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Running title: Vascular risk factors and C-IMT progression

Traditional Risk Factors are Causally Related to Carotid Intima-Media Thickness Progression: Inferences from Observational Cohort Studies and Interventional Trials.

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ABSTRACT

In the present review, associations between traditional vascular risk factors (VRFs) and carotid intima-medial thickness progression (C-IMTp) as well as the effects of therapies for VRFs control on C-IMTp were appraised to infer causality between each VRF and C-IMTp. Cohort studies indicate that smoking, binge drinking, fatness, diabetes, hypertension and hypercholesterolemia are associated with accelerated C-IMTp. An exception is physical activity, with mixed data. Interventions for the control of obesity, diabetes, hypertension and hypercholesterolemia decelerate C-IMTp. Conversely, scarce information is available regarding the effect of smoking cessation, stop of excessive alcohol intake and management of the metabolic syndrome. Altogether, these data support a causative role of several traditional VRFs on C-IMTp. Shortcomings in study design and/or ultrasonographic protocols may account for most negative studies, which underlines the importance of a careful consideration of methodological aspects in investigations using C-IMTp as the outcome.

Key words: atherosclerosis, risk factors, carotid intima-medial thickness, atherosclerosis progression, ultrasonography, causality.

1. INTRODUCTION

Changes in subclinical atherosclerosis over time has been utilized to investigate which environmental or endogenous conditions accelerate atherosclerosis progression and which life-style or pharmacological interventions retard, or even halt, this process. Progression of subclinical atherosclerosis may be assessed by measuring changes of the intima-medial thickness of carotid arteries (carotid intima-medial thickness progression or C-IMTp) using non-invasive ultrasonographic techniques. Numerous studies have been published reporting associations between exposure to traditional cardiovascular risk factors (VRFs), their control and C-IMTp. The results of these studies are rather heterogeneous, possible due to differences in study population, sample size, length of follow-up, methodology of C-IMT measurement and statistical analyses.

In the present narrative review, we examine critically the literature on this topic to provide support or to question inferences of causal VRFs – C-IMTp relationships.

2. MATERIALS AND METHODS

PubMed was searched for original articles with full text available published until June 2019, by combining the following terms: 1) “carotid IMT OR carotid intima* media* thick*” AND 2) “progression OR chang*”, limiting the search to human studies written in English. Given the vast number of published studies that are either small, short-term and/or without proper methodologies, this review was restricted to studies that fullfil the following minimal prespecified inclusion criteria:

1. time between baseline and final C-IMT assessment ≥ 12 months
2. proper statistical power ($\alpha = 0.05$, $\beta > 80\%$)
3. reported assessment of reproducibility of C-IMT measurements
4. statistical analysis with mandatory adjustment for age and gender and optional adjustment for a variable series of other potential confounders.

Figure 1 shows the flowchart of study selection, as well as the number of studies excluded and the reasons for exclusion. Selected studies included observational population-based studies and clinical trials. In the latter, data from the placebo groups were considered, whenever available, to describe relationships between putative risk factors and C-IMTp, whereas data from the actively treated group/s were considered to describe the effect of the intervention/s on C-IMTp. Each title and/or abstract identified by the search strategy was independently reviewed by two investigators (BF, PW), who determined the potential eligibility of the study. Full texts of potentially suitable articles were obtained and further screened for inclusion. Controversies were discussed and solved with a third investigator (DB). Selected studies were tabulated according to main distinct categories of traditional risk factors reported to influence C-IMTp.

Given the methodological heterogeneity of ultrasonographic protocols, detailed data were obtained regarding the carotid segment/s, carotid side (left and/or right) and arterial interface (far-wall and/or near-wall) considered in each study. In addition, since risk factors and their control could affect IMT and atherosclerotic plaques differently, it was specified whether IMT measurements incorporated plaques or not. Collected data was scrutinized by three investigators (MA, DS, LV) for potential influences of these methodological features on study results.

Due to the heterogeneity of study types (observational or interventional), type of population (healty subjects or other), ultrasonographic protocols, follow-up length, etc., a metanalytical approach was deemed unsuitable and the results are presented in a narrative style as reported in each study.

3. RESULTS

Unmodifiable vascular risk factors and C-IMTp

Aging, male gender and familial history of premature cardiovascular events are among the most powerful VRFs and each of them has been consistently associated with accelerated C-IMTp [1-9]. These risk conditions are not modifiable and do not represent targets of therapy. Conversely, we focus on modifiable VRFs. Though several of these conditions are very commonly interrelated (e.g. obesity with hypertension or diabetes, physical activity with food intake and metabolic syndrome, etc.), they will be considered separately, as far as possible, in an attempt to appreciate the relationship between each specific modifiable VRF and C-IMTp.

Life style

Cigarette smoking, physical inactivity, excessive alcohol intake and unhealthy diet are the most consolidated life-style associated VRFs. The following paragraphs describe the relationship between these conditions and C-IMTp as well as the effect of lifestyle modifications.

Cigarette smoking and C-IMTp

The relationship between smoking status and C-IMTp was investigated in general populations and specific patients cohorts (Table 1; supplementary material). In the KIHD cohort study, a population-based sample of middle-aged Finnish men, smokers had a 2.1-fold (P=0.007) age-adjusted C-IMTp compared with nonsmokers during 2-years follow-up [10]. Significant effects of cigarette smoking were observed also in the ARIC, a population-based cohort study of middle-aged American adults among which, in a 3-years follow-up, current smokers and former smokers showed a 50% and 25% higher C-IMTp, respectively, than never smokers [11].

In a small group of patients with metabolic syndrome (n=301), four groups were identified according to smoking status at entry and at 12 months: never smokers, past smokers, quitters, and persistent smokers. After 12 months of follow-up even a C-IMT regression was observed in never smokers, past smokers and quitters (by -2.78%, -0.33%, and -1.16%, respectively), whereas persistent smokers showed a progression of 33.3% from baseline [12]. Current or even past smoking emerged by multivariate analyses as independent predictors of C-IMTp in many other population-based cohort studies [4,7,8,13-19], as well as in patients with hypercholesterolemia [20], type 1 diabetes (T1DM) [21], or cardiovascular disease (CVD) [22]. Moreover, the impact of smoking on C-IMTp appeared to be greater in subjects affected by diabetes and hypertension, as shown in the ARIC study [11].

The higher C-IMTp observed in former smokers than in never smokers suggests that previous exposure to cigarette smoke may engender a kind of “memory” effect [4,11]. Yet, no data about the time elapsed since smoking cessation is provided in these studies and therefore, how long this putative memory of smoke on C-IMTp could persist is currently unknown.

Even passive smoking was recognized as a cardiovascular risk factor for CVD [23]. In the ARIC Study, subjects who were in close contact with smokers for more than one hour per week in the past year had, in a 3-years follow-up, a 20% higher C-IMTp than those not exposed [11]. All together, these observational data suggest that both active and passive smoking are risk factors for C-IMTp.

Smoking cessation and C-IMTp

Curiously, only one study investigated the effect of active intervention on smoking cessation on C-IMTp and, paradoxically, there was a greater increase of C-IMT among subjects who were continuously abstinent compared to those who smoked continuously (p

=0.020) in a 3-years follow-up [24] (Table 1; supplementary material). A possible explanation to this counterintuitive finding is that the significantly higher weight gain in abstinents (by two BMI points, >10-fold vs continuers) could have offset the favorable effect of smoke quitting. It is worth noting that in this study IMT was measured only in the distal 1 cm of each common carotid artery, a segment hardly affected by atherosclerosis (see below paragraph on “controversies”). Indeed, the authors openly recognize that the effect of smoking cessation of C-IMTp in the internal carotid or bulb may have been different to that observed in the common carotid artery.

Alcohol consumption and C-IMTp

The association between binge drinking (heavy acute intake of alcoholic beverages) and C-IMTp was investigated in a population-based sample of middle-aged Finnish men from the KIHD study (Table 2; supplementary material) [25,26]. After a 4-years follow-up, heavy binge drinkers (≥480 ml of vodka) had a significantly higher C-IMTp than less heavy ones (≤240 ml of vodka) [25]. A similar but not significant trend was observed with the beer-drinking pattern [25]. These results were corroborated after 11-years follow-up [26]. We did not find studies about the association between excessive chronic daily alcohol consumption and C-IMTp.

Cessation of excessive alcohol consumption and C-IMTp

We did not find eligible studies on the effect of cessation of either binge or daily excessive alcohol consumption on C-IMTp.

Dietary style and C-IMTp

A few observational studies investigated the association between spontaneous dietary habits and C-IMTp (Table 3; supplementary material). In the IRAS, a multi-center

observational study conducted in a multi-ethnic cohort of middle-aged adults, the impact of various food patterns on C-IMTp was investigated in a subgroup of non-diabetic subjects followed for 5 years [27]. The results showed that a high intake of low-fiber bread and cereal, red and processed meat, cottage cheese, tomato foods, regular soft drinks and sweetened beverages, along with a low intake of wine, rice, pasta and poultry is associated with an accelerated C-IMTp. In another publication of the same study, an inverse but marginally significant association between whole grain intake and C-IMTp was observed [28].

In the Los Angeles Atherosclerosis Study [29], a prospective study in middle-aged adults without CVD followed for 2 years, the intake of viscous fiber and pectin was inversely associated with C-IMTp.

Plasma carotenoid levels, which may reflect carotenoid intake, were also inversely associated with C-IMTp [30-32].

A positive association was found between dietary sodium intake and C-IMTp during 5.3 years of follow-up in Korean adults aged 40 years and older.[33]

Thus, different food components have been associated with the rate of C-IMTp in observational studies. However, observations may be affected by confounding factors such as deleterious or protective habits that cluster with a certain self-chosen food intake.

Dietary changes and C-IMTp

Interventional studies investigating the effect of specific foods or dietary patterns on C-IMTp are summarized in Table 3; supplementary material. A low fat “prudent-like” phase A diet or the Mediterranean Diet, the most widely recommended “heart-friendly” dietary patterns, have been both associated with positive effects on C-IMTp. In fact, in elderly men with long-standing hyperlipidaemia, prescription of a phase A diet (≤30% of energy from fat, saturated fat <1/3 of total fat, cholesterol <300 mg/day, <15% of energy from protein,

≥55% of energy from carbohydrates and not more than 2-3% of energy from alcohol) was associated with a significant reduction in C-IMTp (p=0.047) as compared with a control group without dietary advice [34]. Besides, in a post-hoc analysis of the PREDIMED Study, the effects on C-IMTp of a Mediterranean Diet enriched with either nuts or virgin olive oil, as compared with a low-fat control diet, were evaluated in 187 high-risk asymptomatic Spanish adults. After 1-year, no significant between-group difference in C-IMTp was observed. However, in a subgroup of subjects with elevated baseline C-IMT (>0.9 mm), both types of Mediterranean Diets, but not the control diet, not only reduced C-IMTp but even induced C-IMT regression [35]. Moreover, in a 2.4-years follow-up of another PREDIMED subcohort of 175 high-risk asymptomatic adults from Barcelona (Spain), a Mediterranean Diet supplemented with nuts but not with virgin olive oil was associated with a delayed C-IMTp, whereas a significant C-IMT progression was observed in participants allocated to the control diet group [36]. Whether these positive effects depend on specific nutrients of the Mediterranean Diet or to the whole Mediterranean style is unknown.

In people with diabetes, increasing the intake of fruit (+1 serving; 150 g/day), vegetables (+2 servings; 150 g/day), and dairy products (+1 serving; 200-250 g/day) slowed the 12-months C-IMTp compared with a control group on usual diet [37].

Positive results were also obtained with n-3 fatty acids supplementation. In a randomized open study in Japanese type 2 diabetics, C-IMT of the group treated with eicosapentaenoic acid (EPA, 1800 mg/day) for about 2 years showed a significant regression compared with the untreated control group [38].

In hypertensive patients, the level of adherence to a fish-rich dietary intervention, assessed through changes in the PUFA/SFA ratio, was inversely related to C-IMTp [39].

Negative results were obtained with isoflavone soy supplementation in postmenopausal women [40]. However, a reduced C-IMTp was observed in women who were in menopause since less than 5 years, suggesting that the beneficial effect of isoflavone soy

supplementation could be achieved only if the treatment is started close to the beginning of menopause.

The vitamin most frequently tested for a putative anti-atherosclerotic effect was vitamin E. Contrarily to the positive results of early observational studies [41], most randomized trials aimed at evaluating the effect of vitamin E on C-IMTp have shown no effect [42-44]. Curiously, whereas vitamin C alone failed to reduce C-IMTp in randomized studies, a positive effect was observed with a combination of vitamins E and C [45,46].

Overall, the evidence supports that the Mediterranean diet style may halt C-IMTp whereas the strength of available evidence for a role of any specific food, nutrient or micronutrient supplement is rather weak.

Physical activity and C-IMTp

A few observational studies investigated the relationship between levels of physical activity and C-IMTp (Table 4; supplementary material). In the Los Angeles Atherosclerosis Study, physical activity during leisure time in 500 healthy adults was inversely associated with the 3-years C-IMTp [47]. A paradoxical positive association between workplace physical activity and C-IMTp was observed in this study, in agreement with results of another prospective study in Finnish men followed for 11 years [48]. This paradox might be explained by confounding factors not considered in the multivariate analyses or, alternatively, by opposing effects on C-IMTp of different neuro-hormonal changes during physical activity performed in leisure time (usually pleasant) versus working time (often stressful). In another study carried out in a healthy European population, the average intensity of daily physical activity, objectively measured using an accelerometer, was unrelated to the 3-years C-IMTp [49]. However, C-IMTp was significantly lower in subjects with vigorous activity than in those with light-to-moderate activity. Thus, results of observational studies on physical activity and C-IMTp are not consistent, but suggest that

a deceleration of C-IMTp, if any, might be related to how vigorous the physical activity is and in which context it is carried out.

Physical activity interventions and C-IMTp

In patients with type 2 diabetes, a 1-year intervention based on 3 weekly exercise sessions of either “high-intensity interval training” or “moderate continuous training” (both on top of resistance training) significantly reduced C-IMTp as compared with controls, who only received standard counseling and information regarding general physical activity [50].
In contrast, in a group of adolescents, no differences in C-IMTp were observed between a sport practice group (≥ 300 min/week of organized sports) and a control group (non-sport practice) during 1-year of follow-up [51]. A possible explanation to this discrepancy between results is that C-IMTp in healthy adolescents may be too slow, as compared with diabetic adults, to detect treatment effects in a 1-year period of intervention.

Combined dietary and physical activity interventions and C-IMTp

Table 5 (supplementary material) shows data on the effect of diet plus physical activity on C-IMTp. In perimenopausal and postmenopausal women, a 4-years lifestyle intervention (reduced calories, total and saturated fat and cholesterol dietary intake and increased leisure time physical activity) halved C-IMTp vs a control group (0.004 mm/y vs 0.008 mm/y, P=0.02) [52]. Moreover, not merely a reduced C-IMT progression but even a regression was observed in Japanese hypercholesterolemic patients [53] and in obese adolescents [54,55] subjected to a dietary and physical activity intervention for 2-years and 1-year, respectively. However, in another controlled study, a similar lifestyle intervention for 4 years in postmenopausal women did not affect C-IMTp [56]. Similarly, no effects on C-IMTp of intensive combined lifestyle changes were reported in sedentary hypertensive and hypercholesterolemic men in the HYRIM trial [57]. Altogether, these results are rather

contradictory and therefore, a favorable effect of diet plus physical activity on C-IMTp may be not generalizable but detectable only in distinct groups subjected to specific interventions.

Obesity and C-IMTp

The association between obesity and C-IMTp was investigated in observational studies, but using different measures of body fatness and in dissimilar populations (Table 6; supplementary material). Altogether, most studies support the concept that obesity has a deleterious effect on C-IMTp. Indeed, with the exception of the ARIC study [58], BMI was an independent predictor of C-IMTp in a sample of middle-aged employees [59] and in current smokers [24]. In addition, waist circumference was directly associated with C-IMTp in a population based cohort [60] and waist-to-hip ratio was associated with accelerated C-IMTp both in a population based cohort [61] and in patients with coronary artery disease (CAD) [22]. Thus, though available data are not fully consistent, body fat seems to associate with accelerated C-IMTp at least in some population or patients' categories.

Weight loss in obesity and C-IMTp

Either weight loss obtained through medical nutritional interventions [62-64] or bariatric surgery [65-67] has been associated with a reduced C-IMTp in several studies (Table 6; supplementary material). Of particular interest is the study of Buscemi et al.[62] which shows a significant correlation between *changes* in body weight and *changes* in C-IMT. Conversely, treatment of obese patients with rimonabant for 30 months, though effective in reducing body weight compared to placebo, did not influence C-IMTp [68]. Therefore, it is possible that weight loss induced by drugs may not exert the favourable effect on C-IMTp obtained in obese patients with reduced energy intake or increased energy expenditure.

Other studies investigated the effect of weight loss on C-IMTp in children [63,64]. In obese children with non-alcoholic fatty liver disease, C-IMT did not change significantly after a 1-year intervention program of hypocaloric diet and physical exercise [64]. Though the absence of progression might be interpreted as a positive outcome, the lack of a control group in this study impedes to seize the true impact of the intervention. However, the C-IMT *regression* observed in overweight children subjected to weight-reducing life-style changes in another study [63] suggests a favorable effect of weight loss on C-IMTp even in children.

Metabolic syndrome and C-IMTp

The Metabolic Syndrome (MetS) is a prevalent condition characterized by central obesity, hypertension, hypertriglyceridemia, low HDL-C levels and insulin resistance.

In the Young Finns Study cohort, patients with MetS at baseline had an accelerated C-IMTp during 6-years of follow-up compared with those without [60] (Table 7; supplementary material). Similar findings were reported in middle-aged Japanese women [69], in middle-aged men free of diabetes and CVD [70], in an elderly population [71] and in apparently healthy adults [72] followed for variable periods. In the population-based Tromsø Study, MetS at baseline was associated with C-IMTp during 13-years follow-up in subjects below 50 years of age at baseline [73]. Only in the ELSA study, the presence of MetS was not associated with C-IMTp: however, this was a randomized trial conducted in hypertensive patients with higher baseline C-IMT. In this particular population, the strong effect of hypertension and of hypertensive treatment could have masked the effect of MetS [74]. Statistical models, applied to data from the Los Angeles Atherosclerosis Study, suggest that the atherogenicity of MetS is mediated by its components, with possible gender-based differences; for example, triglycerides were significantly associated with C-IMTp only in women [75].

In at least two [70,72] of these studies [69-74], a change from a normal metabolic status at baseline to the presence of MetS at follow-up (or the presence of MetS at both visits) was associated with an increased C-IMTp, compared to patients with MetS at baseline but not at follow-up, in whom a reduced C-IMTp was observed [69,76].

Treatment of the metabolic syndrome and C-IMTp

The lack of interventional studies in MetS with assessment of C-IMTp impedes to strengthen the notion of MetS as a risk factor for C-IMTp.

Glucose derangement and C-IMTp

The influence of abnormalities in glucose metabolism on C-IMTp has been investigated in several observational studies (Table 8; supplementary material). Results of the IRAS study [14] suggest that C-IMTp relates to the severity of the glucose metabolism derangement. In fact, in a 5-years follow-up, C-IMTp was the lowest in subjects with normal glucose tolerance, greater in patients with impaired glucose tolerance, and the greatest in those with either known or newly diagnosed T2DM. These results are in line with other studies showing that baseline T2DM [4,9,16,17,77-79] and onset of T2DM during follow-up [17] are associated with an increased C-IMTp. Studies performed solely in patients with T2DM [3,80] show an annual C-IMTp significantly higher than that reported in general populations. Results of studies that used biochemical markers of glucose derangement coincide with those that compared discrete clinical diagnostic categories. In fact, fasting glucose predicted C-IMTp in population studies [13,19,81]. Similarly, HbA1c levels were directly associated with C-IMTp in three [3,82,83] out of four studies carried out in patients with T2DM [3,82-84]. Significant associations with C-IMTp were also reported for glycated albumin (GA) [83], HbA1c/GA ratio [83] and 2-h post-challenge glucose [82]. HOMA index was associated with C-IMTp in a prospective cohort study [13].

In summary, most of these studies indicate that pre-diabetes and overt T2DM are associated with an accelerated C-IMTp.

For obvious reasons (immediate need of insulin treatment), no observational data are available on the natural history of C-IMTp in T1DM. As well, data are lacking regarding C-IMTp in less prevalent disorders of glucose metabolism, such as gestational or secondary diabetes.

Diabetes control and C-IMTp

Hypoglycaemic drug therapies (acarbose [85], voglibose [86], nateglinide [87], alogliptin [88], sitagliptin [89]), tested versus placebo or an untreated group, retarded C-IMTp, whereas gliclazide [90], repaglinide [91] or glibenclamide combined with metformin [90] outperformed in comparison with glibenclamide monotherapy (Table 8; supplementary material). One study evaluated the effect of troglitazone on C-IMTp in patients with T2DM before the drug was withdrawn from the market due to liver toxicity. Compared with placebo, troglitazone treatment did not reduce C-IMTp in insulin-requiring type 2 diabetics [92]. Similarly, rosiglitazone did not affect C-IMTp in patients with T2DM [93,94] or pre-diabetes [95]. Conversely, pioglitazone (the only thiazolidinedione still in commerce), reduced C-IMTp in patients with impaired glucose tolerance (versus placebo) [96] and in patients with T2DM, as compared with either glimepiride [97] or with non-thiazolidinedione oral anti-diabetic drugs [98]. These data suggest that the anti-atherosclerotic effect of thiazolidinediones may be compound specific. Yet, studies by Xiang et al. showed that, in women with a history of gestational diabetes, both troglitazone [99] and pioglitazone [100] slowed C-IMTp, possibly indicating a singular efficacy of thiazolidinediones in this specific patient population.

In the ORIGIN-GRACE study [101], patients with CVD and/or traditional VRFs plus a) impaired fasting glucose, b) impaired glucose tolerance, or c) early T2DM received insulin

glargine or standard glycemic care. The effects of insulin glargine and standard care did not differ significantly in terms of C-IMTp.

The result of this study suggest that insulin treatment in patients with T2DM, though often needed to control hyperglycemia, may not favorably impact C-IMTp.

The case seems to be different in hypoinsulinemic conditions. The effect of intensive glycemic control on C-IMTp in patients with T1DM was assessed in the EDIC study [21], which was a long-term follow-up of the DCCT study [102]. In the DCCT study, patients had been treated for 6.5 years with either conventional therapy (one or two daily injections of insulin, without adjustment of insulin dosage) or with intensive therapy (insulin three or more times daily, with dosage adjusted according to the results of glucose self-monitoring). During the subsequent EDIC study, all patients received intensive therapy and were reevaluated at one, six and twelve years after EDIC start. In the EDIC study, [21] C-IMTp was lower in patients that, in the original DCCT study, had been treated intensively than in those that had been treated conventionally [102]. This suggests that early initiation of intensive insulin treatment in T1DM may retard atherosclerosis progression.

In summary, in T2DM, drugs used to control glucose metabolism affect C-IMTp differently, and some of them retard it significantly. Moreover, precocious intensive insulin therapy slowed C-IMTp in T1DM. Overall, these results support a pathogenic role of abnormalities in glucose metabolism on C-IMTp.

Hypertension and C-IMTp

Diagnosis of hypertension [4,8,9,14-16] and blood pressure levels [4,7,13,19,75,77,103-106] were both directly associated with C-IMTp, with one exception [81] (Table 9; supplementary material). Moreover, several blood pressure variables associated with C-IMTp differently [17,107-110]. Specifically, in the KIHD study, baseline systolic blood pressure (SBP) but not diastolic blood pressure (DBP) had a strong and graded positive

relationship with C-IMTp [108]. Another study suggests that C-IMTp already starts to accelerate at SBP levels of about 120 mmHg [108]. Finally, pulse pressure [17,107,108] and blood pressure changes [109,110] were also associated with increased C-IMTp.

Control of hypertension and C-IMTp

In population-based cohorts, baseline use of anti-hypertensive medication was associated with reduced C-IMTp during follow-up [8,111] (Table 9; supplementary material).

The Campania Salute Network assessed whether different targets of SBP (tight control: SBP<130 mmHg or usual control: SBP 130-140 mmHg) achieved during follow-up are associated with different C-IMTp in a group of 4,148 treated hypertensive patients. After a median follow-up of 74 months, C-IMTp was similar in both groups without significant difference related to SBP target. However, it should be stressed that participants had a long-lasting history of hypertension, were under antihypertensive treatment and, in most cases, were already in good blood pressure control. Thus, it is possible that in many cases the maximal effect achievable with antihypertensive treatment had already been obtained in many patients, thus reducing the chance to detect substantial changes in C-IMTp [112].

Many randomized clinical trials evaluated the effect of anti-hypertensive therapy on C-IMTp. Favorable effects were obtained with either diuretics [113], β-blockers [114-117], ACE inhibitors [44,118,119], angiotensin II receptor antagonists [116], calcium channel blockers [113-115,118,120] or α1 receptor -selective blockers [121]. Only a few studies with ACE inhibitors failed to detect significant effects. [95,122,123]

A study suggests that reducing SBP to less than 115 mmHg results in a greater reduction of C-IMTp compared to less intensive treatment [124]. This study showed that, in diabetic patients, an aggressive therapy aimed at decreasing SBP to values ≤115 mmHg and LDL-C to values ≤70 mg/dl halted C-IMTp, whereas C-IMT progressed in less intensively treated patients. However, it is not discernible whether the beneficial effect is related to the

intensity of the anti-hypertensive treatment or, rather, to the combined lipid and blood pressure intensive control. The consistent results of both observational studies and blood pressure lowering interventions (with the exception of some ACE inhibitors), strongly support a pathogenic role of high blood pressure on C-IMTp.

Dyslipidemia and C-IMTp

Total cholesterol and LDL-C levels were directly associated with C-IMTp in population based cohorts [4,7,10,15,60,125-128], in healthy subjects [18,129-131] and in patients with diabetes [82] (Table 10; supplementary material).

Similar direct associations with C-IMTp were reported for triglycerides [126,132], whereas HDL-C levels associated inversely with C-IMTp in population based cohorts [13,17,111,126,133], in patients with VRFs [82,130,134,135] or CAD [22].

Studies performed in different patient populations investigated also associations of C-IMTp with lipid ratios, lipoprotein species, apolipoproteins and modified lipoproteins. Significant direct associations were reported for TC/HDL-C [9,132], TG/HDL-C [132], ApoB/HDL-C [132], VLDL-C [135], $VLDL_{1+2}$-C [135], ApoB levels [126] or ApoB/ApoA-I ratio [136].

Levels of HDL2-C and HDL3-C associated inversely with C-IMTp [135].

The association of C-IMTp with lipoprotein(a) levels [137,138] was not fully consistent. Indeed, levels of lipoprotein(a) were associated with C-IMTp in one high-risk condition (i.e. T2DM) [137] but not in another (heterozygous familial hypercholesterolemia)[138].

Control of dyslipidemia and C-IMTp

Many studies demonstrated a favorable effect of lipid management on C-IMTp (Table 10; supplementary material). In two observational cohort studies, baseline or long-term use of drugs affecting lipid metabolism was an independent predictor of reduced C-IMTp [111,139]. Moreover, a plethora of clinical trials with different statins consistently showed a

slower C-IMTp in patients actively treated with a statin versus placebo [20,57,140-150] or versus a less potent statin [151], with only few exceptions [152,153]. Indeed, treatment of different patient groups with lovastatin [140-143], pravastatin [20,144-146,153,154], rosuvastatin [147-149], fluvastatin [57,155], atorvastatin [150] or pitavastatin [156] was superior in decreasing C-IMTp than either placebo or a lower-dose of the same statin or a statin with less LDL-C lowering efficacy. An exception to these results was a study with pitavastatin and atorvastatin, in which the former produced a greater percent reduction in C-IMTp than the later, even if they were used at equipotent LDL-C lowering doses [151]. The effect of statins on C-IMTp was not evident in only one study in T2DM patients, where treatment with cerivastatin (substituted with simvastatin when cerivastatin was withdrawn) did not influence C-IMTp differently to placebo [152].

Though the beneficial effects of statins on C-IMTp might be related, at least in part, to purported lipid-independent pleiotropic anti-atherogenic actions, as suggested by a post-hoc analysys of a statin trial [157], LDL-C lowering non-statin drug interventions also reduce C-IMTp [158,159], supporting LDL-C exposure as a major player in C-IMTp. Contrarily, the addition of ezetimibe on top of a statin, though more effective in terms of LDL-C reduction, was not superior in reducing C-IMTp than a statin alone [160-162]. A relatively negligible incremental effect on C-IMTp of ezetimibe on top of an already intensive treatment with statins (a kind of saturation) may be a plausible explanation to these negative findings. In addition, the single trial which reported a counter-intuitive inverse correlation between LDL-C changes and C-IMTp was with ezetimibe [163].

Exceptional insight may be gained from the results of lipid-lowering trials performed in patients with familial hypercholesterolemia (FH), as these patients have long-life and extremely high LDL-C levels as the main or even single VRFs.

An open study investigated the effect of simvastatin 80 mg on both carotid and femoral IMT progression in FH patients [164]. After a 2-years follow-up, IMT significantly

decreased in both districts. In the first controlled study with statins in FH, namely ASAP, patients with heterozygous FH were randomized to atorvastatin 80 mg/day or simvastatin 40 mg/day [165]. After 2 years, IMT decreased in patients treated with atorvastatin, and increased in those treated with simvastatin. After completion of the ASAP study, patients were invited to continue a 2-year extension study with atorvastatin 80 mg/day [166]. Participants who received atorvastatin in both periods had a complete arrest of C-IMTp whereas those who shifted from simvastatin to atorvastatin had significant IMT regression. These results indicate that a high-dose/high-potent statin is required to halt atherosclerosis progression in patients with FH.

In the ENHANCE study, patients with heterozigous FH were randomized to simvastatin 80 mg with either placebo or ezetimibe 10 mg. In line with previous trials with ezetimibe in non FH hypercholesterolemic patients [160-162,167], addition of ezetimibe to the statin did not result in significant differences in C-IMTp despite a greater reduction in LDL-C levels [168]. Altogether, the negative results of trials in non-familial and familial hypercholesterolemic patients raise the possibility of a compound-specific inefficacy of ezetimibe on C-IMTp.

Only one study evaluated the effect of statins on C-IMTp in children with FH [169]. In this trial, a trend towards C-IMT regression was observed in those treated with pravastatin (20 to 40 mg/day) and a trend toward C-IMT progression was seen in the placebo group. The two trends differed significantly [169].

Altogether, most of the interventional studies with statins and other non-statin drugs (except ezetimibe) support a pathogenic role of LDL-C on C-IMTp.

Though a favourable effect of LDL-apheresis, partial ileal bypass or other non-pharmacological LDL-C lowering interventions on C-IMTp might have reinforced the role of LDL-C on C-IMTp, we did not find studies with these interventions that fulfill the minimal methodological requirements prespecified in this review.

Studies with experimental lipid-modifying compounds provide insight about the influence of distinct lipoprotein species on C-IMTp. In RADIANCE 1, patients with heterozygous FH were randomized to either atorvastatin monotherapy or atorvastatin combined with torcetrapib, an inhibitor of the cholesterol ester transfer protein (CETP) which potently increases HDL-C. After 2-years follow-up, mean IMT decreased in the atorvastatin plus placebo group whereas it paradoxically increased in the atorvastatin plus torcetrapib group, notwithstanding the CETP inhibitor increased HDL-C by more than 50% [170]. Similar results were obtained in the RADIANCE 2 study in patients with mixed dyslipidemia [171] or in a pooled analysis [106].

It is possible that, in these studies, the increase in systolic blood pressure observed in patients treated with torcetrapib partially offset the potential benefit expected by lipid modification. Overall, proper interventional studies focused on HDL-C are lacking to corroborate the above described observational data about a protective role of HDL-C on C-IMTp.

Anyway, at the time being, a causal role of HDL-C itself on vascular disease is strongly debated and interventions that increase HDL-C levels have not demonstrated convincing changes in cardiovascular health overall [172-174].

4. THE UNRESOLVED CONTROVERSY ABOUT THE CLINICAL SIGNIFICANCE OF C-IMT PROGRESSION

The clinical relevance of C-IMTp fully relies on its ability to predict clinical outcomes. Although C-IMT changes are supposed to be an expression of changes in systemic atherosclerosis and, as a result, a marker of the risk of major clinical atherosclerotic events, some studies have confuted this intuitive relationship. These studies include two meta-regression analyses [175,176], in which average changes in C-IMT induced by active treatments (vs either placebo or a comparative drug) were correlated with the log-

transformed odds ratio for the clinical outcomes considered in each trial, using random-effects. Utilization of study group averages instead of individual data has been viewed as one among a series of possible factors that might explain the failure of these meta-regression analyses in demonstrating the expected ability of C-IMTp to predict clinical outcomes [177]. However, disappointing negative results were also reported in more recent meta-analyses of cohort studies in general populations [178], in patients with T2DM [179] and in high risk individuals [180] that, instead, computed individual data. In these latter studies, however, the analyses were focused on the relationship between clinical events and changes in IMT of the common carotid artery, which is the carotid segment more reproducibly assessed through vascular ultrasound but also the one less affected by atherosclerosis. Thus, a critical issue to consider in this controversy is the ultrasonographic protocol used to measure C-IMTp. In fact, protocols used so far to quantify C-IMTp may not appropriately reflect the focal process of atherosclerosis that account for vascular events. This possibility is suggested by a post-hoc analyses of the IMPROVE Study [181]. This multinational cohort investigation was aimed to evaluate the association between C-IMTp within 15 months and the rate of subsequent vascular events in a European population of adult patients at high cardiovascular risk. The study, indeed, shows that the only C-IMTp variable associated with cardiovascular outcomes is the newly devised "Fastest-$IMT_{max\text{-}prog}$", which is the greatest C-IMTp observed among the progression values of IMT_{max} of the entire carotid tree [181]. Yet, the Fastest-$IMT_{max\text{-}prog}$ was not a prespecified computation of the study and, therefore, replication in other large prospective studies carried out in general populations and patient groups is warranted to corroborate these findings.

5. SO, ARE TRADITIONAL RISK FACTORS CAUSATIVE OF ACCELERATED C-IMTp?

In this review, we found that the reported associations between exposure to traditional cardiovascular risk factors (VRFs), their therapeutic control and C-IMTp comply with several of the Bradford Hill's criteria of causality [182,183] as follows:

a) *temporality* is implicit in the observational cohort studies and in the intervention studies herein reviewed;

b) *consistency* is fairly good. Indeed, most of the established modifiable risk factors, including cigarette smoking, binge drinking, fatness (at least in some patient categories), hyperglycemia, hypertension, the metabolic syndrome and hypercholesterolemia, were associated with an accelerated C-IMTp. An exception was physical activity, as observational studies provided mixed results;

c) a *biological gradient* was recognizable with some risk factors, as C-IMTp related to the severity of the glucose metabolism derangement and with the extent of smoking exposure;

d) the *plausibility* is supported by the knowledge that traditional risk factors accelerate atherosclerosis development by a variety of biological mechanisms and the recognition that carotid IMT is a surrogate of subclinical atherosclerosis;

e) *experiment:* life-style changes or pharmacologic interventions to control hypercholesterolemia, hypertension, obesity and diabetes decelerate carotid wall thickening consistently.

Knowledge gaps still remain to draw conclusive inferences of causality between some risk conditions and C-IMTp. In particular, the available information on the effect of smoking cessation (one single negative study), alcohol abandonment and metabolic syndrome management is very limited or lacking.

Worth noting, several studies included in this review (n=24 out of 161 studies) did not find associations between traditional risk factors and C-IMTp or favorable changes in C-IMTp with interventions that reduce the alluded risk factors. However, a detailed scrutiny of these studies allowed us to identify, in most cases, one or more explanations to these

negative results: a) the population was very young and had baseline IMT in the normal range [51,64]; b) the time of observation was relatively short (1 year) to detect significant associations or changes in the sample investigated [51,64,93,94,167] and/or c) IMTp was evaluated only in the distal 1 cm of the common carotid artery, a segment hardly affected by atherosclerosis [24,40,42,43,51,64,81,84,92,122,123]. Actually, negative studies without one or more of these features (3 observational[49,74,112] and 5 interventional [56,57,95,101,152] were uncommon, which underline the importance of an attentive consideration of methodological aspects in the design of studies aimed to ascertain the clinical significance of C-IMTp.

In conclusion, the fairly consistent cause-effect relationship between traditional VRFs and C-IMTp evidenced in the present review and the potential relevance for research and patient care of having a non-invasive tool to monitor athero-progression strengthen the need to gain further knowledge on methodological aspects of C-IMTp quantitation and on the clinical significance and practical usefulness of C-IMTp assessment.

LIST OF ABBREVIATIONS

C-IMTp = carotid intima-medial thickness progression

VRFs= cardiovascular risk factors

C-IMT = carotid intima-medial thickness

T1DM = type 1 diabetes mellitus

CVD = cardiovascular disease

EPA = eicosapentaenoic acid

PUFA = poly-unsatured fatty acids

SFA = saturated fatty acids

T2DM = type 2 diabetes mellitus

CAD = coronary artery disease

MetS = Metabolic Syndrome

GA = glycated albumin

SBP = systolic blood pressure

DBP = diastolic blood pressure

LDL = low density lipoprotein

HDL = high density lipoprotein

TC = total cholesterol

TG = triglycerides

VLDL = very high density lipoprotein

FH = familial hypercholesterolemia

KIHD = Kuopio Ischaemic Heart Disease

ARIC = Atherosclerosis Risk in Communities

IRAS = Insulin Resistance Atherosclerosis Study

PREDIMED = Prevencion con Dieta Mediterranea

HYRIM = Hypertension High Risk Management trial

ELSA = The European Lacidipine Study on Atherosclerosis

ORIGIN = Outcome Reduction with an Initial Glargine Intervention

GRACE = Glucose Reduction and Atherosclerosis Continuing Evaluation Study

EDIC = Epidemiology of Diabetes Interventions and Complications

DCCT = Diabetes Control and Complications Trial

RADIANCE = Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor

IMPROVE = Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events

CONFLICT OF INTEREST

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

SUPPLEMENTARY MATERIAL

Supplementary tables 1-10 related to this article can be found in Supplementary material online.

Supplemental table 1. Cigarette smoking.

Study population (n) [Ref]	Age, y*	Male, %	Follow-up, y (mean values)	Carotid Segments**	Carotid side	Arterial interface measured	Intervention type	Results	Plaques included in IMT
Evidence of association between smoking habits and C-IMT progression									
Population based cohort (n=128) [10]	42, 48, 54 or 60***	100	2	CC	Right and Left	Far wall	NA	Smoking was a significant predictor of C-IMTp	no
MetS patients (n=301) [12]	68.3	69	1	CC	Right and Left	Far wall	NA	C-IMT regression was observed in never and past smokers and quitters (by -2.78%, -0.33%, and -1.16%, respectively), whereas persistent smokers showed a progression of 33.3% from baseline.	no
Population based cohort (n=3409) [4]	65.4	38	6.5	CC	Right and Left	Near and Far wall	NA	Smoking was a significant predictor of C-IMTp	no
Population based cohort (n=3426) [7]	56.3	41	16	CC	Right	Far wall	NA	Smoking was positively associated with C-IMTp	yes
Healthy subjects (n=364) [18]	48.5	100	2.3	CC	Left	Far wall	NA	Smoking was a significant predictor of C-IMTp	no
Hypercholesterolemic patients (n=426) [20]	57	100	3	CC Bulb	Right and Left	Far wall	NA	C-IMTp was higher in smokers compared to nonsmokers	yes
Population based cohort (n=1192) [14]	53.7 (NGT) 56.6 (IGT) 56.6 (UD) 56.7 (DD)	44	5.2	CC ICA	Right and Left	Near and Far wall	NA	Smoking was positively associated with C-IMTp	yes
Population based cohort (n=1207) [15]	53.7 (NGT) 56.6 (IGT) 56.6 (UD) 56.7 (DD)	44	5.2	CC ICA	Right and Left	Near and Far wall	NA	Smoking was positively associated with C-IMTp	yes
Population based cohort (n=10914) [11]	54	43	3	CC Bulb ICA	Right and Left	Far wall	NA	Smoking was associated with a 50% increase in C-IMTp. Exposure to environmental tobacco smoke was associated with a 20% increase in C-IMTp.	no
Stroke- and myocardial infarction-free subjects (n=712) [8]	54.7	38	4.3	CC Bulb ICA	Right and Left	Far wall	NA	Smoking was a significant predictor of C-IMTp	no
Population based cohort (n=842) [13]	36.4	42	2.4	CC Bulb ICA	Right and Left	Far wall	NA	Smoking was positively associated with C-IMTp	yes
Population based cohort (n=3383) [16]	51.7	49	3	CC Bulb	Right and Left	Far wall	NA	Smoking was a significant predictor of C-IMTp	yes

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Population based cohort (n=12644) [17]	45–64 (range)	45	9	CC Bulb ICA	Right and Left	Far wall	NA	Smoking was positively associated with C-IMTp	yes
Population based cohort (n=336) [19]	32.3	38	5.8	CC Bulb ICA	Right and Left	Far wall	NA	Smoking was a significant predictor of C-IMTp	yes
T1DM patients (n=1116) [21]	35	52	12	CC Bulb ICA	Right and Left	Not available	NA	Smoking was a significant predictor of C-IMTp	no
CAD patients (n=141) controls (n=139) [22]	61.6 (CAD patients) 56.3 (controls)	49	3	CC Bulb ICA	Right and Left	Near and Far wall	NA	Smoking was positively associated with C-IMTp in CAD patients.	yes
Smoking cessation: evidence level of causality									
Current smokers (n=795) [24]	45.2	42	3	CC	Right and Left	Far wall	smoking cessation pharmacotherapies (n=795)	Smoking status was not a significant predictor of C-IMTp.	no

*mean value reported or otherwise indicated, **carotid segments where IMT was measured, ***age-stratified sample of men 42, 48, 54, or 60 years old, CC=common carotid, ICA=internal carotid artery, NA=not applicable, NGT=normal glucose tolerance, IGT=impaired glucose tolerance, UD=undiagnosed diabetes, DD=diagnosed diabetes, T1DM=type 1 diabetes mellitus, CAD=coronary artery disease.

Supplemental table 2. Alcohol consumption.

Study population (n) [Ref]	Age, y*	Male, %	Follow-up, y (mean values)	Carotid Segments**	Carotid side	Arterial interface measured	Intervention type	Results	Plaques included in IMT
Evidence of association between alcohol consumption and C-IMT progression									
Population-based cohort (n=1022) [25]	42, 48, 54 or 60***	100	4	CC	Right and Left	Far wall	NA	Alcohol consumption was positively associated with C-IMTp	no
Population-based cohort (n=751) [26]	42, 48, 54 or 60***	100	11	CC	Right and Left	Far wall	NA	Alcohol consumption was positively associated with C-IMTp	no

*mean value reported or otherwise indicated, **carotid segments where IMT was measured, ***age-stratified sample of men 42, 48, 54, or 60 years old, CC=common carotid, NA= not applicable.

Supplemental table 3. Diet style.

Study population (n) [Ref]	Age, y*	Male, %	Follow-up, y (mean values)	Carotid Segments**	Carotid side	Arterial interface measured	Intervention type	Results	Plaques included in IMT
Evidence of association between diet style and C-IMT progression									
Middle age subjects (n=500) [29]	40-60 (range)	54	3	CC	Right and Left	Far wall	NA	Viscous fiber intake and pectin intake were inversely associated with C-IMTp	no
Cohort of utility employees (n=480) [30,31]	49.9	53	1.5	CC	Right and Left	Far wall	NA	Lutein, beta-cryptoxanthin, zeaxanthin and alpha-carotene levels were inversely associated with C-IMTp	no
Middle-aged subjects (n=840) [32]	55.6	100	6	CC	Right and Left	Far wall	NA	Lycopene, alpha-carotene and beta-carotene levels were inversely associated with C-IMTp	no
Healthy adults (n=2494) [33]	60.2	38	5.4	CC	Right and Left	Far wall	NA	Dietary sodium intake was positively associated with C-IMTp	no
Middle-aged subjects (n=840) [32]	55.6	100	6	CC	Right and Left	Far wall	NA	Lycopene, alpha-carotene and beta-carotene levels were inversely associated with C-IMTp	no
Middle-aged subjects (n=802) [27]	40–69 (range)	44	5	CC ICA	Right and Left	Far wall	NA	Higher intakes of less healthful foods and lower intakes of more healthful foods were positively associated with C-IMTp	yes
Middle aged subjects (n=1178) [28]	55.2	44	5	CC ICA	Right and Left	Near and Far wall	NA	Whole-grain intake was inversely associated with C-IMTp	yes
Dietary changes: evidence level of causality									
Elderly subjects (n=464) [34]	70	100	3	CC	Not available	Far wall	diet (n=233) no diet (n=231)	Dietary intervention slowed C-IMTp compared with controls (0.044±0.091 vs 0.062±0.105 mm; P=0.047)	no
High-cardiovascular-risk asymptomatic subjects (n=187) [35]	67	49	1	CC	Right and Left	Far wall	MedDiet+virgin olive oil (n=66) MedDiet+nuts (n=59) control diet (n=62)	No significant between-group differences in C-IMTp were observed. Among participants with baseline IMT≥0.9 mm, C-IMTp versus control showed significant differences of -0.079 mm (-0.145 to -0.012) for the MedDiet+virgin olive oil and -0.072 mm (-0.140 to -0.004) for the MedDiet+nuts	no
T2DM patients (n=118) [37]	56 (diet) 57 (controls)	56	1	CC	Right and Left	Far wall	diet (n=58) controls (n=60)	C-IMT regression was higher in the diet group compared with control group (-0.02±0.04 vs -0.004±0.04 mm; p=0.009)	no
Postmenopausal women (n=325) [40]	60.8 (isoflavone group) 60.9 (placebo group)	0	2.7	CC	Right	Far wall	isoflavone soy protein (n=162) placebo (n=163)	C-IMTp was similar in the soy protein and in the placebo group [0.0048 (0.0034-0.0062) vs 0.0057 (0.0043-0.0071) mm/y, p=ns]	no

T2DM patients (n=60) [38]	59.0 (EPA group) 61.2 (control group)	60	2.1	CC	Right and Left	Far wall	EPA (n=30) controls (n=30)	C-IMTp was slower in the EPA group compared with the control group (−0.029±0.112 mm vs 0.016±0.109 mm, p=0.029)	no
Hypertensive patients (n=56) [39]	64	48	1	CC	Left	Far wall	three weekly meals of fish (n=56)	Changes in the PUFA/SFA ratio were inversely associated with C-IMTp	no
Patients with prior coronary artery bypass graft surgery (n=146) [41]	54.2	100	2	CC	Right	Near and Far wall	high supplementary vitamin E users (n=22), low supplementary vitamin E users (n=124)	C-IMTp was slower in high supplementary vitamin E users compared with low vitamin E users (0.008±0.023 mm/y vs 0.023±0.020 mm/y, p=0.03)	no
Chronic smokers (n=331) [42]	63.5	43	4	CC	Right	Not available	vitamin E (n=170) placebo (n=161)	C-IMTp was similar between vitamin E and placebo [0.0035 (- 0.0008, 0.0078) mm/y vs – 0.0005 [-0.0049, 0.0039] mm/y, p=ns)	no
Subjects in primary prevention, >40 years old and with LDL >130 mg/dL (n=258) [43]	56.2	48	3	CC	Right	Far wall	vitamin E (n=121), placebo (n=137)	C-IMTp was similar between vitamin E and placebo (0.0040±0.0007 vs 0.0023±0.0007 mm/y, p=ns)	no
Hypercolesterolemic men and post-menopausal women (n=458) [45]	45-69 (range)	49	3	CC	Right and Left	Far wall	placebo (n=110) vitamin E (n=115) vitamin C (n=120) vitamin E and C (n=113)	Only combination of vitamin E and C slowed C-IMTp compared with placebo (0.011 vs 0.020 mm/y, p=0.008)	no
Hypercolesterolemic men and post-menopausal women (n=440) [46]	45-69 (range)	49	6	CC	Right and Left	Far wall	placebo (n=105) vitamin E and C (n=335)	Combination of vitamin E and C slowed C-IMTp compared with placebo (0.010 vs 0.014 mm/y, p=0.034)	no
High-cardiovascular-risk asymptomatic subjects (n=164) [36]	66	46	2.4	CC Bulb ICA	Right and Left	Far wall	MedDiet+virgin olive oil (n=57) MedDiet+nuts (n=46) control diet (n=61)	IMT progressed in the control diet group [0.052 mm (−0.014 to 0.118)] regressed in the MedDiet+nuts group [−0.084 mm (−0.158 to −0.010)], remained stable in the MedDiet+extra virgin olive oil group [−0.003 mm (−0.071 to 0.065)]	no
Subjects at high risk of CVD (n=693) [44]	65.0 (Vitamin E) 65.67 (placebo)	77	4.5	CC Bulb ICA	Right and Left	Near and Far wall	Vitamin E (n=349) placebo (n=344)	C-IMTp was similar between vitamin E and placebo (0.0180±0.0022 vs 0.0174±0.0020, p=ns)	yes

*mean value reported or otherwise indicated, **carotid segments where IMT was measured, CC=common carotid, ICA=internal carotid artery, NA=not applicable, AFG=altered fetal growth, NFG=normal fetal growth, T2DM= type 2 diabetes mellitus, CVD=cardiovascular disease

Supplemental table 4. Physical activity.

Study population (n) [Ref]	Age, y*	Male, %	Follow-up, y (mean values)	Carotid Segments**	Carotid side	Arterial interface measured	Intervention type	Results	Plaques included in IMT
Evidence of association between physical activity and C-IMT progression									
Middle aged subjects (n=500) [47]	50	54	3	CC	Right and Left	Far wall	NA	C-IMTp was the highest in sedentary subjects (0.143±0.017 mm/y), intermediate in moderately active subjects (0.102±0.001 mm/y) and the lowest in vigorously active subjects (0.055±0.015 mm/y) (p for trend <0.0001)	no
Population based cohort (n=612) [48]	49.5	100	11	CC	Right and Left	Far wall	NA	Occupational physical activity was positively associated with C-IMTp	no
Healthy subjects (n=495) [49]	44	49	3	CC Bulb ICA	Right and Left	Far wall	NA	C-IMTp was not associated to sedentary behaviour or to the average intensity of physical activity	no
Physical activity interventions: evidence level of causality									
T2DM patients (n=51) [50]	58.5	52.5	1	CC	Right	Far wall	Controls (n=22) MCT (n = 16) HIIT (n = 13)	Intervention induced C-IMT regression in both MCT group (from 0.738±0.158 to 0.712±0.111 mm, p<0.05) and HIIT group (from 0.734±0.159 to 0.724±0.119 mm, p<0.05)	no
Adolescents (n=74) [51]	11.6	48	1	CC	Right	Far wall	Sport (n=14) Controls (n=60)	C-IMTp was similar between sport group and controls [−0.001 (−0.010 to 0.008) mm vs 0.006 (−0.013 to 0.024) mm]; p=ns	no

*mean value reported or otherwise indicated, **carotid segments where IMT was measured, CC=common carotid, ICA=internal carotid artery, NA=not applicable, T2DM= type 2 diabetes mellitus, CAD=coronary artery disease, MCT=moderate continuous training, HIIT=high-intensity interval training

Supplemental table 5. Combined lifestyle modifications.

Study population (n) [Ref]	Age, y*	Male, %	Follow-up, y (mean values)	Carotid Segments**	Carotid side	Arterial interface measured	Intervention type	Results	Plaques included in IMT
Combined dietary and physical activity interventions: evidence level of causality									
Hypercholesterolemic patients (n=1390) [53]	56.9	29	2	CC	Right and Left	Far wall	lifestyle modification (n=437) lifestyle modification plus lipid-lowering drug (n=159) controls (n=794)	Lifestyle modification induced C-IMT regression both alone (−4.8 % in women and -6.8% in men) or in association with lipid-lowering drugs (-8% in women and -16.7% in men)	no
Obese children (33 NAFLD and 46 non-NAFLD) [54]	17	100	1	CC	Right and Left	Far wall	diet, exercise and psychological support (n=79)	Intervention induced C-IMT regression in both NAFLD (from 0.41±0.06 to 0.37±0.08 mm, p<0.05) and non-NAFLD (from 0.41±0.06 to 0.35±0.05 mm, p<0.05) obese adolescents	no
Obese adolescents (n=77) [55]	16.7	38	1	CC	Right and Left	Far wall	interdisciplinary intervention (n=77)	Intervention induced C-IMT regression	no
Postmenopausal women (n=420) [56]	57	0	4	CC Bulb	Right and Left	Near and Far wall	lifestyle change (n=203), Health Education (n=217)	C-IMTp was similar between Lifestyle Change and Health Education groups (0.067 vs 0.078 mm, p=ns)	yes
Drug-treated hypertensive patients (n=568) [57]	56.8 fluvastatin 57.5 placebo 57.9 fluvastatin and lifestyle modification 56.4 placebo and lifestyle modification	100	4	CC Bulb	Right	Not available	fluvastatin (n=142) placebo (n=143) fluvastatin and lifestyle modification (n=141) placebo and lifestyle modification (n=142)	Lifestyle intervention had no effect on C-IMTp. C-IMTp was 0.049±0.165 mm in the placebo and lifestyle modification group and 0.076±0.101 mm in the placebo group (p=ns). C-IMTp was 0.065±0.097 mm in the fluvastatin and lifestyle modification group and 0.049±0.094 mm in the fluvastatin group (p=ns).	yes
Middle-aged subjects (n=354) [52]	49	0	4	CC Bulb ICA	Right and Left	Near and Far wall	lifestyle intervention (n=166) controls (n=188)	In perimenopausal/postmenopausal women, lifestyle intervention slowed C-IMTp compared to controls (0.004 vs 0.008 mm/y, p=0.02)	yes

*mean value reported or otherwise indicated, **carotid segments where IMT was measured, CC=common carotid, ICA=internal carotid artery, NAFLD=non-alcoholic fatty liver disease

Supplemental table 6. Obesity

Study population (n) [Ref]	Age, y*	Male, %	Follow-up, y (mean values)	Carotid Segments**	Carotid side	Arterial interface measured	Intervention type	Results	Plaques included in IMT
Evidence of association between obesity and C-IMT progression									
Population based cohort (n=9316) [58]	55	44	9	CC	Right and Left	Far wall	NA	BMI was not a significant predictor of C-IMTp	no
Middle-aged subjects (n=573) [59]	48.8 (men) 51.5 (women)	54	3	CC	Right and Left	Far wall	NA	BMI was a significant predictor of C-IMTp	no
Current smokers (n=795) [24]	45.2	42	3	CC	Right and Left	Far wall	NA	BMI was a significant predictor of C-IMTp	no
Population based cohort (n=1809) [60]	32	44	6	CC	Left	Far wall	NA	Waist circumference was positively associated with C-IMTp	no
Population based cohort (n=774) [61]	42, 48, 54, 60***	100	4	CC	Right and Left	Far wall	NA	Waist-to-hip ratio was positively associated with C-IMTp	no
CAD patients (n=141) controls (n=139) [22]	61.6 (CAD patients) 56.3 (controls)	49	3	CC Bulb ICA	Right and Left	Near and Far wall	NA	Waist-to-hip ratio was positively associated with C-IMTp in CAD patients	yes
Weight loss in obesity: evidence level of causality									
Obese patients (n=54) [62]	41.2 (success group) 40.5 (failure group)	19	10	CC	Right and Left	Far wall	nutritional treatment (n=54)	IMT significantly increased in the failure group (10 year weight change >0.5 kg; 0.06±0.02 mm; p=0.004) and significantly decreased in the success group (10 year weight change ≤0.5 kg; −0.07±0.03 mm; p=0.027)	no
Overweight children (n=82) [63]	10	66	1	CC	Right and Left	Far wall	diet (n=41) diet and exercise (n=41)	A regression of IMT was observed in both children on diet [-0.015 mm (-0.025 to -0.006); p=0.02] and on diet/exercise [-0.018 mm (-0.028 to -0.008); p<0.001]	no
Obese children with NAFLD (n=120) [64]	11.9	54	1	CC	Right and Left	Not available	diet and exercise (n=120)	IMT did not change significantly: from 0.54 (0.52-0.57) to 0.53 (0.48-0.54) mm, p=ns	no
Obese women (n=58)[66]	48.5	0	1	CC	Right and Left	Far wall	gastric bypass (n=20) sleeve gastrectomy (n=20) Controls (n=18)	A regression of IMT was observed in both gastric bypass group (-0.11±0.1 mm; p<0.05) and sleeve gastrectomy group (-0.08±0.09 mm; p<0.05) whereas no changes were observed in the control women who had conventional therapy (+0.01±0.11 mm; p<ns)	no
Obese patients (n=111) [67]	42.5	17	1	CC	Right and Left	Near and Far wall	Bariatric surgery (n=111)	A regression of IMT was observed in both women (from 0.619±0.11 to 0.587±0.10 mm;	no

								p=0.005) and men (from 0.675±0.10 to 0.622±0.11 mm; p=0.0.37)	
Patients with abdominal obesity and MetS (n=661) [68]	62.8	51	2.5	CC Bulb ICA	Right and Left	Near and Far wall	rimonabant (n=326) placebo (n=335)	C-IMTp was similar in the rimonabant group (0.010±0.095 mm) and in the placebo group (0.012±0.091 mm) (p=ns)	yes

*mean value reported or otherwise indicated, **carotid segments where IMT was measured, ***age-stratified sample of men 42, 48, 54, or 60 years old, CC=common carotid, ICA=internal carotid artery, NA= not applicable, T1DM=type 1 diabetes mellitus, CAD=coronary artery disease, T2DM=type 2 diabetes mellitus, NAFLD=non-alcoholic fatty liver disease, MetS=metabolic syndrome.

Supplemental table 7. Metabolic syndrome.

Study population (n) [Ref]	Age, y*	Male, %	Follow-up, y (mean values)	Carotid Segments**	Carotid side	Arterial interface measured	Intervention type	Results	Plaques included in IMT
Evidence of association between metabolic syndrome and C-IMT progression									
Population based cohort (n=1809) [60]	32	44	6	CC	Left	Far wall	NA	C-IMTp was 0.079±0.007 mm in subjects with MetS and 0.042±0.002 mm in subjects without MetS (p<0.0001)	no
Population based cohort (n=1673) [69]	48.8 (men) 46.8 (women)	49	1.2	CC	Right	Far wall	NA	Presence of MetS was positively associated with C-IMTp.	no
Population based cohort (n=370) [71]	66 (median)	34	2.15	CC	Right and Left	Far wall	NA	Presence of MetS was positively associated with C-IMTp	no
Healthy subjects (n=293) [72]	36.6	47	6	CC	Right	Not available	NA	Presence of MetS was positively associated with C-IMTp	no
Middle-aged subjects (n=500) [75]	48.7 (men) 51.4 (women)	54	3	CC	Right and Left	Far wall	NA	Atherogenic effects of MetS were mediated through its components; triglycerides were significantly associated with C-IMTp in women only. SBP was significantly associated with C-IMTp in men and women.	no
Population based cohort (n=1673) [76]	31.5	49	6	CC	Left	Far wall	NA	The recovery group (MetS at baseline but not at follow up) had reduced C-IMTp compared with the persistent group (0.036±0.005 vs 0.079±0.010 mm; p<0.001)	no
Middle-aged subjects (n=316) [70]	58	100	3.2	CC Bulb	Right and Left	Far wall	NA	Presence of MetS was positively associated with C-IMTp	yes
Population based cohort (n=2974) [73]	55.5 (men with MetS) 56.2 (men without MetS) 60.4 (women with MetS) 56.0 (women without MetS)	48	13	CC Bulb	Right and Left	Near and Far wall	NA	MetS was a significant predictor of C-IMTp only in subjects below 50 years of age, but not in other age groups	no
Hypertensive patients (n=1444) [74]	56	55	4	CC Bulb ICA	Right and Left	Near and Far wall	NA	Presence of MetS was not associated with C-IMTp	yes

*mean value reported or otherwise indicated, **carotid segments where IMT was measured, CC=common carotid, ICA=internal carotid artery, NA=not applicable, MetS=metabolic syndrome.

Supplemental table 8. Glucose derangement.

Study population (n) [Ref]	Age, y*	Male, %	Follow-up, y (mean values)	Carotid Segments**	Carotid side	Arterial interface measured	Intervention type	Results	Plaques included in IMT
Evidence of association between glucose derangement and C-IMT progression									
Population based cohort (n=3409) [4]	65.4	38	6.5	CC	Right and Left	Near and Far wall	NA	Diabetes was a significant predictor of C-IMTp	no
Population based cohort (n=3534) [78]	69	41	2	CC	Right and Left	Far wall	NA	Diabetic subjects showed enhanced C-IMTp compared with nondiabetic subjects [0.018 (0.016, 0.023) vs 0.011 (0.007, 0.015) mm/y, p=0.03]	no
T2DM patients (n=68) [79]	59.9	63	3.5	CC	Right and Left	Near and Far wall	NA	C-IMTp was higher in women than in men (0.018±0.027 vs 0.007±0.022 mm/y, p=0.021)	no
T2DM patients (n=287) [80]	59.1 (men) 58.5 (women)	45	4	CC	Right and Left	Far wall	NA	C-IMTp was higher in men than in women (0.030±0.025 vs 0.022±0.019 mm, p=0.0006)	no
Population based cohort (n=261) [81]	56.7 (lowest IMT tertile) 59.6 (middle IMT tertile) 62.4 (highest IMT tertile)	51	5	CC	Right	Far wall	NA	Fasting glucose was positively associated with C-IMTp	no
T2DM patients (n=152) [82]	63.5	39	2	CC	Right and Left	Far wall	NA	HbA1c and 2-h post-challenge glucose level were positively associated with C-IMTp	no
T2DM patients (n=218) [83]	62 (median)	56	2	CC	Right and Left	Far wall	NA	Glycemic indices HbA1c, glycated albumin (GA) and GA/A1c ratio were significantly associated with C-IMTp.	no
T2DM patients (n=499) [84]	58 (HbA1c <7.5) 54 (HbA1c >7.5)	34	3	CC	Right and Left	Far wall	NA	HbA1c was not a predictor of C-IMTp	no
Population based cohort (n=1536) [77]	49.8	40	3.5	CC ICA	Right and Left	Far wall	NA	Diabetes was a significant predictor of C-IMTp	yes
Population based cohort (n=1192) [14]	53.7 (NGT) 56.6 (IGT) 56.6 (UD) 56.7 (DD)	44	5.2	CC ICA	Right and Left	Near and Far wall	NA	C-IMTp was the lowest in subjects with NGT (0.038±0.013 mm/y), intermediate in patients with IGT (0.042±0.018 mm/y), and the highest in patients with undiagnosed and diagnosed diabetes (0.075±0.0.026 mm/y and 0.072±0.019 mm/y)	yes
Population based cohort (n=473) [9]	46.3 (Japanese American) 45 (white American)	100	5	CC Bulb ICA	Right and Left	Near and Far wall	NA	Diabetes was associated with C-IMTp only in Japanese American	yes
Population based cohort (n=3383) [16]	51.7	49	3	CC Bulb	Right and Left	Far wall	NA	Diabetes was positively associated with C-IMTp	yes

				ICA					
Population based cohort (n=12644) [17]	45–64 (range)	45	9	CC Bulb ICA	Right and Left	Far wall	NA	Diabetes was positively associated with C-IMTp	yes
T2DM patients (n=287) [3]	61.7	43	3.1	CC Bulb ICA	Right and Left	Far wall	NA	HbA1c was a significant predictor of C-IMTp.	yes
Population based cohort (n=842) [13]	36.4	42	2.4	CC Bulb ICA	Right and Left	Far wall	NA	Fasting glucose was positively associated with C-IMTp	yes
Population based cohort (n=336) [19]	32.3	38	5.8	CC Bulb ICA	Right and Left	Far wall	NA	Fasting glucose was a significant predictor of C-IMTp	yes
Diabetes control: evidence level of causality									
IGT patients (n=132) [85]	54.8 (acarbose) 55.6 (placebo)	53	3.9	CC	Not available	Far wall	acarbose (n=66) placebo (n=66)	Acarbose slowed C-IMTp compared with placebo (0.02±0.07 vs 0.05±0.06 mm, p=0.027)	no
T2DM patients (n=70) [87]	61.3 (nateglinide) 61.8 (controls)	53	1	CC	Right and Left	Far wall	nateglinide (n=34) controls (n=36)	Nateglinide reduced C-IMTp compared to controls (-0.017±0.054 vs 0.024±0.066 mm/y, p=0.0064)	no
T2DM patients (n=322) [88]	64.4 (alogliptin) 64.8 (controls)	58	2	CC	Right and Left	Far wall	alogliptin (n=161) controls (n=161)	Alogliptin reduced C-IMTp compared to controls (-0.026±0.009 vs 0.005±0.009 mm, p=0.022)	no
T2DM patients (n=274) [89]	63.8 (sitagliptin) 63.6 (controls)	59	2	CC	Right and Left	Far wall	sitagliptin (n=137) controls (n=137)	Sitagliptin reduced C-IMTp compared to controls (-0.029±0.013 vs 0.024±0.013 mm, p=0.005)	no
T2DM patients (n=175) [91]	52 (repaglinide) 51 (glibenclamide)	53	1	CC	Right and Left	Far wall	repaglinide (n=88) glibenclamide (n=87)	Repaglinide was more effective than glibenclamide on C-IMTp (-0.029±0.021 vs -0.005± 0.01 mm, p=0.02)	no
Insulin treated T2DM patients (n=276) [92]	52.4 (troglitazone) 52.6 (placebo)	67	2	CC	Right	Far wall	troglitazone (n=142) placebo (n=134)	C-IMTp was similar between troglitazone and placebo (0.0030±0.021 vs 0.0066±0.021 mm/y, p=ns)	no
IGT patients (n=382) [96]	54 (pioglitazone) 53 (placebo)	46	2.3	CC	Right	Far wall	pioglitazone (n=188) placebo (n=194)	Pioglitazone slowed C-IMTp compared with placebo [0.00476 (0.00239 to 0.00714 vs 0.00969 (0.00724 to 0.01215) mm/y, p=0.001)	no
T2DM patients (n=361) [97]	60	64	1.4	CC	Right and Left	Far wall	pioglitazone (n=175) glimepiride (n=186)	Pioglitazone was more effective than glimepiride on C-IMTp (−0.001 vs +0.012 mm, p=0.02)	no
Women with gestational diabetes (n=192) [99]	34.8 (troglitazone) 34.2 (placebo)	0	4	CC	Right	Far wall	troglitazone (n=93)	Troglitazone slowed C-IMTp compared with placebo (0.0065 vs 0.0094 mm/y, p=0.048)	no

							placebo (n=99)		
Women with prior gestational diabetes (n=61) [100]	40	0	3	CC	Right	Far wall	pioglitazone (n=61)	Patients were enrolled from the previous study (see Xiang AH 15623809). Pioglitazone slowed C-IMTp in patients previously treated with placebo (0.0031 vs 0.0100 mm/y, p=0.006). C-IMTp remained stable in patients previously treated with troglitazone (0.0037 vs 0.0060 mm/y; p=0.26).	no
T2DM patients (n=200) IR patients (n=355) [93]	68 (rosiglitazone) 67 (placebo)	46	1	CC Bulb	Right	Far wall	rosiglitazone (n=277) placebo (n=278)	C-IMTp was similar between rosiglitazone and placebo (0.049±0.007 vs 0.060±0.007 mm, p=ns)	yes
T1DM patients (n=1116) [21]	35	52	12	CC ICA	Right and Left	Not available	conventional treatment (n=553) intensive treatment (n=563)	Intensive treatment was more effective than conventional treatment on C-IMTp (0.072±0.011 vs 0.086±0.010 mm, p=0.048)	no
T1DM patients (n=1229) [102]	35	52	6	CC ICA	Right and Left	Not available	conventional treatment (n=611) intensive treatment (n=618)	Intensive treatment was more effective than conventional treatment on C-IMTp [0.032 (0.010 to 0.055) vs 0.046 (0.023 to 0.068) mm; p=0.01]	yes
T1DM patients (n=1116) [21]	35	52	12	CC ICA	Right and Left	Not available	conventional treatment (n=553) intensive treatment (n=563)	Intensive treatment was more effective than conventional treatment on C-IMTp (0.072±0.011 vs 0.086±0.010 mm, p=0.048)	no
T1DM patients (n=1229) [102]	35	52	6	CC ICA	Right and Left	Not available	conventional treatment (n=611) intensive treatment (n=618)	Intensive treatment was more effective than conventional treatment on C-IMTp [0.032 (0.010 to 0.055) vs 0.046 (0.023 to 0.068) mm; p=0.01]	yes
T2DM patients (n=101) [86]	58.6 (voglibose) 60.4 (controls)	55	3	CC Bulb ICA	Right and Left	Far wall	voglibose (n=51) controls (n=50)	Addition of voglibose reduced C-IMTp compared to controls (-0.021±0.144 vs 0.098±0.122 mm/y, p< 0.0001)	yes
T2DM patients (n=118) [90]	60.3 (glibenclamide) 60.8 (gliclazide) 62.8 (glibenclamide + metformin)	49	3	CC Bulb ICA	Right and Left	Far wall	glibenclamide (n=59) gliclazide (n=30) glibenclamide + metformin (n=29)	Glibenclamide plus metformin and gliclazide were more effective than glibenclamide alone on C-IMTp (0.041±0.105, 0.044±0.106, 0.114±0.131 mm/y respectively, p=0.029 and p=0.035 respectively)	yes
T2DM patients (n=57) [94]	62.6 (rosiglitazone) 66.1 (placebo)	79	1	CC Bulb	Right and Left	Not available	rosiglitazone (n=28)	C-IMTp was similar between rosiglitazone and placebo (0.04 vs 0.05 mm, p=ns)	yes

				ICA			placebo (n=29)		
IGT or IFG patients (n=1256) [95]	54	45	3.09	CC Bulb ICA	Right and Left	Near and Far wall	rosiglitazone (n=635) placebo (n=621)	C-IMTp was similar between rosiglitazone and placebo (0.0063±0.0011 vs 0.0090±0.0011 mm/y; p=ns)	yes
T2DM patients (n=186) [98]	56.7 (pioglitazone) 57.2 (controls)	63	2.5-4	CC Bulb ICA	Right and Left	Far wall	pioglitazone (n=89) controls (n=97)	Pioglitazone slowed C-IMTp compared to controls (from 1.060±0.2368 to 0.992±0.1921 mm; p=0.0042 for pioglitazione; from 1.021±0.2136 to 0.990±0.2158, p=ns for controls)	yes
Dysglycemic patients at high risk for CVD (n=1091) [101]	63.0 (insulin glargine) 63.2 (standard care)	64	4.9	CC Bulb ICA	Right and Left	Near and Far wall	insulin glargine (n=533) standard care (n=558)	C-IMTp was similar between insulin glargine and standard care 0.0234±0.0015 vs 0.0264±0.0015 mm/y, p=ns)	yes
T1DM patients (n=1116) [21]	35	52	12	CC ICA	Right and Left	Not available	conventional treatment (n=553) intensive treatment (n=563)	Intensive treatment was more effective than conventional treatment on C-IMTp (0.072±0.011 vs 0.086±0.010 mm, p=0.048)	no
T1DM patients (n=1229) [102]	35	52	6	CC ICA	Right and Left	Not available	conventional treatment (n=611) intensive treatment (n=618)	Intensive treatment was more effective than conventional treatment on C-IMTp [0.032 (0.010 to 0.055) vs 0.046 (0.023 to 0.068) mm; p=0.01]	yes

*mean value reported or otherwise indicated, **carotid segments where IMT was measured, CC=common carotid, ICA=internal carotid artery, NA=not applicable, NGT=normal glucose tolerance, IGT=impaired glucose tolerance, UD=undiagnosed diabetes, DD=diagnosed diabetes, T2DM= type 2 diabetes mellitus, RA=rheumatoid arthritis, T1DM= type 1 diabetes mellitus, MetS=metabolic syndrome, IR=insulin resistance, IFG=impaired fasting glucose, CVD=cardiovascular disease

Supplemental table 9. Hypertension.

Study population (n) [Ref]	Age, y*	Male, %	Follow-up, y (mean values)	Carotid Segments**	Carotid side	Arterial interface measured	Intervention type	Results	Plaques included in IMT
Evidence of association between hypertension and C-IMT progression									
Population based cohort (n=3409) [4]	65.4	38	6.5	CC	Right and Left	Near and Far wall	NA	SBP and/or hypertension were strong, independent predictors of C-IMTp	no
Population based cohort (n=3426) [7]	56.3	59	16	CC	Right	Far wall	NA	Favourable changes in SBP during follow-up decreased C-IMTp	yes
Middle-aged subjects (n=500) [75]	48.7 (men) 51.4 (women)	54	3	CC	Right and Left	Far wall	NA	SBP was positively associated with C-IMTp	no
Population based cohort (n=3364) [103]	65 (normal subjects) 74 (subjects with CKD)	41	4	CC	Right and Left	Far wall	NA	SBP was positively associated with C-IMTp	no
Insulin treated T2DM patients (n=276) [104]	52.2	33	2	CC	Right	Far wall	NA	SBP was positively associated with C-IMTp	no
Population based cohort (n=1038) [105]	42, 48, 54 or 60***	100	4	CC	Right and Left	Far wall	NA	SBP was a significant predictor of C-IMTp	yes
Population based cohort (n=261) [81]	56.7 (lowest IMT tertile) 59.6 (middle IMT tertile) 62.4 (highest IMT tertile)	51	5	CC	Right	Far wall	NA	SBP was not associated with C-IMTp	no
Population based cohort (n=1026) [108]	52.6	100	4	CC	Right and Left	Far wall	NA	Men with SBP <120, 120 to 126, 127 to 134, 135 to 143, and >143 mmHg had, respectively, an increase in mean IMT of 0.074, 0.090, 0.110, 0.136, and 0.158 mm per 4 years ($p<0.001$). Pulse pressure was positively associated with C-IMTp	no
Population based cohort (n=957) [107]	65.2 (men) 65.1 (women)	41	4	CC	Right and Left	Far wall	NA	Pulse pressure was positively associated with C-IMTp	yes
Hypertensive patients (n=100) [109]	56	61	1	CC Bulb	Right and Left	Near and Far wall	NA	SBP change was a significant predictor of C-IMTp	yes
Population based cohort (n=1192) [14]	53.7 (NGT) 56.6 (IGT) 56.6 (UD) 56.7 (DD)	44	5.2	CC ICA	Right and Left	Near and Far wall	NA	Hypertension was a significant predictor of C-IMTp	yes
Population based cohort (n=1207) [15]	53.7 (NGT) 56.6 (IGT)	44	5.2	CC ICA	Right and Left	Near and Far wall	NA	Hypertension was positively associated with C-IMTp	yes

	56.6 (UD) 56.7 (DD)								
Population based cohort (n=1536) [77]	49.8	40	3.5	CC ICA	Right and Left	Far wall	NA	Mean blood pressure was a significant predictor of C-IMTp	yes
Hypertensive postmenopausal women (n=618) [110]	55	0	1	CC ICA	Right and Left	Near and Far wall	NA	SBP reduction during follow up was a significant predictor of C-IMTp	no
Stroke- and myocardial infarction-free subjects (n=712) [8]	54.7	38	4.3	CC Bulb ICA	Right and Left	Far wall	NA	Hypertension was a significant predictor of C-IMTp	no
Population based cohort (n=473) [9]	46.3 (Japanese American) 45 (white American)	100	5	CC Bulb ICA	Right and Left	Near and Far wall	NA	Hypertension was positively associated with C-IMTp only in white Americans	yes
Population based cohort (n=3383) [16]	51.7	49	3	CC Bulb ICA	Right and Left	Far wall	NA	Hypertension was positively associated with C-IMTp	yes
Population based cohort (n=842) [13]	36.4	42	2.4	CC Bulb ICA	Right and Left	Far wall	NA	Mean arterial pressure was positively associated with C-IMTp	yes
Population based cohort (n=336) [19]	32.3	38	5.8	CC Bulb ICA	Right and Left	Far wall	NA	SBP was a significant predictor of C-IMTp	yes
Patients with FH (n=904) or mixed dyslipidemia (n=752) [106]	50.4 (atorvastatin) 51.8 (atorvastatin/torcetrapib)	56	2	CC Bulb ICA	Right and Left	Near and Far wall	NA	SBP was positively associated with C-IMTp in the atorvastatin/torcetrapib group	yes
Population based cohort (n=12644) [17]	45–64 (range)	45	9	CC Bulb ICA	Right and Left	Far wall	NA	Pulse pressure was positively associated with C-IMTp	yes
Control of hypertension: evidence level of causality									
Population based cohort (n=3441) [111]	60.3	47	9.4	CC	Right and Left	Far wall	NA	Antihypertensive use (β=−2.06; p=0.0004) and time on antihypertensive medications (β=−0.29; p<0.0001) were associated with lower C-IMTp	no
Hypertensive patients (n=155) [116]	62.3 (olmesartan) 62.1 (atenolol)	61	2	CC	Right and Left	Far wall	olmesartan (n=78) atenolol (n=77)	Olmesartan and atenolol produced comparable significant regressions in C-IMT (−0.090±0.015 vs −0.082±0.014 mm, p=ns)	no
Post-stroke hypertensive patients (n=326) [112]	69.3	63	1	CC	Right and Left	Far wall	Cilnidipine (n=326)	Cilnidipine reduced C-IMTp in patients with thicker baseline C-IMT [-0.09 (-0.13 to -0.05) mm] compared to normal group [-0.01 (-0.03 to 0.01 mm); p<0.001	yes

Hypertensive patients (n=55) [118]	48 (amlodipine) 49 (lisinopril)	59	1	CC	Right and Left	Far wall	amlodipine (n=28) lisinopril (n=27)	Amlodipine was more effective than lisinopril on C-IMTp [-0.048 (-0.066 to -0.031) vs -0.027 (-0.046 to -0.007) mm, p<0.05)	no
T2DM patients (n=98) [119]	56.4 (enalapril) 56.3 (controls)	62	2	CC	Right and Left	Near and Far wall	enalapril (n=48) controls (n=50)	Enalapril slowed C-IMTp compared with controls (0.02±0.02 vs 0.01±0.02 mm/y; p<0.05)	no
Hypertensive patients (n=242) [120]	55-80	52	4	CC	Right	Far wall	nifedipine (n=115) amiloride/HCTZ (n=127)	C-IMT progressed significantly on amiloride/HCTZ but not on nifedipine 0.034±0.007 vs -0.004±0.009 mm, p=0.002)	no
Patients with vascular disease (n=617) [122]	60 (ramipril) 61 (placebo)	65	4	CC	Right and Left	Far wall	ramipril (n=308) placebo (n=309)	C-IMTp was similar between ramipril (from 0.80 to 0.83 mm) and placebo (from 0.79 to 0.81 mm) (p=ns)	no
Patients with increased albuminuria (n=642) [123]	51	65	4	CC	Left	Far wall	fosinopril (n=319) placebo (n=323)	C-IMTp was similar between fosinopril and placebo (0.031±0.008 vs 0.043±0.009 mm, p=ns)	no
T2DM patients (n=499) [124]	55 (aggressive treatment) 57 (standard treatment)	34	3	CC	Right and Left	Far wall	aggressive treatment for BP and LDL targets (n=252) standard treatment (n=247)	IMT regressed in the aggressive group (from 0.808 to 0.796 mm) and progressed in the standard group (from 0.797 to 0.837 mm, p<0.001).	no
Hypertensive patients (n=1519) [114,115]	55.9 (atenolol) 56.1 (lacidipine)	55	4	CC Bulb	Right and Left	Far wall	atenolol (n=764) lacidipine (n=755)	Lacidipine was more effective than atenolol on C-IMTp (0.0087±0.0015 vs 0.0145±0.0015 mm/y, p=0.0073)	yes
Stroke- and myocardial infarction-free subjects (n=712) [8]	54.7	38	4.3	CC Bulb ICA	Right and Left	Far wall	NA	Antihypertensive medication were significant predictor of C-IMTp	no
Hypertensive patients (n=4148) [112]	52	59	6.2	CC Bulb ICA	Right and Left	Near and Far wall	NA	IMT increased in both patients with tight [from 1.50 (1.46–1.53) to 1.69 (1.65–1.73) mm; p<0.05] or usual SBP control (from 1.55 (1.52–1.58) to 1.75 (1.72–1.78) mm; p<0.05], without differences between groups (p=ns)	yes
Hypertensive patients (n=377) [113]	54.1	52	3.7	CC Bulb ICA	Right and Left	Far wall	verapamil (n=244) chlortalidone (n=254)	Verapamil was more effective than chlorthalidone on C-IMTp (–0.082 vs –0.037 mm/y, p<0.02).	yes
Subjects at high risk CVD (n=693) [44]	65.2 ramipril 10 mg 65.6 ramipril 2.5 mg 65.6 placebo	77	4.5	CC Bulb ICA	Right and Left	Near and Far wall	ramipril 10 mg (n=227) ramipril 2.5 mg (n=232) placebo (n=234)	C-IMTp was 0.0217±0.0027, 0.0180±0.0026 and 0.0137±0.0024 mm/y respectively for placebo, ramipril 2.5 mg and ramipril 10 mg (p=0.033)	yes

IGT or IFG patients (n=1256) [95]	54	45	3.09	CC Bulb ICA	Right and Left	Near and Far wall	ramipril (n=637) placebo (n=619)	C-IMTp was similar between ramipril and placebo (0.0083±0.0011 vs 0.0069±0.0011, p=ns)	yes

*mean value reported or otherwise indicated, **carotid segments where IMT was measured, ***age-stratified sample of men 42, 48, 54, or 60 years old, CC=common carotid, ICA=internal carotid artery, NA=not applicable, NGT=normal glucose tolerance, IGT=impaired glucose tolerance, UD=undiagnosed diabetes, DD=diagnosed diabetes, CKD=chronic kidney disease, T2DM=type 2 diabetes mellitus, FH= familial hypercholesterolemia, CVD=cardiovascular disease, MetS=metabolic syndrome, IFG=impaired fasting glucose

Supplemental table 10. Dyslipidemia.

Study population (n) [Ref]	Age, y*	Male, %	Follow-up, y (mean values)	Carotid Segments**	Carotid side	Arterial interface measured	Intervention type	Results	Plaques included in IMT
Evidence of association between dyslipidemia and C-IMT progression									
Population based cohort (n=3409) [4]	65.4	38	6.5	CC	Right and Left	Near and Far wall	NA	SBP and/or hypertension were strong, independent predictors of C-IMTp	no
Population based cohort (n=3426) [7]	56.3	59	16	CC	Right	Far wall	NA	Favorable changes in LDL and HDL cholesterol during follow-up were associated with reduced C-IMTp	yes
Population based cohort (n=128) [10]	42, 48, 54 or 60***	100	2	CC	Right and Left	Far wall	NA	LDL cholesterol was a significant predictor of C-IMTp	no
Population based cohort (n=1809) [60]	32	44	6	CC	Left	Far wall	NA	LDL cholesterol was positively associated with C-IMTp	no
Employees (n=220) [127]	50.9	100	5	CC	Right and Left	Far wall	NA	Total cholesterol was positively associated with C-IMTp	no
Population based cohort (n=128) [128]	42, 48, 54 or 60***	100	2	CC	Right and Left	Far wall	NA	LDL cholesterol was a significant predictor of C-IMTp	no
Healthy subjects (n=364) [18]	48.5	100	2.3	CC	Left	Far wall	NA	LDL cholesterol was a significant predictor of C-IMTp	no
Postmenopausal women (n=199) [130]	60.6 (estradiol) 61.6 (placebo)	0	2	CC	Right	Far wall	NA	LDL cholesterol was positively associated with C-IMTp, HDL was inversely associated with C-IMTp	no
Healthy subjects (n=571) [131]	44.0	42	3	CC	Right	Far wall	NA	Total cholesterol was a significant predictor of C-IMTp	no
T2DM patients (n=152) [82]	63.5	39	2	CC	Right and Left	Far wall	NA	LDL cholesterol was positively associated with C-IMTp, HDL was inversely associated with C-IMTp	no
Middle-aged subjects at moderate risk for CAD (n=134) [132]	45-75 (range)	55	1.5	CC	Right and Left	Near and Far wall	NA	Triglycerides levels and the ratios TC/HDL-C, TG/HDL-C and Apo B/HDL-C were significant predictor of C-IMTp	no
Population based cohort (n=3441) [111]	60.3	47	9.4	CC	Right and Left	Far wall	NA	HDL cholesterol was inversely associated with C-IMTp. Statin use at baseline was a significant predictor of C-IMTp.	no
Middle-aged subjects (n=500) [133]	40-60 (range)	54	3	CC	Right and Left	Far wall	NA	HDL cholesterol was inversely associated with C-IMTp	no
Hypertensive patients (n=112) [134]	59	49	2	CC	Right and Left	Far wall	NA	HDL cholesterol was a significant predictor of C-IMTp	no
Middle-aged subjects at moderate risk for CAD (n=110) [135]	45-75 (range)	56	1.5	CC	Right and Left	Far wall	NA	HDL cholesterol, HDL-2, HDL-3, VLDL-C and $VLDL_{1+2}$-C were significant predictors of C-IMTp	no

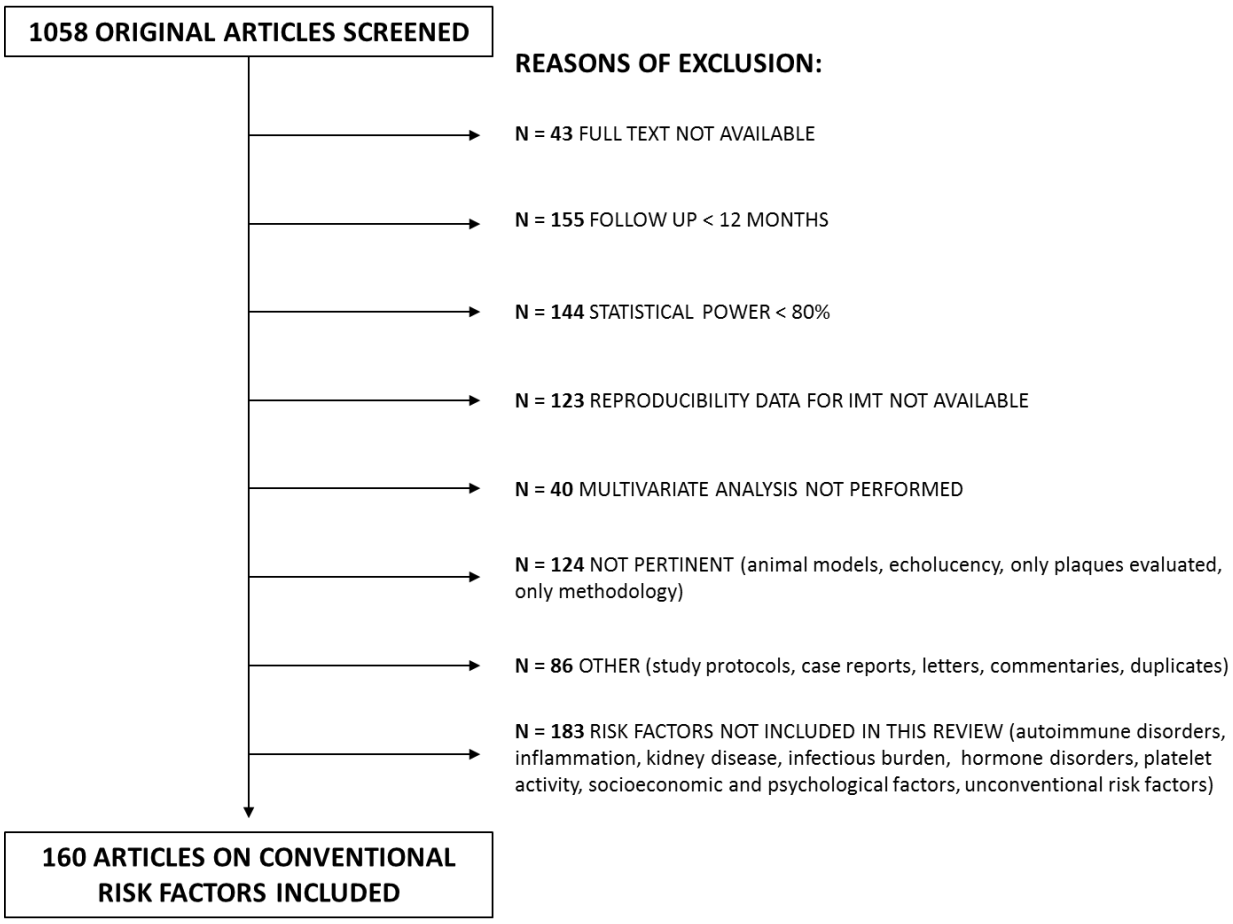
Population based cohort (n=2743) [125]	55.8 (men) 56.6 (women)	48	13	CC Bulb	Right and Left	Near and Far wall	NA	Total cholesterol was positively associated with C-IMTp	no
Middle-aged subjects (n=313) [126]	58	100	3.2	CC Bulb	Right and Left	Far wall	NA	Total cholesterol, LDL cholesterol, triglycerides, apoB levels were positively associated with C-IMTp. HDL cholesterol was inversely associated with C-IMTp	yes
Postmenopausal women (n=84) [129]	58.7	0	5	CC Bulb	Right	Far wall	NA	LDL cholesterol was positively associated with C-IMTp	yes
Middle-aged subjects (n=305) [136]	58	100	8.8	CC Bulb	Right and Left	Far wall	NA	ApoB/ApoA-I ratio was positively associated with C-IMTp	yes
Population based cohort (n=1207) [15]	53.7 (NGT) 56.6 (IGT) 56.6 (UD) 56.7 (DD)	44	5.2	CC ICA	Right and Left	Near and Far wall	NA	LDL cholesterol was positively associated with C-IMTp	yes
Population based cohort (n=842) [13]	36.4	42	2.4	CC Bulb ICA	Right and Left	Far wall	NA	HDL cholesterol was inversely associated with C-IMTp	yes
Population based cohort (n=12644) [17]	45–64 (range)	45	9	CC Bulb ICA	Right and Left	Far wall	NA	HDL cholesterol was inversely associated with C-IMTp	yes
CAD patients (n=141) controls (n=139) [22]	61.6 (CAD patients) 56.3 (controls)	49	3	CC Bulb ICA	Right and Left	Near and Far wall	NA	HDL cholesterol was inversely associated with C-IMTp	yes
Population based cohort (n=473) [9]	46.3 (Japanese American) 45 (White American)	100	5	CC Bulb ICA	Right and Left	Near and Far wall	NA	The ratio total cholesterol/HDL cholesterol was positively associated with C-IMTp only in Japanese Americans	yes
FH patients (n=287) [138]	48 (atorvastatin) 49 (simvastatin)	40	2	CC Bulb ICA	Right and Left	Near and Far wall	NA	Lp(a) level was not associated with C-IMTp	yes
T2DM patients with Lp(a) ≤30 mg/dl (n=60) or Lp(a) >30 mg/dl (n=86) [137]	63 (Lp(a) ≤30 mg/dl) 64 (Lp(a) >30 mg/dl)	64	4	NA	Right and Left	Not available	NA	Lp(a) level was a significant predictor of C-IMTp	no
Control of dyslipidemia: evidence level of causality									
Population based cohort (n=3441) [111]	60.3	47	9.4	CC	Right and Left	Far wall	NA	HDL cholesterol was inversely associated with C-IMTp. Statin use at baseline was a significant predictor of C-IMTp.	no
CAD patients (n=74) [142]	37-67 (range)	91	4	CC	Right	Far wall	lovastatin (n=49) placebo (n=25)	Lovastatin slowed C-IMTp compared with placebo (-0.028±0.003 vs 0.015±0.005 mm/y, p<0.001)	no
Hypercholesterolemic patients (n=161) [150]	58 (atorvastatin) 61 (pravastatin)	71	1	CC	Right and Left	Far wall	atorvastatin (n=79)	Atorvastatin was more effective than pravastatin on C-IMTp (-0.034±0.021 vs 0.025±0.017 mm; p=0.03)	no

							pravastatin (n=82)		
Patients with C-IMT >1.1 mm and LDL >100 mg/dl (n=303) [156]	66.3	57	1	CC	Right and Left	Far wall	'moderate' pitavastatin (n=152) 'intensive' pitavastatin (n=151)	Only 'intensive' pitavastatin reduced C-IMTp [-0.045 (-0.071 to -0.019) mm, p<0.001 vs baseline], whereas 'moderate' pitavastatin had no significant effect [-0.0055 (-0.038 to 0.028) mm, p=ns vs baseline]	no
Hypercholesterolemic patients (n=146) [151]	67.0	53	1	CC	Right and Left	Not available	atorvastatin (n=73) pitavastatin (n=73)	Pitavastatin was more effective than atorvastatin on C-IMTp (from 0.902±0.196 to 0.857±0.212 mm vs 0.884±0.166 vs 0.875±0.180, p<0.05)	no
Patients with prior coronary artery bypass graft surgery (n=78) [158,159]	54.2	100	4	CC	Right	Near and Far wall	colestipol/niacin (n=39) placebo (n=39)	Colestipol/niacin slowed C-IMTp compared with placebo (-0.05±0.08 vs 0.05±0.08 mm, p<0.001)	no
T2DM patients (n=427) [160]	55 (aggressive treatment plus ezetimibe) 57 (aggressive treatment no ezetimibe) 57 (standard treatment)	33	3	CC	Right and Left	Far wall	aggressive treatment plus ezetimibe (n=69) aggressive treatment no ezetimibe (n=154) standard treatment (n=204)	C-IMT regressed similarly in patients with aggressive treatment, with or without ezetimibe [-0.025 (-0.05 to 0.003) vs -0.012 (-0.03 to 0.008) mm, p=ns), but progressed in the standard treatment [0.039 (0.02 to 0.06) mm, intergroup p < 0.0001]	no
CAD or CAD equivalent patients (n=208) [161,162]	65	80	1.2	CC	Right and Left	Far wall	ezetimibe (n=111) niacin (n=97)	Niacin showed superior efficacy to ezetimibe on C- IMTp (−0.0142±0.0041 vs −0.0007±0.0035 mm, p<0.01)	no
CAD or CAD equivalent patients (n=161) [163]	65	80	1.2 (n=111) 0.6 (n=50)	CC	Right and Left	Far wall	ezetimibe (n=161)	There was an inverse relationship between LDL-C and C-IMTp: greater reductions in LDL-C were associated with greater C-IMTp	no
T2DM patients (n=499) [124]	55 (aggressive treatment) 57 (standard treatment)	34	3	CC	Right and Left	Far wall	aggressive treatment for BP and LDL targets (n=252) standard treatment (n=247)	IMT regressed in the aggressive group (from 0.808 to 0.796 mm) and progressed in the standard group (from 0.797 to 0.837 mm, p<0.001).	no
Population based cohort (n=2974) [139]	55.8 (men) 56.6 (women)	48	13	CC Bulb	Right and Left	Near and Far wall	NA	Long-term use of lipid lowering drugs was a significant predictor of C-IMTp	no
Hypercholesterolemic patients (n=426) [20,145]	57	100	3	CC Bulb	Right and Left	Far wall	pravastatin (n=214) placebo (n=212)	Pravastatin slowed C-IMTp compared with placebo (0.017 vs 0.031 mm/y, p=0.005)	yes

Hypertensive patients (n=568) [57]	56.8 (fluvastatin) 57.5 (placebo) 57.9 (fluvastatin and lifestyle modification) 56.4 (placebo and lifestyle modification)	100	4	CC Bulb	Right	Not available	fluvastatin alone (n=142) placebo alone (n=143) fluvastatin and lifestyle modification (n=141) placebo and lifestyle modification (n=142)	Fluvastatin slowed C-IMTp compared with placebo [mean difference -0.074 (-0.146 to -0.012) mm, p=0.0214)	yes
Asymptomatic subjects with early carotid atherosclerosis (n=919) [140,141]	61.7	52	3	CC Bulb ICA	Right and Left	Near and Far wall	lovastatin/placebo (n=231) warfarin/placebo (n=229) lovastatin/warfarin (n=229) placebo/placebo (n=230)	Lovastatin slowed C-IMTp compared with placebo (-0.009± 0.003 vs 0.006±0.003 mm/y; p=0.001)	yes
Asymptomatic subjects with early carotid atherosclerosis (n=919) [143]	61.7	52	3	CC Bulb ICA	Right and Left	Near and Far wall	lovastatin/placebo (n=231) warfarin/placebo (n=229) lovastatin/warfarin (n=229) placebo/placebo (n=230	Women experienced the greatest C-IMT regression with lovastatin/warfarin combination (-0.0104±0.0052 mm/y), men with lovastatin alone (-0.0151±0.0048 mm/y)	yes
CAD patients (n=151) [144]	63	85	3	CC Bulb ICA	Right and Left	Near and Far wall	pravastatin (n=75) placebo (n=76)	Pravastatin slowed C-IMTp compared with placebo in the common carotid (0.0295±0.0058 vs 0.0456±0.0057, p=0.03)	yes
Hypercholesterolemic patients (n=305) [146]	55	53	3	CC Bulb ICA	Right and Left	Near and Far wall	pravastatin (n=151) placebo (n=154)	Pravastatin slowed C-IMTp compared with placebo (-0.0043±0.0028 vs 0.0089±0.0027 mm/y, p<0.0007)	yes
Low risk subjects (n=876) [147-149]	57.6	60	2	CC Bulb ICA	Right and Left	Near and Far wall	rosuvastatin (n=624) placebo (n=252)	Rosuvastatin slowed C-IMTp compared with placebo [-0.0014 (−0.0041 to 0.0014) vs 0.0131 (0.0087 to 0.0174) mm/y, p<0.001]	yes
T2DM patients (n=182) [152]	58.8 (cerivastatin) 58.2 (placebo)	47	2	CC Bulb ICA	Right and Left	Near and Far wall	Cerivastatin[#] (n=103) placebo (n=79)	C-IMTp was similar between statin and placebo [0.002 (-0.0112 to 0.0149) vs -0.006 (-0.0223 to 0.0109), p=ns]	no
Hypercholesterolemic patients (n=269) [157]	55	53	3	CC Bulb ICA	Right and Left	Near and Far wall	pravastatin (n=136) placebo (n=133)	While in the placebo group a positive rate of C-IMTp was observed, in pravastatin group no IMT progression was recorded. C-IMTp did not correlate with the extent of LDL-C lowering.	yes

FH patients (n=139) [164]	46.2	55	2	CC Bulb ICA	Right and Left	Near and Far wall	simvastatin (n=139)	Simvastatin decreased C-IMTp from 0.92 (0.91-0.94) to 0.87 (0.85-0.89) mm (p<0.001)	no
FH patients (n=280) [165]	48	39	2	CC Bulb ICA	Right and Left	Near and Far wall	atorvastatin (n=141) simvastatin (n=139)	Atorvastatin showed superior efficacy to simvastatin on C-IMTp [-0.031 (-0.007 to -0·055) vs 0.036 (0.014 to 0.058); p=0.0001]	yes
FH patients (n=255) [166]	48	39	2	CC Bulb ICA	Right and Left	Near and Far wall	atorvastatin (n=255) In the previous 2 y, 123 were taking simvastatin and 132 atorvastatin	A complete arrest of C-IMTp (from 0.89 to 0.90 mm, p=ns) was observed in patients previously taking atorvastatin. A significant regression (from 0.95 to 0.92 mm, p=0.01) was observed in patients previously taking simvastatin.	yes
FH patients (n=642) [168]	45.7 (simvastatin) 46.1 (simvastatin/ezetimibe)	49	2	CC Bulb ICA	Right and Left	Far wall	simvastatin (n=320) simvastatin/ezetimibe (n=322)	C-IMTp was similar between simvastatin/ezetimibe and simvastatin alone (0.0111±0.0038 vs 0.0058±0.0037 mm, p=ns)	yes
FH children (n=211) [169]	13.0	47	2	CC Bulb ICA	Right and Left	Far wall	pravastatin (n=104) placebo (n=107)	Pravastatin slowed C-IMTp compared with placebo (-0.010±0.048 vs 0.005±0.044, p=0.02)	yes
FH patients (n=850) [170]	45.2 (atorvastatin) 46.8 (atorvastatin/torcetrapib)	49	2	CC Bulb ICA	Right and Left	Near and Far wall	atorvastatin (n=427) atorvastatin/torcetrapib (n=423)	C-IMTp was similar between atorvastatin/torcetrapib and atorvastatin alone (0.0047±0.0028 vs 0.0053±0.0028 mm/y, p=ns)	yes
Mixed dyslipidaemia patients (n=683) [171]	56.5 (atorvastatin) 57.9 (atorvastatin/torcetrapib)	64	2	CC Bulb ICA	Right and Left	Near and Far wall	atorvastatin (n=344) atorvastatin/torcetrapib (n=339)	C-IMTp was similar between atorvastatin/torcetrapib and atorvastatin alone (0.025±0.005 vs 0.030±0.005 mm/y, p=ns)	yes
FH (n=904) or mixed dyslipidaemia patients (n=752) [106]	50.4 (atorvastatin) 51.8 (atorvastatin/torcetrapib)	56	2	CC Bulb ICA	Right and Left	Near and Far wall	atorvastatin (n=829) atorvastatin/torcetrapib (n=827)	C-IMTp was higher with atorvastatin/torcetrapib than with atorvastatin alone (0.0076±0.0011 vs 0.0025±0.0011 mm/y; p=0.0014)	yes

*mean value reported or otherwise indicated, **carotid segments where IMT was measured, ***age-stratified sample of men 42, 48, 54, or 60 years, CC=common carotid, ICA=internal carotid artery, NA=not applicable, NGT=normal glucose tolerance, IGT=impaired glucose tolerance, UD=undiagnosed diabetes, DD=diagnosed diabetes, T2DM= type 2 diabetes mellitus, CAD=coronary artery disease, FH=familial hypercholesterolemia, MI= myocardial infarction, [#]when cerivastatin was withdrawn from the market, 0.4 mg cerivastatin was replaced by 20 mg simvastatin


1058 ORIGINAL ARTICLES SCREENED
REASONS OF EXCLUSION:
N = 43 FULL TEXT NOT AVAILABLE
N = 155 FOLLOW UP < 12 MONTHS
N = 144 STATISTICAL POWER < 80%
N = 123 REPRODUCIBILITY DATA FOR IMT NOT AVAILABLE
N = 40 MULTIVARIATE ANALYSIS NOT PERFORMED
N = 124 NOT PERTINENT (animal models, echolucency, only plaques evaluated, only methodology)
N = 86 OTHER (study protocols, case reports, letters, commentaries, duplicates)
N = 183 RISK FACTORS NOT INCLUDED IN THIS REVIEW (autoimmune disorders, inflammation, kidney disease, infectious burden, hormone disorders, platelet activity, socioeconomic and psychological factors, unconventional risk factors)
160 ARTICLES ON CONVENTIONAL RISK FACTORS INCLUDED

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