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Circulation: Heart Failure

ORIGINAL ARTICLE

Temporal Trends and Clinical Trial Characteristics Associated With the Inclusion of Women in Heart Failure Trial Steering Committees

A Systematic Review

Yousif Eliya, MSc*; Sera Whitelaw, MSc*; Lehana Thabane, PhD; Adriaan A. Voors, MD, PhD; Pamela S. Douglas, MD; Harriette G.C. Van Spall, MD, MPH

BACKGROUND: Trial steering committees (TSCs) steer the conduct of randomized controlled trials (RCTs). We examined the gender composition of TSCs in impactful heart failure RCTs and explored whether trial leadership by a woman was independently associated with the inclusion of women in TSCs.

METHODS: We systematically searched MEDLINE, EMBASE, and CINAHL for heart failure RCTs published in journals with impact factor ≥10 between January 2000 and May 2019. We used the Jonckheere-Terpstra test to assess temporal trends and multivariable logistic regression to explore trial characteristics associated with TSC inclusion of women.

RESULTS: Of 403 RCTs that met inclusion criteria, 127 (31.5%) reported having a TSC but 20 of these (15.7%) did not identify members. Among 107 TSCs that listed members, 56 (52.3%) included women and 6 of these (10.7%) restricted women members to the RCT leaders. Of 1213 TSC members, 11.1% (95% CI, 9.4%–13.0%) were women, with no change in temporal trends (P=0.55). Women had greater odds of TSC inclusion in RCTs led by women (adjusted odds ratio, 2.48 [95% CI, 1.05–8.72], P=0.042); this association was nonsignificant when analysis excluded TSCs that restricted women to the RCT leaders (adjusted odds ratio 1.46 [95% CI, 0.43–4.91], P=0.36).

CONCLUSIONS: Women were included in 52.3% of TSCs and represented 11.1% of TSC members in 107 heart failure RCTs, with no change in trends since 2000. RCTs led by women had higher adjusted odds of including women in TSCs, partly due to the self-inclusion of RCT leaders in TSCs.

Key Words: heart failure ■ leadership ■ randomized controlled trials ■ women

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Randomized controlled trials (RCTs) are considered the gold standard for evaluating the effectiveness of therapeutic interventions, generating the highest-quality evidence to influence clinical practice.[1,2] Clinical trial oversight is essential to ensure that trials are conducted according to Good Clinical Practice and with methodological rigor. Although there are acknowledged variations in oversight practices,[3] the United Kingdom Medical Research Council Guidelines for Good Clinical Practice recommends that trial oversight should include an element of expert advice that is independent of the study investigators and coordinating institution.[4,5] This oversight is usually provided by a trial steering or executive committee (TSC).

The executive roles provided by TSCs are integral to the leadership of RCTs. TSC responsibilities include approving trial design and analysis plans, assessing the progress of the trial, reviewing safety and efficacy data

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WHAT IS NEW?

- Of 403 randomized controlled trials (RCTs) published in high impact factor journals from 2000 to 2019, 31.5% reported having a trial steering committee (TSC), of which 84.3% reported the identity of TSC members.
- Among 107 TSCs that reported members, women were included in 52.3%, representing 11.1% of 1213 TSC members.
- Women had higher adjusted odds of TSC inclusion in RCTs led by women, partly related to self-inclusion of trial leaders in the TSCs.

WHAT ARE THE CLINICAL IMPLICATIONS?

- RCTs should be required to report TSC member names for transparency.
- RCT leaders should consider both expertise and gender diversity in TSC selection.
- TSC registries and objective selection criteria may help diversify TSCs with members other than the RCT leaders.

Nonstandard Abbreviations and Acronyms

HF	heart failure
RCT	randomized controlled trial
TSC	trial steering committee

provided by the data monitoring committees, communicating the trial's progress to relevant parties, and guiding the presentation of trial results.[3–6] An appropriate representation of gender, ethnic, and patient representative groups within TSCs—especially for international trials—may be of importance for steering executive decisions and ensuring high-quality research. Diverse research teams can facilitate higher-quality science of greater relevance to diverse clinical populations.[7] However, the under-representation of women in academic cardiology—especially in clinical trial leadership positions – remains a concern.

Although women are under-represented as heart failure (HF) RCT leaders, trial leadership by women is associated with several benefits. Women represent 15.6% and 12.9% of lead and senior authors of HF RCTs, respectively.[8] Senior authorship by a woman is independently associated with twice the odds of first authorship by a woman, reflecting the gender lines along which mentorship and collaboration may occur.[8] Trial leadership by a woman, defined as first or last authorship by a woman, is independently associated with greater enrollment of females as well as racially and ethnically diverse trial participants (H.G.C. Van Spall, unpublished data, 2021).[9]

The gender gap in cardiovascular clinical trial leadership appears to extend beyond trial leaders and include TSCs.[10,11] Like diverse RCT leaders, diverse TSC members may steer the conduct of trials to better engage and meet the needs of diverse patient populations (H.G.C. Van Spall, unpublished data, 2021).[7,9–11] However, the gender composition of TSCs in HF RCTs is unknown and the association between the gender of trial leaders and TSC members has not been explored. Furthermore, the possible benefits of gender-inclusive TSCs remain to be assessed. The aim of this systematic review was to examine temporal trends in the gender composition of TSCs in HF RCTs published in high impact factor journals and to explore whether trial leadership by a woman is independently associated with inclusion of women in TSCs. A secondary aim was to explore whether the proportion of women in TSCs is independently associated with the proportion of females enrolled as trial participants in HF RCTs.

METHODS

Study Overview

The conduct and reporting of this study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] Data may be shared as per the Population Health Research Institute Data Sharing Policy, which requires approval of the proposed use of the data by a review committee at Population Health Research Institute. Interested parties should contact the study's PI directly for a copy of the policy.

Data Sources and Searches

Guided by a professional information specialist, we conducted a systematic search of the literature. We searched 3 online databases, MEDLINE, EMBASE, and CINAHL, using a combination of medical subject headings and keywords, which included heart failure and randomized controlled trials. The search strategy for MEDLINE is available in the Data Supplement.

Study Selection

We independently screened all titles and abstracts obtained from the search against predefined eligibility criteria. We performed all stages of the systematic review process independently and in duplicate. We included RCTs that were available in the English language, were published between January 1, 2000 and May 7, 2019, and that recruited adults (≥18 years old) with HF. We empirically chose an impact factor threshold of >10 in 2019 to represent high-impact RCTs.[13] We included full-text articles that reported primary outcomes of RCTs. We excluded post hoc, intermediate or secondary analyses, commentaries, editorials, conference abstracts, reviews, and study protocols.

Outcomes

Outcomes for the primary aim included the inclusion of women in TSCs and the proportion of TSC members who were women. The outcome for the secondary aim was the percentage of female participants enrolled in the RCTs.

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Data Extraction and Authors' Gender Classification

Four reviewers (S.W., Y.E., K.S., and M.A.) independently extracted the following information in duplicate: year of publication, journal impact factor, region of coordinating center, location of recruitment (inpatient, ambulatory), type of consent (informed consent, other), type of intervention (health service, drug, device, surgery, exercise/rehabilitation), level of randomization (individual, cluster), type of follow-up (face-to-face, database), scope of trial (national, international), recruitment location (inpatient, ambulatory), number of centers (single center, multicenter), funding type (public, industry), sex-specific eligibility criteria, journal of publication, and number of RCT participants. Three reviewers (S.W., Y.E., and T.A.) independently extracted, in duplicate, gender of RCT participants, total number of authors, gender of authors in first and last position, and gender of TSC members. We classified trials that included any industry funding (partial or full) as industry-funded trials. We classified trials as having TSCs if the trial reported a steering committee. If the trial did not make reference to a steering committee, we included the executive committee, study board, operational committee, or study oversight committee as a proxy for steering committee. If a trial included a large secondary TSC that included site investigators, we only included the primary TSC in the analysis. We ascertained the gender of authors and TSC members using the Web of Science search engine, publication records, institutional websites and social media, or professional networking profiles.[14] If the gender was not apparent from any of these sources, we contacted the lead author of the study for clarification. The senior author (H.V.) audited the data extraction and resolved uncertainties regarding trial inclusion, data extraction, and gender classification.

Statistical Analysis

We performed descriptive analyses and presented continuous variables using medians and interquartile ranges and categorical variables using numbers and percentages. We used the χ^2 test to assess between-group difference in categorical variables and the nonparametric Mann-Whitney *U* test for continuous variables. We assessed temporal trends of the gender distribution of TSC members using the Jonckheere-Terpstra proportion trend test. We used multivariable logistic regression to explore RCT characteristics independently associated with inclusion of women in the TSC. We reported our regression results as odds ratios with corresponding 95% CIs and *P* values.

Sensitivity Analysis

To account for associations due to self-inclusion of RCT leaders in their own TSCs, we: (1) analyzed TSC gender composition after excluding men and women trial leaders from the TSCs; and (2) repeated multivariable logistic regression analysis after excluding TSCs in which women were limited to the trial leaders (ie, lead or senior authors).

Association Between Women TSC Members and Recruitment of Female RCT Participants

We used multivariable linear regression to explore the association between the proportion of women TSC members per RCT and the proportion of females enrolled in the RCT, adjusting for trial characteristics independently associated with this outcome.[9] These included type of intervention, region of coordinating center, number of centers, location of recruitment, sex-specific eligibility criteria, and gender of trial leaders (defined as lead or senior authors).

All *P* values were 2 sided, with alpha=0.05, and were reported to the nearest 0.001 decimal places for significant *P* values and to the nearest 0.01 for nonsignificant *P* values. Data were analyzed using SPSS (version 23; IBM Corporation).

RESULTS

We obtained 10 596 unique titles and abstracts from our systematic literature search. After title/abstract screening, we assessed 2318 full-text articles and identified 403 RCTs that satisfied the eligibility criteria for inclusion in our review (Figure 1).

Characteristics of Included RCTs

Among the 403 RCTs, 127 (31.5% [95% CI, 27.0%–36.3%]) reported having TSCs but 20 of these (15.7%) did not report the identity of TSC members. Of the 107 RCTs that reported TSC member names, a majority were led by men (90.4%), coordinated in North America (48.6%), multicenter (94.4%), and tested drug interventions (70.1%). All 107 RCTs randomized individual patients and obtained informed consent. Men comprised most of the lead (94.4%) and senior (87.9%) authors. The median number of trial participants among the 107

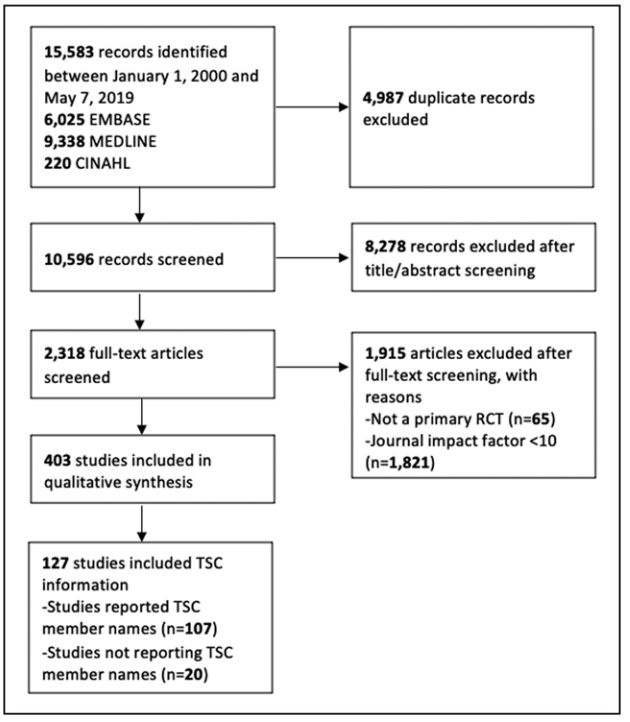

Figure 1. Study selection and flow diagram.
HF indicates heart failure; RCT, randomized controlled trial; and TSC, trial steering committee.

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RCTs was 642 (interquartile range [IQR], 248–2033) per trial and the median proportion of female participants was 25.9 (IQR, 19.0–35.4) per trial (Table 1).

Gender Composition of Steering Committee Members and Temporal Trends

Of the 107 TSCs in which members were named, only 56 (52.3%) included women. Among the 56 TSCs that included women, 13 (23.2%) included at least one woman who led the RCT and 6 (10.7%) were limited exclusively to the women who led the RCT (Figure 2). Twenty-five of 56 RCTs (44.6%) included only one woman, and 6 (10.7%) had a woman TSC chair. The mean percentage of women in TSCs was greater in trials led by a woman (22.2% [95% CI, 13.5%–31.0%]) than by men (7.9% [95% CI, 5.6%–10.2%]; mean difference 14.4% [95% CI, 7.5%–21.3%], $P<0.001$).

Of 1213 TSC members in 107 RCTs (median, 9, IQR, 6–13 per trial), only 135 (11.1% [95% CI, 9.4%–13.0%]) were women. The number of TSC members per RCT remained stable from a median of 9 (IQR, 7–17) in 2000 to 2003 to 9 (IQR, 6–11) in 2016 to 2019. Women comprised 28 out of 276 (10.1%) TSC members in 2000 to 2003, 39 out of 253 (15.4%) in 2004 to 2007, 30 out of 313 (9.6%) in 2008 to 2011, 14 out of 176 (8.0%) in 2012 to 2015, and 24 out of 195 (12.3%) in 2016 to 2019. The proportion of women TSC members did not significantly change over the study period ($P=0.55$; Figure 3).

Multivariable Regression Analysis of RCT Characteristics Associated With Women as TSC Member

Among the 107 RCTs analyzed, trial leadership by a woman was independently associated with TSC inclusion of women (adjusted odds ratio, 2.48 [95% CI, 1.05–8.72], $P=0.042$ relative to men-only leadership teams). No other trial characteristics were associated with inclusion of women in TSCs (Table 2).

Sensitivity Analysis: the Role of Self-Inclusion of RCT Leaders in TSCs

In a sensitivity analysis that excluded both women and men trial leaders from the 107 TSCs, the mean percentage of women in the TSCs remained greater in trials led by a woman (11.8% [95% CI, 8.0%–22.9%]) versus men (9.1% [95% CI, 6.4%–11.8%]; mean difference 2.6% [95% CI, −5.3% to 10.6%], $P=0.50$), although the difference was no longer statistically significant. In multivariable regression that excluded 6 RCTs that limited women in the TSC exclusively to those who led the trial, no significant association was found between RCT leadership by women and TSC inclusion of women (adjusted odds ratio, 1.46 [95% CI, 0.43–4.91], $P=0.36$).

Association Between Women TSC Members and Enrollment of Female RCT Participants

After adjusting for trial characteristics known to be independently associated with enrollment of female RCT participants,[9] we found no association between proportion of women TSC members and proportion of female RCT participants per trial ($r=0.081$, $P=0.43$).

Gender of Steering Committee Members According to Journal Publication

The 107 RCTs that reported TSCs were published in eight major medical journals. Most RCTs were published in *New England Journal of Medicine* (n=29), *Journal of the American Medical Association* (n=12), and *European Journal of Heart Failure* (n=16).

DISCUSSION

This is the first known systematic review to assess temporal trends in the gender composition of TSCs in HF clinical trials, explore trial characteristics independently associated with inclusion of women in TSCs, assess independent associations between the gender composition of TSCs and sex distribution of those enrolled as participants in HF RCTs. We found that among 403 HF RCTs published in high-impact medical journals between 2000 and 2019, 127 (31.5%) included TSCs but 20 of these (15.7%) did not identify members. Of the 107 TSCs that listed members, just over half included women. Among these 56 TSCs, 25 (44.6%) included only one woman and 6 (10.7%) limited the inclusion of women to trial leaders. Women comprised only 11.1% of 1213 TSC members in the 107 trials, with no significant change in the gender representation of TSC members since 2000. The mean proportion of women in TSCs was greater in RCTs led by women than men, but this difference was not statistically significant when analysis excluded RCT leaders from the TSCs. Women had greater odds (adjusted odds ratio, 2.48 [95% CI, 1.05–8.72]) of TSC inclusion in RCTs led by women, but sensitivity analysis revealed that this association was partly due to inclusion of women trial leaders in their TSCs. There was no significant association between the proportion of women in TSCs and the proportion of females enrolled as trial participants (Figure 4).

Our findings that women are not included in nearly half of all TSCs and represent only 11.1% of TSC members are similar to recent analyses of cardiovascular trial leadership committees in which women represented only 10.1% of leadership positions.[10] The representation of women in TSCs in HF RCTs is even lower than the

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Table 1. Characteristics of RCTs, Stratified by Inclusion of Women in the TSC

Clinical trial characteristic	Total RCTs (N=107)	RCTs with woman in TSC (n=56)	RCTs without women in TSC (n=51)	*P* value*
No. of participants per trial, median (IQR)	642 (248–2033)	1066 (357–2305)	448 (180–1237)	0.014
Proportion of participants per trial who were female, median (IQR)	25.9 (19.0–35.4)	27.9 (21.6–40.0)	23.3 (25.7–35.0)	0.026
Gender of lead author,† N (%) of RCTs				
Man	101 (94.4)	51 (91.1)	50 (98.0)	0.12
Woman	6 (5.6)	5 (8.9)	1 (2.0)	
Gender of senior author, N (%) of RCTs				
Man	94 (87.9)	47 (83.9)	47 (92.2)	0.19
Woman	13 (12.1)	9 (16.1)	4 (7.8)	
Woman lead or senior author, N (%) of RCTs	18 (16.8)	13 (23.2)	5 (9.8)	0.06
Inclusion of > 1 woman in TSC, N (%) of RCTs	31 (29.0)	31 (55.4)	N/A	…
Inclusion of women in TSC limited to lead / senior author, N (%) of RCTs	6 (5.6)	6 (10.7)	N/A	…
Gender of TSC chair, N (%) of RCTs				
Man	63 (58.9)	29 (51.8)	34 (66.7)	…
Woman	6 (5.6)	6 (10.7)	N/A	
Not reported	38 (35.5)	21 (37.5)	17 (33.3)	
Primary outcome results, N (%) of RCTs				
Positive	51 (47.7)	24 (42.9)	27 (52.9)	0.30
Neutral	56 (52.3)	32 (57.1)	24 (47.1)	
Unit of randomization, N (%) of RCTs				
Individual	107 (100.0)	56 (100.0)	51 (100.0)	…
Type of consent, N (%) of RCTs				
Informed consent	107 (100.0)	56 (100.0)	51 (100.0)	…
Region of coordinating center, N (%) of RCTs				
North America	52 (48.6)	29 (51.8)	23 (45.1)	0.67
Europe	52 (48.6)	26 (46.4)	26 (51.0)	
Asia	3 (2.8)	1 (1.8)	2 (3.9)	
Recruitment, N (%) of RCTs				
Inpatient	17 (15.9)	8 (14.3)	9 (17.6)	0.63
Ambulatory	90 (84.1)	48 (85.7)	42 (82.4)	
Eligibility criteria, N (%) of RCTs				
Reported	107 (100.0)	56 (100.0)	51 (100.0)	…
Type of intervention, N (%) of RCTs				
Health service	8 (7.5)	6 (10.7)	2 (3.9)	0.73
Exercise	4 (3.7)	2 (3.6)	2 (3.9)	
Drug	75 (70.1)	37 (66.1)	38 (74.5)	
Device	18 (16.8)	10 (17.9)	8 (15.7)	
Surgery	2 (1.9)	1 (1.8)	1 (2.0)	
No. of centers, N (%) of RCTs				
Multicenter	101 (94.4)	51 (91.1)	50 (98.0)	0.12
Single center	6 (5.6)	5 (8.9)	1 (2.0)	
Type of follow-up, N (%) of RCTs				
Face-to-face	107 (100.0)	56 (100.0)	51 (100.0)	…
Scope of trial, N (%) of RCTs				
National	37 (34.6)	25 (44.6)	12 (23.5)	0.022
International	70 (65.4)	31 (55.4)	39 (76.5)	

(*Continued*)

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Table 1. Continued

Clinical trial characteristic	Total RCTs (N=107)	RCTs with woman in TSC (n=56)	RCTs without women in TSC (n=51)	*P* value*
Type of funding, N (%) of RCTs				
Industry	78 (72.9)	37 (66.1)	41 (80.4)	0.25
Public	21 (19.6)	14 (25.0)	7 (13.7)	
Public and industry	8 (7.5)	5 (8.9)	3 (5.9)	
Year of publication, N (%) of RCTs				
2000–2003	22 (20.6)	13 (23.2)	9 (17.6)	0.88
2004–2007	26 (24.3)	13 (23.2)	13 (25.5)	
2008–2011	22 (20.6)	11 (19.6)	11 (21.7)	
2012–2015	16 (15.0)	7 (12.5)	9 (17.6)	
2016–2019	21 (19.6)	12 (21.4)	9 (17.6)	

Analysis included 107 RCTs that reported the names of TSC members. IQR indicates interquartile range; RCT, randomized control trial; and TSC, trial steering committee.

*P values are from χ^2 test for categorical variables and the independent sample Mann-Whitney test for continuous variable.

†Gender of authors was determined using manual online searches of authors' public profiles matched by affiliation status and based on year of publication.

representation of women in other aspects of clinical trial leadership. For example, women represent only 15.6% and 12.9% of lead and senior authors in HF RCTs, with no significant change in temporal trends.[8] It is unclear whether this is because women were less likely to be invited to TSCs or because they were more likely to decline TSC participation than men. The representation of women in HF research leadership is lower than in clinical HF, a specialty in which there are substantially fewer women clinicians and faculty appointees than men.[11] For example, within the subspecialty of HF in the United States, 74.5% are men and 25.5% women representing greater gender balance than in cardiology overall.[11,15]

The proportion of women in TSCs was greater in RCTs led by women than men, and women had greater adjusted odds of inclusion in TSCs when RCTs were led by women. Although these results appear to imply that research collaborations occur along gender

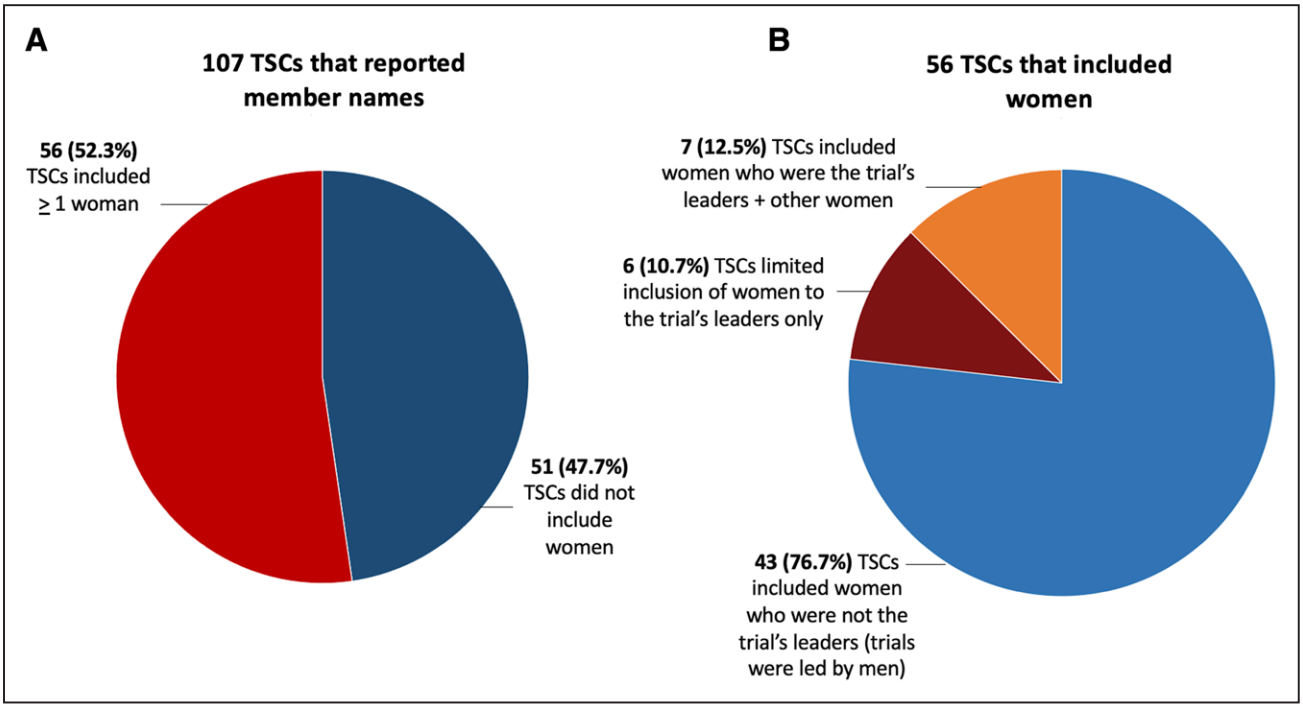

Figure 2. Gender composition of 107 trial steering committees (TSCs) that reported names of members.
A, Among the 107 TSCs that reported member names, 56 included at least 1 woman and 50 did not include any women. **B**, Among the 56 TSCs that included women, 43 did not included any women trial leaders, and 13 included at least 1 woman trial leader. The 43 TSCs that did not include any women trial leaders corresponded to trials led exclusively by men. Both men and women leaders of randomized clinical trials were commonly included in their own TSCs.

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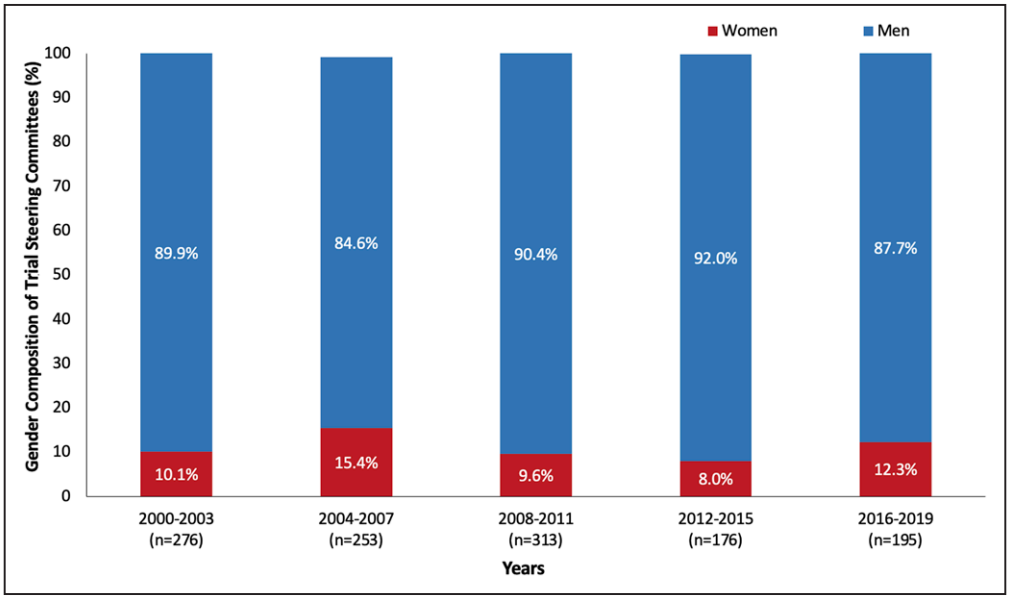

Figure 3. Gender composition of 1213 trial steering committee (TSC) members in 107 heart failure randomized controlled trials published between 2000 and 2019.
Each bar represents all TSC members in trials published within the study period, and the red component represents women. The proportion of steering committee members who were women did not significantly change over the study period (*P*=0.55).

lines—potentially consistent with prior research on RCT authorship[8,16,17]—we found that they were partly related to self-inclusion of trial leaders in their TSCs. In a sensitivity analysis that excluded all trial leaders from the TSCs, the proportion of women TSC members was numerically greater in women-led versus men-led trials, although the difference was no longer statistically significant. In sensitivity analyses that excluded RCTs in which women TSC membership was restricted to women RCT leaders, the independent association between RCT leadership by women and TSC inclusion of women was no longer statistically significant. A substantial proportion of trials led by women did not include women other than the trial leaders, and a substantial proportion of trials led by men did not include women at all. These results highlight the that both men and women trialists must make concerted efforts to include qualified women beyond the trial leaders in steering committees.

Table 2. Multivariable Analysis of Clinical Trial Characteristics Associated With Inclusion of Women in Trial Steering Committees in Randomized Controlled Trials of Heart Failure (N=107)

Variable	aOR (95% CI)	*P* value
Type of intervention		
Other*	1.00 (Reference)	…
Device/surgery	1.18 (0.23–5.55)	0.89
Drug	0.83 (0.20–4.56)	0.79
No. of centers		
Single center	1.00 (Reference)	…
Multicenter	0.28 (0.03–1.25)	0.09
Type of funding†		
Public	1.00 (Reference)	…
Industry	1.21 (0.38–3.70)	0.21
Woman trial leader‡		
No	1.00 (Reference)	…
Yes	2.48 (1.05–8.72)	0.042

aOR indicates adjusted odds ratio.

*Type of intervention other category included health services, exercise, and rehabilitation.

†Type of funding was defined as industry if a trial with mixed funding that also included industry source.

‡Trial leadership was defined as lead or senior author. Gender of authors was determined using manual online searches of authors' public profiles matched by affiliation status and based on year of publication.

We did not find an independent association between the gender of TSC members and enrollment of female trial participants after adjusting for gender of the trial leader (ie, lead or senior author). Our findings may be explained by the high degree of overlap between women authors and women TSC members. Females have been systematically under-enrolled relative to disease distribution in practice-changing clinical trials.[9,18–20] There are sex-related differences in cause, drug metabolism, and treatment response, and adequate sex representation is important to allow for the testing of sex-treatment interactions and to increase the generalizability of trial results.[9,20–22] Federal agencies recommended increasing the recruitment of women in clinical trials so that trial composition reflects disease distribution in clinical settings.[23–25] A systematic review of 317 HF contemporary RCTs published in high-impact medical journals over a 19-year span found that trials led by women were independently associated with greater enrollment of women

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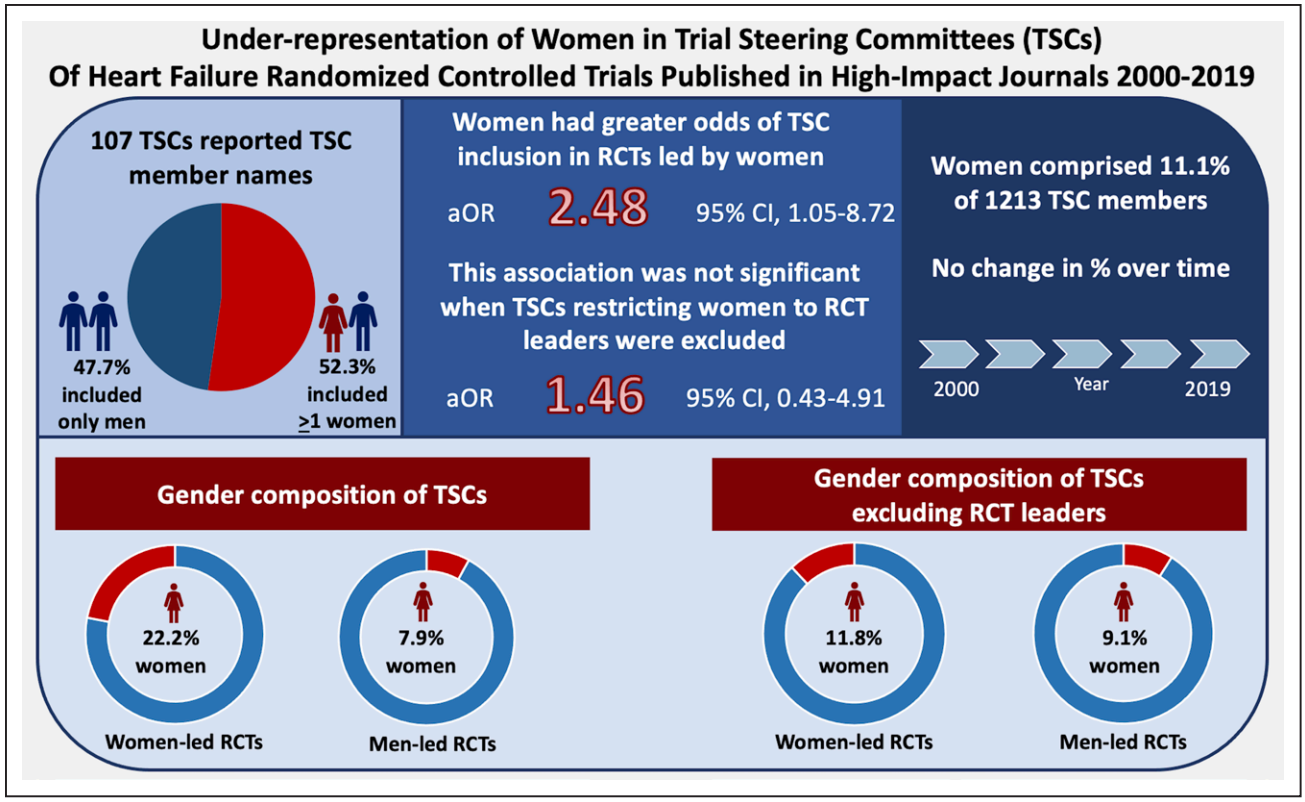

Figure 4. Central illustration.
Women comprised 11.1% of 1213 trial steering committee (TSC) members in the 107 HF TSCs that identified members. There was no significant change in gender composition of TSCs between 2000 and 2019. Women had higher adjusted odds of TSC inclusion in randomized controlled trials (RCTs) led by a woman, but this association was partly due to self-inclusion of RCT leaders in TSCs. aOR indicates adjusted odds ratio.

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participants after adjusting for other trial characteristics.[9] TSC members have the potential to influence trial procedures such as recruitment mechanisms, eligibility criteria, consent procedures, and follow-up plans; and to address some of the factors implicated in the under-enrollment of females as trial participants.[9,20] The small number of trials led by women, small number of RCTs with women TSC members, and high degree of overlap between women trial leaders and TSC members in our cross-section of RCTs made it difficult to reliably assess independent associations between women TSC members and diversity of trial participants.

The possible benefits of diversity in TSCs are multifold, and the lack of consistent documentation and reporting of TSCs in clinical trials is a concern. TSC inclusion may offer women a formal opportunity to engage in research collaborations and increase their research profile, thereby attracting more women investigators to lead cardiovascular research.[8,10] Greater gender representation in TSCs may bring more diverse perspectives and approaches, affording the potential to produce higher-quality research. To improve transparency and allow for conflicts of interest, qualifications, and diversity to be assessed, the membership of TSCs should be reported in all trial publications. Institutional TSCs, such as those associated with The Heart Failure Clinical Research Network, are encouraged to establish a public registry that reports the names of TSC members.

Self-inclusion of men and women trial leaders in their TSCs suggests ambiguity in TSC selection criteria. Although there are no established guidelines or procedures on how to select TSC members, there are several approaches that can be utilized to increase the diversity on TSCs. Current trial regulatory bodies recommend that independent members—other than study investigators, authors, and sponsor representatives—be included in TSCs.[4] At the individual level, established scientists who have participated in TSCs could mentor and sponsor diverse early career cardiologists to participate in TSC. Research institutes, societies, and industries could establish transparent selection criteria for TSC membership and a database of men and women with research expertise who could be drawn on for TSC representation.[11] The selection criteria should not only be based on competence, expertise, experience, and leadership but also demonstrate commitment to diversity, considering the systematic barriers that candidates have experienced by virtue of their demographics.[11] The selection criteria for executive and steering committees, along with the demographic composition, should be reported in trial design methodology publications. Research institutes, clinical trialists, and industry partners involved in TSC selection could receive

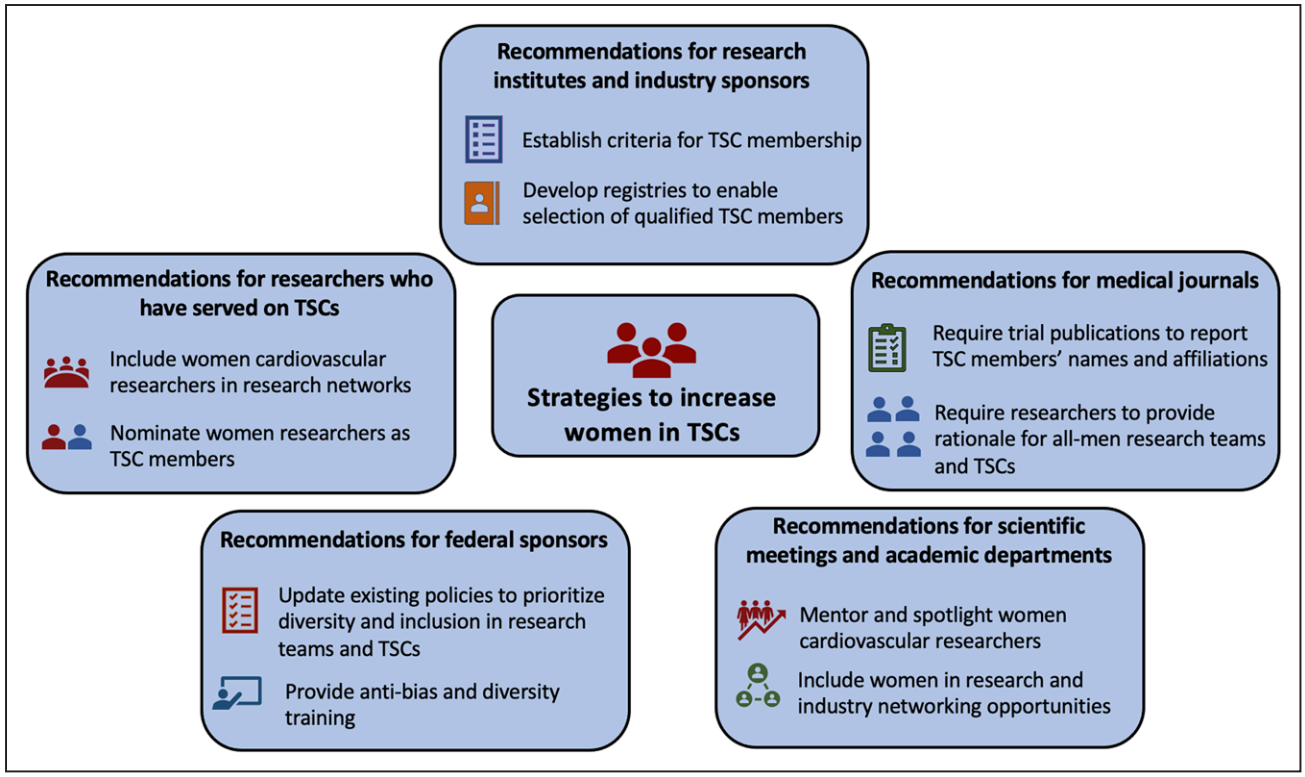

Figure 5. Recommendations to facilitate gender equality in the selection of trial steering committees (TSCs) for research bodies including research programs, academic, and grant funding agencies.

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diversity and anti-bias training. Federal funding agencies and organizations could update their existing policies to promote diversity and inclusion in clinical trial leadership committees.[26] Journals can engage in efforts to reduce gender disparities in research by requesting and evaluating the rationale for all-men authors and TSCs in RCTs that they are considering for publication. In addition, journals could require that all published protocols and trials report the names and affiliations of TSC members to promote transparency and encourage diversity. The CardioVascular Clinical Trialists forum has an internship program aimed to prepare diverse future leaders in cardiovascular clinical trial research, and the experience includes serving on TSCs.[27] Similar initiatives could be implemented by scientific meetings, research institutes, and local academic departments to support the development of women leaders and to facilitate international visibility and networking opportunities (Figure 5).

The strengths of our study included the rigorous systematic review methodology, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Our systematic review included a large number of RCTs published in high impact factor medical journals over a 2-decade time span, further decreasing the possibility that our findings are due to chance. The use of duplicate independent data extraction and independent audits reduced the likelihood of single reviewer bias or chance findings.

There are a few study limitations that must be acknowledged. We restricted this review to English language articles published in medical journals with impact factor ≥10. The gender distribution of TSC members and reported associations may not be generalizable to trials excluded from this review. The gender data was obtained from online sources and relies on accurate information provided by the primary sources. We could not account for nonbinary gender. We did not account for the clustering of TSC membership patterns across RCTs led by the same institutes or that shared the same authors, collaborative networks, and TSC members. The multivariable regression analysis was exploratory and the model may be overfitted due to the low ratio of events to the degrees of freedom for dependent variables.[28]

CONCLUSIONS

Among 403 HF RCTs published in high-impact medical journals between 2000 and 2019, 127 (31.5%) reported having a TSC. Among the 107 HF RCTs that reported TSC member names, women represented 11.1% of 1213 TSC members and were not included in nearly half of all TSCs. The proportion of women in TSCs has not significantly changed since 2000. Women had 2.5 times the adjusted odds of TSC inclusion in RCTs led by women relative to men, partly due to inclusion of women trial leaders in the TSCs. There was no independent association between the proportion of women in TSCs and proportion

of women enrolled as trial participants. Both men and women lead investigators should consider inclusion of women who are independent of the trial leadership in their TSCs to increase diversity. The impact of diversifying TSCs on research quality remains to be investigated.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Supplemental Methods

REFERENCES

1. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med.* 2000;342:1887–1892. doi: 10.1056/NEJM200006223422507
2. Guyatt GH, Haynes RB, Jaeschke RZ, Cook DJ, Green L, Naylor CD, Wilson MC, Richardson WS. Users' Guides to the Medical Literature: XXV. Evidence-based medicine: principles for applying the Users' Guides to patient care. Evidence-Based Medicine Working Group. *JAMA.* 2000;284:1290–1296. doi: 10.1001/jama.284.10.1290
3. Conroy E, Lewis S, Lane A, Sydes M, Norrie J, Murray G, Harman NL, Gamble C. Trial steering committees for randomised controlled trials: updating and redeveloping guidance and terms of reference informed by current practice and experience. *Trials.* 2013;14:P128.
4. Vijayananthan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. *Biomed Imaging Interv J.* 2008;4:e5. doi: 10.2349/biij.4.1.e5
5. Daykin A, Selman LE, Cramer H, McCann S, Shorter GW, Sydes MR, Gamble C, Macefield R, Lane JA, Shaw A. What are the roles and valued attributes of a Trial Steering Committee? Ethnographic study of eight clinical trials facing challenges. *Trials.* 2016;17:307. doi: 10.1186/s13063-016-1425-y
6. Lane JA, Gamble C, Cragg WJ, Tembo D, Sydes MR. A third trial oversight committee: functions, benefits and issues. *Clin Trials.* 2020;17:106–112. doi: 10.1177/1740774519881619
7. Campbell LG, Mehtani S, Dozier ME, Rinehart J. Gender-heterogeneous working groups produce higher quality science. *PLoS One.* 2013;8:e79147. doi: 10.1371/journal.pone.0079147
8. Whitelaw S, Thabane L, Mamas MA, Reza N, Breathett K, Douglas PS, Van Spall HGC. Characteristics of heart failure trials associated with underrepresentation of women as lead authors. *J Am Coll Cardiol.* 2020;76:1919–1930. doi: 10.1016/j.jacc.2020.08.062
9. Whitelaw S, Sullivan K, Eliya Y, Alruwayeh M, Thabane L, Yancy CW, Mehran R, Mamas MA, Van Spall HGC. Trial characteristics associated with under-enrolment of females in randomized controlled trials of heart failure with reduced ejection fraction: a systematic review. *Eur J Heart Fail.* 2021;23:15–24. doi: 10.1002/ejhf.2034
10. Denby KJ, Szpakowski N, Silver J, Walsh MN, Nissen S, Cho L. Representation of women in cardiovascular clinical trial leadership. *JAMA Intern Med.* 2020;180:1382–1383. doi: 10.1001/jamainternmed.2020.2485
11. Van Spall HGC, Lala A, Deering T, Casadei B, Zannad F, Kaul P, Mehran R, Pearson G, Shah M, Gulati M, et al. Ending gender inequality in cardiovascular clinical trial leadership. *J Am Coll Cardiol.* 2021;77:2960–2972. doi: 10.1016/j.jacc.2021.04.038
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535. doi: 10.1136/bmj.b2535
13. Web of Science Group. 2019 journal citation report: full journal list. Accessed April 20, 2020. https://clarivate.com/webofsciencegroup/article/announcing-the-2019-journal-citation-.
14. Web of Science Group. Author search. Accessed April 20, 2020. https://clarivate.libguides.com/woscc/authorid.
15. Blumenthal DM, Olenski AR, Yeh RW, DeFaria Yeh D, Sarma A, Stefanescu Schmidt AC, Wood MJ, Jena AB. Sex differences in faculty rank among academic cardiologists in the United States. *Circulation.* 2017;135:506–517. doi: 10.1161/CIRCULATIONAHA.116.023520
16. Asghar M, Usman MS, Aibani R, Ansari HT, Siddiqi TJ, Fatima K, Khan MS, Figueredo VM. Sex differences in authorship of academic cardiology literature over the last 2 decades. *J Am Coll Cardiol.* 2018;72:681–685. doi: 10.1016/j.jacc.2018.05.047
17. Ouyang D, Sing D, Shah S, Hu J, Duvernoy C, Harrington RA, Rodriguez F. Sex disparities in authorship order of cardiology publications. *Circ Cardiovasc Qual Outcomes.* 2018;11:e005040. doi: 10.1161/CIRCOUTCOMES.118.005040
18. Sullivan K, Doumouras BS, Santema BT, Walsh MN, Douglas PS, Voors AA, Van Spall HGC. Sex-specific differences in heart failure: pathophysiology, risk factors, management, and outcomes. *Can J Cardiol.* 2021;37:560–571. doi: 10.1016/j.cjca.2020.12.025
19. Van Spall HGC. Exclusion of pregnant and lactating women from COVID-19 vaccine trials: a missed opportunity. *Eur Heart J.* 2021. doi: 10.1093/eurheartj/ehab103
20. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA.* 2007;297:1233–1240. doi: 10.1001/jama.297.11.1233
21. Michos ED, Van Spall HGC. Increasing representation and diversity in cardiovascular clinical trial populations. Nat Rev Cardiol. 2021. doi: 10.1038/s41569-021-00583-8
22. DeFilippis EM, Van Spall HGC. Is it time for sex-specific guidelines for cardiovascular disease? *J Am Coll Cardiol.* 2021;78:189-192. doi: 10.1016/j.jacc.2021.05.012
23. National Institutes of Health. Monitoring Adherence to The NIH Policy on The Inclusion of Women and Minorities as Subjects In Clinical Research Fiscal Year 2009-2010. Accessed April 10 2020. http://orwh.od.nih.gov/research/inclusion/pdf/Inclusion-ComprehensiveReport-FY-2009-2010.pdf.
24. FDA Regulations Guidance and Reports related to Women's Health. Accessed April 10 2020. http://www.fda.gov/scienceresearch/specialtopics/womenshealthresearch/ucm472932.htm.
25. American Heart Association. Women and special populations. Accessed June 22, 2020. https://professional.heart.org/professional/Communities/WomenandSpecialPopulations/UCM_475317_Women-and-Special-Populations.jsp.
26. Wang TY, DesJardin JT. Time to end "manels" in clinical trial leadership. *JAMA Intern Med.* 2020;180:1383–1384. doi: 10.1001/jamainternmed.2020.2489
27. Global Cardio Vascular Clinical Trialists Forum. Accessed February 2, 2021. https://www.globalcvctforum.com/young-trialists.
28. Ogundimu EO, Altman DG, Collins GS. Adequate sample size for developing prediction models is not simply related to events per variable. *J Clin Epidemiol.* 2016;76:175–182. doi: 10.1016/j.jclinepi.2016.02.031

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