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EXPERT OPINION

CARDIOVASCULAR RESEARCH Onlife

COVID-19, the wake-up call for implementing sex and gender in cardiovascular disease

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The COVID-19 pandemic has once again shown that gender diversity, ethnic disparities, lifestyle factors, and socio-economic circumstances are crucial determinants of health. The relatively higher hospitalization and mortality rates seen in (elderly) men who are overweight and among ethnic minorities with poorer living conditions have been striking all over the world.[1] Factors including higher education attainment and household income, younger age, better physical fitness, and a healthier living environment are all determinants of favourable COVID-19 outcomes. In addition, sex and age differences in gene expression of angiotensin-converting enzyme 2 (ACE2) and immune response, which are linked to several loci on the X-chromosome, importantly contribute to a lower susceptibility for the infection and better survival in women.[2–5] However, sex differences in reactions to various treatment options have been reported and should be investigated further and applied if appropriate.[5] It is unclear yet whether the long-term sequelae of a prior COVID-19 infection, with persistent and significant impairment of exercise capacity and health status, are comparable among men and women.

These recent findings should act as a wake-up call to speed up the incorporation of sex- and gender, ethnic diversity, and socioeconomic factors in both basic science and clinical practice in many areas of medicine.[6] When focusing on ischemic heart disease (IHD), the evolving techniques in invasive and non-invasive imaging and adequate gender powered studies have revealed many clinically relevant sex- and age-dependent differences in the pattern of coronary and myocardial ageing.[7] Women have more frequent angina with less extensive obstructive coronary artery disease (CAD) and less severe ischemia than men.[8,9] In addition, coronary vasomotor disorders contribute importantly to the burden of anginal symptoms. Only recently, the first position paper has been published with clear guidance for patients with angina based on non-obstructive CAD (INOCA) with/without coronary vasomotor disorders.[10] As this is the dominant pattern of stable IHD in women, the proposed diagnostic and therapeutic pathways are an important leap forward in better care for our female patients, as their appropriate diagnosis is often deferred or delayed.

Sex and gender differences in inflammation dominate in the pathophysiology of coronary and myocardial ageing and are also expressed in its risk factors and comorbidities.[11] Immune reactivity increases in women during and after menopause transition. Autoimmune rheumatic and endocrine disorders such as rheumatic arthritis, systemic lupus erythematosus, antiphospholipid syndrome, Sjøgren-syndrome, irritable bowel disease, and thyroid disorders are more prevalent in women than in men and are associated with an increased IHD risk.[6] In addition, sex-specific risk factors such as hypertensive pregnancy disorders and gender aspects of psychosocial chronic stress also contribute to the activation of the endothelium in a proinflammatory state.[11,12] Clinically relevant sex differences in heart failure may be attributable to the different predisposition to obstructive CAD in men vs. INOCA and coronary vasomotor disorders/endothelial inflammation in women.[13] We should learn to take the life-course and comorbidities more into account in order to do justice to individual health problems in our male and female patients.

Sex-based differences in CVD, risk factors, and co-morbidities interact with each other and often intermingle in symptom presentation. In daily life, this often does not match with the description of symptoms in our guidelines that focus on a single disease entity, mostly from the male patient perspective. Daily occurring examples are residual symptoms of angina, dyspnoea, and loss of energy after a recent percutaneous coronary intervention. It happens too often that repeated coronary angiograms are done to check for stent re-stenoses, whereas a serious elevated blood pressure is the real cause of these symptoms and easy to treat. Hypertension is one of the major triggers for coronary vascular dysfunction and co-exists with obstructive and non-obstructive CAD. It also affects circumferential strain which may induce abnormal coronary reactivity. The latest Global Burden of Disease 2019 data showed that elevated systolic blood pressure is the number one risk factor for mortality worldwide, especially in women.[14] Elevated blood pressure is also the main cause of atrial fibrillation and a major reason for 'frequent flyers' to our emergency departments. The combined high prevalence of heart failure with preserved ejection fraction (HFpEF) in elderly women affects their symptom presentation and is often not recognized as such.[13]

The COVID-19 pandemic has shown that sex and gender matters, and prevention programmes now focus on managing risk factors to lower the risk. This is not different in cardiology, but our efforts reflected by the consecutive EUROASPIRE programmes have been disappointing. The primary focus on obstructive CAD and associated coronary interventions over the past decades have put the female patient at a disadvantage for many years to come. Moreover, whereas women account for half of the population, they are still described as 'minority' groups in subchapters in many cardiology guidelines. In the midst of the current crisis,

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we must not forget that the past year also marks the 5th anniversary of the sustainable development goals (SDGs): of which SDG 3 (health) and SDG 5 (gender equality) are cornerstones to improve women's health. A challenge that the cardiology community should take up with both hands.

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Biography: Professor Angela Maas, MD, PhD, is a clinical cardiologist since 1988 and is a chair of the women's cardiac health programme at the Radboud University Medical Center in Nijmegen, The Netherlands. The focus of her research is the early identification of women at increased CV risk, coronary vasomotor disorders, and ACS in women. She has initiated several multicentre collaborative projects with other disciplines to improve healthy ageing in women. She was awarded by the Dutch Society of female physicians (2010), the Radboud University (2014), and was knighted by the King in 2017. She one of the most influential female doctors in Dutch healthcare and is the 2020/21 Women's representative of the Dutch Government to the United Nations.