Innovations in Treating Aortic Diseases: The Abdominal Aorta

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Patients with an abdominal aortic aneurysm (AAA) could benefit from earlier diagnosis to improve long-term outcomes. Candidate serum biomarkers for earlier AAA diagnosis include D-dimer, fibrinogen, low-density lipoprotein, high-density lipoprotein, lipoprotein(a), and the proteolytic enzymes known as matrix metalloproteinases. Furthermore, biomarkers such as brain natriuretic peptide significantly stratify perioperative risk in AAA repair. Statins significantly improve outcomes after AAA repair. They may also significantly slow AAA growth to allow pharmacologic arrest of AAA development. Recent trials have focused attention on fluid management for AAA repair. Although restrictive fluid management may significantly improve clinical outcomes, current evidence does not clearly support crystalloid or colloid for AAA repair. There may be an increased risk of renal dysfunction associated with hetastarch therapy. Endovascular repair has revolutionized the clinical management of AAAs. Recent trials have shown its significant outcome advantages. Furthermore, it is also applicable in high-risk operative cohorts and, in the future, may be suited for earlier AAA repair. This technology continues to advance with the development of branched and fenestrated grafts as well as total percutaneous endovascular AAA repair. Regardless of these advances, the clinical management of endoleaks will remain a major clinical focus. Taken together, these advances in the management of AAAs likely will significantly influence future clinical approaches to this challenging patient cohort.

KEY WORDS: abdominal aortic aneurysm, D-dimer, fibrinogen, lipoprotein(a), brain natriuretic peptide, matrix metalloproteinases, statins, doxycycline, fluid therapy, colloid, crystalloid, hetastarch, endovascular aortic repair, fenestrated aortic graft, branched aortic graft

THIS REVIEW covers recent major developments in the clinical management of patients with an abdominal aortic aneurysm (AAA). This introduction surveys the major themes that are covered in greater detail in the subsequent sections of the article.

Patients with an AAA could benefit from an earlier diagnosis to prevent the increased morbidity and mortality from aorta-related complications. An earlier diagnosis is possible by means of serum biomarkers such as D-dimer and fibrinogen. Serum lipid profiles, including low-density lipoprotein, high-density lipoprotein, and lipoprotein(a) also correlate significantly with the presence of an AAA. The proteolytic enzyme family known as matrix metalloproteinases may not be only a candidate diagnostic biomarker for an AAA, but also represents a therapeutic target for doxycycline. Besides diagnosis, biomarkers can also assist in the stratification of perioperative risk for AAA repair. Preoperative brain natriuretic peptide levels significantly predict a major adverse clinical outcome after AAA repair.

Although statins significantly improve clinical outcomes after AAA repair, they may also significantly slow the growth rate of an AAA. Pharmacologic delay of AAA growth and development may be possible in the future with agents such as doxycycline and statins.

Recent trials suggest that restrictive perioperative fluid management may significantly improve clinical outcomes after AAA repair. Current evidence suggests that clinical outcomes after AAA repair are not significantly determined by the choice of crystalloid or colloid. Although there may be an increased risk of renal dysfunction associated with hetastarch therapy, this finding requires clinical confirmation.

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BIOMARKERS IN AN AAA

The management of an AAA might benefit significantly from the measurement of circulating AAA biomarkers to facilitate earlier diagnosis and a refined prognosis.[1] Because thrombosis is often associated with an AAA, fibrinogen and D-dimer have been investigated for their diagnostic potential for an AAA.[1,2] A recent meta-analysis showed that elevations in fibrinogen (n = 7,805: 10.7% with an AAA, collated from 10 studies) and D-dimer (n = 667: 39.6% with AAA collated from 6 studies)

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significantly predict the presence of an AAA.[2] An even more recent large observational trial (N = 1,392: 27.2% with an AAA) confirmed the significant diagnostic use of D-dimer; values greater than 400 and 900 ng/mL had predictive odds ratios of 12.1 (95% confidence interval, 7.1-20.5) and 24.7 (95% confidence interval, 13.7-44.6), respectively.[3] Furthermore, elevated D-dimer levels significantly correlated with AAA growth and overall outcome risk.[3] These results were confirmed in a recent smaller study (N = 165: 45.5% with an AAA).[4] Although this study also showed a possible role for C-reactive protein as a diagnostic AAA marker, the dominant diagnostic marker remained D-dimer.[4] Although these coagulation markers significantly suggest an AAA, this is not the case for tissue plasminogen activator. A recent meta-analysis (N = 693: 33.8% with an AAA, collated from 5 studies) showed an insignificant association between tissue plasminogen activator and an AAA ($p = 0.40$).[5] The role of C-reactive protein as a diagnostic AAA marker merits further investigation.

Besides disordered coagulation, an AAA is often associated with aortic atherosclerosis, a process that is intimately related to disordered lipid metabolism.[6] Consequently, it is likely that lipoproteins will correlate with the development of an AAA. A recent meta-analysis (N = 9079: 8.9% with an AAA, collated from 8 trials) showed that lower high-density lipoprotein cholesterol (mean difference = 0.15 mmol/L; 95% confidence interval, 0.07-0.24 mmmol/L; $p = 0.0006$) and higher low-density lipoprotein cholesterol (mean difference = 0.25 mmol/L; 95% confidence interval, 0.08-0.42 mmol/L) significantly correlated with the presence of an AAA.[7] A recent large observational trial (N = 3,327) showed that low high-density lipoprotein cholesterol was significantly protective against an AAA (odds ratio = 0.72; 95% confidence interval, 0.56-0.93).[8] Clearly, an important question is whether statins affect the natural history of an AAA, given that dyslipidemia is a major risk factor for an AAA. This is discussed in detail later in this review.

Lipoprotein(a) also has been the subject of extensive research as a biomarker in vascular disease.[9] Lipoprotein(a) consists of low-density lipoprotein combined with a glycoprotein known as apolioprotein(a). A recent massive meta-analysis (N = 58,000: 40 studies) confirmed the significance of lipoprotein(a) in coronary heart disease (relative risk = 2.08; 95% confidence interval, 1.67-2.58).[9] The logical question that follows is whether lipoprotein(a) is associated with an AAA. A recent meta-analysis (N = 2,278: 43.1% with an AAA, collated from 5 trials) showed that elevated lipoprotein(a) levels were significantly associated with the presence of an AAA (standardized mean difference = 0.26; 95% confidence interval, 0.08-0.44; $p = 0.005$).[10] This observation may represent a future therapeutic target in the prevention of AAAs.

Proteolytic degradation of the abdominal aortic wall by enzymes such as the matrix metalloproteinases also has been linked to the development of AAAs.[11] These proteolytic enzymes may be measured in the plasma and so may serve as biomarkers for AAAs. A recent meta-analysis (N = 838: 30.8% with an AAA, collated from 8 trials) showed that elevated levels of matrix metalloproteinase-9 were significantly associated with AAAs (standardized mean difference = 0.70; 95% confidence interval, 0.23-1.17; $p = 0.004$).[11] This enzyme group recently has been studied as a therapeutic target with doxycycline, a known inhibitor of matrix metalloproteinases. In 2 pilot studies, a short course of doxycycline was shown to significantly reduce the proteolytic activity in the human abdominal aortic wall.[12,13] Further randomized trials are indicated to explore the therapeutic efficacy of doxycycline in AAAs.

Brain natriuretic peptide also has been investigated extensively in the assessment of operative risk in vascular surgical patients, including the patient subset with AAAs.[14] Two recent meta-analyses have strengthened the evidence for the predictive power of this biomarker in patients undergoing operative repair for an AAA.[15,16] The first meta-analysis (N = 3,281, collated from 9 trials across noncardiac surgery, including AAA repair) showed that preoperative brain natriuretic peptide levels were significantly predictive of perioperative death and myocardial infarction (odds ratio = 44.2; 95% confidence interval, 7.6-257) as well as other major adverse events (odds ratio = 14.7; 95% confidence interval, 5.7-38.2).[15] The second meta-analysis (N = 4,856, collated from 15 trials across noncardiac surgery, including AAA repair) confirmed that preoperative brain natriuretic peptide is a powerful independent predictor of postoperative major adverse cardiovascular events both in the short term (odds ratio = 19.7; 95% confidence interval, 13.18-29.65; $p < 0.0001$) and the long term (odds ratio = 17.70; 95% confidence interval, 3.11-100.80; $p < 0.0001$).[16] Further trials should examine the optimization of patients for AAA repair based on a multimodal approach including preoperative measurement of brain natriuretic peptide.[14,17] Ideally, this powerfully predictive biomarker would be measured weeks before surgery to allow time for subsequent adequate optimization in the high-risk groups.[17] This type of stratified approach could lead to further improvement in important clinical outcomes after AAA repair both in the short term and in the long term.[18] Biomarkers together could also lead to further refinement of the already effective population-based screening protocols for AAAs.[19,20] Given the plethora of identified candidate biomarkers, it is likely that as a group they will lead to further refinement of the clinical management of AAAs.

STATIN THERAPY IN AAAs

Statin therapy significantly improves clinical outcomes after AAA repair. The supporting evidence already has been reviewed in an earlier article focused on statin therapy.[21] Recent trials have extended this outcome benefit after AAA repair to enhanced renal outcomes and lower health resource utilization with overall lower hospital costs.[22,23]

Given the enhanced ability to detect AAAs with screening tools such as biomarkers and abdominal ultrasound, interventions to prevent the expansion of detected AAAs could have an enormous therapeutic application. A recent meta-analysis (N = 697: 5 observational studies) has shown that in patients with small AAAs statins were significantly associated with reduced AAA expansion (standardized mean difference = 0.50, 95% confidence interval, 0.75-0.25; $p = 0.0001$).[24] Based on the positive results from this meta-analysis, the investigators suggested that a large prospective randomized trial was indicated to confirm this observation. The inhibitory effect of statins on AAA growth also has sparked considerable research into their