EDITORIAL

Sex- and Gender-specific Diabetes Guidelines: Not Just Gallantry

Suhas Gopal Erande*

Once bitten, twice shy—are we?

When scientific studies and randomized controlled trials (RCTs) did not include women, and observations of men were extrapolated to women, the thalidomide tragedy happened in 1953. The drug Contergan (Grunenthal Pharma), sold as an antiemetic, sedative, and sleeping pill, resulted in nearly 10,000 deformed births.[1]

Pharmacology had already noted fatal cardiac arrhythmia with cisapride (excess QT prolongation in women) and also zolpidem causing prolonged sedation and even vehicular accidents in women (excess store and slower release of zolpidem from adipose tissue).

The United States Food and Drug Administration (USFDA) suggested inclusion of women in RCTs as late as the 1990s, and now even animal experiments need to incorporate female studies.

Since sex and gender can result in different epidemiological, pathophysiological, clinical, investigative, and even drug response differences in diabetes, clinical practice guidelines (CPGs) are one pertinent way to approach diabetes in women specifically to reduce cardiovascular morbidity and mortality and improve quality of life (QoL). Categorical standard-of-care–driven systems can be expected to reduce complications.

Even with advanced therapy and the latest interventions, major adverse cardiovascular events (MACE) in diabetic women remains suboptimal compared to men. We need a change in stance![2]

World Health Organization Definition of Sex and Gender

Sex refers to different biological and physiological characteristics of men and women (reproductive organs, hormones, and chromosomes).

Gender refers to socially constructed features (roles, norms, relationships of and between men and women, etc.). Sex and gender interact, forming a Gordian node, and it is difficult to separate them. For simplicity, we define sex not by karyotyping everyone but by simple clinical methods. We avoid interchangeable use of sex and gender.

Is Diabetes in Women Different?

It is noteworthy that diabetes affects women across their lifespan, and it is very distinctive compared to men.[3] Readers can refer here for detailed deliberations.[4]

Not only that diabetes affects women differently, but women respond differently to the antidiabetic drugs as well. Metformin gives more gastrointestinal (GI) side effects in women but better glycemic control than in men. Similarly, newer sodium-glucose cotransporter 2 (SGLT2) inhibitors [more genitourinary (GU) mycotic infections] and glucagon-like peptide-1 (GLP1) agonists give more GI side effects in women than in men; however, these drugs are more beneficial for women (especially more weight reduction). Differences in body surface area, in fat mass and volume of drug distribution, and different estimated glomerular filtration rate (eGFR) may be important here. So women may need different dosing of drugs.

Are Other Societies Adopting Gender Specific Guidelines?

This initiative has been taken by the cardiology societies and academicians for a very long period of time. The American College of Cardiology (ACC) focuses on heart failure (HF)/HF in women in the cardiology magazine (February 2, 2024), delving deep into differences in HF (women vs men), and mentions that women are more likely to be obese and have a higher risk of HF, especially heart failure with preserved ejection fraction (HFpEF), nonischemic variety, compared to men. It further mentions that diabetic women are at even higher risk of HF and have adverse left ventricle (LV) remodelling [increased LV thickness and left ventricular mass index (LVMI)]. Further, smoking is a bigger risk factor in women (double the risk compared to men). The ACC/American Heart Association (AHA) atherosclerotic cardiovascular disease (ASCVD) risk calculator and the eGFR calculators incorporate sex as a variable in their formula.

Once again, ACC distinguishes hypertension and women interface.[5] This pertains to different epidemiology, pathophysiology, differences in screening and diagnosis, and different responses to drug treatment. It has been observed that lifestyle modification is more helpful in hypertensive women.

It seems that cardiologists, though not officially publishing sex/gender-aligned CPGs, are at least intensively focusing on women from a cardiovascular disease (CVD) point of view.[6–9] Cardiology World has ascertained that the historic Framingham risk scale underestimates CV risk in women. Even the latest SCORE2 method underestimates CVD risk in middle-aged women.

National Lipid Association (NLA) has been discussing lipid guidelines for women for ~9 years.

What Are Clinical Practice Guidelines?

Institute of Medicine (IOM) defines CPGs as statements that include recommendations intended to optimize patient care. They are informed by systematic review of evidence and assessment of harms and benefits of alternative care options. CPGs help collect the best evidence to help clinical decision making and to avoid discrepancy in practices while maintaining cost and quality. CPGs are systematically developed, but they may vary widely in quality. Increasing scientific literature and publications may confuse physicians while managing patients. Critically appraised and synthesized scientific evidence remains very important. Canadian academicians have taken a lead in sex- and gender-differentiated guidelines, though in bits and pieces. For example, the Canadian Diabetic Association (CDA) recommends aspirin for reducing nonfatal myocardial infarction (MI) in men but not in women (without a history of CVD). The same CDA notes that type 1 diabetes mellitus (T1DM) in adolescent girls be regularly screened for eating disorders and be offered more support for weight management and body image issues.

Diabetologist, Akshay Hospital, Pune, Maharashtra, India; *Corresponding Author

How to cite this article: Erande SG. Sex- and Gender-specific Diabetes Guidelines: Not Just Gallantry. J Assoc Physicians India 2025;73(10):11–12.

Is the Gender Bias Decreasing?

It is interesting to note the proportion of women included in various diabetes and cardiology RCTs over the last 75 years.[10] Framingham (2,873 W, 2,336 M), DCCT (615 W, total 1,441), EMPAREG (7,020 W, 28.5%), DECLARE-TIMI (17,610 W, 37.4%), LEADER (9,340 W, 35.7%), REWIND (9,901 W, 46.3%), SUSTAIN-6 (3,297 W, 36.8%), SOUL (9,650 W, 28.9%)

Though it has been illustriously noted that HF is a bigger problem in women (especially diabetic women), the inclusion of women in the latest HF trials has not been optimal. For example, PARADIGM-HF (22% women), DAPA-HF (23%), EMPEROR-Reduced (24%), GALACTIC-HF (21.3%), and VICTORIA (23.9%). Greater benefit of ARNI in women (PARAGON-HF trial) and the newer agent Omecamtiv Mecarbil needs more studies to help diabetic HF women. In fact, PARAGON-HF is one of the very few recent studies that included a sizeable number of women (51.6% in ARNI arm and 51.8% in valsartan arm, where ~43% of patients were diabetic).[11] Women with HFpEF reaped better rewards than men in this study. CPGs have large RCTs as their backbone, so more women in RCTs can better balance the CPGs from sex- and gender-point-of-view.

Conclusion: Will Gender Specific Clinical Practice Guidelines Help?

Looking at various epidemiological, pathophysiological, clinical, and pharmacological differences in diabetic men and women, gender-aligned CPGs definitely will be a good help and navigator to improve patient outcomes and better QoL for diabetic women. The academicians and researchers would note that inclusion of women even in problem areas like diabetes and HF and dyslipidemia has not been adequate over the last 75 years. With newer diabetes drugs like GLP-1 analogs offering more benefits in women, or calcium channel blockers (CCBs) proving better for women (hypertension), or cardiac resynchronization therapy (CRT) more rewarding in women (HF) compared to implantable cardioverter-defibrillator (ICD), we have some better offerings for diabetic women. McKinsey Health Institute January 2024 Insight Report (World Economic Forum) urges closing the gap between women's lifespan (longer than men) and their longer healthspan (shorter than men) to improve lives and economies by 1 trillion United States Dollar (USD) by 2040. Organizations like the National Institutes of Health, USA, Canadian Institutes of Health Research, and European Commission in Europe are increasingly rewarding (financially) excellence in integrated sex- and gender-research in biomedical sciences.

Time to form sex- and gender-aligned diabetes and medical guidelines is now!

Orcid

Suhas Gopal Erande https://orcid.org/0000-0003-1566-6350

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Suggested Reading

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