



A Model- and Systems-Based Approach to Efficacy and Safety Questions Related to Generic Substitution

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Background:

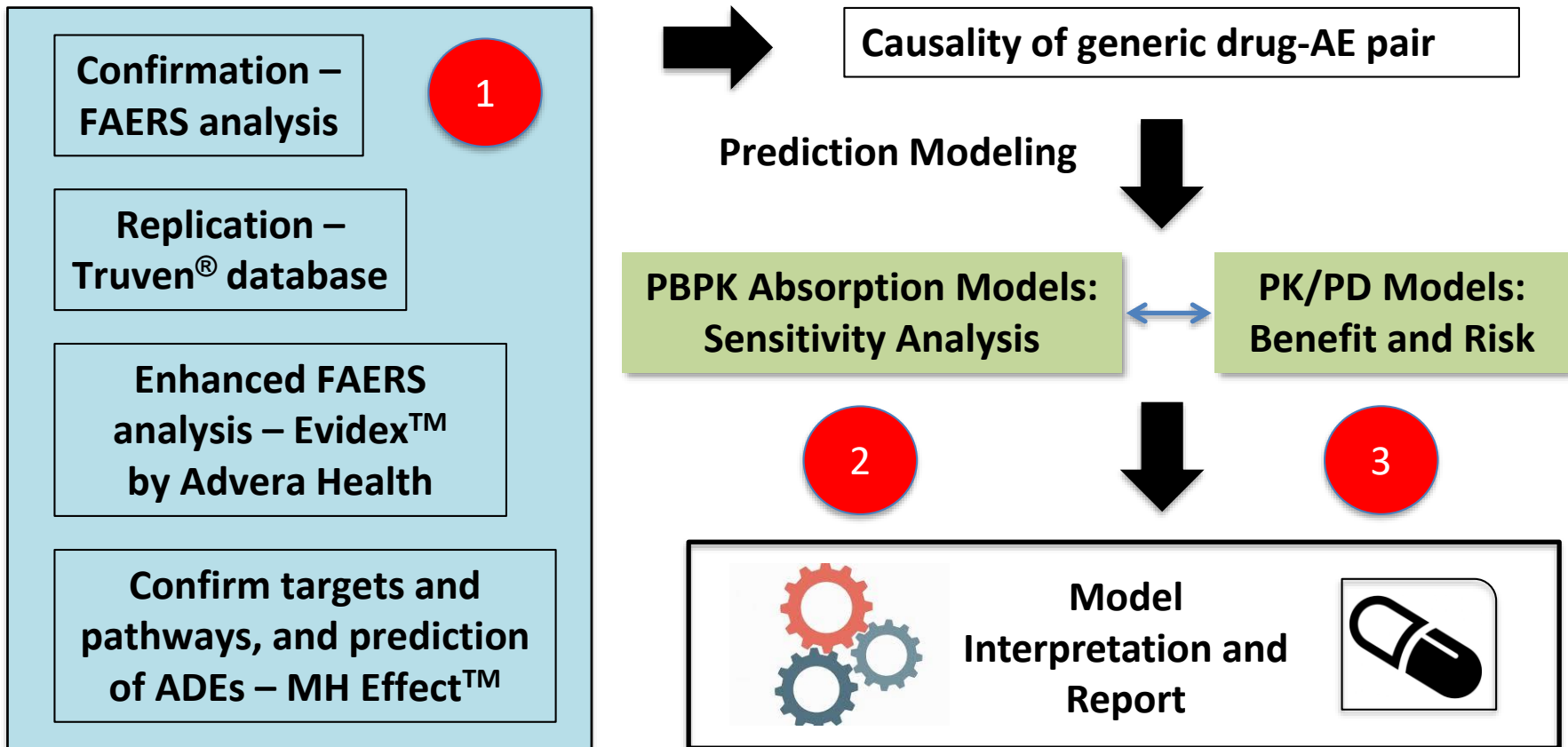
- ~88% of prescription drugs filled in the U.S. are **generic**
- ~\$1.68 Trillion of estimated cost savings for U.S. health system between 2005 and 2014
- U.S. FDA occasionally receives complaints about purported adverse events due to lack of efficacy or safety after switching from brand to generic
- Assessment of whether or not these complaints are real can be challenging

Research Strategy:

- To develop a quantitative and integrative approach that will separate post-marketing “**signals from noise**”
- If the “signal” is credible, develop a strategy using quantitative methods and modeling to provide insight into **causal mechanisms**

Analysis Workflow

ADE: FAERS, consumer complaints, www.peoplespharmacy.com, clinical studies, ISMP and other public databases



Drugs and Formulations Selected To Demonstrate a Wide Range of Applications

Case I: anti-epileptic drugs considers BCS classification that can have a significant effect on absorption. BCS class II (carbamazepine, lamotrigine and phenytoin) and BCS class III (gabapentin and levetiracetam)

Case II: metoprolol XL examines a complex CR formulation to predict PK and PD profiles from a PSA and differences in *in vitro* dissolution

Case III: anticoagulants that belong to the same therapeutic class (DOACs) that are not yet available as generics to gain a mechanistic understanding of potential bioequivalence

Signal Detection

- Formulation problems were reported within the first use of metoprolol XL and were public knowledge within 1-year of launch
- Hypotheses for detecting formulation issues:
 - **Generic uptake/market share** will be decreased
 - Patients will **discontinue** treatment and/or **switch back** to trade formulations at a higher rate
 - **Event rates** for indicated conditions will be **elevated** for generic vs. trade formulations
- To provide an active comparison:
 - **Amlodipine/Benazepril** was approved on same date and launched at about the same with **no known formulation issues**

Clinical Event Rates

		Rate Ratio Generic vs. Trade (METO)						
		MI	HF	Hypertension	Hypotension	Syncope	Angina	Tachycardia
ER Visits	Primary	2.06	1.31	1.18	1.33	1.43	1.50	1.29
	Secondary	2.42	1.20	1.31	1.22	1.39	1.49	1.21
Hospitalizations	Primary	1.00	1.00	1.08	0.92	0.99	1.22	1.12
	Secondary	1.11	1.08	1.44	1.25	0.95	1.39	1.12
		Rate Ratio Generic vs. Trade (AMLO)						
		MI	HF	Hypertension	Hypotension	Syncope	Angina	Tachycardia
ER Visits	Primary	0.86	0.77	0.68	0.84	0.85	1.07	0.91
	Secondary	0.95	0.83	0.82	0.82	0.86	0.95	0.88
Hospitalizations	Primary	0.98	0.78	0.56	1.11	1.03	0.52	0.98
	Secondary	0.95	0.90	0.93	1.02	1.09	0.89	0.93

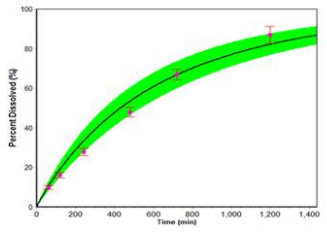
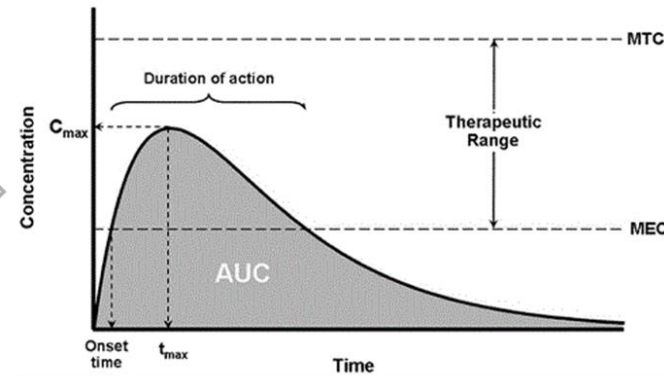
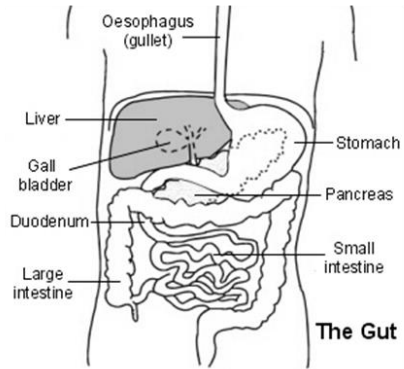
Physiologically-Based Absorption Modeling

Formulation

In vitro and *in silico* dissolution testing

In vivo dissolution and *in silico* absorption modeling

In silico bioequivalence testing

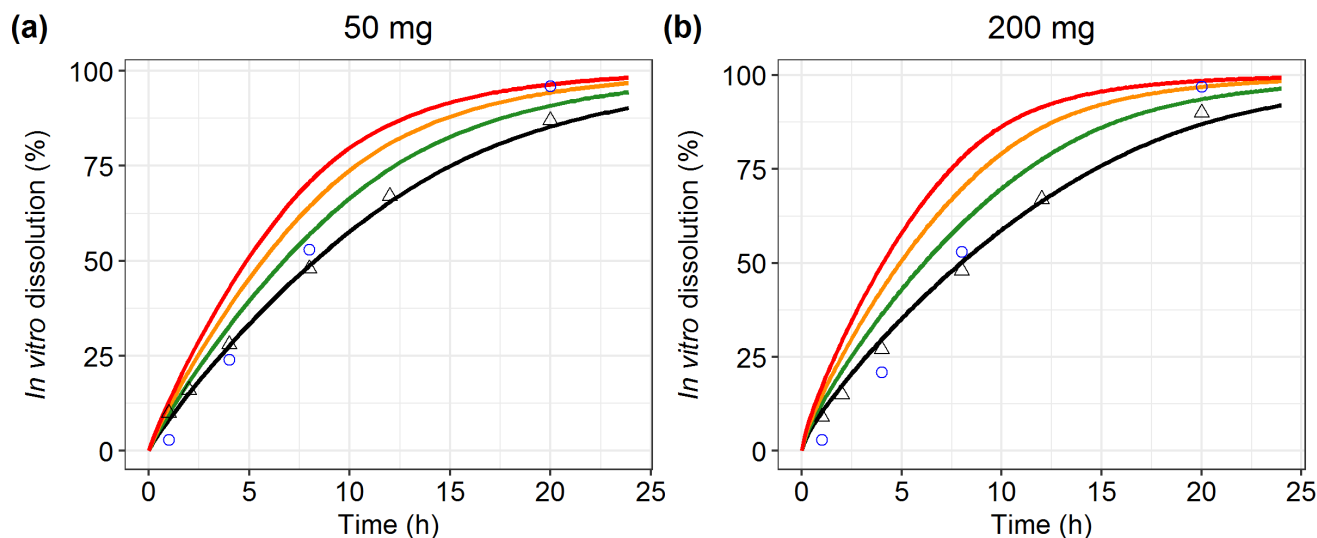


DDDPlus™

Advanced Compartment and Transit (ACAT) module in GastroPlus™

Prediction of *In Vitro* Dissolution Based on the Formulation's Composition & Manufacturing Conditions

In vitro Dissolution profiles



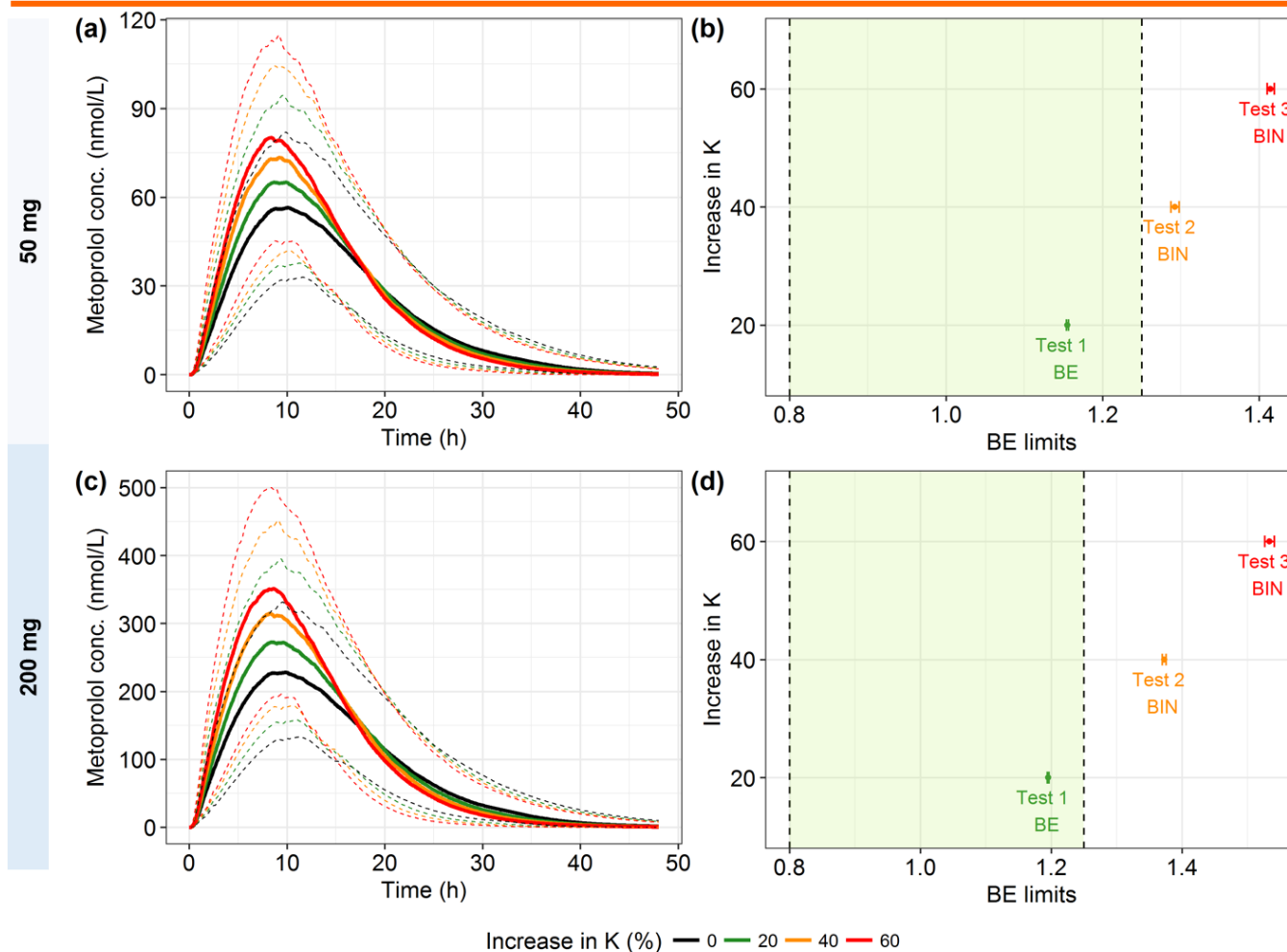
Similarity (F2) test

Increase in K (%) — 0 — 20 — 40 — 60 — Generic formulation (Wockhardt) — Toprol XL

Product (% increase in K, actual K value)	F2	
	Value	Conclusion
Reference (0%, K = 0.006)	n/a	n/a
Test 1 (20%, K = 0.0072)	57	similar
Test 2 (40%, K = 0.0084)	44	different
Test 3 (60%, K = 0.0096)	37	different

Product (% increase in K, actual K value)	F2	
	Value	Conclusion
Reference (0%, K = 0.018)	n/a	n/a
Test 1 (20%, K = 0.0216)	52	similar
Test 2 (40%, K = 0.0252)	40	different
Test 3 (60%, K = 0.0288)	33	different

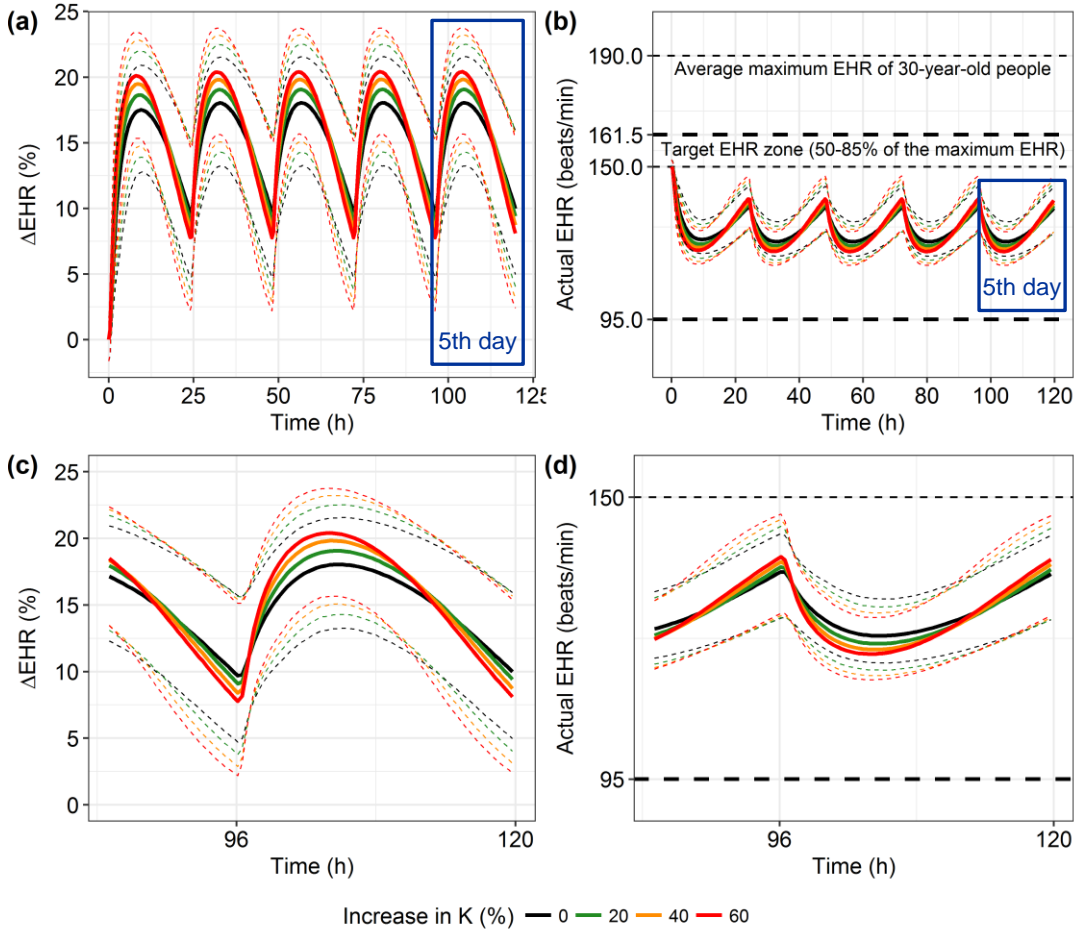
Effect of Drug Release on PK & Bioequivalence



K : drug release rate constant, The graphs in the left panel show the median (solid line), 5th and 95th percentiles (lower and upper dashed lines, respectively) of the concentration vs. time profiles (200 subjects). Bioequivalence (BE) was declared if a 90% confidence interval for the ratio of the geometric means of C_{max} and AUC falls within 80 to 125% (green shaded area). The graphs in the right panel shows the BE testing using the more sensible parameter C_{max} . BIN: bio-in-equivalence.

Effect of Drug Release on PD & Therapeutic Equivalence

PBPK/PD
200 mg

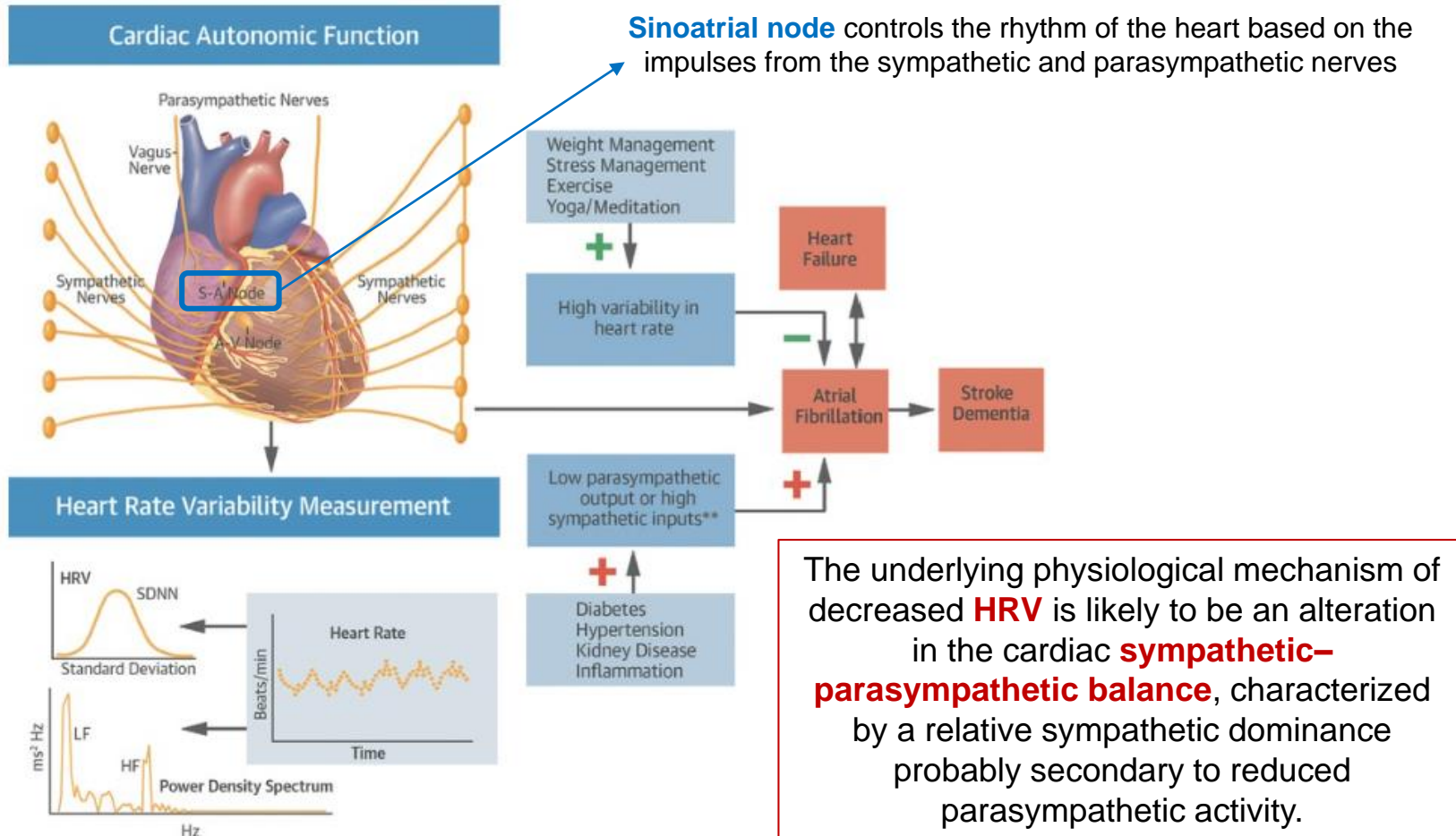


Zoom-in on the 5th day

K: drug release rate constant, The graphs show the median (solid line), 5th and 95th percentiles (lower and upper dashed lines, respectively) of the PD profiles. EHR: exercise-induced heart rate, ΔEHR : percentage reduction in EHR.

Considering Anatomy & Physiology of the Heart

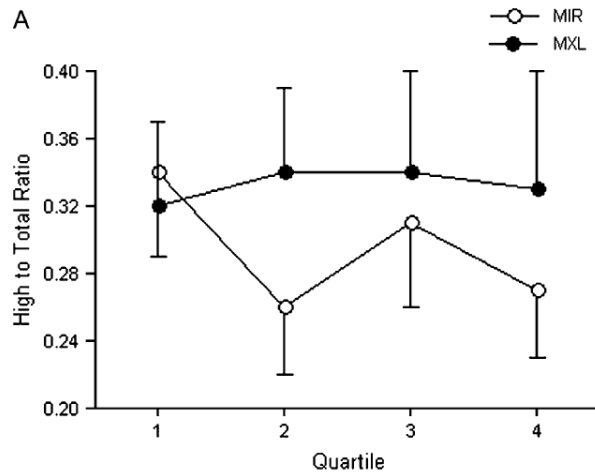
CENTRAL ILLUSTRATION Cardiac Autonomic Function and AF: Potential Interplay



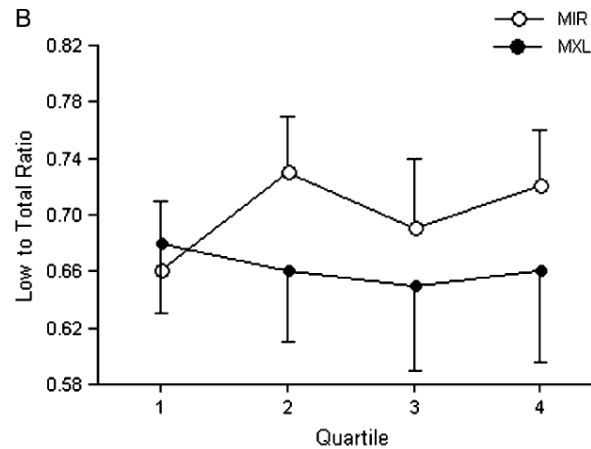
Ongoing Research: Heart Rate Variability (HRV)

Data Used for Model Development

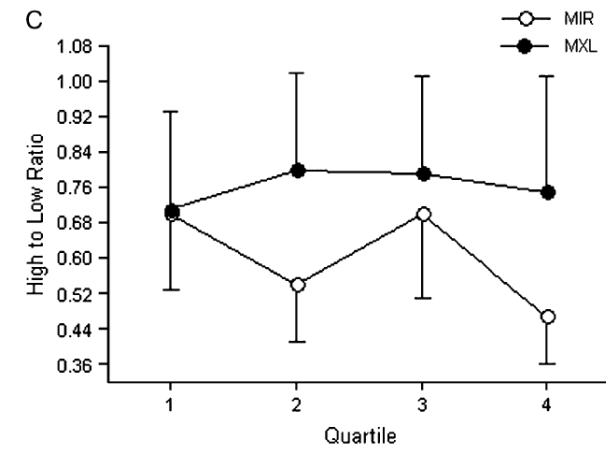
Normalized measures of parasympathetic activity



Normalized measures of sympathetic activity



Index of parasympathetic to sympathetic balance



HRV analyses from 24-hour Holter data were divided into quartiles:

- quartile 1 (3 AM to 9 AM),
- quartile 2 (9 AM to 3 PM),
- quartile 3 (3 PM to 9 PM),
- quartile 4 (9 PM to 3 AM).

Fig. 1. (A) Comparison of high to total frequency variability ratios (normalized measures of parasympathetic activity) for immediate-release metoprolol (open circles) and extended-release metoprolol (black circles). Data are presented as mean \pm SE; $P < .05$. (B) Comparison of low to total frequency variability ratios (normalized measures of sympathetic activity) for immediate-release metoprolol (open circles) and extended-release metoprolol (black circles). Data are presented as mean \pm SE; $P < .05$. (C) Comparison of high to low frequency variability ratios (index of parasympathetic to sympathetic balance) for immediate-release metoprolol (open circles) and extended-release metoprolol (black circles). Data are presented as mean \pm SE; $P < .08$.

Case Example: Metoprolol XL (BCS I, 2006)

- Indication: antihypertensive
- Generics: at least 3 from various manufacturers

✧ Report from physician to FDA on 06-23-2014

Patient: male

Complaints: chest pains

Reaction: increase HR, increase BP, dizziness, migraine

AE resulted in. switch back to brand name product

Suspect Drug: **metoprolol after substitution**

POSSIBLE

<https://www.nytimes.com/2014/06/24/health/warning-unheeded-heart-drugs-are-recalled.html>

Lesko *et al.* accepted for publication in *J Clin Pharmacol.*, 2017

Basu *et al.* accepted for publication in *J Clin Pharmacol.*, 2017

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Collaboration with Drs. Lesko (CPSP), Trame (CPSP), Vozmediano (CPSP), Bihorel (CPSP), Brown (COP-POP), Fang (FDA), Lionberger (FDA)



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