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BREAKOUT SESSION

Gender-specific Research for Emergency Diagnosis and Management of Ischemic Heart Disease: Proceedings from the 2014 *Academic Emergency Medicine* Consensus Conference Cardiovascular Research Workgroup

Basmah Safdar, MD, MSc, John T. Nagurney, MD, MPH, Ayodola Anise, MHS, Holli A. DeVon, PhD, RN, Gail D'Onofrio, MD, MS, Erik P. Hess, MD, MSc, Judd E. Hollander, MD, Mariane J. Legato, MD, Alyson J. McGregor, MD, MS, Jane Scott, ScD, MSN, Semhar Tewelde, MD, and Deborah B. Diercks, MD, MSc

Abstract

Coronary artery disease (CAD) is the most common cause of death for both men and women. However, over the years, emergency physicians, cardiologists, and other health care practitioners have observed varying outcomes in men and women with symptomatic CAD. Women in general are 10 to 15 years older than men when they develop CAD, but suffer worse postinfarction outcomes compared to age-matched men. This article was developed by the cardiovascular workgroup at the 2014 *Academic Emergency Medicine* (*AEM*) consensus conference to identify sex- and gender-specific gaps in the key themes and research questions related to emergency cardiac ischemia care. The workgroup had diverse stakeholder representation from emergency medicine, cardiology, critical care, nursing, emergency medical services, patients, and major policy-makers in government, academia, and patient care. We implemented the nominal group technique to identify and prioritize themes and research questions using electronic mail, monthly conference calls, in-person meetings, and Web-based surveys between June 2013 and May 2014. Through three rounds of nomination and refinement, followed by an in-person meeting on May 13, 2014, we achieved consensus on five priority themes and 30 research questions. The overarching themes were as follows: 1) the full spectrum of sex-specific risk as well as presentation of cardiac ischemia may not be captured by our standard definition of CAD and needs to incorporate other forms of ischemic heart disease (IHD); 2) diagnosis is further challenged by sex/gender differences in

From the Department of Emergency Medicine, Yale University (BS, GD), New Haven, CT; the Department of Emergency Medicine, Massachusetts General Hospital (JTN), Boston, MA; the Department of Emergency Medicine, Mayo Clinic (EPH), Rochester, MN; the Department of Emergency Medicine, Department of Emergency Medicine, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA; the Department of Emergency Medicine, Warren Alpert Medical School of Brown University (AJM), Providence, RI; the Department of Emergency Medicine, University of Maryland (ST), College Park, MD; the Department of Emergency Medicine, University of California, Davis Medical Center (DBD), Davis, CA; The Patient-Centered Outcomes Research Institute (AA), Washington, DC; College of Nursing, University of Illinois at Chicago (HAD), Chicago, IL; the Section of Cardiology, Department of Medicine, Columbia University (MJL), New York, NY; and the National Heart, Lung and Blood Institute (NHLBI) (JS), Washington, DC
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Participants of the cardiovascular breakout session: Blair Alden Parry, John Ashurst, Anise Ayodola, Kevin Barr, Lance Becker, Jeremy Brown, Robert Cannon, Anna Marie Chang, Alan Cherney, Ted Christopher, Laura Costelloe, Steven Deutsch, Holli DeVon, Gail D'Onofrio, Carole Douriez, Nina Gentile, Liz Goldberg, Brooke Harris, Erik Hess, Judd Hollander, Tami Kayea, Jennifer Kruse, Marianne Legato, Richard MacKenzie, Tracy Madsen, Alyson McGregor, Andrew Miller, Chris Moore, Brynn Mumma, Anthony Napoli, Katie O'Conor, Sarah Perman, Basmah Safdar, Jane Scott, Todd Seigel, Shameen Smamji, Howard Smithline, Danica Stone, Doria Suprina, Deepak Vatti, Kevin Weaver, Michael Weigner, Jane Wigginton, Charles Wira, and Jennette Wolfe.
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Address for correspondence and reprints: Basmah Safdar, MD, MSc; e-mail: basmah.safdar@yale.edu.

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presentation and variable sensitivity of cardiac biomarkers, imaging, and risk scores; 3) sex-specific pathophysiology of cardiac ischemia extends beyond conventional obstructive CAD to include other causes such as microvascular dysfunction, takotsubo, and coronary artery dissection, better recognized as IHD; 4) treatment and prognosis are influenced by sex-specific variations in biology, as well as patient–provider communication; and 5) the changing definitions of pathophysiology call for looking beyond conventionally defined cardiovascular outcomes to patient-centered outcomes. These emergency care priorities should guide future clinical and basic science research and extramural funding in an area that greatly influences patient outcomes.

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Coronary artery disease (CAD) is the most common cause of death in the United States for both men and women.[1] Sex- and gender-specific differences have been demonstrated at all levels of CAD and ischemic heart disease (IHD) management and merit special attention.[2,3] Conventional cardiac risk factors attribute variable risk to men and women. For example, hypertension and hyperlipidemia pose a higher risk of acute myocardial infarction (AMI) in men, while diabetes and smoking pose a greater risk in women,[4,5] although no single factor is accurately predictive of AMI in symptomatic patients with chest pain syndrome. On May 13, 2014, *Academic Emergency Medicine,* in partnership with the Society of Academic Emergency Medicine (SAEM), convened a consensus conference to address sex and gender gaps in emergency care. This article outlines the consensus recommendations made by the cardiovascular workgroup in identifying the five priority themes for evaluating and managing IHD: presentation, diagnosis, pathophysiology, treatment, and outcomes.

METHODS

These recommendations were assembled through an iterative consensus-driven process using a four-part nominal group technique as described in the executive summary.[6] A diverse group of stakeholders and experts assembled by the conference leadership participated in the preconference biannual face-to-face meetings. These were in addition to the monthly phone call discussions and progressively refined preconference surveys using the nominal group technique between June 2013 and May 2014. These participants were identified from 1) direct contact with cardiovascular experts in emergency and related fields, 2) emergency medicine (EM) researchers in the cardiovascular and resuscitation area and sex and gender areas, 3) the *AEM* database of peer reviewers, and 4) individuals who self-referred through widespread marketing of the consensus conference.

We sought open-ended feedback about key themes and questions from the *AEM* reviewer database with a preconference survey. The institutional regulatory body at the University of Colorado approved this protocol. A total of 113 members responded; 21 (19%) were female, and 96 (85%) were emergency physicians. The remaining 15% included pediatricians, obstetricians and gynecologists, cardiologists, toxicologists, internists, geriatricians, intensivists, and PhD researchers. Their average postresidency years in practice was 17.6 years. All but five classified themselves as academicians. Their feedback related to CAD care was categorized into nine main themes and 124 research questions. Five of these themes are incorporated in the consensus recommendations. Additional themes that did not qualify for the consensus process are summarized in Table 1.

After the initial nomination and refinement, the preconference workgroup completed a second electronic survey, using a five-point Likert scale (1 being not important at all and 5 being very important) to identify major themes and questions in their degree of importance with respect to patient outcomes. We preselected the questions that were voted to be very important or important based on their average scores. This allowed us to build consensus and debate on questions of variable importance as well as allow new ideas to be explored on the day of the conference. A third survey based on the first two iterations was circulated to all of the conference registrants 2 weeks prior to the conference. Twenty people responded and their feedback was incorporated in the prefinal iteration.

On May 13, 2014, a total of 45 stakeholders (28 females; 62%) assembled to participate in the final iteration of the consensus process (see list in the article note): five (11%) EM residents, three (7%) fellows, 25 (56%) faculty, three (7%) nurses, one (2%) patient, two (4%) paramedics, and six (13%) others, including a cardiologist, PhD researchers, policy makers, and representatives of funding agencies. We used Poll Everywhere for anonymous voting and paper surveys as back-up. The work described in this article represents the results of both the iterative electronic surveys and the in-person meeting on the day of the consensus conference.

Data were either entered manually or transferred electronically into an electronic spreadsheet (Microsoft Excel for Mac, version 2011). Descriptive analyses using means, medians, and percentage calculations were used to tabulate the results.

CONSENSUS RESULTS

The iterative consensus process identified five major themes related to IHD emergency care. The questions with high agreement on importance are described with the recommendations. Related questions went through further voting at the consensus conference and are tabulated in Table 2.

Consensus Recommendation 1: Acute Presentation of IHD

Sex and gender differences in presenting symptoms, and delays in seeking care for IHD, have been well

Table 1
Recurrent Themes/Questions Identified Through Open-Feedback That Did Not Qualify for the Consensus Process

1. Risk factors:
   - Investigate unexplored unique sex-specific risk factors as related to hormones and genes and targeted therapies.
   - Cellular effects of sex hormones during cardiac ischemia and reperfusion.
   - Role of estrogen and menopause in prevention/acceleration of cardiovascular disease.
   - Microarray genetic panels to see if there are unique genetic markers that can diagnose ACS or determine length of resuscitation efforts by sex.
2. Management:
   - Algorithm for chest pain evaluation by sex and for repeat bounce-back evaluations.
   - Do women have a higher rate of recidivism for their chest pain than men and why?
   - Can physician education improve the diagnosis of ischemia, especially due to microvascular dysfunction as opposed to CAD, and outcomes in these patients?
   - Sex differences in pharmacology of cardiac medications.
   - Differential benefits or risks of angiography and interventions by different types of MI.
   - Evaluating the cost-effectiveness of different diagnostic approaches for ACS and CHF stratified by sex and age.
   - Are there biologic differences affecting outcomes after emergent procedures (e.g., PCI or CABG) in men and women.
   - Differences in adherence patterns and interventions aimed at behavioral change.
   - Role of nutrition, exercise, lifestyle, and stress on heart disease and prevention.
3. Prognosis:
   - Investigating differences in prognosis between obstructive CAD and other anatomical etiologies is critical.
   - Sex differences in prognosis by differences in degree of troponin elevation.
   - In ED patients with chest pain, what sex-specific patient-centered outcome measures are associated with morbidity and mortality from ACS.
   - Equitability of outcome measures based on sex and age.
   - Effect of pregnancy on outcomes.
   - Genetic causes of differences in cardiac mortality.
4. Access:
   - Access to primary and specialty care for cardiac issues—disparities by gender and socioeconomic status.
   - Gender, race, and social factors that could impede certain groups from agreeing to participate in research and how they can be overcome.
   - Underlying mechanisms and drivers of disparities, what are patient preferences, physician decision-making, or other causes? How do patients feel about disparities?
   - Establishing sustainable, EM-specific funding sources for diagnosing CHF and ACS (to develop and validate clinical decision aids and to support randomized controlled trials to establish patient-centric outcomes for diagnostic approaches).

ACS = acute cardiac syndromes; CABG = coronary artery bypass graft; CHF = congestive heart failure; MI = myocardial infarction; PCI = percutaneous coronary intervention.

documented. It is essential to note that chest pain or discomfort is the most common symptom in both men and women. However, women are more likely than men to present without chest pain or to have atypical symptoms such as jaw, neck, or back pain; nausea; dyspnea; fatigue; paroxysmal nocturnal dyspnea; or palpitations. This is important as patients without chest pain are more likely to delay seeking care, receive less aggressive therapies, and have two times the mortality compared to patients with chest pain.[7] Women persistently delay in presenting to a health facility with acute ischemia by up to 2 to 3 hours compared to men.[8] Recent literature documents that women younger than 45 years of age are more likely to present without any chest pain and have a greater in-hospital mortality than similarly aged men. These differences attenuate with age.[9] It is possible that the presence of chest pain may relate to MI type, with non-ST elevation myocardial infarction (NSTEMI) patients being twofold more likely to present without chest pain than ST elevation myocardial infarction (STEMI) patients.[9] This may be a factor in differences in sex presentation, as women are more likely to present with NSTEMI than STEMI. It is also possible that women and men respond differently to history-taking, and this may influence providers' behaviors.

In a sex- and gender-specific model, we need to investigate the following:

1. In patients with symptoms of IHD, do sex and gender differences in symptoms result in differences in assessment, treatment, and/or patient behavior?

Consensus Recommendation 2: Diagnosis of IHD
Timely ED diagnosis of symptomatic IHD hinges on the use of appropriate sex-specific biomarkers, diagnostic imaging, and risk stratification tools.

Biomarkers. Several studies have investigated the relationship between cardiac biomarkers and sex. Troponin, considered the criterion standard for diagnosis of acute cardiac ischemia, was found to be lower in women than in men in the Fragmin during Instability in Coronary Artery Disease (FRISC I) trial.[10] Women were also less likely to have a troponin T level above the limit for AMI.[10] Apple et al.[11] further validated these findings by testing eight troponin assays, finding that two had at least a 1.2- to 2.5-fold higher 99th percentile for males versus females and that mean concentrations were significantly higher for males

Similar sex-specific differences have been documented for other biomarkers. Levels of high-sensitivity

Table 2
Rank Order of Consensus-driven Research Questions

Rank	Consensus-based Questions (Voted in Degree of Important From Highest to Lowest)	Mean Likert Score*
1.	In ED patients with microvascular disease does the development of disease-specific pharmacologic interventions improve outcomes?	4.62
2.	In ED chest pain patients, should short- and long-term sex-specific outcomes be analyzed for contemporary risk scores?	4.48
3.	In patients with ACS regardless of sex, what is the incremental value of dynamic changes in biomarker values and at what intervals, compared to static, one-time measurements that improves diagnosis?	4.36
4.	In ED patients with recurrent chest pain, what is the prevalence of alternate causes of chest pain in addition to obstructive CAD?	4.23
5.	In ED patients with chest pain, what should be the optimal sex-specific management for patients diagnosed with nonobstructive CAD?	4.12
6.	In patients presenting with symptoms of cardiac ischemia, should we develop uniform definitions for microvascular disease, coronary vasospasm, syndrome X, and microvascular angina to determine their prevalence in ED patients?	4.09
7.	In patients with suspected IHD are there sex differences in the description of symptoms?	3.83
8.	In the context of cardiovascular testing, what is the effect of gender on the contrast between patients' stated and applied preferences?	3.75
9.	In both healthy and cardiac-diseased populations, are there sex-specific differences in the pathophysiology of acute ischemia?	3.73
10.	In patients with suspected IHD does a gender-specific assessment of symptoms at the time of first medical contact (prehospital setting) result in improved diagnosis of IHD?	3.65
11.	In patients with suspected IHD does the use of simpler clinical (risk score such as TIMI) or noninvasive tests (e.g., carotid intima-media thickness) improve the efficiency for the diagnosis of IHD in men vs. women?	3.27
12.	Are there sex-specific predictors of coronary artery dissection that help improve detection?	2.84

*Range is 0–5.
ACS = acute coronary syndromes; CAD = coronary artery disease; IHD = ischemic heart disease; TIMI = Thrombosis in Myocardial Infarction.

C-reactive protein (CRP) and brain natriuretic peptide (BNP) are higher in women than men in healthy populations.[12,13] In the TACTICS-TIMI 18 trial, all subjects had acute coronary syndrome (ACS) and underwent coronary angiography. Women comprised 34% of the cohort and were more likely than men to have lower creatinine kinase-MB (CK-MB) and troponin T values, and higher high-sensitivity CRP and BNP values, without a difference in the prevalence of chronic renal insufficiency.[14] The authors of this study noted that a higher proportion of women were without significant epicardial coronary obstructive disease and hypothesized that there may be sex differences in pathophysiology. They concluded that men may have presented with plaque rupture, platelet-rich thrombus, and small emboli that would account for their elevated troponin levels, while more women may have presented with small-vessel disease, vessel inflammation, or congestive heart failure. This would explain the women's disproportionately higher levels of CRP and BNP. Of note, the prognostic value of the biomarkers in this trial was similar in men and women. A proposed multimarker approach identified a larger proportion of high-risk women than did a single biomarker approach. The authors also noted that marker-positive patients of both sexes enjoyed improved outcomes with an early invasive strategy. Women without marker elevation had better outcomes with an early conservative strategy.[14] Similar findings were reported from the RITA-3 trial.[15]

Given that differences exist in the baseline levels of cardiac biomarkers by sexes in both healthy and cardiac-diseased populations, the suggestion has been made to establish sex-specific thresholds.[11,14,16] Preliminary findings of the High-STEACS (High Sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome) trial, a study testing lower thresholds for high-sensitivity troponins for the diagnosis of AMI and 1-year mortality, demonstrated that high-sensitivity troponin and sex-specific analytic threshold assay increased the diagnosis of AMI in women while having only a minimal effect in men. Improvement in diagnostic accuracy as measured by the area under the curve was far greater for women than for men as well.[17]

In a sex- and gender-specific model, we need to investigate the following:

1. In patients with IHD, is there a sex-specific single- or multimarker strategy that has the best diagnostic accuracy for the diagnosis, prognosis, and guidance of treatment?
2. In patients with IHD, what are the optimal analytic cutoff points by sex for cardiac markers of myocyte necrosis, inflammation, and hemodynamic function?
3. In patients with microvascular angina, are there sex-specific single- or multimarker panels that can be used for diagnosis, prognosis, and guidance of therapy?

Imaging. There is evidence that women are less likely than men to receive cardiac imaging to diagnose or rule

out IHD.[18] The reasons behind this gender difference are unclear. Some evidence suggests that it is because women are less likely than men to have CAD, so providers test them less often.[19] Others have questioned this and demonstrated that gender bias with respect to cardiac testing persists even after adjustment for presenting characteristics and cardiac risk.[20] Specifically, some findings suggest that women are less likely to receive recommendations for cardiovascular imaging and counseling on possible cardiac etiologies for their chest pain.[21]

There has been support for the traditional risk stratification imaging tests despite their acknowledged limitations. For example, the exercise tolerance test (ETT) is known to generate a higher percentage of false-positive tests in women than in men because of more frequent resting ST-T wave changes and lower ECG voltage. SPECT Sestamibi also may provide false-positives because of breast attenuation of cardiac images.[3,22] Despite these limitations, both the 2002 and 2005 consensus statements from the American Heart Association recommended ETT, SPECT imaging, and stress echo as appropriate diagnostic tools for women who fall within the appropriate risk groups based on clinical information.[3,23] The subsequent guidelines do not differentiate imaging recommendations by sex. Broad-based guidelines recommend use of additional data that demonstrate functional capacity, such as the Duke treadmill score, to refine the prognostic information provided by these tests.[3,22,23] A counterpoint was raised for the utility of the ETT in women by demonstrating that it added little to Bayesian path probability for the accurate diagnosis of CAD.[24] In this study, a significant number of female subjects were young and were falsely misclassified after stress testing. However, the sensitivity of this test in relation to microvascular angina was not studied.

Newer imaging options have gained a foothold in the diagnosis of CAD. The cardiac computed tomography angiogram (CTA) has been demonstrated to be effective at ruling out CAD and predicting at least 1 year of freedom from major adverse cardiac events (MACEs) in patients without evidence of coronary occlusion.[25] This was true for both sexes. In another recent randomized trial comparing cardiac CTA to standard care, women had lower ACS rates than men. They also had a greater reduction in length of stay, lower hospital admission rates, and a lesser cumulative radiation dose. There were no missed ACS diagnoses in either sex.[26] However, the risk–benefit ratio between using a test that requires ionizing radiation compared to one that does not require radiation remains unclear.[26] Ashurst et al.[27] have discussed the sex-specific radiation risks with stress testing. The selection of tests may be limited due to differences, such as renal function, between men and women. Specifically, the choice of test of renal function, serum creatinine versus glomerular filtration rate, affected the percent of patients by sex who would have been ineligible for a cardiac computerized axial tomography angiogram.[28]

Recent evidence is also shifting the focus of imaging from an anatomy-based CAD diagnosis to a more physiologic one (IHD).[3] This is because women are more likely than men to suffer from microvascular cardiac disease, specifically in the precapillary coronary arterioles.[29] These mechanisms are detailed below in the section under "microvascular dysfunction." As a result, imaging limited to epicardial artery anatomy may be less useful in women than men. Yiu et al.[30] demonstrated that a cardiac CTA may have less value in women under age 60 years (when microvascular disease is more prevalent) than in older women or men. Conversely, diagnostic tests that measure cardiac perfusion, microcirculatory resistance, and coronary flow reserve may be more useful in women.[31–34] Adjuncts to test for endothelial cell reactivity such as an impaired vasomotor response to acetylcholine may also need to be considered in clinical investigation.[29] Future research in risk assessment for women will compare these new methods with the traditional risk stratification models, with particular attention to diagnosis and prognosis for patients with microvascular disease and a new tier of cardiac outcomes.

In a sex- and gender-specific model, we need to investigate the following:

1. In patients with suspected IHD, do sex-specific recommendations for traditional imaging modalities (exercise tolerance test, SPECT imaging, stress echo) for the diagnosis of acute IHD optimize cost-effective use of resources as measured by standard cost-effectiveness analytic techniques?
2. In patients with suspected IHD, does the use of newer imaging testing (coronary CTA, MRP, PET scan) in women improve the diagnosis of IHD and prediction of prognosis?
3. In patients presenting with IHD, are the sensitivity and specificity of each diagnostic modality for symptomatic patients different in women compared to men?
4. In ED patients with suspected IHD, what are the screening and definitive modalities for diagnosis of microvascular disease for women compared to men?

Risk Stratification Tools. Several validated prediction tools for risk stratification of ED chest pain patients have been developed. Of these, the Thrombolysis in Myocardial Infarction (TIMI) risk score,[35] the Global Registry of Acute Coronary Events (GRACE) risk score,[36] the HEART (History, ECG, Age, Risk factors, Troponin) Score,[37] the Vancouver Chest Pain rule,[38] the Quantitative Pretest Probability (QPTP) ACS instrument,[39] and the Emergency Department Assessment of Chest Pain Score (EDACS)[40] are of particular contemporary relevance. Both the TIMI and the GRACE risk scores were initially developed in hospitalized patients with known ACS. The GRACE score, although rigorously developed in over 40,000 patients,[36] has not been extensively studied in a the ED chest pain population. The TIMI risk score, however, has been validated in over 17,000 ED chest pain patients[35] and, when included as a component of an accelerated diagnostic protocol with cardiac troponins at 0 and 2 hours, has been demonstrated to be highly (>99%) sensitive and reasonably (23%) specific for MACE at 30 days.[41] The HEART score has been broadly validated in the ED chest pain population and been demonstrated to be highly sensitive and reasonably specific,[42] and a

prospective clinical trial comparing a clinical pathway in which clinicians take into consideration the HEART score versus usual care is currently under way. The Vancouver chest pain rule has been derived from ED populations,[38] but has been demonstrated to have suboptimal sensitivity in validation studies.[43] The QPTP instrument was developed and validated by Mitchell and colleagues,[39] is highly sensitive and reasonably specific for ACS, and has demonstrated effectiveness in two clinical trials.[44,45]

Of these contemporary risk scores, only the EDACS score[40] includes patient sex as a variable in the final model. The investigators developed their risk model by explicitly incorporating the input of practicing clinicians, in addition to considering statistical prognostic performance, and chose a final model that included patient sex with no substantial deleterious effect on statistical performance. Although the EDACS score has only been validated in one study,[40] the approach to model development in this case was both scientifically rigorous and sensitive to end-user needs.

As high-sensitivity troponins become more widely used, it is likely that risk scores for ED chest pain patients will require additional refinement and validation. We recommend that investigators transparently report the statistical contribution of sex in multivariate risk model development and consider incorporating sex as a key variable in the model. Doing so will serve as a foundation to developing sex-specific approaches to diagnosis and therapy.

In a sex- and gender-specific model, we need to investigate the following question:

1. Are there common etiologies of chest pain in women that are systematically categorized as low ischemia risk by contemporary risk scores (e.g., coronary vasospasm, microvascular dysfunction, takotsubo cardiomyopathy, anxiety, depression) that nonetheless are associated with significant morbidity, recidivism, and health care utilization?

Consensus Recommendation 3: Pathophysiology of IHD

Obstructive CAD. The classic definition of CAD is based on "at least 50% stenosis of the diameter of a vessel with reference diameter of more than 1.5 mm as measured by calipers."[46] Clinically significant obstructive CAD was later further qualified as stenosis of 50% or more of the left main coronary artery or stenosis of 70% or more of a major epicardial or branch vessel for treatment. It is more common in men and has been linked with poor outcomes. The prognosis of nonobstructive (<50%) CAD is less well established. Recently a study of 25,000 patients undergoing computed tomography angiogram showed that both obstructive and nonobstructive CAD carries higher mortality rates compared with patients without CAD. Although obstructive CAD confers almost twice the mortality risk, single-vessel disease and nonobstructive disease were linked with higher mortality in women than in men.[47] Long considered benign, nonobstructive disease has been associated with an annual cardiac event rate of 2.5% compared to a higher rate with obstructive disease.[48]

In a sex- and gender-specific model, we need to investigate the following question:

1. In patients with obstructive CAD, does optimal treatment and prognosis differ in women compared to men?

Microvascular Dysfunction. A growing body of literature indicates multiple alternate mechanisms of cardiac chest pain, most of which are more prevalent in women than in men. They include large-vessel (coronary) dysfunction commonly seen as coronary artery spasm[49] and small-vessel (microvascular) dysfunction. The latter represents a heterogeneous group of disorders, including slow flow phenomenon,[50] microvascular angina,[51] microvascular spasm,[52] and cardiac syndrome X.[53] These conditions often coexist with nonobstructive CAD and are distinguished on the basis of exertional or rest angina, timing of pain, presence or absence of typical cardiac risk factors, changes in coronary flow reserve, lactate measurements in the coronary sinus, and microvascular resistance. Despite being known for over three decades, there is lack of consensus on uniform definitions for each entity, further hindering large multicenter research.[54]

Diagnosis by common modalities is a challenge. The criterion standard for measuring vasoreactivity is administration of intravenous ergonavine, acetylcholine, or adenosine during angiography. However, interventional cardiologists have not uniformly adopted this practice due to a controversial risk of stroke or death, despite an acceptable safety profile.[55] Some noninvasive forms of testing have shown promise such as hemodynamic measurements of coronary flow reserve by cardiac PET scan or magnetic resonance imaging. However, their widespread use has been limited by cost and availability. Enhanced screening methods need to be developed in patients with recurrent or persistent chest pain, in partnership with cardiology and radiology.

In a sex- and gender-specific model, we need to investigate the following:

1. In ED patients with persistent chest pain, can we identify predictors of microvascular dysfunction?
2. In ED patients with recurrent chest pain, can historical features, ECG patterns, noninvasive diagnostic studies, or biomarkers be used to screen patients for microvascular dysfunction?
3. In ED patients with recurrent chest pain, are there certain patients who should be referred for definitive diagnostic testing for microvascular dysfunction?

Takotsubo. Broken heart syndrome, or takotsubo, is another less common cause of ischemia that presents like ACS and predominantly affects women. Patients have transient apical hypokinesis and normal or nonobstructed coronary arteries. Mechanisms and triggers appear sex-specific and are related to stress-induced catecholamine release and estrogen deficiency.[56,57] Men with this condition are more prone to a physical stress and malignant arrhythmia due to a disproportionately corrected QTc[58] and thus present in cardiac arrest or cardiogenic shock.[59] Women with their small left ventricular size seem more prone to stunning due to rapid

rise in catecholamines in the setting of emotional stress.[59] Estrogen effect on takotsubo may be multifactorial. Estrogen counteracts the sympathetic nervous system via modulation of the central nervous system, adrenal glands, and endothelial vasoreactivity.[60] Postmenopausal women are particularly prone to this condition due to a decreased sensitivity in vagal tone and baroreflex, decreased β-adrenoreceptor responsiveness, and increased α-1 adrenoreceptor.[61] Sympathetic dominance replaces parasympathetic as the main regulator of the cardiovascular system. Therefore, during stress there is an increase in heart rate and vasoconstriction. Changes in the density or sensitivity of adrenergic receptors from the base to the apex during menopause could explain the pathophysiology in women. A more recent study illustrated that estrogen supplementation partially prevents stress-induced cardiovascular responses both by indirect action on the nervous system and by direct action on the heart. Emergency treatment of takotsubo in the presence of ECG changes is similar to AMI treatment, and prognosis is excellent for this self-limited condition.

In a sex- and gender-specific model, we need to investigate the following:

1. In patients presenting with takotsubo, is there a sex-specific treatment strategy that improves outcomes?

Coronary Artery Dissection. Coronary artery dissection contributes to fewer than 1% of IHD cases.[62] However, it predominantly occurs in women, especially in the peripartum period and in patients with autoimmune conditions. Little evidence exists for the appropriate management of these patients, with high rates of recurrence identified in patients undergoing angioplasty. Some recommend bypass graft for therapy.[62] More work is needed to better understand early recognition and optimal management of these patients.

Consensus Recommendation 4: Treatment of Acute IHD

No studies have led to sex-specific IHD treatment recommendations for women or men, although women with NSTEMI are less likely to receive guideline-recommended therapies, including both invasive procedures and pharmacotherapies.[63–65] A meta-analysis by the Cochrane collaboration pointed out that women incur an early hazard, but still derive significant long-term benefits in terms of lower death rates or AMI (relative risk = 0.73; 95% confidence interval = 0.59 to 0.91) for invasive versus conservative strategies. The ESC guidelines recommend that a routine early invasive strategy be considered in women on the same principles as in men, that is, after careful risk stratification for both ischemic and bleeding risks including clinical and ECG evaluation, analysis of biomarkers, comorbidities, and use of risk scores.[65] Despite increased difficulty in diagnosis and more comorbidities, women do not have a worse long-term prognosis then men. This may be partially explained by the higher prevalence of nonobstructive CAD found on angiography in women.[66]

Real-world data from the CRUSADE registry with over 35,000 patients found that women were less likely to receive treatment with heparin, angiotensin-converting enzyme inhibitors, and glycoprotein IIb/IIIa receptor antagonists in the first 24 hours and were less likely to be discharged on aspirin, angiotensin-converting enzyme inhibitors, and statins.[67] In addition, women with NSTEMI have a higher bleeding risk than men.

Large-scale clinical trials have not tailored either invasive interventions or pharmacotherapies to specific sexes. In fact, there is no clinical trial in patients with NSTEMI that was designed to determine the urgency with which acute intervention could benefit the patient. Unlike STEMI, where many trials begin in the out-of-hospital setting, in NSTEMI it is often not clear when the first dose of medication is given and whether it is even given in the ED. As a result, there are no data on which to determine whether upstream (in the ED) management of patients with NSTEMI should be done, let alone be gender-specific.

In addition to medical therapy, gender-specific clinician–patient communications styles and conversational dynamics may affect treatment. A systematic review exploring the influence of gender dyad concordance on clinician–patient communication revealed that the gender mix of the patient and clinician significantly affected the length of the consultation, the amount of psychosocial content discussed, the degree of patient-centeredness of the conversation, and the proportion of dominant versus submissive voice ratings.[68] Compared to other gender dyads, female clinician/female patient dyads were characterized by the highest number of clinician utterances, the greatest number of patient utterances, and the greatest amount of both psychosocial and biomedical content. Female clinician/female patient dyads were also considered by patients to be the most patient-centered and had higher submissive voice ratings compared to opposite gender dyads. In contrast, in male clinician/female patient dyads, clinicians made the highest number of presumptions about patients and were considered by patients to be the least patient-centered. A participant-level meta-analysis of six randomized trials testing the effect of decision aids delivered during the clinical encounter did not find any association between gender mix and trial-based outcomes such as patient knowledge, decisional conflict, or engagement in the decision-making process. However, this meta-analysis did report a higher frequency of concordance between patients' reported preferences and the actual clinical decision made in female clinician/male patient dyads, compared to male clinician/female patient dyads.[69]

Clinician–patient communication styles may also have implications for obtaining consent for cardiovascular procedures. Compared with men, women undergo fewer diagnostic tests and interventions for IHD.[70] Some suggest that women may be less likely to accept clinicians' recommendations for cardiac catheterization, suggesting that patient preference may play a role in the differential rate of cardiovascular investigations between sexes.[70] This could be due to the fact that women are less frequently counseled about diagnostic testing options or recommended for cardiac testing in the ED.[21] The consensus discussion emphasized the use of "real" patient encounters versus hypothetical scenarios given to

patients to improve communication. Future studies exploring the relationship between clinician and patient gender mix in in the ED setting could employ alternative methods to generate insights such as videographic analysis of the clinician–patient discussion.

In a sex- and gender-specific model, we need to investigate the following:

1. In patients with NSTEMI, does treatment with any agent if given in the first few hours improve outcomes?
2. In patients with suspected IHD, do sex-specific troponin cutoffs improve the identification of patients with a high likelihood of benefiting from early invasive therapy versus conservative management?

Consensus Recommendation 5: Outcomes for IHD

Standardized reporting outcomes and definitions have been described by EM and cardiology. These include the definitions of coronary occlusion and MACE and are traditionally the outcomes used in clinical trials.[71] The focus on outcomes in cardiac clinical trials and clinical risk stratification has primarily been the identification of coronary artery occlusion. Although this is an essential outcome to identify, recent studies suggest that in women it may not identify the full spectrum of cardiovascular disease risk.

The greatest advancement in the understanding of additional outcome measures in women comes from the findings of the Women's Ischemia Syndrome Evaluation (WISE) study.[29] Pivotal for the growth in understanding of potential additional outcomes measures is a deviation from the goal of identification of CAD to the identification of IHD.[72] This implies that functional identification of ischemia rather than the evaluation of structural abnormalities may be beneficial in women. While obstructive CAD is more common in men, outcomes such as admissions and recidivism due to IHD (angina from either coronary artery or microvascular disease) are more common in women, accounting for up to 300,000 annual admissions. Hemingway et al.,[73] in a large international study using the ROSE questionnaire, showed a 20% higher risk of angina in women across all age groups as compared to men.

The WISE data suggest that some of the persistent chest pain could be due to alternate forms of atherosclerosis such as microvascular disease.[34,74,75] As diagnostic strategies are developed that incorporate the diagnosis of microvascular disease, traditional outcomes used to define MACE (death, urgent target vessel revascularization, recurrent MI) may occur at a rate that makes clinical trials unfeasible. Alternative outcome measures that include quality of life, functional status, exercise capacity, unscheduled visits to providers and EDs, symptom relief, and other patient-centered outcomes may need to be used. While patients with alternate forms of ischemia have low mortality rates, they are often linked with high rates of persistent chest pain, frequent presentation to health care facilities, admission for additional testing, and higher costs.[54,76] Once correctly diagnosed, these patients respond well to symptom management with calcium channel blocker, beta blockers, ranolazine, and imipramine. There is little information about cardiac risk management in these patients.

In addition to the sex and gender disparities that exist in IHD prevalence, identification, and management, there may also be disparities that exist within subgroups of women (e.g., women who belong to racial and ethnic minorities, women who live in geographically rural areas). These subgroups of women will have unique attributes and challenges that may not effectively be addressed within a focus on women generally. Future research needs to focus on vulnerable populations and subpopulations with an emphasis on patient-centered outcomes by involving patients and identifying what really matters to them.

In a sex- and gender-specific model, we need to investigate the following:

1. In women presenting to the ED with chest pain, in addition to MACE, does microvascular disease affect short-term health outcomes?
2. Are there sex differences in functional and patient-centered outcomes that need to be measured?

CONCLUSIONS

Despite laudable progress over the past decades in management of ischemic heart disease, the sex- and gender-specific tools for diagnostics and therapeutics for acute care are lacking. Research in ischemic heart disease care has advanced most recently in areas of imaging, nonobstructive disease, and alternate forms of atherosclerosis. The 2014 *Academic Emergency Medicine* consensus conference cardiovascular workgroup has methodically identified major themes and questions for future investigation. We believe that these recommendations should advance the science of gender medicine in acute care of cardiac ischemia.

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