SUGAR AND THE HEART

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MEDICAL GRAND ROUNDS

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"This is to acknowledge that Philip Raskin, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Raskin will not be discussing "off-label" uses in his presentation."

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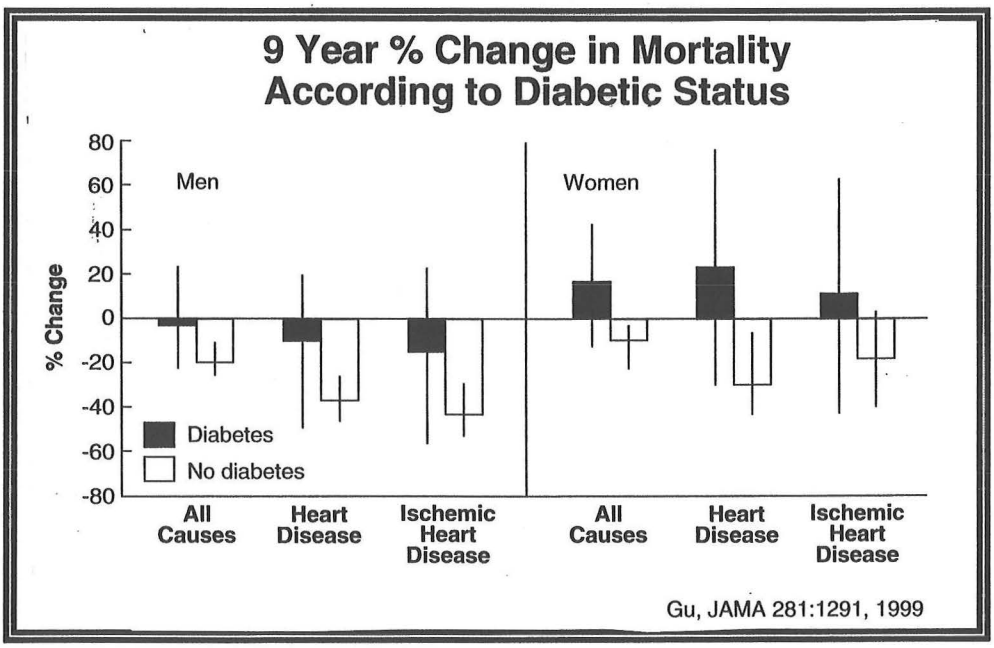
INTRODUCTION

Cardiovascular disease is the major cause of the morbidity and mortality associated with diabetes in the United States. A two to three-fold incidence in cardiovascular disease occurs in both Type 1 and Type 2 diabetic individuals compared to age and gender matched nondiabetic persons. Cardiovascular disease is responsible for the majority of hospital admissions for diabetic individuals and, together with kidney disease, accounts for most of the dollars expended on health care in this population. Because of the enormous and escalating financial and social costs, more attention has been focused recently on the problem of cardiovascular disease in diabetes. Recent data demonstrated a decline in cardiovascular disease mortality in the general U.S. population. However, this does not seem to be the case in the diabetic population, particularly in women (Figure 1). The reason for this fact is not clear.

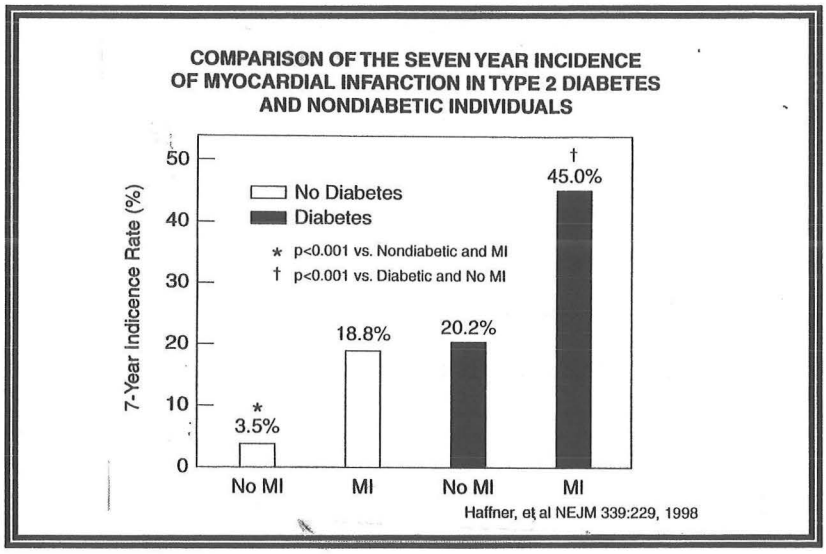
FIGURE 1



These data unfortunately suggest that diabetes is likely to become an even greater contributor to heart disease mortality in the U.S. in the future.[1] In my opinion, the best data regarding diabetes, and the risk of coronary artery disease comes from Haffner et al (Figure 2). In this epidemiological study in Finnish individuals, the incidence of myocardial infarction over 7.5 years

was the same in diabetic individuals who had no prior history of myocardial infarction as it was in non-diabetic persons who had already suffered a heart attack[2]. Thus, all diabetic individuals are at very high risk for coronary heart disease. Physicians generally attend to reducing all risk factors in individuals (both diabetic and nondiabetic) once they have had a cardiac event. Haffner's data suggests this same attention should be provided to **ALL** diabetic individuals, even those who do not have clinical evidence of coronary disease.

FIGURE 2



Because cardiovascular disease in diabetes is such a huge problem, this subject has been reviewed at these proceedings several times in the past few years. Unlike microvascular disease in diabetes which seems to be related primarily to the presence of hyperglycemia, macrovascular disease is multifactorial.[3] The generally accepted modifiable risk factors for cardiovascular disease in diabetes are given in Table 1.

TABLE 1

CARDIOVASCULAR RISK FACTORS IN DIABETES
•Hyperglycemia
•Dyslipidemia
•Hypertension
•Nephropathy
•Cigarette Smoking
•Altered Coagulation Factors
•Hyperinsulinemia/Insulin Resistance

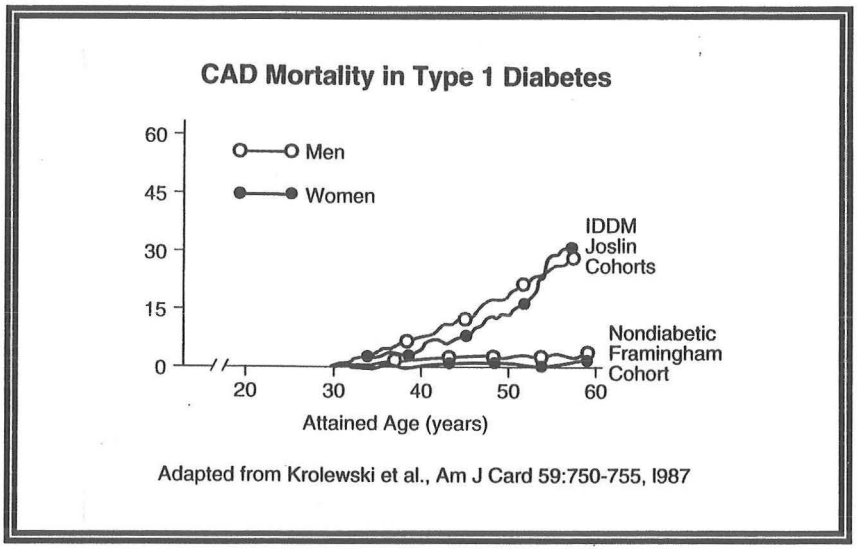
My purpose in this review is to discuss only the evidence that relates to hyperglycemia per se as a risk factor for cardiovascular disease since the other risk factors have been discussed at length in this forum. The material I will cover will include epidemiological data in both diabetic and non diabetic individuals that suggest a relationship between the level of glycemia and cardiovascular risk. I also plan to show interventional data. I will review studies in which changes in glycemia were implemented and the impact those changes had on cardiovascular disease evaluated.

A preponderance of evidence suggests that hyperglycemia is an important independent contributor to the increased cardiovascular disease risk associated with diabetes, (although not nearly as important as it is on the risk for microvascular disease). In fact, the level of glycemia appears to have an impact on cardiovascular disease risk in non diabetic individuals. Hyperglycemia leads to glycation and peroxidation of proteins amongst other biochemical changes. These changes in animal studies cause arterial damage and other direct toxic effects on arterial walls. Logic dictates that chronic exposure of arterial walls to hyperglycemia would enhance atherogenesis.

Epidemiology of Cardiovascular Disease in Diabetes

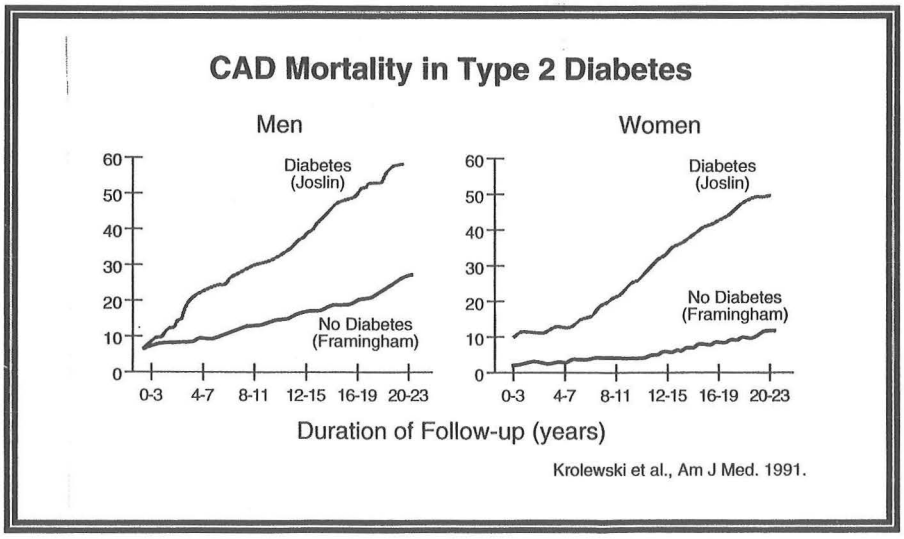
An examination of the natural history of diabetes reveals how common cardiovascular disease is in both Type 1 and Type 2 diabetes. Data generated in the late 1980's from a cohort of 292 patients with Type 1 diabetes followed for 20-40 years revealed an alarmingly high rate of coronary artery disease and coronary artery disease mortality in this population. The cumulative mortality in the diabetic men and women was 3.5-to-4-fold higher than that of a comparison group of nondiabetic individuals from the Framingham Heart Study.[4] (Figure 3) The presence of persistent proteinuria due to the presence of diabetic nephropathy was found to be one of the strongest predictors of the development of coronary artery disease in patients with Type 1 diabetes.

Figure 3



The risk for cardiovascular disease morbidity and mortality is similar in Type 2 diabetes. A cohort of 35 to 64-year-old Type 2 diabetic men and women followed for up to 24 years were compared to a similar nondiabetic population also from the Framingham study. Both populations demonstrated increasing coronary artery disease mortality with duration of follow-up, presumably reflecting the aging process. However, the rate of increase in mortality over the years of follow-up was greater in the diabetic group, reflecting a cumulative effect of exposure to diabetes (Figure 4).[5] Other studies have similarly demonstrated a correlation between the increased risk of coronary heart disease events and duration of diabetes, presumably as a result of the effects of chronic hyperglycemia.[6]

Figure 4



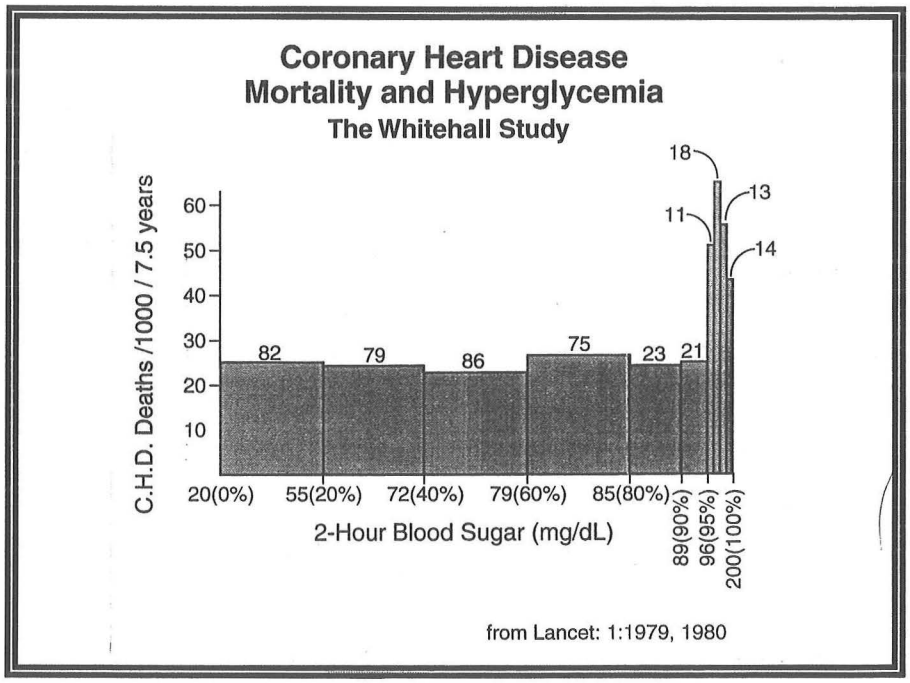
Since cardiovascular disease is multifactorial, the impact of individual components on the increased cardiovascular disease risk in Type 2 diabetes is difficult to ascertain. Data from the Multiple Risk Factor Intervention Trial (MRFIT) in 347,978 men with and without diabetes showed a 3-fold increased risk of cardiovascular disease death in the diabetic men. Serum cholesterol, systolic blood pressure, and cigarette smoking were all significant predictors of cardiovascular disease mortality in both diabetic and nondiabetic men. However, the absolute risk of death from coexistence of multiple risk factors increased more steeply in diabetic men than in nondiabetic men.[7]

While diabetes increases the risk for cardiovascular disease in both men and women, the risk in women is disproportionately greater. An abundance of data suggests that diabetes increases the risk for cardiovascular disease and cardiovascular disease mortality in women 4-to-6-fold as compared to 2-to-3 fold for diabetic men, and any advantage that would otherwise exist due to the premenopausal state is eliminated.[5,8-10] The reasons for this increased risk for cardiovascular disease in women remain unknown.

Many epidemiological studies suggest that severity of hyperglycemia is an independent predictor of cardiovascular disease. The Whitehall study (Figure 5) examined the relationship of coronary heart disease mortality to blood glucose levels 2 hours after a 50 g oral glucose load in 18,403 British men aged 40 to 60 years with glucose tolerance ranging from normal to diabetic levels. Coronary heart disease mortality at 7.5 years of follow-up was increased 1.5-to-2.5-fold in subjects whose 2 hour post oral glucose, blood glucose value was between 96 and 199 mg/dl or those with frank diabetes (2 hour post oral glucose, blood glucose level $\geq$200 mg/dl).[11] The Honolulu Heart Study also examined the role of postprandial blood glucose levels on the risk of coronary heart disease in 8,006 diabetic and nondiabetic men aged 45 to 70 years. After 12 years of followup, the data showed that the risk of fatal and total coronary heart disease increased significantly as 1-h glucose values increased, such that the age-adjusted rate for fatal coronary heart disease was three times greater in the fifth glycemic quintile than in the first.[12] The rate of sudden death increased in a stepwise manner with post glucose challenge, plasma glucose levels with a rate in diabetic men approximately 3 times that of the nondiabetic men. Even more important was the observation that sudden death was increased 1.7-fold in the men with "high-normal" glucose tolerance (post oral glucose value of 151-224 mg/dl [some of these individuals probably had diabetes]) and more than 2.5-fold in the group with asymptomatic

hyperglycemia (i.e. undiagnosed diabetes).[13] After 23 years of followup this relationship was again demonstrated for total mortality, coronary heart disease mortality, and incidence of coronary heart disease, even after adjustment for other coronary heart disease risk factors such as age, smoking, body mass index, and abnormal lipids.[14] These findings strongly support the idea that there is a direct relationship between glycemic level and cardiovascular risk in nondiabetic and as yet undiagnosed diabetic individuals. The corollary to these data is that both aggressive glucose control in diabetic individuals as well as active screening for diabetes may be necessary in order to effectively reduce the burden of hyperglycemia-related coronary heart disease.

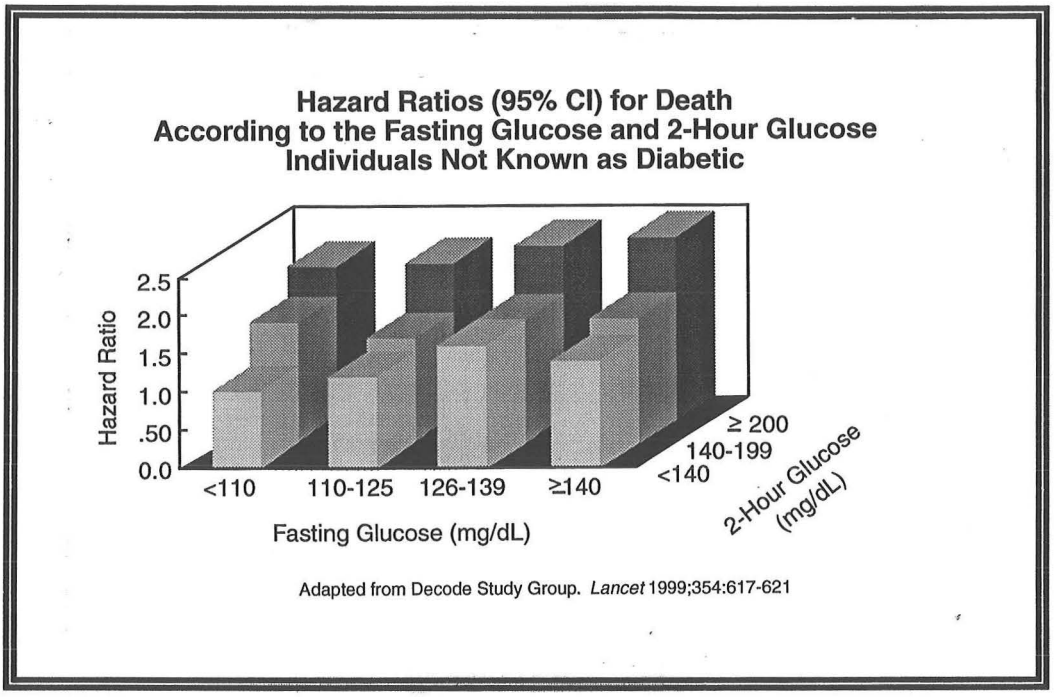
Figure 5



Recently, even more compelling evidence that glycemia may constitute a risk factor for coronary artery disease in nondiabetic individuals comes from the Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe, the so called DCODE Study.[15] This analysis includes data pooled from 13 prospective European cohort studies using fasting and 2 hour post 75 gram glucose load, plasma glucose levels. The study included 25,364 individuals (18,048 men and 7,316 women) aged 30 years or older with unknown glucose tolerance at baseline, and 1275 individuals with a prior diagnosis of diabetes. They compared mortality associated with the American Diabetes Association's fasting plasma glucose criteria as compared to the World

Health Organization's post challenge, plasma glucose criteria after a mean followup of 7.3 years. (Figure 6)

FIGURE 6



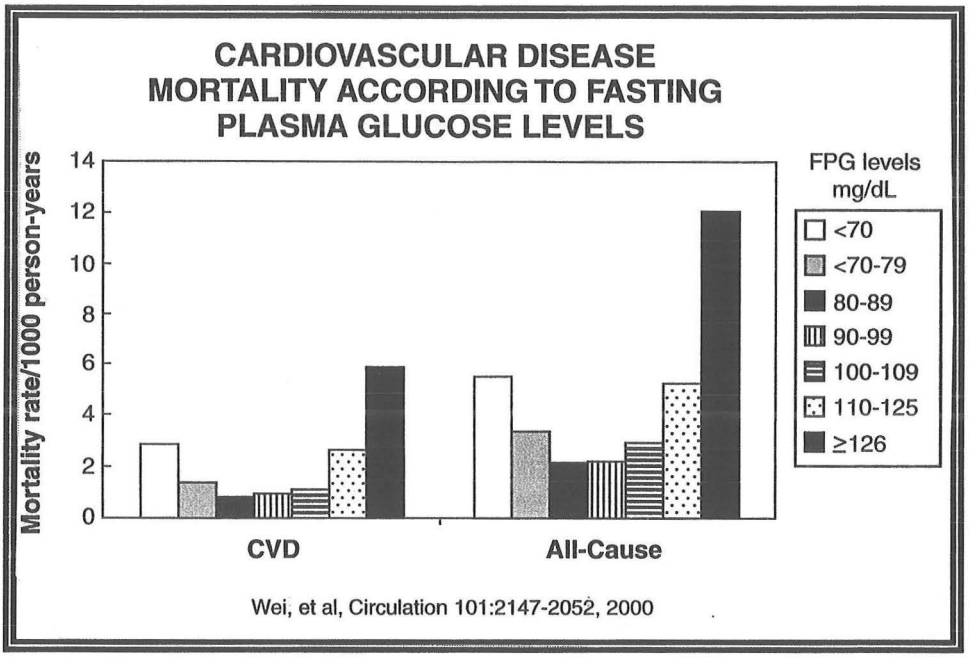
Based on these data, the authors concluded that "fasting glucose concentrations alone do not identify individuals at increased risk of death associated with hyperglycemia. The oral glucose tolerance test provides additional information, and enables detection of individuals with impaired glucose tolerance who have the greatest attributable risk of death".

These data are in agreement with those from the Funagata Diabetes Study.[16] This study compared cardiovascular and total mortality in Japanese individuals relative to their classification of having normal fasting glucose (FPG<110 mg/dl), impaired glucose tolerance (2 hr post 75 gram oral glucose, plasma glucose level >140-199 mg/dl), impaired fasting glucose (FPG 110-126 mg/dl), or diabetes (FPG>126 mg/dl). They concluded that impaired fasting glucose was not a risk factor for cardiovascular disease but impaired glucose tolerance was.

A recent paper from Wei et al[17] based on epidemiological data provides additional, but somewhat confusing information. This survey was based on 40,069 men and women aged 20 to 82 years of age (mean age 43) from either the Aerobics Center Longitudinal Study or the San Antonio Heart Study. The purpose was to investigate the association between fasting plasma

glucose levels and cardiovascular disease and all-cause mortality in the participants of these studies. They documented a U-shaped relationship (Figure 7) between fasting plasma glucose levels and cardiovascular disease mortality.

FIGURE 7

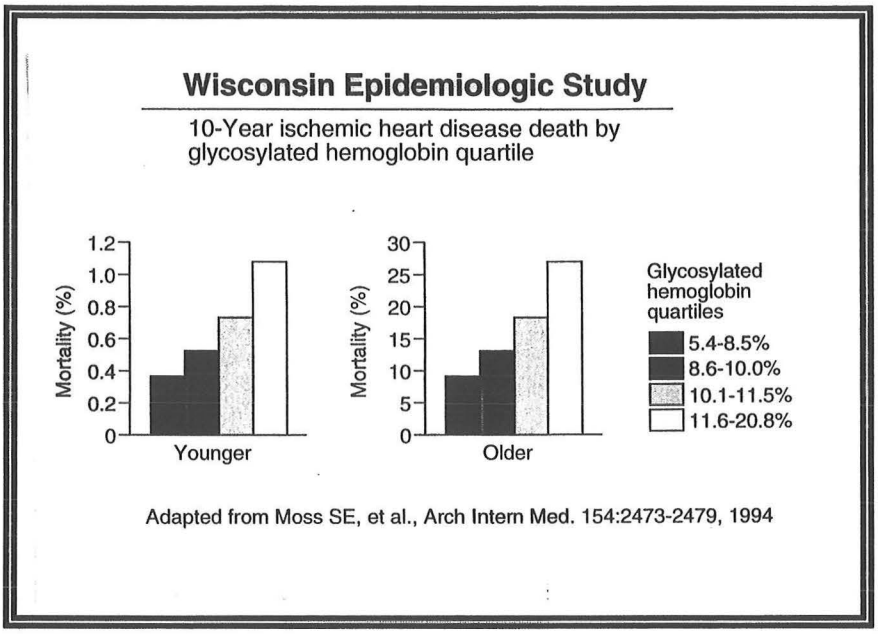


In addition to glucose levels diagnostic of diabetes (FPG ≥126 mg/dl) and those consistent with a "diagnosis" of impaired fasting glucose (FPG 110-125 mg/dl), low fasting plasma glucose levels (FPG < 70 mg/dl) were also associated with high mortality. This relationship remained after a multivariate adjustment for other usual risk factors. The risk for cardiovascular disease mortality was increased 3.3 times for individuals with a fasting plasma glucose level < 70 mg/dl, and 2.4 times for those individuals who had a fasting plasma glucose level from 70 - 79 mg/dl compared with the risk in individuals whose fasting glucose level was 80-109 mg/dl. The precise interpretation of these data are unclear.

The data relating glycemia to cardiovascular risk seem clearer in individuals with overt diabetes. In these individuals, cardiovascular disease risk appears to be associated with both level of hyperglycemia and the duration of diabetes. The Wisconsin Epidemiologic study (Figure 8) examined the relationship between chronic glucose exposure, using glycated hemoglobin measurements, and the incidence and progression of diabetic macrovascular complications. In this study, the rate of mortality from ischemic heart disease over 10 years increased in both the

younger onset (presumably Type 1) and older onset (presumably Type 2) diabetic populations.[18] (Figure 8)

FIGURE 8



Additional data analysis demonstrated that a 1% rise in the glycosylated hemoglobin level had the effect of increasing risk for ischemic death by 10%.[19] (Figure 9) Similarly, in the Finnish Kuusisto Study, in which 1,298 men and women aged 65 to 74 years were followed for 3.5 years, the level of HbA_{1c} and the duration of diabetes were found to be strong predictors of coronary heart disease mortality and all coronary heart disease events.[6] In another Finnish study, middle-aged patients with Type 2 diabetes followed for 10 years had increasing cardiovascular disease mortality with increasing glycemic levels whether on diet treatment or an oral antidiabetic or insulin regimen.[20] (Figure 10) Fifteen year follow-up data on this cohort is now available, and reinforces the observations on the risk of cardiovascular disease mortality associated with glycemia.[21]

FIGURE 9

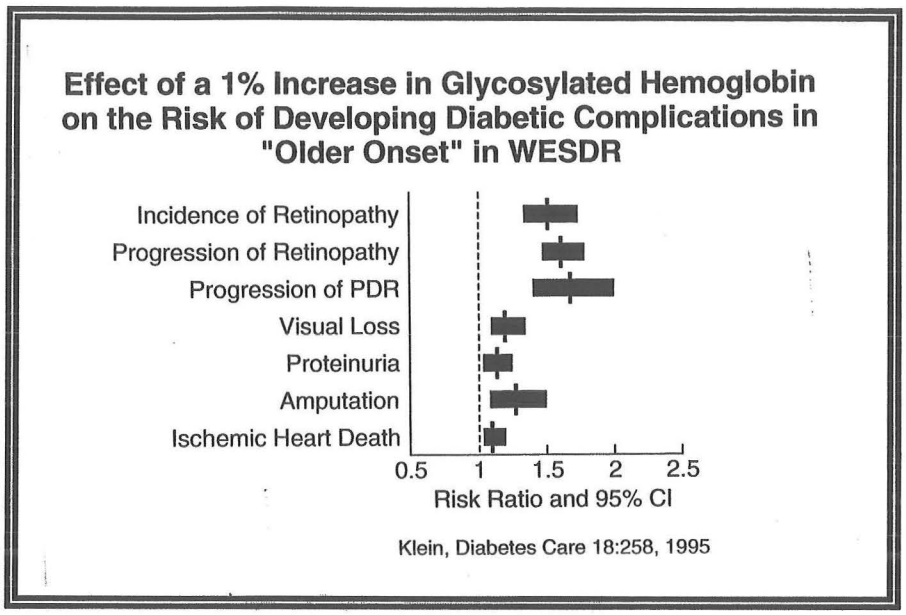
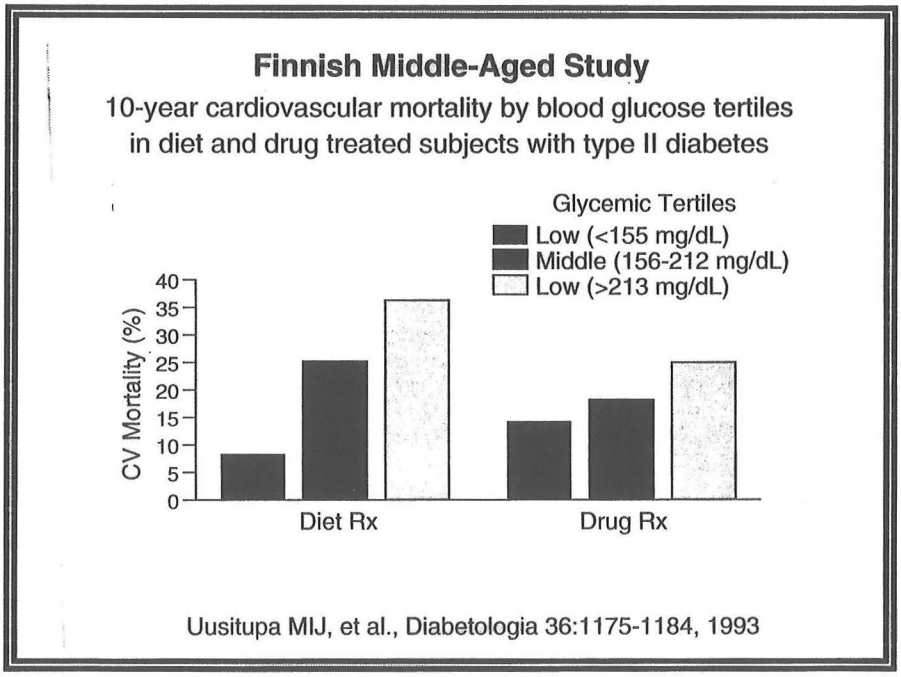


FIGURE 10



Results which strikingly highlight the risk of atherosclerosis associated with hyperglycemia come from the Pathological Determinants of Atherosclerosis in Youth (PADY) study. This was a posthumous study in 1,532 young people (ages 15-34) who died of various, mostly traumatic,

causes. In individuals who had glycosylated hemoglobin levels of 8% or greater, the prevalence of fatty streaks in the right coronary artery was two-fold greater, and raised lesions in that artery were three times that of individuals whose glycohemoglobin levels were below 8%.[22] This evidence strongly supports hyperglycemia as an independent marker of early risk for cardiovascular disease.

Data from the Bedford Survey highlight the risk of diabetes associated with hyperglycemia and gender. This study demonstrated that the 10-year age-adjusted mortality rates in both men and women with established diabetes and "borderline" diabetes (i.e. 2 hour post 50 gram oral glucose challenge, capillary blood glucose level of 120-199 mg/dl) increased in a stepwise manner, from normal to diabetes. In women, however, an approximate 4-fold increase in risk occurred with the onset of "borderline" diabetes, which was maintained with the onset of frank diabetes.[23-24] Diabetes may need to be diagnosed in its early stages to make a real impact on cardiovascular disease development.

The Effects of Glucose Control on Cardiovascular Risk

A number of large prospective studies have provided data to support the concept that improvement in glycemic control can reduce cardiovascular risk in diabetic individuals. Conflicting data do exist, however.

Perhaps the best of the studies that relate changes in diabetes control to changes in cardiovascular risk is the DCCT. In this large prospective trial, 1441 individuals with Type 1 diabetes were randomly assigned to either conventional treatment or intensive diabetes management with either three or four daily insulin injections or an insulin pump. These individuals were followed for up to nine years with an average follow up of 6.5 years. In addition to a remarkable reduction in the development and progression of the microvascular complications[25], there was a 41% reduction in the risk of macrovascular disease (myocardial infarction and peripheral vascular disease) in the intensively treated cohort.[26] Although this was not a "statistically significant" result (the p value = 0.065 for cardiac events and 0.08 for combined cardiac and peripheral events) (Table 2), I believe that it was a "biologically significant" result. One must remember that individuals in the DCCT were young (average age 28 at study

entrance), had diabetes for a short duration, were only followed for an average of 6.5 years and were ineligible for the study if they had either pre-existing clinical coronary artery disease, an abnormal electrocardiogram, hypercholesterolemia, or hypertension. In addition, the treatment was associated with a reduction in at least one cardiovascular risk factor. Those individuals in the intensive treatment group had a reduction in the development of hypercholesterolemia by 34%, both a statistically and biologically significant change.[26]

Table 2

EFFECT OF INTENSIVE DIABETES TREATMENT ON MACROVASCULAR EVENTS IN THE DCCT

Events	Absolute Risk (events per 100 pt years)		Risk Reduction	P
	Intensive Rx	Conventional Rx		
Cardiac	0.29	0.06	18%	0.065
Peripheral	0.55	0.43	22%	----
Combined	0.84	0.49	41%	0.08

DCCT, Amer J Card 75:894, 1995

In the Stockholm Diabetes Intervention Study, 59 patients with Type 1 diabetes were followed for 12 years. Intensive glucose control, defined as a HbA_{1c} level below 7%, was associated with a reduction in carotid wall stiffness and improvement in endothelial function.[27] These differences may translate into slower development of atherosclerosis.

As in the DCCT, a trial of intensive insulin treatment in newly diagnosed, non-obese, Type 2 Japanese diabetic patients (Kumamoto Study) resulted in significant reductions in microvascular disease associated with improved glucose control. However, there were too few cardiovascular events to detect an effect of intensive management on macrovascular disease.[28]

The United Kingdom Prospective Diabetes Study (UKPDS) followed 4,209 newly diagnosed Type 2 diabetic patients over 10 years who were randomized to either an intensive treatment or standard treatment policy. In this study, much like the DCCT, intensive diabetes treatment and lower HbA_{1c}

levels (HbA_{1c} = 7.0% in the intensive policy group vs 7.9% in the conventional policy group) resulted in a significant reduction in all microvascular events. There was also a reduction in the incidence of myocardial infarction in the intensive policy group which just missed statistical significance (p=0.052).[30] Of course, I feel this is also a biologically significant result, especially given the fact that there was no provision in the UKPDS protocol for the treatment of hypercholesterolemia.
The investigators in the UKPDS will follow the patients for an additional 5 years to observe whether the reduction in myocardial infarction and cardiovascular disease mortality reaches statistical significance. Of interest, is a subset of the UKPDS subjects who were obese and were separately randomized (three arms) to conventional treatment or intensive treatment with either sulfonylureas or insulin or metformin. Those treated with metformin had a statistically significant reduction in diabetes related endpoints and myocardial infarction as compared to conventional treatment or treatment with insulin or sulfonylureas. The precise meaning of these data are unclear.[31]

The Veteran's Affairs Cooperative Study on Glycemic Control and Complication in the Diabetes (VACSDM) replicated the difference of the DCCT in HbA_{1c} levels between standard and intensive treatment groups in this 2.5 year study in Type 2 diabetic patients. Unlike the DCCT and Kumamoto study, the cardiovascular event rate was high, but with a trend toward more events in the intensively treated group.[29] The middle-aged or older male subjects in this study had diabetes of long duration, had been poorly controlled, and many had cardiovascular disease at study entry. The duration of the study may have been too short, or the disease, already too far progressed, to see any benefit of improved glucose control on cardiovascular disease.

Perhaps the most interesting study regarding the effect of improved glycemic control on subsequent cardiovascular disease in diabetes is the "Diabetes Mellitus Insulin Glucose-Infusion in Acute Myocardial Infarction(DIGAMI) Study.[32] This study was a randomized prospective study carried out in 19 Swedish hospitals that included 620 diabetic individuals. All of the individuals had suffered an acute myocardial infarction within the previous 24 hours, and the diagnosis of diabetes required a blood glucose level of greater than 198 mg/dl while in the coronary care unit. All subjects were randomly assigned to either a standard treatment protocol(not clearly defined in the paper), or were treated with an insulin-glucose infusion in the coronary care unit for at least 24 hours followed by 4 daily insulin injections for at least 3 months following discharge from the hospital. These individuals were followed for 3 to 4 years. The HbA_{1c} at baseline was the same for both groups.

There were significant differences between the groups at both 3 months and 12 months in terms of HbA_{1c} levels. (Table 3)

TABLE 3

DIGAMI STUDY

(Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction)

Glycemic Control

	Control Group	Infusion Group
	HbA1c(%)	
Randomization	**8.0**	**8.2**
3 Months	**7.4**	**6.9***
12 Months	**7.5**	**6.9***

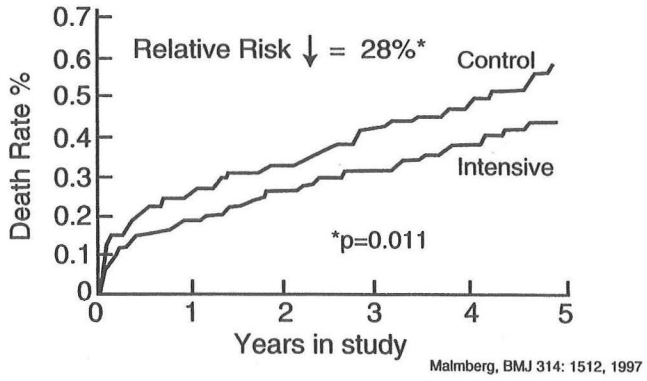
***p<0.001 vs control group**

Malmberg, Brit Med J 214:1512, 1997

Figure 11 shows the results after 5 years of followup. Individuals treated with the glucose-insulin infusion in the peri-infarct period that was followed by a four daily insulin injection treatment program had a 28% lower risk of dying as compared to those individuals who received standard treatment. The effect was even greater for individuals who had never been treated with insulin prior to their myocardial infarction where the risk of dying was 51% lower. (Figure 12)

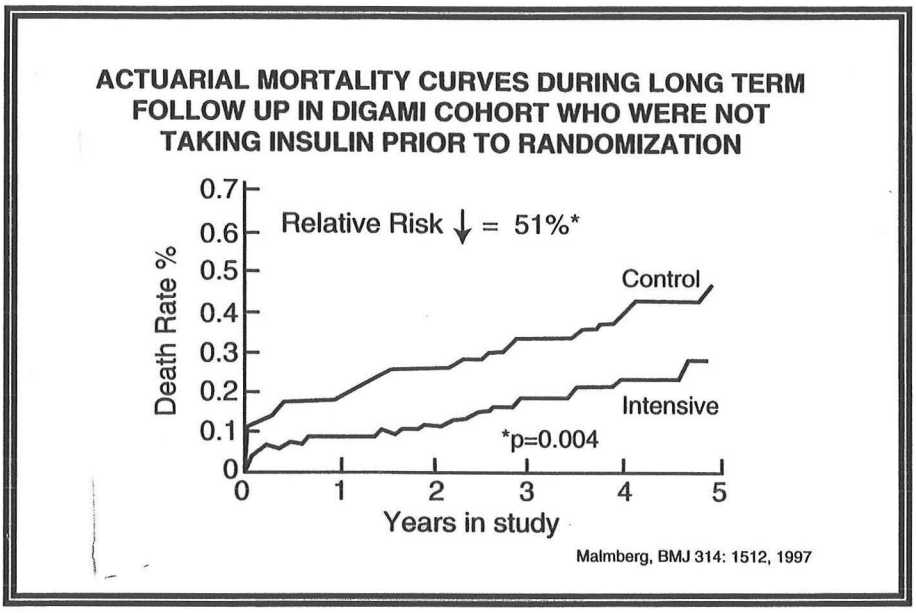
FIGURE 11

ACTUARIAL MORTALITY CURVES DURING LONG TERM FOLLOW UP IN TOTAL DIGAMI COHORT



Malmberg, BMJ 314: 1512, 1997

Figure 12



CONCLUSIONS

Cardiovascular disease is the major cause of mortality and morbidity in diabetic individuals. It is also the major reason for the high health care costs of diabetes. While microvascular disease (retinopathy, nephropathy, and neuropathy) rarely occur in nondiabetic individuals, cardiovascular disease occurs in both diabetic and nondiabetic individuals alike. However, diabetic persons develop cardiovascular disease earlier in life and often have more severe disease than do nondiabetic individuals. Women with diabetes are particularly affected in a negative way, losing all the protection of their gender from cardiovascular disease. Interestingly, there are data that suggest that higher post prandial blood glucose levels in the nondiabetic population may also predispose to cardiovascular disease. Clearly more information and research are needed in this area. There are newer medications being developed that are especially directed toward reducing post prandial glucose levels. Interventional trials with these medications might be done to investigate what impact the reduction in post prandial hyperglycemia might have on subsequent development of cardiovascular disease in nondiabetic individuals.

I have suggested several times in this protocol that screening for diabetes and/or impaired fasting glucose or even impaired glucose tolerance might be worthwhile. Tables 4 and 5 lists the American Diabetes Association's recommendations for screening for diabetes.

Table 4

SCREENING FOR TYPE 2 DIABETES IN ASYMPTOMATIC INDIVIDUALS

In all ≥ 45 years of age - repeat at 3 year intervals
At a younger age and more frequently if
- **–obese**
- **–first degree family history of diabetes**
- **–member of high risk population**
- **–gestational diabetes or previous baby > 9 lbs**
- **–previous IGT or IFG**
- **–hypertension**
- **–dyslipidemia**

ADA Position Statement, Diabetes Care 23 (Suppl 1):S20,

Table 5

SCREENING FOR TYPE 2 DIABETES IN ASYMPTOMATIC INDIVIDUALS

TESTS

- **Fasting plasma glucose level (preferred)**
- **75 gram oral glucose tolerance test**

ADA Position Statement, Diabetes Care 23 (Suppl 1):S20, 2000

Finally, it is clear that diabetic individuals are at very high risk for cardiovascular disease. It is probable that hyperglycemia, per se, is an important risk factor for cardiovascular disease and is independent of all the other accepted cardiovascular risk factors. However, since cardiovascular disease in diabetes, as it is in the nondiabetic individual, is a multifactorial problem, attention must

be given to all the modifiable risk factors. My thoughts on cardiovascular risk factor management in diabetic individuals are given in Table 6. Therapy of course, must be individualized. These treatment goals may not be appropriate for all individuals. For example, in elderly persons with many medical problems or in persons with severe heart disease, the risk of hypoglycemia or hypotension probably outweighs the benefits of aggressive blood glucose and blood pressure control.

Table 6

CARDIOVASCULAR RISK FACTOR MANAGEMENT IN DIABETES

- **Blood Glucose**
  - **Glycated Hemoglobin Level in Range of Individuals Without Diabetes**
- **Blood Pressure**
  - **BP< 135/85 mm Hg - Lower May Be Better**
- **Blood Cholesterol**
  - **LDL - Cholesterol Level < 100 mg/dl**
- **Smoking Cessation**
- **Physical Activity**
- **Aspirin Therapy**

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