Discussing the Treatment of AAAs in Women and Early Results From the LUCY Study

The LUCY trial advisory board members provide their interpretation of the initial impact of the study's early results.

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Abdominal aortic aneurysms (AAAs) are characterized as a disease that predominately affects men. However, although AAAs occur more frequently in men, women have AAAs that expand 40% to 80% faster[1,2] and rupture at smaller diameters than compared with men's AAAs.[3] Perhaps unsurprisingly, women are also more likely to present in an emergent or ruptured state and have greater rates of morbidity and mortality from AAA interventions.[4,5]

Endovascular aneurysm repair (EVAR) was developed to reduce mortality and morbidity associated with open surgical repair. Despite the recent widespread use of EVAR, women are more frequently ineligible for treatment with currently approved devices than men.[6-11] A recent meta-analysis by Ulug et al published in *The Lancet* concluded that, among more than 1,900 patients

TABLE 1. META-ANALYSIS AND SYSTEMIC REVIEW OF AAA TREATMENT IN WOMEN

Conclusions	% of Women	% of Men	Patients	# of Studies Reviewed
Less women are eligible for EVAR	34%	54%	400 women; 1,507 men	5
More women were declined intervention	34%	19%	245 women; 1,365 men	4
30-day mortality higher in women	2.3%	1.4%	11,076 women; 52,018 men	9

Adapted from Ulug, P, Sweeting MJ, von Allmen RS, et al. Morphological suitability for endovascular repair, non-intervention rates, and operative mortality in women and men assessed for intact abdominal aortic aneurysm repair: systematic reviews with meta-analysis. Lancet. 2017;389:2482-2491.

across five studies, only 34% of women with AAAs are eligible for EVAR compared with 54% of men, based on anatomic restrictions (Table 1).[12] Women who do receive an EVAR intervention for their AAA have greater rates of perioperative complications and higher 30-day mortality compared with men.[13]

As with clinical trials in general,[14-16] enrollment of women in EVAR clinical trials is disproportionately low. Although 21% of AAAs in the United States occur in women,[17] only 6% to 15% of patients enrolled in endovascular AAA investigational device exemption studies are female.[6-11] A review of more than 1,000 CT scans of unrepaired AAAs concluded that the three most common anatomic characteristics that preclude EVAR treatment were small access vessel diameter, short neck length, and increased neck angulation.[17] Because these technically challenging characteristics are identified in women more frequently, development of endovascular therapies that accommodate a wider range of aortoiliac anatomies have great potential to minimize the burden of AAA in women.

The Ovation® Abdominal Stent Graft System (Ovation System, Endologix) is a polymer-based, trimodular bifurcated system comprised of a main body and two limbs, designed to accommodate a wide range of aortic anatomies. The Ovation System is delivered via a flexible hydrophilic 14-F (outer diameter) catheter, the lowest profile of any current commercially available stent graft in the United States. Once in place, a patient-specific seal is achieved in situ by introducing a low-viscosity radiopaque fill polymer through a network of inflatable channels and sealing rings that curves to the native anatomy of the aorta. Unlike conventional endovascular devices, the polymer-based sealing technology in the Ovation System does not rely on the traditional aortic neck length to achieve seal but instead requires an inner wall diameter between 16 and 30 mm, at 13 mm below the inferior renal artery. The low-profile delivery system and polymer-based sealing technology of the Ovation System could potentially expand the eligibility of women who have smaller access vessels and more complex aortic neck morphology.

The LUCY (Evaluation of FemaLes who are Underrepresented Candidates for Abdominal Aortic AneurYsm Repair) study is the first prospective study to specifically evaluate EVAR in women. The LUCY study is a multicenter, postmarket study with 225 patients enrolled who were treated with the Ovation System, including 76 women in the treatment group and 149 men in the control group, at 39 centers in the United States between August 2015 and February 2017. Patients were considered eligible for this study if they had an AAA requiring elective intervention, and had suitable anatomy for treatment with the Ovation System. Complete inclusion and exclusion criteria are reported on www.clinicaltrials.gov. Data were collected on enrolled participants during the procedure, and participants were then seen for follow-up evaluation at 1 month (30 days ± 10 days), and 1 year (365 ± 60 days) after their intervention. The primary endpoint was major adverse events (MAEs) at 30 days. Multiple secondary endpoints explore the clinical benefits in both arms of the study. MAEs were adjudicated by a clinical events committee that was composed of three independent physicians. The following results are limited to the 30-day data.

Consistent with the prior literature, women in the LUCY study had more complex vascular anatomy, including smaller access vessels and more aortic neck angulation at their preoperative assessment than men.

Despite these anatomic differences, women and men in the LUCY study had comparable procedural outcomes with the Ovation System. Initial data have shown no significant differences in procedure times, device time, or proximal adjunctive device usage between the two groups. Women and men continued to have similar benefits from the Ovation System EVAR intervention through 30 days including no occlusion, stenosis, migration, or type III endoleaks in either arm, and no type I endoleaks in the women.

Women have traditionally had limited eligibility and worse outcomes after EVAR. The initial results of the LUCY study suggest that women treated with the Ovation System have similar procedural outcomes, no death, no conversion, low 30-day MAE rates, and low rates of endoleaks at 30 days compared with the men in the study. Furthermore, an analysis comparing the outer diameters of several EVAR delivery systems and the max diameter of the iliac access vessels of LUCY patients shows that Ovation would expand eligibility for women with AAA by at least 28%.[18]

The LUCY study Advisory Board have provided some initial thoughts on the early study data and its potential impact on the future treatment of women with AAA.

What are some of the biggest challenges with treating women with AAAs?

Dr. Ash: There is a dichotomy when considering AAA in women. On one hand, there is evidence to support the idea that when women present with AAA, they have a faster rate of AAA growth, a higher rupture risk, and a propensity for AAA rupture at smaller diameters. These facts would lead one to believe that perhaps we should be more aggressive in treating women who present with AAA. On the other hand, we also know that historically, women demonstrate a higher perioperative morbidity and mortality when it comes to AAA repair. Those poor 30-day outcomes have likely curbed our collective enthusiasm for repairing AAA in women using minimally invasive endograft technologies. This is compounded by the fact that women are often underrepresented in endovascular AAA studies due to anatomic limitations that exclude them from participation (ie, small diameter vessels). So, therein lies the dilemma: which is more tenuous for women, the disease process and its progression or the treatment itself?

Dr. Chandra: Numerous trials have found that women with AAA have worse outcomes as compared with men, despite having aneurysms that grow faster and rupture earlier. Women frequently do not fit the indication for use of available devices, experience more complications, and have worse outcomes. The reason behind this is not clear, but is likely multifactorial, including the anatomic challenges of women—such as small access and more challenging neck anatomy—but also likely involves delay in diagnosis due to inadequate attention given to women.

Dr. Hunter: The first challenge with treating women is the misconception that women are less likely to suffer from cardiovascular disease in all forms, AAA being just one aspect. Similarly, there is an underidentification of women with AAA and a misperception that women should not be screened as aggressively as men. There is this belief that women respond poorly to AAA repair with a higher risk of adverse effects, so therefore they should not be treated.

There is also a debate regarding what size AAA (ie, 4.5 cm vs 5.5 cm) in women should be treated. The question arises whether the aortic size index, the size of the patient's aneurysm compared with the patient's body surface area, could be a more patient-specific metric than aneurysm size alone to determine rupture risk and treatment timing.[19] We know women pose certain challenges in treatment, but the LUCY trial aims to help identify outcomes that can be positive for women.

Dr. Rzucidlo: Women are less often offered repair of an AAA, oftentimes due to the higher 30-day mortality rate for EVAR for women compared with men. At the same time, there are fewer women who are eligible candidates to be treated with the current endovascular grafts on the market. The meta-analysis published in *The Lancet*[12] by Ulug et al showed that more than one out of three women were declined intervention compared with only two out of 10 men. That study further showed that more than half the men in the study were eligible for endovascular repair compared with only one-third of the women. Furthermore, women were noted to have nearly twice the mortality of men, which would certainly influence physician decision making when offering women endovascular repair (Table 1).

This could be secondary to women having aortic anatomy less conducive to endovascular repair due to small diameter and short infrarenal neck, as well as a small iliac artery diameter not allowing access and placement of endovascular grafts. These results are consistent in all endovascular graft trials; however, women are underrepresented in EVAR trials and therefore physicians do not have accurate information for recommendation of repair and outcomes in women with aneurysms.

Dr. Vouyouka: The natural history of AAA in women and the indications for repair are not well defined. Most

of the large, randomized studies that determined what size AAA rupture, what is the natural history, and when it be should repaired (eg, UKSAT, ADAM trial, etc.), include very few, if any women, with no power to make conclusions in women. Therefore, for years, we have been managing AAA in women based on conclusions from data derived from studies done in men.

The structural anatomy of the aorta in women is quite different than in men. During their reproductive years, women do have compliant aorta for some treatment, but once in menopause, that compliance changes significantly, and the aorta becomes stiffer than those of men at the same age. Many studies in human and mice have indicated this. This loss of compliance may explain, in part, why women rupture at a smaller aneurysm size than men, and why when they receive successful endovascular repair that excludes pressure from the aortic sac, the AAA shrinks faster than men.

Although not proven, it is a reasonable theory that because of significant loss of wall compliance, women may respond better to grafts that do not rely on radial force to seal and exclude the aneurysm. Theoretically, the Ovation graft might be a better device for women who do not have compliant aorta compared to men, because it does not exert much radial force to the aortic neck and relies mostly on the polymer rings to achieve sealing.

Women are more likely to have short and angulated aortic necks and small access vessels. They also are more likely to have iliac occlusive disease with their AAA and less likely to have iliac aneurysms. Women in the past were less likely to be offered endovascular repair or when they did, there were more immediate complications because women were treated with devices that were developed based on the male aortic anatomy, pathology, and wall physiology. For these reasons, the low profile of the Ovation device and its shorter neck requirement compared with other devices makes this graft very appropriate for treating women with AAA.

What do you hope to accomplish with the LUCY study?

Dr. Chandra: By focusing on women in this study, we accomplish a few important things. First, we bring attention to the fact that women also get aneurysms. Traditionally, women have received treatment for aneurysms at a lower rate than men (this difference is greater than the difference in incidence), and they die more frequently than men. Again, this is likely multifactorial, but the fact that women get diagnosed at an older age and with more comorbidities suggests that women are presenting with more advanced disease because we have not been looking for them. Second, the LUCY study is providing a strong database of female aortic aneurysm anatomy, which offers an invaluable look at what makes women different. Subanalyses can and will be performed, for example, with finite element analysis and other techniques to better understand the aorta of women and the pathophysiology of aneurysm disease in women. Hopefully this can help us answer some of the questions about why aneurysmal disease in woman is so different in behavior and outcome. Finally, our ultimate goal is to improve the treatment and outcomes in women, given the current disparity. The early results of the LUCY study look very promising in this regard.

Dr. Hunter: One goal for the LUCY trial was to highlight the need for women with AAA to be screened and treated for this condition. Early outcomes show that with proper screening and treatment, women may benefit with decreased morbidity and mortality.

Follow-up for the LUCY trial will allow us to gain insight to the pathophysiology of the female aorta. I think the uniqueness of the graft begins a discussion for making advancements in the procedure toward outpatient treatment of AAAs.

Dr. Rzucidlo: The purpose of the LUCY trial was to increase awareness that women are underrepresented in all cardiovascular trials and to show the uniqueness of the Ovation device. The LUCY trial results clearly show that with the Ovation System, treatment of women with endovascular repair is safe, with similar outcomes to men. Therefore, I hope that with increased awareness of these results, more screening will be done to find women who have aneurysms, and more importantly have primary care physicians refer more women to vascular surgeons to allow for endovascular treatment.

Dr. Vouyouka: I hope that this trial will prove that the Ovation device has taken into account all the specific challenges regarding female aortas and shown equally good or better outcomes compared with immediate and long-term results in men.

Dr. Ash: It has been suggested that perhaps the increased perioperative morbidity and mortality in women might be due to factors that are unique to their sex, for example, less than ideal anatomy for EVAR. This may explain why historically women are less likely to receive percutaneous treatment of their aneurysmal disease. It may also explain why their operating room times are generally longer and why they are at higher risk of concomitant peripheral vascular compromise necessitat-

ing additional intraoperative or postoperative revascularization procedures. The question becomes, are these increased rates of morbidity and mortality in women due to their unique disease process or their less than ideal anatomy? Or are they the result of using devices and technology that are less than ideal for these gender-based differences out of necessity and availability?

How has/will the LUCY study and its results change your treatment of female AAA patients?

Dr. Hunter: I hope it highlights that the Ovation System has a favorable profile to be used as the treatment of AAAs. I think the device also highlights advancements in the treatment process, including minimally invasive techniques and all the advancements that come with PEVAR, including shorter procedural times, MAC anesthesia, and decreased use of central lines and Foley catheters.

Dr. Rzucidlo: The LUCY trial is the first prospective, consecutively enrolled, multicenter study designed to assess outcomes in women compared with men treated with the Ovation stent graft platform. The initial LUCY trial results show that women with smaller neck diameters, greater juxtarenal angle, and smaller access vessels were able to have 100% technical success and similar 30-day outcomes compared with men when using the Ovation System. In fact, no significant MAEs were noted between the female and male arms. In addition, no women were reported to have type Ia endoleaks, secondary intervention, occlusion/stenosis, or migration. Given these results, I will definitely consider using the Ovation System as my primary device in the treatment of women with aneurysms.

Dr. Vouyouka: The initial results of LUCY may make the Ovation device my preferred device to use when I treat women. I am anxious to see if the long-term results will be as hypothesized and if women treated with Ovation have less neck dilatation or graft migration and type 1 endoleak compared with historical data.

Dr. Ash: I cannot predict whether the LUCY study results will change the way we treat women with AAA; shifting treatment paradigms can be a long and arduous process. Nonetheless, the LUCY study may be a starting point for this important discussion. The study could challenge the way we have traditionally viewed AAA in women—and perhaps then, over time, the ways in which we treat AAA in this patient population.

The results may well pose questions that deserve additional consideration and even further investigation. For example, if we can show that women are on par with men in terms of morbidity and mortality outcomes in this specific study, then we must ask ourselves, why is that the case? Are women's traditionally poor outcomes truly a result of their unique disease processes or are these suboptimal outcomes, in fact, the result of the technology and devices that are currently available to us and are not particularly ideal for a woman's unique anatomy? Knowing that women with AAA demonstrate, for example, a faster rate of growth and a higher rate of rupture at smaller diameters, one might ask: considering those known risks, if a device or a technology were available and if it were proven to be safe in women (when compared with the data we currently have available to us), would we treat women differently, or sooner?

Dr. Chandra: I have always thought that, anatomically, the Ovation technology makes sense and works better for treating women with AAA. Initial data from LUCY confirms my assumption, and I look forward to longer-term data as well. If those data continue to support these results, I will likely continue to use this technology to treat those patients when appropriate.

Why is the Ovation System a suitable graft for women with AAA? Which Ovation feature(s) would you attribute the positive LUCY 30-day results to?

Dr. Rzucidlo: The uniqueness of the Ovation device allows for women with AAA who have angulated narrow infrarenal necks and typical small iliac artery access to have their aneurysms repaired safely and with good outcomes. This is through the innovative design of the Ovation stent graft system with small diameter devices that enable access for more patients.

Dr. Ash: In my experience, the Ovation System is an attractive choice for treating women with AAA because of its low-profile (14-F outer diameter), which makes it suitable for small vessel diameters and/or concomitant aortoiliac occlusive disease, and its conformable delivery system, which handles like a catheter rather than a sheath. The design of the limbs also makes treating narrow distal aortas and tortuous vessels less of an issue. The limbs are very resistant to kinks and they seem to perform very well in terms of long-term patency.

Dr. Chandra: Numerous features, including the low-profile aspect and the polymer-based technology, which allow us to deal with more complex neck anatomy as well.

Dr. Hunter: The Ovation System is suitable for the treatment of all aneurysms, but there are unique features that benefit women, including the small device size that allows for easy deliverability and access to smaller vessels. The unique fixation system allows for smaller neck size and prevention of migration and neck enlargement.

What do you think the impact of the LUCY study will have on the physician community?

Dr. Vouyouka: The immediate results are very promising and I think with effective circulation of the study results, the Ovation device has the potential to become the primary device of AAA treatment in women.

Dr. Ash: Time will tell. In 1993, the National Institutes of Health mandated that women and minorities be included in government-funded health research. Still, there are disparities that exist when it comes to the representation of women in clinical trials. Since that time, we have also come to understand that women and men are oftentimes very different in how they present, in how they progress, and in how their disease processes are treated. In fact, according to the Institute of Medicine, every cell in our bodies has a sex, which means that men and women are different at even a cellular level.

Ultimately, where the LUCY study is concerned, we will need to wait for the final data—both at 30 days and beyond. At minimum, I hope that the study's results start a dialogue among physicians about aneurysms in women and how we assess and treat them. Perhaps we can look at women with aneurysms in a different light if we can demonstrate both the safety and efficacy of elective AAA repair in this population.

Dr. Chandra: I hope it will bring more attention to at-risk women for physicians to look for and identify aneurysms earlier. Obviously, we need to wait for the longer-term results, but the early data are very encouraging, indicating that the Ovation System can potentially bridge some of the outcome gaps for many women with aortic aneurysmal disease.

Dr. Hunter: I hope the LUCY study will start the discussion in the physician community for more aggressive screening and treatment of women with AAA, initiate treatment at a smaller aneurysm size, and to shift the treatment to percutaneous treatment for most patients. I think LUCY highlights the favorable attributes of the device with 100% procedural deployment success with freedom from endoleaks and secondary intervention in women.

I think it should expand the options for patients and particularly women who may not have been considered a candidate.

Ovation's deliverability, proprietary fixation system, long-term mortality rate, data in women, and long-term freedom from rupture rate should make it the "endograft of choice" for endovascular therapy of AAAs.

Dr. Rzucidlo: When these results are published, primary care and referring physicians will be able to rely on these groundbreaking results to support a decision to allow women, who have in the past been refused repair, to be evaluated and hopefully treated for their aneurysms. ■

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