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Exclusion of Older Adults and Women from Recent Trials of Acute Coronary Syndromes

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Abstract

Objective—The prevalence of coronary heart disease increases with advancing age. However, there is evidence that older patients and women were underrepresented in coronary heart disease clinical trials prior to the year 2000. To determine whether the participation of the elderly and women in published clinical trials has increased during recent years, we conducted a review of recent clinical trials of acute coronary syndromes (ACS).

Design and Measurements—We conducted a search of MEDLINE and the Cochrane Central Register of Controlled Trials to identify clinical trials of ACS published from May, 2007 to May, 2009. Trials were excluded if they enrolled <50 patients, were sub-studies of previously published trials, or initiated treatment more than 3 weeks after the acute cardiac event.

Results—Eighty trials, enrolling a total of 68,016 subjects, met our pre-established criteria. Nearly 30% (n= 23) had explicit exclusion criteria based on age. Only 13.8% of study participants were ≥ 75 years and 27.7% of subjects were women. These percentages remain below the representation of all U.S. adults experiencing an ACS in recent years who were ≥ 75 years of age (41.9%) or women (41.5%). The average age of all study participants was 61.6 years (SD=3.8). There was a significant association between the mean age of a study participant and the proportion of women enrolled in the trial.

Conclusion—Older adults and women remain underrepresented in recent clinical trials of patients hospitalized with an ACS. These exclusions may hinder efforts to inform evidence-based clinical decision-making in these high-risk patient populations.

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Ms. Zhao: analysis and interpretation of data, revising manuscript critically for important intellectual content, and final approval of the version to be published.

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Introduction

Individuals 65 years and older represent nearly two thirds of patients discharged from the hospital after an acute myocardial infarction,¹ and coronary heart disease is the leading cause of death in persons 75 years and older.² In a recent population-based study examining changing trends in the characteristics of patients hospitalized with acute myocardial infarction over the past 3 decades, patients hospitalized during the most recent study years were significantly older, more likely to be female, and had a greater prevalence of important comorbidities.³ Due to the dramatic demographic shifts that are occurring in the U.S. population, these trends are likely to continue, resulting in ever growing numbers of older persons hospitalized with coronary heart disease.

Women are disproportionately represented among the older adult U.S. population.⁴ While men are at greater risk for developing coronary heart disease than women prior to menopause, sex differences in the risk of acute coronary disease narrow after menopause. Furthermore, the majority of published studies have shown that women experience higher death rates after acute myocardial infarction than men, irrespective of age, and women are more likely to experience serious complications of acute myocardial infarction than men.^{5, 6}

Despite this background, older patients and women have historically been underrepresented in clinical trials of coronary heart disease.⁷⁻⁹ Gurwitz et al reported that 60% of randomized controlled trials of acute myocardial infarction published between 1960 and 1991 excluded persons over 75 years old.⁷ Lee and colleagues reported the exclusion of persons 75 years and older in 48% of trials published between 1991 and 1995, and 32% between 1996 and 2000.⁸ Despite these trends, the average age of study participants did not change meaningfully prior to 2000,⁸ and the participation of older adults and women remained substantially below their disease prevalence in the overall U.S. population.

Although guidelines pertaining to the inclusion of elderly participants in clinical trials have existed for more than 2 decades,¹⁰ these two previous reviews suggested ongoing enrollment biases in cardiovascular clinical trials. More recently, in 2001, the National Institutes of Health released guidelines on the inclusion of women in clinical trials to encourage increased representation.¹¹

In the present systematic review, we examined whether the percentage of older persons and women participating in published clinical trials has increased during recent years. This was accomplished by conducting a review of clinical trials of acute coronary syndromes (ACS) published between May, 2007 and May, 2009.

METHODS

Systematic Review and Study Selection

A literature search using MEDLINE and the Cochrane Central Register of Controlled Trials identified studies of patients with ACS published from May, 2007 to May, 2009. Relevant studies were identified using the MeSH terms *myocardial infarction*, *unstable angina*, or *acute coronary syndrome* and were limited to the subject headings *clinical trials (phase 1, 2, 3, and 4)*, *controlled clinical trials*, and *randomized clinical trials (RCTs)*. Studies acquired through the Cochrane database were identified using the subject headings *myocardial infarction*, *unstable angina*, and *acute coronary syndrome*. The search for published articles through electronic databases was supplemented by examination of relevant meta-analyses, review articles, and major cardiology textbooks. One-thousand and ninety-two potential studies were identified during this preliminary review process.

The abstracts of all initially identified studies were reviewed for possible inclusion in this systematic review. Inclusion criteria consisted of RCTs of cardiac medications and common cardiac procedures, including percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG), used in the in-hospital treatment of ACS (defined as unstable angina, acute myocardial infarction (AMI), or both). We excluded studies enrolling less than 50 patients, those published in a language other than English, those that were sub-studies of previously published trials, and studies not including the target population (e.g., trials enrolling patients with heart failure only). In addition, since this review was focused on therapies initiated during hospitalization for ACS, trials initiating treatment more than 3 weeks after the acute cardiac event were excluded. After eliminating studies using these exclusion criteria, a total of 80 trials were included in our final analyses. (Figure 1)

Data Collection

The 80 trials included in this review were abstracted for source of support (i.e., industry, government, or foundation funding), pharmacotherapy, use of cardiac procedures, study phase, number of study sites, trial location (U.S site involved vs. no U.S. site involved), number of patients, diagnostic category (unstable angina, AMI, both), mean age and sex distribution of the trial population, and any age exclusion criteria specified for enrollment. We determined the percentage of study subjects aged 75 years and older and the percentage of women enrolled in each trial. All 80 trials reported the distribution of the trial population by sex. However, the percentage of patients aged 75 years and older was reported in only 3 trials. We contacted all authors to obtain information on the enrollment of patients 75 years of age and older. In instances where the author did not respond, we estimated enrollment of patients 75 years of age and older based on mean ages and standard deviations, using a standardized algorithm that has been used in previously published systematic reviews.¹² The primary and secondary outcomes employed in each trial were categorized as follows: mortality; nonfatal cardiac events including angina, recurrent myocardial infarction, arrhythmia, cardiomyopathy, congestive heart failure, or cardiogenic shock; cardiac function and infarct size estimates based on diagnostic testing results; quality of life and/or functional status; stroke; bleeding; restenosis necessitating revascularization; or other, which included outcomes that did not fit into the other categories (i.e., embolization, mean arterial pressure).

Abstraction of data from all studies was conducted by one reviewer (K.D.) and a 10% sample was independently validated by a second reviewer (J.S.) to assess inter-rater reliability. Specifically, the suitability for study inclusion and the accuracy of the abstracted data were verified. No disagreement was found between reviewers for proper inclusion or each trial's sample size. The two authors also had excellent agreement for the mean age of trial enrollees, for the percentage of study subjects who were women, and for the trials with explicit age exclusions (κ range, 0.90–0.94).

Data Analysis

Trial characteristics are presented as percentages of the overall trial population. Differences between trials that had explicit age exclusions and those that did not were analyzed using *t* tests for continuous variables and χ^2 tests for categorical variables. In order to evaluate associations between specific study characteristics and the presence of an age exclusion, we calculated relative risks (RRs) and accompanying 95% confidence intervals (CIs).

Multivariable regression analysis was employed to examine the association of trial sample size, therapeutic class being investigated, cardiac procedures involved in the treatment of trial enrollees, trial location, source of trial funding, and number of sites involved in the trial (single vs. multicenter trial) with the presence of age exclusions. In addition, a weighted regression analysis, to account for the varying population sizes across studies, was

performed to assess the association between the mean study population age and the proportion of trial enrollees who were female. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Study Characteristics

The study characteristics of the 80 ACS trials that met our pre-defined inclusion criteria are summarized in Table 1. The trials enrolled a total of 68,016 patients, 13.8% (95% CI = 12.5, 15.1) of whom were 75 years and older and 27.7% of whom were women. The majority of ACS trials (73.8%) enrolled fewer than 500 subjects and approximately half (53.8%) were single center trials. Trials enrolling more than 500 patients had a slightly older average mean age (62.1, 95% CI = 61.3, 62.9) compared to smaller trials (61.7, 95% CI = 60.6, 62.8) and multi-center trials had an older mean age (62.1, 95% CI = 61.1, 63.2) than single center trials (61.5, 95% CI = 60.2, 6). Approximately one quarter of multinational studies included U.S. sites. Among the 52 trials that reported on their source of funding, 40% indicated that at least some financial support was derived from industry. The average age of patients was slightly older in studies that were government funded (mean = 63.1, 95% CI = 60.4, 65.7) compared to those without government funding (mean = 61.5, 95% CI = 60.6, 62.4).

Antithrombotic and antiplatelet medications were the most frequent pharmacotherapies investigated in these trials (Table 1). The majority of trials (78%) also involved some type of invasive treatment, alone or in combination with medical therapy. The majority of study participants (92%) underwent PCI or CABG as part of the trial protocol. Study populations most commonly consisted of patients with a diagnosis of AMI (70%). Cardiac function and infarct size were evaluated as outcomes in more than 60% of studies, and non-fatal cardiac events and mortality were also commonly reported outcomes (50% and 46%, respectively). Of special note, none of the studies included in our review evaluated quality of life or functional status as either primary or secondary trial outcomes.

Age Exclusions

Nearly 30% (n=23) of studies had explicit age exclusion criteria included as part of the study protocol. An upper age limit of 80 years was the most frequently used age cut-off (n=11) and an additional 8 studies excluded patients 75 years and older. While the mean age for all study subjects was 61.6 years (SD=3.8; 95% CI = 61.0, 62.6), the mean age of participants in trials with age-based exclusions was 60.1 years (SD=2.2; 95% CI = 59.1, 61.0) as compared to 62.5 (SD=4.1; 95% CI = 61.4, 63.6) years in trials without age exclusions ($P=0.001$).

In multivariable regression models, no trial related characteristics were identified as being significantly associated with the presence of an age exclusion.

Age and Sex

Information on age and sex was available in all ACS trials included in our study (n=80), and women were included in all trials. Women accounted for more than a quarter (27.7%) of the 68,016 patients enrolled in these trials. There was an association between the presence of age-based exclusions and the proportion of the trial population that was female. In trials with age-based exclusions, 25.1% of subjects were women as compared with 28.1% of subjects in trials without age exclusions ($P<0.001$). There was a significant linear relationship between the mean age of the trial population and the percentage of women enrolled in the trial ($P=.001$; $R^2=.21$; Figure 2).

DISCUSSION

Although the prevalence of, and mortality associated with, coronary heart disease increases substantially with advancing age in American men and women, older patients remain underrepresented in ACS clinical trials.^{7, 8} We found that the elderly and women continue to be substantially underrepresented in recently published ACS clinical trials, with only 13.8% of study participants aged 75 years and older; only about a quarter of participants are women. These percentages remain well below the representation of the elderly (41.9%) and women (41.5%) among all patients in the U.S. who experience an ACS.¹

Two previous systematic reviews have examined the representation of older adults in clinical trials of AMI and ACS prior to 2000;^{7, 8} the percentage of studies with explicit age-based exclusions declined markedly over that period of time, from about 60% with explicit exclusions for studies published before 1990 to 32% between 1996 and 2000. In the present review of studies published from May, 2007 to May, 2009, we found that less than 30% of ACS studies had explicit age-based exclusions. In addition, we observed a shift toward the inclusion of patients from older age strata as the threshold for exclusion, with the majority of studies employing 80 years of age as the cutoff, as compared with the limit of 75 years that has been most commonly used in the past. While the less frequent use of explicit age-based exclusions might be considered as a positive step forward for increasing the number of older subjects enrolled in ACS clinical trials, we found that the average age of study participants has changed very little since prior to 2000, suggesting that the elimination of age exclusions does not necessarily enhance the participation of older adults in clinical trials of cardiovascular disease.

One potential explanation for the relatively stable average age of trial participants is that a greater number of younger subjects (i.e., <40 years) may have participated in ACS trials during more recent years. It is possible that greater numbers of younger patients may be presenting with ACS or the use of more sensitive measures for defining MI over time may lead to the increasing inclusion of younger patients. However, recent population based studies indicate that the average age of patients hospitalized with ACS is increasing.¹³

The contemporary management of patients with ACS frequently involves the use of invasive interventional procedures, such as primary angioplasty. Mirroring these practice pattern changes over the past decade, we observed a shift in the treatment strategies studied in more recent ACS clinical trials, as compared with prior to 2000. For example, prior to 2000, less than 6% of trial participants were treated with primary angioplasty compared to our findings indicating that nearly three quarters of subjects were enrolled in trials involving PCI.⁸

Physicians may be less likely to recommend that their elderly patients with ACS undergo invasive procedures compared to younger patients due to their perceived higher risk of complications or frailty.¹³ Several studies have also shown that elderly patients with ACS are often erroneously viewed by their physicians to be at low risk, and, therefore, may not be referred for more aggressive treatment.¹³ Additionally, older and female patients with ACS more often delay their presentation to hospitals after the onset of acute coronary symptoms, which may impact on eligibility to participate in some trials.^{14, 15}

Women account for a greater proportion of the older American adult population than do men.⁹ For example, in 2008, for every 100 men aged 75 years and older, there were 161 women.⁴ For that reason, age-based exclusions in ACS trials may have a secondary effect of excluding women. Similar to the results of earlier reviews,^{7, 8} we found a strong association between older average age of trial subjects and the percentage of women participants in the trial. Increasing the number of older subjects in clinical trials will likely lead to an increase in the proportion of women participants.

Conducting clinical trials with older adults can be challenging for various reasons including an increased prevalence of multiple comorbidities and polypharmacy. These factors may lead to the exclusion of older subjects from clinical trials, even in the absence of age-based exclusions. For example, numerous trials exclude patients with co-morbidities such as renal insufficiency, hypertension, and diabetes, all of which increase in prevalence with advancing age. We suspect that these exclusions impact on the enrollment of both older subjects and women. While these exclusions are often understandable from the standpoint of completing a study safely and efficiently, the results of studies that exclude these patients may be less generalizable to patients cared for outside of the context of clinical trials. The results of studies that include a very narrow, highly selected subset of the ACS patient population may not be applicable to the broader patient population and may lead to uncertainty and confusion in clinical decision-making.

This study has a number of limitations. Since our analysis included clinical trials of ACS conducted between May, 2007 and May, 2009, the total number of studies included was relatively small. However, our results represent a contemporary view of ACS trial populations. Additionally, only 26% of the trials included in our systematic review enrolled 500 subjects and the majority of studies did not report information on the phase of the trial. This somewhat limits the generalizability of our findings. In addition, although we attempted to contact all authors to obtain information on the age distribution of included trials, the proportion of patients 75 years was calculated in a number of trials using well established algorithms.¹² We also conducted a sensitivity analysis, examining only trials with >1000 patients, and the results were unchanged. We did not examine the proportion of older patients and women in STEMI and Non-STEMI patients separately. In addition, we did not have information on the proportion of older patients screened as compared to the number enrolled and we were unable to determine the proportion of patients excluded from trial participation due to comorbidities common in older patients that were exclusion criteria for trials included in our review. In multi-continent studies, we were unable to report the proportion of older adults and women enrolled by site.

In summary, older adults and women remain underrepresented in recent clinical trials of patients hospitalized with ACS. These exclusions will continue to hinder efforts to inform evidence-based clinical decision-making in these high-risk patients. New strategies and policies need to be considered to encourage, enhance, and facilitate the inclusion of older patients and women in clinical trials. Changing trends in the inclusion of the elderly and women should continue to be monitored on a periodic basis to assess the generalizability of study findings to these high-risk patient populations.

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Figure 1.

Numbers of clinical trials of acute coronary syndromes that were excluded from the final review and reasons for exclusion.

Figure 2.

Women as a percentage of trial populations, stratified by mean age

Regression line represents the average increase in percentage of women as the average mean age among the trials increases ($P=.001$; $R^2=.21$).

Table 1**Study Characteristics**

	Trials, No	Patients, No.	Age	75 y No. (%)	Women No. (%)
Publication Dates					
May 2007 – May 2009	80	68016		9196 (13.8)	18828 (27.7)
Trial Enrollment, No. of patients					
50–99	23 (28.8)	1686		148 (8.8)	484 (28.7)
100–499	36 (45.0)	7980		1060 (13.3)	2126 (26.6)
500–999	12 (15)	9001		1219 (13.5)	2216 (24.6)
1000–4999	6 (7.5)	12516		1256 (10.0)	3332 (26.6)
5000	3 (3.8)	36833		5513 (15.0)	10670 (29.0)
No. of sites					
Single center	43 (53.8)	8013		918 (11.5)	2165 (27.0)
Multi-center	37 (46.3)	60003		8278 (13.8)	16663 (27.8)
Location					
No U.S. sites involved	66 (82.5)	18753		2576 (13.7)	4880 (26.0)
U.S. sites involved	14 (17.5)	49293		6978 (14.2)	13948 (28.3)
Therapeutic class [†]					
Antiplatelet	27 (33.8)	52181		7449 (14.3)	14636 (28.0)
Antithrombotic	27 (33.8)	53190		7627 (14.4)	15054 (28.3)
Chinese Medicine	3 (3.8)	253		26 (10.3)	105 (42.7)
Lipid-lowering agent	7 (8.8)	1093		125 (11.4)	283 (25.9)
None	12 (15.0)	3239		481 (14.9)	844 (26.1)
Other	14 (17.5)	4558		529 (11.6)	1294 (28.4)
Thrombolytic	5 (6.3)	4748		639 (13.5)	1399 (29.5)
Vasodilator	3 (3.8)	1819		168 (9.2)	414 (22.8)
Other	14 (17.5)	4558		529 (11.6)	1294 (28.4)
Invasive Procedure					
PCI	59 (73.8)	61995		8468 (13.7)	17092 (27.6)
CABG	3 (3.7)	332		67 (20.2)	103 (31.0)
None	18 (22.5)	5689		661 (11.6)	1633 (28.7)
Funding Source [†]					
Industry	32 (40)	57480		7921 (13.8)	16207 (28.2)
Government	15 (18.8)	4388		520 (11.9)	1052 (24.0)
Industry & Government	3 (3.8)	903		151 (16.7)	215 (23.8)
Foundation	8 (10.0)	6867		720 (10.5)	1784 (26.0)
Not reported	28 (35)	4826		546 (11.3)	1183 (24.5)
Diagnostic categories					

	Trials, No	Patients, No.	Age 75 y No. (%)	Women No. (%)
MI only	56 (70.0)	25976	3077 (11.8)	6697 (25.8)
Unstable angina only	1 (1.2)	85	3 (3.5)	34 (4.0)
Both	23 (28.8)	41955	6116 (14.6)	12097 (28.8)
Outcomes [†]				
Cardiac function/infarct size	50 (62.5)	13033	1628 (12.5)	3211 (24.6)
Non-fatal cardiac event	41 (50.0)	62393	8604 (13.8)	17321 (27.8)
Mortality	37 (46.3)	55645	7772 (14.0)	15430 (27.7)
Restenosis and revascularization	28 (35.0)	39972	5977 (15.0)	11351 (28.4)
Bleed	17 (21.3)	30943	4431 (14.3)	8603 (27.8)
Stroke	11 (13.8)	26108	2666 (10.2)	6866 (26.3)
Quality of life/functional status	0	0	0	0
Other [*]	6 (7.5)	1166	163 (14.0)	353 (30.3)

[†]Total number of observations is larger than the total number of trials due to non-mutually exclusive categories

^{*} Other category includes cholesterol levels, inflammatory marker levels, change in mean arterial pressure, and distal embolization/thrombosis.