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Representation of Women in Randomized Clinical Trials of Cardiovascular Disease Prevention

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Background—The 2007 American Heart Association guidelines for cardiovascular disease prevention in women drew heavily on results from randomized clinical trials; however, representation of women in trials of cardiovascular disease prevention has not been systematically assessed.

Methods and Results—We abstracted 156 randomized clinical trials cited by the 2007 women's prevention guidelines to determine female representation over time and by clinical indication, prevention type, location of trial conduct, and funding source. Both women and men were represented in 135 of 156 (86.5%) trials; 20 trials enrolled only men; 1 enrolled only women. Among all trials, the proportion of women increased significantly over time, from 9% in 1970 to 41% in 2006. Considering only trials that enrolled both women and men, female enrollment was 18% in 1970 and increased to 34% in 2006. Female representation was higher in international versus United States–only trials (32.7% versus 26.7%) and primary versus secondary prevention trials (42.6% versus 26.6%). Female enrollment was comparable in government/foundation-funded versus industry-funded trials (31.9% versus 31.5%). Representation of women was highest among trials in hypertension (44%), diabetes (40%), and stroke (38%) and lowest for heart failure (29%), coronary artery disease (25%), and hyperlipidemia (28%). By contrast, women accounted for 53% of all individuals with hypertension, 50% with diabetes, 51% with heart failure, 49% with hyperlipidemia, and 46% with coronary artery disease. Sex-specific results were discussed in only 31% of primary trial publications.

Conclusions—Enrollment of women in randomized clinical trials has increased over time but remains low relative to their overall representation in disease populations. Efforts are needed to reach a level of representation that is adequate to ensure evidence-based sex-specific recommendations. (*Circ Cardiovasc Qual Outcomes*. 2010;3:00-00.)

Key Words: cardiovascular disease ■ randomized clinical trials ■ women

Cardiovascular disease (CVD) is the primary cause of death among women.¹ With increasing recognition of the importance of heart disease in women, interest in and emphasis on research concerning women and heart disease have grown substantially.^{2,3} Despite this, there remains a concerning gap in the knowledge, understanding, and general awareness of CVD in women. Evidence-based medicine for the prevention and treatment of CVD is guided largely by the results of randomized clinical trials (RCTs). The generalizability of clinical trial results to both women and men depends on the conduct of clinical trials that have sufficient representation of both sexes. Previous analyses have highlighted underrepresentation of women in cardiovascular clinical trials.^{4–6} The demonstration by many studies of a sex-specific response to certain cardiovascular therapies underscores the importance of adequate representation of women in clinical trials populations.^{4,7–9}

The American Heart Association (AHA) 2007 update of the guidelines for CVD prevention in women drew heavily on the results of RCTs.¹⁰ However, representation of women in the clinical trials on which these guidelines were based has

not been systematically assessed. Therefore, we performed a systematic review of all RCTs used to support the AHA guidelines recommendations for CVD prevention in women to determine the overall representation of women in these trials and temporal trends in inclusion of women in CVD prevention trials.

Methods

Source of Data and Study Selection

Three of the authors (C.M., T.Y.W., J.S.B.) independently reviewed all RCTs listed in both the evidence tables used to build the updated AHA guidelines for CVD prevention in women and the evidence tables in the document.¹⁰ Information available in the evidence tables included the name of the trial, year of publication, mean age for the entire patient population, total number of patients enrolled, number of women, therapeutic class, clinical indication, and prevention type (primary or secondary). The reviewers searched for the original articles and abstracted additional information including source of funding, locations in which the trials were conducted, and presence of specific results on women (sex-specific reporting) in the trial. Detailed standardized definitions for data collection were approved by the 3 reviewers, and an Access database (Microsoft Corp) was developed for collection of this information. Secondary analyses of RCTs

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WHAT IS KNOWN

- Women are underrepresented in cardiovascular clinical trials.

WHAT THE STUDY ADDS

- Recent guidelines for cardiovascular disease prevention in women are based on studies in which women represented only one third of the population.
- Enrollment of women in randomized clinical trials has increased during the past 4 decades.
- The proportion of women in randomized clinical trials remains much lower than the proportion of women in the diseased population.
- Specific reasons of low enrollment are hard to define.
- Producing and assessing adequate evidence in women requires specific requirements in trial design such as power calculation adjustment by sex, sex-based stratification, and reporting sex-specific results in publications.

(n=32) were excluded from the current analysis to prevent duplicate counting of the participants. Of the initial 188 citations reviewed in the AHA guidelines, our study included 156 unique RCTs.

Categorization of RCTs

RCTs were categorized by year of publication, therapeutic class of intervention (aspirin for prevention and antiplatelet therapy, aldosterone, β -blocker, angiotensin-converting enzyme inhibitors and angiotensin receptor blocker therapy, lipid-lowering therapy [statins and nonstatins], diabetes mellitus medication, and antioxidant therapy/vitamin supplementation), clinical indication (coronary artery disease [CAD], heart failure, hyperlipidemia, hypertension, diabetes mellitus, stroke), prevention type (primary, secondary, or both), trial location (United States only, international, or both), and funding source (industry or government/foundation).

Data Analysis

General characteristics of RCTs enrolling both women and men were reported in 6 areas of interest (Table 1). Each factor was reported by the number of trials reporting the information and the total number of subjects from whom the information was collected, highlighting the total number of women and then the estimated percentage of women for each characteristic. The factors of interest were the timing of each trial (based on publication year), therapeutic class, clinical indication, prevention type, trial location, and funding source. Unadjusted generalized linear modeling was used to report the estimated percentage of women expected in each category. Overall differences in subgroups are also reported using generalized linear modeling. The above categories were chosen upfront, and all subgroup comparisons were preplanned. Because of the very large samples sizes that would result in even minor differences attaining conventional statistical significance, we do not show probability values but rather present data for these comparisons descriptively for interpretation in the context of clinical relevance.

The relationship between the number of women enrolled in the RCTs (grouped into 2 categories—CAD trials and all other RCTs) and the mean age of the patient population was explored. For plotting, the number of women enrolled was reported in quintiles on the x axis and the mean age (with standard deviation) of each quintile

Table 1. General Characteristics of RCTs

	No. of Trials	Overall Population	No. of Women	Women, %*
Publication year				
1970–1974	2	1214	221	18.2
1975–1979	3	6998	1857	26.5
1980–1984	9	16 818	2604	15.5
1985–1989	8	58 836	17 442	29.6
1990–1994	16	27 380	9722	35.5
1995–1999	34	190 958	57 907	30.3
2000–2006	63	329 940	155 772	34.4
Therapeutic class				
Other	9	47 350	23 106	23.2
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	30	234 028	72 084	30.8
Aspirin for prevention	3	25 320	12 391	48.9
Aldosterone antagonist	2	8295	2364	28.5
Antiplatelet for coronary artery disease (secondary prevention)	21	97 893	26 064	27.8
β -Blockers	25	84 930	30 256	35.6
Diabetes mellitus medication	10	9645	3755	38.9
Lipid-lowering agent, nonstatins	9	4047	1518	37.5
Lipid-lowering agent, statins	18	73 693	19 837	26.9
Antioxidants/vitamins	14	51 041	11 832	23.2
Clinical indication				
Other	1	4495	2583	57.7
CAD	74	311 775	76 868	24.7
Heart failure	14	46 280	13 205	28.5
Diabetes mellitus	7	10 234	4066	39.7
Hyperlipidemia	13	50 599	14 104	27.9
Hypertension	25	205 081	91 002	44.4
Stroke	1	3680	1379	37.5
Prevention type				
Primary	18	87 886	37 465	42.6
Secondary	98	391 495	104 237	26.6
Both	19	152 763	61 505	40.3
Location				
United States only	18	45 148	12 066	26.7
International	91	293 441	96 094	32.7
Both	26	293 555	95 047	32.4
Funding source				
Government/foundation	47	169 309	54 016	31.9
Industry	64	423 047	133 227	31.5
Not reported	24	39 788	15 964	40.1

RCTs enrolled both women and men (n=135).

*Unadjusted estimated percentages.

was reported on the y axis. The standard deviation of the mean age in each individual trial was not recorded; hence the standard deviation reported here reflects the deviation from the mean of the individual mean ages reported for each trial. To take into account that trials had different sample sizes, the means were weighted by the

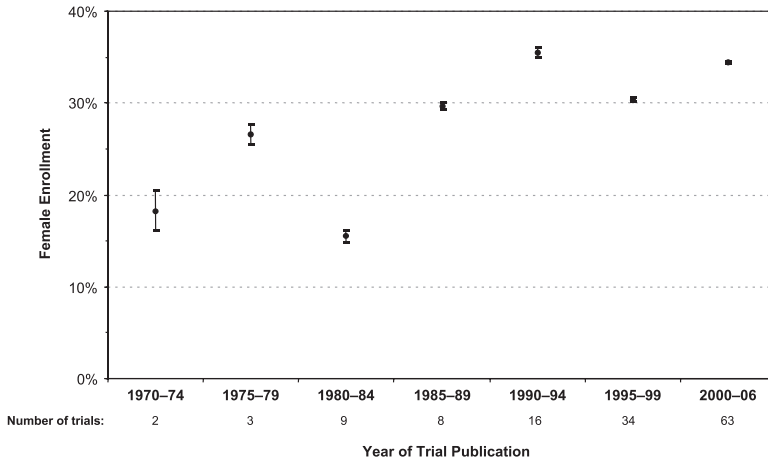


Figure 1. Unadjusted rates of female enrollment in randomized clinical trials by year of publication of trial results. Trials that enrolled only men or only women are excluded.

total number of subjects enrolled in the individual trials over the total number of individuals reported on in each quintile.

Trends over time were displayed overall and by prevention type, trial location, funding source, and sex-specific reporting.

The independent associations of age, year of publication, therapeutic class, clinical indication, prevention type, trial location, and funding source with proportion of women enrolled in RCTs were estimated using multivariable generalized linear modeling. To do this, the SAS GENMOD procedure was used with sex as the outcome of interest, a logit link function assumed, and study included as a fixed effect. The candidate variables chosen were based on previous studies and clinical input.

Finally, the proportions of women enrolled in CAD, heart failure, hypertension, hyperlipidemia, and diabetes trials were compared with the proportions of women represented in the general populations with each of these diseases (data obtained from the AHA Heart Disease and Stroke Statistics, 2008).¹ The proportion of women among those who died from each of these diseases was also provided for context.¹

All statistical tests were 2-sided and considered significant at $P < 0.05$. No adjustments were made for multiple comparisons. Data analysis was performed using SAS version 8.2 (SAS Institute, Cary, NC).

Results

Clinical Trials

Overall, 156 trials were analyzed. Both women and men were represented in 135 of 156 (86.5%) trials; 20 enrolled only men and 1 enrolled only women. Of the 135 trials enrolling both men and women, the majority were performed in patients with CAD ($n=74$), followed by hypertension ($n=25$) and heart failure ($n=14$). Secondary prevention trials ($n=98$) were more frequent than primary prevention trials ($n=18$), and the distribution by location of enrollment was as follows: United States only ($n=18$), international ($n=91$), and both US and international enrollment ($n=26$) (Table 1).

Representation of Women in RCTs

Among the overall 801 198 patients enrolled in these 156 trials, 245 525 (30.6%) were women. Representation of women overall increased from 9% in 1970 to 41% in 2006. After excluding single-sex trials ($n=21$; 20 men-only, 1 women-only), the statistical significance of this finding remained (18% in 1970 to 34.4% in 2006) (Figure 1).

Considering RCTs enrolling both sexes, trials performed internationally enrolled more women than those performed in

the United States only (32.7% versus 26.7%), and primary prevention trials enrolled more women than secondary prevention trials (42.6% versus 26.6%). The percentage of women enrolled in government/foundation-funded trials compared with industry-funded trials was comparable (31.9% versus 31.5%). A significant trend for increasing enrollment of women was observed within each category except for trials conducted in the United States only (Figure 2, A through C).

Enrollment of women differed by therapeutic class. Rates of female enrollment were highest in trials of aspirin (49%), diabetes mellitus medications (39%), or lipid-lowering agents/nonstatins (38%) and lowest for antiplatelet in secondary prevention (28%), statins (27%), and vitamins/antioxidants (23%) (Table 1). Enrollment of women also varied by clinical indication, with higher enrollment in hypertension (44%), diabetes (40%), and stroke (38%) trials and lower enrollment in trials of heart failure (29%), CAD (25%), and hyperlipidemia (28%) (Figure 3). The number of women enrolled in RCTs differed across trial mean age categories. There was a skew toward greater mean age in the quintiles of higher proportions of women enrolled (4th and 5th quintiles), but there was no such pattern observed for non-CAD indication trials (Figure 4).

In multivariable analysis including prevention type (primary, secondary, or both), therapeutic class (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aspirin prevention, aldosterone, antiplatelet agents, β -blockers, diabetes mellitus medication, lipid-lowering agents [statins and nonstatins], antioxidants, and vitamins), clinical indication (CAD, heart failure, diabetes, hyperlipidemia, hypertension, or stroke), type of funding (government/foundation, industry, or not recorded), location of enrollment (US, international, or both), age, and year of the trial population, all variables were independently associated with the proportion of women enrolled in the trials (Table 2).

Inclusion of Women in RCTs Relative to Representation in the Disease Population

Figure 5 displays the representation of women within the trials examined in this study compared with their representation in the general population within major disease groupings (CAD, heart failure, diabetes, hyperlipidemia, and

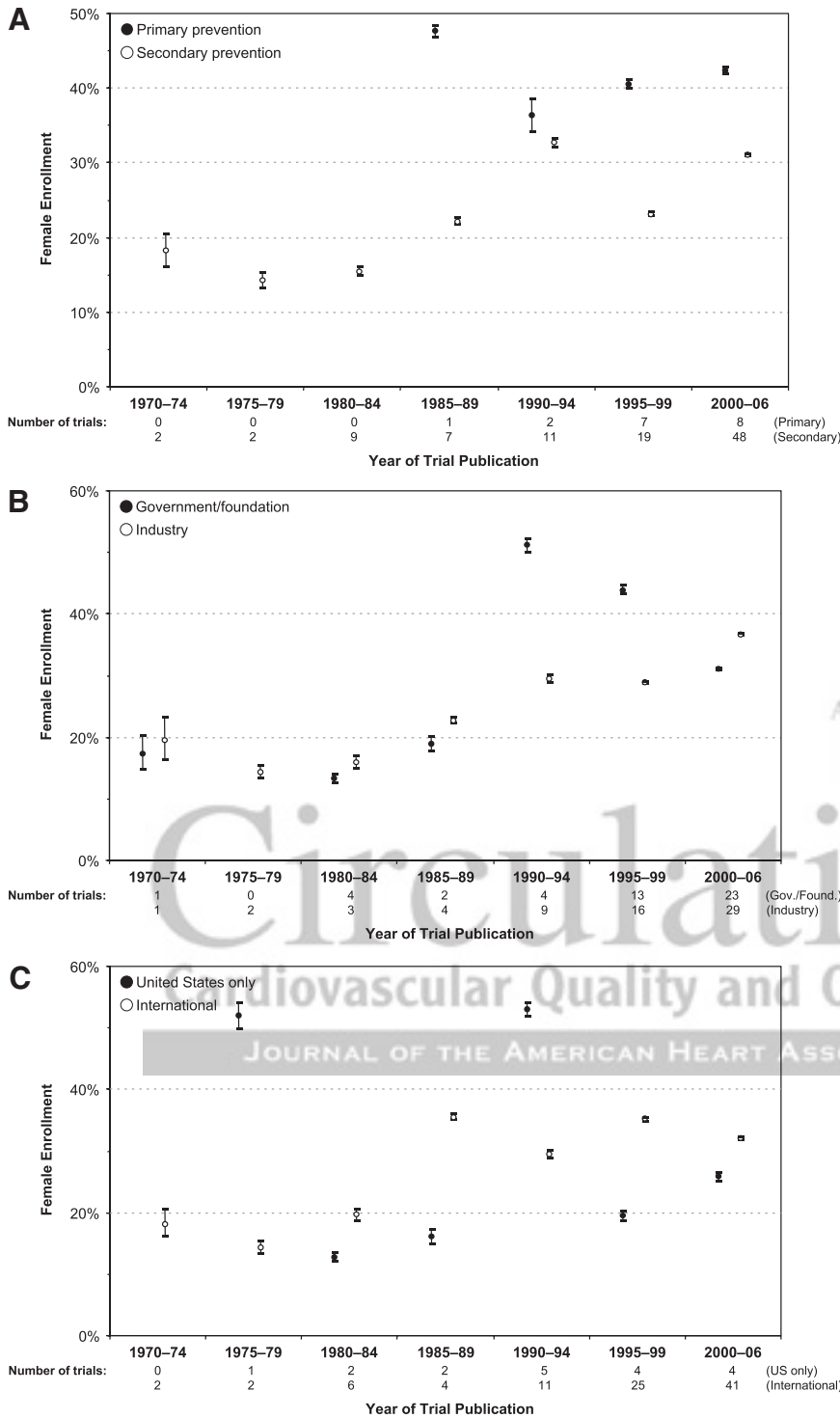


Figure 2. Unadjusted rates of female enrollment by publication year of women in primary and secondary prevention trials (A); in government/foundation-funded and industry-funded trials (B); and in United States-only and international trials (C).

hypertension). In addition, the proportions of all deaths accounted for by women within each disease grouping are shown. Women were enrolled in trials testing therapies for specific disease indications in lower proportions than their representation in the populations suffering from each major disease. Similarly, in contrast to their representation in clinical trials, the proportion of deaths within each disease state that were accounted for by women (50% to 60%) was substantially higher than their clinical trial representation.

Sex-Specific Results Reporting

Sex-specific reporting of results in the main trial publications was available in approximately one third of the studies. There was no change in sex-specific reporting of results over time (Figure 6).

Discussion

Overall, we found that women represented only 30% of patients enrolled in the clinical trials used to support the 2007

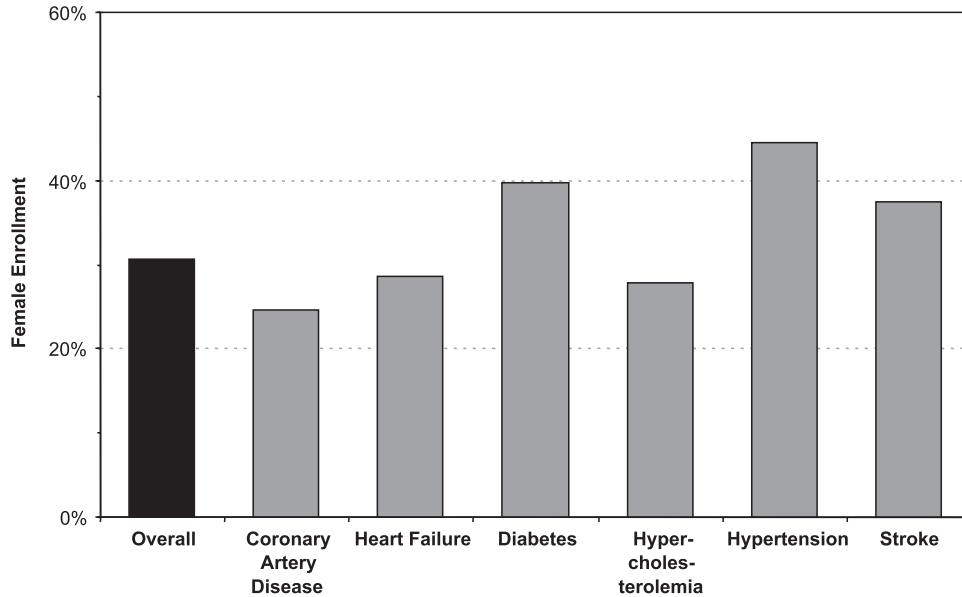


Figure 3. Percentage of women enrolled in randomized clinical trials overall and by clinical indication.

AHA guidelines for CVD prevention in women. Enrollment of women varied substantially depending on clinical indication, prevention type, and geographic location of the conduct of the study and was significantly lower than their representation in the general populations with diseases for which specific therapies would be targeted. Further, only about one third of the trials specifically reported results for women and men by subgroup.

Overall Representation of Women in Randomized Clinical Studies

After increasing awareness of the importance of appropriate representation of women in clinical trials, in 1993, the National Institutes of Health Revitalization Act legally required inclusion of women and men in clinical trials consistent with the known sex-related prevalence of the disease under investigation to provide appropriate data on the efficacy of treatments for both women and men.^{11,12} Despite the release of these guidelines, the increase in the proportion of women enrolled in National Heart, Lung, and Blood Institute

studies several years later was much less than expected, and the positive trend observed was driven primarily by 2 large, single-sex studies of women (the Women’s Health Initiative and Women’s Health Study).⁶ In our analysis, we show that the current guidelines for CVD prevention in women were formulated based on trial data in which female representation was only 30% overall. Whether this is sufficient support for guidelines in women is unknown.

Female representation was higher in primary prevention trials and in studies conducted internationally only but was similar in trials funded by industry and government/foundation sources. Although European authorities have not yet released guidance on sex-specific trial representation, we found a higher proportion of women in international trials than in US-only trials.¹³ These observations suggest that female representation in clinical trials does not necessarily correlate with the existence of specific legislation or policy on women’s representation.

Because it is unclear whether single factors drive their inclusion (we showed significant relationships with all factors

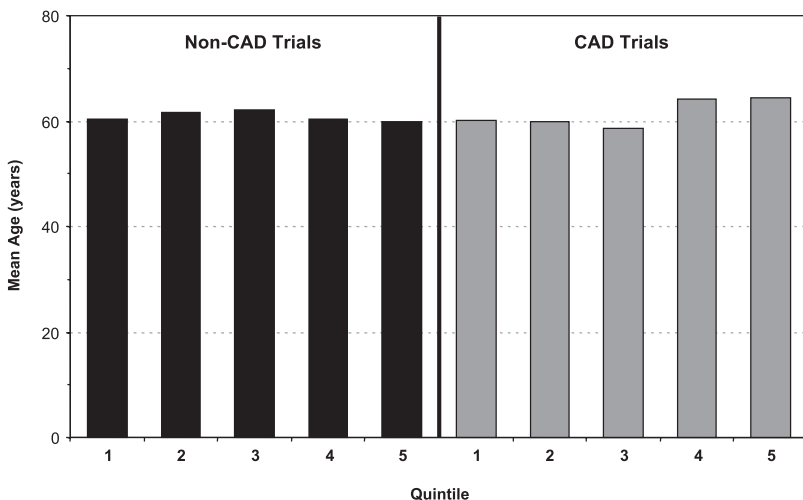


Figure 4. Number of women enrolled by mean age of patient population in randomized clinical trials grouped into 2 categories: CAD trials and all other RCTs (non-CAD trials). The quintiles of women enrolled in RCTs are as follows: 20th percentile: RCT enrolled <108 women; 20th to 40th percentile: RCT enrolled 108 to 284 women; 40th to 60th percentile: RCT enrolled 284 to 590.5 women; 60th to 80th percentile: RCT enrolled 590.5 to 2456 women; 80th to 100th percentile: RCT enrolled >2456 women.

Table 2. Factors Associated With Enrollment of Women in RCTs

Predicting Factors	Estimate	SE	df	χ^2	P Value
Age			2	45 402.65	<0.0001
Linear term	-0.2433	0.0055			
Square term	0.0024	0			
Publication year	0.0091	0.0008	1	139.56	<0.0001
Therapeutic class			9	2756.53	<0.0001
ACE/ARB	0.0537	0.0154		12.13	0.0005
ASA prevention	0.3412	0.0237		207.47	<0.0001
Aldosterone antagonist	0.0822	0.0320		6.59	0.0103
Antiplatelet for CAD	0.2192	0.0161		184.77	<0.0001
β -Blockers	0.3423	0.0197		302.32	<0.0001
DM medication	-0.2047	0.0740		7.65	0.0057
LL nonstatins	0.7099	0.0424		280.73	<0.0001
LL statins	-0.4171	0.0198		442.09	<0.0001
Other	0.3374	0.0198		289.44	<0.0001
Antioxidants/vitamins	0	0.0000		.	.
Clinical indication			5	3429.82	<0.0001
CAD	-0.6095	0.0368		274.58	<0.0001
CHF	-0.6078	0.0396		235.34	<0.0001
Diabetes mellitus	0.1778	0.0800		4.94	0.0263
Hyperlipidemia	0.0062	0.0415		0.02	0.8804
Hypertension	-0.162	0.0389		17.34	<0.0001
Other	-5.7591	0.1789		1036.12	<0.0001
Stroke	0	0.0000		.	.
Prevention type			2	1135.97	<0.0001
Both	0.2185	0.0093		554.34	<0.0001
Primary	0.4042	0.0129		982.96	<0.0001
Secondary	0	0.0000		.	.
Location			2	204.64	<0.0001
Both	0.219	0.0154		202.61	<0.0001
International	0.1791	0.0145		153.4	<0.0001
United States	0	0.0000		.	.
Funding source			2	1071.83	<0.0001
Government/foundation	-0.4407	0.0154		823.66	<0.0001
Industry	-0.2329	0.0140		278.29	<0.0001
Not recorded	0	0.0000		.	.

ACE indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARB, angiotensin receptor blocker; ASA, aspirin; CHF, congestive heart failure; DM, diabetes mellitus; and LL, lipid-lowering.

examined), specific actions to address underrepresentation of women will be difficult to implement until further study has been completed. We showed that enrollment of women differed based on clinical indication; in particular, the proportion of women was higher in hypertension and diabetes trials compared with heart failure and CAD trials. The fact that women were more likely to be included in primary prevention than in secondary prevention trials could suggest a number of possible explanations: that higher-risk women could be less willing to participate in trials, that physicians may have biases in screening them for inclusion, or that there are other social or medical reasons that make their participa-

tion challenging. Indeed, previous studies showed that women perceiving greater risk of harm or being less aware of cardiovascular risk factors were less willing to participate in clinical trials.^{14–16} In one study, among hospitalized patients approached for participation in cardiovascular trials, there was no difference in patient refusal rate by sex, but the type of trial was significantly associated with enrollment, with higher-acuity trials having higher rates of refusal.¹⁷

Other possible explanations for the lower proportion of women enrolled in clinical trials could include the presence of specific exclusion criteria such as older age and child-bearing potential. In addition, CVD affects women later in life, and so, particularly in earlier trials with age cutoffs that excluded the elderly, women may have been more likely to be excluded than men.^{4,18} The above speculation is also supported by our results suggesting that when the mean age of the CAD trial population was above 60 years, the proportion of women enrolled was higher, but no such pattern was observed in trials of non-CAD diseases in which onset is earlier.

Inclusion of Women Relative to Representation in Affected Patient Populations

Studies investigating female enrollment have noted that women as well as the elderly remain largely underrepresented both in US and international cardiovascular clinical trials relative to their representation in disease populations.^{4,18} Similarly, a recent analysis demonstrated that cardiovascular studies used by the Centers for Medicaid and Medicare Services for coverage determination did not include women and the elderly in proportions consistent with their prevalence in the Medicare population.¹⁹ Our data support the finding that the proportion of women enrolled in RCTs continues to inadequately reflect their representation in the disease populations being treated. We also show that women account for at least half of the deaths in the affected patient populations studied—a proportion that is strikingly higher than their representation in the trials supporting the guidelines—thereby underscoring the importance of having adequate representation of women in clinical trials to solidify the evidence base supporting practice guidelines. Without this evidence, we cannot fully understand and address the implications of potential sex-specific responses to cardiovascular therapies and improve cardiovascular outcomes in women.

Time Trends in Reporting Sex-Specific Results

In this analysis, we also showed that differences in treatment effect by sex were not commonly presented in the literature and that this practice has not changed over time despite federal legislation^{11,12} and national calls for such analyses.²⁰ The Food and Drug Administration recently embarked on a bioinformatics modernization effort that will help to track female participation in clinical trials and assess the safety and effectiveness of new drugs to detect sex differences, if any.²¹ Notably, 13% of the studies on which the CVD prevention guidelines for women were based had all-male study populations. Although there are no compelling reasons to believe that the treatments studied in these trials would necessarily behave differently in women than in men, sex-specific

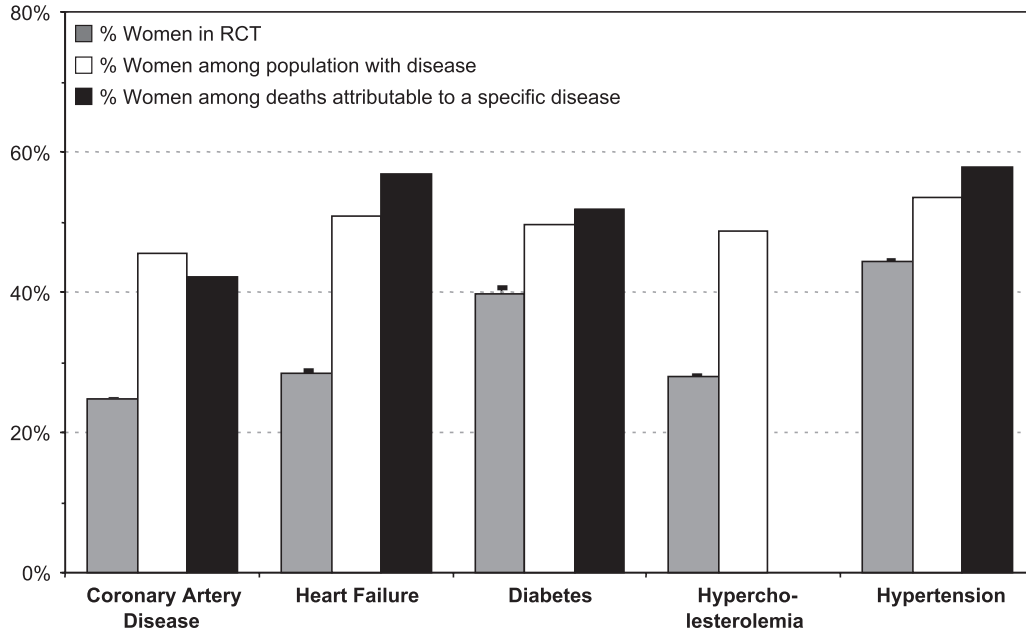


Figure 5. Proportion of women in RCTs compared with the proportion of women among the population with a given disease and proportion of women among deaths attributable to the disease. The upper 95th percentile of the confidence interval for the proportion of women in RCTs is shown by the whisker. Hyperlipidemia is defined as low-density lipoprotein cholesterol >130 mg/dL. Proportion of women among deaths not reported in Heart and Stroke Report statistics.

differences in the pathophysiology of CVD, in baseline characteristics, and in response to treatment might affect direct translation of these results from men to women.^{2,3} One important example is the consideration of medication dosing according to body weight and renal function and use in accordance with underlying risk profile that may alter the risk-benefit ratio of a given therapy.^{4,22} Methodological approaches to help support the generalizability of clinical trial results to both sexes—such as power calculation adjustment by sex or sex-based stratification—should also be considered in clinical trial design.

Limitations

Because our intent was to study individual RCTs and their inclusion of women as the strongest foundation of evidence supporting treatment, meta-analyses and cohort studies included in the evidence tables of the AHA prevention guidelines for women were excluded from this analysis. Overall, female representation in cohort studies supporting the guidelines for CVD prevention may be higher than in RCTs, but inherent biases arising from study design and biases in patient selection for treatment in these nonrandomized comparisons limit the strength of evidence that can be derived from them.



Figure 6. Trend over time of sex-specific reporting in RCTs.

Thus, we thought that a focus on inclusion of women in RCTs was of primary importance to understand and improve representation of women in the foundation of evidence supporting their treatment.

Conclusion

Overall, women represented 30% of patients enrolled in RCTs supporting the 2007 AHA guidelines for CVD prevention in women. The proportion of women in RCTs differed by clinical indication, prevention type, and location of trial conduct. Only one third of the trials specifically reported results for women. Although enrollment of women has increased over time, their inclusion in RCTs remains low relative to their representation in affected patient populations. Causes of low female enrollment are difficult to ascertain, thus undermining attempts to develop specific corrective actions. In addition to further study to discern the underpinnings of and obviate disparities in female representation in clinical trials, a plan for adequate representation of women and reporting of sex-specific results should be a key requirement in the design and publication of RCTs that will serve as part of the evidence base for treatment recommendations.

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References

- Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics: 2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;117:e25–e146.
- Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Mankad S, Sharaf BL, Rogers WJ, Wessel TR, Arant CB, Pohost GM, Lerman A, Quyyumi AA, Sopko G, WISE Investigators. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study, I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol*. 2006;47(3 Suppl):S4–S20.
- Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Pepine CJ, Mankad S, Sharaf BL, Rogers WJ, Pohost GM, Lerman A, Quyyumi AA, Sopko G, WISE Investigators. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study, II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol*. 2006;47(3 Suppl):S21–S29.
- Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA*. 2001;286:708–713.
- Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med*. 2002;162:1682–1688.
- Harris DJ, Douglas PS. Enrollment of women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute. *N Engl J Med*. 2000;343:475–480.
- Walsh JME, Pignone M. Drug treatment of hyperlipidemia in women. *JAMA*. 2004;291:2243–2252.
- Boersma E, Harrington RA, Moliterno DJ, White H, Théroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet*. 2002;359:189–198.
- Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA*. 2006;295:306–313.
- Mosca L, Banka CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, Ganiats TG, Gomes AS, Gornik HL, Gracia C, Gulati M, Haan CK, Judelson DR, Keenan N, Kelepouris E, Michos ED, Newby LK, Oparil S, Ouyang P, Oz MC, Petitti D, Pinn VW, Redberg RF, Scott R, Sherif K, Smith SC Jr, Sopko G, Steinhorn RH, Stone NJ, Taubert KA, Todd BA, Urbina E, Wenger NK. Expert Panel/Writing Group; American Heart Association; American Academy of Family Physicians; American College of Obstetricians and Gynecologists; American College of Cardiology Foundation; Society of Thoracic Surgeons; American Medical Women's Association; Centers for Disease Control and Prevention; Office of Research on Women's Health; Association of Black Cardiologists; American College of Physicians; World Heart Federation; National Heart, Lung, and Blood Institute; American College of Nurse Practitioners. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation*. 2007;115:1481–1501.
- National Institutes of Health. NIH guidelines on the inclusion of women and minorities as subjects in clinical research. *Fed Reg*. 1994;3:143.
- US Congress Publication L No 103-43, *National Institutes of Health Revitalization Act of 1993*. June 10, 1993.
- Ruiz Cantero MT, Pardo MA. European Medicines Agency policies for clinical trials leave women unprotected. *J Epidemiol Community Health*. 2006;60:911–913.
- Ding EL, Powe NR, Manson JE, Sherber NS, Braunstein JB. Sex differences in perceived risks, distrust, and willingness to participate in clinical trials: a randomized study of cardiovascular prevention trials. *Arch Intern Med*. 2007;167:905–912.
- Peterson ED, Biswas MS, Coombs L. Willingness to participate in cardiac trials. *Am J Geriatr Cardiol*. 2004;13:11–15.
- Biswas MS, Calhoun PS, Bosworth HB, Bastian LA. Are women worrying about heart disease? *Womens Health Issues*. 2002;12:204–211.
- Sen Biswas M, Newby LK, Bastian LA, Peterson ED, Sugarman J. Who refuses enrollment in cardiac clinical trials? *Clin Trials*. 2007;4:258–263.
- Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. *JAMA*. 1992;268:1417–1422.
- Dhruva SS, Redberg RF. Variations between clinical trial participants and Medicare beneficiaries in evidence used for Medicare national coverage decisions. *Arch Intern Med*. 2008;168:136–140.
- Wizemann TM, Pardue M-L, eds. *Exploring the Biological Contributions to Human Health: Does Sex Matter?* Washington, DC: The National Academies Press; 2001.
- Oliva A, Pinnow E, Levin R, Uhl K. Improving women's health through modernization of our bioinformatics infrastructure. *Clin Pharmacol Ther*. 2008;83:192–195.
- LaPointe NMA, Chen AY, Alexander KP, Roe MT, Pollack CV Jr, Lytle BL, Ohman ME, Gibler BW, Peterson ED. Enoxaparin dosing and associated risk of in-hospital bleeding and death in patients with non-ST-segment elevation acute coronary syndromes. *Arch Intern Med*. 2007;167:1539–1544.