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INVITED EDITORIAL

Eliminating Gender Disparities in Coronary Heart Disease Treatment: Are We There Yet?

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During the past two decades, the recognition of cardiovascular disease (CVD) as the leading cause of mortality among women has increased [1]. While the incidence of acute coronary syndromes (ACS) and the prevalence of ischemic heart disease in women is lower compared to men, women continue to have increased mortality following ACS [2, 3]. The substantially higher mortality may, in part, be explained by variations in patient factors at presentation such as older age and an increase in comorbidities, but other system-related factors include delay in recognition and treatment [4]. The latest American College of Cardiology/American Heart Association guidelines and European Society of Cardiology guidelines for the management of ST and non-ST elevation myocardial infarction (MI) recommend similar pharmacotherapy goals in both men and women, including beta-blockers, lipid-lowering agents, angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), and low-dose aspirin, to decrease mortality and morbidity after a MI [5–8]. Nevertheless, several large registry studies have revealed that women are undertreated with guideline-directed medical therapy and are less likely to achieve secondary prevention targets for hyperlipidemia, hyperglycemia, physical activity, and body mass index, leading to a greater burden of CVD and an increased risk for readmissions [9–11].

In this issue of *Cardiovascular Drugs and Therapy*, Vynckier et al. [12] report limited gender differences in the medical management of patients with coronary heart disease (CHD). This study involved an analysis of EUROASPIRE V (European Action on Secondary and Primary Prevention by Interventions to Reduce Events)—a cross-sectional study conducted between 2016 and 2017 in 27 countries. Patients were eligible for inclusion if hospitalized for acute myocardial ischemia as defined by ICD-10 coding for unstable angina or angina pectoris, acute MI, elective or emergency percutaneous coronary intervention (PCI), or elective or emergency coronary artery bypass grafting (CABG), within a time period of 6 months to 2 years prior to the date of study interview. Data was analyzed for 8251 patients—74.2% men and 25.8% women. Of note, women were significantly older and were more likely to have myocardial ischemia as the recruiting event. Women also had higher use of anti-hypertensive drugs and glucose-lowering medications, which may be explained by the greater burden of comorbidities in women as compared with men; women were more frequently noted to have a history of stroke, heart failure, and diabetes as compared to their male counterparts [12].

Importantly, the authors describe that there were no gender differences in the prescription or use of optimal medical therapy, such as aspirin, antiplatelet medications, and beta-blockers, at discharge and interview [12]. This is in contrast to older studies such as the CRUSADE initiative, which contained patients at USA hospitals between 2000 and 2002 and reported that women were significantly less likely to receive medications such as aspirin at discharge after non-ST elevation MI (NSTEMI) as compared with men [13]. In this study, Vynckier et al. describe that women had lower statin use at the time of the interview (82.8% vs 77.7%; $p = 0.002$) despite there being no difference in statin prescription at discharge (88.7% vs 87.6%; $p = 0.89$). Similarly, earlier studies such as the SWEDEHEART registry also demonstrated a statistically significant gender difference in the use of statins 1 year after MI [9]. The reason for this gender difference in this study by Vynckier et al. cannot be clearly explained—there was no difference seen with regard to statin intolerance or patient's refusal of taking the statin. However, it is important to note that there was a trend in one group to have more refusal of taking the statin (33.0% vs. 38.8%, $p = 0.06$); therefore, there may be a more significant difference in men and

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women if statin refusal and intolerance are combined together. Female gender is traditionally considered a risk factor for statin intolerance (associated muscle symptoms or abnormal liver enzymes) [14]. Furthermore, the authors did not report whether LDL-C goals were achieved similarly between genders; previous studies have demonstrated that women are less likely to meet LDL-C targets compared to men. Meeting goals for lipid control is likely multifactorial with various factors at the patient, provider, or health care system level playing a role. Interestingly, one study revealed that having an informal caregiver was independently associated with meeting the secondary prevention goal of LDL-C < 70 mg/dL among men but not among women [15] which illustrates that differences among men and women with regard to statin use are rather complex and gender roles within the cultural context and psychosocial factors may also influence adherence and outcomes.

While there was no difference in overall use or prescription of renin-angiotensin-aldosterone system inhibitors between men and women in this study by Vynckier et al., ACE-I were more often prescribed and used in men while ARB were more often prescribed and used in women at both discharge and time of interview [12]. A previous study has described that the female gender can be a significant determinant of cough with ACE-I (OR 1.92, 95% CI 1.68–2.18) [16]. Additionally, women were more likely to use antidepressants and antianxiety medications at the time of the interview [12]. This finding concurs with other studies that have exhibited higher rates of anxiety and depression in female patients with CHD [17]. It is also important to highlight the finding that there were no statistically significant gender differences in prescribed and attended cardiac rehabilitation programs in men and women, which is in contrast to previous research that described women to be significantly less likely to be referred to cardiac rehabilitation [18].

The limitations of this study by Vycnkier et al. are significant and need to be carefully considered in order to understand the broader impact. Several multinational registries have revealed a gap in the utilization of medications and timing of therapeutic intervention in women during the acute period after an MI [19]. In this present study, Vynckier et al. specifically focus on long-term and post-discharge management of CHD rather than acute management. In the past, gender disparities have been reported in the long-term management of CHD as well. A retrospective population-based cohort study from 2004 to 2011 in British Columbia demonstrated that women were significantly less likely to be on optimal medical therapy at 1 year after discharge. In that study, as well as the presently described study, there were no differences in treatment adherence among men and women [20].

In addition, in this study, the overall interview rate was low—only 56% of those eligible were interviewed. Furthermore, medications used at the time of the interview were self-reported which has the possibility of introducing potential bias since the participants were aware of being monitored. While the use of a large registry that spans several institutions across many countries is of great benefit as it reflects real-life practice and increases generalizability, it comes with its own limitations. Patients were recruited in this registry by utilizing ICD-10 coding to identify major events such as angina, acute MI, CABG, and PCI; however, the coding did not take into account the differences in extent or severity of the disease. It is also important to consider that this study by Vynckier et al. did not stratify results based on age and race/ethnicity, so the results may be concealing significant disparities that exist across subsets of the population, particularly for racial minorities and younger women [20]. Medicare claims data from the past has illustrated similar prescription patterns at hospital discharge after ACS, but 30–35% lower a 12-month medication use after an MI in Black and Hispanic women compared with Caucasian men [21].

Vynckier et al. propose that secondary prevention has improved over the years possibly due to increasing awareness of gender disparities. However, these results should not be taken with complacency. Some of the previously observed discrepancies in care between men and women have been attributed to differences in disease phenotype and pathophysiology—this area still requires further research and investigation. Physicians may be more likely to withhold therapies in certain patients if they associate statins and dual antiplatelet agents solely with obstructive atherosclerotic coronary artery disease. However, current guidelines recommend similar treatments after MI regardless of findings on coronary angiogram, and these patients should still be treated with optimal medical therapy. Vynckier et al. show that women were less likely to have received revascularization with CABG (20.4% vs 13.2%; $p < 0.001$) or PCI (82.1% vs 74.9%; $p < 0.001$) by the time of the interview follow-up [12]. It has been previously demonstrated that women presenting with ACS are more likely than men to have non-obstructive coronary artery disease (< 50% stenosis in all vessels), which does not require revascularization [22]. These differences must be better understood in order to continue closing the gap and warrant continued efforts to promote the inclusion of women in research studies.

Previous data from the EUROASPIRE survey, specifically EUROASPIRE IV, showed that females had worse control of risk factors such as dyslipidemia and diabetes after a myocardial infarction [23]. While the current analysis of EUROSPIRE V by Vynckier et al. is promising in that it suggests that we may be closer in narrowing the gender gap for secondary prevention in terms of treatment, substantial differences may still exist regarding target achievement for blood pressure goals, cholesterol levels, HbA1c, body-mass index, and physical activity. To conclude, the authors provide the most contemporary analysis on gender differences for the

medical management of patients with CHD. Although these results are encouraging, there are still strides that need to be taken to further close the gender gap.

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