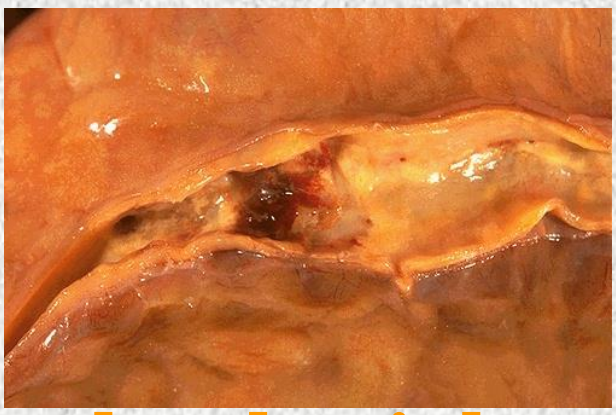
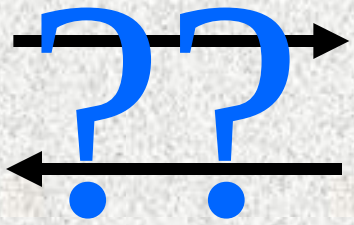
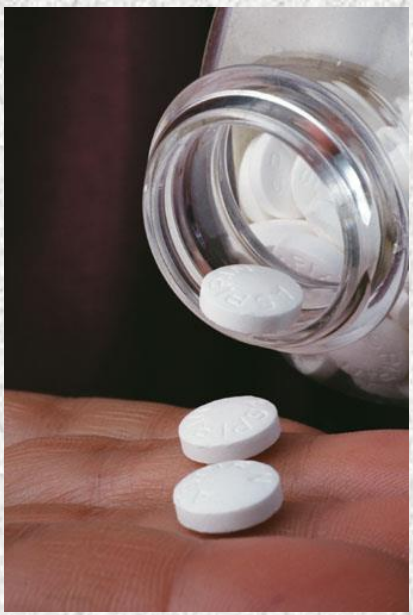


Whither the Arrow of Causality?

Pathophysiology of Cardiovascular Mortality



Poor Glycemic Control



Ron Innerfield, MD, FACE

Chief,
Epidemiology & Clinical Trials,
The National Diabetes Center

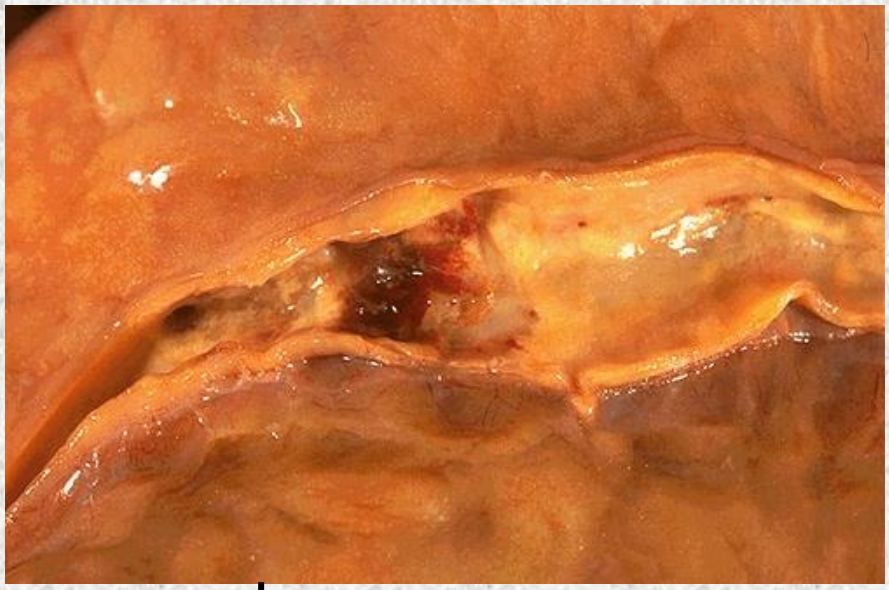
Medical Director,
Medical & Scientific Affairs,
pharmanet

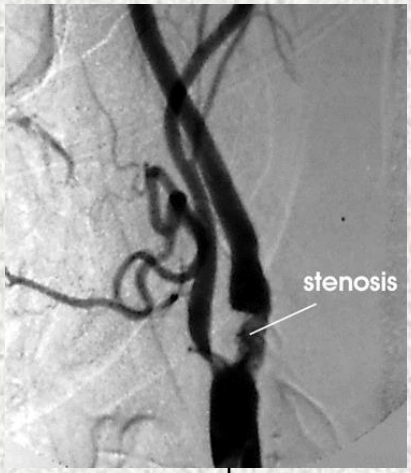
BACKGROUND:-

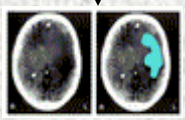
Type 2 diabetes mellitus and cardiovascular disease share common antecedents ("insulin resistance syndrome") which include vasoactive cytokines. Poor glycemic control in Type 2 diabetes associates very strongly with macrovascular mortality. Nevertheless, improving glycemia long-term does not reduce macrovascular mortality. (Only in the setting of acute MI does tight control of hyperglycemia with insulin appear to causally impact mortality.)

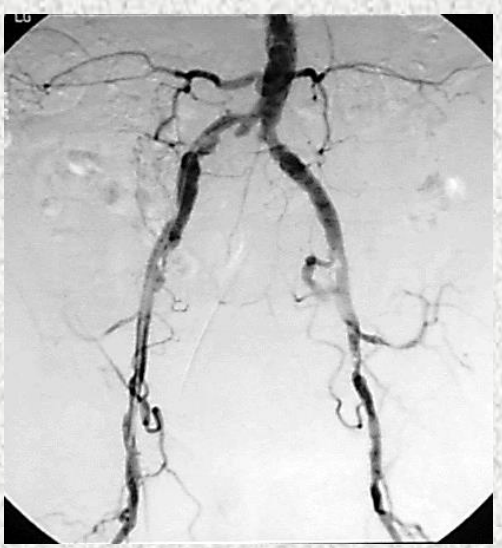
Impaired glucose tolerance - which is characterized by relative normoglycemia – associates by itself significantly with macrovascular disease which in turn associates strongly with increased levels of inflammatory vasoactive cytokines. Hyperglycemia - relentlessly progressive in type 2 diabetes - further associates quite powerfully with increased levels of inflammatory vasoactive cytokines.

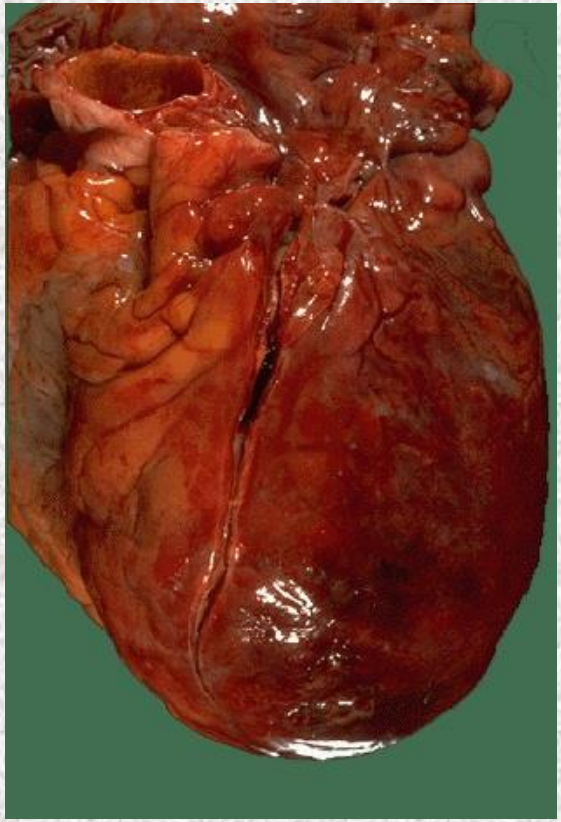
The Problem











METHODOLOGY:-

1) Are glycemic control and cardiovascular mortality strongly associated?

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

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

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

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

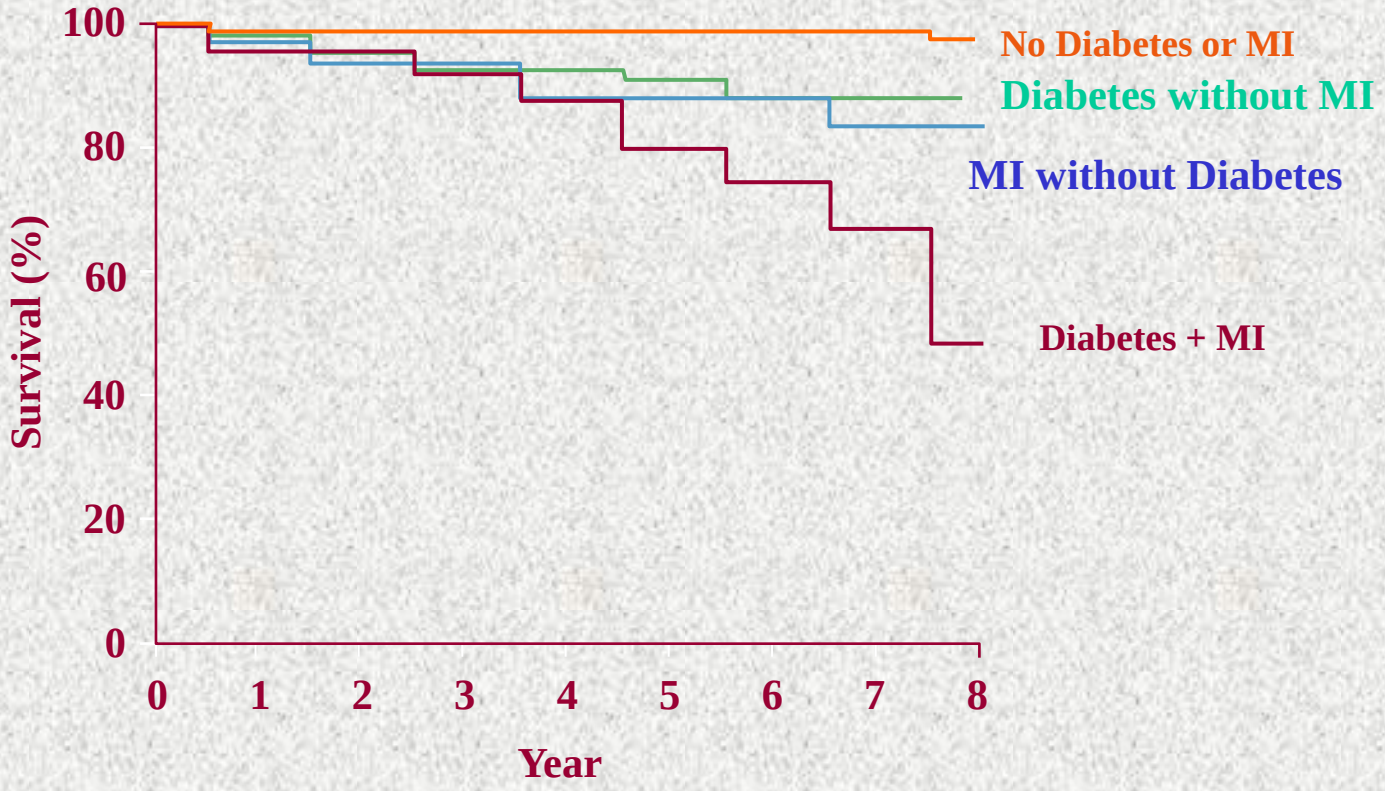
6) If so, can interventions which *reduce* cardiovascular or mortality be shown to *favorably impact* upon glycemic control or incidence of type 2 diabetes?

7) Can short-term control impact mortality? Under what circumstances?

1) Are glycemic control and cardiovascular mortality strongly associated?

Type 2 Diabetes is a CV Risk Factor

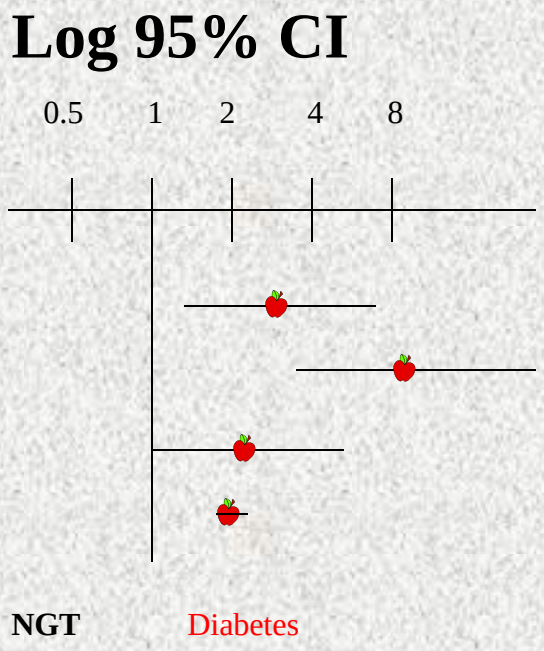
Diabetes and Prior MI Predict Mortality Equally



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.

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

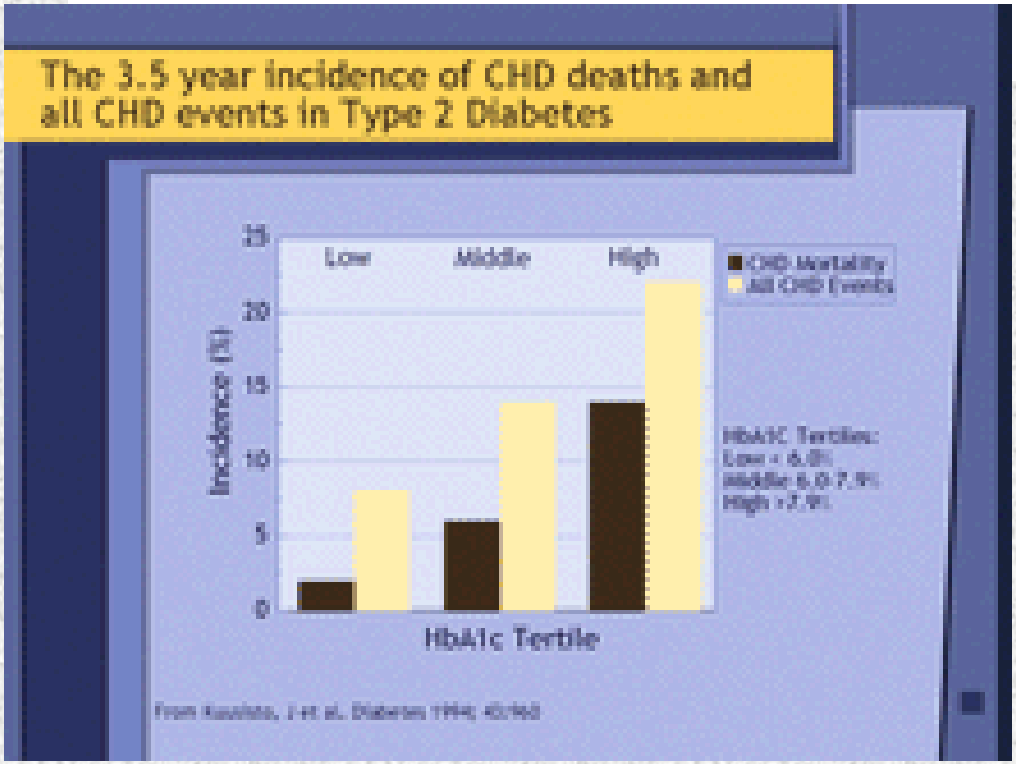
3. Age-Sex Adjusted Relative Risk

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

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

Just Published:- 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.

UMDS

Dr. Harry Keen (1968)[2]

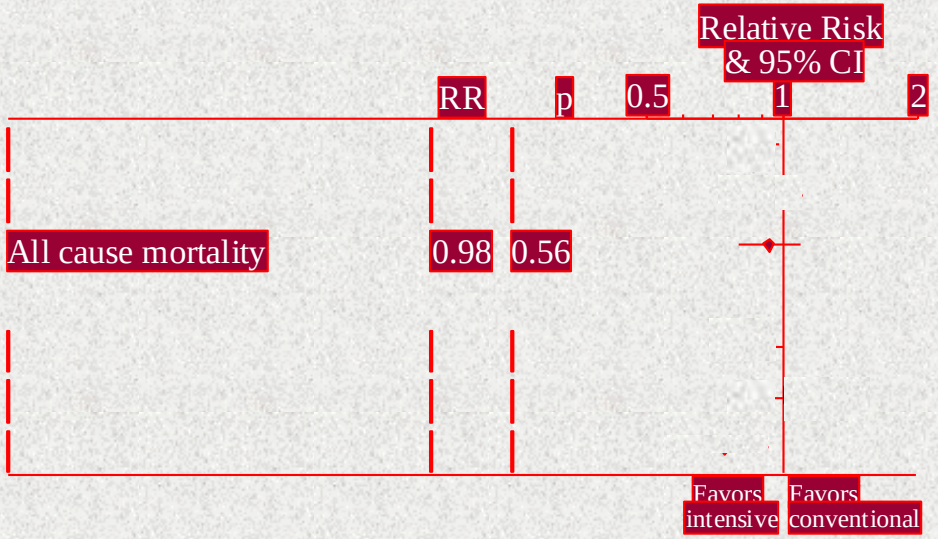
"It is, of course, possible to formulate three standard hypotheses to explain the relationship - that A causes B, that B causes A, or that both A and B are caused by C. We have chosen to examine what is perhaps the most likely and potentially the most useful of these explanations - that hyperglycemia 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)

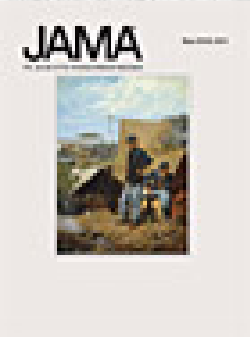
2) If the suspicion is that poor control causes excess cardiovascular mortality, can long-term control of diabetes be shown to reduce long-term cardiovascular mortality?

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

- A:- Nope
  - (UGDP-1971)

Aggregate Clinical Endpoints in the UGDP



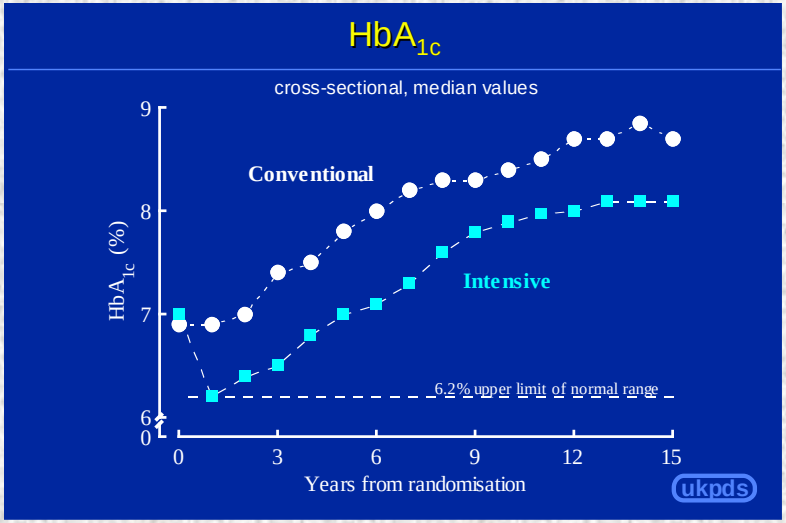


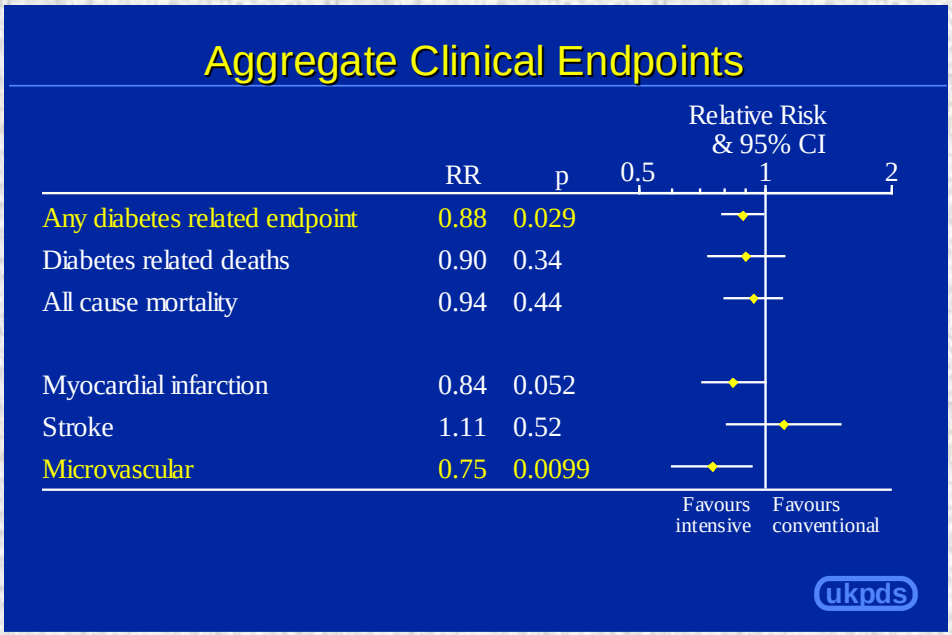
JAMA 1971 Nov;218(9):1400-10

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.

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

- A:- Nope
  - (UKPDS-1999)





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?

Cytokines….[3a]

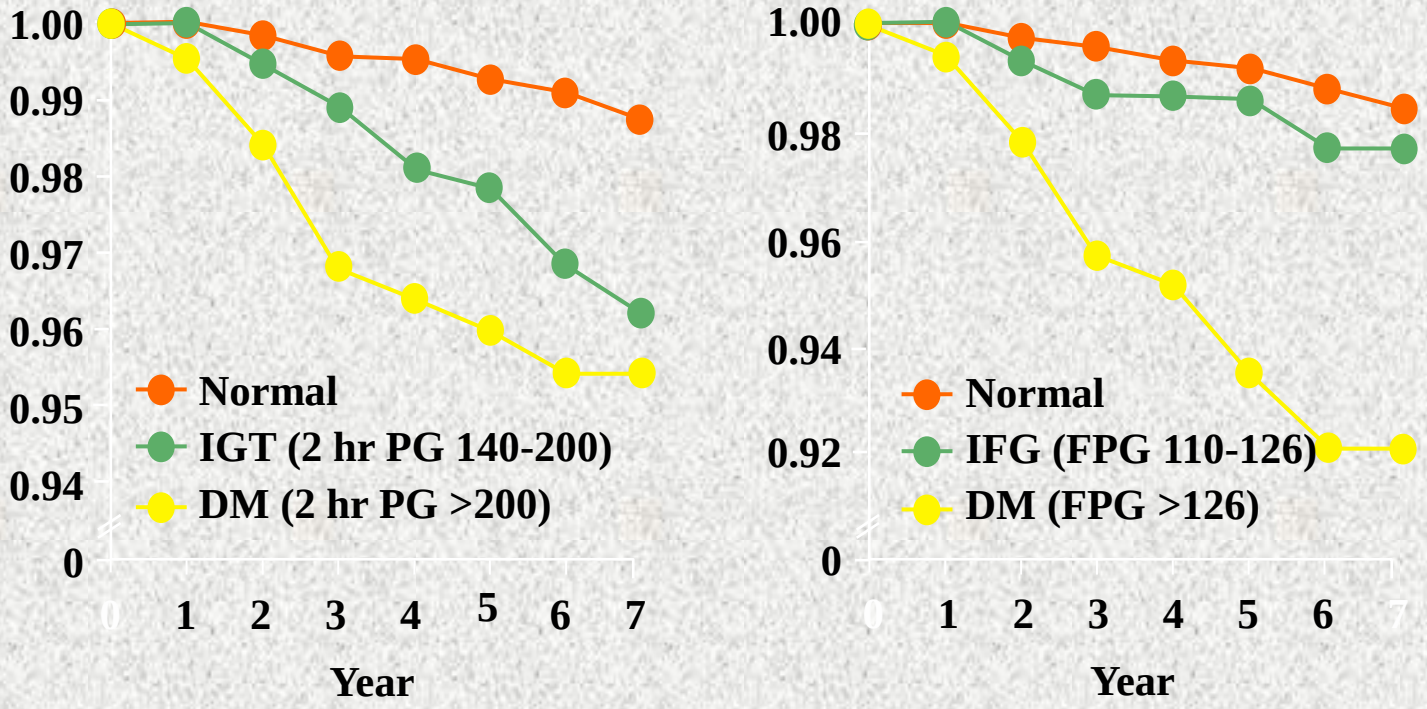
There is some newly emerging data that atherosclerosis, type 2 diabetes, and obesity are all characterized by increased plasma or serum levels of inflammatory vasoactive cytokines. M. Visser and colleagues (*JAMA*[1999] 282:2131-2135) have reported that, "*Higher BMI is associated with higher CRP concentrations, 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?

THE FUNAGATA DIABETES STUDY

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

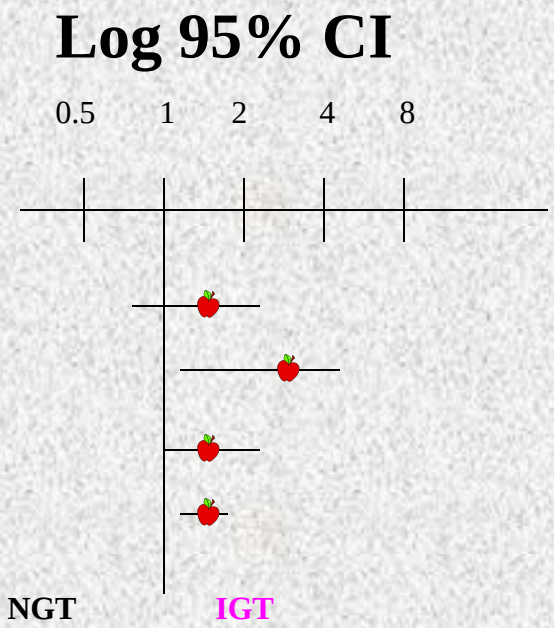
Cumulative Cardiovascular Survival



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.

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

Study	Ratio	p value
• Bedford Mortality Study (1982)[1]		
– **Males**	1.42	ns
– **Females**	**2.76**	**<0.05**
• Paris Prospective Study (1993)[2]	1.6	ns
• Malmohus County Study (1997)[3]	1.8	<0.01



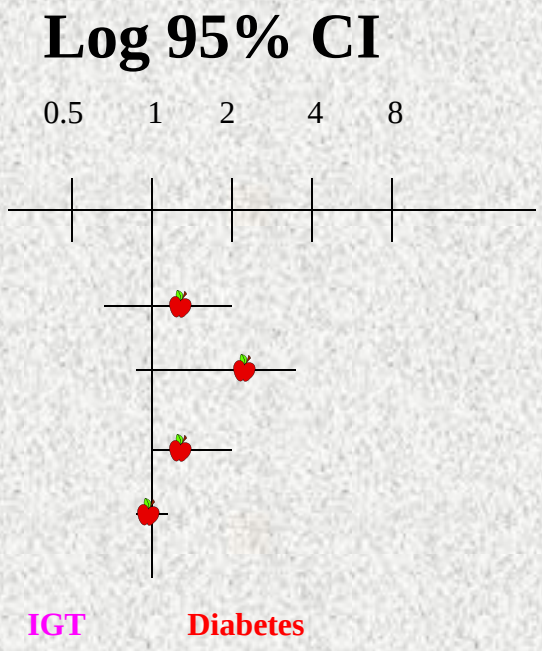
1. Odds Ratio

2. Relative Risk

3. Age-Sex Adjusted Relative Risk **(minus SFU Pts)**

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)**

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

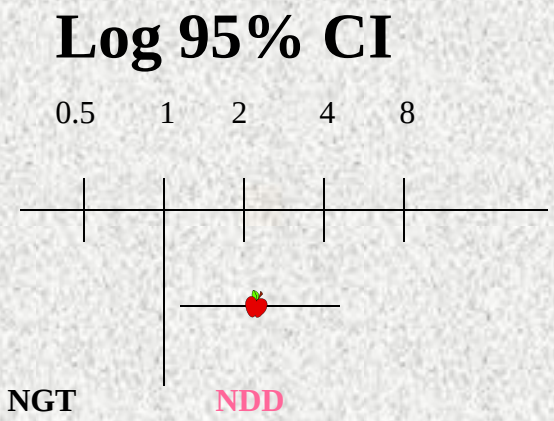
The Osservatorio Geriatrico Regione Campania Group. Amato L, Paolisso G, Cacciatore F, Ferrara N, Ferrara P, Canonico S, Varricchio M, Rengo F *Diabetes Metab* [1997] **23**:213-8

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?

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

Study	Ratio	p value
• Paris Prospective Study (1993)[1]	2.2	<0.05



1. Relative Risk

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

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

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.]

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

- **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 30% reduction (P=0.042) in the hazard of becoming diabetic."

[95% CI of 0.695 point estimate of odds ratio (0.494 to 0.978)]

THE LANCET

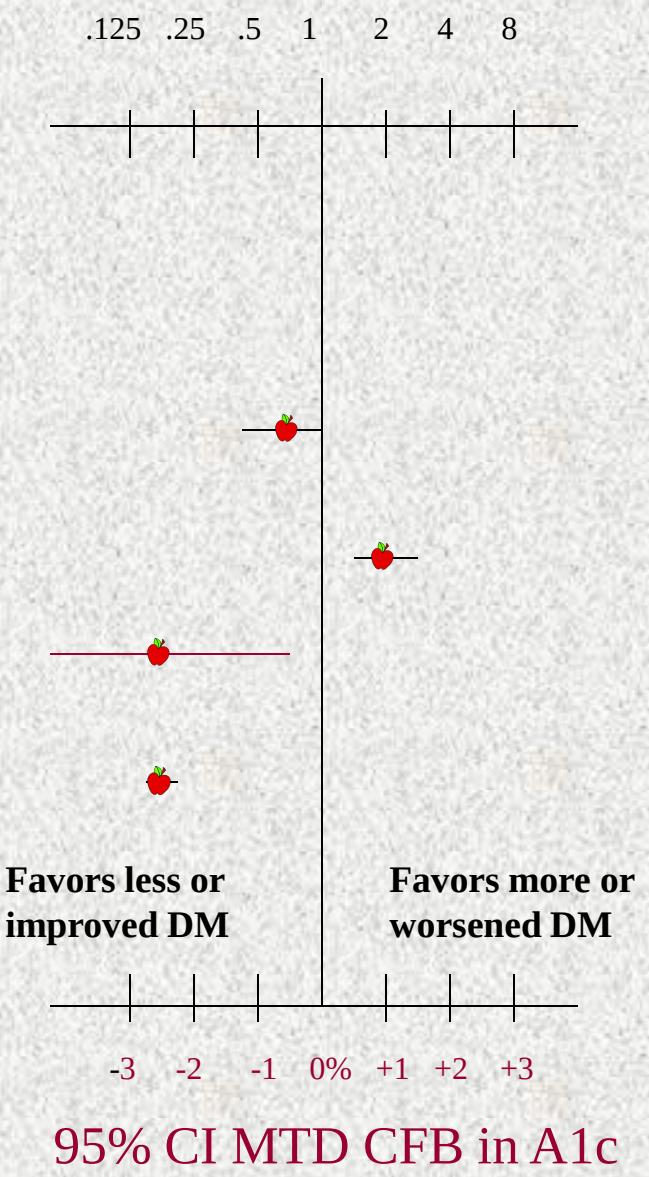
Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy (**Lancet,** Volume 355, Number 9200 22 January 2000)

"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%)

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



7) Can short-term control impact long-term mortality? If so, then under what circumstances?

Q:-Does Altering *Glycemic Control* Over the Short-Term in Any Setting Have A Long-Term Impact Upon Cardiovascular Disease or Mortality[7]?

- A:- Well, only by insulin and only in the setting of acute MI…. (DIGAMI)

Glycometabolic State at Admission: Important Risk Marker of Mortality in Conventionally Treated Patients With Diabetes Mellitus and Acute Myocardial Infarction (*Circulation.* 1999;99:2626-2632.)

Long-Term Results From the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study

Klas Malmberg, MD, PhD; Anna Norhammar, MD; Hans Wedel, PhD; Lars Rydén, MD, PhD

"***Mortality in diabetic patients with AMI is predicted by age, previous heart failure, and severity of the glycometabolic state at admission but not by conventional risk factors or sex. Intensive insulin treatment reduced long-term mortality despite high admission blood glucose and Hb A_{Ic}***."

Beneficial Hemodynamic Effects of Insulin in Chronic Heart Failure[7]

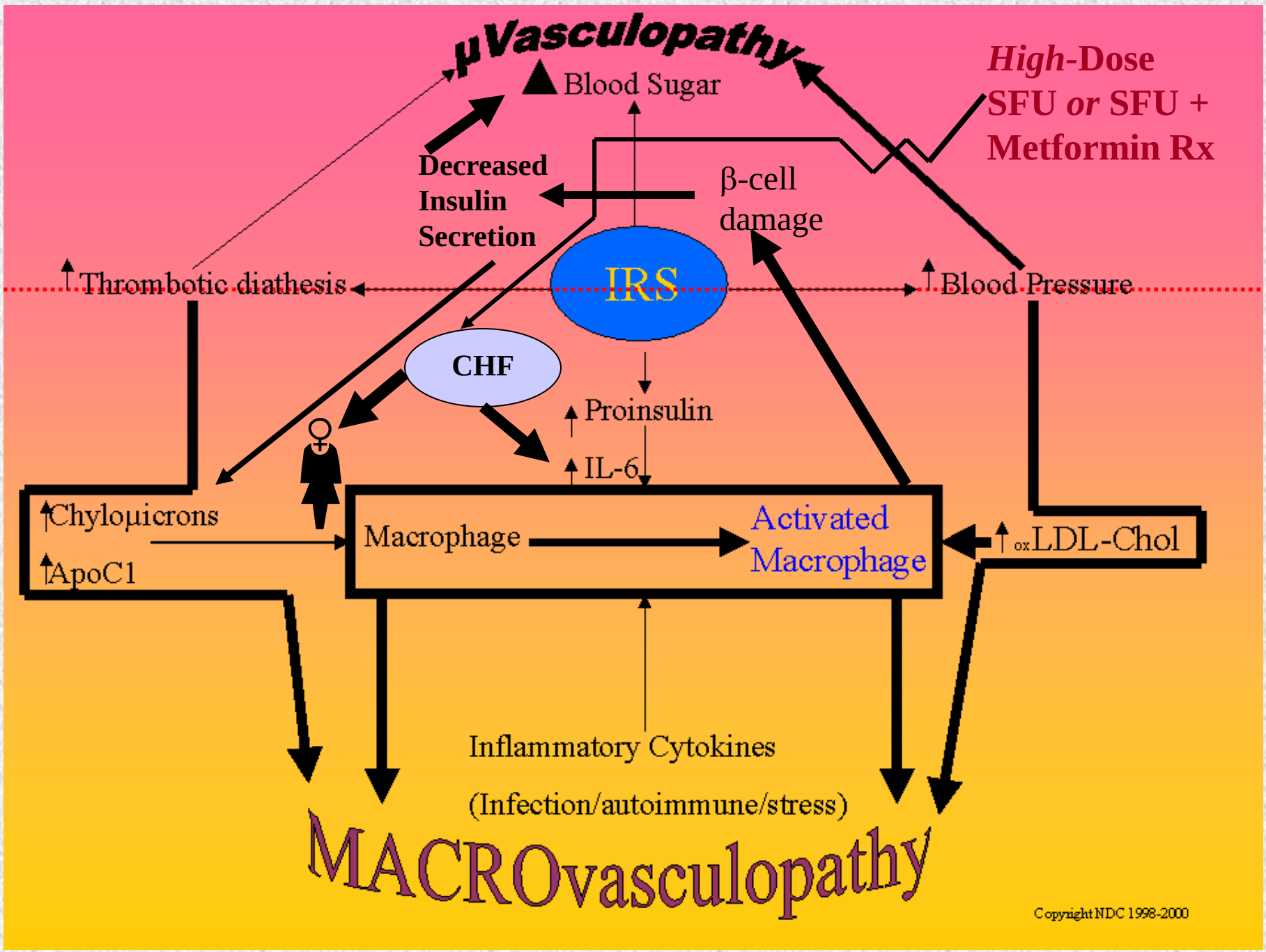
W A Parsonage, D Hetmanski, A J Cowley Heart 2001;85:508-513

DESIGN: Single blind, placebo controlled study. PATIENTS: Ten patients with stable chronic heart failure. INTERVENTIONS: Hyperinsulinaemic euglycaemic clamp and non-invasive haemodynamic measurements. MAIN OUTCOME MEASURES:- Change in resting heart rate, blood pressure, cardiac output, and regional splanchnic and skeletal muscle blood flow.

RESULTS:- Insulin infusion led to a dose dependent increase in skeletal muscle blood flow of 0.36 (0.13) and 0.73 (0.14) ml/dl/min during low and high dose insulin infusions ($p < 0.05$ and $p < 0.005$ v placebo, respectively). Low and high dose insulin infusions led to a fall in heart rate of 4.6 (1.4) and 5.1 (1.3) beats/min ($p < 0.05$ and $p < 0.005$ v placebo, respectively) and a modest increase in cardiac output. There was no significant change in superior mesenteric artery blood flow.

CONCLUSION:- In patients with chronic heart failure insulin is a selective skeletal muscle vasodilator that leads to increased muscle perfusion primarily through redistribution of regional blood flow rather than by increased cardiac output. These results provide a rational haemodynamic explanation for the apparent beneficial effects of insulin infusion in the setting of heart failure.

How might these current data be conceptualized into a model of diabetic pathophysiology?


μVasculopathy
Blood Sugar
High-Dose
SFU or SFU +
Metformin Rx
Decreased
Insulin
Secretion
β-cell
damage
IRS
Thrombotic diathesis
Blood Pressure
CHF
Proinsulin
IL-6
Chyloμicrons
ApoC1
Macrophage
Activated
Macrophage
oxLDL-Chol
Inflammatory Cytokines
(Infection/autoimmune/stress)
MACROvasculopathy
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CONCLUSIONS:-

1) Patients - particularly females - with *new onset type 2 diabetes* should be suspected of being at *high risk* for cardiovascular mortality.

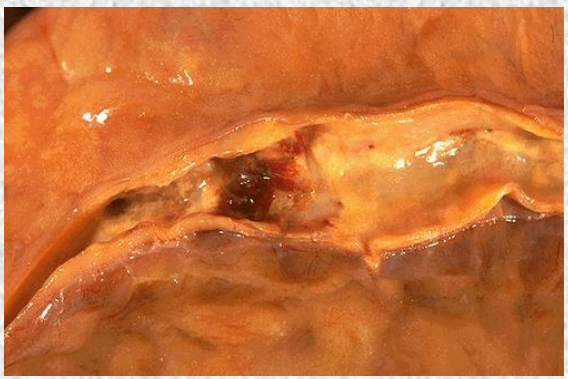
2) Long-term pharmacologic interventions to very tightly control type 2 diabetes are otherwise ineffective in reducing cardiovascular mortality.

3) Current therapeutic hierachy should therefore weight intensive lipid, hypertensive, and coagulation control over efforts to control blood sugar.

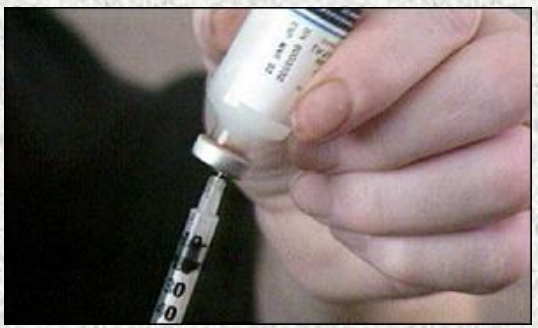
3) Tight control of glycemia should be limited to insulin and only within the context of acute MI or of patients suspected of being at very high risk from cardiovascular mortality **such as those with congestive heart failure**.

4) ADA Treatment Guidelines for Type 2 glycemic control of target A1c at 7% and action point at 8% should be maintained and not tightened except as above.

5) The NIH ACCORD trial -Prevention of Cardiovascular Disease in Diabetes Mellitus ("Action to Control Cardiovascular Risk in Diabetes" - currently underway to test the "extremely tight control hypothesis" should be 2-tailed for this variable and the informed consent so disposed.

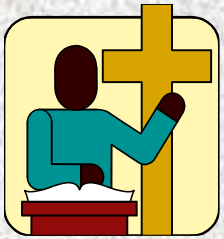


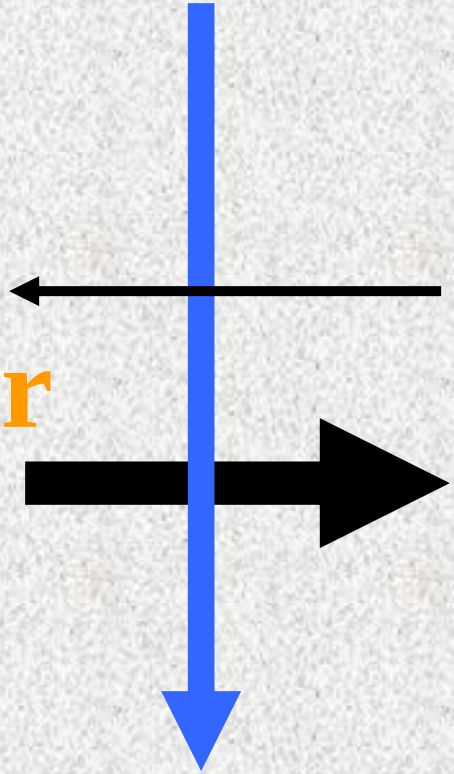
Intensive Glycemic Control with Insulin



High-Risk

Cardiovascular Disease, CHF, &





Poor Glycemic Control

The National Diabetes Center

pharmanet