Young FADOI and gender medicine: sex gender differences in cardiovascular disease

Tiziana Ciarambino,[1] Miriam Gino,[2] Paola Gnerre,[3] Elena Barbagelata,[4] Nunzia Barone,[5] Francesca Saladini,[6] Federica Lorenzi,[7] Marta Zanon,[8] Maria Cristina Pasquini,[9] Cecilia Politi[1]

[1]Department of Internal Medicine, F. Veneziale Hospital, Isernia; [2]Department of Internal Medicine, Rivoli Hospital, Rivoli (TO); [3]Department of Internal Medicine, San Paolo Hospital, Savona; [4]Department of Internal Medicine, Sestri Levante Hospital, Sestri Levante (GE); [5]Emergency Department, Lagonegro Hospital, Lagonegro (PZ); [6]Department of Cardiology, Camposampiero Hospital, Camposampiero (PD); [7]Department of Internal Medicine, Sandro Pertini Hospital, Roma; [8]Department of Internal Medicine, dall'Angelo Hospital, Venezia; [9]Department of Oncology, Maggiore Hospital, Crema (CR), Italy

ABSTRACT

We have evaluated gender-related differences in cardiovascular disease. In particular, in coronary heart disease, atrial fibrillation, arterial hypertension, venous thromboembolism and diabetes mellitus.

Coronary disease: gender-related differences

Introduction

Bernardine Healy, in an editorial of 1991 on the NEJ *The Yentl Syndrome*,[1,2] showed how cardiovascular disease in women is understudied, under diagnosed and undertreated. The adverse ischemic heart disease is leading cause of death, less common in young women, where myocardial infarction (MI) mortality is two-fold higher in women younger than 50 years compared with age-matched men. The literature suggests that when women look like men, with *male-pattern* obstructive cardiovascular diseases (CHD), they are more likely to be diagnosed and treated like men. Two new analyses suggest that the Yentl syndrome is alive and well 10 years later. The first event in women takes about 10-20 years later than men. Women are more likely than men to have high-risk presentations and less likely to manifest central chest pain.[1,3] Pain in the upper back, arm, neck, and jaw, as well as unusual fatigue, dyspnea, indigestion, nausea/vomiting, palpitations, weakness, and a sense of dread, occur more frequently in women compared with men. The absence of chest pain or silent heart attack is more common in women than in men (35% *vs* 28%). So, women often turn later to the doctor and are treated less aggressively.[1] Cardiovascular disease is the most common cause of death and hospitalization in worldwide. Recognition of important gender differences plays an important role in cardiovascular disease prevention. New sensitivity about gender differences, and particularly attention among women, will be necessary for more analytic view about cardiovascular disease in both sexes.

Correspondence: Tiziana Ciarambino, Department of Internal Medicine, Santa Maria della Pietà Hospital Nola (NA), Italy.
Tel.: +39.081.5666037.
E-mail: tiziana.ciarambino@gmail.com

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Possible causes

The Framingham study already described the risk factors for CHD in women; then the INTERHEART, conducted in 52 countries around the world, identified nine risk factors, measurable and modifiable. These factors measurable and modifiable are: i) smoking; ii) hypertension; iii) diabetes; iv) dyslipidemia; v) abdominal obesity (waist/hip ratio); vi) stress and psychosocial factors; vii) physical inactivity; viii) low intake of fruits and vegetables; ix) alcohol. More risk factors greatly multiply the probability of infarction.[4,5] These risk factors explain more than 90% of myocardial infarctions and in about 96% of CHD in women. For example, in women, it has been shown that family and marital stress increase the risk of

ischemic heart disease. In women there is another condition that simulates the coronary heart disease. This condition is the Takotsubo syndrome.[6-16] Depression is one aspect of psychosocial stress and more women become ill with depression after myocardial infarction than men. In addition, non-editable factors are identified, as genetic causes and endothelial dysfunction, as reported:

- *Genetic causes*: the genes of pseudo-autosomal region of the X chromosome encode enzymes involved in oxidative stress, cell survival, apoptosis and fat distribution. As modulated by its *silencer*, the dual presence of the X chromosome in women is therefore a protective factor.[6]
- *Endothelial dysfunction*: the WISE study showed that the prevalence of micro vascular disease in women, is due by typically feminine condition with endothelial dysfunction, impaired arterial compliance, micro vascular dysfunction in vessels that are smaller and deeper. In women prevails coronary dissection, a rare, but increasing and typical of young women of childbearing age (80% of cases), with very high mortality and related to hormonal influence.[10] Endothelial progenitor cells maintain the integrity and vascular homeostasis; their function (migratory capacity and to form colonies) appears to be controlled by estrogen and appears to be an independent marker of vascular integrity. A lower migratory capacity in women appears to be related to increased endothelial dysfunction.[11]

Age: gender-related differences

In elderly women, the destabilization of atherosclerotic plaque and plaque rupture occur with a very similar process to that of men. On the contrary, in old women, acute coronary syndrome and sudden death recognize as pathophysiological mechanism mainly the erosion of plaque in the presence of a strong local inflammation, with a mortality rate approximately double in women than in men.[7,8] In the study GUSTO IIb, the incidence of ST-segment elevation myocardial infarction is lower in women, but, in some studies, an increased mortality after adjustment for comorbidities and age has been reported, due to more frequent post-infarct mechanical complications (mitral regurgitation acute heart failure, ventricular septal defect, ruptured papillary muscle and heart breaking).[9]

Physiological aspects and pharmacokinetic parameters: gender-related differences

Many physiological aspects, especially hormone metabolism influence therapeutic responses. Gender differeces are due to pharmacokinetic parameters, biovailbility, distribution, metabolism excretion and differences in weight and body surface area, extent and distribution of adipose tissue, plasma volume, rate of gastric emptying, concentration of plasma proteins, cytochrome system activity liver wings, function of membrane transporters [the verb in this sentence is missing; please rephrase]. A significant mortality reduction in women has emerged in the meta-analysis that included major studies on the use of β-blockers in secondary prevention. While the use of angiotensin-converting-enzyme inhibitor (ACE-I) showed similar reductions in mortality by gender. Analysis sub-group in patients treated with angiotensin receptor blockers (ARBs) indicates favorable effects on mortality regardless of gender.[17] In women, acetylsalicylic acid for secondary prevention showed a statistically significant reduction in the risk of stroke, while it is not showed a consistent reduction of myocardial infarction or mortality.[18]

Percutaneous and surgical revascularization: gender-related differences

As for the percutaneous and surgical revascularization, women candidate for percutaneous angioplasty (PCI)/by pass aortic are on average older than men with higher prevalence of comorbidities (diabetes, hypertension, heart failure). Some authors have correlated the smaller size of the coronary arteries with worse outcomes, suggesting that the lower success rate of revascularization and the highest rate of complications are correlated with technical difficulties of surgical intervention. Other studies have not confirmed these data after adjustment for body surface area and risk factors, although the incidence of re-stenosis after PCI seems to be higher in women. Numerous studies have shown the delayed percutaneous revascularization in women, even if the effect of gender on mortality is minimal.[19] Considering the different clinical presentation and inadequate control of risk factors in women, the diagnosis is often delayed. In fact, there are gender differences in the use of procedures, unless women do not meet the standards of a male model, and that definitely determines the worst cardiovascular prognosis in women than in men. Yet, as shown by the COURAGE study, women receive less drug prescriptions to treat coronary ischemia despite a similar benefit and similar frequency of adverse drug events in the two genders.[20]

Atrial fibrillation: gender-related differences

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting more than 3 million people in the United States.[21] The lifetime risk for developing AF for men and women aged more than 40 years is

1:4, respectively.[22] A rising number of papers analyze sex-gender differences in treatment and mortality among patients with AF.[23] Women with AF seem to have an increased risk for cardiovascular events, including stroke[24] and underutilization of oral anticoagulant (OAC) treatment among women has been suggested to be a contributing factor.[25] However, studies have reported significant gender differences in the anti-arrhythmic strategy. In particular, in ATA-AF study the preferred anti-arrhythmic strategy was heart rate control in 54.7% of female, compared to 48.4% of male subjects, while the rhythm control was preferred in 29.5% of male compared to 25.1% of female subjects. Compared with males, female patients less frequently underwent electrical cardio version, as well as ablation and implantation or revision of pacemaker/implantable cardioverter defibrillator. At discharge, amiodarone and ACE-I were preferred in male subjects, while ARBs and diuretics were more frequently prescribed in female subjects.[26] Other studies have reported a significant negative association between the $CHADS_2$ score and left atrial emptying fraction only in women.[27] Many studies reported that despite a similar extent of remodeling, the pattern in women had greater atrial myocardial deformation and smaller RA size.[28] The GARFIELD-AF study found that women had a higher risk of stroke than men even after adjustment of risk factors (congestive heart failure, age, hypertension, diabetes mellitus, prior stroke, vascular disease and history of bleeding). The results from the GARFIELD-AF study, found that the mortality was only slightly elevated in women (4.48) compared with men (4.04).[29] To this regard, there was a greater proportion of women over 75 years at the time of diagnosis of non-valvular AF.[30] However, there was also a trend toward a greater prevalence of comorbid vascular disease in men (than women) and comorbid hypertension in women. Otherwise, the prevalence of other risk factors for stroke (diabetes, prior stroke) is similar in men and women. The Framingham study found that gender differences in blood pressure gradually narrow with age. Eventually, women develop higher blood pressure than men (beyond 60 years of age) with the accelerated onset of arterial stiffening beyond menopause (especially in women with a history of hypertension).[31] For example, women require less warfarin to maintain a therapeutic international normalized ratio than men at an equivalent age and dosing reduces proportionally with increasing age. The greater risk of bleeding in men may be explained by their more aggressive OAC therapy dosing relative to women. Conversely, the lower impact of OAC treatment on stroke rates in women may be due to poorer anticoagulation control as determined by *atrial fibrillation follow-up investigation of rhythm management* (AFFIRM).[32] An important consideration concerning women is the impact of age on prescribing practice and adherence to medication, since a higher proportion of women than men were elderly (75 years or older). There is also evidence that women with AF have a significantly greater residual risk of stroke (compared with men) when treated using warfarin.

Arterial hypertension: gender-related differences

Introduction

One of the largest studies that gives us information regarding the prevalence of hypertension and in particular according to gender, is the NHANES III study,[33] which involves non-institutionalized population of the United States. The authors found that 24% of American subjects were hypertensive and that this percentage was slightly higher among males (24.7%) compared to females (23.4%).[33] When they looked at the different distribution according to the age range, they observed that the prevalence of hypertension was higher among man compared to female up to 59 years of age, then there is a reverse trend from 60 years of age among Mexicans and non-Hispanic blacks, and from 70 years of age among non-Hispanic whites.[33] From 80 years of age the prevalence of hypertension becomes 14.2% higher in women compared to men.[33] Moreover, the authors observed a different trend of systolic and diastolic blood pressure (BP) according to gender. Systolic BP is higher in young men compared to young females. In fact, in young men the most frequent form of hypertension is isolated systolic hypertension; then among females there is a steeper rise of systolic BP up to the seventh decade, after that, systolic BP is similar in the two genders or slightly higher in males.[33] Diastolic BP is higher in men compared to females during adulthood, while in older ages diastolic BP levels are similar in the two genders.[33]

Age: gender-related differences

In a recent study it was demonstrated that women after gestational hypertension presented an increased risk of future hypertension and of an earlier hypertension development compared to women that did not experienced gestational hypertension during pregnancy.[34]

BP rises after menopause in most women and it has been postulated that withdrawal of endogenous estrogen, a potent vasodilator, plays a key role in postmenopausal hypertension.[35] Several mechanisms may be supposed to be responsible for this BP rise: increase of salt sensitivity, decrease of nitric oxide production, overexpression of type 1 angiotensin II receptor.[36] Estrogens are supposed to protect from high BP levels by strengthening the correlation between pressure and salt excretion and promoting nitric-oxide synthetize

activity and nitric oxide production. In particular, a previous study that involves more that >22,000 Italian female patients showed that menopause has a double risk of developing sustained hypertension.[37] Another problem that arises with menopause is hormone replacement therapy (HRT) and in literature is still debated the possible unfavorable role of HRT. In a recent paper[38] that involves 43,405 non-hypertensive women before menopause, it was demonstrated that HRT was associated with a significant increased risk of elevated BP levels correlated to the duration of the therapy. In contrast, in another study that evaluated transdermal estrogen replacement therapy, a BP reduction was found.[39] In 2014, Cannoletta *et al*. concluded that HRT was associated with negative effects when it was started some years after the beginning of menopause. The authors reported that if HRT was started earlier and, in particular, with transdermal estradiol or with an association including progesterone (especially drospirenone), seemed to have a favorable effect on BP reduction.[40]

Pharmacological treatment: gender-related differences

Regarding pharmacological effect according to gender we have to take into account the unequal representation of both genders in population studies (usually 44% of female) and the lack of specific results according to genders.[41,42] In the European Society of Hypertension guidelines the authors reported the results of a sub-analysis of 31 randomized controlled studies that demonstrated a similar BP reduction in both genders with similar effect with any drugs (calcium antagonists, ARB, ACE-I, β-blockers, diuretics).[43] However, in literature some differences were described for diuretics with better response among women. During menopause, women presented a greater salt-sensitivity, so diuretics may be useful to promote renal sodium excretion and BP reduction,[36] moreover a beneficial effect on calcium metabolism, with a consequent inferior risk of hip fracture, was described.[44] Diuretics present also different side effects according to gender: among women sodium and potassium reduction, while an increased risk of gout among men.[44] Moreover among women cough with ACE-I and peripheral edema with calcium antagonist are more common.[44,45] Finally, sexual dysfunction, a typical male gender side effect, is described also in women correlated to β-blockers, thiazide diuretics and centrally active agents, while this effect is less pronounced with ARBs.[45] Data from US populations[46,47] showed that BP control in adult to elderly females (65-80 years of age) is lower compared to males. It is still debated if this phenomenon is due to a less intensive treatment, because of medical inertia, to a less adherence in this gender, or to the higher prevalence of resistance hypertension, in this age range, among females.

Venous thromboembolism: gender-related differences

Venous thrombosis, including deep vein thrombosis and pulmonary embolism (PE) occurs at an annual incidence of about 1 per 1000 adults.[48] Venous thromboembolism (VTE) is predominantly a disease of older age, and is rare prior to late adolescence.[49] Incidence rates increase markedly with age for men and women. The overall age-adjusted annual incidence rate is higher for men (130 per 100,000) than for women (110 per 100,000).[50] Incidence rates are somewhat higher in women during childbearing years (16-44 years) compared with men of similar age, whereas incidence rates in individuals aged >45 years are generally higher in men (Figure 1). PE accounts for an increasing proportion of VTE with increasing age in both sexes.[49]

VTE is a complex (multifactorial) disease, involving interactions between acquired or inherited predispositions to thrombosis and VTE risk factors, including increasing patient age and obesity, hospitalization for surgery or acute illness, nursing-home confinement, active cancer, trauma or fracture, immobility or leg paresis, superficial vein thrombosis, and, in women, pregnancy and puerperium, oral contraception, and hormone therapy.[51]

Venous thromboembolism in pregnancy and the puerperium

In the western world, venous thromboembolism in pregnancy and the puerperal period has been either the most common cause of maternal death[52] or ranked closely behind sepsis and preeclampsia/eclampsia. Although the absolute incidence of venous thromboembolism in pregnancy is slow (1 or 2 cases per 1000 pregnancies),[53] this risk is approximately 5-fold higher in pregnant women than in non-pregnant women of the same age due to the changes in the coagulation and venous system associated with pregnancy. Venous stasis is probably caused by progesterone induced vasodilation and pelvic venous compression by uterus. Furthermore, the hemostatic system is progressively activated to prepare the delivery: the activity of protein S is reduced and the activated protein C resistance is progressively high. Thrombotic events are spread across the 3 trimesters.[54]

The risk increases further in the puerperium (the 6-week period after delivery), probably owing to endothelial damage to the pelvic vessels. Recent data indicate that an increased relative risk persists until 12 weeks after delivery.[55] Multiple risk factors often coexist in women who developed VTE in pregnancy and

one of the strongest risk factors is previous pregnancy-related VTE event.[56] Treatment of VTE in pregnancy involves unfractionated heparin or low-molecular weight heparin (LMWH), which do not cross the placenta or enter breast milk. In contrast to vitamin K antagonists that do cross placenta and can cause embryopathy. However, since warfarin crosses minimally into breast milk, it can be used in breast-feeding women during the post-partum period. LMWH is generally safe and easy to use with either once daily or twice daily dosing.[56] The new anticoagulant (dabigatran, rivaroxaban, apixaban and edoxaban) may cross the placenta and should be avoided in pregnancy.[56]

Venous thromboembolism and combined hormonal contraceptive: lights and shadows

Contraceptive pills are among the most popular contraception methods worldwide. Despite their reliable contraception action, these pills may present side effects including VTE. Use of combined hormonal contraceptives (CHC) increased a two- to four-fold the risk of VTE compared with non-user, although the absolute risk of VTE with use of any types of combined oral contraceptives in young women is less than one in 1000 user a year.[57] Sex hormones alter procoagulant protein levels, platelet function, and the vessel wall in a manner that may translate into gender-based differences in thrombosis.[58] All currently used oral contraceptives are equally effective in preventing pregnancy but different combination pills show different VTE risk. Evaluation of these different tendencies may play an important role in choosing the safest pill when starting pill use.[59] The estrogen dose was positively associated with the risk of VTE for preparations containing desogestrel and gestodene most commonly used. The oral contraceptives currently prescribed which contain 30 µg of ethinylestradiol are associated with a higher risk of venous thrombosis than contraceptives containing 20 µg.[60,61] Furthermore the risk of VTE is associated with different types of progestogens in combined oral preparations. It was shown that third-generation CHCs users had a higher risk of VTE than second-generation users.[62,63] The use of drospirenone in a CHC has been shown to increase the risk of VTE, compared with second-generation contraceptives. The risk among women using combined oral contraceptives decreased with duration of use.[64] Women who use transdermal patches or vaginal rings for contraception have a 7.9 and 6.5 times increased risk of confirmed VTE compared with non-users of the same age, corresponding to 9.7 and 7.8 events per 10,000 exposure years. Progestogen-only pills and hormone releasing intrauterine devices did not confer any increased risk of VTE.[65] CHCs have been associated with an increased risk of arterial thrombosis but the magnitude of the risk and the effect of different hormonal contents remain unclear.[66,67] The European Medicines Agency (EMA) and the Italian Pharmaceutical Agency (*Agenzia Italiana del Farmaco* - AIFA) have concluded that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks, and that the well-known risk of VTE with all CHCs is small. It is important that women are made aware of the risk of VTE and its signs and symptoms, and that doctors take into consideration a woman's individual risk factors when prescribing a contraceptive.[68] Universal screening for thrombophilia before the administration of oral contraceptives is not warranted. However, selective screening of women with a family history of thrombosis and thrombophilia before administration of hormonal therapy might be cost-effective.

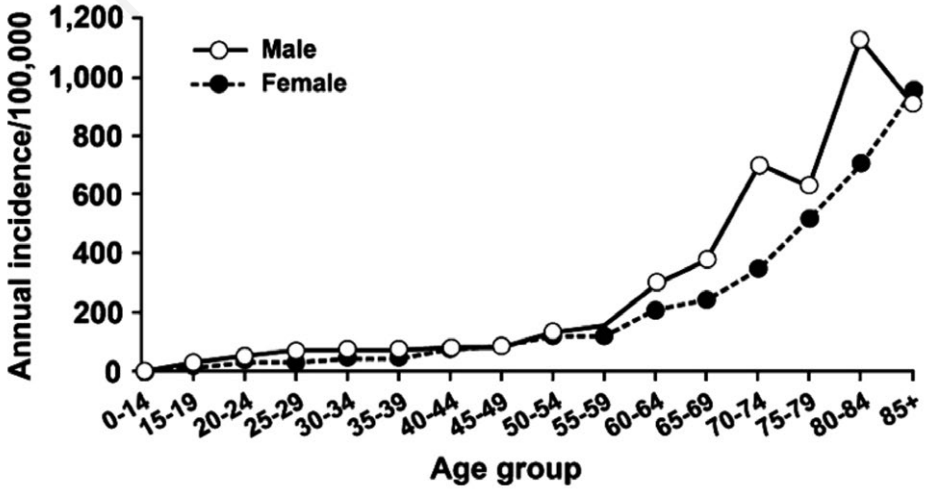

Figure 1. Annual incidence of venous thromboembolism by age and sex.

Diabetes and cardiovascular risk: gender-related differences

Introduction

The prevalence of diabetes mellitus (DM) is increasing at a rapid rate. Currently, ≈1 in 13 people living in the United States has DM, and 90% to 95% of these individuals have type 2 DM (T2DM). Overall, the prevalence of T2DM is similar in women and men.[69] Cardiovascular disease (CVD) is a major cause of morbidity and mortality for both men and women with diabetes, with huge socioeconomic costs. In the US, mortality rates have declined among men with diabetes, but not among women.[70] Estimates of CVD mortality in men with diabetes have varied from 1 to 3 times the rate in men free of the disease, whereas estimates in women with diabetes have ranged from 2 to 5 times the rate in women without diabetes.[71,72] A potential reason for differences in outcomes between men and women with T2DM is differential cardiovascular risk factor control and management.

Coronary heart disease and diabetes: gender-related differences

Type 2 diabetes has long been known as a risk factor for coronary heart disease and is estimated to increase the risk of a fatal event by twofold.[69] The association between diabetes and coronary heart disease has been suggested to be stronger in women than in men, prompting the idea that diabetes eliminates, or substantially attenuates, the advantages of being female.[73]

The relative risk for fatal coronary heart disease associated with diabetes is 50% higher in women than it is in men, even after differences in other major cardiovascular risk factors have been taken into account.[72] This greater excess coronary risk may be explained by more adverse cardiovascular risk profiles among women with diabetes, combined with possible disparities in treatment that favor men. Despite the fact that in many industrialized countries women have lower mortality rates than men, when we look at people with diabetes, the advantage for women is reduced or even absent.[74] Compared to males, females with diabetes have a worse cardiovascular profile, which could explain their higher cardiovascular mortality, mainly at age <60. Diabetic females have higher prevalent abdominal obesity, increasing the risk of hypertension, a worse lipid profile (low levels of high-density lipoproteins cholesterol, small particle size of low-density lipoproteins cholesterol, and high levels of triglycerides), and a more marked endothelial dysfunction, a greater degree of fibrinolysis/thrombosis, and also an increased prevalence of hypoglycemic events compared to that of male diabetic patients.[75] These phenomena might explain the increased incidence of cardiovascular events and mortality among female patients.[76] Besides innate differences in sex physiology, disparities between sexes in the treatment of major cardiovascular risk factors also exist.[77] These can be attributed to an underestimation of patient risk and a less aggressive approach and poorer compliance of females.[71] Nevertheless, two Italian studies did not find any relevant differences between females and males in terms of the quality of diabetes care,[77-79] suggesting that factors other than gender disparities in treatment intensity are responsible.

Myocardial infarction occurs earlier and has higher mortality in women with DM compared with men, and revascularization rates (angioplasty, coronary artery bypass grafting) are lower in women with DM compared with men. T2DM is an especially powerful risk factor in young women, increasing their risk of CHD, including ACS, by 4- to 5-fold.[80]

Evolving sex-specific research has demonstrated that although men and women share similar risk factors for CHD, certain risk factors are more potent in women. These include tobacco abuse, T2DM, depression, and other psychosocial risk factors. The INTERHEART study identified DM as a potentially modifiable risk factors for MI.[81]

Heart failure and diabetes: gender-related differences

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.[82] 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 non-diabetic population.[83] In a more recent report, 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.[84] 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.

Stroke and diabetes: gender-related differences

DM is widely recognized as a risk factor for stroke in both women and men.[85] Whether this sex difference also exists for stroke remains uncertain. Findings from previous studies have been inconsistent, with some in-

vestigators reporting either a stronger, similar, or weaker effect of diabetes on stroke risk in women 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. Compared with men with DM, women with DM had a 27% greater relative risk (RR) for stroke when baseline differences in other cardiovascular risk factors were taken into account [RR=1.27; 95% confidence interval (CI), 1.10-1.46].[86] These data add to the existing evidence that men and women experience diabetes-related diseases differently and suggest the need for further work to clarify the biological, behavioral, or social mechanisms involved.

The most recent American Heart Association (AHA) guidelines on the prevention of stroke in women classified DM as a risk factor that is stronger or more prevalent in women.[87] In the Nurse's Health Study, among middle-aged women, those with T2DM had an almost 2-fold higher risk (RR=1.8; 95% CI, 1.7-2.0) of total stroke than non-diabetic women. Among 30,000 women and men with T2DM, women with HbA1c levels ≥8.0% had a significantly elevated risk of stroke, whereas men did not.[88]

Conclusions

It is imperative that women with DM are accurately informed about CVD risk factors, educated on how to reduce them, and aggressively treated to avoid adverse outcomes. Additional research involving women is needed to explore and reduce disparities in CVD risk between men and women with T2DM.

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