ASK THE EXPERTS

The Biggest Breakthrough in AAA Therapy in the Next Decade Will Involve . . .

Experts contemplate necessary advancements in the next era of AAA management, including new imaging technology, an understanding of the role of genetics and genomics, and EVAR improvements.

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With the new technology of plastic materials, metals could be replaced by cheaper materials that interact less aggressively with fabric. I don't understand why we still use metals as components of endografts. We also need to get rid of radiation exposure or at least decrease its dose. I am aware of a new technology that uses automated vessel mapping techniques combined with electromagnetic tracking to provide real-time navigation with nonfluoroscopic interventional image guidance. In the future, high-resolution color imaging could become standard, and robotic technology will be more affordable and very precise. We are still waiting for preventive treatments for aneurysms and dissections, and medication to avoid or decrease aneurysmal growth is still elusive.

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Without question, the biggest breakthrough in abdominal aortic aneurysm (AAA) therapy in the last 20 years has been the advent of endovascular repair. Percutaneous endovascular aneurysm repair (EVAR) is the polar opposite of open repair in terms of invasiveness; not surprisingly, morbidity associated with EVAR is greatly reduced. Although early mortality results with EVAR are equal or better, longer-term studies have demonstrated a reduction in that benefit and, in some studies, a benefit with open repair. As a result, the most important breakthrough in AAA therapy for the next decade will be to improve long-term mortality with endovascular repair.

Even at this time, many of those breakthroughs are likely already occurring. Current and newer-generation devices are better designed and more durable, thus they are less likely to fail over time, resulting in endoleaks and aneurysm rupture. Devices are lower profile and easier to implant, which makes the overall procedure quicker, less morbid, and less stressful on the patient. Improved techniques allow patients to have quicker and less-invasive procedures, leading to earlier discharges and reduced infection rates. In addition, implantation strategies have evolved to anticipate potential failure modes and prevent them altogether. Devices are also being designed to address anatomic challenges, such as compromised proximal necks.

At the same time, we must recognize that there is likely physiology inherent to AAA that we don't fully understand at this time. Designing treatment paradigms to account for this may also be important for improving mortality. Clearly, EVAR is and should be the preferred therapy for AAA. Improving long-term mortality will be a part of bringing EVAR to its next stage.

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Conservative management of small aneurysms has been defined by seminal trials, including the ADAM trial[1] in the United States and the UK Small Aneurysm trial.[2] These studies supported a stance of watchful waiting for small, run-of-the-mill AAAs. However, I believe significant progress will be made to refine the management of small AAAs over the next decade, as we develop new insights into AAA progression, genetics, and pathogenesis.

The most immediate update will come from the eagerly awaited results of N-TA^{3}CT.[3] This National Institutes of Health–funded trial of men and women with small AAAs (3.5–5.0 cm and 3.5–4.5 cm, respectively) randomized participants to daily doxycycline versus placebo for 2 years. The primary aim of N-TA^{3}CT was to assess change in AAA size, with secondary analyses to investigate inflammatory markers, such as levels of matrix metalloproteinase (MMP)-9, interferon-gamma, and C-reactive protein. Additionally, the wealth of prospectively collected data (including biomarkers and CT scans every 6 months) will be a platform for many more studies to understand AAA progression and pathophysiology.

Another area for major advancement is understanding the role of genetics and genomics in regard to AAA. Numerous genome-wide association studies and candidate gene association studies identified single nucleotide polymorphisms in genes for MMP-3, sortilin-1, low-density lipoprotein receptor, low-density lipoprotein receptor–related protein 1, tissue inhibitor of MMP-1, and many others associated with AAA.[4] However, the odds ratios reported in large genomics studies suggest that AAA pathogenesis is a multifactorial process involving genetic factors as well as environmental factors such as smoking.[4] Although genome-wide association studies have been widely used over the last decade, the next decade brings even more opportunity for large-scale, population-based genomics research and integration of genomics data with proteomics, metabolomics, and epigenetic findings, among others. The growing use and availability of sophisticated bioinformatics systems (also known as *big data tools*) will ultimately provide insight into AAA pathophysiology.

Finally, I expect that advances in imaging technology will lead to important developments in morphometric analysis of AAA. These developments may include progress in finite element analysis and calculations of peak wall stress, better understanding of geometric factors involved in predicting AAA rupture, or development of new biomechanical models.

Developments and improvements in imaging, together with greater insight into underlying biologic pathways, will have the most impact on surveillance and small AAA management. Eventually, we may arrive at a point where imaging characteristics, biomarkers, and/or genotyping are integrated to individualize surveillance protocols and better predict risks of rupture, thus bringing AAA management into the era of precision medicine.

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Endoleak represents the most frequent and substantial cause of aneurysm sac enlargement after EVAR. Type I and III endoleaks are relatively well understood and most often occur due to anatomic challenges and device issues. Type II endoleaks vary in origin and are a source of controversy in terms of whether they can be prevented and, in particular, when and how they should be treated once they occur. As such, they represent one of the greatest opportunities for breakthrough innovation in EVAR besides miniaturization of the delivery system such that outpatient EVAR becomes the standard of care.

Type II endoleaks can emerge in the early postoperative period or arise later. Most—but not all—type II endoleaks observed in the early postoperative period spontaneously resolve. The frequency of spontaneous resolution, although welcome, presents a dilemma regarding whether to intervene, with the chance that the endoleak on the table will not be in the majority. Adding to this challenge, the risk of rupture due to type II endoleaks is relatively rare, which may further cause operators to err on the side of conservative management.

Late-onset type II endoleaks may carry a more significant risk of sac enlargement and therefore have been referred to as *malignant type II endoleak.* Risk factors for this type of refractory type II endoleak include internal iliac embolization, external iliac artery landing, patient age > 80 years, thrombus in the lumen, large inferior mesenteric/lumbar arteries, or a greater number of lumbar arteries. There have been several reports of possible preventive measures including use of the Nellix EVAS (endovascular aneurysm sealing) system (Endologix, Inc.) and preemptive branch vessel embolization, but further study is needed to validate them.[1-6]

Meanwhile, endotension is a phenomenon in which the sac diameter has increased, but there is no clear endoleak present. Its causes are usually unknown, and we cannot accurately measure and quantify the blood flow involved. Mechanisms for this have been suggested, including the pressure inside the graft propagating to the wall due to the permeability of the fabric and serum leakage through the fabric. It has been reported that the incidence of endotension is decreasing with the use of newer EVAR devices.

Long-term studies have shown that aneurysm sac enlargement due to either endoleak or endotension is a significant risk factor for endograft infection, which is a deadly condition.[7] Therefore, as I mentioned, elucidation of the pathology of EVAR aneurysm enlargement and its prevention is a key future task.

Breakthroughs in the prevention and treatment of type II endoleak and endotension are needed. We have previously reported that aortic wall enhancement (AWE) was observed in the venous phase of contrast CT after EVAR, which results in postoperative sac reduction.[8] When AWE was observed at 1 month postprocedure, the aneurysm was reduced in many cases. AWE saw an inverse correlation with type II endoleak and was an independent factor with respect to sac diameter reduction. Although it is not yet known whether the mechanism of AWE relates to inflammation and absence of it is a sign of aortic wall ischemia/atrophy (absence of the vasa variorum), the presence or absence of AWE may be a helpful signal regarding the likelihood of postoperative aneurysm expansion and may shed light on to this conundrum and eventually lead to prevention of this worrisome and annoying Achilles heel of EVAR.

Past breakthroughs in EVAR have predominately come from the device and technical side, but the next breakthrough may be in better understanding of the aneurysm sac, including the associated genomics, and eventually controlling enlargement. ■

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