Mural Thrombus and the Progression of Abdominal Aortic Aneurysms: A Large Population-based Prospective Cohort Study

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WHAT THIS PAPER ADDS

The role of the intraluminal thrombus (ILT) is still heavily debated with regard to whether it accelerates growth or is simply a passive bystander. This large prospective cohort study reveals unique information about patients with abdominal aortic aneurysms (AAA) and the possible interactions between the AAA and the ILT. There appears to be a weak, yet significant, correlation between the initial thrombus size and an increased growth rate, but whether the ILT is harmful, protective, or both remains unclear.

Objective: To investigate whether the relative size of intraluminal thrombus (ILT) in abdominal aortic aneurysms (AAAs) is associated with AAA growth.

Methods: This large observational study was based on a randomised population-based screening trial. Six hundred and fifteen AAAs were diagnosed in men aged 65—74 years. The relative cross-sectional area covered by the mural thrombus was estimated by a semiautomatic method using ultrasound equipment to measure the area of the ellipses, and adapting the inner ellipse (IA) to the luminal border of the thrombus and the outer ellipse to the area inside the media border (OA). The relative thrombus area was then calculated as ((OA—IA)/OU) $\times$ 100%. Four hundred and sixteen of the patients with AAA were eligible for analysis.

Results: The mean size of the AAA was 40.6 mm, and the mean observation time was 1.78 years. In the group with AAAs measuring 30—34 mm, 42% had ILT, with a mean relative size of 12% of the outer area. In the group with AAAs measuring >64 mm, the presence of ILT increased to 100%, with a mean relative size of 70% of the outer area. Univariate analysis showed relative ILT size, aortic diameter, smoking history, and diastolic blood pressure were significantly positively associated with growth rate, while the presence of diabetes mellitus was significantly negatively associated with growth rate. The relative ILT size remained significantly positively associated with the growth rate after a multivariate linear regression adjusting for potential confounders.

Conclusion: These findings suggest that ILT may play a part in the progression of AAAs.

Article history: Received 14 September 2012, Accepted 12 May 2014, Available online 23 June 2014

Keywords: Abdominal aortic aneurysms, Intraluminal thrombus, Ultrasonographic scan

INTRODUCTION

In virtually any aneurysm of clinically important size, intraluminal thrombus (ILT) can be found.[1,2] It is believed that the ILT is a natural phenomenon that is based on the deposition of blood components when an abdominal aortic aneurysm (AAA) grows to a certain size. Whether the presence of ILT has any influence on the natural history of the AAA continues to be a matter of debate. It may be that the ILT's structural elastic integrity buffers the mechanical stress on the AAA wall.[3] Alternatively, it has been thought that biologically active substances infiltrate through the aortic wall by centrifugal convection and centripetal filtration, destabilising the matrix-rich aortic media,[4,5] increasing the inflammatory response and therefore increasing the risk of progression and rupture. The complex biological interaction between the ILT and the aortic wall appears to be divided into layers. The biological activity in the blood—ILT zone encourages platelet aggregation.[5] Together with endothelial injury, the platelets become activated by the biomechanical circumstances occurring in the in-flow part of the AAA and are then deposited when released further down in the aneurysm.[6,7] Earlier experimental studies suggested that the presence of ILT is associated with a higher risk of accelerated growth and rupture.[1,4,8] The two latter complications are the major concerns among clinicians. A recent study looked at the association between the AAA thrombus volume and cardiovascular events and AAA

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1078-5884/$ — see front matter

http://dx.doi.org/10.1016/j.ejvs.2014.05.014

growth.[9] Although a smaller study, the thrombus volume showed a significant association with both cardiovascular events and AAA growth.

One component of the creation and growth of ILT relies on platelets. Observational human-based studies suggest that these complex interactions take place in the ILT of an AAA,[5] and small human cohort studies suggest a potential benefit of antiplatelet treatment of medium-sized AAAs.[10] Nevertheless, the association between the role of ILT with the progression of AAA is poorly understood. Several diagnostic modalities have been used to try to describe the association, each with its own strengths and drawbacks. In this study, ultrasonography was chosen for its portability and therefore its ability to screen a large number of patients.

The aim of this study was to analyse whether ILT may be an independent risk factor for the ongoing enlargement in AAA diameter after adjusting for the other risk factors of AAA growth.

MATERIALS AND METHODS

In this prospective cohort study, data from the population-based Viborg Vascular (VIVA) trial were used.[11] More than 50,000 white men aged 65–74 years living in the Central Denmark Region were randomised 1:1 using the Civil Registration System registry either to receive an invitation to vascular screening or to participate in a control group (clinicaltrials.gov identifier: NCT00662480). The control group consisted of those not randomised for participation because there was no current population-based screening programme for AAA in Denmark during the study period. The participation rate in the VIVA study was 75% (18,628/25,065). From October 2008 until January 2011 trained project nurses diagnosed 615 patients with an AAA ($\geq$30 mm) by abdominal ultrasound examination (Logiq E, using a curved array probe 4C-RS with a 4-MHz setting; GE Healthcare, Fairfield, CT, USA). AAAs $<$50 mm in antero-posterior diameter were followed up annually by ultrasound; AAAs $>$50 mm and those that showed progression above 50 mm during the control visits were referred to a vascular surgery department in the Central Denmark Region for evaluation. Those growing rapidly were also followed up until they were $>$50 mm and then referred. At the baseline visit, informed consent was obtained from all those invited before their participation. Only those who were randomised to participate and agreed to join gave their written consent.

The study was approved by the local ethics committee and the data protection authorities, and was performed in accordance with the Declaration of Helsinki.

After diagnosing an AAA, an informative baseline consultation was offered for information, interview, weight, height, preventive actions (i.e., initiation of aspirin treatment, smoking cessation), examination of systemic blood pressure, ankle blood pressure measurement, first-degree relative with AAA, and an additional abdominal ultrasound scanning to secure high-quality videos and pictures of the AAA.

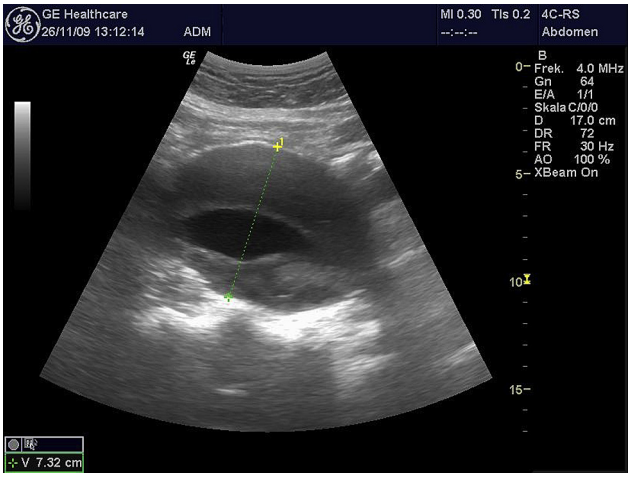

Figure 1. Large abdominal aortic aneurysm in longitudinal view showing anterior to posterior measurements.

AAAs were detected in 615 patients, 590 of whom had images that were sufficient for determining the relative maximal ILT area at the baseline. One hundred and seventeen of the AAAs were $\geq$50 mm in size and were therefore referred for a computed tomography angiography and surgical evaluation. The remaining 498 patients were offered annual follow-up visits. Of these, 416 had undergone a follow-up scan at the time of the data analysis and had sufficient images stored at baseline and at follow-up, as well as a complete baseline assessment.

AAA measurements

As in the VIVA screening study, the systolic longitudinal anterior to posterior maximal inner diameter was measured as shown in Fig. 1. The interobserver variability of these standardised measurements has been estimated to be as low as 0.86 mm.[12]

Systolic cross-sectional recordings were also performed with a semi-automated built-in program (Figs. 2 and 3). The systolic measurement was determined by a combination of

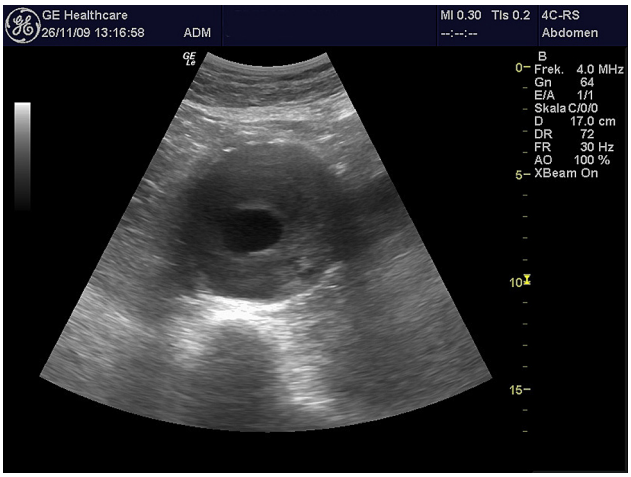

Figure 2. Same abdominal aortic aneurysm as in Fig. 1 in cross-sectional view, visualising the large intraluminal thrombus, the blood–intraluminal thrombus interface and the central lumen.

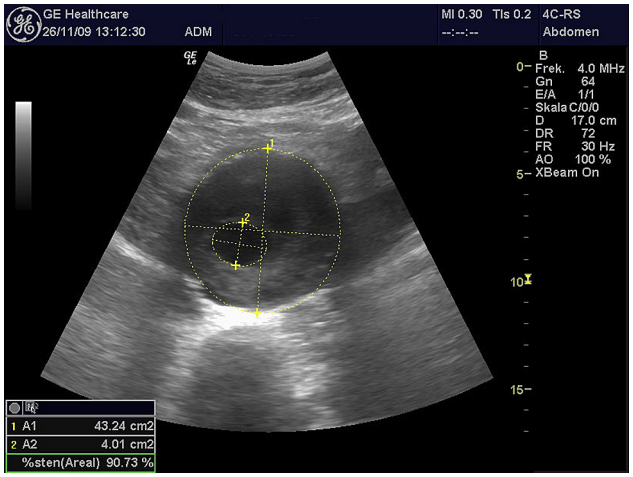

Figure 3. Same abdominal aortic aneurysm as Fig. 1 in cross-sectional view, with area measurements using the built-in semi-automated program to calculate the relative intraluminal thrombus size.

colour Doppler and visual determination by scrolling through the cineloop. The relative area covered by the mural thrombus was estimated by a semiautomatic method using ultrasound to measure the area of the ellipses adapting an inner ellipse (IA) to the luminal border of the thrombus and the outer ellipse as the area inside the media border (OA). The relative thrombus area was then calculated as ((OA−IA)/OU) × 100% (Figs. 2 and 3). When an AAA was tortuous, the best approximation was used. Only the transverse section and not the longitudinal section was used in the area measurements. The cross-sectional area measurements were later validated by the first author, who reviewed all of the cineloops, ensuring the validity of the stored data in the VIVA database. The examiner was personally trained by the most experienced project nurse on the equipment used in the VIVA trial in how to correctly perform the same cross-sectional area measurements. To test the validity of the internal measurement, a small ($n = 25$) study was performed, which showed a correlation coefficient between the first and last observations of the OA, IA, and relative ILT size of 0.99, 0.80, and 0.85, respectively. The intra-observer variation (2 × SD) of the determination of the relative size of the ILT area was 0.12. The validation process was blinded for the known size and growth rate of the AAA.

Bland–Altman plotting (not shown) revealed that the difference in the observations tended to be highest in the smaller AAAs, in which the ILT can be difficult to visualise. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed to strengthen the reporting of the observational studies in epidemiology.

Statistical methods

The categorical variables were coded (No = 0, Yes = 1). The annual growth rate was estimated by an individual linear regressions analysis using all of the observations of the maximal systolic inner AP diameter. Linear regression assumes a linear relationship between the size and the observation time that has been demonstrated multiple times, most recently by RESCAN.[13] Although a mixed-effect model could have been used, they are more difficult to interpret and are known not to supply outcomes that differ from the outcomes of the method that was used in this study.[14] The observations were made at the annual follow-up visits. The normality of the distributions was tested by probability plots. The annual growth rate, which was the dependent variable, was not normally distributed, but slightly left skewed, which was considered acceptable, especially as supplemental testing of the influence of the transformation did not alter the result. Consequently, the

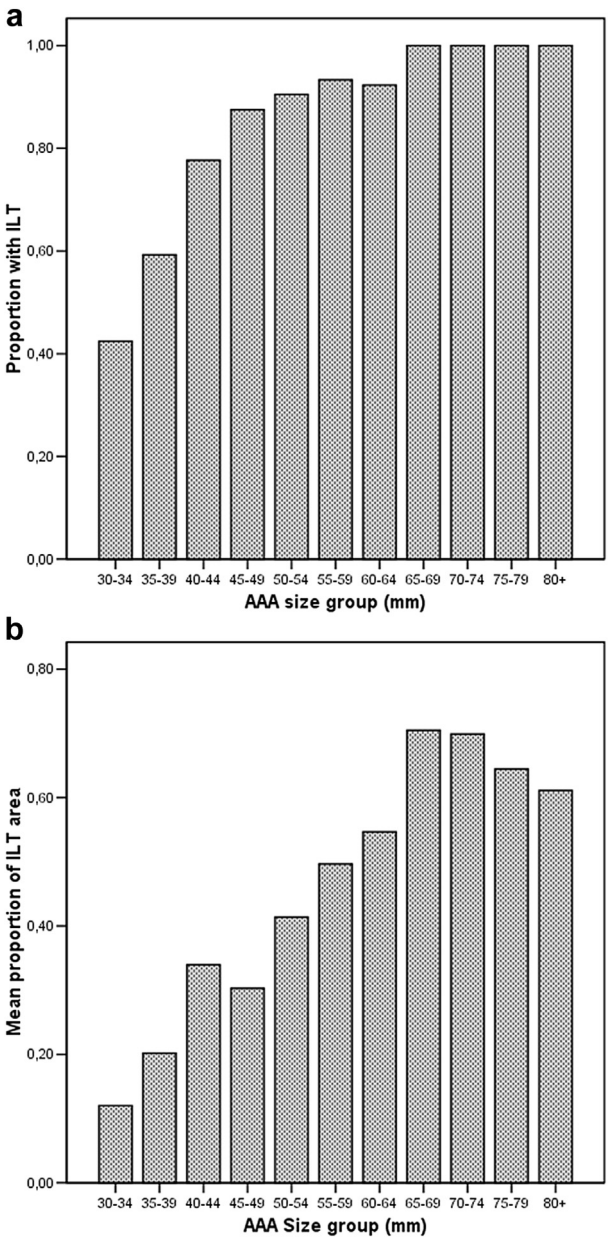

Figure 4. (A) Proportion of abdominal aortic aneurysms (AAAs) that contain intraluminal thrombus (ILT) as a function of AAA size. (B) The mean proportion of the ILT as a function of AAA size.

annual growth rate was left untransformed to allow for a less complicated interpretation. The baseline cross-sectional relative area of the ILT was used in both the univariate and the multivariate linear regression analyses. The linear assumptions for the regression analysis were tested by scatter plots, and the normality of the residuals was tested by histograms, as well as normal probability plots to determine the distribution of the residual values.

To identify potential confounders of the size of the mural thrombus and aneurysm growth rate, the relative area covered by the ILT and its growth rate were used as dependent variables for testing the association with potential confounders, such as smoking, daily use of alcohol, systolic and diastolic blood pressure, ankle brachial index (ABI), hypertension, and diabetes. Associations with a *p*-value $<.10$ were considered to be potential confounders and were used in the final multivariate analyses in combination with the non-significant, well-known confounders.

To evaluate the potential role of the ILT on the size and growth rate, size and growth were used as dependent variables, and the relative area of the ILT was used as the independent variable with and without adjustment for the above-mentioned potential confounders of smoking, daily use of alcohol, systolic and diastolic blood pressure, ABI, hypertension, peripheral arterial disease, and diabetes. SPSS version 12.0 (IBM, Armonk, NY, USA) was used for the statistical analysis.

It is likely that some of the smaller AAAs had a small fresh thrombus, but were classified as having no thrombus. All of the observations where the ILT = 0 were excluded and the statistical analysis was performed again to investigate the effect of potential misclassifications.

RESULTS

The mean maximal systolic diameter of the AAA was 40.6 ± 11.8 mm, the mean observation time was 1.78 years (range 0.6—3.0 years), and the mean annual growth rate was 2.55 ± 2.80 mm/year.

Concerning the presence of ILT, 42% of the patients in the group with AAAs of 30—34 mm had ILT, with a mean relative size of 12% of the OA. In the group of patients with AAAs >64 mm, the presence of ILT increased to 100%, with a mean relative size of 70% of the OA. Thereafter, the relative size of the ILT decreased in patients with very large AAAs (Fig. 4A, B).

The baseline characteristics of the patients with AAAs are shown in Table 1 along with the statistical tests that attempted to identify the potential confounders. On univariate analysis the relative ILT size ($r = .20$), aortic diameter ($r = .30$), diastolic blood pressure ($r = .16$), aspirin users over nonusers (2.42 vs. 3.01 mm/year), and smoking versus non-smoking (3.16 vs. 2.39 mm/year) was significantly positively associated with the growth rate, whereas the presence of diabetes mellitus (1.4 vs. 2.8 mm/year) was significantly negatively associated with the growth rate.

The multivariate analysis testing the size of the ILT as an independent risk factor of aneurysm progression is shown in Table 2, with adjustment for the potential confounders.

Table 1. Baseline characteristics of the 416 abdominal aortic aneurysm (AAA) patients are shown with the statistical tests attempting to identify potential confounders.

Categorical variables	*n*	Relative max ILT area (SD)	*p*	Growth rate in mm/year (SD)	*p*
Hereditary predisposition	N = 388	.24 (.23)		2.70 (2.53)	
	Y = 28	.30 (.30)	.92	2.80 (2.97)	.89
Smoking status	**N = 242**	**.24 (.23)**		**2.39 (2.35)**	
	Y = 174	**.24 (.24)**	**.65**	**3.16 (2.80)**	**.00**
Diabetes mellitus	**N = 372**	**.25 (.23)**		**2.83 (2.60)**	
	Y = 44	**.22 (.24)**	**.35**	**1.43 (1.92)**	**.01**
Hypertension	N = 191	.25 (.25)		2.77 (2.59)	
	Y = 225	.24 (.24)	.92	2.68 (2.58)	.77
Use of statin	N = 192	.25 (.23)		2.93 (2.73)	
	Y = 224	.24 (.25)	.26	2.55 (2.45)	.12
Use of low-dose aspirin	**N = 207**	**.24 (.23)**		**3.01 (2.67)**	
	Y = 209	**.24 (.24)**	**.76**	**2.42 (2.46)**	**.033**
Previous acute myocardial infarction	N = 325	.24 (.23)		2.83 (2.63)	
	Y = 91	.24 (.23)	.16	2.35 (2.39)	.23
Continuous variables *n* = 416		**Pearson's *r*[a]**	***p***	**Pearson's *r*[a]**	***p***
Age		.002	.98	−.073	.14
BMI		−.065	.21	−.025	.61
Systolic blood pressure		−.043	.42	.088	.08
Diastolic blood pressure		.070	.19	**.160**	**.00**
Plasma total cholesterol		.052	.33	.093	.07
Lowest ABI		.016	.76	.055	.28
Initial AAA size		**.483**	**.00**	**.304**	**.00**
Growth rate		**.198**	**.00**		

Note. Suspected confounders and significant findings are highlighted in bold. ILT = intraluminal thrombus; N = no; Y = yes; BMI = body mass index; ABI = ankle—brachial index.

[a] Pearson's correlation coefficient "r".

Table 2. Multivariate linear regression analysis using the relative maximum abdominal aortic aneurysm (AAA) area covered by the intraluminal thrombus (ILT) as the independent predictor, and the AAA growth rate as the dependent variable.

AAA growth rate	Unstandardised coefficients		Standardised coefficients	*p*	95% CI for B	
	B	SE	Beta		Lower bound	Upper bound
(Constant)	−4.131	1.389		.003	−6.862	−1.401
ILT	**0.193**	**0.085**	**0.117**	**.024**	**0.026**	**0.361**
AAA size	**0.101**	**0.027**	**0.197**	**.000**	**0.049**	**0.154**
Smoking	**0.882**	**0.282**	**0.154**	**.002**	**0.327**	**1.436**
DM	−0.944	0.498	−0.092	.059	−1.924	0.036
PAD	−0.466	0.319	−0.072	.144	−1.092	0.160
DBP	**0.028**	**0.012**	**0.116**	**.018**	**0.005**	**0.051**

Note. Suspected confounders and significant findings are highlighted in bold. CI = confidence interval; Smoking = smoking status; DM = diabetes mellitus; PAD = peripheral arterial disease; DBP = diastolic blood pressure.

The relative ILT size remained significantly positively associated with the growth rate, as did the initial size of the AAA, smoking, and diastolic blood pressure. Diabetes was not found to be significantly associated with AAA growth.

The ILT size was heavily confounded, especially by the size of the AAA, as the crude correlation coefficient between the ILT size and expansion rate was 0.2, and the adjusted partial correlation coefficient was only 0.14, but still statistically significant ($p = .024$).

Calculating the effect size revealed that a relative 10% increase in maximal relative ILT area was associated with an increased growth of 0.15 mm/year.

The proportion of the maximum ILT area is depicted as a function of the growth rate in Fig. 5. The best fitting line (correlation) is observed to have a slight positive slope. The 160 AAAs without ILT are bundled together in the left part of the figure. It is known that some of these AAAs may have been misclassified because it is difficult to see new fresh thrombus in a small AAA. When the 160 AAAs were excluded, the correlation coefficient decreased to 0.11 ($p = .08$).

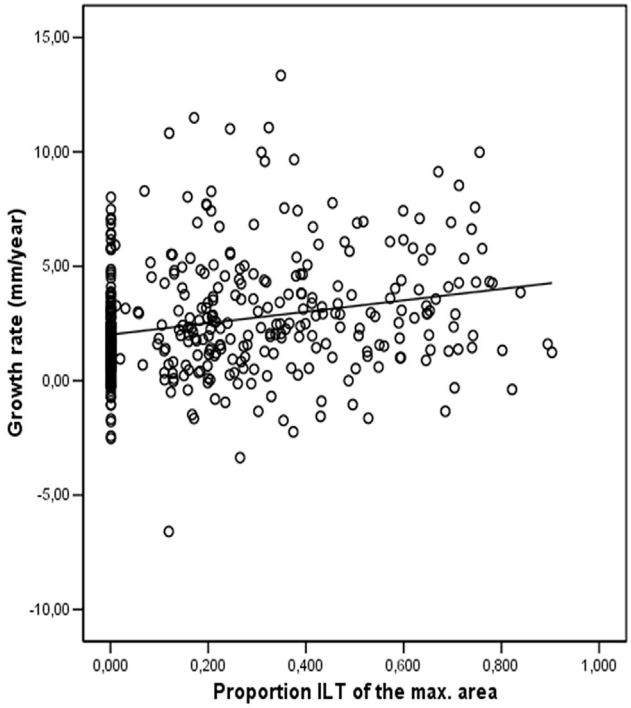

Figure 5. Correlation between relative intraluminal thrombus (ILT) area and growth rate ($r = .2$, $p < 0.01$).

DISCUSSION

This observational prospective cohort study reports observational evidence that suggests that ILTs are involved in the growth of AAAs independently of the aortic diameter, among other confounders. After adjusting for potential confounders, a weak correlation was found between the initial, relative ILT cross-sectional area and the AAA growth rate. Furthermore, a positive correlation between the growth rate and initial AAA size and a positive smoking status was found. A negative association was found among diabetics.

As with all observational studies, the classic sources of bias and study limitations must be considered and addressed.

Selection bias

The randomised population-based design of the VIVA trial, with a participation rate of 75% (18,628/25,065), minimises the probability of selection bias and suggests a high degree of external generalisability.

Information bias

Information bias would require a systematic bias of the measurement of the aortic diameter or the estimation of the relative size of the thrombus.

Measurement bias

All measurements were performed in systole, thus avoiding increased variation in the measurements.[12] The video sequence was intended to be recorded where the AAA was at its maximum size, but ILT might be relatively thicker at another section. This introduces a random error and creates bias only towards the null hypothesis. Occasionally, the picture quality complicated the measurement of the IA, especially in smaller aneurysms with small fresh thrombus formation; however, the relative ILT area was set to zero if in doubt. This type of information bias tends to

underestimate a correlation. When working with area measurements the potential errors will be squared, introducing greater uncertainty. It was noted, in particular, that the smaller AAAs with smaller ILTs had a higher mean difference in the Bland—Altman plot (not shown). The poorer definition of the lateral walls, due to the direction of the ultrasound beams, did, at times, complicate the area measurements. The internal validity of the determination of the relative size of the ILT area was rather high. On the one hand, variation in the measurements creates a bias towards the null hypotheses, which makes it more difficult to detect an association and is more serious when no associations are found, as this study is an attempt to "prove a concept" rather than to estimate the true predictive value. On the other hand, the outer area of an AAA proved to be a quite valid and reproducible size.

Misclassification

Some of the smaller AAAs were most likely misclassified as a result of having a small ILT to not having ILT. Of the 416 AAAs, 160 were classified as not having thrombus. After excluding the 160 with no ILT, the same analysis was performed on the remaining 256. The result revealed a decreased and insignificant correlation. Keeping in mind that the 160 AAAs comprised more than a third of the total cohort, the selection alone could reduce the correlation and make it non-significant. However, some of the AAAs may have been misclassified, and a 100% correct result based on the ultrasound images cannot be provided.

The follow-up periods were relatively short, although it is recognised in epidemiology that longer observation time can itself cause information bias owing to changes in the level of the baseline risk factors. However, a short observation period increases the influence of the variation of the measurements and is thus an obvious bias towards the null hypothesis and cannot explain a significant association.

The observational evidence suggests that ILT plays a role in the growth of an AAA, although it has been difficult to deliver solid evidence because of the numerous complex biological and biophysical interactions taking place simultaneously.

Prior studies, in combination with this study, suggest a possible benefit for aspirin users compared with non-users.[10] It should be noted that Table 1 clearly shows that there was no difference in the relative maximum ILT area in those specific groups. Aspirin has both an anti-inflammatory and a direct effect on thrombocytes, and it is believed that both effects are important. In animal studies, platelet inhibition impairs the progression of aneurysms containing ILTs,[14] and the use of low-dose aspirin was also associated with a lower growth rate in this cohort (Table 1). The experimental trials with non-inflammatory antiplatelet therapy show impairment in the development and growth of AAAs;[15] therefore, the mechanism may not solely be because of aspirin's anti-inflammatory effects. One of the largest meta-analyses of smaller AAAs found only minor and insignificant effects for cardioprotective drugs.[13] Data on statins were not included in the analysis because all of the non-users were prescribed statins at the baseline, and only a few did not follow the regimen; the baseline use was not associated with AAA or thrombus growth.

The size of the AAA is a heavy confounder because of its powerful and consistent association with both the size and relative ILT area, an association that is supported by this study (Table 1). To counter this, the statistics used seriously risked an over-adjustment towards the null hypothesis; despite this, a weak significant correlation was still found. This implies that the ILT could be considered as an independent risk factor for AAA growth in this study. It has been shown in a smaller cohort study that the burden of the thrombus volume creates a higher risk of cardiovascular events and a higher risk of accelerated AAA growth.[9]

Chronic obstructive pulmonary disease (COPD) is reported to be associated with AAA growth,[16] but, unfortunately, no robust data on this subject were available. Only records of COPD medication were available, and these did not show a trend for its association with growth rate.

A review of the largest screening trials found significant effects in current smokers over non- and prior smokers, a finding that is supported by this study, although only data on current and non-smokers were available.[13] There were no differences in the relative ILT areas when comparing smokers with non-smokers.

A significant beneficial effect in diabetics that appeared to be protective against AAA growth was found. There has been speculation about why diabetics demonstrate a slower AAA growth rate, and some consider glycosylation at a molecular level to be an important factor.

Taking the risk of over-adjustment in the statistical method into consideration, the rather weak correlation found in this study is most likely underestimated, as any solid bias away from the null hypothesis, except for a small number of potentially misclassified AAAs, was not identified.

It should be emphasised that the demonstrated positive association does not say anything about causality and the demonstrated effect size, and is hardly clinically relevant. The development and size of the ILT could just as well be protective. However, believing that the creation of the ILT does not have a biological purpose, is most likely incorrect, as there are few, if any, pathophysiological processes known that do not either harm or protect. The ILT itself could also be partially harmful and partially protective, theoretically resulting in poor associations.

The findings of this study are applicable only to white men with AAAs aged 65—74 years.

The data were supplied by the randomised VIVA trial, which yields good external generalisability for this study.

Serious confounding and misclassification appears to be unlikely, as adjustments for the known risk factors of aneurysm progression were performed. However, in principle, residual confounding may be present.

When searching the published literature, no large human-based prospective analyses investigating ILT and the natural history of AAA were found. This, to the best of the

authors' knowledge, is the largest cohort to date. The weak, but significant, correlation between the relative ILT maximum area and AAA growth may be underestimated owing to a statistical over-adjustment for confounders. The measurement bias of a few small AAAs could influence this result, making the correlation smaller.

When dealing with AAAs and ILTs the "chicken and egg" issue is present. It is still unclear whether large ILTs grow large AAAs or if it is the other way around. Furthermore, this study was purely observational, and correlation does not imply causality.

Whether ILTs are independently responsible for accelerating the growth of AAAs is still unclear, but the weak correlation found in this study could be another "piece of the puzzle". It is believed ILTs are both protective and harmful, thus making it difficult to find solid associations. This, of course, needs to be backed up by further research.

However, the OA measurement was found to be a valid and reproducible measurement, and every AAA >64 mm in this study had ILT.

FUNDING

VIVA was financed by the European FAD project (FP-7, HEALTH F2-2008-200647) and the Health Research Fund of Central Denmark Region. Salaries were primarily funded by the Vascular Research Unit, Department of Vascular Surgery, Viborg Regional Hospital, Denmark; otherwise they were from the Karl G. Andersons fund.

CONFLICT OF INTEREST

None.

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