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Continuation of mortality reduction after the end of randomized therapy in clinical trials of lipid-lowering therapy

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BACKGROUND: Long-term follow-up of clinical trials with lipid-lowering medications has suggested a continuation of event reduction after study completion.

OBJECTIVE: To evaluate the persistence of the benefit of lipid-lowering therapy in decreasing mortality after the end of clinical trials, when all patients were advised to take the same open-label lipid-lowering therapy.

METHODS: Through searches of MEDLINE, the Cochrane Library, the Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov until June 2010 we identified randomized clinical trials of lipid-lowering agents with a second report describing results after the end of the trial.

RESULTS: Among the 459 trials reviewed, only 8 including 44,255 patients and 8144 deaths qualified for the meta-anlaysis. All-cause and cardiovascular mortality were lower in the active intervention group during the first phase (0.84, 95% confidence interval [CI] 0.76–0.93; $P = .0006$ and 0.72, 95% CI 0.63–0.82, $P < .0001$, respectively) when 71 ± 23% of the patients randomized to receive active therapy actually received it compared with 13 ± 5% of patients who received active therapy although they were randomized to placebo ($P = .0001$). The lower mortality among those initially randomized to active therapy persisted during the second phase (odds ratio 0.90, 95% CI 0.84–0.97, $P = .0035$, and 0.82 95% CI 0.73–0.93, $P = .0014$), when patients in both randomized groups received active therapy in the same proportions (5 ± 2% for both groups). Numerous sensitivity analyses support the conclusions of the paper.

CONCLUSION: The decrease in mortality with lipid-lowering therapy in clinical trials persists after discontinuation of randomized therapy when patients in the treatment and placebo groups receive active therapy.

Clinical trials and meta-analyses of lipid-lowering therapy have shown a decrease in morbid and mortal cardiovascular events during therapy.[1–4] Although in some instances the benefits of treatment were observed

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soon after the initiation of therapy, in older studies, event reduction became evident after months or years of treatment, implying that coronary arterial structure and function improve with time during lipid-lowering therapy.[5,6] It is possible that the improvement may accrue over time and result in better long-term outcome. The benefit of low-density lipoprotein (LDL) lipid-lowering is probably determined by its duration as well as by its intensity.[7] Investigators of clinical trials have published findings of a persistent benefit of lipid-lowering therapy after the end of randomized trials, when all participants were advised to take active therapy.[8] The purpose of this meta-analysis was to examine the persistence of the effect on all-cause mortality and coronary heart disease (CHD) mortality in patients on lipid-lowering therapy after discontinuation of randomized treatment. We also aimed to relate this effect to the actual percentages of patients in the intervention and control groups who actually received active therapy during the first and the second phases of each study.

Methods

The methods used in the meta-analysis have been published elsewhere.[9] Of the 488 relevant titles identified from the MEDLINE, Cochrane Library, Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov (Fig. 1), 27 appropriate studies were reviewed, and only 8 fulfilled the inclusion criteria (randomized, pertaining to lipid-lowering medications, and with data on all-cause mortality, Tables 1 and 2).[6,8,10–24] In the Helsinki study, where two follow-up reports were retrieved, the one with the longest follow-up (18 years) was used in the primary analysis.[19] Use of the report with the 13-year follow-up[24] did not

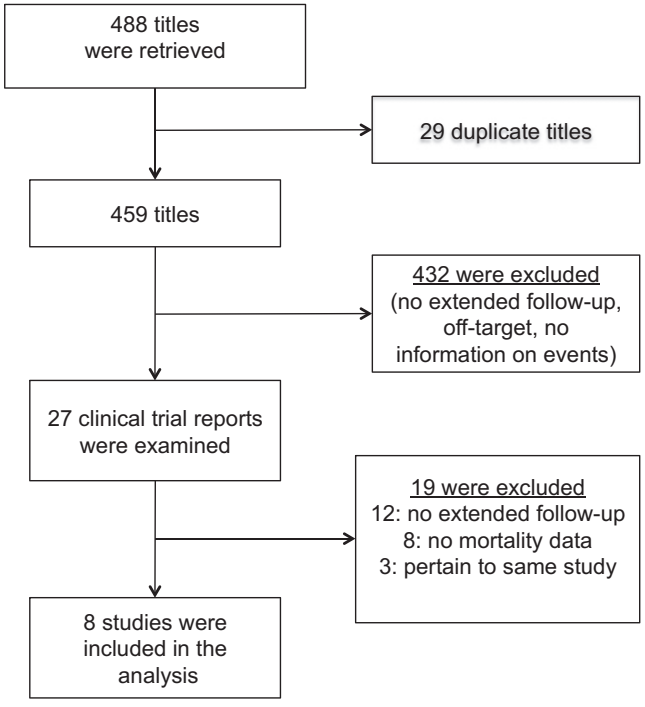

Figure 1 Identification and selection of studies.

Table 1 Study indications, medications and inclusion criteria

Study	Medication class	Intervention	Control	Prevention type	Mean age	% men	Inclusion criteria	References
4S	Statin	Simvastatin	Placebo	Secondary	58	81	CHD and total chol 5.5–8.0 mmol/L	10,11
ALERT	Statin	Fluvastatin	Placebo	Primary	50	66	Renal transplant recipients, TC 4.0–9.0 mmol/L	12,13
ASCOT	Statin	Atorvastatin	Placebo	Primary	63	81	HT ≥3 CV risk factors, TC ≤ 6.5 mmol/L	8,14
CDP-NIACIN	Niacin	Niacin	Placebo	Secondary	52	100	Previous MI	15,16
CPPT	BAS	Cholestyramine	Placebo	Primary	48	100	LDL-C>190 mg/dL and free of CHD	6,17
HELSINKI	Fibrate	Gemfibrozil	Placebo	Primary	47	100	Non HDL-C>200 mg/dL	18,19,24
LIPID	Statin	Pravastatin	Placebo	Secondary	62	83	Previous MI or unstable angina pectoris, TC 4.0–7.0 mmol/L	20,21
WOSCOPS	Statin	Pravastatin	Placebo	Primary	55	100	TC ≥6.5 mmol/L and no history of MI	22,23

ALERT, Assessment of Lescol in Renal Transplantation; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BAS, bile acid sequestrant; CHD, coronary heart disease; Coronary Drug Project-Niacin; CPPT, Coronary Primary Prevention Trial; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease; MI, myocardial infarction; TC, total cholesterol; WOSCOPS, West of Scotland Coronary Prevention Study.