Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: Meta-analysis of 119 clinical trials involving 100,667 patients

Short Title: cIMT progression as surrogate marker for CVD risk

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Abstract

Background: To quantify the association between effects of interventions on carotid intima-media thickness (cIMT) progression and their effects on cardiovascular disease (CVD) risk.

Methods: We systematically collated data from randomized controlled trials. cIMT was assessed as the mean value at the common-carotid-artery; if unavailable, the maximum value at the common-carotid-artery or other cIMT measures were utilized. The primary outcome was a combined CVD endpoint defined as myocardial infarction, stroke, revascularization procedures, or fatal CVD. We estimated intervention effects on cIMT progression and incident CVD for each trial, before relating the two using a Bayesian meta-regression approach.

Results: We analyzed data of 119 randomized controlled trials involving 100,667 patients (mean age 62 years, 42% female). Over an average follow-up of 3.7 years, 12,038 patients developed the combined CVD endpoint. Across all interventions, each 10 μm/year reduction of cIMT progression resulted in a relative risk for CVD of 0.91 (95% credible interval 0.87-0.94), with an additional relative risk for CVD of 0.92 (0.87-0.97) being achieved independent of cIMT progression. Taken together, we estimated that interventions reducing cIMT progression by 10, 20, 30, or 40 μm/year would yield relative risks of 0.84 (0.75-0.93), 0.76 (0.67-0.85), 0.69 (0.59-0.79), or 0.63 (0.52-0.74). Results were similar when grouping trials by type of intervention, time of conduct, time to ultrasound follow-up, availability of individual-participant data, primary vs. secondary prevention trials, type of cIMT measurement, and proportion of female patients.

Conclusions: The extent of intervention effects on cIMT progression predicted the degree of CVD risk reduction. This provides a missing link supporting the usefulness of cIMT progression as a surrogate marker for CVD risk in clinical trials.

Key Words: Intima-media thickness ■ Cardiovascular disease ■ Surrogate marker ■ Clinical trials ■ Meta-analysis.

Non-standard Abbreviations and Acronyms

CI credible interval

cIMT Carotid intima-media thickness

CVD cardiovascular disease

RCT randomized controlled trial

RR relative risk

Clinical Perspective

What Is New?

- We analyzed data of 119 randomized controlled trials that involved 100,667 patients and 12,038 incident cardiovascular disease events.
- We used a Bayesian meta-regression approach to evaluate progression of carotid intima-media thickness as a surrogate marker for cardiovascular events.
- Our analysis revealed a statistically significant association between treatment effects on progression of carotid intima-media thickness and treatment effects on cardiovascular disease risk.

What Are the Clinical Implications?

- Our paper provides the key missing link supporting the usefulness of carotid intima-media thickness progression as a surrogate marker for cardiovascular disease risk in clinical trials.
- Using progression of carotid intima-media thickness as a surrogate endpoint in future randomized controlled trials may facilitate and speed up the development and licensing of new therapies.

Introduction

Carotid intima-media thickness (cIMT), the thickness of the intimal and medial layer of the carotid artery wall, can be measured non-invasively using ultrasound imaging and is considered a marker for the early stage of atherosclerosis.[1] Mean values of cIMT in adults range around 650-900 µm and increase – on average – at a rate of 0-40 µm/year.[2,3] A large number of randomized controlled trials (RCTs) have demonstrated that therapeutic interventions may slow progression of cIMT. However, it is uncertain whether effects on cIMT progression translate into reduced risk of cardiovascular disease (CVD) events, that is whether cIMT progression is a valid surrogate marker for CVD.

In 2005, Espeland *et al.* first proposed cIMT progression as a surrogate marker for CVD risk based on findings in seven statin trials,[4] but their arguments were based on limited data and most researchers were reluctant to rely on cIMT results alone.[5] In 2009, ARBITER-6 HALTS was the first RCT to be terminated early based on findings for cIMT progression, showing superiority of extended-release niacin over ezetimibe.[6] This decision was controversial due to the uncertain validity of the rate of progression of cIMT as a surrogate marker for clinical endpoints.[7,8] Two subsequent literature-based meta-regression analyses on this topic have yielded conflicting results: Goldberger *et al.*[9] observed an association of effects on cIMT progression and risk of myocardial infarction, whereas Costanzo *et al.*[10] found no statistically significant association of changes in mean or maximal cIMT with risk of myocardial infarction or stroke. Both of these meta-analyses have been criticized because of methodological flaws.[11]

To address this uncertainty, we conducted a comprehensive analysis of 119 RCTs involving a total of 100,667 patients. Our aims were to: (i) quantify the reduction in CVD risk associated with reducing cIMT progression by therapeutic intervention; (ii) explore cIMT progression as a surrogate marker for different types of CVD endpoints as well as all-cause mortality; and (iii) investigate differences according to the intervention type, method of cIMT assessment, and other trial characteristics.

Methods

The datasets supporting the conclusions of this article are not made publicly available due to legal restrictions arising from the data distribution policy of the PROG-IMT/Proof-ATHERO collaborations and from the bilateral agreements between the consortium's coordinating center and participating studies, but they may be requested directly from individual study investigators. Studies that shared individual-participant data have obtained informed consent of the study participants and ethical approval by their respective institutional review boards.

The report of the results of our study adhere to the PRISMA-IPD guidelines (**Table I in the Supplement**); the objectives and statistical methods in this paper have been described previously[12]. We identified relevant RCTs published before 3 February 2020 through systematic searches of ten medical knowledge databases, six clinical trial registries, and reference lists of relevant publications and reviews (**Table II in the Supplement**). Trials were eligible for inclusion if they: (1) had assigned patients randomly to two or more arms; (2) had applied well-defined inclusion criteria; (3) had measured cIMT at trial baseline and at one or more follow-up visits; and (4) had recorded incident CVD outcomes. We requested anonymized patient-level data from these trials, performed comprehensive plausibility checks, and were able to resolve any data-related queries through direct correspondence with trial investigators. For trials for which patient-level data was unavailable, four authors (PW, LT, EA, MWL) independently extracted the relevant data from the published literature and resolved any discrepancies by consensus.

As a measure of cIMT, we gave preference to assessments of mean values at the common-carotid-artery. If unavailable, we used maximum values at the common-carotid-artery or cIMT at other sections of the carotid artery instead. In trials quantifying cIMT values at different sites (i.e. left or right side, near or far vessel wall, or at different insonation angles), the arithmetic mean of these measurements was used. The primary outcome was a combined CVD endpoint defined as myocardial infarction, stroke, revascularization procedures (e.g. coronary or carotid revascularization), or fatal CVD. For trials without data on cause-specific death, all-cause mortality was included in the primary outcome instead. **Table III in the Supplement** provides details on the assessment of cIMT progression and primary outcome definition in each trial.

Statistical analysis

We conducted analyses according to a pre-specified analysis plan. For factorial trials, we analyzed the intervention contrast anticipated to have the greatest effect on CVD risk. For trials with more than two trial arms, we compared the arm that was – based on prior trials – anticipated to have the greatest effect to the arm anticipated to have the least effect (or no effect in case of placebo). For all trials, the latter group was used as reference.

The principal analysis consisted of three steps. First, we quantified intervention effects on cIMT progression. For each trial for which patient-level data was available, we used a linear mixed model to estimate the difference in yearly cIMT progression between trial arms. The model included fixed effects for assigned treatment, time in study, and the interaction of the two, plus an intercept and time variable allowed to vary randomly at the patient level. For each trial for which literature-based data was available (i.e. tabular data extracted from the trials' publications), we annualized differences in cIMT progression and calculated standard errors from *P* values, if necessary.

Second, we quantified intervention effects on the CVD outcome. For each trial with patient-level data, we fitted a Cox proportional-hazards model to estimate the log hazard ratio and its standard error comparing the trial arms. If estimates were inestimable due to a low event number, we applied an augmentation procedure to allow incorporation of the trial in the meta-analysis.[13] For each trial with literature-based data, we calculated the log risk ratio and its standard error based on the number of events and patients in each trial arm. For trials in which one arm had zero events, the number of events and non-events were each augmented by +0.5 in both trial arms. Hazard ratios and risk ratios are collectively described as measures of relative risk (RR).

Third, to test whether effects on CVD risk depended on effects on cIMT progression, we used a Bayesian meta-regression approach that models both effects simultaneously, while taking into account the estimated precisions in these two effects.[14] The principal analysis involved (i) a model with an intercept of zero (i.e. forcing the regression line through the origin and thereby assuming that all the effects on CVD risk operate through cIMT progression) and (ii) a model with a non-zero intercept (i.e. allowing for an effect on CVD risk independent of cIMT progression). The meta-regression also took into account the within-study correlation of the

two effects, which was estimated using bootstrapping in the trials with patient-level data and >30 events.[15] For other trials, an overall correlation coefficient pooled using random-effects meta-analysis was used instead. Further details on methods for assessing surrogacy are provided in the **Methods in the Supplement**.

Subsidiary analyses evaluated surrogacy for individual disease endpoints and in trials grouped by intervention type, time of conduct, time to ultrasound follow-up, availability of individual-participant data, primary vs. secondary prevention trials, type of cIMT measure, and proportion of female patients. A Bayesian approach was taken for estimation of the meta-regression model parameters and for prediction (for details, see the **Methods in the Supplement**). Analyses were performed using Stata 15, R 2.5.1 and JAGS 4.3.0. PW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Results

Among 10,260 articles screened, we identified 119 trials involving 100,667 patients that met the pre-specified inclusion criteria (**Figure I in the Supplement**). 103 trials (87%) had two arms, seven had three arms, one had four arms, seven had a 2x2 factorial design, and one had a 3x2 factorial design (**Table 1**). The trials employed antidiabetic (18 trials), antihypertensive (19 trials), dietary/vitamin (20 trials), lipid-lowering (33 trials), and/or other interventions (37 trials). Mean age at baseline was 62 years (standard deviation 8); 42% were female. Over an average follow-up duration of 3.7 years, 12,038 patients developed the primary CVD endpoint. The median proportion of patients with repeat cIMT measurements across trials was 90%. Seven large cardiovascular outcome trials had measured cIMT only in a subset of patients (**Table 1**). Mean cIMT measured at the common-carotid-artery was available in 91 trials, maximum cIMT at the common-carotid-artery in 49 trials, and other cIMT measures in 11 trials. Across contributing trials, the mean rate of cIMT progression was +9.1 µm/year (95% confidence interval: 7.1 to 11.1) in control arms and +1.0 µm/year (-0.6 to 2.7) in interventions arms. Across all contributing trials, the RR for CVD with intervention was 0.88 (0.83-0.92).

Results of the principal analysis are provided in **Figure 1**. Across all interventions, in the model assuming an intercept of zero, each 10 µm/year reduction of cIMT progression was associated with a RR for CVD of 0.88 (95% credible interval [CI] 0.85-0.91). In the model allowing for

a non-zero intercept, the RR for CVD was 0.91 (0.87-0.94) per 10 µm/year slower cIMT progression, with a further RR of 0.92 (0.87-0.97) achieved independent of cIMT progression. Based on the non-zero intercept model, the proportion of variance in the CVD outcome explained by cIMT progression was 98% albeit with a wide 95% CI (71-100%). Taken together, we estimated that interventions that reduce cIMT progression by 10, 20, 30, or 40 µm/year would yield RRs of 0.84 (0.75-0.93), 0.76 (0.67-0.85), 0.69 (0.59-0.79), or 0.63 (0.52-0.74).

Due to presence of effects on CVD risk unexplained by cIMT progression, subsequent analyses focused on the non-zero intercept model. In outcome-specific analyses (**Figure 2**), RRs per 10 µm/year slower cIMT progression were 0.88 (0.82-0.94) for myocardial infarction, 0.92 (0.86-1.00) for stroke, 0.90 (0.83-0.98) for revascularization procedures, 0.91 (0.83-1.01) for fatal CVD, and 0.96 (0.89-1.04) for all-cause mortality. There was no evidence for differences in the RR for CVD associated with slower cIMT progression nor in the intercept across trials grouped by intervention type (**Figure 3** and **Figure 4**). Similarly, there was no evidence for differences in these RRs in trials grouped by time of conduct, time to ultrasound follow-up, availability of individual-participant data, primary vs. secondary prevention trials, type of cIMT measurements, and proportion of female patients (**Figure 4**, *P* values for heterogeneity >0.05). In a sensitivity analysis that omitted trials with extreme effect sizes (i.e. cIMT progression changes >80 µm/year or RR for CVD <0.25 or >4.0), the RR for CVD per 10 µm/year slower cIMT progression was 0.91 (0.87-0.95). Results were also highly robust across leave-one-out cross-validation analyses (**Figure II in the Supplement**). Trial-specific estimates are provided in **Table IV in the Supplement**.

Discussion

In this large-scale meta-analysis involving data from 119 RCTs and 100,667 patients, we showed that interventions reducing cIMT progression are also likely to reduce CVD event rates (summarized in **Figure 5**). Specifically, a 10 µm/year slower cIMT progression was associated with a RR of 0.91 (95% CI 0.87-0.94) for the principal outcome of CVD, with the differences in RR for CVD largely explained by the differences in cIMT progression. The same model also indicated a non-zero intercept, overall and for different types of interventions, highlighting that

a small but significant proportion of the intervention effect acted independently of cIMT progression. By estimating CVD risk reductions according to specific reductions in cIMT progression, we provide guidance to future trials in the cardiovascular field.[5] Results were robust for a range of disease endpoints and across clinically important trial characteristics, including type of intervention or type of cIMT measurement.

Exploring the association between cIMT and CVD risk has some history. cIMT measured at a single time-point is associated with incident CVD and provides incremental predictive value over and beyond conventional CVD risk factors.[190-192] For cIMT progression over time, our earlier analyses of observational studies within the PROG-IMT collaboration indicated no statistically significant association with subsequent CVD risk in individuals of the general population,[2] patients with diabetes mellitus,[193] or patients at high CVD risk[194]. This null association could be explained by the challenges of precisely estimating cIMT progression in individuals over time. In contrast, our present report focuses on groups of patients in RCTs and is therefore better suited to provide answers about the surrogate value of cIMT progression: averaging across patients improves the signal-to-noise ratio, confounders are expected to be balanced due to randomization, trial cohorts might be more homogeneous, and cIMT protocols may be of higher quality in clinical trial settings.

Prior RCT data on cIMT progression as a surrogate marker for CVD risk are limited. Because most RCTs reporting both cIMT and endpoints (with few exceptions[63,70,97,127,170]) have not been designed as CVD outcome trials and as a range of intervention effect sizes is needed for meaningful results, meta-analysis is the method of choice to investigate this question.[195] Three such pooled analyses had been undertaken before. Espeland *et al.* demonstrated that statin treatment reduced cIMT progression and CVD risk in a concordant manner.[4] In a meta-analysis involving 28 RCTs of different intervention types, Goldberger *et al*. observed an association between reduced cIMT progression and lower risk for non-fatal myocardial infarction, but noted marked between-trials heterogeneity.[9] A meta-analysis by Costanzo *et al*. involving 41 RCTs demonstrated no statistically significant relationship between slower cIMT progression and risk of cardiovascular outcomes.[10] Compared to these earlier reports, our meta-analysis stands out by (i) exclusively conducting within-trial comparison (thereby upholding the principle of randomization); (ii) increasing statistical power by involving >5 times as many patients as the previously largest report[10]; (iii) enhancing validity by accessing patient-level

data of 28 trials; and (iv) using modern statistical methods that incorporate uncertainties both around the intervention effects on cIMT progression and CVD risk as well as their within-trial correlation.

What do we know about the suitability of cIMT progression as a surrogate marker for CVD risk? Ultrasound-based cIMT measurement fulfills several requirements of a surrogate marker,[196] including (i) high correlation with thickness of the vessel wall measured in histological samples[197]; (ii) acceptable reproducibility[198], which was further enhanced by clear recommendations for measurement and technical improvements[199]; (iii) close correlation with risk factors and prevalent CVD[190-192]; (iv) established correlation with atherosclerosis in other vascular beds[196]; (v) association with occurrence of clinical events[190-192]; (vi) the ability to change over time[2,193]; and (vii) the possibility to influence cIMT with interventions[200]. In the present analysis, we have provided evidence for the last missing requirement not credibly proven by earlier studies, namely that a change in cIMT progression is related to the change in risk of CVD events.

Importantly, using cIMT progression as a surrogate endpoint in future RCTs may facilitate and speed up development and licensing of new therapies. To illustrate this point, we conducted a sample size calculation for a hypothetical future trial. For this calculation, we assumed 80% power, several parameters similar to our individual-participant data (i.e. 2-year cumulative incidence of CVD 6.57%, a standard deviation of cIMT 178 µm, and a correlation between baseline and follow-up cIMT 0.79), no losses to follow-up, and a perfect relationship between treatment effects on cIMT progression and those on the CVD outcome. To have 80% power to detect a hazard ratio of 0.84, a future 2-year CVD outcome trial would require 8,600 patients in each trial arm. In comparison, a future 2-year cIMT progression trial would require 470 patients per trial arm to detect a 10 µm/year reduction in cIMT progression (corresponding to the above hazard ratio) at 2-years, also with a power of 80%. Consequently, a cIMT trial would only require 5.5% of the sample size of a comparable CVD endpoint trial.

In addition to demonstrating the association between intervention effects on cIMT and intervention effects on CVD risk, we found that the regression line had a small but significant non-zero intercept, in the overall analysis and in all subgroups of trials investigated. The non-zero intercept – which indicates that a small proportion of the intervention effect on CVD risk

bypasses cIMT – may be explained by "pleiotropic" effects; meaning that the intervention influences the clinical endpoint via multiple pathways. While effects of interventions on the extent of atherosclerosis may be captured by cIMT progression, any effects on other pathophysiological mechanisms related to CVD events, such as endogenous thrombogenesis and fibrinolysis,[1] may bypass cIMT progression and thereby lead to a non-zero intercept. Alternative pathways have been described for many major cardiovascular substance groups, including lipid-lowering medications (e.g. statins,[1,201,202] fibrates,[203] niacin,[204] resins,[205] and omega-3 fatty acids[206]), antidiabetic medications (e.g. AMPK activators,[207] thiazolidinediones,[207] DPP-4 inhibitors,[207,208] GLP-1 receptor agonists,[207,208] SGLT-2 inhibitors[208]), or antihypertensive medications (e.g. beta-blockers,[209] calcium channel-inhibitors,[210,211] angiotensin-II antagonists,[212] ACE inhibitors[212]). Nevertheless, this finding does not negate the main result that an intervention effect on cIMT predicts the effect on CVD risk.

A major strength of our study is that we systematically collated and analyzed worldwide data on cIMT progression and CVD outcomes published up to February 2020. Access to patient-level data allowed us to include hitherto unpublished data and thereby reduce publication bias. Supplementing our analysis with published data enhanced generalizability and statistical power. Strengths of our meta-regression analysis include that it upholds randomization within trials, allows for between-trials heterogeneity, makes no distributional assumption about the true intervention effects on cIMT progression across trials (unlike standard bivariate random-effects meta-analysis), and improved precision by incorporating within-trial correlations of intervention effects on cIMT progression and CVD risk.

Our analysis also has limitations. First, our principal analysis combined trials of varying types of interventions. While we conducted a sensitivity analysis by medication class, further research is required to precisely quantify the differences in the surrogate value of cIMT by intervention type. Second, our analysis involved a broad range of types of trial populations. While sensitivity analysis revealed no evidence for differential effects in the setting of primary vs. secondary prevention trials, further study is needed on specific trial populations, such as patients with diabetes or chronic kidney disease. Third, the definition of the primary combined CVD endpoint varied across the included trials. However, the differences were relatively minor (see **Table III in the Supplement**), so we are confident that this does not constitute a major

source of systematic bias. Finally, while ultrasound scanning protocols may have differed across contributing trials – in particular before consensus guidelines were available[213], there was no evidence for effect modification by type of cIMT measure or baseline years of the trials.

Conclusions

In conclusion, effects of interventions on cIMT progression and on CVD risk are associated, endorsing the usefulness of cIMT progression as a surrogate marker in clinical trials. Using cIMT progression as a surrogate marker may be a useful tool to guide future development for cardiovascular drugs.

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Conflict of Interest Disclosures

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Supplemental Material

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Full list of the PROG-IMT and the Proof-ATHERO study groups and their affiliations

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Table 1. Key features of the trials included in this report

Trial	Years of baseline	Country	Access to IPD	No. of trial arms	Type of intervention*					No. of patients	Type of population	Mean age (SD), years	% female	CVD risk		cIMT progression				
					Antidiabetic	Antihypertensive	Dietary / vitamins	Lipid-lowering	Other					Median follow-up, years	No. of events	Maximum follow-up, years	% with cIMT data	Mean CCA-IMT	Max CCA-IMT	Other cIMT
ACAPS[16,17]	1989-1990	USA	●	2x2	-	-	-	●	●	919	Elevated CVD risk	62 (8)	48	5.0	18	6.0	100	-	●	-
ACT NOW[18,19]	2004-2006	USA	-	2	●	-	-	-	-	602	Dysglycemia	52 (10)	58	2.2†	13	4.0	63	●	-	-
ALLO-IMT[20]	2009-2010	UK	●	2	-	-	-	-	●	80	Pre-existing CVD	68 (10)	43	1.0	11	1.2	100	●	●	-
AMAR[21]	2004-2005	Russia	-	2	-	-	●	-	-	257	Elevated CVD risk	61 (9)	0	2.0‡	21	2.0	76	●	-	-
ARBITER[22]	1999-2001	USA	-	2	-	-	-	●	-	161	Elevated CVD risk	60 (12)	29	1.0‡	6	1.0	86	●	●	-
ARBITER 2[23]	2001-2003	USA	-	2	-	-	-	●	-	167	Pre-existing CVD	67 (10)	9	1.0‡	10	1.0	89	●	-	-
ARBITER 6-HALTS[6,24,25]	2006-2009	USA	-	2	-	-	-	●	-	363	Pre-existing CVD	65 (10)	20	1.2‡	11	1.2	57	●	●	-
ARTSTIFF[26]	2008-2011	International	-	3	-	●	-	-	-	133	Hypertension	53 (10)	37	1.0‡	0	1.0	87	●	-	-
ASAP-FINLAND[27-29]	1994-1995	Finland	-	2	-	-	●	-	-	520	Hyperlipidemia	60 (6)	51	6.0‡	22	6.0	85	●	-	-
ASAP-NL[30,31]	1997-1998	Netherlands	-	2	-	-	-	●	-	330	Hyperlipidemia	49 (11)	61	2.0‡	5	2.0	85	●	-	-
ASFAST[32]	1998-2000	International	-	2	-	-	●	-	-	315	Kidney disease	56 (13)	32	3.3†	73	3.6	77	-	●	-
ATIC[33,34]	2001-2002	Netherlands	-	2	-	-	-	-	●	93	Kidney disease	53 (12)	43	2.0‡	4	1.5	80	●	-	-
Ahn et al.[35]	2005-2006	Korea	-	2	-	-	-	-	●	130	Pre-existing CVD	64 (11)	38	2.0‡	18	2.0	73	-	-	●
Andrews et al.[36,37]	2011-2015	USA	-	2	-	-	-	-	●	80	Kidney disease	57 (12)	20	0.2‡	1	0.2	79	●	-	-
BCAPS[38]	1994-1996	Sweden	-	2x2	-	●	-	●	-	793	Elevated CVD risk	62 (5)	54	3.0†	18	3.0	99	●	-	-
BKREGISTRY-II[39]	2000-2003	Korea	●	2	-	-	-	●	-	205	Pre-existing CVD	60 (10)	32	0.5	3	1.1	59	●	-	-
BVAIT[40]	2000-2006	USA	-	2	-	-	●	-	-	506	General population	61 (10)	39	3.1†	20	2.5	97	●	-	-
CAIUS[41]	1991-1992	Italy	-	2	-	-	-	●	-	305	Hyperlipidemia	55 (6)	47	3.0‡	5	3.0	100	-	●	-
CAMERA[42]	2009-2011	UK	●	2	●	-	-	-	-	173	Pre-existing CVD	63 (8)	23	1.5	12	2.3	100	●	-	-
CAPPA[43]	2009	Korea	-	2	-	-	-	-	●	420	Dysglycemia	60 (9)	50	3.0‡	6	3.0	99	●	●	-
CAPTIVATE[44]	2004-2005	International	-	2	-	-	-	●	-	892	Hyperlipidemia	55 (9)	39	2.0‡	32	1.0	99	-	-	●
CERDIA[45]	1999-2001	Netherlands	●	2	-	-	-	●	-	250	Dysglycemia	58 (11)	53	2.1	14	2.5	99	●	●	-
CHICAGO[46]	2003-2005	USA	-	2	●	-	-	-	-	462	Dysglycemia	60 (8)	37	1.4‡	13	1.4	78	●	●	-
CIMT phase 1[47,48]	2008-2009	Denmark	-	2	●	-	-	-	-	412	Dysglycemia	61 (9)	32	1.5‡	20	1.5	100	●	●	-

CLAS[49-51]	1980-1984	USA	-	2	-	-	-	●	-	162	Pre-existing CVD	54 (5)	0	7.0†	82	4.0	48	●	-	-
CONTRAST[52,53]	2004-2009	Netherlands	●	2	-	-	-	-	●	714	Kidney disease	64 (14)	38	2.4	173	3.1	20	●	●	-
Cao et al.[54]	2008-2011	China	-	2	-	-	●	-	-	287	Elevated CVD risk	71 (13)	53	2.0‡	36	2.0	100	-	-	●
DAPC[55,56]	2004-2006	International	-	2	-	-	-	-	●	329	Dysglycemia	64 (7)	48	2.0‡	3	2.0	90	●	●	-
DAPHNE[57]	NR	Netherlands	-	2	-	●	-	-	-	80	Pre-existing CVD	59 (7)	0	3.0‡	16	3.0	100	-	-	●
DOIT[58]	1997-1999	Norway	-	2	-	-	●	-	-	561	Elevated CVD risk	70 (5)	0	3.0‡	63	3.0	83	●	-	-
EGE STUDY[59,60]	2005-2006	Turkey	●	2x2	-	-	-	-	●	644	Kidney disease	59 (14)	46	3.0	60	3.0	100	●	-	-
ELITE (early MP)[61,62]	2005-2008	USA	-	2	-	-	-	-	●	271	General population	55 (4)	100	5.0	1	5.0	92	●	-	-
ELITE (late MP)[61,62]	2005-2008	USA	-	2	-	-	-	-	●	372	General population	65 (6)	100	5.0	5	5.0	94	●	-	-
ELSA[63]	NR	International	-	2	-	●	-	-	-	2334	Hypertension	56 (7)	45	4.0‡	60	4.0	87	-	-	●
ELVA[64]	NR	Sweden	-	2	-	●	-	-	-	129	Hyperlipidemia	60 (10)	49	3.0‡	4	3.0	71	●	-	-
ENCORE[65,66]	2003-2008	USA	●	3	-	-	●	-	-	144	Elevated CVD risk	52 (10)	67	0.4	1	1.1	98	●	-	-
ENHANCE[67]	2002-2004	International	●	2	-	-	-	●	-	720	Hyperlipidemia	47 (9)	49	2.0	52	2.3	100	●	●	-
EPAT[68]	1994-1998	USA	-	2	-	-	-	-	●	222	Hyperlipidemia	61 (7)	100	2.0‡	7	2.0	90	●	-	-
FIELD[69,70]	1998-2000	International	-	2	-	-	-	●	-	9795	Dysglycemia	62 (7)	37	6.0‡	1295	5.0	2	-	●	-
FIRST[71,72]	2008-2010	USA	-	2	-	-	-	●	-	682	Pre-existing CVD	61 (9)	32	2.1‡	30	2.0	84	-	●	-
FRANCIS[73,74]	2011-2012	Netherlands	-	2	-	-	-	-	●	320	Elevated CVD risk	53 (11)	70	5.0‡	9	5.0	100	●	-	-
GRACE[75]	2003-2005	International	●	2x2	●	-	●	-	-	1189	Dysglycemia	63 (8)	36	5.8	374	5.1	100	●	●	-
Gresele et al.[76]	2003-2005	International	●	2	-	-	-	-	●	442	Pre-existing CVD	67 (9)	21	0.6	8	0.6	57	●	●	-
HART[77]	1999-2000	International	●	2	-	-	●	-	-	925	Pre-existing CVD	69 (7)	24	5.0	152	5.6	100	●	●	-
HERS[78,79]	1993-1994	USA	-	2	-	-	-	-	●	2763	General population	67 (7)	100	4.1†	552	4.7	16	-	●	-
HYRIM[80]	1997-1999	Norway	●	2x2	-	-	-	●	●	568	Hypertension	57 (9)	0	4.1	47	4.6	99	-	●	-
INSIGHT[81-83]	1994-1996	France	-	2	-	●	-	-	-	6321	Elevated CVD risk	65 (7)	54	3.5†	347	4.0	5	●	-	-
J-STARS[84-88]	2004-2009	Japan	-	2	-	-	-	●	-	1589	Pre-existing CVD	66 (8)	31	4.9†	290	5.0	50	●	-	-
JART[89]	2008-2010	Japan	-	2	-	-	-	●	-	348	Hyperlipidemia	64 (9)	51	2.0‡	9	2.0	40	●	●	-
KAPS[90]	1984-1989	Finland	-	2	-	-	-	●	-	447	Hyperlipidemia	57 (4)	0	3.0‡	28	3.0	95	-	●	-
KEEPS[91]	2005-2008	USA	-	3	-	-	-	-	●	727	General population	53 (3)	100	4.0‡	1	4.0	100	●	-	-
KIMVASC[92]	2011-2012	UK	●	2	-	-	●	-	-	80	Pre-existing CVD	77 (5)	45	0.5	1	0.5	99	●	-	-
Katakami et al.[93]	1998	Japan	-	3	●	-	-	-	-	159	Dysglycemia	61 (9)	51	3.3†	0	3.3	74	-	-	●
Koyasu et al.[94]	2006-2008	Japan	-	2	●	-	-	-	-	90	Pre-existing CVD	66 (8)	9	1.0‡	0	1.0	90	-	●	-
LAARS[95]	NR	International	-	2	-	●	-	-	-	280	Hypertension	59 (9)	50	2.0‡	0	2.0	72	●	-	-
LIFE-ICARUS[96]	1996-1997	International	●	2	-	●	-	-	-	83	Hypertension	67 (6)	27	4.9	8	3.1	98	●	-	-
LIPID[97-100]	1990-1992	International	-	2	-	-	-	●	-	9014	Pre-existing CVD	61 (8)	17	6.1†	3229	4.0	4	●	-	-
Luijendijk et al.[101,102]	2007-2009	Netherlands	-	2	-	-	-	●	-	155	Pre-existing CVD	36 (12)	38	3.3†	0	4.4	100	●	-	-
MARS[103,104]	1985-1989	USA	-	2	-	-	-	●	-	270	Hyperlipidemia	58 (7)	9	2.2†	54	4.0	27	●	-	-
MAVET[105]	1994-1995	Australia	-	2	-	-	●	-	-	409	Elevated CVD risk	64 (6)	55	4.0‡	6	4.0	81	-	●	-

MECANO[106,107]	2005-2006	Netherlands	-	2	-	-	-	-	●	185	Kidney disease	51 (13)	36	1.5‡	6	2.0	88	●	-	-
MEDICLAS[108,109]	2003-2005	Netherlands	●	2	-	-	-	-	●	48	Elevated CVD risk	42 (10)	0	3.0	1	3.2	77	●	-	-
METEOR[110]	2002-2004	International	-	2	-	-	-	●	-	984	Elevated CVD risk	57 (6)	40	2.0‡	3	2.0	89	●	●	-
MG600[111]	2010-2011	Brazil	●	2	-	-	●	-	-	35	Hypertension	55 (7)	100	0.5	0	0.5	100	●	●	-
MIDAS[112]	NR	USA	-	2	-	●	-	-	-	883	Hypertension	59 (9)	22	3.0‡	47	3.0	100	-	●	-
MITEC[113,114]	2000-2002	France	-	2	-	●	-	-	-	209	Elevated CVD risk	60 (8)	36	3.0‡	0	3.0	41	●	-	-
Makimura et al.[115]	2008-2010	USA	-	2	-	-	-	-	●	60	Elevated CVD risk	41 (2)	35	1.0‡	0	1.0	97	●	-	-
Masia et al.[116]	2006-2007	Spain	●	2	-	-	-	-	●	68	Elevated CVD risk	52 (11)	10	6.0	4	6.9	99	●	●	-
Mitsuhashi et al.[117]	NR	Japan	-	2	-	-	-	-	●	62	Dysglycemia	63 (7)	35	2.6†	1	2.6	100	-	-	●
Mortazavi et al.[118]	NR	Iran	-	2	-	-	●	-	-	54	Kidney disease	57 (12)	50	0.5‡	1	0.5	96	●	-	-
NTPP[119]	2005-2010	Japan	-	2	-	-	-	●	-	123	Elevated CVD risk	59 (9)	54	3.0‡	0	3.0	79	●	●	-
Nakamura et al. II[120]	2001	Japan	●	2	-	-	-	-	●	50	Kidney disease	53 (7)	40	6.9	8	4.1	100	●	●	-
Ntaios et al.[121]	2005	Greece	●	2	-	-	●	-	-	103	Elevated CVD risk	73 (5)	45	1.5	18	1.5	100	●	-	-
OPAL[122,123]	1997-1999	International	●	3	-	-	-	-	●	866	General population	59 (7)	100	3.1	9	3.7	100	●	●	-
PART-2[124]	NR	New Zealand	-	2	-	●	-	-	-	617	Pre-existing CVD	61 (8)	18	4.7†	150	4.0	87	●	-	-
PEACE[125]	2007-2008	Japan	-	2	-	-	-	●	-	303	Hyperlipidemia	66 (9)	43	1.0‡	2	1.0	74	●	●	-
PERFORM[126,127]	2006-2008	International	-	2	-	-	-	-	●	19120	Pre-existing CVD	67 (8)	37	2.4†	2910	3.0	5	●	-	-
PERIOCARDIO[128]	2010-2012	Australia	●	2	-	-	-	-	●	273	Elevated CVD risk	41 (10)	42	1.0	3	1.4	99	●	●	-
PHOREA[129]	1995-1996	Germany	-	3	-	-	-	-	●	321	General population	59 (4)	100	0.9‡	1	0.9	54	-	●	-
PHYLLIS[130,131]	1995-1997	Italy	-	4	-	●	-	●	-	508	Elevated CVD risk	58 (7)	60	2.6†	6	2.6	82	-	●	-
PLAC II[132-134]	1987-1990	USA	-	2	-	-	-	●	-	151	Elevated CVD risk	63 (NR)	15	3.0‡	14	3.0	100	-	●	-
PPAR[135]	2002-2003	International	-	2	●	-	-	-	-	200	Elevated CVD risk	59 (10)	20	1.0‡	17	1.0	100	-	-	●
PREDIMED[136,137]	2008-2009	Spain	-	3	-	-	●	-	-	7447	Elevated CVD risk	67 (6)	57	4.8	288	2.4	2	●	●	-
PREVEND IT[138-141]	1998-1999	Netherlands	●	2x2	-	●	-	●	-	864	Kidney disease	51 (12)	35	3.9	102	4.7	94	●	-	-
PREVENT[142,143]	1992-1997	International	-	2	-	●	-	-	-	825	Elevated CVD risk	57 (10)	20	3.0‡	196	3.0	46	-	●	●
PROBE[144,145]	2002-2003	Japan	-	2	●	-	-	-	-	587	Dysglycemia	58 (NR)	37	4.0‡	14	3.3	30	●	●	-
RADIANCE I[146,147]	2003-2004	International	●	2	-	-	-	●	-	904	Hyperlipidemia	46 (13)	51	2.0	44	2.3	98	●	●	-
RADIANCE II[147,148]	2004-2006	International	●	2	-	-	-	●	-	752	Hyperlipidemia	57 (8)	36	2.0	37	2.4	98	●	●	-
RAS[149]	2002-2003	Sweden	-	2	●	-	-	-	-	557	Elevated CVD risk	67 (6)	54	1.0‡	5	1.0	80	●	-	-
REGRESS[150,151]	1989-1991	Netherlands	-	2	-	-	-	●	-	885	Elevated CVD risk	56 (8)	0	2.0‡	148	2.0	29	●	-	-
REMOVAL[152,153]	2011-2014	International	-	2	●	-	-	-	-	428	Dysglycemia	56 (9)	41	3.0‡	17	3.0	99	●	●	-
RIS[154]	1987-1989	Sweden	●	2	-	-	-	-	●	164	Elevated CVD risk	66 (5)	0	5.9	47	7.3	99	●	●	-
SANDS[155-157]	2003-2004	USA	-	2	-	-	-	-	●	499	Elevated CVD risk	56 (9)	66	3.0‡	18	3.0	100	●	-	-
SCIMO[158,159]	1992-1994	Germany	-	2	-	-	●	-	-	223	Elevated CVD risk	58 (9)	20	2.0‡	55	2.0	77	-	●	-
SECURE[160]	1994-1995	Canada	●	3x2	-	●	●	-	-	731	Elevated CVD risk	66 (7)	24	4.4	103	5.3	100	-	●	-
SEKONA[161]	2004-2005	Germany	-	2	-	-	-	-	●	600	Elevated CVD risk	49 (6)	11	3.0‡	110	3.0	66	●	-	-

SENDCAP[162]	1990-1993	UK	-	2	-	-	-	●	-	164	Dysglycemia	51 (8)	29	3.0‡	4	3.0	77	-	●	-
SPEAD-A[163,164]	2011-2013	Japan	-	2	●	-	-	-	-	341	Dysglycemia	65 (9)	42	2.0‡	4	2.0	94	●	●	-
SPIKE[165-167]	2012	Japan	-	2	●	-	-	-	-	282	Dysglycemia	64 (7)	40	2.0‡	6	2.0	97	●	●	-
STARR[168]	2001-2003	International	●	2x2	●	●	-	-	-	1320	Dysglycemia	53 (11)	55	4.2	30	4.5	100	●	●	-
STOP-NIDDM[169,170]	1996-1998	Germany	-	2	●	-	-	-	-	1429	Dysglycemia	55 (8)	51	3.3†	47	3.9	8	●	-	-
Safarova et al.[171]	2007-2009	Russia	●	2	-	-	-	●	-	60	Pre-existing CVD	55 (6)	0	3.0	40	2.8	100	●	-	-
Sander et al. (Cp neg)[172,173]	1995-1998	Germany	-	2	-	-	-	-	●	147	Pre-existing CVD	64 (12)	44	3.0‡	9	2.0	100	●	-	-
Sander et al. (Cp pos)[172,173]	1995-1998	Germany	-	2	-	-	-	-	●	125	Pre-existing CVD	65 (14)	43	3.0‡	19	2.0	100	●	-	-
Spring et al.[174]	NR	Switzerland	-	2	-	-	-	●	-	100	Pre-existing CVD	67 (11)	22	0.5‡	2	0.5	89	●	-	-
Stanley et al.[175]	2011-2013	USA	-	2	-	-	-	-	●	50	Elevated CVD risk	51 (7)	16	0.5‡	1	0.5	86	●	-	-
Stanton et al.[176]	NR	UK	-	2	-	●	-	-	-	69	Hypertension	48 (11)	41	1.0‡	1	1.0	80	●	-	-
TART[177]	1997-1998	USA	-	2	●	-	-	-	-	299	Dysglycemia	52 (9)	66	2.0	12	2.0	92	●	-	-
TEAAM[178]	2004-2009	USA	-	2	-	-	-	-	●	308	General population	68 (5)	0	3.0‡	16	3.0	99	●	-	-
TRIPOD[179]	1995-1998	USA	-	2	●	-	-	-	-	266	Dysglycemia	34 (7)	100	2.9	0	4.0	72	●	-	-
Tasic et al.[180]	NR	Serbia	-	2	-	●	-	-	-	40	Hypertension	64 (9)	35	0.8‡	6	0.8	100	●	-	-
VEAPS[181]	1996-1999	USA	-	2	-	-	●	-	-	353	Hyperlipidemia	56 (9)	52	3.0†	18	3.0	94	●	-	-
VHAS[182,183]	NR	Italy	-	2	-	●	-	-	-	1414	Hypertension	54 (7)	51	2.0‡	33	4.0	27	-	-	●
VIP[184]	2005-2007	Netherlands	-	2	-	-	-	-	●	119	Kidney disease	53 (12)	33	3.0‡	10	3.0	86	●	-	-
VITAL[185]	2002-2004	Netherlands	●	2	-	-	-	-	●	199	Elevated CVD risk	49 (12)	41	1.5	12	2.5	99	●	-	-
WISH[186]	2004-2007	USA	-	2	-	-	●	-	-	350	General population	61 (7)	100	2.7	1	3.0	93	●	-	-
Yang et al.[187]	2013-2017	China	-	2	-	-	-	-	●	119	Elevated CVD risk	54 (11)	72	0.5‡	0	0.5	100	-	-	●
Yun et al.[188]	2010-2013	China	-	2	●	-	-	-	-	135	Pre-existing CVD	62 (5)	40	2.3†	23	4.5	93	●	-	-
Zou et al.[189]	2010	China	-	2	-	-	●	-	-	96	Elevated CVD risk	57 (5)	59	1.0‡	0	1.0	89	●	-	-
Total: 119 trials	**1980-2017**		**30**		**18**	**19**	**20**	**33**	**37**	**100667**		**62 (8)**	**41.9**	**3.7**	**12038**	**3.5**	**90**	**91**	**49**	**11**

Table V in the Supplement provides full names of the contributing trials. ***Table III in the Supplement** provides detailed information on the interventions in each trial. †Mean. ‡Maximum. Abbreviations: CCA-IMT=common-carotid-artery intima-media thickness. cIMT=carotid intima-media thickness. CVD=cardiovascular disease. IPD=individual-participant data. NR=not reported. SD=standard deviation.

Figure legends

Figure 1. Intervention effects on cIMT progression plotted against intervention effects on risk for the primary CVD endpoint. The intercept of the primary model was 0.92 (95% CI 0.87-0.97). Each bubble represents a trial. Trials with point estimates outside of this area are indicated with the symbol x. The areas of the bubbles are proportional to the inverse variance of the log relative risk for the primary CVD endpoint. The shaded areas around lines-of-fit are 95% prediction intervals. For purpose of presentation, the graph area was limited to -80 to 80 μm/year on the horizontal axis and 0.25 to 4 on the vertical axis. Abbreviations: CI=credible interval. cIMT=carotid intima-media thickness. CVD=cardiovascular disease. RR=relative risk.

Figure 2. Intervention effects on risk for individual CVD endpoints and all-cause mortality per 10 μm/year slower cIMT progression. *The RRs for intercepts are the effects achieved independent of cIMT progression. Abbreviations: CI=credible interval. cIMT=carotid intima-media thickness. CVD=cardiovascular disease. RR=relative risk.

Figure 3. Intervention effects on cIMT progression plotted against intervention effects on risk for the primary CVD endpoint, according to type of intervention. The RRs for intercepts as well as *P* values for heterogeneity of intercept and slope are provided in **Figure 4**. The areas of the bubbles are proportional to the inverse variance of the log relative risk for the primary CVD endpoint. For purpose of presentation, the graph area was limited to -80 to 80 μm/year on the horizontal axis and 0.25 to 4 on the vertical axis. Trials with point estimates outside of this area are indicated with the symbol x. Abbreviations: cIMT=carotid intima-media thickness. CVD=cardiovascular disease. RR=relative risk.

Figure 4. Intervention effects on risk for the primary CVD endpoint per 10 μm/year slower cIMT progression, according to trial characteristics. Abbreviations: CCA-IMT=intima-media thickness of the common-carotid-artery. CI=credible interval. cIMT=carotid intima-media thickness. IPD=individual-participant data. RR=relative risk. **P* values for heterogeneity. §The RRs for intercepts are the effects achieved independent of cIMT progression.‖Numbers of trials across some subgroups do not sum up to 119 because of missing information or contribution of trials to multiple subgroups.

Figure 5. Summary of key findings of our study. Abbreviations: CI=credible interval. cIMT=carotid intima-media thickness. CVD=cardiovascular disease. RCTs= randomized controlled trials.

Supplemental Material

Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: Meta-analysis of 119 clinical trials involving 100,667 patients

Table of Contents

Supplemental Methods

To test whether intervention effects on cardiovascular disease (CVD) risk depended on intervention effects on carotid intima-media thickness (cIMT) progression we used a meta-regression that accounted for the estimated precision in both effects.[14] Specifically, we followed the methods of Daniels and Hughes (1997) as set out below.

In the *i*th trial the true treatment difference on the clinical outcome (CVD incidence) is θ_i and the true treatment difference on the cIMT progression is γ_i. We have estimates $\hat{\theta}_i$ and $\hat{\gamma}_i$ of these quantities from each trial along with estimated standard errors σ_i and δ_i. The correlation between $\hat{\theta}_i$ and $\hat{\gamma}_i$, denoted ρ_i, is estimated using bootstrapping in the trials with individual patient-level data and >30 events as previously described by Riley *et al* in Web Appendix 5 of their paper [15]. The following model is assumed to apply:

$$\begin{pmatrix} \hat{\theta}_i \\ \hat{\gamma}_i \end{pmatrix} \sim N\left(\begin{pmatrix} \theta_i \\ \gamma_i \end{pmatrix}, \begin{pmatrix} \sigma_i^2 & \rho_i\sigma_i\delta_i \\ \rho_i\sigma_i\delta_i & \delta_i^2 \end{pmatrix} \right) \quad (1)$$

$$\theta_i|\gamma_i \sim N(\alpha + \beta\gamma_i, \tau^2) \quad (2)$$

where τ^2 denotes between-trials heterogeneity in the regression of θ_i on γ_i, α is an intercept parameter denoting treatment effects on the clinical outcome that do not act through effects on cIMT progression (i.e. indirect effects), and β is the association between treatment differences on cIMT progression and the clinical outcome. A necessary condition for cIMT progression to be a surrogate marker is for $\beta \neq 0$. Furthermore, if $\tau^2 = 0$ then we could predict θ_i perfectly from γ_i.

This model is similar to a standard meta-regression model except for one key difference. A standard meta-regression model would consider the estimated treatment effects on cIMT progression as covariates to form the regression $\theta_i|\hat{\gamma}_i \sim N(\alpha + \beta\,\hat{\gamma}_i, \tau^2)$. In contrast, the Daniels and Hughes method allows for the uncertainty in the estimation by assuming a bivariate normal distribution between the two estimated treatment effects. Furthermore, unlike a full bivariate random effects meta-analysis, the Daniels and Hughes model makes no distributional assumption about the true treatment effects on cIMT progression. Further details and a comparison of these modelling approaches have been described by Bujkiewicz *et al*[214].

Estimation and Priors

A Bayesian approach was taken to estimate the model parameters and for prediction. Specifically, the following prior distributions were specified for the model parameters:

$$\alpha \sim N(0, 1000)$$

$$\beta \sim N(0, 1000)$$

$$\gamma_i \sim_{iid} N(0, 1000)$$

$$\tau \sim N(0, 100)I(0,)$$

where $I(0,)$ denotes a positive truncated distribution (i.e. τ follows a Half Normal distribution) and iid denotes independent and identically distributed.

Sensitivity to the choice of prior distribution for the between-trials variance, τ^2, was assessed by using an alternative inverse-Gamma prior, $\tau^2 \sim IG(0.001, 0.001)$. Results from the primary model (allowing for a non-zero intercept) were robust to this alternative prior specification; the relative risk (RR) (95% credible interval) per 10 μm/year slower progression was 0.91 (0.87-0.94) under this alternative specification.

Prediction

The 95% prediction interval around the regression line (**Figure 1** and **Figure 3**) is derived as follows. Given a true value of cIMT progression, γ^*, the posterior predictive distribution for the log RR for the clinical outcome, θ^*, is derived from Equation (2) using MCMC to compute the distribution:

$$f(\theta^*|\gamma^*) \sim N(\alpha + \beta\gamma^*, \tau^2)$$

$$f(\theta^*|\gamma^*) = \sum_{m=1}^{M} f\,(\theta^*|\gamma^*, \alpha_{(m)}, \beta_{(m)}, \tau^2_{(m)})$$

The mean and variance of the predictive distribution can also be derived using the summary statistics from the MCMC run; namely using the posterior means $\hat{\alpha}$, $\hat{\beta}$, and $\widehat{\tau^2}$ and the posterior variances s_α^2, s_β^2, and covariance $s_{\alpha\beta}$.

$$E[\theta^*|\gamma^*] = \hat{\alpha} + \hat{\beta}\gamma^*$$

$$Var(\theta^*|\gamma^*) = E[V(\theta^*|\gamma^*, \alpha, \beta, \tau^2)] + V(E[\theta^*|\gamma^*, \alpha, \beta, \tau^2]) =$$

$$= \widehat{\tau^2} + s_\alpha^2 + (\gamma^*)^2 s_\gamma^2 + 2\gamma^* s_{\alpha\beta}$$

Leave-one-out predictive validity

Leave-one-out cross-validation was used to assess the predictive validity of the model. Specifically, for each study in turn, the model was re-estimated leaving out the data from that study. A posterior predictive distribution for the left-out study was then obtained for the primary outcome, using information on the estimated cIMT effect, $\hat{\gamma}_i$, its variance, δ_i^2, and the size of the trial (as obtained from the precision of the clinical outcome, σ_i^2). The observed RR for the clinical outcome was compared with the 95% prediction interval and estimates outside of the intervals were flagged.

Specifically, the predictive distribution for the estimated intervention effect on CVD incidence (the log RR) for study i (left-out of analysis) is:

$$(\hat{\theta}_i | \, \hat{\gamma}_i) \sim N\left(\theta_i + \frac{\sigma_i}{\delta_i}\rho_i(\hat{\gamma}_i - \gamma_i), (1-\rho_i)^2\sigma_i^2\right)$$

with $\theta_i = \alpha + \beta\gamma_i$. Estimates from this predictive distribution were obtained directly from MCMC samples.

Figure II in the Supplement shows results from the leave-one-out cross-validation, where studies have been ordered by the observed precision of the clinical outcome. Only 3 out of the 119 studies (2.5%) fell outside the 95% prediction intervals.

Supplemental Tables

Supplemental Table I. PRISMA-IPD Checklist

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	Title page
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	page 1
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	page 2
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	page 2
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	PMID: 20435179
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	page 3
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	page 3 & Table II in the Supplement
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table II in the Supplement
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	page 3 & Figure I in the Supplement
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	page 3 & Figure I in the Supplement
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or	

		extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	pages 3-4
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	page 3
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	pages 3-4 & Table III in the Supplement
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	pages 3-4 & Table 1 & Table III in the Supplement & Table IV in the Supplement
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	pages 4-5
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	pages 4-5
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	pages 4-5
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	pages 4-5
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	page 5 & Table 1 & Figure I in the Supplement
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	page 5 & Table 1 & Table III in the Supplement & Table V in the Supplement
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	page 3
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	page 6 & Figure 3 & Figure 4 & Figure II in the Supplement

Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Table 1 & Figure 1 & Table IV in the Supplement
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	pages 5-6 & Figure 1 & Figure 2 & Figure 3 & Figure 4
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	page 6 & Figure 2 & Figure 3 & Figure 4 & Figure II in the Supplement
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	page 6 & Figure 3 & Figure 4
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	page 6
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	page 9
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	pages 7-9
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	pages 7-9
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	page 10

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Supplemental Table II. Sources and searches

Name	Full name, URL	Search syntax
Clinicaltrials.gov	Clinicaltrials.gov, https://clinicaltrials.gov/	- Intima media thickness - Intima media thickening
MedPilot	MedPilot, https://www.medpilot.de/ [this portal went offline in 2015]	(intima AND media) AND (thickening OR thickness OR mortality OR death OR stroke OR (myocardial AND infarction))
Cochrane	Cochrane Library, http://onlinelibrary.wiley.com/cochranelibrary/search	- Intima media thickness - Intima media thickening
Embase	Embase®, https://www.embase.com	- Intima media thickness - Intima media thickening
EU CTR	EU Clinical Trials Register, https://www.clinicaltrialsregister.eu/ctr-search/search	- Intima media thickness - Intima media thickening
ISI	Web of knowledge, http://login.webofknowledge.com	(1: Topic=(controlled trial); 2: Topic=(carotid intima media); 3: Topic=(carotid atherosclerosis) 4: #3 OR #2; 5: #4 AND #1)
mRCT	metaRegister of Controlled Trials, http://www.isrctn.com/page/mrct	- Intima media thickness - Intima media thickening
PMC	NCBI PubMed.gov Central, https://www.ncbi.nlm.nih.gov/pmc/	- Intima media myocardial infarction RCT - Intima media stroke RCT - Intima media death RCT - Intima media mortality RCT
PubMed	NCBI PubMed.gov, https://www.ncbi.nlm.nih.gov/pubmed/	((carotid intima media) OR (carotid atherosclerosis)) AND ("Controlled Clinical Trials as Topic"[Mesh] OR "Clinical Trial"[Publication Type])
Reference	References found cited in other studies and review publications on intima-media thickness	Not applicable
WHO	World Health Organization International Clinical Trials Registry Platform, http://apps.who.int/trialsearch/	- Intima media thickness - Intima media thickening
ISRCTN	ISRCTN registry, http://www.isrctn.com/	- Intima media thickness - Intima media thickening
ANZCTR	Australian New Zealand Clinical Trials Registry, http://www.anzctr.org.au/	- Intima media thickness - Intima media thickening
CHICTR	Chinese Clinical Trial Registry, http://www.chictr.org.cn/enIndex.aspx	- Intima media thickness - Intima media thickening
NTR	Netherlands Trial Register, https://www.trialregister.nl/trials	- Intima media thickness - Intima media thickening
UMIN-CTR	UMIN Clinical Trials Registry, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/index.cgi?function=02	- Intima media thickness - Intima media thickening
IFPMA	IFPMA Clinical Trials Portal, http://clinicaltrials.ifpma.org/clinicaltrials/en/myportal/index.htm [these links became nonfunctional between 2014 and 2018]	- Intima media thickness - Intima media thickening

Supplemental Table III. Definition of the primary CVD outcome and methods used to assess cIMT progression

Trial	Primary outcome definition						Assessment of cIMT progression					
	MI	Stroke	Revascularization	Fatal CVD	All-cause mortality	Other	Types of cIMT available	Near wall	Far wall	Right side	Left side	Analyzed with a linear-mixed model
ACAPS	●	●	-	●	-		meanmax CCA	●	●	●	●	●
ACT NOW	●	●	●	●	-		meanmean CCA	-	●	●	-	●
ALLO-IMT	●	●*	-	●	-		meanmean CCA, meanmax CCA	●	●	●	●	●
AMAR	●	●	-	●	-		meanmean CCA	-	●	●	●	-
ARBITER	●	●	●	●	-		meanmean CCA, meanmax CCA	-	●	●	●	-
ARBITER 2	●	●	●	-	●	PVD	meanmean CCA	-	●	●	●	-
ARBITER 6-HALTS	●	-	●	●	-		meanmean CCA, meanmax CCA	-	●	●	●	-
ARTSTIFF	●	●	-	●	-		meanmean CCA	-	●	●	-	-
ASAP-FINLAND	-	-	-	-	●		meanmean CCA	-	●	●	●	-
ASAP-NL	●	●	-	●	-		meanmean CCA	●	●	●	●	-
ASFAST	●	●	-	●	-		meanmax CCA	-	●	●	●	●
ATIC	●	●	-	●	-		meanmean CCA	-	●	●	-	●
Ahn et al.	●	●	●	-	●		meanmax CCA+BIF+ICA	●	●	●	●	-
Andrews et al.	●	●	-	●	-		meanmean CCA	-	●	-	-	●
BCAPS	●	●	-	●	-		meanmean CCA	-	●	●	-	-
BKREGISTRY-II	●	●	-	●	-		meanmean CCA	-	●	-	●	●
BVAIT	-	-	-	-	-	CVD	meanmean CCA	-	●	●	-	●
CAIUS	●	●	●	●	-		meanmax CCA	●	●	●	●	●
CAMERA	●†	●	●	●	-		meanmean CCA	-	●	●	●	●
CAPPA	●†	●	-	●	-		meanmean CCA, meanmax CCA	-	●	●	-	●
CAPTIVATE	●	●	●	●	-		meanmean CCA+BIF+ICA	●	●	●	●	-
CERDIA	●	●	-	●	-		meanmean CCA, meanmax CCA	●	●	●	-	●
CHICAGO	●	●	●	●	-		meanmean CCA, meanmax CCA	-	●	●	●	-
CIMT phase 1	-	-	-	-	●	CVD	meanmean CCA, meanmax CCA	-	●	●	●	-
CLAS	●	-	●	●	-		meanmean CCA	-	●	●	-	-
CONTRAST	●†	●	●	●	-		meanmean CCA, meanmax CCA	●	●	●	●	●
Cao et al.	●	●	●	●	-		meanmax CCA+BIF+ICA	●	●	●	●	-
DAPC	●	●	-	●	-		meanmean CCA, meanmax CCA	-	●	-	●	●
DAPHNE	●	●	●	●	-		meanmean CCA+BIF+ICA	●	●	●	●	●
DOIT	-	-	-	-	-	CVD	meanmean CCA	-	●	-	-	-
EGE STUDY	-	-	-	●	-		meanmean CCA	-	●	●	●	●
ELITE (early MP)	●	●	-	●	-		meanmean CCA	-	●	●	-	●
ELITE (late MP)	●	●	-	●	-		meanmean CCA	-	●	●	-	●
ELSA	●	●	-	●	-		meanmax CCA+BIF+ICA	-	●	●	●	●
ELVA	●	●	-	●	-		meanmean CCA	-	●	●	-	-
ENCORE	-	●	-	-	-		meanmean CCA	●	●	●	●	●
ENHANCE	●	●	●	●	-		meanmean CCA, meanmax CCA	-	●	●	●	●
EPAT	●	●	●	●	-		meanmean CCA	-	●	●	-	●
FIELD	●	●	●	●	-		meanmax CCA	●	●	●	●	-
FIRST	●	●	●	●	-	HF	meanmax CCA	-	●	●	●	●
FRANCIS	●	●	●	●	-		meanmean CCA	-	●	●	●	●
GRACE	●‡	●	●	●	-		meanmean CCA, meanmax CCA	●	●	●	●	●
Gresele et al.	●‡	●	-	●	-		meanmean CCA, meanmax CCA	●	-	●	-	●
HART	●	●	-	●	-		meanmean CCA, meanmax CCA	●	●	●	●	●
HERS	●	●*	-	●	-		meanmax CCA	●	●	●	●	●
HYRIM	●†	●	-	●	-		meanmax CCA	-	●	●	-	●
INSIGHT	●	●	-	●	-		meanmean CCA	-	●	●	-	-

J-STARS	●	●*	-	-	●		meanmean CCA	-	●	●	●	●
JART	●	●	●	-	●		meanmean CCA, meanmax CCA	-	●	●	●	-
KAPS	●	●	●	●	-		meanmax CCA	-	●	●	●	-
KEEPS	●	●	-	●	-		meanmean CCA	-	●	●	●	●
KIMVASC	●	●	-	●	-		meanmean CCA	-	●	●	●	●
Katakami et al.	-	-	-	-	-	CVD	maxmeanmax CCA+BIF+ICA	●	●	●	●	-
Koyasu et al.	●	●	-	●	-		meanmax CCA	●	-	●	●	-
LAARS	●	●	-	●	-		meanmean CCA	-	●	●	●	-
LIFE-ICARUS	●‡	●	●	●	-		meanmean CCA	-	●	●	●	●
LIPID	●	●	●	●	-		meanmean CCA	-	●	●	-	-
Luijendijk et al.	●	●	-	●	-		meanmean CCA	●	-	●	●	-
MARS	●	●	●	●	-		meanmean CCA	●	●	●	-	-
MAVET	-	-	-	●	-		meanmax CCA	-	●	●	-	●
MECANO	●	●	●	●	-		meanmean CCA	●	-	●	●	●
MEDICLAS	●	●	-	●	-		meanmean CCA	●	●	●	-	●
METEOR	●	●§	-	●	-		meanmean CCA, meanmax CCA	●	●	●	●	●
MG600	●	●	-	●	-		meanmean CCA, meanmax CCA	●	●	●	●	●
MIDAS	●	●	●	●	-		meanmax CCA	●	●	●	●	-
MITEC	-	-	-	●	-		meanmean CCA	-	●	●	●	-
Makimura et al.	●	●	-	●	-		meanmean CCA	●	-	●	-	●
Masia et al.	●‡	●	●	●	-		meanmean CCA, meanmax CCA	-	●	●	●	●
Mitsuhashi et al.	●	●	-	●	-		maxmeanmax CCA+BIF+ICA	●	●	●	●	-
Mortazavi et al.	-	●	-	-	●		meanmean CCA	-	●	●	●	-
NTPP	●	●	-	●	-		meanmeanCCA, meanmax CCA	●	-	●	●	-
Nakamura et al. II	●	●	-	●	-		meanmean CCA, meanmax CCA	-	●	●	●	●
Ntaios et al.	●	●*	-	●	-		meanmean CCA	●	●	●	●	●
OPAL	●†	●	-	-	-		meanmean CCA, meanmax CCA	●	●	●	●	●
PART-2	●	●	-	●	-	HF	meanmean CCA	-	●	●	●	-
PEACE	●	-	-	-	●		meanmean CCA, meanmax CCA	●	●	●	●	-
PERFORM	●	●	●	●	-		meanmean CCA	-	●	●	●	●
PERIOCARDIO	-	-	-	-	-	CVD	meanmean CCA, meanmax CCA	-	●	●	●	●
PHOREA	●	●	-	●	-		meanmax CCA	-	●	●	●	-
PHYLLIS	●	●	-	●	-		meanmax CCA	●	●	●	●	-
PLAC II	●	-	-	●	-		meanmax CCA	●	●	●	●	●
PPAR	●	●	-	-	●		meanmean CCA+BIF+ICA	●	-	●	●	●
PREDIMED	●	●	-	●	-		meanmean CCA, meanmax CCA	-	●	●	●	-
PREVEND IT	●†	●	●	●	-		meanmean CCA	-	●	-	●	●
PREVENT	●	●	●	●	-		meanmax CCA	●	●	●	●	●
PROBE	●	●	-	-	●		meanmean CCA, meanmax CCA	-	●	●	●	-
RADIANCE I	●†	●	-	-	-		meanmean CCA, meanmax CCA	●	●	●	●	●
RADIANCE II	●†	●	-	-	-		meanmean CCA, meanmax CCA	●	●	●	●	●
RAS	●	●	-	-	●		meanmean CCA	-	●	●	-	-
REGRESS	●	●*	●	-	●		meanmean CCA	-	●	●	-	-
REMOVAL	●	●	●	●	-		meanmeanCCA, meanmax CCA	-	●	●	●	●
RIS	●	●	-	●	-		meanmean CCA, meanmax CCA	-	●	●	-	●
SANDS	●	●	●	●	-		meanmean CCA	-	●	●	●	-
SCIMO	●	●	●	●	-		meanmax CCA	-	●	●	●	-
SECURE	●	●	-	●	-		meanmax CCA	●	●	●	●	●
SEKONA	●	●	-	-	●		meanmean CCA	-	●	●	●	-
SENDCAP	●	-	-	-	-		meanmax CCA	-	●	●	●	-
SPEAD-A	●	●	-	●	-		meanmeanCCA, meanmax CCA	●	-	●	●	●
SPIKE	●	●	-	-	●		meanmean CCA	●	-	●	●	●
STARR	●‡	●	-	●	-		meanmean CCA, meanmax CCA	●	●	●	●	●
STOP-NIDDM	●‡	●	●	●	-	HF, PVD	meanmean CCA	-	●	●	●	-
Safarova et al.	●	●	●	●	-		meanmean CCA	-	●	●	●	●
Sander et al. (Cp neg)	●	●	-	●	-		meanmean CCA	-	●	●	●	-
Sander et al. (Cp pos)	●	●	-	●	-		meanmean CCA	-	●	●	●	-
Spring et al.	●	●	-	●	-		meanmean CCA	●	●	●	●	-
Stanley et al.	●	●	-	●	-		meanmean CCA	-	●	-	●	-

Stanton et al.	●	●	-	●	-	meanmean CCA	-	●	●	●	-
TART	●	●	-	●	-	meanmean CCA	-	●	●	-	●
TEAAM	●	●	-	●	-	meanmean CCA	-	●	●	●	●
TRIPOD	●	●	-	●	-	meanmean CCA	-	●	●	-	●
Tasic et al.	●	●	-	●	-	meanmean CCA	-	●	●	●	-
VEAPS	●	●*	●	●	-	meanmean CCA	-	●	●	-	●
VHAS	●	●	●	●	-	meanmax CCA+BIF+ICA	-	●	●	●	-
VIP	●	●	-	-	●	meanmean CCA	-	●	●	●	●
VITAL	●†	●	●	●	-	meanmean CCA	-	●	●	-	●
WISH	●	●	-	●	-	meanmean CCA	-	●	●	-	●
Yang et al.	●	●	●	●	-	meanmax CCA+BIF+ICA	●	●	●	●	●
Yun et al.	●	●	-	●	-	meanmean CCA	●	-	●	●	-
Zou et al.	●	●	-	●	-	meanmean CCA	●	●	●	●	-

*includes transient ischemic attack. †includes coronary heart disease. ‡includes stable angina pectoris. §ischemic stroke. Abbreviations: BIF=cIMT measured at the carotid bifurcation. cIMT=carotid intima-media thickness. CCA=cIMT measured at the common-carotid-artery. CVD=cardiovascular disease. HF=heart failure. ICA=cIMT measured at the internal-carotid-artery. MI=myocardial infarction. PVD=peripheral vascular disease. **Table V in the Supplement** provides full names of the contributing trials.

Supplemental Table IV. Intervention effects on progression of individual outcomes and different cIMT types

Trial	Trial arm	RR (95% CI)						Mean difference in progression (95% CI)		
		CVD	MI	Stroke	Revascularisation	Fatal CVD	All-cause mortality	Mean CCA-IMT	Max CCA-IMT	Other cIMT
ACAPS	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	[Reference]	NR
	Lovastatin (10-40mg)	0.38 (0.14, 1.07)	0.83 (0.25, 2.72)	<0.01 (<0.01, >100)	NR	<0.01 (<0.01, >100)	0.28 (0.06, 1.36)	NR	-3 (-8, 2)	NR
	Warfarin (1mg)	0.64 (0.25, 1.65)	0.38 (0.10, 1.42)	4.02 (0.45, 35.98)	NR	0.20 (0.02, 1.72)	0.29 (0.06, 1.38)	NR	1 (-3, 6)	NR
ACT NOW	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	Pioglitazone (30-45mg)	0.44 (0.14, 1.41)	1.97 (0.18, 21.65)	0.99 (0.02, 49.57)	0.25 (0.05, 1.15)	0.99 (0.02, 49.57)	2.96 (0.31, 28.30)	-5 (-9, -1)	NR	NR
ALLO-IMT	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Allopurinol (300mg)	0.36 (0.09, 1.34)	1.03 (0.06, 16.46)	0.66 (0.11, 3.94)	NR	1.00 (<0.01, >100)	<0.01 (<0.01, >100)	-68 (-142, 6)	-61 (-148, 27)	NR
AMAR	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Allicor (300mg)	0.58 (0.24, 1.39)	0.52 (0.16, 1.63)	0.58 (0.11, 3.11)	NR	0.77 (0.22, 2.67)	0.66 (0.20, 2.21)	-37 (-60, -14)	NR	NR
ARBITER	Pravastatin (40mg)	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Atorvastatin (80mg)	1.04 (0.22, 4.99)	1.56 (0.27, 9.07)	0.35 (0.01, 8.37)	3.11 (0.33, 29.31)	1.04 (0.02, 51.68)	1.04 (0.02, 51.68)	-59 (-112, -6)	-153 (-323, 17)	NR
ARBITER 2	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	NR
	Niacin (1g)	0.39 (0.11, 1.47)	0.92 (0.13, 6.38)	0.31 (0.01, 7.42)	0.23 (0.03, 2.01)	NR	0.46 (0.04, 4.97)	-30 (-63, 3)	NR	NR
ARBITER 6-HALTS	Ezetimibe (10mg)	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR
	Niacin (2g)	0.21 (0.05, 0.95)	0.31 (0.03, 2.99)	NR	0.13 (<0.01, 2.58)	0.19 (0.02, 1.60)	NR	-12 (-20, -3)	-15 (-25, -4)	NR
ARTSTIFF	Olmesartan (20mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Olmesartan (40mg)	1.05 (0.02, 51.61)	1.05 (0.02, 51.61)	1.05 (0.02, 51.61)	NR	1.05 (0.02, 51.61)	3.14 (0.13, 75.02)	28 (-28, 84)	NR	NR
	Olmesartan (80mg)	0.94 (0.02, 46.17)	0.94 (0.02, 46.17)	0.94 (0.02, 46.17)	NR	0.94 (0.02, 46.17)	0.94 (0.02, 46.17)	-1 (-47, 45)	NR	NR
ASAP-FINLAND	Placebo	[Reference]	NR	NR	NR	NR	[Reference]	[Reference]	NR	NR
	Vitamin C (250mg) or Vitamin E (136IU) or both	2.11 (0.63, 7.02)	NR	NR	NR	NR	2.11 (0.63, 7.02)	-4 (-7, -0)	NR	NR
ASAP-NL	Simvastatin (40mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Atorvastatin (80mg)	0.69 (0.12, 4.08)	0.69 (0.12, 4.08)	1.04 (0.02, 51.96)	NR	1.04 (0.07, 16.44)	0.52 (0.05, 5.66)	-12 (-24, 1)	NR	NR
ASFAST	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR
	Folic acid (15mg)	0.84 (0.56, 1.26)	1.23 (0.70, 2.17)	0.45 (0.20, 1.01)	2.24 (0.80, 6.30)	0.89 (0.52, 1.53)	1.00 (0.71, 1.41)	NR	-10 (-35, 15)	NR
ATIC	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Pravastatin (40mg) + α-tocopherol (300mg) + Folic acid (5mg) + Pyridoxine hydrochloride (100mg) + Cyanocobalamin (1mg)	0.98 (0.14, 6.66)	1.96 (0.18, 20.85)	0.98 (0.02, 48.30)	NR	0.33 (0.01, 7.80)	0.33 (0.01, 7.80)	-87 (-107, -67)	NR	NR
Ahn et al.	Atorvastatin (10mg) + Aspirin (100mg) + Clopidogrel (75mg)	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	NR	[Reference]
	Atorvastatin (10mg) + Aspirin (100mg) + Clopidogrel (75mg) + Cilostazol (200mg)	0.83 (0.35, 1.96)	0.52 (0.05, 5.55)	1.03 (0.07, 16.14)	1.03 (0.31, 3.39)	NR	0.52 (0.05, 5.55)	NR	NR	-80 (-154, -6)
Andrews et al.	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Allopurinol (300mg)	3.15 (0.13, 75.12)	1.05 (0.02, 51.70)	1.05 (0.02, 51.70)	NR	3.15 (0.13, 75.12)	3.15 (0.13, 75.12)	-87 (-261, 87)	NR	NR
BCAPS	Placebo	[Reference]	NR	NR	NR	NR	NR	[Reference]	NR	NR
	Fluvastatin (40mg)	0.64 (0.25, 1.64)	NR	NR	NR	NR	NR	-8 (-15, -2)	NR	NR
	Metoprolol (25mg)	0.39 (0.14, 1.07)	NR	NR	NR	NR	NR	-1 (-7, 6)	NR	NR
BKREGISTRY-II	Usual therapy	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Usual therapy + Atorvastatin (10mg)	0.44 (0.04, 4.84)	<0.01 (<0.01, >100)	0.88 (0.05, 14.03)	NR	1.00 (<0.01, >100)	1.00 (<0.01, >100)	48 (-47, 142)	NR	NR
BVAIT	Placebo	[Reference]	NR	NR	NR	NR	[Reference]	[Reference]	NR	NR
	Folic acid (5mg) + Vitamin B6 (50mg) + Vitamin B12 (0.4mg)	0.81 (0.34, 1.93)	NR	NR	NR	NR	0.20 (<0.01, 4.11)	-1 (-2, 1)	NR	NR
CAIUS	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR

	Pravastatin (40mg)	1.53 (0.26, 9.03)	1.02 (0.15, 7.15)	1.02 (0.02, 51.07)	3.06 (0.13, 74.52)	3.06 (0.13, 74.52)	3.06 (0.13, 74.52)	NR	-11 (-18, -3)	NR
CAMERA	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	NR
	Metformin (1.7g)	0.56 (0.17, 1.86)	0.18 (0.02, 1.51)	>100 (<0.01, >100)	0.46 (0.09, 2.38)	>100 (<0.01, >100)	NR	7 (-5, 19)	NR	NR
CAPPA	Aspirin (100mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Cilostazol (200mg)	1.02 (0.21, 5.02)	0.68 (0.12, 4.04)	3.07 (0.13, 75.01)	NR	1.02 (0.02, 51.39)	1.02 (0.06, 16.27)	-21 (-33, -9)	-25 (-45, -6)	NR
CAPTIVATE	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR	NR	[Reference]
	Pactimibe (100mg)	1.65 (0.82, 3.34)	3.30 (0.92, 11.92)	2.97 (0.12, 72.79)	1.26 (0.58, 2.75)	2.97 (0.31, 28.48)	NR	NR	NR	14 (0, 28)
CERDIA	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Cerivastatin (0.4mg) / Simvastatin (20mg)	0.34 (0.11, 1.08)	<0.01 (<0.01, >100)	0.35 (0.07, 1.80)	NR	<0.01 (<0.01, >100)	0.72 (0.16, 3.22)	2 (-7, 12)	8 (-3, 19)	NR
CHICAGO	Glimepiride (1-4mg)	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Pioglitazone (15-45mg)	0.30 (0.08, 1.07)	0.33 (0.01, 8.07)	0.33 (0.01, 8.07)	0.37 (0.10, 1.38)	0.99 (0.02, 49.75)	2.97 (0.12, 72.63)	-9 (-17, -1)	-17 (-30, -4)	NR
CIMT phase 1	Placebo	[Reference]	NR	NR	NR	NR	[Reference]	[Reference]	[Reference]	NR
	Metformin (2g)	0.82 (0.35, 1.93)	NR	NR	NR	NR	5.00 (0.24, >100)	8 (-2, 18)	7 (-4, 19)	NR
CLAS	Placebo	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	[Reference]	NR	NR
	Colestipol (30g) + Niacin (4.2g)	0.66 (0.48, 0.90)	0.37 (0.18, 0.74)	NR	0.94 (0.59, 1.52)	0.34 (0.07, 1.64)	NR	-25 (-37, -13)	NR	NR
CONTRAST	Low-flux haemodialysis	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR
	On-line haemodiafiltration	1.12 (0.83, 1.52)	0.81 (0.53, 1.24)	1.17 (0.60, 2.27)	1.23 (0.84, 1.79)	0.47 (0.16, 1.35)	0.95 (0.75, 1.20)	3 (-38, 44)	4 (-47, 55)	NR
Cao et al.	Lifestyle intervention	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR	[Reference]
	Lifestyle intervention + Oligomeric proanthocyanidin (200mg)	0.28 (0.13, 0.58)	0.25 (0.10, 0.66)	0.48 (0.04, 5.27)	0.28 (0.06, 1.31)	0.97 (0.02, 48.34)	0.97 (0.02, 48.34)	NR	NR	-56 (-90, -21)
DAPC	Aspirin (100mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Cilostazol (200mg)	0.52 (0.05, 5.72)	1.05 (0.02, 52.49)	0.52 (0.05, 5.72)	NR	3.14 (0.13, 76.58)	5.24 (0.25, >100)	-36 (-57, -14)	-74 (-104, -43)	NR
DAPHNE	HCTZ (1-16mg)	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR	NR	[Reference]
	Doxazosin (12.5-100mg)	1.22 (0.50, 2.96)	8.56 (0.48, >100)	0.19 (<0.01, 3.84)	0.95 (0.30, 3.03)	0.95 (0.02, 46.78)	NR	NR	NR	2 (-10, 15)
DOIT	No dietary advice	[Reference]	NR	NR	NR	NR	[Reference]	[Reference]	NR	NR
	Dietary advice	0.75 (0.47, 1.20)	NR	NR	NR	NR	0.81 (0.43, 1.50)	-6 (-12, -0)	NR	NR
EGE STUDY	Low-flux membrane	[Reference]	NR	NR	NR	[Reference]	[Reference]	[Reference]	NR	NR
	High-flux membrane	0.91 (0.55, 1.50)	NR	NR	NR	0.91 (0.55, 1.50)	0.87 (0.60, 1.25)	-3 (-14, 8)	NR	NR
	Ultrapure dialysate	1.05 (0.63, 1.75)	NR	NR	NR	1.05 (0.63, 1.75)	1.14 (0.80, 1.65)	3 (-7, 14)	NR	NR
ELITE (early MP)	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	17β-estradiol (1mg)	0.33 (0.01, 7.93)	0.33 (0.01, 7.93)	0.98 (0.02, 48.94)	NR	0.98 (0.02, 48.94)	0.33 (0.01, 7.93)	-3 (-6, -1)	NR	NR
ELITE (late MP)	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	17β-estradiol (1mg)	1.50 (0.25, 8.87)	1.50 (0.25, 8.87)	1.00 (0.02, 50.14)	NR	1.00 (0.02, 50.14)	3.00 (0.12, 73.17)	1 (-1, 3)	NR	NR
ELSA	Atenolol (50-100mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	NR	[Reference]
	Lacidipine (4-6mg)	0.80 (0.49, 1.33)	1.04 (0.54, 2.01)	0.63 (0.27, 1.45)	NR	0.49 (0.15, 1.63)	0.75 (0.37, 1.54)	NR	NR	-2 (-11, 7)
ELVA	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Metoprolol CR/XL (100mg)	3.24 (0.35, 30.35)	3.24 (0.35, 30.35)	1.08 (0.02, 53.64)	NR	1.08 (0.02, 53.64)	1.08 (0.02, 53.64)	-24 (-45, -2)	NR	NR
ENCORE	Usual care	[Reference]	NR	[Reference]	NR	NR	NR	[Reference]	NR	NR
	DASH diet	0.36 (<0.01, >100)	NR	0.36 (<0.01, >100)	NR	NR	NR	29 (-39, 98)	NR	NR
	DASH diet + Weight management	0.35 (<0.01, >100)	NR	0.35 (<0.01, >100)	NR	NR	NR	-12 (-79, 55)	NR	NR
ENHANCE	Simvastatin (80mg) + Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Simvastatin (80mg) + Ezetimibe (10mg)	1.09 (0.63, 1.87)	1.18 (0.68, 2.07)	<0.01 (<0.01, >100)	1.47 (0.41, 5.21)	2.02 (0.18, 22.27)	2.03 (0.18, 22.44)	2 (-4, 8)	2 (-5, 10)	NR
EPAT	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	NR
	17β-estradiol (1mg)	0.40 (0.08, 2.02)	0.50 (0.05, 5.44)	3.00 (0.12, 72.85)	0.50 (0.05, 5.44)	0.33 (0.01, 8.09)	NR	-5 (-11, -0)	NR	NR
FIELD	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR
	Fenofibrate (200mg)	0.90 (0.81, 0.99)	0.89 (0.76, 1.05)	0.90 (0.73, 1.12)	0.81 (0.71, 0.92)	1.10 (0.87, 1.40)	1.10 (0.95, 1.28)	NR	-2 (-23, 19)	NR
FIRST	Atorvastatin + Placebo	[Reference]	NR	NR	NR	NR	[Reference]	NR	[Reference]	NR
	Atorvastatin + Fenofibrate (135mg)	0.88 (0.44, 1.77)	NR	NR	NR	NR	0.25 (0.03, 2.24)	NR	-2 (-15, 11)	NR

FRANCIS	Usual care	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	Treat-to-target	0.27 (0.06, 1.29)	0.14 (<0.01, 2.62)	0.32 (0.01, 7.75)	0.96 (0.14, 6.69)	0.14 (<0.01, 2.62)	0.68 (0.22, 2.10)	-4 (-8, -0)	NR	NR
GRACE	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Insulin glargine (target fasting glucose≤5.3mg/dL)	0.99 (0.81, 1.22)	1.02 (0.76, 1.35)	1.36 (0.83, 2.23)	0.83 (0.61, 1.13)	0.95 (0.61, 1.48)	0.95 (0.72, 1.25)	-2 (-5, 1)	-3 (-6, -0)	NR
	ω3 fatty acids (1g)	1.09 (0.89, 1.33)	1.27 (0.95, 1.70)	0.81 (0.49, 1.32)	0.92 (0.68, 1.25)	1.22 (0.78, 1.90)	0.89 (0.68, 1.18)	-0 (-4, 3)	-0 (-3, 3)	NR
Gresele et al.	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	NCX 4016 (1.6g)	0.67 (0.16, 2.82)	0.45 (0.09, 2.34)	>100 (<0.01, >100)	NR	1.00 (<0.01, >100)	1.00 (<0.01, >100)	-29 (-100, 43)	-58 (-141, 25)	NR
HART	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Folic acid (2.5mg) + Vitamin B6 (50mg) + Vitamin B12 (1mg)	0.88 (0.64, 1.21)	0.86 (0.57, 1.29)	1.28 (0.60, 2.73)	NR	0.63 (0.32, 1.22)	0.69 (0.48, 0.99)	5 (2, 8)	7 (3, 10)	NR
HERS	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	[Reference]	NR
	Conjugated equine estrogen (0.625mg) + Medroxyprogesterone acetate (2.5mg)	1.03 (0.89, 1.20)	0.93 (0.75, 1.17)	1.13 (0.87, 1.47)	NR	1.23 (0.87, 1.72)	1.07 (0.84, 1.35)	NR	4 (-4, 12)	NR
HYRIM	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	[Reference]	NR
	Fluvastatin (40mg)	0.80 (0.45, 1.42)	0.74 (0.40, 1.36)	0.74 (0.17, 3.32)	NR	0.50 (0.04, 5.46)	0.80 (0.21, 2.97)	NR	-1 (-6, 3)	NR
	Lifestyle intervention	0.69 (0.38, 1.23)	0.69 (0.37, 1.27)	1.37 (0.31, 6.14)	NR	0.51 (0.05, 5.60)	1.28 (0.34, 4.75)	NR	-1 (-6, 4)	NR
INSIGHT	Nifedipine (30mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	HCTZ (25mg) + Amiloride (2.5mg)	0.97 (0.79, 1.19)	0.89 (0.67, 1.19)	1.10 (0.79, 1.53)	NR	0.86 (0.60, 1.25)	0.99 (0.80, 1.23)	6 (-1, 12)	NR	NR
J-STARS	Placebo	[Reference]	[Reference]	[Reference]	NR	NR	[Reference]	[Reference]	NR	NR
	Pravastatin (10mg)	1.00 (0.82, 1.24)	0.57 (0.17, 1.92)	0.96 (0.74, 1.24)	NR	NR	1.22 (0.79, 1.88)	-20 (-34, -5)	NR	NR
JART	Pravastatin (10-20mg)	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR
	Rosuvastatin (5-10mg)	0.29 (0.06, 1.37)	0.51 (0.05, 5.53)	1.01 (0.06, 16.04)	0.14 (<0.01, 2.78)	NR	0.34 (0.01, 8.22)	-24 (-44, -4)	-70 (-132, -8)	NR
KAPS	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR
	Pravastatin (40mg)	0.64 (0.31, 1.34)	0.37 (0.10, 1.39)	0.50 (0.09, 2.69)	0.80 (0.22, 2.93)	0.66 (0.11, 3.93)	0.75 (0.17, 3.30)	NR	-19 (-31, -7)	NR
KEEPS	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Estrogen (0.45mg)	1.20 (0.02, 60.03)	1.20 (0.02, 60.03)	1.20 (0.02, 60.03)	NR	1.20 (0.02, 60.03)	3.59 (0.15, 87.63)	1 (-1, 3)	NR	NR
	t-17β-estradiol (1μg)	3.72 (0.15, 90.78)	3.72 (0.15, 90.78)	1.24 (0.02, 62.18)	NR	1.24 (0.02, 62.18)	1.24 (0.02, 62.18)	1 (-2, 3)	NR	NR
KIMVASC	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Vitamin K2 (0.1mg)	>100 (<0.01, >100)	>100 (<0.01, >100)	1.00 (<0.01, >100)	NR	>100 (<0.01, >100)	>100 (<0.01, >100)	68 (-52, 188)	NR	NR
Katakami et al.	Glibenclamide (1.25-7.5mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	NR	[Reference]
	Glicazide (20-120mg)	2.19 (0.04, >100)	2.19 (0.04, >100)	2.19 (0.04, >100)	NR	2.19 (0.04, >100)	2.19 (0.04, >100)	NR	NR	-32 (-54, -10)
	Glibenclamide (1.25-5mg) + Metformin (500-750mg)	1.98 (0.04, 97.79)	1.98 (0.04, 97.79)	1.98 (0.04, 97.79)	NR	1.98 (0.04, 97.79)	1.98 (0.04, 97.79)	NR	NR	-61 (-90, -32)
Koyasu et al.	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	[Reference]	NR
	Acarbose (150mg)	1.00 (0.02, 49.31)	1.00 (0.02, 49.31)	1.00 (0.02, 49.31)	NR	1.00 (0.02, 49.31)	1.00 (0.02, 49.31)	NR	-150 (-261, -39)	NR
LAARS	Atenolol (50mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	[Reference]	NR	NR
	Losartan (50mg)	0.97 (0.02, 48.64)	0.97 (0.02, 48.64)	0.97 (0.02, 48.64)	NR	0.97 (0.02, 48.64)	NR	4 (-7, 15)	NR	NR
LIFE-ICARUS	Atenolol (50-100mg)	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	Losartan (50-100mg)	1.17 (0.29, 4.70)	>100 (<0.01, >100)	0.58 (0.05, 6.38)	<0.01 (<0.01, >100)	1.20 (0.07, 19.14)	0.76 (0.13, 4.57)	-8 (-22, 6)	NR	NR
LIPID	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	Pravastatin (40mg)	0.78 (0.74, 0.83)	0.72 (0.63, 0.83)	0.83 (0.68, 1.01)	0.82 (0.74, 0.91)	0.76 (0.67, 0.87)	0.78 (0.70, 0.88)	-16 (-23, -8)	NR	NR
Luijendijk et al.	No treatment	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Atorvastatin (80mg)	0.94 (0.02, 46.66)	0.94 (0.02, 46.66)	0.94 (0.02, 46.66)	NR	0.94 (0.02, 46.66)	0.94 (0.02, 46.66)	-5 (-14, 5)	NR	NR
MARS	Placebo	[Reference]	NR	[Reference]	NR	NR	[Reference]	[Reference]	NR	NR
	Lovastatin (80mg)	0.70 (0.43, 1.14)	NR	0.34 (0.01, 8.23)	NR	NR	2.03 (0.19, 22.12)	-43 (-68, -18)	NR	NR
MAVET	Placebo	[Reference]	NR	NR	NR	[Reference]	[Reference]	NR	[Reference]	NR
	Vitamin E (500IU)	0.50 (0.09, 2.69)	NR	NR	NR	0.50 (0.09, 2.69)	0.53 (0.24, 1.15)	NR	4 (-2, 10)	NR
MECANO	Cyclosporine A	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR

	Everolimus	1.85 (0.35, 9.88)	0.93 (0.06, 14.60)	2.78 (0.11, 67.39)	0.31 (0.01, 7.49)	2.78 (0.29, 26.25)	3.71 (0.42, 32.55)	-5 (-7, -2)	NR	NR
MEDICLAS	Lopinavir (800mg) + Ritonavir (200mg) + Zidovudine (600mg) + Lamivudine (266mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Lopinavir (1066mg) + Ritonavir (266mg) + Nevirapine (400mg)	>100 (<0.01, >100)	>100 (<0.01, >100)	1.00 (<0.01, >100)	NR	>100 (<0.01, >100)	>100 (<0.01, >100)	-6 (-22, 10)	NR	NR
METEOR	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Rosuvastatin (40mg)	2.81 (0.15, 54.27)	2.81 (0.15, 54.27)	0.40 (<0.01, 20.20)	NR	0.40 (<0.01, 20.20)	1.21 (0.05, 29.50)	-8 (-11, -6)	-12 (-17, -7)	NR
MG600	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	[Reference]	[Reference]	NR
	Magnesium chelate (600mg)	1.00 (<0.01, >100)	1.00 (<0.01, >100)	1.00 (<0.01, >100)	NR	1.00 (<0.01, >100)	NR	100 (-73, 272)	46 (-267, 360)	NR
MIDAS	HCTZ (25-50mg)	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR
	Isradipine (5-10mg)	1.24 (0.71, 2.16)	1.14 (0.42, 3.12)	2.00 (0.50, 7.93)	1.10 (0.47, 2.56)	1.00 (0.20, 4.92)	0.89 (0.35, 2.28)	NR	1 (-5, 7)	NR
MITEC	Amlodipine besylate (5mg)	[Reference]	NR	NR	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Candesartan cilexetil (8mg)	1.09 (0.02, 54.42)	NR	NR	NR	1.09 (0.02, 54.42)	1.09 (0.02, 54.42)	8 (-17, 33)	NR	NR
Makimura et al.	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Tesamorelin (2mg)	0.94 (0.02, 45.63)	0.94 (0.02, 45.63)	0.94 (0.02, 45.63)	NR	0.94 (0.02, 45.63)	0.94 (0.02, 45.63)	-40 (-70, -10)	NR	NR
Masia et al.	Standard care	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Intensified care	1.33 (0.19, 9.46)	0.68 (0.06, 7.51)	1.00 (<0.01, >100)	>100 (<0.01, >100)	1.00 (<0.01, >100)	3.98 (1.07, 14.72)	-5 (-15, 5)	-2 (-27, 23)	NR
Mitsuhashi et al.	Control	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	NR	NR	[Reference]
	Cilostazol (100-150 mg)	0.33 (0.01, 7.87)	1.00 (0.02, 48.83)	0.33 (0.01, 7.87)	NR	1.00 (0.02, 48.83)	NR	NR	NR	-35 (-63, -7)
Mortazavi et al.	Placebo	[Reference]	NR	[Reference]	NR	NR	[Reference]	[Reference]	NR	NR
	Magnesium (107mg)	2.59 (0.11, 60.69)	NR	0.86 (0.02, 41.88)	NR	NR	2.59 (0.11, 60.69)	-28 (-44, -12)	NR	NR
NTPP	Pravastatin (10mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Pitavastatin (1-2mg)	1.05 (0.02, 52.08)	1.05 (0.02, 52.08)	1.05 (0.02, 52.08)	NR	1.05 (0.02, 52.08)	1.05 (0.02, 52.08)	-1 (-32, 30)	-5 (-45, 35)	NR
Nakamura et al. II	No medication	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	AST-120 (6g)	0.21 (0.04, 1.03)	0.34 (0.03, 3.70)	0.16 (0.02, 1.43)	NR	1.00 (<0.01, >100)	0.34 (0.03, 3.70)	-40 (-52, -28)	-29 (-34, -24)	NR
Ntaios et al.	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Folic acid (5mg)	1.00 (0.40, 2.51)	0.96 (0.24, 3.84)	0.98 (0.28, 3.38)	NR	1.00 (<0.01, >100)	1.00 (<0.01, >100)	-13 (-57, 31)	NR	NR
OPAL	Placebo	[Reference]	[Reference]	[Reference]	NR	NR	NR	[Reference]	[Reference]	NR
	Tibolone (2.5mg)	2.06 (0.38, 11.24)	3.11 (0.32, 29.88)	1.02 (0.06, 16.28)	NR	NR	NR	7 (3, 10)	10 (4, 17)	NR
	Estrogen (0.625mg) + Progesterone (2.5mg)	1.46 (0.24, 8.72)	0.96 (0.06, 15.42)	1.96 (0.18, 21.62)	NR	NR	NR	4 (1, 8)	5 (-1, 12)	NR
PART-2	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Ramipril (5/10mg)	0.95 (0.72, 1.26)	0.92 (0.69, 1.23)	1.76 (0.52, 5.94)	NR	0.45 (0.20, 1.01)	0.64 (0.35, 1.18)	3 (-6, 11)	NR	NR
PEACE	Pitavastatin (target LDL-C<100mg/dL)	[Reference]	[Reference]	NR	NR	NR	[Reference]	[Reference]	[Reference]	NR
	Pitavastatin (target LDL-C<80mg/dL)	1.01 (0.06, 15.95)	0.34 (0.01, 8.17)	NR	NR	NR	3.02 (0.12, 73.55)	-16 (-46, 14)	-40 (-95, 15)	NR
PERFORM	Aspirin (100mg)	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	Terutroban (30mg)	1.01 (0.95, 1.08)	1.23 (0.98, 1.55)	1.02 (0.93, 1.11)	0.97 (0.83, 1.12)	1.05 (0.90, 1.22)	1.01 (0.91, 1.13)	11 (-3, 25)	NR	NR
PERIOCARDIO	Usual care	[Reference]	NR	NR	NR	NR	NR	[Reference]	[Reference]	NR
	Peridontal therapy	1.75 (0.16, 19.27)	NR	NR	NR	NR	NR	-14 (-33, 5)	-26 (-51, -2)	NR
PHOREA	No medication	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	[Reference]	NR
	17β-estradiol (1mg) + Gestodene (0.025mg on days 17-28)	0.99 (0.02, 49.47)	0.99 (0.02, 49.47)	0.99 (0.02, 49.47)	NR	0.99 (0.02, 49.47)	0.99 (0.02, 49.47)	NR	22 (-6, 50)	NR
	17β-estradiol (1mg) + Gestodene (0.025mg on days 17-28 every third cycle)	2.94 (0.12, 71.48)	0.98 (0.02, 49.02)	2.94 (0.12, 71.48)	NR	2.94 (0.12, 71.48)	2.94 (0.12, 71.48)	NR	11 (-15, 37)	NR
PHYLLIS	HCTZ (25mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	NR	[Reference]	NR
	Fosinopril (20mg)	0.14 (<0.01, 2.74)	0.14 (<0.01, 2.74)	1.00 (0.02, 50.01)	NR	1.00 (0.02, 50.01)	NR	NR	-2 (-8, 4)	NR
	HCTZ (25mg) + Pravastatin (40mg)	0.14 (<0.01, 2.76)	0.14 (<0.01, 2.76)	1.01 (0.02, 50.41)	NR	1.01 (0.02, 50.41)	NR	NR	-3 (-9, 2)	NR
	Fosinopril (20mg) + Pravastatin (40mg)	0.99 (0.20, 4.82)	0.33 (0.03, 3.14)	2.98 (0.12, 72.39)	NR	2.98 (0.12, 72.39)	NR	NR	-2 (-7, 4)	NR
PLAC II	Placebo	[Reference]	[Reference]	NR	NR	[Reference]	[Reference]	NR	[Reference]	NR
	Pravastatin (10-40mg)	0.41 (0.13, 1.24)	0.41 (0.13, 1.24)	NR	NR	1.01 (0.15, 7.01)	0.61 (0.15, 2.45)	NR	-16 (-31, -2)	NR

PPAR	Placebo	[Reference]	[Reference]	[Reference]	NR	NR	[Reference]	NR	NR	[Reference]
	Rosiglitazone (8mg)	0.52 (0.20, 1.36)	0.60 (0.20, 1.77)	0.48 (0.04, 5.21)	NR	NR	0.48 (0.04, 5.21)	NR	NR	-13 (-52, 26)
PREDIMED	Low-fat diet	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Mediterranean diet + Olive oil	0.85 (0.65, 1.11)	0.94 (0.60, 1.47)	0.81 (0.56, 1.19)	NR	0.83 (0.50, 1.41)	1.00 (0.78, 1.28)	-10 (-26, 6)	-18 (-50, 14)	NR
	Mediterranean diet + Nuts	0.76 (0.57, 1.01)	0.81 (0.51, 1.30)	0.55 (0.36, 0.85)	NR	1.03 (0.63, 1.70)	1.02 (0.79, 1.31)	-7 (-24, 10)	1 (-32, 34)	NR
PREVEND IT	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	Pravastatin (40mg)	0.99 (0.67, 1.46)	0.91 (0.56, 1.48)	1.18 (0.55, 2.49)	0.47 (0.09, 2.58)	0.54 (0.13, 2.17)	1.13 (0.69, 1.83)	0 (-6, 6)	NR	NR
	Fosinopril (20mg)	0.81 (0.55, 1.20)	1.20 (0.73, 1.96)	0.53 (0.24, 1.14)	0.19 (0.02, 1.65)	0.50 (0.12, 1.99)	1.04 (0.64, 1.68)	-4 (-10, 2)	NR	NR
PREVENT	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	[Reference]	NR
	Amlodipine (10mg)	0.75 (0.59, 0.96)	0.74 (0.57, 0.95)	0.98 (0.29, 3.35)	0.60 (0.44, 0.83)	NR	0.73 (0.26, 2.10)	NR	-19 (-30, -8)	NR
PROBE	Non-pioglitazone	[Reference]	NR	NR	NR	NR	NR	[Reference]	[Reference]	NR
	Pioglitazone (15-45mg)	1.00 (0.36, 2.82)	NR	NR	NR	NR	NR	-5 (-19, 10)	-11 (-31, 8)	NR
RADIANCE I	Atorvastatin + Placebo	[Reference]	[Reference]	[Reference]	NR	NR	NR	[Reference]	[Reference]	NR
	Atorvastatin + Torcetrapib (60mg)	1.35 (0.74, 2.45)	1.51 (0.77, 2.98)	0.91 (0.31, 2.71)	NR	NR	NR	4 (0, 8)	6 (-2, 14)	NR
RADIANCE II	Atorvastatin + Placebo	[Reference]	[Reference]	[Reference]	NR	NR	NR	[Reference]	[Reference]	NR
	Atorvastatin + Torcetrapib (60mg)	1.68 (0.86, 3.27)	1.58 (0.74, 3.37)	2.03 (0.51, 8.11)	NR	NR	NR	4 (-2, 10)	0 (-12, 12)	NR
RAS	Placebo	[Reference]	[Reference]	[Reference]	NR	NR	[Reference]	[Reference]	NR	NR
	Rosiglitazone (8mg)	0.67 (0.11, 3.97)	1.00 (0.02, 50.40)	1.00 (0.02, 50.40)	NR	NR	0.67 (0.11, 3.97)	-7 (-20, 6)	NR	NR
REGRESS	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	Pravastatin (40mg)	0.61 (0.45, 0.82)	0.59 (0.25, 1.42)	0.58 (0.14, 2.41)	0.62 (0.43, 0.88)	0.58 (0.14, 2.41)	0.69 (0.22, 2.16)	-15 (-46, 16)	NR	NR
REMOVAL	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Metformin (2000mg)	1.07 (0.42, 2.73)	0.48 (0.12, 1.88)	0.95 (0.14, 6.71)	1.91 (0.17, 20.89)	1.91 (0.17, 20.89)	2.39 (0.47, 12.16)	-5 (-12, 2)	-13 (-18, -8)	NR
RIS	Usual care	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Intensified care	0.77 (0.43, 1.37)	0.92 (0.46, 1.84)	0.45 (0.16, 1.30)	NR	0.35 (0.04, 3.32)	0.45 (0.21, 0.95)	6 (-7, 20)	2 (-15, 18)	NR
SANDS	Standard care	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	Intensified care	1.23 (0.49, 3.05)	1.96 (0.36, 10.61)	0.98 (0.06, 15.58)	0.98 (0.25, 3.88)	0.98 (0.06, 15.58)	0.59 (0.14, 2.43)	-17 (-27, -7)	NR	NR
SCIMO	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR
	ω3 fatty acids (1.65g)	0.89 (0.56, 1.41)	0.25 (0.03, 2.18)	0.33 (0.03, 3.13)	1.08 (0.65, 1.81)	0.33 (0.01, 8.02)	0.50 (0.05, 5.39)	NR	10 (-10, 30)	NR
SECURE	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	[Reference]	NR
	Ramipril (10 or 2.5mg)	0.86 (0.57, 1.28)	0.92 (0.58, 1.45)	0.67 (0.28, 1.59)	NR	1.00 (0.18, 5.43)	1.06 (0.51, 2.19)	NR	-3 (-12, 7)	NR
	Vitamin E (400IU)	1.12 (0.76, 1.65)	1.01 (0.66, 1.56)	1.94 (0.78, 4.81)	NR	0.19 (0.02, 1.66)	0.60 (0.30, 1.22)	NR	0 (-9, 9)	NR
SEKONA	Usual care	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	NR
	Intensified care	0.81 (0.57, 1.14)	0.76 (0.51, 1.14)	0.81 (0.14, 4.81)	0.58 (0.41, 0.84)	NR	1.08 (0.42, 2.76)	-23 (-42, -5)	NR	NR
SENDCAP	Placebo	[Reference]	[Reference]	NR	NR	NR	NR	NR	[Reference]	NR
	Bezafibrate (400mg)	0.34 (0.04, 3.22)	0.34 (0.04, 3.22)	NR	NR	NR	NR	NR	1 (-19, 22)	NR
SPEAD-A	Conventional treatment	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Alogliptin (25mg)	0.11 (<0.01, 2.05)	0.20 (<0.01, 4.13)	0.33 (0.01, 8.12)	0.33 (0.01, 8.12)	1.00 (0.02, 50.09)	1.00 (0.02, 50.09)	-15 (-28, -2)	-28 (-53, -3)	NR
SPIKE	Conventional treatment	[Reference]	[Reference]	[Reference]	NR	NR	[Reference]	[Reference]	[Reference]	NR
	Sitagliptin (25-100mg)	1.00 (0.21, 4.87)	1.00 (0.06, 15.83)	2.00 (0.18, 21.80)	NR	NR	0.33 (0.01, 8.11)	-27 (-45, -8)	-17 (-33, 0)	NR
STARR	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	[Reference]	NR
	Ramipril (15mg)	1.31 (0.64, 2.69)	1.30 (0.57, 2.96)	1.33 (0.30, 5.95)	NR	1.00 (<0.01, >100)	0.60 (0.14, 2.50)	-5 (-10, -1)	-5 (-10, -1)	NR
	Rosiglitazone (8mg)	0.86 (0.42, 1.76)	0.90 (0.40, 2.05)	0.73 (0.16, 3.28)	NR	1.00 (<0.01, >100)	0.33 (0.07, 1.62)	-3 (-7, 1)	-3 (-8, 1)	NR
STOP-NIDDM	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	NR
	Acarbose (300mg)	0.47 (0.26, 0.86)	0.08 (0.01, 0.64)	0.50 (0.09, 2.74)	0.55 (0.27, 1.15)	0.50 (0.05, 5.53)	NR	-6 (-11, -1)	NR	NR
Safarova et al.	Atorvastatin	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	Atorvastatin + Niacin (1500mg)	0.72 (0.38, 1.34)	0.70 (0.37, 1.33)	<0.01 (<0.01, >100)	0.34 (0.09, 1.32)	1.00 (<0.01, >100)	2.41 (0.22, 26.92)	-12 (-99, 76)	NR	NR
Sander et al. (Cp neg)	Placebo	[Reference]	[Reference]	[Reference]	NR	NR	[Reference]	[Reference]	NR	NR

	Roxithromycin (300mg)	0.79 (0.22, 2.82)	0.99 (0.06, 15.48)	0.66 (0.11, 3.82)	NR	NR	0.99 (0.14, 6.82)	-10 (-43, 23)	NR	NR
Sander et al. (Cp pos)	Placebo	[Reference]	[Reference]	[Reference]	NR	NR	[Reference]	[Reference]	NR	NR
	Roxithromycin (300mg)	1.13 (0.49, 2.59)	1.02 (0.06, 15.89)	0.73 (0.24, 2.16)	NR	NR	0.68 (0.12, 3.92)	-40 (-70, -10)	NR	NR
Spring et al.	Standard statin treatment	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	[Reference]	NR	NR
	Atorvastatin (80mg)	1.08 (0.07, 16.84)	1.08 (0.07, 16.84)	1.08 (0.02, 53.54)	NR	1.08 (0.02, 53.54)	NR	-40 (-404, 324)	NR	NR
Stanley et al.	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Tesamorelin (2mg)	0.26 (0.01, 6.12)	0.79 (0.02, 38.05)	0.26 (0.01, 6.12)	NR	0.79 (0.02, 38.05)	0.79 (0.02, 38.05)	-60 (-150, 30)	NR	NR
Stanton et al.	Amlodipine (5-10mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Lisinopril (5-20mg)	0.34 (0.01, 8.13)	1.03 (0.02, 50.42)	0.34 (0.01, 8.13)	NR	1.03 (0.02, 50.42)	1.03 (0.02, 50.42)	21 (1, 41)	NR	NR
TART	Placebo	[Reference]	[Reference]	[Reference]	NR	NR	NR	[Reference]	NR	NR
	Troglitazone (400mg)	1.01 (0.33, 3.05)	1.34 (0.31, 5.89)	0.67 (0.11, 3.96)	NR	NR	NR	-4 (-9, 2)	NR	NR
TEAAM	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	Testosterone (75mg)	2.92 (0.96, 8.86)	1.46 (0.25, 8.62)	6.82 (0.36, >100)	2.44 (0.48, 12.36)	2.92 (0.12, 71.18)	0.65 (0.11, 3.83)	0 (-3, 3)	NR	NR
TRIPOD	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	[Reference]	NR	NR
	Troglitazone (400mg)	1.00 (0.02, 50.03)	1.00 (0.02, 50.03)	1.00 (0.02, 50.03)	NR	1.00 (0.02, 50.03)	NR	-3 (-6, -0)	NR	NR
Tasic et al.	Atenolol (50mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Fosinopril (20mg)	0.50 (0.10, 2.43)	0.67 (0.12, 3.57)	0.33 (0.01, 7.70)	NR	1.00 (0.02, 47.98)	1.00 (0.02, 47.98)	-141 (-219, -63)	NR	NR
VEAPS	Placebo	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	DL-α-tocopherol (400IU)	0.80 (0.32, 1.97)	0.99 (0.36, 2.78)	0.20 (<0.01, 4.11)	0.50 (0.09, 2.68)	0.99 (0.06, 15.77)	1.99 (0.18, 21.73)	2 (-0, 4)	NR	NR
VHAS	Chlorthalidone (25mg)	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR	[Reference]
	Verapamil (240mg)	1.06 (0.54, 2.09)	0.89 (0.34, 2.29)	1.25 (0.34, 4.64)	1.33 (0.30, 5.94)	1.25 (0.34, 4.64)	1.25 (0.34, 4.64)	NR	NR	-1 (-15, 13)
VIP	Withdrawal of mycophenolate mofetil	[Reference]	[Reference]	[Reference]	NR	NR	[Reference]	[Reference]	NR	NR
	Withdrawal of calcineurin inhibitor	0.44 (0.12, 1.61)	0.34 (0.04, 3.17)	1.02 (0.02, 50.42)	NR	NR	0.51 (0.10, 2.67)	-3 (-11, 6)	NR	NR
VITAL	Usual care	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]	NR	NR
	Intensified care	1.41 (0.45, 4.46)	1.53 (0.25, 9.13)	1.00 (<0.01, >100)	1.01 (0.25, 4.05)	>100 (<0.01, >100)	>100 (<0.01, >100)	16 (-11, 44)	NR	NR
WISH	Placebo	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	[Reference]	NR	NR
	Isoflavone Soy Protein (25g)	3.00 (0.12, 73.14)	1.00 (0.02, 50.12)	3.00 (0.12, 73.14)	NR	1.00 (0.02, 50.12)	1.00 (0.02, 50.12)	-1 (-3, 1)	NR	NR
Yang et al.	Control	[Reference]	[Reference]	[Reference]	NR	[Reference]	[Reference]	NR	NR	[Reference]
	Puerarin (400mg)	0.98 (0.02, 48.75)	0.98 (0.02, 48.75)	0.98 (0.02, 48.75)	NR	0.98 (0.02, 48.75)	0.98 (0.02, 48.75)	NR	NR	-48 (-93, -2)
Yun et al.	Control	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	[Reference]	NR	NR
	Acarbose (150mg)	0.47 (0.21, 1.05)	0.30 (0.07, 1.41)	0.53 (0.10, 2.81)	NR	0.64 (0.16, 2.56)	NR	-38 (-42, -34)	NR	NR
Zou et al.	Lutein (20mg)	[Reference]	[Reference]	[Reference]	NR	[Reference]	NR	[Reference]	NR	NR
	Lutein (20mg) + Lycopene (20mg)	1.00 (0.02, 49.38)	1.00 (0.02, 49.38)	1.00 (0.02, 49.38)	NR	1.00 (0.02, 49.38)	NR	-38 (-92, 16)	NR	NR

Abbreviations: CCA-IMT=intima-media thickness of the common-carotid-artery. CI=confidence interval. CVD=cardiovascular disease. DASH=dietary approaches to stop hypertension. HCTZ=hydrochlorothiazide. LDL-C=low-density lipoprotein cholesterol. MI=myocardial infarction. NR=not reported. RR=relative risk. **Table V in the Supplement** provides full names of the contributing trials. [Reference] indicates reference group.

Supplemental Table V. Full names and links to publications of contributing trials

Trial acronym	Full trial name	Link
ACAPS	Asymptomatic Carotid Artery Progression Study	https://doi.org/10.1016/0197-2456(92)90012-o https://doi.org/10.1161/01.CIR.90.4.1679
ACT NOW	Actos Now for Prevention of Diabetes Study	https://doi.org/10.1056/NEJMoa1010949 https://doi.org/10.1161/ATVBAHA.112.300346
ALLO-IMT	ALLO-IMT Study	https://doi.org/10.1136/heartjnl-2014-305683
AMAR	Atherosclerosis Monitoring and Atherogenicity Reduction Study	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4637943/
ARBITER	Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol Trial	https://doi.org/10.1161/01.CIR.0000034508.55617.65
ARBITER 2	Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol Trial 2	https://doi.org/10.1161/01.CIR.0000148955.19792.8D
ARBITER 6-HALTS	Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 - HDL and LDL Treatment Strategies in Atherosclerosis Trial	https://doi.org/10.1007/s10557-007-6020-8 https://doi.org/10.1056/NEJMoa0907569 https://doi.org/10.1016/j.jacc.2010.03.017
ARTSTIFF	Effect of Olmesartan Medoxomil on Arterial Stiffness and Thickness in Subjects With Metabolic Syndrome Study	https://doi.org/10.1161/HYPERTENSIONAHA.114.03282
ASAP-FINLAND	Antioxidant Supplementation in Atherosclerosis Prevention Study	https://doi.org/10.1046/j.1365-2796.2000.00752.x https://doi.org/10.1161/01.ATV.20.12.2677 https://doi.org/10.1161/01.CIR.0000050626.25057.51
ASAP-NL	Atorvastatin vs Simvastatin on Atherosclerosis Progression Study	https://doi.org/10.2165/00044011-200020020-00001 https://doi.org/10.1016/S0140-6736(00)04053-8
ASFAST	Atherosclerosis and Folic Acid Supplementation Trial	https://doi.org/10.1016/j.jacc.2005.10.064
ATIC	Anti-Oxidant Therapy in Chronic Renal Insufficiency Study	https://doi.org/10.1001/archinte.167.12.1262 https://doi.org/10.1111/j.1523-1755.2005.00680.x
Ahn et al.	Ahn et al.	https://doi.org/10.1007/s00380-010-0093-1
Andrews et al.	Andrews et al.	https://doi.org/10.1371/journal.pone.0205831 https://doi.org/10.1681/ASN.2016050521
BCAPS	Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study	https://doi.org/10.1161/01.CIR.103.13.1721
BKREGISTRY-II	BK Registry II Study	https://doi.org/10.1177/107424840400900306
BVAIT	B-Vitamin Atherosclerosis Intervention Trial	https://doi.org/10.1161/STROKEAHA.108.526798
CAIUS	Carotid Atherosclerosis Italian Ultrasound Study	https://doi.org/10.1016/S0002-9343(96)00333-6
CAMERA	Carotid Atherosclerosis - Metformin for Insulin Resistance Study	https://doi.org/10.1016/S2213-8587(13)70152-9
CAPPA	Cilostazol versus Aspirin for Primary Prevention of Atherosclerotic Events	https://doi.org/10.1007/s00380-019-01421-1
CAPTIVATE	Carotid Atherosclerosis Progression Trial Investigating Vascular ACAT Inhibition Treatment Effects	https://doi.org/10.1001/jama.301.11.1131
CERDIA	Cerivastatin in Diabetes Trial	https://doi.org/10.2337/diacare.27.12.2887
CHICAGO	Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone Trial	https://doi.org/10.1001/jama.296.21.joc60158
CIMT phase 1	Copenhagen Insulin and Metformin Therapy Trial	https://doi.org/10.1136/bmjopen-2015-008376 https://doi.org/10.1111/j.1463-1326.2008.00959.x
CLAS	Cholesterol Lowering Atherosclerosis Study	https://doi.org/10.1161/01.CIR.88.1.20 https://doi.org/10.1161/01.CIR.93.1.34 https://doi.org/10.1001/jama.1990.03450230049028
CONTRAST	Convective Transport Study	https://doi.org/10.1186/1468-6708-6-8 https://doi.org/10.1681/ASN.2011121140
Cao et al.	Cao et al.	https://doi.org/10.11909/j.issn.1671-5411.2015.04.014
DAPC	Diabetic Atherosclerosis Prevention by Cilostazol	https://doi.org/10.1161/CIRCULATIONAHA.109.892414 https://doi.org/10.1186/1475-2840-5-16
DAPHNE	Doxazosin Atherosclerosis Progression Study in Hypertensives in the Netherlands	https://pubmed.ncbi.nlm.nih.gov/12572707
DOIT	Diet and Omega-3 Fatty Acid Intervention Trial	https://doi.org/10.1016/j.numecd.2008.01.006
EGE STUDY	Ege Study	https://doi.org/10.1681/ASN.2012090908 https://doi.org/10.5414/CN108251
ELITE (early MP)	Early versus Late Intervention Trial with Estradiol (early menopause)	https://doi.org/10.1097/GME.0000000000000343 https://doi.org/10.1056/NEJMoa1505241
ELITE (late MP)	Early versus Late Intervention Trial with Estradiol (late menopause)	https://doi.org/10.1097/GME.0000000000000343 https://doi.org/10.1056/NEJMoa1505241
ELSA	European Lacidipine Study on Atherosclerosis	https://doi.org/10.1161/01.CIR.0000039288.86470.DD

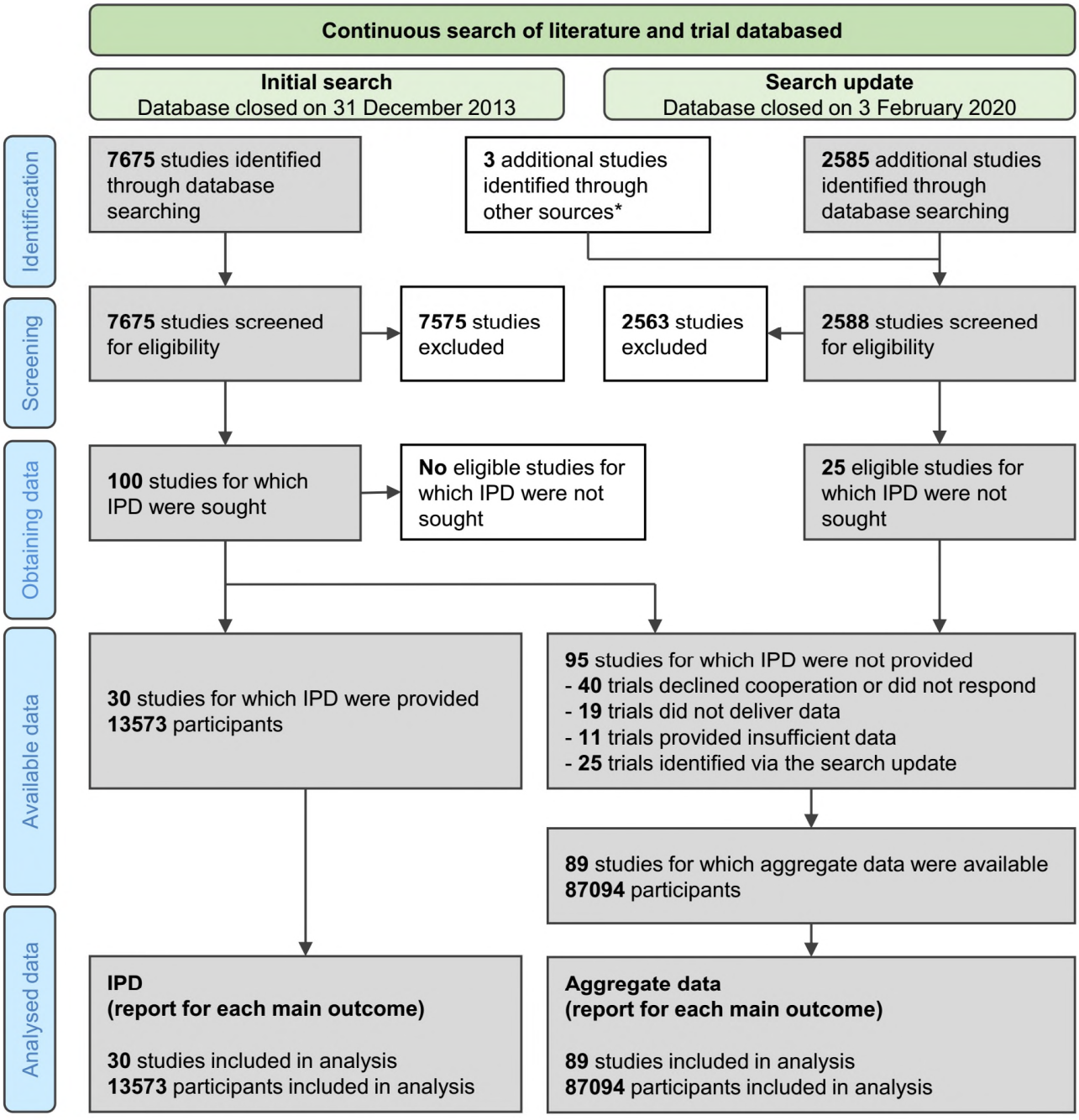
ELVA	Effect of Long-Term Treatment of Metoprolol CR/XL on Surrogate Variables for Atherosclerotic Disease	https://doi.org/10.1161/hs0202.102332
ENCORE	Exercise and Nutritional Interventions for Cardiovascular Health Study	https://doi.org/10.1001/archinternmed.2009.470 https://doi.org/10.1161/HYPERTENSIONAHA.109.146795
ENHANCE	Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression Trial	https://doi.org/10.1056/NEJMoa0800742
EPAT	Estrogen in the Prevention of Atherosclerosis Trial	https://doi.org/10.7326/0003-4819-135-11-200112040-00005
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes Study - Helsinki Cohort	https://doi.org/10.1016/S0140-6736(05)67667-2 https://doi.org/10.1016/j.jacc.2008.09.049
FIRST	Evaluation of Choline Fenofibrate (ABT-335) on cIMT in Subjects with Type IIb Dyslipidemia with Residual Risk in Addition to Atorvastatin Therapy Trial	https://doi.org/10.1007/s10557-012-6395-z https://doi.org/10.1161/ATVBAHA.113.302926
FRANCIS	Franciscus Rheumatoid Arthritis and Cardiovascular Intervention Study	https://doi.org/10.1136/annrheumdis-2018-214075 https://doi.org/10.1016/j.atherosclerosis.2018.02.019
GRACE	Glucose Reduction and Atherosclerosis Continuing Evaluation Study	https://doi.org/10.2337/dc12-2129
Gresele et al.	Gresele et al.	https://doi.org/10.1016/j.jvs.2012.05.064
HART	Homocysteine and Atherosclerosis Reduction Trial	https://doi.org/10.1177/1358863X08092102
HERS	Heart and Estrogen/Progestin Replacement Study	https://doi.org/10.1161/01.atv.0000033514.79653.04 https://doi.org/10.1001/jama.280.7.605
HYRIM	Hypertension High Risk Management Study	https://doi.org/10.1016/j.atherosclerosis.2004.08.033
INSIGHT	International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment - France Cohort	https://doi.org/10.1161/01.CIR.103.24.2949 https://doi.org/10.1016/S0140-6736(00)02527-7 https://doi.org/10.2165/00003495-200363140-00001
J-STARS	Japan Statin Treatment Against Recurrent Stroke	https://doi.org/10.1161/STROKEAHA.119.024968 https://doi.org/10.5551/jat.41533 https://doi.org/10.1161/STROKEAHA.117.018387 https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.11.113 https://doi.org/10.1016/j.ebiom.2015.08.006
JART	Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function and Atherosclerosis in Japanese Patients with Mild-to-Moderate Hypertension Study	https://doi.org/10.1253/circj.CJ-11-0887
KAPS	Kuopio Atherosclerosis Prevention Study	https://doi.org/10.1161/01.CIR.92.7.1758
KEEPS	Kronos Early Estrogen Prevention Study	https://doi.org/10.7326/M14-0353
KIMVASC	KIMVASC Study	https://doi.org/10.1007/s12603-015-0619-4
Katakami et al.	Katakami et al.	https://doi.org/10.1007/s00125-004-1547-8
Koyasu et al.	Koyasu et al.	https://doi.org/10.1016/j.clinthera.2010.07.015
LAARS	Losartan Vascular Regression Study	https://doi.org/10.1016/S0149-2918(02)80028-5
LIFE-ICARUS	Losartan Intervention For Endpoint Reduction in Hypertension - Insulin Carotids US Scandinavia Study	https://doi.org/10.1097/01.hjh.0000163160.60234.15
LIPID	Long-term Intervention with Pravastatin in Ischemic Disease Trial	https://doi.org/10.1161/01.CIR.97.18.1784 https://doi.org/10.1016/S0002-9149(99)80133-7 https://doi.org/10.1056/NEJM199811053391902 https://doi.org/10.1016/j.ehj.2003.12.024
Luijendijk et al.	Luijendijk et al.	https://doi.org/10.1016/j.ijcard.2014.06.016 https://doi.org/10.1016/j.cct.2011.11.011
MARS	Monitored Atherosclerosis Regression Study	https://doi.org/10.7326/0003-4819-119-10-199311150-00002 https://doi.org/10.7326/0003-4819-124-6-199603150-00002
MAVET	Melbourne Atherosclerosis Vitamin E Trial	https://doi.org/10.1097/01.hjr.0000219108.10167.46
MECANO	Minimization of maintenance immunosuppression early after renal transplantation	https://doi.org/10.1111/tri.13322 https://doi.org/10.1111/ajt.14048
MEDICLAS	Metabolic Effects of Different Classes of Antiretrovirals Study	https://doi.org/10.1086/597475 https://doi.org/10.1097/QAD.0b013e32832c4947
METEOR	Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin	https://doi.org/10.1001/jama.297.12.1344
MG600	Effects of Magnesium Supplementation on Vascular Structure and Function in Hypertensive Patients Study	https://doi.org/10.1097/HJH.0000000000001129
MIDAS	Multicenter Isradipine Diuretic Atherosclerosis Study	https://doi.org/10.1001/jama.1996.03540100029024
MITEC	Media Intima Thickness Evaluation with Candesartan Cilexetil Study	https://doi.org/10.1177/14746514070070010401 https://doi.org/10.2147/VHRM.S3409
Makimura et al.	Makimura et al.	https://doi.org/10.1210/jc.2012-2794
Masia et al.	Masia et al.	https://doi.org/10.1093/jac/dkp250
Mitsuhashi et al.	Mitsuhashi et al.	https://doi.org/10.1507/endocrj.51.545

Mortazavi et al.	Mortazavi et al.	https://doi.org/10.1159/000346427
NTPP	NTPP	https://doi.org/10.5551/jat.22095
Nakamura et al. II	Nakamura et al. II	https://doi.org/10.1159/000077536
Ntaios et al.	Ntaios et al.	https://doi.org/10.1016/j.ijcard.2009.01.023
OPAL	Osteoporosis Prevention and Arterial Effects of Tibolone Study	https://doi.org/10.1016/S0197-2456(03)00096-5 https://doi.org/10.1093/eurheartj/ehi695
PART-2	Prevention of Atherosclerosis with Ramipril Trial	https://doi.org/10.1016/S0735-1097(00)00736-1
PEACE	Pitavastatin Evaluation of Atherosclerosis Regression by Intensive Cholesterol-lowering Therapy Study	https://doi.org/10.1177/2047487312451539
PERFORM	Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin with Terutroban in Patients with a History of Ischemic Stroke or Transient Ischemic Attack Trial	https://doi.org/10.1016/S0140-6736(11)60600-4 https://doi.org/10.1161/STROKEAHA.114.004775
PERIOCARDIO	PerioCardio Study	https://doi.org/10.1161/HYPERTENSIONAHA.114.03359
PHOREA	Postmenopausal Hormone Replacement against Atherosclerosis Trial	https://doi.org/10.1016/S0735-1097(00)00969-4
PHYLLIS	Plaque Hypertension Lipid-lowering Italian Study	https://doi.org/10.1097/00004872-200101000-00011 https://doi.org/10.1161/01.STR.0000147041.00840.59
PLAC II	Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries Trial	https://doi.org/10.1016/0002-9149(94)90297-6 https://doi.org/10.1016/S0002-9149(99)80580-3 https://doi.org/10.1016/S0002-9149(99)80471-8
PPAR	Peroxisome Proliferator–activated Receptor Study	https://doi.org/10.1016/j.ahj.2007.03.029
PREDIMED	Prevención con Dieta Mediterránea Trial	https://doi.org/10.1056/NEJMoa1200303 https://doi.org/10.1161/ATVBAHA.113.302327
PREVEND IT	Prevention of Renal and Vascular Endstage Disease Intervention Trial	https://doi.org/10.1016/S0002-9149(00)01042-0 https://doi.org/10.1161/01.CIR.0000146378.65439.7A https://doi.org/10.1161/01.STR.0000155731.92786.e9 https://doi.org/10.1016/j.ahj.2011.03.028
PREVENT	Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial	https://doi.org/10.1016/s0002-9149(97)00611-5 https://doi.org/10.1161/01.cir.102.13.1503
PROBE	Pioglitazone Anti-atherosclerosis Effect on Prospective Randomized Open Blinded Endpoint Trial	https://doi.org/10.1185/03007990903328124 https://doi.org/10.5551/jat.4663
RADIANCE I	Rating Atherosclerosis Disease Change by Imaging with a New CETP Inhibitor 1 Study	https://doi.org/10.1056/NEJMoa071359 https://doi.org/10.1185/030079907X182121
RADIANCE II	Rating Atherosclerosis Disease Change by Imaging with a New CETP Inhibitor 2 Study	https://doi.org/10.1185/030079907X182121 https://doi.org/10.1016/S0140-6736(07)61088-5
RAS	Rosiglitazone Atherosclerosis Study	https://doi.org/10.1111/j.1365-2796.2007.01767.x
REGRESS	Regression Growth Evaluation Statin Study	https://doi.org/10.1016/S0002-9149(99)80469-X https://doi.org/10.1016/S0735-1097(98)00170-3
REMOVAL	Reducing with Metformin Vascular Adverse Lesions	https://doi.org/10.1111/dom.12840 https://doi.org/10.1016/S2213-8587(17)30194-8
RIS	Risk Factor Intervention Study	https://doi.org/10.1046/j.1365-2796.2001.00818.x
SANDS	Stop Atherosclerosis in Native Diabetics Study	https://doi.org/10.1001/jama.299.14.1678 https://doi.org/10.1016/j.jacc.2008.10.031 https://doi.org/10.1111/j.1751-7176.2009.00121.x
SCIMO	Study on Prevention of Coronary Atherosclerosis by Intervention with Marine Omega-3 Fatty Acids	https://doi.org/10.1016/S0008-6363(02)00229-8 https://doi.org/10.7326/0003-4819-130-7-199904060-00003
SECURE	Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E	https://doi.org/10.1161/01.CIR.103.7.919
SEKONA	Sekundärprävention bei Patienten mit Koronarer Herzkrankheit durch Anschlussheilbehandlung und anschließender konzeptintegrierter Nachsorge	https://doi.org/10.1177/2047487312465526
SENDCAP	St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention	https://doi.org/10.2337/diacare.21.4.641
SPEAD-A	Study of Preventive Effects of Alogliptin on Diabetic Atherosclerosis	https://doi.org/10.5551/jat.18333 https://doi.org/10.2337/dc15-0781
SPIKE	Sitagliptin Preventive Study of Intima-Media Thickness Evaluation	https://doi.org/10.2337/dc15-2145 https://doi.org/10.1111/jdi.12559 https://doi.org/10.1186/s12933-018-0666-3
STARR	Study of Atherosclerosis with Ramipril and Rosiglitazone	https://doi.org/10.1016/j.jacc.2008.12.072
STOP-NIDDM	Study to Prevent Non-Insulin-Dependent Diabetes Mellitus - Dresden Cohort	https://doi.org/10.1001/jama.290.4.486 https://doi.org/10.1161/01.STR.0000125864.01546.f2
Safarova et al.	Safarova et al.	https://pubmed.ncbi.nlm.nih.gov/21649590
Sander et al. (Cp neg)	Sander et al. (Chlamydia pneumoniae negative)	https://doi.org/10.1161/01.CIR.103.10.1390 https://doi.org/10.1161/01.CIR.0000036748.26775.8D
Sander et al. (Cp pos)	Sander et al. (Chlamydia pneumoniae positive)	https://doi.org/10.1161/01.CIR.103.10.1390 https://doi.org/10.1161/01.CIR.0000036748.26775.8D

Spring et al.	Spring et al.	https://doi.org/10.1160/TH07-04-0265
Stanley et al.	Stanley et al.	https://doi.org/10.1001/jama.2014.8334
Stanton et al.	Stanton et al.	https://doi.org/10.1042/cs1010455
TART	Troglitazone Atherosclerosis Regression Trial	https://doi.org/10.2337/dc05-2462
TEAAM	Testosterone's Effects on Atherosclerosis Progression in Aging Men	https://doi.org/10.1001/jama.2015.8881
TRIPOD	Troglitazone in Prevention of Diabetes Study	https://doi.org/10.1210/jc.2004-1685
Tasic et al.	Tasic et al.	https://doi.org/10.2298/SARH0604106T
VEAPS	Vitamin E Atherosclerosis Prevention Study	https://doi.org/10.1161/01.CIR.0000029092.99946.08
VHAS	Verapamil in Hypertension and Atherosclerosis Study	https://doi.org/10.1097/00004872-199715110-00019 https://doi.org/10.1097/00004872-199816110-00014
VIP	Vascular Imaging Project	https://doi.org/10.1097/TP.0b013e3182958552
VITAL	Vital Study	https://doi.org/10.1016/j.amjcard.2012.04.045
WISH	Women's Isoflavone Soy Health Trial	https://doi.org/10.1161/STROKEAHA.111.620831
Yang et al.	Yang et al.	https://doi.org/10.1016/j.clinthera.2018.08.014
Yun et al.	Yun et al.	https://doi.org/10.1155/2016/1602083
Zou et al.	Zou et al.	https://doi.org/10.1017/S0007114513002730

Supplemental Figures

Supplemental Figure I. PRISMA Flow chart



The PRISMA IPD flow diagram

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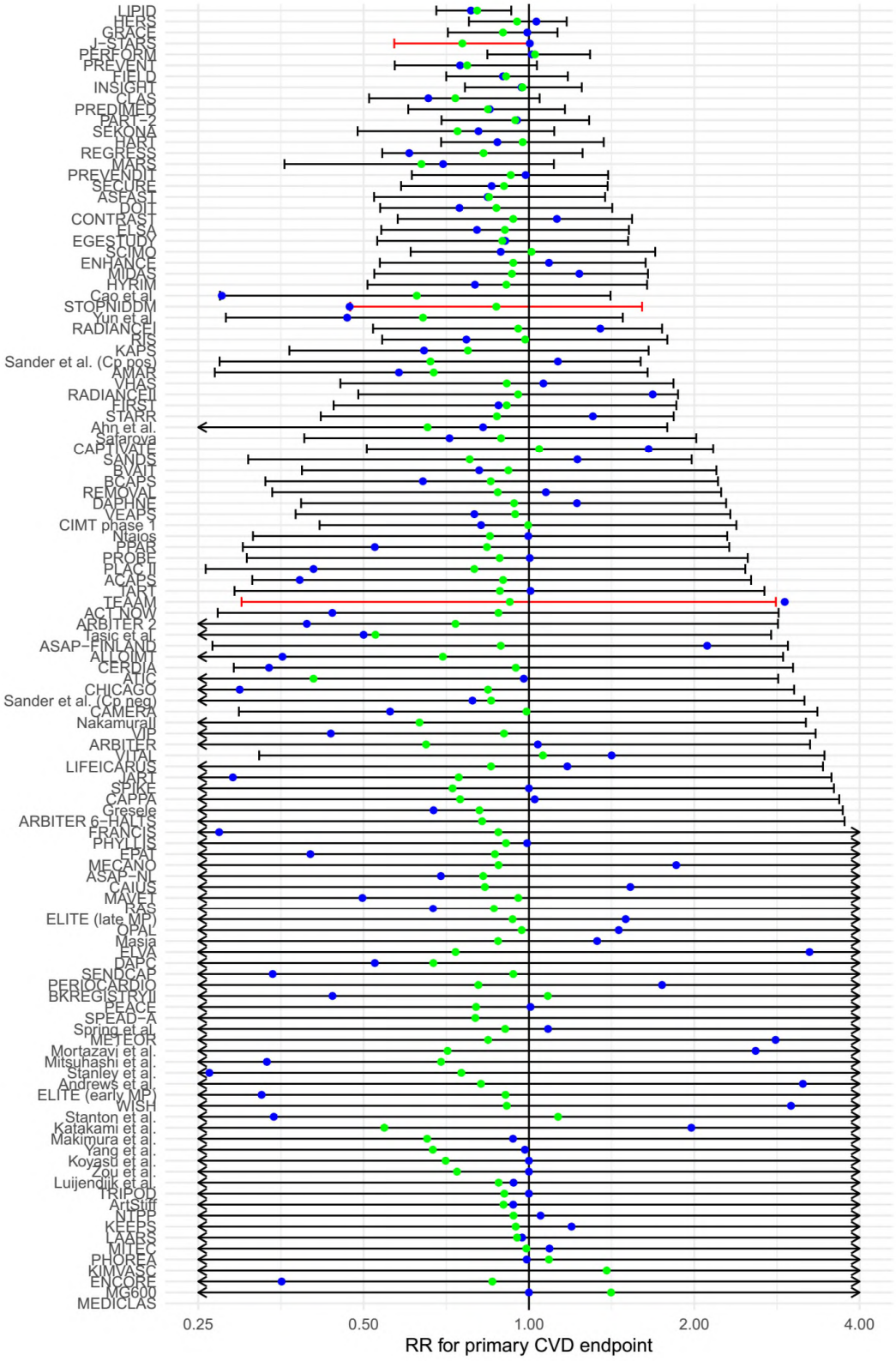
*identified through screening of reference lists and review articles

Supplemental Figure II. Leave-one out cross-validation analysis showing 95% prediction intervals for each study



Green circles denote predicted RRs, blue circles are the observed RRs. Lines are coloured red for prediction intervals in which the observed RR is outside the interval. Abbreviations: RR=relative risk. **Table V in the Supplement** provides full names of the contributing trials.

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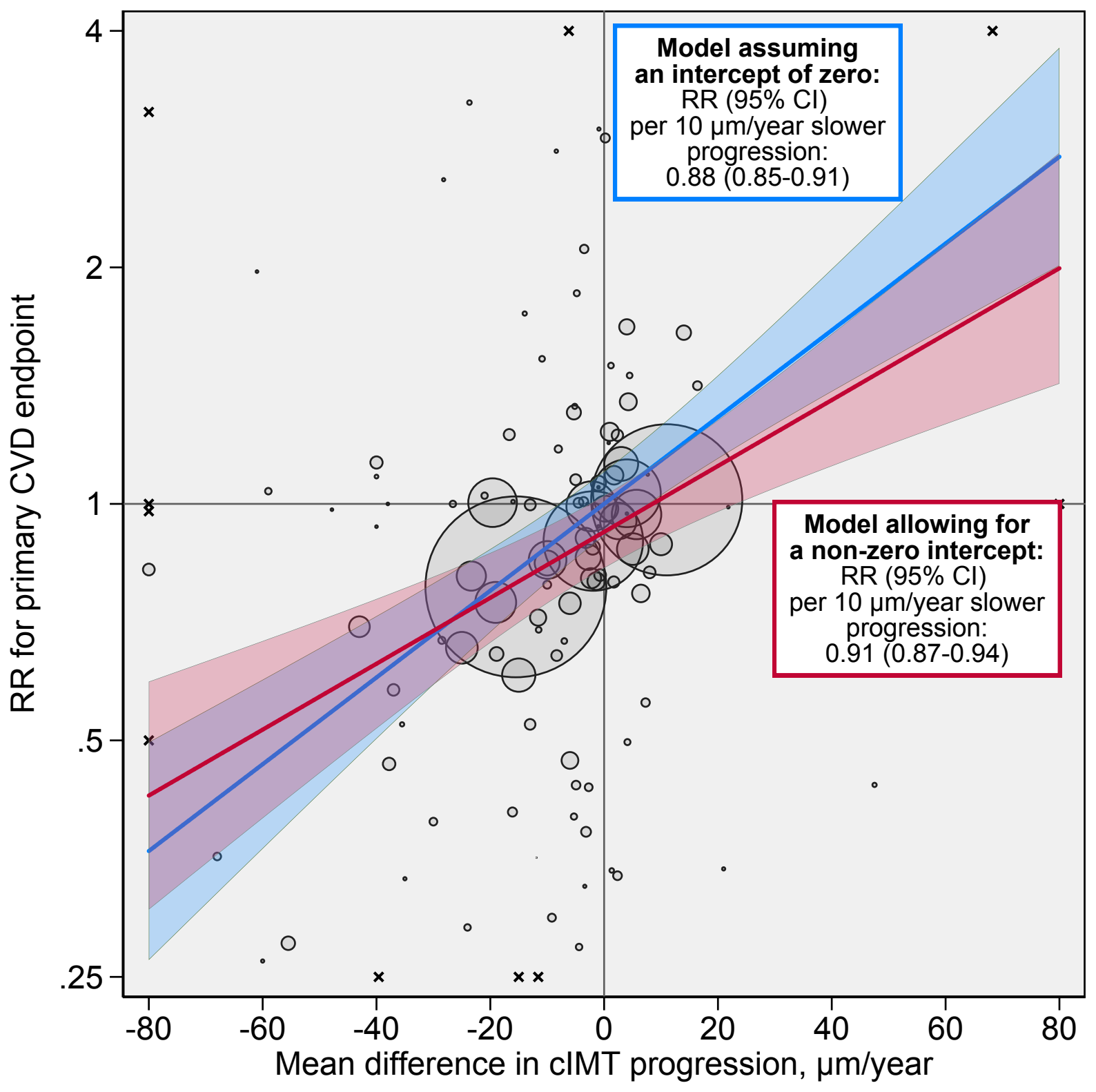
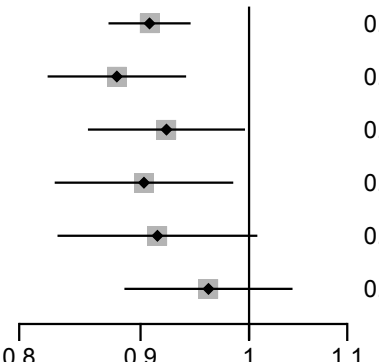
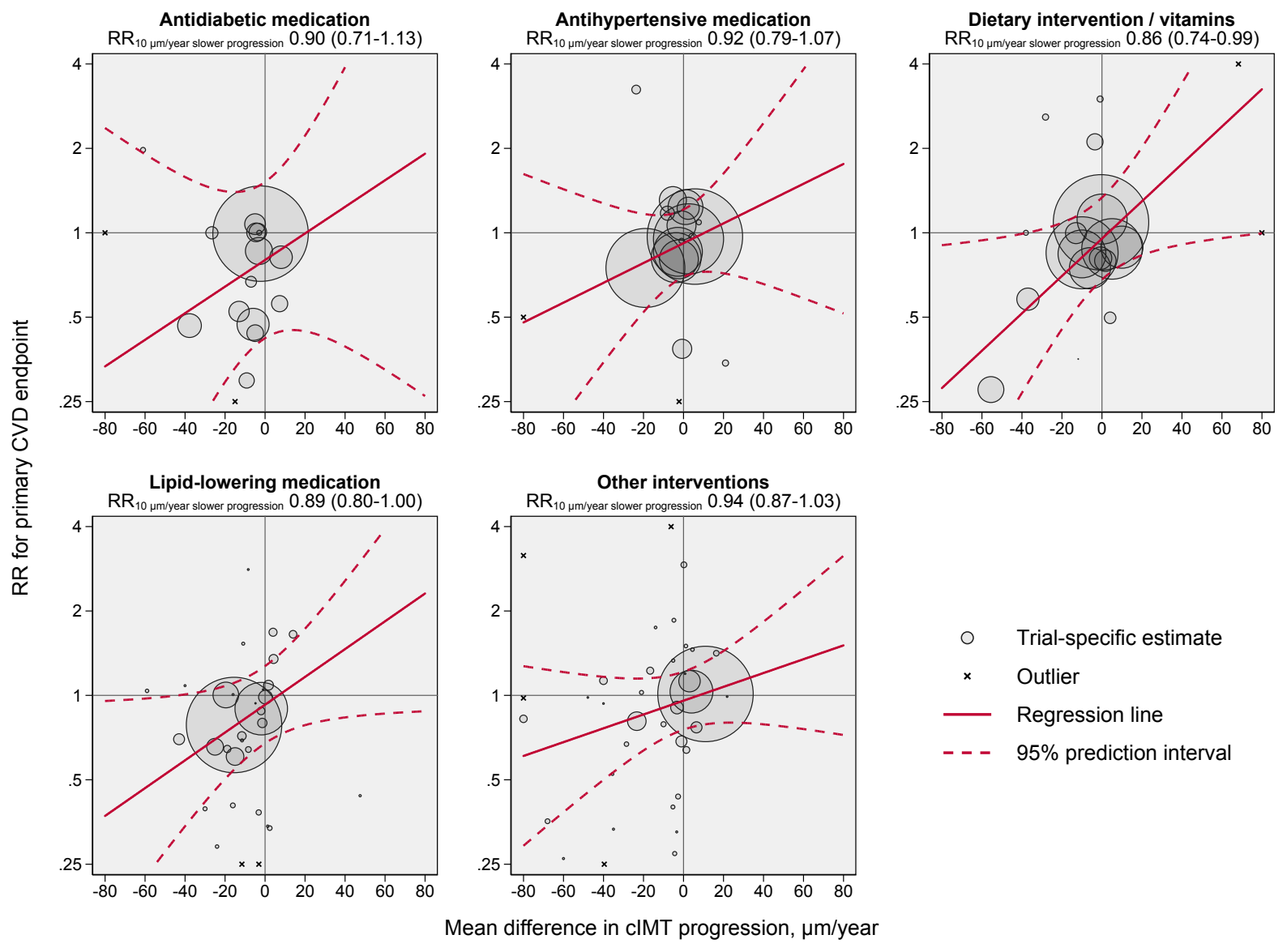
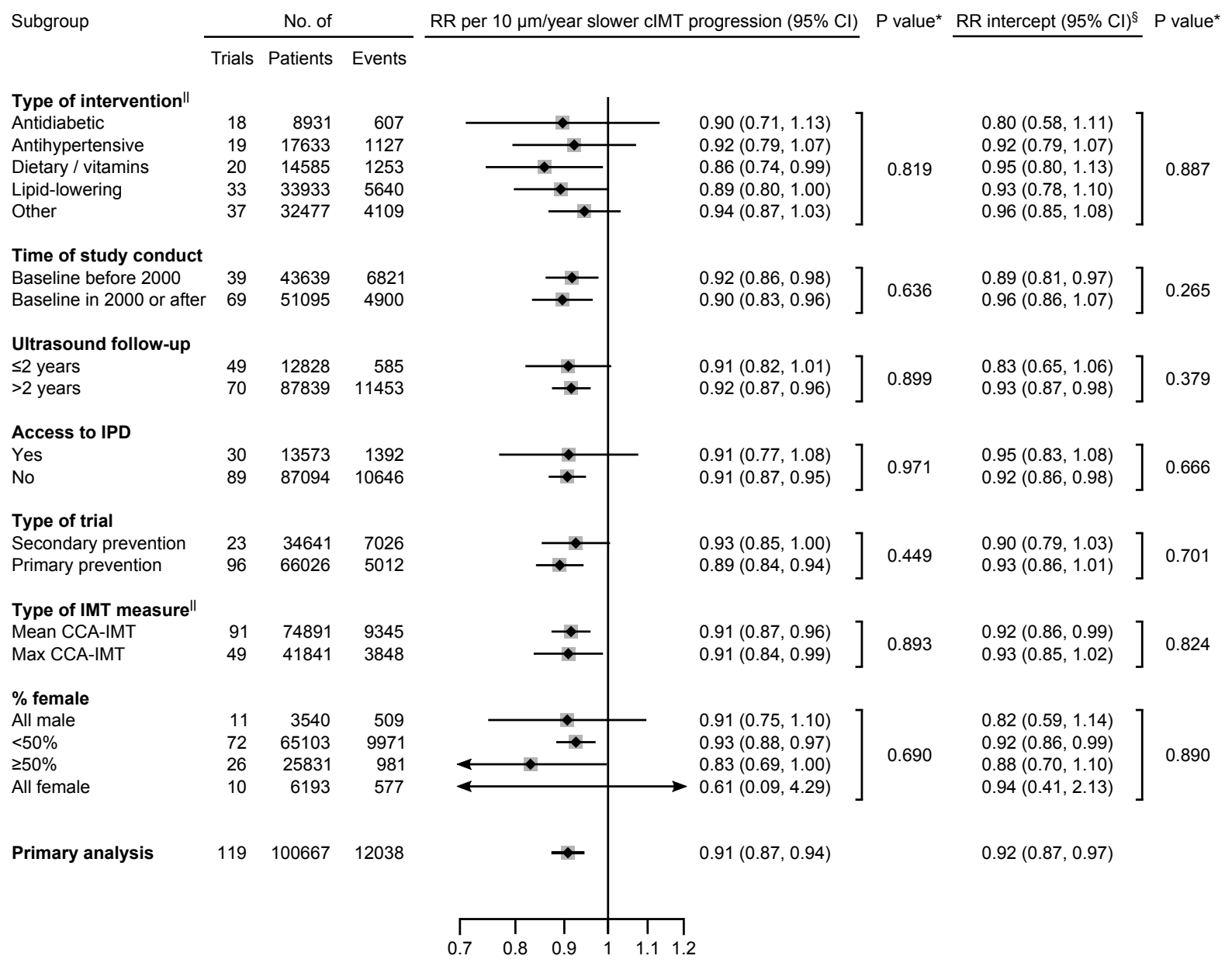

Model assuming an intercept of zero:
RR (95% CI) per 10 µm/year slower progression:
0.88 (0.85-0.91)
Model allowing for a non-zero intercept:
RR (95% CI) per 10 µm/year slower progression:
0.91 (0.87-0.94)
RR for primary CVD endpoint
4
2
1
.5
.25
-80
-60
-40
-20
0
20
40
60
80
Mean difference in cIMT progression, µm/year

Outcome	No. of Trials	No. of Patients	No. of Events	RR per 10 μm/year slower cIMT progression (95% CI)	P value	RR intercept (95% CI)*	P value
Primary CVD endpoint	119	100667	12038	0.91 (0.87-0.94)	<0.001	0.92 (0.87-0.97)	0.005
Myocardial infarction	105	94603	3856	0.88 (0.82-0.94)	<0.001	0.92 (0.85-1.00)	0.047
Stroke	103	93928	3533	0.92 (0.86-1.00)	0.039	0.97 (0.88-1.07)	0.519
Revascularization	41	55635	3764	0.90 (0.83-0.98)	0.021	0.88 (0.78-1.00)	0.042
Fatal CVD	90	87488	2439	0.91 (0.83-1.01)	0.072	0.91 (0.81-1.03)	0.135
All-cause mortality	95	91082	5338	0.96 (0.89-1.04)	0.344	0.94 (0.87-1.02)	0.128




Antidiabetic medication
RR10 µm/year slower progression 0.90 (0.71-1.13)
Antihypertensive medication
RR10 µm/year slower progression 0.92 (0.79-1.07)
Dietary intervention / vitamins
RR10 µm/year slower progression 0.86 (0.74-0.99)
Lipid-lowering medication
RR10 µm/year slower progression 0.89 (0.80-1.00)
Other interventions
RR10 µm/year slower progression 0.94 (0.87-1.03)
RR for primary CVD endpoint
Mean difference in cIMT progression, µm/year
Trial-specific estimate
Outlier
Regression line
95% prediction interval


Subgroup
No. of
Trials
Patients
Events
RR per 10 µm/year slower cIMT progression (95% CI)
P value*
RR intercept (95% CI)§
P value*
Type of intervention‖
Antidiabetic 18 8931 607 0.90 (0.71, 1.13) 0.80 (0.58, 1.11)
Antihypertensive 19 17633 1127 0.92 (0.79, 1.07) 0.92 (0.79, 1.07)
Dietary / vitamins 20 14585 1253 0.86 (0.74, 0.99) 0.819 0.95 (0.80, 1.13) 0.887
Lipid-lowering 33 33933 5640 0.89 (0.80, 1.00) 0.93 (0.78, 1.10)
Other 37 32477 4109 0.94 (0.87, 1.03) 0.96 (0.85, 1.08)
Time of study conduct
Baseline before 2000 39 43639 6821 0.92 (0.86, 0.98) 0.89 (0.81, 0.97)
Baseline in 2000 or after 69 51095 4900 0.90 (0.83, 0.96) 0.636 0.96 (0.86, 1.07) 0.265
Ultrasound follow-up
≤2 years 49 12828 585 0.91 (0.82, 1.01) 0.83 (0.65, 1.06)
>2 years 70 87839 11453 0.92 (0.87, 0.96) 0.899 0.93 (0.87, 0.98) 0.379
Access to IPD
Yes 30 13573 1392 0.91 (0.77, 1.08) 0.95 (0.83, 1.08)
No 89 87094 10646 0.91 (0.87, 0.95) 0.971 0.92 (0.86, 0.98) 0.666
Type of trial
Secondary prevention 23 34641 7026 0.93 (0.85, 1.00) 0.90 (0.79, 1.03)
Primary prevention 96 66026 5012 0.89 (0.84, 0.94) 0.449 0.93 (0.86, 1.01) 0.701
Type of IMT measure‖
Mean CCA-IMT 91 74891 9345 0.91 (0.87, 0.96) 0.92 (0.86, 0.99)
Max CCA-IMT 49 41841 3848 0.91 (0.84, 0.99) 0.893 0.93 (0.85, 1.02) 0.824
% female
All male 11 3540 509 0.91 (0.75, 1.10) 0.82 (0.59, 1.14)
<50% 72 65103 9971 0.93 (0.88, 0.97) 0.92 (0.86, 0.99)
≥50% 26 25831 981 0.83 (0.69, 1.00) 0.690 0.88 (0.70, 1.10) 0.890
All female 10 6193 577 0.61 (0.09, 4.29) 0.94 (0.41, 2.13)
Primary analysis 119 100667 12038 0.91 (0.87, 0.94) 0.92 (0.87, 0.97)
0.7
0.8
0.9
1
1.1
1.2

Contributing data

Meta-analysis

International collaboration
119 RCTs
100,667 participants
12,038 incident CVD events

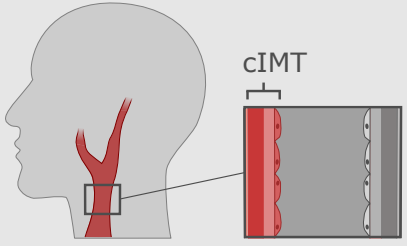
Mean age: 62 years

42% female

Key finding

Intervention effect

cIMT progression



CVD events

Myocardial infarction
Revascularization
Stroke
Fatal CVD

Relative risk for CVD

0.91

(95% CI: 0.87-0.94)

per 10 μm/year reduction of cIMT progression