

ENROLLMENT OF WOMEN IN CARDIOVASCULAR CLINICAL TRIALS FUNDED BY THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

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ABSTRACT

Background With the recognition that certain aspects of cardiovascular disease are specific to sex, the U.S. government has sought to ensure that federally funded clinical research yields adequate high-quality information about heart disease in women.

Methods We tabulated the numbers of men and women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute (NHLBI) between 1965 and 1998, recording both total numbers and the numbers for each type of cardiovascular disease. We analyzed the data according to the sex-specific prevalence of disease and assessed changes in enrollment over time. We performed a similar analysis after excluding all single-sex trials.

Results A total of 398,801 subjects (215,796 women and 183,005 men) were enrolled in NHLBI-funded studies of cardiovascular disease. The overall enrollment rate for women (54 percent) exceeded the prevalence of cardiovascular disease in women in the general population (49 percent) and increased over time ($P=0.002$). With single-sex trials excluded, the enrollment rate for women was 38 percent, which did not change significantly over time. In studies of coronary artery disease and hypertension the rates of enrollment of women were similar to or exceeded the prevalence of these disorders in women. The enrollment rate increased significantly over time in studies of coronary artery disease ($P<0.001$) but not in studies of hypertension or arrhythmia. Women were under-enrolled in studies of heart failure, and the rate of enrollment did not change significantly over time. When single-sex trials were excluded from the analysis of enrollment rates according to the prevalence of disease, the results were similar. There was no change in enrollment rates over time for any category of disease.

Conclusions Federal efforts to increase the representation of women in clinical trials have been moderately successful primarily because of the institution of a small number of large, single-sex trials involving coronary artery disease. There has been no change in the sex composition of cohorts in the majority of studies of cardiovascular disease. (N Engl J Med 2000; 343:475-80.)

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CARDIOVASCULAR disease is the most common cause of death in both men and women in the United States and is increasingly recognized as having sex-specific features. Clinical and epidemiologic studies have shown that men and women with cardiovascular disease differ with respect to disease processes, clinical presentations, and outcomes.¹⁻³ The recognition of sex-based differences in cardiovascular disease is a compelling reason for ensuring that the enrollment of women in cardiovascular clinical trials is proportional to the prevalence of cardiovascular disease among women in the general population.

In 1965, the National Heart Institute, as the National Heart, Lung, and Blood Institute (NHLBI) was then known, funded its first cardiovascular clinical trial, the Coronary Drug Project. Since then, the institute has funded a total of 126 cardiovascular clinical trials. The enrollment of women in clinical trials came under scrutiny in the mid-1980s, with the realization that less information about treatment was available for women with cardiovascular disease than for men with the disease.⁴ Various federal mandates and other initiatives have subsequently sought to increase the enrollment of women in clinical trials. We performed a study to determine how successful these efforts have been in increasing the enrollment of women in cardiovascular clinical trials conducted by the NHLBI. In addition, we determined whether the pattern of enrollment differed according to the type of cardiovascular disease under study.

METHODS**Clinical Trials**

On October, 1, 1999, in response to a request filed under the Freedom of Information Act, the NHLBI provided one of us with a list of all cardiovascular clinical trials conducted between 1965 and 1998. The information included a brief description of each trial, the date of its inception, and the numbers of enrolled men and women (including boys and girls in studies of congenital heart disease). Actual numbers were provided for studies conducted before 1995 and predicted numbers for more recent studies. Of the 126 clinical trials, 5 were initiated before the NHLBI required that re-

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searchers document the sex of subjects enrolled in clinical trials; since the sex of the 1291 subjects enrolled in these 5 trials was not recorded, they were excluded from the analysis. The 121 remaining trials were categorized according to the type of cardiovascular disease being investigated (heart failure, coronary artery disease, hypertension, congenital heart disease, arrhythmias, or other). The numbers of men and women were tabulated according to the category of disease and according to whether the study was a mixed or single-sex trial (there were 54,449 men in 8 trials that enrolled only men and 138,542 women in 14 trials that enrolled only women).

Sex-Specific Prevalence

Data on the sex-specific prevalence of cardiovascular disease in general and of coronary artery disease, hypertension, and heart failure were obtained from the American Heart Association (www.americanheart.org) and compared with the enrollment rates for men and women in the 121 clinical trials. Given the heterogeneity of arrhythmias, data on their sex-specific prevalence may be misleading. For this reason and because the data were not easily obtained, arrhythmias and congenital heart disease were not included in the comparison. For cardiovascular disease in general, coronary artery disease, and heart failure, data on patients between the ages of 45 and 74 years were used. The data were tabulated on the assumption that the size of the population was the same for each decade of age. The sources of the data were the third National Health and Nutrition Examination Survey, the National Center for Health Statistics, and the American Heart Association. For hypertension, data on patients between the ages of 20 and 74 years were used, and the source of the data was the National Center for Health Statistics.

Statistical Analysis

The percentage of women enrolled in each trial was calculated. A linear regression analysis was performed to assess the relation between the starting date of the trial and the proportion of women enrolled. The results are expressed as correlation coefficients. All reported P values are two-tailed.

RESULTS

A total of 398,801 subjects, including 215,796 women and 183,005 men, were enrolled in cardiovascular clinical trials funded by the NHLBI between 1965 and 1998 (Table 1). The overall enrollment rate for women (54 percent) exceeded the prevalence of cardiovascular disease in women in the general population between the ages of 45 and 74 years (49 per-

cent). In addition, the enrollment of women as a percentage of overall enrollment increased significantly over time ($r=0.57$, $P=0.002$) (Fig. 1). However, half the women were enrolled in two large, single-sex trials investigating the primary prevention of coronary artery disease: the Women's Health Study (an investigation of the protective effects of aspirin and vitamin E in 39,876 women, started in 1991) and the Women's Health Initiative (an investigation of hormone-replacement therapy and diet in 68,135 women, started in 1992). With all single-sex trials excluded from the analysis, the total number of enrolled subjects was 205,810, of whom 38 percent were women (Table 2). Furthermore, in trials that enrolled both men and women, the percentage of women did not increase significantly over time ($r=0.08$) (Fig. 2).

In mixed and single-sex studies of coronary artery disease and hypertension, the enrollment rates for women were proportional to or greater than the prevalences of these disorders among women in the general population (Table 1). The enrollment of women increased significantly over time in studies of coronary artery disease ($r=0.74$, $P<0.001$) but not in studies of hypertension ($r=0.31$, $P=0.29$). In contrast, in all trials that investigated heart failure, women were underenrolled (Table 1), and the enrollment of women in trials investigating heart failure or arrhythmia did not change significantly over time.

With single-sex clinical trials excluded from the analysis, the enrollment rate for women was proportional to the sex-specific prevalence for studies of coronary artery disease and hypertension but not for studies of heart failure (Table 2). For all three disorders, there was no significant change over time in the proportion of women enrolled in studies ($r=0.07$ to 0.11 , $P=0.64$ to 0.86) (Fig. 3). However, there was an abrupt increase in the proportion of women enrolled in studies of coronary artery disease in the mid-1980s, with minimal subsequent changes.

TABLE 1. ENROLLMENT OF WOMEN AND MEN IN ALL NHLBI-FUNDED CLINICAL TRIALS, 1965–1998.*

DISORDER	NO. OF TRIALS	TOTAL ENROLLMENT	MEN	WOMEN	PREVALENCE†
			no.	no. (%)	%
Coronary artery disease	74	328,342	140,492	187,850 (57)	40
Hypertension	24	27,461	15,004	12,457 (45)	44
Congestive heart failure	6	17,349	12,922	4,427 (26)	43
Arrhythmia	11	18,822	13,411	5,411 (29)	NA
Congenital disorder	3	1,125	651	474 (42)	NA
Other cardiac diseases	3	5,702	525	5,177 (91)	NA
Total	121	398,801	183,005	215,796 (54)	49

*NHLBI denotes the National Heart, Lung, and Blood Institute, and NA not available.

†The prevalence is the estimated prevalence of the disorder among women in the general population.

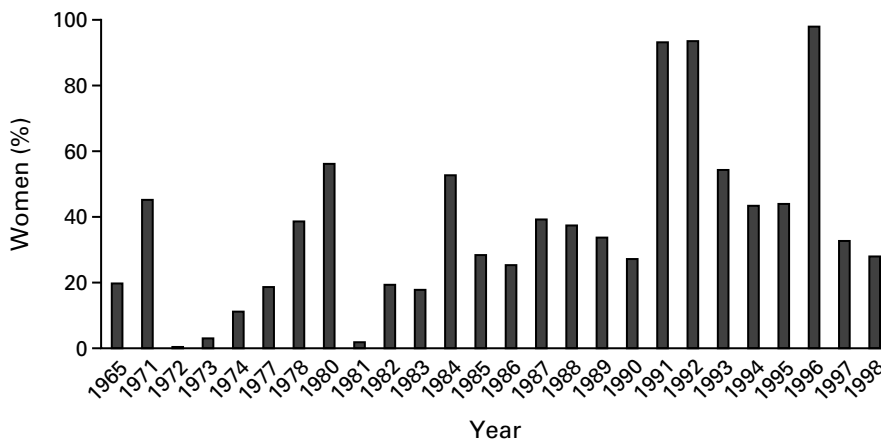


Figure 1. Percentage of Women among Enrollees in All Cardiovascular Clinical Trials Funded by the National Heart, Lung, and Blood Institute between 1965 and 1998, According to the Year the Trial Was Started. Years are shown for trials for which data on sex were available.

TABLE 2. ENROLLMENT OF WOMEN AND MEN IN NHLBI-FUNDED, MIXED-SEX CLINICAL TRIALS, 1965–1998.*

DISORDER	NO. OF TRIALS	TOTAL ENROLLMENT	MEN	WOMEN	PREVALENCET†
		no.			
Coronary artery disease	52	140,609	86,562	54,047 (38)	40
Hypertension	21	26,792	14,485	12,307 (46)	44
Congestive heart failure	6	17,349	12,922	4,427 (26)	43
Arrhythmia	11	18,822	13,411	5,411 (29)	NA
Congenital disorder	3	1,125	651	474 (42)	NA
Other cardiac diseases	2	1,113	525	588 (53)	NA
Total	95	205,810	128,556	77,254 (38)	49

*NHLBI denotes the National Heart, Lung, and Blood Institute, and NA not available.

†The prevalence is the estimated prevalence of the disorder among women in the general population.

DISCUSSION

Efforts to increase the enrollment of women in studies of cardiovascular disease funded by the NHLBI have been partially successful. In studies of coronary artery disease performed since the mid-1980s and in studies of hypertension performed since the mid-1960s, the rates of enrollment of women have been proportional to the sex-specific prevalence of disease.

Two shifts in thinking have contributed to efforts to increase the representation of women in cardiovascular clinical trials. The first was scientific and was based on a growing appreciation of the differences in the pathophysiology, presentation, treatment, and outcomes of cardiovascular disease in women and in men. Since comparatively little information was available to guide decisions about the treatment of cardiovascular disease in women, there was a call for clin-

ical trials that would generate the data necessary for the practice of evidence-based medicine involving female patients. The second shift was societal — the movement away from a protectionist approach to the selection of research subjects, as women demanded greater autonomy in all matters of health, including the decision to participate in clinical trials. The combination of these two forces has led to a number of federal regulations designed to include more women in clinical trials in general, and in cardiovascular studies in particular.

Federal recognition of the need to include larger numbers of women in clinical trials began in 1985, with the recommendation of the Public Health Service’s Task Force on Women’s Health Issues that more attention be paid to research on women’s health.⁵ In response, the National Institutes of Health (NIH) Advisory Committee on Women’s Health Issues stip-

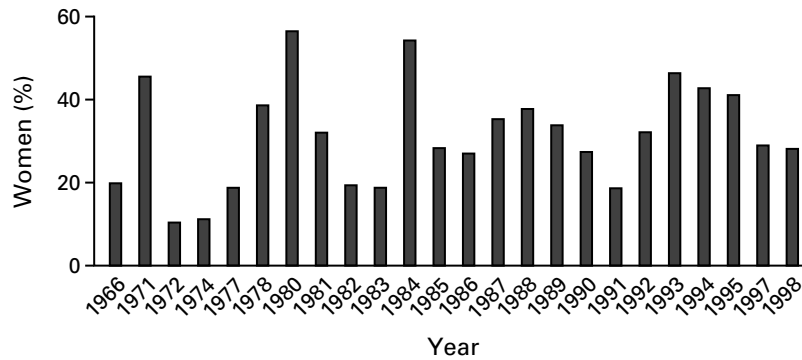


Figure 2. Percentage of Women among Enrollees in Cardiovascular Trials Involving Men and Women, According to the Year the Trial Was Started.

Years are shown for trials for which data on sex were available. Single-sex trials are not included.

ulated that if women were to be excluded from a clinical trial, a satisfactory explanation would have to be provided by the researchers before their grant application would be approved.⁶ In 1990, the General Accounting Office concluded that these recommendations had been unevenly applied.⁷ The NIH and the Alcohol, Drug Abuse, and Mental Health Administration, in turn, instituted the requirement that all grant applications for clinical studies include a study design with a sex composition that was “appropriate to the known incidence/prevalence of the disease or condition studied.”⁸ In addition, the Office of Research on Women’s Health was established to ensure fair representation of the sexes in all studies funded by the NIH. In 1992, the Public Health Service Action Plan for Women’s Health was initiated to “implement policy regarding inclusion of women in National Institutes of Health–supported clinical research.”⁹ In 1993, the National Institutes of Health Revitalization Act (Public Law 103-43) required the inclusion of women in every clinical trial involving a disorder that affects women and directed the NIH to “ensure that the trial is designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women [and men] differently.”¹⁰⁻¹² The costs of including women would not be a “permissible consideration” for waiving the requirement.

Since there have been no substantial increases in the proportion of women enrolled in mixed-sex trials over the past 30 years, our data indicate that, apart from single-sex trials, the temporal patterns of enrollment of women and men in NHLBI-funded cardiovascular clinical trials appear to be unrelated to the federal mandates with regard to the sex composition of study cohorts. The one observed increase in the enrollment of women — in studies of coronary artery disease in the mid-1980s — is abrupt and difficult to attribute to the federal mandates, since it

predated most of them. The growing awareness of the importance of biologic differences between men and women and the enunciation of the right of women to participate in clinical trials may have played a part.

The federal regulations have altered the sex composition of clinical trials primarily through the institution of large trials restricted to women. Although these trials are an appropriate solution to the problem, they should not be allowed to obscure the underrepresentation of women in studies of particular types of cardiovascular disease. Most of the trials that have enrolled only women have investigated coronary artery disease; few of these trials have focused on hypertension, and none on heart failure or arrhythmias. Thus, the Women’s Health Initiative and other clinical trials that have enrolled women exclusively do not cover the broad spectrum of cardiovascular diseases that affect women as well as men.

In a 1993 editorial, Angell cautioned against the development of a new medical specialty for women’s health, stating, “It would marginalize the care of women and leave the mainstream to men, where the lack of attention to women’s health would then be officially sanctioned.”¹³ Care must be taken to ensure that with the current pattern of enrollment in NHLBI-funded cardiovascular clinical trials, including several large trials focused on a limited number of issues in coronary artery disease in women, broader issues in coronary artery disease and in cardiovascular disease in general are not neglected. However, to the extent that trials restricted to women can provide answers to specific questions, some of which have already been addressed in men, they may help correct the underenrollment of women in studies of coronary artery disease before the mid-1980s.

Although the enrollment of women in studies of coronary artery disease has exceeded the prevalence of the disease as a result of single-sex trials, the enrollment of women in mixed-sex trials has been com-

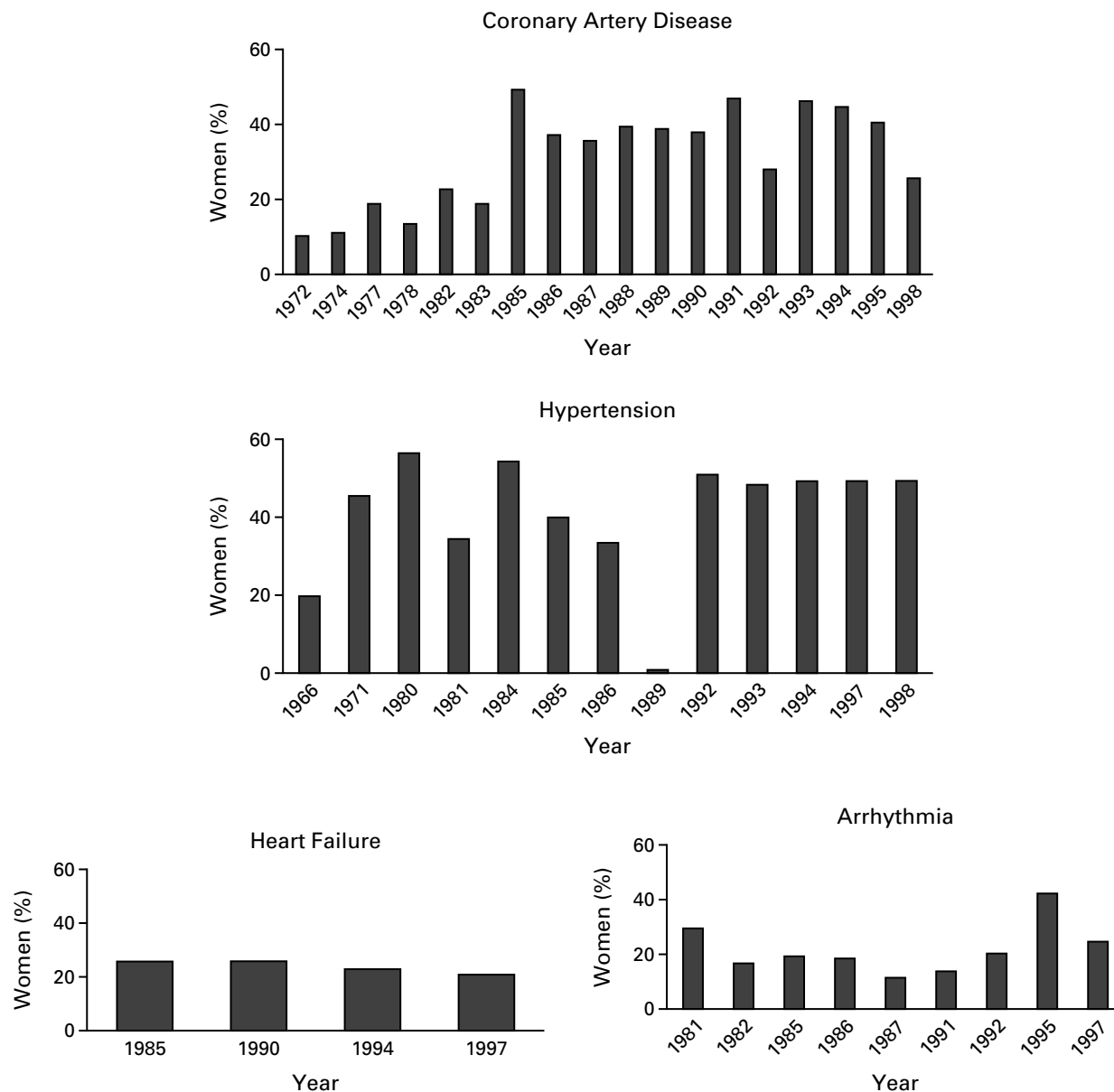


Figure 3. Percentage of Women among Enrollees in Clinical Trials According to the Type of Cardiovascular Disorder and the Year the Trial Was Started.

mensurate with the prevalence of the disease in women. This is an important point, because trials such as the Women's Health Initiative address a limited set of questions, and broader questions must be examined in clinical trials involving both men and women. However, for such trials to address sex-related differences effectively, as required by federal regulations, subgroup analyses must be included in the study design, and the study population must be large enough to draw valid conclusions separately for women and

for men. Recent data suggest that such analyses are performed infrequently.¹⁴

Previous justifications for the underenrollment of women in clinical trials included concern about the safety of women of childbearing potential and of pregnant women and their fetuses; barriers to participation, such as the general unwillingness of women to volunteer for participation in studies; and the tendency for women to withdraw from studies before their completion. The adequate enrollment of women

in studies of hypertension and coronary artery disease, however, strongly discounts these claims, indicating that women are both eligible for and willing to participate in cardiovascular clinical trials. Thus, the overall underrepresentation of women in studies of cardiovascular disease in general and in studies of heart failure specifically cannot be attributed to such factors. Other barriers may be present.

In view of the importance of sex-based differences in cardiovascular disease, we must obtain the data required to tailor treatment for women. The pattern of enrollment of women in studies of coronary artery disease and hypertension is encouraging, but improvement is needed in other areas. The positive findings also make it clear that the persistent underenrollment of women in certain areas is not due to barriers to their recruitment and retention. Policies designed to increase the enrollment of women in NHLBI-funded cardiovascular clinical trials have had mixed results. In fact, the proportion of women enrolled in trials involving both men and women has not changed significantly, despite a series of federal regulations intended to increase the enrollment of women and ensure the evaluation of sex-related differences in findings.

What steps can be taken to ensure success in all areas? The problem falls on the shoulders of researchers, funding agencies, and policy makers. More stringent NIH requirements or stricter enforcement of current regulations may seem punitive to investigators and may act as a disincentive to the performance of valuable research. The legal requirements that the levels of enrollment of men and women in NHLBI-funded clinical trials be statistically appropriate and that sex be considered as an independent variable are expensive as well as time-consuming; our data cannot be used to determine the success of this law. Single-

sex clinical trials are potentially appropriate for addressing the persistent underenrollment of women and for resolving clinical issues that are specific to sex. However, they are not an adequate solution as long as the majority of cardiovascular clinical trials continue to underenroll women. The successful resolution of this difficult problem is critical for the prevention and management of cardiovascular disease in women and men.

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