ORIGINAL RESEARCH

Systematic Incorporation of Sex-Specific Information Into Clinical Practice Guidelines for the Management of ST-Segment–Elevation Myocardial Infarction: Feasibility and Outcomes

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***Background*—**Clinical practice guideline (CPG) developers have yet to endorse a consistent and systematic approach for considering sex-specific cardiovascular information in CPGs. This article describes an initiative led by the Canadian Cardiovascular Society to determine the feasibility and outcomes of a structured process for considering sex in a CPG for the management of ST-segment–elevation myocardial infarction.

***Methods and Results*—**A sex and gender champion was appointed to the guideline development committee. The feasibility of tailoring the CPG to sex was ascertained by recording (1) the male–female distribution of the study population, (2) the adequacy of sex-specific representation in each study using the participation/prevalence ratio, and (3) whether data were disaggregated by sex. The outcome was to determine whether recommendations for CPGs based on an assessment of the evidence should differ by sex. In total, 175 studies were included. The mean percentage of female participants reported in the studies was 24.5% (SD: 6.6%; minimum: 0%; maximum: 51%). The mean participation/prevalence ratio was 0.62 (SD: 0.16; minimum: 0.00; maximum: 1.19). Eighteen (10.2%) studies disaggregated the data by sex. Based on the participation/prevalence ratio and the sex-specific analyses presented, only 1 study provided adequate evidence to confidently inform the applicability of the CPG recommendations to male and female patients.

***Conclusions*—**Implementing a systematic process for critically appraising sex-specific evidence for CPGs was straightforward and feasible. Inadequate enrollment and reporting by sex hindered comprehensive sex-specific assessment of the quality of evidence and strength of recommendations for a CPG on the management of ST-segment–elevation myocardial infarction. **(*J Am Heart Assoc*. 2019;8:e011597. DOI: 10.1161/JAHA.118.011597.)**

Key Words: acute coronary syndrome • guideline • sex • women

Clinical practice guidelines (CPGs) are a key step to translating evidence into clinical practice. Guidelines are developed through national guidelines committees made up of groups of experts in the treatment of specific clinical conditions. In the setting of cardiovascular disease (CVD), the transformation of landmark randomized controlled trials (RCTs) into current practice guideline–directed therapy recommendations has resulted in dramatic decreases in 30-day mortality and readmissions as well as improved patient care.[1–3] Despite a general understanding that manifestations and outcomes of diseases may differ for male and female patients, and despite a near-linear rise in sex- and gender-specific research publications since the 1990s, the uptake of sex and gender influences into CPGs has been slow, with only 20% of CPGs recommending sex-specific diagnostic or treatment strategies.[4,5] Although the terms are frequently used interchangeably, *sex-related factors* refer to biological constructs, including hormones, genes, anatomy, and physiology. *Gender-related factors* are socially constructed, culturally specific dimensions including gender roles, identity, relations, and institutionalized gender. Tannenbaum et al provide a number of clinical examples in which the consequences of not including evidence about women and men separately in CPGs can range from missed opportunities to

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Accompanying Table S1 and Data S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011597

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Clinical Perspective

What Is New?

- One of the first steps in moving beyond a one-size-fits-all approach to management of patient care involves the generation and application of practice recommendations that systematically account for each patient's biological sex.
- Because of both low enrollment of female participants in the evidence used for the clinical practice guidelines on care for ST-segment–elevation myocardial infarction and inadequate reporting of sex-specific outcomes, the quality of the literature studied was insufficient to produce sex-specific recommendations; however, 96% of the studies in this analysis reported the percentage of female participants included in the studies, indicating that reporting outcomes by sex is feasible.

What Are the Clinical Implications?

- The state of the evidence should be transparently reported by sex to allow clinicians to implement sex-specific care, to avoid missed opportunities for improving outcomes, and to accelerate the delivery of personalized medicine at the point of care.

inappropriate prescription of drugs.[5] Based on one such situation, Health Canada issued a postmarketing warning to cut the dosage of a common sleeping pill in half for female patients because morning blood levels of the drug were higher in female compared with male patients.[5] If quality of care for both male and female patients is to be improved, sex and gender differences must be incorporated into CPG development.

Guidelines committees typically use standard methodologies for the development of guidelines, including the critical appraisal of the selected literature and phrasing of recommendations for clinical practice based on established quality-criteria instruments.[4] A consistent criterion in quality assessment for the development of guidelines is the specific description of the target population. Two internationally developed instruments, the Appraisal of Guidelines, Research and Evaluation (AGREE-II) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE), identify sex and gender as items that may be considered.[6–8] However, these instruments do not provide guidance on how to synthesize the sex and gender evidence. Other barriers to the systematic inclusion of evidence of sex- and gender-related factors in the process of guideline development include (1) a tendency for working groups to develop recommendations for the "general" patient population, (2) a lack of awareness that attention to sex- and gender-related factors may improve the quality of the guidelines, and (3) the absence of a structured process for identifying and systematically evaluating the evidence on sex and gender differences.[9] In appreciation of these challenges, Keuken[4] designed and piloted a training course, "Attention to Sex Differences in Guidelines Development"; however, Keuken's article has been cited only 11 times in Scopus and 3 times in PubMed since its publication in 2007. Furthermore, PlumX Metrics (https://plumanalytics.com/learn/about-metrics/) indicates that although the abstract has been read 305 times, it has been exported or saved just 46 times. It would appear that the use of a specific process to ensure sex-based guideline development has yet to be endorsed by the broader CPG community. This article describes the process and experience of a motivated group in Canada to implement sex and gender integration during the development of a CPG for the management of ST-segment–elevation myocardial infarction (STEMI). We determined the feasibility and outcomes of a systematic procedure for evaluating the quality of evidence and strength of recommendations based on sex- and gender-specific information.

Methods

All data and supporting materials have been provided with the published article. Institutional review board approval was not required given the nature of the study (review of frequencies of female participants in published RCTs).

Project Initiation

The lack of progress in the integration of sex and gender in the development of CPGs elicited a conversation about changing the status quo at a workshop hosted by the Canadian Women's Heart Health research committee (Toronto, Canada, February 2017). As an action item from that discussion, the scientific director of the Institute of Gender and Health of the Canadian Institutes of Health Research, Dr Cara Tannenbaum, wrote a letter to the chair of the guidelines committee of the Canadian Cardiovascular Society (CCS), Dr Sean McMurtry, highlighting the opportunity for collaboration. This action resulted in a jointly sponsored pilot project to determine the feasibility and outcomes of incorporating sex and gender into a CPG on the topic of the management of STEMI.

Process

Author C.M.N. introduced the pilot project at the inaugural teleconference of the STEMI guidelines committee. With the agreement of the STEMI guidelines chairs, a designated sex and gender champion (C.M.N.) was added to the guidelines committee as a member. Next, the process for assessing the

RCTs based on sex-specific information was outlined by C.M.N. in a short presentation to the STEMI guidelines committee. For the purposes of the guideline development, a medical librarian conducted a systematic search to identify relevant publications, including systematic reviews and meta-analyses for each topic. In a standardized manner, 2 reviewers independently screened each title and abstract identified in the literature search. All studies that appeared to address the individual PICO (patient, problem, or population; intervention; comparison, control, or comparator) research questions were obtained in full-text format. On review of the full-text publication, more detailed eligibility criteria were applied, and decisions were made about inclusion of individual studies for full analysis. Disagreements were resolved through discussion and consensus. Publications were eligible for inclusion if they met the predefined PICO criteria, employed randomized or nonrandomized study designs, and were published in the English language in a peer-reviewed journal. Summaries of the literature review and detailed methodology regarding the literature assessment are provided online (https://www.ccs.ca/). Records from database searches were downloaded and imported into EndNote databases to facilitate the sex-based analyses.

To inform whether the data supported sex-specific recommendations, 2 of the pilot project investigators (C.M.N. and M.S.M.) recorded the following information for each selected study in a data collection sheet (adapted from Keuken's additional file description of the training course modules):[4] (1) What is the sex composition of the study population (percentage male and female with the condition)? (2) Are both sexes sufficiently represented in each trial? (The participation/prevalence ratio [PPR] was calculated.) (3) Are differences between male and female participants analyzed in the RCT? For the latter question, if the answer was *yes*, the following question was posed: How were the subgroup analyses reported? Although our original intent was to assess both sex- and gender-specific information in the RCTs, initial reviews of the RCTs, reinforced by our own previous work, elucidated significant challenges in identifying and measuring gender variables.[10–12] For this reason, the decision was taken to focus this pilot project on sex-specific information only, using the adapted Keuken framework. The specific topics of the CPG using PICO questions (Table S1) were related to the management of STEMI patients. These included prehospital oxygen administration, prehospital opioid administration, prehospital administration of $P2Y_{12}$ inhibitors, prehospital ECG interpretation and catheterization laboratory activation, prehospital scope of practice for interfacility acute STEMI transport, and prehospital direct transport of patients with STEMI for primary percutaneous coronary intervention.

Challenges

The question of whether both sexes were sufficiently represented presented a unique methodological challenge, particularly in the context of myocardial infarction. CVD has long been thought of as a disease that mostly affects men. The crude age-standardized mortality rates for ischemic heart disease, for example, are 3- to 4-fold higher in male compared with female patients.[13] However, despite the lower incidence rate for female patients, CVD is recognized as the number 1 killer among women. It is not clear whether the sex differences are due exclusively or in part to differences in

Table 1. Percentages and PPRs of Female Participants Included in Studies Analyzed

	No. of Studies Included in Guidelines (N=180)	No. of Studies With Data on Sex	% Female		PPR			
			Mean (SD)	Median	Mean (SD)*	Median	Min	Max
Meta-analyses	22	10	24.2 (2.13)	24.00	0.61 (0.06)	0.61	0.52	0.70
RCT multicenter	7	7	24.1 (3.47)	24.70	0.61 (0.92)	0.62	0.45	0.71
RCT	73	71	22.8 (7.69)	22.00	0.58 (0.20)	0.57	0.00	1.19
RCT pragmatic	1	1	29.0	29.0	0.67	0.67	0.67	0.67
Prospective cohort	28	27	25.7 (5.04)	26.50	0.67 (0.13)	0.68	0.48	1.03
Retrospective cohort	38	32	26.9 (6.32)	26.70	0.65 (0.13)	0.66	0.46	1.10
Retrospective registry	6	4	27.8 (3.70)	28.10	0.70 (0.09)	0.71	0.58	0.81
Road network analysis	1	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Review	2	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Editorial	2	. . .	. . .	. . .	. . .	. . .	. . .	. . .

Max indicates maximum; min, minimum; PPR, participation/prevalence ratio; RCT, randomized controlled trial.
*PPR ≥0.80 and ≤1.12 indicates female patients are appropriately represented.

age-related established risk factors. The lower incidence of CVD in premenopausal women may to be related to the protective effect of endogenous hormones, but this is but this is not well established.[13] Other hypotheses that have been explored include sex heterogeneity in insulin resistance, favorable LDL (low-density lipoprotein) characteristics in women, and differences in the aging processes influencing arterial stiffness.[13] Given the increasing risk of CVD in postmenopausal women and/or age-related changes in risk factors, the sex-specific representation of patients in RCTs could best be represented by real-world, country-specific, sex-based incidence curves of CVD over the life span.

Analysis

The 3 feasibility indicators for tailoring CPGs by sex were ascertained as follows. The male–female distribution of the study population was recorded by extracting data from each study's "table 1" about the sex of the participants in each study. The proportion of studies with the availability of these data was calculated. The adequacy of sex-specific representation in each of the clinical trials was determined using the PPR.[14] The PPR is a metric used to identify the representation of a specific population included in a study relative to their representation in the disease population. For the purposes of this analysis, the real-world, sex-specific incidence of acute coronary syndrome admissions in Canada was determined from the Canadian Institute of Health Information, Canada's population health statistics agency and a repository of all hospital diagnostic billing claims from Canada's different healthcare jurisdictions. The representation of female patients in each study was calculated by dividing the number of female participants in the trial by the total study enrollment. The PPR is calculated by dividing the representation of female patients in a study by their representation in the real world for the disease of interest. A PPR that is relatively close to 1 indicates that the sex composition of the study approximates that of the disease population. By convention, a PPR <0.8 or >1.2 indicates that one sex was underrepresented or overrepresented, respectively, relative to the population of patients hospitalized for an acute myocardial infarction.

To determine whether data were disaggregated by sex, each study was reviewed to identify whether the results were stratified by sex and/or presented either in graphic form (eg, forest plot) or as text in the results and/or discussion section of the study (eg, "differences were found in subgroup analyses . . . among females [P<01]").[15] The reported sex-specific point estimates were recorded. The statistical analyses sections of all included studies were reviewed to identify whether the statistical analysis included a multivariate analysis that adjusted for sex. If appropriate, the results and discussion sections were also reviewed to identify whether the addition of sex in the modeling was reported. If all 3 criteria were met for any given PICO question—information about the male:female distribution of study participants, adequate sex-specific representation in the trial population, and results data disaggregated by sex—then the investigators judged that adequate evidence was provided to confidently inform the applicability of the CPG recommendations to male and female patients.

Results

The 21 PICO questions (Table S1) yielded a total of 180 studies, of which 175 studies (Data S1) were included in the sex-based analyses (1 node network analysis, 2 reviews, and 2 editorials were excluded). There were 22 meta-analyses, 7 multicenter RCTs, 73 RCTs, 1 pragmatic RCT, 28 prospective cohort studies, 38 retrospective cohort studies, and 6 retrospective studies using registry data. Figure shows the flowchart for the process by which all studies were assessed for meeting the 3 feasibility criteria.

Representation of Sufficient Numbers of Male and Female Participants in the Studies Included in the CPG

Data on the sex composition of the participants were available from 96% of the studies.

Using Canadian Institute for Health Information (CIHI) data, we determined that the proportion of female patients

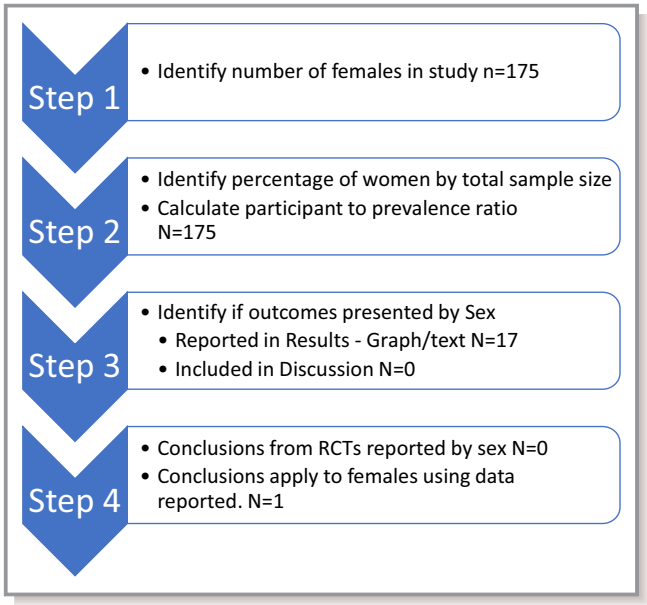

Figure. Process of sex-based analysis of studies used for clinical practice guidelines. RCTs indicates randomized controlled trials.

hospitalized in Canada in 2015 who were hospitalized with an acute myocardial infarction was 39.5% based on CIHI data (20 399 female of 51 635 total patients). In comparison, the mean percentage of female participants reported in the studies was 24.5% (SD: 6.6%; minimum: 0%; maximum: 51%). The mean PPR was 0.62 (SD: 0.16; minimum: 0.00; maximum: 1.19). The mean PPR by study type is presented in Table 1.

Disaggregating Results by Sex

Only 18 (17 RCTs and 1 cohort study) of the 175 studies (10.3%) conducted analyses that accounted for sex (Table 2). Although a number of studies (19/175) statistically controlled for sex, the results of adjusting for sex in a multivariate model were rarely reported (4/10), and interactions with sex were not examined. Seventeen of 103 RCT studies provided subgroup analyses based on sex by illustrating the results in a forest plot and/or describing them in the text (Table 3). In 15 cases, the significance value of the interaction term between sex and the outcome of interest was nonsignificant ($P \geq 0.05$), and it was assumed that there was no difference in outcomes based on sex. Furthermore, in the subgroup analyses, 13 of 17 RCTs reported point estimates (odds or hazard ratios) with differences between female and male participants that were either contradictory (eg, <1 for female, >1 for male) or noteworthy for differences in magnitude. However, there were no further discussions regarding the sex difference, and conclusions of the studies discussed the combined (female and male) sample without regard to sex differences. No study commented on the potential limitation of the number of female participants in the RCT, particularly given that almost all the 95% CIs of the odds or hazard ratios for female participants presented in the forest plots were wide, suggesting small sample sizes.

Similarly, in 19 of 72 cohort studies, a significant difference was identified in the proportions of male and female patients in the groups being compared, with statistical adjustment for sex, performed through modeling or regression analyses. Of the 19 studies that adjusted for sex, 4 studies reported that sex remained or was no longer independently predictive of the outcome. Overall, the majority of the studies analyzed in this article reported on a treatment-related outcome for STEMI for which sex differences in outcome could not be excluded. Based on the PPR, the type of study, or the analyses used, only 1 of the 175 studies provided sufficient data to determine that the study's conclusions were clearly and objectively valid for female and male patients separately.[16]

Table 2. Differences Between Sexes Reported in Results

Types of Studies	No. of Studies (N=175)	Differences Between Female and Male Participants Reported in Results, n (%)	
		Forest Plots/Text Include Sex in Results	Outcome Adjusted for Sex*
Meta-analyses	22	1 (4.5)	0
RCTs (multicenter and single-center combined)	80	16 (20.0)	2 (2.7)
RCT pragmatic	1	0	0
Prospective cohort	28	0	2 (7.1)
Retrospective cohort	38	1 (2.6)†	12 (31.6)
Retrospective registry	6	0	3 (50)
Total	175	18	19

RCTs indicates randomized controlled trials.
*Adjusted for sex in multivariate analyses.
†Cohort study presented sex-stratified results.

Discussion

The results of this study indicated that it was highly feasible to put in place a structured process among guideline developers to better inform sex-specific assessments of the quality of evidence and strength of recommendations for cardiovascular CPGs. Appointing a champion or expert who was knowledgeable about sex differences was acceptable to the CCS executive and CPG development committees and facilitated oversight and decision-making with respect to the type and appropriateness of assessments for each trial included in the literature review. The outcome of the project demonstrated that barriers were associated with the published evidence base to inform the development of sex-specific CPGs for the management of STEMI. Given both low enrollment of female participants in the studies and inadequate reporting of sex-specific outcomes, the quality of the literature studied was insufficient to assess the quality of the evidence and emit sex-specific recommendations.

These findings are consistent with other studies reporting persistent underrepresentation of either male or female patients in the most influential RCTs of cardiology over the past 20 years.[17] Age- and sex-specific representation are improving but remain modulated by the cardiovascular condition studied, the funding source, and the specific exclusion criteria of each trial. In a review of clinical trials supporting approval by the US Food and Drug Administration, Scott et al reported that based on the PPR, female patients were appropriately represented in trials for hypertension and atrial fibrillation but not for trials in heart failure, coronary artery disease, and acute coronary syndrome.[18] Male patients were underrepresented in drug trials of new agents for treatment of primary pulmonary hypertension. In the present assessment, the PPR for all clinical trials on STEMI care was <0.8 for female

Table 3. Studies That Reported Outcomes by Sex in RCTs

Types of Studies	No. of Studies	Outcomes Stratified by Sex (Forest Plots and/or Text Included, n (%)	Outcomes Reported by Sex	Analyses by Sex Reported in the Conclusion
Meta-analyses	22	1 (4.5)	1 forest plot reported more early deaths and strokes in women in fibrinolysis group (1.4% vs 0.9%)	Conclusion states that fibrinolytic therapy is beneficial in a much wider range of patients than is currently given
RCTs (single center and multicenter)	80	13 (16.3)	13 forest plots reported ORs or HRs (1) that go in opposite directions (<1/>1) by sex or (2) that are different for female and male patients	All conclusions reported results for sample without reporting differences noted in subgroup analyses by sex
		1 (1.3)	1 forest plot reported OR by sex for combined mortality and MI but not bleeding/strokes	Conclusion in abstract: fondaparinux significantly reduces mortality and reinfarction without increasing bleeding and strokes
		1 (1.3)	1 forest plot reported (OR <1=stent better [95% CI]): female, 0.53 (0.35–0.81); male: 0.54 (0.39–0.74)	Conclusion in abstract: at experienced centers, stent implantation (with or without abciximab therapy) should be considered the routine reperfusion strategy
		1-text (1.3)	Decrease in chest pain in female patients who received morphine vs metoprolol (P<0.001), no difference in men	Conclusion in abstract: in suspected acute myocardial infarction, if chest pain persists after IV β-adrenergic blockage treatment, morphine will offer better pain relief than increased dosages of metoprolol
RCT pragmatic	1	0	Adjusted for sex in modeling of death from any cause	Routine use of supplemental oxygen in patients with suspected MI who did not have hypozemia was not found to reduce 1-year all-cause mortality

HR indicates hazard ratio; MI, myocardial infarction; OR, odds ratio; RCTs, randomized controlled trials.

patients. These results are supported in data presented at the European Society of Cardiovascular Congress in 2017, where Roeters van Lennep reported that despite enforcement, the number of female participants in major trials was "disappointingly low."[19] In addition, in an editorial entitled "Participation of Women in Clinical Trials," Pilote and Raparelli state that given the current numbers of women participating in trials, the likelihood that the results are generalizable to women is of immediate concern.[20] Changes in protocol design elements may increase representativeness, and there is certainly a role for regulatory agencies to attenuate the discrepancy between cardiovascular trials and population demographics.[17] Without adequate participation and analysis in cardiovascular clinical trials, it will not be possible to provide equal care for female and male patients with CVD.

Although the majority of studies included in this CPG reported the sex of the participants, few analyses were stratified by sex. There are several possible reasons why investigators did not disaggregate results by sex or consider the importance of doing so. First, analysts may have mistakenly concluded that if the sex distribution of participants was equal between the intervention and control groups, then sex could not be a confounder. In fact, the sex-specific representation of male and female participants in the intervention and control groups of an RCT is independent of whether sex is related to the incidence of disease or the response to treatment. Second, there is the mistaken assumption that in subgroup analyses, there is no difference in outcomes by sex if the interaction term between female and male is not statistically significant. In his commentary on subgroup analyses in clinical trials, Sleight points out that an explanation for negative or nonsignificant results in a subgroup is that the statistical power to detect a result is reduced by either a low event rate or a low number of participants in a particular subgroup (eg, female sex).[21] In other words, absence of evidence is not evidence of absence.

Third, there is the flawed notion that adjusting for sex is similar to identifying sex-related differences in outcomes. However, controlling for binary variables such as sex (coded as 0/1) in multivariate analyses in effect gives all cases the "proportion" of the variable coded as 1, which may have obscured differences. This means that when sex was coded as 1=male and 0=female, the regression coefficient was based on a participant being 75.5% male. This is particularly relevant in samples with fewer female participants (eg, patients with

STEMI), for which female data are statistically attenuated because of the lower proportions of women with the event.

Fourth, the P in PICO mandates consideration of sex, so if the intent is for clinical trials to inform practice, then CPG developers need to insist that outcomes for male and female participants be stratified separately. Recommendations based on evidence that does not report sex-specific outcomes make the assumption that outcome effects are homogeneous for male and female patients, which is not always true.

Finally, we did not address whether the RCTs measured gender as a study variable. Sex and gender are often erroneously used and/or measured interchangeably in health-care research. Given that sex and gender are not independent of each other, solely assessing one or the other cannot account for identified variations in health.[11,22] Gender, independent of sex, has been shown to be associated with poor outcomes after early acute coronary syndrome.[11] Different family, social, and institutional roles and attitudes of men and women in recent decades play a role in the symptom presentation of acute myocardial infarction as well as time to treatment. A wide range of behavioral factors; psychosocial processes; and personal, cultural, and societal factors can create, suppress, or amplify underlying biological health differences. How gender intersects with other social factors such as race, age, ethnicity, culture, and sexual orientation is critical to delivering a personalized health approach for every patient. Unless researchers begin to routinely report on gender, this variable cannot be incorporated into CPGs. The routine integration of a gender-based framework into health research is a necessary requirement to advance this field.[23]

Limitations

A number of factors limit the generalizability of our findings. It may be that the PICO questions we posed were ill-suited to capture the literature on sex differences. We focused primarily on health-services–related outcomes and not pathophysiology or drug treatment per se. However, in a recent study, Langabeer et al report that female patients continue to have more bleeding, heart failure, and other major adverse cardiac events following STEMI, and they attribute this finding to limited guidance on discharge dispositions.[24] It may be that other PICO questions would result in a greater proportion of studies including sufficient numbers of female patients and disaggregating the results by sex. The studies used in our analyses were several years old. More recent cardiovascular studies are paying attention to sex bias in cardiovascular health services research, which is encouraging for future CPG development. Huded et al found that a standardized 4-step protocol reduced the door-to-balloon time disparity for female patients in STEMI care as well as 30-day mortality.[18] Unfortunately, the study was released in February 2018, after completion of the guideline, so it was not included. Finally, our literature search did not specifically include key words for sex differences.[25] In the future, use of a validated algorithm designed to identify sex- and gender-specific health literature may improve the yield of systematic searches for CPGs that aim to inform sex- and gender-specific care.[25] Including STEMI incidence data from a Canadian population, and not necessarily the population evaluated in each study, could have affected the PPR values. As a final point, to calculate the PPR, we used the prevalence that represented all female patients hospitalized in 2015 for acute myocardial infarctions in Canada, which included both STEMIs and non-STEMIs. Because the trials incorporated in the guidelines attempted to include only STEMI patients, a better comparison may have been the prevalence of STEMI patients who were female.

Addressing the Gaps

Several steps could address the gaps discovered through this project. An easy first step would be for all CPG development committees to implement the structured approach described for considering sex- and gender-specific information during CPG generation. Appointing a sex and gender expert to oversee the data-extraction process for sex-specific information did not interfere with the timeline of the guideline development. Ensuring that guidelines committees calculate and report median PPRs of the trials used in the development of the guidelines would provide an objective measure to determine the sex-specific strength of the guidelines. Overall, 96% of the studies in this analysis reported the percentage of female participants included in the studies, so this approach is feasible. Reporting outcomes by sex, even if underpowered, to demonstrate efficacy or safety for male and female patients as separate categories will enable future meta-analyses. If signals suggest that sex differences exist, then proper sample size calculations for future trials will enable robust analyses. Enforcing journal standards for reporting will also improve publications so that primary efficacy and safety outcomes are available stratified by sex.

Conclusion

Incorporating a systematic appraisal of sex evidence as part of CPG development is straightforward and feasible. Major challenges with the published literature on the management of STEMI, including inadequate enrollment of female participants in RCTs, lack of publication of main outcomes stratified by sex, and lack of inclusion of gender as a study variable rendered sex-specific assessments of the quality of evidence and strength of recommendations impossible at the current time.

Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. PICO QUESTIONS.

1. Does the regionalization of STEMI Networks improve clinical outcomes?
2. What is the maximum acceptable delay for STEMI patients presenting to non-PCI capable centers?
3. What is the maximum acceptable delay for STEMI Patients presenting to PCI-capable centers?
4. Should STEMI patients transferred to a PCI center for Primary PCI go directly to cath lab or to ED of PCI center?
5. Does Fibrinolytic Therapy Improve Outcomes For Patients Who Are Undergoing PCI within 120 Minutes of First Medical Contact?
6. Does Routine Early angiography/PCI within 24 hours after Fibrinolysis Improve Outcomes Compared with Delayed or Ischemia-Guided angiography/PCI after Fibrinolysis? (Pharmacoinvasive PCI)
7. Does Fibrinolysis Prior to PCI Improve Outcomes for STEMI Patients with Cardiogenic shock who cannot undergo timely Primary PCI?
8. Does the routine use of supplemental oxygen improve clinical outcomes for STEMI patients?
9. Is the routine administration of opioids safe when used for pain control amongst STEMI patients?
10. Does the prehospital administration of P2Y12 inhibitors improve clinical outcomes for STEMI patients?
11. Does prehospital ECG diagnosis of STEMI and prehospital catheterization laboratory activation improve clinical outcomes of STEMI patients undergoing primary PCI?
12. Do STEMI patients required transport with advanced care or critical care paramedics for interfacility transportation for PPCI?
13. What is the maximum transport time for patients to be transferred from the prehospital setting for primary PCI?
14. Should STEMI patients with multivessel disease undergo complete revascularization or culprit only revascularization?
15. Should STEMI patients with multivessel disease and cardiogenic shock undergo complete revascularization or culprit only revascularization?
16. Does routine upfront thrombectomy improve outcomes in primary PCI?
17. Is radial access superior to femoral access in patients undergoing urgent PCI for STEMI?
18. Does intracoronary fibrinolysis improve outcomes in primary PCI?
19. Do intravenous or intracoronary Glycoprotein IIb/IIIa inhibitors improve outcomes in primary PCI?
20. Do intravenous or intracoronary Glycoprotein IIb/IIIa inhibitors improve outcomes in primary PCI?
21. Does Bivalirudin improve outcomes in primary PCI compared to low-molecular weight heparin or unfractionated heparin?

Data S1.

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