Review

A review of the carotid and femoral intima-media thickness as an indicator of the presence of peripheral vascular disease and cardiovascular risk factors

Koon-Sung Cheng[a], Dimitri P. Mikhailidis[b], George Hamilton[a], Alexander M. Seifalian[a],*

[a]*Vascular Haemodynamic Unit, University Department of Surgery, Royal Free and University College Medical School, University College London and The Royal Free Hospital, Pond Street, London NW3 2QG, UK*
[b]*Department of Clinical Biochemistry, Royal Free and University College Medical School, University College London, London, UK*

Abstract

Peripheral vascular disease (PVD) is a common condition often associated with cardiovascular risk factors and events. With the aid of B-mode ultrasound scanning, evidence is emerging that these risk factors and events are significantly related to an increased carotid and femoral intima-media thickness (IMT). More importantly, treatment of these risk factors is associated with a decrease or a diminished progression of the IMT, paralleled by a reduction in cardiovascular events and an improvement in the symptoms associated with PVD. This evidence is particularly strong for lipid lowering therapy. Additional predictors of cardiovascular risk like the IMT, could now influence the decision to intervene with medication. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Peripheral vascular disease (PVD) is a common condition, particularly in the elderly [1]. The Edinburgh Artery Study (EAS) [1] has shown a prevalence of 4.5% for symptomatic PVD and 24.6% for asymptomatic subjects [ankle brachial pressure index (ABPI) of <0.9] between 55 and 74 years of age. With the aid of B-mode ultrasound scanning, it is possible to study the morphology of the arterial wall and its viscoelastic behaviour [2–6]. However, unlike compliance and elastic modulus, the ultrasonic measurement of the intima-media thickness (IMT) is independent of the blood pressure [7,8]. Measuring the IMT may be the best method of detecting early atherosclerosis and assessing the subsequent risk of vascular events [4,9–18].

Several population studies have shown that the carotid IMT is significantly increased in patients with PVD [4–6]. However, there is a paucity of data with regard to the relationship between the femoral IMT and PVD [3,19]. In this review we consider the evidence relating PVD and cardiovascular risk factors and events to the carotid and femoral IMT. The effect of risk factor management on the IMT, cardiovascular events and symptoms associated with PVD is also considered.

2. B-mode ultrasound scanning

The IMT is measured non-invasively by means of B-mode duplex scanning [4,6,8,15,20,21]. It is defined by the two parallel echogenic lines (double line pattern), which correspond to the lumen–intima and the media–adventitia interfaces (Fig. 1). Ultrasonically, these interfaces are well defined only in the far arterial wall. Even when the near wall IMT is well visualized, its measurement is gain-dependent and unreliable [20,22].

There are several problems associated with the ultrasonographic measurement of the carotid and femoral

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*Corresponding author. Tel.: +44-20-7830-2901 (direct) or +44-20-7794-0500 Ext. 3936; fax: +44-20-7431-4528.
E-mail address: a.seifalian@rfc.ucl.ac.uk (A.M. Seifalian).
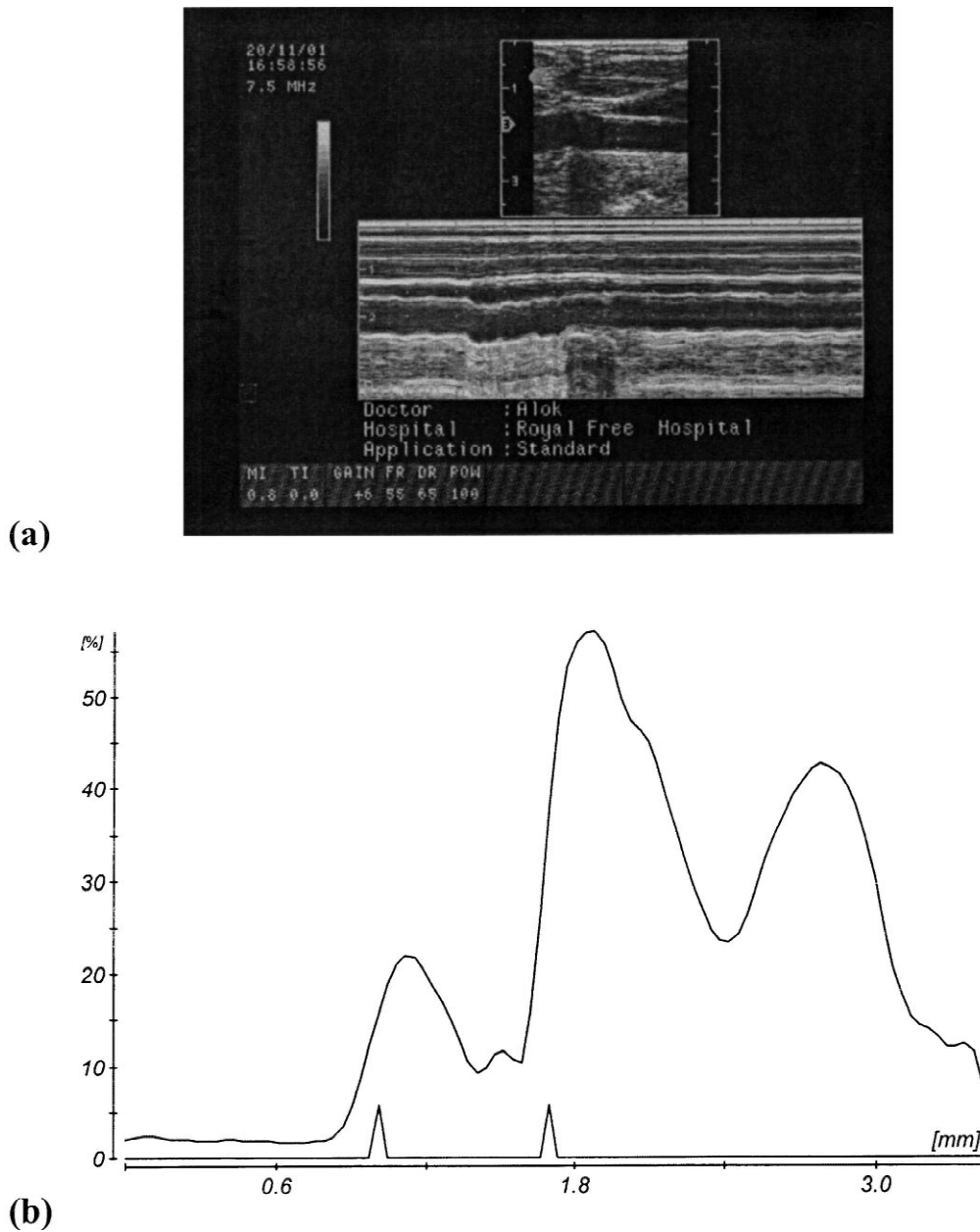
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Fig. 1. (a) B-mode and M-mode image of the common carotid artery (CCA) in a 72-year-old woman. (b) The distance density curve has been generated automatically from the radio frequency (RF) signal and the distance between markers (lumen–intima and media–adventitia interfaces) represent the IMT (in this case 0.70 mm).

IMT; namely, the resolution of the equipment, operator variability and the definition of carotid/femoral IMTs. With the advancement in technology and computer software, accurate measurement and the interpretation of the carotid and femoral IMT can be made with greater reliability and reproducibility. Computer software can now automatically define the IMT to within 0.01 mm.

A critical component in IMT measurement is the variation or error in the readings, which leads to non-identical results of repeated measurements from the same subject. In general, the inter- and intra-observer errors are acceptable [23–25]. Methods to reduce these errors have

been suggested [25,26]. In one study, automated edge detection as opposed to the manual tracing of the echo interfaces not only simplified the reading of ultrasonic images but also produced results with low variability [26]. The same authors also demonstrated a reduction ($P<0.01$) in the inter-observer error by using ultrasound images from both carotid arteries rather than from one. In another report, the use of external reference points to measure the carotid IMT reduced the intra-observer error by 38.2% [25].

There is no uniformity in the definition of carotid or femoral IMT. The EAS [4] measured the carotid artery

2 cm below the bifurcation from both sides and the carotid IMT was defined as the maximum of these two readings. The Rotterdam study [6] used the average value from the two common carotid arteries, each with three recordings obtained from the distal 1 cm. The AXA study [15], so-called because it screened employees from the AXA Insurance Company in France, took multiple readings of the thickness every 100 μm along a 1 cm longitudinal length of the artery 2 to 3 cm proximal to its bifurcation. The carotid IMT was defined as the average of the left and right sides. The Atherosclerosis Risk In Communities (ARIC) study [13] used the average of the readings taken from the common carotid artery, the carotid bifurcation and the internal carotid artery of both sides. Measurement of the maximum carotid IMT and the mean IMT over a length of 1 cm is similar but the latter had a better reproducibility in one observational study [27].

The relationship between ultrasonic and histological determination of the IMT has been reported in several observational studies [22,28–30]. There is a general consensus that ultrasonic estimation gives a slightly higher IMT reading [22,28,29]. This discrepancy could be explained by post-mortem tissue shrinkage as well as tissue contraction during histological fixation.

3. The association between cardiovascular risk factors and IMT

Both the carotid and femoral IMTs increase significantly with age and the IMT is greater in men compared with women (Table 1) [4,15,16,31–34]. In the National Institute for Longevity Sciences–Longitudinal Study of Aging (NILS–LSA) [31], the carotid IMT increased significantly ($P<0.01$) with age in both genders. The mean carotid IMT was 0.61±0.15 mm (mean±S.D.) for men and 0.58±0.14

mm for women and there was a significant difference between the two genders ($P<0.01$). There was also a significant increase in the IMT in subjects with plaques in the carotid bulb ($P<0.0001$). Furthermore, the carotid IMT was estimated to increase by 0.06 mm and 0.04 mm for every 10 years in the presence and absence of plaques in the carotid bulbs, respectively.

These findings were supported by the EAS [4], which showed a continuous increase in the carotid IMT with age ($P\leq0.01$) and that the overall mean IMT was significantly higher in men than in women after age adjustment ($P\leq0.01$). Men were shown to develop atherosclerosis earlier (by about 5 to 10 years) than women. Men were also more liable to suffer from what they described as moderate to severe atherosclerotic disease (defined by carotid IMT >2 mm) in later life. This carotid IMT is very high indeed, but the same authors did state that the IMT value was the maximum value of both sides and that the overall prevalence of moderate to severe disease was low in the population studied (1.2%). They also estimated that the mean carotid IMT in this population increased by 0.012 mm per year in men and 0.010 mm per year in women.

The AXA study [15] also demonstrated significant relationships between the carotid and femoral IMTs with age and cardiovascular risk factors such as body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, glucose and smoking.

These three studies [4,15,31] are population based; they included subjects with cardiovascular risk factors and disease. One interesting observational study assessed the carotid and femoral IMTs of healthy subjects (n=98) aged from 20 to 60 years [32]. The mean carotid IMT was found to be 0.573±0.07 mm for men and 0.556±0.057 mm for women. The respective figures for the mean femoral IMT were 0.562±0.074 mm and 0.543±0.063 mm. The carotid IMT was estimated to increase by 0.0034 mm per year in

Table 1
The relationship between IMT and age

	NILS–LSA [31]	EAS [4]	AXA [15]	Lausanne [32]
Number of subjects	979	1106	788	98
Men (% of total)	51	49.5	41.4	46
Age/years (mean±S.D.) or range	58.5±10.9	60–80	17–65	20–60
Mean carotid IMT/mm (mean±S.D.)	0.59±0.14 for M&W 0.61±0.15 for M 0.58±0.14 for W	0.91 for M 0.84 for W	0.56±0.12 for M 0.51±0.06 for W	0.573±0.07 for M 0.556±0.057 for W
Probability of carotid IMT increase with age	$P<0.01$	$P\leq0.01$	$P<0.001$	$P\leq0.001$ in M $P\leq0.03$ in W
Mean femoral IMT/mm (mean±S.D.)			0.5±0.11 for M 0.43±0.06 for W	0.562±0.074 for M 0.543±0.063 for W
Probability of femoral IMT increase with age			$P<0.001$	$P<0.002$ for M NS for W
Increase in carotid IMT/per year (mm)	0.006 with plaques 0.004 without plaques	0.012 in M 0.01 in W	0.007 in M 0.006 in W	0.0034 in M 0.0018 in W
Increase in femoral IMT/per year (mm)			0.005 in M 0.003 in W	0.0031 in M 0.0012 in W

Keys: NILS–LSA, National Institute for Longevity Sciences–Longitudinal Study of Aging. EAS, Edinburgh Artery Study. AXA, AXA Insurance Company. M, Men. W, Women. NS, Not significant.

men ($P<0.001$) and 0.0018 mm in women ($P<0.03$). For the femoral IMT, these rates were 0.0031 mm ($P<0.002$) and 0.0012 mm (not significant), respectively, per year. The carotid and femoral IMTs as well as their rates of increase in this latter study are much less than in either the EAS or NILS–LSA, probably because of the effect of age (younger subjects) and the fact that it screened subjects free of cardiovascular disease.

Lifestyle can affect the carotid IMT [35]. In the Monitored Atherosclerosis Regression Study (MARS) [35], dietary cholesterol, body mass index and smoking were significant predictors of the annual progression of carotid IMT ($P<0.05$) in 98 subjects with coronary artery disease. Cigarette smoking alone has also been shown to increase the IMT of both the carotid and femoral arteries [36–40]. In a study of 184 cigarette smokers (aged 44.3 ± 9.0 years) for whom smoking was the only cardiovascular risk factor, the carotid ($P=0.02$) and femoral ($P<0.0001$) IMTs were significantly larger than in 56 non-smokers matched for age and gender [39]. In a larger population study [36] of 2073 subjects, the lowest mean carotid IMT was found in the never smokers not exposed to environmental tobacco smoke (mean$\pm$standard error: 0.706 ± 0.013 mm). Exposure to passive smoking was associated with an increased carotid IMT (0.734 ± 0.012 mm) and the greatest carotid IMT was seen in the active smokers (0.807 ± 0.009 mm). There is also evidence to suggest that the increase in carotid IMT is related to the duration and the number of cigarettes smoked [37,41] and to the male gender [38,41]. The latter finding suggests that the female gender protects against smoking-induced thickening of the arterial wall as well as from the effects of ageing.

Alcohol is another lifestyle factor, which can affect the carotid IMT [42]. The sub-analysis of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) demonstrated that alcohol binging ($\geq$ a whole bottle of vodka or $\geq$six beers at a time) was associated with the highest atherosclerosis progression in men.

Diabetes mellitus is associated with an increased carotid IMT [43–47]. One fascinating demonstration of the progressive increase in the carotid IMT from subjects with normal glucose tolerance to patients with established type 2 diabetes is provided by the Insulin Resistance Atherosclerosis Study (IRAS) [47]. The carotid IMT increased most notably at the level of established diabetes (0.802, 0.822, 0.831, and 0.896 mm for subjects with normal glucose tolerance, impaired glucose tolerance, patients with newly diagnosed type 2 diabetes, and established type 2 diabetes, respectively). One sub-analysis of the IRAS suggests that ethnicity may influence the carotid IMT [48]. Black participants were shown to have significantly a greater carotid IMT than the non-Hispanic whites, which in turn, had a thicker IMT than the Hispanics.

In a study of 70 type 2 diabetics, the carotid IMT was greater ($P=0.028$) than in 52 non-diabetic controls [46]. In another study of 287 type 2 diabetics (mean age 61.6

years) without a history of coronary heart disease or stroke [45], the carotid IMT progressed by 0.04 ± 0.004 mm/year (which is 10 times the rate of progression compared to the NILS–LSA [31]). This is a cause for considerable concern since these findings suggest that diabetics free of cardiovascular disease have a carotid IMT progression rate ten times that of their non-diabetic counterparts. The same authors [45] also found that the independent predictors of IMT progression were the baseline carotid IMT ($P<0.001$), the average glycated haemoglobin (HbA$_{1c}$) ($P<0.001$) and age ($P=0.001$). Furthermore, predictors of non-fatal coronary heart disease (angina pectoris and myocardial infarction) were the initial IMT [odds ratio 4.9, 95% confidence interval (CI) 1.7–14.1] and a low average high-density lipoprotein (HDL)-cholesterol (odds ratio 0.2, 95% CI 0.1–1.8). This supports the view that a carotid IMT above a certain value is associated with an increased risk of coronary heart disease [12], stroke [12] and PVD [6].

The duration of type 2 diabetes is also an important factor in relation to an increased carotid IMT [43]. Other independent predictors of an increased carotid IMT in diabetic patients include age, hyperlipidaemia, body mass index and the presence of coronary heart disease [43,46]. Therefore, the IMT retains its predictive value and its relationship with several cardiovascular risk factors in type 2 diabetes; a condition associated with an increased vascular morbidity and mortality.

Hypercholesterolaemia and familial hypercholesterolaemia (FH) are associated with an increased carotid and femoral IMTs [14,16,34,49,50]. In a study performed by the Prevention Cardio-Vasculaire en Medecine du Travail (PCVMETRA) group, the carotid and femoral IMTs of 101 asymptomatic men aged 28 to 60 years free of cardiovascular risk factors apart from cigarette smoking were analysed [34]. Subjects with hypercholesterolaemia (total cholesterol$\geq$6.2 mmol/l) had significantly raised ($P<0.01$) carotid and femoral IMTs when compared with normo-cholesterolaemic men (total cholesterol<5.2 mmol/l). The carotid and femoral IMTs were significantly correlated with increased total cholesterol ($r=0.47$, $P<0.001$ and $r=0.35$, $P<0.001$, respectively) and low-density lipoprotein (LDL)-cholesterol ($r=0.33$, $P<0.001$ and $r=0.34$, $P<0.001$, respectively). Furthermore, the femoral IMT was suggested to be a powerful predictor of coronary risk in both men and women but this was partly conditional on age.

In another study of 60 subjects aged from 32 to 65 years, an elevated serum cholesterol was a significant independent determinant of early atherosclerosis in both the carotid and femoral arteries based on measurement of the IMT [16]. Patients with FH also have elevated carotid and femoral IMTs as shown in a study of 248 patients with FH, particularly in subjects with evidence of cardiovascular disease [49].

Hypertension is also associated with an increased carotid

IMT [51–54]. In one study of 22 healthy men (aged 37 ± 4 years) with borderline hypertension (defined as systolic of 130 to 140 mmHg or diastolic of 85 to 89 mmHg) [52], the carotid IMT was significantly higher than in 22 control subjects (0.75 ± 0.07 vs. 0.58 ± 0.06 mm, $P < 0.001$). This finding was supported by a larger study of 97 subjects with borderline hypertension [51]. The Plaque Hypertension Lipid Lowering Italian Study (PHYLLIS) suggested that the systolic and pulse pressures together with age were the most significant factors associated with an increased carotid IMT in hypertensive patients with moderate hypercholesterolaemia (LDL-cholesterol 4.14–5.17 mmol/l).

The relationship between IMT and rheological and haemostatic factors is less well defined [55–57]. This is also true for homocysteine and lipoprotein(a) [58–63]. The EAS [55] found significant associations between the carotid IMT and blood viscosity ($P \leq 0.001$), plasma viscosity ($P \leq 0.01$), plasma fibrinogen ($P \leq 0.01$) and haematocrit ($P \leq 0.05$) in men. Cortellaro et al. [56] found Factor VII as the only independent haemostatic variable associated with an increased carotid IMT ($P < 0.01$) in 64 patients with PVD. In another study, raised plasma fibrinogen was associated with the maximal femoral IMT [19]. However, no association was demonstrated between carotid IMT and fibrinogen or factor VII in a study of 121 healthy subjects aged 18 to 56 years [57].

One study of homocysteine did not demonstrate any links with the carotid and femoral IMTs [58] but in four other studies, an association was shown [59–62]. In a cross-sectional study of 474 elderly men aged 60–74 years in Japan [62], the odds ratio for having carotid IMT thickening with high levels of plasma homocysteine was 5.8. This relationship however, was only demonstrated in subjects without hypertension. Therefore the pro-atherogenic effect of hypertension may mask the effect of homocysteine on the vascular wall. In a smaller study of 144 subjects free of atherosclerotic lesions [61], homocysteinaemia was independently and positively associated with the carotid IMT ($P < 0.02$). In another study of 75 healthy subjects (mean age 49 years, range 22–75) with untreated moderate homocysteinaemia (mean plasma homocysteine concentration: 10.5 ± 2.81 μmol/l; range 5.7–19.6), the plasma homocysteine concentration was independently associated with the carotid IMT ($P < 0.001$) after adjustment for cardiovascular risk factors [60]. In a larger study [59] of 513 asymptomatic men and women aged 45–69 years, who were examined at the baseline of the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study, men with high levels (>11.5 μmol/l) of homocysteine had a significantly higher average carotid IMT of 1.12 mm compared to 1.02 mm in men with low levels (<11.5 μmol/l) of homocysteine ($P = 0.029$). This average carotid IMT of 1.12 mm in these men is quite high compared to 0.61 mm in the NILS–LSA [31] men of a similar age group but this may be accounted for by the fact that the ASAP subjects had FH.

Lipoprotein(a) has also been implicated as a risk factor of carotid atherosclerosis independent of other risk factors [63]. So far, evidence suggests an association between rheological and haemostatic factors as well as homocysteinaemia and lipoprotein(a) with an increased carotid IMT [19,55,56,59–63]. These observations suggest that atherosclerosis is linked to impaired fibrinolytic potential, lipid peroxidation, platelet activation and endothelial disturbance. The exact mechanisms by which these factors interact and cause atherogenesis are still unknown.

4. The association between IMT and clinical events

Evidence suggests that the carotid IMT is associated with cardiovascular disease [10,11,13,17,18]. In the ARIC study [13] of 13 870 black and white men and women aged between 45 to 64 years, the mean carotid IMT was consistently greater in those with prevalent clinical cardiovascular disease than in disease-free participants. The greatest difference was demonstrated in subjects with intermittent claudication.

In a review of carotid IMT studies, Aminbakhsh and Mancini [12] estimated that if the IMT progressed by 0.034 mm or more (approximately 10 times the normal increase in the carotid IMT for a healthy man per year [32]), the risk of future cardiovascular events was significantly raised. The same authors also calculated that the risk of first myocardial infarction was enhanced with an IMT of ≥ 0.822 mm and that an increased risk of a stroke was associated with an IMT of ≥ 0.75 mm. Another observational study of 30 coronary patients (who had survived a myocardial infarct) aged 30 to 50 years, demonstrated a significantly greater carotid IMT ($P < 0.0001$) when compared to 30 age-matched men without coronary disease [17].

The significant association between a raised carotid IMT and stroke is also supported by other studies [10,11,18]. The Cardiovascular Health Study Collaborative Research Group reported a significantly higher risk of stroke with elevated carotid IMT even after adjustment for the traditional risk factors in subjects at or over 65 years of age [18]. The Rotterdam Study calculated that the odds ratio for stroke per standard deviation increase in the carotid IMT (0.163 mm) was 1.41 [11]. In another observational study of 47 stroke patients, the carotid IMT was significantly elevated when compared with control subjects (0.96 vs. 0.70 mm, $P < 0.0001$) [10].

5. Relationship between PVD and IMT

The EAS (Table 2) demonstrated that PVD was significantly associated with an increased carotid IMT ($P \leq 0.05$) [4]. The age- and sex-adjusted mean carotid IMT for

Table 2
The relationship between IMT and peripheral vascular disease (PVD)

	EAS [4]	Rotterdam Study [6]	SMART Study [5]
Number of subjects	1106	970	172
Age (years)	60–80	$\geq$55 (68$\pm$7)	61$\pm$11
Men (%)	49	39	66
Mean carotid IMT/mm (mean$\pm$S.D.)	0.91$\pm$0.01 for M	0.81$\pm$0.19 for M	
	0.84$\pm$0.01 for W	0.76$\pm$0.19 for W	
Carotid IMT/mm for symptomatic and asymptomatic PVD subjects (mean$\pm$S.D.)			0.98$\pm$0.34
Carotid IMT/mm for asymptomatic PVD subjects (mean$\pm$S.D.)	0.87$\pm$0.04 for ABPI$\leq$0.9 (n=198)		
	0.80$\pm$0.02 for ABPI>0.9 (n=844)		
	$P\leq$0.01		
Carotid IMT/mm for claudicants (mean$\pm$S.D.)	0.90$\pm$0.05 for IC (n=122)	0.87$\pm$0.16 for IC (n=12)	
	0.81$\pm$0.02 for asymptomatic (n=984)	0.76$\pm$0.16 for asymptomatic	
	$P\leq$0.01		

Keys: EAS, Edinburgh Artery Study. SMART, Secondary Manifestations of ARTerial disease. M, Men. W, Women. IC, Intermittent claudication.

the 198 subjects with an ABPI≤0.9 was 0.87±0.04 mm compared to 0.80±0.02 mm for the 844 subjects with an ABPI>0.9 (*P*≤0.01) [4]. For the 122 participants with intermittent claudication, this value was 0.90±0.05 mm compared to 0.81±0.02 mm for the 984 asymptomatic subjects (*P*≤0.01) [4].

The Rotterdam study [6] showed that a carotid IMT≥ 0.89 mm was strongly associated with the prevalence of PVD. However, a gradual linear increase between the two variables was not demonstrated. The odds ratio for PVD in subjects with a carotid IMT≥0.89 mm compared to subjects with an IMT<0.89 mm was 2.8 after adjusting for age, gender and cardiovascular risk factors. There were 12 subjects with intermittent claudication with a mean ABPI of 0.84±0.32 and a mean carotid IMT of 0.87±0.16 mm compared to a mean ABPI of 1.12±0.22 and IMT of 0.76±0.16 mm for subjects free of intermittent claudication (*n*=958). These latter findings are limited by the fact that only 12 of the 970 subjects had symptomatic PVD.

In the Secondary Manifestations of ARTerial disease (SMART) Study [5], the prevalence of ABPI≤0.9 was 16% in abdominal aortic aneurysm (AAA) patients with a carotid IMT≤0.90 mm compared to 25% when the carotid IMT was >0.90 mm. The findings indicated that a higher carotid IMT was associated with PVD in this pre-defined group of patients.

A raised carotid IMT was also linked to a greater risk of cardiovascular disease in subjects with PVD [13,64]. One study showed that the ultrasonographic presence of carotid plaques together with clinical manifestation of PVD were reliable positive predictors for coronary artery disease [64]. In the ARIC study [13], the correlation between an elevated carotid IMT and prevalent clinical cardiovascular disease was most marked in subjects with intermittent claudication.

Similarly, subjects at a high cardiovascular risk have an increased probability of developing PVD [3]. Suurkula et al. [3] compared 143 hypertensive men with a high cardiovascular risk to 46 hypertensive men at low risk. The definition of high risk was the presence of one or more of the following: serum cholesterol above 6.5 mmol/l, diabetes mellitus or cigarette smoking. Subjects with high cardiovascular risk had a lower ABPI in both legs compared to the low risk group (*P*<0.0001). They also had a significantly thicker femoral IMT than the low risk group (1.65±0.66 mm versus 1.33±0.79 mm, *P*=0.0009) as well as more and larger atherosclerotic plaques in the common femoral artery.

6. Risk factor management and the carotid and femoral IMT

Lipid lowering reduces cardiovascular events and mortality including the incidence of carotid bruits, stroke, angina pectoris and intermittent claudication [65–72]. It also significantly reduces or prevents the progression of carotid and femoral IMT [73–78]. Treatment should aim at restoring LDL-cholesterol, HDL-cholesterol and triglyceride concentrations to normality [65,68–70,79].

A 3-year study on the effects of pravastatin (40 mg/day) on 53 subjects with heterozygous FH showed a significant net difference in the mean and maximal carotid IMT compared to untreated, low risk control subjects (*P*<0.05) [73]. The greatest reduction in the carotid IMT was seen in subjects (*n*=17) with a history of myocardial infarction (*P*<0.01). No such difference was seen with the femoral IMT in this study. However, in the Regression Growth Evaluation Statin Study (REGRESS) involving 255 men with coronary artery disease (total cholesterol 4 to 8 mmol/l) [78], pravastatin (40 mg/day) significantly reduced the combined carotid and femoral IMT (*P*<0.0085) as well as the femoral IMT (*P*<0.004) after 2 years.

Aggressive lowering of cholesterol by high dose atorvastatin (80 mg/day) [75] or by LDL apheresis [76] reduced the progression of the carotid IMT. In the apheresis study [76], 42 men with primary hypercholesterolaemia (total cholesterol>8.0 mmol/l) and extensive coronary artery disease were randomised to biweekly apheresis of LDL-cholesterol plus simvastatin 40 mg/day (*n*=21) or simvastatin 40 mg/day for 2 years. The apheresis group showed a decrease in the carotid IMT, whereas the simvastatin-only group demonstrated an increase in the IMT (*P*<0.001). In the ASAP study, 2 year treatment with high dose atorvastatin (80 mg/day) decreased the carotid IMT in 160 patients with FH, whereas treatment with simvastatin (40 mg/day) produced an increased carotid IMT in 165 subjects (*P*=0.0017) [75]. The change in the IMT correlated with the % LDL-cholesterol reduction (*r*=0.14, *P*=0.01) rather than changes in HDL-cholesterol or lipoprotein(a). The authors justified the use of simvastatin 40 mg daily as it was the highest dosage available at that time. However, several "non-LDL" differences have been reported when comparing various statins [79].

The Kuopio Atherosclerosis Prevention Study (KAPS) [74] randomised 424 men aged 44 to 65 years with LDL-cholesterol≥4.0 mmol/l and total cholesterol<7.5 mmol/l to pravastatin (40 mg/day) or placebo for 3 years. The baseline mean common carotid IMT was 1.35 mm, with pravastatin producing a treatment effect (rate of progression was 66% less than the placebo group (95% CI: 30 to 95%; pravastatin 0.010 mm/year; placebo 0.029 mm/year; *P*<0.002). However, no significant treatment effect was observed on the femoral IMT. Patients with average or below average cholesterol levels (4–7 mmol/l) also benefited from pravastatin therapy [80]. A sub-analysis (*n*=522) of the Long-term Intervention with Pravastatin in Ischaemic Disease study (LIPID) [80] showed that pravastatin (40 mg/day) significantly reduced the total cholesterol, LDL-cholesterol and triglyceride levels (all

$P<0.0005$). Pravastatin also decreased the mean carotid IMT by 0.014 mm compared to an increase of 0.048 mm in the placebo group after 4 years ($P<0.0001$).

One interesting observational study showed that a decrease in the carotid IMT in subjects with PVD after 8 weeks of treatment with atorvastatin [21]. This effect may be the result of a reduction in the inflammatory reaction at the vessel wall.

Treatment of hypertension reduces the carotid IMT [81–83]. In the Celiprolol Intima-Media Enalapril Efficacy Study (CELIMENE) of 98 patients with essential hypertension [81], both celiprolol and enalapril produced significant decreases in the carotid IMT associated with a significant reduction in the carotid pulse pressure after 9 months. The Verapamil in Hypertension and Atherosclerosis Study (VHAS) [83] showed that treatment with verapamil (240 mg/day) was superior to chlorthalidone (25 mg/day) in decreasing the carotid IMT (-0.082 vs. -0.037 mm/year, $P<0.02$) in 498 hypertensive patients over 48 months. More importantly, it demonstrated that the better carotid IMT regression with verapamil was paralleled by a lower cardiovascular event rate ($P<0.05$). Low-dose metoprolol (25 mg/day) together with fluvastatin (40 mg/day) also significantly reduced the rate of progression of the carotid IMT compared to placebo in a trial of 793 asymptomatic subjects with carotid plaque ($P=0.002$) [84].

A significant reduction in the carotid IMT was seen in type 2 diabetics ($n=60$) treated with cilostazol (100–200 mg twice to four times daily) for 12 months when compared to the placebo group ($n=60$) in the absence of differences between the groups in terms of risk factors such as body mass index, blood pressure, blood sugar, HbA_{1c} and lipid profiles [85]. This finding suggests that cilostazol may reduce atherosclerosis in type 2 diabetic patients without altering conventional cardiovascular risk factors. Asymptomatic type 2 diabetic subjects with hyperlipidaemia also benefit from gemfibrozil in the same way as non-diabetic subjects [86]. Anti-platelet therapy with aspirin or ticlopidine also reduces the progression of the carotid IMT in type 2 diabetic patients [87].

Lifestyle modification can affect the carotid IMT [35]. MARS [35] demonstrated that a reduction in the body mass index by 5 kg/m^2, a reduction of dietary cholesterol intake by 100 mg/day and quitting a 10 cigarettes/day habit reduced the progression of carotid IMT by a staggering 0.13 mm/year. Weight reduction has also been shown to correlate significantly with a decreased progression of the carotid IMT [88]. In a 4-year study involving 20 obese subjects treated by gastroplasty compared to 10 obese subjects and 35 lean participants, the surgical group demonstrated a mean weight reduction of 22 kg (19% body weight) compared to the obese group, whose weight was unchanged ($P<0.001$) [88]. There was also an improvement in the blood pressure, cholesterol and insulin levels ($P<0.05$). The progression of the carotid IMT in the surgical group was not significantly different from that of the lean group (0.024 vs. 0.025 mm per year). However, the control obese group showed a faster progression of the carotid IMT than the surgical and lean groups (0.068 vs. 0.025 mm per year, $P<0.05$).

The use of hormone replacement therapy (HRT) has been associated with a decreased mean and maximum carotid IMT (Rotterdam study) [89]. Only women using HRT for at least 1 year showed such benefit compared to the non-users (mean IMT$\pm$S.E., 0.719 ± 0.01 vs. 0.742 ± 0.004 mm, $P=0.03$; max IMT$\pm$S.E., 0.952 ± 0.015 vs. 0.983 ± 0.006 mm, $P=0.04$) [89].

Anti-platelet therapy in patients with vascular disease reduces the risk of cardiovascular events and death rather than improving the symptoms of PVD [90,91]. A systematic review of 39 randomised trials of antiplatelet therapy showed a significant reduction ($P=0.02$) in serious vascular events (non-fatal myocardial infarction and non-fatal stroke) and vascular death in PVD patients treated with an anti-platelet agent when compared with a placebo [91]. In the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study [90], clopidogrel was superior to aspirin with a relative risk reduction (of myocardial infarction, stroke or other vascular death) of 8.7% (95% CI, 0.3–16.5%) and fewer side effects. The greater risk reduction (23.8%, $P=0.0028$) was seen in the PVD subset of the CAPRIE trial. However, this subgroup analysis is limited by the fact that it was not included in the initial protocol of the CAPRIE study [91].

7. Conclusions

At present, we can use the Framingham equation to predict the risk of cardiovascular event in an individual patient. However, we are unable to determine which of the high-risk patients will develop a cardiovascular event. Therefore, we need to refine our risk assessments. There is consistent evidence that an elevated carotid IMT is associated with increased cardiovascular risk and event as well as PVD. Evidence is also emerging to suggest that the femoral IMT has similar significant associations. More importantly, treatment of these risk factors causes a reduction or prevents the progression of the IMT, paralleled by a decrease in cardiovascular risk and events. The IMT may be regarded as the closest investigation to an arterial biopsy. Therefore, the morphological and dimensional information obtained from duplex scans may be used in addition to classical risk factors for risk assessment. Indeed, new guidelines (ATPIII) from the United States actually state that additional predictors of risk (e.g., imaging) could influence a clinician's decision to intervene with medication [92]. B-mode scanning could become an important non-invasive, accurate and reproducible method to assess cardiovascular risk in the future.

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