CHAPTER 18

HEART DISEASE AND DIABETES

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SUMMARY

Heart disease remains a major cause of morbidity and mortality in type 2 diabetes and is estimated to account for 10%–11% of all vascular deaths. Surveys of the U.S. population have demonstrated an age-standardized differential for heart disease in adults with mostly type 2 diabetes that varies from 1.9 to 2.5. The age-standardized prevalence is about 50% higher in men than women overall and for most categories of heart disease, except congestive heart failure. Although rates of diabetes are higher in nonwhites than in non-Hispanic whites, it should be noted that non-Hispanic whites with diabetes generally report heart disease rates about 50% higher than Hispanic subjects with diabetes, with an intermediate prevalence in non-Hispanic blacks. Despite an approximate doubling in type 2 diabetes prevalence from the 1980s to the 2010s, the prevalence of heart disease in diabetes has remained stable.

Classic heart disease risk factors, such as elevated low-density lipoprotein (LDL) cholesterol, blood pressure, reduced high-density lipoprotein (HDL) cholesterol, and smoking, have been clearly demonstrated to be important determinants of heart disease in diabetes. However, several studies, including a very large, multinational meta-analysis, indicate that the excess prevalence of heart disease in diabetes is not accounted for by measured classic cardiovascular disease (CVD) risk factors, including levels of triglyceride, HDL cholesterol, non-HDL cholesterol, C-reactive protein, fibrinogen, and renal function. In addition, novel biomarkers have not been found to add significance in prediction of heart disease. The association between fasting glucose and heart disease displays a J-shaped curve in several studies, indicating that the risk for heart disease in subjects with fasting plasma glucose 100–125 mg/dL is only modestly elevated compared to the twofold higher risk in those with values ≥126 mg/dL, the current cut point for diagnosis of type 2 diabetes. Glycosylated hemoglobin (A1c) has also been shown to have a graded association with heart disease. The association between insulin resistance and heart disease is inconsistent, at least in part because of methodologic differences among studies. Furthermore, these studies may be complicated by cross-reactivity with proinsulin, which is a marker for beta cell failure and may be more strongly associated with heart disease than insulin levels. Obesity is the most important risk factor for type 2 diabetes but has not been shown to have an independent association with heart disease. Although similar associations with heart disease have been found for body mass index and waist measurements in a large meta-analysis of general population cohort studies, these were lost after adjustment for other risk factors, possibly because obesity is in the causal pathway between these risk factors and heart disease development. Similarly, conflicting data have been reported as to whether the presence of the metabolic syndrome in subjects with diabetes is independently associated with heart disease. In contrast to body weight, physical inactivity in those with diabetes appears to have an independent association with heart disease.

Clinical trials involving risk factor modification in diabetes have helped to clarify their roles in heart disease development, as well as the benefits and limitations of modern treatment modalities for diabetes and its complications, and have led to significant modification in treatment guidelines. Whether improvement of glycemic control reduces heart disease has long been a central question, since older trials had not demonstrated benefit. However, extended follow-up of earlier studies of improved glycemic control in both type 1 and type 2 diabetes have demonstrated a long-term so-called “legacy” benefit for heart disease, not immediately evident after completion of the active intervention phase. Intervention trials testing intensive versus standard glycemic control, however, have found no evidence of benefit of improved glycemic control on cardiovascular outcomes. In one of these trials, cardiovascular and all-cause mortality increased in the intensive control group, while a meta-analysis of 13 trials of intensive glycemic control found no significant impact on all-cause mortality. Severe hypoglycemia, longstanding diabetes, and preexisting heart disease appeared to contribute to the increased mortality and the lack of benefit for intensive glycemic control, and *post hoc* analyses suggested that this intervention may be most effective in more recently diagnosed subjects. With respect to lipid-lowering clinical trials, by contrast, studies have shown unequivocally that statin treatment, in both secondary as well as primary prevention trials, significantly reduces heart disease with a similar risk reduction to that seen in nondiabetic subjects. However, fenofibrate given as monotherapy or as add-on therapy to simvastatin does not confer heart disease benefit in diabetes, except possibly in the subgroup with high triglyceride and low HDL cholesterol levels. While older trials of

Received in final form December 18, 2014, with an update on January 20, 2017.

blood pressure lowering demonstrated benefit, a more recent large trial of intensive blood pressure control did not find that achieving a lower goal leads to a reduction in cardiovascular events overall, although ischemic stroke incidence was decreased. Several trials were unable to demonstrate a significant benefit for low-dose aspirin as primary preventive therapy in diabetes. Finally, although there have been few studies of comprehensive risk factor management, one small, long-term trial was highly successful in reducing cardiovascular events by intensive glycemic blood pressure and LDL cholesterol control. In addition, a meta-analysis of physical activity trials in patients with diabetes showed a reduction in myocardial infarction and all-cause mortality. However, a large 10-year clinical trial focusing on weight reduction in people with diabetes through an intensive lifestyle change program showed no cardiovascular benefit despite improvement in risk factors.

In conclusion, despite intensive management of risk factors, the high risk for heart disease among people with diabetes remains a major health concern.

INTRODUCTION

Although coronary heart disease (CHD) is the major cause of morbidity and mortality in patients with type 2 diabetes, historically the diabetes-CHD association received little systematic study, even after the publication of Kelly West's monumental book *Epidemiology of Diabetes Mellitus and Its Vascular Lesions* (1) and the development of standard World Health Organization (WHO) (2) and National Diabetes Data Group (3) criteria for the definition of diabetes in the 1980s.

According to the Centers for Disease Control and Prevention (4), the proportion of diabetes in the United States that is type 1 is 5%, and type 2 diabetes accounts for 90%–95%. The epidemiology and etiology of type 1 (insulin-dependent) diabetes has been reviewed (5) and is described in detail in Chapter 2 *Prevalence and Incidence of Type 1 Diabetes Among Children and Adults in the United States and Comparison With Non-U.S. Countries*. Although type 1 diabetes carries a cardiovascular disease (CVD) mortality risk similar to type 2 diabetes (6), this chapter mainly addresses type 2 diabetes, citing papers reporting fasting plasma glucose (FPG) or diabetes by history.

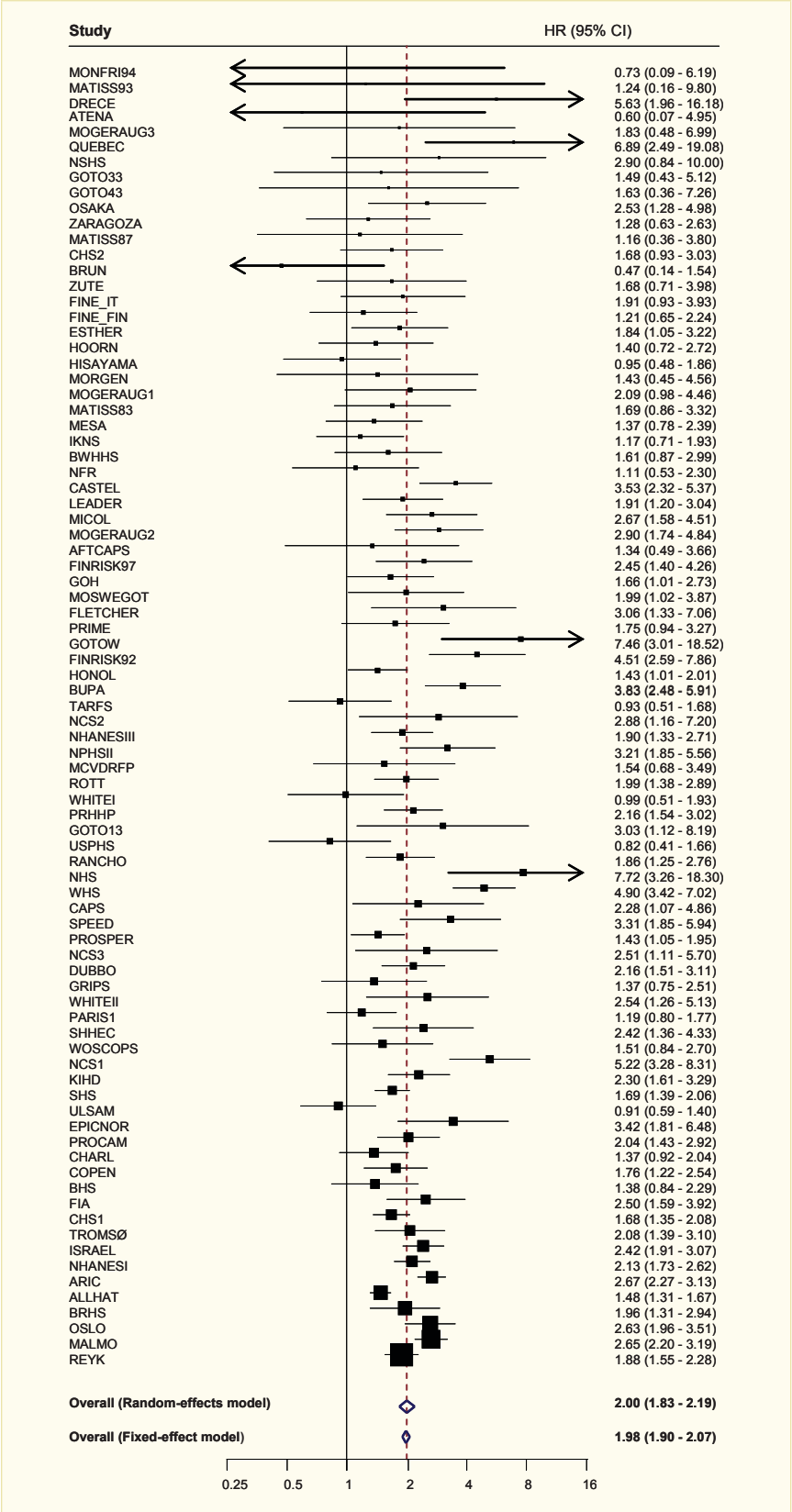
The literature on the association between diabetes and CVD has increased exponentially since *Diabetes in America, 2nd edition*, was published in 1995 (7). In this chapter, each section usually starts with a review and, whenever possible, concludes showing a large systematic review or meta-analysis that addresses each topic. In order to improve generalizability and statistical power, no attempt was made to exclude prospective studies done outside the United States, which were included in these meta-analyses. Point estimates are provided from each cohort study. Unless otherwise noted, individuals in most cohort studies were of European or Scandinavian ancestry and about one-third of cohorts were from the United States.

Diabetes is clearly an established risk factor for CHD (8,9), but how much its effect varies by age, sex, or levels of conventional risk factors is uncertain (10,11). Key risk factors characteristic of diabetes are discussed, specifically hyperglycemia; dyslipidemia (elevated triglycerides and low high-density lipoprotein [HDL] cholesterol); hypertension; components of the metabolic syndrome; central obesity; insulin (hyperinsulinemia); biomarkers, such as C-reactive protein; lack of physical activity; and smoking. Hypertension, or high blood pressure, is usually included in discussions of the metabolic syndrome but does not cluster with metabolic syndrome components in factor analysis. Nevertheless, hypertension is the most common risk factor in adults with diabetes and is clearly a risk factor for heart disease and stroke. The extent to which diabetes is associated with fatal versus nonfatal myocardial infarction is also unknown (12,13). Further, how much of the effect of diabetes on vascular risk can be accounted for by conventional vascular risk factors (dyslipidemia, hypertension, obesity, smoking) is unresolved (14). Different uncertainties apply regarding the best measures of dysglycemia in people without diabetes. FPG has been reported to be log-linearly and importantly associated with risk of vascular disease at all concentrations, including below the classic fasting threshold for diabetes of 126 mg/dL (6.99 mmol/L). Available data on this topic are inconclusive (15,16). In 2009, the U.S. Preventive Services Task Force stated that prospective data for FPG concentration and CHD were inconsistent and had serious limitations (17).

Figure 18.1 shows study-specific hazard ratios (HR) for CHD in people with diabetes at baseline compared with people without diabetes (18). The overall summary risk estimates from the Forest plot indicate that the overall effect is an approximate doubling of risk of CHD among those with diabetes compared to those without diabetes. Regression analyses were stratified, where appropriate, by sex and trial group and adjusted for age, smoking status, body mass index (BMI), and systolic blood pressure. Studies are ordered (top to bottom) by increasing number of CHD cases. Sizes of data markers are proportional to the inverse of the variance of the hazard ratios. The data sources shown in this Forest plot reveal the heterogeneity of associations by cohort.

Obesity is increasing steadily worldwide, especially in industrializing countries (19). In the United States, the prevalence of obesity defined by a BMI ≥30 kg/m^2 is 30%–35% in both middle-aged (40–59 years) and older adults (≥60 years) (20).

FIGURE 18.1. Study-Specific Hazard Ratios for Coronary Heart Disease in People With Diabetes at Baseline Compared to People Without Diabetes



Regression analyses were stratified, where appropriate, by sex and trial group, and adjusted for age, smoking status, body mass index, and systolic blood pressure. Studies are ordered (top to bottom) by increasing number of coronary heart disease cases. Studies with <11 coronary heart disease cases were excluded from analysis. Sizes of data markers are proportional to the inverse of the variance of the hazard ratios. CI, confidence interval; HR, hazard ratio.

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Losing weight is difficult, and interventions that work in younger adults cannot be assumed to successfully translate into an older population, where low muscle mass, physical frailty, osteoporosis, comorbid disease, and cultural differences may increase risk. Sustained weight loss may be required to produce meaningful changes in health outcomes, particularly for CVD.

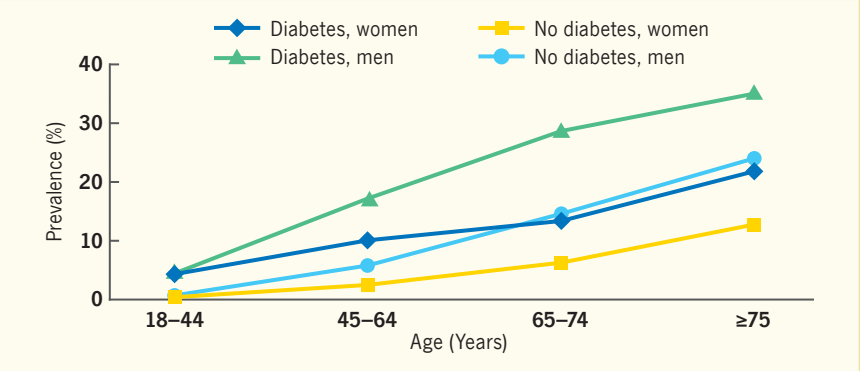
The clinical trial evidence is reviewed for interventions designed to produce healthy changes in heart disease risk factors and reduce heart disease comparing adults with or without diabetes.

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

In new analyses conducted for *Diabetes in America, 3rd edition*, nationally based surveys of the U.S. population consistently demonstrate that the prevalence of heart disease (no matter how defined) is higher among adults with diabetes than adults without diabetes (Tables 18.1–18.4, Appendices 18.1–18.4). In both adults with and without diabetes, the prevalence of heart disease increases with age (Figure 18.2). The age-standardized differential for overall heart disease (ratio in persons with diabetes to those without) varies from 1.9 to 2.5, reflecting the different heart disease conditions included in each survey: 29.7% versus 16.4% for the National Health Interview Survey (NHIS), 22.4% versus 9.4% for the National Health and Nutrition Examination Survey (NHANES), and 15.3% versus 6.2% for the Behavioral Risk Factor Surveillance System (BRFSS), for those with and without diabetes, respectively. National data based on hospital discharges demonstrate similar trends, but with a lower differential between adults with and without diabetes (Table 18.4, Appendix 18.4).

Examination of these national surveys demonstrates that the age-standardized prevalence of heart disease is consistently higher among men than women, both among those with and without diabetes (Tables 18.1–18.4, Appendices 18.1–18.4). The only exception was congestive heart failure in the NHANES 2007–2010 where prevalences were similar in men and women. These tables also demonstrate substantial variation in the age-standardized prevalence of heart disease among race/ethnicity groups. American Indians/Alaska Natives reported the highest rates of CHD or angina and heart attack or myocardial infarction in the BRFSS 2010. For the NHIS and NHANES (which did not have sufficient numbers of American Indian/Alaska Native respondents to report separately), non-Hispanic whites generally reported the highest rates. However, non-Hispanic blacks in the NHANES reported more heart failure than other race/ethnicity groups.

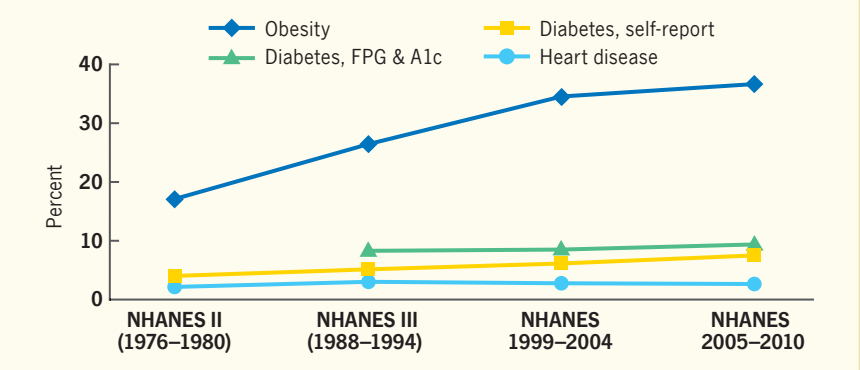
FIGURE 18.2. Prevalence of Coronary Heart Disease, by Diabetes Status, Age, and Sex, U.S., 2009–2010



Coronary heart disease and diabetes status are self-reported.

SOURCE: National Health Interview Surveys 2009–2010

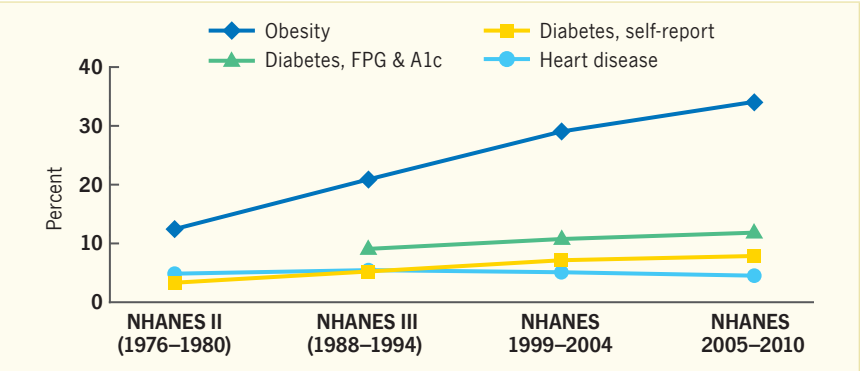
FIGURE 18.3. Trends in the Age-Standardized Prevalence of Obesity, Diabetes, and Heart Disease Among Adult Women Age 20–74 Years, U.S., 1976–2010



Obesity is defined as body mass index ≥30 kg/m². Diabetes is defined as self-report and/or A1c ≥6.5% and/or FPG ≥126 mg/dL. Heart disease is self-reported and includes heart attack or heart failure. Estimates are age-standardized to the National Health Interview Survey 2010 total population using age categories 18–44, 45–64, and ≥65 years. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.

SOURCE: National Health and Nutrition Examination Surveys (NHANES) II (1976–1980), III (1988–1994), and 1999–2010

FIGURE 18.4. Trends in the Age-Standardized Prevalence of Obesity, Diabetes, and Heart Disease Among Adult Men Age 20–74 Years, U.S., 1976–2010



Obesity is defined as body mass index ≥30 kg/m². Diabetes is defined as self-report and/or A1c ≥6.5% and/or FPG ≥126 mg/dL. Heart disease is self-reported and includes heart attack or heart failure. Estimates are age-standardized to the National Health Interview Survey 2010 total population using age categories 18–44, 45–64, and ≥65 years. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; FPG, fasting plasma glucose.

SOURCE: National Health and Nutrition Examination Surveys (NHANES) II (1976–1980), III (1988–1994), and 1999–2010

TABLE 18.1. Age-Standardized Prevalence of History of Heart Disease Among Adults Age ≥18 Years, by Diabetes Status, Sex, and Race/Ethnicity, NHIS, U.S., 2009–2010

	PERCENT (STANDARD ERROR)					
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
CHARACTERISTICS	Coronary Heart Disease		Angina Pectoris		Heart Attack	
Total	16.2 (0.58)	6.9 (0.20)	7.6 (0.49)	3.1 (0.13)	11.4 (0.55)	4.9 (0.18)
Sex						
Men	20.5 (0.96)	9.7 (0.35)	9.7 (0.81)	3.7 (0.22)	14.4 (0.90)	6.8 (0.28)
Women	11.8 (0.72)	4.7 (0.21)	5.5 (0.50)	2.5 (0.15)	8.4 (0.61)	3.3 (0.18)
Race/ethnicity						
Non-Hispanic white	17.8 (0.79)	7.2 (0.23)	8.9 (0.68)	3.3 (0.16)	12.3 (0.74)	5.1 (0.20)
Non-Hispanic black	13.5 (1.10)	5.7 (0.47)	5.5 (0.93)	2.5 (0.32)	11.3 (1.12)	4.0 (0.37)
All Hispanic	10.8 (1.11)	5.4 (0.55)	4.9 (0.86)	2.0 (0.30)	8.0 (1.16)	3.4 (0.42)
Mexican American	10.4 (1.53)	6.0 (0.72)	4.2 (1.22)	1.6 (0.38)	7.6 (1.63)	3.8 (0.68)
Other Hispanic	11.8 (1.52)	4.8 (0.83)	5.9 (1.10)	2.3 (0.47)	8.6 (1.56)	3.0 (0.52)
Other/Multiracial	15.4 (2.61)	5.0 (0.86)	6.1 (1.55)	1.8 (0.38)	8.6 (2.03)	3.4 (0.72)
	Other Heart Condition		Any Heart Condition, Including Angina		Any Heart Condition, not Including Angina	
Total	16.8 (0.68)	10.4 (0.23)	29.7 (0.74)	16.4 (0.26)	28.7 (0.74)	15.8 (0.26)
Sex						
Men	17.6 (1.03)	11.0 (0.37)	32.7 (1.17)	19.1 (0.43)	31.8 (1.16)	18.7 (0.43)
Women	16.1 (0.88)	9.9 (0.28)	26.8 (0.97)	14.5 (0.32)	25.6 (0.97)	13.7 (0.31)
Race/ethnicity						
Non-Hispanic white	18.8 (0.93)	11.3 (0.29)	32.2 (0.98)	17.6 (0.31)	31.1 (0.98)	17.0 (0.30)
Non-Hispanic black	15.7 (1.68)	8.1 (0.48)	29.7 (1.79)	13.8 (0.62)	28.7 (1.77)	13.2 (0.60)
All Hispanic	10.8 (1.21)	6.2 (0.53)	20.2 (1.59)	11.2 (0.77)	19.1 (1.53)	10.5 (0.72)
Mexican American	11.0 (1.75)	6.1 (0.73)	19.8 (2.34)	11.8 (0.91)	18.8 (2.27)	11.2 (0.91)
Other Hispanic	10.5 (1.69)	6.3 (0.80)	21.0 (2.04)	10.7 (1.19)	19.6 (1.98)	9.9 (1.09)
Other/Multiracial	8.3 (1.74)	5.8 (0.81)	20.3 (2.74)	9.7 (1.25)	19.8 (2.69)	9.2 (1.23)

History of heart disease and diabetes status are self-reported. Data are standardized to the NHIS 2009–2010 diabetic population using age categories 18–44, 45–64, and ≥65 years.

SOURCE: National Health Interview Surveys (NHIS) 2009–2010

TABLE 18.2. Age-Standardized Prevalence of History of Heart Disease Among Adults Age ≥20 Years, by Diabetes Status, Sex, and Race/Ethnicity, NHANES, U.S., 2007–2010

	PERCENT (STANDARD ERROR)					
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
CHARACTERISTICS	Congestive Heart Failure		Coronary Heart Disease		Angina	
Total	10.0 (1.06)	2.8 (0.22)	11.4 (0.81)	4.8 (0.31)	7.7 (0.89)	2.7 (0.28)
Sex						
Men	9.5 (1.12)	4.0 (0.39)	14.1 (1.58)	7.8 (0.54)	7.6 (1.39)	3.5 (0.44)
Women	10.3 (1.80)	1.9 (0.26)	9.0 (1.28)	2.4 (0.26)	7.8 (1.38)	2.1 (0.30)
Race/ethnicity						
Non-Hispanic white	10.4 (1.62)	2.6 (0.24)	13.8 (1.37)	5.0 (0.35)	8.6 (1.30)	2.8 (0.35)
Non-Hispanic black	12.0 (1.41)	4.1 (0.58)	5.7 (1.31)	2.1 (0.42)	6.2 (1.39)	1.4 (0.42)[1]
All Hispanic	7.0 (0.93)	2.6 (0.56)	9.6 (0.94)	3.7 (0.54)	6.1 (1.15)	2.7 (0.73)
Mexican American	6.3 (0.72)	2.0 (0.42)	9.5 (1.23)	4.5 (0.67)	5.1 (1.22)	2.9 (0.98)[1]
Other Hispanic	8.2 (1.86)	3.4 (1.09)[1]	9.7 (1.54)	2.6 (0.55)	7.9 (2.77)[1]	2.4 (0.59)
Other/Multiracial	6.6 (2.41)[1]	3.9 (1.64)[2]	9.9 (2.98)[1]	5.9 (1.95)[1]	6.5 (2.68)[2]	2.1 (0.66)[1]
	Heart Attack		Any Heart Condition, Including Angina		Any Heart Condition, not Including Angina	
Total	10.8 (0.93)	4.6 (0.30)	22.4 (1.41)	9.4 (0.45)	20.2 (1.15)	8.4 (0.43)
Sex						
Men	12.9 (1.38)	7.3 (0.56)	24.5 (2.09)	13.4 (0.76)	22.6 (1.91)	12.7 (0.78)
Women	8.7 (1.16)	2.5 (0.26)	20.3 (2.08)	6.3 (0.49)	17.7 (1.71)	5.0 (0.42)
Race/ethnicity						
Non-Hispanic white	12.2 (1.35)	4.7 (0.37)	24.9 (2.07)	9.5 (0.52)	22.5 (1.76)	8.5 (0.48)
Non-Hispanic black	8.6 (1.04)	4.6 (0.63)	19.9 (1.75)	8.2 (0.85)	17.8 (1.68)	7.7 (0.87)
All Hispanic	9.9 (1.45)	3.2 (0.34)	17.2 (1.60)	8.4 (0.86)	15.7 (1.62)	6.8 (0.68)
Mexican American	9.3 (1.70)	3.6 (0.48)	16.8 (1.58)	8.7 (0.77)	14.9 (1.63)	6.9 (0.67)
Other Hispanic	10.7 (2.65)	2.7 (0.58)	18.0 (3.49)	8.0 (1.37)	17.3 (3.28)	6.6 (1.16)
Other/Multiracial	[3]	4.7 (1.58)[1]	15.4 (4.04)	9.1 (2.26)	12.8 (3.22)	9.0 (2.25)

History of heart disease and diabetes status are self-reported. Data are standardized to the National Health Interview Surveys 2009–2010 diabetic population using age categories 20–44, 45–64, and ≥65 years.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys (NHANES) 2007–2010

TABLE 18.3. Age-Standardized Prevalence of History of Heart Disease Among Adults Age ≥18 Years, by Diabetes Status, Sex, and Race/Ethnicity, BRFSS, U.S., 2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)			
	Diabetes	No Diabetes	Diabetes	No Diabetes
	Coronary Heart Disease or Angina		Heart Attack or Myocardial Infarction	
Total	15.3 (0.25)	6.2 (0.07)	14.4 (0.25)	6.0 (0.07)
Sex				
Men	17.8 (0.41)	8.3 (0.13)	17.4 (0.40)	8.6 (0.13)
Women	12.8 (0.30)	4.6 (0.08)	11.4 (0.28)	4.0 (0.07)
Race/ethnicity				
Non-Hispanic white	16.5 (0.30)	6.2 (0.07)	15.0 (0.28)	5.9 (0.07)
Non-Hispanic black	11.6 (0.66)	5.7 (0.31)	11.3 (0.60)	6.4 (0.32)
All Hispanic	12.9 (0.78)	5.3 (0.35)	12.6 (0.87)	5.5 (0.40)
Non-Hispanic Asian	9.6 (1.91)	4.0 (0.68)	8.3 (1.68)	3.8 (0.67)
Native Hawaiian/Other Pacific Islander	[3]	5.8 (2.39)[2]	18.1 (8.78)[2]	9.9 (3.03)[1]
American Indian/Alaska Native	20.2 (2.59)	9.9 (1.39)	27.1 (3.08)	11.4 (1.42)

History of heart disease and diabetes status are self-reported. Data are standardized to the BRFSS 2010 diabetic population using age categories 18–44, 45–64, and ≥65 years.
[1] Relative standard error >30%–40%
[2] Relative standard error >40%–50%
[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: Behavioral Risk Factor Surveillance System (BRFSS) 2010

TABLE 18.4. Age-Standardized Percent of Hospitalizations Listing Heart Disease Among Adults Age ≥18 Years, by Diabetes Status, Sex, and Race, NHDS, U.S., 2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)					
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
	Myocardial Infarction		Angina		Cardiac Dysrhythmia	
Total	2.9 (0.19)	2.8 (0.09)	0.9 (0.10)	0.6 (0.04)	9.6 (0.31)	11.9 (0.17)
Sex						
Men	3.5 (0.32)	3.6 (0.15)	1.1 (0.17)	0.8 (0.08)	10.6 (0.46)	14.0 (0.28)
Women	2.3 (0.21)	2.1 (0.10)	0.6 (0.12)	0.3 (0.04)	8.7 (0.42)	10.2 (0.21)
Race						
White	3.1 (0.27)	2.7 (0.11)	0.8 (0.11)	0.5 (0.04)	10.3 (0.41)	12.4 (0.21)
Black	2.2 (0.38)	2.5 (0.25)	0.8 (0.27)[1]	0.4 (0.09)	7.5 (0.64)	9.6 (0.45)
Not stated	2.5 (0.30)	2.9 (0.23)	1.0 (0.29)	0.8 (0.18)	8.4 (0.72)	11.0 (0.44)
	Congestive Heart Failure		Coronary Heart Disease		Cardiovascular Disease	
Total	13.1 (0.37)	10.8 (0.17)	20.8 (0.45)	13.9 (0.19)	41.3 (0.54)	33.7 (0.25)
Sex						
Men	13.3 (0.53)	11.7 (0.26)	26.0 (0.72)	18.5 (0.31)	46.3 (0.80)	39.8 (0.39)
Women	12.9 (0.51)	10.2 (0.22)	16.2 (0.54)	10.1 (0.22)	36.8 (0.73)	28.9 (0.33)
Race						
White	12.7 (0.48)	10.0 (0.19)	22.2 (0.60)	14.2 (0.23)	42.0 (0.71)	33.5 (0.31)
Black	16.3 (0.95)	15.5 (0.59)	16.1 (0.94)	12.0 (0.52)	41.5 (1.24)	36.0 (0.74)
Not stated	9.6 (0.69)	10.1 (0.39)	19.2 (1.11)	13.3 (0.48)	35.8 (1.33)	32.1 (0.69)

Diabetes is defined as ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0, and 775.1. Heart disease is defined by ICD-9 codes as follows: myocardial infarction 410, angina pectoris 413, cardiac dysrhythmia 427, congestive heart failure 428, coronary heart disease 410–414, and cardiovascular disease 410–414, 426–438, and 440–448. Data are standardized to the National Health Interview Survey 2009–2010 diabetic population using age categories 18–44, 45–64, and ≥65 years. Standard errors were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. ICD-9, International Classification of Diseases, Ninth Revision.

SOURCE: National Hospital Discharge Survey (NHDS) 2010

While the above variations in the prevalence of heart disease are consistent with those described in *Diabetes in America, 2nd edition* (7), large secular trends have been noted from the 1970s to the 2010s. Figures 18.3 and 18.4 present prevalences of obesity, diabetes, and heart disease for women and men, respectively, from four different NHANES time periods covering 1976–2010. Over this time, the prevalence of obesity increased dramatically, from 17% to 37% in women and 12% to 34% in men. Over this same period, the prevalence of self-reported diabetes also increased from 4% to 7% in women and 3% to 8% in men, a similar percent increase as for obesity. However, the prevalence of heart disease remained stable or declined for both sexes. This finding was also true when men and women with and without diabetes were examined separately; however, estimates in men or women with diabetes were unstable due to smaller sample sizes (data not shown). Although heart disease prevalence has been stable, population attributable risk (PAR, here defined as the number of cases of heart disease that would not occur if diabetes could be eliminated) may not have been. In other words, the prevalence

of heart disease has remained stable, even though the prevalence of diabetes has increased—that is, the association between diabetes and heart disease has decreased, and the PAR has declined.

One limitation of much national survey data is the reliance on self-reported diabetes and heart disease. However, as seen in Figures 18.3 and 18.4, the prevalence of diabetes based on FPG and glycosylated hemoglobin (A1c) levels has demonstrated the same trends as self-reported data over the last three survey time periods. Therefore, the reported variations by age, sex, and race/ethnicity are likely real.

RISK FACTORS FOR THE DEVELOPMENT OF CORONARY HEART DISEASE IN PERSONS WITH DIABETES

HYPERGLYCEMIA

Because a diagnosis of diabetes requires hyperglycemia, it is difficult to separate the effect of diabetes *per se* on CVD risk from the effect of glycemia in persons who have glucose levels below diabetes diagnostic threshold levels. (Though often referred to as prediabetes, this term can be misleading as less than half of those with hyperglycemia go on to develop diabetes.) An early attempt was made by Epstein (21), who reviewed 29 prospective studies of glycemia and CHD to determine whether any observed CVD association was independent of cholesterol, blood pressure, and cigarette smoking. In five of 13 studies of postchallenge glucose in adults with no diagnosis of diabetes, a positive association was found that remained significant after adjusting for the other risk factors; no studies of fasting or casual glucose showed an independent association with CHD, nor did any of the four studies that included women. In 1999, Coutinho *et al.* (15) examined the association between glucose and incident CVD in a meta-analysis of 20 published studies of adults without a diagnosis of diabetes, which included 95,783 individuals followed for about 12 years. Only two of these 20 studies included women. The authors found a progressive association with a risk that extended below the diabetic diagnostic threshold, but no adjustment for other risk factors was made.

The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study group analyzed individual data from 22 European cohort studies, which included 29,714 adults (without a diagnosis of diabetes) who were followed for an average of 11 years, in order to determine whether the glucose association with CVD was linear or showed a threshold effect and whether it was independent of classic CHD risk factors (22). Although DECODE is known as a European study, Minnesota railroad workers were by far the largest single DECODE cohort (n=2,315), and two Japanese cohorts (n=504 and 496) were included as well. Most DECODE studies had data that allowed adjustment for cholesterol, blood pressure, and cigarette smoking. In the pooled analysis for fatal CVD, a J-shaped association was found with a threshold effect for FPG (97.2 mg/dL [5.39 mmol/L]) and a linear association with 2-hour postchallenge glucose. Risks were increased at blood glucose levels less than those thought to be diagnostic of diabetes. In DECODE, the 2-hour postchallenge oral glucose tolerance test (OGTT) glucose was a stronger CVD risk factor than impaired fasting glucose (IFG).

The Multiple Risk Factor Intervention Trial (MRFIT) cohort study (23) included 347,978 men, age 35–57 years, at high risk for CHD, who were screened in 20 U.S. centers and followed for an average of 12 years. The outcome was CVD mortality. Among 5,163 men who reported taking medication for diabetes, 1,092 men died, including 603 CVD deaths. Absolute risk for CVD death was much higher for diabetic than nondiabetic men at every age stratum, racial/ethnic background, and risk factor level—overall, three times higher even after adjustment for age, race/ethnicity, income, serum cholesterol, systolic blood pressure, and number of cigarettes smoked per day ($p<0.0001$).

The European Prospective Investigations into Cancer (EPIC) Norfolk cohort study (one of several EPIC studies) was the first large prospective cohort study of A1c and CVD in diverse populations (European, North American, Austral-Asian, Japanese, and Caribbean) unselected for diabetes (24); ethnicities were self-reported, and many individuals were of mixed race ethnicity. A graded association was observed between A1c levels and the risk for CVD and death in both sexes. Results were not materially changed after the exclusion of participants with known diabetes. The one-quarter of the cohort who had A1c <5.0% (<31 mmol/mol) had the lowest risk of death and CVD.

The risk of diabetic complications is a continuum with A1c and includes values below the diabetes threshold (defined as <6.5% [<48 mmol/mol] by the American Diabetes Association [ADA]). The absence of a clear threshold explains concerns about the use of A1c for screening, because a large percentage of individuals otherwise identified as having prediabetes would be classified as normal by A1c and might therefore not receive preventive interventions (25).

The most definitive data come from The Emerging Risk Factors Collaboration at the University of Cambridge, which collected data from 102 prospective studies, reported in their 2010 publication. This meta-analysis was designed to address uncertainties about the magnitude of associations of diabetes and fasting glycemia with the risk of CHD using individual records from 698,782 people without known vascular disease who had 52,765 incident fatal or first-ever nonfatal vascular events during 8.49 million person-years at risk (18). Overall, the risk for CHD was about twofold greater in adults with diabetes at baseline compared to those without, as shown in Figure 18.1 (18). These hazard ratios did not change appreciably after further adjustment for lipid, inflammatory, or renal markers. Hazard ratios for CHD were higher in women than in men, higher at age 40–59 years than at ≥70 years, and higher for fatal than nonfatal CVD. FPG had a U- or J-shaped association with vascular risk,

with no significant associations between 3.90 mmol/L (70.3 mg/dL) and 5.59 mmol/L (100.7 mg/dL). Compared with FPG concentrations of 3.90–5.59 mmol/L, hazard ratios for CHD were: 1.07 (95% confidence interval [CI] 0.97–1.18) for <3.90 mmol/L; 1.11 (95% CI 1.04–1.18) for 5.60–6.09 mmol/L (100.9–109.7 mg/dL); and 1.17 (95% CI 1.08–1.26) for 6.10–6.99 mmol/L (109.9–126 mg/dL). In people without a history of diabetes, IFG or impaired postchallenge glucose did not significantly improve vascular disease prediction when added to information about conventional risk factors. Based on an adult population-wide 10% prevalence of type 2 diabetes, diabetes was estimated to account for 10%–11% of vascular deaths (18).

LIPIDS AND LIPOPROTEINS

A majority of patients with type 2 diabetes have unfavorable levels of lipids and lipoproteins, often present years before the diagnosis of diabetes (26). Even when total and low-density lipoprotein (LDL) cholesterol levels are similar to those in persons without diabetes, LDL particles are typically smaller and denser than LDL particles observed in nondiabetic individuals (27). Patients with type 2 diabetes also often have lower HDL cholesterol and higher triglyceride levels than persons without diabetes, and this dyslipidemia is a marker for highly atherogenic small, dense LDL, often associated with normal or only slightly elevated levels of LDL (28).

In another meta-analysis including 10,158 incident CHD cases from 262,525 participants in 29 studies, Sarwar *et al.* (29) reported on triglycerides and risk of CHD in 3,582 incident cases of fatal and nonfatal CHD and 6,175 controls, using data from 44,237 men and women included in both the EPIC-Norfolk and Reykjavik studies. Repeat lipid measurements were obtained an average of 4 years apart in 1,933 EPIC-Norfolk participants and an average of 12 years apart in 379 Reykjavik participants. The EPIC-Norfolk study did not obtain fasting samples, so it adjusted only for history of diabetes. The Reykjavik study included FPG and history of diabetes data. The long-term stability of log-triglyceride values (within-person correlation coefficients) was 0.64 (95% CI 0.60–0.68) over 4 years and 0.63 (95% CI 0.57–0.70) over 12 years, similar to stability of blood pressure and total serum cholesterol. After adjusting for baseline values of established risk factors, including a history of diabetes, the strength of the association was attenuated but still significant. In a comparison of individuals in the top third with those in the bottom third of usual log-triglyceride values, over time the adjusted odds ratio for CHD was 1.57 (95% CI 1.10–2.24) in the EPIC-Norfolk study and 1.76 (95% CI 1.39–2.21) in the Reykjavik study.

Ethnic and/or cultural differences have been observed in triglyceride levels. For example, in a 7.8-year prospective study of patients with type 2 diabetes and no history of CVD from 59 hospitals throughout Japan (940 men and 831 women, mean age 58 years), the serum triglyceride level was a leading predictor of CHD (myocardial infarction or angina) (30). This risk was higher in patients who also had high cholesterol levels. The 1.6-fold increased CHD risk for an increment of 1 mmol/L (39 mg/dL) in LDL cholesterol was almost identical to that observed in the United Kingdom Prospective Diabetes Study (UKPDS) (31).

Although many prospective studies have reported associations of cardiovascular diseases with circulating lipid markers and/or inflammatory markers, most were too short or too small to provide reliable estimates under different circumstances or to consider within-person variability. The Emerging Risk Factors Collaboration, with a central database on over 1.1 million participants from 104 prospective population-based studies, as reported in the 2007 publication, had adequate sample size to provide subsets with information on specific lipid and inflammatory markers as precursors of major cardiovascular morbidity and cause-specific CVD mortality (32). This group also collected repeat measurements of relevant characteristics in approximately 340,000 participants, allowing estimation of and correction for within-person variability. Re-analysis of individual data yielded approximately 69,000 incident fatal or nonfatal first-ever major cardiovascular outcome recorded during 11.7 million person-years at risk. Primary analyses used age-specific regression models in people without known CVD at baseline and fatal or nonfatal first-ever CHD as outcomes (32).

A meta-analysis from this group (33) assessed the role of lipids and apolipoproteins in vascular risk, using individual records of 302,430 people without baseline vascular disease from 68 long-term prospective studies, mostly in Europe and North America. During 2.79 million person-years of follow-up, 8,857 nonfatal myocardial infarctions and 3,928 CHD deaths occurred. Hazard ratios, adjusted for conventional risk factors, were calculated for 1-standard deviation (SD) higher values: 0.52 log triglyceride, 15 mg/dL (0.39 mmol/L) HDL cholesterol, 43 mg/dL (1.11 mmol/L) non-HDL cholesterol, 29 mg/dL apolipoprotein AI (apo AI), 29 mg/dL apolipoprotein B (apo B), and 33 mg/dL (0.85 mmol/L) for directly measured LDL. CHD rates per 1,000 person-years comparing the bottom versus the top tertile of baseline lipid and lipoprotein tertiles were 2.6 and 6.2 for triglycerides, 6.4 and 2.4 for HDL cholesterol, and 2.3 and 6.7 for non-HDL cholesterol. Hazard ratios were at least as strong for nonfasting and fasting blood samples. The hazard ratio for CHD was 0.35 (95% CI 0.30–0.42) with a combination of 80 mg/dL (2.07 mmol/L) lower non-HDL cholesterol and 15 mg/dL higher HDL cholesterol. For the subset with apolipoproteins or directly measured LDL, hazard ratios were 1.50 (95% CI 1.38–1.62) with the ratio of non-HDL/HDL cholesterol, 1.49 (95% CI 1.39–1.60) with the ratio of apo B/apo AI, 1.42 (95% CI 1.06–1.91) with non-HDL cholesterol, and 1.38 (95% CI 1.09–1.73) with directly measured LDL. The authors concluded that lipid assessment for vascular disease can be simplified by measurement of either total and HDL cholesterol levels or apolipoproteins without need for fasting samples or without considering triglyceride levels.

Expert opinion remains divided about whether assessment of apo AI and apo B should replace HDL and total cholesterol levels in assessment of vascular risk (34,35,36). Uncertainty also persists about the merits of modification or even measuring triglycerides or HDL cholesterol (29,37), and it is not clear to what extent these associations with apo AI and apo B depend on cholesterol or triglyceride levels or vary by fasting state (38).

HYPERTENSION

Hypertension is common in patients with diabetes and often precedes it (26,39). In the UKPDS (40), 38% of newly diagnosed diabetic patients had systolic/diastolic blood pressures ≥160/90 mmHg or were being treated for hypertension. Because overweight and obesity are associated with both diabetes and hypertension, it is difficult to determine which plays a leading role, but it is clear that hypertension further increases the risk of CVD in the diabetic patient (41).

In an epidemiologic analysis of UKPDS data (42), the risk of each macrovascular complication of type 2 diabetes was strongly associated with systolic blood pressure, with no evidence of a threshold effect. Myocardial infarction occurred about twice as frequently as microvascular endpoints at each level of blood pressure. The decrease in risk of macrovascular or microvascular disease for each 10 mmHg lower level mean systolic blood pressure was about 11% for myocardial infarction and 13% for microvascular complications.

In the community-based Multi-Ethnic Study of Atherosclerosis (MESA), 3,513 volunteers were at baseline free of hypertension, defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medications. Over a median 4.7-year follow-up, 27% developed incident hypertension. Compared with participants who had normal baseline FPG levels, those with diabetes (but not IFG) had a significantly increased relative risk (RR) of developing hypertension (RR 1.41, 95% CI 1.17–1.71, p=0.001) (43).

Aggressive targets for lower blood pressure treatment in type 2 diabetes guidelines have been questioned in two studies. Zhao *et al.* (44) reported a prospective cohort study of diabetic patients, including 17,536 African Americans and 12,618 whites from seven public hospitals and affiliated clinics in Louisiana. In 2000–2009, they identified 7,260 incident CHD cases, with data suggesting a U-shaped association or even inverse association between blood pressure and CHD risk such that blood pressure <120/70 mmHg was associated with an increased risk of CHD in both African American and white patients with diabetes. Sundstrom *et al.* (45) investigated 34,009 consecutive patients with type 2 diabetes and no known CVD (age ≥35 years; mean age 64 years at baseline) at 84 primary care centers in central Sweden, who were seen between 1999 and 2008. Over an additional 1-year follow-up in 2009, among persons whose systolic blood pressure was reduced to levels <130 mmHg, the risk of myocardial infarction or overall CVD morbidity or mortality did not decrease.

THE METABOLIC SYNDROME

The classic metabolic syndrome includes five CVD risk factors that are more common in individuals with diabetes than in those without. Five key factors were described in 1992 by Bierman (46), who recognized that almost all potentially modifiable CVD risk factors (except cigarette smoking and total cholesterol) were associated with diabetes. The initial choice of the components—hypertension, high triglycerides, low HDL cholesterol levels, waist girth or waist-to-hip ratio, and in some definitions, high insulin levels or diabetes—was logical, but the cut points defining normality were arbitrary.

There are important differences in recommended diagnostic criteria for the metabolic syndrome (Table 18.5). The National Cholesterol Education Program (Adult Treatment Panel III) (NCEP) defined the metabolic syndrome as the presence of three or more of five components (47). In 2005, the International Diabetes Federation (IDF) considered that central obesity was a requirement for the diagnosis of the metabolic syndrome along with any two other features (48). In contrast, the WHO criteria stated that glucose intolerance or type 2 diabetes together with two other features is a *sine qua non* for a metabolic syndrome diagnosis (49). The NCEP, IDF, and WHO definitions have all been shown to predict incident type 2 diabetes and CVD. However, limited data are available to assess which of these definitions best predicts diabetes or heart disease (50,51). Although laboratory features, such as increased C-reactive protein, raised alanine aminotransferase, hyperuricemia, and microalbuminuria, are common in the presence of the metabolic syndrome, they are not included in metabolic syndrome diagnostic criteria.

Controversy over the scientific basis for the definition of this cluster of risk factors stems from the arbitrariness of the included (and excluded) variables and their cut points, the loss of risk prediction when continuous risk factors are categorized, and the unproven assumption that there is a single underlying biology (52,53). Nevertheless, the metabolic syndrome is a commonly used phenotype for clinicians, drawing attention to the importance of previously neglected risk factors, such as central obesity and elevated triglycerides, and to the potential importance of interventions when modest elevations in risk factors occur together (54).

Cohort studies from Italy (55), Finland and Sweden (56), and the United States (57) have shown that adults with a combination of at least three metabolic syndrome risk factors have more than a threefold increased risk of CVD.

In the Kuopio Ischemic Heart Study, the increased CVD risk associated with the metabolic syndrome occurred in the absence of diabetes (58). In contrast, the NHANES II Mortality Study, a cohort study of a representative sample of adults in the United States, did not find that the metabolic syndrome significantly increased the risk of heart disease when participants with diabetes were excluded (59). In the

TABLE 18.5. Metabolic Syndrome Definitions

CRITERIA	NATIONAL CHOLESTEROL EDUCATION PROGRAM ADULT TREATMENT PANEL III	WORLD HEALTH ORGANIZATION	EUROPEAN GROUP FOR THE STUDY OF INSULIN RESISTANCE	AMERICAN COLLEGE OF ENDOCRINOLOGY
Required		Insulin in top 25%; glucose ≥6.1 mmol/L [≥110 mg/dL]; 2-hour glucose ≥7.8 mmol/L [≥140 mg/dL]	Insulin in top 25%	High risk*; BMI >25 kg/m² or waist ≥102 cm (men) or ≥88 cm (women)
Number of abnormalities:	≥3 of:	And ≥2 of:	And ≥2 of:	And ≥2 of:
Glucose	≥6.1 mmol/L [≥110 mg/dL]		≥6.1 mmol/L [≥110 mg/dL]	≥6.1 mmol/L [≥110 mg/dL]; 2-hour glucose ≥7.8 mmol/L [≥140 mg/dL]
HDL cholesterol	<1.0 mmol/L [<40 mg/dL] (men); <1.3 mmol/L [<50 mg/dL] (women)	<0.9 mmol/L [<35 mg/dL] (men); <1.0 mmol/L [<40 mg/dL] (women)	<1.0 mmol/L [<40 mg/dL]	<1.0 mmol/L [<40 mg/dL] (men); <1.3 mmol/L [<50 mg/dL] (women)
		or	or	
Triglycerides	≥1.7 mmol/L [≥150 mg/dL]	≥1.7 mmol/L [≥150 mg/dL]	≥2.0 mmol/L [≥180 mg/dL]	≥1.7 mmol/L [≥150 mg/dL]
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)	Waist:hip ratio >0.9 (men) or >0.85 (women); BMI ≥30 kg/m²	Waist ≥94 cm (men) or ≥80 cm (women)	
Hypertension	≥130/85 mmHg	≥140/90 mmHg	≥140/90 mmHg	≥130/85 mmHg

* For the American College of Endocrinology definition, high risk of being insulin resistant is indicated by the presence of at least one of the following: diagnosis of CVD, hypertension, polycystic ovary syndrome, nonalcoholic fatty liver disease, or acanthosis nigricans; family history of type 2 diabetes, hypertension, or CVD; history of gestational diabetes or glucose intolerance; nonwhite ethnicity; sedentary lifestyle; BMI ≥25 kg/m² or waist circumference ≥94 cm for men and ≥80 cm for women; and age >40 years. Conversions for cholesterol, glucose, and triglyceride values are provided in *Diabetes in America Appendix 1 Conversions*. BMI, body mass index; CVD, cardiovascular disease.

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NHANES, the metabolic syndrome was inferior to established risk factor models like the Framingham CVD risk score for either type 2 diabetes or CVD (60).

OBESITY

Obesity was the first recognized and remains the strongest single risk factor for type 2 diabetes; the obesity epidemic that began in the United States in the early 1980s was closely associated with the epidemic of diabetes (61). A subsequent epidemic of CVD was predicted, but thus far, the amount of CVD in the United States continues to decline in both sexes and in most race/ethnicity groups. This paradox of decreasing CVD despite increasing obesity has been attributed to improved lifestyle, use of better lipid-lowering and blood pressure medications, smoking cessation, and more revascularization surgery, as reviewed by Barrett-Connor (61).

Opinions differ about the best assessment of adiposity measures for the prediction of diabetes or CVD, whether methods should differ by age, sex, and race/ethnicity, and about their value for CVD risk prediction independent of other obesity-associated risk factors. National and international guidelines have differing recommendations about the value of clinical measures of adiposity for prediction of CVD risk in primary prevention (62). Recommendations range from omission of all adiposity measures to inclusion of new screening tests. WHO has recommended assessment of both BMI and waist circumference, at least in adults with a BMI 25.0–34.9 kg/m² (63). The ADA states that established BMI cut points indicating elevated diabetes risk are inappropriate for Asian Americans and that identifying a specific BMI cut point to identify Asian Americans with or at risk for future diabetes will be beneficial to the potential health of millions of Asian Americans (64).

Varying guideline recommendations reflect differing results from previous studies. For example, in a large, multinational, retrospective case-control study, waist-to-hip ratio was three times more strongly related to risk of acute myocardial infarction than BMI (65). These recommendations were rarely tested by prospective studies with comparisons of BMI, waist circumference, and waist-to-hip ratio in the same cohort (66,67,68,69,70,71,72). Prospective studies of adiposity often lacked concomitant measurement of lipids and other conventional risk factors, which precluded assessment of adiposity measures in the context of standard risk prediction scores (70,73). Furthermore, studies often reported relative risks (measures of association without measures of risk discrimination and reclassification) and were unable to make an optimum assessment of predictive ability (versus etiologic importance) (74,75). Finally, studies of CVD outcomes with data on long-term *change* in BMI, waist circumference, and waist-to-hip ratio (e.g., from midlife to old age) have been limited. In the Rancho Bernardo study, subclinical CHD based on coronary artery calcium plaque in persons without known CVD was increased 25 years after baseline measurements of modifiable CVD risk factors, including FPG, blood pressure, cholesterol, triglycerides, and BMI; Rancho Bernardo is one of the few studies that has prospectively examined risk of subclinical CVD with documentation of BMI over time (61). In adjusted analyses, only FPG and blood pressure were not associated with subclinical CHD (76).

The Emerging Risk Factors Collaboration studied the separate and combined associations of BMI, waist circumference, and waist-to-hip ratio with risk of first CVD

event (77), using individual records from 58 cohorts to calculate hazard ratios per 1-SD higher baseline values (4.56 kg/m² higher BMI, 12.6 cm higher waist circumference, and 0.083 higher waist-to-hip ratio); it also reported measures of risk discrimination and reclassification, as well as serial adiposity assessments to calculate regression dilution ratios. Individual records were available for 221,934 people from 17 countries with 14,297 incident CVD outcomes during 1.87 million person-years at risk. Serial adiposity assessments were made in up to 63,821 people (mean interval 5.7 years [SD 3.9]). In people with a BMI ≥20 kg/m², hazard ratios for CVD were 1.23 (95% CI 1.17–1.29) with BMI, 1.27 (95% CI 1.20–1.33) with waist circumference, and 1.25 (95% CI 1.19–1.31) with waist-to-hip ratio, after adjustment for age, sex, and smoking status. After further adjustment for baseline systolic blood pressure, diabetes history, and total and HDL cholesterol, corresponding hazard ratios were still significant at 1.07 (95% CI 1.03–1.11) with BMI, 1.10 (95% CI 1.05–1.14) with waist circumference, and 1.12 (95% CI 1.08–1.15) with waist-to-hip ratio. In contrast, addition of information on BMI, waist circumference, or waist-to-hip ratio to a CVD risk prediction model that included conventional risk factors did not improve risk discrimination. Findings were similar when adiposity measures were considered in combination.

Reproducibility of adiposity measures using serial measurements (taken over several years in up to 63,821 people) was greater for BMI than for waist circumference or waist-to-hip ratio. Overall, BMI, waist circumference, and waist-to-hip ratio, assessed singly or in combination, did not importantly improve CVD risk prediction in largely Caucasian populations in developed countries, when additional information was available for blood pressure, diabetes history, smoking, and lipids. These results may be interpreted to mean that adiposity is not an independent CVD risk factor or that obesity is in the causal pathway to these covariables. This latter interpretation will require clinical trials to resolve. In additional analyses, relative risks were not appreciably altered after additional adjustment for C-reactive protein, fibrinogen, alcohol consumption, or socioeconomic status.

To summarize, in this collaborative analysis from the Emerging Risk Factors Collaboration, hazard ratios per 1-SD higher baseline values (4.56 kg/m² higher BMI) were calculated. In people with a BMI ≥20 kg/m², hazard ratios for CVD were 1.23 (95% CI 1.17–1.29) with BMI, 1.27 (95% CI 1.20–1.33) with waist circumference, and 1.25 (95% CI 1.19–1.31) with waist-to-hip ratio, after adjustment for age, sex, and smoking status. Findings were similar when adiposity measures were considered in combination. Reproducibility was greater for BMI than for waist circumference or waist-to-hip ratio. Thus, BMI, waist circumference, and waist-to-hip ratio, whether assessed singly or in combination, do not independently improve CVD risk prediction in people in developed countries when additional information is available for systolic blood pressure, history of diabetes, and lipids.

These results are contrary to the large, retrospective Global Case-Control Study of Risk Factors for Acute Myocardial Infarction (INTER-HEART) (65), which reported waist-to-hip ratio was three times more strongly related to myocardial infarction than BMI.

INSULIN

Insulin resistance, usually measured as the fasting insulin level, or insulin resistance using the homeostasis model assessment of insulin resistance (HOMA-IR) in epidemiologic studies, is thought to precede the development of diabetes by one or two decades. Early epidemiologic studies suggesting that endogenous hyperinsulinemia was a precursor of CVD have been reviewed (78,79,80). A 1990 review of epidemiologic data by Stout (81) concluded that insulin and insulin resistance were strongly implicated in the genesis of atherosclerotic disease. The atherogenic potential of insulin was summarized separately by Ferrara *et al.* (82) and McKeigue and Davey (83), who did not find an insulin-CVD association in women or in non-Caucasian ethnic groups. A meta-analysis of 12 studies published through 1996 showed a small but significant positive association of hyperinsulinemia with CVD, such that an increase of 50 pmol/L (8.3 microIU/mL) of fasting insulin yielded a summary relative risk of 1.18 (84). There was highly significant heterogeneity among studies, however, suggesting race/ethnicity or different insulin assay methods as possible explanations for the differences. Another study in Finnish patients with type 2 diabetes found that hyperinsulinemia predicted CHD death in men, but not women, but the association in men was not independent of HDL and triglyceride levels (85). In Italian patients with type 2 diabetes, comparing the lowest and highest quartiles of HOMA-IR positively predicted an increased risk of CVD (86). In contrast, neither hyperinsulinemia nor insulin sensitivity based on HOMA-IR was independently associated with CVD in the UKPDS (87,88). The Insulin Resistance Atherosclerosis Study (IRAS), a cross-sectional, four-center study in the United States, however, found that low insulin sensitivity assessed by a frequently sampled intravenous glucose tolerance test and minimal model analysis was an independent risk factor for CHD, but fasting and 2-hour insulin levels were not (89).

One explanation for these contradictory results could be differences in insulin assays. Most insulin radioimmunoassays fail to discriminate between intact insulin and proinsulin-like molecules. Increased proinsulin is a marker for beta cell failure and appears to be an important risk factor for CVD. Although a 6.5-year follow-up study of South Asian subjects showed that the association between proinsulin and CHD was no longer significant after controlling for body weight (90), a 27-year follow-up of Swedish men found that proinsulin, but not specific insulin or immunoreactive insulin, predicted fatal and nonfatal CHD independent of other risk factors (91). A cross-sectional study of older North American men and women without diabetes also found proinsulin was more strongly and consistently associated with CHD than intact insulin (92).

In a meta-analysis of 19 population-based studies of circulating levels of three insulin markers (fasting insulin, nonfasting insulin, and proinsulin) and CHD risk, 14 studies reported on fasting insulin levels involving 2,649 CHD cases, eight reported nonfasting insulin levels involving 1,980 CHD cases, and three reported proinsulin levels involving 413 CHD cases. In comparisons of individuals in the top third insulin levels with those in the bottom third, the odds ratio for CHD was 1.12 (95% CI 0.98–1.28) for raised fasting insulin, 1.35 (95% CI 1.14–1.60) for raised non-fasting insulin, and 2.23 (95% CI 1.65–3.00) for raised proinsulin (93); this is the strongest evidence for the superiority of proinsulin as a CHD risk factor.

BIOMARKERS

Since 2004, there has been an incremental increase in "novel risk factors"—each claiming to improve the prediction of CVD and the identification of patients who need intervention. Many of these markers are higher in overweight patients and in persons with diabetes. The evidence that they add predictive power to conventional risk factors is weak. In the Atherosclerosis Risk in Communities (ARIC) cohort, 10 of the "most exciting new" CVD risk markers added nothing of significance to the prediction of CVD beyond that explained by the classic risk factors (94). Similar results were reported from the Framingham Heart Study (95).

C-Reactive Protein

In an individual participant meta-analysis from the Emerging Risk Factors Collaboration (96), individual records of 160,309 people without a history of vascular disease from 54 long-term prospective studies were followed for 1.31 million person-years at risk, with 27,769 fatal or nonfatal CVD outcomes. In within-study regression analyses adjusted for within-person variation in risk factor levels, $\log_e$ C-reactive protein concentration was linearly associated with several conventional risk factors and inflammatory markers and nearly log-linearly associated with ischemic vascular disease and nonvascular mortality. Risk ratios for CHD per 1-SD higher C-reactive protein concentration were 1.63 (95% CI 1.51–1.76) when adjusted for age and sex only and 1.37 (95% CI 1.27–1.48) when also adjusted for conventional risk factors, and these risk ratios were still significant after further adjustment for fibrinogen. The C-reactive protein concentration also showed a continuous association with a diversity of other chronic diseases, including cancer and lung disease. The relevance of C-reactive protein to such a range of disorders is unclear.

Fibrinogen

One of the earliest recognized biomarkers for CVD risk was fibrinogen, originally thought to be of interest mainly as a coagulation factor but now recognized as an important anti-inflammatory factor associated with CVD (see the preceding *Obesity* section).

IMPORTANT COVARIATES

Important major covariates of CVD risk include physical activity and smoking, as well as diet and weight loss, which are also discussed in the *Clinical Trials* section.

Physical Activity

The Health Professionals' Follow-up Study (HPFS) (97) followed 2,803 men without physical impairment who reported a diagnosis of diabetes at age ≥30 years; men reported their physical activity every 2 years during 14 years of follow-up. Relative risks of CVD and death were estimated using Cox proportional hazards with adjustment for potential confounders. The multivariate relative risks of CVD incidence corresponding to quintiles of increasing total physical activity were 1.0, 0.87, 0.64, 0.72, and 0.67 (p=0.07). The corresponding multivariate relative risks for total mortality were 1.0, 0.80, 0.57, 0.58, and 0.58 (p=0.005). Walking was associated with reduced risk of total mortality, and walking pace was inversely associated with CVD, fatal CVD, and total mortality independent of walking hours.

The EPIC-Norfolk cohort study designed and tested a new four-part physical activity questionnaire, asking about (1) work-related physical activity; (2) leisure physical activity, including housework; (3) amount of energy expended during exercise based on sweating, rapid heart rate, and hours per week; and (4) stair climbing. Analyses based on these questions were derived from the responses of 4,423 men and 5,711 women, age 45–79 years (without CHD at baseline) from 10 European countries, who had complete data on physical activity and CHD outcomes and were followed for an average of 10.9 years for fatal CHD (98). A total of 548 men and 310 women had a validated CHD event. In both sexes, event rates were higher in those with the metabolic syndrome compared to those without: 17.4% versus 9.4% in men and 10.2% versus 3.4% in women. Significant downward trends in CHD event rates with increasing physical activity were strongest in men and women with the metabolic syndrome (37.6% of men and 30.2% of women). There was statistical evidence for significant effect modification (p for interaction=0.1 for men, p=0.06 for women, p=0.006 for both sexes combined), indicating that physical activity affected the association between CHD risk and the metabolic syndrome. Thus, interventions to increase physical activity targeting specific metabolic syndrome components are likely to decrease CHD risk in individuals with the metabolic syndrome.

Smoking

Overwhelming epidemiologic evidence has been found that smoking cessation decreases the risk of CVD or CHD. Yudkin (99) reported the benefits of smoking cessation for persons with and without diabetes; using data from MRFIT (100), he estimated that smoking cessation would prolong the life of a 45-year-old man with diabetes by a mean of 3 years compared with 4 years for a 45-year-old man without diabetes (99). Using data from the Framingham Offspring Study, Clair *et al.* (101) reported that recently quitting smoking was associated with an average weight gain of 2.7 kg in participants without diabetes and 3.6 kg in those with diabetes, but quitting still reduced CVD events by half. Results were stronger in the much larger group without a history of diabetes; among participants with diabetes, there were qualitatively similar

lower risks that did not reach statistical significance, possibly because of limited study power.

SUBCLINICAL ATHEROSCLEROSIS

The MESA evaluated 6,603 volunteers age 45–84 years to determine whether screening for coronary artery calcium (CAC) and carotid intimal-medial thickness (CIMT) could improve CVD risk stratification over traditional risk factors in people with the metabolic syndrome or diabetes (102). Overall, 1,686 individuals (25%) had the metabolic syndrome but no diabetes, and 881 (13%) had diabetes. Projected annual CHD event rates were 1.0% in participants with the metabolic syndrome and 1.5% in those with diabetes. Those with the metabolic syndrome or CAC scores ≥100 had annual CHD rates of ≥2%; those with the metabolic syndrome or CAC scores ≥400 had the highest annual CHD rates of 3.5% and 4%, respectively, versus 0% in subjects with neither the metabolic syndrome nor diabetes. Ethnicity and risk factor-adjusted hazard ratios ranged from 2.6 to 9.5 in those with neither the metabolic syndrome nor diabetes; in those with the metabolic syndrome, hazard ratios ranged from 3.9 to 11.9; and in those with diabetes, from 2.9 to 6.2 (all $p<0.05$ to $p<0.001$). In each group, findings were similar for CVD. CAC significantly contributed to prediction ($p<0.001$) more than traditional risk factors, whereas CIMT added negligibly to prediction over traditional risk factors. Importantly, more than one-third of those with type 2 diabetes had no CAC, and for these individuals, CHD risk was lower than that for many persons without diabetes and one-tenth that of those with diabetes who had CAC scores of ≥400. The authors concluded that adults with the metabolic syndrome or diabetes have low risks for CHD when CAC or CIMT is not increased; prediction of CHD and CVD events is improved more by CAC than by CIMT.

CLINICAL TRIALS: CONTROL OF GLYCEMIA OR OTHER CVD RISK FACTORS AND CVD RISK

Summaries of major trials involving glycemic, lipid, blood pressure, antiplatelet, and lifestyle management are shown in Tables 18.6–18.10. The following text highlights the results and interpretation of these trials. This section also provides systematic reviews of published clinical trials where available.

Extensive epidemiologic evidence documents the direct relation of diabetes with CHD and CVD (Tables 18.1–18.4, Appendices 18.1–18.4). In a meta-analysis comprising 9,123 persons with diabetes from 13 observational studies, Selvin *et al.* (103) showed a pooled relative risk of CVD in those with type 1 diabetes of 1.15 (95% CI 0.92–1.43) and type 2 diabetes of 1.18 (95% CI 1.10–1.26) for each 1% increase in A1c. Using NHANES III data from 19,025 adults, Saydah *et al.* (104) reported A1c ≥8% (≥64 mmol/mol) versus <6% (<42 mmol/mol) was associated with a hazard ratio of 3.38 (95% CI 1.98–5.77) for CVD mortality.

These observational epidemiologic studies suggested a direct relation of extent of glycemic control with risk of CHD and CVD events and promoted interest in examining whether intensive glycemic control in a randomized clinical trial setting is associated with reductions in future CHD or CVD events. The potential roles of intensive blood pressure control, lipid modification, antiplatelet therapy, multiple risk factor control, and lifestyle management in reducing CVD event risk have been the subject of a number of clinical trials in the prediction or prevention of diabetes.

TRIALS OF INTENSIVE GLYCEMIC CONTROL

Diabetes Control and Complications Trial/Epidemiology of Diabetes and Interventions and Complications Study

The Diabetes Control and Complications Trial (DCCT) (105) examined whether intensive versus conventional control of glucose with insulin therapy (accomplishing mean A1c levels of approximately 7% [53 mmol/mol] vs. 9% [75 mmol/mol], respectively) would reduce development or progression of microvascular complications in 1,441 patients with type 1 diabetes (Table 18.6). Substantial reductions were observed in the development or progression of retinopathy, microalbuminuria, albuminuria, and clinical neuropathy within the intensive glycemic control group. While 41% fewer CVD events occurred in the intensively treated individuals, these results did not achieve statistical significance, possibly due to the small number of events in this relatively young population. DCCT participants continued to be followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study; after 11 years, when the differences in A1c between the groups had disappeared, the rate of CVD complications continued to diverge, indicating a possible "metabolic memory" from earlier glycemic control. The extended follow-up showed 46 CVD events among 31 patients in the intensive control group compared to 98 events in 52 patients in the conventional control group, with a statistically significant 42% reduction in events (p=0.02) (106).

United Kingdom Prospective Diabetes Study

The UKPDS tested the hypothesis that intensive glycemic control could reduce CVD disease in persons with type 2 diabetes. A group of 3,867 patients with newly diagnosed type 2 diabetes was randomized to treatment with sulfonylureas or insulin compared to diet alone (107). Mean A1c levels of 7.0% and 7.9% (63 mmol/mol) in the intensive versus standard glycemic control groups, respectively, were obtained, and microvascular events were reduced by 21%–34%. The combined incidence of nonfatal myocardial infarction and sudden death did not reach statistical significance (16% risk reduction, p=0.052), although the randomized substudy of overweight patients did show metformin therapy significantly reduced CVD events (108). The results of the 10-year post-trial follow-up showed loss of the A1c differences between groups, that microvascular event reduction of 24% (p=0.001) between the groups persisted, and a statistically significant reduction in myocardial infarction (15%, p=0.01) and all-cause

TABLE 18.6. Clinical Trials of Intensive Glucose Control on Cardiovascular Disease Risk

STUDY, YEARS (REF.)	INTERVENTION	CONTROL	SAMPLE SIZE	FOLLOW-UP (YEARS)	CARDIOVASCULAR ENDPOINT	RELATIVE RISK REDUCTION	P VALUE
DCCT/EDIC, 1983–2005 (105,106)	Intensive insulin	Conventional insulin therapy	1,441	17 total (6.5 on therapy)	Total CVD	42%	0.02
UKPDS, 1977–2007 (107,108,109)	Intensive sulfonylurea, insulin, metformin	Conventional with diet	3,867	10 / extended follow-up addition 10 years	MI	16% / 15%	0.052 / 0.01
ACCORD, 2001–2007 (110)	Intensive therapy targeting A1c <6.0%	Standard therapy for A1c 7.0%–7.9%	10,251	3.5	Nonfatal MI, nonfatal stroke, or CVD death	10%	0.16
ADVANCE, 2001–2008 (111)	Gliclazide plus other oral drugs to achieve A1c <6.5%	Standard drugs	11,140	5	Nonfatal MI, nonfatal stroke, or CVD death	6%	0.32
VADT, 2000–2008 (112)	Intensive control	Standard drugs	1,791	5.6	Total CVD events	12%	0.14
ORIGIN, 2003–2011 (114)	Insulin glargine	Standard drugs	12,537	6.2	Nonfatal MI, nonfatal stroke, or CVD death	2% increase	0.63
EMPA-REG, 2010–2015 (127)	Empagliflozin	Standard drugs	7,020	3.1	CVD death, nonfatal MI, nonfatal stroke	14%	0.04
ELIXA, 2010–2015 (131)	Lixisenatide	Standard drugs	6,068	1.1	CVD death, MI, stroke, angina	-2%	0.81
LEADER, 2010–2016 (132)	Liraglutide	Standard drugs	9,340	3.8	CVD death, nonfatal MI, nonfatal stroke	13%	0.01
SUSTAIN-6, 2013–2016 (133)	Semaglutide	Standard drugs	3,297	2.0	CVD death, nonfatal MI, nonfatal stroke	26%	0.02

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin A1c; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CVD, cardiovascular disease; DCCT/EDIC, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI, myocardial infarction; ORIGIN, Outcome Reduction With Initial Glargine Intervention trial; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

SOURCE: References are listed within the table.

mortality (21%, p=0.01) emerged. Even greater reductions in myocardial infarction and all-cause mortality were seen in the overweight, metformin-treated subjects (33% and 27%, respectively) (109). These results add to those of the DCCT/EDIC in type 1 diabetes patients in supporting a long-term glycemic legacy effect from the on-trial intensive glycemic control strategy, at least in those with primarily uncomplicated, shorter duration diabetes as was the case for the DCCT and UKPDS.

Action to Control Cardiovascular Risk in Diabetes; Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; Veterans Affairs Diabetes Trial; and Outcome Reduction With Initial Glargine Intervention Trials

In light of the continued uncertainty of the effects of intensive glycemic control on macrovascular outcomes in patients with type 2 diabetes, these four trials more formally tested this hypothesis, employing an even more intensive glucose target of A1c <6.0% compared to 7.0%–7.9% in the conventional control groups over 3.5 years. Patients enrolled in these studies had more advanced diabetes of longer duration than the earlier studies, many with prior macrovascular disease.

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (110), 10,251 patients were enrolled with a mean baseline A1c of 8.3% (67 mmol/mol) and mean age of 62 years. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) (111) had slightly older patients (mean age 66 years) but with a lower mean A1c (7.5% [58 mmol/mol]), and the Veterans Affairs Diabetes Trial (VADT) cohort (112) had the youngest average age (60 years) but the highest baseline A1c (9.4% [79 mmol/mol]). All three trials failed to show benefit in cardiovascular outcomes, and while ACCORD showed a reduction in nonfatal myocardial infarction of 24% (p=0.004), both cardiovascular and all-cause mortality (HR 1.22, p=0.04) were actually increased. In the VADT, severe hypoglycemia was the strongest predictor of CVD mortality. In contrast, a subsequent analysis of ACCORD showed CVD deaths occurred in those who did not respond to the intensive therapy (113). A *post hoc* subgroup analysis of ACCORD and ADVANCE showed those without preexisting macrovascular disease did benefit, experiencing fewer CVD events. These observations are consistent with the hypothesis of lack of benefit of intensive glycemic control among those with prolonged, more advanced diabetes who have known macrovascular disease and support the concept that intensive glycemic control may benefit

less complicated, more newly diagnosed persons with diabetes who have not had longstanding poor glycemic control and more advanced diabetes. Further, in those with more advanced diabetes, it may be difficult to realize benefit from intensive glycemic control initiated many years after initial diagnosis of diabetes.

Finally, the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial tested the effects of normalizing FPG in 12,537 individuals with CVD risk factors plus either IFG, impaired glucose tolerance, or type 2 diabetes. Subjects who were randomized to either insulin or standard care (and to n-3 fatty acids or placebo) showed no difference in cardiovascular events between the two groups (114).

Changes to Glycemic Goal. The findings from these trials led in part to a 2013 revision in the ADA guidelines for glycemic control, where A1c <8% is considered acceptable for those with more complicated type 2 diabetes, such as when accompanied by macrovascular disease, with a goal of <7% still reasonable for those with shorter duration diabetes and with uncomplicated diabetes (115). Because it is possible that the early follow-up of 5 years was too short to show reduced mortality, in 2010, the ADA recommended tighter glucose control in patients with recently diagnosed diabetes, long life expectancy, and no significant CVD (116). A working group report on hypoglycemia and diabetes commissioned by the ADA and the Endocrine Society concurred that a A1c goal of <7% is appropriate for newly diagnosed or less complicated diabetes, with less stringent goals for those with more complicated diabetes (117). The report noted that while hypoglycemia was associated with an increased risk of death in ACCORD, ADVANCE, and VADT, its effects on other diabetic complications make it difficult to establish risk and benefits with respect to these complications. The importance of patient education, dietary and exercise modifications, careful glucose monitoring, medication adjustment, and careful surveillance by the clinician in preventing hypoglycemic episodes was emphasized.

In 2011, Boussageon *et al.* (118) published a meta-analysis of 13 randomized clinical trials to determine whether all-cause mortality and deaths from cardiovascular events were associated with intensive glucose-lowering treatment in people with type 2 diabetes. The quality of the clinical trials was assessed by the Jadad score. Of 34,533 patients, 18,315 received intensive glucose-lowering treatment, and 16,218 received standard treatment. Intensive treatment did not significantly alter all-cause mortality (risk ratio 1.04, 99% CI 0.91–1.19) or cardiovascular death (risk ratio 1.11, 95% CI 0.86–1.43). Intensive therapy was associated with reductions in the risk of nonfatal myocardial infarction (risk ratio 0.85, 95% CI 0.74–0.96, p<0.001) and microalbuminuria (risk ratio 0.90, 95% CI 0.85–0.96, p<0.001) but caused a more than twofold increase in the risk of severe hypoglycemia (risk ratio 2.33, 95% CI 1.62–3.36, p<0.001). The authors calculated that 117–150 patients would need to be treated over a period of 5 years to prevent one myocardial infarction, whereas one severe episode of hypoglycemia would occur in every 15–52 patients. In an analysis restricted to high-quality studies (Jadad score >3), intensive treatment was not associated with any significant risk reductions but resulted in a 47% increase in risk of congestive heart failure (p<0.001) (118).

Another systematic review considered the quality and agreement of 11 current English language guidelines for oral diabetes medications applied in the United States, United Kingdom, and Canada (119). Ten guidelines agreed that thiazolidinediones are associated with higher rates of edema and congestive heart failure compared with other oral diabetes medications. Seven guidelines agreed that metformin is the favored first-line oral agent.

A different question is whether glucose control improves outcomes in hospitalized diabetes patients who had an acute myocardial infarction and who were seen in an intensive care unit and required prolonged ventilator support or coronary artery bypass surgery (120,121,122,123,124). The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE SUGAR) Study, the largest in-patient glucose control study to date, was designed to confirm whether intensive control (glucose 81–108 mg/dL [4.50–5.99 mmol/L]) improves outcomes compared with usual care (glucose <180 mg/dL [<10.00 mmol/L]). In this study, the intensive glucose criterion group treated with insulin had increased incidences of severe hypoglycemia and 90-day mortality (125). These results led to modification of the then-current consensus guidelines by the ADA and the American Association of Clinical Endocrinologists, which were revised to recommend a target glucose of 140–180 mg/dL (7.77–10.00 mmol/L) for the majority of critically ill patients and pre-meal and random blood glucose targets <140 mg/dL and <180 mg/dL, respectively, in all hospitalized patients (126).

Cardiovascular Outcomes Trials of Newer Glucose-Lowering Agents

Since 2015, results of several key cardiovascular outcomes trials of newer glucose-lowering agents have been reported. The first of these was the EMPA-REG trial (127) of patients with diabetes and prior cardiovascular disease involving the sodium glucose transporter-2 (SGLT2) inhibitor empagliflozin. The trial showed a significant 14% relative risk reduction in the composite cardiovascular endpoint, with greater reductions in death from cardiovascular causes (38%), hospitalization for heart failure (35%), and death from all causes (32%) compared to usual care and placebo. To further demonstrate whether the EMPA-REG findings were a class effect, other SGLT2 inhibitor cardiovascular trials, Canagliflozin Cardiovascular Assessment (CANVAS) trial with canagliflozin (128), Dapagliflozin Effect on Cardiovascular Events (DECLARE) trial with dapagliflozin (129), and Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS CV) trial with ertugliflozin (130), are in progress. These

TABLE 18.7. Clinical Trials of Lipid Modification on Cardiovascular Disease Risk

STUDY, YEARS (REF.)	INTERVENTION	CONTROL	SAMPLE SIZE	FOLLOW-UP (YEARS)	CARDIOVASCULAR ENDPOINT	RELATIVE RISK REDUCTION	P VALUE
HPS Diabetes Subgroup, 1994–2001 (136)	Simvastatin 40 mg	Placebo	5,963	5	Total CVD events	22%	<0.0001
CARDS, 1997–2003 (137)	Atorvastatin 10 mg	Placebo	2,838	3.9	Total CVD events	37%	0.001
FIELD, 1998–2005 (139)	Fenofibrate 200 mg	Placebo	9,795	5	Nonfatal MI or CHD death	11%	0.16
ACCORD Lipid, 2001–2009 (140)	Fenofibrate, plus simvastatin	Simvastatin	5,518	4.7	Nonfatal MI, nonfatal stroke, or CVD death	8%	0.32

ACCORD, Action to Control Cardiovascular Risk in Diabetes; CARDS, Collaborative Atorvastatin Diabetes Study; CVD, cardiovascular disease; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes study; HPS, Heart Protection Study; MI, myocardial infarction.

SOURCE: References are listed within the table.

trials will help demonstrate the extent to which any cardiovascular benefits may be due to changes in other risk factors beyond the effects on glycemic control. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial (131) of subjects with diabetes and a prior myocardial infarction or unstable angina involved the glucagon-like peptide-1 receptor antagonist (GLP-1 RA) lixisenatide, a derivative of exenatide. This trial did not show benefit (HR 1.02 for a composite endpoint of major adverse cardiovascular events [cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke]) from the relatively short 25-month median follow-up. But in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (132) involving 3.8 years median follow-up, there was a significant 13% reduction in the composite cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and stroke) and a reduction of cardiovascular mortality with the GLP-1 RA liraglutide compared to placebo. Liraglutide, unlike lixisenatide, has nearly 100% homology to human GLP-1. In the short Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) (133), use of semaglutide compared to placebo was associated with a reduction in the composite cardiovascular outcome of 26%, with an even greater 39% reduction in stroke. Other GLP-1 RA cardiovascular endpoint trials, including the Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL) with exenatide LR (134) and the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) with dulaglutide (135) are due to report in 2018 and 2019, respectively. Importantly, these trials will help clarify the mechanisms for the cardiovascular benefits seen in SUSTAIN-6 regarding whether they are a class effect.

LIPID-MODIFYING CLINICAL TRIALS

Management of dyslipidemia in persons with diabetes has focused on lowering LDL cholesterol. The strongest evidence for CVD risk reduction derives from statin clinical trials (Table 18.7). A subgroup of the Heart Protection Study (HPS) enrolled 5,963 patients with type 1 or type 2 diabetes who were assigned to simvastatin 40 mg treatment or placebo. The active medication was associated with a 22% (p<0.0001) risk reduction of a first major coronary event (136). This was followed by the Collaborative Atorvastatin Diabetes Study (CARDS), in which atorvastatin 10 mg daily versus placebo resulted in a 37% (p=0.001) reduction in major cardiovascular events (137). Moreover, in a large meta-analysis of 18,686 subjects with diabetes randomized to statin therapy versus placebo, each mmol/L reduction in LDL cholesterol resulted in a 21% reduction in CVD events, similar to the risk reduction seen in nondiabetic individuals (138).

Given the predominance of low HDL cholesterol and/or high triglycerides in persons with diabetes, researchers have examined whether therapy with fibric acid derivatives could reduce CVD events. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial (139), 9,795 patients with type 2 diabetes not taking a statin at entry were randomized to fenofibrate 200 mg daily versus placebo; after an average of 5 years follow-up, there was no significant risk reduction in the primary outcome of CHD death or non-fatal myocardial infarction, although in a subgroup analysis, fenofibrate reduced total CVD events. The authors suggested that subjects beginning statin use during the course of the study (as a result of changing guidelines recommending statins in those with diabetes) may have contributed to this null effect. The ACCORD Lipid Substudy (140) randomized a subset (n=5,518) of participants all treated with simvastatin to receive either masked fenofibrate or placebo; after nearly 5 years, no reduction in CVD outcomes was seen in the combination group among the overall study sample (HR 0.92, 95% CI 0.79–1.08, p=0.32). However, among the subset of participants with high triglycerides (≥200 mg/dL [≥2.26 mmol/L]) and low HDL cholesterol (<35 mg/dL [<0.91 mmol/L]), a significant reduction (HR 0.69, p=0.03) in CVD outcomes was observed. Nevertheless, the failure to show additional benefit from fenofibrate therapy in prevention of CVD events over statin therapy in the overall cohort of adults with diabetes has contributed to continued support for the use of statin therapy alone for management of dyslipidemia in persons with diabetes, and combination therapy is not recommended due to lack of demonstrated additional benefit beyond statins (115).

TABLE 18.8. Clinical Trials of Blood Pressure Control on Cardiovascular Disease Risk

STUDY, YEARS (REF.)	INTERVENTION	CONTROL	SAMPLE SIZE	FOLLOW-UP (YEARS)	CARDIOVASCULAR ENDPOINT	RELATIVE RISK REDUCTION	P VALUE
HOT, 1992–1997 (141)	Felodipine and other agents for randomization to ≤80 mmHg vs. ≤90 mmHg DBP	NA	18,790 (1,501 with diabetes)	3.8	Major CVD event in those treated to 90 mmHg vs. 80 mmHg	RR 2.06 (95% CI 1.24–3.44)	0.005 for trend
ACCORD BP, 2001–2009 (142)	<120 mmHg SBP	130–140 mmHg	4,733	4.7	Nonfatal MI, nonfatal stroke, or CVD death	12% (41% for stroke)	0.20 (0.01 for stroke)

ACCORD BP, Action to Control Cardiovascular Risk in Diabetes, Blood Pressure study; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; HOT, Hypertension Optimal Treatment trial; MI, myocardial infarction; NA, not applicable; RR, relative risk; SBP, systolic blood pressure.

SOURCE: References are listed within the table.

TABLE 18.9. Clinical Trials of Antiplatelet/Aspirin Use on Cardiovascular Disease Risk

STUDY, YEARS (REF.)	INTERVENTION	CONTROL	SAMPLE SIZE	FOLLOW-UP (YEARS)	CARDIOVASCULAR ENDPOINT	RELATIVE RISK REDUCTION	P VALUE
Antithrombotic Trialists Diabetes Subset (meta-analysis of trials through 1997) (144)	Antiplatelet	Placebo	4,961	Various	Major vascular events	7%	NS
HOT, 1992–1997 (141)	75 mg aspirin	Placebo	18,790 (1,501 with diabetes)	3.8	Major CVD event	15% (36% for MI)	Not given
PPP, 1994–1998 (145)	100 mg per day aspirin	Placebo	4,495 diabetes and no diabetes	3.7	MI, stroke, or CVD death	10% in diabetes / 41% in no diabetes	NS for diabetes
POPADAD, 1997–2006 (146)	Aspirin alone or with antioxidant	Placebo alone or with antioxidant	1,276	8	Total CVD	2%	NS
JPAD, 2002–2008 (147)	Aspirin 81 or 100 mg	Placebo	2,539	4.37	Total CVD	20%	0.16

CVD, cardiovascular disease; HOT, Hypertension Optimal Treatment trial; JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; MI, myocardial infarction; NS, nonsignificant; POPADAD, Prevention of Progression of Arterial Disease and Diabetes trial; PPP, Primary Prevention Project.

SOURCE: References are listed within the table.

TRIALS OF BLOOD PRESSURE CONTROL

Clinical trial results supporting a lower blood pressure goal have been surprisingly mixed (Table 18.8). In the Hypertension Optimal Treatment (HOT) trial (141), the subset of patients with diabetes who reached the lowest blood pressure target (diastolic blood pressure <80 mmHg) compared to 85–<90 mmHg had a 51% relative risk reduction for major adverse CVD events. However, in the ACCORD blood pressure component, 4,733 ACCORD participants were randomized to treatment designed to achieve a systolic blood pressure of <120 mmHg versus <140 mmHg (142); there was no significant benefit (HR 0.88, 95% CI 0.73–1.06, p=0.20) for the reduction of CVD events overall in those in the intensive blood pressure-lowering arm, although a statistically significant 41% reduction in stroke was found among those in the intensive blood pressure-lowering arm. Intensive treatment was associated with a higher incidence of serious adverse events (3.3% vs. 1.3%, p<0.001). The 2013 systolic/diastolic blood pressure goal of <140/80 mmHg for most persons with diabetes (revised from <130/80 mmHg) by the ADA (115) is supported by the lack of randomized clinical trial evidence for prevention of CVD events from achieving systolic blood pressure <140 mmHg. Moreover, the 2014 Eighth Joint National Committee (JNC-8) report stated the evidence was appropriate to recommend an initiation and target level of blood pressure of <140/90 mmHg (143).

TRIALS OF ANTIPLATELET/ASPIRIN MANAGEMENT

Compared to the role of aspirin in secondary prevention, data among adults with diabetes are limited (Table 18.9). In the Antithrombotic Trialists meta-analysis of antiplatelet therapy (144), there was a 22% benefit in CVD risk in the overall cohort that was attenuated to only a 7% (nonsignificant) benefit in a subset of almost 5,000 patients with diabetes. Among hypertensive subjects enrolled in the HOT study, including 1,501 participants with diabetes, aspirin was associated with a 36% reduction in risk for myocardial infarction and 15% reduction in risk for major CVD events (141). Three other randomized clinical trials examining the role of aspirin in primary prevention of CVD that included subjects with diabetes have been reported. The Primary Prevention Project (PPP) showed 100 mg per day aspirin versus placebo to result in only a nonsignificant 10% reduction in death, myocardial infarction, or stroke among the 1,031 patients with type 2 diabetes compared to a 41% risk reduction in those without diabetes (145). Further, the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) showed no significant reduction in risk of CVD events in the 1,276 patients with type 1 or type 2 diabetes who were randomized to 100 mg aspirin daily versus placebo (146). The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes

TABLE 18.10. Clinical Trials of Comprehensive Risk Factor Control and Lifestyle Management on Cardiovascular Risk

STUDY, YEARS (REF.)	INTERVENTION	CONTROL	SAMPLE SIZE	FOLLOW-UP (YEARS)	CARDIOVASCULAR ENDPOINT	RELATIVE RISK REDUCTION	P VALUE
Steno-2 Trial, 1993–2006 (148,149)	Intensive therapy to lower LDL cholesterol, blood pressure, and glucose	Usual care	160	7.8	Total CVD events	53%	<0.001
Diabetes Prevention Program, 1996–2001 (152)	Intensive lifestyle with 7% weight loss and 150 minutes physical activity, or metformin	Usual care	3,234	2.8	Incident diabetes (not a CVD outcomes trial)	58% from lifestyle 31% from metformin	<0.001
Look AHEAD, 2001–2012 (154,156)	Intensive lifestyle	Usual care	5,145	11	Total CVD events	5%	0.51

CVD, cardiovascular disease; LDL, low-density lipoprotein; Look AHEAD, Action for Health in Diabetes.
SOURCE: References are listed within the table.

(JPAD) study also showed only a nonsignificant 20% reduction in risk of CVD events associated with aspirin 81 or 100 mg per day versus placebo in 2,539 patients with type 2 diabetes (147).

TRIALS OF COMPREHENSIVE RISK FACTOR AND LIFESTYLE MANAGEMENT

Few trials have been published involving multiple risk factor intervention among persons with diabetes (Table 18.10). The Steno-2 trial was conducted among 160 patients with type 2 diabetes who were randomized to intensive therapy designed to lower glucose, LDL cholesterol, and blood pressure; after a 7.8-year follow-up, those in the intensive therapy arm had a significantly lower risk of CVD events (HR 0.47, 95% CI 0.24–0.73) (148). A further 5.5-year follow-up of this study cohort showed a subsequent 46% lower total mortality, 57% lower CVD death rate, and 59% lower risk of subsequent CVD events (149).

Meta-analysis of clinical trials of at least 12 weeks duration in patients with type 2 diabetes evaluated the ability of structured exercise training or physical activity advice to lower A1c levels compared with a control group; 47 randomized clinical trials (n=8,538 subjects) were included (150). Structured aerobic exercise, structured resistance training, and both combined were each associated with declines in A1c levels compared with control participants. The relative risk reductions for myocardial infarction and all-cause mortality were significantly lower in the patients who initially received the intensive treatment compared with those in the conventional treatment arm. Moreover, the initial benefit in terms of microvascular complications observed at the end of the intervention trial remained unaltered at follow-up.

In another trial, structured exercise training of >150 minutes per week was associated with greater A1c declines than that of <150 minutes per week. Physical activity advice was associated with lower A1c only when combined with dietary advice (151).

The intensive lifestyle approach employed in the Diabetes Prevention Program (DPP) (152) involved a targeted weight loss of 7% and 150 minutes per week of physical activity. The mean age of the 3,234 participants was 51 years; mean BMI was 34.0 kg/m^2; 68% were women; 45% were members of minority groups. The intervention resulted in a 58% reduction in the onset of new type 2 diabetes when the trial was stopped early based on observed benefits in preventing diabetes, with an average follow-up of 2.8 years. In an extended follow-up, the Diabetes Prevention Program Outcomes Study (DPPOS) (153) examined whether regression from prediabetes (defined as consistently having FPG 5.6–6.9 mmol/L [100–125 mg/dL] and/or 2-hour plasma glucose levels of 7.8–11.0 mmol/L [140–198 mg/dL] on annual OGTT *during the DPP period* and never having met the criteria for the diagnosis of diabetes) to normal glucose regulation has a carry-over effect in reducing long-term diabetes risk. The DPPOS showed a 56% reduced risk of developing diabetes in those who returned to normal glucose; however, no effect of lifestyle intervention for the prevention of cardiovascular outcomes was established, and there was no evidence of fewer cardiovascular events in the DPPOS despite the reduced risk of diabetes and improved CVD risk factors.

The largest trial to address the value of behavioral intervention for CVD prevention in adults with known diabetes is the Look AHEAD: Action for Health in Diabetes study of 5,145 U.S. adults with BMI ≥25 kg/m^2 and type 2 diabetes. This study (151) compared an intensive lifestyle group, consisting of weekly group and individual counseling in the first 6 months followed by three sessions for the next 6 months and refresher sessions afterwards, to diabetes support and education alone, involving three group sessions annually in the first 4 years and decreasing to one thereafter. Look AHEAD showed that those in the intensive group lost significantly more weight (6.2% vs. 0.9% of starting weight), had greater improvement in fitness, blood pressure, HDL cholesterol, and triglycerides, and were significantly more likely to experience remission in their diabetes (154). In October 2012, the National Institutes of Health announced early termination of this trial after ≤11 years due to absent differences in CVD events and lack of a reasonable likelihood of showing a CVD difference if the study were continued for the planned 13 years (155). Other analyses from Look AHEAD (156) reported that the initial differences in benefit in risk factors and physical activity between groups diminished substantially during later years of the trial, and at the end of the 9.6-year

median follow-up, the primary outcome of cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization due to angina did not differ when comparing the intervention and control groups (HR 0.95, p=0.51).

CONCLUSION

Among people with diabetes in the United States, the prevalence of CVD remains about twofold greater than in people without diabetes. This disparity represents a major health care challenge. Understanding the determinants of the excess risk for CVD in patients with diabetes remains far from complete. The relevance of dysglycemia is unclear in both nondiabetic and prediabetic subjects, which raises questions about the role of hyperglycemia *per se*. Some clinical trial data suggest that intensive management of moderate hyperglycemia may cause harm in high-risk subjects. Also, despite the worrying increase in obesity and diabetes prevalence, there is little evidence that measures of obesity are related to CVD independent of other risk factors or that weight reduction through change in lifestyle yields benefit for CVD prevention. Traditional risk factors, such as dyslipidemia, hypertension, and smoking, clearly are important, although some studies call into question the importance of mild elevations in blood pressure. Furthermore, despite the importance of low HDL cholesterol as a risk factor, benefit beyond LDL cholesterol-targeted statin therapy for lipoprotein medications is unproven. An improved understanding of the natural history of atherosclerosis in diabetes and its risk factors during the earlier phases of diabetes development may open the door to earlier and perhaps more innovative cardioprevention therapies.

LIST OF ABBREVIATIONS

A1c. . . . . glycosylated hemoglobin
ACCORD . . . . . Action to Control Cardiovascular Risk in Diabetes
ADA . . . . . American Diabetes Association
ADVANCE . . . . Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
Apo . . . . . apolipoprotein
BMI . . . . . body mass index
BRFSS . . . . . Behavioral Risk Factor Surveillance System
CAC . . . . . coronary artery calcium
CHD. . . . . coronary heart disease
CI. . . . . confidence interval
CIMT . . . . . carotid intimal-medial thickness
CVD . . . . . cardiovascular disease
DCCT. . . . . Diabetes Control and Complications Trial
DECODE . . . . . Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe
DPP . . . . . Diabetes Prevention Program
DPPOS. . . . . Diabetes Prevention Program Outcomes Study
EDIC . . . . . Epidemiology of Diabetes Interventions and Complications study
EPIC. . . . . European Prospective Investigations into Cancer
FPG . . . . . fasting plasma glucose
GLP-1. . . . . glucagon-like peptide-1
GLP-1 RA . . . . . GLP-1 receptor antagonist
HDL. . . . . high-density lipoprotein
HOMA-IR . . . . . homeostasis model assessment of insulin resistance
HOT . . . . . Hypertension Optimal Treatment trial
HR . . . . . hazard ratio
IDF. . . . . International Diabetes Foundation
IFG. . . . . impaired fasting glucose
LDL . . . . . low-density lipoprotein
Look AHEAD . . Action for Health in Diabetes
MESA. . . . . Multi-Ethnic Study of Atherosclerosis
MRFIT . . . . . The Multiple Risk Factor Intervention Trial
NCEP. . . . . National Cholesterol Education Program (Adult Treatment Panel III)
NHANES . . . . . National Health and Nutrition Examination Survey
NHIS . . . . . National Health Interview Survey
OGTT. . . . . oral glucose tolerance test
PAR . . . . . population attributable risk
RR . . . . . relative risk
SD . . . . . standard deviation
SGLT2 . . . . . sodium glucose transporter-2
SUSTAIN-6 . . . Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes
UKPDS. . . . . United Kingdom Prospective Diabetes Study
VADT . . . . . Veterans Affairs Diabetes Trial
WHO . . . . . World Health Organization

CONVERSIONS

Conversions for A1c, cholesterol, glucose, insulin, and triglyceride values are provided in *Diabetes in America Appendix 1 Conversions*.

DUALITY OF INTEREST

Drs. Barrett-Connor, Wingard, Wong, and Goldberg reported no conflicts of interest, with the following potential exceptions. Dr. Barrett-Connor served as an advisory panel member and contracted advisor for Eli Lilly. Dr. Wong received research support through the University of California, Irvine, from Bristol Myers-Squibb.

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APPENDICES

APPENDIX 18.1. Crude and Age-Standardized Prevalence of History of Heart Disease Among Adults Age ≥18 Years, by Diabetes Status, Sex, and Race/Ethnicity, U.S., 2009–2010

	PERCENT (STANDARD ERROR)					
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
CHARACTERISTICS	Coronary Heart Disease		Angina Pectoris		Heart Attack	
Total						
Crude	16.2 (0.60)	3.5 (0.11)	7.6 (0.49)	1.7 (0.07)	11.4 (0.54)	2.5 (0.09)
Age-standardized	16.2 (0.58)	6.9 (0.20)	7.6 (0.49)	3.1 (0.13)	11.4 (0.55)	4.9 (0.18)
Sex						
Men						
Crude	20.3 (0.99)	4.6 (0.17)	9.7 (0.81)	1.9 (0.12)	14.2 (0.88)	3.2 (0.14)
Age-standardized	20.5 (0.96)	9.7 (0.35)	9.7 (0.81)	3.7 (0.22)	14.4 (0.90)	6.8 (0.28)
Women						
Crude	12.0 (0.73)	2.5 (0.11)	5.5 (0.51)	1.5 (0.08)	8.5 (0.62)	1.9 (0.09)
Age-standardized	11.8 (0.72)	4.7 (0.21)	5.5 (0.50)	2.5 (0.15)	8.4 (0.61)	3.3 (0.18)
Race/ethnicity						
Non-Hispanic white						
Crude	18.5 (0.82)	4.1 (0.14)	9.1 (0.67)	2.0 (0.10)	12.7 (0.73)	3.0 (0.12)
Age-standardized	17.8 (0.79)	7.2 (0.23)	8.9 (0.68)	3.3 (0.16)	12.3 (0.74)	5.1 (0.20)
Non-Hispanic black						
Crude	13.2 (1.13)	2.6 (0.21)	5.5 (0.97)	1.1 (0.15)	10.9 (1.10)	1.8 (0.17)
Age-standardized	13.5 (1.10)	5.7 (0.47)	5.5 (0.93)	2.5 (0.32)	11.3 (1.12)	4.0 (0.37)
All Hispanic						
Crude	9.8 (1.05)	1.8 (0.19)	4.4 (0.78)	0.8 (0.10)	7.4 (1.07)	1.1 (0.12)
Age-standardized	10.8 (1.11)	5.4 (0.55)	4.9 (0.86)	2.0 (0.30)	8.0 (1.16)	3.4 (0.42)
Mexican American						
Crude	9.0 (1.38)	1.7 (0.23)	3.7 (1.03)	0.6 (0.12)	7.0 (1.45)	1.0 (0.15)
Age-standardized	10.4 (1.53)	6.0 (0.72)	4.2 (1.22)	1.6 (0.38)	7.6 (1.63)	3.8 (0.68)
Other Hispanic						
Crude	11.4 (1.54)	2.1 (0.32)	5.7 (1.10)	0.9 (0.17)	8.2 (1.49)	1.1 (0.20)
Age-standardized	11.8 (1.52)	4.8 (0.83)	5.9 (1.10)	2.3 (0.47)	8.6 (1.56)	3.0 (0.52)
Non-Hispanic Asian						
Crude	15.8 (2.93)	2.0 (0.33)	6.2 (1.64)	0.9 (0.20)	9.2 (2.42)	1.1 (0.23)
Age-standardized	15.4 (2.61)	5.0 (0.86)	6.1 (1.55)	1.8 (0.38)	8.6 (2.03)	3.4 (0.72)
	Other Heart Condition		Any Heart Condition, Including Angina		Any Heart Condition, not Including Angina	
Total						
Crude	16.8 (0.69)	6.8 (0.15)	29.7 (0.75)	10.0 (0.17)	28.7 (0.75)	9.6 (0.17)
Age-standardized	16.8 (0.68)	10.4 (0.23)	29.7 (0.74)	16.4 (0.26)	28.7 (0.74)	15.8 (0.26)
Sex						
Men						
Crude	17.4 (1.05)	6.7 (0.21)	32.4 (1.20)	10.6 (0.26)	31.5 (1.19)	10.3 (0.26)
Age-standardized	17.6 (1.06)	11.0 (0.37)	32.7 (1.17)	19.1 (0.43)	31.8 (1.16)	18.7 (0.43)
Women						
Crude	16.2 (0.89)	6.9 (0.20)	27.0 (1.00)	9.6 (0.22)	25.8 (0.99)	9.1 (0.21)
Age-standardized	16.1 (0.88)	9.9 (0.28)	26.8 (0.97)	14.5 (0.32)	25.6 (0.97)	13.7 (0.31)
Race/ethnicity						
Non-Hispanic white						
Crude	19.3 (0.93)	8.1 (0.20)	33.0 (0.98)	11.8 (0.22)	32.0 (0.97)	11.4 (0.22)
Age-standardized	18.8 (0.93)	11.3 (0.29)	32.2 (0.98)	17.6 (0.31)	31.1 (0.98)	17.0 (0.30)
Non-Hispanic black						
Crude	15.5 (1.75)	5.2 (0.28)	29.2 (1.89)	7.9 (0.36)	28.2 (1.86)	7.6 (0.35)
Age-standardized	15.7 (1.68)	8.1 (0.48)	29.7 (1.79)	13.8 (0.62)	28.7 (1.77)	13.2 (0.60)
All Hispanic						
Crude	9.8 (1.16)	3.1 (0.22)	18.6 (1.50)	5.0 (0.29)	17.5 (1.43)	4.6 (027)
Age-standardized	10.8 (1.21)	6.2 (0.53)	20.2 (1.59)	11.2 (0.77)	19.1 (1.53)	10.5 (0.72)
Mexican American						
Crude	9.7 (1.56)	2.7 (0.27)	17.6 (2.03)	4.6 (0.33)	16.7 (1.93)	4.2 (0.32)
Age-standardized	11.0 (1.75)	6.1 (0.73)	19.8 (2.34)	11.8 (0.91)	18.8 (2.27)	11.2 (0.91)
Other Hispanic						
Crude	10.1 (1.68)	3.7 (0.39)	20.4 (2.10)	5.7 (0.49)	19.0 (2.02)	5.2 (0.47)
Age-standardized	10.5 (1.69)	6.3 (0.80)	21.0 (2.04)	10.7 (1.19)	19.6 (1.98)	9.9 (1.09)
Non-Hispanic Asian						
Crude	8.6 (2.00)	3.1 (0.37)	20.8 (3.17)	4.7 (0.55)	20.4 (3.15)	4.4 (0.54)
Age-standardized	8.3 (1.74)	5.8 (0.81)	20.3 (2.74)	9.7 (1.25)	19.8 (2.69)	9.2 (1.23)

History of heart disease and diabetes status are self-reported. Where noted, data are standardized to the National Health Interview Surveys 2009–2010 diabetic population using age categories 18–44, 45–64, and ≥65 years.

SOURCE: National Health Interview Surveys 2009–2010

APPENDIX 18.2. Crude and Age-Standardized Prevalence of History of Heart Disease Among Adults Age ≥20 Years, by Diabetes Status, Sex, and Race/Ethnicity, U.S., 2007–2010

	PERCENT (STANDARD ERROR)					
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
CHARACTERISTICS	Congestive Heart Failure		Coronary Heart Disease		Angina	
Total						
Crude	10.3 (1.11)	1.4 (0.12)	11.8 (0.85)	2.4 (0.17)	7.9 (0.91)	1.5 (0.14)
Age-standardized	10.0 (1.06)	2.8 (0.22)	11.4 (0.81)	4.8 (0.31)	7.7 (0.89)	2.7 (0.28)
Sex						
Men						
Crude	9.6 (1.23)	1.8 (0.18)	14.3 (1.75)	3.7 (0.30)	7.7 (1.45)	1.8 (0.21)
Age-standardized	9.5 (1.12)	4.0 (0.39)	14.1 (1.58)	7.8 (0.54)	7.6 (1.39)	3.5 (0.44)
Women						
Crude	10.9 (1.89)	1.1 (0.14)	9.4 (1.30)	1.3 (0.14)	8.0 (1.45)	1.2 (0.16)
Age-standardized	10.3 (1.80)	1.9 (0.26)	9.0 (1.28)	2.4 (0.26)	7.8 (1.38)	2.1 (0.30)
Race/ethnicity						
Non-Hispanic white						
Crude	11.1 (1.66)	1.5 (0.16)	14.6 (1.37)	2.9 (0.23)	8.9 (1.30)	1.7 (0.20)
Age-standardized	10.4 (1.62)	2.6 (0.24)	13.8 (1.37)	5.0 (0.35)	8.6 (1.30)	2.8 (0.35)
Non-Hispanic black						
Crude	12.1 (1.42)	2.0 (0.35)	5.7 (1.28)	1.1 (0.19)	6.1 (1.34)	0.7 (0.22)[1]
Age-standardized	12.0 (1.41)	4.1 (0.58)	5.7 (1.31)	2.1 (0.42)	6.2 (1.39)	1.4 (0.42)[1]
All Hispanic						
Crude	6.0 (0.87)	0.7 (0.14)	8.5 (1.05)	1.0 (0.17)	5.9 (1.20)	0.9 (0.27)
Age-standardized	7.0 (0.93)	2.6 (0.56)	9.6 (0.94)	3.7 (0.54)	6.1 (1.15)	2.7 (0.73)
Mexican American						
Crude	5.0 (0.67)	0.5 (0.08)	8.1 (1.50)	1.1 (0.22)	4.8 (1.30)	1.1 (0.38)[1]
Age-standardized	6.3 (0.72)	2.0 (0.42)	9.5 (1.23)	4.5 (0.67)	5.1 (1.22)	2.9 (0.98)[1]
Other Hispanic						
Crude	7.7 (1.89)	1.0 (0.33)[1]	9.3 (1.85)	0.7 (0.17)	7.9 (2.90)[1]	0.7 (0.16)
Age-standardized	8.2 (1.86)	3.4 (1.09)[1]	9.7 (1.54)	2.6 (0.55)	7.9 (2.77)[1]	2.4 (0.59)
Other/Multiracial						
Crude	6.4 (2.15)[1]	1.7 (0.40)	9.7 (3.41)[1]	2.7 (0.90)[1]	6.5 (2.77)[2]	1.6 (0.42)
Age-standardized	6.6 (2.41)[1]	3.9 (1.64)[2]	9.9 (2.98)[1]	5.9 (1.95)[1]	6.5 (2.68)[2]	2.1 (0.66)[1]
	Heart Attack		Any Heart Condition, Including Angina		Any Heart Condition, not Including Angina	
Total						
Crude	11.1 (0.97)	2.5 (0.20)	23.1 (1.47)	5.0 (0.27)	20.8 (1.21)	4.5 (0.27)
Age-standardized	10.8 (0.93)	4.6 (0.30)	22.4 (1.41)	9.4 (0.45)	20.2 (1.15)	8.4 (0.43)
Sex						
Men						
Crude	13.1 (1.42)	3.6 (0.31)	24.9 (2.30)	6.4 (0.60)	23.0 (2.13)	6.1 (0.41)
Age-standardized	12.9 (1.38)	7.3 (0.56)	24.5 (2.09)	13.4 (0.76)	22.6 (1.91)	12.7 (0.78)
Women						
Crude	9.1 (1.17)	1.5 (0.17)	21.4 (2.26)	3.6 (0.28)	18.7 (1.83)	2.9 (0.25)
Age-standardized	8.7 (1.16)	2.5 (0.26)	20.3 (2.08)	6.3 (0.49)	17.7 (1.71)	5.0 (0.42)
Race/ethnicity						
Non-Hispanic white						
Crude	12.9 (1.38)	2.8 (0.24)	26.6 (2.07)	5.6 (0.35)	24.1 (1.73)	5.1 (0.33)
Age-standardized	12.2 (1.35)	4.7 (0.37)	24.9 (2.07)	9.5 (0.52)	22.5 (1.76)	8.5 (0.48)
Non-Hispanic black						
Crude	8.9 (1.03)	2.1 (0.30)	19.9 (1.67)	4.0 (0.47)	17.8 (1.64)	3.7 (0.44)
Age-standardized	8.6 (1.04)	4.6 (0.63)	19.9 (1.75)	8.2 (0.85)	17.8 (1.68)	7.7 (0.87)
All Hispanic						
Crude	8.9 (1.38)	1.1 (0.17)	15.5 (1.72)	2.7 (0.28)	13.9 (1.70)	2.0 (0.22)
Age-standardized	9.9 (1.45)	3.2 (0.34)	17.2 (1.60)	8.4 (0.86)	15.7 (1.62)	6.8 (0.68)
Mexican American						
Crude	8.1 (1.50)	1.1 (0.19)	14.6 (1.61)	2.7 (0.34)	12.5 (1.57)	1.9 (0.22)
Age-standardized	9.3 (1.70)	3.6 (0.48)	16.8 (1.58)	8.7 (0.77)	14.9 (1.63)	6.9 (0.67)
Other Hispanic						
Crude	10.4 (2.89)	1.2 (0.30)	17.0 (3.93)	2.7 (0.39)	16.4 (3.72)	2.2 (0.42)
Age-standardized	10.7 (2.65)	2.7 (0.58)	18.0 (3.49)	8.0 (1.37)	17.3 (3.28)	6.6 (1.16)
Other/Multiracial						
Crude	[3]	2.8 (0.68)[1]	15.4 (4.81)[1]	4.5 (0.78)	12.6 (3.62)	4.4 (0.75)
Age-standardized	[3]	4.7 (1.58)[1]	15.4 (4.04)	9.1 (2.26)	12.8 (3.22)	9.0 (2.25)

History of heart disease and diabetes status are self-reported. Where noted, data are standardized to the National Health Interview Surveys 2009–2010 diabetic population using age categories 20–44, 45–64, and ≥65 years.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Health and Nutrition Examination Surveys 2007–2010

APPENDIX 18.3. Crude and Age-Standardized Prevalence of History of Heart Disease Among Adults Age ≥18 Years, by Diabetes Status, Sex, and Race/Ethnicity, U.S., 2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)			
	Diabetes	No Diabetes	Diabetes	No Diabetes
	Coronary Heart Disease or Angina		Heart Attack or Myocardial Infarction	
Total				
Crude	15.3 (0.26)	3.2 (0.04)	14.4 (0.25)	3.2 (0.05)
Age-standardized	15.3 (0.25)	6.2 (0.07)	14.4 (0.25)	6.0 (0.07)
Sex				
Men				
Crude	17.6 (0.42)	3.9 (0.07)	17.3 (0.41)	4.2 (0.08)
Age-standardized	17.8 (0.41)	8.3 (0.13)	17.4 (0.40)	8.6 (0.13)
Women				
Crude	12.9 (0.30)	2.6 (0.05)	11.5 (0.29)	2.4 (0.05)
Age-standardized	12.8 (0.30)	4.6 (0.08)	11.4 (0.28)	4.0 (0.07)
Race/ethnicity				
Non-Hispanic white				
Crude	17.2 (0.31)	3.6 (0.05)	15.6 (0.29)	3.5 (0.05)
Age-standardized	16.5 (0.30)	6.2 (0.07)	15.0 (0.28)	5.9 (0.07)
Non-Hispanic black				
Crude	11.1 (0.65)	2.7 (0.15)	10.8 (0.59)	3.1 (0.16)
Age-standardized	11.6 (0.66)	5.7 (0.31)	11.3 (0.60)	6.4 (0.32)
All Hispanic				
Crude	11.7 (0.75)	2.1 (0.13)	11.3 (0.82)	2.0 (0.14)
Age-standardized	12.9 (0.78)	5.3 (0.35)	12.6 (0.87)	5.5 (0.40)
Non-Hispanic Asian				
Crude	9.2 (1.90)	1.3 (0.21)	7.8 (1.58)	1.3 (0.21)
Age-standardized	9.6 (1.91)	4.0 (0.68)	8.3 (1.68)	3.8 (0.67)
Native Hawiaiian/Other Pacific Islander				
Crude	[3]	1.5 (0.49)[1]	[3]	2.6 (0.75)
Age-standardized	[3]	5.8 (2.39)[2]	18.1 (8.78)[2]	9.9 (3.03)[1]
American Indian/Alaskan Native				
Crude	19.7 (2.71)	5.4 (0.81)	25.7 (3.12)	6.3 (0.81)
Age-standardized	20.2 (2.59)	9.9 (1.39)	27.1 (3.08)	11.4 (1.42)

History of heart disease and diabetes status are self-reported. Where noted, data are standardized to the Behavioral Risk Factor Surveillance System 2010 diabetic population using age categories 18–44, 45–64, and ≥65 years.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: Behavioral Risk Factor Surveillance System 2010

APPENDIX 18.4. Crude and Age-Standardized Percent of Hospitalizations Listing Heart Disease Among Adults Age ≥18 Years, by Diabetes Status, Sex, and Race, U.S., 2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)					
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
	Myocardial Infarction		Angina		Cardiac Dysrhythmia	
Total						
Crude	3.0 (0.19)	2.4 (0.07)	1.0 (0.12)	0.5 (0.03)	11.2 (0.35)	11.0 (0.16)
Age-standardized	2.9 (0.19)	2.8 (0.09)	0.9 (0.10)	0.6 (0.04)	9.6 (0.31)	11.9 (0.17)
Sex						
Men						
Crude	3.6 (0.31)	3.5 (0.14)	1.2 (0.20)	0.8 (0.07)	12.2 (0.52)	14.6 (0.29)
Age-standardized	3.5 (0.32)	3.6 (0.15)	1.1 (0.17)	0.8 (0.08)	10.6 (0.46)	14.0 (0.28)
Women						
Crude	2.5 (0.23)	1.7 (0.08)	0.7 (0.14)	0.3 (0.03)	10.4 (0.47)	8.8 (0.18)
Age-standardized	2.3 (0.21)	2.1 (0.10)	0.6 (0.12)	0.3 (0.04)	8.7 (0.42)	10.2 (0.21)
Race						
White						
Crude	3.2 (0.26)	2.5 (0.09)	0.8 (0.13)	0.5 (0.04)	12.8 (0.48)	12.6 (0.21)
Age-standardized	3.1 (0.27)	2.7 (0.11)	0.8 (0.11)	0.5 (0.04)	10.3 (0.41)	12.4 (0.21)
Black						
Crude	2.2 (0.39)	1.8 (0.18)	0.8 (0.29)[1]	0.3 (0.07)	7.8 (0.66)	7.3 (0.33)
Age-standardized	2.2 (0.38)	2.5 (0.25)	0.8 (0.27)[1]	0.4 (0.09)	7.5 (0.64)	9.6 (0.45)
Not stated						
Crude	2.6 (0.32)	2.2 (0.17)	1.3 (0.37)	0.6 (0.13)	9.2 (0.75)	8.8 (0.33)
Age-standardized	2.5 (0.30)	2.9 (0.23)	1.0 (0.29)	0.8 (0.18)	8.4 (0.72)	11.0 (0.44)

Appendix 18.4 continues on the next page.

APPENDIX 18.4. (continued)

CHARACTERISTICS	PERCENT (STANDARD ERROR)					
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
	Congestive Heart Failure		Coronary Heart Disease		Cardiovascular Disease	
Total						
Crude	14.6 (0.40)	9.9 (0.15)	22.4 (0.47)	12.2 (0.16)	44.9 (0.56)	30.1 (0.23)
Age-standardized	13.1 (0.37)	10.8 (0.17)	20.8 (0.45)	13.9 (0.19)	41.3 (0.54)	33.7 (0.25)
Sex						
Men						
Crude	14.5 (0.57)	12.1 (0.26)	27.8 (0.74)	18.7 (0.32)	49.8 (0.82)	40.3 (0.40)
Age-standardized	13.3 (0.53)	11.7 (0.26)	26.0 (0.72)	18.5 (0.31)	46.3 (0.80)	39.8 (0.39)
Women						
Crude	14.6 (0.55)	8.5 (0.17)	17.7 (0.57)	8.2 (0.17)	40.7 (0.76)	23.7 (0.27)
Age-standardized	12.9 (0.51)	10.2 (0.22)	16.2 (0.54)	10.1 (0.22)	36.8 (0.73)	28.9 (0.33)
Race						
White						
Crude	15.0 (0.53)	10.2 (0.19)	24.6 (0.62)	13.5 (0.21)	47.5 (0.73)	32.4 (0.29)
Age-standardized	12.7 (0.48)	10.0 (0.19)	22.2 (0.60)	14.2 (0.23)	42.0 (0.71)	33.5 (0.31)
Black						
Crude	16.3 (0.96)	11.5 (0.45)	15.8 (0.93)	8.6 (0.38)	41.6 (1.28)	26.9 (0.61)
Age-standardized	16.3 (0.95)	15.5 (0.59)	16.1 (0.94)	12.0 (0.52)	41.5 (1.24)	36.0 (0.74)
Not stated						
Crude	10.4 (0.71)	7.9 (0.30)	20.5 (1.16)	10.4 (0.37)	38.2 (1.40)	25.1 (0.55)
Age-standardized	9.6 (0.69)	10.1 (0.39)	19.2 (1.11)	13.3 (0.48)	35.8 (1.33)	32.1 (0.69)

Diabetes is defined as ICD-9 codes 250, 357.2, 362.0, 366.41, 648.0, and 775.1. Heart disease is defined by ICD-9 codes as follows: myocardial infarction 410, angina pectoris 413, cardiac dysrhythmia 427, congestive heart failure 428, coronary heart disease 410–414, and cardiovascular disease 410–414, 426–438, and 440–448. Where noted, data are standardized to the National Health Interview Survey 2009–2010 diabetic population using age categories 18–44, 45–64, and ≥65 years. Standard errors were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. ICD-9, International Classification of Diseases, Ninth Revision.

[1] Relative standard error >30%–40%

SOURCE: National Hospital Discharge Survey 2010