Surrogate Markers of Abdominal Aortic Aneurysm Progression
Anders Wanhainen, Kevin Mani, Jonathan Golledge

Abstract—The natural course of many abdominal aortic aneurysms (AAA) is to gradually expand and eventually rupture and monitoring the disease progression is essential to their management. In this publication, we review surrogate markers of AAA progression. AAA diameter remains the most widely used and important marker of AAA growth. Standardized reporting of reproducible methods of measuring AAA diameter is essential. Newer imaging assessments, such as volume measurements, biomechanical analyses, and functional and molecular imaging, as well as circulating biomarkers, have potential to add important information about AAA progression. Currently, however, there is insufficient evidence to recommend their routine use in clinical practice. (Arterioscler Thromb Vasc Biol. 2016;36:236-244. DOI: 10.1161/ATVBAHA.115.306538.)

Key Words: aortic aneurysm, abdominal • biomarkers • magnetic resonance imaging • molecular imaging • ultrasonography

The natural course of most abdominal aortic aneurysms (AAA) is to gradually expand and in some cases eventually rupture. There is currently no recognized specific pharmacological treatment to reduce growth or rupture risk of an AAA.1 Standard of care for patients with small AAAs (<55 mm) is limited to surveillance with open or endovascular surgical repair considered for large (>55 mm), rapidly growing (>10 mm/y) or symptomatic AAAs.2 Because most AAAs are asymptomatic, ultrasound-based screening programs targeting risk groups (commonly men aged ≥65 years) have been established in some countries.3 Such programs, along with the growing use of abdominal imaging for other problems, have led to an increase in the identification of patients with small AAAs. Predicting the progress of small AAAs is, therefore, a key management priority.

Morphological Markers
AAA Diameter
The most commonly used surrogate marker of rupture risk is the maximal AAA diameter. Because of its ease of use, safety, wide availability, and low cost, ultrasound is the most commonly used imaging modality for this purpose, an intra- and interobserver variabilities (2 SDs) in the range of 2 to 7 mm and 2 to 10 mm, respectively,4,5 represent an important limitation that may have significant impact on clinical decision making. Modern computed tomography (CT) and magnetic resonance imaging (MRI) with advanced image processing methods, such as multiplanar reformation, are perceived to have higher accuracy and reproducibility, with a reported intra- and interobserver variability of <2 mm.6 Although CT or MRI is frequently the preferred imaging modalities for monitoring growth rates in small clinical trials, they are less suitable for mass screening and large-scale trials. Similar reproducibility for ultrasound and CT has been reported in some but not identifying weak areas prone to rupture. Recently, functional and molecular imaging and circulating biomarkers have also been proposed as potential means to monitor the progression of AAA pathobiology. This review focuses on the current evidence on the value of different surrogate markers of AAA progression.

Maximum AAA diameter has traditionally been used as the main marker of disease progression although there are concerns about the reproducibility of readings and the sensitivity to detect true disease progression. Aneurysm volume has been suggested as a more sensitive anatomical marker for monitoring expansion, and biomechanical analyses have been proposed for

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Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org
DOI: 10.1161/ATVBAHA.115.306538

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Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>FDG</td>
<td>18-fluorodeoxyglucose</td>
</tr>
<tr>
<td>AAA</td>
<td>abdominal aortic aneurysm</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>ILT</td>
<td>intraluminal thrombus</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PWS</td>
<td>peak wall stress</td>
</tr>
<tr>
<td>PWRI</td>
<td>peak wall rupture index</td>
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</table>

in all studies when a standardized protocol is used. One of the challenging aspects to assessing maximum AAA diameter is the variety of methods that can potentially be used and the lack of reporting of the exact techniques used in individual studies. Variations may occur in the plane of acquisition (eg, coronal or sagittal), the axis of measurement (eg, axial or orthogonal), the position of the measuring calipers (eg, inner to inner or outer to outer), the relationship with the cardiac cycle (systole versus diastole), and the selected region of the AAA. It has been suggested that diameters measured perpendicular to the aorta centerline (orthogonal), rather than within the axial plane, are more representative of the true AAA diameter. With ultrasound, measurements within the anteroposterior, rather than the transverse plane, have been reported to be more reproducible.

There is no current consensus on how to place the calipers when measuring the diameter with ultrasound. Methods used include the outer-to-outeter method, where calipers are placed on the outer layer of the aortic wall; the inner-to-inner method, where calipers are placed on the inner layer of the aortic wall; and the leading edge-to-leading edge method, where calipers are placed on the outer layer of the anterior wall and the inner layer of the posterior wall (Figure 1). Much of the reported variation in ultrasound measured AAA diameter is likely because of the variation in caliper placement. The UK Small Aneurysm Trial is based on the measurement of AAA diameter on the outer-to-outeter method, and this method has been adopted into the current UK intervention criteria.

A systematic review of 15 studies reported considerable variation in small AAA growth rates (mean, −0.3 to +4.0 mm/y). The variation could not be explained by differences in initial AAA diameter alone. The authors suggested that methodological issues, such as differences in imaging modalities, variation in the plane of measurement, and cursor positioning, likely explained the large heterogeneity. Frequently, important methodological aspects were not reported. Furthermore, growth rates were estimated in a variety of different ways using (last–first diameter)/time, linear regression, or more complex techniques such as multilevel modeling, which has been shown to affect the growth estimation.

Grondal et al reported that AAA diameter measurement by ultrasound was influenced by the pulse wave propagation, with an average maximal diameter difference of 1.9 mm between diastole and systole. Thus, ECG-gated imaging may further increase precision by reducing the effects of hemodynamic variations and has been used in clinical trials. A rapid increase in AAA diameter (>10 mm/y) is claimed to be a risk factor for rupture and is generally accepted as an indication for repair. The average annual growth rate for AAAs is 5% to 10% of the initial diameter; however, there is considerable heterogeneity in growth rates reported across studies. Furthermore, large individual variability in growth patterns exist, with most AAAs remaining static for periods of time followed by expansion (staccato growth), some growing at a continuous linear rate, and others having long periods of stability. In a study by Vega de Céñiga et al, only 15 (11.5%) of 195 patients with 4 to 4.9 cm AAAs followed with 6 monthly CT scans over a mean of 50 months showed a continuous growth pattern. Although individual patient factors may partially explain the observed irregular expansion patterns, measurement error and variation of assessment techniques are likely an important contributor to this heterogeneity. Some authors claim that management decisions should not be based on the presumption that observed growth rates of AAAs can be extrapolated to predict future growth rates, and that rapid increase in AAA diameter should not be an indication for elective AAA repair.

Despite its limitation, AAA diameter remains the most widely used and important marker of disease progression. The methods used to measure AAA diameter should be standardized and reported to minimize measurement error and increase generalizability.

### AAA Volume

AAA volume has been reported to be a more sensitive and accurate predictor of AAA progression and to have excellent generalizability.

![Figure 1. Schematic of different methods to place the calipers when measuring the anteroposterior abdominal aortic diameter with ultrasound. Because of a better ultrasound reflection and lower variability, the anteroposterior diameter is preferable to the transverse diameter.](image-url)
reproducibility (coefficients of variation of <3%).24 Changes in aneurysm morphology do not always result in maximum diameter changes, and volume measurements take this into account. Moreover, measuring volume overcomes variation introduced by measuring in different planes and axes.25 In a study by Parr et al.,24 almost half of the patients with volumetric growth greater than the reader variability (ie, outside the 95% limits of agreements and therefore considered true growth) did not have corresponding diameter increases. Kontopodis et al.26 reported that volumetric growth of 34 small AAAs was a better predictor of requirement for surgical repair than AAA diameter growth. Currently, there is, however, no defined threshold volumes at which surgical repair should be recommended.25

AAA volume can be measured with a variety of techniques, including CT, MRI, and ultrasound. Noncontrast CT has been reported to be comparable with contrast-enhanced CT for aortic volume analysis.27 Recent studies on 3-dimensional (3D) ultrasound report reproducibility similar to CT although this remains to be validated in other cohorts.28 There has been considerable progress in segmentation software, allowing a rapid semiautomatic or even completely automatic calculation of accurate volumes.6

Surveillance after endovascular aortic repair by CT or ultrasound is recommended by current guidelines.2 Continued sac expansion is suggestive of an endoleak and an important risk factor for secondary aneurysm rupture. Several studies have suggested that aortic volume is a much more sensitive indicator than aortic diameter for sac expansion after endovascular aortic repair.29–31 It has been suggested that a 2% increase in aortic volume is indicative of an endoleak after endovascular aortic repair.32 More widespread examination of the accuracy of AAA volume measurements in diagnosing endoleak is required. Currently, because most patients are followed with standard ultrasound, it would not be possible to introduce this method of diagnosing endoleak into clinical practice.

### AAA Thrombus

Most AAAs have large quantities of intraluminal thrombus (ILT), which can be measured by imaging (Figure 2). The volume of ILT may influence biomechanical properties, which may affect the risk of rupture. Furthermore, cellular and metabolic activity within the thrombus could have secondary effects to weaken the adjacent aortic wall.24 Parr et al.24 studied a group of 39 patients who underwent repeat CT imaging and reported an association between larger ILT volume and greater AAA growth, independent of initial aortic diameter. In addition, high ILT volume predicted an increase rate of cardiovascular events in a group of 98 patients.33 In a large population-based cohort study from Viborg, Denmark, 416 men with screening-detected AAAs were followed up for mean of 1.8 years with ultrasound. After adjusting for potential confounders (AAA diameter, smoking, blood pressure, and diabetes), a weak but significant correlation (correlation coefficient, 0.14) was found between the initial relative ILT cross-sectional area and the AAA growth rate.34 In a recent study from the Netherlands, an unorganized loose ILT, characterized by high thrombus signal intensity on T1-weighted MRI, was associated with higher AAA growth rates, and the authors suggested that MR thrombus characterization was a promising technique to identify fast growing aneurysms.35

### Biomechanical Imaging

AAA rupture is thought to occur at sites where aortic wall stress surpasses the aortic wall strength. Aneurysm wall strength and wall stress are affected by various factors, including wall thickness, presence of thrombus, aneurysm geometry, blood pressure, and flow dynamics within the aorta. Morphological assessment of the aorta together with knowledge of blood pressure and flow dynamics may, therefore, offer a better tool for predicting AAA progression and rupture than simple diameter or volume measurements.

Finite element analysis has been used for the biomechanical evaluation of AAAs. This technique involves acquisition of morphological 3D imaging often with CT or MRI, vessel reconstruction, and segmentation, followed by finite element computation using dedicated software. Recently, the feasibility of wall stress analysis using 3D ultrasound was reported,36 which would be beneficial considering that ultrasound is the routine method for small AAA follow-up. The estimates of peak wall stress (PWS) can be highly complicated requiring detailed processing and advanced understanding of fluid mechanics. Recently, software has been developed to enable more user-friendly PWS estimation and also calculation of a peak wall rupture index (PWRI). Areas with increased PWS and PWRI can be identified (Figure 3).

To facilitate clinical applicability of finite element analysis, efforts have been made to translate the biomechanical calculations such as PWRI, to clinically tangible data through identification of a PWRI-equivalent diameter of the AAA.37 Several retrospective studies indicate that finite element analysis can identify areas with increased risk of aneurysm expansion and rupture.38–40 A study of 30 asymptomatic, 15 symptomatic, and 15 ruptured AAA suggested that PWRI was the parameter that...
best distinguished between asymptomatic and symptomatic AAAs. The same group reported that regions of the AAA with increased PWRI had increased histopathological degeneration on examination of aortic wall specimens obtained at surgical repair. The findings suggest a potential means of linking biomechanical imaging to the molecular pathology of AAA.

A recent meta-analysis reported that PWS was significantly greater in a series of 144 patients with ruptured or symptomatic AAAs than 204 individuals with asymptomatic AAAs. A serious limitation of current biomechanical imaging measurements is that none has been prospectively validated against the main outcome they are supposed to predict (ie, AAA rupture). It remains to be established whether the measurement of PWS or PWRI in surveillance programs will improve management of small AAAs. Because most small AAAs are currently monitored by standard ultrasound, this would require a significant change in practice.

**Functional and Molecular Imagings**

AAA surveillance programmes are currently based on morphological assessment; however, the traditional imaging modalities cannot assess the pathological process that is ongoing in a degenerative aneurysm. The potential role of functional imaging is to differentiate aneurysms with pathological properties that indicate more aggressive disease or to monitor the response to medical interventions. Functional imaging involves the use of tracers to assess cellular activity or aortic wall cell composition, combined with morphological imaging such as CT or MR to visualize the AAA.

**Positron Emission Tomography**

The functional imaging that is currently most used in clinical practice is positron emission tomography fused with CT imaging (PET/CT). 18-fluorodeoxyglucose or FDG-PET is often used in oncological staging or assessment of autoimmune rheumatologic disease, as increased glucose metabolism indicates the presence of inflammation or cell proliferation. FDG-PET/CT imaging is used for diagnosis of mycotic aneurysms, aortic graft infections, and sometimes for evaluation of symptomatic aneurysms. Increased FDG-uptake has been reported in symptomatic AAAs. In an analysis of 12 asymptomatic AAAs with FDG-PET/CT imaging, no aneurysm wall–specific uptake could be identified in any patient. Thus, currently, the role of FDG-PET/CT in evaluation asymptomatic small AAAs is unclear. It is possible that the use of other radionucleotide markers, such as those representative of angiogenesis, maybe more useful.

**MRI and Functional Imaging**

Functional imaging with MRI has the benefit that it combines morphological and mechanical imaging of the aorta with the assessment of aortic wall composition and cellular activity. In addition, MRI does not involve ionizing radiation, which may be an issue because most patients with asymptomatic small AAAs require repeat imaging. Functional MRI imaging of phagocytic activity of macrophages has been reported in humans, using superparamagnetic iron oxide as the MR contrast agent. These particles have been used in imaging of macrophage activity in atherosclerosis. There are initial reports that suggest uptake of iron oxide in the aortic wall is representative of macrophage activity. One study, which included 29 patients, reported iron oxide uptake to be associated with a threefold increased expansion rate. These promising results remain to be validated. The inherent properties of iron oxide as a contrast agent for MRI may affect the clinical applicability of these results because results are highly dependent on imaging technique and protocol. Recently, PET-MR was introduced and may offer increased possibilities in imaging of cardiovascular disease.

**Circulating Markers**

Circulating markers representative of the pathological processes occurring within AAA could be valuable for many reasons. First, they could be used in clinical trials investigating novel drug therapies for AAA to determine the likely success of therapies under investigation. Second, blood markers could...
be used to identify patients who are at high risk of AAA rupture requiring early surgical intervention or those at low risk of AAA rupture in whom AAA surveillance could be continued. Third, they could be used to identify patients who are at risk of complications after AAA repair, eg, to detect continued perfusion of the AAA (endoleak) after endovascular repair.

**Current Research to Identify Circulating Markers of AAA Progression**

A large number of circulating markers have been associated with AAA presence and size. These include markers related to thrombus remodeling (eg, D-dimer), the extracellular matrix (eg, aminoterminal propeptide of type III procollagen), proteolytic enzymes (eg, matrix metalloproteinase-9), lipids (eg, high-density lipoprotein), and inflammation (eg, interleukin-6).53,54

In contrast, there have been fewer studies investigating circulating markers associated with AAA progression. Studies of this type are difficult to design and carry out for many reasons. First, during surveillance of patients, there are frequently losses to follow-up because of patients undergoing AAA repair or serious complications.17 Second, monitoring AAA growth is not straightforward because of the complexity of measuring AAA diameter accurately outlined above.23,24

Currently, no circulating markers have been accepted to be sufficiently valuable to be introduced into clinical practice.

**Circulating Markers Associated With AAA Growth**

Tables 1 and 2 illustrate some of the marker investigated for the association with small AAA growth.55–70 Of the marker examined, only 2, namely D-dimer and plasmin–antiplasmin complex, have been associated with AAA growth after adjusting for initial AAA diameter in at least 2 distinct studies (Table 1).55–57 In the largest of these studies, in which 299 patients with small AAAs were included, it was reported that the use of plasma D-dimer plus initial aortic diameter enable the identification of groups with growth as disparate as 0.4 and 2.5 mm/y.56 Other markers investigated

### Table 1. Examples of Circulating Biomarkers Assessed for Associated With Small AAA Growth in At Least 2 Studies

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Patient Number</th>
<th>Imaging Modality</th>
<th>Measurement of AAA Growth</th>
<th>Measure Error of Imaging</th>
<th>Measure Error of Assay</th>
<th>Association With AAA Growth</th>
<th>Significant After Adjustment†</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer</td>
<td>96</td>
<td>US and CT</td>
<td>Maximum of AP, transverse and lateral orthogonal diameter</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes in MR (100-ng/mL increase associated with growth of 0.6 mm)</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>299</td>
<td>US</td>
<td>Maximum of AP and transverse diameters</td>
<td>95% CI &lt;3 mm</td>
<td>CV 2%–3%</td>
<td>r=0.39</td>
<td>Yes in MR, ROC and CART (using DD and diameter could define groups with growth 0.4–2.5 mm/y)</td>
<td>56</td>
</tr>
<tr>
<td>PAP</td>
<td>70</td>
<td>US</td>
<td>AP diameter</td>
<td>ICC 0.98</td>
<td>CV 3%</td>
<td>r=0.39</td>
<td>Yes in MR and ROC</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>US and CT</td>
<td>Maximum of AP, transverse and lateral orthogonal diameter</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes in MR OR, 1.01 (95% CI, 1.00–1.02)</td>
<td>55</td>
</tr>
<tr>
<td>CRP</td>
<td>260</td>
<td>CT</td>
<td>Internal orthogonal diameter</td>
<td>NR</td>
<td>CV 6%</td>
<td>Rise in CRP from baseline to 12 m highly correlated with growth (r=0.71)</td>
<td>Yes in MR</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>545</td>
<td>US</td>
<td>Maximum of AP and transverse diameters</td>
<td>95% CI &lt;3 mm</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>142</td>
<td>US</td>
<td>AP diameter</td>
<td>IOV 1.4 mm</td>
<td>NR</td>
<td>No</td>
<td>NA</td>
<td>17</td>
</tr>
<tr>
<td>MMP-9</td>
<td>178</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>CV 4%</td>
<td>No</td>
<td>No</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>CT</td>
<td>AP diameter</td>
<td>NR</td>
<td>NR</td>
<td>r=0.32</td>
<td>NR</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>US and CT</td>
<td>Maximum of AP, transverse and lateral orthogonal diameter</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>55</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>142</td>
<td>US</td>
<td>AP diameter</td>
<td>IOV 1.4 mm</td>
<td>NR</td>
<td>r=−0.22</td>
<td>Yes in MR; no in ROC</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>US and CT</td>
<td>Maximum of AP, transverse and lateral orthogonal diameter</td>
<td>NR</td>
<td>NR</td>
<td>Yes positive association</td>
<td>No</td>
<td>55</td>
</tr>
<tr>
<td>PIIINP</td>
<td>99</td>
<td>US</td>
<td>AP diameter</td>
<td>IOV 1.7 mm</td>
<td>NR</td>
<td>r=0.24</td>
<td>Yes in MR marginal improvement in ROC</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>139</td>
<td>US</td>
<td>NR</td>
<td>NR</td>
<td>CV 5%</td>
<td>r=0.15–0.55</td>
<td>NR</td>
<td>63</td>
</tr>
</tbody>
</table>

AAA indicates abdominal aortic aneurysm; AP, anterior-posterior; CART, classification and regression tree analysis; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; CV, coefficient of variation; DD, D-dimer; ICC, interobserver correlation coefficient; IOV, inter-observer variation (2 SD); MMP-9, matrix metalloproteinase 9; MR, multivariate regression; NA, not applicable; NR, not reported; PAP, plasmin–antiplasmin complex; r, correlation coefficient; PIIINP, Procollagen-III-N-terminal propeptide; and ROC, receiver operator characteristic curve; and US, ultrasound.

†For initial diameter.
Table 2. Examples of Circulating Biomarkers Assessed for Associated With Small AAA Growth in Single Studies

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Patient Number</th>
<th>Imaging Modality</th>
<th>Measurement of AAA Growth</th>
<th>Measure Error of Imaging</th>
<th>Measure Error of Assay</th>
<th>Association With AAA Growth</th>
<th>Significant After Adjustment*</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPA</td>
<td>70</td>
<td>US</td>
<td>AP diameter</td>
<td>NR</td>
<td>CV 28%</td>
<td>r=0.37</td>
<td>NR</td>
<td>64</td>
</tr>
<tr>
<td>PRX-1</td>
<td>80</td>
<td>US</td>
<td>NR</td>
<td>IOV 1.4 mm</td>
<td>CV 9%</td>
<td>r=0.3</td>
<td>Yes added to diameter</td>
<td>65</td>
</tr>
<tr>
<td>TWEAK</td>
<td>79</td>
<td>US</td>
<td>AP diameter</td>
<td>NR</td>
<td>CV 8%</td>
<td>r=−0.263</td>
<td>Yes in MR</td>
<td>66</td>
</tr>
<tr>
<td>EP</td>
<td>99</td>
<td>US</td>
<td>AP diameter</td>
<td>IOV 1.7 mm</td>
<td>CV 10%</td>
<td>r=0.31</td>
<td>Yes in MR marginal improvement in ROC</td>
<td>62</td>
</tr>
<tr>
<td>P-Elastase</td>
<td>79</td>
<td>US</td>
<td>AP diameter</td>
<td>NR</td>
<td>NR</td>
<td>r=0.30</td>
<td>NR</td>
<td>67</td>
</tr>
<tr>
<td>OPN</td>
<td>198</td>
<td>US</td>
<td>Maximum of AP and transverse diameters</td>
<td>CR 1.2 mm; LOA −0.8 to 1.6 mm</td>
<td>ICCC 0.99</td>
<td>r=0.24</td>
<td>Yes in MR</td>
<td>68</td>
</tr>
<tr>
<td>OPG</td>
<td>146</td>
<td>US</td>
<td>Maximum of AP and transverse diameters</td>
<td>NR</td>
<td>NR</td>
<td>r=0.20</td>
<td>Yes in MR</td>
<td>69</td>
</tr>
</tbody>
</table>

AAA indicates abdominal aortic aneurysm; AP, anterior-posterior; CR, coefficient of repeatability; CV, coefficient of variation; EP, serum elastin peptides; ICCC, interassay concordance correlation coefficient; IOV, interobserver variation (2 SD); LOA, limits of agreement; MR, multivariate regression; NR, not reported; OPG, osteoprotegerin; OPN, osteopontin; P-Elastase, P- elastase-a1-antitrypsin-complexes; PRX-1, peroxiredoxin-1; r, correlation coefficient; ROC, receiver operator characteristic curve analysis; tPA, tissue-type plasminogen activator; TWEAK, soluble tumor necrosis factor-like weak inducer of apoptosis; and US, ultrasound.

*For initial diameter.

have been examined in single cohorts only, or findings have been inconsistent across studies (eg, C-reactive protein and matrix metalloproteinase-9; Tables 1 and 2).

Circulating Markers Associated With AAA Rupture

Few studies have investigated the association of circulating markers with subsequent AAA rupture. Studies investigating predictors of AAA rupture are difficult to perform and are subject to bias because they require large sample sizes, given that rupture of small AAAs is rare and most large AAAs undergo surgical repair. Currently, no circulating biomarkers have been convincingly shown to predict AAA rupture. Satta et al reported the assessment of 18 patients whose AAA subsequently ruptured were compared with 55 patients whose AAA remained intact during follow-up. The investigators reported that serum concentrations of the collagen turnover marker procollagen-IIIN-terminal propeptide were significantly higher in patients who later developed AAA rupture although it was not stated whether this association was independent of initial AAA diameter.

Future Progress in Identifying Circulating Markers of AAA Progression

Table 3 illustrates some advantages and disadvantages of techniques in current use or under investigation for predicting AAA progression. Given the potential ease of measuring blood markers in clinical trials and clinical practice, there is continued interest in such tools. Further work is, however, needed to identify groups of markers, which are reflective of the pathological processes present in AAA and which can be used as surrogate markers in clinical trials and clinical practice. Many proteomics and metabolomics studies have been performed in an attempt to screen for markers; however, currently, these techniques have many limitations, such as the difficulty in detecting less abundant proteins within blood samples and problems in processing high numbers of

Table 3. Theoretical Advantages and Disadvantages of Imaging and Circulating Biomarkers as Surrogate Markers of AAA Progression

<table>
<thead>
<tr>
<th>Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum AAA diameter</td>
<td>Well-established predictor of AAA rupture. Used in clinical practice to decide clinical care</td>
<td>Substantial variation in methods used to measure. Slow changes during monitoring which are within the reported measurement error</td>
</tr>
<tr>
<td>Total AAA volume</td>
<td>Maybe a more sensitive marker of AAA progression as changes during follow-up have been reported to be more commonly greater than the measurement error in comparison to diameter</td>
<td>Techniques to measure are less well defined and available in clinical practice</td>
</tr>
<tr>
<td>AAA peak wall stress</td>
<td>Considers overall anatomical and hemodynamic aspects and may provide a better individual assessment of rupture risk</td>
<td>Techniques to measure are less well defined and available in clinical practice and currently requires CTA or MRA</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>May provide a localized measure of the activity of aortic wall pathology</td>
<td>Current predictive power not well defined and technology for assessment less available than other imaging</td>
</tr>
<tr>
<td>Circulating markers</td>
<td>Relatively easy to examine</td>
<td>Identifying markers specific for AAA problematic</td>
</tr>
</tbody>
</table>

AAA indicates abdominal aortic aneurysm; CTA, computed tomographic angiogram; FDG-PET: fluorodeoxyglucose (18F) positron emission tomography; and MRA, magnetic resonance angiogram.
samples reproducibly. Recently, many investigators have reported circulating micro-RNAs associated with AAA presence, such as miR-155, miR-191-3p, miR-455-3p, miR-1281, and miR-411. Techniques to screen large numbers of circulating micro-RNAs and lipids are better developed than for proteins, and therefore it is possible that these fields of investigation maybe more fruitful in identifying effective markers. Ultimately, any markers identified by these screening techniques will need to be tested in large numbers of patients from different populations to assess their value in different situations such as determining the response to treatment or predicting which AAAs should receive early or delayed intervention.

Conclusions

AAA diameter remains the most widely used and important marker of AAA progression although it has many limitations. Newer imaging assessments, such as volume measurements, biomechanical analyses, and functional and molecular imaging, as well as circulating biomarkers have potential to be adopted in practice in the future.

Disclosures

None.

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**Significance**

Abdominal aortic aneurysm is a common and potentially lethal disease. Predicting the progression of small abdominal aortic aneurysms is essential in clinical practice and research. Here, we review the current evidence on the value of different surrogate markers of abdominal aortic aneurysm progression, such as abdominal aortic aneurysm diameter and volume measurement, biomechanical analyses, functional and molecular imagings, and circulating biomarkers.
Surrogate Markers of Abdominal Aortic Aneurysm Progression
Anders Wanhainen, Kevin Mani and Jonathan Golledge

Arterioscler Thromb Vasc Biol. 2016;36:236-244; originally published online December 29, 2015;
doi: 10.1161/ATVBAHA.115.306538
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the
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