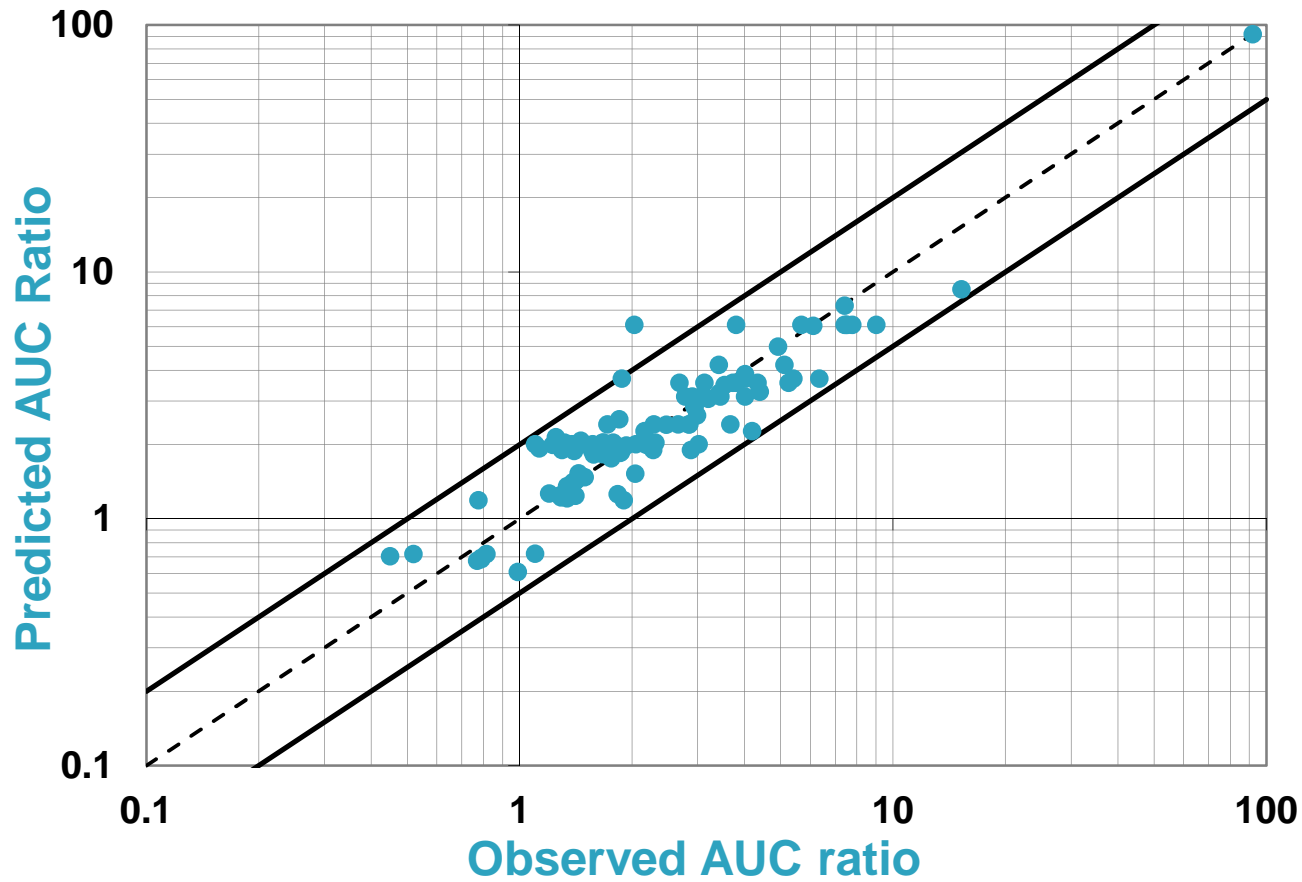**Step 2: External validation**
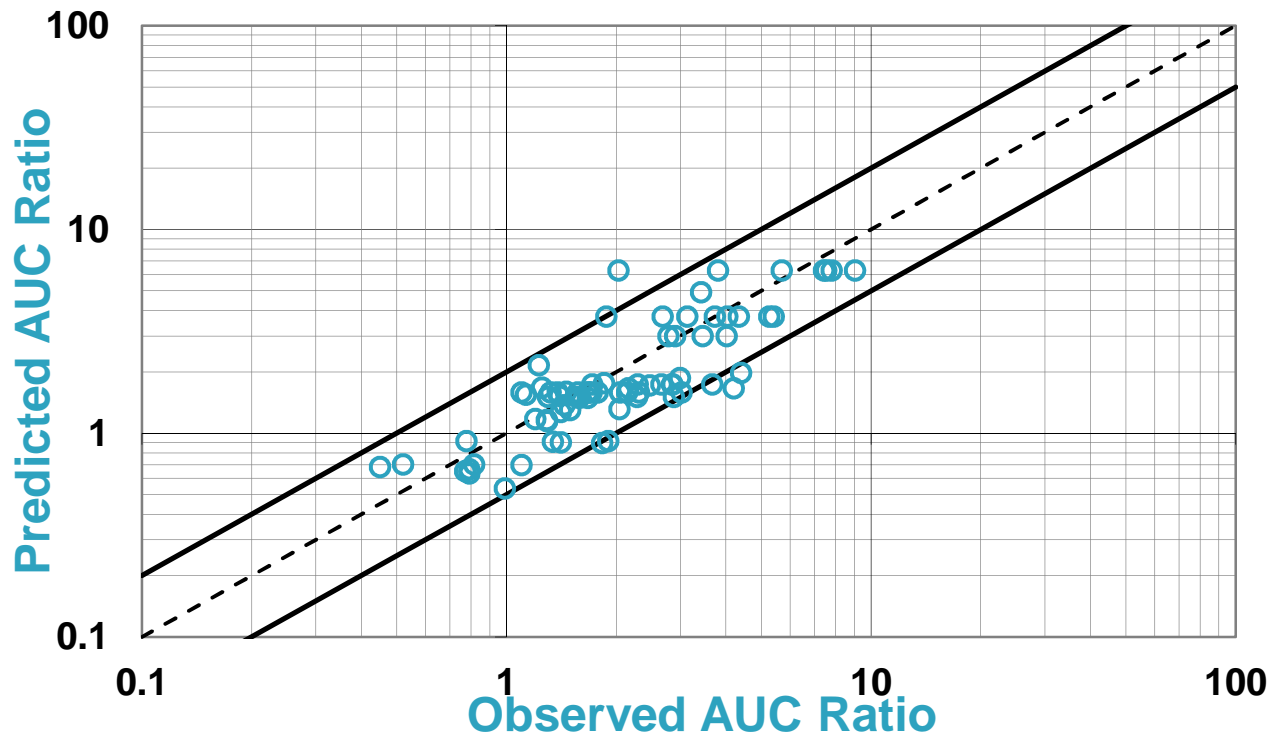
N = 75 AUC ratios

ME = -0.27
MAE = 0.72

5 outliers (6.7%)

Results: CYP2C19 Gene Polymorphism

Step 3: Final Estimation

N = 99 AUC ratios

ME = -0.15
MAE = 0.62

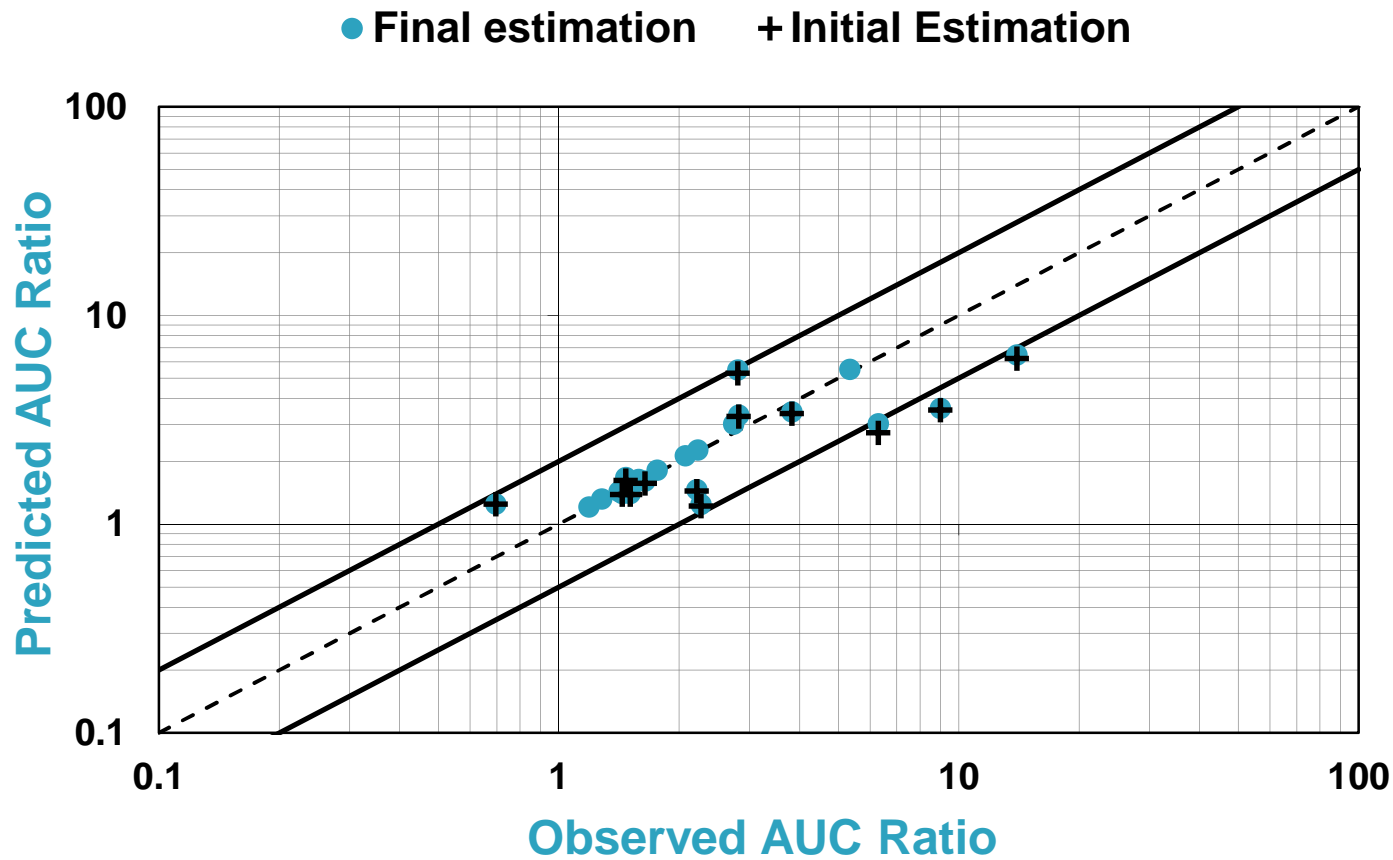1 outlier (1%)

Results: CYP2C19 Gene Polymorphism

Drug	CR	90% CI	Drug	CR	90% CI
Mephobarbital R	0.99	0.99-1.0	Pantoprazole	0.80	0.76-0.83
Proguanil	0.89	0.87-0.90	Lansoprazole R	0.74	0.68-0.79
Lansoprazole S	0.87	0.85-0.88	Voriconazole	0.68	0.60-0.74
Omeprazole	0.84	0.82-0.86	Escitalopram	0.45	0.33-0.57
Diazepam	0.84	0.81-0.86	Amitriptyline	0.28	0.18-0.40

Genotype	Frequency in Caucasians	Phenotype	FA	90% CI
*2*2	2.8%	PM	0.005	0.002-0.008
*1*2	16.4%	IM	0.30	0.25-0.36
*2*17	3.2%	Unknown	0.80	0.50-1.19
*1*17	22.8%	EM	1.59	1.24-1.85
*17*17	2.8%	UM	2.03	1.28-2.62

Results: CYP2C19-mediated DDI

▸ 22 AUC ratios from 18 studies (10 inhibitors)

● Final estimation   + Initial Estimation

Initial estimation (step 2)
N=13
ME = -1.2
MAE = 1.76

Final estimation (step 3)
N=22
ME = -0.62
MAE = 1.05

3 outliers (13.6%)

▶

Results: CYP2C19-mediated DDI

| Inhibitor	Daily dose (mg)	IR	90% CI
Fluvoxamine	50 – 150	0.98	0.95-0.99
Fluconazole	100 – 400	0.78	0.62-0.90
Voriconazole	400 – 800	0.64	0.43-0.82
Moclobemide	300	0.61	0.39-0.80
Ticlopidine	300	0.51	0.29-0.72
Fluoxetine	60	0.44	0.24-0.66
Omeprazole	40 - 80	0.43	0.24-0.64
Clopidogrel	75	0.28	0.13-0.48
Pantoprazole	80	0.26	0.12-0.45

Results: Extrapolation

▸ The model provides predictions of the AUC ratio for all possible substrate/ genotype (n=125) pairs, including rare genotypes

● PM *2*2   ■ UM *17*17

CYP2C19 substrates ranked by Contribution Ratio (CR) values
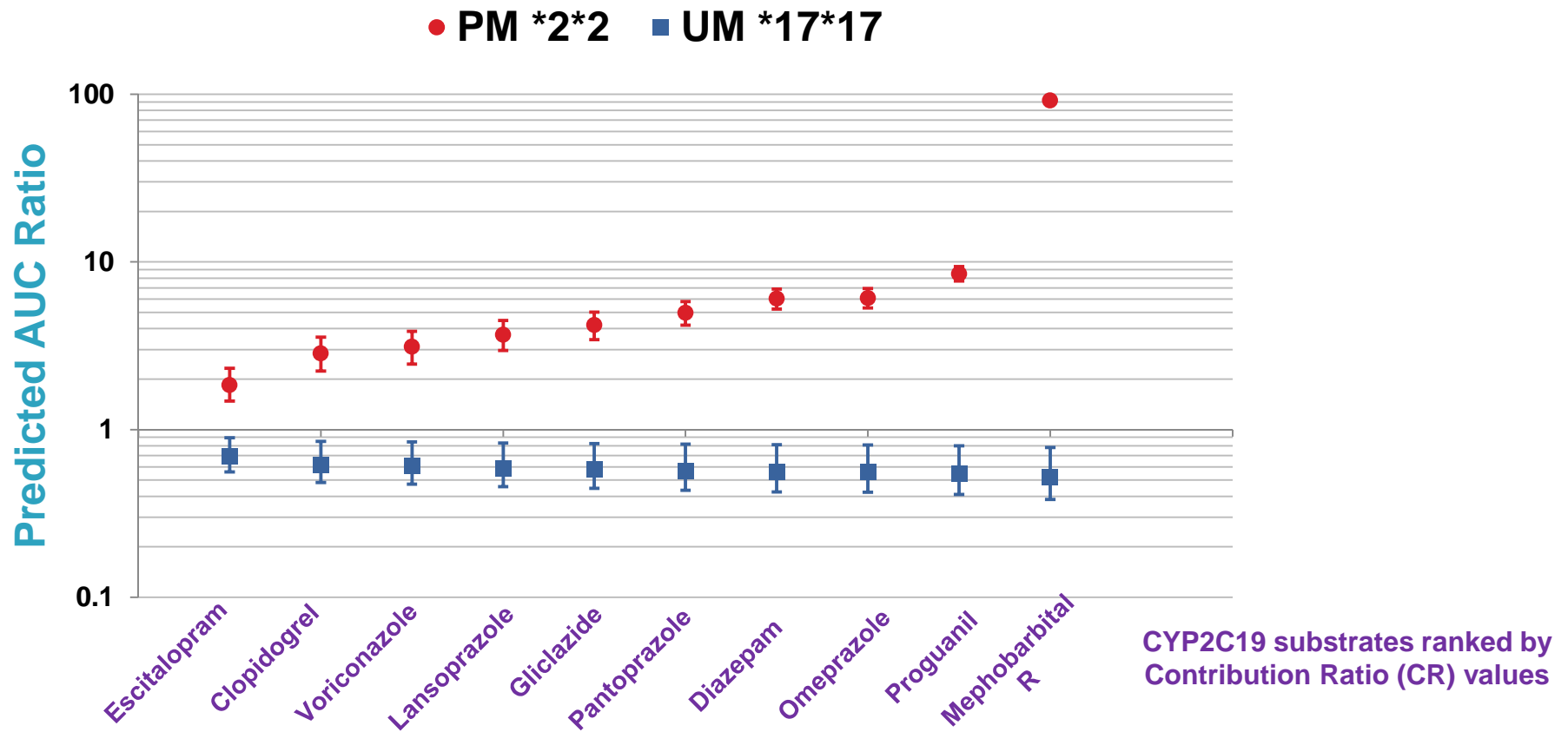
Results: Extrapolation
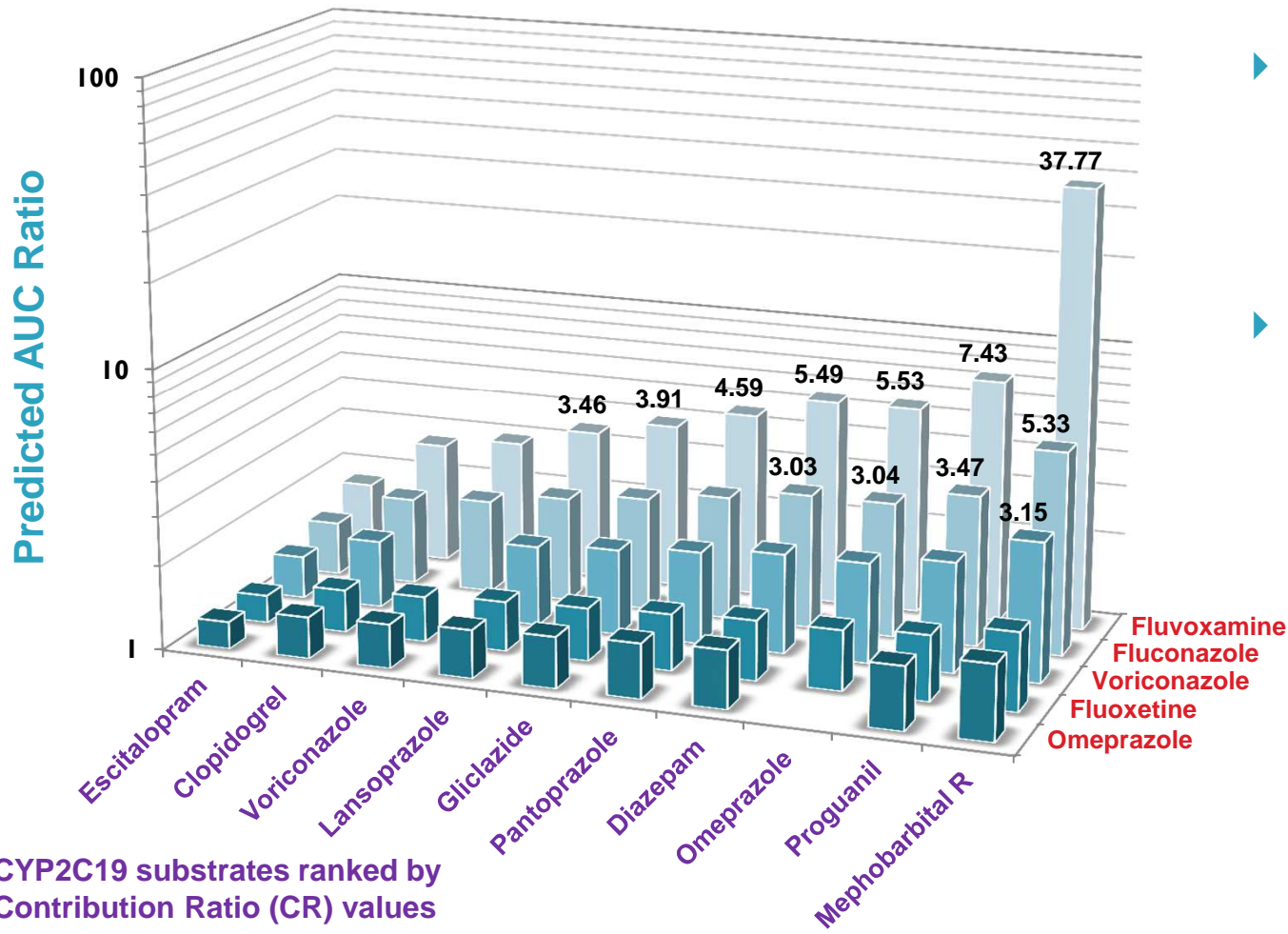
- Predictions of the AUC ratio available for a number of unpublished cases
- DDI with potential clinical relevance may be identified

Discussion

‣ In the past, this *in vivo* quantitative approach has been applied to DDI and gene polymorphism separately (CYP3A4, CYP2D6), with good predictive performance (Ohno, Tod)

‣ Sequential unified approach for CYP2C19

‣ Limitations of the study
  ‣ Few published data on rare genotypes *1*17 and *2*17
  ‣ Few published data on DDI

‣ Limitations of the approach
  ‣ One cytochrome pathway (at a time)
  ‣ Oral drugs
  ‣ Linear pharmacokinetics
  ‣ Competitive inhibition
  ‣ Average prediction of AUC ratio
  ‣ Prediction of DDI in EM only

‣ *Ohno et al. Clin Pharmacokinet 2007,46:681 & Clin Pharmacokinet 2008,47:649*
Tod et al. Clin Pharmacol Ther 2011, 90:582 & Clin Pharmacokinet 2011, 50:519

Discussion

- Proof-of-concept of the FDA statement
    - Information from CYP genetic subgroups may be used to predict drug interactions (and vice-versa)
    - Contribution ratio: common parameter in both equations

- Implications for routine patient care
    - Prediction of AUC changes in hundreds of clinical situations
    - Predicted AUC ratios may be used by clinicians to adjust the dose regimens of CYP substrate drugs in clinically relevant situations

- Implications for new drug development
    - The contribution ratio is an informative parameter to be determined
    - Pre-clinical screening of DDI and gene polymorphism effect

- Future developments
    - Prediction of DDI in CYP mutants PM or UM