Pharmacogenetics of β-blockers: CPIC Proposal for *ADRB1*, *GRK5* and *CYP2D6*

Cameron D. Thomas, Pharm.D.
Postdoctoral Fellow in Genomic Medicine
Julie A. Johnson, Pharm.D.
Dean and Distinguished Professor

UF College of Pharmacy
UNIVERSITY of FLORIDA

Objectives

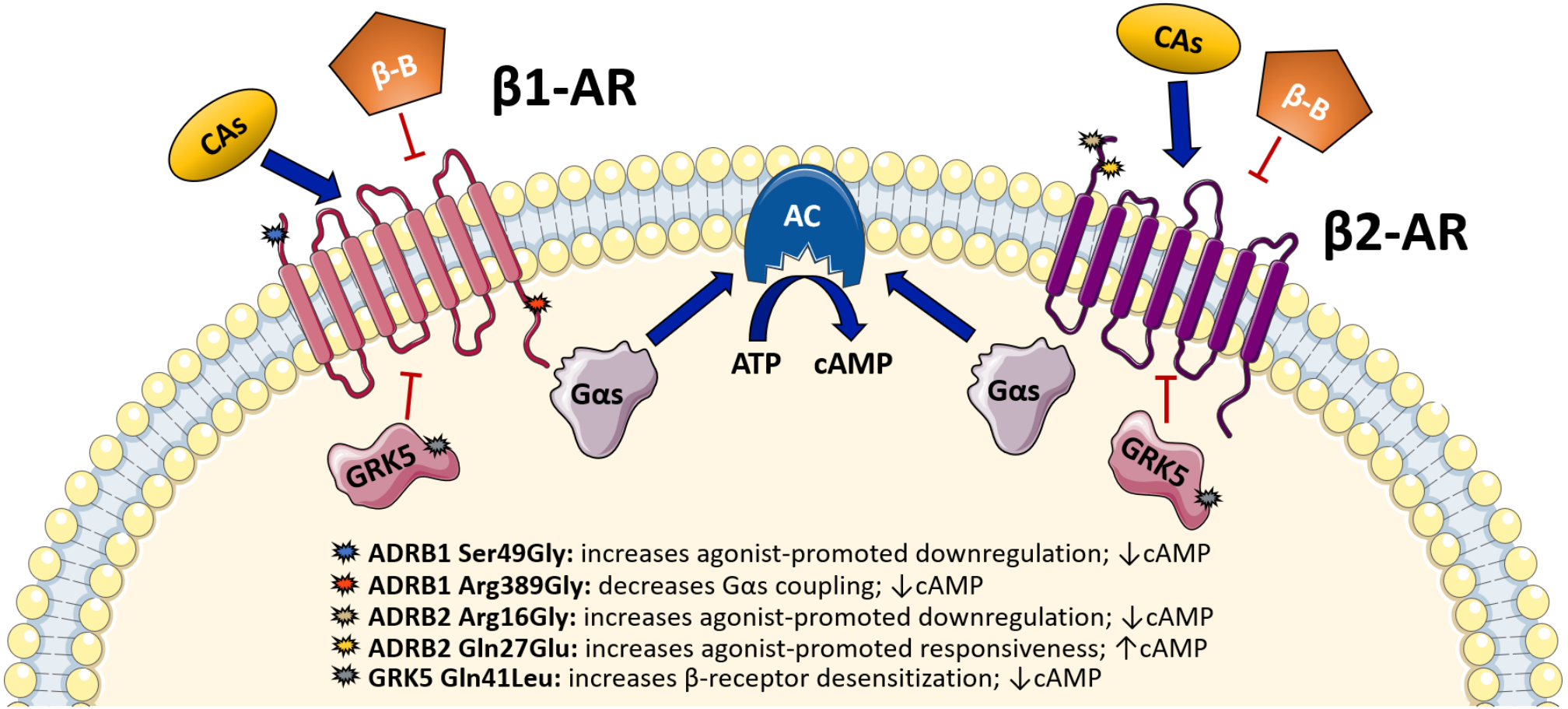
- Describe pharmacogenetic factors affecting β-blocker metabolism and response
- Provide insight into the robustness of the genetic associations
- Discuss clinical interpretations for potential translation of variants influencing β-blocker response into practice

β-blockers

- Among most commonly used of all drugs
  - Common indications: Heart failure, ischemic heart disease, hypertension
  - Four beta-blockers in top 50 prescribed drugs in 2020 (not including combo products)
    - Metoprolol #6 – 68M
    - Carvedilol #29 – 23M
    - Atenolol #36 – 20M
    - Propranolol #41 – 18M
- Modulate sympathetic nervous system activation to produce:
  - ↓ chronotropic
  - ↓ inotropic
  - ↓ dromotropic
- Variation within genes that affect β-blocker pharmacokinetic and pharmacodynamic properties contribute to wide inter-patient variability in response

https://clincalc.com/DrugStats/Top200Drugs.aspx

Pharmacodynamic Pathways of β1 and β2 Receptors and Resulting cAMP Generation



Thomas, Johnson. *Expert Opin Drug Metab Toxicol*. 2020. PMID: 32726152

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Phenotype and Variant Allele Frequencies

	EUROPEAN	AFRICAN	ASIAN
PHENOTYPE FREQUENCIES			
CYP2D6			
PM	6	2	2
IM	38	45	29
NM	51	44	66
UM	4	4	2
VARIANT ALLELE FREQUENCIES			
ADRB1			
rs1801252 (Gly49)	13	16	5
rs1801253 (Gly389)	31	37	38
GRK5			
rs2230345 (Leu41)	2	16	0

IM: intermediate metabolizer; NM: normal metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer. CYP2D6 phenotype frequencies from https://cpicpgx.org/. *ADRB1* and *GRK5* variant allele frequencies from dbGaP, with the resulting encoded variant allele amino acid in parentheses.

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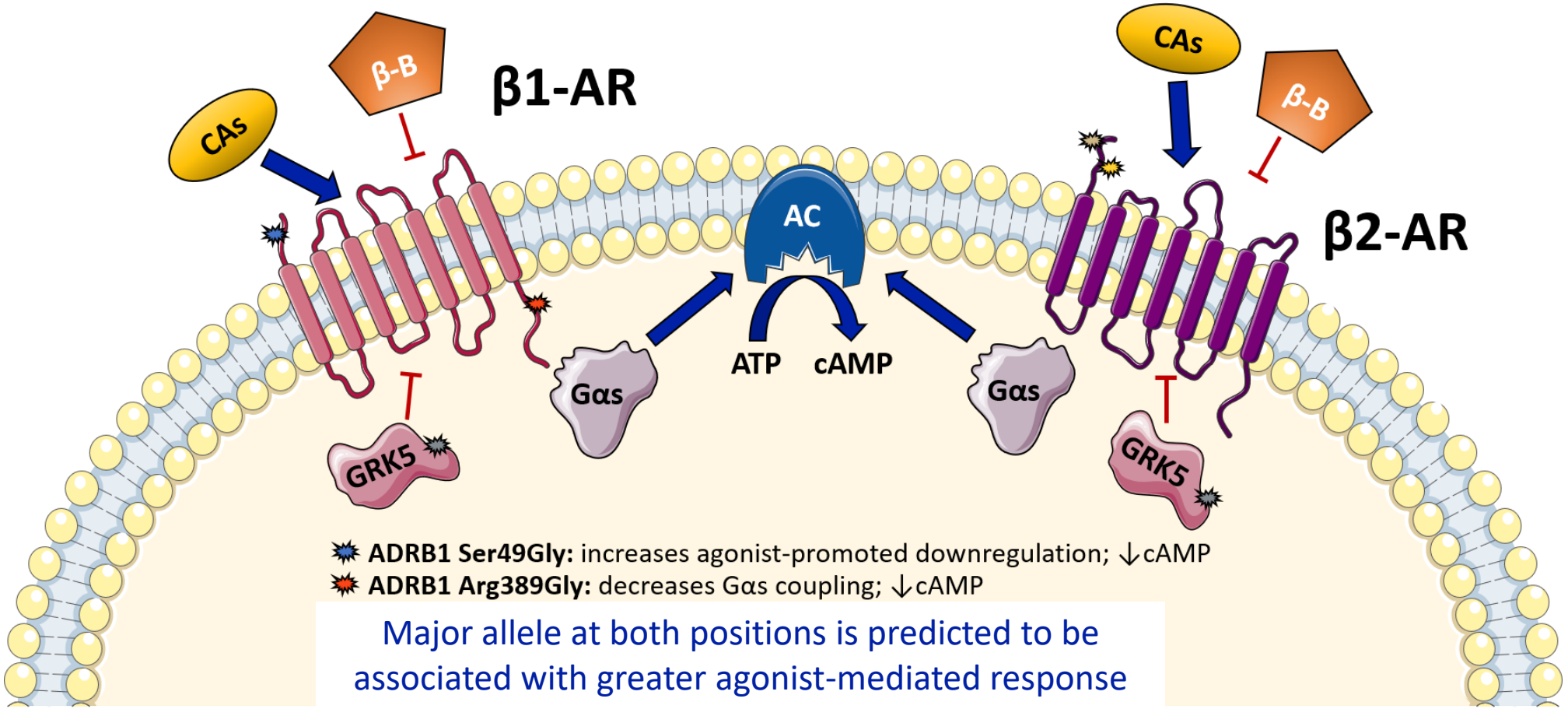
ADRB1

β1-adrenergic receptors are modulated by desensitization and downregulation



Major allele at both positions is predicted to be associated with greater agonist-mediated response

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ADRB1 is a determinant of antihypertensive response to β-blockers

Representative examples:

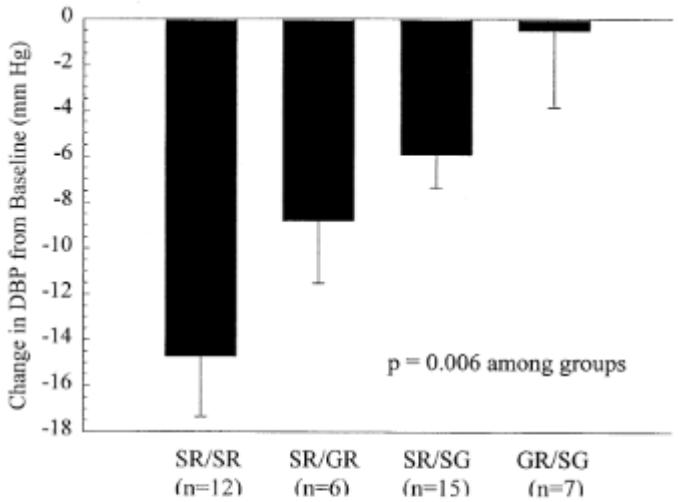


Fig 2. BP response to metoprolol by β_1–adrenergic receptor (β_1AR) haplotype pair (diplotype). Data are presented as mean reduction and SE. SR, Ser49Arg389 haplotype; SG, Ser49Gly389 haplotype; GR, Gly49Arg389 haplotype. P = .006, between groups for change in DBP from baseline to treatment.

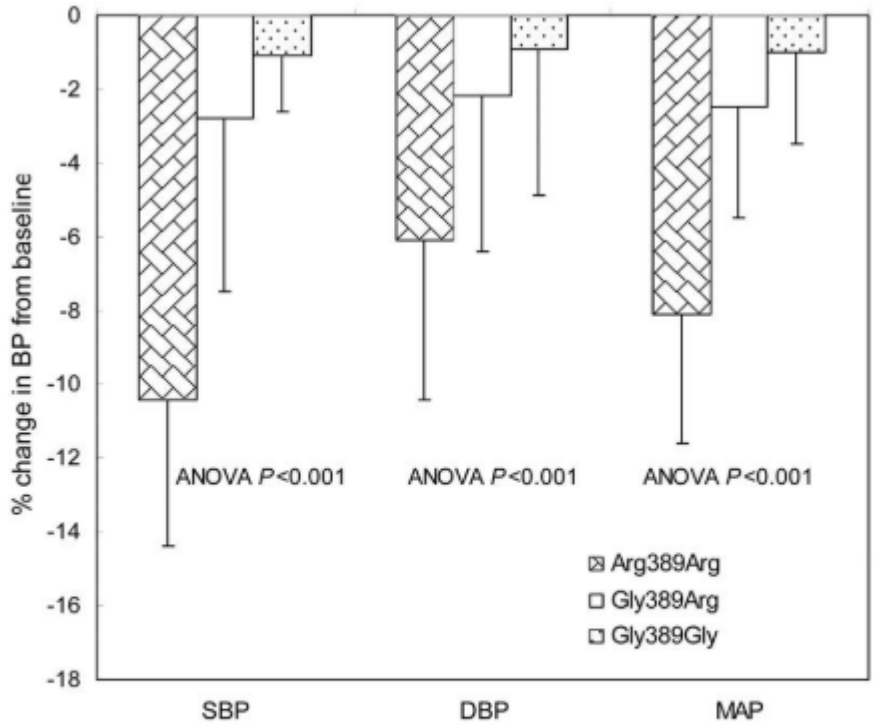


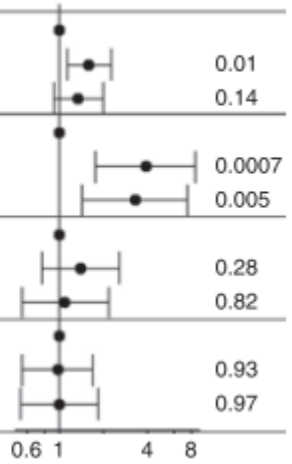
Fig 2. Blood pressure response to metoprolol monotherapy in patients with hypertension stratified according to β_1-adrenergic receptor Gly389Arg genotypes (Arg389Arg, n = 33; Gly389Arg, n = 19; Gly389Gly, n = 9). Data are presented as mean percentage decrease with SD. SBP, Systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Johnson, et al. *Clin Pharmacol Ther*. 2003;74:44-52.
Liu, et al. *Clin Pharmacol Ther*. 2006;80:23-32.

ADRB1 Ser49-Arg389 carriers associated with increased risk for MACE (death, MI, stroke)

Figure 1 Associations of the *ADRB1* Ser49-Arg389 haplotype with primary and secondary outcomes. Hazard ratios are based on reduced model adjusted for age, sex, and race/ethnicity. *Crude incidence per 1,000 patient years. MI, myocardial infarction.

Event	No. copies Ser49-Arg389	Incidence*	Hazard ratio (95% Confidence interval)	P
Primary outcome	0	10.8	1.00 (reference)	
	1	17.8	1.59 (1.12–2.27)	0.01
	2	15.6	1.35 (0.91–1.99)	0.14
All-cause mortality	0	1.9	1.00 (reference)	
	1	7.4	3.88 (1.76–8.52)	0.0007
	2	6.3	3.26 (1.42–7.49)	0.005
Nonfatal MI	0	3.7	1.00 (reference)	
	1	5.6	1.40 (0.76–2.57)	0.28
	2	4.7	1.09 (0.55–2.15)	0.82
Nonfatal stroke	0	5.1	1.00 (reference)	
	1	5.1	0.97 (0.56–1.69)	0.93
	2	5.3	0.99 (0.54–1.82)	0.97



Ser49-Arg389 carriers vs. non-carriers: HR, 1.51 (95% CI, 1.07-2.12); p=0.02

Pacanowski, et al. *Clin Pharmacol Ther*. 2008;84:715-21.

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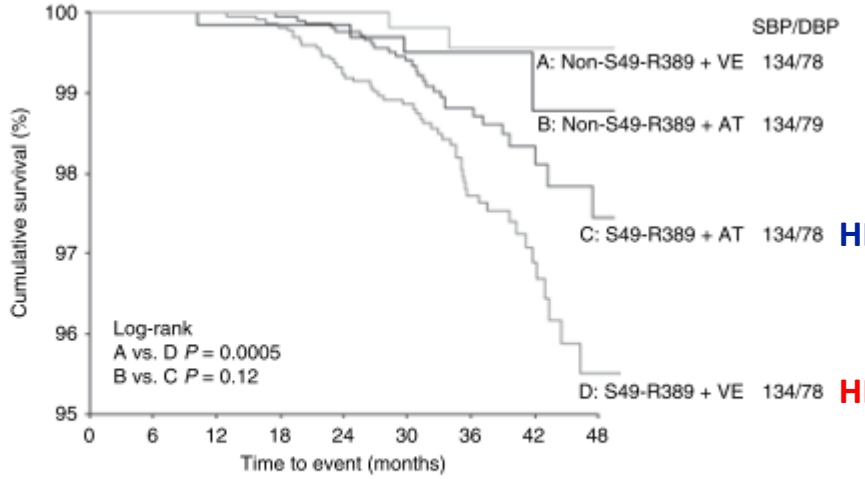
ADRB1 Ser49-Arg389 is favorable response allele for β-blocker therapy in ischemic heart disease

Figure 2 All-cause mortality and mean on-treatment blood pressure by *ADRB1* Ser49-Arg389 haplotype and atenolol/verapamil sustained-release (SR) therapy. HR, hazard ratio; 95% CI, 95% confidence interval; S49-R389, Ser49-Arg389 haplotype; AT, atenolol; VE, verapamil SR; SBP, systolic blood pressure; DBP, diastolic blood pressure.



No. at risk									
Non-S49-R389 + AT	626	624	624	624	623	494	324	135	78
Non-S49-R389 + VE	653	652	651	651	651	508	337	131	63
S49-R389 + AT	2116	2096	2096	2095	2091	1669	1125	454	243
S49-R389 + VE	2235	2229	2228	2224	2211	1737	1169	478	234

HR, 2.31 (95% CI, 0.82-6.55); p=0.11

HR, 8.58 (95% CI, 2.06-35.8); p=0.003

Pacanowski, et al. *Clin Pharmacol Ther*. 2008;84:715-21.

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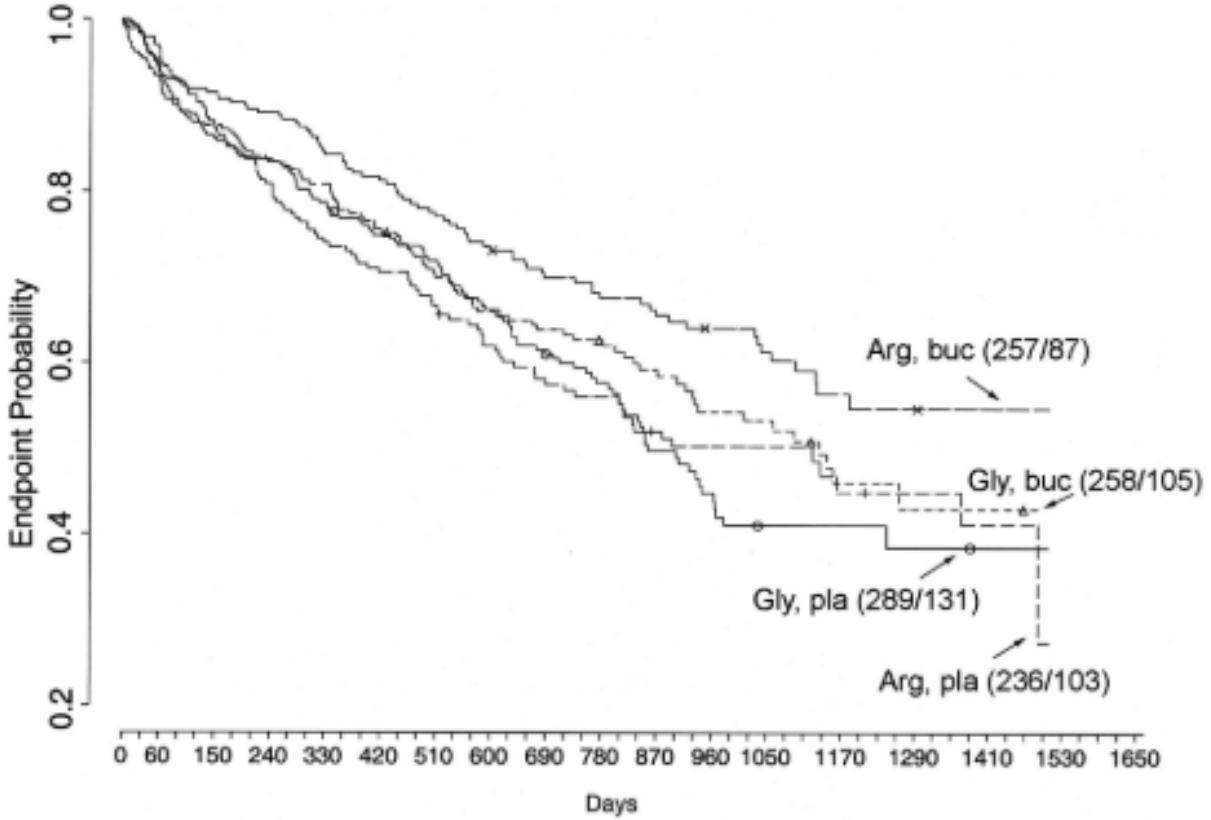
ADRB1 Arg389 is the favorable β-blocker response allele in heart failure

- BEST: NYHA class III-IV HFrEF
- The risks for death and hospitalization were not significantly different between bucindolol and placebo arms among Gly389 carriers
- Conclusion: benefits of bucindolol in the studied HF population were confined to those with the Arg389Arg genotype



Gly-389 carriers: HR, 0.87 (95% CI, 0.67–1.11); p=0.25

Arg389Arg: HR, 0.66 (95% CI, 0.50–0.88); p=0.004

Liggett, et al. *Proc Natl Acad Sci USA*. 2006;103:11288-93.

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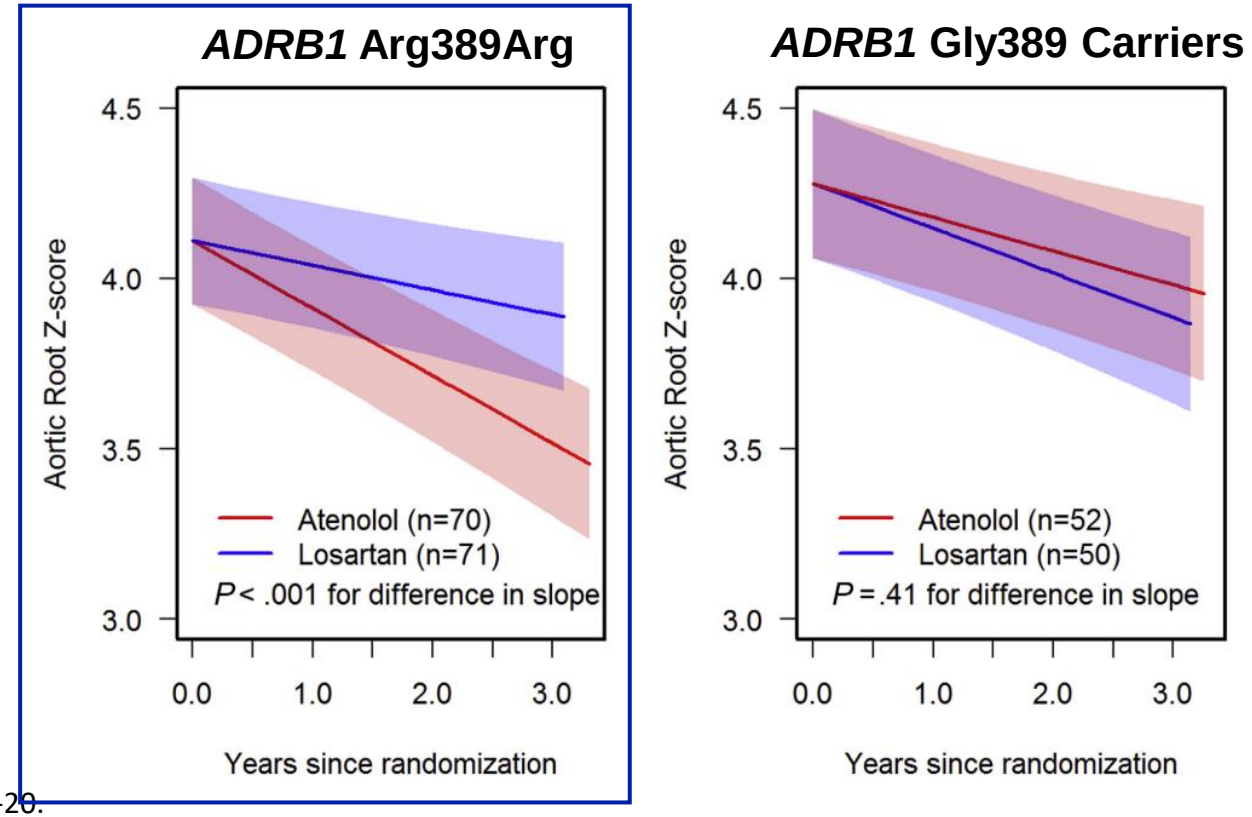
ADRB1 Arg389Gly associated with atenolol response in children and young adults with Marfan syndrome

- Pharmacogenetic substudy of a randomized trial of atenolol vs losartan in 250 participants with Marfan syndrome

Arg389Arg: greater improvements in aortic-root z-score for atenolol-treated compared with losartan-treated participants



Van Driest, et al. *J Pediatr*. 2020;222:213-20.

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Positive associations identified between *ADRB1* and hemodynamic and clinical outcomes

Hemodynamics: strongest data exist for an association between *ADRB1* and DBP response to β-blockers

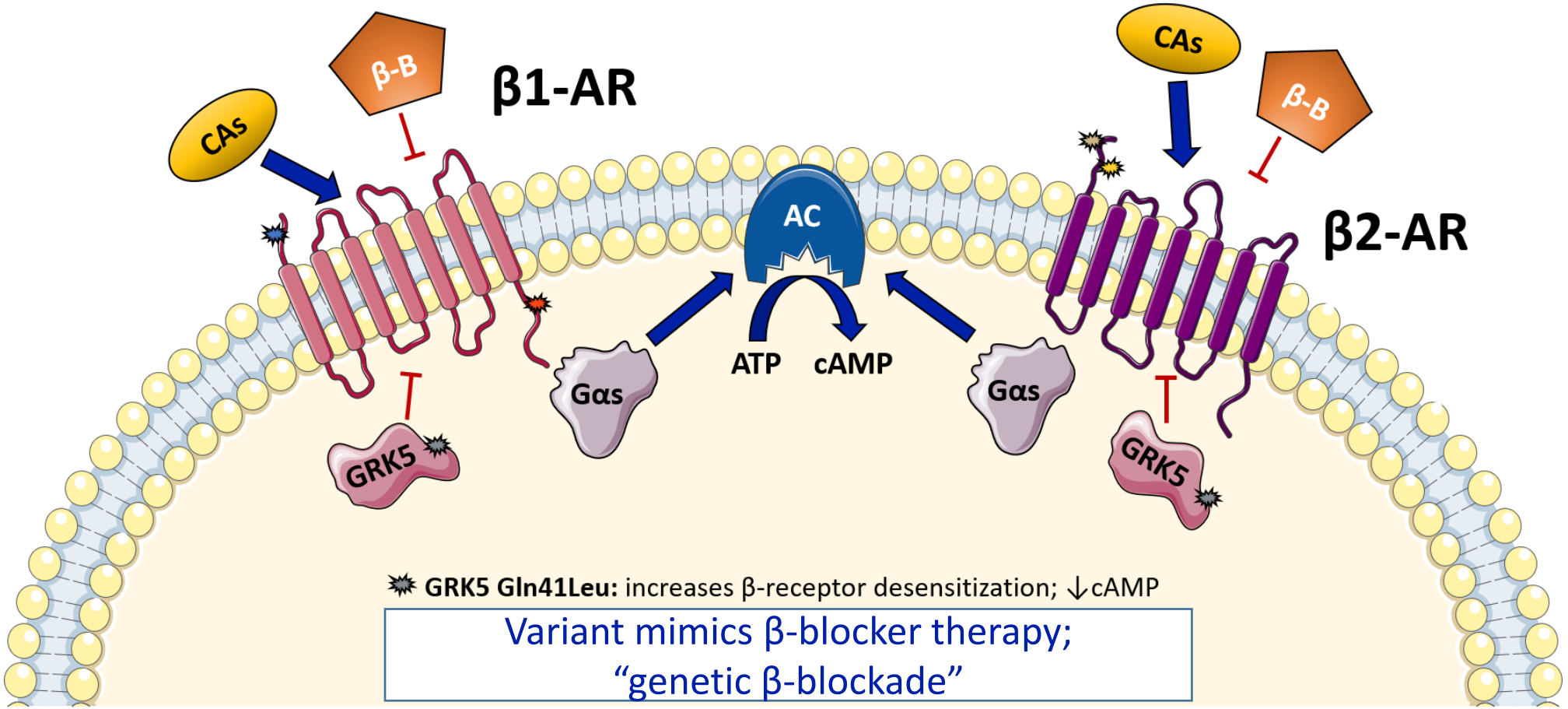
β-blocker therapy may offset the risk for MACE observed with the *ADRB1* Ser49-Arg389 haplotype

Studies support greater benefits from β-blocker therapy among HFrEF patients with the Arg389Arg genotype compared to Gly389 carriers.

Associations identified between *ADRB1* and: metoprolol, atenolol, bucindolol, carvedilol, thus implying a class effect

GRK5

G protein-coupled receptor kinases (GRKs) desensitize β-receptors



Thomas, Johnson. *Expert Opin Drug Metab Toxicol*. 2020.
Liggett, et al. *Nat Med*. 2008;14:510-7.

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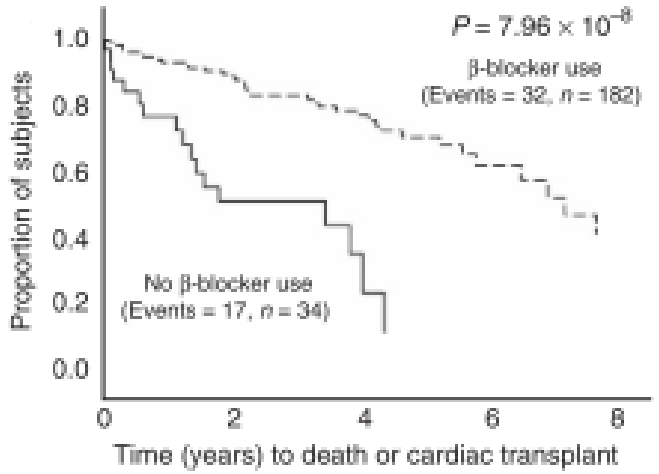
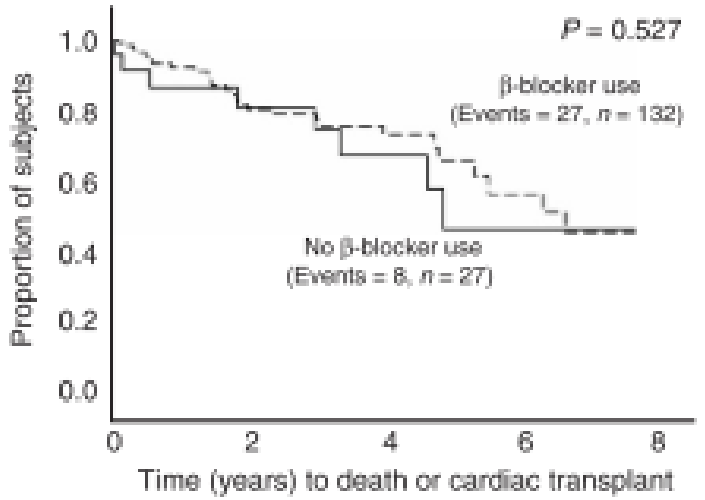
β-blocker therapy mimics the survival advantage of *GRK5* Leu41

HFrEF (LVEF < 40%; NYHA class II-IV); all participants of African ancestry

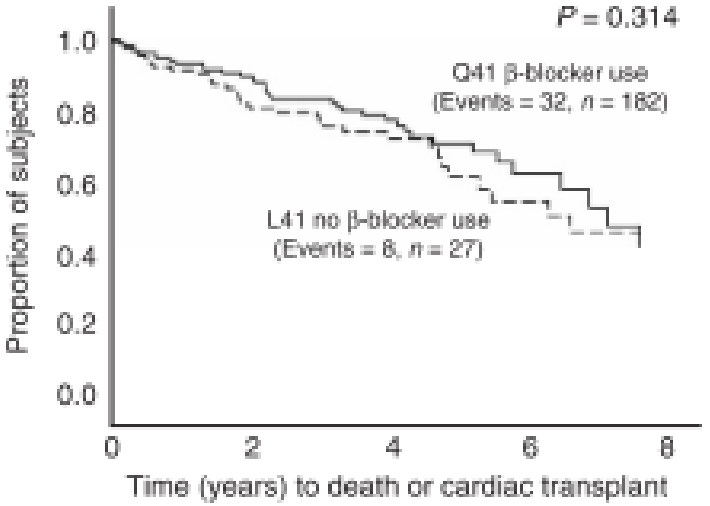
Comparison of *GRK5* Gln41Gln subjects with and without b-blocker use.



Comparison of *GRK5* Leu41 carriers with and without b-blocker use.



Comparison of *GRK5* Gln41Gln subjects treated with β-blockers to *GRK5* Leu41 carrier subjects without β-blocker use.



Liggett, et al. *Nat Med*. 2008;14:510-7.

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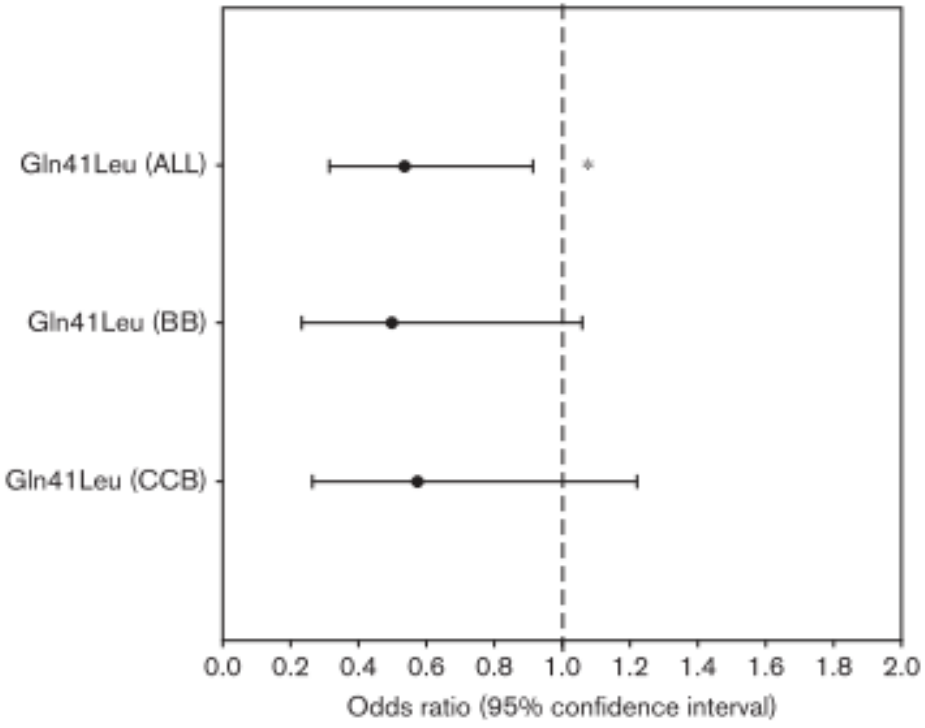
GRK5 Leu41 associated with decreased odds of adverse cardiovascular outcomes

- Hypertensive cohort with CAD
- Outcome: death, MI, or stroke
- Leu41 carriers vs. Gln41Gln; p=0.022
- Generalizability of protective role of Leu41 allele
  - Heart failure
  - Hypertension + coronary artery disease
- *GRK5* Leu41 does not influence BP response to antihypertensives



Lobmeyer, et al. *Pharmacogenet Genomics*. 2011;21:42-9.

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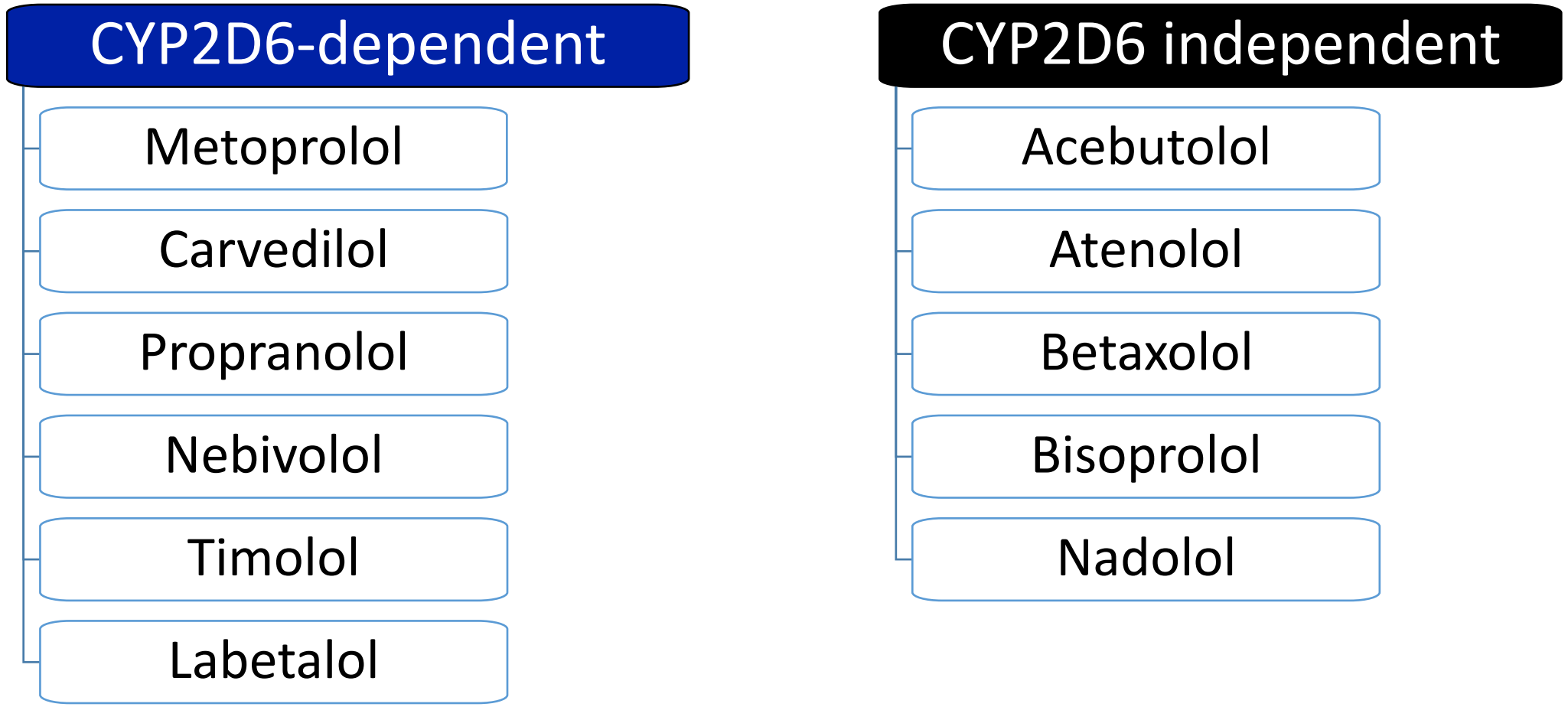
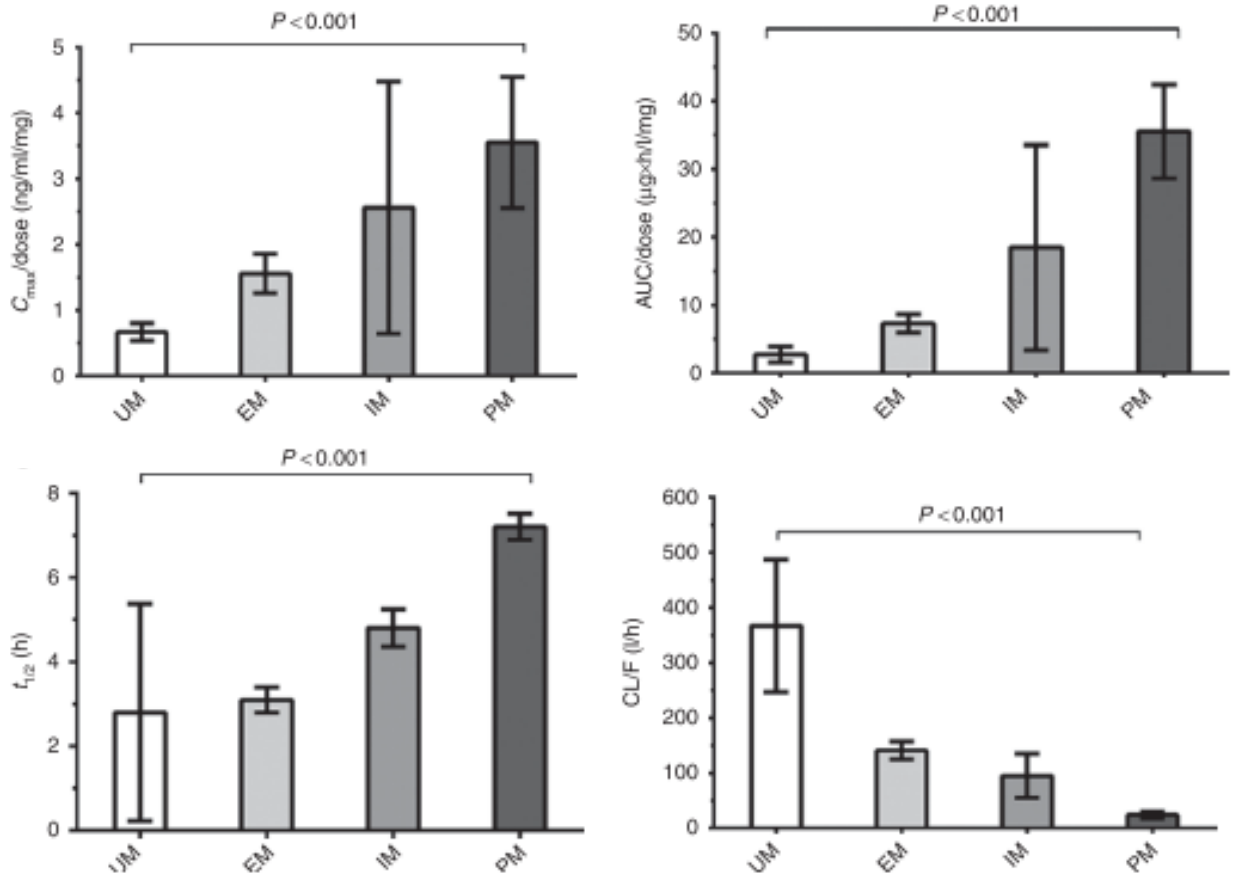
CYP2D6

There is evidence CYP2D6 affects the pharmacokinetics of CYP2D6-dependent β-blockers



CYP2D6 phenotype affects metoprolol pharmacokinetics and change in HR



CYP2D6 Phenotype

Table 3 Changes from baseline in HR, SBP, and DBP in PMs, IMs, EMs, and UMs of CYP2D6 treated with metoprolol

Parameter	PM	IM	EM	UM	*P*
Change in HR (beats/min)	−16.6±6.9	−18.6±5.1	−11.4±6.6	−11.2±8.2	0.0001
Change in SBP (mm Hg)	−9.4±9.0	−6.5±11.1	−7.1±9.8	−9.4±5.1	0.91
Change in DBP (mm Hg)	−9.3±5.1	−8.3±7.5	−7.0±6.6	−7.5±4.8	0.37

CYP2D6, cytochrome P450 2D6; DBP, diastolic blood pressure; EM, extensive metabolizer; HR, heart rate; IM, intermediate metabolizer; PM, poor metabolizer; SBP, systolic blood pressure; UM, ultrarapid metabolizer.

Blake, et al. *Clin Pharmacol Ther*. 2013;94:394-9.
Hamadeh, et al. *Clin Pharmacol Ther*. 2014;96:175-81.

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There is limited clinical utility for *CYP2D6* and β-blocker pharmacotherapy

- *CYP2D6* associated with HR response but no other response phenotypes, in part explained by usual upward titration of dose and HR being used to define target dose
- Impact of *CYP2D6* on HR response is evident at lower doses while patient is still on the linear portion of the dose-response curve
- *CYP2D6* not associated with:
  - BP responses
  - Adverse reactions (e.g., headache, dizziness, fatigue, dyspnea)
- PM/IM may achieve goal HR response at a lower than expected dose
- Possible clinical utility if *CYP2D6* available in the electronic health record to better understand likely dose requirements for beta-blockade

Thomas, Johnson. *Expert Opin Drug Metab Toxicol*. 2020. PMID: 32726152

Summary: *ADRB1*, *GRK5*, and *CYP2D6*

- *ADRB1* Arg389Arg, or Ser49-Arg389, associated with improved treatment outcomes with β-blocker therapy
- *GRK5*: Gln41Gln associated with ↑ risk of adverse cardiovascular outcomes, which is offset by β-blocker therapy
- *CYP2D6*
  - If available to the clinician, may provide clinical utility given PM/IM patients may achieve the target HR response at a lower doses
  - Ordering *CYP2D6* test to guide β-blocker therapy not justified

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Recommending a CPIC guideline for β-blockers: Genes likely to be included in guideline are *ADRB1, GRK5,* and *CYP2D6,* though literature review would need to include other genes, including *ADRB2, GRK4* and possibly others

Julie A. Johnson, Pharm.D.

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