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Representation of Elderly Persons and Women in Published Randomized Trials of Acute Coronary Syndromes

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DEMOGRAPHIC CHANGES IN THE US population have resulted in an increase in the numbers of elderly patients and women seeking treatment for cardiovascular disease. In 1975, 24% of patients hospitalized for myocardial infarction (MI) were at least 75 years old. By 1995, this percentage had risen to 37%.¹ Similarly, the percentage of women MI patients has risen from 35% in 1975 to 43% in 1995.¹ Beyond their high prevalence in the MI population, elderly persons and women fare worse following cardiac events. For example, up to 60% of MI deaths occur in patients aged 75 years or older.² Elderly patients and women also experience more MI complications including heart failure, shock, and ventricular rupture.³ Despite these higher risks, published cardiovascular clinical trials have historically underenrolled elderly persons and women relative to younger persons and men.^{2,4}

Awareness of these potential biases has stimulated government efforts designed to encourage clinical research to be more representative of the treated population. In 1989, the US Food and Drug Administration (FDA) published *Guideline for the Study of Drugs*

Context Elderly persons and women were underrepresented in randomized controlled trials (RCTs) prior to 1990. Since then, efforts have been made to correct these biases, but their effect is unclear.

Objective To determine whether the percentage of elderly persons and women in published clinical trials of acute coronary syndromes has increased and how this enrollment compared with disease prevalence.

Data Sources The MEDLINE and Cochrane databases were searched for English-language articles from January 1966 to March 2000 regarding myocardial infarction, unstable angina, or acute coronary syndromes. Additional data sources included meta-analyses, review articles, and cardiology textbooks. Estimates of community-based myocardial infarction rates came from the National Registry of Myocardial Infarction and the Worcester Heart Study.

Study Selection Published RCTs of acute coronary syndrome patients were included and trials enrolling 50 patients or fewer, those without clinical end points, papers published in a language other than English, and unpublished manuscripts were excluded. Of 7645 studies identified, 593 RCTs were selected for review.

Data Extraction The RCTs were abstracted by 2 of the authors for year of publication, source of support (ie, funding), pharmacotherapy, study phase, number of study sites, trial location, number of patients, mean age of the study population, and any age exclusion criteria for enrollment.

Data Synthesis The number of published RCTs with explicit age exclusions has declined from 58% during 1966-1990 to 40% during 1991-2000. Trial enrollment of patients aged 75 years or older increased from 2% for studies published during 1966-1990 to 9% during 1991-2000, but remains well below their representation among all patients with myocardial infarction (37%) in the United States. Enrollment of women has risen from 20% for studies published between 1966-1990 to 25% during 1991-2000, but remains well below their proportion of all patients with myocardial infarction (43%) in the United States.

Conclusions Attempts at making cardiovascular RCTs more inclusive appear to have had limited success; thus, women and elderly persons remain underrepresented in published trial literature relative to their disease prevalence. Because safety and efficacy can vary as a function of sex and age, these enrollment biases undermine efforts to provide evidence-based care to all cardiac patients.

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Likely to be Used in the Elderly, which stated that the population studied should reflect the population likely to be treated.⁵ Similarly, in 1990 the National Institutes of Health noted that women had been excluded from clini-

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cal trials without satisfactory explanation.⁶ In 1993, the National Institutes of Health Revitalization Act issued guidelines for the inclusion of women as subjects in clinical trials.^{7,8} These guidelines stated that it is “imperative to determine whether the intervention or therapy being studied affects women differently.”

We investigated the degree to which growing public and governmental awareness of sex and age biases altered the “representativeness” of cardiovascular clinical trials. Specifically, we examined trends among published randomized controlled trials (RCTs) of acute coronary syndromes (ACS) over the last 25 years to determine whether the percentage of women and elderly persons has increased and how this enrollment compared with disease prevalence.

METHODS

Systematic Review and Study Selection

A literature search using MEDLINE and the Cochrane database of Clinical Trials identified studies published from January 1966 to March 2000. Relevant studies in MEDLINE were identified using the MeSH terms *myocardial infarction*, *unstable angina*, or *acute coronary syndromes* and were limited to the subject headings *clinical trials (phase 1, 2, 3, and 4)*, *controlled clinical trials*, and *randomized clinical trials*. Relevant studies in the Cochrane database were identified by the subject headings *myocardial infarction*, *unstable angina*, and *acute coronary syndromes*. The search was supplemented by review of meta-analyses, review articles, and major cardiology textbooks. We identified 7645 potential studies through this initial review process.

Abstracts from all initially identified studies were reviewed for potential inclusion in the study. We included those RCTs of pharmacotherapies and primary angioplasty used in the in-hospital treatment of ACS (defined as unstable angina, acute MI, or both). Exclusion criteria consisted of trials enrolling fewer than 50 patients, those

solely reporting nonclinical end points, those published in non-English-language publications, and unpublished manuscripts. After applying these exclusion criteria, our study included 593 unique cardiovascular RCTs.

Data Collection

Included trials were abstracted for year of publication, source of support (ie, funding), pharmacotherapy, study phase, number of study sites, trial location, number of patients, mean age of the study population, and any age exclusion criteria for enrollment. Our prospectively defined primary end points were the percentage of women enrolled and the percentage of enrolled patients who were at least 75 years of age. While definitions of “elderly” vary, this age cut point has been used in multiple prior studies. Distributions by sex were reported in 528 of the trials. The percentage of patients aged 75 years or older was reported in 268 trials and calculated in an additional 139 trials from mean ages and SDs.

The initial data abstraction by one reviewer (P.Y.L.) was validated by a 10% audit by a separate reviewer (S.K.P.) to confirm appropriateness for study inclusion, as well as the accuracy of abstracted data. No disagreement was found between reviewers regarding appropriate inclusion, and only 1 disagreement was found for a trial’s total sample size. Agreement between reviewers was also high for the mean age of study patients and percentage of patients aged 75 years or older and for the percentage of trials with explicit age exclusions (κ range, 0.92-0.95).

Data Analysis

Trial characteristics were reported as percentages of the overall trial population. Differences were assessed by *t* test for continuous variables and by χ^2 test for categorical variables and were considered significant at $P = .05$. Our primary analyses centered on determining whether enrollment of elderly persons and women in RCTs of ACS increased since 1990 compared with those conducted from 1966 through 1990.

We secondarily examined trends in study enrollment among the first and second half of this past decade. Because studies performed in the Veterans Affairs system were almost exclusively performed in men, we separated these studies from the overall results when assessing degree of enrollment of women.

Using multivariable regression analysis, we also investigated the independent influence of trial sample size, class of drugs under study, source of funding (government vs industry), study location (US vs non-US), year of publication, and whether the study was a single-center or a multicenter trial. Linear regression was used to assess the degree to which study characteristics were associated with the percentage of women included in the trial. Because the majority of trials failed to enroll any patients aged 75 years or older (thereby skewing the data), logistic regression was used to determine characteristics associated with enrolling any elderly patients. During model development, we tested for nonlinear associations and for the potential influence of out-of-range values. SAS version 8.1 (SAS Institute, Cary, NC) was used for all analyses.

Finally, we compared the percentage of elderly persons and women enrolled in trial populations with those potentially eligible in community-based MI patient populations. In this comparison, we excluded 59 trials that enrolled only unstable angina patients. Comparisons were made for both the overall MI trial population as well as that of MI trials performed at sites in the United States only. Estimates of community-based MI populations came from data from the National Registry of Myocardial Infarction (NRMID)⁹ and from the Worcester Heart Study populations.¹

RESULTS

Study Characteristics

Characteristics of the 593 ACS trials are summarized in TABLE 1. Just over half of the trials were published since 1990. The majority of the trials were multi-

center and performed in a single country. Sites in the United States participated in about a third of all ACS trials. Industry funding was the most common source of reported study support. More than 70% of trials enrolled fewer than 500 patients with trial enrollment increasing over time from a median of 181 patients per trial in the period 1966 through 1970 to 309 patients per trial in the period 1995

through 2000. Thrombolytic agents were the most common therapeutic class investigated, followed by anti-thrombotics. The majority of trials were performed in patients with MI.

Representation of Elderly Patients in Trials

The percentage of RCTs of ACS with explicit protocol exclusions for age actually increased over time, reaching a

high of 66.3% during the 1980s (TABLE 2). After 1990, explicit age exclusions declined. The most common age cutoff among trials with an explicit age exclusion was 75 years. Although some trials did not have protocol-based age exclusions, they still failed to enroll any elderly patients. For example, in the period 1966 through 1990, only 19% of trials enrolled any patients aged 75 years or older. After 1990, enrollment of elderly patients improved. However, even among ACS trials published in the period 1996 through 2000, more than half still failed to enroll at least 1 patient aged 75 years or older (Table 2).

Between 1966 and 1990, patients aged 75 years or older accounted for only 2% of all patients enrolled in ACS trials. Since 1990, enrollment of elderly patients in RCTs of ACS has risen to 9%. Finally, in just those studies published after 1995 (n=141) or those published studies that initiated patient recruitment after 1995 (n=29), the percentage of elderly patients enrolled increased to 10% and 13%, respectively. While these are positive trends, the demographics of patients hospitalized with ACS have also changed over time, altering the trial recruitment pool. For example, FIGURE 1A displays a consistent, wide gap between the proportion of MI patients in the United States aged 75 years or older and their enrollment in all RCTs of MI. A similar gap between MI patient population and trial enrollment exists among the subset of trials performed exclusively in the United States. After accounting for trial characteristics, trial enrollment of elderly patients has not improved more rapidly in US-only trials than in non-US trials ($P=.86$ for interaction).

Representation of Women in Trials

The percentage of women enrolled in RCTs of ACS increased from 20% during the period 1966 through 1990 to 25% during the period 1991 through 2000 ($P<.001$). Among the most recent trials published after 1995 and those published trials initiating enrollment af-

Table 1. Characteristics of Trials (N = 593)*

	Trials, No. (%)	Patients, No.	Age ≥ 75 y, %	Women, %
Publication years				
1966-1970	28 (4.7)	7400	0.9	19.1
1971-1980	63 (10.6)	40 846	1.2	15.0
1981-1990	202 (34.1)	175 699	3.2	21.6
1991-1995	159 (26.8)	294 620	7.3	24.0
1996-2000	141 (23.8)	201 357	10.3	26.7
All	593	719 922	6.7	23.8
Trial enrollment, No. of patients				
50-99	132 (22.3)	9457	3.2	19.1
100-499	292 (49.2)	67 003	4.1	21.2
500-999	60 (10.1)	40 685	3.3	20.6
1000-4999	79 (13.3)	176 771	4.8	21.8
≥ 5000	30 (5.1)	426 006	9.4	25.9
No. of sites				
Single center	208 (35.1)	35 247	6.2	21.5
Multicenter	385 (64.9)	684 675	6.8	23.9
Location				
No US sites involved	424 (71.5)	341 508	5.8	22.0
US sites involved	169 (28.5)	378 414	7.7	25.7
Therapeutic class†				
Thrombolytic	176 (26.0)	259 179	8.0	24.1
Antithrombotic	103 (15.2)	167 878	8.6	27.0
Antiarrhythmic	80 (11.8)	45 430	7.6	22.6
β -Blocker	70 (10.3)	56 517	3.7	20.6
Antiplatelet	69 (10.2)	91 712	6.9	24.0
ACE inhibitor	49 (7.2)	135 412	9.2	23.6
Primary angioplasty	39 (5.8)	22 511	2.8	21.0
Vasodilator	35 (5.2)	91 986	13.1	23.3
Calcium channel blocker	29 (4.3)	20 692	1.1	19.5
Magnesium	19 (2.8)	64 411	13.8	25.6
Lipid-lowering agent	8 (1.2)	25 294	0	14.8
Funding source				
Industry	224 (37.8)	341 938	7.4	25.2
Government	107 (18.0)	87 583	2.6	18.1
Both	92 (15.5)	219 763	7.9	25.2
Not reported	170 (28.7)	68 348	7.5	20.0
Diagnostic categories				
MI only	465 (78.4)	447 778	5.8	21.5
Unstable angina only	59 (9.9)	13 497	2.2	26.6
Both	69 (11.6)	258 647	12.4	28.5

*ACE indicates angiotensin-converting enzyme; MI, myocardial infarction.

†Total number of observations for therapeutic classes is larger than the total number of trials due to combination trials that included more than 1 therapeutic class.

ter 1995, the percentage of women enrolled increased to 27% and 29%, respectively. However, as was seen among elderly patients, the difference between the percentage of US women with MI and the percentages of women with MI enrolled in RCTs in both the United States and overall has remained fairly constant over time (Figure 1B). Additionally, a nearly linear relationship was noted between the mean age of patients enrolled in clinical trials and the percentage of women enrolled in these trials (FIGURE 2). Assuming this relationship remained constant, eliminating the age disparity in the study population through targeted enrollment would simultaneously eliminate the gap in the percentage of women enrolled in trials.

Predictors of Trial Enrollment

In our multivariable analyses, year of trial publication and enrollment of more than 5000 patients were the strongest predictors of enrolling any elderly patients and enrolling more women. After controlling for these and other characteristics, antithrombotic and vasodilator trials were significantly more likely to include elderly patients than other therapeutic classes ($P < .05$ for both). Importantly, funding source (government vs industry) and location of the trials (United States vs other) were not

significant predictors of trials that enrolled any elderly patients ($P = .33$ and $.19$, respectively). Funding source was also not a predictor of higher enrollment of women, but studies with sites in the United States did enroll more women ($P < .01$).

COMMENT

The 1990s truly represent the decade of evidence-based cardiovascular medicine, with more trials being published in this decade than in the past 3 decades combined. While these RCTs have been the "evidence base" for cardiovascular care guidelines, they were predominantly conducted in younger (< 75 years) and in male populations. Moreover, elderly persons and women remain highly underenrolled in the published literature. It remains to be seen whether efforts initiated over the past decade to promote inclusion of elderly persons and women in clinical research will eventually be successful.

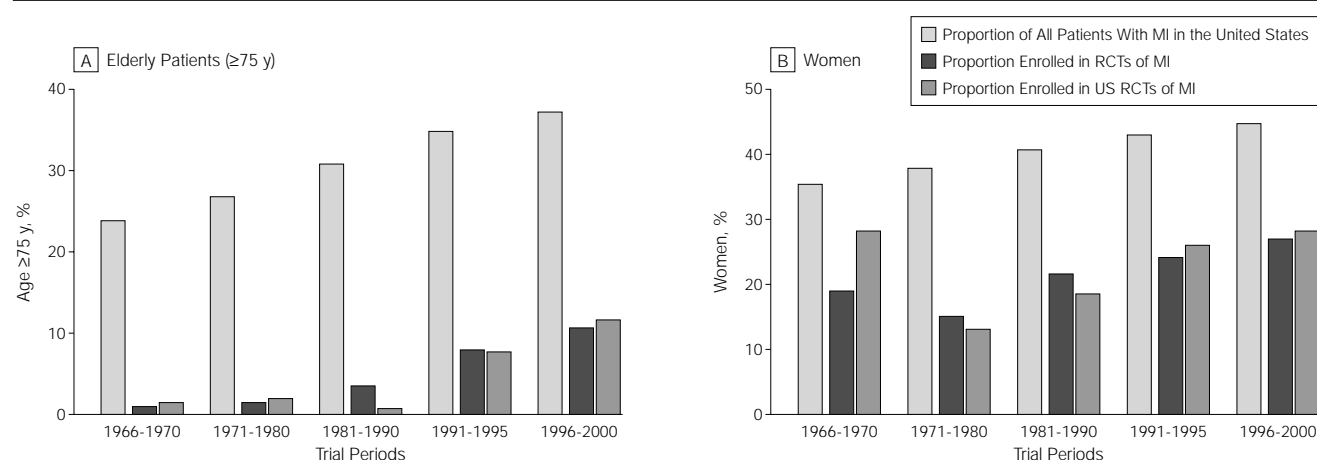
The problems of age- and sex-based biases in cardiovascular RCTs performed prior to 1990 were previously documented by Gurwitz and colleagues.² They found that between 1966 and 1990, more than 60% of MI trials excluded persons older than 75 years. Gurwitz et al and other researchers have also pointed out that women were being systematically underrepresented in cardiovascular clinical trials.^{2,4} However, since the late 1980s, these and other publications have raised the consciousness of the public and the medical community concerning biases against elderly persons and women in clinical research.^{4,10,11} Additionally, beginning in 1989, US regulatory agencies have enacted a series of guidelines and funding criteria explicitly designed to reverse these age and sex biases.^{5,7,8}

A recent review of 52 cardiovascular clinical trials funded by the National Heart, Lung, and Blood Insti-

Table 2. Enrollment and Exclusion of Elderly Patients in Clinical Trials of Acute Coronary Syndromes

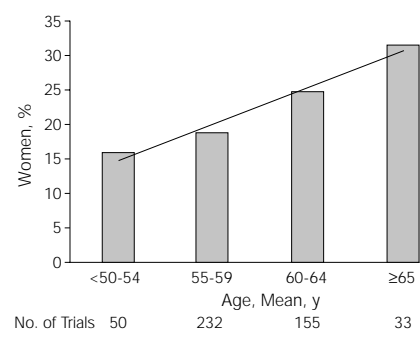
Trial Years	Mean Patient Age, y	Age ≥ 75 y Exclusion, %	Trials Not Enrolling Any Patients Aged > 75 y, %
1966-1970	60.0	32.1	45.0
1971-1980	55.8	42.9	70.7
1981-1990	58.4	66.3	89.4
1991-1995	61.4	47.8	75.9
1996-2000	61.9	31.9	55.2

Figure 1. Representation of Elderly Patients and Women in Randomized Trials of MI



Lightest gray bars based on the Worcester Heart Attack Study.¹ MI indicates myocardial infarction; RCTs, randomized controlled trials.

Figure 2. Trial Populations of Women With Myocardial Infarction, Stratified by Mean Age



Regression line represents the average increase in percentage of women as the average mean age among the trials increases.

tute (NHLBI) gave the first insight into the impact of these trial inclusiveness policies.¹² This study found that, after excluding 2 large single-sex trials of cardiovascular disease (Women's Health Study and Women's Health Initiative), NHLBI-sponsored trials failed to include an appropriate representation of women relative to their disease prevalence.

Our broader analysis examined trial enrollment of women and elderly persons in published RCTs of ACS. Our study also included trials sponsored by government, industry, and foundations, as well as those conducted outside the United States. Consistent with the prior review,¹² we found that both women and elderly persons remain highly underrepresented in the published literature. After accounting for changes in disease demographics, neither group has experienced substantial gains in trial representation (Figure 1).

We also noted that, to date, studies published from sites in the United States were not significantly better than those from sites outside the United States at enrolling elderly persons. Likewise, government sponsorship of a trial was not a significant predictor of more inclusive trial enrollment. This further casts doubts on whether regulatory recommendations and US funding may yet influence trial enrollment patterns. Fi-

nally, we noted that much of the sex disparity in trial enrollment appears to be a byproduct of underenrollment of elderly persons (Figure 2). If efforts to increase enrollment of elderly persons in trials are successful, this may simultaneously eliminate sex disparities.

Given the lag time between the initiation of trial enrollment and eventual publication in a peer-reviewed journal, it remains possible that legislation and regulations have had positive effects and that ongoing clinical trials may actually enroll a higher percentage of women and elderly patients. However, among studies published 5 or more years after FDA regulatory changes or those that initiated enrollment after 1995, women and elderly patients remain underrepresented relative to their disease prevalence (Figure 1). Thus it may take many years for these regulations to have an effect.

The reasons for underenrollment of elderly persons in cardiovascular RCTs remain unclear. Gurwitz et al¹³ and Krumholz et al¹⁴ have postulated that physicians might be reluctant to subject elderly patients to more invasive or risky therapies such as the use of thrombolytics. However, our study paradoxically demonstrated that in certain cases, trials involving more risky therapies (eg, antithrombotics) actually tended to be as likely or more likely to include elderly patients. Others have attributed underenrollment to a perceived difficulty in recruiting or retaining elderly patients in randomized trials. However, existing evidence indicates that elderly patients can be successfully recruited when targeted¹⁵ and appear to be compliant with medication use or follow-up appointments when enrolled.^{16,17} Also, investigators may be reluctant to expose elderly patients with more advanced disease or comorbid illness to experimental therapies. While this concern for patient safety can be appreciated, the net effect of this "protectionism" has been to exclude elderly patients with cardiac disease from evidence-based care.

When treating elderly patients, clinicians must extrapolate from existing trial

data for younger patients—a process that can be fraught with hazards, as demonstrated by recent studies. For example, the benefits of thrombolytic therapy, unequivocally demonstrated in younger patients, has recently been associated with higher short-term mortality in MI patients aged 75 years or older.¹⁸ The SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shock) trial also found that patients younger than 70 years with extensive MIs had a survival benefit with an interventional approach, yet elderly patients fared better with a conservative approach.¹⁹ Therefore, the universal extension of trial results from a younger, mostly male population to women and elderly patients of both sexes may be inappropriate.

Finally, this paucity of information regarding the safety and efficacy of therapies in women and elderly persons may lead some physicians to withhold treatment in these subgroups. Numerous studies have found that women and (more particularly) elderly persons with cardiac disease are less likely to receive evidence-based drugs and interventions.^{14,20,21} The extent to which these undertreatment patterns can be reversed by expanding our knowledge in these important subgroups of patients awaits confirmation.

Limitations

This study excluded both non-English-language trial publications as well as trials with fewer than 50 patients. However, given that larger trials tended to enroll more elderly patients and women, these exclusions most likely make our results conservative. While this study was also limited to cardiovascular trials, reviews in other areas of medicine such as oncology have demonstrated similar results.²² We also examined only the published literature, and, as noted above, ongoing trial enrollment patterns may be different from those completed and published. Finally, because trials rarely publish the characteristics of their screened populations, it was impossible to deter-

mine the degree to which underrepresentation of women and elderly persons can be explained by other exclusion criteria (eg, comorbid illness), patient refusal to participate, or lack of recruitment. Clarification of these reasons should be an important area for future study.

Conclusions

Despite growing awareness in the last decade of potential age and sex biases, there has been only limited improvement in the inclusion of elderly persons and women among cardiovascular RCTs, as evidenced in the published literature. More than half of all re-

cently published trials still failed to enroll any patients aged 75 years or older, and women were consistently enrolled at approximately half of their prevalence in the affected population.

Given that treatment risks and benefits may alter as a function of patient sex and (more particularly) age, regulatory agencies will need to continue to monitor enrollment patterns to ensure that future trials are tested in representative populations. Agencies that fund clinical studies also should provide additional resources to promote enrollment of representative patient populations. These efforts are urgently needed if we are to provide evi-

dence-based care to all cardiac patients.

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Acquisition of data: Lee, Pasquali.

Analysis and interpretation of data: Lee, Hammill, Peterson.

Drafting of the manuscript: Lee, Peterson.

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Statistical expertise: Hammill, Peterson.

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Study supervision: Peterson.

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