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Commentary

A commentary on "Gender disparities in coronary artery disease: current state of affairs and future directions"

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Commentary

Coronary artery disease (CAD) is a significant health issue in the United States. Siddiqui and colleagues recently published a manuscript titled "Gender disparities in coronary artery disease: a review of factors influencing clinical outcomes," which excellently describes the current state of affairs and outcomes of CAD between men and women [1]. It is important to recognize that while men and women share common cardiovascular risk factors such as diabetes, hyperlipidemia and obesity, each of these risk factors have more severe consequences in women compared to men [2]. However, the presence of estrogen is a critical turning point in cardiovascular disease. Estrogen plays a critical role in halting atherosclerotic progression. This hormone works by downregulating both the renin-angiotensin-aldosterone system (RAAS) and fibrinolytic pathways. Both pathways will eventually lead to hypertension and CAD if left unchecked [3]. In menopause, the sudden decrease in estrogen unleashes these harmful pathways, which not only catalyze the progression of CAD but also worsens weight gain and hyperlipidemia [3]. Ultimately, leading to worsening cardiovascular outcomes at earlier ages. Furthermore, estrogen has antioxidant characteristics that mitigate free radial damage to the endothelium [4]. The hormone also contributes to distribution of body fat, in menopause there is an increased risk of abdominal obesity which predisposes to insulin resistance and later DM [4,5]. In addition to estrogen, women also are predisposed to irregularities in sirtuin expression [6]. Sirtuins is a family of seven proteins involved in critical physiologic and aging functions such as cellular homeostasis, cellular metabolism, DNA damage, and senescence [6]. When expressed normally, Sirtuins are protective against cardiovascular disease [6]. Sirtuin1 is an important protein with anti-aging properties, cell circadian rhythm, and cell apoptosis [6,7]. There is a push to explore this protein thanks to its anti-aging characteristics [7]. It also plays a key part in nitric oxide homeostasis and epigenetic regulation. Sirtuin1 influences the expression of p53, immune regulation and glucose metabolism [7,8]. As such its dysregulation is linked to the development of diabetes, neurodegenerative disorders such as Parkinson's Disease and Alzheimer's Disease, non-alcoholic fatty liver disease, and autoimmune disorders [8]. However, especially in pregnancy, decreased expression of sirtuin1 is believed to contribute to the pathophysiology of preeclampsia as defects in sirtuin2, 3, and 4 are found to be present [6]. Following this discovery, sirtuin activating compounds and nicotinic adenine dinucleotide (NAD) boosters are being explored as potential therapeutic agents for the treatment of various cardiovascular diseases [6]. To date, the sirtuin activating agent resveratrol has shown promise in increasing sirtuin1 activity and preventing abnormal cardiac remodeling in those with hypertension [9]. Moreover, adverse pregnancy outcomes (APO) encompassing preeclampsia, gestational DM, and pre-term delivery are increasingly becoming acknowledged as perpetrators of CAD. While not evident in the short run, APOs were found to have contributed to downstream cardiovascular disease decades after the last pregnancy and delivery [10,11]. Siddiqui and colleges make an interesting point in highlighting non-traditional risk factors for cardiovascular disease. Among the not well recognized, depression

and intimate partner violence are both significant risk factors for the development of CAD. While they do not directly cause cardiovascular disease, these conditions lead to chronic stress, which can manifest as somatic symptoms through autonomic dysregulation and predispose the victim to unhealthy and maladaptive lifestyle choices [12–14]. Expanding on this topic, post-traumatic stress disorder (PTSD) was shown to expedite the development of cardiovascular disease through autonomic dysregulation. The prevalence of PTSD is 10-12% in women and 5-6% in men [15]. Exposure to chronic stress alters the hypothalamic-pituitary-adrenal axis as well as the autonomic nervous system, leading to elevated levels of catecholamines, which in turn elevate basal heart rate and blood pressure [16]. Anxiety disorders were also studied in their association with cardiovascular disease. A meta-analysis conducted by Emdin *et al.* found that anxiety will increase the risk of CAD by 41% and stroke by 71% [17]. Overall, anxiety disorders in conjunction with depression ought to be better recognized as important risk factors for cardiovascular disease [18].

Furthermore, women are especially at higher risk of complications and death due to coronary artery disease. In acute coronary syndromes (ACS) such as MI manifesting as a ST-elevation MI (STEMI) or non-ST-elevation MI (NSTEMI), women were found to have non-conventional symptoms of ACS [19,20]. While chest pain and shortness of breath are both ubiquitous symptoms, women can have nausea, vomiting, fatigue, dizziness, and syncope [19,20]. Pain is often found in the jaw, interscapular region, or neck [19,20]. Due to the under recognition of atypical symptoms manifesting as MI, women are less likely to receive fibrinolytic therapy, percutaneous coronary intervention (PCI), or both compared to men [21]. Similarly, women are less likely to achieve a timely door-to-balloon time [22]. In the last two decades, trends in the incidence of myocardial infarction (MI) have remained similar for men; on the other hand, women were noted to have an increasing incidence of MI starting at earlier ages [23]. Compared to men, women were found to have more focal CAD compared to men [24]. With physiologic equivocal lesions based on fractional flow reserve (FFR), women reported frequent angina and worse quality of life compared to men [24]. Spontaneous coronary artery dissection (SCAD) is the separation of the intimal layers of the coronary artery without significant trauma or pre-existing atherosclerosis. Despite accounting for 1–4% of ACS events, 90% of the patients with SCAD are women [25]. SCAD does not have the traditional or atypical risk factors found in both sexes. Typically, SCAD is associated with emotional stressors, changes in hormone concentrations and connective tissue disease [25]. These differences are not unique to Western nations. In a Saudi Arabian study, unstable angina is more likely to be diagnosed in women and men had higher rates of STEMI compared to women. Women had less left anterior descending artery occlusion incidence compared to men [26]. Medical therapy was pursued more often in women and women also received less interventions. Elsewhere, women who present with STEMI had higher rates of stroke, in hospital and out of hospital mortality after undergoing percutaneous intervention (PCI) in a Singaporeon center [27].

Apart from ACS, women who present with chest pain should also be evaluated for non-obstructive CAD/coronary microvascular dysfunction (CMD). CMD is defined as anginal symptoms without significant coronary artery disease on angiography. As 50% of women who undergo coronary angiograms for angina symptoms will have normal findings, CMD is an important diagnosis to consider in this population [28]. Angina due to non-obstructive CAD is often attributed to coronary vasospasms, hypercoagulable state, and oxidative stress [28]. As a result, these patients with non-obstructive CAD can have symptoms at rest, not determined by their excursion. APOs, systemic inflammatory syndromes (such as autoimmune disorders), and prior chemotherapy for breast cancer are all unique risk factors for the development of CMD in women [28]. While the sex-difference of CMD is not well elucidated, experts postulate that the loss of estrogen catalyzes the loss of healthy endothelium [29]. Therefore, to better understand and risk-stratify women, it is imperative to have a comprehensive history and physical that thoroughly explores each unique risk factor women can have. Traditional stenosis-style approaches to risk stratification of CAD often lead to the underdiagnosis and delayed/poor treatment of these women [30]. Furthermore, risk stratification calculators such as the Framingham Risk Score fail to account for these unique risk factors [30].

Medical management of these diseases is the same as men, anti-anginal regimens consisting of beta-blockers, calcium channel blockers, and nicorandil. Additionally, risk factor-specific therapies such as angiotensin-converting enzyme inhibitors (ACEi) and statins are beneficial. However, studies have shown that women are less frequently prescribed statins, beta-blockers, and ACEi [31,32]. Once rejected, hormone replacement therapy (HRT) is now being re-evaluated for potential cardiovascular benefit. Recent studies demonstrate that the initiation of HRT within 10 years of menopause can mitigate the risk of cardiovascular disease [33]. Clear benefit was seen in those 50–59; however, experts warn that HRT can increase cardiovascular risk in those older than 70 and should be used with caution in women ages 60–69 [34].

As mentioned by Siddiqui and colleges, it is concerning that gender disparities exist in research. In the early clinical trials investigating ACS and CAD, women were underrepresented which hinders the generalizability of these trials [1]. Experts found that socioeconomic determinants of health including education, capital, and race are all contributing factors to this problem [1,2]. Even in the outpatient setting, women were found to delay seeking medical help [35]. They are less likely to be prescribed cardioprotective medications and undergo invasive interventions for the evaluation and treatment of CAD [2,35,36]. Black women, especially, suffer a higher cardiovascular disease burden compared to their white counterparts. To address these issues, one intervention being one within hospitals is the AHA's Get With the Guidelines initiative (GWTG) [37]. This movement incorporates a multidisciplinary team to educate clinicians on better guideline-based practices to reduce variability amongst the treated populations [37]. Other interventions include sex-sensitive data gathering for clinical trials, all-female intervention teams and routine domestic violence screening [38]. However, policies aimed to directly intervene on gender disparities have been slow to implement. The difficulty of the creation and enforcement of these interventions are attributed to lack of political commitment, deep-seated gender norms, lack of awareness and lack of funding [38,39].

One limitation of this piece is there is a lack of recent research on the effectiveness of implementation programs or interventions designed to reduce gender disparities. While Siddiqui *et al.* mention programs to spread awareness, hormone replacement therapy and even the use of artificial intelligence (AI) as potential solutions, these interventions have little evidence supporting their efficacy. As such, discussion on solutions is limited, and for now remains theoretical.

Overall, the problem of reducing disparities between men and women remains an elusive challenge. Future research and efforts should focus on increasing female representation in clinical research and on incorporating female-specific risk factors, such as psychosocial history, menses, and socioeconomic status, into the risk stratification calculus. Therefore, a multidisciplinary approach (including both medical and political perspectives) is required not only to address this disparity but also to raise awareness of the problem among physicians.

Conflict of Interest

None.

References

1. Siddiqui A, Gill R, Ringor M, Dugal JK, Malhi A, Abdallah A, et al. Gender disparities in coronary artery disease: a review of factors influencing clinical outcomes. Neth Heart J. 2025 Dec;33(12):377–84.
2. Kim HL. Sex differences in coronary atherogenesis: a narrative review. Ewha Med J. 2024 Apr;47(2):e15.
3. Kryczka KE, Kruk M, Demkow M, Lubiszewska B. Fibrinogen and a Triad of Thrombosis, Inflammation, and the Renin-Angiotensin System in Premature Coronary Artery Disease in Women: A New Insight into Sex-Related Differences in the Pathogenesis of the Disease. Biomolecules. 2021 Jul 15;11(7):1036.
4. Niranjan MK, Koiri RK, Srivastava R. Expression of estrogen receptor alpha in response to stress and estrogen antagonist tamoxifen in the shell gland of Gallus gallus domesticus: involvement of anti-oxidant system and estrogen. Stress. 2021 May;24(3):261–72.
5. Janssen I, Powell LH, Kazlauskaite R, Dugan SA. Testosterone and visceral fat in midlife women: the Study of Women's Health Across the Nation (SWAN) fat patterning study. Obesity (Silver Spring). 2010 Mar;18(3):604–10.
6. Ding YN, Wang HY, Chen XF, Tang X, Chen HZ. Roles of Sirtuins in Cardiovascular Diseases: Mechanisms and Therapeutics. Circ Res. 2025 Feb 28;136(5):524–50.
7. Martins IJ. Anti-aging genes improve appetite regulation and reverse cell senescence and apoptosis in global populations. Scientific Research. 2016;5:9–26.
8. Martins IJ. Single gene inactivation with implications to diabetes and multiple organ dysfunction syndrome. Journal of Clinical Epigenetics. 2017 Aug 1;3(3):1–8.
9. Zheng X, Hai J, Yang Y, Zhang C, Ma X, Kong B, et al. Effects of resveratrol supplementation on cardiac remodeling in hypertensive patients: a randomized controlled clinical trial. Hypertens Res. 2023 Jun;46(6):1493–503.
10. Crump C, Sundquist J, McLaughlin MA, Dolan SM, Govindarajulu U, Sieh W, et al. Adverse pregnancy outcomes and long term risk of ischemic heart disease in mothers: national cohort and co-sibling study. BMJ. 2023 Feb 1;380:e072112.
11. Venkatesh KK, Khan SS, Yee LM, Wu J, McNeil R, Greenland P, et al; Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b), and nuMoM2b–Heart Health Study (HHS) Investigators. Adverse Pregnancy Outcomes and Predicted 30-Year Risk of Maternal Cardiovascular Disease 2-7 Years After Delivery. Obstet Gynecol. 2024 Jun 1;143(6):775–84.
12. Carney RM, Freedland KE. Depression and coronary heart disease. Nat Rev Cardiol. 2017 Mar;14(3):145–55.
13. Krittanawong C, Maitra NS, Qadeer YK, Wang Z, Fogg S, Storch EA, et al. Association of depression and cardiovascular disease. The American journal of medicine. 2023 Sep 1;136(9):881–95.
14. Zeng J, Qiu Y, Yang C, Fan X, Zhou X, Zhang C, et al. Cardiovascular diseases and depression: A meta-analysis and Mendelian randomization analysis. Molecular psychiatry. 2025 Sep;30(9):4234–46.
15. Olff M. Sex and gender differences in post-traumatic stress disorder: an update. European journal of psychotraumatology. 2017 Sep 29;8(sup4):1351204.
16. Coughlin SS. Post-traumatic stress disorder and cardiovascular disease. The open cardiovascular medicine journal. 2011 Jul 11;5:164.
17. Emdin CA, Odutayo A, Wong CX, Tran J, Hsiao AJ, Hunn BH. Meta-Analysis of Anxiety as a Risk Factor for Cardiovascular Disease. Am J Cardiol. 2016 Aug 15;118(4):511–9.
18. Vogelzangs N, Seldenrijk A, Beekman AT, van Hout HP, de Jonge P, Penninx BW. Cardiovascular disease in persons with depressive and anxiety disorders. Journal of affective disorders. 2010 Sep 1;125(1-3):241–8.
19. Joseph NM, Ramamoorthy L, Satheesh S. Atypical Manifestations of Women Presenting with Myocardial Infarction at Tertiary Health Care Center: An Analytical Study. J Midlife Health. 2021 Jul-Sep;12(3):219–24.
20. DeVon HA, Mirzaei S, Zègre-Hemsey J. Typical and Atypical Symptoms of Acute Coronary Syndrome: Time to Retire the Terms? J Am Heart Assoc. 2020 Apr 7;9(7):e015539.
21. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, et al Get With the Guidelines Steering Committee and Investigators. Sex differences in medical care and early death after acute myocardial infarction. Circulation. 2008 Dec 16;118(25):2803–10.
22. Mirzaei S, Steffen A, Vuckovic K, Ryan C, Bronas UG, Zegre-Hemsey J, et al. The association between symptom onset characteristics and prehospital delay in women and men with acute coronary syndrome. Eur J Cardiovasc Nurs. 2020 Feb;19(2):142–54.
23. Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, et al. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction: the ARIC Community Surveillance Study. Circulation. 2019 Feb 19;139(8):1047–56.
24. Brouwers S, Munhoz D, Storozhenko T, Sakai K, Arslani K, Engstrom T, C et al. Gender differences in coronary artery disease patterns. European Heart Journal. 2024 Oct;45(Supplement_1):ehae666–1401.
25. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. American Heart Association Council on Peripheral Vascular Disease; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Stroke Council. Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement From the American Heart Association. Circulation. 2018 May 8;137(19):e523–57
26. Sayed AI. Gender Differences in Coronary Artery Disease, Clinical Characteristics, and Angiographic Features in the Jazan Region, Saudi Arabia. Cureus. 2022 Oct 12;14(10):e30239.
27. Ngiam JN, Thong EH, Loh PH, Chan KH, Chan MY, Lee CH, et al. An Asian Perspective on Gender Differences in In-Hospital and Long-Term Outcome of Cardiac Mortality and Ischemic Stroke

after Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction. J Stroke Cerebrovasc Dis. 2022 Jan;31(1):106215.

28. Kuruvilla S, Kramer CM. Coronary microvascular dysfunction in women: an overview of diagnostic strategies. Expert Rev Cardiovasc Ther. 2013 Nov;11(11):1515–25.
29. Reynolds HR, Bairey Merz CN, Berry C, Samuel R, Saw J, Smilowitz NR, de Souza ACDAH, et al. Coronary Arterial Function and Disease in Women With No Obstructive Coronary Arteries. Circ Res. 2022 Feb 18;130(4):529–51.
30. Brown HL, Warner JJ, Gianos E, Gulati M, Hill AJ, Hollier LM, et al. Promoting Risk Identification and Reduction of Cardiovascular Disease in Women Through Collaboration With Obstetricians and Gynecologists: A Presidential Advisory From the American Heart Association and the American College of Obstetricians and Gynecologists. Circulation. 2018 Jun 12;137(24):e843–52
31. Zhao M, Woodward M, Vaartjes I, Millett ERC, Klipstein-Grobusch K, Hyun K, et al. Sex Differences in Cardiovascular Medication Prescription in Primary Care: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2020 Jun 2;9(11):e014742.
32. Alhassan HA, Mann H, Chiu L, Malik B, Countouris M, Johnson AE. Sex Differences in Pharmacologic Optimal Medical Therapy for Ischemic Heart Disease. JACC Adv. 2026 Mar 23:102691
33. Hodis HN, Mack WJ. Menopausal Hormone Replacement Therapy and Reduction of All-Cause Mortality and Cardiovascular Disease: It Is About Time and Timing. Cancer J. 2022 May-Jun 01;28(3):208–223.
34. Rossouw JE, Aragaki AK, Manson JE, Szmuilowicz ED, Harrington LB, Johnson KC, et al. Menopausal Hormone Therapy and Cardiovascular Diseases in Women With Vasomotor Symptoms: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials. JAMA Intern Med. 2025 Nov 1;185(11):1330–9.
35. Kaul P, Armstrong PW, Sookram S, Leung BK, Brass N, Welsh RC. Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction. Am Heart J. 2011 Jan;161(1):91–7.
36. Daly C, Clemens F, Lopez Sendon JL, Tavazzi L, Boersma E, Danchin N, et al. Gender differences in the management and clinical outcome of stable angina. Circulation. 2006 Jan 31;113(4):490–8.
37. Alcalde-Rubio L, Hernández-Aguado I, Parker LA, Bueno-Vergara E, Chilet-Rosell E. Gender disparities in clinical practice: are there any solutions? Scoping review of interventions to overcome or reduce gender bias in clinical practice. Int J Equity Health. 2020 Sep 22;19(1):166.
38. Crespí-Lloréns N, Hernández-Aguado I, Chilet-Rosell E. Have Policies Tackled Gender Inequalities in Health? A Scoping Review. Int J Environ Res Public Health. 2021 Jan 5;18(1):327.
39. Sgraja S, Mollenhauer J, Seeland U, Kloepfer M, Kurscheid C, Amelung V. Closing the Gap: Implementing Gender-Sensitive Care to Address Healthcare Disparities. Eur J Public Health. 2024 Oct 28;34(Suppl 3):ckae144.607.