Thrombus volume is associated with cardiovascular events and aneurysm growth in patients who have abdominal aortic aneurysms

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Background: **Patients with abdominal aortic aneurysms (AAA) are predisposed to cardiovascular events and often experience continual expansion of their aneurysm. Cardiovascular events and expansion rates are positively correlated with aneurysm size. AAA is usually associated with intraluminal thrombus, which has previously been implicated in AAA pathogenesis. This study prospectively assessed the association of infrarenal abdominal aortic thrombus volume with cardiovascular events and AAA growth.**

Methods: **Ninety-eight patients with AAAs underwent computed tomography angiography (CTA). The volume of infrarenal aorta thrombus was measured by a previously validated technique. Patients were monitored prospectively for a median of 3 years (interquartile range [IQR], 2.0-3.6 years), and cardiovascular events (nonfatal stroke, nonfatal myocardial infarction, coronary revascularization, amputation, and cardiovascular death) were recorded. Of the original patients, 39 underwent repeat CTA a median of 1.5 years (IQR, 1.1-3.3 years) after entry to the study. Kaplan-Meier and Cox proportional analysis were used to examine the association of aortic thrombus with cardiovascular events and average weighted AAA growth.**

Results: **There were 28 cardiovascular events during follow-up. The incidence of cardiovascular events was 23.4% and 49.2% for patients with small (smaller than the median) and large (median or larger) volumes of aortic thrombus, respectively, at 4 years (P = .040). AAA thrombus volume of median or larger was associated with increased cardiovascular events (relative risk [RR] 2.8, 95% confidence interval [CI], 1.01-5.24) independent of other risk factors, including initial AAA diameter, but was only of borderline significance when patients were censored at the time of AAA repair (RR, 2.35; 95% CI, 0.98-5.63). In the subset of patients with CTA follow-up, the median annual increase in AAA volume was 5.1 cm^3 (IQR, 0.8-10.3 cm^3). Annual AAA volume increase was positively correlated with initial AAA diameter (r = 0.44, P = .006) and thrombus volume (r = 0.50, P = .001). Median or larger aortic thrombus volume was associated with rapid AAA volume increase (≥5 cm/y), independent of initial aortic diameter (RR, 15.0; 95% CI, 1.9-115.7; P = .009).**

Conclusion: **In this small cohort, infrarenal aortic thrombus volume was associated with the incidence of cardiovascular events and AAA progression. These results need to be confirmed and mechanisms underlying the associations clarified in large further studies. (J Vasc Surg 2011;53:28-35.)**

Abdominal aortic aneurysms (AAA) are a common pathology affecting approximately 7% of men and 1% of women aged ≥65 years.[1] Patients who have AAAs have two principal concerns. Firstly, AAAs are associated with an excess risk of death and cardiovascular complications, such as myocardial infarction and ischemic stroke,[2,3] distinct from the risk of AAA rupture. Secondly, AAAs tend to expand over time to a size often requiring surgery and where AAA rupture is more prevalent.[4] Previous studies indicate that about 60% of small AAAs measuring ≥40 mm enlarge to a diameter requiring surgery within 5 years.[5,6]

The determinants of AAA progression and cardiovascular events in these patients are currently poorly defined. The most consistent prognostic factor for cardiovascular events and AAA progression is the initial AAA diameter.[2,3-14] AAA is usually associated with intraluminal thrombus, which contains leukocytes, proinflammatory cytokines, and proteolytic enzymes and is implicated in AAA development, progression, and rupture.[15-23] AAA thrombus products are also released into the circulation, where they have potential to stimulate leukocytes and other changes that might promote atherosclerotic plaque activation and acute coronary and cerebrovascular events.[24-28] To our knowledge, no previous study has examined the association of AAA thrombus with subsequent cardiovascular events; thus, the study had two aims:

- Aim 1: Examine the association of AAA thrombus volume with future cardiovascular events.
- Aim 2: Assess the association of AAA thrombus with AAA growth.

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METHODS

Ethics approval for this study was provided by Human Research Ethics Committees of the Townsville Health Service District and James Cook University.

Patients and clinical definitions. Patients were prospectively recruited from the vascular surgery clinic at The Townsville Hospital, Queensland, Australia, between May 2003 and July 2008. Inclusion criteria included:

1. Verbal and written informed consent;
2. A computed tomography angiogram (CTA) by the treating physician to further assess the patients, with indications for CTA including aneurysm morphology assessment before surgery, inadequate ultrasound assessment, requirement for more detailed AAA diameter assessment, and analysis of concurrent atherothrombosis; and
3. An initial maximal axial infrarenal aortic diameter of ≥30 mm measured on CTA.

Exclusion criteria included refusal to participate, previous surgical repair of the abdominal aorta, and contraindication to CTA, such as abnormal serum creatinine concentration and contrast allergy. Numbers and demographics of patients excluded were not recorded.

Intermittent claudication was diagnosed by a consultant vascular physician from an appropriate history along with clinical signs of lower limb ischemia and CTA evidence of occlusive or stenotic peripheral artery disease. Hypertension and diabetes were defined by history or treatment for these conditions. Cigarette smoking classification was based on smoking history and defined ultimately as ever or never smoked. Coronary heart disease (CHD) was defined by a history of myocardial infarction, angina, or coronary revascularization. Body mass index (BMI) was calculated as kg/m^2.

CT angiography. Contrast-enhanced CT images were obtained using a 64-slice multiscanner (Philips, North Ryde, NSW, Australia), under a set acquisition protocol. The images were recorded at 3-mm intervals, with a slice thickness of 3-mm, to construct 3-mm contiguous image slices for analysis. A contrast agent (100 mL; Ultravist 300, Bayer, Wayne NJ), delivered by an automatic CT injection driver system (MEDRAD, Warrendale, Pa) was given intravenously. A low dose preliminary CT locater was set above the renal arteries, which triggered the CTA when the Hounsfield unit (HU) at the center of the aorta reached 130 after the delivery of the contrast agent.

Workstation protocols. AAA thrombus volume was measured using a previously validated protocol with an interobserver coefficient of variation of about 5%.[29] Images from the origin of the lowest renal artery (excluding accessory arteries) to the bifurcation of the aorta were transferred to MxView Visualization Workstation software (Philips, Bothell, Wash) for analysis. Previously defined HUs (center level, 0 HU; window width, 140 HU) were used for the thrombus threshold. The volume-of-interest tool was used to draw an encircling line around the aorta to form a region of interest. The region of interest was individually drawn for each slice to ensure that only the aorta was included.

The selected images were saved onto the workstation and reloaded into the three-dimensional (3D) mode. The software program computed the volume of thrombus in cm^3. Maximal axial infrarenal aortic diameter was assessed using the "CTA viewer function" on the Philips Workstation. The region was scouted to find the area of maximal diameter, taking many measurements with electronic calipers. Maximal diameter was recorded in millimeters (to the nearest 0.1 mm).

Clinical data. The following information was collected by a vascular physician at entry into the study: sex, age, height, weight, smoking status, diabetes mellitus, hypertension, CHD, and medication history. After the initial consultation, a CTA was arranged and the patients were subsequently monitored according to the AAA diameter. Follow-up was yearly for patients with small AAAs measuring 30 to 39 mm and every 6 months for those with an initial AAA diameter ≥40 mm. The primary outcome recorded during follow-up was admission for cardiovascular events (nonfatal stroke, nonfatal myocardial infarction, coronary revascularization, amputations, and cardiovascular death) to assess aim 1. Outcome data were recorded during follow-up visits and subsequently checked by review of patients' records by two independent researchers (for all patients) and by additional phone calls to selected patients who had no chart entry in previous 2 years and whose primary residence was outside The Townsville Hospital catchment area. Ultrasound imaging was used to monitor most AAAs, but some patients underwent repeat CTA because of concern that the AAA had expanded to a size requiring surgery, difficulty in imaging by ultrasound, or concern over the accuracy of the ultrasound imaging. Only patients undergoing repeat CTA were included to assess aim 2 due to the lack of comparability between diameters derived by ultrasound imaging and CT.[30]

Growth measurements. Initial and follow-up CTAs were assessed for maximal axial infrarenal aortic diameter and total infrarenal aortic volume using previously validated techniques.[29] These measurements were used to calculate the weighted annual change in AAA volume. We used this assessment method because we have previously found volume is more sensitive to change than diameter.[31]

Statistical analysis. Data were prospectively entered into an Excel spreadsheet (Microsoft, Redmond, Wash) and later transferred to SPSS 17 software (SPSS Inc, Chicago, Ill) for further analysis.

To assess aim 1, the total cohort of patients was included. Median initial aortic thrombus in this group was 29.6 cm^3 (interquartile range [IQR], 13.6-54.5). Aortic thrombus volume of small (thrombus volume <25.0 cm^3) and large (thrombus volume ≥25.0 cm^3) was defined by rounding down thrombus median to the nearest 5 cm^3.

To assess aim 2, the 39 patients with a repeat CTA assessment were included. Median initial aortic thrombus in this group was 16.4 cm^3 (IQR, 10.6-32.0 cm^3). Aortic thrombus was defined as small (thrombus volume <15.0

Table I. Risk factors of patients at recruitment in relation to abdominal aortic aneurysm *(AAA)* thrombus volumes

Characteristic[a]	*Total*	*Thrombus <25.0 cm³*	*Thrombus ≥25.0 cm³*	P
Patients	98	43	55	
Age, years	73 (67-77)	72 (67-75)	74 (68-78)	.245
Male	75 (76.5)	28 (65.1)	47 (85.5)	.029
Follow-up, years	3.0 (2.0-3.6)	3.2 (2.0-3.7)	2.8 (1.9-3.4)	.358
Max AAA axial diameter, mm	47.2 (34.9-54.6)	34.4 (32.2-42.6)	52.8 (49.5-58.1)	<.001
Body mass index, kg/m^2	28.2 (25.0-30.8)	28.7 (25.6-32.0)	27.8 (24.5-30.3)	.150
Intermittent claudication	29 (29.6)	18 (41.9)	11 (20.0)	.026
Diabetes mellitus	20 (20.4)	8 (18.6)	12 (21.8)	.803
Ever smoked	86 (87.8)	36 (83.7)	50 (90.9)	.357
Hypertension	75 (76.5)	33 (76.7)	42 (76.4)	>.99
Coronary heart disease	59 (60.2)	25 (58.1)	34 (61.8)	.836
Medication use				
Warfarin	13 (13.3)	7 (16.3)	6 (10.9)	.552
Aspirin	62 (63.3)	27 (62.8)	35 (63.6)	>.99
Calcium channel blocker	24 (24.5)	13 (30.2)	11 (20.0)	.344
ACE inhibitor	42 (42.9)	22 (51.2)	20 (36.4)	.156
Statin	65 (66.3)	24 (55.8)	41 (74.5)	.057
β-Blocker	35 (35.7)	18 (41.9)	17 (30.9)	.293

ACE, Angiotensin-converting enzyme.
[a]Continuous results are presented as medians (interquartile range) and compared by Mann-Whitney *U* test; nominal results are presented as number (%) and are compared by Fisher exact test (two-tailed significance).

cm^3) and large (thrombus volume ≥15.0 cm^3) by rounding down thrombus median to the nearest 5 cm^3.

Initially continuous variables were assessed using Kolmogorov-Smirnov test, histograms, and normal quantile-quantile plots, which demonstrated that they were not normally distributed. Continuous variables were compared with Mann-Whitney *U* test and nominal variables with the Fischer exact test. Kaplan-Meier analysis was used to determine freedom from cardiovascular events.

In the primary analysis, patients were censored at loss to follow-up or death from causes other than cardiovascular events. In a secondary analysis, patients were also censored at the time of AAA repair to exclude confounding effects of surgical intervention. Cox proportional analysis was used to assess the effects of known risk factors on cardiovascular events. Relative risk (RR) is presented with 95% confidence intervals (CI). Categoric variables were dummy-coded. Known risk factors examined for inclusion in the final model were age, gender, smoking status, diabetes mellitus, hypertension, dyslipidemia, CHD, maximal axial infrarenal aortic diameter, intermittent claudication, and use of calcium channel blockers, statins, warfarin, aspirin, angiotensin converting enzyme inhibitor, and β-blockers.

Association of risk factors with cardiovascular events was examined with a stepwise selection procedure using backward and forward likelihood ratios. Variables not in the stable model were included individually in the model. Risk factors that led to a ≥10% change in the coefficient of the model were retained in the final model as a potential confounder. Variables not included in the final model did not significantly affect the results. Determinants of rapid AAA growth were assessed using logistic regression.

RESULTS

Characteristics of patients at recruitment. The risk factors of the 98 patients in relation to the volume of infrarenal AAA thrombus are reported in Table I. The median infrarenal axial AAA diameter was 47.2 mm, and 19 patients had an AAA with axial diameter >55 mm at study entry. Thrombus volume was greater in large AAAs, men, and in patients who did not have intermittent claudication (Table I). Thrombus volume was not associated with warfarin or aspirin use.

Cardiovascular events. Patients were monitored for a median of 3.0 years (IQR, 2.0-3.6 years). Cardiovascular events that occurred during follow-up were nonfatal myocardial infarction in 13, coronary revascularization in 4, stroke in 1, below knee amputation in 1, and cardiovascular death in 9. Patients with a large volume of AAA thrombus had a higher incidence of cardiovascular events (Fig 1). The incidence of cardiovascular events at 4 years in patients with small compared with large AAA thrombus was 23.4% (95% CI, 16.0%-30.8%) vs 49.2% (95% CI, 39.8-58.6), respectively ($P = .040$). The incidence of cardiovascular events at 4 years in patients with small vs large maximal AAA diameters was 24.5% (95% CI, 16.7%-32.3%) vs 46.6% (95% CI, 37.9-55.3), respectively ($P = .074$; Fig 2). AAA thrombus volume ≥25.0 cm^3 was associated with increased incidence of new cardiovascular events independent of other risk factors by Cox analysis (RR, 2.3; 95% CI, 1.01-5.24; Table II). Sex was identified as a confounding factor. All other variables, including initial AAA diameter, did not significantly affect the results.

AAA surgery. During follow-up, 37 patients underwent AAA repair, comprising 12 open and 25 by endovas-

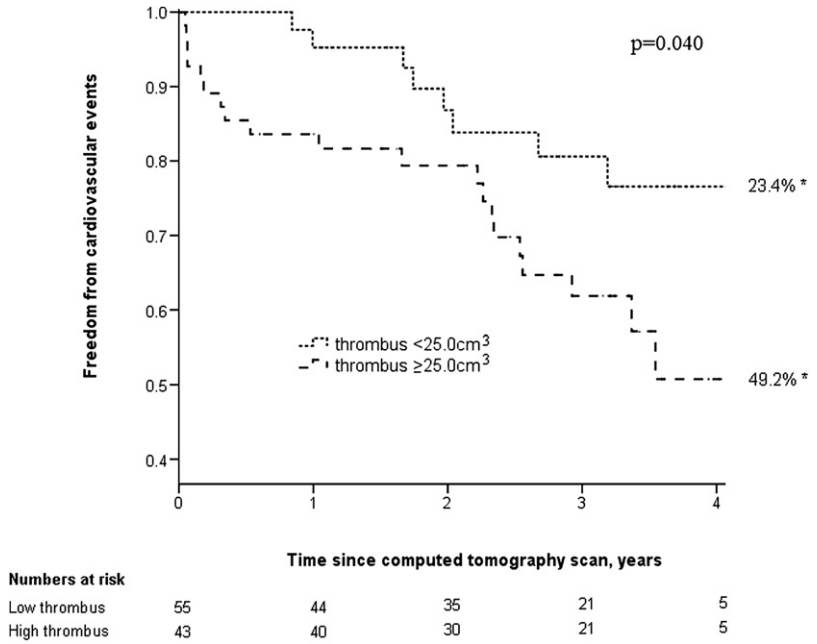

Fig 1. Kaplan-Meier analysis shows freedom from cardiovascular events in patients with small (<26.0 cm^3) and large (>26.0 cm^3) abdominal aortic aneurysm thrombus volumes. *Cardiovascular event rate at 4 years.

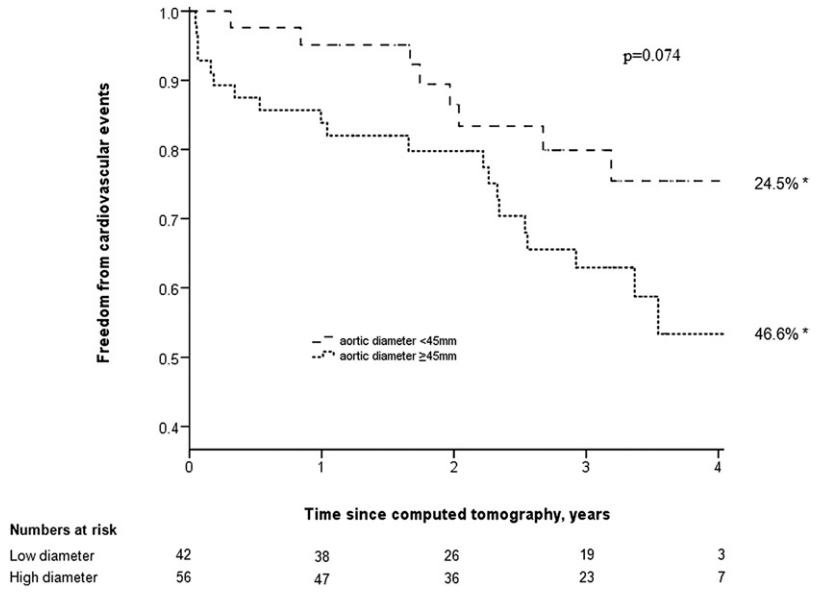

Fig 2. Kaplan-Meier analysis shows freedom from cardiovascular events in patients with small- (<45.0 mm) and large-diameter (≥45.0 mm) abdominal aortic aneurysms. *Cardiovascular event rate at 4 years.

cular repairs. No patients died within 30 days of surgery. A secondary analysis of cardiovascular events examined the association of AAA thrombus, censoring these patients at AAA repair. The findings of this analysis were similar to the primary analysis. The incidence of cardiovascular events at 4 years for patients with small compared with large AAA thrombus volumes was 26.9% (95% CI, 18.3-35.5) vs 48.9% (95% CI, 40.6-59.5), respectively ($P = .049$). The incidence of cardiovascular events at 4 years for patients with small compared with large maximal axial AAA diameters was 26.1% (95% CI, 17.5-34.7) vs 48.6% (95% CI, 38.1%-59.1%), respectively ($P = .065$). Patients with AAA thrombus volume ≥25.0 cm^3 had an increased incidence of cardiovascular events (RR, 2.35; 95% CI, 0.98-5.63) after

Table II. Cox proportional analysis examining prognostic factors for cardiovascular events

Prognostic factor	*Sample size (n = 98)*	*Cardiovascular events, No. (n = 28)*	*RR (95% CI)*	P
Thrombus volume				
<25.0 cm^3	43	8	1 (Ref)	.046
≥25.0 cm^3	55	20	2.30 (1.01-5.24)	
Sex[a]				
Male	75	19	1 (Ref)	.115
Female	23	9	1.95 (0.85-4.46)	
Max axial aortic diameter[b]				
<45.0 mm	42	8	1 (Ref)	.857
≥45.0 mm	56	20	1.1 (0.27-4.72)	

CI, Confidence interval; *RR,* relative risk.
[a]Identified as a confounder (ie, <10% change in thrombus coefficient).
[b]Not identified as a confounder but included to illustrate the effect of diameter when thrombus is included in analysis.

Table III. Risk factors of patients at recruitment in relation to abdominal aortic aneurysm *(AAA)* expansion at or exceeding the median or below the median

		Annual AAA volume increase		
Characteristic[a]	*Total*	*<5.0 cm^3/y*	*≥5.0 cm^3/y*	P
Patients	39	19	20	
Age, years	73 (69-77)	74 (69-77)	71 (68-75)	.518
Male	27 (69.2)	13 (68.4)	14 (70.0)	.981
Follow-up, years	1.5 (1.1-3.3)	1.4 (0.9-3.3)	1.6 (1.1-3.3)	.771
Max AAA diameter, mm	42.1 (33.0-47.0)	22.0 (30.3-43.3)	44.8 (41.0-49.3)	.001
Total AAA volume, cm^3	73.6 (46.6-95.2)	49.6 (40.4-60.0)	86.0 (75.2-107.3)	<.001
Thrombus volume	16.4 (10.6-32.0)	11.1 (9.2-13.7)	27.1 (21.4-44.3)	<.001
Warfarin	2 (5.1)	1 (5.3)	1 (5.0)	>.99
Intermittent claudication	15 (38.5)	10 (52.6)	5 (25.0)	.105
Diabetes mellitus	9 (23.1)	6 (31.6)	3 (15.0)	.237
Ever smoked	32 (82.1)	15 (78.9)	17 (85.0)	.695
Hypertension	29 (74.4)	16 (84.2)	13 (65.0)	.273
Coronary heart disease	22 (56.4)	14 (73.7)	8 (40.0)	.054

[a]Continuous results are presented as medians (interquartile range) and compared by Mann-Whitney *U* test; nominal results are presented as number (%) and are compared by the Fisher exact test (two-tailed significance).

adjusting for other risk factors, although the association was no longer significant ($P = .056$).

AAA growth. Repeat CT scans of the AAAs were done in 39 patients a median of 1.5 years (IQR, 1.1-3.3 years) after their initial imaging and before any surgery. Included in these 39 are 15 patients who were selected for AAA repair and another 24 patients whose treating physicians decided to obtain a further CT. The risk factors of the 39 patients who underwent repeat CTA in relation to slow (<5 cm^3) and rapid (≥5 cm^3) annual abdominal aortic volume expansion are reported Table III. Rapid expansion was associated with larger initial AAA diameter and thrombus volume ($P \leq .001$). Annual median (IQR) AAA volume was 5.1 cm^3 (0.8-10.3 cm^3), and diameter increase was 1.3 mm (−0.2 to 2.7 mm). Annual abdominal aortic volume change was positively correlated with maximal axial initial AAA diameter ($r = 0.44$, $P = .006$) and thrombus volume ($r = 0.50$, $P = .001$; Fig 3). Initial AAA thrombus volume ≥15.0 cm^3 was associated with rapid volumetric growth ≥5 cm^2/y (RR, 15.0; 95% CI, 1.9-115.7, $P = .009$). Initial AAA diameter, smoking, and diabetes mellitus were not significantly associated with rapid growth after adjusting for thrombus volume.

DISCUSSION

The main finding of this study was that the volume of AAA thrombus was associated with subsequent cardiovascular events and rapid AAA growth. This association was independent of initial AAA diameter, at least in our primary analysis. Few previous studies have examined the association of thrombus quantity with AAA growth,[18,19] and we are unaware of any previous investigation that has examined the relationship of thrombus volume and cardiovascular outcomes.

Large AAA diameter has been independently associated with increased risk of perioperative cardiovascular complications[32] and 3-year cardiovascular death[2,33] after endoluminal aneurysm repair. A similar association is found in patients whose small AAAs were treated conservatively.[2,3,7-9] Five large studies have reported that initial abdominal aortic diameter predicts future cardiovascular events,[7-9] all-cause mortality,[3,7,8] and cardiovascular mor-

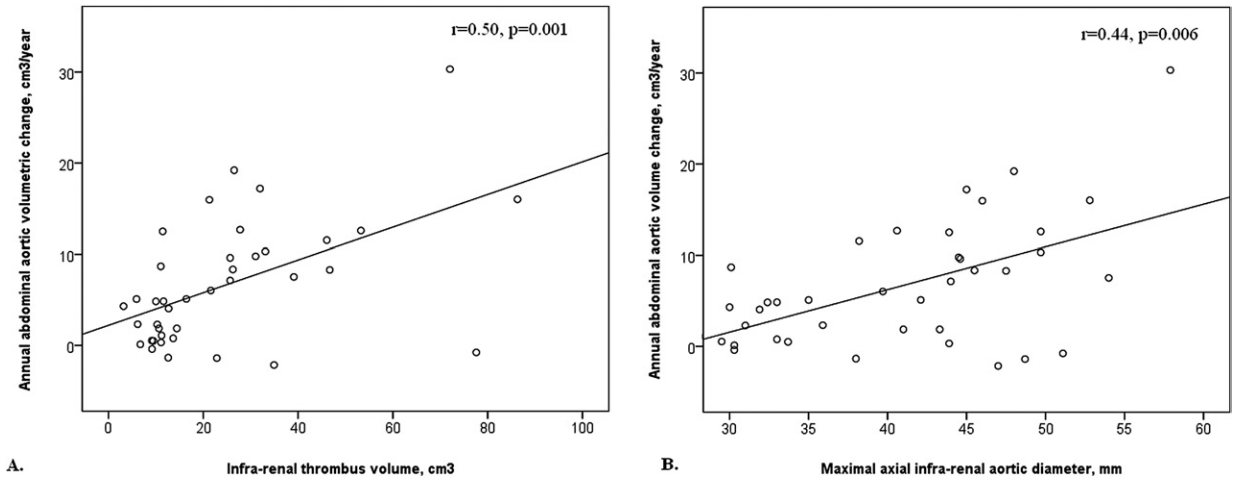

Fig 3. Scatterplots display the association of annual abdominal aortic volume change with **(A)** thrombus volume and **(B)** maximal axial abdominal aortic diameter.

tality,[2,3,7] even when not in the aneurysmal range.[3] Thus, there are convincing data of the association between aortic diameter and cardiovascular events; however, the reason for this association is currently unknown.

A recent study by our group found thrombus volume was closely correlated with maximum axial aortic diameter ($r = 0.74$; $P < .0001$) in patients with AAA or aortic ectasia.[29] This association between AAA diameter and thrombus is in keeping with the findings of previous smaller studies.[34,35] Currently, the factors determining thrombus deposition are not known and were not examined in this study. AAA thrombus products have been demonstrated within the systemic circulation and have potential to influence pathways implicated in atherothrombosis.[24-28] We therefore postulated that AAA thrombus products could be one of a number of causal links between aortic diameter and cardiovascular events. Our findings support this hypothesis and suggest the association between AAA thrombus and outcome warrants further assessment in larger studies.

Initial AAA diameter is recognized as the most powerful and consistent predictor of AAA growth.[4,5,11,13,36-41] Two previous studies have examined the association between AAA thrombus and growth.[18,19] Wolf et al[19] reviewed CT scans of 80 patients who underwent repeat CT scans >6 months apart. On the section with the largest cross-sectional diameter, the researchers used hard copy images to measure maximal diameter, aneurysm area, lumen area, thrombus thickness, and arc of aortic wall covered by thrombus and calculated AAA volume, thrombus volume, and thrombus percentage. They reported that large thrombus arc, thrombus percentage, and thrombus area were highly significantly associated with increased AAA expansion ($P < .001$ in all variables). There was no report of the reproducibility of the measurement techniques used and the association was not adjusted for initial AAA diameter. A recent longitudinal prospective study[18] examined 195 AAA patients (range, 40-49 mm) with two CT scans >6 months apart. The authors assessed continuous (increased growth rates) vs discontinuous growth. Aneurysms with no thrombus or concentric thrombus were associated exclusively with discontinuous and slower growth rates ($P = .05$). These two previous studies, along with the current investigation, provide support for a role of thrombus in AAA progression.

AAA thrombus has been demonstrated to contain large numbers of polymorphonuclear leukocytes and high concentrations of matrix metalloproteinases, elastase, and plasmin.[16,17,42] Elastase has been suggested to inhibit mesenchymal cells binding to fibrin and thereby impair repair of aortic injury.[43] Plasmin activation of matrix metalloproteinases at the thrombus and aortic wall interface has been postulated to enhance proteolysis.[16] These mechanisms provide a potential link between AAA thrombus and progression. In keeping with these findings, a recent study reported an association between reduced small AAA progression and aspirin prescription, and two preclinical studies have suggested that antiplatelet interventions inhibit AAA progression.[44-46]

In our primary assessment of risk factors for cardiovascular events, we did not censor patients at the time of AAA repair because these events are still common after surgery. In a secondary analysis, we censored patients who required AAA repair at the time of surgery. The findings of this analysis were similar to our primary assessment, except that the association of thrombus volume with cardiovascular events adjusted for other risk factors was only of borderline significance.

The current study has a number of limitations. Firstly, the small sample size made analysis difficult. Interaction terms could not be used to assess the relationship between thrombus and AAA diameter in relation to cardiovascular events. The results may be confounded by the relationship between thrombus and AAA diameter, in addition to other

variables. A larger study is needed to adequately assess this aspect before any conclusions can be reached.

Secondly, follow-up periods were short. Larger studies with longer-term follow-up are required to confirm the associations we report.

Thirdly, a large portion of patients in the high thrombus group had an AAA repair, potentially confounding results.

Fourthly, volumetric analysis of thrombus may have certain limitations. Because the length of the infrarenal aorta varies between individuals, this method may overestimate the thrombus burden in patients with greater length. However, because volumetric analysis assesses thrombus quantity, this should provide an estimation of the thrombus available for potential thrombus-derived product production and release into the circulation.

Finally, the findings of this study are based on patients with AAA who underwent CT assessment only. Whether the findings can be related to all small AAAs remains to be established.

CONCLUSIONS

To our knowledge, this is the first study to demonstrate an association between AAA thrombus volume and subsequent cardiovascular events. This association could reflect cardiovascular risk factors we have not been able to adjust for in this study or may result from the systemic effects of circulating thrombus products. Further studies are required to assess the clinical importance of the association.

AUTHOR CONTRIBUTIONS

Conception and design: JG, AP
Analysis and interpretation: AP, JG
Data collection: AP, MM, BB, AS
Writing the article: AP, PB, JG
Critical revision of the article: AP, JG, PB, MM, AS, BB
Final approval of the article: AP, JG, PB, MM, AS, BB
Statistical analysis: AP, JG, PB
Obtained funding: JG
Overall responsibility: AP

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