

# The EVAR Landscape in 2011

A status report on AAA therapy.

BY FRANK J. CRIADO, MD, FACS, FSVM

**A**bdominal aortic aneurysm (AAA) ranks high among the most significant cardiovascular diseases. It has been estimated that in the United States, 1.1 million individuals between the ages of 50 and 84 have an AAA;<sup>1</sup> the actual number may well be larger. Of these, more than 100,000 new cases are diagnosed, and in excess of 50,000 patients undergo aneurysm repair each year (Figure 1). At least 15,000 deaths annually can be attributed to an AAA, and most are related to rupture of the aneurysm, making it the 13th leading cause of death overall.<sup>1,2</sup> Men are disproportionately affected (5:1), but women tend to have worse treatment outcomes and a higher mortality rate in the face of rupture.<sup>3,4</sup> Definitive treatment has been available since the early 1950s when surgical techniques for resection and graft replacement were developed. AAA repair emerged as a relatively common operation in the 1960s and 1970s and—truly—became a signature procedure in vascular surgery. But dark clouds loomed on the horizon as its invasive nature resulted in frequent major morbidity and even death. More troublesome yet, many patients were excluded from treatment when deemed inoperable on the basis of medical or, rarely, anatomical contraindications to surgical treatment. Thus, the AAA landscape remained incomplete and suboptimal for decades (from a patient-care perspective), as the open surgical approach left many without a viable treatment option.

## THE EMERGENCE OF EVAR

Dr. Juan Parodi understood these unmet needs perhaps more clearly and earlier than anyone else and, through sharp inventiveness, two key partnerships (with Drs. Julio Palmaz and Héctor Barone), and sheer perseverance and hard work, succeeded in developing a

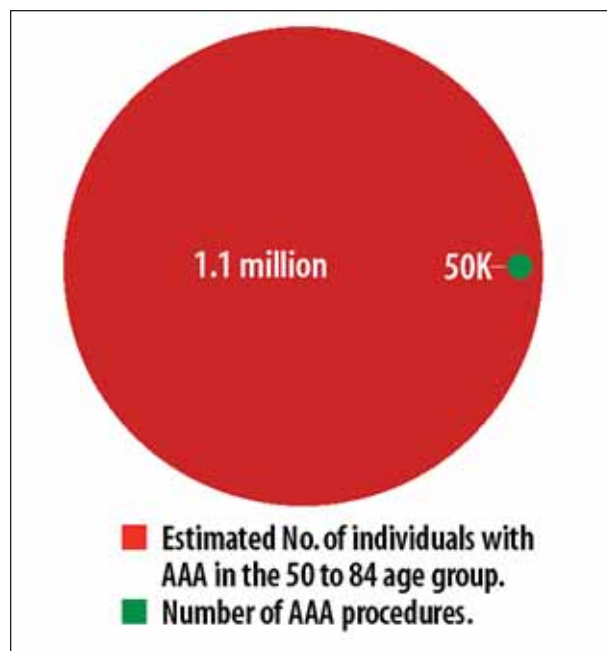


Figure 1. Of the 1.1 million people between ages 50 and 84 diagnosed with an AAA, approximately 50,000 undergo aneurysm repair. Created with information from Kent KC, et al. *J Vasc Surg.* 2010;52:539-548.<sup>1</sup>

catheter-based technique that essentially duplicated the universally adopted endoaneurysmorrhaphy surgical strategy but obviating the need for a major intra-abdominal operation and aortic cross-clamping through a totally intraluminal approach. The world's first endovascular stent graft operation for AAA repair (EVAR) was performed by Drs. Parodi, Palmaz, and Barone at the Instituto Cardiovascular de Buenos Aires in Argentina on September 7, 1990.<sup>5</sup> Not surprisingly,

(Images courtesy of respective manufacturers.)








September 1999		November 2002	May 2003	October 2004	April 2008	December 2010
<b>Ancure</b> Guidant	<b>AneuRx</b> Medtronic	<b>Excluder</b> Gore	<b>Zenith</b> Cook	<b>Powerlink</b> Endologix	<b>Talent</b> Medtronic	<b>Endurant</b> Medtronic
						

Figure 2. A timeline of FDA approvals for EVAR stent grafts.

but unbeknown to them at the time, they were not alone in these endeavors. Most notably, Volodos in the Ukraine,<sup>6</sup> Lazarus in the United States,<sup>7</sup> and a few others,<sup>8</sup> were working independently and concurrently on similar less-invasive solutions for aortic aneurysm repair. The revolutionary new technique was destined to change everything and signaled the beginning of the next era in aortic surgery. Furthermore, and beyond aneurysm therapy, these developments propelled the entire field and, in truth, vascular surgery as a whole in a transformative new direction from where it would not turn back.<sup>5</sup>

### EVAR DEVICES, NOW AND THEN

Stent graft devices have evolved rapidly over the last 2 decades. In the 1990s, we witnessed the emergence of several early designs that encountered many challenges—both anticipated and unforeseen—related mostly to the rather hostile aortic environment the implanted devices had to endure. US Food and Drug Administration (FDA) approval of the first two stent grafts to pass regulatory muster in September 1999 (AneuRx [Medtronic, Inc., Minneapolis, MN] and Ancure [Guidant Corporation]) marked the end of the infancy phase for these technologies. Significant iterative improvements and design breakthroughs were just around the corner. Commercial availability of the Ancure device was short-lived because the manufacturer (Guidant Corporation) decided to remove it from the market in 2003, but the AneuRx stent graft proved quite resilient, and it has gone through seven evolutionary iterations and remains available in the US market today. In all, six FDA-approved EVAR endograft devices are currently available in the US market (Figure 2). In 2002, Gore & Associates (Flagstaff, AZ) received FDA approval for the Excluder device, which was soon followed by Cook Medical's (Bloomington, IN) Zenith and

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Endologix's (Irvine, CA) Powerlink in 2003 and 2004, respectively. The latest entry was Medtronic's Endurant, which was granted regulatory approval in December 2010. It is widely viewed as a next-generation technology,<sup>9</sup> with a design that incorporated a number of important lessons learned over the past decade, including a lower profile, enhanced deliverability, flexibility, and deployment, and a suprarenal fixation apparatus with integrated anchoring pins that penetrate deep into the aortic wall. That said, it is important to recognize that all currently approved and commercially available devices seem to perform remarkably well when used on-label and in adherence to the manufacturers' instructions for use. Integrity issues appear to have been overcome through better designs and testing strategies.

Nonetheless, unsatisfactory outcomes continue to occur in the EVAR universe, and most such failures (today) are related to off-label use of stent grafts when physicians choose to "push the envelope" for treatment of patients and anatomies that are well outside the approved indications. And although true that medical practice realities may at times call for such action, it is most important for all involved—patients included—to realize and be informed that device performance and anticipated clinical outcomes may be

quite different (ie, inferior) when a stent graft is used in such manner.

## DEVICE FAMILIES

Stent graft devices are often depicted as belonging to a first generation, second generation, etc. Regrettably, no one has ever defined precisely just what a *generation* is with regard to stent grafts. We felt it would be more useful to describe devices as belonging to families, and just as in human societies, families are best characterized by ancestral origins. With that in mind, *EVAR device families* are defined by their manufacturers (see *Device Families* sidebar).

## CURRENT AND FUTURE DEVELOPMENTS

A number of shortcomings and unmet needs remain unresolved and have appropriately become the primary drivers for ongoing development. Three of these stand out:

**AAA anatomies featuring short and angulated proximal necks.** Endurant is the first device to become commercially available in the United States that was largely developed to address such a need. The FDA-approved on-label indication that was sought and granted does not reflect such capabilities, but early and midterm results from Europe are quite encouraging regarding the performance of the Endurant device in

patients with disadvantaged proximal necks.<sup>9</sup> The Aorfix stent graft (Lombard Medical Technologies Inc., Tempe, AZ) is another advanced design created with the specific purpose of treating severely angulated proximal necks but while adhering to an infrarenal fixation strategy. It was first granted CE Mark regulatory approval in Europe in 2001, and an on-label indication that includes AAA anatomies with a proximal neck angulation up to 90° was added in 2009; this is the first and only regulatory approval (anywhere in the world) for angulations of such degree.

**Lower profile.** This remains a worthy and appealing objective, both to obviate access issues and improve deliverability, as well as to facilitate and strengthen the evolving shift to percutaneous EVAR. It would not be far-fetched to predict that several stent grafts with an outer diameter profile of < 16 F are likely to become available within the next 5 years. Recent European regulatory approval of the 14-F Ovation endograft system (TriVascular, Inc., Santa Rosa, CA) is a strong sign of the ongoing trend. The 14-F Incraft AAA stent graft system (Cordis Corporation, Bridgewater, NJ) is another such example, but the device remains to be fully tested in the clinical arena.

**Branches.** This is undeniably a major issue because branch management strategies represent the next fron-

## DEVICE FAMILIES

### APTUS, INC.

- Aptus<sup>a</sup>



### COOK MEDICAL

- Zenith
- Zenith Flex
- Zenith LP<sup>a</sup>



### CORDIS CORPORATION

- Incraft<sup>a</sup>



### ENDOLOGIX

- Powerlink
- Nellix<sup>a</sup>



### GORE & ASSOCIATES

- Excluder



### LOMBARD

- Aorfix<sup>a</sup>



### MEDTRONIC, INC.

- AneuRx
- Talent
- Endurant



### TRIVASCULAR

- Ovation<sup>a</sup>



### VASCUTEK

- Anaconda<sup>a</sup>



<sup>a</sup>Investigational device in the United States.

(Images courtesy of respective manufacturers.)

tier in EVAR technologies, with the promise to expand applicability and optimize performance. Among manufacturers, Cook Medical pioneered these efforts with the development of fenestrated designs more than 10 years ago.<sup>10</sup> A relatively large experience has been accumulated worldwide, but the procedures have proven prolonged and complex, and the devices are extremely expensive and require customization. Building on that very solid platform, Cook and other major manufacturers are now shifting their focus to more standard, simpler endograft solutions that could be used in an off-the-shelf manner for the majority of cases.<sup>11</sup> The brand-new Ventana fenestrated-cuff design (Endologix) reflects this trend.<sup>12</sup> It would not be unrealistic to expect rapid advances and increased availability of such devices within the next few years.

In addition to the previously described primary targets for current and future research and design efforts in the EVAR technology arena, I would be remiss not to mention the Endologix Nellix device that represents the first serious attempt at out-of-the-box thinking in the EVAR technology field.<sup>13</sup> Instead of relying on the now-established endovascular principle of proximal-neck fixation and seal with subsequent aneurysm sac exclusion/depressurization followed by sac shrinkage, the Nellix system relies on the brand-new concept of treating the sac. The aneurysm itself is in fact anchored with a set of two thin polytetrafluoroethylene polymer-filled endobags that freeze the sac in a way that will (presum-

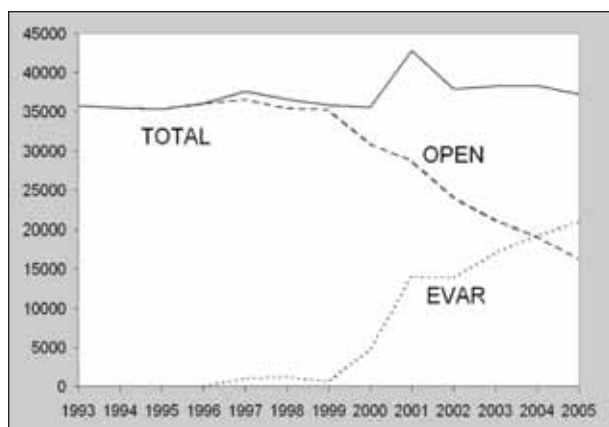


Figure 4. Total, open, and endovascular repairs of intact aortic aneurysms from 1993 to 2005. Reprinted from the *Journal of Vascular Surgery*, 49/3, Giles et al, 543-550, Copyright 2009, with permission from Elsevier.<sup>14</sup>

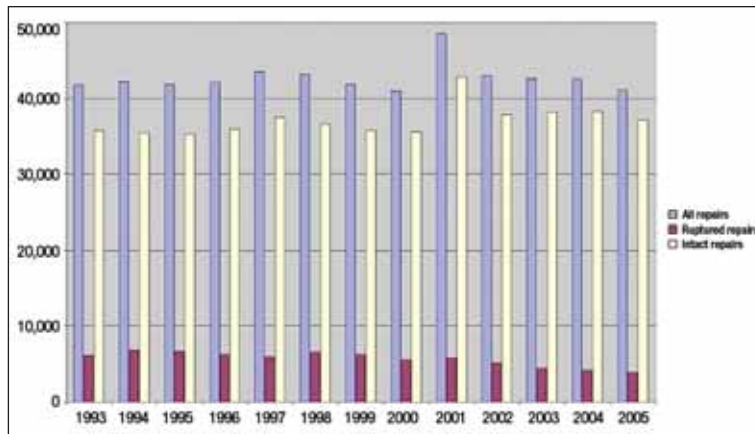


Figure 3. AAA repairs from 1993 to 2005 in the Nationwide Inpatient Sample. Reprinted from the *Journal of Vascular Surgery*, 49/3, Giles et al, 543-550, Copyright 2009, with permission from Elsevier.<sup>14</sup>

ably) prevent any further anatomical morphing or changes. Clinical experience to date is limited ( $n = 34$  patients enrolled in an international phase I trial), but device performance and clinical outcomes have been quite encouraging. Regulatory approval in Europe is anticipated as early as 2012. The future potential of a device such as this is significant because it could conceivably eliminate type II endoleaks and be able to treat no-neck aneurysms.

The Aptus EVAR system (Aptus Endosystems, Inc., Sunnyvale, CA) is another innovative design because of its endostaple-based fixation. The system was tested in a pivotal US clinical trial. Although the endostaple and graft performance overall seemed satisfactory, a num-

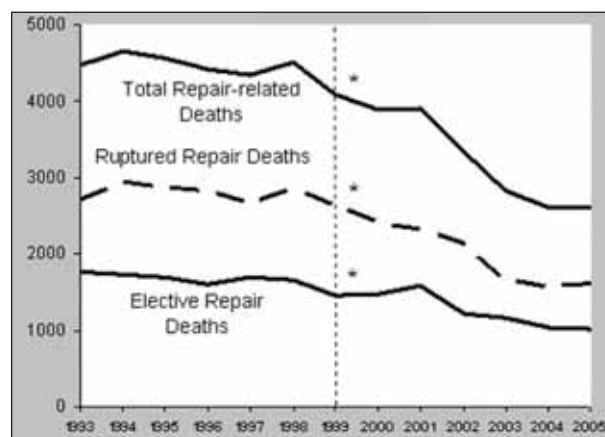


Figure 5. Annual deaths from 1993 to 2005 after AAA repair (total, ruptured, and elective). An asterisk indicates that the decline in deaths after the introduction of EVAR was greater than the decline before EVAR ( $P < .0001$ ). Reprinted from the *Journal of Vascular Surgery*, 49/3, Giles et al, 543-550, Copyright 2009, with permission from Elsevier.<sup>14</sup>



“EVAR’s rapid preeminence has resulted in many lives saved, a strong resolve toward uncovering undiagnosed aneurysms, and the promise of a much better less-invasive future for AAA treatment . . .”

ber of patients developed significant thromboembolic arterial complications that led to a root-cause investigation and—ultimately—redesign of the stent graft. The most recent iteration has been granted CE Mark approval. Also, the manufacturer is pursuing US regulatory approval and commercialization of the endostapler as a stand-alone product.

## EVIDENCE-BASED TREATMENT OF AAA

The EVAR-1 (United Kingdom Endovascular Aneurysm Repair 1) and DREAM (Dutch Randomised Endovascular Aneurysm Management) trials<sup>15,16</sup> have contributed significantly to establish and advance the scientific foundation of EVAR by providing level 1 evidence to serve as the most legitimate platform on which to base contemporary therapy. A much clearer picture emerged with reports of a 3.5-fold decrease in operative mortality with EVAR (5% with open repair [OR] vs 1.5% for EVAR). The mortality advantage held out to 4 years, and—not unexpectedly—there was no difference in all-cause mortality. Long-term complications and secondary interventions favored OR over EVAR. In the most recent publication of the EVAR-1 trial results with follow-up extended up to 10 years (median 6 years), the AAA-related mortality benefit had been lost by the end of the study, and there were a number of late aneurysm ruptures and new complications appearing up to 8 years postprocedure.<sup>17</sup> Secondary interventions became necessary in 30% of the patients out to 8 years, and the same rate was observed during the DREAM trial out to 6 years.

Although the EVAR-1 and DREAM trials do show favorable results for EVAR, on closer scrutiny, the emerging overall picture is somewhat mixed and not without doubt. This relates mainly to late failures, including late aneurysm rupture and the relatively high rate of reinterventions. At the same time, it is important to note these trials were planned and conducted more than 10 years ago. Since then, a great many lessons have been learned, and technologies have improved significantly; today’s devices are more

advanced, better-designed, and thoroughly tested. There is also a much larger procedural experience, with improved operator skills and better case selection strategies, all leading to enhanced success rates with EVAR. It would not be unreasonable to postulate that endovascular experts today can achieve far better results than those produced by the EVAR-1 and DREAM investigators all those years ago.

## EVAR HAS TRANSFORMED THE AAA THERAPY LANDSCAPE

Despite the previously described real and perceived shortcomings, EVAR developments and continuing technology evolutions have had an enormous impact on the way aneurysms are treated. The total number of AAA repairs has changed little if at all, but the relative preponderance of one procedure over the other and their outcomes have been affected dramatically.<sup>17</sup> Since the introduction of EVAR in the US market in 1999–2000, elective aneurysm repairs have increased by 8%, whereas repair of ruptured AAAs has plummeted by 35% (Figure 3). By 2004, EVAR had overtaken OR as the most common form of AAA repair in the United States (Figure 4), and by 2005, EVAR accounted for 56% of all intact aneurysm repairs but only 27% of the operative mortality—another life-saving achievement. Overall, since 1993, AAA-related deaths have decreased by 42%, and for every component of such drop (including total repair-related deaths, ruptured AAA repair deaths, and elective repair deaths), the decline rate in mortality has proven significantly steeper after the introduction of EVAR into our armamentarium (Figure 5). OR mortality, on the other hand, remained quite stable, with an average of 4.6%. This can be contrasted with an EVAR mortality of 1.3%, which, of course, represents a highly significant difference in favor of the endovascular approach. It is mainly such procedural mortality advantage and the overall great appeal of less-invasive therapies that have led to the almost-explosive creation of a most significant EVAR device market worldwide that was valued at \$820 million (USD) in 2008, with the potential for exponential growth to \$1.6 billion by 2015 in a recent and well-respected forecast.<sup>18</sup>

## CONCLUSION

This brings us to the bottom line on AAA therapy in 2011. The landscape is populated by fast-evolving technologies, new treatment paradigms, and an incredibly fast and profound shift from time-honored surgical concepts and approaches to endovascular treatment in the majority of cases. EVAR’s future potential is unlimited.

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ed, but shortcomings and unresolved issues remain. Prominent among these are the high long-term rates of complications and reinterventions, as well as lingering uncertainties about device performance and durability beyond 10 years. On the upside, however, EVAR's rapid preeminence has resulted in many lives saved, a strong resolve toward uncovering undiagnosed aneurysms, and the promise of a much better less-invasive future for AAA treatment (and vascular therapy overall) in the years to come. ■

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