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ORIGINAL RESEARCH ARTICLE

Women's Participation in Cardiovascular Clinical Trials From 2010 to 2017

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BACKGROUND: Cardiovascular disease is the leading cause of death among women worldwide, yet, women have historically been underrepresented in cardiovascular trials.

METHODS: We systematically assessed the participation of women in completed cardiovascular trials registered in ClinicalTrials.gov between 2010 and 2017, and extracted publicly available information including disease type, sponsor type, country, trial size, intervention type, and the demographic characteristics of trial participants. We calculated the female-to-male ratio for each trial and determined the prevalence-adjusted estimates for participation of women by dividing the percentage of women among trial participants by the percentage of women in the disease population (participation prevalence ratio; a ratio of 0.8 to 1.2 suggests comparable prevalence and good representation).

RESULTS: We identified 740 completed cardiovascular trials including a total of 862 652 adults, of whom 38.2% were women. The median female-to-male ratio of each trial was 0.51 (25th quartile, 0.32; 75th quartile, 0.90) overall and varied by age group (1.02 in ≤55 year old group versus 0.40 in the 61- to 65-year-old group), type of intervention (0.44 for procedural trials versus 0.78 for lifestyle intervention trials), disease type (0.34 for acute coronary syndrome versus 3.20 for pulmonary hypertension), region (0.45 for Western Pacific versus 0.55 for the Americas), funding/sponsor type (0.14 for government-funded versus 0.73 for multiple sponsors), and trial size (0.56 for smaller [n≤47] versus 0.49 for larger [n≥399] trials). Relative to their prevalence in the disease population, participation prevalence ratio was higher than 0.8 for hypertension, pulmonary arterial hypertension and lower (participation prevalence ratio 0.48 to 0.78) for arrhythmia, coronary heart disease, acute coronary syndrome, and heart failure trials. The most recent time period (2013 to 2017) saw significant increases in participation prevalence ratios for stroke (P=0.007) and heart failure (P=0.01) trials compared with previous periods.

CONCLUSIONS: Among cardiovascular trials in the current decade, men still predominate overall, but the representation of women varies with disease and trial characteristics, and has improved in stroke and heart failure trials.

This article is part of the Science Goes Red™ collection. Science Goes Red™ is an initiative of Go Red for Women®, the American Heart Association's global movement to end heart disease and stroke in women.

Key Words: cardiovascular disease ■ clinical trial ■ coronary disease ■ female

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Clinical Perspective

What Is New?

- The authors present a thoughtful analysis of women enrollment in cardiovascular trials based on data available from ClinicalTrials.gov. The overall percentage of women enrolled in the 740 eligible trials was 38.2%, which is lower than the previous report driven data from pivotal cardiovascular drug trials.
- In addition to updating participation rates adjusting by disease prevalence, this study incorporates funding sources, intervention type, sponsor type, and region as subgroups.
- Regarding the participants' age, the lowest participation rates were among women aged 61 to 65 years old (26%).

What Are the Clinical Implications?

- There are challenges in recruiting women to participate in clinical trials of cardiovascular diseases, especially for the trials of heart failure and targeting the elderly.

The appropriate representation of women in clinical trials is recognized as a worrisome issue.[1] In particular, given the burden of cardiovascular morbidity and mortality in both sexes, and increasing appreciation of sex differences in cardiovascular disease, several publications have focused on the inclusion of women in cardiovascular trials. A systematic review on 325 cardiovascular trials published in three leading medical journals from 1997 to 2009 estimated that 1 in 3 participants were women. After accounting for age- and sex-specific differences in disease prevalence, however, the enrollment rates of women were lower than expected, estimated at 3% to 13% across a spectrum of cardiovascular diseases.[2] Using publicly available US Food and Drug Administration reviews of trials in support of 36 cardiovascular medications from 2005 to 2015, Scott et al found large variations in participation of women (range, 22% to 81%; mean per trial, 46%).[3] In 118 heart failure trials with at least 400 participants, only 27% were women, with no significant temporal trends.[4]

Previous studies have analyzed trials based only on the journal or regulatory agency or size, potentially biasing results and explaining the inconsistencies among different studies. Conversely, none of them have performed a comprehensive review of all registered trials regardless of journal impact factor, geography, or size. Therefore, we used data from ClinicalTrials.gov to provide a systematic analysis of the representation of women across a broad range of cardiovascular clinical trials. Among all available trial registration platforms, this site has the longest history, the largest number of trials, and the widest geographic coverage.

METHODS

The data, analytical methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure from the corresponding author on reasonable request.

Source of Data and Study Selection

We searched clinical trials registered in ClinicalTrials.gov, a resource provided by the US National Library of Medicine and managed by the National Institutes of Health. The search terms were "cardiovascular diseases" as disease condition, "interventional studies (clinical trials)" as study type, "completed" as recruitment status, and "with results" as result status. Searches were limited to only include trials with adults or older participants and with a primary completion date between January 1, 2010 and December 31, 2017. Because very few trials completed in 2018 or 2019 had uploaded their results, we did not include trials completed after 2017.

Trials were excluded if (1) the disease type was not one of the 8 preidentified major cardiovascular diseases (stroke, heart failure, coronary heart disease or acute coronary syndrome or atherosclerosis, arrhythmia, myocardial infarction or ischemia, hypertension, pulmonary hypertension, and multiple outcomes including the aforementioned diseases [Table I in the online-only Data Supplement]); (2) the number of participants was less than 20; or (3) the sex proportion was not stated/could not be identified.

Data Extraction

Data were extracted by X.J. and 20% of the data was independently verified by C.C. and W.B. Only trials that met the aforementioned criteria were selected for the data extraction process. The following trial characteristics were extracted: (1) National Clinical Trial number, (2) primary completion date, (3) trial locations, (4) intervention type, (5) disease type, (6) sponsor type, (7) sponsor name, (8) total sample size, (9) proportion of women, (10) mean age, and (11) funding sources. The intervention type was further categorized into drugs, devices, lifestyle, procedures, or multiple interventions. The sponsor type was categorized into industry, research institute (hospital/medical center and university), government, industry and research institute, government and research institute, multiple sponsors (excluding the National Institutes of Health), and multiple sponsors (including the National Institutes of Health). Trial location was categorized according to the World Health Organization classifications of regions (European, the Americas, Western Pacific, Southeast Asia, and Eastern Mediterranean). Trials conducted in more than 1 region were identified as "global." Age groups included ≤55, 56 to 60, 61 to 65, and >65 years. Trial sizes were divided into 4 groups by quartiles (quartile 1, ≤47; quartile 2, 48 to 124; quartile 3, 125 to 398; quartile 4, ≥399).

Statistical Analysis

We computed the proportion of women by disease type, sponsor type, age, intervention, region, and trial size. The

median of the female to male ratio of each trial was calculated and stratified by disease type, sponsor type, age, intervention, region, trial size, and year of trial completion.

Participation to prevalence ratio (PPR), a measure to describe the representation of women in trial with respect to their proportion in disease population, was computed using the formula below, as previously described.[3,5,6]

$$\text{PPR} = \frac{\text{Percentage of women among trial participants (\%)}}{\text{Percentage of women among disease population}}$$

The corresponding proportion of women in each disease population was obtained from the most recent or large epidemiologic population-based data available in the literature (Table I in the online-only Data Supplement). The influence of disease prevalence on actual female participation rates could be adjusted by measuring PPR. The PPR rate of 1 suggests that sex distribution in the respective trial is comparable to that of the disease population. Women were underrepresented or overrepresented when the PPR was <0.8 or >1.2, respectively, relative to women in the disease population.[3]

The difference among groups was assessed by Kruskal–Wallis test. Pairwise comparisons in continuous variables were performed with the Mann–Whitney U test. A nonparametric test for trend[7], which is an extension of the Wilcoxon rank-sum test, was applied to test the trends of PPR change by time. All analyses were conducted by using STATA version 14.0 (StataCorp, College Station, TX).

RESULTS

General Characteristics of Trials and the Proportion of Women Participants

In total, 1947 trials were screened and 740 trials were included in the data extraction and analysis process (Figure 1), resulting in a total of 862 652 participants, of whom 38.2% were women.

Among the 740 trials, 57.6% evaluated drug interventions, 51.6% were solely sponsored by industry, and 56.8% were conducted in the Americas (Table). The mean age of trial participants of both sexes was 60.8 years and ranged from 25 to 89 years. The proportion of women in cardiovascular trials varied by disease type, sponsor, age group, intervention, region, and trial size. Higher proportions of women were represented in trials sponsored by research institutes, involving pulmonary hypertension, and conducted in America. Of note, the lowest proportion of women were in trials where the average age was between 61 and 65 years (26.0%), despite the largest number of trials taking place in that same age group (n=218; 31.6%). Trials solely sponsored by government had the lowest proportion of women participants compared with other sponsors (15.9%).

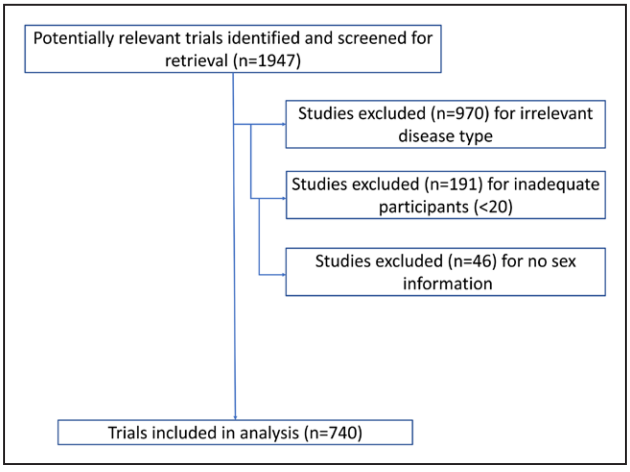

Figure 1. Flowchart of trial selection process.

Women Representation in Cardiovascular Clinical Trials

Figure 2 illustrates the median female to male ratios stratified by several categories. The median female to male ratio was smaller with older age (1.02 to 0.40 for <55 and 61 to 65 years) and different by the extent of intervention (0.78 to 0.44 for lifestyle and procedure). The female to male ratio also varied by disease type (3.20 to 0.34 for pulmonary hypertension and acute coronary syndrome), regions (0.45 in the Western Pacific to 0.55 in the Americas), nature of sponsorship (0.14 for government to 0.73 for multiple sponsors), and trial size (0.56 for smaller [n≤47] versus 0.49 for larger [≥399] trials).

Taking the prevalence of diseases into consideration, significant differences among different intervention types, disease types, and sponsor types were observed (P<0.05). Women were reasonably represented in hypertension (PPR=0.82) and pulmonary hypertension trials (PPR=1.33). The PPR of pulmonary hypertension trials was higher and that of heart failure trials was lower compared with all the other categories (P<0.0018) (Figure 3). Women were represented at a rate lower than their share in the respective disease population (PPR<0.8) for arrhythmia (PPR=0.78), coronary heart disease (PPR=0.67), stroke (PPR=0.73), acute coronary syndrome (PPR=0.66), heart failure (PPR=0.48) and multiple outcomes (PPR=0.75). Trials cosponsored by government and research institutes and solely sponsored by government had lower PPRs than all the other categories (P<0.0024). Regarding the mean age of trial participants, the <55 age group had a higher PPR compared with all other age groups (P<0.0083). Drug trials had higher PPRs than device ones (P=0.0009). However, there was no significant difference in PPRs among trials of different sizes.

To further explore trends in women representation by disease type, median PPRs in 2-year increments from 2010 to 2017 by major cardiovascular disease type are shown in Figure 4. The PPR of pulmonary hypertension decreased during the 8 years, but was consistently greater than 1.2. The PPR of coronary heart disease trials for 2016 to 2017 was lower than in previous years. The most recent 5 years (2013 to 2017) saw significant

Table. Basic Characteristics of the 740 Clinical Trials, 2010 to 2017

Category	Number of Trials, N (%)	Female, N (%)
Overall	740	329 633 (38.2)
Disease	740	329 633 (38.2)
Stroke	87 (11.8)	114 561 (52.3)
Arrhythmia	106 (14.3)	86 036 (40.5)
Coronary heart disease	141 (19.1)	25 783 (27.3)
Acute coronary syndrome	61 (8.2)	37 012 (26.9)
Pulmonary hypertension	36 (4.9)	4853 (76.3)
Heart failure	102 (13.8)	12 948 (28.6)
Hypertension	136 (18.4)	22 875 (42.4)
Multioutcome	71 (9.6)	25 565 (27.3)
Sponsor	738	329 560 (38.2)
Industry	381 (51.6)	194 915 (34.8)
Research institute	152 (20.6)	102 289 (53.8)
Government	30 (4.1)	767 (15.9)
Industry + research institute	70 (9.5)	14 909 (25.5)
Research institute + government	9 (1.2)	1082 (30.7)
Multiple sponsors (excluding NIH)	24 (3.3)	4552 (34.7)
Multiple sponsors (including NIH)	74 (10.0)	11 119 (33.5)
Age, y	690	319 090 (38.8)
≤55	119 (17.2)	11 479 (50.3)
56–60	170 (24.6)	18 917 (38.1)
61–65	218 (31.6)	67 353 (26.0)
≥66	183 (26.5)	221 341 (45.0)
Intervention	738	329 633 (38.2)
Drug	425 (57.6)	450 156 (31.6)
Device	151 (20.5)	41 655 (31.0)
Lifestyle intervention	54 (7.3)	16 693 (33.9)
Procedure	19 (2.6)	10 859 (31.6)
Others + multi-interventions	89 (12.1)	343 289 (48.1)
Region	740	329 633 (38.2)
Global	139 (18.8)	104 882 (31.9)
European	86 (11.6)	68 318 (37.4)
Americas	420 (56.8)	128 579 (46.5)
Western Pacific	70 (9.5)	25 086 (37.2)
Southeast Asia	3 (0.4)	107 (28.1)
Eastern Mediterranean	3 (0.4)	162 (30.6)
Nonstated	19 (2.6)	2499 (42.3)
Trial size	740	329 633 (38.2)
Quartile 1 (≤47)	177 (24.0)	2148 (37.8)
Quartile 2 (48–124)	187 (25.3)	5906 (37.9)
Quartile 3 (125–398)	188 (25.5)	15 651 (35.8)
Quartile 4 (≥399)	188 (25.5)	305 928 (38.4)

NIH indicates the National Institutes of Health.

increases in PPRs for stroke (P<0.001) and heart failure (P=0.01) trials. Specifically, stroke trials among participants with mean age of >65 years that were conducted in the Americas (P=0.009) and sponsored by research institutes (P=0.03) showed the greatest increase in PPR (Figure I in the online-only Data Supplement). Longitudinal increases of PPR in heart failure trials were consistent across all categories with the exception of those conducted in the Americas.

DISCUSSION

Our analyses highlighted the critical patterns in the representation of women in 740 cardiovascular clinical trials with 862 652 participants registered on ClinicalTrials.gov between 2010 to 2017. Overall, 38.2% of the trial participants were women. Women's representation in trials compared to disease prevalence varied by disease, being higher in pulmonary hypertension, comparable in hypertension, and lower in stroke, arrhythmia, coronary heart disease, acute coronary syndrome, and heart failure. Furthermore, participation of women in cardiovascular trials was particularly low in trials where the average participant age was between 61 and 65 years, in government-sponsored trials, in procedure interventions, and in trials conducted in the Western Pacific region. These findings provide key insights into factors impacting women's representation in cardiovascular trials, including both success factors as well as areas where women remain underrepresented. Future efforts should build on previous successes and target key areas for improvement with multifactorial approaches to enhance recruitment of women.

Our findings were generally consistent with prior publications. In 2002, Heiat et al reviewed the randomized controlled trials of heart failure between 1985 to 1999 and highlighted the underrepresentation of women.[8] More recently, Tahhan et al reported that older patients and women remain underrepresented in heart failure trials since 2001.[4] Although there was an increase in PPR from 2016 to 2017, it was still <0.8 for heart failure trials throughout our study period of 2010 to 2017. Expanding to cardiovascular disease in general, Scott et al[3] evaluated the participation of women in 36 clinical trials supporting the US Food and Drug Administration's approval of cardiovascular drugs, and reported disease-specific differences in female representation. They found that the representation of women was below the prevalence estimate for trials in heart failure, coronary heart disease, and acute coronary syndrome. Our study included 740 trials registered on ClinicalTrials.gov with different intervention and sponsor types. We found that women were overrepresented in pulmonary hypertension trials and relatively well-represented in hypertension trials. We confirmed results from Scott et al[6] that women were underrepresented in heart failure, coronary heart disease, and acute coronary syndrome trials.

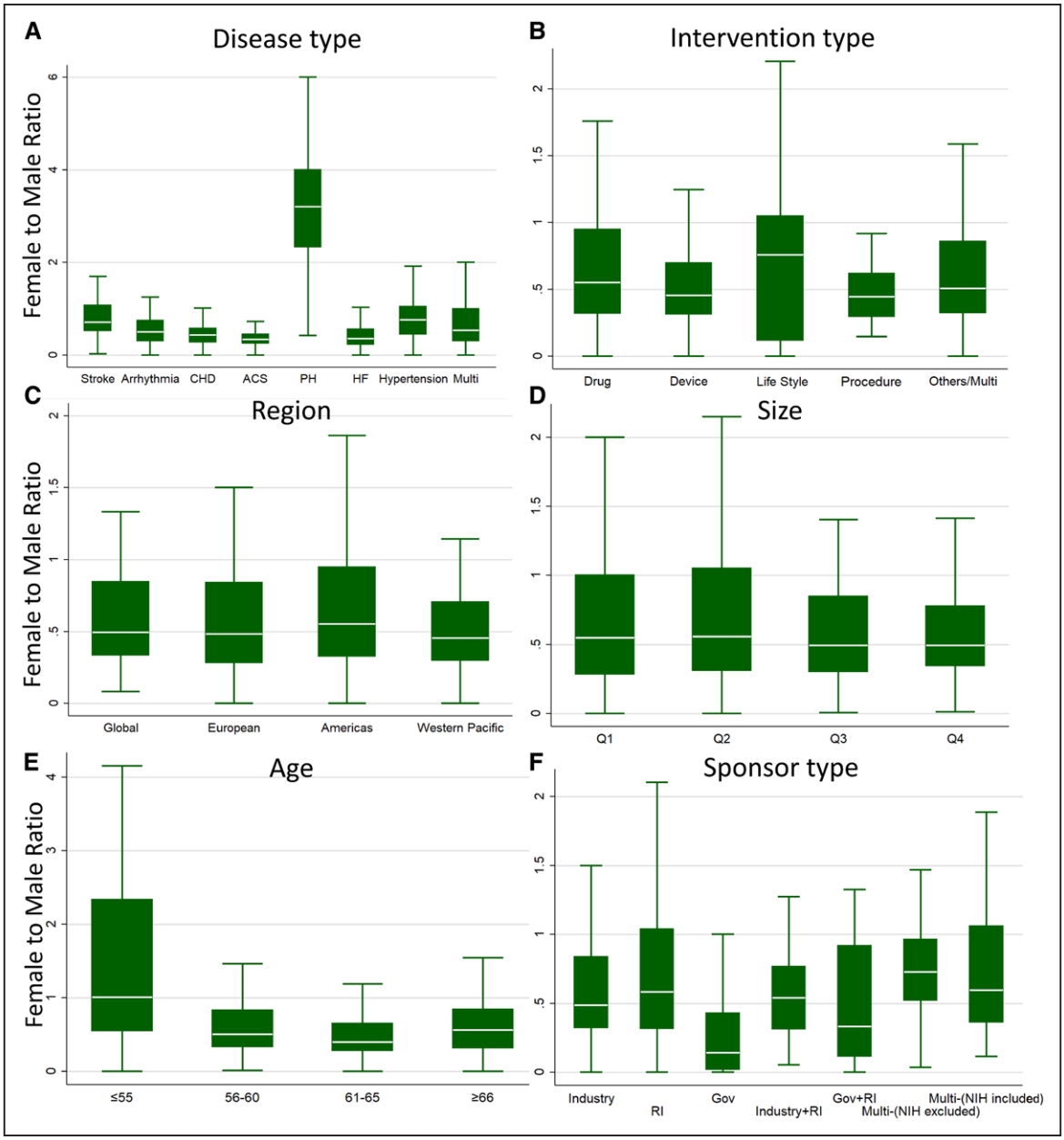

Figure 2. Median female-to-male ratio in 740 trials.
These trials were stratified by (A) disease type; (B) intervention type; (C) region; (D) trial size; (E) age; or (F) sponsor type. Quartile ranges for trial size: Q1, ≤47; Q2, 48 to 124; Q3, 125 to 398; and Q4, ≥399. *Significantly (P<0.01) different from all other categories in the pairwise comparisons. ACS indicates acute coronary syndrome; CHD, coronary heart disease; Gov, government; HF, heart failure; Multi, the trials with two or more disease types, intervention types or sponsor types; PH, pulmonary hypertension; Q, quartile, and RI, research institute. #To show greater details in each panel, we did not include any value larger than the 1.5 times of the interquartile range in this figure.

To the best of our knowledge, the current study was the first to include results from multiple factors such as sponsor type and region. Multisponsor trials were more likely to recruit women, especially those involving the National Institutes of Health and trials originating in the Americas, perhaps illustrating the success of the National Institutes of Health's Office of Research on Women's Health's initiatives in drawing attention to the issue of appropriate representation of women in trials. This finding suggests that such an effort may be warranted in low-representation regions. Trials sponsored by government (not including the National Institutes of Health) showed a relatively lower female participation, which was caused by a large proportion of such trials being sponsored by Veteran Affairs Office of Research and Development (28 out of 30).

The lower participation rate of women in cardiovascular clinical trials logically begs the question, "Why don't women participate in trials at rates similar to men?" Hypothetically, multiple opportunities exist for a patient to fall out of the enrollment pathway, and

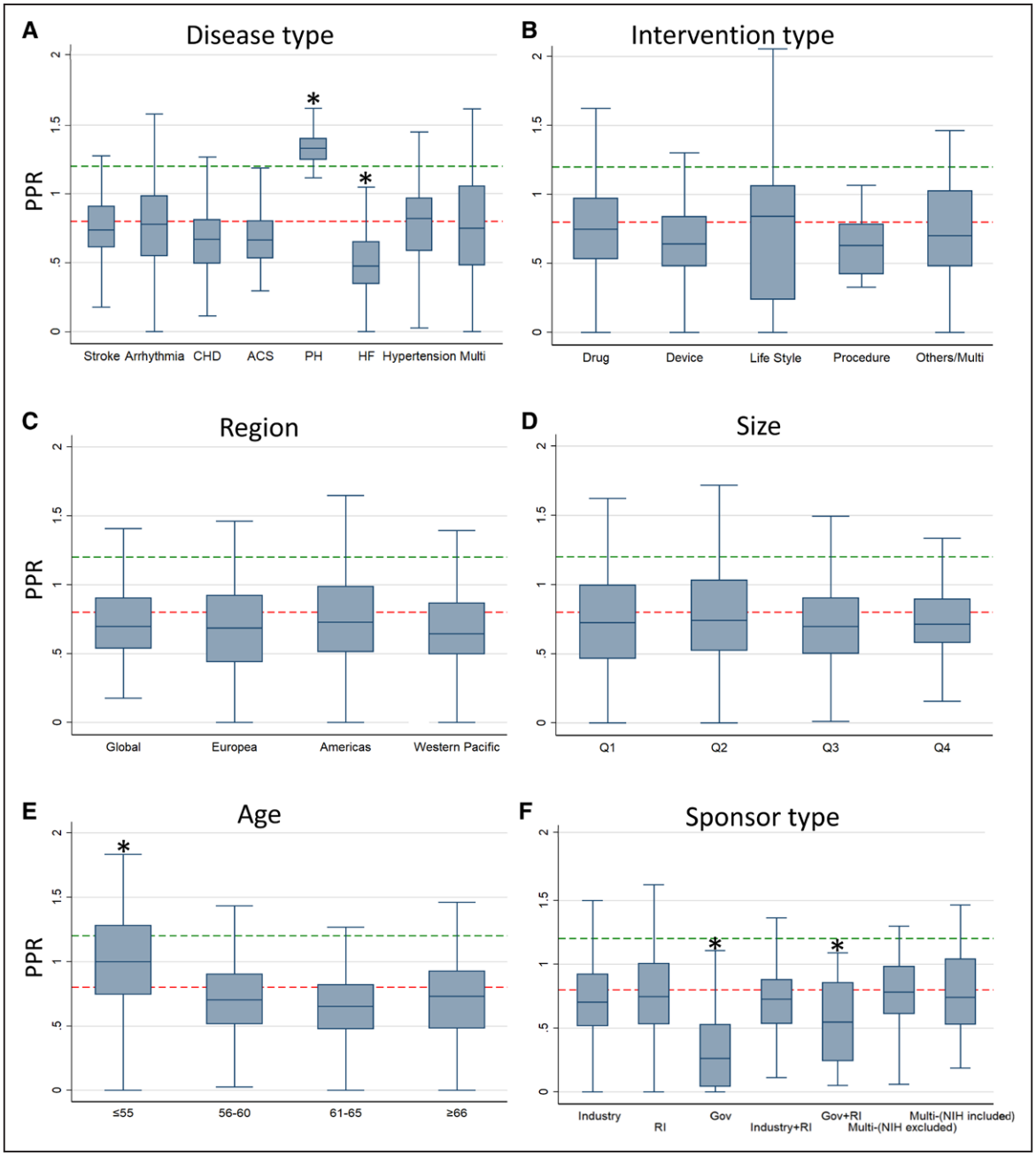

Figure 3. Median participation prevalence ratio (PPR) in 740 trials.
Trials are stratified by (A) disease type; (B) intervention type; (C) region; (D) trial size; (E) age; or (F) sponsor type. Quartile ranges for trial size: Q1, ≤47; Q2, 48 to 124; Q3, 125 to 398; and Q4, ≥399. ACS indicates acute coronary syndrome; CHD, coronary heart disease; Gov, government; HF, heart failure; Multi, the trials with two or more disease types, intervention types or sponsor types; PH, pulmonary hypertension; Q, quartile, and RI, research institute. *Significantly (P<0.01) different from all other categories in the pairwise comparisons #To show greater details in each panel, we did not include any value larger than the 1.5 times of the interquartile range in this figure.

several of these opportunities can likely be influenced by both patient-related and trial site–related factors.

First, a patient must be made aware of the opportunity to participate, which requires that either the patients identify the opportunity via consumer channels or that study sites approach adequate numbers of female patients for participation. Women must also have access to centers participating in trials in order to enroll, which can require both that referrals are appropriately made and that patients can support participation logistics such as transportation and child care. Last, women must understand and be comfortable with the clinical trial process, with the process of informed consent, and with the overall clinical trial experience. Cultural background or biases, investigator communication approach, and written trial materials can all likely influence patient comfort with enrolling.

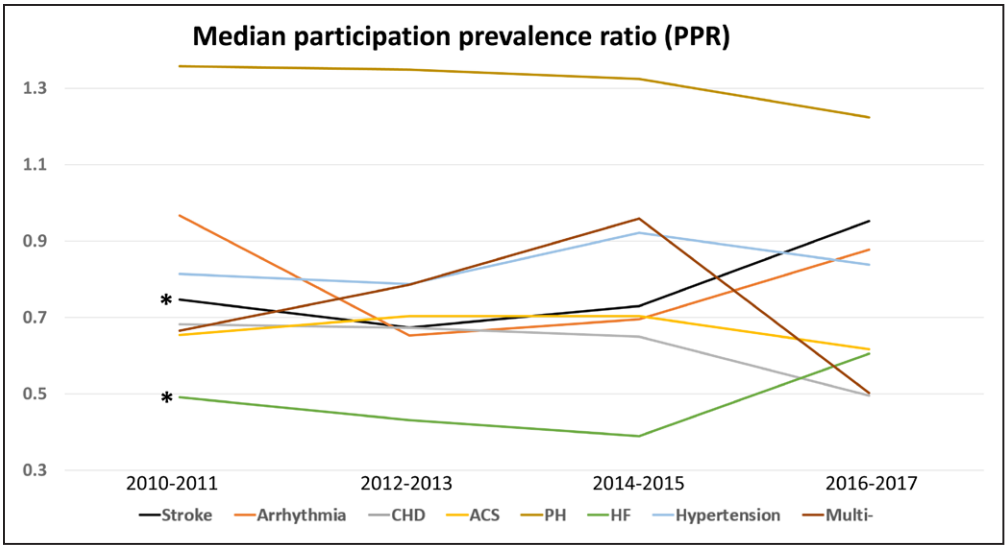

Figure 4. Median participation prevalence ratio (PPR) between 2010 to 2017 by 2-year increment in 740 cardiovascular trials by disease type. ACS indicates acute coronary syndrome; CHD, coronary heart disease; HF, heart failure; Multi, multiple outcomes; Multi, the trials with 2 or more disease type; and PH, pulmonary hypertension. *Significant (P<0.05) trend from 2013 to 2017.

Ding et al conducted a randomized study of patient willingness to participate in cardiovascular prevention trials and found that men had 15% greater willingness to participate than women.[9] Among the reasons for this gap was the fact that women perceived a greater risk of harm from trial participation. Women had also been shown to take fewer risks than men under stress, and large health-based decisions could certainly be a source of stress.[10] Randomized clinical trials present an added element of risk and uncertainty, and women have been shown to be more reluctant than men to consider participation.[11]

Women also make decisions differently than men, which means that the same enrollment process may yield different enrollment rates by sex. Women may take more time to make a decision, and they may require more sources of input.[12] Women are more likely to have a decision influenced by friends, family, researchers, or other external influences. They are also more likely to have their decision influenced by altruistic motivations.[13]

Increasing the number of women who choose to enroll in clinical trials requires novel approaches to the recruitment and enrollment process. In the WIN-Her Initiative (Women Opt-In for Heart Research), an ongoing research effort by Boston Scientific Corporation, quantitative surveys and qualitative interviews were performed in women with cardiovascular disease to explore previous experiences and attitudes surrounding participation in cardiovascular research trials. This research identified that potential barriers to female trial participation included the minimal understanding of trial process and logistics, limited clinical trial information from physicians, and misperceptions around the risks and benefits of participation. Results suggested that sex-specific clinical trial educational materials may enhance women's participation in clinical trials—an approach currently being evaluated in the ASAP-TOO left atrial appendage closure trial (Assessment of the WATCHMAN Device in Patients Unsuitable for Oral Anticoagulation).

Novel trial design solutions may be needed to ensure that sex-specific results may be meaningfully obtained. Such solutions may include prespecification of sex as a subgroup of interest in formal interaction testing, and adequately powering the trial to ensure that a large enough group of each sex is enrolled for sex-stratified assessment. These approaches were exemplified in the recent PARAGON-HF trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker Global Outcomes in Heart Failure and Preserved Left Ventricular Ejection Fraction),[14] which recruited more women (n=2479; 52%) than most previous heart failure trials, and reported a strong sex-by-treatment interaction, where greater benefit was seen in women than in men with heart failure and preserved ejection, given sacubitril/valsartan compared with valsartan (interaction P<0.006). Future trials may consider building sex-specific analyses into the trial design by using sex-specific trial enrollment materials (as previously described in the WIN-Her Initiative), incorporating such analyses into the statistical analysis plan and/or interim data analyses by Data Safety Monitoring Boards, and carefully monitoring sex distribution during recruitment with steps taken to cap recruitment of men and/or encourage enrollment specifically of women during the course of the trial.

Our study cannot provide insights into the reasons for low female participation previously discussed;

however, it is the first to comprehensively review a data source not limited to journal publications, including both drug, device, and other trials whether large or small, and to simultaneously evaluate the impacts of funding source and geographic region. Our key findings on female participation by age, intervention, disease, sponsor type, and region identified main areas for improvement and suggested potential measures to do so. Our study also has several limitations. First, we only used data from ClinicalTrials.gov from 2010 to 2017. Although it is the largest platform for clinical trial registration, future studies will benefit from including other data sources for longer time periods. Second, our search only found 3 trials conducted in Southeastern Asia and 3 trials in the Eastern Mediterranean Region. This paucity may reflect the reality of a small number of trials in these regions or bias from our data source. Last, we could not find region-specific estimates of disease prevalence for all diseases, and thus applied global estimates when calculating PPRs. This practice may attenuate variations in female participation across different regions.

In summary, we systematically screened cardiovascular trials registered on ClinicalTrials.gov from 2010 to 2017 and identified 740 trials for analyses of women representation. We found that the overall representation was low (38%). After adjustment for disease prevalence, heart failure, coronary heart disease, and acute coronary syndrome trials still had a PPR<0.8. Device, procedure, and multi-interventional trials had lower representation from women than drug or lifestyle trials. Women were relatively better represented in trials conducted in the Americas or multiple regions than those in Europe or the Western Pacific. Government-sponsored trials (excluding the National Institutes of Health) had particularly low representation. The increase in female participation for stroke and heart failure trials in recent years is worth further investigation to generate useful insights. More important, effective strategies to improve women representation in cardiovascular clinical trials are needed. These strategies should consider multiple factors included in this study as well as practical and innovative psychological, cultural, and gender-specific measurements.

ARTICLE INFORMATION

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