

Heart Failure:

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

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CHAIRMAN

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



Speaker's Bureau:

AstraZeneca

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Etiology and Prevalence of Diabetic Heart Failure

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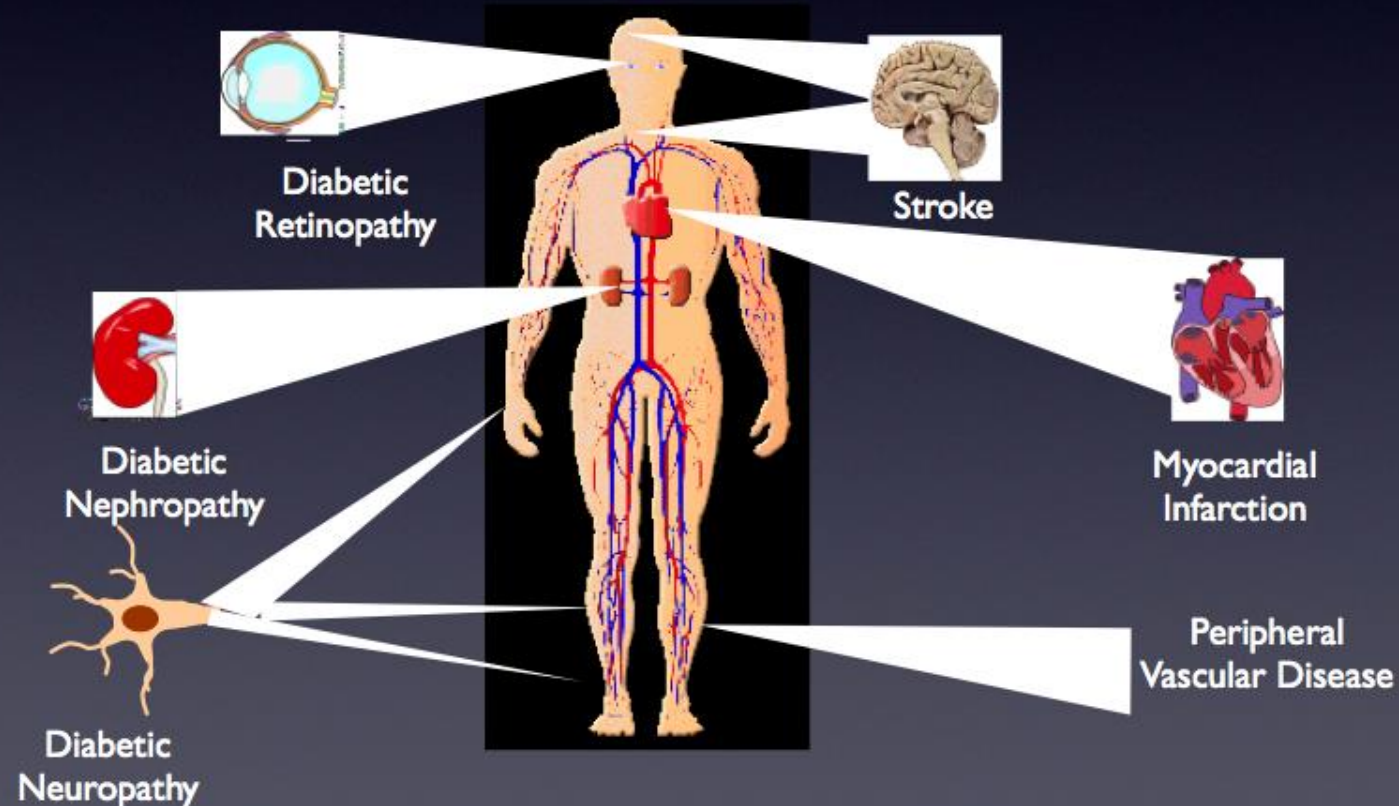
Heart Failure

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

The frequent, forgotten, and often fatal complication of diabetes

Microvascular

Macrovascular

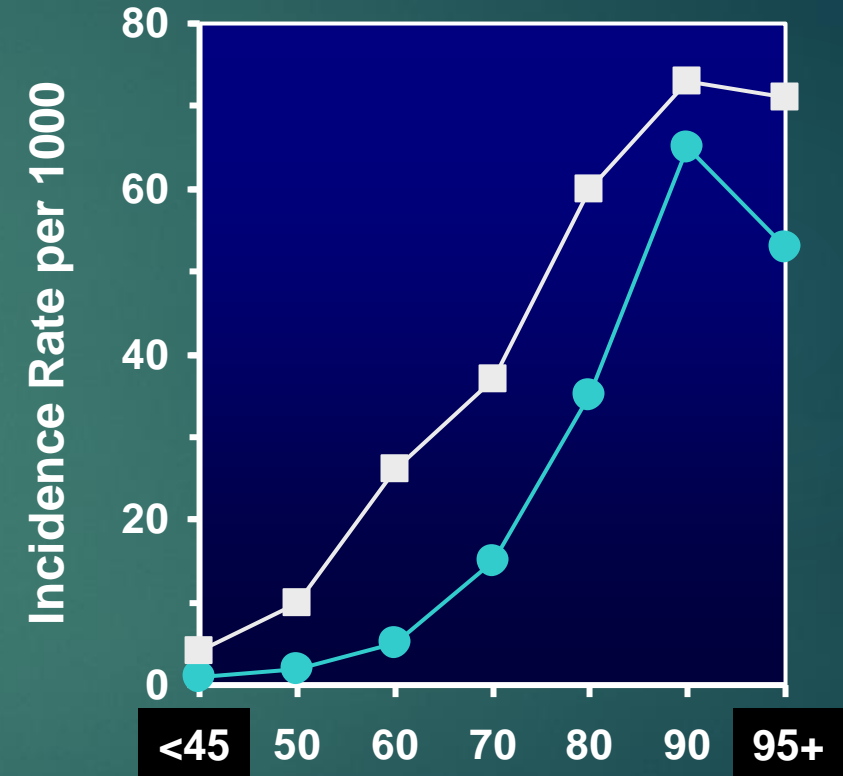
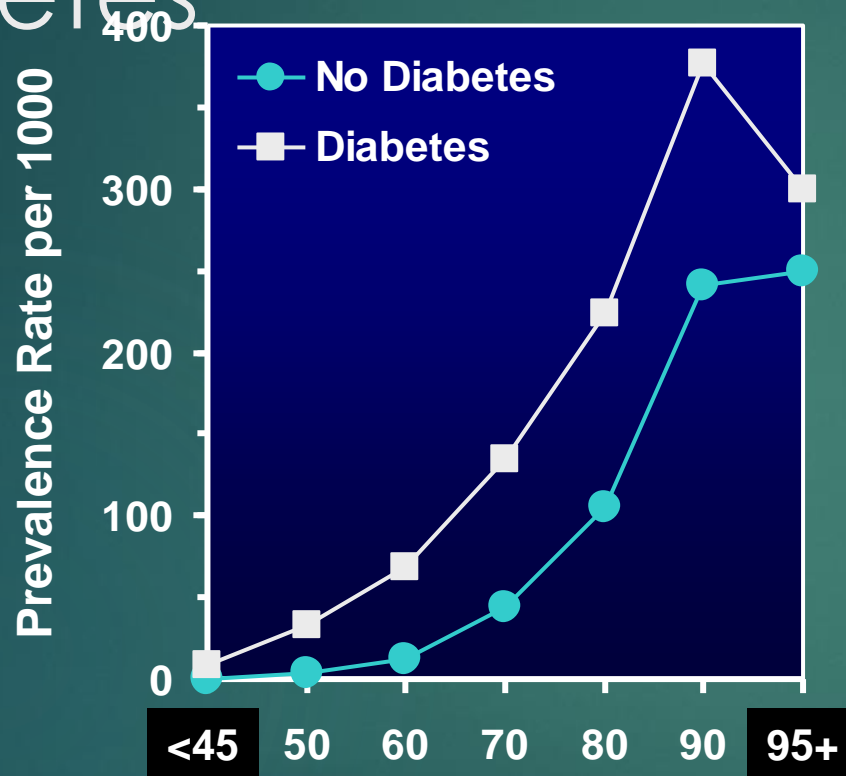


The Rest of the Story?

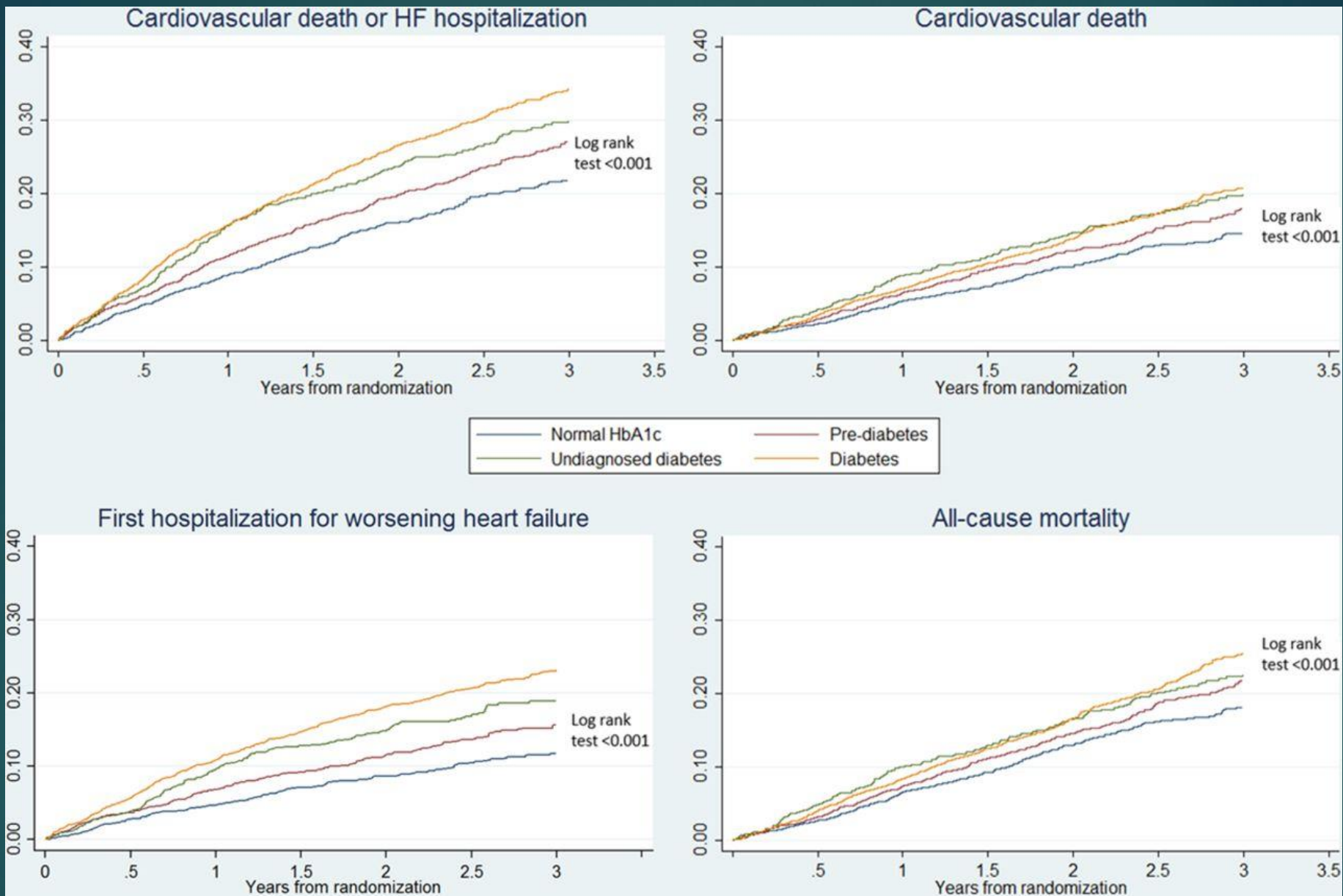
Two CVD Disorders

- 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)

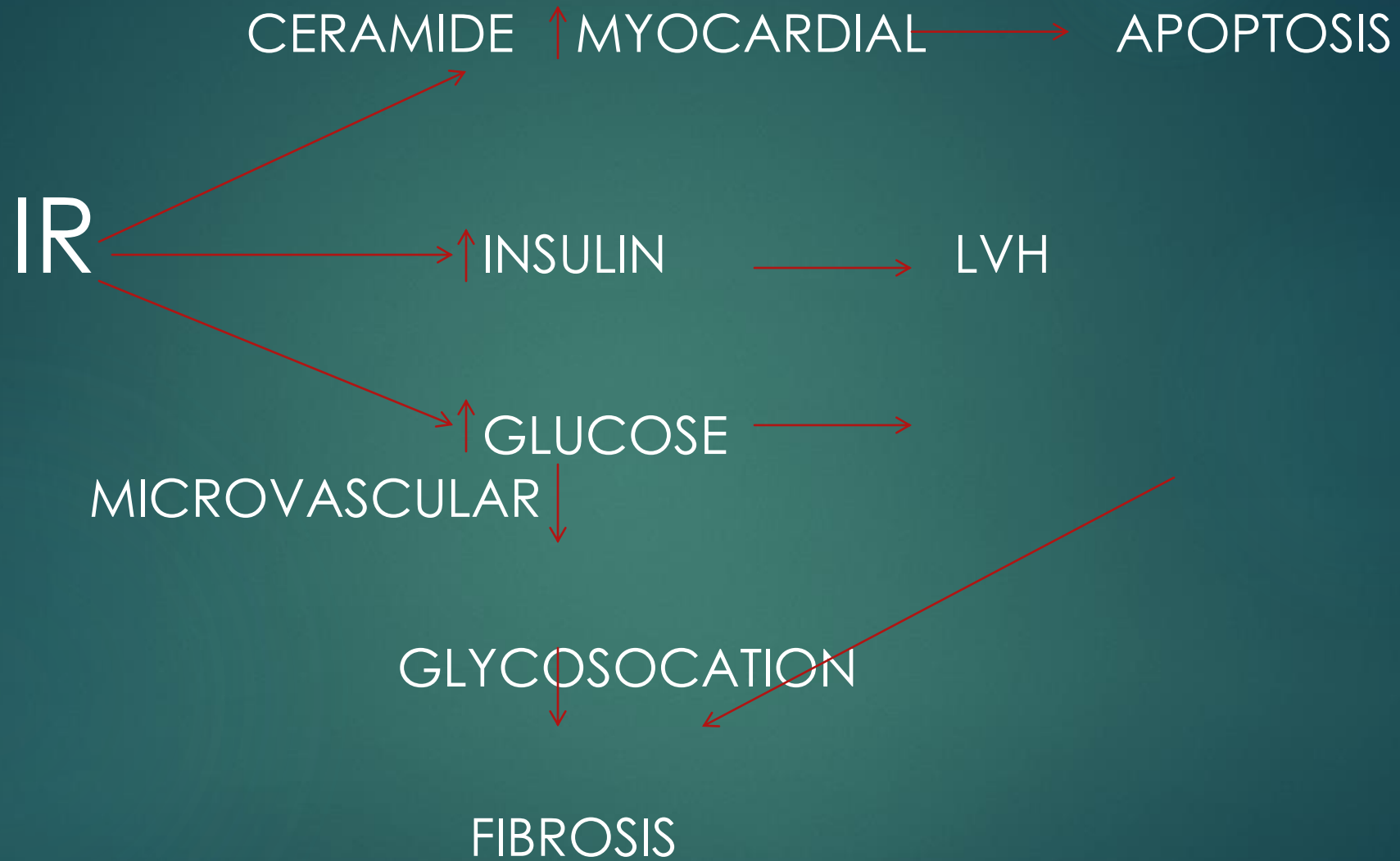
- 1) ENDOTHELIAL DYSFUNCTION
- 2) AUTONOMIC NEUROPATHY
 - IMPAIRED VASODILATION TO SYMPATHETIC RESPONSE
 - IMPAIRED CONTRACTILITY

- 3) METABOLIC
 - ↓ GLUCOSE LACTATE METABOLISM
 - ENHANCED FFA METABOLISM

↓
LIPID ACCUMULATION

↓
LIPOTOXICITY

↓
APOPTOSIS



PROPOSED ETIOLOGY OF DIABETIC CARDIOMYOPATHY

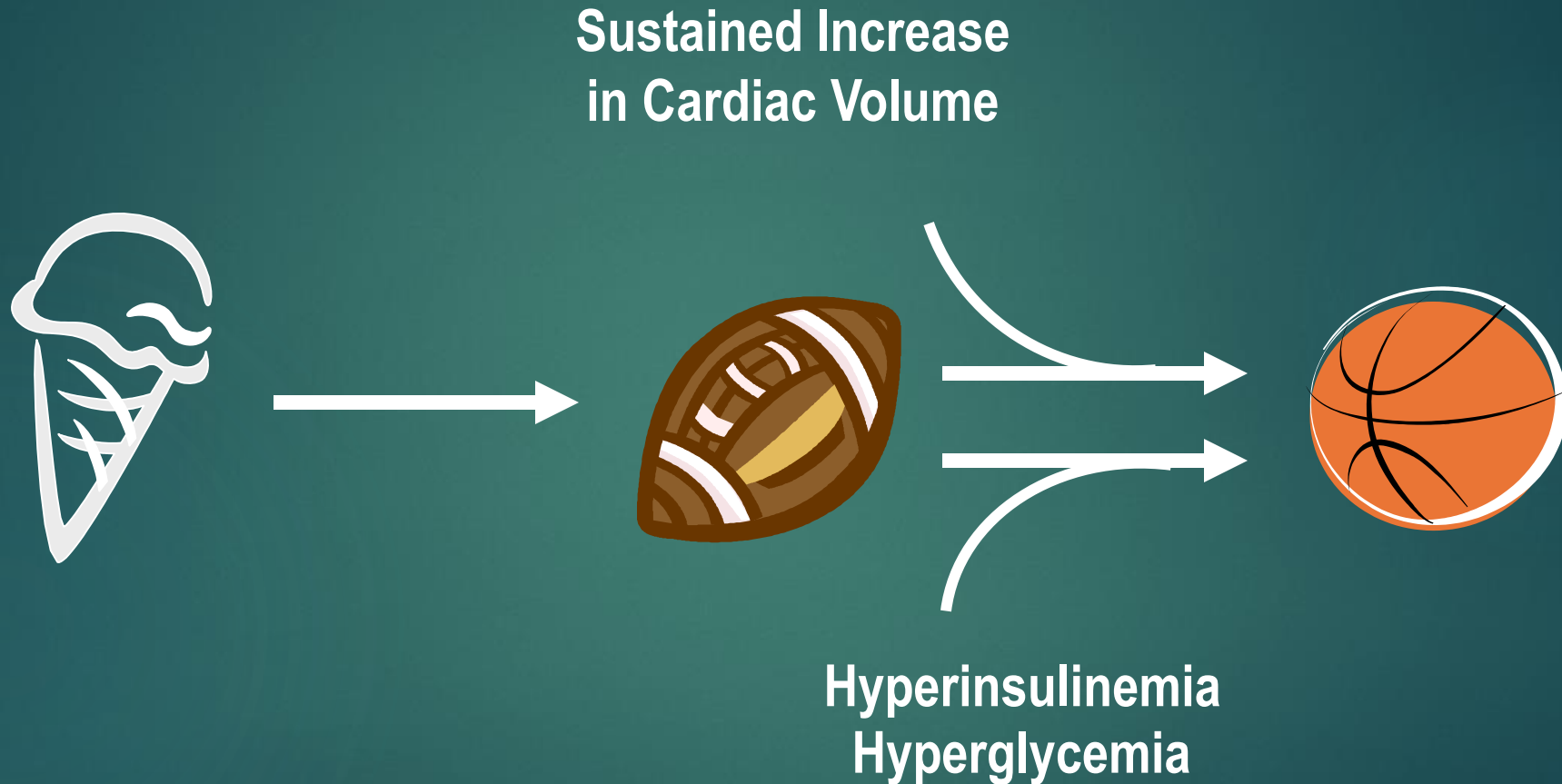
LV Hypertrophy and Diabetes

- ▶ Framingham Study: Women with diabetes had a ventricular mass 22% greater than their nondiabetic peers¹
- ▶ Tayside Study: LV hypertrophy present in 32% of normotensive patients with type 2 diabetes independent of CAD, ACEIs, or HTN²
- ▶ Echocardiographic study of 371 subjects with type 2 diabetes showed that 71% had LV hypertrophy³
- ▶ Relative risk of death in African Americans with^{*,4}:
 - ▶ LV hypertrophy: 2.4
 - ▶ LV systolic dysfunction (EF <45%): 2.0
 - ▶ Coronary artery disease: 1.6

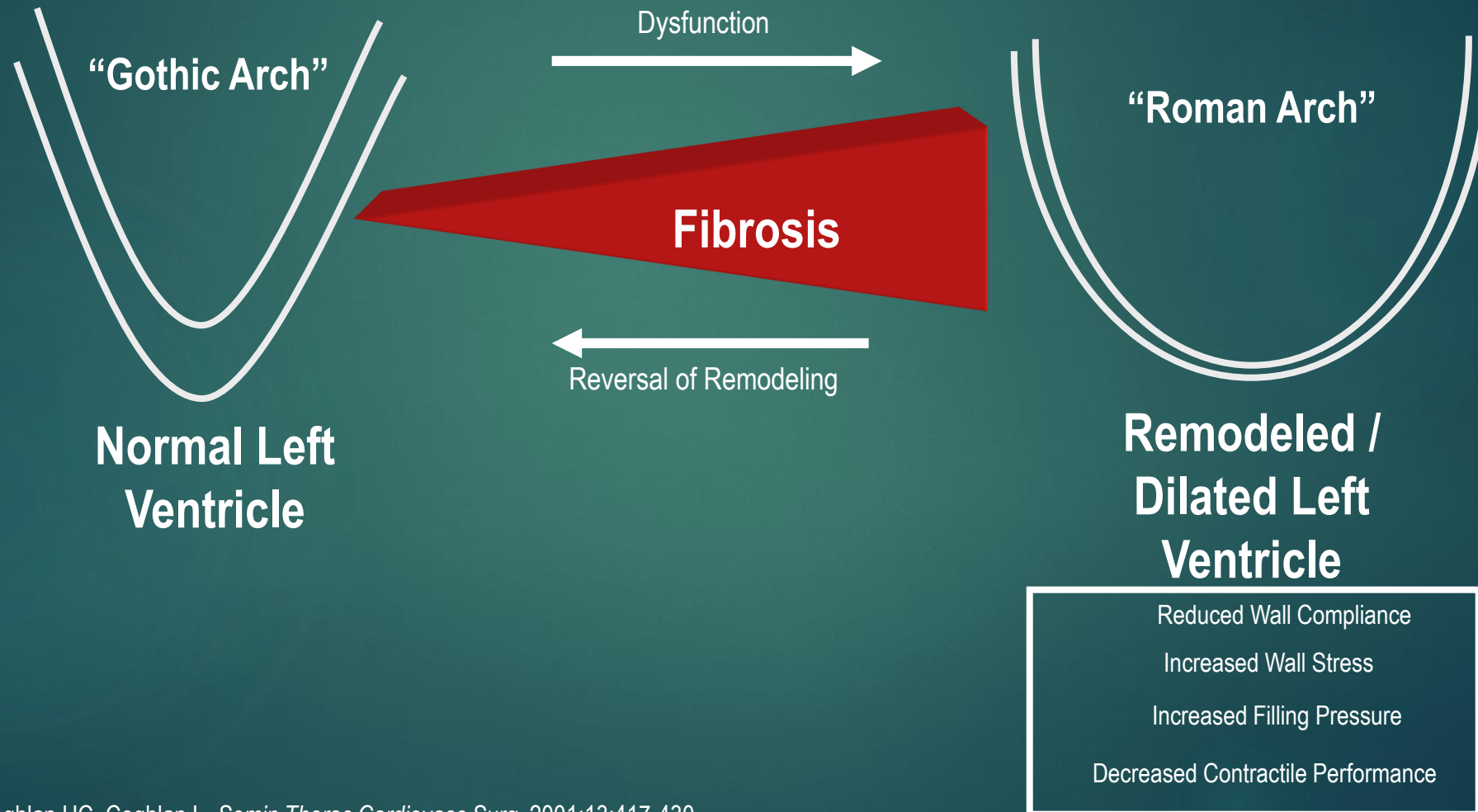
*Based on cohort study from a hospital registry with a mean follow-up of 5 years. 26.1% of those studied had diabetes.

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.

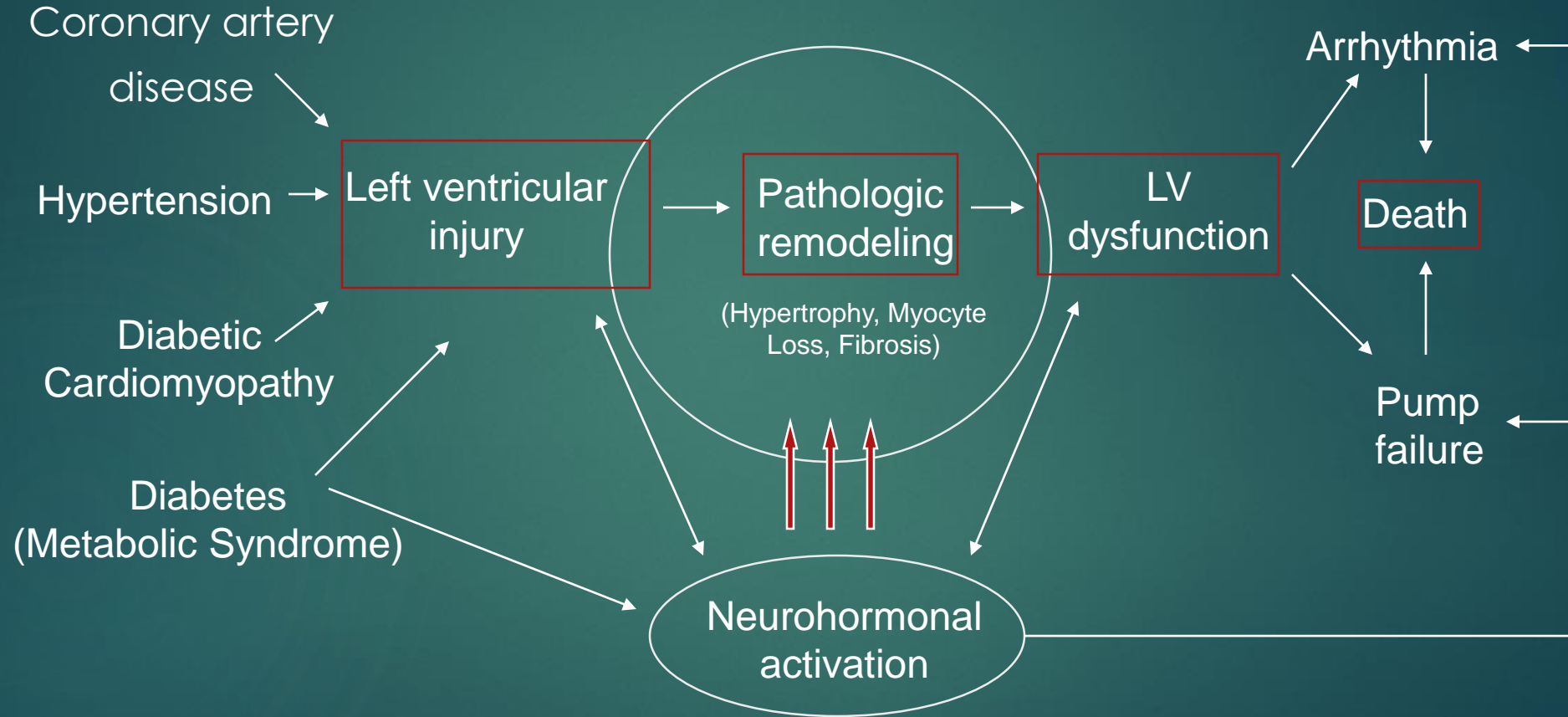
Myocardial Remodeling



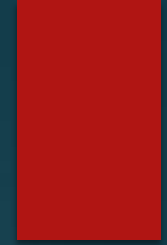
Cardiac Remodeling



Progression of Cardiovascular Disease

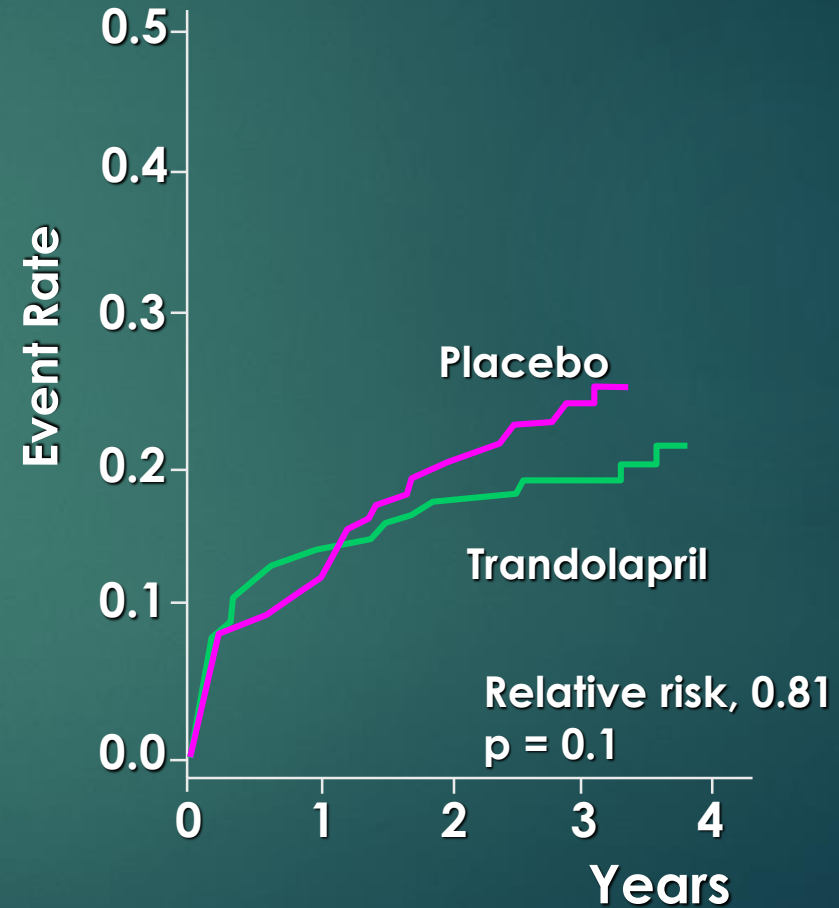
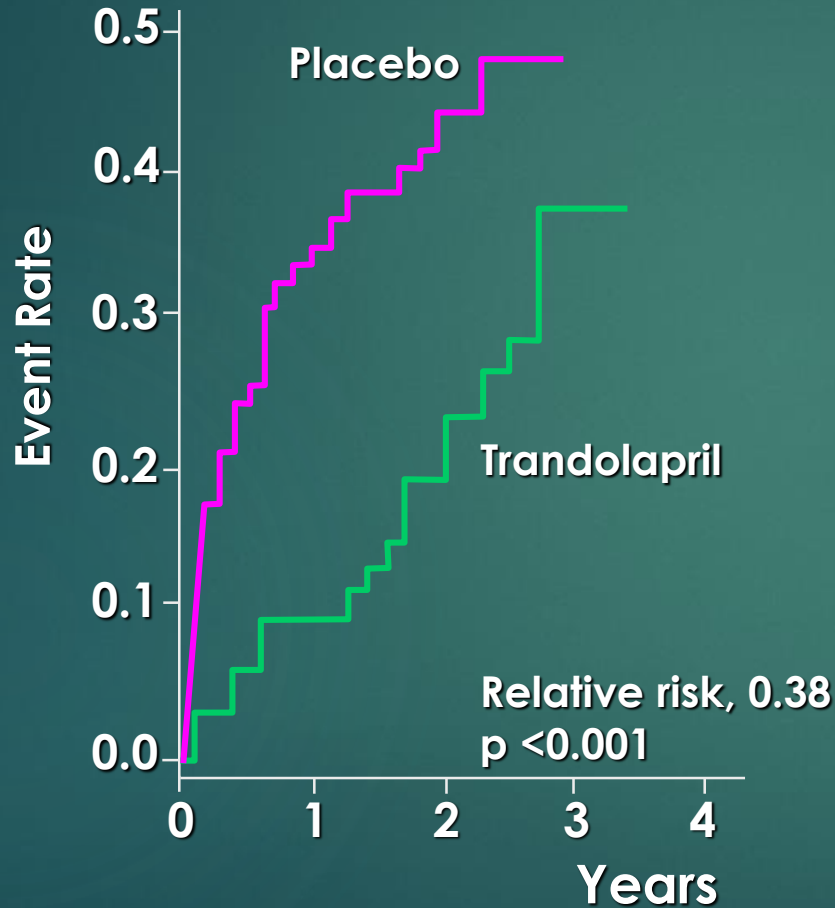


TRACE: Effect of Trandolapril on CHF Progression after Acute MI

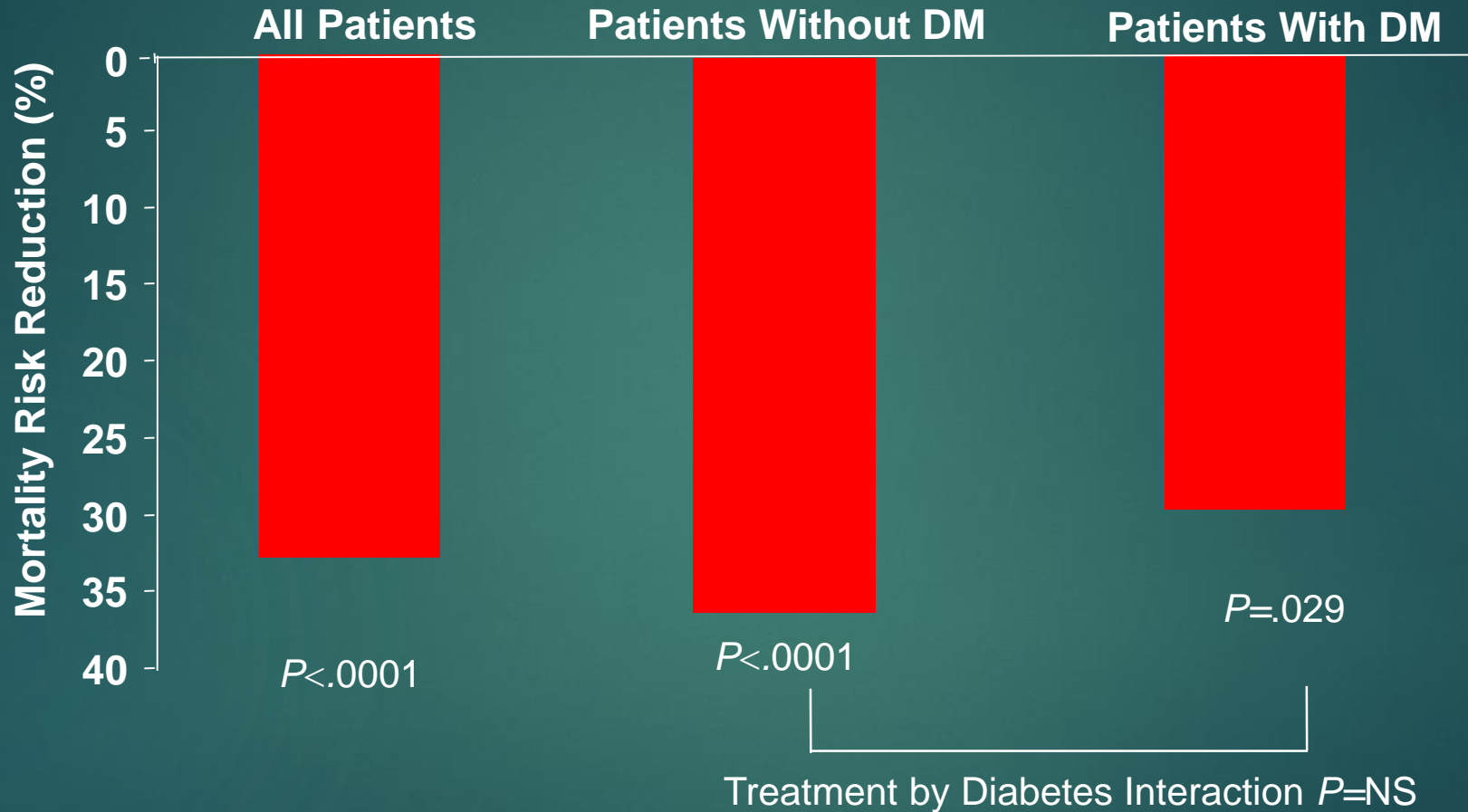


Diabetics

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

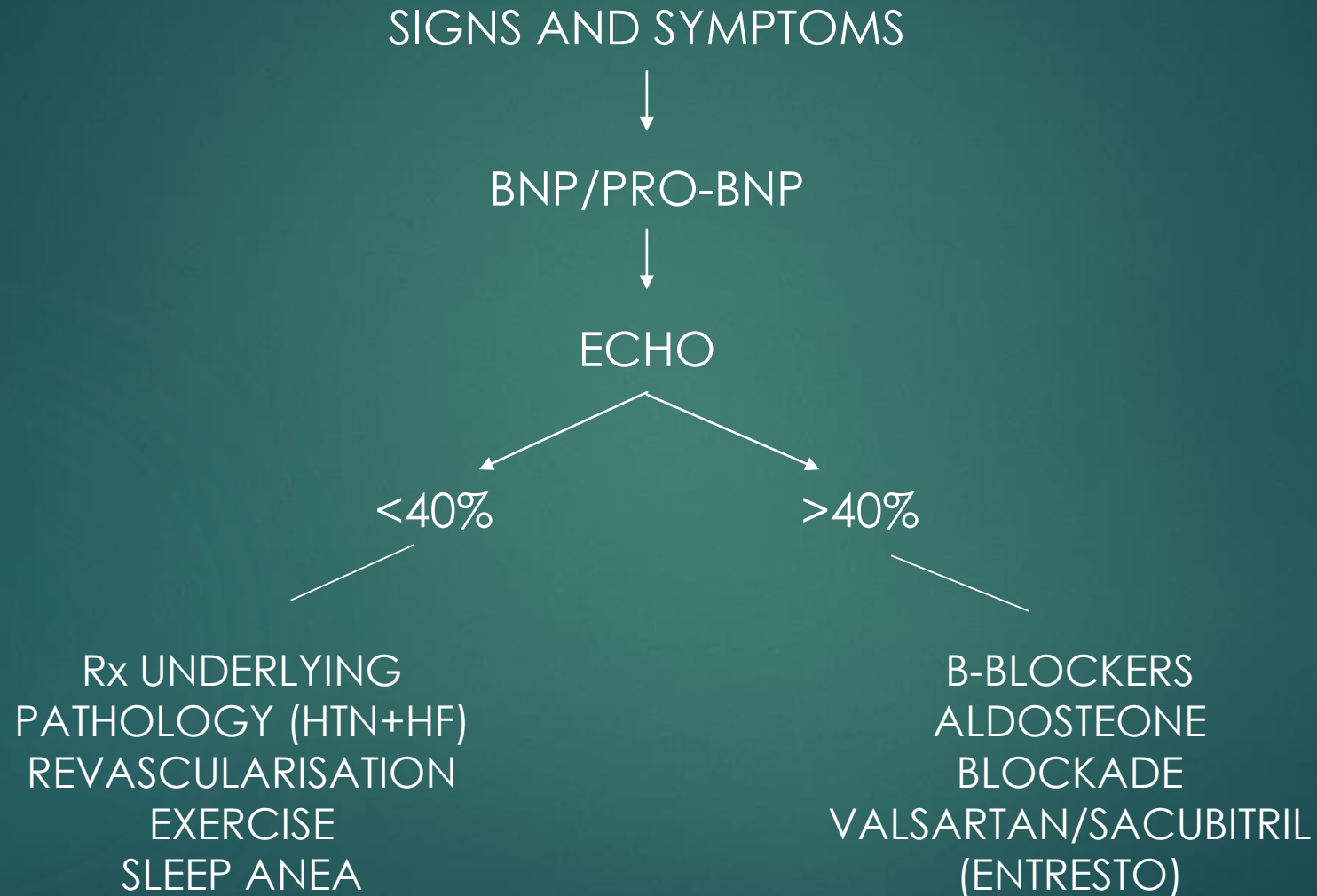
HPnEF

- 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_nEF (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

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