Supplemental Material

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

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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

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

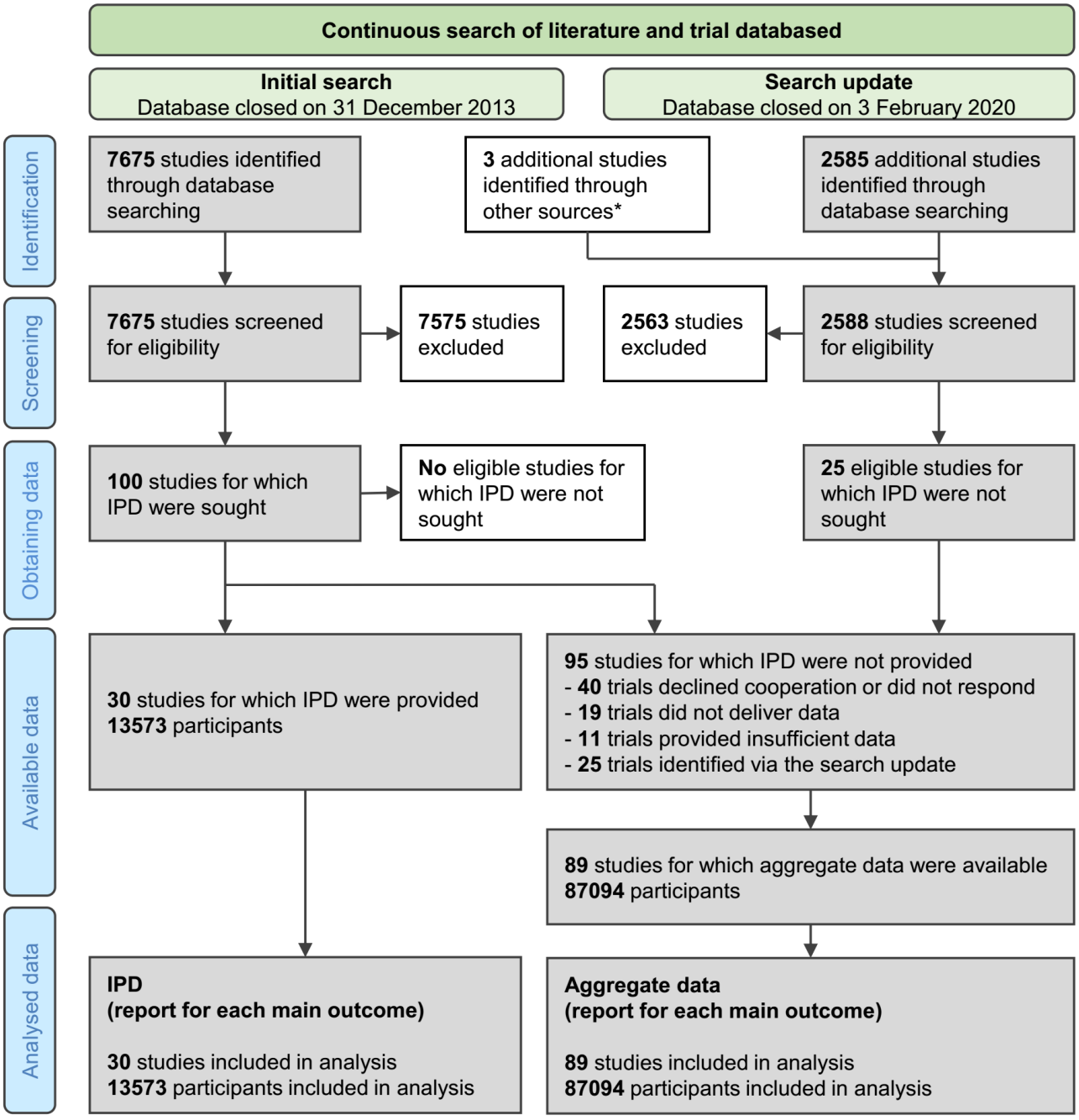
ELVA	Effect of Long-Term Treatment of Metoprolol CR/XL on Surrogate Variables for Atherosclerotic Disease	https://doi.org/10.1161/hs0202.102332
ENCORE	Exercise and Nutritional Interventions for Cardiovascular Health Study	https://doi.org/10.1001/archinternmed.2009.470 https://doi.org/10.1161/HYPERTENSIONAHA.109.146795
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

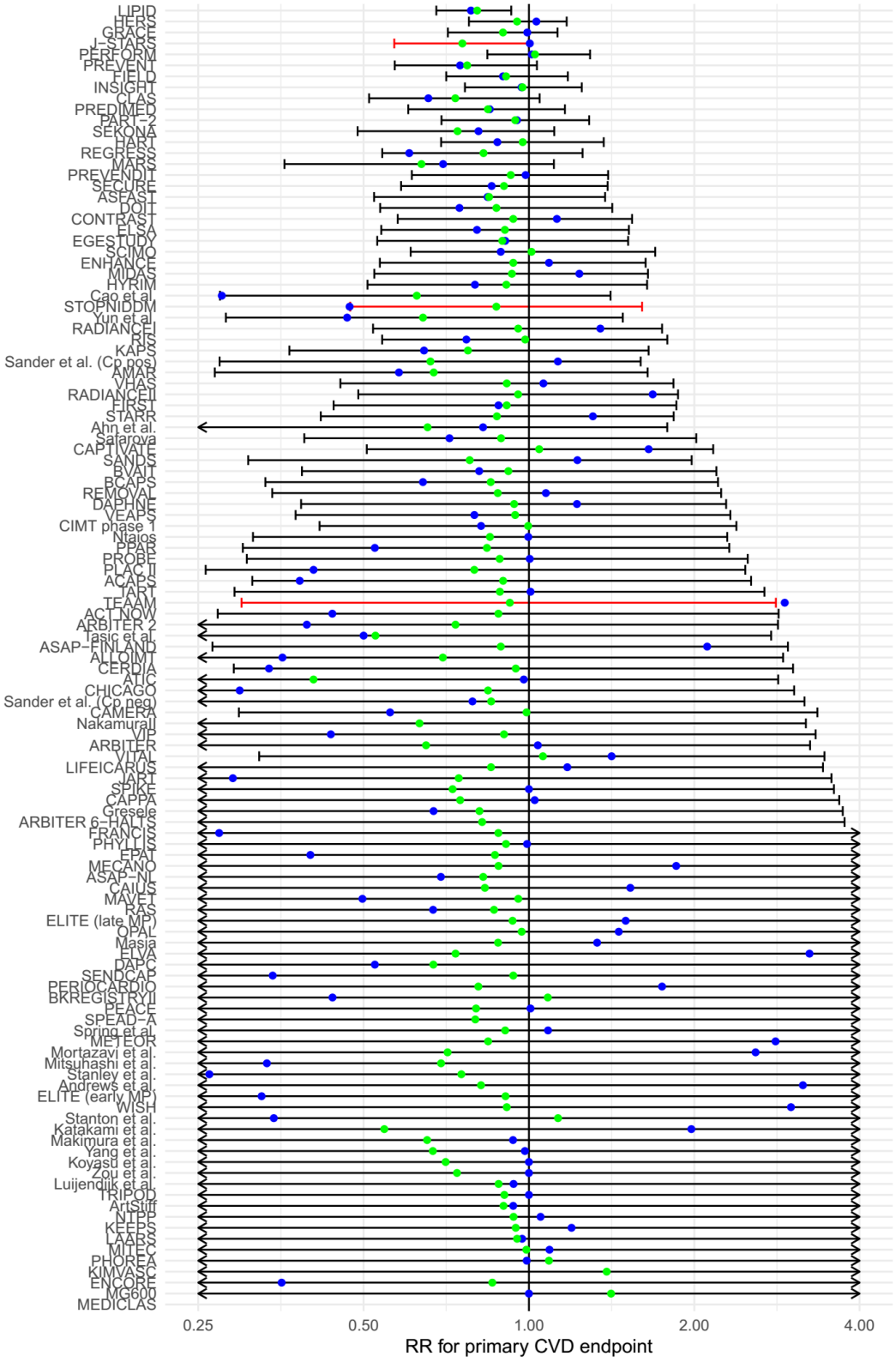
Supplemental Figure I. PRISMA Flow chart



The PRISMA IPD flow diagram

*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.

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

Stefan Agewall, MD, PhD
Oslo University Hospital
Ullevål and Institute of Clinical Sciences
University of Oslo
Oslo, Norway

Tadao Akizawa, MD, PhD
Division of Nephrology,
Department of Medicine
Showa University School of Medicine
Tokyo, Japan

Elias Allara, MD
Department of Public Health and Primary Care
University of Cambridge
Cambridge, UK
and
National Institute for Health Research Blood and Transplant Research Unit in Donor Health and Genomics
University of Cambridge
Cambridge, UK

Mayuko Amaha, MD
Division of Nephrology
Shinmatsudo Central General Hospital
Chiba, Japan

Mauro Amato, PhD
Centro Cardiologico Monzino IRCCS
Milan, Italy

Steen Andersen, MD, DMSc
Steno Diabetes Center
Gentofte, Denmark

Sigmund A. Anderssen, PhD
Department of Sports Medicine
Norwegian School of Sports Sciences
Oslo, Norway

Aleksandra Araszkiewicz, MD, PhD
Department of Internal Medicine and Diabetology
Poznan University of Medical Sciences
Poznan, Poland

Gülay Aşçi, MD
Nephrology Department
Ege University School of Medicine
Bornova-Izmir, Turkey

Folkert W. Asselbergs, MD, PhD
Department of Cardiology
University Medical Center Utrecht
Utrecht, the Netherlands

Jang-Ho Bae, MD, FACC
Heart Center
Konyang University Hospital
Daejeon, South Korea
and
Department of Cardiology
Konyang University College of Medicine
Daejeon, South Korea

Tatyana Balakhonova, MD, PhD
Ultrasound Vascular Laboratory
National Medical Research Center of Cardiology
Moscow, Russia

Damiano Baldassarre, PhD
Department of Medical Biotechnology and Translational Medicine
University of Milan
Milan, Italy
and
Centro Cardiologico Monzino IRCCS
Milan, Italy

John A. Bartlett, MD
Division of Infectious Diseases and International Health,
Department of Medicine
Duke University Medical Center
Durham, North Carolina, USA
and
Duke Global Health Institute
Durham, North Carolina, USA

Edith Beishuizen, MD
Department of Internal Medicine
HMC+ (Bronovo)
the Hague, the Netherlands

Oscar Beloqui, MD, PhD
Department of Internal Medicine
University Clinic of Navarra
Navarra, Spain

Gerald Berenson, MD
Department of Medicine, Pediatrics, Biochemistry, Epidemiology
Tulane University School of Medicine and School of Public Health and Tropical Medicine
New Orleans, USA

Göran Bergström, MD, PhD
Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy
University of Gothenburg
Gothenburg, Sweden
and
Department of Clinical Physiology
Sahlgrenska University Hospital, Region Västra Götaland
Gothenburg, Sweden

Enrique Bernal, MD, PhD
Infectious Diseases Unit
Reina Sofia Hospital
Murcia, Spain

Joline W. J. Beulens, PhD
Department of Epidemiology & Biostatistics
Amsterdam UMC- Location Vumc
Amsterdam, the Netherlands

Sebastjan Bevc, MD, PhD
Department of Nephrology
University Medical Centre Maribor
Maribor, Slovenia
and
Faculty of Medicine
University of Maribor
Maribor, Slovenia

Lokpal Bhatia, MD, MRCP, PhD
Faculty of Medicine
University of Southampton - Southampton General Hospital
Southampton, UK
and
Southampton NIHR Biomedical Research Centre
University Hospital Southampton - Southampton General Hospital
Southampton, UK

Horst Bickel, PhD
Department of Psychiatry and Psychotherapy
Technische Universität München
Munich, Germany

Stefan Blankenberg, MD
Department of Cardiology
University Hospital Hamburg-Eppendorf
Hamburg, Germany
and
2nd Department of Medicine
Johannes Gutenberg-Universität
Mainz, Germany

Peter J. Blankestijn, MD
Department of Nephrology
University Medical Center Utrecht
Utrecht, the Netherlands

James A. Blumenthal, PhD
Department of Psychiatry and Behavioral Sciences
Duke University Medical Center
Durham, NC 27710, USA

Lena Bokemark, MD, PhD
Wallenberg Laboratory for Cardiovascular Research
University of Gothenburg
Gothenburg, Sweden

Michiel L. Bots, MD, PhD
Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht
Utrecht, the Netherlands

Frank P. Brouwers, MD, PhD
Department of Cardiology
Haga Teaching Hospital
the Hague, the Netherlands

Christopher D. Byrne, FRCP, FRCPath, PhD
Human Development and Health Academic Unit, Faculty of Medicine, The Institute of Developmental Sciences
University of Southampton - Southampton General Hospital
Southampton, UK

Laura Calabresi, PhD
Department of Pharmacological and Biomolecular Sciences
University of MilanMilan, Italy

Philip C. Calder, PhD
Faculty of Medicine
University of Southampton - Southampton General Hospital
Southampton, UK
and
Southampton NIHR Biomedical Research Centre
University Hospital Southampton - Southampton General Hospital
Southampton, UK

Yong-Jun Cao, MD, PhD
Department of Neurology
Second Affiliated Hospital of Soochow University
Suzhou, China

Samuela Castelnuovo, PhD
Centro Dislipidemie
ASST Grande Ospedale Metropolitano Niguarda
Milan, Italy

Alberico Catapano, PhD
Department of Pharmacological and Biomolecular Sciences
University of Milan
Milan, Italy
and
IRCCS Multimedica
Milan, Italy

Chen-Huan Chen, MD
Faculty of Medicine
National Yang-Ming University
Taipei, Taiwan

Pei-Chun Chen, PhD
Clinical Informatics & Medical Statistics Research Center
Chang Gung University
Taoyuan, Taiwan

Kuo-Liong Chien, MD, PhD
Institute of Epidemiology and Preventive Medicine
National Taiwan University
Taipei, Taiwan

Ana R. Cunha, PhD
Department of Clinical Medicine
State University of Rio de Janeiro
Rio de Janeiro, Brazil

Francois Dabis, MD, PhD
Centre de Recherche INSERM U.897
Université Victor Segalen Bordeaux 2
Bordeaux Cedex, France

Jesse Dawson, MD, FRCP, FESO
Institute of Cardiovascular and Medical Sciences
University of Glasgow
Glasgow, UK

Eric de Groot, MD, PhD
Imagelabonline & Cardiovascular
Eindhoven and Lunteren, the Netherlands

Ralph A. DeFronzo, MD
Diabetes Division
University of Texas Health Science Center
San Antonio, USA

Moise Desvarieux, MD, PhD
Department of Epidemiology
Mailman School of Public Health, Columbia University
New York, USA
and
METHODS Core, Centre de Recherche Epidémiologie et Statistique Paris Sorbonne Cité (CRESS)
Institut National de la Santé et de la Recherche Médicale (INSERM) UMR 1153
Paris, France

Chrysostomos Dimitriadis, MD
University Department of Nephrology
Hippokration General Hospital
Thessaloniki, Greece

Marcus Dörr, MD
Department B for Internal Medicine
University Medicine Greifswald
Greifswald, Germany
and
German Center for Cardiovascular Research (DZHK)
Greifswald, Germany

Pierre Ducimetiere, PhD
Faculty of Medicine
University Paris Descartes
Paris, France

Helen Eddington, MD
Institute of Applied Health Research
University Hospitals Birmingham
Birmingham, UK

Robert Ekart, MD, PhD
Department of Dialysis
University Medical Centre Maribor
Maribor, Slovenia

Petra Elders, MD, PhD
Department of General Practice
Amsterdam UMC- Location Vumc
Amsterdam, the Netherlands

Jean Philippe Empana, MD, PhD
Paris Cardiovascular Research Centre (PARCC)
University Paris Descartes
Paris, France

Gunnar Engström, MD, PhD
Department of Clinical Sciences in Malmö
Lund University
Malmö, Sweden

Mark A. Espeland, PhD
Department of Biostatistical Sciences
Wake Forest School of Medicine
Winston-Salem, NC, USA

Christine Espinola-Klein, MD
2nd Department of Medicine
Johannes-Gutenberg University
Mainz, Germany

Ramon Estruch, MD, PhD
Endocrinology & Nutrition Service
Hospital Clínic de Barcelona
Barcelona, Spain

Marat Ezhov, MD, PhD
Laboratory of Lipid Disorders
National Medical Research Center of Cardiology
Moscow, Russia

Beat Frauchiger, MD
Department of Internal Medicine
Kantonsspital Frauenfeld
Frauenfeld, Switzerland

Alfonsa Friera, MD
Radiology Department
Universidad Autónoma de Madrid
Madrid, Spain

Rafael Gabriel, MD, PhD
National School of Public Health
Instituto de Salud Carlos III
Madrid, Spain

Greg Gamble, MSc
Department of Medicine
The University of Auckland
Auckland, New Zealand

Lu Gao, BSc, MSc
MRC Biostatistics Unit
University of Cambridge
Cambridge, UK

Hertzel C. Gerstein, MD, MSc, FRCPC
Department of Medicine and Population Health Research Institute
McMaster University
Hamilton, Ontario, Canada
and
Hamilton General Hospital
Hamilton, Ontario, Canada

Paolo Gresele, MD, PhD
Division of Internal and Cardiovascular Medicine, Department of Medicine
University of Perugia
Perugia, Italy

Liliana Grigore, MD, PhD
SISA Center for the Study of Atherosclerosis
Bassini Hospital
Cinisello Balsamo, Italy

Diederick E. Grobbee, MD, PhD
Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht
Utrecht, the Netherlands

Muriel P. C. Grooteman, MD, PhD
Department of Nephrology
Amsterdam UMC
Amsterdam, the Netherlands

Giuseppe Guglielmini, PhD
Division of Internal and Cardiovascular Medicine, Department of Medicine
University of Perugia
Perugia, Italy

Markolf Hanefeld, MD, DHC, PhD
Center for Clinical Studies
Technical University Dresden
Dresden, Germany

Apostolos I. Hatzitolios, MD, PhD, FESH
1st Propedeutic Department of Internal Medicine
Aristotle University of Thessaloniki
Thessaloniki, Greece

Bo Hedblad, MD, PhD
Department of Clinical Sciences in Malmö
Lund University
Malmö, Sweden

Frans A. Helmond, PhD
Merck Research Laboratories
Kenilworth, NJ, USA

Loghman Henareh, MD, PhD
Department of Medicine, Huddinge (MedH), H7
Stockholm, Sweden

Peter Higgins, MD, MRCP
Institute of Cardiovascular and Medical Sciences
University of Glasgow
Glasgow, UK

Alan Hinderliter, MD
Department of Medicine
University of North Carolina
Chapel Hill, NC, USA

Radovan Hojs, MD, PhD
Department of Nephrology
University Medical Centre Maribor
Maribor, Slovenia
and
Faculty of Medicine
University of Maribor
Maribor, Slovenia

Hirokazu Honda, MD, PhD
Division of Nephrology, Department of Medicine, Showa University School of Medicine
Tokyo, Japan

Satoshi Hoshide, MD, PhD
Department of Medicine
Jichi Medical University
School of Medicine
Tochigi, Japan

Menno V. Huisman, MD, PhD
Department of Thrombosis and Hemostasis
Leiden University Medical Center
Leiden, the Netherlands

Joseph Hung, MBBS, FRACP, FACC
School of Medicine and Pharmacology
University of Western Australia
Nedlands, Australia
and
Department of Cardiovascular Medicine
Sir Charles Gairdner Hospital
Nedlands, Australia

Bernhard Iglseder, MD
Department of Geriatric Medicine
Gemeinnützige Salzburger Landeskliniken Betriebsgesellschaft GmbH
Christian-Doppler-Klinik
Salzburg, Austria
and
Department of Geriatric Medicine
Paracelsus Medical University
Salzburg, Austria

M. Arfan Ikram, MD, PhD
Department of Epidemiology
Erasmus University Medical Center
Rotterdam, the Netherlands

Raffaele Izzo, MD, PhD
Department of Advanced Biochemical Sciences
Federico II University
Naples, Italy

Lisa M. Jamieson, PhD
Australian Research Centre for Population Oral Health
University of Adelaide
Adelaide, SA, Australia

Tomas Jogestrand, MD, PhD
Department of Laboratory Medicine (LABMED), H5, Division of clinical physiology
Stockholm, Sweden

Stein Harald Johnsen, MD, PhD
Department of Neurology
University Hospital of Northern Norway
Tromsø, Norway
and
Department of Clinical Medicine
University of Tromsø
Tromsø, Norway

Aleksandar Jovanovic, MD, PhD
Faculty of Medicine
University of Prishtina
Prishtina\Kosovska Mitrovica, Serbia

Anna Kablak-Ziembicka, MD, PhD
Department of Interventional Cardiology
Collegium Medicum
Jagiellonian University
Krakow, Poland

Philip A. Kalra, MD, PhD
Department of Renal Medicine
Salford Royal Hospital
Manchester, UK

Kostas Kapellas, PhD
Australian Research Centre for Population Oral Health
University of Adelaide
Adelaide, SA, Australia

Kazuomi Kario, MD, PhD
Department of Medicine
Jichi Medical University
School of Medicine
Tochigi, Japan

John J. P. Kastelein, MD, PhD, FESC
Department of Vascular Medicine
Academic Medical Centre, University of Amsterdam
Amsterdam, the Netherlands

Akihiko Kato, MD
Blood Purification Unit
Hamamatsu University Hospital
Hamamatsu, Japan

Jussi Kauhanen, MD
Institute of Public Health and Clinical Nutrition
University of Eastern Finland, Kuopio Campus
Kuopio, Finland

Maryam Kavousi, MD, PhD, FESC
Department of Epidemiology
Erasmus University Medical Center
Rotterdam, the Netherlands

Masanori Kawasaki, MD, PhD
Department of Cardiology
Gifu University Graduate School of Medicine
Gifu, Japan

Kerstin Kempf, PhD
Düsseldorf Catholic Hospital Group (VKKD)
Düsseldorf, Germany

Stefan Kiechl, MD
Department of Neurology
Medical University of Innsbruck
Innsbruck, Austria
and
VASCage GmbH
Research Centre on Vascular Ageing and Stroke
Innsbruck, Austria

Jang-Young Kim, MD, PhD
Department of Cardiology
College of Medicine Yonsei University
Wonju, South Korea

Kazuo Kitagawa, MD, PhD
Department of Neurology
Tokyo Women's Medical University
Tokyo, Japan

Sverre E. Kjeldsen, MD, PhD
Department of Cardiology
Oslo University Hospital
Oslo, Norway

Gerhard Klingenschmid, MD
Department of Neurology
Medical University of Innsbruck
Innsbruck, Austria

Sang Back Koh, MD, PhD
Preventive Medicine, College of Medicine
Yonsei University
Wonju, South Korea

Svetlana Kostic, MSc, MD
Primarius Institute for Therapy and Rehabilitation
Niš, Serbia

Manuel F. Landecho, MD, PhD
Department of Internal Medicine
University Clinic of Navarra
Navarra, Spain

Tatjana Lazarevic, MA
Faculty of Medicine
University of Kragujevac
Kragujevac, Serbia

Moo-Sik Lee, MD, PhD
Department of Preventive Medicine
Konyang University
Daejeon, South Korea
and
College of Medicine
Konyang University Hospital
Daejeon, South Korea

Seung Hwan Lee, MD, PhD
Department of Cardiology
Yonsei University
Wonju, South Korea

Wattana Leowattana, MD, PhD
Department of Clinical Tropical Medicine
Mahidol University
Rachatawee, Bangkok, Thailand

Ximing Liao, BSc, MSc, PhD
Department of Neurology
Goethe University
Frankfurt am Main, Germany

Yao-Ping Lin, MD, PhD
Department of Medicine
Taipei Veterans General Hospital
Taipei, Taiwan

Hung-Ju Lin, MSc
Department of Internal Medicine
National Taiwan University Hospital
Taipei, Taiwan

Lars Lind, MD, PhD
Department of Medicine
Uppsala University
Uppsala, Sweden

Chun-Feng Liu, MD, PhD
Department of Neurology
Second Affiliated Hospital of Soochow University
Suzhou, China

Jing Liu, MD, PhD
Department of Epidemiology
Beijing Anzhen Hospital, Capital Medical University
Beijing, China

Eva Lonn, MD, MSc, FRCPC, FACC
Department of Medicine and Population Health Research Institute
McMaster University
Hamilton, Ontario, Canada
and
Hamilton General Hospital
Hamilton, Ontario, Canada

Larrye E. Loss, PharmD, MBA, PMP
AstraZeneca
Gaithersburg (Maryland), USA

Dianna Magliano, PhD
Department of Epidemiology and Preventive Medicine
Monash University, Alfred Hospital
Melbourne, Australia

Francesca Mallamaci, MD
Institute of Biomedicine (CNR)
Centre of Clinical Physiology and Division of Nephrology
Reggio Calabria, Italy

Costantino Mancusi, MD
Department of Advanced Biochemical Sciences
Federico II University
Naples, Italy

Maria V. Manzi, MD
Department of Advanced Biochemical Sciences
Federico II University
Naples, Italy

Stephan Martin, MD, PhD
Düsseldorf Catholic Hospital Group (VKKD)
Düsseldorf, Germany

Ellisiv B. Mathiesen, MD, PhD
Department of Clinical Medicine
University of Tromsø
Tromsø, Norway

Wolfgang Mayer-Berger, MD
Rehabilitationsklinik für Herz-, Kreislauf-, Gefäßerkrankungen und Psychokardiologie
Klinik Roderbirken
Leichlingen, Germany

Barry P. McGrath, PhD, MBBS
Department of Vascular Sciences
Monash University,
Dandenong Hospital
Melbourne, Australia

Stela McLachlan, PhD
Usher Institute
University of Edinburgh
Edinburgh, UK

John McNeil, PhD, MBBS
School of Public Health and Preventive Medicine
Monash University
Melbourne, Australia

Brendan McQuillan, MBBS, PhD, FRACP
School of Medicine and Pharmacology
University of Western Australia
Nedlands, Australia
and
Department of Cardiovascular Medicine
Sir Charles Gairdner Hospital
Nedlands, Australia

Patrick Mercié, MD
Service de Médecine Interne
CHU de Bordeaux
Bordeaux, France

Rino Migliacci, MD, PhD
Division of Internal Medicine
Cortona Hospital
Cortona, Italy

Dragan Mijalković, MD
Institute for Treatment and Rehabilitation
Niška Banja, Serbia

Firouzeh Moeinzadeh, MD
Department of Internal Medicine
Isfahan University of Medical Sciences
Isfahan, Iran

Mojgan Mortazavi, MD
Nephrology Departement
Isfahan University of medical sciences
Isfahan, Iran

Titus Francis Msoka, MD, PhD
Department of Internal Medicine
Kilimanjaro Christian Medical Centre
Moshi, Tanzania

Veronica A. Myasoedova, MD, PhD
Unit for the Study of Aortic, Valvular, and Coronary Pathologies
Centro Cardiologico Monzino IRCCS
Milan, Italy

Michiaki Nagai, MD, PhD
Department of Internal Medicine, General Medicine and Cardiology
Hiroshima City Asa Hospital
Hiroshima, Japan

Tsukasa Nakamura, MD, PhD
Division of Nephrology
Shinmatsudo Central General Hospital
Chiba, Japan

Prabath W.B. Nanayakkara, MD, PhD, FRCP
Department of Clinical Neurophysiology
Amsterdam UMC
Amsterdam, the Netherlands

Dariusz Naskręt, MD, PhD
Department of Internal Medicine and Diabetology
Poznan University of Medical Sciences
Poznan, Poland

Mario F. Neves, MD, PhD
Department of Clinical Medicine
State University of Rio de Janeiro
Rio de Janeiro, Brazil

Pythia T. Nieuwkerk, PhD
Department of Medical Psychology
Amsterdam UMC- Location AMC
Amsterdam, the Netherlands

Giel Nijpels, MD, PhD
Department of General Practice
EMGO Institute for Health and Care Research
VU University Medical Center
Amsterdam, the Netherlands

Giuseppe D. Norata, PhD
SISA Center for the Study of Atherosclerosis
Bassini Hospital
Cinisello Balsamo, Italy
and
Department of Pharmacological and Biomolecular Sciences
University of Milan
Milan, Italy

George Ntaios, MD, MSc, PhD, FESO
Department of Medicine
University of Thessaly
Larissa, Greece

Ercan Ok, MD
Nephrology Department
Ege University School of Medicine
Bornova-Izmir, Turkey

Shuhei Okazaki, MD, PhD
Department of Neurology
Osaka University Graduate School of Medicine
Osaka, Japan

Michael H. Olsen, MD, PhD, DMSc
Department of Internal Medicine, Holbaek Hospital
University of Southern Denmark
Odense, Denmark

Alexander N. Orekhov, PhD, DSc
Laboratory of Angiopathology
Skolkovo Innovation Center
Moscow, Russia

Aikaterini Papagianni, MD
University Department of Nephrology
Hippokration General Hospital
Thessaloniki, Greece

Hyun-Woong Park, MD
Department of Internal Medicine
Gyeongsang National University Hospital
Jinju, South Korea

Grace Parraga, PhD
Department of Medical Biophysics
Western University
London, Canada

Margaretha Persson, MD
Department of Clinical Science
Lund University
Malmö, Sweden

Matthieu Plichart, MD, PhD
Paris Cardiovascular Research Centre (PARCC)
University Paris Descartes
Paris, France
and
Assistance Publique
Hôpitaux de Paris, Hôpital Broca
Paris, France

Joseph F. Polak, MD, MPH
Tufts University School of Medicine
Tufts Medical Center
Boston, USA

Holger Poppert, MD, PhD
Department of Neurology
Technische Universität München
Munich, Germany

David Preiss, PhD, FRCPath, MRCP
MRC Population Health Research Unit, Clinical Trial Service Unit, Nuffield Department of Population Health
University of Oxford
Oxford, UK

Jackie F. Price, MD
Usher Institute
University of Edinburgh
Edinburgh, UK

Tadeusz Przewlocki, MD, PhD
Department of Interventional Cardiology
Collegium Medicum
Jagiellonian University
Krakow, Poland

Joel S. Raichlen, MD
AstraZeneca
Wilmongton, DE, USA

Peter Reaven, MD
Department of Medicine
University of Arizona
Phoenix, USA

Marcus Redaèlli, MD
Department für Humanmedizin
Universität Witten/Herdecke
Witten, Germany

Peter Reiss, MD, PhD
Department of Global Health
Amsterdam UMC- Location AMC
Amsterdam, the Netherlands
and
Amsterdam Institute for Global Health and Development
University of Amsterdam
Amsterdam, the Netherlands

Kathrin Reuber, MSc
Department of Neurology
Goethe University
Frankfurt am Main, Germany

Martin Röhling, PhD
Westdeutsches Diabetes- und Gesundheitszentrum
Verbund Katholischer Kliniken Düsseldorf
Düsseldorf, Germany

Emilio Ros, MD, PhD
Endocrinology & Nutrition Service
Hospital Clínic de Barcelona
Barcelona, Spain

Signe Rosenlund, MD
Steno Diabetes Center
Gentofte, Denmark

Peter Rossing, MD, DMSc
Steno Diabetes Center
Gentofte, Denmark

Maria Rosvall, MD, PhD
Department of Clinical Sciences in Malmö
Lund University
Malmö, Sweden

Tatjana Rundek, MD, PhD
Department of Neurology
University of Miami Miller School of Medicine
Miami, USA

Mohammad Saadatnia, MD
Al-Zahra Hospital
Isfahan University of Medical Sciences
Isfahan, Iran

Maya Safarova, MD
Atherosclerosis Department
National Medical Research Center of Cardiology
Moscow, Russia

Dirk Sander, MD
Department of Neurology
Benedictus Hospital Tutzing & Feldafing
Feldafing, Germany
and
Department of Neurology
Technische Universität München
Munich, Germany

Kerstin Sander, MD, PD
Department of Psychosomatic
Berchtesgadener Land, Germany

Eiichi Sato, MD
Division of Nephrology
Shinmatsudo Central General Hospital
Chiba, Japan

Naveed Sattar, MD, PhD
BHF Glasgow Cardiovascular Research Centre
University of Glasgow
Glasgow, UK

Christos Savopoulos, MD, PhD
1st Propedeutic Department of Internal Medicine
Aristotle University of Thessaloniki
Thessaloniki, Greece

Frank Scheckenbach, MSc, PhD
Department of Neurology
Goethe University
Frankfurt am Main, Germany

Caroline Schmidt, PhD
Wallenberg Laboratory for Cardiovascular Research
University of Gothenburg
Gothenburg, Sweden

Irene Schmidtmann, PhD
Institut fuer Medizinische Biometrie, Epidemiologie und Informatik (IMBEI)
Universitaetsmedizin Mainz
Mainz, Germany

Ulf Schminke, MD
Department of Neurology
Greifswald University Clinic
Greifswald, Germany

Michael Schneider, MD
Mannheim Institute for Public Health
Ruprecht-Karls University Heidelberg
Mannheim, Germany
and
Dept HR Services & Expertise Center
Boehringer Ingelheim Pharma GmbH & Co. KG
Ingelheim am Rhein, Germany

Lisa Seekircher, DI, Mag., BSc
Department of Neurology
Medical University of Innsbruck
Innsbruck, Austria

Norman Sharpe, MD
Heart Foundation
Ellerslie, Auckland, New Zealand

Andrew Sherwood, PhD
Department of Psychiatry and Behavioral Sciences
Duke University Medical Center
Durham, NC 27710, USA

Matthias Sitzer, MD
Department of Neurology
Klinikum Herford
Herford, Germany
and
Department of Neurology
Goethe University
Frankfurt am Main, Germany

Michael Skilton, PhD
Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders
University of Sydney
Sydney, NSW, Australia

Patrick J. Smith, PhD, MPH
Department of Psychiatry and Behavioral Sciences
Duke University Medical Center
Durham, NC, USA

Igor A. Sobenin, MD, PhD, DSc
Laboratory of Medical Genetics
Institute of Experimental Cardiology, National Medical Research Center of Cardiology
Moscow, Russia
and
Laboratory of Angiopathology
Institute of General Pathology and Pathophysiology
Moscow, Russia

J. David Spence, MD, FRCPC, FAHA
Stroke Prevention & Atherosclerosis Research Centre
Western University
London, Canada

Sathanur R. Srinivasan, PhD
Center for Cardiovascular Health, Department of Epidemiology, Biochemistry
Tulane University School of Public Health and Tropical Medicine
New Orleans, USA

Daniel Staub, MD
Department of Angiology
University Hospital Basel
Basel, Switzerland

Coen D. A. Stehouwer, MD, PhD, FESC
Department of Internal Medicine and Cardiovascular Research Institute Maastricht (CARIM)
Maastricht University Medical Centre
Maastricht, the Netherlands

Helmuth Steinmetz, MD
Department of Neurology
Goethe University
Frankfurt am Main, Germany

Radojica Stolić, MD, PhD
Department of Internal Medicine, Faculty of Medical Sciences
University of Kragujevac
Kragujevac, Serbia

Erik Stroes, MD, PhD
Department of Vascular Medicine
Academic Medical Centre, University of Amsterdam
Amsterdam, the Netherlands

Ta-Chen Su, MD, PhD
Department of Internal Medicine
National Taiwan University Hospital
Taipei, Taiwan

Carmen Suarez, MD, PhD
Internal Medicine Department
Universidad Autónoma de Madrid
Madrid, Spain

Michael J. Sweeting, PhD
Department of Health Sciences
University of Leicester
Leicester, UK
and
Department of Public Health and Primary Care
University of Cambridge
Cambridge, UK

Ivan S. Tasić, MD, PhD
Faculty of Medicine
University of Niš
Niš, Serbia
and
Institute for Treatment and Rehabilitation
Niška Banja, Serbia

Pieter M. ter Wee, MD, PhD
Department of Nephrology
Amsterdam UMC
Amsterdam, the Netherlands

Rodolphe Thiébaut, MD, PhD
Centre de Recherche INSERM U.897
Université Victor Segalen Bordeaux 2
Bordeaux Cedex, France

Simon G. Thompson, DSc
Department of Public Health and Primary Care
University of Cambridge
Cambridge, UK

Peter L. Thompson, MD, FRACP, FACC, MBA
Heart Research Institute of WA and Department of Cardiovascular Medicine
Sir Charles Gairdner Hospital
Nedlands, Australia

Estefania Toledo, MD, MPH, PhD
Department of Preventive Medicine and Public Health
University of Navarra
Pamplona, Spain
and
Centro de Investigación Biomédica en Red-Fisiopatología de la Obesidad y la Nutrición (CIBERobn)
Instituto de Salud Carlos III (ISCIII)
Madrid, Spain

Elena Tremoli, PhD
Centro Cardiologico Monzino IRCCS
Milan, Italy

Devjit Tripathy, MD, PhD
Division of Diabetes
University of Texas Health Science Center
San Antonio, USA

Giovanni Tripepi, MSc, PhD
Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension Unit
Institute of Physiology of the National Research Council (CNR)
Reggio Calabria, Italy
Lena Tschiderer, DI, BSc, PhD
Department of Neurology
Medical University of Innsbruck
Innsbruck, Austria

Tomi-Pekka Tuomainen, MD, PhD
Institute of Public Health and Clinical Nutrition
University of Eastern Finland, Kuopio Campus
Kuopio, Finland

Aleksandra Uruska, MD, PhD
Department of Internal Medicine and Diabetology
Poznan University of Medical Sciences
Poznan, Poland

Heiko Uthoff, MD, PD
Department of Angiology
University Hospital Basel
Basel, Switzerland

Michiel A. van Agtmael, MD, PhD
Department of Internal Medicine
Amsterdam UMC, Vrije Universiteit
Amsterdam, the Netherlands

Wiek van Gilst, PhD
Department of Experimental Cardiology
University Medical Center Groningen
Groningen, the Netherlands

Gary P. van Guilder, PhD
Department of Health and Nutritional Sciences
South Dakota State University
Brookings, South Dakota, USA

Marit G. A. van Vonderen, MD, PhD
Department of Internal Medicine
Medical Center Leeuwarden
Leeuwarden, the Netherlands

Fabrizio Veglia, PhD
Centro Cardiologico Monzino IRCCS
Milan, Italy

Frank L. J. Visseren, MD
Department of Vascular Medicine
University Medical Center Utrecht
Utrecht, the Netherlands

Henry Völzke, MD
Institute for Community Medicine
SHIP/Clinical-Epidemiological Research
Greifswald, Germany
and
German Center for Cardiovascular Research (DZHK)
Greifswald, Germany

Ari Voutilainen, PhD
Institute of Public Health and Clinical Nutrition
University of Eastern Finland, Kuopio Campus
Kuopio, Finland

Kristian Wachtell, MD, PhD, DrMedSci
Department of Cardiology
Oslo University Hospital
Oslo, Norway

Matthew Walters, MD, FRCP
School of Medicine, Dentistry and Nursing
University of Glasgow
Glasgow, UK

Miao Wang, MD
Department of Epidemiology
Beijing Anzhen Hospital, Capital Medical University
Beijing, China

Thapat Wannarong, MD
Stroke Prevention & Atherosclerosis Research Centre
Western University
London, Canada
and
Department of Internal Medicine, Faculty of Medicine
Siriraj Hospital, Mahidol University
Bangkok, Thailand

Gillian Whalley, PhD
Faculty of Social and Health Sciences
Unitec
Auckland, New Zealand

Johann Willeit, MD
Department of Neurology
Medical University of Innsbruck
Innsbruck, Austria
Miles D. Witham, BMBCh, PhD
AGE Research Group, NIHR Newcastle Biomedical Research Centre
Newcastle University and Newcastle-upon-Tyne Hospitals Trust
Newcastle, UK

Wuxiang Xie, MD, PhD
Department of Epidemiology
Beijing Anzhen Hospital, Capital Medical University
Beijing, China

Kiyofumi Yamada, MD, PhD
Departments of Neurosurgery
Gifu University Graduate School of Medicine
Gifu, Japan

David N. Yanez, PhD
Department of Biostatistics
University of Washington
Seattle, USA

Shinichi Yoshimura, MD, PhD
Departments of Neurosurgery
Gifu University Graduate School of Medicine
Gifu, Japan

Wen-Chung Yu, MD
Division of Cardiology
Taipei Veterans General Hospital
Taipei, Taiwan
and
Institute of Clinical Medicine
National Yang-Ming University
Taipei, Taiwan

Salim Yusuf, MD, DPhil, MRCP
Department of Medicine and Population Health Research Institute
McMaster University
Hamilton, Ontario, Canada
and
Hamilton General Hospital
Hamilton, Ontario, Canada

Dong Zhao, MD, PhD
Department of Epidemiology
Beijing Anzhen Hospital, Capital Medical University
Beijing, China

Zhi-Yong Zou, MD
Institute of Child and Adolescent Health, School of Public Health
Peking University
Beijing, China

Sophia Zoungas, MD, FRACP, PhD
School of Public Health and Preventive Medicine
Monash University
Melbourne, Australia

Dorota A. Zozulińska-Ziółkiewicz, MD, PhD
Department of Internal Medicine and Diabetology
Poznan University of Medical Sciences
Poznan, Poland

Principal investigator of the PROG-IMT consortium

Matthias W. Lorenz, MD, PD
Department of Neurology
Goethe University
Frankfurt am Main, Germany

Principal investigator of the Proof-ATHERO consortium

Peter Willeit, MD, MPhil, PhD
Department of Neurology
Medical University of Innsbruck
Innsbruck, Austria
and
Department of Public Health and Primary Care
University of Cambridge
Cambridge, UK