



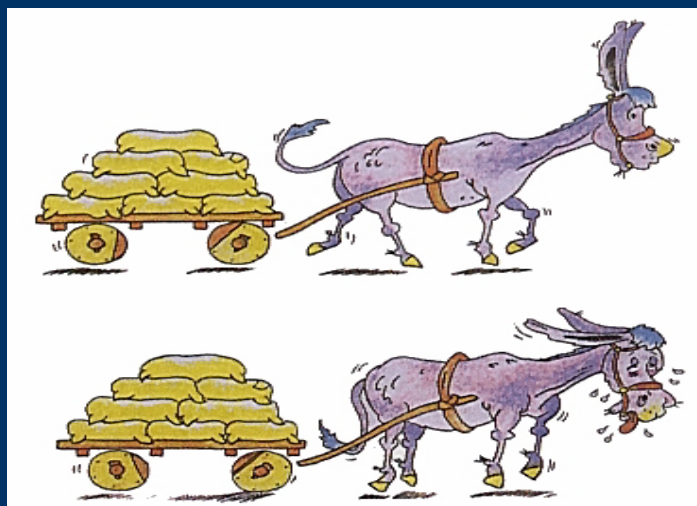
LA TERAPIA FARMACOLOGICA NEL PAZIENTE ANZIANO

Fattori Farmacogenetici e Farmacogenomici (della
terapia) dello Scompenso cardiaco

Paolo Biagi USL 7 Siena
Montepulciano

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM)

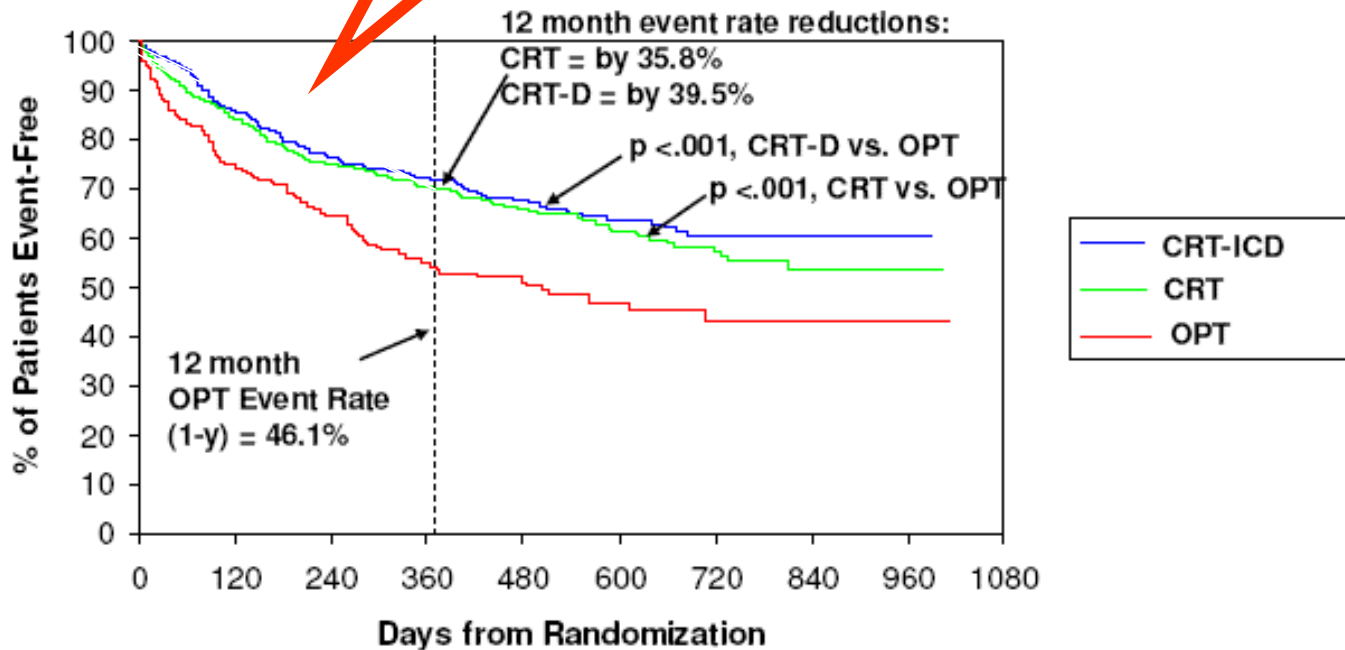


Stage C Therapy (Reduced LVEF with Symptoms)

Recommended Therapies:

- General measures as advised for Stages A and B
- Drug therapy for all patients
 - **Diuretics for fluid retention**
 - **ACEI**
 - **Beta-blockers**
- Drug therapy for selected patients
 - **Aldosterone Antagonists**
 - **ARBs**
 - **Digitalis**
 - **Hydralazine/nitrates**
- ICDs in appropriate patients
- Cardiac resynchronization in appropriate patients
- Exercise Testing and Training

EVENTS DESPITE THERAPY



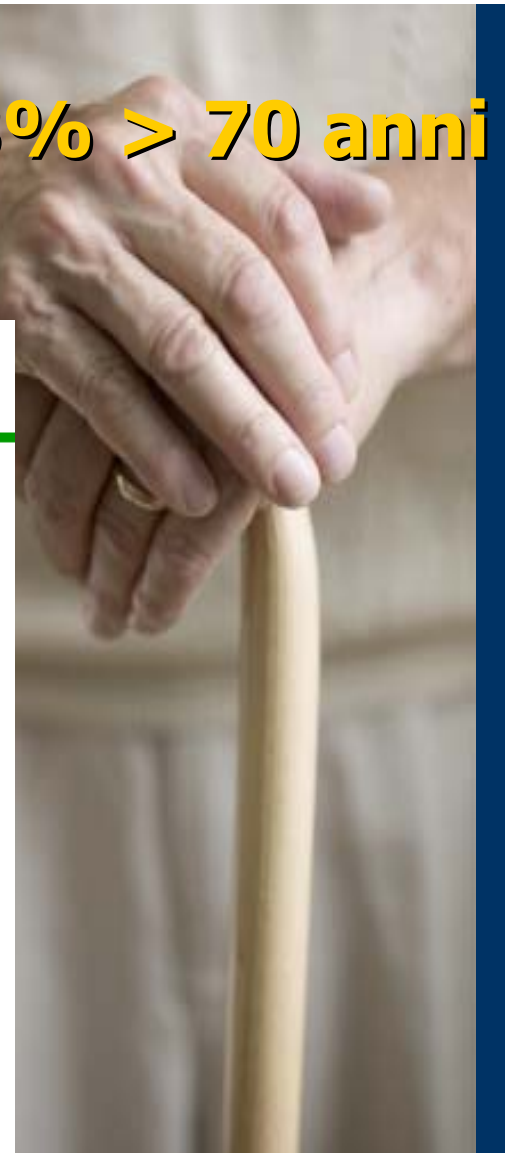


83% > 70 anni

Spectrum of heart failure in older patients: results from the National Heart Failure project.

Havranek EP, Masoudi FA, Westfall KA, Wolfe P, Ordin DL, Krumholz HM.
Am Heart J 2002 Mar;143(3):412-7

Elderly patients with HF are a heterogeneous group and appear to differ substantially from patients enrolled in clinical trials. Evidence-based guidance for treatment in the context of multiple comorbid conditions, poor renal function, HF with preserved left ventricular systolic function, and residence in long-term care facilities is urgently needed.



Pharmacogenetics

Links differences in gene structure (inherited polymorphism) to drug metabolism and response

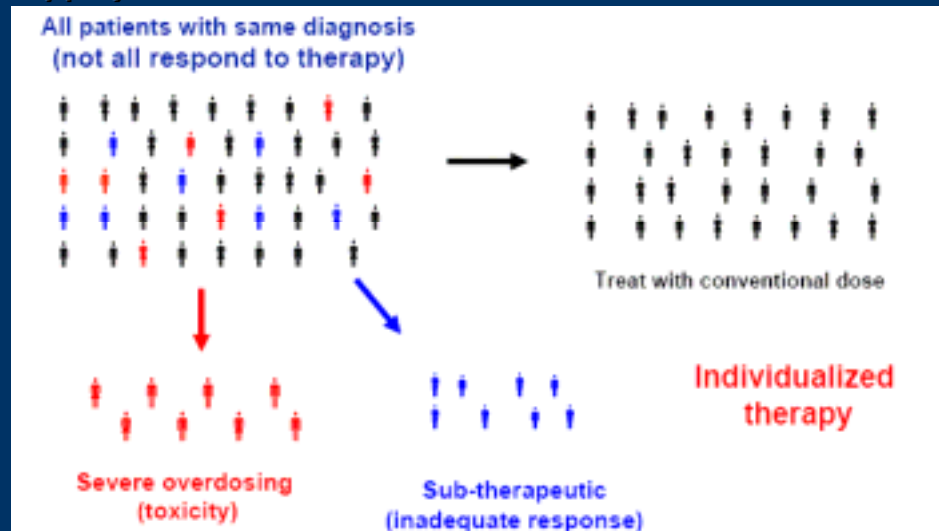
Genetic Polymorphism

(Genotype)



Drug metabolism & response

(Phenotype)

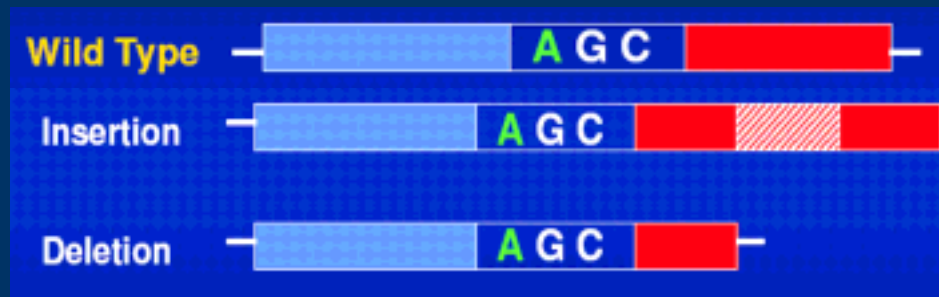


Genomic variation

SNPs: Single Nucleotide polymorphisms and
Variable number tandem repeats



Insertions/deletions



Examples of Genes Implicated in Variable Outcomes of Drug Therapy in Cardiovascular Medicine

Drug	Gene	Reported Association
Pharmacokinetic mechanisms		
Digoxin	<i>ABCB1</i>	Variable drug levels resulting from variable bioavailability and clearance
Warfarin	<i>CYP2C9</i>	Greater anticoagulation with hypofunctional alleles
Losartan, irbesartan	<i>CYP2C9</i>	Greater blood pressure drop with hypofunctional alleles
Metoprolol, timolol, propafenone	<i>CYP2D6</i>	Poor metabolizers display greater β -blockade
Procainamide	<i>NAT2</i>	Poor acetylators at greater risk for drug-induced lupus
Pharmacodynamic mechanisms		
QT-prolonging drugs	<i>KCNH2, KCNE2, KCNQ1, KCNE1, SCN5A</i>	Increased torsade de pointes risk
β -Blockers	<i>ADRB1, ADRB2</i>	Altered extent of heart rate slowing or blood pressure lowering
ACE inhibitors	<i>ACE</i>	Decreased response in subjects with the DD genotype
β -Blockers	<i>ACE</i>	Increased response in subjects with the DD genotype
Fluvastatin	<i>ABCA1</i>	Fluvastatin resistance
Pravastatin	<i>CETP</i>	Variable regression of atherosclerosis
Estrogen	<i>ESR1</i>	Variable HDL elevation during estrogen therapy
Lipid-lowering therapy	<i>LIPC</i>	Variable lipid lowering
Antiplatelet drugs	<i>ITGB3</i>	Variable antiplatelet effects ex vivo
Antihypertensive drugs	<i>AGTR1</i>	No relation to antihypertensive effects
Amiloride	Epithelial sodium channel genes	Antihypertensive effect in black subjects
Antihypertensive drugs	<i>GNAS</i>	Variable blood pressure lowering
Diuretics	<i>ADD1</i>	Variable stroke incidence, variable blood pressure response (especially when analyzed as a function of ACE polymorphism)

Genetic polymorphism and HF therapeutics

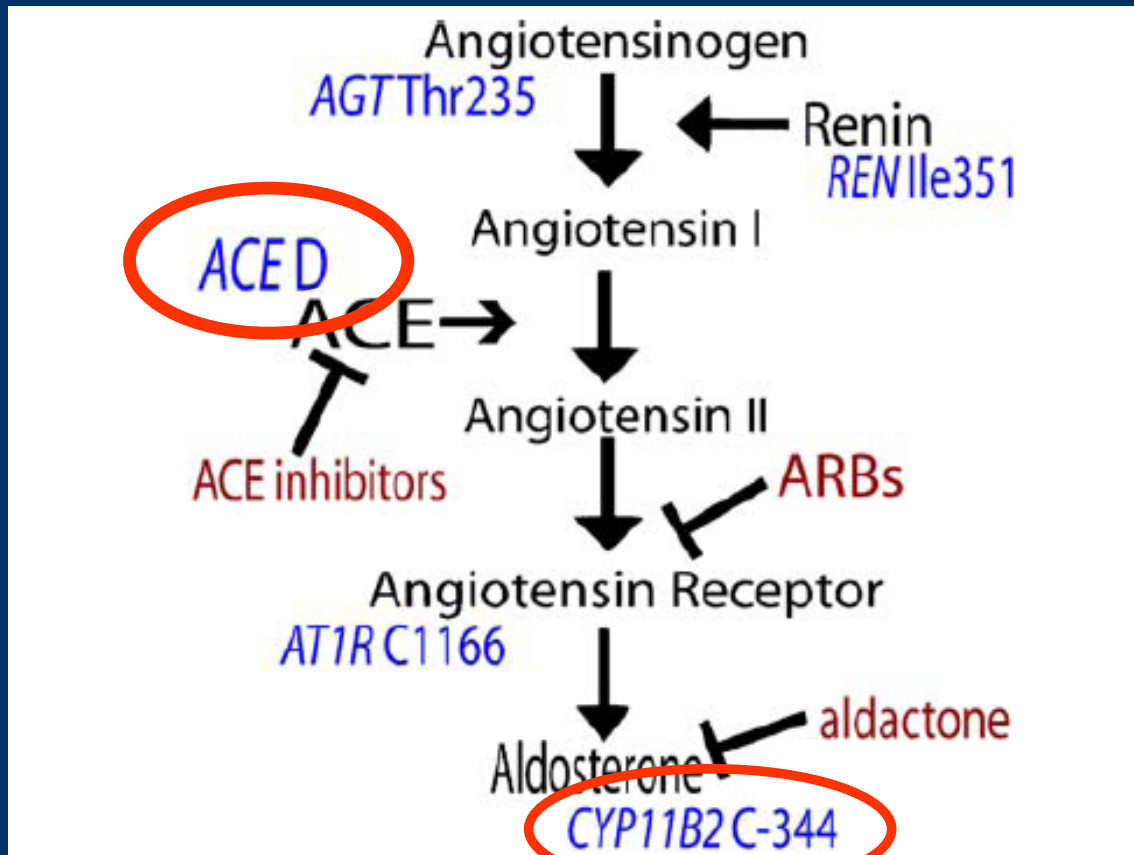
Gene	Polymorphysm	Functional significance	Potential Therapeutic Influence	
RAAS	ACE	D/I	ACE D higher ACE activity and Ang II levels	ACE inhibitors Beta blockers
	Aldosterone Synthase (CYP11B2)	Promoter -344 T/C	-344C higher transcriptional activity and aldosterone production	ACE inhibitors Aldosterone receptor antagonist
β adrenergic Receptors	β1AR	Arg389Gly	Arg: ↑adrenergic signal	β blockers
	β1AR	Gly49Ser	Gly: enhanced down regulation	β blocker
	β2AR	Gly16Arg Gln27Gly	Receptor down regulation	β blockers
α adrenergic receptor signaling	α2C receptor	α2C deletion	Deletion: ↓uptake of norepinephrine	β blockers
Nitric oxide	Endothelial NOS (NOS3)	Asp298Glu	Asp: associated with lower NOS3 activity	ACE inhibitor

Why is clinical application of pharmacogenetics important?

% pts with < therapeutic effect

Angiotensin 2 Antagonists	10-25%
ACE inhibitors	10-25%
Beta-blockers	15-25%
Beta-2 adrenergic agonists	40-70%

Renin–angiotensin–aldosterone system and polymorphisms



Stage C Therapy (Reduced LVEF with Symptoms)

Angiotensin Enzyme Converting Inhibitors (ACEIs)



ACEIs are recommended **for all patients with current or prior symptoms of HF and reduced LVEF**, unless contraindicated.

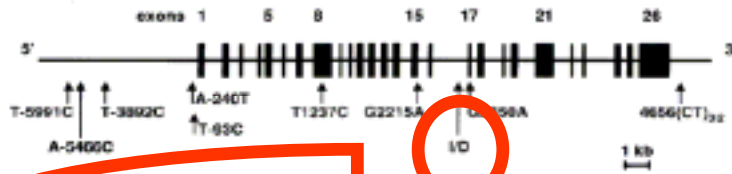


Routine combined use of an ACEI, ARB, and aldosterone antagonist is **not recommended** for patients with current or prior symptoms of HF and reduced LVEF.

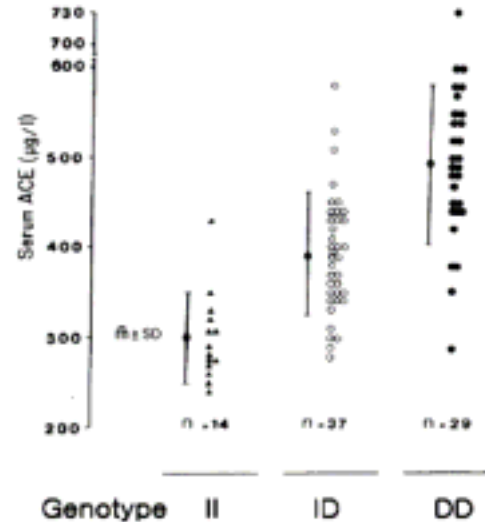


Angiotensin-Converting Enzyme gene

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



Identification of 10 bi-allelic polymorphisms in ACE gene

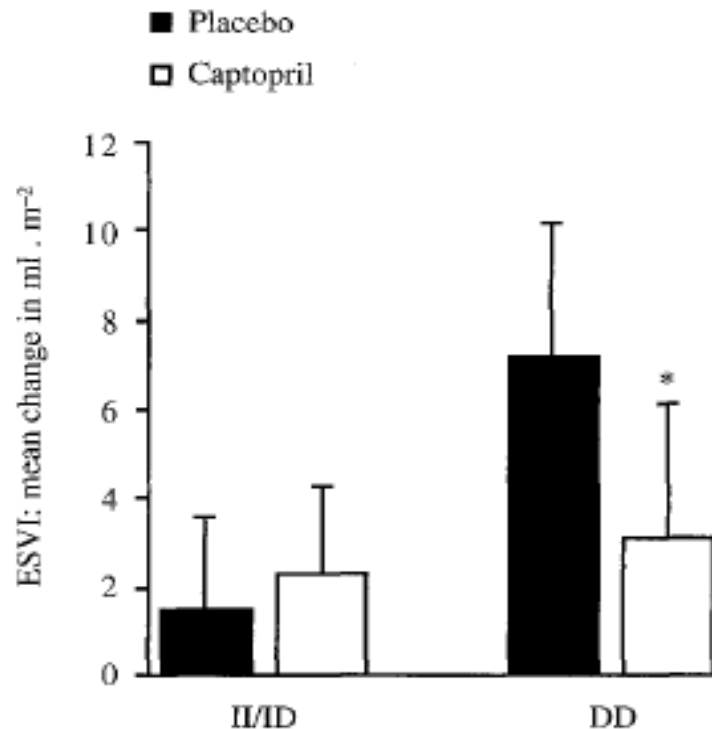


A Biallelic Deletion Polymorphism in Intron 16 of the ACE Gene



Captopril after Thrombolysis Study (CATS)

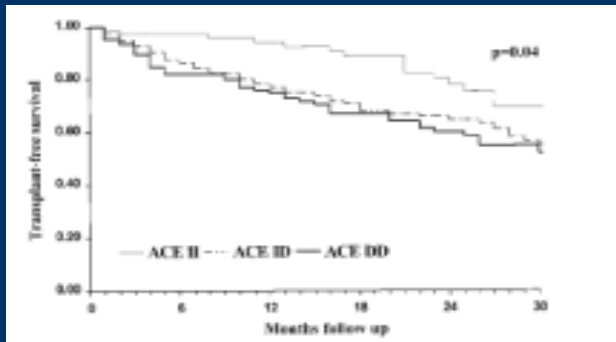
Relationship between angiotensin-converting enzyme (ACE) genotype (insertion/deletion [I/D] polymorphism) and ACE inhibition on end-systolic volume index (ESVI) in patients who received either captopril or placebo after thrombolysis for a first anterior myocardial infarction. **After 1 year, patients with the DD ACE genotype developed significant ventricular dilatation, which was effectively blunted by captopril (*P < 0.05).**



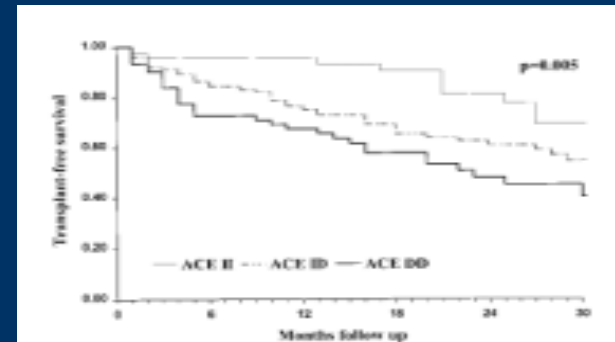
Pharmacogenetic Interactions Between β -Blocker Therapy and the Angiotensin-Converting Enzyme Deletion Polymorphism in Patients With Congestive Heart Failure

Dennis M. McNamara, MD; Richard Holubkov, PhD; Karen Janosko, RN, MSN; Amy Palmer, MA; Jue J. Wang, MS; Guy A. MacGowan, MD; Srinivas Murali, MD; Warren D. Rosenblum, MD; Barry London, MD, PhD; Arthur M. Feldman, MD, PhD

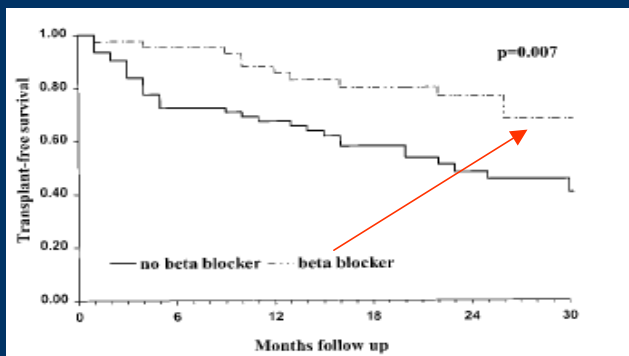
Circulation. 2001;103:1644-1648.)



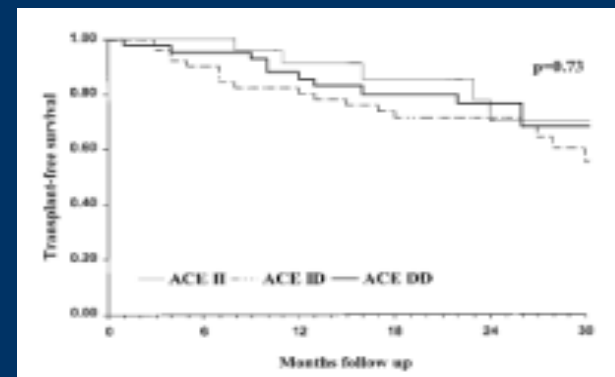
Transplant-free survival compared by *ACE* genotype.



Transplant-free survival by *ACE* genotype. Patients not treated with b-blockers at time of study entry



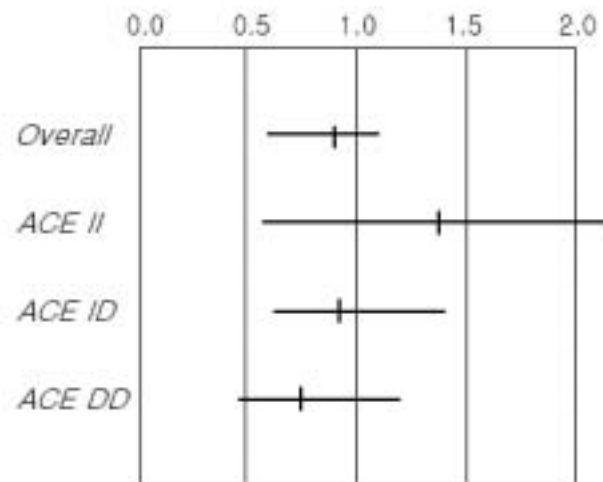
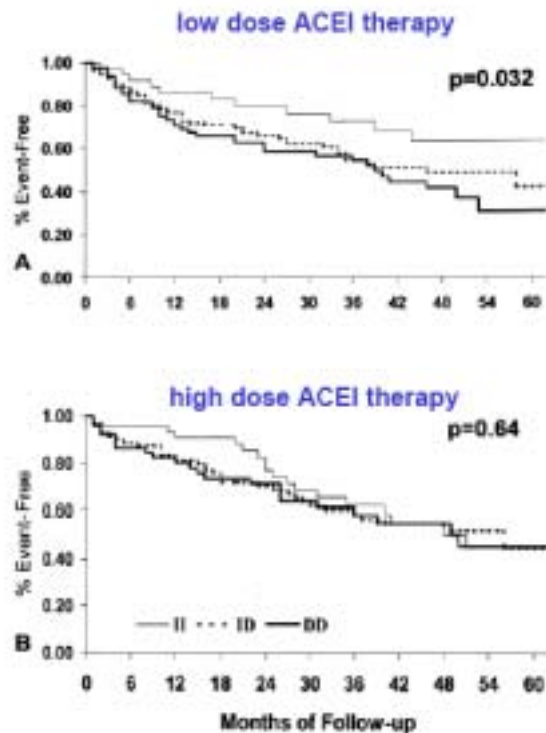
Transplant-free survival compared by b-blocker use for patients with *ACE DD* genotype only



Transplant-free survival by *ACE* genotype. Patients receiving b-blocker therapy,

GRACE (Genetic Risk Assessment of Cardiac Event) study

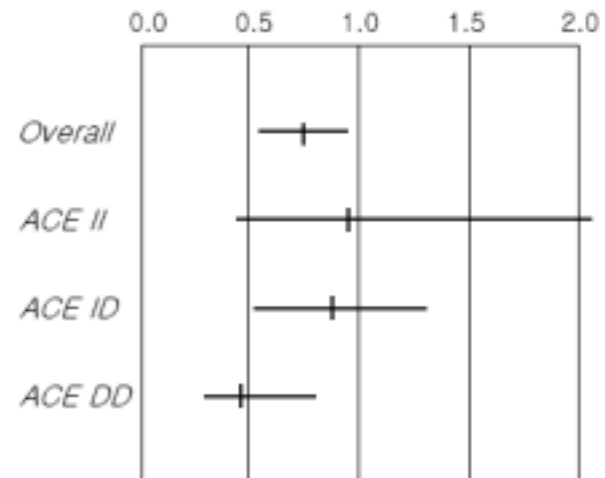
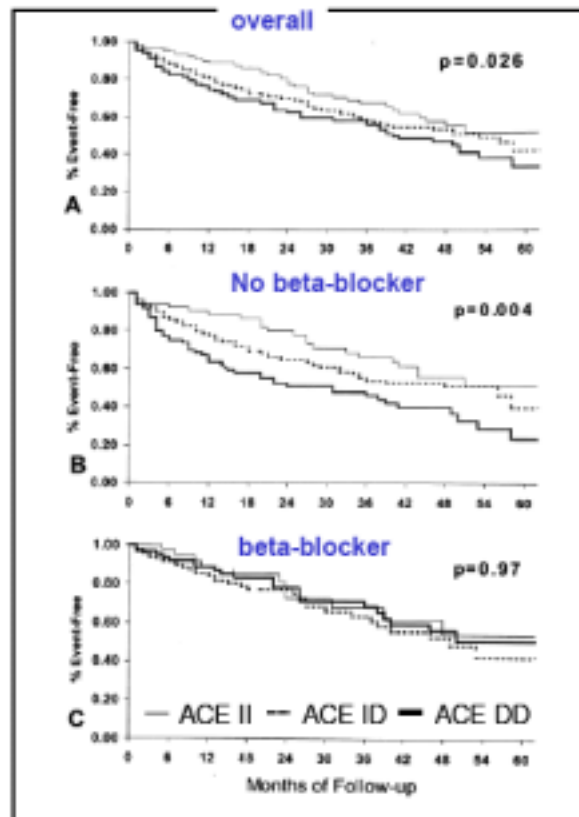
479 patients with ischemic/nonischemic CMP(LVEF: 0.25 ± 0.08)



Relative risk of death/transplantation
by ACE inhibitor dose use

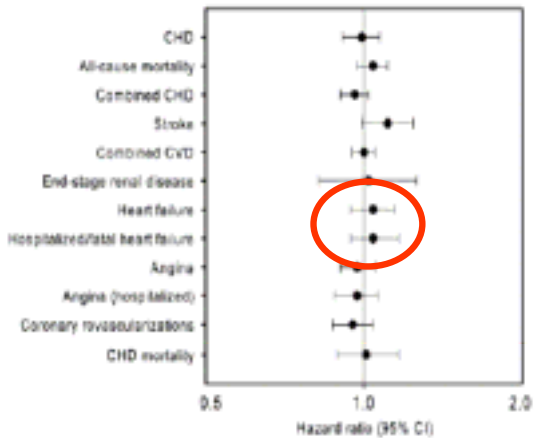
GRACE (Genetic Risk Assessment of Cardiac Event) study

479 patients with Ischemic/nonischemic CMP(LVEF:0.25 ± 0.08)

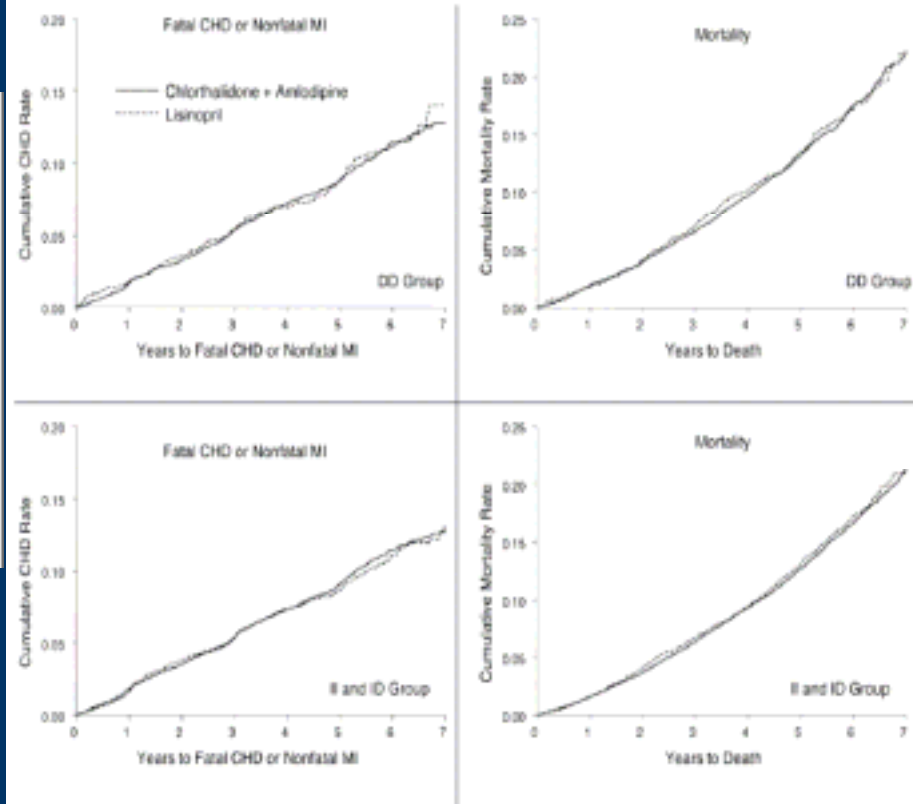


Relative risk of death/transplantation by beta-blocker use

Pharmacogenetic Association of the Angiotensin-Converting Enzyme Insertion/Deletion Polymorphism on Blood Pressure and Cardiovascular Risk in Relation to Antihypertensive Treatment
The Genetics of Hypertension-Associated Treatment (GenHAT) Study



Cox proportional hazard ratios and 95% CIs for ACE DD genotype vs ID and II genotype group.



Does the Angiotensin-converting enzyme (ACE) gene insertion/deletion polymorphism modify the response to ACE inhibitor therapy? – A systematic review

Background: Pharmacogenetic testing to individualize ACE inhibitor therapy remains controversial. We conducted a systematic review to assess the effect modification of the insertion/deletion (I/D) polymorphism of the ACE gene on any outcome in patients treated with ACE inhibitors for cardiovascular and/or renal disease.

Methods: Our systematic review involved searching six electronic databases, then contacting the investigators (and pharmaceutical industry representatives) responsible for the creation of these databases. Two reviewers independently selected relevant randomized, placebo-controlled trials and abstracted from each study details on characteristics and quality.

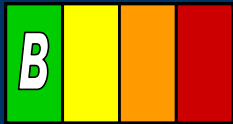
Results: Eleven studies met our inclusion criteria. Despite repeated efforts to contact authors, only four of the eleven studies provided sufficient data to quantify the effect modification by genotypes. We observed a trend towards better response to ACE inhibitors in Caucasian DD carriers compared to II carriers, in terms of blood pressure, proteinuria, glomerular filtration rate, ACE activity and progression to end-stage renal failure. Pooling of the results was inappropriate, due to heterogeneity in ethnicity, clinical domains and outcomes.

Conclusion: Lack of sufficient genetic data from the reviewed studies precluded drawing any convincing conclusions. Better reporting of genetic data are needed to confirm our preliminary observations concerning better response to ACE inhibitors among Caucasian DD carriers as compared to II carriers.

Stage C Therapy (Reduced LVEF with Symptoms)

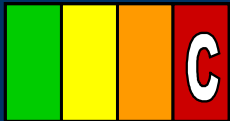
Aldosterone Antagonists

I IIa IIb III



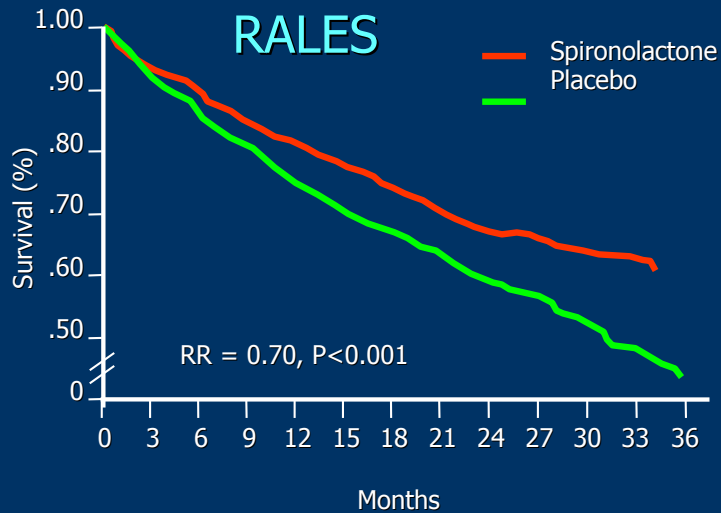
Addition of an aldosterone antagonist is recommended **in selected patients with moderately severe to severe symptoms of HF and reduced LVEF** who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be less than or equal to 2.5 mg/dL in men or less than or equal to 2.0 mg/dL in women and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists.

I IIa IIb III

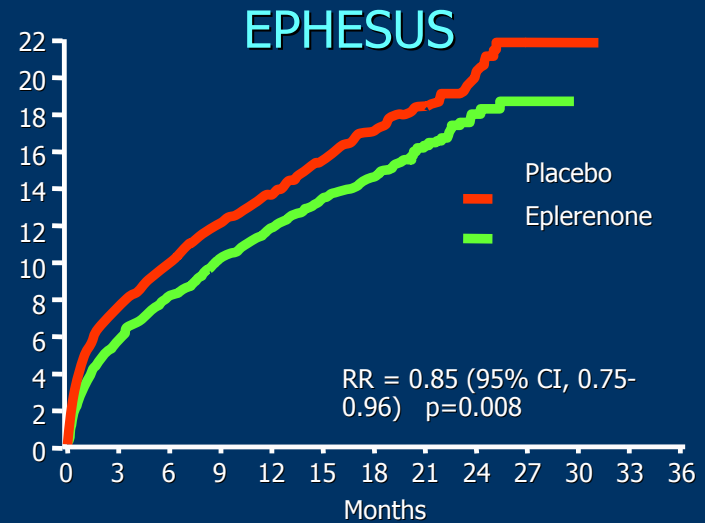


Routine combined use of an ACEI, ARB, and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF.

Aldosterone Antagonist



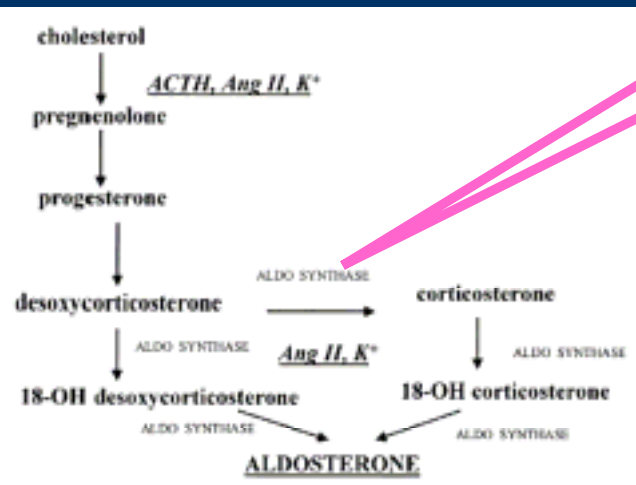
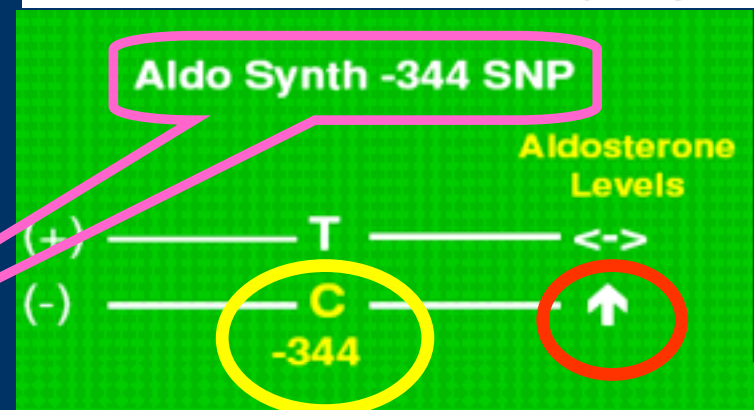
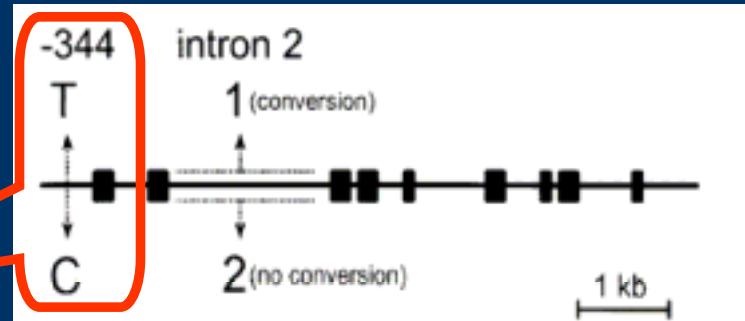
NYHA III-IV, LVEF \leq 35%



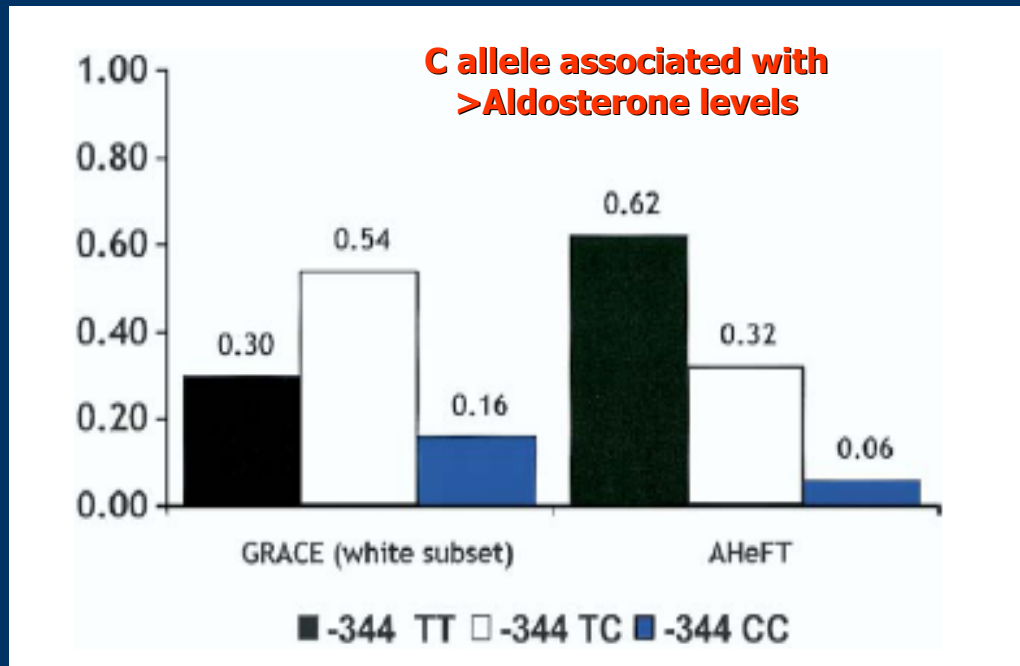
post-AMI, LVEF \leq 40%

CYP11B2 Gene Polymorphism

- Polymorphism in the promoter area i.e. transcriptional regulatory region
- The nucleotide in -344 position can be either cytosine (C) or thymidine (T)
- **Three CYP11B2 genotypes:**
-344CC,
-344CT,
-344TT



Aldosterone Synthase Promoter
Polymorphism Predicts Outcome in
African Americans With Heart Failure
Results From the A-HeFT Trial

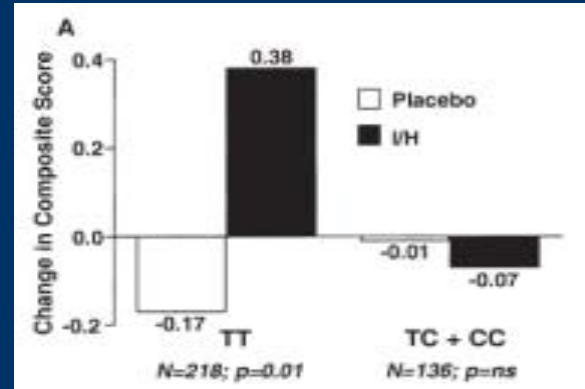
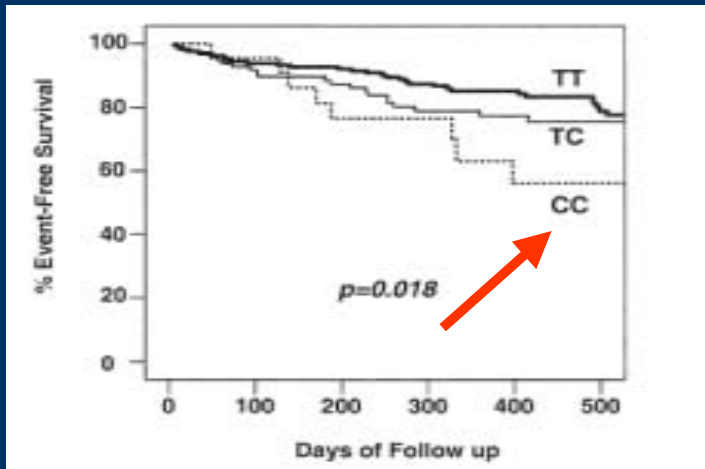


Genotype frequencies for the **aldosterone synthase (CYP11B2) 344 T/C polymorphism** in the white heart failure cohort in the **GRACE trial** and the African American heart failure cohort from **GRAHF substudy**.

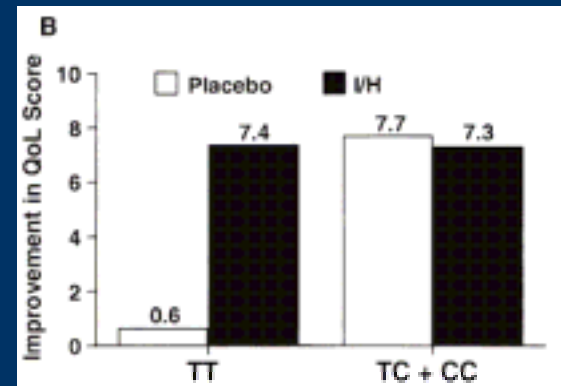
The prevalence of the T allele is significantly higher ($p < 0.001$) in African Americans.

Aldosterone Synthase Promoter Polymorphism Predicts Outcome in African Americans With Heart Failure

Results From the A-HeFT Trial



Impact of therapy with isosorbide dinitrate and hydralazine (I/H) on outcomes in HF



Change in quality-of-life scores

Aldosterone Synthase polymorphisms might alter response to drugs that modify the aldosterone pathway

Stage C Therapy (Reduced LVEF with Symptoms) Angiotensin Receptor Blockers (ARBs)



ARBs approved for the treatment of HF are recommended in patients with current or prior symptoms of HF and reduced LVEF **who are ACEI-Intolerant**.



ARBs are reasonable to use as alternatives to ACEIs as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications.



Polymorphism in the human CYP2C9

Allele	Trivial name	Effect of nucleotide changes	Enzyme activity	0 200 400 600 800 1000 1200 1400 1600 bp
CYP2C9*1	CYP2C9 _{wt}		100	1 2 3 4 5 6 7 8 9
CYP2C9*2	Cys 144	Arg ₁₄₄ Cys	12%	1 2 3 4 5 6 7 8 9 C ₄₅₀ T
CYP2C9*3	Leu 359	Ile ₃₅₉ Leu	<5%	1 2 3 4 5 6 7 8 9 A ₁₁₇₃ C A ₁₆₁ T

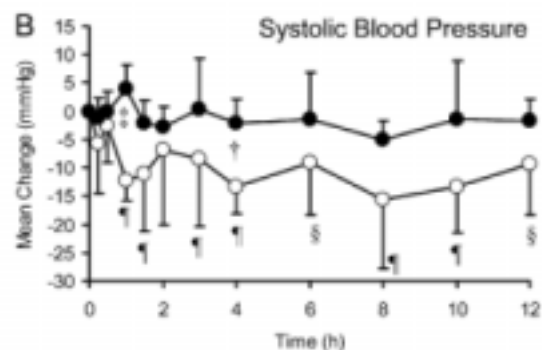
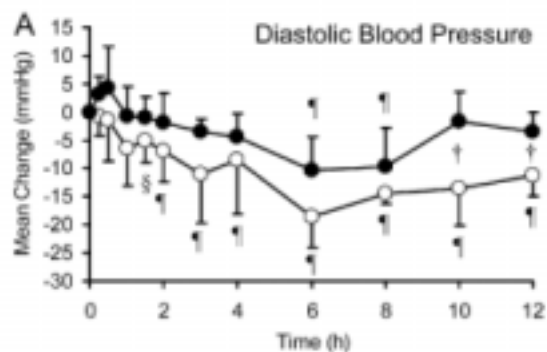
[†]substrate dependent

Substrate drugs:

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

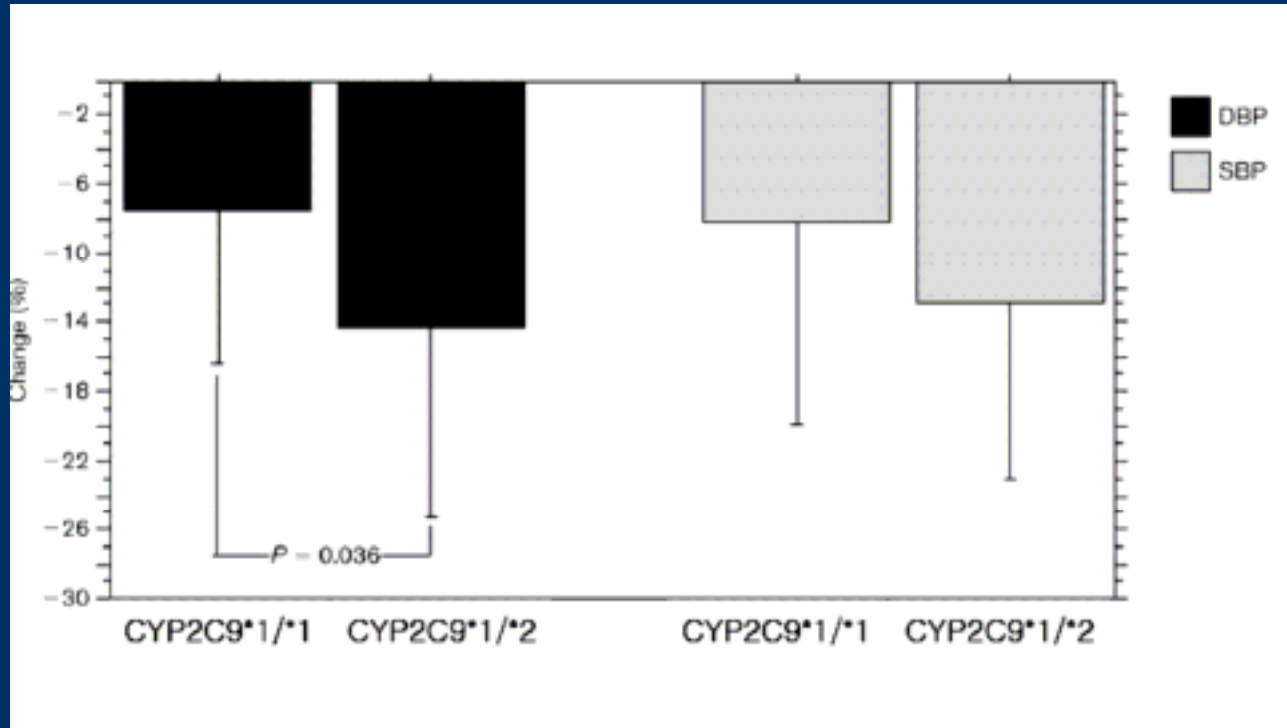


Effect of the CYP2C9*3 allele on pharmacogenetics of Losartan in healthy Japanese subjects

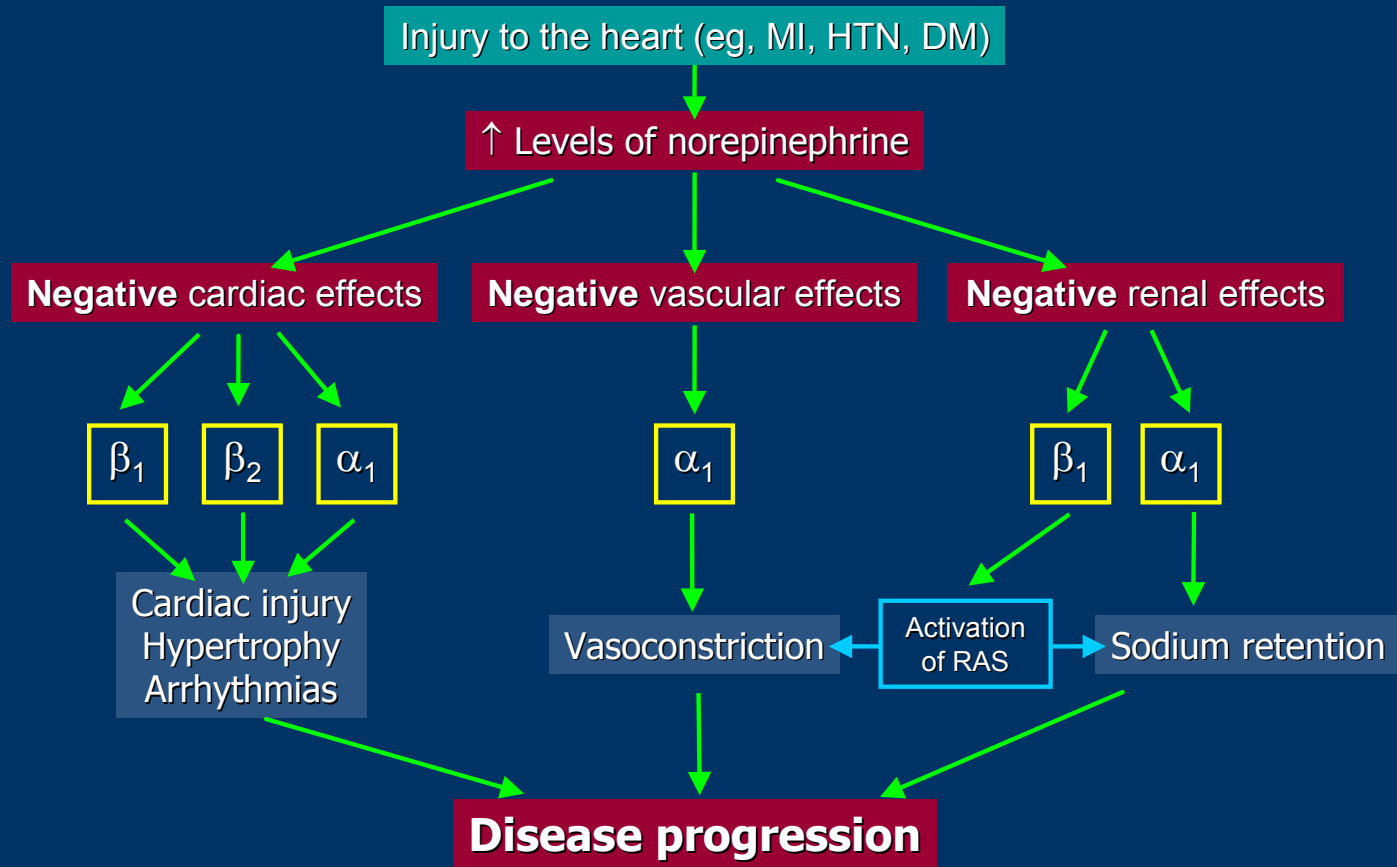


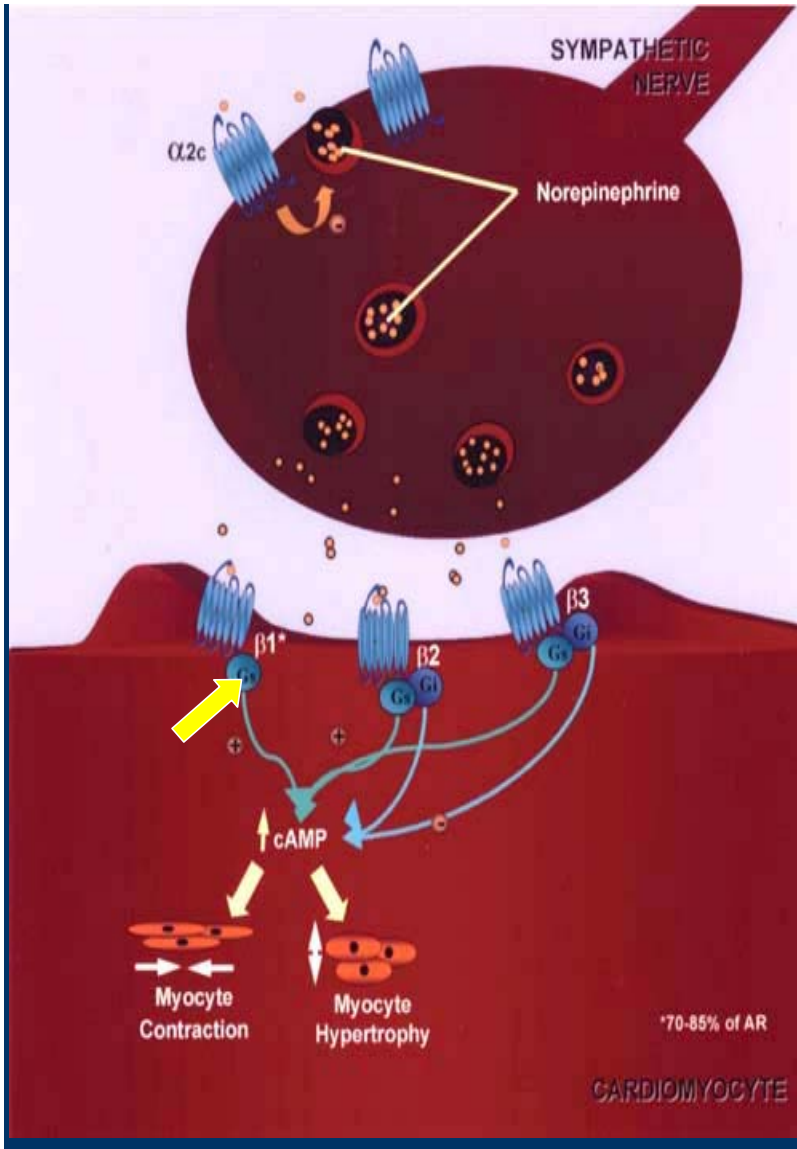
- CYP2C9*1/*3
- CYP2C9*1/*1

SILVHIA (Swedish irbesartan LV hypertrophy investigation vs atenolol) trial



Deleterious Effects of Norepinephrine in CV Disease





Representation of a synaptic gap with the main components of the cardiac adrenergic signaling. **Release of norepinephrine is regulated by presynaptic α_{2c} -adrenergic receptor (AR).** After being released, norepinephrine binds to **β -AR, that are G-protein-coupled transmembrane receptors.** On binding to ligands, **the stimulatory G-protein (G_s) activates adenylate cyclase and the inhibitory G-protein (G_i) reduces its activity.** **Both β_1 - and β_2 -AR are normally coupled to G_s protein, but β_2 -AR may also couple to G_i .** The stimulation and function of these receptors modulate effector molecules responsible for regulating cardiomyocyte contraction and hypertrophy.

Stage C Therapy (Reduced LVEF with Symptoms)

Beta-Blockers



Beta-blockers (using 1 of the 3 proven to reduce mortality, i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) are recommended **for all stable patients with current or prior symptoms of HF and reduced LVEF**, unless contraindicated.



Chronic Heart Failure

β blockers

responder

non-responder

CAUSE

Plasma Concentration
of β blocker



**Polymorphisms
Drug Metabolizing Enzyme**

Function of **Target
Molecules** of β blocker



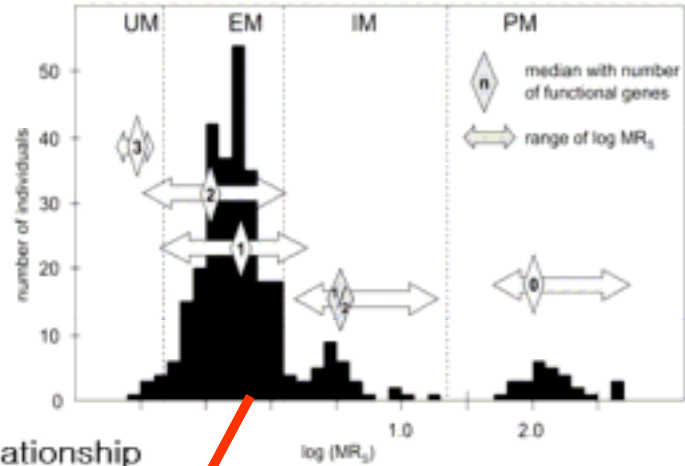
**Polymorphisms
AR and Target Molecules**

Drugs metabolized by cytochrome P450 2D6 (CYP2D6)

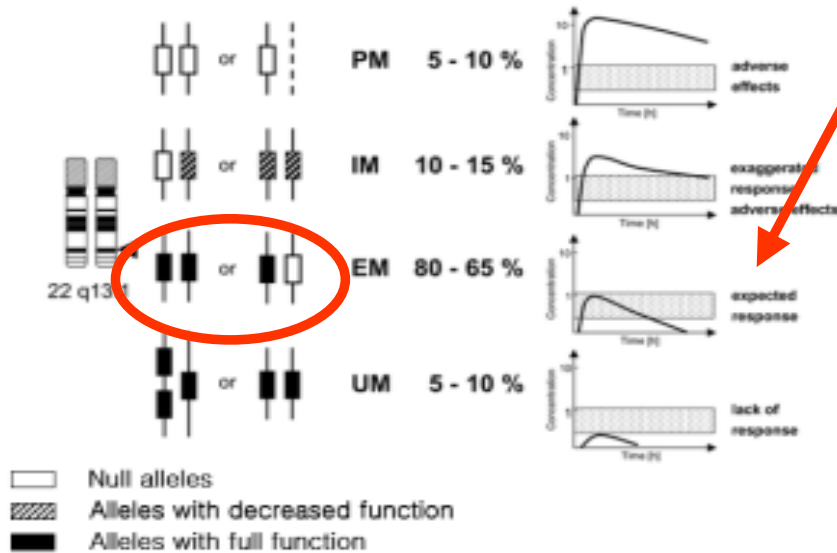
Analgesics
Anti-ADHD drugs
Antiarrhythmics
Antidementia drugs
Tricyclic antidepressants
Antidiabetic
Anti-estrogen
Antihypertensives
Antiemetics
Antihistamines
Antipsychotics
Appetite suppressants
Beta-adrenergic blockers
Calcium antagonists
MAO-inhibitors
Recreational drugs
Vasodilators



Alprenolol
Bufuralol
Bunitrolol
Bupranolol
Carvedilol
Metoprolol
Propranolol
Timolol



Schemes of CYP2D6 genotype-phenotype relationship



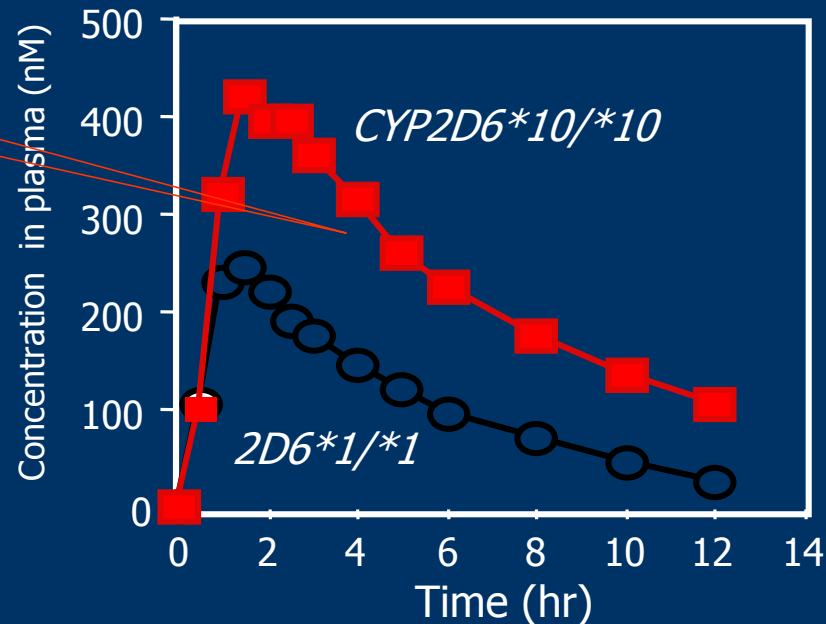
CYP2D6*1 and *2
 alleles code for
 normal enzyme
 activity (**EM**)

Metoprolol Clearance in Healthy Subjects

1. CYP2D6*1 and *2 alleles code for normal enzyme activity (**EM**)
2. 20 variant alleles, including CYP2D6*4 and *5, code for null enzyme activity (**NM**)
3. CYP2D6*9, *10 (which includes *10A, *10B, and *10C), *17, *36, and *41 variant alleles code for decreased enzyme activity (**PM**)
4. Gene duplication resulting in extra copies classified as ultra-extensive metabolizers (**UM**)

pharmacokinetic parameter	consequences for the PM relative to EM
bioavailability	2-5 fold
systemic exposure	
C_{max}	2-6 fold
AUC	2-5 fold
half life	2-6 fold
metabolic clearance	0.1-0.5 fold

Journal of Clinical Pharmacology, 2004;44:447-456





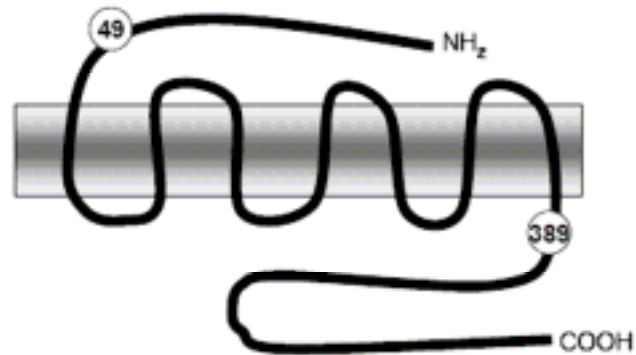
Receptor Polymorphism	Effect in Vitro	Expected Effect in Vivo
α_{2C} Del322-325	Decreased function	Increased norepinephrine release at synapse
β_1 Arg389	Increased function	Increased response at cardiomyocyte

α_{2C} -Adrenergic receptor
 (activation inhibits norepinephrine release)

β_1 -Adrenergic receptor
 (activation stimulates contractility)

Cardiomyocyte

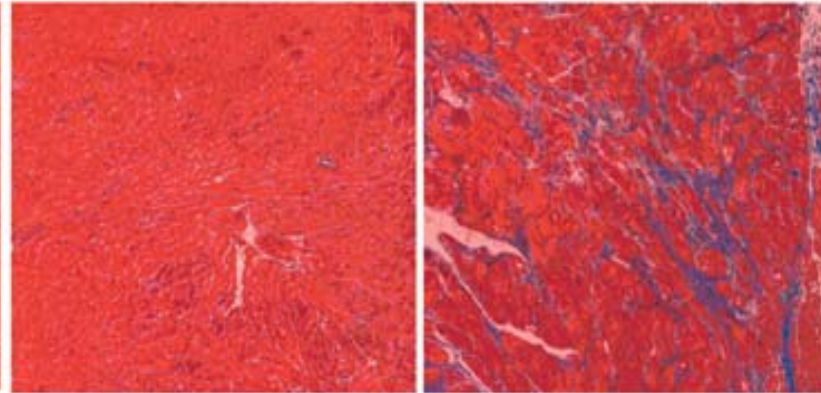
β_1 adrenergic receptor



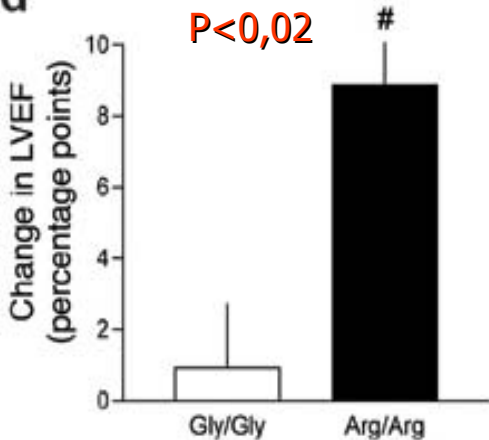
Codon	Polymorphism	Allele frequency	Function in vitro
β_1			
389	Arg/Gly	0.70/0.30	Arg = gain of function (\uparrow cAMP)
49	Ser/Gly	0.85/0.15	No data

Gly 389

Arg389



d



224 ptz

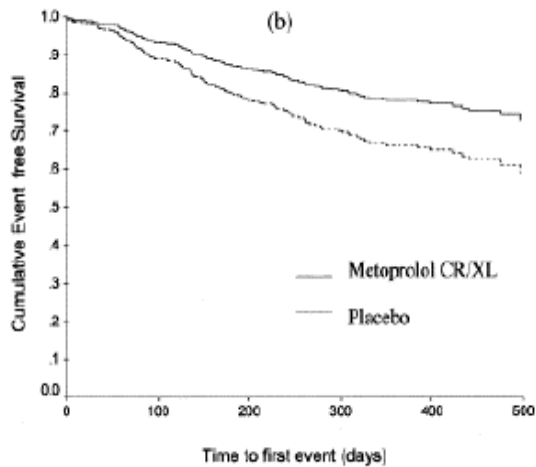
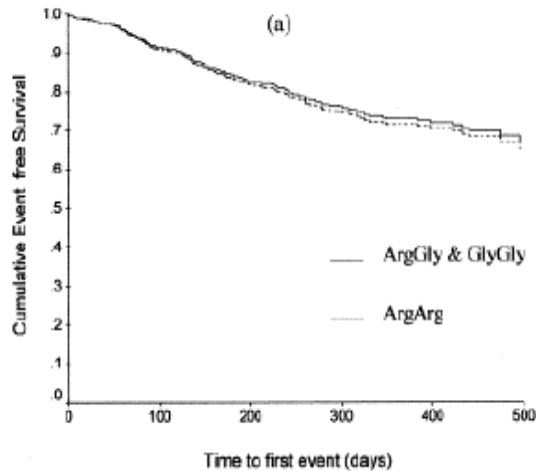
Beta 1-adrenergic receptor polymorphisms confer differential function and predisposition to heart failure

...hemodynamic responses to beta-receptor blockade were greater in Arg389 mice, and homozygosity for Arg389 was associated with improvement in ventricular function during carvedilol treatment in heart failure patients.

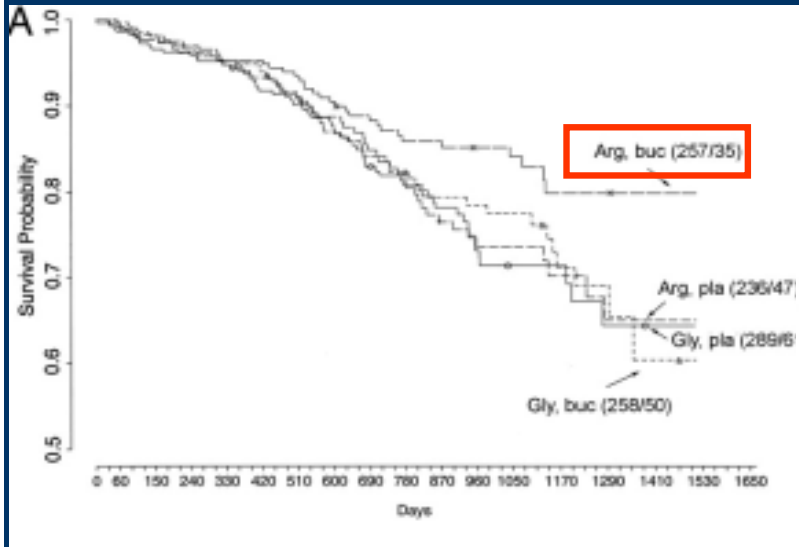
- Arg homozygous demonstrate increased efficacy of b-AR agonists by 3-4 fold
- increased myopathic potential

MERIT-HF substudy

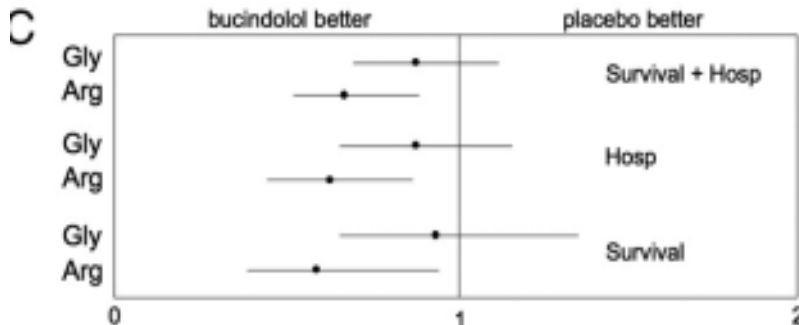
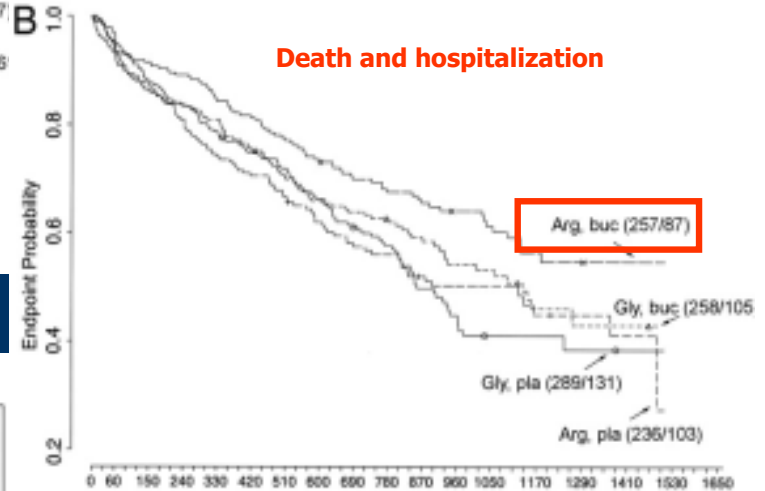
Metoprolol CR/XL 200 mg/d vs placebo



BEST Substudy



	Whites	Blacks
Heterozygotes	42%	50%
Gly homozygotes	9%	20%
Arg homozygotes	49%	30%
Gly carriers	51%	70%

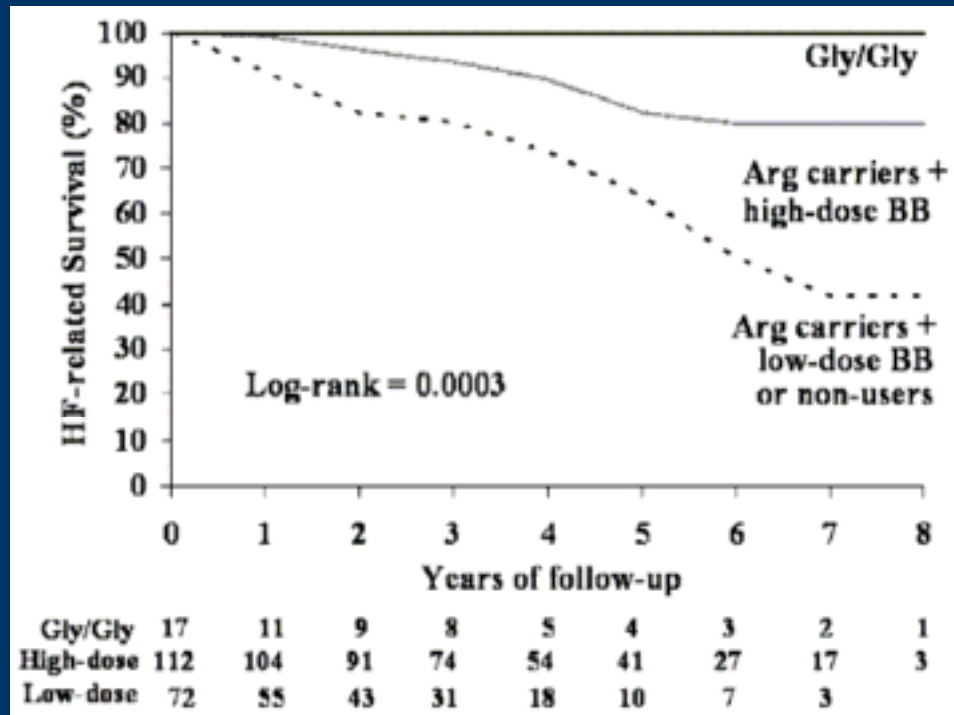


BEST Substudy

	Bucindolol vs Placebo					
	Arg389 Homozygous			Gly389 Carriers		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Death	0.62	0.40-0.95	.02	0.90	0.62-1.30	0.57
Death + hospitalizations	0.64	0.46-0.88	.006	0.86	0.64-1.15	0.29
Combined	0.66	0.50-0.88	.004	0.87	0.67-1.11	0.25

	Arg Homozygous	Arg/Gly Heterozygous	Gly Homozygous	Gly Carriers
Placebo group (n = 525)	236	237	52	289
Bucindolol group (n = 515)	257	216	42	258
Total	493	453	94	547

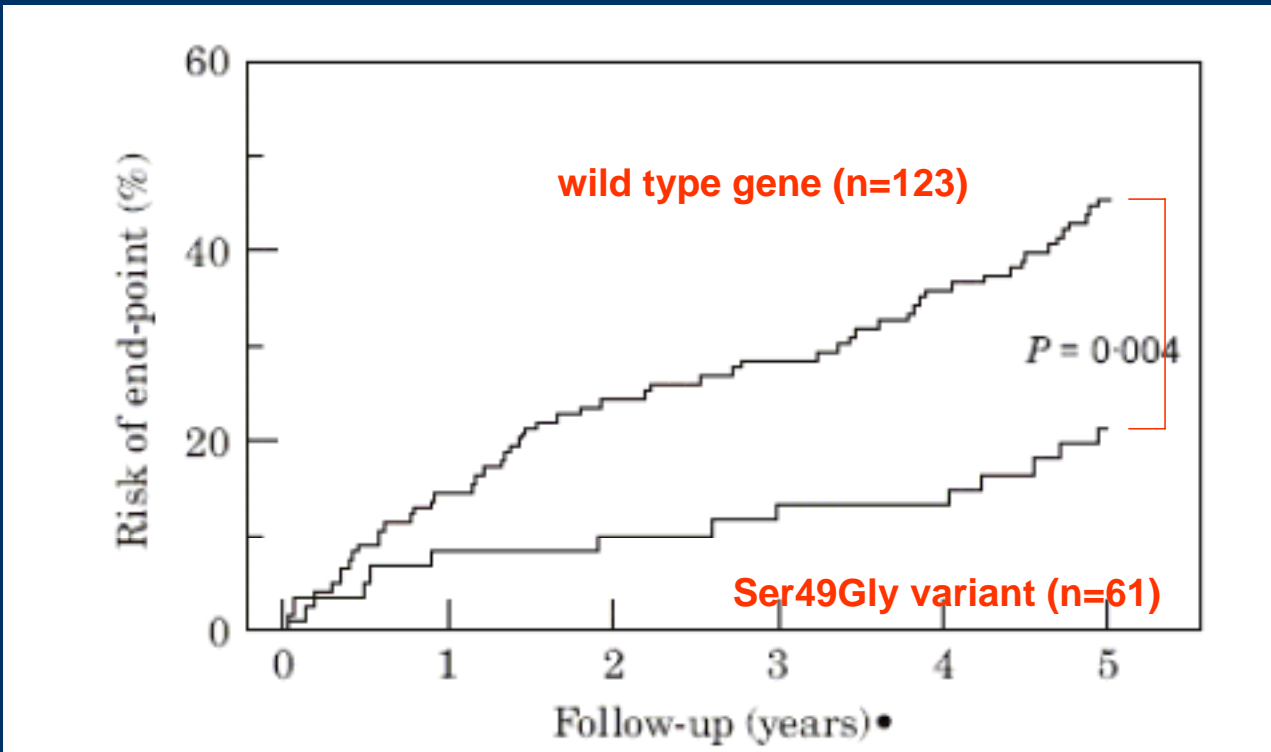
Impact of β 1-Adrenergic Receptor Polymorphisms on Susceptibility to Heart Failure, Arrhythmogenesis, Prognosis, and Response to Beta-Blocker Therapy



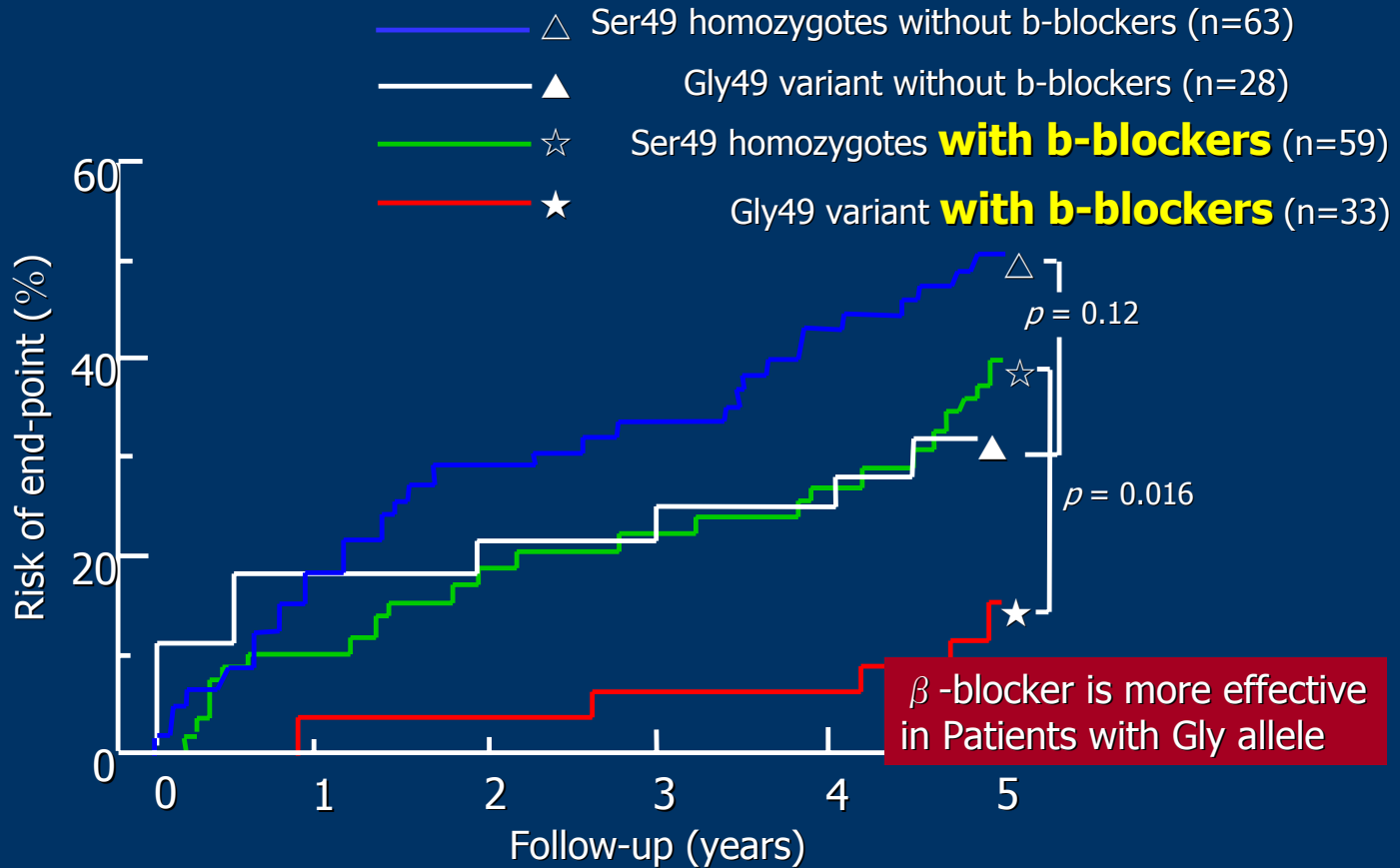
HF-related survival according to the 1-Arg389Gly polymorphism and use and dosage of beta blockers (BB)

A novel polymorphism in the gene coding for the beta₁-adrenergic receptor associated with survival in patients with heart failure

β₁AR Ser49Gly and Risk of death or cardiac transplantation

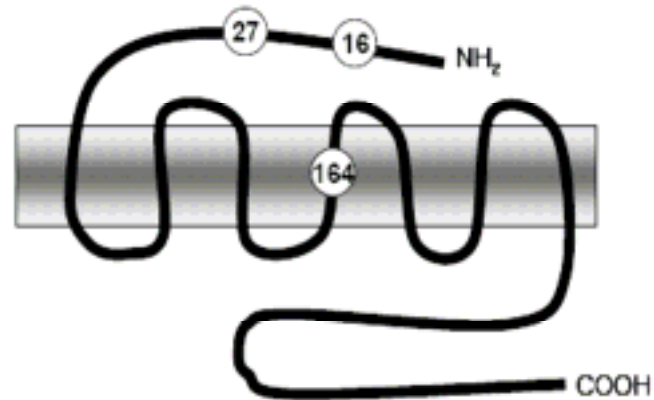


β_1 AR Ser49Gly and Risk of death or cardiac transplantation for patients with HF according to the use of beta-blockers



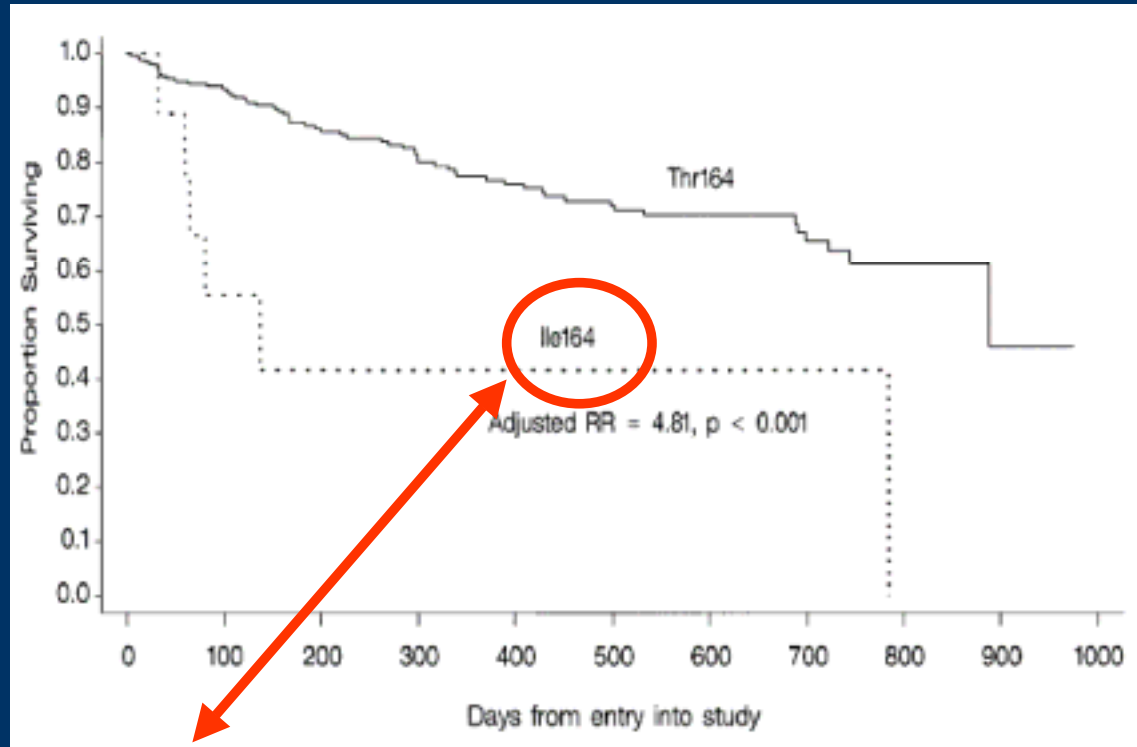
Increased down regulation

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

The Ile164 β_2 -Adrenergic Receptor Polymorphism Adversely Affects the Outcome of Congestive Heart Failure




Allele frequency <1%

β_2 AR Gln27Glu adrenergic receptor polymorphism

Ratio of Responders	
Gln/Gln	26%
Gln/Glu	62%
Glu/Glu	

Responder ; Improved LVEF by 10%
Improved FS by 5%

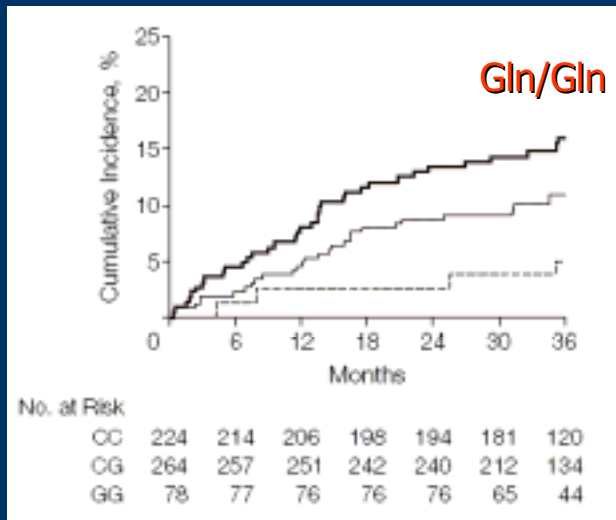


Gln27Glu is a potential determinant for the response to carvedilol in heart failure

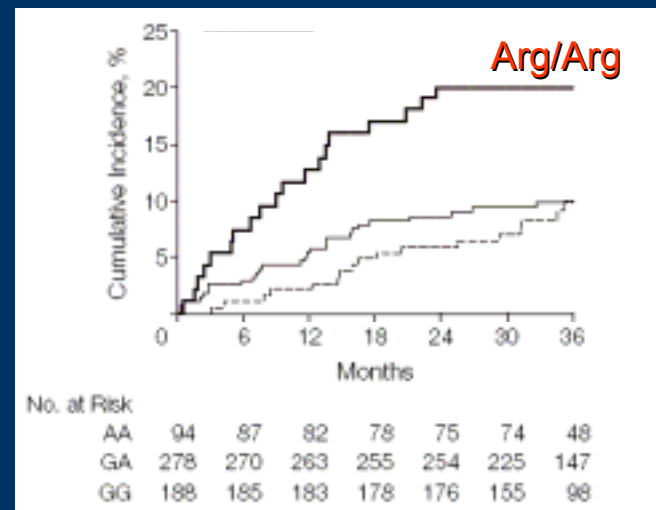
Kaye, DM, et al Pharmacogenetics (2003) 13 ; 379-382

Decreased down regulation

β_2 -Adrenergic Receptor Genotype and Survival Among Patients Receiving β -Blocker Therapy After an Acute Coronary Syndrome



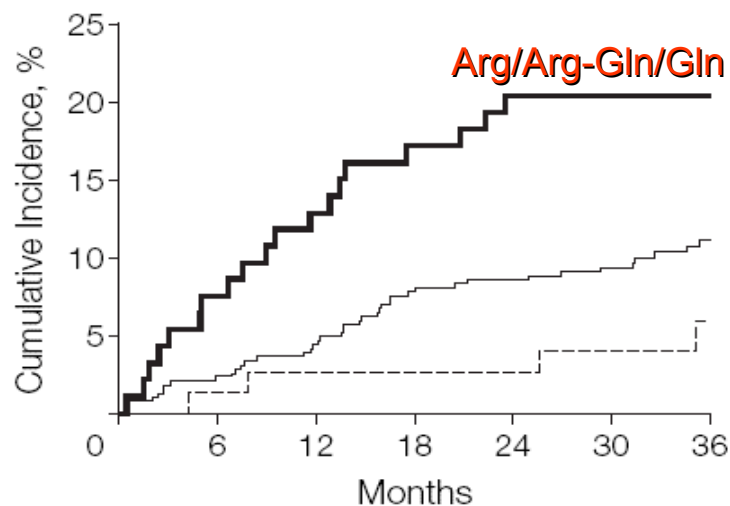
Mortality of Patients Receiving Beta-Blocker Therapy by *ADRB2* 79 C to G= **Genotype (Gln27Glu)**



Mortality of Patients Receiving Beta-Blocker Therapy by *ADRB2* 46 G to A= **Genotype (Gly16Arg)**

β_2 -Adrenergic Receptor Genotype and Survival Among Patients Receiving β -Blocker Therapy After an Acute Coronary Syndrome

Mortality of Patients Receiving Beta-Blocker Therapy by *ADRB2* Composite Genotype



No. at Risk

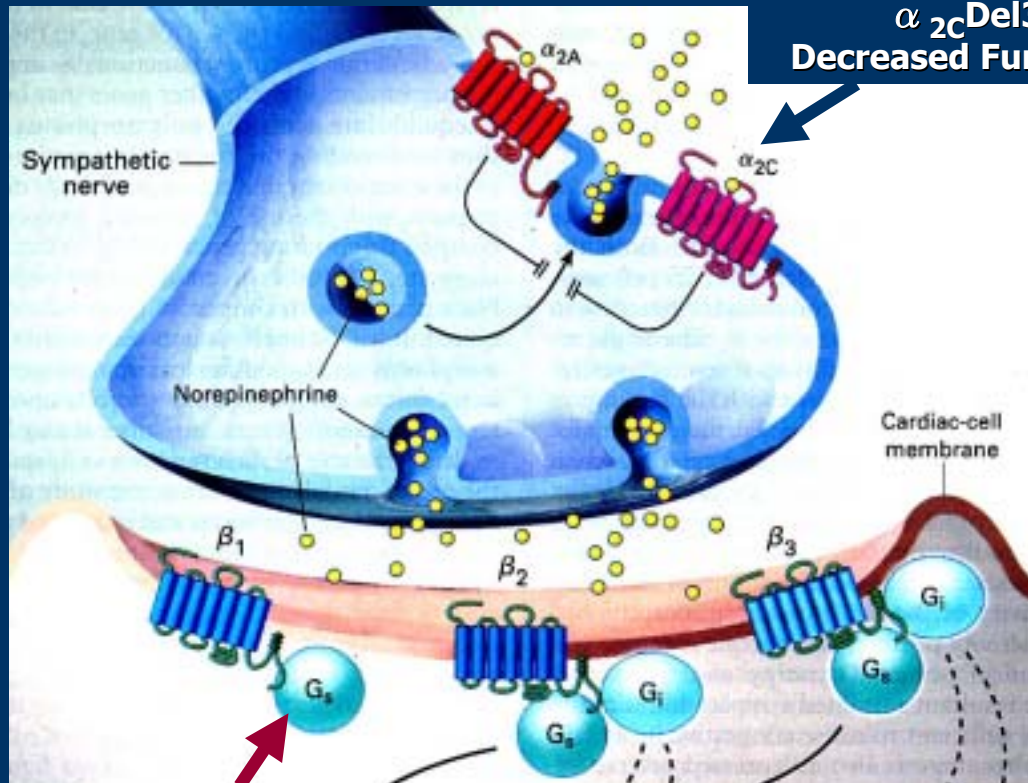
C	93	86	81	77	74	73	48
B	386	376	368	355	352	312	200
A	75	74	73	73	73	63	43

Role of β 1- and β 2-adrenoceptor polymorphisms in heart failure: a case-control study

Genotypes	Cases		Controls		OR (95% CI)
	No.	(%)	No.	(%)	
<i>β1-AR</i>					
Gly389Gly	21	(8.2)	18	(7.8)	Reference
Arg389Gly	116	(45.3)	90	(39.1)	1.5 (0.7–3.1)
Arg389Arg	119	(46.5)	122	(53.1)	1.1 (0.5–2.2)
<i>Allele frequency</i>					
Gly		(31.0)		(27.0)	
Arg		(69.0)		(73.0)	
<i>β2-AR (codon 16)</i>					
Arg16Arg	40	(15.6)	34	(14.8)	Reference
Arg16Gly	119	(46.5)	115	(50.0)	0.8 (0.5–1.5)
Gly16Gly	97	(37.9)	81	(35.2)	1.0 (0.5–1.8)
<i>Allele frequency</i>					
Arg		(39.0)		(40.0)	
Gly		(61.0)		(60.0)	
<i>β2-AR (codon 27)</i>					
Gln27Gln	124	(48.4)	120	(52.2)	Reference
Gln27Glu	97	(37.9)	79	(34.3)	1.2 (0.8–1.8)
Glu27Glu	35	(13.7)	31	(13.5)	1.1 (0.6–2.1)
<i>Allele frequency</i>					
Gln		(67.0)		(69.0)	
Glu		(32.0)		(31.0)	

Odds ratio (ORs) for heart failure adjusted for age and sex and 95% confidence intervals (95% CI) according to β 1- and β 2-adrenoceptor genotypes

Heart failure and Polymorphism of α_{2c} AR



α_{2c} Del322-325
Decreased Function in vitro

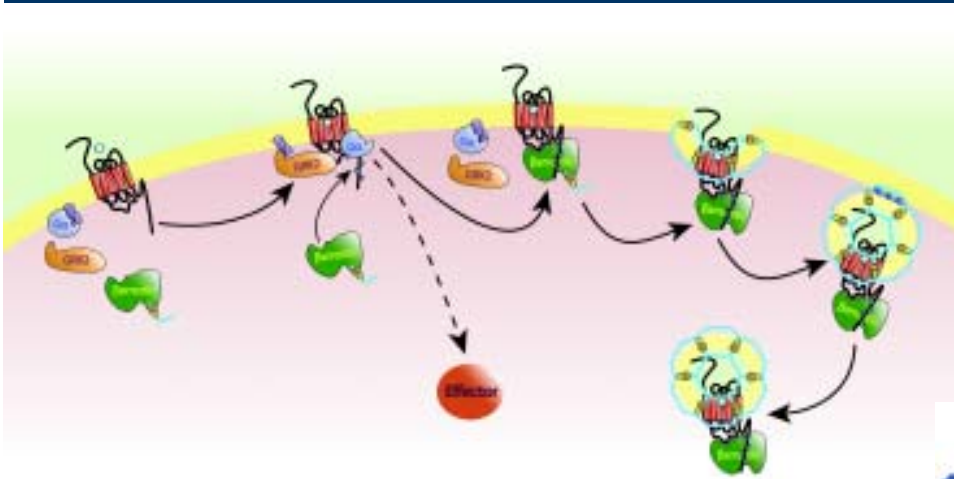
α_{2c} AR Del322-325

	Allele frequency	
	CHF	healthy
Black	0.62	0.41
White	0.11	0.04
Yellow	???	???

β_1 Arg389Gly
Increased
Function in vitro

These two polymorphism of receptors act synergistically to increase the risk of heart failure in black.

Downregulation of β -AR signaling

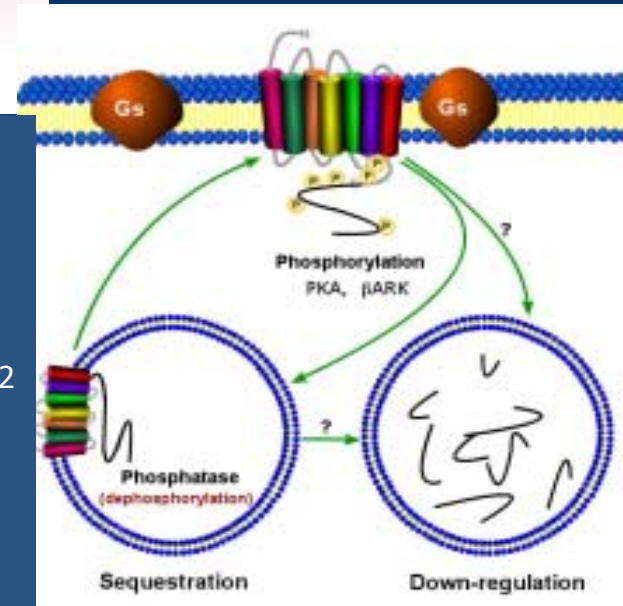


GRK2

- predominant function in the acute regulation of β -AR signaling
- No nonsynonymous polymorphism

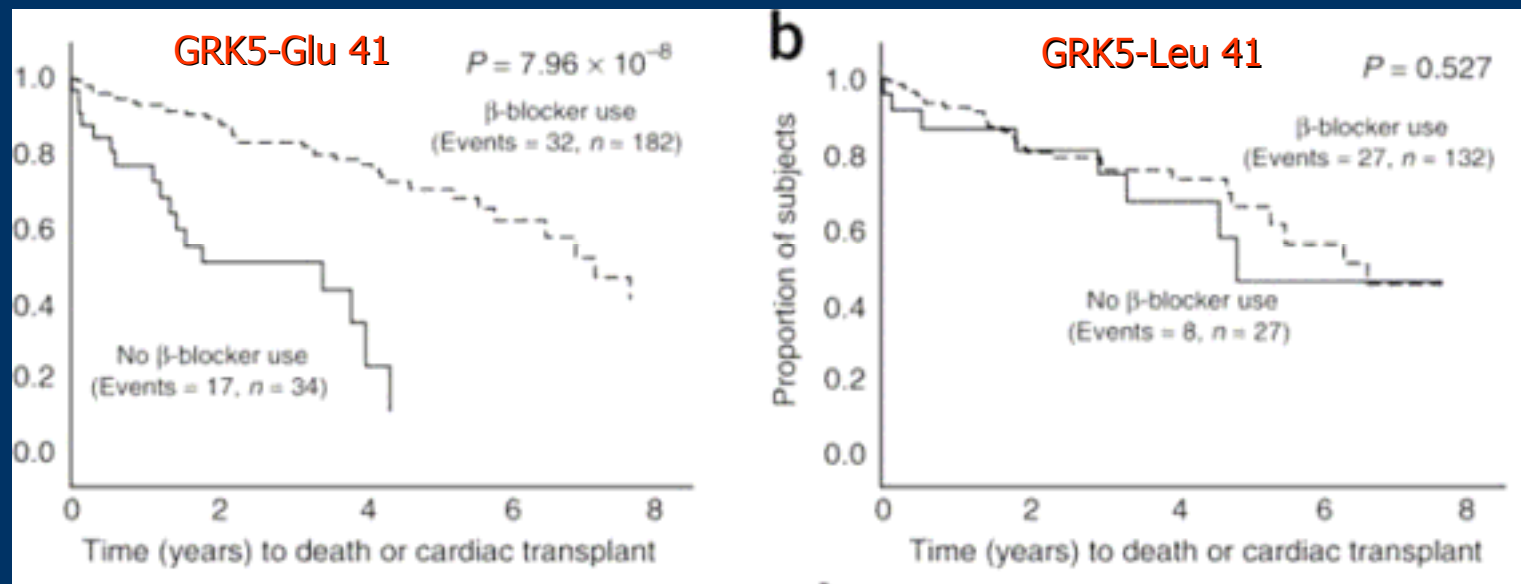
• GRK5

- **more important for chronic regulation of β -AR signaling**
- 4 nonsynonymous polymorphism at cDNA nucleic acid position 122 (A/T), 840 (G/A), 1274 (C/T) and 1624 (C/G)
- **amino acid change at residues 41 glutamine to leucine (GRK5-Glu41Leu variant)**
- **Allele frequency >2% (African American GRK5-Leu41 41%)**



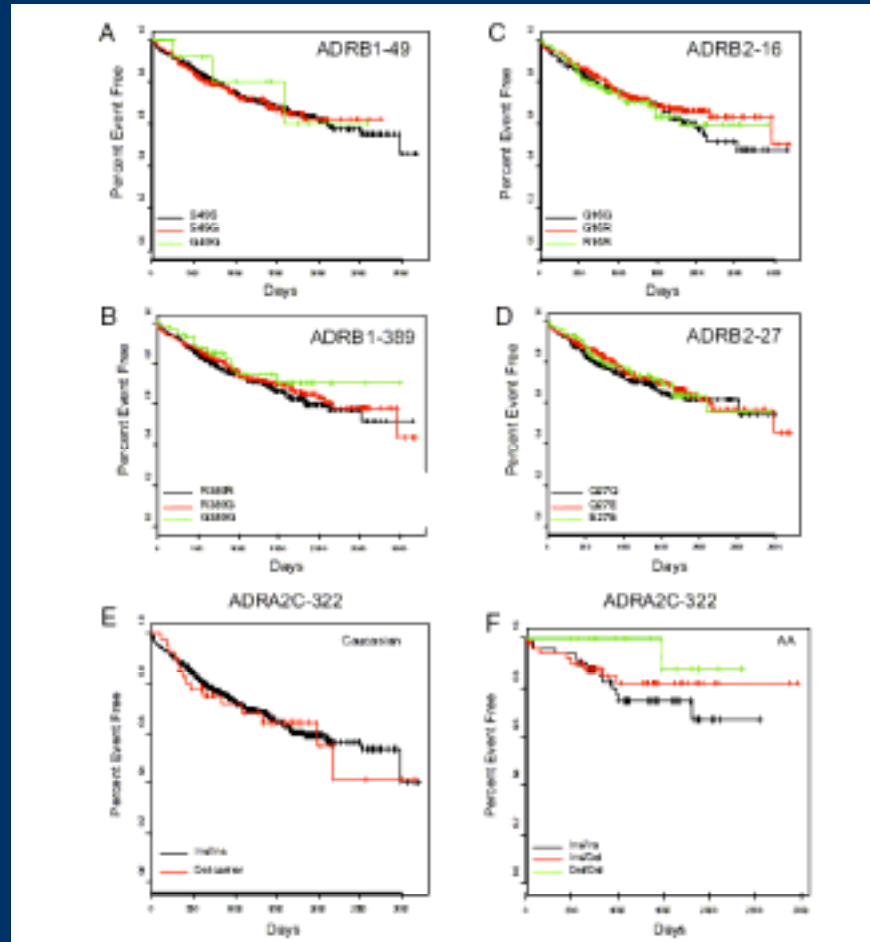
A GRK5 polymorphism that inhibits β -adrenergic receptor signaling is protective in heart failure

Stephen B Liggett^{1,6,7}, Sharon Cresci^{2,2}, Reagan J Kelly^{3,2}, Faisal M Syed¹, Scot J Matkovich², Harvey S Hahn¹, Abhinav Diwan⁴, Jeffrey S Martini⁴, Li Sparks¹, Rohan R Parekh⁴, John A Spertus⁵, Walter J Koch⁴, Sharon L R Kardia² & Gerald W Dorn II^{1,2}



“Enhanced β -AR desensitization of excessive catecholamine signaling by GRK5-Leu41 provides a ‘genetic β -blockade’ that improves survival in African Americans with heart failure, suggesting a reason for conflicting results of β -blocker clinical trials in this population”

Lack of Association Between Adrenergic Receptor Genotypes and Survival in Heart Failure Patients Treated With Carvedilol or Metoprolol

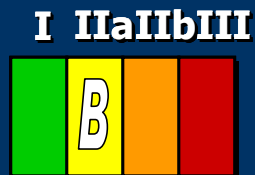


Results of Genetic Studies in beta-blocker–Treated Heart Failure Patients With Survival End Points

	ADRB1 S49G	ADRB1 R389G	ADRB2 G16R	ADRB2 Q27E	ADRA2C Del322-325	ADRB1 49/389 SR, SQ, GR	ADRB2 16/27 RQ, GE, GQ
Current cohort	p = 0.47	p = 0.87	p = 0.73	p = 0.30	p = 0.85 Caucasian, p = 0.094 African American	NS	NS
Shin et al. (21)	NS	NS	NS	NS	NS	NS	2 copies RQ HR: 1.91, 95% CI: 1.09 to 3.36 (p = 0.024)
de Groote et al. (29)	NS	NS	NS	NS	—	NS	2 copies GQ p = 0.01 (univariate)
White et al. (30), MERIT-HF	—	p = 0.74	—	—	—	—	—
Liggett et al. (16), BEST	—	R389R bucindolol-treated patients had better survival compared with R389R placebo- treated patients HR: 0.62, 95% CI: 0.40 to 0.96 (p = 0.03)	—	—	Unpublished	—	—

Stage C Therapy (Reduced LVEF with Symptoms)

Digitalis



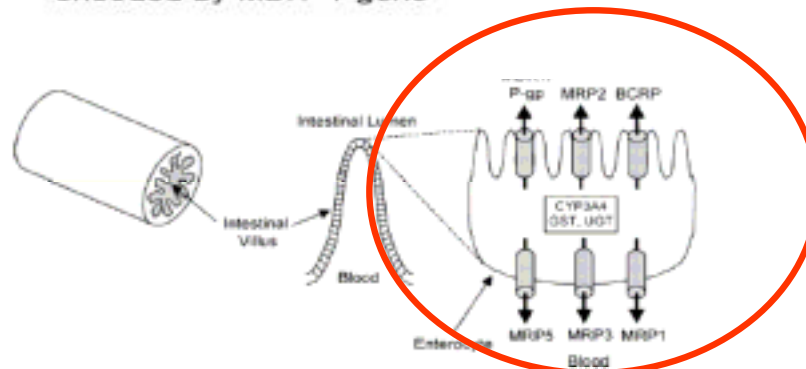
Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF **to decrease hospitalizations for HF.**



Polymorphism in drug transport

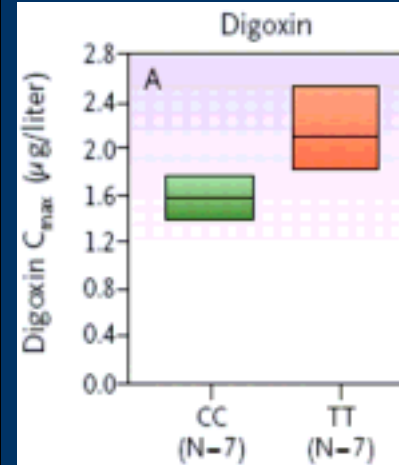
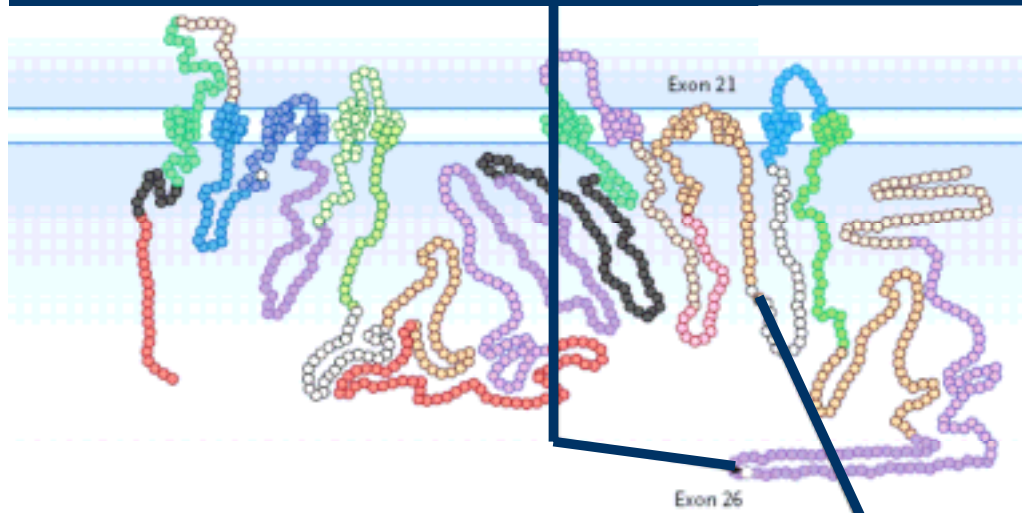
P-glycoprotein

- 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



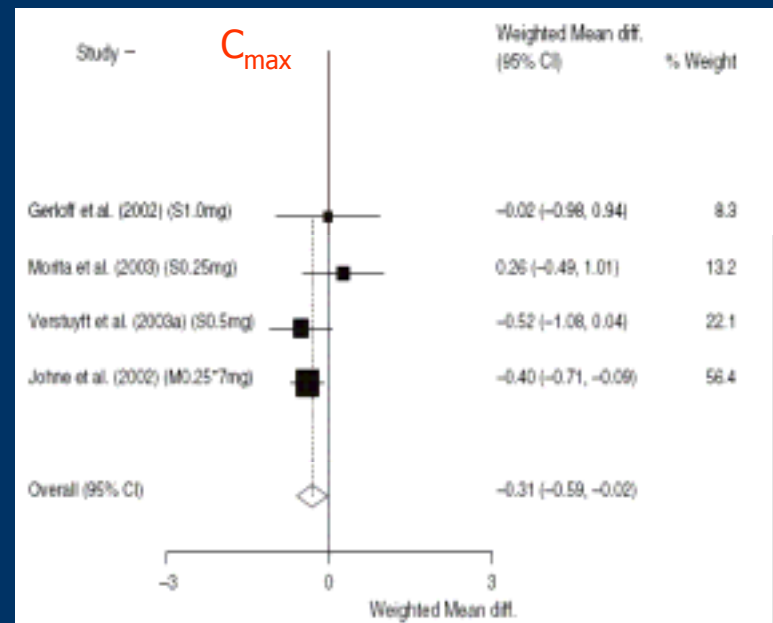
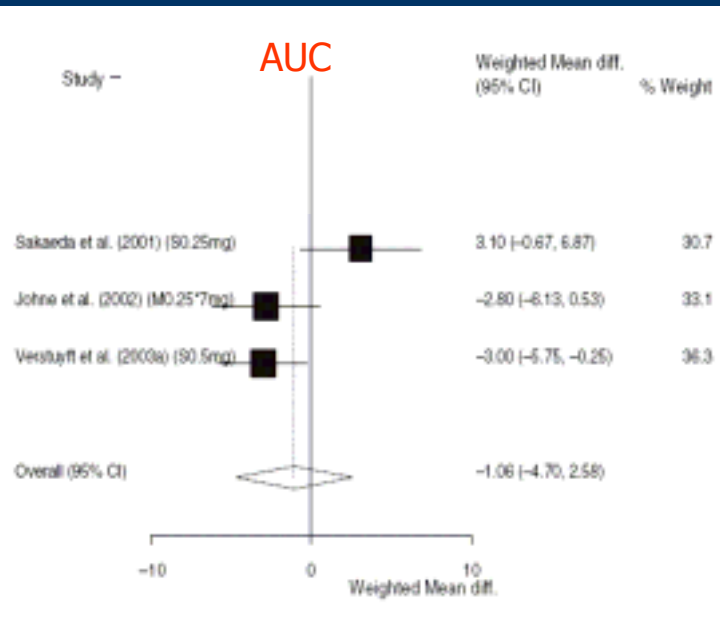
Functional Consequences of Genetic Polymorphisms in the Human P-Glycoprotein Transporter Gene *ABCB1* (or *MDR1*)

3435C→T
I1145I



2677G→T
A893S

Meta-analysis of the influence of *MDR1* C3435T polymorphism on digoxin pharmacokinetics and *MDR1* gene expression



Conclusionsmeta-analysis of available studies indicates that the synonymous *MDR1* C3435T SNP does not affect the pharmacokinetics of digoxin and the expression of *MDR1* mRNA.

The Management of Heart Failure

The Past, the Present, and the Future

Eugene Braunwald, MD

The genetic determinants of the responses to drugs have important implications for the clinical course and management of HF.

We are now on the threshold of many additional advances in pharmacogenetics, advances that during the next decade or two will enhance both risk stratification of patients with or likely to develop HF and selection of the most appropriate therapy.



AmpliChip® CYP450 Test
The first FDA cleared microarray



Fitting the drug to the patient

Susan Mayor, *BMJ* 2007;334:452-453



Thank you