

# PHARMACOGENETICS

## Cardiovascular Diseases

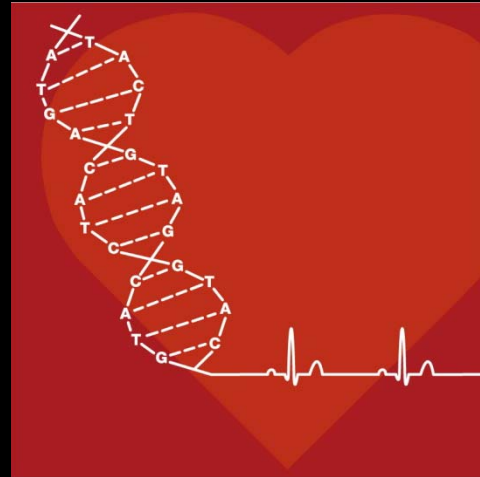
Bruce D. Gelb, M.D.

Center for Molecular Cardiology

Departments of Pediatrics and Genetics &  
Genomic Sciences



MOUNT SINAI  
SCHOOL OF  
MEDICINE



# TOPICS

---

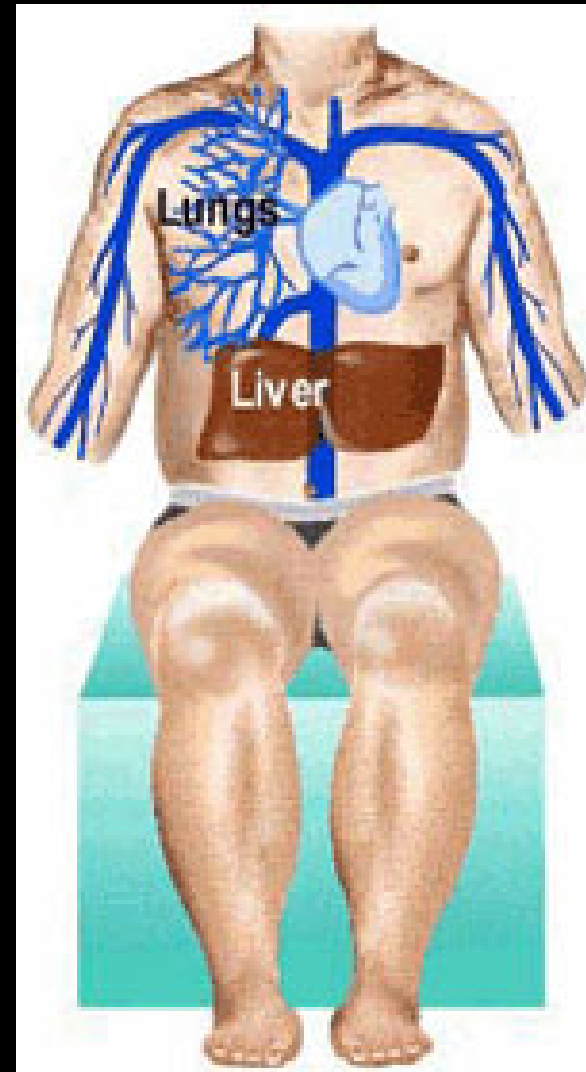
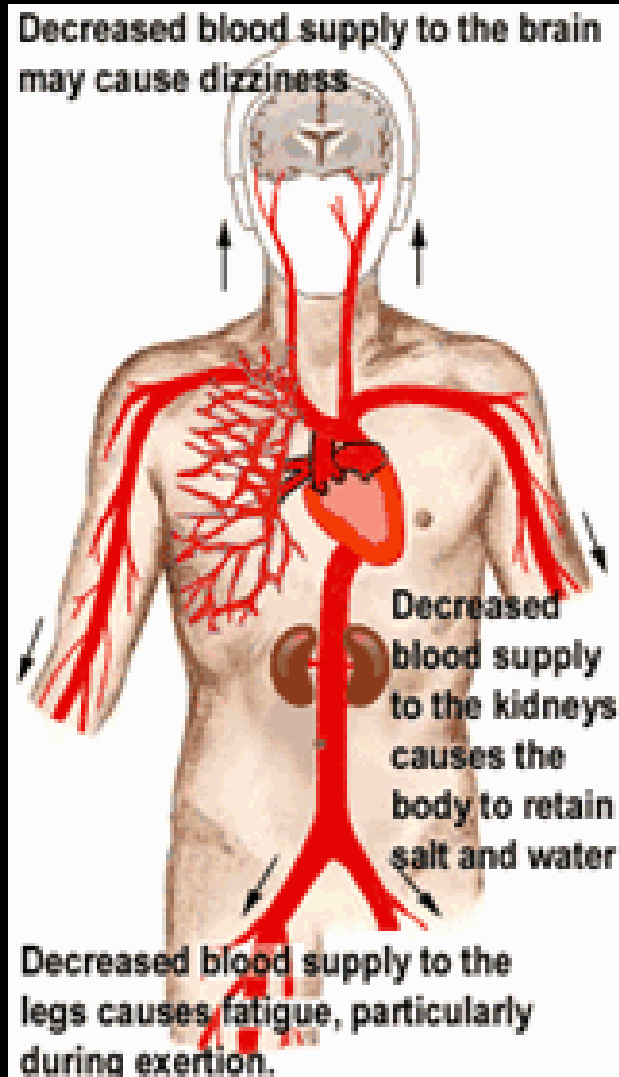
- Congestive Heart Failure
    - Renin-Angiotensin-Aldosterone System
    - $\beta$  Adrenergic System
    - Nitric Oxide
  - Long QT Syndrome
    - Congenital
    - Drug Induced
-

# CONGESTIVE HEART FAILURE

---

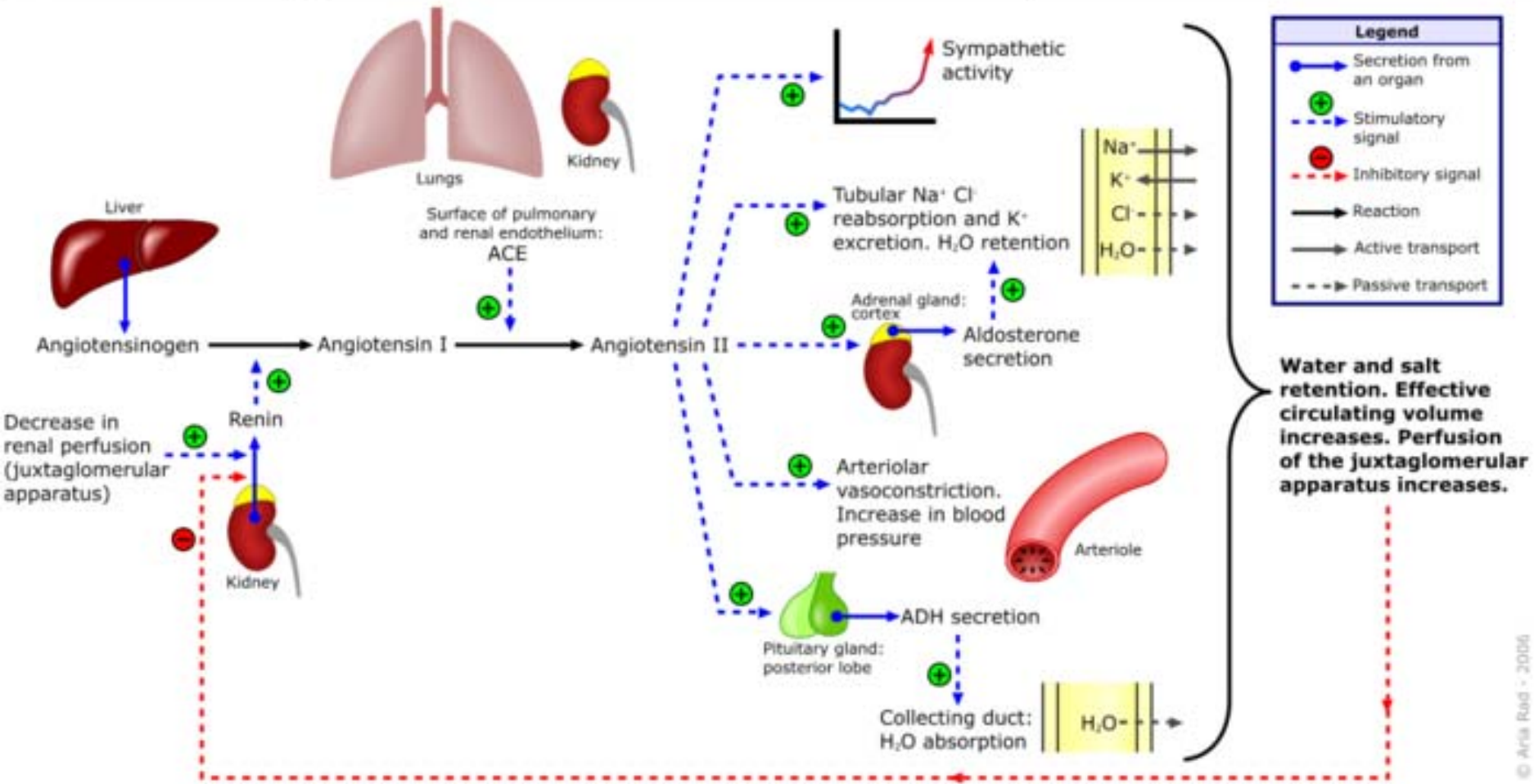
- Major Cause of Morbidity and Mortality
  - Different Forms
    - Systolic Dysfunction
    - Diastolic Dysfunction
  - Heterogeneous Causes
    - Primary Myocardial Disease (e.g., Cardiomyopathies)
    - Secondary Myocardial Disease (e.g., Myocarditis)
    - Inadequate O<sub>2</sub>/Nutrient Supply (e.g., Atherosclerosis)
-

# CONGESTIVE HEART FAILURE



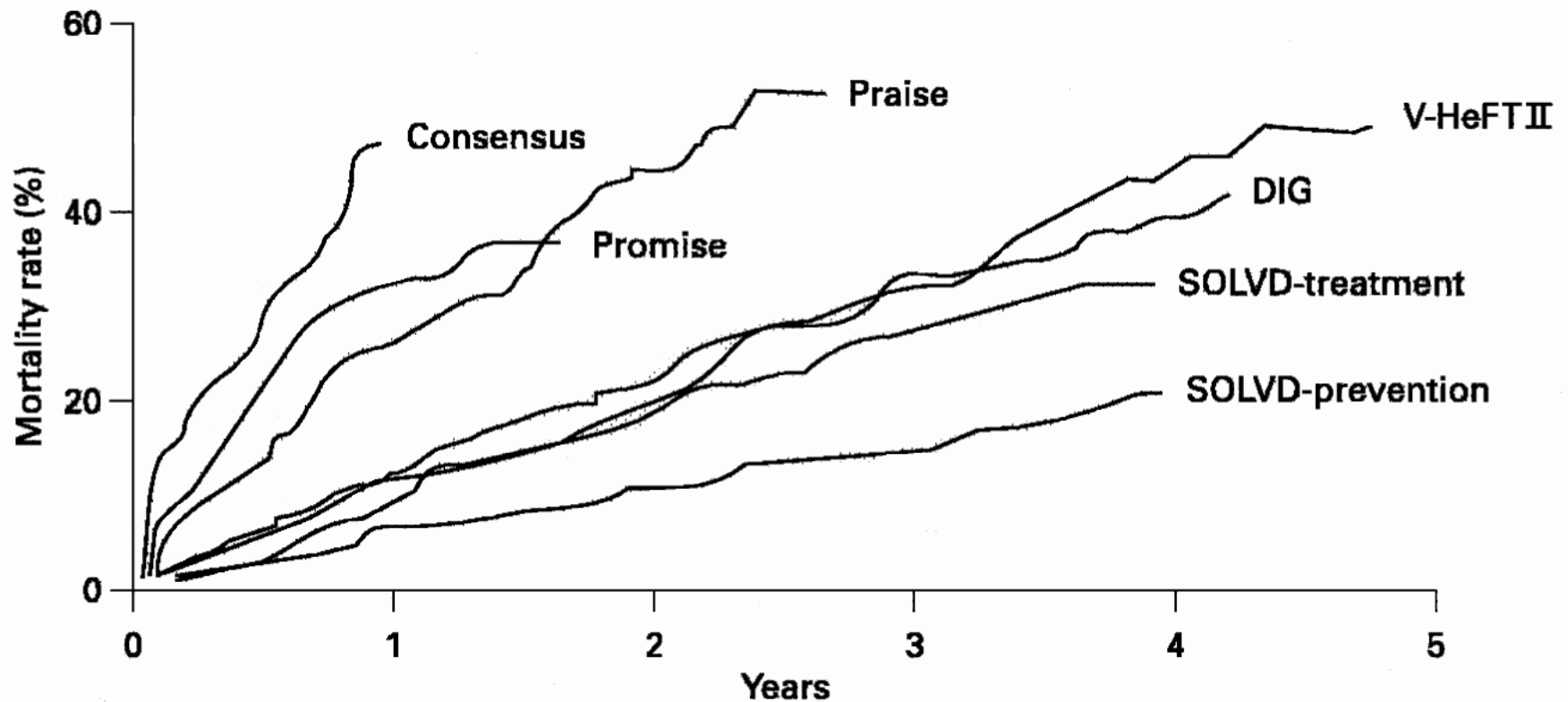
# CONGESTIVE HEART FAILURE

## Renin-angiotensin-aldosterone system



# Congestive Heart Failure

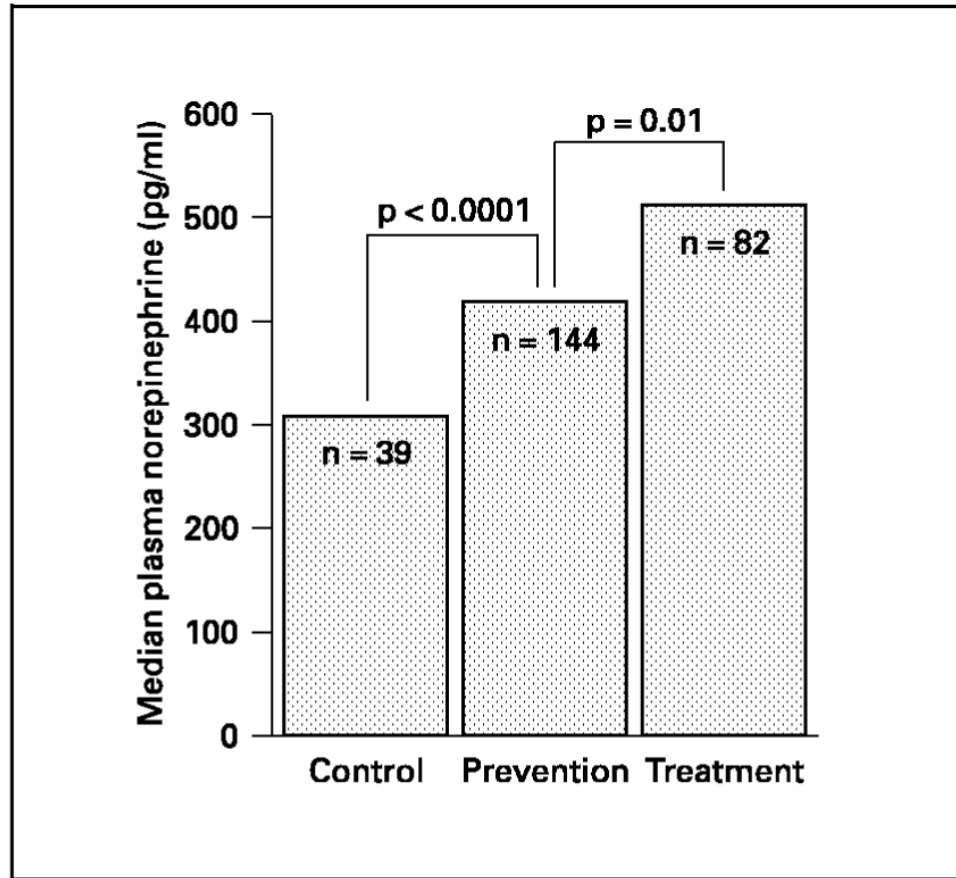
## OUTCOMES



Cohn, *Cardiology* 1999

# SOLVD TRIAL

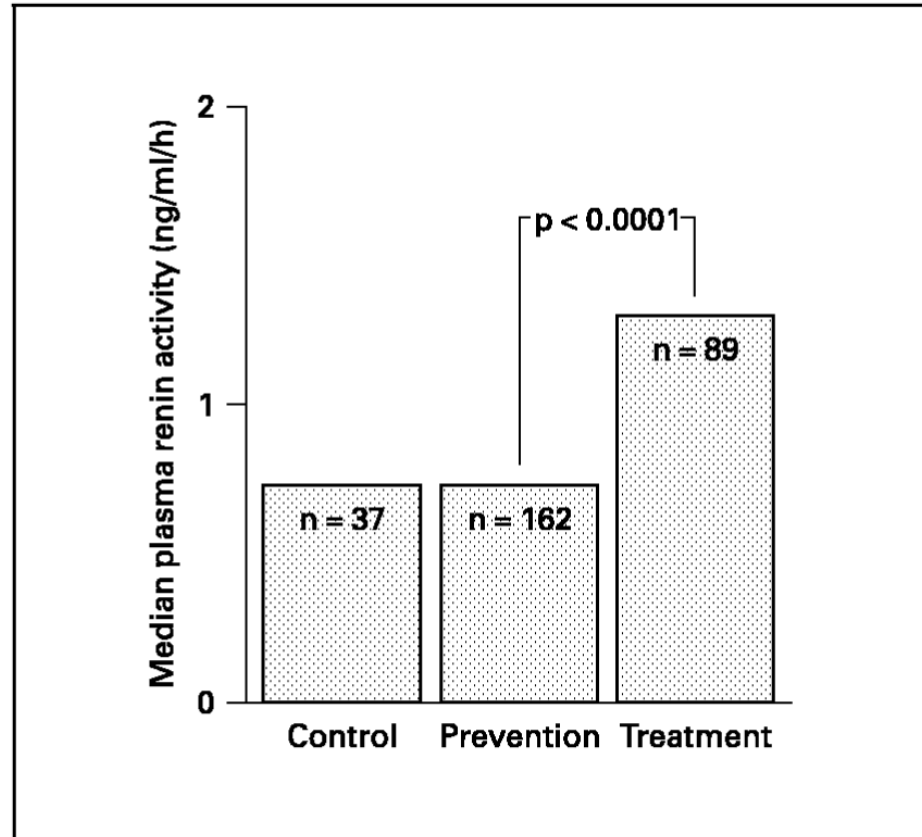
## Neuroendocrine Activation in CHF



Francis *et al.*, *Circulation* 1990

# SOLVD TRIAL

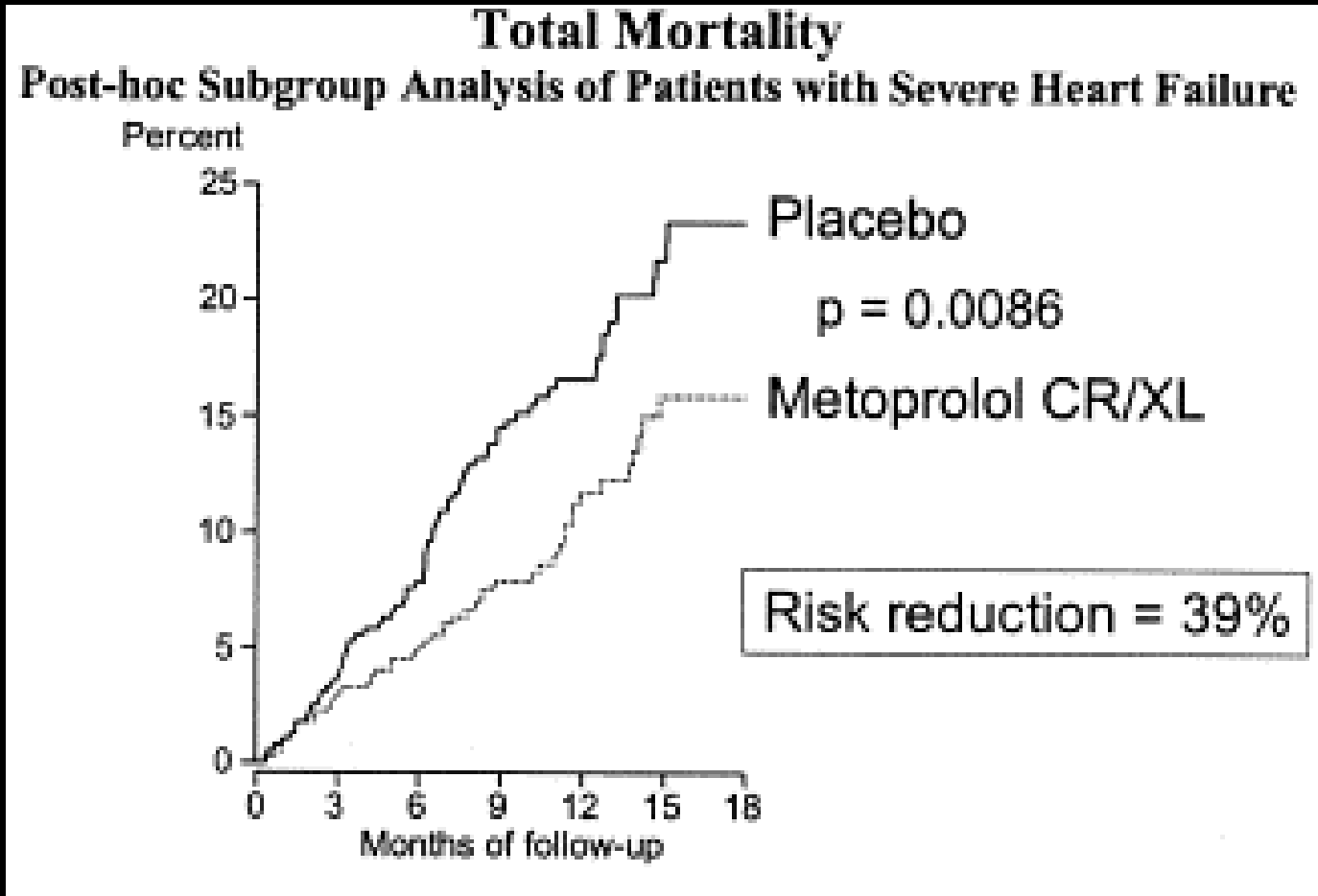
## Neuroendocrine Activation in CHF



Francis *et al.*, *Circulation* 1990

# Congestive Heart Failure

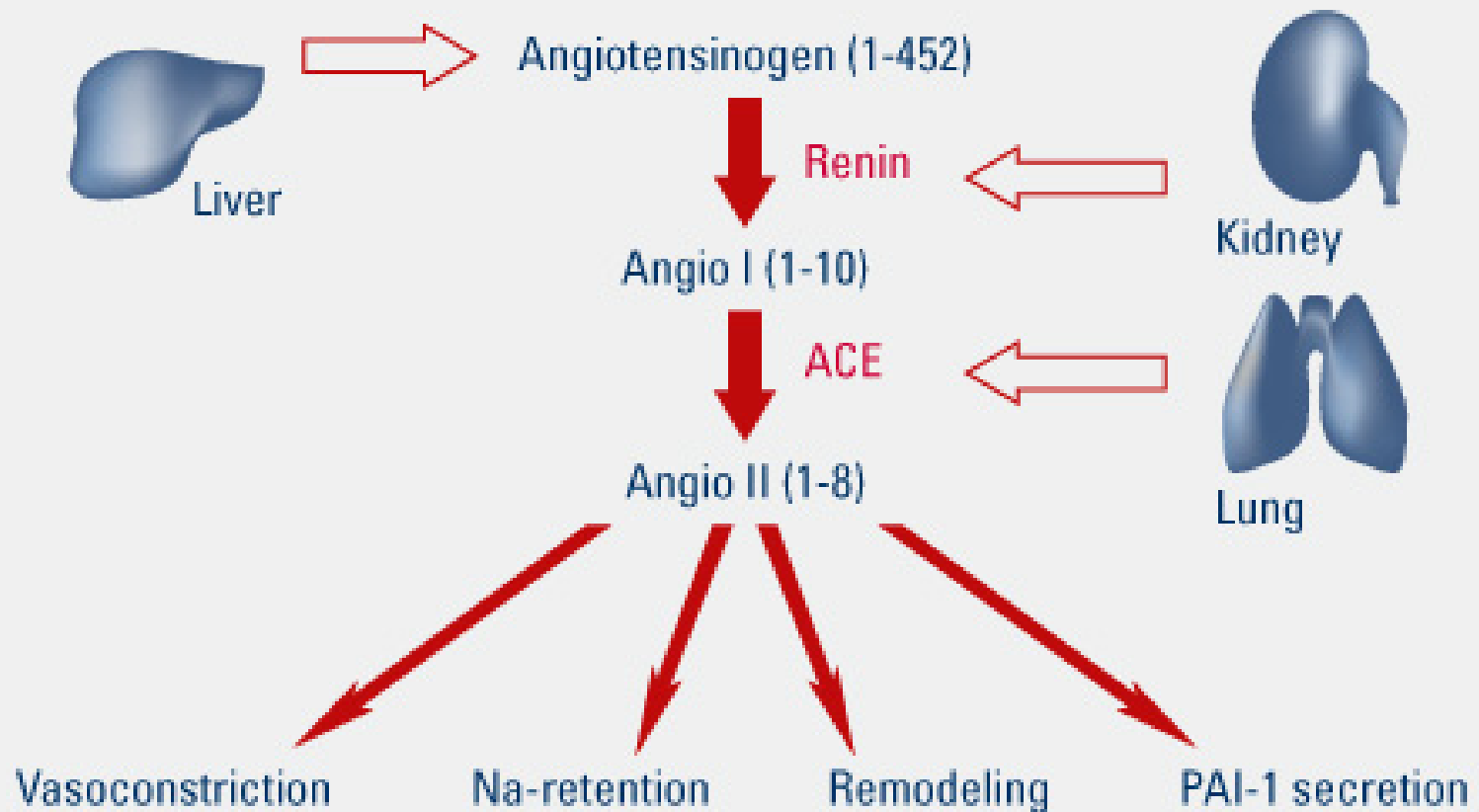
## $\beta$ Blocker Therapy



Goldstein *et al.*, JACC 2001

# RAAS

**Renin-Angiotensin System – involved in many pathological processes**

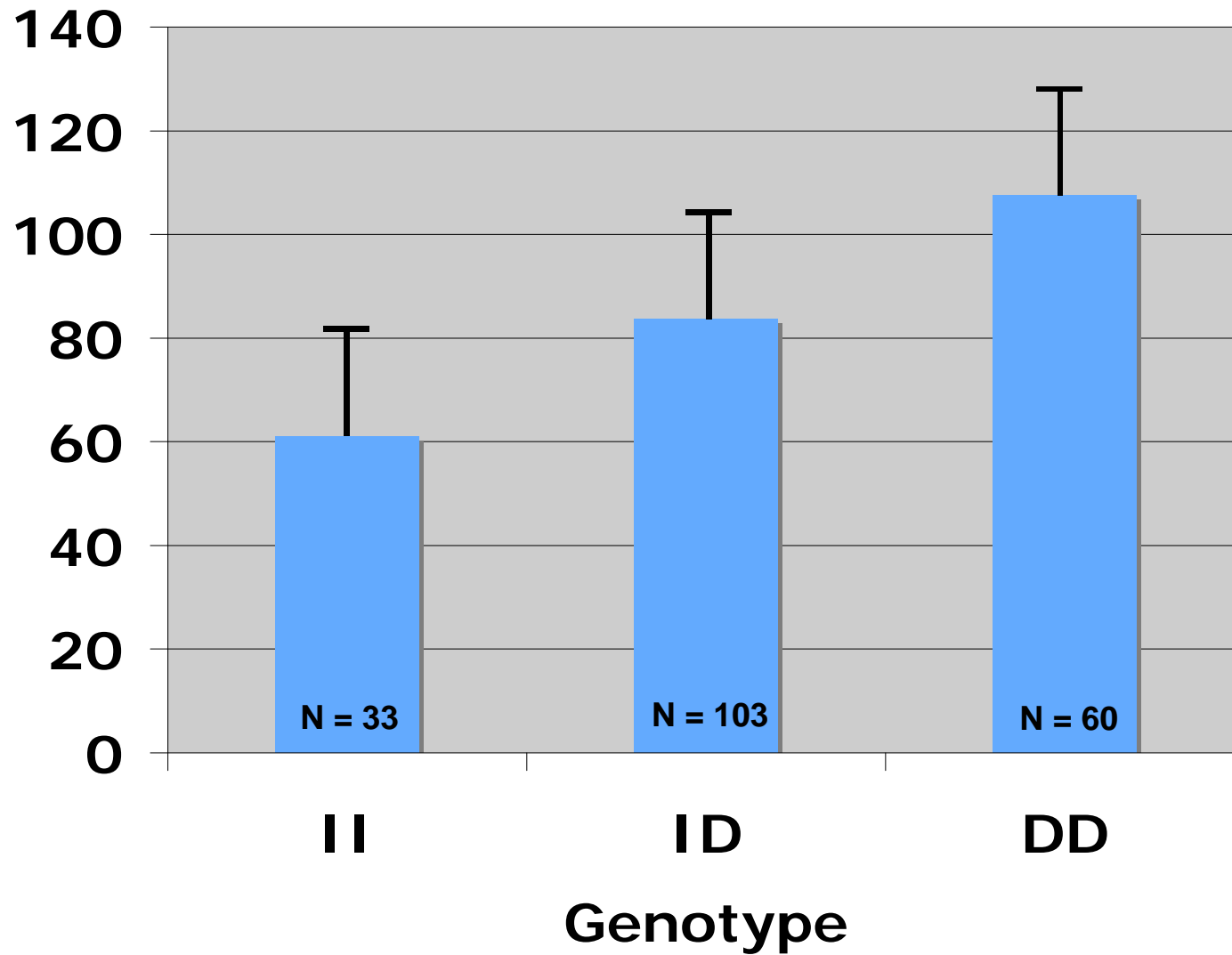


# Insertion and Deletions

*Angiotensin Converting Enzyme Gene DII polymorphism*

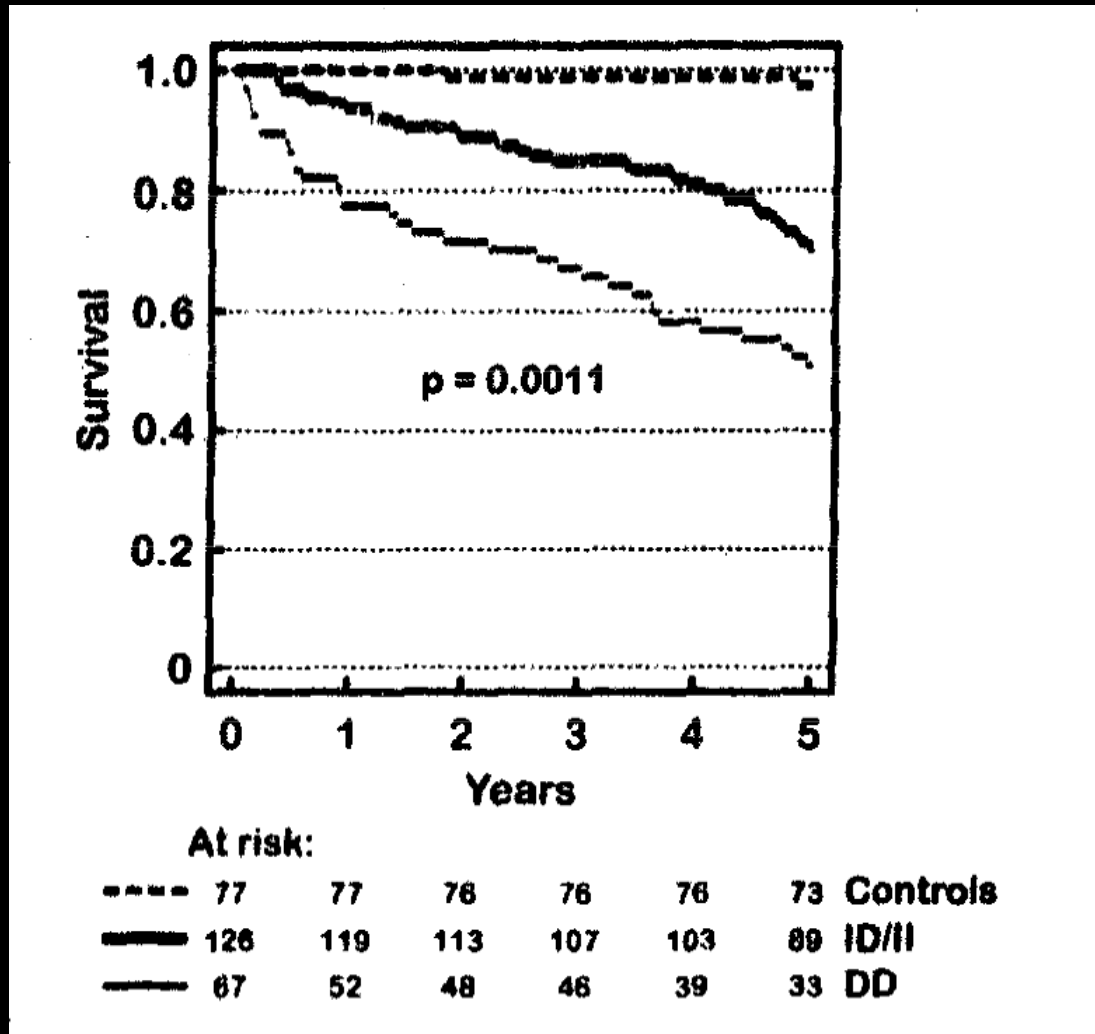
*Intron 16 (ACE gene 26 exons on Chromosome 17q23)*





# ACE GENOTYPE

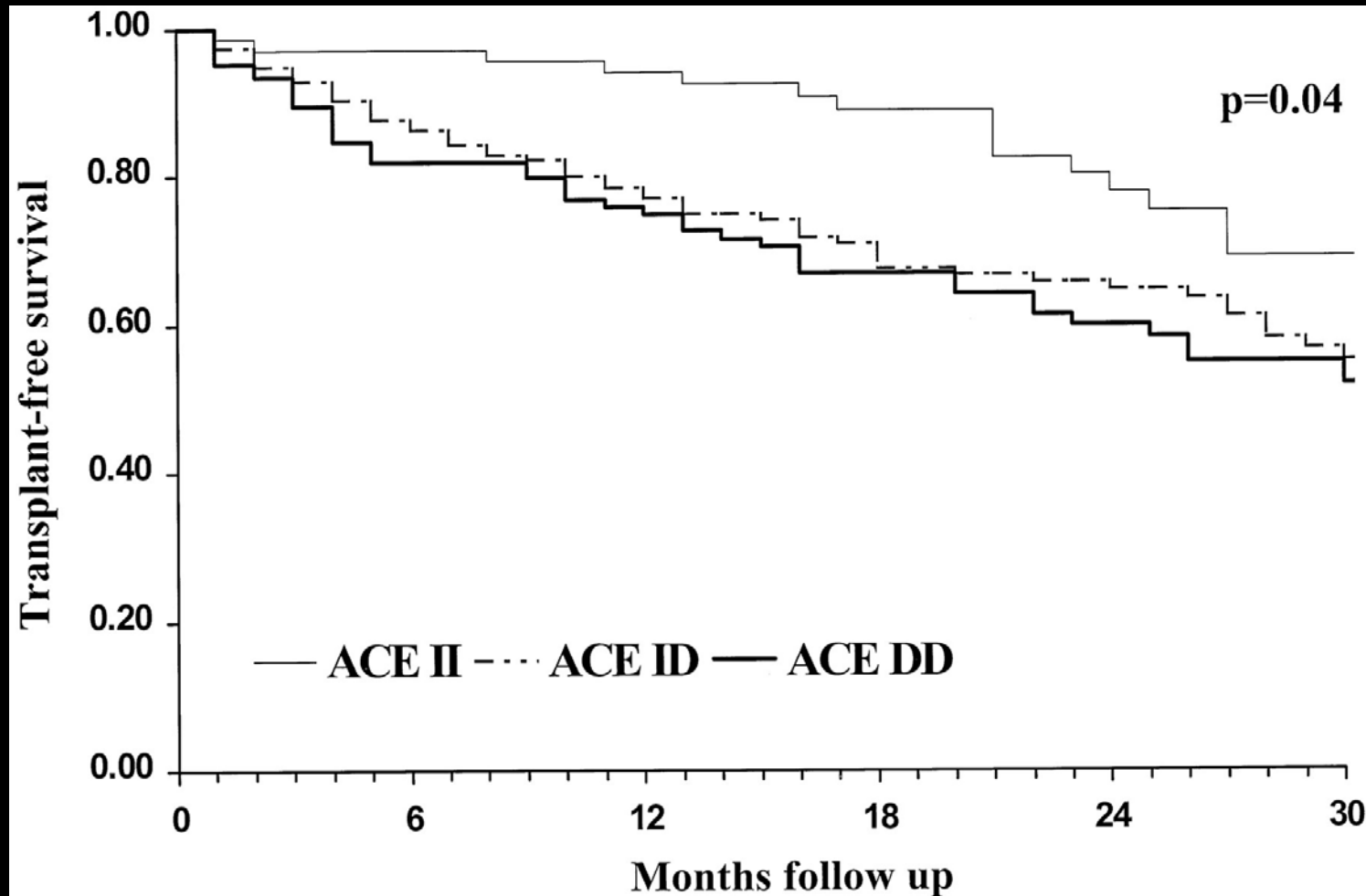
## Mortality in CHF



Andersson and Sylven, *JACC* 1996

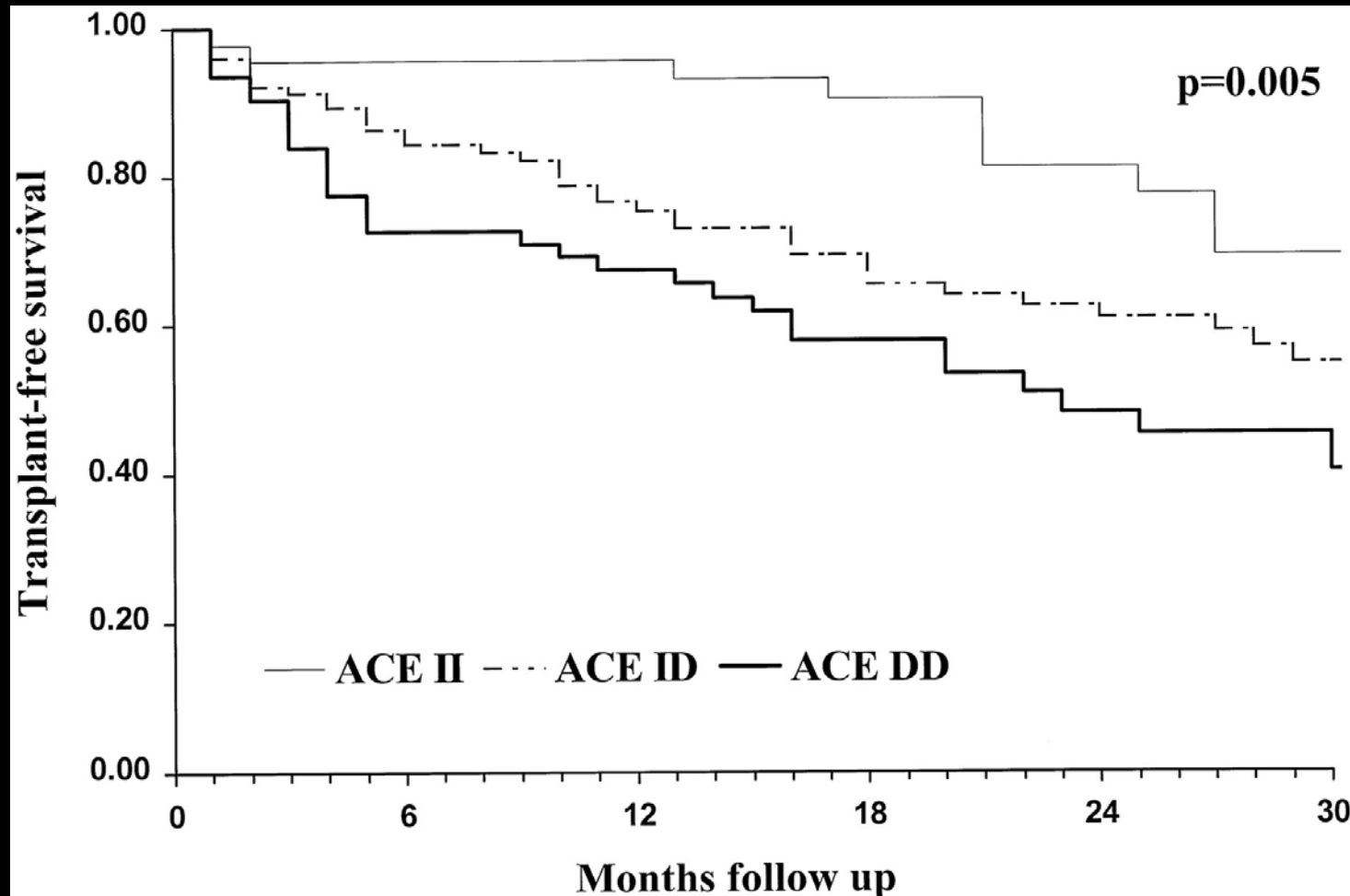
# GRACE TRIAL

## Transplant-Free Survival and ACE Genotype



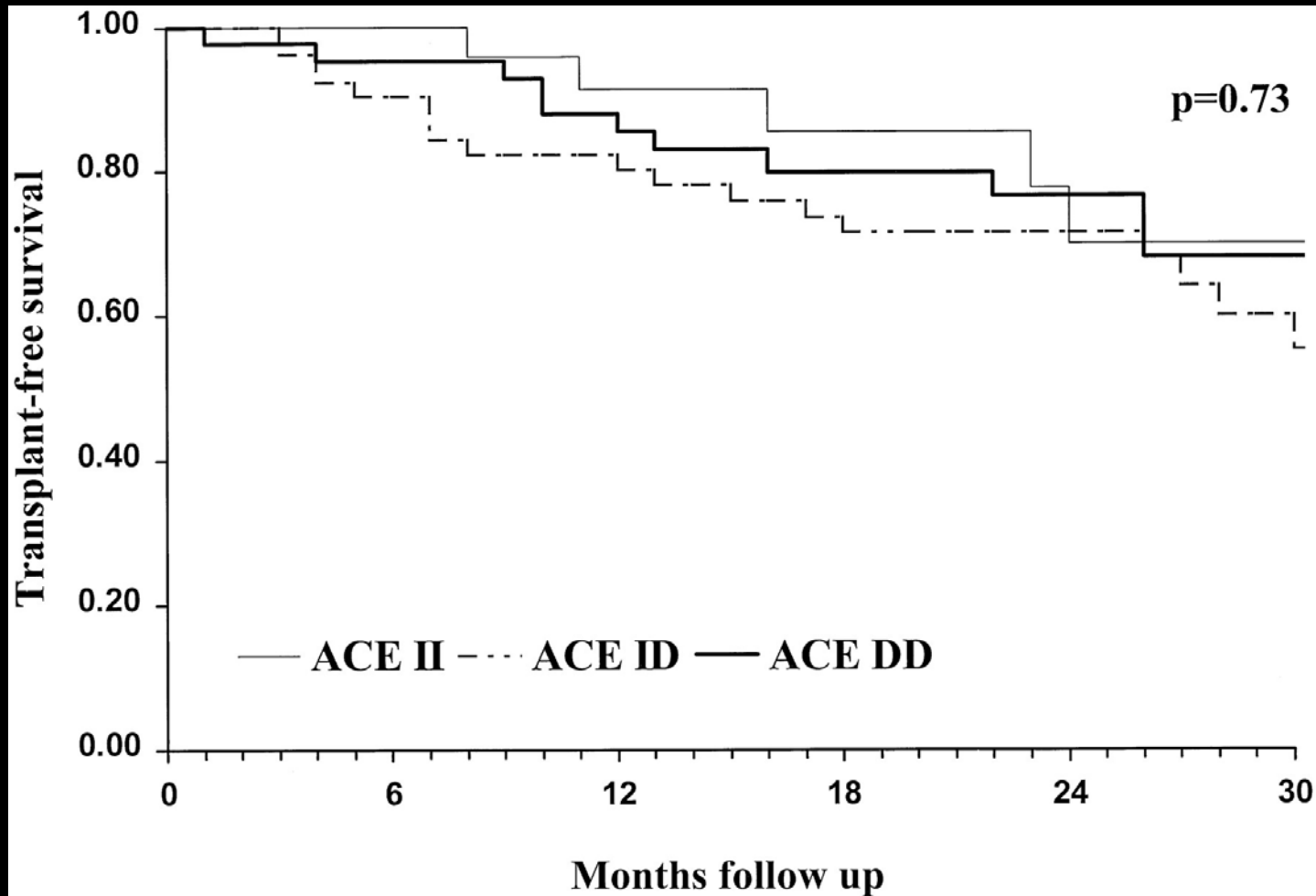
# GRACE TRIAL - NO $\beta$ BLOCKER

## Transplant-Free Survival, ACE Genotype



# GRACE TRIAL - $\beta$ BLOCKER TX

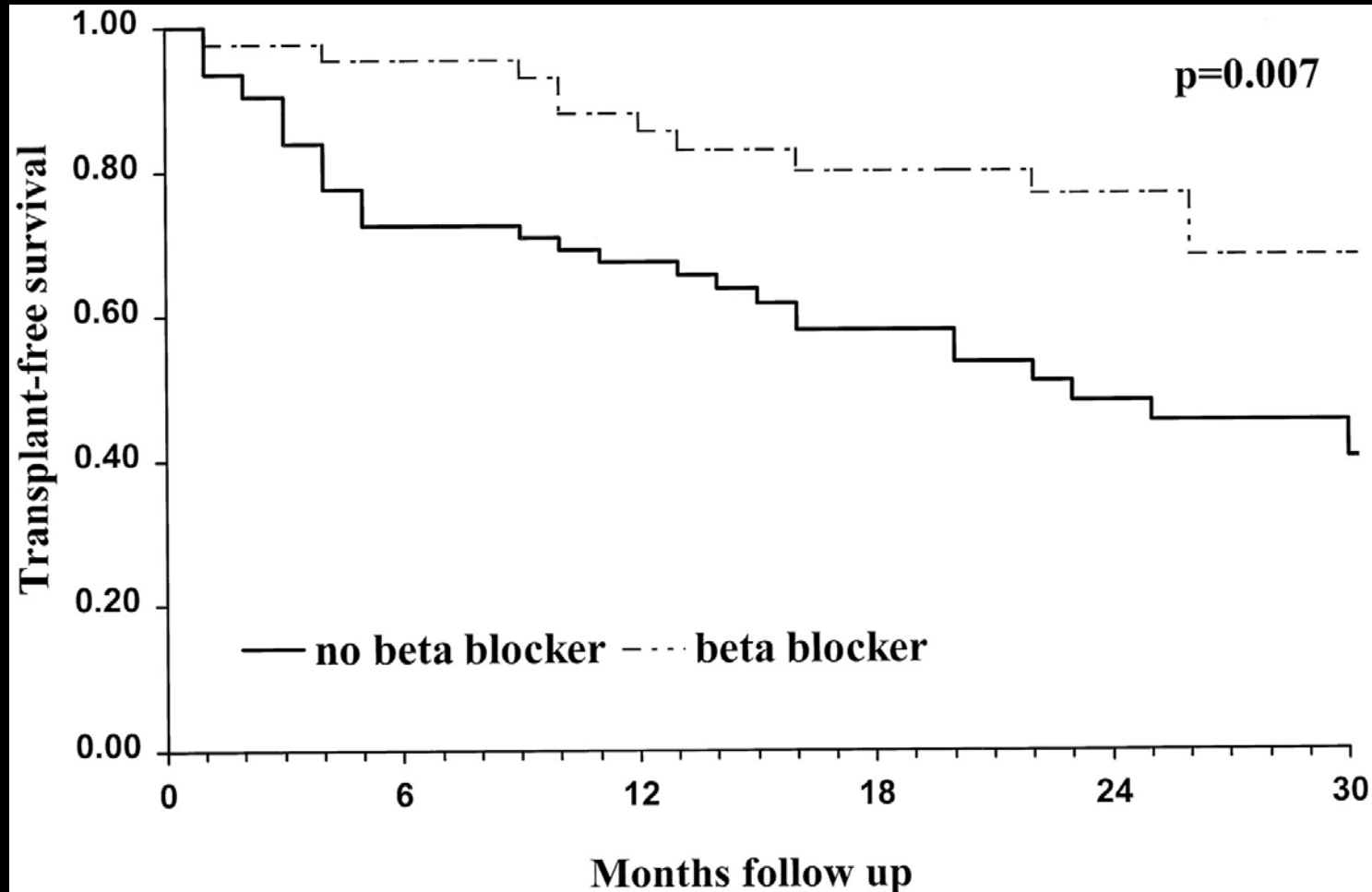
## Transplant-Free Survival, ACE Genotype



McNamara *et al*, *Circulation* 2001

# GRACE TRIAL

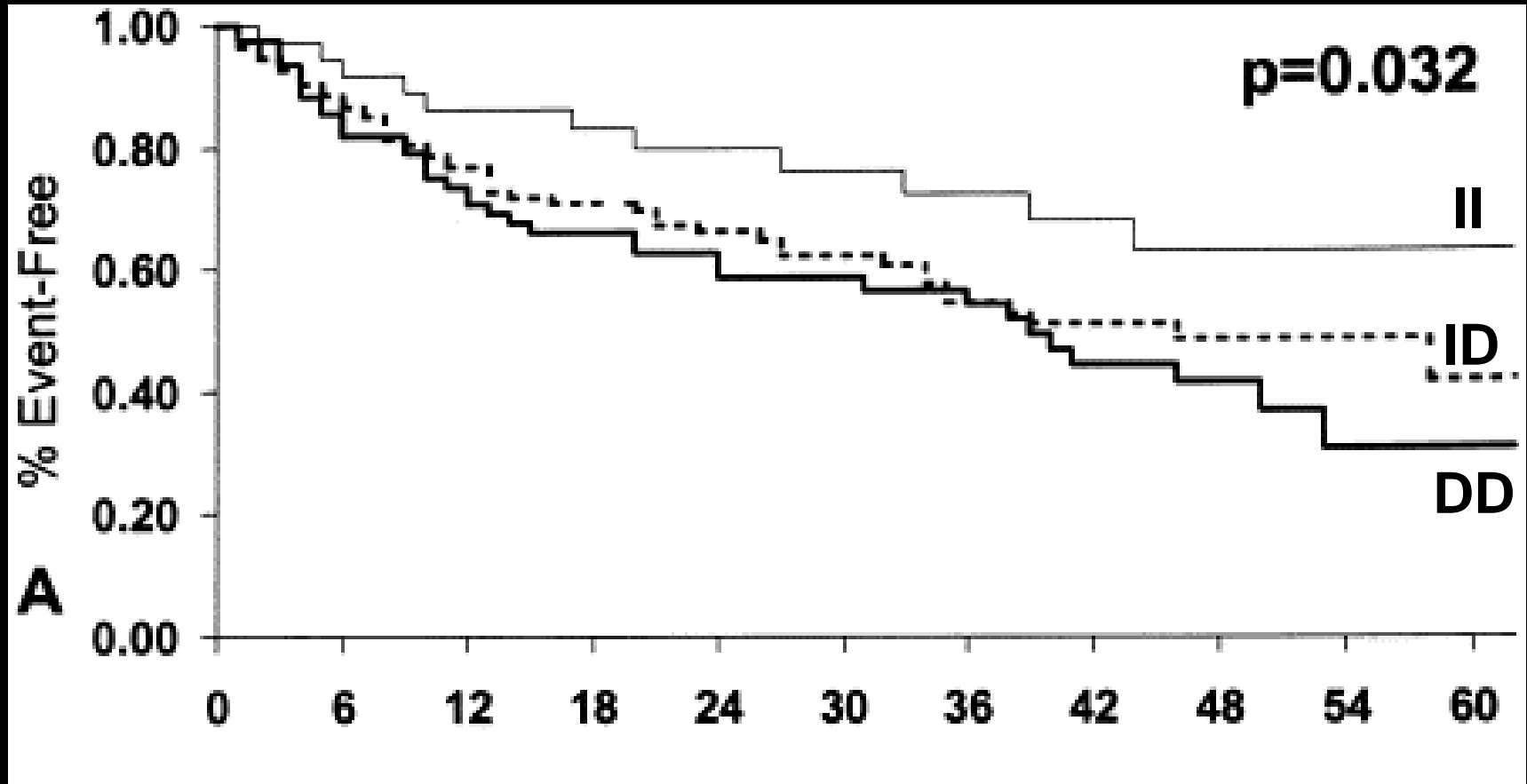
## Transplant-Free Survival, ACE DD Genotype



McNamara *et al*, *Circulation* 2001

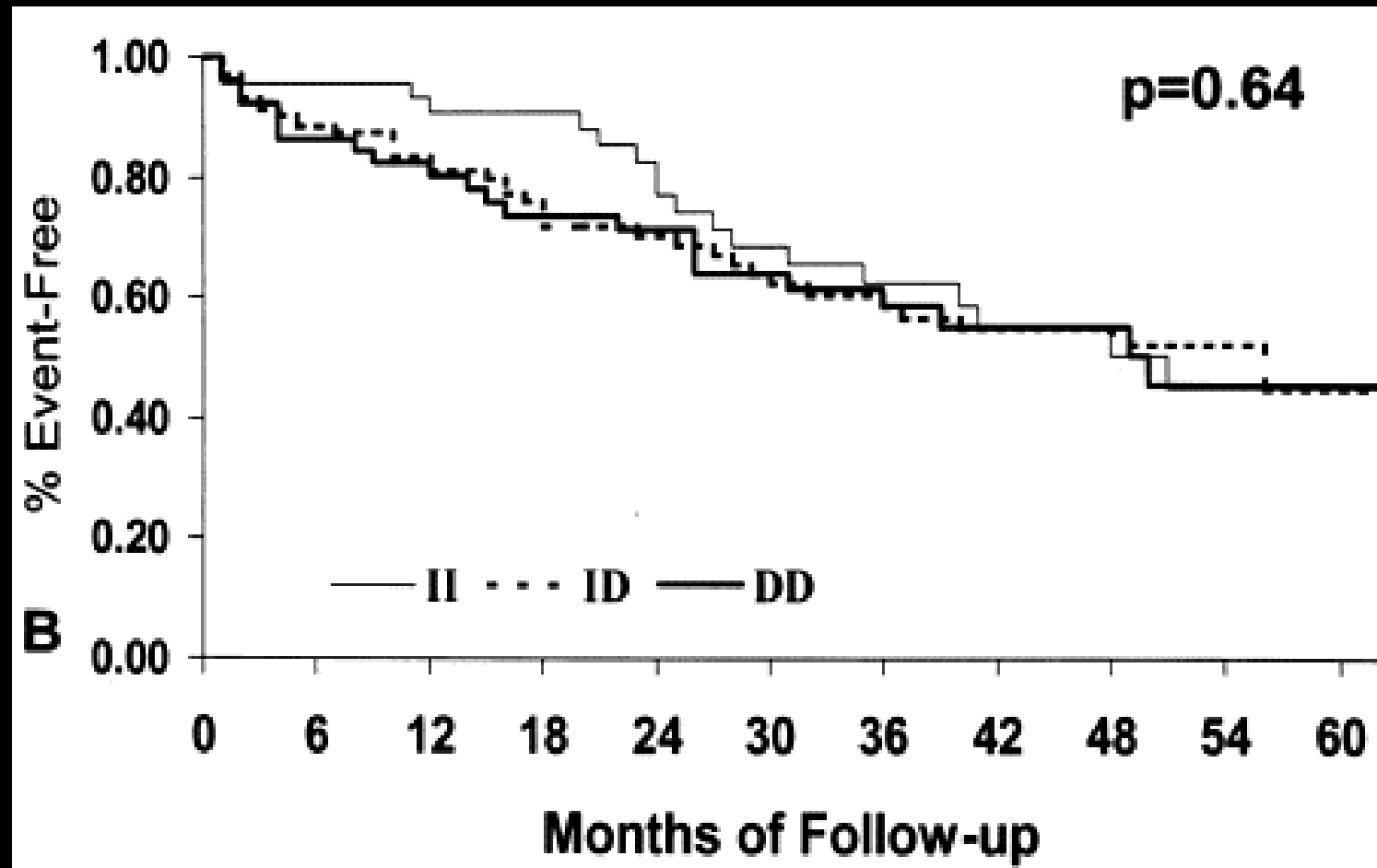
# GRACE TRIAL

## Transplant-Free Survival with Low Dose ACEI



# GRACE TRIAL

## Transplant-Free Survival with High Dose ACEI



McNamara *et al.*, JACC 2004

# $\beta$ Adrenergic Receptors

- $\beta_1$  and  $\beta_2$ 
  - Conserved 7 Transmembrane Domains
  - Ring Shape in the Lipid Bilayer
  - Distinct Cytoplasmic Domains
- Normal Heart
  - $\beta_1 > \beta_2$ 
    - 4:1
- CHF
  - $\Downarrow$   $\beta_1$  Numbers
  - $\Downarrow$   $\beta_2$  Responsiveness

# $\beta$ Adrenergic Receptors

## CODING POLYMORPHISMS

Receptor	Codon	Region	AA	Allele Freq	Function
$\beta_1$	49	Extracell	Ser/Gly	85/15	$\uparrow$ Downreg
$\beta_1$	389	Cytoplasm	Arg/Gly	70/30	$\downarrow$ Fxn
$\beta_2$	16	Extracell	Arg/Gly	40/60	$\uparrow$ Downreg
$\beta_2$	27	Extracell	Gln/Glu	55/45	$\downarrow$ Downreg
$\beta_2$	164	TMD 4	Thr/Ile	95/5	$\downarrow$ Fxn

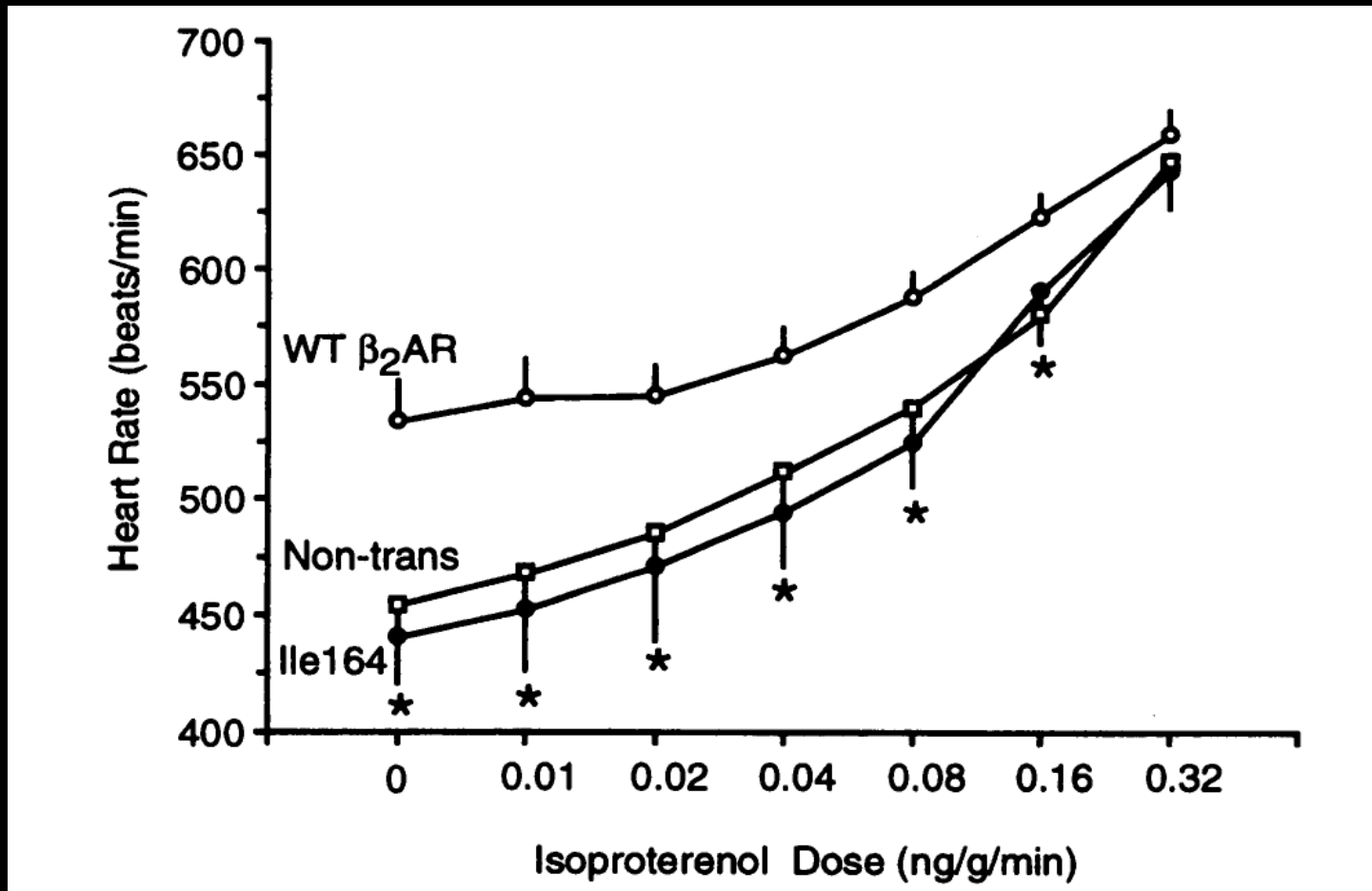
# $\beta_2$ Adrenergic Receptor

## Ile164 VARIANT

---

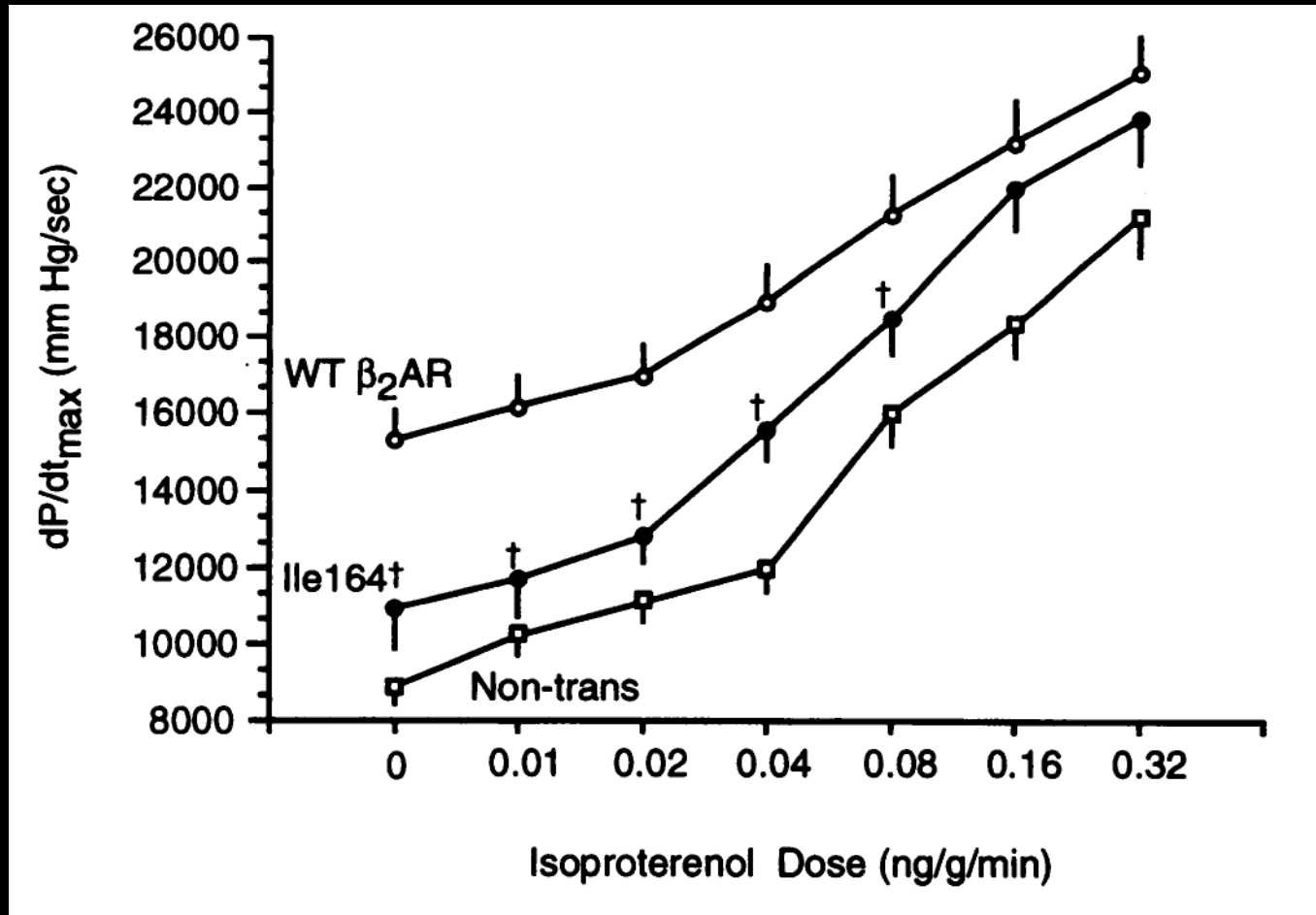
- Functional Effects
  - Lower Binding Affinity
    - Isoproterenol, Epinephrine, Norepinephrine
  - Response to Agonist
    - Lower Adenylate Cyclase Activity
- Transgenic Mice
  - Cardiac-Specific Expression
  - Decrease HR and dP/dT
    - Basally and with Agonist Stimulation

# $\beta_2$ Adrenergic Receptor Ile164 VARIANT



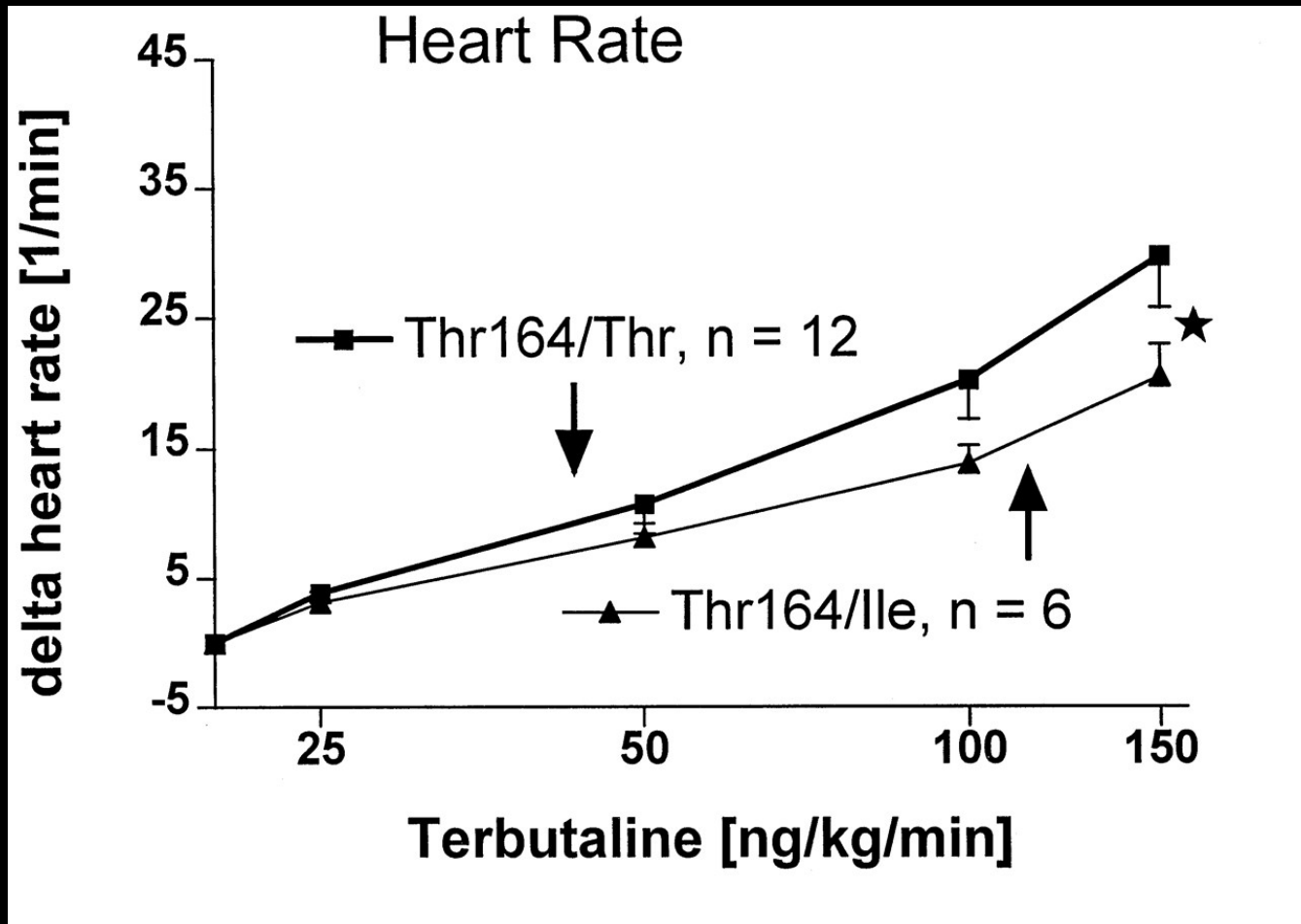
Turki *et al.*, *PNAS* 1996

# $\beta_2$ Adrenergic Receptor Ile164 VARIANT



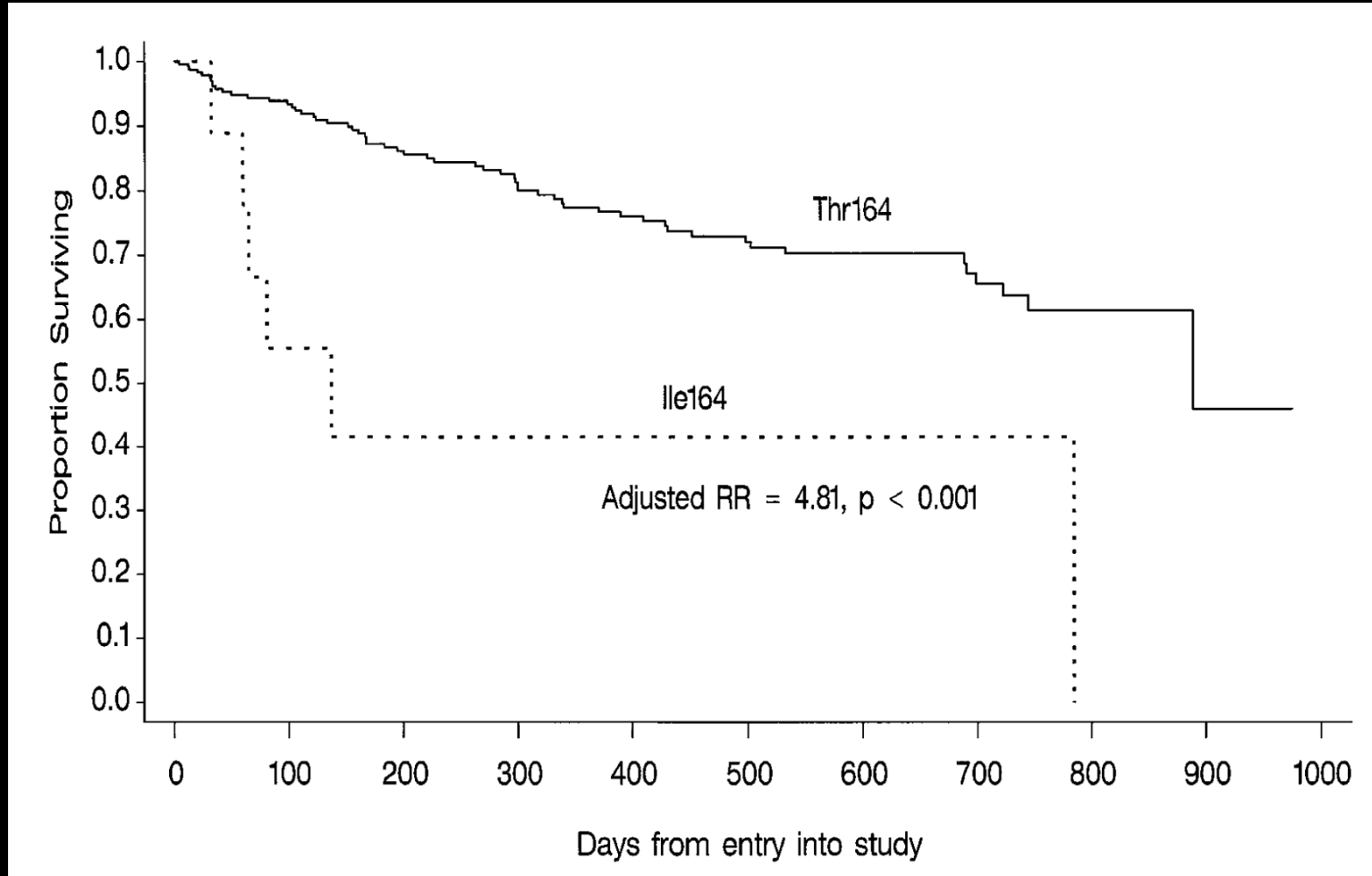
Turki *et al.*, PNAS 1996

# $\beta_2$ Adrenergic Receptor Ile164 VARIANT



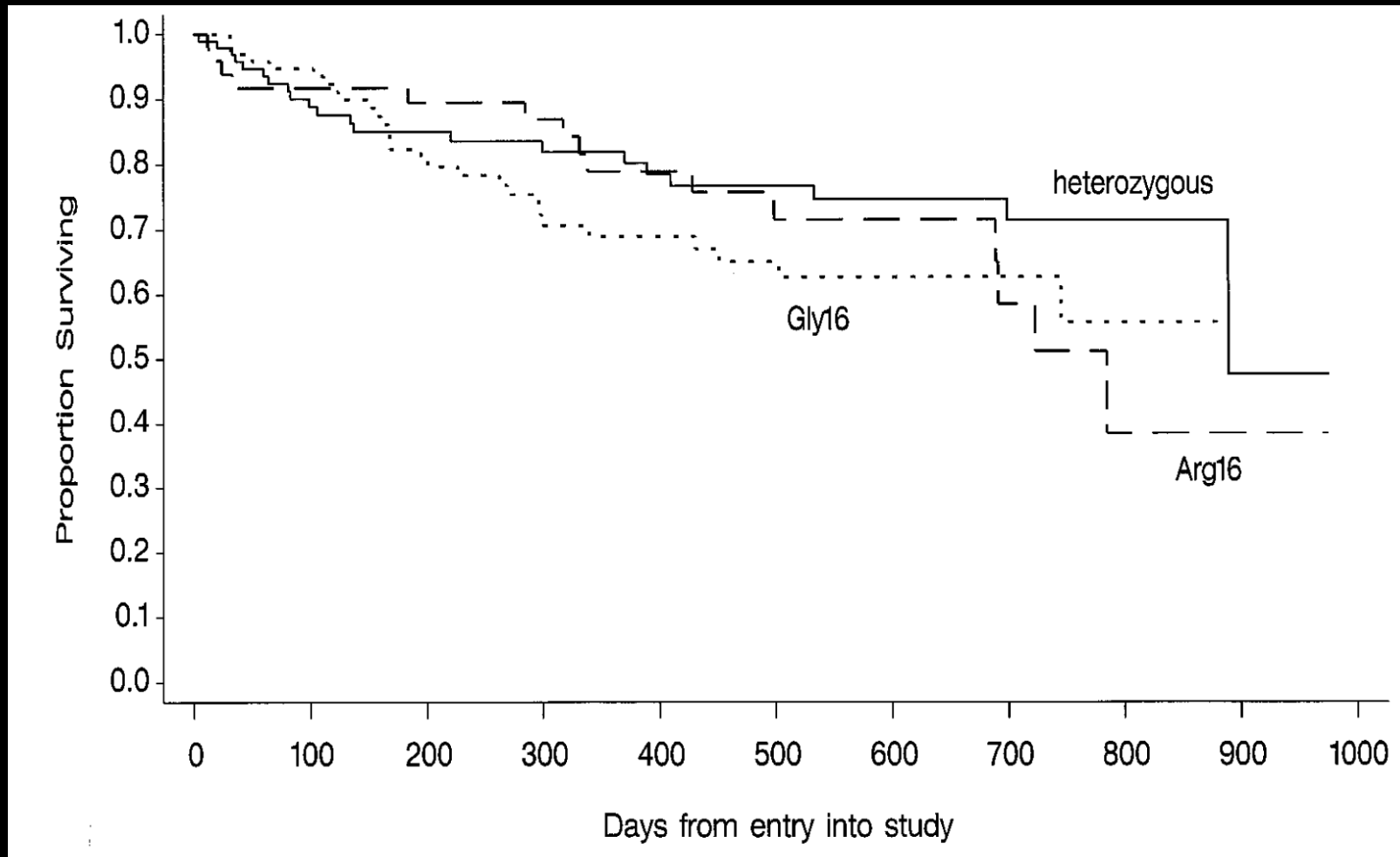
Brodde *et al.*, *Circulation* 2001

# $\beta_2$ Adrenergic Receptor Ile164 VARIANT



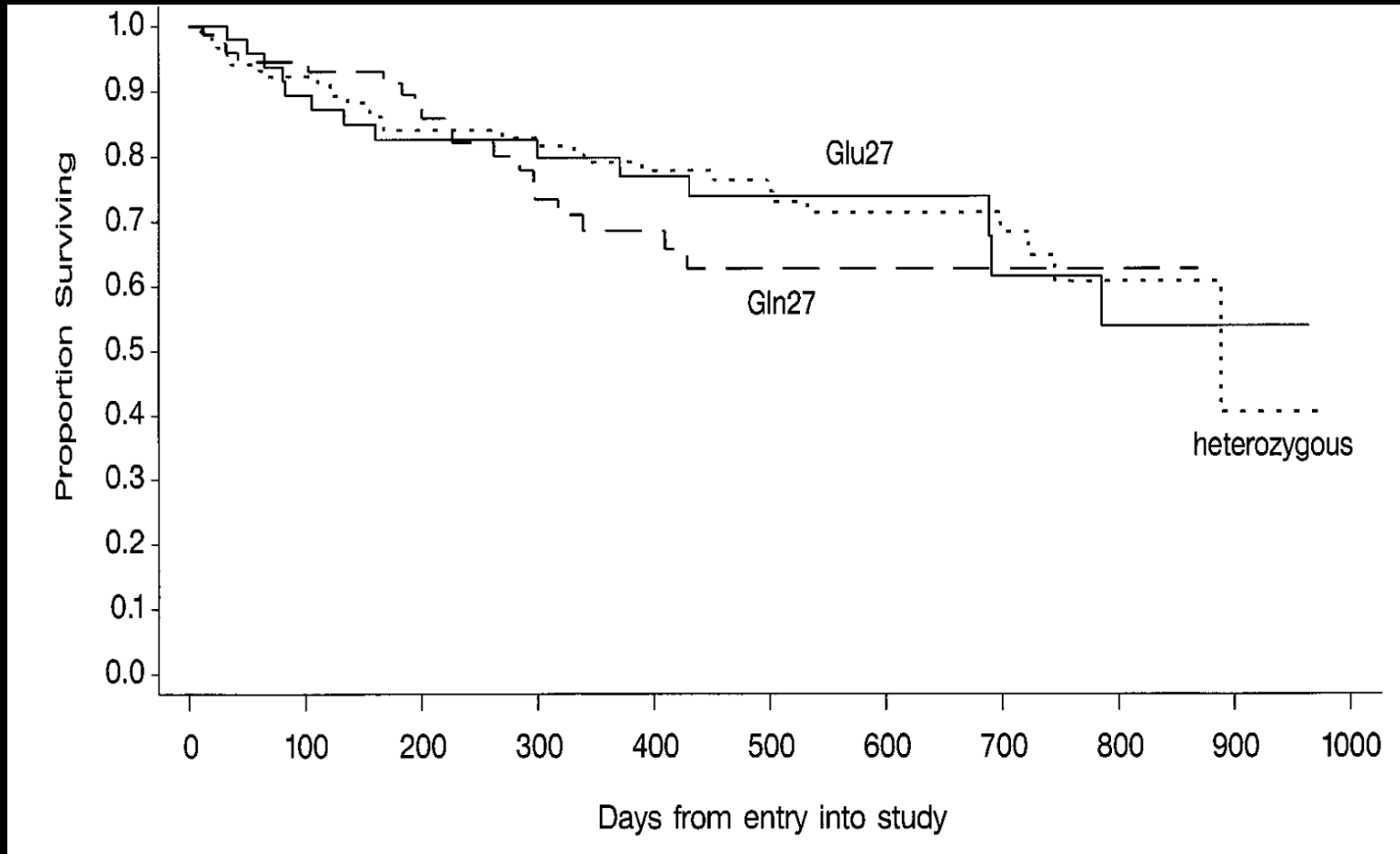
Ligett *et al.*, *J Clin Invest* 1998

# $\beta_2$ Adrenergic Receptor Gly16 VARIANT



Ligett *et al.*, *J Clin Invest* 1998

# $\beta_2$ Adrenergic Receptor Glu27 VARIANT



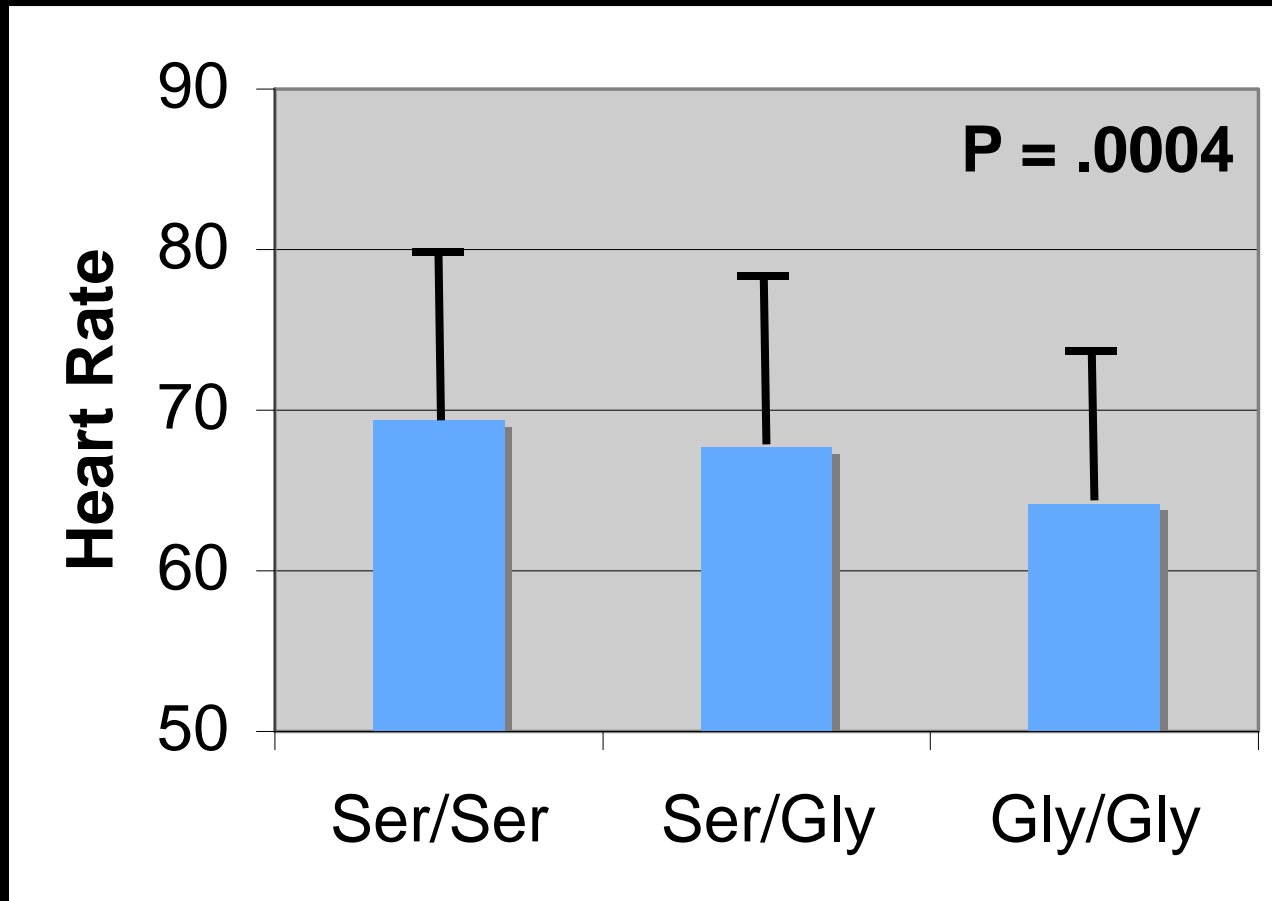
Ligett *et al.*, *J Clin Invest* 1998

# $\beta$ Adrenergic Receptors

## CODING POLYMORPHISMS

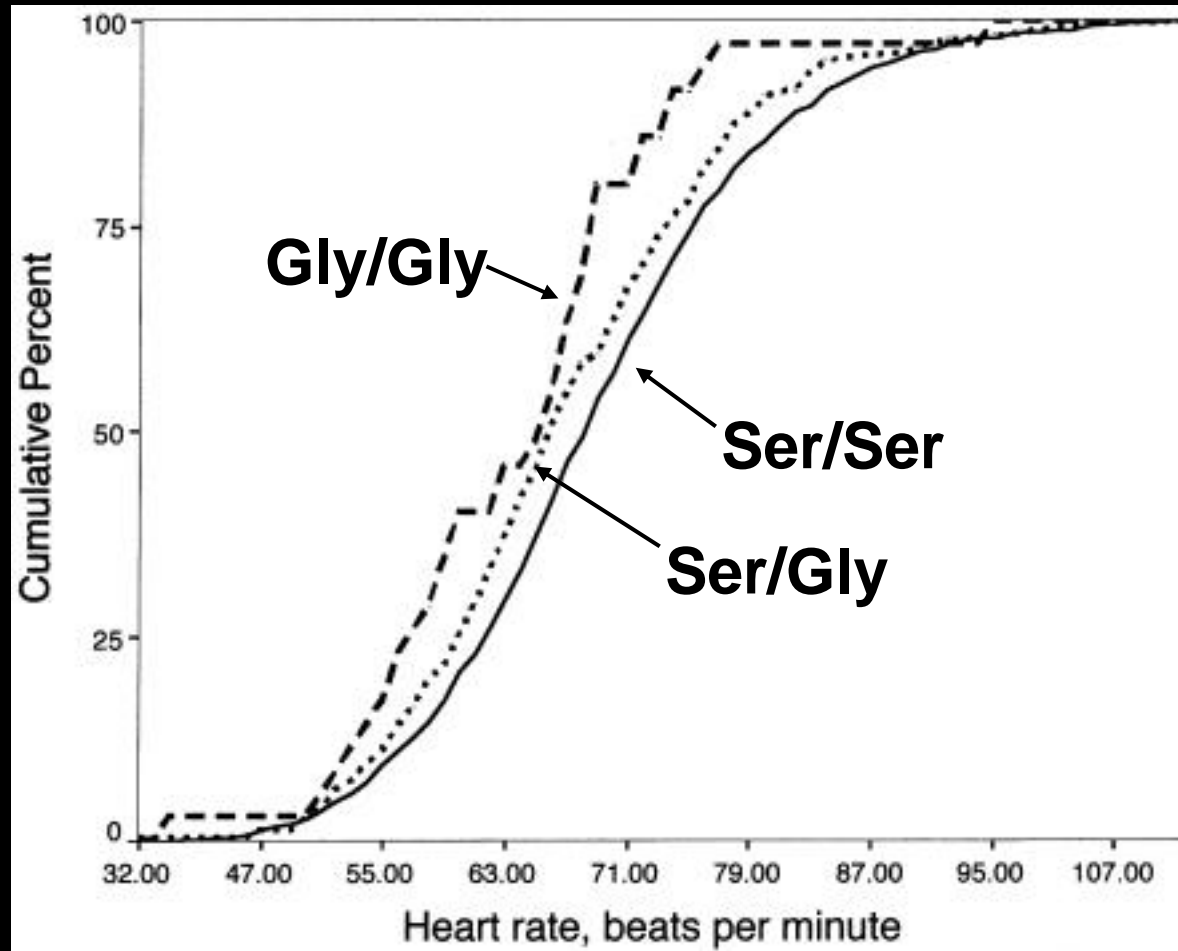
Receptor	Codon	Region	AA	Allele Freq	Function
$\beta_1$	49	Extracell	Ser/Gly	85/15	$\uparrow$ Downreg
$\beta_1$	389	Cytoplasm	Arg/Gly	70/30	$\downarrow$ Fxn
$\beta_2$	16	Extracell	Arg/Gly	40/60	$\uparrow$ Downreg
$\beta_2$	27	Extracell	Gln/Glu	55/45	$\downarrow$ Downreg
$\beta_2$	164	TMD 4	Thr/Ile	95/5	$\downarrow$ Fxn

# $\beta_1$ Adrenergic Receptor Gly49 VARIANT



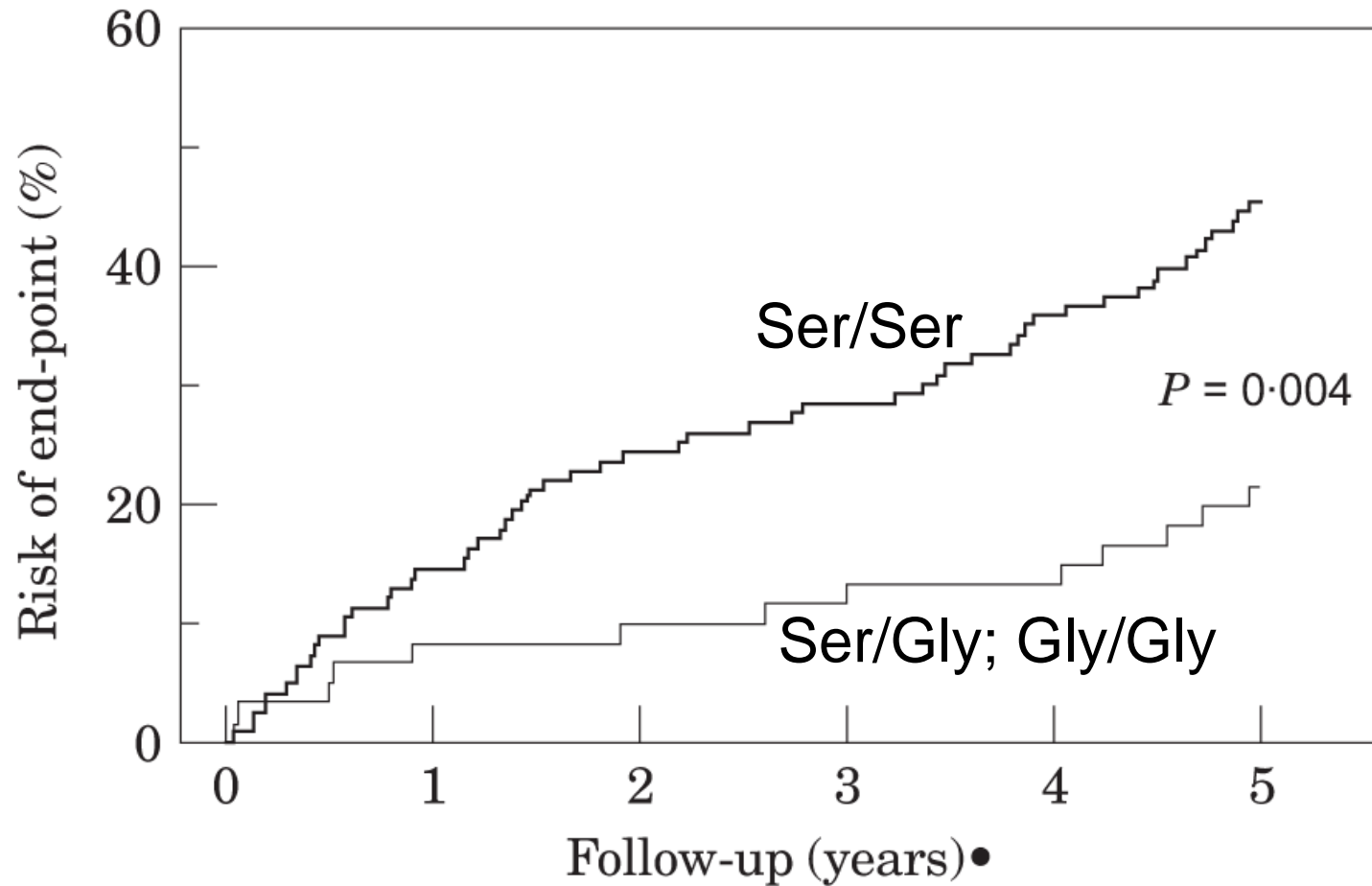
Ranade *et al.*, *Am J Hum Genet* 2002

# $\beta_1$ Adrenergic Receptor Gly49 VARIANT



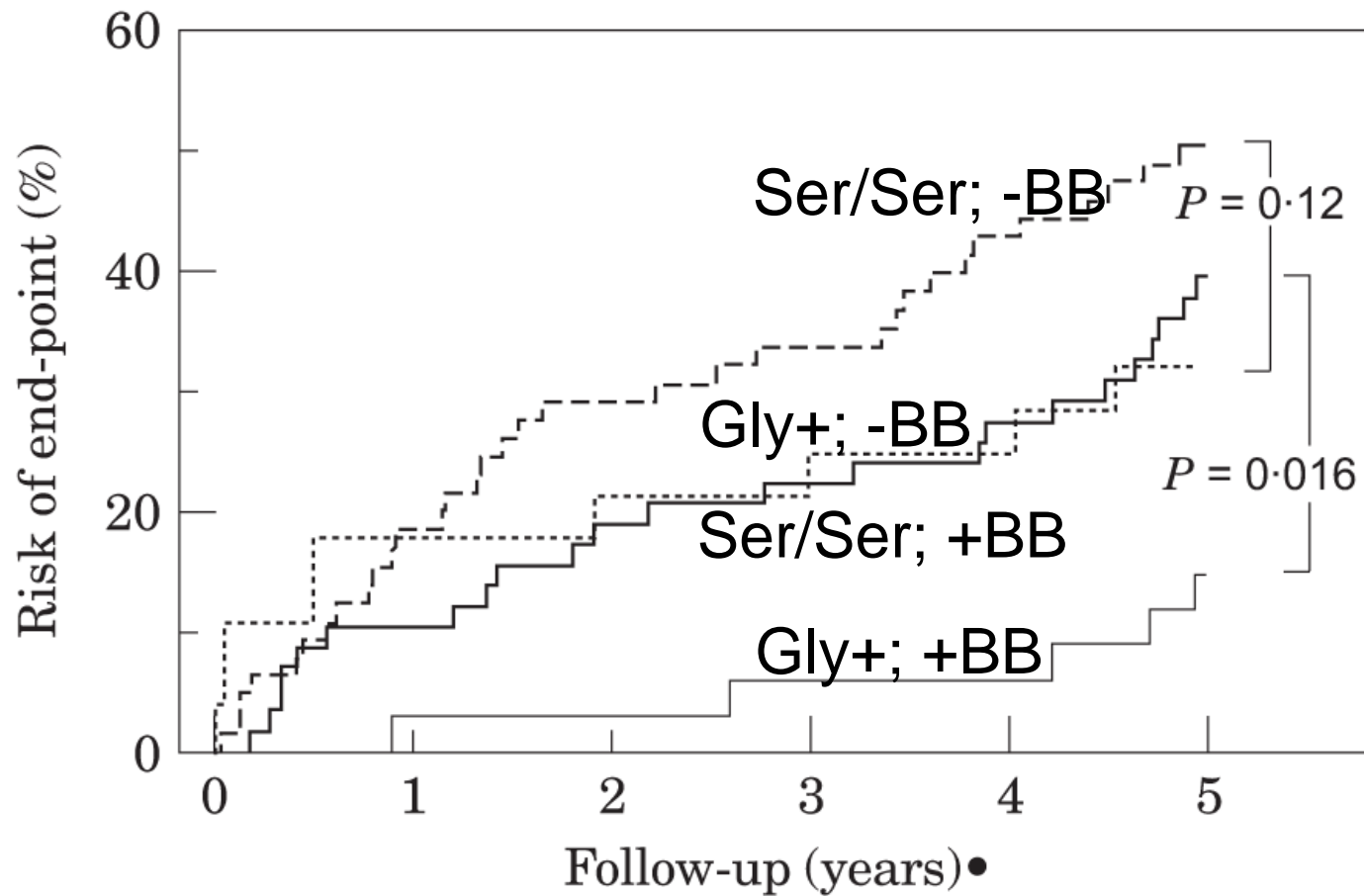
Ranade *et al.*, *Am J Hum Genet* 2002

# $\beta_1$ Adrenergic Receptor Gly49 VARIANT



Borjesson *et al.*, *Eur Heart J* 2000

# $\beta_1$ Adrenergic Receptor Gly49 VARIANT



Borjesson *et al.*, *Eur Heart J* 2000

# Nitric Oxide Synthase

---

- Nitric Oxide
    - Diffusible Free Radical Gas
    - Very Short Half-Life
    - Synthesized from L-Arginine
      - Nitric Oxide Synthase (NOS)
    - Dilatory Effects on Vascular Tone
    - Cardiac Effects
  - NOS
    - Three Forms: nNOS, iNOS, eNOS
-

# eNOS

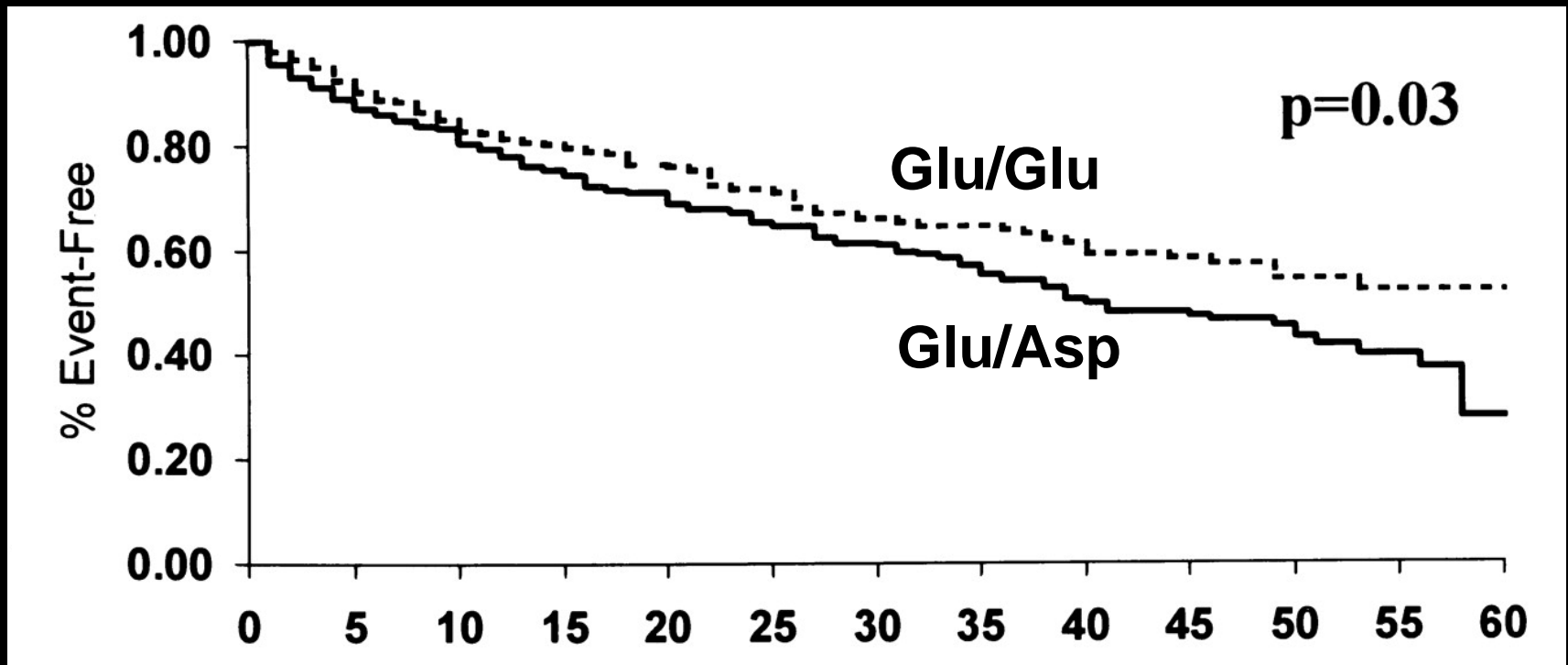
## Glu298Asp Polymorphism

---

- Asp298
    - Shorter Half-Life
    - Linked to Cardiovascular Risk
    - Decreased  $\text{VO}_{2\text{max}}$  in CHF
    - Decreased Survival
-

# eNOS

## Glu298Asp Polymorphism



McNamara *et al.*, *Circulation* 2003

# eNOS

## ACEI INTERACTION

---

- Mouse eNOS KO
    - Lose Salutary Effects of ACEI
      - Ischemia/Reperfusion Injury
  - GRACE Study
    - Asp298 Effects on Survival
      - Only with Low-Dose ACEI
-

# CHF

## PHARMACOGENETICS WRAP UP

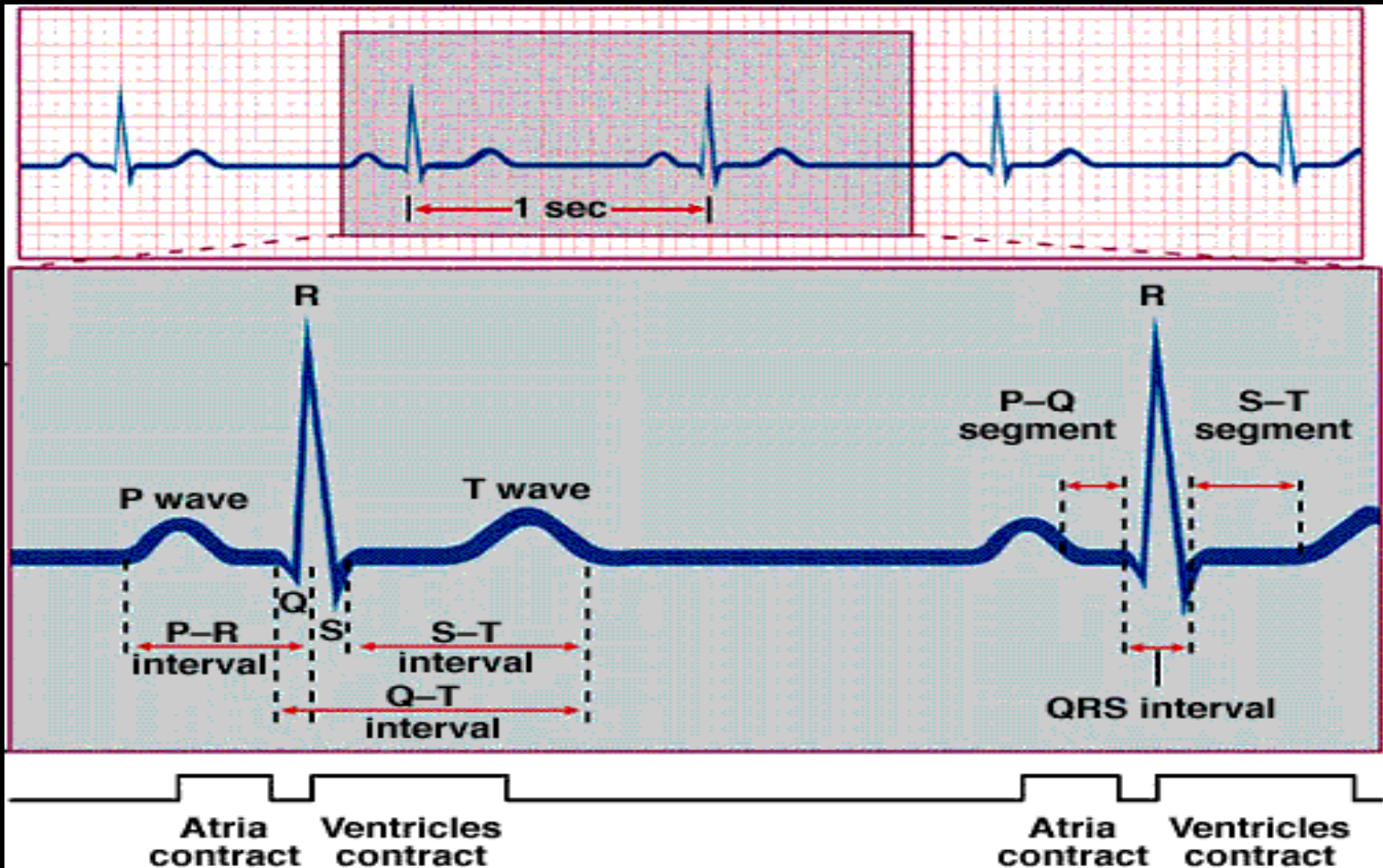
---

- Interactions
    - RAAS
    - $\beta$ -Adrenergic Receptors
    - NOS Signaling
  - Clinical Utility
    - Remains Unproven
    - Variable Response to Drugs
      - Suggests Opportunities
-

# Long QT Syndrome

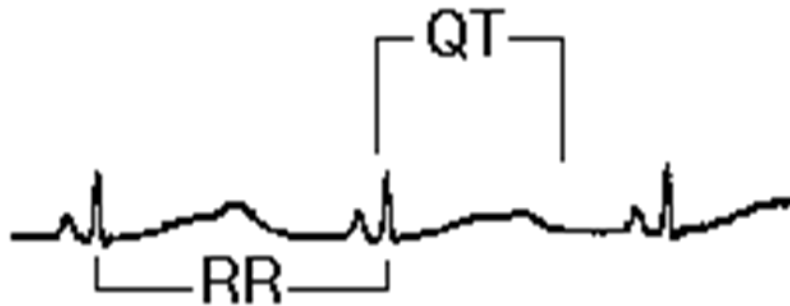
**What is it?**

# Electrocardiogram INTERVALS



# QT Interval RATE CORRECTION

## Bazette's Formula



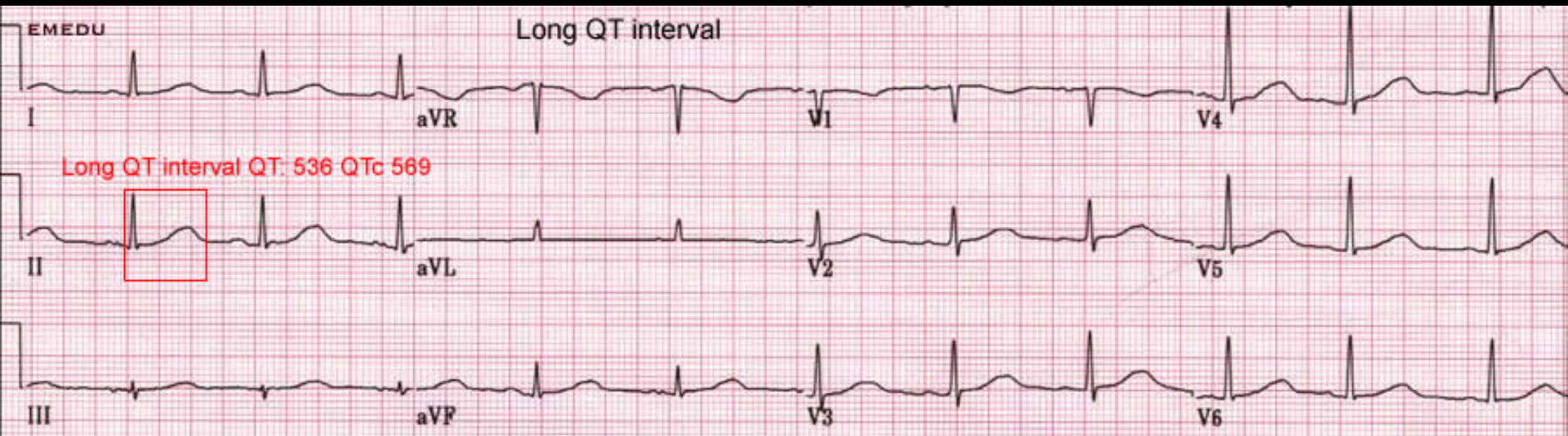
$$QT_c = \frac{QT}{\sqrt{RR}} = \frac{0.71}{\sqrt{1.11}} = 0.67 \text{ seconds}$$

# QTc

## NORMAL RANGES

<u>QTc (msec)</u>	<u>Male</u>	<u>Female</u>
Normal	<430	<450
Borderline	431-450	451-470
Prolonged	>450	>470

# Long QT

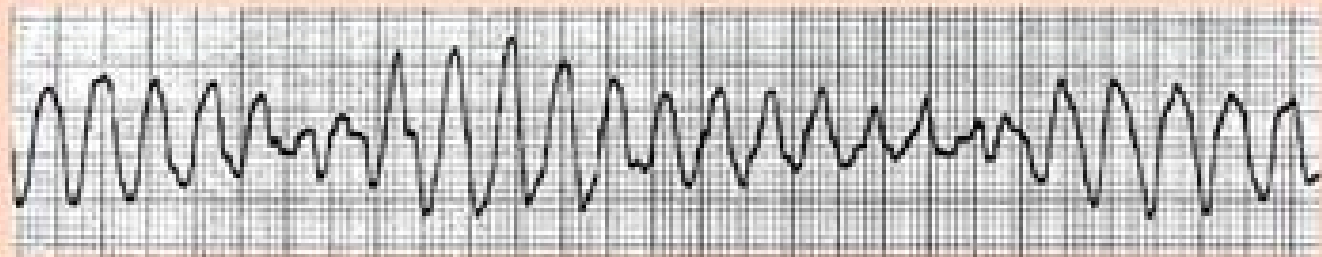


**QT = 536 msec**

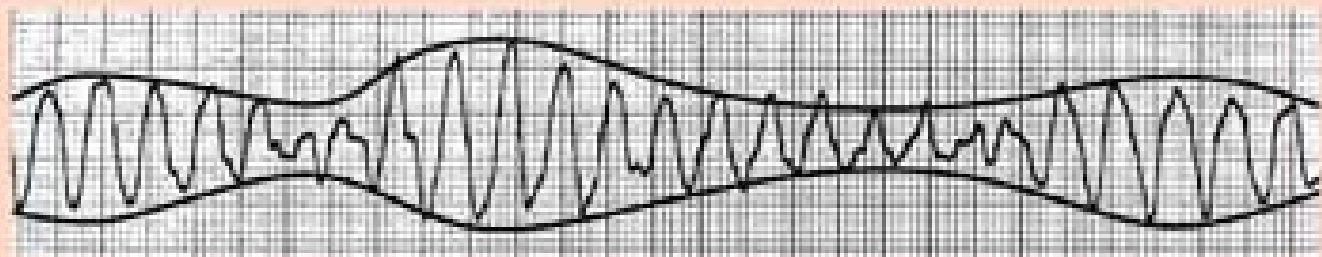
**QTc = 569 msec**

# Long QT

## Torsades de Pointes



outline looks like a party streamer



# Long QTc

## CAUSES

- Congenital
  - Genetic Channelopathies
- Acquired
  - Highly Heterogeneous
  - Drug Induced

# Medications

## CAUSING QT PROLONGATION

---

### Drugs Commonly Involved

Disopyrimide

Dofetilide

Ibutilide

Procainamide

Quinidine

Sotalol

Bepridil

# Medications

## WITHDRAWALS DUE TO DI-LQTS

Terodiline	1991	Anti-Muscarinic
Astemizole	1998	Anti-Histamine
Mibefradil	1998	Anti-Hypertensive
Terfenadine	1998	Anti-Histamine
Grepafloxacin	1999	Antibiotic
Cisapride	2000	Promotility
Levomethadyl	2004	Analgesic

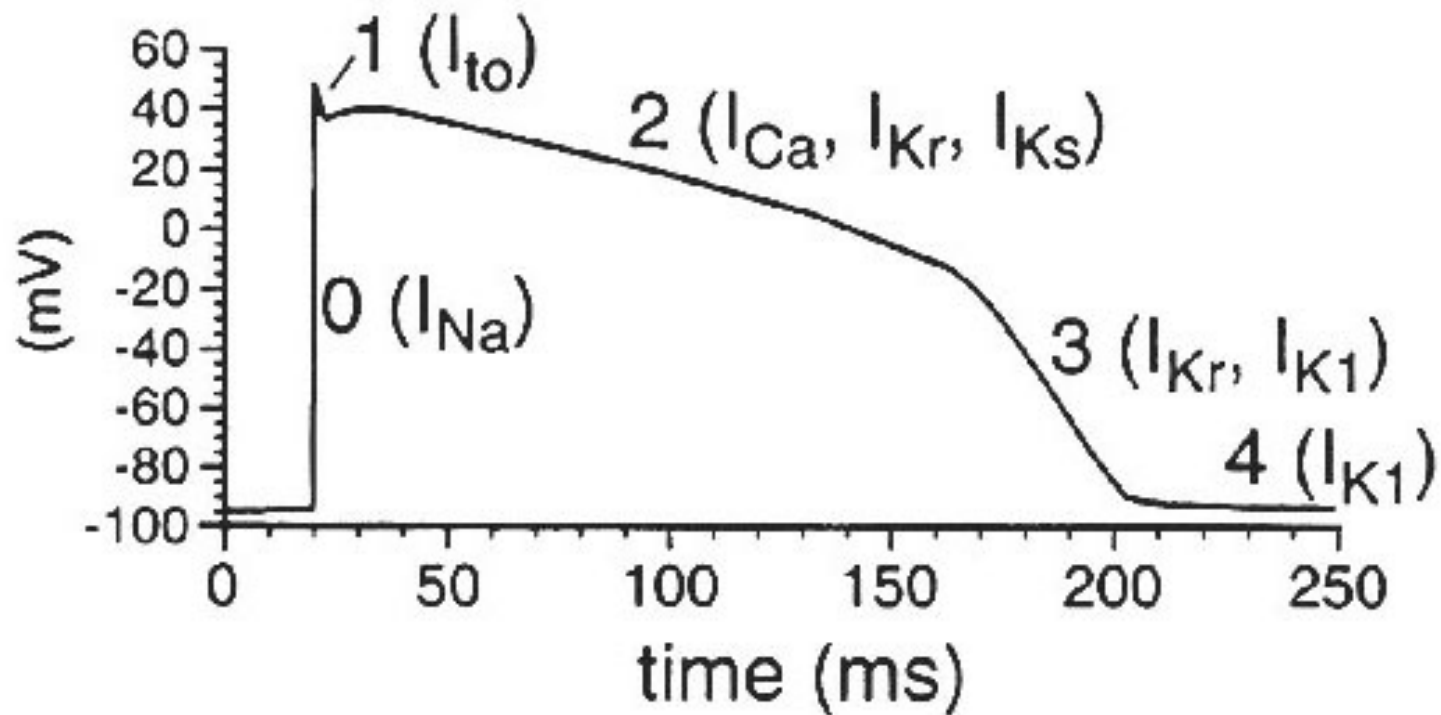
# Drug Screening

## THOROUGH QT/QTc STUDY

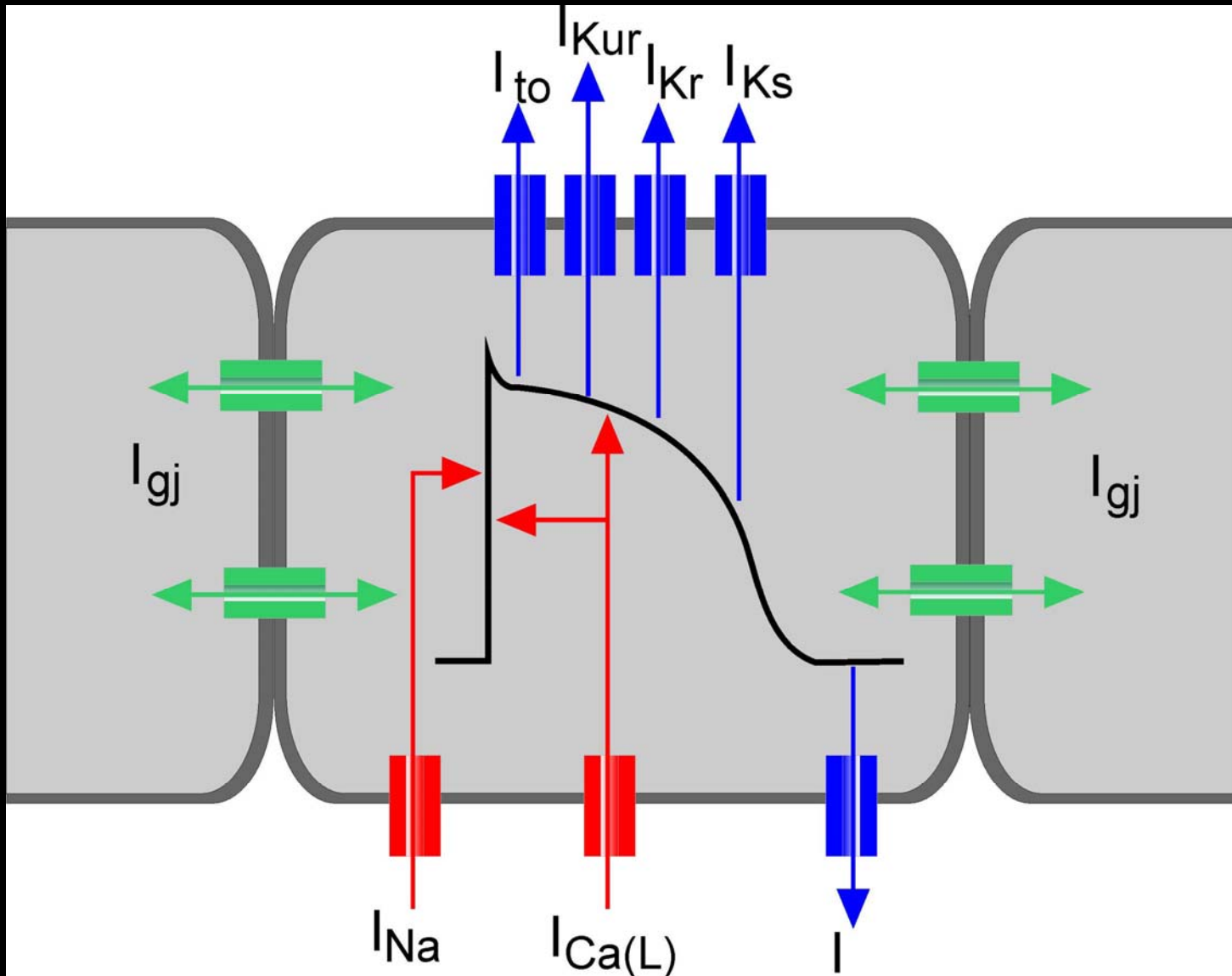
---

- ECG Evaluations
    - Multiple Doses
    - Threshold
      - Increased Mean QTc of 5 msec
      - Upper Bound of 95% of 10 msec
  - Drugs Failing
    - Further Evaluate Torsadogenic Potential
-

# Cardiac Action Potential



# Cardiac Action Potential



# Cardiac Action Potential

---

$I_{Na}$  SCN5A

$I_{Ks}$  KCNQ1 + KCNE1

$I_{Kr}$  KCNH2 + KCNE2

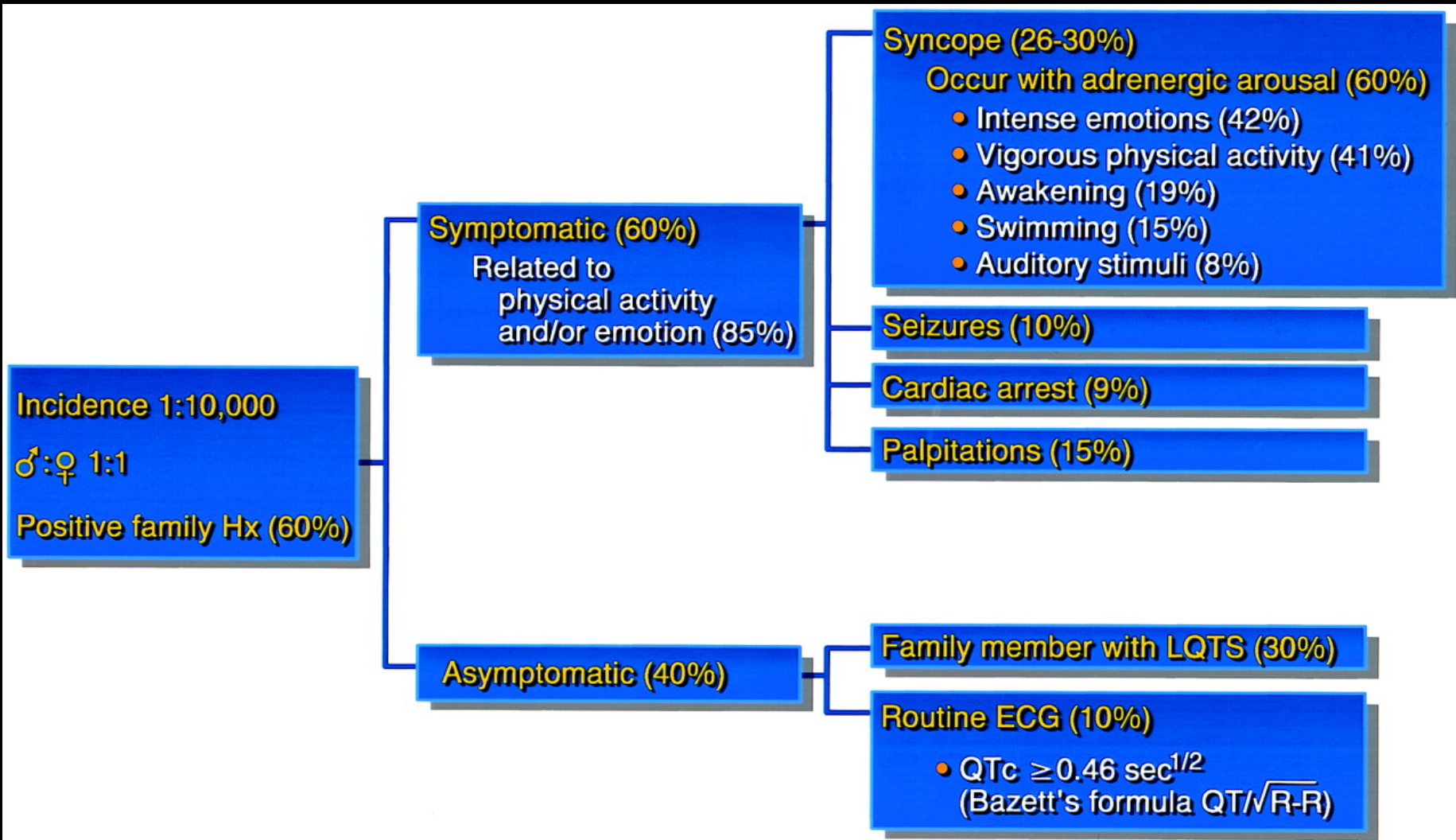
# LQTS

- Jervell and Lange-Nielsen Syndrome
  - Described in 1957
  - Autosomal Recessive
  - Less than 10% of LQTS
  - Includes Hearing Loss
  - Severe Cardiac Phenotype
    - Long QT Interval
    - High Rate of Cardiac Events at Young Age
- Romano-Ward Syndrome
  - Described in 1963
  - Autosomal Dominant
  - Cardiac Phenotype Only

# LQTS

- LQT1
  - *KCNQ1* Loss-of-Function Mutations
  - 30-35% of LQTS
  - Exertion and Swimming Trigger TdP
  - Beta-Blocker Therapy Very Effective
- LQT2
  - *KCNH2/HERG* Loss-of-Function Mutations
  - 30-35% of LQTS
  - Auditory Trigger TdP
  - Beta Blocker Therapy Effective
- LQT3
  - *SCN5A* Gain-of-Function Mutations
  - 5-10% of LQTS
  - Sleep Triggers TdP
  - Beta Blockers of ?? Effectiveness

# LQTS



# KCNH2

- Human Ether-a-Go-Go Related Gene (HERG)
  - *Drosophila* ether-a-go-go
    - Leg Shaking in Response to Ether
    - Potassium Channel with 6 TMDs
    - Voltage Gated
  - Forms  $I_{Kr}$  with MinK-Related Peptide-1
    - Encoded by KCNE2
  - Mutated in LQT2

# Drug-Induced Torsades de Pointes

## RISK FACTORS

- Female
- Older Age
- Hypokalemia
- Anorexia Nervosa/Starvation
- CHF
- High Serum Drug Level
- Baseline QT Prolongation
- Ion Channel Polymorphisms
- Severe Hypomagnesemia
- Atrial Fibrillation

# Torsades de Pointes Risk

## REPOLARIZATION RESERVE

---

- Repolarization Reserve
  - Orderly and Rapid Repolarization Normally
    - No Risk of Reentrant Circuits or EADs
    - Depend Upon Delayed Rectifiers  $I_{Kr}$  and  $I_{Ks}$
  - Identified Risk Factors
    - Reduced Reserve
    - Increased Susceptibility for TdP
      - $I_{Kr}$  Blocking Drug
      - Subtle Genetic Defect

# Drug-Induced QT Prolongation

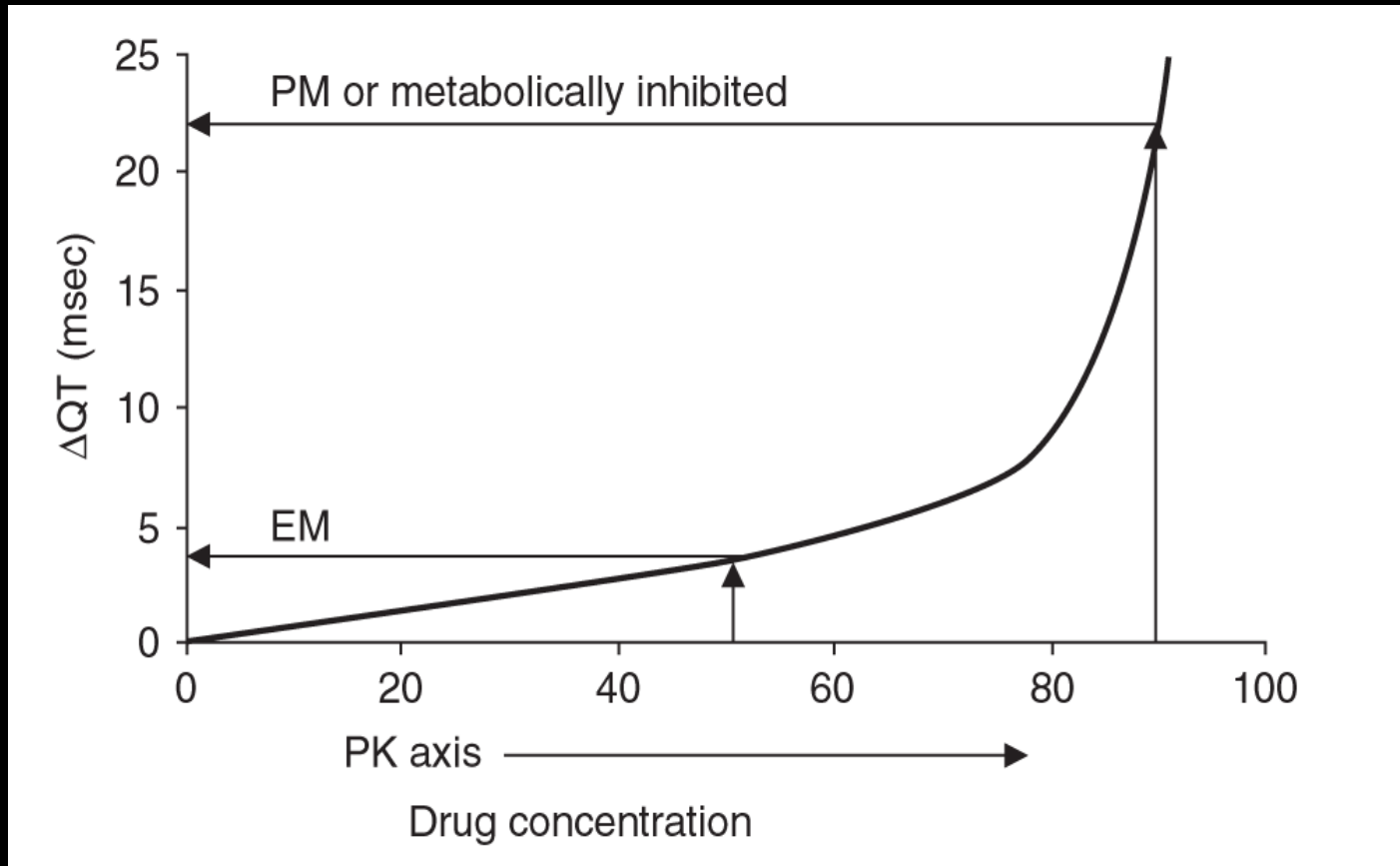
## Pharmacokinetics and Genetics

---

- P450 Metabolism
    - *CYP2D6*
      - Copy Number Variants
      - Many Coding SNPs
      - Can Be Used to Predict Levels
        - Poor Metabolizer
        - Extensive Metabolizer
    - *CYP3A4*
      - No Knockout Alleles
      - Variable Metabolic Efficiency
        - Alters Expression Levels
      - Not Practical for Predicting Drug Levels
-

# Drug-Induced QT Prolongation

## Pharmacokinetics and Genetics



Judson *et al.*, *Mol Diag Ther* 2006

# Drug-Induced QT Prolongation

## Pharmacokinetics and Genetics

---

- Interactions with Other Factors
    - Other Drugs Requiring P450 Metabolism
    - Foods
      - Example: Grapefruit Juice
  - Predicted Effects on QT Interval
    - Direct Drug Effect
    - Drug Metabolite Effect
-

# Drug-Induced QT Prolongation

## Pharmacodynamics and Genetics

---

- Interaction with LQTS
  - QT-Prolonging Drugs
    - Contraindicated for LQTS Patients
  - Incomplete ECG Penetrance
    - Sudden Death Risk is not Population Level
    - Can Be Unmasked by QT-Prolonging Drugs
  - Estimated LQTS Prevalance of 1:2000

# Drug-Induced QT Prolongation

## Pharmacodynamics and Genetics

Variant	Afr-Am	Cauc	Effects
KCNE2 T8A	<1	1	TMP/SMX, quinidine, amiodarone
KCNE2 Q9E	3	<1	Erythromycin
KCNH2 K897T	8	33	Increased QTc and TdP
KCNH2 R1047L	<1	4	Dofetilide
SCN5A S1103Y	12	<1	Assoc w LQTS
KCNE1 D85N	<1	2	LQTS and DI-QT Prolongation

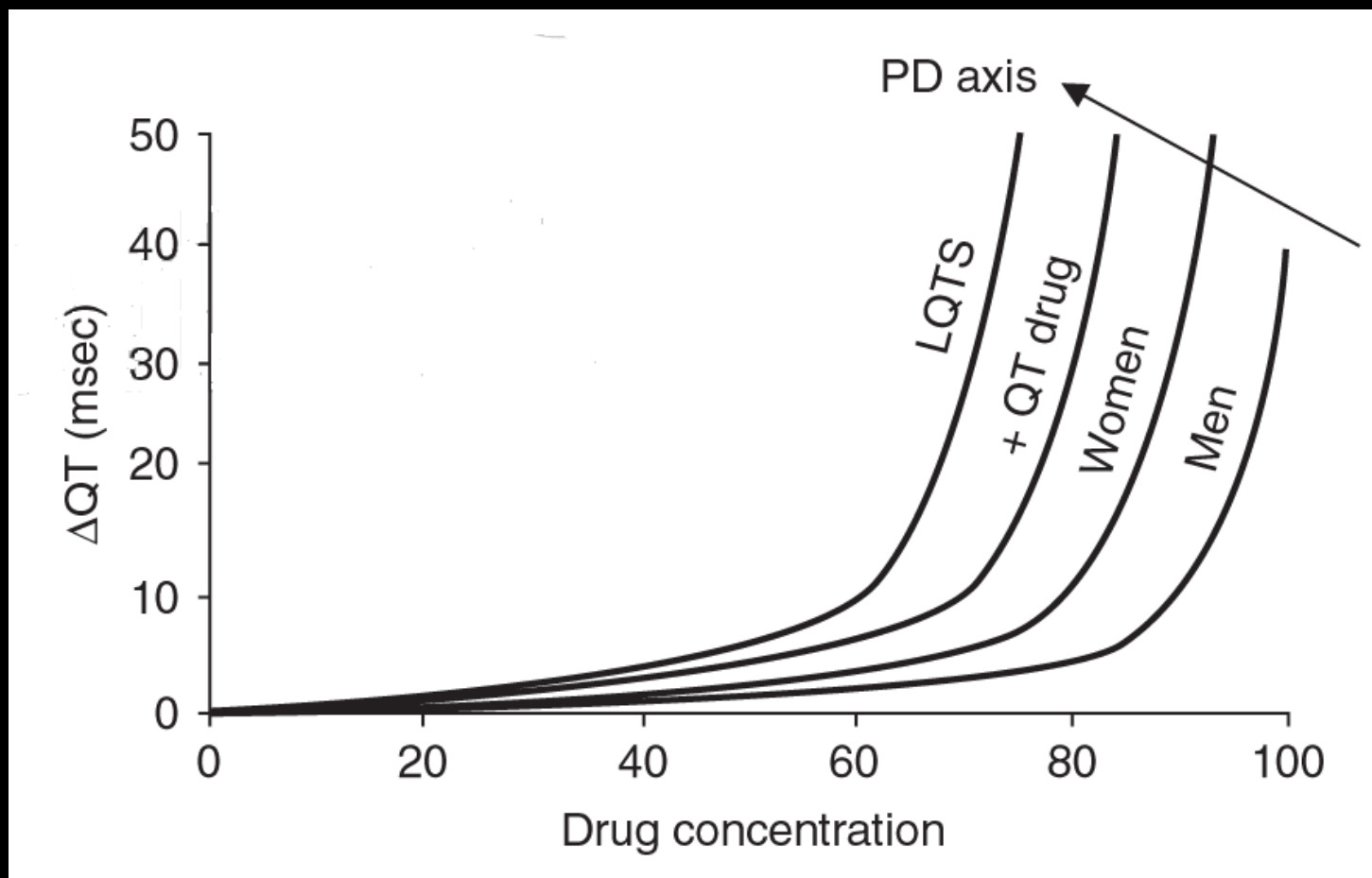
# Drug-Induced QT Prolongation

## Pharmacodynamics and Genetics

---

- $\beta$  Adrenergic Receptors
  - Regulate Channel Dynamics
  - $\beta_2$  Gly16 and Gln27
    - Associated with  $\uparrow$  TdP Risk
- Sex Hormones
  - Estradiol/Progesterone
    - Possible Role in Regulating QT Interval
      - Alter Cardiac Potassium Channel Expression

# Drug-Induced QT Prolongation FINAL MODEL



Judson *et al.*, *Mol Diag Ther* 2006