Journal of the American College of Cardiology
Vol. 52, No. 8, 2008

Published by Elsevier Inc.
ISSN 0735-1097/08/$34.00

CORRESPONDENCE

Research Correspondence

Enrollment of Women in National Heart, Lung, and Blood Institute-Funded Cardiovascular Randomized Controlled Trials Fails to Meet Current Federal Mandates for Inclusion

To the Editor: In 1986, the National Institutes of Health (NIH) established a policy for the inclusion of women in clinical research that was subsequently enacted into public law when Congress approved the NIH Revitalization Act of 1993 (1). This Act states that women and minorities must be included in phase 3 clinical trials in numbers adequate to allow for valid analyses of differences in intervention effect. To evaluate the impact of these legislative reforms, we sought to describe the enrollment of women in federally funded cardiovascular (CV) randomized controlled trials (RCTs) during the past 10 years by searching the NIH registry of clinical trials for phase 3 or 4 CV RCTs funded by the National Heart, Lung, and Blood Institute (NHLBI). Studies with primary outcomes of myocardial infarction, stroke, or death published between 1997 and 2006 were included. Trials were excluded if they were still recruiting as of November 16, 2006, included children, or were restricted to women. We categorized the trials by disease process, the acuity of the patient at study enrollment, and the risk of the intervention. The categories of disease were coronary artery disease (CAD), electrophysiologic disease, congestive heart failure (CHF), and hypertension. Acute trials enrolled patients during the acute phase of illness. High-risk studies involved an invasive procedure. Relationships between the mean proportion of women (percent of women) enrolled and the categories described above were compared with the Student t test ($\alpha = 0.05$) and one-way analysis of variance. The mean percent of women enrolled by disease process was then compared with the percent of women in the general population age ≥20 years with the disease process as reported by the American Heart Association (AHA) Heart Disease and Stroke Statistics report (2). Gender-specific prevalence data were not available from the AHA report for sudden cardiac death. Thus, data from the AVID (Antiarrhythmics Vs Implantable Defibrillators) (3) and MUSTT (Multicenter Unsustained Tachycardia Trial) (4) registry papers and a large population-based retrospective cohort study of all out-of-hospital cardiac arrests in Seattle and neighboring King County, Washington (5), were used. Stata software (LP Intercooled Stata, version 9.0, Stata Corporation, College Station, Texas) was used for statistical analyses.

Of 11,918 NIH studies, 1,488 were funded by the NHLBI. Of these, 982 studied CV disease and 851 were no longer recruiting at the query date. After excluding trials that were not phase 3 or 4 RCTs performed in adults, 141 remained, of which 53 reported primary outcomes of stroke, myocardial infarction, or death. We excluded 3 trials that were restricted to women and 31 published outside of the time window. This resulted in 19 RCTs (Online Table): 8 CAD, 7 electrophysiologic disease, 3 CHF, and 1 hypertension (Fig. 1). The enrollment of women ranged from 10% to 47%. The mean enrollment of women for all trials was 27%. Only 13 trials explicitly presented subgroup analyses based on gender in the primary report. All studies were published in high-impact journals, and many have been cited in major societal guidelines.

There was no significant difference in the mean percent of women enrolled by type of disease, acuity, or risk of intervention (all p = NS). Comparison of the mean percent of women enrolled in CV RCTs by disease category with the published percent of women among those with disease according to the AHA report (2) showed that enrollment in CAD (29% vs. 46%), CHF (23% vs. 50%), sudden cardiac death (17% vs. 16% in MUSTT registry [4], 23% in AVID registry [3], and 32% in Seattle/King EMS study [5]), and atrial fibrillation (39% vs. 59%) fell short of the comparative proportions. The mean percent of women enrolled in all trials was 27% versus 53% of all patients with CVD who are women (2).

Despite a federal mandate for significant inclusion of women in federally sponsored clinical trials, women are under-represented in NIH-supported CV RCTs. This lack of legislative impact was first reported more than a decade ago (6). Our current study of CV RCTs published in the past decade shows an ongoing lack of progress in the enrollment of women. We excluded 3 gender-specific CV RCTs (7–9) that otherwise were eligible for inclusion for 2 reasons. First, previous work (6) demonstrating an increase in the enrollment of women in CV clinical trials funded by the NHLBI between 1965 and 1998 found that this increase was largely due to the inclusion of the Women's Health Study (9) and the Women's Health Initiative (7). When excluded, the enrollment of women decreased from 54% to 38% with no significant increase in enrollment over time. Thus, the relevant question to be answered by our updated analysis was whether the proportion of enrollment in mixed-gender trials has improved.

Second, the stated goal of the NIH Revitalization Act is to "ensure that the trial is designed and carried out in a manner sufficient to provide for valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial" (1). The existence of 3 large single-gender studies (2 evaluating hormone-replacement therapy) does not substitute for the spirit of the mandate, and although they are important, these studies cannot be expected to answer the breadth of questions that arise in the care of women with heart disease.

The inadequate proportion of women enrolled in NIH-sponsored CV RCTs merits attention. Although this mission falls under the responsibility of the NIH, the lack of success in

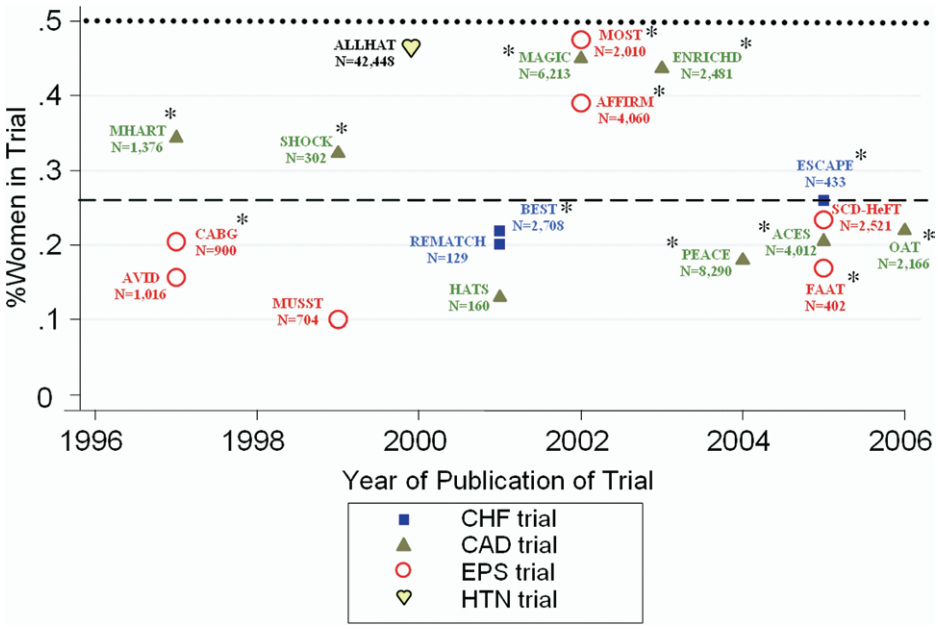

Figure 1 **Enrollment of Women in NHLBI-Sponsored Phase 3 to 4 Cardiovascular Randomized Cardiovascular Trials From 1997 to 2006**

Each trial is represented by a marker showing the type of cardiovascular disease process it studies (CHF = congestive heart failure, CAD = coronary artery disease, EPS = electrophysiologic disease, HTN = hypertension). An **asterisk** by a trial name denotes that subgroup analyses based on gender were published in the primary report. The **dotted line** represents an arbitrarily chosen reference point of 50% enrollment, and the **dashed line** represents the average enrollment of women over 10 years: 27%. NHLBI = National Heart, Lung, and Blood Institute.

increasing female participation does not seem to be due to a lack of purpose. In our experience, enrollment of women and minorities is emphasized at every stage of trial conduct, from protocol design to grant approval to scrutiny of periodic enrollment reports with the study leadership. In fact, the enrollment of women in overall NIH trials has increased significantly since 1993 such that more women than men were enrolled in NIH-sponsored phase 3 clinical trials (10), but our study shows that, in mixed-gender CV RCTs, women are still underrepresented. In conclusion, close monitoring by the NIH and the support of a federal mandate have not been successful in increasing the enrollment of women in cardiovascular RCTs. Investigation of the reasons for female under-representation warrants ongoing research.

Esther S. H. Kim, MD, MPH
Thomas P. Carrigan, MD
***Venu Menon, MD, FACC**

*Department of Cardiovascular Medicine, Desk F15
9500 Euclid Avenue
Cleveland, Ohio 44195
E-mail: menonv@ccf.org

doi:10.1016/j.jacc.2008.05.025

REFERENCES

1. U.S. Congress Public Law No. 103-43. National Institutes of Health Revitalization Act of 1993. June 10, 1993.
2. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:e69–171.
3. Anderson JL, Hallstrom AP, Epstein AE, et al. Design and results of the Antiarrhythmics Vs Implantable Defibrillators (AVID) registry. The AVID Investigators. Circulation 1999;99:1692–9.
4. Buxton AE, Lee KL, DiCarlo L, et al., for the Multicenter Unsustained Tachycardia Trial Investigators. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. N Engl J Med 2000;342:1937–45.
5. Kim C, Fahrenbruch CE, Cobb LA, Eisenberg MS. Out-of-hospital cardiac arrest in men and women. Circulation 2001;104:2699–703.
6. 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;343:475–80.
7. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
8. Schulman SP, Thiemann DR, Ouyang P, et al. Effects of acute hormone therapy on recurrent ischemia in postmenopausal women with unstable angina. J Am Coll Cardiol 2002;39:231–7.
9. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293–304.
10. Department of Health and Human Services NIH. Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research. Comprehensive Report: Tracking of Human Subjects Research As Reported in Fiscal Year 2005 and Fiscal Year 2006. Bethesda, MD: NIH, Spring 2007.

APPENDIX

For a supplementary table with a list of included phase 3 or 4 cardiovascular randomized controlled trials sponsored by the NHLBI published between 1997 and 2006 with primary outcomes of MI, stroke, or death, please see the online version of this article.