A histopathological classification scheme for abdominal aortic aneurysm disease

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ABSTRACT

Objective: Two consensus histopathological classifications for thoracic aortic aneurysms (TAAs) and inflammatory aortic diseases have been issued to facilitate clinical decision-making and inter-study comparison. However, these consensus classifications do not specifically encompass abdominal aortic aneurysms (AAAs). Given its high prevalence and the existing profound pathophysiologic knowledge gaps, extension of the consensus classification scheme to AAAs would be highly instrumental. The aim of this study was to test the applicability of, and if necessary to adapt, the issued consensus classification schemes for AAAs.

Methods: Seventy-two AAA anterolateral wall samples were collected during elective and emergency open aneurysm repair performed between 2002 and 2013. Histologic analysis (hematoxylin and eosin and Movat Pentachrome) and (semi-quantitative and qualitative) grading were performed in order to map the histological aspects of AAA. Immunohistochemistry was performed for visualization of aspects of the adaptive and innate immune system, and for a more detailed analysis of atherosclerotic lesions in AAA.

Results: Because the existing consensus classification schemes do not adequately capture the aspects of AAA disease, an AAA-specific 11-point histopathological consensus classification was devised. Systematic application of this classification indicated several universal features for AAA (eg, [almost] complete elastolysis), but considerable variation for other aspects (eg, inflammation and atherosclerotic lesions).

Conclusions: This first multiparameter histopathological AAA consensus classification illustrates the sharp histological contrasts between thoracic and abdominal aneurysms. The value of the proposed scoring system for AAA disease is illustrated by its discriminatory capacity to identify samples from patients with a nonclassical (genetic) variant of AAA disease. (JVS—Vascular Science 2021;2:260-73.)

Clinical Relevance: The pathophysiology of abdominal aortic aneurysm (AAA) disease remains an enigma. Histological evaluation is critical for appreciation of the tissue remodeling and spatial aspects of AAA disease. Histopathological classification schemes have been devised for aortic pathology. Unfortunately, these schemes do not specifically address the most common aortic pathology, AAA disease. In order to facilitate interstudy comparisons and pathophysiologic understanding of AAA disease, we here present a multiparameter consensus histopathological AAA classification scheme. The scheme clearly discriminates AAA disease from thoracic aortic aneurysm disease. Systematic implementation of this AAA classification system indicates a substantial biological variation for AAA disease, and stresses the need for adequate group sizes in order to adequately cover the natural variability. Examples illustrating the diagnostic value of the classification system are provided.

Keywords: Abdominal aortic aneurysm; Classification; Histology; Thoracic aortic aneurysm; Vascular remodeling
Histopathological classification is crucial for aortic disease diagnosis and classification, and for a better understanding of aortic pathology. To facilitate clinical decision-making and interstudy comparisons, two consensus classifications with harmonized nomenclature and categorization for respectively thoracic aortic aneurysms (TAAs) and inflammatory aortic diseases have recently been issued. Notably, these consensus classifications do not specifically encompass abdominal aortic aneurysms (AAAs), by far the most prevalent form of aortic disease.

Given its high prevalence and the existing knowledge gaps, extension of the consensus classification scheme to AAA would be of major value. However, inclusion of AAA in the consensus classifications is potentially interfered by fundamental pathophysiologic differences between TAA and AAA. For instance, more than TAA, AAA disease comes with gross alternations of the vessel wall structure and associates with an extensive clinical and molecular variability, all of which may translate in a histopathological diversity. The goal of this study was to evaluate whether the existing aortic diseases consensus classification schemes can be applied to AAA. Because it was concluded that the schemes incompletely cover the histopathological spectrum of AAA disease, a first outline for classification system for AAA disease was devised.

METHODS

Patients and tissue sampling. Materials used in this study were formalin-fixed and paraffin-embedded samples from the Leiden University Medical Center (LUMC) tissue bank that were stored at room temperature. Samples were collected either as control samples within clinical trials (LUMC Medical Ethical Review Board protocol numbers: P00.146; P06.019; P08.017), or under the former opt-out guidelines for clinical trials (LUMC Medical Ethical Review Board protocol numbers: P00.146; P06.019; P08.017), or under the current code available at: www.coreon.org). Removal of excess aneurysm wall is a standard procedure during open aneurysm repair. As such, this excess vessel wall material in the study was considered “waste” material by Dutch law, and, therefore exempted from ethical consent (WGBO Art. 7.467) when used in anonymously as is the case for the tissue bank.

This study was performed on 72 AAA anterolateral wall samples collected during elective (n = 45) and emergency (n = 27) open aneurysm repair performed between 2002 and 2013 in the LUMC or the Elisabeth-TweeSteden Ziekenhuis, the Netherlands. These samples were randomly selected from a patient number list of the vascular tissue bank from the Department of Vascular Surgery, Leiden, the Netherlands. This tissue bank contains more than 250 AAA samples. It was anticipated that this sample size would provide sufficient power to map the variation in morphological characteristics.

Considering the median age of 70 years of the patients with AAA, and the reported association between atherosclerotic disease and AAA disease, two types of reference samples were considered relevant: first, infrarenal aorta samples without signs of atherosclerotic disease derived from kidney grafts of young organ donors (details of these control samples have been previously described). These controls represent the ‘normal’ aorta. The second set of references were infrarenal, non-aneurysmal aortic wall specimens from elderly (kidney) organ donors. These latter reference samples covered the full spectrum of advanced atherosclerotic disease (revised American Heart Association grading according to Virmani), late fibroatheroma, thin cap fibroatheroma, and fibrocalcific plaque.

Aortic tissues were formalin-fixed, decalcified (Kristensen’s fluid), and paraffin-embedded. Quality control showed that long-term storage of the tissue blocks did not interfere with the (immuno) histochemical stainings. Blocks were serially sectioned (4 μm) and hematoxylin and eosin (H&E) and Movat’s Pentachrome stained. A subset (n = 5) of samples that had been split, which halves had either been or not been decalcified, was stained for Alizarin Red S. See Supplementary Protocol 1 (online only) for protocols. Images were captured by means of digital microscopy (Philips IntelliSite Pathology Solution Ultra-Fast Scanner, Eindhoven, the Netherlands).

The authors declare that all supporting data are available within the article and its supplementary files.

Histological analysis. From each patient, one section was randomly chosen and used for histological grading. Histological hallmarks of AAA disease were first explored by two independent observers (L.E.B., C.S.G.) and the senior author (J.H.L.), and applied to the panel, whereafter validation was performed by experts in the field (J.A.C., J.G., J.F.H., G.T.J., R.L., L.M., P.W.V., D.W., B.X., D.Y.). Histological analysis was based on Movat Pentachrome and H&E stains.

ARTICLE HIGHLIGHTS

- **Type of Research:** Human study
- **Key Findings:** Existing consensus classification schemes for aortic disease do not adequately capture the aspects of abdominal aortic aneurysl (AAA) disease. Therefore, an AAA-specific 11-point histopathological consensus classification was devised.
- **Take Home Message:** Systematic implementation of this AAA classification system indicates a substantial biological variation for AAA disease and stresses the need for adequate group sizes in order to adequately cover the natural variability of AAA disease.
stainings. Semi-quantitative grading was based on integration of the data for the full tissue section (average grade), whereas qualitative scores were based on the most severe aspect present.

Regional heterogeneity within AAA samples in the longitudinal axis was explored by analyzing grading the sequential tissue blocks from single patients (n = 4).

Immunohistochemistry (IHC) was performed on randomly chosen subsets of the sample set (n = 72). Details for the IHC protocols, including primary antibodies used ([Apolipoprotein B-100 (ApoB100); n = 5], T-cells [CD4/8; n = 20], B-cells [CD20; n = 20], mature B-cells [CD21; n = 4], macrophages/foam cells [CD68; n = 20], plasma cells [CD138; n = 4], chemotactic signal for B-cells [CXCL13; n = 4], erythrocyte membranes [Glycoporphin-A; n = 5], neutrophils [Myeloperoxidase; n = 20], and mast cells [Tryptase; n = 20]) are provided in Supplementary Protocol 1 and Supplementary Table I (online only).

Tonsil tissue was used as a positive control for inflammatory cells and CXCL13, whereas ApoB100 was validated on liver tissue.

**Statistical analysis.** Analyses were performed with IBM SPSS Statistics 27.0 (Amsterdam, the Netherlands).

Cohen’s kappa coefficients (κ) were used to assess intra-observer repeatability.

Pearson correlation analysis was performed to explore associations between clinical and histological characteristics.

**RESULTS**

Aggregated patient characteristics of the 70 cases included in the analysis, 44 of elective and 26 of acute aneurysm repair, are summarized in Table I. Individual data, and the data for the two excluded cases is provided in Supplementary Table II (online only).

**Application of the existing consensus statements for classifying AAA.** Upon systematic application of the ‘non-inflammatory’ consensus classification scheme (Supplementary Table IIIa), it was concluded that this scheme only partially covers the pathological changes in AAA. More specifically, key aspects, such as mucoid extracellular matrix accumulation; elastic fiber fragmentation, thinning, and disorganization; laminar medial collapse and smooth muscle cell (SMC) disorganization, are either absent in AAA or are not adequately captured by the thresholds defined in the classification. In fact, although TAA is characterized by isolated medial fibrosis, AAA associates with comprehensive elastolysis, more pronounced SMC (nuclei) loss, and transmural fibrosis with full loss of the characteristic three-layered aortic wall structure (see Supplementary Figure 1.1, online only, for illustrations of the contrasts). SMC disorganization was observed in two AAA samples (Supplementary Figure 1.2, online only), which, in retrospect, were from a patient with Marfan syndrome and a patient with multiple aortic branch vessel aneurysms (iliac, femoral, and popliteal) and four second-degree family members with an AAA (Supplementary Table II, online only), suggestive for a non-classic, syndromic AAA variant. On basis of the distinct histological morphology and the clinical information, these samples were excluded from the analysis.

The “inflammatory” consensus classification scheme focused on inflammatory aorta diseases (ie, atherosclerosis, atherosclerosis with excessive inflammation [eg, “inflammatory atherosclerotic aneurysm”] and (peri) aortitis). AAA is not explicitly included as a separate entity, but is brought forward as complication of severe aortitis (“inflammatory atherosclerotic aneurysm”). The working group issued an initial classification scheme focusing on aortitis and peri-aortitis. In contrast to the semi-quantitative “non-inflammatory” consensus classification scheme, this “inflammatory” classification scheme is merely descriptive. Systematic evaluation of this “inflammatory” classification scheme (Supplemental Table IIIb, online only) showed that the initial scheme focusing on peri-aortitis and aortitis incompletely covered the AAA characteristics. To be more specific, although the inflammatory reaction observed in AAA could be subclassified as “mixed inflammatory pattern,” this generic term has limited discriminatory capacity, as it does not cover the profound and extensive remodeling that hallmarks AAA disease.

In the light of a suggested association between AAA and (severe) atherosclerosis in the consensus statement, systematic grading of the atherosclerotic lesions was performed in all 72 AAA samples included in this study. Although the evaluation confirmed presence of isolated atherosclerotic lesions in 97% (n = 68) of the cases, few of the lesions were classified as advanced. In fact, the most advanced lesions present were either classified as early (lipid pools [47%; n = 32]) or intermediate lesions (isolated necrotic cores [51%; n = 35]). Notably, clusters of intermediate/late stage lesions and dominance of stabilized fibrous calcified lesions, as observed in the non-aneurysmal aorta of the elderly controls, were absent in AAA. Clear contrasts were also observed for the spatial organization and distribution of the leukocyte subpopulations in AAA and aortic atherosclerosis (Supplementary Figure 1.3, online only). Consequently, it was concluded that convincing support for an assertion that an AAA is a variant of severe aortic atherosclerosis is lacking.

Based on the inventory, it was concluded that the two consensus classification schemes for aortic pathology fail to adequately appreciate the histopathological aspects and biological diversity of AAA disease.

**Mapping the histological spectrum of end-stage AAA disease.** To adequately appreciate the histopathological variability of AAA disease, we performed an inventory of its (patho)histomorphological characteristics. Aspects
emerging from this evaluation are incorporated in an 11-point semi-quantitative classification system that includes the following aspects: wall thickness, elastolysis, mesenchymal cell loss, fibrosis, neovascularization, adventitial adipogenic degeneration, calcification, lymphoid infiltration, lymphoid follicles, atherosclerotic lesions, and intraluminal thrombus organization. Individual aspects of the grading system are detailed in Table II (classification system), and illustrated in Supplementary Figs 2.1-2.9 (online only) (representative images illustrating the different categories in the classification).

This classification system was applied on the 70 AAA samples, and results are summarized in a heat map (Table III). Excellent (>0.8) Cohen’s kappa coefficients were observed for all histological parameters (see top of Table III).

From the systematic evaluation of the diverse histological aspects of AAA disease, the picture emerges of AAA being characterized by a series of consistent findings (almost complete elastolysis, micro-calcifications), as well as more varying factors (aortic wall thickness, fibrosis/mesenchymal cell loss, inflammation, atherosclerotic lesions, and the extent of neovascularization and intraluminal thrombus [ILT] organization). This histomorphological variability of AAA disease is illustrated in Figs 1-4. The scoring system did not identify specific signatures for ruptured and unruptured AAA samples (Table III).

A notable observation was the diffuse presence of cholesterol crystals at the transition zone of the ILT and the intima. To test whether the atherosclerotic lesions in AAA relate to lipoprotein accumulation or alternatively to erythrocyte membrane-derived cholesterol deposition, ApoB100 (lipoproteins) and Glycophorin-A (erythrocyte membrane) stainings were performed. Atherosclerotic lesions were all ApoB100-positive and Glycophorin-A-negative (Supplemental Figs 3.1 and 3.2, online only).

Specific stainings were also performed for a better characterization of tertiary lymphoid follicle-like structures in the adventitia and the diffuse, unorganized lymphoid infiltrates that were located in the intima, media, or adventitia. Tertiary lymphoid-follicle-like structures were identified on basis of the anatomical features (structures resembling lymph nodes, but that are located in locations that are normally devoid of canonical lymphoid organs, such as the aorta). It was concluded that these diffuse infiltrates mainly represent T-cells, and that the presence of B-cells and plasma cells was limited to the tertiary lymphoid follicle-like structures (Supplementary Fig 4.1, online only). These lymphoid follicles were positive for lymphoid homeostatic factor CXCL13, but negative for B-cell maturation marker CD21 (Supplementary Fig 4.2, online only).

Aspects of the adaptive immune cell signature in AAA disease are illustrated in Supplementary Fig 5 (online only). Macrophage infiltration was observed throughout all vessel walls, including in close proximity of the necrotic cores and within tertiary lymphoid follicle-like structures (Supplementary Fig 5.1, online only). Similarly, neutrophils and mast cells diffusely present throughout all vessel walls (Supplementary Fig 5.2 and 5.3, online only), where they primarily associated with microvessels (inner and medial wall segments) and or tertiary lymphoid follicle-like structures in the adventitial aspect of the aneurysm wall.

Exploration of regional variety within AAA samples from single patients indicated a modest variation in the core features (Supplementary Table IV, online only); the greatest variation was observed for atherosclerotic lesions.
Table II. Eleven-point histomorphological AAA classification

| Histological aspect                  | Scoring | Main results                                                                 | Commentary                                                                                                                                                                                                 |
|--------------------------------------|---------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mesenchymal cell loss, % (pattern)   | 1       | 10-30                                                                        | In 50% of AAA samples, the estimated mesenchymal cell loss exceeded 80%. Cutoffs applied differ from the thresholds of “non-inflammatory” consensus classification because the >30% lower limit of the most advanced group was inadequate to appreciate the differential extent of cell loss in AAA disease. |
|                                      | 2       | 30-80, patchy                                                                 |                                                                                                                                                                                                            |
|                                      | 3       | 30-80, diffuse                                                                |                                                                                                                                                                                                            |
|                                      | 4       | >80, patchy                                                                   |                                                                                                                                                                                                            |
|                                      | 5       | >80, diffuse                                                                  |                                                                                                                                                                                                            |
| Pathological ECM remodeling          |         |                               |                                                                                                                                                                                                            |
| Intimal/medial fibrosis, % (pattern) | 1       | 10-30                                                                        | (Sub) normal aortic wall structure with a clear intima-media border absent in all AAA samples. Fibrosis grading in the “non-inflammatory” classification focuses on a granular fibrotic pattern in the media as seen in TAA and was inadequate to cover the extent and pattern of fibrosis in AAA disease. Moreover, the media is indistinguishable from the intima due to fibrosis. Therefore, cutoffs were adapted and applied to the intimal-medial zones collectively. |
|                                      | 2       | 30-80, patchy                                                                 |                                                                                                                                                                                                            |
|                                      | 3       | 30-80, diffuse                                                                |                                                                                                                                                                                                            |
|                                      | 4       | >80, patchy                                                                   |                                                                                                                                                                                                            |
|                                      | 5       | >80, diffuse                                                                  |                                                                                                                                                                                                            |
| Elastin                              | 1       | Remnants of elastin visible                                                   | All AAA samples were characterized by extreme elastolysis. If present, elastin was only observed as patchy remnants.                                                                                                                                                  |
|                                      | 2       | No elastin visible                                                            |                                                                                                                                                                                                            |
| Aorta wall thickness, mm             | Q4      | 1.49-3.05                                                                    | No clear association between wall thickness and rupture. Included as a more quantitative matrix aspect, whereas mesenchymal cell loss and pathological ECM remodeling essentially capture qualitative AAA matrix aspects.                                                                 |
|                                      | Q3      | 1.10-1.48                                                                    |                                                                                                                                                                                                            |
|                                      | Q2      | 0.80-1.09                                                                    |                                                                                                                                                                                                            |
|                                      | Q1      | 0.41-0.79                                                                    |                                                                                                                                                                                                            |

Inflammation
| Table II. Continued. | | | |
|---|---|---|---|
| A. Transmural lymphoid infiltrates | Scoring | Main results | Commentary |
| | 0 | Low number of perivascular lymphocytes | Transmural unorganized infiltrations and lymphoid follicles were concurrently present in the majority (65%) of AAA. Follicles were mainly (65%) early TLO-like structures. T-cells were distributed transmurally, while B-cells were primarily located in adventitial lymphoid follicles (Supplementary Fig 7.1, online only). Indications were found for gross B-cell immaturity in TLO-like structures (Supplementary Fig 7.2, online only). |
| | 1 | Small unorganized lymphoid infiltrates | |
| | 2 | Large unorganized lymphoid infiltrates | |
| B. TLO-like structures in adventitia | Scoring | Main results | Commentary |
| | 0 | No lymphoid follicles | |
| | 1 | Early TLO-like structure | |
| | 2 | Late developed TLO-like structure | |
| Neovascularization | Scoring | Main results | Commentary |
| | 0 | Into part 1 | Neovascularization up to the ILT was observed. |
| | 1 | Into part 2 | |
| | 2 | Into part 3 | |
| | 3 | Into part 4 | |
| Atherosclerotic lesions | Scoring | Main results | Commentary |
| | 0 | None visible | Atherosclerotic lesions were present in 97% of AAA samples, of which mainly foam cells/lipid pools (46%) and necrotic cores (50%). Although the location and morphologic characteristics of some necrotic cores differed from classic aortic atherosclerotic lesions (Supplementary 6, online only), lesion characteristics could well be graded on basis of morphologic aspects of the Virmani classification (Supplementary Fig 5.4, online only). |
| Table II. Continued. | Histological aspect | Scoring | Main results | Commentary |
|----------------------|--------------------|---------|--------------|------------|
|                      | 1 Foam cells/lipid pool(s) directly under ILT |         |              |            |
|                      | 2 Foam cells/lipid pool(s) not directly under ILT |         |              |            |
|                      | 3 Necrotic core deeply embedded in aortic wall, without classic overlying fibrous cap |         |              |            |
|                      | 4 Superficial necrotic core, resembling classic atherosclerotic lesion |         |              |            |
|                      | 5 Calcified sheet, of so-called stabilized, fibrous calcified lesions |         |              |            |
| ILT organization     | 0 No ILT | Reorganizing ILTs were present in 28% of the AAA samples were and the majority of ILTs were organized (53%). | An adherent ILT is a common aspect in AAA, often with cholesterol crystals at the level of intimai border zone and different degrees of reorganization/maturation. | |
|                      | 1 Fibrin and/or cholesterol rich ILT, clearly delineated from intima |         |              |            |
|                      | 2 Reorganizing ILT: incorporation into intima (fading of clear demarcation zone between aneurysm wall and thrombus, including regions of intramural hemorrhage (s), no immune cell infiltration in ILT |         |              |            |
|                      | 3 Reorganizing ILT: incorporation into intima, immune cell infiltration in ILT |         |              |            |
|                      | 4 Organized: matrix deposition and spindle shaped cell (mesenchymal cells) ingrowth in ILT, with (out) calcifications |         |              |            |
Associations between clinical and discriminative histological parameters (viz. elastolysis, adipogenic adventitial degeneration, and microcalciﬁcations were excluded) were explored by univariate Pearson correlation analysis (Supplementary Table V, online only). An inverse, robust association was found between aortic wall diameter and aortic wall thickness ($R = 0.40; P < .05$).

**DISCUSSION**

Although the consensus classiﬁcation schemes for aortic diseases prove highly instrumental for classifying TAA, it is concluded that the existing schemes fail to adequately cover the histological aspects of AAA disease. Therefore, a novel classiﬁcation scheme is proposed to cover the unique characteristics and histological variability of AAA disease. Systematic application of this scheme highlighted extensive vascular remodeling as the universal core feature, but also pointed to an under-appreciated heterogeneity for other key aspects (eg, inﬂammation, aspects of atherosclerosis, and ILT reorganization). No contrasts were observed between stable and ruptured AAA.

The issued histological consensus classiﬁcation schemes for, respectively, inﬂammatory and non-inﬂammatory (degenerative) ascending aortic pathology are developed as standardized grading systems for aortic pathology. Given the parallels between TAA and AAA disease, we speculated that these classiﬁcation systems could also be applied to AAA. However, following a systematic evaluation, it was concluded that aspects such as the profound transmural remodeling with extreme ﬁbrosis and elastolysis, extensive mesenchymal cell loss, and completely distorted aortic wall structure in AAA disease are not adequately covered by the “non-inﬂammatory” classiﬁcation scheme.

AAAs are not included as a distinct entity in the “inﬂammatory” consensus scheme, although specific reference is made to “inﬂammatory aneurysms;” a type of aortic aneurysm that is clinically distinct from AAA, and that is characterized by wall thickening ($>4$ mm), extensive ﬁbrosis, and extensive adhesions. The consensus scheme does refer to AAA as a complication of aortic atherosclerotic disease. A critical question is whether...
Table III. Visual representation (heat map) of histopathological heterogeneity of end-stage AAA disease

| Patient No. | Fibrosis in intima/media zone (<0.80) | Mesenchymal cell loss in intima/media zone (<0.87) | Inflammation-transmural lymphoid infiltration (<0.88) | Inflammation-lymphoid follicles in adventitia (<0.93) | Atherosclerotic lesions (<0.89) | Wall thickness (intima + media) (<0.93) | Extent of neovessel formation (<0.92) | Intraluminal thrombus organization (<0.88) | Calcification (<0.99) | Elastic fiber degradation (<0.80) | Adventitial adipogenic degeneration (<1.0) |
|-------------|--------------------------------------|--------------------------------------------|---------------------------------------------|-----------------------------------------------|--------------------------------|-----------------------------|-------------------------------|------------------------------------------|------------------|-------------------------------|-------------------------------------|
| Elective    |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 1           |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 2           |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
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| 45          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| Acute-ruptured |                                  |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 46          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
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| 55          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 56          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 57          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 58          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 59          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 60          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 61          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 62          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 63          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 64          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 65          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 66          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 67          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
| 68          |                                      |                                            |                                             |                                               |                                |                             |                               |                                           |                  |                               |                                     |
that these clefts reflect a cholesterol flux from membrane remnants of erythrocytes that caught in the thrombus. Erythrocyte membrane remnants have been recognized as a dominant cholesterol source in coronary atherosclerosis, and it was reasoned that such a mechanism could drive atherosclerotic lesion formation in AAA. ApoB100 and Glycophorin-A staining was performed to respectively discriminate between lipoprotein or erythrocyte membrane-driven atherosclerotic lesion formation in AAA disease. Consistent ApoB100 positivity but Glycophorin-A negativity suggests that the cholesterol fluxes in atherosclerotic lesions in AAA are essentially lipoprotein-driven.

Aspects of inflammation are obviously a core aspect of the "inflammatory" consensus scheme. In the consensus scheme, inflammation is grossly divided into two main categories: atherosclerosis (including inflammatory [atherosclerotic] aneurysms), and noninfectious and infectious (peri)arthritis. The question arises whether AAA aligns with one of the two main categories. The inflammatory signature of AAA is clearly distinct from atherosclerotic disease. For example, abundant adventitial follicles, a key histological feature of AAA disease, are rare in the context of atherosclerotic disease and in fact only, transiently, present in direct association with a thin cap or instable lesion type. Moreover, although immune aspects are clearly present in the AAA wall, absence of systemic involvement and the extensive vascular remodeling classify AAA as an entity that is clearly distinct from (peri)arthritis included in the consensus classification.

Because the "non-inflammatory" and "inflammatory" consensus classifications fail to cover the characteristics of AAA disease, a novel and unique AAA-specific classification scheme was devised based on a systematic histological inventory of 72 AAA samples. This first inventory resulted in an 11-point classification scheme that covers diverse histomorphological key aspects of AAA, some of which had been brought forward earlier as a histological characteristic of AAA disease. The inventory identified the extensive matrix remodeling (near) complete loss of elastin, transmural fibrosis, and loss of the distinct boundaries between the three structural layers of the aorta) as the universal core features of AAA disease. In fact, re-evaluation of the patient records of two cases that presented with mild vascular remodeling implied that these aneurysms were not classical AAAs, but that they were part of a general dilating vascular disease (respectively, Marfan disease and an unknown familial trait). The pattern of matrix

### Table III. Continued.

| Patient No. | Acute-symptomatic | Mesenchymal cell loss in intima/media zone (≤ 0.80) | Inflammation-transmural lymphoid infiltration (≤ 0.88) | Inflammation-lymphoid follicles in adventitia (≤ 0.93) | Atherosclerotic lesions (≤ 0.89) | Wall thickness (intima-media) | Extent of neovessel formation (≤ 0.92) | Intraluminal thrombus organization (≤ 0.88) | Calcification (≤ 0.99) | Elastic-fiber degradation (≤ 0.80) | Adventitial adipogenic degeneration (≤ 1.0) |
|-------------|-------------------|---------------------------------------------------|------------------------------------------------------|-----------------------------------------------------|---------------------------------|-----------------------------|-------------------------------------|---------------------------------|-----------------------------|----------------------------------|
| 69          |                   | [fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl][fl]}
remodeling observed clearly differentiates AAA from TAA disease, which associates with a more localized, mucoid (glycoprotein rich) matrix remodeling and focal elastolysis.

Further histological aspects of AAA disease include scattered micro-calci
cfactions throughout the former intima and media and extensive neovascularization. Macro-calci
cfactions were less commonly observed, and predominantly associated with (remodeled) necrotic cores from (previous) atherosclerotic lesions.

Extensive neovascularization with vessels mainly originating from the medio-adventitial border and extending up into the ILT has been attributed to wall hypoxia caused by the luminal thrombus. Despite the attractiveness of this hypothesis, it could be argued that direct oxygen exchange through the aortic wall and the blood passing through the aorta is minimal due to absent erythrocyte-endothelium interaction and the high aortic flow, and that the aortic wall oxygen supply essentially relies on the vasa vasora network. Alternatively, it has been speculated that the abundant neovascularization in AAA disease may relate to abundance of proangiogenic signals such as HIF1a, VEGF, and CXCL8.

Common, albeit not universal, observations for AAA were adventitial adipogenic degeneration, a process thought to reflect dysregulated mesenchymal cell differentiation and remodeling of the intraluminal thrombus. Although adhering thrombus is grossly removed during surgery, remnants of adhering thrombus were present in the majority of the samples. Movat stainings revealed different grades of remodeling, with ingrowth of the wall (mesenchymal cell influx, matrix deposition, and angiogenesis) in the abluminal thrombus in a subset of samples.

More variable aspects included the presence of scattered atherosclerotic lesions (see above), and presence of lymphocytic infiltrates and tertiary lymphoid-like structures. Lymphocytic infiltrates, diffusely distributed throughout all vascular wall layers, mainly consisted of T-cells and generally presented in close proximity of microvessels. Tertiary lymphoid-like structures presented as a garland of follicles located at the former medial-adventitial border zone. These structures were dominated by B- and T-cells, and associated with CXCL13 expression, a chemokine critically involved in organizing B-cell follicles and germinal center formation. Similar to tertiary lymphoid-like structures observed in atherosclerosis, full lymphoid maturation was missing: most lymphoid structures lacked the characteristic germinal centers (H&E staining), and lymphoid B-cells were all negative for the maturation marker CD21. Moreover, it was observed that the plasma cells located non-classically in the peripheral niches of the tertiary lymphoid-like structures rather than central in the germinal center core.
Although systematic application of this first AAA classification system indicates a number of universal features for AAA, considerable variation was observed for other aspects (e.g., inflammation, atherosclerotic lesions, and ILT organization). This apparent biological variation has potential implications for AAA research, with the need for robust group sizes in order to adequately cover the biological variability. The value of the scoring system is illustrated by two cases from the biobank that did not align with the classification.

Limitations. The scheme is a first approach to generate a general multiparameter histopathological classification system for AAA disease. As such, the classification system may not fully encompass all aspects of the AAA disease spectrum. For example, due to the absence of protocolized size estimations and an accompanying large measurement variability, we refrained from including growth data as parameter. A further limitation is the lack of wall samples of AAA smaller than 50 mm. Also, the interpretation of atherosclerotic lesions in AAA sections is hampered by the shielding of the ILT, which may interfere with the natural history of atherosclerotic disease progression (such as interference with the intimal luminal blood interaction). Wall samples in this analysis were randomly chosen from an existing tissue bank. No stratification for specific factors such as age, sex, or comorbidities was performed. Although associations were found between the histological classification system components and clinical parameters, the power of this study was too low for regression analysis. As such, it is unclear whether the observed associations are covariants or causative. Finally, the proposed classification system should be considered as a “work in progress,” with room for future adaptations and/or extensions such as extension to smaller AAA and/or inclusion of aspects of the ILT, an aspect that could not be fully addressed in this study.

AUTHOR CONTRIBUTIONS
Conception and design: LB, JH, JL
Analysis and interpretation: LB, JC, JG, RL, LM, DW, BX, DY, JL
Data collection: LB, CG, CR, PV, JL
Writing the article: LB, JL
Critical revision of the article: LB, CG, JC, JG, JL, GJ, RL, LM, CR, PV, DW, BX, DY, JL
Final approval of the article: LB, CG, JC, JG, JL, GJ, RL, LM, CR, PV, DW, BX, DY, JL
Statistical analysis: LB, CG
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Overall responsibility: JL
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