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Review

Sex-Specific Considerations in Guidelines Generation and Application

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ABSTRACT

New knowledge about male–female differences in pathophysiology, diagnosis, and treatment is shifting the practice of medicine from a one-size-fits all approach to a more individualized process that considers sex-specific interventions at the point of care. In this article, we review how clinical practice guideline committees can incorporate a structured framework to determine whether sex-specific assessments of the quality of the evidence or the particular recommendations should be made. The process can be operationalized by societies who author clinical practice guidelines by developing formal policies to approach biological sex in a systematic way, and by ensuring that writing committees include an individual who will champion the formal appraisal of the literature for associations between sex and the outcomes of interest. Ongoing challenges are discussed, and solutions are provided for how to disaggregate the evidence, how to assess bias, how to improve search strategies, and what to do when the data are

RÉSUMÉ

Les nouvelles connaissances sur les différences homme-femme en matière de physiopathologie, de diagnostic et de traitement réorientent la pratique de la médecine pour passer d'une approche universelle à un processus plus individualisé qui considère les interventions en fonction du sexe au point d'intervention. Dans le présent article, nous passons en revue la façon dont les comités sur les lignes directrices de pratique clinique peuvent intégrer un cadre structuré pour déterminer si des évaluations de la qualité des données probantes en fonction du sexe ou si des recommandations particulières devraient être faites. Le processus peut être mis en œuvre par les sociétés qui rédigent les lignes directrices de pratique clinique en élaborant des politiques formelles pour aborder de manière systématique le sexe biologique et en s'assurant que les comités de rédaction regroupent des individus qui soutiendront l'évaluation formelle de la littérature sur les associations entre le sexe et les critères

Including sex-specific evidence in clinical practice guidelines is integral to attaining the delivery of personalized medicine. Sound decisions about patient screening, diagnosis, and treatment should be evidence-informed by genetic and sex hormone differences between male and female patients that determine disparate manifestations of disease and drug response.[1] One of the first steps in moving beyond a one-size-fits-all approach to management involves the generation and application of practice recommendations that systematically account for each patient's biologic sex, in addition to other intersecting factors such as gender, age, race, and socioeconomic status (Box 1). Sex is defined and shaped by the genetic, sex hormone, physiological, and anatomical differences between male and female individuals. Gender, on the other hand, encompasses social and cultural factors that include gender identity, gender roles, and gender relations.[2] Sex and gender are important to report as risk factors and effect modifiers in clinical trials and clinical practice guidelines—and might be difficult to disentangle in the real-world setting. Here we focus on consideration of biological sex.

Sex Matters in Cardiovascular Disease

Cardiovascular medicine is arguably most advanced in its understanding of clinically significant biologic differences between the sexes, from prevention to treatment.[3,4] Risk factors for heart disease and stroke are known to vary between men and women.[5,6] Clinical presentations of acute coronary syndrome differ, men experience earlier onset disease, and

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insufficient to make sex-specific recommendations. Application of sex-specific recommendations will involve routinely asking whether the presentation, diagnostic workup, or management might change for each patient if they were the opposite sex.

d'intérêt. Nous traitons des enjeux actuels, et nous donnons des solutions sur la manière de désagréger les données probantes, sur la manière d'évaluer les biais, sur la manière d'améliorer les stratégies de recherche et sur ce qu'il faut faire lorsque les données sont insuffisantes pour formuler des recommandations en fonction du sexe. L'application de recommandations en fonction du sexe obligera à se demander systématiquement s'il est possible que le tableau clinique, le bilan diagnostique ou la prise en charge aient varié pour chacun des patients s'ils avaient été de sexe opposé.

women more frequently have non—ST-segment elevation myocardial infarction and nonobstructive pathophysiology.[3] Sex differences appear in the manifestation and outcome of acute heart failure, atrial fibrillation, aneurysm formation, peripheral vascular disease, and aortic valve decompensation.[7-11] Sex-specific thresholds are recognized for troponin as a biomarker for acute myocardial injury.[12] Reference values differ for the electrocardiogram, cardiac compartmental volumes, and arterial vessel size in male and female individuals.[13] Even common cardiovascular drugs exhibit sex-specific trends in efficacy and toxicity.[14]

The lag time between discovery and implementation of sex-specific considerations accounts for disparities in cardiovascular morbidity and mortality.[3-5,15] When sex-specific biases are addressed, the gap in male—female 30-day mortality after ST-elevation myocardial infarction diminishes by half, from 6.1% to 3.2%.[16] Door-to-balloon time for women can be significantly reduced using a 4-step protocol that bypasses cardiology consultation and relies instead on guideline-directed therapy, immediate transfer for catheterization and initial radial approach.[16] Translation of this evidence into practice through clinical guidelines will promote uptake of these protocols into routine clinical care.

Sex-Specific Knowledge in Other Specialities

Other fields of medicine are starting to recognize the value of applying sex-specific knowledge to improve aspects of patient diagnosis and treatment. In oncology, fecal occult blood testing and flexible sigmoidoscopy have been found to be more sensitive to detecting colon cancer in men, underscoring a need for new screening methods in women.[17] Preliminary data show that the magnitude of benefit of immune checkpoint inhibitors for advanced cancers such as melanoma and non—small-cell lung cancer is greater for men.[18] Clinicians should discuss these findings during the assessment of risk vs benefit in shared decision-making with female patients about treatment strategies. The same approach applies to known sex differences in immune function that affect the onset and progression of autoimmune disease, response to vaccination, and susceptibility to infection.[19,20] Providing patients with information about the root causes of increased bronchial hyper-responsiveness in women might attenuate higher rates of female morbidity from asthma.[21] General practitioners now use sex-specific alcohol thresholds when counselling patients about high-risk drinking.[22] Lower drug dosing has also been proposed for women prescribed zolpidem for insomnia to avoid next-day driving impairment because of sex differences in drug pharmacokinetics and pharmacodynamics, and for desmopressin for nocturia to avoid severe hyponatremia.[23,24]

Box 1. Factors in personalized clinical practice guidelines

- Genetics
- Epigenetics
- Sex
- Gender
- Age
- Ethnicity, race, and culture
- Religion
- Occupation
- Socioeconomic status
- Place of residence

The Role of Clinical Practice Guidelines

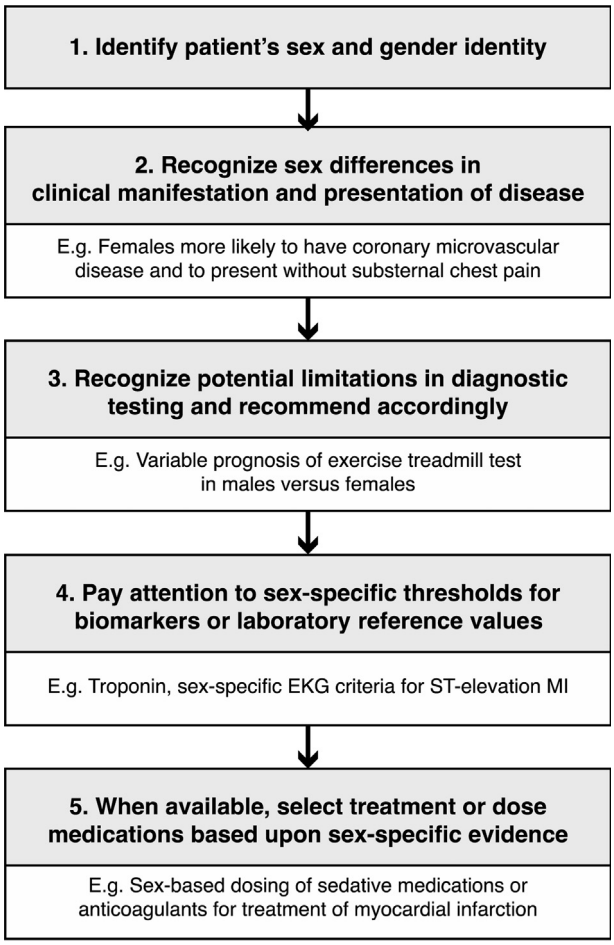
Continuing professional development groups are calling for this new knowledge about sex differences to be integrated into ongoing activities.[25] Students in graduate and undergraduate programs expect to see this information embedded in health care curricula.[26] Clinical practice guidelines can play a critical role in filling these gaps.

Guidelines for sex-specific conditions such as prostate cancer, fertility, and pregnancy have long existed, however sex-specific integration of evidence into clinical practice guidelines that apply to both sexes has been inconsistent.[27,28] A review of 118 Canadian clinical practice guidelines published between 2013 and 2015 revealed that only 20% of guidelines contained sex-related diagnostic or management recommendations.[27] Topics on osteoporosis tended to be better covered than others such as depression.[28]

Data Gaps Improving

Reliance on male cells, animals, and humans in medical research with inattention to sex effects partially explains historical shortcomings in female-specific evidence, as does the lack of female representation in clinical trials. In trials of cardiovascular disease prevention, the proportion of women was only 9% in 1970, rising to 41% in 2006.[29] From 2001 to 2007, only 5% of Cochrane reviews addressing interventions for cardiovascular disease included data disaggregated according to sex.[30] Fast forward to 2015—the US Food and Drug Administration examined 36 trials supporting cardiovascular drug approvals from 2005 to 2015 and concluded that women had finally become adequately represented in trials for select conditions such as hypertension and atrial fibrillation.[31] This upward trend in representation of female participants in

cardiovascular trials is being mirrored in other specialties. A review of sex-related reporting in all 60 clinical trials published in the *Lancet* and the *New England Journal of Medicine* from April to July 2016 revealed that participation of women was 41%—up from 37% in 2009—and that 48% of trials reported sex disaggregated analyses in the results section.[32] In 2016-2017, 23% of all Cochrane systematic reviews conducted subgroup analyses of the effectiveness of health interventions according to sex—up from 5% in 2007.[33] A change in the requirements from health research funding agencies and medical journals to include sex, gender, or both in clinical research is driving further improvements.[2,34] Because of the near-linear rise over the past decade in medical research publications that consider male and female participants separately, and an increase in the number of systematic reviews that are disaggregating outcomes according to sex, the evidence on which to base sex-specific guideline recommendations is now becoming more readily accessible to guideline developers.[35]



Adapted with permission from Alyson McGregor, 2018

Figure 1. Cognitive steps to integrate sex-specific considerations. EKG, electrocardiogram; MI, myocardial infarction. Modified from McGregor et al.[36] with permission from Creative Commons License (CC BY 4.0).

The Need for Cognitive Restructuring

In anticipation of this bolus of evidence and its associated generation of sex-specific guideline recommendations, McGregor et al. invite clinicians to consider the cognitive steps required to transform the current nonindividualized model of care to one that routinely applies sex-specific recommendations.[36] Thinking differently involves asking how the presentation, diagnostic work-up, or management would change for each patient if they were the opposite sex. Figure 1 illustrates a stepwise structured process that can be used to apply sex-specific evidence during teaching and practice.

The first step is to accurately identify each patient's biological sex. Chromosomal sex (XX vs XY) might be distinct from gender identity (how a person self-identifies through behaviour, expression, and dress), so might require clarification by the patient. The second step is to reflect on whether the underlying pathophysiology and presenting symptoms could change on the basis of sex. Next, consideration should be given to sex biases in diagnostic testing or biomarker thresholds during the workup of each patient. For example, female patients are more likely to have nonobstructive coronary artery disease or a nonplaque cause of ischemia, which will not be detected using catheterization. Finally, treatment strategies and drug dosing might be differentially effective for male and female patients and should be adjusted accordingly. Although decision-making might remain unaltered in many cases, walking through this thought process will prepare clinicians to implement sex-specific recommendations when required and avoid missed opportunities for improving outcomes.

Spotlight on the "P" in PICO Guideline Development

When a structured cognitive process is in place for delivering personalized care, seamless integration into guideline development should occur. At present, appropriate methodology exists but remains underutilized. Guideline developers are instructed to ensure that their guidelines are rigourous and apply to the target population. Instruments such as Agree II provide a cue for making certain that each guideline specifically describes the population to whom the guideline is meant to apply.[37] Clear articulation of a Population, Intervention, Comparator, Outcome (PICO) statement is also recommended to ensure that the scope of the guideline meaningfully informs care for particular groups of patients. Guidelines can be developed for 1 sex only, although the disease condition affects both sexes. The 2014 American Heart Association/American Stroke Association's guideline for the prevention of stroke in women is one such case.[5] More commonly, however, the PICO statement does not restrict attention to male or female patients, and the description of the patient populations tends to revolve around disease risk, in the absence of other identifying characteristics such as age or sex.[27,28]

An example of a useful format for identifying the target population and subsequently providing sex-specific recommendations can be found in the 2017 Canadian Task Force on Preventive Health Care guideline on screening for abdominal aortic aneurysm in primary care.[38] Guideline developers generated recommendations for the same condition separately for male and female patients aged 65 years and older, and summarized the

recommendations in the same document. Recommendations are listed for each sex according to age group, along with the strength of the recommendation, the quality of the supporting evidence, an accompanying rationale, and stratified evidence tables. The reporting format is straightforward, informative, and conveniently accessible for clinicians (Box 2).

A Structured Framework for Sex-Specific Guideline Generation

When conceiving a clinical practice guideline, many questions of interest might have biological reasons for differences in pathophysiology between male and female individuals that could affect therapeutic choices. If so, it is reasonable to incorporate a systematic appraisal of the included literature to determine whether sex specific assessments of the quality of the evidence or the particular recommendations should be made (Fig. 2). The process can be operationalized by societies who author clinical practice guidelines by developing formal policies to approach biological sex in a systematic way, and by ensuring that writing committees include an individual who will champion the formal appraisal of the literature for associations between sex and the outcomes of interest.

Literature searches, including the development of the PICO questions, can proceed in the usual way. Assessments of the risk for sex-specific bias in the included reports can be evaluated using the participation to prevalence ratio (PPR), a metric that links the participation of each sex to the prevalence of the disease of interest in the population (a real-world example of how to calculate the PPR is in the Supplementary Material).[31] By convention, a PPR > 0.8 is considered adequate or bias-free enrollment. In addition to the usual measurement of outcomes in the population studied in each article, it should be determined whether sex-specific outcomes are reported and, if so, whether these outcomes justify sex-specific recommendations. The authors should consider whether or not the quality of evidence is the same for both sexes. The text accompanying the recommendations should clearly identify whether or not recommendations hold for both sexes uniformly, or are different for each sex. Practical tips for implementation of sex-specific recommendations should also be offered.

Box 2. Example of a sex- and age-specific guideline recommendation

Canadian Task Force on Preventive Health Care
Recommendations on screening for abdominal aortic aneurysm in primary care[38]

1. "We recommend one-time screening with ultrasonography for abdominal aortic aneurysm of men aged 65 to 80 years (weak recommendation; moderate quality of evidence)."
2. "We recommend not screening men older than 80 years of age for abdominal aortic aneurysm (weak recommendation; low quality of evidence)."
3. "We recommend not screening women for abdominal aortic aneurysm, regardless of age (strong recommendation; very low quality of evidence)."

Ongoing Challenges

Sex and gender terminology

Conflation of the terms sex and gender in included studies for guideline generation might pose a challenge, making it difficult to know how the data were collected and which subgroup is represented in the analyses. Trials generally report the baseline characteristics of participants as male/female or men/women, but might not state explicitly if they are referring to sex or gender. The term sex should be used when biological factors are being considered. Participants should be referred to as male or female, on the basis of the sex they were assigned at birth on their birth certificate, determined by self-report during data collection (using survey questions such as "are you male/female" or "what sex were you assigned at birth"), or by anatomic or genetic designation. Most trials conducted to date intend to record the sex of the participants, but often use the term gender inappropriately.[27,28] The term gender should only be used when participants are asked to describe their current gender identity and lived gender, expressed on a continuum of how that person feels and behaves, independent of biological sex (eg, male, female, nonbinary, gender fluid, 2-spirit etc).[39] Sex and gender should be queried and reported in clinical research.[2,39]

Search strategy

Clinical practice guidelines that include both sexes might not include sex-specific terminology in the search strategy, thereby missing important sources of evidence for one sex or the other. This problem can be circumvented by clearly articulating PICO statements that *a priori* specify subgroups of interest according to sex, age, or other identifying characteristics (Box 1). Standardized application of the validated search strategy used by Song et al. for uncovering publications that report sex-specific diagnostic and treatment evidence could enhance the discovery of relevant evidence on male- or female-only populations to help inform statements for each PICO subgroup.[40]

Sex-specific representation and statistical power

Representation and statistical power are 2 distinct, nonoverlapping concepts as pertains to formulating sex-specific recommendations from clinical trials. Adequate representation of male and female participants refers to the way in which the study population mirrors the sex distribution of the disease in the target population. Commonly designated as the PPR, this indicator of inclusion can be calculated by dividing the number of male or female participants in a trial by the total study enrollment, and then dividing this latter proportion by the proportion of male or female patients affected by the disease in the population of interest (see the Supplementary Material).[31] As mentioned, a PPR that is relatively close to 1 indicates that the sex composition of the study approximates that of the disease population. A PPR of < 0.8, or greater than 1.2 indicates that 1 sex was underrepresented or over-represented, respectively, relative to the population of individuals affected by the condition under study. Agencies such as the US Food and Drug Administration use the PPR to gauge adequate representation of women and other diverse populations in clinical trials, and it can also

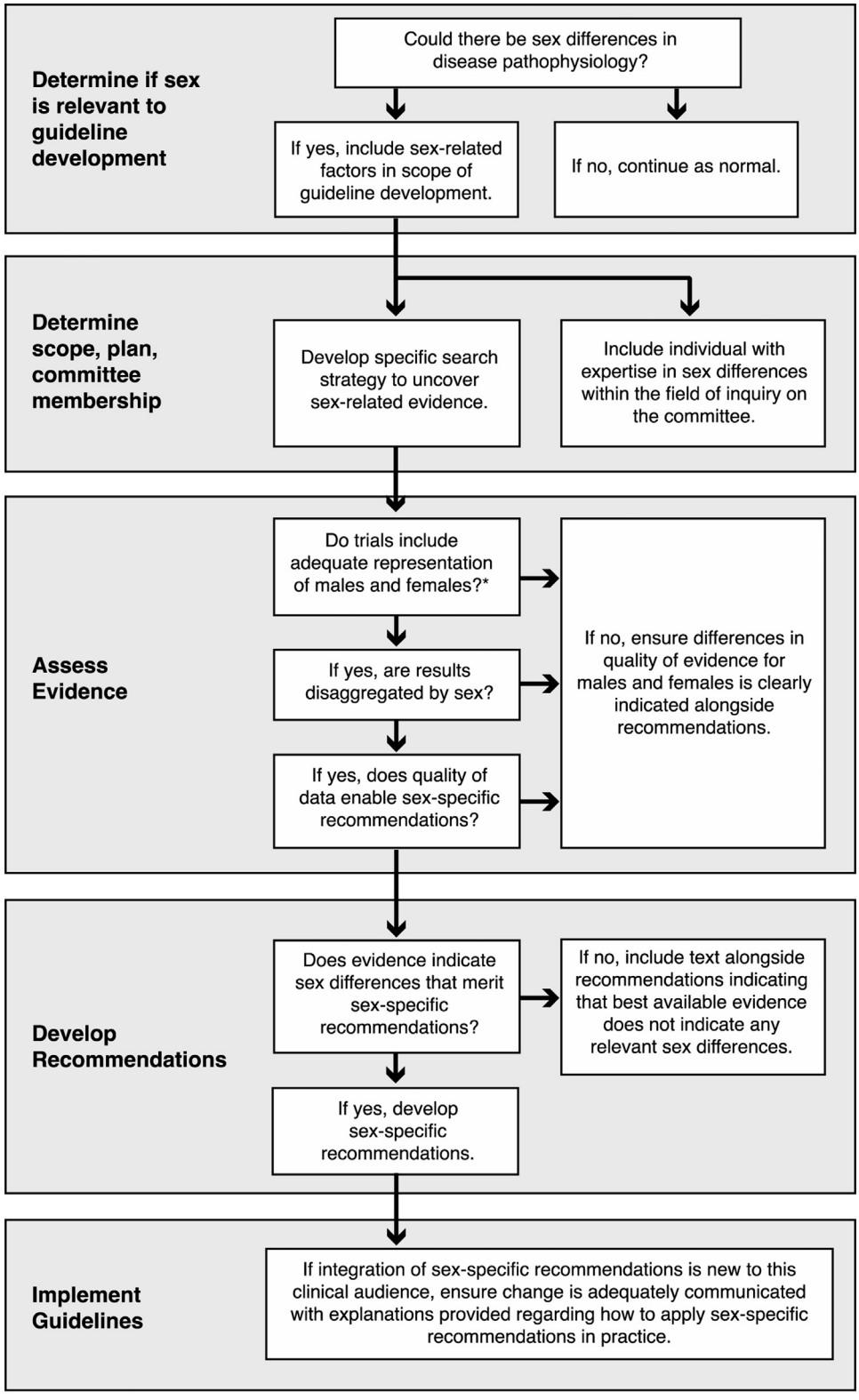


Figure 2. Structured framework for generating sex-specific guidelines.

be used to assess sex-specific bias in included reports for clinical practice guidelines.[31] However, including representative numbers of women in drug trials is insufficient to inform guideline recommendations if the efficacy outcomes and frequency of adverse events are not disaggregated and reported according to sex, and if the analyses are underpowered to detect real differences.

Statistical power refers to the likelihood that a trial will detect a difference when there is a real difference to be detected between subgroups of individuals. Depending on the magnitude of the expected difference, prespecified sample sizes of individuals are required to determine with confidence whether the anticipated difference occurs. Because sex differences are rarely specified *a priori* in trial design, post hoc analyses that might be underpowered to detect real differences are frequently used to compare drug efficacy and safety between male and female participants, making it difficult to recommend treatment decisions on the basis of a more individualized assessment of benefit and risk. In the latter case, the effect of sex on study outcomes is commonly illustrated in a Forest plot showing subgroup risk differences. When a trial does not *a priori* intend to identify sex differences, and disparate outcomes are observed for male and female participants, multivariate analyses should be conducted to account for confounding variables such as age or comorbidity.

Going forward, pharmaceutical companies are encouraged to pose clinically relevant sex-specific questions *a priori*, with hypotheses driven substantively by preliminary data obtained from phase I or II pharmacokinetic and pharmacodynamic trials, or age and sex-based model simulations.[41,42] Tests for interaction, which are more valid than separate subgroup tests, can then be used to determine whether a differential sex-specific treatment effect exists.[42] In the meantime, there is value in having trials report data disaggregated according to sex, even if underpowered, to enable pooling of sex-specific data during meta-analysis.[2]

Summarizing the evidence when sex-specific information is lacking

Guideline producers should specifically identify up front if the literature does not support sex-specific recommendations. This statement, at the beginning of the recommendations section, not only qualifies the usefulness of the guidelines to practitioners but also calls on the research community to do better, in cases in which more evidence is required. In 2017-2018 the Canadian Cardiovascular Society applied the structured framework shown in Figure 2 to the development of guidelines for the prehospital management of ST-elevation myocardial infarction. After endorsement by the executive committee of the Canadian Cardiovascular Society, and discussion with the guideline steering committee, a sex and gender champion was appointed. The champion determined the male−female distribution of the study population, created a data extraction sheet, and for each study that was identified for inclusion in the guideline recorded the following: (1) the extent to which both sexes were represented in each trial; and (2) whether data were disaggregated according to sex. One hundred seventy-five studies were included. The mean percentage of women reported in the studies was 24.5% (SD, 6.6 %; range, 0%-51%). Fifteen studies performed a subgroup analysis according to sex. At the end of the process, the authors concluded that the data were insufficient to make sex-specific recommendations for the prehospital management of ST-elevation myocardial infarction. A decision was taken to include the following statement in the publication of the guideline to help inform future research and let users know that decisions for female patients could not be supported by existing evidence: "Although we found that it was straightforward and feasible to incorporate a systematic appraisal of sex and gender considerations of included literature as part of (this) clinical practice guideline development, there were major challenges with the published literature, including inadequate enrollment of women in randomized trials, lack of publication of main outcomes stratified according to sex, and lack of inclusion of gender as a study variable. It was therefore infeasible to make sex- and gender-specific assessments of either the quality of evidence or strength of recommendations for the clinical questions evaluated. Although we make the agnostic assumption that the recommendations in this guideline hold equally for men and for women, we acknowledge that the published literature is inadequate to confirm this clearly and objectively."

Conclusion

A compelling scientific rationale combined with improved access to sex-specific information in research trials is heralding a change in the way medicine is practiced. Guideline developers have started applying a structured framework for including sex and other identifying characteristics in clinical practice recommendations. The process is feasible, capturing simple, streamlined, and critical information to help inform sound decision-making for male and female patients. When data are unavailable to support separate recommendations, the state of the evidence should be transparently reported to drive future research that will fill current gaps in knowledge and accelerate the delivery of personalized medicine at the point of care.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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