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# Does Carotid Intima-Media Thickness Regression Predict Reduction of Cardiovascular Events?

## A Meta-Analysis of 41 Randomized Trials

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**Objectives** The purpose of this study was to verify whether intima-media thickness (IMT) regression is associated with reduced incidence of cardiovascular events.

**Background** Carotid IMT increase is associated with a raised risk of coronary heart disease (CHD) and cerebrovascular (CBV) events. However, it is undetermined whether favorable changes of IMT reflect prognostic benefits.

**Methods** The MEDLINE database and the Cochrane Database were searched for articles published until August 2009. All randomized trials assessing carotid IMT at baseline, at end of follow-up, and reporting clinical end points were included. A weighted random-effects meta-regression analysis was performed to test the relationship between mean and maximum IMT changes and outcomes. The influence of baseline patients' characteristics, cardiovascular risk profile, IMT at baseline, follow-up, and quality of the trials was also explored. Overall estimates of effect were calculated with a fixed-effects model, random-effects model, or Peto method.

**Results** Forty-one trials enrolling 18,307 participants were included. Despite significant reduction in CHD, CBV events, and all-cause death induced by active treatments (for CHD events, odds ratio [OR]: 0.82, 95% confidence interval [CI]: 0.69 to 0.96, $p = 0.02$; for CBV events, OR: 0.71, 95% CI: 0.51 to 1.00, $p = 0.05$; and for all-cause death, OR: 0.71, 95% CI: 0.53 to 0.96, $p = 0.03$), there was no significant relationship between IMT regression and CHD events ($tau^2$ 0.91, $p = 0.37$), CBV events ($tau^2 -0.32$, $p = 0.75$), and all-cause death ($tau^2 -0.41$, $p = 0.69$). In addition, subjects' baseline characteristics, cardiovascular risk profile, IMT at baseline, follow-up, and quality of the trials did not significantly influence the association between IMT changes and clinical outcomes.

**Conclusions** Regression or slowed progression of carotid IMT, induced by cardiovascular drug therapies, do not reflect reduction in cardiovascular events. (J Am Coll Cardiol 2010;56:2006–20) © 2010 by the American College of Cardiology Foundation

Carotid intima-media thickness (IMT) increase predicts the risk of cardiovascular events (1), with relatively stronger prognostic power for cerebral as compared with coronary vascular events (2). In fact, increased IMT is considered to represent a manifestation of subclinical atherosclerosis, and, therefore, it has been included in the list of organ damage conditions in the European hypertension guidelines (3) and in the European prevention guidelines (4). The lack of invasiveness and repeatability makes IMT measurement an attractive biomarker, potentially useful as a therapeutic target in subjects at increased cardiovascular risk (5). Therefore, IMT changes (either regression or slowed progression) have been employed as surrogate clinical end points in several randomized clinical studies using lipid-lowering (Online Appendix references 1–21), antihypertensive (Online Appendix references 6,22–28), oral antidiabetic (Online Appendix references 23,29–31), and antioxidant drugs (Online Appendix references 32–35) in subjects at intermediate to high cardiovascular risk.

However, although clinical events were generally reported in these trials, none of them was designed to verify whether changes in IMT are associated with consistent changes in the cardiovascular subjects' risk profile (6). Yet, this information would be relevant for the interpretation of IMT variations as surrogate clinical end points and use as therapeutic targets for monitoring and optimization of cardiovascular therapies in several categories of subjects at increased cardiovascular risk (5,7).

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Therefore, the aim of the present study was to assess, using a meta-regression analysis of all available randomized trials, whether reduced progression or regression of IMT is associated with reduced incidence of major cardiovascular events in subjects at intermediate to high cardiovascular risk.

## Methods

**Search strategy and data extraction.** This study was designed according to the QUOROM (Quality of Reporting Meta-analyses) statement (8). Inclusion criteria for a study to be included were as follows: evaluation of carotid IMT at baseline and at end of follow-up; report of major clinical cardiovascular end points (coronary heart disease events [CHD] including acute coronary syndrome, CHD death, revascularization, angina pectoris; cerebrovascular [CBV] events, including transient ischemic attack and stroke, or all-cause death); comparison of active drug treatments or of an active drug versus placebo, or of different doses of active drugs; and randomized protocol design. Observational studies without longitudinal follow-up and cross-sectional studies were excluded.

The MEDLINE database, the Cochrane database, and the ISI Web of Science were searched for articles published in English and other languages until August 2009. Studies were identified through PubMed searches of the MEDLINE database with the following headings: IMT, carotid atherosclerosis, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-COA) reductase inhibitor, statin, lipid lowering, fibrate, nicotinic acid, a:cholesterol acyltransferase (ACAT) inhibitor, cholesteryl-ester transfer protein (CETP) inhibitor, diet, life-style, antihypertensive, angiotensin-converting enzyme (ACE) inhibitor, calcium-channel blocker, angiotensin-receptor blocker, antidiabetic agent, insulin, diuretic, beta-blocker, alpha-antagonist, randomly, random, randomized controlled trials, atherosclerosis. We searched reference lists of the retrieved articles to identify other eligible studies, and information from colleagues was used to identify more recently published articles.

**Abbreviations and Acronyms**

CBV = cerebrovascular
CHD = coronary heart disease
CI = confidence interval
IMT = intima-media thickness
LDL = low-density lipoprotein
OR = odds ratio

Two reviewers independently selected potentially eligible trials according to fulfillment of inclusion criteria. Selected trials were compared, and any discrepancies were resolved by discussion and consensus. Two reviewers independently read the full text of retained studies and included trials that met the inclusion criteria. Articles finally selected for the review were checked to avoid inclusion of data published in duplicate. Data on baseline characteristics, presence of diabetes mellitus, hypertension, smoking, carotid IMT measurement at baseline and end follow-up, lipid serum level, outcomes as all-cause mortality and CHD and CBV events were abstracted. We also calculated for each trial a composite outcome including CHD and CBV events; a cardiovascular hard event outcome including acute coronary syndrome, cardiac death, and stroke; and a cardiovascular soft event outcome including stable angina, coronary revascularization, heart failure hospitalization, and transient ischemic attack. When a potentially eligible trial was retrieved, but the paper lacked essential information to be included in the analysis (i.e., number of

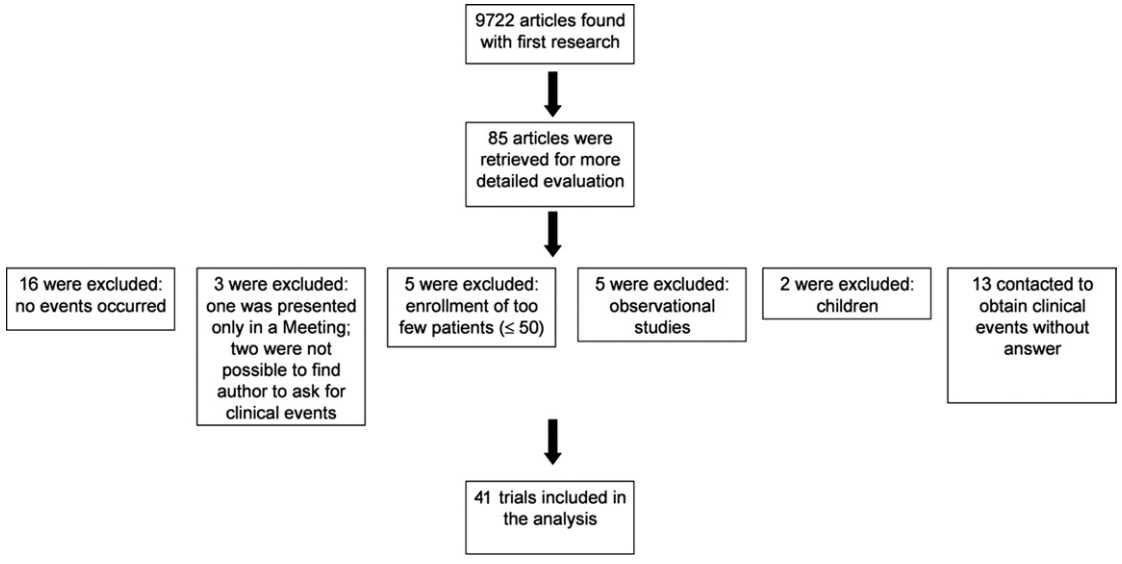


**Figure 1** Meta-Analysis Flow Chart

Flow chart showing the progress through the stages of the meta-analysis.

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**Table 1** Baseline Characteristics of Trials Included in Overview

| Trial Name/ First Author | Year | Treatment Category | Treatment | Control | Population Intervention | Age (yrs) | Treatment (n) | Control (n) |
|---|---|---|---|---|---|---|---|---|
| ACAPS | 1994 | Lipid lowering | Lovastatin | Placebo | Primary | 62 | 460 | 459 |
| Angerer et al. | 2001 | Antioxidants | Fish oil/PUFA | Placebo | Secondary | 58 | 87 | 84 |
| ARBITER | 2002 | Lipid lowering | Atorvastatin | Pravastatin | Secondary | 60 | 79 | 82 |
| ARBITER 2 | 2004 | Lipid lowering | Niacin+statin | Statin | Secondary | 67 | 87 | 80 |
| ASAP | 2001 | Lipid lowering | Atorvastatin | Simvastatin | Secondary | 48 | 160 | 165 |
| ASFAST | 2006 | Antioxidants | Folic acid/vitamin B12 | Placebo | Secondary | 56 | 156 | 159 |
| ATIC | 2007 | Lipid lowering | Pravastatin | Placebo | Secondary | 53 | 47 | 46 |
| BCAPS statin only | 2001 | Lipid lowering | Fluvastatin | Placebo | Primary | 62 | 395 | 398 |
| BCAPS statin+ beta-blocker | 2001 | Anti-HTN | Metoprolol | Placebo | Primary | 62 | 396 | 397 |
| Beishuizien et al. | 2004 | Lipid lowering | Cerivastatin | Placebo | Primary | 59 | 125 | 125 |
| BVAIT | 2009 | Antioxidants | Folic acid/vitamin B12 | Placebo | Primary | 61 | 254 | 252 |
| CAIUS | 1996 | Lipid lowering | Pravastatin | Placebo | Primary | 55 | 151 | 154 |
| CAPTIVATE | 2009 | Lipid lowering | Pactimibe+statin | Statin | Secondary | 55 | 443 | 438 |
| DAPHNE | 2002 | Anti-HTN | Doxazosin | HCT | Secondary | 59 | 41 | 39 |
| ELSA | 2002 | Anti-HTN | Lacidipine | Atenolol | Primary | 56 | 755 | 764 |
| ENHANCE | 2008 | Lipid lowering | Simvastatin+ezetimibe | Simvastatin | Primary | 46 | 357 | 363 |
| EPAT | 2001 | Other | Estradiol | Placebo | Primary | 61 | 97 | 102 |
| FAST | 2002 | Lipid lowering | Pravastatin | Placebo | Primary | 66 | 83 | 163 |
| FIELD | 2008 | Lipid lowering | Fenofibrate | Placebo | Secondary | 62 | 87 | 83 |
| Hodis et al. | 2006 | Oral antidiabetics | Troglitazone | Placebo | Primary | 53 | 142 | 134 |
| HYRIM | 2004 | Lipid lowering | Fluvastatin | Placebo | Primary | 57 | 142 | 143 |
| KAPS | 1995 | Lipid lowering | Pravastatin | Placebo | Primary | 57 | 224 | 223 |
| Mazzone et al. | 2006 | Oral antidiabetics | Pioglitazone | Glimepiride | Secondary | 59 | 230 | 228 |
| METEOR | 2007 | Lipid lowering | Rosuvastatin | Placebo | Primary | 57 | 702 | 282 |
| MIDAS | 1996 | Anti-HTN | Isradipine | HCT | Primary | 58 | 442 | 441 |
| MITEC | 2009 | Anti-HTN | Candesartan | Amlodipine | Primary | 60 | 100 | 109 |
| Mitsuhashi et al. | 2004 | Other | Cilostazol | Placebo | Primary | 63 | 31 | 31 |
| PHYLLIS | 2004 | Lipid lowering | Pravastatin | Placebo | Primary | 58 | 254 | 254 |
| PLAC II | 1995 | Lipid lowering | Pravastatin | Placebo | Secondary | | 75 | 76 |
| PREVEND IT | 2005 | Lipid lowering | Pravastatin | Placebo | Primary | 51 | 317 | 325 |
| RADIANCE 1 | 2007 | Lipid lowering | Torcetrapib+atorvastatin | Atorvastatin | Primary | 46 | 450 | 454 |
| RADIANCE 2 | 2007 | Lipid lowering | Torcetrapib+atorvastatin | Atorvastatin | Primary | 57 | 377 | 375 |
| RAS | 2007 | Oral antidiabetics | Rosiglitazone | Placebo | Primary | 68 | 277 | 278 |
| REGRESS | 1998 | Lipid lowering | Pravastatin | Placebo | Secondary | 56 | 131 | 124 |
| RIS | 1996 | Lipid lowering | Life-style | Usual care | Secondary | 66 | 81 | 83 |
| SANDS | 2008 | Lipid lowering | Standard statin treatment | Aggressive (statin + ezetimibe) | Primary | 56 | 223 | 204 |
| Shinoda-Tagawa et al. | 2002 | Other | Cilostazol | Placebo | Secondary | 60 | 43 | 46 |
| Stanton et al. | 2001 | Anti-HTN | Amlodipine | Lisinopril | Secondary | 49 | 35 | 34 |
| STARR ACE inhibitor | 2009 | Anti-HTN | Ramipril | Placebo | Primary | 54 | 715 | 710 |
| STARR glitazone | 2009 | Oral antidiabetics | Rosiglitazone | Placebo | Primary | 54 | 709 | 716 |
| VEAPS | 2002 | Antioxidants | Vitamin E | Placebo | Primary | 56 | 162 | 170 |
| VHAS | 1998 | Anti-HTN | Verapamil | Chlorthalidone | Secondary | 54 | 244 | 254 |
| Yu et al. | 2007 | Lipid lowering | Atorvastatin | Atorvastatin | Secondary | 66 | 57 | 55 |

See Online Appendix for references and description of study acronyms.

ACE = angiotensin-converting enzyme; BMI = body mass index; CHD = coronary heart disease; HCT = hydroclorothiazide; HTN = hypertension; NR = not reported; PUFA = polyunsaturated fatty acids.

events, detailed information about IMT), the authors were contacted to request further information (Fig. 1).

Both mean and maximum IMT values were considered. Mean IMT was defined as the mean of all measurements on common carotid artery or, when this value was not available, a single measurement on common carotid artery. Maximum IMT was defined as the mean of all maximum measurements, or when this value was not available, the measurement at bulb or the single maximum value.

The quality of the trials was evaluated giving a score for each study using the Detsky method (9) (Table 1).

Of 9,722 articles identified by the initial search, 85 were retrieved for more detailed evaluation, and 41 were included in the study (Fig. 1). Details of included trials and populations are listed in Table 1. In particular, 21 trials compared

**Table 1** Continued

| Women (%) | BMI (kg/m$^2$) | Follow-Up (yrs) | Smokers (%) | Hypertension (%) | Diabetes (%) | CHD (%) | Detsky Quality Score | Event Rate Year | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | % Treatment | % Control |
| 48 | 26 | 3 | 12 | 29 | 2 | 0 | 19 | 0.4 | 0.7 |
| 18 | NR | 2 | 15 | 48 | 0 | 53 | 19 | 1.1 | 3.6 |
| 29 | NR | 1 | 10 | 69 | 10 | 46 | 18 | 3.8 | 3.7 |
| 9 | NR | 1 | 10 | 75 | 27 | 43 | 21 | 3.4 | 8.8 |
| 61 | 26 | 2 | 32 | NR | NR | 31 | 21 | 0.6 | 0.6 |
| 51 | 26 | 3.6 | 10 | 90 | 23 | 21 | 20 | 9 | 8.8 |
| 43 | 27 | 2 | 35 | 31 | 0 | 0 | 20 | 2.1 | 6.5 |
| 54 | 26 | 3 | 31 | 12 | 3 | 4 | 17 | 0.6 | 0.9 |
| 54 | 26 | 3 | 31 | 12 | 3 | 4 | 17 | 0.4 | 1.1 |
| 40 | 31 | 2 | 24 | 50 | 100 | 0 | 19 | 0 | 1.6 |
| 39 | 30 | 3 | 3 | NR | NR | NR | 18 | 1.2 | 1.5 |
| 47 | 25 | 3 | 24 | NR | NR | 0 | 18 | 0.7 | 0.4 |
| 39 | 28 | 1.25 | 16 | 29 | 5 | 65 | 21 | 4.5 | 2.4 |
| 0 | 26 | 3 | 46 | 100 | 0 | 39 | 19 | 3.3 | 1.7 |
| 45 | 27 | 3.75 | 20 | 100 | NR | NR | 18 | 0.9 | 1.1 |
| 51 | 27 | 2 | 28 | 16 | 2 | 28 | 21 | 1.4 | 1.1 |
| 100 | 29 | 2 | 0 | 0 | 3 | 0 | 19 | 1.5 | 2 |
| 73 | 23 | 2 | 53 | 41 | 23 | 14 | 18 | 3 | 4 |
| 37 | 29 | 5 | 14 | 56 | 100 | 20 | 20 | 0.5 | 1.2 |
| 67 | 32 | 2 | NR | 67 | 100 | 0 | 18 | 2.1 | 2.2 |
| NR | 29 | 4 | 15 | 100 | NR | 0 | 17 | 1.1 | 1.6 |
| 0 | NR | 3 | 26 | 33 | 2 | 8 | 19 | 1.3 | 2.5 |
| 63 | 32 | 1.3 | NR | 70 | 100 | 18 | 20 | 2 | 6.1 |
| 40 | 27 | 2 | 22 | 28 | 0 | 0 | 21 | 0.4 | 0.2 |
| 22 | 28 | 3 | 20 | 100 | 0 | 4 | 20 | 3.3 | 1.8 |
| 63 | 31 | 3 | NR | 100 | 100 | NR | 21 | 0.7 | 0.6 |
| 35 | 24 | 1 | NR | 60 | 100 | 0 | 16 | 0 | 6.5 |
| 60 | NR | 3 | 16 | 100 | NR | 0 | 18 | 0.3 | 0.5 |
| NR | NR | 3 | NR | NR | NR | 100 | 18 | 1.8 | 4.4 |
| 37 | NR | 2 | 39 | 24 | 4 | 3 | 20 | 1.4 | 2.3 |
| 49 | 27 | 2 | 20 | 24 | 3 | 0 | 21 | 0.4 | 0.1 |
| 64 | 30 | 2 | 16 | 50 | 21 | 0 | 21 | 0.4 | 0 |
| 51 | 30 | 1 | 13 | 57 | 36 | 7 | 21 | 1.1 | 0.7 |
| 0 | 26 | 2 | 32 | 26 | NR | 100 | 18 | 5.3 | 10.1 |
| 0 | 27 | 3.4 | 35 | 100 | NR | | 17 | 2.2 | 2.1 |
| 67 | 34 | 3 | 19 | NR | 100 | 0 | 17 | 1.5 | 1.1 |
| 49 | 23 | 3.2 | NR | 57 | 100 | NR | 17 | 0 | 1.4 |
| 40 | NR | 1 | 27 | 100 | 0 | 0 | 19 | 2.9 | 2.9 |
| 55 | 30 | 3 | 11 | 41 | 0 | 0 | 20 | 0.7 | 1.1 |
| 55 | 30 | 3 | 11 | 40 | 0 | 0 | 20 | 1.1 | 0.7 |
| NR | NR | 3 | 36 | 0 | 0 | 0 | 20 | 2.1 | 2.7 |
| 48 | 27 | 4 | 18 | 100 | NR | NR | 18 | 1 | 1.9 |
| 17 | NR | 1 | 43 | 51 | 28 | 100 | 19 | 10.5 | 7.3 |

statins or other lipid-lowering drugs treatments versus placebo or active treatments (Online Appendix references 1–21), 8 trials compared antihypertensive drugs versus active treatment or placebo (Online Appendix references 6,23–8), 4 trials compared oral antidiabetic agents versus active treatment or placebo (Online Appendix references 22,29–31), and 4 trials compared antioxidant agents versus placebo (Online Appendix references 32,35). Additionally, 1 trial compared an a:cholesterol acyltransferase inhibitor versus placebo (Online Appendix reference 36), 1 trial compared estrogens versus placebo (Online Appendix reference 37), 2 trials compared phosphodiesterase inhibitors versus placebo (Online Appendix references 38,39), and 2 trials compared cholesteryl-ester transfer protein inhibitors versus placebo

**Table 2** IMT Values

| Trial Name/ First Author | Mean IMT | | Max IMT | | Change Mean IMT | | Change Max IMT | | ΔMean IMT (%) | ΔMax IMT (%) | Total Cholesterol, Mean (mg/dl) | LDL, Mean (mg/dl) | HDL, Mean (mg/dl) | Triglycerides, Mean (mg/dl) | ΔLDL (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Treatment (mm) | Control (mm) | Treatment (mm) | Control (mm) | Treatment (mm/yr) | Control (mm/yr) | Treatment (mm/yr) | Control (mm/yr) | | | | | | | |
| ACAPS | 1.14 | 1.14 | 1.32 | 1.315 | NR | NR | −0.0060 | 0.0060 | NA | −2.7 | 235 | 155 | 52 | 318 | −28 |
| Angerer et al. | 1.26 | 1.31 | 1.54 | 1.65 | 0.035 | 0.025 | 0.0300 | 0.0150 | 1.6 | 1.9 | NR | 155 | 50 | 193 | 4 |
| ARBITER | 0.625 | 0.615 | 0.935 | 0.808 | −0.034 | 0.025 | −0.1370 | 0.0020 | −9.5 | −15.9 | 229 | 152 | 49 | 207 | −18 |
| ARBITER 2 | 0.893 | 0.868 | NR | NR | 0.014 | 0.044 | NR | NR | −3.4 | NA | 154 | 89 | 40 | 163 | 3 |
| ASAP | 0.86 | 0.87 | 1.09 | 1.07 | −0.0155 | 0.018 | −0.0110 | 0.0310 | −7.7 | −7.8 | 386 | 315 | 46 | 165 | −7 |
| ASFAST | 0.86 | 0.86 | 1.06 | 1.08 | NR | NR | −0.0067 | 0.0100 | NA | −9.0 | 197 | 126 | 42 | 186 | NA |
| ATIC | 0.68 | 0.65 | NR | NR | −0.025 | 0.03 | NR | NR | −16.5 | NA | 224 | 138 | 48 | 164 | −31 |
| BCAPS statin only | 0.8945 | 0.909 | 1.9315 | 1.9055 | 0.0037 | 0.012 | 0.0567 | 0.0703 | −2.8 | −2.1 | 237 | 160 | 54 | 103 | −23 |
| BCAPS statin+beta-blocker | 0.9115 | 0.892 | 1.9225 | 1.884 | 0.0073 | 0.008 | 0.0513 | 0.0757 | −0.2 | −3.8 | 240 | 163 | 54 | 103 | NA |
| Beishuizien et al. | 0.759 | 0.757 | 0.823 | 0.815 | 0.0015 | 0.003 | −0.0085 | −0.0050 | −0.4 | −0.9 | 212 | 135 | 47 | 164 | −31 |
| BVAIT | 0.075 | 0.076 | NR | NR | 0.002 | 0.0003 | NR | NR | 6.8 | NA | 217 | 134 | 57 | 130 | NA |
| CAIUS | 0.89 | 0.85 | 1.06 | 1.04 | −0.0032 | 0.0077 | −0.0430 | 0.0089 | −3.8 | −14.8 | 259 | 182 | 54 | 138 | −20 |
| CAPTIVATE | 0.785 | 0.775 | 0.937 | 0.927 | 0.0152 | 0.004 | 0.0136 | 0.0104 | 1.8 | 0.4 | 219 | 140 | 52 | 136 | 6 |
| DAPHNE | 1.05 | 1.08 | 1.39 | 1.43 | −0.005 | −0.0267 | −0.0500 | −0.0600 | 6.1 | 2.1 | 240 | 151 | 38 | 178 | −3 |
| ELSA | 1.1589 | 1.1619 | 1.3115 | 1.3131 | 0.0101 | 0.0125 | NR | NR | −0.8 | NA | 227 | 145 | 53 | 136 | 1 |
| ENHANCE | 0.69 | 0.7 | 0.8 | 0.8 | 0.0056 | 0.0029 | 0.0088 | 0.0052 | 0.8 | 0.9 | 400 | 319 | 47 | 159 | −16 |
| EPAT | 0.766 | 0.764 | NR | NR | −0.0019 | −0.0016 | NR | NR | −0.1 | NA | 253 | 166 | 55 | 160 | −6 |
| FAST | 1.267 | 1.316 | 1.267 | 1.316 | −0.088 | 0.025 | −0.0880 | 0.0250 | −17.5 | −17.5 | 251 | 164 | 56 | 152 | −13 |
| FIELD | 1.03 | 1.01 | 1.3 | 1.29 | 0.004 | 0.004 | 0.0100 | 0.0080 | 0.0 | 0.8 | 190 | 119 | 44 | 142 | −23 |
| Hodis et al. | 0.809 | 0.821 | NR | NR | 0.003 | 0.0066 | NR | NR | −0.9 | NA | 197 | 176 | 50 | 115 | NA |
| HYRIM | 0.793 | 0.804 | 1.496 | 1.628 | 0.012 | 0.0185 | 0.0350 | 0.0535 | −3.3 | −4.7 | 225 | 148 | 50 | 157 | NA |
| KAPS | 1.66 | 1.66 | 2 | 2 | 0.0097 | 0.0283 | 0.0280 | 0.0400 | −3.4 | −1.8 | 259 | 189 | 46 | 150 | −31 |
| Mazzone et al. | 0.771 | 0.779 | 1.038 | 1.042 | −0.0008 | 0.0092 | 0.0015 | 0.0200 | −1.7 | −2.3 | NR | 113 | 48 | 175 | 4 |
| METEOR | 0.76 | 0.76 | 1.15 | 1.17 | 0.0004 | 0.0088 | −0.0014 | 0.0130 | −2.2 | −2.5 | 229 | 155 | 50 | 130 | −49 |
| MIDAS | 1.17 | 1.17 | 1.45 | 1.44 | 0.0403 | 0.0497 | 0.0513 | 0.0693 | −2.4 | −3.7 | 217 | 147 | 48 | 327 | NA |
| MITEC | 0.758 | 0.726 | NR | NR | −0.0053 | −0.013 | NR | NR | 3.1 | NA | 178 | 107 | 44 | 147 | 0 |
| Mitsuhashi et al. | 1.08 | 1.08 | NR | NR | 0.04 | 0.12 | NR | NR | −7.4 | NA | 191 | 104 | 52 | 155 | −3 |
| PHYLLIS | 1.065 | 1.06 | 1.205 | 1.22 | NR | NR | −0.0231 | 0.0133 | NA | −7.8 | 266 | 183 | 54 | 142 | −20 |
| PLAC II | NR | NR | NR | NR | 0.0593 | 0.0675 | 0.0900 | 0.1040 | NA | NA | 235 | 166 | 41 | 171 | −30 |
| PREVEND IT | NR | NR | NR | NR | NR | NR | NR | NR | −0.5 | NA | NR | NR | NR | NR | NR |
| RADIANCE 1 | 0.71 | 0.72 | 1.13 | 1.15 | 0.005 | −0.005 | 0.0050 | 0.0050 | 2.8 | 0.0 | 213 | 139 | 53 | 97 | −13 |
| RADIANCE 2 | 0.83 | 0.83 | 1.32 | 1.3 | 0.0065 | 0.004 | 0.0125 | 0.0150 | 0.6 | −0.4 | 186 | 101 | 48 | 167 | 9 |
| RAS | 1.46 | 1.43 | 1.95 | 1.92 | 0.049 | 0.06 | 0.0880 | 0.1010 | −0.8 | −0.7 | 213 | 135 | 52 | 116 | 7 |
| REGRESS | 0.87 | 0.86 | 1.08 | 1.07 | −0.025 | 0.0000 | −0.0250 | 0.0050 | −5.8 | −5.6 | 239 | 168 | 38 | 163 | −29 |

*Continued on next page*

**Table 2** Continued

| Trial Name/ First Author | Mean IMT | | Max IMT | | Change Mean IMT | | Change Max IMT | | ΔMean IMT (%) | ΔMax IMT (%) | Total Cholesterol, Mean (mg/dl) | LDL, Mean (mg/dl) | HDL, Mean (mg/dl) | Triglycerides, Mean (mg/dl) | ΔLDL (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Treatment (mm) | Control (mm) | Treatment (mm) | Control (mm) | Treatment (mm/yr) | Control (mm/yr) | Treatment (mm/yr) | Control (mm/yr) | | | | | | | |
| RIS | 0.89 | 0.89 | 1.07 | 1.03 | 0.0206 | 0.0176 | 0.0088 | 0.0206 | 1.1 | −3.8 | 263 | 181 | 48 | 177 | −8 |
| SANDS | 0.82 | 0.79 | NR | NR | −0.0062 | 0.013 | NR | NR | −7.1 | NA | 184 | 103 | 46 | 160 | −27 |
| Shinoda-Tagawa et al. | 1.1 | 1.09 | NR | NR | −0.0063 | 0.0563 | NR | NR | −18.3 | NA | 209 | 126 | 56 | 138 | −1 |
| Stanton et al. | 0.763 | 0.792 | NR | NR | −0.048 | −0.027 | NR | NR | −2.7 | NA | 214 | 136 | 55 | 147 | NA |
| STARR ACE inhibitor | 0.66 | 0.66 | 0.75 | 0.76 | 0.0009 | 0.0016 | 0.0028 | 0.0023 | −0.3 | 0.2 | NR | NR | NR | NR | NA |
| STARR glitazone | 0.66 | 0.67 | 0.75 | 0.76 | 0.0005 | 0.0019 | 0.0021 | 0.0030 | −0.6 | −0.4 | NR | NR | NR | NR | NA |
| TRIPOD | 0.58 | 0.58 | NR | NR | 0.004 | 0.0023 | NR | NR | −1.5 | NA | NR | 154 | 57 | 135 | 3 |
| VEAPS | 0.746 | 0.76 | NR | NR | 0.015 | 0.016 | 0.0120 | 0.0120 | 0.7 | NA | 238 | 153 | 50 | 142 | −1 |
| VHAS | 0.857 | 0.896 | 0.88 | 0.947 | −0.2 | −0.08 | NR | 0.0060 | −0.5 | 0.0 | 230 | 111 | 46 | 159 | NA |
| Yu et al. | 1.18 | 1.21 | NR | NR | NR | NR | −0.0060 | 0.0150 | −5.0 | NA | 173 | 155 | 52 | 318 | −11 |

In this table are shown mean and maximum IMT baseline value and their change during follow-up. Delta mean and maximum IMT correspond to the achieved between-group difference from baseline to end of follow-up. Delta low-density lipoprotein (LDL) corresponds to the achieved between-group difference from baseline to end of follow-up expressed in percent of LDL. See Online Appendix for references and description of study acronyms.

HDL = high-density lipoprotein; IMT = intima-media thickness; Max = maximum; NA = not available; other abbreviations as in Table 1.

(Online Appendix references 40,41). The extended titles of the trials included in the study are listed in the Online Appendix.

**Meta-regression analysis.** Weighted random-effects meta-regression analysis was performed with the metareg command (10) (STATA version 10.0, StataCorps, College Station, Texas) to test the relationship between changes in IMT from baseline to end of follow-up and incidence of clinical events. For this analysis, the achieved differences between IMT change (millimeters per year) in the control group and the active treatment group both for mean and maximum IMT (delta mean IMT and delta maximum IMT, respectively) were considered. To explore the influence of potential effect modifiers on the association between IMT changes and outcomes, separate meta-regression analyses were performed also, including the following covariates, each separately: mean age, sex, body mass index, smokers, diabetes, hypertension, total serum cholesterol at baseline, low-density lipoprotein (LDL) at baseline and achieved difference between groups (from baseline to end of follow-up), systolic and diastolic blood pressure at baseline and achieved difference between groups (from baseline to end of follow-up), IMT mean and maximum at baseline, length of follow-up, Detsky quality score (9), and study publication year. Meta-regression analysis was also performed to test the association between LDL cholesterol reduction and the outcomes.

For all meta-regression analyses, a random-effects model was used to take into account the mean of a distribution of effects across studies. In fact, random-effects modeling more appropriately provides wider confidence intervals (CIs) for the regression coefficients than does a fixed-effect analysis, if residual heterogeneity exists (11). The weight used for each trial was the inverse of the sum of the within-trial variance and the residual between trial variance, in order to correspond to a random-effects analysis. To estimate the additive (between-study) component of variance, tau$^2$, the restricted maximum likelihood (REML) method was used to take into account the occurrence of residual heterogeneity, not explained by the potential effect modifiers (11).

Finally, to investigate a potential relationship between mean and maximum IMT modification and LDL serum level change, we performed a linear regression analysis weighted by the size of each study.

**Outcome meta-analysis.** Odds ratios (ORs) of the effect of randomized treatments were calculated using the metan routine (STATA version 10.0, StataCorps) (12). The OR and CI for each outcome was separately calculated for each trial, with grouped data, in intention-to-treat analyses. The choice to use OR was driven by the retrospective design of the meta-analysis on the basis of published studies that vary in design, subjects' population, treatment regimen, primary outcome measure, and quality (12–14). Overall estimates of effect were calculated with a fixed-effects model, random-effects model, or Peto method where appropriate. The assumption of homogeneity between the treatment effects in different trials was tested with the Q and the I-square statistic. If the assumption of homogeneity

**Table 3** Baseline and End Follow-Up Blood Pressure

| Trial Name/ First Author | Treatment Group | | Control Group | | Treatment Group | | Control Group | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline SBP (mm Hg) | Baseline DBP (mm Hg) | Baseline SBP (mm Hg) | Baseline DBP (mm Hg) | Change in SBP (mm Hg) | Change in DBP (mm Hg) | Change in SBP (mm Hg) | Change in DBP (mm Hg) | ΔSBP (%) | ΔDBP (%) |
| ACAPS | 130 | 76 | 131 | 77 | NA | NA | NA | NA | NA | NA |
| Angerer et al. | NR | NR | NR | NR | NA | NA | NA | NA | NA | NA |
| ARBITER | NR | NR | NR | NR | NA | NA | NA | NA | NA | NA |
| ARBITER 2 | NR | NR | NR | NR | NA | NA | NA | NA | NA | NA |
| ASAP | 127 | 77 | 128 | 77 | NA | NA | NA | NA | NA | NA |
| ASFAST | 144 | 83 | 141 | 79 | NA | NA | NA | NA | NA | NA |
| ATIC | 136 | 79 | 134 | 78 | −2 | 1 | 0 | −2 | −1.5 | 3.8 |
| BCAPS statin only | 140 | 85 | 139 | 84 | 4 | 0 | 3 | 0 | 0.7 | 0.0 |
| BCAPS statin+beta-blocker | 138 | 85 | 139 | 85 | 2 | 0 | 3 | 0 | −0.7 | 0.0 |
| Beishuizien et al. | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| BVAIT | 128 | 80 | 129 | 80 | NA | NA | NA | NA | NA | NA |
| CAIUS | 133 | 81 | 134 | 81 | NA | NA | NA | NA | NA | NA |
| CAPTIVATE | 128 | 128 | 78 | 78 | NA | NA | NA | NA | NA | NA |
| DAPHNE | 163 | 100 | 164 | 101 | NA | NA | NA | NA | NA | NA |
| ELSA | 164 | 101 | 163 | 101 | −22 | −15 | −22 | −16 | 0.0 | 1.0 |
| ENHANCE | 125 | 78 | 124 | 78 | NA | NA | NA | NA | NA | NA |
| EPAT | 128 | 129 | 78 | 77 | NA | NA | NA | NA | NA | NA |
| FAST | NR | NR | NR | NR | NA | NA | NA | NA | NA | NA |
| FIELD | 142 | 88 | 140 | 88 | −6 | −8 | −2 | −8 | −2.8 | 0.0 |
| Hodis et al. | 137 | 80 | 134 | 79 | NA | NA | NA | NA | NA | NA |
| HYRIM | 140 | 88 | 140 | 88 | −1 | NA | 1 | NA | −1.4 | 0.0 |
| KAPS | 136 | 86 | 137 | 86 | NA | NA | NA | NA | NA | NA |
| Mazzone et al. | 130 | 78 | 129 | 77 | NA | NA | NA | NA | NA | NA |
| METEOR | 124 | 77 | 125 | 78 | NA | NA | NA | NA | NA | NA |
| MIDAS | 151 | 97 | 149 | 96 | −16 | −13 | −19 | −13 | 2.0 | 0.0 |
| MITEC | 156 | 91 | 156 | 92 | −25 | −14 | −25 | −16 | 0.0 | 2.2 |
| Mitsuhashi et al. | 135 | 71 | 130 | 72 | 5 | −2 | 5 | −1 | 0.0 | −1.4 |
| PHYLLIS | 160 | 98 | 160 | 98 | −18 | −13 | −17 | −13 | −0.6 | 0.0 |
| PLAC II | NR | NR | NR | NR | NA | NA | NA | NA | NA | NA |
| PREVEND IT | 130 | 76 | 130 | 76 | NA | NA | NA | NA | NA | NA |
| RADIANCE 1 | 116 | 73 | 116 | 73 | 4 | 2 | 1 | 2 | 2.6 | 0.0 |
| RADIANCE 2 | 121 | 75 | 120 | 75 | 7 | 2 | 1 | 1 | 5.0 | 1.3 |
| REGRESS | 134 | 80 | 137 | 82 | NA | NA | NA | NA | NA | NA |
| RAS | 141 | 83 | 142 | 83 | 1 | −2 | 3 | 0 | −2 | −2 |
| RIS | 145 | 80 | 151 | 83 | 5 | 1 | 4 | −4 | 0.7 | 6.1 |
| SANDS | 127 | 73 | 131 | 75 | −11 | −7 | −2 | −2 | −7.0 | −6.8 |
| Shinoda-Tagawa et al. | 138 | 80 | 134 | 77 | −3 | −4 | 0 | 0 | −2.2 | −5.1 |
| Stanton et al. | 165 | 99 | 164 | 101 | −21 | −14 | −20 | −15 | −0.6 | 1.0 |
| STARR ACE inhibitor | 134 | 81 | 135 | 82 | −8 | −5 | −3 | −3 | −3.7 | −2.5 |
| STARR glitazone | 135 | 82 | 135 | 82 | −7 | −5 | −5 | −4 | −1.5 | −1.2 |
| TRIPOD | 113 | 70 | 115 | 71 | −4 | −4 | −3 | −3 | −0.9 | −1.4 |
| VEAPS | 128 | 77 | 128 | 76 | NA | NA | NA | NA | NA | NA |
| VHAS | 168 | 102 | 168 | 102 | −25 | −15 | −28 | −16 | 1.8 | 1.0 |
| Yu et al. | NR | NR | NR | NR | NA | NA | NA | NA | NA | NA |

Delta systolic blood pressure (SBP) and diastolic blood pressure (DBP) correspond to the achieved between-group difference from baseline to end of follow-up, expressed in percent. See Online Appendix for references and description of study acronyms.

Abbreviations as in Tables 1 and 2.

was rejected ($p < 0.10$), additional analyses were done with a random-effects model and sensitivity analysis (15). Furthermore, in case events rate were ≤1%, analysis was also performed with the Peto method (16). Pooled ORs were logarithmically transformed and weighted for the inverse of variance. The significance level for the overall estimates of effect and for meta-regression analyses was set at $p \leq 0.05$. Participants could only contribute with 1 event to the calculation of each outcome, but could contribute with 1 event for each of the separate analyses of different outcomes.

**Sensitivity analysis.** Sensitivity analysis was performed to verify the robustness of the results. In detail, to assess the

influence of the baseline profile risk, separate meta-regression analysis and meta-analysis were performed for primary and secondary prevention trials. To evaluate the specific effect of treatment category, meta-regression analysis and meta-analysis were performed separately for treatment category (lipid lowering, antihypertensive, antidiabetic, antioxidant therapy). To assess the influence of mean and maximum IMT baseline value, we used them as covariates in meta-regression analysis (see Results, Meta-regression analysis), and we also made a meta-regression analysis including only trials with a mean or maximum IMT ≥1 mm (17). Furthermore, progression and regression of mean and maximum IMT were also assessed separately. Then, the influence of several potential effect modifiers on the association between IMT changes and outcomes was also explored (see Results, Meta-regression analysis). Finally, as previously stated, IMT measurements were expressed in millimeters per year; however, we also performed the meta-regression analysis by using the achieved differences between IMT percent change in the control group and the active treatment group both for mean and maximum IMT.

To explore nonlinearity in the associations between each outcome and delta mean and maximum IMT (18), the splined models (19) were used. This analysis allows a cubic association in each of several subintervals of continuous factor's range, but requiring linearity at the beginning and end of the range and requiring that the pieces join smoothly (19).

**Publication bias.** To evaluate potential publication bias, a weighted linear regression was used, with the natural log of the OR as the dependent variable and the inverse of the total sample size as the independent variable. This is a modified Macaskill's test, which gives more balanced type I error rates in the tail probability areas in comparison with other publication bias tests (20).

## Results

**Characteristics of included trials.** The baseline characteristics of the 41 trials (18,307 participants) included in the meta-analysis are shown in Tables 1, 2, and 3; 9,313 subjects were assigned to a statin and 8,994 to another drug or to placebo. The duration of follow-up ranged from 0.5 to 5 years, and the mean was 2.4 ± 0.96 years.

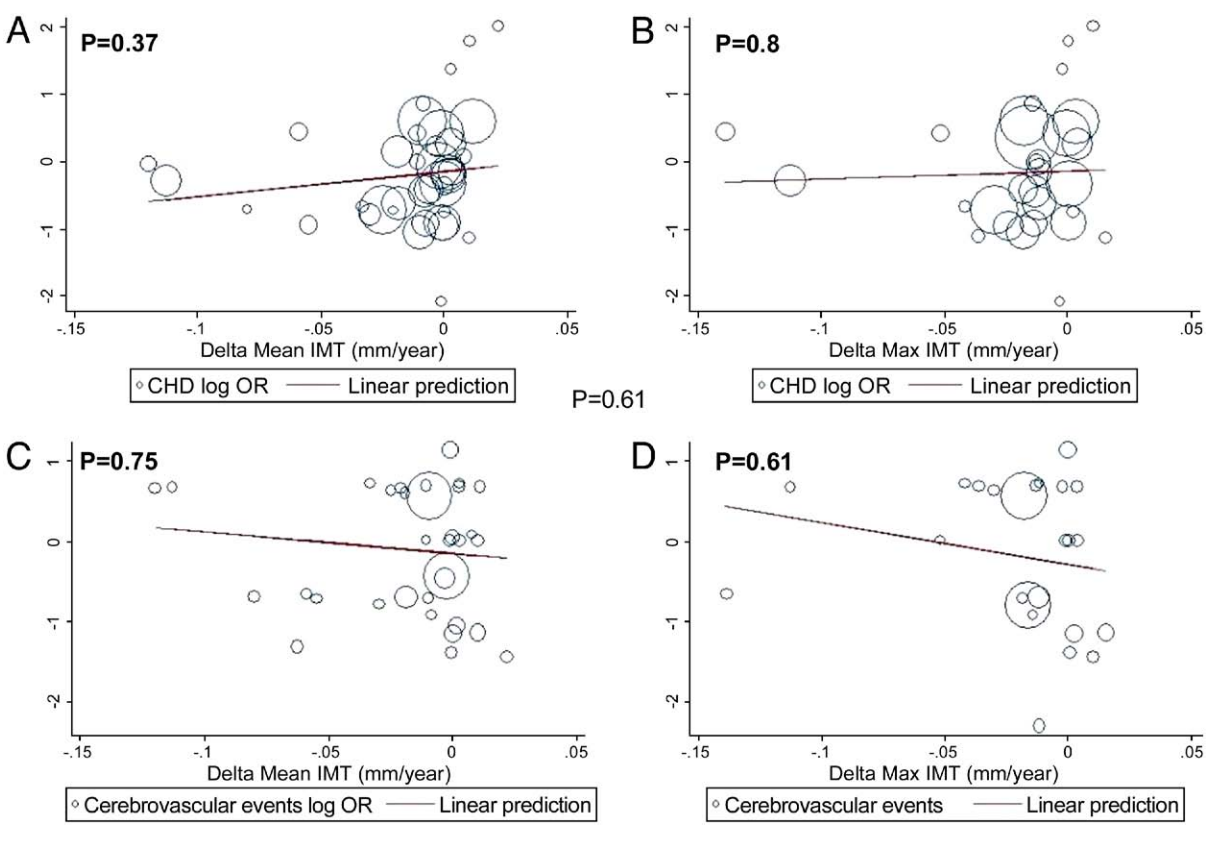


**Figure 2** Meta-Regression Analysis Between Delta Mean and Maximum IMT, CHD, and CBV Events

Meta-regression analysis between delta mean and maximum (max) intima-media thickness (IMT) for **(A, B)** coronary heart disease (CHD) events and **(C, D)** cerebrovascular (CBV) events. The log of odds ratios (ORs) is reported on the y-axis, and the covariate is reported on the x-axis. Bubble size for each study is proportional to the inverse of the variance.

The overall mean age of subjects was 58 ± 5 years, and 43% were women.

**Meta-regression analysis.** When all data from the 41 trials were pooled, there was no significant relationship between delta mean and delta maximum IMT changes from baseline to end of follow-up and CHD, CBV events, composite outcome, and all-cause death (Figs. 2 and 3, Tables 4 and 5). Likewise, no relationship was found when only hard cardiovascular events (cardiac death, myocardial infarction, and stroke) were considered (Online Appendix Fig. 1 and Table 1).

In addition, lack of relationship was confirmed when pre-specified potential effect modifiers (listed in Methods) were considered in the meta-regression analysis (Table 6).

In contrast, meta-regression analysis of lipid-lowering trials demonstrated a significant relationship between LDL lowering and reduction of CHD events (Online Appendix Fig. 2) and composite outcome (Online Appendix Fig. 3), with a trend for CBV events (Online Appendix Fig. 2), and no statistically significant association for all-cause death (Online Appendix Fig. 3).

However, no significant relationship between change in mean or maximum IMT and LDL serum modification was found (Online Appendix Figs. 4 and 5). For further details about these statistical analysis, refer to the legends of the respective figures.

**Sensitivity analysis.** Sensitivity analysis was performed to separately assess the association between IMT changes and outcomes for primary (n = 23) and secondary (n = 18) prevention trials, for lipid lowering (n = 21), antihypertensive (n = 8), antidiabetic (n = 4), and antioxidant therapy (n = 4). Similar to the overall pooled analysis, no significant relationship between IMT changes and outcomes was observed in any of these separate analysis (Tables 4 and 5). Analyzing the influence of covariates listed in Methods, the only notable result was that in primary prevention, change in systolic blood pressure significantly influenced the association between maximum IMT changes and CHD risk modification ($Exp^{(b)}$1.33, standard error 0.12, 95% CI: 1.08 to 1.65, change in $tau^2$ = 3.19, p = 0.015).

We also performed a meta-regression analysis considering separately progression and regression of carotid mean and maximum IMT, and also in this case, no significant association between change in IMT and outcomes was observed (Online Appendix Table 2). The influence of mean and maximum baseline IMT value was considered, including them as covari-

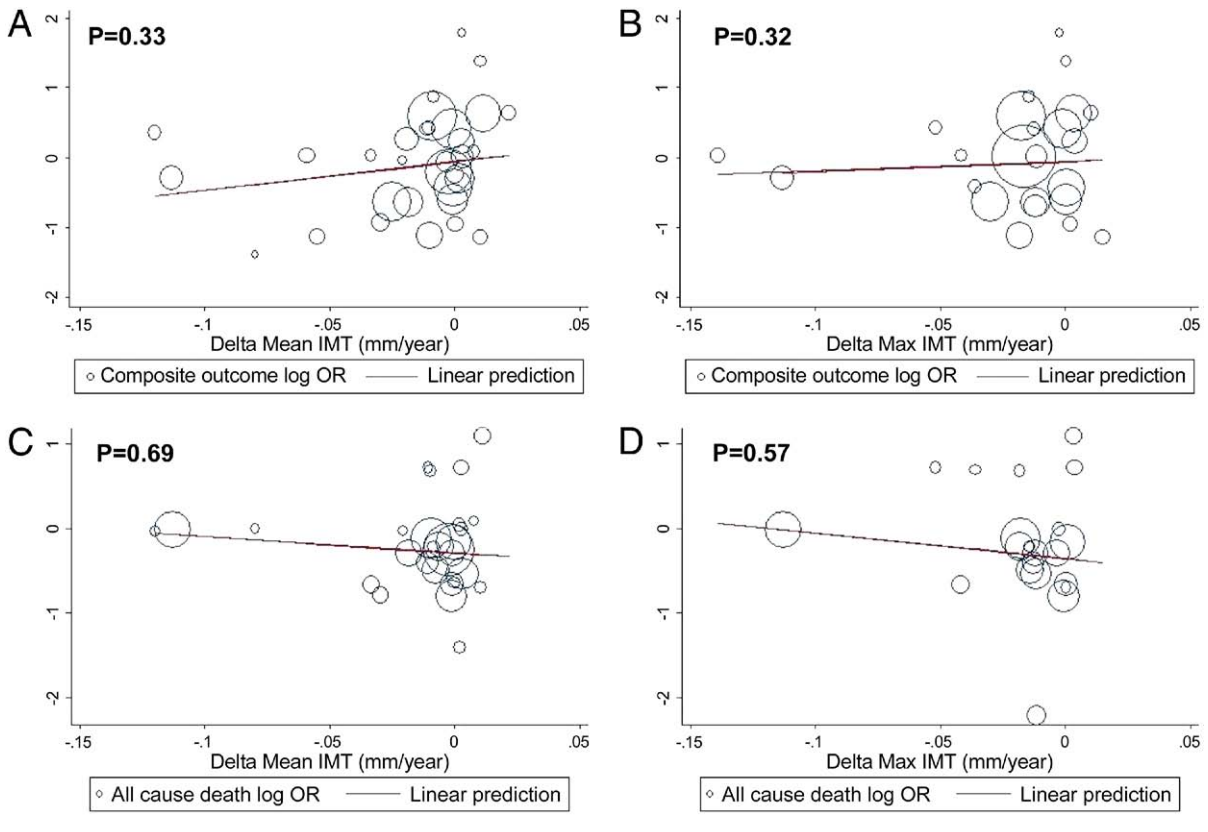


**Figure 3** Meta-Regression Analysis Between Delta Mean and Maximum IMT, Composite Outcome, and All-Cause Death

Meta-regression analysis between delta mean and maximum (max) intima-media thickness (IMT) for **(A, B)** composite outcome and **(C, D)** all-cause death. Log of odds ratios (OR) is reported on the y-axis, and the covariate is reported on the x-axis. Bubble size for each study is proportional to the inverse of the variance.

**Table 4** Exp(b) of Delta Mean Intima-Media Thickness Change (mm/yr) From Baseline, 95% CI, Change in Tau², Statistical Significance, and REML Statistics for Every Outcome

| | Exp(b) | SE | 95% CI | Change in Tau² | p tau² | REML |
|---|---|---|---|---|---|---|
| All-cause death | | | | | | |
| All trials (n = 28) | 0.14 | 0.68 | 0–>1,000† | −0.41 | 0.69 | 0 |
| Lipid lowering (n = 12) | 0.09 | 0.49 | 0–>1,000† | −0.44 | 0.67 | 0 |
| Antihypertensive (n = 6) | 0* | 0* | 0–0* | −0.22 | 0.83 | 0 |
| Antidiabetics (n = 3) | 0* | 0* | 0–0* | −0.6 | 0.65 | 0 |
| Antioxidant (n = 2) | NA | NA | NA | NA | NA | NA |
| Primary prevention (n = 19) | 0.09 | 0.47 | 0–>1,000† | −0.47 | 0.65 | 0 |
| Secondary prevention (n = 9) | 18.12 | 266 | 0–0* | 0.2 | 0.85 | 0 |
| Cerebrovascular events | | | | | | |
| All trials (n = 33) | 0.06 | 0.56 | 0–>1,000† | −0.32 | 0.75 | 0.01 |
| Lipid lowering (n = 13) | 0.01 | 0.01 | 0–0* | −0.58 | 0.57 | 0 |
| Antihypertensive (n = 7) | 0* | 0* | 0–0* | −1.61 | 0.17 | 0 |
| Antidiabetics (n = 4) | 0* | 0* | 0–0* | −0.19 | 0.86 | 0 |
| Antioxidant (n = 3) | 0.97 | 0.09 | 0.31–3.02 | −0.33 | 0.8 | 0 |
| Primary prevention (n = 18) | 0.02 | 0.32 | 0–0* | −0.28 | 0.78 | 0.04 |
| Secondary prevention (n = 14) | 0.08 | 0.89 | 0–0* | −0.22 | 0.83 | 0 |
| Coronary heart disease events | | | | | | |
| All trials (n = 38) | 45.25 | 188.9 | 0.01–>1,000† | 0.91 | 0.37 | 0.1 |
| Lipid lowering (n = 18) | 0.99 | 4.33 | 0–>1,000† | 0 | 0.99 | 0 |
| Antihypertensive (n = 8) | >1,000† | 0* | 0–0* | 0.36 | 0.73 | 0.33 |
| Antidiabetics (n = 4) | 0* | 0* | 0–0* | 2.4 | 0.14 | 0 |
| Antioxidant (n = 3) | 0* | 0* | 0–0* | −0.8 | 0.57 | 0 |
| Primary prevention (n = 23) | 12.64 | 61.52 | 0–>1,000† | 0.52 | 0.61 | 0.04 |
| Secondary prevention (n = 15) | 24.3 | 176 | 0–0* | 0.44 | 0.67 | 0.18 |
| Composite end point | | | | | | |
| All trials (n = 32) | 58.75 | 242 | 0.013–>1,000† | 0.99 | 0.33 | 0.12 |
| Lipid lowering (n = 14) | 2.35 | 10.56 | 0.01–>1,000† | 0.19 | 0.19 | 0.01 |
| Antihypertensive (n = 7) | 0.05 | 1.68 | 0–0* | −0.10 | 0.93 | 0.18 |
| Antidiabetics (n = 4) | 0* | 0* | 0–0* | 1.91 | 0.20 | 0 |
| Antioxidant (n = 3) | 0.95 | 0.04 | 0.57–1.6 | −1.22 | 0.44 | 0 |
| Primary prevention (n = 18) | 69.46 | 359.05 | 0–>1,000† | −0.82 | 0.42 | 0.76 |
| Secondary prevention (n = 14) | 6.55 | 44 | 0–0* | 0.28 | 0.78 | 0.2 |

The number of trials included in the analysis is reported in parentheses. Symbols indicate that value is *too small or †too large to be reported.
CI = confidence interval; NA = not available; REML = restricted maximum likelihood.

ate in the analysis (Table 6), and performing a meta-regression analysis in trials with mean or maximum IMT ≥1 mm. Again, in both cases no significant association was found.

The analysis was also performed by using the IMT percent change from baseline; however, the results did not significantly differ (data not shown).

Exploring a potential nonlinearity in the associations between the outcomes and delta mean and maximum IMT through the splined models (19) did not show any significant nonlinear relationship for all outcomes.

**Outcomes analysis.** Pooling all trials included in the meta-analysis, the risk of all-cause death was significantly reduced by active treatments (OR: 0.71, 95% CI: 0.53 to 0.96, comparison p = 0.03, heterogeneity p = 0.91) (Online Appendix Fig. 6). A trend for risk reduction by active treatments was observed for CHD events (OR: 0.87, 95% CI: 0.74 to 1.03, comparison p = 0.09, heterogeneity p = 0.03) (Online Appendix Fig. 7), for CBV events (OR: 0.90, 95% CI: 0.77 to 1.05, comparison p = 0.08, heterogeneity p = 0.09) (Online Appendix Fig. 8), and for the composite outcome of CHD and CBV events (OR: 0.90, 95% CI: 0.77 to 1.05, comparison p = 0.19, heterogeneity p = 0.05) (Online Appendix Fig. 9). All trends became significant when the unsuccessful phase III trials using cholesteryl-ester transfer protein and a:cholesterol acyltransferase inhibitors (CAPTIVATE, RADIANCE 1, and RADIANCE 2) were excluded (for CHD events, OR: 0.82, 95% CI: 0.69 to 0.96, comparison p = 0.02, heterogeneity p = 0.11; for CBV events, OR: 0.71, 95% CI: 0.51 to 1, comparison p = 0.05, heterogeneity p = 0.31; and for composite events, OR: 0.84, 95% CI: 0.72 to 0.99, comparison p = 0.04, heterogeneity p = 0.19).

For more details about results by treatment category, refer to Online Appendix Figures 6 through 9.

**Publication bias.** Macaskill's modified test did not show any publication bias for each outcome (20).

## Discussion

The main finding of the study is that carotid IMT changes (regression or progression) do not correlate with changes in

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**Table 5** Exp[(b)] of Delta Maximum Intima-Media Thickness Change (mm/yr) From Baseline, 95% CI, Change in Tau$^2$, Statistical Significance, and REML Statistics for Every Outcome

| | Exp[(b)] | SE | 95% CI | Change in Tau$^2$ | p tau$^2$ | REML |
|---|---|---|---|---|---|---|
| **All-cause death** | | | | | | |
| All trials (n = 21) | 0.05 | 0.26 | 0–>1,000† | −0.57 | 0.57 | 0 |
| Lipid lowering (n = 12) | 0.02 | 0.11 | 0–>1,000† | −0.67 | 0.52 | 0 |
| Antihypertensive (n = 3) | 0 | 0 | 0–0* | −0.27 | 0.83 | 0 |
| Antidiabetics (n = 3) | 0 | 0 | 0–0* | −0.73 | 0.60 | 0 |
| Antioxidant (n = 2) | NA | NA | NA | NA | NA | NA |
| Primary prevention (n = 15) | 0.03 | 0.16 | 0–>1,000† | −0.65 | 0.53 | 0 |
| Secondary prevention (n = 6) | 0 | 0 | 0–0* | 0.51 | 0.64 | 0 |
| **Cerebrovascular events** | | | | | | |
| All trials (n = 24) | 0 | 0.05 | 0–>1,000† | −0.52 | 0.61 | 0.13 |
| Lipid lowering (n = 11) | 0 | 0.35 | 0–0* | −0.51 | 0.62 | 0 |
| Antihypertensive (n = 4) | 0 | 0 | 0–0* | −0.93 | 0.45 | 0.35 |
| Antidiabetics (n = 3) | 0 | 0 | 0–0* | 0.16 | 0.89 | 0 |
| Antioxidant (n = 4) | 0.97 | 0.08 | 0.32–2.97 | −0.33 | 0.80 | 0 |
| Primary prevention (n = 13) | 0 | 0 | 0–0* | −0.66 | 0.52 | 0.05 |
| Secondary prevention (n = 10) | 0.87 | 10.57 | 0–0* | −0.01 | 0.99 | 0 |
| **Coronary heart disease events** | | | | | | |
| All trials (n = 29) | 3.21 | 15 | 0–>1,000† | 0.25 | 0.80 | 0.18 |
| Lipid lowering (n = 19) | 0.14 | 0.61 | 0–>1,000† | −0.45 | 0.66 | 0 |
| Antihypertensive (n = 5) | >1,000† | 0* | 0–0* | 0.34 | 0.76 | 0.79 |
| Antidiabetics (n = 3) | 0 | 0 | 0–0* | 2.55 | 0.24 | 0 |
| Antioxidant (n = 2) | NA | NA | NA | NA | NA | NA |
| Primary prevention (n = 17) | 26.9 | 153 | 0–>1,000† | 0.58 | 0.57 | 0.11 |
| Secondary prevention (n = 12) | 0.11 | 0.89 | 0–>1,000† | −0.28 | 0.78 | 0.32 |
| **Composite end point** | | | | | | |
| All trials (n = 24) | 4 | 17 | 0–>1,000† | 0.32 | 0.75 | 0.16 |
| Lipid lowering (n = 12) | 0.32 | 1.31 | 0–>1,000† | −0.28 | 0.79 | 0 |
| Antihypertensive (n = 4) | 0 | 0 | 0–0* | −1.97 | 0.19 | 0 |
| Antidiabetics (n = 3) | 0 | 0 | 0–0* | 1.98 | 0.30 | 0.1 |
| Antioxidant (n = 3) | 0.95 | 0.04 | 0.57–1.6 | −1.23 | 0.44 | 0 |
| Primary prevention (n = 13) | 20.54 | 123.94 | 0–0* | −0.50 | 0.63 | 0.16 |
| Secondary prevention (n = 11) | 0.74 | 4.86 | 0–>1,000† | −0.05 | 0.96 | 0.21 |

The number of the trials included in the analysis is reported in parentheses. Symbols indicate that value is *too small or †too large to be reported.
Abbreviations as in Table 4.

the occurrence of major cardiovascular events induced by several drug treatments in different categories of subjects at intermediate to high cardiovascular risk (Figs. 2 and 3). Thus, IMT changes do not accurately predict the benefits of therapies with proven favorable effects on cardiovascular risk profile. This observation held true when the relationship was separately assessed for different categories of active drugs, when it was separately assessed in subjects with and without previous cardiovascular disease, and when several common effect modifiers were introduced in the analytic statistical modeling.

Although carotid IMT is currently included among organ damage indicators in major cardiovascular guidelines (3,4), and increased IMT impacts on therapeutic strategy in individual subjects (4), its use as a surrogate end point in clinical trials and interpretation of IMT changes as predictors of clinical benefits remain debated, as also recently reported by the U.S. Preventive Services Task Force (21,22). This is at variance with other organ damage indicators such as left ventricular hypertrophy and microalbuminuria, for which association between regression and favorable cardiac and renal outcomes has been demonstrated (23–25). However, the findings of the current study do not detract from the value of carotid IMT as a risk population marker or from the value of IMT assessment in individual subjects (2,18), in particular for high IMT value to be a proxy elsewhere in the body (26).

The lack of association between IMT changes and clinical outcomes is surprising, and the biologic explanations for why carotid IMT and clinical outcomes are dissociated can be only hypothesized and likely subject to considerable debate. As a first hypothesis, it is known that the process of IMT increase is a complex phenomenon, not only determined by atherosclerotic risk factors (27), and the role of IMT as a marker of atherosclerosis has been for this reason debated (2,28,29). Thus, it is conceivable that the multifactorial determinants of IMT may reduce the clinical strength and statistical significance of IMT changes as predictors of cardiovascular outcomes when interventions on more direct atherosclerotic risk factors (e.g., LDL and blood pressure lowering) are used. The second additional and relevant

**Table 6** Potential Effect Modifiers of Delta Mean and Maximum IMT Percentage Change From Baseline With Change in Tau$^2$ and Statistical Significance for Every Outcome

| | Delta Mean IMT | | Delta Max IMT | |
|---|---|---|---|---|
| | Change in Tau$^2$ | p Value | Change in Tau$^2$ | p Value |
| All-cause death | | | | |
| Age | −0.60 | 0.56 | −0.69 | 0.59 |
| Women | −0.40 | 0.69 | −0.38 | 0.71 |
| BMI | −0.28 | 0.78 | −0.65 | 0.52 |
| Smokers | −0.03 | 0.97 | 0.13 | 0.9 |
| Diabetes mellitus | −0.21 | 0.84 | −0.34 | 0.74 |
| Hypertension | −0.31 | 0.76 | −0.48 | 0.64 |
| Total serum cholesterol | −0.37 | 0.72 | −0.32 | 0.76 |
| LDL baseline | −0.38 | 0.71 | −0.39 | 0.7 |
| Delta LDL | −0.24 | 0.81 | −0.23 | 0.82 |
| Systolic blood pressure baseline | −0.16 | 0.87 | 0 | 1 |
| Diastolic blood pressure baseline | −0.49 | 0.63 | 0.32 | 0.76 |
| Delta systolic blood pressure | −0.49 | 0.63 | −0.6 | 0.57 |
| Delta diastolic blood pressure | −0.45 | 0.66 | −0.81 | 0.45 |
| Mean IMT baseline | −0.31 | 0.76 | −0.47 | 0.65 |
| Maximum IMT baseline | −0.33 | 0.75 | −0.43 | 0.67 |
| Follow-up | −0.29 | 0.77 | −0.19 | 0.85 |
| Jadad quality score | −0.55 | 0.58 | −0.69 | 0.5 |
| Year | −0.43 | 0.67 | −0.62 | 0.54 |
| Cerebrovascular events | | | | |
| Age | −0.18 | 0.86 | −0.12 | 0.9 |
| Women | −0.06 | 0.95 | −0.09 | 0.93 |
| BMI | −0.07 | 0.94 | −0.10 | 0.92 |
| Smokers | −0.76 | 0.46 | −0.09 | 0.93 |
| Diabetes mellitus | −0.22 | 0.83 | −0.09 | 0.93 |
| Hypertension | −0.12 | 0.90 | 0.59 | 0.56 |
| Total serum cholesterol | 0.04 | 0.97 | 0.23 | 0.82 |
| LDL baseline | −0.12 | 0.90 | −0.04 | 0.96 |
| Delta LDL | −0.17 | 0.87 | −1.00 | 0.33 |
| Systolic blood pressure baseline | 0.10 | 0.92 | 0.43 | 0.68 |
| Diastolic blood pressure baseline | −0.11 | 0.92 | 0.08 | 0.94 |
| Delta systolic blood pressure | 0.11 | 0.92 | −0.39 | 0.71 |
| Delta diastolic blood pressure | 0.55 | 0.59 | −0.94 | 0.38 |
| Mean IMT baseline | −0.16 | 0.87 | −0.08 | 0.94 |
| Maximum IMT baseline | −0.91 | 0.38 | −0.28 | 0.78 |
| Follow-up | −0.06 | 0.95 | −0.02 | 0.99 |
| Jadad quality score | −0.36 | 0.72 | −0.06 | 0.96 |
| Year | −0.33 | 0.74 | −0.36 | 0.72 |

*Continued on next page*

hypothesis that can explain our findings concerns the assumption that carotid wall injuries are representative of the status of the whole arterial bed in the body, including the coronary tree. Indeed, this has not been proven in the majority of subjects, by pathological post-mortem studies (30–34) and by clinical studies (35–38), indicating clearly that in the majority of patients, carotid lesions, including atherosclerotic plaques, are dissociated from coronary lesions. Finally, as atherosclerotic plaques grow longitudinally along the carotid axis >2 times faster than they thicken, IMT might be a less sensitive measure of plaque evolution (39). In fact, it was demonstrated that carotid plaques are a more sensitive and representative measure of the atherosclerotic burden than IMT, with higher predictive value for cardiovascular events (40,41). In addition, the lack of a clear relation between change in IMT and LDL, and the fact that IMT association with coronary heart disease is influenced by change in systolic blood pressure, might strengthen the hypothesis that IMT is influenced by mechanisms such as the shear stress and wall reactivity rather than pure atherosclerotic processes. These observations may explain why IMT is a very good population risk marker, whereas its value as a therapeutic target in individual subjects may be limited.

**Study limitations.** First, like all meta-analyses not based on individual data, the findings should be considered only as hypothesis-generating and not as definitive evidence of a

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**Table 6 Continued**

| | Delta Mean IMT | | Delta Max IMT | |
|---|---|---|---|---|
| | Change in Tau$^2$ | p Value | Change in Tau$^2$ | p Value |
| Coronary heart disease events | | | | |
| Age | 0.87 | 0.39 | −0.56 | 0.58 |
| Women | 1.01 | 0.32 | −0.11 | 0.91 |
| BMI | 1.11 | 0.28 | 0.59 | 0.56 |
| Smokers | 0.54 | 0.59 | −0.53 | 0.6 |
| Diabetes mellitus | 0.87 | 0.39 | −0.26 | 0.8 |
| Hypertension | 1.3 | 0.2 | 0.13 | 0.9 |
| Total serum cholesterol | 1.15 | 0.26 | 0.08 | 0.94 |
| LDL baseline | 1.00 | 0.32 | −0.23 | 0.82 |
| Delta LDL | 1.18 | 0.25 | 0.24 | 0.81 |
| Systolic blood pressure baseline | 1.4 | 0.17 | −0.09 | 0.93 |
| Diastolic blood pressure baseline | 1.36 | 0.18 | 0.11 | 0.91 |
| Delta systolic blood pressure | 0.53 | 0.6 | 0.61 | 0.55 |
| Delta diastolic blood pressure | 0.72 | 0.48 | 0.30 | 0.77 |
| Mean IMT baseline | 1.04 | 0.31 | −0.22 | 0.83 |
| Maximum IMT baseline | 0.78 | 0.44 | −0.04 | 0.97 |
| Follow-up | 1.09 | 0.28 | −0.02 | 0.98 |
| Jadad quality score | 0.69 | 0.5 | −1.35 | 0.19 |
| Year | 0.74 | 0.47 | −0.05 | 0.96 |
| Composite outcome | | | | |
| Age | −0.18 | 0.86 | −0.09 | 0.38 |
| Women | −0.06 | 0.95 | −0.09 | 0.93 |
| BMI | −0.07 | 0.94 | −0.01 | 0.92 |
| Smokers | −0.76 | 0.46 | −0.09 | 0.93 |
| Diabetes mellitus | −0.22 | 0.83 | −0.09 | 0.93 |
| Hypertension | −0.12 | 0.9 | 0.59 | 0.56 |
| Total serum cholesterol | 0.04 | 0.97 | 0.23 | 0.82 |
| LDL baseline | 0.10 | 0.92 | −0.04 | 0.96 |
| Delta LDL | −0.17 | 0.87 | −1.00 | 0.33 |
| Systolic blood pressure baseline | 0.10 | 0.92 | 0.42 | 0.68 |
| Diastolic blood pressure baseline | −0.04 | 0.97 | 0.08 | 0.94 |
| Delta systolic blood pressure | 0.11 | 0.92 | −0.39 | 0.71 |
| Delta diastolic blood pressure | 0.55 | 0.59 | −0.93 | 0.38 |
| Mean IMT baseline | −0.16 | 0.87 | −0.91 | 0.38 |
| Maximum IMT baseline | −0.08 | 0.94 | −0.28 | 0.78 |
| Follow-up | −0.06 | 0.95 | −0.02 | 0.99 |
| Jadad quality score | −0.36 | 0.72 | −0.06 | 0.96 |
| Year | 0.89 | 0.38 | 0.07 | 0.94 |

Abbreviations as in Tables 1 and 2.

lack of association between IMT changes and clinical outcomes. Indeed, they should foster adequate intervention prospective studies to assess whether IMT changes may be considered a valid surrogate end point for monitoring of cardiovascular risk profile in individual patients.

In addition, as it is inherent to meta-analyses, the uncertain definition and allocation of end points may differ among trials, especially for soft end points. However, confirmation of our findings when only hard cardiovascular end points were considered support our results and limits the potential confounding effect of this limitation (see Online Appendix Fig. 1 and Table 1).

Furthermore, several of the covariates included were trial level, because of unavailability of access to individual study participant data. However, it has been reported that, when the number of studies and of subjects in studies is not small, meta-regression with aggregated data is reliable and meaningful (42).

Although the selection of potential effect modifiers was made taking into account general characteristics, baseline risk, IMT results, and quality of the trials, meta-regression analysis could only be based on published results of the trials. Thus, complete information about potential effect modifiers were not available for all trials included in the study. In addition, we selected trials that measured carotid IMT and trials that reported clinical events; thus, large outcomes trials not reporting IMT where excluded. Therefore, the relationships between

some baseline measures (LDL, and so forth) are less robust than those from larger outcomes trials.

Technical aspects concerning the reproducibility of serial within-individual changes and lack of standardization of IMT measurements may also play a role to explain the findings of the present study in which trials using different methodological approaches were pooled. Indeed, carotid IMT measurements are prone to generate variability in follow-up studies, mostly sonographer dependent. However, in controlled clinical trials, measurement variability has been decreasing, owing to technical improvements, standardization, and training (43). Furthermore, in multicenter trials, images are handled and IMT measurements recorded off line in a core ultrasound laboratory that limits, likely substantially, technical errors in measurements. Yet, to take into account this potential limitation, we performed a sensitivity analysis with the year of trial publication as covariate that did not show a significant influence on results (Table 6). In addition, considering the potentially suboptimal standardization of IMT measurement in small studies, we performed a sensitivity analysis excluding studies that did not measure IMT in a central core laboratory, and our results again did not significantly change.

## Conclusions

Although IMT increase indicated an increased cardiovascular risk, favorable changes induced by drug therapies do not consistently reflect improved clinical outcome.

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**Key Words:** atherosclerosis ■ cardiovascular risk ■ intima-media thickness.

**APPENDIX**

**For study acronym definitions, supplementary references, and supplementary figures, please see the online version of this article.**