# ADVENTURES IN CARDIOVASCULAR RESEARCH: A Personal Journey

EUGENE BRAUNWALD, M.D.

Henry Neufeld Memorial Lecture
Jerusalem
April 22, 2013

# Calcium antagonists in secondary prevention after acute myocardial infarction: The Secondary Prevention Reinfarction Nifedipine Trial (SPRINT)

H. N. NEUFELD

*Heart Institute, Sheba Medical Center Tel-Hashomer, Israel*

Eur Heart J 1986;7(suppl B):51

# Genetic Aspects of Arteriosclerosis

**Uri Goldbourt and Henry N. Neufeld**

Arteriosclerosis 1986;6:357

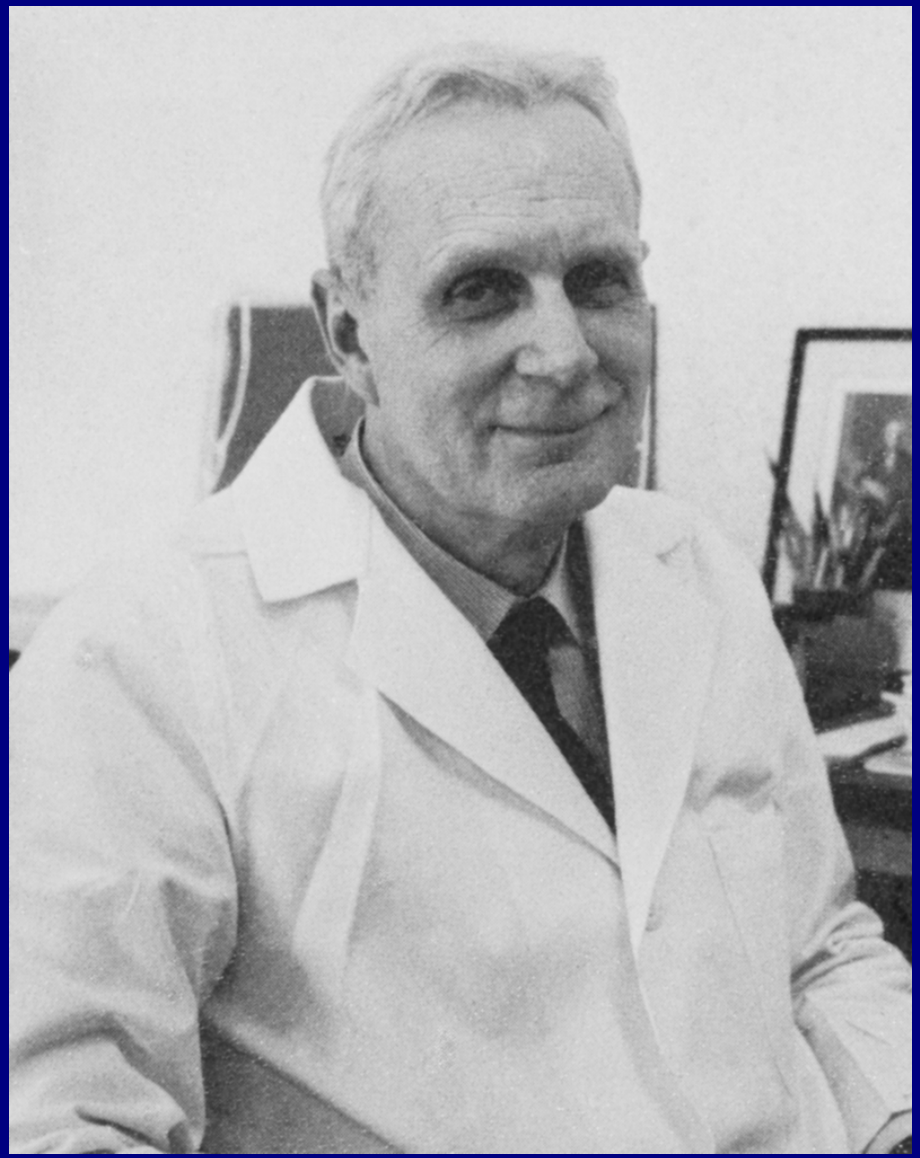
# Disclosures

## Research Support for Clinical Trials

| | |
|---|---|
| Squibb | SAVE, CARE |
| Bristol Myers Squibb | PROVE IT (TIMI 22)<br>SAVOR (TIMI 53) |
| Astra Zeneca | SAVOR (TIMI 53) |
| Lilly/Daiichi Sankyo | TRITON (TIMI 38)<br>ENGAGE (TIMI 48) |
| Johnson & Johnson | ATLAS 2 (TIMI 51) |
| GSK | SOLID (TIMI 52) |
| Merck | TRA-2P (TIMI 50)<br>REVEAL (TIMI 55) |

# BELLEVUE HOSPITAL – 1950
# Thursday Night Cardiac Clinic

# Ludwig Eichna
# 1909-2003



# CARDIOLOGY IN 1952

| | |
|---|---|
| CV mortality (Age adjusted) | 3x current |
| ARF | Very common in US; ARF hospitals |
| Arrhythmias | Quinidine and Dig.; No pacemakers |
| Heart Failure | Digitalis, mercurials, very low $Na^+$ diet |
| AMI | No CCUs; early mortality 30% |
| Imaging | NO echocardiography, nuclear, coronary art., contrast ventriculography |

# CARDIOLOGY IN 1952

| | |
|---|---|
| Cardiac cath | Rt. heart cath. (12 labs in U.S.)<br>NO Lt. heart cath. |
| Clinical trials | None |
| Evidence-based medicine | |
| Hypothesis-based clinical investigation | |
| Risk Factor Concept | No |
| Surgery | Closed mitral valvotomy;<br>no open-heart surgery |
| NHI | Budget ~ $200,000/yr |
| AHA | Research budget ~ $40,000/yr |

# CARDIOLOGY IN 1952 (ctd)

Two Potential Opportunities for Advancing the Field:

1) Cardiac Catheterization

2) Cardiac Surgery (Closed)

Mitral Valvotomy, Repair of PDA, and Coarctation

VALVULAR HEART DISEASE

HYPERTROPHIC CARDIOMYOPATHY

HEART FAILURE

LIPID LOWERING

MYOCARDIAL ISCHEMIA AND INFARCTION

# 1953

**WE MUST BE ABLE TO**

**MEASURE PRESSURES**

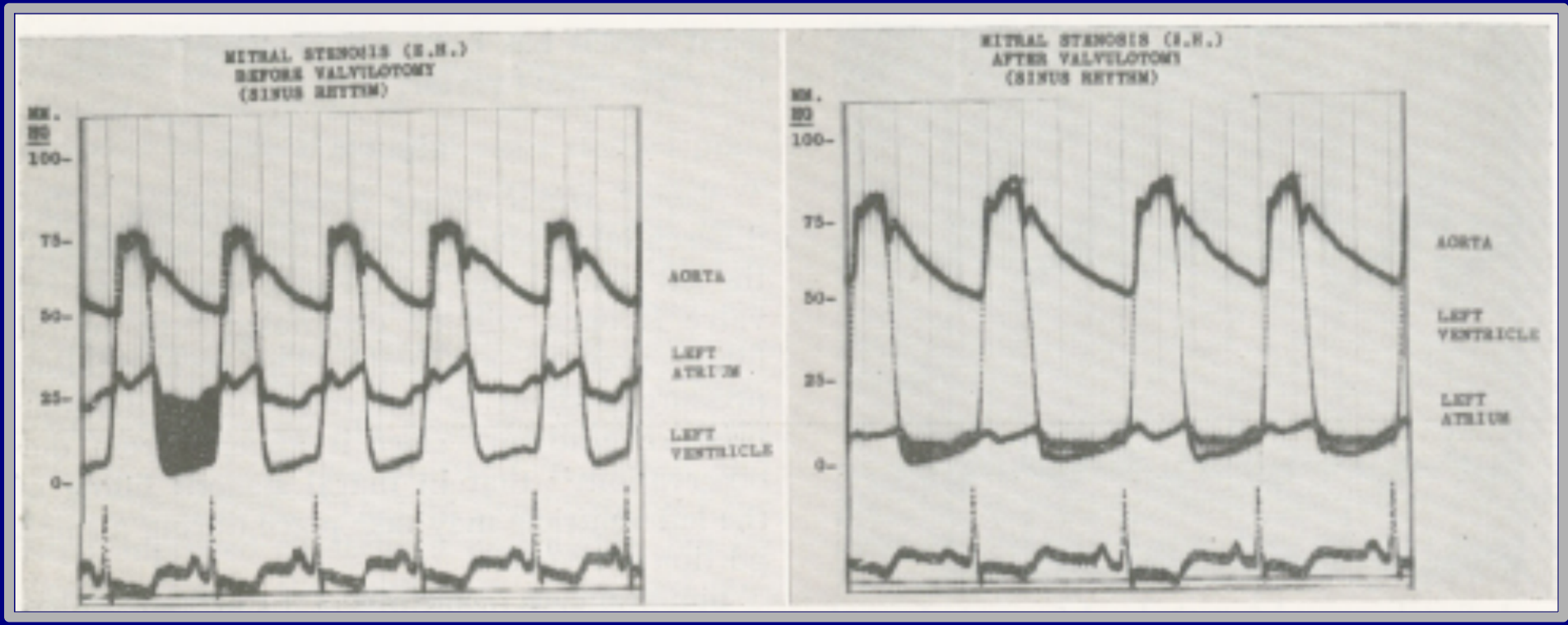
**IN THE LEFT SIDE OF THE HEART!**

# The Hemodynamics of the Left Side of the Heart as Studied by Simultaneous Left Atrial, Left Ventricular, and Aortic Pressures; Particular Reference to Mitral Stenosis

*By* Eugene Braunwald, M.D., Howard L. Moscovitz, M.D., Salomao S. Amram, M.D., Richard P. Lasser, M.D., Samuel O. Sapin, M.D., Aaron Himmelstein, M.D., Mark M. Ravitch, M.D. and Alvin J. Gordon, M.D.

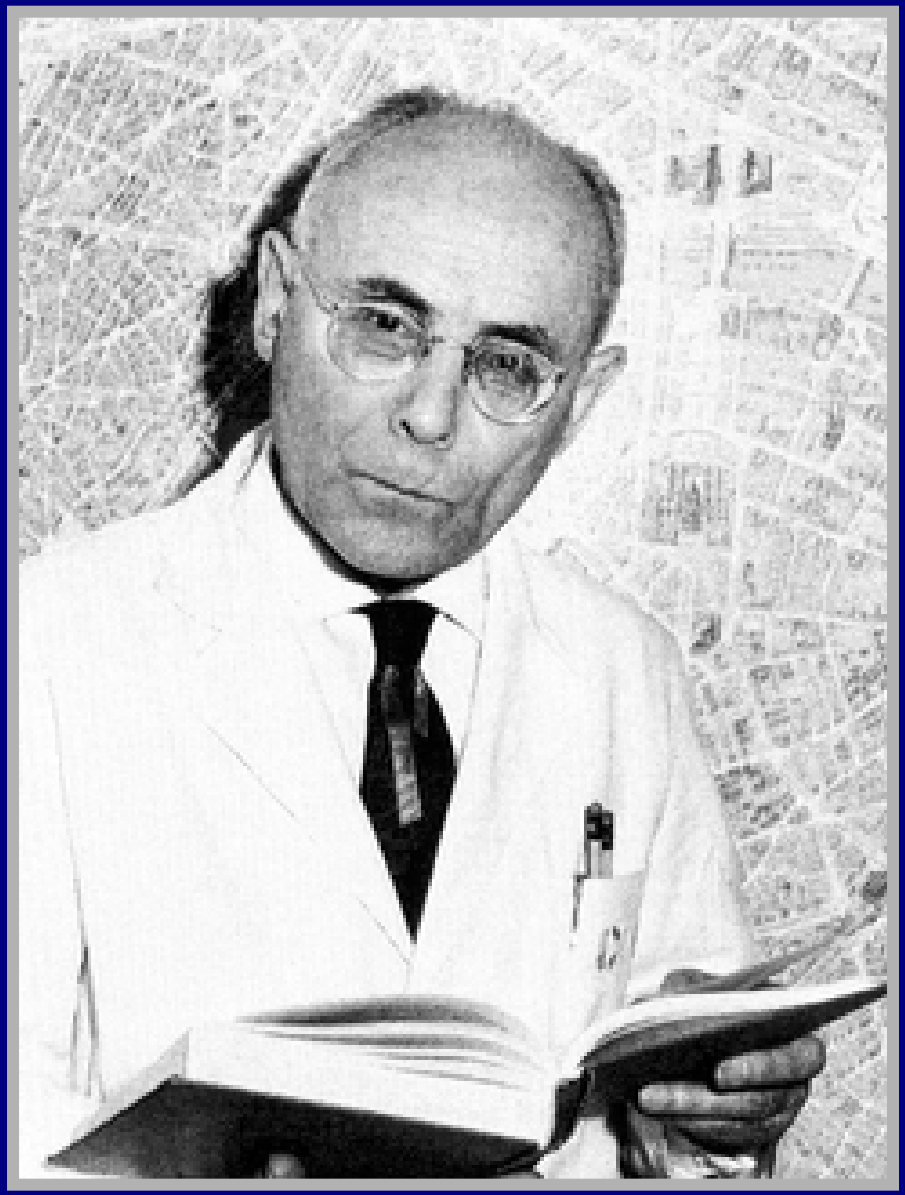
Circulation 1955;12:69

# FIRST DIRECT MEASUREMENT OF TRANSVALVULAR GRADIENT




Circulation 1955;12:69

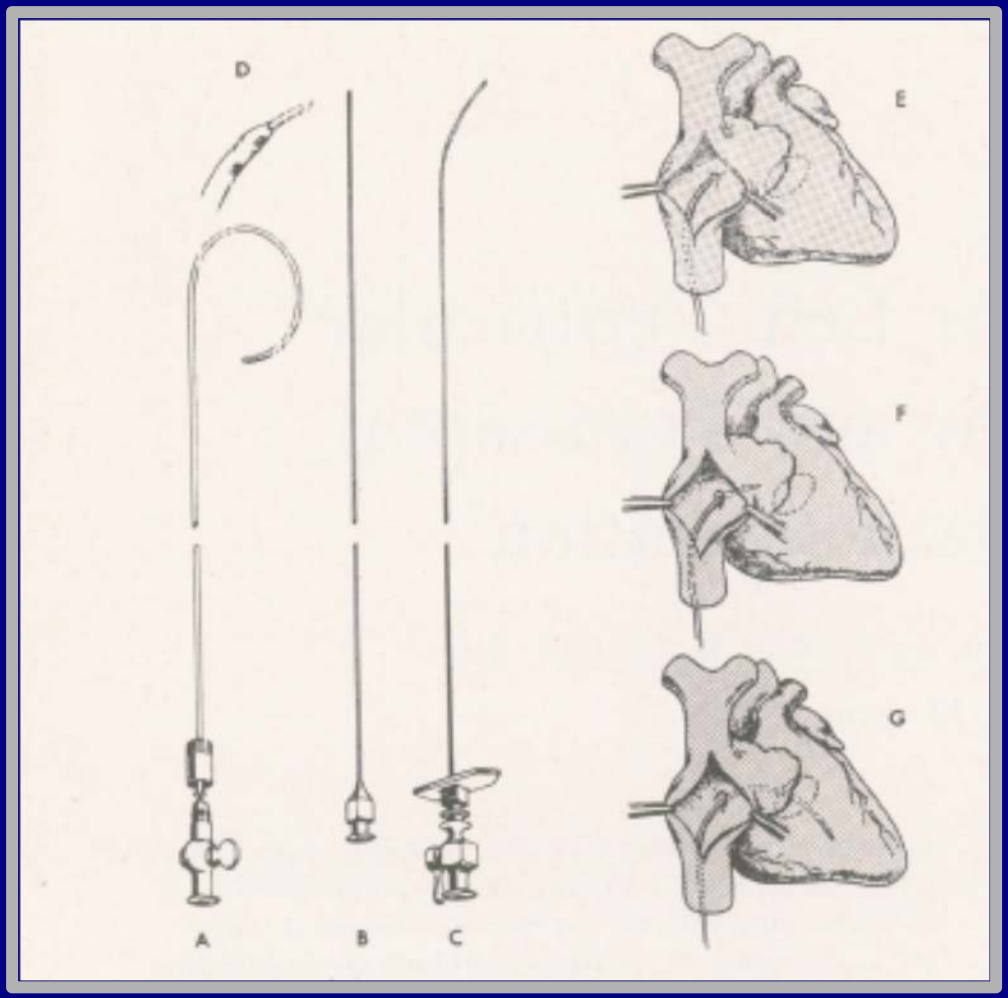
# Andre Cournand, M.D.
# 1895-1988



# Left Heart Catheterization by the Transseptal Route

## A Description of the Technic and Its Applications

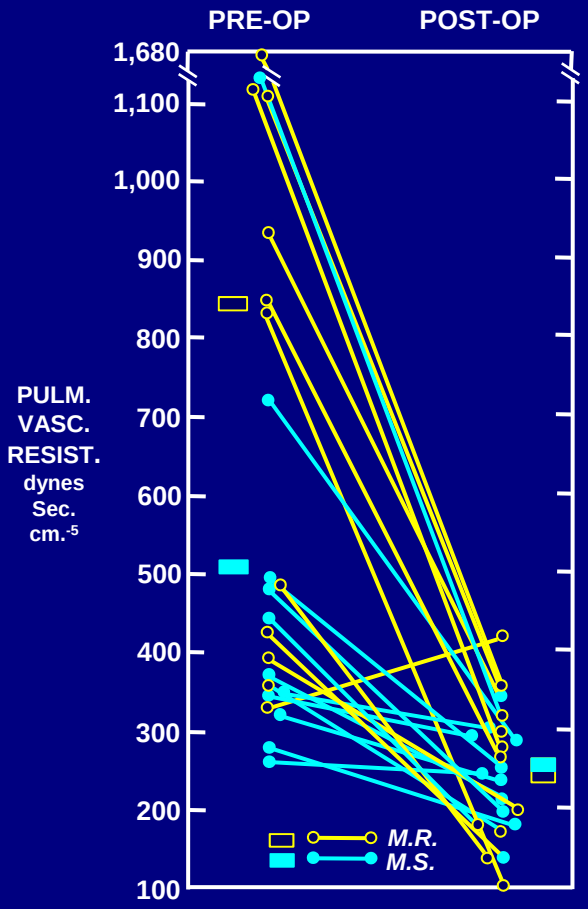
*By* JOHN ROSS, JR., M.D., EUGENE BRAUNWALD, M.D.,
AND ANDREW G. MORROW, M.D.




Circulation 1960;22:927

# EFFECTS OF MITRAL-VALVE REPLACEMENT ON THE PULMONARY VASCULAR DYNAMICS OF PATIENTS WITH PULMONARY HYPERTENSION*

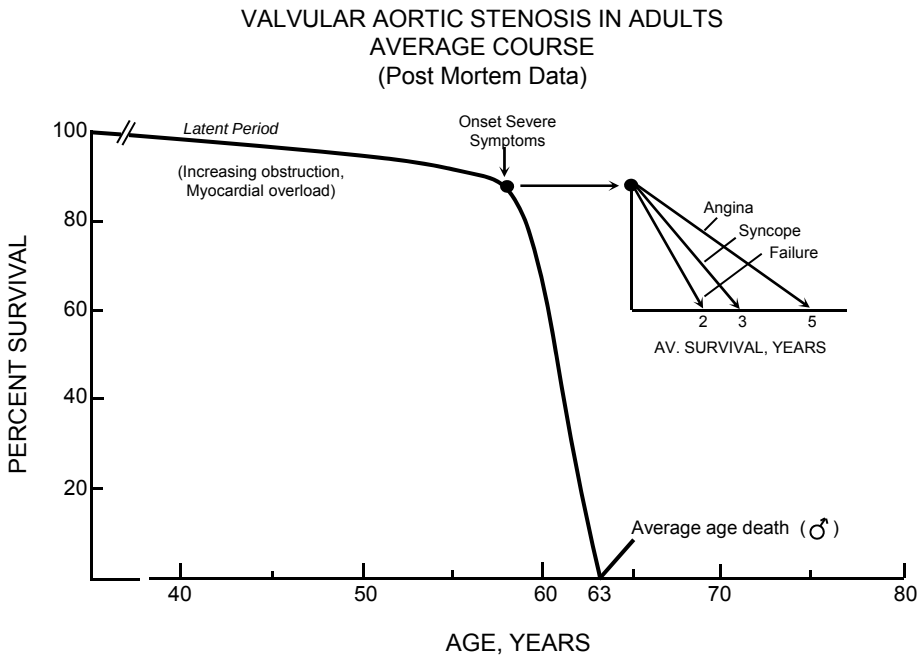
EUGENE BRAUNWALD, M.D.,† NINA S. BRAUNWALD, M.D.,‡ JOHN ROSS, JR., M.D.,§ AND ANDREW G. MORROW, M.D.¶




N Engl J Med 1965;273:509

# Aortic Stenosis

*By* JOHN ROSS, JR., M.D. AND EUGENE BRAUNWALD, M.D.




Circulation 1968;37:V61

VALVULAR HEART DISEASE

HYPERTROPHIC CARDIOMYOPATHY

HEART FAILURE

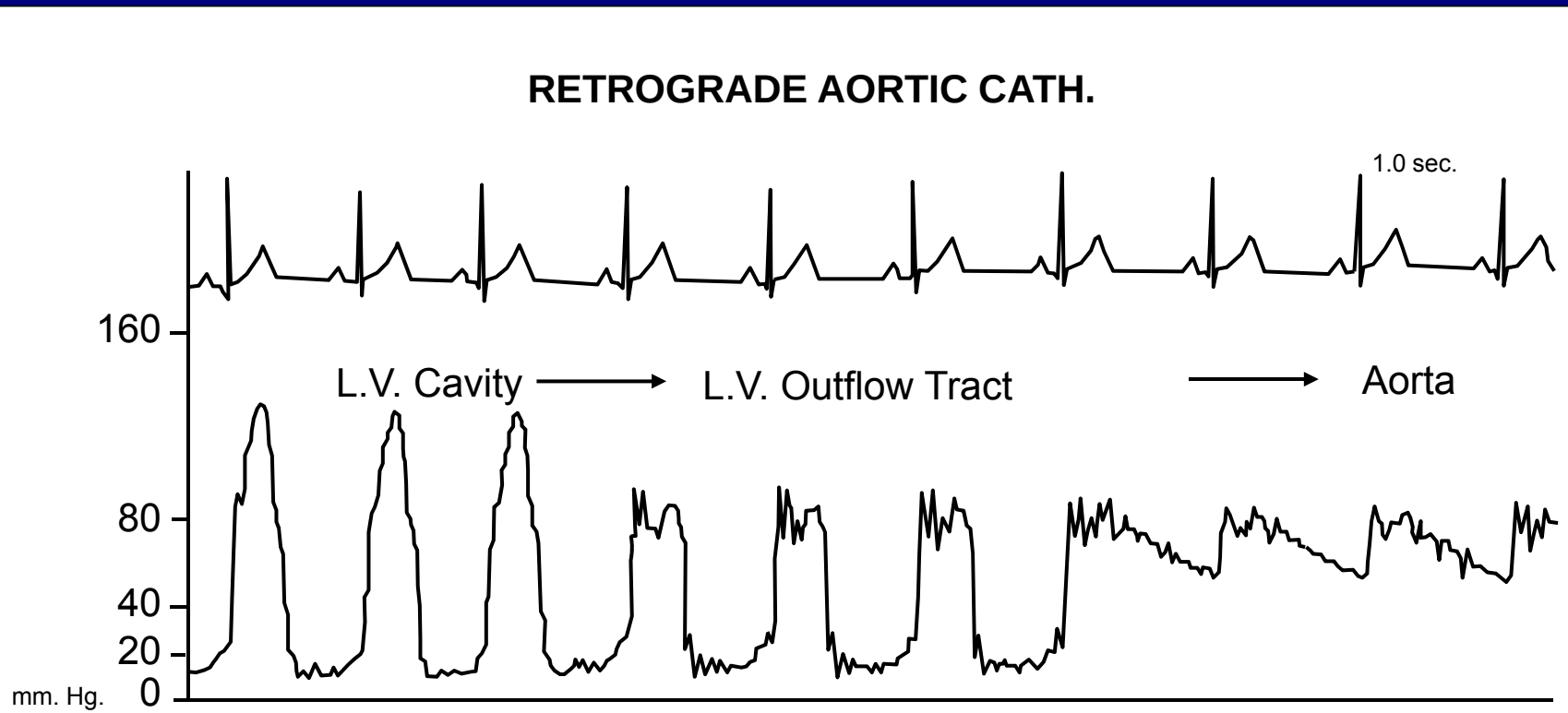
LIPID LOWERING

MYOCARDIAL ISCHEMIA AND INFARCTION

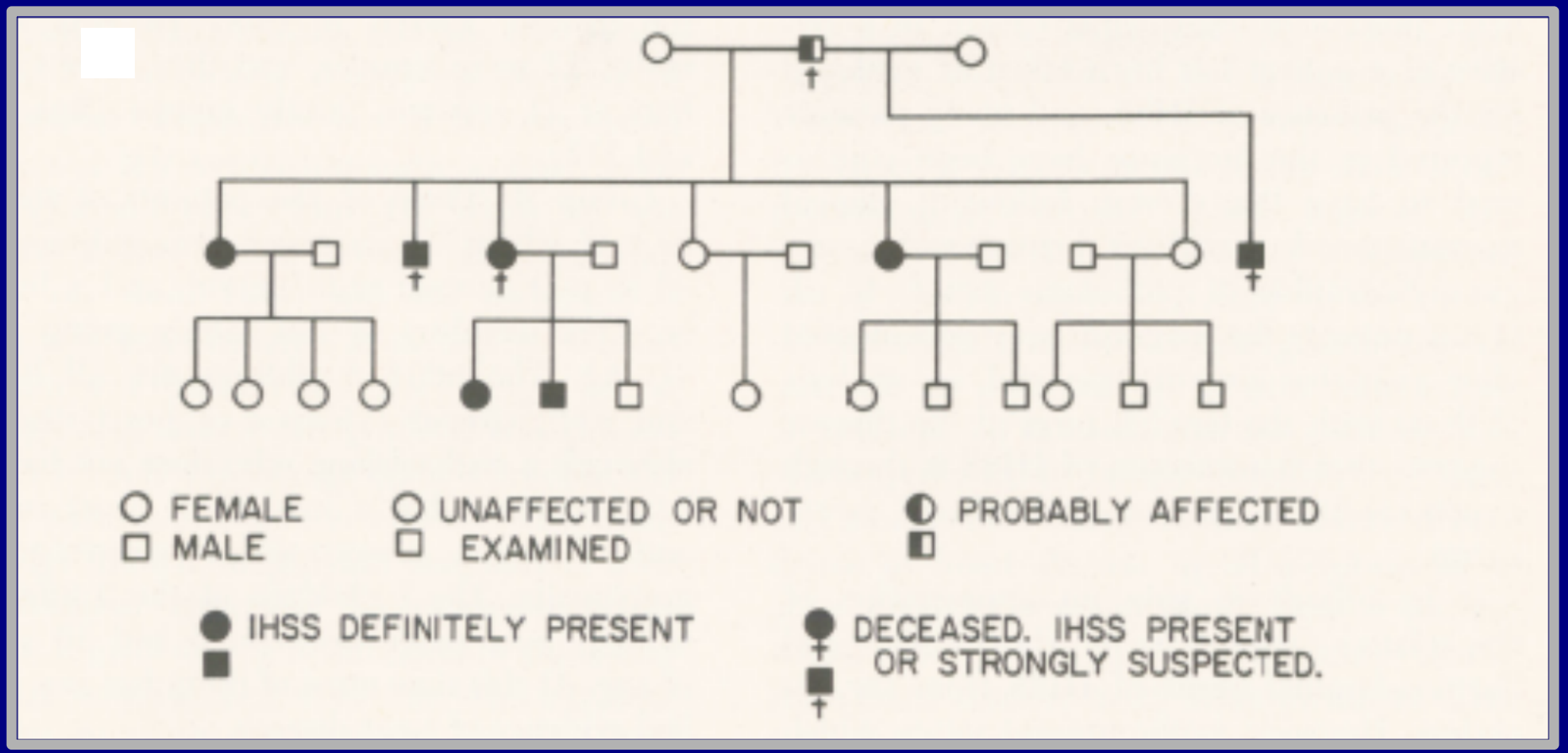
# Functional Aortic Stenosis

## A Malformation Characterized by Resistance to Left Ventricular Outflow without Anatomic Obstruction

*By* Andrew G. Morrow, M.D., and Eugene Braunwald, M.D.



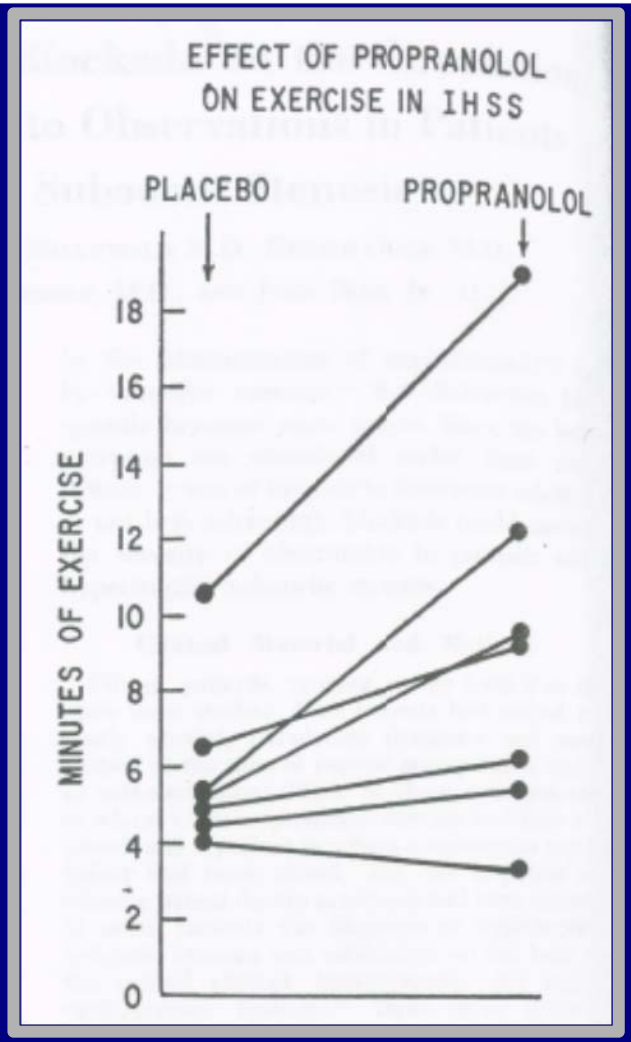

Circulation 1959;20:181



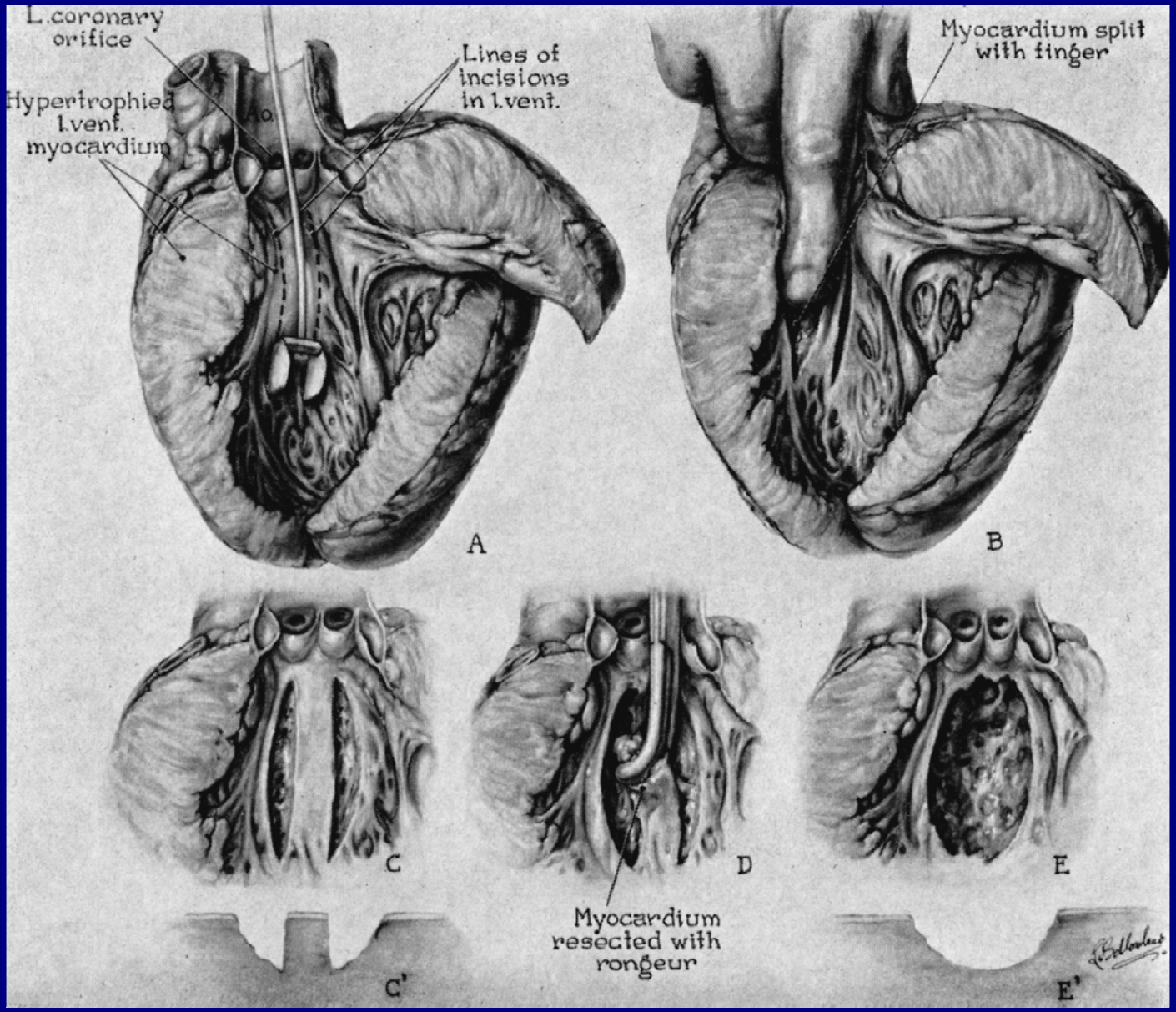

Braunwald E, et al
Circulation 1964;30 Suppl4:3-119

# Effects of Beta Adrenergic Blockade on the Circulation, with Particular Reference to Observations in Patients with Hypertrophic Subaortic Stenosis

*By* Donald C. Harrison, M.D., Eugene Braunwald, M.D., Gerald Glick, M.D., Dean T. Mason, M.D., Charles A. Chidsey, M.D., and John Ross, Jr., M.D.




Circulation 1964;29:84




Morrow AG, et al
Circulation 1964;30 Suppl4:3-119

# Idiopathic Hypertrophic Subaortic Stenosis

## Clinical Analysis of 126 Patients with Emphasis on the Natural History

*By* STUART FRANK, M.D., AND EUGENE BRAUNWALD, M.D.

Circulation 1968;37:759

6 sudden deaths
(of 10 deaths)

# HCM

| | |
|---|---|
| 1959 | Obstruction 2$^{o}$ to muscular hypertrophy |
| 1960 | Familial association/autosomal dominant |
| 1962 | Variability of obstruction |
| 1962 | Provocation by isoprotereno |
| 1964 | Medical treatment with beta blockade |
| 1964 | Surgical treatment with myectomy |
| 1968 | Frequency of sudden death |

VALVULAR HEART DISEASE

HYPERTROPHIC CARDIOMYOPATHY

HEART FAILURE

LIPID LOWERING

MYOCARDIAL ISCHEMIA AND INFARCTION

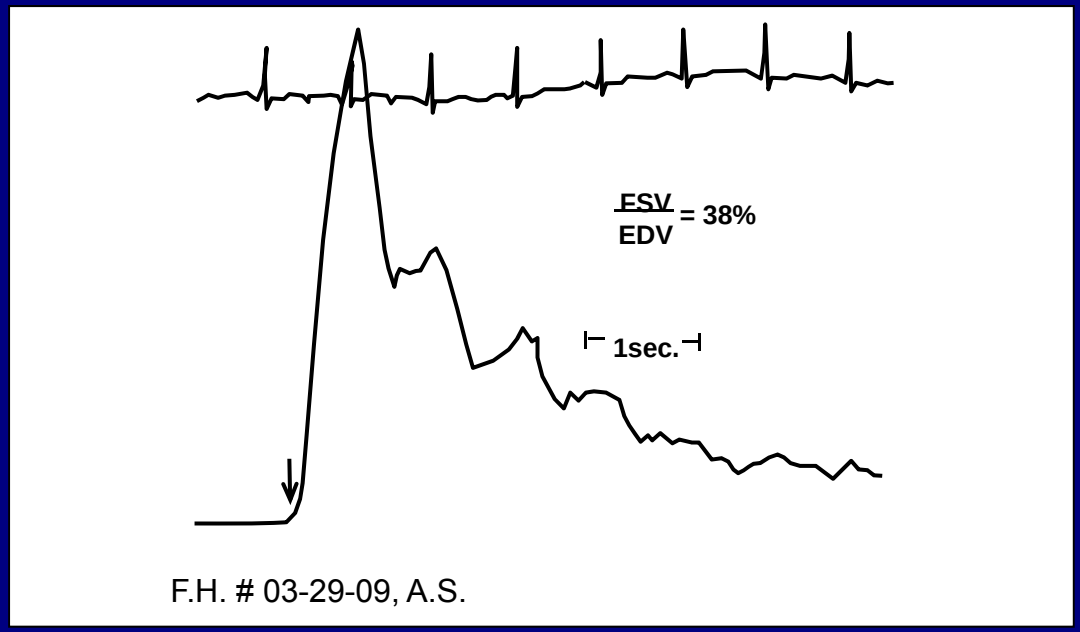
# FIRST MEASUREMENT OF EJECTION FRACTION

## Determination of Fraction of Left Ventricular Volume Ejected per Beat and of Ventricular End-Diastolic and Residual Volumes

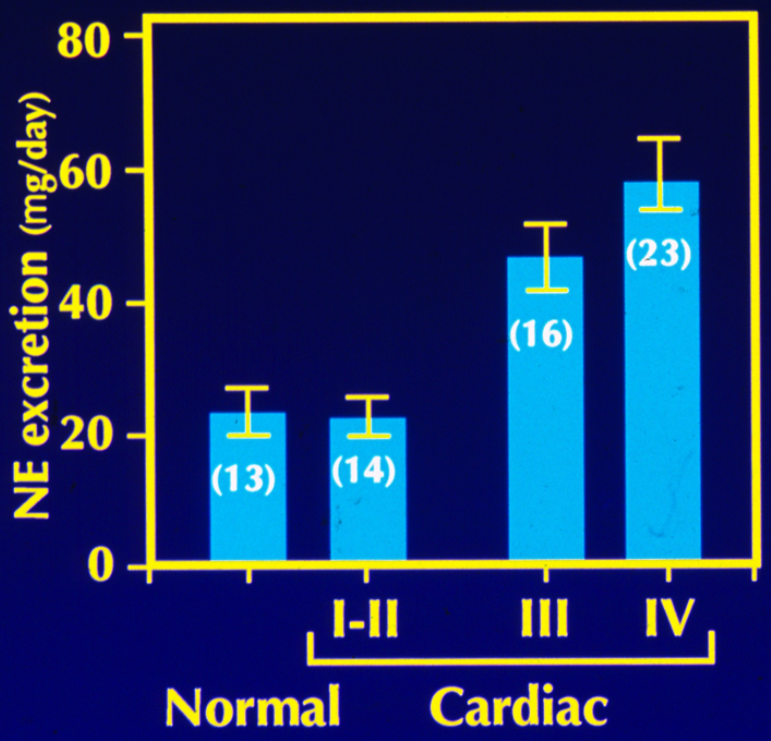
### Experimental and Clinical Observations with a Precordial Dilution Technic

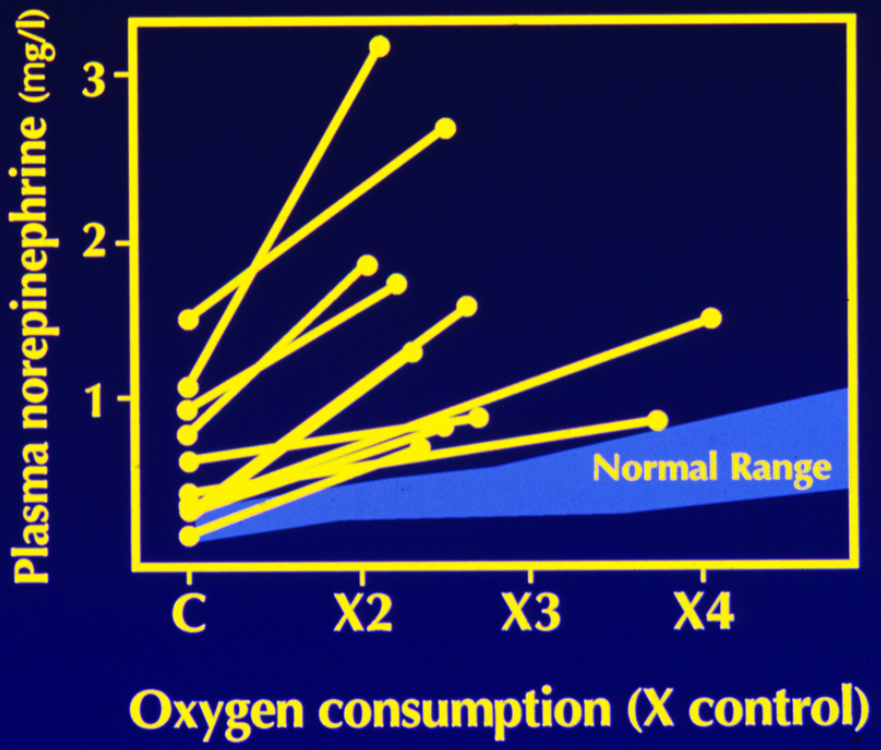
*By* Roland Folse, M.D., and Eugene Braunwald, M.D.

Circulation 1962;25:674



# FIRST NEURO-HORMONAL ABNORMALITY IN HEART FAILURE



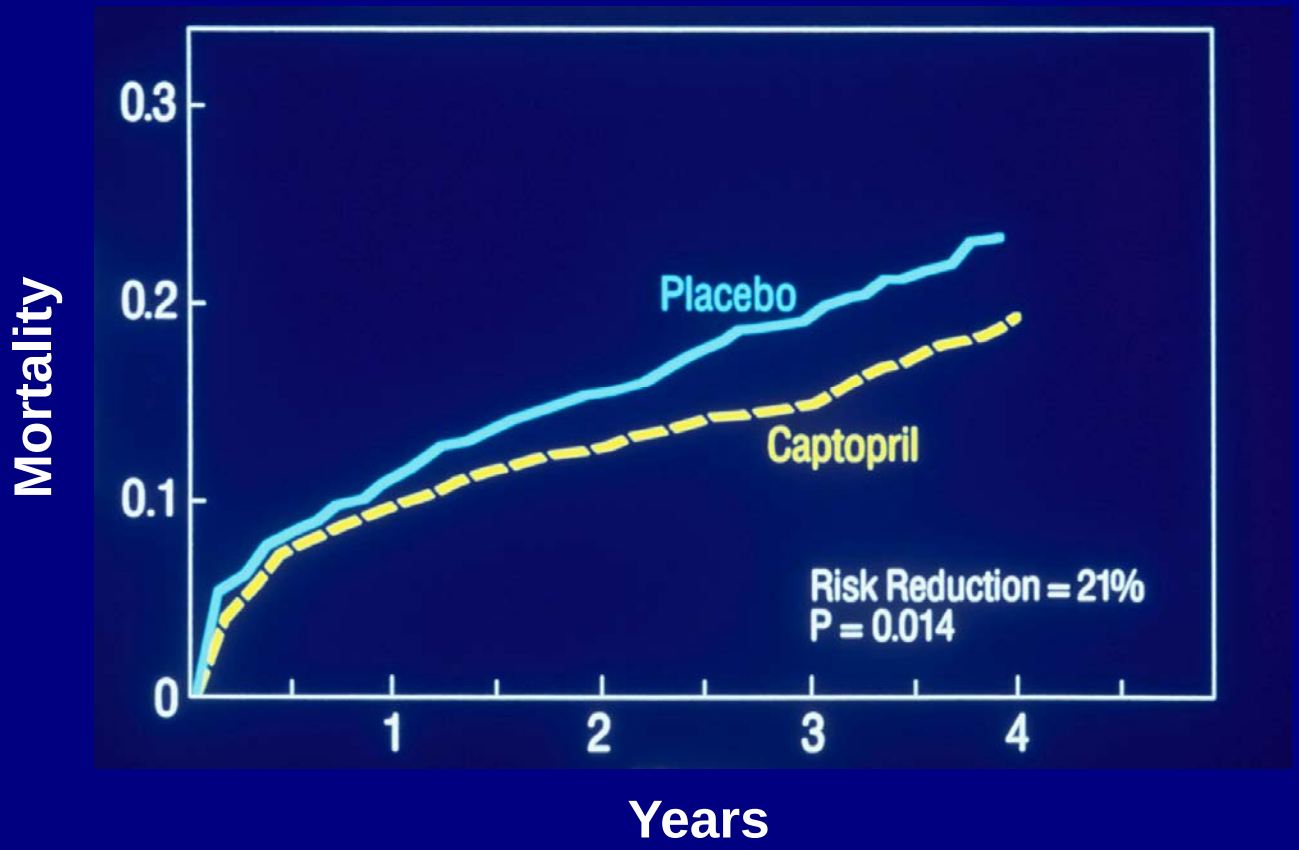




Chidsey CA, Harrison DC, Braunwald E: N. Engl. J. Med. 267:650, 1962

# SECOND NEURO-HORMONAL ABNORMALITY IN HEART FAILURE: ACTIVATION OF THE RA SYSTEM

## THE SAVE TRIAL

<10 days post AMI, LVEF <40%




Pfeffer, Braunwald et al
NEJM 1992;327:669

VALVULAR HEART DISEASE

HYPERTROPHIC CARDIOMYOPATHY

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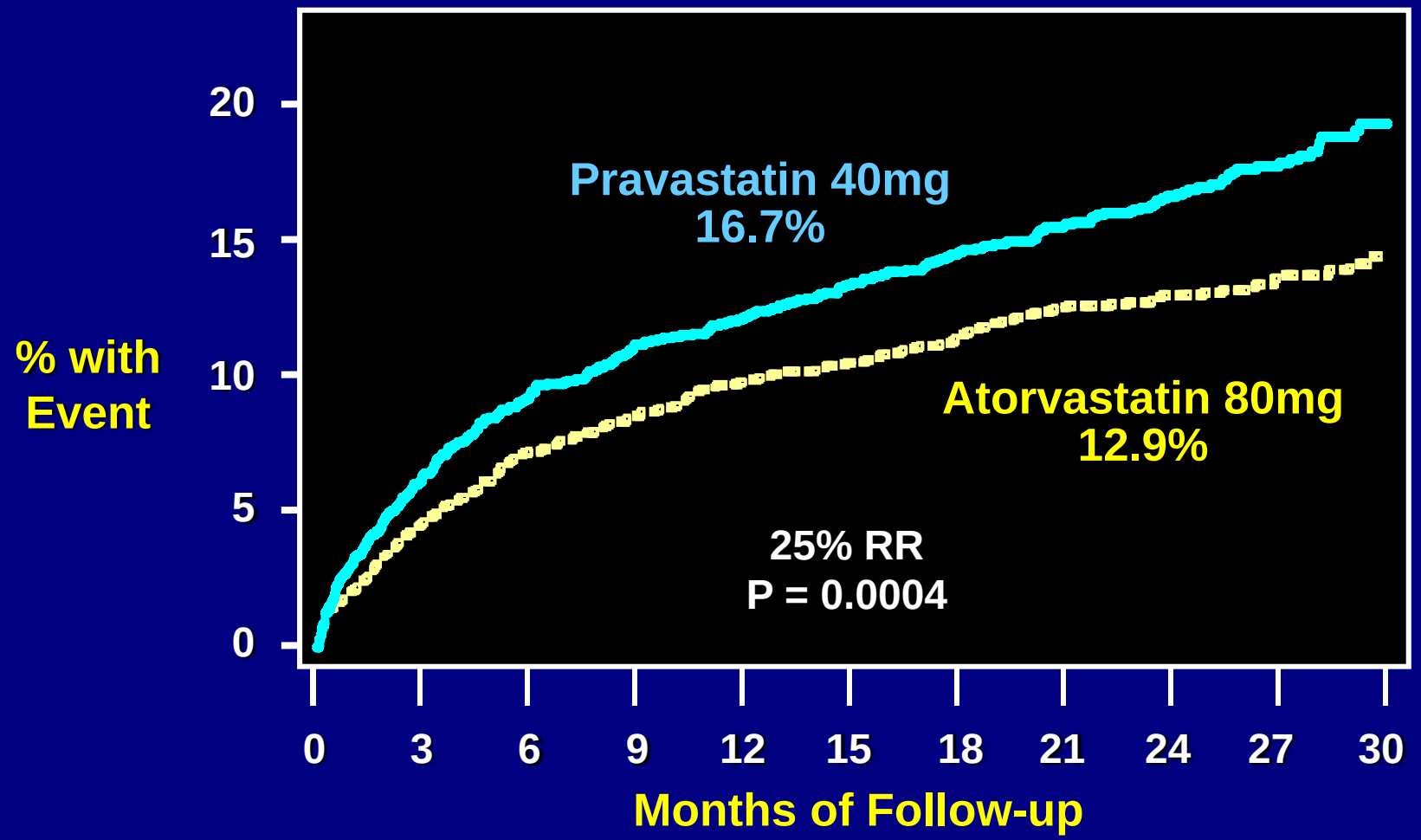
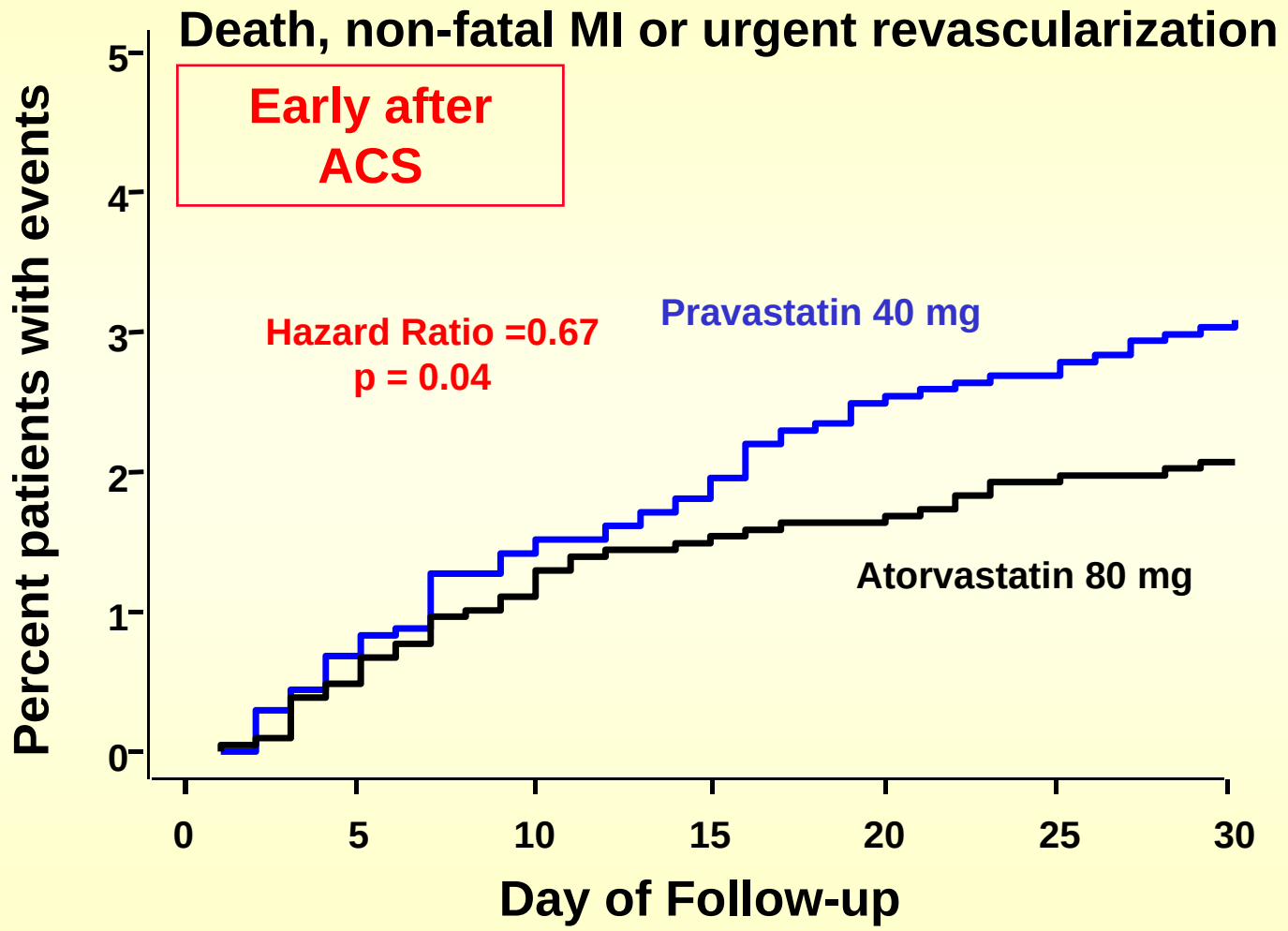
# PROVE IT – TIMI 22
# All-Cause Death, Non-Fatal MI, or Urgent Revascularization



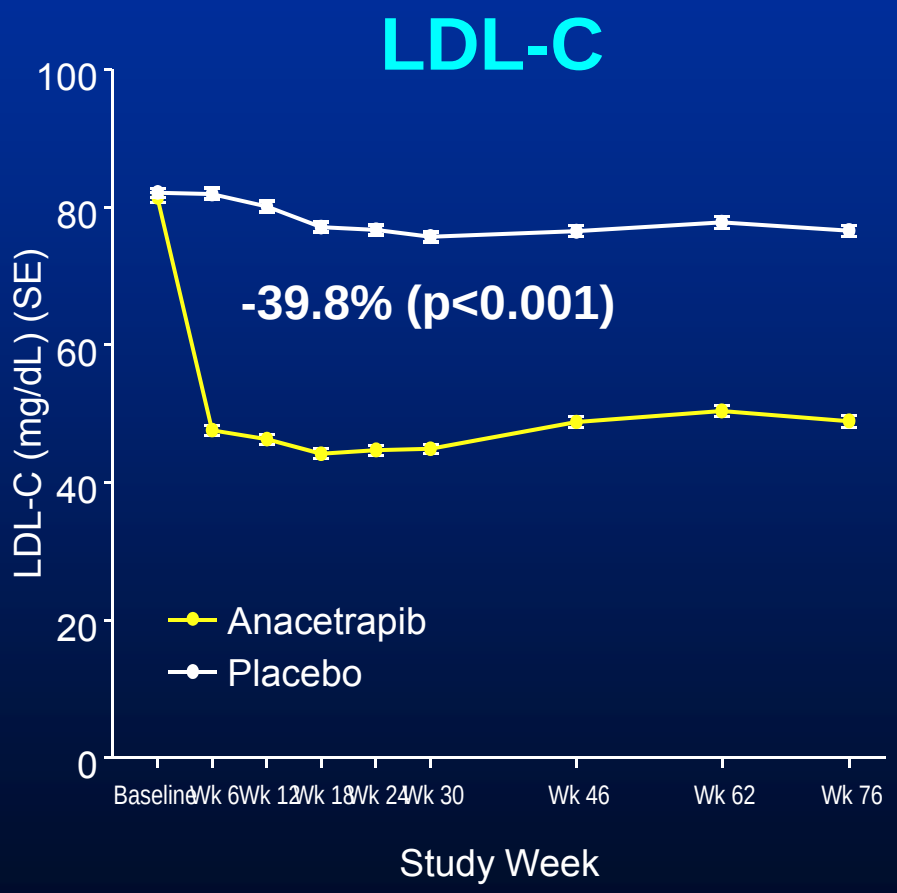
# PROVE IT-TIMI 22

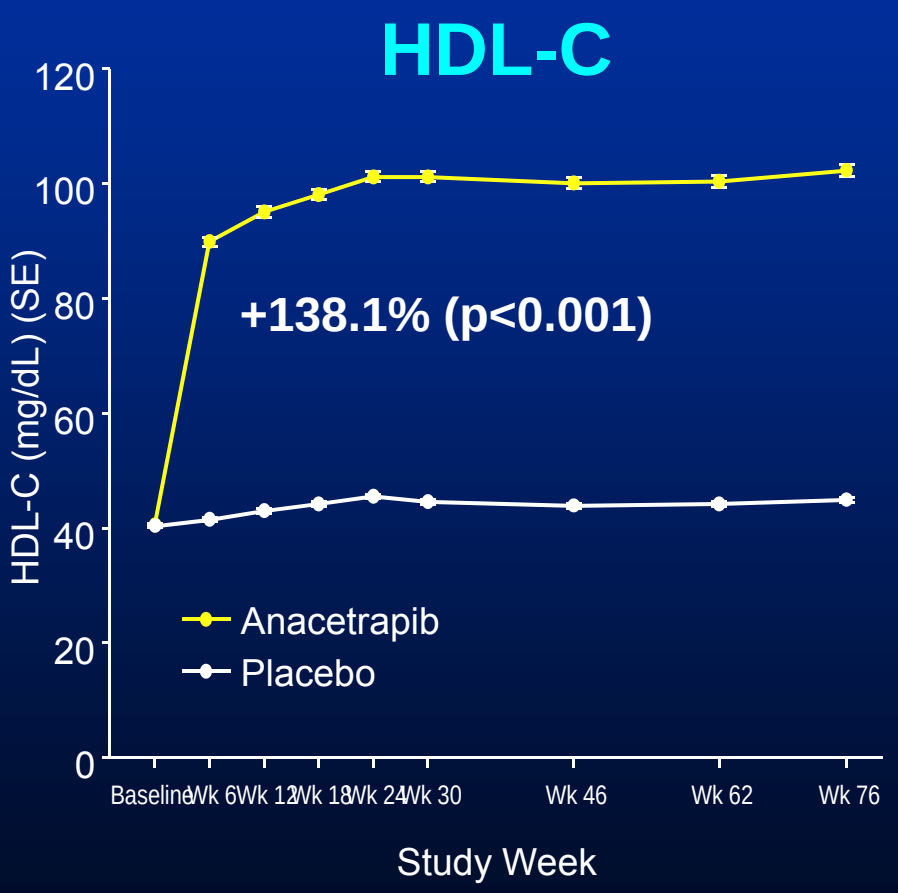



Cannon CP, N Engl J Med 2004; 350:1495-04

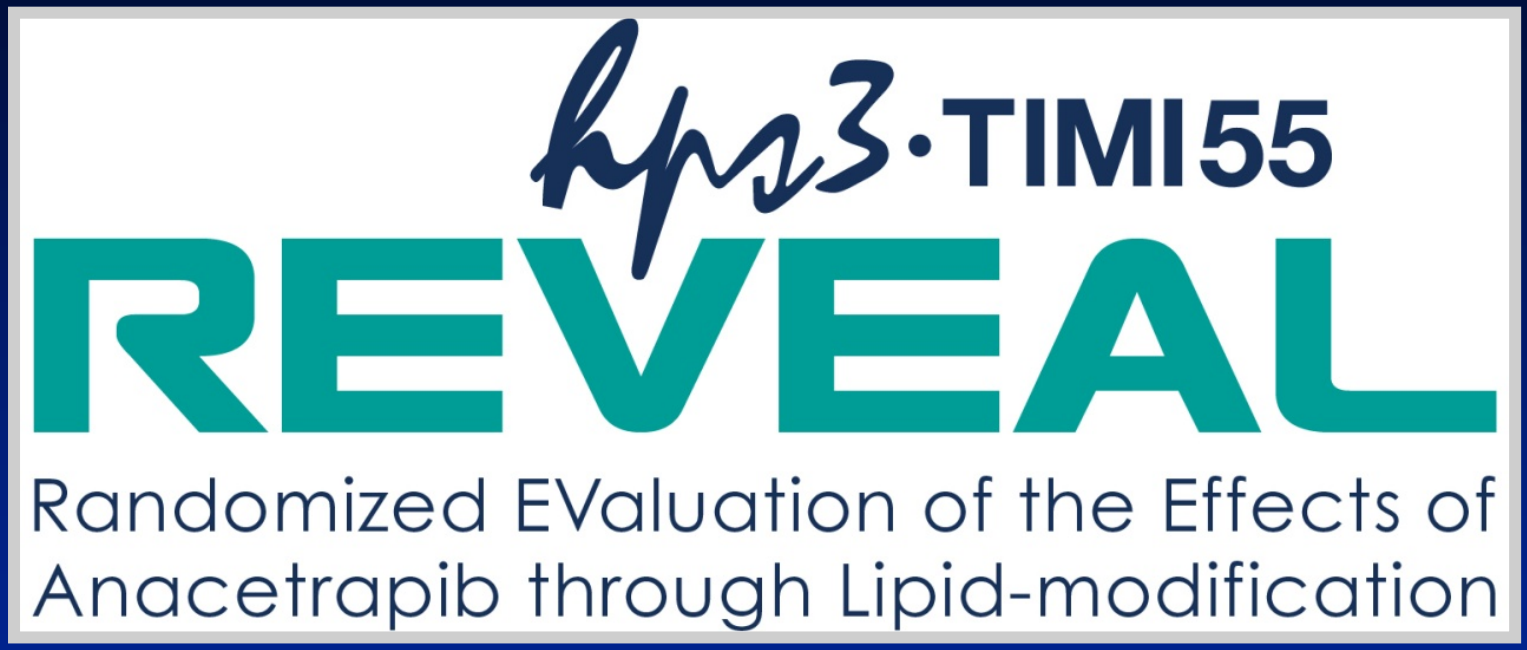
define
Determining the EFficacy and Tolerability of CETP INhibition with AnacEtrapib

# Effects of CETP Inhibition on LDL-C and HDL-C




Cannon CP et al. NEJM 2010;363:2406


hps3·TIMI55
REVEAL
Randomized EValuation of the Effects of
Anacetrapib through Lipid-modification

VALVULAR HEART DISEASE

HYPERTROPHIC CARDIOMYOPATHY

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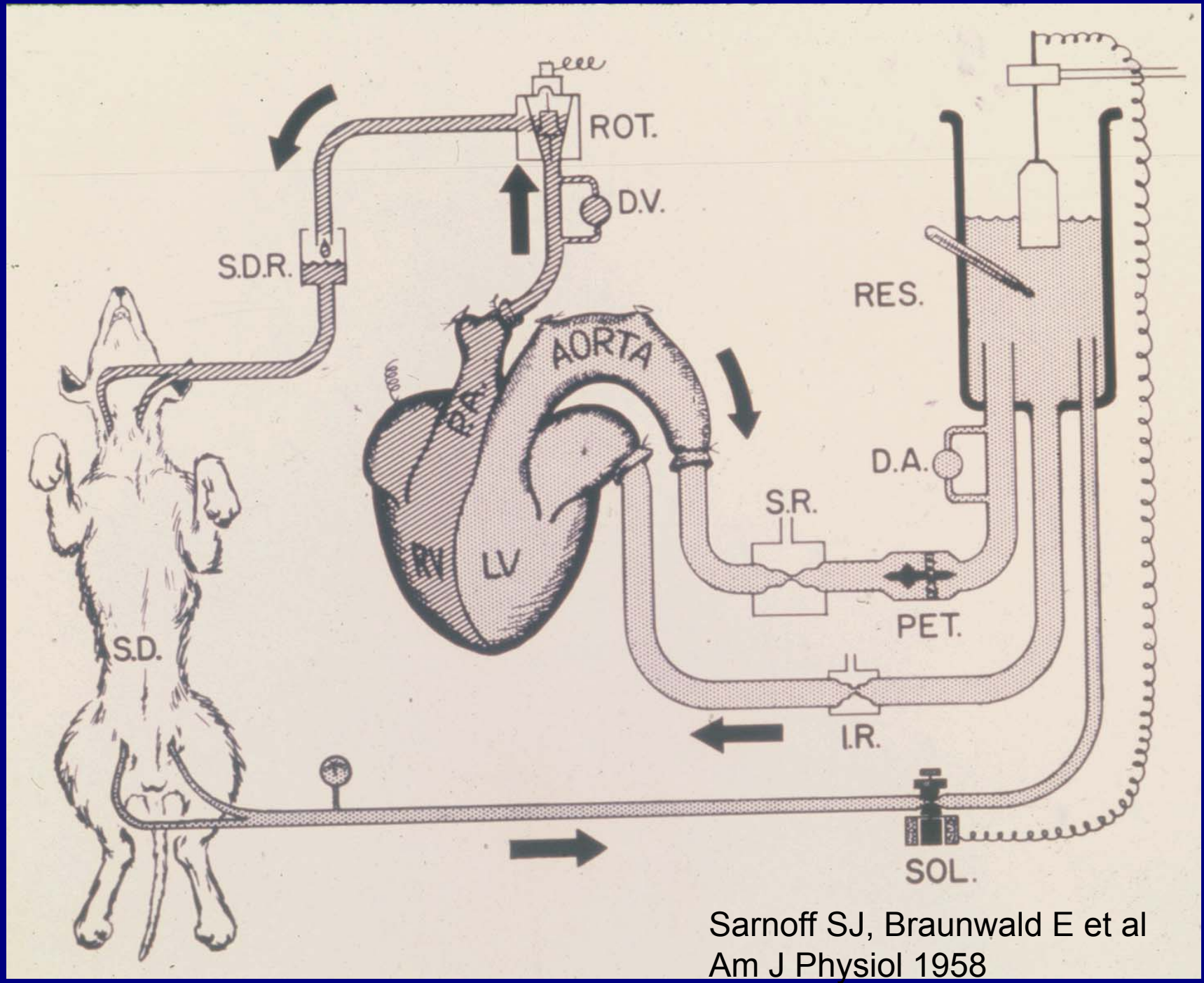
**Elucidation of determinants of myocardial $O_2$ consumption ($O_2$ demand)**




Sarnoff SJ, Braunwald E et al
Am J Physiol 1958

# DETERMINANTS OF MYOCARDIAL $O_2$ CONSUMPTION

- Tension development
- Contractility
- Heart rate

} 92%

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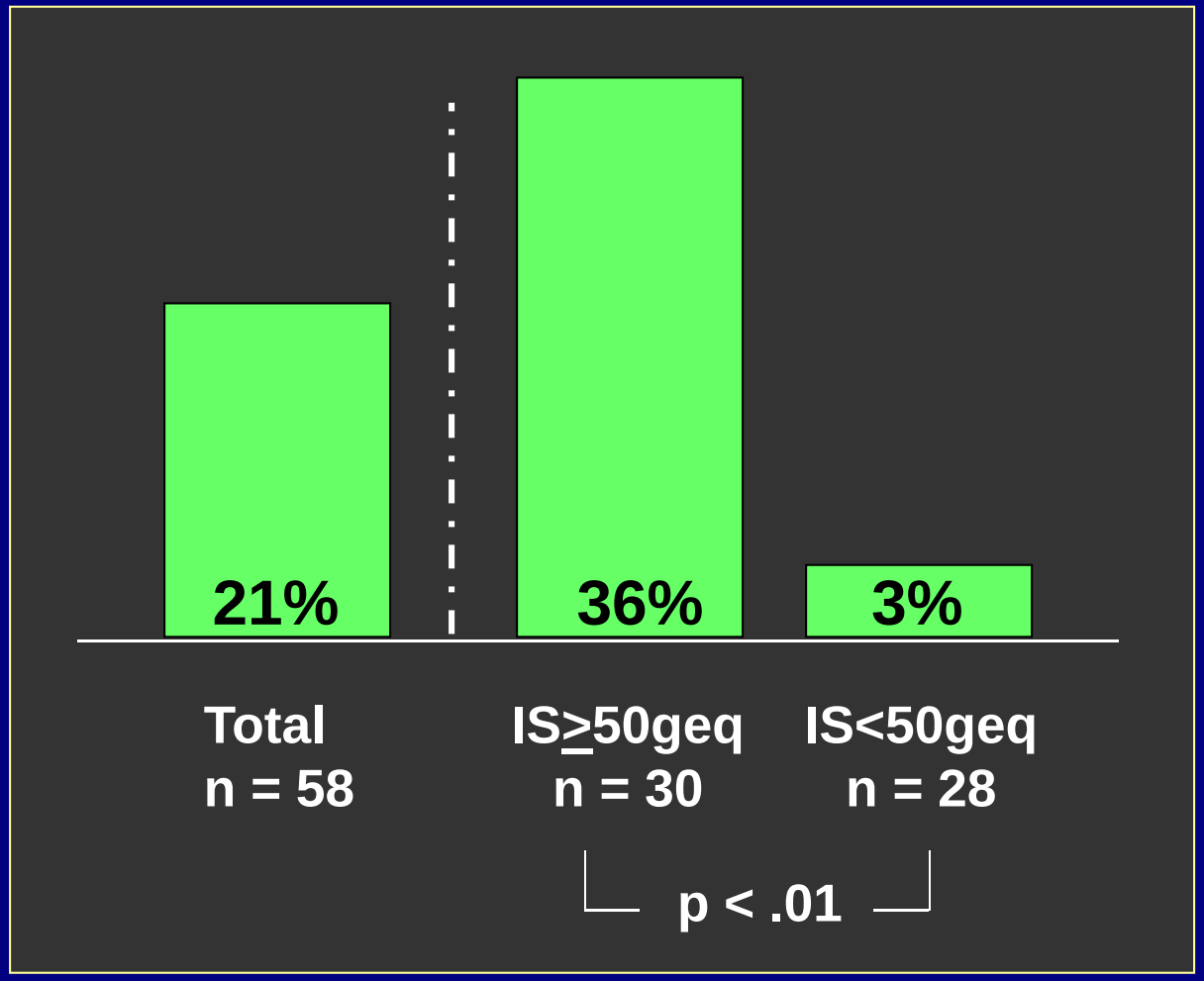
- Basal
- Depolarization
- Activation
- Maintenance of active state
- Shortening against a load – Fenn effect

Braunwald: Bowditch Lecture
American Physiol. Society, 1967

# INFARCT SIZE AND ACUTE MORTALITY




1968

# Factors Influencing Infarct Size Following Experimental Coronary Artery Occlusions

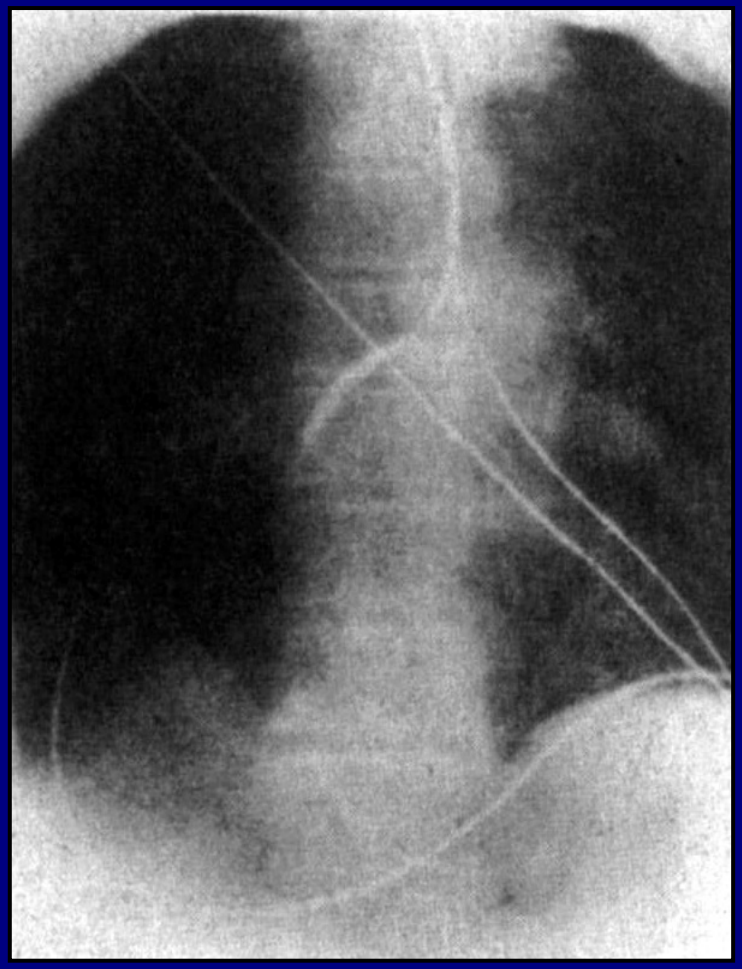
*By* PETER R. MAROKO, M.D., JOHN K. KJEKSHUS, M.D., BURTON E. SOBEL, M.D., TAN WATANABE, M.D., JAMES W. COVELL, M.D., JOHN ROSS, JR., M.D., AND EUGENE BRAUNWALD, M.D.

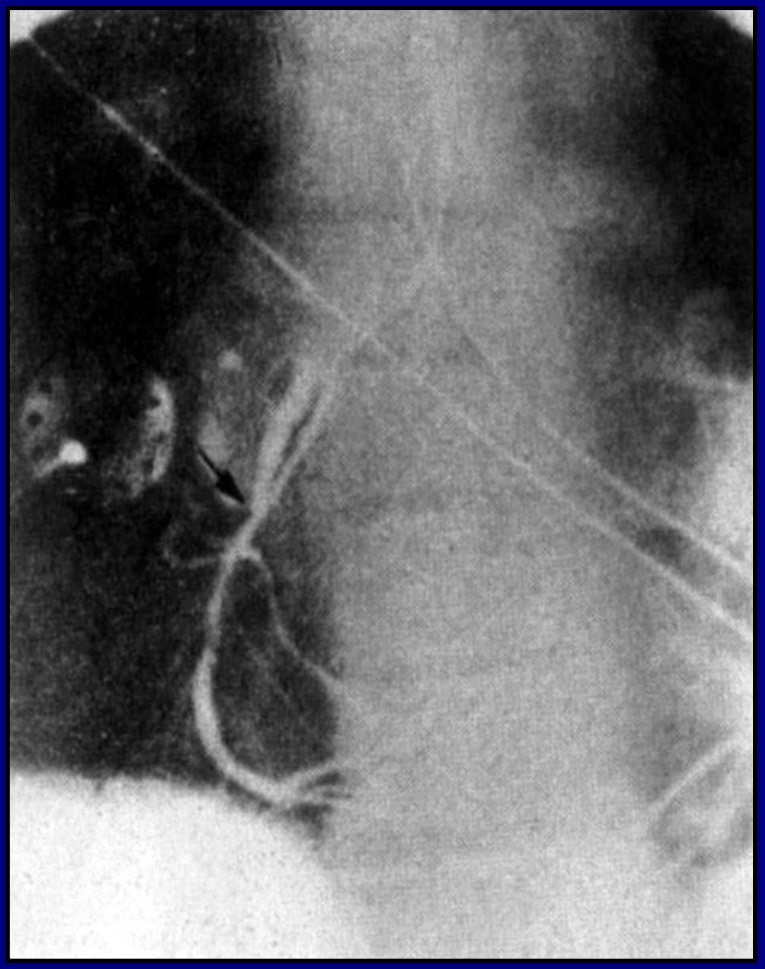
Circulation 1971;43:67

“In patients with myocardial ischemic injury resulting from coronary occlusion, measures designed for reduction of myocardial oxygen demands and improvement of coronary perfusion when effected promptly after a patient has been brought to a hospital, might reduce the ultimate size of the infarct.”

Maroko PR et al.
Circulation 1971;43:67

# REPERFUSION OF RCA





Chazov EI
Ter. Arkh. 1976

The New England
Journal of Medicine



Volume 305 OCTOBER 1, 1981 Number 14

# MYOCARDIAL SALVAGE AFTER INTRACORONARY THROMBOLYSIS WITH STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION

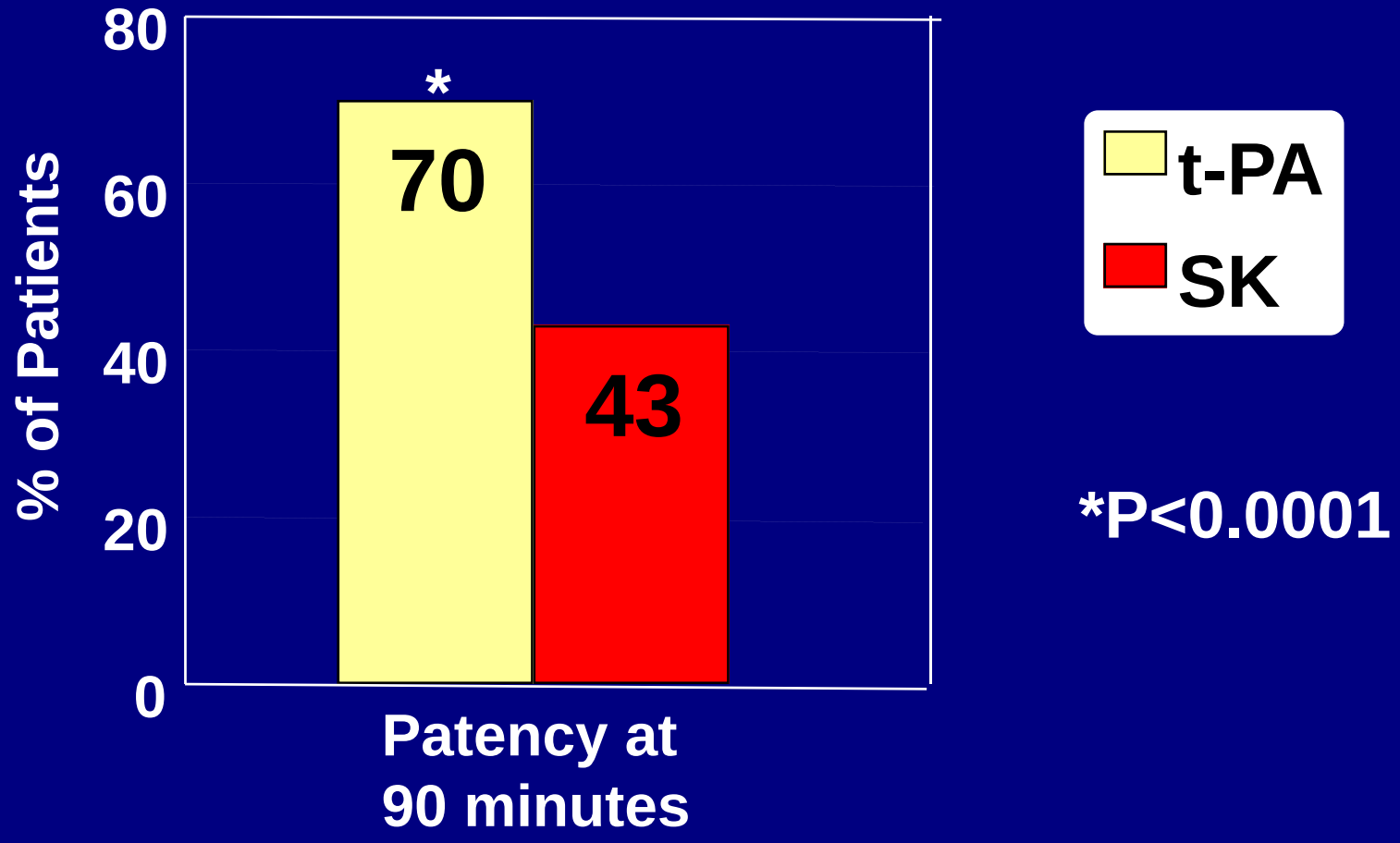
## Assessment by Intracoronary Thallium-201

JOHN E. MARKIS, M.D., MICHAEL MALAGOLD, M.D., J. ANTHONY PARKER, M.D., KENNETH J. SILVERMAN, M.D., WILLIAM H. BARRY, M.D., ANN V. ALS, M.D., SVEN PAULIN, M.D., WILLIAM GROSSMAN, M.D., AND EUGENE BRAUNWALD, M.D.

# TIMI

*Primary Outcome*

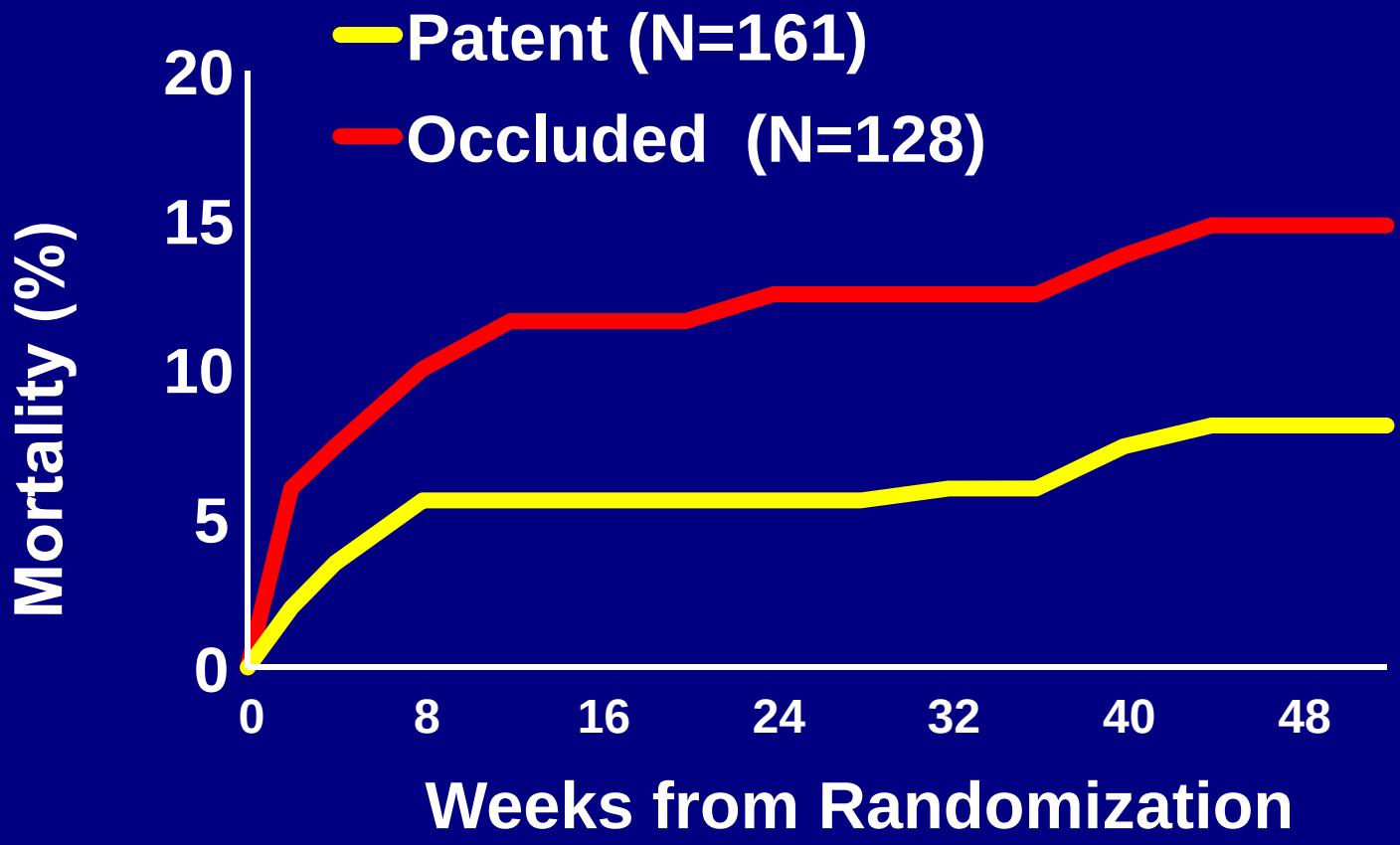
## Comparison of t-PA and Streptokinase




*P<0.0001

Braunwald E. NEJM 1985

# Impact of 90 Minute Patency on Mortality




Dalen J, Gore J, Braunwald E
Am J Cardiol 1988; 62:179-85

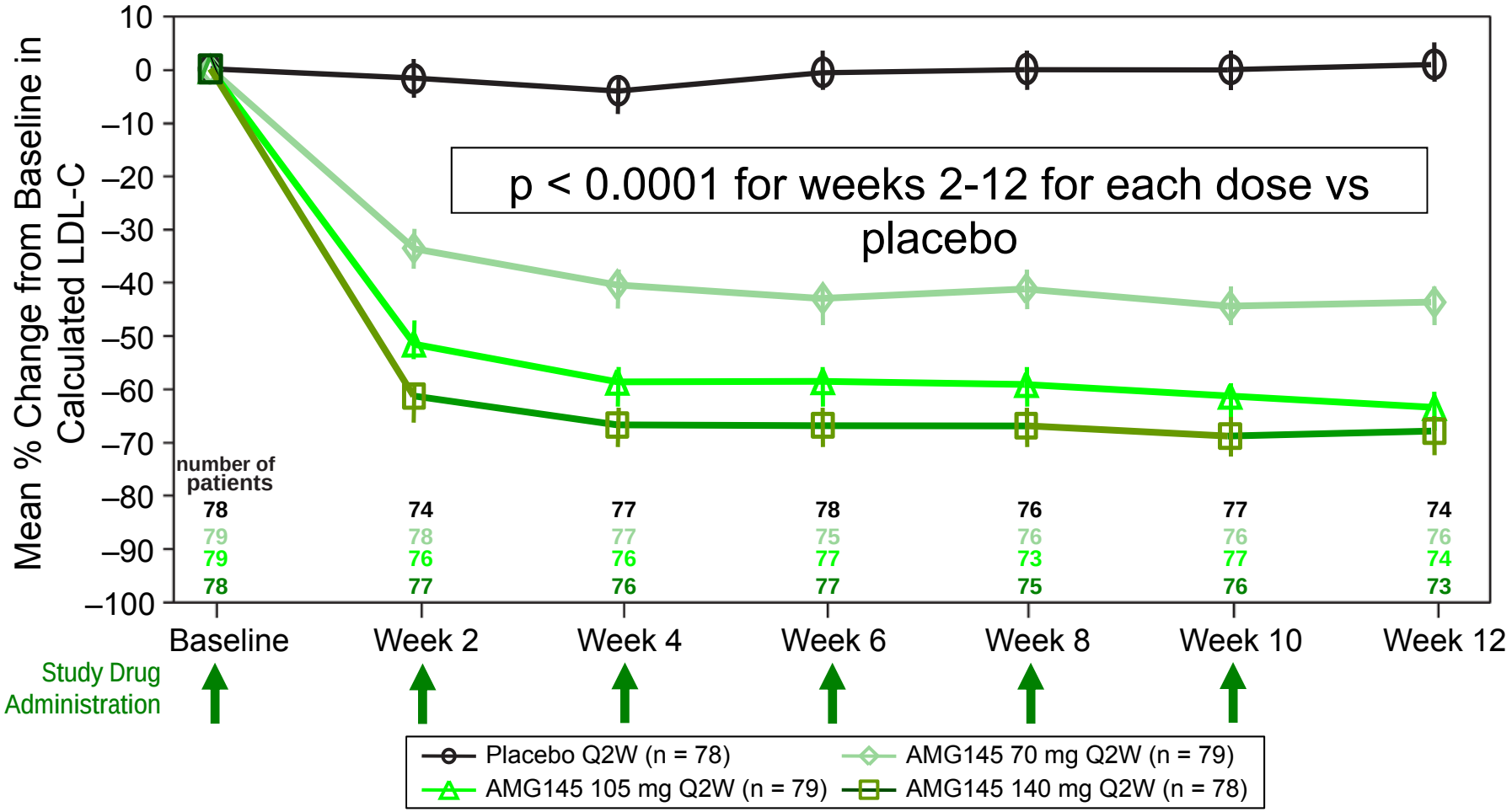
THE LANCET

# Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging phase 2 study

*Robert P Giugliano, Nihar R Desai, Payal Kohli, William J Rogers, Ransi Somaratne, Fannie Huang, Thomas Liu, Satishkumar Mohanavelu, Elaine B Hoffman, Shannon T McDonald, Timothy E Abrahamsen, Scott M Wasserman, Robert Scott, Marc S Sabatine, for the LAPLACE-TIMI 57 Investigators**

***Lancet* 2012:380:2007**

# AMG 145 Q2W Dose Response:
## % Change in LDL-C Through 12 Wks






LDL-C calculated using the Friedewald equation

# ONGOING TIMI TRIALS

| Trial | Population | Drug | # of Pts |
|---|---|---|---|
| ENGAGE-TIMI 48 | AF | Xa antagonist Edoxaban | 20,500 *** |
| IMPROVE-IT ▲ | Post ACS | Ezetimibe | 18,000 *** |
| SOLID –TIMI 52 | Post ACS | Lp-PLA2 antagonist Darapladib | 13,000 *** |
| SAVOR-TIMI 53 | Diabetes with CAD | DPP4 inhibitor Saxagliptin | 16,500 *** |
| PEGASUS - TIMI 54 | Post MI | $P2Y_{12}$ antagonist Ticagrelor | 21,000 ** |
| REVEAL hps 3 - TIMI 55 | Chronic CAD | CETP inhibitor Anacetrapib | 30,000 ** |

*** Enrollment complete, in F.U. ** Enrollment ongoing
▲ DCRI-TIMI Collaboration

# TAKE HOME MESSAGES (1)

- **Immense importance of medical school experience with inspiring mentor(s)**
- **Identify important problem; the question(s) you ask are of overriding importance.**

# TAKE HOME MESSAGES (2)

- **Requirements for a satisfying career in research:**
  - **Regard research as an end in itself – not a means to an end**
  - **Feel deeply the thrill of the chase and the joy of discovery, i.e. answering an important question**

# TAKE HOME MESSAGES (3)

- **Research is not a “one person show” but requires input from colleagues and trainees**
- **Critical importance of team building**