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Sex/Gender Disparities in Randomized Controlled Trials of Statins: The Impact of Awareness Efforts

Abstract

Purpose: Studies have demonstrated gender differences in the burden of cardiovascular outcomes for patients with dyslipidemia. Progress in identification of the sex/gender composition in Randomized Controlled Trials (RCTs) is crucial for understanding the distribution of therapeutics effectiveness in the population according to sex/gender.

The purpose of this study was to investigate the evolving pattern of sex/gender disparity in participants of RCTs on statins between 1990 and 2010. A secondary objective was to evaluate changes in the pattern of the average age of participants of RCTs on statins between 1990 and 2010.

Methods: This review focused on RCTs on statins that reported participants' numbers by sex/gender. Studies were identified from an initial PubMed search using several combinations of MeSH terms. The search was limited to the RCTs on adults in English-language publications. The dates for search were set between January 1, 1990 and December 31, 2010.

Results: In the 1990s, RCTs on statins with an average of more than 500 participants included 18.6% women [95% Confidence Interval (95% C.I.): 16.31%, 21.13%]. By the first decade of the 2000s, women comprised, on average, 31.45% [29.45%, 32.52% (95% C.I.)] of the total cohort of RCTs with more than 500 participants. Regression analysis illustrated a significant increase in the recruitment of women for RCTs of statins (p -value < 0.01). Furthermore, analysis of the average age of participants illustrated a significant trend (p -value = 0.03) towards an increase in the average age of the participants in RCTs on statin between 1990 and 2010: the average age of participants in the 1990s was 58 years [56, 60 (95% C.I.)] and in the 2000s it was 62 years [56, 60 (95% C.I.)].

Conclusion: This study demonstrates significant progress in the inclusion of women in RCTs on statins. This finding reflects the efforts of different agencies and groups to increase the representation of women in clinical trials.

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There is a vast gender disparity regarding epidemiology and burden of illness of cardiovascular disease (CVD) [1]. Women have a considerably higher risk of cardiovascular-related morbidity and mortality than men [2,3]. Since 1984, the number of CVD deaths for females has exceeded those for males in the United States [4]. The coronary heart disease death rate for American women aged 35 to 44 years increased annually between 1997 and 2002 [4], and in 2009, CVD was the cause of death in 401,495 females [4] (51.0% of the deaths from CVD) [4].

Women aged 45 and older are less likely than men of the same age to survive a year after their first heart attack [4]. This pattern of morbidity and mortality is likely related to cardiovascular risk factor control [5, 7]. Compared with men, women receive less aggressive diagnostic workups and therapy for CVD [8, 9]. Studies consistently demonstrated that women are more likely than men to have LDL-C levels above treatment goals [7-10]. This issue has been observed in several studies from around the globe, despite different patient populations, different clinical practice guidelines and different timeframes [11]. A meta-analysis of randomized, controlled statin trials evaluating the gender specific incidence of cardiovascular events illustrated that statins reduced the risk of cardiovascular events in both men and women, but that women on statins may not have the same reductions in mortality and stroke as their male counterparts [12]. A meta-analysis of studies on adherence to statins by men and women reported that women had a 10% greater odds of non-adherence (odds ratio 1.10, 95% confidence interval: 1.07-1.13) [13].

The concept of a gender gap is useful for identifying at-risk groups for prevention and treatment efforts. Scientists, health-care providers, the public and policy makers have made substantial efforts to improve our understanding of the sex/gender differences in cardiovascular disease [14]. In 1994, the US National Institutes of Health (NIH) issued a guideline for the study and evaluation of gender/sex differences in clinical trials to ensure that the safety and efficacy of drugs would be adequately investigated in the full range of patients who would use the therapy [15]. Progress in the gender/sex composition of Randomized Controlled Trials (RCTs) is crucial for understanding the distribution of therapeutics effectiveness in the population according to sex/gender. This paper investigates the evolving pattern of gender/sex disparity in participants of RCTs on statins between 1990 and 2010 to illustrate the impact of the efforts from agencies and groups, such as the 1994 US NIH guideline, to increase the representation of women in clinical trials. Furthermore, as both the female sex and advanced age has been identified as predisposing factors for

statin-associated myopathy in clinical practice [16], as a secondary objective, this paper evaluated changes in the pattern of average age of participants of RCTs on statins between 1990 and 2010.

Methods

This paper focused on RCTs of statins that reported participants' numbers by sex/gender. Of note, gender is shaped by environment and experience and a person's self-representation as male or female or how that person is responded to in social situations on the basis of the individual's gender representation [17]. In contrast, sex is the classification of female or male according to reproductive organs and functions assigned by chromosomal complement [17]. Throughout this paper the words, "gender" or "sex" has been utilized interchangeably in accordance to the original articles that has been cited as references.

Studies were identified from a PubMed search using several combinations of medical subject heading (MeSH) terms (Appendix 1). As this article is not intended to be a systematic review, only a PubMed search was done. The search strategy framework was defined as follows to extract the RCTs: the search was limited to RCTs on adult humans in English-language publications. The dates for search were set between January 1, 1990 and December 31, 2010. Filters were used for extracting RCTs as described above and then abstracts were checked manually to include or exclude the studies. The studies were chosen with a minimum duration of 6 months, a minimum sample size of 500 patients and a primary cardiovascular endpoint (Appendix 2). The included studies are tabulated in Appendix 3.

The percentage of women who participated in RCTs, as well as the mean age of participants, was analyzed using Chi-square and ANOVA, respectively, in accordance with the dates that the RCTs were published. Since the RCTs had different lengths of study and follow-up times, and the date of publication was used as an endpoint for analysis, the data were categorized into two 10-year periods for analysis. ANOVA was used for continuous data (average age) and Chi-square was utilized for categorical data (percentage of female participant) for comparisons between the two 10-year intervals. Results of regression analyses are illustrated in Figure 1 and Figure 2. The data for each individual study were not analyzed as a trend over time as the length of each study was different. Also, the data were analyzed according to the size of trials to determine if trends of change were consistent for much larger trials (larger than 4000) compared to all trials larger than 500 or 1000 participants.

Results

The ratio of male to female participants in RCTs on statins decreased significantly in the decade of 2000s compare with the 1990s ($p=0.03$). The RCTs on statins with more than 500 participants in the 1990s included 18.6% women, on average (Table 1). Women comprised between 16.31% and 21.13% [95% Confidence Interval, (95% C.I.)] of the total cohort in RCTs on statins. In the decade of 2000s, women comprised between 29.45% and 32.52% (95% C.I.) and on average 31.45% of the total cohort of RCTs with more than 500 participants. Figure 1 illustrates the trend in the percentage of recruited women in the total cohort of RCTs with more than 500 participants by timeline between 1990 and 2010. Regression analysis illustrated a significant increase in the recruitment of women for RCTs on statins ($p<0.01$). Analysis was also conducted on only the larger RCTs (Table 1), including RCTs with more than 1000 participants (24 studies) and RCTs with more than 4000 participants (19 studies), and demonstrated the same significant increase in women participation (approximately 12.5% increase, $p<0.05$).

Furthermore, analysis on average age illustrated a significant trend ($p=0.03$) in increasing the average age of participants in RCTs on statin between 1990 and 2010 (Table 2). The average age of participants in the 1990s was 58 years [56, 60 (95% C.I.)] and in the 2000s was 62 years [56, 60 (95% C.I.)]. Figure 2 illustrates the trend in the mean age of the participants in the total cohort of RCTs on statins by timeline between 1990 and 2010. Regression analysis illustrated a significant increase in average age of participants in RCTs on statins ($p<0.001$). The same patterns of rise in the mean age of participants were observed for larger RCTs (Table 1), with an approximate 5 years increase in average age ($p=0.01$).

Discussion

In the new millennium, with a growth in “personalized medicine”, sex/gender aspects in clinical medicine has become extremely important [18]. Gender-based medicine studies the biological and physiological differences between the human sexes and how these sex differences affect differences in disease progression and treatment [18]. Traditionally, medical research

TABLE 1. Trend in percentage of women participation in total cohort of RCTs by timeline

Size of RCTs	Number of studies included	1990-1999	2000-2010	P- Value
Larger than 4000	19	17.5% [14.67, 20.74]	30.23% [27.73, 32.78]	0.03
Larger than 1000	24	17.3% [14.8, 20.41]	30.76% [28.62, 33]	0.02
Larger than 500	30	18.6% [16.31, 21.13]	31.45% [29.45, 33.52]	0.03

Numbers are non-weighted average percentage (%) of women participation in total cohort of RCTs for each decade. Confidence Intervals [a, b] were calculated using Wilson 95% C.I. method.

TABLE 2. Trend in mean age of participants in total cohort of RCTs by timeline

Size of RCTs	Number of studies included	1990-1999	2000-2010	P- Value
Larger than 4000	19	57 (2) [54, 60]	64 (5) [61, 67]	0.01
Larger than 1000	24	57 (3) [55, 60]	63 (5) [61, 66]	0.01
Larger than 500	30	58 (2) [56, 60]	62 (6) [60, 65]	0.03

Numbers are non-weighted mean age (year) and standard deviation (SD) of participants in total cohort of RCTs for each decade. [a, b] are 95% Confidence Intervals.

has mostly been conducted using men as the basis for clinical studies. The findings of these studies have often been applied across the sexes and healthcare providers have assumed a uniform approach in treating both male and female patients. While in the past the majority of therapeutic strategies and evaluations were aimed mostly at men, in the last decades there has been vast efforts to change this paradigm.

As differences in the clinical manifestations of prevalent diseases and responses to medical treatments in women and men become apparent, medical researchers have begun to understand the importance of taking sex/gender into account in clinical research [18]. This is at least partially due to sex differences in pathophysiology. Women and men differ in response to treatment of diabetes and various cardiovascular diseases. For example, gender differences in response to dyslipidemia treatment with statins, including greater difficulty in reaching cholesterol targets, can be related to the use of a less aggressive approach in women, poorer adherence of women to statins, or sex/gender physiopathological differences [19]. Differences in pathophysiology due to sex/gender differences can lead to differences in drug response due to dissimilarities in pharmacodynamics and pharmacokinetics [20, 21]. Evidence of sex-based differences in statin metabolism implicates differences in body-fat content between men and women [22]: females tend to have a higher percentage of body fat, which affects the volume of distribution of some drugs and can significantly increase the half-life of a variety of medications, including the more lipophilic statins [22]. As mentioned earlier, a meta-analysis of studies on adherence to statins by men and women indicated

that women had a 10% greater odds of non-adherence (odds ratio 1.10, 95% confidence interval: 1.07-1.13) [13]. The combination of sex/gender differences in pathophysiology, drug metabolism and adherence to treatment supports sex-based evaluation and treatment for cardiovascular diseases such as dyslipidemia.

Melloni and colleagues conducted a study where 156 randomized clinical trials cited by the 2007 women's prevention guidelines were abstracted to determine female representation over time [23]. This study found that 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 enrolment was 18% in 1970 and increased to 34% in 2006. 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%). In 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. The present study adds information on this subject as it illustrates an approximate 13% increase in the proportion of women participated in RCTs on statin between 1990s and 2000s. This result is consistent with the Melloni study [23], where female enrolment increased from 18% in 1970 to 34% in 2006. The findings of the present study is also consistent with the near doubling of the rate of awareness of heart disease in women between 1997 and 2009 [14]. "The Heart Truth" is a campaign that started in 2002 to increase awareness of the risk of heart

FIGURE 1. Trend in percentage of women participation in total cohort of RCTs by timeline for RCTs larger than 500 participants

FIGURE 2. Trend in mean age of participants in total cohort of RCTs by timeline for RCTs larger than 500 participants

disease in women. The campaign is sponsored in the United States by the National Heart, Lung, and Blood Institute, and in Canada by the Heart and Stroke Foundation of Canada.

In 2008, a study evaluated the enrolment of women in the National Heart, Lung, and Blood Institute (NHLBI)-sponsored phase 3 to 4 cardiovascular randomized cardiovascular trials from 1997 to 2006, to evaluate the impact of national legislative reforms in The United States to increase the enrolment of women in federally-funded cardiovascular RCTs [24, 25]. In 1986, NIH established a policy for the inclusion of women in clinical research, which was subsequently enacted into public law when Congress approved the NIH Revitalization Act of 1993 [24, 25]. 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. This study [24, 25] included 19 RCTs, comprising eight CAD trials, seven electrophysiological disease trials, three CHF trials, and one hypertension trial. The enrolment of women ranged from 10% to 47%. The mean enrolment of women for all trials was 27%. This study concluded that despite a federal mandate for significant inclusion of women in federally sponsored clinical trials, women were under-represented in NIH-supported cardiovascular RCTs. The present study concluded the same pattern of under-representation for women in RCTs on statins. The proportion of female participants has increased overtime; however, the average was still only 31% in 2000s, which is considerably below an ideal number (50%) for women participation in RCTs on statins.

A report published in 2011 from the Institute of Medicine Committee on Women's Health Research recommended 1) the government ensure adequate participation of women in trials and analyses and 2) reporting of data, both efficacy and adverse effects, by sex [14]. The availability of such data will inform future guidelines and facilitate the translation of research findings into practice. The following recommendations were proposed for future cardiovascular trials in women [14]: include equal representation of women and men; limit exclusion criteria and remove the upper age limit to improve the generalizability of results and the projection of effectiveness in clinical practice; conduct and publish gender-specific analyses for both efficacy and safety; conduct cost-effectiveness analysis for both genders; publish gender-specific data; document non-adherence to interventions according to gender; and, conduct gender-specific power calculations. The present study demonstrated a steady and significant increase in the proportion of women recruited for RCTs on statins as well as in the average age of participants.

Both female sex and advanced age has been identified as predisposing factors for statin-associated myopathy among other factors [16]. Data on adherence to statin therapy from "real world settings" (clinical practice) demonstrated that both female sex and advanced age are predisposing factors for non-adherence [16]. In 2001, a systematic review [26] evaluated whether the percentage of elderly persons and women in published clinical trials of acute coronary syndromes has increased and how this enrolment compared with disease prevalence. This review primarily included English-language articles from January 1966 to March 2000 regarding myocardial infarction, unstable angina, or acute coronary syndromes from MEDLINE and Cochrane databases. Estimates of community-based myocardial infarction rates were obtained from the National Registry of Myocardial Infarction and the Worcester Heart Study. The number of published RCTs with explicit age exclusions was demonstrated to decline from 58% during the period from 1966-1990 to 40% during 1991-2000. Trial enrolment of patients aged 75 years or older increased from 2% for studies published during the period from 1966-1990 to 9% during 1991-2000, but remained well below their representation among all patients with myocardial infarction (37%) in the United States. Enrolment of women has risen from 20% for studies published during the period from 1966-1990 to 25% during 1991-2000, but remained well below their proportion of all patients with myocardial infarction (43%) in the United States. The present analysis also concluded that the percentage of women enrolled in RCTs of statins increased over time but was still significantly below 50% and that the average age of the participants increased significantly between 1990 and 2010.

A gender gap has also been observed not just in clinical research but in evidence-based guidelines development as well. The incorporation of gender data into evidence-based medicine is the next step to be addressed; for example, despite well-recognized gender differences in coronary heart disease management in UK critical care units, the UK National Health Service guidelines for management are not gender-specific [15]. As another example, the 2007 American Heart Association guidelines for cardiovascular disease prevention in women were established based on results from randomized clinical trials; however, of the 156 trials considered in the development of the guidelines, 20 trials enrolled only men [23]. Sex-specific results were discussed in only 31% of primary trial publications [23]. The level of representation for women in RCTs should be adequate to ensure that evidence-based sex-specific recommendations are applicable for women.

In conclusion, this study demonstrated significant progress in the inclusion of women in RCTs on statins. This finding

reflects the efforts of different agencies and groups to increase the representation of women in clinical trials. Despite significant improvement in participation and recruitment of women into RCTs, additional clinical investigations of gender differences in pathophysiology, response to treatment and adherence to treatment protocols are needed in order to eliminate fundamental inequalities between men and women in the treatment of disease. Ideally, the proportion of enrolment for women in mixed-gender trials should be 50% of the total cohort; however, the present study and previous studies illustrated that this number is still significantly below 50% despite improvements in enrolment. Exploring gender differences is a driving force for ensuring that biomedical research is conducted on women and for raising awareness about the biological and physiological differences between men and women [27]. In the era of personalized medicine, greater attention to gender differences in drug disposition is crucial as a platform for therapeutics development and utilization [28]. At this juncture, attention to the impact of gender differences on the pathophysiology and management of prevalent diseases, such as cardiovascular diseases and diabetes, is needed. This calls for further study to determine the causes of possible gender disparities in order to tailor interventions for each risk factor while addressing the possible impacts of gender differences. Also, it is important to disseminate this gender/sex specific data to reduce gender disparities in preventive care and improve clinical outcomes for women.

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Appendix 1 - List of MeSH that utilized for search

MeSH – medical subject heading

Humans
 Male
 Female
 Adult
 Double-Blind Method
 Therapeutic Use
 Hydroxymethylglutaryl-CoA Reductase Inhibitors
 Anticholesteremic Agents
 rosuvastatin, atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin
 Cholesterol
 LDL
 Lipids
 Hypercholesterolemia
 Cardiovascular Diseases
 Myocardial Infarction
 Coronary Disease
 Myocardial Ischemia
 Heart Failure
 Angina Pectoris
 Carotid Disease
 Cerebral Hemorrhage
 Cerebral Infarction
 Transient Ischemic Attack

Stroke
 Arteriosclerosis
 Pulmonary Embolism
 Venous Thrombosis
 Peripheral Vascular Diseases

Appendix 2 – Database (PubMed) search strategy and selection of the studies

The limits: RCTs on adult human beings in English-language publications.

The date for search: between January 1, 1990 and December 31, 2010.

Citations obtained from combination use of MeSH terms before exclusion = 328

Exclusion criteria: not mutually exclusive

Citations deleted due to less than 6 months duration of study = 89

Citations deleted due to sample size smaller than 500 patients = 72

Citations deleted due to measured primary endpoint was not cardiovascular outcome = 137

Citations deleted due to repeat publication of the same RCT = 23

Total citations included in analysis = 30 studies

Appendix 3 – List of RCTs included in the analysis

1990 – 1999

EXCEL[29], 4S [30], REGRESS [31], CARE [32], PREDICT [33], LIPID [34], FLARE [35], ACAPS [36], WOSCOPS [37], AFCAPS [38]

2000 – 2010

HPS [39], PROSPER [40], ASCOT-LLA [41], CARDS [42], PREVENT IT [43], ALLIANCE [44], 4D [45], A-Z [46], REVERSAL [47], PROVE IT [48], TNT [49], IDEAL [50], MEGA [51], ASPE [52], SPARCL [53], CORONA [54], JUPITER [55], GISSI-HF [56], METEOR [57], SEARCH [58]