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Systematic Review of Circulating, Biomechanical, and Genetic Markers for the Prediction of Abdominal Aortic Aneurysm Growth and Rupture

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***Background*—**The natural course of abdominal aortic aneurysms (AAA) is growth and rupture if left untreated. Numerous markers have been investigated; however, none are broadly acknowledged. Our aim was to identify potential prognostic markers for AAA growth and rupture.

***Methods and Results*—**Potential circulating, biomechanical, and genetic markers were studied. A comprehensive search was conducted in PubMed, Embase, and Cochrane Library in February 2017, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Study selection, data extraction, and methodological quality assessment were conducted by 2 independent researchers. Plausibility of markers was based on the amount of publications regarding the marker (more than 3), pooled sample size (more than 100), bias risk and statistical significance of the studies. Eighty-two studies were included, which examined circulating (n=40), biomechanical (n=27), and genetic markers (n=7) and combinations of markers (n=8). Factors with an increased expansion risk included: AAA diameter (9 studies; n=1938; low bias risk), chlamydophila pneumonia (4 studies; n=311; medium bias risk), S-elastin peptides (3 studies; n=205; medium bias risk), fluorodeoxyglucose uptake (3 studies; n=104; medium bias risk), and intraluminal thrombus size (5 studies; n=758; medium bias risk). Factors with an increased rupture risk rupture included: peak wall stress (9 studies; n=579; medium bias risk) and AAA diameter (8 studies; n=354; medium bias risk). No meta-analysis was conducted because of clinical and methodological heterogeneity.

***Conclusions*—**We identified 5 potential markers with a prognostic value for AAA growth and 2 for rupture. While interpreting these data, one must realize that conclusions are based on small sample sizes and clinical and methodological heterogeneity. Prospective and methodological consonant studies are strongly urged to further study these potential markers. **(*J Am Heart Assoc*. 2018;7:e007791. DOI: 10.1161/JAHA.117.007791.)**

Key Words: abdominal aortic aneurysm • biomechanical marker • circulating biomarker • genetic marker • growth • rupture

The natural course of an abdominal aortic aneurysm (AAA) is a steady increase of the diameter, and eventually, if left untreated, the aneurysm might rupture.[1] In most cases of AAA, this pathophysiological process remains asymptomatic until rupture. Such an event can be prevented by surgical AAA repair. The decision to perform surgery is commonly based on 3 characteristics being the: (1) maximum AAA diameter exceeding 5.0 cm in women and 5.5 cm in men; (2) experience of symptoms; or (3) aneurysm growth rate exceeds 1 cm/year.[2,3] The first 2 characteristics are relatively easy to identify by imaging or by questioning the patient. However, AAA growth rate can only be considered retrospectively, because a prognostic value for expansion has not yet been acknowledged.

In the current AAA management, no marker for aneurysm progression or rupture has been implemented as common practice. This might be explained by little existing evidence and lack of experience with prognostic markers. Although numerous potential markers of aneurysm growth and rupture have been examined, a systematic review with a detailed and structured evaluation of markers for AAA expansion and rupture is lacking.

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An accompanying Data S1 is available at http://jaha.ahajournals.org/content/7/13/e007791/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In the management of abdominal aortic aneurysm (AAA) disease, the use of prognostic parameters is still limited to current AAA diameter and growth speed.
- In this article, we have systematically reviewed the literature for prognostic markers of aneurysm growth and rupture. In addition to AAA diameter, also chlamydophila pneumonia, S-elastin peptides, 18F-fluorodeoxyglucose uptake, and intraluminal thrombus have potential to predict AAA expansion.
- Peak wall stress measurement in AAA and S-elastin peptides appear useful tools for predicting aneurysm rupture, along with AAA diameter.

What Are the Clinical Implications?

- Because of heterogeneity in threshold values, the aforementioned markers are not yet ready for clinical use, although intraluminal thrombus and peak wall stress appear closest to clinical application.
- The current article provides insight into multiple promising markers that can help predict aneurysm growth and rupture in patients with AAA.

The aim of this systematic review was to identify promising markers of aneurysm expansion and rupture to aid clinicians in AAA management. We searched for retro- and prospective observational studies in which the prognostic value of circulating bloodmarkers, biomechanical properties, and genetic variations for AAA expansion or rupture are investigated.

Methods

The data, analytical methods, and study materials will be available from the corresponding author upon reasonable request for purposes of reproducing the results.

Search Strategy

A comprehensive search was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[4] Separate searches were performed in PubMed, Embase, and Cochrane Library on February 27, 2017 exploring: circulating, biomechanical, and genetic markers. The search strategies can be found in Data S1. Study titles and abstracts were screened, and full texts were examined when a study appeared to fulfill the inclusion criteria. In addition, reference lists were searched to identify potentially missing studies.

Study Selection and Data Extraction

Studies were independently selected by 2 reviewers, and differences in selected studies were discussed. In case of disagreement during the selection process, a third author would make the final decision.

Studies examining markers for a correlation with AAA expansion or rupture were included. No limits were placed on year of publication. Inclusion was limited to studies published in English and full publications. No attempt was performed to search for "gray literature." Case reports, reviews, animal studies, and studies regarding inflammatory AAA were excluded.

Data extraction was performed independently by 2 reviewers and merged by consensus. Using data extraction forms, the following data were extracted: study population (sex, age), sample size, results reported either as Pearson or Spearman correlations, area under curve, odds ratio, fold increase/decrease, means or medians alongside a measure of variance (eg, range, interquartile range, and SDs), and statistical significance (*P* values).

Quality Appraisal of Individual Studies

Risk of bias was assessed using guidelines provided by Hayden et al for evaluating the quality of prognosis studies in systematic reviews.[5] Accordingly, 6 potential bias items were addressed: (1) study participation; (2) study attrition; (3) prognostic factor measurement; (4) outcome measurement; (5) measurement and account of confounders; and (6) analysis methods. Every item has 3 to 7 questions; per item, an equal amount of points were attributed, resulting in a total percentile score of bias items excluded. We classified studies as low risk (75% or more bias items excluded), intermediate risk (50–75% bias items excluded), or high risk of bias (less than 50% of bias items excluded). Risk of bias is presented and studies are sorted accordingly.

Statistical Analysis

Reported outcomes of studies include correlation coefficients, statistical significance, sample size, and quality appraisal. The principal measure reported for each study was the correlation between the given biomarkers (ie, circulating, biomechanical, or genetic) and a presented outcome change with growth or rupture of AAA. Factors that pose an increased risk of growth or rupture were considered plausible if it was: (1) demonstrated to be a marker in 3 or more publications and these publications demonstrated consistent results; (2) a pooled sample size of more than 100 patients; (3) demostrated as a low risk of bias in at least one third of the studies; and (4) statistically significant in two thirds of the studies.

In consensus, the authors concluded that a meta-analysis could not be performed because of clinical and methodological heterogeneity, which is consistent with current thought.[6] Additionally, a meta-analysis of correlation coefficients is only considered to be reliable if more than 30 studies are able to be pooled for the same outcome.[7] In the present review, a maximum of 9 studies were able to be identified per marker.

Results

Search Results

The searches resulted in 760 studies (Figure), of which 605 were excluded based on title or abstract (no AAA [n=352]; no biomarker of growth or rupture [n=141]; case report, comment or oral presentation only [n=34]; not English [n=37]; not human [n=9]; or other [n=32]). Consequently, 155 articles were retrieved for full-text evaluation, of which 73 were excluded (no biomarker of growth or rupture [n=54]; review [n=14], no AAA [n=4]; or inflammatory AAA [n=1]). A total of 82 articles were included: 40 studies concerned circulating biomarkers; 27 studies concerned biomechanical markers; 7 studies concerned genetic markers; and 8 studies described a circulating biomarker together with a biomechanical or a genetic marker.

Circulating Biomarkers

In 48 studies, 63 circulating biomarkers were investigated (Table 1). Most investigated circulating markers are part of the immune response (18 markers); then the coagulation cascade (14 markers); connective tissue turnover (12 markers); and lipids (9 markers). Remaining categories concerned smoking, kidney function, hormones, and others. The following focuses on markers described in 3 or more publications.

Aminoterminal Propeptide of Type III Procollagen

A significant correlation with expansion was found in 1 study (r=0.24), in which 99 follow-up patients were included.[8] The quality appraisal attributed this study with medium bias risk. In 2 studies (1 medium and 1 high bias risk) no correlation was found in 91 follow-up patients in total.[9,10] However, Satta et al did reach significance after 2 years of follow-up.[9]

Chlamydophila Pneumoniae

In 4 studies, chlamydophila pneumoniae was investigated as a marker for expansion[11–14] and in 2 as a marker for rupture.[15,16] In none of the patients was an inflammatory AAA suspected. All studies on expansion had significant outcomes. Lindholt et al demonstrated in 2 separate studies (total patients n=194) that AAA expansion rate was faster in patients with a higher immunoglobulin A titer. Falkensammer et al found the same results for seropositive versus seronegative patients. In a third separate publication, Lindholt et al demonstrated a significant correlation (r=0.29) with expansion in 70 follow-up patients. Nyberg et al found no difference in seropositivity between ruptured AAA patients and controls.[15] A second study of Nyberg et al on the same cohort demonstrated that AAA patients had no increased risk of rupture as compared with controls when these patients were also seropositive for Helicobacter Pylori, Herpes Simplex, or Cytomegalovirus.[16] Overall, the quality of studies was intermediate: 4 had medium risk, 1 had low risk, and 1 had high risk of bias.

Complement Reactive Protein

Complement reactive protein was examined as marker for expansion in 5 studies[17–21] and in 2 as marker for rupture.[22,23] De Haro et al and Wiernicki et al were the only groups to demonstrate significant correlations with expansion. De Haro et al included 260 patients, had a low risk of bias, and measured a strong correlation (r=0.71; P<0.05). According to Norman and Flondell-Sité et al, who included 723 patients in total and were both qualified as low risk of bias, complement reactive protein levels did not differ between follow-up patients with high versus low expansion rate. Speelman et al also found no correlation, but included only 18 follow-up patients and had a medium risk of bias. Domanovits et al measured higher complement reactive protein levels in patients presenting with a ruptured AAA than in patients preceding elective repair (low risk of bias and total n=225). Tambyraja et al, also with a low bias risk, measured 4 times higher complement reactive protein levels in symptomatic patients than in asymptomatic patients (total n=112).

Cotinine

Cotinine was examined in 3 studies as marker for AAA expansion. Wilmink et al,[24] whose study was appraised with a medium bias risk, followed 447 AAA patients and found no difference in cotinine levels between follow-up patients with an expanding AAA (growth >2 mm per year) versus a stable AAA. Lindholt et al demonstrated significant correlations (r=0.23 and r=0.24) in 2 separate studies[13,25] (low and medium bias risks), after including 149 follow-up patients in total from the same screening program.

D-Dimer

The association between D-dimer and expansion was demonstrated by Golledge et al (r=0.39; n=299).[26] In 2 studies, an increased D-dimer level was found in patients suffering from AAA rupture (total n=139).[27,28] All studies had a low risk of bias.

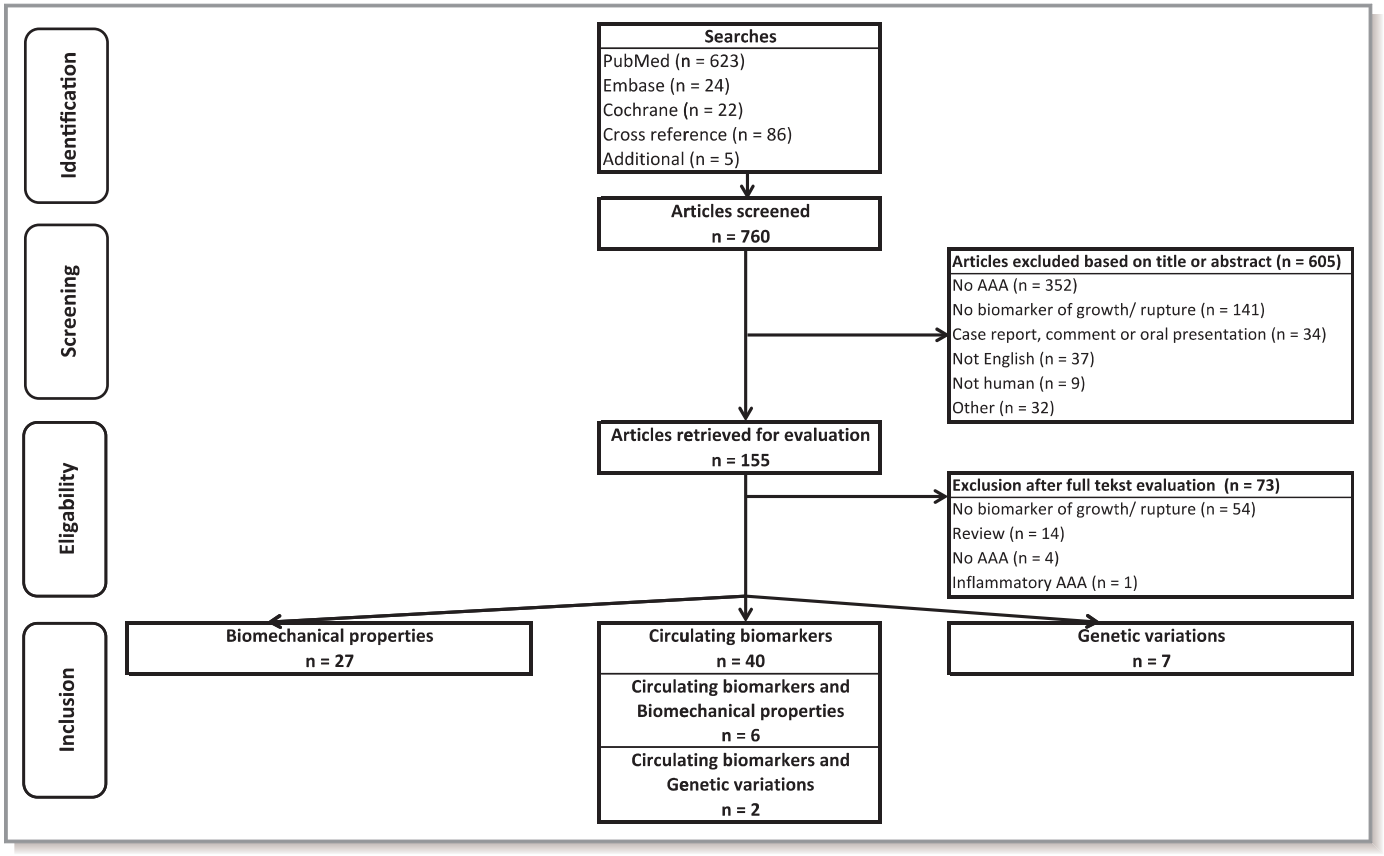

Figure. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the literature search. AAA indicates abdominal aortic aneurysm.

Fibrinogen

Levels of fibrinogen were measured in ruptured AAA patients versus symptomatic and asymptomatic patients. All studies had a low risk of bias. In 2 studies, fibrinogen was lower in ruptured than in nonruptured patients (total n=269),[22,27] whereas Tambyraja et al measured higher levels in 12 symptomatic than in 39 asymptomatic AAA patients.[23]

Homocysteine

Homocysteine and AAA expansion were investigated in 3 studies, all with a low risk of bias. Halazun et al[29] were the only group to describe a significant correlation (r=0.28; n=108). The other 2 studies observed no association between homocysteine and AAA expansion (total n=248).[13,21]

Interleukin-6

Interleukin-6 and AAA expansion were examined in 3 studies, but none observed a significant association.[21,30,31] Jones et al found no correlation in 466 follow-up patients (low bias risk). Flondell-Sité et al (low bias risk) observed no difference in interleukin-6 between 178 high- versus low-expansion-rate AAA patients. Treska et al (high bias risk) included 90 patients and demonstrated no difference between patients who required surgery during follow-up versus asymptomatic patients.

Matrix Metalloproteinase 9

In 3 studies, circulating matrix metalloproteinase 9 was tested as a marker for expansion. Flondell-Sité et al, the largest study with the lowest risk of bias, found no correlation with AAA expansion in 163 follow-up patients.[32] In 2 smaller studies (medium bias risk), with 54 patients in total, significant correlations were described (r=0.32 and r=0.33).[10,33] Wilson et al (medium bias risk) demonstrated higher matrix metalloproteinase 9 levels in patients with a ruptured AAA than in patients preceding elective repair.[34]

Plasminogen Activator Inhibitor 1

Lindholt et al observed a significant, but weak, correlation between plasminogen activator inhibitor 1 (PAI-1) and AAA expansion (r=0.02; n=70; low bias risk).[13] In 3 studies (total

Table 1. Circulating Biomarkers That Have Been Investigated for an Association With AAA Expansion or Rupture

Marker	Total Studies (n)	Significant Outcome	Total Patients (n)
Coagulation			
Activated protein C—protein C inhibitor[32]	1	0 of 1 studies	163
Activated prothrombin time (APTT)[27]	1	1 of 1 studies	44
D-dimer (see Table 4)[26–28]	3	3 of 3 studies	438
Factor XII[40]	1	1 of 1 studies	48
Fibrinogen (see Table 4)[22,23,27]	3	3 of 3 studies	381
Plasmingon activator inhibitor 1 (PAI-1; see Table 4)[13,27,28,35]	4	4 of 4 studies	304
Plasmin-antiplasmin-complex[36]	1	1 of 1 studies	70
Platelets[27]	1	0 of 1 studies	44
Prothrombin time[27]	1	0 of 1 studies	44
Prothrombin fragment 1+2[27]	1	1 of 1 studies	44
Serpine-1[32]	1	0 of 1 studies	163
Tissue plasminogen activator (tPA; see Table 4)[13,27,28,35]	4	4 of 4 studies	304
tPA serpine-1[32]	1	0 of 1 studies	163
Urokinase-like PA[13]	1	0 of 1 studies	70
Connective tissue			
Aminoterminal propeptide of type III procollagen (see Table 4)[9,10,12]	3	1 of 3 studies	190
Carboxyterminal propeptide of type 1 procollagen[41]	1	0 of 1 studies	86
Elastase[25]	1	1 of 1 studies	79
Matrix metalloproteinase 1 (MMP-1)[34]	1	1 of 1 studies	68
MMP-2[32,34]	2	0 of 2 studies	231
MMP-3[34]	1	0 of 1 studies	68
MMP-9 (see Table 4)[10,18,32,34]	4	3 of 4 studies	285
S-elastin peptides (see Table 4)[8,10,36–38]	5	5 of 5 studies	365
Transforming growth factor beta-1[13]	1	0 of 1 studies	70
Tissue inhibtor metalloproteinase-1 (TIMP-1; see Table 4)[18,32,34]	3	0 of 3 studies	249
α-1 antitrypsine[10,18,39,40] (see Table 4)	4	2 of 4 studies	127
α-1 antitrypsine, Factor XII, D-dimer, and IgG[40]	1	0 of 1 studies	48
Lipids			
Albumin[23]	1	1 of 1 studies	51
Apolipoprotein A1[42]	1	1 of 1 studies	180
Apolipoprotein B[42]	1	1 of 1 studies	180
Cholesterol[42,59]	2	0 of 2 studies	295
Glycosylphosphatidylinositol phospholipase D[43]	1	1 of 1 studies	133
High-density lipoprotein[21,59]	2	0 of 2 studies	295
Low-density lipoprotein[59]	1	0 of 1 studies	117
Lipoprotein A[42]	1	0 of 1 studies	180
Triglyceride[42,59]	2	2 of 2 studies	297
Immune response system			
Chlamydophila pneumoniae (see Table 4)[11–16]	6	4 of 6 studies	465
CRP (see Table 4)[17–23]	7	4 of 7 studies	1421
Cytomegalovirus[44]	1	0 of 1 studies	119
Helicobacter pylori[45]	1	0 of 1 studies	119
Herpes simplex 1[16]	1	0 of 1 studies	119
Interleukin-1ß[30]	1	0 of 1 studies	90
Interleukin-2[30]	1	0 of 1 studies	90
Interleukin-6 (see Table 4)[21,30,31]	3	0 of 3 studies	734
Interleukin-8[30]	1	1 of 1 studies	90
Interferon gamma[95]	1	1 of 1 studies	50
Leukocytes[22]	1	1 of 1 studies	225
Macrophage inhibiting factor[13,47]	2	1 of 2 studies	168
Neutrophil gelastinase-associated lipocalin[48]	1	1 of 1 studies	40
Osteopontin[84]	1	1 of 1 studies	198
Osteoprotegerin[49]	1	1 of 1 studies	146
Peroxiredoxin[50]	1	1 of 1 studies	80
Tumor necrosis factor-α[21,30]	2	1 of 2 studies	268
Tumor necrosis factor–like weak inducer of apoptosis[51]	1	1 of 1 studies	43
Smoking			
Cotinine (see Table 4)[13,24,25]	3	2 of 3 studies	596
Smoking[25]	1	1 of 1 studies	79
Kidney function			
Creatinine[21,52]	2	2 of 2 studies	274
Cystatine C[52,53]	2	2 of 2 studies	238

Continued

Continued

Table 1. Continued

Marker	Total Studies (n)	Significant Outcome	Total Patients (n)
Hormones			
Endothelin-1,2[54]	1	0 of 1 studies	65
Endothelin-1[21]	1	0 of 1 studies	178
Insulin-like growth factor 1[55]	1	1 of 1 studies	115
Insulin-like growth factor 2[55]	1	0 of 1 studies	115
Others			
Forced expiratory volume in 1 sec[25]	1	0 of 1 studies	79
Homocysteine (see Table 4)[13,21,29]	3	1 of 3 studies	356

Markers are categorized by its (patho)physiological system. Per marker, the amount of included studies with significant outcomes are shown, as well as the total number of patients in studies pooled. AAA indicates abdominal aortic aneurysm.

n=234; 1 medium risk of bias, 2 low risk), ≈4-fold higher levels of PAI-1 were found in patients with a ruptured AAA than in nonruptured AAA patients.[27,28,35]

S-Elastin Peptides

In 3 studies, S-elastin peptides (SEP) was investigated as a marker for expansion[8,10,36] and 2 as a marker for rupture.[37,38] Lindholt et al performed 3 different studies, including 205 follow-up patients in total, all demonstrating significant correlations with expansion (r=0.51 [medium bias risk], r=0.33 [medium bias risk], and r=0.31 [low bias risk]). In 100 AAA patients with a rupture during follow-up, SEP had a significantly predictive value (area under curve=0.68; medium bias risk).[37] Petersen et al, appraised with a low risk of bias, found a significant difference between 15 patients with a ruptured AAA versus 45 patients preceding elective repair.[38] Note that 1 research group, using patients from the same AAA screening cohort, performed 4 of 5 studies. The degree of patient overlap between studies, if any, is not clear.

Tissue Inhibitor Metalloproteinase 1

Speelman et al[18] (n=18) and Flondell-Sité et al[32] (n=163) investigated tissue inhibitor metalloproteinase 1 as marker for expansion. Their studies had, respectively, low and medium bias risk. Wilson et al[34] (medium bias risk) examined tissue inhibitor metalloproteinase 1 as marker for rupture in 68 patients. None found significant outcomes.

Tissue Plasminogen Activator

Lindholt et al demonstrated a significant correlation between circulating tissue plasminogen activator and AAA expansion (r=0.37; n=70; low bias risk).[13] Remarkably, Adam et al and Hobbs et al measured lower levels of tissue plasminogen activator in patients with a ruptured AAA versus nonruptured (total n=139; low and medium risk of bias, respectively),[27,35] whereas Skagius et al observed 1.7-fold higher levels in 50 ruptured AAA patients than in 45 electively treated AAA (low bias risk).[28]

α-1 Antitrypsine

Significant correlations with expansion were found in 2 studies (1 low and 1 medium bias risk; r=0.55 and r=0.42) with 61 follow-up patients in total,[10,39] whereas 2 studies (1 low and 1 medium bias risk) could not reproduce such significant correlations in 66 follow-up patients.[18,40] Pulinx et al, however, did reach significance when initial AAA diameter was included in their multivariate model.[40]

Other included biomarkers that have not been mentioned above are markers in the field of connective tissue,[41] lipids,[42,43] the immune system,[44–51] kidney function,[52,53] and hormones[54,55] (see Table 1).

Biomechanical Markers

A total of 33 studies investigated 28 biomechanical AAA properties as a marker for expansion or rupture (Table 2). Markers were categorized as anatomic properties (13 markers), radiographic properties (3 markers), or as vessel wall properties (9 markers). The fourth category contains 3 software-calculated predictive indices. The following focuses on markers described in 3 or more publications.

AAA Diameter

In 9 studies, AAA diameter was described as a marker for expansion[8,17,19,21,40,56–59] and in 9 as a marker for rupture.[34,37,60–66] Overall, the data are reliable because 2570 patients in total were included and 8 studies were appraised with low bias risk, 7 with medium risk, and only 3 with high risk. In 7 studies, significant correlations with expansion were demonstrated in 958 patients in total (r=0.30–0.83),[8,21,40,56–58] and Norman et al measured faster growth in patients with a large (≥4 cm; n=112) versus small AAA (3–4 cm; n=433).[19] In 6 studies, with a total of 552 patients, significant outcomes were demonstrated for AAA diameter as a marker for rupture. In 5 studies, larger diameters were measured in ruptured (and symptomatic) AAA when compared with asymptomatic patients,[34,60,61,64,65] and 1 study

Table 2. Biomechanical Markers That Have Been Investigated for an Association With AAA Expansion or Rupture

Marker	Total Studies (n)	Significant Outcome	Total Patients (n)
Anatomical properties			
AAA diameter[8,17,19,21,34,37,40,56–66]	18	15 of 18 studies	2570
AAA expansion[76,77]	2	1 of 2 studies	1125
AAA surface area[76]	1	0 of 1 studies	52
AAA volume[71]	1	1 of 1 studies	34
Aortic diameter asymmetry[78]	1	1 of 1 studies	200
Aortic tortuosity[78]	1	1 of 1 studies	200
ILT area[57,76]	2	2 of 2 studies	469
ILT circumference[78]	1	0 of 1 studies	200
ILT location[79]	1	1 of 1 studies	34
ILT thickness[71,78]	2	1 of 2 studies	234
ILT volume[33,60,71]	3	3 of 3 studies	139
Lumbar 3 vertebral body diameter[78]	1	1 of 1 studies	200
Peak wall stress equivalent diameter[75]	1	0 of 1 studies	243
Predictive indices			
PWRI[60,75]	2	2 of 2 studies	303
PWRI equivalent diameter[60,75]	2	1 of 2 studies	303
Rupture potential index[61,62]	2	1 of 2 studies	66
Radiographical properties			
LaPlace[66]*	1	0 of 1 studies	48
Medium filter texture parameter kurtosis[67]	1	1 of 1 studies	40
^{18}F-FDG uptake[67–70]†	4	4 of 4 studies	119
Vessel wall properties			
Stiffness (β)[56,65]	2	0 of 2 studies	108
Minimal strenght[61]	1	0 of 1 studies	53
Mean wall stress[18,74]	2	1 of 2 studies	99
Peak wall stress [60,62–64,66,72–75]	9	7 of 9 studies	579
Pressure strain elastic modules (Ep)[56,65]	2	0 of 2 studies	108
Von Mises strain[61]‡	1	1 of 1 studies	53
Von Mises stress[61]‡	1	1 of 1 studies	53
Wall displacement[61]	1	1 of 1 studies	53
Wall strength[62]	1	1 of 1 studies	13

Markers are categorized by different properties, which can be measured after radiographic scanning. The total amount of studies and significant outcomes are presented as well as the total number of patients in studies pooled. AAA indicates abdominal aortic aneurysm; ^{18}F-FDG, Fluorodeoxyglucose; ILT, Intraluminal thrombus; PWRI, Peak wall rupture index.

*LaPlace=law of LaPlace (pressure=surface tension/radius).

†^{18}F-FDG uptake as measured by positron emission tomography.

‡Von Mises strain and stress are calculations of tensile stress according to Maximum Distortion Energy Theory of Failure.

demonstrated aneurysm diameter as a prognostic marker for rupture (area under curve=0.67).[37] In 3 studies, of which 2 were with high bias risk, no difference was found in diameter between ruptured AAA patients versus patients preceding elective repair (total n=80).[62,63,66]

Fluorodeoxyglucose Uptake

Maximum fluorodeoxyglucose (^{18}F-FDG) uptake after positron emission tomography scanning was studied as a marker for expansion in 3 studies[67–69] and in 1 study as a marker for rupture.[70] All 3 studies demonstrated significant inverse correlations with aneurysm expansion (r=−0.50 [medium bias risk], r=−0.38 [low bias risk], and r=−0.32 [medium bias risk]; total n=104). Reeps et al, however, found higher uptake in symptomatic versus asymptomatic AAA patients (n=15; medium bias risk).

Intraluminal Thrombus Volume

In 3 studies, intraluminal thrombus (ILT) volume was focused on. In 2 studies as a marker for expansion[33,71] and in 1 as a marker for rupture,[60] all studies had medium risk of bias. Speelman et al measured significantly higher expansion rates in patients with a large ILT volume (≥32% of the total aneurysm sac) versus a small ILT volume (total n=30). Kontopodis et al found a significant correlation (r=0.60) with expansion in 34 follow-up patients. Erhart et al measured larger ILT volumes in ruptured AAA than in follow-up patients (total n=75).

Peak Wall Stress

Aortic peak wall stress (PWS) was investigated as a marker for AAA rupture in 9 studies.[60,62–64,66,72–75] In 7 studies, significantly higher PWS (ranging 1.29–1.66-fold higher) was found in ruptured (and symptomatic) AAA patients than in asymptomatic AAA patients (2 low risk, 4 medium risk, and 1 high risk of bias; total n=536). According to Truijers et al, PWS was higher in 10 ruptured AAA than in 10 diameter-matched asymptomatic patients. In 2 studies, no difference was found between ruptured and electively treated AAA. However, the latter 2 included only 43 patients in total and both had high risk of bias.

Other biomechanical markers that have not been mentioned above, but are included, concern anatomical properties (see Table 2).[76–79]

Genetic Variations

In 9 studies, 20 genetic markers were elaborated on (Table 3). None of the following markers were described in more than 1 study. These genetic markers are therefore not evaluated as

Table 3. Genetic Variations That Have Been Investigated for an Association With AAA Expansion or Rupture

Marker	Total Studies (n)	Significant Outcome	Total Patients (n)
APOE gene[81]	1	1 of 1 studies	57
IL-6 gene[31]	1	0 of 1 studies	466
Cystatin C gene[83]	1	0 of 2 studies	412
CCR5 gene[80]	1	1 of 1 studies	70
OPN gene[84]	1	0 of 1 studies	198
Chromosome 9p21[85]	1	0 of 1 studies	741
Haptoglobin 2-1[20]	1	1 of 1 studies	83
LRP1 gene[82]	1	1 of 1 studies	141
MMP-9 p-2502 gene[82]	1	1 of 1 studies	141
MTHFR gene[82]	1	1 of 1 studies	141
miR-125a-5p[86]	1	1 of 1 studies	169
miR-136-5p[86]	1	0 of 1 studies	169
miR-195-5p[86]	1	1 of 1 studies	169
miR-221-3p[86]	1	1 of 1 studies	169
miR-223-3p[86]	1	1 of 1 studies	169
miR-30a-5p[86]	1	0 of 1 studies	169
miR-326[86]	1	1 of 1 studies	169
miR-335-p[86]	1	1 of 1 studies	169
miR-421[86]	1	1 of 1 studies	169
miR-99a-5p[86]	1	1 of 1 studies	169

The total amount of studies and significant outcomes are presented as well as the total number of patients in studies pooled. AAA indicates abdominal aortic aneurysm.

extensively as circulating and biomechanical markers in this review.

CCR5 gene was the only gene examined as a marker for rupture. Ghilardi et al demonstrated a higher percentage of *CCR5* gene Δ32 deletion mutation in ruptured AAA patients (n=21) than in electively treated AAA patients (n=49; 48% versus 18%, respectively).[80]

The following markers were all investigated in AAA follow-up patients and were associated with the aneurysm growth rate. Gerdes et al identified that *APOE* mutations are associated with higher growth rates in 57 patients.[81] Wiernicki et al measured higher growth rates in 41 patients with a Haptoglobin 2-1 phenotype than in 13 with a Haptoglobin 1-1 phenotype.[20] Duellman et al included 141 patients and demonstrated that mutations in the following genes are associated with a growth speed of 3.25 mm per year or more: *LRP1* (odds ratio, 5.0), *MMP9* p-2502 (odds ratio, 2.2), and *MTHFR* (odds ratio, 3.0).[82] No such differences were measured with the following genes: *IL-6* (n=466)[31]; *Cystatin C* (n=412)[83]; *OPN* (n=198)[84]; and 9p21 (n=741).[85] Of 20 investigated genetic markers, 10 were investigated by Wanhainen et al[86] in 169 follow-up patients (all concerning microRNA as marker for expansion), of which 8 markers demonstrated significant differences between slow and fast growing AAA.

Discussion

Numerous markers have been investigated as a predictive factor for AAA expansion and rupture. All markers described in 3 or more studies were described in more detail and are summarized in Table 4. Thus, we focused on 14 markers, of which 5 were investigated as a marker for expansion, 1 as a marker for rupture, and 8 as a marker for both. Markers were qualified as high potential based on sample size, quality appraisal of the study, and significant outcomes. The highest potential as a prognostic marker for AAA expansion are in descending order: AAA diameter, chlamydophila pneumoniae; SEP; and ^{18}F-FDG uptake. Factors with high potential as marker for aneurysm rupture are in descending order: PWS, AAA diameter, and PAI-1. The following 2 markers were described in only 2 studies, but had remarkable results and are therefore separately mentioned: ILT as a marker for expansion and S-elastin peptides as a marker for rupture. Little research has been done on genetic markers for rupture and growth, given that this is a relatively new area of research. We therefore evaluated none of the genetic markers in detail.

AAA diameter is broadly accepted as a predictive factor for both aneurysm growth and rupture and is thus implemented in important AAA follow-up guidelines.[2,3] Our systematic review confirmed the strong prognostic value for expansion given that 8 of 9 studies had significant outcomes, with mainly low bias risks and low *P* values in a total of 1503 patients. However, correlation coefficients do have a relatively broad range, with values varying from r=0.30 to r=0.83. Overall, these studies demonstrate that large aneurysms grow faster than small AAA do.

Chlamydophila pneumoniae was already identified as a causative factor for inflammation and atherosclerosis of the aorta.[87] The bacterial infection induces degenerative processes in the aortic wall, which might explain the strong correlation of antibodies against chlamydophila pneumoniae with AAA expansion. All 4 studies, with mainly medium bias risks, had significant outcomes and consistent results, of which 3 had very low *P* values. Therefore, it seems to be a reliable marker for AAA expansion in case of seropositivity.

SEP are derived from the enzymatic degradation of insoluble elastic polymers in the vessel wall by matrix metalloproteinase.[88] In all studies, this marker was significantly correlated with AAA expansion and bias risks were medium. However, 1 group performed 4 of 5 studies using patients from the same AAA screening cohort. Therefore,

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Table 4. All Markers for AAA Expansion or Rupture That Have Been Described in 3 or More Studies Have Been Evaluated in More Detail

Marker Subject	Reference	Risk of Bias	Measurement	Study Group	Control Group	N (Total)	Correlation	Fold Change	*P* Value
Cicrculating markers									
Aminoterminal propeptide of type III procollagen (PIIINP)									
Expansion	Lindholt et al (2001)[8]	Medium	Pearson	Follow-up	. . .	99	0.24	. . .	Significant
Expansion	Lindholt et al (2000)[10]	Medium	Spearman	Follow-up	. . .	36	No correlation	. . .	0.180
Expansion	Satta et al (1997)[9]	High	Pearson	Follow-up	. . .	55	0.15	. . .	0.260
Chlamydophila pneumonia									
Expansion	Lindholt et al (2003)[13]	Low	Spearman	Follow-up	. . .	70	0.29	. . .	0.006
Expansion	Lindholt et al (1999)[11]	Medium	Fold change	Follow-up: IgA titre ≥20	Follow-up: IgA titer <20	139	. . .	1.48	0.003
Expansion	Lindholt et al (2001)[12]	Medium	Fold change	Follow-up: IgA titer ≥64	Follow-up: IgA titer <64	55	. . .	1.69	<0.050
Expansion	Falkensammer et al (2007)[14]	High	Fold change	Follow-up: seropositive	Follow-up: seronegative	47	. . .	1.67	0.046
Rupture	Nyberg et al (2007)[15]	Medium	Fold change	Rupture	Controls	77	. . .	1.01	0.397
Rupture	Nyberg et al (2008)[16]	Medium	Fold change	Rupture	Controls	77	. . .	NA	Ns
CRP									
Expansion	De Haro et al (2012)[17]	Low	Spearman	Follow-up	. . .	260	0.71	. . .	<0.050
Expansion	Norman et al (2004)[19]	Low	Fold change	Follow-up: expansion ≥3 mm/year	Follow-up: expansion <3 mm/year	545	. . .	NA	Ns
Expansion	Flondell-Sité et al (2009)[21]	Low	Fold change	Follow-up: expansion ≥2.5 mm/year	Follow-up: expansion <2.5 mm/year	178	. . .	1.07	0.721
Expansion	Wiernicki et al (2010)[20]	Medium	Spearman	Follow-up		83	. . .	0.32	0.003
Expansion	Speelman et al (2010)[18]	Medium	Partial correlation	Follow-up	. . .	18	0.06	. . .	0.720
Rupture	Domanovits et al (2002)[22]	Low	Fold change	Rupture	Elective	225	. . .	4.80	<0.050
Rupture	Tambyraja et al (2007)[23]	Low	Fold change	Symptomatic	Asymptomatic	112	. . .	4.40	<0.001
Cotinine									
Expansion	Lindholt et al (2003)[13]	Low	Spearman	Follow-up	. . .	70	0.23	. . .	0.038
Expansion	Lindholt et al (2003)[25]	Medium	Spearman	Follow-up	. . .	79	0.24	. . .	0.040
Expansion	Wilmink et al (1999)[24]	Medium	Fold change	Follow-up: expansion ≥2 mm/year	Follow-up: expansion <2 mm/year	447	. . .	1.00	Ns

Continued

Table 4. Continued

Marker Subject	Reference	Risk of Bias	Measurement	Study Group	Control Group	N (Total)	Correlation	Fold Change	*P* Value
D-dimer									
Expansion	Golledge et al (2011)[26]	Low	Spearman	Follow-up	. . .	299	0.39	. . .	<0.001
Rupture	Adam et al (2002)[27]	Low	Fold change	Rupture	Symptomatic	44	. . .	2.52	0.005
Rupture	Skagius et al (2008)[28]	Low	Fold change	Rupture	Elective	95	. . .	4.53	<0.001
Fibrinogen									
Rupture	Adam et al (2002)[27]	Low	Fold change	Rupture	Symptomatic	44	. . .	0.53	0.033
Rupture	Domanovits et al (2002)[22]	Low	Fold change	Rupture	Asymptomatic	225	. . .	0.94	0.049
Rupture	Tambyraja et al (2007)[23]	Low	Fold change	Symptomatic	Asymptomatic	112	. . .	1.28	<0.001
Homocysteine									
Expansion	Lindholt et al (2003)[13]	Low	Spearman	Follow-up	. . .	70	0.06	. . .	0.535
Expansion	Halazun et al (2007)[29]	Low	Spearman	Follow-up	. . .	108	0.28	. . .	0.003
Expansion	Flondell-Sité et al (2009)[21]	Low	Fold change	Follow-up: expansion ≥2.5 mm/year	Follow-up: expansion <2.5 mm/year	178	. . .	1.00	0.940
IL-6									
Expansion	Jones et al (2001)[31]	Low	Spearman	Follow-up	. . .	466	No correlation	. . .	Ns
Expansion	Flondell-Sité et al (2009)[21]	Low	Fold change	Follow-up: expansion ≥2.5 mm/year	Follow-up: expansion <2.5 mm/year	178	. . .	2.29	0.820
Expansion	Treska et al (2000)[30]	High	Fold change	Surgery during follow-up	Asymptomatic	90	. . .	2.19	Ns
MMP-9									
Expansion	Flondell-Sité et al (2010)[32]	Low	Spearman	Follow-up	. . .	163	No correlation	. . .	Ns
Expansion	Lindholt et al (2000)[10]	Medium	Spearman	Follow-up	. . .	36	0.33	. . .	0.010
Expansion	Speelman et al (2010)[18]	Medium	Partial correlation	Follow-up	. . .	18	0.32	. . .	<0.050
Rupture	Wilson et al (2008)[34]	Medium	Fold change	Rupture	Elective	68	. . .	3.37	0.006
Plasminogen activator inhibitor 1									
Expansion	Lindholt et al (2003)[13]	Low	Spearman	Follow-up	. . .	70	0.02	. . .	0.015
Rupture	Adam et al (2002)[27]	Low	Fold change	Rupture	Symptomatic	44	. . .	4.92	0.023
Rupture	Skagius et al (2008)[28]	Low	Fold change	Rupture	Elective	95	. . .	4.33	0.002
Rupture	Hobbs et al (2007)[35]	Medium	Fold change	Rupture	Elective	95	. . .	3.73	0.001

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Table 4. Continued

Marker Subject	Reference	Risk of Bias	Measurement	Study Group	Control Group	N (Total)	Correlation	Fold Change	*P* Value
S-elastin peptides									
Expansion	Lindholt et al (2001)[36]	Low	Pearson	Follow-up	. . .	70	0.31	. . .	0.050
Expansion	Lindholt et al (2001)[8]	Medium	Pearson	Follow-up	. . .	99	0.33	. . .	Significant
Expansion	Lindholt et al (2000)[10]	Medium	Spearman	Follow-up	. . .	36	0.51	. . .	0.010
Rupture	Petersen et al (2001)[38]	Low	Fold change	Rupture	Elective	60	. . .	0.80	0.001
Rupture	Lindholt et al (2001)[37]	Medium	AUC met 95% CI	Rupture	. . .	100	0.68	. . .	Significant
TIMP-1									
Expansion	Flondell-Sité et al (2010)[32]	Low	Spearman	Follow-up	. . .	163	No correlation	. . .	Ns
Expansion	Speelman et al (2010)[18]	Medium	Partial correlation	Follow-up	. . .	18	0.12	. . .	0.510
Rupture	Wilson et al (2008)[34]	Medium	Fold change	Rupture	Elective	68	. . .	0.50	0.456
Tissue plasminogen activator (tPA)									
Expansion	Lindholt et al (2003)[13]	Low	Spearman	Follow-up	. . .	70	0.37	. . .	0.002
Rupture	Adam et al (2002)[27]	Low	Fold change	Rupture	Symptomatic	44	. . .	0.16	0.023
Rupture	Skagius et al (2008)[28]	Low	Fold change	Rupture	Elective	95	. . .	1.71	<0.001
Rupture	Hobbs et al (2007)[35]	Medium	Fold change	Rupture	Elective	95	. . .	0.22	0.036
α-1 antitrypsine									
Expansion	Vega de Céniga et al (2009)[39]	Low	Spearman	Follow-up	. . .	25	0.55	. . .	0.004
Expansion	Pulinx et al (2011)[40]	Low	AUC met 95% CI	Follow-up	. . .	48	No correlation	. . .	Ns
Expansion	Lindholt et al (2000)[10]	Medium	Spearman	Follow-up	. . .	36	0.42	. . .	0.050
Expansion	Speelman et al (2010)[18]	Medium	Partial correlation	Follow-up	. . .	18	0.00	. . .	0.990
Biomechanical markers									
AAA diameter									
Expansion	De Haro et al (2012)[17]	Low	Spearman	Follow-up	. . .	435	0.31	. . .	>0.050
Expansion	Norman et al (2004)[19]	Low	OR	Follow-up ≥4 cm	Follow-up <4 cm	545	. . .	7.20	0.050
Expansion	Tong et al (2015)[58]	Low	Pearson	Elective and Rupture	. . .	33	0.70	. . .	0.010
Expansion	Flondell-Sité et al (2010)[21]	Low	Pearson	Follow-up	. . .	178	0.39	. . .	0.001

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Table 4. Continued

Marker Subject	Reference	Risk of Bias	Measurement	Study Group	Control Group	N (Total)	Correlation	Fold Change	*P* Value
Expansion	Pulinx et al (2011)[40]	Low	AUC met 95% CI	Follow-up	. . .	48	0.83	. . .	0.001
Expansion	Behr-Rasmussen et al (2014)[57]	Low	Pearson	Follow-up	. . .	416	0.30	. . .	0.001
Expansion	Lindholt et al (2001)[8]	Medium	Spearman	Follow-up	. . .	124	0.30	. . .	0.010
Expansion	Lindholt et al (2001)[8]	Medium	Pearson	Follow-up	. . .	99	0.48	. . .	0.000
Expansion	Wilson et al (1999)[56]	High	Spearman	Follow-up	. . .	60	0.60	. . .	<0.050
Rupture	Fillinger et al (2003)[64]	Low	Fold change	Rupture and symptomatic	Elective	61	. . .	1.03	0.000
Rupture	Fillinger et al (2002)[66]	Low	Fold change	Rupture	Elective	40	. . .	1.13	0.100
Rupture	Lindholt et al (2001)[37]	Medium	ROC curve	Rupture	. . .	100	0.67	. . .	0.011
Rupture	Wilson et al (2003)[65]	Medium	Fold change	Rupture	Follow-up	210	. . .	1.12	0.001
Rupture	Maier et al (2010)[61]	Medium	Fold change	Rupture and symptomatic	Elective	53	. . .	1.33	0.006
Rupture	Erhart et al (2015)[60]	Medium	Fold change	Rupture	Follow-up	60	. . .	1.42	<0.001
Rupture	Wilson et al (2008)[34]	Medium	Fold change	Rupture	Elective	68	. . .	1.67	<0.001
Rupture	Venkatasubramaniam et al (2004)[63]	High	Fold change	Rupture	Elective	27	. . .	1.11	0.197
Rupture	Vande Geest et al (2006)[62]	High	Fold change	Rupture	Elective	13	. . .	1.11	0.260
Fluorodeoxyglucose (^{18}F-FDG)									
Expansion	Kotze et al (2014)[67]	Low	Spearman	Follow-up	. . .	40	−0.38	. . .	0.015
Expansion	Morel et al (2015)[69]	Medium	Spearman	Follow-up	. . .	39	−0.32	. . .	0.049
Expansion	Kotze et al (2011)[68]	Medium	Spearman	Follow-up	. . .	25	−0.50	. . .	0.011
Rupture	Reeps et al (2008)[70]	Medium	Fold change	Symptomatic	Elective	15	. . .	2.14	<0.001
ILT volume									
Expansion	Speelman et al (2010)[33]	Medium	Fold change	Follow-up: ILT volume ≥32%	Follow-up: ILT volume <32%	30	. . .	NA	<0.010
Expansion	Kontopodis et al (2014)[71]	Medium	Spearman	Follow-up	. . .	34	0.60	. . .	0.001
Rupture	Erhart et al (2015)[60]	Medium	Fold change	Rupture	Follow-up	75	. . .	2.00	0.015
Peak wall stress (PWS)									
Rupture	Fillinger et al (2003)[64]	Low	Fold change	Rupture and symptomatic	Elective	61	. . .	1.38	<0.001
Rupture	Fillinger et al (2002)[66]	Low	Fold change	Rupture	Elective	40	. . .	1.29	0.030
Rupture	Gasser et al (2014)[75]	Medium	Fold change	Rupture	Follow-up	243	. . .	1.62	<0.001

Continued

Table 4. Continued

Marker Subject	Reference	Risk of Bias	Measurement	Study Group	Control Group	N (Total)	Correlation	Fold Change	*P* Value
Rupture	Erhart et al (2015)[60]	Medium	Fold change	Rupture	Follow-up	75	…	1.57	<0.001
Rupture	Truijers et al (2007)[72]	Medium	Fold change	Rupture	Follow-up	20	…	1.30	0.040
Rupture	Heng et al (2008)[73]	Medium	Fold change	Rupture	Elective	70	…	1.66	0.008
Rupture	Venkatasubramaniam et al (2004)[63]	High	Fold change	Rupture	Elective	27	…	1.65	0.004
Rupture	Vande Geest et al (2006)[62]	High	Fold change	Rupture	Elective	13	…	1.08	0.620
Rupture	Vande Geest et al (2008)[74]	High	Fold change	Rupture	Elective	30	…	1.09	0.550

Presented are: the subject of the marker (on which aspect the marker was investigated: AAA expansion or rupture); first author and date of publication of the reference; the risk of bias; statistical method of measurement; the moment of data retrieval (during conservative follow-up of maximum aortic diameter, at time of presentation with symptomatic AAA or AAA rupture), and, if applicable, main clinical characteristic of the study and control groups (varying per study); the total sample size (cases and controls pooled); the correlation coefficient (negative correlation: −1 to 0; and positive correlation: 0 to 1) or the fold change (decrease: 0–1; and increase: above 1) of study group vs control group; and *P* values. Note that significant ($P<0.05$) outcomes are indicated by an asteriks. AAA indicates abdominal aortic aneurysm; AUC, area under the curve; CI, confidence interval; CRP, complement reactive protein; IL-6, interleukin-6; ILT, intraluminal thrombus; MMP-9, matrix metalloproteinase 9; NA, not applicable; Ns, not significant; OR, odds ratio; ROC, receiver operating characteristic; TIMP-1, tissue inhibitor of matrix metalloproteinase 1.

other groups should first reproduce these data before SEP can be applied as a marker for expansion.

Metabolic activity in the aneurysm wall can be measured by positron emission tomography. Locations of high ^{18}F-FDG uptake in the aneurysm wall were demonstrated to accumulate MMP and other factors of aortic deterioration.[89] It therefore seems contradictive that an inverse correlation was found between ^{18}F-FDG uptake and expansion in all 3 studies. The current explanation is that an inflammatory period precedes a phase of rapid growth and is then followed by a period of stasis with low metabolic activity.[67–70] However, this phenomenon is clearly not fully explained yet. Overall, ^{18}F-FDG uptake studies were appraised with medium bias risks and had consistent results with relatively low *P* values. Therefore, it seems a reliable marker for AAA expansion.

An ILT is the source of many pro-proteolytic processes that stimulate aortic wall degradation.[90] We designated this marker as promising because of a clear association of ILT volume with expansion, even though relatively small patient numbers were included in only 2 studies. However, Kontopodis, Nguyen, and Behr-Rahsmussen et al also demonstrated the ILT to be correlated with AAA expansion in 694 follow-up patients in total (ie, ILT thickness, signal intensity, and surface area, respectively).[57,71,91] In total, 5 studies have elaborated on ILT size as a marker for expansion in 758 patients, with, on average, a medium bias risk. These data plead for the ILT size as a promising prognostic growth marker. However, there have been several studies demonstrating a correlation between ILT presence and AAA diameter.[58,71] The presented associations between ILT and AAA expansion might be the result of multicolinearity attributed to the strong correlation between AAA diameter and its growth speed. Therefore, before clinical implementation, more homogenous studies must be produced. In those studies, AAA diameter should be corrected for as a confounding factor before ILT can be considered a reliable growth marker.

A potential marker for rupture is PWS. To determine stress on the aneurysm wall, a technique called finite element analysis is used. This is a numerical method to approximate the forces that are applied on the aortic wall. Because aneurysms are not symmetrical dilations, pressure in the aneurysm sac is heterogeneously divided. Finite element analysis enables software programs to calculate the PWS on the aneurysm wall.[63] In 7 of 9 studies, PWS retrospectively differentiated between ruptured and nonruptured AAA, but none investigated it as a prognostic value. In 2 studies, no significant differences were found, but both had high bias risks and a total patient number of only 43. Given that significant differences were found in 536 patients, we suggest that PWS has a high potential to contribute in AAA management.

AAA diameter has long since also been acknowledged as a risk factor for aneurysm rupture and is used as an indicator

for elective repair surgery.[2,3] Our results are in line with this common use, although 3 of 9 studies found no differences between ruptured AAA versus patients preceding elective repair. It must be noted that in those 3 studies, aneurysm diameters of the elective repair groups were all larger than current guidelines apply (6.8±1.5, 6.1±0.5, and 6.1±0.2 cm).

Another marker for rupture with promising results is PAI-1, a known marker for coronary heart disease that plays an essential role in fibrinolysis.[92] Its levels were ≈4 times higher in 102 patients with a ruptured AAA than in asymptomatic patients. However, given that the massive retroperitoneal hematoma and blood clotting could be the cause of PAI-1 activation, its use a prospective marker for rupture must be reconsidered. Activation of this pathway should first be fully elucidated before it is investigated as a marker for AAA rupture in a prospective trial.

SEP have been investigated as a marker for rupture by 2 separate groups. Promising results were demonstrated given that both groups found highly significant associations. However, only 2 groups have reported on this marker yet in a total of 160 patients. Before it is implemented in a clinical setting, it should be studied more extensively.

Genetic variations and microRNA are relatively new markers for AAA expansion and rupture. Therefore, little is known about its potential as prognostic tools, when compared with circulating and biomechanical markers. Gene mutations in the *FBN1*[93] and *COL3A1*[94] genes, responsible for Marfan's disease and Ehlers-Danlos vascular type disease, respectively, are perhaps the best-known genetic disorders leading to aortic aneurysms. However, despite the broad amount of studies describing these 2 important genetic mutations, no studies about *FBN1 or COL3A1* met our inclusion criteria. This might be explained by the fact that these disorders commonly cause thoracic and thoracoabdominal aortic aneurysms, and also that growth rate and rupture are often totally unpredictable in these cases.

One major limitation of this review is the inability to pool data attributed to high clinical and methodological heterogeneity. Also, we considered biomarkers in the evidence that demonstrated a statistically significant association with an outcome (AAA rupture or growth); however, we recognize that this may have severe limitations given that this choice is subject to type II errors, particularly in the case of studies with small sample sizes. Furthermore, the potential markers provided such heterogenic threshold values that direct clinical implementation is not possible based on the current data. More specifically, prospective and methodological consonant research is necessary for the promising markers that we have identified, in which threshold values for follow-up and surgical intervention must be determined.

This review has identified several circulating and biomechanical markers with potential value for the prognosis of AAA expansion and rupture. As possible markers for expansion, we suggest the use of AAA diameter, chlamydophila pneumonia in case of seropositivity, SEP, inverse fluorodeoxyglucose uptake, and ILT size. Markers with the best prognostic value for rupture are PWS and AAA diameter. Prospective trials are now required to determine threshold values for the clinical implementation of these markers. In conclusion, there are several potential markers for AAA expansion and rupture, which could contribute to better decision making in the management of AAA.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

MeSH terms:

PubMed: “aortic aneurysm, abdominal" AND "aneurysm, ruptured" OR "aortic rupture" OR "aneurysm" AND "growth" AND "biomarkers" OR "proteins" OR "RNA" AND "humans" NOT "aorta, thoracic" AND "genetic variation” OR "genetic markers" OR "mutation";

Embase: “abdominal aorta aneurysm” AND “aneurysm rupture OR “aorta rupture” AND “biological marker”;

Cochrane Library: “abdominal aortic aneurysm” OR “abdominal aortic aneurisms” AND “rupture” AND “biomarker” OR “screening”.