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## Clinical Research

# Temporal Trends of Women Enrollment in Major Cardiovascular Randomized Clinical Trials

Inna Y. Gong, MD, PhD,[a] Nigel S. Tan, MD,[a,b] Sammy H. Ali, MD,[c] Gerald Lebovic, PhD,[d,e] Muhammad Mamdani, PharmD, MA, MPH,[e,f,g,h] Shaun G. Goodman, MD, MSc,[b] Dennis T. Ko, MD, MSc,[a,e,i] Andreas Laupacis, MD, MSc,[a,e,h] and Andrew T. Yan, MD[a,b]

[a] *Department of Medicine, University of Toronto, Toronto, Ontario, Canada*

[b] *Terrence Donnelly Heart Centre, St. Michael's Hospital, Toronto, Ontario, Canada*

[c] *Department of Medicine, St Mary's General Hospital, Kitchener, Ontario, Canada*

[d] *Applied Health Research Centre, Keenan Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada*

[e] *Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada*

[f] *The Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada*

[g] *Li Ka Shing Centre for Healthcare Analytics Research and Training (LKS-CHART), Toronto, Ontario, Canada*

[h] *Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada*

[i] *Institute for Clinical Evaluative Sciences, Schulich Heart Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada*

***See editorial by Pacheco and Bairey Merz, pages 552–554 of this issue.***

## ABSTRACT

**Background:** Although it is known that women do not participate in trials as frequently as men, there are limited recent data examining how women recruitment has changed over time.

**Methods:** We conducted MEDLINE search using a validated strategy for randomized trials published in *New England Journal of Medicine*, *Lancet*, and *Journal of the American Medical Association* between 1986 and 2015, and included trials evaluating pharmacologic or nonpharmacologic therapies. We abstracted data on demographics, intervention type, clinical indication, and trial design characteristics, and examined their relationships with women enrollment.

**Results:** In total, 598 trials met inclusion criteria. Women enrollment increased significantly over time (21% between 1986 and 1990 to 33% between 2011 and 2015; $P_{\text{for trend}} < 0.001$) and did not differ by journal or funding source. Women enrollment varied with clinical indication, comprising 37% for non–coronary artery disease vascular

## RÉSUMÉ

**Contexte :** Si l'on sait que les femmes ne participent pas aux essais cliniques aussi fréquemment que les hommes, rares sont cependant les données récentes sur l'évolution du nombre de femmes recrutées au fil du temps.

**Méthodologie :** Nous avons utilisé une stratégie validée pour rechercher dans MEDLINE les essais cliniques randomisés portant sur des traitements tant pharmacologiques que non pharmacologiques publiés dans les revues *New England Journal of Medicine*, *Lancet* et *Journal of the American Medical Association* entre 1986 et 2015. Nous avons abrégé les données sur les caractéristiques démographiques, le type d'intervention, l'indication clinique et le plan de l'essai et avons examiné leurs liens avec le recrutement des femmes.

**Résultats :** Au total, 598 essais cliniques satisfaisaient aux critères d'inclusion. Le recrutement des femmes a augmenté de façon

Cardiovascular disease (CVD) is the leading cause of death among women and represents an important health concern in women.[1-3] Importantly, sex differences in CVD epidemiology, pathophysiology, clinical presentation, treatment efficacy, and prognosis have been described.[4-6] Randomized controlled trials (RCTs) provide the most rigorous evidence to assess the impact of interventions and to inform clinical practice guidelines. Accordingly, adequate women participation in trials reflective of the disease population is imperative for delineating treatment risks and benefits, and informing treatment guidelines in women with CVD. Yet, previous studies have consistently demonstrated that women were under-enrolled in RCTs as compared with men.[7,8] This raises concern for the generalizability of RCT results across the whole spectrum of

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Corresponding author: Dr Andrew T. Yan, Division of Cardiology, St Michael's Hospital, 30 Bond Street, Room 6-030 Donnelly, Toronto, Ontario M5B 1W8, Canada. Tel.: +1-416-864-5465; fax: +1-416-864-5159.

E-mail: yana@smh.ca

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trials, 30% for coronary artery disease trials, 28% for heart failure trials, and 28% for arrhythmia trials ($P < 0.001$), which were all significantly lower than the expected proportion in disease populations ($P < 0.001$). Women enrollment varied with trial type (31%, 29%, and 26% for pharmacologic, device, and procedural trials, respectively; $P = 0.001$). These findings were corroborated using multivariable analysis. We found significant positive correlations between women enrolled, and mean age and total number of participants. Fewer women were enrolled in trials reporting statistically significant results than those who did not ($P = 0.001$).

**Conclusions:** Although enrollment of women has increased over time, it remains lower than the relative proportion in the disease population. Future studies should elucidate the reasons for persistent underrepresentation of women in clinical trials.

significative avec le temps (de 21 % entre 1986 et 1990 à 33 % entre 2011 et 2015; $p_{\text{pour la tendance}} < 0{,}001$), sans aucune variation en fonction de la revue ou de la source de financement. Le recrutement des femmes variait en fonction de l'indication clinique : 37 % dans les essais sur les maladies vasculaires ne portant pas sur les artères coronaires, 30 % dans les essais sur les coronaropathies, 28 % dans les essais sur l'insuffisance cardiaque et 28 % dans les essais sur l'arythmie ($p < 0{,}001$), des chiffres qui sont dans tous les cas significativement inférieurs à la proportion attendue dans chaque population des patients atteints ($p < 0{,}001$). Le recrutement des femmes variait en fonction du type d'essai clinique (31 %, 29 % et 26 % pour les essais portant respectivement sur des produits pharmaceutiques, des dispositifs et des interventions; $p = 0{,}001$). Ces constatations ont été corroborées par une analyse multivariée. Nous avons observé des corrélations positives significatives entre le nombre de femmes recrutées et l'âge moyen et le nombre total de participants. Les femmes étaient moins nombreuses à être recrutées dans les essais rapportant des résultats statistiquement significatifs que dans ceux dont les résultats ne l'étaient pas ($p = 0{,}001$).

**Conclusions :** Même s'il a augmenté au fil du temps, le nombre de femmes recrutées demeure inférieur à la proportion relative dans la population totale des personnes atteintes. Des études ultérieures sont nécessaires pour permettre de comprendre les raisons de cette sous-représentation persistante des femmes dans les essais cliniques.

patient population. For many cardiovascular conditions, it is unclear whether there are true sex-based differences in treatment efficacy.[6] For instance, in the Digitalis Investigation Group (DIG) study, digoxin was associated with increased mortality in women with heart failure compared with men.[9]

With increasing awareness of the low rate of enrollment of women in RCTs, the National Institutes of Health (NIH) instituted a policy to promote inclusion of women in trials, which subsequently became law in 1993, mandating women and minorities be included in NIH-funded trials.[10] Despite progress made since 1993 for increasing women enrollment, participation of women in RCTs continues to be less than expected.[11,12] Recent trends in how recruitment of women in trials has changed are required. Hence, we evaluated temporal trends of women enrollment in cardiovascular trials across the whole spectrum of cardiovascular conditions published in 3 major general medical journals over the past 3 decades, and compared women enrollment in trials with sex-based disease prevalence observed in the disease population. Secondarily, given the limited data examining the relationship between women enrollment and trial design characteristics such as size of the trial and endpoints used, we also explored the association between women enrollment and trial characteristics that may reflect quality of the trial.

## Methods

### Data sources and searches

We used a previously validated method for retrieving RCTs[13,14] to search MEDLINE using the following terms: cardiac, cardiology, cardiovascular, coronary, heart, and myocardial. Studies published between 1986 and 2015 in *New England Journal of Medicine*, *Journal of the American Medical Association*, and *Lancet* were included. We selected these 3 general medical journals to search for cardiovascular trials as they are well-regarded high-impact journals with the greatest potential to influence guidelines and clinical practice.

### Study selection

Standardized criteria were applied to all studies to determine suitability for inclusion. The studies selected met the following inclusion criteria: study was an RCT of adult patients (> 18 years of age); primary intent of the trial intervention was for treatment, or primary or secondary cardiovascular prevention; the primary outcome included at least 1 clinical outcome (examples include death, myocardial infarction, stroke, cause-specific or all-cause hospitalization, revascularization, arrhythmia, or surgical procedures such as valve replacement or cardiac transplant). The exclusion criteria were trials with primary nonclinical or surrogate outcomes, such as angiographic restenosis, left ventricular ejection fraction, infarct size, biomarker changes, exercise testing, cardiovascular risk factors, and symptom-based scoring systems; trials evaluating cardiovascular consequences and safety of noncardiovascular agents; trials with interim analysis or reanalysis of previously published trials (either subgroup analysis or extended follow-up).

### Data extraction

The data were abstracted by 2 authors independently using a standardized form. Full manuscripts were obtained for all potentially eligible articles. For 23 articles where uncertainty arose regarding eligibility, a third author was involved to determine the decision for inclusion. For all eligible articles, we collected baseline demographic information including number and/or percentage of women enrolled, clinical indication for the trial, trial intervention, primary outcome, funding source (industry or government/nonprofit), and sex

of the corresponding author (or first author, if there was no clear corresponding author).

Full details on categorization of trials have been described previously.[14] Briefly, the clinical trials were stratified into 6 time intervals determined *a priori*: 1986-1990, 1991-1995, 1996-2000, 2001-2005, 2006-2010, and 2011-2015. We identified the clinical indication for the trial and divided trials into the following groups: coronary artery disease (CAD), heart failure (HF), non-CAD/vascular (ie, cerebrovascular and peripheral vascular disease trials), arrhythmia, and other cardiovascular diseases (including cardiac arrest, cardiac transplant, aortopathy, and valve disease). Study interventions were classified into one of the following 4 groups: pharmacologic, procedural (including percutaneous coronary intervention, cardiovascular surgery, or electrophysiology studies and ablations), devices (including permanent pacemakers, implantable cardioverter defibrillators, cardiac resynchronization therapy, transcatheter aortic valve implantation, intra-aortic balloon pump, Swan-Ganz catheters, and left ventricular assist devices), and other interventions (including lifestyle modification or interventions not meeting other criteria). We collected data on the primary and secondary endpoints of each trial, including whether a composite primary endpoint was used and what components comprised each composite.

### Data analysis

Continuous variables are presented as means with standard deviations (SD) or as medians with interquartile ranges. Categorical variables are presented as frequencies and percentages.

Temporal trends in the percentage of women enrolled in clinical trials over the 6 time periods were examined using the Jonckheere-Terpstra test. The associations of women enrollment with trial characteristics including year of publication, journal of publication, type of intervention, clinical indication, and trial funding were examined using the Mann-Whitney *U*, Kruskal-Wallis or Jonckheere-Terpstr tests, as appropriate. We compared the observed percentage of women enrolled in trials by clinical indication with the expected percentage of women enrollment defined by the disease's prevalence in the general population using the 1-sample *t*-test. We used data from the American Heart Association heart disease and stroke statistics for 2015 trends[3] to compare the unselected population-based sex-specific disease prevalence with women enrollment in trials between 2011 and 2015. The relationships between women enrollment and age of participants in the trial and size of trial were examined using nonparametric Spearman's correlation test.

The relationships between age and year of publication, clinical indication for the trial, and type of trial intervention were examined using the Jonckheere-Terpstra or Kruskal-Wallis test, as appropriate. Differences in women enrollment in relation to the use of composite endpoint, inclusion of all-cause mortality or a minor component in the primary endpoint, and significant trial results were compared using the Mann-Whitney *U* test. A minor component (eg, dyspnea, nonfatal angina, or arrhythmia) was defined based on a previously published hierarchical categorization to categorize primary endpoint components based on clinical importance.[15]

A multivariable fractional (logit) regression model was employed to evaluate the independent associations of year of publication, publication journal, intervention type, clinical indication for the trial, and age with women enrollment.

The association between women enrollment and the sex of the corresponding author (or first author) was examined using the Mann-Whitney *U* test.

Statistical significance was defined as a 2-sided $P$ value $< 0.05$. All data were analysed using SPSS version 22 (IBM Corp., Armonk, NY) and Stata 15.1 (StataCorp, College Station, TX).

## Results

### Characteristics of clinical trials

Our search strategy identified 2607 trials, of which 604 met the inclusion criteria. Six trials lacked information on women enrollment, resulting in a total of 598 trials being included in this study (Fig. 1). Table 1 summarizes the characteristics of these trials. Of trials included, 18 (3.0%) did not enroll female participants, whereas 7 (0.5%) did not enroll male participants. The largest proportion of included trials were published in *New England Journal of Medicine*; the majority of trials studied CAD (65%), evaluated pharmacologic interventions (67%), and used a composite endpoint (68%), with a median of 3 components within composite outcomes (interquartile range, 1-3). The primary outcome was statistically significant in 46% of trials.

### Enrollment of women in trials

Among 2,965,314 patients in all included trials, 32.4% were women. Women enrollment according to trial characteristics is shown in Table 1. The mean percentage of women enrolled in trials significantly increased from 20.7% in 1986-1990 to 32.6% in 2011-2015 ($P_{\text{for trend}} = 0.001$). Women

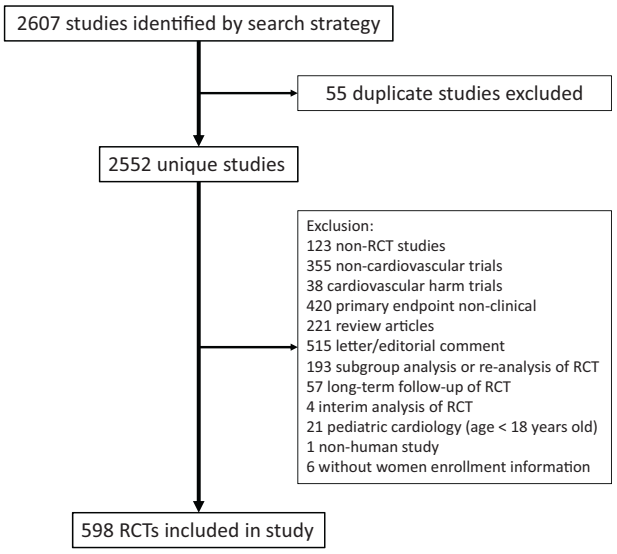


**Figure 1.** Study selection flow diagram. RCT, randomized controlled trials.

**Table 1.** Characteristics of included randomized controlled trials and percentage of women enrollment stratified by trial characteristics

| | Number of trials (%) | Mean percentage of women enrollment (SD) | *P* value |
|---|---|---|---|
| Journal | | | 0.24 |
| *NEJM* | 310 (51.8) | 28.6 (15.8) | |
| *Lancet* | 189 (31.6) | 30.9 (15.5) | |
| *JAMA* | 99 (16.6) | 32.2 (19.2) | |
| Year | | | 0.001 |
| 1986-1990 | 32 (5.4) | 20.7 (17.5) | |
| 1991-1995 | 71 (11.9) | 25.4 (15.5) | |
| 1996-2000 | 97 (16.2) | 29.0 (16.3) | |
| 2001-2005 | 141 (23.6) | 31.4 (17.6) | |
| 2006-2010 | 146 (24.4) | 31.3 (16.0) | |
| 2011-2015 | 111 (18.6) | 32.6 (14.1) | |
| Type of trial intervention | | | 0.001 |
| Pharmacologic | 403 (67.4) | 30.7 (16.6) | |
| Procedural* | 106 (17.7) | 25.7 (14.6) | |
| Devices | 41 (6.9) | 28.7 (15.4) | |
| Other interventions† | 48 (8.0) | 33.5 (17.4) | |
| Clinical indication | | | < 0.001 |
| Coronary artery disease | 387 (64.7) | 29.7 (17.0) | |
| Noncoronary/vascular | 23 (3.8) | 36.8 (10.5) | |
| Heart failure | 64 (10.7) | 28.4 (15.4) | |
| Arrhythmia | 53 (8.9) | 27.9 (14.8) | |
| Other cardiovascular diseases‡ | 71 (11.9) | 32.0 (16.0) | |
| Funding source | | | 0.23 |
| Industry | 192 (32.1) | 31.2 (19.6) | |
| Government/nonprofit | 402 (67.2) | 29.5 (14.5) | |

*JAMA*, *Journal of the American Medical Association*; *NEJM*, *New England Journal of Medicine*; PCI, percutaneous coronary intervention; SD, standard deviation.
* Procedural: PCI, cardiovascular surgery, electrophysiology study ± ablation.
† Other intervention: lifestyle modification or interventions not meeting the other criteria.
‡ Other cardiovascular disease: cardiac arrest, cardiac transplant, aortopathy, valve disease.

enrollment did not differ significantly by publication journal or type of funding.

Women enrollment varied significantly based on the clinical indication for the trial. The mean percentage of women enrolled ranged from 36.8% for non-CAD/vascular trials, 29.7% for CAD trials, 28.4% for HF trials, and 27.9% for arrhythmia trials ($P < 0.001$).

Women enrollment varied significantly based on the type of intervention studied in the trial. The percentage of women enrolled ranged from 33.5% for trials in the "other" category (including lifestyle modification or interventions not otherwise categorized), 30.7% for pharmacologic trials, 28.7% for device trials, and 25.7% for procedural trials ($P = 0.001$).

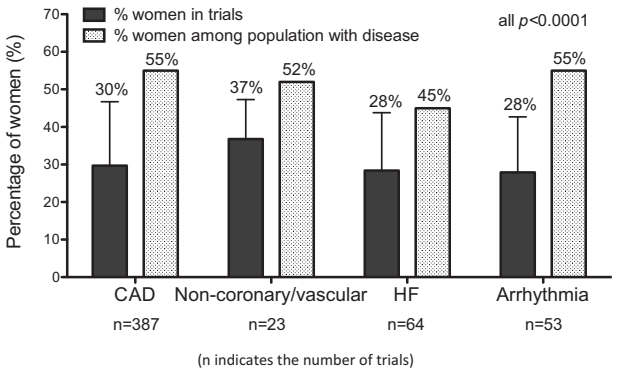


**Figure 2.** Percentage of women enrolled in trials compared with the percentage of women in the general population with a given disease. CAD, coronary artery disease; HF, heart failure.

Multivariable analysis showed that women enrollment was independently associated with time and increased between 1986 and 2015 ($P_{\text{for trend}} < 0.001$). Similar to univariate comparisons, women enrollment was significantly less in procedural trials ($P < 0.001$) and significantly more in non-CAD/vascular trials ($P < 0.001$).

## Comparison of women enrollment with disease population prevalence

We compared the percentages of women in trials relative to unselected population-based disease representation for major CVDs. We found a consistent pattern of women accounting for a higher percentage of the disease population in general compared with the clinical trial cohorts (Fig. 2) for each major category of cardiovascular conditions (all $P < 0.001$). For instance, the percentage of women with HF was 55% in the disease population, compared with 28% enrollment in trials. Similarly, the percentage of women with CAD was 45% in the general population, compared with 30% enrollment in trials.

## Relationship of women enrollment and trial characteristics

There was a significant positive relationship between women enrollment and mean age at recruitment (Spearman's $r = 0.33$, $P = 0.001$). The mean age of trial participants in trials with greater than median percentage of women enrolled was 65 (SD 7) years old, significantly older than mean age of 62 (SD 5) in trials with less than the median percentage of women enrolled ($P < 0.001$). We also found a significant

**Table 2.** Endpoint characteristics of included randomized clinical trials and percentage of women enrollment

| | Number of trials (%) | Mean percentage of women enrollment (SD) | *P* value |
|---|---|---|---|
| Use of a composite primary endpoint | | | 0.016 |
| Yes | 406 (67.9) | 31.3 (16.8) | |
| No | 192 (32.1) | 27.1 (15.1) | |
| Significant *P* value for primary endpoint | | | 0.001 |
| Yes | 273 (45.7) | 27.4 (15.2) | |
| No | 325 (54.3) | 32.0 (17.0) | |
| Primary endpoint includes all-cause mortality | | | 0.001 |
| Yes | 353 (59.0) | 27.9 (14.7) | |
| No | 245 (41.0) | 32.8 (18.2) | |
| Primary endpoint includes any minor outcome | | | 0.14 |
| Yes | 65 (10.9) | 32.2 (14.8) | |
| No | 533 (89.1) | 29.7 (16.5) | |

SD, standard deviation.

positive relationship between year of publication and mean age (Spearman's r = 0.22, $P < 0.001$). The temporal relationship between women enrollment and year of publication remained significant after adjusting for age in the multivariable analysis ($P_{\text{for trend}} = 0.001$).

There were significant associations between age and clinical indication and type of trial intervention ($P < 0.001$). Notably, CAD trials and procedural trials enrolled relatively younger patients compared with other trial types.

Trials using a composite endpoint had a significantly greater proportion of women enrollment (Table 2). There was a significant correlation between women enrollment and number of endpoints incorporated in the composite outcome (Spearman's $r = 0.10$, $P = 0.01$). Trials with a primary endpoint including all-cause mortality had significantly less women enrollment, whereas trials with a primary endpoint including a minor component were not associated with women enrollment (Table 2). Proportionally fewer women were enrolled in trials reporting statistically significant results than those that did not (15.2% vs 17.0%, $P = 0.001$; Table 2).

The median (interquartile range) percentages of women enrolled in trials with a female (n = 50) and male (n = 532) corresponding (or first) author were 32.0 (25.2-43.5) and 27.0 (21.0-36.0), respectively. The trials with women as the corresponding (or first) author had significantly higher proportion of women enrollment ($P = 0.004$).

## Discussion

Although prior studies evaluated temporal trends of women enrollment for a variety of CVDs, there is a scarcity of data examining the relationship between trial design characteristics and women enrollment. Herein, we found that although women enrollment progressively increased during our study period between 1986 and 2015 (absolute increase of 12%), women enrollment continues to be substantially less than the expected proportion in the disease population they comprise. We found that women enrollment significantly varied depending on type of intervention and clinical indication for the trial, and participants in trials with greater women enrollment were older. Proportionally fewer women were enrolled in trials that included all-cause mortality as a component of the composite primary endpoint, and in trials with a statistically significant primary outcome.

Our findings that inclusion of women in trials remained lower compared with men are consistent with prior studies examining women enrollment in cardiovascular trials. For instance, mean proportion of women enrolled was 30% in CAD trials included in this study, similar to the range of 25% to 33% found in previous studies.[7,8,16] Likewise, for HF trials, mean proportion of women enrolled was 28%, consistent with previous studies ranging from 21% to 29%.[7,8,11,17-19] Prior studies tended to be composed of selected categories of trials (such as NIH-funded studies only, certain cardiovascular disease types, or Food and Drug Administration–approved drugs only). In contrast, the present study was not limited to federally funded studies or subcategory of trials; rather, we intended to incorporate a wider spectrum of major cardiovascular studies. For instance, our study is one of few to include recent trials that better reflect contemporary CVD burden to examine women enrollment across cardiovascular intervention types.

Indeed, we observed that women enrollment varied based on type of intervention and cardiovascular clinical indication for the trial. We found that women enrollment was highest for other interventions such as lifestyle modification trials, and least for device or procedural trials. These findings corroborate with prior older studies demonstrating under-representation of women in cardiovascular device trials.[20] Moreover, prior studies have shown underutilization of evidenced-based interventional procedures in women.[21] For instance, fewer women undergo coronary angiography or percutaneous coronary intervention for acute coronary syndrome compared with men,[22-25] which may limit their eligibility to enter procedural trials requiring coronary anatomy. Women enrollment was highest for non-CAD/vascular trials compared with HF, CAD, or arrhythmia trials. These results corroborate the findings by Melloni et al.[8] demonstrating that women representation was higher in primary prevention than secondary prevention trials. There may be several plausible reasons contributing to this, including sex-based risk perception differences that may hinder trial participation. When

compared with men, women tended to perceive fewer benefits and more risk from higher-acuity trial participation, which might undermine their willingness to participate.[26-28]

Our study findings indicate that the proportion of women enrolled in trials still inadequately reflect their disease representation in the general population, and the lack of substantial improvement over time is concerning. These results corroborate with 2 very recent studies by Scott et al.[29] and Nguyen et al.,[30] which respectively examined women enrollment using trial data from new Food and Drug Administration drug applications and trial data from most cited trials, demonstrating that women under-representation continues to persist. Women account for up to 50% of mortality in disease populations, which further emphasizes the importance of women representation in trials to determine appropriate evidence-based interventions with minimal sex bias to inform clinical practice.[3] Of note, recent data suggest that there is a plateau in mortality of CAD, particularly for women $<$ 55 years old.[31] To improve outcomes in women, trials evaluating novel cardiovascular interventions ought to be generalizable to women encountered in routine clinical practice.

To the best of our knowledge, our study is the first to explore the relationship between women enrollment and trial design characteristics (ie, size of trial, use of clinically important outcomes in the composite endpoint, trials with significant results), to determine whether more definitive trials enrolled more or fewer women. We demonstrated that trials with greater women enrollment had an overall older population at recruitment. Important sex differences in epidemiology, clinical presentation, treatment patterns, and prognosis have previously been described.[4] For example, women with ACS generally present 10 years later than men; as such, women may have more comorbidities, higher risk profiles at presentation, and higher mortality rates compared with their male counterparts.[32,33] Their enrollment may therefore be limited by inherent selection bias towards healthier, younger patients with fewer comorbidities who meet strict inclusion criteria of RCTs.[12,34] Indeed, preferential recruitment of younger trial participants with fewer comorbidities has been demonstrated previously.[35,36] Moreover, CVD likely manifests differently depending on demographic factors such as age and sex, likely due to differences in pathophysiology, clinical presentation, and treatment response.[37-41] For instance, women are more likely to be asymptomatic or present with atypical symptoms such as exertional fatigue rather than classic angina.[42] This has important treatment implications and is likely partly responsible for the treatment-risk paradox with underutilization of evidence-based interventional procedures and medical therapies in women.[21] Taken together, it is plausible that the clinical definitions of disease in trial inclusion criteria are more reflective of presenting characteristics of men rather than women and may constitute a barrier for women recruitment. Further contemporary studies are needed to understand whether cardiovascular trial eligibility criteria are overly restrictive and determine its influence on women accrual.[43]

We demonstrated that there were proportionally fewer women in trials with a composite endpoint incorporating outcomes of greater clinical significance such as all-cause mortality. Furthermore, although larger trials enrolled more women, fewer women were enrolled in trials reporting statistically significant results than those that did not. The explanation for these finding and the possibility of sex-based efficacy difference between women and men remains elusive and may be multifactorial.[44,45] We speculate that larger trials and those with difficulty reaching target enrollment might recruit more women and other minority groups. Nevertheless, these findings further highlight that continued research is needed to elucidate barriers to women recruitment, develop, and implement actionable strategies to encourage women inclusion in cardiovascular trials to achieve the expected proportion as observed in the disease population, to ensure generalizability of trial results to women.

To this end, qualitative and quantitative studies are needed to investigate both internal and external factors contributing to women-specific barriers to trial participation. For instance, despite a high proportion of women with CVD, a disproportional lower number of women highlight it as their major health concern, which likely limits motivation to participate in trials.[26,46] As such, research staff should be made aware of the distinct needs of women requiring additional education and resources.[47] There may be logistical barriers for women including childcare, inflexibility of work hours, and transportation costs to study sites. For those that require aide, incorporation of flexible clinic hours or at-home follow-ups, providing transportation and childcare may alleviate some of these barriers. Moreover, there are long-standing cultural and societal norms that contribute to sex-based dynamics in autonomy and choice of voluntary participation, in which women tend to seek approval from their family for decision-making support.[48] Women also perceive more harm than benefit from trial participation.[26-28] We examined the relationship between sex of the senior author and women enrollment. Our results demonstrate that the representation of women corresponding authors was much less as compared with men, and intriguingly, trials with a female corresponding author had greater women enrollment. These findings support the notion that increased female investigators, physicians, and clinical trial staff to interact with women participants may foster greater trust and understanding. Another aspect to be addressed is insufficient sex-stratified analysis and reporting of trial results.[49] Strategies such as *a priori* statistical planning with power calculation to incorporate sex-stratified analysis and collection of sex-specific data may in turn increase women enrollment by ensuring adequate inclusion of sufficient women for planned analysis. Finally, women contribution should be acknowledged and feedback should be obtained from women participating in trials to inform future efforts.

We acknowledge several limitations in our study. We focused on 3 major medical journals, and it is not known whether trials published in other journals demonstrate the same findings for women enrollment. However, this strategy allowed us to focus on cardiovascular trials published in high-impact journals with greater potential to influence guidelines and clinical practice. We evaluated a finite number of trial factors to explain enrollment patterns of women in clinical trials and were not able to examine important granular details such as the percentage of women screened vs enrolled, whether women were approached equally for participation, and percentage of women eligible but declined participation. Similarly, we could not determine whether women under-representation may be potentially related to explicit *a priori* strict exclusion criteria

(and their appropriateness), or invisible selection bias against women recruitment. For example, women may have had more comorbidities (given their older age at disease presentation), such as renal dysfunction or history of a haemorrhagic event, resulting in (potentially legitimate) exclusion. Although limited prior studies compared women screened vs enrolled, a recent study by Scott et al.[29] evaluated the impact of eligibility criteria on women enrollment in 5 of 45 trials with screening data available. They found that the percentage of women screened was similar to the percentage of women eventually enrolled, supporting the notion that women themselves may be less likely to consider trial participation as well as less likely to be considered for trial screening. Although this study did not evaluate enrollment of elderly participants or minorities over time, prior studies have described their under-representation in trials.[12,17] As such, addressing limitations to their enrollment is also imperative to enroll a trial population reflective of the population with CVD to inform clinical practice guidelines. Overall, we acknowledge that there are many intricacies to address the precise reasons for women under-representation that are beyond the scope of this study, and these should be the focus of future research.

## Conclusions

Despite their CVD burden and mortality, women continue to be under-represented in major cardiovascular trials compared with men, and relative to their expected proportion in the disease population. Trials with clinically important outcomes as part of the composite endpoint and trials with significant results had less women representation. Our findings support the need for further studies (both quantitative and qualitative) to delineate the precise reasons for low women enrollment to guide strategies for encouraging women participation, to minimize sex selection bias in evidence-based recommendations. It is imperative to remember that generalizability of a trial is based on the degree to which trial participants reflect the characteristics of the patient population that the intervention should be applied. These efforts will likely bridge the persistent sex-based gaps in treatment provision and clinical outcomes.

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## Disclosures

The authors have no conflicts of interest to disclose.

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