



## Editorial

### Levelling the field of cardiovascular disease in women

Cardiovascular disease (CVD) is the leading cause of mortality in women<sup>1,2</sup>. Worrying 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 report<sup>3</sup>. A significant increase in myocardial infarction (MI) in female patients is also observed<sup>4,5</sup>. 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 women<sup>6</sup>. 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 surgery<sup>7</sup>. 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 57<sup>th</sup> 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 strategies<sup>8</sup>. 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 2022<sup>9</sup>.

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 far<sup>10</sup>.

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 women<sup>11</sup>. 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 journals<sup>12</sup>. 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 number<sup>11</sup>. 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

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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<sup>13,14</sup>. 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'<sup>15-19</sup>. 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 2030<sup>20</sup>. 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.

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**Giulia Botti<sup>1</sup>, Valeria Paradies<sup>2</sup>, Mirvat Alasnag<sup>3</sup> & Alaide Chieffo<sup>1,\*</sup>**

<sup>1</sup>Interventional Cardiology Unit, Cardio-Thoracic-Vascular Department, IRCCS San Raffaele Scientific Institute, Milan, Italy, <sup>2</sup>Department of Cardiology, Maasstad Hospital, Rotterdam, The Netherlands & <sup>3</sup>Cardiac Center, King Fahd Armed Forces Center, Jeddah, Saudi Arabia

\*For correspondence:  
chieffo.alaide@hsr.it

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