Status of Women in Cardiovascular Clinical Trials

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The Burden of Cardiovascular Disease in Women

Cardiovascular disease (CVD) is the most common cause of death in American women and accounts for a full one-third of all deaths.1 Although the common perception may be that CVD affects mainly men, there is equal prevalence of this disease between the genders by the age of 40, and by the age of 60 more women than men are affected. More women than men have died from CVD causes on a yearly basis since the mid 1980s, and whereas the CVD mortality has steadily declined in men over the past 30 years, it has remained steady in women until very recently when CVD mortality was noted to decrease for both genders.2

Inclusion of Women in Clinical Trials: A Historical Perspective

The importance of CVD as a major source of morbidity and mortality in U.S. women has become the focus of public education efforts such as the “Go Red for Women” campaign sponsored by the American Heart Association and the “Red Dress” project sponsored by the Department of Health and Human Services, the National Institutes of Health (NIH), and the National Heart Lung and Blood Institute (NHLBI). These programs are, in part, a response to the increasing awareness of cardiovascular disease as a major source of morbidity and mortality in U.S. women.

The 1992 GAO Report7 on Women’s Health showed that more than 60% of drug trials had inadequate representation of women (with “standard of representativeness” being a “comparison of the proportion of women among clinical trial participants with the proportion of women among those persons with the disease for which the drug is intended”) and that even when women were included in drug trials, sex-specific analyses were often not performed. In 1993, the FDA issued a new guideline, “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs,” which explicitly reversed the 1977 policy of exclusion and aimed to reduce the risk of fetal exposure through protocol design including emphasis on the process of informed consent, the need for contraception for women of childbearing potential participating in early drug trials, and pregnancy testing in appropriate circumstances.8 The 1993 guideline also called for data collection and data analyses to be performed to assess for differences in drug effect attributable to gender. In a continuing effort to improve inclusion of women in drug trials, the FDA published another regulation known as the “Demographic Rule” in 1998.9 This regulation applies to investigational new drug applications

NIH Revitalization Act reinforced existing NIH policies for inclusion of women and minorities and stated that in the case of Phase III clinical trials, 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.”5

While federally-funded clinical trials are under the mandate for inclusion of women set by the NIH Revitalization Act, the majority of drug trials (around 80%) are sponsored by pharmaceutical companies.6 These trials are ultimately regulated by the Food and Drug Administration (FDA), but unlike the NIH, the FDA does not have a federal mandate for inclusion in clinical trials under its regulation. According to a 1992 General Accounting Office (GAO) Report on Women’s Health,7 drug trials under the guidance of the FDA were found to have inadequate inclusion of women, and this under-representation was attributable, in large part, to the thalidomide experience and fears of birth defects resulting from drug testing in women of childbearing potential. In fact, a 1977 FDA regulation excluded women of childbearing potential from early drug studies. Sadly, this regulation may have led to the under-representation of women of all ages in trials in all phases of development.

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(INDs) and new drug applications (NDA) and requires the submission of information on clinical trial participation, safety, and effectiveness by gender, age, and racial subgroups. A regulation in 2000 permitted the FDA to temporarily suspend studies of drugs for life-threatening conditions if participants were excluded because of reproductive potential.

As a result of these regulations, a follow-up GAO report in 2001 found that women were the majority of clinical drug trial participants for more than half of the NDAs reviewed and that women accounted for 52% of the total trials enrollees in these NDAs. There was, however, wide variability in the proportion of women enrolled in the different stages of drug development such that only 22% of participants in initial safety trials used to set dosing for larger trials were women. The report also found that the FDA did not adequately oversee NDAs for the presentation of data for women and sex-specific analysis of data. It further found that the FDA did not have adequate procedures in place to monitor compliance with its regulations for inclusion.

**Participation of Women in Cardiovascular Clinical Trials Since the NIH Revitalization Act**

Because of large single-sex studies such as the Women’s Health Study and the Women’s Health Initiative, the overall number of women enrolled in NIH sponsored trials has increased substantially since the NIH Revitalization Act. In fact, there have been more women than men enrolled in NIH-sponsored phase 3 clinical trials since 1993; however, in mixed-gender cardiovascular trials, women are still under-represented. This was clearly shown a decade ago in a study which investigated the enrollment of women in CV clinical trials funded by the NHLBI between 1965 to 1998. The overall enrollment of women in these trials during that time period was 54%, but when the Women’s Health Study and the Women’s Health Initiative were excluded from analysis, the proportion of women enrolled decreased to 38%, and there was no significant increase in enrollment over time. In other words, while the absolute number of women included in federally-funded CV clinical trials increased over the 30-year span, the proportion of women in mixed-gender trials remained about the same. An updated analysis of the enrollment of women in mixed-gender NHLBI-sponsored randomized-controlled trials with primary outcomes of stroke, myocardial infarction, or death published between 1997 and 2006 showed the mean proportion of women included in these trials to be 27% (Figure), and only 13 of 19 studies included in this analysis reported gender-based outcomes in their primary report. These two studies highlight the lack of progress in the proportion of women enrolled in mixed-gender NIH-supported cardiovascular trials even fifteen years after the NIH Revitalization Act was passed into law.

Lack of progress in the inclusion of women in cardiovascular clinical trials is not limited to federally-funded studies. An analysis of trials included in Cochrane meta-analyses (Cochrane Systematic Reviews) for the inclusion of women in cardiovascular clinical trials and for the reporting of gender-based analyses showed similar results. Of 258 clinical trials studied, women constituted only 27% of the pooled population and of 196 trials which included both genders, only 33% reported gender-based outcomes. When analyzed by year of publication before or after 1993, there was no difference in the frequency of gender-based analyses.

Although it may be utopian to enroll women in sufficient numbers to perform adequately powered analyses for intervention effect in every clinical trial, there is currently no clearly established lowest benchmark for adequate enrollment. Neither the NIH Revitalization Act nor the FDA guidelines for inclusion of women in clinical trials explicitly set a mandated target recruitment proportion. One suggested measure of numeric adequacy is to compare enrollment to the sex-specific prevalence of the disease. Even by this standard, however, women continue to be under-represented in cardiovascular randomized clinical trials sponsored by the NHLBI (Table).

**Implications of Under-Representation of Women in Cardiovascular Clinical Trials**

The inadequate representation of women in cardiovascular clinical trials has significant implications. Translation of research evidence into clinical practice is effective only in
Barriers to Enrollment in Cardiovascular Clinical Trials

Enrollment of women in cardiovascular clinical trials has proven to be a challenge despite federal mandates for inclusion and increasing public education efforts. Cardiac risk may be underestimated in women,\(^2\) resulting in reduced referrals to cardiology practices where recruitment for cardiovascular clinical trials are performed. Gender bias may also lead to the misinterpretation of symptoms of coronary heart disease in women leading to less referral for cardiac testing and specialty care.\(^2\)^\(^2\) Women are less likely to be referred to the cardiac catheterization laboratory during acute coronary syndromes\(^2\)^\(^4\)\(^-\)\(^6\) and less likely to receive percutaneous intervention,\(^2\)^\(^7\) thus precluding their inclusion into interventional clinical trials.

Study protocols for recruitment and traditional exclusion criteria for participation in cardiovascular clinical trials may also contribute to the under-enrollment of women subjects. Women present with manifest heart disease later in life\(^2\) and older patients tend to be excluded from clinical trials.\(^2\)^\(^8\)\(^9\) This potential age-gender interaction has been supported by a study which showed that the proportion of women in myocardial infarction trials increases with an increase in the mean age of the population studied.\(^2\)^\(^0\)

Some possible barriers to the recruitment of women that have been outlined by the NIH\(^1\) are fear and distrust of the research enterprise, lack of knowledge, lack of transportation, interference with work or family responsibilities, subject burden as a result of participation in a clinical study, and financial costs. Although the psychological, social, and economic backdrop of these barriers is complex, some practical recruitment and retention strategies used by the ENRICHD study,\(^2\)^\(^2\) which included 44\% women, can serve as an example of potential methods that work. In this trial, extraordinary efforts were made to include a diverse staff in terms of gender and ethnicity to match the demographics of the patients being enrolled. Patient follow-up was done occasionally by home visits, and transportation, meals, and support of dependents were also provided when needed.\(^2\)^\(^3\) While these measures may be labor intensive and costly, innovative methods which target important gender-specific barriers to enrollment are required to increase the enrollment of women as guidelines and federal mandates alone have been ineffective.

The lack of willingness of women to participate in high-risk cardiovascular clinical trials may also be a contributing factor. Women may differ from men in their perception of risk from cardiovascular disease and in the risk benefit ratio from the intervention being tested as well as in their risk taking behaviors.\(^2\)^\(^4\) An accurate measure of this phenomenon can be obtained by the conduct of robust concurrent funded registries that identify the proportion of women both in the parent trial and in the community at large. Questionnaires that study the attitudes of women, the elderly, and minorities to clinical trial participation should be an integral component of the consent process. It also remains the responsibility of local site investigators to institute recruitment strategies that will promote the participation of women, and local impediments to recruitment and retention in clinical trials need to be recognized and addressed.

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Table. Comparison of the Mean Proportion of Women in NHLBI Sponsored Phase 3-4 Cardiovascular Randomized Controlled Trials Published Between 1997 and 2006 to Proportion of Women Among the General Population With Cardiovascular Disease

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>% Women Among Those With Disease</th>
<th>% Women (mean)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Artery Disease</td>
<td>29%</td>
<td>46%</td>
<td>AHA</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>23%</td>
<td>52%</td>
<td>ADHERE</td>
</tr>
<tr>
<td>Sudden Cardiac Death</td>
<td>17%</td>
<td>23%</td>
<td>MUSTT registry</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>39%</td>
<td>55%</td>
<td>AHA</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47%</td>
<td>53%</td>
<td>AHA</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>27%</td>
<td>53%</td>
<td>AHA</td>
</tr>
</tbody>
</table>

AHA indicates American Heart Association; ADHERE, Acute Decompensated Heart Failure National Registry; NHFP, National Heart Failure Project (patients >65 years old); Seattle/King EMS, Retrospective cohort study of all out-of-hospital arrests in Seattle and King County, WA, since 1970s.

populations that are adequately represented. In those areas where a gender treatment interaction is suspected, gender specific trials that are adequately powered are necessary. As an example, there have been 3 major non-ST segment elevation acute coronary syndrome (NSTEMI) trials which have raised questions about whether early invasive therapy for NSTEMI benefits men and women differently. The FRISC II\(^1\)\(^7\) and RITA 3\(^1\)\(^8\) trials showed no benefit of early invasive therapy over conservative therapy in women with NSTEMI, whereas there was a benefit of early invasive therapy seen in men. In contrast, the TACTICS-TIMI 18\(^1\)\(^9\) trial showed that early invasive therapy was equally beneficial for men and women. Adequately powered gender specific trials in response to these conflicting results have yet to be published.

In a second example, aspirin therapy for the primary prevention of cardiovascular disease has different effects in men and women. In a meta-analysis of 6 trials including more than 95 000 individuals, aspirin was found to have a significant reduction in composite cardiovascular events in both men and women, 14\% and 12\%, respectively; however, the reduction in cardiovascular events was driven by different types of events for men and women. In men, there was a 32\% reduction in myocardial infarction but no significant effect on stroke or cardiovascular mortality. In women, there was a 17\% reduction in stroke but no significant effect on MI or cardiovascular mortality.\(^2\)^\(^0\)

Gender-based analyses are thus essential to elucidate differences in treatment effect of cardiac interventions and to determine differences in side-effect profiles. Continued under-enrollment of women in clinical trials of cardiac interventions may lead to institution of ineffective or even harmful treatment regimens. Conversely, potentially effective cardiac treatments for women may be dismissed when gender-specific analyses are not performed.
Moving Toward Adequate Representation

The first step toward adequate representation of women in cardiovascular clinical trials is addressing the lack of knowledge among physicians and the general public of the burden of cardiovascular disease in women. Heart disease awareness campaigns such as the Red Dress Campaign and patient advocacy groups such as the National Coalition for Women with Heart Disease encourage women with heart disease to empower themselves in the same way that the Susan G. Komen Breast Cancer Foundation has empowered the fight against breast cancer. These efforts should be applauded and generously supported.

On the regulatory end, there are continued efforts by federal agencies to increase the enrollment of women in cardiovascular trials. As an example, the FDA’s Center for Devices and Radiological Health recently held a workshop on “Gender Differences in Cardiovascular Device Trials” in preparation for plans to publish a Guidance Document “on gender and race-specific analysis of healthcare data that is aware among physicians and the general public of the burden of cardiovascular disease in women.” This workshop was the second FDA workshop to explore this issue and included participants from government agencies, industry, clinical investigators, and patient advocacy groups. Recognizing the conflict between adequate enrollment of women and cost-effective trial execution, convening all shareholders for the development of practical guidelines in the conduct of new drug and device trials is an important step toward achieving adequate representation of women in cardiovascular clinical trials reviewed by the FDA.

Finally, in an effort to improve the prevention, diagnosis, and treatment of heart disease and stroke in women, several advocacy groups supported the Heart Disease Education, Analysis and Research, and Treatment for Women Act (HEART for Women Act) which was passed by the House of Representatives in September 2008. This bill (H.R. 1014) will be presented to the 111th Congress and seeks to raise awareness of heart disease among medical professionals and the women they treat by authorizing educational grants and awareness campaigns, providing gender and race-specific information for clinicians and researchers by requiring gender- and race-specific analysis of healthcare data that is already being reported to the federal government, and authorizing the expansion of the WISEWOMAN (Well-Integrated Screening and Evaluation for Women Across the Nation) program which provides cardiovascular screening to low-income women.

Much work has been done to increase the awareness of the impact of cardiovascular disease on American women, and there have been many strides in regulations to improve the enrollment of women in cardiovascular trials since the 1985 Public Health Service Report. Translating the knowledge of under-representation of women in cardiovascular clinical trials to achieving adequate enrollment will require further investigation into the causes of under-enrollment and heightened expectations for adequate representation.

Disclosures

None.

References


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