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INVITED EDITORIAL

Protecting women heart in Type 2 diabetes mellitus: why, how, and when?

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This editorial refers to 'Higher risk of adverse cardiovascular outcomes in females with type 2 diabetes mellitus: an umbrella review of systematic reviews' by C.Y.L. Yaow *et al*. https://doi.org/10.1093/eurjpc/zwad133

Cardiovascular diseases (CVD) are the leading global cause of morbidity and mortality in adults for decades.[1] Through major advances in acute and chronic management, we are witnessing the transition in some countries with malignant disease taking the lead, but more granular view reveals this is largely limited to men, as only Danish and Israeli women share these benefits with men.[2] Several reasons can contribute to higher cardiovascular mortality in women, including atypical clinical presentation, more comorbidities, and lower rates of medical referral[3] (*Figure 1*). In addition, women are less likely to be prescribed with medication to prevent incident cardiovascular disease. This was nicely demonstrated by Zhao *et al.*[4] in a systematic review and meta-analysis that included 2.2 million patients, where women were less likely prescribed with statins, aspirin, and neurohormonal medication than men.

It is essential to understand that lower reported incidence and prevalence of CVD in women is not related to the absence of the disease but rather to the limited capacity to diagnose disease. During the lifetime, women have additional risk factors beyond classical ones, which are present regardless of the biological sex. Pregnancy-related complications, hysterectomy, and hormonal variations throughout the entire lifetime impact the burden for development of the cardiovascular diseases.[5] With diabetes mellitus (DM) in spotlight, despite men have higher prevalence,[3] women carry a higher cardiovascular events risk. Particularities in women's CVD in DM pathophysiology include smaller hearts, more heart failure with preserved ejection fraction, obesity, and metabolic syndrome; importantly, all promote insulin resistance, limit physical activity, and worsen DM outcomes. Additionally, these changes are more pronounced when diabetes is diagnosed before menopause because of hormonal protection loss that leads to lipids' metabolism acceleration to promote earlier organ damage. Across the field of CVD, there are reports to highlight higher risk in women. This spans from risk factors as smoking, where women had 25% higher adjusted risk for coronary heart disease, to heart failure.[6]

As increased cardiovascular risk was consistent within the variety of trials and systematic reviews, an umbrella review was needed to confirm these findings. Yaow *et al.*[7] fill this gap with their elegant work about the diabetes mellitus impact on cardiovascular outcomes. They included 27 interventional and observational reviews, assessed also by external tools for objective qualitative characterization, that described similar numbers of low-, moderate-, and high-quality articles. The authors acknowledge the presence of heterogeneity of the included studies and the need for robust results from balanced epidemiology data to address the sex differences. Primary finding is that women had higher rates of overall coronary heart disease, acute coronary syndromes, and heart failure rates compared with men. Additionally, all-cause mortality, cardiovascular mortality, and coronary heart disease mortality were higher in diabetic women compared with their male counterparts. In this context, it was highlighted that women are diagnosed later, in advanced stages of the disease, when it is more likely to have a cardiovascular event.

The current review did not include data about diabetes medication or any analysis based on therapies. Nowadays, antidiabetic prescription considers cardiovascular outcomes, although decades ago the therapeutic resources for DM were limited, mainly based on insulin, sulfonylureas, thiazolidinediones, and biguanides.[8] Currently, there is increasing evidence these therapies are associated with worse prognosis. This likely resulted in no differences in all-cause mortality rates between women and men before 2001.

This umbrella review also reports that women in the general population have lower prescriptions of preventive medication, as the results of interventional reviews with glucagon-like peptide-1 receptor agonists, sodium glucose co-transporter-2 inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, statins, and aspirin mainly based on randomized controlled trials (RCT) did not meet significant differences in major adverse cardiac events (MACE) between the two groups. Supporting this hypothesis, the sub-group analysis based on percutaneous coronary intervention (PCI) trials identified higher odds rates for MACE and higher mortality rates in women compared with men, suggesting the presence of advanced disease and a higher number of comorbidities in females. Additionally, supporting evidence come from external meta-analysis[9] that showed women are less invasively treated

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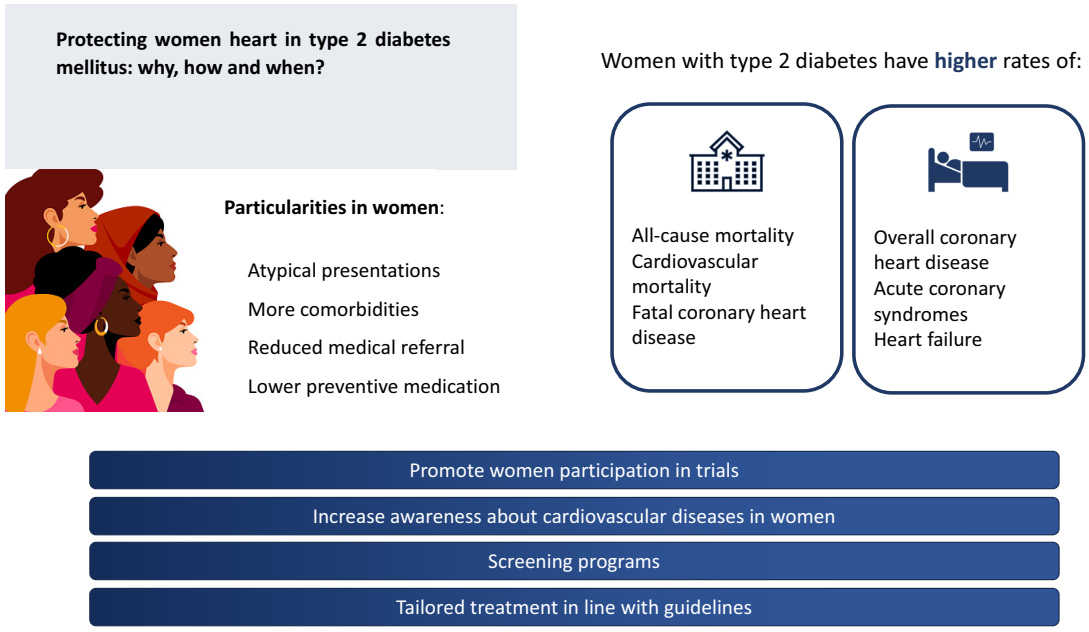

Figure 1

with primary PCI, with longer waiting times for invasive interventions in acute coronary syndromes compared with men.

Finally, women under-representation in clinical trials deserves some attention.[9,10] It may cause spurious perception about the epidemiology and lead to difficulties in result interpretation due to insufficient power for statistical analysis. To the best of our knowledge, there are no trials investigating cardiovascular outcomes in diabetic women; limited data are available about diabetes endpoints in pregnancy and peri-partum period. Limited evidence exists for cardiovascular rehabilitation programmes in women only population. The small number of women included in RCT limits the gender analysis understanding, as most of these are powered only for men. In near future, this may change as there are trials investigating medical and invasive therapies in women only.[11,12] This would also contribute to our understanding of pharmacokinetic differences between genders that currently are largely ignored.

Overall, women under-representation leads to limited capacity of proper recognition of the diseases, with the consequence of an abnormal perception of the global cardiovascular burden in women's cardiovascular disease. Gender discrimination is visible across the trial designs (eligibility, design, recruitment) or participants barriers, including educational, social, cultural, or financial support.[13] In the last years, regulatory agencies require specific criteria of minimum females' participation, but this is focusing on younger than 65-year-old White women, which ignores then global ageing of the population and multi-ethnicity.[14]

The guidelines usually are accepted globally although many trials were conducted only in few countries. In their review,[7] authors reported significant geographical differences, when divided in Asian, North American, and Western Europe regions, possibly related to the higher impact of modern risk factors in Western areas—more obesity, processed food consumption, and smoking compared with Asian countries. Also, we need to consider the existence of cardiovascular screening programmes in the Asian population. Despite big three regions analysed, there is still a scarcity in the global overview of women cardiovascular burden. Middle East, Africa, Central and Eastern Europe, Australia, and South America regions have not been included in the current analysis. Geographical preferences lead to social and ethnic discrimination and limit researchers and physicians understanding of the actual CVD impact and biological differences. In specific regions, women face additional unequal rights in terms of healthcare access in men's favour, in a 'man' orientated manner.

The current paper[7] highlights a lack of understanding in women's global cardiovascular burden. Current 2021 European guidelines for cardiovascular prevention[15] acknowledge sex-related differences requiring specific health concerns, with physiological differences in heart structure, function, adverse drug reactions, and overall general awareness. Nowadays, the gaps in evidence were reached within the recently published European guidelines for the management of cardiovascular diseases in patients with diabetes,[16] where new recommendations for a systematic survey of cardiovascular symptoms have been summarized, with additional diagnostic tests requested in suspected heart failure. This umbrella review brings clinical value, empowering women needs for diagnosis processes improvements, along with adequate treatment to improve cardiovascular outcomes. The authors address women with diabetes, although existing data show that the worse prognosis is consistent with additional risk factors, suggesting gender-related increased risk.

In conclusion, this umbrella review[7] addresses the worldwide problem of cardiovascular disease in diabetic women and identifies several potential action points (*Figure 1*). Women around the world should have same access to healthcare, both for preventive and curative strategies, supporting awareness in women's cardiovascular disease. Women should benefit equally as men from tailored treatment for cardiovascular diseases and associated comorbidities in line with current recommendations. Physicians must be aware of the high burden of cardiovascular diseases in women and implement screening programmes and prescription of the available therapeutic resources. We look forward to alleviating the gender bias, along with greater inclusion of diverse ethnic and geographic groups in future cardiovascular trials.

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Data availability

There are no new data associated with this article.

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