JOURNAL OF INSURANCE MEDICINE

J Insur Med 2001;33:50–103

EVIDENCE BASED MEDICINE

DIABETES MELLITUS AND LIFE INSURANCE

Anthony F. Milano, MD, MPH

A comprehensive review of the literature of diabetes mellitus, its progression and complications is written with respect to the life insurance industry.

Address: Business Men's Assurance Co of America, PO Box 419076, Kansas City, MO 64141-6076.

Correspondence: Anthony F. Milano, MD, MPH, Reinsurance Medical Director and Vice President.

Key words: Diabetes mellitus, life insurance.

Received: August 29, 2000

Accepted: October 20, 2000

DEFINITION

Diabetes is a complex metabolic disease with differing causes, treatments, prognosis, complications and morbid multi-system end-outcomes characterized by inappropriate hyperglycemia and impaired metabolism of sugar and other energy-yielding foods, having distinct genetic and pathogenic mechanisms linked to defects in insulin secretion, insulin utilization or both.

CLASSIC SIGNS AND SYMPTOMS

Abrupt or insidious onset of: hyperglycemia and glucosuria (elevated blood and urine sugar); polydipsia, polyuria, polyphagia, (excessive thirst, urination and hungar); weakness, weight change and blurred vision.

EPIDEMIOLOGY OF DIABETES MELLITUS[1,2,3]

Incidence:

798,000 new cases diagnosed per year in the United States,

Overall Prevalence:

Overall total: 15.7 million (5.9% of the United States population)
Diagnosed: 10.3 million people
Undiagnosed: 5.4 million people

Prevalence by age:

Age 65 or older: 6.3 million; 18.4% of all people in this age group,
Age 20 or older: 15.6 million; 8.2% of all people in this age group,
Under age 20: 123,000; 0.16% of all people in this age group.

Prevalence by gender in adults (≥20-years old):

Men: 7.5 million; 8.2% of all men have diabetes,
Women: 8.1 million; 8.2% of all women.

Prevalence in children and teenagers:

123,000 in the United States.

Prevalence by race/ethnicity in adults:

Non-Hispanic whites: 11.3 million; 7.8% of all non-Hispanic whites,

Non-Hispanic blacks: 2.3 million; 10.8% of all non-Hispanic blacks,

Mexican Americans: 1.2 million; 10.6% of all Mexican Americans,

Other Hispanic/Latino Americans: ±15%,

Native Hawaiians: twice the diagnosed prevalence of white Hawaiians,

American Indians and Alaska natives: prevalence varies by tribes, bands, pueblos and villages,

Asian Americans and Pacific Islanders; twice the prevalence of white Hawaiians.

General population mortality among persons with diabetes:

1993: 400,000 all-cause deaths among diabetics ≥25 years old,

1994: 7th leading cause; whites, blacks, Chinese, Philippine,

4th leading cause; females and American Indians,

5th leading cause Hawaiians

6th leading cause; Japanese

CLASSIFICATION OF DIABETES[4]

1. Type 1 diabetes: (usual age onset: 0–19); also called insulin dependent diabetes mellitus, IDDM, juvenile onset diabetes; constitutes 5% to 10% of all diagnosed cases.

2. Type 2 diabetes: (usual age onset: ≥ 20 years); non-insulin dependent diabetes, NIDDM, adult onset diabetes (AOD); constitute 90% to 95% of all diagnosed cases, insidious onset, milder symptoms and ketosis resistant.

Risk Factor Summary: Older age, probable polygenetic disorders[5], obesity[6], positive family history, history of gestational diabetes, impaired glucose tolerance, physical inactivity[7], race/ethnicity. African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Pacific Islanders are at particularly high risk for type 2 diabetes.

MODY[8,9]: Maturity-onset Diabetes of the Young. These are rare cases of NIDDM that most commonly develops in thin adolescents and is associated with autosomal dominant inheritance and diminished or deranged insulin secretion. In the RW pedigree, polymorphic markers on chromosome 20q appear to determine the early abnormalities of insulin secretion, and not insulin resistance in persons predisposed to MODY[10]

3. Gestational diabetes:[11,12] Pregnancy-onset glucose intolerance develops in 2% to 5% of pregnancies but disappears when pregnancy is over. Even with mild, asymptomatic hyperglycemia, rigorous treatment, often with insulin is required to protect against fetal morbidity and mortality. Risk Factors: Occurs more frequently in the obese, African Americans, Hispanic/Latino Americans, American Indians, and persons with a family history of diabetes. Women who have had gestational diabetes have about a 40% increased risk for developing type 2 diabetes within 5 to 10 years.

4. Secondary diabetes: Accounts for 1% to 2% of all diagnosed cases of diabetes.

Risk Factors: Genetic Syndromes: lipodystrophy, myotonic dystrophy, ataxia, telangectasia; *Pharmaceuticals:* thiazides, steroids, phenytoin; *Malnutrition:* anorexia, starvation; *Pancreatic Disease:* hemochromatosis, pancreatectomy, pancreatic surgery; *Hormonal:* Cushing's syndrome, pheochromocytoma, acromegaly, gigantism.

5. Impaired glucose tolerance: A new diagnostic category characterized by fasting plasma glucose values of 110 to 125 mg/dl. This was formerly referred to as borderline, latent, subclinical, and chemical diabetes. It is estimated that 13.4 million persons, 7.0% of the population, have IGT; however one-third eventually develop type 2 diabetes. These patients are not at risk for most long term diabetic complications, but they are at risk for cardiovascular (macrovascular) complications.

THE NEW DIAGNOSTIC CRITERIA FOR DIABETES[13]

1. Overnight Fasting Plasma Glucose:

- Routine diagnostic screening test;

Table 1. Short Term Death Rates-DCCT Findings[23]

NIDDM Subset & Macrovascular Disease	~ Death Rate (%/y)
Newly diagnosed diabetes	1–3
Known duration = 5–20 y	5–8
Previous myocardial infarction	8–10
Previous amputation	10–12
Stroke	16

- Normal fasting plasma glucose: <110 mg/dL
- Impaired glucose tolerance: 110 to 125 mg/dL
- Diabetes mellitus: confirmed fasting plasma glucose ≥126 mg/dL.
- (Confirmation by repeat testing another day)

2. Random Plasma Glucose

- ≥200 mg/dL is diagnostic in the presence of classic symptoms of diabetes

3. 2-Hour Oral Glucose Tolerance Test

- ≥200 mg/dL, (diagnostic if confirmed on another day) performed according to World Health Organization standards

4. High Risk Pregnant Women*

- ≥25 years of age
- Greater than normal body weight
- Positive family history
- High prevalence ethnic group
- *Test for gestational diabetes during the 24th to 28th week

5. Glycosuria

Although glycosuria strongly suggests diabetes, urine testing should never be used exclusively because some persons have a low renal threshold for glucose.

LABORATORY MARKERS FOR THE DEGREE OF DIABETES CONTROL[14]

The objective of treatment is to regulate the blood glucose to as close to normal as possible to prevent or slow the development of acute and chronic complications and tertiary end-points of diabetes mellitus listed below.

Degree of control is the average level of blood glucose over time-elapsed

For underwriting, assessment of the degree of control over time-elapsed involves the following tests:

1. Glycated hemoglobin (Hemoglobin A1c, HbA1c, glycosylated hemoglobin, glycohemoglobin)[15,16]

Measures: glucose-hemoglobin combination is the clinical ''gold standard'' and primary indicator of degree of control. Reflects the average plasma glucose value during the prior 12 weeks. *It is highly sensitive.*

2. Fructosamine (glycated proteins)[17,18]

Measures: glucose-serum albumin combination; Reflects average daily serum glucose levels during the prior 2–4 weeks; *Highly specific.*

3. Fasting Plasma Glucose (fasting blood sugar, FBS)

Plasma glucose obtained after an overnight fast

A current FBS that is substantially worse than historical levels may indicate a worsening in the disease and should be underwritten cautiously

4. Random or postprandial (PP) glucose

Non-fasting plasma glucose
Little underwriting value

5. Urine glucose (glycosuria)

Little underwriting value due to differing renal thresholds

OVERVIEW OF MORTALITY, MORBIDITY, AND BURDENS OF DIABETES IN THE UNITED STATES[19,20,21,22] (see Table 1)

Metabolic

Diabetic ketoacidosis (DKA); indicates an acute insulin deficiency requiring exogenous-

ly administered insulin for survival; a shift to fat metabolism and difficult to manage ''brittle'' disease.

Hyperglycemia (high blood sugar); indicates poor compliance or inadequate treatment

Hypoglycemia (low blood sugar); indicates excessive medication or insufficient caloric intake

Macrovascular

Cardiac, cerebral and peripheral vascular complications secondary to the accelerated development of atherosclerotic disease in the large arteries resulting in angina, myocardial infarction, stroke, claudication with 7,000 amputations per year in the United States, and death rates 2 to 4 or more times higher than normal populations

Microvascular

Nephropathy and retinopathy secondary to damaged small vessels and other tissues by glucose metabolic products resulting in 40% new cases end-stage renal disease (ESRD) yearly and 12,000 to 24,000 new cases blindness per year

Neuropathic

Autonomic neuropathy, and orthostatic hypotension: mild to severe peripheral in 60% to 70% of diabetics resulting in impaired sensation, extremity pain, slowed digestion or diarrhea. Currently, there is no cure for diabetic neuropathy.

Hypertension

60% to 65% of diabetics are hypertensive; the coexistence of hypertension is a very unfavorable prognostic factor with mortality at or greater than 3 times that of normotensive diabetics;

Dental disease

Periodontal disease occurs in 30% type 1 diabetics age 19 or older.

Complications of pregnancy

Congenital malformation rate: preconception care − 0% to 5%, no preconception care − 10%.

Intra-uterine mortality rate: non-diabetic − 1.5%, diabetic − 3% to 5%.

Other complications

Hyperosmolar non-ketotic coma, acutely life-threatening,

All-cause illness susceptibility and premature mortality to influenza, pneumonia, etc.

Cost (United States, 1992);

Total (direct and indirect): $98.2 billion. Direct medical costs: $44.1 billion; Indirect $54.1 billion (disability, work loss, mortality etc).

PATTERNS OF SURVIVAL AND EXCESS MORTALITY

Objectives

1. Diabetes mellitus outcome indicators of premature mortality, morbidity, and shortened survival examined and analyzed in this section are: age of onset, disease duration, gender, degree of metabolic control, intensity of care, micro & macrovascular, neuropathic & infectious complications, and, co-morbid risk factors including alcohol abuse, build, hyperlipidemia, hypertension, & smoking.

2. Specifically reviewed are relevant historical and current clinical & statistical follow-up studies to:

Discern the basic mortality and survival associated with uncomplicated diabetes mellitus compared to defined populations.

3. Determine the additional mortality impact of co-morbid conditions on diabetic subgroups.

Historical Survey of Mortality & Survival by Age of Onset, Disease Duration, and Gender

Natural History of Diabetes Mellitus and the Determination of Basic Mortality: The

Table 2. Distribution by Age & Sex

Age group (y)	0–19	20–39	40–59	60–79	80 up	Total
Male	252	305	832	467	17	1871
Female	247	299	811	695	29	1982
Total number	499	505	1643	30.1	46	3853
Percent (%)	13.0	13.1	42.6	30.1	1.2	100.0

milestone Joslin Clinic, Equitable Life and Lincoln National multi-year prospective studies on select diabetic populations are historically reviewed and systematically compared with abbreviated meta-analysis in the search to discern inherent patterns of survival and mortality:

1. Joslin Clinic Study: 1939–1963[24]

Subjects Studied and Follow-up

3,853 patients (white Massachusetts residents—all others excluded) in five cohorts with early diagnosis of diabetes mellitus within one year of first Joslin Clinic Visit,

"Index years" of entry: July 1, 1939; 1944; 1949; 1954; Clinical follow-up every 18-months, 92.6% follow-up to October 1, 1993 (see Tables 2 through 4).

SUMMARY

- Age 0–20: excess mortality far higher than all other age groups combined; Hazard Ratio = 4.3,
- Age 20–79: mortality ratios decrease, but EDRs increase in both sexes,
- All Age Groups: female mortality is much higher than male mortality.
- EDRs increase with increasing disease duration.
- Cumulative Survival Ratios progressively decrease with increasing duration

2. Equitable Life Study: 1951–1970[25]

Purposes, Subjects Studied & Follow-up

- Analyze survival of uncomplicated diabetes by duration in applicants & policyholders
- 20-year follow-up on DECLINED as well as ISSUED applicants,
- 2,900 diagnosed diabetic applicants issued substandard policies,
- 7,633 diagnosed diabetic applicants were declined insurance,
- 9,919 out of 10,538 applicants (94.1%) were successfully traced to 1971 (see Tables 5 through 9)

CONCLUSIONS

MRs, as a measure of severity, tend to increase with disease duration,

- Declined group; 20-yr Cum MR = 395%
- Issued group; 20-yr Cum MR = 167%
- Proportional hazard; 2.4
- MRs, for a particular duration; more favorable for older age groups,

EDRs for all durations vary within narrow limits:

- Issued group: average EDR = 1.4 to 3.2/1,000/year
- Declined group: average EDR = 8.7 to 16/1,000/year
- Proportional hazard; 5.0

Build

- Underweight: highest MR; 485%
- Overweight: lowest mortality ratios; 260 & 290%
- Standard build: MR = 310%; EDRs—no significant variation by build class,

Hypertension

- All categories, higher MRs and EDRs
- Systolic hypertension is a more ominous predictor of mortality than diastolic

Table 3. *RESULTS:* Mortality Analysis by Age, Sex and Time Elapsed (Duration) Since Diagnosis: (adapted from Singer & Levinson)*

		Cumulative MR			Cumulative SR			EDR		
Age	Interval (y)	Male (%)	Female (%)	Average (%)	Male (%)	Female (%)	Average (%)	Male (%)	Female (%)	Average (%)
0–19	0–5	192	1360	776	99.6	96.9	98.3	0.8	6.2	3.5
	5–10	315	1070	693	97.7	95.5	96.6	3.8	3.0	3.4
	10–15	275	840	558	97.4	95.0	96	0.7	1.0	0.9
	15–20	465	1090	776	88.6	86.9	87.6	19	18	19
	20–25	490	1080	785	82.4	82.6	82.5	14	10	12
	0–25	490	1080	785	82.4	82.6	82.5	4.2	5.9	5.1
20–39	0–5	103	520	312	100	96.9	98.5	0.1	6.7	3.4
	5–10	142	350	246	98.5	95.7	97.1	2.9	1.9	2.4
	10–15	139	355	247	97.4	91.9	94.7	2.1	7.9	5
	15–20	175	300	238	89.8	91.1	90.5	16	1.4	8.7
	20–25	168	285	227	88.4	88.3	88.4	2.9	5.4	4.2
	0–25	168	285	227	88.4	88.3	88.4	3.5	4.9	4.2
40–59	0–5	140	168	154	97.1	96.7	96.9	5.9	6.5	6.2
	5–10	147	190	169	91.7	89.3	90.5	12	15	13.5
	10–15	152	197	175	83.2	78.7	81.0	19	23	21
	15–20	152	205	179	73.5	63.5	68.5	22	45	33.5
	20–25	152	205	179	68.0	54.5	61.3	31	28	30
	0–25	152	205	179	68.0	54.5	61.3	12	16	14
60–79	0–5	109	168	139	98.4	88.4	93.4	4.4	24	14.2
	5–10	120	167	144	86.8	74.8	80.8	24	31	27.5
	10–15	119	162	141	79.8	60.8	70.3	16	33	24.5
	15–20	120	163	142	63.4	38.2	50.8	38	73	55.5
	0–20	120	163	142	63.4	38.2	50.8	13	29	21

* (Basis of expected mortality: Massachusetts Life Tables)

Table 4. *CONCLUSIONS:* 0–25 year Cumulative Mortality (%) & Excess Death Rate Rate / 1,000

Age at	Mortality Ratios			Excess Death Rates		
Diagnosis	M*	F*	Av.	M	F	Av.
0–19	490	1080	785	4.2	5.9	5.1
20–39	168	285	227	3.5	4.9	4.2
40–59	152	205	179	12	16	14
60–79	120	163	142	13	29	21

Key: M* = male F* = female

3. Lincoln National 4th Major Reinsurance Study on Diabetes & Mortality: 1976–1995[26]

Purpose: Compare the current (1976–1995) diabetes underwriting outcome mortality experience to the prior studies of 1975, 1971 and 1961.

Subjects Studied and Follow-up

Issue years: 1965–1984
Number of policies: 11,176
Number of claims: 790
Policy years of exposure: 72,840
Maximum exposure per policy in years: 26
Average policy duration in years: 6.5

Classification of Insured Cases

- General cases: Treated diabetics without complication or comorbidity,
- Complicated cases: Treated diabetes with complications or comorbidities,
- Miscellaneous cases: Two categories;
- Diabetics treated with diet & insulin plus an oral hypoglycemic agent,
- Applicants not classifiable as general or complicated cases,
- Selected cases: General cases treated by

Table 5

Age at Application	<30	30–39	40–49	50–59	60 up	Total	Av. Age-y
Numbered issued	472	776	940	616	96	2900	41.2
Numbered declined	1615	1514	2001	1773	735	7638	42.2
Total number	2087	2290	2941	2389	831	10,538	41.9
Percent (%)	19.8	21.7	27.9	22.7	7.9	100.0	

Table 6. *RESULTS:* **Mortality by Age and Diabetes Duration Prior to Application; (Issued & Declined Cases)***

Age at Application	Duration (y)	MR (%)	Est. 7-y Surv. Rate	EDR
1–19	All	450	.9725	3.1
20–29	0–5	595	.9578	5.1
	5–10	985	.9335	8.8
	10–15	1770	.8791	17
	15–20	1590	.8917	15
	20 up	1640	.8853	16
	All Dur.	1090	.9246	10
30–39	0–5	315	.9536	4.6
	5–10	370	.9417	6.2
	10–15	820	.8791	16
	15–20	905	.8695	18
	20 up	1130	.8386	23
	All Dur.	545	.9187	9.8
40–49	0–5	295	.8993	9.9
	5–10	340	.8808	13
	10–15	335	.8803	13
	15–20	400	.8565	16
	20 up	415	.8597	16
	All Dur.	325	.8876	12
50–59	0–5	210	.8567	11
	5–10	320	.7829	24
	10–15	405	.7573	29
	15–20	425	.7242	34
	20 up	420	.7523	30
	All Dur.	235	.8224	16
60–69	0–5	210	.7667	20
	5–10	235	.7263	25
	10–15	330	.6338	44
	15–20	395	.5749	57
	20 up	260	.7451	25
	All Dur.	240	.7344	25

* (basis of expected mortality: Equitable Life Select & Ultimate Mortality Tables 1958–1963)

diet and insulin, good control, no risk factors (see Table 10).

COMMENT

The impact of diabetes is markedly higher in the 0–19 age category representing the severity of juvenile diabetes as compared to all other age groups. Mortality ratios successively diminish with increasing age-onset to age 60-years; At age 60 & up, mortality increases moderately (see Table 11).

COMMENT

- Above table reflects disease severity at any age at diagnosis
- Persistent mortality patterns are noted for each treatment regimen
- Rx by diet alone produced the lowest mortality
- Rx by diet & insulin—the highest mortality
- Rx by diet plus an oral agent—mortality intermediate between the above two

*( ) indicates actual number of claims (see Table 12)

COMMENT

- Rx by diet-alone: mortality crests & stabilizes at 12-years duration
- Rx by diet plus insulin: mortality crests & stabilizes at 12-years duration
- Rx by diet plus oral agent: mortality becomes catastrophic beyond the 12-year mark suggesting that disease duration contributes to severity by the development of complications in this category (see Table 13)

Table 7. 20-year Cumulative Mortality & Survival Analyses *by Disease Duration & Insurance Action at the Time of Application*

Basis of expected mortality: Equitable Life Select and Ultimate Mortality Tables 1958–1963

	Issued Group			Declined Group		
Interval-y	MR%	EDR	7-y Surv Rate	MR%	EDR	7-y Surv Rate
0–5	128	1.4	.9561	300	12	.8768
5–10	210	5.6	.9279	385	15	.8675
10–15	265	6.1	.9337	635	22	.8316
15–20	255	6.6	.9258	645	25	.8109
20 up	235	5.8	.9313	665	24	.8204
All	167	3.2	.9453	395	16	.8589

Table 8. 20-year Cumulative Mortality & Survival Analyses *by Post-Application Duration of Follow-Up*

	Issued Group			Declined Group		
Interval-y	MR%	EDR	SR%	MR%	EDR	SR%
0–2	167	1.4	99.7	440	8.7	98.3
2–5	130	0.5	99.6	410	14.0	94.3
5–10	152	3.9	97.7	420	21.0	84.9
10–15	168	9.0	93.3	405	24.0	75.0
15–20	167	8.1	89.6	395	18	68.5
All 0–20	167	3.2	89.6	395	16	68.5

COMMENT

- Mortality, reflecting treatment-dependent severity, is stable in the 1st interval,
- Mortality rises in successive durations indicating rapid blunting of the effects of risk selection
- Mortality continue to rise differentially in the diet/insulin treated group after the 15th year (see Table 14)

COMMENT

- Mortality is the highest in the underweight vs. normal weight sub-group (345% vs. 220%)
- Mortality is minimally more in the overweight vs. normal weight (238% vs. 220%) (see Table 15)

COMMENT

- Highest excess mortality: extreme builds & renal complications (albuminuria),
- Rx with oral agents & insulin reflect severe disease: 601% mortality.

Summary: Three-Study Comparison of Mortality & Survival by Age-onset, Duration, and Sex

AGE ONSET

Joslin Clinic: 25-year clinical follow-up

- Disease severity measured by age onset & duration since diagnosis,
- Below age 20, excess mortality far exceeds that of all other age groups,
- Female mortality was significantly greater & long-term survival significantly less than males in almost all age/duration categories,

From Age 20–79

- Mortality ratios decrease but excess death rates increase with advancing age,

Table 9. Comparative Experience by Build and Blood Pressure (Issued and Declined Cases, All Ages and Durations Combined)

Category	MR%	EDR	7-y Surv. Rate	Hazard
Standard Build	310	11	.8955	
Underweight	485	12	.8981	1.56
10–20% overweight	260	12	.8708	
21% overweight up	290	13	.8660	
Blood Pressure				
S<140, D<90	265	8.2	.9122	
S 140–159, D<90	335	18	.8296	1.26
S≥160, D<90	505	39	.7046	1.91
S<140, D 90–99	375	15	.8625	1.42
S 140–159, D 90–99	420	23	.8048	1.58
S≥160, D≥90–99	460	37	.7100	1.74
S<160, D≥100	275	12	.8796	1.04
S≥160, D≥100	580	33	.7502	2.19
BP Summary				
Normotensive	265	8.2	.9122	
Av. All HTN (S, D, Both)	421	25.3	.7916	1.59

Table 10. *RESULTS: Mortality by Age at Diagnosis—General Cases**

Age at Diagnosis	Mortality Ratio (%)
0–19	524
20–29	412
30–39	202
40–49	236
50–59	176
60 & up	215

* Basis of expected mortality: 1975–80 Select and Ultimate Tables

- Survival ratios inordinately decrease with advancing age,
- Progressively better prognosis in both sexes with advancing age.

Equitable Life: 20-plus years follow-up

- Study included both issued and declined applicants for life insurance,
- Below age 30, excess mortality exceeds that of all other age groups,
- Mortality ratios decrease but excess death rates tend to increase with advancing age at application,
- 20-year cumulative survival:

Issued: 89.6%; declined: 68.5% (indicating the value of risk selection),

Lincoln National Reinsurance: 20-year follow-up

- Disease severity measured by age onset:
- Below age 20, excess mortality far exceeds that of all other age groups,
- Mortality decreases with advancing age of diagnosis to age 60 when a moderate increase occurs.

DURATION

Joslin Clinic

- Mortality remained level with time elapsed (increasing duration) from diagnosis,
- Excess death rates significantly increase with both disease duration and advancing age,
- Female mortality, both mortality ratios and excess death rates, exceeds that of males,
- Cumulative survival progressively decreases with increasing disease duration.

Table 11. *Mortality by Age at Diagnosis & Treatment Type—General Cases*

Age at Dx	Diet Alone	Diet & Oral Agent	Diet & Insulin	All
<40	118% (11)*	326% (24)	426% (98)	335% (133)
40–49	153% (34)	303% (52)	366% (20)	236% (106)
50 & up	138% (45)	242% (71)	— (4)	185% (120)
All	140% (90)	273% (147)	390% (122)	240% (359)

Table 12. *Mortality by Duration at Issue & Treatment Type—General Cases*

Duration at Issue	Diet Alone	Diet & Oral Agent	Diet & Insulin	All
0–6	139% (67)	250% (91)	355% (33)	203% (191)
7–12	143% (17)	245% (31)	423% (36)	255% (84)
13 & up	143% (6)	***523% (25)***	392% (53)	374% (84)
All	140% (90)	273% (147)	390% (122)	240% (359)

Table 13. *Mortality by Policy Duration & Treatment Type—General Cases*

Policy Duration	Diet Alone	Diet & Oral Agent	Diet & Insulin	All
1–5	96% (19)	249% (40)	220% (23)	177% (82)
6–10	164% (34)	323% (51)	335% (34)	255% (119)
11–15	178% (25)	346% (38)	587% (33)	313% (96)
16 up	123% (12)	164% (18)	629% (32)	240% (62)
All	140% (90)	273% (147)	390% (122)	240% (359)

Table 14. *Mortality by Relative Weight and Treatment Type—General Cases*

Relative Weight*	Diet Alone	Diet & Oral Agent	Diet & Insulin	All
Underweight	188% (11)	318% (14)	497% (34)	345% (54)
Normal	123% (43)	266% (74)	329% (63)	220% (180)
Overweight	154% (36)	273% (59)	470% (25)	238% (120)
All	140% (90)	273% (143)	390% (122)	240% (359)

Table 15. *Mortality in Complicated and Miscellaneous Cases*

Complication	Mortality Ratio (%)	Number
Hypertension, current or history	248	110
Circulatory impairment	253	34
Albuminuria	388	19
General or extreme builds	426	51
Endocrine, nervous, other	331	42
Multiple conditions indicated	311	77
All	297	333
Miscellaneous Cases		
Diabetes merely suspected	170	15
History only of diabetes	149	16
Oral medication & insulin	601	10
Cases not classified	315	57

Equitable Life

Mortality and survival by age & duration prior to application

- Issued Group: MRs increased from 128% to 265% up to 15-years prior to application, EDRs increased from 1.4 to 6.6 extra deaths per 1,000 over 15-years,
- Declined Group: MRs are consistently 2.5 to 3.0 times greater on declined cases EDRs increased to about 25 extra deaths per 1,000 over 20-years,

Mortality and survival by post insurance duration of follow-up

- Issued Group: Cumulative mortality (MRs) remained stable at 167% over 20-years,

Table 16. Authors Abbreviated Meta-analysis of Historical Mortality by Age at Dx & Disease Duration

Age	Study	0–5	6–10	11–15	16–20	>20
0–19	Joslin	776	693	558	776	785
	Equitable	450	450	450	450	450
	Lincoln	355	423	392	(390)	(390)*
	Average	527	522	467	613	618
20–39	Joslin	312	350	247	238	227
	Equitable	455	—	—	—	—
	Lincoln	203	335	335	374	374
	Average	323	343	291	306	300
40–59	Joslin	154	169	175	179	179
	Equitable	253	339	370	413	418
	Lincoln	211	211	(523)	(523)	273
	Average	206	237	273	296	290
60–79	Joslin	139	144	141	142	142
	Equitable	210	235	330	395	260
	Lincoln	185	185	(523)	(523)	273
	Average	178	188	236	269	225

* figures in parenthesis not used in calculation

EDRs increased modestly to 8.1 deaths per 1,000 at 29-years,
SRs decreased from 99.7% to 89.6% with follow-up duration to 20-years.

- Declined Group: Higher initial MRs & EDRs remained stable,
  SRs diminished to 68.5%.

Lincoln National Reinsurance

Mortality by disease duration at issue & treatment type (general cases)

1. Diet alone: Lowest mortality, stable in three successive intervals, average 140%,

2. Diet & insulin: Highest mortality overall, MRs increase to 12-years duration, then stabilize, Average mortality is 390%,

3. Diet & oral agent: Stable mortality to 12-years (245%), 523% mortality ratio after 12th year, Increases abruptly to 523% by 13th year of disease duration,

(NOTA BENE: Advancing duration is associated with increasingly higher mortality & morbidity in this treatment category)

Mortality by policy duration and treatment type (general cases)

1. Diet alone: Mortality increased with duration but overall was stable at 140%

2. Diet & oral agent: Mortality increased from 249% to 346% at 15 years, Overall 20-year mortality averaged 273%,

3. Diet & insulin: Mortality rose from an initial 220% to 629% at 16-years & beyond. Beneficial effects of selection dissipate rapidly in this Rx category (see Table 16 and 17).

Current Age, Sex & Duration-specific SMRs for Diabetes Mellitus: Berger 1999[27]

OBJECTIVE: analyze the incidence, prevalence and mortality of diabetes in a population of 280,539 inhabitants and determine Standardized Mortality Ratios (SMRs)

STUDY DESIGN: the incidence, prevalence, and deaths from diabetes at all ages of a prospectively followed population in the county of Skaraborg, Sweden, since 1991 (see Table 18).

RESULTS

1. Annual incidence of diabetes per 100,000 inhabitants (mean ± 95% CI) in 1991–1995:

- Type 1 diabetes; 14.7 ± 3.2diagnosed at 24.1 ± 2.2 years of age,
- Type 2 diabetes; 265.6 ± 16.1 diagnosed at 66.6 ± 0.6 years of age.

Table 17. Three-Study Composite Relative Risk (%) Associated with Oral Agent or Insulin-treated Diabetes Mellitus by: Age at Diagnosis & Disease Duration

*Experience of the Joslin Clinic 1939–1963; Equitable Life 1951–1970; Lincoln National 1976–1995**

Age	Disease Duration (years)					
Onset	0–5	6–10	11–15	16–20	20 up	All
0–19	427	422	367	513	518	449
20–39	223	243	191	206	200	213
40–59	106	137	173	196	190	160
60–79	78	88	136	169	125	119

* Excess Mortality of Diabetes Mellitus Controlled by Diet Alone − 40%

- Incidence of type 2 was significantly higher in men ($P < 0.001$),
- No significant change in the age at diagnosis,

2. Prevalence of diabetes increased by 6% each year (although the incidence & age at Dx were constant).

3. Relative mortality risk for diabetic patients:

- Almost four times higher than expected,
- Median age at death; *increased significantly* from 77.2 to 80.2 years ($P < 0.05$)

CONCLUSIONS

Prevalence but not incidence of diabetes increased from 1991–1995,
Although diabetics showed a high relative mortality, increased survival apparently explains the increase in prevalence of diabetes in Skaraborg, Sweden.

COMMENTS

- The difference between age 'age at diagnosis' and 'actual age' is an indicator of DM duration,
- Relative risk for death by age at diagnosis, actual age (marker for disease duration) and sex, pattern the order of magnitude of the composite relative risk developed in the abbreviated meta-analysis of the Joslin Clinic, Equitable Life, and Lincoln National Life studies above.

Table 18. *OUTCOMES:* Relative mortality risk (SMRs) for diabetics by sex, age at diagnosis, and actual age

Actual Age (years)		Age at diagnosis (years)				
		0–19	20–39	40–59	60–79	80–99
0–19		7.1 (2.2–22.1)				
	M	3.6 (0.5–26.2)				
	F	12.7 (3.1–52.0)				
20–39		5.6 (2.6–11.9)	5.7 (2.3–13.8)			
	M	3.4 (1.1–10.8)	3.3 (0.8–13.4)			
	F	10.4 (3.8–28.5)	10.8 (3.4–34.3)			
40–59		7.8 (5.2–11.7)	3.1 (2.0–4.7)	3.5 (2.7–4.6)		
	M	7.3 (4.3–12.2)	3.2 (1.9–5.2)	3.3 (2.4–4.5)		
	F	8.3 (4.3–16.2)	2.6 (1.2–5.8)	3.6 (2.2–5.9)		
60–79		3.4 (1.9–6.1)	2.8 (2.0–3.8)	1.7 (1.5–1.9)	1.6 (1.5–1.8)	
	M	3.3 (1.6–6.8)	2.5 (1.7–3.7)	1.4 (1.2–1.6)	1.5 (1.3–1.7)	
	F	3.3 (1.2–9.0)	3.0 (1.8–4.9)	2.0 (1.7–2.4)	1.8 (1.3–2.1)	
80 +		0.7 (0.2–3.0)	1.2 (0.9–1.6)	0.9 (0.8–0.9)	1.1 (0.9–1.2)	
	M	1.0 (0.7–1.5)	1.0 (0.7–1.5)	0.8 (0.7–0.9)	1.0 (0.8–1.1)	
	F	1.3 (0.2–10.8)	1.4 (0.9–2.0)	0.9 (0.8–1.0)	1.1 (1.0–1.3)	
Total mean		6.0 (4.5–8.0)	3.1 (2.4–3.9)	2.1 (1.9–2.4)	1.2 (1.2–1.3)	1.1 (0.9–1.2)
	M	4.4 (3.0–6.5)	2.4 (1.8–3.1)	1.9 (1.7–2.1)	1.1 (1.0–1.2)	1.0 (0.8–1.1)
	F	8.7 (5.5–13.6)	4.4 (3.0–6.5)	2.3 (2.0–2.7)	1.4 (1.2–1.5)	1.1 (1.0–1.3)

Data are means (95% Confidence Intervals)

Prognosis of Type 1 DM[28]

1. Life expectancy continues to improve & survival is longer since the 1940s and earlier,

2. Epidemiologic data are available to 1980 but at this point, *continuing prospective studies must continue another 40-years and beyond* to ultimately and scientifically validate the beneficial results of current therapies.

3. The goal of good control has now a very definitive objective with precise tools: Daily capillary blood sugar with measurement of glycated hemoglobin.

4. The DCCT for type 1 and UKPDS for type 2 clinical studies: Recently scientifically validated the view that intensive insulin treatment, regular measurement of glycohemoglobin and daily use of capillary blood sugar effect good glycemic control & exerts positive effect on limiting microangiopathy, its associated morbidity & mortality, & enhancement of quality of life.

5. Increasing experience of healthy long-term survivors, after 40–50 years of type 1 diabetes.

Prognosis of Type 2 DM

1. With disease onset after age 60 and no complications, comorbidities or risk factors, diabetes has little effect on longevity.

2. The UKPDS clinical study: Additional secondary risk factors of obesity, atherosclerosis, and dyslipidemia can also benefit, although to a lesser degree, from modern approaches to secondary prevention.

MORTALITY & SURVIVAL ASSOCIATED WITH DEGREE OF CONTROL, COMPLICATIONS AND COMORBIDITIES

General: A similar spectrum of metabolic, microvascular, macrovascular, neuropathic and other complications accompany all forms of diabetes mellitus to greater or lesser degree. However the morbidity and mortality risk of co-morbid cardiac, peripheral & cerebrovascular, and other impairments associated with diabetes is profound when compared to their underlying risk in the general population.

Laboratory Markers of Control and Glycemic Goals: Monitoring and control of glycemic status is the capstone of diabetes care. Since hyperglycemia is the defining hallmark of the diabetic state, determinations of mean or average fasting glucose levels over weeks and months provide the patient and health care team with an objective measure of glycemia over an extended period of time useful for assessing the efficacy of therapy and to make adjustments in diet, exercise, and medications to achieve the best possible glucose control.

Glycated hemoglobin (GHb) testing[29], also commonly referred to as glycosylated hemoglobin, glycohemoglobin, HbA1c, or HbA1, is a term used to describe a stable hemoglobin-glucose chemical bond, which is directly proportional to the ambient glucose concentration. The level of GHb in a blood sample provides a glycemic history of the previous 120 days, the average red blood cell lifespan.

Clinical implications of hyperglycemia[30]

1. Potential for tissue hypoxia and resultant diabetic microangiopathy caused by the increased affinity and binding of oxygen by glycohemoglobin.

2. Routine use of GHb testing is recommended in all diabetic patients as a surrogate of mean blood glucose determination for two reasons:

3. Determine the degree of glucose control at initial assessment,

4. Facilitate routine continuing care.

Glycated serum proteins (GSPs), fructosamine[31], measures the chemical combination (glycation) of glucose molecules with serum albumin. Fructosamine determinations reflect time-integrated average glucose concentrations over the 2- to 4-week half life of these serum proteins.

Sensitivity and Specificity of GHbs and GSPs[32] *Subjects Studied, Follow-up, Results and Conclusions:* In a study of a sample population of 1,000 consecutive HbA1c reflexes at HORL

Table 19. Reference Ranges for Glycemic Control: Glycated Protein Testing[33]

Diabetic Population: HbA1c Values ≅ Average Fasting Plasma Glucose Levels.♣

HbA1c	FPG mg%	mM/L	HbA1c	FPG mg%	mM/l
6	106	5.83	14	338	18.59
7	135	7.425	15	367	20.185
8	164	9.02	16	396	21.78
9	193	10.615	17	425	23.375
10	222	12.21	18	454	18.59
11	251	13.805	19	483	26.565
12	280	15.4	20	512	28.16
13	309	16.995			

♣ This analysis is for 400 diabetic patients. The samples were collected in a clinic and analyzed by CRL. The line is: Y = a + b(X); a = −68, b = 29.

Table 20. Insurance Population: Fasting and Non-Fasting Plasma Glucose♣

HbA1c	Pl. Glucose%	mM/L	HbA1c	Pl. Glucose%	mM/L
6	121	6.655	14	313	17.215
7	145	7.975	15	337	18.535
8	169	9.295	16	361	19.855
9	193	10.615	17	385	21.175
10	217	11.935	18	409	22.495
11	241	13.255	19	433	23.815
12	265	14.575	20	457	25.135

♣ This analysis is based on 8,000 HbA1c values: The line is: Y = a + b(X); a = −23, b = 24

(Home Office Reference Laboratory, Lenexa, Kansas), the following results were noted:

1. 771 samples had an elevated glucose result (>115 mg/dl to age 55, and >125 mg/dl over age 55).
2. Of these 771 samples, only 31.5% (243) also had elevated HbA1c.
3. 466 specimens had elevated fructosamine (>2.1 mM/L); of these, 57.7% (269) had elevated HbA1c.
4. There were 229 HbA1c reflexes that were the result of an elevation in fructosamine alone.
5. Sixty-one resulted in an elevated HbA1c.

CONCLUSION

1. In the short term, using HbA1c as the most sensitive indicator of glycemic control, fructosamine was almost twice as specific as glucose in detecting this state.
2. The overall correlation between fructosamine and HbA1c was 78.5%.
3. The correlation between glucose levels and HbA1c was only 41% (see Table 19 through 21).

Glycohemoglobin Assay Methods[36,37]

In keeping with the need to standardize glycohemoglobin test results so that clinical laboratory results are comparable to those reported in the Diabetes Control and Complications Trial (DCCT) where relationships to mean blood glucose and risk for vascular complications have been established, Clinical Reference Laboratory, Lenexa, Kansas used assay methods based primarily on structural differences as approved by NGSP (Immunoassay, BMC Tina Quant). Occasionally, approved methods based on charge differences (Ion-exchange HPLC, Bio-Rad Diamat) were also used.

Table 21. Measures of Control—Comparative Parameters[34,35]

Indicator	Normal				
HbA1c %	≤6.0	6.1–8.0	8.1–9	9.1–10	>10
Fructosamine mmol/l	≤2.1	2.2–2.5	2.6–2.9	3.0–3.3	>3.3
FBS mg/dl	<110	111–164	165–193	194–222	>222

Table 22. *RESULTS:* **Proportional Hazards models for a 1% baseline change in HbA1c; Hazard Ratios (HR) at the 95% confidence limit (CI) as follows**

<30-year old:	Underlying cause of death (diabetes):	HR = 1.25; (CI, 1.13 to 1.38),
	Ischemic heart disease:	HR = 1.18; (CI, 1.00 to 1.40),
	All causes:	HR = 1.12; (CI, 1.04 to 1.21),
>30-year old:	Diabetes:	HR = 1.32; (CI, 1.21 to 1.43),
	Ischemic heart disease:	HR = 1.10; (CI, 1.04 1.17),
	Stroke:	HR = 1.17; (CI, 1.05 to 1.30),
	Cancer:	HR = 0.99; (CI, 0.88 to 1.10).
	All causes:	HR = 1.12; (CI, 1.08 to 1.16).

Hyperglycemia as a Risk Factor for Death: Is there a glycemic threshold for mortality risk?

Moss et al[38] reported on a cohort-design based in a primary care setting. Participating were:

1. 996 diabetics younger than 30-years old (median follow-up 10-years); Mean HbA1c = 12.6%,
2. 1,370 diabetics, age 30-years or older (median follow-up 8.3-years); Mean HbA1c = 11.1%.
3. The main outcome measure was cause-specific mortality as determined from death certificates (see Table 22).

CONCLUSIONS: Glycosylated hemoglobin levels are significantly related to mortality from diabetes.

Balkau et al[39] have recently provided current 1998 information on the relationship of glycemia to mortality in initially non-diabetic adults in a 20-year mortality study of non-diabetic, working men, age 44–55 years, in three European cohorts known as the:

- Whitehall Study (n = 10,025),
- Paris Prospective Study (n = 6,629),
- Helsinki Policeman Study (n = 631).

These men were identified by their 2-h glucose levels following an oral glucose tolerance test and by the absence of a prior diagnosis of diabetes. As the protocol for the oral glucose tolerance test and methods for measuring glucose differed between studies, mortality was analyzed according to the percentiles of the 2-h and fasting glucose distributions, using the Cox's proportional hazards model.

RESULTS: Men in the upper 20% of the 2-h glucose distributions and those in the upper 2.5% for fasting glucose had a significantly higher risk of all-cause mortality in comparison with men in the lower 80% of these distributions, with age-adjusted hazard ratios of 1.6 (95% CI 1.4–1.9) and 2.0 (1.6–2.6) for the upper 2.5%. For death from cardiovascular and CHD, men in the upper 2.5% of the 2-h and fasting glucose distributions were at higher risk, with age-adjusted hazard ratios for CHD of 1.8 (1.4–2.4) and 2.7 (1.7–4.4), respectively.

CONCLUSIONS: If early intervention aimed at lowering blood glucose concentrations can be shown to reduce mortality, it may be justified to lower the levels of both 2-h and fasting glucose, which define diabetes.

IN SUM: Harris and Eastman[40] commenting on this investigation found this to be very large and long term study indicating that glycemia can be implicated as a risk factor only for all-cause mortality in men in the highest 2.5th percentile of fasting glucose, for heart disease mortality in men in the highest 2.5th percentile of 2-h glucose, and for all-cause and cancer mortality in the >20th percentile of 2-h glucose.

Hyperglycemia: Risk for Microvascular Complications & Mortality

Diabetes Control & Complications Trial Research Group, Type I DM and Degree of Control[41]

The **DCCT** is a 10-year study conducted by the National Institutes of Health involving

Table 23. Risk for Development & Progression of Long-term Complications of Diabetes with Intensive versus Conventional Therapy

	Primary Prevention			Secondary Intervention			Both Cohorts Risk
Complications	ConRx rate/100 pt-yr	IntRx pt-yr	Risk Red %	Con Rx rate/100 pt-yr	IntRx pt-yr	Risk Red %	Reduction %
Retinopathy	4.7	1.2	76	7.8	3.7	54	63
Urine Alb Excretion							
≥40 mg/24 hr	3.4	2.2	34	5.7	3.6	43	39
≥300 mg/24 hr	0.3	0.2	44	1.4	0.6	56	54
Clinical neuropathy (5 years)	9.8	3.1	69	16.1	7.0	57	60
Macrovascular Dis.	0.8	0.5	41	(albeit not significantly)			

1,441 volunteers ages 13–39 with insulin–dependent diabetes mellitus (IDDM) at 29 medical centers in the United States and Canada, which demonstrated that the maintenance of near-normal blood glucose levels was the key factor in the salutary effect of intensive therapy (versus conventional therapy) for the control of microvascular complications caused by the development of microangiopathy.

The **DCCT** quantitatively defined the relationship between GHb and average glycemia. Since GHb assays are not standardized among laboratories, however, it is not yet possible for health care providers to relate the GHb test result to average blood glucose except in a general way. If it were only a question of normal versus abnormal test values, standardization of GHb assays would not be nearly so important: each laboratory could establish a non-diabetic reference range as ''normal'' or ''abnormal.'' Instead, GHb values in patients with diabetes are a continuum . . . ranging from normal in a small percentage of patients, whose average blood glucose is normal or close to normal, to markedly elevated values . . . reflecting an extreme degree of chronic hyperglycemia.

DCCT general guidelines in relating GHb to mean blood glucose are as follows:

- Highly correlated ($r = 0.80$, $P < 0.0001$), linear relationship between average glycemia and GHb.
- Roughly, each 1% increase in GHb was related to a 30 mg/dl (1.99 mM/L) increase in average blood glucose.

The DCCT was not able to study the dose-response of blood glucose levels on the occurrence of complications; rather, the risk for development and progression of the chronic microvascular complications of diabetes—*retinopathy, nephropathy, and neuropathy*—exists on a continuum closely related to the degree of glycemic control, as measured by glycohemoglobin (GHb) determinations.

DCCT Results: See Table 23.

CONCLUSIONS OF THE DCCT STUDY

1. The relation between the rate of development of retinopathy and glycemic exposure, expressed as the HbA1c value over time showed a continuously increasing risk of sustained progression with increasing mean glycosylated hemoglobin values.

2. Similarly, the risk of severe hypoglycemia increased continuously with lower monthly glycosylated hemoglobin values.

3. Secondary analyses do not support the existence of a specific target value for glycosylated hemoglobin at which the benefits of intensive therapy are maximized and the risks minimized.

4. Although patients with non-insulin-dependent diabetes mellitus (NIDDM) were not studied, other reports indicate that hypergly-

Table 24. *RESULTS:* Lifetime (Relative) Risk for Blindness and End-Stage Renal Disease by HbA1c Level

	Age Onset of Diabetes* τ							
	45 years		55 years		65 years		75 years	
%HbA1c	Bl	ESRD	Bl	ESRD	Bl	ESRD	Bl	ESRD
7	0.3	2.0	0.1	0.9	<0.1	0.3	<0.1	0.1
8	1.1	2.7	0.5	1.3	0.2	0.5	<0.1	0.1
9	2.6	3.5	1.2	1.6	0.5	0.6	0.1	0.1
10	5.0	4.3	2.5	2.1	1.0	0.8	0.3	0.2
11	7.9	5.0	4.4	2.5	1.9	0.9	0.5	0.2

* transition probability from retinopathy to blindness
τ transition probability from proteinuria to end-stage renal disease

cemia is associated with the presence or progression of complications in NIDDM.

5. Diminished cumulative risk for microvascular complications with ***optimized glycemic control:***

Mean glucose values of ≤155 mg/dl (≤8.5 mmol/L);
Normal FBS = <110 mg/dL or 6.05 mmol/l;
Hemoglobin A1c levels of ≤7.2%, (≤6.05% = normal).

Vijan Markovian Model and Type II Diabetes Mellitus[42]

Vijan describes a Markovian model that was constructed to analyze the risk for retinopathy and nephropathy in patients with **Type 2 diabetes** as defined in the DCCT. The simulated patients progressed sequentially through increasingly severe disease states; death could occur in any disease state.

Blindness: defined as corrected visual acuity of 20/200 or worse and was restricted to blindness caused by retinopathy or its sequelae (for example, macular edema).

Microalbuminuria: defined as an albumin level of 30 to 300 mg/g of creatinine;

Proteinuria: defined as a protein level greater than 300 mg/g of creatinine;

End-stage Renal Disease: defined as renal disease requiring dialysis or transplantation (see Table 24).

Results for Patients Who Become Blind

Age onset 45 years; average time spent blind was 11 years;
Age onset 55 years; average time spent blind was 8.3 years;
Age onset 65 years; average time spent blind was 5.2 years;
Age onset 75 years; average time spent blind was 3.2 years.

Results for Patients Who Develop End-stage Renal Disease

Age onset 45 years; average time spent in this disease state was 5.2 years;
Age onset 55 years; average time spent in this disease state was 4.6 years;
Age onset 65 years; average time spent in this disease state was 4.0 years;
Age onset 75 years; average time spent in this disease state was 2.7 years.

CONCLUSIONS: Highest risk for developing end-stage outcomes:

1. Younger age onset diabetes,
2. Poor glycemic control: HbA1c level ≥8.0%.

Hyperglycemia: Risk for Macrovascular Complications & Mortality

Andersson and Svardsudd[43] studied the influence of long-term glycemic control on ma-

crovascular mortality in a cohort totaling 441 newly detected type II diabetic individuals diagnosed between 1972 and 1987 and followed until 31 December 1989.

METHODS: Mortality rates were age-standardized against the Swedish national population of 31 December 1986 using 5-year age intervals. Survival analyses were performed using the Cox proportional hazards regression method with P values <5% accepted as indicating significance.

RESULTS: The levels of characteristics significantly related to mortality, together with other clinical characteristics, are shown in Table 13 for the surviving and deceased type 2 diabetic patients (see Tables 25 and 26):

CONCLUSIONS: ***Mortality and Morbidity***

1. There was no obvious threshold level distinguishing good from poor FBG values,
2. The lower the FBG levels, the better the outcome.
3. Diabetic subjects with average long-term FBG ≥7.8 mmol/l (141mg/dl)
4. All-cause mortality rate (Relative Risk) of 1.4, and, Cardiovascular Relative Risk of 1.6;
5. 5% & 60% respectively higher mortality versus diabetic subjects with average FBG < 7.8 mmol/l.
6. All-cause and cardiovascular mortality rose with less long-term metabolic control in all age groups independent of sex and treatment modalities.
7. Using Pitman's nonparametric permutation test, the results showed a significant positive correlation between average FBG and survival whether or not confounders present at baseline—(age at diagnosis, heart disease, cerebrovascular disease, or kidney disease)—were taken into account (P = 0.0001).
8. *Long-term Survival Analysis* (incident cases):

Average FBG <6.7 mmol/l: 10-year survival ≅72%

Average FBG ≥10.0 mmol/l: 10-year survival ≅62%.

Impact of Impaired Glucose Tolerance on Cardiac Function[44]

The importance of the Celentano study is that it was the first to provide data on abnormal cardiac function and structure in patients with only minor abnormalities of glucose homeostasis—impaired glucose tolerance (IGT)—using well standardized diagnostic criteria. Specifically, they found that ***left ventricular end-systolic dimension,*** indexed to body surface area, was greater in those with NIDDM ($p < 0.05$) and in those with impaired glucose tolerance ($p < 0.05$) with respect to normo-glycemic persons (1.94 ± 0.29 versus 1.76 ± 0.31) independent of the confounding role of myocardial ischemia, body weight, and blood pressure.

Metabolic Syndrome X (Insulin Resistance)[45,46]

The combination of insulin resistance, abnormal glucose tolerance, dyslipidemia and hypertension has been termed metabolic syndrome X. Despres and colleagues[47] have concluded that high fasting insulin concentrations appear to be an independent predictor of ischemic heart disease but evidence does not demonstrate conclusively that improved glucose tolerance lowers the risk of CHD. Regenauer[48] discussed the epidemiology and prognostic aspects of syndrome X concluding that extra mortality rates of the individual impairments should not be applied on a purely additive basis. *At this time prudent risk assessment should consider the adequate control and stability of the individual impairments while also assessing the status of the cardiovascular system.*

UKPDS and Degree of Control (Summary of Results)[49,50,51,52,53,54,55,56,57,58]

- No patients with NIDDM were included in the DCCT.
- The United Kingdom Prospective Diabetes Study (UKPDS) was organized to evaluate the effect of intensive therapy on outcomes in Type 2 diabetes.

Table 25. Clinical Characteristics of Type 2 Diabetics by Vital Status

	Survivors	Deceased
Number	250	161
Men (%)	50.0 (43.8–56.2)	52.2 (44.5–59.9)
Age at diagnosis (years)	62.9 (61.5–64.4)	71.8 (70.3–73.3)
Mean follow-up time (years)	8.6 (8.1–9.2)	5.6 (5.0–6.1)
Average FBG (mmol/l)	8.2 (7.9–8.4)	8.8 (8.5–9.2)
Average BMI (kg/m-squared)	28.9 (28.3–29.5)	27.7 (27.4–28.1)
Diagnosis (%)		
Cardiovascular disease	44.4 (38.2–50.6)	80.7 (74.6–86.8)
Cerebrovascular disease	10.0 (6.3–13.7)	23.0 (16.5–29.5)
Peripheral vascular disease	5.6 (2.8–8.4)	9.9 (5.3–14.5)
Nephropathy	5.6 (2.8–8.4)	12.4 (7.3–17.5)
Hypertension	66.0 (60.1–71.9)	58.4 (50.8–66.0)
Type of diabetes treatment (%)		
Diet only	50.0 (43.8–56.2)	46.8 (39.0–54.6)
Tablets	44.4 (38.2–50.6)	48.1 (40.3–55.9)
Insulin	5.6 (2.8–8.4)	5.1 (1.6–8.6)

95% CIs are given in parentheses. Average FBG and BMI denote values recorded during the whole study period. A diagnosis of concomitant disease denotes any recording of the disease during the study period.(8.2 mmol/l ≅149 mg glucose/dl; 8.8 mmol/l ≅160 mg/dl).

OVERALL RESULTS

1. The type 2 group with its additional secondary risk factors—obesity, atherosclerosis, dyslipidemia—also benefit, although to a lesser degree, from the modern approaches to secondary prevention,

2. Standardized mortality ratios for 5,071 patients recently diagnosed with NIDDM compared with general population indicate poorer prognosis with disease duration in males and females[59] (see Table 27),

In the Steno type 2 randomized study[60] (Steno Diabetes Centre, Copenhagen, Denmark), Gaede and co-workers carried out a randomized, open, parallel trial of stepwise intensive treatment or standard treatment of multifactorial risk factors in microalbuminuric patients with NIDDM, mean age 55.1 years. This included behavior modification and pharmacological therapy targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria with 3.8 years clinical follow-up.

RESULTS

Multifactorial intensive therapy group versus the standard group had significantly lower rates of progression to:

Nephropathy: odds ratio 0.27 (95% CI, 0–10–0.75)

Retinopathy: odds ratio 0.45 (95% CI, 0.21–0.95)

Autonomic neuropathy: odds ratio 0.32 (95% CI, 0.12–0.78)

CONCLUSION

Intensified multifactorial intervention in patients with type 2 diabetes and microalbuminuria has beneficial effects on long-term complications.

UKPDS Mortality

CAUSE-SPECIFIC: Myocardial Infarction-specific Mortality Associated with NIDDM: Turner and colleagues[61] evaluated baseline risk factors for coronary artery disease and

Table 26. Stratifying All-cause Mortality for Age at Diagnosis and Glycemic Control

Age at Diabetes Diagnosis	Average FBG Range of Control			Mortality (%)
	mmol/l	≅	mg/dl	
<55	<6.7		(<122)	9.5
	6.7–7.7		122–140	9.5
	7.8–8.7		141–159	12.5
	8.8–9.9		160–180	12.5
	≥10.0			12.5
55–64	<6.7		(<122)	15.4
	6.7–7.7		122–140	23.2
	7.8–8.7		141–159	23.2
	8.8–9.9		160–180	23.2
	≥10.0			48.0
65–69	<6.7		(<122)	16.7
	6.7–7.7		122–140	40.0
	7.8–8.7		141–159	40.0
	8.8–9.9		160–180	41.7
	≥10.0			54.6
70–74	<6.7		(<122)	38.5
	6.7–7.7		122–140	40.0
	7.8–8.7		141–159	45.8
	8.8–9.9		160–180	45.8
	≥10.0			76.5
≥75	<6.7		(<122)	46.3
	6.7–7.7		122–140	46.3
	7.8–8.7		141–159	50.0
	8.8–9.9		160–180	76.5
	≥10.0			76.5

Table 27

Risk Factor	Hazard Ratio (Risk of Death)
LDL ≥ 4.5 mmol/L	2.0
HDL ≥ 1.25 mmol/L	<1.0
Age years to 65	2.25
HbA1c level 6.0%	1.0
HbA1c level ≥ 7.0%	1.75
Systolic BP:	
120 mm Hg	1.0
130 mm Hg	1.75
150–160 mm Hg	2.0
Never smokers & ex-smokers	1.0
Current smokers	1.5

cardiovascular- specific mortality in patients with type 2 diabetes mellitus.

DESIGN: A stepwise selection procedure, adjusting for age and sex, was used in 2693 subjects with complete data to determine which risk factors for coronary artery disease should be included in a Cox proportional hazards model.

SUBJECTS: 3055 white patients (mean age 52) with recently diagnosed type 2 diabetes mellitus and without evidence of disease related to atheroma. Median duration of follow up was 7.9 years. 335 patients developed coronary artery disease within 10 years.

OUTCOME MEASURES: Angina with confirmatory abnormal electrocardiogram; nonfatal and (cause-specific) fatal myocardial infarction.

RESULTS

1. Coronary artery disease was significantly associated with increased concentrations of low density lipoprotein cholesterol, decreased concentrations of high density lipoprotein cholesterol, and increased triglyceride concentration, haemoglobin A1c, systolic blood pressure, fasting plasma glucose concentration, and a history of smoking.

2. The estimated hazard ratios for the upper third relative to the lower third were 2.26 (95% confidence interval 1.70 to 3.00) for low density lipoprotein cholesterol, 0.55 (0.41 to 0.73) for high density lipoprotein cholesterol, 1.52 (1.15 to 2.01) for haemoglobin A1c, and 1.82 (1.34 to 2.47) for systolic blood pressure.

3. The estimated hazard ratio for smokers was 1.41 (1.06 to 1.88).

CONCLUSIONS

1. A quintet of potentially deadly but modifiable risk factors for coronary artery disease exists in patients with type 2 diabetes mellitus.

2. These risk factors are increased concentrations of low density lipoprotein cholesterol, decreased concentrations of high density lipoprotein cholesterol, raised blood pressure, hyperglycaemia, and smoking (see Table 28).

Table 28. *CAUSE-SPECIFIC MORTALITY:*
Standardized mortality ratios for 5,071 patients recently diagnosed with non-insulin dependent diabetes mellitus compared with general population are displayed below

Years since Random-ization	No of patients	Observed	Expected	Standardized mortality ratio	P value
Men					
0 to <5	2982	153	182	0.94	0.78
5 to <10	2287	161	118	1.36	<0.001
≥10	588	42	26	1.62	0.002
Women					
0 to <5	2079	89	72	0.96	0.64
5 to <10	1581	84	55	1.52	<0.001
≥10	409	28	12	2.42	<0.0001

CAUSE-SPECIFIC MORTALITY CONCLUSIONS

1. Poorer prognosis with disease duration in both men and women
2. Prognosis is more severe in women compared to men with increasing disease duration.

ALL-CAUSE MORTALITY ASSOCIATED WITH NIDDM

Hanefeld et al[62] analyzed the risk factors for subsequent CHD and all-cause mortality during the 11 year follow-up of the Diabetes Intervention Study (DIS) on, at baseline, 1139 subjects, aged 30–55 years at the time of diabetes detection and classified as diet controlled after a 6-week screening phase, were included.

RESULTS

1. Of the patients 112 (15.2%) suffered from myocardial infarction, 197 (19.82%) of 994 had died.
2. The odds ratios for all-cause mortality compared to the general population at the age of 36–45 years were: males 5.1; females 7.0.

Glycosuria, Ketonuria[63,64] and Ketoacidosis[65]

Urine glucose tests cannot provide accurate information regarding current blood glucose levels because glucose profiles, especially in IDDM are highly labile, and the renal threshold for glucose excretion is variable[66]**.** Reagent strips to make the measurements more precise have been developed.

Diagnosed and Treated Diabetics

- 0.25 mg / dl urine (dipstick trace to 1+), no additional rating is usually necessary,
- ≥0.26 mg / dl urine, obtain and use HbA1c for accurate risk assessment
- More than trace ketones present in several specimens in current 3-months, consider the presence of superimposed illness, inadequate insulin intake or pernicious vomiting as these symptoms may indicate ketoacidosis.

Undiagnosed New Applicants: If urine glucose levels are ≥ 0.26 mg / dl with cause unknown: use HbA1c for risk accurate assessment.

Brittle Diabetes and Recurrent Ketoacidosis (DKA)

'Brittle diabetes' is defined as insulin-dependent diabetes mellitus associated with glycemic instability of any type, leading to life

disruption with recurrent and/or prolonged hospitalizations.[67] DKA is relatively uncommon and is not usually the first presenting sign of diabetes. Brittleness is often episodic and perceived causes of brittleness are usually psychosocial.[68] Nevertheless, in the study by Kent et al:[69]

Mortality rate was 19% (5) of 26 females reassessed after a mean of 10.5 (SD 1.4) years.

Causes of death were not certain, but were probably ketoacidosis, hypoglycemia and renal failure

Of the 21 survivors, only 2 (10%) were still considered to have brittle diabetes,

DM complications were more common & frequent (67%) than a matched stable DM control group (25%),

Pregnancy complications occurred in 13 of 28 pregnancies (46%) in severely unstable patients compared with 2 of 27 patients (7%) in stable controls,

Pediatric mortality, diabetic ketoacidosis

While the treatment of children with type 1 diabetes mellitus has dramatically improved since the introduction of insulin in 1922, significant acute mortality still remains. In a retrospective review of diabetes[70] associated mortality in younger children and adolescents at the Children's Hospital of Pittsburgh between the years 1950 and 1985, 55 deaths were identified of which 20 occurred during the initial presentation of diabetes and 35 occurred between 2 months and 11 years following diagnosis of DM. DKA was associated with 64% of the total mortality. 85% of the early onset and 54% of the late onset deaths were ketoacidosis related.

Diabetes "control" versus diabetes "management"

Malone et al[71] noted that the terms ''diabetic control'' and ''diabetic management'' are not synonymous. Diabetes control (less than 25 grams urine sugar/24 hours) implies normal glucose metabolism, typically monitored by periodic determinations of plasma glucose and urine reducing sugar concentrations (URS). A group of 220 diabetic children attending a camp complied 74% of the time with the request to collect and test their urine for URS. Fifty percent of random URS values determined by the children varied from those obtained on the same specimens of urine by laboratory technicians. Good control was found in 18 of 54 children.

Insulin Pumps and Glucose Monitoring

Silverstein and Rosenbloom[72] have given an excellent overview in the recent advances of diabetes management and prevention of diabetes including the research and development of improved methods of glucose monitoring, and more physiologic ways of insulin delivery. The two most promising methods of minimally invasive blood glucose monitoring are the Glucowatch, using the technique of reverse iontophoresis to measure interstitial fluid glucose levels every 20 minutes and an implantable sensor, in which a catheter through a pump is impregnated with glucose oxidase at the tip. This device monitors blood glucose every few minutes, but like a holter monitor, must be downloaded in the physician's office.

Implantible Subcutaneous Sensors

Still under development are (1) implantible subcutaneous sensors with a high and low blood glucose alarm and (2) sensors in which the patient will be able to download the data using a home PC. Advances in insulin delivery have included the availability of new insulin analogs simulating the increase in endogenous insulin release with rapid acting analogs simulating the increase in insulin production that normally occurs after meals.[73] In addition, use of the insulin pump has increased markedly since publication of the DCCT with the greatest increase being among adolescents and pregnant mothers.[74]

Pancreas and Islet Transplantation for Patients with Diabetes

Research is continuing on curing the disease using islet cell transplantation and pre-

venting the disease with agents such as insulin (DPT-1 Trial) and nicotinamide (ENDIT). No data are available concerning long-term mortality and morbidity outcomes. Registry data on patients with type 1 diabetes mellitus indicate that only 8% are free of the need for insulin therapy at one year. However, in addition to the side effects of life-long immunosuppression,[75,76] the procedure itself has significant morbidity and carries a small, but not negligible risk of mortality.

Very recently, Shapiro and his colleagues[77] reported that seven of seven transplant recipients with type 1 diabetes who received an average of approximately 800,000 islets (delivered to the liver by injection into the portal vein) maintained normal blood glucose concentrations and glycosylated hemoglobin values without exogenous insulin for an average of one year. The keys to this impressive outcome include transplanting very high quality islets as soon as possible after harvest from cadaveric donors and substantially modifying the conventional immunosuppressive regimen. The modifications involved eliminating glucocorticoids, using a low dose of tacrolimus, a conventional dose of sirolimus, and adding daclizumab. Editorializing in the same issue of the Journal, R. Paul Robertson[78] of the Pacific Northwest Research Institute, Seattle, WA 98122 noted that if such remarkable preliminary success continues over the next few years, it is the supply-and-demand issue that will determine whether islet transplantation will become a readily accessible therapeutic option for patients with diabetes. The American Diabetes Association's technical review on this subject may be consulted for further information.[79]

Underwriting Action

Amidst rapidly emerging and very hopeful advances in the management, control and prevention of diabetes mellitus, the underwriter must carefully understand the clinical setting at its basics to *preclude sepsis, myocardial infarction, patient non-compliance, "brittleness", inadequate insulin treatment, inanition, pregnancy, complications, co-morbidities, risk factors etc.* Type I diabetic patients still have a mortality in excess of non-diabetic individuals not withstanding the fact that the ***median life expectancy for IDDM has increased by more than 15 years.***[80] However, there should be no cause for underwriting concern in adults—and at this point adolescents—with early recognition, prompt and adequate treatment, good management & control, and long-term prevention of DKA especially as brittle diabetes has a tendency to stabilize with time.

MACROVASCULAR COMPLICATIONS: CARDIOVASCULAR DISEASE

General: The risk of cardiac disease is increased from two to 10-fold in NIDDM. As indicated in the Joslin Clinic and Equitable Life studies earlier, the relative risk of cardiovascular disease in diabetic women (compared with non-diabetic women) is increased even more than for diabetic men. Risk factors include obesity, hypertension, dyslipidemia (low HDLs and high VLDLs with small dense LDLs), hyperglycemia, and, HbA1c (as an independent risk factor).[81,82]

Myocardial Infarction

MIDAS Study:[83] The effect of diabetes mellitus (DM) on mortality rate was studied in 42,595 patients in the statewide Myocardial Infarction Data Acquisition System **(MIDAS),** which included patients with myocardial infarction from 90 nonfederal hospitals in New Jersey during the years 1986 and 1987. Of these patients, 9,695 (22.8%) had DM. DM was more prevalent among female, black, and older patients.

DM was associated with higher mortality rates, both in-hospital (21.5% vs 19.2%, $p < 0.001$) and during 3-year follow-up (46.7% vs 37.8%, $p < 0.001$). This relation persisted in men and women, blacks and whites, and all age groups.

DM was an independent predictor of mortality by multivariate Cox proportional hazards regression analysis after adjustments

Table 29

(MIDAS) RESULTS:	Age-group	Relative Risk for Death ($p < 0.001$)
	30–49	1.87
	50–69	1.36
	70–89	1.17
CONCLUSION:	DM and acute MI	
3-year mortality		46.7%
Annual mortality		15.6%
3-year survival		53.3%

were made for gender, race, age, hypertension, left ventricular dysfunction, chronic liver disease, & anemia. *This effect of DM was most pronounced in the younger age groups* (see Table 29).

GISSI-2 Study[84]

Carried out on a total of 11,667 patients who were randomized within 6-hours of the onset of acute myocardial infarction symptoms for thrombolytic treatment with either streptokinase or recombinant tissue-type plasminogen activator (Actylise).

RESULTS

1. The prevalence of diabetes was higher in women than in men,

- 8.75% compared with 1.85%, ($p < 0.01$); for insulin-dependent women,
- 23.7% compared with 13.8% ($p < 0.01$) for non-insulin-dependent diabetic patients.

2. The type of fibrinolytic agent used did not affect mortality rates;

3. Six-month and Total Mortality Rates: See Table 30.

CONCLUSIONS

Males

The increase in in-hospital mortality of diabetic patients was moderate and similar for men with insulin- and non-insulin-dependent diabetes (8.7% and 10.1%, respectively, versus 5.8% in non-diabetic patients;

Females

1. Mortality was markedly higher for insulin-dependent and only slightly higher for non-insulin-dependent patients (24.0% and 15.8% respectively, vs 13.9% for non-diabetic patients);

2. Adjusted relative risks were 1.9 (95% confidence interval 1.2 to 2.9) for insulin-dependent diabetic women, and, 1.4 (95% confidence interval 1.1 to 1.8) for non-insulin-dependent diabetic men.

3. Post-discharge mortality rate showed a

Table 30

	In Hospital Mortality			6-months Post Discharge		
	Mortality (%)	Odds Ratio (95% CI)	p* Value	Mortality (%)	Odds Ratio (95% CI)	p* Value
MEN						
No diabetes	5.8	1		3.1	1	
Diabetes						
Insulin-dependent	8.7	1.7 (0.8–3.3)	NS	2.2	0.7 (0.3–2.4)	NS
Non-insulin-dependent	10.1	2.0 (1.6–2.6)	<0.001	4.4	1.5 (1.0–2.2)	<0.05
WOMEN						
No diabetes	13.9	1		4.3	1	
Diabetes						
Insulin-dependent	24.0	2.2 (1.4–3.5)	<0.001	13.7	7.3 (3.1–17.4)	<0.001
Non-insulin-dependent	15.8	1.2 (0.9–1.6)	NS	5.5	1.3 (0.8–2.4)	NS

(p values are in comparison with values in non diabetic patients. CI = confidence interval).

similar gender difference, and in insulin-dependent women, prognosis was ominous (even in the absence of left ventricular damage before discharge).

Corpus Christi Heart Project:[85] The effect of diabetes on survival after myocardial infarction (MI) was examined in a prospective population-based study of 1,199 individuals hospitalized with MI in a bi-ethnic community of Mexican-Americans and non-hispanic whites.

TOTAL NUMBER: diabetics = 523; non-diabetics = 676.

RESULTS & MORTALITY: Adjusting for age, sex, and ethnicity;

Cumulative total mortality over 44 months of follow-up:

1. ***Diabetics:*** 37.4% (Ann Mort = 10.1%); ***Non-diabetics:*** 23.3% (Ann Mort = 6.3%) ($P < 0.001$), with similar adverse post-MI mortality in both Mexican-Americans and non-Hispanic whites.

2. Kaplan-Meier estimates for 28-day case fatality rates were 10.1% among diabetics, and 5.0% among non-diabetic individuals.

3. Kaplan-Meier estimates for long-term (43 months) all-cause mortality starting 1 month after the index event were 30.4% among diabetic cases and 19.3% among non-diabetic cases ($P < 0.001$).

4. Diabetes remained significantly predictive of *long-term mortality, RR 1.45,* 95% CI 1.08–1.94).

Rancho Bernardo Study[86] This study reports the 14-year sex-specific effect of non-insulin-dependent diabetes mellitus on the risk of fatal ischemic heart disease in a geographically defined population of men and women aged 40 through 79 years. There were 207 men and 127 women who had diabetes at baseline based on medical history or fasting hyperglycemia who were compared with 2,137 adults who had fasting euglycemia and a negative personal and family history of diabetes.

RESULTS & MORTALITY: Relative hazard of ischemic heart disease (IHD) death in diabetics vs non diabetics after adjusting for age, systolic blood pressure, cholesterol, body mass index, and cigarette smoking using the Cox regression model was: 1.8 in men and 3.3 in women ***(Average RH = 2.5)***

CONCLUSION: The sex difference in the independent contribution of diabetes to fatal heart disease was largely explained by the persistently more favorable survival rate of women (than men) without diabetes.

Table 31

SURVIVAL:	CABG Rx; 5-year Survival = 80.6%:		PTCA Rx; 5-year survival = 65.5%
MORTALITY:	Age	Mortality Ratio	Mortality Ratio
	45	1,970	4,000
	55	896	2,000
	65	231	727

BARI Investigators—Treatment with PTCA or CABG[87,88,89]

RESULTS AND CONCLUSIONS

1. Treated type I or type II diabetes mellitus, (19% of a randomized cohort of 1829 patients),

2. 5-year survival—DM patients: 80.6% CABG group, and 65.5% for PTCA group,

3. 5-year survival—non-DM patients: 89.3% for CABG Group, and 86.3% for PTCA group.

4. PTCA-treated diabetics experienced far worse mortality outcomes; a difference of 15 percentage points in 5-year survival was found in favor of CABG.

5. *Overall Annual Non-diabetic vs Diabetic Mortality in Coronary Heart Disease Patients*

Non-diabetic Mortality: CABG Group: 2.1% per year for multi-vessel disease

PTCA Group: 2.7% per year for multi-vessel disease

Diabetic Mortality: CABG Group: 4.0% per year for multi-vessel disease

PTCA Group: 7.0% per year for multi-vessel disease

6. Age-specific Magnitude of Risk for Diabetics with CABG-or PTCA-Treated CHD: See Table 31.

Table 32

	No Diabetes	Diabetes	*P*
All patients –n	1,859 (87%)	268 (13%)	
Mortality	n (%)	n (%)	
<30 days	56 3.0	18 6.7	<0.01
30 days to 2 years	64 3.6	19 7.8	<0.01
2 years (total)	120 6.5	37 13.9	<0.0001

Western Sweden Study[90]

RESULTS

1. In this prospective follow-up study carried out on 2,127 patients in western Sweden in whom CABG was undertaken between June 1988 and June 1991 and in whom concomitant procedures were not performed, diabetic patients (n = 268) differed from non-diabetic patients (n = 1,859) in that more women were included, and the patients had a more frequent history of myocardial infarction (MI), congestive heart failure, intermittent claudication, and obesity.
2. Mortality During 2-Years of Follow-up: See Table 32.
3. Factors in Clinical History Associated with 2-Year Mortality (univariate analysis): See Table 33.
4. Overall cardiac death rate:
   Diabetics: 9.9%;
   Non-diabetics: 4.6%; ($P < 0.001$)
5. 2-year cumulative survival after CABG:
   Diabetics: 86.1%;
   Non-diabetics: 93.5%.
6. Independent Predictors of Death During 2 Years of Follow-up (multivariate analysis): See Table 34.
7. Post CABG Morbidity During 2 Years of Follow-up: See Table 35.

CONCLUSIONS

1. Even after CABG, diabetic patients with ischemic heart disease remain a high-risk group with twice the mortality of non-diabetics both peri-operatively and long term.
2. Diabetes per se confers an increased long-term mortality risk after CABG.

No history of myocardial infarction or congestive heart failure

Haffner study[91]

Stable 1-vessel CAD, ejection fraction >45% treated medically or with CABG; relative risk = 1.50

Stable 2-vessel CAD disease, ejection fraction >45%, treated medically or with CABG; RR = 2.0

3-vessel CAD disease, or ejection fraction <50, relative risk is greater than 2.0

Herlitz (Western Sweden study)

Post CABG annual mortality in diabetics with otherwise uncomplicated

Table 33

Clinical Factor	2-year Mortality (%)	*P*
Age (years) (≥65/≤65)	10.9/4.5	<0.0001
Sex (M/F)	6.5/11.8	<0.001
History		
Myocardial infarction (yes/no)	8.4/6.0	<0.05
Congestive heart failure (yes/no)	15.5/6.0	<0.0001
Hypertension (yes/no)	9.7/6.1	<0.01
Renal dysfunction (yes/no)	12.9/5.3	<0.0001
Cerebrovascular disease (yes/no)	12.4/7.0	<0.05
Intermittent claudication (yes/no)	13.9/6.5	<0.0001
Previous CABG (yes/no)	16.4/7.0	<0.0001
Three-vessel disease ((yes/no)	8.2/4.8	<0.01
Ejection fraction <40 (yes/no)	12.4/6.3	<0.01

Table 34

Factor	Beta	Relative Risk	*P*
Cong. heart failure	0.622 ± 0.205	1.86 (1.25–2.78)	<0.01
Renal dysfunction	0.595 ± 0.203	1.81 (1.22–2.70)	<0.01
Age ≥65 years	0.581 ± 0.214	1.79 (1.17–2.72)	<0.01
Diabetes	0.574 ± 0.224	1.78 (1.14–2.76)	<0.05
Intermittent claud.	0.506 ± 0.222	1.66 (1.07–2.56)	<0.05

Data are means ± SE or relative risk (95% CI).

Table 35

Morbid Factor	Diabetics	Nondiabetics	*P*
Anterior MI (>30 days)	4.2%	2.1%	0.06
Fatal AMI	0.4%	0.5%	>0.2
Nonfatal AMI	3.7%	1.6%	<0.05
Developed Stroke	6.3%	2.5%	<0.001
Fatal Stroke	1.2%	0.6%	>0.2
Nonfatal Stroke	5.25	1.9%	<0.001

CHD = 3.4%

Untreated or treated silent ischemia: It is well known that patients with diabetes mellitus may not have chest pain during MI (possibly secondary to autonomic dysfunction).[92,93,94]

Canto et al.[95] analyzing a total of 434,877 patients with confirmed MI enrolled June 1994 to March 1998 in the largest observational study to date **(NRMI-2),** indicated that MI patients without chest pain had a 23.3% in-hospital mortality rate compared with 9.3% among patients with chest pain (adjusted odds ratio for mortality, 2.21 [95% confidence interval, 2.17–2.26]).

Risk factors associated with lack of pain:

- Diabetes-38.5%, prior heart failure-51.0%, prior stroke 47%, Age >75 years-44.9%, non-white-33.7%, women-38.6%, (any combination of risk factors-as high as 63.4%).
- Prinzmetal's (variant) angina[96] may be silent with the risk for sudden death.

CEREBROVASCULAR DISEASE

Stroke: *The World Health Organization definition of stroke is "rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin."*[97]

This definition excludes transient ischemic attack (TIA), subdural hematoma, and hemorrhage or infarction caused by infection or tumor. Approximately 90% of strokes are ischemic of which about 41% are thrombotic and 59% embolic.[98]

Primary intracerebral hemorrhage (ICH) accounts for the remaining 10% of strokes.[99] The prevalence of cerebral infarcts, especially lacunar infarcts is increased, and the prevalence of subarachnoid hemorrhage, cerebral hemorrhage, and transient ischemic attacks are decreased in the diabetic patient.[100]

Diabetes as a risk factor for stroke:[101] Because of local cerebral acidosis caused by ischemia and hyperglycemia in diabetics, morbidity and mortality are increased. Serum glucose >120 mg/dl (6.7mM) have a higher morbidity and mortality from stroke. Hemiparesis may last 4-weeks or longer. However, focal neurologic findings, such as seizures and hemiparesis, that disappear with correction of dehydration and hyperglycemia are

features of hyperosmolar nonketotic diabetic coma rather than stroke.

Risk Factors Predicting Incidence & Outcome:[102] Age, race, hypertension, level of physical activity[103], diabetic nephropathy, and coronary and peripheral vascular disease are risk factors for stroke in the diabetic patient; whereas obesity, smoking, hyperlipidemia, and glycemic control are questionable.

Increased Mortality from Stroke in Diabetics

The Bell paper comments on a carefully matched Finnish study (*Webster P. The natural history of stroke in diabetic patients. Acta Med Scand 1980; 207: 417–424*)[104] in which the survival of diabetic patients was compared with a group of randomly selected non-diabetic patients and a group of age- and sex-matched non-diabetic control subjects with a stroke.

Stroke 5-Year Survival & Mortality: Non-diabetics: 40%; Mortality: 60%: Annual Mortality: 12%

Diabetics: 20%; Mortality: 80%: Annual Mortality: 16%

(Expected General Population Survival = 80%)

Increased Morbidity from Stroke in Diabetics

5-year recurrence rate: 20% to 40% (50% greater mortality associated with second CVA)

Morbidity is related to the serum glucose cut-off point of 120 mg/dl (6.6mM):

>120 mg/dl is associated with increased likelihood of cerebral edema and >4 weeks (slowed) recovery of hemiparesis.

Transient Ischemic Attack (TIA)[105]

Transient ischemic attack (TIA) is *defined as "an episode of focal loss of brain function attributed to ischemia that lasts less than 24 hours, is localized to a portion of the brain supplied by one vascular system, has no persistent deficit, and is not attributable to any other cause."*[106]

Most TIAs are caused by small thromboemboli originating in atheromas in the heart or neck vessels and are quite brief in duration; 24% − 5 minutes, 50% − 30 minutes, 60% − 1 hour.

Risk Factors Predicting Outcome:[107] Post-TIA survival is significantly decreased by older age, smoking, previous stroke, ischemic heart disease, peripheral arterial disease, and diabetes mellitus.

TIA MORTALITY & SURVIVAL[108]

United States:[109] Annual mortality is 5% to 6% following a TIA, mainly due to myocardial infarction, (At age 60, this equates to an observed of 50–60 deaths/1,000 compared with a general population expected of 10–12 deaths/1,000). (Annual mortality was reportedly as high as 8% in a prior paper by Easton et al.)[110]

Asian:[111] 71 patients with TIA were followed for 22 years. Most of the 34 deaths were due to stroke; cerebral hemorrhage-15 deaths, cerebral infarction-6 deaths, myocardial infarction-1death.

Age-gender groups: (Mayo Clinic, Rochester Minnesota, second age-and sex-matched community-based study):[112] Young women: best overall survival; older women: worst overall survival;

Males: relative risk highest at age 50 with subsequent decline.

Risk of Stroke:[113] Overall post-TIA risk of stroke:

- First month: 5%; First year: 12%; Five year: 30%; Annual after first year: 7%
- Risk of stroke is about seven times higher than in an age-matched general population
- Higher risk with extensive neurologic (hemispheric) TIAs,
- Higher risk with recent or increasingly frequent TIAs,
- Risk by age; older age, risk increases by 45% for each 10 year increment of age
- TIAs associated with high grade carotid stenosis[114]

Amaurosis fugax: (retinal TIAs); the incidence of stroke is much higher than in the general population[115] but prognosis is more

Table 36. Five-year Incidence, Type of Stroke & Risk Factors

60–99% Stenosis Group	Percent	Risk factors
Territory of large artery;	9.9%	silent brain infarct, diabetes, higher degree stenosis,
Lacunar stroke;	6.0%	≥age 75, hypertension, diabetes, higher degree stenosis
Cardio-embolic stroke;	2.1%	history of myocardial infarction, angina, hypertension

Table 37. Five-year Risk of Mortality

	Any cause	Stroke	MI	Vascular	non-Vascular
Asymptomatic stenosis (<60%):	17.5%	1.9%	3.4%	6.2%	7.1%
Symptomatic stenosis (60%-99):	21.0%	1.0%	2.0%	10.7%	8.8%

favorable compared to those with hemispheric brain TIAs.[116]

CAROTID ARTERY SURGERY[117,118,119]

GENERAL

The North American Symptomatic Carotid Endarterectomy Trial Collaborators **(NASCETC)** studied 1820 patients with unilateral symptomatic carotid-artery stenosis and asymptomatic contralateral stenosis from 1988 to 1997.

RESULTS

The risk of stroke at five years after study entry increased with the severity of the stenosis:
Stenosis: <60% luminal diameter among 1604 patients: risk of first stroke − 8.0% (1.6% annually),

Stenosis: 60–99% of luminal diameter in 216 patients: risk of first stroke − 16.2% (3.2% annually)

80% of 1st strokes were not heralded by transient ischemia (see Table 36).

Annualized Risk of Stroke

In area of asymptomatic occluded artery; 1.9% (relatively low risk),

perioperative (30-day) risk of stroke and death in asymptomatic patients; 5%-12.3% (see Table 37).

Annual (Multi-study) Mortality Rates[120,121]

- 3.4%-4.9% with significant early & late morbidity & mortality among diabetic patients,
- Leading cause of death is ischemic heart disease
- Improved survival after carotid endarterectomy in TIA or CVA patients with at least 70% stenosis, (however, beneficial effect lasted only 3-years)

Ocular Ischemic Syndrome (OIS): *The OIS is defined as ocular symptoms and sign attributable to severe carotid artery obstruction.*[122] Decreased vision and pain are symptoms of the OIS, while signs in the anterior segment include rubeosis iridis and uveitis. Posterior segment signs include narrowed retinal arteries, dilated but non-tortuous retinal veins, dot and blot retinal hemorrhages, optic disc and retinal neovascularization, and cotton-wool spots. *Carotid angiography* usually discloses at least a 90% atherosclerotic obstruction within the ipsilateral arterial system (see Table 38).

Mortality

- 5-Year mortality rate = 40%: Annual mortality = 8% (similar to TIA)
- Causes of death: Cardiac 63%, Stroke 19%, Other impairments 18%.

Conclusion OIS is clinical manifestation of advanced, diffuse and severe arteriosclerosis

Table 38

Associated systemic diseases	Percent (%)
Hypertension	73
Diabetes mellitus	56
Ischemic heart disease	48
Cerebrovascular accident	27
Peripheral vascular disease	19

affecting other target organs such as the heart, brain, and kidneys.

PERIPHERAL VASCULAR DISEASE (PVD)

In the general population, peripheral atherosclerosis is a strong predictor of cardiovascular disease and death. Peripheral vascular disease (PVD) may *be defined as claudication, any loss of a lower limb pulse, peripheral vascular surgery, dysvascular lower extremity amputation, or abdominal aortic aneurysm.*

Cause of Death of Lower Limb Amputees

The Dundee Limb Fitting Center (DLFC)[123] reviewed 100 sequential deaths of lower limb amputees admitted for prosthetic management to determine cause of death and survival times over a 25-year period, and, compare this with the recorded causes of death and survival times for the Tayside population for the year of study; Average age of amputation—70 years (see Table 39 and 40).

Table 39. Mortality, Morbidity & Survival Results
(Source for Tayside (control) group for 70 year old people—Registrar General for Scotland 1987)

Causes of Amputation	
PVD non-diabetic	61
PVD with diabetes mellitus	32
Tumor	4
Other	3

Causes of Death	Tayside%	DLFC%
Myocardial infarction	25.2	42
Other heart disease	2.9	9
Carcinomatosis	23.5	14
Cerebrovascular accident	12.3	6
Pulmonary disease	10.2	5
Bronchopneumonia	5.4	13
PVD	0.5	5
Septicemia	0.2	3
Renal failure	1.0	1
Hypoglycemia	0.9	1
Total	79.5	1 operative death
	(4111 cases)	(100 cases)

CONCLUSION: 25-year median survival of lower limb amputees:

- No diabetes and PVD: 3 yrs. 10 months;
- Diabetes and PVD: 3 yrs. 5 months;
- Peer group survival (no PVD): >10 yrs.

Table 40

Comparative Median Survival Times:	Tayside	DLFC
Median survival overall:	>10 years	3 yrs. 9 months.
PVD		
• 61 cases non diabetic		3 yrs. 10 months.
• 32 cases diabetes mellitus)		3 yrs. 5 months.
Myocardial infarction:		2 yrs. 11 months. (25 of 61 patients (41%) with PVD) (15 of 32 patients (46.9%) with DM)
Bronchopneumonia:		5 yrs. 11 months.
Above-knee amputation:		1 yr. 11 months.
Below-knee amputation:		4 yrs. 0 months.

Table 41. MEDIAN SURVIVAL for the whole 25-Year Study ($p < 0.006$)

1. All vascular cases (1464 overall)	4 yr 0 month
2. Above-knee 3 yr 6 month	
Below-knee	4 yr 2 month
Vascular (non-diabetic − 1,019)	4 yr 2 month
Diabetic Cases (445)	3 yr 8 month
3. 70-year-old Control Group (1988)	
Male	10.34 yr
Female	13.40 yr

Lower limb amputee survival (DLFC), Dundee Limb Fitting Center (DLFC):[124]

PURPOSE

- A total of 1710 primary lower limb amputees were studied over a 25-year period at the DLFC from 1965–1989 and their survival time calculated.
- Vascular related amputees (1464 overall) had an overall median survival of 4 years.

RESULTS

Source for Tayside (control) group for 70-year-old people—Registrar General for Scotland 1988: See Table 41.

CONCLUSION

Associated diabetic cases have significantly shorter survival than the pure PVD associated amputee, 3 yr 8 month as compared with 4 yr 2 month ($p < 0.006$).

PVD Survival, Mortality & Morbidity with Rehabilitation after amputation for vascular disease[125]

PURPOSES AND METHODS: Compare 5-year survival, mortality & continuing morbidity in PVD amputees fitted with prosthesis, with and without diabetes mellitus.

DESIGN: From August 1979 to August 1987, 128 consecutive patients—**median age 62 years**—with lower limb amputation due to peripheral vascular disease (PVD), who were fitted with prosthesis and provided intensive rehabilitation to restore bipedal gait, were evaluated:

99 male (77.3%), 29 female (22.7%), 67 diabetic (52.3%)

RESULTS: **(Kaplan-Meyer product-limit estimates):** Five-year Survival for 128 Patients with Lower Limb Amputation Caused by PVD: See Table 42.

CONCLUSIONS: **5-Year Survival, Mortality & Morbidity**

Post amputation five-year survival

Diabetics; 42.4% (Average Annual Mortality-11.5%)

Non-diabetics; 85.5% ($p = 0.0002$) (Average Annual Mortality-2.9%)

Late mortality risk: six times greater in diabetics than non-diabetics.

Five year opposite limb preservation: Diabetics-69.5%, Non-diabetics-90.2% ($p = 0.0013$).

COMMENT: CLEVELAND CLINIC REPORTED COMPARATIVE SURVIVAL RATES FOR PVD:[126]

5-years: 75%, 10-years: 40%, 15-years: 26%

Average mortality: 5% to 10% per year

Average loss of life expectancy: 10-years

Results of Peripheral Vascular Bypass in Juvenile-onset Diabetes Mellitus[127]

PURPOSES: This study was performed to evaluate the results of peripheral vascular reconstruction for arterial occlusive disease in patients with juvenile-onset diabetes mellitus. The results of 67 bypass procedures performed on 60 patients with juvenile-onset diabetes mellitus (JODM) between Jan. 1, 1984 and Dec. 31, 1989, were reviewed (see Table 43).

RESULTS: **Outcomes & Survival (24-months follow-up)**

1. Actuarial patency (primary vein graft group) 66.0% ± 10.7
2. Limb salvage rates 83.4% ± 8.0
3. Cumulative 2 year survival, entire group 84.1%

Table 42. Mean Survival Time

Variable	Categories	# Patients	(months)	% 5-yr Survival
Sex	male	99 (77.3%)	93.5 ± 12.6	61.3
	female	29 (22.7%)	95.4 ± 22.1	67.3
Associated	diabetes	67 (52.4%)	55.6 ± 5.5	42.4
Disease	other	61 (47.6%)	86.4 ± 4.5	85.5

Table 43. Demographic Characteristics of Patients with JODM

Total Patients	60
Men	31
Women	29
Mean age (range)	44.4 yrs (29–59)
Mean age diabetes onset	9.8 yrs (1–19)
Mean duration of diabetes (range)	34.6 yrs (20–52)
Preoperative risk factors	
IDDM	60 (100%)
Hypertension	27 (45%)
Neuropathy	60 (100%)
Retinopathy	55 (92%)
Renal Failure	27 (45%)
Dialysis	21 (35%)
Previous Kidney Transplant	14 (23%)
Smoking	
Current	29
Previous	13
Never	15
Unknown	6

CONCLUSIONS

1. Small vessel disease does not appear to play a significant role in the diabetic lower extremity. This subgroup has a very high incidence of ocular and renal microangiopathy, and renal failure (45%). However, graft patency and limb salvage rates were acceptable when compared with other peripheral vascular bypass series for ischemia in AODM and non-diabetic populations suggesting that occlusive disease in the large vessels is the principal cause for ischemia-related limb loss in these patients.

2. The 2-year cumulative survival rate of 84% is low in this young group of patients. However, considering the substandard life expectancies by age at diagnosis (0–19) in general cases reported in the Lincoln National Reinsurance Study, a mortality ratio of 524% indicates that median survival is decreased by nearly 25 years when compared with the general population.

Relationship of Severity of Lower Limb PVD to Mortality and Morbidity

The paper by Howell et al[128] describes a 6-year review of 247 consecutive patients undergoing lower extremity noninvasive vascular assessment to investigate the relationship of risk of death, myocardial infarction, stroke, and limb loss to the severity of peripheral vascular disease.

There were 130 men and 117 women with a mean age of 65 ± 15 years. Patients were categorized into four groups according to their **ankle-brachial pressure indexes (ABI)** at their first visit as follows: (decreasing ABI indicates an increase in PVD severity) See Table 44.

Developmental Course & Mortality of PVD in Non-insulin Dependent Diabetics

The report by Kreines et al[129] analyzed the course of peripheral vascular disease (PVD) in 619 patients with type 2 diabetes recruited within 1-year of diagnosis and followed quarterly for up to 14 years (see Table 45).

Relationship between CALC and mortality

40.3% of 144 women who developed CALC died versus 21% of 300 without CALC, a relationship not seen among the men, (RR = 1.9)

Table 44

	Ankle-Brachial Index	Patients	Total Diabetes *n* (%)	Mean Age (yr)
Group I	normal (≥0.92)	97	14 (14)	59.6 ± 16.1
Group II	mild disease (0.50 to 0.91)	86	16 (19)	67.3 ± 13.4
Group III	moderate disease (0.31 to 0.49)	39	17 (44)	71.1 ± 10.3
Group IV	ischemic disease (≤0.30)	25	4 (16)	73.4 ± 12.1
		247	51 (21)	

RESULTS: **Distribution of End Events at 6-year Follow-up**

End Events	I	II	III	IV	Total
n	97	86	39	25	247
Death *n* (%)	19 (20)	22 (26)	12 (31)	16 (64)	69 (28)
(Annual mortality)	***(3.3)***	***(4.3)***	***(5.2)***	***(10.7)***	***(4.7)***
MI *n* (%)	8 (8)	15 (17)	8 (21)	5 (20)	36 (15)
Stroke *n* (%)	5 (5)	9 (10)	3 (8)	3 (12)	20 (8)
Amputation *n* (%)	1 (1)	6 (7)	5 (13)	8 (32)	20 (8)
Vascular Surgery *n* (%)	4 (4)	26 (30)	10 (26)	7 (28)	47 (19)

Table 45. 13-year duration actuarially determined cumulative risks

	Males	Females
Intermittent claudication (IC),	37.9%	24.3%,
Non palpable dorsal pedal pulse (NPUL),	34.5%	37.6%,
Arterial calcification (CALC),	60.9%	32.2%

Relationship between NPUL and mortality in both sexes

Men: 50% of 68 men with NPUL died versus 27.6% of the 96 without NPUL (P = 0.0053), (RR = 1.8). In men, the only significant risk factors were diminished vibration perception that was related to NPUL ($P < 0.05$), and the serum tryglyceride that was related to IC ($P < 0.05$).

Women: 36.4% of 173 women with NPUL died versus 21.4% of the 280 without NPUL (P = 0.0007), (RR = 1.7).

MICROVASCULAR DISEASE

Nephropathy

Nephropathy is the diabetic complication associated with the highest mortality.[130,131] The kidney, as a window on the vasculature is an elegant and excellent surrogate marker for cardiovascular disease. Even mild anomalies are easy to detect.

Risk factors for nephropathy & measures to prevent progression to overt ESRD[132]

- Elevated blood pressure: maintain mid-normal range blood pressure of 125/75 preferably with use of ACE inhibitors or possibly angiotensin II—receptor blockers;
- Albuminuria or proteinuria: reduce level to <1 g per day;
- Poor glycemic control (high level of insulin resistance): maintain HgbA1c ≤7.0%;
- Smoking
- High dietary intake of protein? Restrict dietary protein intake to ≤0.8 grams/kilo body weight/day
- Hyperlipidemia

Pathogenesis: It begins incipiently with low levels of albumin excretion (microalbuminuria) as early as five years after IDDM onset and progresses to macroalbuminuria with accompanying hypertension after IDDM of 12 to 20 years duration. Finally, the nephrotic syndrome and the decrease in glo-

Table 46. *Comparative mortality by age & primary cause of ESRD, durations 0–5 years combined*

Age group	5-year Annual Survival	Mortality Ratio (%)	Excess Death Rate / 1000
42,107 Patients with ESRD due to diabetic nephropathy			
15–24	0.345	16,000	191
25–34	0.297	11,400	214
35–44	0.253	9,200	237
45–54	0.234	7,100	245
55–64	0.185	1,820	270
65–74	0.115	1,130	320
75–84	0.074	515	327
85 up	0.171(2y)	385	434
All Ages	0.186	1,640	269
112,540 Patients with ESRD due to other causes			
15–24	0.788	3,900	46
25–34	0.675	4,000	74
35–44	0.634	3,300	84
45–54	0.608	1,400	87
55–64	0.368	1,150	165
65–74	0.218	850	232
75–84	0.105	460	284
85 up	0.051	265	279
All Ages	0.361	780	160

merular filtration rate (GFR) progress to end-stage renal disease (ESRD).[133,134,135,136]

The 1995 mortality results of Singer and Balakrishna:[137] (Mortality Abstract 637M1) analysis of mortality by age and disease duration in medicare patients with diabetes mellitus on dialysis for end-stage renal disease (ESRD) from 1982 to 1987 is a dreadful & morbid revelation summarized in Table 46 and 47.

Conclusion: The diabetic nephropathy group has the highest mortality of all the primary cause groups of ESRD patients.

Prediction of Creatinine Clearance (CC) from Serum Creatinine: In the insurance environment, it is useful to be able to quickly predict creatinine clearance when a 24-hour urine volume cannot be collected.

Cockcroft and Gault[138] developed the following formula in 1975 to roughly predict creatinine clearance in adult males expressed as follows:

Table 47. *Comparative mortality by duration, all ages combined (primary cause diabetes or all others)*

Interval years	Mortality Ratio (%)	Excess Death Rate / 1000
ESRD due to diabetic nephropathy		
0–1	1,070	249
1–2	1,190	265
2–3	1,210	232
3–4	1,400	272
4–5	(1,580)	267
0–4	1,210	254
ESRD due to all other causes		
0–1	1,160	185
1–2	1,140	156
2–3	1,240	171
3–4	1,410	184
4–5	(1,140)	137
0–4	1,190	177

Creatinine Clearance
= (140 − age)(wt kg) ÷ 72
× Serum Creatinine (mg/100 ml)
(15% less in females)

- They demonstrated an almost linear decrease of about 50% (23.6 to 12.1 mg / kg) over the 3rd to 9th decades (presumably related to a decrease in muscle mass with aging)
- A correction to lean or ideal body weight is advised when abnormalities are pronounced.
- A limitation is that CC can be greatly over estimated in the early phase of acute renal failurebefore the serum creatinine has risen appreciably

Levy et al[139] in 1999 reported a new formula to more accurately predict renal function. Glomerular filtration rate (GFR) rather than creatinine clearance may provide a more accurate estimate of renal function, according to the Modification of Diet in Renal Disease (MDRD) Study expressed as follows:

$$\mathbf{GFR = 170 \times [Scr]^{-0.999} \times [Age]^{-0.176}}$$
$$\mathbf{\times [0.762 \text{ if female}]}$$
$$\mathbf{\times [1.180 \text{ if patient is black}]}$$
$$\mathbf{\times [BUN]^{-0.170} \times [Albumin]^{-0.318}}$$

Table 48. Albumin Excretion and Overall 5-year Mortality

24-hour albumin excretion rate	5-year Mortality	Annual Mortality
• Normoalbuminuria: AER <30 mg/24 hours:	8%	1.6%
• Microalbuminuria: AER 30–299 mg/24 hours:	20%	4.0%
• Macroalbuminuria: AER ≥300 mg/24 hours:	35%	7.0%

Table 49. All-cause Mortality Predictors (Cox multivariate regression analysis)

Predictor	Relative Risk	95% CL
• CHD	2.9	1.6–5.1
• Log_{10} AER	1.9	1.4–2.6
• HbA1c	1.2	1.0–1.4
• Age (years)	1.08	1.93–1.13

Table 50. Cardiovascular Mortality Predictors

Micro & Macroalbuminuria: (Cox multivariate regression analysis)

Predictor	Relative Risk	95% CL
• CHD (preexisting)	6.1	2.8–13.5
• *Macroalbuminuria*	2.5	1.1–5.8
• HbA1c level %	1.3	1.1–1.6
• sBP (10 mm Hg)	1.2	1.0–1.4

Normoalbuminuria: (Cox univariate regression)

AER increases to median 8 mg/24 hours; Relative Risk for all cause mortality = 2.7

Factors contributing to greater accuracy of the new equation for calculating GFR include:

- Use of a creatinine assay (the kinetic alkaline picrate reaction) that is least subject to artifact,
- Equation validation in a control cohort of patients differing from the tested cohort,
- Prediction of GFR over a wide range of values,
- Inclusion of variables for ethnicity and serum albumen
- No reliance on timed urine collections

Table 51. Relative Risk of Death for NIDDM Patients

Variable	Relative Risk	95% CL	*P* value
Treatment			
Oral agent	2.29	1.01–5.20	<0.05
Insulin	4.85	2.17–10.85	<0.001
Retinopathy			
Nil	1.00		
Background	2.37	1.33–4.22	<0.001
Proliferative	4.01	1.52–10.56	<0.001
Hypertension	2.24	1.23–4.09	<0.01
CHD (ECG codes)	4.60	2.64–8.02	<0.001
Stroke	4.73	2.37–9.45	<0.001

Comment: Implementation of the GFR equation into insurance clinical laboratory reports is not yet a routine practice.

Microalbuminuria & proteinuria: These are highly significant laboratory markers of diseased blood vessels:[140,141]

- Nephropathy (early to late end-stage renal disease with nephrotic syndrome),
- Glomerulosclerosis (Kimmelstiel-Wilson Disease)
- Accelerated atherosclerosis,
- Generalized microvascular and macrovascular disease,[142]

Aged population: important independent risk factor for mortality[143]

Indicators of end-organ damage in hypertension.[144]

Mortality Impact of Albuminuria in NIDDM

Gall et al. in a 5-year prospective study from 1/1/87 to 1/1/93 reported the relationship of albumin excretion rate (AER) with mortality in 328 white NIDDM patients with a mean age of 54-years and determined the relative importance of micro- and macroalbuminuria compared with other cardiovascular risk factors[145] (see Tables 48 through 51).

Effect of Treatment with Ace Inhibitors on Nephropathic Mortality:[146,147,148,149] See Table 52.

Survival[150]: ***Life expectancy has been advanced up to 15 years in type 1 DM*** mostly

Table 52. Mortality Implications of the HOPE Study and MICRO-HOPE Sub-study[148,149]

Outcome	Relative Risk	(95% CL)	*P* value
MI, stroke, or death from cardiovasc. causes	0.78	(0.70–0.86)	<0.001
Death from cardiovascular causes	0.74	(0.64–0.87)	<0.001
Myocardial infarction	0.80	(0.70–0.90)	<0.001
Stroke	0.68	(0.56–0.84)	<0.001
Death from non-cardiovascular causes	1.03	(0.85–1.26)	0.74
Death from any cause	0.84	(0.75–0.95)	0.005
Mortality, Morbidity, Survival-Outcomes: Ramipril Relative Risk Reduction:			
Mortality			
Composite outcomes	25%	(12–36)	0.004
Myocardial infarction	22%	(6–36)	
Stroke	33%	(10–50)	
Cardiovascular death	37%	(21–51)	
Total mortality	24%	(8–37)	
Revascularization	17%	(2–30)	
Overt nephropathy	24%	(3–40)	0.027

attributable to improved treatment of diabetic nephropathy by blocking the renin-angiotension system & stabilizing micro-angiopathic proliferation.

Outpatient Random Urine Sampling to Predict Persistent Microalbuminuria[151]

Sensitivity: 91%
Specificity: 83.2%
Positive Predictive Value: 76.3%

Microalbumin/Creatinine Ratio (P/C): 24-hour urine collection[152]

1. Defined as the number of grams of protein per gram of creatinine excreted in 24 hours.
2. Normal value should not exceed 0.2 grams,
3. Slightly higher values to .42 grams (upper limit of normal) in insurance urine samples may reflect a delay in analysis with creatinine degeneration,
4. Should not be used for risk assessment in isolation from other data as a number of factors can affect numerator & denominator i.e., state of hydration, physical activity, etc.

Table 53. Reduction of Relative Risk of Neuropathy—Results of DCCT: NEJM 1993

Cohort	Intensive Treatment	Conventional Treatment	% Risk Reduction
Development prevented	3.1	9.8	69
Progression prevented	7.0	16.1	57

Neuropathy

Neuropathy, characterized as peripheral (mono & polyneuropathy) or autonomic (cardiovascular, gastrointestinal & genitourinary) has a variety of differing forms, manifestations and associated mortality and morbidity in diabetes.[153,154,155] Common clinical expressions include mild peripheral sensorimotor paresthesias of the feet or toes. With time, severity progresses to hypoesthesia and insensate feet become vulnerable to trauma, infection, foot ulcers and amputation. DCCT results below indicated a major beneficial impact with greatly enhanced risk reduction for the development and progression of neuropathy with intensive Rx: See Table 53.

Autonomic neuropathy may affect the cardiovascular, gastrointestinal and genitouri-

nary systems with catastrophic clinical syndromes including gastroparesis with pernicious nausea & vomiting, and diabetic diarrhea alternating with constipation. Genitourinary neuropathy causes impotence, and bladder hypotonia or atonia resulting in overflow incontinence.[156,157]

Cardiovascular neuropathy red flags include resting tachycardia, postural hypotension, systolic & diastolic decreased blood pressure, sympathetic and parasympathetic failure resulting in decreased glomerulo filtration rate, lack of respiratory variation in heart rate and most ominously, painless myocardial infarction & silent ischemia.[158,159]

10-year mortality rate for autonomic neuropathy summarized by Watkins[160] as follows:

Symptomatic diabetics: 27% 10-year mortality: Asymptomatic diabetics: 10% 10-year mortality

Hazard ratio: 2.7

Retinopathy[161,162]

General: Diabetes mellitus is a leading cause of blindness in the United States.[162] In the pre-DCCT era, retinopathy occurred in almost all IDDM and most NIDDM patients with long duration diabetes.

Non-proliferative retinopathy—also called background retinopathy—is generally benign unless it occurs near the macula, and consists of microaneurysms & hard exudates. *It is not a marker for excess mortality.* As retinopathy progresses, terminal capillaries become obstructed causing retinal ischemia.

Infarctions of the nerve layer appear as soft (cotton-wool) exudates with new vessel proliferation *proliferative retinopathy* in response to angiogenic growth factors released by the ischemic retina. It is a *marker for renal and vascular disease.*[164] Symptomatic or asymptomatic vascular disease may be present, along with nephropathy, proteinuria, vitreous hemorrhage, retinal edema and blindness.

Retinopathy versus mortality[164]: Klein and associates[165] investigated the association of ocular disease with all-cause mortality and cause-specific mortality in a geographically defined population-based cohort study in an 11-county area in Wisconsin.

STUDY POPULATION

- Participants were all younger-onset diabetic persons (diagnosed as having diabetes at <30 years of age and taking insulin) and a random sample of older-onset diabetic persons (diagnosed as having diabetes at ≥30 years of age).
- Diabetic retinopathy, macular edema, visual acuity, and cataract were measured using standardized protocols at baseline examinations from 1980 to 1982, in which 996 younger-onset and 1370 older-onset persons participated.
- Participants were followed up for 16 years.

MAIN OUTCOME MEASURE: All-cause and cause-specific mortality as determined from death certificates.

RESULTS

In the younger-onset group, after controlling for age and sex, retinopathy severity, macular edema, cataract, history of cataract surgery, and history of glaucoma at baseline, were associated with all-cause and ischemic heart disease mortality.

In the older-onset group

1. After controlling for age and sex, retinopathy and visual impairment were related to all-cause, ischemic heart disease, and stroke mortality. No ocular variable under study was related to cancer mortality.

2. Retinopathy severity was related to all-cause and stroke mortality, and visual impairment was related to all-cause, ischemic heart disease, and stroke mortality.

In the younger-onset group, after controlling for systemic risk factors, visual impairment was associated with all-cause and ischemic heart disease mortality.

CONCLUSIONS

1. Presence of more severe retinopathy or visual impairment in diabetic patients is a risk indicator for increased risk of ischemic heart disease death. Presence of these ocular conditions may identify individuals who should be under care for cardiovascular disease.

2. In the post DCCT era, The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group was organized to assess whether the benefits of intensive therapy to reduce the risk of occurrence and severity of microvascular complications (retinopathy & nephropathy) persists for four years after the end of the Diabetes Control and Complications Trial.[166]

3. The reduction of the risk of progressive retinopathy and nephropathy resulting from intensive therapy persisted during the four years of follow-up in the EDIC study despite increasing hyperglycemia.

4. Those who will benefit most from eye screening are patients with poor glycemic control.[167]

MORTALITY IMPACT OF C0-EXISTING RISK FACTORS

Hypertension

Recent guidelines have emphasized that the target blood pressure levels for patients with diabetes should be lower than in other hypertensive groups.[168,169] A decrease in cardiovascular events is especially important to patients with diabetes, who have at least a 2-fold increase in cardiovascular mortality that is further increased by concomitant hypertension.[170] Hypertension is associated with both the progression of renal and cardiovascular disease and its control is linked to a decreased rate in their concomitant excess mortality and morbidity in IDDM & NIDDM patients.[171,172]

The Heart Outcomes Prevention Evaluation (HOPE) Study[173] cited elsewhere, provides compelling evidence for the role of ACE inhibition in patients with diabetes. Ramipril treatment was associated with a:

25% reduction in a composite endpoint of cardiovascular death, MI, and stroke;

24% decrease in total mortality, beneficial effects were observed with a reduction in systolic blood pressure of only 2.4 mm Hg and diastolic of 1 mm Hg after 4 years.

The 1990 WHO Multinational Study by Morrish[174] of co-existing risk factors and their contribution to mortality in diabetic patients indicated the following:

STUDY DESIGN

- 497 diabetics ages 35–54; 254 males, 243 females,
- Stratified by age, gender, diabetes type (equal numbers IDDM & NIDDM), duration,
- Follow-up period 1975–1987.
- Overall mortality = 92 deaths (see Table 54).

CONCLUSION

Hypertension and proteinuria have the most consistent associations with mortality in the different analyses with the effect of hypertension appearing stronger in IDDM and proteinuria in NIDDM.

The 1996 WHO Multinational Study reported by Wang and colleagues in 1996[175] was more complete & statistically powerful, determined the extent that mortality in IDDM and NIDDM patients is in excess of that in the general population and examined its relation to hypertension and proteinuria in diabetic patients.

STUDY DESIGN: Stratified random sample of 4,714 diabetics (2310 men, 2404 women) ages 35–55 clinically followed from 1975 to 1987.

- Excess mortality, compared with the background population, was assessed in terms of standardized mortality ratios (SMRs) for each of the 10 international cohorts
- The relationship between excess mortality & proteinuria/hypertension was examined by DM type & sex.

Table 54. *Results for IDDM*

Risk Factors	Relative Risk for All-Cause Mortality (Univariate Cox Regression)	
Variable	Males (n = 117)	Females (n = 123)
Systolic BP	1.5	1.4
Diastolic BP	1.4	1.0
Serum cholesterol	1.0	0.9
Plasma creatinine	1.5	1.2
Body mass index	0.9	0.9
Duration	1.3	1.1
Proteinuria	2.1	2.9
ECG abnormal	0.5	3.2
Hypertension	**4.3**	**7.2**
Smoking	1.0	1.1
Results for NIDDM		
	Males (n = 132)	Females (n = 114)
Systolic BP	1.2	1.0
Diastolic BP	1.2	0.8
Serum cholesterol	1.0	1.5
Plasma creatinine	0.5	1.6
Body mass index	1.3	1.1
Duration	1.1	1.2
Proteinuria	**2.5**	**5.0**
ECG abnormal	1.9	0.8
Hypertension	2.0	1.5
Smoking	1.7	1.3

Table 55. Demographics

	Total #	Male #	Female #
Diabetics:	4,714	2,310	2,404
IDDM:	1,266	663	603
NIDDM:	3,448	1,647	1,801
Deaths	1,088 (23%)		
IDDM deaths	367 (34%)		

- Definition of hypertension: systolic BP ≥ 160 mmHg; diastolic BP ≥ 95 mmHg
- Definition of proteinuria: light to heavy turbidity (see Tables 55 and 56).

COMMENT

1. SMRs were in general higher in patients with IDDM (ranging from 188 to 686 for men and from 336 to 790 for women).

Table 56. *Mortality Results of 1996 WHO Study*

1. All-cause Standardized Mortality Ratios (SMRs) by DM Type and Gender

Variable	Standardized Mortality Ratios
IDDM male	437 (188 to 686)
IDDM women	563 (336 to 790)

2. Cardiovascular SMRs by Diabetes Mellitus Type and Gender

	IDDM		NIDDM	
Cause	Male	Female	Male	Female
CHD	504	1155	414	749
Stroke	736	747	284	371

3. Relative Risk (SMRs): With Hypertension and Proteinuria

IDDM males:	11	IDDM females:	18
NIDDM males:	5	NIDDM females:	8

4. Relative Risk (SMRs): Absence of Proteinuria and Hypertension

IDDM males:	284	IDDM females:	360
NIDDM males:	192	NIDDM females:	236

2. For both diabetes types and in both sexes, SMRs decreased with increasing age and increased with increasing diabetes duration.

3. IDDM patients with both hypertension and proteinuria experienced a strikingly high mortality risk:
11-fold for men with IDDM and 18-fold for women with IDDM,

5-fold for men with NDDM and 8-fold for women with NIDDM,

4. Even in the absence of proteinuria and hypertension, SMRs were significantly increased in both IDDM (284 men & 360 women) and NIDDM (192 men & 236 women) patients.

CONCLUSIONS

1. Considerable international differences were found not only in mortality rates for the two types of diabetes but also in the extent of excess mortality among centers.

2. IDDM had the highest excess mortality,

3. Significant excess mortality was demon-

strated even in patients without proteinuria and hypertension for both sexes and for both types of diabetes

Isolated Systolic Hypertension

After the fact analyses of studies performed more than 10 years ago, such as the Systolic Hypertension in the Elderly Program (SHEP), indicated that antihypertensive therapy may reduce the rate of cardiovascular disease (CHD) events in the diabetes patient subgroup.[176]

SHEP Study Participants

4736 diabetic males and females age ≥ 60 at baseline with isolated systolic hypertension (ISH), (blood pressure ≥ 160 mm Hg; diastolic BP <90 mm Hg at baseline, 583 NIDDM and 4149 non-diabetic patients,

RESULTS

1. The SHEP antihypertensive drug regimen lowered BP of both diabetic and non-diabetic patients;
2. 5-year major CHD rate was 34% lower for the treated group compared to placebo, both for diabetics (95% CI, 6%-54%) and non-diabetics (95% CI 21%-45%),
3. Absolute risk reduction with treatment compared with placebo was twice as great for diabetic versus non-diabetic patients (101/1000 vs 51/1000 randomized participants at the 5-year follow-up), reflecting the higher risk of diabetic patients.

CONCLUSION

Low-dose diuretic-based (chlorthalidone) treatment is effective in preventing major CVD events, cerebral and cardiac, in both NIDDM and non-diabetic older patients with ISH.

The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators[177] paralleled SHEP Study outcomes

1. Active treatment reduced the total rate of stroke from 13.7 to 7.9 endpoints per 1000 patient-years (42% reduction; $p = 0.003$).
2. Non-fatal stroke decreased by 44% ($p = 0.007$).
3. All fatal and non-fatal cardiac endpoints, including sudden death, declined by 26% ($p = 0.03$) and all fatal and non-fatal cardiovascular endpoints by 31% ($p < 0.001$).
4. Cardiovascular mortality was slightly lower on active treatment (-27%, $p = 0.07$), but,
5. All cause mortality was not influenced (-14%; $p = 0.22$)

CONCLUSION

Anti-hypertensive treatment of 1000 patients for 5-years may prevent 29 strokes or 53 major cardiovascular endpoints.

Systolic Hypertension in Europe (Syst-EUR) study: Quite recently, Tuomilehto and colleagues[178] indicated that in 492 diabetic patients of 4695 patients (age ≥ 60-years) with systolic blood pressure of 160 to 219 mm Hg and diastolic pressure below 95 mm Hg, the calcium channel blocker (CCB), nitrendipine, was associated with a decrease in the rate of cardiac events as well as cardiovascular mortality;

1. Overall mortality: reduced 55%—from 45.1 deaths/1000 patients to 26.4 deaths/1000 patients
2. Mortality from cardiovascular disease: reduced by 76%,
3. All cardiovascular events combined: reduced by 69%,
4. Fatal and non-fatal strokes: reduced by 73%,
5. All cardiac events combined: reduced by 63%.

CONCLUSIONS

1. Nitrendipine-based antihypertensive therapy is particularly beneficial in older patients with diabetes and isolated systolic hypertension;
2. Long-acting calcium channel blockers are not harmful in diabetic patients.

Isolated Diastolic Hypertension[179]

Hypertension Optimal Treatment (HOT) Randomized Trial Study Group:[180] Principal results on 18,790 patients from 26 countries, ages 50 to 80 years (mean 61.5 years) with hypertension and diastolic blood pressure between 100 mm Hg and 115 mm Hg (mean 105 mmHg), whether measured at home or clinic,[181] were:

1. In diabetes patients, there was 51 % reduction in major cardiovascular events in target group ≤ 80 mm Hg BP compared with target group ≤ 90 mm Hg (p for trend = 0.005).
2. Acetylsalicylic acid reduced major cardiovascular events by 15% (p = 0.03) and all myocardial infarction by 36% (p = 0.002), with no effect on stroke,
3. There were seven fatal bleeds in the ASA group and eight in the placebo group, and 129 versus 70 non-fatal major bleeds in the two groups respectively (p < 0.001).
4. A sub-study showed that the lower the blood pressure achieved, the better the quality of life.

FACET Study:[182] a post-hoc analysis suggested that fosinopril was associated with fewer vascular events than amlodipine.

The Swedish Trial in Old Patients (STOP-2)[183] however, recently found that ACE inhibitors were superior to calcium channel blockers in preventing MI and congestive heart failure in the subgroup of elderly patients with diabetes.

'STOP-2' RESULTS: From 1950 to 1989

1. Use rate of anti-hypertensive medications increased from 2.3% to 24.6% among men, and from 5.7% to 27.7% among women,
2. Age-adjusted prevalence of systolic blood pressure of ≥ 160 mm Hg or diastolic blood pressure of ≥ 100 mm Hg declined from 18.5 % to 9.2% among men and from 28.0% to 7.7% among women,
3. Age-adjusted reductions in the prevalence of ECG evidence of LVH, from 4.5% to 2.5% among men and from 3.6% to 1.1% among women.

Framingham Heart Study:[184] 10,333 participants in the Framingham Heart Study who were 45 to 74 years of age underwent a total of 51,756 examinations from 1950 to 1989. Data were obtained on blood pressure, the use of anti-hypertensive medications, electrical evidence of left ventricular hypertrophy (LVH) on electrocardiograms.

CONCLUSIONS

Increasing use of anti-hypertensive medication has resulted in a reduced prevalence of high blood pressure and a concomitant decline in LVH (and considerable mortality) in the general population from cardiovascular disease since the late 1960s.

Lipids and Diabetes Mellitus:[185,186,187,188,189] Patients with diabetes mellitus (DM) have a marked increase in coronary heart disease (CHD) events relative to those without DM.

MORTALITY

1. In the 6-year ***Canterbury, New Zealand Study*** on a cohort of 447 subjects of predominantly European origin (median age 62-years) with type 2 diabetes mellitus reported by Florkowski et al.,[190] mortality rates were compared with the general New Zealand population by calculating standardized mortality ratios (SMR) and the hazard ratio (HR) of prognostic factors evaluated with Cox's proportional hazard model.

Six-year survival was 70% (95% CI 66–74).

- SMR was 2.53 (95% CI 1.99–2.68) for the female cohort
- SMR was 2.03 (95% CI 1.60–2.59) for the male cohort.

Factors assessed at baseline (1989) that were independently prognostic of total mortality included age, male sex, pre-existing coronary artery disease (CAD) (HR 2.2, 95% CI 1.5–3.3) and plasma cholesterol (HR for 1.4 mmol l(-1) change: 1.49, 95% CI 1.2–1.9). HDL-cholesterol was protective in women (HR for 0.4 mmol l (-1) change: 0.72, 95% CI 0.51–1.00).

Predictors of CAD mortality (in those subjects free of CAD in 1989) included:

Table 57

Simvastatin treated diabetics	Non-diabetics
Total mortality: 0.57 (95% CI, 0.30–1.08; P = 0.087),	0.71 (95% CI, 0.58–0.87; p = 0.001)
Major CHD events (death or MI): 0.45 (95% CI, 0.27–0.74; P = 0.002),	0.68 (95% CI, 0.60–0.77; P < 0.0001)
Any atherosclerotic event: 0.63 (95% CI, 0.60–0.77; p < 0.0001),	0.74 (95% CI, 0.68–0.82; p < 0.0001)

- Plasma cholesterol (HR for 1.4 mmol l(-1) change: 1.86 95% CI 1.20–2.89)
- Glycated haemoglobin (HR for 1.8% change: 1.9 95%CI 1.04–3.47),
- Male sex, peripheral vascular disease, and smoking

2. In the ***Multiple Risk Factor Intervention Trial (MRFIT)*** Reported by Stamler and colleagues[191],

- *Relative risk* for CVD mortality for diabetic compared with non-diabetic men ranged from 2.83 to 4.46 at varying levels of serum cholesterol. Of interest, unlike absolute excess risk, RR was lower at higher serum cholesterol levels.
- *Absolute risk* for CVD mortality:
  Non-diabetic men: 32.28/10,000 person-year (46.12–13.84),
  Diabetic men: 68.71 (130.43–61.72) or more than double.

In a landmark report from the ***Scandinavian Simvastatin Survival Study (4S)***[192] using a clinical case definition of DM (202 diabetics compared with 4,242 non-diabetic patients with previous myocardial infarction, angina pectoris, serum cholesterol 5.5–8.0 mmol/l, and serum triglycerides ≤2.5 mmol/l), simvastatin-treated patients had significantly fewer CHD end-events compared with placebo-treated control subjects. Over the 5.4-year median follow-up period, simvastatin treatment produced mean changes in serum lipids in diabetic patients similar to those observed in non-diabetics.

RESULTS

Relative risks (RRs) of main endpoints were as in Table 57.

Table 58

Risk	LDL cholesterol	HDL cholesterol*	Triglyceride
High	≥130	<35	≥400
Borderline	100–129	35–45	200–399
Low	<100	>45	<200

* Data are given in milligrams per deciliter. For women, the HDL cholesterol values should be increased by 10%.

CONCLUSIONS

The results strongly suggest that cholesterol lowering with simvastatin:

1. Improves the prognosis of diabetic patients with CHD,

2. The absolute clinical benefit is greater in diabetics with CHD than in non-diabetics with CHD because diabetics have a higher absolute risk of recurrent CHD events & other atherosclerotic events.

3. Significant decreases in total mortality, major coronary events, and revascularizations were also observed in simvastatin-treated patients with impaired fasting glucose levels (≤6.0 mmol/L [≤110 mg dL]) or DM and known CHD.[193]

4. Similar reductions in cardiovascular events in diabetics using pravastatin were reported by the cholesterol and recurrent events **(CARE) trial investigators.**[194]

Categories of Risk: The American Diabetes Association has recently published its Clinical Practice Recommendations 2000 for the management of dyslipidemia.[195] The categories of CHD risk by lipoprotein levels in type 2 diabetic patients are shown in Table 58.

Management of Dyslipidemia: Aggressive

therapy of diabetic dyslipidemia will probably reduce the risk of CHD in patients with diabetes. Primary therapy should be directed first at lowering LDL levels. The goal is to reduce LDL concentrations to levels recommended for patients with preexisting CHD (<100 mg/dl [2.60 mmol/l]). The initiation level for behavioral interventions is also an LDL cholesterol of >100 mg/dl (2.60 mmol/l)]. The initial therapy should be to use statin therapy with the addition of a resin if necessary to reach the LDL goal.

However, limited data are available from clinical trials especially in diabetic patients without clinical CVD. In the absence of such data, because of the high mortality for diabetic patients with first myocardial infarction, *aggressive treatment of dyslipidemia is also indicated.*

- For patients without previous CHD, the goal for LDL cholesterol is <100 mg/dl (2.60 mmol/l); the initiation level for pharmacological therapy is set at an LDL level >130 mg/dl (3.35 mmol/l).
- However, in patients with multiple risk factors, some authorities recommend the initiation of drug therapy when LDL levels are between 100 and 130 mg/dl[196]
- The initial therapy for hypertriglyceridemia is improved glycemic control.
- Additional triglyceride lowering can be achieved with very high dose statins (for subjects with both high LDL and triglyceride levels) or fibric acid derivatives (gemfibrozil or fenofibrate).

Obesity and Diabetes Mellitus: Existing evidence regarding the relationship between weight and mortality and the effects of weight change is conflicting.

Colditz and colleagues[197] at the Channing Laboratory, Harvard Medical School, carried out a study to determine the relation of body mass index (weight/height2) with the risk of clinical *NIDDM in a cohort* of 113,861 US women aged 30–55 years in 1976. During the 8 years of follow-up (826,010 person-years), 873 definite cases were identified among women initially free from diagnosed diabetes.

RESULTS

1. Among women of average body mass index, 23–23.9 kg.m2, the relative risk was 3.6 times that of women having a body mass index <22 kg/m2. The risk continued to increase above this level of body mass index.

2. The authors observed a much weaker association with weight at age 18, and this association was eliminated after adjustment for current body mass index (BMI).

3. Thus, weight gain after age 18 was a major determinant of risk.

4. For an increase of 20–35 kg, the ***relative risk was 11.3,***

5. For an increase of more than 35 kg, the ***relative risk was 17.3.***

6. These data indicate that, at even average weight, women are at increased risk of clinical NIDDM,

7. The relation of body mass index and risk of diabetes is continuous.

Higgins and colleagues[198] identified the benefits and adverse effects of weight loss from observations derived from the Framingham Study in men and women, ages 35–54, (20-year FU) in Framingham, Mass.

1. During 20 years follow-up, death rates were highest in those whose BMI decreased and in those with the highest BMI at study entry.

2. Relative risks for death from cardiovascular disease, coronary heart disease,

3. All cause mortality was significantly greater by 33% to 61% in men whose BMI decreased after adjusting for age and risk factors for cardiovascular disease.

4. In women, weight loss and weight gain were associated with higher relative risks for cardiovascular disease and coronary heart disease, but only the 38% increase in total mortality rate among women who lost weight was statistically significant after adjusting for age.

They concluded that weight loss was associated with improvements in blood pres-

sure and cholesterol levels but also with continued cigarette smoking, prevalent and incident cardiovascular disease, diabetes mellitus, other diseases, and higher death rates. Leanness and maintenance of stable weight were beneficial to risk factors, and to the prevention of morbidity and death.

Chaturvedi and associates however, in the Department of Epidemiology and Public Health, University College, London, U.K., examined morbidity and mortality risks associated with body weight in people with IDDM and NIDDM.

In the IDDM cohort[199] of 644 men and 576 women with IDDM from nine centers worldwide and followed from 1975 to 1988, the following results were noted:

1. Body weight was positively associated with blood pressure, and in men, with cholesterol,
2. Fasting blood glucose was higher was higher in the most obese groups in women only,
3. There were 204 male deaths, and 148 female deaths,
4. A J-shaped relationship existed between body weight and all-cause mortality
5. Highest mortality rates occurred in the leanest BMI category.
6. The age-, duration-, and center-adjusted mortality rate ratio (95% CI) comparing BMI category $<$29 kg/m2 with BMI category $\geq$22 and $<$24 kg/m2 was 2.64 (1.59–4.38) in men and 1.54 (0.77–3.06 in women.
7. Additional adjustments for smoking, blood pressure, glucose, cholesterol, and proteinuria did not qualitatively alter these findings

CONCLUSIONS

Except in very lean people with IDDM, body weight is not significantly associated with mortality,

Efforts to improve glycemic control should not be restricted by concerns about the effects of weight gain on mortality.

In the NIDDM cohort[200] study of 1,416 men and 1,544 women, a morbidity follow-up was performed in 1983, and a mortality follow-up continued until 1988. Data were analyzed according to geographical groups: Europeans, East Asians, and Native Americans. The relationship between weight change and mortality was analyzed for Europeans only.

RESULTS

1. Generally, BMI was positively associated with age, blood pressure, and cholesterol,
2. BMI was negatively associated with diabetes duration, retinopathy prevalence, & insulin use,
3. No clear relationship between BMI and mortality across geographical groups,
4. In Europeans, weight loss in the leanest subjects at baseline (BMI $<$ 26 kg/m2) was associated with a ***three-fold increase in mortality risk*** compared with those who had maintained a steady weight (relative risk [RR] 3.05, 95% CI, 1.26–7.36).
5. Only in the most obese group was weight loss associated with a mortality risk reduction (BMI $>$ 29 kg/m2, RR 0.84, 95% CI 0.40–1.74)

CONCLUSIONS

1. The positive association of BMA with age, blood pressure, and cholesterol and the negative association with diabetes duration, retinopathy, and insulin use may explain why there is no strong relationship between BMI and mortality in NIDDM.
2. Weight loss, particularly in the relatively lean diabetic person, may be associated with an increased mortality risk.

Smoking and Diabetes Mellitus

In the *EURODIAB IDDM Complications Study*[201] which was a prevalence survey of 3,250 men and women aged 15–60 years with IDDM from 31 diabetes centers in 16 European countries, Chaturvedi and associates determined that the:

1. Relative risk (RR) of developing microvascular complications (microalbuminuria

and retinopathy) between insulin-dependent diabetics who were smokers versus IDDM non-smokers was 2.0.

2. Current smokers had higher prevalence of microalbuminuria and total retinopathy than those who never smoked,

3. Ex-smokers had a higher prevalence of macroalbuminuria and proliferative retinopathy than those who never smoked,

4. Both current and ex-smokers had similar prevalence of microalbuminuria.

In the *MRFIT Study* (previously cited—see section on Lipids and DM)

1. Absolute risk for heavy diabetic smokers than diabetic non-smokers: 89.64/ vs. 56.28/ 10,000 person-yr

2. RR for diabetic compared with non-diabetic men ranged from 2.38 (smokers of 16–25 cigarettes/day) to 4.56 (non-smokers).

In the Epidemiology of Diabetes Complications Study (EDC)[202] in the United States, comparing similar complication outcomes between IDDM smokers and IDDM non-smokers of comparable ages and sex distributions and duration characteristics between the two continents;

1. Prevalence of macroalbuminuria was higher in EDC (27%) than in EURODIAB (12%),

2. Rates of microalbuminuria were similar (33 versus 25% respectively

CONCLUSIONS

1. Advanced renal disease is more prevalent in IDDM in EDC (Pittsburgh, PA) than in Europe,

2. This is not explained by hypertension, glycemic control, or smoking.

American Diabetes Association Recommendations Regarding Smoking: The rational for the prevention and cessation of smoking in diabetics is substantial. The guidelines are based on the body of evidence summarized in the ADA's technical review on smoking and diabetes.[203]

Alcohol and Diabetes Mellitus

1. Lindegard and Hilborn[204] studied the effects of *alcohol abuse* in 1987 and found a very strong correlation with excess mortality and brain infarct.

2. Valmadrid et al[205] analyzed the association between alcohol consumption and risk of cardiovascular outcomes in a population-based prospective cohort study from 1984 through 1996, with a follow-up of 12.3 years.

Setting and Participants:

- A total of 983 older-onset diabetic individuals (mean [SD] age, 68.6 [11.0] years; 45.2% male; 98.5% white) were interviewed about their past-year intake of alcoholic beverages during the 1984–1986 follow-up examination of a population-based study of diabetic persons in southern Wisconsin.

Main Outcome Measure:

- Time to mortality from CHD by category alcohol intake.

MORTALITY RESULTS

1. Alcohol use was *inversely associated* with risk of CHD mortality in older-onset diabetic subjects.

2. The CHD mortality rates for never and former drinkers were 43.9 and 38.5 per 1000 person-years, respectively,

3. Rates for those with alcohol intakes of less than 2, 2 to 13, and 14 or more g/d were 25.3, 20.8, and 10.0 per 1000 person-years, respectively.

4. Compared with never drinkers and controlling for age, sex, cigarette smoking, glycosylated hemoglobin level, insulin use, plasma C-peptide level, history of angina or myocardial infarction, digoxin use, and the presence and severity of diabetic retinopathy, former drinkers had a relative risk (RR) of 0.69 (95% confidence interval [CI], 0.43–1.12);

5. Excess Mortality (Relative Risk): See Table 59.

6. Further adjustments for blood pressure, body mass index, education, physical activity, diabetes duration, hypertension history, overt nephropathy, peripheral neuropathy, lipid measures, or intake of medications such as as-

Table 59

Excess Mortality (Relative Risk)	For those who drank the following amounts of alcohol:
• 0.54 (95% CI, 0.33–0.90):	Less than 2 g/day (less frequent than 1 drink a week):
• 0.44 (95% CI, 0.23–0.84):	2 to 13 g/day:
• 0.21 (95% CI, 0.09–0.48):	14 or more g/day (about 1 drink or more a day):

pirin and anti-hypertensive agents did not change the associations observed.

CONCLUSION

1. Their results suggest an overall beneficial effect of alcohol consumption in decreasing the risk of death due to CHD in people with older-onset diabetes

2. Perhaps the prudent wisdom—'*Poco di Tutti*'—(a little of everything) is operative here (italics mine).

WHAT WILL THE FUTURE BRING?

Duration of life

There is no denying that a diagnosis of diabetes shortens the expectation of duration of life. Given our current knowledge regarding diabetes mellitus, the early set of criteria used from the late 1930s to the present in underwriting were understandably strict especially in regard to age of onset (above 20), disease duration (less than 10 years) in a person regularly employed. With the historical, clinical, and epidemiologic experience gained over subsequent decades, these criteria have changed and the life-insurability of applicants with diabetes has become relatively routine.

Prognostic insights gained over the last 40 years coupled with continuing diagnostic and treatment advances in medicine, endocrinology and the technological development of non-invasive glucose sensors and implantable insulin pumps discussed in this paper, all the result of well-designed studies in the modern (glycemic) era, provide useful understanding of future trends to minimize diabetes projected extra mortality (see Table 60).

Table 60. Relative Risk 'Best' Assumptions for Future Mortality in the Millenium*

AGE at Dx	DISEASE DURATION (years)			
	0–5 (%)	6–10 (%)	11–15 (%)	≥16 (%)
10–19	300	300	300	350
20–39	250	275	275	275
40–59	200	200	250	250
60 up	175	175	175	175

* 1. My personal best-case predictive scenarios of anticipated improving relative risk (RR) in the millenium associated with continuing diagnostic and intensive treatment advances, by age-onset and disease duration. We presume perennial good glycemic control (several results of glycohemoglobin <130% of normal), good risk factor control, negative family history, documented absence of micro-vascular & macro-vascular complications and co-morbidities, normal weight and blood pressure.

* 2. Note: A special—controlled by diet-alone category—of diabetes mellitus has a relative risk of slightly less than 150% with any age-onset & disease duration

* 3. From birth to age 10 years relative risk remains exceedingly high but childhood treatment advances in the next 5–10 years are expected to routinely stabilize the dire consequences of early childhood DM.

* 4. Assuming a 20-year old sample population with newly diagnosed DM, 40–50 years of prospective clinical follow-up will be necessary to bio-statistically validate the above assumptions.

REFERENCES

1. Surveillance Report: The Public Health of Diabetes Mellitus in the United States. Centers for Disease Control and Prevention. Diabetes Surveillance 1997. *http://www.cdc.gov/nccdphp/ddt/survl/surveill.htm*
2. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. JAMA 1999; 281: 1291–1297
3. Muller WA. Diabetes Mellitus—long time survival. J Ins Med 1998; 30: 17–27

4. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National estimates and general information on diabetes in the United States. NIH Publication No. 98–3926, Atlanta, GA: U.S. Department of health and Human Services, Centers for Disease Control and Prevention, November 1997. *http://www.niddk.nih.gov/health/diabetes/pubs/dmstats/dmstats.htm*
5. Aitman TJ, London MRC Clinical Science Center. Nature, Medicine, January, 1999
6. Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 1990; 132: 501–513.
7. Hu FB, Sigal RG, Rich-Edwards JW et al. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. JANA 1999; 282: 1433–1439.
8. Tattersall RB. Mild familial diabetes with dominant inheritance. Q J Med 1974; 43: 339.
9. Froguel P, Vaxillaire M, Sun F, et al. Close linkage of glucokinase locus on chromosome 7p to early onset non-insulin-dependent diabetes mellitus. Nature 1992: 356: 162.
10. Herman WH, Fajans SS, Ortiz FJ, et al. Abnormal insulin secretion, not insulin resistance, is the genetic or primary defect of MODY in the RW pedigree. Diabetes 1994; 43(1): 40–46.
11. Diabetes during pregnancy—United States, 1993–1995. MMWR 1998 (May 29);47: 408–414
12. Metzger BE, Cho NH, Roston SM, Radvany RR. Prepregnancy weight and antepartum insulin secretion predict glucose tolerance five years after gestational diabetes mellitus. Diabetes Care 1993; 16 (12): 1598–1605.
13. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997 July; 20 (7): 1183–97.
14. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. Diabetes care 1995; 19: 896–909
15. Little RR, Wiedmeyer HM, England JD, et al. Interlaboratory standardization of measurements of glycohemoglobin. Clin Chem 1992; 38: 2472–78.
16. Goldstein DE, Little RR, England JD, et al. Methods for quantitating glycosylated hemoglobins: high performance liquid chromatography and thiobarbituric acid colorimetry. In: Clarke WL, Larner J, Pohl SL, eds. Methods in Diabetes Research, Vol. 2.: Clinical methods. New York: John Wiley, 1986: 475–504.
17. Ludvigsen CW, Sprague G, Smith KM. Fructosamine—clinical usefulness and determination of reference ranges. J Ins Med 1989; 21:No. 3, 203–208
18. Miller PK, Ludvigsen CW, Roberts BD. Letter to the editor; Prostate specific antigen and fructosamine (sensitivity and specificity of glycated serum proteins and glycohemoglobin). J Ins Med 1990; 22(1):67–68.
19. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National estimates and general information on diabetes in the United States. NIH Publication No. 98–3926, Atlanta, GA: U.S.Department of health and Human Services, Centers for Disease Control and Prevention, November 1997. *http://www.niddk.nih.gov/health/diabetes/pubs/dmstats/dmstats.htm*
20. Cohen DL, Neil HAW, Thorogood M, Mann JI. A population-based study of the incidence of complications associated with type 2 diabetes in the elderly. Diabetic Medicine 1991; 8: 928–933.
21. Brownlee M. Glycation products and the pathogenesis of diabetic complications. Diabetes Care 1992; 15: 1835.
22. MacLeod CA, Murchison LE, Russell EM, Dingwall-Fordyce I. Measuring outcomes of diabetes: a retrospective survey. Diabetic Medicine 1989; 6: 59–63.
23. Colwell J. DCCT findings: Applicability and implications for NIDDM. Diabetes Reviews 1994; 2: 277.
24. Singer RB, Levinson L. 905-Natural history of diabetes.(Joslin Clinic 1939–1963). Medical Risks: Patterns of Mortality and Survival 1976; 9–22 to 25.
25. Goodkin L, Wolloch L, Gottcent RA, Reich F. Diabetes—A Twenty Year Mortality Study. Trans. Life Ins. Med. Dir. Amer. 1974; 217–269. Rep. In: Medical Risks; Patterns of Mortality and Survival: Editors: RB Singer, L Levinson; D.C.Heath and Co. 1976, pp9–2 to 9–7.
26. Mast JL. Findings from LNRC's fourth major study on diabetics and mortality. Reinsurance Reporter 1996; 148:18–30.
27. Berger B, Stenstrom G, Sundkvist G. Incidence, prevalence and mortality of diabetes in a large population. A report from the Skaraborg Diabetes Registry. Diabetes Care 1999 May; 22 (5): 773–778.
28. Claude R Catellier, MD. Be it resolved that given our current knowledge regarding diabetes mellitus that insurance companies are liberal in their underwriting of this condition (negative). Presentation at the annual Canadian Life Insurance Medical Officers Association (CLIMOA); Chateau Frontenac, Quebec, Canada, May 17, 2000.
29. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. Diabetes Care 1995; 19: 896–909.
30. Ditzel J. Oxygen transport impairment in diabetes. Diabetes 1976; (Suppl II): 832–837.
31. Ludvigsen CW, Sprague G, Smith KM. Fructosamine—clinical usefulness and determination of

reference ranges. J Ins Med 1989; 21: No. 3, 203–208.
32. Miller PK, Ludvigsen CW, Roberts BD. Letter to the Editor; Prostate specific antigen and fructosamine. J Ins Med 1990; 22: No. 1, 67–68.
33. Stout R (personal communication). Reference Ranges for Glycemic Control. Clinical Reference Laboratory (CRL), Lenexa, Kansas, Sept. 17,1998.
34. Stout R (personal communication). Reference ranges for glycemic control. Clinical Reference Laboratory (CRL), Lenexa, Kansas, September 17, 1998.
35. Moss SE, Klein R, Klein BEK, Meuer S. The association of glycemia and cause-specific mortality in a diabetic population. Arch Int Med 1994; 154: 2473–2479.
36. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. Diabetes Care 1995; 18: 896–909.
37. National Glycohemoglobin Standardization Program (NGSP). *http://www.missouri.edu/~diabetes/ngsp.html*
38. Moss SE, Klein R, Klein BEK, Meuer SM. The association of glycemia and cause-specific mortality in a diabetic population. Arch Intern Med 1994; 154: 2473–2479.
39. Balkau B, Shipley M, Jarrett RJ, et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. Diabetes Care 1998 Mar; 21(3):360–7.
40. Harris MI, Eastman RC. Is there a glycemic threshold for mortality risk? [editorial]. Diabetes Care 1998 Mar; 21(3):331–3
41. The Diabetes Control and Complications Trial Research Group, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977–986.
42. Vijan S, Hofer TP, Hayward RA. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. Ann. Int. Med. 1997: 127: 788–795.
43. Andersson DKG, Svardsudd K. Long-term glycemic control relates to mortality in type II diabetes. Diabetes Care 1995; 18: 1534–1543.
44. Celentano A, Vaccaro O, Tammaro P, et al. Early abnormalities of cardiac function in non-insulin dependent diabetes mellitus and impaired glucose tolerance. Am J Cardiol 1995; 76: 1173–1176.
45. Reaven GM. Banting Lecture 1988: role of insulin resistance in human disease. Diabetes 1988 (9); 37: 1595–1607.
46. Davidson MB. Clinical implications of the insulin resistant syndromes. Am J Med 1995; 99:420
47. Depres JP, Lamarche B, Maureague P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 1996 April 11; 334 (15): 952–957.
48. Regenauer A. Prognostic aspects of the metabolic syndrome. J Ins Med 1998; 30 (3):180–190.
49. Nathan DM. Inferences and implications: (Do results from the Diabetes Control and Complications Trial apply in NIDDM?) Diabetes Care 1995; 18: 251–257.
50. Turner RC, Cull CA, et al. UK Prospective Diabetes Study 16, (UKPDS). Overview of 6 years therapy of type II diabetes: A progressive disease. Diabetes 1995; 44: 1249–1258.
51. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998: 352: 837.
52. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:854.
53. Nathan DM. Some answers, more controversy, from UKPDS. UK Prospective Diabetes Study. Lancet 1998; 352: 832.
54. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998; 317: 703.
55. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. UK Prospective Diabetes Study Group. BMJ 1998; 317:720.
56. Abriara C, Colwell JA, Nuttall FQ, et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes. Diabetes Care 1995; 18: 1113–1123.
57. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. Diabetes 1994; 43: 960–967.
58. Standl E, Balletshofer B, Dahl B, et al. Predictors of 10-year macrovascular and overall mortality in patients with NIDDM: the Munich General Practitioner Project. Diabetologia 1996; 39: 1540–1545.
59. Turner RC. The U.K. Prospective Study: a review. Diabetes Care 1998; 21 (Suppl 3): C35–38.
60. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomized study. Lancet 1999 Feb 20; 353 (9153): 617–622.

61. Turner RC; Millns H; Neil HA; Stratton IM; Manley SE; Matthews DR; Holman RR. Diabetes Research Laboratories, Nuffield Department of Medicine, University of Oxford, Radcliffe Infirmary. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ 1998 Mar 14;316(7134):823–8. PMID: 9549452 UI: 98210620
62. Hanefeld M; Fischer S; Julius U; Schulze J; Schwanebeck U; Schmechel H; Ziegelasch HJ; Lindner J. Medical Faculty C. G. Carus, Technical University Dresden, Germany. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. Diabetologia 1996 Dec;39(12):1577–83 PMID: 8960845 UI: 97120174
63. Malone JI, Rosenbloom AL, Grgic A, et al. The role of urine sugar in diabetic management. Am J Dis Child 1976; 130: 1324.
64. Frishman D, Ardito DM, Graham SM. Performance of glucose monitors. Lab Med 1992; 23: 179.
65. Faich GA, Fishbein HA, Ellis SE. The epidemiology of diabetic acidosis: a population-based study. Am J Epidemiol 1983; 117: 551.
66. Malone JI, Rosenbloom AL, Grgic A, Weber FT. The role of urine sugar in diabetic management. Am J Dis Child 1976 Dec; 130(12):1324–1327.
67. Gill GV, Lucus S, Kent LA. Prevalence and characteristics of brittle diabetes in Britain. Walton Diabetes Centre, Walton Hospital, Liverpool, UK. QJM 1996 Nov; 89(11): 839–843.
68. Tattersall R, Gregory R, Selby C, et al. Course of brittle diabetes: 12 year follow-up. Department of Diabetes, University Hospital, Nottingham. BMJ 1991 May 25: 302(6787): 1240–1243.
69. Kent La, Gill GV, Williams G. Mortality and outcome of patients with brittle diabetes and recurrent ketoacidosis. Diabetic Clinic, Royal Liverpool University Hospital, UK. Lancet 1994 Sep 17; 344(89250: 765–766.
70. Scibilia J, Finegold D, Dorman J, et al. Acta Endocrinol Suppl (Copenh) 1986; 279: 326–333.
71. Malone JI, Hellrung JM, Malphus EW, et al. Good diabetic control—a study in mass delusion. J Pediatr 1976 Jun; 88(6): 943–947. J Matern Fetal Med 2000 Jan-Feb; 9(1):42–45.
72. Silverstein JH, Rosenbloom AL. New developments in type 1 (insulin-dependent) diabetes. Department of Pediatrics, University of Florida College of Medicine, Gainesville, USA. Clin Pediatr (Phila) 2000 May; 39(5): 257–266.
73. Melki V, Renard E, Lassmann-Vague V, et al. Improvement in HbA1c and blood glucose stability in IDDM patients treated with lispro insulin analog in external pumps. Service de Diabetologie, Hospital de Rangueil, CHU Toulouse, France. Diabetes Care 1998Jun; 21(6): 977–982.
74. Gabbe SG. New concepts and applications in the use of the insulin pump during pregnancy.Department of Obstetrics and Gynecology, University of Washington School of Medicine, seattle 09195–6460, USA. J Matern Fetal Med 2000 Jan-Feb; 9(1): 42–45.
75. Original Articles—NEJM (rating: 672) Original Text. A.M. James Shapiro, Jonathan R.T. Lakey, Edmond A. Ryan, Gregory S. Korbutt, Ellen Toth, Garth L. Warnock, Norman M. Kneteman, Ray V. Rajotte. NEJM 2000 July 27 (Full text pub)
76. From the Surgical-Medical Research Institute and the Department of Surgery (A.M.J.S., J.R.T.L., G.S.K., G.L.W., N.M.K., R.V.R.) and the Department of Medicine (E.A.R., E.T.), University of Alberta, Edmonton, Alta., Canada. Address reprint requests to Dr. Shapiro at 2D4.37 Department of Surgery, University of Alberta Hospitals, Mackenzie Health Sciences Center, 8440 112 St., Edmonton, AB T6G 2B7, Canada, or at.
77. Shapiro AMJ, Lakey JRT, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000 July; 343(4):230–238
78. Robertson RP. Successful islet transplantation for patients with diabetes—fact or fantasy? N Engl J Med 2000 July: 343 (4): 289–290.
79. Robertson RP, Davis C, Larsen J, Stratta R, Sutherland DER: Pancreas and islet transplantation for patients with diabetes mellitus (Technical Review).
80. Borch-Johnsen K. Improving prognosis of type 1 diabetes. Mortality, accidents, and impact on insurance. Steno Diabetes Centre, Gentofte, Denmark.. Diabetes Care 1999 Mar;22 Suppl 2:B1–3
81. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham Study. JAMA 1979; 241: 2035.
82. Singer DE, Nathan DM, Anderson KM, et al. Association of HbA1c with prevalent cardiovascular disease in the original cohort of the Framingham Heart Study. Diabetes 1992; 41:202.
83. Abbud ZA, Shindler DM, Wilson AC, Kostis JB. Effect.of diabetes mellitus on short- and long term mortality rates of patients with acute myocardial infarction: A statewide **(MIDAS) study.** Am Heart J 1995; 130: 51–8.
84. Zuanetti G, Latini R, Maggioni AP, et al. Influence of diabetes on mortality in acute myocardial infarction: Data from the **GISSI-2 Study.** J Am Coll Cardiol 1993; 22: 1788–94.
85. Orlander PR, Goff DC, Morrissey M, et al. The relation of diabetes to the severity of acute myocardial infarction and post-myocardial infarction

survival in Mexican-Americans and non-Hispanic whites. The **Corpus Christi Heart Project.** Diabetes 1994; 43: 897–902.
86. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? **The Rancho Bernardo Study**. JAMA 1991; 265: 627–631.
87. The Bypass Angioplasty Revascularization Investigation **(BARI) Investigators.** Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996; 335: 217–225.
88. Gum PA, O'Keefe JH Jr, Borkon AM et al. Bypass surgery versus coronary angioplasty for revascularization of treated diabetic patients. Circulation 1997 Nov 4; 96 (9 Suppl): II-7–10.
89. Barsness GW, Peterson ED, Ohman EM, et al. Relationship between diabetes mellitus and long-term survival after coronary bypass and angioplasty. Circulation 1997 Oct 21; 96 (8): 2551–2556.
90. Herlitz J, Wognsen GB, Emanuelsson H, et al. Mortality and morbidity in diabetic and nondiabetic patients during a 2-year period after coronary artery bypass grafting. Diabetes Care 1996; 19: 698–703.
91. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type II diabetes and in non-diabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339: 229–234.
92. Acharya DU, Shekhar YC, Aggarwal A, Anand IS. Lack of pain during myocardial infarction in diabetics: is autonomic dysfunction responsible? Am J Cardiol 1991; 68: 793–796.
93. Nesto RW, Watson FS, Kowalchuk GJ, et al. Silent myocardial and infarction in diabetics with peripheral vascular disease: Assessment by dipyridamole Thallium-201 scintigraphy. Am Heart J 1990; 120: 1073–1077.
94. O'Brien IA, McFadden JP, Corrall RJM. The influence of autonomic neuropathy on mortality in insulin-dependent diabetes. Quart J Med 1991; 79: 495–502.
95. Canto JG, Shlipak MG, Rogers WJ, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. National Registry of Myocardial Infarction 2 (NRMI-2). JAMA June 28,2000; 283: 3223–3229.
96. Nakamura M, Takeshita A, Nose Y. Clinical characteristics associated with myocardial infarction, arrhythmias, and sudden death in patients with vasospastic angina. Circulation 1987; 75: 1110.
97. Bonita R. Epidemiology of stroke. Lancet 1992; 339: 342–344.
98. Kistler JP. The risk of embolic stroke: another piece of the puzzle. N Engl J Med 1994; 331: 1517–1519.
99. Caplan LR. Intracerebral hemorrhage. Lancet1992; 339: 656–658.
100. Bell DSH. Stroke in the diabetic patient. Diabetes Care 1994; 17: 213–219
101. Stegmayr B, Asplund K. Diabetes as a risk factor for stroke. A population perspective. Diabetologia 1995; 38: 1061–1068.
102. Sacco RL. Risk factors and outcomes for ischemic stroke. Neurology (suppl. 1) 1995; 45:S10-S14.
103. Hu FB, Stampfer MJ, Colditz GA, et al. Physical activity and risk of stroke in women. JAMA 2000; 283: 2961–2967.
104. Webster P. The natural history of stroke in diabetic patients. Acta Med Scand 1980; 207: 417–424.
105. Roehmhodt ME, Palumbo PJ, Whisnant JP, Elusback LR. Transient ischemic attack and stroke in a community-based diabetic cohort. Mayo Clin Proc 1983; 58:56–58.
106. Matchar DB, McCrory DC, Barnett HJM, Feussner JR. Medical treatment for stroke prevention. Ann Int Med 1994; 121: 41–53.
107. Hornig CR, Lammers C, Buttner T, et al. Long-term prognosis of infratentorial transient ischemic attacks and minor strokes. Stroke 1992; 23: 199–204.
108. Roehmhodt ME, Palumbo PJ, Whisnant JP, Elusback LR. Transient ischemic attack and stroke in a community-based diabetic cohort. Mayo Clin Proc 1983; 58:56–58.
109. Biller J, Saver JL. Transient ischemic attacks—populations and prognosis. Mayo Clin Proc 1994; 69: 493–494.
110. Easton JD, Hart RG, Sherman DG, Kaste M. Diagnosis and management of ischemic stroke: Part I. Threatened stroke and its management Curr Prob Cardiol 1983; 8; 76.
111. Wang X. Chinese patients with transient ischemic attack. Chinese Med J 1990; 103: 699–703.
112. Evans BA, Sicks JD, Whisnant JP. Factors affecting survival and occurrence of stroke in patients with transient ischemic attacks. Mayo Clin Proc 1994; 69: 416–421.
113. Warlow C. Secondary prevention of stroke. Lancet 1992; 339: 724–727.
114. Moore WS, Barnett HJM, Beebe HG, et al. Guidelines for carotid endarterectomy: a multi-disciplinary consensus statement from the ad hoc committee, American Heart Association. Circulation 1995: 91: 566–579.
115. Streifler JY, Benavente OR, Harbison JW, et al. Prognostic implications of retinal versus hemispheric TIA in patients with high grade carotid stenosis: observations from NASCET (abstract). Stroke 1992; 23:159.

116. Brown RD, Evans BA, Wiebers DO, et al. Transient ischemic attack and minor ischemic stroke: an algorithm for evaluation and treatment. Mayo Clin Proc 1004; 69: 1027–1039.
117. Inzitari D, Eliasziw M, Gates P, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis: for the North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 2000; 342 (No. 23): 1693–1700.
118. North American Symptomatic Carotid Endarterectomy Trial Collaborators: Beneficial effect of carotid endarterectomy in symptomatic patients with high grade stenosis. N Engl J Med 1991; 325: 445–453.
119. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. N Engl J Med 1998; 339: 1415.
120. Executive Committee For the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995: 273; 1421–1428.
121. The CASANOVA Study Group. Carotid surgery versus medical therapy in asymptomatic carotid stenosis. Stroke 1991; 22: 1229–1235.
122. Brown GC, Magargal LE. The ocular ischemic syndrome. Int Opthalmol1988; 11:239–251
123. Stewart CPU, Jain AS. Cause of death of lower limb amputees. Dundee Limb Fitting Centre (DLFC), Broughty Ferry, Scotland. Prosthetics and Orthotics International 1992; 16: 129–132.
124. Stewart CPU, Jain AS, Ogston SA. Lower limb amputee survival. Dundee Limb Fitting Centre (DLFC), Broughty Ferry, Scotland. Prosthetics and Orthotics International 1992; 16: 11–18.
125. DeLuccia N, DeSouza Pinto MAG, Guedes JPB, Albers MTV. Rehabilitation after amputation for vascular disease: a follow-up study. Prosthetics and Orthotics International 1992:16: 124–128.
126. Cleveland Clinic J Med 1993; Jan / Feb: 12
127. Kwolek CJ, Pomposelli FB, Tannenbaum GA, et al. Peripheral vascular bypass in juvenile-onset diabetes mellitus: Are aggressive revascularization attempts justified? J Vasc Surg 1992; 15: 394–401.
128. Howell MA, Colgan MP, Seeger RW, et al. Relationship of severity of lower limb peripheral vascular disease to mortality and morbidity: A six-year follow-up study. J Vasc Surg 1989; 9: 691–697.
129. Kreines K, Johnson E, Albrink M, et al. The course of peripheral vascular disease in non-insulin dependent diabetes. Diabetes Care 1985; 8: 235–243.
130. Messent JW, Elliott TG, Hill RD, et al. Prognostic significance of microalbuminuria in insulin-dependent diabetes mellitus: a twenty-three year follow-up study. Kidney Int 1992, April; 41 (4): 836–839.
131. Stephenson JM, Kenny S, Stevens LK, et al. Proteinuria and mortality in diabetes: the WHO Multinational Study of Vascular Disease in Diabetes. Diabet Med 1995 Feb; 12 (2): 149–155.
132. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Eng J Med 1999; 341 (15): 1127–1133.
133. Andersen AR, Christiansen JS, Andersen JK, et al. Diabetic nephropathy in type 1 (insulin-dependent diabetes): an epidemiological study. Diabetetologia 1982; 25: 496.
134. Remuzzi G, Ruggenenti P, Benigni A. Perspectives in Clinical Nephrology: Understanding the nature of renal disease progression. Kidney International 1997; 51: 2–15.
135. Orth SR, Ritz E. The nephrotic syndrome.N Engl J Med 1998 April; 338 (17): 1202–1211.
136. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. N Engl J Med 1998 Nov; 339 (20): 1448–1556.
137. Singer RB, Balakrishna SS. Mortality in medicare patients on dialysis for end-stage renal disease (ESRD), 1982–1987. J Ins Med 1995 Summer; 27 (1): 28–32.
138. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–34.
139. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130; 461.
140. Wass V, Cameron JS. Cardiovascular disease and the nephrotic syndrome: the other side of the coin. Nephron 1981; 27: 58–61.
141. Ordonez JD, Hiatt RA, Killebrew EJ, Fireman BH. The increased risk of coronary heart disease associated with nephrotic syndrome. Kidney International 1993; 44: 638–642.
142. Alzaid AA. Microalbuminuria in patients with NIDDM: An overview. Diabetes Care 1996; 19: 70–89
143. Klein R, Klein BEK, Moss SE. Prevalence of microalbuminuria in older-onset diabetes. Diabetes Care 1993; 16 (10): 1325–1330.
144. Nielsen S, Hansen KW, Schmitz A, et al. Albuminuria and 24-h ambulatory blood pressure in normal albuminuric and microalbuminuric NIDDM Patients: A longitudinal study. Diabetes Care 1995 Nov; 18 (11): 1434–1441.
145. Gall M, Borch-Johnsen K, Hougaard P, et al. Albuminuria and poor glycemic control predict

mortality in NIDDM. Diabetes 1995; 44: 1303–1309.
146. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of Angiotensin-converting enzyme inhibition in non-insulin- dependent diabetes mellitus. Arch Int Med 1996; 156: 286–289.
147. Kiberd BA, Jindal KK. Routine treatment of insulin-dependent diabetic patients with ACE inhibitors to prevent renal failure: an economic evaluation. Am J Kid Dis 1998 Jan: 31 (1): 49–54.
148. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor,ramipril, on cardiovascular events in high risk patients. N Engl J Med January 20, 2000; 342 (3): 145–153.
149. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet January 22, 2000; 355 (No. 9200): 253–259.
150. Borch-Johnsen. Increase in life expectancy in type 1 diabetes mellitus. Diab Care 1999; 22: BI
151. Bouhanick B, Berrut G, Chameau AM, et al. Predictive value of testing random urine sample to detect microalbuminuria in diabetic subjects during outpatient visit. Diabetes Metab 1992;18: 54–58.
152. Advances in the assessment of the prognostic implications of proteinuria: microalbuminuria and the protein / creatinine ratio.J Ins Med 1994; 26 (2): 272–277
153. Vinik AI, Holland MT, LeBeau JM, et al. Diabetic neuropathies. Diabetes Care 1992; 15: 1926–1975.
154. McNeely MJ, Boyko EJ, Ahroni JH, et al. The independent contributions of diabetic neuropathy and vasculopathy in foot ulceration: how great are the risks? Diabetes Care 1995; 18: 216–219.
155. Dyck PJ, Kratz KM, Karnes MS, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: The Rochester Diabetic Neuropathy Study. Neurology 1993; 43: 817–824.
156. Ewing DJ, Clarke BF. Autonomic neuropathy: its diagnosis and prognosis. Clin Endocrinol Metab 1986; 15: 855–888.
157. Levitt NS, Stansberry KB, Wynchank S, Vinik AI. The natural progression of autonomic neuropathy and autonomic function tests in a cohort of people with IDDM. Diabetes Care 1996; 19: 751–754.
158. Sundvist G, Lilja B. Autonomic neuropathy predicts deterioration in glomerular filtration rate in patients with IDDM. Diabetes Care 1993; 16: 773–779.
159. Nesto RW, Watson FS, Kowalchuk GJ, et al. Silent myocardial ischemia and infarction in diabetics with peripheral vascular disease: Assessment by dipyridamole thallium-201 scintigraphy. Am Heart J 1990; 120: 1073–1077.
160. Watkins PJ, Diabetic autonomic neuropathy. N Engl J Med 1990; 322: 1078–1079.
161. Krolewski AS, Warram JH, Christlieb AR, et al. Risk of diabetic proliferative retinopathy in juvenile-onset type I diabetes: a 40-year follow-up study. Diabetes Care 1986; 9: 443–452
162. Krolewski AS, WarramJH, Rand LI, et al. Epidemiologic approach to the etiology of type 1 diabetes mellitus and its complications. N Engl J Med 1987; 317: 1390.
163. Diabetes in America. 2nd ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995.
164. Palmberg P, Smith M, Waltman S, et al. The natural history of retinopathy in insulin-dependent juvenile-onset diabetes. Opthalmology 1981; 88: 613.
165. Klein R, Klein BE; Moss SE, Cruickshanks KJ. Association of ocular disease and mortality in a diabetic population. Department of Ophthalmology and Visual Sciences, University of Wisconsin Medical School, Madison 53705–2397, USA. Arch Ophthalmol 1999 Nov;117(11):1487–95
166. The Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000; 342: 381–389.
167. Vijan S, Hofer TP, Hayward RA. Cost-utility analysis of screening intervals for diabetic retinopathy in patients with type 2 diabetes mellitus. JAMA 2000,; 283: 889–896.
168. Guidelines Subcommittee. 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. J Hypertens 1999; 17: 151–183.
169. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997; 157: 2413–2445
170. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434–444.
171. Grossman E, Messerli FH. Diabetic and hypertensive heart disease. Ann Intern Med 1996; 125:304–310.
172. Hemmelder MH, de Zeeuw D, Gansevort RT, de Jong PE. Blood pressure reduction initiates the

antiproteinuric effect of ACE inhibition. Kidney International 1996, 49: 174–180.
173. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor,ramipril, on cardiovascular events in high risk patients. N Engl J Med January 20, 2000; 342 (3): 145–153.
174. Morrish NJ, Stevens LK, Head J, et al. A prospective study of mortality among middle-aged diabetic patients (the WHO Multinational Study of Vascular Disease in Diabetics) II: associated risk factors. Diabetologia 1990; 33: 542–548.
175. Wang SL, Head J, Stevens L, Fuller JH. World Health Organization Multinational Study Group. Excess mortality and its relation to hypertension and proteinuria in diabetic patients: The World Health Organization Multinational Study of Vascular Disease in Diabetes. Diabetes Care April, 1996; 19 (4): 305–312.
176. Curb JD, Pressel SL, Cutler JA, et al. for the Systolic Hypertension in the Elderly Program Cooperative Research Group. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. JAMA 1996; 276: 1886–1892.
177. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *(Effect on cardiovascular, cerebrovascular and overall mortality).* The Lancet 1997; 350: 757–764.
178. Tuomilehto J, Rastenyte D, Birkenhager WH, et al: For the Systolic Hypertension in Europe Trial Investigators. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. N Engl J Med March 1999; 340 (9): 677–684.
179. Mosterd A, D'Agostino RB, Silbershatz H, et al. Trends in the prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1950 to 1989: Framingham Heart Study. N Engl J Med 1999; 340: 1221–1227.
180. Hansson L, Zanchetti A, Carruthers SG, et al.Effects of intensive blood-pressure lowering and low-dose aspirin in patients with *(diastolic)* hypertension: Principle results of the hypertension optimal treatment (HOT) randomized trial. The Lancet 1998 (June 13); 351: 1755–1761.
181. Kjeldsen SE, Hedner T, Jamerson K, et al. Hypertension optimal treatment (HOT) study: home blood pressure in treated hypertensive subjects. Hypertension 1998 Apr; 31 (4): 1014–1020.
182. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril versus Amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998 April: 21 (4): 597–603.
183. Hansson L, Lindholm LH, Ekbom T, et al. Randomized trial of old and new antihypertensive drugs in elderly patients. Lancet 1999; 354: 1751–1756.
184. Mostard A, D'Agostino RB, Silbershatz H, et al. National Heart, Lung, and Blood Institute's Framingham Heart Study. Trends in the prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1950 to 1989. N Engl J Med April 1999; 340 (16): 1221–1227.
185. Morrish NJ, Stevens LK, Head J, Fuller JH et al. A prospective study of mortality among middle-aged diabetic patients (the London cohort of the WHO Multinational Study of Vascular Disease in Diabetics)II: associated risk factors. Diabetologia 1990; 33: 542–548.
186. Florkowski CM, Scott RS, Moir CL, Graham PJ. Lipid but not glycaemic parameters predict total mortality from type 2 diabetes mellitus in Canterbury, New Zealand. Diabet Med 1998 May; 15 (5): 359.
187. American Diabetes Association consenus statement. Detection and management of lipid disorders in diabetes. Diabetes Care 1993; 16: 828.
188. Betteridge J. Diabetic dyslipidemia. The American Journal of Medicine 1994; 96: 6A–25S.
189. Goldschmid MG, Barrett-Connor E, Edelstein SL, et al. Division of Diabetes Translation, Centers for Disease Control, Atlanta, GA. Dyslipidemia and ischemic heart disease mortality among men and women with diabetes. Circulation 1994 Mar; 89 (3): 991–997.
190. Florkowski CM, Scott RS, Moir CL, Graham PJ. Lipid but not glycaemic parameters predict total mortality from type 2 diabetes mellitus in Canterbury, New Zealand. Diabet Med 1998 May; 15 (5): 386–92
191. Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care 1993; 16: 434–444.
192. Pyorala K, Pedersen TR, Kjekshus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandanavian Simvastatin Survival Study (4S). Diabetes Care 1997 Apr; 20 (4): 469–471.
193. Haffner SM, Alexander CM, Cook TH et al. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandanavian Simvastatin Survival Study. Arch Int Med 1999 Dec 13–27; 159 (22): 2661–2667.

194. Goldberg RB, Mellies MJ, Sacks FM, et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The CARE Investigators. Circulation 1998 Dec 8; 98 (23): 2513–2519.
195. American Diabetes Association. Management of Dyslipidemia in Adults With Diabetes. Clinical Practice Recommendations 2000. Diabetes Care 2000 Jan; 23, Supplement 1: 1–9.
196. Haffner SM, Lehto S, Rönnemaa T, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction.
197. Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 1990 Sep; 132 (3): 501–513.
198. Higgins M, D'Agostino R, Kannell W, et al. Benefits and adverse effects of weight loss. Observations from the Framingham Study. National heart, Lung and Blood Institute, Bethesda, MD. Ann Intern Med 1993 Oct 1; 119 (7 Pt 2): 758–763.
199. Chaturvedi N, Stevens LK, Fuller JH. Mortality and morbidity associated with body weight in people with IDDM. The WHO Multinational Study of Vascular Diseases in Diabetics. Diabetes Care 1995 Jun; 18 (6): 761–765.
200. Chaturvedi N, Fuller JH. Mortality risk by body weight and weight change in people with NIDDM. The WHO Multinational Study of Vascular Disease in Diabetes. Diabetes Care 1995 Jun; 18 (6): 766–774.
201. Chaturvedi N, Stephenson JM, Fuller JH, et al. The relationship between smoking and microvascular complications in the EURODIAB IDDM complications study. Diabetes Care 1995 Jun; 18 (6); 785–792.
202. Lloyd CE, Stephenson J, Fuller JH, Orchard TJ. A comparison of renal disease across two continents: the epidemiology of diabetes complications study and the EURODIAB IDDM Complications Study. Craduate School of Public Health, University of Pittsburgh, Pennsylvania, USA. Diabetes Care 1996 Mar; 19(3): 219–225.
203. Haire-Joshu D, Glasgow RE, Tibbs TL: Smoking and diabetes (Technical Review).
204. Lindegard B, Hillborn M. Associations between brain infarction, diabetes and alcoholism: observations from the Gothenburg population cohort study. Acta Neurol Scand 1987; 75: 195–200.
205. Valmadrid CT, Klein R, Moss SE, Klein BEK, Cruickshanks KJ. Alcohol Intake and the Risk of Coronary Heart Disease Mortality in Persons With Older-Onset Diabetes Mellitus. JAMA 1999 July 21; 282 (3): 239–246.