Invited Editorial for article: Sex differences on new-onset heart failure in patients with known or suspected coronary artery disease; EJPC-D-21-00198R1

Title: Sex related risk of heart failure in suspected or known coronary artery disease: Adding a piece to the puzzle

Authors: Vasiliki Tsampasian[1], Vass S Vassiliou[2]

[1] Norwich Medical School and University of East Anglia, UK

[2] Norfolk and Norwich University Hospital, UK

Corresponding Author

Prof Vass S Vassiliou

Second Floor, Bob Champion Research and Education

Colney Lane, Norwich, NR4 7UQ

UK

Email: v.vassiliou@uea.ac.uk

Sex related risk of heart failure in suspected or known coronary artery disease: Adding a piece to the puzzle

Cardiovascular disease represents the most common cause of death with a high mortality burden globally[1]. Over the recent years, sex related differences have been observed with cardiovascular disease affecting millions of women and accounting for four times more deaths than breast cancer[2]. Mortality rates are higher amongst women of older age and poor outcomes have been associated with failure of acknowledging the disease in the first place, although inadequate recognition and treatment has been correlated with high cardiovascular risk in young female individuals as well[3,4].

Studies have shown that despite the advanced treatment options of coronary artery disease (CAD), women that have suffered a myocardial infarction (MI) carry a higher risk of mortality and recurrent MI and have surprisingly lower rates of revascularisation after an acute event compared to their male counterparts[5–7]. Additionally, it has been demonstrated that women are at higher risk of developing heart failure following an acute MI, regardless of the severity of the coronary artery disease as determined by invasive angiography[5]. What then makes women more prone to the development of heart failure in the long term? Could they have higher ischaemic burden? Or do they have significantly impaired myocardium and lower left ventricular ejection fraction (LVEF) from the baseline that just worsens with time?

In this issue of European Journal for Preventive Cardiology Núñez et al. present a very well contacted analysis adding a piece to this puzzle and seek to answer some of these questions[8]. The team have provided data from a large prospective registry that included 5,899 patients who underwent stress Cardiovascular Magnetic Resonance (CMR) imaging for known or suspected CAD over a period of fifteen years. Patients were followed up for a mean period of

four and a half years. The main focus and primary clinical endpoint of the study was the risk of new-onset heart failure, an arguably underexamined endpoint in previously published data and studies. The diagnosis of new-onset heart failure was based on either an acute hospitalisation for heart failure or on the ambulatory heart failure diagnosis made by the physician in the outpatient setting according to the ESC guidelines[9]. The authors also analysed the impact of the ischaemic burden and left ventricular systolic function as assessed by CMR on the risk of new onset heart failure in both males and females.

Women had significantly higher rates of new-onset heart failure during the entire follow up period, with the risk being 1.6 times higher than men. The strong correlation between female sex and higher risk of new-onset heart failure persisted even after multivariate adjustment accounting for the impact of competing events that included all-cause mortality, MI and revascularisation that took place during the follow-up period. Interestingly, the biggest proportion of the new-onset heart failure diagnoses in women was represented by acute heart failure hospitalisations rather than outpatient-based evaluation in the clinic setting. Although there were no statistically significant differences between men and women in terms of the ischaemic and necrosis burden as assessed by stress CMR, an important finding was noted regarding the LVEF. At reduced LVEF values, the risk of new-onset heart failure was high in both males and females. However, in the subgroup analysis of the patients with preserved LVEF defined as ≥55%, women had significantly higher incidence of new-onset heart failure.

This real-life registry demonstrated that even after adjustment for all the traditional cardiovascular risk factors including age, revascularisation procedures and ischaemic burden, female sex remained independently associated with higher risk of new-onset heart failure in

the context of known or suspected CAD. Moreover, baseline ventricular function plays a key role, with women with preserved EF exhibiting higher risk than their male counterparts.

The authors should be congratulated for their study. Their findings however, generate important questions: What makes women with suspected or known CAD and preserved ejection fraction more likely to develop heart failure? Does this subgroup represent an underdiagnosed entity that is not treated with appropriate medical therapy and, subsequently, leads to increased rates of hospitalisation for heart failure? One cannot help but think of coronary microvascular dysfunction, a pathophysiological process that is increasingly gaining more interest as it is often missed and, subsequently, undertreated leading to increased incidence of cardiovascular events and hospitalisations[10]. As part of the ischaemia with non-obstructive coronary arteries (INOCA), coronary microvascular dysfunction is often expressed with clinical symptoms suspicious of CAD in the absence of flow limiting coronary disease. Several large studies have unanimously demonstrated a significantly higher female prevalence of young and middle-aged groups[10]. Hospitalisation for heart failure with preserved ejection fraction is one of the most frequently encountered adverse events of coronary microvascular dysfunction with an observed incidence of up to ten times higher than asymptomatic women[11]. Despite the lack of evidence-based pharmacological therapy for improving prognosis, medical treatment with standard anti-anginal medication is recommended, starting with beta-blockers, calcium channel blockers or ranolazine[10]. Answers to this question will come from them Women's Ischaemia Treatment Reduces Events In Non-Obstructive CAD (WARRIOR) study (NCT03417388) comparing high-intensity statin, ACE-Is or ARBs, and aspirin to usual care in 4422 symptomatic women with INOCA in a randomised multicentre setting.

This study by Núñez et al. identifies the increased risk of subsequent heart failure in women with known or suspected CAD, particularly in those with preserved LVEF. For medical professionals the results highlight the importance of close monitoring, early identification, appropriate investigations and prompt initiation of medical therapy in women, with a lower comparative threshold to men in those with preserved LVEF. Future research studies focusing on the pathophysiological mechanisms behind the observed findings can guide us with appropriately sex-tailored precise management of these patients.

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