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Cardiovascular Risk in Women with Type 2 Diabetes: Still an Enigma?

The Lancet Women and Cardiovascular Disease Commission: reducing the global burden by 2030 — has aptly summarized — "cardiovascular disease in women remains understudied, under-recognized, underdiagnosed, and undertreated" [1]. Historically, the Framingham study was one of the first large-scale studies conducted in 1974 that suggested an excess risk of heart failure (HF) and cardiovascular (CV) death in women with type 2 diabetes (T2D) compared to men [2, 3]. Two large meta-analyses conducted subsequently also suggested an increased rate of stroke, coronary artery disease (CAD), and all-cause mortality (ACM) in women with T2D compared to men including people from Asia-Pacific [4, 5]. Notwithstanding, several other studies did not find any gender-related difference in HF, CAD, stroke, CV death, and ACM in people with T2D [6–10]. Therefore, the relative impact of T2D on CV disease and mortality remains intriguing, gender-wise.

In this issue of *Clinical Diabetology*, Weerawickrama et al. [11] have attempted to assess the prevalence of CV risk factors and compare the capability of the World Health Organization/International Society of Hypertension (WHO/ISH) risk prediction score and Framingham Risk Score (FRS) to predict CV disease risk in Sri Lankan women with T2D but without overt CV disease. This assumes relevance given the dearth of such risk prediction tools in South Asian women with T2D in general and Sri Lankans in particular. The authors further divided the patients into premenopausal, early post-menopausal (< 5 years), and late post-menopausal (> 5 years). Of note, more than 97% of patients in all three groups had central obesity although close to 40% had body mass index (BMI) < 25 kg/m^2. Perhaps, choosing a cutoff BMI of < 23 kg/m^2 (as advocated for Asians) would have identified more patients with overweight or obesity. The study also demonstrated a higher incidence of dyslipidemia among premenopausal women than postmenopausal women; however, statistical analysis was not documented to see if it reached statistical significance. There was a significant discrepancy in risk prediction by the WHO/ISH and FRS. The WHO/ISH score chart had high specificity but poor sensitivity. In contrast, FRS had low specificity but high sensitivity meaning therefore that the WHO/ISH score chart would fail to appropriately predict risk for women with high CV risk. In contrast, FRS would classify the same group as moderate or high risk. This was explained by the fact that FRS included high-density lipoprotein cholesterol (HDL-C) in the risk calculation and in the present study close to 20% of patients had low HDL-C. Perhaps including a third commonly used scoring system the QRISK3 would have been more helpful as it covers more extensive parameters and can be region-specific as it has options to choose from the ethnicity section including Indian, Pakistani, Bangladeshi, etc. [12]. Nevertheless, this study opens

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up the discussion on why women would be different from men regarding CV risk in T2D.

There could be several factors underpinning the uncertain CV risk in women with T2D compared to men. Altered CV risk in women could be akin to — i. psycho-socio-cultural differences; ii. Geno-phenotype differences; iii. women-related factors: polycystic ovarian syndrome, primary ovarian insufficiency, and menopause; iv. pregnancy-related factors: gestational hypertension, preeclampsia, gestational diabetes, and preterm birth (< 37 weeks); v. pharmacokinetic-dynamic (PK-PD) factors; vi. differential response to anti-diabetes and CV drugs, and vii. exaggerated adverse events, compared with men. Several studies have reported poorly controlled diabetes, blood pressure (BP), and lipid levels, and delays in diagnosis and treatment of T2D and CV diseases in women due to psycho-socio-cultural differences, compared to men [13–15]. Higher BMI, a higher frequency of atypical angina, a higher rate of coronary microvascular dysfunction (CMD) such as MINOCA/INOCA (Myocardial Infarction/Ischemia and No Obstructive Coronary Artery Disease), and longer corrected QT interval (QTc) in women owing to the biological effects of female sex hormones akin to geno-phenotype difference [16, 17]. Both women-related and pregnancy-related factors are associated with a varying increased risk of T2D, hypertension, CV disease, and CAD [18]. Concerning PK-PD differences, women have a higher percentage of body fat, lower plasma volume, and lesser organ blood flow that can alter the PK-PD of lipophilic vs. hydrophilic drugs, plasma/tissue drug concentrations, hepatic enzyme activity (cytochrome 450 and P-glycoprotein family) as well as drug clearance [19]. For example – in women, levels of metoprolol and propranolol in plasma are higher due to a lower volume of distribution and a slower clearance causing a greater reduction in exercise-induced heart rate and BP compared to men. However, metoprolol has been found to exert a greater effect on stress-induced angina in men compared with women despite higher plasma levels in the latter. Likewise, levels of plasma statin concentrations are generally 15–20% higher in women than in men. However, women metabolize lipophilic statins faster due to higher concentrations of cytochrome 4503A4. Similarly, women have faster clearance of verapamil and amlodipine due to the lower activity of P-glycoprotein and higher activity of CYP3A4 [19].

Concerning the differential effect of anti-diabetes drugs, the MASTERMIND consortium (n = 22,379), a UK Clinical Practice and Research Datalink, showed a significantly greater response with thiazolidinediones (TZDs) and lesser response to SUs in obese women compared with men. Moreover, a significantly higher weight gain and edema risk with TZDs was observed in obese women compared with men [20]. Similar findings were observed in the TODAY (made Treatment Options for Type 2 Diabetes in Adolescents and Youth) trial showing a better glycemic response with TZDs in obese women compared to non-obese women and obese men [21]. Women also showed differential responses to glucagon-like peptide-1 receptor agonists (GLP-1RAs). While weight loss with short-acting exenatide at 1 year was significantly higher in women, a significantly lower glycemic efficacy was observed in women compared with men [22]. Moreover, a recent meta-analysis of cardiovascular outcome trials (CVOTs) found a pronounced effect of GLP-1RAs and a lesser beneficial effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on the composite of major cardiovascular events in women compared to men [23].

With regards to CV drugs, in primary prevention studies, while aspirin lowered the risk of stroke it did not reduce myocardial infarction or CV death in women compared with men [24]. Similarly, the effects of statins in primary prevention are less evident in women [25]. Angiotensin-converting enzyme inhibitors (ACEi) have shown a significant reduction in heart failure hospitalization (HHF) and mortality in men than in women in earlier heart failure trials [26]. Likewise, few studies showed beta-blockers did not improve survival in women with hypertension and/ or heart failure [27]. Digoxin therapy was less effective in women in reducing HHF than in men in the DIG (Digitalis Intervention Group) trial [28]. A meta-analysis of glycoprotein (GP) IIb/IIIa antagonist trials found no treatment benefit in women than in men with non-ST elevated acute coronary syndromes [29].

Finally, a higher frequency of adverse events of drugs could cause poor compliance in women. An increased incidence of cough (ACEi), myopathy (statins), edema (amlodipine), hemorrhagic complications (anticoagulants/ anti-platelets/ thrombolytics), electrolyte abnormalities (diuretics) in women compared with men could be associated factor [19]. Drug-induced torsades-de-pointes are more frequent in women than in men due to longer corrected QT interval (QTc) [19]. Table 1 summarizes the possible mechanism underpinning the altered CV risk in women.

However, any interpretation of these data should be made in light of certain limitations. Most of the data have been collected through observational and cohort studies and these findings could merely be an association. There are clear inconsistencies between observational studies, randomized trials, and meta-analyses. Unfortunately, women with T2D have been

Table 1. Possible Mechanism Underpinning Altered Cardiovascular Risks in Women [13–29]

Areas of differences	Overall effect	Other effects observed
1. Psycho-socio--cultural difference	i. Poorly controlled diabetes, BP, and lipid levels, ii. Delays in diagnosis and treatment of T2D and CV diseases	—
2. Geno-phenotype difference	i. Higher percentage of body fat, ii. Higher BMI, iii. Higher frequency of atypical angina, iv. Higher rates of CMD such as MINOCA/INOCA, v. Longer QTc	—
3. Women-related factors	i. Polycystic ovarian syndrome (PCOS) ii. Premature ovarian insufficiency (POI) iii. Menopause	i. PCOS is associated with an increased risk of T2D, HTN, and CVD ii. POI is associated with an increased risk of CVD and CHD
4. Pregnancy--related factors	i. Pregnancy-induced hypertension (PIH) ii. Preeclampsia iii. Gestational diabetes mellitus (GDM) iv. Premature/ pre-term delivery (<37 weeks)	i. PIH, preeclampsia, and GDM are associated with an increased risk of future HTN, T2D, CVD, and CHD ii. Mothers having preterm delivery have shown an increased risk of HTN, T2D, and CVD
5. PK-PD difference	i. Lower plasma volume, ii. Lesser organ blood flow iii. Altered PK-PD of lipophilic vs. hydrophilic drugs iv. Altered plasma/tissue drug concentrations v. Altered hepatic enzyme activity (cytochrome 450 and P-glycoprotein family) vi. Altered drug clearance	i. Levels of metoprolol and propranolol in plasma are higher ii. Plasma statin concentrations are 15–20% higher iii. Metabolize lipophilic statins faster iv. Faster clearance of verapamil and amlodipine
6. Differential effects of anti-diabetes drugs	i. Greater response with TZDs ii. Lesser response to SUs iii. Lesser HbA1c but higher weight reduction with GLP-1RAs iv. More pronounced effect of GLP-1RAs on MACE outcome v. Less pronounced effect of SGLT2i on MACE outcome	i. Higher weight gain and edema risk with TZDs
7. Differential effects of CV drugs	i. The effect of statins in primary prevention is less evident ii. Lesser effect of ACEi on HHF iii. Lesser effect of BB on survival in HTN and HF iv. Lesser effect of digoxin on HHF in HF v. Lesser effect of GP-IIb/IIIa antagonists in ACS	i. Lower risk of stroke but not MI or CV death with statin in primary prevention ii. Increased ACM with digoxin in HF
8. Differential adverse events	i. Two-fold increase in cough with ACEi ii. Higher incidence of myopathy with statins iii. Higher incidence of amlodipine-induced edema iv. Higher incidence of hemorrhagic complications with anticoagulants, anti-platelets, and thrombolytics v. Increased electrolyte abnormalities with diuretics	i. Higher drug-induced torsades-de-pointes

ACM — all-cause mortality; ACS — acute coronary syndrome; BB — beta-blockers; BMI — body-mass-index; BP — blood pressure; CHD — coronary heart disease; CMD — coronary microvascular dysfunction; CV — cardiovascular; CVD — cardiovascular disease; GLP1-RAs — glucagon-like peptide-1 receptor agonists; GP-IIb/IIIa — glycoprotein-IIb/IIIa; HF — heart failure; HHF — hospitalization due to heart failure; HTN — hypertension; MI — myocardial infarction; MACE — major adverse cardiovascular events; MINOCA/INOCA — myocardial infarction/ischemia due to non-obstructive coronary disease; PCOS — polycystic ovarian syndrome; PK-PD — phenotype-genotype; SGLT2i — sodium-glucose transporter-2 inhibitors; SUs — sulfonylureas; T2D — type 2 diabetes; TZD — thiazolidinedione

underrepresented in randomized controlled trials. This was evident in older statins and aspirin trials. Notwithstanding, even most of the recent CVOTs trials exclude women of childbearing age where renin-angiotensin system blockers (RASB) are contraindicated owing to potential teratogenicity which could potentially impact the inclusion of women of reproductive age in clinical trials. Needless to say, more research is required to exactly know the biological mechanism underpinning the risk of CV disease in women.

Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and take responsibility for the integrity of the work. They confirm that this paper will not be published elsewhere in the same form, in English or in any other language, including electronically.

Conflict of interest

The authors declare no conflict of interest.

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