2007. 4. 20 춘계 순환기 통합 학술대회, 부산

Pharmacogenetics in Heart Failure

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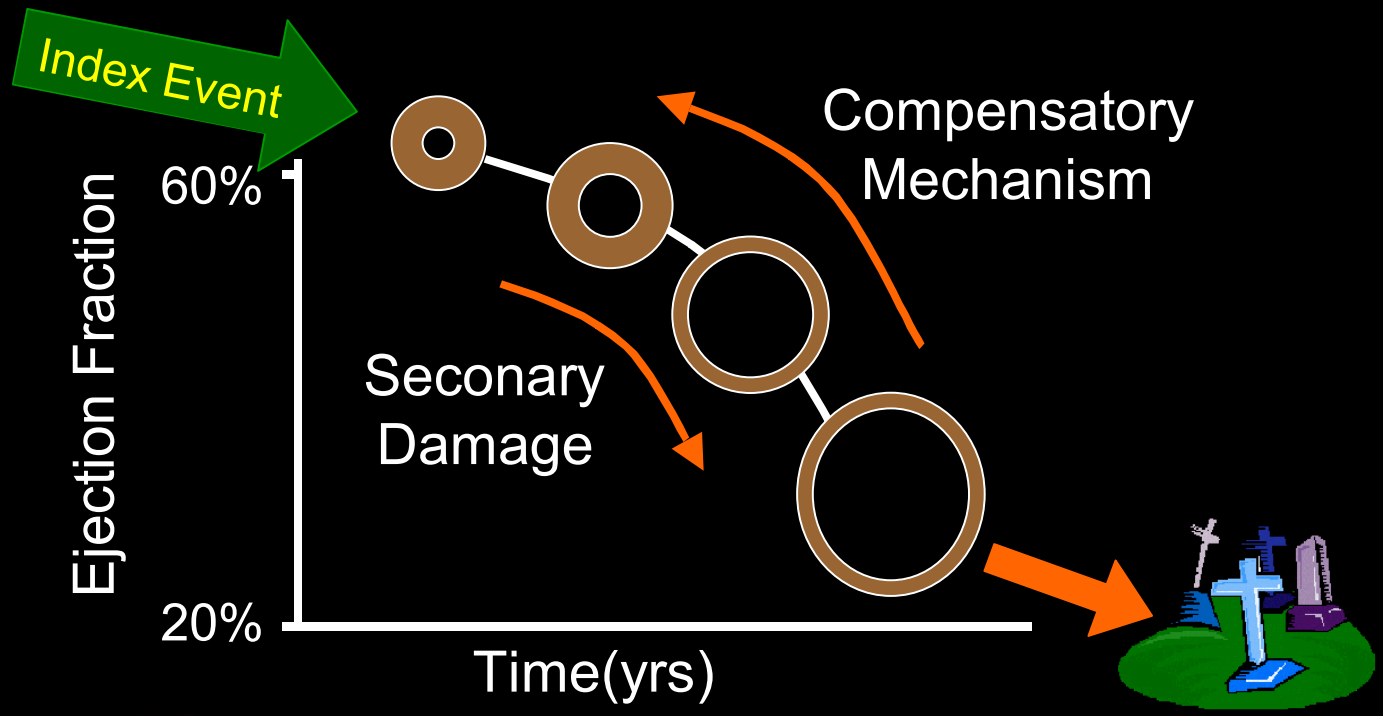
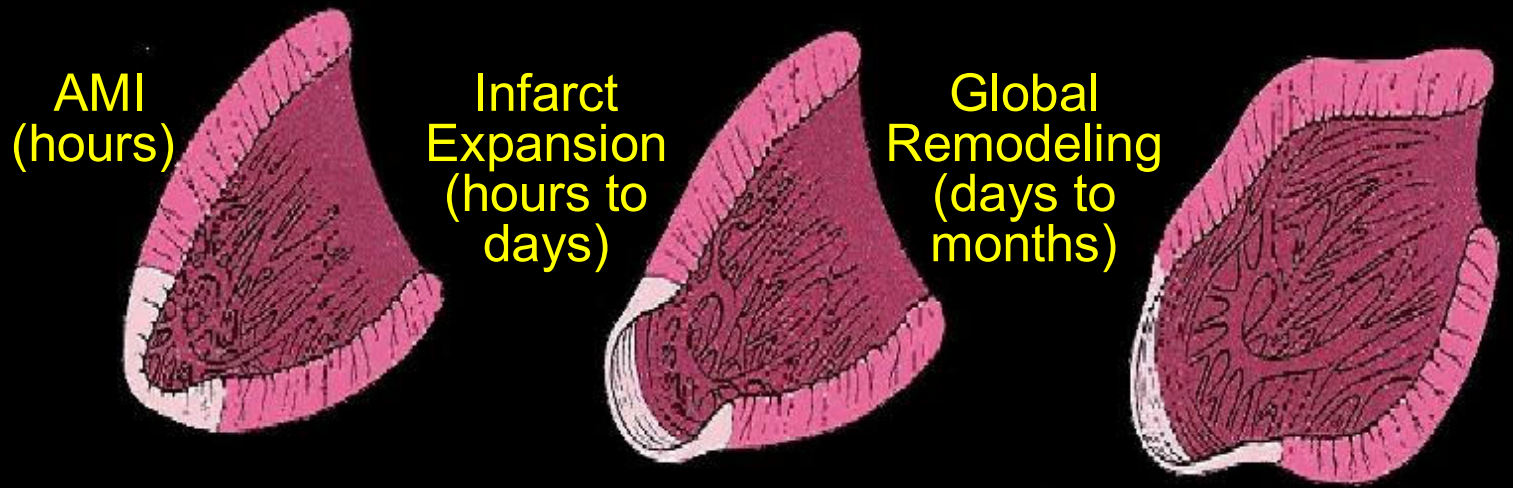
김영대

Progression of Hypertrophy to Failure





Courtesy of MC Cho, Choongbuk University

Post-MI ventricular remodeling in reperfusion era

Thrombolysis	71.8%
IV β-blockers	25.1%
Aspirin	85.8%

614 patients enrolled in GISSI-3 study (19,349)
2-D echocardiograms at 24-48 h, discharge, 6 wk, 6 Mo

Patient groups	Late1 (LV volume reduction) (n = 193) (31%)	Late2 (LV volume stability) (n = 154) (25%)	Late3 (mild/moderate LV dilation) (n = 172) (28%)	Late4 (severe LV dilation (n = 95) (16%)	Statistical significance*
EDVi (mL/m^2)					$P = .0001$
S1	79 ± 20	82 ± 20	79 ± 20	82 ± 22	
S2	87 ± 22	87 ± 23	81 ± 23	79 ± 23	
S3	80 ± 23	86 ± 23	87 ± 25	95 ± 30	
S4	75 ± 19	87 ± 23	90 ± 25	106 ± 32	
ESVi (mL/m^2)					$P = .0001$
S1	41 ± 16	44 ± 16	43 ± 16	47 ± 18	
S2	46 ± 18	47 ± 19	44 ± 18	45 ± 20	
S3	42 ± 18	47 ± 20	48 ± 20	56 ± 24	
S4	38 ± 14	47 ± 20	50 ± 22	64 ± 27	
%WMA					$P = .0041$
S1	23 ± 14	27 ± 15	26 ± 15	29 ± 17	
S2	21 ± 14	25 ± 15	24 ± 16	28 ± 16	
S3	19 ± 14	23 ± 15	22 ± 16	27 ± 17	
S4	18 ± 14	22 ± 16	21 ± 16	27 ± 16	
EF (%)					$P = .0001$
S1	48 ± 7	47 ± 7	47 ± 8	44 ± 8	
S2	48 ± 7	47 ± 8	47 ± 8	45 ± 10	
S3	49 ± 7	47 ± 8	46 ± 8	42 ± 9	
S4	50 ± 7	47 ± 8	46 ± 9	41 ± 9	

Giannuzzi P, et al. Am Heart J 2001;141:131

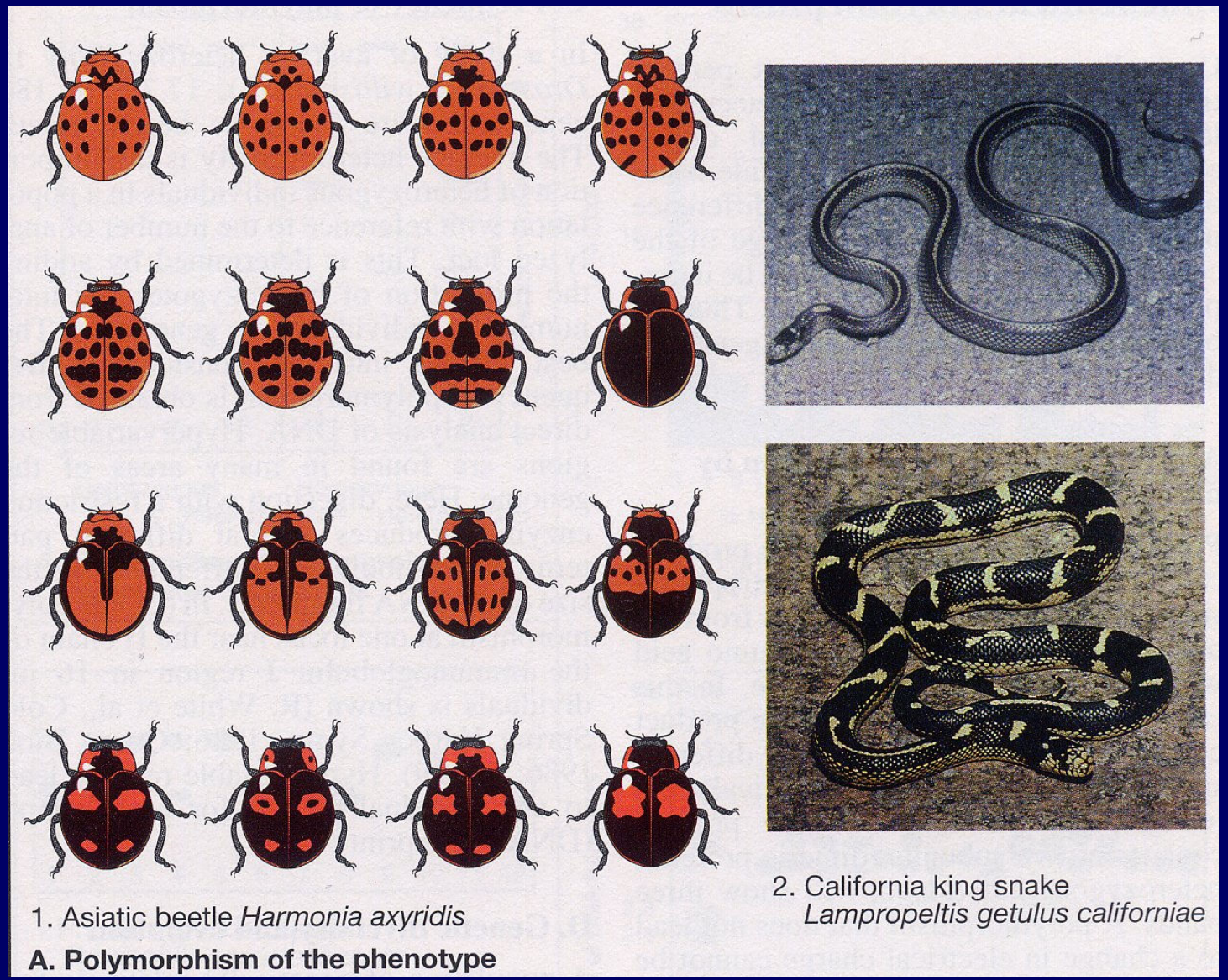
Genetic basis of left ventricular remodeling after myocardial infarction

103 patients with first MI: polymorphism of ACE I/D, AGT M235T
LVEDVI and LVESVI at 7±4 days and 3.9 ±1.3 months after MI

	Coefficient	S.E.	Partial F	P-value
Prediction of $LVEDV_2$ Intercept = 35.419. R^2 = 0.618				
LVESV1	0.873	0.078	124.104	0.0001
ACE I/D genotype	−8.414	2.791	9.090	0.0033
Diabetes Mellitus	8.310	2.847	9.454	0.0044
Gender	10.428	3.592	8.428	0.0046
Period2	2.082	1.039	4.106	0.0479

Ohmichi N, et al. Int J Cardiol 1996;53:265

Genetic polymorphism



1. Asiatic beetle *Harmonia axyridis*

A. Polymorphism of the phenotype

2. California king snake
Lampropeltis getulus californiae

Candidate genes in heart failure

1. RAAS system

ACE I/D

Angiotensinogen M235T, T174M, G-6A

AII receptor AT1R A1166C,
AT2R A3123C, G1675A

Aldosterone synthase CYP11B2 C-334T

2. Sympathetic system

A2ARα2c Wt/Del322-325

B1AR Ser49Gly, Arg389Gly

B2AR Arg16Gly, Gln27Glu,

3. Endothelin

END1 G8002A

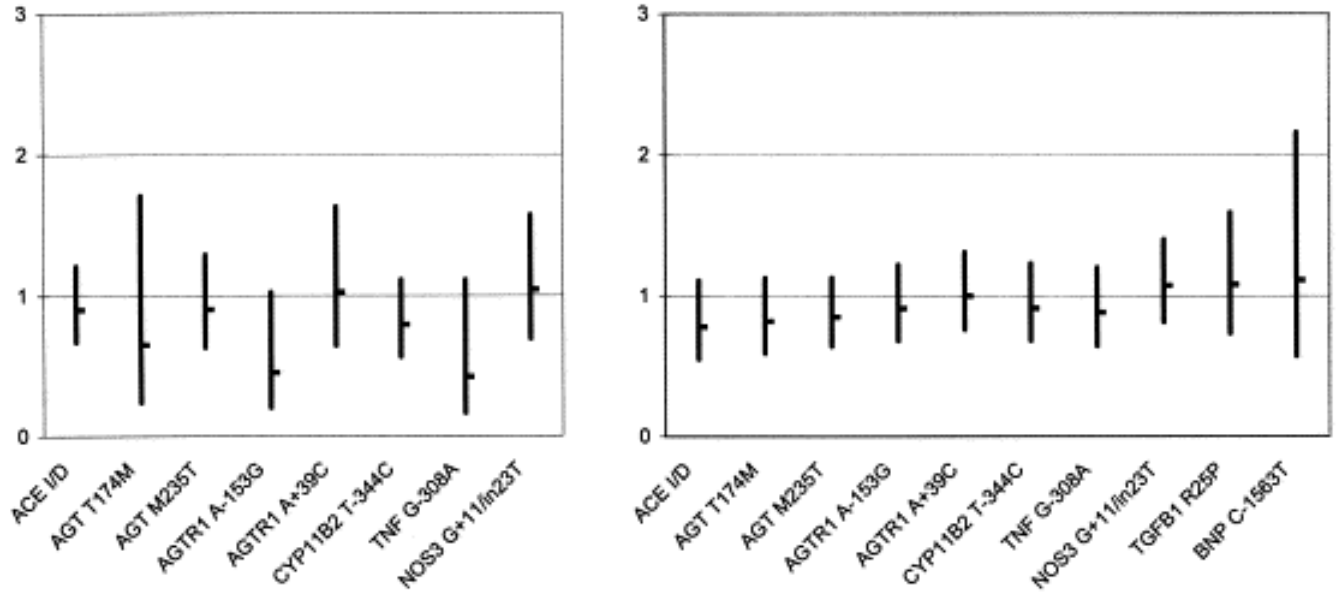
ETAR C1363T, C69T

4. Miscellaneous

Bradykinine receptor, TNF, NOS, APOE, AMPD, etc.

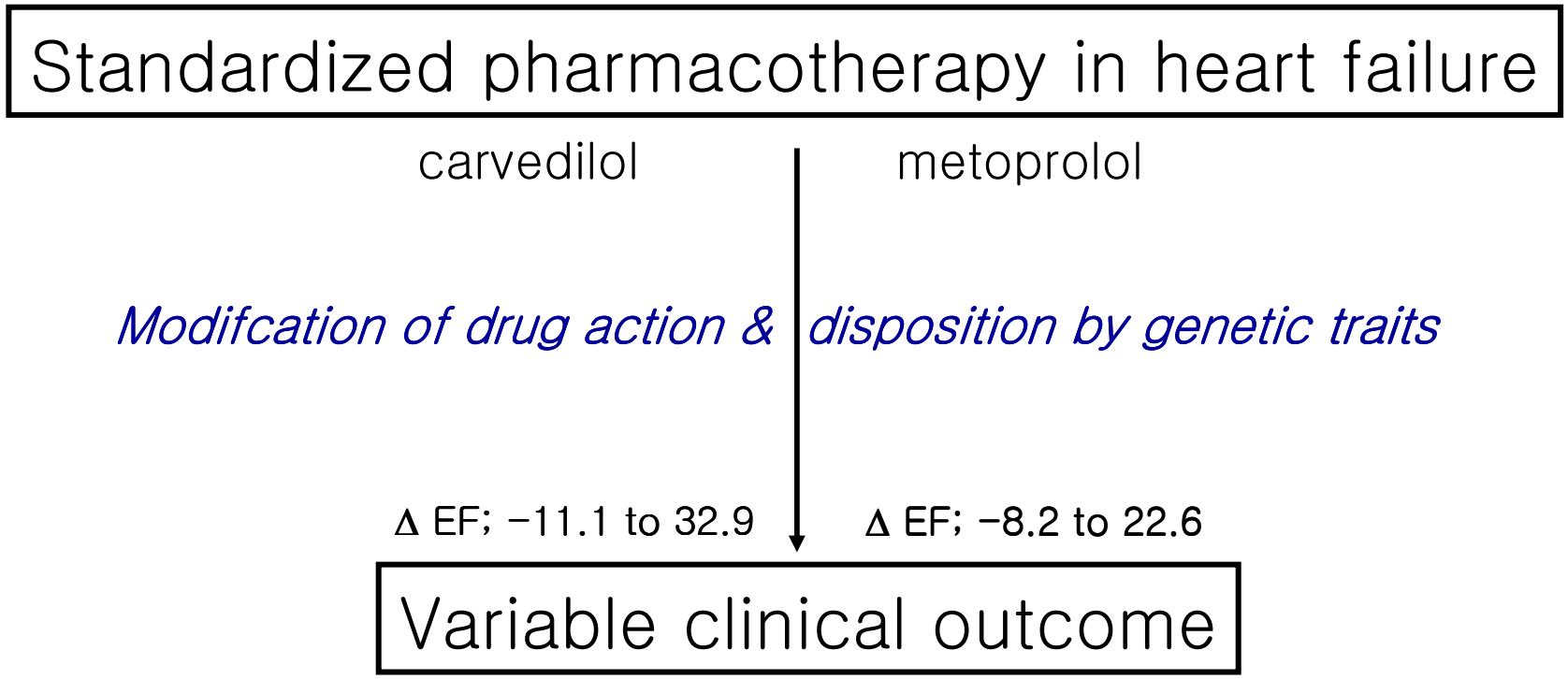
1. Susceptibility genes
   질병의 발생에 관여
2. Modifier genes
   질병의 경과에 관여

Lack of Association between Polymorphisms of Eight Candidate Genes and Idiopathic DCMP CARDIGENE Study



Tiret L, et al. J Am Coll Cardiol 2000;35:29.

Pharmacogenetics in Heart Failure



Contents

1. Pharmacogenetics of drug action
   genetic polymorphism in target of drug

2. Pharmacogenetics of drug disposition
   genetic polymorphism in drug metabolism
   genetic polymorphism in drug transport

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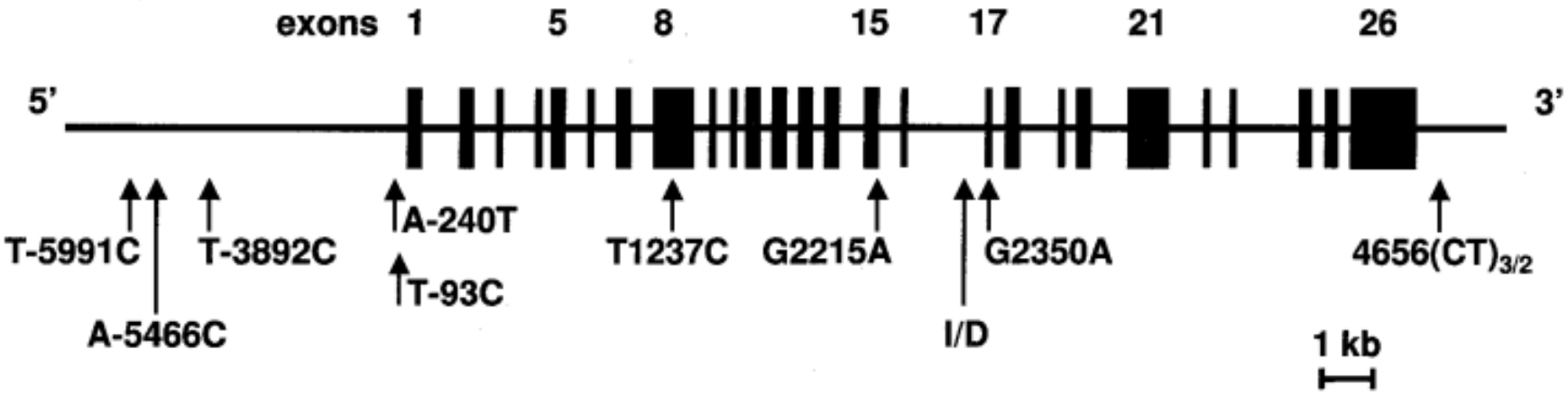
   genetic polymorphism in drug metabolism
   genetic polymorphism in drug transport

Angiotensin-Converting Enzyme gene

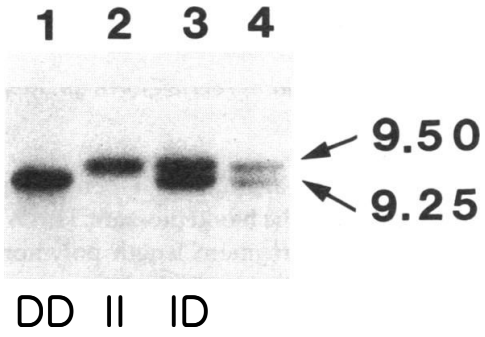
- located in the long arm of chromosome 17 (17q23)
- 21 kb long
- 26 exon and 25 introns
- more than 160 polymorphisms



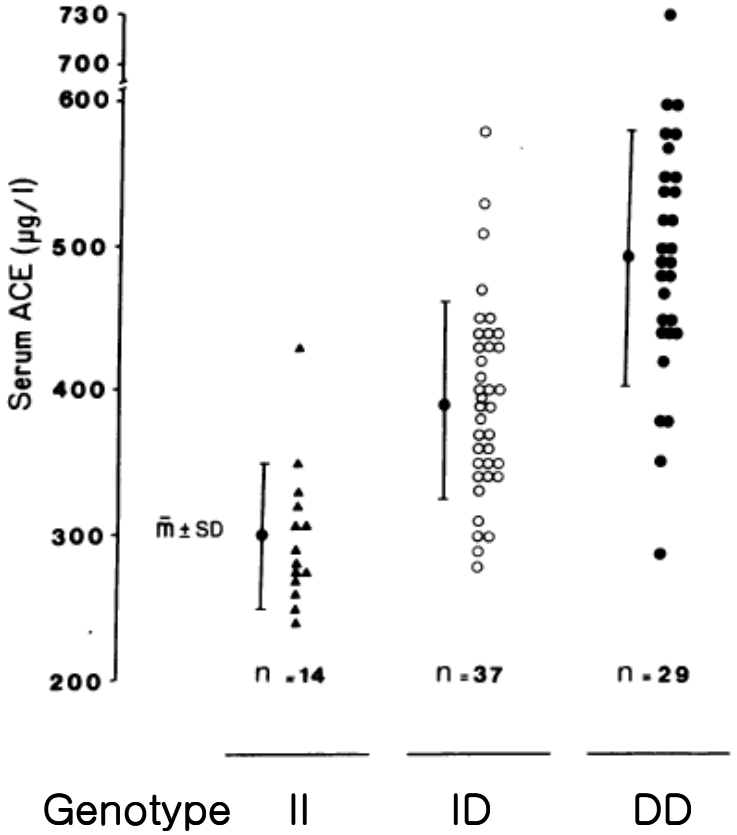
Location of 10 bi-allelic polymorphisms in ACE gene

Insertion/Deletion polymorphism of ACE gene

- 278-bp Alu element in intron 16 of the ACE gene



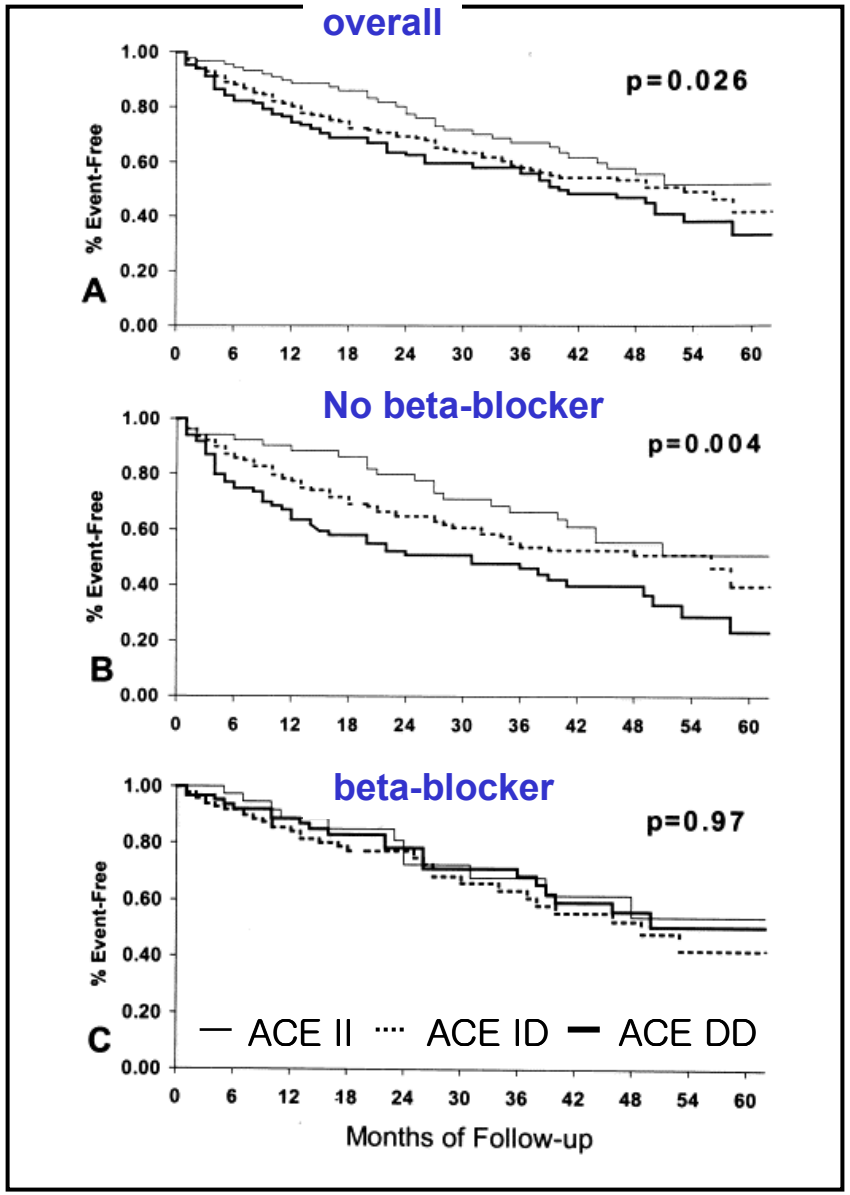
- Functionally neutral, but in strong linkage-disequilibrium with another unobserved functional mutation
- Equivocal or weak association with hypertension, LVH, cardiomyopathy.

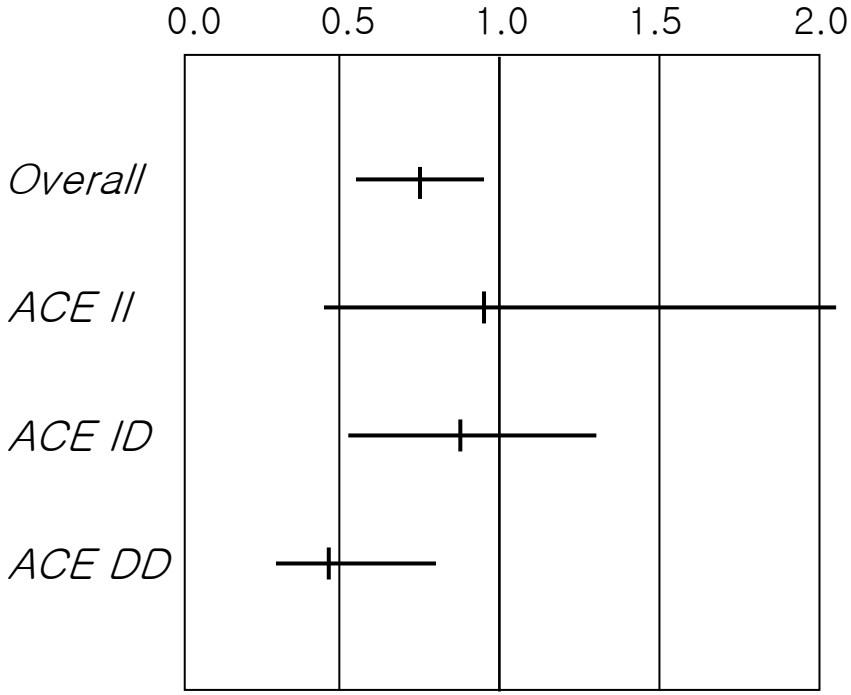


Rigat B, et al. J Clin Invest 1990 199086:1343.

GRACE (Genetic Risk Assessment of Cardiac Event) study

479 patients with ischemic/nonischemic CMP(LVEF;0.25 ± 0.08)





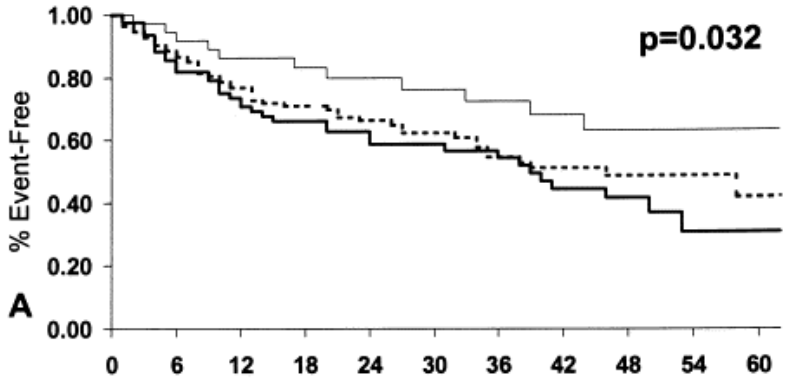
Relative risk of death/transplantation by beta-blocker use

McNamara DM, et al. J Am Coll Cardiol 2004;44:2019

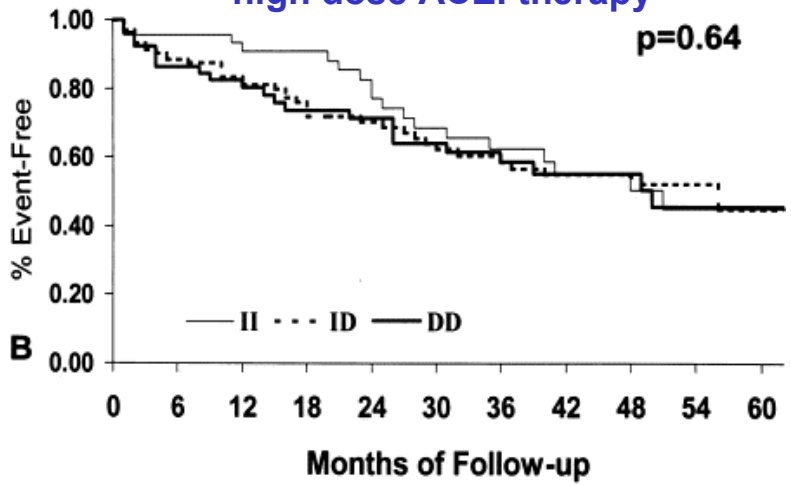
GRACE (Genetic Risk Assessment of Cardiac Event) study

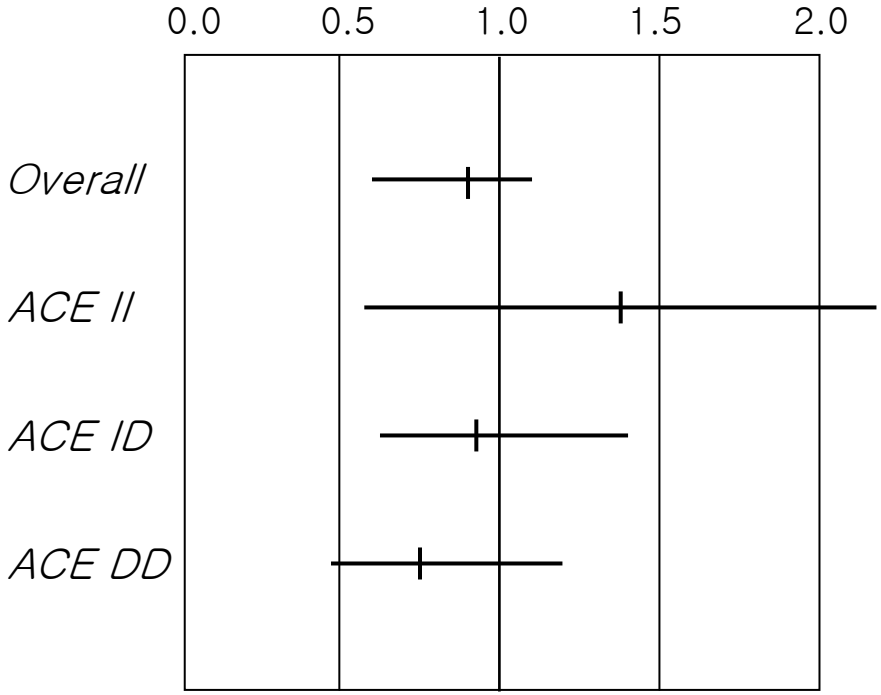
479 patients with ischemic/nonischemic CMP(LVEF;0.25 ± 0.08)

low dose ACEI therapy



high dose ACEI therapy



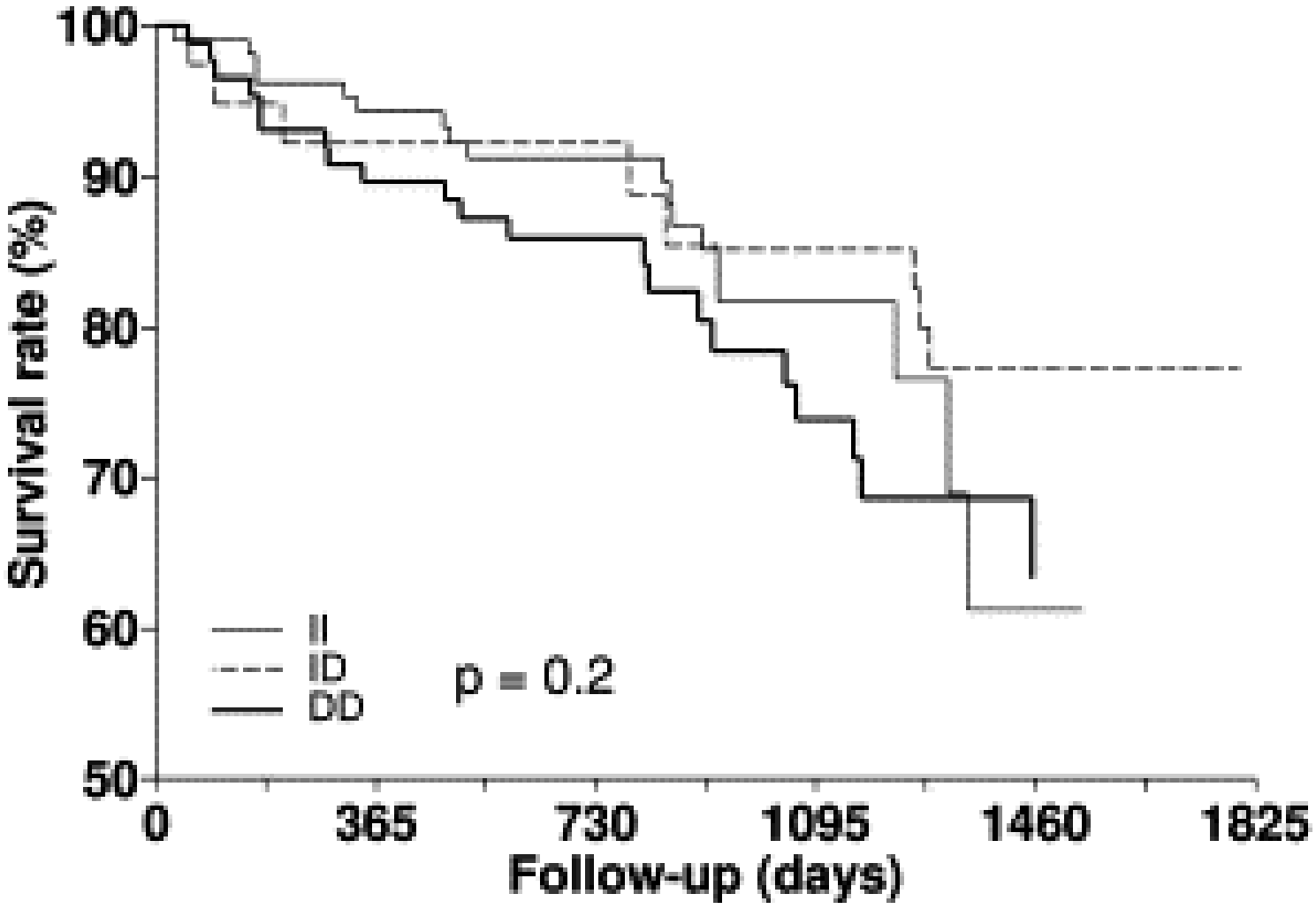


Relative risk of death/transplantation by ACE inhibitor dose use

McNamara DM, et al. J Am Coll Cardiol 2004;44:2019

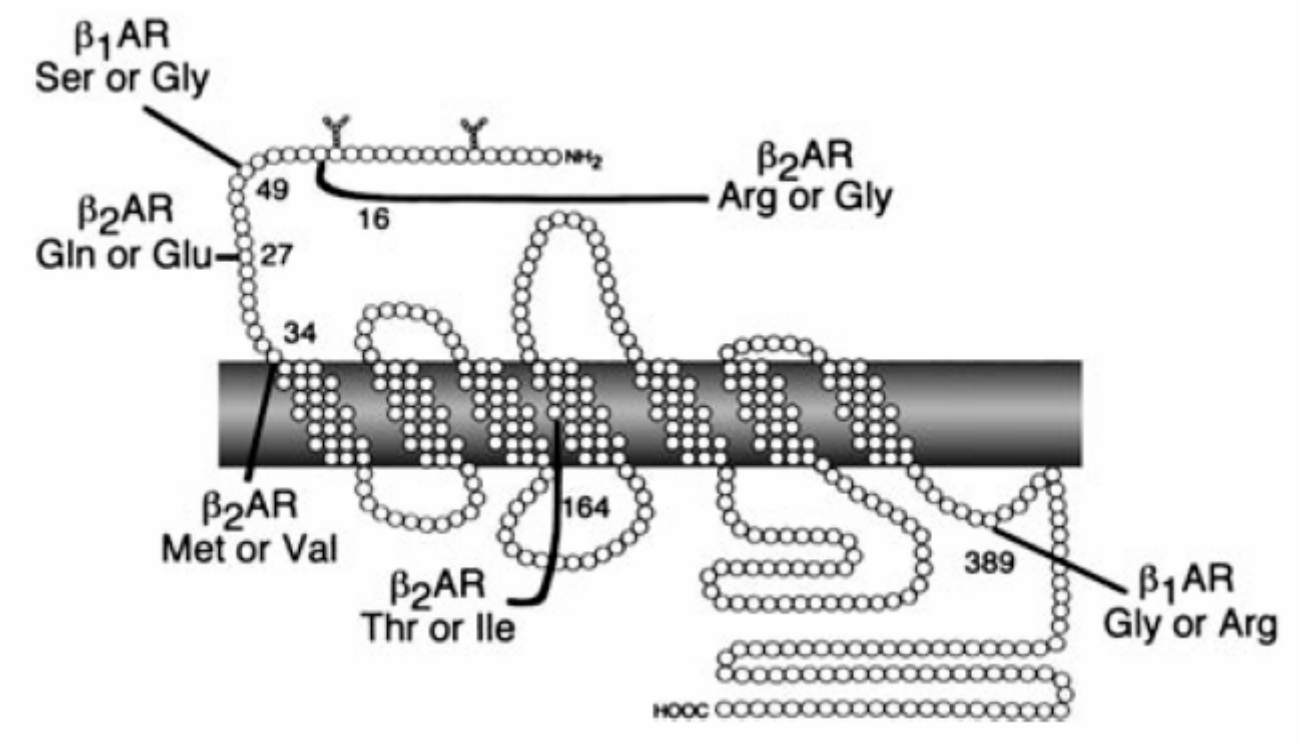
β-blocker therapy and ACE (I/D) polymorphism in chronic HF; France study

199 β-blocker naive patients with CHF (LVEF;0.30 ± 0.10)



deGroote P, et al. Eur J Heart Fail 2004;6:17.

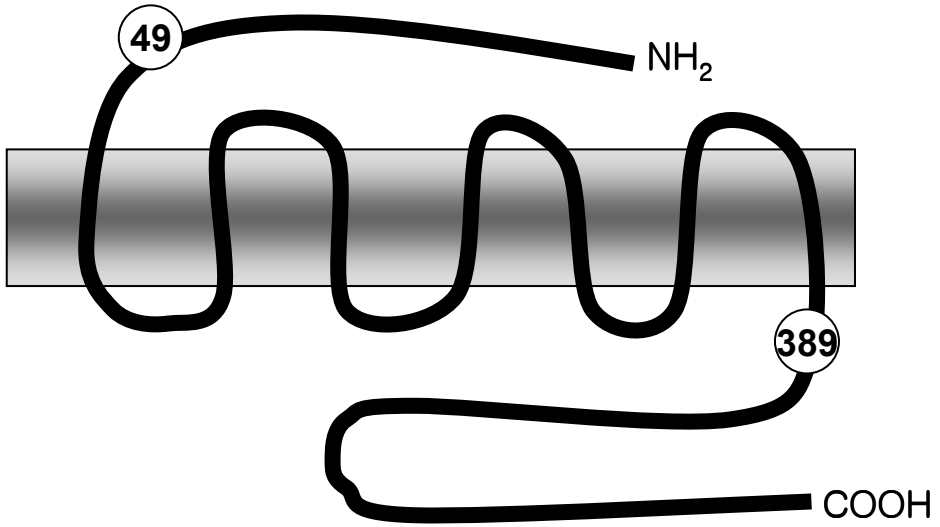
β Adrengergic Rereceptor



β_1-AR: encoded by intronless gene, consists of 477 amino acids
β_2-AR: similar genomic structure, consists of 413 amino acids

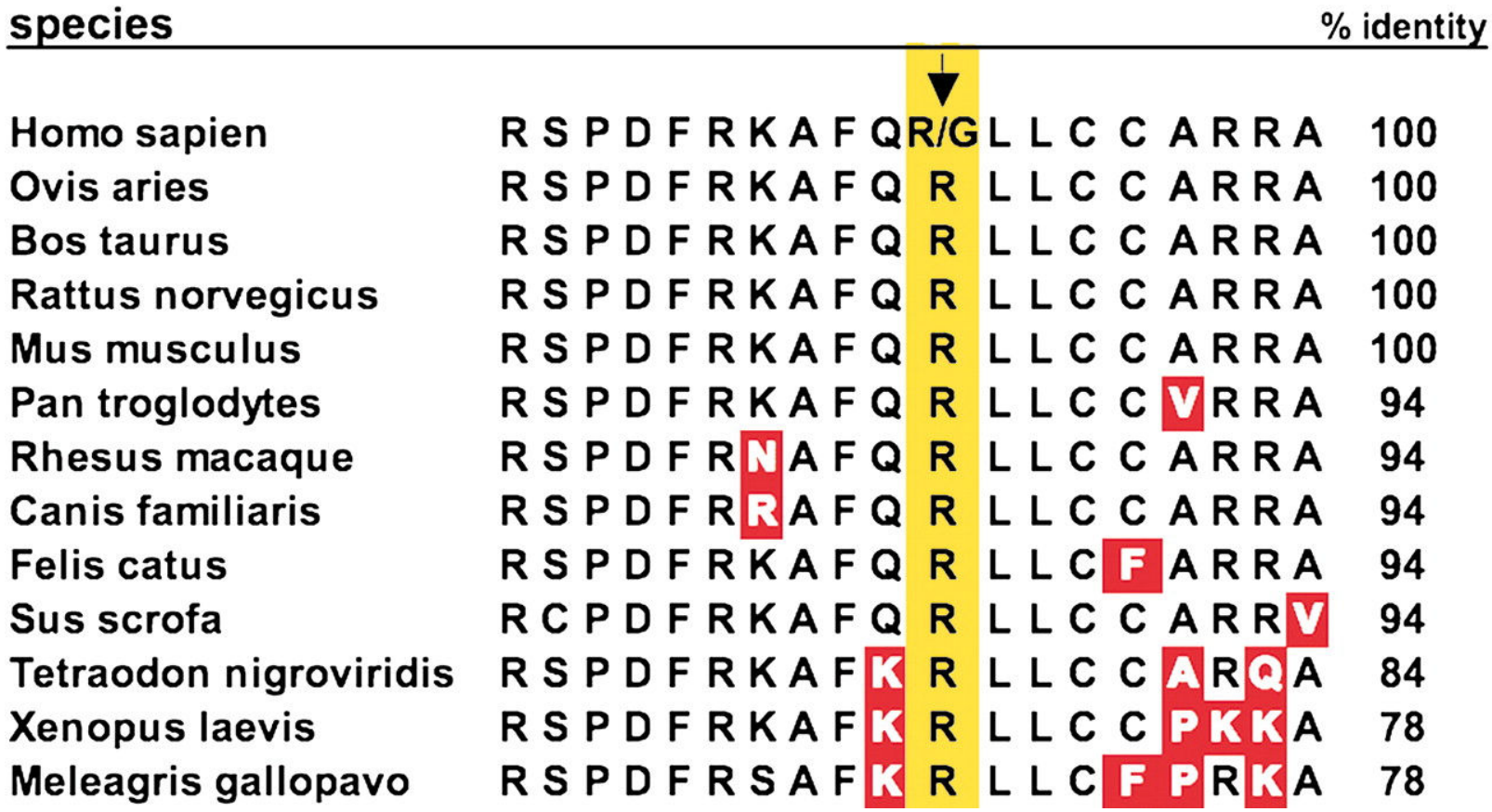
Localization of β-adrenergic receptor polymorphisms in the Human

β_1 adrenergic receptor



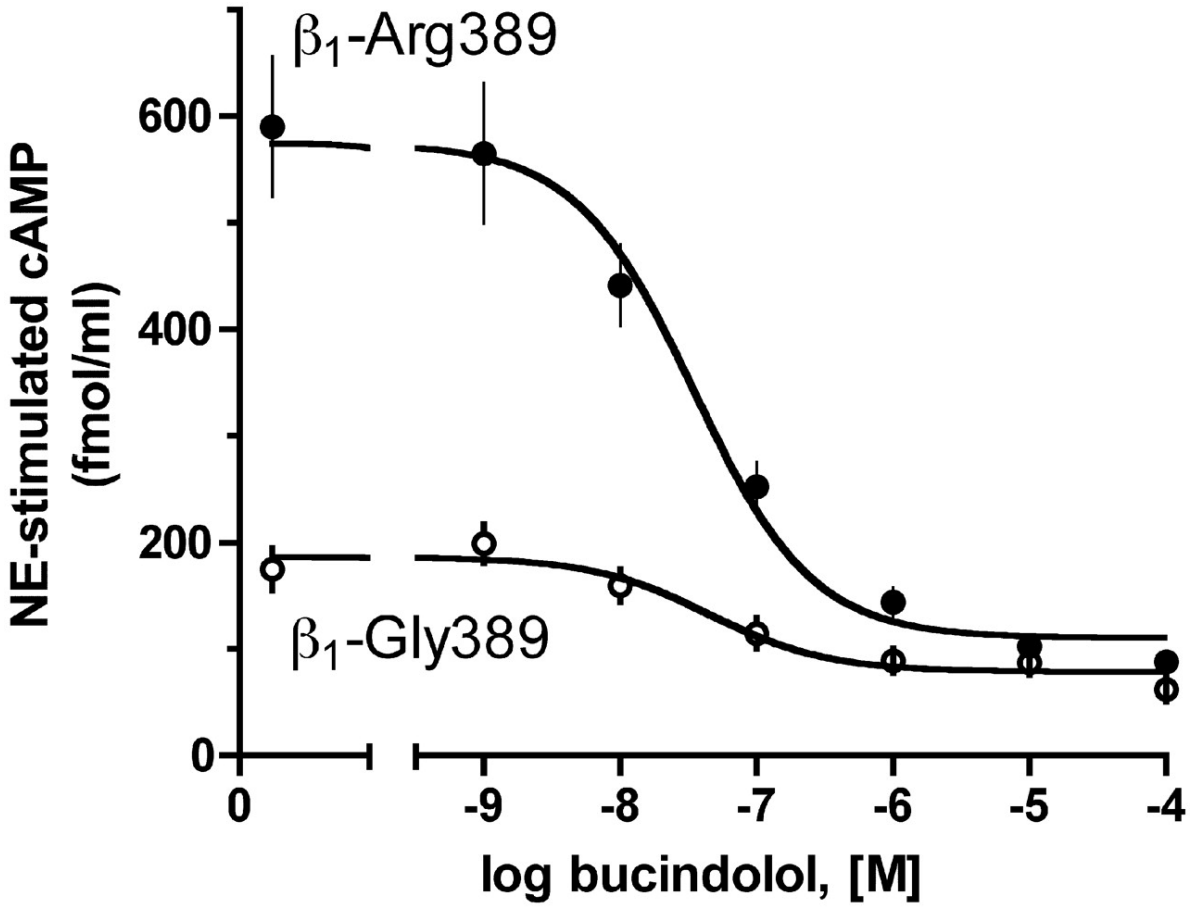
Codon	Polymorphism	Allele frequency	Function in vitro
β_1			
389	Arg/Gly	0.70/0.30	Arg = gain of function (↑cAMP)
49	Ser/Gly	0.85/0.15	No data

β_1AR Ser389Gly polymorphism in human

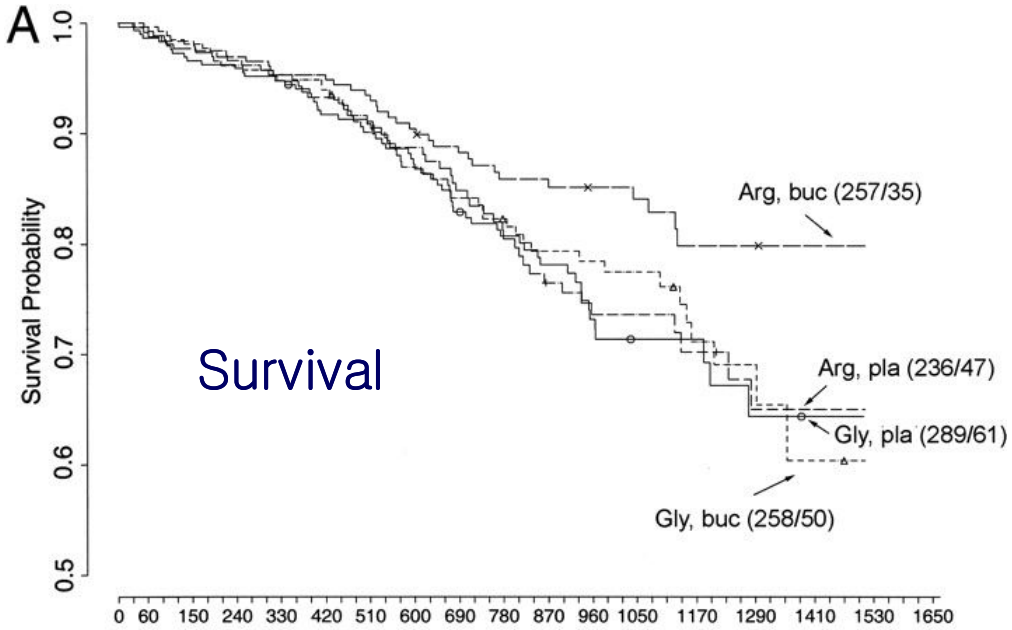


Ligget SB, et al. Proc Natl Acad Sci USA 2006;103:11288.

Different response according to β_1AR Arg389Gly polymorphism to agonist and antagonist

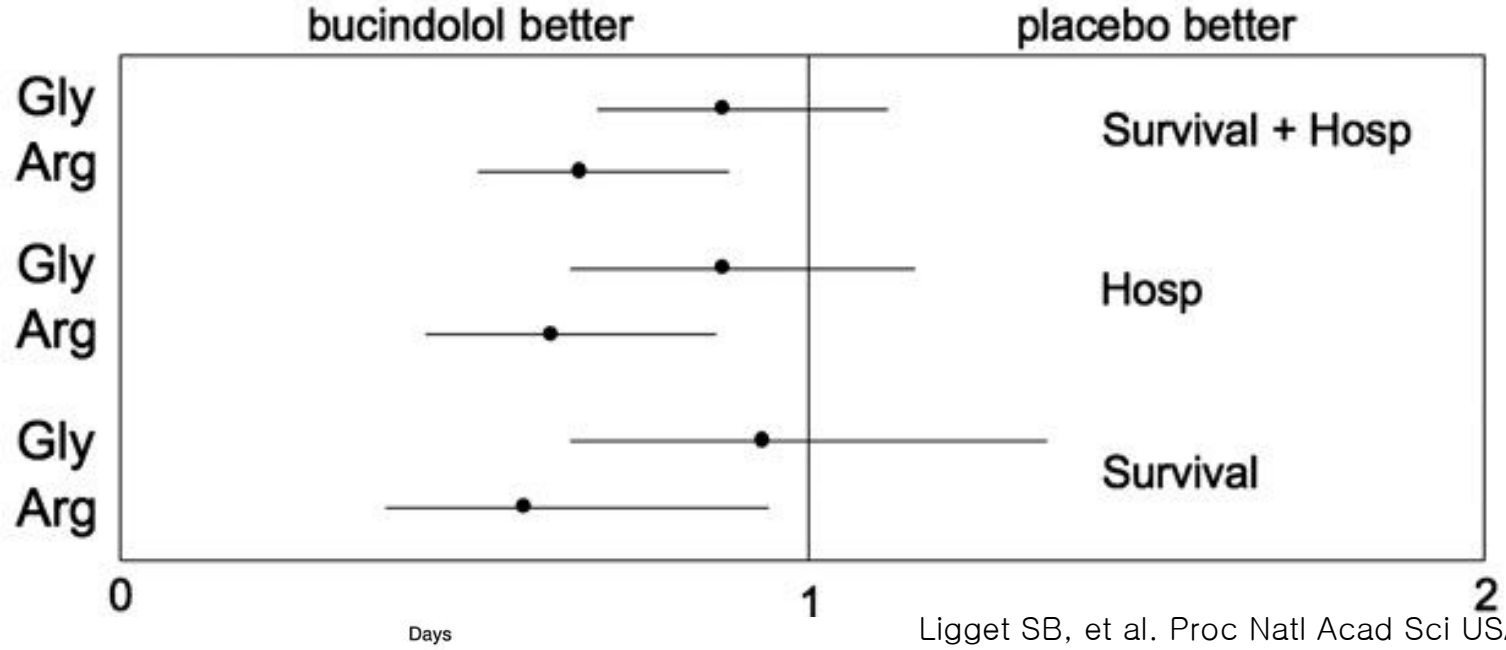


Ligget SB, et al. Proc Natl Acad Sci USA 2006;103:11288.



BEST (Beta-blocker Evaluation In Survival Trial)

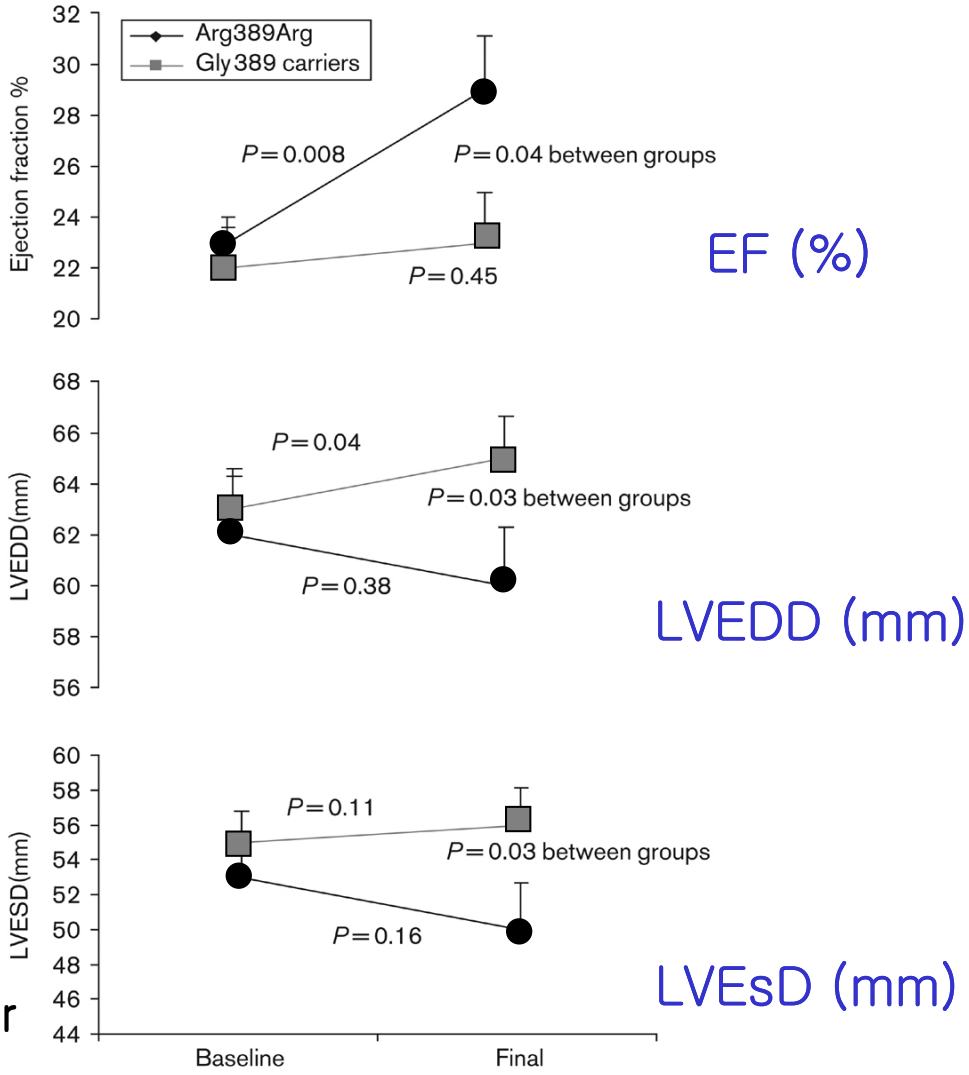
- NYHA class III-IV
- 1040 patients genotyped
- Arg homozygote vs Gly carrier



Ligget SB, et al. Proc Natl Acad Sci USA 2006;103:11288.

β1-AR polymorphism and LV remodeling change
in response to β-blocker therapy

- 61 β-blocker naive patients with systolic LV dysfunction NYHA II-III, LVEF ≤ 40 %
- β1 AR genotyping Serg49Gly, Arg389Gly
- Titration with metoprololCR/XL upto 200 mg/d or maximum tolerable dose
- Echocardiographic follow-up after 3 month

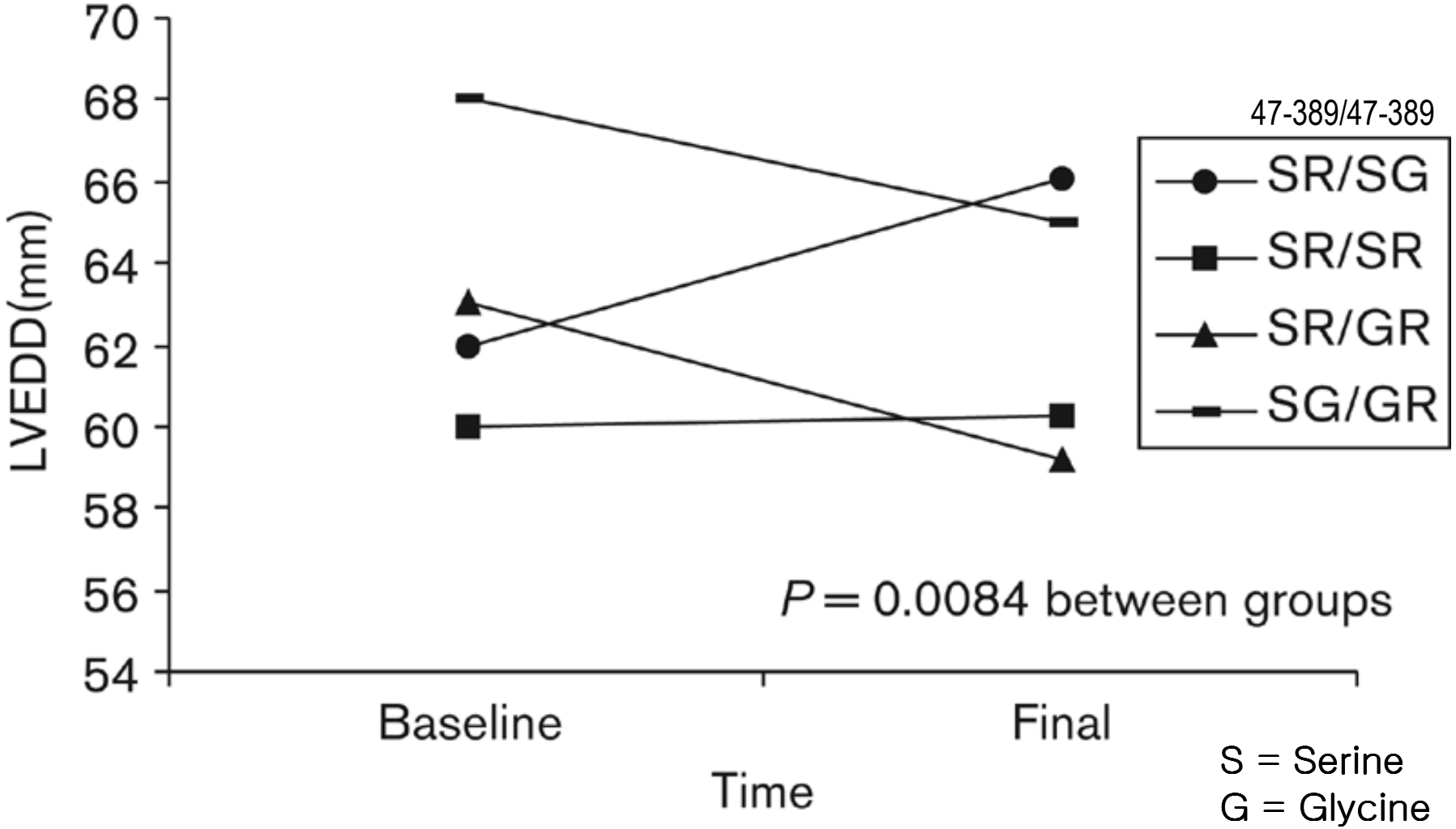


Arg389Arg

Gly389 carrier

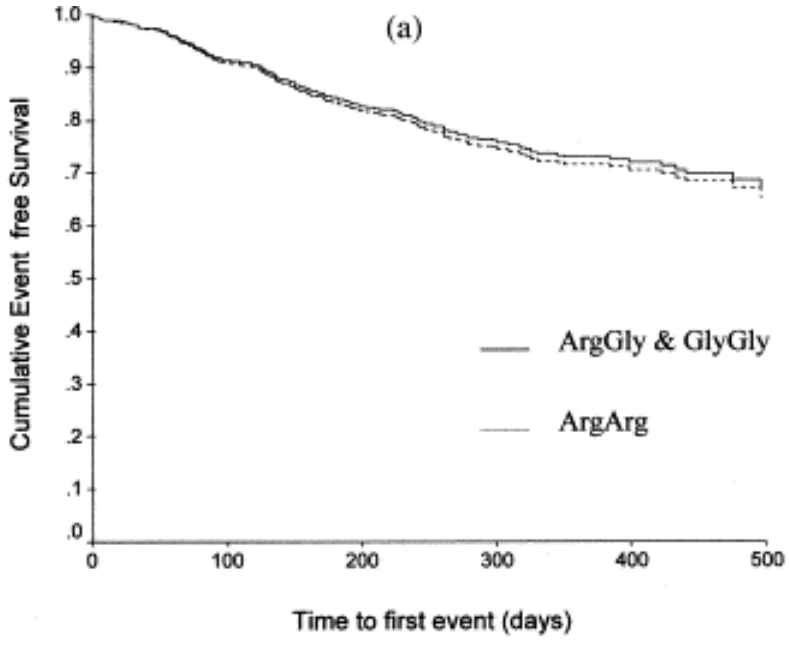
Terra SG, et al. Phramacogenet Genomics 2005;15:227

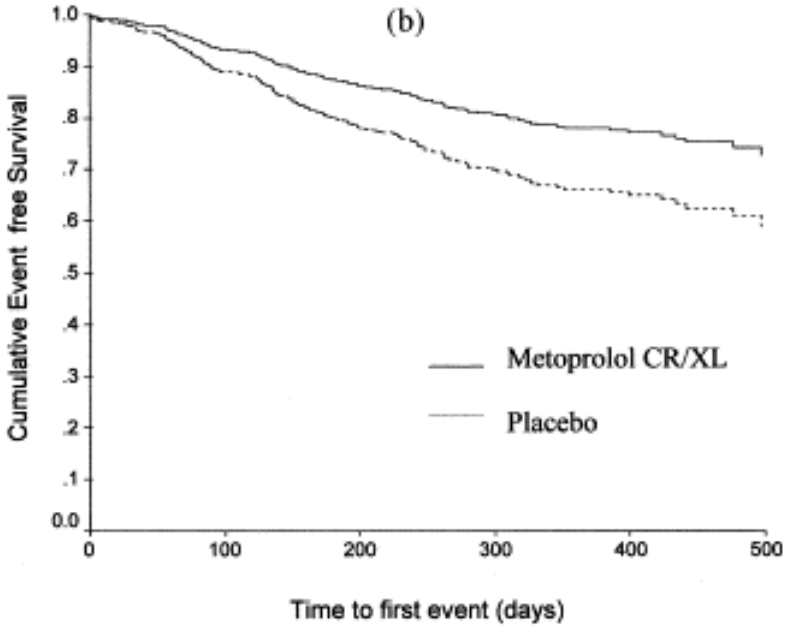
β1-AR polymorphism and LV remodeling change
in response to β-blocker therapy



S = Serine
G = Glycine
R = Arginine

Terra SG, et al. Phramacogenet Genomics 2005;15:227





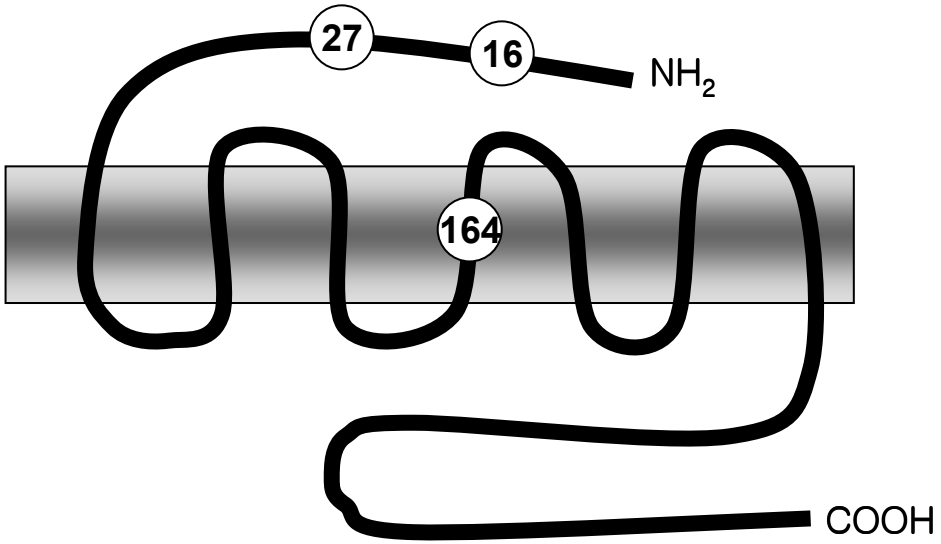
MERIT-HF substudy

- NYHA class II-IV
- Metoprolol CR/XL 200 mg/d vs placebo
- 600 patients genotype Arg389Gly polymorphism
- combined effect of total mortality + hospitalization

MERIT-HF Study Group. Eur J Heart Fail 2003;5:463

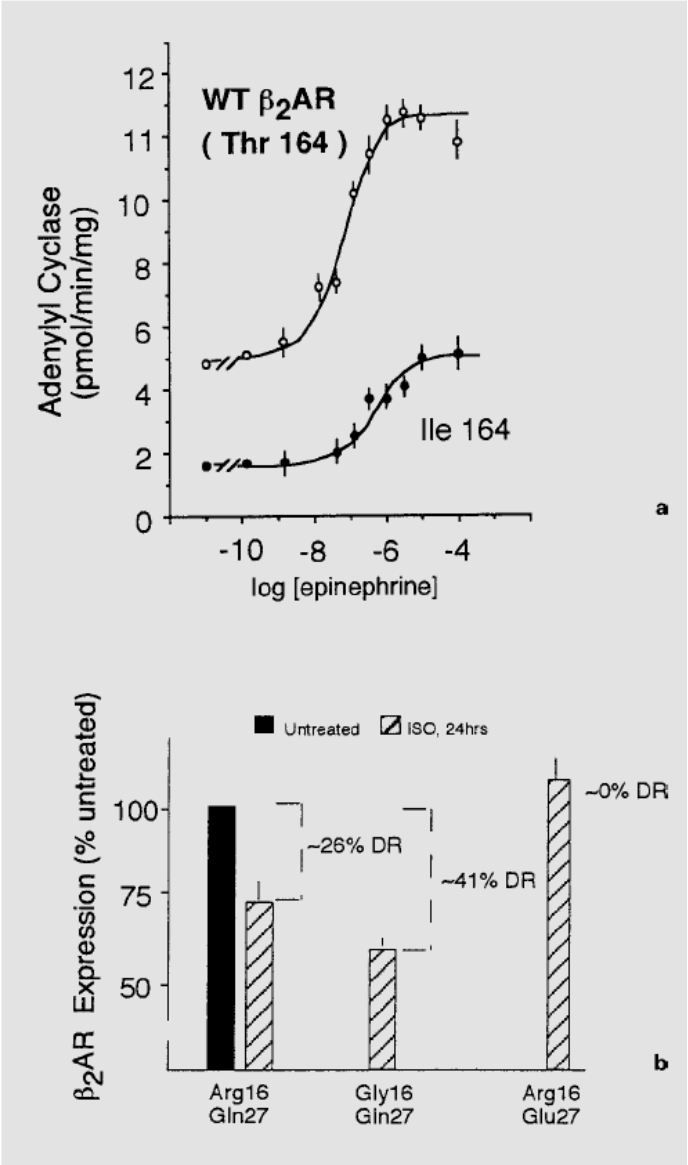
Localization of β-adrenergic receptor polymorphisms in the Human

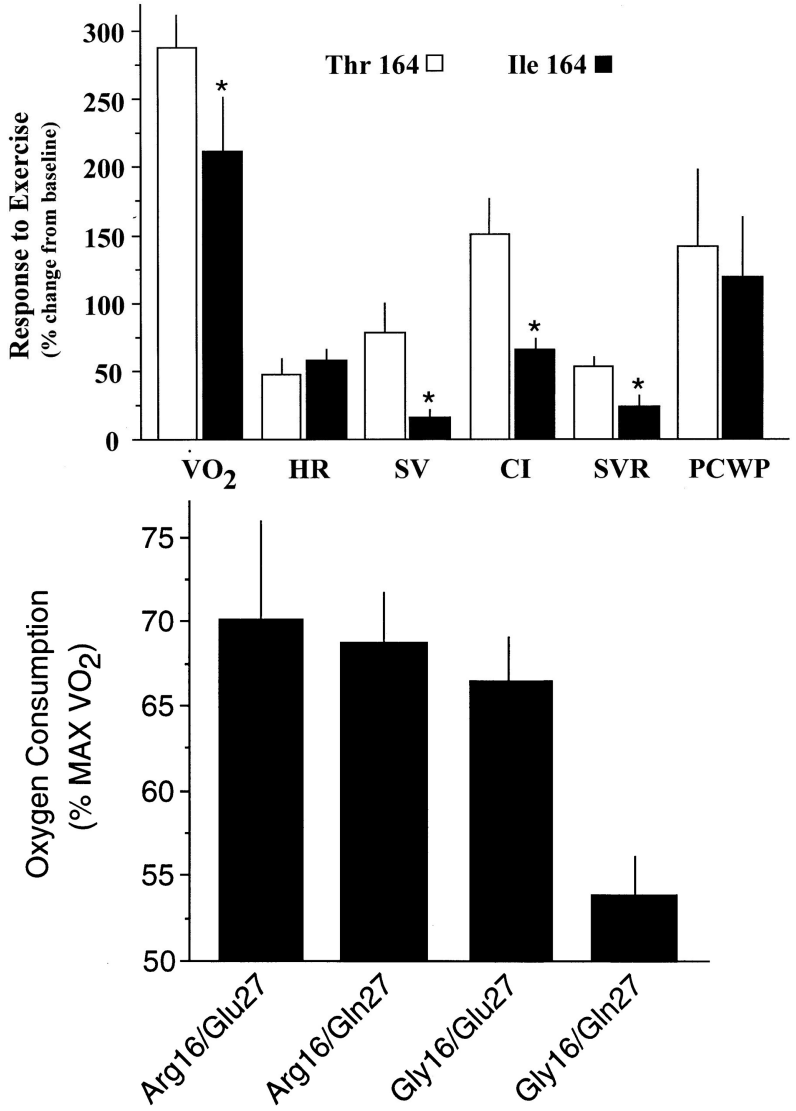
β_2 adrenergic receptor



Codon	Polymorphism	Allele frequency	Function in vitro
β_2			
16	Arg/Gly	0.40/0.60	Gly = enhanced downregulation
27	Gln/Glu	0.55/0.45	Glu = resistance to downregulation
164	Thr/Ile	0.95/0.05	Ile = loss of function

β_2AR polymorphism and pharmacologic response





Wagoner LE,et al. Circ Res 2000;86:834.

β_2AR polymorphism and pharmacologic response

- 80 CHF patients treated with *carvedilol*
- β_2 AR genotyped
  Arg16Gly, Gln27Glu
- Echocardiographic follow-up
  Good responder:
  LVEF increase of 10% or more
  LVFS increase of 5% or more

Rate of Good responder

#16 Gly/Gly Arg/Gly : Arg/Arg = 44% : 38%, P=NS

#27 Gln/Gln : Glu/Glu Gln/Glu = 26% : 63%, P=0.003

Kaye DM, et al. Pharmacogenetics 2003;18:379.

Other genetic polymorphisms

1. Angiotensinogen
2. Endothelial nitric oxide synthase (NOS3)
3. AMP deaminase-1
4. Tumor necrosis factor
5. Matrix metalloproteinase

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1. Pharmacogenetics of drug action
   genetic polymorphism in target of drug

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   genetic polymorphism in drug metabolism
   genetic polymorphism in drug transport

Polymorphism in drug metabolism

Cytochrome *P* 450 (CYP)

CYP 1 (family), A (subfamily), 2 (gene)

	CYP2D6, %			CYP2C19, %		CYP2C9, %	
	Absent	Present	Ultrarapid	Absent	Present	Absent	Present
African/African-American	8	92	?	4–7	93–96	0.003	>99
Asian	1	98	1	12–22	78–88	0.08	>99
White	7	92	1	3	97	0.36	>99

Abernethy DR, et al. Circulation 2000;101:1749.

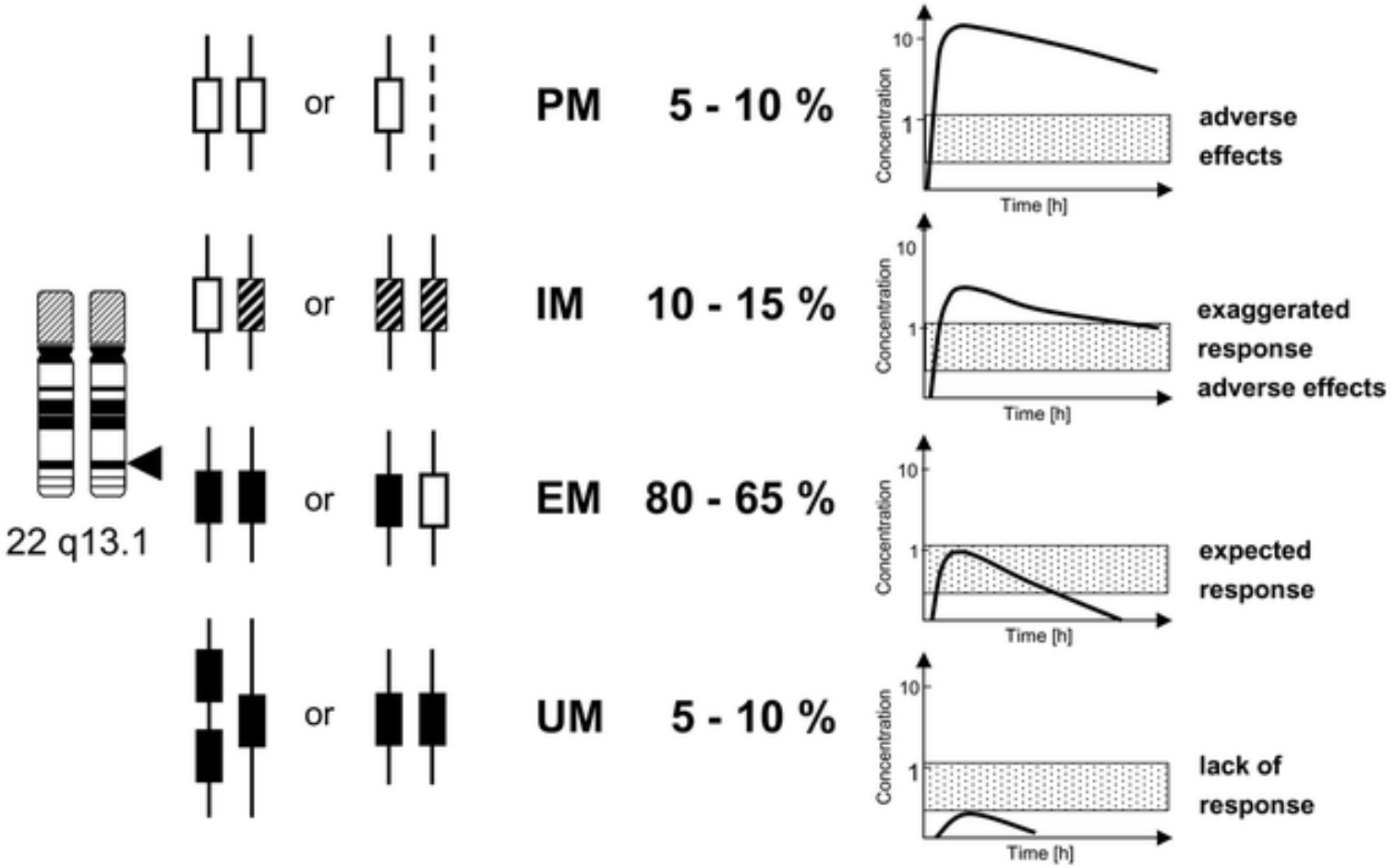
Drugs metabolized by cytochrome P450 2D6 (CYP2D6)

Analgesica
Anti-ADHD drugs
Antiarrhythmics
Antidementia drugs
Tricyclic antidepressants
Antidiabetic
Antiestrogen
Antihypertensives
Antiemetics
Antihistamines
Antipsychotics
Appetite suppressants
Beta-adrenergic blockers
Calcium antagonists
MAO-inhibitors
Recreational drugs
Vasodilators

Alprenolol
Bufuralol
Bunitrolol
Bupranolol
Carvedilol
Metoprolol
Propranolol
Timolol

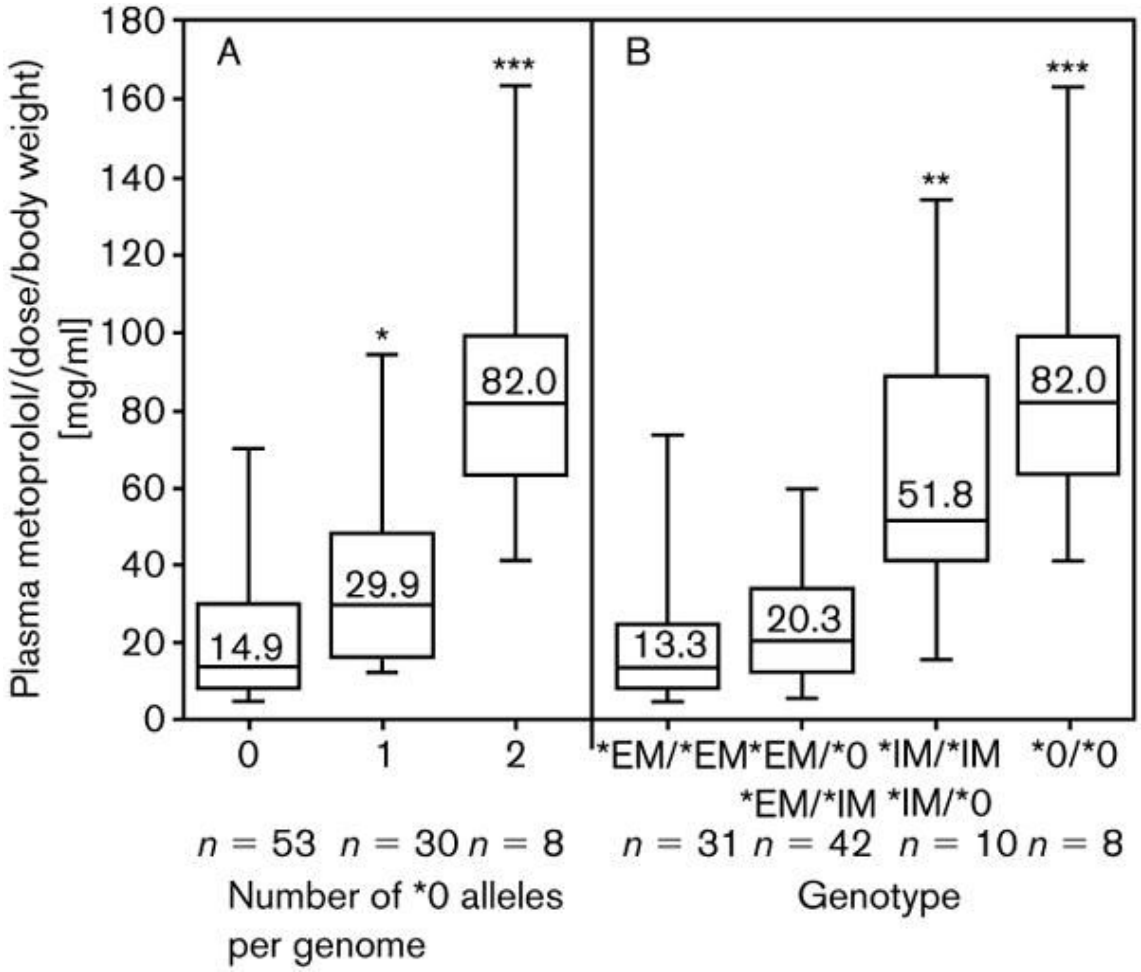
Zanger UM, et al. Naunyn-Schmiedebergs Arch Pharmacol 2004;369:23.

Schemes of CYP2D6 genotype-phenotype relationship



Zanger UM, et al. Naunyn-Schmiedebergs Arch Pharmacol 2004;369:23.

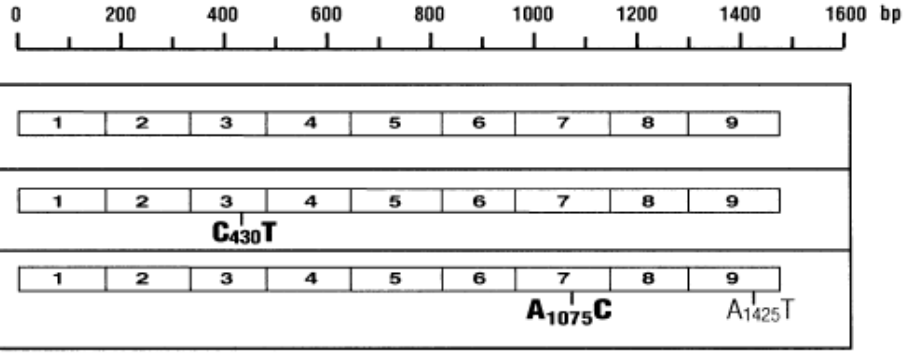
Metoprolol plasma concentration by CYP2D6 genotype



Rau T, et al. Pharmacogenetics 2002;12:465.

Polymorphism in the human CYP2C9

Allele	Trivial name	Effect of nucleotide changes	Enzyme activity
*CYP2C9*1*	$CYP2C9_{wt}$		100
*CYP2C9*2*	Cys 144	Arg_{144} Cys	12%
*CYP2C9*3*	Leu 359	Ile_{359} Leu	<5%



†substrate dependent

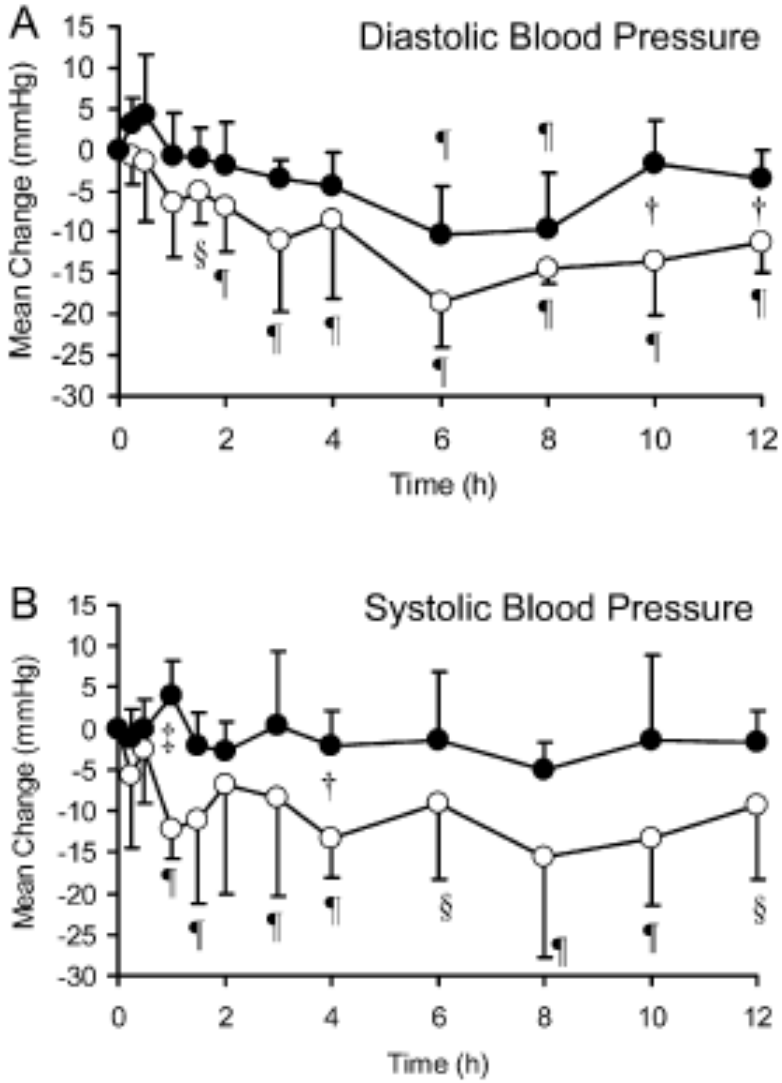
Substrate drugs:
Phenytoin, S-warfarin, tolbutamide, glipizide, glibenclamide, torsemide, losartan, irbesartan.non-steroidal anti-inflammatory drugs

Prodrug losartan $\xrightarrow[\textit{activation}]{\text{CYP2C9}}$ EXP3174

Irbesartan $\xrightarrow[\textit{inactivation}]{}$ Metabolite

Goldstein JA. Br J Clin Pharmacol 2001;52:349

Effect of the CYP2C9*3 allele on pharmacogenetics of Losartan in healthy Japanese subjects



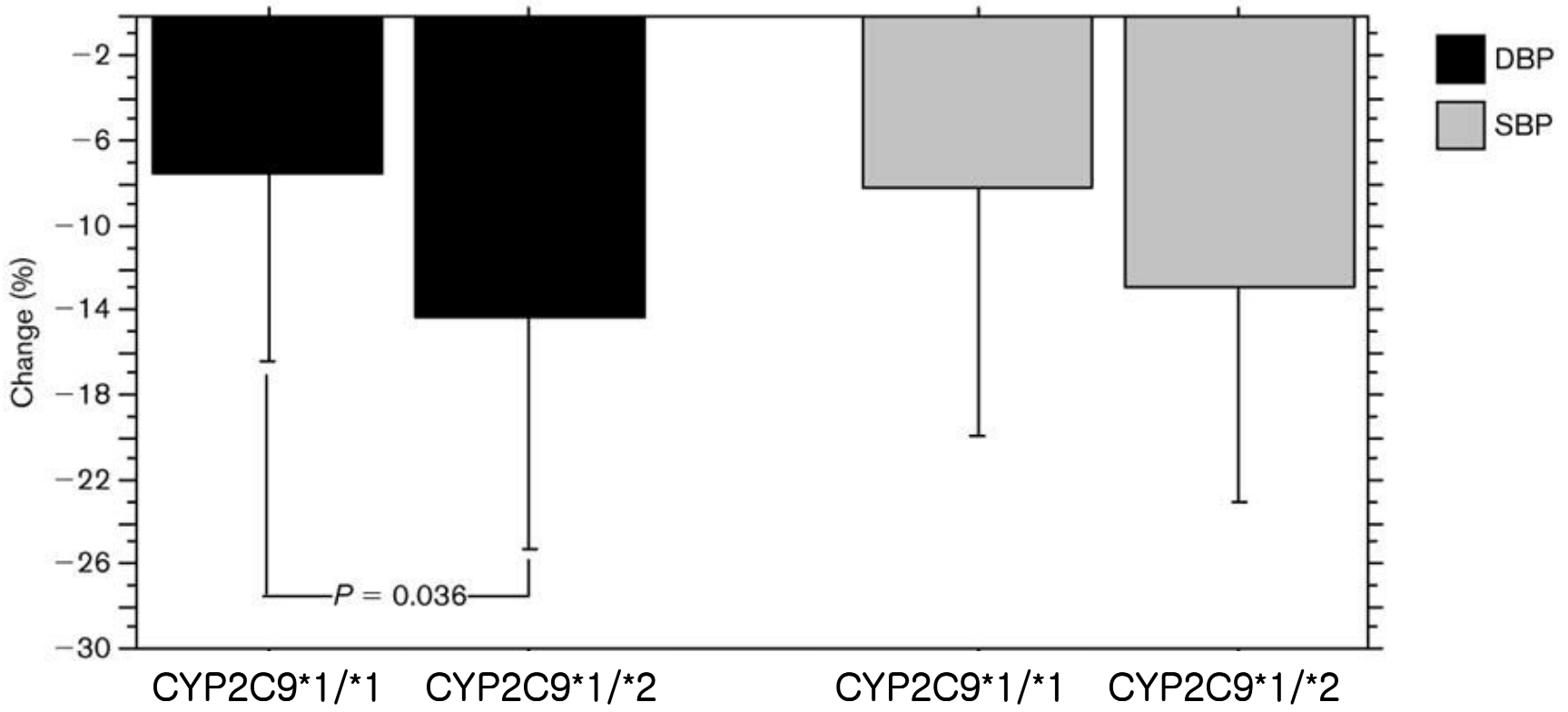
● CYP2C9*1/*3

○ CYP2C9*1/*1

Sekino K, et al. Eur J Clin Pharmacol 2003;59:589.

CYP2C genotype predicts the BP response to irbesartan

SILVHIA (Swedish irbesartan LV hypertrophy investigation vs atenolol)trial

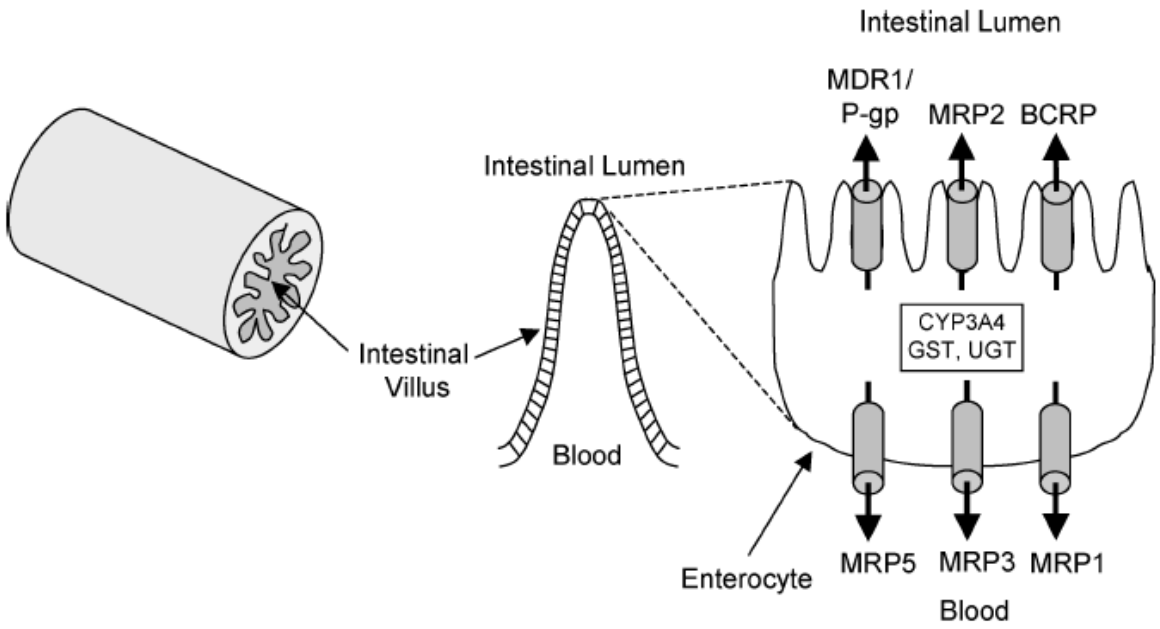


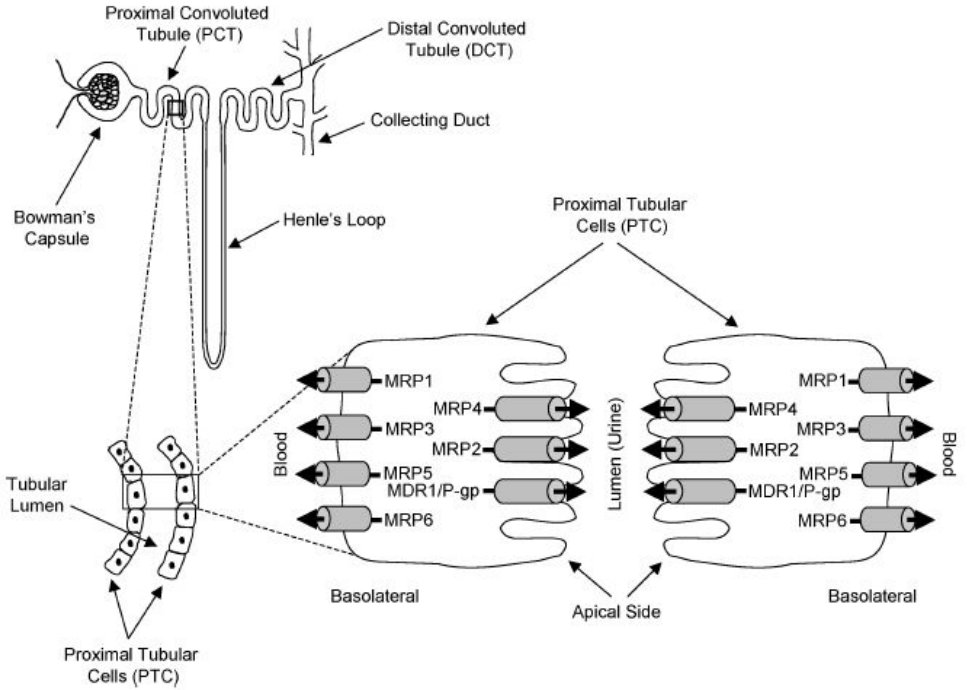
Hallberg P, et al. J Hypertens 2002;20:2089.

Polymorphism in drug transport

P-glycoprotein

- a member of ATP-binding cassette superfamily
- drug transporter across the cell membrane
  - responsible for the resistance to anticancer drug
  - renal drug transporter
  - efflux pump from CNS for selected drugs
  - barrier to drug absorption in the intestinal wall
- encoded by MDR-1 gene


Intestinal Lumen
MDR1/
P-gp
MRP2
BCRP
Intestinal Lumen
CYP3A4
GST, UGT
Intestinal
Villus
Blood
Enterocyte
MRP5
MRP3
MRP1
Blood


Proximal Convoluted
Tubule (PCT)
Distal Convoluted
Tubule (DCT)
Collecting Duct
Bowman's
Capsule
Henle's Loop
Proximal Tubular
Cells (PTC)
MRP1
MRP4
MRP3
MRP2
MRP5
MDR1/P-gp
MRP6
Blood
Lumen (Urine)
Blood
Tubular
Lumen
Basolateral
Apical Side
Basolateral
Proximal Tubular
Cells (PTC)

A Partial List of drug substrates transported by human P-gp

Anticancer

Actinomycin D
Daunorubicin
Doxorubicin
Etoposide
Imatimib
Mitoxantrone
Paclitaxel
Irinotecan
Topotecan
Vinblastine
Vincristine

Antihypertensive

Celiprolol
Losartan
Nicardipine
Reserpine
Talinolol

Cholesterol drugs

Atorvastatin
Lovastatin

Antibiotics

Clarithromycin
Erythromycin
Levofloxacin
Rifampin
Sparfloxacin
Tetracyclin

Antimycotics

Itraconzole
Ketoconazole

Antiepilptics

Phenobarbital
Phenytoin

Immuno suppressants

Cyclosporin
Sirolimus
Taclolimus
Valspodar

Antacids

Cimetidine
Ramitidine

Glucocorticoids

Aldosterone
Cortisol
Dexamethasone

Antiviral

Amprenavir
Indinavir
Nelfinavir
Ritonavir
Saquinavir

Antidepressants

Amitriptyline
Fluoxetine
Paroxetine
Sertraline
St John's wort

Antiemetics

Domperdon
Ondansetron

Antihistamine

Fexofenadine
Terfenadine

Opiods

Methadone
Morphine
Pentazocine

Antiarrhythmics

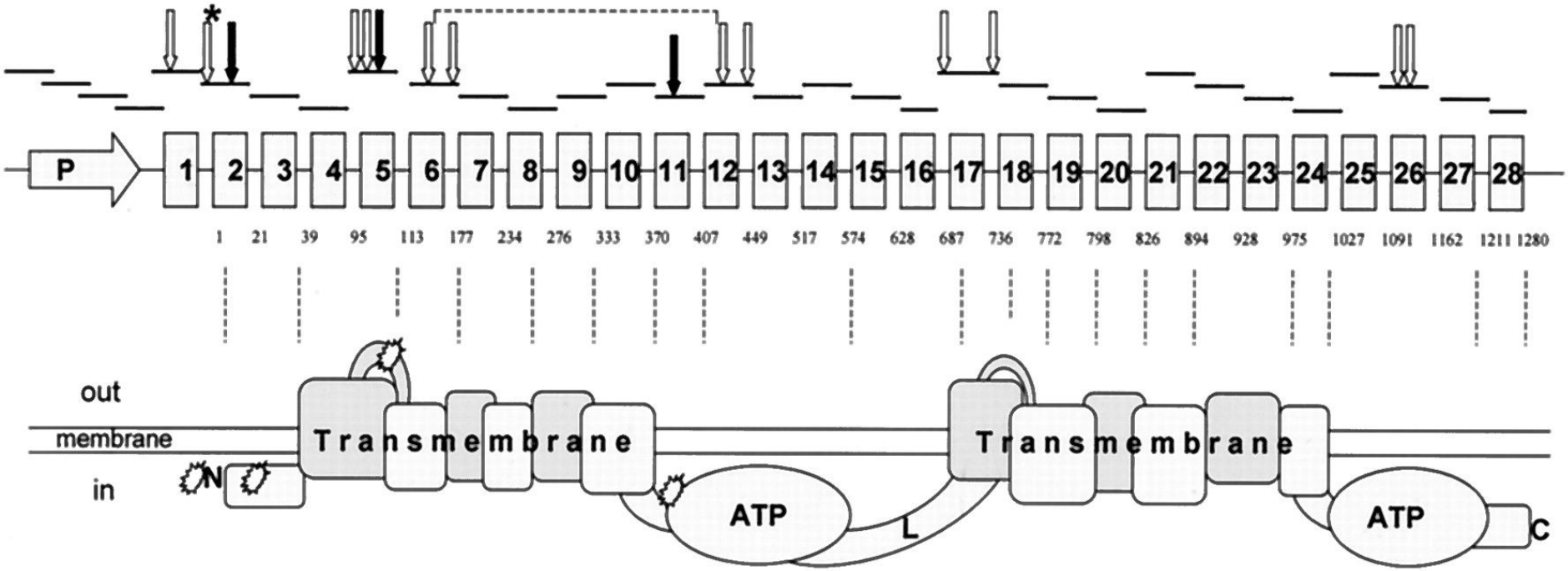
Amiodarone
Digoxin
Propafenone
Quinidine
Verapamil

Others

Bromocriptine
Colchicine
Emetine
Ivermectin
Leperamide
Melfoquine
Progesterone
Retinoic acid
Rhodamine 123
Spironolactone

Choudhuri S, Klaassen CD. Int J Toxicol 2006;25:231.

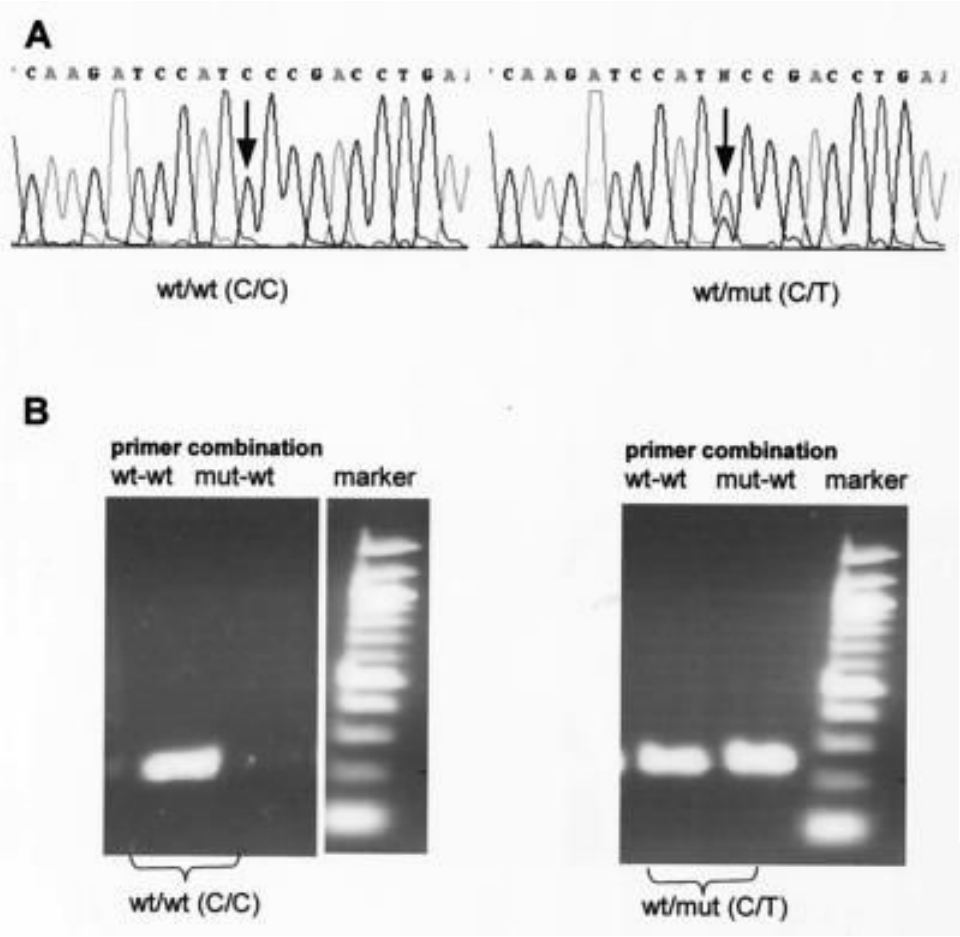
MDR-1 gene

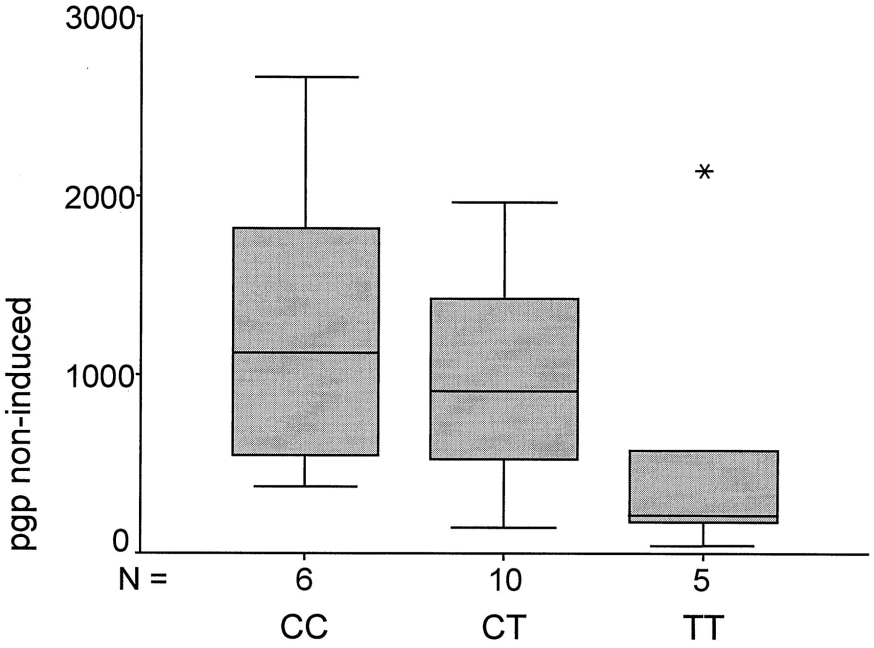


P-glycoprotein

Hoffmyer S, et al Porc Natl Acad Sci USA 200;97:3473.

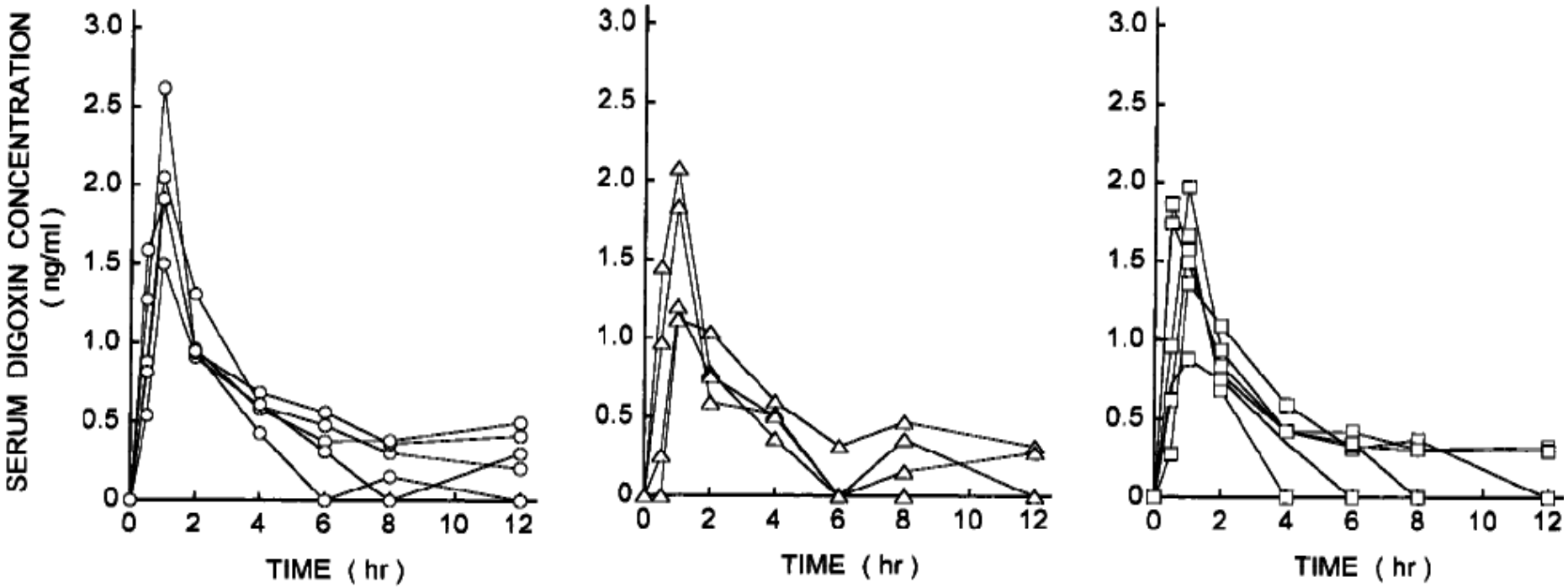
MDR1 C3435T polymorphism





MDR1 genotype-related pharmacokinetics of digoxin In healthy Japanese subjects

MDR-1 C3435T polymorphism



Sakaeda T, et al. Pharmaceutical Res 2001;10:1400

Summary

1. 심부전에서 약물의 target이 되는 분자의 유전형 다형성은 약물 작용 (action)의 차이를 초래할 수 있으며 임상연구는 이는 임상결과의 차이로 귀결될 가능성을 시사하고 있다.

2. 약물의 대사나 수송에 관여하는 분자의 다형성은 약물의 농도에 변화를 야기함으로써 약물 효과나 부작용이 다르게 나타날 수 있다. 임상과의 관련성은 향후의 연구를 필요로 한다.

Randomized, open-label, multi-center study to evaluate the impact of dosage of angiotensin-receptor blocker valsartan and genetic polymorphism on the post-MI LV remodeling

경북의대
계명의대
대구가톨릭의대
영남의대
대구파티마 병원

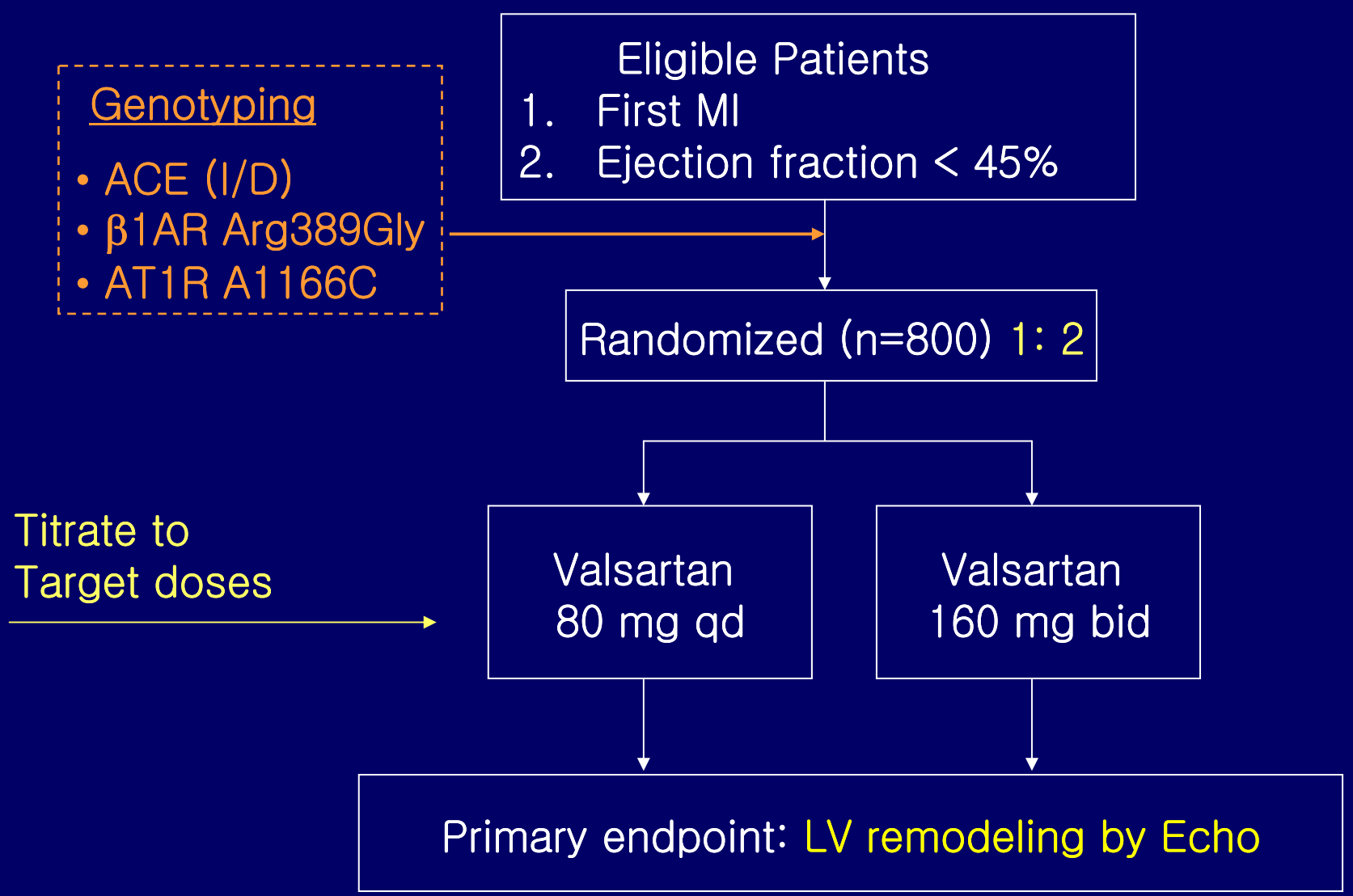
울산의대
동강병원

고신의대
대동병원
동아의대
메리놀병원
부산의대
인제의대
좋은강안병원

성균관의대

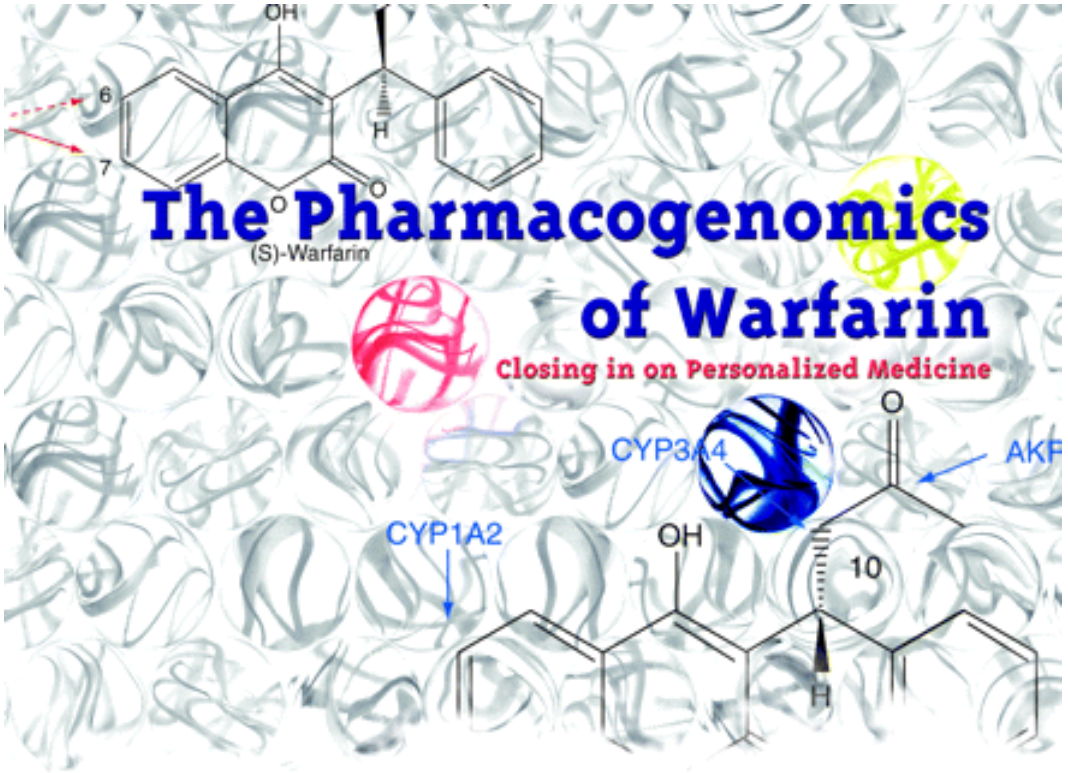
경상의대

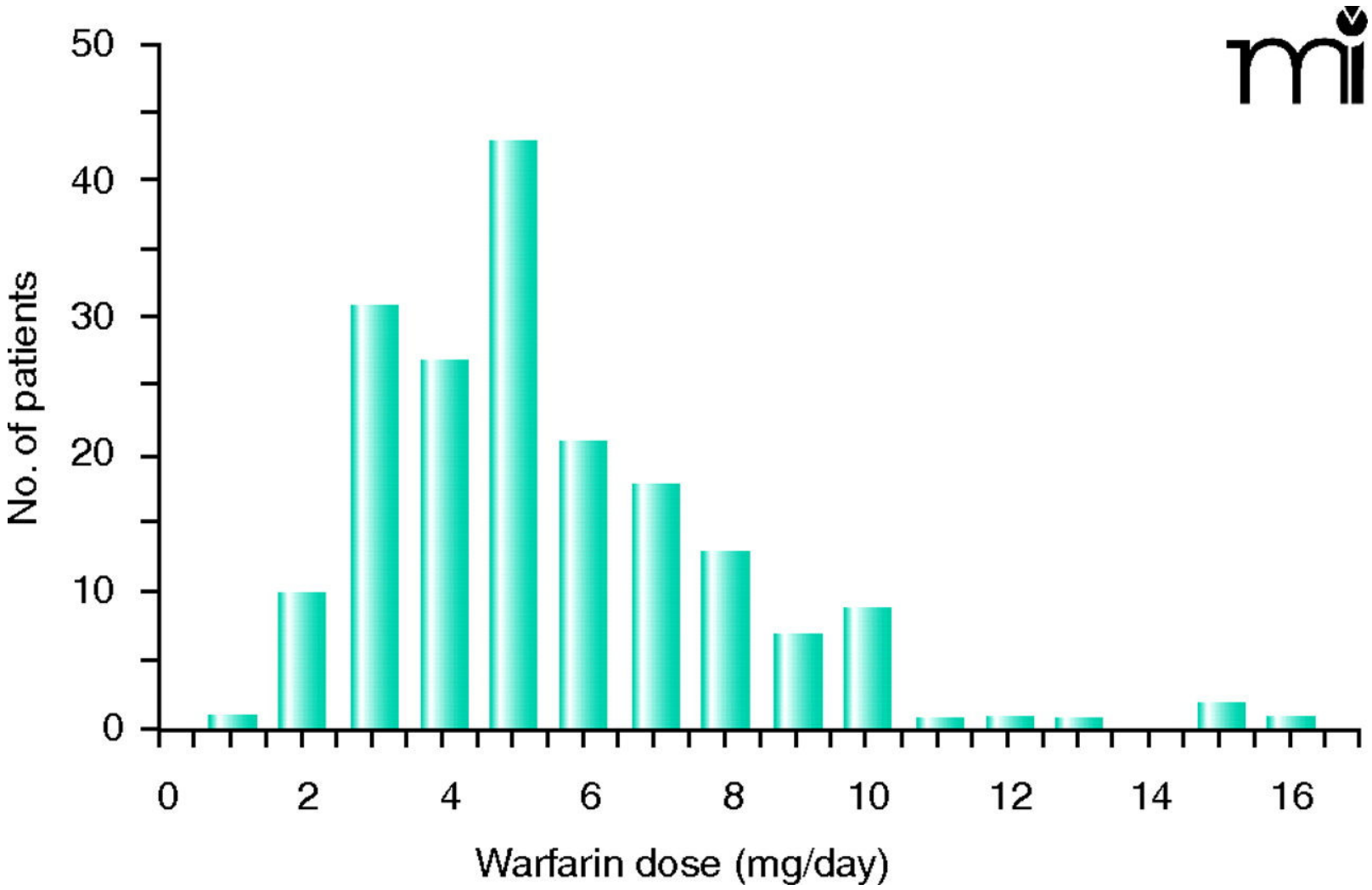
Study design

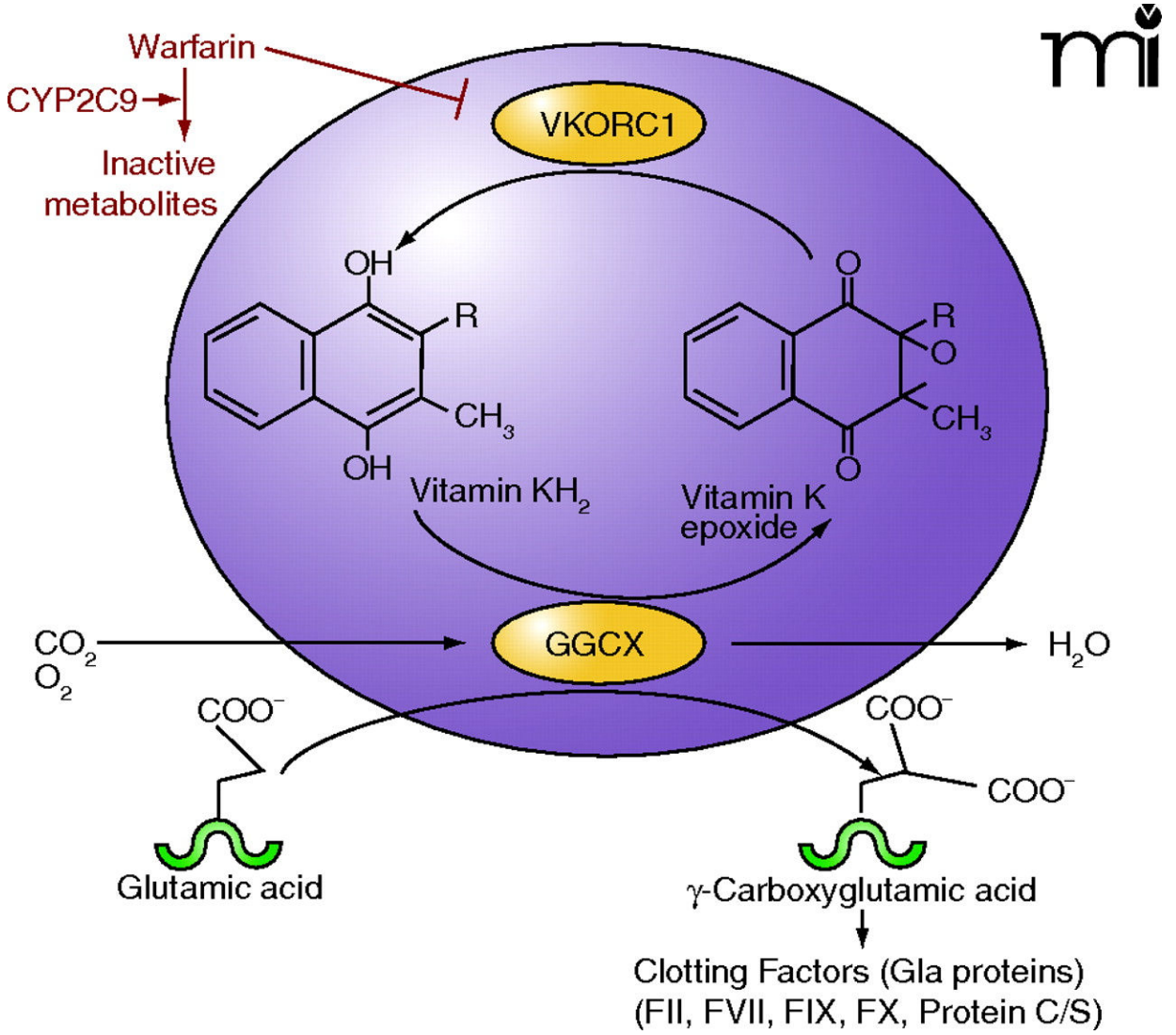


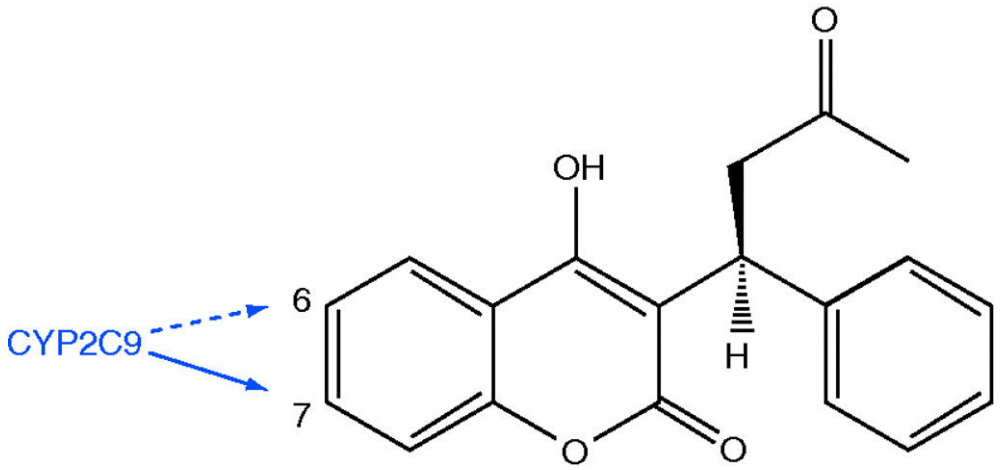
자갈치 Jagalchi fish market, 2005. 9.26

Thank you for attention!

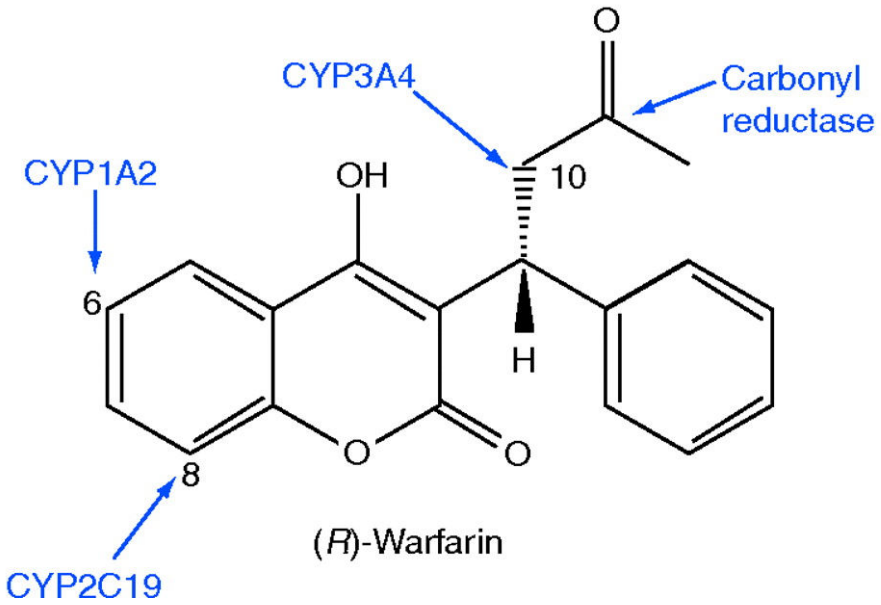

OH
6
7
H
O
O
(S)-Warfarin
The Pharmacogenomics
of Warfarin
Closing in on Personalized Medicine
CYP3A4
AKR
CYP1A2
OH
O
10
H


50
40
30
20
10
0
No. of patients
0
2
4
6
8
10
12
14
16
Warfarin dose (mg/day)

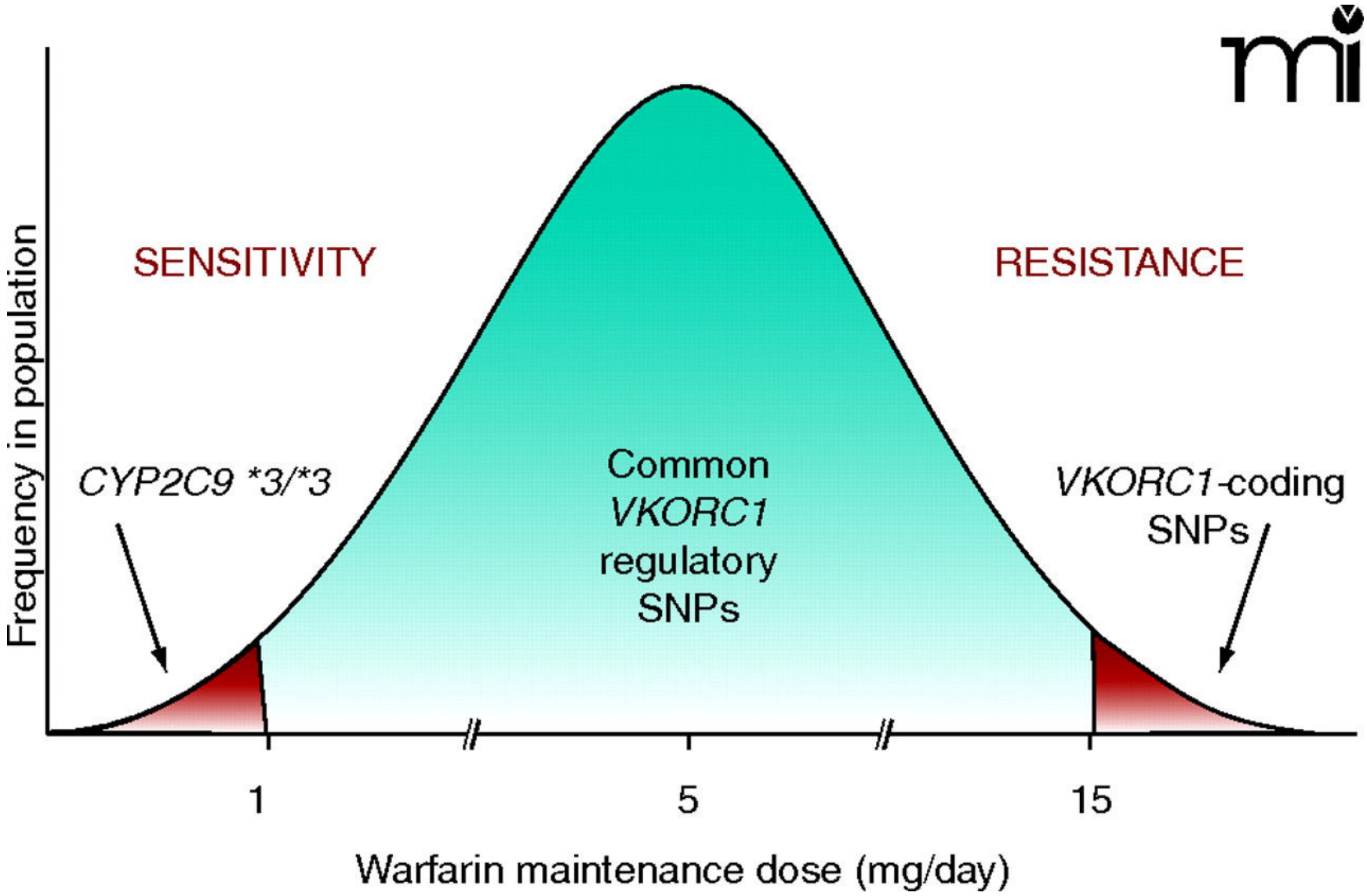

Warfarin
CYP2C9
Inactive metabolites
VKORC1
OH
R
CH3
OH
Vitamin KH2
O
R
O
CH3
O
Vitamin K epoxide
CO2
O2
GGCX
H2O
COO⁻
Glutamic acid
COO⁻
COO⁻
γ-Carboxyglutamic acid
Clotting Factors (Gla proteins)
(FII, FVII, FIX, FX, Protein C/S)



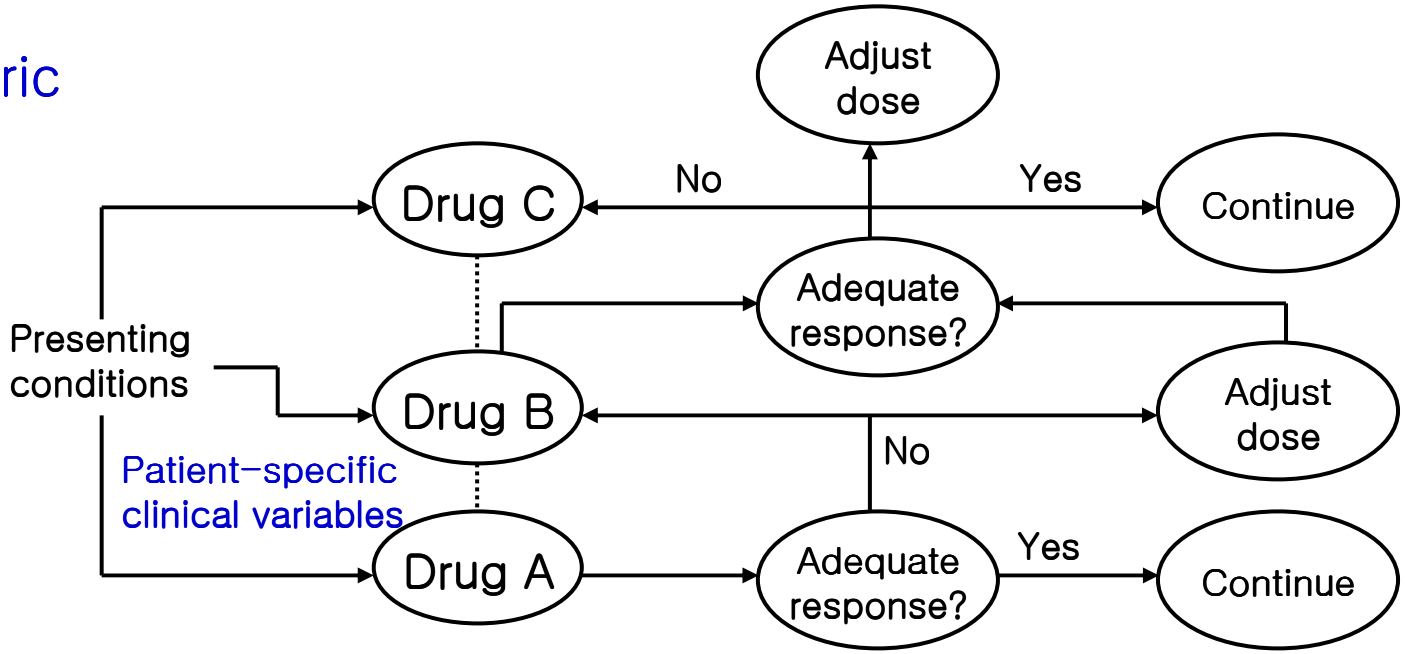
(*S*)-Warfarin



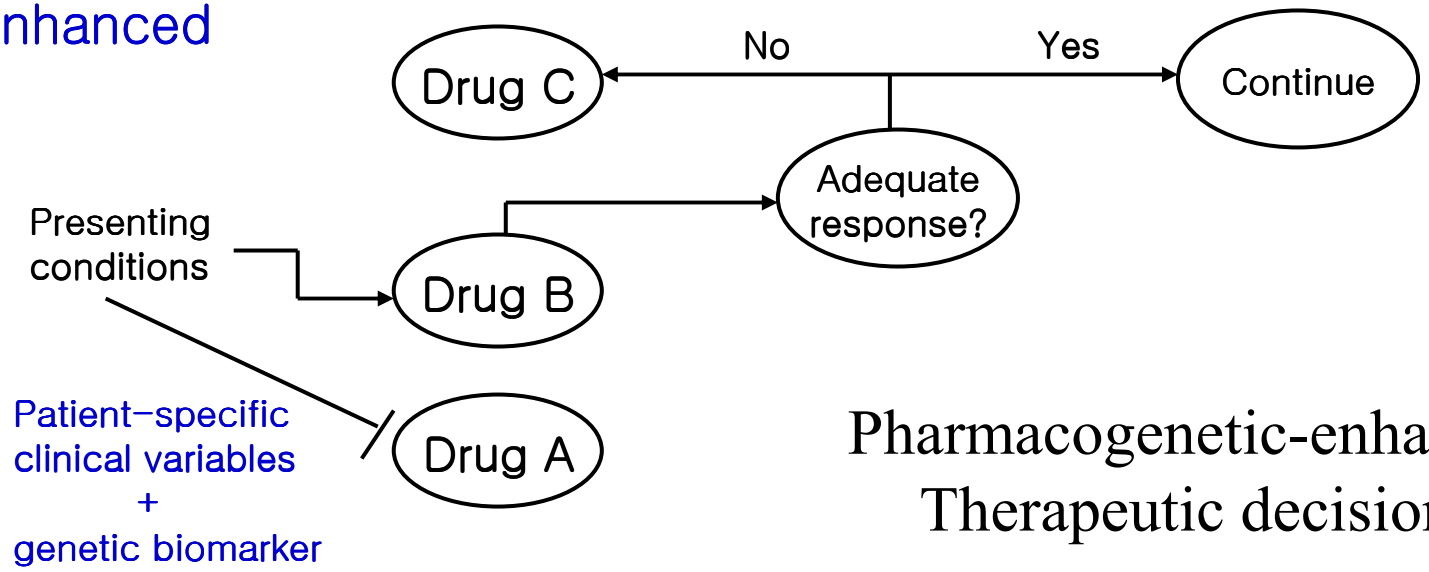
(*R*)-Warfarin


SENSITIVITY
RESISTANCE
Frequency in population
CYP2C9 *3/*3
Common
VKORC1
regulatory
SNPs
VKORC1-coding
SNPs
1
5
15
Warfarin maintenance dose (mg/day)

Empiric

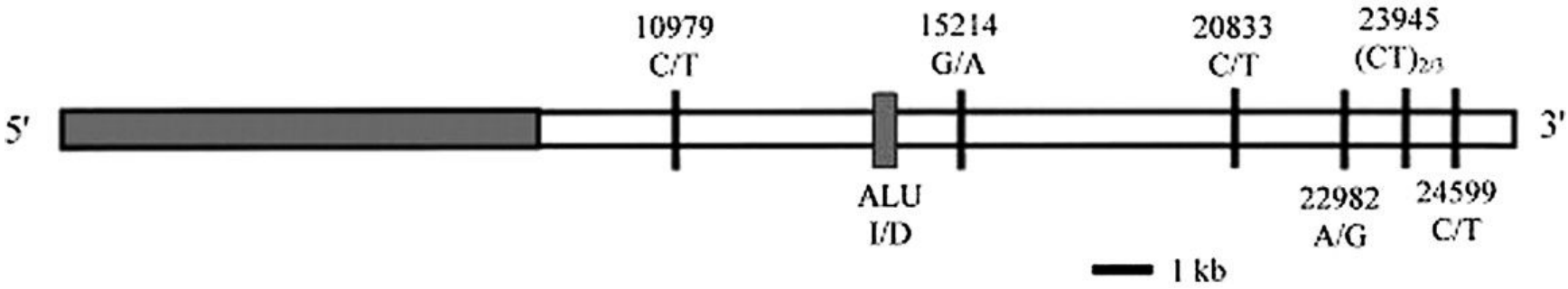


Pharmacogenetics-enhanced



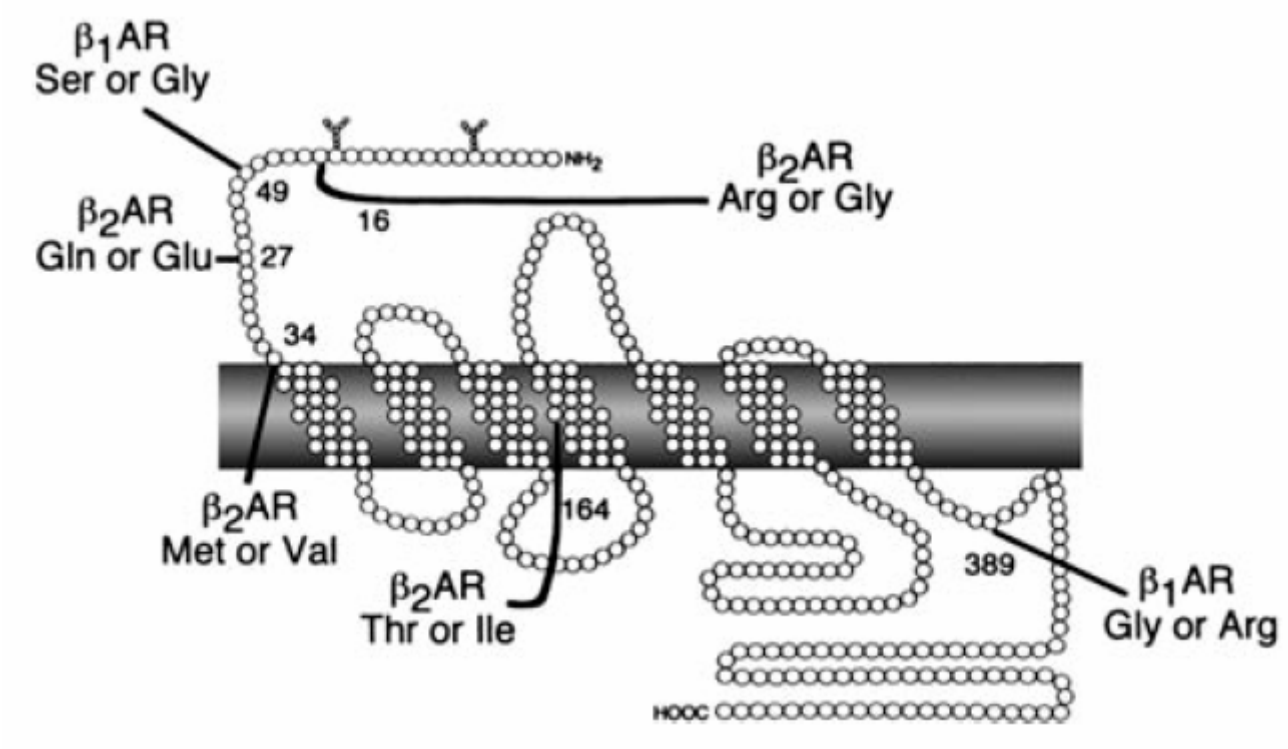
Pharmacogenetic-enhanced Therapeutic decisions

Angiotensin-Converting Enzyme gene

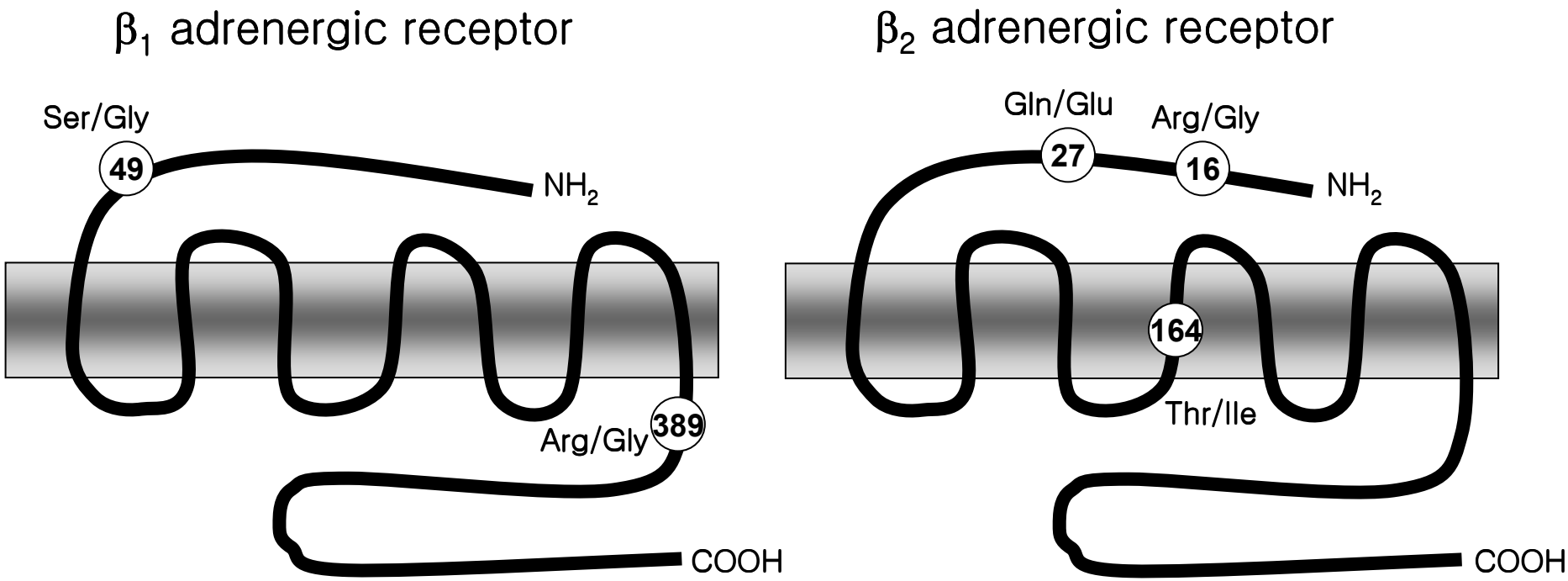


Location of 7 bi-allelic polymorphisms in ACE gene

Localization of β_1- and β_2-adrenergic polymorphisms in the Human population

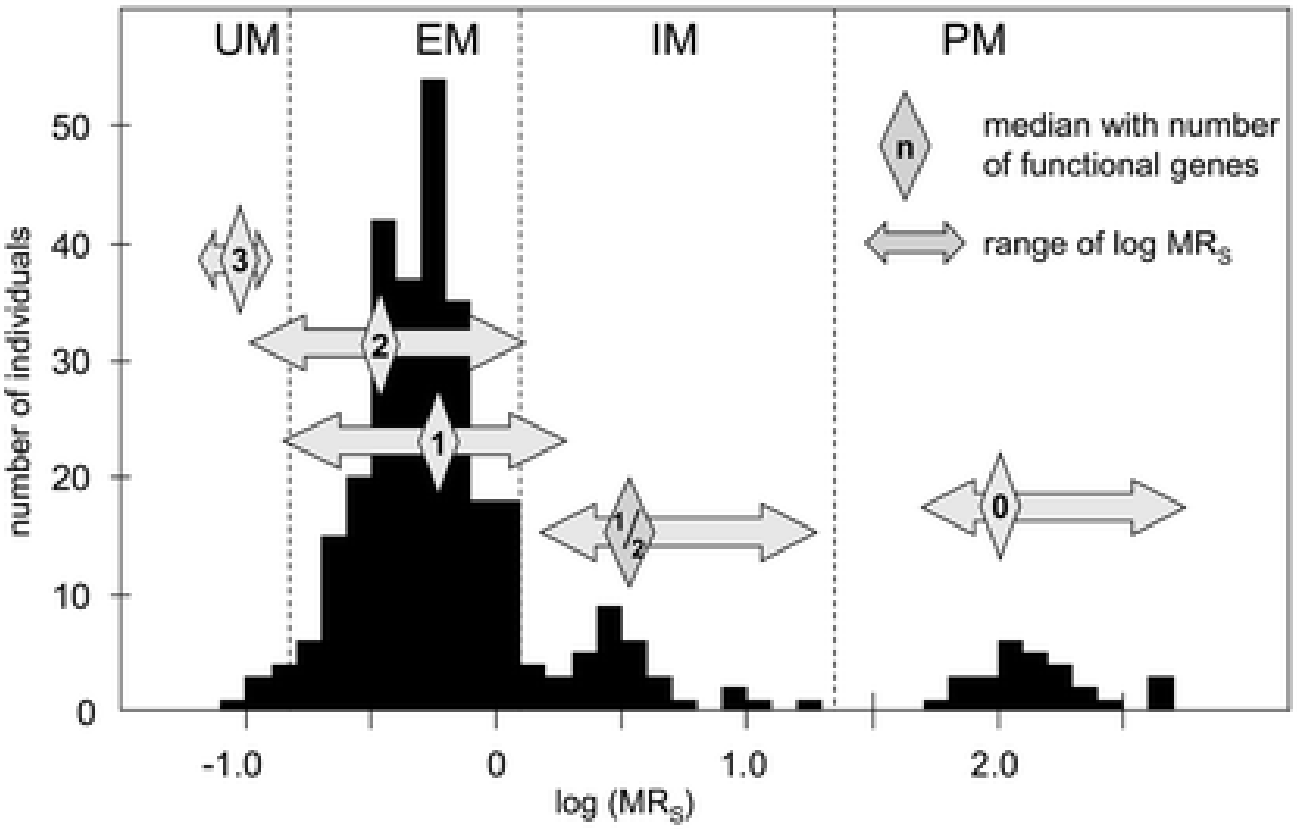


Localization of β-adrenergic polymorphisms in the Human

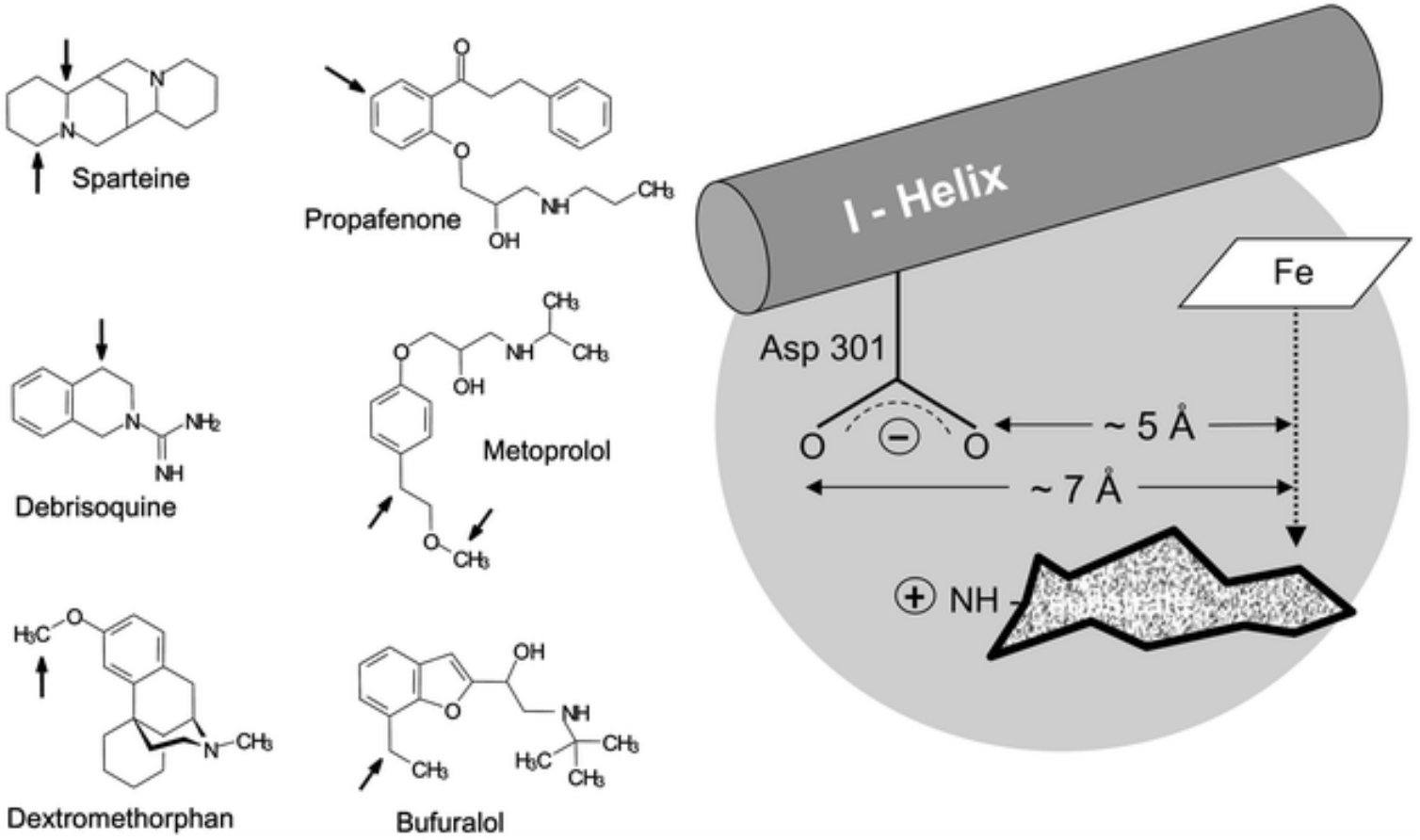


Codon	Polymorphism	Allele frequency	Function in vitro
β_1			
389	Arg/Gly	0.70/0.30	Arg = gain of function (↑cAMP)
49	Ser/Gly	0.85/0.15	No data
β_2			
16	Arg/Gly	0.40/0.60	Gly = enhanced downregulation
27	Gln/Glu	0.55/0.45	Glu = resistance to downregulation
164	Thr/Ile	0.95/0.05	Ile = loss of function

Cytochrome P450 2D6



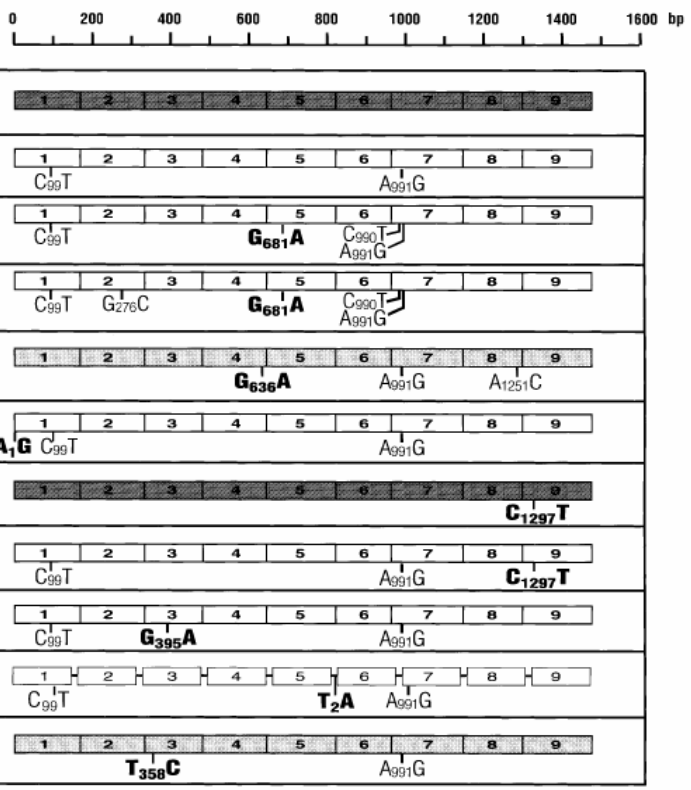
Zanger UM, et al. Naunyn-Schmiedebergs Arch Pharmacol 2004;369:23.



Zanger UM, et al. Naunyn-Schmiedebergs Arch Pharmacol 2004;369:23.

Clinical relevance of genetic polymorphisms in the human CYP2C subfamily

Allele	Trivial name	Effect of nucleotide changes	Enzyme activity
*CYP2C19*1A*	$CYP2C19_{wt1}$		Active
*CYP2C19*1B*	$CYP2C19_{wt2}$	Ile_{331} Val	Active
*CYP2C19*2A*	$CYP2C19_{m1A}$	Splicing defect	Inactive
*CYP2C19*2B*	$CYP2C19_{m1B}$	Glu_{92} Asp Splicing defect	Inactive
*CYP2C19*3*	$CYP2C19_{m2}$	Stop codon	Inactive
*CYP2C19*4*	$CYP2C19_{m3}$	GTG Initiation codon	Inactive
*CYP2C19*5A*	$CYP2C19_{m4}$ $CYP2C19_{TRP433}$	Arg_{433} Trp	Inactive
*CYP2C19*5B*		Arg_{433} Trp	Inactive
*CYP2C19*6*	$CYP2C19_{m5}$	Arg_{132} Gln	2% Rel. Activity
*CYP2C19*7*	$CYP2C19_{m6}$	Splicing defect $G_1T_2 \rightarrow G_1A_2$	
*CYP2C19*8*	$CYP2C19_{m7}$	Trp_{120} Arg	9% Rel. Activity



Allele	Trivial name	Effect of nucleotide changes	Enzyme activity
*CYP2C9*1*	$CYP2C9_{wt}$		Active
*CYP2C9*2*	Cys 144	Arg_{144} Cys	Intermediate
*CYP2C9*3*	Leu 359	Ile_{359} Leu	Higher K_m† and/or lower V_{max}

†substrate dependent

Goldstein JA. Br J Clin Pharmacol 2001;52:349

“ Variability is the law of life,”
Sir William Osler

심부전-개인에 따른 큰 차이
Variability

Genetic basis of left ventricular remodeling after myocardial infarction

103 patients with first MI: polymorphism of ACE I/D, AGT M235T
LVEDVI and LVESVI at 7±4 days and 3.9 ±1.3 months after MI

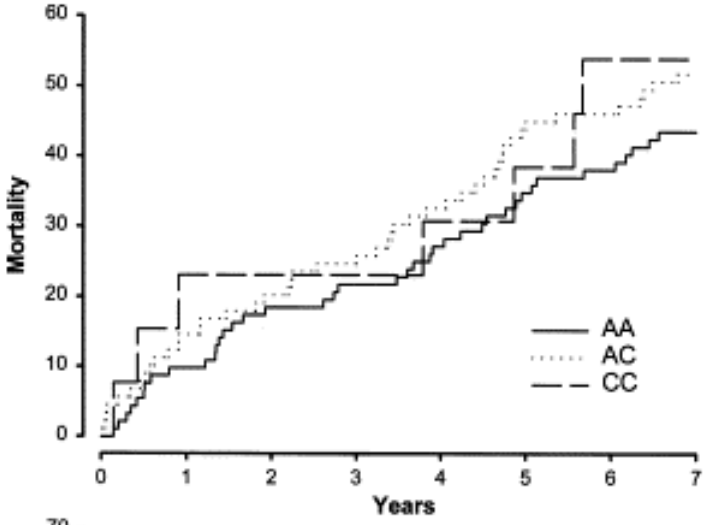
	Coefficient	S.E.	Partial F	P-value
Predictors of $LVEDVI_2$				
Intercept = 35.419, R^2 = 0.618				
$LVESVI_1$	0.873	0.078	124.104	0.0001
ACE I/D genotype	−8.414	2.791	9.090	0.0033
Diabetes mellitus	8.310	2.847	9.454	0.0044
Gender	10.428	3.592	8.428	0.0046
$Period_2$	2.082	1.039	4.106	0.0479
Predictors of $LVESVI_2$				
Intercept = 2.514, R^2 = 0.471				
$LVESVI_1$	0.709	0.081	77.389	0.0001
Smoking	8.867	3.495	6.436	0.0128
ACE I/D genotype	−7.252	2.862	6.418	0.0129
$Period_2$	2.063	1.058	3.803	0.0540

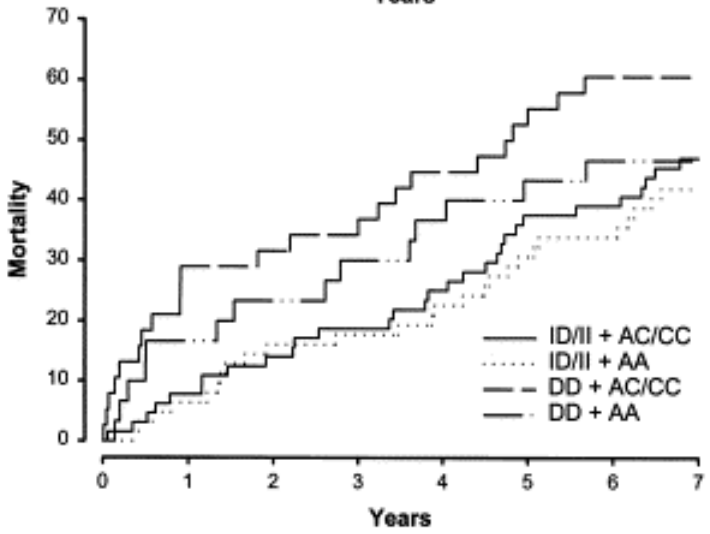
Ohmichi N, et al. Int J Cardiol 1996;53:265

Candidate gene for CHF
1. Susceptibility genes
2. Modifier genes

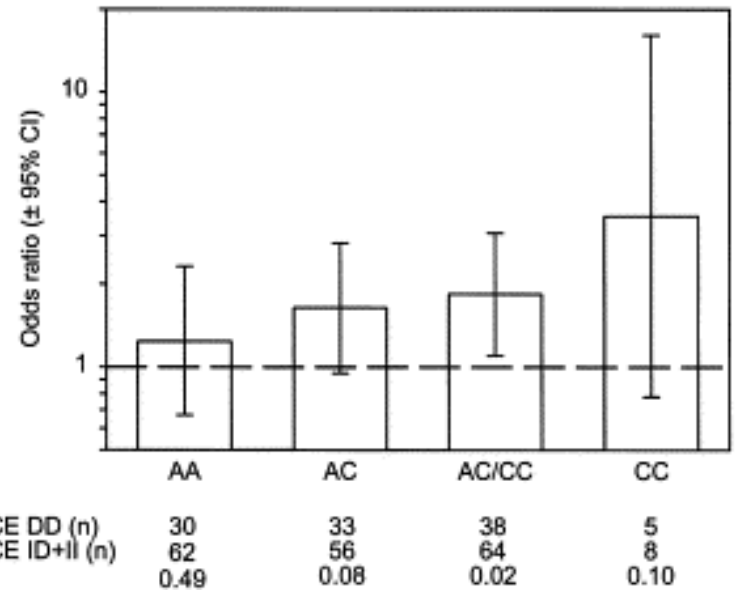
1. 상관관계는 뚜렸하지 않다.
2. 1 보다는 상대적으로 상관관계가 있는 듯

A-II type 1 receptor gene polymorphism and long term survival In patients with idiopathic congestive heart failure





ATRG genotype	AA	AC	CC
n (%)	92 (47)	89 (46)	13 (7)
ACE genotype			
II	17 (9)	20 (10)	2 (1)
ID	45 (23)	36 (19)	6 (3)
DD	30 (15)	33 (17)	5 (3)



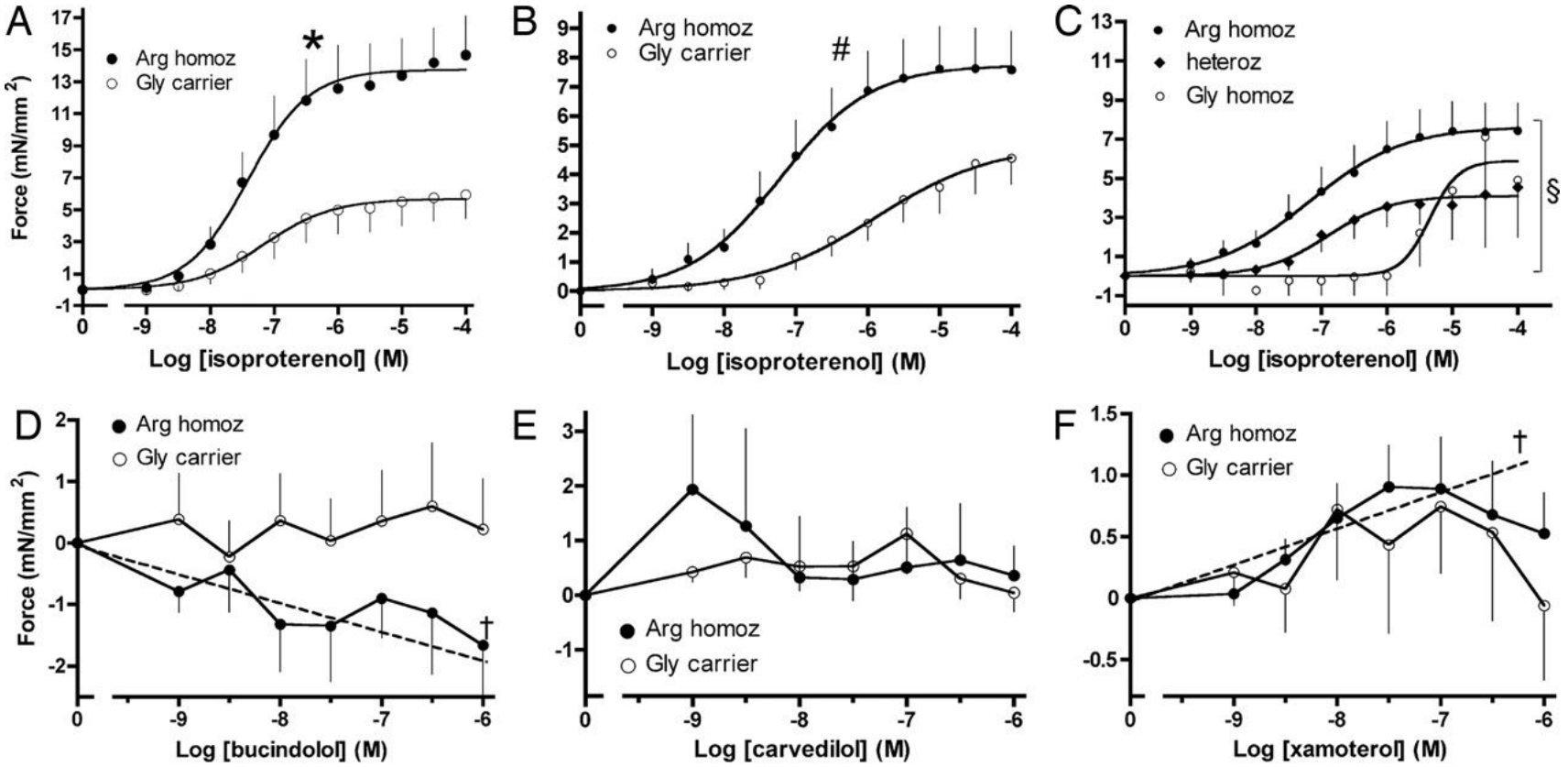
Anderson B, et al. Eur J Heart Fail 1999;1:363.

Correlation of polymorphisms of the neurohumoral system and clinical parameters (chi-square test P values) in heart failure among Chinese

Gene/peptide	Mortality rate at 1 year	LVEF	LVDD	RVDD
ACE (DD/DI/II)	0.25	0.11	0.98	0.10
ACE (allele frequency)	0.11	0.71	0.86	0.89
Angiotensinogen (M235T)	0.98	0.78	0.90	0.90
ATIR (AI166C)	0.91	0.49	0.83	0.04
Serum ACE (unit/L)	0.59	0.21	0.52	0.04
Serum aldosterone (pmol/L)	0.21	0.35	0.40	0.04
Plasma ANP (pg/mL)	0.009	0.001	0.045	0.29

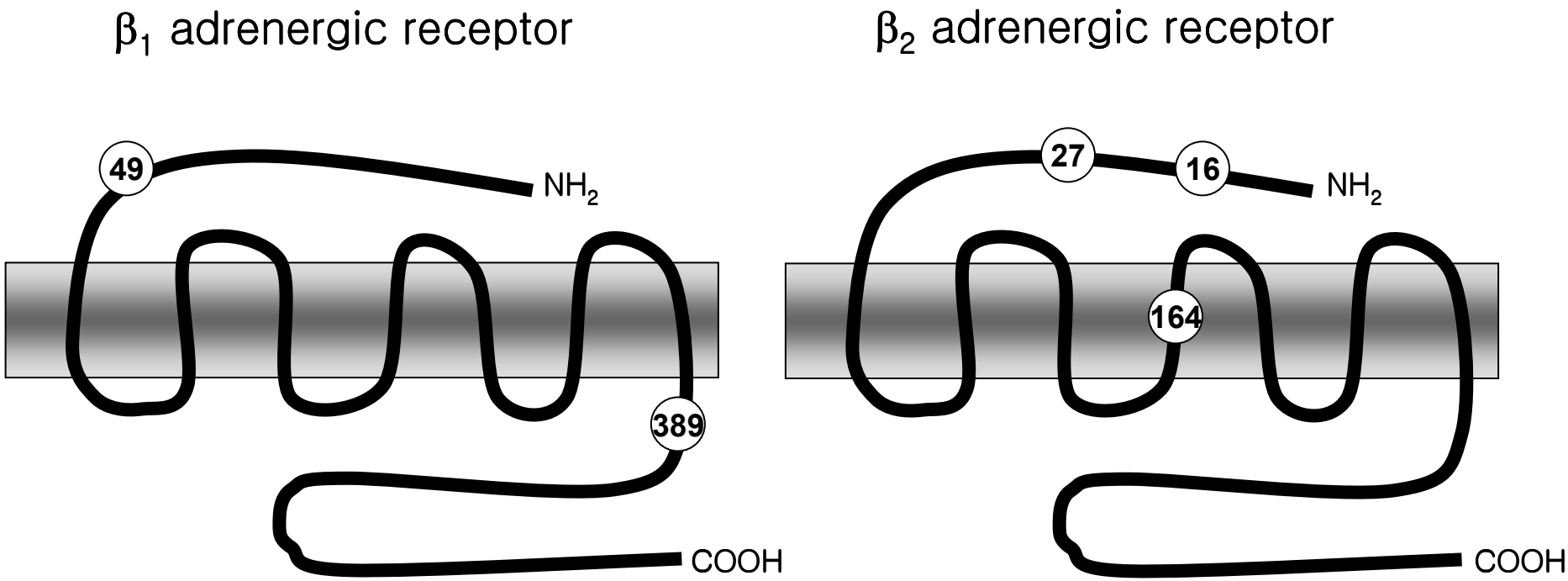
Sanderson JE, et al. Am Heart J 1999;137:653-7.

β_1AR genotype and drug-response correlations



Ligget SB, et al. Proc Natl Acad Sci USA 2006;103:11288.

Localization of β-adrenergic receptor polymorphisms in the Human



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49	Ser/Gly	0.85/0.15	No data
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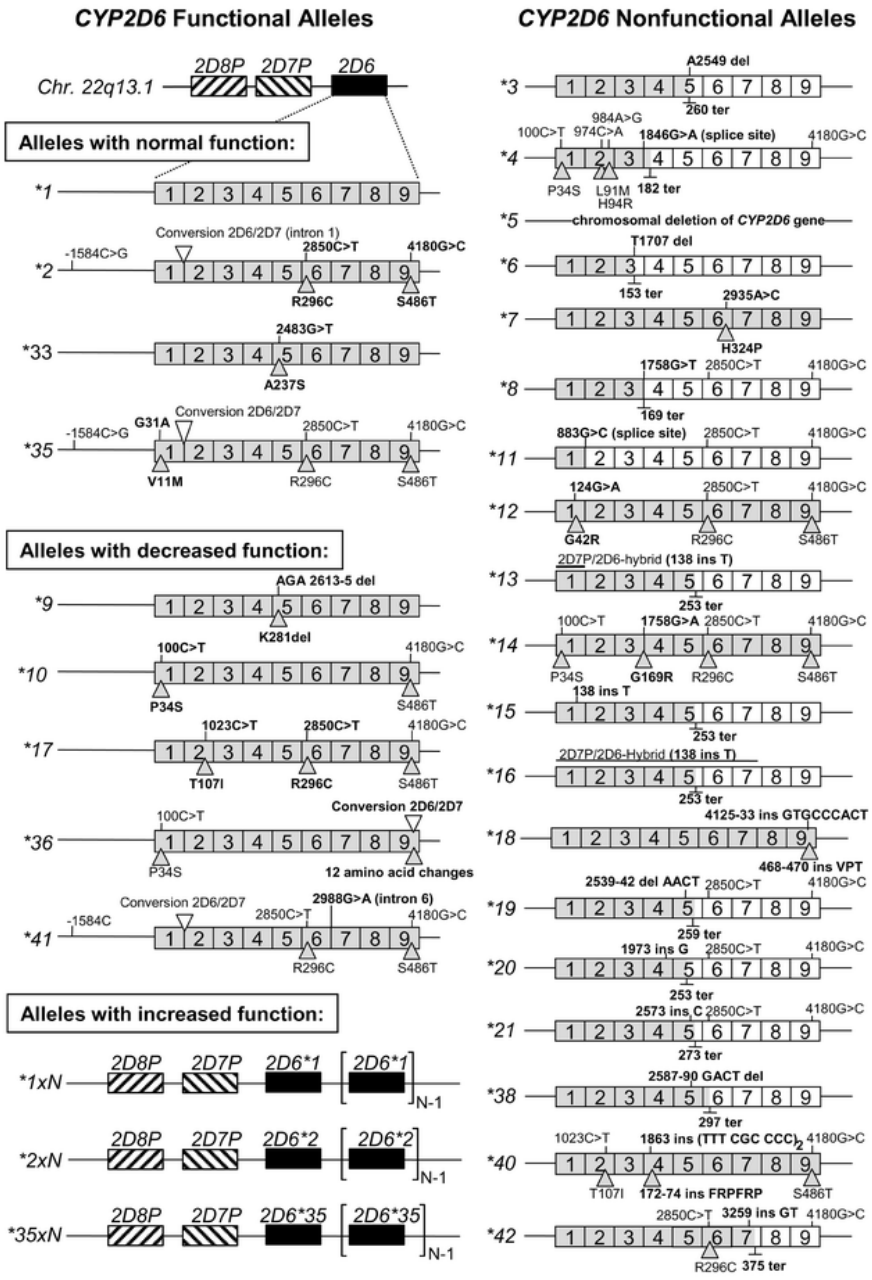
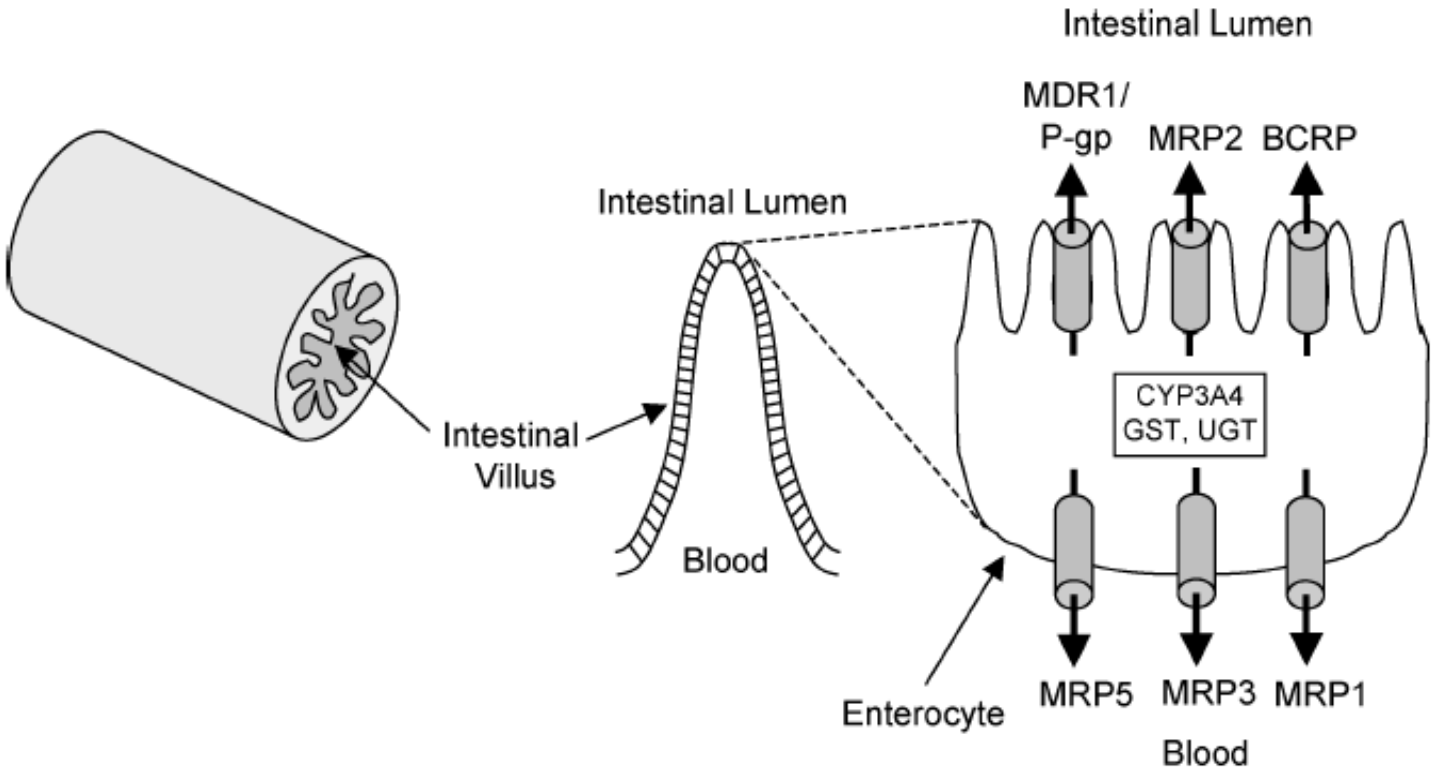
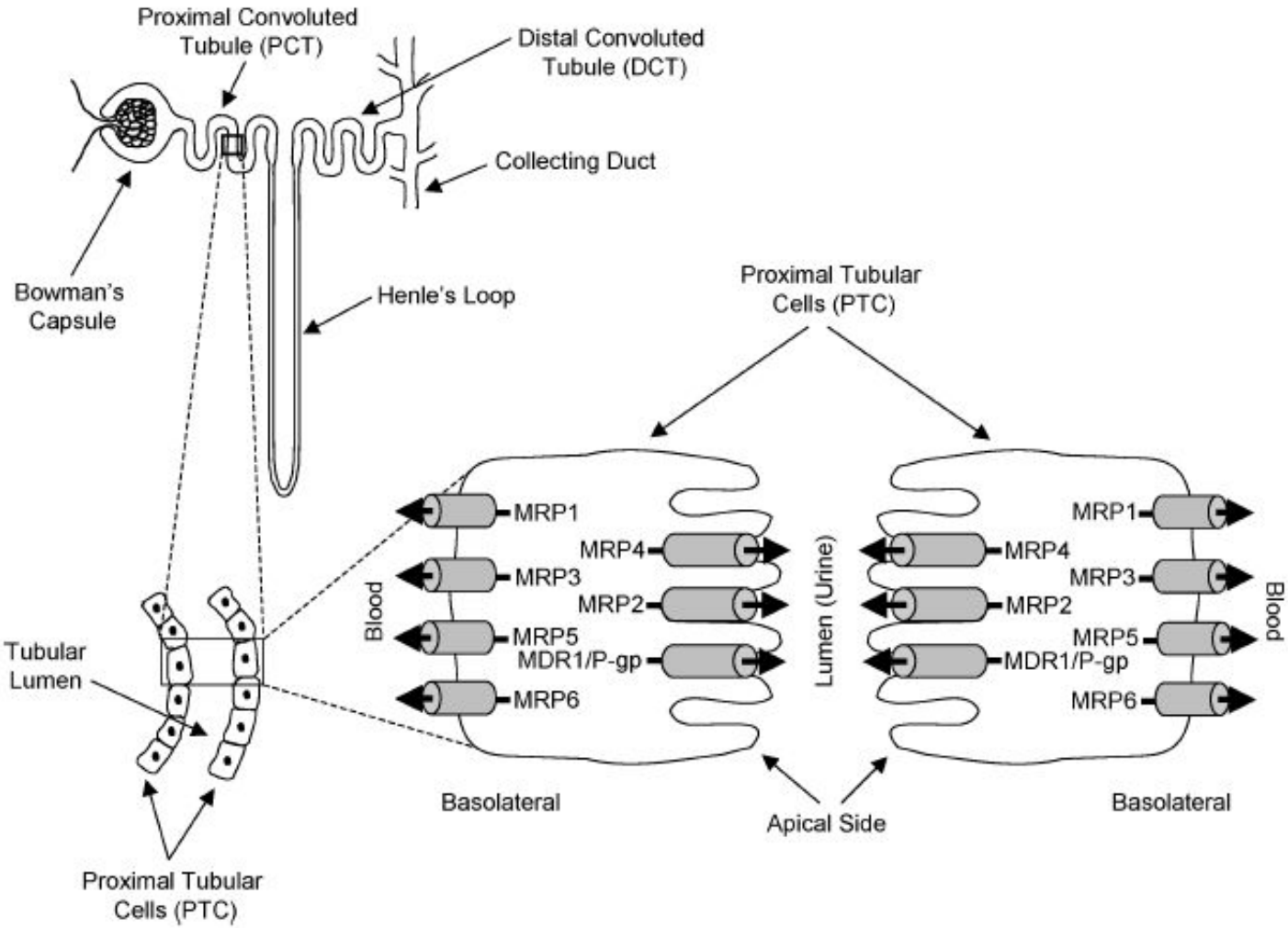
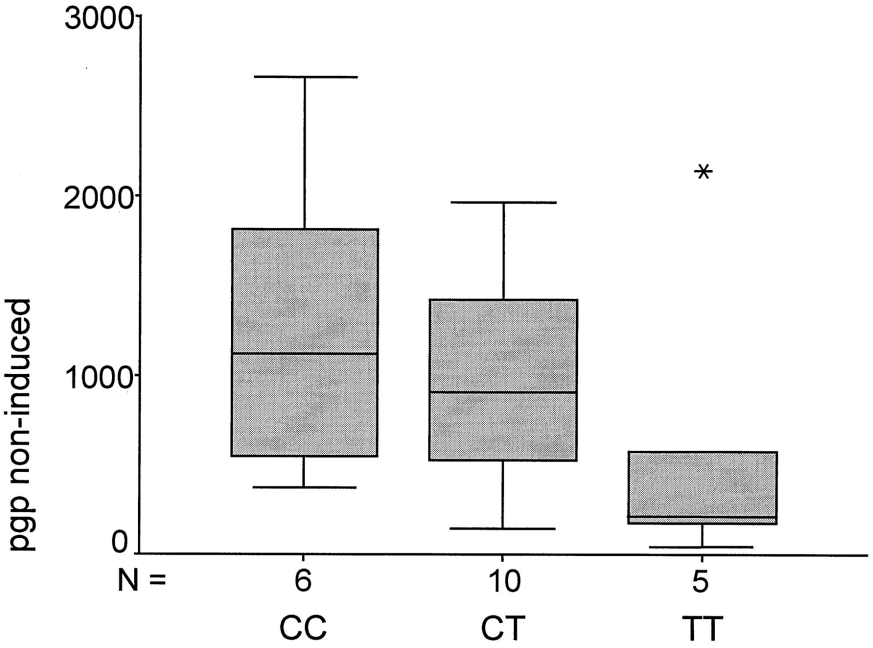
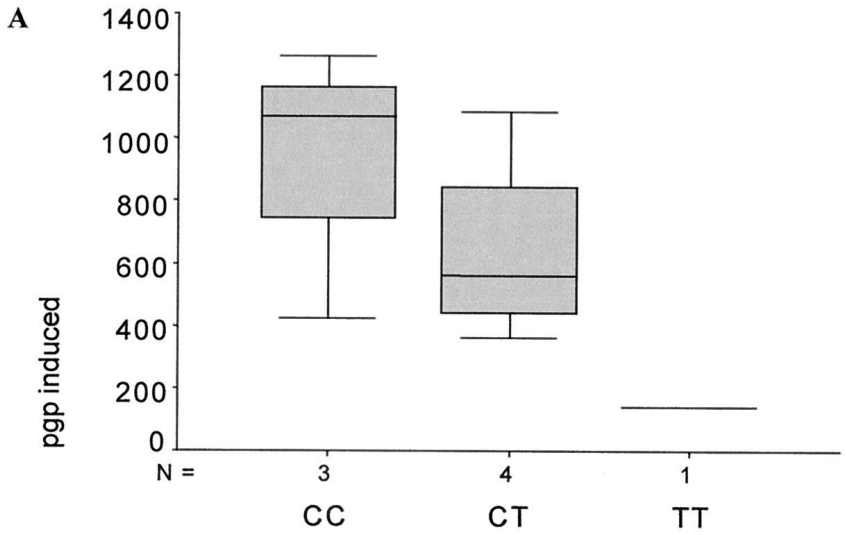


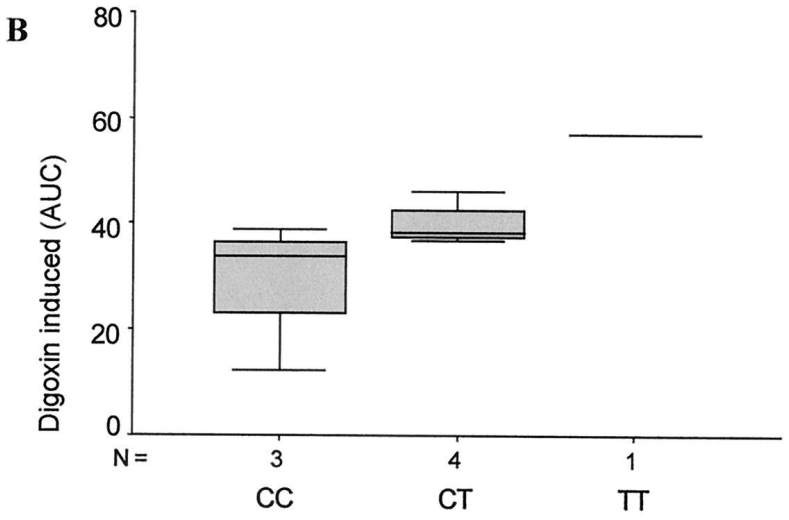
Zanger UM, et al. Naunyn-Schmiedebergs Arch Pharmacol 2004;369:23.


Intestinal Lumen
MDR1/
P-gp
MRP2
BCRP
Intestinal Lumen
CYP3A4
GST, UGT
Intestinal
Villus
Blood
Enterocyte
MRP5
MRP3
MRP1
Blood


Proximal Convoluted Tubule (PCT)
Distal Convoluted Tubule (DCT)
Collecting Duct
Bowman's Capsule
Henle's Loop
Proximal Tubular Cells (PTC)
Tubular Lumen
Proximal Tubular Cells (PTC)
Blood
MRP1
MRP4
MRP3
MRP2
MRP5
MDR1/P-gp
MRP6
Lumen (Urine)
MRP1
MRP4
MRP3
MRP2
MRP5
MDR1/P-gp
MRP6
Blood
Basolateral
Apical Side
Basolateral

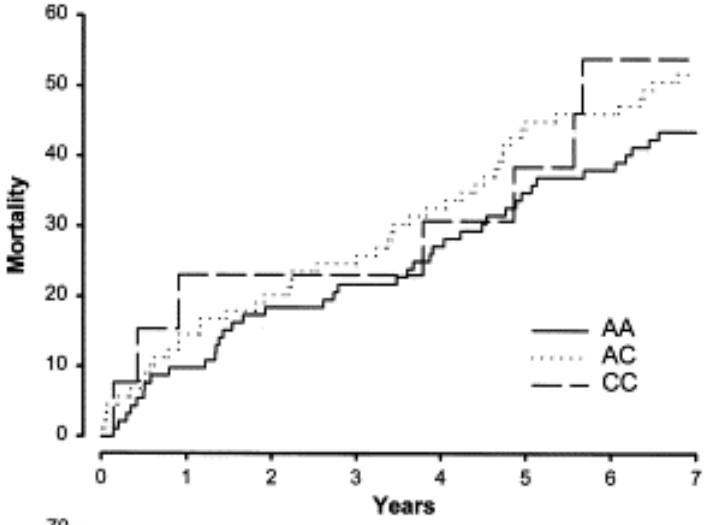


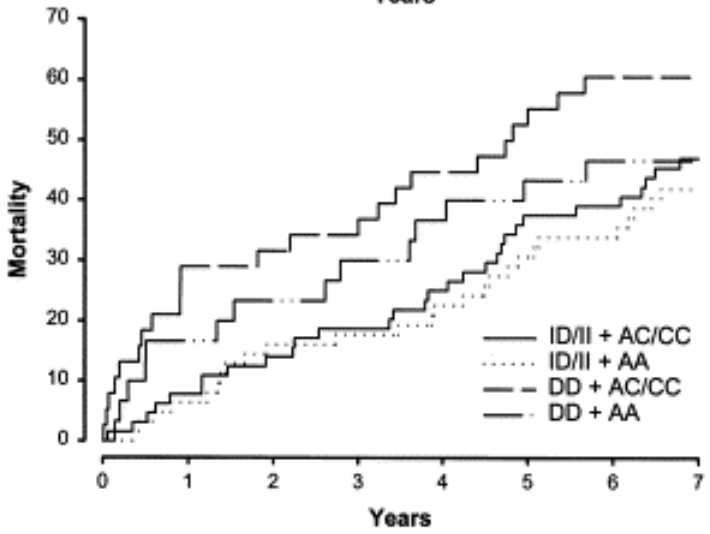




Hoffmyer S, et al Porc Natl Acad Sci USA 200;97:3473.

Angiotensin-II type 1 receptor





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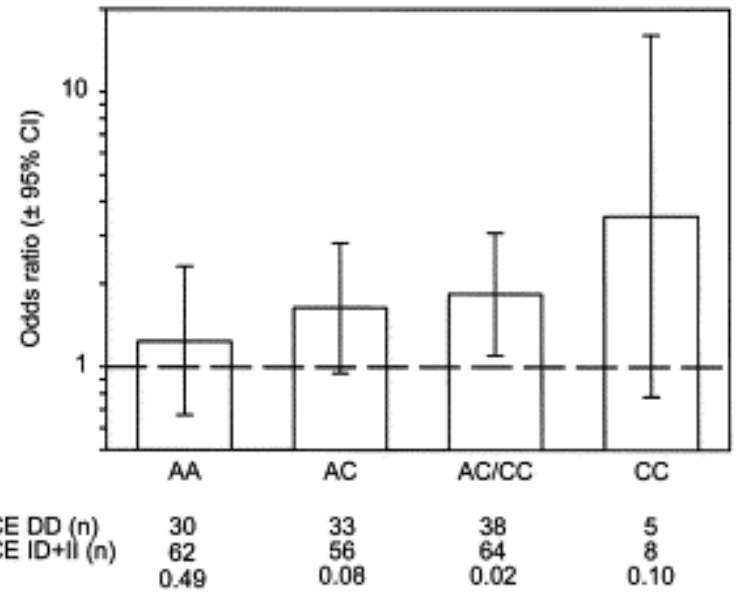
II	17 (9)	20 (10)	2 (1)
ID	45 (23)	36 (19)	6 (3)
DD	30 (15)	33 (17)	5 (3)



Anderson B, et al. Eur J Heart Fail 1999;1:363.