

# Sex- and gender-specific precision medicine for chronic coronary syndromes: challenges and opportunities

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Humanity is roughly divisible into equal shares of men and women. For cardiovascular diseases (CVDs)—a global leading cause of death—the risk factor distribution, prevalence, presentations, and management in men and women appear distinctly different.<sup>1-3</sup> Such large differences in manifestations and healthcare, if properly understood, constitute a huge resource to leverage relevant health modifiers. The biological effects of sex chromosomes and hormones, the unique pregnancy potential, as well as the macroscopic and deep phenotypic differences between men and women (such as body size, sex attributes, liver and kidney function, and pharmacodynamics) are typically nonmodifiable and directly related to sex. In contrast, social behaviors developed specifically around one or the other sex are defined as gender differences and are increasingly acknowledged as impacting patient outcomes.<sup>3,4</sup> The challenge (and great opportunity) of sex- and gender-specific precision medicine is to unravel the contribution of biological differences from that related to social and healthcare disparities. Identifying, understanding, and targeting the differences provide a basis for the effective implementation of measures for healthcare improvement in patients of both sexes.

In the general population, men versus age-matched women have more cardiovascular risk factors, a 20% higher incidence of typical CVD, and a 30% higher risk of all-cause death.<sup>5</sup> Whether the higher incidence and mortality in men can be entirely ascribed to quantitatively or qualitatively different age-stratified CVD risk factors is a matter of debate. For sure, among hospitalized

patients with acute and chronic coronary syndromes, women are older and have a greater risk factor burden compared with men. Moreover, at ages above 75 years, the male-to-female ratio drops below 1<sup>1-3</sup>; epicardial artery anatomy is less obstructive in women, and the adjusted recurrence of CVD events is variably reported as higher, similar, or lower than in men.<sup>6-8</sup> Thus, the cardiovascular phenotype of women in the general population is markedly different from that within the CVD subgroup. Women in the population have a lower incidence of CVD compared with men, presumably owing to the smaller risk factor burden and/or potential baseline biological protection. Women who reach the threshold of manifesting CVD instead are selected among those relatively few women in the population who have a large or specific cluster of risk factors or in whom advanced age may have compensated for the otherwise lower biological CVD risk.<sup>1</sup> Of note, these women may have worse outcomes than men, which may be attributable, at least in part, to the underdelivery of appropriate treatments (Yentl syndrome),<sup>3-5</sup> a higher rate of early hemorrhagic complications,<sup>3</sup> and/or the distinctly lower average economic, educational, and political status.<sup>9</sup>

Many investigators have reported on the presentations and outcomes of men and women after acute coronary syndromes; fewer have done so for patients with chronic coronary syndromes (CCS), especially after angiography.<sup>10,11</sup> A Danish report of more than 29 000 patients with CCS undergoing angiography between 2004 and 2016 showed a female share of 30%, improved

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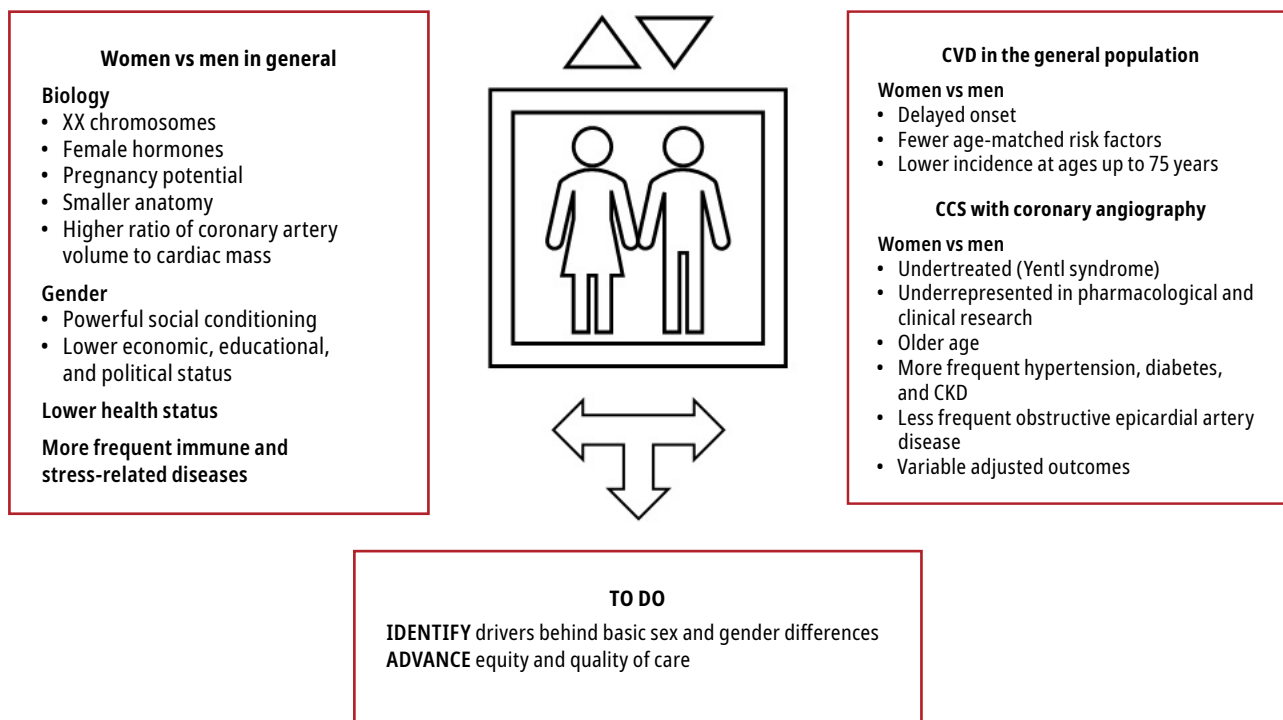
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**FIGURE 1** Key points related to biological, social, and clinical characteristics of women and men with chronic coronary syndromes undergoing angiography  
Abbreviations: CCS, chronic coronary syndromes; CKD, chronic kidney disease; CVD, cardiovascular disease

temporal trends in outcomes regardless of sex, and lower absolute risks in women.<sup>10</sup> A Korean registry of more than 17 000 patients undergoing coronary artery stenting for both acute and chronic coronary syndromes also reported a 30% female share and showed that, compared with men, women with CCS were older, more frequently suffered from hypertension and diabetes, and had similar 3-year outcomes.<sup>11</sup>

In this context, the Prospective Registry of Stable Angina Management and Treatment (PRESAGE) reported by Duda-Pyszny et al<sup>12</sup> is a most welcome contribution. PRESAGE is a single-cardiac center database of 11 021 patients with CCS undergoing angiography in a large Eastern European city (Katowice, Poland—320 000 inhabitants; birthplace of Nobel Prize laureate Maria Goeppert-Mayer), enrolled between 2006 and 2016 and followed for in-hospital bleeding and 12-month all-cause death, nonfatal myocardial infarction (MI), other acute coronary syndrome, and nonfatal stroke.<sup>12</sup> As in other datasets, women constituted a sizable minority (35%), were 4 years older than men, and more frequently presented with 2 major metabolic risk factors, that is, hypertension and diabetes. Compared with men, women also had greater body weight, more commonly premature CVD in their family history, lower hemoglobin levels, and worse renal function. Conversely, smoking status, chronic obstructive pulmonary disease, prior MI, prior coronary artery revascularization, epicardial artery disease (including multivessel, left main, and chronic

total occlusions), left ventricular ejection fraction below 35%, peripheral artery disease, and high white blood cell count were significantly more common among men.<sup>12</sup> Major in-hospital bleeding complications more frequently occurred in women than in men; this should encourage the use of the transradial angiographic access in women.<sup>3</sup> However, the unadjusted rates of death and cardiac events at 1 year were significantly higher in men. After correction for 12 prognostic factors (in order of increasing weight: creatinine levels, age, white blood cell count, low left ventricular ejection fraction, prior MI, hemoglobin levels, New York Heart Association class III, left main disease, peripheral artery disease, chronic obstructive pulmonary disease, significant coronary artery stenosis, and New York Heart Association class IV), sex was unrelated to outcomes. These findings indicate, as in many previous datasets, that patient- rather than sex-related characteristics have a significant influence on adverse events. Of note, women received less frequently therapy with statins and antithrombotic agents than men.<sup>12</sup>

A remarkable feature of PRESAGE, given its careful prospective data collection, is the stark contrast between male and female phenotypes, with women more frequently having metabolic risk factors (hypertension, diabetes, and overweight), presumable extra-epicardial vessel disease, and abdominal organ involvement (pancreas, kidneys), as opposed to men who presented with predominant chest and limb involvement (myocardium, lungs, coronary and peripheral

arteries). When medical history, smoking status, anatomy, and laboratory data are considered, PRESAGE seems to point towards a prevailing metabolic–anemic–small vessel disease in women as opposed to an athero-inflammatory–prothrombotic mechanism in men. This supports the hypothesis that CCS in men and women may represent markedly different entities.

Along with previous data, PRESAGE reiterates a number of relevant questions: 1) Are the differences between women and men in terms of incidence, presentation, and outcomes of acute and chronic coronary syndromes a mere consequence of diverse quantitative and qualitative exposures to risk factors for CVD? 2) What is the specific role of sex? Studies reporting clear sex differences in gene regulatory network activity within atherosclerotic tissues,<sup>13</sup> a greater ratio of coronary artery volume to cardiac mass in women,<sup>14</sup> and the relatively high prevalence of coronary artery erosions, dissections, small vessel disease, and Takotsubo and autoimmune syndromes in women<sup>1,3</sup> suggest that sex-related biological differences do indeed exist. 3) What is the specific role of gender bias in medical research? Studies on pharmacotherapy and interventions show a strong female underrepresentation.<sup>1,3,6-8</sup> 4) What is the specific role of healthcare disparities? A recent study reporting clear undertreatment with cardiac resynchronization therapy devices in women over an 11-year time interval suggests that gender differences in access to treatments and perception of disease do still exist.<sup>15</sup> The 2020 World Economic Forum also highlighted wide, geographically heterogeneous gender gaps in health status disfavoring women, with patchy rates of improvement across the globe.<sup>9</sup>

In conclusion, women with CCS on average constitute a generally smaller population than men with CCS at ages up to 75 years; however, they represent a high-risk group, given their advanced age, cluster of risk factors, comorbidities, atypical clinical and angiographic presentations, hemorrhagic complications, and not-always-appropriate treatments. Primary goals are to recognize and understand true biological sex differences and implement effective measures in order to reduce healthcare inequalities. Key points are summarized in **FIGURE 1**.

## ARTICLE INFORMATION

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