

In Brief

The increased risk for coronary heart disease in women with either type 1 or type 2 diabetes has been well documented. Interventions directed towards primary, secondary, and tertiary prevention should be promptly implemented in these women to improve long-term outcomes.

Coronary Heart Disease in Women With Diabetes

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More than 8 million women in the United States have diabetes.¹ Approximately 10% have type 1 diabetes, which is characterized by insulin deficiency and an absolute requirement for exogenous insulin. The remaining 90% have type 2 diabetes, which is characterized by defects in insulin secretion and sensitivity. Regardless of the pathophysiological defect causing hyperglycemia, there is a growing appreciation of the acceleration in risk for coronary heart disease (CHD) in women with any form of diabetes. In fact, diabetes erases any protective female advantage in regard to CHD, which is the number one cause of death for diabetic men and women.²

This review summarizes prevalence data for CHD in women with diabetes and risk factors as they pertain to women, presents a proposed rationale for the impact of diabetes on CHD risk, and discusses primary, secondary, and tertiary preventive strategies directed toward modification of these risk factors. A discussion on the use of postmenopausal hormone replacement therapy (HRT) is also included.

Prevalence of CHD in Women With Diabetes

The Framingham study first reported in 1979 that men and women with diabetes had a similar risk for CHD.² This represented a doubling of overall

risk compared to men without diabetes and a fivefold increase for women. Since this report, the increase in CHD risk in women with diabetes has been confirmed in other epidemiological studies.² In fact, there is concern that, with the alarming increase in prevalence of diabetes, the prevalence of CHD mortality is also increasing, particularly for women. While a decline in CHD mortality of 36 and 27% was recently reported among nondiabetic men and women, respectively, a decline of only 13% was observed in men with diabetes and, more alarmingly, an increase of 23% was observed in women with diabetes.³

Women with diabetes not only are at greater risk for CHD, but also experience more adverse outcomes following a vascular event. Following a myocardial infarction (MI), both early (28-day) (22 vs. 14%) and late (2-year) (28.9 vs. 19.6%) mortality is greater in women than in men with diabetes.^{4,5}

This increase in CHD morbidity and mortality in women is observed at the time of diagnosis of diabetes, as well as in normoglycemic women who develop diabetes at a later date, suggesting both a delay in the diagnosis of dysglycemia (i.e., blood glucose levels that do not meet criteria for diagnosis of diabetes or impaired glucose tolerance [IGT]) but trend toward the

higher range) as well as the presence of prior contributing risk factors.⁶ For women with or at risk for type 2 diabetes, as well as for many with type 1 diabetes, abnormalities in glucose tolerance serve as one manifestation of Syndrome X, or the insulin resistance syndrome, which includes dyslipidemia, hypertension, and central obesity. These disorders, taken together, are associated with an increased risk for cardiovascular disease (CVD). The prevalence of the insulin resistance syndrome is estimated to be ~24% of the total adult population but increases with increasing plasma glucose concentrations.⁷ These metabolic abnormalities may affect women to a greater extent than men, as will be discussed below.

Risk Factors for CHD in Women With Diabetes

Several potential interacting factors may contribute to the acceleration of CHD risk in women with diabetes. These include a greater tendency to poor glycemic control, more severe elevations in blood pressure and circulating lipids, the development of central obesity, higher rates of depression, and low socioeconomic status.

Although there are no definitive data demonstrating higher levels of hemoglobin A_{1c} (A1C) in women, wide fluctuations in glucose independent of A1C have been proposed as a contributor to the development of both microvascular and macrovascular disease.⁸ In women, factors that can influence stability of glycemic control over time include a higher frequency of eating disorders, use of hormonal contraception, menstrual variability in glucose control and insulin sensitivity, pregnancy, and variability in glucose control through perimenopause.

The term "dyslipidemia" is used to describe the lipid abnormalities associated with the insulin resistance syndrome. These abnormalities include elevated triglycerides, low HDL cholesterol, and small, dense, atherogenic LDL cholesterol particles. High triglycerides and low HDL have a greater adverse impact on risk for vascular disease in women.⁹ Measurement of the non-HDL cholesterol, which indirectly accounts for this triad of lipid abnormalities, is emerging as the most significant predictor of CHD risk in both women and men with diabetes.⁹ This measurement is calculated by subtracting the HDL from the total cholesterol

and is recommended as a secondary target for lipid-lowering therapy once LDL cholesterol is at goal level.

Diabetes is more likely to be associated with elevations in both systolic and diastolic blood pressure in women than in men. This is independent of age, obesity, body fat distribution, and fasting insulin.¹⁰ Together with hyperglycemia, hypertension predisposes to the development of microalbuminuria and proteinuria, which in turn further aggravate the risk for vascular complications.

The majority of women with type 2 diabetes in the United States are obese. Weight gain, even of a modest degree, increases the risk for type 2 diabetes and CHD in women. A waist-to-hip ratio > 0.76 is associated with a more adverse metabolic risk profile than are peripheral or gynecoid obesity.¹¹

Other factors contributing to the increase in CHD risk include cigarette smoking, which is the single most potent risk factor for atherosclerosis. Women with diabetes are more likely to be of low socioeconomic status than are those without diabetes. This, together with a higher prevalence of depression among women with diabetes, may contribute to a decrease in self-care practices that target metabolic indices of glucose, blood pressure, and lipid control, as well as weight loss practices.¹²

Primary Prevention of CHD by Primary Prevention or Early Diagnosis of Diabetes

The first rule of any prevention strategy is the identification of individuals who are at high risk for a disease. Because diabetes is now identified as the equivalent to established CHD, emphasis should be placed on the identification of women who have abnormalities of glucose metabolism. Currently, ~30% of women with diabetes are unaware of this fact. The American Diabetes Association (ADA) recommends that all women above the age of 45 years be screened with a fasting glucose test every 3 years. Individuals at high risk, including those with a history of gestational diabetes, obesity, a family history of diabetes, or who are members of racial/ethnic groups for which prevalence rates are high, should be screened both more frequently and at an earlier age.

A group often overlooked as being at high risk for type 2 diabetes is that composed of young women with

irregular menses, acne and hirsutism, or infertility. These clinical findings suggest a diagnosis of polycystic ovary syndrome, which affects ~5% of premenopausal women, 20% of whom have either impaired and overtly abnormal glucose tolerance.¹³ Approximately 40% of these young women are obese, with their young age of presentation providing an opportunity to address not only the gynecological aspects of this disorder, but also the potential metabolic consequences.

A woman with or at risk for diabetes is also at risk for CHD. Therefore, an important issue in primary prevention is the avoidance of hyperglycemia. The Diabetes Prevention Program (DPP) recently identified the effectiveness of an intensive lifestyle intervention consisting of a program of moderate exercise in combination with diet modifications targeted to achieve a 7% weight loss, in reducing the rate of progression to type 2 diabetes in women with IGT. Metformin was also effective, although to a lesser degree, in women with a body mass index (BMI) > 35 kg/m².¹⁴ The DPP thus gives additional scientific support to the efforts of both health care providers and communities to encourage practices that reduce sedentary behavior, the ingestion of fat calories, and, ultimately, obesity.

Exercise. Institution of a regular program of aerobic exercise can help to promote weight loss, improve insulin sensitivity, lower blood pressure, and raise HDL cholesterol. Current recommendations suggest 30 minutes of moderate physical activity several days a week. Multiple short (10-minute) bouts of exercise in the form of brisk walking produces similar changes in cardiorespiratory fitness and weight loss to that achieved with regimens involving longer, less frequent intervals.¹⁵ In the face of end-organ complications, such as neuropathy or established vascular disease, exercise prescriptions require modification but not elimination.

Aspirin therapy. Based on results of two prospective clinical trials demonstrating significant reductions in CHD events with aspirin therapy in the presence of diabetes, the ADA recommends the use of aspirin in the primary prevention of CHD events for all women > 30 years of age who have diabetes and one of the following risk factors: family history of CHD, cigarette smoking, hypertension, overweight (BMI > 27.3 kg/m²), microal-

buminuria or proteinuria, cholesterol > 200 mg/dl, LDL cholesterol > 100 mg/dl, HDL cholesterol < 55 mg/dl, or triglycerides > 200 mg/dl. The dose of aspirin used can vary between 75 and 325 mg/day. Many physicians recommend a dose of 81 mg/day because this is readily available in stores, effective in inhibiting thromboxane synthesis, and carries a lower risk of gastrointestinal bleeding than do higher doses. In patients with a contraindication to aspirin therapy, antiplatelet therapy with clopidogrel can be considered.¹⁶

In summary, identification of women with risk factors warranting interventions directed toward primary prevention of both diabetes and CHD is relatively straightforward. A careful medical history with attention to menstrual history and family history of diabetes or CHD, together with measurement of BMI, waist and hip circumference, and blood pressure is effective in identifying high-risk individuals for whom intervention is recommended.

Secondary Prevention of CHD in Women With Diabetes

Once a woman is diagnosed with diabetes, her medical management becomes similar to that for a woman with established CHD. Modification of these strategies is essential in young women who are anticipating pregnancy or in those without any additional risk factors. Recommended secondary prevention strategies include attention to glycemic, blood pressure, and lipid control, together with use of aspirin.¹⁶

Glycemic control. The ADA recommends an A1C of < 7% for the majority of individuals with diabetes. This recommendation is based on results of the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study (UKPDS), which demonstrated reductions in risk for microvascular and macrovascular complications at this level of glycemic control.^{17,18} In regard to CHD, an epidemiological analysis of data from the UKPDS revealed a 14% reduction in risk for CHD for each 1% reduction in A1C. In women, an independent association has been described between A1C and prevalence of CHD, further supporting ADA recommendations for glycemic control.¹⁹ A reduction in total calories and fat calories, an increase in fiber consumption, and regular spacing of meals, together with a regular exercise program, can help women achieve

these glycemic goals. If the target A1C cannot be achieved with nonpharmacological therapy, then the use of oral medications or insulin is required.

Hypertension. Antihypertensive therapy with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) is initiated for individuals with diabetes with a persistent blood pressure >130/80 mmHg or microalbuminuria. The Micro-HOPE trial demonstrated the efficacy of the ACE inhibitor ramipril in reducing risk for MI (22%), stroke (33%), cardiovascular death (37%), total mortality (24%), and revascularization (17%) in individuals with diabetes >55 years of age with one other CHD risk factor.²⁰ This prompted the recommendation that ACE inhibitors be prescribed for this group of individuals independent of blood pressure or albuminuria. If an ACE inhibitor is not tolerated, an ARB can be substituted.¹⁶

Women of childbearing age who are not using contraception should not receive an ACE inhibitor or ARB because of known harmful effects to developing fetuses. Women who become pregnant while taking one of these agents should discontinue the agent immediately. There are acceptable options for controlling hypertension and reducing microalbuminuria in women with diabetes that can be used safely during pregnancy. In a small study, the non-dihydropyridine calcium-channel blocker (non-DCCB) diltiazem was demonstrated to have a similar renal protective component to an ACE inhibitor.

As demonstrated in the UKPDS, several antihypertensive agents with different mechanisms of action are frequently required to achieve desired levels of blood pressure control in many individuals with diabetes. An ACE inhibitor or ARB is usually recommended as first-line therapy. β -Blockers have similar efficacy in reducing CHD outcomes in the presence of diabetes as demonstrated in the UKPDS.²¹

In those individuals requiring more than two drugs to control hypertension, data regarding safety and efficacy are more controversial. The use of low doses of thiazide diuretics is acceptable in individuals with diabetes. In one study, doses of 12.5–25 mg/day of chlorthalidone were associated with improved cardiovascular outcomes in a group of elderly men and women with diabetes. Questions

regarding the long-term safety of the dihydropyridine calcium-channel blockers (DCCBs) in diabetes have been raised. An increase in risk for cardiac events with DCCBs and an increase risk for coronary heart failure with use of the α -blocker doxazosin during the ALLHAT trial limits the use of these agents to add-on therapy to an ACE inhibitor or ARB. Use of a non-DCCB such as diltiazem or verapamil can be acceptable alternative first-line agents if patients do not tolerate other recommended therapies.¹⁶

Lipids. Both the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and the ADA recommend an LDL cholesterol < 100 mg/dl as the primary target for any individual with diabetes.^{16,22} Pharmacological therapy is recommended for those individuals with an LDL cholesterol > 130 mg/dl in the absence of CHD and > 100 mg/dl in the presence of CHD. Following this, the non-HDL cholesterol becomes a secondary target, with enhancement of lipid-lowering therapy recommended for a non-HDL cholesterol > 160 mg/dl in the absence of CHD and > 130 mg/dl in the presence of CHD.

Data from several large lipid-lowering trials suggest that women with CHD and those with diabetes are as likely as or more likely than those without diabetes to benefit from lipid-lowering therapy with a statin. Separate subgroup analyses have not been performed for men and women with diabetes.²³ Relative risk reductions of recurrent CHD events ranging from 24 to 34% are reported in women and from 19 to 42% in the presence of diabetes. Variability in results is because of differences in lipid entry criteria among the trials. Prospective trials investigating the efficacy of lowering of non-HDL cholesterol are not currently available.

Smoking. Diabetes and smoking each independently increase risk for a CHD event fourfold in women. Together, the impact may be additive. Therefore, counseling regarding the importance of smoking cessation with the addition of group support and/or pharmacological therapy with bupropion or nicotine patches is recommended.¹⁶ Women who smoke should be strongly urged to stop.

Depression. Lower mood scores and a higher prevalence of depression are reported by women than by men with diabetes. Indeed, depression has been implicated as an independent

risk factor for CHD in women with diabetes. Whether antidepressant medication affects this risk is unknown. However, treating underlying depression with psychotherapy or medication may bring about an improvement in mood that can help women manage complicated medical recommendations for optimal metabolic control.

HRT and CVD in Women With Diabetes

Two recent, randomized, controlled clinical trials comparing HRT with placebo have prompted the recommendation that this form of therapy is of no benefit in either the primary or secondary prevention of CVD. In the Heart and Estrogen/Progestin Replacement Study (HERS), a greater frequency of recurrent CVD events occurred in the group randomized to HRT than in those randomized to placebo during the first year. In the Women's Health Initiative (WHI), an increase in the combined endpoints, which included CVD events, prompted early discontinuation of the study. Based on the results of these two studies, HRT is not recommended for any woman, with or without diabetes, as a therapeutic strategy for primary or secondary prevention of CHD.^{24,25} The mean age of women participating in HERS was 67 years and that of women in WHI was 63 years. It is important to note that the majority of women with diabetes who are considering estrogen replacement therapy (ERT) or HRT in the early postmenopausal period are significantly younger than those who participated in either of these studies.

The chief indication for HRT is for relief of menopausal symptoms, such as hot flashes, vaginal dryness, disordered sleep, and mood disturbances, which occur in some women. Women with diabetes experience physiological and metabolic changes similar to those of women without diabetes as they transition through the perimenopausal to the menopausal state and thus have similar indications and contraindications to the use of postmenopausal ERT and HRT. There is no evidence to suggest that women with diabetes should be denied postmenopausal ERT and HRT, although it is important for these women to be aware of their enhanced risk for CHD and to have appropriate interventions to modify other risk factors, such as hypertension and dyslipidemia. The decision to use these regimens is high-

ly individualized and requires careful discussion and consideration of the potential benefits and risks as they are currently understood.

Confounding clinical decisions regarding the initiation of HRT is a recently published study from HERS in which HRT reduced the incidence of diabetes by 35%.²⁶ However, this observation is insufficient to recommend the use of hormones for prevention of either diabetes or heart disease. Results from the WHI regarding the use of ERT alone in hysterectomized women have not yet been published, and there are no prospective data to guide health care providers in advising in favor of or against this therapy.

Tertiary Prevention of CHD in Women With Diabetes

Although the risk of a CHD event in a person with diabetes but without documented CHD is equivalent to that of a person with established CHD, the risk of a recurrent event in someone with both diabetes and established CHD is increased greater than twofold.²⁷ Aggressive medical therapy with tight glycemic control, blood pressure control, lipid-lowering therapy, and the use of aspirin or another anti-platelet agent should be adjusted to achieve targets described above.

Data from a study of more than 600 people with diabetes (232 women) admitted to the hospital with an acute MI revealed that early institution of intensive insulin therapy improved survival up to 3.4 years following discharge.²⁸ The blood glucose level at admission was observed to be the strongest predictor of a fatal outcome, supporting the need for glycemic control in the outpatient as well as the inpatient area.

β -Blockers improve long-term survival and decrease the risk of a recurrent MI in individuals with and with-

out diabetes.²⁹ In a large review of more than 200,000 high-risk individuals (including 92,000 women and 60,000 people with diabetes), a 36% reduction in mortality was observed at 2 years post-MI among subjects with diabetes who were prescribed β -blockers.

Until recently, many physicians have been reluctant to prescribe β -blockers in the presence of diabetes because of concerns regarding the risk of severe hypoglycemia. An increased incidence of hypoglycemic episodes was not observed in the UKPDS in the group treated with the β -blocker atenolol compared to those receiving the ACE inhibitor captopril.²¹ The available information suggests that the benefits of β -blockers outweigh the risks and thus that β -blockers should be prescribed for women with diabetes who experience an MI or who have established CHD. Counseling regarding a potential change in symptoms of hypoglycemia with recommendations for an increase in the frequency of home blood glucose monitoring can help offset any potential increase in risk for a severe hypoglycemic episode.

Screening for CHD

According to the ADA Consensus Development Conference for the Diagnosis of Coronary Heart Disease in Diabetes, stress testing should be performed in individuals with diabetes who meet any of the criteria listed in Table 1.³⁰ There is a lack of agreement about the type of stress test that is optimal in the evaluation of underlying CHD. For women who are able to exercise, testing on a treadmill allows the evaluation of both workload capacity and potential ischemia. For those with an abnormal electrocardiogram at baseline, myocardial perfusion imaging allows for assessment of the distribution of blood flow

Table 1. Criteria for Cardiac Stress Testing in People With Diabetes³⁰

- Typical or atypical cardiac symptoms
- Resting electrocardiogram suggestive of ischemia or infarction
- Peripheral or carotid occlusive disease
- Sedentary, age \geq 35 years planning vigorous exercise program
- Two or more risk factors in addition to diabetes
 - Total cholesterol $>$ 240 mg/dl, LDL cholesterol $>$ 160 mg/dl, or HDL cholesterol $<$ 35 mg/dl
 - Blood pressure $>$ 140/90 mmHg
 - Smoking
 - Family history of premature coronary artery disease
 - Positive test for micro- or macroalbuminuria

in response to exercise. For those who are unable to exercise or who are unlikely to achieve target heart rates during exercise, a pharmacological stress test with adenosine or dipyridamole can be performed in combination with perfusion imaging. A dobutamine echocardiogram evaluates the presence of myocardial wall motion abnormalities in response to a stimulus that increases cardiac workload.

Gender-based discrepancies exist in the accuracy of existing diagnostic studies. Women have a higher rate of false-positive exercise stress testing than do men. A negative exercise stress test also has a lower negative predictive value. For this reason, many health care providers order perfusion imaging in combination with exercise as a means of improving the accuracy of the test in women. Women with diabetes and a positive stress test are eligible for cardiac catheterization to evaluate the extent of underlying CHD.

Electron beam computed tomography (EBCT) quantifies the presence and severity of coronary artery calcifications as a noninvasive measure of stenotic lesions $\geq 50\%$ in the coronary arteries. Data are insufficient to support any recommendation regarding the use of EBCT as a diagnostic modality for screening women for CHD.

Bypass Angioplasty Revascularization Investigation 2 in Type 2 Diabetes (BARI 2D)

BARI 2D is an important and novel clinical trial funded by the National Institutes of Health that will address the observed acceleration in morbidity and mortality in men and women with type 2 diabetes and angiographically defined CHD. Until now, most studies of primary and secondary prevention for CHD have included only a small percentage of diabetic subjects. BARI 2D is seeking to recruit 2,800 men and women with type 2 diabetes from more than 30 centers to participate in this trial. It is the first large-scale clinical trial that combines expertise from the subspecialties of cardiology and endocrinology to address the efficacy of early revascularization versus aggressive medical therapy, and insulin versus insulin-sensitizing agent therapy on mortality and vascular events in individuals with diabetes. More information about BARI 2D can be obtained by visiting the website www.bari2d.org.

Summary

Diabetes stands out as a disorder that equalizes the risk for CHD between men and women at any age. Lifetime attention to fasting and postprandial glycemic control with diet, exercise, and medications; control of blood pressure and dyslipidemia; use of aspirin; and effective treatment of any underlying depression may all help to reduce this risk. In women with diabetes and established CHD, intensification of hypoglycemic therapy at the time of presentation may favorably influence long-term outcomes. Therapy with β -blockers should be prescribed in the absence of contraindications. Information from prospective long-term clinical trials targeted to answer questions regarding optimal treatment strategies for both CHD and diabetes will help to guide therapy in the future.

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