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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ORIGINAL RESEARCH ARTICLE

Carotid Intima-Media Thickness Progression as Surrogate Marker for Cardiovascular Risk

Meta-Analysis of 119 Clinical Trials Involving 100 667 Patients

Editorial, see p 643

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 used. The primary outcome was a combined CVD end point 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 2 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 end point. Across all interventions, each 10 µm/y 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/y 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), respectively. Results were similar when grouping trials by type of intervention, time of conduct, time to ultrasound follow-up, availability of individual-participant data, primary versus 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.

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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 study 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 end point in future randomized, controlled trials may facilitate and speed up the development and licensing of new therapies.

Carotid intima-media thickness (cIMT), the thickness of the intimal and medial layer of the carotid artery wall, can be measured noninvasively using ultrasound imaging and is considered a marker for the early stage of atherosclerosis.[1] Mean values of cIMT in adults range around 650 to 900 µm and increase—on average—at a rate of 0 to 40 µm/y.[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 on the basis of findings in 7 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 (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis) 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 because of the uncertain validity of the rate of progression of cIMT as a surrogate marker for clinical end points.[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 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: (1) quantify the reduction in CVD risk associated with reducing cIMT progression by therapeutic intervention; (2) explore cIMT progression as a surrogate marker for different types of CVD end points as well as all-cause mortality; and (3) 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 because of legal restrictions arising from the data distribution policy of the PROG-IMT (Individual Progression of Carotid Intima Media Thickness as a Surrogate for Vascular Risk)/Proof-ATHERO (Prospective Studies of Atherosclerosis) 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 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Individual Patient Data) guidelines (Table I in the Data Supplement); the objectives and statistical methods in this paper have been described previously.[12] We identified relevant RCTs published before February 3, 2020, through systematic searches of 10 medical knowledge databases, 6 clinical trial registries, and reference lists of relevant publications and reviews (Table II in the Data Supplement). Trials were eligible for inclusion if they: (1) had assigned patients randomly to 2 or more arms; (2) had applied well-defined inclusion criteria; (3) had measured cIMT at trial baseline and at ≥1 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 were unavailable, 4 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 (ie, 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 end point defined as myocardial infarction, stroke, revascularization procedures (eg, 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 Data Supplement provides details on the assessment of cIMT progression and primary outcome definition in each trial.

Statistical Analysis

We conducted analyses according to a prespecified analysis plan. For factorial trials, we analyzed the intervention contrast anticipated to have the greatest effect on CVD risk. For trials with more than 2 trial arms, we compared the arm that was, based on previous 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 3 steps. First, we quantified intervention effects on cIMT progression. For each trial for which patient-level data were 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 2, plus an intercept and time variable allowed to vary randomly at the patient level. For each trial for which literature-based data were available (ie, 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 because of 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 on the basis of the number of events and patients in each trial arm. For trials in which 1 arm had zero events, the number of events and nonevents 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 2 effects.[14] The principal analysis involved: (1) a model with an intercept of zero (ie, forcing the regression line through the origin and thereby assuming that all the effects on CVD risk operate through cIMT progression), and (2) a model with a nonzero intercept (ie, allowing for an effect on CVD risk independent of cIMT progression). The meta-regression also took into account the within-study correlation of the 2 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 Data Supplement.

Subsidiary analyses evaluated surrogacy for individual disease end points and in trials grouped by intervention type, time of conduct, time to ultrasound follow-up, availability of individual-participant data, primary versus 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 Data 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 prespecified inclusion criteria (Figure I in the Data Supplement). 103 trials (87%) had 2 arms, 7 had 3 arms, 1 had 4 arms, 7 had a 2x2 factorial design, and 1 had a 3x2 factorial design (Table). The trials used antidiabetic (18 trials), antihypertensive (19 trials), dietary/vitamin (20 trials), lipid-lowering (33 trials), 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 end point. 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). 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/y (95% confidence interval, 7.1–11.1) in control arms and +1.0 µm/y (–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 per 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 nonzero intercept, the RR for CVD was 0.91 (0.87–0.94) per 10 µm/y slower cIMT progression, with a further RR of 0.92 (0.87–0.97) achieved independent of cIMT progression. Using the nonzero intercept model, the proportion of variance in the CVD outcome explained by cIMT progression was 98% albeit with a wide 95% CI (71% to 100%). Taken together, we estimated that interventions that reduce cIMT progression by 10, 20, 30, or 40 µm/y 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), respectively.

Owing to presence of effects on CVD risk unexplained by cIMT progression, subsequent analyses focused on the nonzero intercept model. In outcome-specific analyses (Figure 2), RRs per 10 µm/y 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

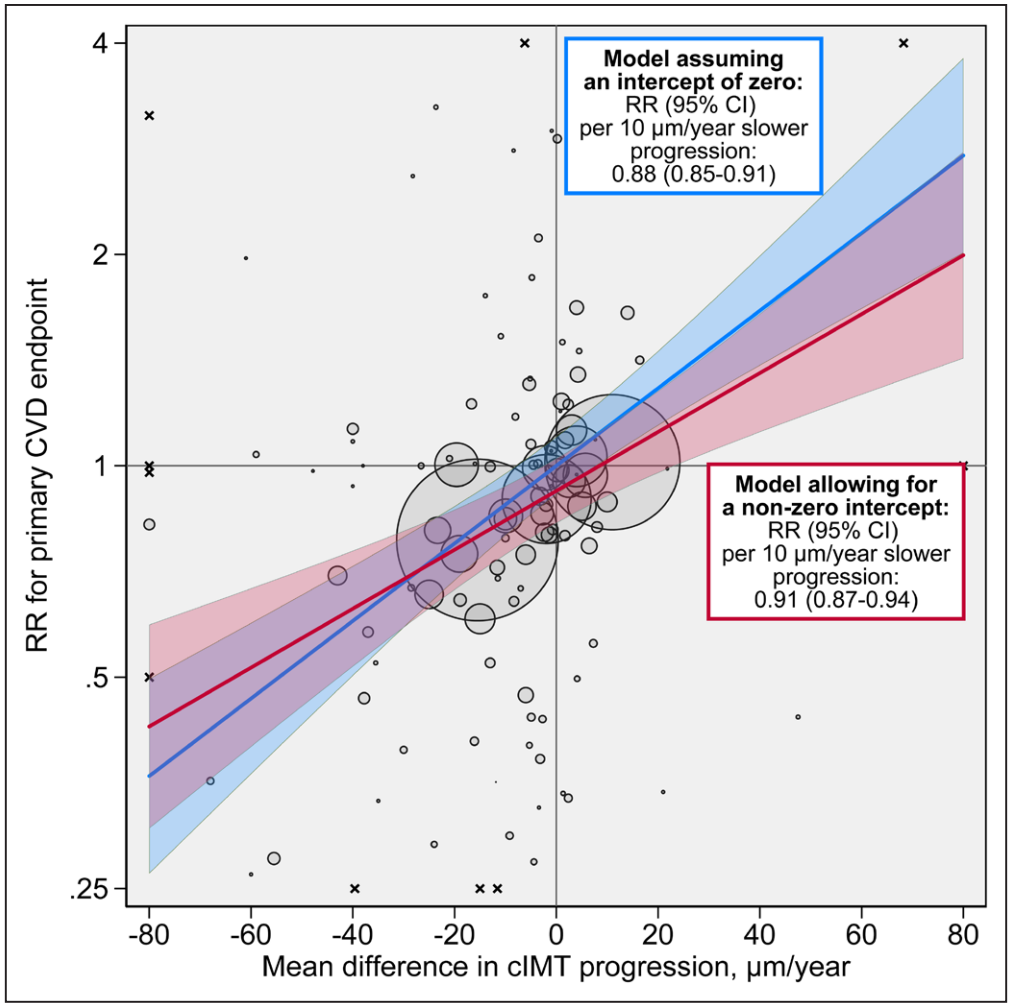

Figure 1. Intervention effects on carotid intima-media thickness progression plotted against intervention effects on risk for the primary cardiovascular disease end point.

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 cardiovascular disease (CVD) end point. 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/y on the horizontal axis and 0.25 to 4 on the vertical axis. CI indicates credible interval; cIMT, carotid intima-media thickness; and RR, relative risk.

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). There was also 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 versus secondary prevention trials, type of cIMT measurements, or proportion of female patients (Figure 4, *P* values for heterogeneity >0.05). In a sensitivity analysis that omitted trials with extreme effect sizes (ie, cIMT progression changes >80 µm/y or RR for CVD <0.25 or >4.0), the RR for CVD per 10 µm/y 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 Data Supplement). Trial-specific estimates are provided in Table IV in the Data 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). To be specific, a 10 µm/y 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 nonzero 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

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

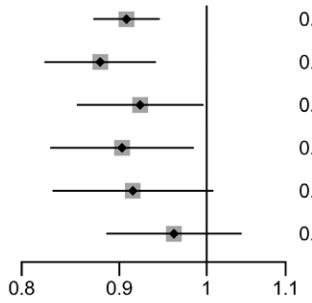

Figure 2. Intervention effects on risk for individual cardiovascular disease end points and all-cause mortality per 10 µm/y slower carotid intima-media thickness progression.

*The relative risks (RRs) for intercepts are the effects achieved independent of carotid intima-media thickness (cIMT) progression. CI indicates credible interval; and CVD, cardiovascular disease.

of disease end points 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

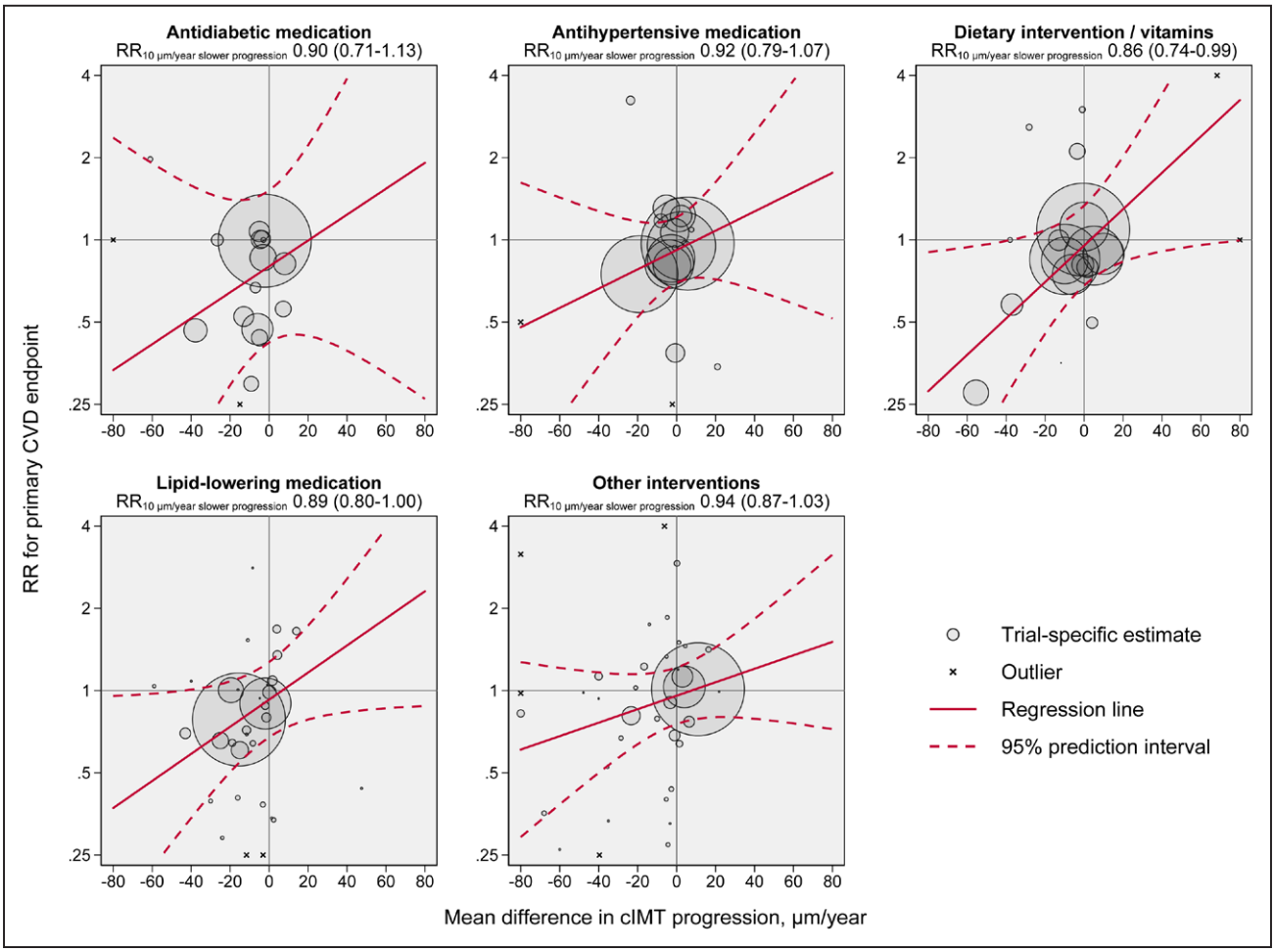

Figure 3. Intervention effects on carotid intima-media thickness progression plotted against intervention effects on risk for the primary cardiovascular disease end point, according to type of intervention.

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 cardiovascular disease (CVD) end point. For purpose of presentation, the graph area was limited to –80 to 80 µm/y 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. cIMT indicates, carotid intima-media thickness; and RR, relative risk.

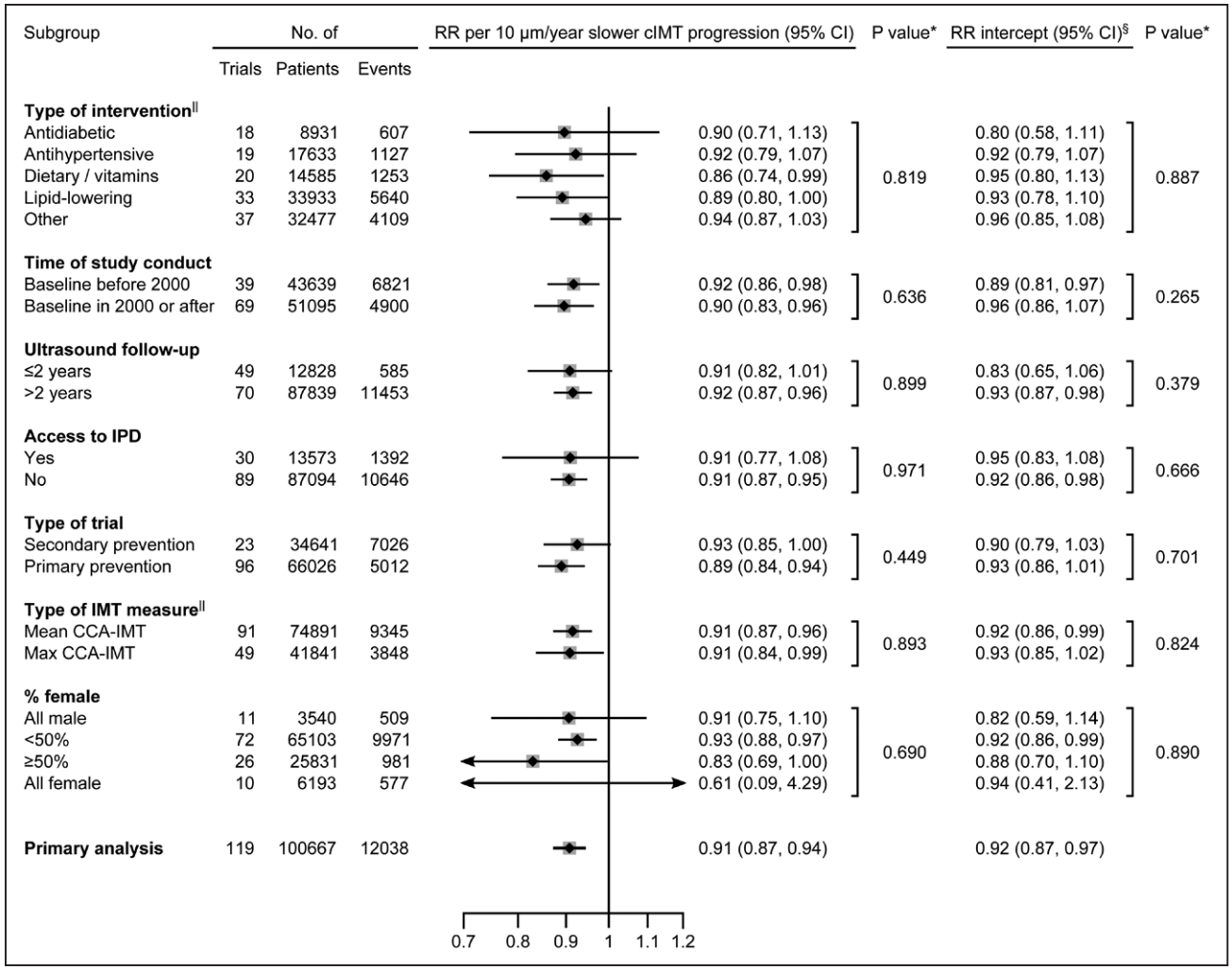

Figure 4. Intervention effects on risk for the primary cardiovascular disease end point per 10 µm/y slower carotid intima-media thickness progression, according to trial characteristics.

**P* values for heterogeneity. §The relative risks (RRs) for intercepts are the effects achieved independent of carotid intima-media thickness (cIMT) progression. ‖Numbers of trials across some subgroups do not sum to 119 because of missing information or contribution of trials to multiple subgroups. CCA-IMT indicates intima-media thickness of the common-carotid-artery; CI, credible interval; and IPD, individual-participant data.

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 because of randomization, trial cohorts might be more homogeneous, and cIMT protocols may be of higher quality in clinical trial settings.

Previous RCT data on cIMT progression as a surrogate marker for CVD risk are limited. Because most RCTs reporting both cIMT and end points (with few exceptions)[63,70,97,127,170] have not been designed as CVD outcome trials and because 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 nonfatal 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 with these earlier reports, our meta-analysis stands out by: (1) exclusively conducting within-trial comparison (thereby upholding the principle of

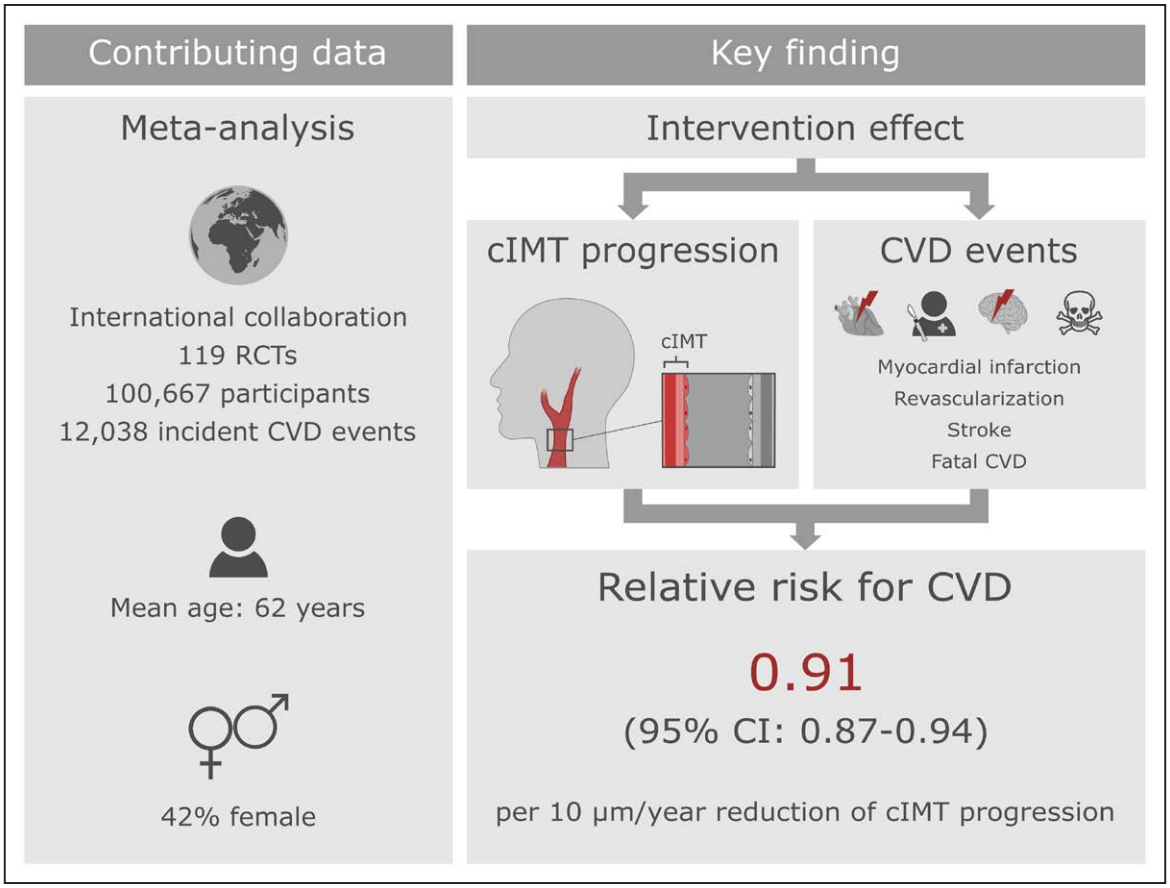

Figure 5. Summary of key findings of our study.
CI indicates credible interval; cIMT, carotid intima-media thickness; CVD, cardiovascular disease; and RCTs, randomized, controlled trials.

randomization); (2) increasing statistical power by involving >5 times as many patients as the previously largest report;[10] (3) enhancing validity by accessing patient-level data of 28 trials; and (4) 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: (1) high correlation with thickness of the vessel wall measured in histological samples;[197] (2) acceptable reproducibility,[198] which was further enhanced by clear recommendations for measurement and technical improvements[199]; (3) close correlation with risk factors and prevalent CVD;[190–192] (4) established correlation with atherosclerosis in other vascular beds;[196] (5) association with occurrence of clinical events;[190–192] (6) the ability to change over time;[2,193] and (7) 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.

It is important that using cIMT progression as a surrogate end point 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 (ie, 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 8600 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/y 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 end point 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 nonzero intercept, in the overall analysis and in

Table 1. Key Features of the Trials Included in This Report

Trial	Years of Baseline	Country	Access to IPD	No. of Trial Arms	Type of Intervention*				
					Anti-Diabetic	Anti-Hypertensive	Dietary / Vitamins	Lipid-Lowering	Other
ACAPS[16,17]	1989–1990	USA	●	2x2	-	-	-	●	●
ACT NOW[18,19]	2004–2006	USA	-	2	●	-	-	-	-
ALLO-IMT[20]	2009–2010	UK	●	2	-	-	-	-	●
AMAR[21]	2004–2005	Russia	-	2	-	-	●	-	-
ARBITER[22]	1999–2001	USA	-	2	-	-	-	●	-
ARBITER 2[23]	2001–2003	USA	-	2	-	-	-	●	-
ARBITER 6-HALTS[6,24,25]	2006–2009	USA	-	2	-	-	-	●	-
ARTSTIFF[26]	2008–2011	International	-	3	-	●	-	-	-
ASAP-FINLAND[27–29]	1994–1995	Finland	-	2	-	-	●	-	-
ASAP-NL[30,31]	1997–1998	Netherlands	-	2	-	-	-	●	-
ASFAST[32]	1998–2000	International	-	2	-	-	●	-	-
ATIC[33,34]	2001–2002	Netherlands	-	2	-	-	-	-	●
Ahn et al[35]	2005–2006	Korea	-	2	-	-	-	-	●
Andrews et al[36,37]	2011–2015	USA	-	2	-	-	-	-	●
BCAPS[38]	1994–1996	Sweden	-	2x2	-	●	-	●	-
BKREGISTRY-II[39]	2000–2003	Korea	●	2	-	-	-	●	-
BVAIT[40]	2000–2006	USA	-	2	-	-	●	-	-
CAIUS[41]	1991–1992	Italy	-	2	-	-	-	●	-
CAMERA[42]	2009–2011	UK	●	2	●	-	-	-	-
CAPPA[43]	2009	Korea	-	2	-	-	-	-	●
CAPTIVATE[44]	2004–2005	International	-	2	-	-	-	●	-
CERDIA[45]	1999–2001	Netherlands	●	2	-	-	-	●	-
CHICAGO[46]	2003–2005	USA	-	2	●	-	-	-	-
CIMT phase 1[47,48]	2008–2009	Denmark	-	2	●	-	-	-	-
CLAS[49–51]	1980–1984	USA	-	2	-	-	-	●	-
CONTRAST[52,53]	2004–2009	Netherlands	●	2	-	-	-	-	●
Cao et al[54]	2008–2011	China	-	2	-	-	●	-	-
DAPC[55,56]	2004–2006	International	-	2	-	-	-	-	●
DAPHNE[57]	NR	Netherlands	-	2	-	●	-	-	-
DOIT[58]	1997–1999	Norway	-	2	-	-	●	-	-
EGE STUDY[59,60]	2005–2006	Turkey	●	2x2	-	-	-	-	●
ELITE (early MP)[61,62]	2005–2008	USA	-	2	-	-	-	-	●
ELITE (late MP)[61,62]	2005–2008	USA	-	2	-	-	-	-	●
ELSA[63]	NR	International	-	2	-	●	-	-	-
ELVA[64]	NR	Sweden	-	2	-	●	-	-	-
ENCORE[65,66]	2003–2008	USA	●	3	-	-	●	-	-
ENHANCE[67]	2002–2004	International	●	2	-	-	-	●	-
EPAT[68]	1994–1998	USA	-	2	-	-	-	-	●
FIELD[69,70]	1998–2000	International	-	2	-	-	-	●	-
FIRST[71,72]	2008–2010	USA	-	2	-	-	-	●	-
FRANCIS[73,74]	2011–2012	Netherlands	-	2	-	-	-	-	●
GRACE[75]	2003–2005	International	●	2x2	●	-	●	-	-

(*Continued*)

Table 1. Continued

No. of Patients	Type of Population	Mean Age (SD), yrs	% Female	CVD Risk		cIMT Progression				
				Median Follow-Up, yrs	No. of Events	Maximum Follow-Up, yrs	% With cIMT data	Mean CCA-IMT	Max CCA-IMT	Other cIMT
919	Elevated CVD risk	62 (8)	48	5.0	18	6.0	100	-	●	-
602	Dysglycemia	52 (10)	58	2.2†	13	4.0	63	●	-	-
80	Preexisting CVD	68 (10)	43	1.0	11	1.2	100	●	●	-
257	Elevated CVD risk	61 (9)	0	2.0‡	21	2.0	76	●	-	-
161	Elevated CVD risk	60 (12)	29	1.0‡	6	1.0	86	●	●	-
167	Preexisting CVD	67 (10)	9	1.0‡	10	1.0	89	●	-	-
363	Preexisting CVD	65 (10)	20	1.2‡	11	1.2	57	●	●	-
133	Hypertension	53 (10)	37	1.0‡	0	1.0	87	●	-	-
520	Hyperlipidemia	60 (6)	51	6.0‡	22	6.0	85	●	-	-
330	Hyperlipidemia	49 (11)	61	2.0‡	5	2.0	85	●	-	-
315	Kidney disease	56 (13)	32	3.3†	73	3.6	77	-	●	-
93	Kidney disease	53 (12)	43	2.0‡	4	1.5	80	●	-	-
130	Preexisting CVD	64 (11)	38	2.0‡	18	2.0	73	-	-	●
80	Kidney disease	57 (12)	20	0.2‡	1	0.2	79	●	-	-
793	Elevated CVD risk	62 (5)	54	3.0†	18	3.0	99	●	-	-
205	Preexisting CVD	60 (10)	32	0.5	3	1.1	59	●	-	-
506	General population	61 (10)	39	3.1†	20	2.5	97	●	-	-
305	Hyperlipidemia	55 (6)	47	3.0‡	5	3.0	100	-	●	-
173	Preexisting CVD	63 (8)	23	1.5	12	2.3	100	●	-	-
420	Dysglycemia	60 (9)	50	3.0‡	6	3.0	99	●	●	-
892	Hyperlipidemia	55 (9)	39	2.0‡	32	1.0	99	-	-	●
250	Dysglycemia	58 (11)	53	2.1	14	2.5	99	●	●	-
462	Dysglycemia	60 (8)	37	1.4‡	13	1.4	78	●	●	-
412	Dysglycemia	61 (9)	32	1.5‡	20	1.5	100	●	●	-
162	Preexisting CVD	54 (5)	0	7.0†	82	4.0	48	●	-	-
714	Kidney disease	64 (14)	38	2.4	173	3.1	20	●	●	-
287	Elevated CVD risk	71 (13)	53	2.0‡	36	2.0	100	-	-	●
329	Dysglycemia	64 (7)	48	2.0‡	3	2.0	90	●	●	-
80	Preexisting CVD	59 (7)	0	3.0‡	16	3.0	100	-	-	●
561	Elevated CVD risk	70 (5)	0	3.0‡	63	3.0	83	●	-	-
644	Kidney disease	59 (14)	46	3.0	60	3.0	100	●	-	-
271	General population	55 (4)	100	5.0	1	5.0	92	●	-	-
372	General population	65 (6)	100	5.0	5	5.0	94	●	-	-
2334	Hypertension	56 (7)	45	4.0‡	60	4.0	87	-	-	●
129	Hyperlipidemia	60 (10)	49	3.0‡	4	3.0	71	●	-	-
144	Elevated CVD risk	52 (10)	67	0.4	1	1.1	98	●	-	-
720	Hyperlipidemia	47 (9)	49	2.0	52	2.3	100	●	●	-
222	Hyperlipidemia	61 (7)	100	2.0‡	7	2.0	90	●	-	-
9795	Dysglycemia	62 (7)	37	6.0‡	1295	5.0	2	-	●	-
682	Preexisting CVD	61 (9)	32	2.1‡	30	2.0	84	-	●	-
320	Elevated CVD risk	53 (11)	70	5.0‡	9	5.0	100	●	-	-
1189	Dysglycemia	63 (8)	36	5.8	374	5.1	100	●	●	-

(*Continued*)

Table 1. Continued

Trial	Years of Baseline	Country	Access to IPD	No. of Trial Arms	Type of Intervention*				
					Anti-Diabetic	Anti-Hypertensive	Dietary / Vitamins	Lipid-Lowering	Other
Gresele et al[76]	2003–2005	International	●	2	-	-	-	-	●
HART[77]	1999–2000	International	●	2	-	-	●	-	-
HERS[78,79]	1993–1994	USA	-	2	-	-	-	-	●
HYRIM[80]	1997–1999	Norway	●	2x2	-	-	-	●	●
INSIGHT[81–83]	1994–1996	France	-	2	-	●	-	-	-
J-STARS[84–88]	2004–2009	Japan	-	2	-	-	-	●	-
JART[89]	2008–2010	Japan	-	2	-	-	-	●	-
KAPS[90]	1984–1989	Finland	-	2	-	-	-	●	-
KEEPS[91]	2005–2008	USA	-	3	-	-	-	-	●
KIMVASC[92]	2011–2012	UK	●	2	-	-	●	-	-
Katakami et al[93]	1998	Japan	-	3	●	-	-	-	-
Koyasu et al[94]	2006–2008	Japan	-	2	●	-	-	-	-
LAARS[95]	NR	International	-	2	-	●	-	-	-
LIFE-ICARUS[96]	1996–1997	International	●	2	-	●	-	-	-
LIPID[97–100]	1990–1992	International	-	2	-	-	-	●	-
Luijendijk et al[101,102]	2007–2009	Netherlands	-	2	-	-	-	●	-
MARS[103,104]	1985–1989	USA	-	2	-	-	-	●	-
MAVET[105]	1994–1995	Australia	-	2	-	-	●	-	-
MECANO[106,107]	2005–2006	Netherlands	-	2	-	-	-	-	●
MEDICLAS[108,109]	2003–2005	Netherlands	●	2	-	-	-	-	●
METEOR[110]	2002–2004	International	-	2	-	-	-	●	-
MG600[111]	2010–2011	Brazil	●	2	-	-	●	-	-
MIDAS[112]	NR	USA	-	2	-	●	-	-	-
MITEC[113,114]	2000–2002	France	-	2	-	●	-	-	-
Makimura et al[115]	2008–2010	USA	-	2	-	-	-	-	●
Masia et al[116]	2006–2007	Spain	●	2	-	-	-	-	●
Mitsuhashi et al[117]	NR	Japan	-	2	-	-	-	-	●
Mortazavi et al[118]	NR	Iran	-	2	-	-	●	-	-
NTPP[119]	2005–2010	Japan	-	2	-	-	-	●	-
Nakamura et al II[120]	2001	Japan	●	2	-	-	-	-	●
Ntaios et al[121]	2005	Greece	●	2	-	-	●	-	-
OPAL[122,123]	1997–1999	International	●	3	-	-	-	-	●
PART-2[124]	NR	New Zealand	-	2	-	●	-	-	-
PEACE[125]	2007–2008	Japan	-	2	-	-	-	●	-
PERFORM[126,127]	2006–2008	International	-	2	-	-	-	-	●
PERIOCARDIO[128]	2010–2012	Australia	●	2	-	-	-	-	●
PHOREA[129]	1995–1996	Germany	-	3	-	-	-	-	●
PHYLLIS[130,131]	1995–1997	Italy	-	4	-	●	-	●	-
PLAC II[132–134]	1987–1990	USA	-	2	-	-	-	●	-
PPAR[135]	2002–2003	International	-	2	●	-	-	-	-
PREDIMED[136,137]	2008–2009	Spain	-	3	-	-	●	-	-

(*Continued*)

Table 1. Continued

No. of Patients	Type of Population	Mean Age (SD), yrs	% Female	CVD Risk		cIMT Progression				
				Median Follow-Up, yrs	No. of Events	Maximum Follow-Up, yrs	% With cIMT data	Mean CCA-IMT	Max CCA-IMT	Other cIMT
442	Preexisting CVD	67 (9)	21	0.6	8	0.6	57	●	●	-
925	Preexisting CVD	69 (7)	24	5.0	152	5.6	100	●	●	-
2763	General population	67 (7)	100	4.1†	552	4.7	16	-	●	-
568	Hypertension	57 (9)	0	4.1	47	4.6	99	-	●	-
6321	Elevated CVD risk	65 (7)	54	3.5†	347	4.0	5	●	-	-
1589	Preexisting CVD	66 (8)	31	4.9†	290	5.0	50	●	-	-
348	Hyperlipidemia	64 (9)	51	2.0‡	9	2.0	40	●	●	-
447	Hyperlipidemia	57 (4)	0	3.0‡	28	3.0	95	-	●	-
727	General population	53 (3)	100	4.0‡	1	4.0	100	●	-	-
80	Preexisting CVD	77 (5)	45	0.5	1	0.5	99	●	-	-
159	Dysglycemia	61 (9)	51	3.3†	0	3.3	74	-	-	●
90	Preexisting CVD	66 (8)	9	1.0‡	0	1.0	90	-	●	-
280	Hypertension	59 (9)	50	2.0‡	0	2.0	72	●	-	-
83	Hypertension	67 (6)	27	4.9	8	3.1	98	●	-	-
9014	Preexisting CVD	61 (8)	17	6.1†	3229	4.0	4	●	-	-
155	Preexisting CVD	36 (12)	38	3.3†	0	4.4	100	●	-	-
270	Hyperlipidemia	58 (7)	9	2.2†	54	4.0	27	●	-	-
409	Elevated CVD risk	64 (6)	55	4.0‡	6	4.0	81	-	●	-
185	Kidney disease	51 (13)	36	1.5‡	6	2.0	88	●	-	-
48	Elevated CVD risk	42 (10)	0	3.0	1	3.2	77	●	-	-
984	Elevated CVD risk	57 (6)	40	2.0‡	3	2.0	89	●	●	-
35	Hypertension	55 (7)	100	0.5	0	0.5	100	●	●	-
883	Hypertension	59 (9)	22	3.0‡	47	3.0	100	-	●	-
209	Elevated CVD risk	60 (8)	36	3.0‡	0	3.0	41	●	-	-
60	Elevated CVD risk	41 (2)	35	1.0‡	0	1.0	97	●	-	-
68	Elevated CVD risk	52 (11)	10	6.0	4	6.9	99	●	●	-
62	Dysglycemia	63 (7)	35	2.6†	1	2.6	100	-	-	●
54	Kidney disease	57 (12)	50	0.5‡	1	0.5	96	●	-	-
123	Elevated CVD risk	59 (9)	54	3.0‡	0	3.0	79	●	●	-
50	Kidney disease	53 (7)	40	6.9	8	4.1	100	●	●	-
103	Elevated CVD risk	73 (5)	45	1.5	18	1.5	100	●	-	-
866	General population	59 (7)	100	3.1	9	3.7	100	●	●	-
617	Preexisting CVD	61 (8)	18	4.7†	150	4.0	87	●	-	-
303	Hyperlipidemia	66 (9)	43	1.0‡	2	1.0	74	●	●	-
19 120	Preexisting CVD	67 (8)	37	2.4†	2910	3.0	5	●	-	-
273	Elevated CVD risk	41 (10)	42	1.0	3	1.4	99	●	●	-
321	General population	59 (4)	100	0.9‡	1	0.9	54	-	●	-
508	Elevated CVD risk	58 (7)	60	2.6†	6	2.6	82	-	●	-
151	Elevated CVD risk	63 (NR)	15	3.0‡	14	3.0	100	-	●	-
200	Elevated CVD risk	59 (10)	20	1.0‡	17	1.0	100	-	-	●
7447	Elevated CVD risk	67 (6)	57	4.8	288	2.4	2	●	●	-

(*Continued*)

Table 1. Continued

Trial	Years of Baseline	Country	Access to IPD	No. of Trial Arms	Type of Intervention*				
					Anti-Diabetic	Anti-Hypertensive	Dietary / Vitamins	Lipid-Lowering	Other
PREVEND IT[138–141]	1998–1999	Netherlands	●	2x2	-	●	-	●	-
PREVENT[142,143]	1992–1997	International	-	2	-	●	-	-	-
PROBE[144,145]	2002–2003	Japan	-	2	●	-	-	-	-
RADIANCE I[146,147]	2003–2004	International	●	2	-	-	-	●	-
RADIANCE II[147,148]	2004–2006	International	●	2	-	-	-	●	-
RAS[149]	2002–2003	Sweden	-	2	●	-	-	-	-
REGRESS[150,151]	1989–1991	Netherlands	-	2	-	-	-	●	-
REMOVAL[152,153]	2011–2014	International	-	2	●	-	-	-	-
RIS[154]	1987–1989	Sweden	●	2	-	-	-	-	●
SANDS[155–157]	2003–2004	USA	-	2	-	-	-	-	●
SCIMO[158,159]	1992–1994	Germany	-	2	-	-	●	-	-
SECURE[160]	1994–1995	Canada	●	3x2	-	●	●	-	-
SEKONA[161]	2004–2005	Germany	-	2	-	-	-	-	●
SENDCAP[162]	1990–1993	UK	-	2	-	-	-	●	-
SPEAD-A[163,164]	2011–2013	Japan	-	2	●	-	-	-	-
SPIKE[165–167]	2012	Japan	-	2	●	-	-	-	-
STARR[168]	2001–2003	International	●	2x2	●	●	-	-	-
STOP-NIDDM[169,170]	1996–1998	Germany	-	2	●	-	-	-	-
Safarova et al[171]	2007–2009	Russia	●	2	-	-	-	●	-
Sander et al (Cp neg)[172,173]	1995–1998	Germany	-	2	-	-	-	-	●
Sander et al (Cp pos)[172,173]	1995–1998	Germany	-	2	-	-	-	-	●
Spring et al[174]	NR	Switzerland	-	2	-	-	-	●	-
Stanley et al[175]	2011–2013	USA	-	2	-	-	-	-	●
Stanton et al[176]	NR	UK	-	2	-	●	-	-	-
TART[177]	1997–1998	USA	-	2	●	-	-	-	-
TEAAM[178]	2004–2009	USA	-	2	-	-	-	-	●
TRIPOD[179]	1995–1998	USA	-	2	●	-	-	-	-
Tasic et al[180]	NR	Serbia	-	2	-	●	-	-	-
VEAPS[181]	1996–1999	USA	-	2	-	-	●	-	-
VHAS[182,183]	NR	Italy	-	2	-	●	-	-	-
VIP[184]	2005–2007	Netherlands	-	2	-	-	-	-	●
VITAL[185]	2002–2004	Netherlands	●	2	-	-	-	-	●
WISH[186]	2004–2007	USA	-	2	-	-	●	-	-
Yang et al[187]	2013–2017	China	-	2	-	-	-	-	●
Yun et al[188]	2010–2013	China	-	2	●	-	-	-	-
Zou et al[189]	2010	China	-	2	-	-	●	-	-
Total: 119 trials	1980–2017		30		18	19	20	33	37

(*Continued*)

Table 1. Continued

No. of Patients	Type of Population	Mean Age (SD), yrs	% Female	CVD Risk		cIMT Progression				
				Median Follow-Up, yrs	No. of Events	Maximum Follow-Up, yrs	% With cIMT data	Mean CCA-IMT	Max CCA-IMT	Other cIMT
864	Kidney disease	51 (12)	35	3.9	102	4.7	94	●	-	-
825	Elevated CVD risk	57 (10)	20	3.0‡	196	3.0	46	-	●	●
587	Dysglycemia	58 (NR)	37	4.0‡	14	3.3	30	●	●	-
904	Hyperlipidemia	46 (13)	51	2.0	44	2.3	98	●	●	-
752	Hyperlipidemia	57 (8)	36	2.0	37	2.4	98	●	●	-
557	Elevated CVD risk	67 (6)	54	1.0‡	5	1.0	80	●	-	-
885	Elevated CVD risk	56 (8)	0	2.0‡	148	2.0	29	●	-	-
428	Dysglycemia	56 (9)	41	3.0‡	17	3.0	99	●	●	-
164	Elevated CVD risk	66 (5)	0	5.9	47	7.3	99	●	●	-
499	Elevated CVD risk	56 (9)	66	3.0‡	18	3.0	100	●	-	-
223	Elevated CVD risk	58 (9)	20	2.0‡	55	2.0	77	-	●	-
731	Elevated CVD risk	66 (7)	24	4.4	103	5.3	100	-	●	-
600	Elevated CVD risk	49 (6)	11	3.0‡	110	3.0	66	●	-	-
164	Dysglycemia	51 (8)	29	3.0‡	4	3.0	77	-	●	-
341	Dysglycemia	65 (9)	42	2.0‡	4	2.0	94	●	●	-
282	Dysglycemia	64 (7)	40	2.0‡	6	2.0	97	●	●	-
1320	Dysglycemia	53 (11)	55	4.2	30	4.5	100	●	●	-
1429	Dysglycemia	55 (8)	51	3.3†	47	3.9	8	●	-	-
60	Preexisting CVD	55 (6)	0	3.0	40	2.8	100	●	-	-
147	Preexisting CVD	64 (12)	44	3.0‡	9	2.0	100	●	-	-
125	Preexisting CVD	65 (14)	43	3.0‡	19	2.0	100	●	-	-
100	Preexisting CVD	67 (11)	22	0.5‡	2	0.5	89	●	-	-
50	Elevated CVD risk	51 (7)	16	0.5‡	1	0.5	86	●	-	-
69	Hypertension	48 (11)	41	1.0‡	1	1.0	80	●	-	-
299	Dysglycemia	52 (9)	66	2.0	12	2.0	92	●	-	-
308	General population	68 (5)	0	3.0‡	16	3.0	99	●	-	-
266	Dysglycemia	34 (7)	100	2.9	0	4.0	72	●	-	-
40	Hypertension	64 (9)	35	0.8‡	6	0.8	100	●	-	-
353	Hyperlipidemia	56 (9)	52	3.0†	18	3.0	94	●	-	-
1414	Hypertension	54 (7)	51	2.0‡	33	4.0	27	-	-	●
119	Kidney disease	53 (12)	33	3.0‡	10	3.0	86	●	-	-
199	Elevated CVD risk	49 (12)	41	1.5	12	2.5	99	●	-	-
350	General population	61 (7)	100	2.7	1	3.0	93	●	-	-
119	Elevated CVD risk	54 (11)	72	0.5‡	0	0.5	100	-	-	●
135	Preexisting CVD	62 (5)	40	2.3†	23	4.5	93	●	-	-
96	Elevated CVD risk	57 (5)	59	1.0‡	0	1.0	89	●	-	-
100 667		62 (8)	41.9	3.7	12 038	3.5	90	91	49	11

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

all subgroups of trials investigated. The nonzero 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 end point 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 nonzero intercept. Alternative pathways have been described for many major cardiovascular substance groups, including lipid-lowering medications (eg, statins,[1,201,202] fibrates,[203] niacin,[204] resins,[205] and omega-3 fatty acids[206]), antidiabetic medications (eg, AMP-activated protein kinase activators,[207] thiazolidinediones,[207] dipeptidyl peptidase–4 inhibitors,[207,208] glucagon-like peptide–1 receptor agonists,[207,208] sodium-glucose transport protein–2 inhibitors[208]), or antihypertensive medications (eg, β-blockers,[209] calcium channel-inhibitors,[210,211] angiotensin-II antagonists,[212] angiotensin-converting enzyme 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 upheld randomization within trials, allowed for between-trials heterogeneity, made 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. Whereas sensitivity analysis revealed no evidence for differential effects in the setting of primary versus secondary prevention trials, further study is needed on specific trial populations, such as patients with diabetes mellitus or chronic kidney disease. Third, the definition of the primary combined CVD end point varied across the included trials. However, the differences were relatively minor (see Table III in the Data Supplement), so we are confident that this does not constitute a major source of systematic bias. Last, while ultrasound scanning protocols may have differed across contributing trials, in particular those 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.

ARTICLE INFORMATION

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Supplemental Materials

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