AHA Scientific Statement

Sex Differences in the Cardiovascular Consequences of Diabetes Mellitus

A Scientific Statement From the American Heart Association

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The prevalence of diabetes mellitus (DM) is increasing at a rapid rate. In the United States in 2012, 29.1 million Americans, or 9.3% of the population, had DM.[1] Currently, ≈1 in 13 people living in the United States has DM, and 90% to 95% of these individuals have type 2 DM (T2DM).[2] Overall, the prevalence of T2DM is similar in women and men. In the United States, ≈12.6 million women (10.8%) and 13 million men (11.8%) ≥20 years of age are currently estimated to have T2DM.[2]

Among individuals with T2DM, cardiovascular disease (CVD) is the leading cause of morbidity and mortality and accounts for >75% of hospitalizations and >50% of all deaths.[3] Although nondiabetic women have fewer cardiovascular events than nondiabetic men of the same age, this advantage appears to be lost in the context of T2DM.[4,5] The reasons for this advantage are not entirely clear but are likely multifactorial with contributions from inherent physiological differences, including the impact of the sex hormones, differences in cardiovascular risk factors, and differences between the sexes in the diagnosis and treatment of DM and CVD.[6] In addition, there are racial and ethnic factors to consider because women of ethnic minority backgrounds have a higher prevalence of DM than non-Hispanic white (NHW) women.

This scientific statement was designed to provide the current state of knowledge about sex differences in the cardiovascular consequences of DM, and it will identify areas that would benefit from further research because much is still unknown about sex differences in DM and CVD. Areas that are discussed include hormonal differences between the sexes and their possible effects on the interaction between DM and CVD, sex differences in epidemiology, ethnic and racial differences and risk factors for CVD in DM across the life span, sex differences in various types of CVD and heart failure, and sex differences in the effects of treatments for DM, including both medications and lifestyle. In addition, there is discussion about risk factors that are specific to women, including gestational diabetes mellitus (GDM) and polycystic ovarian syndrome (PCOS), which affect CVD risk. Table 1 focuses on sex differences in CVD risk factors and outcomes in DM, and Table 2 provides information about sex differences in CVD treatments and interventions in DM. Table 3 contains some of the important ideas for research in sex differences in the cardiovascular consequences of DM.

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Sex Differences in the Hormonal Milieu Between Women and Men: Could They Differentially Influence Coronary Risk in DM?

For years, it has been recognized that the incidence of coronary heart disease (CHD) in women lags behind that of men by ≈10 years,[7] thus generating hypotheses that differences in endogenous sex steroid levels contribute to sex differences in CHD. It also has been recognized for years that DM confers greater risk for CHD death in women compared with men.[8]

Early Rancho Bernardo Study publications noted that men with DM by history or by fasting plasma glucose had a 2.4-fold excess risk of ischemic heart disease death compared with men without DM, whereas women who had DM had a 3.5-fold excess risk compared with women without DM that was independent of multiple covariates (P=0.048 for effect modification by sex).[9] As they age, women with DM eventually have a risk of CHD death similar to that of men with DM.[8] Therefore, is it possible that differences in endogenous sex steroids contribute to the sex differences in the association between DM and CHD death? Testosterone and estrogens may play a significant role in the development of CHD in both women and men. Early studies, including those from Rancho Bernardo, noted that sex steroid levels were frequently undetectable among older adults.[10] However, low levels of total testosterone in men predicted incident coronary events, and extremes of bioavailable or unbound testosterone in women predicted coronary events.[10] These data suggest that high bioavailable testosterone may be harmful for women because of its association with obesity, DM, and metabolic syndrome components,[11–13] whereas low total testosterone effects in men may be enacted through different mechanisms. Whether testosterone levels are associated with the greater degree of CVD risk factor clustering observed with DM in women[14] needs to be addressed.

Therefore, the answer to the question of whether sex steroids influence the different risk factor levels and clustering of CVD risk factors in women and men remains uncertain. The conflicting results of exogenous estrogen trials compared with endogenous estrogen studies and exogenous testosterone trials compared with endogenous testosterone observations highlight the possibility that randomized sex steroid trials may not reflect naturally occurring mechanisms.[15] Our traditional approach to manipulating the hormonal milieu to understand how it influences CHD risk needs to be supplemented with other approaches. Assessing trajectories or repeated measures of risk factors, including sex steroids, before the onset of obesity and DM helps to elucidate the pathophysiology of hormonal sex differences and how they contribute to CHD in both sexes.

Table 1. Sex Differences in CVD Risk Factors and Outcomes in DM

	Sex Differences
Risk factor	
Sex hormones: testosterone	High bioavailable or unbound testosterone predicts incident coronary events
	Low levels of total testosterone predict incident coronary events
Generalized obesity	Higher prevalence of obesity in women, particularly postmenopausal women, than men
HDL-C	Women have higher HDL-C compared with men
Hypertension	Women with DM have more hypertension at >60 y of age (ie, postmenopausal)
	Men with DM and hypertension are at greater risk for renal injury than women (perhaps because of sex hormone differences)
Cardiovascular risk profile	More adverse in women with DM: impaired endothelium-dependent vasodilation, worse atherogenic dyslipidemia, prothrombotic coagulation profile, higher metabolic syndrome prevalence
	Compared with men, women have worse HbA_{1c} and blood pressure control
	CHD predictors in T1DM (Pittsburgh Epidemiology of Diabetes Complications Study)
	Women only: abdominal adiposity, insulin resistance, HbA_{1c}
	Men and women: inflammatory markers (fibrinogen, white blood cell count), microalbuminuria
Adiposity	Abdominal adiposity was more strongly associated with cardiovascular mortality in women compared with men with DM in a Finnish population
Outcome	
CHD	Women with DM have a 2-fold excess CHD risk compared with men
	Myocardial infarction occurs earlier and has higher mortality in women with DM compared with men
	Revascularization rates (angioplasty, coronary artery bypass grafting) are lower in women with DM compared with men
Heart failure	Risk of incident heart failure is greater in women than men
Stroke	Male stroke patients have a higher prevalence of DM than female stroke patients
	DM is a stronger risk factor for stroke in women compared with men
PAD	DM is a more significant risk factor for the development of claudication in women compared with men
	Women with PAD and DM respond less well to exercise training compared with women without DM and men with and without DM
	Decreased long-term survival in women undergoing revascularization and increased postsurgical mortality are seen in women but not men with DM

CHD indicates coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; PAD, peripheral arterial disease; and T1DM, type 1 diabetes mellitus.

Table 2. Sex Differences in CVD Treatments and Interventions in DM

CVD Treatment/Intervention	Sex Differences
Prescription of pharmacotherapy	Compared with men, women have lower frequency of lipid-lowering (statin) therapy, lower aspirin use, and lower ACE inhibitor and β-blocker use
	Lower medication adherence in women compared with men in some but not all studies
Statin therapy*	Equally effective for secondary CVD prevention in both men and women
	No prospective evidence for primary CVD with statins in women; however, on the basis of expert opinion and cholesterol theory of atheroma progression, statins are recommended for primary prevention in women
	Atheroma regression and LDL lowering greater with statins in women than in men in the Study of Coronary Atheroma by Intravascular Ultrasound
	Statin therapy side effects:
	Women may have a greater likelihood of developing DM on statins
	Myalgia may be more frequent in women
	Increase in creatinine phosphokinase or abnormal liver function may be more frequent in men
Fenofibrate	Greater lipid-lowering impact and greater reduction in CVD end point in women compared with men, although sex interaction for the latter was not significant (from the FIELD study)
ACE inhibitors, β-blockers, spironolactone*	Guidelines support use for the treatment of heart failure for both men and women
Aspirin therapy	Primary prevention:
	Consider low-dose aspirin (75–162 mg/d) for individuals with 10-y CVD risk of at least 10% who do not have an increased risk of bleeding and have at least 1 additional CVD risk factor
	Men ≥50 y of age
	Women ≥60 y of age
	Not recommended for adults with DM at low risk with no additional CVD risk factors
	Men <50 y of age
	Women <60 y of age
Lifestyle treatment	Cardiovascular events and mortality:
	Da Qing Diabetes Prevention Study of Chinese adults with prediabetes demonstrated a sex difference in cardiovascular mortality of the lifestyle intervention that favored women (although smoking prevalence was higher in men than women)
	No sex differences in cardiovascular outcomes in individuals with DM in the Japanese Diabetes Complications Study (stroke) or the Look AHEAD Study (cardiovascular mortality/major cardiovascular events)
	Observational studies suggest that women with DM may require greater frequency/intensity of physical activity than men to reduce cardiovascular events
	Fitness:
	Look AHEAD showed greater improvements in cardiorespiratory fitness in men compared with women
	Diabetes Aerobic and Resistance Exercise trial and a meta-analysis showed similar improvements in fitness in response to exercise training
	Glycemic control/DM prevention:
	Women with T1DM may have greater improvement in HbA_{1c} with exercise than men
	Data on the effect of exercise on HbA_{1c} in men and women with T2DM are inconclusive
	Men and women with prediabetes had similar weight loss and DM prevention rates in the US Diabetes Prevention Program and the Finnish National Diabetes Prevention Study

ACE indicates angiotensin-converting enzyme; CVD, cardiovascular disease; DM, diabetes mellitus; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; HbA_{1c}, hemoglobin A_{1c}; LDL, low-density lipoprotein; Look AHEAD, Action for Health in Diabetes; T1DM, type 1 diabetes mellitus; and T2DM, type 2 diabetes mellitus.
*Fewer women than men are represented in studies evaluating the effect of these interventions on the stated outcomes.

Epidemiology, Ethnic and Racial Differences, and Risk Factors for CVD in DM Across the Life Span

Epidemiology

Introduction to Sex Differences in Cardiovascular Outcomes Within Racial/Ethnic Groups

Sex differences in cardiovascular consequences of DM are modified in distinct racial/ethnic subgroups for 2 reasons (Figures 1 and 2). First, patients from a specific racial/ethnic subgroup with DM show sex differences in biological and social/cultural factors, which may modify key cardiovascular consequences of DM.[16] Second, understanding the cardiovascular consequences of DM within racial/ethnic subgroups with DM is important to guide prevention targets to reduce cardiovascular health disparities.[16] In this section, we use the Williams[17] definition of race/ethnicity as "a complex multidimensional construct" that includes biological, geographic, and socioeconomic factors.

Table 3. Recommendations for Future Research

Epidemiology, ethnic and racial differences, and risk factors for CVD in DM	Future research is needed to expand limited data on sex differences in cardiovascular outcomes among racial/ethnic subgroups with DM.
	More research is needed to determine sex differences in the biological, social, and cultural factors that lead to worse cardiovascular outcomes for many minority populations with DM.
CHD and heart failure in women	Most contemporary recommendations for the prevention, diagnostic testing, and medical and surgical treatments of CHD in women are extrapolated from studies conducted predominantly in middle-aged men. Underrepresentation of women in trials of cardiovascular clinical procedures and therapies and, when women are enrolled, inadequate provision of sex-specific analyses limit the ability to define the specific benefits and risks experienced by women.
	Specific factors requiring further investigation include the following:
	Hormonal effects on myocardium
	Sex differences in the response to therapies known to affect heart failure such as ACE inhibitor, aldosterone inhibitor, and angiotensin receptor blocker medications
	Sex differences in glucose and insulin metabolism, none of which have been systematically studied
Hypertension and stroke	Hypertension is less well controlled in women than men. Reasons are not apparent because women typically see physicians more frequently and are at least as compliant with medications as men. However, therapeutic guidelines for women and men are the same.
	New studies are needed to determine whether the mechanisms that cause hypertension are the same for men and women.
	More detailed prospective data are needed on the relationship between DM and stroke types in women and men, as well as more data on the effects of DM duration or control on stroke incidence.
PAD	Relatively little is known about sex differences in the diagnosis, symptoms, and treatments of DM in combination with PAD.
	More studies needed to evaluate the sex differences in prevalence of coexisting DM and PAD.
PCOS and GDM	Both GDM and PCOS are naturally occurring models of alterations in sex steroids and insulin resistance. Studies of GDM and PCOS could help us understand the sex-specific cardiovascular consequence of DM in women.
	Prospective studies are needed that examine the incidence of CVD in PCOS and GDM and specifically whether associations exist apart from recognized risk factors for CVD, particularly DM and hyperandrogenism.
	Cohort studies are needed to examine whether a history of PCOS and GDM can distinguish risk for women in midlife, apart from recognized CVD risk factors.
	Studies are needed to determine whether early interventions during the reproductive period may modify CVD risk.
	Specific data on the risk of stroke in women with a history of GDM are needed.
Treatments	
Pharmacotherapy	Sex differences in the pharmacological treatment of DM are not well understood. More studies are needed.
Pharmacotherapy during pregnancy	Overall, there are few studies of pharmacotherapy during pregnancy; more are needed.
	Studies are needed to determine whether pravastatin use during pregnancy is associated with poorer outcomes compared with no use, apart from any impact on preeclampsia.
	Studies are needed to determine whether metformin use during pregnancies with T2DM affects birth outcomes or can reduce insulin use.
Lifestyle	Several RCTs that used lifestyle interventions to improve cardiovascular-related outcomes or cardiovascular risk factors have not conducted sex differences analyses, so important opportunities exist for investigators to conduct secondary data analyses that assess sex differences in lifestyle interventions.
	Attention should be given to whether there is adequate power to assess sex differences in post hoc analyses of lifestyle intervention studies.

ACE indicates angiotensin-converting enzyme; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; GDM, gestational diabetes mellitus; PAD, peripheral arterial disease; PCOS, polycystic ovary syndrome; RCT, randomized, controlled trial; and T2DM, type 2 diabetes mellitus.

Racial/Ethnic Differences in Cardiovascular Consequences of DM

First, we provide robust data describing the racial/ethnic differences in the cardiovascular consequences of DM, followed by the much more limited data on sex differences in the cardiovascular consequences of DM within specific racial/ethnic groups, an area that still warrants further exploration.

In 2011 in the United States, there was no significant difference in the age-adjusted prevalence of CHD or stroke in non-Hispanic blacks (NHBs; 33.0%) and NHWs (33.9%) who were ≥35 years of age and reported a diagnosis of DM.[18] Compared with the other 2 subpopulations, Hispanic Americans with DM had the lowest prevalence of CHD/stroke (24.5%). These general CVD trends among US adults with DM persisted from 1997 to 2011 (Figure 1).[18] Other studies found that after adjustment for multiple cardiovascular risk factors and confounders, several minority populations had a lower risk of incident CVD than NHWs, including Hispanic Americans, Asian Americans, and NHBs.[19,20] Data on American Indians and Alaskan natives are less extensive, but in 1 large study (n=42 143), age-adjusted CHD rates were lower (5.5% versus 7.2%; $P<0.05$) and CVD rates were higher (6.9% versus 5.5%) in American Indian adults with DM in the general population compared with commercially insured US adults with DM.[21]

In contrast to the lower rates of CVD observed in many racial/ethnic subpopulations with DM, it appears that

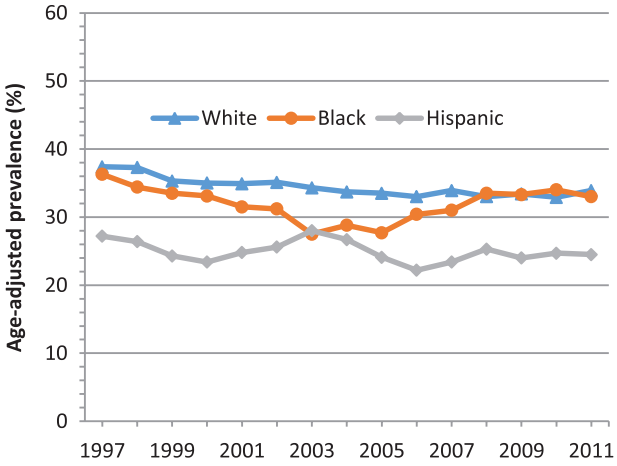

Figure 1. Prevalence of coronary heart disease/stroke by race and ethnicity in adults with diabetes mellitus.

cardiovascular mortality rates are higher in many racial subpopulations than in NHWs with DM. For example, in the Multicenter Investigation of the Limitation of Infarct Size, higher mortality rates were identified in NHB versus NHW patients with DM after myocardial infarction.[22] This difference was due primarily to worse mortality among NHB women (48%) compared with NHW and NHB men (21% and 23%, respectively) and NHW women (32%).[22]

Sex Differences Within Racial/Ethnic Population Subgroups

With the exception of the data by Tofler et al,[22] there are limited data on sex differences within racial/ethnic subgroups with DM; the data that do exist are mixed in terms of the influence of sex on cardiovascular outcomes. The most recent epidemiological data among NHBs with DM demonstrate a consistently higher prevalence of CHD/stroke in NHB women compared with NHB men from 1997 to 2011, with similar findings emerging among Hispanic Americans from 2005 to 2011.[18] In contrast, among NHWs with DM, there was a consistently lower prevalence of CHD/stroke in women compared with men from 1997 to 2011[18] (Figure 2). Finally, 2 separate studies observed protective associations between female sex and lower coronary artery calcium (CAC) scores among NHBs with T2DM.[23,24]

Given the lack of consistent data on the influence of sex on cardiovascular outcomes among racial and ethnic subpopulations, it is important to consider the sex and racial/ethnic differences in factors that are known contributors to cardiovascular outcomes in patients with DM and the social and cultural factors that may influence cardiovascular outcomes. The next 2 sections address these factors.

Metabolic Factors That May Contribute to the Exacerbation of Diabetic Heart Disease and Differ by Sex or Race/Ethnicity

Generalized Obesity

The relative effect of DM on CVD is generally worse in women than men because of an interaction with sex differences in obesity.[16,25,26] Because women have a higher prevalence of obesity than men, sex differences in obesity have the potential to magnify existing sex differences in diabetic heart disease.[27] The effect of obesity on the sex difference

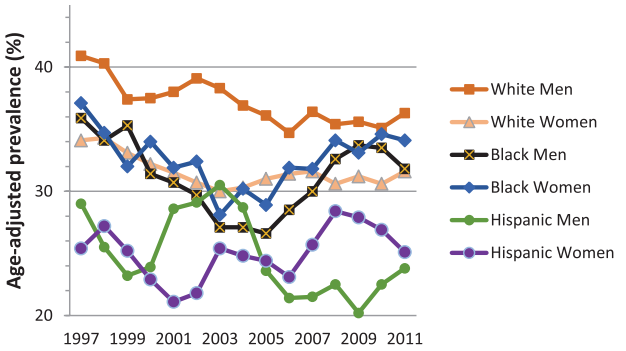

Figure 2. Prevalence of coronary heart disease/stroke by sex, race, and ethnicity in adults with diabetes mellitus.

in diabetic heart disease may be enhanced by age. National Health and Nutrition Examination Survey (NHANES) data in the 10-year period between 2003 to 2004 and 2011 to 2012 revealed that the prevalence of obesity in adults, in general, remained stable at 35%.[27] However, for women ≥60 years of age, the prevalence of obesity increased from 32% to 38%.[27] Therefore, in postmenopausal women, the CVD risk of DM is compounded by the combined impact of obesity and aging.

Central Obesity

Visceral adiposity is the main fat depot contributing to the development of DM and heart disease.[28–32] Even after adjustment for either body mass index (BMI) or waist circumference (WC), measurements of visceral adipose tissue are lower in NHB than NHW women.[33–36] Consequently, the WC that predicts insulin resistance and cardiometabolic risk is 5 to 10 cm higher in NHB than NHW women because NHBs have more subcutaneous compared with visceral fat at a given WC than NHW women.[37,38] However, this racial difference in the WC of risk may not be clinically important because in every BMI category the prevalence of obesity is ≈50% higher in NHB than NHW women.[27] This means that the lower proportion of visceral adipose tissue in NHB women may not provide protection because it is offset by a higher overall fat mass, including visceral adipose tissue, as a result of higher BMI in NHBs than NHWs.

In contrast, DM and CVD occur at a lower BMI and WC in Asian than in white or black women.[39,40] Thus, a normal BMI by standard criteria in Asian women should not be interpreted by healthcare providers to mean that DM or diabetic cardiovascular risk or disease is absent.[39,40]

Hypertension

Hypertension adversely affects every aspect of diabetic heart disease, and although the prevalence of hypertension does not differ by sex, it does by race.[41] Almost 50% of NHBs compared with one third of NHWs and Hispanics have hypertension.[41] Therefore, hypertension has the potential to magnify the severity of diabetic heart disease in NHB women.

High-Density Lipoprotein Cholesterol

Women have higher high-density lipoprotein cholesterol (HDL-C) than men, and nondiabetic NHBs have higher HDL-C levels than NHWs.[41] In addition to being active in reverse cholesterol transport, HDL-C has antithrombotic, anti-inflammatory, and antioxidant activity.[42] However, HDL-C levels are actually suppressed, not elevated, in insulin-resistant

NHB women.[42–44] Furthermore, preliminary evidence suggests that HDL-C particles are less effective as anti-inflammatory and antioxidant agents in postmenopausal NHB compared with NHW women.[45]

Social and Cultural Factors Contributing to Disparities

Multilevel factors at the individual, population, and health system levels contribute to sex and racial/ethnic disparities in CVD in DM.[16] The majority of research has focused on the contribution of these factors to racial/ethnic disparities and less to sex disparities. Therefore, future research should focus on how social and cultural factors influence sex disparities.

Sex Differences in the Cardiovascular Complications of DM: CHD and Heart Failure

Coronary Heart Disease

DM is a potent risk factor for CHD and was deemed a risk equivalent for CHD by the Adult Treatment Panel in 2001.[46] Emerging research data highlight sex differences in the basic biology, pathophysiology, preventive strategies, diagnostic procedures, medical and interventional therapies, and clinical outcomes of disorders.[47] There is a 3-fold excess fatal CHD risk in women with T2DM compared with nondiabetic women (95% confidence interval [CI], 1.9–4.8),[48] with a higher adjusted hazard ratio (HR) of fatal CHD in women with DM (HR=14.74; 95% CI, 6.16–35.27) compared with men with DM (HR=3.77; 95% CI, 2.52–5.65).[49] Myocardial infarction occurs earlier in women with DM compared with men,[5] with higher mortality from the myocardial infarction.[25] In a Finnish cohort study,[5] the presence of DM reduced the so-called female advantage for CVD risk; indeed, mortality from CHD was 3 times higher in women compared with men with DM. Similar findings were observed in the NHANES cohort; ischemic heart disease mortality increased ≈11% from the 1971 to 1975 cohort followed up through 1986 compared with the 1982 to 1984 cohort followed up through 1992.[50] Biologically, a more adverse cardiovascular risk profile is observed in women with DM compared with men, consisting of impaired endothelium-dependent vasodilation, a prothrombotic coagulation profile, worse atherogenic dyslipidemia, and more metabolic syndrome with or without DM.[51–54] Other postulated contributors to this paradoxical increase in DM-related cardiovascular events have ranged from a differential application of risk factor management strategies or perhaps a differential effect of these management strategies[55]; these may be important targets for improvement in these disparities. Evidence has emerged demonstrating a potential sex disparity in the intensity of cardiovascular risk reduction whereby worse hemoglobin A_{1c} (HbA_{1c}) control, lower frequency of lipid-lowering therapy, lower aspirin use, and lower blood pressure control were noted in women.[56] Women with DM are less likely to receive appropriate care both in outpatient clinic settings[57] and after acute coronary syndromes.[58] Revascularization rates of CHD with angioplasty and coronary artery bypass surgery are lower in women than men with DM,[59,60] all contributing to more CHD-related complications in women with DM.

Heart Failure

Heart failure is strongly related to DM, probably at least in part by its strong association with ischemic heart disease. The risk of heart failure increases by 40% in the presence of DM,[61] and the age-adjusted odds ratio (OR) for the development of heart failure was 2.8 (95% CI, 2.2–3.6) in patients with DM compared with nondiabetic patients in Iceland.[62] There is a sex difference in this risk, shown first in the Framingham Heart Study in which heart failure risk was 2-fold higher in men ($P<0.05$) and 5-fold higher in women with DM ($P<0.01$) compared with the respective nondiabetic population.[63] There was no statistical test for effect modification by sex in this analysis. In a more recent report,[64] despite no difference in hospitalization among women with DM compared with men, the association between the diagnosis of heart failure and that of DM had a characteristic horseshoe shape over a 70-year age span with a relatively early rise followed by a progressive decrease with advancing age, as previously described.[61] This association was greater among women in the fourth and fifth decades of age compared with men. The underlying reason for the increased risk of developing heart failure in women with DM compared with men with DM is not entirely clear but most likely relates to the sex disparities at play in CHD diagnosis and treatment.

Sex Differences: DM and Hypertension

Normotensive women typically have lower blood pressures than men.[65] However, with menopause, more women exhibit hypertension than do men of comparable age.[65] Hypertension is a common occurrence in individuals who have both T2DM and type 1 DM (T1DM),[66] and there are sex differences in the development of hypertension with T2DM that seem to be age related. In the Western New York Health Study, the strongest indicators for development of hypertension were impaired fasting glucose and weight gain after 25 years of age.[67] In an Austrian cohort of individuals with T2DM, more men 20 to 60 years of age had hypertension, whereas more women ≥60 years of age had hypertension than men.[68] In a Chinese cohort, individuals who had impaired fasting glucose at baseline were more likely to develop T2DM at the 5-year follow-up if they were hypertensive, >60 years of age, and female. In a Spanish cohort, the incidence of T2DM and hypertension increased from 89.8% in 2003 to 92.9% in 2009, and the percentages were higher for women or individuals >65 years of age.[66] Interestingly, in a Swedish study of individuals who were all 50 years of age, men had a greater prevalence of hypertension or metabolic syndrome that included T2DM than did women, but in women, the prevalence of hypertension with metabolic syndrome was greater.[69] Therefore, within various ethnic cohorts, DM and hypertension are strongly linked, and this is especially true in postmenopausal women.

The mechanisms responsible for hypertension in T2DM have not been completely elucidated. However, there is a strong interaction between obesity and both T2DM and hypertension. Animal studies have shown that obesity is associated with activation of the sympathetic nervous system, mediated mainly by activation of the pro-opimelanocortin–melanocortin 3/4 receptors.[70–72] Leptin, which is produced by adipocytes, has been shown to be one of the factors that upregulate the pro-opimelanocortin–melanocortin 3/4 receptor system.[70]

Other factors that may contribute to hypertension in individuals with DM include chronic kidney disease. In the Kidney Early Evaluation Program study, NHWs were more likely to have metabolic syndrome with hypertension, DM, and a greater decrease in estimated glomerular filtration rate than blacks.[73] In the same cohort, male sex was associated with hypertension, DM, lower estimated glomerular filtration rate, and albuminuria, which were predictive of end-stage renal disease, whereas age, male sex, DM, lower estimated glomerular filtration rate, and albuminuria were predictive of mortality.[74] As noted above, men are thought to be at greater risk for renal injury, especially hypertensive individuals with DM, resulting perhaps from the presence of androgens.[75] In contrast, women are thought to be somewhat protected from renal injury associated with DM and hypertension perhaps because of the presence of estrogens.[75,76] Because we now know that androgen levels are decreased with obesity and chronic diseases,[77] including hypertension and DM, the model that androgens are bad and estrogens are good is overly simplistic to adequately account for the mechanisms responsible for hypertension in DM and obesity.

With regard to hypertension in individuals with DM, the new guidelines for the management of high blood pressure in adults (the Eighth Joint National Committee)[78] state that for individuals ≥18 years of age, the physician should initiate pharmacological treatment to lower blood pressure to a goal of systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg. In the nonblack population, that is, whites or Hispanics, the drugs should include thiazide-type diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. In NHBs, including those with DM, initial treatment should include a thiazide-type diuretic and calcium channel blockers.[78] The guidelines unfortunately remain non–sex-specific, despite the clinical and translational studies that have provided evidence that the mechanisms responsible for hypertension in men and women may be different. For example, studies of blood pressure control in aging hypertensive animal models have shown that the renin-angiotensin system and the sympathetic nervous system are the major contributors. However, in aging females of the same strain, not only the renin-angiotensin system and sympathetic nervous system but also the endothelin system and eicosanoids such as 20-hydroxyeicosatetraenoic acid contribute to hypertension.[65] Furthermore, although the dogma in hypertension research is that oxidative stress contributes to the development and maintenance of hypertension, these studies have been done primarily in males only. Several investigators have now shown that oxidative stress does not contribute to hypertension in females,[79–81] unless there is an inflammatory or immune-mediated component to the hypertension such as in preeclampsia or lupus erythematosus. Whether these sex differences in mechanisms responsible for hypertension hold true for humans remains to be determined so that treatment for both sexes will be improved.

Sex Differences in the Risk of Stroke Among Individuals With DM

DM is widely recognized as a risk factor for stroke in both women and men.[82–84] On a population level, ≈26.3% of strokes are attributable to DM.[85] In terms of the different types of stroke, a >2-fold risk for ischemic stroke has been observed consistently among those with DM, with an ≈50% increased risk of hemorrhagic stroke.[83] DM has been particularly associated with increased risk of lacunar-type infarction.[85–87]

Sex Differences in the Association of DM as a Stroke Risk Factor

The prevalence of DM among stroke patients differs by sex, with male stroke patients having a higher prevalence of DM. In a recent meta-analysis of 45 studies of sex differences in the prevalence of risk factors for stroke, men were more likely to smoke and to have a history of DM, whereas women tended to be older and were more likely to have a history of hypertension and atrial fibrillation.[88]

In contrast, individual studies of the sex differences in risk of stroke associated with DM have been inconsistent, with some studies showing women with DM at higher risk,[5,83,86,89] similar risk,[90] or lower risk[91,92] compared with men with DM. In a recent comprehensive systematic review and meta-analysis using data from 64 cohorts including >12 000 strokes, DM was a stronger risk factor for stroke in women than in men. The overall adjusted relative risk (RR) for total stroke associated with DM was 2.28 (95% CI, 1.93–2.69) for women and 1.83 (95% CI, 1.60–2.08) for men. No test for interaction by sex was provided. Compared with men with DM, women with DM had a 27% greater RR for stroke when baseline differences in other cardiovascular risk factors were taken into account (RR=1.27; 95% CI, 1.10–1.46).[93] One study suggested an almost 4-fold risk for lacunar infarction among women (HR=3.85; 95% CI, 2.22–6.70) compared with a 2-fold risk in men (HR=2.04; 95% CI, 1.21–3.44) when DM is present.[86] No *P* value was reported for interaction by sex for lacunar infarctions. The most recent American Heart Association guidelines on the prevention of stroke in women[94] classified DM as a risk factor that is stronger or more prevalent in women.

Differences in Stroke Mortality for Women and Men With DM

Long-term survival after first stroke is lower among individuals with DM; this was particularly true for women and younger patients in a Swedish study.[95] In the Women's Pooling Project, individuals with DM without CVD had a risk of fatal stroke similar to that of nondiabetic subjects with a history of prior stroke after adjustment for other cardiovascular risk factors.[96] These results suggest that DM may be classified as a stroke risk equivalent and that more aggressive treatment strategies may be warranted to prevent stroke in this high-risk group.

Type of DM and Diabetic Control

DM is a strong risk factor for stroke in both women and men. However, many studies fail to distinguish between T1DM and T2DM. Moreover, adult associations of T1DM are influenced by the longer total duration of disease. Both types of DM were associated with substantially increased risks of stroke among women in the Nurse's Health Study. Among middle-aged women, those with T1DM had a 4-fold higher risk (RR=4.7; 95% CI, 3.3–6.6) and those with T2DM an

almost 2-fold higher risk (RR=1.8; 95% CI, 1.7–2.0) of total stroke than nondiabetic women. The multivariate-adjusted risk of ischemic stroke was increased 6-fold (RR=6.3; 95% CI, 4.0–9.8) in T1DM and 2-fold (RR=2.3; 95% CI, 2.0–2.6) in T2DM. T1DM was also significantly associated with the risk of hemorrhagic stroke (RR=3.8; 95% CI, 1.2–11.8).[97] Whether history of GDM is a risk factor for stroke remains unknown.

Among 30 000 women and men with T2DM, women with HbA_{1c} levels ≥8.0% had a significantly elevated risk of stroke, whereas men did not.[98] Importantly, strict blood glucose control has not been shown to decrease the incidence of stroke among people with DM.[99]

Sex Differences in Peripheral Arterial Disease With DM

Approximately 8 to 12 million people in the United States have peripheral artery disease (PAD), with peripheral atherosclerosis typically manifested in the legs.[100] Studies differ on whether the prevalence of PAD in nondiabetic individuals is greater in women or men,[101,102] but women tend to develop PAD at an older age.[103] The prevalence of PAD in female versus male patients with DM has not been clearly established.[100] In both sexes, there is a substantial overlap between PAD with CHD and cerebrovascular disease, as would be expected, and PAD is considered a CHD risk equivalent. The risk factors for PAD and CHD are comparable and include smoking, DM, age, hypertension, and dyslipidemia, with DM and cigarette smoking having a particularly strong association with PAD.[104] Although the majority of PAD patients are asymptomatic or have atypical symptoms, about one third have intermittent claudication, which is pain, aching, or cramping in the buttocks, thighs, or calves of the legs brought on reproducibly by walking and relieved by rest.

Relatively little has been written about sex differences in the cardiovascular consequences of DM with regard to PAD. In fact, in many studies of PAD, patients with DM have been excluded to permit a more streamlined study design and to reduce confounders. However, some key observations have been made. On the basis of limited data, DM seems to be a more significant risk factor in women than men for the development of claudication. DM in the presence of glycosuria increased the risk of claudication 8.6-fold in women compared with 3.5-fold in men.[105] No 95% CI or test for effect modification by sex was reported. Results from the Framingham Heart Study also showed a 3- to 4-fold increase in risk of CHD, stroke, and heart failure in women who had both DM and intermittent claudication compared with either condition alone.[106] In contrast, men with both DM and intermittent claudication had a 2-fold increase in risk of stroke and a 3-fold greater likelihood of heart failure.[106] No 95% CI or test for effect modification by sex was reported. In an observational Japanese study comparing 730 women and men with PAD, the women were older and more likely to have DM and hyperlipidemia, as well as more severe PAD.[107] An observational study in Taiwan found that women and men with DM had different risk factors for developing PAD.[108] For instance, insulin therapy was a risk factor in women but not in men. In 2012, Wisman et al[109] reported that women with PAD who were <60 years of age were reported to have an increased risk for cardiovascular events compared with men of that age (HR=4.9; 95% CI, 1.8–13.6), whereas no sex difference was seen above 60 years of age. No test for interaction by sex was provided, but the 95% CI does not cross 1.0, so the *P* value is <0.05.

In studies of claudication, women with PAD and DM do not respond as well to exercise training as nondiabetic women, nondiabetic men, or men with DM.[110] Even with excellent adherence to exercise training (84%), women with DM did not improve in measures of walking ability, including claudication onset time and peak walking time.[110] In contrast, nondiabetic women and men and even men with DM showed improvement in these variables.

Associations between sex and survival after lower-extremity revascularization for PAD are altered by the presence of DM. Magnant et al[111] reported similar perioperative mortality rates among women and men undergoing infrainguinal bypass for lower-extremity ischemia but decreased long-term survival in women (54% versus 72% 3-year survival for women versus men, respectively). These authors also observed an effect of sex in combination with DM, with increased postsurgical mortality in women with DM (RR=2.5; 95% CI, 1.4–4.4; *P*<0.002 for association of DM and mortality in women) but not in men with DM (*P*>0.05 for association of DM and mortality in men). No test for interaction by sex was provided. However, given that most studies have not evaluated the role of DM in these effects, for the most part, little is known about these important issues, and this is clearly an area where more research is needed.

PCOS and GDM: Sex-Specific Models of Subclinical DM and CVD

PCOS and GDM are 2 conditions specific to women of reproductive age that identify women at higher risk for the development of DM. PCOS and GDM provide 2 natural models of the interaction of sex steroid hormones and insulin resistance that may inform our understanding of sex-specific CVD before the conversion to DM.

PCOS and Cardiovascular Risk

PCOS is the most common endocrine disorder among women of reproductive age, occurring in at least 6% to 8% of women in the United States[112–114] by criteria of hyperandrogenism and oligoanovulation and as many as 16% to 19% of women by current Rotterdam criteria that include polycystic ovaries.[115–117] Insulin resistance is a key feature of PCOS, and at least half of women with PCOS have insulin resistance, even if they are not overweight or obese.[118] Hyperinsulinemia may increase androgen production, and interventions that improve insulin sensitivity can lower androgens and restore ovulatory cycles. Alternatively, lowering androgens with spironolactone and oral contraceptives can also improve insulin sensitivity, although to a lesser degree.[119] Given the major role for insulin resistance in PCOS, it is not surprising that PCOS is also associated with a greater prevalence of individual CVD risk factors, including obesity, hypertension, dyslipidemia, and the metabolic syndrome.[113,120,121] Women with PCOS also have a higher prevalence of impaired glucose tolerance and DM, especially obese individuals,[122,123] and as early as adolescence.[124]

PCOS and Cardiovascular Events

Despite a higher prevalence of cardiovascular risk factors in PCOS, a higher cardiovascular event risk or mortality rate has not been confirmed, although studies are limited by small sample size or retrospective diagnosis. Because PCOS is diagnosed before menopause, few studies are designed to prospectively evaluate cardiovascular events in PCOS. The study that initially reported a 7-fold predicted risk for cardiovascular events with a sample of 35 women with PCOS[125] found no increase in cardiovascular events after 21 years of follow-up.[126] Another cohort with a similar length of follow-up in a retrospective sample of 309 women with PCOS also found no increase in cardiovascular events or mortality.[127] The largest retrospective cohort study in the United Kingdom of 1028 women with PCOS did not find an increase in CVD mortality over an even longer range of follow-up, averaging 31 years.[128,129]

Surrogates for PCOS and Cardiovascular Events

Epidemiological cohorts in the United States have found that menstrual irregularity, as a surrogate for PCOS, increases cardiovascular risk,[130,131] although it is possibly mediated by BMI.[132] However, the estimated RR for menstrual irregularity was no greater than 1.5 (95% CI, 1.10–2.04 for overweight, very irregular women), which is comparable to the HRs of 1.65 (95% CI, 1.10–2.47) to 2.1 (95% CI, 1.5–2.8) for cardiovascular events from the metabolic syndrome alone in other cohorts.[133,134] Because menstrual irregularity increases the risk for insulin resistance and DM,[135] risk associated with menstrual irregularity may not be attributable to PCOS per se but to insulin resistance, the metabolic syndrome, or obesity. Other PCOS criteria of androgen excess and polycystic ovaries have been associated with an increased risk for coronary occlusion or cardiovascular events in postmenopausal women.[131,136,137] Although few studies have prospectively characterized large samples of women with PCOS and control subjects through the menopausal transition, available data suggest conflicting results as to the persistence of androgen excess and polycystic ovaries.[138] In women without PCOS, androgens and sex hormone–binding globulin may decrease or increase, depending on the stage of the menopausal transition.[139–141] Therefore, although postmenopausal androgen excess and polycystic ovaries may be associated with CVD, longitudinal studies are needed to confirm the persistence of PCOS criteria after menopause and the association with cardiovascular risk.

PCOS and Surrogates for CVD

As a result of data demonstrating the ability of carotid intima-media thickness, CAC, and peripheral endothelial function to predict CVD and outcomes, subclinical measurements of CVD have been studied in PCOS. Subclinical measurements of CVD are generally worse in those with PCOS than in control subjects. PCOS has been more consistently associated with greater carotid intima-media thickness in older,[142] younger,[143–145] and nonobese[146] women. Measurements of peripheral endothelial function have shown greater variability, with some studies finding no difference in flow-mediated endothelial dilation in obese women with PCOS compared with matched control subjects.[147,148] A meta-analysis of several studies reported a significant decrease in flow-mediated endothelial dilation associated with PCOS after accounting for age and BMI, although there was substantial heterogeneity between studies.[149] Differences in carotid intima-media thickness and impairment in peripheral vascular function could be attributed at least in part to insulin resistance, obesity, or dyslipidemia.[144,150–155] Although a few studies report greater CAC in women with PCOS than in those who do not have PCOS,[156–159] these data must be interpreted cautiously because of the influence of obesity on CAC measurements and the low prevalence of detectable CAC among young women (5.1% of women 33–45 years of age).[160] In obesity, x-ray scatter from adjacent soft tissue increases the false-positive rate, with duplicate scans in obese individuals demonstrating the highest rate of false positives with CAC scores <10.[161] The majority of CAC scores in PCOS studies are <10. In the largest study of 144 women with PCOS, which defined positive CAC ≥10, there was no significant difference in CAC prevalence between obese women with PCOS and control subjects.[115] The significant influence of BMI on CAC is demonstrated in a study that did not find significant differences in CAC between 36 women with PCOS and control groups matched for BMI, reporting significant differences only in a second sample not matched for BMI.[156] In the study of 24 obese women with PCOS and BMI-matched control subjects, the range of CAC scores was below 10 in those with PCOS, and BMI was the only significant predictor of CAC among all women.[157] The best evidence for greater CAC in women with PCOS compared with control subjects may be seen at the time near the menopausal transition. PCOS was associated with an almost 2-fold greater unadjusted odds for CAC in 2 studies with sample sizes of 55 to 61 women with PCOS. When adjusted for features of the metabolic syndrome, the association with PCOS remained significant in only 1 study.[158] Therefore, the influence of obesity and insulin resistance and low prevalence of CAC in premenopausal women make it difficult to conclude that CAC is greater in women with PCOS, although further study may be warranted to investigate the menopausal transition.

In summary, subclinical measures of CVD in women with PCOS are more abnormal than in control subjects but may be mediated in part by insulin resistance, obesity, or dyslipidemia. These results must also be viewed cautiously because these measurements have technique- and reader-dependent issues in reliability, have not been validated to predict outcomes specifically in PCOS, and are not recommended clinically for cardiovascular risk assessment in asymptomatic individuals.[162]

GDM and Cardiovascular Risk

GDM is associated with a substantial risk of developing DM later in life.[163,164] In 2011, GDM, along with preeclampsia, was classified as a major risk factor for CVD in women.[165] However, very limited data on the relationship of GDM and subsequent risk of CVD are available. It is unclear whether this risk occurs apart from a diagnosis of postpartum glucose intolerance and DM. In a retrospective study, women with a history of GDM were more likely to experience cardiovascular events and to experience them at earlier ages than women without a history of GDM.[164] However, these women conceived in approximately the 1970s, before the era of universal screening, and it is possible that recall bias or selective

screening affected risk estimates. Moreover, the subjects in the cohort examined had 2 affected family members with DM and therefore were at particularly high risk for DM, and it is unclear whether women with GDM actually had previously unrecognized preconception DM. Other reports have noted that GDM is associated with increased risk of cardiovascular events and hospitalizations for CVD, although DM was not adjusted for in 1 report[166] and the association between GDM and cardiovascular event risk was attenuated by adjustment for DM in the other report.[163] In a Swedish study using health registry data, women with a history of GDM had an OR of 1.51 (95% CI, 1.07–2.14) for CVD, although analyses were not adjusted for intercurrent DM.[167] Administrative data from Ontario, Canada, show that women with GDM are at increased risk of CVD, even after adjustment for subsequent DM.[163]

There are several potential mediators of the association between GDM and CVD events in addition to DM, although they were not examined in the above reports. Compared with women with healthy pregnancies, women with histories of GDM more commonly have cardiovascular risk factors, including hypertension[164,168–171] and unfavorable changes in HDL-C and triglyceride levels.[168–173] Women with histories of GDM had greater vascular resistance, lower stroke volume, lower cardiac output,[174] and greater intima-media thickness compared with women without histories of GDM.[175] Small cross-sectional studies conflict as to whether flow-mediated dilation is impaired among women with a history of GDM.[176]

The Risk for Developing DM After GDM in Women With PCOS

DM is considered a cardiovascular risk equivalent in women and men, an end point that significantly increases cardiovascular risk, particularly in premenopausal women.[177–179] Although the prevalence of DM is greater in women with PCOS than in control subjects, few studies have prospectively followed up a PCOS cohort with an appropriate control group from the same sample. Studies report ORs for the development of DM to be ≈2, although most are not statistically significant because of small sample sizes and because control groups were not matched for family history or BMI.[180–183] Therefore, although a higher prevalence of impaired glucose tolerance and DM in PCOS is well established, few studies can demonstrate a significant increase in the incidence or conversion of impaired glucose tolerance to DM without larger samples or adequately matched control groups.[184] In comparison, it is better established in GDM that there is at least a 7-fold increased risk for developing DM.[185] The risk for developing DM after GDM in women with PCOS is associated with a lower OR of 2 to 3.[186,187] However, significant result differences relate to retrospective versus prospective study design and the baseline risk of the control group.[187]

The Influence of Sex Hormones on Cardiovascular Risk in PCOS and GDM

Studies of subclinical measurements of CVD present an opportunity to assess the influence of sex steroids on vascular disease, in particular to assess changes with interventions. In PCOS, the association of androgens with peripheral vascular dysfunction is variable. In 2 studies, there was no association,[151,188] whereas other studies reported significant associations of testosterone with endothelial dysfunction.[153,154,189] In contrast, an inverse association of the adrenal androgen dehydroepiandrosterone sulfate has been seen with carotid intima-media thickness in PCOS.[145,152] Multiple intervention studies have shown that therapy that increases insulin sensitivity can improve endothelial function[190,191] more than oral contraceptives[192] and in combination with oral contraceptives.[193] However, metformin treatment may have direct and indirect effects on vascular function beyond insulin sensitivity.[190] Trying to attribute changes in vascular function to sex steroids with current data is difficult because oral contraceptive estrogen dose and varying progesterone components may be associated with worsening insulin resistance[192,194] and because oral contraceptives affect lipids and inflammatory markers.[192] Another confounding factor that may be mediated through changing androgens is the change in estrogen concentrations mediated through conversion of androgens by aromatase or through an increase in ovulatory cycles. Studies using spironolactone, a competitive inhibitor of the androgen receptor, have demonstrated improvement in flow-mediated dilation, but the effect may be related to aldosterone antagonism and changes in lipids.[195] Flutamide could better delineate effects specifically mediated by the androgen receptor, but this has not been studied in PCOS in association with measurements of subclinical CVD. Studies have not looked at the influence of sex steroid hormone concentrations during pregnancy on subclinical measurements of CVD in GDM. Lower sex hormone–binding globulin, which may be associated with higher androgens and lower estrogens, has been implicated as a risk factor for GDM, but it may also indicate greater insulin resistance.[196,197]

To summarize, although PCOS and GDM are associated with cardiovascular risk factors and a higher risk for DM, the evidence for cardiovascular events and mortality is less established, in part as a result of limitations in prospectively collected data. Well-characterized longitudinal cohorts are needed to better determine cardiovascular risk and predictors for cardiovascular risk. Without a clear signal of increased risk in women with PCOS and GDM, androgen excess and impaired glucose metabolism during pregnancy cannot be considered sufficient or irreversible risk factors for CVD.

Sex Differences in Pharmacotherapy in T2DM

In general, the clinical assumption has been that women and men with DM and the concomitant CVD risk should be treated with the use of similar treatment algorithms in terms of management with statins, angiotensin-converting enzyme inhibitors, and β-blockers. Consistent across the literature is the observation that women are less consistently prescribed these agents.[198–201] In some but not all studies, lower medication adherence was observed in women than men.[200,202–204] Fewer women are represented in the combined data sets evaluating primary and secondary interventions with statins.[205,206] Despite that and given some conflicts in the data as to whether the impact of the effect is the same, expert opinion, supported by evidence, indicates that statins effectively lower cardiovascular risk for both women and men. Statins should be used in subjects with moderate or high CVD risk according to both new

American Heart Association/American College of Cardiology guidelines and the Framingham risk calculator.[207] Of note, many more women will qualify for treatment with statins according to the newer guidelines, which state that all individuals (regardless of sex) >40 years of age with DM should be treated. Similarly, for heart failure, women are underrepresented in the studies that demonstrate beneficial effects of angiotensin-converting enzyme inhibitors, β-blockers, and spironolactone. The guidelines, based on expert opinion and not refuted by the existing data, support the use of these agents in appropriate patients regardless of sex.[207] For heart failure specifically, new data from the Swedish Heart Failure Registry may further clarify differential response to drug treatment and heart failure between men and women with DM.[207a]

Statins have revolutionized the treatment of cardiovascular risk and should be used in women at high risk for CVD.[207] There are conflicting data as to whether the impact of statins is similar in men and women. In the 2010 report of the Cholesterol Treatment Trialists' Collaboration (a meta-analysis of data from 170 000 participants in 26 randomized trials), people with DM had a 20% reduction in risk overall across primary and secondary prevention trials. Women (n=2625) had a 17% reduction (RR= 0.83; 95% CI, 0.76–0.90) compared with men (n=10 765) who had a 23% reduction (RR=0.77; 95% CI, 0.74–0.80), a significant interaction by sex (P=0.04).[208] The conclusion from this study was that there is a clear benefit for secondary prevention with statins in both women and men. In contrast, the evidence for primary prevention of CVD with statins in women is less marked; the summary estimate of benefit was smaller than that observed in the individual trials, which also examined individuals over short periods of time. Despite that, it is reasonable, on the basis of expert opinion and the cholesterol theory of atheroma progression, to use statins for primary prevention in women at high risk for CVD. Coronary atheroma burden was demonstrated to be less in women than in men in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) study, and atheroma regression by coronary ultrasound and low-density lipoprotein lowering was greater in women treated with statins than in men.[209]

Although not shown conclusively, it has been postulated that women with DM may have their CVD risk factors treated less aggressively than men with DM. In a multicenter cohort of managed care enrollees, women were more likely to have low-density lipoprotein levels <3.35 mmol/L (<130 mg/dL) and less likely to receive intensive lipid-lowering therapy than men.[210] This disparity has been documented in other health systems[56] and in other countries,[6] suggesting that disparities in the management of lipid-lowering therapy may contribute to CVD disparities among individuals with DM.

Statin-induced DM was first highlighted in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial in which statins increased the risk of DM (25%) but decreased the risk of composite cardiovascular events (44%). Composite data were reviewed to evaluate the incidence of DM across 13 trials with 91 140 participants.[211] There was only a 9% increased risk for new DM (OR, 1.09; 95% CI, 1.02–1.17) or 1 in 255 probability of incident DM per 4 years of statin use; in contrast, the decreased risk of a cardiovascular event was 5.4 in 255 per 4 years of statin use.[212,213] Expert opinion suggests that patients at high risk for the development of DM who are treated with statins should be monitored for DM development, but statin avoidance is not recommended. In a recent review on this topic, there was a suggestion that women had a greater likelihood of developing DM on statins.[212] Myalgia is a side effect of statin therapy that often limits tolerability. In a Brazilian cohort study, baseline and 6-month data were evaluated for 495 patients (331 women and 164 men) treated with simvastatin/atorvastatin. Myalgia occurred more frequently in women compared with men (25.9% versus 9.0%; P=0.002), whereas an increase in creatine phosphokinase or abnormal liver function was more frequent in men compared with women (17.9% versus 7.6%; P=0.017),[214] suggesting the potential for dimorphism in side effects. This difference has not been commented on in larger prospective studies.

The effect of fenofibrate on lipids and CVD in women with T2DM was evaluated in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Women (n=3657) and men (n=6138) with T2DM used fenofibrate for 5 years. Fenofibrate reduced a complex predetermined cardiovascular end point by 30% in women (95% CI, 8–46; P=0.008) and 13% in men (95% CI, −1 to 24; P=0.07) with no treatment-by-sex interaction. It also had a greater impact on lipid lowering in women.[215]

In women, hormone replacement therapy significantly reduces CHD (RR=0.68; 95% CI, 0.48–0.96) and mortality (RR=0.61; 95% CI, 0.39–0.95) in primary prevention when it is initiated in women who are <60 years of age or are <10 years since menopause.[216]

Aspirin Therapy: Sex Differences in Recommendations for Aspirin Therapy

The use of aspirin therapy to prevent CVD events in women with DM is uncertain. The Antithrombotic Trialists' (ATT) Collaboration demonstrated a reduction in vascular events for the secondary prevention of myocardial infarction[217] and for nonfatal myocardial infarction in primary prevention trials.[217] In a large primary prevention trial of women, aspirin (100 mg every other day versus placebo) was associated with a lower risk of stroke but not myocardial infarction or CVD death.[218]

Three trials have examined aspirin use among patients with DM. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial was a primary prevention trial that randomized patients with DM and PAD to daily aspirin (100 mg) either with or without antioxidant tablets and found that neither aspirin nor antioxidant therapy reduced either of the prespecified composite CVD end points.[219] In a sex-stratified prespecified subgroup, there was no sex difference (P=0.68), although the HR for men was stronger (HR, 1.33 versus 1.09). The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial tested the efficacy of low-dose aspirin (81 or 100 mg/d) in patients with T2DM without prior CVD. The composite end point showed no difference (HR=0.80; 95% CI, 0.58–1.10; P=0.16).[220] Finally, the Early Treatment Diabetic Retinopathy Study Report 14 (ETDRS) randomized patients with T1DM or

T2DM to aspirin (two 325-mg tablets a day versus placebo). Similar to the other 2 studies in patients with DM, there was no overall benefit in the treatment group, and results were slightly stronger in men compared with women.[221] Finally, in the DM subgroup of the Women's Health Study, women with DM who received aspirin had a lower risk of stroke and ischemic stroke compared with those without DM, although these were secondary end points.[218]

There have been several meta-analyses of aspirin use in DM; most did not show a benefit for aspirin treatment in DM for primary CVD prevention,[217,222–226] although there was a stronger signal for secondary prevention.[222] In addition, the HR between studies in individuals with and without DM was largely similar,[217,223] suggesting that power may be a factor in studies that have focused exclusively on patients with DM. Sex differences may be important. One large meta-analysis showed that aspirin reduced the risk of myocardial infarction in men with DM (HR=0.57; 95% CI, 0.34–0.94) but not women (HR=1.08; 95% CI, 0.71–1.65; *P* for interaction=0.056).[226] Another meta-analysis in DM demonstrated that participants in studies made up of ≥50% men had a lower risk of myocardial infarction when treated with aspirin (HR=0.71; 95% CI, 0.5–1.0; *P*=0.05) compared with participants in studies with <50% men (HR=1.10; 95% CI, 0.75–1.62; *P*=0.61).[224]

Taken together, these data highlight that the benefit of aspirin for primary prevention of CVD in women with DM is far from conclusive. Based on this evidence, a 2010 consensus document written by the American Heart Association, the American College of Cardiology Foundation, and the American Diabetes Association makes the following recommendations for adults with DM and without pre-existing CVD[227]:

- Low-dose aspirin (75–162 mg/d) should be considered for individuals with a 10-year risk of CVD of at least 10% who do not have an increased risk of bleeding; this group consists of men at least 50 years of age and women at least 60 years of age with at least 1 additional CVD risk factor.
- Aspirin should not be recommended for adults with DM at low risk (men <50 years of age and women <60 years of age with no additional CVD risk factors).

The recommendation is to consider low-dose aspirin in adults with DM at intermediate risk (10-year CVD risk, 5%–10%).

Use of Medications During Pregnancies Complicated by T2DM

Oral Hypoglycemic Therapies

During pregnancy, insulin is the mainstay of hypoglycemic therapy for women with T2DM. The American Diabetes Association consensus statement advises that insulin be used even among women previously controlled on oral hypoglycemic therapy[228] on the basis of concerns about adequate glycemic control and fetal safety. The statement acknowledges that observational studies have not found that glyburide or metformin is harmful to mother or fetus but rather that randomized trials comparing these agents directly with insulin therapy among pregnant women with T2DM are lacking. Safety and efficacy data on thiazolidinediones, metglitinides, and incretins are lacking with regard to pregnancy, and their use is currently not supported.

Among women with mild GDM, randomization to glyburide versus insulin yielded equivalent glycemic control and fetal harm.[229] Similar randomized trials in women with T2DM before conception, who generally have higher glucose levels, do not exist. Observational studies among these women have suggested that glyburide is not associated with adverse events, possibly because transplacental passage for this particular sulfonylurea is low.[230] Among women with GDM, randomization to metformin, with supplemental insulin as needed for glycemic control, versus insulin yielded similar neonatal outcomes and had a similar safety profile.[231] Results from randomized trials among women with T2DM before conception do not exist, although such a trial is currently in progress in Canada.[232] Observational studies among women with PCOS who were treated with metformin in the first trimester have not reported major fetal malformations,[233] and the British National Institute for Health and Clinical Excellence endorses metformin use among women with T2DM before conception for these reasons.[234]

Statins

Discontinuation of statin therapy before conception is currently recommended on the basis of surveillance reports that noted malformations in several infants exposed to lipophilic statins (simvastatin, lovastatin, atorvastatin, cerivastatin) in the first trimester, although no malformations were observed in the 14 infants exposed to hydrophilic pravastatin.[235] The magnitude of risk is likely to be small.[236] Of note, the National Institutes of Health is currently sponsoring a trial of pravastatin during pregnancy for preeclampsia prevention.[237]

Antihypertensive Therapy

All antihypertensive agents cross the placenta. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and direct renin inhibitors are associated with fetal cardiac abnormalities with first trimester exposure and renal abnormalities with exposure in the latter half of pregnancy.[238] In a systematic review of case series and case reports, approximately half of infants continued to have poor outcomes in the years after birth.[238] Although data are not available from randomized studies, the availability of other antihypertensive agents suggests that pregnant women should discontinue angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. If it is necessary to initiate another agent, methyldopa, hydralazine, and long-acting calcium channel blockers have not been reported to increase fetal malformations.[239] Of the β-blockers, labetalol has been the most studied and is thought to be safe for the fetus, although as a class β-blockers may slightly increase the risk of specific fetal malformations.[240] Although volume reduction with thiazides has been thought to be potentially harmful to the fetus, women using these agents before pregnancy are unlikely to have major volume shifts resulting from this drug during pregnancy and thus could potentially be continued on thiazides during pregnancy.[241]

Sex Differences in the Effectiveness of Lifestyle Treatments on the Cardiovascular Consequences of DM

For adults with DM, lifestyle measures that optimize dietary quality and physical activity level are a cornerstone of treatment.[242] Improvements in dietary quality, physical activity levels, and weight loss can improve cardiovascular and metabolic factors that have been linked to cardiovascular morbidity and mortality such as blood pressure, dyslipidemia, cardiorespiratory fitness, and insulin resistance/glycemic control.[243–250] It is important to examine whether the effectiveness of lifestyle treatments in DM differs by sex.

There are very limited data, particularly from randomized, controlled trials (RCTs), to enable a determination of whether effects of lifestyle treatments differ by sex in populations with DM.[251–256] Thus, to consider whether sex differences exist in the effects of lifestyle treatments, we expanded the scope of our review to include, in addition to adults with T2DM and T1DM, adults with prediabetes because they are also metabolically at risk for cardiovascular events. We also considered cardiovascular outcomes broadly to include cardiovascular mortality; cardiovascular events of myocardial infarction or stroke; traditional cardiovascular risk factors of blood pressure and dyslipidemia; and biomarkers associated with the development of CVD such as central adiposity (waist-to-hip ratio), cardiorespiratory fitness, endothelial dysfunction, and inflammatory measures. Because of our focus on treatment effects, we excluded cross-sectional studies. We present our findings by strength of evidence, beginning with RCTs followed by observational studies.

Meta-Analysis/RCT Data

Cardiovascular Events/Mortality

Very few RCTs of lifestyle interventions have reported on mortality outcomes, owing in part to the need for long-term follow-up to provide adequate statistical power to detect mortality differences. To the best of our knowledge, to date there is only 1 RCT of insulin-resistant adults, the Da Qing Diabetes Prevention Study, which demonstrated improved mortality from a lifestyle intervention. In the Da Qing study of Chinese adults with prediabetes, sex differences in cardiovascular mortality benefits of the lifestyle intervention favored women (women: HR=0.28; 95% CI, 0.11–0.71; P=0.01; men: HR=0.91; 95% CI, 0.50–1.65; P=0.7). Interaction effects for sex and intervention remained marginally significant for CVD mortality (P=0.06).[256] In this study, participants with prediabetes were randomized to a lifestyle intervention or to a control arm in a 3:1 ratio; intervention participants were randomized to an intervention of a weight-loss diet, regular physical activity, or a weight-loss diet plus physical activity. For individuals with a normal BMI randomized to a dietary intervention in the Da Qing study, the goal was to improve dietary quality by "reducing simple carbohydrate and alcohol intake" rather than targeting weight loss. A limitation of the Da Qing study was a higher rate of smoking in men versus women (61% versus 16%), which may have blunted the intervention effects on mortality in men. The Da Qing study provides a rare opportunity to identify the cardiovascular benefits of lifestyle treatments in an RCT with long-term follow-up of >2 decades. The long-term follow-up of this study was particularly important because group differences in cardiovascular mortality did not emerge until 12 years of follow-up were complete, and these differences became statistically significant only after 23 years of follow-up.

Even when lifestyle interventions improved cardiovascular event rates, RCTs have not reported sex differences in these cardiovascular event outcomes in adults with T2DM. The Japan Diabetes Complications study demonstrated a reduction in stroke among 2033 older adults with T2DM randomized to a combined lifestyle counseling intervention versus usual care. The combined lifestyle intervention targeted medication adherence, weight loss to a goal BMI <22 kg/m^2, and physical activity promotion. No significant sex differences in stroke outcomes were observed (HR=0.68; 95% CI, 0.42–1.11) for women versus men in a Cox multivariate model adjusted for age, systolic blood pressure, and dyslipidemia.[251] The Action for Health in Diabetes (Look AHEAD) trial studied a combined lifestyle intervention of behavioral counseling to lose weight by reducing total calorie and dietary fat intake and by achieving physical activity goals of at least 175 minutes of weekly moderate- to vigorous-intensity physical activity. In the Look AHEAD trial, there was no significant effect of the combined lifestyle intervention on the primary outcome of cardiovascular mortality/major cardiovascular events. In addition, there were no sex differences in the intervention effects (male subjects: HR=0.93; 95% CI, 0.78–1.11; female subjects: HR=0.97; 95% CI, 0.79–1.20; P=0.73 for interaction by sex).[252] One limitation of the Look AHEAD trial was the exclusion of subjects who were unable to complete a valid maximal exercise test.[252]

Biomarkers Associated With CVD: Fitness

Fitness levels are strongly linked to short- and long-term mortality in middle-aged and older adults with and without DM, so fitness is an important cardiovascular biomarker in people with DM.[257–260] Data on improvements in fitness outcomes after physical activity interventions do not clearly reveal whether sex differences exist. The Look AHEAD study showed greater improvements in cardiorespiratory fitness for men compared with women at both the 1- and 4-year follow-up, even with adjustment for baseline fitness levels.[243,261] In contrast, both women and men with T2DM appeared to have similar improvements in fitness in response to exercise training interventions in the Diabetes Aerobic and Resistance Exercise trial[253] and in a meta-analysis of physical activity interventions among people with T2DM.[262]

Biomarkers Associated With CVD: Glycemic Control

Sex differences in the effect of lifestyle treatments on glycemic biomarkers may be present in people with T1DM, and data are mixed on the presence of sex differences in people with T2DM and prediabetes. In a meta-analysis of patients with T1DM, a higher percentage of women in a "lifestyle treatment" study that included physical activity were associated with a greater improvement in HbA_{1c}.[263] In people with T2DM, a meta-analysis noted the opposite effect: Women were less likely than men to show improvement in HbA_{1c} in a meta-analysis of people treated with an intervention that included physical activity counseling or supervised physical activity.[264] However, 3 other meta-analyses of the effects of exercise or weight loss on glycemic control in adults with T2DM did not

report sex difference data, so it is uncertain whether sex differences were present.[246,265,266] In a sensitivity analysis of the Diabetes Prevention Program RCT, which included only intervention participants who lost 3% to 7% of their weight, men improved more than women with regard to 2-hour postprandial glucose ($P<0.01$) and insulin resistance ($P<0.03$).[255] Although this finding suggests that the metabolic benefits of achieving weight loss goals for people with prediabetes may be superior for men than for women, lifestyle interventions appear to benefit women and men similarly in terms of both weight-loss outcomes and incidence rates for T2DM.[254,256] Specifically, in the Finnish National Diabetes Prevention Program study, which randomized primary care adults with prediabetes (n=2798) to a weight-loss diet and physical activity lifestyle intervention versus control, mean weight loss was similar by sex (men, −1.3 kg; women, −1.1 kg).[254] In addition, 2 large studies of participants with prediabetes showed no sex differences in the incidence rates of T2DM resulting from a combined weight-loss diet and physical activity lifestyle intervention.[254,256]

Observational Cohort or Case-Control Studies

Mortality

In observational studies of people with T2DM, some sex differences in mortality responses to lifestyle behaviors have been observed that favor men over women. In a cohort study of Finnish people with T2DM and their family members, abdominal adiposity was more strongly associated with cardiovascular mortality in women (HR=18.8; 95% CI, 3.2–111.4) compared with men (HR= 3.7; 95% CI, 0.2–73.1).[267] Although there were 4654 participants in this study, wide CIs suggest heterogeneity in the influence of abdominal adiposity on cardiovascular mortality. Interestingly, BMI was not significantly associated with cardiovascular mortality in either sex.[267] Although the effects of abdominal adiposity treatments were not assessed in this Finnish cohort, the study demonstrates that abdominal adiposity appears more hazardous in women than in men. It also demonstrated that men with DM (predominantly T2DM) had greater benefits of intermediate amounts of walking on all-cause mortality than women with DM ($P=0.037$ for interaction by sex between walking and all-cause mortality). Mortality rates for men declined significantly with walking across 3 tertiles (for the highest tertile: HR=0.61; 95% CI, 0.46–0.81; for the middle tertile: HR=0.75; 95% CI, 0.58–0.97; for the lowest tertile: HR=1.0 [reference]).[268] In contrast, mortality was significantly better only for women in the highest tertile of walking (HR=0.54; 95% CI, 0.38–0.78) compared with the lowest tertile (reference HR=1.0).[268]

Cardiovascular Events

Data from 2 large observational studies support sex differences in the effects of lifestyle habits on cardiovascular events in people with T1DM. In the European Diabetes (EURODIAB) Prospective Complications Study of 1415 people with T1DM, the benefits of mild or vigorous intensity weekly physical activity on preventing the development of a biomarker of cardiovascular disease[269,270] were significant only in men (mild activity: adjusted OR=0.27; 95% CI, 0.10–0.76; vigorous activity: adjusted OR=0.38; 95% CI, 0.14–0.99), not in women (mild activity: adjusted OR=0.74; 95% CI, 0.28–1.96; vigorous activity: adjusted OR=0.54; 95% CI, 0.19–1.49).[271] No test for effect modification by sex was reported. In the Pittsburgh Epidemiology of Diabetes Complications Study of participants with T1DM, the standard cardiovascular risk factors of age, blood pressure, smoking, and ratio of total cholesterol to HDL-C were found to poorly predict rates of incident CHD.[272] Thus, the investigators looked for other measures that predicted incident CHD. In women only, measures of abdominal adiposity, insulin resistance, and HbA_{1c} predicted incident CHD; in both women and men, inflammatory markers (fibrinogen and white blood cell count) and microalbuminuria predicted incident CHD.[272] Although lifestyle treatments were not incorporated into this CHD predictive model, there were sex differences in measures that are responsive to lifestyle change, including abdominal adiposity, insulin resistance, and glycemic control.[243–250]

We are unaware of sex difference data for physical activity treatments on cardiovascular events in observational studies of people with T2DM, but physical activity was associated with lower cardiovascular event rates in the Nurses' Health Study cohort of women with T2DM.[273] In this study, women who performed moderate to vigorous physical activity for at least 2 compared with <1 h/wk had lower cardiovascular event rates of combined CHD and stroke.[273] Greater frequency of walking activity was also associated with lower cardiovascular event rates in the same study.[273]

Summary

To determine improvements in cardiovascular events and mortality requires long-term follow-up, and the limited data available suggest that lifestyle interventions may improve cardiovascular mortality more in women with prediabetes than their male counterparts.[256] There are also suggestions that abdominal adiposity and insulin resistance may be stronger predictors of cardiovascular events in both women with prediabetes and women with T1DM.[267,272] Because insulin resistance and abdominal adiposity were predictive of cardiovascular events in women with prediabetes, it is possible that the beneficial effects of lifestyle interventions to improve insulin resistance and abdominal adiposity may be one reason that the Da Qing intervention was more successful in women with prediabetes than in men. Observational studies suggest that women with DM may require greater frequency and intensity of physical activity than their male counterparts to reduce cardiovascular events. From a practical standpoint, at least 2 h/wk of activity was associated with lower cardiovascular events for women with T2DM in the Nurses' Health Study cohort,[273] and this finding is consistent with the US physical activity guidelines and the joint American Diabetes Association/American College of Sports Medicine guidelines for people with DM, which recommend at least 150 minutes of weekly physical activity for all adults.[274,275]

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*Modest.

†Significant.

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*Modest.

†Significant.

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