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Age and gender bias in statin trials

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Summary

Cardiovascular disease is strongly age-related, and is the leading cause of death in older people. Several well-publicized trials have recently reported that statin drugs (HMG CoA reductase inhibitors) are effective in lowering cholesterol and in reducing the risk of myocardial infarction and stroke. In order to determine whether the results of these trials are relevant to our ageing population, we examined the representation of older people and women in randomized controlled trials of statin drugs. A systematic search of the medical literature from 1990 to 1999 was done to identify randomized placebo-controlled trials of statin drugs which evaluated clinical end-points—myocardial infarction, stroke or death. We identified 19 trials: 15 secondary prevention and four primary prevention. The mean age, age range and gender of the participants in these trials were determined. In the secondary prevention trials, the total number of patients randomized was 31 683, with a combined mean age of 58.1 years. No trial enrolled people beyond the age of 75 years, and only 23% of the trial population was female. The four primary prevention trials randomized a combined total of 14 557 subjects with a mean age of 56.9 years. Only 10% of study participants were female. Statin drug trials have suffered from age and gender bias, having been mainly conducted in middle-aged male populations. The extrapolation of evidence from these trials to older people and women needs further evaluation.

Introduction

Cardiovascular disease is the leading cause of death in older people,[1] but they are less likely to receive cardioprotective treatment or interventions recommended by guidelines.[2] Lowering cholesterol has been shown to reduce the risk of coronary heart disease and stroke.[3,4] The current National Cholesterol Education Programme's guidelines for the management of high serum cholesterol raise questions about the extrapolation of evidence to older people on the basis of trials carried out in middle-aged patients, but recommend that physicians maintain a positive attitude towards the potential benefits of cholesterol reduction in the older patient.[5]

Serum cholesterol is a strong predictor of coronary heart disease and all-cause mortality in middle-aged populations,[6] but there has been conflicting evidence regarding the risk associated with hypercholesterolaemia in older populations.[7,8] The pathophysiology of coronary heart disease is not fundamentally different in younger and older patients. The relative risk predicted by high serum cholesterol appears to decrease in people over 75 years of age,[9] but because older people have

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much more atherosclerosis and cardiovascular disease, elevated cholesterol has more attributable risk for coronary events in the old compared with the young.[10] Statins (hydroxy-methyl-glutaryl-CoenzymeA reductase inhibitors) have been shown in several large-scale intervention studies to be effective in lowering cholesterol and in reducing coronary events and stroke.[11] Subgroup analysis of these trials has been interpreted as showing statins to be effective in older populations.[12] However, older people and women are often under-represented in clinical trials,[13] and this bias in trials may give rise to bias in clinical practice, particularly in this era of evidence-based medicine.[14] We examined the representation of people aged 70 years and over, and of women, in the published randomized controlled trials of statin drugs.

Methods

We conducted a computerized search of the MEDLINE database for the last 10 years (1990–1999) and identified randomized controlled trials of statin drugs. Search terms used were hydroxy-methyl-glutaryl-CoA-reductase inhibitors, statins, lovastatin, simvastatin, pravastatin, fluvastatin, or atorvastatin, and myocardial infarction, cerebrovascular accident or stroke. Searches were limited to articles published in the English language, and to those conducted on human subjects. We also searched the reference lists of published trials of statin drugs, the published overviews, EMBASE, the Cochrane collaboration database and approached the pharmaceutical industry for any additional information. The inclusion criteria for our study were: (i) randomized placebo-controlled trials of statin drugs alone; (ii) mortality and/or myocardial infarction and/or stroke were study end-points; and (iii) the intervention period lasted at least 6 months. We excluded studies which did not examine clinical outcome end-points, those which were not placebo-controlled and trials of multi-factorial interventions. Those trials meeting our eligibility criteria were then scrutinized to identify the age range and gender of patients enrolled, and the gender distribution and mean age of the combined trial populations were calculated.

Results

We identified 19 trials which met our eligibility criteria. Of these, 15 were secondary prevention[11,15–28] and four were primary prevention studies.[29–32]

Among the secondary prevention trials, (Table 1) six trials randomized >1000 patients each, and four of these trials essentially contributed the bulk of patients.[11,15,23,27] The total number of patients randomized in 15 secondary prevention trials was 31 683. The mean age of this combined study population was 58.1 years.

The LIPID study,[27] a substantial secondary prevention study with over 9000 patients, had a mean study population age of 62 years. The other studies with mean ages in low 60s rather than in the low 50s were all much smaller.[17,21,24] In general, the study population mean age increased slightly with advancing year of publication from 1991 to 1999. The age ranges of patients randomized in various secondary prevention trials indicate that none of the trials enrolled anyone beyond the age of 75 years. Two of the larger secondary prevention trials, EXCEL[15] and 4S,[23] enrolled patients only up to the age of 70 years.

The gender distribution of the secondary prevention trials was highly skewed towards men. Of 31 683 patients in the combined study population, 24 447 were male (77%). REGRESS[25] randomized only male patients. EXCEL[15] had significant female participation (41%). Only two trials[11,15] in the secondary prevention group gave any data about the ethnicity of the study population; both were North American and had 92% White participation.

In the primary prevention category (Table 2), two trials, WOSCOP[30] and AFCAPS[32] contributed most of the patients. The total number of patients randomized in these four trials was 14 557, and the mean age of the combined study population was 56.9 years. WOSCOP only enrolled patients up to the age of 64 years; AFCAPS included patients up to the age of 73 years. ACAPS,[29] which was a smaller primary prevention study included patients up to age 79 years, but the mean age was still only 62 years.

WOSCOP[30] and KAPS[31] enrolled men only and AFCAPS[32] enrolled 85% men. ACAPS had more significant female representation (48%). Overall, of the 14 557 subjects in the combined study population, 13 129 were male (90%). Two trials gave information about the ethnicity of the study population: ACAPS[29] and AFCAPS.[32] Both were North American studies, and reported that 92% and 89%, respectively, of their study populations were White.

Discussion

Statins have recently received a lot of attention, given their benefits in reducing coronary heart disease, stroke and mortality.[11,23,27,30] However,

Table 1 Secondary prevention trials

Name of trial and year of publication	Patients randomized (*n*)	Mean follow-up (months)	Mean age of trial population at baseline (years)	Age range of patients at baseline (years)	Sex ratio of trial populations (males : females)	Reduction achieved in LDL-cholesterol (%)	Significant change in clinical outcome (MI/Stroke/Death) achieved	Ethnicity of trial populations
EXCEL, 1991[15]	8245	12	54	18–70	59 : 41	24%	No	92% White
MARS, 1991[16]	270	26	58	37–67	91 : 9	38%	No	NA
SAHNI, 1991[17]	157	6	64.2	NA	71 : 29	20%	No	NA
Pravastatin Multinational Trial, 1993[18]	1062	12	55	20–69	77 : 23	26%	MI↓	NA
CCAIT, 1994[19]	331	24	52	27–70	81 : 19	29%	No	NA
PLAC I, 1994[20]	408	36	57	NA	79 : 21	28%	MI↓	NA
PLAC II, 1994[21]	151	36	63	50–75	85 : 15	29%	MI↓	NA
MAAS, 1994[22]	404	48	55.6	30–67	89 : 11	31%	No	NA
4S, 1994[23]	4444	64	58.1	35–70	82 : 18	38%	MI↓, death↓	NA
Lovastatin Restenosis, 1994[24]	404	6	62	NA	72 : 28	34%	No	NA
REGRESS, 1995[25]	885	24	55.5	⩽70	Men only	29%	MI↓	NA
CARE, 1996[11]	4159	60	59	21–75	86 : 14	32%	MI↓, stroke↓	92% White 8% other
PREDICT, 1997[26]	695	6	58.2	31–75	84 : 16	24%	No	NA
LIPID, 1998[27]	9014	72	62	31–75	83 : 17	25%	MI↓, stroke↓, death↓	NA
FLARE, 1999[28]	1054	9	60	NA	83 : 17	33%	MI↓, death↓	NA

NA, not available; MI, myocardial infarction.

Table 2 Primary prevention trials

Name of trial and year of publication	Patients randomized (*n*)	Mean follow-up (months)	Mean age of trial population at baseline (years)	Age range of patients at baseline (years)	Sex ratio of trial populations (males : Females)	Reduction achieved in LDL-cholesterol (%)	Significant change in clinical outcome (MI/Stroke/Death) achieved	Ethnicity of trial populations
ACAPS, 1994[29]	910	34	62	40–79	52 : 48	28	No	92% White
WOSCOP, 1995[30]	6595	57	55.3	45–64	Men	26	MI↓, death↓	NA
KAPS, 1995[31]	447	36	57	44–65	Men	27	No	NA
AFCAPS, 1998[32]	6605	62	58	45–73	85 : 15	25	MI↓	89% White 3% Black 7% Hispanic

NA, not available; MI, myocardial infarction.

people over 75 years of age have been excluded from these trials (Table 1). Three of the larger secondary prevention trials have reported benefits of cholesterol lowering that are similar in young and 'old'. These reports are based on subanalysis of the 4S study[23] which enrolled patients up to the age of 70 years, and the CARE[11] and LIPID[27] studies which enrolled patients up to the age of 75 years. Thus at the moment, there is no substantial data for patients over the age of 75 years.

There are even fewer data for older women, despite the fact that hypercholesterolaemia may be associated with higher relative risk for coronary heart disease in older women than in older men.[33] Indeed, in general, there is little evidence for the benefits of statin therapy in women of any age. One of the few trials to enroll women in substantial proportions was EXCEL[15] (mean age 54 years and 41% women), and this trial was of short duration and did not show any significant benefits in reducing mortality, myocardial infarction or stroke. Neither was there any statistically significant reduction in mortality, myocardial infarction or stroke in ACAPS,[29] a primary prevention study enrolling 48% women. Significant benefits have only been demonstrated for women when primary prevention trials and secondary prevention trials have been pooled.[34,35] The under-representation of women may relate in part to excluding women of childbearing age. However, the exclusion of older women cannot be justified. CARE enrolled more older women than younger women, but even within the 65–75 year age range, the male : female ratio was $>4:1$.[12]

The high attributable risk of hypercholesterolaemia for CHD in older populations means that primary prevention may be particularly important in this group. The main primary prevention studies WOSCOP[30] and AFCAPS[32] had predominantly middle-aged men as their target populations. It is not known whether data from these trials can be extrapolated to older populations.

Ethnicity has largely been ignored in these trials, despite being of major interest for several reasons. The numbers of older Asian and Black people in both Britain and North America are currently increasing. These ethnic population groups have high vascular risk, and in the next 50 years, the major predicted global increase in vascular disease will be in Asia and Africa, where dramatic shifts in the population age structure are occurring. A Cochrane systematic review of hypertension[36] has highlighted the importance of ethnicity in vascular risk reduction, significant mortality benefits occurring with hypertension treatment in African American women of any age, but in Caucasian women only if aged 55 years or more. It is clearly

unsatisfactory to base treatment and prevention strategies for these important major populations on data extrapolated from middle-aged White men.

In conclusion, evidence is still lacking from randomized controlled trials on which to base lipid-lowering treatment strategies for older patients (>75 years) and women. The ongoing PROSPER study of pravastatin[37] in older people should address some of these issues, having enrolled 2806 men and 2998 women aged 70–82 years. Populations with high cardiovascular risk, namely older people, women, and ethnic groups with known high risk, are potentially major targets for risk-lowering interventions in clinical practice, and should not be excluded from clinical trials.

References

1. Graves EJ. Detailed diagnosis and procedures. National Hospital Discharge Survey, 1989. *Vital Health Stat* 1991; **108**:1–236.
2. McLaughlin TJ, Soumerai S. Adherence to national guidelines for drug treatment of acute myocardial infarction, evidence for under treatment in women and the elderly. *Arch Intern Med* 1996; **156**:799–805.
3. Holme I. Cholesterol reduction and its impact on coronary artery disease and total mortality. *Am J Cardiol* 1995; **76**:10–17C.
4. Herbert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke and total mortality. An overview of randomised trial. *JAMA* 1997; **278**:313–21.
5. Expert panel on detection, evaluation and treatment of high blood cholesterol in adults. The second report of the National Cholesterol Education Programme (NCEP) Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *Circulation* 1994; **89**:1329–445.
6. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. *JAMA* 1987; **257**:2176–80.
7. Krumholz HM, Seeman TE, Merill SS, Mendes de Leon CF, Vacarino V, Silverman DI. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA* 1994; **272**:1335–40.
8. Corti MC, Guralnik JM, Salive ME, Harris T, Ferrucci L, Glyn RJ, Havlik RJ. Clarifying the direct relationship between total cholesterol levels and death from coronary heart disease in older patients. *Ann Intern Med* 1997; **126**:753–60.
9. Grundy SM, Cleeman JI, Rifkind BM, Kuller LH, for the coordinating committee of the national cholesterol education programme. Cholesterol lowering in the elderly population. *Arch Intern Med* 1999; **139**:1670–78.
10. Malenka DJ, Baron JA. Cholesterol and coronary heart disease; the importance of patient specific attributable risk. *Arch Int Med* 1998; **148**:2247–52.
11. Sacks FM, Pfeffer MA, Moyee LA, Rouleau JL, Rutherford JD, Cole TG, Brown I, Arnold JMO, Wun CC, Davis BR, Braunwald E, for the cholesterol and recurrent events trial investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; **335**:1001–9.
12. Lewis SJ, Moye LA, Sacks FA, Johnstone DE, Timmis G, Limachar M, Kell S, Glasser SP, Grant J, Davis BR, Pfeffer MA, Braunwald E, for the CARE investigator. Effect of Pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. *Ann Intern Med* 1998; **129**:681–9.
13. Schmucker DL, Vessell SV. Underrepresentation of women in clinical drug trials. *Clin Pharmacol Ther* 1993; **54**:11–15.
14. Evans JG. Evidence-based and evidence-biased medicine. *Age Ageing* 1995; **24**:461–3.
15. Bradford RH, Shear CL, Chermos AN, Dujovne C, Downtown M, Franklin FA, Gould L, Hesney M, Higgins J, Hurley DP, Nash DT, Pool JL, Schnaper H. Expanded clinical evaluation of lovastatin (EXCEL) study results. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. *Arch Intern Med* 1991; **151**:43–9.
16. Blankenhorn DH, Azen SP, Kramsch DM, Mack VJ, Hoddis HN, DeBoer LWV, Mahrer PR, Vailas LI, Hirsch LJ and MARS Research Group. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study Group (MARS). *Ann Intern Med* 1993; **119**:969–76.
17. Sahni R, Maniet AR, Voci G, Banka VS. Prevention of restenosis by lovastatin after successful coronary angioplasty. *Am Heart J* 1991; **121**:1600–7.
18. The pravastatin multinational study group for cardiac risk patients. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/l plus two additional artherosclerotic risk factors. *Am J Cardiol* 1993; **72**:1031–7.
19. Waters D, Higginson L, Gladstone P, Kimball B, May ML, Boccuzzi SJ, Lesperance J, the CCAIT Study Group. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. (CCAIT) *Circulation* 1994; **89**:959–67.
20. Pitt B, Mancini GBJ, Ellis SG, Rosman HS, Park J, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): Reduction in atherosclerosis progression and clinical events. *JACC* 1995; **26**:1133–9.
21. Crouse JR, Byington RP, Bond MG, Espeland MA, Craven TE, Sprinkle JW, McGovern ME, Furberg CD. Pravastatin, lipids and artherosclerosis in the carotid arteries (PLAC II). *Am J Cardiol* 1995; **75**:455–9.
22. MAAS investigators. Effects of simvastatin on coronary artheroma, the multicentre antiatheroma study (MAAS). *Lancet* 1994; **344**:633–8.
23. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease (4S). *Lancet* 1994; **344**:1383–9.
24. Weintraub WS, Boccuzzi SJ, Klein JI, Kosiniski AS, King III SB, Gedarholm JG, Talley D, DeMaio SJ, O'Neill WW, Frazier JE, Robbins DC, Alexander RW and the lovastatin restenosis trial study group. Lack of effect of lovastatin on Restenosis after coronary angioplasty. *N Engl J Med* 1994; **331**:1331–7.
25. Jukema JW, Brushchke AVG, van Boven AJ, Reiber JHC, Bal ET, Zwinderman AH, Jansen H, Boerma GJM, Lie KI

on behalf of the REGRESS study group. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995; **91**:2528–40.

26. Bertrand ME, McFadden EP, Fruchart J, Van Belle E, Commeau P, Grollier G, Bassand J, Cassagnes J, Mossard J, Castiagne A, Lablanche JM, for the PREDICT trial investigator. Effect of pravastatin on angiographic restenosis after coronary balloon angioplasty. *JACC* 1997; **30**:863–9.
27. The long-term intervention with pravastatin in ischaemic disease (LIPID) study group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol level. *N Engl J Med* 1998; **339**:1349–57.
28. Servwys PW, Foley DP, Jackson G, Bonnier H, Macaya C, Vrolix M, Branzi A, Shepherd J, Suryapranata H, Feyterpj, Melkert R, Pfister PJ, on behalf of FLARE study group. A randomised placebo controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty. Final result of the fluvastatin angiographic restenosis (FLARE) trial. *Eur Heart J* 1999; **20**:58–60.
29. Furberg CD, Adams HP, Applegate WB, Byington RP, Espeland MA, Hartwell T, Lefkowitz DS, Riley WA, Young B, for the asymptomatic carotid artery progression study (ACAPS) research group. Effect of lovastatin on early carotid artherosclerosis and cardiovascular events. *Circulation* 1994; **90**:1679–87.
30. Shepherd J, Cobbe SM, Ford I, Isles CG, Lormier AR, Macfarlane PW, McKillop JH, Packard CJ, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; **333**:1301–7.
31. Salonen R, Nyyssonen K, Porkkala E, Rummukainen J, Belder R, Park J, Salonen JT. Kuopio Atherosclerosis Prevention Study (KAPS): A population based primary prevention trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation* 1995; **92**:1758–64.
32. Downs JR, Clearfield M, Weis S, Whitney E, Shpiro DR, Beere PA, Stein EA, Kruyer W, Gotto AM, for the AFCAPS/TexCAPS research group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol level. *JAMA* 1998; **279**:1615–22.
33. Corti MC, Guralnik JM, Salive ME, Harris T, Field TS, Wallace RB, Berkman LF, Seeman TE, Glynn RJ, Havlik RJ. HDL cholesterol predicts coronary heart disease mortality in older persons. *JAMA* 1995; **274**:539–44.
34. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease, a meta-analysis of randomised controlled trials. *JAMA* 1999; **282**:2340–6.
35. Clemenson ND, Ebrahim S. Statins and risk of coronary heart disease (letter). *JAMA* 2000; **283**:2935–6.
36. Quan A, Kerlikowske K, Gueyffier F, Boissel JP, INDANA investigators. Pharmacotherapy for hypertension in women of different races (Cochrane Review). In: *The Cochrane Library,* Issue 4. Oxford Update software, 2000.
37. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen ELEM, Buckley BM, Ford I, Jukema J, Hyland M, Gaw A, Lagaay AM, Perry IJ, Macfarlane PW, Meinders AE, Sweeney BJ, Twomey C, Stott DJ, on behalf of the PROSPER study group. The design of a prospective study of pravastatin in the elderly at risk. *Am J Cardiol* 1999; **84**:1192–7.