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REVIEW ARTICLE

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 a 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 careful consideration of methodological aspects in investigations using C-IMTp as the outcome.

Keywords: Atherosclerosis, risk factors, carotid intima-medial thickness, atherosclerosis progression, ultrasonography, causality.

1. INTRODUCTION

Changes in subclinical atherosclerosis over time have 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, possibly due to differences in the study population, sample size, length of follow-up, the methodology of C-IMT measurement and statistical analyses.

In the present narrative review, we examined the literature critically 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 fulfill the following minimal prespecified inclusion criteria:

1). The time between baseline and final C-IMT assessment ≥ 12 months.
2). Proper statistical power ($\alpha = 0.05$, $\beta > 80\%$).
3). Reported assessment of the 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.

Fig. **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 the 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 were 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 (healthy subjects or others), ultra-

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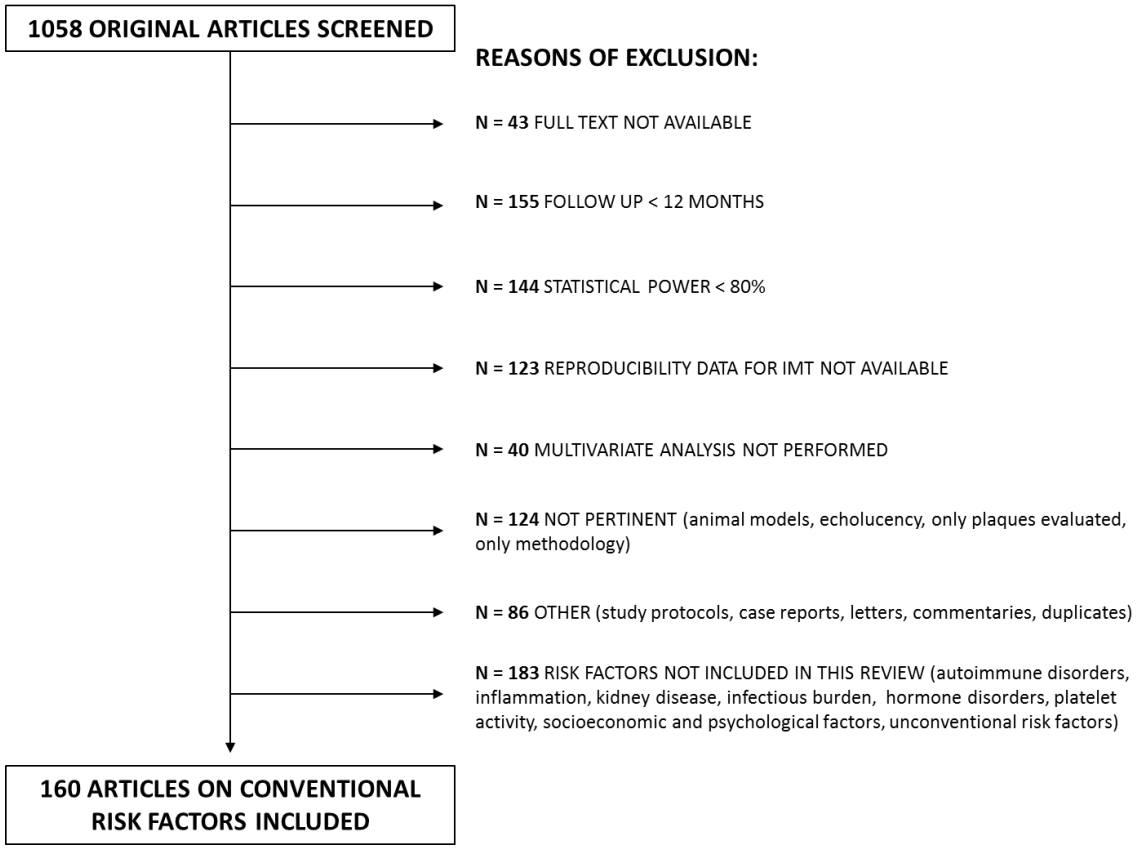

Fig. (1).

sonographic 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

3.1. 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 focused 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.

3.2. Life Style

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

3.3. Cigarette Smoking and C-IMTp

The relationship between smoking status and C-IMTp was investigated in general populations and specific patient 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 as compared with nonsmokers during 2-years follow-up [10]. Significant effects of cigarette smoking were also observed 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]. Altogether, these observational data suggest that both active and passive smoking are risk factors for C-IMTp.

3.4. Smoking Cessation and C-IMTp

Curiously, only one study investigated the effect of the active intervention of smoking cessation on C-IMTp and, paradoxically, there was a greater increase in C-IMT among subjects who were continuously abstinent as 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 on C-IMTp in the internal carotid or bulb may have been different from that observed in the common carotid artery.

3.5. 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.

3.6. 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.

3.7. 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 on 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 certain self-chosen food intake.

3.8. 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, an increase in 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 as compared with a control group on a usual diet [37].

Positive results were also obtained with n-3 fatty acid supplementation. In a randomized open study on 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 as 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 for 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, while 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 the role of any specific food, nutrient or micronutrient supplement is rather weak.

3.9. 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 the 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, the 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.

3.10. 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 sports practice group ($\geq$300 min/week of organized sports) and a control group (non-sports practice) during 1-year of follow-up [51]. A possible explanation for 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.

3.11. 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.

3.12. 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.

3.13. 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). The study of Buscemi *et al.* [62] showed a significant correlation between *changes* in body weight and *changes* in C-IMT. Conversely, the 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.

3.14. Metabolic Syndrome and C-IMTp

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 as compared with those without having MetS [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 a 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 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, as compared to patients with MetS at baseline but not at follow-up, in whom a reduced C-IMTp was observed [69,76].

3.15. Treatment of Metabolic Syndrome and C-IMTp

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

3.16. 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 the 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 bio-

chemical 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 for 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.

3.17. 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 antidiabetic 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 suggests 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 than in the original DCCT study, that 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 the pathogenic role of abnormalities in glucose metabolism on C-IMTp.

3.18. 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.

3.19. 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 differences related to the SBP target. However, it should be stressed that participants with 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, consequently 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 in C-IMTp as compared to less intensive treatment [124]. This study showed that, in diabetic patients, 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.

3.20. 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 also investigated 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 were 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].

3.21. 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 a 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 analysis 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 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 heterozygous 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], the 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 towards 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 into 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 a 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 offsets 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.

Nevertheless, 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 accounts for vascular events. This possibility is suggested by posthoc 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 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.

It is 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

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

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

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