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Are there Sex Differences in Acute Coronary Syndrome Presentation? A Guide through the Maze

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In 1772, Heberden first reported his personal experience of angina pectoris as a retrosternal pain characterized by a crushing, burning, or squeezing sensation.¹ Decades of later work by a host of other scientists uncovered angina as a cardinal manifestation of myocardial ischemia, although the biology underlying the manifestation of angina remains poorly understood.² Perception of anginal symptoms is an important survival mechanism in patients with acute coronary syndrome (ACS), alerting the need for urgent medical care.

Prior studies indicate that there may be sex differences in ACS presentation, with the absence of chest pain or discomfort as a symptom of ACS being more common among women than men in large cohort studies (37% vs 27%).³ However, there is controversy as to whether these observed sex differences in ACS presentation warrant sex-specific public health messages.^{3,4,5} This issue becomes of particular relevance given that younger women are more than twice as likely to die from an acute myocardial infarction compared to men,⁶ yet obstructive coronary artery disease is much less likely in younger women than men.

In this issue of the journal, Khan and colleagues⁷ examine sex (biologic) and gender (sociocultural) differences in ACS presentation among 1,015 patients (30% women) aged 18–55 years hospitalized for ACS. They further investigate potential determinants of ACS presentation occurring without chest pain. The authors apply a standardized validated survey instrument in order to identify pre-specified determinants of sex differences in clinical presentation, utilization of care, and outcomes after the occurrence of premature ACS. Diagnosis of ACS was determined by the treating physician based on clinical presentation and either diagnostic ECG changes or elevated cardiac enzymes; the absence of chest pain and low intensity of any chest pain was coded as ACS presentation without chest pain.

In this study, chest pain was the most common symptom and highly prevalent in both men and women (86.3% vs 81.0%, respectively, $p=0.03$). While the small difference between men and women is consistent with other studies, the proportion of ACS presentation without chest pain was about half of that reported in earlier studies, albeit Khan et al.⁷ applied a stricter definition for chest pain.^{3,4,5,8} Women presenting without chest pain had more non chest pain symptoms than men, a finding compatible with other studies.^{3,4,5} In general, women in this study were more likely than men to report non-chest pain symptoms such as weakness, flushing, back pain, right arm/shoulder pain, nausea, vomiting, headache, and neck or throat pain. However, the authors were unable to identify a consistent pattern of symptoms for ACS presentation with or without chest pain in either women or men.

Amongst the potential pre-specified determinants of sex differences in ACS presentation, Khan et al⁷ found that being a woman and baseline tachycardia were the only factors that were independently associated with ACS presentation without chest pain. An analysis restricted to patients who underwent angiography further identified higher household income and left main disease as additional factors independently associated with ACS presentation without chest pain. On the contrary, ACS type, troponin levels, and angiographically defined coronary stenosis did not differ between those with or without chest pain.

The study by Khan et al extends the prior literature by demonstrating that sex specific differences in ACS presentation occur earlier in life. Similar findings were documented from an analysis of the National Registry of Myocardial Infarction database by Canto and colleagues who observed that women were more likely than men to suffer a myocardial infarction without chest pain, and that this sex difference was more pronounced in the youngest age group and diminished with older age.⁸ These results have also been suggested in an earlier report from the Framingham Heart Study.⁹ In contrast, authors of a recently published study of patients with suspected coronary disease found that anginal symptoms were similar between men and women with angiographically defined obstructive coronary disease,¹⁰ although that study was not powered to examine sex-specific differences by age.

Previously hypothesized differences in the later age of onset of ACS along with a higher risk of comorbidities in women compared to men as explanations for sex differences in ACS presentation may not explain the result observed by Khan et al⁷ since their study population was 55 years old or younger. Hence, observations of sex-specific differences in ACS symptom presentation call for a more tenable mechanism. Transmission of angina pain is mediated by the activation of sympathetic and vagal nerves which may relate to differences in symptoms experienced during an ACS.² Afferent fibers arising from sympathetic nerves concentrate along the distribution of the left anterior coronary artery while parasympathetic afferents predominate along the distribution of the right coronary and circumflex arteries; hence the diseased artery in an ACS may affect the relative predominance of the sympathetic to vagal nerve activation.¹¹ Thus, activation of the parasympathetic nervous system, which may account for symptoms such as nausea and emesis, may characterize pain in patients with right dominant systems.¹¹ It is possible that sex differences in ACS presentation such as a higher frequency of non chest pain symptoms observed in women in the current⁷ and prior studies^{3,4,5,8} may reflect the predilection for a right dominant coronary system in women. Additionally, the role of sex hormones on endorphin rise during an ACS may also partly explain the lower likelihood of women experiencing chest pain compared with men.¹²

Although all participants in the study by Khan et al.⁷ were admitted for an ACS, their results shed light on the potential for physicians to miss a case of ACS when the cardinal symptom of chest pain is not experienced or elicited. More so, ~ 4% of the hospitalized ACS patients studied by Khan et al. did not present with any of the 37 symptoms included on their survey tool. How these estimates compare to those of individuals who developed an ACS but did not seek appropriate care owing to the lack of symptoms remain to be determined.

In light of their findings, Khan et al. rightfully stressed the need for a standardized symptom assessment in order to raise the index of suspicion in patients experiencing an ACS without chest pain. Limiting such an effort will be the many at risk ACS candidates who will not seek preventive or acute medical care, especially in this younger age group. Furthermore, diagnosis of any disease with a lower prevalence but higher mortality such as coronary artery disease in younger women is more challenging. Future research aimed at elucidating the basis for sex differences in ACS symptoms and outcomes is warranted. Meanwhile, it is

prudent for public health messages to target both men and women regarding ACS symptom presentation with or without chest pain in order to encourage earlier and more widespread access to appropriate and lifesaving care.

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