HEART FAILURE

The Frequent and Often Fatal Complications of Diabetes

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Increased Frequency of Heart Failure with Diabetes

- Framingham x 2♂ x 5♀ ages 45-75 years
- <65 years x 4♂ x 8♀
- 10,000 DM2s in an HMO
  - 12% HF at entry
  - Remainder 3.3% per year diagnosed with CHF
- Nursing home patients 39% with diabetes versus 23% without diabetes developed CHF after 43 months
- Elderly population prevalence of diabetes was 30%
- In UKPDS prevalence of HF proportional to HbA1c – 1%-15%

•Kannel WB JAMA (1979) 241:2035-38

•Nichols GA Diabetes Care (2001) 24:1614-9

•Aronov WS Chest (1999) 115:867-8

•Amato L Diabetes, Metab (1997) 23:213-8

•Straton IM BMJ (2000) 321:405-12

Increased Frequency of Heart Failure With Diabetes (2)

- 30% - 40% of hospital admissions with CHF have diabetes
- HF is an independent risk factor for developing diabetes – over 3 years 29% vs. 18% of HF patients developed diabetes
- Diabetes patients are underrepresented (25%) in major studies on HF due to exclusion criteria of DM or renal decompensation

•Reis SE J Am Coll Cardiol (1997) 30:733-8
•Bell DSH Diabetes (2001) 50:A456
•Suskin NJ Am Coll Cardiol (1998) 31:249A
•Bell DSH Diabetes Care (2003) 26:2433-41

Diastolic Dysfunction

- Documented in young DM1s
- 30% on standard ECHOS
- With more rigorous Dopler methods early diastolic function can be diagnosed
- 52% DMs in Olmstead Co. Minnesota
- 60% in Quebec Canada
- Discharge diagnosis of idiopathic cardiomyopathy more common in the diabetic patient

•Schannwell CM Cardiology (2002) 98:33-39

•Di Bonito P Diabet Med (1996) 13:321-4

•Redfield MM JAMA (2003) 289:194-202

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

•BErtoni AG Diabetes Carw (2003) 26:2791-5

Diabetic Cardiomyopathy (1)

- Diastolic dysfunction is proportional to HbA1c level
  - Increased myocardial AGEs leading to cross-linking of collagen
  - Myocardial glycation (reversed by aminoguanidine) alters calcium homeostasis which leads to myocardial dysfunction
  - Hyperglycemia activates PKC-β leading to myocardial necrosis, fibrosis, and ventricular dysfunction
  - Hyperglycemia increases free radicals and oxidants inducing myocardial inflammation, decreased NO levels and endothelial dysfunction

Diabetes Cardiomyopathy (2)

- Diastolic dysfunction is proportional to HbA1c level
  - Elevated FFA level associated with hyperglycemia since FFAs and/or their oxydation products are directly toxic to the myocadium
  - In animal studies, lysis of collagen, aminoguanidine, PKC-β inhibitors, poly (ADP-Ribose) polymerase-1 inhibition and TZDs all improve ventricular function

•Devereux RB Circulation (2000) 2271-6

•Bauters C Cardiovasc Diabetol (2003) 2:1-167

•Ziegelhoffer A Mol Cell Biochem (1997) 176:191-8

•Wakasaki H Proc Natl Acad Sci USA (1997) 94:9320-5

•Young ME Circulation (2002) 105:1861-70

Diabetic Cardiomyopathy (3)

- Diastolic dysfunction is proportional to the level of microalbuminuria
  - Even after adjusting for age, gender, BMI, BP, LV mass, CAD and duration of DM in the Strong Heart Study, micoralbuminuria is a marker of endothelial dysfunction
  - Permeability in myocardial microcirculation leads to myocardial fibrosis and stiffening
  - HOPE study showed association of microalbuminuria with CHF

•Liu JE J AM Coll Cardiol (2003) 42:2002-8

•Bell DSH Diabetes Care (2003) 26:2949-51

•Arnold JM Circulation (2003) 107:1284-90

Hypertension and Left Ventricular Hypertrophy

- 75% of DMs are hypertensive
  - Hyperglycemia
  - Insulin resistance
- LVH can occur in the absence of hypertension
  - Framingham 10% normotensive women
  - Tayside 32% of non-hypertensive, non ACE utilizing DM2s without known CAD
- Related to IR syndrome

Galderis M Am J Cardiol (1991) 68:85-89

Strathers AD Lancet (2002) 359:1430-2

Phillips RA J Clin Endocrinol Metab (1998) 4284-4288

Cardiotoxic Triad

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

•Genda A Clin Cardiol (1986) 9:375-382

•Ahmed SS Am Heart J (1975) 89:153-158

•Factor SM The Diabetic Heart (1991) 89:-101

Autonomic Dysfunction

- Impaired myocardial performance and hyperglycemia through activation of intracellular pathways (e.g. PKC) activate the RAS and SNS to avoid systemic hypoperfusion
- Accelerated myocardial necrosis and apoptosis and further myocardial dysfunction and spiraling increases in activation of the RAS and SNS
- Remodeling of the ventricle by change in shape and size of the cardiac chambers occurs secondary to the RAS and SNS stimulation

Bristow MR Lancet (1998) 352(suppl1) S18

Autonomic Dysfunction (2)

- Activation of RAS and SNS leads to increased carnitine palmityl transferase-1 (CPT-1) a mitochondrial enzyme promoting transportation of FFAs into the mitochondria thus promoting the use of FFAs rather than glucose by the myocardium and increasing myocardial workload.
- Activation of RAS and SNS alter gene expression in the myocardium
  - Isoforms of myosin heavy chain changed to a fetal pattern of less α (FAST) and more β (slow) isoforms, ANP and skeletal α Actin genes reexpressed.

•Panchal AR J Card Fail (1998) 4:12-6

•Bristow M Lancet (2000) 356:1621-2

Autonomic Dysfunction (3)

- A downregulation of the gene encoding the key ionotrophic protein sarcoplasmic reticular Ca^{++} ATPase (SERCA-2) occurs with induction of the fetal gene program leading to a decrease in ventricular function
- Probably an adaptation to protect the surviving myocardium

Lowes BD J Am Coll Cardiol (1999) 33(suppl A) 216

Screening for CHF in the Diabetic Population

- DM places patients in the highest risk category
- 20% of diabetics with E # less than 45% have no symptoms
  - GXT or 6 min walk test
- In SOLVD E # <45%
  - 32% Rales
  - 26% edema
  - 26% neck vein distention
  - 17% S3
- Two dimensional and pulsed Doppler echocardiography recommended if HF suspected

•Hunt SA J Am Coll Cardiol (2001) 38:2101-13

•Marantz PR JAMA (1988) 77:607-12

•Bittner JAMA (1993) 270:1702-7

•Bourassa MG, J Am Coll Cardiol (1993) 22:14-19A

Screening for CHF in the Diabetic Population (2)

- Screening should be performed with Brain Naturetic Peptide
  - Like ANP elevated with ventricular dysfunction or CHF
  - Unlike ANP not affected by hyperglycemia
  - Sensitivity 92%
  - Specificity 72%
- Economic test to identify patients with ventricular dysfunction of CHF who should be further evaluated with ECHO cardiography

•McKenna K Diabet Med (2000) 17:512-7.

•McDonagh TA Lancet (1998) 351:9-13.

Deaths From Heart Disease

Decrease in mortality over 9 years

	Nondiabetic	Diabetic
Men	36.4%	13.1%
Women	27%	+23%

Gu K et al. *JAMA*. 1999;281:1291–1297.

Potential Explanations for Reduction in CV Mortality

- Decreased incidence of heart disease 25%
- Decreased case fatality rate
  - MI, cardiac arrest 12%
- Secondary prevention –medical and surgical 63%

Hunnick MGM, JAMA (1997) 277:535-542.

Unal B, Circulation (2004)109:1101-7.

Potential Benefits of Glycemic Control the Diabetic Subject With CHF

- Lowering serum glucose results in opening of the K_{ATPase} channels and decreased myocardial work load
- Lowering of FFA levels decreases sympathetic activity myocardial calcium levels and risk of arrhythmia
- Decreases utilization of FFA increases utilization of glucose and decreases myocardial oxygen consumption, cardiac workload and ischemia and improves ventricular function
- Reverses FFA induced myocardial apoptosis in animals

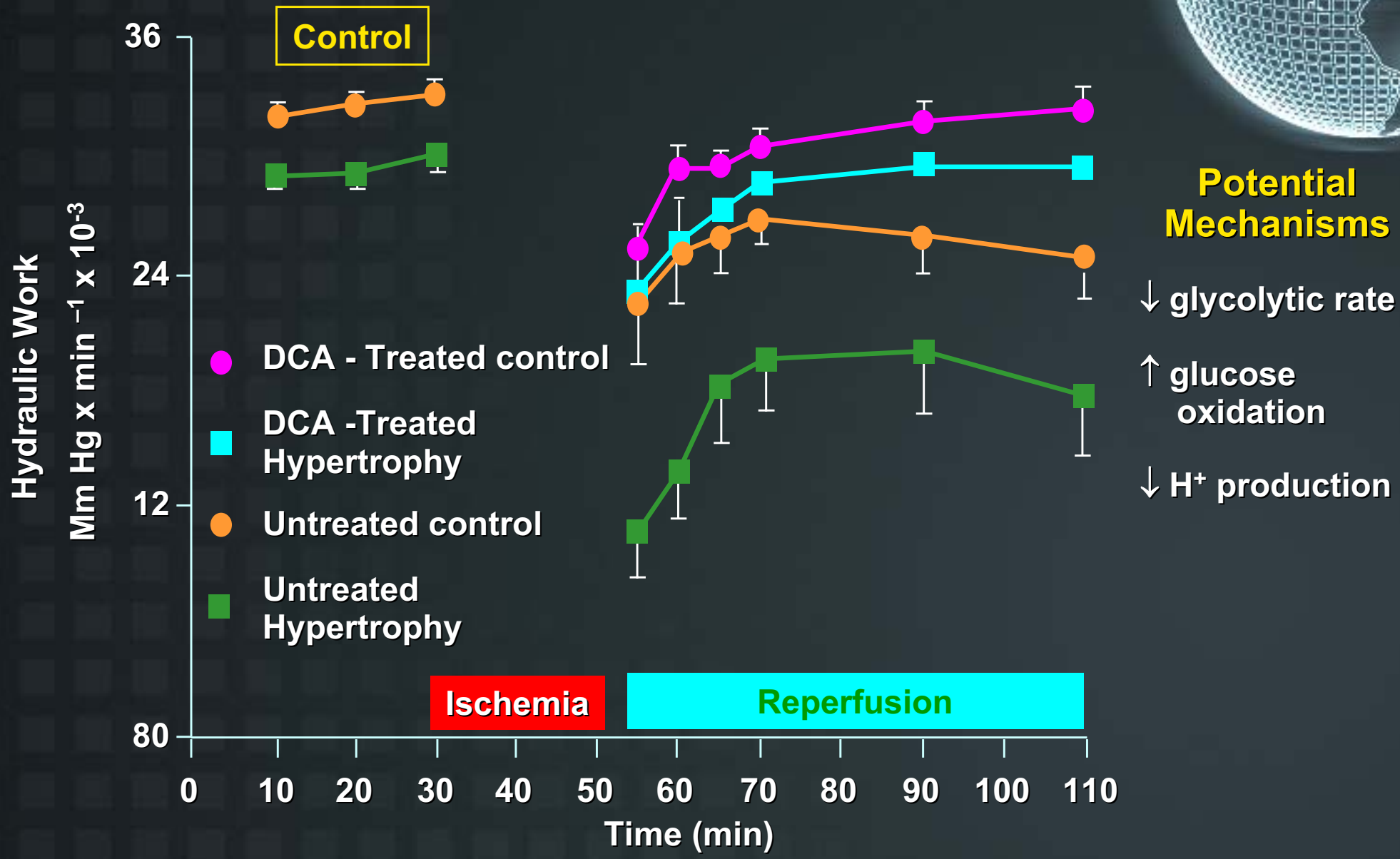
Oliver MF, Lancet (1994) 343:155-158
Myos OD, J Clin Invest (1971) 50:1386-1389

Dichloracetate Mimics FFA Reduction

- Stimulates activity of pyruvate dehydrogease
- Stimulates glucose utilization by the myocardium
- Increases lactate extraction
- Decreases myocardiac oxygen consumption
- Improves ventricular function

Bersin RM, J Am Coll Cardiol (1996) 23:1617-1624

Dichloroacetate Normalizes Post-Ischemic Cardiac Dysfunction



Potential Mechanisms

- ↓ glycolytic rate
- ↑ glucose oxidation
- ↓ H^+ production

Walmbolt, RB et al. J Am Coll Cardiol 2000; 36: 1378-1385

Pancreas Transplant With Portal Delivery Of Insulin

Doppler Echocardiographic Parameters

	Pre	6 months post
A1c	9.7%	5.6%
LVEF (%)	54.0	56.5
LVMI (g/m^2)	86.7	72.0
PWTD (mm)	8.9	8.0
E/A	1.2	1.4
IVRT (msec)	90.5	85.0

PWTD – Posterior wall telediastolic diameter

IVRT – Isovolumetric relaxation time

Henley SH Diabetes Care (1999) 22:320-7

Coppelli A Transplantation (2003) 76:974-6

TZDs and Edema - Usual Scenario

1) TZDs do not have a negative effect on the myocardium
2) TZDs induce dependent edema
   a) Increased renal Na retention
   b) Vasodilatation and stimulation of the RAS and SS
   c) Increase in VEGF production
3) Neck veins not distended
4) BNP normal

Bell DSH, Diabetes (2003) 26:2433-2341.

TZDs and CHF - Rare Scenario

1) Pre-existing diastolic dysfunction
2) Increase plasma volume by as much as 6%
3) CHF develops prematurely
4) Neck veins distended
5) BNP elevated
6) Potential for improved prognosis
7) Undiagnosed ventricular dysfunction is associated with an increased incidence of cardiac arrhythmia and sudden death

Nesto RW, Bell DSH et al, Circulation(2003) 108:2941-2948.

Retrospective Study of TZDs and CHF

- 16,000 medicare beneficiaries over age 65
- Hospitalized with 1° diagnosis of CHF 1988-1989
- Mean age 77yrs
- 77% pulmonary edema on CXR
- Multivariate analysis with 78 variables including ejection #
- With TZDs 6% increase in re-admission with CHF
- 13% decrease in mortality (p=0.009), 95% CI, 0.78-0.97

Massoudi A, Diabetes (2004)53(suppl 2): A29

Correction Of Anemia In Diabetic CHF

- Diabetic patients with Hb less than 12.5 grams/ % treated with Erythropoetin and IV iron
- NYHA class increased by 36.8%
- Dyspnea by 69.7% on visual scale
- Ejection # by 7.6%
- Hospitalizations by 96.6%

Silverberg DS Nephrol Dial Transplant (2003) 18 (1) 161-6

Obstructive Sleep Apnea, Diabetes and CHF

- OSA is more prevalent in both diabetes and CHF
- Increased sympathetic tone is the common denominator
- Increases sympathetic activity increases BP, myocardial stress and insulin resistance
- CPAP Rx decreases sympathetic activity and afterload and ANP and increases LVEF and stroke volume

Somers VKK, J Clin Invest (1995) 96:1897-1904.

Kaye DM, Circulation (2001) 103:2336-2338.

Treatment –Digoxin and Diuretics

- Improve clinical manifestations of HF
- Improve quality of life for HF patient
- No effect on mortality
- To improve mortality, the remodeling process must at least be halted and preferably reversed

Myocardial Remodeling

- Stimulation of RAS and SNS initially protective
- Sustained stimulation leads to progressive loss of myocutes cellular hypertrophy and a change in size and shape of the left ventricle
- Increase in myocardial mass
- Placement decreases rather that improves myocardial function
- Deterioration in function further stimulates RAS and SNS
- Eventually HF occurs

Eichhorn EJ, Circulation (1996) 94:2285-2296.

Myocardial Remodeling (2)

- Remodeling can be attenuated utilizing drugs that interfere with RAS and SNS
- In the diabetic subject, hyperglycemia plays an important role

Sonag L, Eur Heart J (199) 20:789-795.

Eichhorn EJ, Circulation (1996) 2285:-2286.

Briston MR, (Lancet (1998) 352:s18-114.

ACE Inhibitors and ARBs in Diabetics CHF

- Stimulation of the AT_1 receptor results in myocardial hypertrophy and fibrosis
- With ACE inhibitors bradykinin levels are increased mediating increased nitric oxide and prostacyclin levels and improving hypertrophy and fibrosis
- Prevention of myocardial remodeling
- VALHEF versus CHARM added
  - Probable benefit of adding ARB to ACE in CHF

Weberkt Circulation (1991) 83:1849-1865

Kutz AM, Ann Intern Med (1994) 121:363-371

Mitchell GF, J Am Coll Cardiol (1992) 19:1136-1144

Cohn JN, N eng J Med (2001) 345:1667-1675)

McMurray JJ, Lancet (2003) 362:767-771

ACE Inhibitors in Diabetic CHF

SAVE, SOLVD, GISSI and ATLAS all showed equivalent efficacy in diabetic CHF as non-diabetic CHF

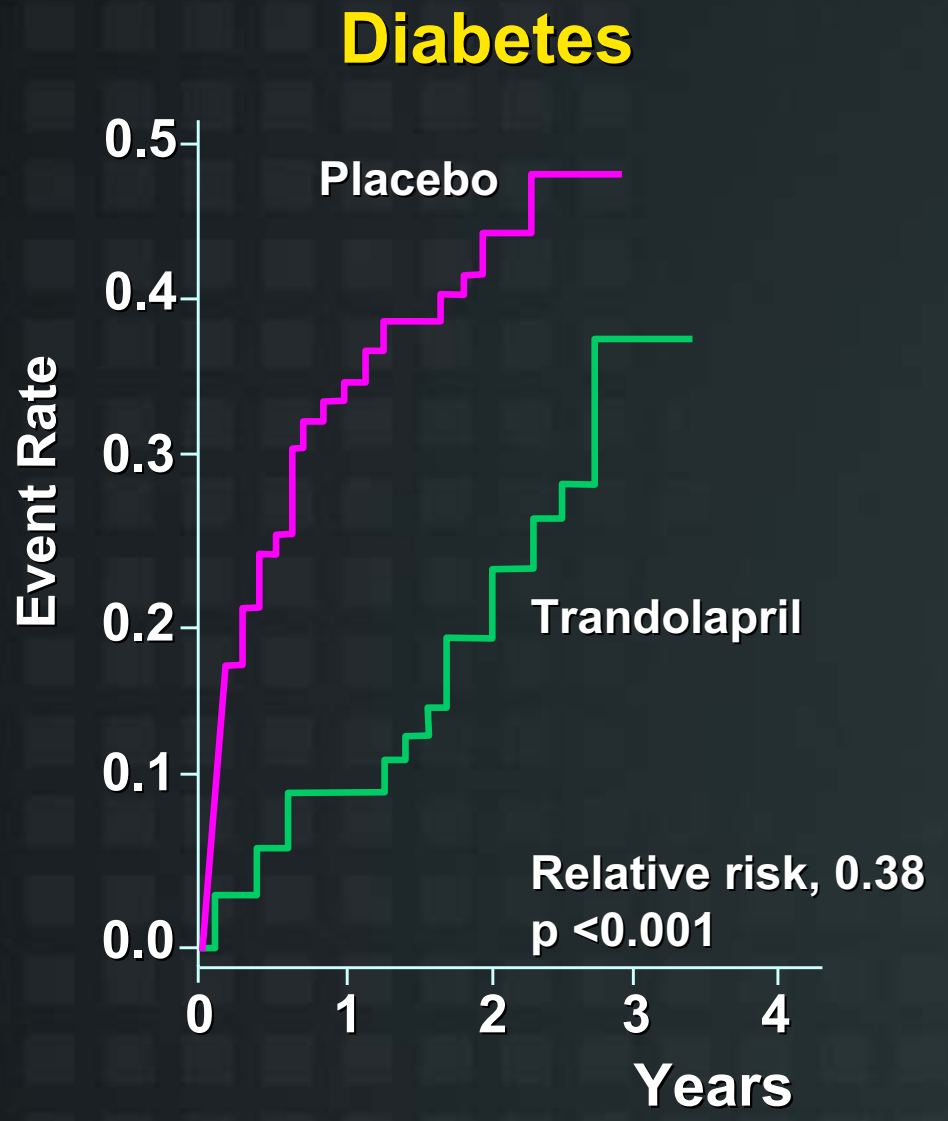
Moye LA, Eur Heart J, 15(supplB) (194) 2-8.

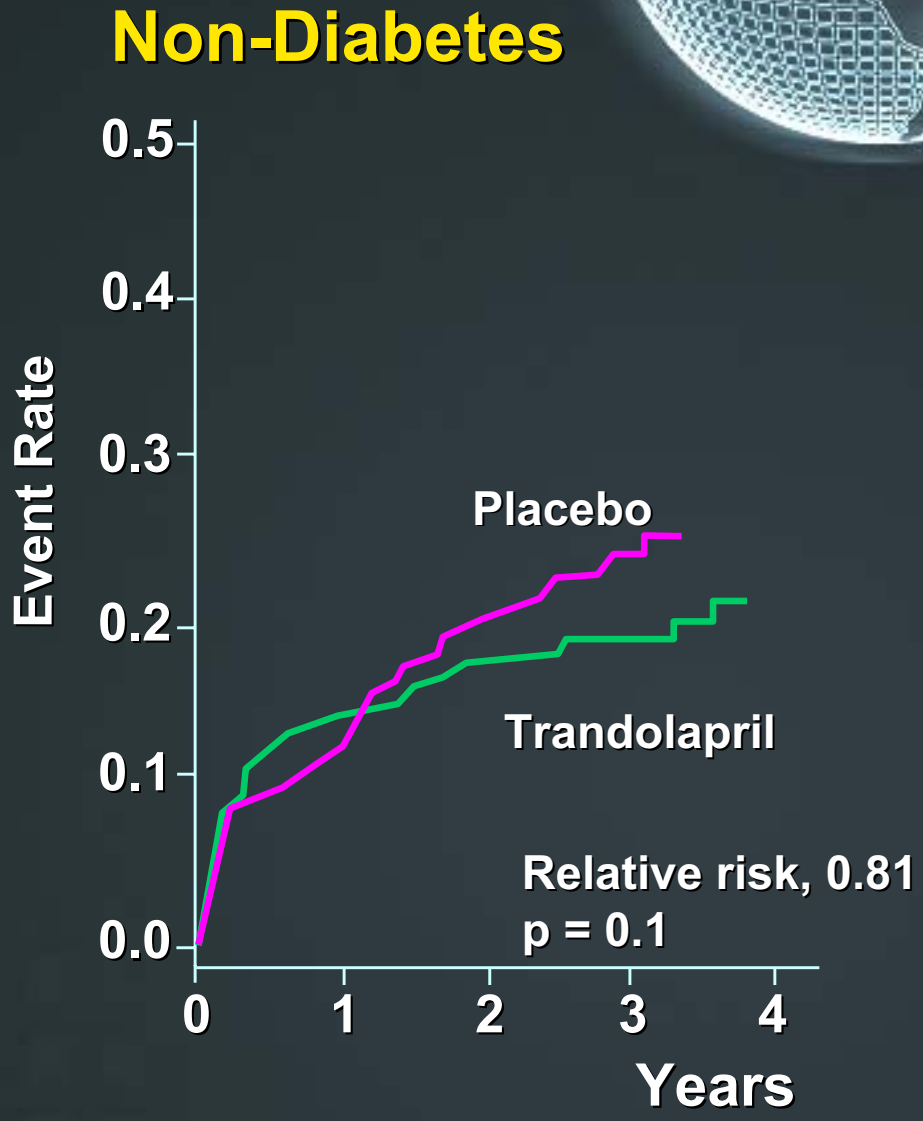
Schindler DM, A J Crdiol (1996) 77:1017-1020.

Zuanetti G, Circulation(1997)96:4239-4245.

Packer M, J Am coll Cardiol (1998)31:249A.

TRACE: Effect of Trandolapril on CHF Progression After Acute MI





TRACE JACC 1999; 34; 83-89

Aldosterone Receptor Blockers in Diabetic CHF

- Excess aldosterone not only associated with Na retention but also with myocardial fibrosis hypertrophy and dysfunction
- ACEIs do not entirely suppress
- Aldosterone antagonists combined with ACEIs + B-Blocker improve mortality
- Associated with an increased incidence of hyperkalemia – more common in diabetic and anemic patients

PHB NEJM (1999) 341:709-717

Anton C, J Clin Pharma Ther (2003) 278(4)285-7

Norepinephrine and the Failing Heart

- Directly toxic to cardiac myocytes at the high concentration experienced with HF
- Angiotension 2 is directly toxic to the myocardium but also increases norepinphrine production
- Acting through the $\propto$1 receptor downregulates the β_1 receptor and upregulates β_2 receptor
- Reversible cardiomyopathy with pheochromocytoma
- Reversible HF with head injury
- IR and hyperinsulinemia associated with increased sympathetic activity

Mann DL, Circulation (1997) 85:790-804

Norepinphrine and the Failing Heart (2)

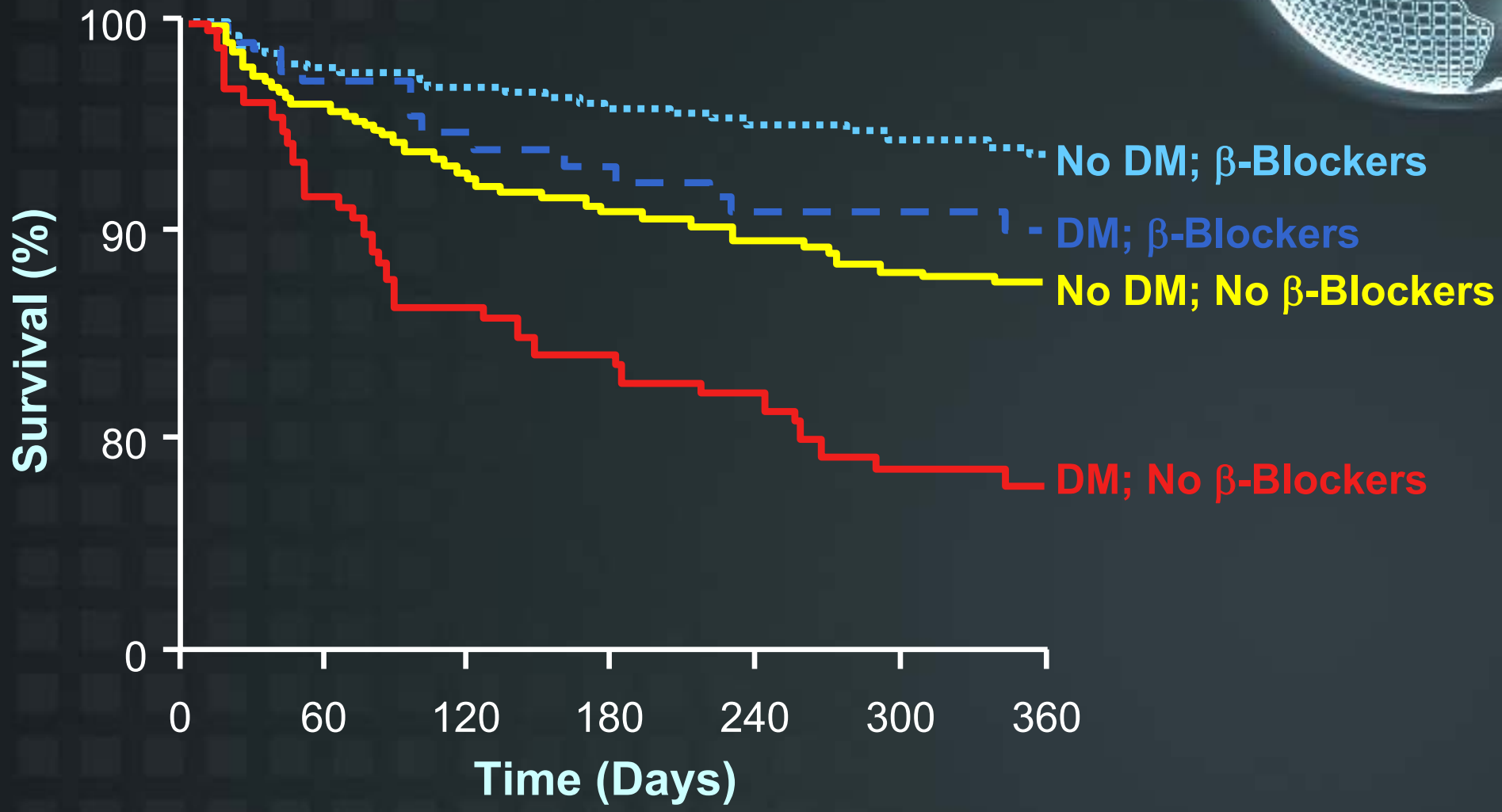
- Upregulates the fetal gene program
  - genes present in the ventricle in fetal life reappear with sympathetic stimulation eg. ANP
  - SERCA 1 downregulated leading to myocardial remodelling
  - Systoliic and diastolic dysfunction due to remodeling occur
  - Reversed with β blockade

B-Blockade in Diabetic CHF

- To effectively prevent myocardial remodeling requires blockade of both the SNS and RAS
- SNS blockade requires inhibition of β_1, β_2 and and $\propto_1$ receptors
- Initial decrease in ejection # is followed by improvement at one month and significant improvement at 3 months with reduced ventricular volumes
- After 18 months LV mass decreased and initially spherical ventricle remodeled to a normal eliptical shape

Waagstein F, Lancet (1993) 342:1441-1446

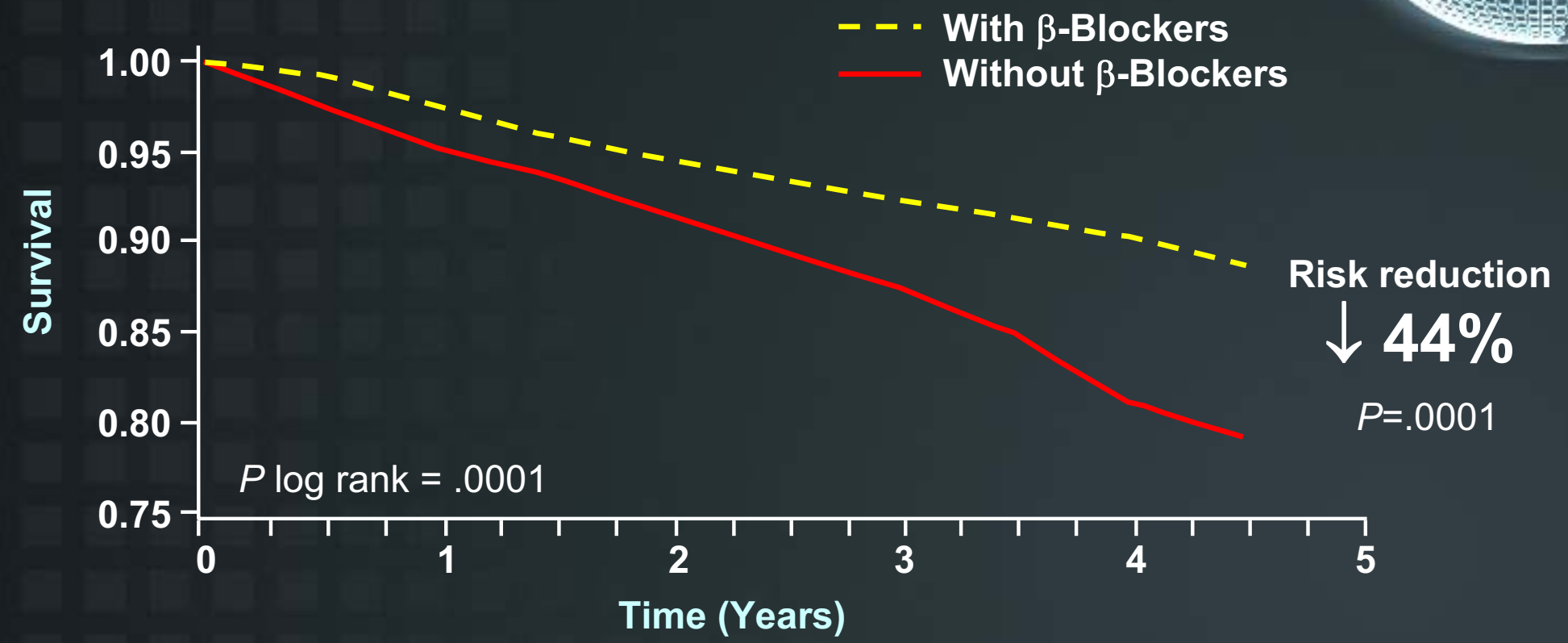
β-Blockers in Diabetics: Post-MI



From a 2024 patient study, 340 had diabetes, and 281 survived hospitalization for acute MI.
Of the 127 diabetics taking β-blockers, 80% received propranolol, 20% received other β-blockers.

Kjekshus J et al. *Eur Heart J*. 1990;11:43–50.

β-Blockers in the Diabetic Patient With CAD: Bezafibrate Infarction Prevention Study



With β-blockers event rate: 7.8%; without β-blockers event rate: 14.0%

2723 Patients with type 2 diabetes and CAD. Of those patients receiving a β-blocker, 39% received propranolol, and 61% received a cardioselective β-blocker

Jonas M et al. *Am J Cardiol*. 1996;77:1273–1277.

β-Blockers and Survival with Diabetic CHF

- 3300 Diabetic subjects with CHF
- Diabetes increased mortality by 25%
- Diabetic subjects on Beta-Blockers 28% lower morality

Haas SJ American Heart Journal (2003) 146:848-53

Ratio of Adrenergic Receptors in the Heart

In the failing heart, the ratio of receptors shifts, increasing the relative proportion of β_2 and α_1 receptors

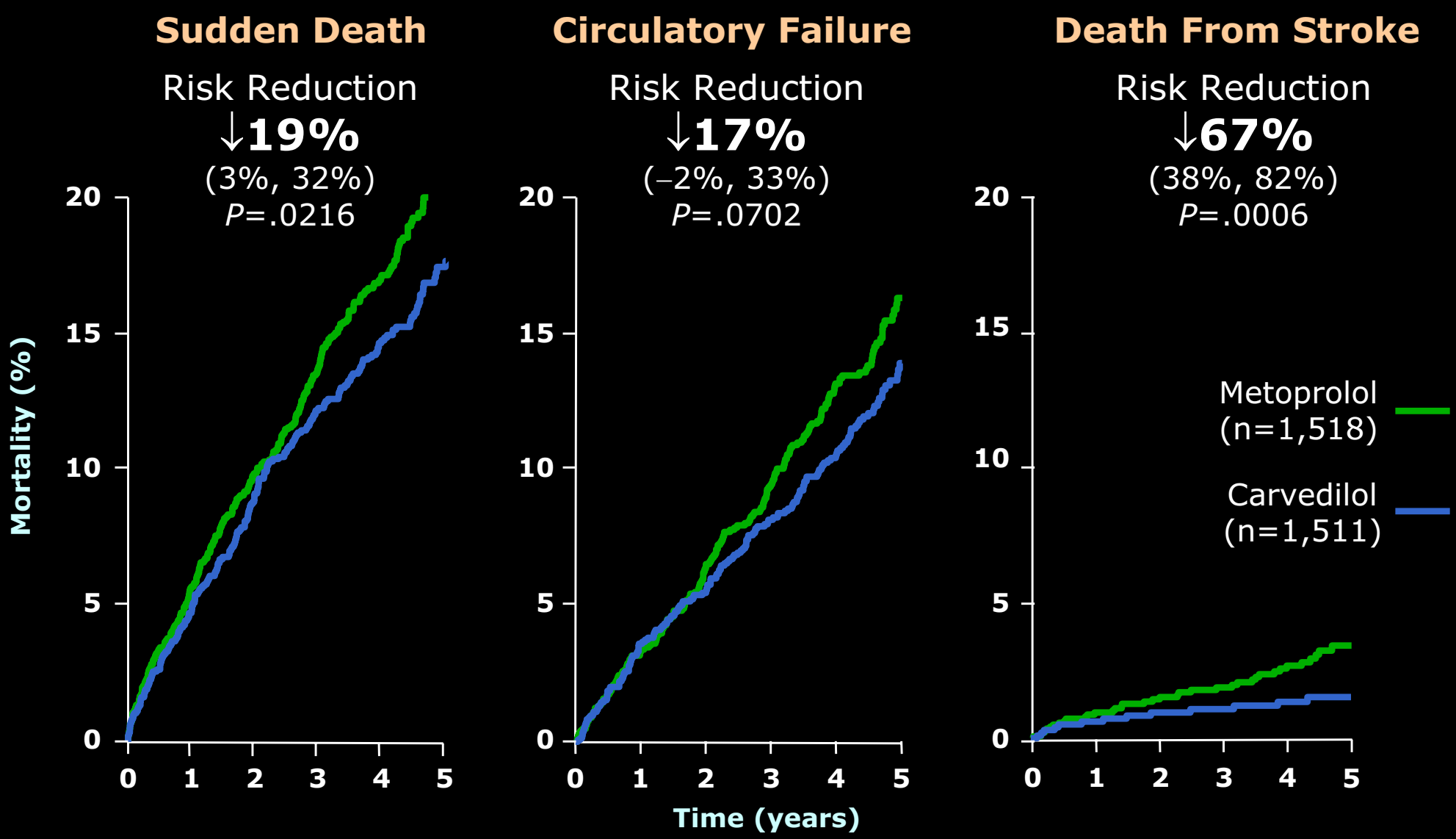
	β_1 :	β_2 :	α_1
Normal Heart	**70 :**	**20 :**	**10**
Failing Heart	**50**	**25**	**25**

Adapted from: Bristow MR. *J Am Coll Cardiol.* 1993;22(4 Suppl A):61A–71A.

B-Blockade in Diabetic CHF (2)

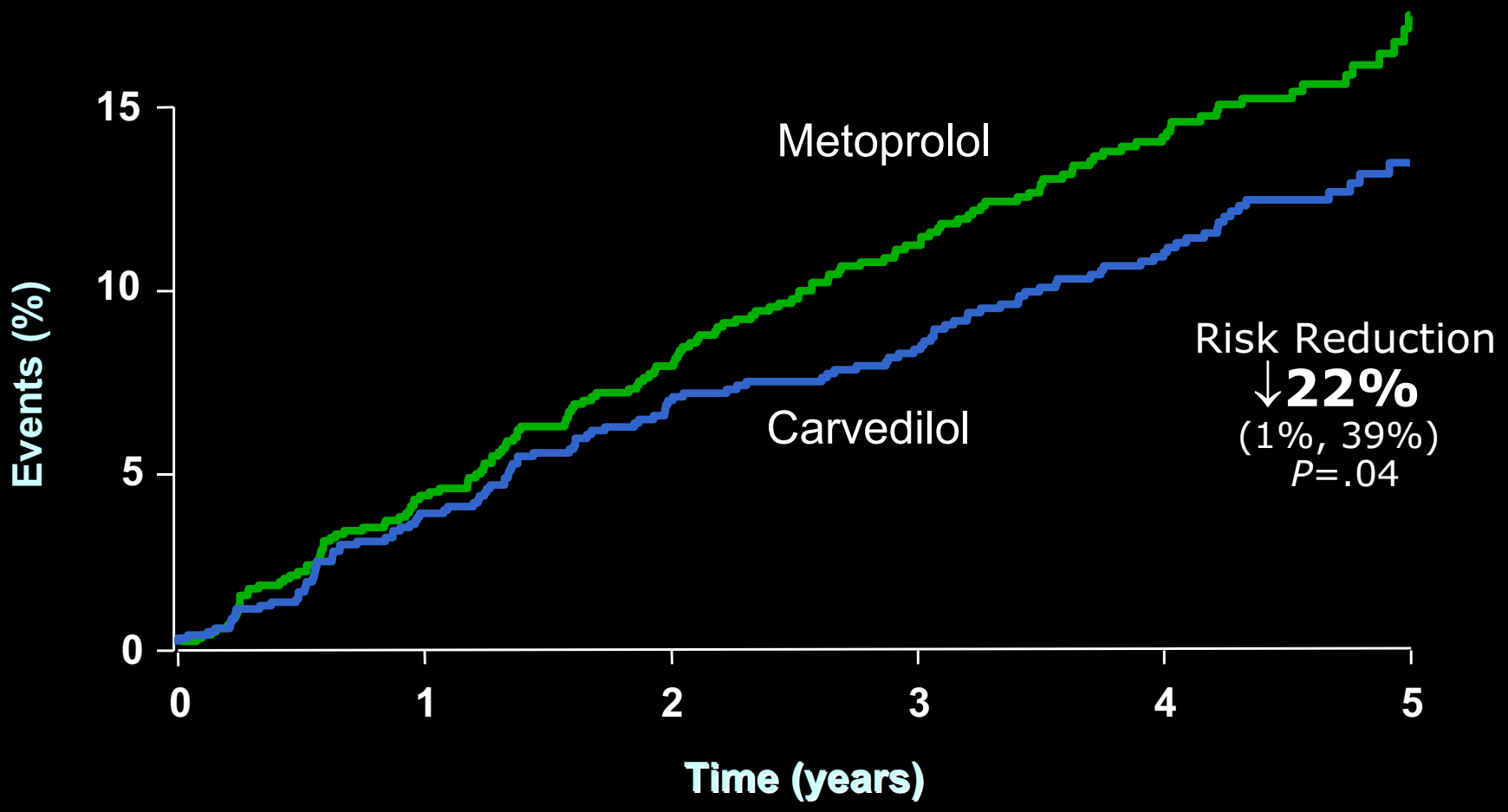
- First generation – (Propanalol Timolol) are contraindicated in CHF due to myocardial depressant effect
- Second generation – Bisoprolol atenolol and metpoprolol - efficacy limited due to specificity for B_1 receptor
- Third generation – Labetolol and carvedilol inhibit both B_1 and B_2 as well as $\propto_1$ receptor

COMET: Mode of Death



Sudden death rates: metoprolol 17.3%, carvedilol 14.4%; circulatory failure rates: metoprolol 13%, carvedilol 11.1%; death from stroke rates: metoprolol 2.5%, carvedilol 0.9%.
Data on file. GlaxoSmithKline.

COMET: New-Onset Diabetes-Related Adverse Events in CHF

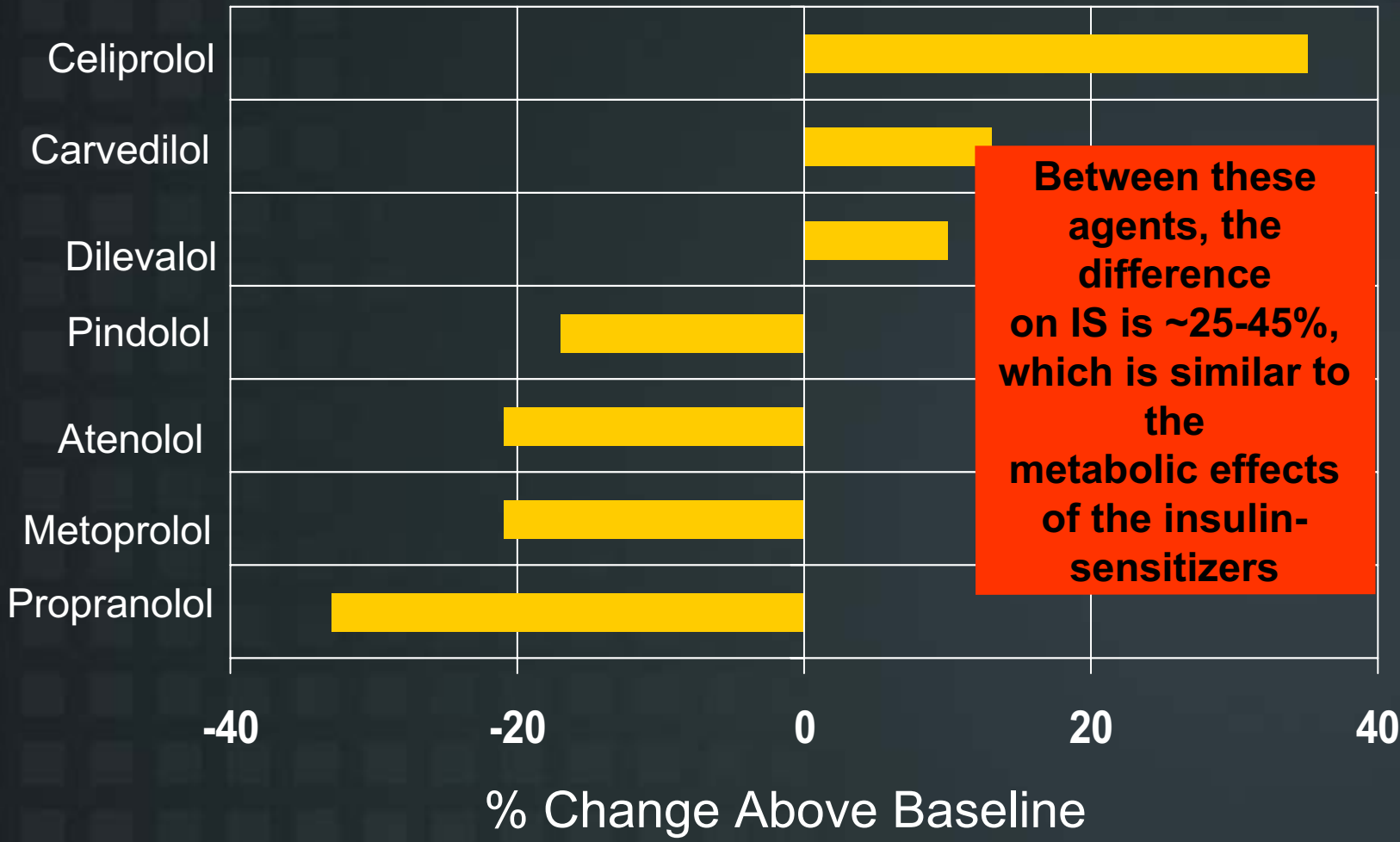


Endpoints include adverse events of diabetic coma, diabetes mellitus, peripheral gangrene (diabetic foot), decreased glucose tolerance, or hyperglycemia in a patient classified as not having diabetes at baseline.

Event rates: metoprolol 13.0%; carvedilol 10.6%.

Data on file. GlaxoSmithKline.

Effect of β-Blockers on Insulin Sensitivity in Hypertensive Patients



Jacob S et al. *Am J Hypertens.* 1998;11:1258–1265.

To maximally reduce morbidity and mortality in the diabetic subject with CHF , it is necessary to achieve….

1. Glycemic Control
2. A lowered insulin resistance
3. Correction of Anemia
4. Treat Sleep Apnea
5. Maximal suppression of the RAS and SS

Heart Failure – The Frequent, Forgotten and Often Final Complications of Diabetes

- Increased incidence and prevalence in the diabetic subject
- Worsened prognosis of CHF in the diabetic subject
- Etiology of the increased incidence, prevalence and worsened prognosis
- Prophylactic strategies and therapies to improve outcomes in the diabetic patient with CHF

Bell DSH, Diabetes Care (2003) 26:2433-41