

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

Novo Nordisk

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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



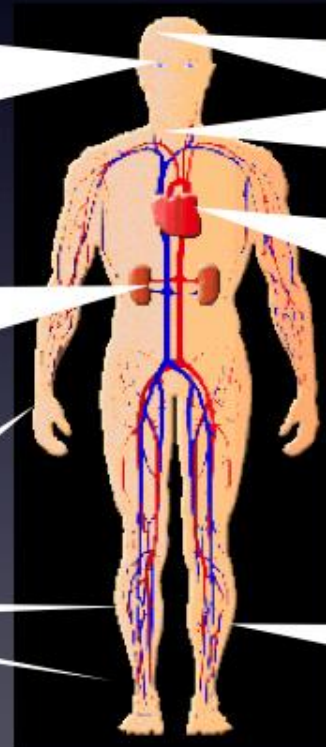
Diabetic Retinopathy



Diabetic Nephropathy



Diabetic Neuropathy



Macrovascular



Stroke



Myocardial Infarction

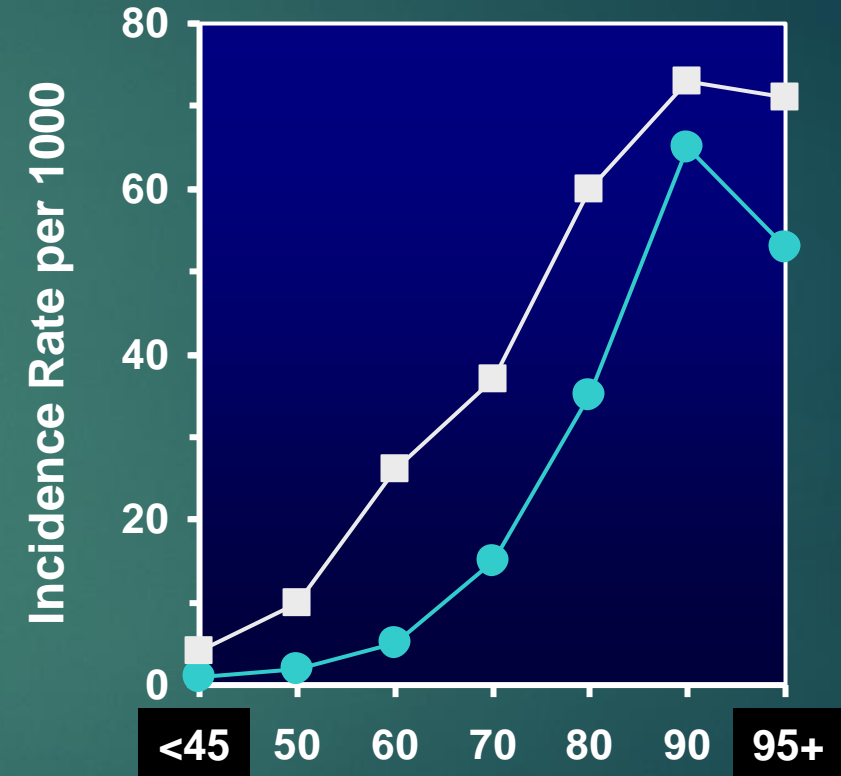
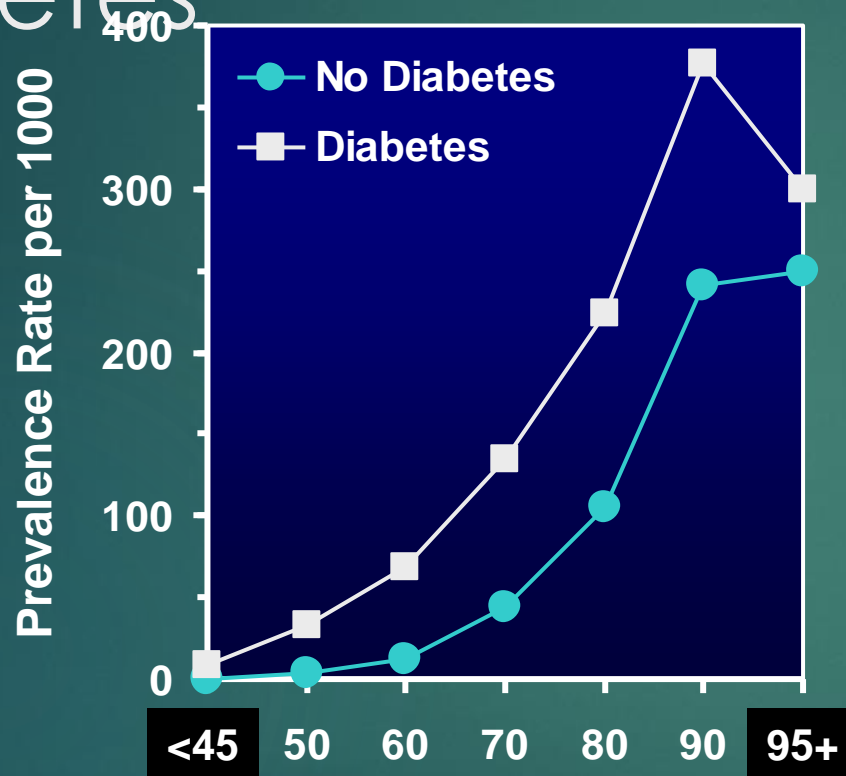
Peripheral Vascular Disease

The Rest of the Story?

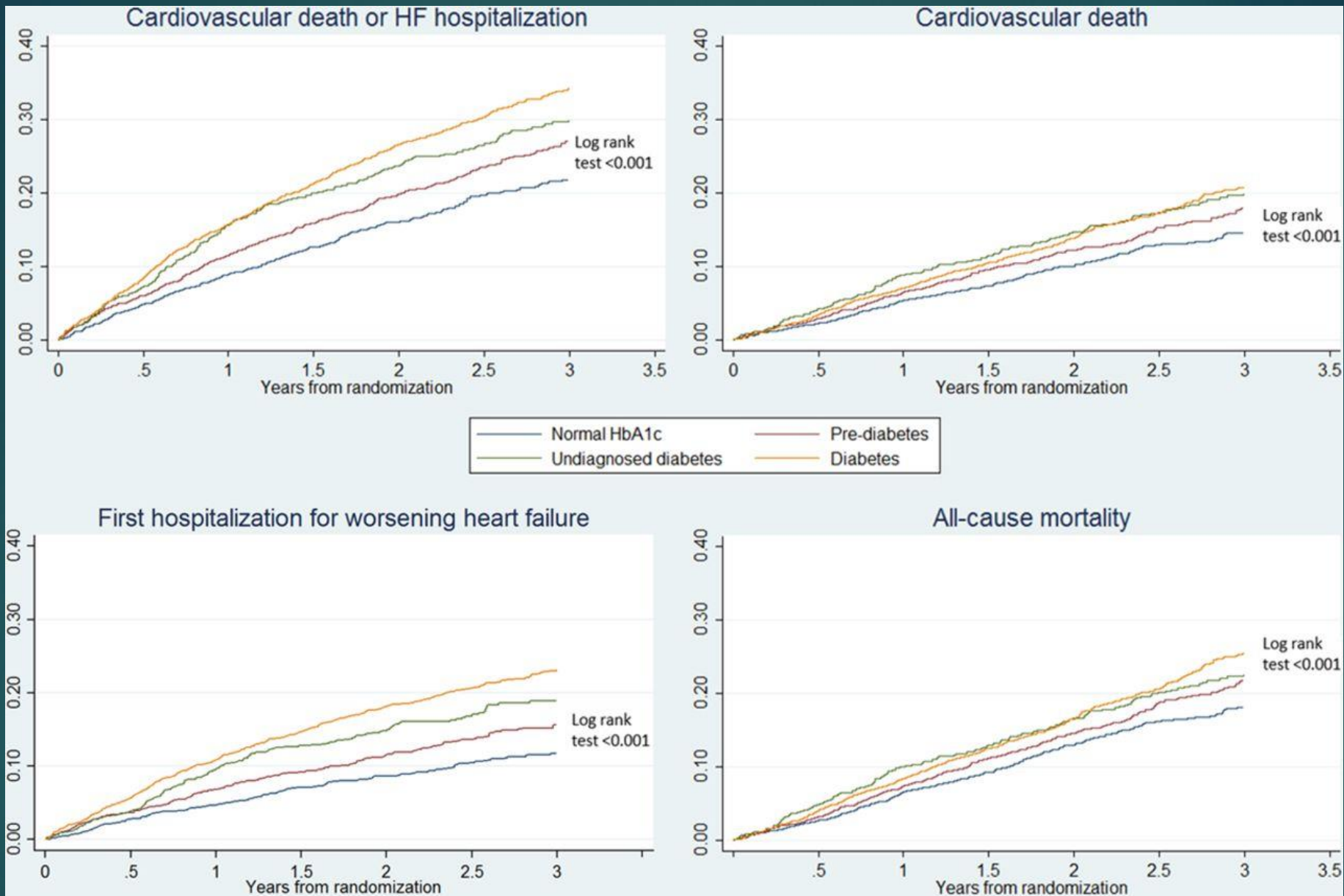
Two CVD Disorders

- 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)

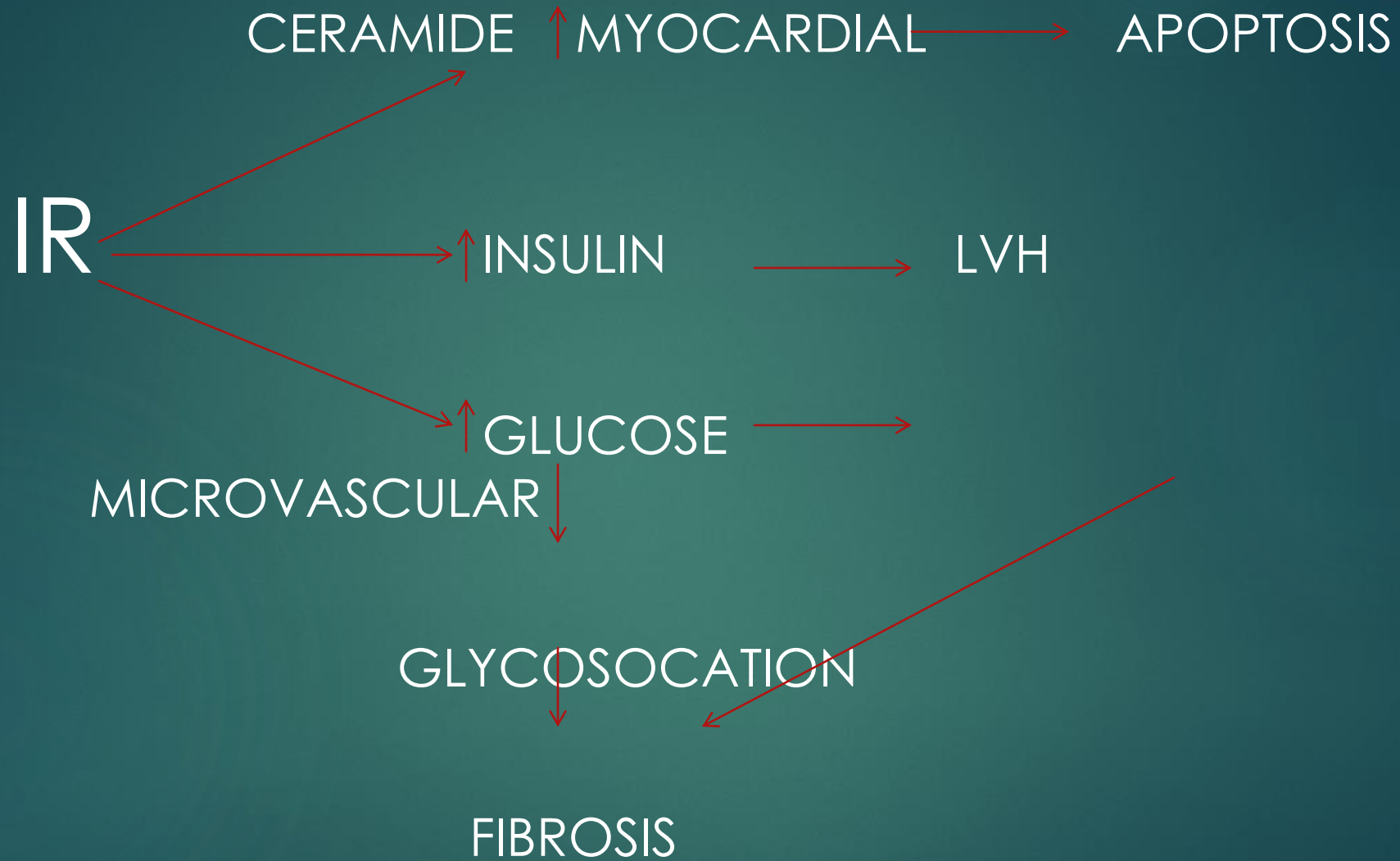
- 1) ENDOTHELIAL DYSFUNCTION
- 2) AUTONOMIC NEUROPATHY
 - IMPAIRED VASODILATION TO SYMPATHETIC RESPONSE
 - IMPAIRED CONTRACTILITY

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

↓
LIPID ACCUMULATION

↓
LIPOTOXICITY

↓
APOPTOSIS



PROPOSED ETIOLOGY OF DIABETIC CARDIOMYOPATHY

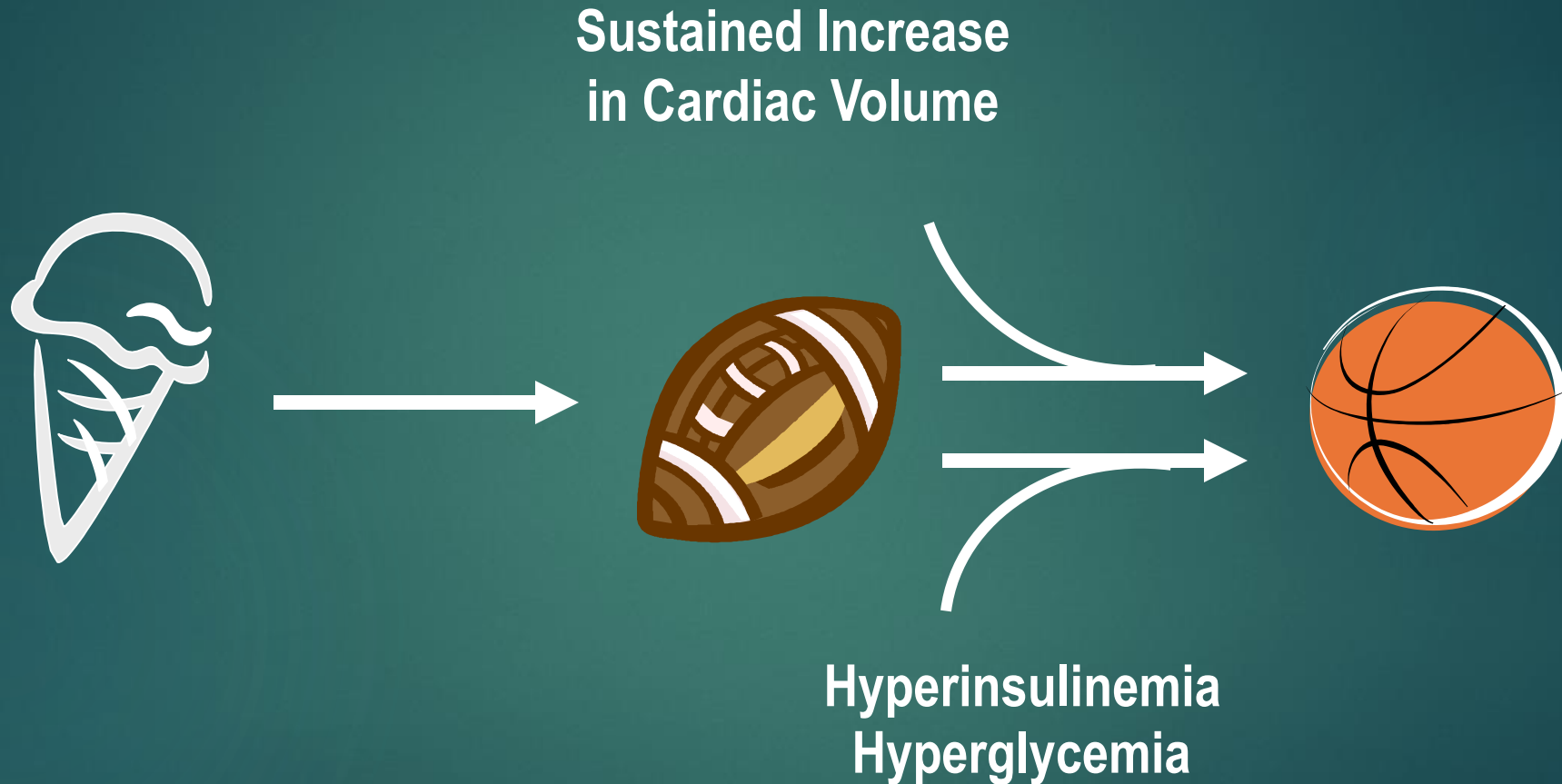
LV Hypertrophy and Diabetes

- ▶ 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

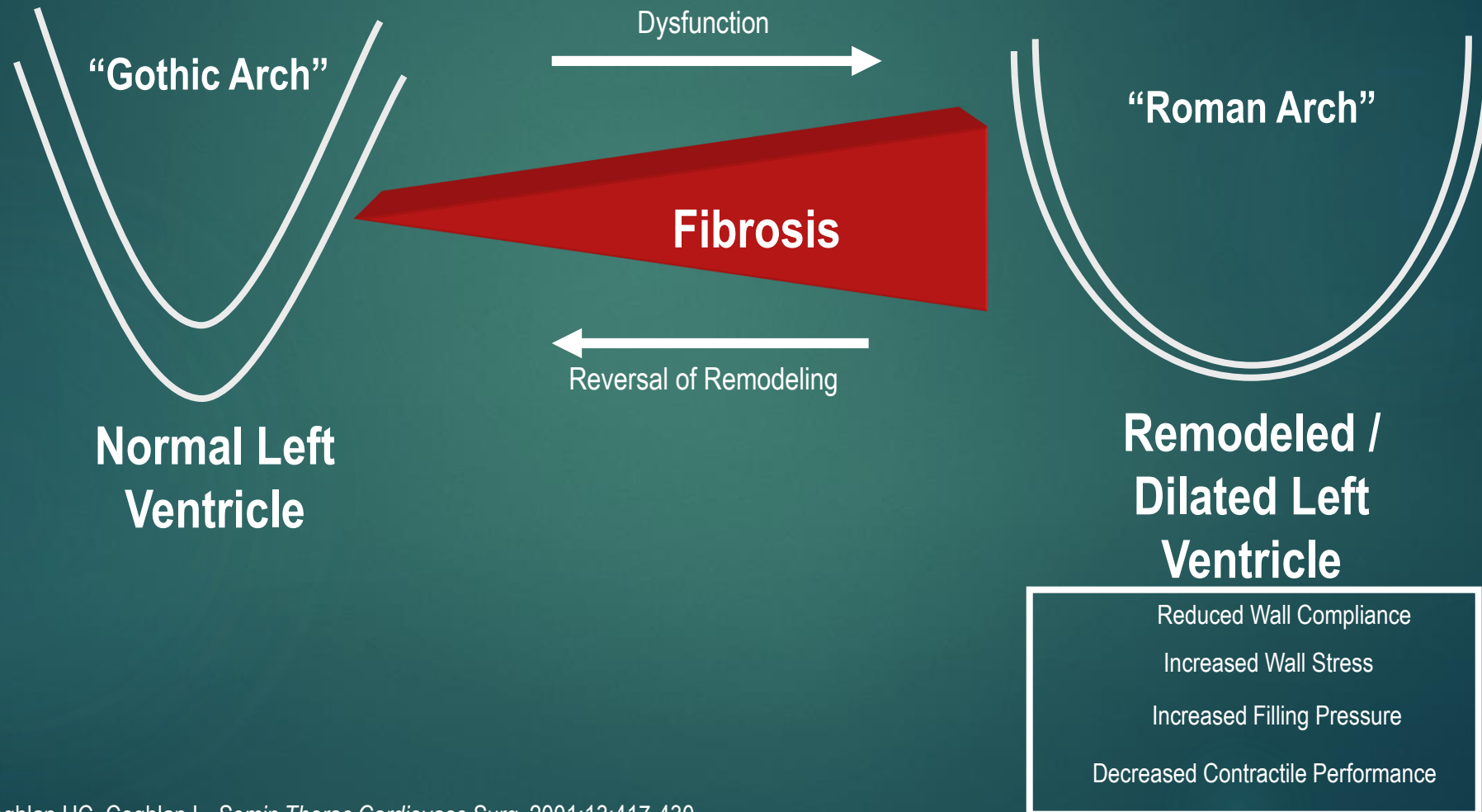
*Based on cohort study from a hospital registry with a mean follow-up of 5 years. 26.1% of those studied had diabetes.

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.

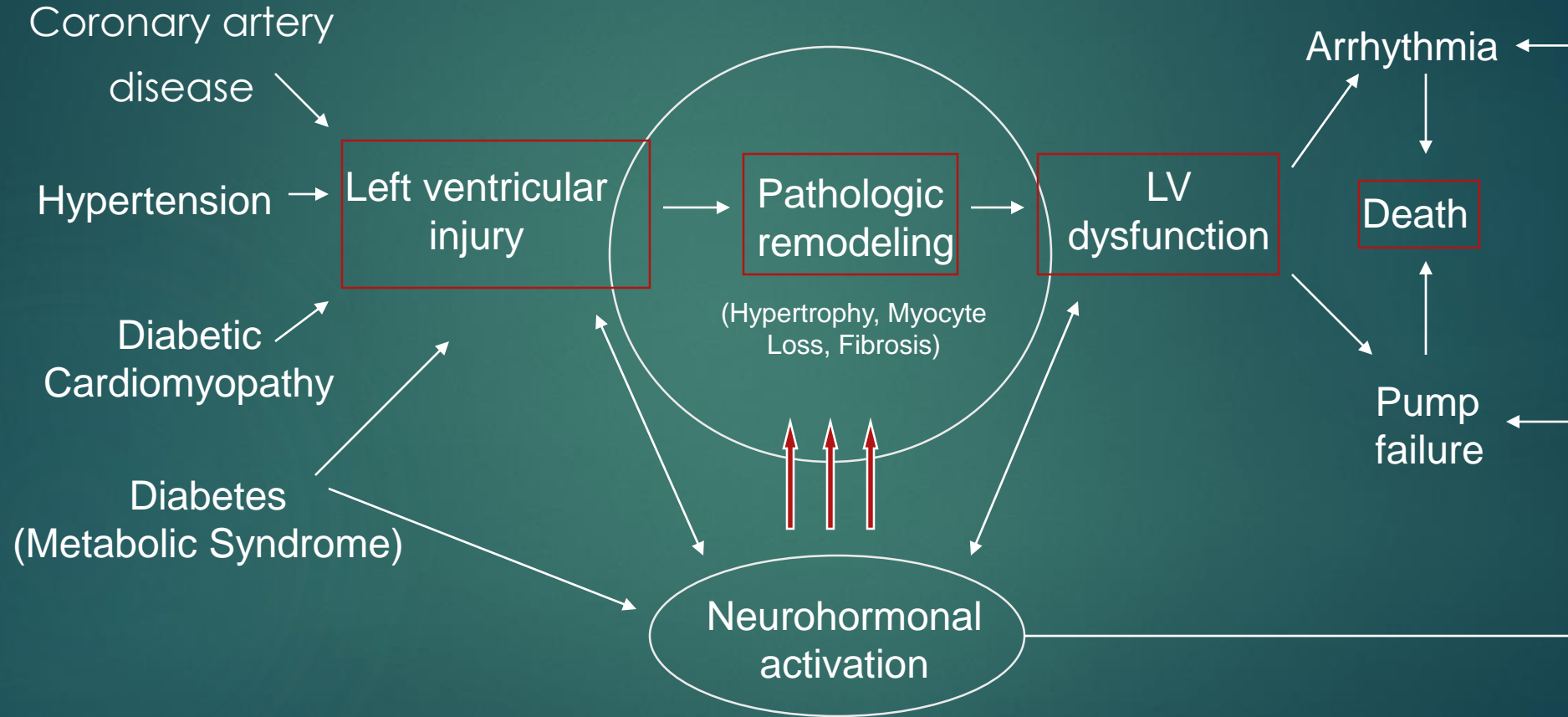
Myocardial Remodeling



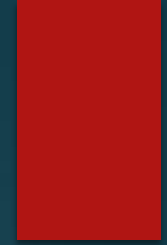
Cardiac Remodeling



Progression of Cardiovascular Disease

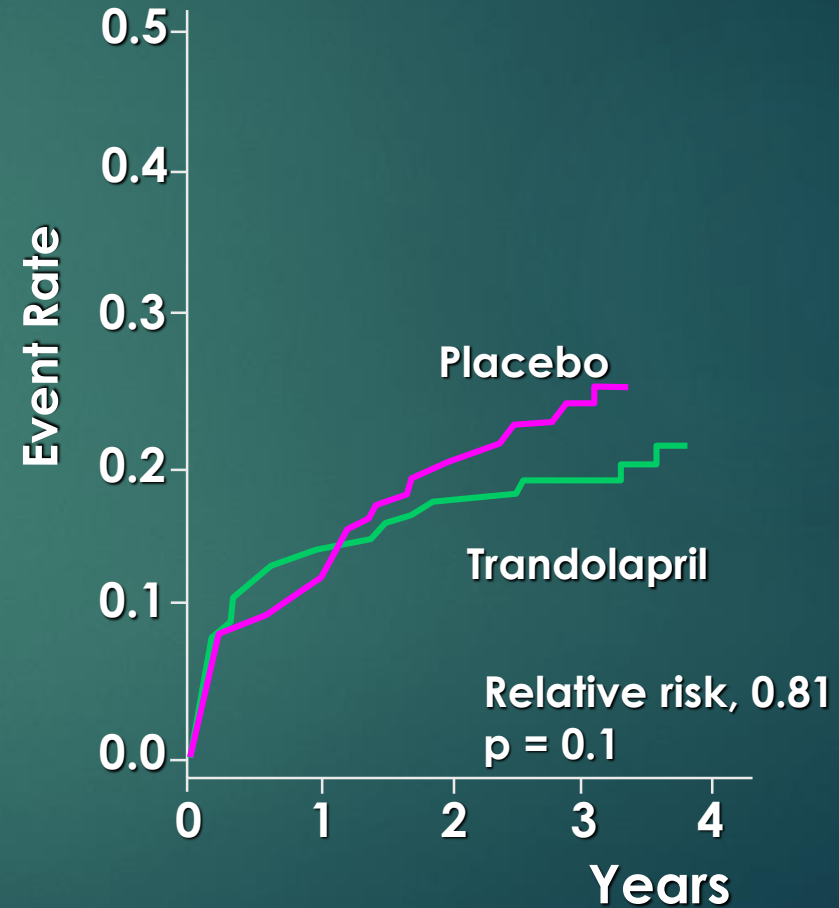
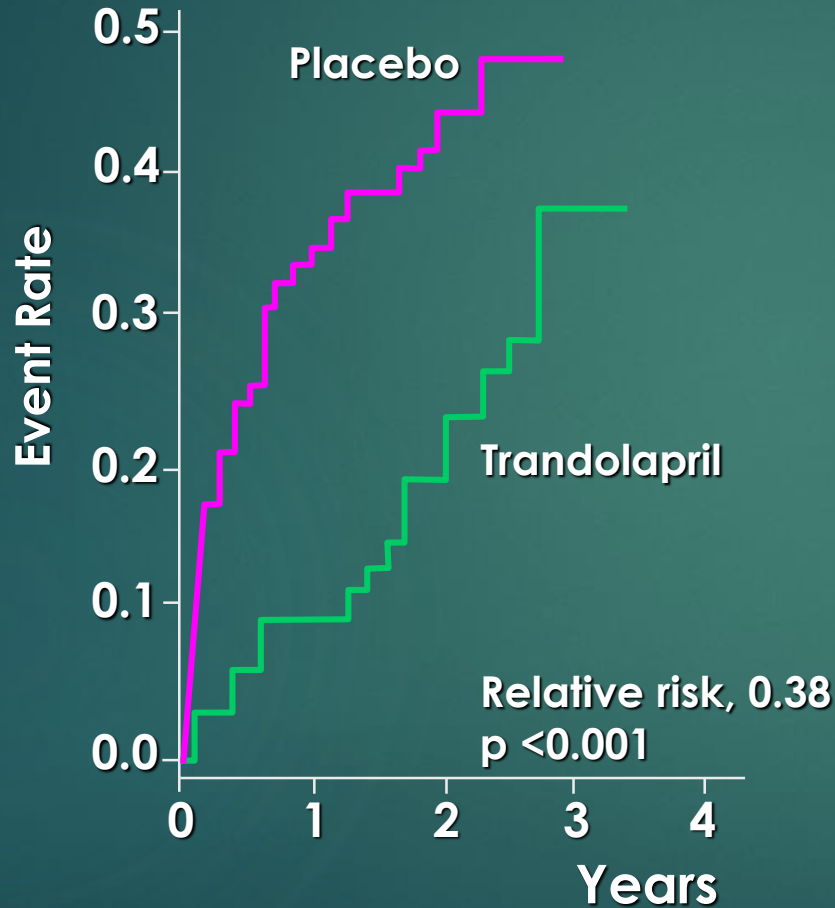


TRACE: Effect of Trandolapril on CHF Progression after Acute MI

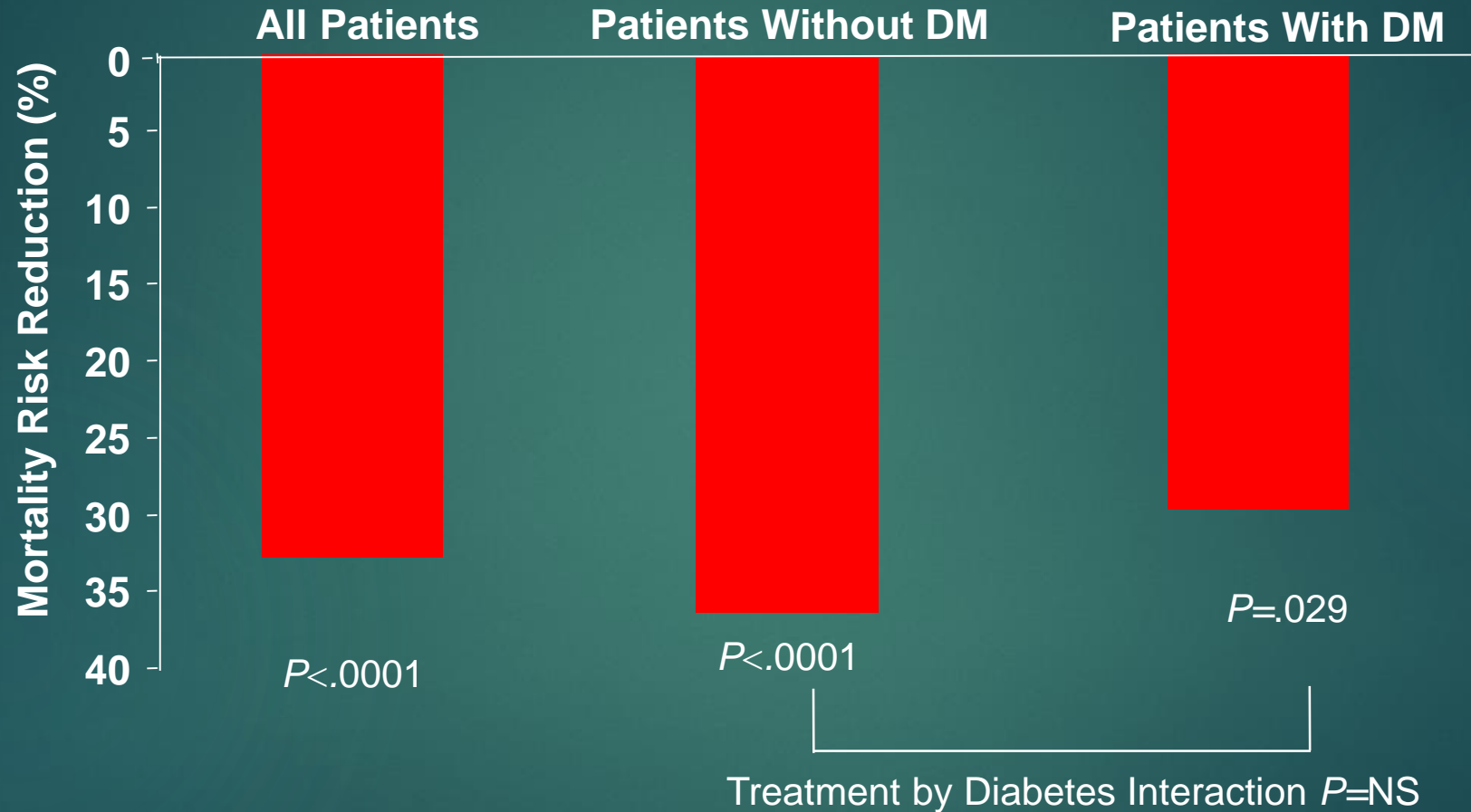


Diabetics

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

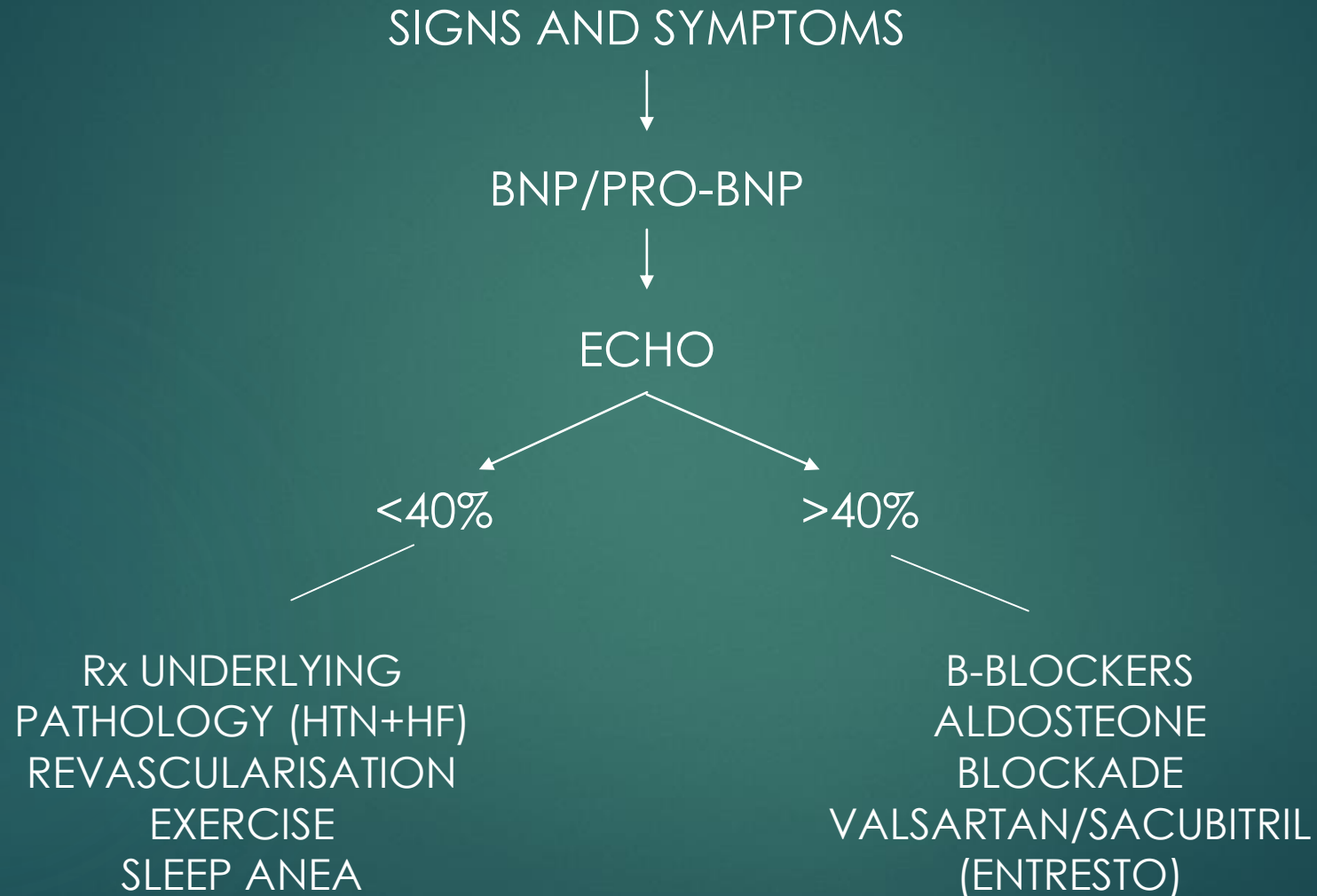
HPnEF

- 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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