

# Heart Failure:

The Frequent, Forgotten and often  
Fatal Complication of Type 2  
Diabetes

DAVID S. H. BELL  
CHAIRMAN

BELL, DSH. DIABETES CARE(2003)26:2433-41.



# Speaker's Bureau:

AstraZeneca

Novo Nordisk

Janssen

# Etiology and Prevalence of Diabetic Heart Failure

David S. H. Bell  
MB, FACE, FRCP, FRCPS(Can), FRCP (Ed)

Professor of Medicine (Retired)  
University of Alabama  
Southside Endocrinology  
Birmingham, AL

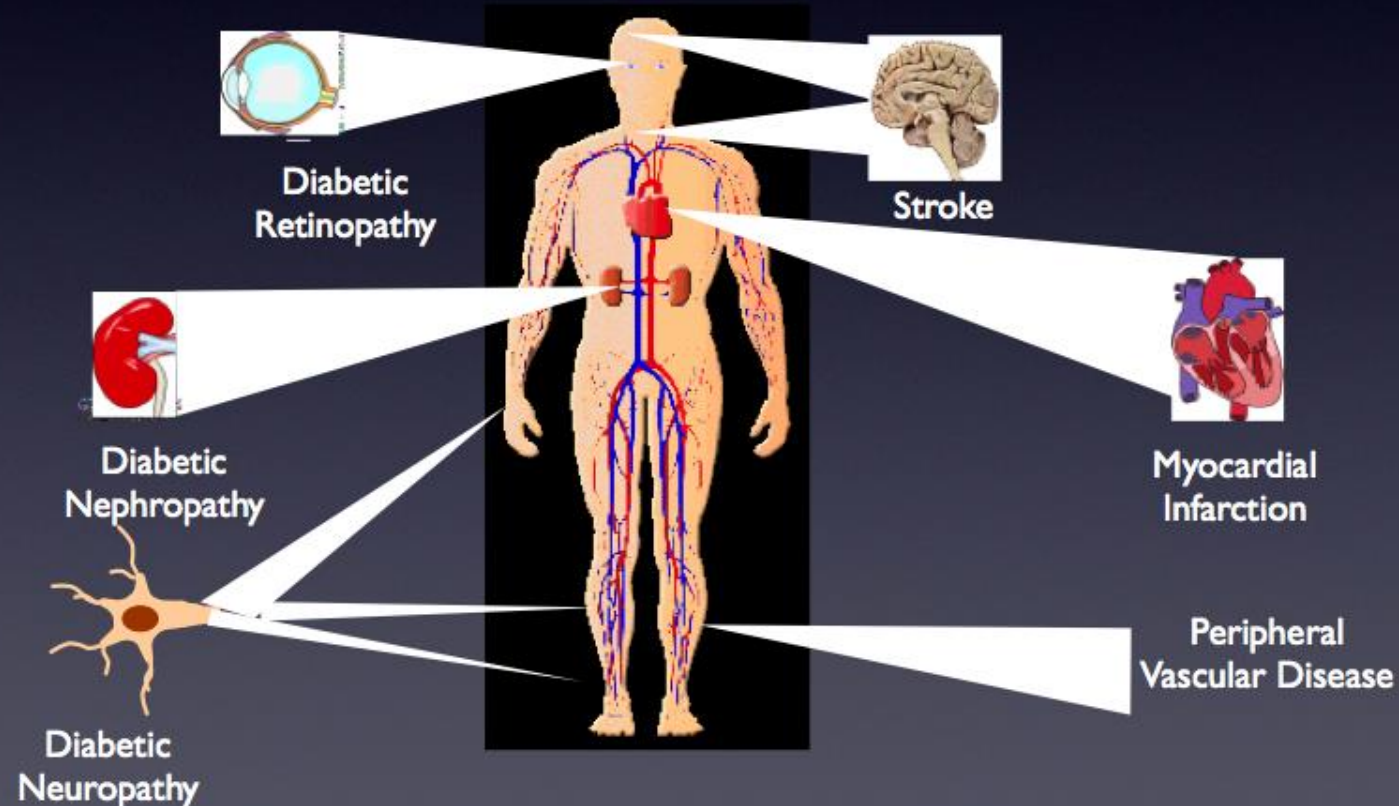
# Heart Failure

DAVID S.H. BELL, MB, FACE *Diabetes Care* 26:2433–2441, 2003

The frequent, forgotten, and often fatal complication of diabetes

## Microvascular

## Macrovascular

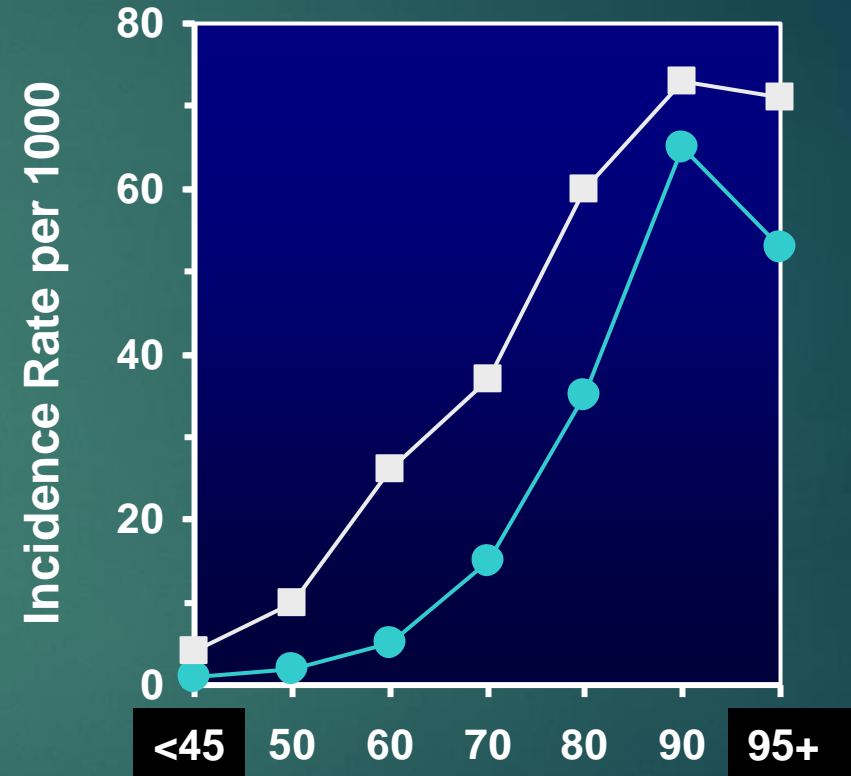
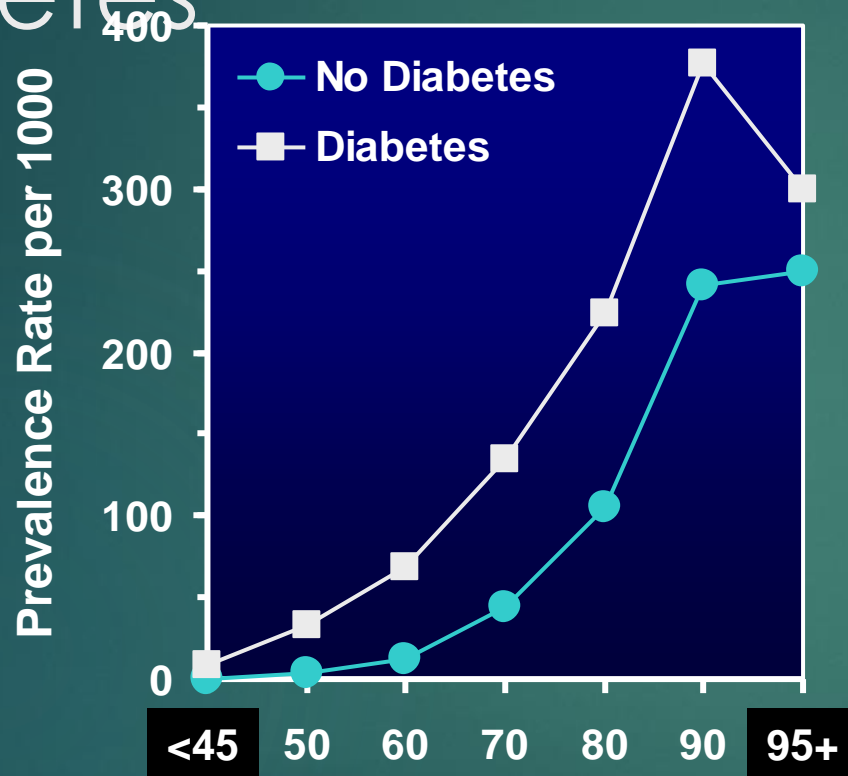


# The Rest of the Story?

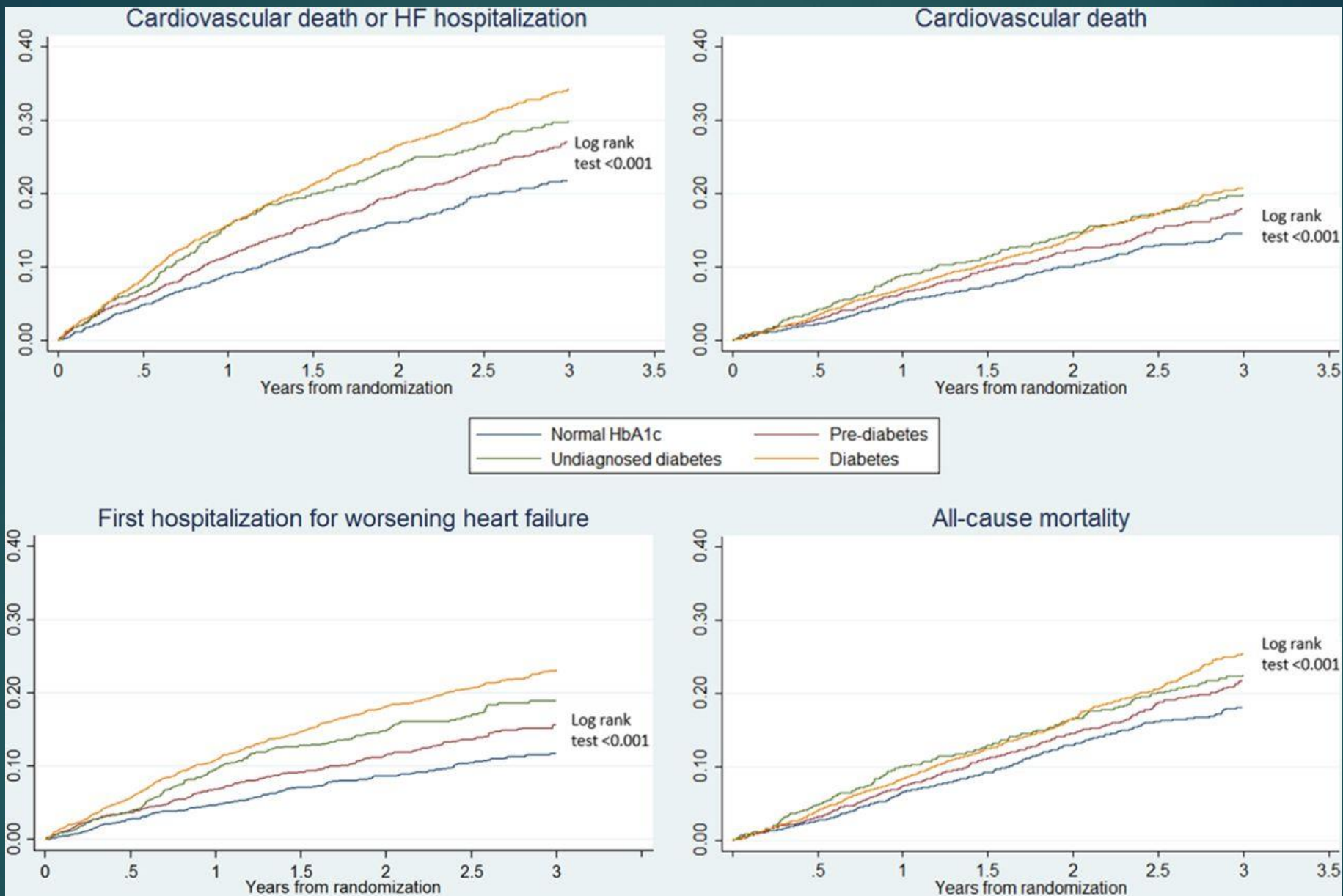
## Two CVD Disorders

- 1) Disorders of perfusion due to atherosclerosis
- 2) Disorders of cardiac structure and function due to LVH and LV dysfunction

# Congestive Heart Failure Is More Common in Patients With Type 2 Diabetes



Age at Baseline



## DIABETES STATUS AND OUTCOMES IN HEART FAILURE

# CHEMO-RELATED CARDIOTOXICITY

- ▶ 83 PATIENTS (54 BREAST, 20 LYMPHOMA, 9 GASTRIC)
- ▶ PRESENCE OF REDUCED E# AND GLOBAL LONGITUDINAL STRAIN IN DIABETIC SUBJECTS



# Cardiotoxic Triad

- ▶ Diabetic cardiomyopathy
- ▶ Hypertension
- ▶ Myocardial ischemia
  - ▶ Macrovascular
  - ▶ Microvascular
    - ▶ No lactate increase during atrial pacing
    - ▶ Endothelial dysfunction leading to vasoconstriction, reperfusion injury, and myocardial fibrosis
    - ▶ Endothelial dysfunction leading to vessel permeability and myocardial fibrosis

# Diabetic Cardiomyopathy

## 1) Diastolic Dysfunction

- 30% by Echo
- 52% - 60% using pulse waved doppler examinations during second stage of valsalva maneuver
- Frequency proportional to  $A_{1C}$
- Degree proportional to level of microalbuminuria

Redfield MM JAMA (2003) 289:194-202

Poirier P Diabetes Care (2001) 24:5-10

Devereux JB Circulation (2000) 101:2271-6

Liu JE J Am Coll Cardiol (2003) 42:2022-8

# MECHANISMS FOR DIABETIC CARDIOMYOPATHY (2)

## 4) BIOCHEMICAL

- Ca AND K CHANNELS
- Na/Ca EXCHANGERS
- Ca BINDING PROTEINS
- MITOCHONDRIAL Ca UNIPORTER

## 5) UPREGULATION OF RAS

## 6) OXIDATIVE STRESS

## 7) GLYCATION OF PROTEINS

## 8) ACTIVATION OF PKC

# MECHANISMS FOR DIABETIC CARDIOMYOPATHY (1)

- 1) ENDOTHELIAL DYSFUNCTION
- 2) AUTONOMIC NEUROPATHY
  - IMPAIRED VASODILATION TO SYMPATHETIC RESPONSE
  - IMPAIRED CONTRACTILITY

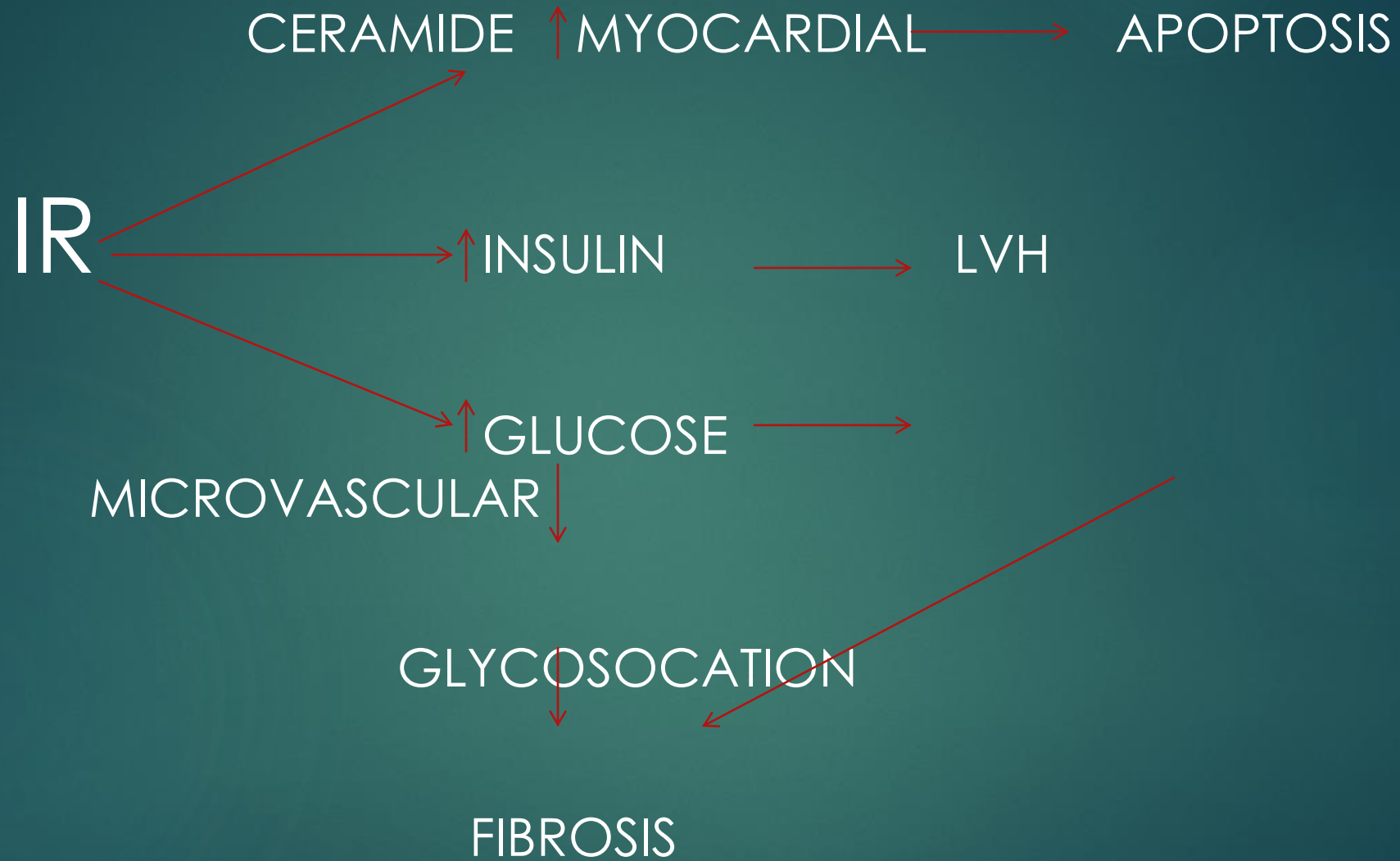
- 3) METABOLIC

- ↓ GLUCOSE LACTATE METABOLISM
- ENHANCED FFA METABOLISM

↓  
LIPID ACCUMULATION

↓  
LIPOTOXICITY

↓  
APOPTOSIS



PROPOSED ETIOLOGY OF DIABETIC CARDIOMYOPATHY

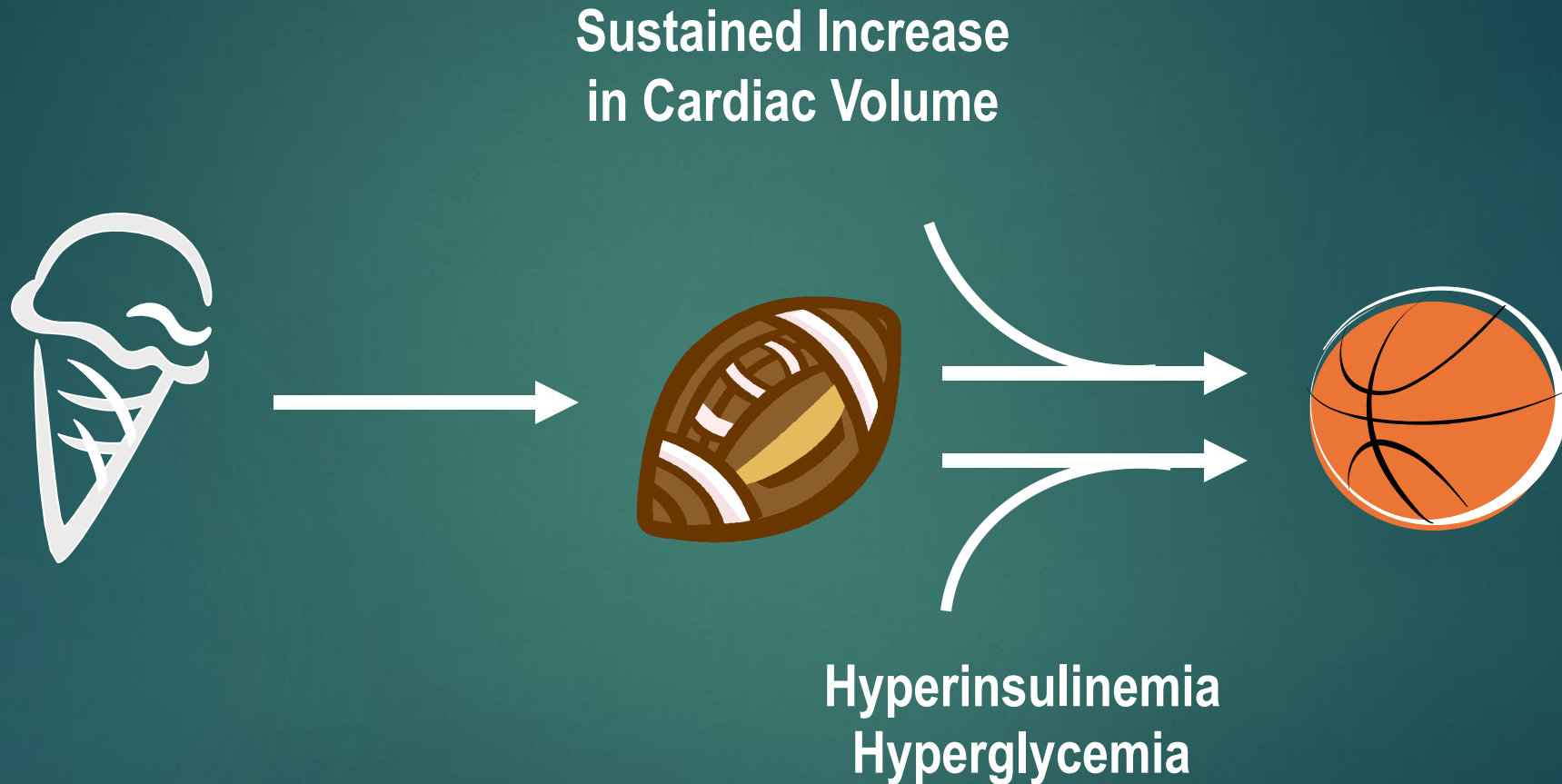
# LV Hypertrophy and Diabetes

- ▶ Framingham Study: Women with diabetes had a ventricular mass 22% greater than their nondiabetic peers<sup>1</sup>
- ▶ Tayside Study: LV hypertrophy present in 32% of normotensive patients with type 2 diabetes independent of CAD, ACEIs, or HTN<sup>2</sup>
- ▶ Echocardiographic study of 371 subjects with type 2 diabetes showed that 71% had LV hypertrophy<sup>3</sup>
- ▶ Relative risk of death in African Americans with<sup>\*,4</sup>:
  - ▶ LV hypertrophy: 2.4
  - ▶ LV systolic dysfunction (EF <45%): 2.0
  - ▶ Coronary artery disease: 1.6

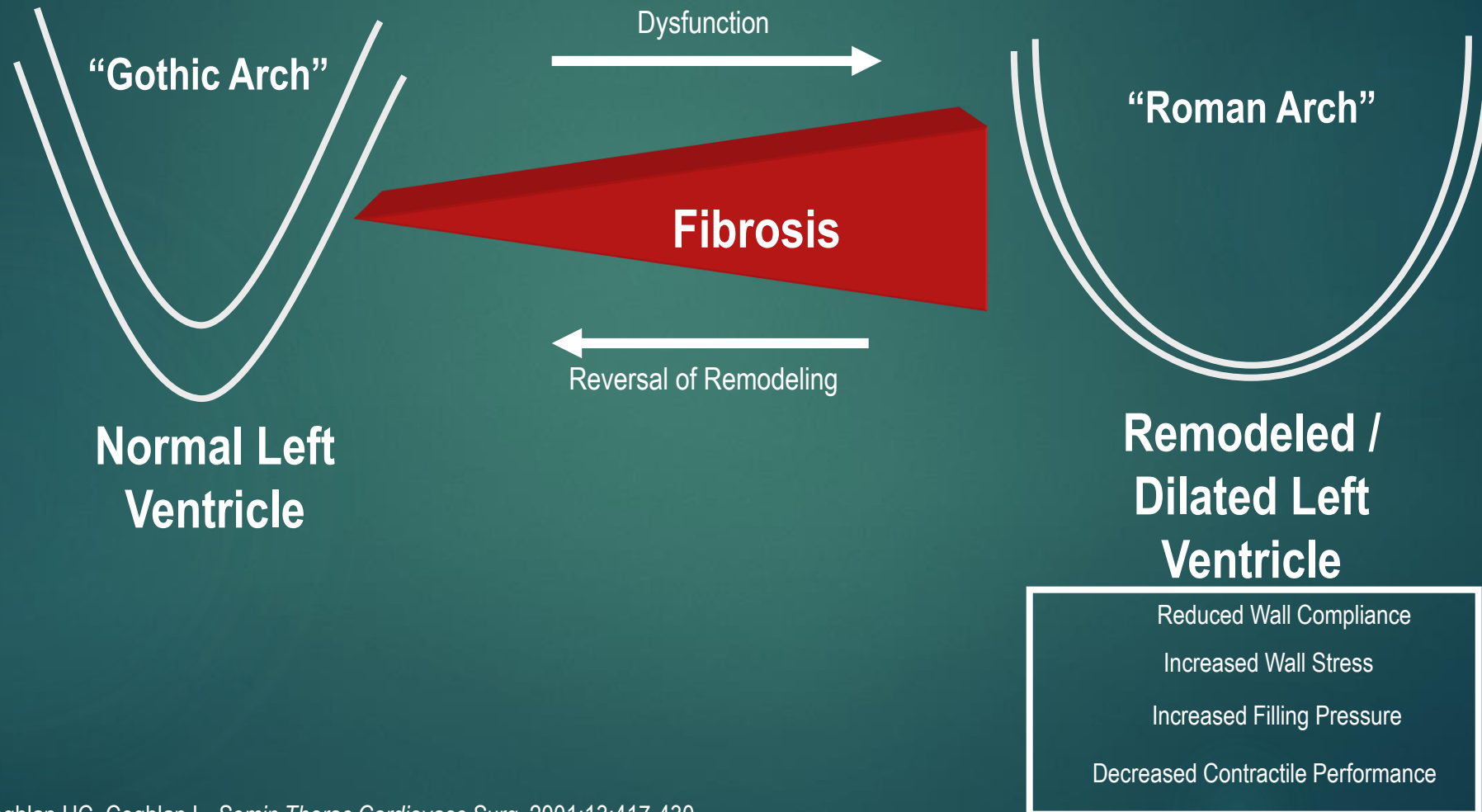
\*Based on cohort study from a hospital registry with a mean follow-up of 5 years. 26.1% of those studied had diabetes.

1. Galderisi M. *Am J Cardiol.* 1991;68:85–89. 2. Struthers AD. *Lancet.* 2002;359:1430–1432. 3. Dawson A et al. *Diabetologia.* 2005;48:1971–1979. 4. Liao Y. *JAMA.* 1995;273:1592–1597.

# Myocardial Remodeling

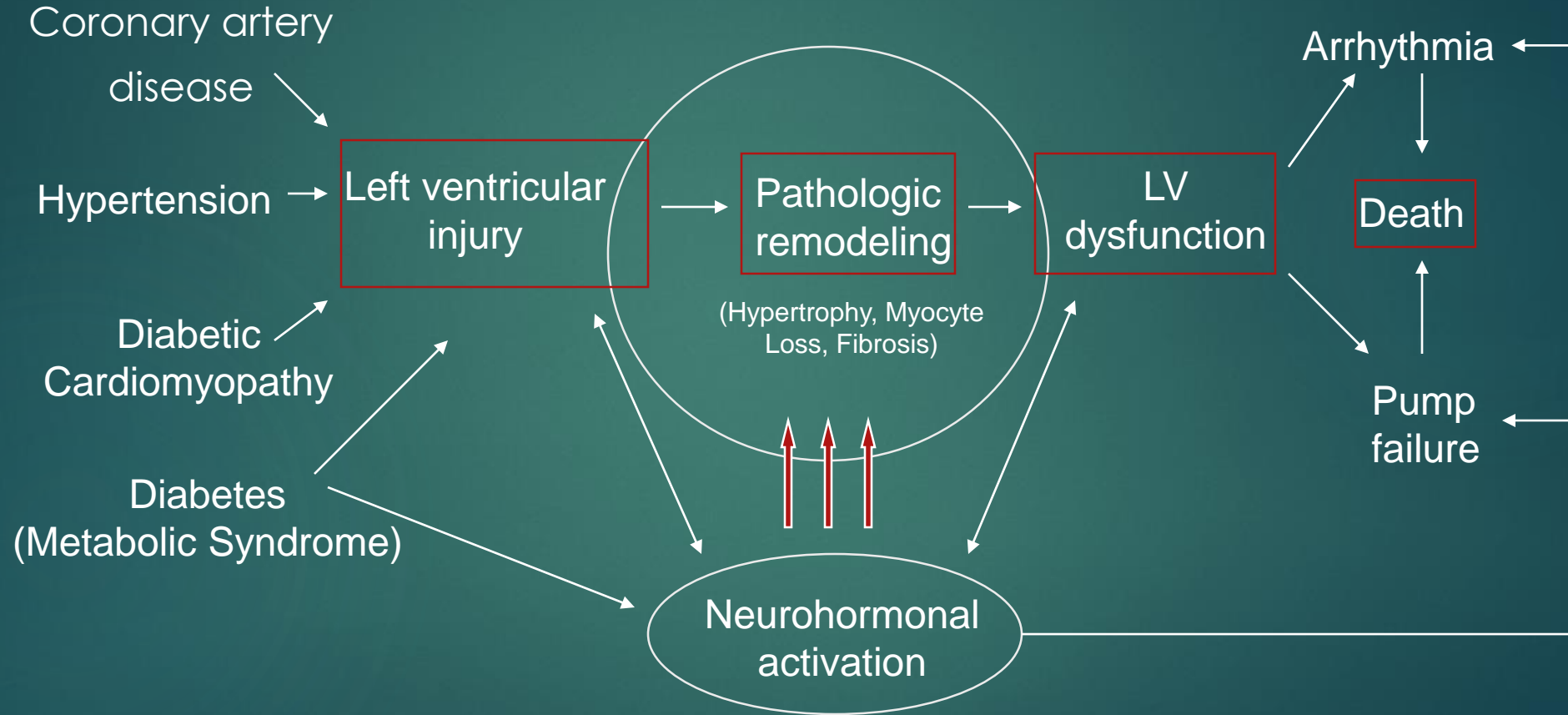


# Cardiac Remodeling





# Progression of Cardiovascular Disease

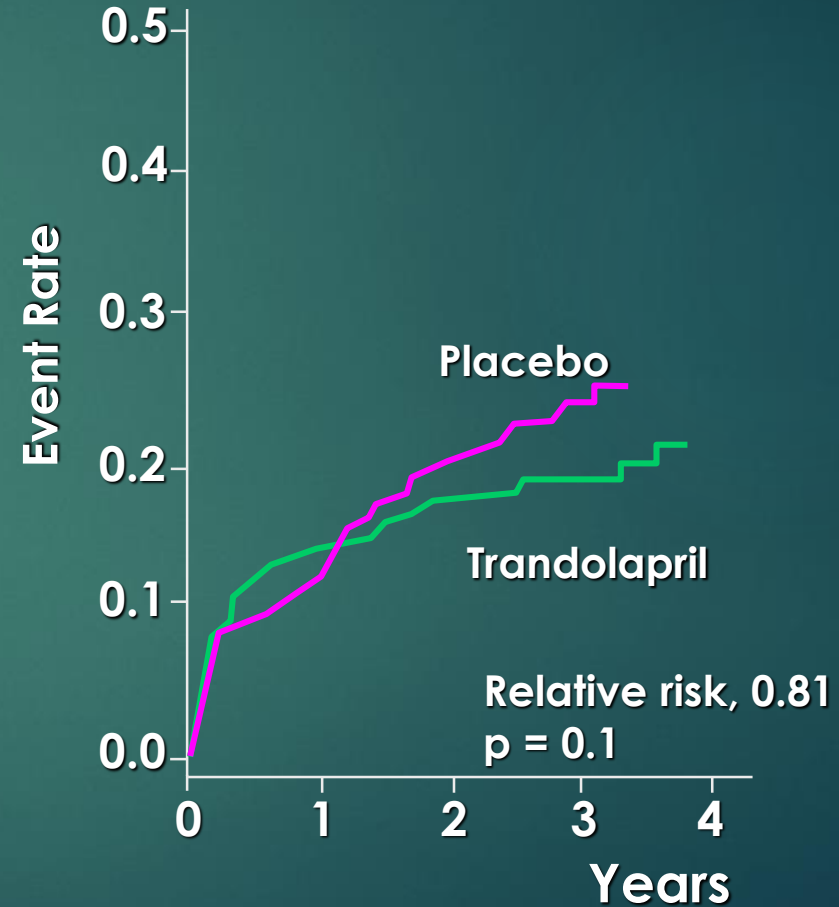
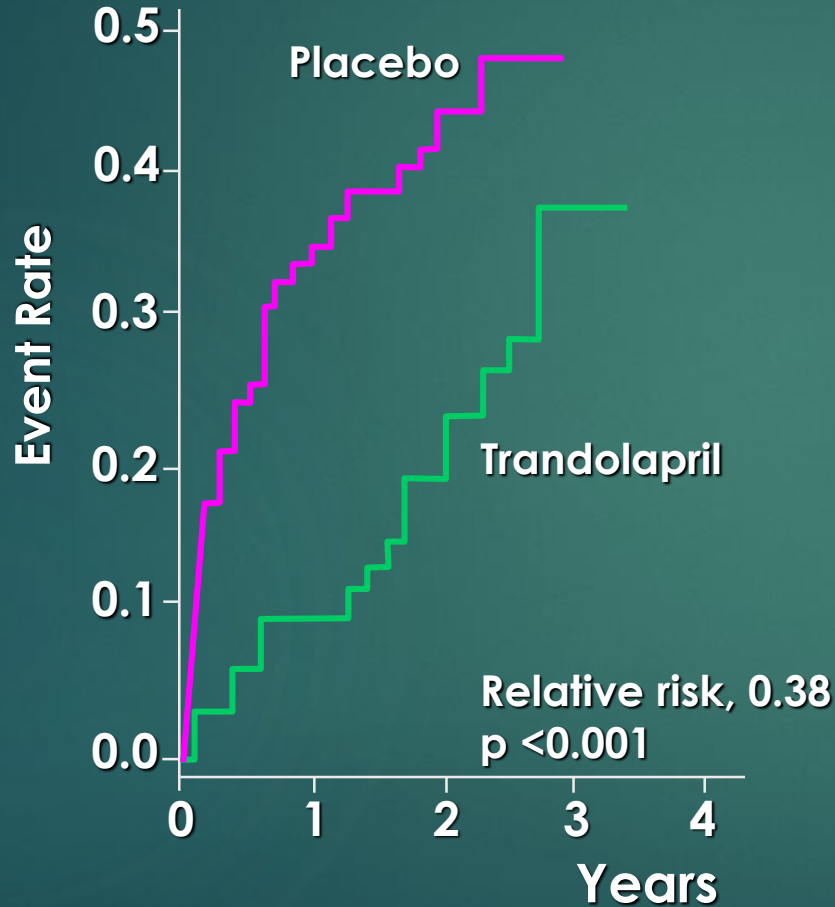


# TRACE: Effect of Trandolapril on CHF Progression after Acute MI

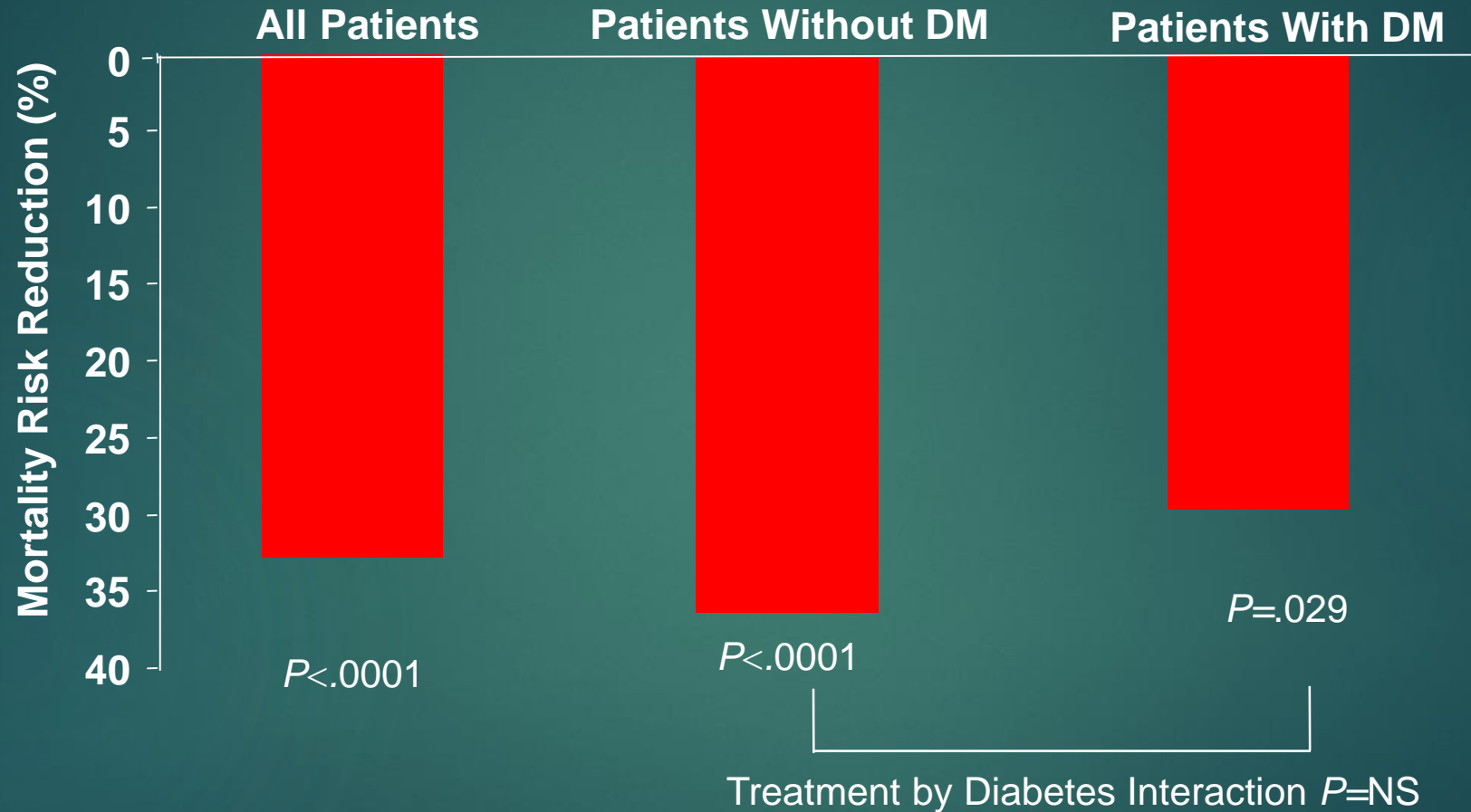


Diabetics

Non-Diabetics



# Meta-Analysis of COREG Placebo-Controlled Outcomes Trials (HF or Post-MI LVD): Mortality



Meta-analysis of trials include: US Carvedilol Trials, ANZ Heart Failure study, CAPRICORN, and COPENICUS.

All patients with LVD in these trials were included in the meta-analysis.

Bell DSH et al. *Curr Med Res Opin.* 2006;22:287–296.

# VALSARTAN/SACUBITRIL

- ▶ SUPPRESSION OF RAS
- ▶ SACUBITRIL INHIBITS NEUTRAL ENDOPETIDASE WHICH DEGRADES VASOACTIVE PEPTIDES (ANP, BNP)
- ▶ SUPPRESSION ENDOGENOUS COUNTER BALANCE TO RAS INHIBITION
- ▶ CONSISTENT REDUCTION OF HEART, WEIGHT AND CARDIAC FIBROSIS INDEPENDENT OF BP CONTROL
- ▶ REDUCES PROTEINURIA, RETINOPATHY IN DIABETIC SUBJECTS
- ▶ IN PARADIGM-HF TRIAL WITH REDUCED EF BETTER THAN ENALARIL FOR DECREASING MORTALITY AND HOSPITALIZATION FOR HF ACROSS THE HbA1c SPECTRUM

# TREATMENT EFFECTS OF SACUBITRIL/VALSARTAN VERSUS ACE INHIBITOR

	<u>RR</u>	<u>95% CI</u>
HF HOSP/CV DEATH	0.87	0.77-0.98
CV DEATH	0.92	0.77-1.09
HF HOSP	0.79	0.67-0.94
MORTALITY (ALL CAUSE)	0.97	0.83-1.14
CLINICAL SCORE	0.86	0.74-1.01

# HEART FAILURE normal EJECTION FRACTION (HFnEF)

- ▶ 40%-60% ADMISSIONS WITH HF
  - ▶ DIABETES 45%
- ▶ OTHER FACTORS AGE, FEMALE HYPERTENSION, OBESITY, AF, CAD

# Diastolic Dysfunction

- ▶ Documented in young diabetic patients, most of whom have type 1 DM
- ▶ 30% incidence on standard echocardiography
- ▶ With more rigorous Doppler methods, early diastolic dysfunction can be diagnosed
- ▶ Diastolic dysfunction seen in 52% of diabetic patients in Olmstead County, Minnesota
- ▶ Diastolic dysfunction seen in 60% of diabetic patients in Quebec, Canada
- ▶ Discharge diagnosis of idiopathic cardiomyopathy more common in the diabetic patient

## HPnEF

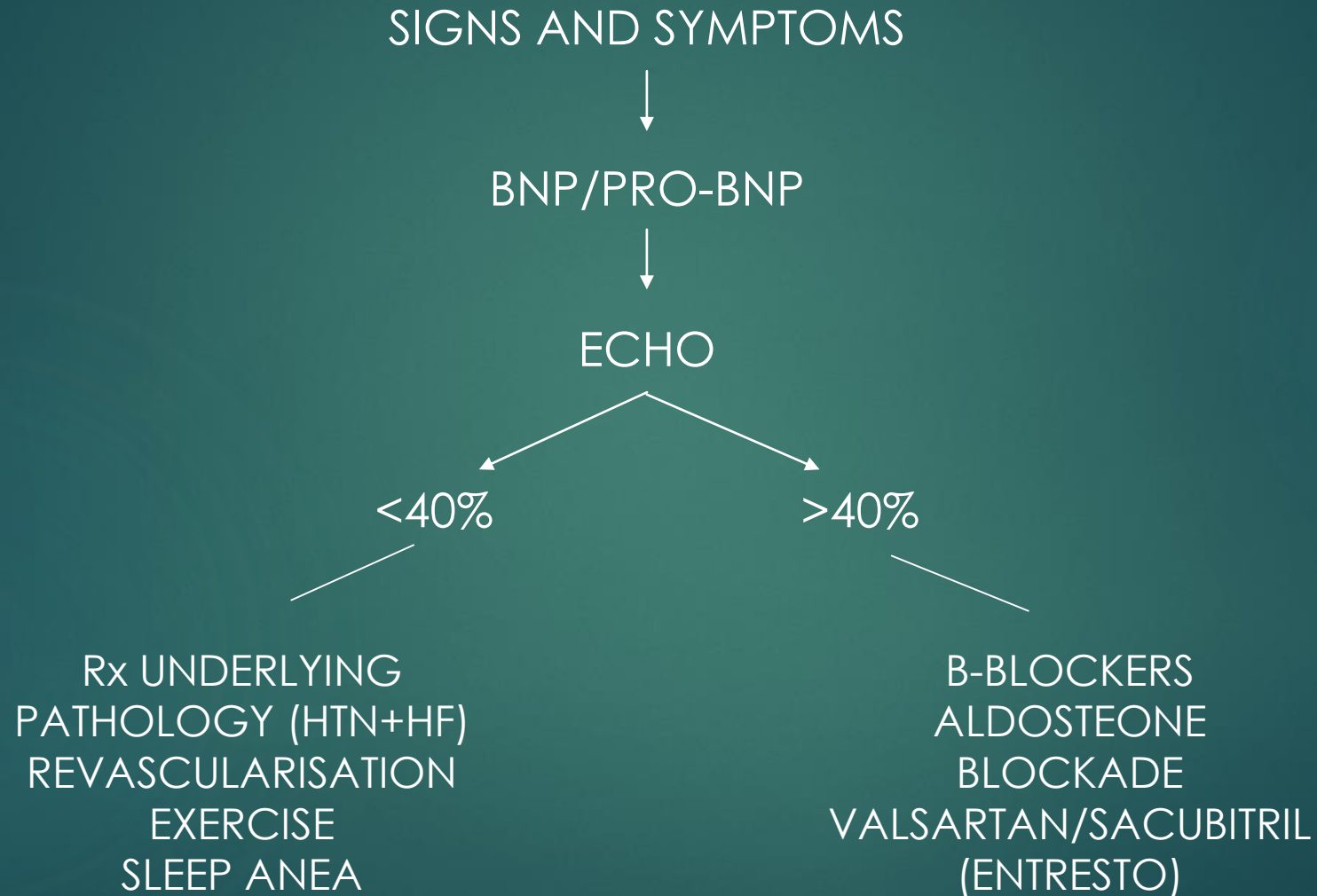
- 1) LARGE CLINICAL TRIALS HAVE NOT SHOWN LIMITED EVIDENCE OF CLINICAL BENEFIT
- 2) AGGRESSIVE MANAGEMENT OF CONTRIBUTING FACTORS – HTN, AF, MYOCARDIAL ISCHEMIA AND SLEEP APNEA BENEFICIAL
- 3) DIURETICS TO IMPROVE DYSPNEA
- 4) AVOID UNBENEFICIAL THERAPIES
- 5) SALT AND WATER RESTRICTON, EXERCISE



# LOWERING LEFT ATRIAL PRESSURE IN HF<sub>n</sub>EF (1)

- 1) THERAPEUTIC OPTIONS LIMITED
- 2) INCREASED LEFT ATRIAL PRESSURE ESPECIALLY DURING EXERCISE IS A KEY CONTRIBUTOR TO SYMPTOMS
- 3) 8 mm PERMANENT SHUNT IN ATRIAL SEPTUM TO LOWER LEFT ATRIAL PRESSURE
- 4) AT 30 DAYS LV FILLING PRESSURE REDUCED FROM 19.7 TO 14.2 mmHg (p=0.005)
- 5) NYHA CLASS IMPROVED IN 63.6% OF SUBJECTS
- 6) NO PULMONARY HYPERTENSION

# DIAGNOSIS AND Rx OF DIABETIC HF



THE END

???

