**SUPPLEMENT**

This supplementary material has been provided by the authors to give readers additional information about their work including eTables 1-16 and eFigures 1-26.

### SUPPLEMENT PART I

### METHODS

### Information sources

Studies were identified by searching Medline via Pubmed, ClinicalTrials.gov and Cochrane Central Register of Controlled Trials from 1994 to December 31th 2019. Our electronic search was supplemented by scanning the reference lists of the retrieved original articles and of previously published systematic review articles to identify additional trials. We also contacted research groups, authors of relevant articles, and prominent clinicians in the field to identify completed relevant trials awaiting publication.1

### Search strategy

### The Medline search strategy was developed by an author (RAG). The search concepts included “lipid lowering therapy”, “statin”, “ezetimibe”, “PCSK9 inhibitor”, “mortality” and “randomized controlled trial”. We used both standardized medical subject heading (MeSH) and text words. No restriction type of documents and methodology filters were used. The Medline search strategy was adjusted to account for differences in syntax and subject headings across electronic bibliographic databases.

### Study selection

Literature search results were uploaded along with titles and abstracts into a reference management software. Two review authors (PVE and RAG) independently screened citation titles and abstracts yielded by the literature search against pre-specified eligibility criteria. Full-text articles were retrieved for citations rated as potentially relevant by at least one of the two review authors. They independently assessed full text articles for eligibility, using a standardized form. Duplicate publications reporting data from the same study were identified by comparing author names, study sites, and sample sizes. Corresponding authors were contacted to obtain clarification on potential overlapping or inconsistencies across multiple reports of the same study.

Disagreements were resolved by discussion between the two review authors, and the reasons for excluding a study were recorded.

### Data extraction

Two review authors (PVE & RAG) independently collected qualitative and quantitative information using a standardized data extraction form. Where possible, outcome measures were extracted from published articles and entered into an Excel database. Corresponding authors and/or principal investigators of eligible primary studies were invited to collaborate in this systematic review by providing us with missing relevant information on pre-specified outcomes. Several authors responded including Paul Ridker for the JUPITER trial 2 Frank Sacks for the Pravastatin projects 3, Patrick Serruys for the LIPS trial 4, Hiroshi Ogawa for the HIJ-PROPER trial 5, John R. Downs for the AFCAPS/TexCAPS trial 6. Authors from the STATCOPE 7, HOPE-3 8 , GLAGOV 9, Post CABG 10, J-STARS 11, PREVEND IT 12, AURORA 13, SHARP 14, ALLIANCE 15 trials did not answer or declined to provide further details.

### Data items

Data extracted from eligible studies included the first author’s name, publication year, study name, number of participants, lipid lowering therapy for the intervention arm, control treatment, mean age for all participants, percentage of female participants, and prevalence of hypertension, diabetes, active smoking, follow-up duration, mean LDL-C levels at baseline and at the end of the trial for the intervention and control arms respectively.

We quantified the extent of LDL-C cholesterol reduction using the relative and absolute magnitude of reduction. The relative magnitude of LDL-C reduction was calculated as the percentage of change in LDL-C from baseline in the intervention arm minus that in the control arm. The absolute magnitude of LDL-C reduction was computed as the change in LDL-C from baseline in the intervention arm minus that in the control arm. 16

### Risk of bias assessment

Two review authors (PVE and RAG) independently appraised the methodological quality of the included studies for each outcome of interest, using a checklist adapted from the Cochrane Collaboration’s Risk of Bias tool.17 The risk of bias was assessed for the six domains that comprised the Cochrane bias tool, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.

**Analysis**

*Analytical sample.* The meta-analytical sample comprised all included primary studies. No primary study was excluded from the meta-analysis based on methodological quality assessment. Primary studies that did not gather data for a primary or secondary outcome of interest were excluded from the meta-analysis for the given outcome only.

*Descriptive summary statistics.* Baseline participant characteristics were reported as means or medians and standard deviations for continuous variables and numbers and percentages for categorical variables as appropriate.

*Effect size estimates.* To account for differences in follow-up duration across primary studies, we computed rate ratio (RR), defined as the ratio of the rate in the intervention group to the rate in the control group [Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration website. http://training.cochrane.org/handbook. 2011. Accessed February 26, 2018]. The rates for the event of interest were adjusted by person-years, a metric that incorporated study duration. Rate ratios were akin to relative risks as follow-up durations were similar for the intervention and control groups within each primary study [Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration website. http://training.cochrane.org/handbook. 2011. Accessed February 26, 2018]. We also computed absolute rate difference (ARD), which was expressed as numbers of events per 1000 person-years.

*Data synthesis.* We performed random-effect meta-analysis using the DerSimonian and Laird’s model for combining natural logarithm of rate ratios. To investigate heterogeneity in rate ratio estimates, we performed stratified random-effect meta-analysis with prespecified cut-off values for baseline LDL-C level (i.e., < 100, 100 to 129, 130 to 159 and ≥ 160 mg/dL), absolute magnitude of LDL-C reduction (i.e., < 35, 35 to 65, and > 65 mg/dL), relative magnitude of LDL-C reduction (i.e., < 30, 30 to 49 and ≥ 50 mg/dL), achieved LDL-C level (i.e., ≥ 116, 110 to 115, 70 to 99, 55 to 69 and < 55 mg/dL) and for annual CV mortality rates of control arms in population studies (<5, 5 to 9.999, 10 to 14.999 and ≥15‰) respectively. We performed separate univariable random-effect meta-regressions for modelling trends in natural logarithm of rate ratios as functions of baseline LDL-C level, absolute magnitude of LDL-C reduction, relative magnitude of LDL-C reduction, achieved LDL-C level, and annual CV mortality rates respectively.18 We assessed the linearity assumption for continuous variables by using fractional polynomial regression. We performed multivariable meta-regression to assess the independent associations between the natural logarithm of rate ratios and the magnitude of LDL-C reduction after adjusting for baseline LDL-C, publication year, mean age for all participants, and percentage of female participants. We further adjusted for annual CV mortality rates.

We estimated pooled ARD using the same meta-analytical approach and then derived number needed to treat (NNT) point estimates along with 95% confidence intervals (CI).19

*Investigation of heterogeneity.* We assessed between-study heterogeneity graphically by examining forest plots and statistically by using the *I*² inconsistency index.20 The *I*² index provides an estimate of the percentage of total variance across studies due to heterogeneity rather than chance. An *I*² index of 0% indicates no evidence of heterogeneity and larger values reflect increasing heterogeneity.20

*Reporting bias:* We investigatedpublication bias graphically by examining a scatter-plot of the rate ratio estimates from primary studies against the standard error.21 A symmetrical funnel shape would be consistent with the absence of selective reporting. Asymmetry was formally evaluated for statistical significance by using Egger’s test.21

*Software.* All data manipulation, figures, and analyses were documented in Stata programs and performed using Stata 14.0 Special Edition (Stata corp, College Station, Texas, USA).

**RESULTS**

**eFigure 1**. PRISMA 2009 Flow Diagram of randomized clinical trials evaluating the effect of low-density lipoprotein cholesterol–lowering therapies using statins and/or ezetimibe and/or PCSK-9 monoclonal antibodies on clinical outcomes

Studies included in quantitative synthesis (meta-analysis)  
(n = 59 for all-cause mortality outcome; n = 58 for CV mortality outcome)

Records excluded  
(n = 5,823 )

Records screened  
(n = 6,154 )

Records after duplicates removed  
(n = 6,154 )

## Identification

## Eligibility

## Included

## Screening

Additional records identified through other sources: ClinicalTrials.gov, Cochrane.org, Navarese’s paper  
(n = 539 + 77 + 34 )

Studies included in qualitative synthesis  
(n = 60 )

Full-text articles assessed for eligibility  
(n = 331 )

Records identified through PUBMED database searching  
(n = 6,804 )

Full-text articles excluded, for Not reporting neither deaths nor cardiovascular events per group, Mean follow-up <12 months, Sub studies of trials   
(n = 261)

**eTable 1.** PICO (Population/problem, Intervention, Comparison, and Outcome) table of the included randomized clinical trials

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Trials, journal, year of publication**  **(enrollment criteria)** | **Population**  **Type of prevention** | **Intervention** | **Comparator** | **Mean FU, years** | **Primary outcome** | **Results for the primary outcome** | **NNT** |
| **WOSCOPS, NEJM 1995 (1)**  (6,595 men, 45 to 64 years of age, with hypercholesterolemia and no history of MI) | Primary prevention | Pravastatin 40 mg | Placebo | 4.9 | Nonfatal MI or death from CHD | 248 definite coronary events in the placebo group, and 174 in the pravastatin group (RRR 31%; 95% CI 17-43%; *P* <0.001) | 44 |
| **KAPS, Circulation 1995 (2)**  (447 men, 44 to 65 years of age, with serum LDL-C levels ≥155 mg/dL and TC levels <290 mg/dl) | Primary prevention | Pravastatin 40 mg | Placebo | 3 | Rate of carotid atherosclerotic progression | Pravastatin reduced the rate of progression by 45% (95% Cl: l6-69%, *P* =0.005) and by 66% (95% Cl: 30-90%, *P* =0.002) in the common carotid arteries | NA |
| **CAIUS, Am J Med 1996 (3)**  (305 subjects, 45 to 65 years of age, LDL-C ≥155 mg/dL) | Primary prevention | Pravastatin 40 mg | Placebo | 3 | Progression of carotid atherosclerosis in asymptomatic patients with isolated moderate hypercholesterolemia | Progression of the carotid intima-media thickness was 0.009 ± 0.0027 versus -0.0043 ± 0.0028 mm/year (*P* <0.0007) in the placebo and pravastatin groups, respectively | NA |
| **AFCAPS/TexCAPS, JAMA 1998 (4)**  (6,605 men aged 45 to 73 years and postmenopausal women aged 55 to 73 years without clinically evident ASCVD with average TC and LDL-C levels and below average HDL-C levels) | Primary prevention | Lovastatin 20-40 mg | Placebo | 5.2 | First acute major coronary event defined as fatal or nonfatal MI, unstable angina, or sudden cardiac death | 183 vs 116 first events in the lovastatin group (RR 0.63; 95% CI, 0.50-0.79; *P* <0.001) | 49 |
| **PATE, J Atheroscler Thromb 2001 (5)**  (665 subjects, aged ≥60 years (73 ± 6 years) with serum TC levels of 220-280 mg/dL | Primary prevention | Pravastatin 10-20 mg (S) | Pravastatin  5 mg (L) | 3.9 | Fatal and nonfatal CV events including CVD, cardiac disease, PVD, and sudden death. CVD included cerebral infarction, cerebral hemorrhage, TIA, and subarachnoidal hemorrhage | The incidence of CV events was significantly lower in group S than in group L (*P* = 0.046, generalized Wilcoxon test; *P* = 0.096, log-rank test). The risk ratio for group S compared with group L was 0.674 (95% CI 0.423-1.074) | NA |
| ***ALLHAT, JAMA 2002 (6)***  (10,355, moderately hypercholesterolemic, hypertensive participants aged 55 years or older with at least 1 additional CHD risk factor) | Primary prevention | Pravastatin 40 mg | Usual care | 4.8 | All-cause mortality | All-cause mortality was similar for the 2 groups (RR 0.99; 95% CI 0.89-1.11; *P* =0.88), with 6-year mortality rates of 14.9% for pravastatin vs 15.3% with usual care | NA |
| **PROSPER, Lancet 2002 (7)**  (5,804 men (n=2804) and women (n=3000) aged 70–82 years with a history of, or risk factors for vascular disease) | Primary prevention  (44% were in secondary prevention) | Pravastatin 40 mg | Placebo | 3.2 | Coronary death, non-fatal MI, and fatal or non-fatal stroke | Pravastatin reduced the incidence of the primary endpoint to 408 events compared with 473 on placebo (HR 0·85, 95% CI 0·74–0·97, *P* =0·014) | 47 |
| **ASCOT-LLA, Lancet 2003 (8)**  (10,305 aged 40–79 years with at least three other CV risk factors) | Primary prevention | Atorvastatin 10 mg | Placebo | 3.3 | Non-fatal MI and fatal CHD | 100 primary events had occurred in the atorvastatin group compared with 154 events in the placebo group (HR 0·64 [95% CI 0·50–0·83], *P* =0·0005) | 94 |
| **CERDIA, Diabetes Care 2004 (9)**  (250 patients with type 2 diabetes for at least 1 year, aged 30–80 years, and without a history of CVD) | Primary prevention | Cerivastatin 0.4 mg replaced by 20 mg simvastatin without deblinding the study | Placebo | 1.28 | The change of mean common carotid IMT, as measured by B-mode ultrasound, over 2 years. | Common carotid IMT at baseline was 0.780 mm in the placebo group and 0.763 mm in the statin group and did not change significantly after 2 years | NA |
| ***PREVEND IT, Circulation 2004* (10)**  (864 microalbuminuric subjects aged 28 to 75 years) | Primary prevention | Pravastatin 40 mg | Placebo | 3.8 | Cardiovascular mortality and hospitalization for cardiovascular morbidity | Subjects treated with pravastatin had a nonsignificant 13% lower incidence of the primary end point than subjects in the placebo group (4.8% versus 5.6%, *P* =0.649 | NA |
| **CARDS, Lancet 2004 (11)**  (2,838 men and women aged 40–75 years with type 2 diabetes and at least one or  more of the following: a history of hypertension, retinopathy, microalbuminuria or macroalbuminuria, or currently smoking) | Primary prevention | Atorvastatin 10 mg | Placebo | 3.9 | Time to first occurrence of the following: acute CHD events, coronary revascularisation, or stroke | 127 patients allocated placebo (2·46 per 100 person-years at risk) and 83 allocated atorvastatin (1·54 per 100 person-years at risk) had at least one major cardiovascular event (RRR 37% [95% CI –52 to –17], *P* =0.001) | 31 |
| **MEGA, Lancet 2006 (12)**  (7,832 patients with hypercholesterolaemia (TC 5·69–6·98 mmol/L) and no history of CHD or stroke) | Primary prevention | Pravastatin 10-20 mg | Usual care | 5.3 | The first occurrence of CHD | Coronary heart disease was significantly lower in the diet plus pravastatin group than in the diet alone group (66 events vs 101 events; HR 0·67, 95% CI 0·49–0·91; *P* =0·01) | 119 |
| ***ASPEN, Diabetes Care 2006* (13)**  (2,410 subjects with type 2 diabetes) | Primary prevention  (21% were in secondary prevention) | Atorvastatin 10 mg | Placebo | 4 | Cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, CABG surgery, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization | When atorvastatin compared versus placebo, composite primary end point rates were 13.7 and 15.0%, respectively (HR 0.90 [95% CI 0.73–1.12]; *P* =0.34) | NA |
| ***SEAS, NEJM 2008* (14)**  (1,873 patients with mild-to moderate,  asymptomatic aortic stenosis) | Primary prevention | Simvastatin 40 mg  plus 10 mg of Ezetimibe | Placebo | 4.35 | Death from CV causes,  aortic-valve replacement, nonfatal MI, hospitalization for unstable angina pectoris, HF, coronary-artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke | The primary outcome occurred in 333 patients (35.3%) in the simvastatin–ezetimibe group and in 355 patients (38.2%) in the placebo group (HR in the simvastatin–ezetimibe group, 0.96; 95% CI 0.83 to 1.12; *P* =0.59) | NA |
| **JUPITER, NEJM 2008 (15)**  (17,802 apparently healthy men and women with LDL-C levels <130 mg/dL and high-sensitivity C-reactive protein levels ≥2.0 mg/l) | Primary prevention | Rosuvastatin 20 mg | Placebo | 1.9 | Myocardial infarction, stroke, arterial revascularization,  hospitalization for unstable angina, or death from cardiovascular causes. | The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (HR for rosuvastatin, 0.56; 95% CI 0.46-0.69; *P* <0.00001) | 82 |
| **STATCOPE, NEJM 2014 (16)**  (885 patients, 40 to 80 years of age, had COPD and a smoking history ≥10 pack-years, receiving supplemental oxygen or treatment with glucocorticoids or antibiotic agents, or had had an emergency department visit or hospitalization for COPD within the past year) | Primary prevention | Simvastatin 40 mg | Placebo | 1.8 | COPD exacerbation rate | The mean number of exacerbations per person-year was similar in the simvastatin and placebo groups: 1.36±1.61 exacerbations and 1.39±1.73 exacerbations, respectively (*P* =0.54) | NA |
| **HOPE 3, NEJM 2016 (17)**  (12,705 participants who did not have cardiovascular disease and were at intermediate risk) | Primary prevention | Rosuvastatin 10 mg | Placebo | 5.6 | Death from cardiovascular causes, nonfatal MI, or nonfatal stroke | The first coprimary outcome occurred in 235 participants (3.7%) in the rosuvastatin group and in 304 participants (4.8%) in the placebo group (HR 0.76; 95% CI 0.64-0.91; *P* =0.002) | 91 |
| ***EMPATHY, Diabetes Care 2018 (18)***  (5,144 patients with hypercholesterolemia, diabetic retinopathy, and no history of coronary artery disease) | Primary prevention | Intensive statin therapy targeting  LDL-C <70 mg/dL | Standard statin therapy targeting  LDL-C 100–120 mg/dL | 3.1 | Incidence of CV events, including cardiac, cerebral, renal, and vascular events, or CV-associated death | The primary end point events occurred in 129 intensive group patients and 153 standard group patients ([HR 0.84:95% CI 0.67–1.07]; *P* =0.15) | NA |
| ***TRACE RA, Arthritis & Rheumatology 2019 (19)***  (3,002 patients fulfilled the 1987 American College of Rheumatology rheumatoid arthritis (RA) Criteria, aged >50 years or had RA disease duration >10 years) | Primary prevention | Atorvastatin 40 mg | Placebo | 2.51 | Cardiovascular death, myocardial infarction, stroke, transient  ischemic attack, or any arterial revascularization. | Among patients allocated atorvastatin 24/1504 (1.6%) had a primary endpoint, compared with 36/1498 (2.4%) on placebo (HR 0.66, 95%CI 0.39-1.11, *P* =0.115) | NA |
| **EWTOPIA 75, Circulation 2019 (20)**  (3,796 patients aged ≥75 years with serum LDL-C level ≥140 mg/dL without history of CAD) | Primary prevention | Ezetimibe  10 mg | Usual care |  | A composite of sudden cardiac death, MI, coronary  revascularization, or stroke | Ezetimibe reduced the incidence of the primary outcome (HR 0.66; 95% CI 0.50-0.86; *P* =0.002). | 37 |
|  |  |  |  |  |  |  |  |
| **4S, Lancet 1994 (21)**  (4,444 patients with angina pectoris or previous MI and serum TC 5.5-8.0 mmol/L on a lipid-lowering diet) | Secondary prevention | Simvastatin 20-40 mg | Placebo | 5.4 | Total mortality | 256 patients (12%) in the placebo group died, compared with 182 (8%) in the simvastatin group (RR 0.70 (95% Cl 0.58-0.85, *P* =0.0003) | 30 |
| **ACAPS, Circulation 1994 (22)**  (919 asymptomatic men and women, 40 to 79 years old, with early carotid atherosclerosis as defined by B-mode ultrasonography and LDL-C between the 60th and 90th percentiles) | Secondary prevention | Lovastatin  20 to 40 mg | Placebo | 3 | 3-year change in mean maximum intimal-medial thickness (IMT) in 12 walls of the carotid arteries | Among participants not on warfarin, regression of the mean maximum IMT was seen after 12 months in the lovastatin group compared with the placebo group; the 3-year difference was statistically significant (*P* =0.001). | NA |
| **PLAC I, J Am Coll Cardiol 1995 (23)**  (408 patients with CAD, low density lipoprotein (LDL) cholesterol ≥130 mg/dL but <190 mg/dL) | Secondary prevention | Pravastatin 40 mg | Placebo | 2.4 | Atherosclerosis progression was  evaluated by quantitative coronary arteriography | Progression of atherosclerosis was reduced by 40% for minimal vessel diameter (p=0.04), particularly in lesions <50% stenosis at baseline. MI was reduced during active treatment (8 in the pravastatin group, 17 in the placebo group; log-rank test, *P* <0.05; RR 60%) | NA |
| **CARE, NEJM 1996 (24)**  (4,159 patients with MI who had plasma TC levels below 240 mg/dL and LDL-C levels of 115 to 174 mg/dL) | Secondary prevention | Pravastatin 40 mg | Placebo | 5 | Fatal coronary event or a nonfatal MI | The frequency of the primary end point was 10.2% in the pravastatin group and 13.2% in the placebo group (RR 24% (95% CI 9-36; *P* =0.003) | 33 |
| **LCAS, Am J Cardiol 1997 (25)**  (429 men and women aged 35 to 75 years with angiographic CHD and mean low-density lipoprotein (LDL) cholesterol of 115 to 190 mg/dL despite diet) | Secondary prevention | Fluvastatin  40 mg | Placebo | 2.5 | Within-patient per-lesion change in minimum lumen diameter (MLD) of qualifying lesions assessed by quantitative coronary angiography | Significantly less lesion progression in all fluvastatin versus all placebo patients, ΔMLD -0.028 versus -0.100 mm (*P* <0.01) | NA |
| **Post CABG, NEJM 1997 (26)**  (1351 patients who had undergone bypass surgery 1 to 11 years before base  line and who had an LDL cholesterol level between 130 and 175 mg/dL and at least one patent vein graft as seen on angiography) | Secondary prevention | Lovastatin  40-80 mg  (Cholestyramine 8 g in 30%) | Lovastatin  2.5-5 mg  (Cholestyramine 8 g in 5%) | 4.3 | The mean percentage per patient of grafts with a decrease of 0.6 mm or more in lumen diameter | The mean percentage of grafts with progression of atherosclerosis was 27% for patients whose LDL cholesterol level was lowered with aggressive treatment and 39% for those who received moderate treatment (*P* =0.001). | NA |
| **LIPID, NEJM 1998 (27)**  (9,014 patients who were 31 to 75 years of age, had a history of MI or hospitalization for unstable angina and initial plasma TC levels of 155 to 271 mg/dL) | Secondary prevention | Pravastatin 40 mg | Placebo | 6.1 | Mortality from coronary heart  disease | Death from coronary heart disease occurred in 8.3 percent of the patients in the placebo group and 6.4 percent of those in the pravastatin group, a relative reduction in risk of 24 percent (95% CI 12-35; *P* <0.001) | 52 |
| **SCAT, Circulation 2000 (28)**  (460 patients, mean age 61 years, total serum cholesterol levels between 4.1 and 6.2 mmol/L, angiographically detectable coronary atherosclerosis in ≥3 major coronary artery segments; and LVEF >35%) | Secondary prevention | Simvastatin 10-40 mg | Placebo | 3.98 | Changes in quantitative coronary angiographic measures | Mean diameters, -0.07 versus -0.14 mm (*P* =0.004); minimum diameters, -0.09 versus -0.16 mm (*P* =0.0001); and percent diameter stenosis, 1.67% versus 3.83% (*P* =0.0003) in simvastatin versus placebo group | NA |
| ***GISSI-P, Italian Heart Journal 2000 (29)***  (4,271 recent acute myocardial infarction patients (≤ 6 months) with total blood cholesterol ≥ 200 mg/dL) | Secondary prevention | Pravastatin 20 mg | No treatment | 2 | Cumulative rate of total mortality, non-fatal MI, and stroke | 256 (6.0%) patients either died or had a non-fatal stroke or a MI, 136 (6.4%) in the control group and 120 (5.6%) in the pravastatin group (RR 0.90, 95% CI 0.71-1.15, *P* =0.41) | NA |
| **FLORIDA, Eur Heart J 2002 (30)**  (540 patients, aged 61±11 years with an AMI and total cholesterol of <6·5 mmol/L) | Secondary prevention | Fluvastatin  80 mg | Placebo | 1 | Ischaemia was measured by ambulatory electrocardiographic monitoring over 48-h at baseline, after 6 weeks and at 12 months | Fluvastatin treatment did not affect ischaemia on ambulatory electrocardiographic, nor the occurrence of any major clinical events as compared to placebo | NA |
| **LIPS, JAMA 2002 (31)**  (1,677 patients, aged 18-80 years, with stable or unstable angina or silent ischemia following successful completion of their first PCI who had baseline TC between 135 and 270 mg/dL) | Secondary prevention | Fluvastatin  80 mg | Placebo | 3.9 | Cardiac death, nonfatal MI, or reintervention procedure | 181 (21.4%) of 844 patients in the fluvastatin group and 222 (26.7%) of 833 patients in the placebo group had at least 1 MACE (RR 0.78, 95% CI 0.64-0.95; *P* =0.01) | 19 |
| **HPS, Lancet 2002 (32)**  (20,536 UK adults (aged 40–80 years) with coronary disease, other occlusive arterial disease, or diabetes) | Secondary prevention | Simvastatin 40 mg | Placebo | 5 | All-cause mortality | All-cause mortality was significantly reduced (1328 [12·9%] deaths among 10 269 allocated simvastatin versus 1,507 [14·7%] among 10,267 allocated placebo; *P* =0.0003) | 57 |
| **GREACE, CMRO 2002 (33)**  (1600 consecutive patients with established CHD) | Secondary prevention | Atorvastatin  10-80 mg | Usual care | 3 | Death, non-fatal MI, unstable angina, congestive HF, revascularisation and stroke | 196 (24.5%) CHD patients on ‘usual’ care had a CHD recurrent event or died vs. 96 (12%) CHD patients on atorvastatin; risk ratio 0.49; CI 0.27-0.73, *P* < 0.0001. | 8 |
| **REVERSAL, JAMA 2004 (34)**  (502 patients, aged 30 to 75 years who required coronary angiography for a clinical indication and demonstrated at least 1 obstruction with angiographic luminal diameter narrowing of 20% or more) | Secondary prevention | Atorvastatin 80 mg | Pravastatin 40 mg | 1.5 | the percentage change in coronary artery atheroma volume | The percentage change in atheroma volume showed a significantly lower progression rate in the atorvastatin (intensive) group (*P* =0.02) | NA |
| **PROVE IT-TIMI 22, NEJM 2004 (35)**  (4,162 patients who had been hospitalized for an ACS within the preceding 10 days) | Secondary prevention | Atorvastatin 80 mg | Pravastatin 40 mg | 2 | death from any cause, MI, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke | the rates of the primary end point at two years were 26.3% in the pravastatin group and 22.4% in the atorvastatin group, reflecting a 16% reduction in the HR in favor of atorvastatin (*P* =0.005; 95% CI 5-26) | 25 |
| **ALLIANCE, JACC 2004 (36)**  (2,442 CHD patients with hyperlipidemia) | Secondary prevention | Atorvastatin 80 mg | Usual care | 4.3 | Cardiac death, non-fatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina  requiring hospitalization | A total of 289 (23.7%) patients in the atorvastatin group compared with 333 (27.7%) patients in the usual care group experienced a primary outcome (HR 0.83; 95% CI 0.71-0.97, *P* =0.02). | 29 |
| ***A to Z, JAMA 2004 (37)***  (4,497 patients with ACS) | Secondary prevention | Simvastatin 40 mg for 1 month followed by 80  mg/d thereafter | Placebo for 4 months  followed by 20 mg/d of simvastatin | 2 | Cardiovascular death, nonfatal MI, readmission for ACS, and stroke. | A total of 343 patients (16.7%) in the placebo plus simvastatin group experienced the primary end point compared with 309 (14.4%) in the simvastatin only group (40 mg/80 mg) (HR 0.89; 95% CI 0.76-1.04; *P* =0.14) | NA |
| ***IDEAL, JAMA 2005 (38)***  (8888 patients aged 80 years or younger with a history of acute MI) | Secondary prevention | Atorvastatin 80 mg | Simvastatin 20 mg | 4.8 | Coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation | A major coronary event occurred in 463 simvastatin patients (10.4%) and in 411 atorvastatin patients (9.3%) (HR 0.89; 95% CI 0.78-1.01; *P* =0.07) | NA |
| **TNT, NEJM 2005 (39)**  (10,001 patients with clinically evident CHD and LDL cholesterol levels <130 mg/dL) | Secondary prevention | Atorvastatin 80 mg | Atorvastatin 10 mg | 4.9 | Death from CHD, nonfatal non–procedure-related  MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke | A primary event occurred in 434 patients (8.7%) receiving 80 mg of atorvastatin, as compared with 548 patients (10.9%) receiving 10 mg of atorvastatin (HR 0.78; 95% CI 0.69-0.89; *P* <0.001) | 44 |
| **SAGE, Circulation 2007 (40)**  (891 65 to 85 years of age and had a documented history of CAD, baseline LDL-C levels between 100 mg/dL and 250 mg/dL, and ≥1 episode of myocardial ischemia with a total duration of ≥3 minutes during 48-hour ambulatory ECG monitoring at the screening visit) | Secondary prevention | Atorvastatin 80 mg | Pravastatin 40 mg | 1 | Absolute change from baseline in total duration of ischemia at month 12 | The primary endpoint was significantly reduced in both groups at month 3 and month 12 (both *z* <0.001 for each treatment group) with no significant difference between the treatment groups | NA |
| ***SEARCH, Lancet 2008 (41)***  (12,064 men and women aged 18–80 years with a history of MI were either currently on or had clear indication for statin therapy, and had a TC concentration of at least 3·5 mmol/L if already on a statin or 4∙5 mmol/L if not.) | Secondary prevention | Simvastatin 80 mg | Simvastatin 20 mg | 6.7 | Coronary death, MI, stroke, or arterial revascularization | Major vascular events occurred in 1,477 (24·5%) participants allocated 80 mg simvastatin versus 1553 (25·7%) of those allocated 20 mg, corresponding to a 6% proportional reduction (RR 0∙94, 95% CI 0.88-1.01; *P* =0.10) | NA |
| **SATURN, NEJM 2011 (42)**  (1,039 patients, 18 to 75 years of age, were eligible if they had at least one vessel with 20% stenosis on clinically indicated coronary angiography and a target vessel for imaging with less than 50% obstruction with a statin in the preceding 4 weeks were required to have an LDL-C >100 mg/dL; those who had received such treatment were  required to have >80 mg/dL) | Secondary prevention | Rosuvastatin 40 mg | Atorvastatin 80 mg | 2 | The progression of coronary atherosclerosis assessed by IVUS | The PAV decreased by 0.99% (95% CI −1.19 to −0.63) with atorvastatin and by 1.22% (95% CI −1.52 to −0.90) with rosuvastatin (*P* =0.17) | NA |
| **IMPROVE-IT, NEJM 2015 (43)**  (18,144 patients with an ACS within the preceding 10 days) | Secondary prevention | Simvastatin 40 mg and ezetimibe 10 mg | Simvastatin 40 mg alone | 6 | Cardiovascular death, nonfatal MI, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke | The primary end point at 7 years was 32.7% in the simvastatin-ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; HR 0.936; 95% CI 0.89-0.99; *P* =0.016) | 50 |
| **ODYSSEY LONG TERM, NEJM 2015 (44)**  (2,341 patients (≥18 years of age) with heterozygous familial hypercholesterolemia (as determined by genotyping or clinical criteria) or with established CHD or a CHD risk equivalent who had LDL-C ≥70 mg/dL and were receiving treatment with statins at the maximum tolerated dose | Secondary prevention  (62%) | Alirocumab 150 mg every 2 weeks | Placebo | 1.56 | The percentage change in calculated LDL cholesterol level from baseline to week 24 | At week 24, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL cholesterol level was −62 % (*P* <0.001); the treatment effect remained consistent over a period of 78 weeks | NA |
| **GLAGOV, JAMA 2016 (45)**  (968 patients, 18 years or older, with at least 1 epicardial coronary stenosis of 20% or greater on clinically indicated coronary angiography and had a target vessel suitable for imaging with 50% or less visual obstruction stable statin dose for at least 4 weeks and to have an LDL-C ≥80 mg/dL between 60 and 80 mg/dL with 1 major or 3 minor CV risk factors) | Secondary prevention | Evolocumab 420 mg monthly | Placebo |  | The nominal change in PAV from baseline to week 78, measured by serial IVUS imaging | The PAV increased 0.05% with placebo and decreased 0.95% with evolocumab (difference, −1.0% [95% CI −1.8% to −0.64%]; *P*  <0.001). | NA |
| **Im E et al., Rev Esp Cardiol 2017 (46)**  (2,000 clinically stable patients who underwent drug eluting stent implantation 12 months previously and received aspirin monotherapy) | Secondary prevention | Atorvastatin 40 mg | Pravastatin 20 mg | 1 | All death, MI, revascularization, stent thrombosis, stroke, renal deterioration, intervention for peripheral artery disease, and admission for cardiac events | The primary endpoint at 12-month follow-up occurred in 25 patients (2.5%) receiving high intensity statin treatment and in 40 patients (4.1%) receiving low-intensity statin treatment (HR, 0.58; 95%CI 0.36-0.92; *P* =0.018). | 62 |
| ***HIJ-PROPER, Eur Heart J 2017 (47)***  (1734 patients with ACS and dyslipidaemia) | Secondary prevention | Pivastatin  1-4 mg and ezetimibe 10 mg | Pivastatin  1-4 mg | 3.86 | All-cause death, non-fatal MI, non-fatal stroke, unstable angina, and ischemia driven  revascularization | Statin plus ezetimibe did not reduce primary endpoint occurrence in comparison with standard statin monotherapy (283/864, 32.8% vs. 316/857, 36.9%; HR 0.89, 95% CI 0.76-1.04, *P* =0.152) | NA |
| **SPIRE-2, N Engl J Med 2017 (48)**  (10,621 patients with previous cardiovascular event or a history of diabetes, chronic kidney disease, or peripheral vascular disease with additional cardiovascular risk conditions or a history of familial hypercholesterolemia and LDL ≥ 100 mg/dL) | Secondary mainly and primary prevention | Bococizumab 150 mg | Placebo | 1 | Nonfatal MI, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death | Major cardiovascular events occurred in 179 and 224 patients, respectively (HR 0.79; 95% CI 0.65-0.97; *P* =0.02). | 118 |
| **REAL CAD, Circulation 2018 (49)**  (13 054 Japanese patients with stable coronary artery disease who achieved LDL-C <120 mg/dL during a run-in period (pitavastatin 1 mg/d)) | Secondary prevention | Pivastatin  4 mg | Pivastatin  1 mg | 3.9 | Cardiovascular death, nonfatal MI, nonfatal ischemic stroke, or unstable angina requiring emergency hospitalization. | High-dose as compared with low-dose pitavastatin significantly reduced the risk of the primary end point (266 patients [4.3%] and 334 patients [5.4%]; HR 0.81; 95% CI 0.69-0.95; *P* =0.01) | 92 |
| **FOURIER, NEJM 2017 (50)**  (27,564 patients with ASCVD and LDL-C ≥70 mg/dL who were receiving statin therapy) | Secondary prevention | Evolocumab | Placebo | 2.2 | Cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization | Evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; HR 0.85; 95% CI 0.79-0.92; *P* <0.001) | 67 |
| **ODYSSEY OUTCOME, NEJM 2018 (51)**  (18,924 patients who had an ACS 1 to 12 months earlier, had a LDL-C level ≥70 mg/dL, a non HDL-C level ≥100 mg/dL, or an apolipoprotein B level ≥80 mg/dL, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose) | Secondary prevention | Alirocumab | Placebo | 2.8 | Death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization | A composite primary end-point event occurred in 903 patients (9.5%) in the alirocumab group and in 1052 patients (11.1%) in the placebo group (HR 0.85; 95% CI 0.78-0.93; *P* <0.001) | 49 |
|  |  |  |  |  |  |  |  |
| ***CORONA, NEJM 2007 (52)***  (5,011 patients at least 60 years of age with NYHA class II, III, or IV ischemic, systolic HF) | HF  (60% had previous MI) | Rosuvastatin 10 mg | Placebo | 2.7 | Death from any cause, any coronary event, death from  cardiovascular causes, and the number of hospitalizations | The primary outcome occurred in 692 patients in the rosuvastatin group and 732 in the placebo group (HR 0.92; 95% CI 0.83 to 1.02; *P* =0.12) | NA |
| ***GISSI-HF, Lancet 2008 (53)***  (4,574 patients aged 18 years or older with chronic HF of NYHA II–IV, irrespective of cause and left ventricular ejection fraction) | HF  (40% had ischemic heart disease) | Rosuvastatin 10 mg | Placebo | 3.9 | time to death | 657 (29%) patients died from any cause in the rosuvastatin group and 644 (28%) in the placebo group (adjusted HR 1·00 [95.5% CI 0·898-1.122], *P* =0.943) | NA |
|  |  |  |  |  |  |  |  |
| ***ALERT, Lancet 2003 (54)***  (2,102 renal transplant recipients with TC 4·0–9·0 mmol/L) | KD  (10% had CHD and 19% diabetes) | Fluvastatin  40 mg | Placebo | 5.1 | Cardiac death, nonfatal MI, or coronary intervention  procedure | Risk reduction with fluvastatin for the primary endpoint (RR 0·83 [95% CI 0.64-1.06], *P* =0.139) was not significant | NA |
| ***German Diabetes and Dialysis Study, NEJM 2004 (55)***  (1,255 subjects with type 2 KD diabetes mellitus receiving maintenance hemodialysis) | KD  (29% had CHD, 44.5% PVD) | Atorvastatin 20 mg | Placebo | 4 | Death from cardiac causes, nonfatal MI, and stroke | 469 patients (37%) reached the primary end point, of whom 226 were assigned to atorvastatin and 243 to placebo (RR 0.92; 95% CI 0.77-1.10; *P* =0.37) | NA |
| ***AURORA, NEJM 2009 (56)***  (2,776 patients, 50 to 80 years of age, who were undergoing maintenancehemodialysis) | KD  (40% had CVD, 26% diabetes) | Rosuvastatin 10 mg | Placebo | 3.8 | Death from cardiovascular  causes, nonfatal MI, or nonfatal stroke | 396 patients in the rosuvastatin group and 408 patients in the placebo group reached the primary end point (9.2 and 9.5 events per 100 patient-years, respectively; HR for the combined end point in the rosuvastatin group vs. the placebo group, 0.96; 95% CI 0.84-1.11; *P* =0.59) | NA |
| **SHARP, Lancet 2011 (57)**  (9,270 patients with chronic kidney disease (3,023 on dialysis and 6,247 not) with no known history of MI or coronary revascularization) | KD  (15% had CVD, 23% diabetes) | Simvastatin 20 mg plus ezetimibe 10 mg | Placebo | 4.9 | Non-fatal MI or coronary death, non-haemorrhagic stroke, or any arterial revascularization procedure) | A 17% proportional reduction in major atherosclerotic events (526 [11.3%] simvastatin plus ezetimibe vs 619 [13.4%] placebo; rate ratio 0·83, 95% CI 0.74-0.94; log-rank *P* =0.0021) | 48 |
|  |  |  |  |  |  |  |  |
| **SPARCL, NEJM 2006 (58)**  (4,731 patients who had had a stroke or TIA within one to six months before study entry, had low-density lipoprotein (LDL) cholesterol levels of 100 to 190 mg/dL, and had no known CHD) | Stroke | Atorvastatin 80 mg | Placebo | 4.9 | First nonfatal or fatal stroke | 265 patients (11.2%) receiving atorvastatin and 311 patients (13.1%) receiving placebo had a fatal or nonfatal stroke (adjusted HR 0.84; 95% CI 0.71-0.99; *P* =0.03; unadjusted *P* =0.05) | 52 |
| ***J-STARS, EBioMedicine 2015 (59)***  (1,578 patients who experienced non-cardioembolic ischemic stroke) | Stroke | Pravastatin 10 mg | No statin | 4.9 | Stroke recurrence and TIA | Stroke and TIA similarly occurred in both groups (2.56 vs. 2.65%/year) | NA |
| **TST, NEJ*M* 2019 (60)**  (2,860 patients with ischemic stroke in the previous 3 months or a TIA within the previous 15 days) | Stroke | Target LDL-C level <70 mg/dL | Target LDL-C range of 90 mg to 110 mg/dL | 3.5 | Ischemic stroke, MI, new symptoms leading to urgent coronary or carotid revascularization, or CV death | The composite primary end point occurred in 121 patients (8.5%) in the lower-target group and in 156 (10.9%) in the higher-target group (adjusted HR 0.78; 95% CI 0.61-0.98; *P* =0.04) | 41 |
|  |  |  |  |  |  |  |  |

**Abbreviations**: ACS: acute coronary syndrome; AMI: acute myocardial infarction; ASCVD: atherosclerotic cardiovascular disease; CAD: coronary artery disease; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; HF: heart failure; HR: hazard ratio; IVUS: intravascular ultrasonography; KD: kidney disease; LDL-C: low-density lipoprotein cholesterol; FU: follow-up; LV: left ventricular; MI: myocardial infarction; NA: non applicable; NEJM: New England Journal of Medicine; NNT: number of patients needed to treat in order to delay 1 primary end-point beyond the mean trial duration; NYHA: New York Heart Association; PAV: percent atheroma volume; PVD: peripheral vascular disease; RR: risk ratio or rate ratio or risk reduction; RRR: relative risk reduction; TC: total cholesterol; TIA: transient ischemic attack.

**eTable 2.** Studies and patients baseline characteristics in the included randomized clinical trials

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Trials, year of publication | Design | Countries | Recruitment period | Mean  age  (years) | HTN  (%) | DM  (%) | Smoker (%) | Female (%) | Mean baseline LDL-C (mg/dL) | | Mean achieved LDL-C (mg/dL) | | Relative LDL-C reduction (%) | Absolute LDL-C reduction (mg/dL) |
| **WOSCOPS** | Multicenter, double-blind placebo controlled RCT | West of Scotland | 1989-95 | 58 | 28.8 | 38 | 44 | 0 | 192 | 142.9 | | 26.2 | | 50.2 |
| **KAPS** | Single-center, double-blind placebo-controlled RCT | Finland | NA | 57.4 | 74 | 2.5 | 26.2 | 0 | 189 | 135 | | 29.7 | | 56 |
| **CAIUS** | Multicenter, double-blind placebo controlled RCT | Italy | NA | 55 | 0 | 0 | 24 | 47 | 180 | 140.2 | | 20.2 | | 36.2 |
| **AFCAPS/TexCAPS** | Multicenter, double-blind placebo-controlled RCT | Texas, US | 1990-93 | 55.2 | 21.9 | 2.3 | 12.4 | 15 | 150 | 115 | | 27.3 | | 41 |
| **PATE** | Multicenter nonblinded RCT | Japan | 1991-93 | 73 | 50.5 | 30 | 8.5 | 20.7 | 165 | 125 | | 5.2 | | 9 |
| ***ALLHAT*** | Multicenter nonblinded RCT  2X2 Factorial design | North America | 1994-2002 | 66.3 | 100 | 35.1 | 23.2 | 48.8 | 146.7 | 104.2 | | 15.8 | | 23.2 |
| **PROSPER** | Multicenter double-blind placebo-controlled RCT | Scotland, Ireland, Netherlands | 1997-2001 | 75.4 | 61.9 | 10.7 | 26.8 | 51.7 | 146.9 | 96.5 | | 33.9 | | 49.8 |
| **ASCOT-LLA** | Multicenter double-blind placebo-controlled RCT  2X2 Factorial design | UK, Ireland, Scandinavian | 1998-2000 | 63 | 100 | 24.6 | 32.7 | 18.8 | 132.8 | 86.9 | | 34.9 | | 46.3 |
| **CERDIA** | Multicenter double-blind placebo-controlled RCT | Netherlands | 2000-03 | 58.5 | 63 | 100 | 24 | 52.5 | 134.9 | 99.6 | | 31.4 | | 42 |
| ***PREVEND IT*** | Single-center double-blind placebo-controlled RCT  2X2 Factorial design | Netherlands | 1998-99 | 51.2 | 0 | 2.5 | 39.9 | 35.3 | 156.4 | 119.7 | | 21.9 | | 34.8 |
| **CARDS** | Multicenter double-blind placebo-controlled RCT | UK, Ireland | 1997-2001 | 62 | 84 | 100 | 22 | 32 | 117 | 74.1 | | 38.5 | | 45.2 |
| **MEGA** | Open-labelled, blinded RCT | Japan | 1994-2002 | 58 | 42 | 21 | 20.5 | 68.5 | 156.4 | 127.8 | | 14.6 | | 22.8 |
| ***ASPEN*** | Multicenter double-blind placebo-controlled RCT | North America, Europe, Australia, New Zealand, South Africa | 1996-2000 | 61 | 55 | 100 | 12.5 | 33.5 | 113.5 | 79 (primary prevention)  78.8 (secondary prevention) | | 29.8 (primary prevention)  26.2 (secondary prevention) | | 34 (primary prevention)  29.4 (secondary prevention) |
| ***SEAS*** | Multicenter double-blind placebo-controlled RCT | North Europe | 2001-02 | 67.6 | 51.5 | 0 | 19 | 38.6 | 139.5 | 52.5 | | 62.2 | | 87.1 |
| **JUPITER** | Multicenter double-blind placebo-controlled RCT | North and South America, Europe, South Africa | 2003-06 | 66 | 0 | 0 | 15.8 | 38.3 | 108 | 54.1 | | 42.9 | | 46.3 |
| **STATCOPE** | Multicenter double-blind placebo-controlled RCT | North America | 2010-11 | 62.2 | NA | 0 | 31.1 | 43.7 | 114.2 | 80.7 | | 23.3 | | 26.6 |
| **HOPE-3** | Multicenter double-blind placebo-controlled RCT  2X2 Factorial design | America, Asia, Europe, South Africa | 2007-10 | 65.7 | 37.9 | 5.8 | 27.7 | 46 | 127.8 |  | | 26.5 | | 34.6 |
| ***EMPATHY*** | Multicenter, open-label, blinded end point RCT | Japan | 2010-13 | 63.1 | 70.9 | 100 | 18.6 | 52.2 | 106.2 | 76.5 | | 26.1 | | 27.7 |
| ***TRACE RA*** | Multicenter double-blind placebo-controlled RCT | UK | 2007-11 | 61 | 21.9 | 0 | 15.6 | 74 | 123.7 | 85.5 | | 24 | | 29.87 |
| **EWTOPIA** | Multicenter, open-label, blinded end-point RCT | Japan | 2009-14 | 80.6 | 88.8 | 25.4 | 5 | 74.5 | 161.6 | 120 | | 7.4 | | 12 |
|  |  |  |  |  |  |  |  |  |  |  | |  | |  |
| **4S** | Multicenter double-blind placebo-controlled RCT | Scandinavia | 1988-94 | 59 | 26 | 4.5 | 25.5 | 18.5 | 188 | 116.6 | | 38 | | 71.4 |
| **ACAPS** | Single-center double-blind placebo-controlled RCT  2X2 Factorial design | US | 1989-90 | 61.7 | 28.8 | 2.3 | 11.9 | 48.5 | 155.6 | 113.1 | | 31.3 | | 48.9 |
| **PLAC I** | Multicenter double-blind placebo-controlled RCT | North America | 1987-94 | 57 | 45.5 | 0 | 16.5 | 22.5 | 164 | 118 | | 29 | | 47.6 |
| **CARE** | Multicenter double-blind placebo-controlled RCT | US, Canada | 1989-96 | 59 | 42.5 | 14.5 | 21 | 14 | 139 | 96.5 | | 27.8 | | 38.6 |
| **LCAS** | Single-center, placebo-controlled RCT | US | 1990-96 | 58.8 | 81.6 | 4.2 | 19.6 | 19 | 145.4 | 110.7 | | 19.9 | | 29.1 |
| **Post CABG** | Multicenter, placebo-controlled RCT  2X2 factorial design | US | 1989-93 | 61.5 | NA | 9 | 12 | 8 | 154.8 | 93 | | 27.8 | | 43 |
| **LIPID** | Multicenter double-blind placebo-controlled RCT | Australia, New Zealand | 1989-97 | 62 | 41.5 | 6.1 | 9.5 | 17 | 150 | 112 | | 25.3 | | 38 |
| **SCAT** | Multicenter double-blind placebo-controlled RCT  2X2 factorial design | Canada, Japan | 1991-95 | 61 | 36 | 11 | 15 | 11 | 129.7 | 90 | | 34.2 | | 44.7 |
| ***GISSI-P*** | Multicenter open-label blinded endpoint RCT  2X2 Factorial design | Italy | 1993-96 | 62 | 36.5 | 13.6 | 11.8 | 13.8 | 151.6 | 129.3 | | 11.8 | | 17.9 |
| **FLORIDA** | Multicenter double-blind placebo-controlled RCT | The Netherlands | 1997-99 | 61 | NA | NA | NA | 17 | 137 | 103 | | 29.5 | | 40 |
| **LIPS** | Multicenter double-blind placebo-controlled RCT | Europe, Canada, Brazil | 1996-98 | 67.6 | 38.6 | 12 | 26.6 | 16.2 | 131.5 | 95.6 | | 27 | | 35.4 |
| **HPS** | Multicenter double-blind placebo-controlled RCT  2X2 Factorial design | UK | 1994-2001 | 65 | 41 | 19 | 14 | 33 | 131.3 | 92.7 | | 29.4 | | 38.6 |
| **GREACE** | Multicenter, open-label RCT | Greece | 1998-2000 | 58.5 | 42.9 | 19.6 | NA | 21.5 | 179.5 | 165 | | 45.2 | | 81 |
| **REVERSAL** | Multicenter, double-blind, active control RCT | US | 1999-2001 | 56.2 | 69 | 19 | 26.5 | 28 | 150.2 | 78.9 | | 21 | | 31.5 |
| **PROVE IT-TIMI 22** | Multicenter double-blind placebo-controlled RCT | North America, Australia | 2000-03 | 58.2 | 50.1 | 17.6 | 36.7 | 21.9 | 106 | 62 | | 31.1 | | 33 |
| **ALLIANCE** | Multicenter, open-label RCT | US | 1995-98 | 61.2 | NA | 22.1 | 19.5 | 17.7 | 146.5 | 97 | | 10.7 | | 16 |
| ***A to Z*** | Multicenter double-blind placebo-controlled RCT | North and South America, Europe, Asia | 1999-2003 | 61 | 50 | 23.5 | 41 | 24.5 | 111.5 | 63 | | 13.2 | | 15 |
| ***IDEAL*** | Multicenter, open-label, blinded end-point RCT | Northern Europe | 1999-2005 | 61.7 | 33 | 12 | 20.6 | 19.1 | 121.5 | 81 | | 19.1 | | 23.2 |
| **TNT** | Multicenter double-blind RCT | North America, Europe, South Africa, Australia | 1998-2004 | 61 | 54.2 | 15 | 13.4 | 19 | 97.5 | 77 | | 23.7 | | 23 |
| **SAGE** | Multicenter double-blind RCT | North America, Europe, Israel, Turkey, Egypt, Australia | 2004-06 | 72.5 | 64.5 | 23.2 | 6.2 | 30.5 | 145.7 | 65.8 | | 23 | | 35 |
| ***SEARCH*** | Multicenter double-blind placebo-controlled RCT | UK | 1998-2008 | 64 | 42 | 11 | 30 | 17 | 97 | 83 | | 14.5 | | 14 |
| **SATURN** | Multicenter double-blind placebo-controlled RCT | North and South America, Europe, Australia | 2008-09 | 57.6 | 70.3 | 15.3 | 32.3 | 26.4 | 119.9 | 62.6 | | 6.3 | | 7.7 |
| **IMPROVE-IT** | Multicenter double-blind placebo-controlled RCT | North and South America, Europe, Asia Pacific, South Africa, Israel | 2005-14 | 63.6 | 61.5 | 27.2 | 33 | 24.3 | 93.8 | 53.7 | | 16.9 | | 15.8 |
| **ODYSSEY LONG TERM** | Multicenter double-blind placebo-controlled RCT | North and South America, South Africa, Europe, | 2012-14 | 60.5 | NA | 34.4 | 20.5 | 37.8 | 122.4 | 57.9 | | 53.4 | | 65.5 |
| **GLAGOV** | Multicenter double-blind placebo-controlled RCT | North and South America, Europe, Asia, Australia, South Africa | 2013-15 | 59.8 | 82.9 | 20.8 | 24.4 | 27.8 | 92.5 | 36.6 | | 60.9 | | 56.4 |
| **Im E et al.** | Multicenter, open-label, blinded endpoint RCT | Korea | 2010-14 | 64 | 60.6 | 28.5 | 21.5 | 29.3 | 74.1 | 67.8 | | 41.7 | | 30.9 |
| ***HIJ-PROPER*** | Multicenter, open-label, blinded endpoint RCT | Japan | 2010-13 | 65.6 | 68.2 | 30.2 | 34.5 | 24.5 | 135.2 | 65.1 | | 14.1 | | 18.7 |
| **SPIRE-2** | Multicenter double-blind placebo-controlled RCT | North and Latin America, Europe, Israel, Australia, New Zealand, Asia, South Africa | 2013-16 | 62.4 | 80.4 | 46.8 | 27.1 | 34.6 | 133.6 | 79.5 | | 43.2 | | 57.9 |
| **REAL CAD** | Multicenter, open-label, blinded endpoint RCT | Japan | 2010-16 | 68 | 75.6 | 40.1 | 16.4 | 17.3 | 87.9 | 76 | | 16.6 | | 14.6 |
| **FOURIER** | Multicenter double-blind placebo-controlled RCT | North and Latin America, Europe, Asia Pacific, South Africa | 2013-17 | 62.5 | 80.1 | 36.6 | 28.2 | 24.5 | 92 | 30 | | 65.2 | | 60 |
| **ODYSSEY OUTCOME** | Multicenter double-blind placebo-controlled RCT | North and Latin America, Europe, Asia, Australia, New Zealand, Israel | 2012-17 | 58.5 | 66.4 | 28.8 | 24.1 | 25.2 | 92 | 66 | | 40.3 | | 37 |
|  |  |  |  |  |  |  |  |  |  |  | |  | |  |
| ***CORONA*** | Multicenter double-blind placebo-controlled RCT | Northern Europe | 2003-07 | 73 | 63 | 29.5 | 8.5 | 24 | 137.1 | 76 | | 44.8 | | 61.2 |
| ***GISSI-HF*** | Multicenter double-blind placebo-controlled RCT | Italy | 2002-08 | 68 | 54.3 | 26.2 | 14 | 22.6 | 121.4 | 85.7 | | 32.4 | | 39.4 |
|  |  |  |  |  |  |  |  |  |  |  | |  | |  |
| ***ALERT*** | Multicenter double-blind placebo-controlled RCT | Northern Europe, Canada | 1996-2002 | 49.7 | 74.9 | 18.8 | 18.5 | 66 | 158.3 | 107.6 | | 24.1 | | 38.2 |
| ***German Diabetes and Dialysis Study*** | Multicenter double-blind placebo-controlled RCT | Germany | 1998-2004 | 65.7 | NA | 100 | 8.6 | 46 | 126 | 72 | | 36.9 | | 46 |
| ***AURORA*** | Multicenter double-blind placebo-controlled RCT | Europe, Canada, Australia | 2003-08 | 64 | NA | 26.3 | 15.5 | 37.9 | 99.5 | 58 | | 40.1 | | 40.1 |
| **SHARP** | Multicenter double-blind placebo-controlled RCT | North America, Europe, New Zealand, Asia | 2003-10 | 62 | NA | 23 | 13 | 37.5 | 107.1 | 71.4 | | 29.3 | | 31.3 |
|  |  |  |  |  |  |  |  |  |  |  | |  | |  |
| **SPARCL** | Multicenter double-blind placebo-controlled RCT | North and South America, Europe, Israel, Australia, New Zealand, South Africa | 1998-2005 | 62.7 | 61.7 | 16.8 | 19.2 | 40.4 | 133.2 | 72.9 | | 41.2 | | 54.6 |
| ***J-STARS*** | Multicenter, open-label, blinded-endpoint, parallel-group RCT | Japan | 2004-09 | 66.2 | 76 | 23.3 | 53.6 | 31.1 | 129.3 | 103.1 | | 16.4 | | 21.2 |
| **TST** | Multicenter, open-label, parallel-group, blinded-endpoint RCT | France, South Korea | 2010-18 | 66.7 | 65.6 | 22.6 | 30.2 | 32.4 | 135 | 65 | | 23 | | 31 |
|  |  |  |  |  |  |  |  |  |  |  | |  | |  |

**Abbreviations**: ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CAD: coronary artery disease; CHD: coronary heart disease; CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; HF: heart failure; HR: hazard ratio; HTN: hypertension; IVUS: intravascular ultrasonography; KD: kidney disease; LDL-C: low-density lipoprotein cholesterol; LFU: lost to follow-up; LV: left ventricular; MI: myocardial infarction; NA: non applicable; NEJM: New England Journal of Medicine; NNT: number of patients needed to treat in order to delay 1 primary end-point beyond the mean trial duration; NYHA: New York Heart Association; PAV: percent atheroma volume; PVD: peripheral vascular disorder; RR: risk ratio or rate ratio; RRR: relative risk reduction; TC: total cholesterol; TIA: transient ischemic attack.

**Of note within tables, trials are ordered in a similar way than in eTables 1&2**

**eTable 3.** Number of events in the less and intensive LDL-C lowering therapies arms for all-cause death

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **TRIALS** | **Population** | **Intervention group** | **Control group** | **All-cause death Intervention group** | **No death Intervention group** | **All-cause death Control group** | **No death Control group** |
| **WOSCOPS** | 6595 | 3302 | 3293 | 106 | 3196 | 135 | 3158 |
| **KAPS** | 447 | 224 | 223 | 4 | 220 | 3 | 220 |
| **CAIUS** | 305 | 151 | 154 | . | . | . | . |
| **AFCAPS/TexCAPS** | 6605 | 3304 | 3301 | 80 | 3224 | 77 | 3224 |
| **PATE** | 665 | 331 | 334 | 14 | 317 | 20 | 314 |
| **ALLHAT** | 10355 | 5170 | 5185 | 631 | 4539 | 641 | 4544 |
| **PROSPER** | 5804 | 2891 | 2913 | 298 | 2593 | 306 | 2607 |
| **ASCOT-LLA** | 10305 | 5168 | 5137 | 185 | 4983 | 212 | 4925 |
| **CERDIA** | 250 | 125 | 125 | 3 | 122 | 4 | 121 |
| **PREVEND IT** | 864 | 433 | 431 | 6 | 427 | 4 | 427 |
| **CARDS** | 2838 | 1428 | 1410 | 61 | 1367 | 82 | 1328 |
| **MEGA** | 7832 | 3866 | 3966 | 55 | 3811 | 79 | 3887 |
| **ASPEN Primary prevention** | 1905 | 959 | 946 | 44 | 915 | 41 | 905 |
| **ASPEN Secondary prevention** | 505 | 252,0 | 253,0 | 26 | 226 | 27 | 226 |
| **SEAS** | 1873 | 944 | 929 | 105 | 839 | 100 | 829 |
| **JUPITER** | 17802 | 8901 | 8901 | 198 | 8703 | 247 | 8654 |
| **STATCOPE** | 895 | 443 | 452 | 28 | 415 | 30 | 422 |
| **HOPE-3** | 12705 | 6361 | 6344 | 334 | 6027 | 357 | 5987 |
| **EMPATHY** | 5042 | 2518 | 2524 | 41 | 2477 | 34 | 2490 |
| **TRACE RA** | 3002 | 1504 | 1498 | 25 | 1479 | 27 | 1471 |
| **EWTOPIA** | 3411 | 1716 | 1695 | 188 | 1528 | 173 | 1522 |
| **4S** | 4444 | 2221 | 2223 | 182 | 2039 | 256 | 1967 |
| **ACAPS** | 919 | 460 | 459 | 1 | 459 | 8 | 451 |
| **PLAC-I** | 408 | 206 | 202 | 4 | 202 | 10 | 192 |
| **CARE** | 4159 | 2081 | 2078 | 180 | 1901 | 196 | 1882 |
| **LCAS** | 429 | 214 | 215 | 3 | 211 | 5 | 210 |
| **Post CABG** | 1351 | 676 | 675 | 32 | 644 | 35 | 640 |
| **LIPID** | 9014 | 4512 | 4502 | 498 | 4014 | 633 | 3869 |
| **SCAT** | 920 | 460 | 460 | 13 | 447 | 6 | 454 |
| **GISSI-P** | 4271 | 2138 | 2133 | 72 | 2066 | 88 | 2045 |
| **FLORIDA** | 540 | 265 | 275 | 7 | 258 | 11 | 264 |
| **LIPS** | 1677 | 844 | 833 | 36 | 808 | 49 | 784 |
| **HPS** | 20536 | 10269 | 10267 | 1328 | 8941 | 1507 | 8760 |
| **GREACE** | 1600 | 800 | 800 | 23 | 777 | 40 | 760 |
| **REVERSAL** | 502 | 253 | 249 | 1 | 252 | 1 | 248 |
| **PROVE IT-TIMI22** | 4162 | 2099 | 2063 | 46 | 2053 | 66 | 1997 |
| **ALLIANCE** | 2442 | 1217 | 1225 | 121 | 1096 | 127 | 1098 |
| **A to Z** | 4497 | 2265 | 2232 | 104 | 2161 | 130 | 2102 |
| **IDEAL** | 8888 | 4439 | 4449 | 366 | 4073 | 374 | 4075 |
| **TNT** | 10001 | 4995 | 5006 | 284 | 4711 | 282 | 4724 |
| **SAGE** | 891 | 446 | 445 | 6 | 440 | 18 | 427 |
| **SEARCH** | 12064 | 6031 | 6033 | 964 | 5067 | 970 | 5063 |
| **SATURN** | 1380 | 691 | 689 | . | . | . | . |
| **IMPROVE IT** | 18144 | 9067 | 9077 | 1215 | 7852 | 1231 | 7846 |
| **ODYSSEY LONG TERM** | 2341 | 1553 | 788 | 8 | 1545 | 10 | 778 |
| **GLAGOV** | 968 | 484 | 484 | 3 | 481 | 4 | 480 |
| **Im et al.** | 2000 | 1000 | 1000 | 5 | 995 | 8 | 992 |
| **HIJ PROPER** | 1721 | 864 | 857 | 42 | 822 | 60 | 797 |
| **SPIRE-2** | 10621 | 5312 | 5309 | 54 | 5258 | 59 | 5250 |
| **REAL CAD** | 12413 | 6199 | 6214 | 207 | 5992 | 260 | 5954 |
| **FOURIER** | 27564 | 13784,0 | 13780,0 | 444 | 13340 | 426 | 13354 |
| **ODYSSEY OUTCOME** | 18924 | 9462 | 9462 | 334 | 9128 | 392 | 9070 |
| **CORONA** | 5011 | 2514 | 2497 | 728 | 1786 | 759 | 1738 |
| **GISSI HF** | 4574 | 2285 | 2289 | 657 | 1628 | 644 | 1645 |
| **ALERT** | 2102 | 1050,00 | 1052,00 | 143 | 907 | 138 | 914 |
| **GDDS** | 1255 | 619 | 636 | 297 | 322 | 320 | 316 |
| **AURORA** | 2773 | 1389 | 1384 | 636 | 753 | 660 | 724 |
| **SHARP** | 9270 | 4650 | 4620 | 1142 | 3508 | 1115 | 3505 |
| **SPARCL** | 4731 | 2365 | 2366 | 216 | 2149 | 211 | 2155 |
| **J-STARS** | 1578 | 793 | 785 | 43 | 750 | 35 | 750 |
| **TST** | 2860 | 1430 | 1430 | 88 | 1342 | 93 | 1337 |

**eTable 4.** Number of events in the less and intensive LDL-C lowering therapies arms for cardiovascular death

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **TRIALS** | **Population** | **Intervention group** | **Control group** | **CV death Intervention group** | **No CV death Intervention group** | **CV death Control group** | **No CV death Control group** |
| **WOSCOPS** | 6595 | 3302 | 3293 | 50 | 3252 | 73 | 3220 |
| **KAPS** | 447 | 224 | 223 | 1 | 223 | 0 | 223 |
| **CAIUS** | 305 | 151 | 154 | 1 | 150 | 0 | 154 |
| **AFCAPS/TexCAPS** | 6605 | 3304 | 3301 | 17 | 3284 | 25 | 3276 |
| **PATE** | 665 | 331 | 334 | 8 | 323 | 6 | 328 |
| **ALLHAT** | 10355 | 5170 | 5185 | 295 | 4875 | 300 | 4885 |
| **PROSPER** | 5804 | 2891 | 2913 | 135 | 2756 | 157 | 2756 |
| **ASCOT-LLA** | 10305 | 5168 | 5137 | 74 | 5094 | 82 | 5055 |
| **CERDIA** | 250 | 125 | 125 | . | . | . | . |
| **PREVEND IT** | 864 | 433 | 431 | 4 | 429 | 4 | 427 |
| **CARDS** | 2838 | 1428 | 1410 | 25 | 1403 | 37 | 1373 |
| **MEGA** | 7832 | 3866 | 3966 | 11 | 3855 | 18 | 3948 |
| **ASPEN Primary prevention** | 1905 | 959 | 946 | 24 | 935 | 19 | 927 |
| **ASPEN Secondary prevention** | 505 | 252,0 | 253,0 | 14 | 238 | 18 | 235 |
| **SEAS** | 1873 | 944 | 929 | 47 | 897 | 56 | 873 |
| **JUPITER** | 17802 | 8901 | 8901 | 35 | 8866 | 43 | 8858 |
| **STATCOPE** | 895 | 443 | 452 | 4 | 439 | 4 | 448 |
| **HOPE-3** | 12705 | 6361 | 6344 | 154 | 6207 | 171 | 6173 |
| **EMPATHY** | 5042 | 2518 | 2524 | . | . | . | . |
| **TRACE RA** | 3002 | 1504 | 1498 | 6 | 1498 | 6 | 1492 |
| **EWTOPIA 75** | 3411 | 1716 | 1695 | 29 | 1687 | 45 | 1650 |
| **4S** | 4444 | 2221 | 2223 | 136 | 2085 | 207 | 2016 |
| **ACAPS** | 919 | 460 | 459 | 0 | 460 | 6 | 453 |
| **PLAC-I** | 408 | 206 | 202 | 3 | 203 | 3 | 199 |
| **CARE** | 4159 | 2081 | 2078 | 112 | 1969 | 130 | 1948 |
| **LCAS** | 429 | 214 | 215 | 1 | 213 | 2 | 213 |
| **Post CABG** | 1351 | 676 | 675 | 22 | 654 | 20 | 655 |
| **LIPID** | 9014 | 4512 | 4502 | 331 | 4181 | 433 | 4069 |
| **SCAT** | 920 | 460 | 460 | 7 | 453 | 4 | 456 |
| **GISSI-P** | 4271 | 2138 | 2133 | 52 | 2086 | 65 | 2068 |
| **FLORIDA** | 540 | 265 | 275 | 6 | 259 | 11 | 264 |
| **LIPS** | 1677 | 844 | 833 | 13 | 831 | 24 | 809 |
| **HPS** | 20536 | 10269 | 10267 | 781 | 9488 | 937 | 9330 |
| **GREACE** | 1600 | 800 | 800 | 20 | 780 | 38 | 762 |
| **REVERSAL** | 502 | 253 | 249 | . | . | . | . |
| **PROVE IT-TIMI22** | 4162 | 2099 | 2063 | 23 | 2076 | 29 | 2034 |
| **ALLIANCE** | 2442 | 1217 | 1225 | 43 | 1174 | 61 | 1164 |
| **A to Z** | 4497 | 2265 | 2232 | 83 | 2182 | 109 | 2123 |
| **IDEAL** | 8888 | 4439 | 4449 | 223 | 4216 | 218 | 4231 |
| **TNT** | 10001 | 4995 | 5006 | 126 | 4869 | 155 | 4851 |
| **SAGE** | 891 | 446 | 445 | 4 | 442 | 10 | 435 |
| **SEARCH** | 12064 | 6031 | 6033 | 565 | 5466 | 572 | 5461 |
| **SATURN** | 1380 | 691 | 689 | 2 | 689 | 2 | 687 |
| **IMPROVE IT** | 18144 | 9067 | 9077 | 537 | 8530 | 538 | 8539 |
| **ODYSSEY LONG TERM** | 2341 | 1553 | 788 | 4 | 1549 | 7 | 781 |
| **GLAGOV** | 968 | 484 | 484 | 3 | 481 | 4 | 480 |
| **Im et al.** | 2000 | 1000 | 1000 | 0 | 1000 | 4 | 996 |
| **HIJ PROPER** | 1721 | 864 | 857 | 26 | 838 | 28 | 829 |
| **SPIRE-2** | 10621 | 5312 | 5309 | 28 | 5284 | 34 | 5275 |
| **REAL CAD** | 12413 | 6199 | 6214 | 86 | 6113 | 112 | 6102 |
| **FOURIER** | 27564 | 13784,0 | 13780,0 | 251 | 13533 | 240 | 13540 |
| **ODYSSEY OUTCOME** | 18924 | 9462 | 9462 | 240 | 9222 | 271 | 9191 |
| **CORONA** | 5011 | 2514 | 2497 | 488 | 2026 | 487 | 2010 |
| **GISSI HF** | 4574 | 2285 | 2289 | 478 | 1807 | 488 | 1801 |
| **ALERT** | 2102 | 1050,00 | 1052,00 | 66 | 984 | 73 | 979 |
| **GDDS** | 1255 | 619 | 636 | 148 | 471 | 162 | 474 |
| **AURORA** | 2773 | 1389 | 1384 | 324 | 1065 | 324 | 1060 |
| **SHARP** | 9270 | 4650 | 4620 | 361 | 4289 | 388 | 4232 |
| **SPARCL** | 4731 | 2365 | 2366 | 78 | 2287 | 98 | 2268 |
| **J-STARS** | 1578 | 793 | 785 | 4 | 789 | 4 | 781 |
| **TST** | 2860 | 1430 | 1430 | 22 | 1408 | 32 | 1398 |

**eTable 5.** Number of events in the less and intensive LDL-C lowering therapies arms for myocardial infarction

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **TRIALS** | **Population** | **Intervention group** | **Control group** | **CV death Intervention group** | **No CV death Intervention group** | **CV death Control group** | **No CV death Control group** |
| **WOSCOPS** | 6595 | 3302 | 3293 | 50 | 3252 | 73 | 3220 |
| **KAPS** | 447 | 224 | 223 | 1 | 223 | 0 | 223 |
| **CAIUS** | 305 | 151 | 154 | 1 | 150 | 0 | 154 |
| **AFCAPS/TexCAPS** | 6605 | 3304 | 3301 | 17 | 3284 | 25 | 3276 |
| **PATE** | 665 | 331 | 334 | 8 | 323 | 6 | 328 |
| **ALLHAT** | 10355 | 5170 | 5185 | 295 | 4875 | 300 | 4885 |
| **PROSPER** | 5804 | 2891 | 2913 | 135 | 2756 | 157 | 2756 |
| **ASCOT-LLA** | 10305 | 5168 | 5137 | 74 | 5094 | 82 | 5055 |
| **CERDIA** | 250 | 125 | 125 | . | . | . | . |
| **PREVEND IT** | 864 | 433 | 431 | 4 | 429 | 4 | 427 |
| **CARDS** | 2838 | 1428 | 1410 | 25 | 1403 | 37 | 1373 |
| **MEGA** | 7832 | 3866 | 3966 | 11 | 3855 | 18 | 3948 |
| **ASPEN Primary prevention** | 1905 | 959 | 946 | 24 | 935 | 19 | 927 |
| **ASPEN Secondary prevention** | 505 | 252,0 | 253,0 | 14 | 238 | 18 | 235 |
| **SEAS** | 1873 | 944 | 929 | 47 | 897 | 56 | 873 |
| **JUPITER** | 17802 | 8901 | 8901 | 35 | 8866 | 43 | 8858 |
| **STATCOPE** | 895 | 443 | 452 | 4 | 439 | 4 | 448 |
| **HOPE-3** | 12705 | 6361 | 6344 | 154 | 6207 | 171 | 6173 |
| **EMPATHY** | 5042 | 2518 | 2524 | . | . | . | . |
| **TRACE RA** | 3002 | 1504 | 1498 | 6 | 1498 | 6 | 1492 |
| **EWTOPIA** | 3411 | 1716 | 1695 | 29 | 1687 | 45 | 1650 |
| **4S** | 4444 | 2221 | 2223 | 136 | 2085 | 207 | 2016 |
| **ACAPS** | 919 | 460 | 459 | 0 | 460 | 6 | 453 |
| **PLAC-I** | 408 | 206 | 202 | 3 | 203 | 3 | 199 |
| **CARE** | 4159 | 2081 | 2078 | 112 | 1969 | 130 | 1948 |
| **LCAS** | 429 | 214 | 215 | 1 | 213 | 2 | 213 |
| **Post CABG** | 1351 | 676 | 675 | 22 | 654 | 20 | 655 |
| **LIPID** | 9014 | 4512 | 4502 | 331 | 4181 | 433 | 4069 |
| **SCAT** | 920 | 460 | 460 | 7 | 453 | 4 | 456 |
| **GISSI-P** | 4271 | 2138 | 2133 | 52 | 2086 | 65 | 2068 |
| **FLORIDA** | 540 | 265 | 275 | 6 | 259 | 11 | 264 |
| **LIPS** | 1677 | 844 | 833 | 13 | 831 | 24 | 809 |
| **HPS** | 20536 | 10269 | 10267 | 781 | 9488 | 937 | 9330 |
| **GREACE** | 1600 | 800 | 800 | 20 | 780 | 38 | 762 |
| **REVERSAL** | 502 | 253 | 249 | . | . | . | . |
| **PROVE IT-TIMI22** | 4162 | 2099 | 2063 | 23 | 2076 | 29 | 2034 |
| **ALLIANCE** | 2442 | 1217 | 1225 | 43 | 1174 | 61 | 1164 |
| **A to Z** | 4497 | 2265 | 2232 | 83 | 2182 | 109 | 2123 |
| **IDEAL** | 8888 | 4439 | 4449 | 223 | 4216 | 218 | 4231 |
| **TNT** | 10001 | 4995 | 5006 | 126 | 4869 | 155 | 4851 |
| **SAGE** | 891 | 446 | 445 | 4 | 442 | 10 | 435 |
| **SEARCH** | 12064 | 6031 | 6033 | 565 | 5466 | 572 | 5461 |
| **SATURN** | 1380 | 691 | 689 | 2 | 689 | 2 | 687 |
| **IMPROVE IT** | 18144 | 9067 | 9077 | 537 | 8530 | 538 | 8539 |
| **ODYSSEY LONG TERM** | 2341 | 1553 | 788 | 4 | 1549 | 7 | 781 |
| **GLAGOV** | 968 | 484 | 484 | 3 | 481 | 4 | 480 |
| **Im et al.** | 2000 | 1000 | 1000 | 0 | 1000 | 4 | 996 |
| **HIJ PROPER** | 1721 | 864 | 857 | 26 | 838 | 28 | 829 |
| **SPIRE-2** | 10621 | 5312 | 5309 | 28 | 5284 | 34 | 5275 |
| **REAL CAD** | 12413 | 6199 | 6214 | 86 | 6113 | 112 | 6102 |
| **FOURIER** | 27564 | 13784,0 | 13780,0 | 251 | 13533 | 240 | 13540 |
| **ODYSSEY OUTCOME** | 18924 | 9462 | 9462 | 240 | 9222 | 271 | 9191 |
| **CORONA** | 5011 | 2514 | 2497 | 488 | 2026 | 487 | 2010 |
| **GISSI HF** | 4574 | 2285 | 2289 | 478 | 1807 | 488 | 1801 |
| **ALERT** | 2102 | 1050,00 | 1052,00 | 66 | 984 | 73 | 979 |
| **GDDS** | 1255 | 619 | 636 | 148 | 471 | 162 | 474 |
| **AURORA** | 2773 | 1389 | 1384 | 324 | 1065 | 324 | 1060 |
| **SHARP** | 9270 | 4650 | 4620 | 361 | 4289 | 388 | 4232 |
| **SPARCL** | 4731 | 2365 | 2366 | 78 | 2287 | 98 | 2268 |
| **J-STARS** | 1578 | 793 | 785 | 4 | 789 | 4 | 781 |
| **TST** | 2860 | 1430 | 1430 | 22 | 1408 | 32 | 1398 |

**eTable 6.** Number of events in the less and intensive LDL-C lowering therapies arms for stroke

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **TRIALS** | **Population** | **Intervention group** | **Control group** | **Stroke Intervention group** | **No Stroke Intervention group** | **Stroke Control group** | **No Stroke Control group** |
| **WOSCOPS** | 6595 | 3302 | 3293 | 46 | 3256 | 51 | 3242 |
| **KAPS** | 447 | 224 | 223 | . | . | . | . |
| **CAIUS** | 305 | 151 | 154 | . | . | . | . |
| **AFCAPS/TexCAPS** | 6605 | 3304 | 3301 | 14 | 3290 | 17 | 3284 |
| **PATE** | 665 | 331 | 334 | 11 | 320 | 15 | 319 |
| **ALLHAT** | 10355 | 5170 | 5185 | 209 | 4961 | 231 | 4954 |
| **PROSPER** | 5804 | 2891 | 2913 | 135 | 2756 | 131 | 2782 |
| **ASCOT-LLA** | 10305 | 5168 | 5137 | 89 | 5079 | 121 | 5016 |
| **CERDIA** | 250 | 125 | 125 | . | . | . | . |
| **PREVEND IT** | 864 | 433 | 431 | 7 | 426 | 4 | 427 |
| **CARDS** | 2838 | 1428 | 1410 | 21 | 1407 | 39 | 1371 |
| **MEGA** | 7832 | 3866 | 3966 | 34 | 3832 | 46 | 3920 |
| **ASPEN Primary prevention** | 1905 | 959 | 946 | 27 | 932 | 29 | 917 |
| **ASPEN Secondary prevention** | 505 | 252,0 | 253,0 | 7 | 245 | 9 | 244 |
| **SEAS** | 1873 | 944 | 929 | 33 | 911 | 29 | 900 |
| **JUPITER** | 17802 | 8901 | 8901 | 33 | 8868 | 64 | 8837 |
| **STATCOPE** | 895 | 443 | 452 | . | . | . | . |
| **HOPE-3** | 12705 | 6361 | 6344 | 70 | 6291 | 99 | 6245 |
| **EMPATHY** | 5042 | 2518 | 2524 | 22 | 2496 | 41 | 2483 |
| **TRACE RA** | 3002 | 1504 | 1498 | 6 | 1498 | 12 | 1486 |
| **EWTOPIA** | 3411 | 1716 | 1695 | 55 | 1661 | 70 | 1625 |
| **4S** | 4444 | 2221 | 2223 | 16 | 2205 | 33 | 2190 |
| **ACAPS** | 919 | 460 | 459 | 0 | 460 | 5 | 454 |
| **PLAC-I** | 408 | 206 | 202 | 0 | 206 | 2 | 200 |
| **CARE** | 4159 | 2081 | 2078 | 54 | 2027 | 78 | 2000 |
| **LCAS** | 429 | 214 | 215 | . | . | . | . |
| **Post CABG** | 1351 | 676 | 675 | . | . | . | . |
| **LIPID** | 9014 | 4512 | 4502 | 169 | 4343 | 204 | 4298 |
| **SCAT** | 920 | 460 | 460 | 4 | 456 | 7 | 453 |
| **GISSI-P** | 4271 | 2138 | 2133 | 20 | 2118 | 19 | 2114 |
| **FLORIDA** | 540 | 265 | 275 | . | . | . | . |
| **LIPS** | 1677 | 844 | 833 | 2 | 842 | 1 | 832 |
| **HPS** | 20536 | 10269 | 10267 | 290 | 9979 | 409 | 9858 |
| **GREACE** | 1600 | 800 | 800 | 9 | 791 | 17 | 783 |
| **REVERSAL** | 502 | 253 | 249 | 1 | 252 | 1 | 248 |
| **PROVE IT-TIMI22** | 4162 | 2099 | 2063 | 21 | 2078 | 20 | 2043 |
| **ALLIANCE** | 2442 | 1217 | 1225 | 35 | 1182 | 39 | 1186 |
| **A to Z** | 4497 | 2265 | 2232 | 28 | 2237 | 35 | 2197 |
| **IDEAL** | 8888 | 4439 | 4449 | 151 | 4288 | 174 | 4275 |
| **TNT** | 10001 | 4995 | 5006 | 117 | 4878 | 155 | 4851 |
| **SAGE** | 891 | 446 | 445 | 1 | 445 | 3 | 442 |
| **SEARCH** | 12064 | 6031 | 6033 | 255 | 5776 | 279 | 5754 |
| **SATURN** | 1380 | 691 | 689 | 3 | 688 | 2 | 687 |
| **IMPROVE IT** | 18144 | 9067 | 9077 | 236 | 8831 | 297 | 8780 |
| **ODYSSEY LONG TERM** | 2341 | 1553 | 788 | 9 | 1544 | 2 | 786 |
| **GLAGOV** | 968 | 484 | 484 | 2 | 482 | 3 | 481 |
| **Im et al.** | 2000 | 1000 | 1000 | 2 | 998 | 3 | 997 |
| **HIJ PROPER** | 1721 | 864 | 857 | 17 | 847 | 18 | 839 |
| **SPIRE-2** | 10621 | 5312 | 5309 | 26 | 5286 | 39 | 5270 |
| **REAL CAD** | 12413 | 6199 | 6214 | 84 | 6115 | 83 | 6131 |
| **FOURIER** | 27564 | 13784,0 | 13780,0 | 117 | 13667 | 226 | 13554 |
| **ODYSSEY OUTCOME** | 18924 | 9462 | 9462 | 111 | 9351 | 152 | 9310 |
| **CORONA** | 5011 | 2514 | 2497 | 103 | 2411 | 115 | 2382 |
| **GISSI HF** | 4574 | 2285 | 2289 | 82 | 2203 | 66 | 2223 |
| **ALERT** | 2102 | 1050,00 | 1052,00 | 74 | 976 | 63 | 989 |
| **GDDS** | 1255 | 619 | 636 | 47 | 572 | 33 | 603 |
| **AURORA** | 2773 | 1389 | 1384 | 57 | 1332 | 55 | 1329 |
| **SHARP** | 9270 | 4650 | 4620 | 114 | 4536 | 157 | 4463 |
| **SPARCL** | 4731 | 2365 | 2366 | 265 | 2100 | 311 | 2055 |
| **J-STARS** | 1578 | 793 | 785 | 54 | 739 | 62 | 723 |
| **TST** | 2860 | 1430 | 1430 | 88 | 1342 | 109 | 1321 |

**eTable 7.** Number of events in the less and intensive LDL-C lowering therapies arms for non-cardiovascular death

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **TRIALS** | **Population** | **Intervention group** | **Control group** | **Non CV death Intervention group** | **No non CV death Intervention group** | **Non CV death Control group** | **No non CV death Control group** |
| **WOSCOPS** | 6595 | 3302 | 3293 | 56 | 3246 | 62 | 3231 |
| **KAPS** | 447 | 224 | 223 | 3 | 221 | 3 | 220 |
| **CAIUS** | 305 | 151 | 154 | . | . | . | . |
| **AFCAPS/TexCAPS** | 6605 | 3304 | 3301 | 63 | 3241 | 52 | 3249 |
| **PATE** | 665 | 331 | 334 | 6 | 325 | 14 | 320 |
| **ALLHAT** | 10355 | 5170 | 5185 | 336 | 4834 | 341 | 4844 |
| **PROSPER** | 5804 | 2891 | 2913 | 163 | 2728 | 149 | 2764 |
| **ASCOT-LLA** | 10305 | 5168 | 5137 | 111 | 5057 | 130 | 5007 |
| **CERDIA** | 250 | 125 | 125 | . | . | . | . |
| **PREVEND IT** | 864 | 433 | 431 | 2 | 431 | 0 | 431 |
| **CARDS** | 2838 | 1428 | 1410 | 36 | 1392 | 45 | 1365 |
| **MEGA** | 7832 | 3866 | 3966 | 44 | 3822 | 61 | 3905 |
| **ASPEN Primary prevention** | 1905 | 959 | 946 | 20 | 939 | 22 | 924 |
| **ASPEN Secondary prevention** | 505 | 252,0 | 253,0 | 12 | 240 | 9 | 244 |
| **SEAS** | 1873 | 944 | 929 | 58 | 886 | 44 | 885 |
| **JUPITER** | 17802 | 8901 | 8901 | 163 | 8738 | 204 | 8697 |
| **STATCOPE** | 895 | 443 | 452 | 24 | 419 | 26 | 426 |
| **HOPE-3** | 12705 | 6361 | 6344 | 180 | 6181 | 186 | 6158 |
| **EMPATHY** | 5042 | 2518 | 2524 | . | . | . | . |
| **TRACE RA** | 3002 | 1504 | 1498 | 19 | 1485 | 21 | 1477 |
| **EWTOPIA** | 3411 | 1716 | 1695 | 159 | 1557 | 128 | 1567 |
| **4S** | 4444 | 2221 | 2223 | 46 | 2175 | 49 | 2174 |
| **ACAPS** | 919 | 460 | 459 | 1 | 459 | 2 | 457 |
| **PLAC-I** | 408 | 206 | 202 | 1 | 205 | 7 | 195 |
| **CARE** | 4159 | 2081 | 2078 | 68 | 2013 | 66 | 2012 |
| **LCAS** | 429 | 214 | 215 | 2 | 212 | 3 | 212 |
| **POST CABG** | 1351 | 676 | 675 | 10 | 666 | 15 | 660 |
| **LIPID** | 9014 | 4512 | 4502 | 167 | 4345 | 200 | 4302 |
| **SCAT** | 920 | 460 | 460 | 6 | 454 | 2 | 458 |
| **GISSI-P** | 4271 | 2138 | 2133 | 20 | 2118 | 23 | 2110 |
| **FLORIDA** | 540 | 265 | 275 | 1 | 264 | 0 | 275 |
| **LIPS** | 1677 | 844 | 833 | 23 | 821 | 25 | 808 |
| **HPS** | 20536 | 10269 | 10267 | 547 | 9722 | 570 | 9697 |
| **GREACE** | 1600 | 800 | 800 | 3 | 797 | 2 | 798 |
| **REVERSAL** | 502 | 253 | 249 | . | . | . | . |
| **PROVE IT-TIMI22** | 4162 | 2099 | 2063 | 23 | 2076 | 37 | 2026 |
| **ALLIANCE** | 2442 | 1217 | 1225 | 78 | 1139 | 66 | 1159 |
| **A to Z** | 4497 | 2265 | 2232 | 21 | 2244 | 21 | 2211 |
| **IDEAL** | 8888 | 4439 | 4449 | 143 | 4296 | 156 | 4293 |
| **TNT** | 10001 | 4995 | 5006 | 158 | 4837 | 127 | 4879 |
| **SAGE** | 891 | 446 | 445 | 2 | 444 | 8 | 437 |
| **SEARCH** | 12064 | 6031 | 6033 | 399 | 5632 | 398 | 5635 |
| **SATURN** | 1380 | 691 | 689 | . | . | . | . |
| **IMPROVE IT** | 18144 | 9067 | 9077 | 678 | 8389 | 693 | 8384 |
| **ODYSSEY LONG TERM** | 2341 | 1553 | 788 | 4 | 1549 | 3 | 785 |
| **GLAGOV** | 968 | 484 | 484 | 0 | 484 | 0 | 484 |
| **Im et al.** | 2000 | 1000 | 1000 | 5 | 995 | 4 | 996 |
| **HIJ-PROPER** | 1721 | 864 | 857 | 16 | 848 | 32 | 825 |
| **SPIRE-2** | 10621 | 5312 | 5309 | 26 | 5286 | 25 | 5284 |
| **REAL CAD** | 12413 | 6199 | 6214 | 121 | 6078 | 148 | 6066 |
| **FOURIER** | 27564 | 13784,0 | 13780,0 | 193 | 13591 | 186 | 13594 |
| **ODYSSEY OUTCOME** | 18924 | 9462 | 9462 | 94 | 9368 | 121 | 9341 |
| **CORONA** | 5011 | 2514 | 2497 | 240 | 2274 | 272 | 2225 |
| **GISSI HF** | 4574 | 2285 | 2289 | 179 | 2106 | 156 | 2133 |
| **ALERT** | 2102 | 1050,00 | 1052,00 | 77 | 973 | 65 | 987 |
| **GDDS** | 1255 | 619 | 636 | 149 | 470 | 158 | 478 |
| **AURORA** | 2773 | 1389 | 1384 | 312 | 1077 | 336 | 1048 |
| **SHARP** | 9270 | 4650 | 4620 | 781 | 3869 | 727 | 3893 |
| **SPARCL** | 4731 | 2365 | 2366 | 138 | 2227 | 113 | 2253 |
| **J-STARS** | 1578 | 793 | 785 | 39 | 754 | 31 | 754 |
| **TST** | 2860 | 1430 | 1430 | 66 | 1364 | 61 | 1369 |

**Methodological quality appraisal**

Assessment of the risk of bias within individual trials is detailed in eTable 1. Main limitation was the risk of bias in allocation concealment as lipid results were not blinded to investigators or participants in most trials. In several trials CV events were not carefully reported or defined as fatal and/or nonfatal events.

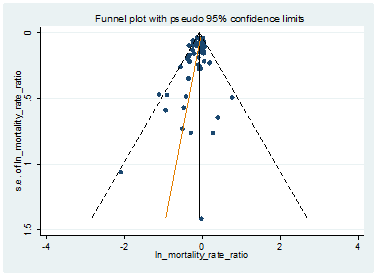
|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **eTable 8 :** Listing of potential sources of bias | | | | | | |
| **TRIALS** | **Random sequence**  **generation** | **Allocation concealment** | **Blinding of participants**  **and personnel** | **Blinding of outcome**  **assessment** | **Incomplete outcome**  **data** | **Selective reporting** |
| **WOSCOPS** | **+** | **±** | **+** | **+** | **+** | **+** |
| **KAPS** | **+** | **+** | **+** | **+** | **-** | **+** |
| **CAIUS** | **+** | **±** | **+** | **+** | **-** | **+** |
| **AFCAPS/TexCAPS** | **+** | **±** | **+** | **+** | **+** | **+** |
| **PATE** | **+** | **±** | **+** | **+** | **+** | **+** |
| **ALLHAT** | **+** | **-** | **-** | **-** | **+** | **+** |
| **PROSPER** | **+** | **±** | **+** | **+** | **+** | **+** |
| **ASCOT-LLA** | **+** | **±** | **+** | **+** | **+** | **+** |
| **CERDIA** | **+** | **±** | **+** | **+** | **-** | **+** |
| **PREVEND IT** | **+** | **±** | **+** | **+** | **±** | **+** |
| **CARDS** | **+** | **±** | **+** | **+** | **+** | **+** |
| **MEGA** | **+** | **-** | **-** | **+** | **+** | **+** |
| **ASPEN Primary prevention** | **+** | **±** | **+** | **+** | **+** | **+** |
| **ASPEN Secondary prevention** | **+** | **±** | **+** | **+** | **+** | **+** |
| **SEAS** | **+** | **±** | **+** | **+** | **+** | **+** |
| **JUPITER** | **+** | **±** | **+** | **+** | **+** | **+** |
| **STATCOPE** | **+** | **±** | **+** | **+** | **-** | **+** |
| **HOPE-3** | **+** | **±** | **+** | **+** | **+** | **+** |
| **EMPATHY** | **+** | **-** | **-** | **+** | **±** | **+** |
| **TRACE RA** | **+** | **±** | **+** | **+** | **+** | **+** |
| **EWTOPIA** | **+** | **-** | **-** | **+** | **+** | **+** |
| **4S** | **+** | **±** | **+** | **+** | **+** | **+** |
| **ACAPS** | **+** | **±** | **+** | **+** | **+** | **+** |
| **PLAC-I** | **+** | **±** | **+** | **+** | **+** | **+** |
| **CARE** | **+** | **±** | **+** | **+** | **+** | **+** |
| **LCAS** | **+** | **±** | **+** | **+** | **±** | **+** |
| **Post CABG** | **+** | **±** | **+** | **+** | **±** | **+** |
| **LIPID** | **+** | **±** | **+** | **+** | **+** | **+** |
| **SCAT** | **+** | **±** | **+** | **+** | **+** | **+** |
| **GISSI-P** | **+** | **-** | **-** | **+** | **+** | **+** |
| **FLORIDA** | **+** | **+** | **+** | **+** | **±** | **+** |
| **LIPS** | **+** | **±** | **+** | **+** | **+** | **+** |
| **HPS** | **+** | **±** | **+** | **+** | **+** | **+** |
| **GREACE** | **+** | **-** | **-** | **+** | **±** | **+** |
| **REVERSAL** | **+** | **+** | **+** | **+** | **±** | **+** |
| **PROVE IT-TIMI22** | **+** | **+** | **+** | **+** | **+** | **+** |
| **ALLIANCE** | **+** | **-** | **-** | **+** | **+** | **+** |
| **A to Z** | **+** | **±** | **+** | **+** | **+** | **+** |
| **IDEAL** | **+** | **-** | **-** | **+** | **+** | **+** |
| **TNT** | **+** | **±** | **+** | **+** | **+** | **+** |
| **SAGE** | **+** | **±** | **+** | **+** | **+** | **+** |
| **SEARCH** | **+** | **±** | **+** | **+** | **+** | **+** |
| **SATURN** | **+** | **±** | **+** | **+** | **±** | **+** |
| **IMPROVE IT** | **+** | **±** | **+** | **+** | **+** | **+** |
| **ODYSSEY LONG TERM** | **+** | **±** | **+** | **+** | **+** | **+** |
| **GLAGOV** | **+** | **±** | **+** | **+** | **+** | **+** |
| **Im et al.** | **+** | **-** | **-** | **+** | **+** | **+** |
| **HIJ PROPER** | **+** | **-** | **-** | **+** | **+** | **+** |
| **SPIRE-2** | **+** | **±** | **+** | **+** | **+** | **+** |
| **REAL CAD** | **+** | **-** | **-** | **+** | **+** | **+** |
| **FOURIER** | **+** | **±** | **+** | **+** | **+** | **+** |
| **ODYSSEY OUTCOME** | **+** | **+** | **+** | **+** | **+** | **+** |
| **CORONA** | **+** | **±** | **+** | **+** | **+** | **+** |
| **GISSI HF** | **+** | **±** | **+** | **+** | **+** | **+** |
| **ALERT** | **+** | **±** | **+** | **+** | **+** | **+** |
| **GDDS** | **+** | **±** | **+** | **+** | **+** | **+** |
| **AURORA** | **+** | **±** | **+** | **+** | **+** | **+** |
| **SHARP** | **+** | **±** | **+** | **+** | **+** | **+** |
| **SPARCL** | **+** | **±** | **+** | **+** | **+** | **+** |
| **J-STARS** | **+** | **-** | **-** | **+** | **+** | **+** |
| **TST** | **+** | **-** | **-** | **+** | **+** | **+** |

**-** High risk of bias ; **±** Unclear risk of bias ; **+** Low risk of bias

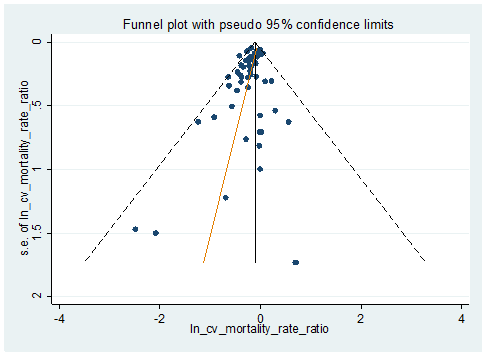
**Publication bias**

We found graphical and statistical evidence of small-study effect, with smaller trials reporting larger effects for all-cause mortality (*P*= .01), CV mortality (*P*= .005), MI (*P*= .005) and non-cardiovascular mortality (*P*= .25) (*P* for Egger test < .05).

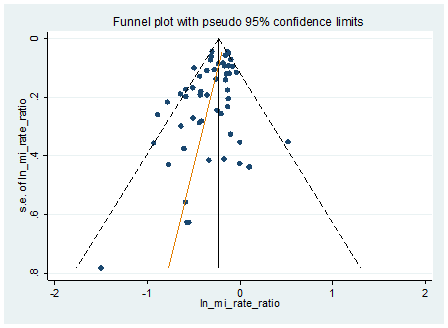
**eFigure 2** Publication Bias: all-cause mortality Markers represent individual studies.



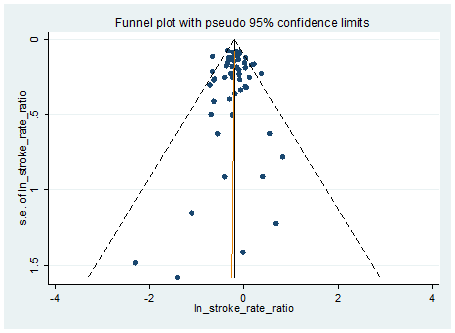
**eFigure 3** Publication Bias: cardiovascular mortality. Markers represent individual studies.



**eFigure 4** Publication Bias: myocardial infarction. Markers represent individual studies.



**eFigure 5** Publication Bias: stroke. Markers represent individual studies.



**eFigure 6** Publication Bias: non-cardiovascular mortality. Markers represent individual studies.

