SCIENTIFIC LETTER

Women, older persons, and ethnic minorities: factors associated with their inclusion in randomised trials of statins 1990 to 2001

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In practice, only a minority of people with coronary heart disease in the UK who could benefit from cholesterol lowering are currently being prescribed statins.[1 2] Clinical trials of cardiovascular medicines, moreover, have also been characterised as "uninclusive", with women, older persons, and ethnic minorities tending to be under represented.[3 4] To explore this further, we examined a series of statins trials to ascertain levels of inclusion of these groups and to determine whether factors such as geographical region, commercial support, and specialised clinical investigation were associated with inclusion.

METHODS

We conducted a Medline search up to 1 August 2001 for randomised trials of statins in adults with a minimum treatment duration of six months (or 26 weeks) which reported lipid changes or stenosis change or cardiovascular events. We considered unpublished and non-English language studies and checked references in relevant papers. To be eligible, trials had to compare a statin with a non-statin drug, an inactive control or "usual care". Adjuvant drug treatment for excessively high lipids during the trial was acceptable. We included factorial trials if appropriate data could be derived. Trials in which all patients had renal failure or diabetes were not eligible. For clarity, we drew upon only one treatment comparison (for example, statin arm versus placebo arm) per trial, taking the comparison first reported. Data were extracted by one researcher (CB), with extraction duplicated by a colleague for key variables. We coded trials to "USA" if all or some of the patients were located in the USA. We also coded trials according to whether support had been provided by the pharmaceutical industry. Trials in which coronary or carotid artery stenosis was measured we coded to "angiographic". Analysis was in STATA 7, using Fisher's exact test and the Kruskal Wallis test. We report probability values of $p \leqslant 0.05$.

RESULTS

In total, 47 randomised controlled trials (RCTs) published in the period 1990 to 2001 inclusive were eligible. The mean follow up period was two years. The total number of patients was 50 245, the median being 270. The statins involved were: pravastatin (22 trials), lovastatin (12), simvastatin (9), fluvastatin (3), and atorvastatin (1). Most trials (38) were secondary or mixed primary/secondary prevention. As table 1 shows, eight trials (17%) reported complete exclusion of women, and the median percentage of women included was only 18.6% (interquartile range (IQR) 11.8–30%). While 14 trials reported separate outcome information for women, only seven of these reported cardiovascular event data, often in a superficial way; only two trials distinguished between men and women in reporting adverse events. In all, 31 trials reported setting a definite upper limit for age, the median being 70 years, but 11 of the remaining trials were equivocal about this. The percentage of people aged 65+ was infrequently reported (13 trials), the median percentage being zero. Eleven trials reported outcome information by age group, although this was often minimal. Only eight trials (17%) reported the ethnic minority proportion in their respective samples.

USA patients were involved in 17 trials. These trials included a higher proportion of women and had an older median age limit (75 *v* 70 years, $p = 0.048$). US trials also reported a higher median percentage of people aged 65+ (21.1% *v* 0%). The eight trials reporting ethnicity were all US trials (median percentage of ethnic minorities 10.5%, IQR 7.5–15%). Because of this small number of trials we did not conduct any further analyses involving ethnicity.

A total of 22 trials recorded a pharmaceutical company as sole source of external support. "Solely pharmaceutical" trials were more likely to exclude women. Although these trials had a greater average number of women per trial, this was because they were relatively large studies compared with the other trials (median numbers 427.5 *v* 157, $p = 0.004$), but their median percentage of women was comparatively small (15.2% *v* 29.9%, $p = 0.01$). The median value of the upper age limit in "solely pharmaceutical" trials was similar to that for the rest of the series. A similar pattern emerged when we compared trials reporting *any* pharmaceutical support (not necessarily sole support) ($n = 38$) with trials reporting no pharmaceutical support ($n = 9$).

We classified 26 trials as "angiographic". These were more likely to exclude women, and had smaller median numbers and percentages of women (15.8% *v* 26%, $p = 0.018$). These trials were less likely to report the proportion of people aged 65+ (12% *v* 48%, $p = 0.009$).

DISCUSSION

To our knowledge this is the most comprehensive analysis of associations with inclusion of women, older people, and ethnic minorities in a series of statins trials; Lee and colleagues' investigation of possible influences on cardiovascular trials included only eight trials of cholesterol reducing drugs.[3] We found that US trials were more inclusive. This might be expected following the National Institutes of Health Revitalization Act of 1993, which promotes representation of women and ethnic minorities in trials, yet the difference was only moderate, apart from the reporting of ethnicity. Angiographic trials tended to be less inclusive; employing an invasive procedure probably militated against including older, higher risk patients, while younger cardiovascular patients would be more likely to be male anyway. Trials dependent on pharmaceutical support tended to have greater numbers of women, but as relatively small proportions of the sample, perhaps because inclusion criteria based on cardiovascular risk led to the selection of more men. The relation between pharmaceutical companies and inclusion by age was not clear.

Table 1 Age and sex related characteristics of randomised controlled trials (RCTs) of statins from 1990 to 2001, according to location, source of funding, and angiographic investigation

	All RCTs	USA	Non-USA	Solely pharmaceutical	Not solely pharmaceutical	Angiographic	Non-angiographic
Number of RCTs	47	17	30	22	25	26	21
Median number of patients (IQR)	270 (77–834)	270 (97–429)	267.5 (77–834)	427.5 (205–1062)	157 (56–305)	250 (97–408)	286 (56–4159)
Number of RCTs completely excluding women (%)	8 (17%)	1 (6%)	7 (23%)	6 (27%)	2 (8%)	6 (23%)	2 (10%)
Median number of women across all trials (IQR)	45 (12–143)	80 (22–195)	22.5 (8–140)	53.5 (0–247)	34 (13–90)	22.5 (8–92)	64 (13–582)
Median percentage women across all trials (IQR)	18.6% (11.8–30%)	22.7% (15–40.8%)	16.5% (10.9–26%)	15.2% (0–19.5%)	29.9% (14.9–46.9%)	15.8% (8.5–22.5%)	26% (15.1–49%)
Number of RCTs stating an upper age limit (%)	31 (66%)	12 (71%)	19 (63%)	18 (82%)	13 (52%)	19 (73%)	12 (57%)
Median upper age limit where reported (IQR)	70 (65–75)	75 (69.5–77)	70 (65–75)	70 (67–75)	70 (65–75)	70 (67–75)	70 (64.5–74)
Number of RCTs reporting proportion aged 65+ years (%)	13 (28%)	4 (24%)	9 (30%)	7 (32%)	6 (24%)	3 (12%)	10 (48%)
Median percentage aged 65+ years where reported (IQR)	0 (0–23%)	21.1% (10.3–60.7%)	0% (0–23%)	0 (0–23%)	10.3 (0–39%)	0 (0– 0)	21.1 (0–33.1)

IQR, interquartile range.

We did not detect a trend for an increasing percentage of women in statins trials during this period, although the landmark Heart Protection Study, published after our end date, clearly has a greater than average proportion.[5] Nevertheless, if this bias is a recurring feature of most trials of cardiovascular drugs, legislation is evidently required beyond the USA. Even so, this still might not provide sufficient remedy.

Ethics committees should encourage trialists to address lacunae in the evidence base. Trialists should ensure study power is appropriate for the event rates of any subgroups to be analysed and state clearly the population to which trial outcomes can reasonably be generalised.

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Erratum

In the article entitled "Dissection of the aorta: a new approach" (*Heart* 2003;**89**:6–8), the author's name is B Mikich, not M Mikich. The error is regretted.