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Type 2 Diabetes

Ron Innerfield, MD, FACE

Medical Director,
Medical & Scientific Affairs

19 July 2002

What is Diabetes?

(Metabolically?....)

Elevated fasting sugar > 126 mg/dl
(or 2hr post prandial sugar > 200 mg/dl)

Insufficient insulin to suppress gluconeogenesis

Variable levels of *insulin resistance* in the liver and periphery (muscle and fat)

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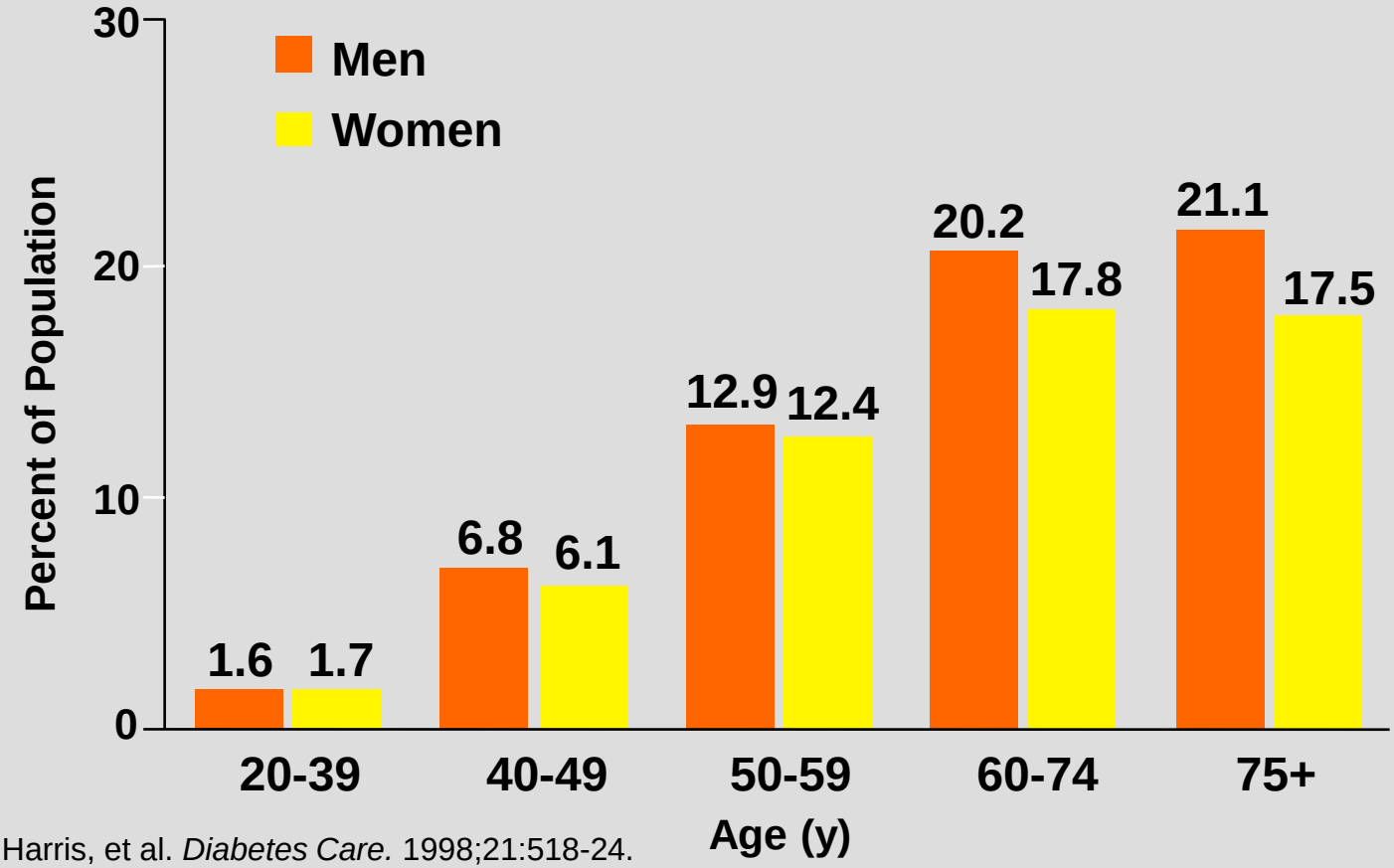
Estimated Prevalence of Diabetes in the US

Adult Men and Women



Harris, et al. *Diabetes Care.* 1998;21:518-24.

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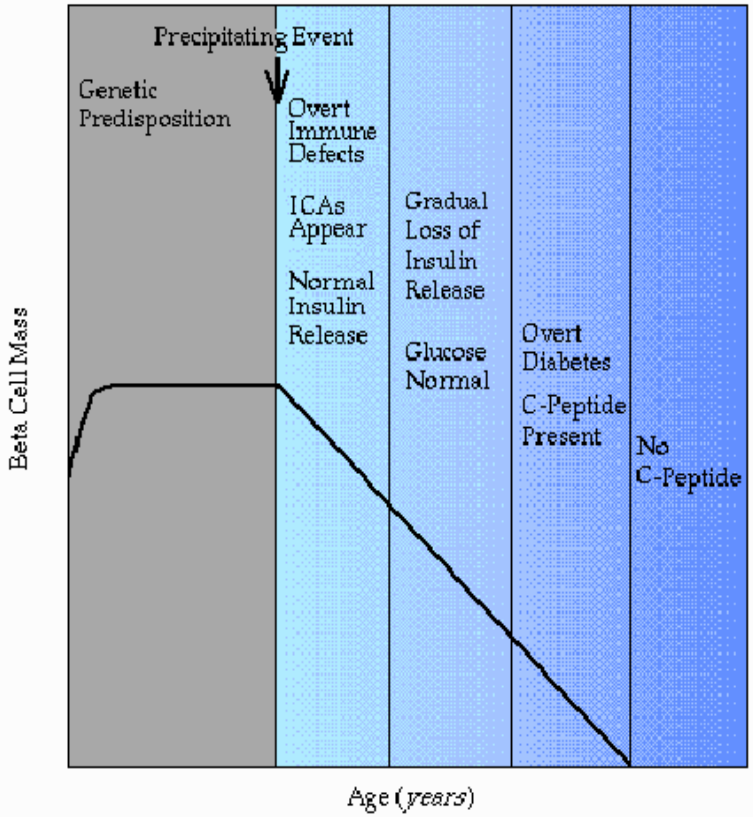
Course of Type 1



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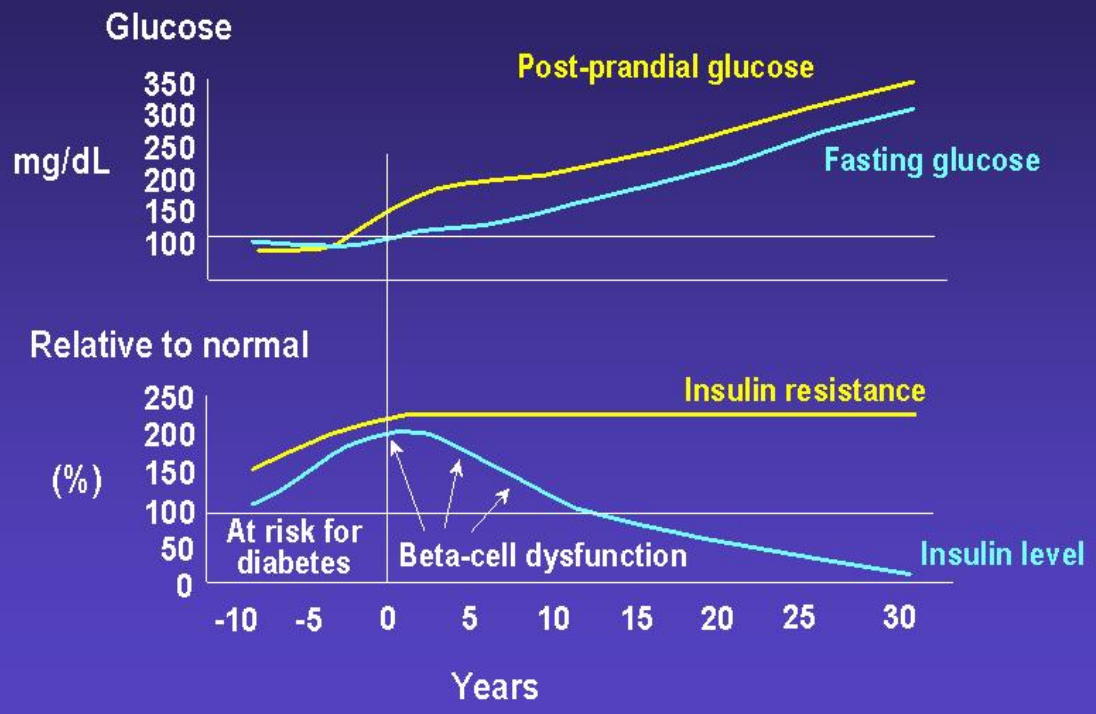
Emerging Strategies

Natural History of Type 2 Diabetes



R.M. Bergenstal, International Diabetes Center

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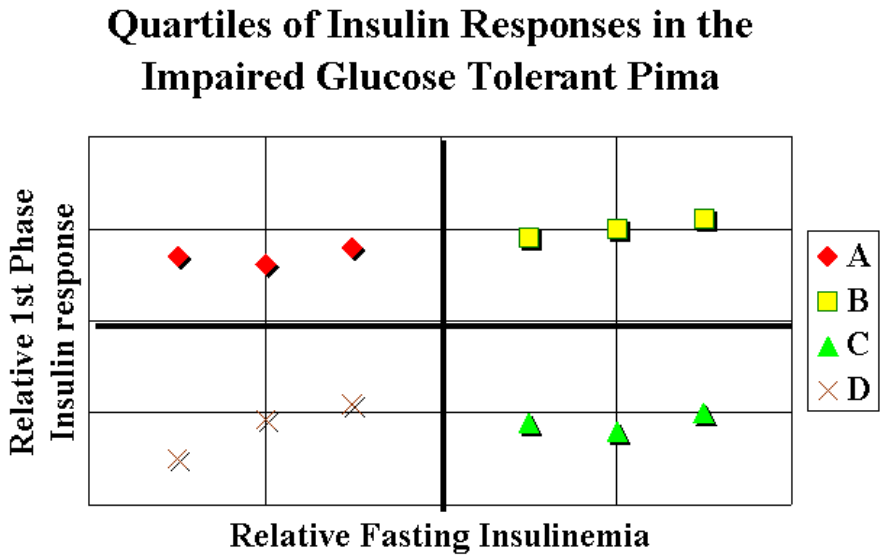
Who progresses to Type 2 from IGT?

Who Progresses to Type 2 DM?



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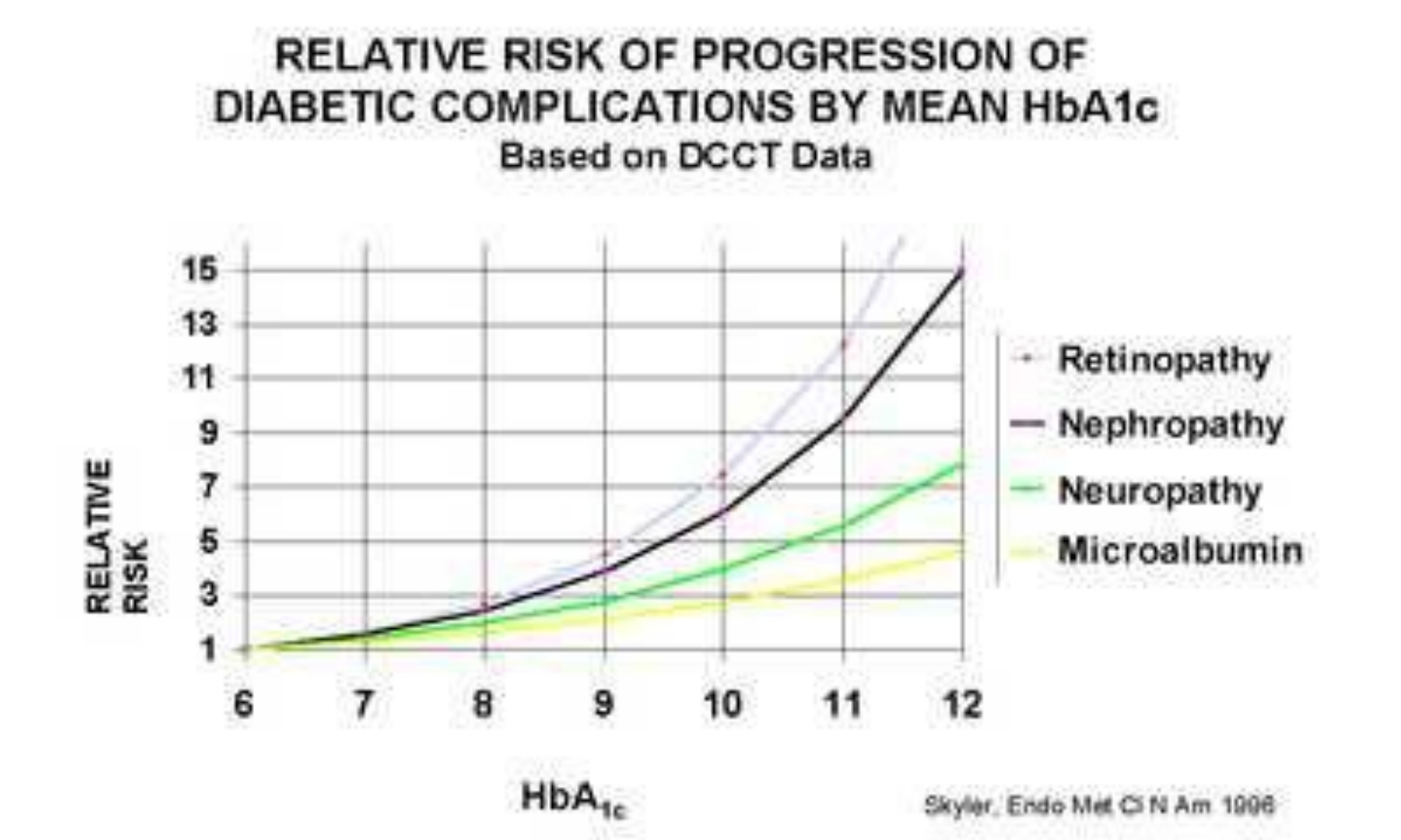
Discrete vs. Continuous?



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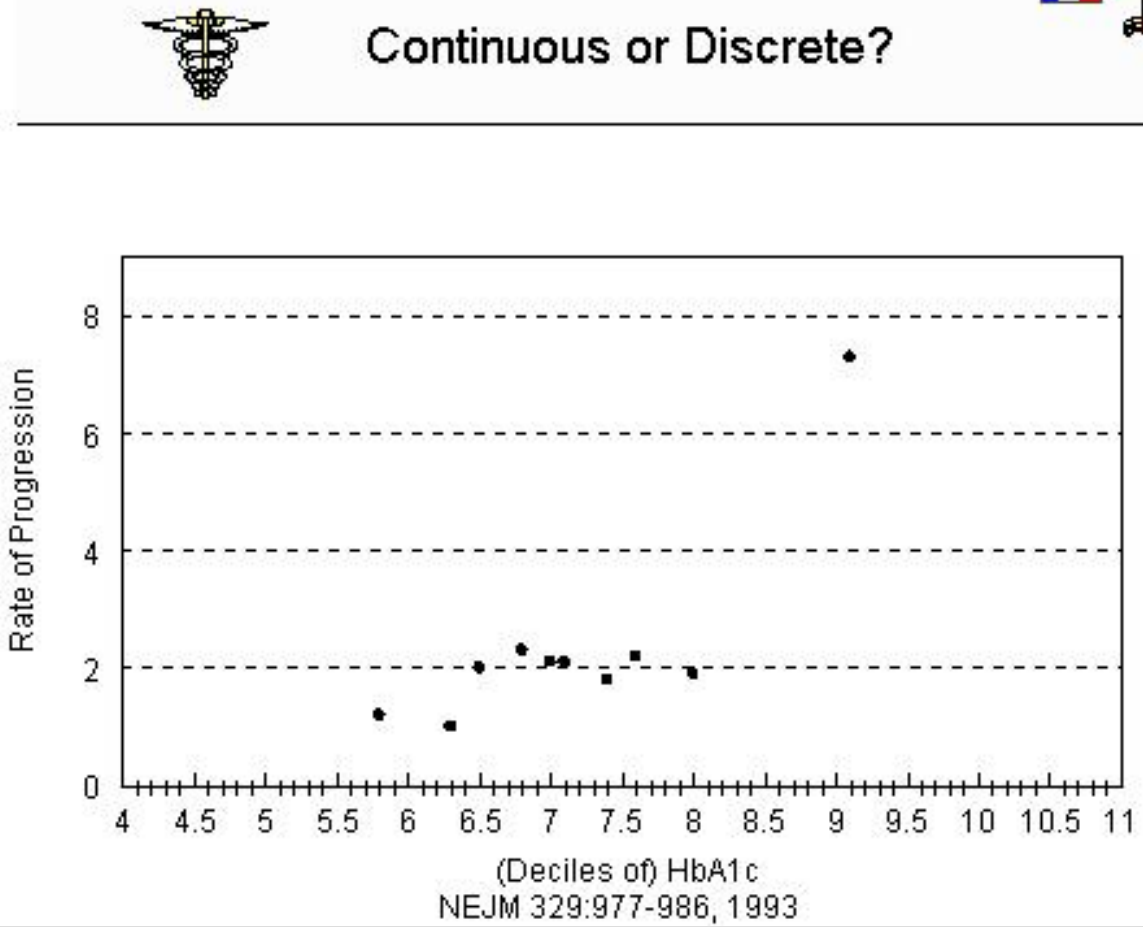
DCCT Data

Continuous or Discrete?



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Pathophysiology of Glycemic Microvasculopathy-1

- **Hemoglobin A1c (HbA1c) is the sugarization or "*Stickiness-index*" which measures the percentage of hemoglobin - a protein, sitting innocently within the membrane-protected environment of the red blood cell, whose function it is to bind O2 in the lungs and release it in the tissues - which is covalently stuck to glucose (*maple syrup*)**

- **Correlates virtually linearly with the level and duration (*average*) of glucose concentration over the preceding three months or so:-**

•60 mg/dl <=> 4%	90 mg/dl <=> 5%
•120 mg/dl<=> 6%	150 mg/dl<=> 7%
•180 mg/dl<=> 8%	210 mg/dl<=> 9%
•240 mg/dl<=> 10%	270 mg/dl<=> 11%
•300 mg/dl<=> 12%	330 mg/dl<=> 13%
•360 mg/dl<=> 14%	390 mg/dl<=> 15%

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Pathophysiology of Glycemic Microvasculopathy-2

- **Correlates with the pathophysiologic glycosylation of (*glucose-stickiness to*) proteins in the vasculature**
- **Correlates with small-vessel complications as glycosylated proteins cause more obstruction to red-cell flow in smaller caliber arteries than in larger caliber arteries**

- **Target is an A1c of 7% Hemogobin sugarization with action suggested if the Hemoglobin sugarization exceeds 8%**
- **Correlates with the life span of the red cell and is therefore dependent on a normal (3 month or so) red-cell survival**

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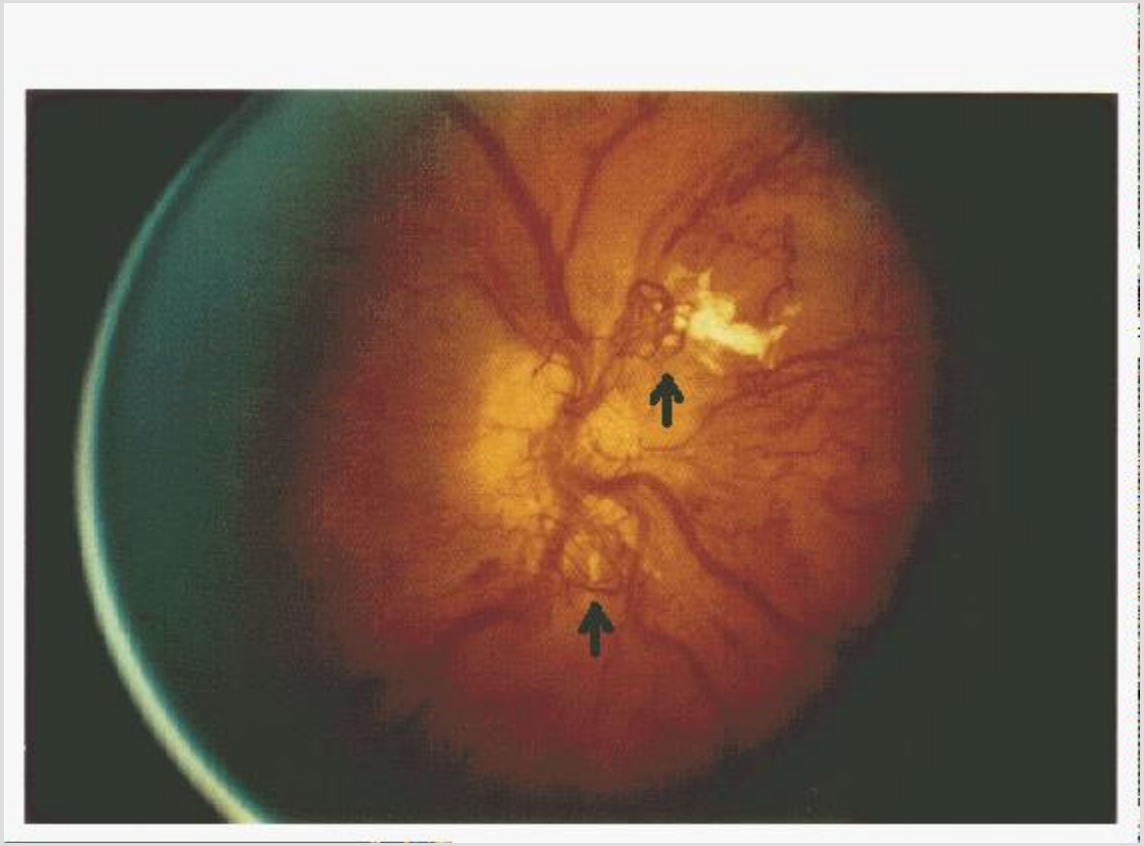
Microvasculopathy



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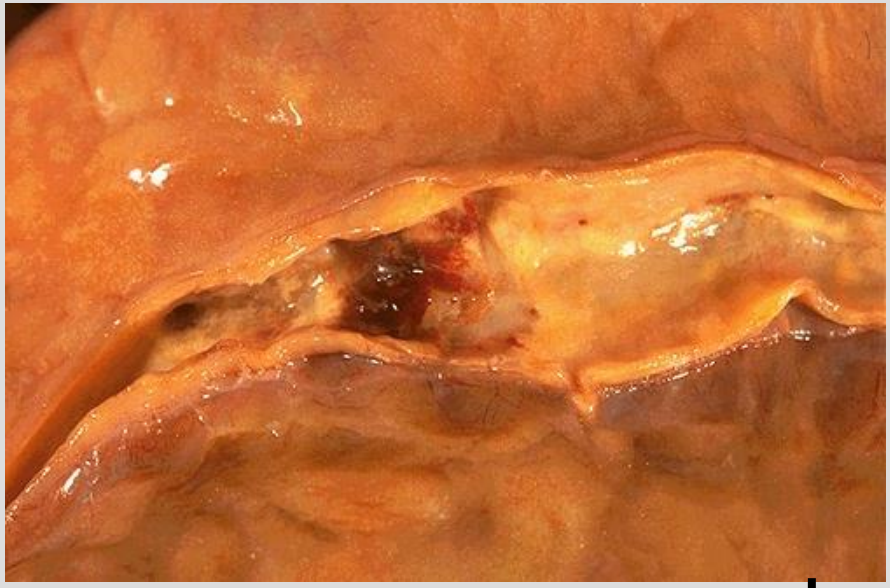

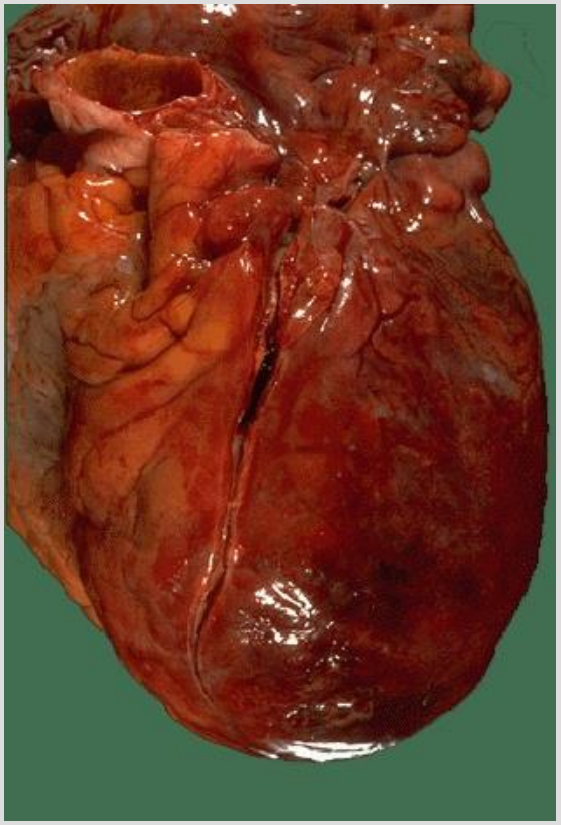

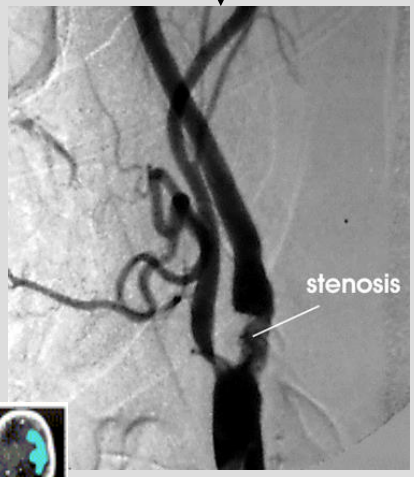

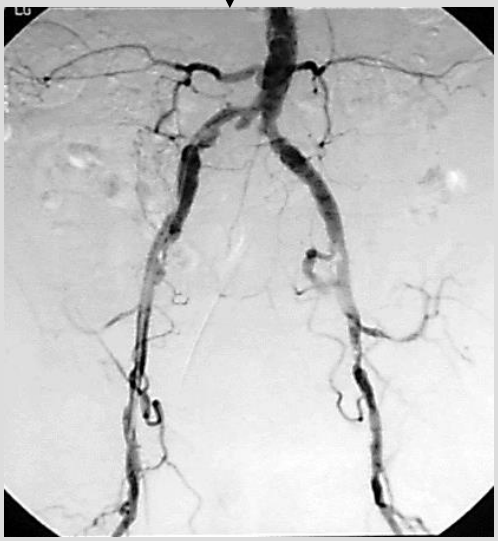

MacroVasculopathy

The Problem

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NIDDK/NHLBI/NDC/AHA/ADA Statement

NHLBI/NIDDK/AHA/ADA/NDC Statement (1 Sep 1999)

Diabetes Mellitus: A Major Risk Factor for Cardiovascular Disease

Statement from Dr. Claude Lenfant, Director, National Heart, Lung, and Blood Institute, and Dr. Phillip Gorden, Director, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

The National Heart, Lung, and Blood Institute (NHLBI) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes Diseases (NIDDK) of the National Instiutes Health (NIH) have collaborated with three leading private health organizations on a major public health statement to alert physicians, patients, and the general public

to the increasing significance of diabetes mellitus as a major risk factor for cardiovascular disease.

In joining this effort, each organization reaffirms its commitment to better understand the causes and unique factors that contribute to excess risk of premature CVD in persons with diabetes, and to develop and implement improved treatments to reduce these complications.

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1) Are glycemic control and cardiovascular mortality strongly associated?

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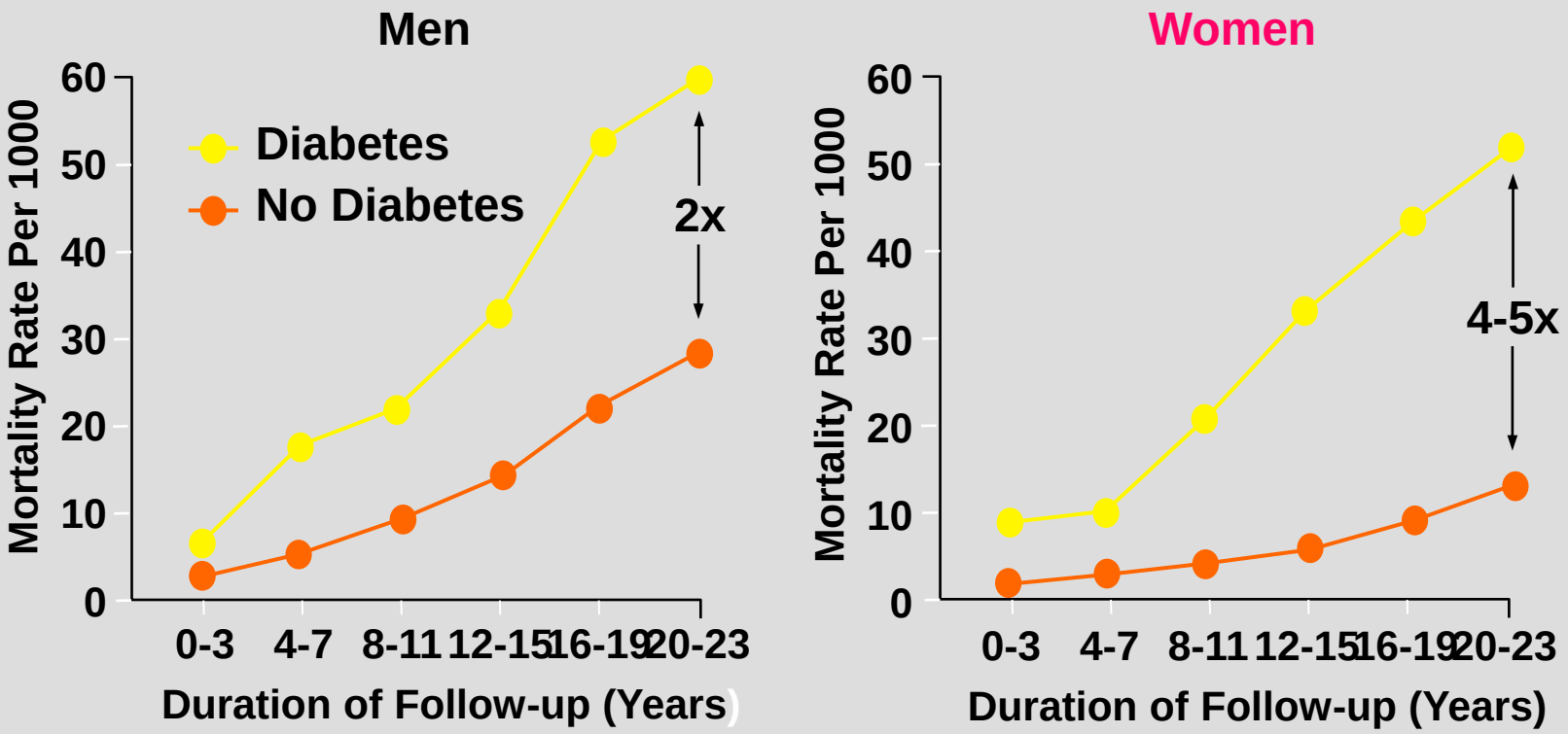
FRAMINGHAM STUDY AND JOSLIN PATIENTS

Diabetes is a CV Risk Factor



Krolewski AS, et al. Evolving natural history of coronary disease in diabetes mellitus. *Am J Med* 1991;90(Supp 2A):56S-61S.

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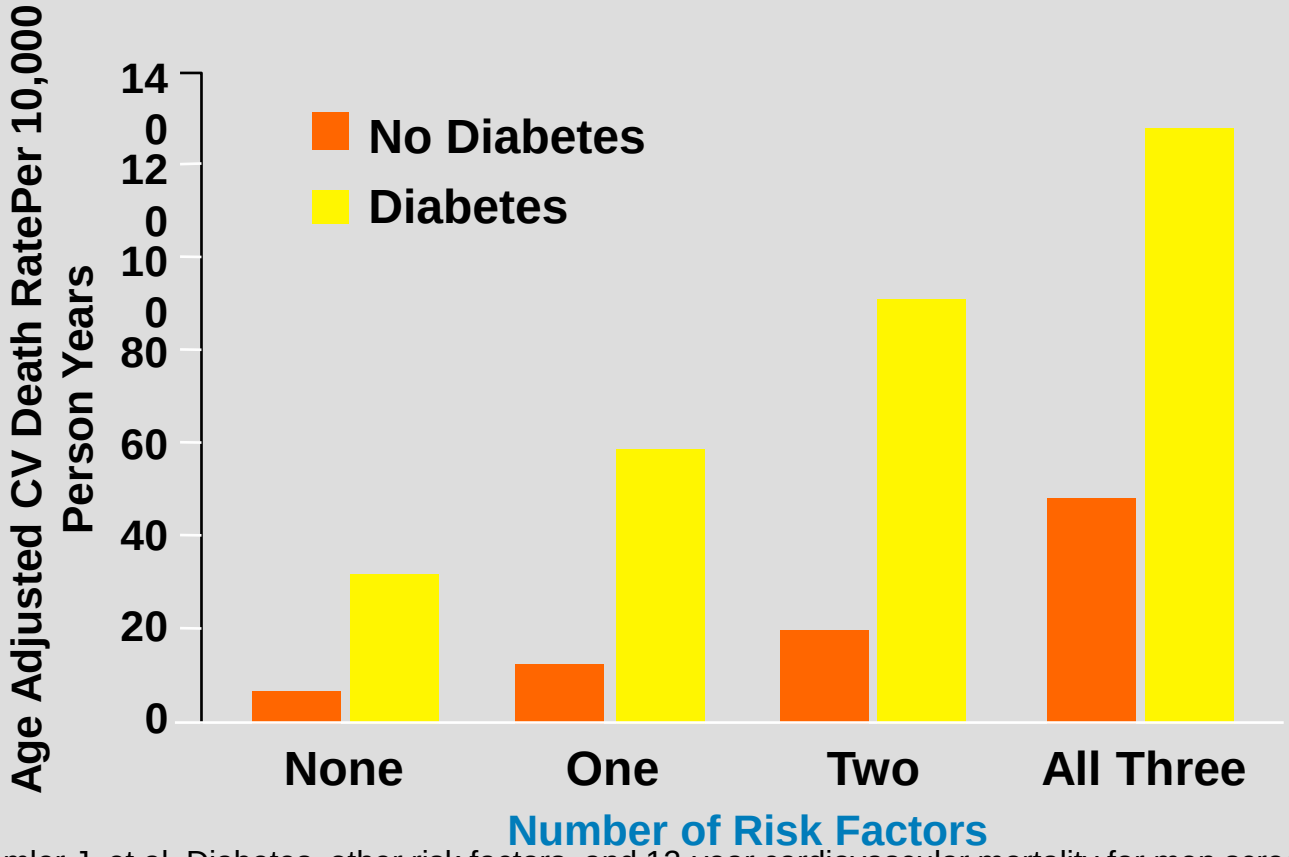
MRFIT

Type 2 Diabetes is a CV Risk Factor

Additive Effects of Hypertension, Hypercholesterolemia, and Smoking



Stamler J, et al. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434-44.

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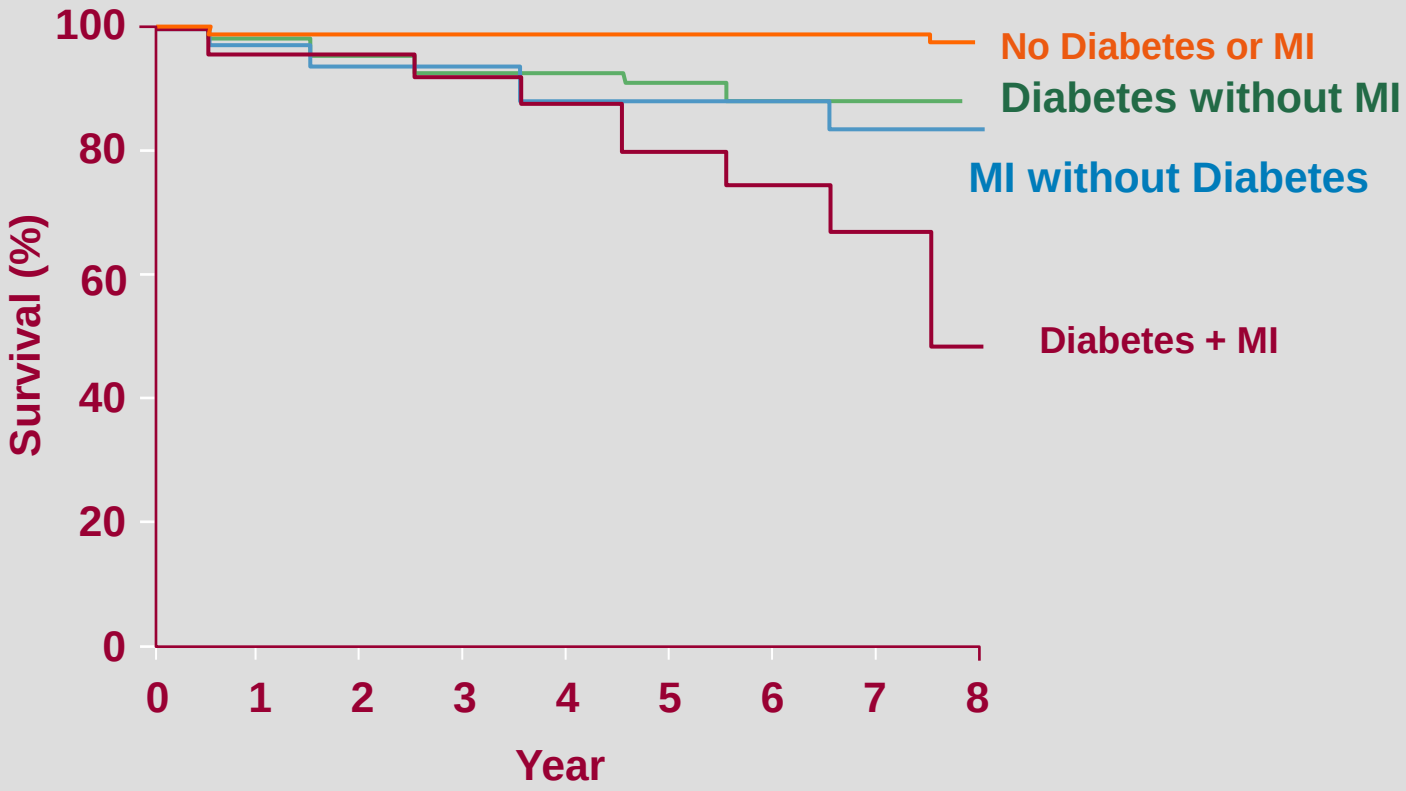
Type 2 Diabetes is a CV Risk Factor

Diabetes and Prior MI Predict Mortality Equally



Haffner SM, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229-34.

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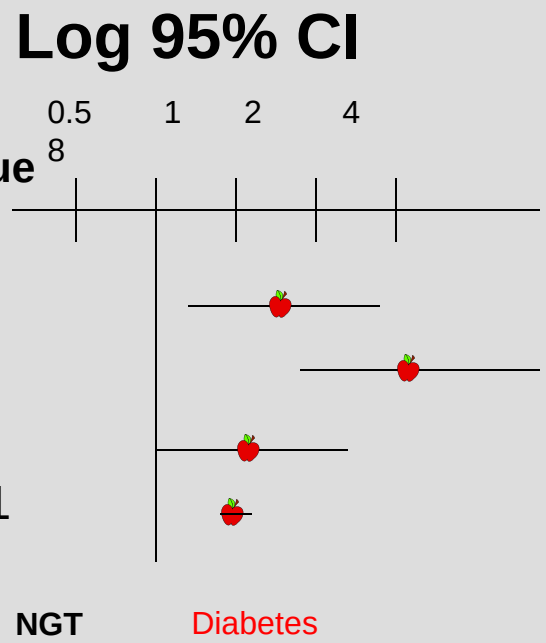
Cardiovascular Mortality in Normal Glucose Tolerance vs. Diabetics[1]

Study	Ratio	p value
SanAntonio Heart Study(1998)[1]		
Males	3.2	<0.05
Females	8.5	<0.05
Paris Prospective Study(1993)[2]	**2.3**	**ns**
Malmohus County Study(1997)[3]	**1.8**	<0.01



1, 2 Relative Risk

3. Age-Sex Adjusted Relative Risk

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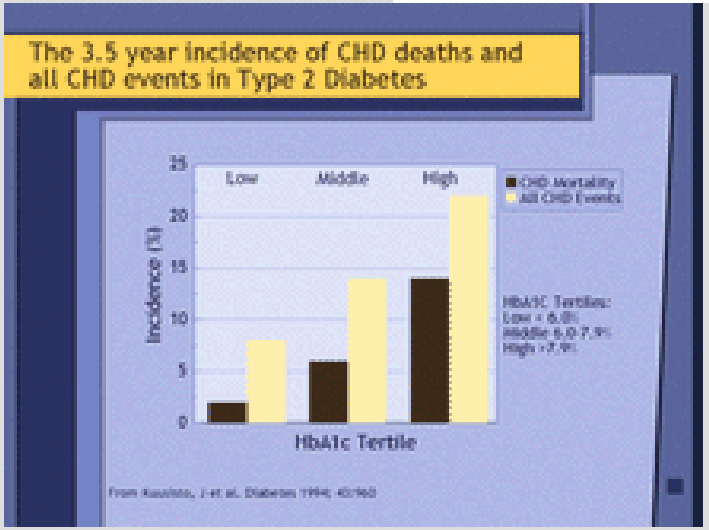
Cardiovascular Mortality in Diabetes[1]

TABLE 2
Hyperglycemia as predictor of cardiovascular mortality in type 2 diabetes: a 15-year follow-up from the time of diagnosis-
The Kuopio 2 Study

	All-cause Mortality Odds Ratio	Cardiovascular Mortality Odds ratio
Men	5.0, P < 0.001	6.2, P < 0.001
Women	5.2, P < 0.001	11.2, P < 0.001

Diabetes Care 1998 Nov;21(11):1861-9



(**Diabetes 1994 Aug;43(8):960-7**)
In a Finnish 3.5 year study at Kuopio 1 (Figure 2), coronary heart disease deaths and events are shown to increase by tertile of hemoglobin A1c. "In NIDDM subjects, only glycated hemoglobin A1c (GHbA1c) at baseline ($P < 0.01$) and duration of diabetes ($P < 0.05$) predicted CHD death (n = 15) and all CHD events (n = 33)." Moreover the HbA1c correlation was still seen across long and short periods of disease duration

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Cardiovascular Mortality in Diabetes[1]

TABLE 1
Hazard Ratios of Cause-Specific Mortality
And Glycemia in Older-Onset Diabetes Patients
(*WESDR*)

Cause of Death	Hazard Ratio for Each 1% Increase in *Baseline* Glycohemoglobin*
Diabetes Mortality	1.32 (1.21-1.43)
Ischemic Heart Disease	1.10 (1.04-1.17)
Stroke	1.17 (1.05-1.30)
Cancer	0.99 (0.88-1.10)

*Adjusted for other risk factors such as smoking, hypertension, etc.

Moss SE et al.
Arch Intern Med 1994 Nov 14;154(21):2473-9

Each 1% increase in Hb A_{Ic} is associated with an 8% increased risk of heart failure (95% CI 5% to 12%) - Iribarren et all, *Circulation.* 2001;103:2668.

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UMDS

Dr. Harry Keen (1968)[2]

"It is, of course, possible to formulate three standard hypotheses to explain the relationship - that A causes B, that B causes A, or that both A and B are caused by C. We have chosen to examine what is perhaps the most likely and potentially the most useful of these explanations - that hyperglycemia contributes causally to the development of the arterial lesions. It is a useful explanation because there is long experience and knowledge of methods aimed at lowering the blood sugar: the possibility of intervening in the progress of a disease process is one which stimulates both the interest of the doctor and the co-operation of the patient." (Keen H, Jarrett, RJ, Chlouverakis C, Boyns DR, The effect of treatment of moderate hyperglycemia on the incidence of arterial disease. *Postgrad. Med.J*. [1968] **44**:960)

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2) If the suspicion is that poor control causes excess cardiovascular mortality, can long-term control of diabetes be shown to reduce long-term cardiovascular mortality?

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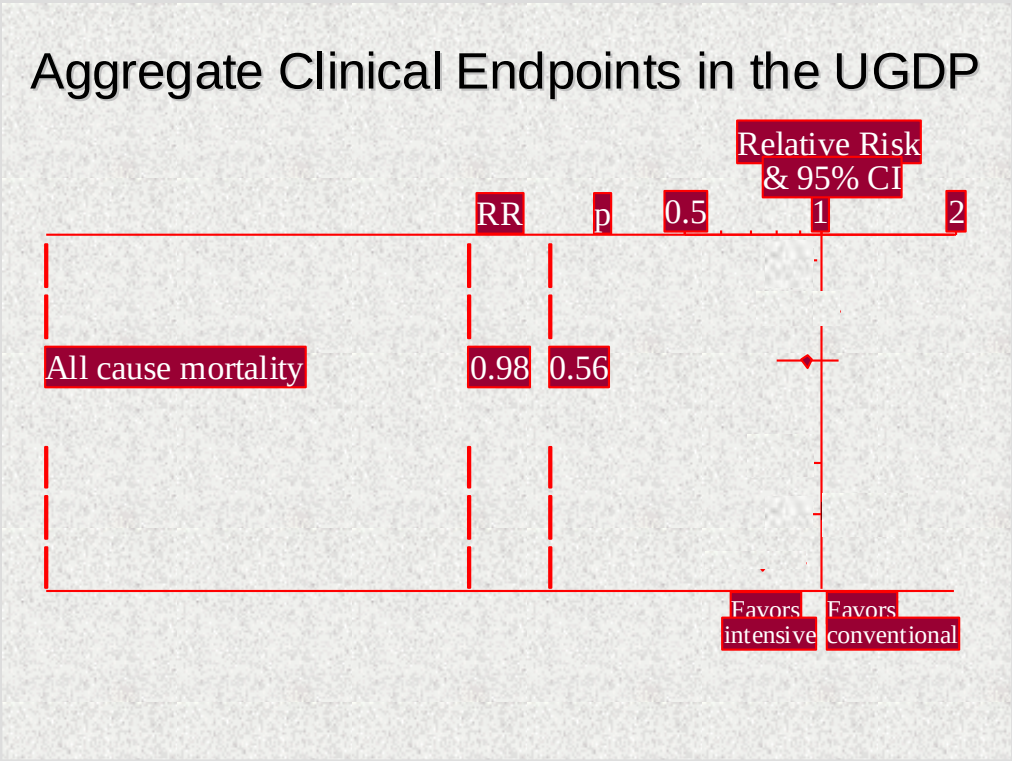
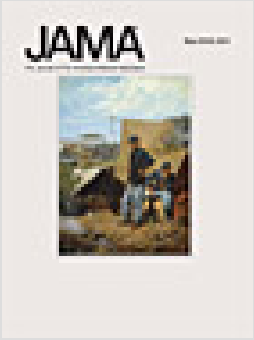
Q:-Does Altering *Glycemic Control* Over the Long-Term Have Any Impact Upon Cardiovascular Mortality? [2]

- **A:- Nope**
  - **(UGDP-1971)**





JAMA 1971 Nov;218(9):1400-10 **Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. 3. Clinical implications of UGDP results.** Goldner MG, Knatterud GL, Prout TE.

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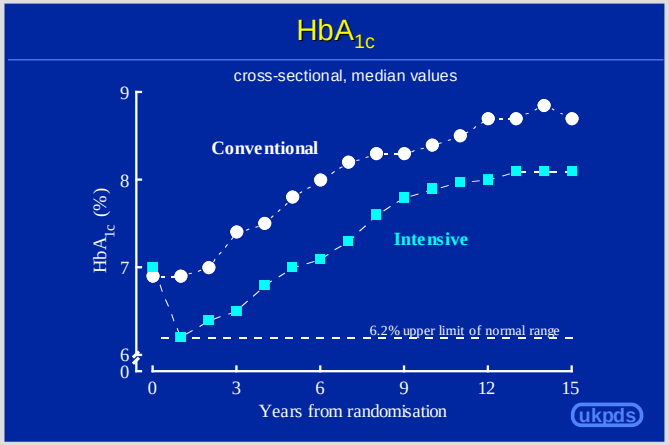
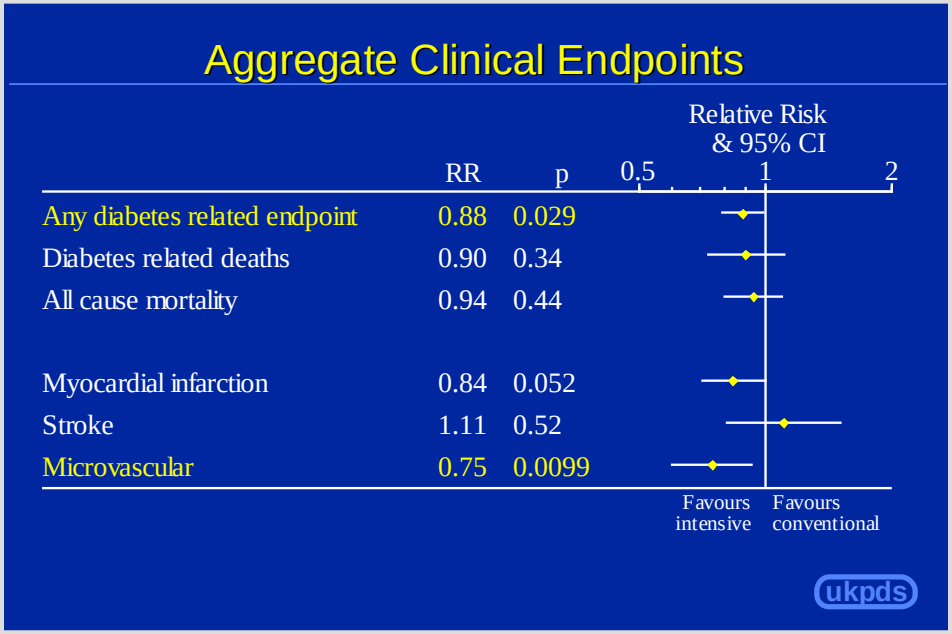
Q:-Does Altering *Glycemic Control* Over the Long-Term Have An Impact Upon Cardiovascular Mortality?[2]

- **A:- Nope**
  - **(UKPDS-1999)**





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3a) If not, can *markers* which may precede diabetes but are not necessarily associated with poor control also be shown to associate with increased cardiovascular mortality?

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Cytokines….[3a]

There is some newly emerging data that atherosclerosis, type 2 diabetes, and obesity are all characterized by increased plasma or serum levels of inflammatory vasoactive cytokines. M. Visser and colleagues (*JAMA*[1999] 282:2131-2135) have reported that, "*Higher BMI is associated with higher CRP concentrations, even among young adults aged 17 to 39 years. These findings suggest a state of low-grade systemic inflammation in overweight and obese persons*." Hak et al reported in1999 (*Arteriosclerosis, Thrombosis, and Vascular Biology* **19**:1986-1991) that C-Reactive Protein associates with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. Also, John Yudkin's group has data recently published (*Arteriosclerosis, Thrombosis, and Vascular Biology* (1999) 19: 972-978) that "adipose tissue is an important determinant of a low level, chronic inflammatory state as reflected by levels of interleukin-6, tumor necrosis factor-, and C-reactive protein, and that infection with H pylori, C pneumoniae, and cytomegalovirus is not …[and] support the concept that such a low-level, chronic inflammatory state may induce insulin resistance and endothelial dysfunction and thus link the latter phenomena with obesity and cardiovascular disease." Additionally, data from the Hoorn study (Jager, A, van Hinsbergh, VW.M., Kostense, PJ., Emeis, JJ., Yudkin, JS., Nijpels, G, Dekker, JM., Heine, RJ., Bouter, LM., Stehouwer, CDA., von Willebrand Factor, C-Reactive Protein, and 5-Year Mortality in Diabetic and Nondiabetic Subjects : The Hoorn Study *Arteriosclerosis, Thrombosis, and Vascular Biology* (1999) **19**: 3071-3078) show that not only does CRP, but also increased levels of von Willebrand's factor "are independently associated with cardiovascular and all-cause mortality in both diabetic and nondiabetic subjects….Mutual adjustment of vWf and CRP did not markedly change the results, favoring the hypothesis that vWf and CRP predict mortality through different pathways."

3b) If so, can *conditions* which may precede diabetes but are not associated with poor control also be shown to associate with increased cardiovascular mortality?

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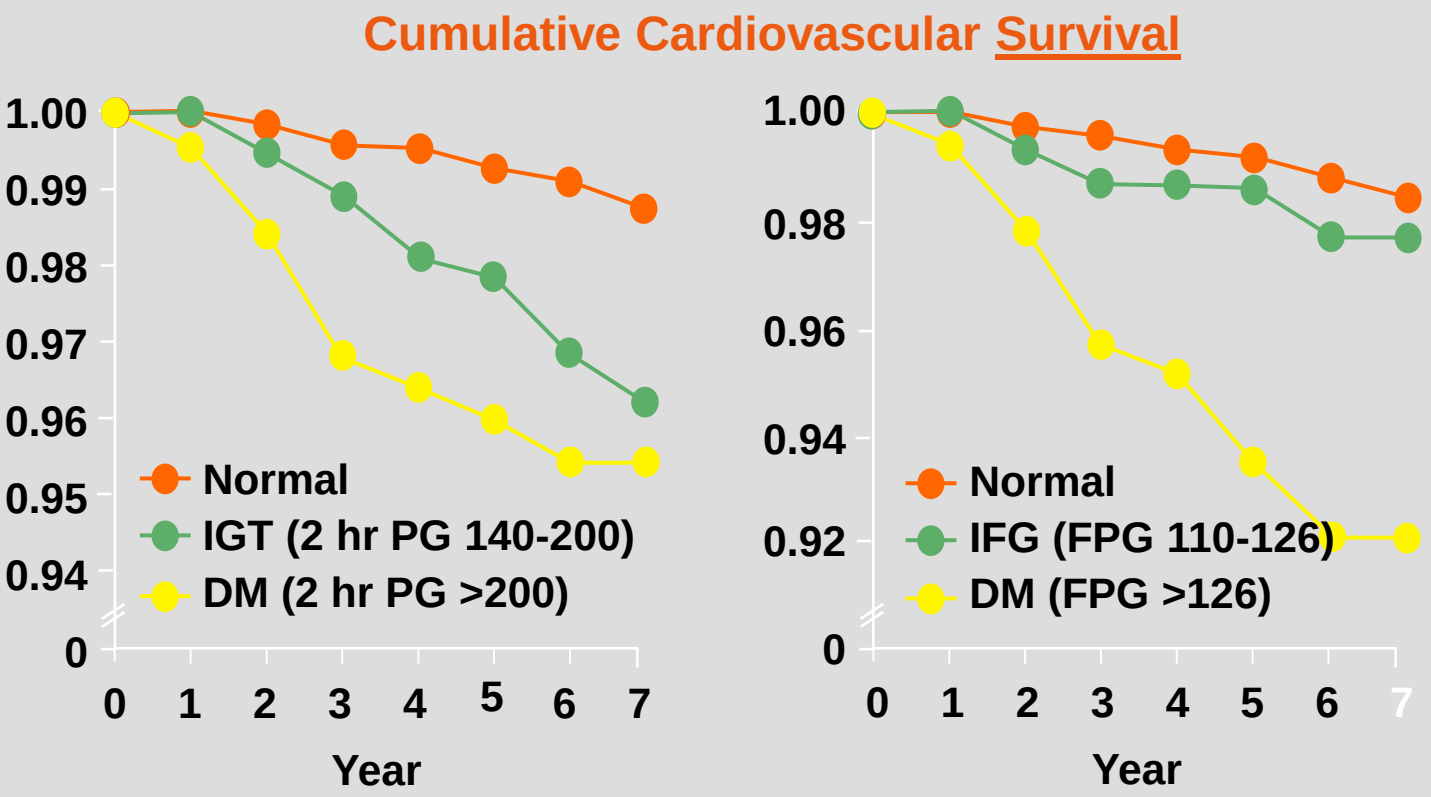
THE FUNAGATA DIABETES STUDY

Impaired Glucose Tolerance is a CV Risk Factor[3b]



Tominaga M, et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, ***but not impaired fasting glucose***. *Diabetes Care* 1999;22:920-4.

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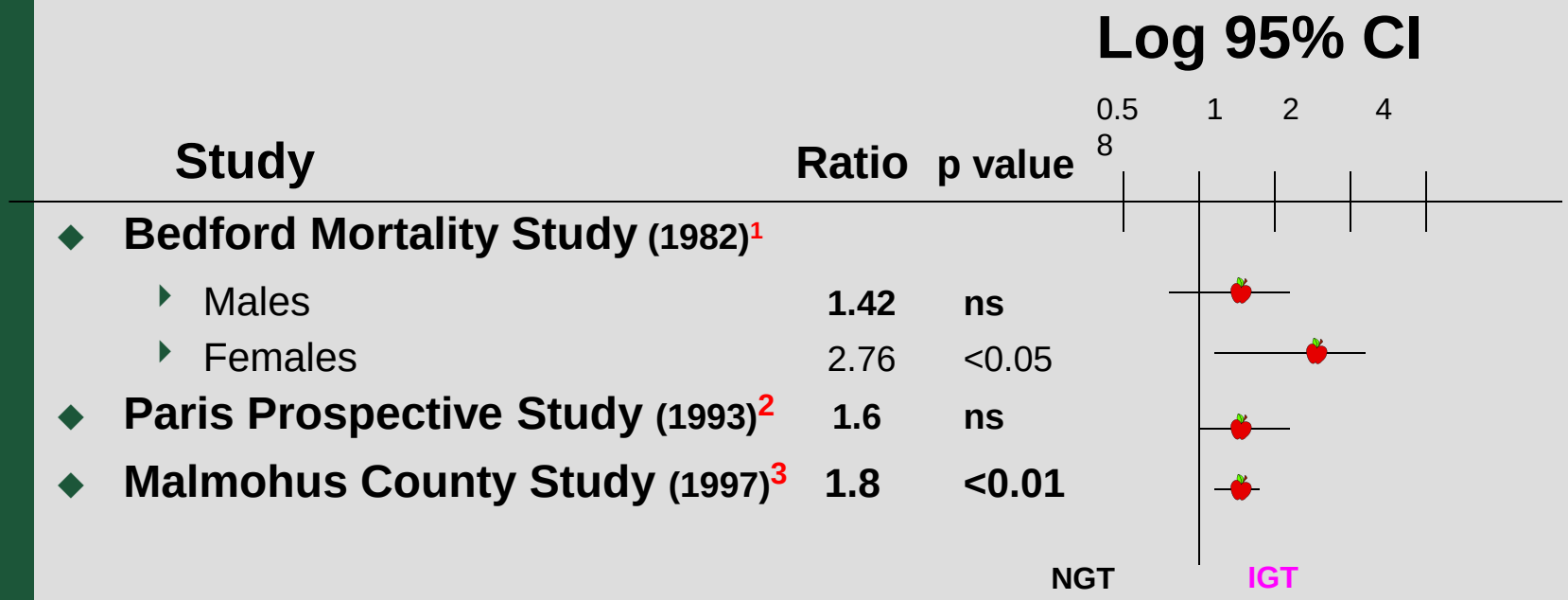
Cardiovascular Mortality in Normal Glucose Tolerance vs Impaired Glucose Tolerance[3b]



1. Odds Ratio
2. Relative Risk
3. Age-Sex Adjusted Relative Risk **(minus SFU Pts)**

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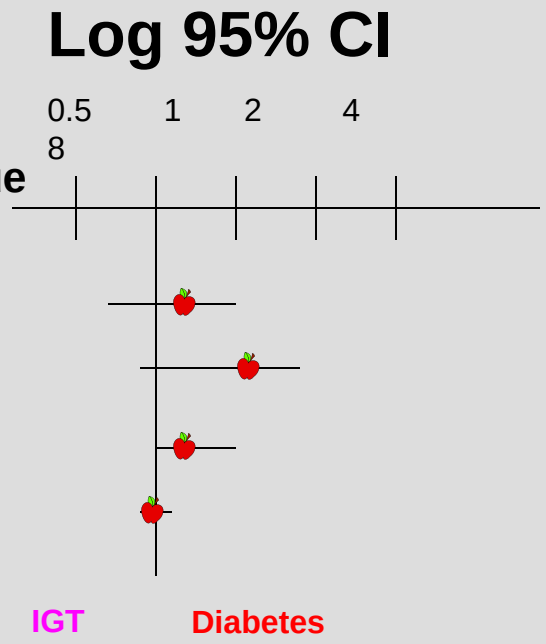
Cardiovascular Mortality in Impaired Glucose Tolerance vs Diabetics[3b]

Study	Ratio	p value
Bedford Mortality Study (1982)[1]		
Males	**1.31**	**ns**
Females	**2.12**	**ns**
Paris Prospective Study(1993)[2]	**1.43**	**ns**
Malmohus County Study(1997)[3]	**1.0**	**ns**



1. Odds Ratio
2. Relative Risk
3. Age-Sex Adjusted Relative Risk **(minus SFU Pts)**

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Congestive Heart Failure Predicts the Development of Non-Insulin-Dependent Diabetes Mellitus in the Elderly[3b,4]

The Osservatorio Geriatrico Regione Campania Group. Amato L, Paolisso G, Cacciatore F, Ferrara N, Ferrara P, Canonico S, Varricchio M, Rengo F *Diabetes Metab* [1997] **23**:213-8

Congestive heart failure (CHF) is an insulin-resistant state which constitutes the main risk factor for the development of non-insulin-dependent diabetes mellitus (NIDDM). Our study investigated the predictive role of CHF on the development of NIDDM in 1,339 elderly subjects with a mean (+/- SD) age of 74.2 +/- 6.4 years. CHF had a 9.5% prevalence, and 14.7% of the subjects had NIDDM. After stratification by age, subjects between 80 and 84 years had the highest prevalence of CHF and a total of 29.6% of CHF patients had NIDDM. In multiple logistic regression analysis, CHF was associated with NIDDM [odds ration (OR) = 2.0, 95% confidence interval (CI) - 1.6-2.5] independent of age, sex, family history of diabetes, body mass index, (BMI), waist/hip ratio, and diastolic blood pressure. When only untreated CHF patients were taken into account, the association between CHF and NIDDM was even stronger (OR = 4.0, 95% CI = 3.4-5.8). When untreated CHF patients were grouped into those with low (I and II) and high (III and IV) New York Heart Association (NYHA) classes, the association of CHF and NIDDM was stronger with the worsening of CHF. In a longitudinal study, CHF predicted NIDDM independently of age, sex, family history of diabetes, BMI, waist/hip ratio, systolic and diastolic blood pressure, and therapy for CHF (OR = 1.4, 95% CI = 1.1-1.8). CHF was associated with a higher prevalence of NIDDM and was a risk factor for its development. Elevated FFA concentrations may play a pivotal role.

4) If so, can the *new onset* of diabetes be shown to associate with increased cardiovascular mortality?

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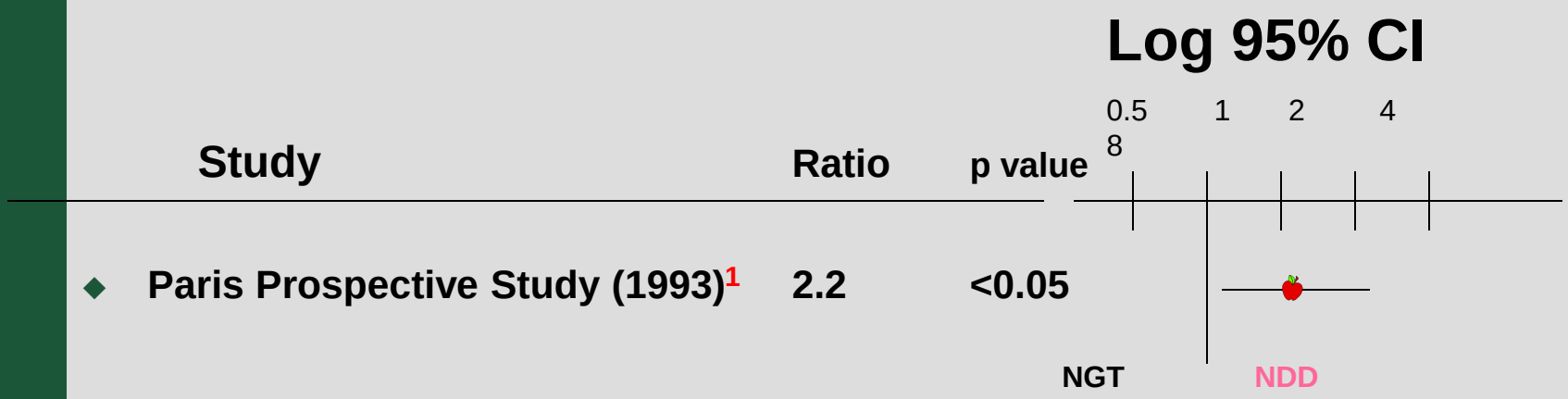
Cardiovascular Mortality in Normal Glucose Tolerance vs "***Newly Diagnosed***" Diabetics[4]



1. Relative Risk

Why was the Paris Prospective Study only able to show statistically significant increased cardiovascular mortality in "***newly diagnosed***" diabetics?

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5) If so, can interventions which exacerbate cardiovascular mortality be shown to negatively impact upon glycemic control or incidence of type 2 diabetes?

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THE SUNDAY TIMES

- May 27 2001 IRELAND

- **Smokers at risk from diabetes** - *Jan Battles*
  - **SMOKERS are almost twice as likely to develop diabetes as nonsmokers, a team of Irish and British scientists has found.**

Of 7,128 men studied, 290 were found to have developed "type 2" or adult-onset diabetes during subsequent assessments. "People who smoked were almost twice as likely to develop diabetes during the follow up," said Ivan Perry, who compiled the research at UCC.

Perry, professor of public health at University College Cork, said the research "provides significant, substantial evidence from a major population-based study for a causal link" between smoking and diabetes. [95% CI Odds Ratio (1.58 to 2.54.) Findings presented in Japan early June of 2001.]

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6) If so, can interventions which improve cardiovascular mortality be shown to positively impact upon glycemic control or incidence of type 2 diabetes?

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- Pravastatin and the Development of Diabetes Mellitus
  - Evidence for a Protective Treatment Effect in the West of Scotland Coronary Prevention Study (***Circulation.*** **2001;103:357.)**

"We concluded that the assignment to pravastatin therapy resulted in a <u>30% reduction (P=0.042) in the hazard of becoming diabetic</u>." [95% CI of 0.695 point estimate of odds ratio (0.494 to 0.978)]

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THE LANCET

Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy

(Lancet, Volume 355, Number 9200 22 January 2000)

"Compared with baseline, mean absolute HbA$_{1c}$ values increased by absolute amounts of 1·5% higher than the upper limit of normal in the ramipril group and 3·4% in the placebo group at 1 year (p=0·04). They fell by 0·1% among participants taking ramipril and rose by 2·2% among participants taking placebo at 2 years (p=0·016)…." 95%CI of CFB MTD @ 2yrs (-0.53 to -4.07%)

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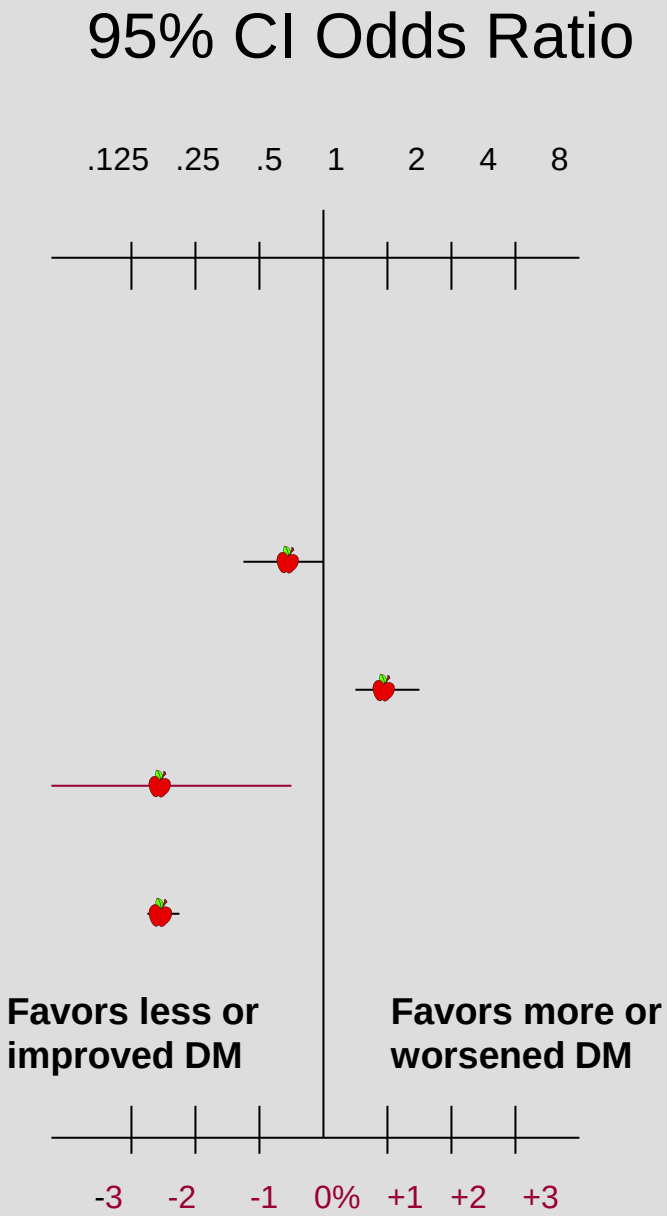
Effects of Atherogenic Interventions on Incidence or Control of Diabetes[5,6]

drug	cv death*	OR/A1c Δ
pravastatin	↓	0.695
smoking	↑	1.96
ramipril	↓	-2.3%
Estrogen*	↓	-2.4%

*Change Carotid Artery Intimal Medial Thickness



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What characterizes Type 2 Diabetes?

(*pathophysiologically*?...)

- 80% Diabetics are Obese with increased leptin levels
  - IL-6 is a cytokine involved in atherogenesis
  - Leptin is defect in ob/ob & db/db mouse obesity models
- Adipocyte [mass]=>Adipocyte [IL-6]
  - **Adipocyte [IL-6]=> Adipocyte[Leptin]**
  - – Increases with weight gain (=> menarche)
  - – Decreases with weight loss (=> amenorrhea)
- Leptin
  - Increases hepatic insulin resistance
  - Decreases pancreatic insulin output
  - Associates with hypertension
  - Clinical trials -> several cases of diabetes
- Is Type 2 Diabetes an *escape* from morbid obesity?

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Other characteristics of Type 2 Diabetes

What Else is Type 2 Diabetes?

A ***VASCULAR*** disease?

A ***hypertensive*** disorder?

A disorder of elevated ***LDL-cholesterol***?

A disorder of ***insulin resistance*** (IRS)?

A ***post-prandial lipid*** disporder?

A disease caused by hyper***pro*** insulinemia?

An ***inflammatory cytokine*** disorder?

An ***obesity*** disorder involving visceral fat?

Any/All of the above?

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Blood Pressure Control?

Should We Intensively Control *Blood Pressure* in Type 2 Diabetes?

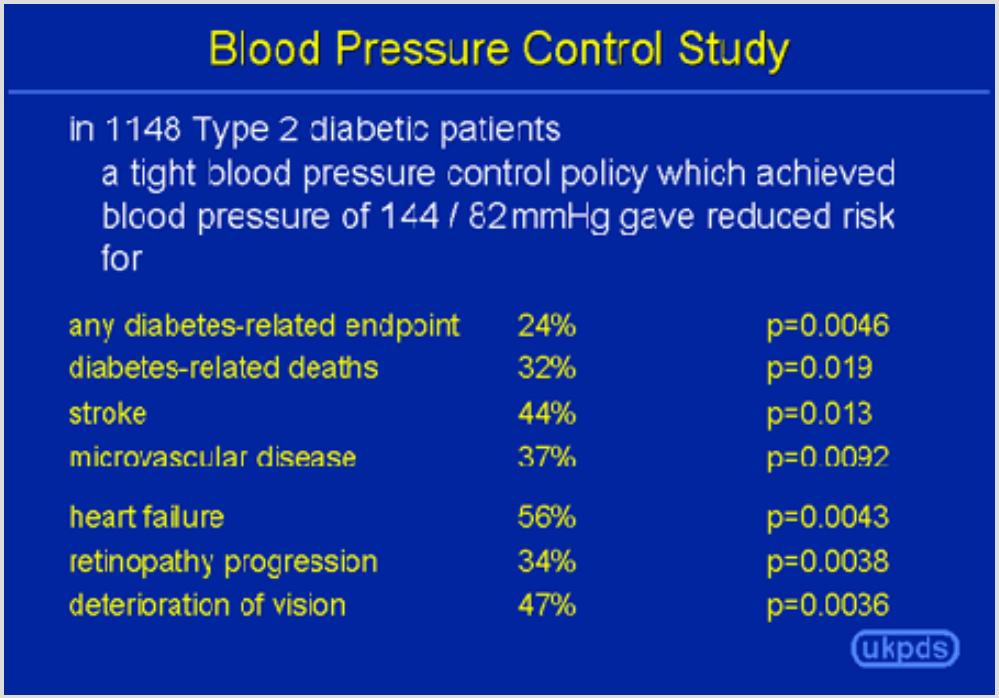
To prevent microvascular complications?

YES (beta-blockers and ACE in UKPDS study)

To prevent *macrovascular* complications?

YES (beta-blockers and ACE in UKPDS study)

YES (ramipril in HOPE Study)



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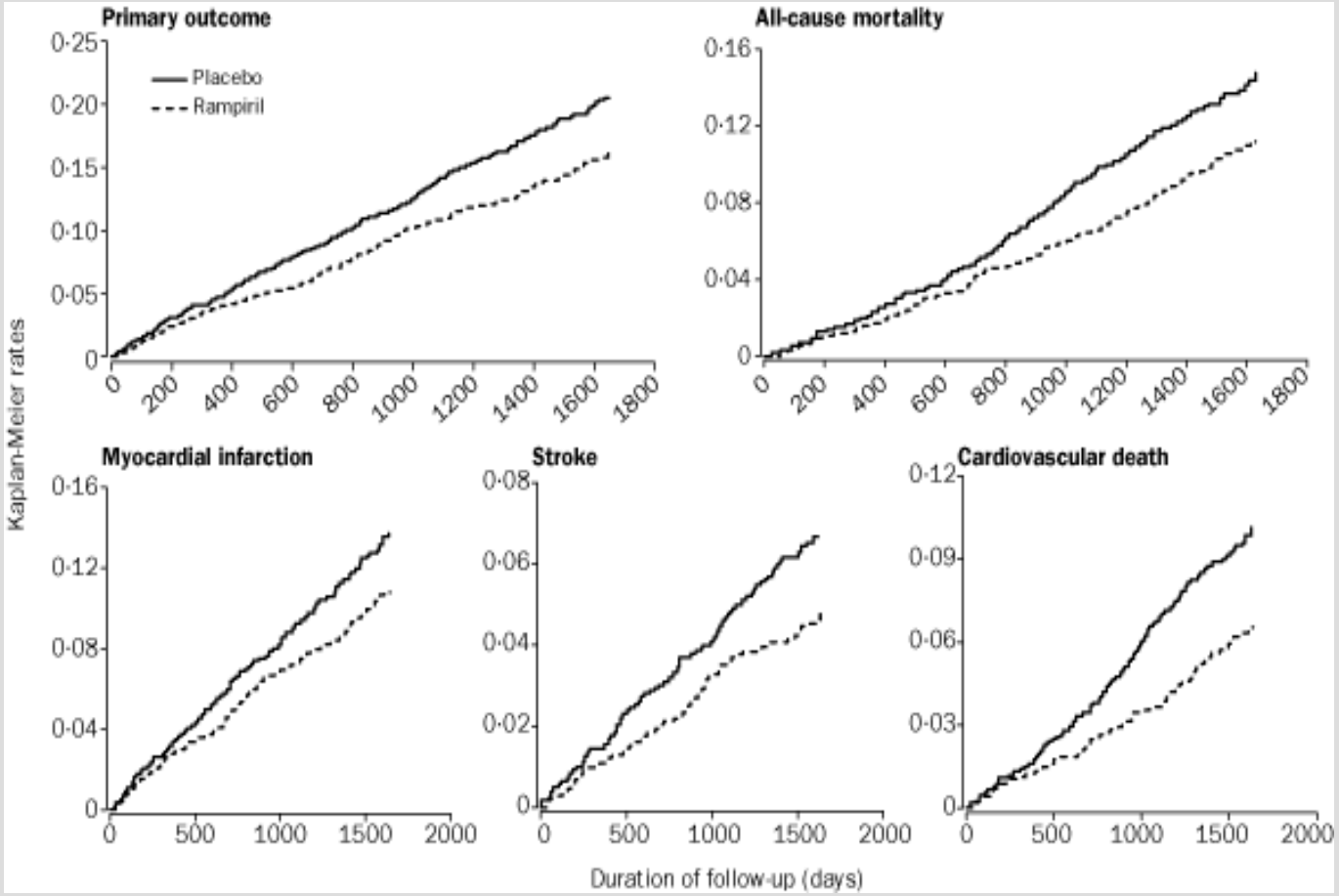
The Hope Trial



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Should We Intensively Control *LDL-cholesterol* in Type 2 Diabetes?

To prevent microvascular complications?

YES

To prevent ***macrovascular*** complications?

YES (simvastatin and pravachol in 4S/WeStCOPS)

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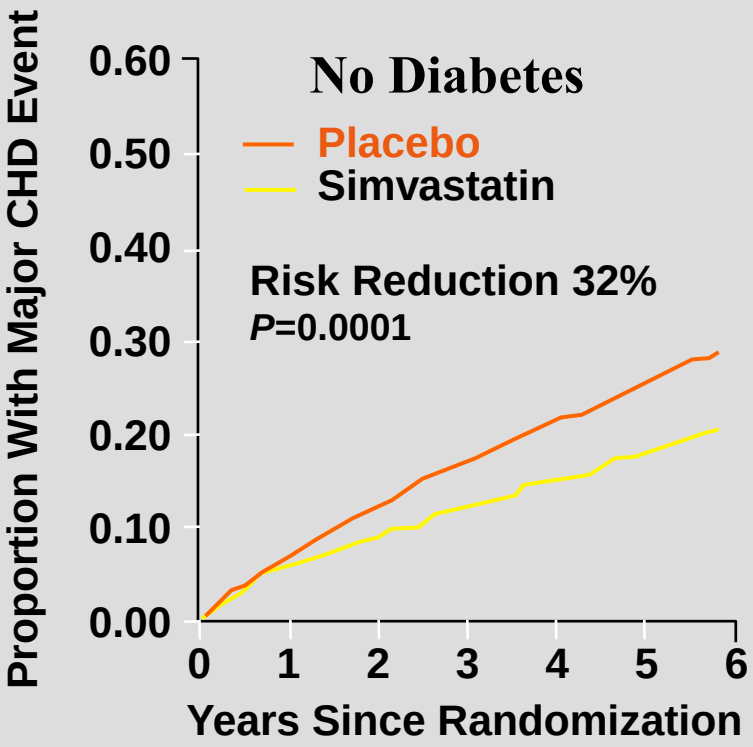
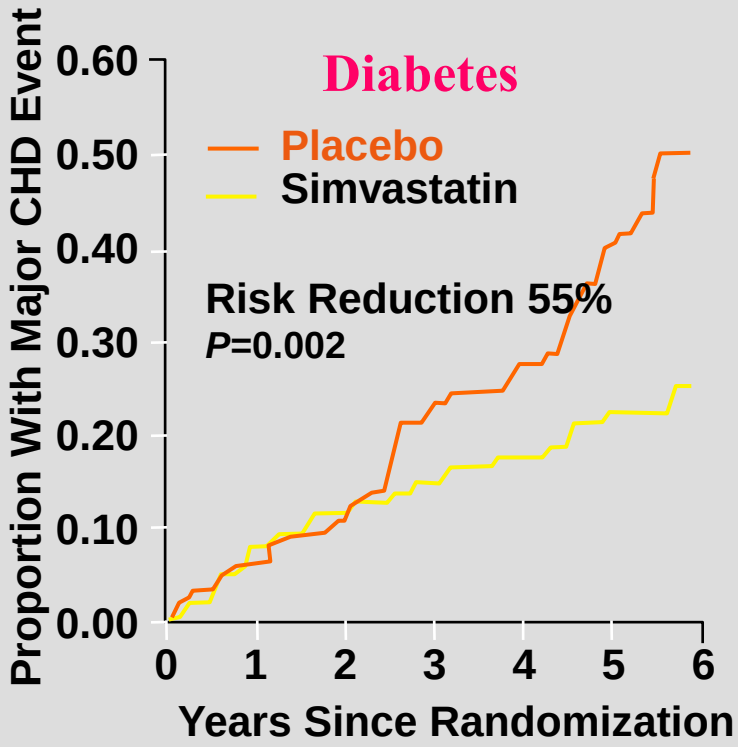
SCANDINAVIAN SIMVASTATIN SURVIVAL STUDY (4S)

Diabetes Subgroup Analysis

Reduction of Major Recurrent CV Events





Pyorala K et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. *Diabetes Care* 1997;20:614-20.

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SSSS Data in Diabetes

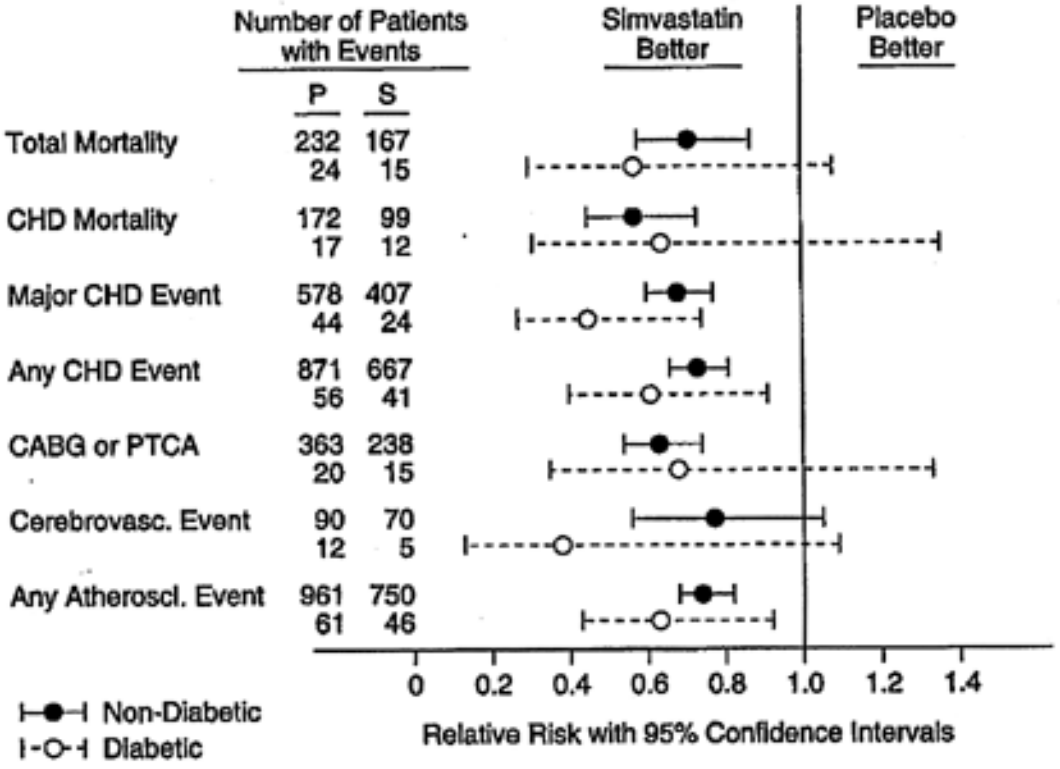

Figure 1—*Reduction in the risk of different endpoints expressed as RR (simvastatin [S] group vs. placebo [P] group) with 95% CIs in nondiabetic and diabetic patients.*

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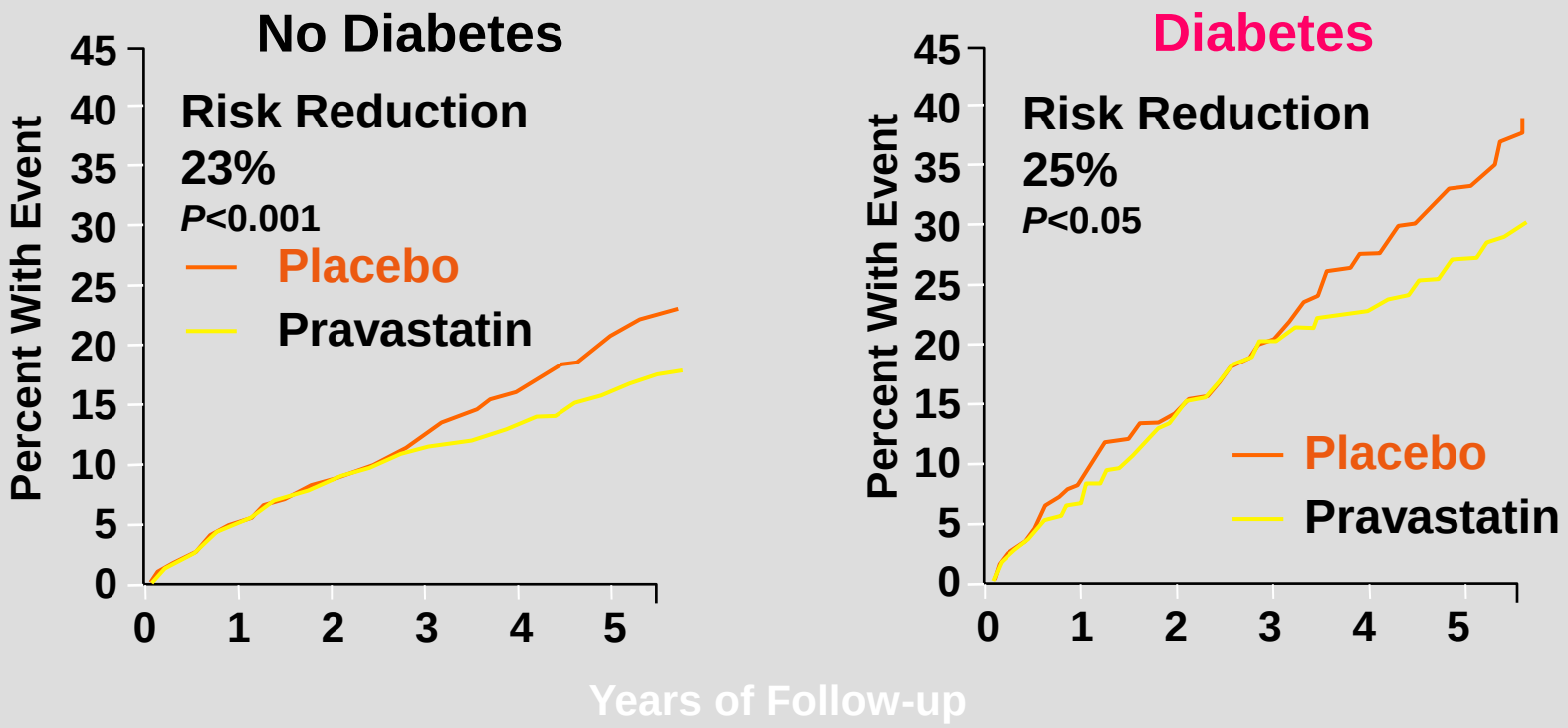
CARE TRIAL

Diabetes Subgroup Analysis

Reduction of Recurrent CV Events



Goldberg RB et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels. Subgroup analysis in the Cholesterol And Recurrent Events (CARE) Trial. *Circulation* 1998;98:2513-19.

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Other interventional areas?

What else should we attempt to control in type 2 diabetes?

- Hypercoagulability?
  - Yes in Macrovascular disease (IIb/IIIa, ASA)
- Triglyceridemia?
- HDL-cholesterol??
- Pro-insulin?
- Insulin resistance?
- Inflammatory cytokines?
- Post-prandial lipid metabolism (Apo-c-i)?
- Weight?
- Weight distribution?

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CV Risk-Reduction With Antiplatelet Therapy

High-Risk Patients
Diabetes Subgroup Meta-analysis

	No Diabetes	Diabetes
n	21,197	21,136
Vascular events Control	16.4%	22.3%
Antiplatelet Rx (usually ASA)	12.8%	18.5%
Risk Reduction	28%	21%

Antiplatelet Trialists Collaboration. Collaborative overview of randomized trials of antiplatelet therapy I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patient. BMJ 1994;308:71-2.

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Syndrome X/IRS

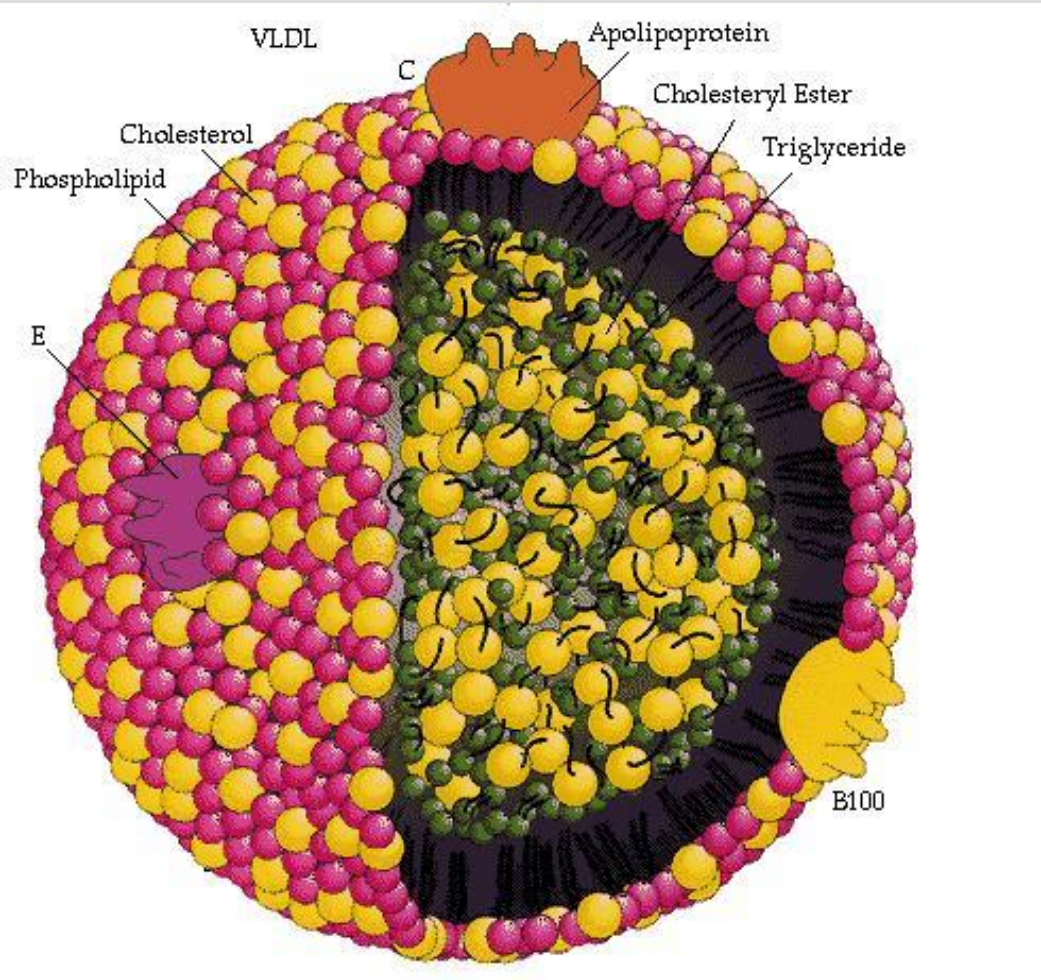
Syndrome X (a *post-prandial* disorder)

Impaired glucose tolerance, hypertension, hyperinsulinemia, hypoHDLemia, diabetes, hypertriglyceridemia, obesity, hyperuricemia, impaired fibrinolysis

Does hyperinsulinemia cause CHD?

- PIMA indians are the prime example of Syndrome X in this country, and yet the incidence of coronary disease is no greater in the PIMA than that of the general (***non-diabetic***) population at large

VLDL Particle



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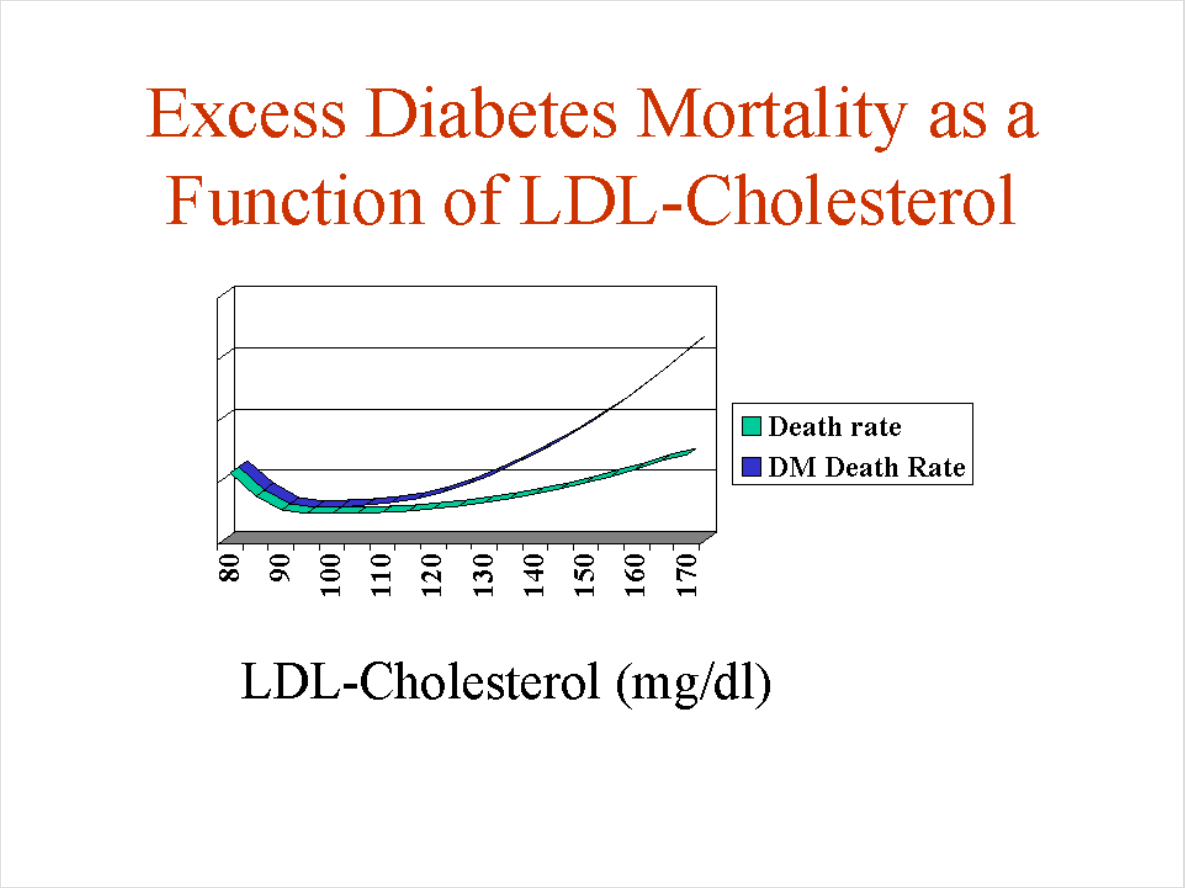
Excess Mortality =f(LDL-cholesterol)



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Atherogenic Components of IRS

What are the atherogenic components in Syndrome X?

INCREASED *LDL-Cholesterol* or Post-Prandial *apo-C-1 PLUS*

Impaired glucose tolerance

Post-prandial

– hyper***pro***insulinemia (Hamsten/Haffner)
– hyper***triglyceride***mia (Hamsten/Reaven)
– hypo***HDL***emia

Hypertension

Impaired fibrinolysis

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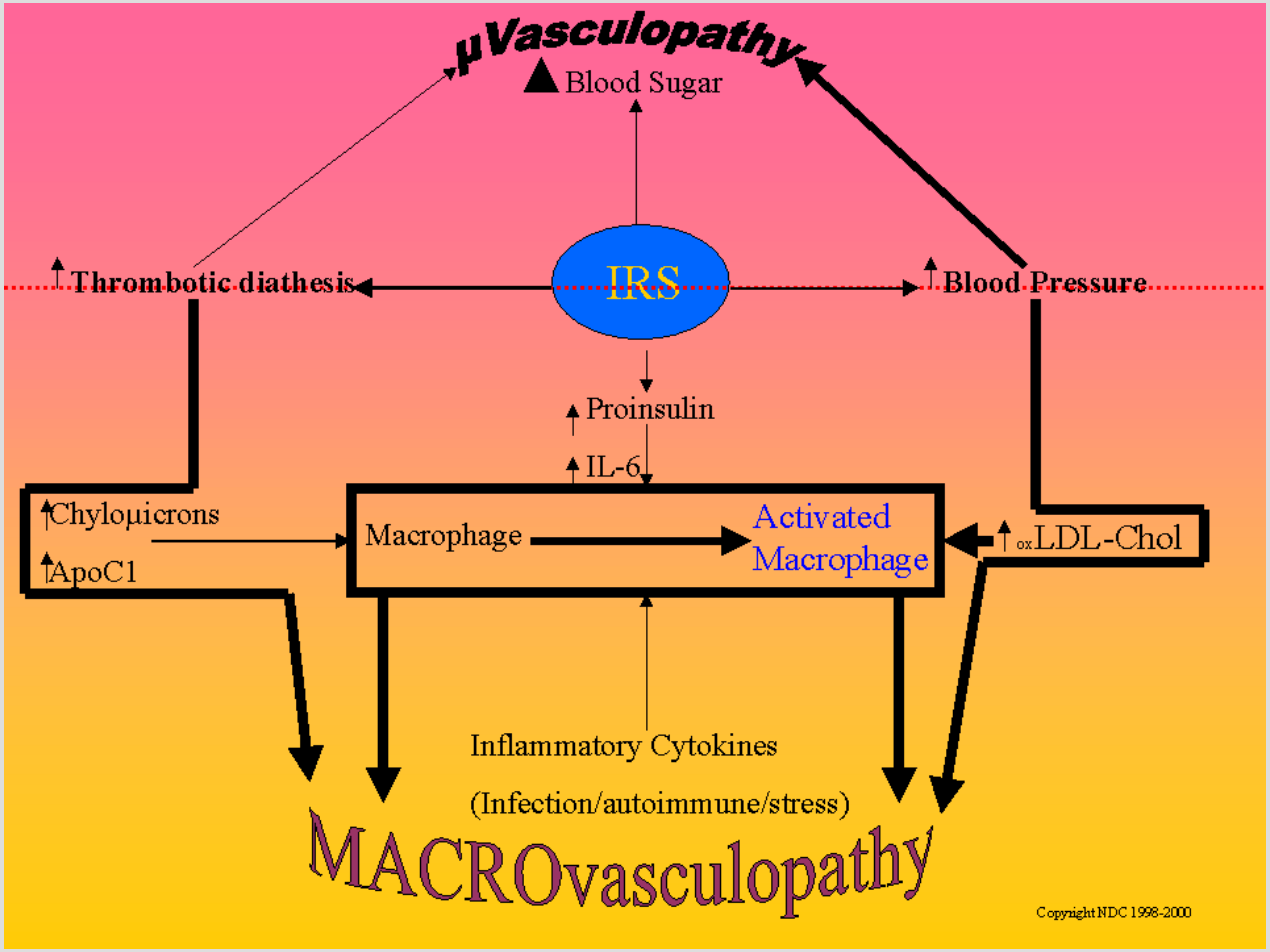
The Grand Unified Theory of Diabetic Complications



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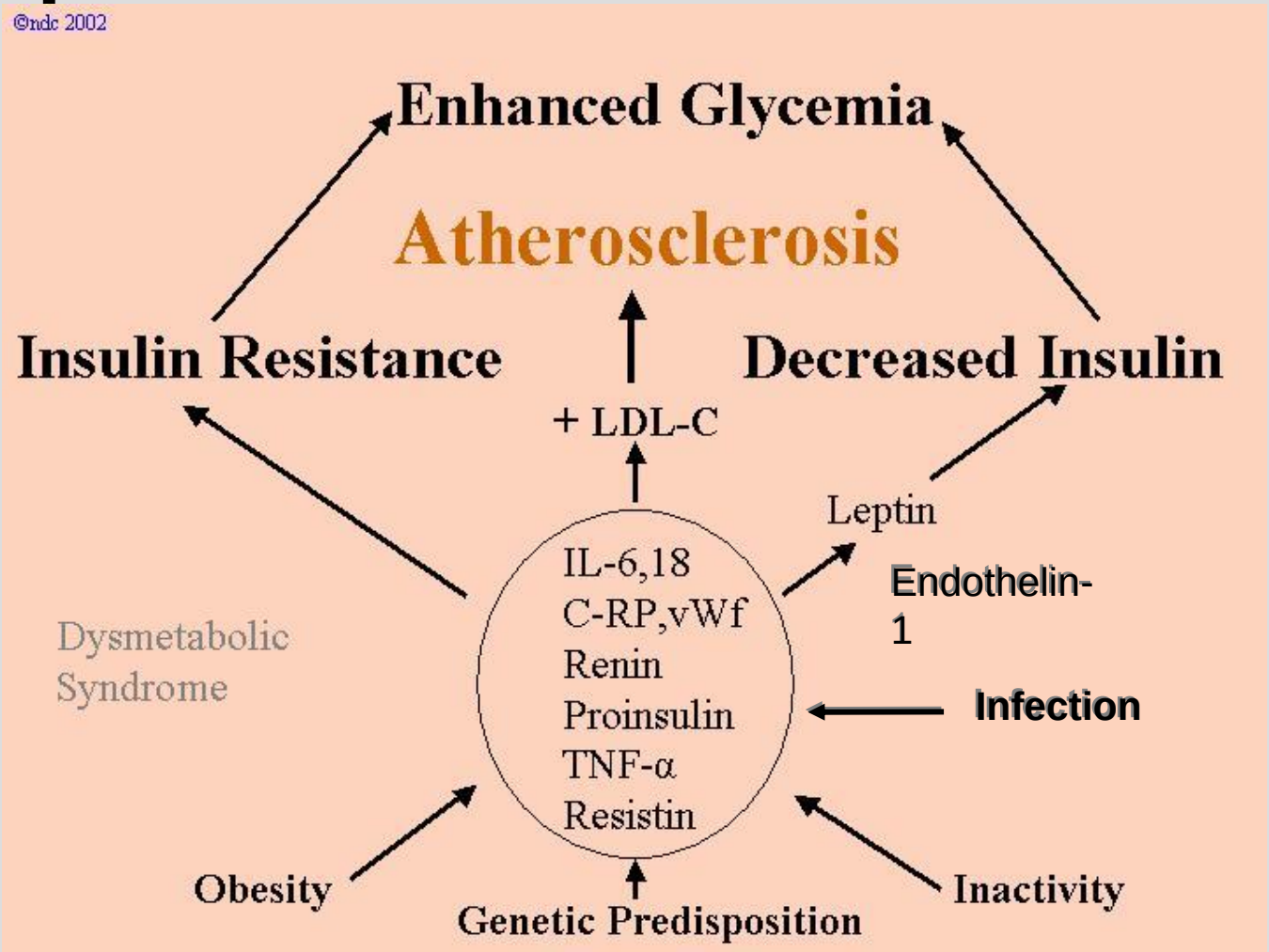
The Grand Unified Theory of Diabetic Complications



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SFU Warning

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (DIABETES, 19, SUPP. 2: 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glipizide and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

As with any other non-deformable material, caution should be used when administering GLUCOTROL XL Extended Release Tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug in this non-deformable sustained release formulation.

PRECAUTIONS

General

Renal and Hepatic Disease: The pharmacokinetics and/or pharmacodynamics of glipizide may be affected in patients with impaired renal or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

GI Disease: Markedly reduced GI retention times of the GLUCOTROL XL Extended Release Tablets may influence the pharmacokinetic profile and hence the clinical efficacy of the drug.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may affect

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k-ATP Channels

ATP sensitive K^+-channels

Metabolically sensitive

Increased glucose => increased ATP => K+-channel closure => insulin release (*SUR-1* beta- cell)

Decreased O_2 =>decreased ATP => K+-channel opening => vasodilation (*SUR-2* heart)

The major compensatory vasodilatory response to ischemia in the myocardium

Mitochondrial k-ATP channels modulate **infarct-size reduction** and represent the **final common pathway of NO expression**

Prototypal effect ***CLOSURE by SFU's***

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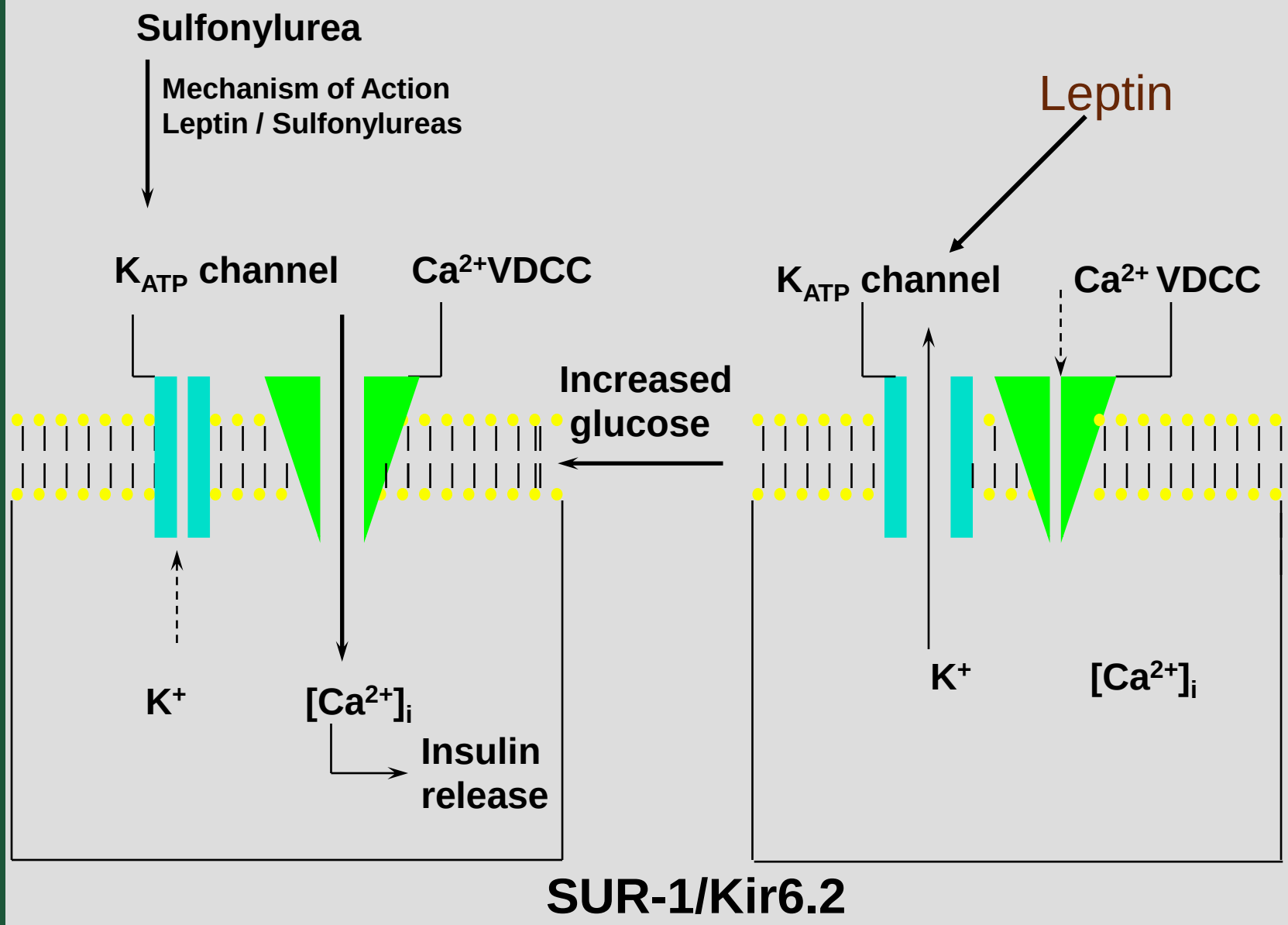
Sulfonylurea
Mechanism of Action
Leptin / Sulfonylureas
Leptin
K_{ATP} channel
Ca^{2+}VDCC
K_{ATP} channel
Ca^{2+} VDCC
Increased glucose
K^+
$[Ca^{2+}]_i$
Insulin release
K^+
$[Ca^{2+}]_i$
SUR-1/Kir6.2

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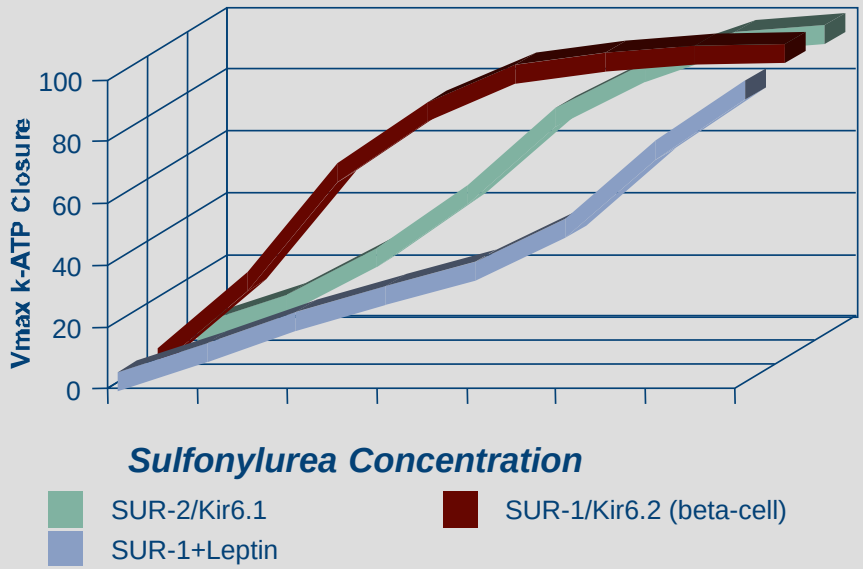
Affinity Plots for k-ATP Channels

Affinity Plots for Sulfonylurea Receptors vs [SFU]



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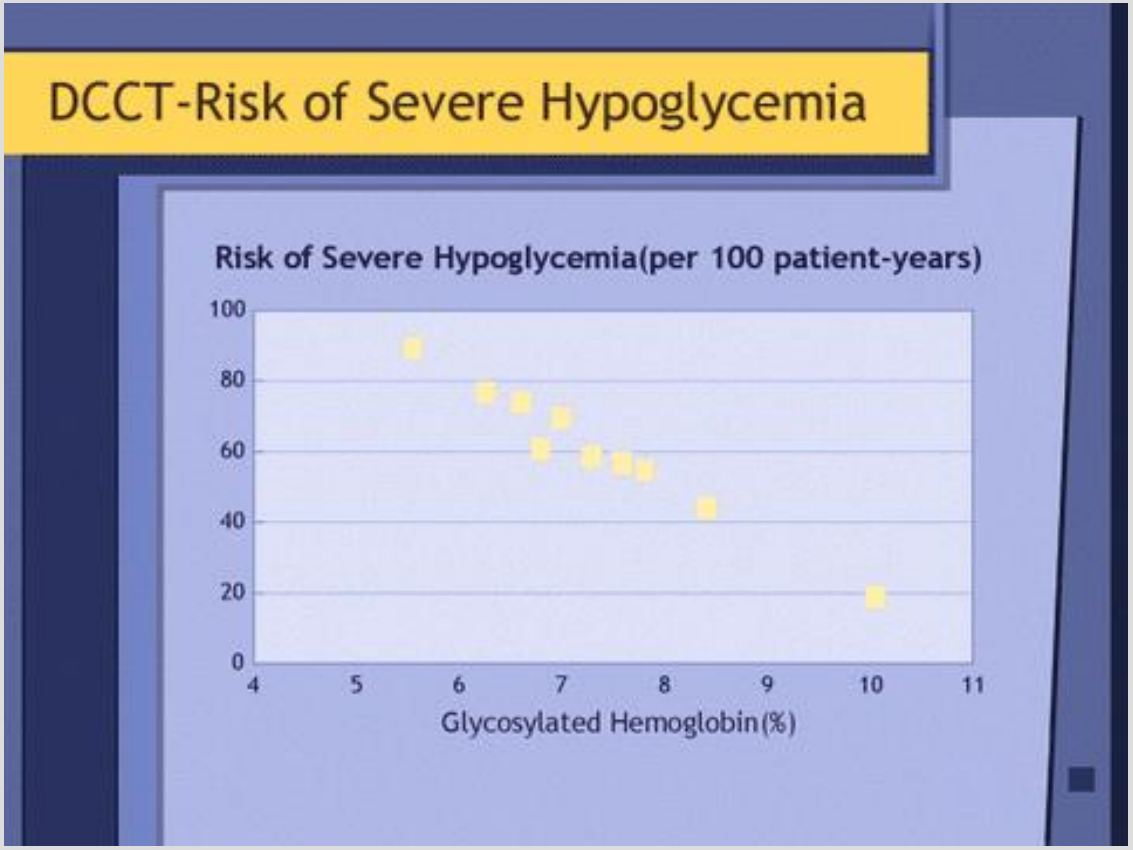
Hypoglycemia and Tight Control



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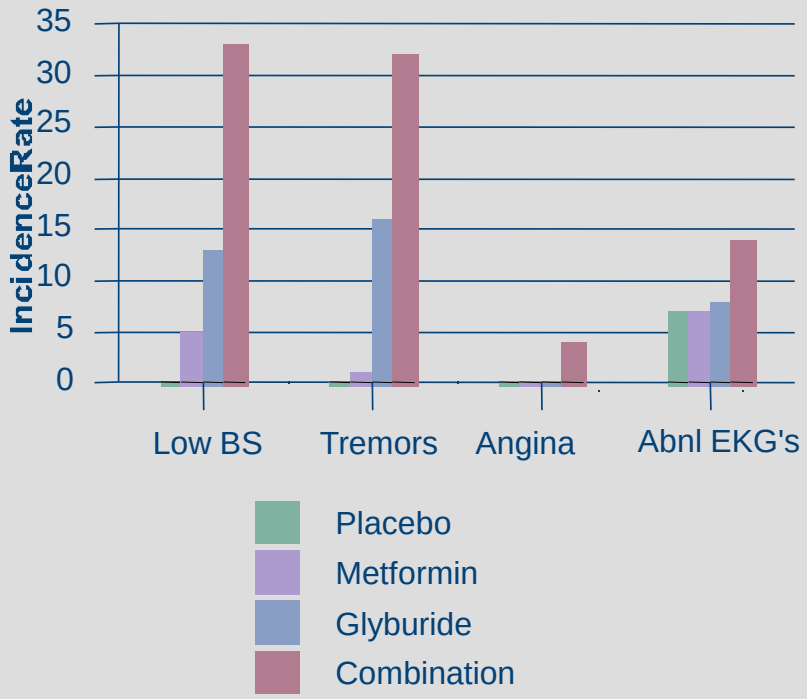
SFU+Metformin Toxicity in US Pivotal Trials



Placebo	0	0	0	7
Metformin	5	1	0	7
Glyburide	13	16	0	8
Combinati	33	32	4	14

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Deaths with SFU+Metformin Rx

Sulphonylurea plus Metformin

- patients primarily randomised to intensive therapy with sulphonylurea were not given additional metformin until their fpg was >15 mmol/L or they developed hyperglycaemic symptoms
- in view of the progressive hyperglycaemia in these patients, a protocol modification was made to secondarily randomise the subset of patients who were on maximum sulphonylurea therapy and had fpg >6 mmol/L to earlier addition of metformin

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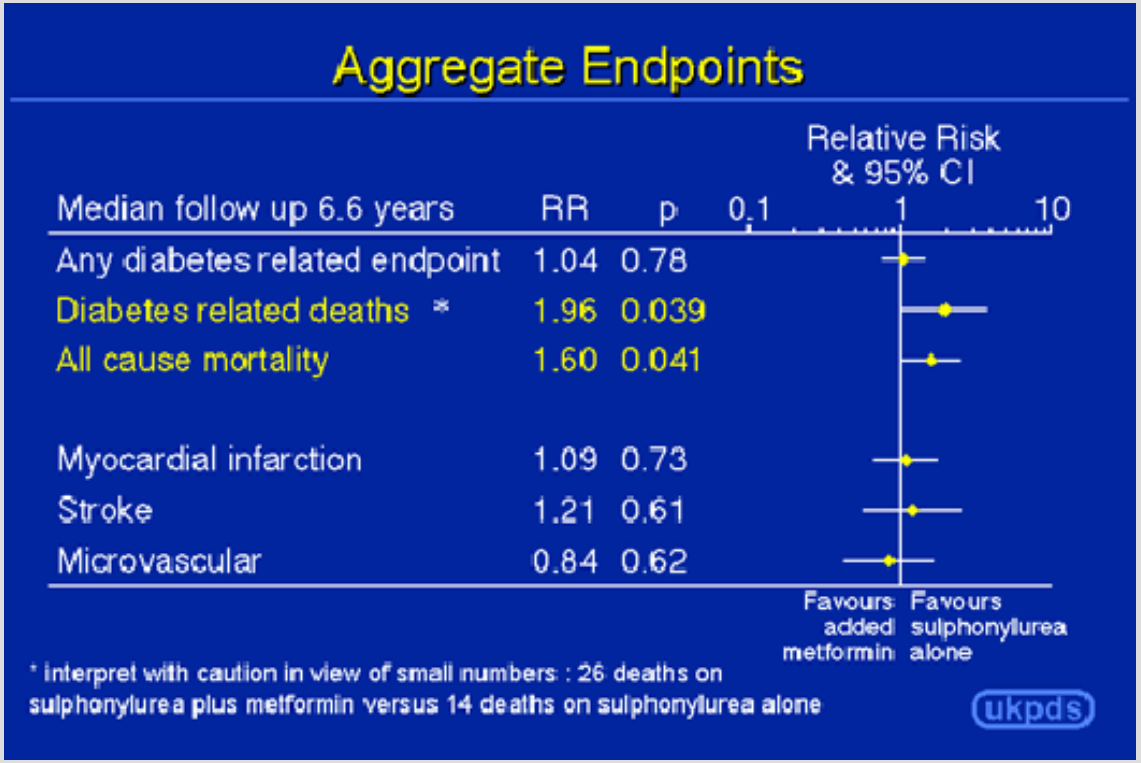
SFU+Metformin in UKPDS

UKPDS Mortality Slide *(SFU+metformin)*



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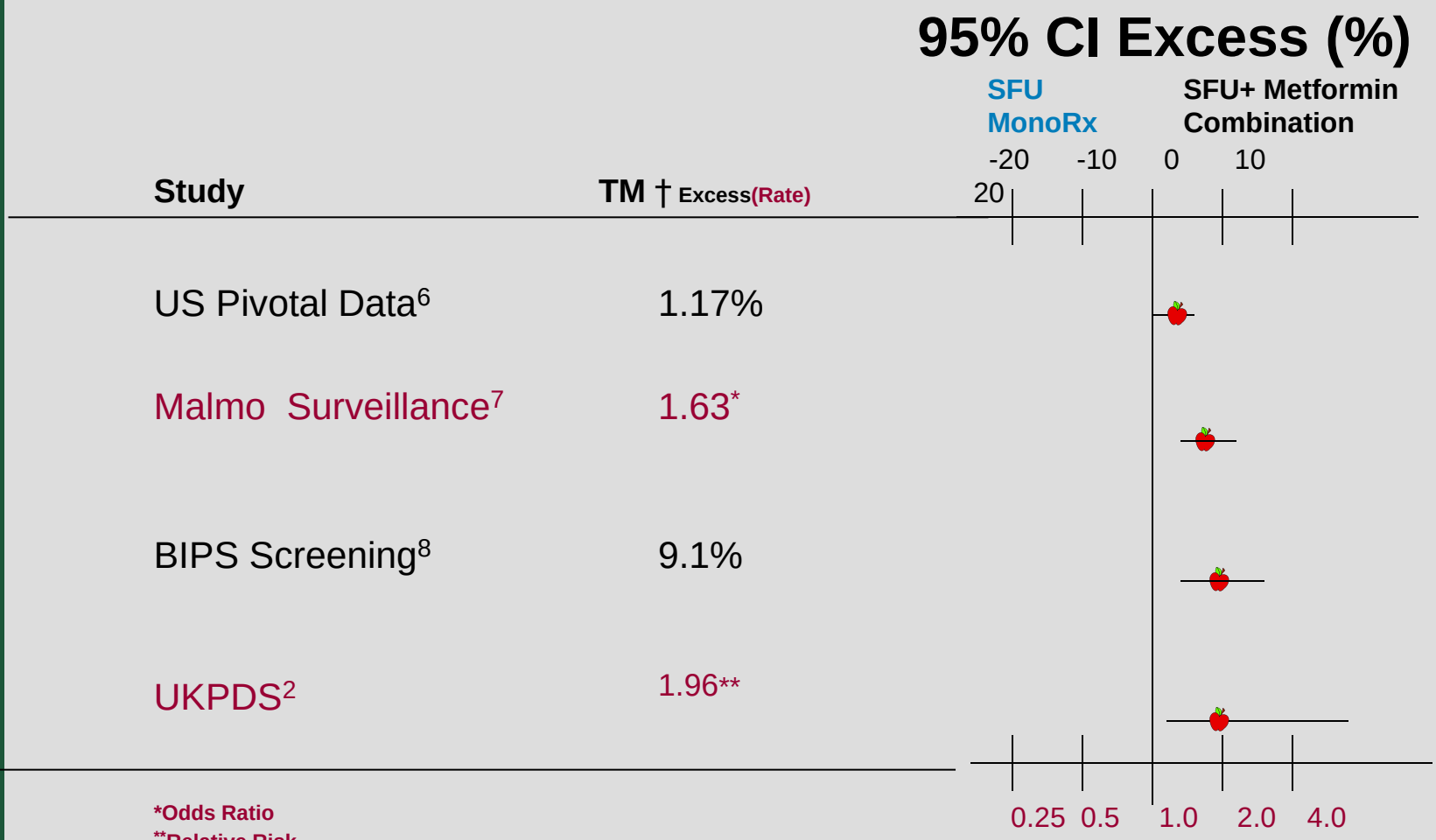
Total Mortality of Metformin-SFU Combination vs SFU Alone *Across* Different Studies



*Odds Ratio
**Relative Risk

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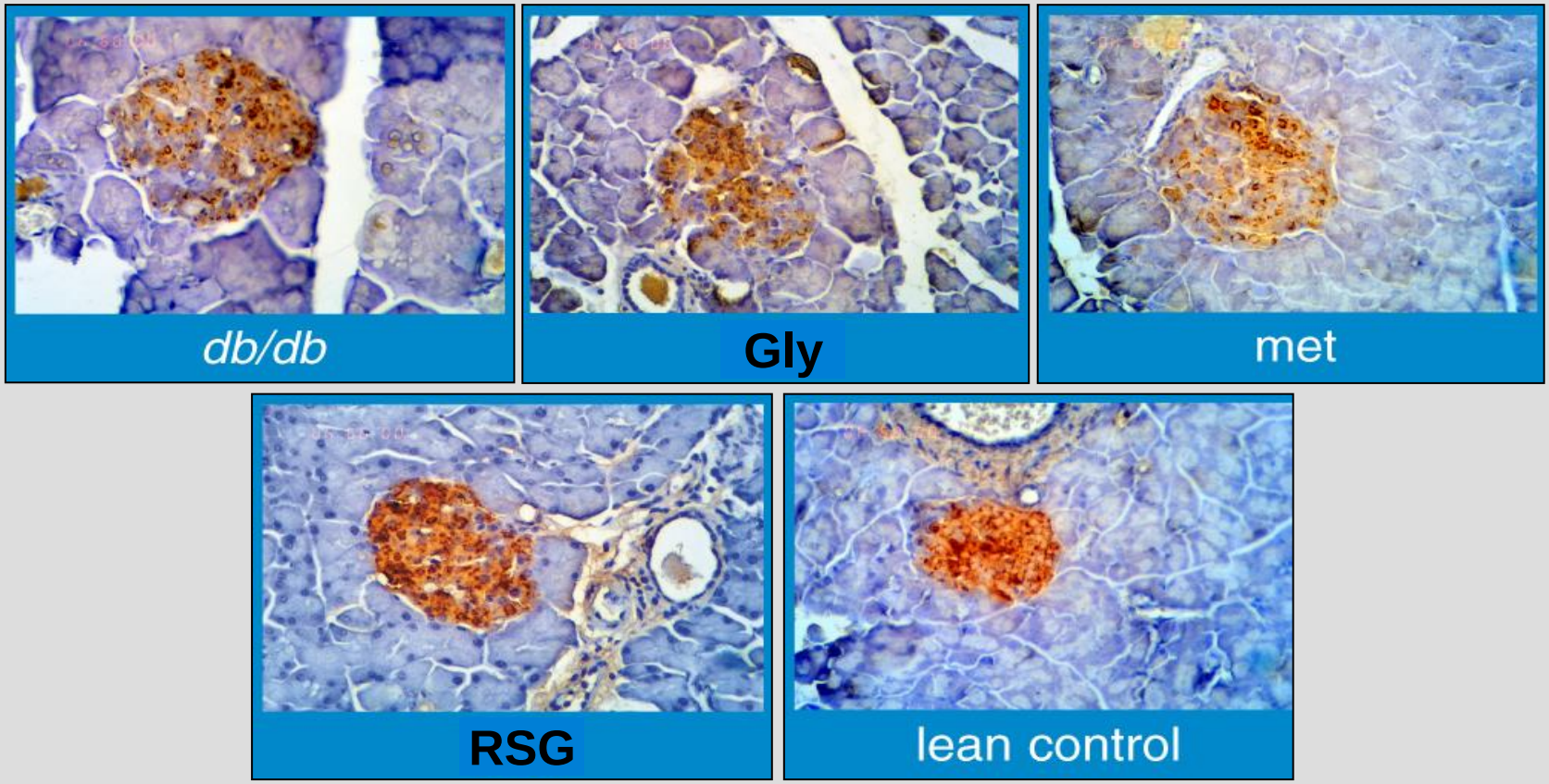
Rosiglitazone Increases Islet Insulin in *db/db* Mice



Clinical significance of the preclinical findings is unknown. 28 days treatment with RSG 1.42 mg/kg, MET 100 mg/kg, GLIB 49.4 mg/kg.Mice treated for 28 days beginning @ ~6–7 weeks of age.Lister CA et al. *Diabetologia* 1999;42(suppl 1):A150 (abstr 556). Lister et al. 35th Annual EASD, Brussels, Belgium, September 28, 1999, poster.

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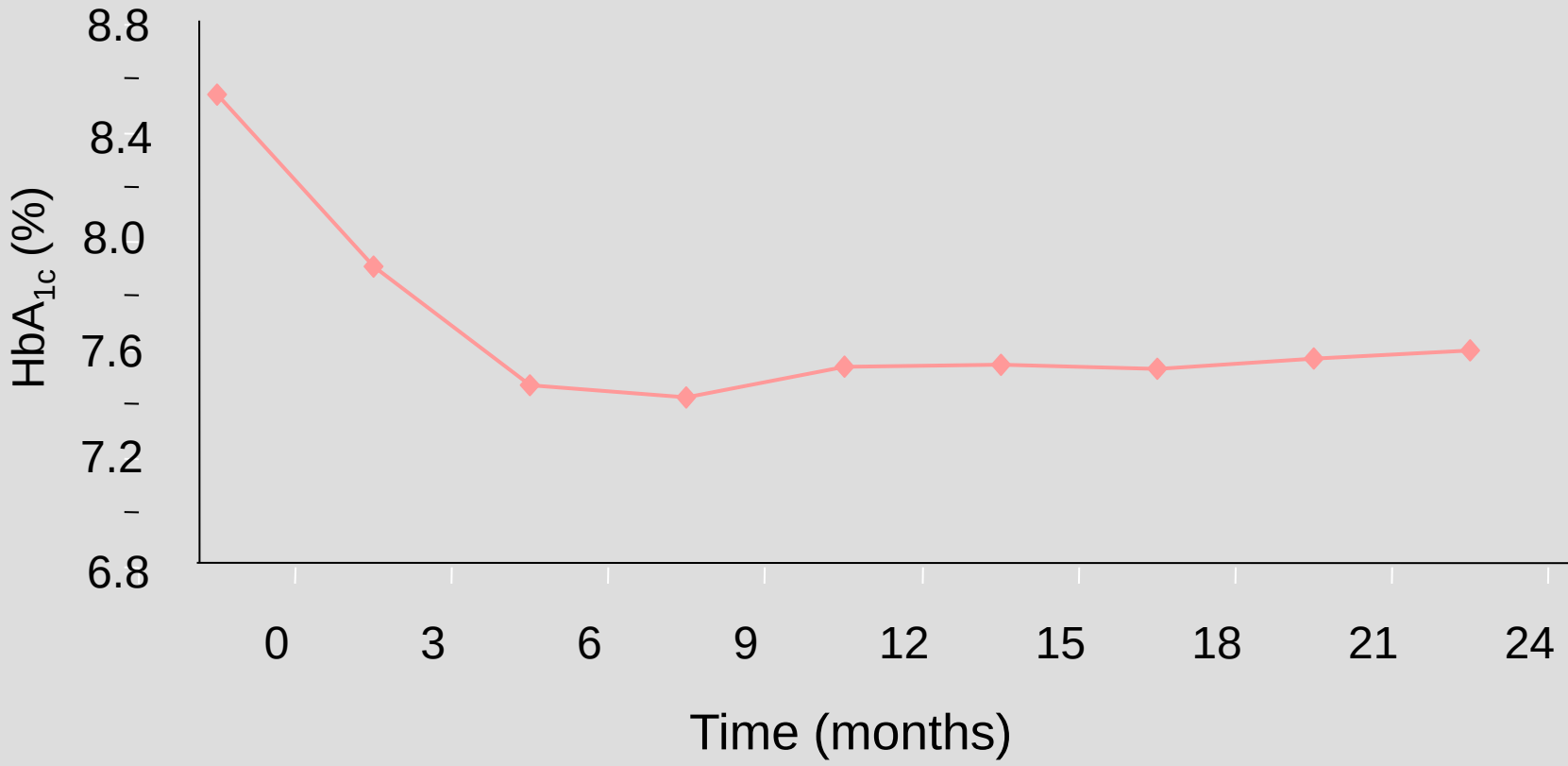
Long-term Rosiglitazone Monotherapy (HbA_{1c})

Rosiglitazone 8 mg/day (n=266)



Studies 011, 024, 084, 105. Data on file. GlaxoSmithKline.

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Strategies

Rx for Diabetes - Strategies

- Intensively treat hypertension (132/80)
- Minimize LDL-cholesterol (<100 mg/dl)
- Decrease postprandial proinsulinemia
- Decrease postprandial triglyceridemia
- Decrease SUR-2/mito k-ATP binding
- Increase fibrinolytic potential
- Decrease inflammation
- Maximize beta-cell survival
- Keep HbA1c < 8%

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