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Carotid Intima-Media Thickness Progression as Surrogate Marker for Cardiovascular Risk: Meta-Analysis of 119 Clinical Trials Involving 100,667 Patients

Running Title: *Willeit & Tschiderer, et al.; cIMT Progression as Surrogate Marker for CVD Risk*

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Abstract

Background: To quantify the association between effects of interventions on carotid intima-media thickness (cIMT) progression and their effects on cardiovascular disease (CVD) risk.
Methods: We systematically collated data from randomized controlled trials. cIMT was assessed as the mean value at the common-carotid-artery; if unavailable, the maximum value at the common-carotid-artery or other cIMT measures were utilized. The primary outcome was a combined CVD endpoint defined as myocardial infarction, stroke, revascularization procedures, or fatal CVD. We estimated intervention effects on cIMT progression and incident CVD for each trial, before relating the two using a Bayesian meta-regression approach.
Results: We analyzed data of 119 randomized controlled trials involving 100,667 patients (mean age 62 years, 42% female). Over an average follow-up of 3.7 years, 12,038 patients developed the combined CVD endpoint. Across all interventions, each 10 μm/year reduction of cIMT progression resulted in a relative risk for CVD of 0.91 (95% credible interval 0.87-0.94), with an additional relative risk for CVD of 0.92 (0.87-0.97) being achieved independent of cIMT progression. Taken together, we estimated that interventions reducing cIMT progression by 10, 20, 30, or 40 μm/year would yield relative risks of 0.84 (0.75-0.93), 0.76 (0.67-0.85), 0.69 (0.59-0.79), or 0.63 (0.52-0.74). Results were similar when grouping trials by type of intervention, time of conduct, time to ultrasound follow-up, availability of individual-participant data, primary vs. secondary prevention trials, type of cIMT measurement, and proportion of female patients.
Conclusions: The extent of intervention effects on cIMT progression predicted the degree of CVD risk reduction. This provides a missing link supporting the usefulness of cIMT progression as a surrogate marker for CVD risk in clinical trials.

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

Non-standard Abbreviations and Acronyms
CI credible interval
cIMT Carotid intima-media thickness
CVD cardiovascular disease
RCT randomized controlled trial
RR relative risk

Clinical Perspective

What is new?

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

What are the clinical implications?

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

Introduction

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

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

To address this uncertainty, we conducted a comprehensive analysis of 119 RCTs involving a total of 100,667 patients. Our aims were to: (i) quantify the reduction in CVD risk associated with reducing cIMT progression by therapeutic intervention; (ii) explore cIMT

progression as a surrogate marker for different types of CVD endpoints as well as all-cause mortality; and (iii) investigate differences according to the intervention type, method of cIMT assessment, and other trial characteristics.

Methods

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

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

extracted the relevant data from the published literature and resolved any discrepancies by consensus.

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

Statistical analysis

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

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

publications), we annualized differences in cIMT progression and calculated standard errors from *P* values, if necessary.

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

Third, to test whether effects on CVD risk depended on effects on cIMT progression, we used a Bayesian meta-regression approach that models both effects simultaneously, while taking into account the estimated precisions in these two effects.[14] The principal analysis involved (i) a model with an intercept of zero (i.e. forcing the regression line through the origin and thereby assuming that all the effects on CVD risk operate through cIMT progression) and (ii) a model with a non-zero intercept (i.e. allowing for an effect on CVD risk independent of cIMT progression). The meta-regression also took into account the within-study correlation of the two effects, which was estimated using bootstrapping in the trials with patient-level data and >30 events.[15] For other trials, an overall correlation coefficient pooled using random-effects meta-analysis was used instead. Further details on methods for assessing surrogacy are provided in the **Methods in the Supplement**.

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

Results

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

interval: 7.1 to 11.1) in control arms and +1.0 μm/year (-0.6 to 2.7) in interventions arms. Across all contributing trials, the RR for CVD with intervention was 0.88 (0.83-0.92).

Results of the principal analysis are provided in **Figure 1**. Across all interventions, in the model assuming an intercept of zero, each 10 μm/year reduction of cIMT progression was associated with a RR for CVD of 0.88 (95% credible interval [CI] 0.85-0.91). In the model allowing for a non-zero intercept, the RR for CVD was 0.91 (0.87-0.94) per 10 μm/year slower cIMT progression, with a further RR of 0.92 (0.87-0.97) achieved independent of cIMT progression. Based on the non-zero intercept model, the proportion of variance in the CVD outcome explained by cIMT progression was 98% albeit with a wide 95% CI (71-100%). Taken together, we estimated that interventions that reduce cIMT progression by 10, 20, 30, or 40 μm/year would yield RRs of 0.84 (0.75-0.93), 0.76 (0.67-0.85), 0.69 (0.59-0.79), or 0.63 (0.52-0.74).

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

>80 µm/year or RR for CVD <0.25 or >4.0), the RR for CVD per 10 µm/year slower cIMT progression was 0.91 (0.87-0.95). Results were also highly robust across leave-one-out cross-validation analyses (**Figure II in the Supplement**). Trial-specific estimates are provided in **Table IV in the Supplement**.

Discussion

In this large-scale meta-analysis involving data from 119 RCTs and 100,667 patients, we showed that interventions reducing cIMT progression are also likely to reduce CVD event rates (summarized in **Figure 5**). Specifically, a 10 µm/year slower cIMT progression was associated with a RR of 0.91 (95% CI 0.87-0.94) for the principal outcome of CVD, with the differences in RR for CVD largely explained by the differences in cIMT progression. The same model also indicated a non-zero intercept, overall and for different types of interventions, highlighting that a small but significant proportion of the intervention effect acted independently of cIMT progression. By estimating CVD risk reductions according to specific reductions in cIMT progression, we provide guidance to future trials in the cardiovascular field.[5] Results were robust for a range of disease endpoints and across clinically important trial characteristics, including type of intervention or type of cIMT measurement.

Exploring the association between cIMT and CVD risk has some history. cIMT measured at a single time-point is associated with incident CVD and provides incremental predictive value over and beyond conventional CVD risk factors.[190-192] For cIMT progression over time, our earlier analyses of observational studies within the PROG-IMT collaboration indicated no statistically significant association with subsequent CVD risk in individuals of the general population,[2] patients with diabetes mellitus,[193] or patients at high CVD risk[194]. This null

association could be explained by the challenges of precisely estimating cIMT progression in individuals over time. In contrast, our present report focuses on groups of patients in RCTs and is therefore better suited to provide answers about the surrogate value of cIMT progression: averaging across patients improves the signal-to-noise ratio, confounders are expected to be balanced due to randomization, trial cohorts might be more homogeneous, and cIMT protocols may be of higher quality in clinical trial settings.

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

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

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

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

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

meta-analysis), and improved precision by incorporating within-trial correlations of intervention effects on cIMT progression and CVD risk.

Our analysis also has limitations. First, our principal analysis combined trials of varying types of interventions. While we conducted a sensitivity analysis by medication class, further research is required to precisely quantify the differences in the surrogate value of cIMT by intervention type. Second, our analysis involved a broad range of types of trial populations. While sensitivity analysis revealed no evidence for differential effects in the setting of primary vs. secondary prevention trials, further study is needed on specific trial populations, such as patients with diabetes or chronic kidney disease. Third, the definition of the primary combined CVD endpoint varied across the included trials. However, the differences were relatively minor (see **Table III in the Supplement**), so we are confident that this does not constitute a major source of systematic bias. Finally, while ultrasound scanning protocols may have differed across contributing trials – in particular before consensus guidelines were available[213], there was no evidence for effect modification by type of cIMT measure or baseline years of the trials.

Conclusions

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

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Conflict of Interest Disclosures

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Supplemental Material

Supplemental Methods

Supplemental Tables I-V

Supplemental Figures I-II

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

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

					Type of intervention*									CVD risk		cIMT progression				
Trial	**Years of baseline**	**Country**	**Access to IPD**	**No. of trial arms**	**Antidiabetic**	**Antihypertensive**	**Dietary / vitamins**	**Lipid-lowering**	**Other**	**No. of patients**	**Type of population**	**Mean age (SD), years**	**% female**	**Median follow-up, years**	**No. of events**	**Maximum follow-up, years**	**% with cIMT data**	**Mean CCA-IMT**	**Max CCA-IMT**	**Other cIMT**
ACAPS[16,17]	1989-1990	USA	●	2x2	-	-	-	●	●	919	Elevated CVD risk	62 (8)	48	5.0	18	6.0	100	-	●	-
ACT NOW[18,19]	2004-2006	USA	-	2	●	-	-	-	-	602	Dysglycemia	52 (10)	58	2.2†	13	4.0	63	●	-	-
ALLO-IMT[20]	2009-2010	UK	●	2	-	-	-	-	●	80	Pre-existing CVD	68 (10)	43	1.0	11	1.2	100	●	●	-
AMAR[21]	2004-2005	Russia	-	2	-	-	●	-	-	257	Elevated CVD risk	61 (9)	0	2.0‡	21	2.0	76	●	-	-
ARBITER[22]	1999-2001	USA	-	2	-	-	-	●	-	161	Elevated CVD risk	60 (12)	29	1.0‡	6	1.0	86	●	●	-
ARBITER 2[23]	2001-2003	USA	-	2	-	-	-	●	-	167	Pre-existing CVD	67 (10)	9	1.0‡	10	1.0	89	●	-	-
ARBITER 6-HALTS[6,24,25]	2006-2009	USA	-	2	-	-	-	●	-	363	Pre-existing CVD	65 (10)	20	1.2‡	11	1.2	57	●	●	-
ARTSTIFF[26]	2008-2011	International	-	3	-	●	-	-	-	133	Hypertension	53 (10)	37	1.0‡	0	1.0	87	●	-	-
ASAP-FINLAND[27-29]	1994-1995	Finland	-	2	-	-	●	-	-	520	Hyperlipidemia	60 (6)	51	6.0‡	22	6.0	85	●	-	-
ASAP-NL[30,31]	1997-1998	Netherlands	-	2	-	-	-	●	-	330	Hyperlipidemia	49 (11)	61	2.0‡	5	2.0	85	●	-	-
ASFAST[32]	1998-2000	International	-	2	-	-	●	-	-	315	Kidney disease	56 (13)	32	3.3†	73	3.6	77	-	●	-
ATIC[33,34]	2001-2002	Netherlands	-	2	-	-	-	-	●	93	Kidney disease	53 (12)	43	2.0‡	4	1.5	80	●	-	-
Ahn et al.[35]	2005-2006	Korea	-	2	-	-	-	-	●	130	Pre-existing CVD	64 (11)	38	2.0‡	18	2.0	73	-	-	●
Andrews et al.[36,37]	2011-2015	USA	-	2	-	-	-	-	●	80	Kidney disease	57 (12)	20	0.2‡	1	0.2	79	●	-	-
BCAPS[38]	1994-1996	Sweden	-	2x2	-	●	-	●	-	793	Elevated CVD risk	62 (5)	54	3.0†	18	3.0	99	●	-	-
BIREGISTRY-II[39]	2000-2003	Korea	●	2	-	-	-	●	-	205	Pre-existing CVD	60 (10)	32	0.5	3	1.1	59	●	-	-
BVAIT[40]	2000-2006	USA	-	2	-	-	●	-	-	506	General population	61 (10)	39	3.1†	20	2.5	97	●	-	-
CAIUS[41]	1991-1992	Italy	-	2	-	-	-	●	-	305	Hyperlipidemia	55 (6)	47	3.0‡	5	3.0	100	-	●	-
CAMERA[42]	2009-2011	UK	●	2	●	-	-	-	-	173	Pre-existing CVD	63 (8)	23	1.5	12	2.3	100	●	-	-
CAPPA[43]	2009	Korea	-	2	-	-	-	-	●	420	Dysglycemia	60 (9)	50	3.0‡	6	3.0	99	●	●	-
CAPTIVATE[44]	2004-2005	International	-	2	-	-	-	●	-	892	Hyperlipidemia	55 (9)	39	2.0‡	32	1.0	99	-	-	●
CERDIA[45]	1999-2001	Netherlands	●	2	-	-	-	●	-	250	Dysglycemia	58 (11)	53	2.1	14	2.5	99	●	●	-
CHICAGO[46]	2003-2005	USA	-	2	●	-	-	-	-	462	Dysglycemia	60 (8)	37	1.4‡	13	1.4	78	●	●	-
CIMT phase 1[47,48]	2008-2009	Denmark	-	2	●	-	-	-	-	412	Dysglycemia	61 (9)	32	1.5‡	20	1.5	100	●	●	-
CLAS[49-51]	1980-1984	USA	-	2	-	-	-	●	-	162	Pre-existing CVD	54 (5)	0	7.0†	82	4.0	48	●	-	-

CONTRAST[52,53]	2004-2009	Netherlands	●	2	-	-	-	-	●	714	Kidney disease	64 (14)	38	2.4	173	3.1	20	●	●	-
Cao et al.[54]	2008-2011	China	-	2	-	-	●	-	-	287	Elevated CVD risk	71 (13)	53	2.0‡	36	2.0	100	-	-	●
DAPC[55,56]	2004-2006	International	-	2	-	-	-	-	●	329	Dysglycemia	64 (7)	48	2.0‡	3	2.0	90	●	●	-
DAPHNE[57]	NR	Netherlands	-	2	-	●	-	-	-	80	Pre-existing CVD	59 (7)	0	3.0‡	16	3.0	100	-	-	●
DOIT[58]	1997-1999	Norway	-	2	-	-	●	-	-	561	Elevated CVD risk	70 (5)	0	3.0‡	63	3.0	83	●	-	-
EGE STUDY[59,60]	2005-2006	Turkey	●	2x2	-	-	-	-	●	644	Kidney disease	59 (14)	46	3.0	60	3.0	100	●	-	-
ELITE (early MP)[61,62]	2005-2008	USA	-	2	-	-	-	-	●	271	General population	55 (4)	100	5.0	1	5.0	92	●	-	-
ELITE (late MP)[61,62]	2005-2008	USA	-	2	-	-	-	-	●	372	General population	65 (6)	100	5.0	5	5.0	94	●	-	-
ELSA[63]	NR	International	-	2	-	●	-	-	-	2334	Hypertension	56 (7)	45	4.0‡	60	4.0	87	-	-	●
ELVA[64]	NR	Sweden	-	2	-	●	-	-	-	129	Hyperlipidemia	60 (10)	49	3.0‡	4	3.0	71	●	-	-
ENCORE[65,66]	2003-2008	USA	●	3	-	-	●	-	-	144	Elevated CVD risk	52 (10)	67	0.4	1	1.1	98	●	-	-
ENHANCE[67]	2002-2004	International	●	2	-	-	-	●	-	720	Hyperlipidemia	47 (9)	49	2.0	52	2.3	100	●	●	-
EPAT[68]	1994-1998	USA	-	2	-	-	-	-	●	222	Hyperlipidemia	61 (7)	100	2.0‡	7	2.0	90	●	-	-
FIELD[69,70]	1998-2000	International	-	2	-	-	-	●	-	9795	Dysglycemia	62 (7)	37	6.0‡	1295	5.0	2	-	●	-
FIRST[71,72]	2008-2010	USA	-	2	-	-	-	●	-	682	Pre-existing CVD	61 (9)	32	2.1‡	30	2.0	84	-	●	-
FRANCIS[73,74]	2011-2012	Netherlands	-	2	-	-	-	-	●	320	Elevated CVD risk	53 (11)	70	5.0‡	9	5.0	100	●	-	-
GRACE[75]	2003-2005	International	●	2x2	●	-	●	-	-	1189	Dysglycemia	63 (8)	36	5.8	374	5.1	100	●	●	-
Gresele et al.[76]	2003-2005	International	●	2	-	-	-	-	●	442	Pre-existing CVD	67 (9)	21	0.6	8	0.6	57	●	●	-
HART[77]	1999-2000	International	●	2	-	-	●	-	-	925	Pre-existing CVD	69 (7)	24	5.0	152	5.6	100	●	●	-
HERS[78,79]	1993-1994	USA	-	2	-	-	-	-	●	2763	General population	67 (7)	100	4.1†	552	4.7	16	-	●	-
HYRIM[80]	1997-1999	Norway	●	2x2	-	-	-	●	●	568	Hypertension	57 (9)	0	4.1	47	4.6	99	-	●	-
INSIGHT[81-83]	1994-1996	France	-	2	-	●	-	-	-	6321	Elevated CVD risk	65 (7)	54	3.5†	347	4.0	5	●	-	-
J-STARS[84-88]	2004-2009	Japan	-	2	-	-	-	●	-	1589	Pre-existing CVD	66 (8)	31	4.9†	290	5.0	50	●	-	-
JART[89]	2008-2010	Japan	-	2	-	-	-	●	-	348	Hyperlipidemia	64 (9)	51	2.0‡	9	2.0	40	●	●	-
KAPS[90]	1984-1989	Finland	-	2	-	-	-	●	-	447	Hyperlipidemia	57 (4)	0	3.0‡	28	3.0	95	-	●	-
KEEPS[91]	2005-2008	USA	-	3	-	-	-	-	●	727	General population	53 (3)	100	4.0‡	1	4.0	100	●	-	-
KIMVASC[92]	2011-2012	UK	●	2	-	-	●	-	-	80	Pre-existing CVD	77 (5)	45	0.5	1	0.5	99	●	-	-
Kataakami et al.[93]	1998	Japan	-	3	●	-	-	-	-	159	Dysglycemia	61 (9)	51	3.3†	0	3.3	74	-	-	●
Kovasu et al.[94]	2006-2008	Japan	-	2	●	-	-	-	-	90	Pre-existing CVD	66 (8)	9	1.0‡	0	1.0	90	-	●	-
LAARS[95]	NR	International	-	2	-	●	-	-	-	280	Hypertension	59 (9)	50	2.0‡	0	2.0	72	●	-	-
LIFE-ICARUS[96]	1996-1997	International	●	2	-	●	-	-	-	83	Hypertension	67 (6)	27	4.9	8	3.1	98	●	-	-
LIPID[97-100]	1990-1992	International	-	2	-	-	-	●	-	9014	Pre-existing CVD	61 (8)	17	6.1†	3229	4.0	4	●	-	-
Luijendijk et al.[101,102]	2007-2009	Netherlands	-	2	-	-	-	●	-	155	Pre-existing CVD	36 (12)	38	3.3†	0	4.4	100	●	-	-
MARS[103,104]	1985-1989	USA	-	2	-	-	-	●	-	270	Hyperlipidemia	58 (7)	9	2.2†	54	4.0	27	●	-	-
MAVET[105]	1994-1995	Australia	-	2	-	-	●	-	-	409	Elevated CVD risk	64 (6)	55	4.0‡	6	4.0	81	-	●	-
MECANO[106,107]	2005-2006	Netherlands	-	2	-	-	-	-	●	185	Kidney disease	51 (13)	36	1.5‡	6	2.0	88	●	-	-
MEDICLAS[108,109]	2003-2005	Netherlands	●	2	-	-	-	-	●	48	Elevated CVD risk	42 (10)	0	3.0	1	3.2	77	●	-	-
METEOR[110]	2002-2004	International	-	2	-	-	-	●	-	984	Elevated CVD risk	57 (6)	40	2.0‡	3	2.0	89	●	●	-

MG600[111]	2010-2011	Brazil	●	2	-	-	●	-	-	35	Hypertension	55 (7)	100	0.5	0	0.5	100	●	●	-
MIDAS[112]	NR	USA	-	2	-	●	-	-	-	883	Hypertension	59 (9)	22	3.0‡	47	3.0	100	-	●	-
MITEC[113,114]	2000-2002	France	-	2	-	●	-	-	-	209	Elevated CVD risk	60 (8)	36	3.0‡	0	3.0	41	●	-	-
Makimura et al.[115]	2008-2010	USA	-	2	-	-	-	-	●	60	Elevated CVD risk	41 (2)	35	1.0‡	0	1.0	97	●	-	-
Masia et al.[116]	2006-2007	Spain	●	2	-	-	-	-	●	68	Elevated CVD risk	52 (11)	10	6.0	4	6.9	99	●	●	-
Mitsuhashi et al.[117]	NR	Japan	-	2	-	-	-	-	●	62	Dysglycemia	63 (7)	35	2.6†	1	2.6	100	-	-	●
Mortazavi et al.[118]	NR	Iran	-	2	-	-	●	-	-	54	Kidney disease	57 (12)	50	0.5‡	1	0.5	96	●	-	-
NTPP[119]	2005-2010	Japan	-	2	-	-	-	●	-	123	Elevated CVD risk	59 (9)	54	3.0‡	0	3.0	79	●	●	-
Nakamura et al. II[120]	2001	Japan	●	2	-	-	-	-	●	50	Kidney disease	53 (7)	40	6.9	8	4.1	100	●	●	-
Ntaios et al.[121]	2005	Greece	●	2	-	-	●	-	-	103	Elevated CVD risk	73 (5)	45	1.5	18	1.5	100	●	-	-
OPAL[122,123]	1997-1999	International	●	3	-	-	-	-	●	866	General population	59 (7)	100	3.1	9	3.7	100	●	●	-
PART-2[124]	NR	New Zealand	-	2	-	●	-	-	-	617	Pre-existing CVD	61 (8)	18	4.7†	150	4.0	87	●	-	-
PEACE[125]	2007-2008	Japan	-	2	-	-	-	●	-	303	Hyperlipidemia	66 (9)	43	1.0‡	2	1.0	74	●	●	-
PERFORM[126,127]	2006-2008	International	-	2	-	-	-	-	●	19120	Pre-existing CVD	67 (8)	37	2.4†	2910	3.0	5	●	-	-
PERIOCARDIO[128]	2010-2012	Australia	●	2	-	-	-	-	●	273	Elevated CVD risk	41 (10)	42	1.0	3	1.4	99	●	●	-
PHOREA[129]	1995-1996	Germany	-	3	-	-	-	-	●	321	General population	59 (4)	100	0.9‡	1	0.9	54	-	●	-
PHYLLIS[130,131]	1995-1997	Italy	-	4	-	●	-	●	-	508	Elevated CVD risk	58 (7)	60	2.6†	6	2.6	82	-	●	-
PLAC II[132-134]	1987-1990	USA	-	2	-	-	-	●	-	151	Elevated CVD risk	63 (NR)	15	3.0‡	14	3.0	100	-	●	-
PPAR[135]	2002-2003	International	-	2	●	-	-	-	-	200	Elevated CVD risk	59 (10)	20	1.0‡	17	1.0	100	-	-	●
PREDIMED[136,137]	2008-2009	Spain	-	3	-	-	●	-	-	7447	Elevated CVD risk	67 (6)	57	4.8	288	2.4	2	●	●	-
PREVEND IT[138-141]	1998-1999	Netherlands	●	2x2	-	●	-	●	-	864	Kidney disease	51 (12)	35	3.9	102	4.7	94	●	-	-
PREVENT[142,143]	1992-1997	International	-	2	-	●	-	-	-	825	Elevated CVD risk	57 (10)	20	3.0‡	196	3.0	46	-	●	●
PROBE[144,145]	2002-2003	Japan	-	2	●	-	-	-	-	587	Dysglycemia	58 (NR)	37	4.0‡	14	3.3	30	●	●	-
RADIANCE I[146,147]	2003-2004	International	●	2	-	-	-	●	-	904	Hyperlipidemia	46 (13)	51	2.0	44	2.3	98	●	●	-
RADIANCE II[147,148]	2004-2006	International	●	2	-	-	-	●	-	752	Hyperlipidemia	57 (8)	36	2.0	37	2.4	98	●	●	-
RAS[149]	2002-2003	Sweden	-	2	●	-	-	-	-	557	Elevated CVD risk	67 (6)	54	1.0‡	5	1.0	80	●	-	-
REGRESS[150,151]	1989-1991	Netherlands	-	2	-	-	-	●	-	885	Elevated CVD risk	56 (8)	0	2.0‡	148	2.0	29	●	-	-
REMOVAL[152,153]	2011-2014	International	-	2	●	-	-	-	-	428	Dysglycemia	56 (9)	41	3.0‡	17	3.0	99	●	●	-
RIS[154]	1987-1989	Sweden	●	2	-	-	-	-	●	164	Elevated CVD risk	66 (5)	0	5.9	47	7.3	99	●	●	-
SANDS[155-157]	2003-2004	USA	-	2	-	-	-	-	●	499	Elevated CVD risk	56 (9)	66	3.0‡	18	3.0	100	●	-	-
SCIMO[158,159]	1992-1994	Germany	-	2	-	-	●	-	-	223	Elevated CVD risk	58 (9)	20	2.0‡	55	2.0	77	-	●	-
SECURE[160]	1994-1995	Canada	●	3x2	-	●	●	-	-	731	Elevated CVD risk	66 (7)	24	4.4	103	5.3	100	-	●	-
SEKONA[161]	2004-2005	Germany	-	2	-	-	-	-	●	600	Elevated CVD risk	49 (6)	11	3.0‡	110	3.0	66	●	-	-
SENDCAP[162]	1990-1993	UK	-	2	-	-	-	●	-	164	Dysglycemia	51 (8)	29	3.0‡	4	3.0	77	-	●	-
SPREAD-A[163,164]	2011-2013	Japan	-	2	●	-	-	-	-	341	Dysglycemia	65 (9)	42	2.0‡	4	2.0	94	●	●	-
SPIKE[165-167]	2012	Japan	-	2	●	-	-	-	-	282	Dysglycemia	64 (7)	40	2.0‡	6	2.0	97	●	●	-
STARR[168]	2001-2003	International	●	2x2	●	●	-	-	-	1320	Dysglycemia	53 (11)	55	4.2	30	4.5	100	●	●	-
STOP-NIDDM[169,170]	1996-1998	Germany	-	2	●	-	-	-	-	1429	Dysglycemia	55 (8)	51	3.3†	47	3.9	8	●	-	-

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

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

Figure Legends

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

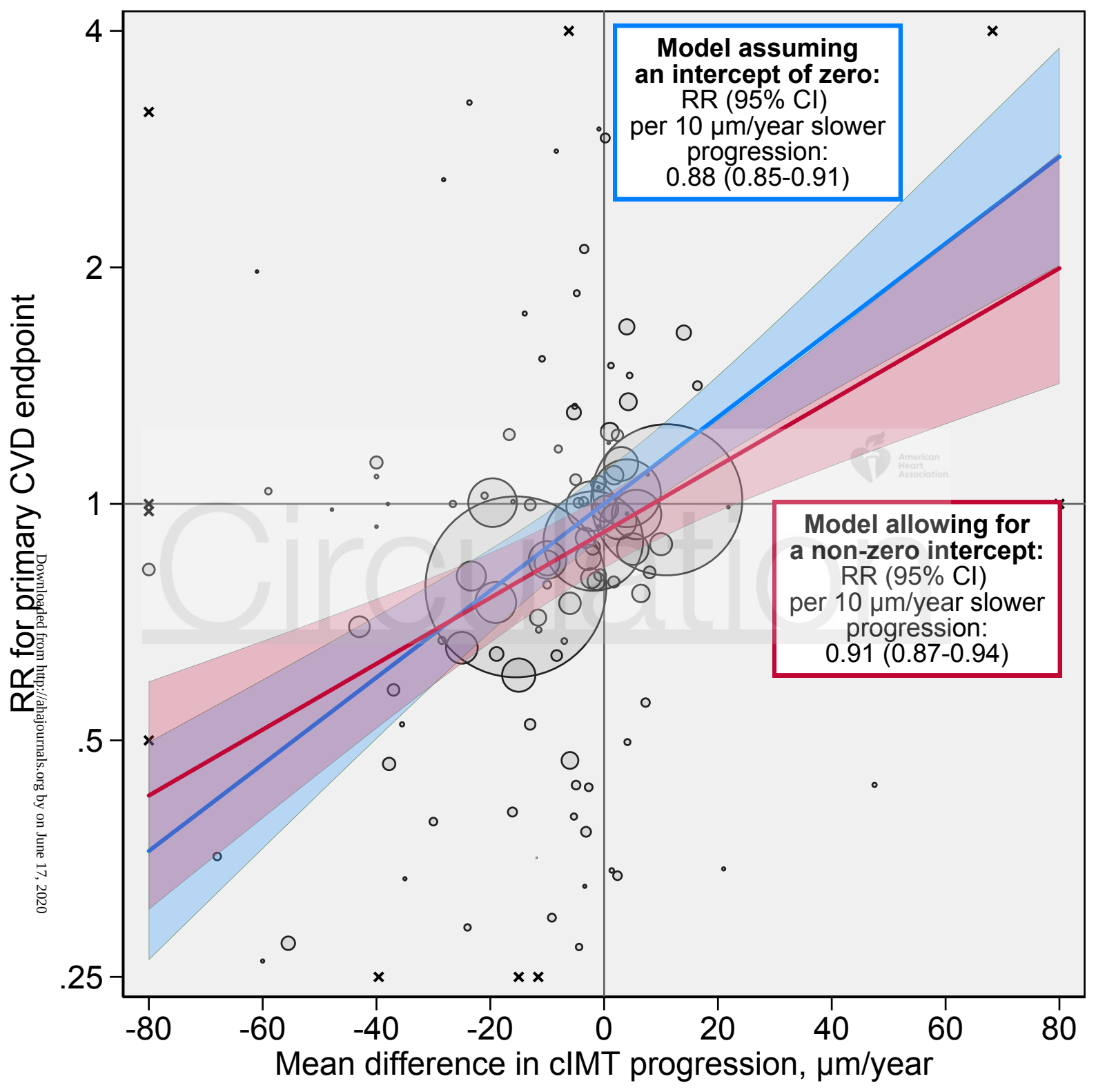
Figure 2. Intervention effects on risk for individual CVD endpoints and all-cause mortality per 10 μm/year slower cIMT progression. *The RRs for intercepts are the effects achieved independent of cIMT progression. Abbreviations: CI=credible interval. cIMT=carotid intima-media thickness. CVD=cardiovascular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

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

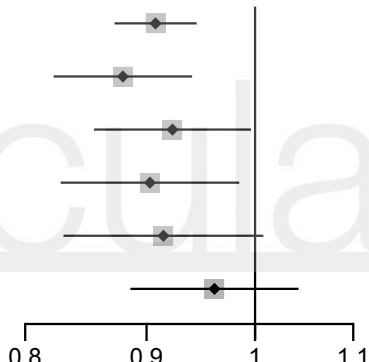
outside of this area are indicated with the symbol x. Abbreviations: cIMT=carotid intima-media thickness. CVD=cardiovascular disease. RR=relative risk.

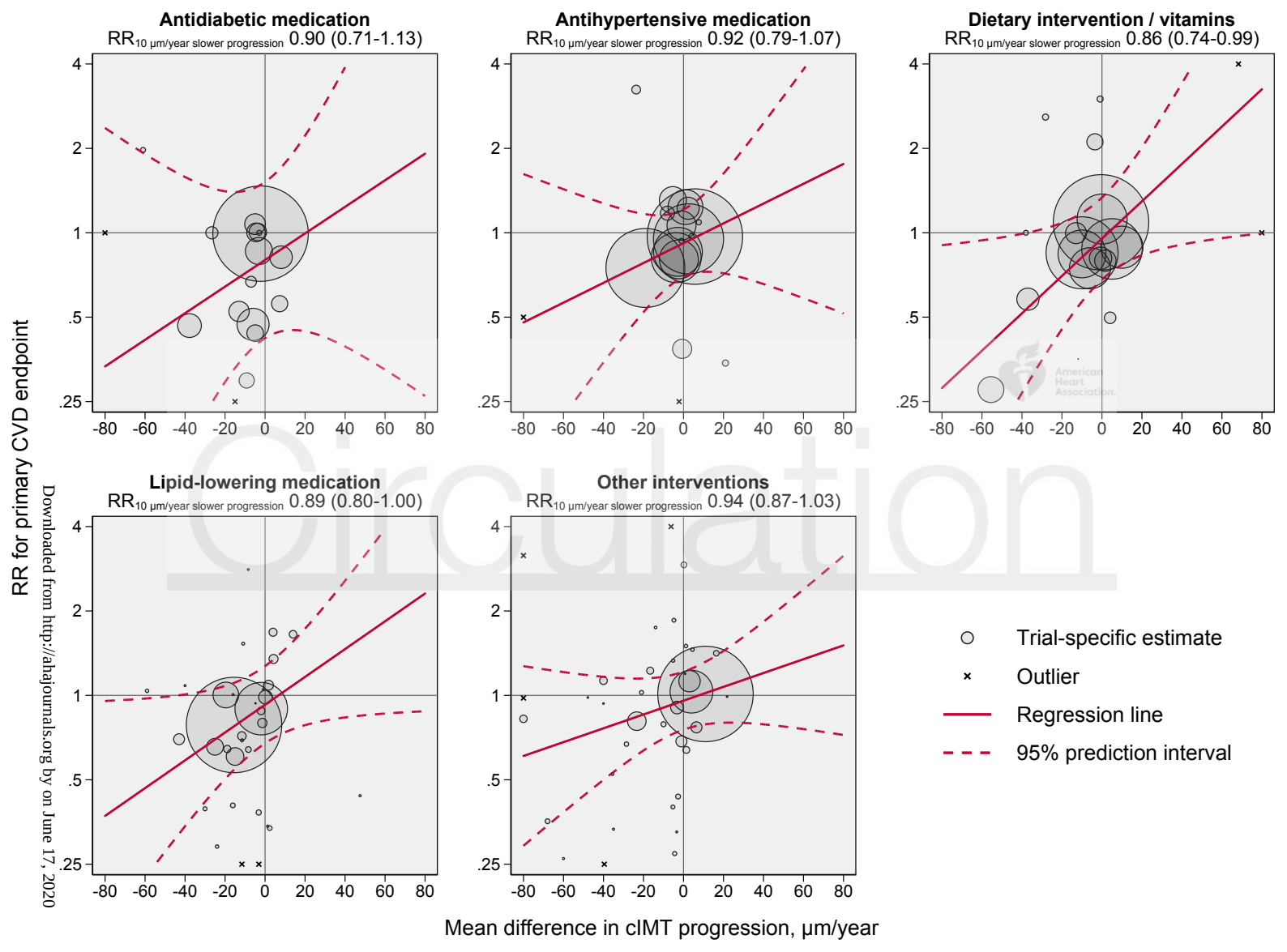
Figure 4. Intervention effects on risk for the primary CVD endpoint per 10 µm/year slower cIMT progression, according to trial characteristics. Abbreviations: CCA-IMT=intima-media thickness of the common-carotid-artery. CI=credible interval. cIMT=carotid intima-media thickness. IPD=individual-participant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

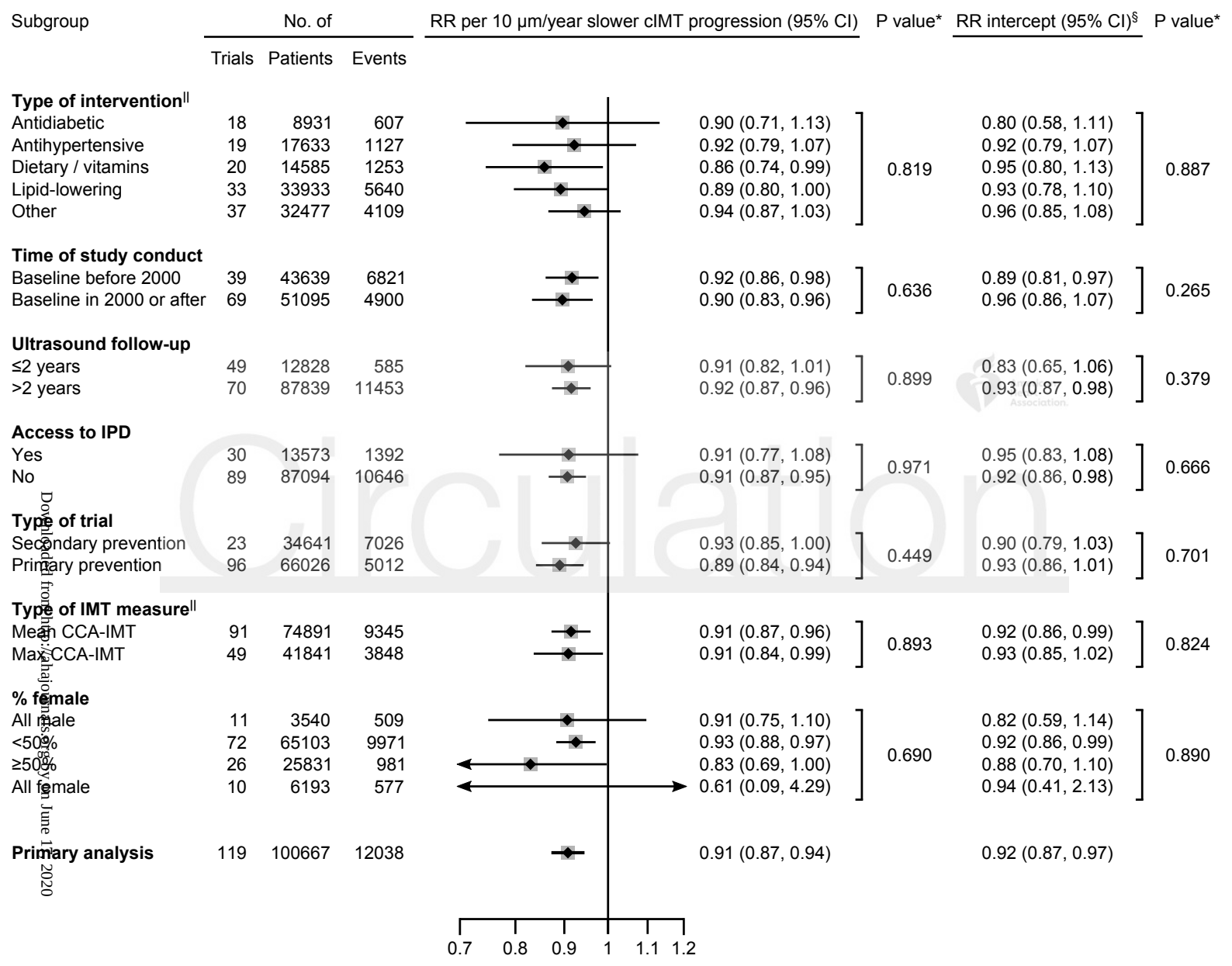
Figure 5. Summary of key findings of our study. Abbreviations: CI=credible interval. cIMT=carotid intima-media thickness. CVD=cardiovascular disease. RCTs= randomized controlled trials.



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







Contributing data

Meta-analysis

International collaboration

119 RCTs

100,667 participants

12,038 incident CVD events

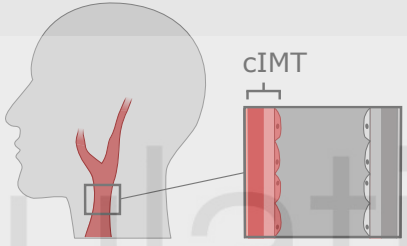
Mean age: 62 years

42% female

Key finding

Intervention effect

cIMT progression



CVD events

Myocardial infarction

Revascularization

Stroke

Fatal CVD

Relative risk for CVD

0.91

(95% CI: 0.87-0.94)

per 10 μm/year reduction of cIMT progression