

Diabetes and Heart failure pathogenesis and therapy

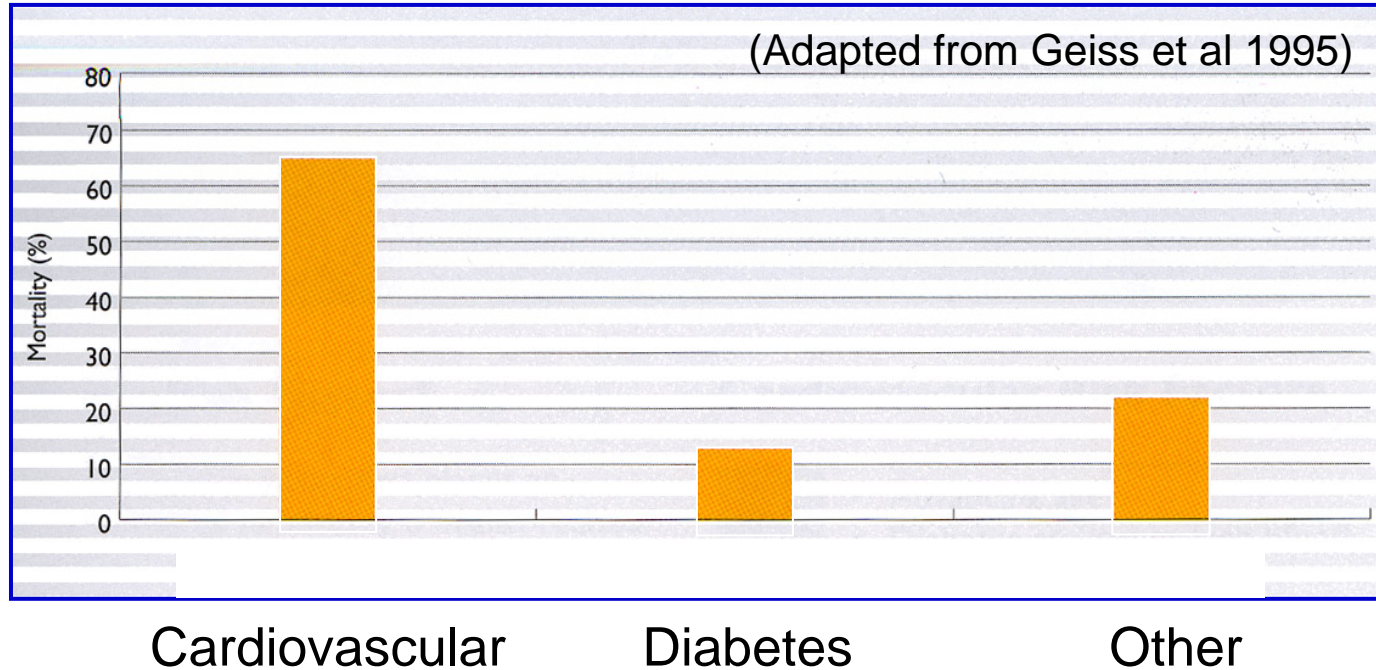
Diabetes and heart failure

- Epidemiology and prognosis

Diabetes and heart failure

Recommendation	Class	Level
ACE-inhibitors are recommended as first-line therapy in diabetic patients with reduced left ventricular dysfunction with or without symptoms of heart failure.	I	C
Angiotensin-II receptor blockers have similar effects in heart failure as ACE-inhibitors and can be used as an alternative or even as added treatment to ACE-inhibitors.	I	C
BBs in the form of metoprolol, bisoprolol, and carvedilol are recommended as first-line therapy in diabetic patients with heart failure.	I	C
Diuretics, in particular loop diuretics, are important for symptomatic treatment of diabetic patients with fluid overload owing to heart failure.	IIa	C
Aldosterone antagonists may be added to ACE-inhibitors, BBs, and diuretics in diabetic patients with severe heart failure.	IIb	C

Background – mortality in diabetes



”Heart failure
...the frequent, forgotten and
often fatal complication of diabetes”

(Bell et al, Diabetes Care 26; 2003)

Diabetes and Risk for Heart Failure

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

Diabetes and Risk for Heart Failure

From the RESOLVD study

n = 663 with CHF NYHA I-IV; mean age 64 years

Category	no	%
Previously known DM	176	27
Newly detected DM	53	8
Elevated FPG (6.1-7.0 mmol/L)	58	9

Proportion with disturbed glucose tolerance
Diabetes mellitus 35% Total with IGT 44%

(Suskin et al Europ Heart J 2000; 21:1368-75)

Heart failure in patients with and without diabetes

Subjects from Kaiser Permanente Northwest (KPNW)
health maintenance organisation

Parameter	Type 2 diabetes n = 8 231	No diabetes n = 8 845
Heart failure	1 167 / 14 %	526 / 6 %
Incid/1 000 pers yrs	31	12
Age (years)	69 ± 10	75 ± 9
Female gender	48 %	46 %

(Nichols et al. Diabetes Care 2004; 27:1879)

Glucose abnormalities and Heart Failure

The Reykjavik Study

n= 19 381

Time period 1967 – 1997

1-6 visits/patient

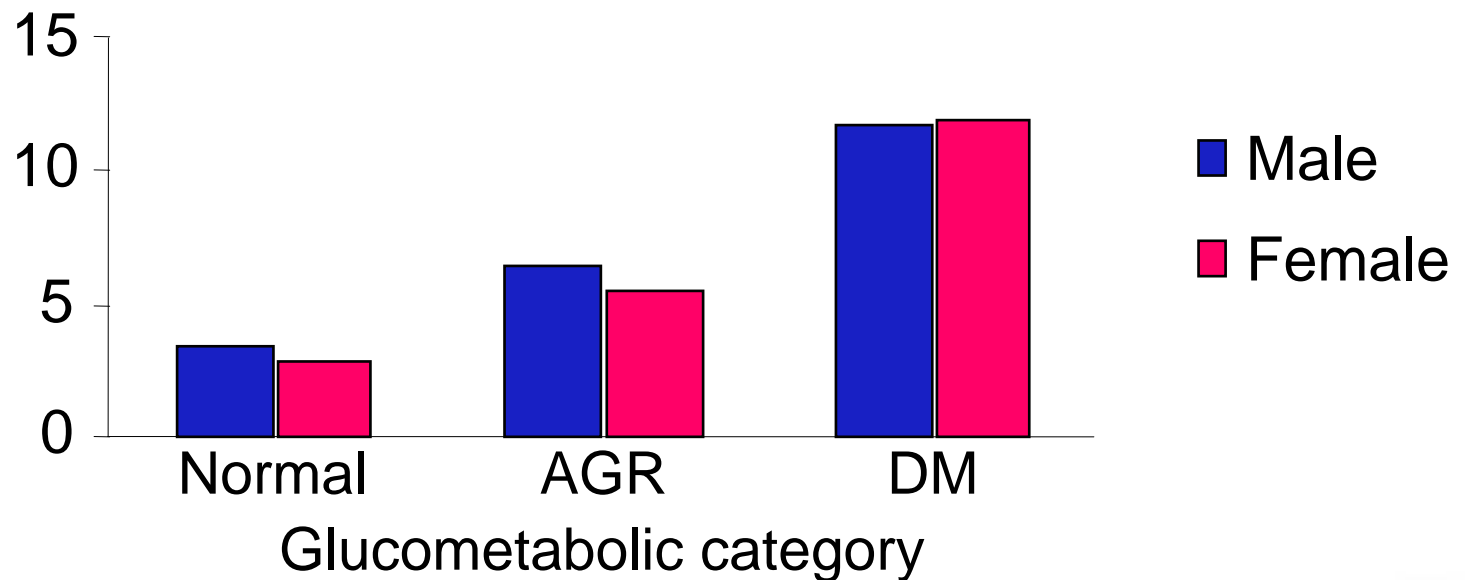
Extensive health and laboratory data including OGTT

Glucose abnormalities and Heart Failure

The Reykjavik Study

Proportion with heart failure according to the glucometabolic state

Prevalence of heart failure (%)



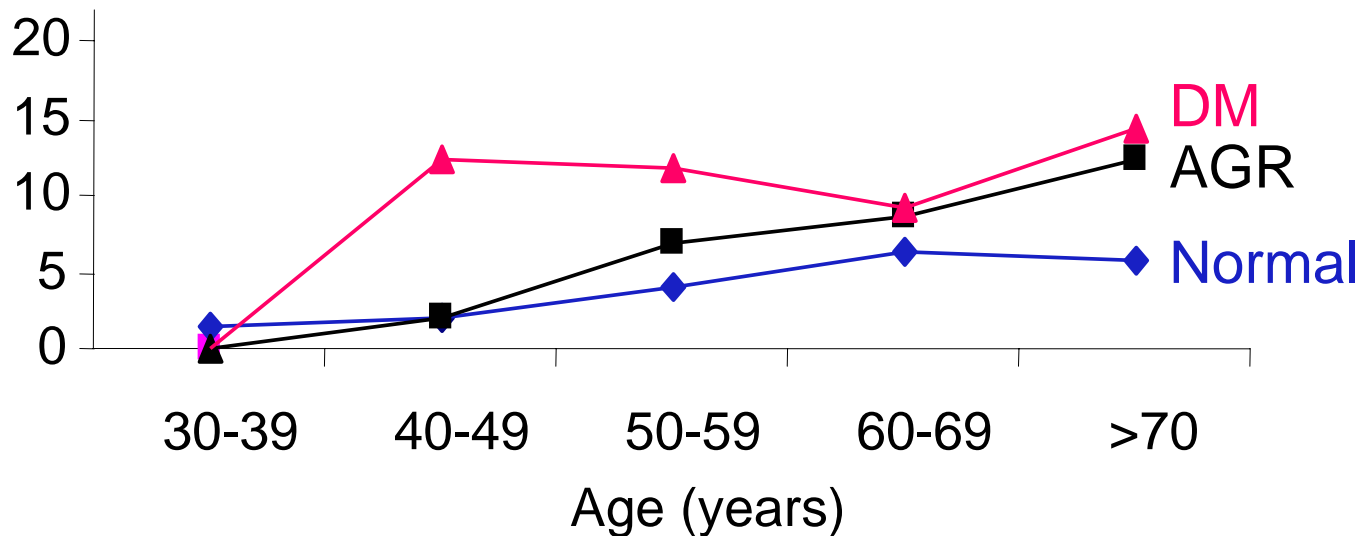
(Thrainsdottir, Aspelund Rydén et al. Diabetes Care 2005; 28: 612)

Glucose abnormalities and Heart Failure

The Reykjavik Study

Prevalence of glucose abnormalities and heart failure related to age and glucometabolic state in men

Prevalence (%)

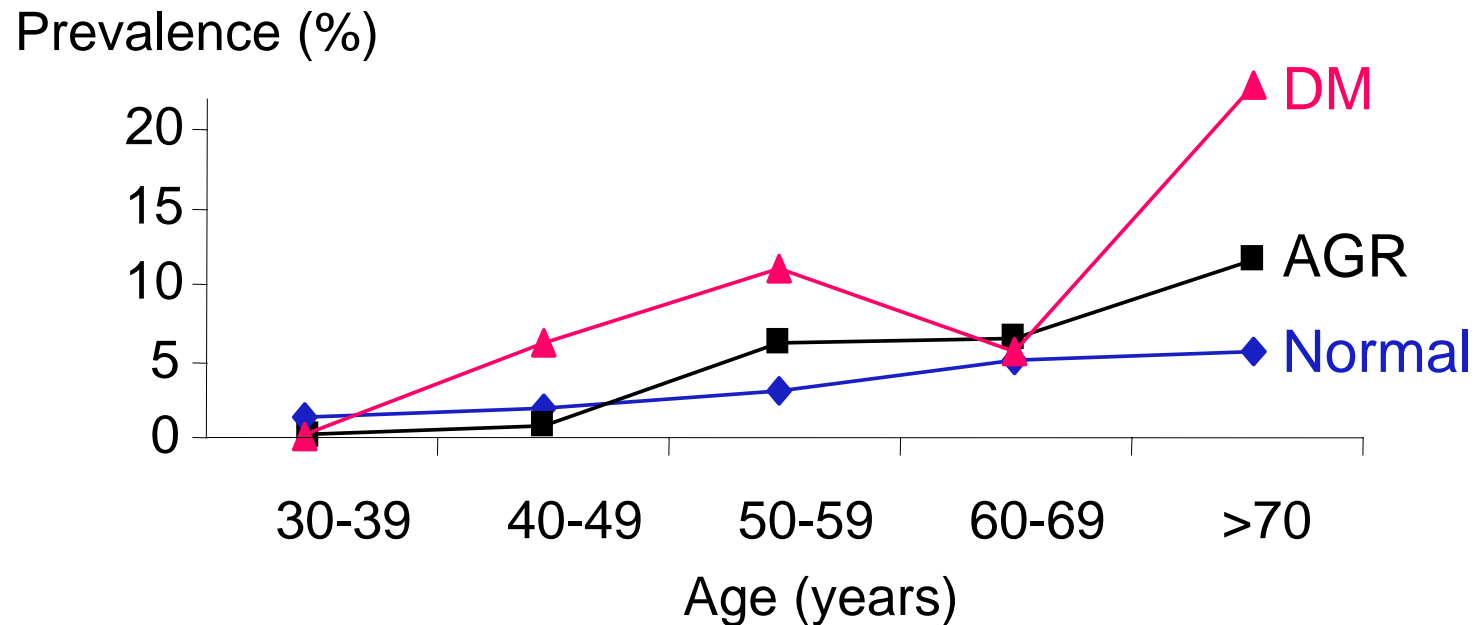


(Thrainsdottir, Aspelund Rydén et al. Diabetes Care 2005; 28: 612)

Glucose abnormalities and Heart Failure

The Reykjavik Study

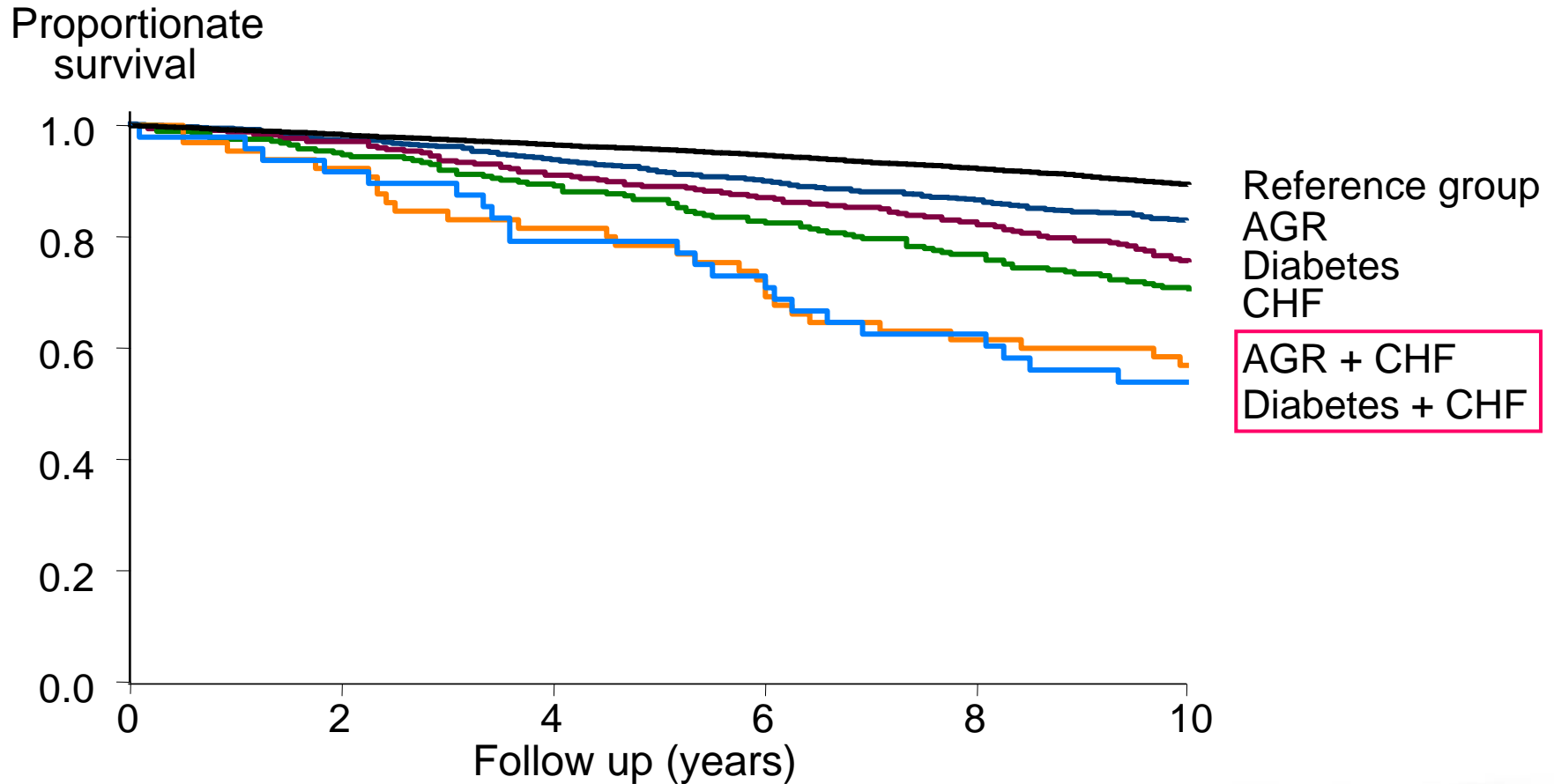
Prevalence of glucose abnormalities and heart failure related to age and glucometabolic state in women



(Thrainsdottir, Aspelund Rydén et al. Diabetes Care 2005; 28: 612)

Reykjavik study

Survival curves related to glucose abnormality & heart failure



(Thrainsdottir, Aspelund Rydén et al Eur J Cardiovasc Prev Rehab 2005;12:465)

Glucose abnormalities and Heart Failure

The Reykjavik Study

Total mortality

Adjusted for age, hypertension, BMI, IHD
Hazard Ratios (CI)

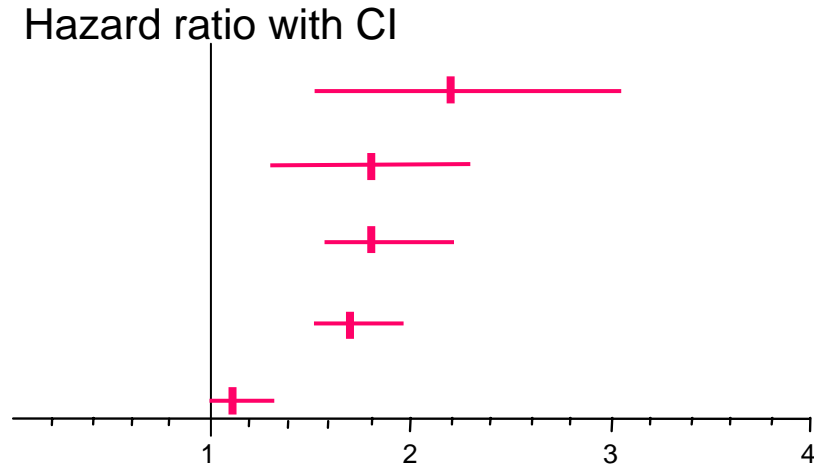
Patient category	Heart failure		p
	Yes	No	
DM Men	1.9 (1.3-2.7)	1.5 (1.3-1.8)	<0.0001
DM Women	2.0 (1.3-3.0)	1.6 (1.3-1.9)	<0.0001
AGR Men	1.9 (1.5-2.5)	1.1 (1.0-1.2)	<0.0001
AGR Women	1.3 (0.9-1.9)	1.2 (1.1-1.3)	<0.0001

(Thrainsdottir, Aspelund Rydén et al Eur J Cardiovasc Prev Rehab 2005;12:465)

Mortality during 30-years follow up time data for all participants (HR; CI) Adjusted for age, SBP, cholesterol, BMI, smoking and IHD

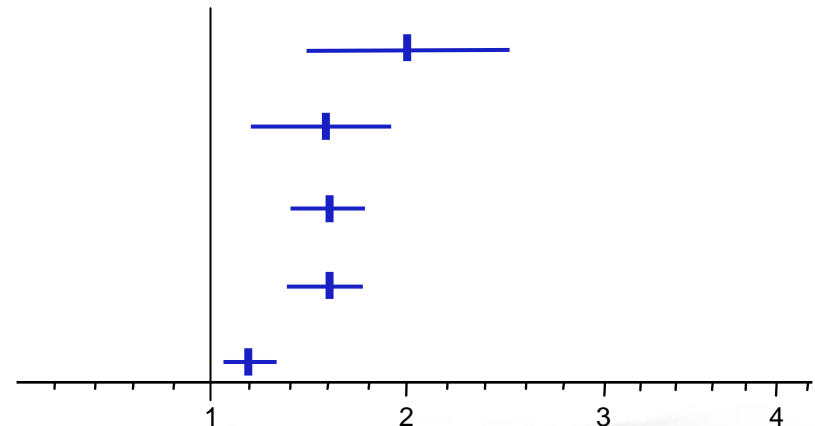
Cardiovascular mortality

- Diabetes and heart failure
- Abnormal glucose regulation and heart failure
- Heart failure
- Diabetes
- Abnormal glucose regulation



All cause mortality

- Diabetes and heart failure
- Abnormal glucose regulation and heart failure
- Heart failure
- Diabetes
- Abnormal glucose regulation



(Thrainsdottir, Aspelund Rydén et al Eur J Cardiovasc Prev Rehab 2005;12:465)

Diabetes and heart failure

Long term survival in diabetes and heart failure

Patients (no) 1 246
Referrals for HF LV ejection fraction <45%
Diabetes Treated or history of FBG >7.0 x 2

Investigations

Echocardiography
Cardio-pulmonary exercise test
Coronary arteriography

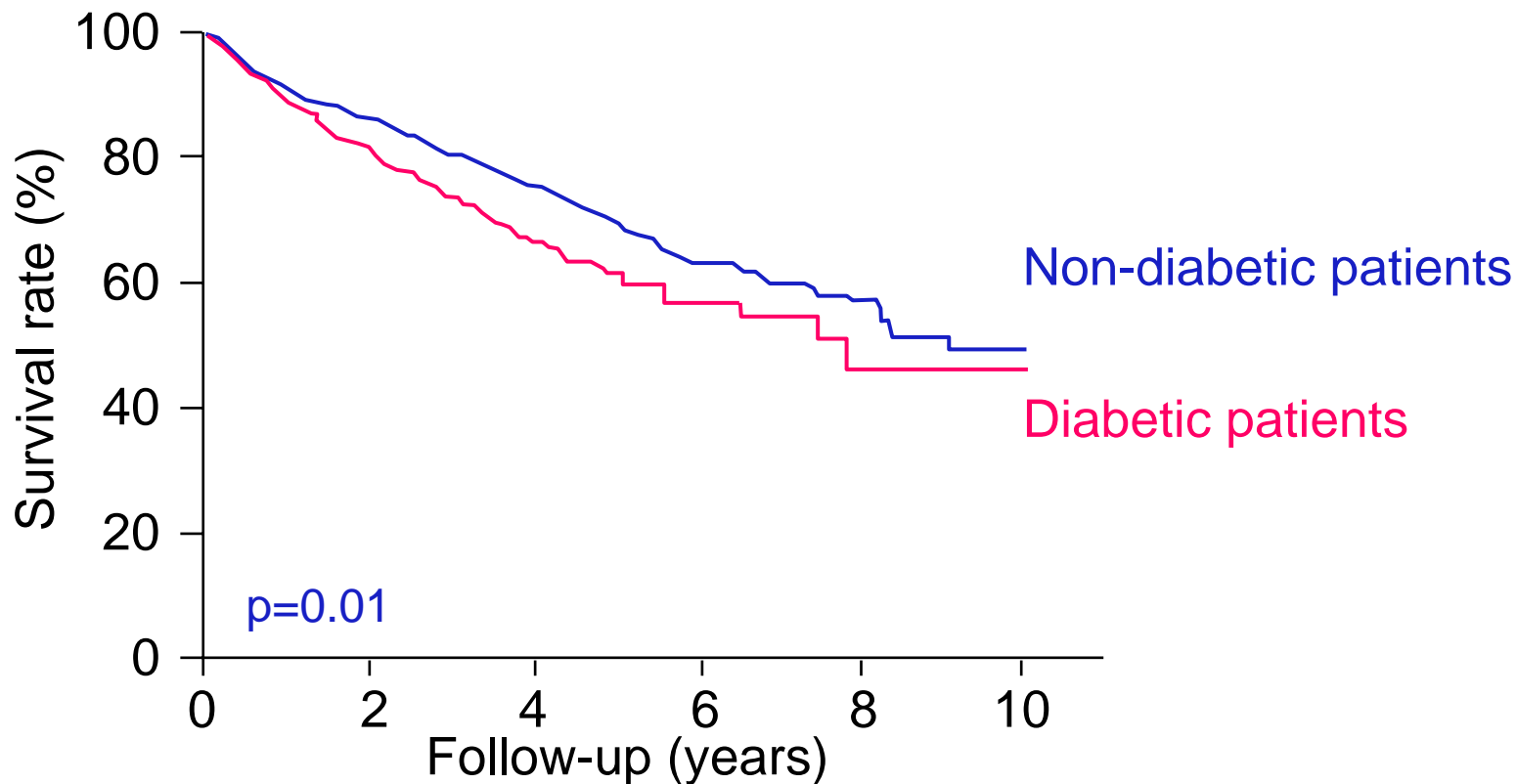
Etiology

Ischemic MI or coronary stenosis >50%

(de Groote et al Europ Heart J 2004; 25:656)

Diabetes and heart failure

Long term survival in diabetes and heart failure



Patients at risk: 1246 839 509 249 118

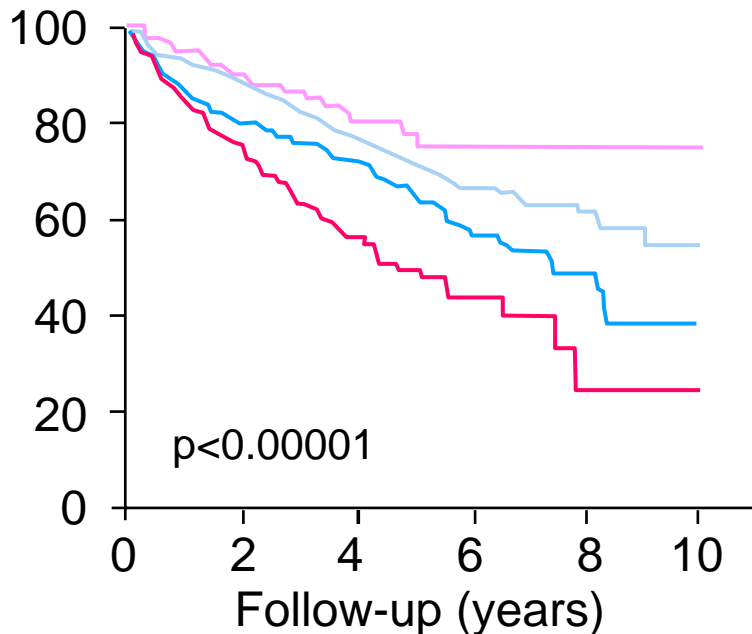
(de Groote et al Europ Heart J 2004; 25:656)

Diabetes and heart failure

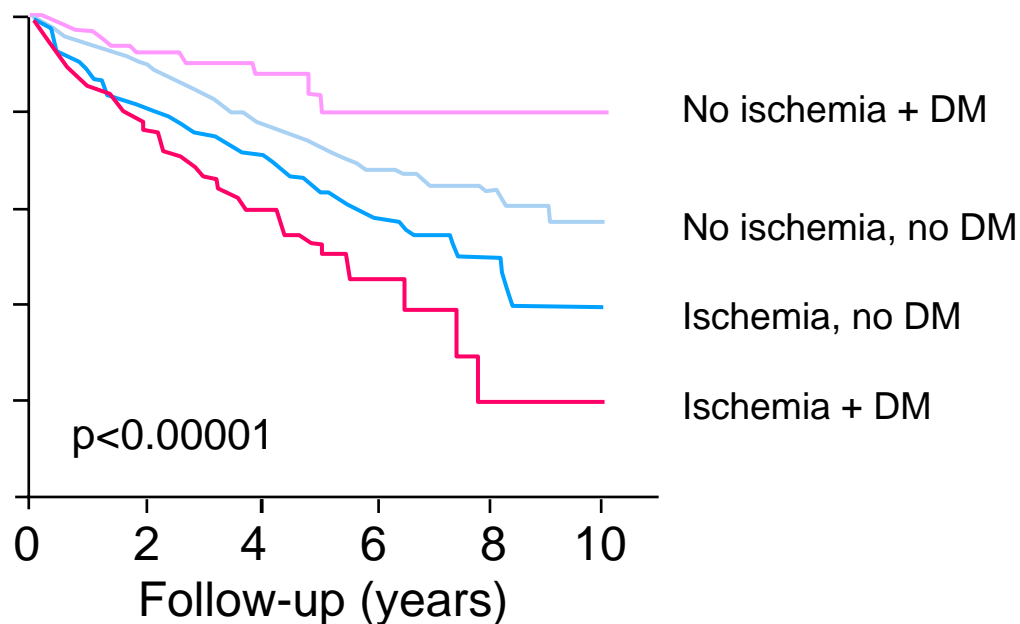
Long term survival in diabetes and heart failure

Diabetes = on hypoglycaemic drugs or FBG > 126 mg/dL

Survival rate (%)



Diabetes = on hypoglycaemic drugs

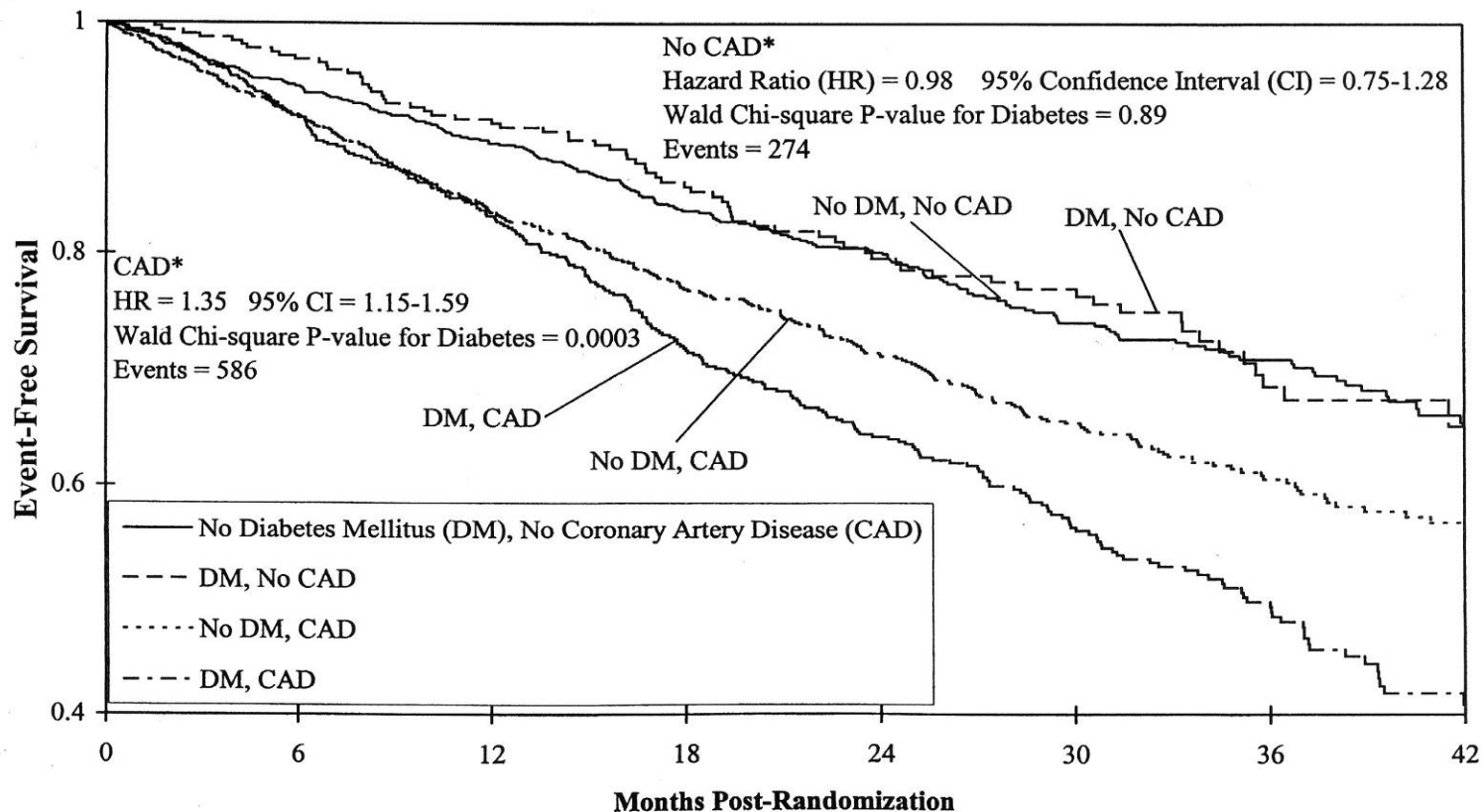


(de Groote et al Europ Heart J 2004; 25:656)

Diabetes and heart failure

Experiences from the BEST trial

Patients 2 708; NYHA III-IV; Diabetes 35% (964)



(Domanski et al J Am Coll Card 2003; 42:914)

Diabetes and heart failure

- Epidemiology and prognosis
- **The diabetic cardiomyopathy**

The Diabetic Cardiomyopathy

Evidence for a diabetes related heart disease

Originally proposed as a specific diabetic angiopathy by Lundbaek 1954

Characteristic features

Diastolic impairment

Lack of response to injury

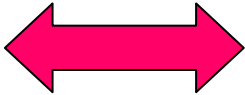

May be related to

Vascular factors (anatomical & functional)

Metabolic disturbances

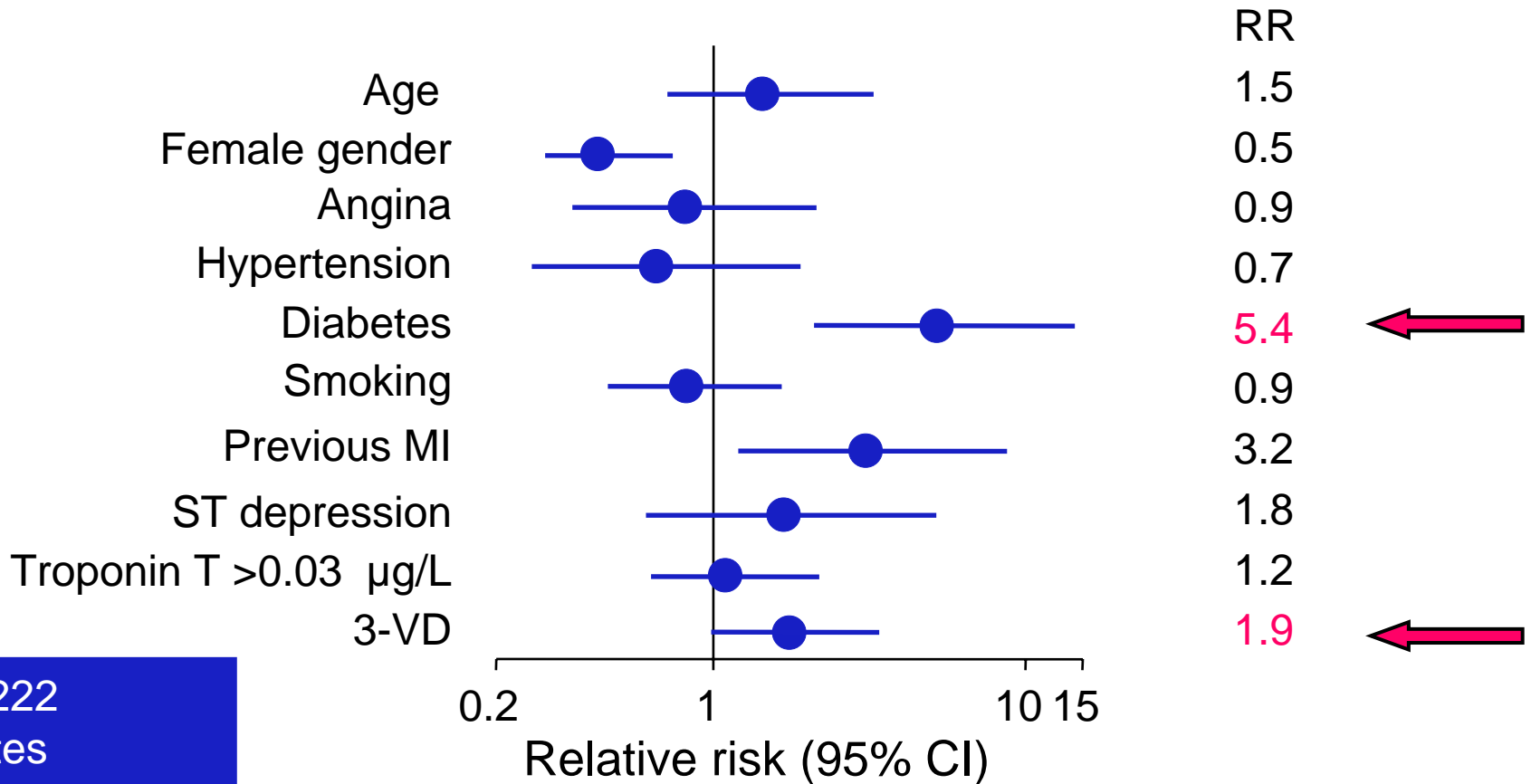
Response to MI in Patients with and without Diabetes Mellitus

Left ventricular function

Parameter	Diabetics	Non-diabetics	p
EF (%)	61	60	NS
Hyperkinesia non-infarct zone			<0.05
Signs of CHF	22	14	<0.001
Diastolic dysfunction	+++	+/-	

(Woodfield et al: Gusto I angiographic part, J Am Coll Card 1996;28:1661)

Mortality predictors in invasively managed patients with ACS (from FRISC 2)



n = 1 222
 Diabetes
 No 1 067
 Yes 155

(Norhammar et al Europ Heart J 2003; 24:838-48)

The Diabetic Cardiomyopathy

Morphological studies

(Hardin Coron Artery Disease 1996;7:99)

(Shehadeh & Regan Clin Cardiol 1995;18:301)

Structural abnormalities

- Myocyte hypertrophy
- Deposition of PAS-positive glycoproteins
- Interstitial edema
- Extracellular matrix accumulation
- Myocyte loss and interstitial fibrosis
- Intramyocardial microangiopathy

Not specific for the diabetic subject

The Diabetic Cardiomyopathy

Pathophysiological aspects

Anatomic

Diabetic cardiomyopathy
Distal and widespread CAD

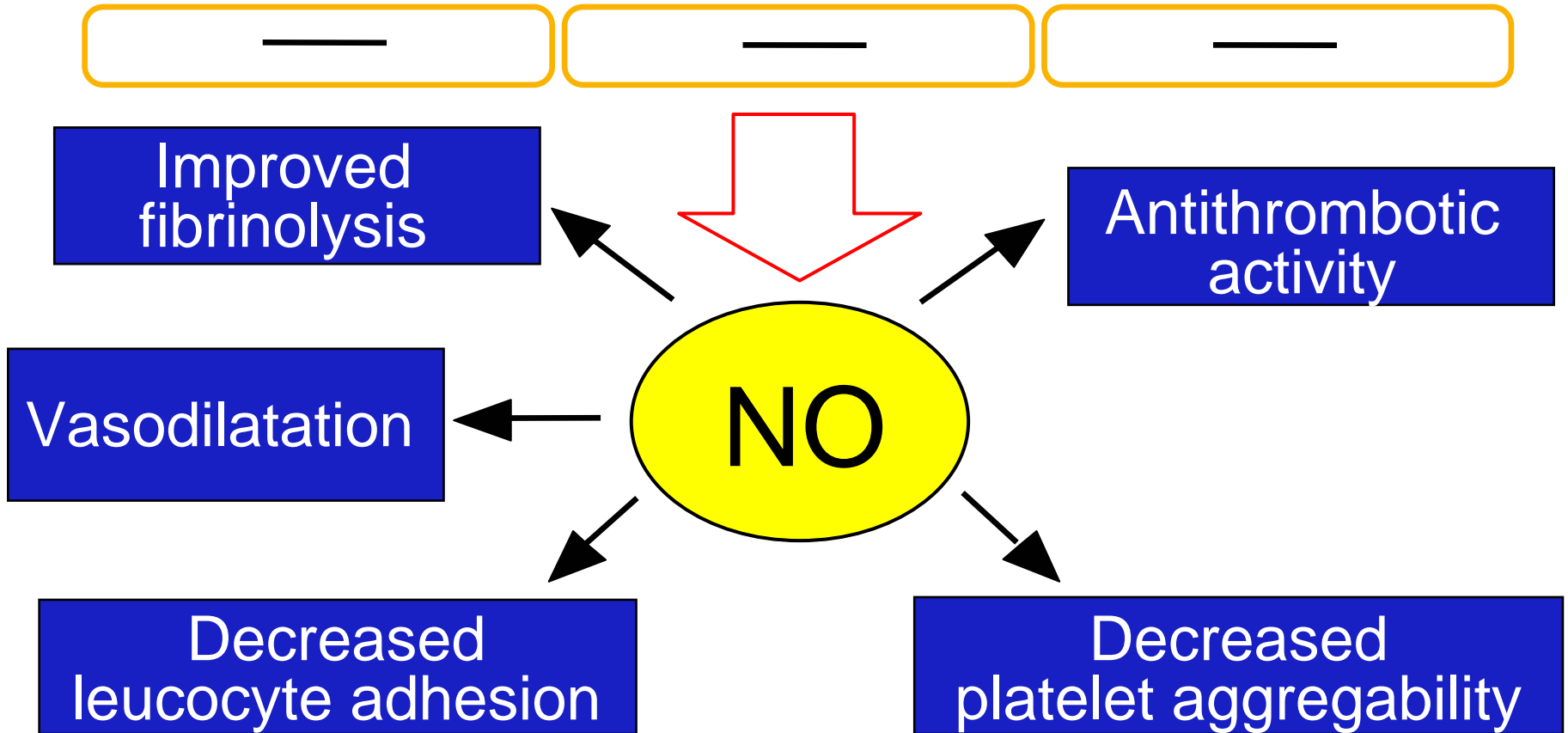
Functional

Autonomic dysfunction
Endothelial dysfunction
Compromised fibrinolytic capacity

Metabolic

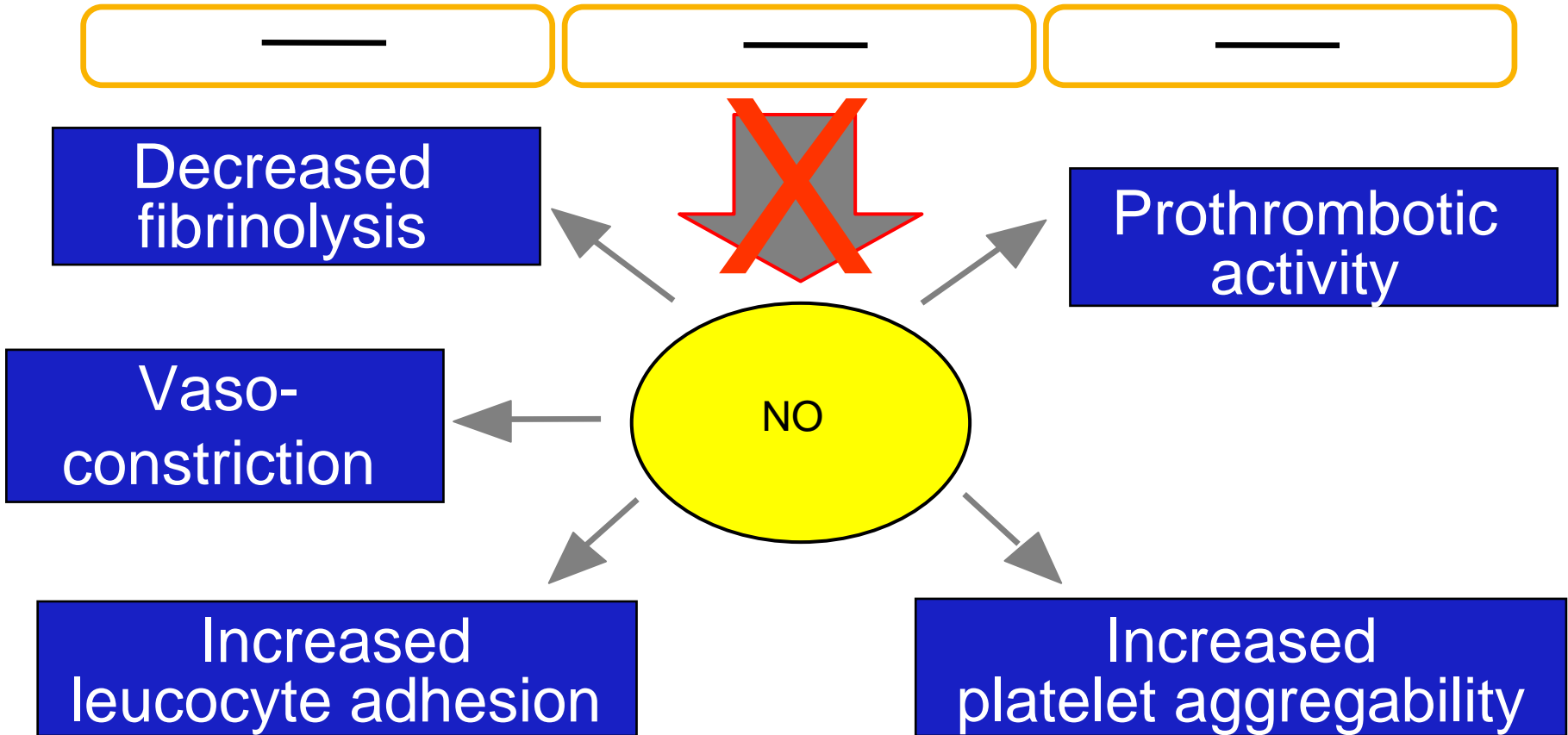
Free fatty acid exposure
Decreased glucose utilisation

Endothelial function



Endothelial function

Important in diabetes mellitus



Diabetes and heart failure

- Epidemiology and prognosis
- The diabetic cardiomyopathy
- **Diagnosing diabetic cardiomyopathy**

TDI for the Detection of Myocardial Dysfunction in Type 2 Diabetes Mellitus

The patient material

Patient characteristics

Type 2 diabetes	n=43
No diabetes	n=34

Clinical condition

No symptoms or signs of heart failure

Two-dimensional echocardiography

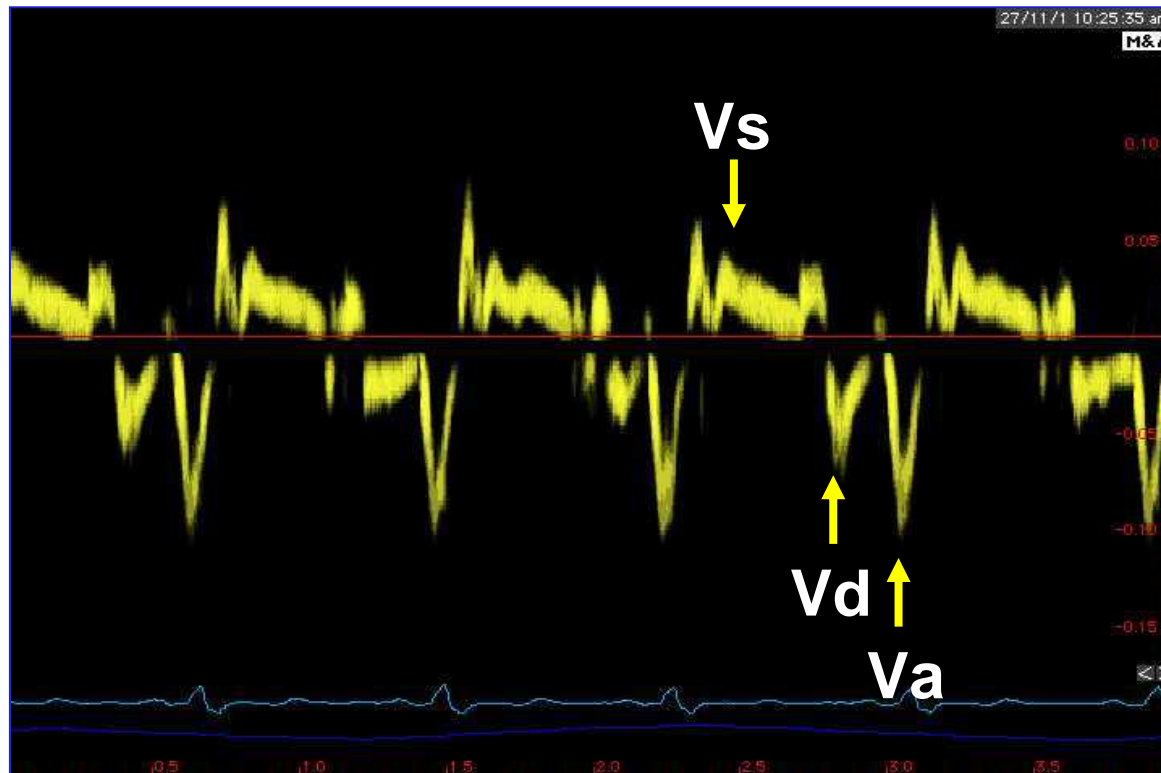
Global LV function	normal
Ejection fraction	normal

(Thrainsdottir et al Diabetes Vasc Dis Res 2005; 2:24)

TDI for the Detection of Myocardial Dysfunction in Type 2 Diabetes Mellitus

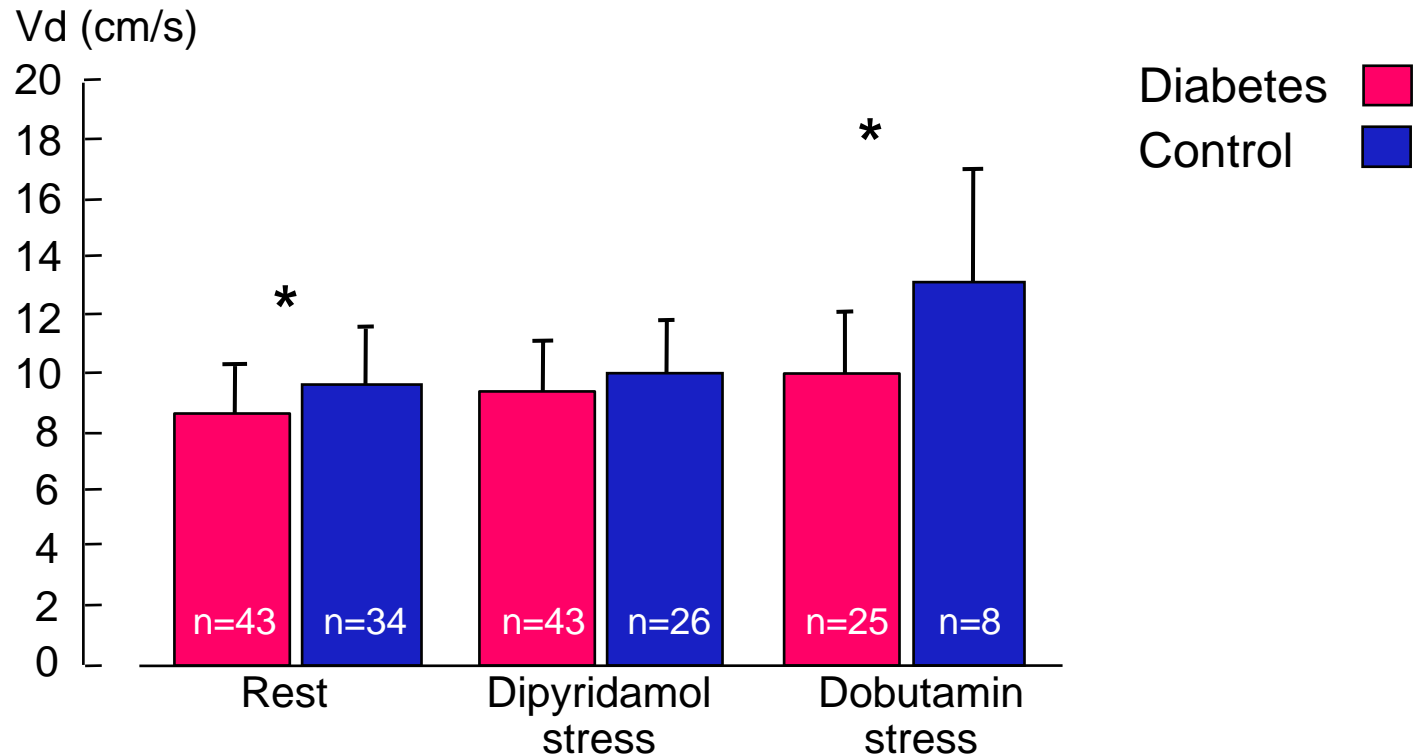
Example of registration

Peak systolic (V_s), early diastolic (V_d) and atrial contraction (V_a)



TDI for the Detection of Myocardial Dysfunction in Type 2 Diabetes Mellitus

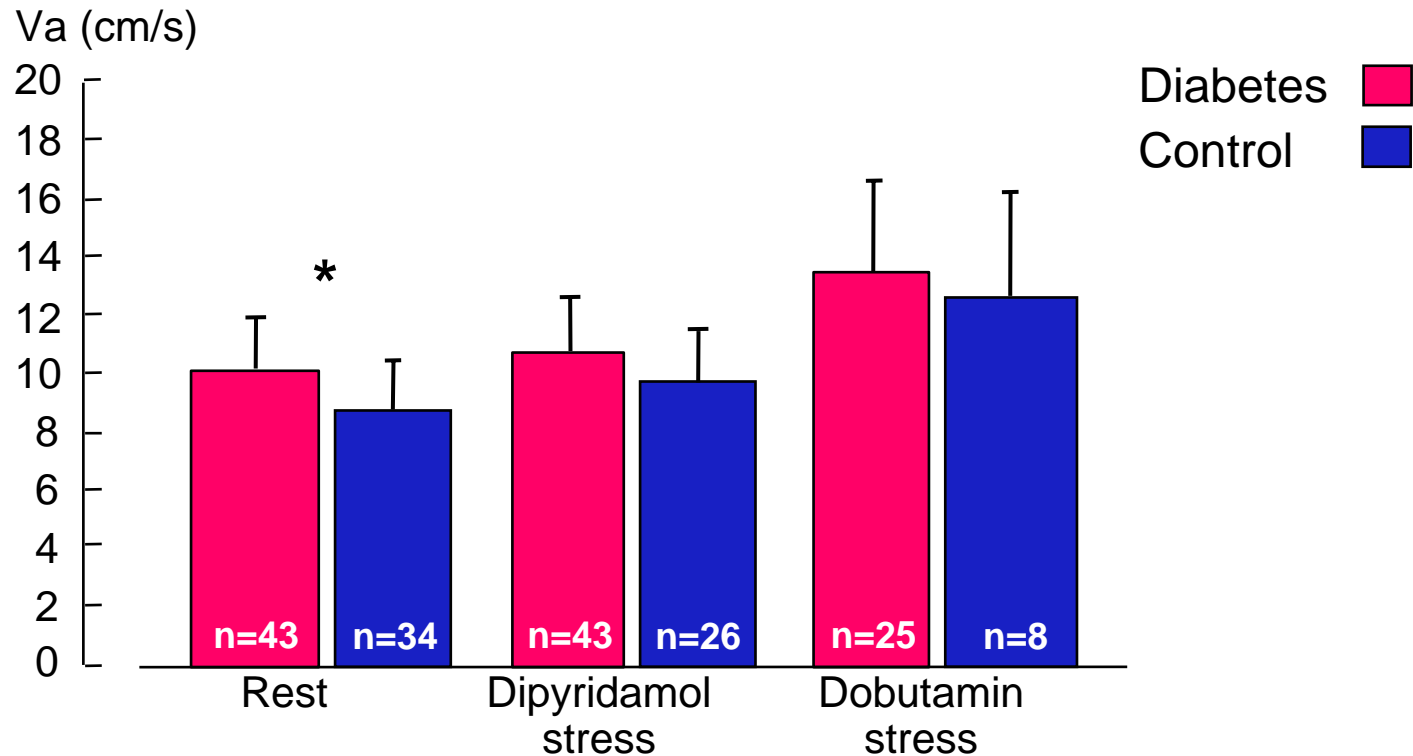
Mean early diastolic velocity (V_d) at rest and stress



(Thrainsdottir et al Diabetes Vasc Dis Res 2005; 2:24)

TDI for the Detection of Myocardial Dysfunction in Type 2 Diabetes Mellitus

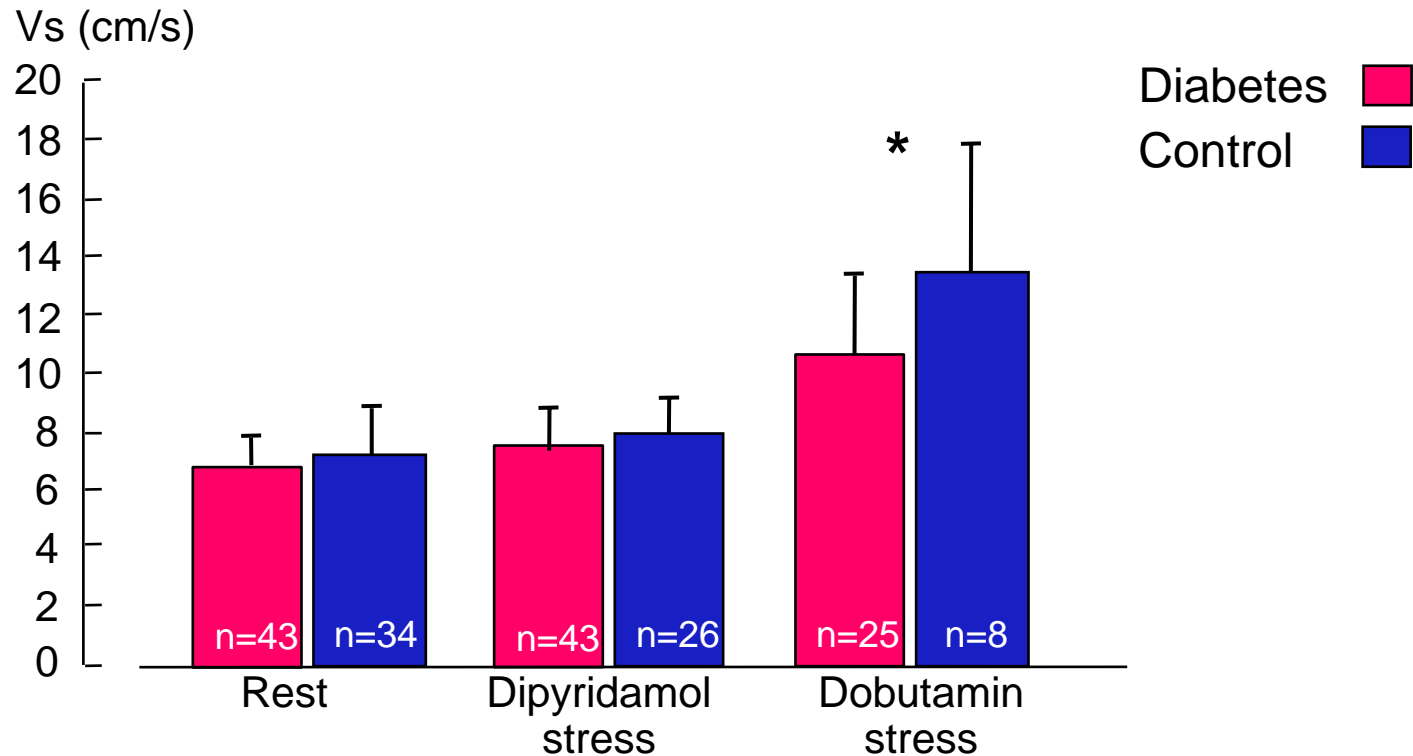
Mean late diastolic velocity (V_a) at rest and stress



(Thrainsdottir et al Diabetes Vasc Dis Res 2005; 2:24)

TDI for the Detection of Myocardial Dysfunction in Type 2 Diabetes Mellitus

Mean systolic velocity (V_s) at rest and stress



(Thrainsdottir et al Diabetes Vasc Dis Res 2005; 2:24)

TDI for the Detection of Myocardial Dysfunction in Type 2 Diabetes Mellitus

Conclusions

Diabetic patients are characterised by
Early signs of diastolic (predominant)
and
Systolic dysfunction

This is identifiable by TDI in patients
without clinical signs of heart failure
and
with apparently normal 2-D echo

(Thrainsdottir et al Diabetes Vasc Dis Res 2005; 2:24)

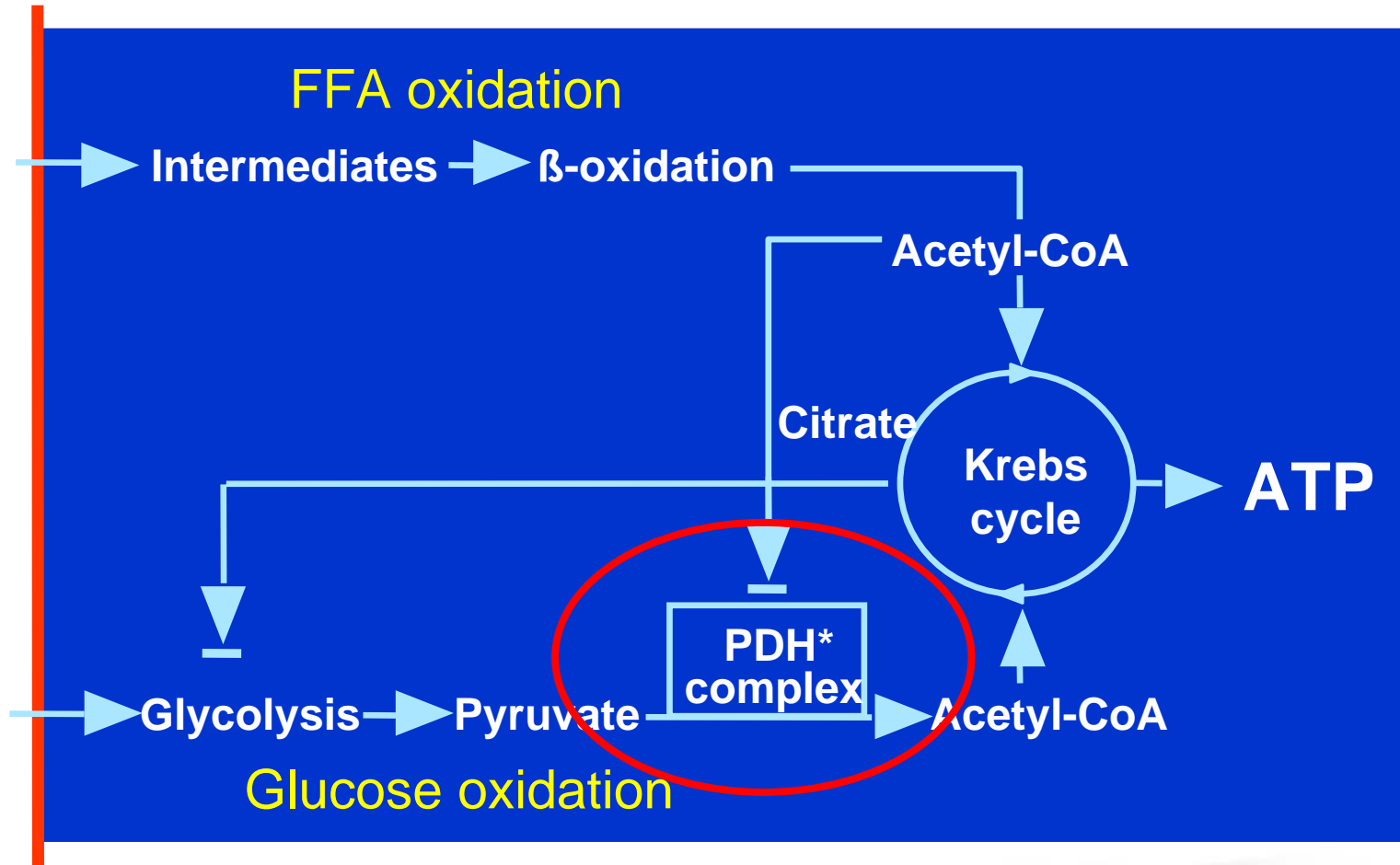
Diabetes and heart failure

- Epidemiology and prognosis
- The diabetic cardiomyopathy
- Diagnosing diabetic cardiomyopathy
- **Myocardial metabolism**

Myocardial Metabolism in Diabetes

FFA
60%
Diabetes
90%

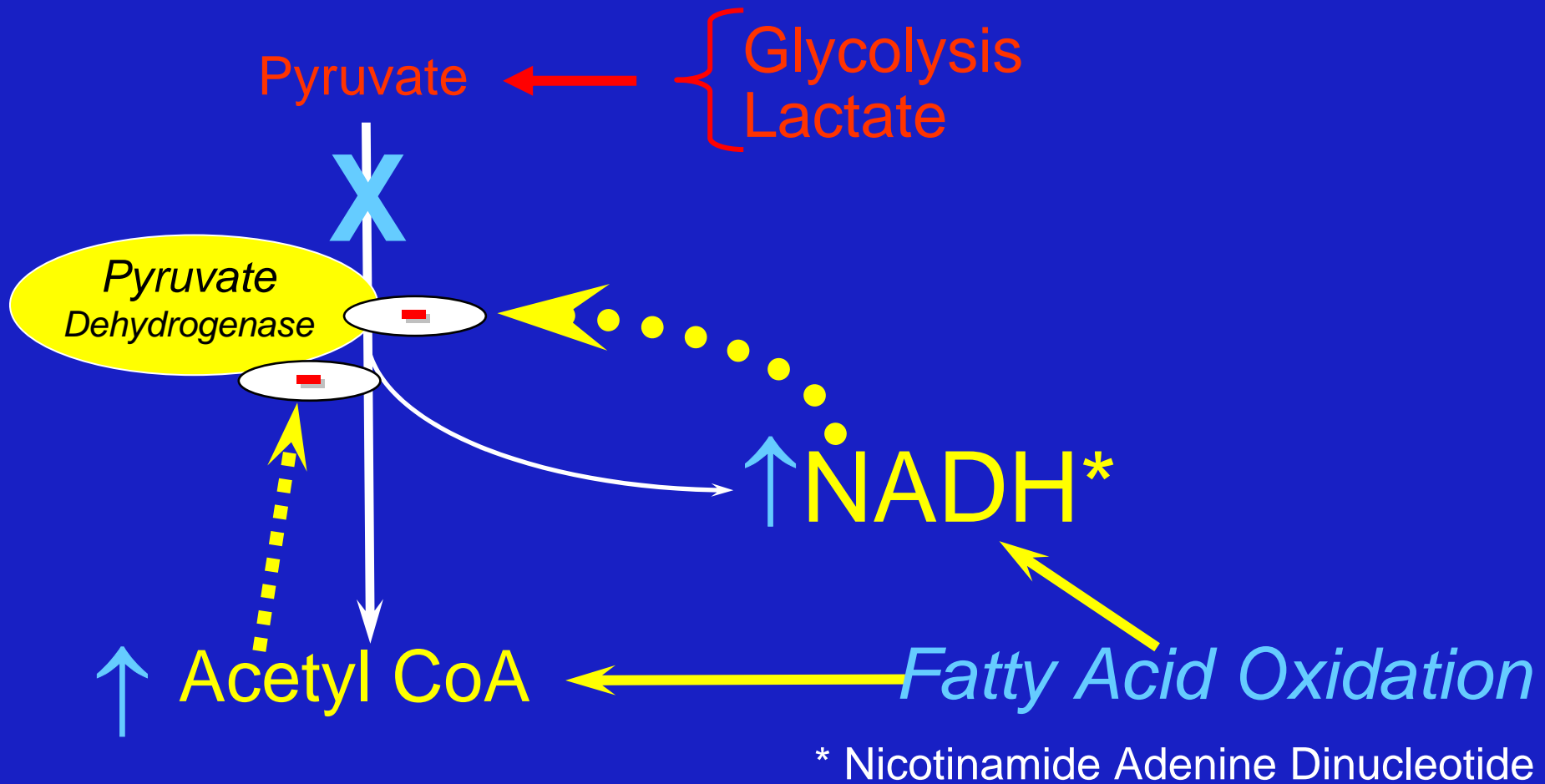
Glucose
40%
Diabetes
10%



* PDH = Pyruvate DeHydrogenase

Myocardial Metabolism

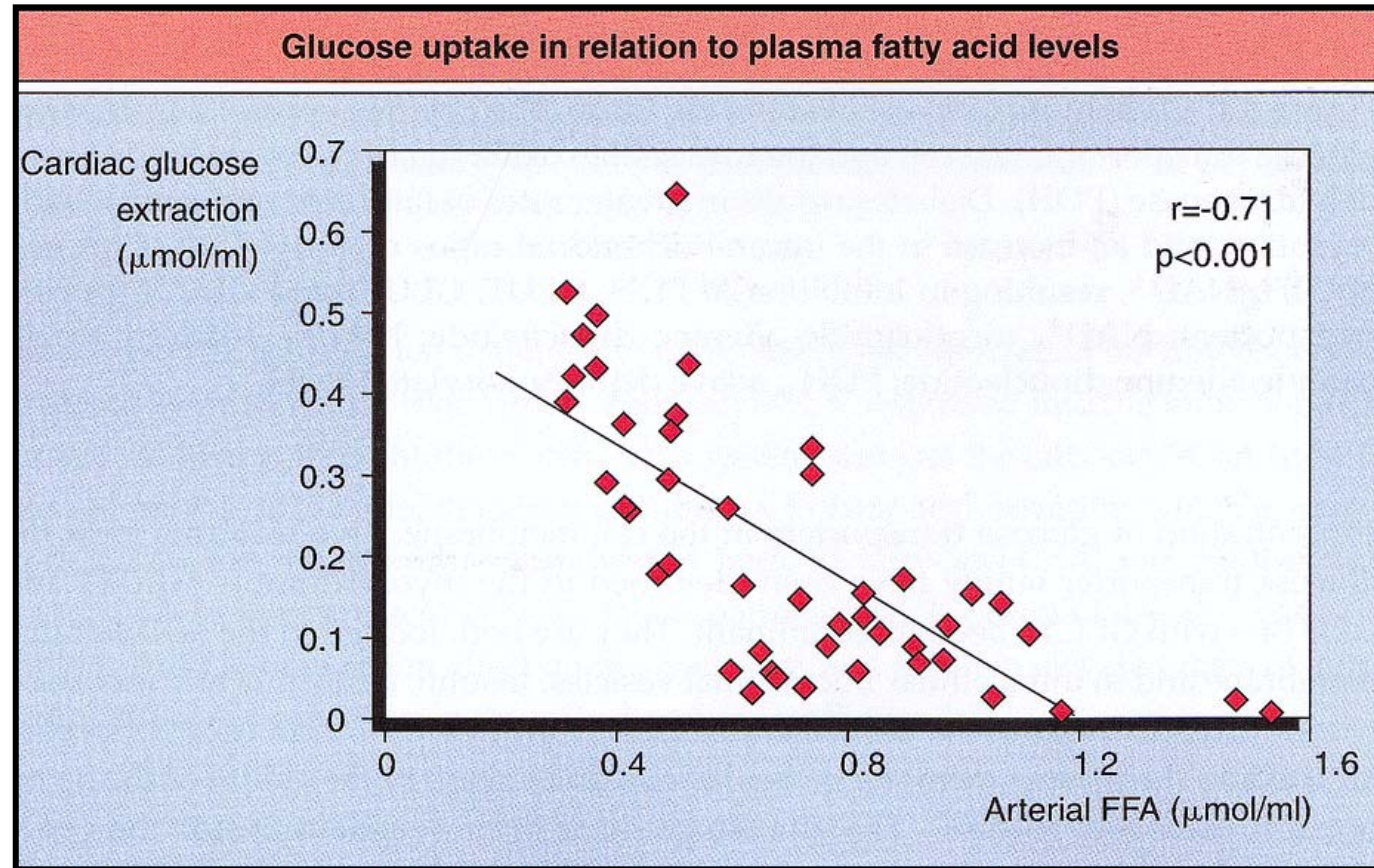
Glucose - Fatty Acid Cycle (Randle)



Myocardial Metabolism

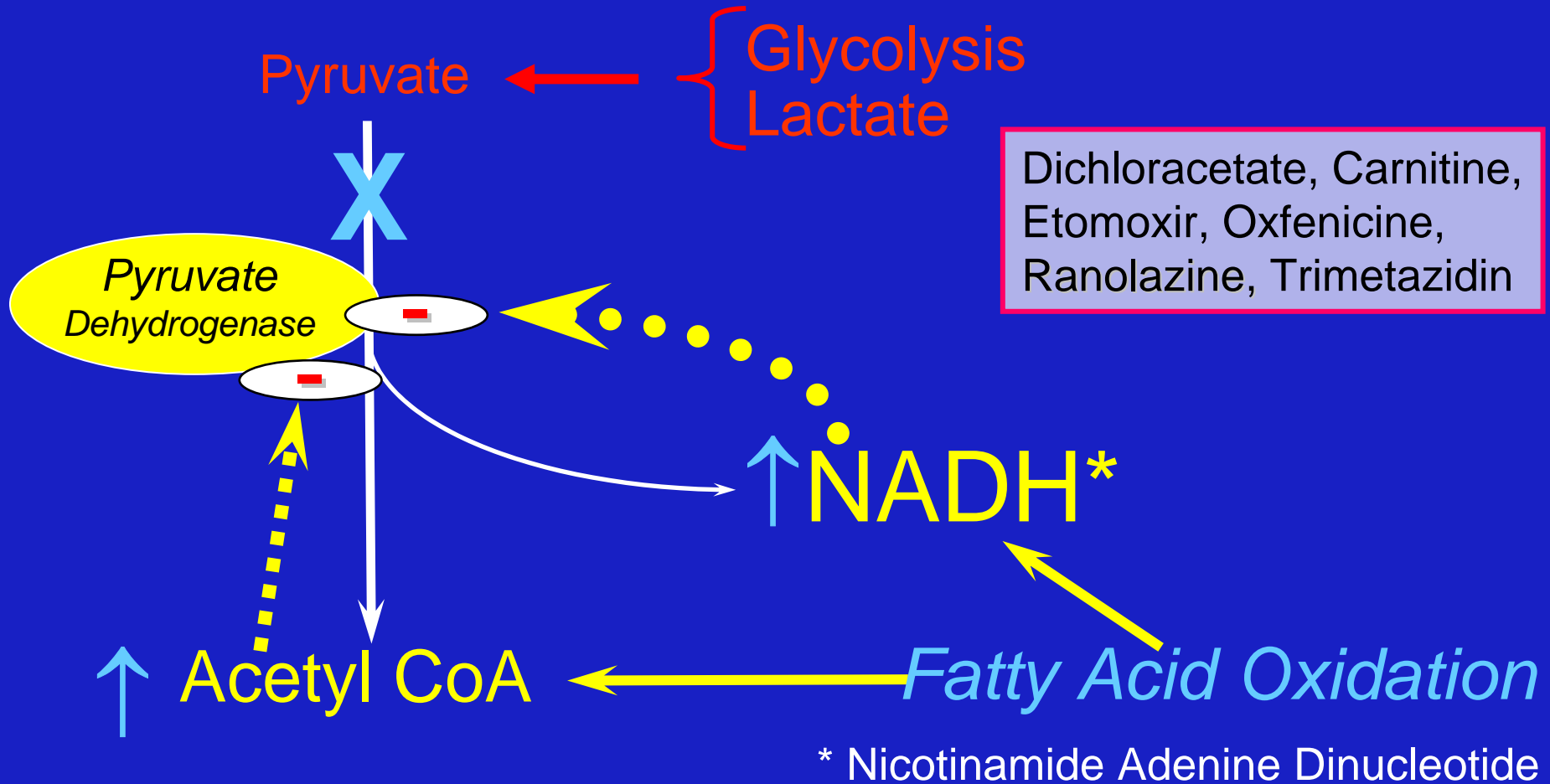
Glucose - Fatty Acid Cycle (Randle)

Inhibition of glucose oxidation by increasing beta-oxidation of free fatty acids

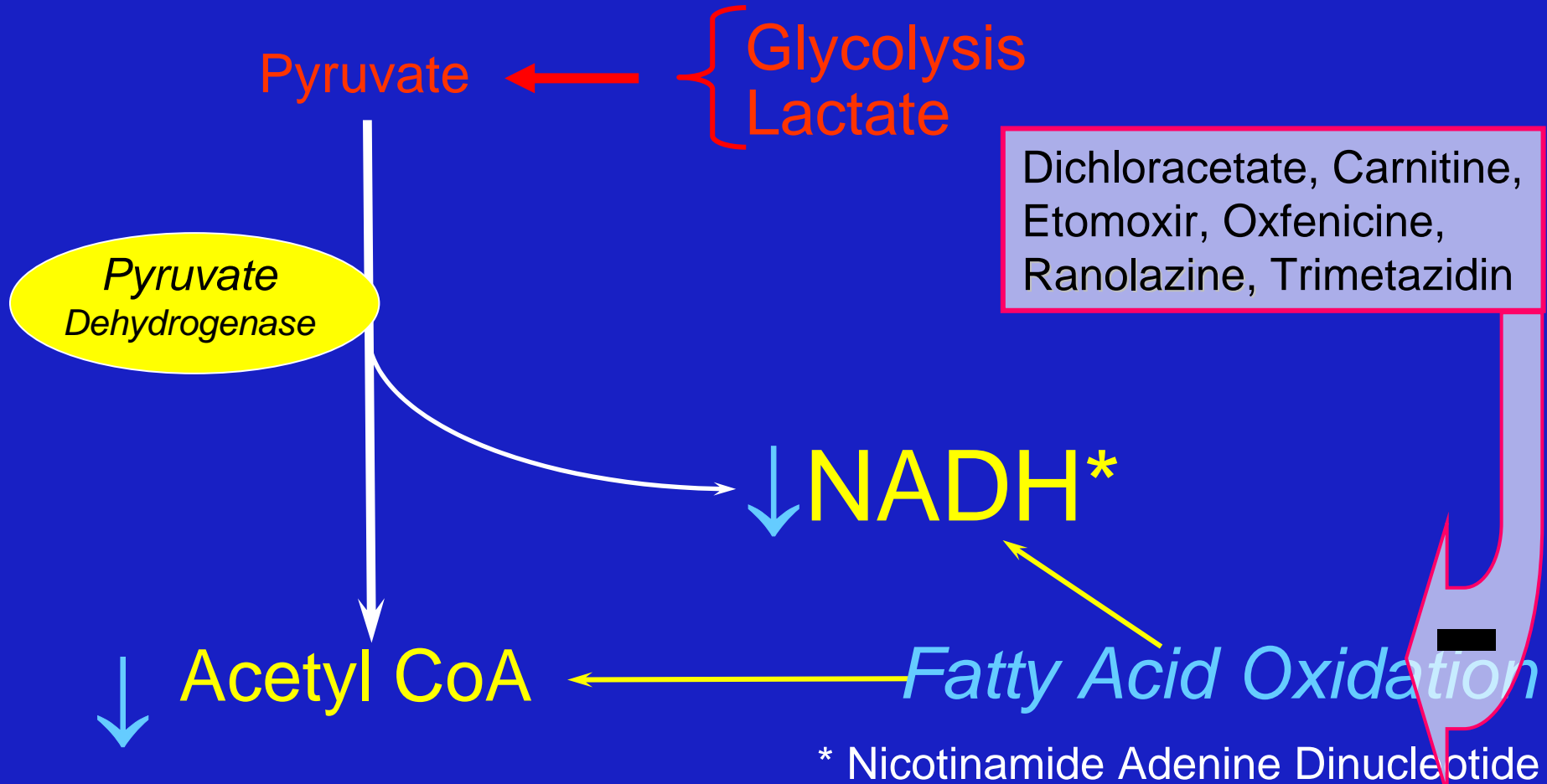


(Wisneski et al. J Clin Invest 1987 79:359)

Metabolic modulation in heart failure



Metabolic modulation in Heart Failure



Myocardial Metabolism in Diabetes

Fatty Acid Oxidation

Promoted by

Stress

Decreased insulin



Effects

Glucose derived Acetyl-CoA



Glucose oxidation < Glycolytic rate

Accumulation of lactate/protons



ATP used for ionic homeostasis



Intracellular Na & Ca



Myocardial mechanical efficiency



Diabetes and heart failure

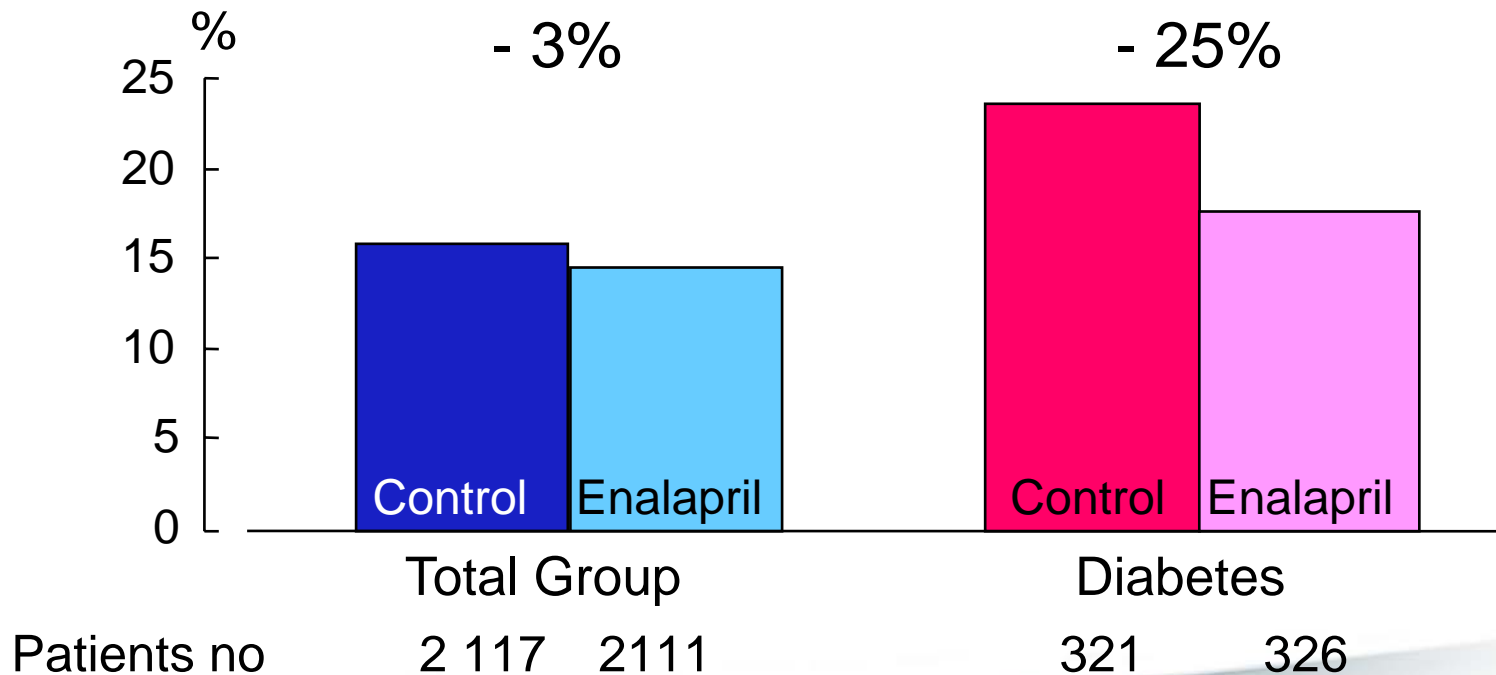
- Epidemiology and prognosis
- The diabetic cardiomyopathy
- Diagnosing diabetic cardiomyopathy
- Myocardial metabolism
- **Treatment of diabetic cardiomyopathy**

Diabetes and heart failure

Effect of ACE-inhibitors

Subgroup analysis from SOLVD-prevention

Total Mortality

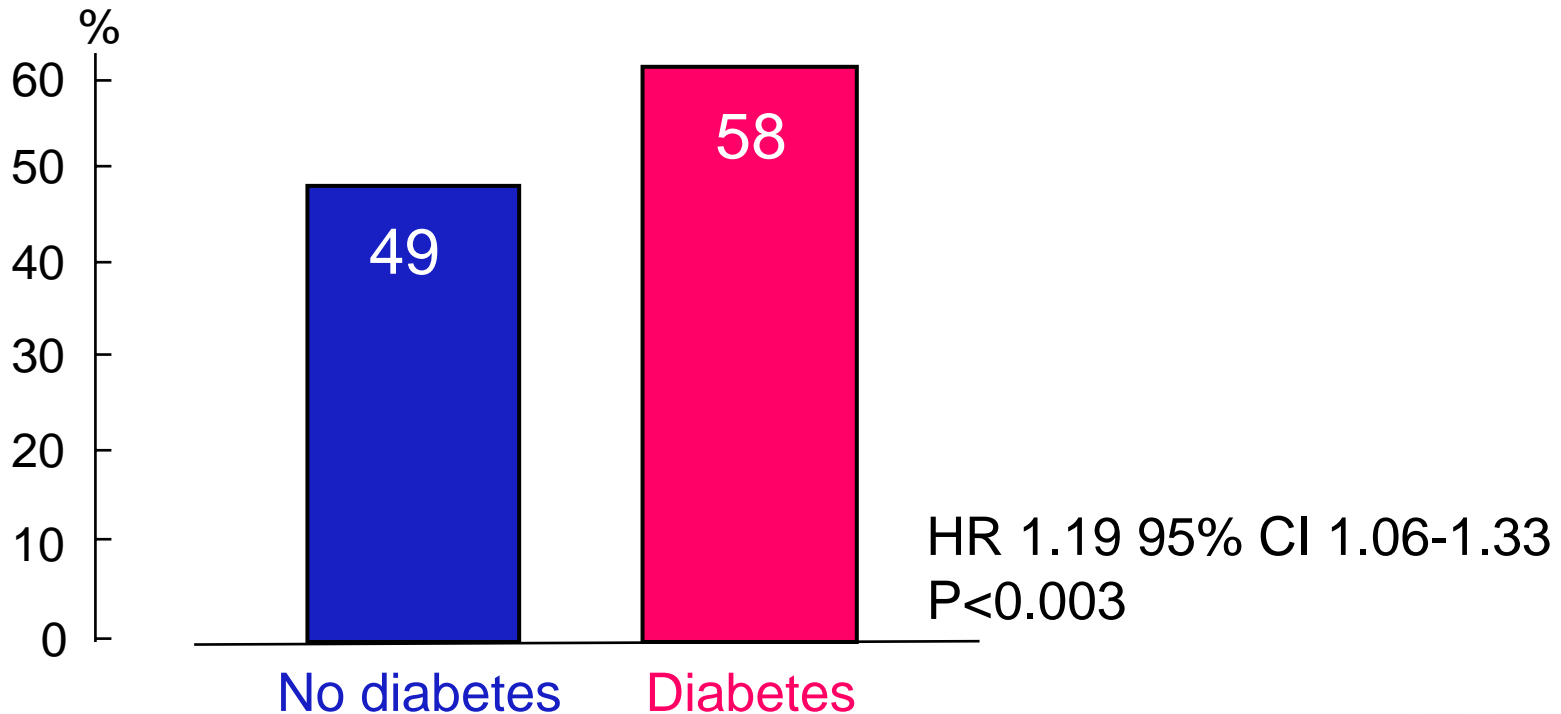


Diabetes and heart failure

Experiences from the BEST trial

Patients 2 708; NYHA III-IV; Diabetes 35% (964)

Mortality or hospitalisation for HF after 2 year



(Domanski et al J Am Coll Card 2003; 42:914)

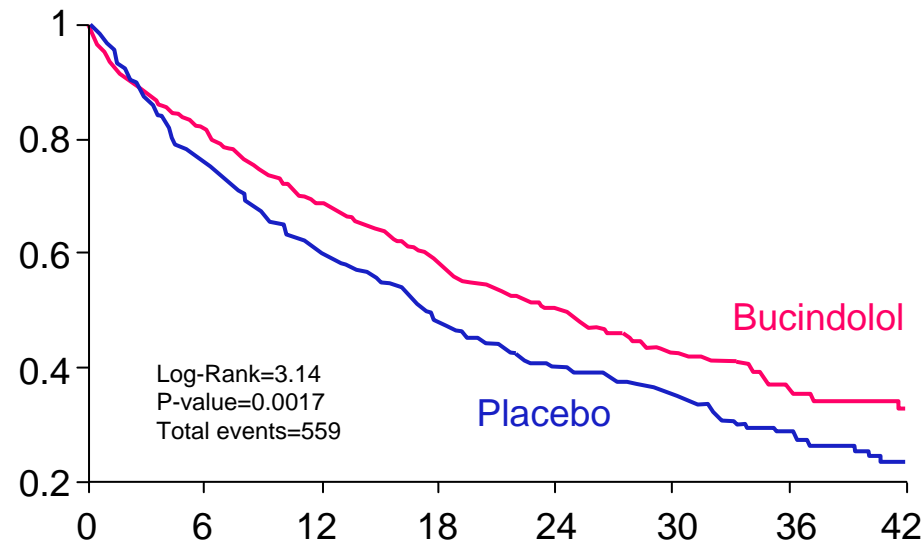
Diabetes and heart failure

Experiences from the BEST trial

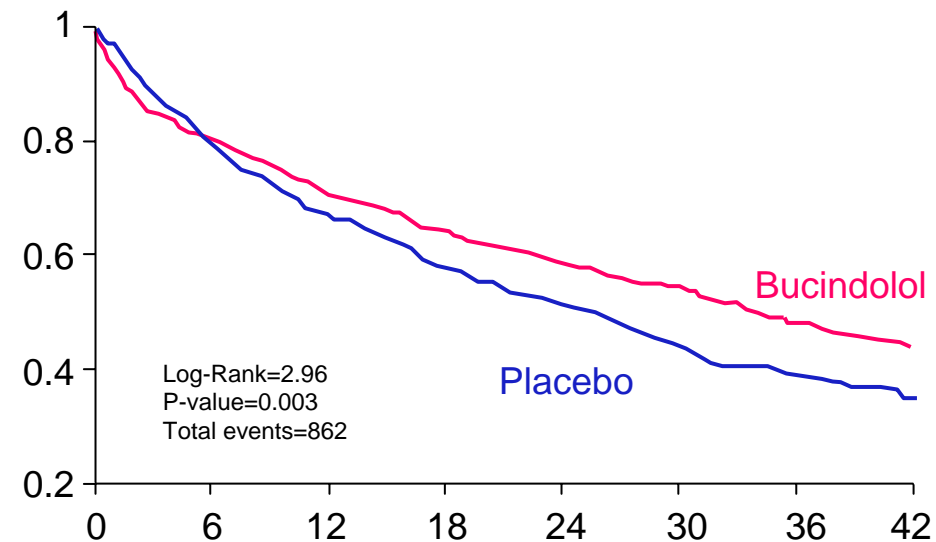
Patients 2 708; NYHA III-IV; Diabetes 35% (964)

Effect of bucindolol on death or heart failure hospitalisation

Diabetes



No diabetes



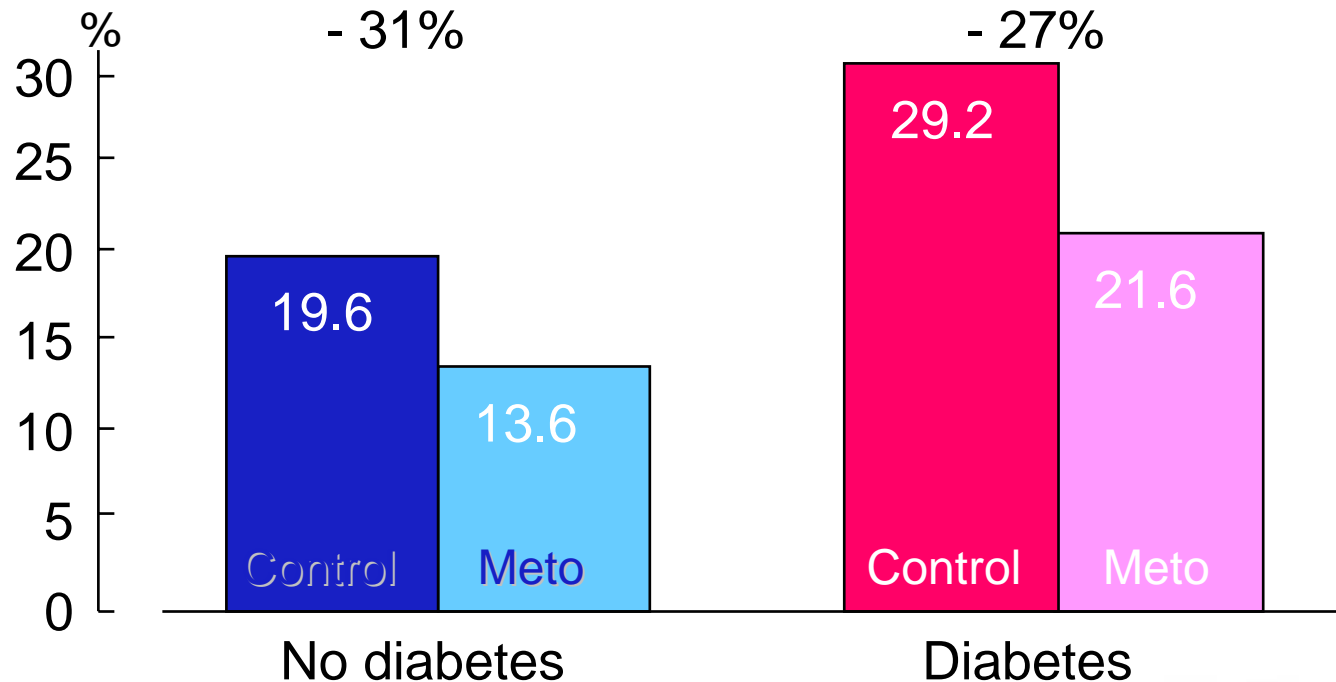
(Domanski et al J Am Coll Card 2003; 42:914)

Diabetes and heart failure

Effect of betablockade

Subgroup analysis from MERIT-HF

Mortality or hospitalisation for HF after 1 year



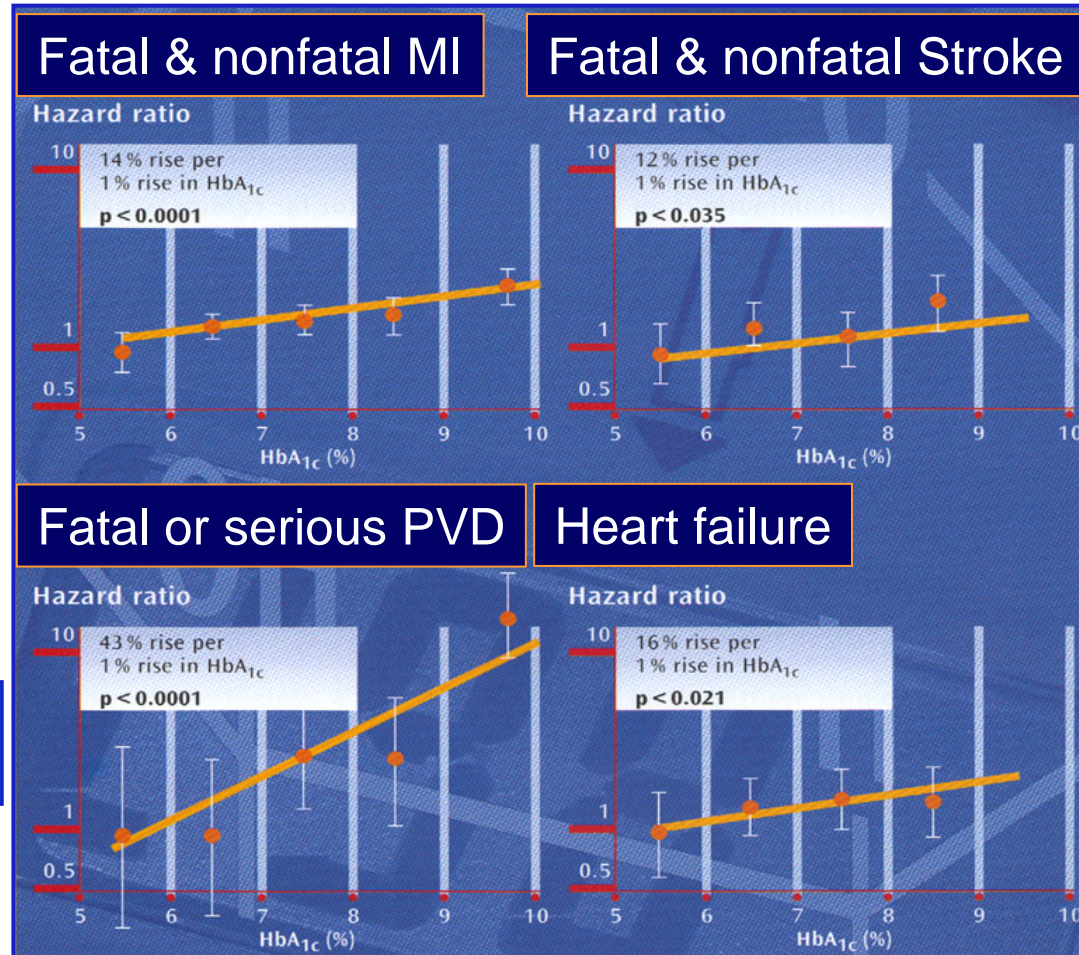
(Hjalmarson et al JAMA 2000;283:1295)

Diabetes and heart failure

- Epidemiology and prognosis
- The diabetic cardiomyopathy
- Diagnosing diabetic cardiomyopathy
- Myocardial metabolism
- Treatment of diabetic cardiomyopathy
- **Future directions**

Diabetes Mellitus and Risk for Cardiovascular Disease

Relation between glycemic control expressed by HbA1c and various manifestations of cardiovascular disease



HbA1c +1% → CHF +8 -15%

(UKPDS Brit Med J 2000;321:405
(Iribarren et al Circulation 2001;103:2668)

Diabetes and heart failure

Effects of Insulin

- decreases blood glucose
- increases myocardial blood flow
- decreases heart rate
- increases cardiac output modestly
- may worsen prognosis??

Parsonage WA et al, Heart 2001;85:508
McNulty Ph et al. Am J Cardiol 2000;85:161
Khoury VK et al. Heart 2003;89:61

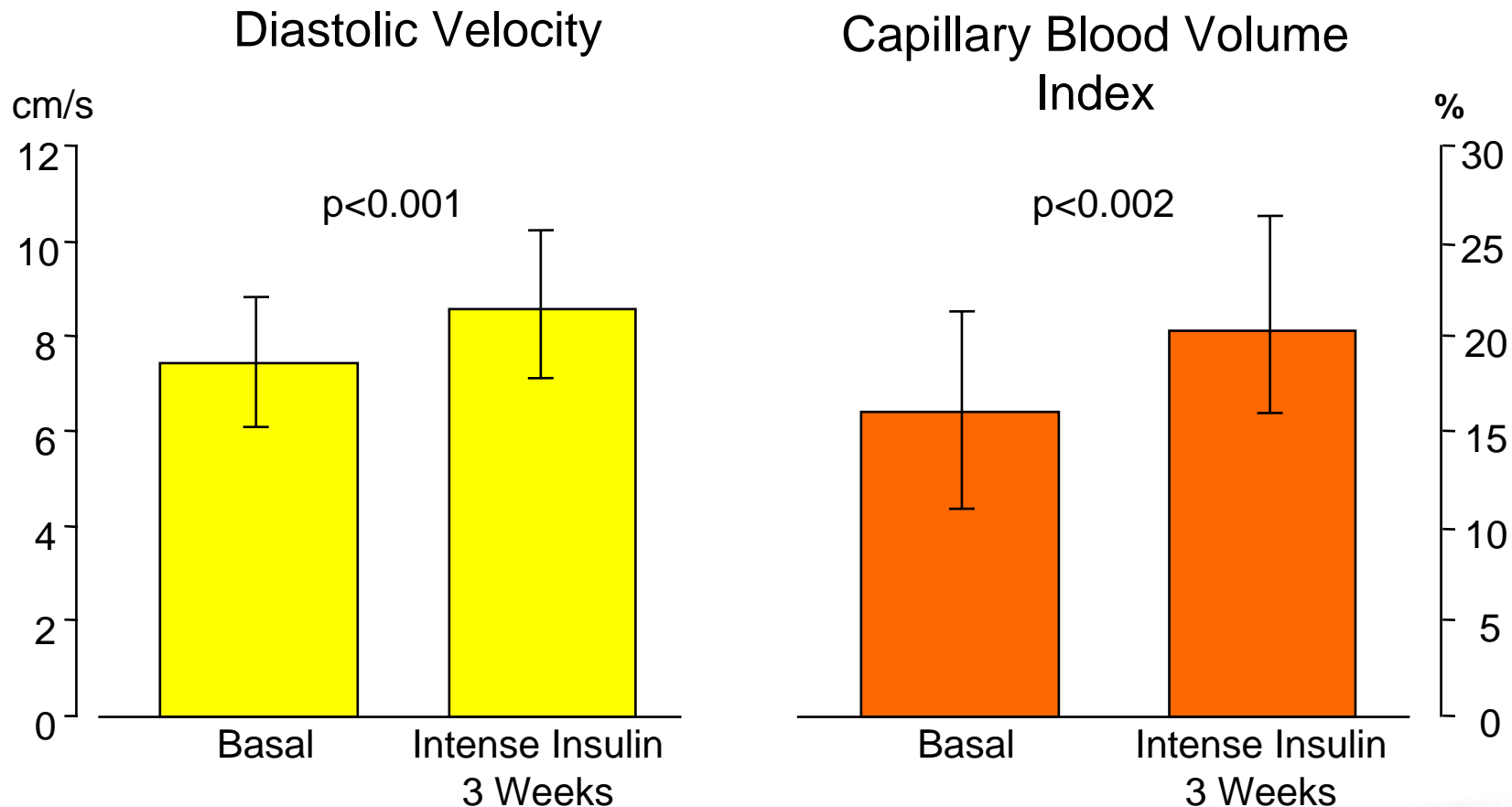
Improved glucose control and myocardial function

Patient characteristics

Parameter	Insulin	OAD	Diet
Male sex (%)	75	80	75
Age (years)	60±8	58 ±8	63 ±6
Diabetes duration	8 ±6	6 ±3	8 ±8
BMI (kg/cm ²)	29 ±4	27 ±5	28 ±3
HbA1c (%)	7.2 ± 1.3	7.1 ± 1.2	5.6 ±0.5
FB-glucose (mmol/l)			
Control	11.3 ± 3.7	10.5 ± 3.0	8.0 ± 2.0
3 weeks	7.4 ±2.4	6.9 ±1.3	7.7 ±1.8

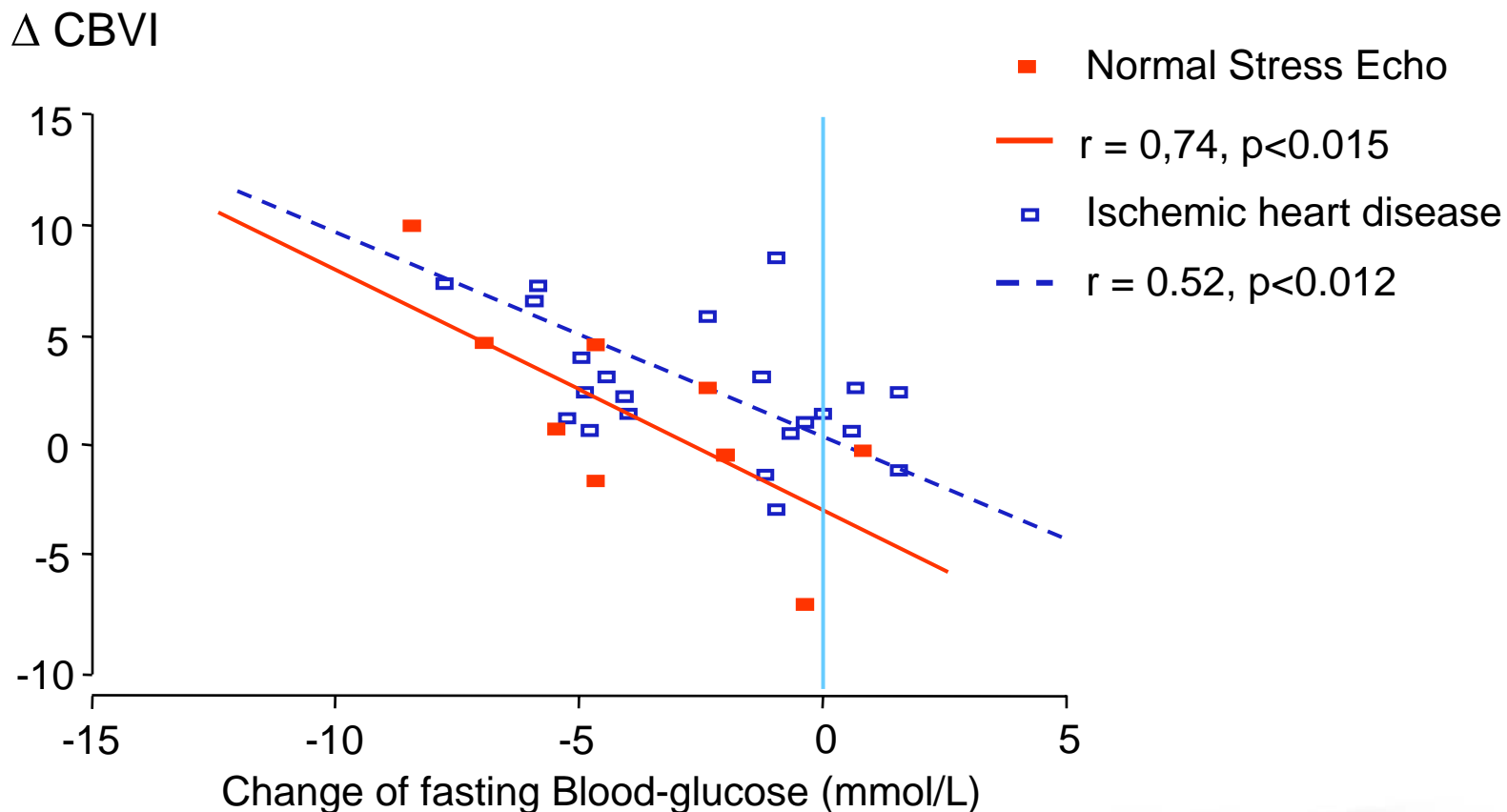
(von Bibra, Rydén et al Heart 2004; 90:1483)

Improved glucose control and myocardial function



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

Improved glucose control and myocardial function



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

Improved glucose control and myocardial function

Conclusions

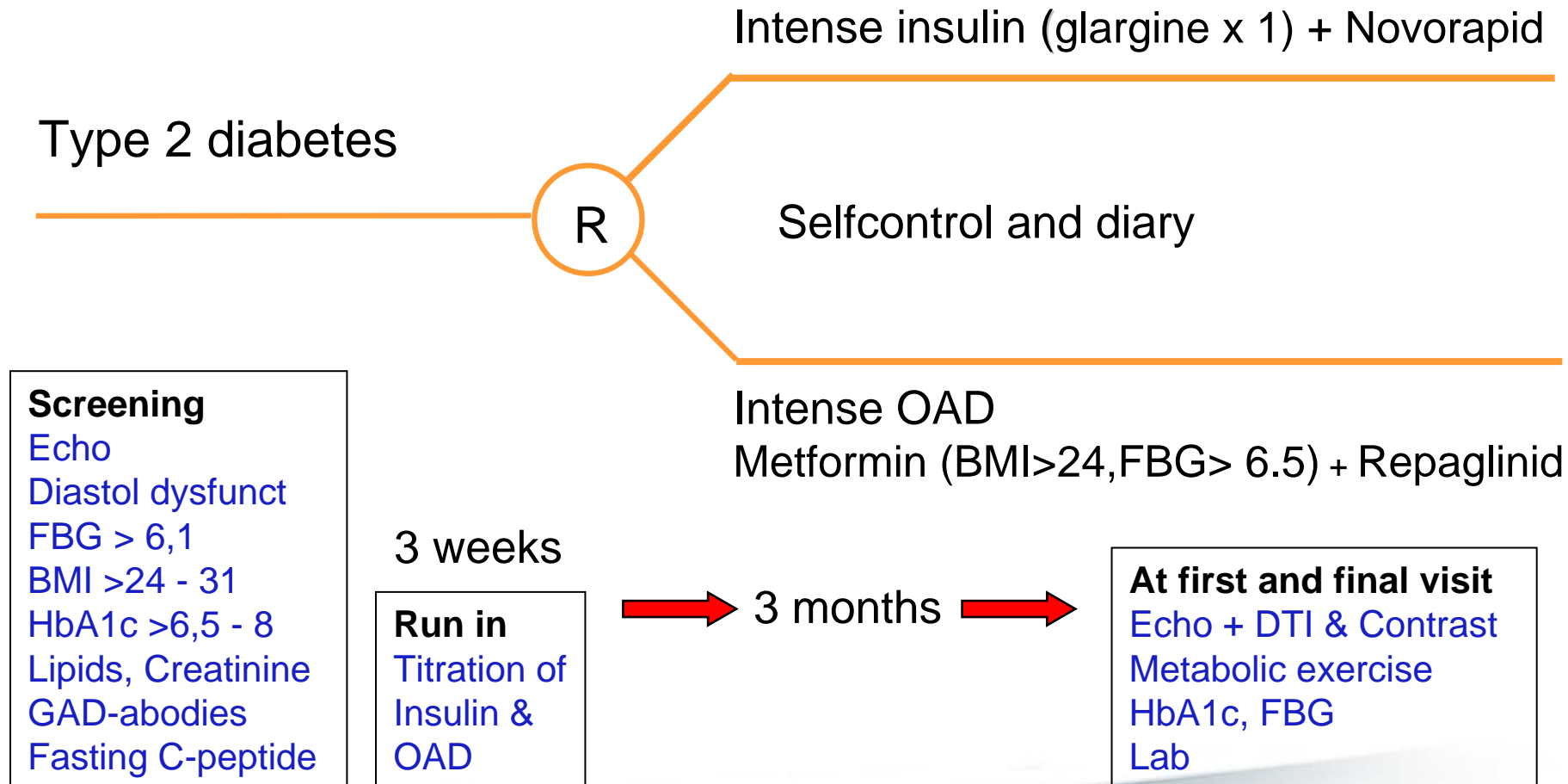
Euglycemia and insulin improve myocardial diastolic function and perfusion

Cardiac abnormalities in type 2 diabetes seem to have a considerable reversibility possibly related to energy production or improved endothelial function

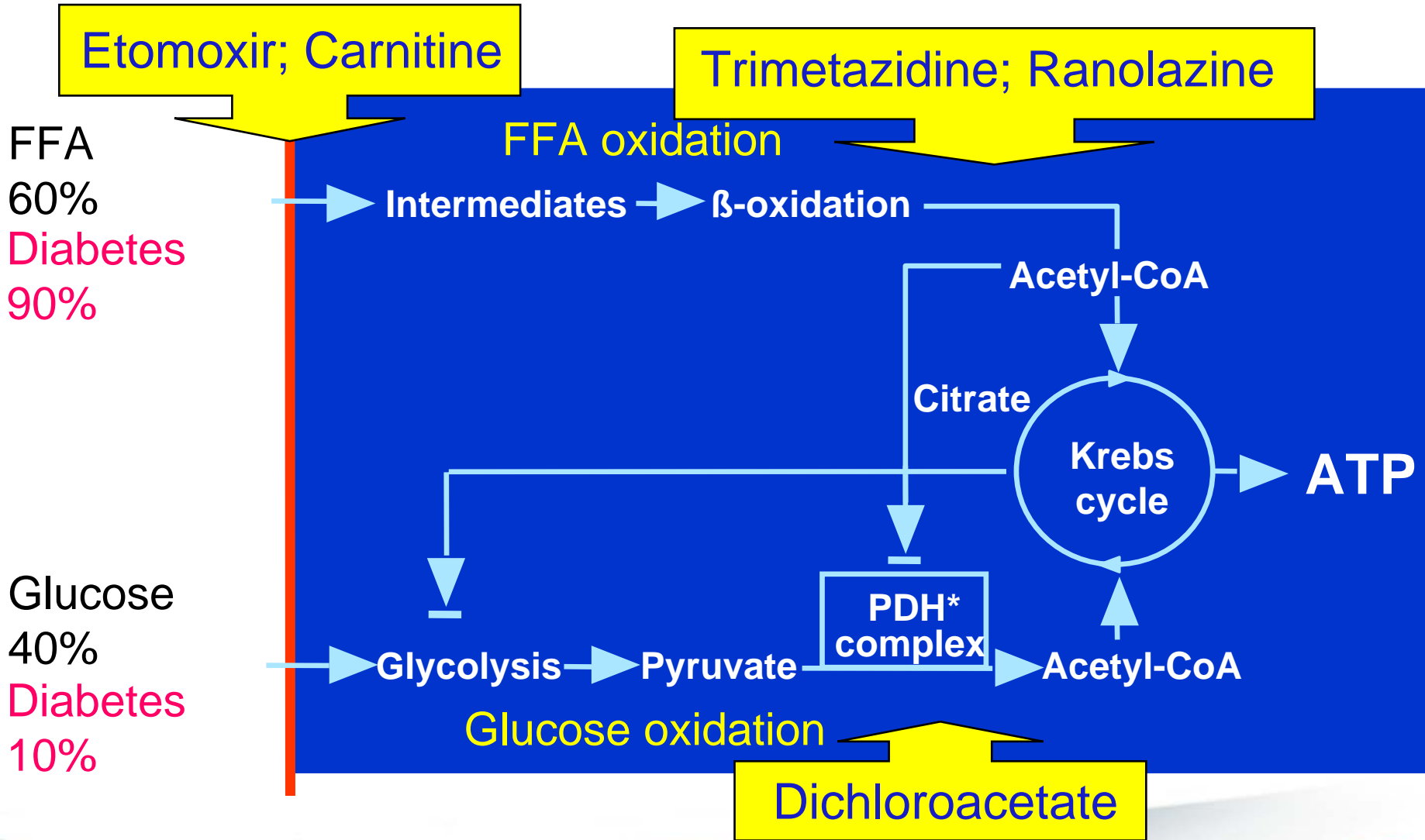
(von Bibra, Rydén et al Heart 2004; 90:1483)

Diabetes And Diastolic Dysfunction

The DADD study protocol



Myocardial Metabolism in Diabetes



Metabolic Modulation in Heart Failure

Initial experiences with Etomoxir

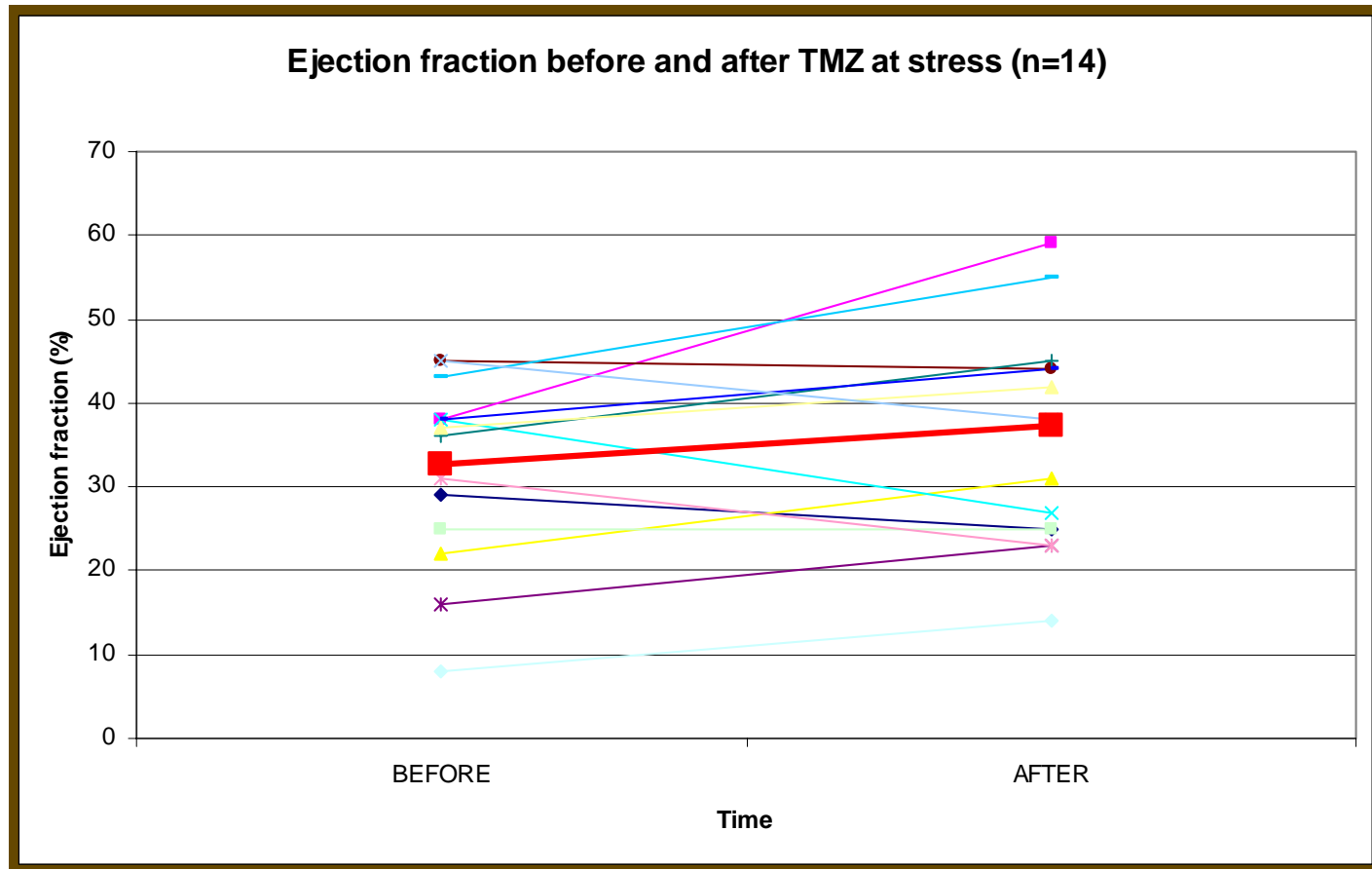
Patients (n=10) NYHA II-III DCM 9; IHD 1
Etomoxir 80 mgx1 3 months

Parameter	Before	After
Rest		
LVEF (%)	22 ± 3	27 ± 2
Exercise		
CO (l/min)	9.8 ± 1.3	13.4 ± 1.5
SV (ml)	84 ± 7	109 ± 9

(Schmidt-Schweda & Holubarsch Clin Sci 2000;99:27)

Diabetes and heart failure

The trimetazidine pilot trial



(Thrainsdottir, Rydén et al J Cardvasc Pharm 2004; 44:101)

Diabetes and heart failure

The trimetazidine pilot trial

Results

Exercise tolerance	no difference
Echocardiography	↑ systolic function
TDI	no difference

Conclusion

No certain improvement in myocardial function
Needs further research

(Thrainsdottir, Rydén et al J Cardvasc Pharm 2004; 44:101)

Diabetes and heart failure

Overall conclusion

The diabetic subject with CHF

- is at high risk
- needs meticulous care
- based on conventional therapy
- perhaps supplemented by a metabolic approach