Aneurysmal disease is associated with lower carotid intima-media thickness than occlusive arterial disease

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Objective: **Patients with aneurysmal and occlusive arterial disease have overlapping cardiovascular risk profiles. The question remains how atherosclerosis is related to the formation of aortic aneurysms. Common carotid artery intima-media thickness (CIMT) is an easily accessible and objective marker of early atherosclerosis. The aim of the current study was to investigate whether there is a difference in atherosclerotic burden as measured by CIMT between patients with aneurysmal and those with occlusive arterial disease.**

Methods: **From 2004 to 2011, the CIMT was measured using B-mode ultrasound scanning in patients undergoing vascular surgery for aortic aneurysmal or occlusive arterial disease at the Erasmus University Medical Center. Cardiovascular risk factors, comorbidities, and medication were recorded. Patients treated for combined aneurysmal and occlusive arterial disease and patients diagnosed with a genetic aneurysm syndrome were excluded. Univariable and multivariable analyses were used to calculate differences in CIMT between aneurysmal and occlusive arterial disease.**

Results: **In total, 904 patients were included in the study: 502 patients with aneurysmal disease (85% male; mean age, 72 years) and 402 patients with occlusive arterial disease (65% male; mean age, 64 years). The mean (standard deviation) CIMT in patients with aneurysmal disease was 0.97 (0.29) mm and was 1.07 (0.38) mm in patients with occlusive arterial disease ($P < .001$). Adjustment for cardiovascular risk factors, comorbidities, and medication showed a mean difference in CIMT of 0.15 mm (95% confidence interval, 0.10-0.20; $P < .001$).**

Conclusions: **The current study shows a lower CIMT in patients with aneurysmal disease than in those with occlusive arterial disease, indicating a lower atherosclerotic burden in patients with aneurysmal disease. These findings endorse the idea that additional pathogenic mechanisms are involved in aortic aneurysm formation. Further studies are needed to clarify the role of atherosclerosis in aortic aneurysm formation. (J Vasc Surg 2013;57:642-7.)**

It is well known that aortic aneurysm disease is correlated with systemic atherosclerotic disease. Patients with aneurysmal disease and those with occlusive arterial diseases, including ischemic heart disease, carotid artery stenosis, and peripheral arterial disease (PAD), have overlapping cardiovascular risk profiles. Furthermore, patients with an abdominal aortic aneurysm (AAA) have a high degree of coronary artery disease as well as atherosclerotic changes in the aortic wall.[1,2]

However, a causal relation between atherosclerosis and aneurysmal disease has not been established. Most patients with atherosclerotic disease do not develop an aneurysm, and aneurysmal disease is not always associated with peripheral arterial, carotid, or coronary disease.[1] Second, although conventional cardiovascular risk factors, such as age, male gender, diabetes mellitus, hypertension, smoking, and dyslipidemia, are often observed in patients with aneurysmal disease, a number of studies report conflicting results on the relationship between these risk factors and AAAs.[3-5] Next, atherosclerosis affects predominantly the intimal and medial layers of the vascular wall, whereas in aneurysmal disease, pathologic changes also involve the adventitial layer. High proteolytic activity, destruction of collagen and elastin, and massive infiltration of inflammatory cells are characteristics of an aneurysmal arterial wall.[6] Given the epidemiologic, biochemical, and structural differences between aneurysmal and occlusive arterial disease, the conventional view of aneurysm formation as a consequence of atherosclerosis is currently challenged.[7]

The aim of the current study was to investigate whether there is a difference in atherosclerotic burden between patients with aneurysmal disease and those with occlusive arterial disease. The atherosclerotic burden was determined by measuring the common carotid artery intima-media thickness (CIMT) using B-mode ultrasound scanning. Thickening of the intimal and medial layers of the common carotid artery is an early expression of generalized atherosclerosis.[8,9] In addition, CIMT serves as a risk predictor for cardiovascular and cerebrovascular events.[10,11]

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METHODS

Study population. The study population consisted of patients undergoing elective open or endovascular surgery for aortic aneurysmal disease or for occlusive arterial disease, between 2004 and 2011 in the Erasmus University Medical Center in Rotterdam, The Netherlands. The aortic aneurysmal disease population was defined as patients having an aortic and/or thoracic aortic aneurysm with a diameter >55 mm or >60 mm, respectively. The occlusive arterial disease population was defined as patients with symptomatic PAD, which included patients with intermittent claudication or critical limb ischemia in combination with a resting and/or postexercise ankle-brachial index <0.9 and/or imaging findings compatible with the clinical symptoms. Patients treated for combined aneurysmal and occlusive arterial disease and patients diagnosed with a genetic aneurysm (eg, Marfan, Loeys-Dietz, or vascular Ehlers-Danlos syndrome) were excluded. The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board.

Patient characteristics. Patients were prospectively enrolled, and the following characteristics were recorded for all patients as part of routine clinical practice before surgery, including the cardiovascular risk factors: age, gender, body mass index, hypertension (blood pressure ≥140/90 mm Hg in nondiabetics, ≥130/80 mm Hg in diabetics, or use of antihypertensive medication), hypercholesterolemia (low-density lipoprotein cholesterol ≥3.5 mmol/L, or use of lipid-lowering medication), diabetes mellitus (fasting plasma glucose ≥7.0 mmol/L, nonfasting glucose ≥11.1 mmol/L, or use of antidiabetic medication), smoking status, and kidney disease (serum creatinine ≥2.0 mg/dL). Furthermore, cardiovascular comorbidities were recorded, including congestive heart failure, ischemic heart disease (history of angina pectoris, myocardial infarction, coronary revascularization, or pathologic Q waves on the electrocardiogram), and cerebrovascular disease (history of ischemic/hemorrhagic stroke or transient ischemic attack). Furthermore, prescription medications were recorded, including statins, β-blockers, renin–angiotensin system inhibitors, diuretics, and antiplatelet drugs.

Atherosclerotic marker. The severity of atherosclerotic disease was assessed by measurements of the CIMT prior to surgery using B-mode ultrasound scanning according to the guidelines from the Mannheim Carotid Intima-Media Thickness Consensus.[12,13] Patients were examined in the supine position with the head turned 45° away from the side being scanned and the neck extended slightly. A longitudinal view of the right and left common carotid artery was obtained using a portable SonoSite Titan Ultrasound System (SonoSite Inc, Bothell, Wash) with an L38-10-5 MHz linear ultrasound transducer or a portable Vivid-I Ultrasound System (Vivid-I; GE Healthcare, Solingen, Germany) with an 8L-RS transducer. Several measurements were made along a minimum of 10 mm at the posterior wall of the right and left common carotid artery. The intima-media thickness was calculated online by built-in software of the ultrasound system from the interface between the lumen and intima to the interface between media and adventitia. The maximum CIMT value of both common carotid arteries was used for the analysis. Atherosclerotic plaques, defined as focal structures of at least 0.5 mm encroaching into the arterial lumen, were excluded from analysis.[13] The sonographers who performed the measurements were blinded for the clinical characteristics of the patients and had an interobserver correlation of 96.2%.[12]

Statistical analysis. Dichotomous data are presented as number and percentage. Continuous variables are presented as mean (standard deviation) or median (interquartile range) when not normally distributed. Categorical data were analyzed with the χ^2 test and continuous variables with analysis of variance or Kruskal-Wallis test, as appropriate. Linear univariable and multivariable regression analyses were performed to evaluate the difference in CIMT between patients with aneurysmal and those with occlusive arterial disease. Multivariable analyses were adjusted for age, gender, body mass index, congestive heart failure, ischemic heart disease, cerebrovascular disease, kidney disease, diabetes mellitus, hypercholesterolemia, hypertension, current smoking, and use of statins, β-blockers, renin–angiotensin system inhibitors, diuretics, and antiplatelet drugs. Additionally, interaction between significant differences in medication use (statins, β-blockers and antiplatelet drugs) and CIMT was tested and, because of nonsignificance, not included in the final model. Covariates were chosen on the basis of biologic plausibility. Multivariable binary logistic regression analysis was used to calculate associations between aneurysmal and occlusive arterial disease. Covariates in the model were the same cardiovascular risk factors, comorbidities, and medication as used in the multivariable linear analyses.

For all tests, $P < .05$ (two-sided) was considered significant. All analyses were performed using IBM SPSS Statistics (version 20.0; SPSS Inc, Chicago, Ill).

RESULTS

A total of 904 patients were included in the study: 502 patients with aneurysmal disease and 402 patients with occlusive arterial disease. The characteristics of the patient populations are listed in Table I.

Atherosclerotic marker. The mean CIMT in the population was 1.02 (0.33) mm (Table I). Patients with aneurysmal disease had a mean CIMT of 0.97 (0.29) mm (median, 0.96 mm; interquartile range, 0.8-1.2), whereas patients with occlusive arterial disease had a mean CIMT of 1.07 (0.38) mm (median, 1.0 mm; interquartile range, 0.8-1.3). Univariate regression analysis showed a mean difference in CIMT of 0.09 mm (95% confidence interval [CI], 0.05-0.14; $P < .001$; Table II). After adjustment for potentially confounding factors, this difference increased to 0.15 mm (95% CI, 0.10-0.20; $P < .001$).

The presence of cerebrovascular disease correlated with the CIMT in multivariable linear regression analysis (β = .03; 95% CI, 0.01-0.13; $P = .022$). In addition, the cardiovascular risk factors age (β = .01; 95% CI, 0.00-0.01;

Table I. Baseline characteristics of patients with aneurysmal and occlusive arterial disease

	Total population (n = 904)	*Aneurysmal disease (n = 502)*	*Occlusive disease (n = 402)*	P *value*
Baseline characteristic				
Male gender, %	685 (75.8)	425 (84.7)	260 (64.7)	<.001
Age, mean (SD), years	68.4 (10.1)	71.6 (7.8)	64.4 (11.2)	<.001
Body mass index, mean (SD), kg/m^2	26.0 (4.2)	26.0 (3.8)	26.0 (4.5)	.920
Cardiovascular comorbidity, %				
Congestive heart failure	106 (11.7)	51 (10.1)	55 (13.6)	.428
Ischemic heart disease	380 (42.0)	217 (43.2)	163 (40.5)	.417
Cerebrovascular disease	142 (15.7)	70 (13.9)	72 (17.9)	.103
Cardiovascular risk factor, %				
Kidney disease	141 (15.5)	75 (14.9)	66 (16.4)	.543
Diabetes mellitus	213 (23.5)	77 (15.3)	136 (33.8)	<.001
Hypertension	610 (67.4)	342 (68.1)	268 (66.6)	.655
Hypercholesterolemia	800 (88.4)	436 (86.8)	364 (98.0)	.084
Smoking, current	393 (43.4)	197 (39.2)	196 (48.7)	.004
Smoking, ever	683 (75.5)	392 (78.0)	329 (81.8)	.163
Medication, %				
Statin	688 (76.1)	363 (72.3)	325 (80.8)	.004
β-blocker	748 (82.7)	428 (85.2)	320 (79.6)	.022
Renin–angiotensin system inhibitor	415 (45.9)	226 (45.0)	189 (47.0)	.577
Diuretic	214 (23.6)	108 (21.5)	106 (26.3)	.092
Antiplatelet drug	591 (65.3)	297 (59.1)	294 (73.1)	<.001
Atherosclerotic marker				
CIMT, mean (SD), mm	1.02 (0.33)	0.97 (0.29)	1.07 (0.38)	<.001

CIMT, Common carotid intima-media thickness; *SD,* standard deviation.

Table II. Differences in CIMT between aneurysmal and occlusive arterial disease

Atherosclerotic marker	*β*	*95% CI for β*	P *value*
CIMT			
Unadjusted	.09	.05-.14	<.001
Adjusted[a]	.15	.10-.20	<.001

CI, Confidence interval; *CIMT,* common carotid intima-media thickness.
[a]Adjusted for age, gender, body mass index, congestive heart failure, ischemic heart disease, cerebrovascular disease, kidney disease, diabetes mellitus, hypertension, current smoking, and use of statins, β-blockers, renin–angiotensin system inhibitors, diuretics, and antiplatelet drugs.

$P < .001$), male gender (β = .09; 95% CI, 0.04-0.14; $P = .001$), and hypercholesterolemia (β = .10; 95% CI, 0.01-0.19; $P = .025$) also correlated with CIMT, as did statin use (β = –.08; 95% CI, –0.14 to –0.01; $P = .020$).

Associations with aneurysmal and occlusive disease. Multivariable binary logistic regression analysis showed that CIMT (per 1 mm) was associated with occlusive arterial disease (odds ratio [OR], 4.5; 95% CI, 2.6-7.7; $P < .001$; Fig). Furthermore, diabetes mellitus (OR, 3.0; 95% CI, 2.1-4.5; $P < .001$) was also associated with occlusive arterial disease, whereas increased age (OR, 0.91; 95% CI, 0.89-0.92; $P < .001$) and male gender (OR, 0.25; 95% CI, 0.17-0.37; $P < .001$) were associated with aneurysmal disease.

DISCUSSION

The results of the current study show that patients with aneurysmal disease have a lower CIMT than patients with occlusive arterial disease. This indicates that the atherosclerotic burden is less in patients with aneurysmal disease than in patients with occlusive arterial disease despite their overlapping cardiovascular risk profiles.

The CIMT measurement was developed for easily accessible, noninvasive visualization of early stages of atherosclerosis. Atherosclerotic disease starts with asymptomatic lesions in the arterial wall, including the carotid arteries.[14] Under the influence of cardiovascular risk factors, early atherosclerotic changes progress to severe atherosclerotic changes in the arterial wall. The CIMT measures the thickness of the intimal and medial layers of the carotid artery using ultrasound scanning, which has been shown to correlate well with histologic findings of atherosclerosis.[15] The CIMT is considered a marker for generalized atherosclerosis, which, among others, is based on a study showing the correlation between atherosclerotic lesions in the coronary arteries and increased IMT in the common carotid artery.[13,16] Increased CIMT is associated with cardiovascular risk factors, including hypertension, smoking, diabetes mellitus, and dyslipidemia.[17] In addition, several studies report a correlation between high CIMT and ischemic events such as coronary events,[18] cerebrovascular events,[19] a combination of coronary and cerebrovascular events,[20] and postoperative cardiovascular events.[12] Aminbakhsh et al[20] concluded that a rise in CIMT of 0.03 mm per year was associated with an overall increased risk of ischemic events. Moreover, Lorenz et al[21] reported in a meta-analysis that an absolute CIMT difference of 0.1 mm, the future risk for myocardial infarction increases with 10% to 15%, and the risk for stroke increases

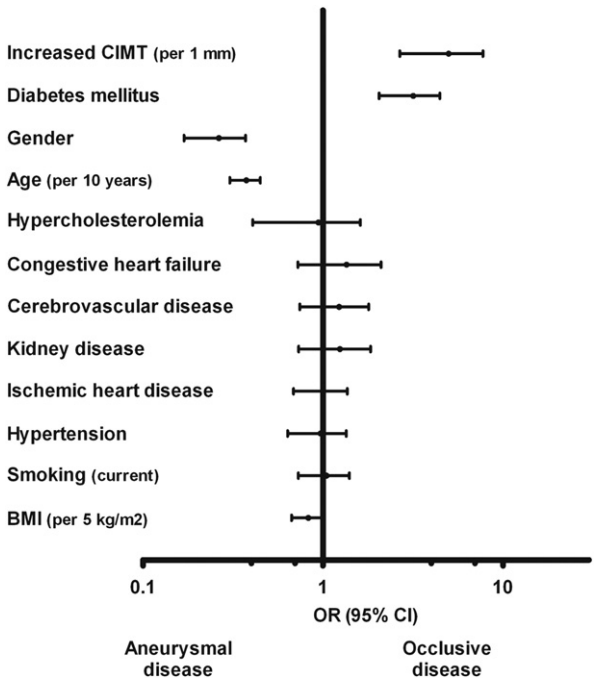

Fig. Multivariable logistic analysis for aneurysmal vs occlusive arterial disease. Adjusted for age, gender, body mass index (*BMI*), congestive heart failure, ischemic heart disease, cerebrovascular disease, kidney disease, diabetes mellitus, hypertension, current smoking, and use of statins, β-blockers, renin–angiotensin system inhibitors, diuretics, and antiplatelet drugs. *CI,* Confidence interval; *CIMT,* common carotid artery intima-media thickness; *OR,* odds ratio.

with 13% to 18%. Treatment of risk factors, notably hyperlipidemia, may decrease CIMT and reduce the risk of cardiovascular events.[22,23] Although most studies assume linearity between CIMT and risk for events, Lorenz et al[21] found that the relationship was nonlinear. Nevertheless, they concluded that linear models fitted well for moderate-to-high CIMT values.[21] In addition, because there is a lack of uniformity in its definition and the methodology used, no CIMT threshold value for high CIMT has been established.[12,24] Taken together, these data show a strong association between increased CIMT and the presence and severity of atherosclerotic disease and indicate that measurement of the CIMT is a valuable clinical tool for assessment of subclinical atherosclerosis and prediction of the risk for ischemic events.[24,25]

The mean CIMT in patients with aneurysmal and occlusive arterial disease was 0.97 and 1.07 mm, respectively, which resembles an absolute difference of about 10%. In the Rotterdam study, which investigated determinants of atherosclerotic disease in the general population, the mean CIMT in healthy people with a mean age of 71 (9) years was 0.79 mm.[11] Another study of a healthy population in the United Kingdom reported an upper limit of 0.81 mm for the CIMT in participants 60 years or older.[26] In contrast to the established relationship between CIMT and atherosclerosis, the results of previous studies on CIMT in patients with aneurysmal disease are conflicting. One study showed a similar increase in CIMT in patients with symptomatic PAD and in patients with AAAs compared with healthy controls (Table III).[27] Two other studies reported that patients with AAAs had a 0.16- to 0.18-mm lower mean adjusted CIMT than PAD patients.[28,29] The current study, which is the largest to date, clearly demonstrates a lower CIMT in patients with aneurysmal disease than in those with occlusive arterial disease, even when corrected for all known factors that might affect the CIMT, including cardiovascular risk factors, comorbidities, and medication. Hence, the results of the study indicate that patients with aneurysmal disease have a lower atherosclerotic burden than patients with occlusive arterial disease. Nevertheless, CIMT values in the aneurysm patients were higher when compared with previously reported CIMT values in age-matched general populations, an indication that patients with aneurysmal disease were not free of atherosclerosis.

Table III. Studies presenting mean difference in CIMT between patients with aneurysmal disease and peripheral arterial disease

	Year of publication	*No. of patients*	*Mean CIMT difference, mm*
Simons et al[28]	1999	172	0.18[b]
Spring et al[27]	2006	67	0.03[a]
Cheuk et al[29]	2007	169	0.16[b]
van de Luijtgaarden et al	2012	904	0.15[c]

CIMT, Common carotid intima-media thickness.
[a]Univariable difference.
[b]Age- and gender-adjusted difference.
[c]Multivariable-adjusted difference.

In addition to differences in CIMT, the current study also found differences in several cardiovascular risk factors and comorbidities between aneurysmal and occlusive arterial disease patients in multivariable analysis. In line with previous reports, age and male gender were associated with aneurysmal disease.[30,31] It is known that with advancing age, the incidence of aortic aneurysms increases and that men are at higher risk for AAAs compared with women. Although the true cause for this matter is still unclear, it seems that genetic susceptibility and risk factor exposure contribute to this phenomenon.[32] Furthermore, also in line with previous reports was the lower prevalence of diabetes mellitus compared with patients having occlusive arterial disease.[33] Although diabetes is a risk factor for atherosclerosis, it seems protective for aortic aneurysm formation.[34] Exact mechanisms for this effect are still unclear, but therapeutic agents for diabetes might stabilize the arterial wall, in order to prevent dilatation.[35] No differences in hypercholesterolemia, hypertension, and smoking were observed between the two patient populations.

Remarkably, the number of patients using statins and antiplatelet drugs was significantly lower among patients

with aneurysmal disease than in patients with occlusive arterial disease. However, given the high cardiovascular risk profile in aortic aneurysm patients, the treatment of these patients should include antiplatelet and statin therapy as part of their cardiovascular risk management.[30]

It is still unclear why some people develop aneurysmal disease, whereas others develop occlusive arterial disease, despite similarities in their cardiovascular risk profiles. Because not all patients with atherosclerosis develop aortic aneurysms, there is ongoing discussion as to whether aneurysmal disease is pathogenetically linked to atherosclerosis or whether the two arterial diseases should be considered as separate entities.[36,37] Even if the classic risk factors for atherosclerosis may influence the evolution and development of aneurysms, the observed difference in CIMT suggests that additional factors are involved in the pathogenesis of aneurysmal disease. About 15% of the AAA patients have a positive family history, which indicates that genetic predisposition plays an important role in aneurysmal disease.[38] However, no major genetic causes for AAAs have yet been identified.[39]

Our study has some limitations. First, as stated earlier, an important difficulty with the CIMT measurement is the lack of uniformity in its definition and the methodology used, which limits quantitative comparisons of absolute CIMT values between studies.[13] In particular, because AAA patients are not free of atherosclerosis, it would be interesting to compare the CIMT values between patients with aneurysmal disease and those of a propensity score-matched control group. Second, patients with PAD might have had higher rates of carotid artery stenosis and, hence, elevated CIMT. However, high CIMT and carotid artery stenosis are not similar in terms of localization, natural history, risk factors, and predictive value for vascular events. Furthermore, in the current study, the CIMT was measured in the common carotid artery, whereas carotid artery stenosis usually is located in the internal carotid artery. In addition, the rates of symptomatic cerebrovascular disease (stroke, transient ischemic attack) were similar in patients with aneurysmal disease and those with PAD, whereas patients who underwent surgery for carotid artery stenosis were excluded from the study. Third, no systematic screening was performed for the genetic defects causing Marfan, Loeys-Dietz, or vascular Ehlers-Danlos syndrome, so patients with specific genetic aneurysm syndromes might have been included in the study. However, the contribution of these syndromes to the study population is probably very small because these syndromes are rare causes of aortic aneurysms. In addition, the mean age of patients with aneurysmal disease is much higher than that of patients with occlusive arterial disease, and patients with the genetic aneurysm syndromes mentioned are generally diagnosed at a younger age.[40]

CONCLUSIONS

The current study shows a lower CIMT in patients with aneurysmal disease than in patients with occlusive arterial disease, indicating a lower atherosclerotic burden in patients with aneurysmal disease. Further research is needed to gain insight into the complex transcriptional mechanisms underlying aneurysm development, in particular, the diverging processes that lead to dilating or occlusive arterial disease in the presence of common cardiovascular risk factors.

AUTHOR CONTRIBUTIONS

Conception and design: KL, RS, HV
Analysis and interpretation: KL, ER, SH
Data collection: KL, EB, TV
Writing the article: KL, EB, ER, TV, DM
Critical revision of the article: ER, SH, RS, DM, HV
Final approval of the article: KL, EB, ER, SH, TV, RS, DM, HV
Statistical analysis: KL, SH
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