Reporting of gender-related information in clinical trials of drug therapy for myocardial infarction

Evidence

Études

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Abstract

Background: Concern has been expressed that women are not adequately represented in clinical trials evaluating treatments for medical conditions they commonly experience. This study was designed to assess the reporting of data on women in recently published trials of drug therapy for myocardial infarction, including those funded by an agency with a gender-related policy.

Methods: All randomized controlled trials and meta-analyses of drug therapies for myocardial infarction published in *The New England Journal of Medicine, The Lancet, The Journal of the American Medical Association,* the *Annals of Internal Medicine* and the *British Medical Journal* from January 1992 to December 1996 were evaluated. On preliminary review, 102 articles met the inclusion criteria; these were reviewed in detail, and 59 were excluded. Two reviewers independently extracted gender-related information from the 43 articles; discrepancies were resolved by consensus.

Results: Women represented up to 48% of the trial participants (mean 24.1%). In the trials funded by an agency with a gender-related policy, only 16.8% of participants, on average, were women. Of the 43 articles in the sample, only 14 (32%) provided gender-related results. Funding from an agency with a gender-related policy did not affect the reporting of gender-related information. Subgroup analyses were provided for 14 (32%) of the 43 trials, including 2 (29%) of 7 trials funded by an agency with a gender-related policy. Of the 12 trials that included interaction analyses (excluding the 2 trials in which secondary analyses were conducted specifically to identify differences between women and men), 7 (58%) conducted an interaction analysis to determine if women responded differently than men; for one of these the interaction analysis was for a secondary outcome measure (drug safety). Only 5 (12%) of the 43 articles mentioned the differences between men and women in the Discussion section; 2 of these were studies that used secondary analyses to examine sex differences. Of the 5, only 1 was funded by an agency with a gender-related policy.

Interpretation: Women were poorly represented in the randomized controlled trials in this sample, regardless of whether the trials were funded by an agency with a gender-related policy. Structured reporting of gender-related information for clinical trials may improve the quality of information available about women and therefore facilitate the application of research findings to the care of women.

Résumé

Contexte : On pense que les femmes ne sont pas représentées comme il se doit dans les études cliniques qui visent à évaluer les traitements de problèmes médicaux fréquents chez elles. Cette étude visait à évaluer la présentation de données sur les femmes dans les études cliniques publiées récemment qui portaient sur la pharmacothérapie des infarctus du myocarde, y compris les études financées par un organisme qui a une politique sur les questions spécifiques aux sexes.

Méthodes : On a évalué toutes les études contrôlées randomisées et les méta-analyses portant sur des pharmacothérapies pour traiter l'infarctus du myocarde qui ont été publiées dans *The New England Journal of Medicine, The Lancet,*

The Journal of the American Medical Association, les *Annals of Internal Medicine* et le *British Medical Journal* de janvier 1992 à décembre 1996. Une étude préliminaire a révélé que 102 articles satisfaisaient aux critères d'inclusion. On a étudié ces articles en détail et l'on en a exclu 59. Deux examinateurs ont extrait des 43 articles, chacun de leur côté, des renseignements spécifiques aux sexes et les divergences de vues ont été réglées par consensus.

Résultats : Les femmes ont représenté jusqu'à 48 % des participants aux études (moyenne de 24,1 %). Dans les études financées par un organisme doté d'une politique sur les questions spécifiques aux sexes, les femmes représentaient 16,8 % seulement des participants en moyenne. Sur les 43 articles contenus de l'échantillon, 14 (32 %) seulement présentaient des résultats spécifiques aux sexes. Le financement provenant d'un organisme doté d'une politique sur les questions spécifiques aux sexes n'a pas joué sur la présentation de rapports sur les aspects spécifiques aux sexes. Des analyses par sous-groupes ont été fournies dans 14 (32 %) des 43 études, dont deux (29 %) des sept études financées par un organisme doté d'une politique sur les questions spécifiques aux sexes. Sur les 12 études comportant des analyses d'interaction (et excluant les deux études au cours desquelles on a effectué des analyses secondaires spécifiquement pour définir des différences entre les femmes et les hommes), on a procédé à une analyse d'interaction dans sept (58 %) cas pour déterminer si les femmes réagissaient différemment des hommes. Dans un cas, l'analyse d'interaction a porté sur une mesure de résultat secondaire (sûreté du médicament). Seulement cinq (12 %) des 43 articles mentionnaient les différences entre hommes et femmes dans la section sur la discussion et il s'agissait, dans deux cas, d'études au cours desquelles on a utilisé des analyses secondaires pour examiner les différences entre les sexes. Sur les cinq études en cause, une seulement était financée par un organisme doté d'une politique sur les questions spécifiques aux sexes.

Interprétation : Les femmes étaient faiblement représentées dans les études contrôlées randomisées de l'échantillon, que les études aient été ou non financées par un organisme doté d'une politique sur les questions spécifiques aux sexes. La production de rapports structurés sur des renseignements spécifiques aux sexes dans le cadre d'études cliniques peut améliorer la qualité des renseignements disponibles sur les femmes et faciliter par conséquent l'application des résultats de recherche aux soins dispensés aux femmes.

Concern has been expressed that women are not adequately represented in clinical trials that evaluate treatments for medical conditions they commonly experience,[1,2] which has resulted in the suggestion that women are "systematically discriminated against in medical research."[3] Because prescribing decisions are based on scientific evidence published in the medical literature, the inadequate representation of and reporting on women in clinical trials may hinder the ability of physicians to apply study findings properly to their clinical practices. The underrepresentation of women has implications because physiologic and social differences may result in women responding differently than men to medical interventions, especially drugs. These differences may be especially relevant in older age groups because of the higher proportion of women in the elderly population.[4] Furthermore, relative to men, women take more medication,[5] have more coexisting conditions and weigh less.[6] These factors increase the likelihood that women will respond differently to drug therapies.

The United States Food and Drug Administration (FDA) has recognized the need for scientific evidence to optimize drug treatment for women and has taken steps to ensure that pre-marketing drug studies evaluate the responses of women.[7] In 1988 the FDA introduced guidelines calling for traditionally excluded patient groups, such as women and the elderly, to be routinely evaluated during the new drug application process. In 1993 the FDA revised its guidelines,[8] recommending that data be analysed by sex to assess the potentially different responses of men and women. These revisions reversed the 1977 policy that recommended excluding women of childbearing age from early clinical trials.[8] The changes underscore the FDA's attempt to promote the participation of women in clinical trials. Health Canada is currently reviewing its regulatory guidelines to ensure the appropriate inclusion of women in clinical trials.[9]

Similarly, major national funding agencies, including the US National Institutes of Health (NIH)[10] and the

Medical Research Council of Canada (MRC),[11] have recently developed guidelines to ensure that the trials they fund include women or that their exclusion is justified. The NIH has the most comprehensive guidelines of any funding agency.[12] The Medical Research Council in the United Kingdom does not have specific gender-related guidelines but does strongly recommend that clinical trials be conducted in such a manner that the results can be generalized beyond the research setting.[13]

Although efforts to include women in clinical trials have been met with enthusiasm by the public and the media and have been generally accepted by the scientific community,[14] it is not clear what impact this acceptance has had on the information about women that is published in reports. We conducted a systematic review of randomized controlled trials (RCTs) of drug therapies for myocardial infarction published in 5 leading general medical journals to assess the reporting of data on women.

Methods

Included in our study were all RCTs and meta-analyses of drug therapies for patients with myocardial infarction published between January 1992 and December 1996 in 5 leading general medical journals (*The New England Journal of Medicine*, *The Lancet*, *The Journal of the American Medical Association*, the *Annals of Internal Medicine* and the *British Medical Journal*). Articles were identified by reviewing the contents list of each issue of each journal during the period of the study and by conducting an original MEDLINE search. The search identified a total of 102 articles for potential inclusion.

All 102 articles were retrieved and independently reviewed by 2 of us (J.P.C. and V.P.) to identify all RCTs of drugs for the treatment of myocardial infarction in adults. After a detailed review of the articles, 59 articles were excluded: 7 were not original investigations, 34 were not RCTs, 10 were not for myocardial infarction and 8 were not drug efficacy trials. The remaining 43 articles became our study sample (Appendix 1).

Characteristics of articles

For each of the 43 articles we evaluated 6 characteristics: the drug therapies evaluated, the source of acknowledged financial support, the funding agency and whether it had a policy regarding the inclusion of women, the number of patients, the age and sex distribution of the patients and the reporting of gender-related data.

Gender-related policies of funding agencies

Information about whether funding agencies had gender-related policies was obtained by a variety of means, including a MEDLINE search, an Internet search and direct contact with the agencies. We analysed separately the presentation of results related to sex in trials funded by agencies with and without gender-related policies.

Reporting of gender-related data

For each of the 43 articles, 2 trained reviewers (J.P.C. and V.P.) examined the way in which data about men and women were reported. Discrepancies were resolved by consensus involving 3 of us (J.P.C., V.P. and P.A.R.). The quality of the gender-related content was rated according to FDA,[8] NIH[10] and MRC[11] guidelines for reporting information about women. Specifically, we evaluated the reporting of information on the number of men and women in the trial,[8,11,12] the use of subgroup analyses by sex,[11,12] the use of interaction analyses to determine whether there were differences in the responses of men and women[8,12] and the discussion of gender-related issues.

Statistical analyses

Descriptive statistics were used to assess the presentation of gender-related information in the trials. Analyses were performed using SPSS (System for Windows, version 7.5.1.; SPSS Inc., Chicago, 1996).

Results

Characteristics of articles

Of the 43 articles in our sample, 12 (28%) were published in *The New England Journal of Medicine*, 20 (46%) in *The Lancet*, 5 (12%) in *The Journal of the American Medical Association*, 2 (5%) in the *Annals of Internal Medicine* and 4 (9%) in the *British Medical Journal*. In total, 53 drug therapies were evaluated. Thrombolytic agents (studied in 22 [51%] of the 43 studies) and angiotensin-converting enzyme inhibitors (in 7 [16%]) were most frequently evaluated (Table 1).

Gender-related policies of funding agencies

Support was acknowledged in 37 (86%) of the 43 articles. For these 37 studies, funding came from industry in 17 (46%), from a North American government in 5 (14%), from a non-North American government in 4 (11%) and from a combination of industry and government in 11 (30%). Seven (16%) of the 43 articles were funded by an agency with a gender-related policy, the NIH in all cases (Table 2).

Gender-related analyses

All 43 articles reported the number of participants in their trials; in total there were 641 178 participants. The median age was relatively young (62 years). Forty-one (95%) of the reports provided no age information by sex, and 5 (12%) provided no information about the sex distribution of their samples. Thirty-eight (88%) of the articles described the sex distribution of the samples; for 37 of these, women were included in the trial. Women represented from 0% to 48% of trial participants (mean 24.1%). The weighted mean proportion of women in the trials was 20.8%. In trials funded by an agency with a gender-related policy, women represented from 15.0% to 18.7% of the trial participants (mean 16.8%).

Table 1: Characteristics of reports of clinical trials of drug therapy for myocardial infarction published between 1992 and 1996

Characteristic	Funding agency; no. (and %) of studies		
	Gender-related policy in place *n = 7*	No gender-related policy in place *n = 36*	Overall *n = 43*
Study size			
<100	0	1 (3)	1 (2)
100–499	1 (14)	7 (19)	8 (19)
500–4999	4 (57)	13 (36)	17 (40)
>5000	2 (28)	15 (42)	17 (40)
Location			
Europe	0	18 (50)	18 (42)
Multicontinent	0	13 (36)	13 (30)
North America	7 (100)	3 (8)	10 (23)
Other	0	2 (6)	2 (5)
Drug evaluated*			
ACE inhibitors	1 (14)	6 (17)	7 (16)
Antiarrhythmic agents	3 (43)	0	3 (7)
Anticoagulants	0	6 (17)	6 (14)
Antiplatelet agents	0	4 (11)	4 (9)
ß-blockers	2 (28)	0	2 (5)
Calcium-channel blockers	1 (14)	0	1 (2)
Nitrates	0	3 (8)	3 (7)
Thrombolytic agents	2 (28)	20 (56)	22 (51)
Miscellaneous	0	5 (14)	5 (12)

Note: ACE = angiotensin-converting enzyme.
*Some studies evaluated more than one drug.

Only 14 (32%) of the 43 articles provided gender-related results; in 2 of these, secondary analyses were conducted because the difference in responses between men and women was the major outcome measure. Funding by an agency with a gender-related policy did not affect the use of subgroup analyses: subgroup analyses were conducted in 14 (32%) of the 43 trials overall and in 2 (28%) of the 7 trials funded by the NIH.

Excluding the 2 trials that used secondary analyses to examine the effect of sex on response, 12 trials conducted subgroup analyses. Of these, 7 (58%) included an interaction analysis to determine if the responses of men and women were different; one of these interaction analyses was for a secondary outcome measure (drug safety). The 7 articles including an interaction analysis represented only 16% of the total sample. Funding from an agency with a gender-related policy did not affect the reporting of interaction analyses: interaction analyses were provided for only 1 (14%) of the 7 trials funded by an agency with such a policy.

Only 5 (12%) of the 43 articles made any mention of gender-related issues in the Discussion section; 2 of these were the studies that used secondary analyses to examine differences between men and women. One of the 5 trials was funded by an agency with a gender-related policy. Of the 5 studies, 2 included both subgroup and interaction analyses, and 1 included only subgroup analyses. A summary of the reports that included gender-related analyses is presented in Fig. 1.

Table 2: Funding agency information for the clinical trials

Agency	Location	No. funded	Policy on gender-related information
National Institutes of Health	United States	7	Yes
British Heart Foundation*	United Kingdom	6	No
Medical Research Council*	United Kingdom	2	No
Swedish National Association on Heart and Chest Diseases	Sweden	2	No
Associazione Nazionale Medici Cardiologi Ospedalieri	Italy	1	No
European Economic Community Directorate General XII	European Economic Community	1	No
Netherlands Thrombosis Foundation	Netherlands	1	Not available
Scottish Home and Health Department	United Kingdom	1	No
Other support		17	Not applicable
Support unacknowledged		6	Not applicable

*One study supported by more than one agency.

Interpretation

Although guidelines have been established by some funding agencies to encourage the inclusion and adequate representation of women in clinical drug trials, the influence of these policies on the published reports of clinical trials is not evident. Our results suggest that women continue to be poorly represented in clinical trials. Even when women are included, the gender-related information that is published is inadequate. It is imperative, therefore, that steps be taken to improve the quality of the information related to women in reports of RCTs. This could be facilitated by structured reporting of gender-related information, an approach consistent with the move toward structured reporting of RCTs.[15]

We found that women, in particular older women, were underrepresented in the RCTs of myocardial infarction therapy reported in leading general medical journals between 1992 and 1996. In the trials we analysed the overall percentage of women was very low, only 20.8%. The poor representation of elderly patients in the articles in our sample (for which the median age was 62 years) relative to women's predominance in the older age groups of the general population suggests that older women are a group most likely to be underrepresented. Gurwitz and associates[2] evaluated the exclusion of elderly people and women from RCTs of drug therapy for acute myocardial infarction in trials published up to 1991. Of 150 920 participants in the 214 trials they identified, only 20% were women. The underrepresentation of women is of particular concern given that the short-term prognosis after myocardial infarction is worse for women than for men and the relative risk of death after myocardial infarction is greater for women than for men.[16] According to FDA guidelines, "patients included in clinical trials should in general reflect the population that will receive the drug when it is marketed."[8] If clinical trials were complying with this recommendation, more women than men and more elderly patients would be participating.

The number of trials that provided basic subgroup information by sex was disappointing. Yusuf and colleagues[17] state that patient characteristics such as sex are ideally suited for subgroup analyses. The final report of the Advisory Committee on Women in Clinical Trials of the MRC[11] suggested that if information was provided by sex for each trial, it would be possible to conduct meta-analyses to determine how women respond to the particular drug therapy under investigation. Subgroup analyses may provide information about underrepresented groups such as women, in particular older women.

Despite the need for interaction analyses to determine if women respond differently to therapy from men, we identified few published trials that examined the effects of interaction by sex. Descriptive statistics are not adequate for this purpose. If different responses are suspected for men and women, there should be a move to "increase the size — and the cost — of clinical trials necessary for statistically valid subgroup analyses by gender."[3] Using this approach will allow the responses of women to drug treatments to be compared with the responses of men. Russek-Cohen and Simon[18] have suggested methods to conduct appropriate interaction analyses.

We found that gender-related issues were seldom mentioned in the Discussion sections of the trial reports (in only 5 [12%] of the reports). Even among the 7 articles that reported interaction analyses, only 3 mentioned these findings in the Discussion, and 2 of these were the articles in which secondary analyses of differences between men and women were the main focus. In each of the trials women constituted no more than one-quarter of the study population, but none of the reports discussed the fact that the underrepresentation of women might limit the degree to which the trial results could be applied to a general population. Women constitute the group to which a large proportion of drug therapy for myocardial infarction should be targeted, and information about them should be reflected in the comments of these trials.

Limitations

Because we evaluated only articles published in 5 leading general medical journals, our findings may not reflect the quality of reports published in other journals. It is also possible that subgroup analyses by sex for the trials we examined were published separately. The number of trials in our sample that were funded by an agency with a gender-related policy was small and may not accurately represent all funded clinical trials. Similarly, because we evaluated

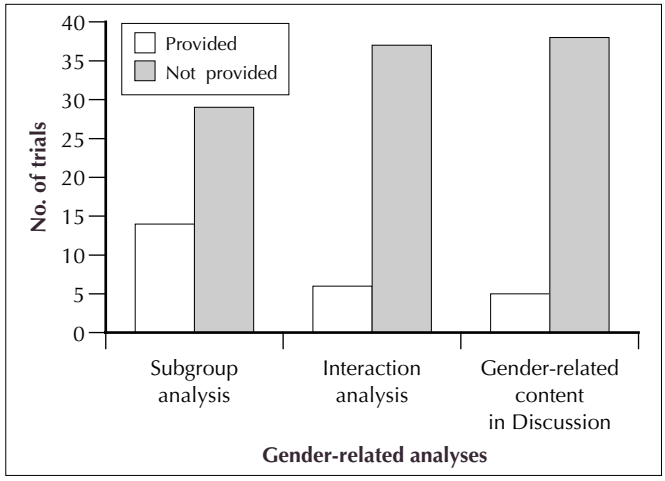

Fig. 1: A comparison of clinical trials of drug therapy for myocardial infarction published between 1992 and 1996 on the basis of whether gender-related analyses were provided.

trials of drug treatments for myocardial infarction, our results may not apply to other medical conditions. However, cardiovascular disease is the leading cause of death in women. If clinical trials relating to medical conditions are to begin including a representative number of women, myocardial infarction is an obvious place to start.

Gender-related policies are relatively new, and it is possible that the trials in our sample were conducted before their effects could be felt. However, the NIH, the only funding agency in our sample with a gender-related policy, has been promoting the inclusion of women in clinical trials since 1987. Although we hope that additional policies will lead to a "trickle-down effect" in future trials, our work suggests that additional measures are necessary before such policies will have a substantial effect on the published reports of clinical trials.

A call for structured reporting of gender-related information

Journal editors can promote the reporting of gender-related data by requiring a structured presentation of such information when results of clinical trials are published. One possible structure is outlined in Table 3. The published reports of any clinical trials evaluating therapy for a condition experienced by women should provide specific information as follows. First, the distribution of men and women should be stated, and the number of women included in the trial should reflect the patient population likely to use the treatment. Second, subgroup analyses should be provided to facilitate meta-analysis. Third, if there is an adequate number of women in the clinical trial, interaction analyses should be conducted to determine if women respond differently than men. Finally, gender should be discussed in any published report of clinical trials of drug therapies that women are likely to use. If women are inadequately represented in the trial, this underrepresentation should be discussed. If differences between men and women are discovered, they should be described. Requiring structured reporting of gender-related data in clinical trial reports may improve the quality of information available on how best to use therapies to treat women in clinical practice.

Table 3: Suggested structured reporting of gender information for reports of clinical trials

Characteristic	Description
Sex distribution	The proportion of women in the trial should reflect the patient population likely to receive the therapy
Subgroup analyses	Data should be presented by subgroups of men and women to allow for meta-analyses
Interaction analyses	Interaction analyses of subgroups should be conducted to determine differences between men and women
Gender-related content in discussion	Gender-related information should be discussed either to state limits to which the results can be generalized to populations outside the clinical trial or to highlight the differences in responses of men and women

Conclusions

We found that women were poorly represented in the RCTs in our sample, whether or not the trial was funded by an agency with a gender-related policy. We have recommended 2 strategies to deal with this problem. The first is to make sure that the people evaluated in clinical trials reflect the population that will likely receive the therapy; thus, women should be adequately represented in the clinical trials of drug therapies that will be used by women. The second is to improve the reporting of gender-related information from the trials that do include women. This could be achieved by implementing structured reporting of gender-related information. With these strategies in place, physicians will be able to apply more accurately the findings of clinical studies to their patients.

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Appendix 1: Clinical trials of drug therapy for myocardial infarction published between 1992 and 1996 and meeting the study criteria*

Third International Study of Infarct Survival (ISIS-3) Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs anistreplase and of aspirin plus heparin vs aspirin alone among 41 299 cases of suspected acute myocardial infarction. *Lancet* 1992;339:753-70.

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