Chapter 19

Heart Disease and Diabetes

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SUMMARY

Based on the 1989 U.S. National Health Interview Survey (NHIS), 3% of men and women age 18-44 years who reported having diabetes also reported having ischemic heart disease. This increased to 14% of those age 45-64 years and 20% of those age ≥65 years. The most common cause of death in adults with diabetes is coronary heart disease. The only national incidence data for the United States come from a 9-year follow-up of the 1971-75 First National Health and Nutrition Examination Survey (NHANES I), in which the age-adjusted death rate per 1,000 person-years was 28.4 for diabetic men and 10.2 for nondiabetic men age 40-77 years at baseline, and 10.5 and 4.1 for diabetic and nondiabetic women, respectively. The excess risk of heart disease occurs with both insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). In contrast to people without diabetes, heart disease in diabetic individuals appears earlier in life, affects women almost as often as men, and is more often fatal. As presented in Chapter 7, adults with diabetes are more likely than those without diabetes to have hypertension and dyslipidemia (low levels of high-density lipoprotein, HDL, and high levels of triglycerides and small dense low-density lipoprotein, LDL), but some of the increased risk of heart disease associated with diabetes appears to be independent of these factors. Insulin and glucose may act as cardiovascular disease risk factors, but data are inconsistent. The Diabetes Control and Complications Trial (DCCT) found that improved control of blood glucose levels in young adults with IDDM reduced their risk of renal and retinal complications and may have also reduced their excess risk of heart disease. In contrast, preliminary results from the Feasibility Trial of the VA Cooperative Study on Glycemic Control and Complications in Type II Diabetes found an increased risk of cardiovascular events in insulin-treated patients with NIDDM. Further studies are needed to determine the role of insulin in the risk of cardiovascular disease.

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METHODOLOGICAL PROBLEMS IN ASSESSING DIABETES AND HEART DISEASE

In the 1985 edition of *Diabetes in America*[1], the chapter on diabetes and heart disease noted the lack of studies based on a standard diagnosis of diabetes, the failure to distinguish IDDM from NIDDM, and problems related to the definition of heart disease. Since then, publications on the relation between diabetes and heart disease have improved in both quantity and quality.

One of the most important advances is the availability of standardized criteria for the definition of diabetes, promulgated by the U.S. National Diabetes Data Group[2] and the World Health Organization[3] (WHO)(Chapter 2). These criteria have permitted meaningful comparisons of individuals with and without diabetes and across studies. Screening with oral glucose tolerance tests (OGTTs) in population-based studies reduces the serious problems of selection bias for who is diagnosed in a clinical setting (e.g., obese adults are more likely to be tested for diabetes than normal-weight individuals, Chapter 2) and of Berkson's bias (e.g., patients seen in clinics or hospitals may be there because they have another condition in addition to clinically recognized diabetes). These types of bias pertain particularly to the epidemiologic study of NIDDM, in which ~50% of those affected are unrecognized until glucose tolerance testing[4,5]. If only the sickest, most obese, or otherwise selected diabetic persons are in the study population, the risk of complications, including heart disease, may be exaggerated.

Unfortunately the criteria for ischemic (also called coronary) heart disease have been less well standardized and still vary from study to study. Further, the most definitive diagnostic methods, such as coronary angiography, are too invasive for population-based studies. Use of history and clinical records is not entirely satisfactory because silent myocardial ischemia or infarction, based on the electrocardiogram, is more common in diabetic persons than in nondiabetic persons[6,7]. The limitations of death certificates are well known. For example, among known diabetic subjects with suspected ischemic heart disease in one study[8], only 41% of death certificates listed diabetes. In a review of 15 other studies of known diabetic individuals[8], 32%-92% of death certificates listed diabetes.

Clinical studies of patients with diabetes usually have the advantages of multiple and more invasive diagnostic tests but suffer from the bias that only symptomatic patients are selected for such investigations; these patients may have more severe disease or symptoms than the general patient population. Clinic populations are prone to selection bias, in that diabetic clinics attract patients with more severe diabetes and cardiology clinics attract those with more severe heart disease.

Prevalence studies suffer from survivor bias by excluding subjects with diabetes who have already died due to heart disease. Unless there has been screening of the population for both heart disease and diabetes, prevalence studies are also subject to ascertainment bias because diabetes may be more often sought in persons with heart disease and vice versa.

Table 19.1

Percent of Adults Reporting Heart Conditions, by Diabetes Status and Age, U.S., 1989

	18-44 years		45-64 years		≥65 years	
	%	No.	%	No.	%	No.
Ischemic heart disease						
IDDM		14		4		2
NIDDM	3.9	34	14.8	145	20.2	167
All diabetic persons	2.7	48	14.3	150	20.0	169
All nondiabetic persons	0.2	7,880	4.7	3,454	11.6	2,068
Heart and rhythm disorders						
IDDM		14		4		2
NIDDM	1.8	34	7.3	145	7.1	167
All diabetic persons	1.2	48	7.1	150	7.0	169
All nondiabetic persons	1.9	7,880	4.0	3,454	6.6	2,068
Arteriosclerosis						
IDDM		14		4		2
NIDDM	6.8	34	7.0	145	7.6	167
All diabetic persons	4.8	48	6.8	150	7.6	169
All nondiabetic persons	0.0	7,880	1.2	3,454	3.6	2,068

IDDM defined as diagnosis at age <30 years and continuous insulin use since diagnosis and body mass index <27 for men and <25 for women; NIDDM, all others identified as having physician-diagnosed diabetes.

Source: Harris MI, National Diabetes Data Group, data from a 1/6 subset of the 1989 National Health Interview Survey

PREVALENCE OF HEART DISEASE IN U.S. DIABETIC VERSUS NONDIABETIC PERSONS

U.S. SURVEY ESTIMATES

Based on the 1989 NHIS, the prevalence of self-reported ischemic heart disease, heart and rhythm disorders, and arteriosclerosis in the United States was higher among adults with self-reported diabetes than without (Table 19.1). The overall prevalence of heart disease increased with age, but the differential between those with and without diabetes was greater among those age <65 years. Among adults with NIDDM, self-reported prevalence of angina and other heart trouble and visits to a cardiologist at age ≥45 years were greater among those using insulin than those not (Table 19.2). Among diabetic individuals age 18-44 years, those with IDDM reported less angina and other heart trouble and fewer visits to a cardiologist than those with NIDDM. Based on the 1989-91 National Hospital Discharge Surveys, men and women age ≥55 years with a discharge diagnosis

Table 19.2

Percent of Adults Reporting Heart Conditions, by Type of Diabetes, Insulin Use, and Age, U.S., 1989

	18-44 years		45-64 years		≥65 years	
	%	No.	%	No.	%	No.
Angina						
IDDM	1.9	101		19		3
NIDDM using insulin	4.9	116	11.5	406	20.0	386
NIDDM not using insulin	3.8	133	11.1	531	14.8	653
All diabetic persons	3.9	354	11.2	963	16.6	1,044
Other heart trouble						
IDDM	10.6	101		19		3
NIDDM using insulin	20.1	115	23.7	410	35.4	386
NIDDM not using insulin	10.9	132	21.1	532	32.3	655
All diabetic persons	14.0	352	21.8	968	33.4	1,046
Cardiologist visit past 12 months						
IDDM	3.6	102		18		3
NIDDM using insulin	13.2	116	25.0	408	32.6	386
NIDDM not using insulin	15.7	132	20.9	536	24.8	670
All diabetic persons	11.2	354	22.3	969	27.6	1,061

IDDM defined as diagnosis at age <30 years and continuous insulin use since diagnosis and body mass index <27 for men and <25 for women; NIDDM, all others identified as having physician-diagnosed diabetes (13 diabetic subjects were unclassified).

Source: Harris MI, National Diabetes Data Group, data from the 1989 National Health Interview Survey Diabetes Supplement

Table 19.3
Prevalence of Heart Disease Diagnoses in U.S. Hospitalizations by Diabetes Diagnosis, Age ≥55 Years, 1989-91

	Percent with heart disease diagnosis			
	Diabetes diagnosis		No diabetes diagnosis	
Heart disease diagnosis (ICD number)	Men (No.=0.92 million)	Women (No.=1.3 million)	Men (No.=5.2 million)	Women (No.=6.1 million)
Hypertensive heart disease (402)	2.5	4.2	1.5	2.1
Acute myocardial infarction (410)	7.3	5.3	5.7	3.5
Other acute ischemic heart disease (411)	7.2	6.5	5.7	4.4
Old myocardial infarction (412)	5.0	3.5	3.6	1.9
Angina pectoris (413)	4.5	4.9	3.8	3.4
Other chronic ischemic heart disease (414)	27.3	20.9	19.7	13.3
Cardiomyopathy (425)	3.4	2.1	2.3	1.3
Cardiac dysrhythmias (427)	18.1	15.1	19.3	15.5
Heart failure (428)	20.1	20.4	11.8	13.1

Data are weighted to represent all U.S. short-stay hospitalizations; all hospitalizations in which a diabetes or heart disease diagnosis was listed on the discharge summary are included in the table.

Source: Harris MI, National Diabetes Data Group, data from the National Hospital Discharge Surveys for 1989-91 (with diabetes diagnosis) and 1990 (without diabetes diagnosis)

of diabetes were more likely than those without this diagnosis to have at least one of all heart disease diagnoses except cardiac dysrhythmia (Table 19.3).

Based on the 1976-80 NHANES II, the most recent NHANES for which data are available, the prevalence of angina by Rose questionnaire was higher among men and women with than without diabetes, as diagnosed by an OGTT (Table 19.4). History of a myocardial infarction as determined by Rose questionnaire was also higher among men (age 55-74 years) and women (age 35-74 years) with diabetes than without. Among diabetic people, the prevalence of angina (age 55-74 years) and history of myocardial infarction (age 35-74 years) was more common among those with known diabetes compared with those diagnosed at the visit with an OGTT.

COMMUNITY-BASED PREVALENCE STUDIES

Several recent population-based studies from the United States have reported the prevalence of coronary heart disease among white, non-Hispanic white, and Hispanic adults who received a standardized OGTT[6,9,10] (Table 19.5). Those with NIDDM generally had the greatest prevalence of myocardial infarction, ischemic ECGs, and coronary heart disease, while

Table 19.4
Prevalence of Angina and Myocardial Infarction by Oral Glucose Tolerance Status, U.S., 1976-80

	35-54 years				55-74 years			
	Men		Women		Men		Women	
	%	No.	%	No.	%	No.	%	No.
Angina								
Diagnosed diabetes	6.7	37	8.6	57	8.6	190	10.3	239
Undiagnosed diabetes	14.1	10	12.4	20	6.7	68	8.1	88
All diabetes	10.0	47	10.5	77	7.6	258	9.1	327
IGT	10.1	49	3.8	75	6.9	172	9.3	182
Normal OGTT	2.3	391	5.3	457	6.4	563	8.0	579
Myocardial infarction								
Diagnosed diabetes	6.7	37	11.6	57	16.5	190	14.0	239
Undiagnosed diabetes	0.0	10	5.2	20	4.6	68	9.0	88
All diabetes	3.7	47	8.4	77	10.6	258	11.3	327
IGT	5.9	49	5.6	75	7.3	172	6.3	182
Normal OGTT	7.1	391	4.6	457	7.3	563	5.7	579

Angina and previous myocardial infarction were measured by Rose questionnaire; previously diagnosed diabetes determined by medical history; other categories were ascertained by World Health Organization criteria applied to the results of 2-hour 75-g oral glucose tolerance tests after exclusion of IDDM; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

Source: Harris MI, National Diabetes Data Group, data from the 1976-80 National Health and Nutrition Examination Survey

those with normal glucose tolerance had the lowest prevalence (Figure 19.1). This was also true in a study of Japanese-American volunteers who received an OGTT[11,12]. In the Rancho Bernardo Study, prevalence of myocardial infarction was higher among diabetic persons diagnosed prior to the study than among those newly diagnosed by OGTT during the study[13]. Adults with NIDDM had an increased prevalence of silent ischemia as well as total ischemia (Table 19.5). Approximately half of all ischemic ECG abnormalities were silent. While this proportion is the same in diabetic and nondiabetic persons, the prevalence of both asymptomatic and symptomatic ischemia was increased in adults with NIDDM. Among patients with IDDM from the Joslin Clinic[14], silent ischemia also accounted for at least half of all coronary artery disease. The association of glucose intolerance with coronary heart disease or myocardial infarction by history or ECG was as great or greater among women as men (Table 19.5, Figure 19.1).

CLINICAL STUDIES

Congestive Heart Failure

Approximately 1% of the U.S. population overall and 10% of the population age >75 years have congestive heart failure (CHF), most commonly due to previous myocardial infarction[15]. Population-based studies such as Framingham, MA[16] and Rochester, MN[17] have reported an excess of CHF in women with diabetes. In

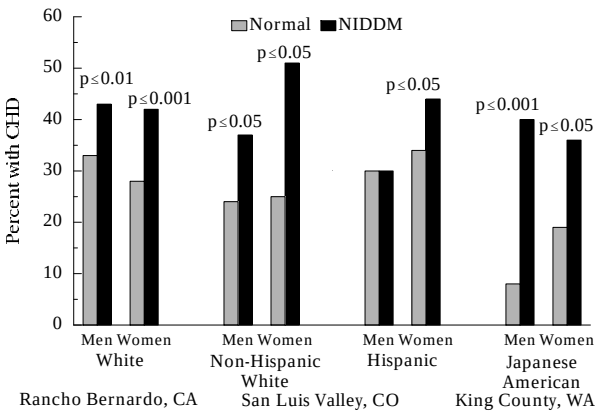
Table 19.5
Age-Adjusted Prevalence of Coronary Heart Disease Among Adults by Oral Glucose Tolerance Status, U.S. Population-Based Studies

Ref.	Population	Race	Sex	Glucose Tolerance	No.	Myocardial infarction (%) History	Myocardial infarction (%) History or ECG[a]	Ischemic ECG (%) Total[b]	Ischemic ECG (%) Silent[c]	Coronary heart disease[d] (%)
6	Rancho Bernardo, CA (population-based, 1984-87, age 50-89 years)	White	M	NIDDM	159		17.1	34.7**	20.9*	43.1**
				IGT	237		18.4*	28.2	13.0	38.5
				Normal	591		13.2	22.3	12.0	32.0
			F	NIDDM	157		13.7**	30.0**	13.7*	41.9***
				IGT	347		9.5	23.3	12.0	34.3*
				Normal	732		7.2	19.6	8.8	28.5
9	San Luis Valley, CO (population-based, 1984-88, age 25-74 years)	Non-Hispanic White	M	NIDDM	79	12.3*	26.5*	16.7	7.7	36.9*
				IGT	34	11.6	18.1	19.0	7.4	37.7
				Normal	307	4.8	12.8	9.7	4.5	23.1
			F	NIDDM	66	4.4	14.2*	25.5*	17.8	50.6*
				IGT	48	1.4	9.5	18.3	15.3	40.1*
				Normal	345	2.0	7.0	15.5	11.8	24.6
		Hispanic	M	NIDDM	107	5.6	11.3	14.2	12.2*	29.7
				IGT	35	8.8	18.0	13.3	2.4	29.1
				Normal	214	6.7	16.3	12.5	5.2	29.7
			F	NIDDM	177	2.8	12.4	18.5	13.6	44.5*
				IGT	56	2.5	11.6	20.9	16.7	36.4
				Normal	226	0.4	8.7	14.9	10.3	32.6
10	San Antonio, TX (population-based, 1979-88, age 25-64 years)	Non-Hispanic White	M	NIDDM	37	13.3	29.9			
				Other	790	4.0	8.2			
			F	NIDDM	41	7.2	11.7			
				Other	995	1.2	2.5			
		Hispanic	M	NIDDM	154	12.6	21.6			
				Other	1,230	3.1	5.6			
			F	NIDDM	240	4.2	10.7			
				Other	1,654	1.1	3.1			
11	King County, WA (volunteers, 1983-85, age 45-74 years)	Japanese-American	M	NIDDM	78			29.5***	16.7**	41.0***
				IGT	72			23.6	12.5	27.8
				Normal	79			6.3	3.8	8.9
12	King County, WA (volunteers, 1986-88, age 45-74 years)	Japanese-American	F	NIDDM	52					36.5*
				IGT	67					35.8*
				Normal	72					19.4

M, male; F, female; ECG, electrocardiogram; IGT, impaired glucose tolerance. [a]History or ECG criteria: Rancho Bernardo — Minn. code 1.1; San Luis Valley — history or ECG Minn. code 1.1-1.2; San Antonio — history or ECG Minn. code 1.1-1.3. [b]Total ischemic ECG criteria: Rancho Bernardo and San Luis Valley — Minn. code 1.1-1.3, 4.1-4.3, 5.1-5.3, 7.1; San Antonio and King County — Minn. code 1.1-1.3, 5.1-5.3, 7.1. [c]Silent ECG criteria: ischemic ECG without history of MI, angina, or chest pain. [d]CHD criteria: Rancho Bernardo — possible MI, angina, or ischemic ECG; San Luis Valley — heart attack, angina, or ischemic ECG; King County — MI, bypass, angina, or ischemic ECG. *p ≤0.05; **p ≤0.01; ***p ≤0.001 compared with normal glucose tolerance group.

Source: References are listed within the table

Figure 19.1
Age-Adjusted Prevalence of Coronary Heart Disease in Diabetic and Nondiabetic Adults



Definition of CHD: Rancho Bernardo—possible MI, angina, ischemic ECG; San Luis Valley—heart attack, angina, ischemic ECG; King County—MI, bypass, angina, ischemic ECG.

Source: References 6, 9, 11, 12

the Multicenter Investigation of the Limitation of Infarct Size (MILIS) Trial[18], insulin-treated diabetes was an independent risk factor for post-infarction CHF, with a stronger effect in women than in men.

The amount of myocardial necrosis is a major determinant of congestive heart failure and death after an acute myocardial infarction. Some studies[19,20] suggest the excess CHF in diabetes is caused by a larger amount of postinfarction myocardial necrosis, compared with nondiabetic persons, but others found an increase in CHF in diabetic versus nondiabetic patients despite comparable infarct size[21-23]. For example, in a prospective study of 100 patients with clinically diagnosed diabetes and 426 patients without diabetes, CHF was found twice as frequently in diabetic as nondiabetic patients (31.2% versus 15.7%) despite smaller infarct size as estimated enzymatically[21]. In another study using radionuclide angiography to study patients with a first acute Q wave anterior myocardial infarction, the 17 noninsulin-treated diabetic patients had more left ventricular regional dysfunction of the *noninfarcted* area at every QRS score (an index of infarct size) than the 28 nondiabetic patients[23].

The pathogenesis of CHF in diabetes is not well understood. The studies cited above provide evidence for a nonatherosclerotic determinant of outcome that is peculiar to diabetes. It is known that atherosclerotic arteries respond paradoxically to acetylcholine, compromising myocardial perfusion. A comparison was made of seven control subjects and 11 patients who had either IDDM or NIDDM and who had normal coronary arteries and normal left ventricular systolic function[24]. In control subjects, acetylcholine caused a progressive increase in the diameter of epicardial arteries; in all diabetic subjects there was diffuse constriction of the coronary arteries. These observations are compatible with the thesis that *nonatherosclerotic* alterations in the coronary circulation in diabetic patients damage the myocardium. A recent review concluded that there is both pathologic myocardial damage and myocellular dysfunction due to diabetes[25].

Cardiomyopathy

In addition to myocardial dysfunction and failure consequent to atherosclerosis, increasing evidence suggests that diabetic individuals have a cardiomyopathy that is independent of atherosclerosis. Most of these clinical investigations have been reviewed[26,27]. Several lines of research suggest that myocardial dysfunction occurs in persons reasonably presumed to be without atherosclerotic heart disease. Echocardiographic studies in children and adolescents with IDDM[28,29] and exercise testing or radionuclide angiography in young adults with IDDM[30-32] suggest myocardial dysfunction.

Two-dimensional echocardiography and stress perfusion scintiography was used to study 88 well-characterized patients with diabetes and 65 volunteers without diabetes[33]. Patients with IDDM or NIDDM had restrictive cardiomyopathy as manifest by mildly reduced left ventricular end-diastolic volume and altered left ventricular compliance independent of coronary artery disease. Cardiac function was compared in 125 patients with IDDM and 50 age- and sex-matched healthy controls[34]. Echocardiography showed significantly increased septal and posterior wall thickness and abnormalities in diastolic function. Echocardiography was used to study 157 young patients who had IDDM and no cardiac symptoms[35]. The patients had more ventricular dysfunction than 54 age- and sex-matched controls. Among diabetic persons, diastolic dysfunction was more than twice as common as systolic dysfunction and occurred earlier (8 versus 18 years after diagnosis of diabetes).

The interpretation that abnormal test results reflect diabetic cardiomyopathy has been challenged by comparing 20 normotensive young adults who had IDDM for an average of 15 years with 20 age-matched nondiabetic individuals[36]. By radionuclide angiography, all normal subjects had an increased ejection fraction with exercise, compared with 45% of those with IDDM. However, when left ventricular systolic performance was assessed by load and rate independent indices, all subjects had normal baseline ventricular

contractility, which provides evidence against cardiomyopathy. Some studies have failed to adjust for the lower activity levels of people with diabetes. When 11 boys with IDDM (diabetes of 4.5 years duration) were compared with 11 nondiabetic boys matched for age, body size, and physical activity, no evidence of functional myocardial disease was found[37].

Population-based studies of myocardial function by diabetic status are rare. Echocardiographic evidence for cardiomyopathy in nearly 5,000 adult men and women from the Framingham, MA studies have been reported[38]. Their evaluation did not include an OGTT, and only 69 men and 42 women had diabetes by Framingham criteria. Nevertheless, women (but not men) with diabetes had significantly increased left ventricular wall thickness and mass, independent of hypertension and other confounders. Subjects with overt cardiovascular disease were excluded, but myocardial dysfunction secondary to occult infarction remains a possibility for this finding, suggested by the observation that younger diabetic women had no apparent increase in left ventricular mass.

Other evidence that diabetes increases the risk of cardiomyopathy comes from the Washington, DC Dilated Cardiomyopathy Study[39]. Cases defined by idiopathic ventricular dilatation and hypokinesis were compared with neighborhood controls. Individuals who had a history of myocardial infarction or coronary artery stenosis were excluded, and diabetes was defined as physician-diagnosed with 90% confirmation by hospital record review. Twenty-nine percent of case patients and 14% of controls had a history of diabetes. Diabetes was associated with dilated cardiomyopathy before and after adjusting for covariates (multiply adjusted relative odds 2.6, 95% confidence interval (CI) 1.5-4.3).

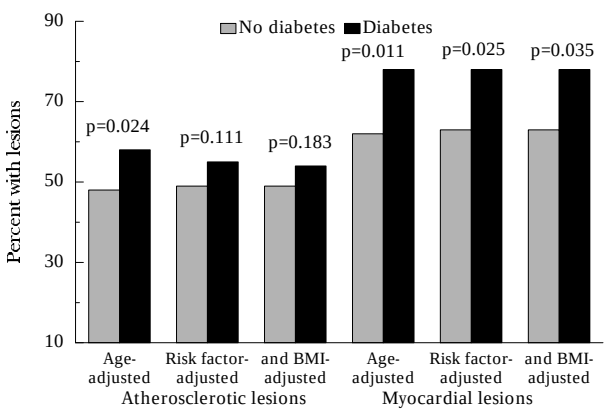
AUTOPSY STUDIES

Although the etiology (some would say existence) of diabetic cardiomyopathy remains unresolved[40], surprisingly few autopsy studies have specifically examined the diabetic heart[41-45]. In the only recent population-based autopsy study, protocol autopsies were evaluated in 83 diabetic and 159 nondiabetic Japanese-American men from the Honolulu Heart Program[19]. Diabetic individuals had an excess of coronary atherosclerosis and of acute, healing, or fibrotic myocardial lesions; the latter but not the former association was independent of major coronary heart disease risk factors (Figure 19.2). This suggests that the atherosclerotic process is mediated by blood pressure, cholesterol, and smoking, while one or more nonatherosclerotic processes also account for some of the excess heart disease in men with diabetes. Unfortunately, in this study the diagnosis of diabetes was made without study-wide glucose tolerance tests and the protocol autopsy appears not to have included a systematic search for microvascular disease.

Autopsy evidence for diabetic cardiomyopathy is sparse. In one study, hearts obtained at autopsy from 67 patients with diabetes, hypertension, or both were examined[44]. Patients with both diabetes and hypertension had the most microscopic fibrosis, but diabetic subjects without hypertension had more fibrosis than patients with hypertension only. It was postulated that myocardial fibrosis contributed to the diastolic dysfunction observed in patients with IDDM.

Although it is plausible that cardiac microvascular disease plays a role in the pathogenesis of diabetic cardiomyopathy, there is little evidence for an excess of small vessel heart disease in people with diabetes. In the only recent autopsy study that looked for microvascular pathology, diabetic subjects who had a myocardial infarction had more microangiopathy compared with diabetic subjects without ischemic heart disease or normoglycemics with myocardial infarction[45]. Microangiopathy was defined by low capillary density. Only 10 diabetic hearts were examined and no appropriate controls without ischemic heart disease or diabetes were studied. Recent studies of endomyocardial biopsies in large numbers of patients

Figure 19.2
Prevalence of Atherosclerotic and Myocardial Lesions in Diabetic and Nondiabetic Men, 1965-84



Data are from the Honolulu Heart Program Autopsy Study; risk factors included in adjustment of the prevalence were age, cigarette smoking, cholesterol, and systolic blood pressure (and body mass index, where indicated); sample size—diabetic 83, nondiabetic 159.

Source: Reference 19

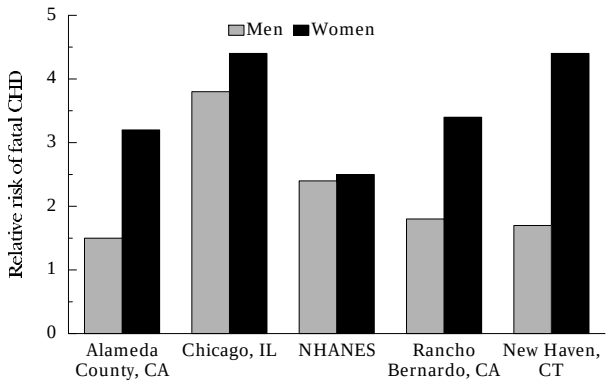
have not confirmed an association between diabetes and small vessel disease[46,47].

INCIDENCE OF HEART DISEASE IN U.S. DIABETIC VERSUS NONDIABETIC PERSONS

Since the 1985 edition of *Diabetes in America*, only four occupational/population-based studies have been published comparing the incidence of heart disease in adults with and without diabetes in the United States[48-51] (Table 19.6). All found an increased risk of incident heart disease (fatal and nonfatal combined) among diabetic individuals. The Nurses' Health Study[50] also reported a twofold higher risk among women with IDDM (onset at age <30 years) compared with women with NIDDM (onset at age ≥30 years). The age-adjusted relative risks for diabetic versus nondiabetic women were 12.2 for IDDM and 6.7 for NIDDM. The higher relative risks for both diabetic groups in the Nurses' Health Study may in part reflect the inclusion of only clinically diagnosed diabetic persons, who presumably have more severe disease than unrecognized cases. Alternatively, the Nurses' Health Study women are relatively young; because heart disease is uncommon in younger women without diabetes, the relative risk for those with diabetes could be higher than in studies of older women.

Several occupation/population-based studies have been published comparing the risk of fatal ischemic heart disease among diabetic and nondiabetic adults. Table 19.7 presents summaries of studies in white adults in the United States[50-56]. The Wisconsin Study[56] relied on physician diagnosis of diabetes and reported data for NIDDM and IDDM separately. The Rancho Bernardo Study[55] relied on an abnormal fasting plasma glucose or history of diabetes and included very few subjects with IDDM. The other five[50-54] were based on self-reported diabetes. In every study, the risk of fatal ischemic heart disease was significantly greater among those with diabetes than those without. In most cases, the increased risk of heart disease mortality associated with diabetes was greater among women than men (Figure 19.3).

Figure 19.3
Multiply Adjusted Risk of Fatal Coronary Heart Disease in Diabetic Compared with Nondiabetic Adults, by Sex



Definition of risk: Alameda–relative risk; Chicago, NHANES, Rancho Bernardo–relative hazard; New Haven–odds ratio.

Source: References 51-55

Table 19.6
Risk of Incident Coronary Heart Disease in Diabetic versus Nondiabetic Adults, U.S. Occupation/Population-Based Studies

Ref.	Population	Type of diabetes	Years followup	Sex	Number Diabetic	Number Nondiabetic	Adjusted risk ratio† Age	Adjusted risk ratio† Multiple
48	Framingham Study (population-based, 1969-79, age 45-84 years)	Unspecified; history or casual glucose	2	M	1,382		2.3	
				F	2,094		2.9	
49	Honolulu Heart Study (Japanese Americans, 1970-72, age 51-72 years)	NIDDM and IGT; history or nonfasting glucose challenge	18	M	376	2,042	1.7	
50	Nurses' Health Study (registered nurses, 1976, age 30-55 years)	NIDDM; self-report	8	F	1,483	114,694	6.7*	3.1*
		IDDM; self-report	8	F	226	114,694	12.2*	
51	New Haven, CT (population-based, 1982, age 65+ years)	Unspecified; self-report	6	M	156	994		1.8
				F	230	1,388		3.2**

M, male; F, female; IGT, impaired glucose tolerance. †Framingham, Honolulu, Nurses Health studies — risk of nonfatal myocardial infarction and fatal coronary heart disease; New Haven — nonfatal and fatal MI; prevalent heart disease at baseline was excluded in all four studies. *95% confidence interval does not contain 1.0; **p ≤0.01

Source: References are listed within the table

Table 19.7

Risk of Fatal Coronary Heart Disease in Diabetic versus Nondiabetic White Adults, U.S. Occupation/Population-Based Studies

Ref.	Population	Type of diabetes	Years followup	Sex	Number Diabetic	Number Nondiabetic	Adjusted risk ratio† Age	Adjusted risk ratio† Multiple
52	Alameda County, CA (population-based, 1965, age ≥40 years)	Unspecified; self-report	9	M	51	1,648		1.5
				F	70	1,982	3.5**	3.1**
53	Chicago, IL (employees, 1967-73, age 35-64 years)	Unspecified; self-report	9	M	377	10,843	4.0***	3.8***
				F	170	7,860	5.9***	4.7***
54	NHANES I (population-based, 1971-75, age 40-77 years)	Unspecified; self-report of physician diagnosis	9	M	189	3,151	2.3	2.4††
				F	218	3,823	2.8	2.6††
55	Rancho Bernardo, CA (population-based, 1972-74, age 40-79 years)	NIDDM; history or fasting glucose	14	M	207	893	1.8**	1.9**
				F	127	1,224	3.3***	3.3***
50	Nurses' Health Study (registered nurses, 1976, age 30-55 years)	NIDDM; self-report of physician diagnosis	8	F	1,483	114,694	6.9††	
56	Wisconsin (population-based, 1980)	NIDDM; physician diagnosis	8.5	M	797	Wisconsin	2.4††	
				F	975	statistics	2.2††	
		IDDM; physician diagnosis	8.5	M	626	Wisconsin	9.1††	
				F	574	statistics	13.5††	
51	New Haven, CT (population-based, 1982, age ≥65 years)	Unspecified; self-report of physician diagnosis	6	M	156	994		1.6
				F	230	1,388		4.5**

NHANES, National Health and Nutrition Examination Survey. †Risk ratio for diabetic versus nondiabetic: Alameda and Nurses studies—relative risk; Chicago, NHANES I, Rancho Bernardo—relative hazard; Wisconsin—standardized mortality ratio; New Haven—odds ratio; ischemic heart disease, ICD9 codes 410-414, with prevalent heart disease at baseline excluded (NHANES I, Nurses' study) or adjusted (New Haven). *p ≤0.05; **p ≤0.01; ***p ≤0.001; ††95% confidence interval does not contain 1.0

Source: References are listed within the table

NATURAL HISTORY OF HEART DISEASE IN DIABETIC VERSUS NONDIABETIC PERSONS

Diabetic individuals who have had a myocardial infarction are more likely than nondiabetic people to experience another infarction or death (Table 19.8)[18,57-65]. In a series of thrombolytic trials, diabetic patients had twice the risk of having another infarction before they left the hospital[57]. In Framingham, MA diabetic men had a 40% increased risk of reinfarction within 2 years of their first infarction, whereas diabetic women had three times the risk ($p \leq 0.001$) compared with those without diabetes[64].

Data from the National Hospital Discharge Surveys[60] suggest that in-hospital deaths may be increased only for diabetic individuals age <55 years (Table 19.8). While these data also suggest that the increased risk of in-hospital death among diabetic patients is greater for men than women (relative risks of 1.8 and 1.4, respectively), studies of patients with acute myocardial infarction in the MILIS[18] suggest the opposite (relative risks of 1.6 for men and 2.6 for women). Similarly, among patients who were treated with thrombolytic agents[57], the risk of in-hospital death was lower for diabetic men than for diabetic women (relative risks of 3.2 and 3.8, respectively). In Framingham[64], the increased risk of death within 2 years of a myocardial infarction was also greater for diabetic women than for diabetic men (relative risks of 2.6 and 1.8, respectively).

The population-based studies summarized in Table 19.8 also indicate that the increased mortality risk among diabetic persons who experience a myocardial infarction persists well past hospitalization. In the Corpus Christi Heart Project[63], diabetic persons had twice the risk of death within 28 days of a myocardial infarction and a 60% increased risk within 44 months compared with nondiabetic persons. In the Minnesota Heart Survey[61], adults with diabetes had a 40% increased risk of death within 6 years of a myocardial infarction, and in the Worcester Heart Attack Study[62], diabetic persons had twice the mortality risk 12 years later. In the Framingham cohort[65], death following a myocardial infarction was significantly increased for diabetic individuals from the time of their first hospitalization through 30 years of followup.

Few studies have examined determinants of the poorer prognosis in patients with diabetes. A comparison was made of 228 patients admitted to a Boston, MA intensive care unit with myocardial infarction and NIDDM and a similar number of nondiabetic patients with infarction[58]. The patients with diabetes had an increased 30-day and 150-day mortality, but they also were older and had more cardiovascular disease before

the infarction. The relative risk was greatest among diabetic patients with the lowest baseline risk (Figure 19.4).

A followup was made of 60 insulin-treated patients admitted to eight hospitals in Arizona, Missouri, and New York and 721 nondiabetic patients, all with myocardial infarctions[59]. Among all subjects, pulmonary rales, ejection fraction <40%, symptoms before myocardial infarction, and >10 ventricular premature complexes per hour predicted mortality. Among diabetic patients, only pulmonary rales were significantly associated with 1-year mortality rates. In a followup of patients hospitalized for their first myocardial infarction in Finland, patients with NIDDM had a poorer prognosis than patients without diabetes; however, they did not differ in infarct size[65b].

The records of 832 consecutive patients in Denmark who were hospitalized for an acute myocardial infarction during a 3-year period were reviewed for mortality[66]. Patients with NIDDM were twice as likely to die within 1 month than nondiabetic patients (42% versus 20%). Among diabetic patients, those who died had significantly higher fasting plasma glucose levels in the 3 years before infarction than those who sur-

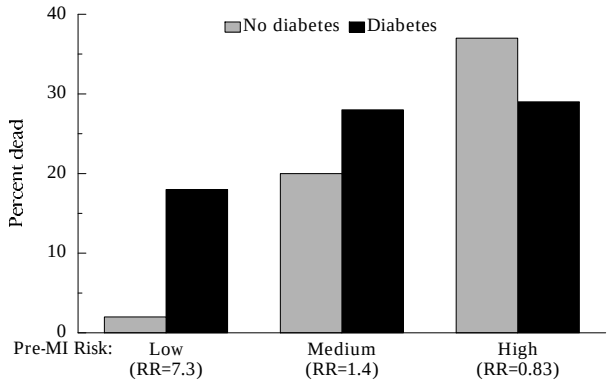
Table 19.8
Risk of Reinfarction and Death Following Acute Myocardial Infarction in Diabetic versus Nondiabetic White Adults, U.S. Studies

Ref.	Population	Type of diabetes	Length of followup	Sex (age)	Number		Risk ratio‡	
					Diabetic	Nondiabetic	Reinfarction	Death
Clinical Studies								
57	Thrombolytic Trials (1985-89)	Unspecified; physician diagnosis	In hospital	M	110	746		1.6
			In hospital	F	38	177		2.6
			In hospital	M and F	148	923	2.0	1.8*
			5 years	M and F	131	826		increased**
58	Mass. General Hosp. (1977-82)	NIDDM; physician diagnosis	30 days	M	122	142		2.1
			30 days	F	106	54		1.0
			30 days	M and F	228	196		1.6*
			150 days	M and F	228	196		1.6**
59	8 hospitals in MPIP (1979-80)	Insulin-treated	36 months	M and F	60	721		3.1***
18	5 hospitals in MILIS study (1978-83)	Unspecified; history or diagnosis	In hospital	M	52	330		3.2
			In hospital	F	33	85		3.8
			In hospital	M and F	85	415		3.7**
			4 years	M	49	324		1.0
			4 years	F	30	83		2.5**
			4 years	M and F	79	407		1.8**
Population-Based Studies								
60	National Hospital Discharge Survey (1979-87)	Unspecified; physician diagnosis	In hospital	M (35-54)	(from >500 hospitals)			1.8††
			In hospital	F (35-54)				1.4
			In hospital	M (≥55)				1.0
			In hospital	F (≥55)				1.0
61	Minneapolis-St. Paul, MN (1970, 1980, 1985)	Unspecified; physician diagnosis	In hospital	M and F	384	2,196		1.5**
			6 years	M and F	155	294		1.4**
62	Worcester, MA (1975, 1978, 1981, 1984, 1986)	Unspecified; physician diagnosis	In hospital	M	467	2,060		1.2
			In hospital	F	476	1,100		1.2*
			In hospital	M and F	943	3,160		1.4††
			12 years	M	379	1,751		1.6††
			12 years	F	353	846		1.6††
			12 years	M and F	732	2,597		2.0††
63	Corpus Christi, TX (1988-90)	Unspecified; history or diagnosis	28 days	M and F	523	676		2.0***
			44 months	M and F	523	676		1.6***
64	Framingham, MA (1948-81)	Unspecified; history or casual glucose	2 years	M	55	359	1.4	1.8**
			2 years	F	37	158	3.1***	2.6**
65	Framingham, MA (1948-80)	Unspecified; history or casual glucose	30 years	M and F	50	294		2.6††
			30 years	M and F	33	242	2.0††	

M, males; F, females; MILIS, Multicenter Investigation of the Limitation of Infarct Size; MPIP, Multicenter Postinfarction Program. ‡Risk ratio for diabetic versus nondiabetic: relative risk—Thrombolytic, Mass. Gen., MPIP, MILIS, NHDS, Worcester; odds ratio—Minneapolis, Framingham; relative hazard—MILIS, NHDS, Minneapolis, Worcester, Corpus Christi; Kaplan-Meier curves—Thrombolytic, MPIP, MILIS, Corpus Christi; data in Minneapolis, Worcester, Corpus Christi, Framingham are adjusted for age and selected covariates. *p ≤0.05, **p ≤0.01, ***p ≤0.001; ††95% confidence interval does not contain 1.0.

Source: References are listed within the table

Figure 19.4
Death Rate Within 30 Days After Admission for Acute Myocardial Infarction



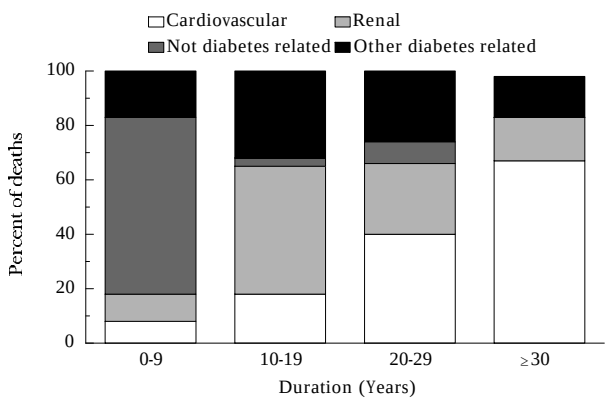
Diabetic patients are compared with nondiabetic patients in strata of pre-MI cardiac risk. Pre-MI risk was determined for each patient from logistic regression of 30-day death on age (coded as continuous), history of congestive heart failure (CHF, yes or no), and history of previous MI (yes or no). This equation was fitted on nondiabetic patients only: ln(odds of 30-day death) = -6.554 + 0.06847(x age), +0.5076(x history of CHF), and +0.1985(x history of previous MI). Strata are tertiles of pre-MI risk.

Source: Reference 58

vived (178 versus 143 mg/dl, $p<0.05$). Glucose levels were similar in those who were treated with oral agents or insulin, but the latter group was less likely to die ($p<0.02$).

In contrast, studies in England[67] and Malta[68] found that prognosis was unrelated to glycemic control. In the case-control study from Malta, the 196 patients with NIDDM and a myocardial infarction had higher mortality, less reperfusion, and more pump failure and cardiogenic shock than the 196 nondiabetic patients with infarctions[68]. Absent heart rate variability, presumably related to autonomic neuropathy, was predictive of both mortality and left ventricular failure. These observations are reminiscent of studies that found that 91% of patients with long-standing IDDM had cardiac autonomic neuropathy; left ventricular function was depressed in 59% of IDDM patients with neuropathy and only 8% of those without[69].

Figure 19.5
Causes of Death in IDDM Patients by Duration of Diabetes



Data are from the Pittsburgh Epidemiology of Diabetes Complications Study.

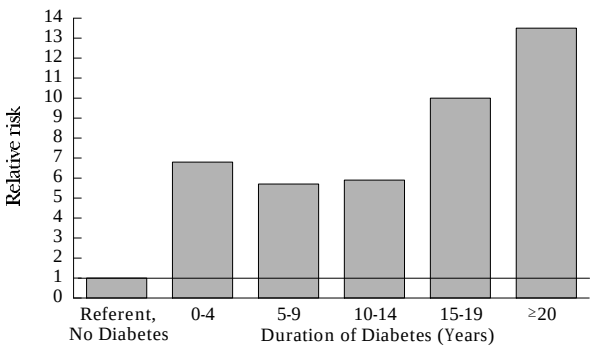
Source: Reference 71

RISK FACTORS FOR DEVELOPMENT OF HEART DISEASE IN DIABETIC VERSUS NONDIABETIC PERSONS

AGE AND DURATION OF DIABETES

The risk of coronary heart disease increases with age in persons with or without diabetes, but diabetes appears to accelerate the process. Nevertheless, coronary heart disease is uncommon before age 30 years in patients with IDDM, even when diabetes began in childhood[14,70]. Data from the Pittsburgh Epidemiology of Diabetes Complications Study[71] show an association between fatal cardiovascular disease and the duration of IDDM (Figure 19.5), suggesting either that diabetes accentuates atherosclerosis only in the presence of existing coronary artery disease or that a minimum duration of exposure to diabetes is required to cause cardiovascular disease. The onset of NIDDM is less obvious than IDDM, and it has been difficult to distinguish between an effect of age and an effect of

Figure 19.6
Relative Risk of Combined Nonfatal Myocardial Infarction and Fatal Coronary Heart Disease in Diabetic versus Nondiabetic Women, by Duration of Diabetes



Data are from the Nurses' Health Study and are stratified by duration of maturity-onset diabetes; referent is nondiabetic women; risks are age-adjusted; 95% confidence intervals: 0-4 years, 4.6-9.0; 5-9 years, 3.6-8.3; 10-14 years, 3.2-10.4; 15-19 years, 5.5-18.3; ≥20 years, 7.1-24.6.

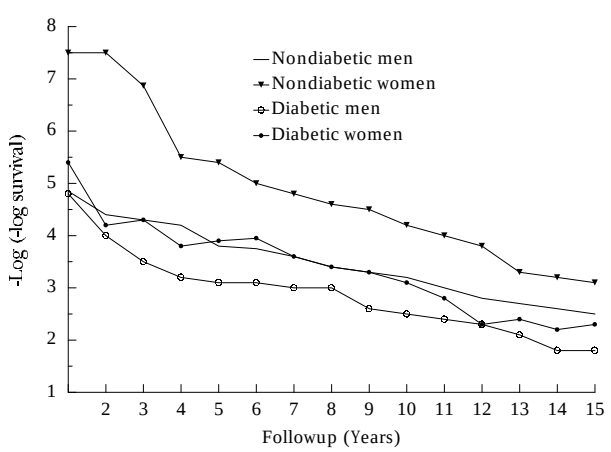
Source: Reference 50

duration of diabetes on heart disease risk. However, in the Nurses' Health Study[50], a longer duration of clinically recognized maturity onset diabetes in women was found to be associated with an increased risk of coronary heart disease, even after age adjustment (Figure 19.6).

GLUCOSE CONTROL

While some studies have found a significant association between glucose levels and the prevalence[72] or incidence[73,73b] of heart disease, others have not[11,48,71,74,75]. Some of this variation may reflect population differences in age or duration of diabetes and adjustment for these factors. Even within a single cohort[73,74], different associations emerge depending on the gender of the subsample and the covariates included in multivariate models. The Pittsburgh Epidemiology of Diabetes Complications Study has examined the association between glucose levels and heart disease in individuals with IDDM[71]. Glycemic control, as measured by glycosylated hemoglobin, was not associated with 4-year incidence of coronary heart disease, after adjustment for either age or duration of diabetes. A Finnish study examined the association of glycosylated hemoglobin and heart disease in individuals with NIDDM[73b]. After adjustment for duration of diabetes, glycemic control was significantly associated with 3.5-year coronary heart disease mortality but not with incidence. It is very difficult to separate the effect of glycemic control from age and duration of diabetes.

Figure 19.7
Age-Adjusted Ischemic Heart Disease Survival by Sex and Diabetes Status, Rancho Bernardo, CA 1982-88



Curves were estimated by a Cox model blocked on both sex and diabetes status and adjusted for age.

Source: Reference 55

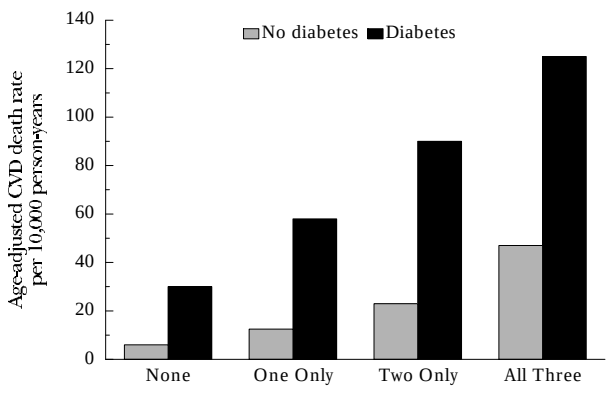
SEX

Diabetes is the only condition that causes women to have heart disease rates similar to those of men. The reason for this effect is uncertain. It is unlikely that it reflects differential loss of men with coronary heart disease through excess mortality. In the Rancho Bernardo Study[55], diabetic women had ischemic heart disease mortality rates similar to both nondiabetic and diabetic men, while nondiabetic women had a clear longevity advantage (Figure 19.7). In addition, case-fatality rates following a myocardial infarction are as great or greater for diabetic women relative to nondiabetic women as for diabetic men (Table 19.8). The increased heart disease risk of diabetic women could be mediated in part by the loss of women's usually favorable lipoprotein profile in the presence of diabetes[76] (see Chapter 7).

HEART DISEASE RISK FACTORS

As noted in Chapter 7, adults with diabetes are more likely than those without diabetes to have heart disease risk factors, especially high blood pressure, low levels of HDL cholesterol, and high levels of triglycerides[77]. However some of the increased risk of heart disease associated with diabetes appears to be independent of these factors. As shown in Tables 19.6 and 19.7, the incidence of heart disease is significantly increased among diabetic individuals in five occupational/population-based studies after adjustment for major heart disease risk factors[50,51,53-55]. In the Multiple Risk Factor Intervention Trial (MRFIT)[78], men with

Figure 19.8
Age-Adjusted CVD Death Rates by Number of CVD Risk Factors for Diabetic and Nondiabetic Men



Subjects are screenees for the MRFIT study; risk factors are hypercholesterolemia, hypertension, and cigarette smoking; CVD, cardiovascular disease.

Source: Reference 78

diabetes had a fivefold increased risk of cardiovascular mortality over a 12-year period compared with men without diabetes, even in the absence of high blood pressure, hypercholesterolemia, and cigarette smoking (Figure 19.8). Diabetes was also associated with an increased risk of cardiovascular death in the presence of any one, two, or all three of these heart disease risk factors (relative risks of 4.8, 4.0, and 2.6, respectively).

MICROALBUMINURIA

In 1984, two groups[79,80] reported an excess mortality in prospectively studied patients with NIDDM who also had microalbuminuria. Although neither study reported cause-specific mortality, 50% and 88% of deaths, respectively, were attributed to cardiovascular disease. There are now at least six publications[79-84], all from the United Kingdom or Denmark, describing an increased risk of death from all causes combined in patients who have NIDDM and microalbuminuria (Table 19.9). Only one of these studies, a population-based study from Oxford, England, separately examined coronary heart disease mortality: a significantly increased risk of death from all causes and from coronary heart disease was found for men and women who had microalbuminuria[84].

Most information on the relation of microalbuminuria to coronary heart disease in patients with diabetes comes from cross-sectional studies (Table 19.10)[82,84-87]. In three of five studies, microalbuminuria was significantly associated with prevalent coronary heart disease based on history or electrocardiogram. The other two studies resulted in statistically nonsignificant results. One found a nearly twofold risk of coronary heart disease in a small sample[86]; in the other, prevalent ischemic heart disease was not associated with increasing gradients of proteinuria[84].

It is uncertain whether the microalbuminuria-coronary heart disease association is independent of an association between microalbuminuria and blood pressure, lipids, or lipoproteins. Microalbuminuria in adults with NIDDM from the San Antonio Heart Study was associated with higher blood pressure but not with a more atherogenic lipid or lipoprotein pattern[88]. In contrast, investigators from Finland found that NIDDM patients with microalbuminuria had higher LDL and very low-density lipoprotein (VLDL) cholesterol levels and lower HDL cholesterol levels compared with nondiabetic subjects but no differences in blood pressure[89]. These divergent results are unexplained.

Microalbuminuria occurs in older adults without diabetes, in whom it predicts an increased risk of vascular disease[83,90]. Studies in nondiabetic individuals suggest that microalbuminuria may be a marker for heart disease rather than a risk factor. For example, von Willebrand factor antigen, a marker for damaged vascular endothelium, was present in higher amounts in

Table 19.9
Prospective Association of Microalbuminuria and Mortality in Adults with NIDDM, International Studies

Ref.	Population	Ascertainment of diabetes	Years followup	Sex	No.	Microalbuminuria (μg/ml)	Mortality end points	Mortality risk†
Clinical Studies								
79	London, England (1966-67, age 33-60 years)	Physician diagnosis	14	M and F	44	≥31 (versus ≤30)	All cause (88% CVD)	3.3**
80	Denmark (1973, age 50-75 years)	Physician diagnosis	9.5	M and F	76	30-140 (versus <15)	All cause (50% CVD)	1.8
81	Denmark (1973, age 50-75 years)	Physician diagnosis	10	M and F	503	41-200 (versus ≤15)	All cause (58% CVD)	2.3***
82	London, England (1985-87, age 31-64 years)	Physician diagnosis	3.4	M and F	141	20-200 (versus <20)	All cause (57% CVD)	4.1*
Population-Based Studies								
83	Fredericia, Denmark (1981-82, age 60-74 years)	Self-report and physician diagnosis or fasting glucose	8-9	M and F	211	Continuous	All cause	coef=0.333***
84	Oxford, England (1982, age 28-89 years)	Self-report and physician diagnosis or fasting glucose	6	M and F	246	40-200 (versus ≤15)	CHD All cause (41% CVD)	Increased 2.2††

M, males; F, females; CVD, cardiovascular disease; CHD, coronary heart disease; NIDDM, noninsulin-dependent diabetes mellitus †Mortality risk: Denmark, (Reference 80)—univariate relative risk; adjusted relative hazard—all other studies *p<0.05, **p<0.01, ***p<0.001, ††95% confidence interval does not include 1.0.

Source: References are listed within the table

Table 19.10
Cross-Sectional Association of Microalbuminuria and Heart Disease in Adults with NIDDM, International Studies

Ref.	Population	Ascertainment of NIDDM	Sex	No.	Microalbuminuria (μg/ml)	Heart disease endpoints	Association
Clinical Studies							
85	London, England (1985-87, age 35-64 years)	Physician diagnosis	M F	78 52	continuous up to 200	Angina, MI, abnormal ECG	p=0.007 (positive) p=0.008 (positive)
82	London, England (1985-87, age 31-64 years)	Physician diagnosis	M F	82 59	20-200	Angina, MI, abnormal ECG	p<0.05*(positive) p<0.01*(positive)
86	Edinburgh, Scotland (1987?, adults)	New NIDDM, physician diagnosis	M and F	149	>30 estimated (ACR>2.5 g/mol)	Angina, MI, abnormal ECG	ns
Population-Based Studies							
87	UKPDS (1982-87, age 25-65 years)	New NIDDM, physician diagnosis	M and F	2,337†	continuous	Abnormal ECG, history of MI	p<0.001*(positive) ns*
					ACR>2.5 g/mol	Abnormal ECG, history of MI	p<0.01 (positive) ns
84	Oxford, England (1982, age 28-89 years)	Known NIDDM, self-report and physician diagnosis or fasting plasma glucose	M and F	246	40-200	Angina, MI, CHD mortality (ICD 410-414)	ns*

ACR, albumin/creatinine ratio; ECG, electrocardiogram; CHD, coronary heart disease; MI, myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study; ns, not statistically significant. *Univariate. †Subjects excluded were those with MI during past year, current angina or heart failure, more than one major vascular episode, serum creatinine >175 μmol/l, severe retinopathy, malignant hypertension.

Source: References are listed within the table

nondiabetic hypertensive men who had microalbuminuria compared with nondiabetic hypertensive men without microalbuminuria[91].

ENDOGENOUS INSULIN

Hyperinsulinemia or insulin resistance has been the leading candidate for the risk factor that explains the excess risk of cardiovascular disease in patients with diabetes[92]. This hypothesis is compatible with studies showing that insulin covaries with dyslipidemia and central obesity, and in some populations, with hypertension. Because hyperinsulinemia (or insulin resistance) precedes the onset of diabetes[93], its role as a cardiovascular disease risk factor is also compatible with the observation that cardiovascular disease risk factors often precede the onset of clinically manifest diabetes[94-96].

All three prospective population-based studies of insulin and cardiovascular disease presented in the 1985 edition of *Diabetes in America* found insulin to be an independent predictor of coronary heart disease or cardiovascular disease in men[97-99]. However, in the only study that included women[97], no association was found. Since that time, two more cross-sectional population-based studies[100,101] and nine more prospective studies[102-109], including extended followup of the original cohorts, have been reported. Both cross-sectional studies and three of the prospective studies included women. These new data have not consistently confirmed the association of hyperinsulinemia and heart disease in men, and none have found an association in women.

The two cross-sectional studies yield different results. Postchallenge hyperinsulinemia was associated with cardiovascular disease in men but not women in a study of 1,263 adults age 40-70 years chosen as a representative sample of an Israeli cohort[100]. In contrast, among a representative sample of 1,069 men and women age 65-74 years from Kuopio, Eastern Finland, 2-hour postchallenge insulin was associated with known previous myocardial infarction in women but not men[101]. No association of fasting insulin with previous myocardial infarction was found.

The prospective studies of insulin levels and cardiovascular disease or coronary heart disease in nondiabetic subjects are shown in Table 19.11. In Finland, 1- and 2-hour insulin levels, but not fasting insulin, were associated with coronary heart disease in men at 5 and 9.5 years followup[98,103], while in South Wales, fasting insulin was associated with coronary heart disease in men at 5 years followup[104b]. In contrast, the Paris Prospective Study found that fasting but not 2-hour insulin predicted coronary heart disease in men at 5 years, while the reverse was true for the 15-year followup[99,104]. In Busselton, Australia, post-challenge insulin levels were associated with cardiovascular disease in men age 60-69 years after 12 but not after 13

years of followup[97,102]. No association was found in women at either followup.

All five of the more recent studies shown in Table 19.11 found no association between high insulin levels and increased coronary heart disease risk. This was true in men from Gothenberg, Sweden[105], in men from the MRFIT[107], and in two studies that presented data on men and women combined: the study of Pima Indians[106] and the San Luis Valley Study[108]. The Rancho Bernardo Study[109] found no association between insulin levels and cardiovascular disease in women and a negative association between post-challenge insulin levels and cardiovascular disease in men (a high insulin was "protective").

Some of these differences among studies may reflect ethnic or geographic variations. Thus far, significant differences have been found only in Caucasian populations, with the strongest and most consistent association in the Helsinki Study[98,103]. In the MRFIT, hyperinsulinemia was a risk factor only in men with apo E 3/2 phenotype, rather than the more usual apo E 3/3 phenotype[107]. The Finnish population is at high risk for cardiovascular disease and dyslipidemia, perhaps reflecting a different distribution of apo E phenotypes.

Some of the variation in Table 19.11 may reflect which diabetic individuals were excluded. Only three studies excluded all diabetic persons defined by current WHO criteria[106,108,109]; none of these found a positive association between insulin and heart disease. While some of the other studies adjusted for hypertension, which is more common among individuals with diabetes[98,99,103,104], they did not adjust for differences in the use of antihypertensive medications that are associated with higher insulin levels[110-112].

Table 19.11

Prospective Association of Endogenous Insulin and Heart Disease in Nondiabetic Adults, International Studies

Ref.	Population	Diabetics excluded†	Years followup	Sex	No.	End Points	Multivariate association of insulin with heart disease	
97	Busselton, Australia	?	12	M	1,634	CHD/CVD	1-hour	p<0.05/.01 (positive)
	(1966, age ≥21 years)	?	12	F	1,697	CHD/CVD	1-hour	ns/ns
102	Busselton, Australia	?	13	M	840	CHD/CVD	1-hour	ns/ns
	(1966, age 40-74 years)	?	13	F	724	CHD/CVD	1-hour	ns/ns
98	Helsinki, Finland	known	5	M	1,042	MI/CHD	Fasting	ns
	(1971-72, age 35-64 years)						1-hour	p<0.01/ns* (positive)
							2-hour	p<0.01/.01 (positive)
103	Helsinki, Finland	known	9.5	M	982	MI and CHD	Fasting	ns
	(1971-72, age 35-64 years)						1-hour	p<0.05 (positive)
							2-hour	p<0.01 (positive)
99	Paris, France	known	5	M	7,246	MI and CHD	Fasting	p<0.01 (positive)
	(1968-73, age 43-54 years)						2-hour	ns
104	Paris, France	insulin-treated	15	M	7,028	CHD	Fasting	ns
	(1968-73, age 43-54 years)						2-hour	p<0.01** (positive)
104b	Caerphilly, South Wales	known and borderline	5	M	2,022	MI and CHD	Fasting	p=0.04 (positive)†
	(1979-83, age 45-59 years)							
105	Gothenburg, Sweden	known	8	M	563	MI and CHD	Fasting	ns*
	(1980, 67 years)						1-hour	ns*
106	Pima Indians, USA	new and known	15 (mean=6.7)	M and F	589	Abnormal ECG	Fasting	ns
	(1975, age ≥25 years)						2-hour	ns
107	MRFIT, USA	known	7-10	M	622	MI and CHD	Fasting	ns
	(1973-76, age 35-57 years)		7-10	M (with Apo E 3/2)	58	MI and CHD	Fasting	p=0.02 (positive)
108	San Luis Valley, USA	new and known	4	M and F	626	MI and CHD	Fasting	ns
	(1984-88, age 25-74 years)						Area	ns
109	Rancho Bernardo, USA	new and known	5	M	538	CHD/CVD	Fasting	ns/ns
	(1984-87, age 50-89 years)						2-hour	ns/p=0.01 (negative)
		new and known	5	F	705	CHD/CVD	Fasting	ns/ns
							2-hour	ns/ns

MRFIT, Multiple Risk Factor Intervention Trial, a nested-case control study within a clinical trial; MI, nonfatal myocardial infarction; CHD, fatal coronary heart disease; CVD, fatal cardiovascular disease; ns, not statistically significant. †Known, previously diagnosed diabetics; new, NIDDM by OGTT according to WHO criteria; *univariate analysis; **highest quintile vs. lower quintiles; †age-adjusted, ns after adjustment for triglycerides, prevalent heart disease, or body mass index.

Source: References are listed within the table

Table 19.12

Prospective Association of Endogenous Insulin and Heart Disease in Adults with Diabetes or IGT, International Studies

Ref.	Population	Type of diabetes	Years followup	Sex	No.	End Points†	Multivariate association of insulin with heart disease	
113	Bedford, UK (population-based, 1962, adults)	Borderline diabetic	10	M and F	241	Fatal CHD Nonfatal CHD	2-hour 2-hour	ns p<0.01* (negative)
114	Paris, France (employees, 1968-73, age 43-54 years)	IGT and NIDDM	11	M	943	Fatal CHD	Fasting 2-hour	ns ns
115	Kuopio, Finland (population-based, 1979-81, age 45-64 years)	New NIDDM	5	M and F	109	Nonfatal MI	Fasting 2-hour	ns ns
106	Pima Indians, USA (population-based, 1975, age ≥25 years)	NIDDM	15 (mean=6.7)	M and F	405	Abnormal ECG	Fasting 2-hour	ns ns

IGT (impaired glucose tolerance) and NIDDM diagnosed by OGTT according to WHO criteria; ns, not statistically significant. †Subjects were free of heart disease at baseline; CHD, coronary heart disease; ECG, electrocardiogram; MI, myocardial infarction. *A high insulin was "protective."

Source: References are listed within the table

The lack of a positive association between endogenous insulin levels and coronary heart disease is shown in Table 19.12 for four prospective population-based or employee-based studies of adults with diabetes or impaired glucose tolerance[106,113-115]. In the Bedford cohort[113], there was a significant inverse association: 2-hour insulin was "protective" for nonfatal coronary heart disease.

Not shown in Table 19.12 are preliminary results from the Diabetes Intervention Study, a German clinical trial of patient education, clofibric acid, and antihypertensive treatment in patients with newly diagnosed NIDDM[116]. In that study, fasting insulin levels in 357 men showed a graded association with new ECG abnormalities ($p<0.05$) and myocardial infarction (not significant) over 10 years; no associations were seen

Table 19.13

Prospective Association of Insulin Treatment and Cardiovascular Disease in Diabetic Adults, International Studies

Ref.	Population	Type of diabetes	Years followup	Sex	No.	End points	Association of insulin treatment with heart disease	
Observational Studies								
54	NHANES I, USA (1971-75, age 40-77 years)	Unspecified	9	M and F	207	Fatal CVD	Insulin/diet	ns (positive)
106	Pima Indians, USA (1975, age ≥25 years)	NIDDM	15 (mean=6.7)	M and F	824	Abnormal ECG*	Insulin (yes/no)	ns**
75	Pima Indians, USA (1975, age ≥45 years)	NIDDM	9	M and F	689	Fatal CHD	Insulin (yes/no)	significant** (positive)
117	Schwabing, Germany (1980?, age 17-84 years)	Unspecified	5	M and F	197	Nonfatal CVD	Insulin dose	p<0.001 (positive)
118	Pittsburgh, USA (1981, adults)	IDDM	6	M and F	548	Fatal CHD	Insulin dose	ns
Randomized Clinical Trials								
119	UGDP, USA (1961-65, adults)	NIDDM***	9-13	M and F	619	Fatal and nonfatal CVD	Insulin standard/diet Insulin variable/diet	ns ns
120	DCCT, USA (1983-89, age 13-39 years)	IDDM	6.5	M and F	1,441	Macrovascular disease	Insulin intensive/conventional	ns (negative)
121	VA Trial, USA (1991?, age 40-69 years)	NIDDM	≥2	M	153	CVD	Insulin intensive/conventional	p=0.04 (positive)

UGDP, University Group Diabetes Program; NHANES, National Health and Nutrition Examination Survey; DCCT, Diabetes Control and Complications Trial; VA, Veterans Administration; ECG, electrocardiogram; CHD, coronary heart disease; ns, not statistically significant; CVD, cardiovascular disease. *Free of ECG abnormalities at baseline; **adjusted for duration of diabetes; ***diagnosed within 12 months of first exam.

Source: References are listed within the table

in 203 women. Insulin levels were measured after randomization and may have been altered by antihypertensive treatment.

EXOGENOUS INSULIN

If endogenous insulin is a heart disease risk factor, one might expect an increased risk of heart disease in patients treated with insulin. On the other hand, if glucose levels are sufficiently reduced by insulin therapy, the risk of heart disease might decrease. In the absence of a trial, it is difficult or impossible to distinguish the effects of insulin use and dose from the severity of diabetes.

As shown in Table 19.13, there have been five observational studies and three randomized clinical trials that have investigated the prospective association between insulin treatment and cardiovascular disease[54,75,106,117-121]. Three of the observational studies found an increased risk of heart disease associated with insulin use; this was statisticially significant in the Pima Indians[75] and in Germany[117]. The Pima Indian study adjusted for differences in duration of diabetes, as insulin use may be a marker for disease of longer duration.

In the DCCT[120], young adults with IDDM who were randomly assigned to the stricter of two insulin treatment protocols had a significant 34% reduction in LDL cholesterol and a nonsignificant 41% reduction in macrovascular disease (Table 19.13). The improvement was not explained by differences in the duration of diabetes, which was similar in the two randomized groups, but could have been due to unmeasured differences in diet or meal frequency in the group assigned to more rigid control.

In contrast is the preliminary report from the Feasibility Trial of the VA Cooperative Study on Glycemic Control and Complications in Type II Diabetes[121]. In this trial, 153 NIDDM patients were followed for 27 months. Those randomly assigned to intensive treatment with insulin experienced significantly more cardiovascular events than those assigned to conventional treatment (p=0.04) (Table 19.13). In the first randomized clinical trial of adults with NIDDM, the University Group Diabetes Program[119], there was no difference in cardiovascular disease risk during 9-13 years followup between those receiving diet or insulin in either standard or variable doses, despite lower glucose levels in adults assigned to variable insulin doses. All subjects had been diagnosed within 12 months of baseline, so duration of diabetes was not a confounding issue. As recently reviewed, the role of insulin as a heart disease risk factor remains controversial[122].

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