

Diabetic Heart

can we protect the heart of diabetic?

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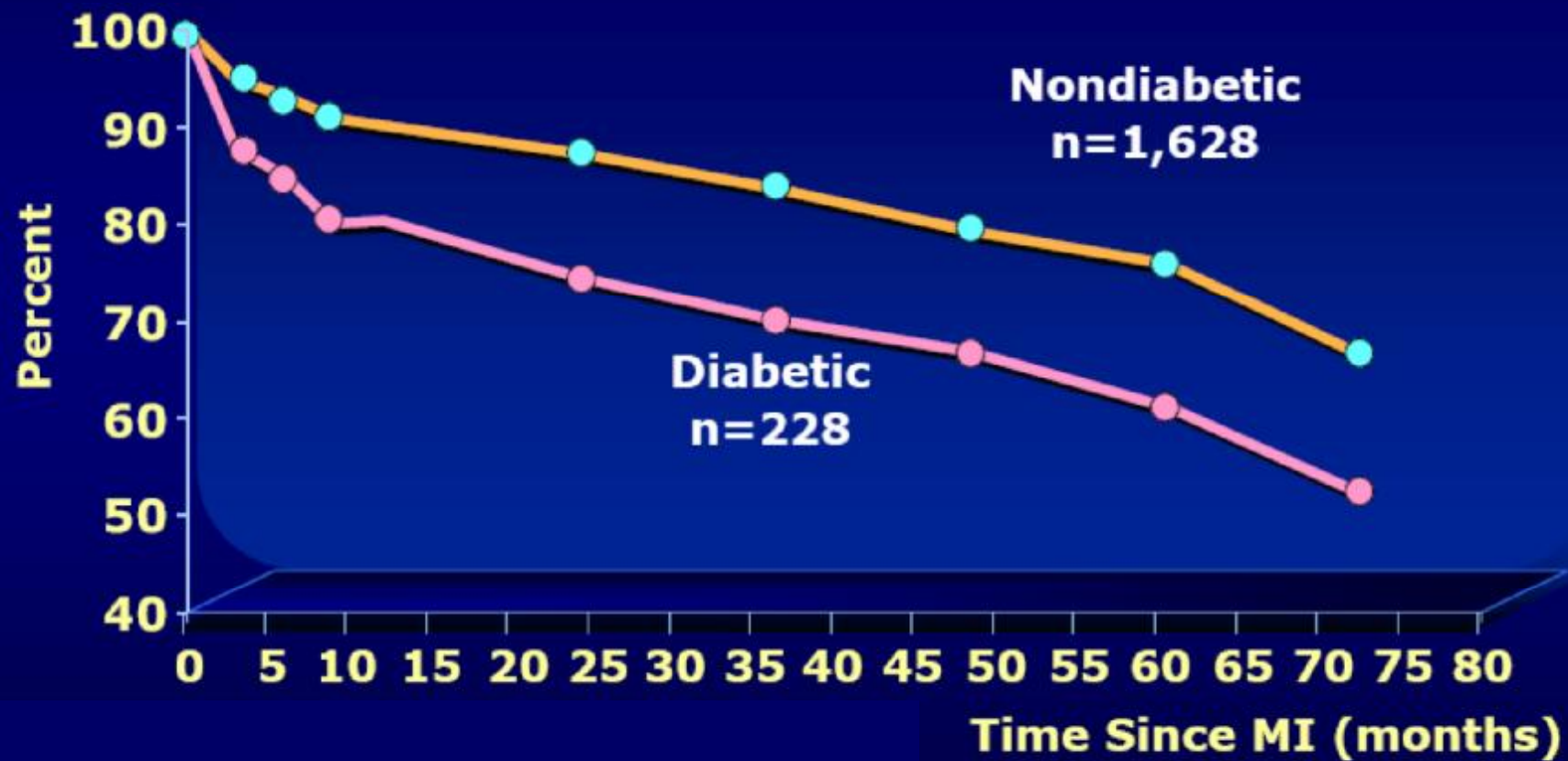
- n CVD are four times more common in Diabetic than non diabetic
- n The macrovascular complications (CAD,PAD,CVA) account for more than 70% of deaths diabetics .
- n occur at a younger age group .

n diabetic with no history of vascular disease have the same risk of having a **heart attack or dying of vascular disease** as nondiabetic individuals with a prior history of vascular disease).

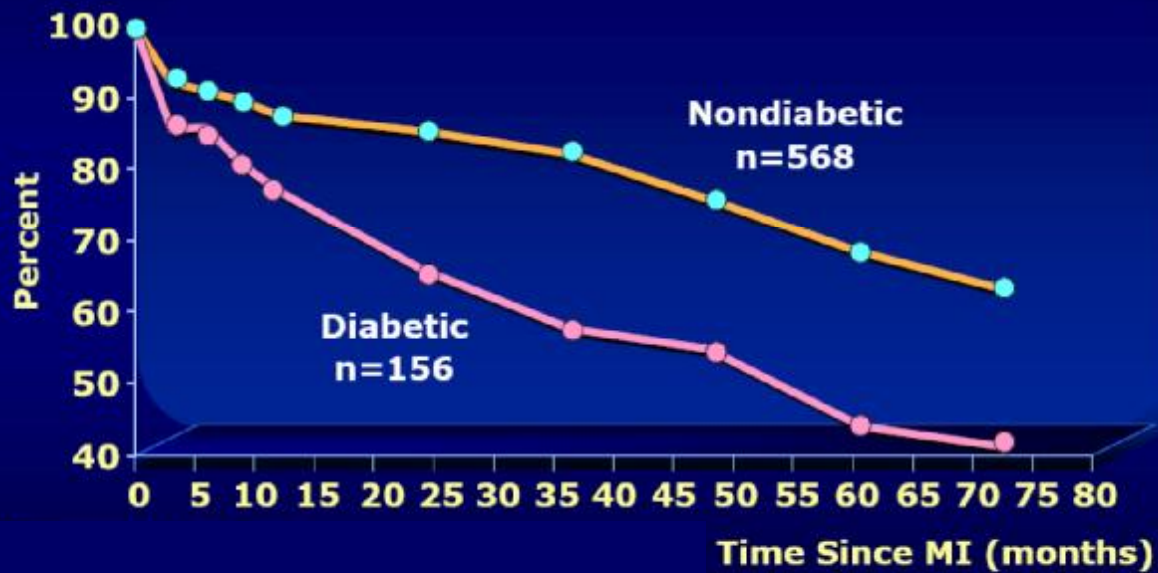
n The risk of CVD conferred by diabetes is so great that the National Cholesterol Education Program (NCEP) Adult Treatment Panel III identifies **diabetes as a CVD risk equivalent**

- n Diabetics have a worse prognosis after an acute Ischemia than non-diabetic patients.
- n The Framingham heart study has shown a higher mortality rate, as well as reinfarction and heart failure rates, in diabetic patients.

Minnesota Heart Survey Post-MI Survival in Men*

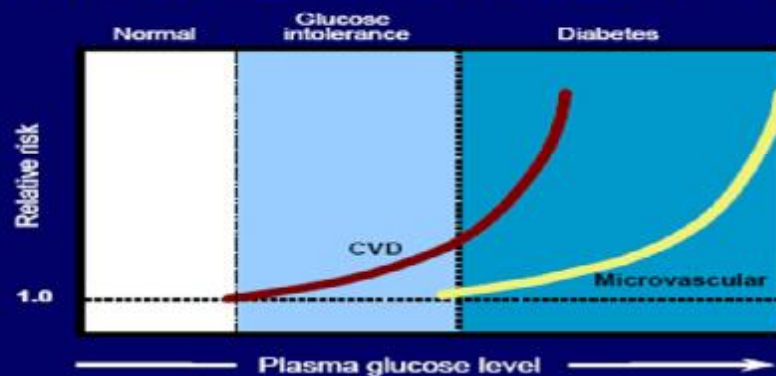


Minnesota Heart Survey Post-MI Survival in Women*



Postprandial Hyperglycaemia – “Early Warning” for Diabetes

Increased risk of CV complications begins in the non-diabetic range of glucose dysregulation¹

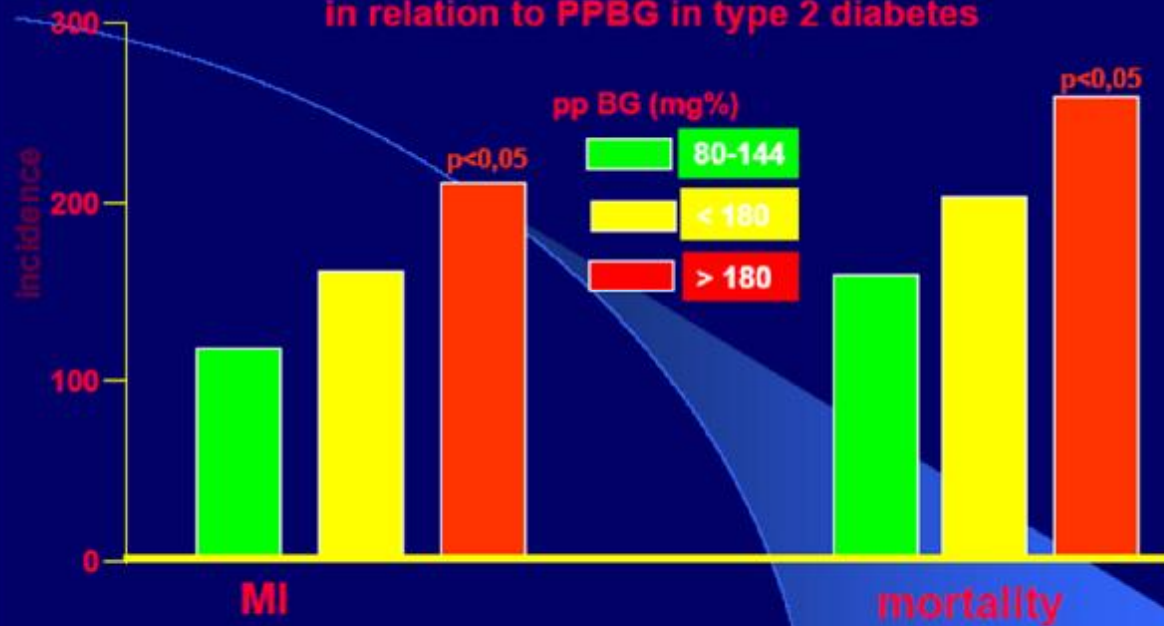


- ◆ Impaired glucose tolerance (IGT) appears first
- ◆ HbA_{1c} & fasting glucose are still normal at this stage^{1,2}
- ◆ Increased risk of CV complications begins before overt diabetes develops.³
- ◆ => Measurement of postprandial glucose allows early identification of at-risk individuals

1. Gerstein HC. Glucose: a continuous risk factor for cardiovascular disease. *Diabet Med* 1997;14(Suppl 3):S25-31.
2. Reaven GM et al. Does Hyperglycaemia or hyperinsulinemia characterize the patient with chemical diabetes? *Lancet* 1972;i:1247-1249.
3. Little RR et al. Relationship of glycosylated hemoglobin to oral glucose tolerance: implications for diabetes screening. *Diabetes* 1988;37:60-64.

Diabetes Interventions Studie (DIS)

MI incidence and mortality
in relation to PPBG in type 2 diabetes



M. Hanefeld et al.; Diabetologia, 1999; 39:1577-1583

Postprandial glucose and cardiovascular risk

Studies showing correlation of PPG and CV risk

Whitehall Study
Helsinki Policemen Study
Paris Prospective Survey
Tecumseh Study
Honolulu Heart Program

Studies showing PPG more predictive than FPG or HbA1c for CV risk

Diabetes Intervention Study (DIS)
DECODE

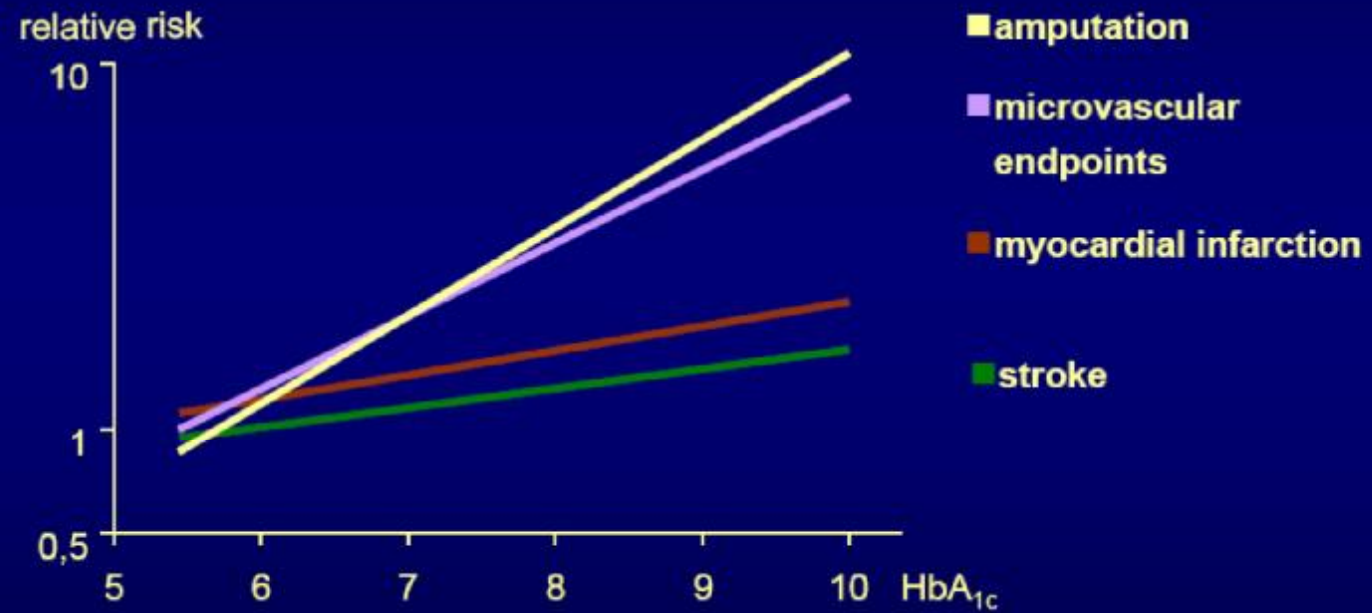
Hypertension

- n Hypertension is, affecting 20–60% of diabetic.
- n It is 1.5 to 3 times higher than that of nondiabetic age-matched groups
- n . Pt with both diabetes and hypertension have approximately **twice the risk of cardiovascular disease** as nondiabetic with hypertension.

- n The challenge is, therefore,
- n to protect the heart of diabetic patients more effectively.
- n Can we achieve this goal ?

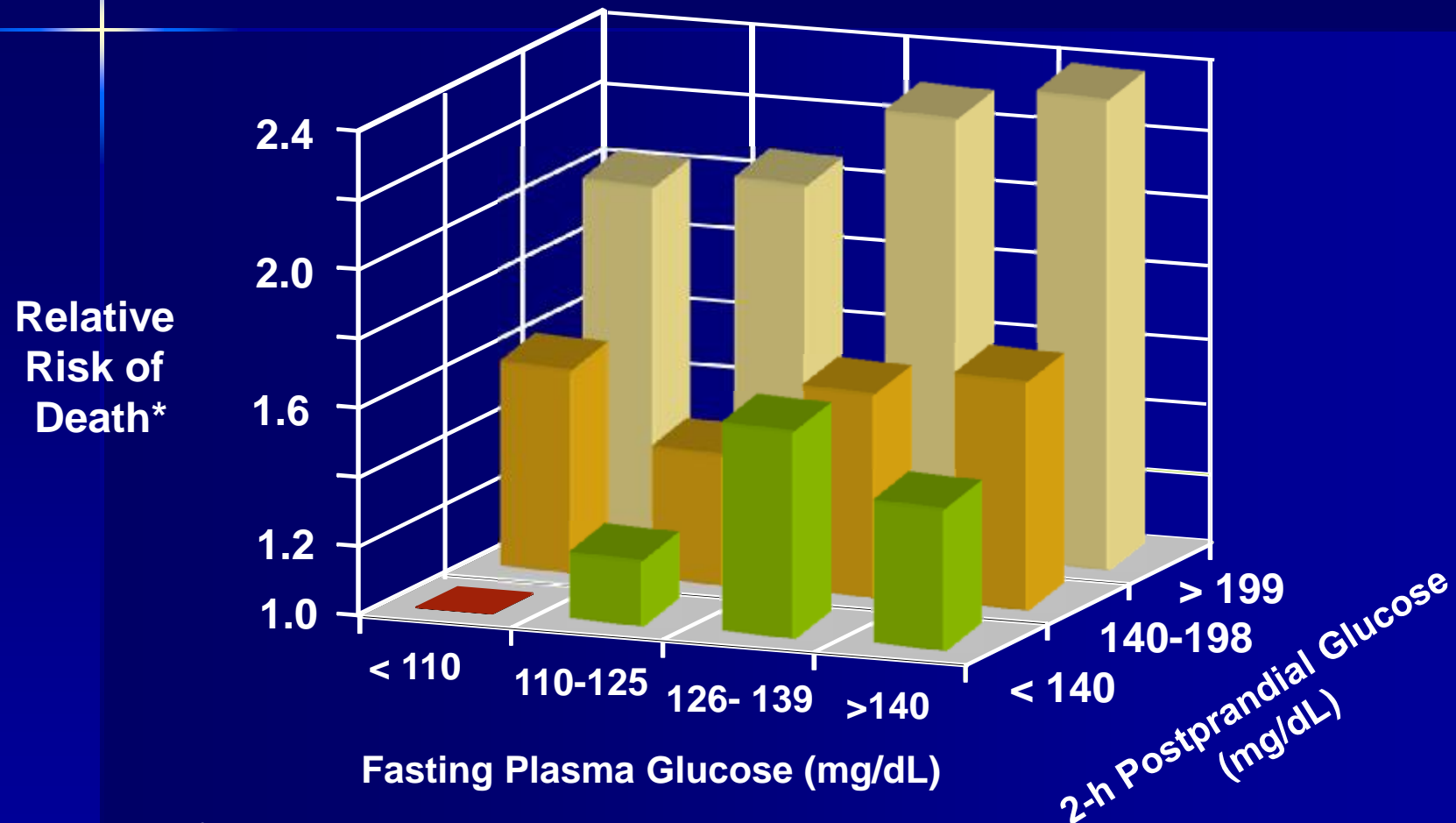
- n Glycemic control
- n Oral hypoglycemia
- n Insuline therapy
- n Statine
- n Cardiovascular drugs

UKPDS: Diabetes Complications



Graph: Novo Nordisk according to Stratton et al., UKPDS 35

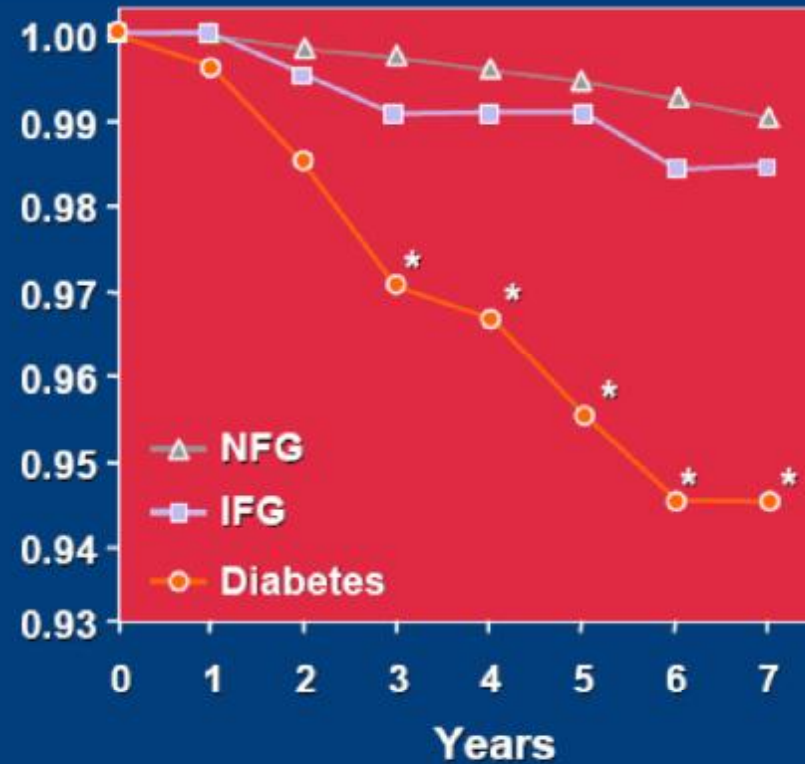
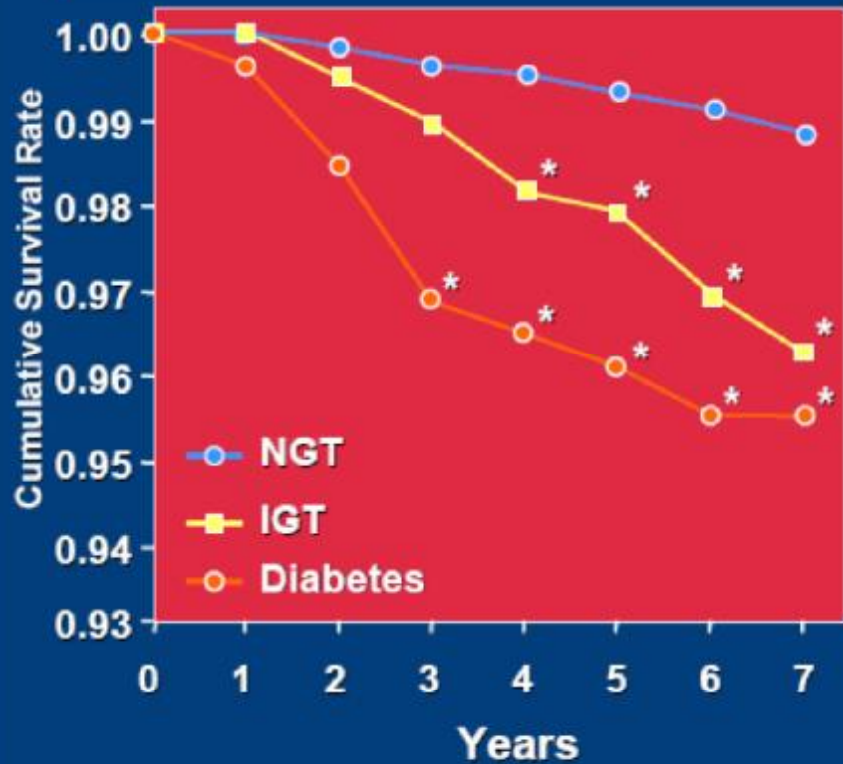
Relative Risk for Death Increases with 2hour Blood Glucose Regardless of the FPG Level



*Adjusted for age, sex, study center

Adapted from DECODE Study Group. *Lancet*. 1999;354:617-621.

Impaired Glucose Tolerance, Not Impaired Fasting Glucose, Predicts CVD



* $P < 0.05$.

Preconditioning

n is the mechanism by which brief periods of sublethal ischaemia can render a heart more resistant to subsequent periods of more prolonged ischaemia

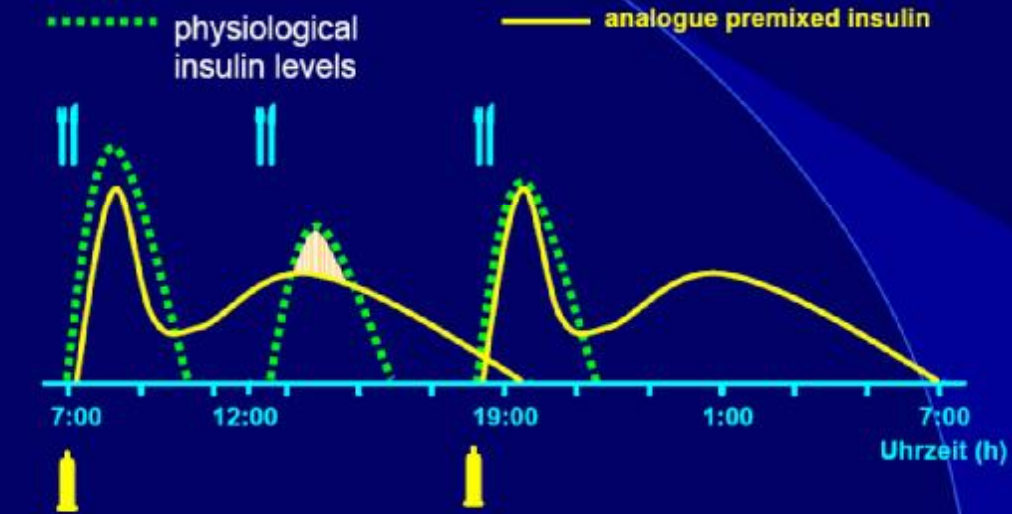
Insulin

- n Using an animal model of reperfusion after low flow ischaemia, it was shown that insulin perfusion increased pre-ischaemic myocardial glycogen content in both diabetic and control hearts.

- n The DIGAMI (diabetes mellitus, insulin glucose infusion in acute myocardial infarction) study enrolled patients with AMI who received insulin and glucose intravenously or conventional treatment. One year follow up results showed a
- n 30% lower mortality rate in the intensive treatment group.
- n Subsequent studies suggested that treatment with intravenous insulin can have positive effects upon several aspects of the disease (besides glucose values).

- Insulin perfusion improved
- n recovery of cardiac performance
 - n and elevated creatine phosphate concentrations in both diabetic and control hearts.
-
- n Results demonstrate greater cardioprotection against ischaemia/reperfusion injury in diabetics and with insulin perfusion.

Conventional insulin therapy CT using analogue premixed insulins



Closer to normal physiology with analogue premixed insulins

Oral hypoglycemic drugs

- n use of sulfonylurea drugs may be harmful by preventing endogenous cardioprotective mechanisms;
- n sulfonylurea drugs increased early mortality in diabetic patients after direct angioplasty for AMI.

Sulfonureas

- n sulfonylureas may abolish the preconditioning response in humans.
- n Selective blockade of myocardial KATP channels with glibenclamide at therapeutic doses is associated with significantly impaired cardioprotection and,
- n thereby, contributes to this increase in mortality.

Glimepiride

- n Unlike glibenclamide, glimepiride does not block the mitochondrial KATP channels of the myocardium.
- n This finding is especially important in older persons with diabetes, in whom preconditioning has been shown to be impaired by attenuated activation of KATP channels.

Glitazones

- n Glitazones—act as insulin sensitisers.
- n Data mainly from preclinical studies suggest that glitazones
- n protect the heart from acute ischaemia/reperfusion injury and
- n also might attenuate cardiac remodelling and heart failure

- n Mechanisms involved in this cardioprotection are multifactorial .

Glitazones decrease

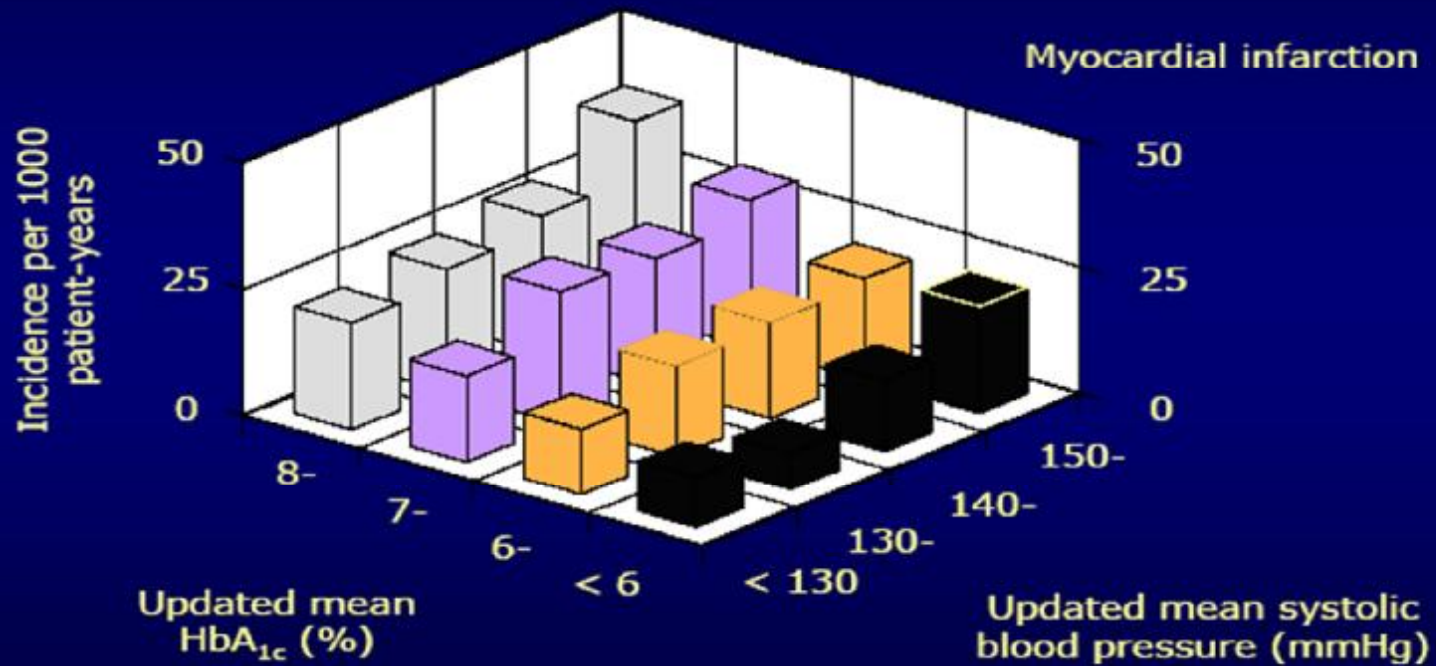
- n triglycerides, fibrinogen, visceral fat, blood pressure, and microalbuminuria,
- n and improve vascular function.

- n However, fluid retention by glitazones may induce or worsen congestive heart failure in diabetics with left ventricular dysfunction.

Reduction of BP

- n The greatest reduction in cardiovascular mortality occurs at achieving a diastolic blood pressure of ~80 mmHg).
- n Epidemiological evidence indicates that there is a benefit to reducing systolic blood pressure to <130 mmHg .
- n Therefore, aggressive blood pressure control should be attempted in all patients with diabetes.

Multifactorial Therapy in UKPDS



Unpublished data (Irene Stratton)

Cardiovascular drugs

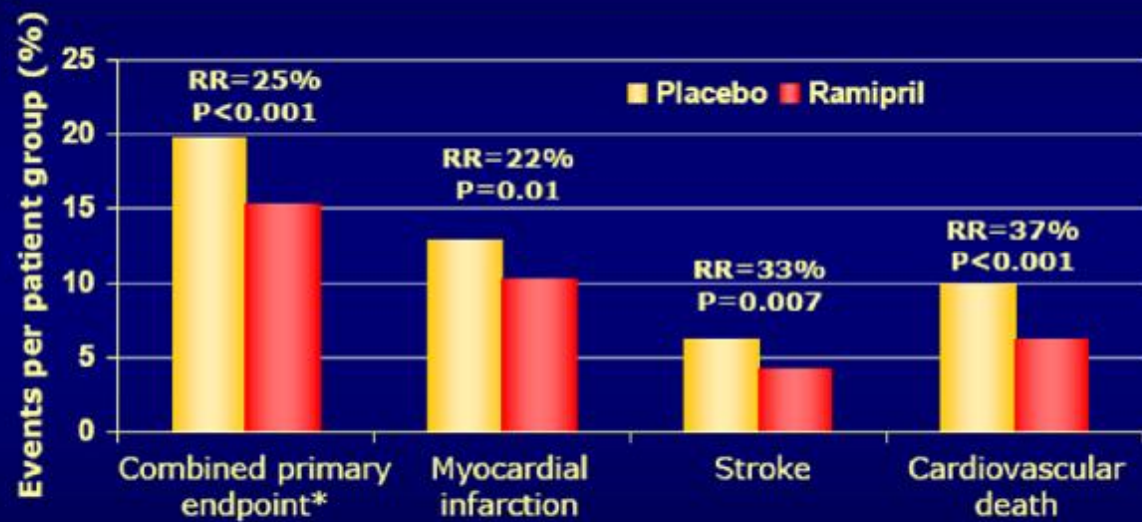
Beta blocker

- n b Blockers have an established role in cardioprotection, both in primary and secondary preventive studies, and there is evidence that their **cardioprotection is even greater in diabetics**.
- n Common belief that b blockers increase the complication rate in diabetes and worsen glycaemic control **has no scientific basis** and **should not limit their use in diabetics** with coronary artery disease.

Angiotensin converting enzyme (ACE) inhibitors

- n As both angiotensin II and renin–angiotensin system activation are important deleterious factors in diabetes,
- n it is not surprising that ACE inhibitors prolong survival in diabetics with **heart failure**
- n and/or **coronary artery disease**,
- n emphasised by current guidelines.

MICRO-HOPE Events Per Patient Group for Primary Endpoint* and Components



*The occurrence of myocardial infarction, stroke or cardiovascular death

RR=Relative risk reduction

HOPE Study Investigators. Lancet. 2000;355:253-259.

www.hypertensiononline.org

- n Anigiotensine converting enzyme inhibitor represents a
- n Vasculoprotective
- n Renoprotective
- n Beneficial for overt neuropathy in diabetes

Micro HOPE SUBSTUDY

angiotensin II receptor blocker

- n Candesartan, an angiotensin II receptor blocker, lowers blood pressure and
 - n preserves left ventricular diastolic function
 - n reduces the thickening of the capillary basement membrane,
 - n decreasing cardiomyocyte diameter,
 - n increasing matrix metalloproteinase-2 activity,
 - n and decreasing inflammatory cytokines.
-
- n These mechanisms may explain why, in diabetics with heart failure and coronary artery disease, angiotensin II receptor blockers are endorsed by current guidelines.

dyslipidemia

- n Diabetic dyslipidaemia is characterised by
- n moderately high concentrations of serum cholesterol
- n and triglycerides,
- n small and dense low density lipoprotein (LDL) particles,
- n and low high density lipoprotein (HDL) cholesterol concentrations.

Lipid risk factors and predictors of CV risk

- Low HDL is an independent risk factor for CHD¹
- TC:HDL ratio is best predictor of coronary artery disease¹
 - superior measure of risk compared to total cholesterol or LDL²
- Small dense LDL particles are more atherogenic and have been associated with an increased risk of MI³
- Triglycerides are NOT an independent risk factor when analysed with other variables eg HDL⁴
- Free fatty acids play a role in CVD by affecting vascular tone (via reducing nitric oxide action/production)

1. Austin MA *et al.* *JAMA* 1988; **260**: 1917-1921

3. Stampfer MJ *et al.* *JAMA* 1996; **276**: 882-888

2. Castelli WP. *Am J Obstet Gynecol* 1999; **180**: S349-S356

4. Turner RC *et al* (UKPDS 23). *BMJ* 1998; **316**: 823-828

Statins

- n Recent clinical trials have demonstrated the benefits of statins in both diabetic and non-diabetic patients, thus supporting aggressive treatment of diabetic dyslipidaemia for coronary artery disease prevention.
- n It is believed that an important part of the derived benefit in diabetics may be due to the **pleiotropic effects of statins**

(improvement in endothelial function, and anti-inflammatory and antioxidant effects).

Thank you