Carotid imaging in cardiovascular risk assessment

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CHAPTER 3

Associations Between Cardiovascular Risk Score and Ultrasound-Determined Subclinical Carotid Atherosclerosis

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ABSTRACT

Aims

Current guidelines in cardiovascular disease prevention advocate the use of carotid ultrasound measurements in risk assessment. The additional predictive power of adding carotid ultrasound parameters to traditional risk assessment tools is thought to be limited, especially in high risk patients. In the present study we aimed to evaluate the prevalence of subclinical carotid atherosclerosis in presumed high-risk vascular outpatients in relation to calculated cardiovascular risk scores.

Methods and Results

Carotid ultrasound was performed in 112 vascular outpatients to measure intima-media thickness and detect plaques. Plaques were observed in 52% of primary prevention patients and 88% of secondary prevention patients. In a low risk statin-naïve primary prevention subgroup (mean calculated risk score: 3.3%/10years) 48% of the patients were found to have plaques present. Intima-media thickness was explained (r^2=0.575; p<0.001) by traditional risk factors in a multiple regression model. Plaque presence only related (r^2=0.372; p<0.001) to hypertension (β=0.347; p=0.036), a positive family history for cardiovascular disease (β=0.396; p=0.016) and fasting glucose levels (β=0.158; p=0.047). Adding carotid ultrasound parameters to risk assessment strategies would result in an additional 23% (plaque presence alone) to 36% (plaque and/or increased intima-media thickness) of our primary prevention patients being reclassified as higher risk patients.

Conclusion

Our findings show that subclinical carotid atherosclerosis is highly prevalent in a vascular clinic setting and is frequently observed in patients with low calculated risk scores. Carotid ultrasound can potentially improve risk assessment strategies in these patients.

INTRODUCTION

Calculation of absolute risk of future cardiovascular events is an important tool in cardiovascular disease prevention strategies. The algorithms for such calculations are based on data from large epidemiological studies, such as the Framingham study (55), the Münster heart study (56) and the SCORE project (57) However, up to 40% of incident myocardial infarctions are not explained by the presence of traditional risk factors on which risk calculations are based, illustrating that significant limitations exist in predicting cardiovascular events. (58) It remains difficult to pinpoint individual patients that may require early or intensive pharmacological interventions, especially in an intermediate risk group.

Ultrasound determined carotid intima-media thickness (IMT) and the presence of carotid plaques are independently associated with incident cardiovascular events, even after adjustment for traditional cardiovascular risk factors (59) (60) (7) (8) (63) (64). The European Society of Cardiology (65), The European Society of Hypertension (66) and the American Heart Association (67) have added recommendations for the use of carotid ultrasound in cardiovascular risk stratification to their guidelines. Large meta-analyses have recently questioned the additional value of carotid ultrasound. There does appear to be an improvement in the predictive potential of risk assessment models containing carotid ultrasound findings but the benefit may be so marginal that it is not clinically relevant, (68) (69) . Although there is no broad consensus on whether to use carotid ultrasound most authors agree that the potential target population is the intermediate risk group. Patients who are already at high cardiovascular risk should receive an intensive risk management strategy regardless of any findings at carotid examination therefore rendering the investigation unnecessary. In the Netherlands a substantial part of the initial cardiovascular risk management is performed by primary healthcare providers, Access to carotid artery imaging is less readily available in this setting than it is in a dedicated vascular unit of a referral hospital. However, patients referred to a vascular clinic have different characteristics compared to a general population. The prevalence of carotid atherosclerosis and correlation to calculated risk in such a specific, presumably high-risk population is not known. In the present study we therefore investigated the prevalence of subclinical carotid atherosclerosis (SCA) defined as increased

IMT and/or plaque presence in vascular outpatients and related SCA to a traditional risk factor scoring system, with a secondary prevention population as reference.

PATIENTS AND METHODS

Patients

Patients were recruited from the vascular outpatient department of our hospital. The population included patients newly referred by their primary healthcare providers as well as patients already under evaluation. Oral and written informed consent was obtained from all patients; the study protocol was approved by the Institutional Review Board. The primary focus of the inclusion were subjects free of clinically manifest cardiovascular disease (CVD), defined as prior myocardial infarction or stroke, coronary revascularization or known peripheral vascular disease. As a reference, a group of patients with a history of CVD were included. There were no predefined exclusion criteria to ensure a representative cross-section of patients. The presence of hypertension was defined as an average of 3 measurements over 140/90 mmHg or the use of anti-hypertensive medication. Subjects were designated as having a positive family history if at least one first degree relative had a cardiovascular event or revascularization intervention before the age of 60 years. Smoking habits were recorded, and patients who had not smoked in the last 12 months were designated as ex-smokers. Absolute risk of a fatal cardiovascular event over 10-years was calculated using the SCORE algorithms as described earlier (57), and values of more than 5% per 10-years risk of a fatal cardiovascular event were considered treatment indications, as recommended by the European Society of Cardiology guidelines (65).

Study design

Carotid ultrasound measurements were performed in a specialized vascular laboratory. Distribution of plaque prevalence and IMT values was assessed in statin-naïve and statin-treated primary prevention patients as well as secondary prevention patients. Subsequently associations of carotid parameters and traditional risk factors were assessed. In the untreated primary prevention group the number of patients with a treatment indication based on calculated

risk scores was compared to the number of patients with potential treatment indications if risk scores were to be augmented by vascular imaging. The presence of moderate to severe carotid plaques and/or increased IMT was arbitrarily used as potential treatment indications for this analysis.

Ultrasound protocol

Carotid ultrasound scans were performed using an Acuson Sequoia 512 (Siemens Medical AG, Munich, Germany) high-resolution ultrasound machine with an 8LS (8MHz) linear transducer. One sonographer (4 years of experience) who has been certified to implement the ultrasound protocol for clinical trials performed and analysed the scans. At the time of scan and analysis the sonographer was blinded for the clinical data of the patient. Subjects were examined in prone position with the head tilted to the side counter lateral to the site of examination. The left and right carotids were both scanned. First, a transverse scan was performed for orientation, starting at the clavicle and moving cranially up to the mandible, hereby locating the height of the carotid bifurcation. Subsequently, longitudinal images were obtained. This technique allows visualization of two echogenic lines, separated by an anechoic space. It has previously been established that these lines indicate the blood-intima and the media-adventitia interfaces, and that the distance between the lines represents a histologically reliable measure for the thickness of the lamina intima and media (70). The caudal tip of the flow divider (i.e. the wall structures between the internal and external carotid arteries) was used as the anatomical landmark to localize the most distal 1cm of the common carotid artery. The artery was visualized at four angles (anterior, two antero-lateral projections and lateral). Subsequently, the carotid bifurcation and internal carotid artery were visualized and assessed for the presence of plaque. The overall gain settings during scanning were kept at 0dB when possible. The sonographer was free to adjust the gain levels if necessary, but within the limits of -7dB to 7 dB to avoid possible influences of extreme gain settings on subsequent IMT quantification. It has been recently shown that a similar ultrasound protocol, limited to plaque detection and IMT measurement in the common carotid artery, produces the same results as more comprehensive protocols that include quantification of IMT in the carotid bifurcation and internal carotid artery (17). The scans were recorded on sVHS video tapes and quantitatively analysed off-line with computer-aided automatic boundary detection where possible and

manual adjustment where necessary, using the ASM II software package version 1.1364 (Gustavson, Chalmers, Sweden). IMT was defined as the average of the maximum values of the far and near walls of the left and right common carotid artery at all four angles. Plaques were defined as focal thickening of >1.5mm or >1.5 times the surrounding IMT. If present the plaques were classified to be mild if only the aforementioned criteria were met. Moderate plaques were defined as lesions encroaching into the lumen. If the lesion caused stenosis the plaque was classified as severe. Subclinical carotid atherosclerosis (SCA) was defined as presence of moderate to severe plaque and/or an IMT of ≥0.9mm, considered the clinically relevant cut-off value (65). All quantifications were performed in cardiac diastole.

Statistical analysis

All data were analyzed using the SPSS 12.0 software package. Data are expressed in means [95% confidence intervals] unless indicated otherwise. All continuous variables followed normal distribution. Differences between groups were analyzed with an independent Student *t*-test; categorical data were compared using a Chi-squared test. Pearson correlation coefficients were calculated to assess associations between vascular parameters and risk scores. Stepwise multiple regression analysis was performed to assess explanatory parameters for plaque presence and variability in IMT values.

RESULTS

Patient characteristics

A total of 112 patients (60 (54%) males) were included in the study of which 88 (79%) were seen in a primary prevention setting and 24 (21%) had a prior history of CVD. The characteristics of the patients are shown in table 1. The secondary prevention patients were significantly older and had smoked more packyears. Diastolic blood pressure was significantly lower in the secondary prevention group. Secondary prevention patients were more frequently treated with anti-platelet therapy, anti-hypertensive medication and statins, possibly partly explaining the lower blood pressure and lipid values.

Of the primary prevention patients 50% were receiving statin therapy for

Table 1 | Characteristics of primary and secondary prevention patients

Variable	Primary prevention (n=88)	Secondary prevention (n=24)	p-value
Age (yrs)	52.1 [49.8-54.4]	58.7 [54.2-63.2]	0.01
Male Gender	49 (54.5%)	13 (54.2%)	-
Waist circumference (cm)	97.8 [95.3-100.3]	98.7 [94.4-103.0]	0.74
Systolic BP (mmHg)	134.1 [130.2-138.1]	132.2 [132.2-123.6]	0.66
Diastolic BP (mmHg)	83.21 [81.0-85.1]	78.2 [74.7-81.7]	0.03
Diabetes Mellitus	12 (13.6%)	2 (8.3%)	0.54
Hypertension	37 (42.0%)	16 (66.7%)	0.02
Hypercholesterolemia	61 (69.3%)	14 (58.3%)	0.42
Family history of CVD	25 (28.4%)	10 (41.7%)	0.20
Current smokers	21 (23.8%)	3 (12.5%)	0.27
Packyears of smoking	8.37 [5.2-11.6]	19.85 [7.7-32.0]	0.01
Anti-platelet therapy	10 (11.4%)	14 (58.3%)	<0.001
Statin therapy	44 (50.0%)	18 (75.0%)	0.13
Anti-hypertensive therapy	33 (37.5%)	14 (58.3%)	0.01
HbA1c (%)	5.3 [5.1-5.4]	5.6 [5.2-5.9]	0.12
Fasting glucose (mmol/L)	5.4 [5.1-5.6]	5.3 [5.1-5.7]	0.90
Total cholesterol (mmol/L)	5.7 [5.4-5.9]	5.2 [4.7-5.7]	0.06
Triglycerides (mmol/L)	1.9 [1.6-2.2]	1.5 [1.2-1.7]	0.02
HDL-cholesterol (mmol/L)	1.6 [1.4-1.7]	1.6 [1.4-1.8]	0.66
LDL-cholesterol (mmol/L)	3.7 [3.4-3.9]	3.1 [2.6-3.7]	0.07
Plaques	46 (52.3%)	21 (87.5%)	0.006
IMT (mm)	0.830 [0.797-0.863]	0.917 [0.873-0.960]	0.01
IMT≥0.9mm	29 (32.9%)	12 (52.2%)	0.56

previously diagnosed hyperlipidemia at time of inclusion. The characteristics of the statin-treated and statin-naïve primary prevention patients are shown in table 2. Plasma levels of LDL cholesterol were significantly lower in the statin-treated group and there was a higher prevalence of type 2 diabetes mellitus and hypertension. Levels of HbA1c and fasting glucose were significantly higher in the statin-treated group.

Table 2 | Characteristics of primary prevention patients

Variable	Statin naïve (n=44)	Statin treated (n=44)	p-value
Age (yrs)	50.0 [46.2-53.1]	54.1 [51.3-56.9]	0.08
Male gender	24 (54.5%)	25 (56.8%)	-
Waist circumference (cm)	95.9 [92.5-99.3]	99.6 [95.8-103.3]	0.15
Systolic BP (mmHg)	132.9 [127.1-138.7]	135.3 [129.7-140.9]	0.55
Diastolic BP (mmHg)	81.5 [78.6-84.4]	84.5 [81.7-87.4]	0.14
Diabetes Mellitus	2 (4.5%)	10 (22.7%)	0.02
Hypertension	13 (29.5%)	24 (54.5%)	0.02
Hypercholesterolemia	19 (43.2%)	44 (100%)	<0.001
Family history of CVD	10 (26.3%)	15 (34.1%)	0.45
Current smokers	12 (27.3%)	9 (20.5%)	0.45
Packyears of smoking	6.9 [3.2-10.6]	10.5 [4.7-16.4]	0.29
Anti-platelet therapy	6 (13.6%)	10 (22.7%)	0.50
Anti-hypertensive therapy	12 (27.3%)	21 (47.7%)	0.05
HbA1c (%)	5.1 [4.9-5.3]	5.4 [5.2-5.7]	0.05
Fasting glucose (mmol/L)	5.1 [4.7-5.4]	5.7 [5.3-6.1]	0.01
Total cholesterol (mmol/L)	6.1 [5.7-6.4]	5.3 [4.9-5.6]	0.02
Triglycerides (mmol/L)	2.0 [1.5-2.3]	1.8 [1.4-2.3]	0.85
HDL-cholesterol (mmol/L)	1.5 [1.3-1.7]	1.6 [1.4-1.7]	0.62
LDL-cholesterol (mmol/L)	4.2 [3.8-4.5]	3.2 [2.8-3.5]	<0.001
SCORE-risk (% per 10 yrs)	3.3 [2.1-4.5]	-	-
Plaques	21 (47.7%)	26 (59.1%)	0.34
IMT (mm)	0.787 [0.743-0.830]	0.875 [0.829-0.919]	0.006
IMT≥0.9mm	12 (27.3%)	18 (40.1%)	0.20

Ultrasound findings

In the primary prevention group 52% had evidence of atherosclerotic plaque in the carotid artery, whereas 88% of secondary prevention patients had plaques (p=0.006, table 1). Within the primary prevention group there was no difference in plaque prevalence between the statin-naive patients and the statin-treated group (48% vs. 59%, respectively; p=0.34). Carotid IMT was significantly higher in

the secondary prevention group (0.830mm for primary prevention patients vs. 0.917mm for secondary prevention patients; p=0.01). The percentage of patients above the clinically relevant cut-off value of 0.9mm did not significantly differ between the groups (33% vs. 52%, respectively; p=0.56). Within the primary prevention group the statin-treated patients had significantly higher IMT values (0.787mm for untreated patients vs. 0.875mm for statin treated patients; p=0.006), but the number of patients above the clinical cut-off value was comparable between the groups (27% vs. 40%, respectively; p=0.20). The distribution of carotid plaque prevalence and increased IMT values is illustrated in figure 1.

The statin-naïve patients had a mean calculated risk of a fatal cardiovascular event (SCORE system) of 3.3% per10yrs [95% CI: 2.1-4.5]. Risk scores correlated with carotid IMT (r=0.647; p<0.001, illustrated in figure 2) and plaque presence (r=0.37; p<0.05). Significant multiple regression models could be made using the following co-variates: age, gender, waist circumference, body mass index, systolic and diastolic blood pressure, blood lipid levels, fasting glucose and HbA1c, the presence of diabetes mellitus, hypertension, hypercholesterolemia, family history of CVD and smoking status. Variability in IMT values was significantly explained (r^2=0.575; p<0.001) by age (β=0.005; p=0.002), systolic blood pressure (β=0.004; p=0.003) and waist circumference (β=0.003; p=0.012). Plaque presence was explained (r^2=0.372; p<0.001) by the presence of hypertension (β=0.347; p=0.036), a positive family history for CVD (β=0.396; p=0.016) and fasting glucose levels (β=0.158; p=0.047). None of the other traditional risk factors significantly contributed to this model.

Of the statin-naïve primary prevention patients 11/44 (25%) had a treatment indication on the basis of a calculated risk of above 5% per 10yrs. The distribution of carotid parameters in patients above and below this treatment threshold is summarized in table 3. Adding of the presence of moderate to severe carotid plaque to the decision process would result in an additional 10/44 (23%) of patients being reclassified in a higher risk group. When taking into account increased IMT values as well as plaque presence, a further 6/44 (14%) patients would be identified as higher risk patients.

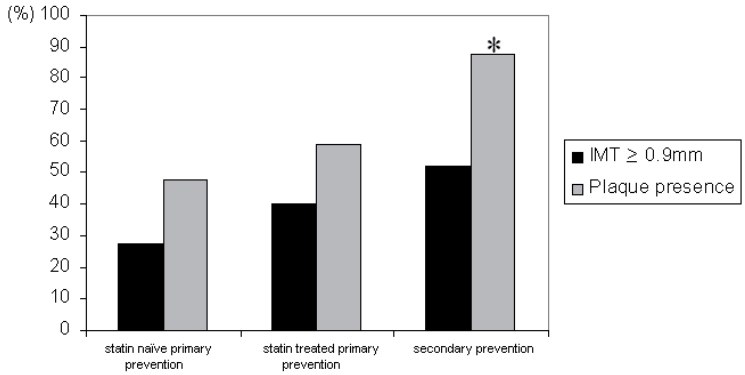

Figure 1 | Distribution of carotid plaques and increased intima-media thickness.
(*) indicates that secondary prevention group had significantly higher plaque prevalence compared with primary prevention patients

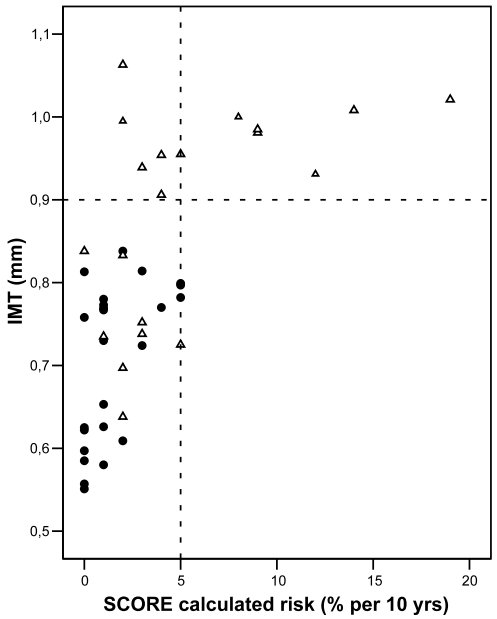

Figure 2 | Relation between subclinical carotid atherosclerosis and calculated risk score in statin naïve primary prevention cases. Dotted lines indicate the treatment threshold advised in ESC guidelines (SCORE ≥ 5% per 10 yrs; x-axis) and a proposed treatment threshold using ultrasound (IMT ≥ 0.9mm; y-axis).

● patients with no treatment indication based on ultrasound parameters
Δ patients with carotid plaque and/or IMT ≥ 0.9mm

Table 3 | Distribution of plaques alone and subclinical carotid atherosclerosis (SCA) defined as moderate to severe plaque and/ or IMT ≥ 0.9mm over risk strata in statin naïve primary prevention patients.

	Analysis based on plaque		Analysis based on plaque and/or IMT		
	No/mild plaque	Moderate/severe plaque	SCA -	SCA +	total
SCORE < 5	23	10	17	16	33
SCORE ≥ 5	5	6	3	8	11
Total	28	16	20	24	44

DISCUSSION

The main findings of our study are that subclinical carotid atherosclerosis is highly prevalent in a vascular outpatient setting and that it is frequently observed in patients with low calculated cardiovascular risk scores.

Carotid ultrasound imaging identified plaques in approximately 50% of our primary prevention patients, whereas nearly all (88%) of the secondary prevention patients had evidence of atherosclerotic carotid plaque. These figures are comparable to prevalence numbers reported in population based studies. Rosvall et al. (72) found 43% carotid plaques in 5163 subjects with and average age of 58 years and van der Meer et al. (19) reported 58% plaques in 6389 subjects of >55 years of age. Both these study samples were recruited from the general population and showed similar patterns of co-morbidity as our patients, although our patients were younger. This is an indication that a population in a referral center such as a vascular outpatient department may reach comparable levels of subclinical atherosclerosis at an earlier age than a general population.

A substantial number of plaques and increased IMT values were found in patients with low calculated risk in our study. Both plaque presence and IMT values correlated with calculated risk scores, but traditional risk factors could only partly explain plaques presence and IMT values. Besides the traditional cardiovascular risk factors, carotid ultrasound parameters have been associated with many factors not included in algorithms for risk calculation. Amongst these are levels of homocysteïne (74), lipoprotein(a) (75) C-reactive protein (76), fibrinogen (23), markers of oxidative stress (24) and endothelial dysfunction (25). The impact of these non-traditional risk factors on SCORE-

calculated risk has been acknowledged in the European Society of Cardiology guidelines (65), stating that patients exhibiting these characteristics may be at higher actual risk than their calculated SCORE results indicate. In addition, the development of atherosclerosis is subject to individual genetic susceptibility. Current guidelines recommend screening for ultrasound measured subclinical carotid atherosclerosis. The presence of SCA should be interpreted as target organ damage rather than a risk factor. It could in this regard be viewed as an easily obtained *in vivo* marker for the cumulative effect of traditional and non-traditional risk factors on the arterial wall. Importantly, both carotid plaque and IMT have been associated with atherosclerotic changes in other vascular beds, including the coronary arteries (80) (27) (82) (29), where these risk factors may also promote atherosclerosis formation.

Previous reports have addressed the added value of carotid ultrasound in risk assessment. The addition of carotid parameters to risk prediction models does appear to improve their performance (84). In a large population-based study as well as recent systematic reviews however the positive effect on predictive power has been shown to be marginal (68) (69) It is therefore still questionable whether the measurements offer clinically relevant benefits in risk assessment. Not all the scanning protocols in these studies included carotid plaques in the analysis. In several earlier reports, plaque presence has been associated with higher risk of future cardiovascular events (8) (85) (32) (33) (34). Therefore, adding plaque detection may improve the predictive value of carotid ultrasound results. The current recommendations therefore advise prudent use of carotid ultrasound in clinical practice by carefully selecting patients in whom the findings offer additional information. Plaque detection combined with IMT measurements appears to offer the most relevant information. It can be argued that patients referred to a specialized vascular clinic where carotid ultrasound is readily available may not be comparable to the general public. The added value of carotid imaging has not been prospectively studied in such a setting. Our study provides data exploring carotid ultrasound in risk assessment in the setting of a vascular referral clinic. The consequences regarding treatment decisions may be considerable. In untreated subjects, imaging may identify a significant number of high risk primary prevention patients (23%-36%, according to our cross-sectional data) with subclinical atherosclerosis. These subjects are not identified as high risk by current risk assessment algorithms. This potential

should be explored further, as the lack of outcome studies poses a critical factor limiting routine use of carotid ultrasound in clinical practice. Although subclinical carotid atherosclerosis has consistently been associated with higher cardiovascular risk, a prospective study incorporating carotid ultrasound in treatment decisions is warranted.

Our study has limitations. We evaluated a small cross-sectional sample. Larger studies in the referral centers where the carotid ultrasounds are available in clinical practice are needed. We defined the presence of moderate to severe plaque and/or increased IMT values as subclinical carotid atherosclerosis. More elaborate plaque classifications are available, including plaque size, echogenicity and regularity of the plaque surface. We did not evaluate these parameters.

Furthermore, our patients were recruited from a vascular referral center in the Netherlands. This limits the possibilities to extrapolate our findings to populations in other countries where the role of primary health care providers in CVD risk management and thresholds for referral may be different.

In conclusion, our findings demonstrate that subclinical carotid atherosclerosis is highly prevalent in a vascular outpatient setting in the Netherlands. It was frequently observed in patients with low calculated risk scores. Our data suggest that utilization of carotid ultrasound may be useful, even in a setting of presumed high-risk patients.

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