

# Abdominal Aortic Aneurysms in Women: The Debate Continues

A look at the available data on diagnosing and treating aneurysmal disease in women and how further study could improve screening and treatment guidelines in the female AAA population.

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There has been significant debate among vascular specialists regarding the existence of sex-related differences in the presentation, treatment, and eventual outcomes of male versus female patients with abdominal aortic aneurysms (AAAs). We know that AAA is a disease that affects men at a much higher rate than their female counterparts, with a 4:1 male-to-female predominance.<sup>1</sup> However, women who present with AAA generally fare worse when compared to their male counterparts. Women are older at presentation, exhibit faster rates of AAA growth, demonstrate a higher risk of rupture, and experience rupture at smaller diameters (Figure 1).<sup>2-5</sup> Historically, women are also less likely to undergo endovascular aneurysm repair (EVAR).<sup>6</sup>

## EPIDEMIOLOGY, ETIOLOGY, AND RUPTURE RISK

Regardless of patient sex, AAAs are generally managed by surveillance until they reach a diameter of 5.5 cm, at which point repair is typically offered to patients. Exceptions to this rule include, but are not limited to, rapid aneurysm growth or saccular aneurysm morphology. These general rules of engagement, however, are based on trials that have historically low rates of female patient enrollment. For example, the UK Small Aneurysm trial and the ADAM trial each enrolled a large number of men (83% and 99.2%, respectively), but a small number of women.<sup>1-5</sup>

The prevalence of aneurysmal disease is affected by age, family history, sex, and tobacco exposure. The prevalence of AAAs larger than 2.9 cm in diameter ranges from 1.9% to 18.5% in men and 1% to 4.2% in women.<sup>7</sup> Currently, the prevalence of AAAs in the female population is

considered to be too low to justify routine screening.<sup>8-11</sup> However, if AAAs in women were defined by aortic dilation > 1.5 times the normal infrarenal aortic diameter (when compared to a standard definition of 3 cm), the prevalence of AAAs in women (aged 65–75 years) increases from 3.5% to 9.8%, and the prevalence of AAAs in men (aged 65–75 years) would decrease from 16.9% to 12.9%.<sup>12</sup> DeRubertis et al reported a 20% AAA occurrence in the female population that they studied. They also noted that women presenting with AAAs tended to be

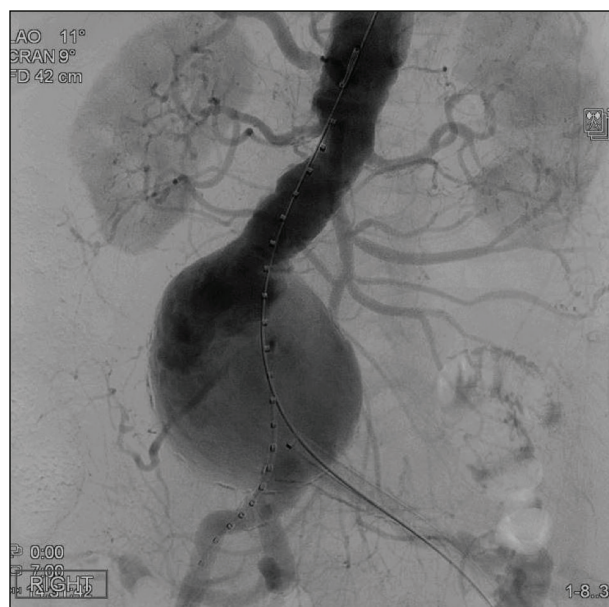


Figure 1. Postprocedural imaging of an 87-year-old woman with a ruptured (contained) 8-cm AAA.

older than their male counterparts and that their aneurysmal disease was associated with a risk factor history that was positive for smoking and cardiovascular disease.<sup>7</sup>

Aneurysmal disease is characterized by the obliteration of elastin and collagen in the media and adventitia, smooth muscle cell loss with thinning of the medial wall, and infiltration of lymphocytes and macrophages with associated neovascularization.<sup>13</sup> We have traditionally assumed that aneurysms are caused by degenerative atherosclerotic disease, but more recently, matrix metalloproteinases (MMPs) have been recognized to significantly affect aortic degeneration and likely play an important role in the development of aneurysms. Data seem to suggest that there may be an estrogen-mediated reduction in macrophage MMP-9 production, which could help to explain some of the differences seen in female and male patients where aneurysmal development and progression are concerned.<sup>12</sup>

### Variation and Relativity

When considering aneurysm size, rupture rates, and growth rates, it is important to recognize that there are significant variations in each of these metrics that seem to be related to native (normal) aortic diameters. In women, aortic diameters are on average 2 mm smaller than in men.<sup>14-16</sup> Sonesson et al also noted that body surface area is lower in women when compared to men.<sup>15</sup> This means that the relative AAA diameter increase from the predicted size was larger in women when compared to men, so that aneurysms of equal size represent a greater relative dilation in women.

Most providers agree that a more rapid AAA growth rate is associated with an increased risk of rupture. Three separate studies have shown faster rates of AAA growth in women when compared to men and have demonstrated that initial aortic diameter and female sex were independent risk factors associated with AAA expansion. Solberg et al reported a 2.43-mm AAA growth rate per year in women compared to a 1.65-mm growth rate per year in men.<sup>17</sup> Additionally, Mofidi et al reported a rate of 3.67 mm in women and 2.03 mm in men, respectively.<sup>4</sup> Finally, Schouten et al reported that a faster AAA growth rate (+1.82 mm per year) and aneurysm diameter (+0.06 mm per year) were independently associated with female sex.<sup>18</sup>

The UK Small Aneurysm trial reported a fourfold higher risk of rupture for women than men. These data were confirmed in a study by Brown et al in patients unfit for elective AAA repair. A threefold higher risk of rupture for women was found, and rupture occurred at smaller diameters in women when compared to men in those who were monitored under ongoing surveillance.<sup>5,19</sup>

### AAA OUTCOMES IN WOMEN

Dillavou et al reported results in 2006 that were retrospectively obtained from data retrieved from the Centers for Medicare & Medicaid Services database (inpatient sample from 1994–2003) queried by ICD-9 diagnosis and procedure codes.<sup>6</sup> These data demonstrated several very distinct differences in the outcomes of AAA patients when comparing the female and male populations. During the time period that was evaluated, roughly a decade, they determined that the overall mortality for ruptured AAAs remained relatively unchanged; however, they noted that the average mortality rate was significantly higher for women presenting with ruptured AAAs (52.8%) than in men (44.2%). They also reported an overall decrease in mortality associated with elective AAA repair, but again, differences were noted in comparing the male to the female cohort. Mortality for men decreased from 5.57% in 1994 to 3.20% in 2003; during the same time period, mortality for women decreased from 7.48% in 1994 to 5.45% in 2003. Multivariate analysis demonstrated that increasing age, female sex, and open surgery (rather than endovascular repair) were significant predictors of mortality in both elective and ruptured AAA repair.

In-hospital mortality is reportedly greater in women after endovascular repair per the Healthcare Cost and Utilization Project.<sup>20</sup> It has also been reported that female sex is a predictor of longer hospital lengths of stay. In 21,769 patients treated with EVAR, female sex was the strongest independent preoperative predictor of length of stay.<sup>21</sup> In their analysis of 20,780 patients who underwent EVAR between 2006 and 2015, Lowry et al confirmed an increased rate of adverse outcomes in female AAA patients. Hospital length of stay, unplanned readmission, and mortality rates were all higher in women compared to men.<sup>22</sup>

These outcomes may be explained by the fact that by the time women reach the standard threshold for elective repair, they oftentimes do not meet the criteria delineated in the instructions for use (IFU) for most standard stent grafts. This was demonstrated by Sweet et al in their retrospective review of CT scans with associated three-dimensional reconstructions from a single center over the course of 13 years.<sup>23</sup> They assessed unrepaired infrarenal aneurysms that measured > 5 cm or aneurysms that measured 4 to 5 cm if the sac diameter was more than twice the diameter of the normal aorta at the level of the renal arteries; 1,063 unique, unrepaired AAAs were analyzed. They determined that neck length, diameter, and angulation differ for women, even after adjustment for patient age and AAA size. EVAR eligibility based on device-specific IFU criteria was directly affected

by patient sex. Neck length < 15 mm was found in 47% of men and 63% of women. Neck angulation exceeding 60° was seen in 12% of men and 26% of women. A minimum iliac diameter of 6 mm was observed in 35% of men and 55% of women. Only 32% of men and 12% of women met all three neck criteria and had iliac diameters > 6 mm.

## CONTROVERSIES IN DIAGNOSIS AND TREATMENT

With the understanding that there are seemingly significant differences in the etiology and epidemiology of AAAs in women, not to mention possible meaningful differences in rates of disease progression, the looming question is whether screening and treatment guidelines for AAA in the female population should be amended to increase detection and alter the manner in which we treat their unique disease process. Several reports of screening programs for women have been cited in contemporary literature. Chabok et al attempted to determine the prevalence of AAAs that were  $\geq 3$  cm in women screened with ultrasound imaging, the risk factors associated with AAAs in this population, and whether high-risk groups could be identified with AAA prevalence of 1% or greater.<sup>24</sup> In their study, AAAs were detected in 82 of the 50,000 women screened, and aneurysms were rarely seen in those younger than 66 years (7/24,499). In patients aged 66 to 85 years, there were 72 AAAs in 25,170 women (0.29%). A history of stroke/transient ischemic attack (TIA), hypertension, smoking, atrial fibrillation, ankle-brachial index < 0.9, and internal carotid artery stenosis of at least 50% was associated with an increased prevalence of AAAs ( $P < .001$ ). In a multivariable linear logistic regression of risk factors, age  $\geq 76$  years, history of stroke/TIA, hypertension, and smoking were independent predictors of AAAs. This report suggested consideration of a targeted AAA screening program for women > 65 years of age.

In another recently published meta-analysis, Ulug et al detailed the findings of a systematic review of studies screening for AAAs that was performed over a 16-year period and included more than 1,000 women who were at least 60 years of age.<sup>25</sup> Studies were identified by searching Medline, Embase, and Cochrane Central Register of Controlled Trials databases. Eight studies were identified, including only three based on population registers. The largest studies were based on self-purchase of screening. In total, 1,537,633 women were screened. The overall AAA prevalence rates were very heterogeneous, ranging from 0.37% to 1.53%; the pooled prevalence was 0.74%. The pooled prevalence increased with both age (> 1% for women > 70 years) and smoking (> 1% for those who had ever smoked and > 2% in current smokers). The prevalence of screen-detected AAAs in older

women was noted to be subject to wide demographic variation; however, in “ever-smokers” and those older than 70 years, the prevalence was > 1%.

Both of these studies confirmed the findings of an earlier publication that also found an increased risk of aneurysmal disease in women older than 70 years who were smokers. In this study, smoking was strongly associated with AAAs in women: 18 of 19 (95%) women with a screen-detected AAAs had a history of smoking compared with 44.2% of those with a normal aorta. The prevalence of AAAs was 0.03% among never-smokers, 0.4% in former smokers, and 2.1% in current smokers.<sup>26</sup>

Based on these data sets, consideration should be given to screening elderly women (those > 65 years) who are past or current smokers. Having said that, most screening programs have routinely diagnosed AAAs at a diameter of 3 cm, which calls into question whether the definition of AAAs in women should be changed to reflect either body surface area or the ratio between the normal infrarenal aortic diameter and the diameter of the aneurysmal segment. Perhaps if either of those two AAA definitions were used to diagnose aneurysms in the previously cited female patient populations, the incidence would be higher than the currently published and accepted prevalence rates.

One additional question remains: Should the threshold of treatment for AAAs in women be the same threshold that is used to determine treatment in men? This question was addressed for men by the UK Small Aneurysm and ADAM trials, but these trials included only 198 women in total. Ulug et al reported on gender differences among patients being assessed for intact AAAs.<sup>27</sup> The authors found that a smaller proportion of women than men were eligible for EVAR (34% vs 54%), a higher proportion of women than men were not offered intervention (34% vs 19%), and 30-day mortality was higher in women than in men for both EVAR (2.3% vs 1.4%) and open repair (5.4% vs 2.8%). These findings underscore the need to design or identify a stent graft specifically for use in women. They also point out that women have smaller aortas than men and suggest that “if a smaller threshold for both diagnosis and intervention were introduced, compared with those recommended for men, women might have a better chance of being offered and surviving intervention at a younger age.”<sup>27</sup>

The LUCY trial has attempted to address this question by prospectively assessing women and men with AAAs to determine the safety of treating these aneurysms in women with the 14-F Ovation abdominal stent graft system (Endologix).<sup>28</sup> The study was designed as a prospective, multicenter, United States postmarket registry. The trial consecutively enrolled men and women at a

respective 2:1 ratio. The primary endpoints were 30-day major adverse events, as well as outcomes at 30-day and 1-year follow-up. Two hundred twenty-five patients were enrolled, including 76 women and 149 men. There were no significant differences in patient demographics. Women were noted to have more complex anatomy (ie, increased juxtarenal angulation and smaller iliac access vessel size). At 30 days, procedural outcomes, major adverse event rates, efficacy (migration, endoleak rates, occlusion, and stenosis), as well as secondary interventions were assessed, and the female and male patients were found to have equivalent outcomes. In this prospective trial, women did not fare worse than their male counterparts and were enrolled at a rate more reflective of the actual incidence of AAA in the female population (~20%). This trial's early results seem to support the supposition that stent grafts more suited to the female anatomy when used in conjunction with on-label indications, may allow women with AAAs to fare just as well as their male counterparts as far as outcomes and success rates are concerned.

## CONCLUSION

The debate surrounding the definition, diagnosis, and treatment of AAAs in women continues. To determine whether updated AAA screening, definition, and treatment guidelines should be considered in the female population, more evidence is needed—specifically more prospective, randomized trials that assess women using contemporary, on-label treatment modalities and devices, some of which are now seemingly much more suitable for addressing the female patient than in the past. Such projects will surely help us to determine whether aneurysmal disease in women deserves its own set of guidelines to aid in improving care for this often overlooked and undertreated patient population. ■

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