Diabetic cardiomyopathy: Does it exist?

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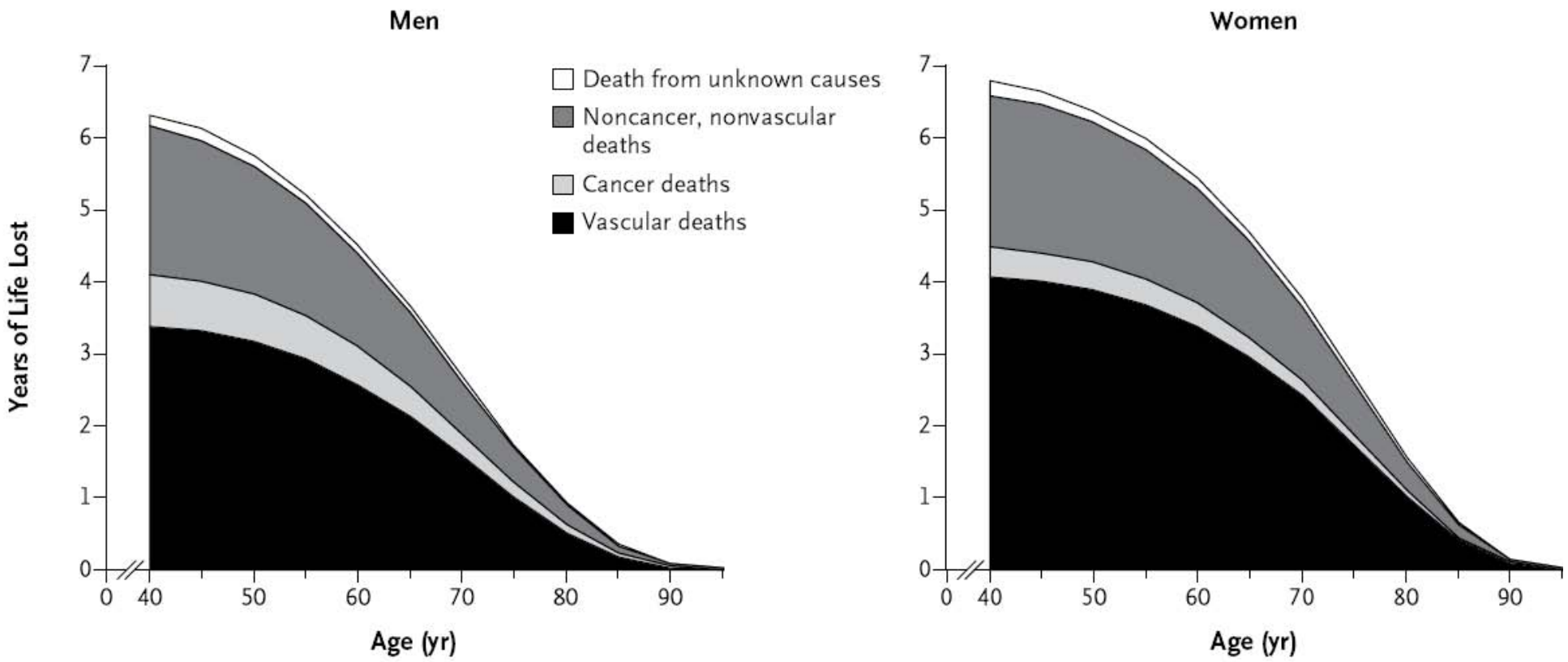
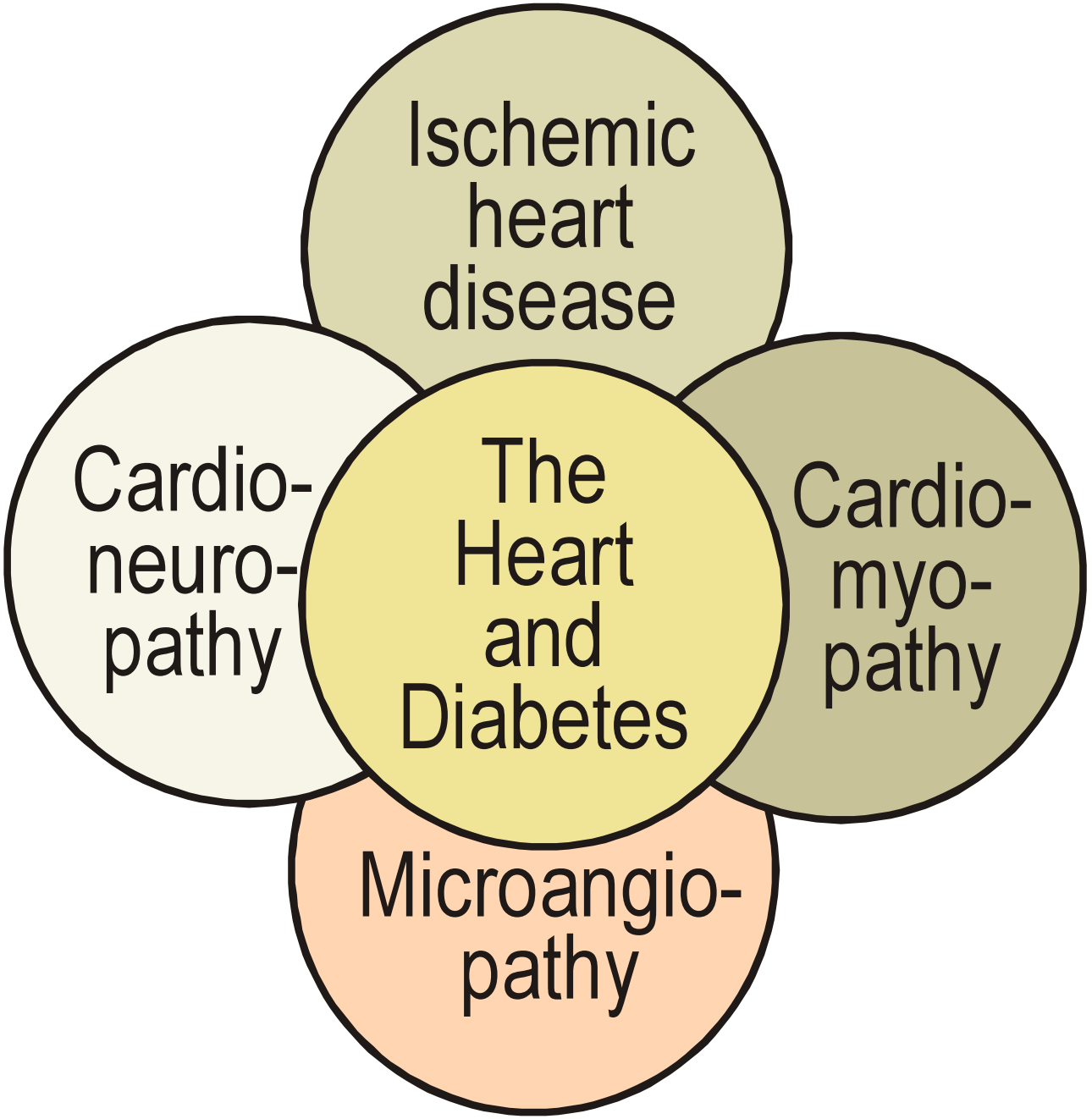
Diabetes mellitus, fasting glucose, and risk of cause-specific death

Estimated future years of life lost owing to diabetes



The Emerging Risk Factors Collaboration. NEJM 2011; 364: 829-841


Ischemic heart disease
Cardio-neuro-pathy
The Heart and Diabetes
Cardio-myo-pathy
Microangio-pathy

Diabetic cardiomyopathy

Originally proposed as a specific diabetic angiopathy
by Lundbaek in 1954

Definition

A term referred to as the presence of myocardial disease in diabetic patients, which cannot be ascribed to extramyocardial coronary artery stenosis.

Definition of diabetic cardiomyopathy

A distinct entity characterized by the presence of abnormal myocardial performance or structure in the absence of epicardial coronary artery disease, hypertension and significant valvular disease

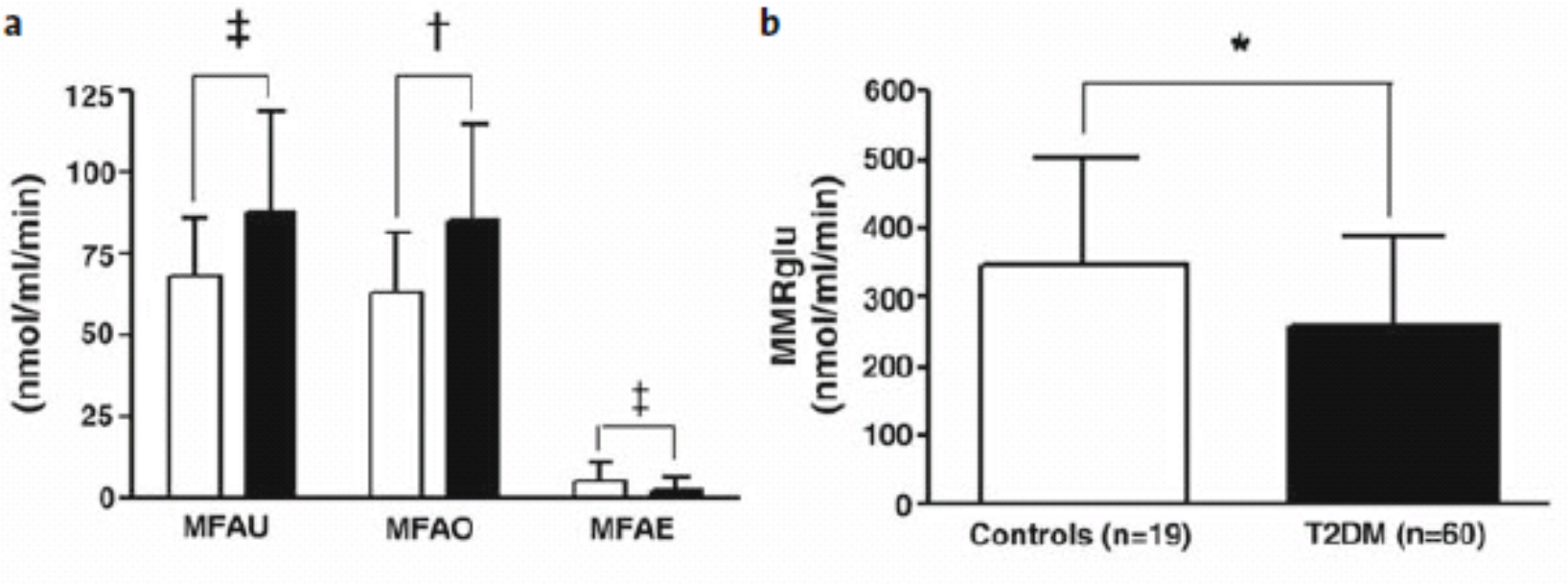
Aneja A et al. Am J Med 121 (2008): 748–757
Fang ZY et al. Endocr Rev 25 (2004): 543–567

Prevalence of diabetes in heart failure trials

Trial	Journal	Year	%
CONSENSUS 1	New Engl J Med	1988	23
SOLVD	New Engl J Med	1991	21
NETWORK	Europ Heart J	1998	10
ATLAS	Europ Heart J	2000	19
MERIT-HF	JAMA	2000	24
RESOLVD	Europ Heart J	2000	35

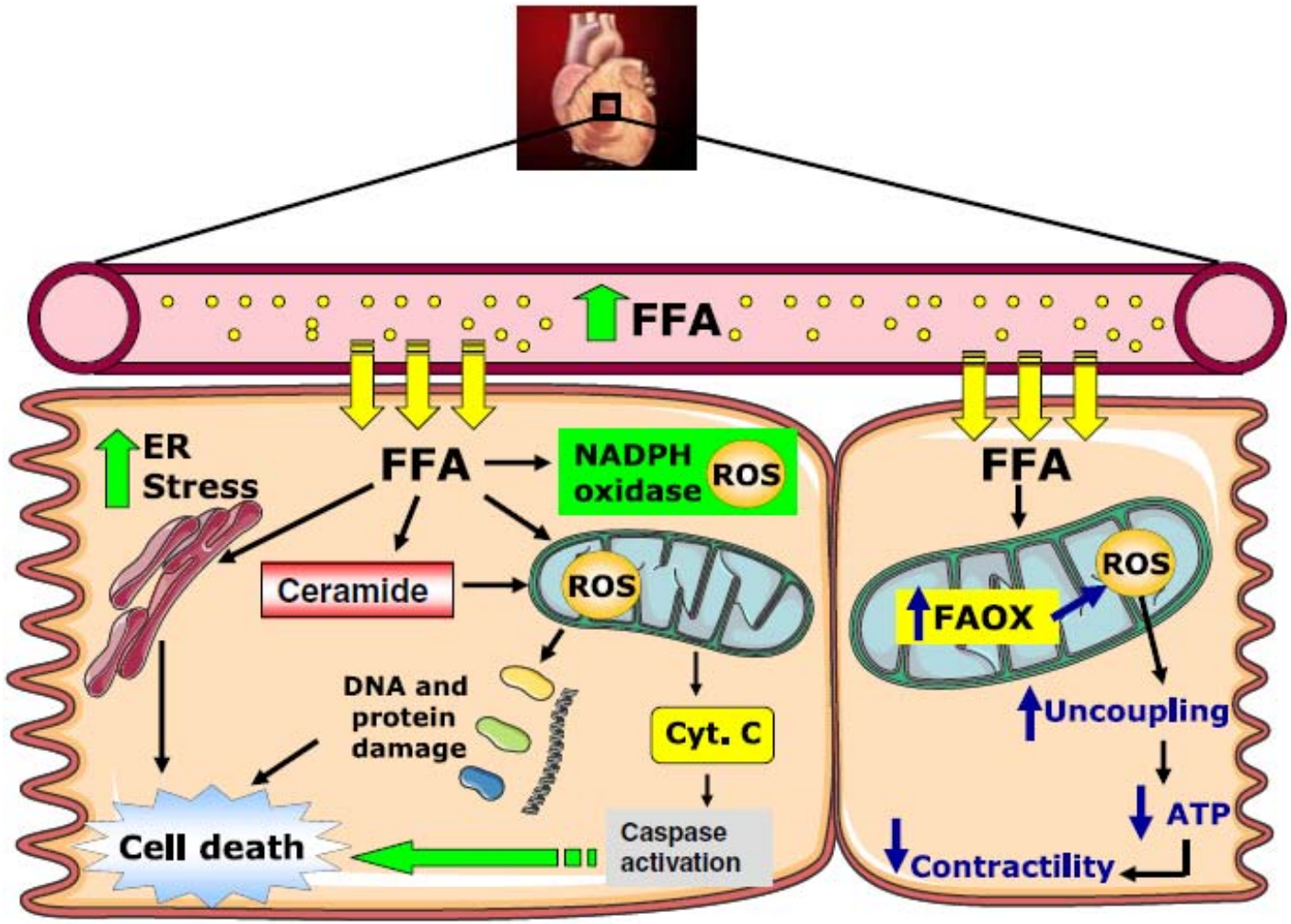
Diastolic heart failure characterizes diabetic cardiomyopathy and accounts for approximately 50% of all cases with heart failure

Nonischemic diabetic cardiomyopathy: Myocardial fatty acid uptake (MFAU), oxidation (MFAO), esterification (MFAE) and metabolic rate of glucose uptake (MMRglu) assessed by PET



Rijzewijk LJ et al. J Am Coll Cardiol 2009; 54:1524-1532

FA-induced cardiac dysfunction in diabetes

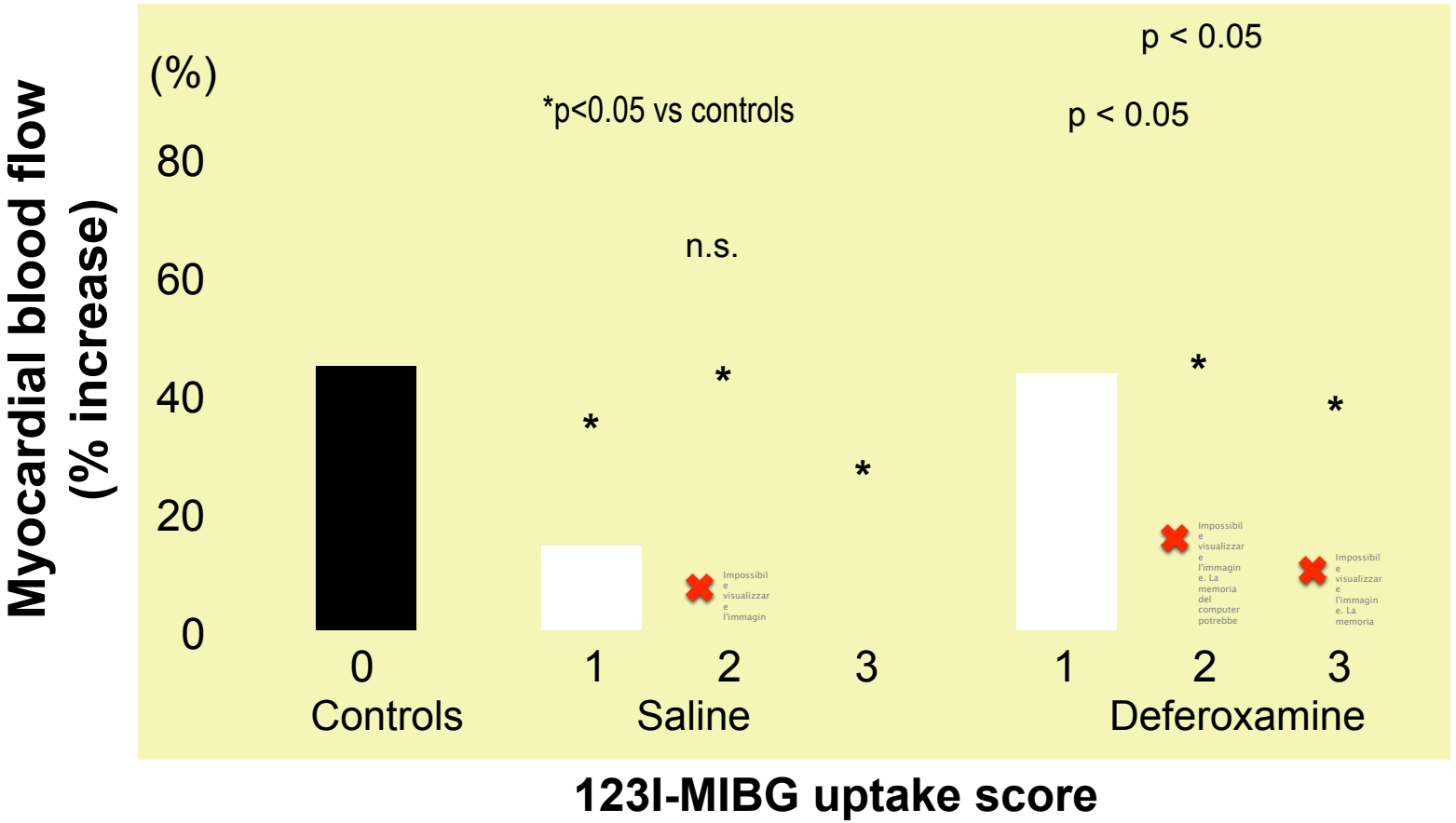


Rijzewijk LJ et al. J Am Coll Cardiol 2009; 54:1524-1532

Iron-catalyzed Fenton reaction

Hattori N, Schnell O et al., Diabetic Medicine (2003) 20: 375-381

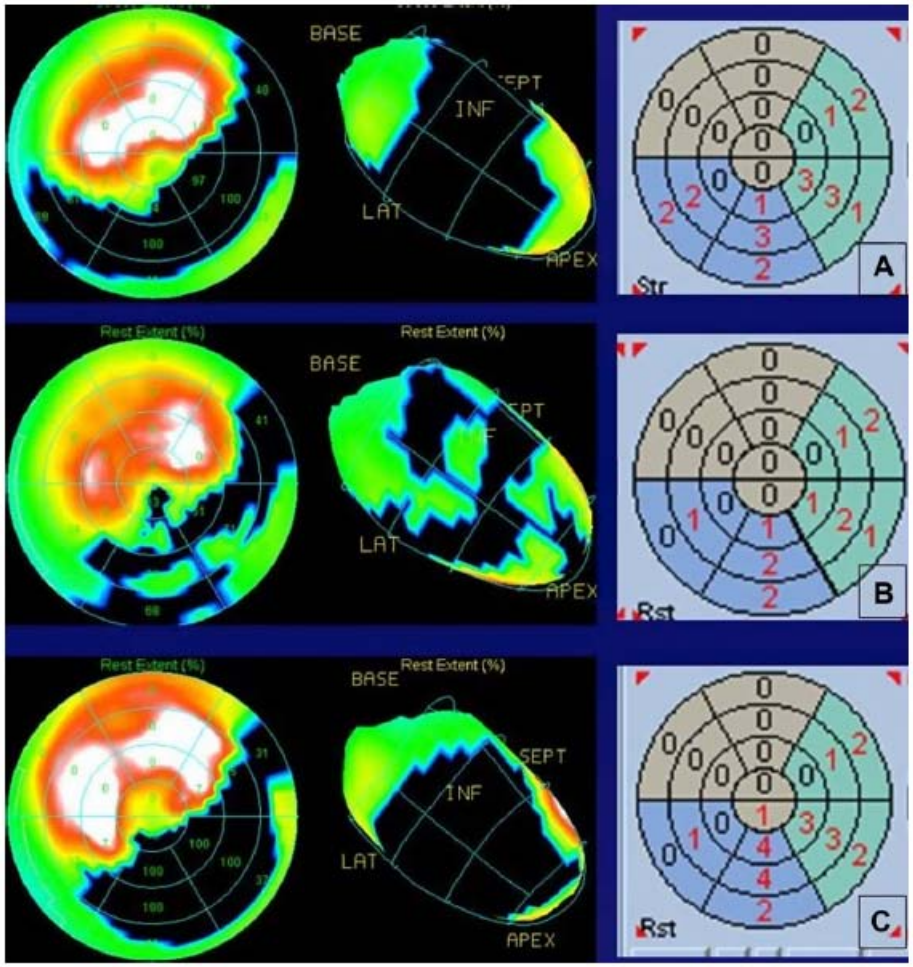
Increase in myocardial blood flow with deferoxamine is related to the extent of cardiac sympathetic denervation



Hattori N, Schnell O et al., Diabetic Medicine (2003) 20: 375-381

Nuclear diagnostic imaging in diabetic cardiomyopathy

Perfusion and neurotransmission



Sasso FC et al. Nutrition, Metabolism Cardiovascular Diseases 2010; 20: 208-216

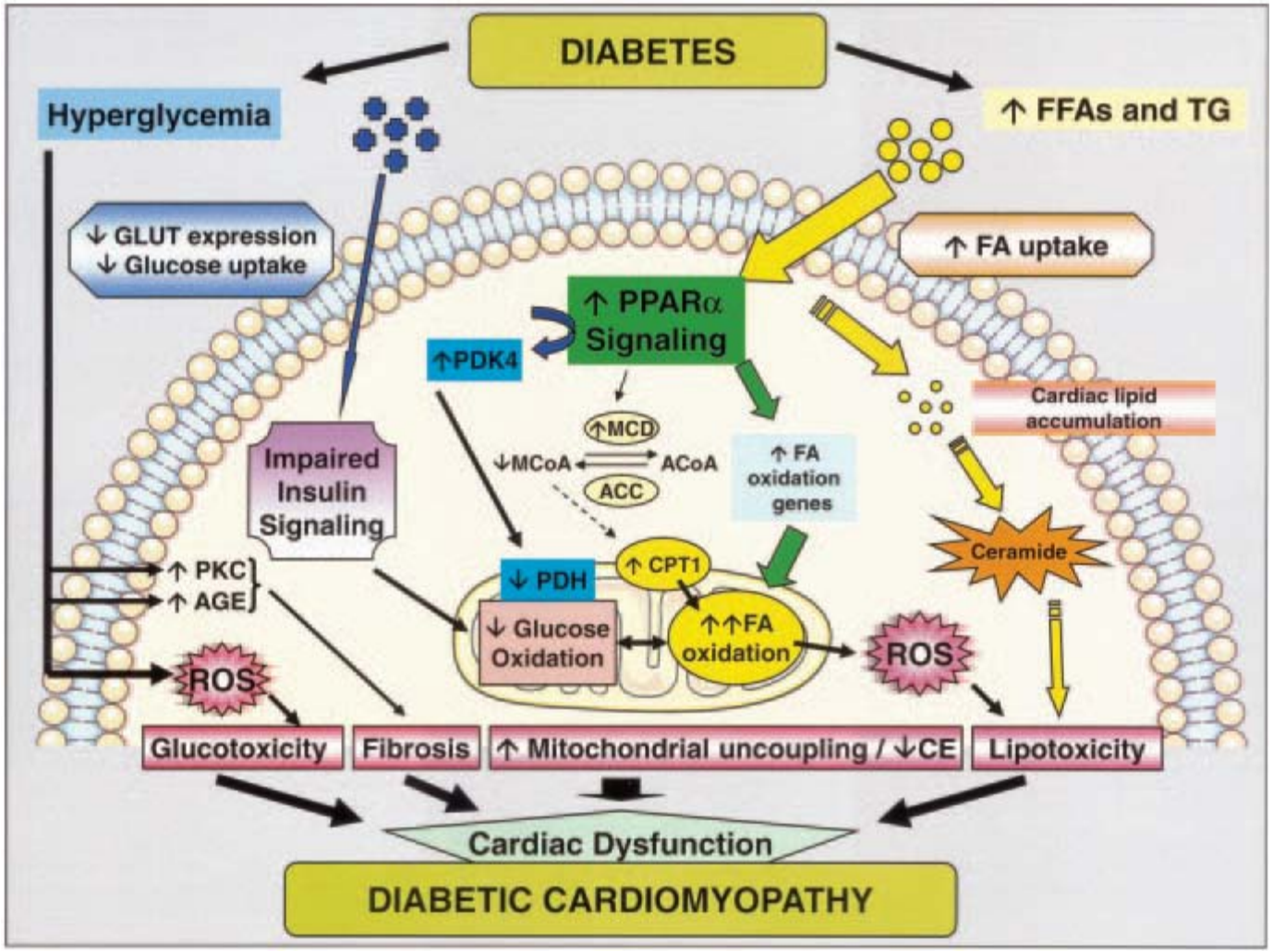
Oxidative stress: a contributor to diabetic cardiomyopathy

- Excess formation of reactive oxygen species (ROS) induced by hyperglycemia, elevated FFA, leptin
- Reduction of antioxidant defenses
- Increase in mitochrondrial ROS generation
- ROS activate genes of pathways involved in the pathogenesis of diabetic cardiomyopathy:

  inflammation
  endothelial dysfunction
  cell death
  cardiovascular remodeling

- Activation of transcription factors, polyol and hexosamine pathways, tyrosine kinase pathways

Hyperglycemia and altered substrate metabolism, ROS, and oxidative stress



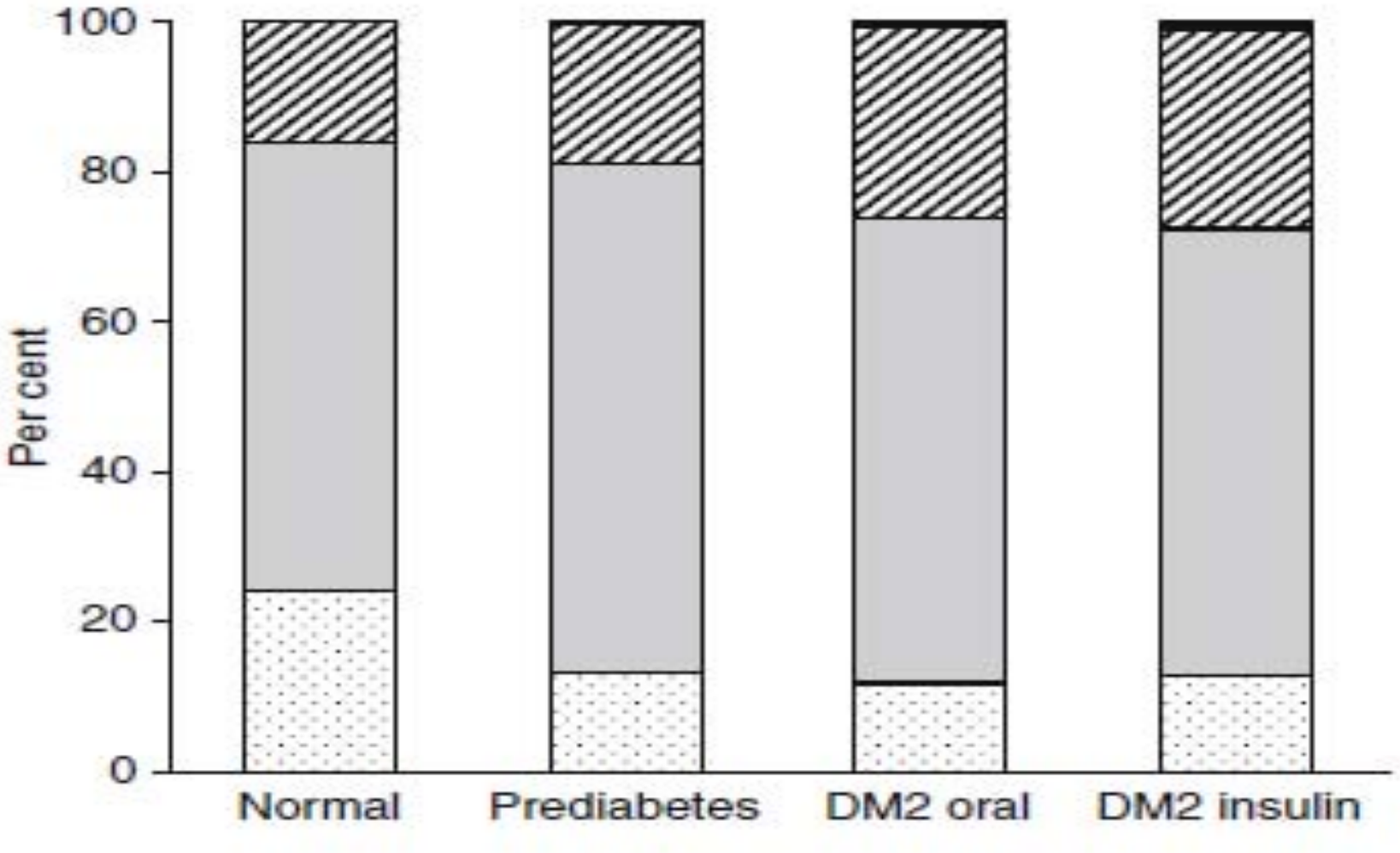
Boudina E, Abel D. Circulation 2007; 115:3213-3223

Natural course of diabetic cardiomyopathy

	Molecular and cellular events	Alterations in structure and morphology	Myocardial performance
Early phase	• Metabolic disturbances: hyperglycemia, increased circulating FFA, insulin resistance • Altered Ca2+ homeostasis • Endothelial dysfunction	• insignificant changes in myocardial structure: normal LV dimensions, wall thickness, and mass	• impaired diastolic compliance with normal systolic function, or no obvious functional changes
Middle phase	• Cardiomyocyte injury, apoptosis, necrosis • Activation of cardiac fibroblasts leading to myocardial fibrosis	• minor changes in structure: slightly increased heart mass, wall thickness or size. • cardiomyocyte hypertrophy • insignificant myocardial vascular changes	• significant changes in diastolic and systolic function
Late phase	• Hypertension • Coronary artery disease • Microangiopathy • Cardiac autonomic neuropathy	• Significant changes in structure: increased heart size, wall thickness and mass • Myocardial microvascular • disease	• Abnormal diastolic and systolic function

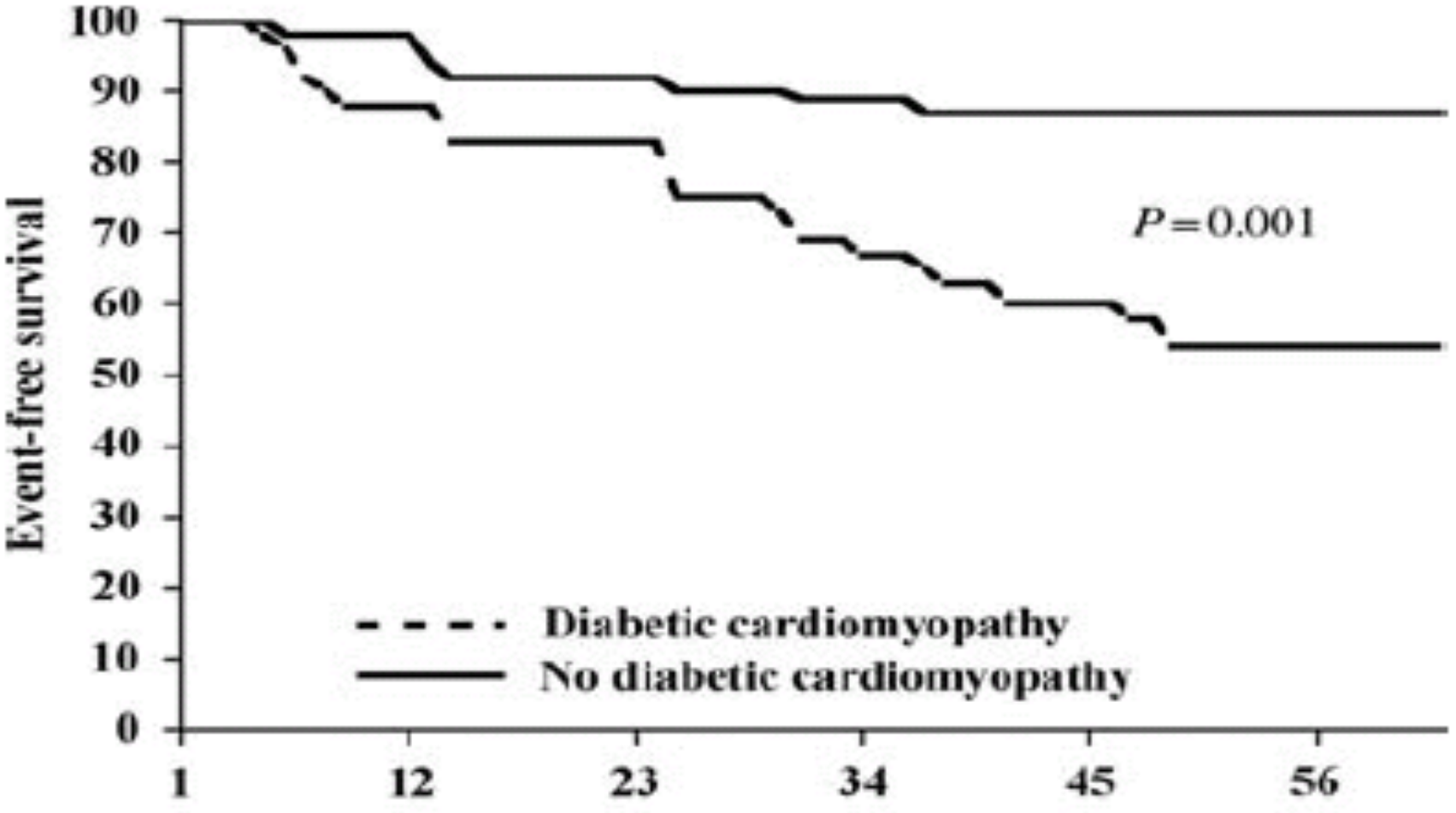
Battiprolu PK et al. Drug Discov Today Dis Mech. 2010; 7(2): e135–e143. doi:10.1016/j.ddmec.2010.08.001

Severity of diastolic dysfunction among patients with various glycemic status



Stahrenberg R et al, Diabetologia 2010; 53:1331-1340

Event-free survival in patients with and without diabetic cardiomyopathy



Kiencke S et al. Eur J Heart Failure 2010; 12:951-957

Structural and morphological features of DCM

- Near-normal end-diastolic volume
- Elevated left ventricular mass relative to chamber volume
- Elevated wall thickness to chamber radius
- Myocardial hypertrophy
- Myocardial fibrosis
- Intramyocyte lipid accumulation

Battiprolu PK et al. Drug Discov Today Dis Mech. 2010; 7(2): e135–e143. doi:10.1016/j.ddmec.2010.08.001

Functional features of DCM

- Abnormal diastolic function (observed in up to 75% of asymptomatic diabetic patients)
- Compromised left ventricular systolic function
- Clinical heart failure

Battiprolu PK et al. Drug Discov Today Dis Mech. 2010; 7(2): e135–e143. doi:10.1016/j.ddmec.2010.08.001

Diagnostic tools and typical findings observed in diabetic cardiomyopathy

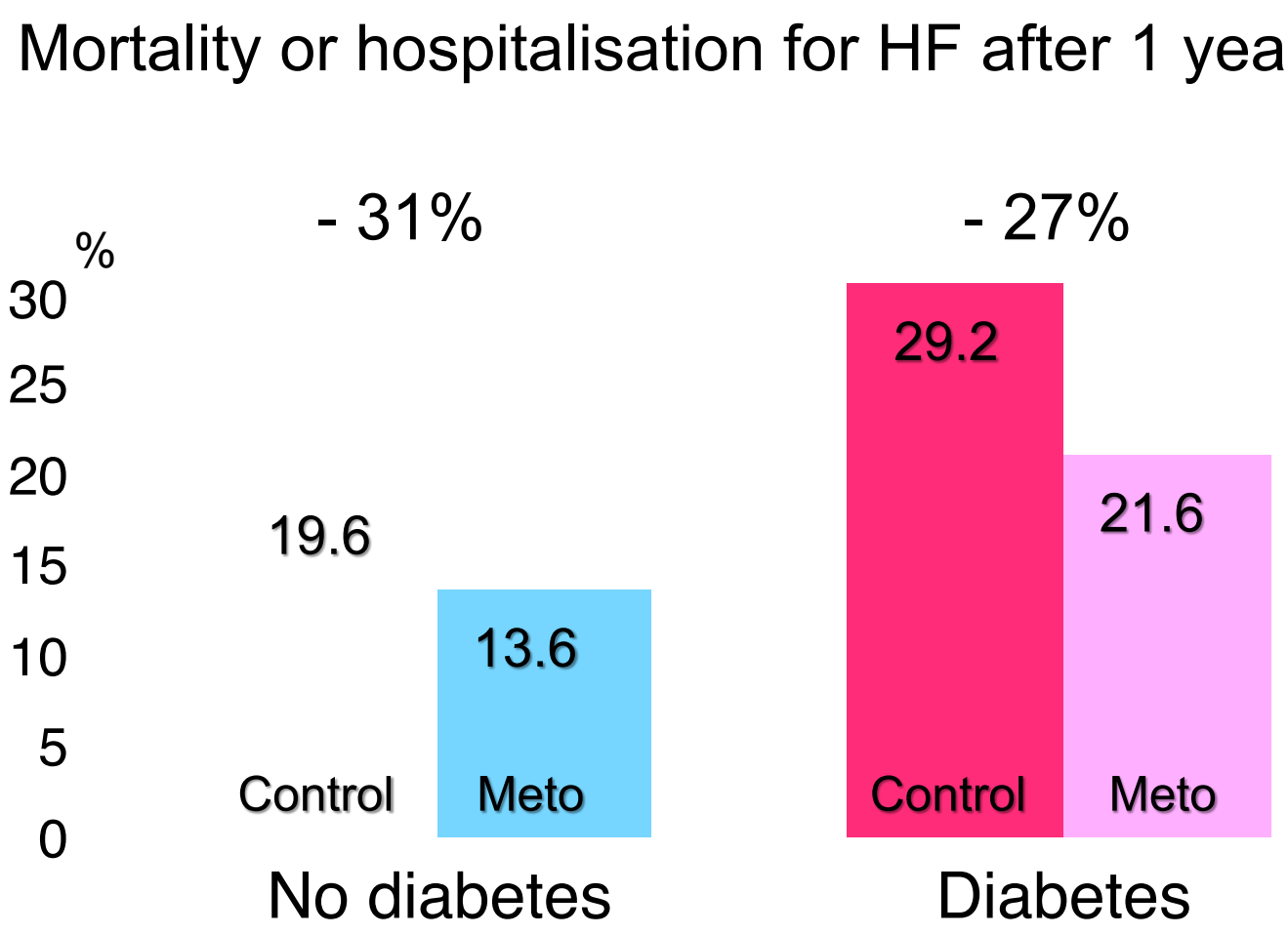
Diagnostic tool	Modality	Results
Echocardiography	• Transmitral Doppler	• Increased left ventricular mass and diameter
	• Pulmonary venous blood flow • Color M-mode • Tissue Doppler imaging Tissue Doppler imaging-strain Tissue Doppler imaging-strain-rate	• Diastolic dysfunction by flows • Systolic dysfunction • Decreased tissue velocities
Magnetic resonance imaging (MRI)	• MRI	• Increased left ventricular mass and diameter
	• Late gadolinium enhancement MRI • 1H-magnetic res. spectroscopy • 31P-magnetic res. spectroscopy	• Diastolic and systolic dysfunction • Myocardial fibrosis • Triglyceride content Myoc. phosphocreatine to ATP ratio
Serum biomarkers	• Serum aminoterminal propeptide of type I and type III, carboxyterminal telopeptide of type I collagen	• Extracellular matrix turnover
	• Matrix metalloproteinases, tissue inhibitor metalloproteinases • B-natriuretic peptide (BNP)	• BNP left ventricular synthesis

Maya L, Villarreal FJ. J Mol Cell Cardiol 48 (2010): 524–529

Effect of angiotensin receptor blockade in heart failure trials by diabetic state

Trial	Patients **no**	Diabetes **%**	Mortality reduction **%**	
CONSENSUS	*253*	*18*	*31*	*after 1 year*
SAVE	*2231*	*22*	*19*	*all cause*
			21	*CVD*
ATLAS	*3164*	*19*	*14*	*with high dose*
GISSI 4	*18131*	*15*	*30*	*after 6 weeks*

Effect of beta-blockade
Subgroup analysis from the MERIT-HF trial

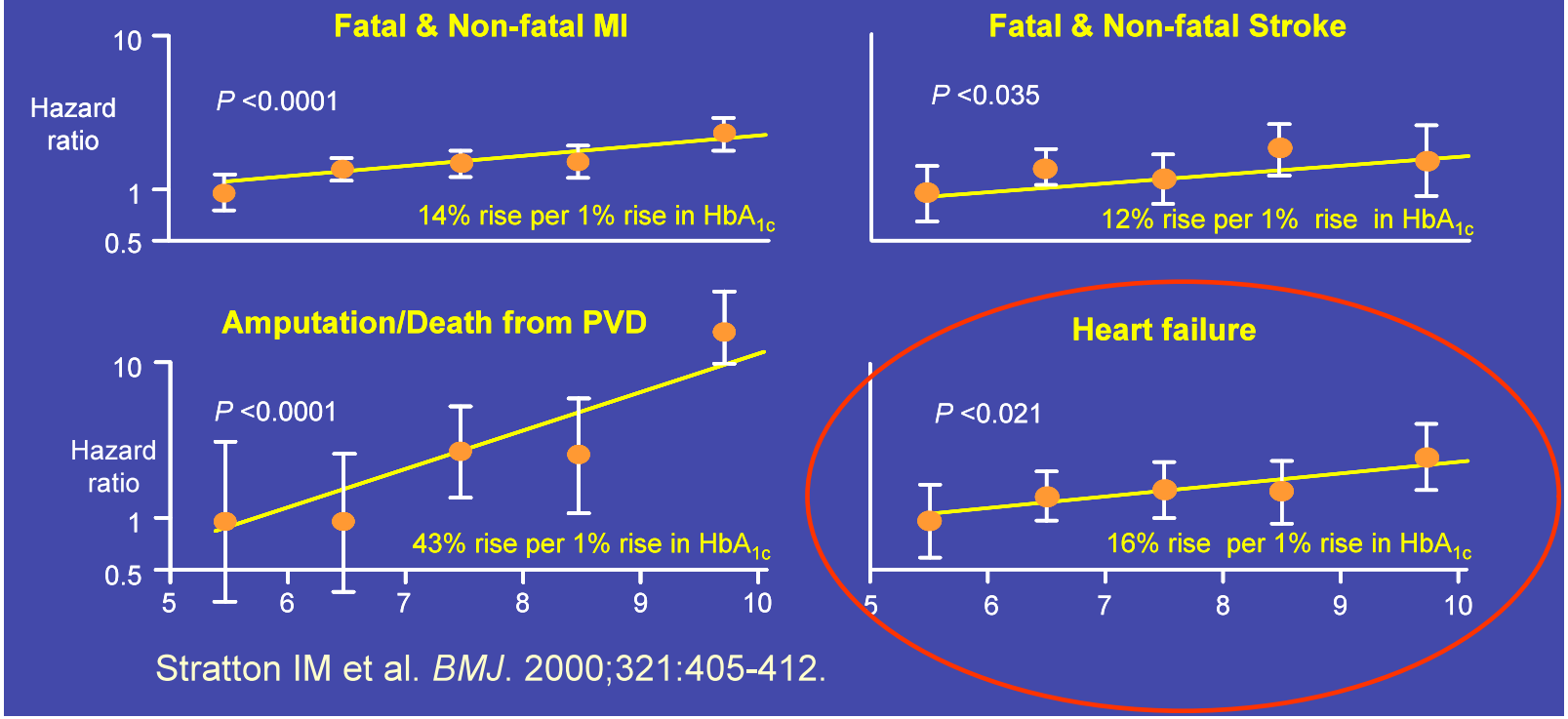


(Hjalmarson et al JAMA 2000;283:1295)

UKPDS: HbA1c and heart failure

Diabetes, Glucose, and CV Disease

- Diabetes (DM) is an established risk factor for CVD
- In DM, higher glucose levels/HbA1c predict higher CV risk



Stratton IM et al. *BMJ*. 2000;321:405-412.

Contradictory effects of insulin on the vascular system

Insulin

IRS-1
↓
PI3-kinase
↓
PDK-1
↓
Akt

Vacular effects

Shc
↓
Grb-2 / Sos
↓
Ras
↓
Raf
↓
MAP-kinase
↓
Downstream-Effectors

NO-dependent vasodilatation

Endothelial independent vasolidatation

Glucose uptake

ET-1

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\+

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Vascular effects

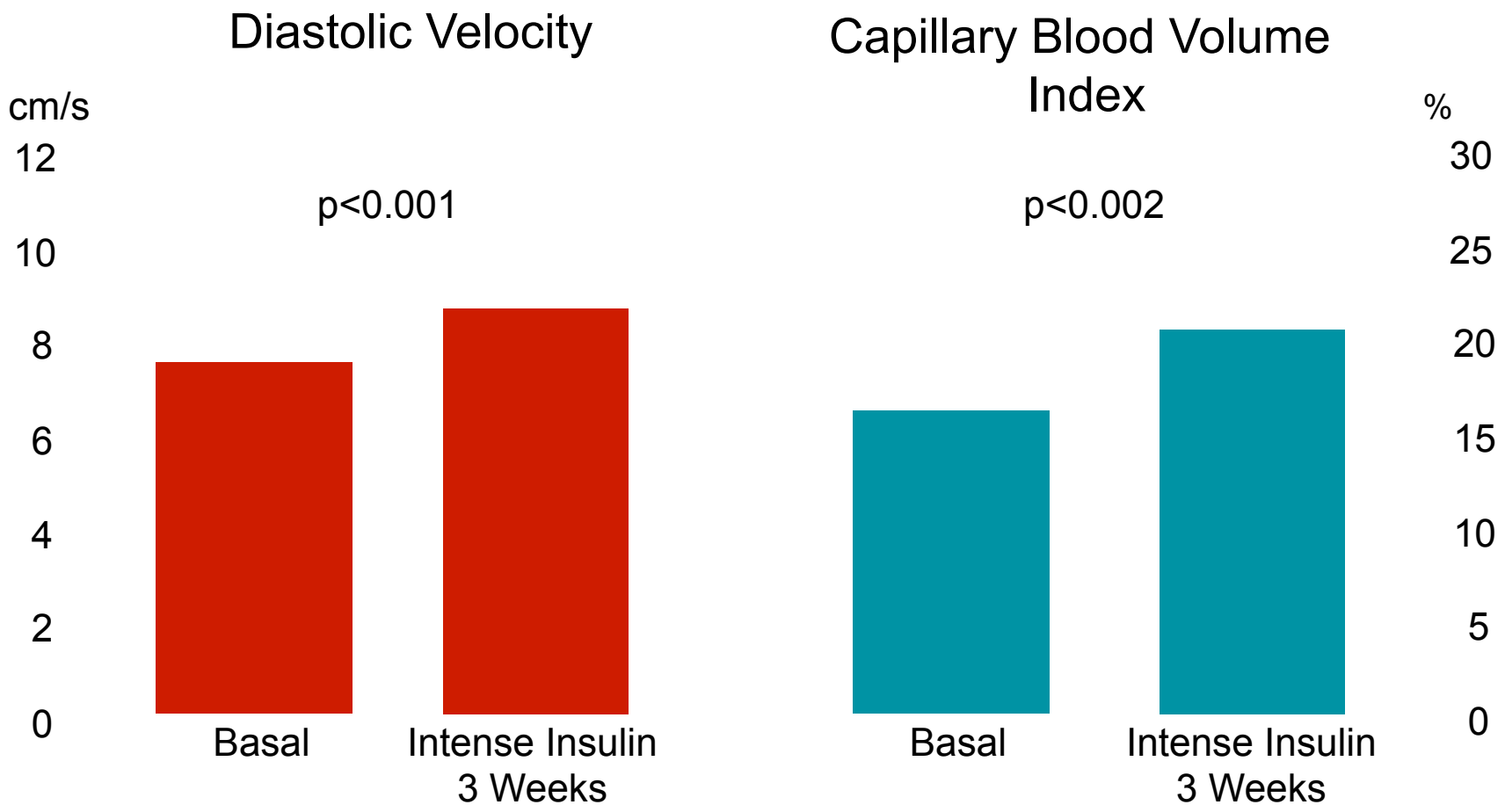
Metabolic effects

Vascular effects

Kim J et al. Circulation 2006;113:1888–1904

Diabetes

Can glucose control improve diastolic function?



von Bibra, Rydén et al Heart 2004; 90:1483

Diabetes

Can glucose control improve diastolic function

Insulin glargine + Insulin Aspart

Type 2 diabetes

Diastolic dysfunction

R

Selfcontrol and diary

Screening
Echo
Diastol dysfunct
FBG > 6,1
BMI >24 - 31
HbA1c >6,5 – 8
Laboratory specimens

8 weeks

Run in
Titration of Insulin & OGLD

Oral glucose lowering agents
Metformin + Repaglinid

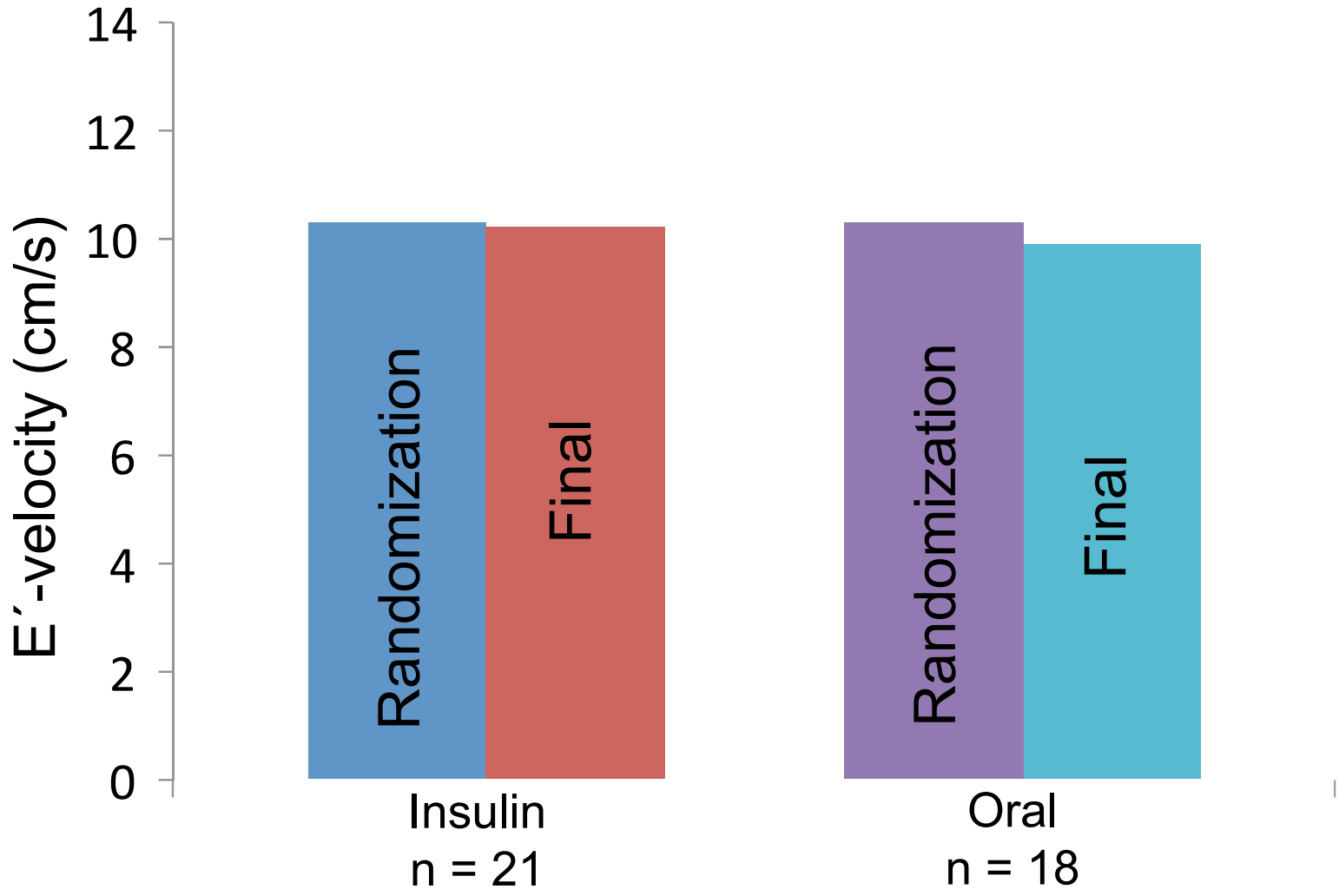
4 months

At first and final visit
Echo + DTI & Contrast
HbA1c, FBG
Lab

(Jarnert et al Eur J Heart Fail 2009; 11:39)

Diabetes

Can glucose control improve diastolic function ?



(Jarnert et al Eur J Heart Fail 2009; 11:39)

Treatment approaches

- **Glycemic control**
  Further studies needed before aggressive glucose normalisation can be recommended as a possibility to improve prognosis
- **Neurohormonal Antagonism**
  The use of ACE-inhibitors, angiotensin receptor blockers, and aldosteron antagonists in preventing the morphological and functional abnormalities being associated with diabetic cardiomyopathy is supported
- **Novel Therapies**
  In experimental stages (e.g. AGE inhibitors, AGE cross-link breakers, copper chelation therapy) or to be studied specifically in patients with diabetic cardiomyopathy (Trimetazidine [modulation of FFA metabolism], Exenatide)

Aneja A et al. Am J Med 121 (2008): 748–757

Echocardiographic findings

The association between diabetic cardiomyopathy and the presence of cardiac hypertrophy and myocardial stiffness, both independent of hypertension, is supported by several studies

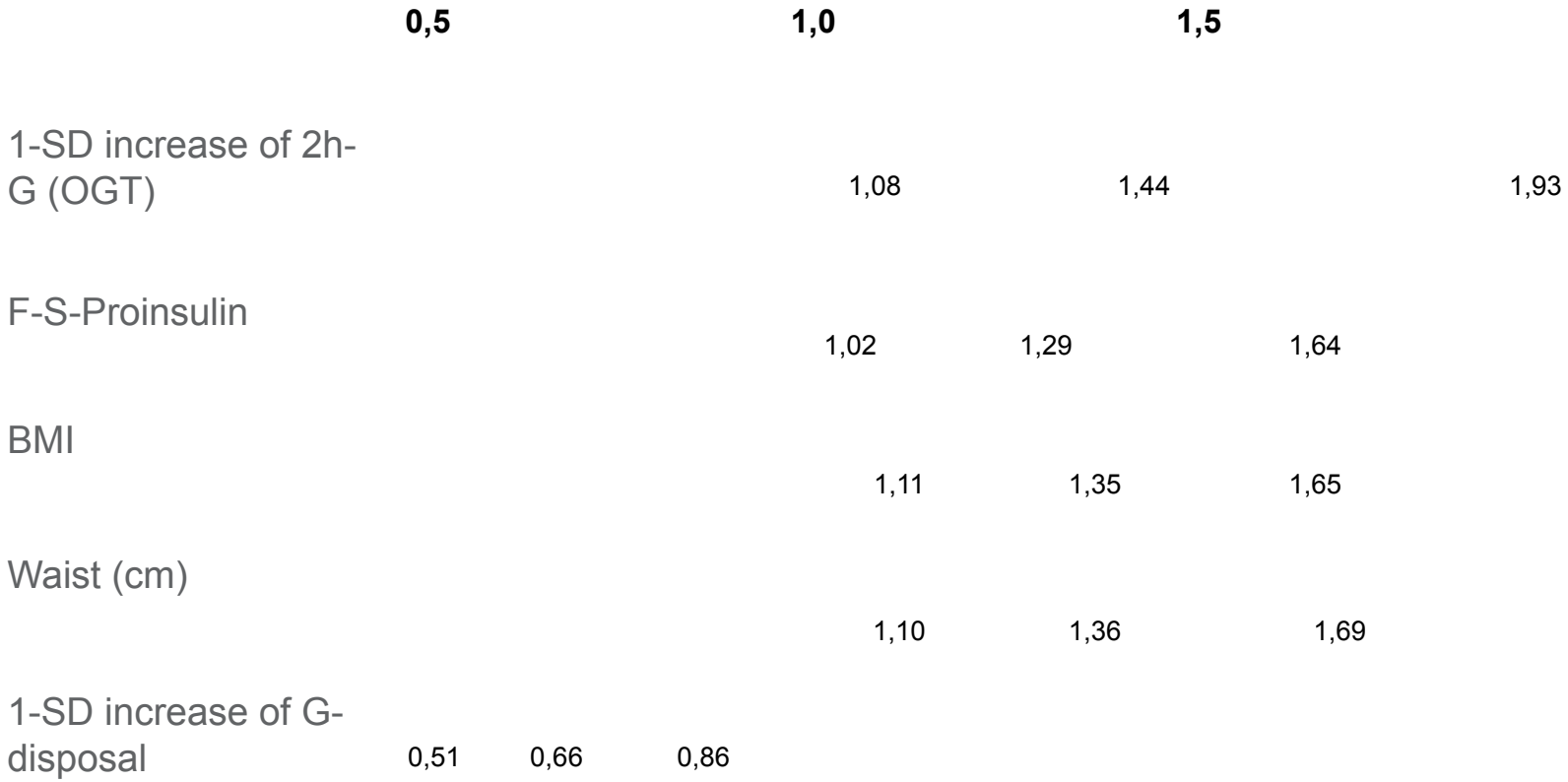
Authors	Year	Findings	Population Sample (n)
Galderisi et al[9]	1991	Increase of LVM in women	111 DM
Framingham Heart Study			381 IGT
Lee et al[10]	1997	Increase of LVM in both genders	2697 DM or IGT
Cardiovascular Health Study			>65 y
Devereux et al[11]	2000	Increase of LVM, reduction of EFS and MFS	1810 DM
Strong Heart Study			
Palmieri et al[12]	2001	Increase of LVM and RWT, reduction of MFS	386 DM + HTN
HyperGEN Study			
Ilercil et al[13]	2001	Increase of LVM and RWT	457 IGT
Strong Heart Study			
Bella et al[14]	2001	Progressive increase of LVM and reduction of EFS and MFS in DM and DM + HTN	642 DM
Strong Heart Study			874 DM + HTN
Liu et al[15]	2001	Progressive reduction of E/A ratio and prolongation of DT in DM and DM + HTN	616 DM
Strong Heart Study			671 DM + HTN
Rutter et al[16]	2003	Progressive increase of LVM, RWT, and LA in IGT and DM	186 DM
Framingham Heart Study			343 IGT

DM = diabetes mellitus; EFS = endocardial fractional shortening; HTN = hypertension; IGT = impaired glucose tolerance; LA = left atrium; LVM = left ventricular mass; MFS = midwall fractional shortening; RWT = relative wall thickness.

Aneja A et al. Am J Med 121 (2008): 748–757

Insulin resistance: Predictor of heart failure

Uppsala Longitudinal Study
(n = 1,188 Men ≥ 70 Jahre; Follow-up 8.9 Jahre)



When adding G-disposal to the Cox-models, obesity parameters were no longer significant CHF predictors

Ingelsson et al. JAMA (2005) 294:334

Stages of diabetic cardiomyopathy

Stages	Characteristics	Functional features	Structural features	Study methods
Early stage	Depletion of GLUT4 Increased FFA Carnitine deficiency Ca^{2+} homeostasis changes Insulin resistance	No overt functional abnormalities or possible overt diastolic dysfunction but normal ejection fraction	Normal LV size, wall thickness, and mass	Sensitive methods such as strain, strain rate, and myocardial tissue velocity
Middle stage	Apoptosis and necrosis Increased AT II Reduced IGF-I Increased TGF-β1 Mild CAN	Abnormal diastolic dysfunction and normal or slightly decreased ejection fraction	Slightly increased LV mass, wall thickness, or size	Conventional echocardiography or sensitive methods such as strain, strain rate, and myocardial tissue velocity
Late stage	Microvascular changes Hypertension CAD Severe CAN	Abnormal diastolic dysfunction and ejection fraction	Significantly increased LV size, wall thickness, and mass	Conventional echocardiography

AT II, Angiotensin II; CAD, coronary artery disease.

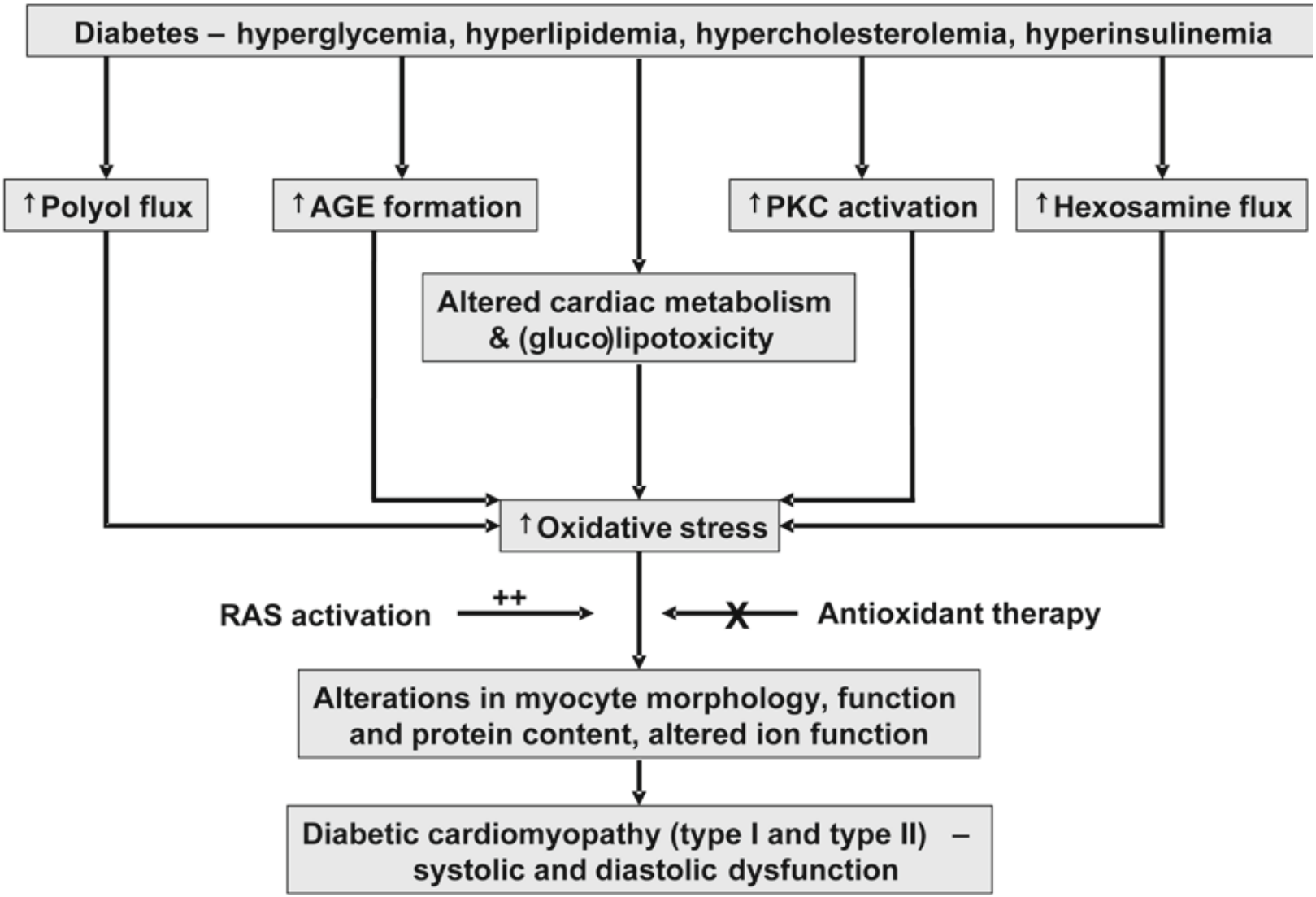
Fang ZY (Sasso FC) et al. Endocrine Reviews 2004; 25:543-567

Epidemiological data*

- **Macrovascular complications (CAD, peripheral vascular disease, stroke) are 2–4 times more frequent in patients with diabetes compared to non-diabetic people[1]**
- **In patients with T2DM, even under treatment of all associated CV risk factors and despite of a reduction of CV events by 50%, the CV mortality still remains high[2]**
- **Frequency of CAD is twice more common in patients with diabetes of both sexes. Death from CAD is 3 times more common in diabetic patients compared with nondiabetics (Framingham Study[3])**
- **The prevalence of heart failure with preservation of systolic function among patients with diabetes is 19%–26%**
  (ATLAS[4]: 19% – V-HeFT II[5]: 20% – SOLVD[6]: 26%)
- **In summary, CV disease is 2–3 times more common, and survival is worse in people with diabetes vs. age- and sex-matched controls**

*Voulgari C. Vasc Health & Risk Man 2010:6 883–6903
[1]Zimmet P. Nature 2001;414:782–787 / [2]Haffner SM et al. N Engl J Med 1998;339:229–234 /
[3]Kannel WB. JAMA 1979;241:2035–2038 / [4]Ryden L et al.Eur Heart J. 2000;21:1967–1978 /
[5]Cohn JN et al. N Engl J Med. 1991;325:303–310 /
[6]Shindler DM et al. Am J Cardiol 1996;77:1017–1020

Contributing factors to oxidative stress



Stratmann B et al. Herz 2010; 35:161-168

Clinical aspects of diabetic cardiomyopathy

- **Diastolic heart failure characterizes diabetic cardiomyopathy and accounts for approximately 50% of all cases with heart failure**
- **Tissue Doppler imaging should be combined with conventional echocardiography to optimize the detection of diastolic dysfunction**
- **Cardiac hypertrophy and fibrosis indicate diabetic cardiomyopathy**
- **Because of a lack of clinical intervention trials, specifically in patients with diabetic cardiomyopathy, currently no evidence-based interventions for the specific treatment of diabetic cardiomyopathy may be present**

Khavandi K et al. Best Pract & Res Clin Endocrin & Metabol 23 (2009) 347–360

Hyperglycemia and altered substrate metabolism, ROS, and oxidative stress

Summary

- Altered Free Fatty Acid Metabolism: Increase in myocardial fatty acid uptake and oxidation, decrease in esterification
- Increase in oxidative stress characterized by an increase in ROS, early inactivation of NO
  Mediated by pathway activation: Polyol-, PKC, Hexosamine-Pathways, formation of AGE
- Impact on NO-dependent vascular effects of insulin action