Indian J Med Res 156, September 2022, pp 365-367 DOI: 10.4103/ijmr.ijmr_1571_22

Editorial



Levelling the field of cardiovascular disease in women

Cardiovascular disease (CVD) is the leading cause of mortality in women^{1,2}. Worrisome data originating from socially deprived regions where women have higher CVD mortality than men have been summarized in the updated version of the Global Burden of CVDs report³. A significant increase in myocardial infarction (MI) in female patients is also observed^{4,5}. However, women are affected by a wide range of conditions, such as MI with non-obstructive coronary disease and ischaemia with non-obstructive coronary disease, which are more common in women⁶. Such diagnoses are also associated with a high rate of misdiagnosis. Despite increasing awareness of sex-based dissimilarities, the underlying mechanisms remain poorly understood. As such, specific indications have rarely been elaborated to provide sex-related management algorithms for women. As a result, guidelines from most international scientific societies rarely include specific recommendations for women.

The lack of sex-tailored therapeutic flowcharts is counterproductive and does not promote a patient-centred approach, which has become integral to clinical practice. Several considerations may offer partial explanation for such apparent incongruity. First, women are significantly under-represented in clinical trials because they are excluded at baseline due to excessive comorbidities or age restrictions, or because they tend to be more frequently referred to surgical rather than interventional procedures. This is often the case with complex and diffused coronary artery disease, especially left main lesions, for which the outcomes in women have historically been in favour of surgery7. As a result, the data available to thoroughly understand the sex-specific features of such CVD in women are scarce and are likely not enough to outline tailored treatment pathways. What confounds this is the emerging data presented at the 57th annual meeting of The Society of Thoracic Surgeons (STS 2021), indicating that women were 14-22 per cent less likely than men to undergo coronary artery bypass graft (CABG) procedures with these revascularization strategies⁸. The ROMA Women (randomization of single *vs.* multiple arterial grafts). Study is a global trial randomizing 2100 female patients undergoing primary isolated non-emergent CABG to either single or multiple arterial grafts. Enrolment is expected to be completed after 2022⁹.

Conversely, recent registries regarding interventional procedures for valvular heart diseases, especially transcatheter aortic valve replacement (TAVR), have enrolled a high percentage of women, allowing for a comprehensive analysis of risk factors, pathophysiology and short and long-term outcomes. However, this knowledge has not been incorporated into sex-specific practices so far¹⁰.

Notable obstacles can also be identified within the medical community: the interest towards understanding and managing CVD in women belongs mainly to female practitioners. Unsurprisingly, the first authors and/or the senior authors of the main registries focussing on sex-specific outcomes in CVDs are women¹¹. However, a strong sex inequality characterizes clinical trial leadership, with women still representing only 10 per cent of lead authors of cardiovascular clinical trials published in high-impact journals¹². Despite the increase in the number of women graduating medical schools who choose to pursue a career in the cardiovascular field, women principal investigators remain a small number¹¹. This evidence is a clear indication that fewer women are granted opportunities in research and academia where they are able to collect, analyze and present their work.

Considering the overall discouraging picture, numerous national and international societies of

This editorial is published on the occasion of World Heart Day - September 29, 2022.

^{© 2022} Indian Journal of Medical Research, published by Wolters Kluwer - Medknow for Director-General, Indian Council of Medical Research

cardiology, as well as independent organizations, have acknowledged the wide range of differences and disparities and have confronted the challenge to create equal opportunities and ultimately to promote the growth of a community of women in cardiology working for women based on merit^{13,14}. Most initiatives focus on reducing the burden of under-recognition and suboptimal treatment of CVD in women, on investing in further sex-specific research and on encouraging and guiding female cardiologists who choose to train and practice in the interventional field. Among the notable, the EAPCI Women Committee, Women in Cardiology - ACC, Women in Innovations (WIN) SCAI and WIN - Asian Pacific Society of Interventional Cardiology deserve to be mentioned as active and charismatic branches of the corresponding international societies and are joined by independent organizations such as 'Women as One'15-19. The wide range of registries, sub-studies and consensus documents produced by such organizations has contributed to building the pillars of our knowledge of CVD in women.

Most recently, a thorough and comprehensive analysis of the existing evidence has been offered by the Lancet Women and CVD Commission, which points out knowledge gaps in research, prevention, treatment and access to care for women, ultimately aiming at offering high-quality, specific recommendations to reduce the burden of CVD in women by 2030²⁰. Alongside the well known prevalence of CVD and the differences with analogous diseases in men, the Commission offers an all-around overview of the multiple facets of the disease in women, with a special focus on under-recognized risk factors, on understudied pathophysiology and on the absence of established global policies to coordinate prevention and treatment of CVD in women.

Besides the well established, traditional risk factors associated with CVD, the Commission highlights the contribution to the global burden of the disease of sex-specific factors, including premature menopause, pregnancy-related risk factors and autoimmune/inflammatory disorders, as well as under-recognized aspects, such as psychological, socio-economic and geographical factors. The latter are mainly due to lack of education, low awareness, substandard quality of care and inequitable access to healthcare in the regions of Asia, Western Europe, Africa and Latin America and surely contribute to the higher prevalence of CVD in such countries. Moreover, the inadequacy of educational and prevention programmes may also be responsible for the increase of MI among young women. Unquestionably, more effort and funding must be put into educating women and increasing the accessibility to healthcare institutions in developing countries.

The Commission also addresses the disease-specific underlying pathophysiological differences, clinical presentations and outcomes and offers recommendations by disease. The key highlighted issue is the lack of sex-specific information and sex-oriented analyses, mainly due to the under-representation of women in clinical trials. Therefore, the Commission recommends measures meant to increase eligibility of female patients for clinical trials by removing age limitations and educating the medical personnel and primary care physicians about the importance of enrolling women, as well as initiatives to ease the follow up process, to limit the study retention.

Ultimately, the medical community should aim at closing the gaps in knowledge, enhancing and promoting awareness of CVD in women and targeting under-recognized risk factors to scale up the quality of care and meet the target of optimized and personalized protocols for female patients. On the other hand, building comprehensive teams of medical professionals and expanding opportunities for female practitioners will have the ultimate goal of improving outcomes for women by obtaining high-quality evidence and by enabling the cardiovascular societies to provide sex-specific recommendations.

Financial support & sponsorship: None.

Conflicts of Interest: Author (AC) reports speaker consultant fees from Abbott, Abiomed, Boston Scientific, Biosensor; all other authors declare no conflicts of interest.

Giulia Botti¹, Valeria Paradies², Mirvat Alasnag³ & Alaide Chieffo^{1,*}

¹Interventional Cardiology Unit, Cardio-Thoracic-Vascular Department, IRCCS San Raffaele Scientific Institute, Milan, Italy, ²Department of Cardiology, Maasstad Hospital, Rotterdam, The Netherlands & ³Cardiac Center, King Fahd Armed Forces Center, Jeddah, Saudi Arabia **For correspondence:* chieffo.alaide@hsr.it

Received July 15, 2022

References

- 1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, *et al.* Heart disease and stroke statistics-2019 update: A report from the American Heart Association. *Circulation* 2019; *139* : e56-528.
- Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, *et al.* Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol* 2017; 70 : 1-25.
- Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, *et al.* Global burden of cardiovascular diseases and risk factors, 1990-2019: Update from the GBD 2019 Study. *J Am Coll Cardiol* 2020; 76 : 2982-3021.
- Gabet A, Danchin N, Juillière Y, Olié V. Acute coronary syndrome in women: Rising hospitalizations in middle-aged French women, 2004-14. *Eur Heart J* 2017; 38: 1060-5.
- Arora S, Rosamond WD, Caughey MC. Response by Arora et al to letter regarding article, "twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction: The ARIC community surveillance study." *Circulation* 2019; 140: e331-2.
- Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, *et al.* An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with european society of cardiology working group on coronary pathophysiology & microcirculation endorsed by coronary vasomotor disorders international study group. *Eur Heart J* 2020; *41* : 3504.
- Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti R, Garcia Garcia HM, *et al.* Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. *Eur Heart J* 2012; *33* : 3105-13.
- 8. The Society of Thoracic Sergeons. Women undergo less aggressive open heart surgery, experience worse outcomes than men. Available from: https://www.sts.org/media/news-releases/women-undergo-less-aggressive-open-heart-surgery -experience-worse-outcomes-men, accessed on September 18, 2022.
- 9. Gaudino M, Alexander JH, Bakaeen FG, Ballman K, Barili F, Calafiore AM, *et al*. Randomized comparison of the clinical

outcome of single versus multiple arterial grafts: The ROMA trial-rationale and study protocol. *Eur J Cardiothorac Surg* 2017; *52* : 1031-40.

- Masiero G, Paradies V, Franzone A, Bellini B, De Biase C, Karam N, *et al.* TAVI specific sex consideration. *Mini Invasive Surg* 2022; 6:4.
- van Spall HG, Lala A, Deering TF, Casadei B, Zannad F, Kaul P, *et al.* Ending gender inequality in cardiovascular clinical trial leadership: JACC review topic of the week. *J Am Coll Cardiol* 2021; 77 : 2960-72.
- Denby KJ, Szpakowski N, Silver J, Walsh MN, Nissen S, Cho L. Representation of women in cardiovascular clinical trial leadership. *JAMA Intern Med* 2020; *180* : 1382-3.
- 13. Ortega RF, Mehran R, Morice, MC. The opportunity of women as one. *JACC: Case Reports* 2020; *2* : 2044-6.
- Buchanan GL, Mehilli J, Kunadian V, Radu MD, Chieffo A. The invisible army of women in interventional cardiology: EAPCI Women mission to make them visible. *EuroIntervention* 2018; 14: e1158-9.
- European Society of Cardiology. The EAPCI Women Initiative. Available from: https://www.escardio.org/Sub-specialtycommunities/European-Association-of-Percutaneous-Car diovascular-Interventions-(EAPCI)/Membership-and-Comm unities/The-EAPCI-Women-Initiative, accessed on September 16, 2022.
- American College of Casrdiology. Women in cardiology section. Available from: https://www.acc.org/membership/ sections-and-councils/women-in-cardiology-section, accessed on September 16, 2022.
- Society of Cardiovascular, Angiography & Interventions. Women in innovations (WIN). Available from: https:// scai.org/membership/professional-development/ women-innovations-win, accessed on Septembeer 18, 2022.
- Asian Pacific Society Of Interventional Cardiology (APSIC). *Home.* Available from: *https://www.apsic.net*, accessed on September 18, 2022.
- Women as One. Available from: https://womenasone.org, accessed on September 18, 2022
- Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, *et al.* The Lancet women and cardiovascular disease Commission: Reducing the global burden by 2030. *Lancet* 2021; 397 : 2385-438.