Diabetes and cardiovascular disease, are women protected or at higher risk?

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For many years, data have accumulated demonstrating that diabetes mellitus (DM) promotes atherosclerosis progression and imparts risk of major adverse cardiovascular events (MACE), including revascularization, myocardial infarction (MI), and cardiac death. Among patients without known cardiovascular disease (CVD), having DM is a “risk equivalent,” meaning that they are at the same risk of MACE as a patient with known CVD.¹ The most recent recommendations on CVD prevention largely overlap for both sexes,² and the guidelines on CVD prevention in women uniformly encourage aggressive risk factor modification for women with diabetes.³ Treating men and women the same might be reasonable if their risks are the same, however, the literature suggests that risks differ between the sexes and that a more nuanced approach is warranted to achieve optimal outcomes.

In this issue, Romero-Farina et al.⁴ report data from a large cohort study examining the relationship between DM, CVD, and sex. Among 1,327 patients with diabetes referred for single-photon emission computed tomography at their facility, the risk of MACE over 8 years of follow-up was lowest in women without known CVD (7.1% versus 14.6% for men without CVD, 17% for men

with CVD, and 20.3% for women with CVD). While women without DM or CVD have lower CVD risk than men, women with DM have similar or higher risk of CVD events compared with men.¹ This has been observed for a wide array of events including stroke, peripheral artery disease, and coronary disease.⁵ Their findings highlight ongoing questions about CVD management and risk assumptions made for women compared to men and for patients with and without DM.

UNIQUE RISK FACTORS FOR WOMEN

Life events specific to women contribute to their risk for developing CVD. Pregnant women who develop gestational DM have a 7-12-fold increased risk of developing DM later in life thus increasing their overall risk for CVD.¹ Women who develop preeclampsia during pregnancy are at 6-fold higher risk for chronic hypertension, a 2-fold risk of developing diabetes, and 2-fold increased risk for ischemic heart disease and stroke.⁶ The rate of preeclampsia is around 2-7% in the general female population, the rate among diabetic women is 10-20%, placing them in an even higher risk group for CVD.⁷ Menopause is another factor that could increase the risk for CVD in women. A cohort study comparing premature natural or surgically induced menopause in women <40 years old to women who underwent menopause at 40-69 years old found a small but statistically significant increase in CVD in the women who underwent early menopause.⁸ This study suggests that estrogen itself likely contributes a small role in the CVD advantage of pre-menopausal women. Furthermore, estrogen-replacement therapy in post-menopausal women does not confer a CVD protective effect and instead, increases the risk of stroke and venous thromboembolism.⁹ A recent study from Canada looked further into why post-menopausal women have more hypertension and dyslipidemia than men.¹⁰ They found that downstream receptors for estrogen, estrogen

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receptor (ER), and G-protein coupled receptor (GPCR) play an important role in mediating estrogen-protective effects. ER plays a role in decreasing ischemia-reperfusion-induced injury and decreasing chronic ischemia, while GPCR activation decreases angiotensin II and blood pressure. The balance of these two receptor activation plays an important role in vascular remodeling.¹⁰

PRIMARY PREVENTION WITH ASPIRIN

Enthusiasm for the role of aspirin in primary prevention has been waning for the past several years. The reason being is that contemporary data showing that any benefits noted for prevention of MACE is offset by a higher risk of bleeding.¹¹ In 2019, the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines suggested that 75-100 mg daily of ASA would be a reasonable treatment for patients at higher atherosclerotic cardiovascular disease (ASCVD) risk without elevated bleeding risk (Class IIb recommendation, LOE-A).¹² The guideline also recommends against aspirin for primary prevention to those over the age of 70 and those with elevated bleeding risk.

This guideline does not offer sex-specific treatment recommendations, however, unique factors for women are discussed and need to be incorporated in their risk assessment. As detailed above, women experience unique risk factors for CVD including preeclampsia, preterm delivery, and small for gestational age infants. Other noted risks include chronic inflammatory diseases which may be more common in women than men.¹³⁻¹⁵ Modest randomized evidence suggests a stronger benefit of aspirin in stroke risk reduction for women, compared to men.¹⁶ This finding may hold true when combined with other data and using meta-regression techniques.¹¹ These should all be considerations when assessing risk and making individual treatment decisions involving women.

STATINS FOR PRIMARY PREVENTION

Current prevention guidelines also do not make sex-specific treatment recommendations for other pharmaceutical prevention cornerstones, such as statins. The data for prevention benefits with statins are overwhelming, however, most of the early data are based largely on men. Byrne et al. published an overview of systematic reviews in 2019 observing that evidence for a primary prevention benefit in women is not as robust as it is for men.¹⁷ In addition to being understudied in women, several plausible mechanisms have been identified to explain why statins may be less beneficial in women.¹⁸ Women have differences in volume of distribution,

differences in adipokine secretion, and higher activity of cytochrome P-450 3A4, responsible for metabolism of lipophilic statins.

SECONDARY PREVENTION AND DUAL ANTIPLATELET THERAPY

An analysis of data from the Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents trial found that patients with diabetes had higher platelet reactivity than those without diabetes.¹⁹ After controlling for this factor in a logistic regression, the risk of coronary events remained elevated in patients with diabetes and the risk was greater magnitude for women than men. One potential reason for this observation may be related to the phenotypic manifestations of coronary atherosclerosis in women compared to men. Substantially more women than men have no obstructive epicardial coronary disease associated with their angina.²⁰ Women may have smaller diameter coronary vessels and more complex lesions, factors that have been linked to an increased risk of both stent thrombosis and target lesion revascularization.²¹ Among women with no obstructive epicardial stenosis, coronary reactivity to adenosine identifies dysfunction in the coronary microvasculature and may represent a target for novel therapies.²² As an example, women may have differential microvascular response to mineralocorticoid blockade.²³

NOVEL TREATMENTS FOR DIABETES AND CARDIOVASCULAR RISK

The newer classes of treatments for diabetes improve blood sugar management and some have demonstrated substantial effects at mitigating risk of MACE. A cohort study of 132,737 patients found that MACE risk was higher for insulin and sulfonylureas compared to dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter 2 inhibitors, and thiazolidinediones.²⁴ Specifically in women, a cohort study using the Marketscan database suggests that women in particular may derive greater benefit from glucagon-like peptide 1 receptor agonists.²⁵

DISPARITIES

In addition to the evidence that women have unique risk factors and may have differential benefits from established treatment options, data show that women are not treated as aggressively as men. In both the outpatient setting and after an acute coronary syndrome, women are less likely than men to receive adequate treatment

with lipid-lowering therapy and aspirin. Women are less likely to undergo revascularization and less likely to have adequate BP control.¹

CONCLUSION

The data from Romero-Farina et al. should serve as an important reminder: women with DM are at substantial risk for MACE; with established CVD, the risk is even greater. Future trials in CVD need to actively recruit women in order to better understand unique risk factors and differences in treatment benefits. In the meantime, clinicians need to use available data to make individualized treatment choices that incorporate risks that are unique in women. Systems need to be developed to minimize disparities in care and outcomes for women with diabetes.

Disclosures

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