

Appendix 3: Sensitivity analyses of the relative risk of death from any cause associated with the use of statins in people at low cardiovascular risk

Sensitivity	No. of studies	No. of participants	RR (95% CI)	<i>I</i> ² value for heterogeneity, %	<i>p</i> value from metaregression*
Continuity correction	23	79 495	0.91 (0.85–0.97)	0	NA
Trials with intention-to-treat analyses	17	74 325	0.90 (0.82–0.99)	10	0.62
Placebo-controlled trials	15	56 138	0.86 (0.78–0.96)	0	0.22
No placebo-controlled trials	4	22 183	0.90 (0.77–1.06)	28	0.22
Trials in which both cardiovascular-related death and nonfatal myocardial infarction could be used to calculate 10-year risk	16	76 310	0.89 (0.81–0.97)	13	0.36
Trials with estimated 10-year risk of cardiovascular disease < 20% (ATP III) ¹²	19	78 321	0.90 (0.84–0.97)	2	NA
Trials with estimated 10-year risk of cardiovascular disease < 20% assuming hypertension is treated ^{†11}	4	9 985	0.78 (0.57–1.06)	0	0.34
Trials with estimated 10-year risk of cardiovascular disease < 20% assuming hypertension is untreated ^{†11}	9	37 642	0.82 (0.66–1.02)	12	0.10
No trials in which any patient had known cardiovascular disease	10	40 015	0.84 (0.74–0.95)	0	0.13
No trials in which any patient had known cardiovascular disease or diabetes	3	19 091	0.81 (0.67–0.97)	0	0.18
No trials in which any patient had cardiovascular disease or diabetes (here, diabetes was assumed to be absent in trials that did not report diabetes)	5	20 167	0.81 (0.68–0.97)	0	0.19
Trials with observed 10-year risk of cardiovascular-related death or nonfatal myocardial infarction < 10%	11	40 748	0.83 (0.73–0.94)	0	0.11
Trials with follow-up period > median (2 yr)	13	49 279	0.92 (0.85–0.99)	0	0.56
Trials with follow-up period ≤ median (2 yr)	6	29 042	0.99 (0.69–1.43)	14	0.56

Note: ATP III = Third Adult Treatment Panel, CI = confidence interval, CV = cardiovascular, CVD = cardiovascular disease, NA = not applicable, NFMI = nonfatal myocardial infarction, RR = relative risk.

*Where possible, we used univariable metaregression analysis to examine whether certain variables influenced the association between therapy and the risk of all-cause mortality. The method used by the Third Adult Treatment Panel calculates sex-specific 10-year risk of “hard” coronary artery disease (myocardial infarction or coronary death) using input parameters age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, treatment of hypertension and smoking status.¹² Input parameters were used in the same manner as in the D’Agostino method. The method used by D’Agostino and colleagues¹¹ calculates the sex-specific 10-year risk of cardiovascular disease (coronary artery disease, stroke, peripheral artery disease, heart failure) using input parameters age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, use of antihypertensive medications, current smoking status and diabetes status. We used sex-specific parameters where found. Otherwise, the same input parameters were used for both males and females, and the resulting risks were combined based on the proportion of males and females in each trial. For dichotomous input parameters (smoking: yes/no, diabetes: yes/no), we used the proportion of participants who smoked and the proportion who had diabetes for each trial (e.g., 0.119% for 11.9% smokers). For trials in which a parameter was not reported, we imputed the value using the median value of the trials that did report the parameter.

†Hypertension was assumed to be “treated” with the exception of three trials in which inclusion criteria permitted untreated or uncontrolled hypertension, or mandated that antihypertensive medications could not be used.