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**The prognostic impact of vascular calcification on abdominal aortic aneurysm progression**

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Short Title: Prognostic impact of vascular calcification on AAA

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## **ARTICLE HIGHLIGHTS**

**Type of Research:** Single-center retrospective cohort study

**Key Findings:** We assessed the prognostic value of arterial calcification to predict abdominal aortic aneurysm (AAA) progression. Morphometric data was gained by analyzing 389 computed tomography angiographies of 102 AAA patients. The median calcification volume (1225.3 vs 519.8 mm<sup>3</sup>,  $P = 0.003$ ) and the median abdominal total customized Agatston calcium (cAC) score (1663.5 vs 718.4,  $P = 0.003$ ) of the infrarenal aorta were significantly increased in slow compared to fast progressing AAA. A log-linear mixed model efficiently predicted AAA expansion based on current diameter and abdominal total cAC score ( $P = 0.042$ ).

**Take Home Message:** An inverse relation of abdominal vascular calcification and AAA progression over short-term periods of six months was identified.

## **Table of Contents Summary**

An inverse relation of increased abdominal vessel wall calcification and short-term AAA progression was detected in this retrospective study with 389 analyzed computed tomography angiographies of 102 AAA patients. Increased vascular calcification stabilizes the aortic aneurysmal wall and likely protects against progressive AAA expansion.

## 1    **What this paper adds**

2    Currently, the maximal aortic diameter is the only clinically applied parameter to assess  
3    abdominal aortic aneurysm (AAA) prognosis. Since the impact of calcification on AAA is yet  
4    unclear, we analyzed the association of vascular calcification with AAA stability and growth and  
5    we assessed the prognostic value of arterial calcification to predict AAA progression.  
6    Morphometric data was gained by analyzing 389 computed tomography angiographies (CTA) of  
7    102 AAA patients. Vascular calcification was found to identify fast AAA progression over short-  
8    term periods of six months, which was additionally confirmed in a log-linear mixed model over  
9    extended monitoring period.

## 1 Abstract

2 **Objective:** The maximal aortic diameter is currently the only clinically applied predictor of  
3 abdominal aortic aneurysm (AAA) progression. It is known that risk of rupture is associated with  
4 aneurysm size, hence accurate monitoring of AAA expansion is crucial. Aneurysmal vessel wall  
5 calcification and its implication on AAA expansion are insufficiently explored. We evaluated the  
6 vascular calcification using longitudinal computed tomography angiographies (CTA) of AAA  
7 patients and its association with AAA growth.

8 **Methods:** We conducted a retrospective study of 102 AAA patients with a total number of 389  
9 abdominal CTAs at six-month intervals, treated and followed-up at the Division of Vascular  
10 Surgery, Department of General Surgery, Medical University of Vienna. Digitally stored CTAs  
11 were reviewed for vascular calcification (volume and score) of the infrarenal aorta and common  
12 iliac arteries as well as for morphometric AAA analysis. In the prognostic setting, slow versus  
13 fast AAA progression was defined as  $< 2$  or  $\geq 2$  mm increase in AAA diameter over six months.  
14 In addition, to analyze the association of vascular calcification and AAA growth rate with  
15 longitudinal monitoring data, a specifically tailored log-linear mixed model was employed.

16 **Results:** An inverse relation of increased abdominal vessel wall calcification and short-term  
17 AAA progression was detected. Compared to fast progressing AAA, the median calcification  
18 volume of the infrarenal aorta (1225.3 vs 519.8 mm<sup>3</sup>,  $P = 0.003$ ), the median total calcification  
19 volume (2014.1 vs 1434.9 mm<sup>3</sup>,  $P = 0.008$ ) and the median abdominal total customized Agatston  
20 calcium (cAC) score (1663.5 vs 718.4,  $P = 0.003$ ) were significantly increased in slow  
21 progressing AAA. Importantly, a log-linear mixed model efficiently predicted AAA expansion  
22 based on current diameter and abdominal total cAC score ( $P = 0.042$ ).

1   **Conclusion:** We assessed the prognostic value of CTA-measured vascular calcification for AAA  
2   progression. Increased vascular calcification stabilizes the aortic aneurysmal wall and likely  
3   protects against progressive AAA expansion, resulting in a significant decrease of aneurysm  
4   growth over time. As a consequence, this may have implications for rupture risk, mortality,  
5   morbidity, and cost.

6   **Keywords:** abdominal aortic aneurysm, growth prediction, vascular calcification, calcification  
7   volume, calcification score, computed tomography angiography

8   **Conflict of Interest:** The authors declare that they have no conflict of interest.

## 1 Introduction

2 An abdominal aortic aneurysm (AAA) is diagnosed if the maximal aortic diameter exceeds 30  
3 mm.<sup>1</sup> If left undiagnosed or untreated, the AAA will continue to grow indefinitely and eventually  
4 rupture, with a 50 - 80% mortality rate.<sup>2</sup> To date, the maximal aortic diameter is solely used as  
5 clinically applied predictor of AAA progression and indication of surgery, while other  
6 parameters such as vascular calcification are still debated.<sup>3</sup> However, the importance of other  
7 parameters for AAA risk stratification is undeniable. The individual risk assessment is often not  
8 well reflected in AAA diameter alone, although large studies such as the Aneurysm Detection  
9 and Management Trial and the United Kingdom Small Aneurysm Trial show that the maximal  
10 AAA diameter is predictive of aneurysm rupture.<sup>4, 5</sup> To improve the effectiveness of individual  
11 AAA risk assessment, new additional potential risk variables should be considered. For  
12 cardiovascular risk assessment, the prognostic value of arterial calcification has been thoroughly  
13 described.<sup>6-8</sup> Considering the inflammatory character of AAA, it is notable that arterial  
14 calcification as an independent risk factor of cardiovascular morbidity and mortality, has been  
15 demonstrated to be a marker of degenerative inflammatory processes.<sup>9-11</sup> It has been reported,  
16 that AAA wall calcification is inconclusively associated with aortic wall stress and  
17 biomechanical vessel wall stability.<sup>12-14</sup> A recent meta-analysis on the prognostic value of  
18 abdominal aortic calcification concluded that high-risk patients with advanced abdominal aortic  
19 calcification have a higher risk of cardiovascular events, elevated all-cause mortality and in  
20 general a poorer prognosis. This study, additionally designed to reveal feasibility, further  
21 addressed the prerequisite for standardized calcification measurements, but also stated the need  
22 for providing more information about abdominal aortic calcification, that may can help clinicians  
23 to better understand and manage AAA patients.<sup>15</sup>

1 In fact, the impact of aortic vessel wall calcification on AAA growth is unclear. Different  
2 methods of assessing aortic diameter and vessel wall calcification are described in the current  
3 literature, with many of them lacking in assessment reproducibility.<sup>15, 16</sup> As a result, there is no  
4 agreement on whether or not a calcification score can be used as a reliable AAA evaluation  
5 parameter.<sup>17-19</sup> Based on our CTA-based assessment accuracy (six-month intervals), we  
6 hypothesize that AAA progression is associated with the degree of vessel wall calcification and  
7 increased vascular calcification may stabilize the aortic aneurysmal wall protecting against  
8 progressive AAA expansion.



## 1   **Methods**

### 2   *Study Population*

3   All studies involving human subjects were conducted according to The Code of Ethics of the  
4   World Medical Association (Declaration of Helsinki), reviewed and registered the study ID  
5   research registry 5637 and approved by the institutional ethics committee (license no.  
6   1729/2014) and all study participants (89 male and 13 female AAA patients, in total 389 CTAs)  
7   gave their written informed consent. Each patient was diagnosed with an AAA and treated as  
8   well as followed-up at the outpatient clinic at a tertiary university hospital (Department of  
9   General Surgery, Division of Vascular Surgery, General Hospital of Vienna, Medical University  
10   of Vienna, Vienna, Austria). The exclusion criteria for patients were recent (< 12 months) tumor  
11   or chemotherapy, systemic autoimmune or hematological disease and organ transplantation.  
12   Patient demographics were recorded by a structured questionnaire and all study participants  
13   underwent serial blood withdrawing and CTA every six months.

### 14   *Morphometric CTA and calcification analyses*

15   Individual morphometric AAA analysis was performed by analyzing CTAs with syngo.via  
16   (version VB40B, Siemens Healthineers, Forchheim, Germany) and impax EE (Agfa-Gevaert,  
17   Mortsel, Belgium) imaging software. Multiple measurements of the same CTA image (maximal  
18   AAA diameter) were done by two independent experts, resulting in a mean intra- and  
19   interobserver variability ranging at 0.14 mm and 0.20 mm, respectively.<sup>20</sup> The measurements  
20   were rounded to within the nearest 0.1 mm. Computed tomography angiographies were  
21   performed with two different CTA scanners (Siemens Somatom Flash or Siemens Somatom  
22   Force) and patient received up to 40 ml of 400 mg/ml Iomeron contrast agent. A tube voltage of

100 or 120 kV and a tube current of 120 ref mAs were applied (collimation: 2x64x0.6 mm). Multiplanar reconstructions were done by using images reconstructed in 1 or 2 mm slices. We measured the vascular calcification applying the “CTA syngo Calcium Scoring” tool of syngo.via software. First, a Hounsfield unit threshold was set individually for each CTA in order to exclude the contrast agent within the vessel lumen next to the calcification plaques. All distributions of pixels with a density above the defined threshold were detected and manually color marked for each calcification plaque. The semiautomatic software allows accurate visualization and quantification of calcified arterial lesions. For the calcification measurements, four anatomic regions (infrarenal aorta, common iliac arteries and combined segments) were defined separately and collectively (**Figure 1**). Subsequently, from the selected areas, the software automatically calculated the segmental calcification volume and calcification score - customized Agatston calcium (cAC) score.<sup>21</sup>

### *Statistical analysis*

The results are presented as median and interquartile range (IQR) for continuous variables and counts with percent sample group for nominal variables. For assessment of statistical significance, non-parametric tests were employed (Mann-Whitney U test for group comparisons of continuous variables). Slow versus fast AAA disease progression was characterized as a < 2 mm or  $\geq 2$  mm increase in AAA diameter over the next 6 months, reflecting previously published cut-offs in the prognostic setting of 4 mm per year.<sup>22</sup>

To analyze the association of vascular calcification and AAA growth rate with longitudinal monitoring data, a specifically tailored log-linear mixed model was employed (incorporating time as the main effect and vascular calcification as effect modifier), accounting for multiple measurements in patients over time. The model-based equation specifies  $y_{\text{timepoint}} = y_{\text{baseline}} * e^{(\lambda * \text{time})}$

time +  $\beta$  \* (calcification value at baseline – mean) \* time), and thus projects AAA size (y) in a certain time period (years) based on the current aneurysm diameter and calcification level at baseline. The natural logarithm of two subsequent maximal AAA diameter measurements was calculated through the time interval between the two measurements (in years) and the interaction of time interval and vascular calcification (volume or score) as measured at the beginning of the time interval. The effect of time interval was modelled as normally distributed random effect at patient level to account for correlations of repeated observations within the same patient. Calcification values were centered at the sample mean before entering the model to allow for direct estimation of the average growth rate. No intercept was included, because at a theoretical time interval of length zero, the AAA growth is zero by definition. Baseline maximal AAA diameter was not included as predictor, because the model explains relative change, and hence, the initial maximal AAA diameter of each time interval is included in the log transformed maximal diameter ratio which is the outcome variable of the model.

Multivariable binary logistic regression was conducted to assess the biomarker value of vascular calcification to predict fast AAA progression when adjusting for other calcification parameters, comorbidities, and medication. During the course of data analysis, only variables with  $p < 0.1$  in univariate analysis were included in multivariable binary logistic regression analysis. Two-sided  $P$ -values below 0.05 were considered statistically significant. The data analysis was conducted with SPSS (version 27.0, SPSS Inc., Chicago, IL, USA).

## 1    **Results**

### 2    *Patient Collective*

3    This retrospective study analyzed 389 CTAs of 102 AAA patients, who were followed-up with  
4    serial blood withdrawing and CTA analyses in six-month intervals. The main objective of this  
5    study was to determine the prognostic impact of vascular calcification on AAA progression.

6    Patient demographics are listed in **Table 1**. The majority of study participants were men, i.e. 89  
7    (87.3%) and 13 (12.7%) women were included. The median age at study entry was 71 years for  
8    men, 73 years for women and the median body mass index was within the range of overweight at  
9    27.4 kg/m<sup>2</sup> and 26.4 kg/m<sup>2</sup> for men and women, respectively. The median AAA diameter at  
10    study entry was 45.4 mm for men and 41 mm for women. The aortic size index ( $P = 0.372$ ) as  
11    well as the total baseline calcification volume ( $P = 0.288$ ) were not significantly different  
12    comparing male AAA patients to female AAA patients. Additionally, we classified the aneurysm  
13    shapes. In our population of male patients, 65 aneurysms were fusiform, 12 saccular, 2 eccentric  
14    and 10 of other or combined shapes. In the female cohort, 7 aneurysms were fusiform, 4 saccular  
15    and 2 of other or combined shapes. The high prevalence of smoking behavior of male AAA  
16    patients is reflected in a median of 45 smoking pack-years. Female AAA patients had a median  
17    of 40 smoking pack-years. Most prevalent comorbidities of the patient collective were  
18    hypertension and hyperlipidemia, each more prevalent in male AAA patients (86.5 vs 84.6% and  
19    78.7 vs 76.9%, respectively). Lipid-lowering agents, antiplatelet medication and antihypertensive  
20    agents were the most often prescribed medications in this patient population. Further details of  
21    patient population characteristics and concomitant medication are listed in **Table 1**.

22    *Increased vascular calcification predicts aneurysm growth and protects against progression*

Differences of morphological and calcification parameters of AAA between groups with slow (< 2 mm) and fast ( $\geq 2$  mm) AAA progression are listed in **Table 2**. For the calcification measurements, four anatomic regions (infrarenal aorta, common iliac arteries and combined segments) were defined separately and collectively (**Figure 1**). We found a significantly larger AAA diameter and intraluminal thrombus (ILT) in the fast progressing group (44.8 vs 49.1 mm,  $P = 0.002$  and 11.5 vs 16 mm,  $P = 0.007$ , respectively). In line, the aortic segment volume (AAA volume with thrombus, 70.3 vs 111.5 cm<sup>3</sup>,  $P < 0.001$ ) and ILT volume (26.3 vs 42.6 cm<sup>3</sup>,  $P = 0.001$ ) showed higher values in fast progressing AAA. This was also reflected in a significantly reduced vessel occlusion rate of slow progressing AAA (36.3 vs 40.2%,  $P = 0.034$ ). The proximal neck length and proximal neck diameter were found to be significantly larger in slow progressing AAA (23.4 vs 13.6 mm,  $P = 0.020$  and 19.8 vs 16.6 mm,  $P = 0.017$ ), as opposed to the aneurysm length, which was significantly longer (71.4 vs 105.2 mm,  $P < 0.001$ ) in fast progressing AAA. In addition, we also evaluated the AAA growth between groups with slow (< 2 mm) and fast ( $\geq 2$  mm) AAA progression over 6 months regarding their aneurysm shape: 161 fusiform, 31 saccular, 4 eccentric and 18 other or combined AAA shapes showed intervals of slow AAA growth. In contrast, fast AAA progression over 6 months was observed in 24 fusiform, 2 saccular, 2 eccentric and 5 other or combined aneurysm shapes.

Our results demonstrate that the volume of infrarenal vessel wall calcification is significantly elevated in slow progressing compared to fast progressing AAA (1225.3 vs 519.8 mm<sup>3</sup>,  $P = 0.003$ ). The difference in representative vascular vessel wall calcifications in patients with slow and fast AAA progression is highlighted in **Figure 2**. In addition, infrarenal vascular calcification, assessed with the cAC score, was likewise significantly increased in slow progressing AAA (1663.5 vs 718.4,  $P = 0.003$ ). These results indicate a prognostic potential of

CTA-measured vascular calcification on AAA progression. We suggest that increased vessel wall calcification stabilizes the aortic aneurysmal wall and protects against progressive AAA expansion, specifically over short-term periods of six months. Moreover, by assessing a combined (infrarenal and common iliac arteries) volume of vascular calcification or cAC score, the prognostic potential of vascular calcification on AAA progression persists (2014.1 vs 1434.9 mm<sup>3</sup>,  $P = 0.008$  and 2769.2 vs 1948.7,  $P = 0.007$ , respectively). However, our findings show that the sole volumes of common iliac artery calcifications cannot predict fast AAA progression (**Table 2**).

Furthermore, we evaluated the biomarker value of vascular calcification volume and cAC score to predict AAA progression in a log-linear mixed model. The total cAC score (infrarenal and common iliac arteries combined) allowed a reliable AAA growth prediction and confirmed the prognostic potential of vascular vessel wall calcification for AAA progression (**Table 3**). As time is the strongest determinant of AAA progression, the measured time intervals (years), always present as highly significant predictors of disease progression. The significant interaction ( $P = 0.042$ ) between calcification parameter (total cAC score) and time indicates that the impact of time on AAA progression can indeed be modified by vessel calcification. For instance: according to the mixed model, a representative AAA patient with a baseline maximal aortic diameter of 47.90 mm and a baseline cAC score of 11575.4 is predicted to have a maximal aortic diameter of 48.66 mm after 6 months. The model-based calculation for this patient corresponds to  $47.90 * e^{(0.040672 * 0.5 + (-0.000001245393) * (11575.4 - 4489.766) * 0.5)}$ . In fact, the radiologic measurement of the patient revealed a maximal aortic diameter of 48.70 mm after six months which is almost identical to the predicted value.

1 The total cAC score was further evaluated by univariate and subsequent multivariable binary  
2 logistic regression analysis to identify fast progressors. After adjusting for morphological and  
3 blood parameters as metric variables as well as comorbidities and patient medication as  
4 categorical variables (**Table 4**), the total cAC score did not hold independent prognostic  
5 information for AAA growth. Maximal AAA diameter ( $P = 0.017$ ) was confirmed as  
6 independent predictor of disease progression in multivariable analysis.

## Discussion

This study demonstrates a protective effect of increased arterial vessel wall calcification on AAA progression, based on accurate, serial CTA analyses (six-month intervals) of substantial sample size. Further, we confirmed the predictive potential of vascular calcification for AAA growth in a log-linear mixed model, accounting for multiple measurements in patients over time. In multivariable analysis (binary logistic regression) of AAA patients, the total cAC score did not prevail and only the maximal AAA diameter was independently associated with faster AAA progression over six months. It is known that the AAA growth rate is associated with the initial aneurysm size and could therefore also be associated with the degree of calcification.<sup>16</sup> However, AAA expansion represents a surrogate parameter and was nevertheless included in multivariable binary logistic regression analysis with risk of overadjustment. Yet, confounding factors could be present, although data acquisition and analysis make severe selection bias most unlikely. The morphometric analyses were performed by blinded observers. However, the non-persistence after adjustment for potential confounders influencing vascular calcification and AAA growth may be a consequence of the heterogeneous AAA etiology. Considering the prognostic potential of vascular calcification on AAA progression, this may lead to an associated reduction of rupture risk, mortality, morbidity, and cost.

Compared to investigations of the coronary arteries, only a few studies have analyzed the role of vascular calcification of the AAA wall and if so, most often in the context of cardiovascular event outcome.<sup>15, 23</sup> As opposed to earlier studies truly analyzing the prognostic potential of vascular calcification on AAA, we used CTA-based quantification of vascular calcification with high reproducibility and definitely much more accurate data compared to other imaging methods such as ultrasonography or plain x-ray.<sup>15, 18, 19, 23</sup> Actually, compared to other studies, our



research additionally shows a many times higher sample size with regard to the number of analyzed CTAs.<sup>15</sup>

Our results are in line with another study reporting that increased calcification reduces AAA progression. However, this prior study achieved an interobserver variability of 1.4 mm and vascular calcification was measured via ultrasonography.<sup>18</sup> In contrast, in our study, multiple measurements of the same CTA image (maximal AAA diameter) were performed by two independent experts, resulting in a mean intra- and interobserver variability ranging at 0.14 mm and 0.20 mm, respectively. A study with reasonable selection bias, but yet calcification analysis of AAA by multidetector-row computed tomography and calcification index, reported results consistent to our findings.<sup>24</sup> Contrarily, a study, which investigated growth models of AAA between 40 and 49 mm of maximal diameter found no significant influence of vascular calcification on AAA growth patterns. However, this study did not quantify vascular calcification parameters (volume and score) like in our study, but classified depending on the grade of calcification in relation to aortic circumference.<sup>25</sup> This might explain these discrepancies.

In general, there are various approaches of measuring vascular calcification such as semiquantitative methods like the abdominal aortic calcification-8 score, the abdominal aortic calcification-24 score or aortic calcification index in addition to computerized methods of calcification quantification such as the Agatston calcium score or Callister method.<sup>21, 26-30</sup> Originally, both, the Callister and Agatston methods are described to be able to only assess calcification in non-contrast enhanced computed tomography images, because the signal generated by the intravascular contrast agent interferes with that generated by the calcification of the vessel wall.<sup>19</sup> However, the preferred imaging modality used to study AAA is CTA.<sup>1</sup> Of note,

we applied a method in our study to quantify the vascular calcification with a computerized method, however, we set the Hounsfield units threshold individually for each CTA in order to adjust for contrast agent and to be able to measure the amount of calcification as precise as possible. Since CTAs can also be used for standardized quantification of arterial vessel wall calcification, we applied the “CTA syngo Calcium Scoring” tool of syngo.via software (Siemens Healthineers, Forchheim, Germany), which is usually used for quantification of calcified coronary lesions.<sup>31, 32</sup> The calcium scoring tool allows accurate visualization and quantification by automatic selection and subsequent essential manual defining for the calcified plaques. The software provides a comprehensive analysis of calcification volume (mm<sup>3</sup>) and score (Agatston method), if analyzed, also of the abdominal arteries (cAC score).<sup>21</sup>

There are several limitations, which must be addressed. First, it should be noted that the data for this study was collected retrospectively. The “CTA syngo Calcium Scoring” tool of syngo.via software was used to quantify abdominal vascular calcification, thus each calcification plaque had to be marked manually offering potential variability of measurements. Data validity ultimately depends on the validity of calcification measurements and the ability to manage for confounding factors. Although our intra- and interobserver reproducibility are notable, we are already investigating and establishing automatic 3D detection, segmentation and modeling of AAA in CTA datasets using deep convolutional neural networks (artificial intelligence) e.g. possible influence of the thrombus volume in AAA growth topic in another manuscript. This research may provide improvement and optimization of measurement accuracy in the future. Even though the total cAC score did not reach statistical significance in the multivariable regression analysis, it can be interpreted that several AAA disease factors are implicated in AAA growth. Vascular calcification appears to be of substantial impact as well, although not in an

independent manner. On the basis of the limited number of AAA patients who displayed rapid AAA progression, the number of included covariates is a compromise between overadjustment with 6 covariates and maintaining the complexity of included AAA disease factors by including several covariates in the multivariable regression analysis. Most AAA patients in this study are Caucasian from central Europe. We conducted 389 abdominal CTA analyses of 102 AAA patients. Compared to current literature with predominantly x-ray or ultrasonography measurements of AAA calcification, we provide a many times higher sample size in addition to increased accuracy of CTA analyses.<sup>15</sup> However, a further prospective study seems favorable and necessary to confirm and add evidence of validity to identify fast AAA progression via vascular calcification. Afterwards, the method to efficiently predict AAA expansion based on current diameter and abdominal total cAC score is expected to be applicable in clinical practice. In addition, after demonstrating the efficacy of computerized clinical decision support with regards to vascular calcification on abdominal aortic aneurysm progression, it is conceivable that the improved prognostic value of aneurysm growth has several positive effects on patient care. This concerns improved patient education and diminished anxiety because of previously more unpredictable AAA growth. We believe that it also improves the assessment accuracy of aneurysm growth or AAA-size related rupture risk by surgeons. Considering AAA as multifactorial disease, it seems logical that the more factors that are included in the growth rate prognosis, the more precise it will be. If the intervals of extensive and costly CTAs can be prolonged (or safely alternated with sonography) as well as surgical AAA repair can be delayed based on this prognosis, patients and health care systems might further benefit.

## **Conclusion**

1 We observed a protective effect of increased CTA-measured vascular calcification on AAA  
2 progression. Vascular calcification may identify fast AAA progression over short-term periods of  
3 six months. This prognostic potential was further confirmed in a log-linear mixed model. As  
4 pathological implication, it is suggested that vascular calcification stabilizes the aortic  
5 aneurysmal wall and protects against progressive AAA expansion. This information may have  
6 impact on patient awareness of disease risk, clinical decision making and could lead to an  
7 associated reduction of rupture risk, mortality, morbidity, and cost.

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**Table 1:** Patient demographics: metric and categorical variables

Abbreviations: n, number of individuals; IQR, interquartile range; AAA, abdominal aortic aneurysm; ILT, intraluminal thrombus; COPD, chronic obstructive pulmonary disease; *P*-value: \*\* < 0.01; \*\*\* < 0.001

**Table 2:** Comparison of morphological and calcification parameters between AAA with slow (< 2 mm) and fast ( $\geq 2$  mm) progression over six months

Abbreviations: n, number of CTA measurements; IQR, interquartile range; AAA, abdominal aortic aneurysm; ILT, intraluminal thrombus; CIA, common iliac artery; cAC score, customized Agatston calcium score; *P*-value: \* < 0.05; \*\* < 0.01; \*\*\* < 0.001

**Table 3:** Log-linear mixed model for AAA growth prediction incorporating time as the main effect and vascular calcification parameters as effect modifiers

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**Table 4:** Multivariable analysis (binary logistic regression) of AAA progression

Abbreviations: CI, confidence interval; cAC score, customized Agatston calcium score; AAA, abdominal aortic aneurysm; LDL, low-density lipoprotein; HDL, high-density lipoprotein; *P*-value: \* < 0.05

**Figure 1. Defined anatomic regions for analysis and measured parameters of vascular calcification in CTA.** The circumferential vascular calcification of four anatomic regions was assessed: infrarenal aorta (red segment), left common iliac artery (blue segment), right common iliac artery (green segment) and combined overall calcification of infrarenal aorta and common iliac arteries (yellow segment). Abbreviations: cAC score, customized Agatston calcium score; CIA, common iliac artery

**Figure 2. Differences of vascular calcification patterns in AAA patients.** Representative CTAs showing an AAA with little vessel wall calcification and increased progression (A) compared to an AAA with a more pronounced vascular calcification, but decreased AAA growth rate (B) over the identical observational period.

1 **Table 1:** Patient demographics: metric and categorical variables

Characteristic	n/n ♂/♀	Male median (IQR) or frequency (%)	Female median (IQR) or frequency (%)	P-value
Age at first visit [years]	89/13	71 (12)	73 (11)	0.421
Weight [kg]	88/13	85 (17)	70 (18)	<b>0.001**</b>
Height [cm]	88/13	176 (6.8)	163 (15.5)	<b>&lt; 0.001***</b>
Body mass index [kg/m <sup>2</sup> ]	88/13	27.4 (5)	26.4 (4.2)	0.397
Body surface area [m <sup>2</sup> ]	88/13	2.1 (0.2)	1.8 (0.3)	<b>&lt; 0.001***</b>
Smoking pack-years [py]	81/12	45 (31)	40 (14.5)	0.546
Mean systolic pressure [mmHg]	87/13	133.3 (19)	140.5 (18)	0.354
Mean diastolic pressure [mmHg]	87/13	78.8 (10)	80.8 (13)	0.240
Maximal AAA diameter [mm] at first visit	89/13	45.4 (10.3)	41 (9.3)	0.104
Aortic size index [cm/m <sup>2</sup> ] at first visit	88/13	2.2 (0.5)	2.3 (0.6)	0.372
Aortic segment volume [cm <sup>3</sup> ] at first visit	86/13	74.2 (59.1)	79 (97.2)	0.889
ILT volume [cm <sup>3</sup> ] at first visit	87/13	11.9 (11.1)	13.8 (15.7)	0.489
Total calcification volume [mm <sup>3</sup> ] at first visit	85/13	2208.0 (3674.90)	1385.4 (1749.15)	0.288
Hypertension	89/13	77 (86.5%)	11 (84.6%)	0.853
Hyperlipidemia	89/13	70 (78.7%)	10 (76.9%)	0.888
Peripheral artery disease	89/13	23 (25.8%)	5 (38.5%)	0.343
Coronary heart disease	89/13	30 (33.7%)	4 (30.8%)	0.835
Myocardial infarction	89/13	17 (19.1%)	2 (15.4%)	0.673
Stroke	89/13	11 (12.4%)	2 (15.4%)	0.761
Diabetes mellitus	89/13	18 (20.2%)	3 (23.1%)	0.905
COPD	89/13	19 (21.3%)	2 (15.4%)	0.621
Antiplatelet therapy	89/13	78 (87.6%)	12 (92.3%)	0.627
Anticoagulation therapy	89/13	21 (23.6%)	1 (7.7%)	0.195
Antihypertensive therapy	89/13	76 (85.4%)	12 (92.3%)	0.501
Lipid-lowering agents	89/13	84 (94.4%)	11 (84.6%)	0.195
Statins	84/11	79 (94%)	9 (81.8%)	0.146

3 Abbreviations: n, number of individuals; IQR, interquartile range; AAA, abdominal aortic aneurysm; ILT,  
4 intraluminal thrombus; COPD, chronic obstructive pulmonary disease; P-value: \*\* < 0.01; \*\*\* < 0.001

**Table 2:** Comparison of morphological and calcification parameters between AAA with slow (< 2 mm) and fast ( $\geq 2$  mm) progression over six months

<i>Parameter</i>	<i>n/n</i>	<i>Slow progression over 6 months - median (IQR)</i>	<i>Fast progression over 6 months - median (IQR)</i>	<i>P-value</i>
<i>Maximal AAA diameter [mm]</i>	214/34	44.8 (11.5)	49.1 (8.4)	<b>0.002**</b>
<i>Maximal ILT diameter [mm]</i>	208/33	11.5 (11.2)	16 (10)	<b>0.007**</b>
<i>ILT volume [cm<sup>3</sup>]</i>	214/33	26.3 (42.3)	42.6 (47)	<b>0.001**</b>
<i>Aortic segment volume [cm<sup>3</sup>]</i>	211/33	70.3 (68.3)	111.5 (76.7)	<b>&lt; 0.001***</b>
<i>Vessel occlusion [%]</i>	214/33	36.3 (36.8)	40.2 (24.1)	<b>0.034*</b>
<i>Aneurysm length [mm]</i>	213/34	71.4 (42.7)	105.2 (46.2)	<b>&lt; 0.001***</b>
<i>Proximal neck length [mm]</i>	214/34	23.4 (27.6)	13.6 (33.9)	<b>0.020*</b>
<i>Proximal neck diameter [mm]</i>	214/34	19.8 (6.1)	16.6 (20.1)	<b>0.017*</b>
<i>Calcification volume of infrarenal aorta [mm<sup>3</sup>]</i>	209/33	1225.3 (1746)	519.8 (1173.1)	<b>0.003**</b>
<i>Calcification volume of left CIA [mm<sup>3</sup>]</i>	204/32	407 (845.6)	328.15 (570.3)	0.194
<i>Calcification volume of right CIA [mm<sup>3</sup>]</i>	208/32	496.4 (740.4)	344.55 (617)	0.094
<i>Total calcification volume [mm<sup>3</sup>]</i>	201/32	2014.1 (3367.9)	1434.9 (2473.05)	<b>0.008**</b>
<i>cAC score of infrarenal aorta</i>	209/33	1663.5 (2380.4)	718.4 (1720.5)	<b>0.003**</b>
<i>cAC score of left CIA</i>	204/32	550.4 (1124.4)	487.15 (774.2)	0.227
<i>cAC score of right CIA</i>	208/32	677.9 (978.3)	465.8 (820.2)	0.102
<i>Total cAC score</i>	201/32	2769.2 (4556.2)	1948.7 (3398.3)	<b>0.007**</b>

Abbreviations: n, number of CTA measurements; IQR, interquartile range; AAA, abdominal aortic aneurysm; ILT, intraluminal thrombus; CIA, common iliac artery; cAC score, customized Agatston calcium score; *P*-value: \* < 0.05; \*\* < 0.01; \*\*\* < 0.001

**Table 3:** Log-linear mixed model for AAA growth prediction incorporating time as the main effect and vascular calcification parameters as effect modifiers

Parameter	Estimate	95% CI lower value	95% CI upper value	P-value
<i>CTA time interval (years)</i>	0.040207 ( $\lambda$ )	0.034724	0.045691	< <b>0.001</b> ***
<i>Calcification volume of infrarenal aorta [mm<sup>3</sup>]</i>	-2.079229 <sup>-6</sup> ( $\beta$ )	-4.661990 <sup>-6</sup>	5.035321 <sup>-7</sup>	0.113
<i>CTA time interval (years)</i>	0.040507 ( $\lambda$ )	0.034918	0.046096	< <b>0.001</b> ***
<i>Total calcification volume [mm<sup>3</sup>]</i>	-1.554397 <sup>-6</sup> ( $\beta$ )	-3.161347 <sup>-6</sup>	5.255276 <sup>-8</sup>	0.058
<i>CTA time interval (years)</i>	0.040212 ( $\lambda$ )	0.034728	0.045695	< <b>0.001</b> ***
<i>cAC score of infrarenal aorta</i>	-1.583818 <sup>-6</sup> ( $\beta$ )	-3.532981 <sup>-6</sup>	3.653442 <sup>-7</sup>	0.109
<i>CTA time interval (years)</i>	0.040520 ( $\lambda$ )	0.034960	0.046080	< <b>0.001</b> ***
<i>Total cAC score</i>	-1.245393 <sup>-6</sup> ( $\beta$ )	-2.444247 <sup>-6</sup>	-4.653900 <sup>-8</sup>	<b>0.042</b> *

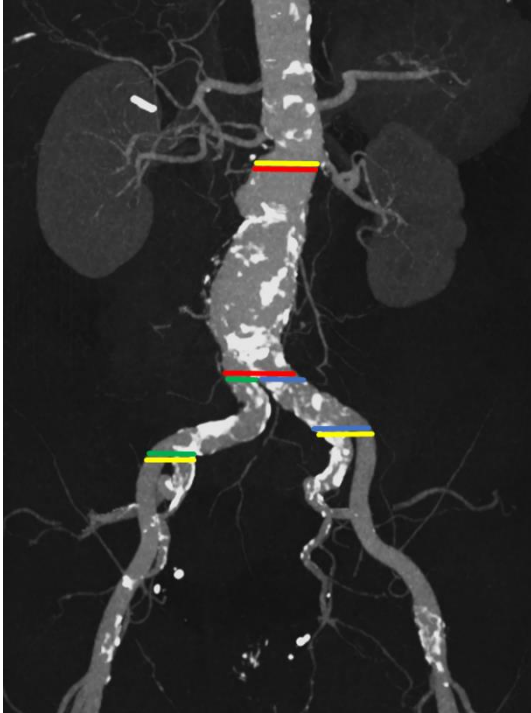
Abbreviations: CI, confidence interval; cAC score, customized Agatston calcium score; P-value: \* < 0.05

**Table 4:** Multivariable analysis (binary logistic regression) of AAA progression

Parameter	Odds ratio	95% CI lower value	95% CI upper value	P-value
<i>Total cAC score</i>	1.000	1.000	1.000	0.200
<i>Maximal AAA diameter</i>	1.082	1.014	1.154	<b>0.017</b> *
<i>Age at first visit</i>	0.943	0.883	1.007	0.079
<i>Hypertension and/or antihypertensive medication</i>	0.542	0.149	1.974	0.353
<i>Total cholesterol</i>	1.003	0.989	1.018	0.668
<i>LDL/HDL ratio</i>	1.035	0.566	1.894	0.910
<i>Constant</i>	0.266			0.667

Abbreviations: CI, confidence interval; cAC score, customized Agatston calcium score; AAA, abdominal aortic aneurysm; LDL, low-density lipoprotein; HDL, high-density lipoprotein; P-value: \* < 0.05

1



Measured parameters of defined anatomic regions:

Calcification volume & cAC score of infrarenal aorta

Calcification volume & cAC score of left CIA

Calcification volume & cAC score of right CIA

Total calcification volume & total cAC score

