Use of a Cocktail to Reduce the Need for Drug Interaction Studies During Drug Development

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Goals and Objectives

- Review the "cocktail" approach discussing
  - Development
  - Validation
  - Biomarkers and probes
- Show data on use of the cocktail for drug interaction screening

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So what is a cocktail?

- Cocktail: A mixture
- In DDI studies, a mixture of drugs given simultaneously (probes)
- Biomarkers are measured to determine the constitutive activity of DMEs and then again with the test drug to determine a potential DDI

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Assessment of DDI's: Old vs. New Approach

- Formerly needed individual DDI studies (8-10 studies)
- Cocktail approach has been endorsed by PhRMA and FDA (per guidance)
- If no cocktail interaction seen, no additional DDI studies on the effect of study drug on other drugs is needed
- Many cocktails published, few validated

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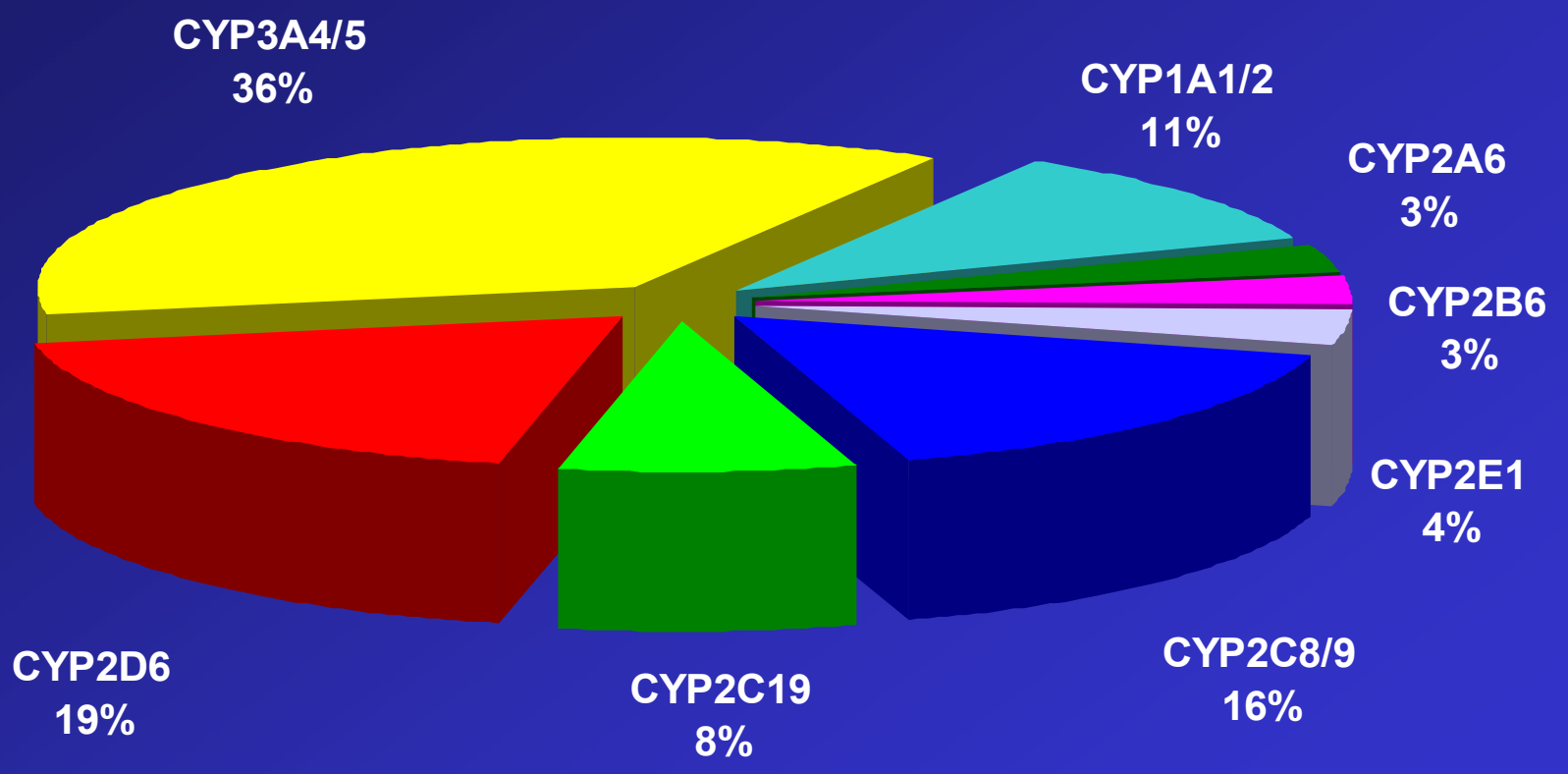
Proportion of Drugs Metabolized by CYP Enzymes



ADM Kashuba

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Do *in vitro* models predict *in vivo* DDIs?

- Yes
  - Saquinavir and ritonavir
  - Terfenadine and macrolides
- No
  - Alprazolam and ritonavir
  - Nevirapine and ketonazole

Bottom line: *In vivo* studies are essential

Davit et al. JCP 1999;39:899-910

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Issues with Cocktail Approach

Use of validated cocktails

- ***In vitro*, drug specific for DME under study**
- **Use of commercially available drugs**
- **Use of safe agents or agents that can be made safer**
- **Screen for drug assay interference with test drug**
- **Validate cocktail by giving separate and combo probes**
- **Use of validated biomarkers**

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What constitutes a valid probe?

- *In vitro*, probe is primarily metabolized by one CYP to a defined metabolite
- *In vivo*, biomarker for probe changes from baseline to induction and inhibition
- Stability of probe in urine or plasma (biomarker doesn't change over time)

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Probe Comparison: Accepted *in vivo* probe versus proposed probe

Simvastatin vs. Midazolam as a CYP3A Probe

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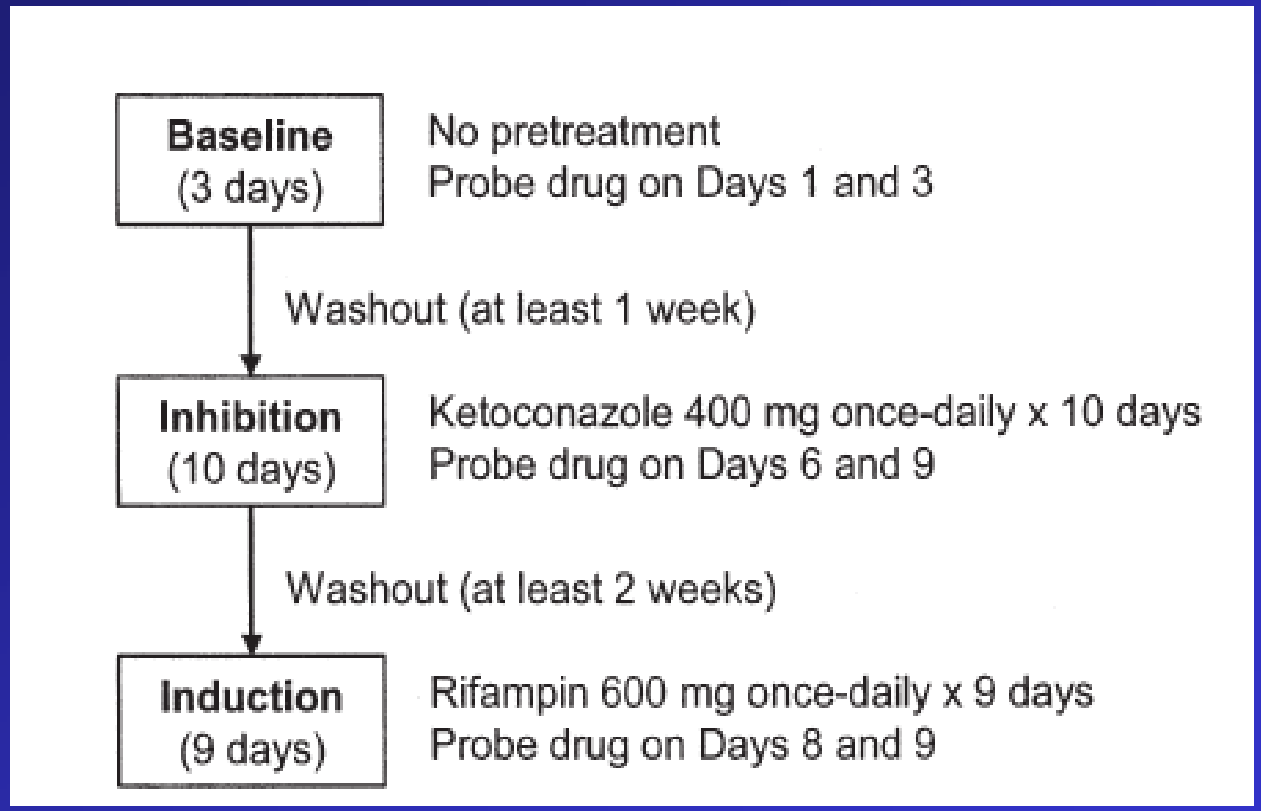
Comparison of Midazolam vs. Simvastatin as CYP3A probe



Chung et al, CP&T 2006;79:350-361

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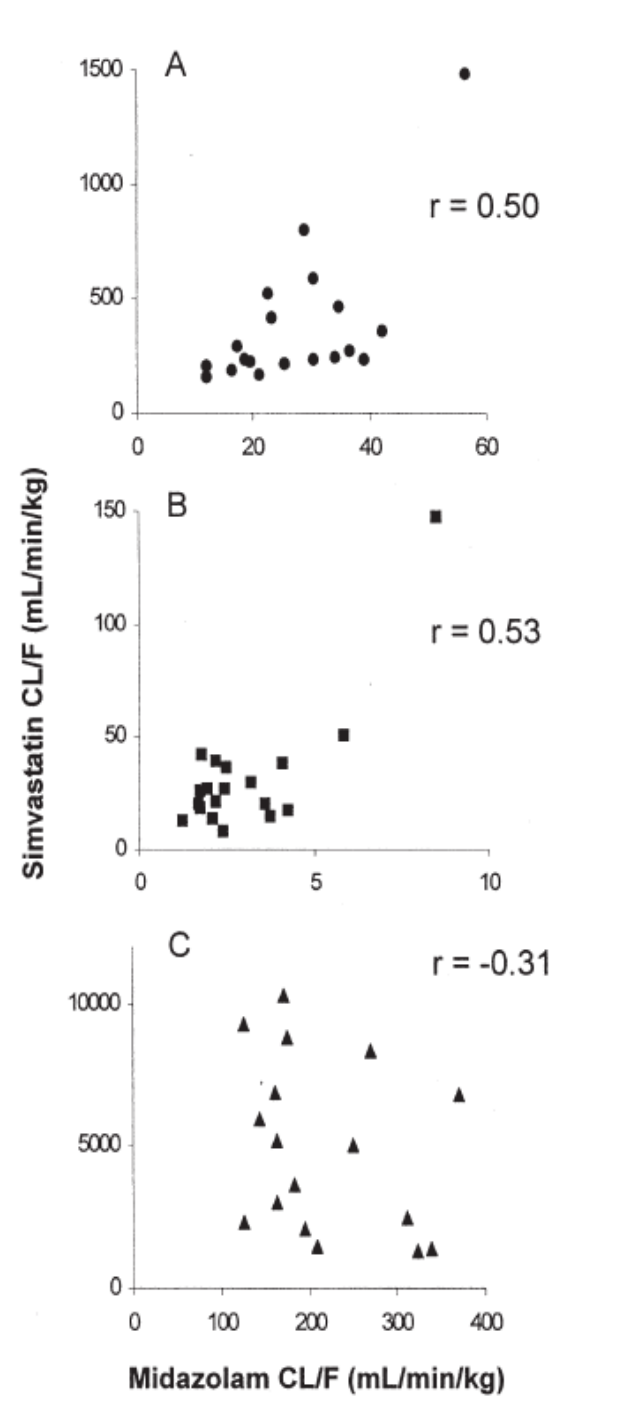

Baseline

Inhibition

Induction

Chung et al, CP&T 2006;79:350-361

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Drug Assay Interference: The Maribivar Story

- Maribivar, anti-CMV oral agent, no effect on CYP3A activity noted *in vitro*
- Cooperstown 5+1 study baseline and after 7 days of maribivar (AAC 2006;50:1130-1135)
- Midazolam PK suggested >75% increase in CL/F
  - Data suggested significant reduction in AUC of MDZ
  - Investigation showed that maribivar suppressed the internal standard for the LC-MS-MS assay, alprazolam
  - Midazolam assay using another LC-MS-MS method (with flurazepam as internal standard) gave results showing no CYP3A effect
- Bottom line: Need to screen test drug or herbal for assay interference

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Validated and Non-validated Biomarkers and Probes

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What are invalid biomarkers or probes?

- Midazolam (CYP3A), 1OHMDZ/MDZ single point ratio
  - For IV Disproven: JCP 2002;42:1079-1082
  - For PO Disproven: JCP 2006;46:229-234
- Erythromycin breath test (CYP3A)
  - Disoproven: Also a PGP substrate (Pharmacogenetics 2000;10:187-216)
- Simvastatin (CYP3A)
  - Disproven, no correlation with MDZ: CP&T 2006;79:350-361

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What are invalid biomarkers or probes?

- Dapsone: (CYP3A)
  - Disproven: Not a CYP3A substrate (Pharmacogenetics 2000;10:187-216
- B-OH Cortisol: (CYP3A)
  - Disproven, no correlation with MDZ: BJCP June 2006
- Diclofenac: (CYP2C9)
  - Variable absorption: EJCP 2000;56:793
- Mephenytoin: (CYP2C19)
  - S/R urine ratios change with storage: Pharmacogenetics 2000;10:187-216

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Problems with Cocktails

- **Pittsburgh: Use of mephenytoin and debrisoquin. Has added oral midazolam and substituted omeprazole however, no validation published (CP&T 1997;62:365-376)**
- **GW: Uses mephenytoin and debrisoquin (Rap Com Mass Spec 1999;13:2305-2319)**
- **Hunan: Uses mephenytoin and single 1OHMDZ/MDZ ratios [not a valid biomarker] (CP&T 2001;70:455-461**
- **AZ: Uses debrisoquin (BJCP 2003;57:162-169)**
- **Karolinska: Uses quinine (not a validated probe), debrisoquin, cannot give other drugs with debrisoquin [losartan, quinine, caffeine, omeprazole] (CP&T 2003;73:517-528)**

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Problems with Cocktails

- **Quebec: No valid CYP3A probe [dapsone used, this is CYP2E1 probe] (BJCP 2004;58:288-297**
- **IU: No CYP2C19 probe, no validation published (CP&T 2001;70:317-326)**
- **German: Uses mephenytoin, no validation published (DMD 2005;33:1859-1866)**
- **Yin (HK): Used debrisoquine, no real validation, incorrect biomarkers used (Rap Comm Mass Spec 2004;18:2921-2933)**
- **Merck German: Not validated, uses diclofenac and mephenytoin (EJCP 2006)**

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The Cooperstown 5+1 Cocktail

CYP3A*	CYP2D6	CYP1A2, NAT-2, XO	CYP2C19	CYP2C9
Midazolam 0.075 mg/kg by mouth	Dextromethorphan 30 mg orally	Caffeine 2 mg/kg orally	Omeprazole 40 mg orally	Warfarin 10 mg + vitamin K 10 mg orally
Blood samples at 0, 5, 30, 60, 90, 120, 180, 240 and 360 minutes (plasma)	12 hour urine or plasma AUC for paraxanthine/caffeine. Serum AUC for DM/DX or urinary DM/DX ratio (12 hr)		Blood sample at 2 hours (plasma)	Blood samples at 3, 6, 12, 24, 36, 48, 72, 96 hours (plasma)

*or Midazolam 0.025 mg/kg IV with blood samples at 0, 5, 30, 60, 120, 240, 360 min

Chainuvati S et al. Clin Pharmacol Ther 2003;74:437-447.

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Biomarkers for Cooperstown 5+1 Cocktail

- **Caffeine (CYP1A2): Urine 1U+1X+AFMU/17U or plasma paraxanthine (17X)/caffeine validated**
- **DM (CYP2D6): Urinary DX/DM or plasma DM CL or AUC DM/DX validated**
- **Warfarin (CYP2C9): S-warfarin AUC validated**

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Biomarkers for Cooperstown 5+1 Cocktail

- Omeprazole (CYP2C19): OMP/5-OH OMP plasma concentration (consider full AUC curve)
- Midazolam (CYP3A isozymes): MDZ plasma clearance

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Cocktail thoughts

- **Need to study genotypic EMs to optimize interaction**
- **Probe sampling needs to be adjusted if *in vitro* data indicates there is CYP inhibition, induction or activation**
- **BE testing required, not significance testing**

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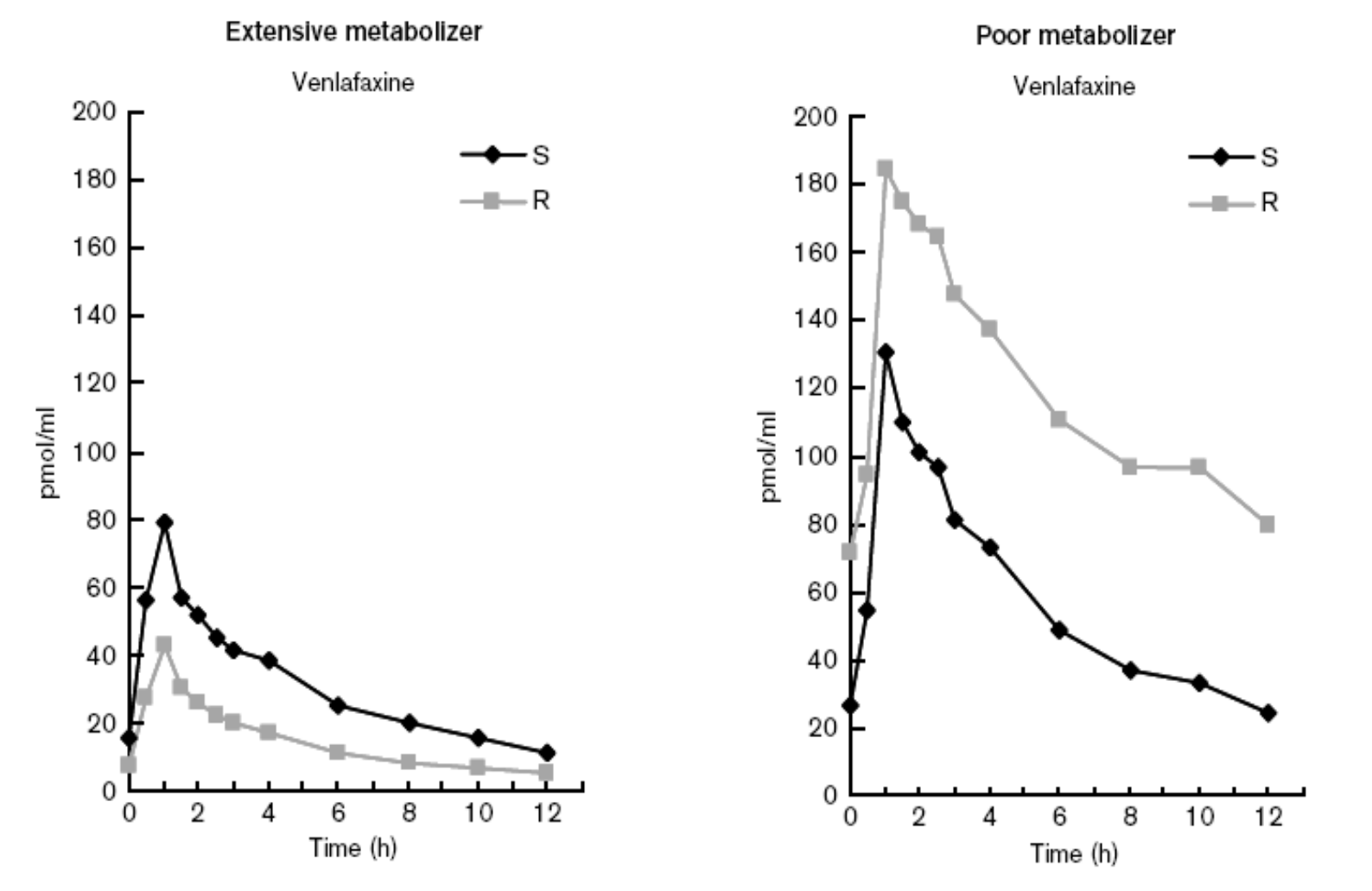
Use of EMs for DDI studies: Venlafaxine and CYP2D6



Eap et al, Pharmacogenetics 2003;13:39-47

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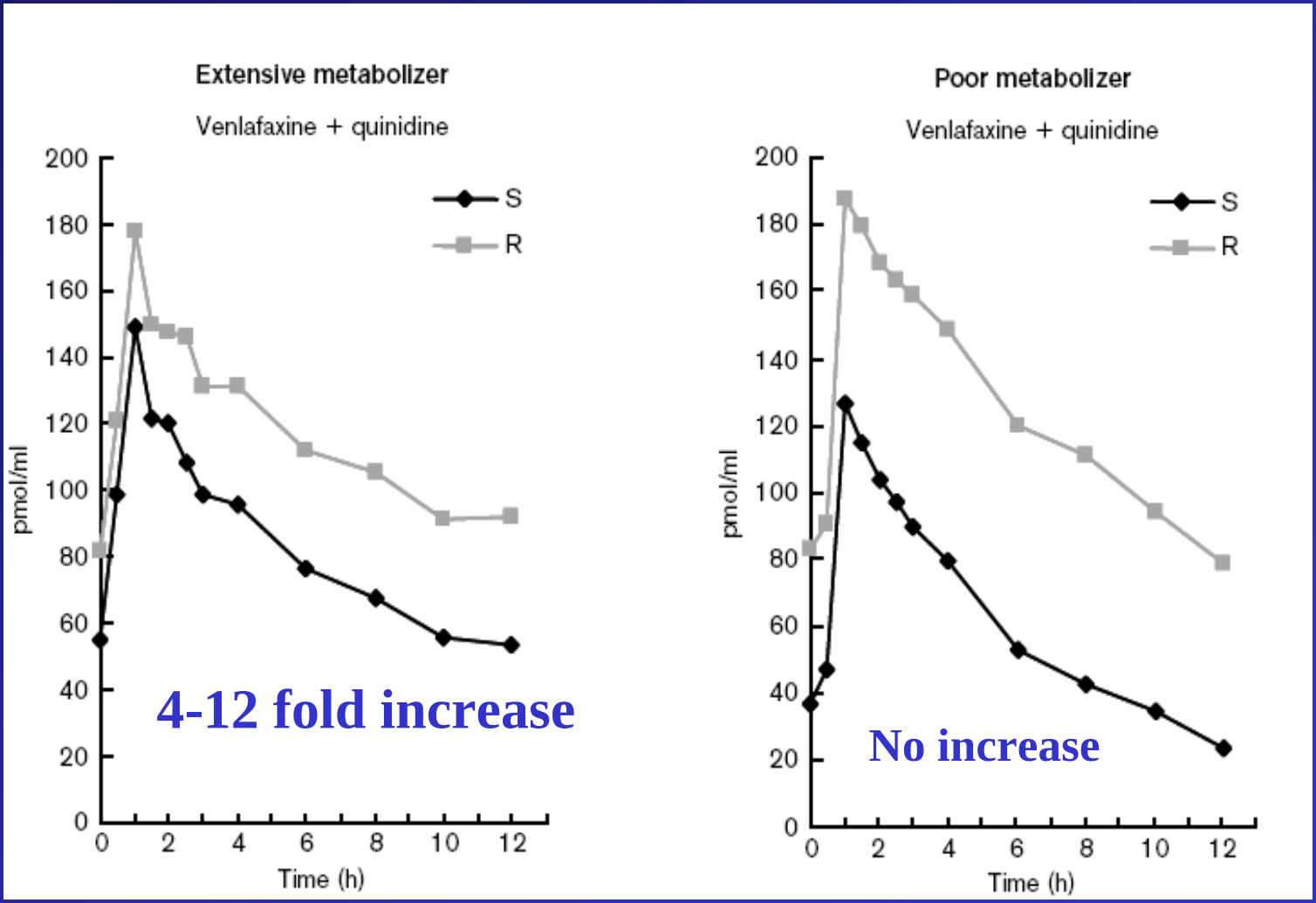
Use of EMs vs. PMs for DDI studies: Venlafaxine + Quinidine and CYP2D6



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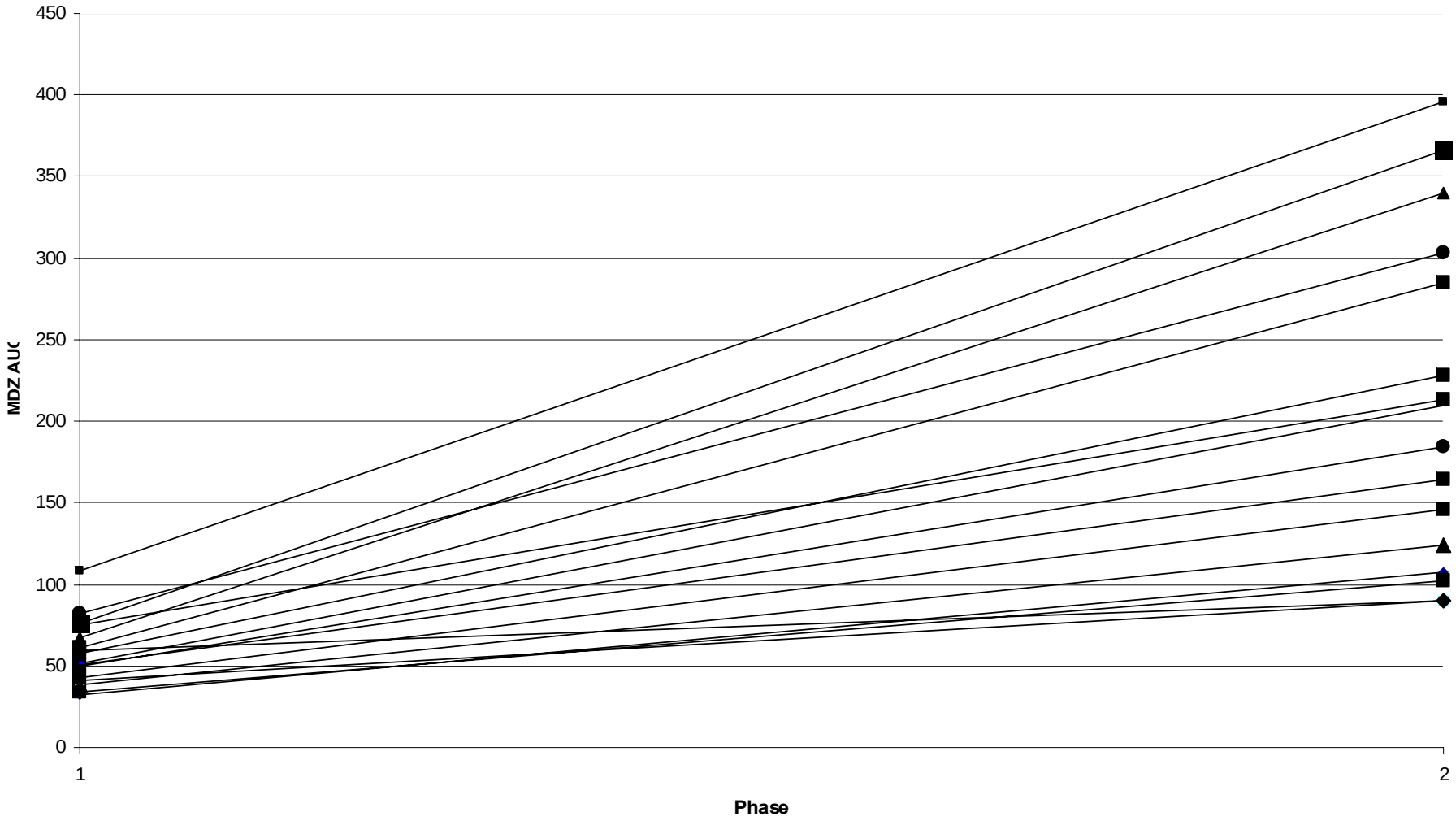
Range of Telithromycin effect on Midazolam



Range is 51-405% decreased clearance

LEE ICAAC 2005

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Examples of drug interaction studies using the Cooperstown 5+1 cocktail

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Maribavir

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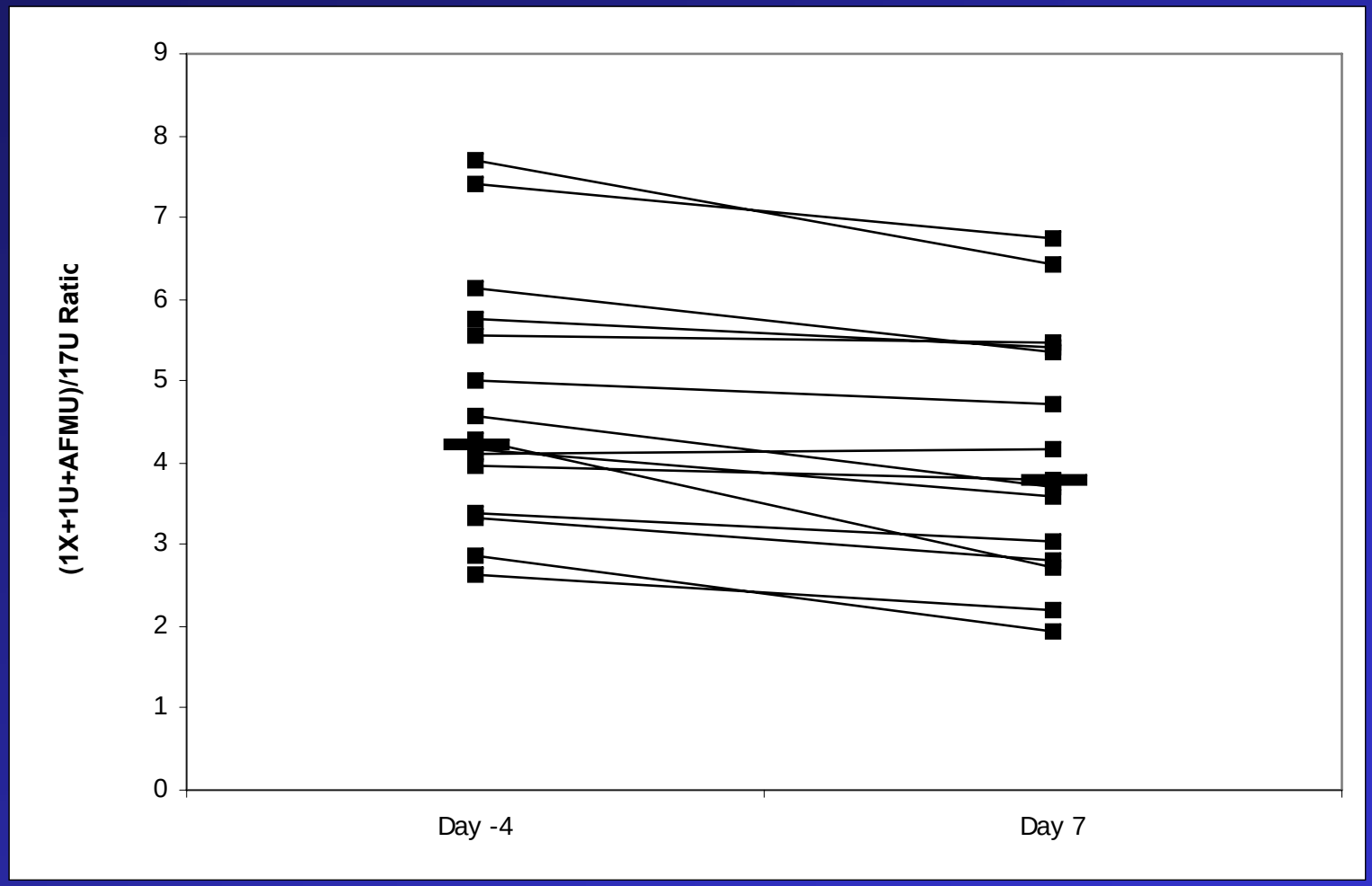
Assessment of CYP1A2 Activity with Caffeine



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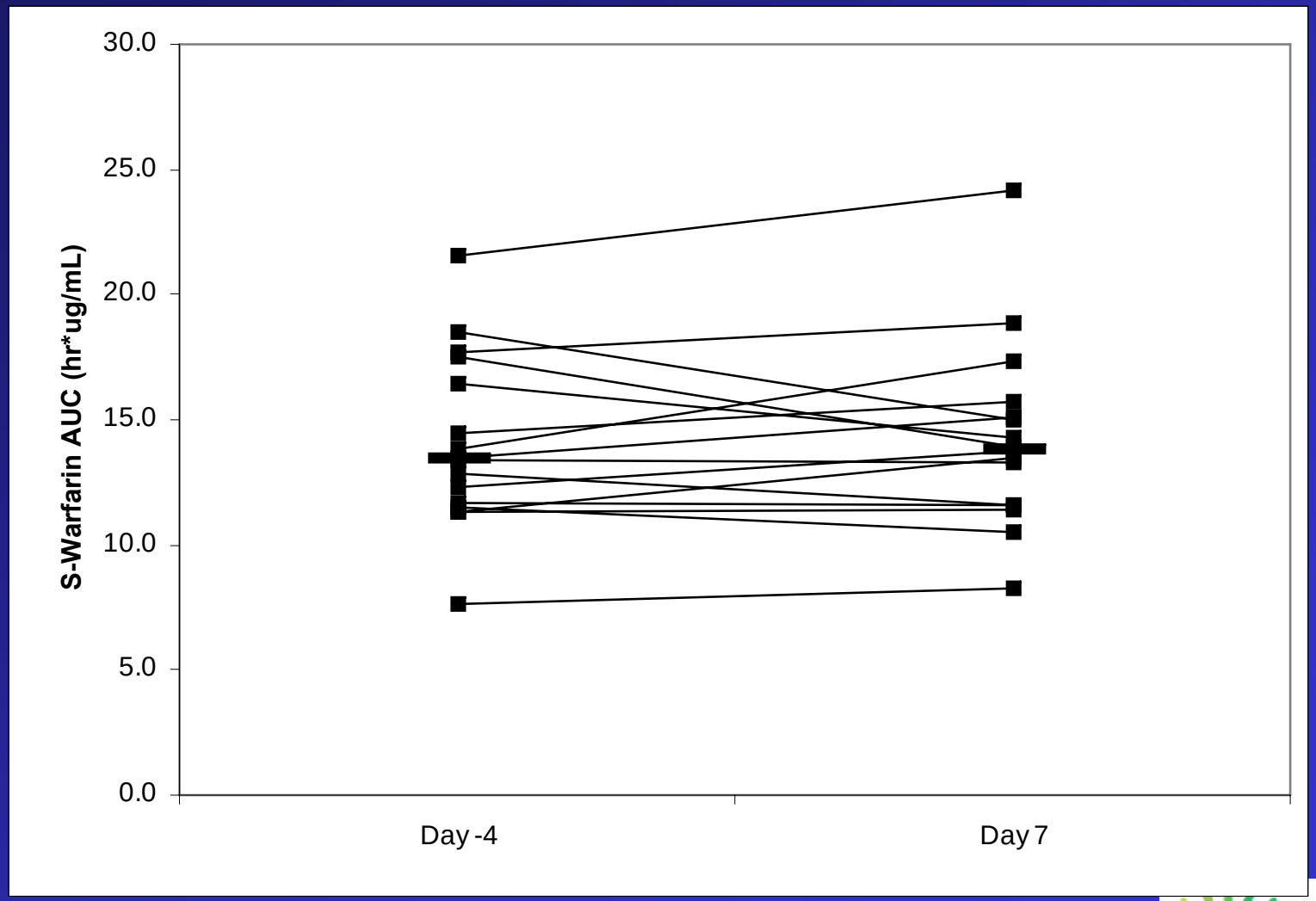
Assessment of CYP2C9 Activity with Warfarin



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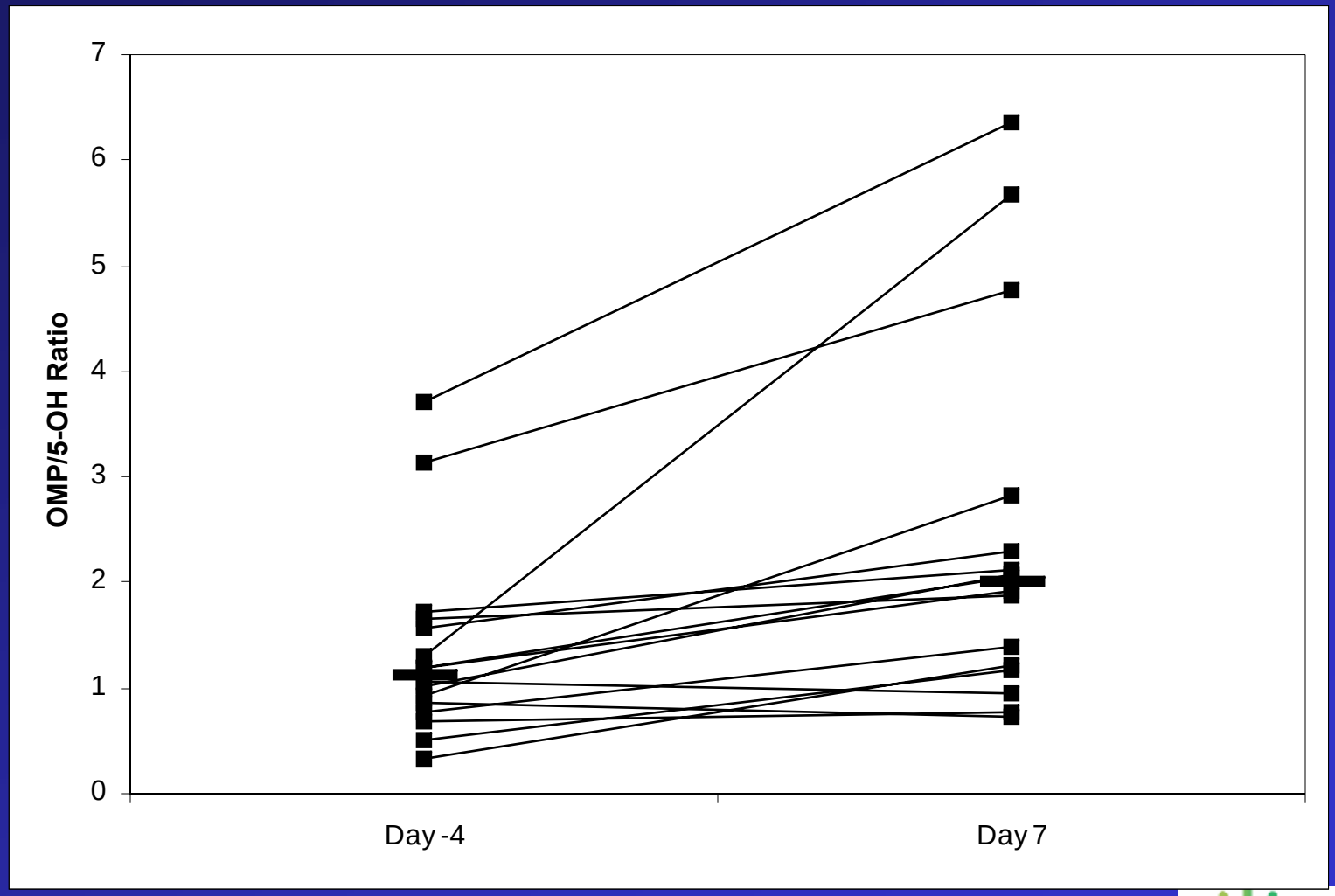
Assessment of CYP2C19 Activity with Omeprazole



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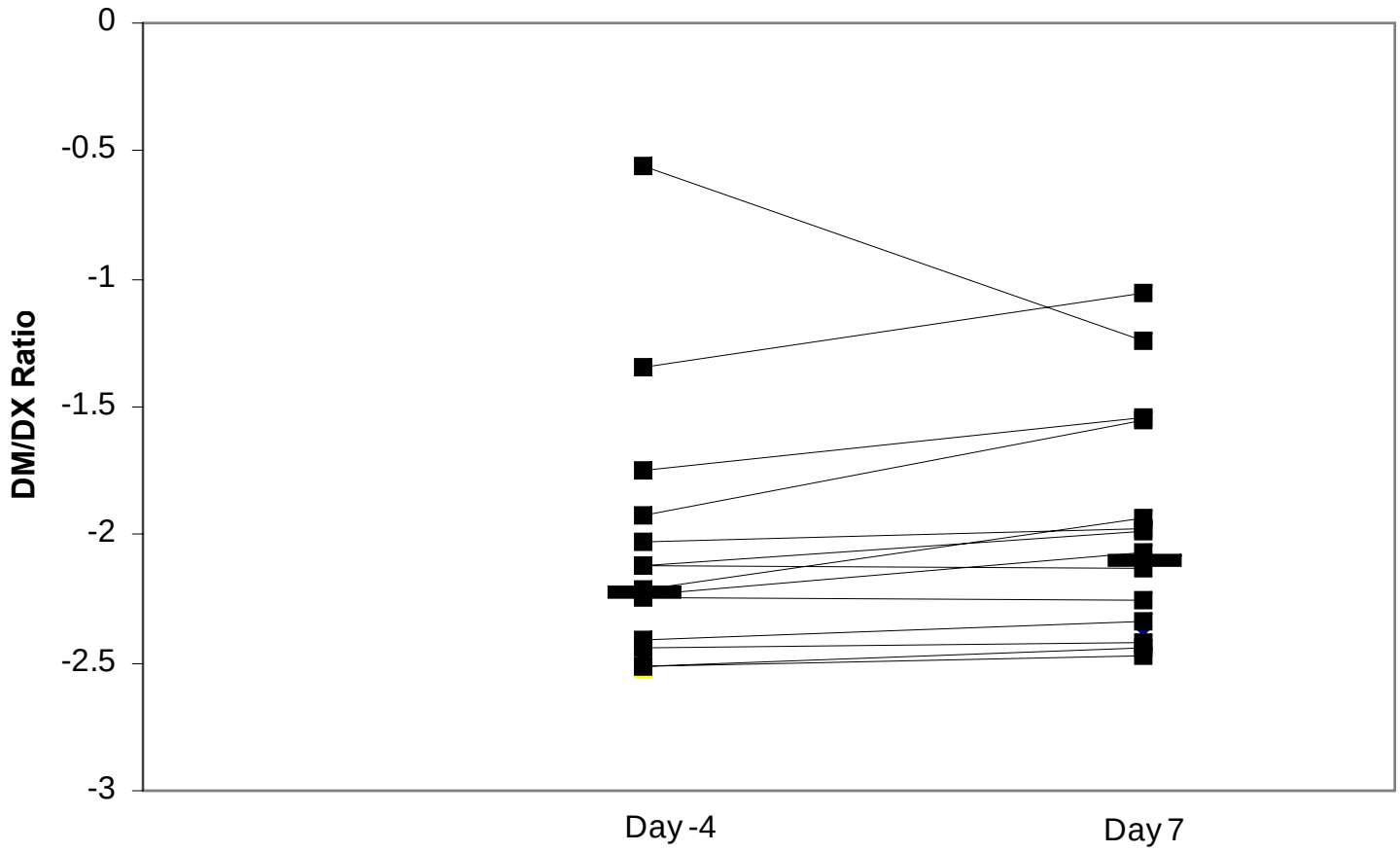
Assessment of CYP2D6 Activity with Dextromethorphan



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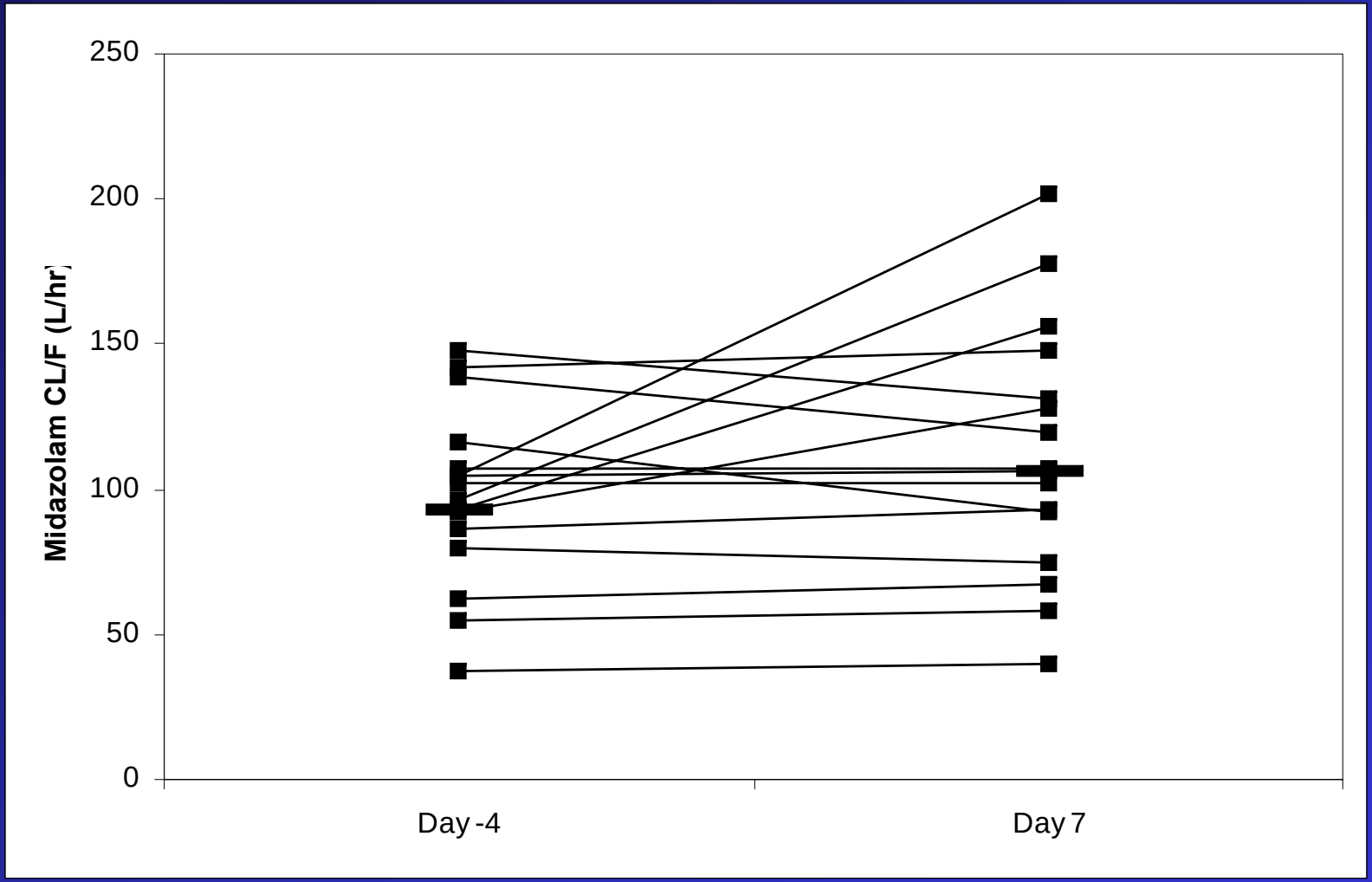
Assessment of CYP3A Activity with Midazolam



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Cocktail BE Testing for Maribavir

Enzyme	Parameter	N	LS-GMR (Day 7/Day -4)	90% CI
CYP1A2	(1X+1U+AFMU)/17U[1]	15	0.86	0.80 - 0.92
CYP2C9	S-warfarin $AUC_{0-\infty}$	16	1.01	0.95 - 1.07
CYP2C19	OMP/5-OH	16	1.71	1.50 - 1.92*
CYP2D6	DM/DX	16	1.18	0.94 - 1.41*
CYP3A	Midazolam CL/F	16	1.13	1.01 - 1.24

Ma et al. AAC April 2006

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Aplaviroc

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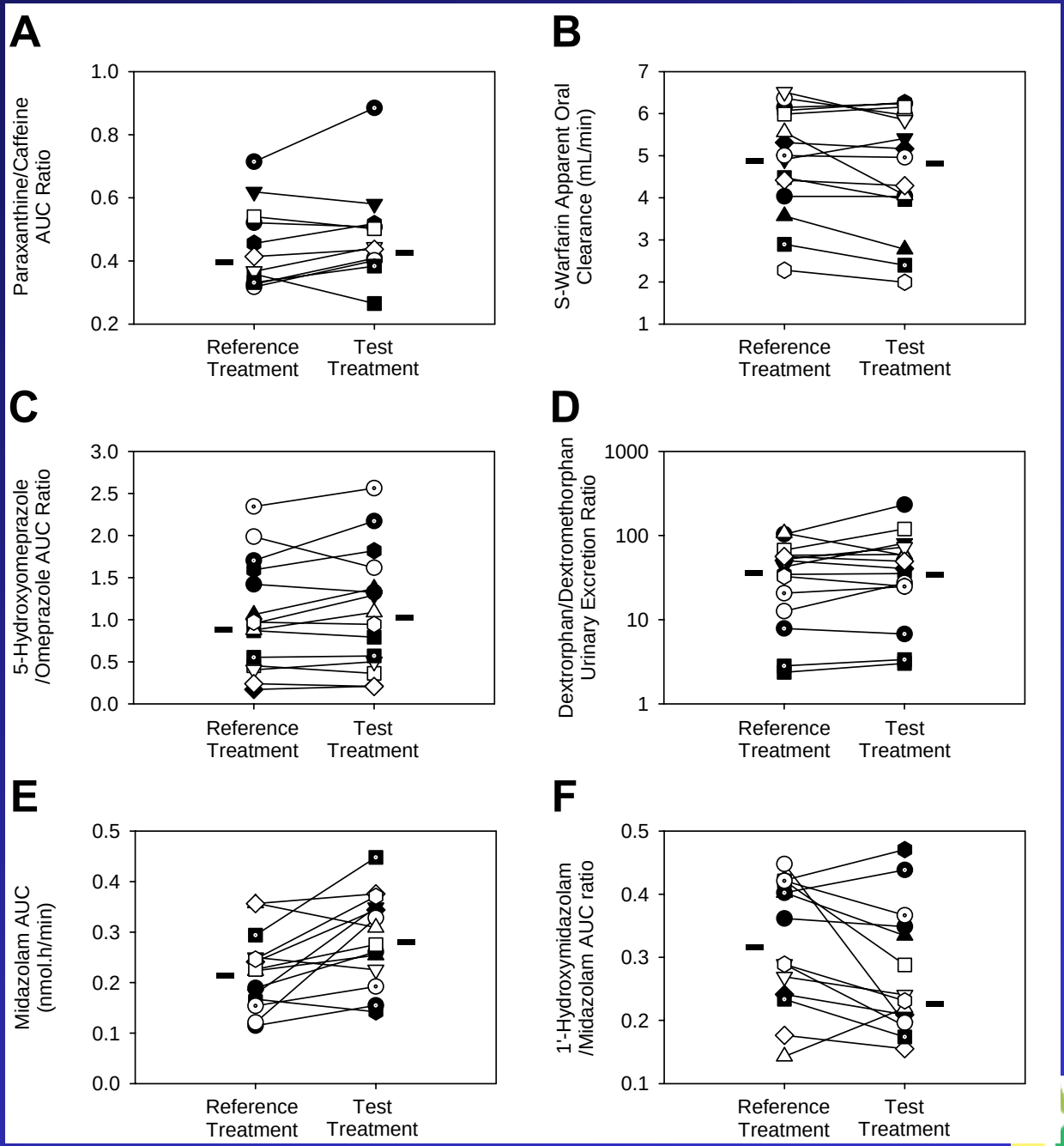
Aplaviroc



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Aplaviroc BE Analysis

CYP Isozyme(s)	Probe	Pharmacokinetic Parameter	Test/Reference Treatment GLS Ratio (90% CI), N
CYP1A2	Caffeine	Paraxanthine/caffeine plasma AUC_{0-12h} ratio	1.06 (0.97, 1.17), N = 11
CYP2C9	Warfarin	S-warfarin apparent oral clearance	0.93 (0.76, 1.15), N = 15
CYP2C19	Omeprazole	5-Hydroxyomeprazole/omeprazole plasma AUC_{0-10h} ratio	1.07 (0.98, 1.16), N = 15
CYP2D6	Dextromethorphan	Dextrorphan/dextromethorphan urinary excretion ratio (0-12 h)	1.17 (0.97, 1.42), N = 15
CYP3A	Midazolam	Midazolam $AUC_{0-\infty}$	1.30 (1.04, 1.63), N = 14
CYP3A	Midazolam	1'-Hydroxymidazolam/midazolam plasma $AUC_{0-\infty}$ ratio	0.86 (0.75, 0.98), N = 14

Johnson B et al. JCP May 2006

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Cocktails…what does the future hold?

- Addition of substances to measure transporter activity
  - PGP: Digoxin
  - OATP1B1: Pravastatin?
  - Phase II: Still a question
- Any additions to a cocktail will need to revalidate

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Use of Cocktails for DDI

- Cocktails can screen for DDIs for the most important CYPs
- Genetic controls (using subjects as their own controls) advantageous in DDI studies
- Studies in EMs for polymorphic enzymes can result in uncovering potential DDIs if they exist.
- Studies in PMs or IMs may result in underestimating DDIs

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Use of Cocktails for DDI

- For DMEs with wide intersubject variability, DDIs may give wide differences in clearance change
- Cost reduction substantial with cocktail study, one study versus numerous studies
- Even with cocktail study, ability to quantitate DDI for label is difficult
- Other factors such as exposure response relationships may determine severity of DDI…generally these are poorly worked out
- True prediction of extent of drug interactions remains elusive

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Questions and Comments

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