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**

Lesko *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)

Analysis Workflow

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

Confirmation – FAERS analysis 1

Replication – Truven® database

Enhanced FAERS analysis – Evidex™ by Advera Health

Confirm targets and pathways, and prediction of ADEs – MH Effect™

→ **Causality of generic drug-AE pair**

Prediction Modeling ↓

PBPK Absorption Models: Sensitivity Analysis ↔ **PK/PD Models: Benefit and Risk**

2 ↓ 3

Model Interpretation and Report

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 bioINequivalence

1

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

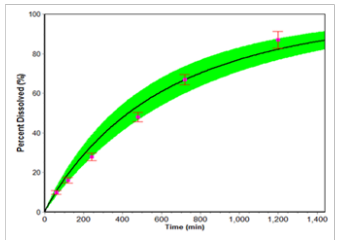
2

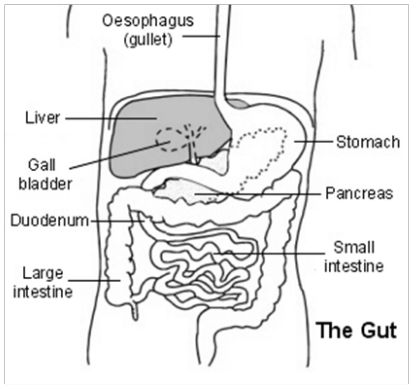
Formulation

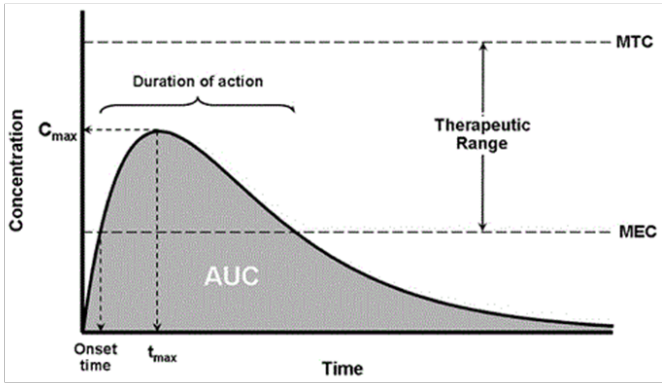
***In vitro* and *in silico* dissolution testing**

***In vivo* dissolution and *in silico* absorption modeling**

***In silico* bioequivalence testing**







DDDPlus™

Advanced Compartment and Transit (ACAT) module in GastroPlus™

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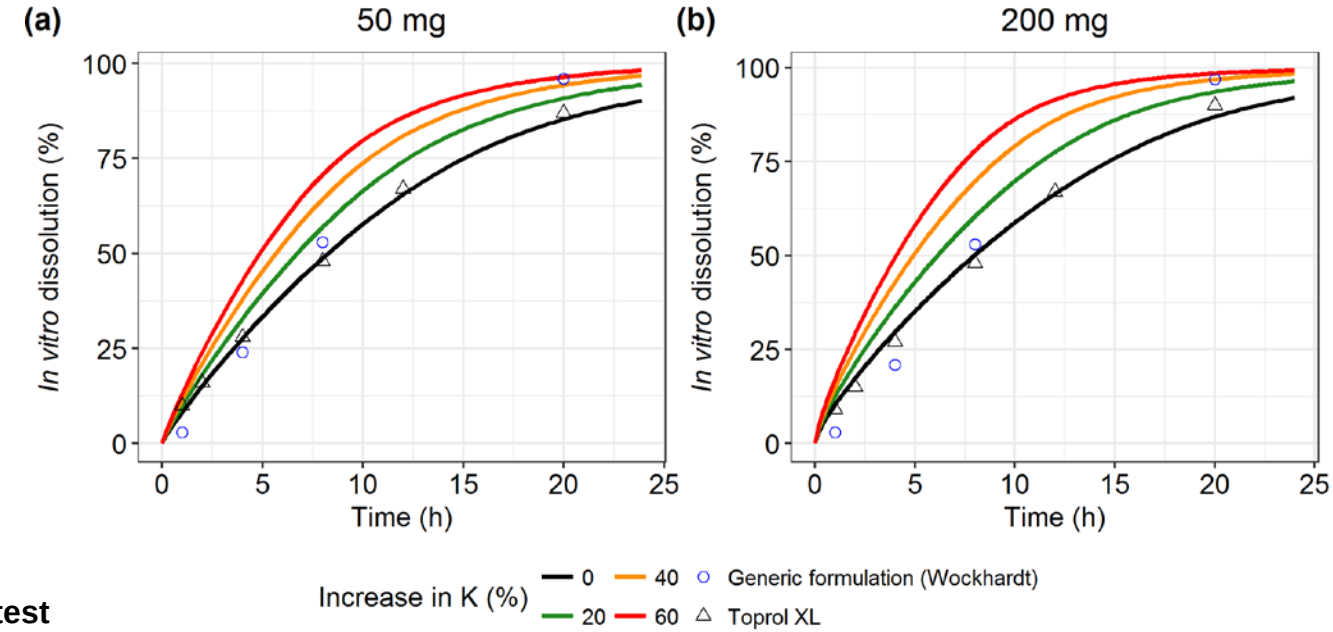
Prediction of *In Vitro* Dissolution Based on the Formulation's Composition & Manufacturing Conditions

***In vitro* Dissolution profiles**



Similarity (F2) test

Product (% increase in K, actual K value)	F2 Value	F2 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	F2 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

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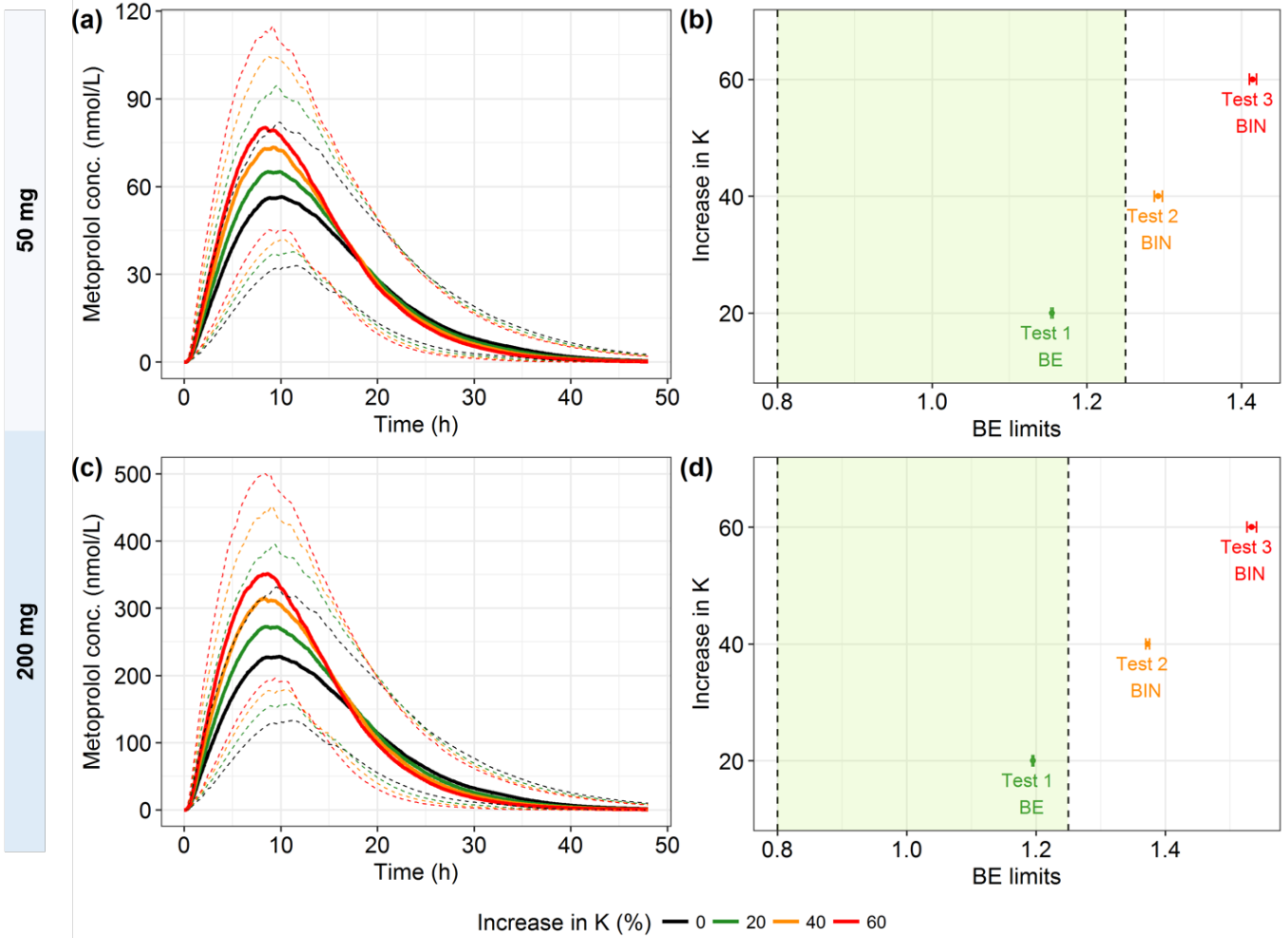
K: drug release rate constant, F2 ≥ 50 indicates similarity. Lower the F2 value, lower the similarity, whereas F2 = 100 indicates absolute similarity.

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.

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Effect of Drug Release on PD & Therapeutic Equivalence

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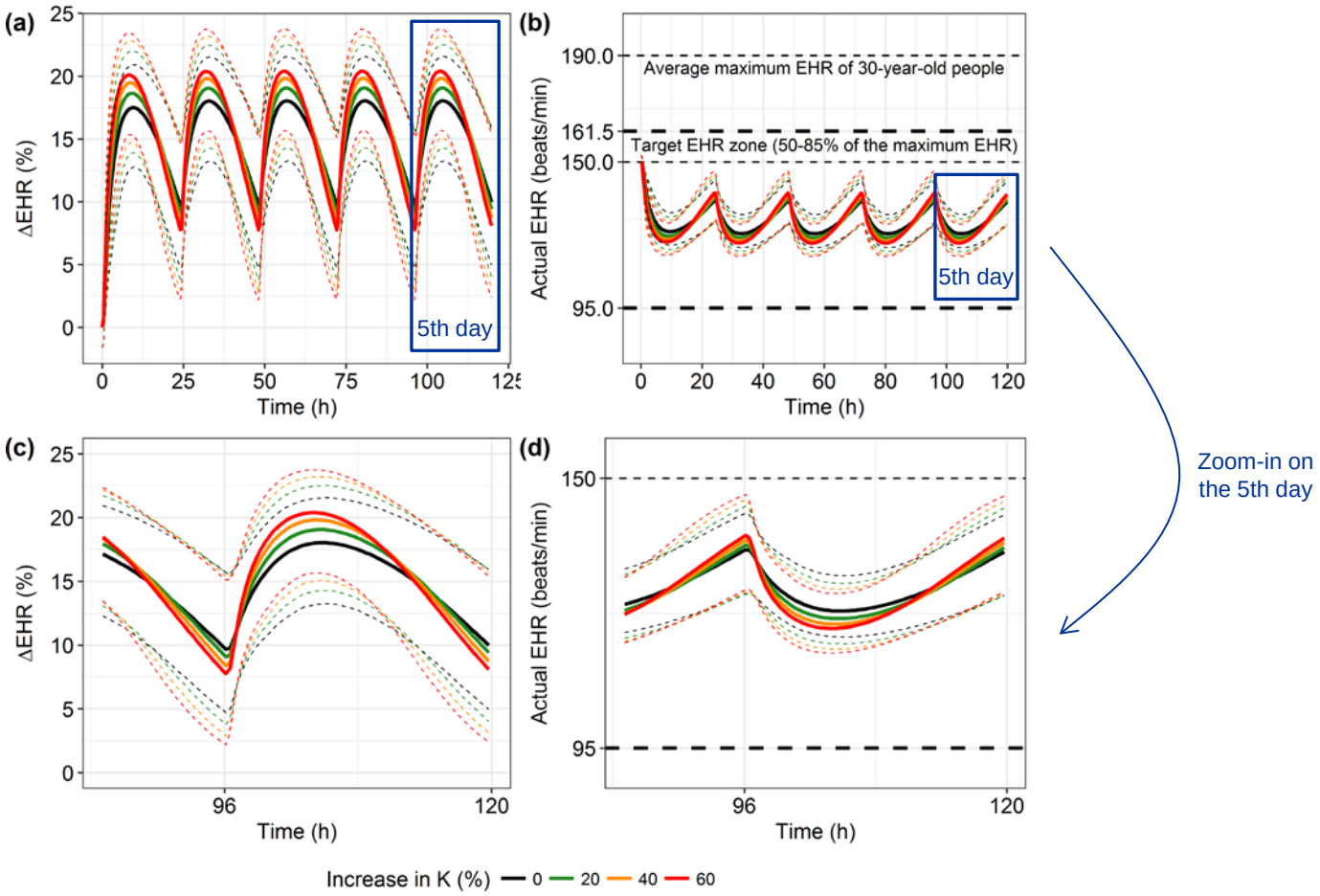
PBPK/PD
200 mg



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.

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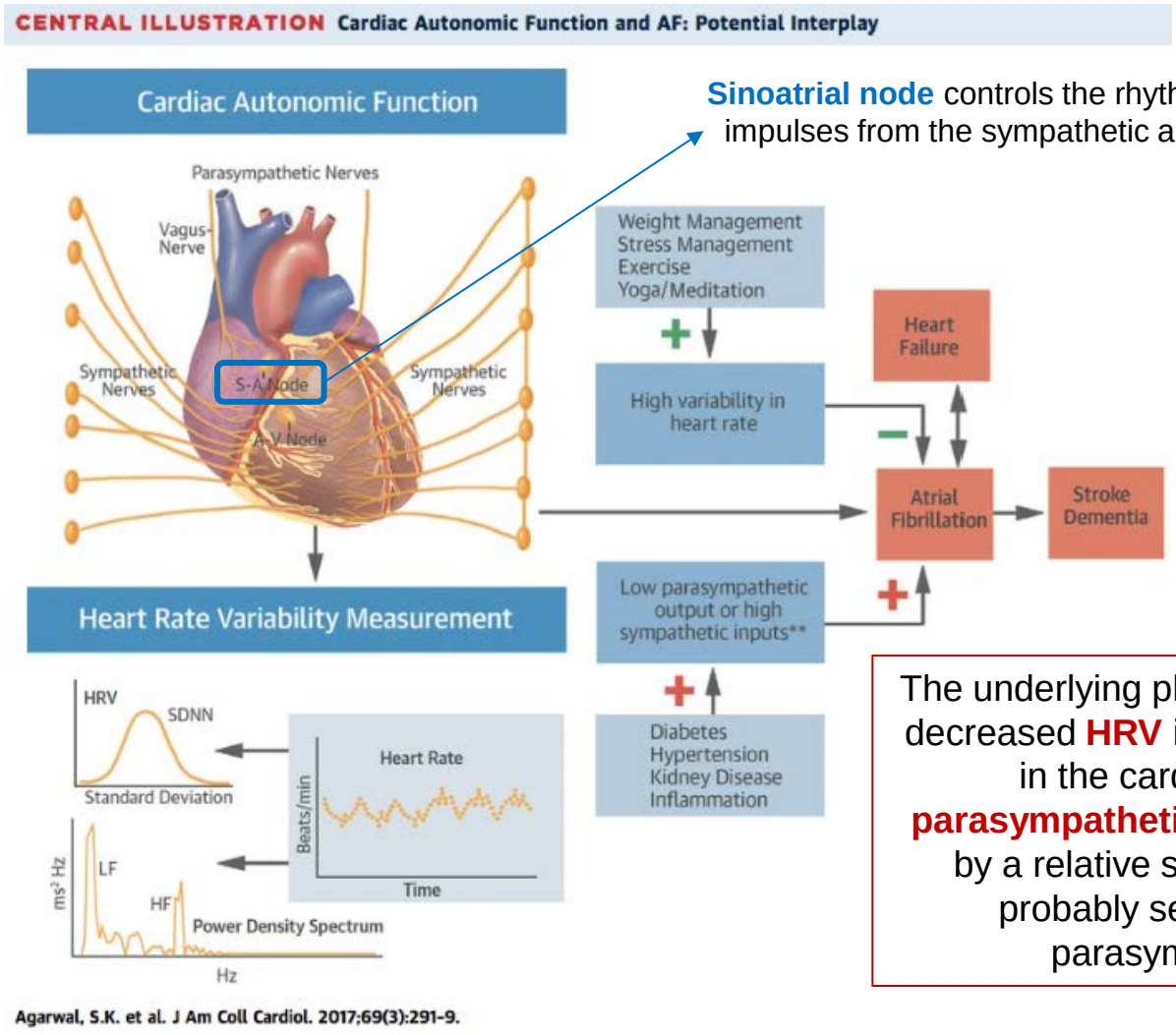
Reference for the target EHR zone: https://www.cdc.gov/physicalactivity/basics/measuring/heartrate.htm

Considering Anatomy & Physiology of the Heart



Sinoatrial node controls the rhythm of the heart based on the impulses from the sympathetic and parasympathetic nerves

Agarwal, S.K. et al. J Am Coll Cardiol. 2017;69(3):291-9.

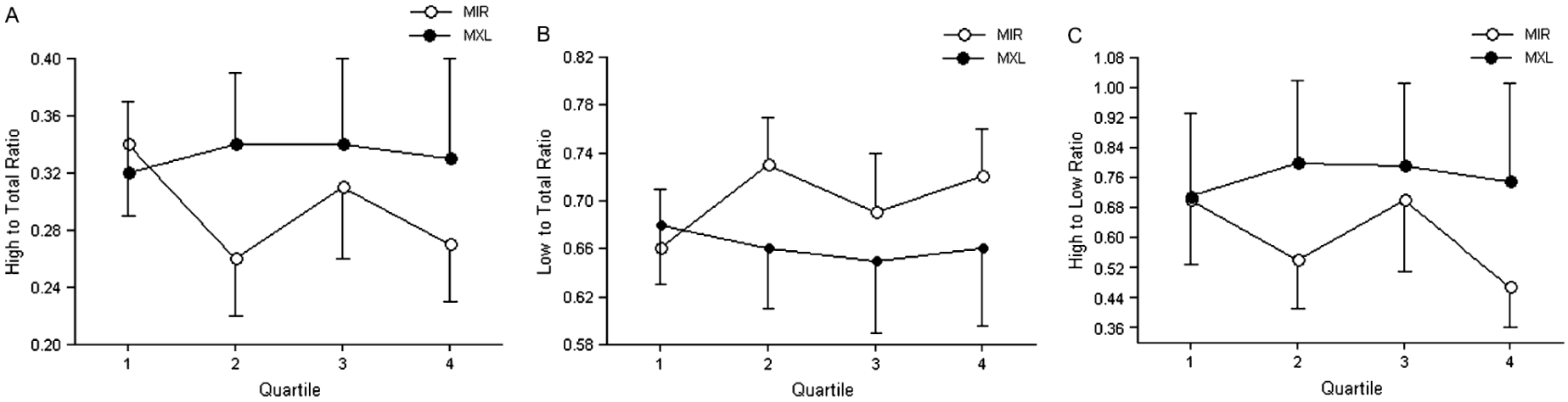
The underlying physiological mechanism of decreased **HRV** is likely to be an alteration in the cardiac **sympathetic–parasympathetic balance**, characterized by a relative sympathetic dominance probably secondary to reduced parasympathetic activity.

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 ± 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 ± 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 ± SE; $P < .08$.

Figure from Aquilante *et al*, (2006) Journal of Cardiac Failure 12(3): 171-176.

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
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