

## Rate of female patients treated for Abdominal Aortic Aneurysm may be extremely low in specific populations

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### Abstract:

**Purpose:** In most current series examining patients undergoing Abdominal Aortic Aneurysm (AAA) repair, women account for around 20% of the study population. Yet, in a single institution in an insular area in the east Mediterranean Sea very few women undergoing AAA treatment have been observed. The objective of the present study is to record rate of female patients among subjects treated for AAA.

**Materials and Methods:** This is a retrospective single center study including all consecutive patients treated for AAA with either Endovascular Aneurysm Repair (EVAR) or open surgical techniques in a single institution providing vascular service for a catchment area of 700.000 population. Patients treated electively and those treated emergently were included. The study period was from 01.01.2010 until 31.12.2019. The main endpoint of the analysis was to define rate of female patients among subjects receiving AAA treatment.

**Results:** Totally, there were 713 procedures. Three-hundred-seventy-five (53%) cases were operated by open repair and 338(47%) by EVAR. Six-hundred-two (84%) patients were treated electively while 111 (16%) patients were treated for ruptured AAA. The vast majority of patients were male (706/713 - 99%) with only few female patients (7/713 - 1%). Rates of women treated for AAA were similar for both elective (6/602 - 1%) and ruptured cases (1/111 - 1%). Smoking was the most prevalent risk factor in male patients (87%), while all female patients were current smokers.

**Conclusion:** There is a remarkable difference among rates of female patients undergoing AAA treatment in a single institution (<1%) and those typically reported in the current literature. Cultural and habitual reasons that resulted in very low smoking rates among women during the past decades may have led to this difference.

**Key Words:** Abdominal aortic aneurysm, Women, Female patients

### INTRODUCTION

Abdominal aortic aneurysm (AAA) is mainly a disease of older male patients. The predisposition of this disease for the male gender has been well established by large scale epidemiologic studies and currently the prevalence of AAA in males is estimated around 3% and in females <1%.<sup>1,2</sup> The total AAA prevalence has been reported to be progressively declining following reduced rates of smoking in the developed world.<sup>3,4</sup> Among the randomized clinical trials (RCTs) investigating the cost-effectiveness of screening for AAA, only the Chichester study included female patients (prevalence was 1,3% in females and 7.6% in males) while the MASS, Viborg and Western Australia studies did not.<sup>5-8</sup> Screening programs in Sweden estimated current prevalence of AAA in older women at 0.5% while similar rates were found in the UK.<sup>4,9</sup> Other contemporary screening protocols do not include women, as that in

Denmark.<sup>1</sup> In summary, the prevalence of AAA in women is currently low, the relative risk in men being 4-fold.

Except for AAA prevalence detected inside screening programs, an important index indicating the magnitude of the disease burden among women, especially with regard to those with clinically relevant AAAs, is the rate of female patients undergoing invasive treatment. Among cases treated for AAA, most series report rates of women around 15-20%.<sup>10-17</sup> In both elective and emergency settings this rate is mostly the same.<sup>10-17</sup> Large administrative databases of elective AAA treatment which include thousands of patients report rates of female patients around 20% while rates around 10% have been recorded inside the randomized trials (RCTs) comparing Endovascular Aneurysm Repair (EVAR) and open repair of intact AAAs.<sup>10-13</sup> Regarding the rate of female patients treated for ruptured AAAs, numbers are mostly similar.<sup>11,14-17</sup>

In a single institution very few women received treatment for AAA and the objective of the current study is to record the rate of female patients inside a cohort of consecutive patients undergoing invasive AAA treatment.

### METHODS

#### *Study design and study population*

This is a retrospective study, being held in a single Tertiary institution providing Vascular service for a catchment area of

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700,000 population. All consecutive patients undergoing AAA repair during the last decade (01/01/2010 - 31/12/2019) were reviewed. Para-renal (aneurysms that included at least one renal artery and extent up to the superior mesenteric artery) and para-visceral AAAs (aneurysms that included the renal arteries and the superior mesenteric artery but extent not beyond the celiac axis) were included but more extensive disease such as thoraco-abdominal (Type I-IV) lesions were excluded from the analysis (6 cases, all of them male patients).<sup>18</sup> Cases were identified from the hospital's electronic database and medical records. All types of repair (open surgical repair and EVAR) for both elective and emergent indications were included. In general, open surgical repair was the primary therapeutic modality at an earlier phase, while there was a progressive shift towards EVAR in the later years. Currently, open surgical repair is reserved for patients with hostile anatomy for EVAR and in young, fit patients with a long life expectancy. In case of open surgical repair of complex AAAs, a transperitoneal approach is most often favored when the aneurysm does not extent in the superior mesenteric artery with supra-renal clamping and the proximal anastomosis being constructed at the level of the most caudal renal artery with a posterior bevel or with renal artery re-implantation when this is needed. If the aneurysm involves the superior mesenteric artery, a retroperitoneal approach is usually preferred with a laterally beveled proximal anastomosis including the superior mesenteric artery and the right renal artery and re-implantation of the left renal artery.

**Primary and secondary outcomes**

The primary outcome of the analysis was to record rate of female patients among subjects that received treatment for AAA during the study period. Secondary outcomes were, procedural time, length of stay in the ICU and/or hospital, peri-procedural mortality and complications. Quantitative data are reported as mean ± Standard deviation if normally distributed or median (Range) if distribution was skewed. Qualitative data are reported as frequencies as appropriate. We planned to compare abovementioned values among men and women in the study cohort.

**RESULTS**

**Primary outcomes**

During the study period we recorded a total of 713 procedures for AAA (684 infrarenal AAAs and 29 cases of complex AAA). Three-hundred-seventy-five cases (53%) were operated by open repair and 338 (47%) by EVAR. Relevant anatomic variables of the study cohort were recorded. Mean AAA neck length was 25±12mm among patients receiving EVAR and 14±11mm among those undergoing open surgical repair (p<0.001). Aortic neck angulation was 25±19 in the former and 30±24 in the later group (p=0.62). Infra-renal neck diameter was not significantly different between groups (EVAR 23±3mm, Open 22±5mm, p=0.83). It becomes apparent that the most common anatomical variable that precluded EVAR was inadequate proximal neck length.

Six-hundred-two(84%) patients were treated in the elec-

tive setting while 111(16%) patients were treated urgently due to AAA rupture. All ruptured cases were treated by open surgical repair. The vast majority of patients were male (706/713 - 99%) with only few female patients (7/713 - 1%). Rates of women treated for AAA were <1% for both elective (6/602) and ruptured cases (1/111) as seen in Figure 1. Female patients were treated by open repair in 4 and by EVAR in 3 cases. Among female patients undergoing open surgery, 1 was operated for ruptured AAA, 1 had adverse anatomy for EVAR due to severe neck angulation and 2 presented proximal extension of the aneurysm involving the renal arteries. The rest of the female patients (n=3) were treated with standard EVAR in two cases and by Chimney EVAR in one case. Among the total number of patients included, 26 (4%) men and 3 (43%) of women presented extension of the AAA above the renal arteries and these patients were treated with Chimney-EVAR in 8 and open surgical repair in 21 cases.

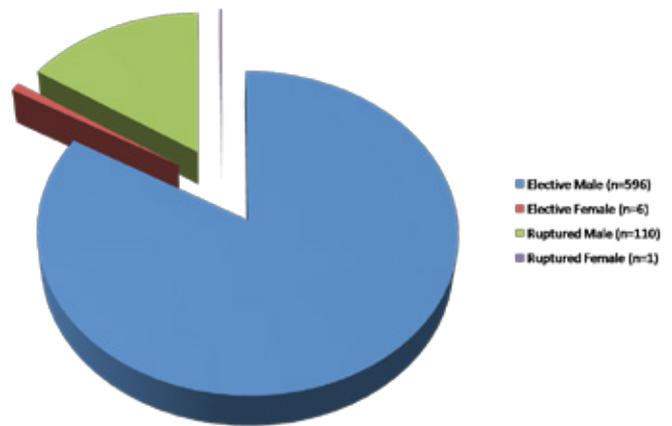


Figure 1. Chart summarizing gender distribution in our study cohort.

**Secondary outcomes**

Demographic information of patients is summarized on Table 1. Remarkably, 87% of male and 100% of female patients were current or ex-smokers. Regarding peri-procedural details, patients undergoing elective AAA repair presented an acceptable 30-day mortality rate (3% for open repair and >1% for EVAR) while mortality for ruptured AAA repair was 38%. Length of ICU and hospital stay was lower among patients undergoing EVAR compared to those receiving open repair, similar to what it is reported in the literature. Clinical information is summarized in Table 2. Unfortunately, the low rate of female patients observed, did not allow for any meaningful statistical comparisons between genders.

Variables	Male (n=706)	Female (n=7)
Age	75 (49-91)	71 (59-81)
Hypertension	600 (85%)	7 (100%)
Hypelipidemia	487 (69%)	5 (71%)
Diabetes	7 (1%)	1 (14%)
Smoking	614 (87%)	7 (100%)
Renal disease	49 (7%)	1 (14%)
Coronary artery disease	70 (10%)	2 (28%)

Table 1. Demographics and comorbidities of the study cohort. Smoking refers to ever smokers. Renal disease is defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m<sup>2</sup>.

	Open Elective (n=264)	Open Ruptured (n=111)	EVAR elective (n=338)
Procedural time	172 (135-323)	224 (145-410)	100 (60-310)
LOS ICU	1 (0-8)	3 (1-12)	0 (0-9)
LOS Hospital	9 (7-18)	13 (9-23)	2 (1-10)
30-Day mortality	8 (3%)	42 (38%)	2 (0.6%)
MI	13 (5%)	18 (16.2%)	4 (1.2%)
Intestinal ischemia	7 (2.6%)	30 (27%)	1 (0.3%)
Acute kidney injury	38 (14%)	45 (41%)	24 (7.1%)
Acute limb ischemia	4 (1.5%)	13 (5%)	1 (0.3%)

**Table 2.** Clinical details and outcomes of patients included in the analysis. LOS: Length of Hospital Stay, ICU: Intensive Care Unit, MI: Myocardial Infarction.

Study	Database	Indication	Study period	Number of patients	Female (%)
Schermerhorn et al <sup>10</sup>	Medicare	Elective	2001-2008	79,932	22%
Mani et al <sup>11</sup>	SwedVasc	Elective	1987-2005	8,663	17%
Budtz-Lilly <sup>12</sup>	VascuNet	Elective	2005-2013	83,253	14%
Greenhalgh et al <sup>13</sup>	EVAR-1	Elective	1999-2003	1,082	10%
Mohan et al <sup>14</sup>	NIS	Ruptured	2001-2010	42,126	23%
Edwards et al <sup>15</sup>	Medicare	Ruptured	2001-2008	10,998	28%
Mani et al <sup>11</sup>	SwedVasc	Ruptured	1987-2005	4,171	14%
Budtz-Lilly <sup>16</sup>	VascuNet	Ruptured	2010-2013	9,320	17%
Powell et al <sup>17</sup>	IMPROVE	Ruptured	2009-2013	613	22%

**Table 3.** Typical values of rates of female patients treated for AAA as reported in representative observational and randomized trials for both elective and urgent indications. NIS: Nationwide Inpatient Sample.

## DISCUSSION

In a single centers' experience we have observed very few cases of female patients treated for AAA. During a 10-year period the rate of women treated for AAA was <1% of the total number of patients. This represents a remarkable difference from the typical values reported in the literature and approximates that of studies that mostly excluded women such as the OVER trial.<sup>19</sup> Regarding elective AAA treatment, the rate of female patients is usually reported around 20% with no significant variability between studies. Large administrative databases including many thousands of cases report rates of this magnitude<sup>10-12</sup>. In table 3 the distribution of patients by gender inside 3 of the most representative administrative databases can be seen (The Medicare, the SwedVasc and the VascuNet registries).

The rate of female patients treated for ruptured AAA is similarly reported around 20%. Again the Medicare, SwedVasc and VascuNet databases, have recorded rates of women treated at 28%, 14% and 18%.<sup>11,15,16</sup> The Nationwide Inpatient Sample being the largest all payer database in the United States reported that 23% of patients were women.<sup>14</sup> The difference between these values has no straightforward explanation but maybe related to different practices in screening in women, indications for elective treatment and time periods for which these values are valid. Nevertheless, all these values are of the same magnitude contrary to those observed in our practice.

Even if the design of the study is different, i.e. in randomized trials, rates of female patients treated for AAA are similar. For example in the EVAR-1 trial which is the largest RCT comparing EVAR and open surgery for intact AAAs, wom-

en represented around 10% of the total number of patients included in the analysis. Regarding ruptured AAAs, the IMPROVE trial, again being the largest among RCTs comparing EVAR and open repair, included 22% women. Therefore, for every study design and for every clinical setting, rate of female patients treated for AAA reported in the literature converge at a value around 20%.

The reason for the large discrepancy between our experience and the abovementioned published data is unknown. The low rate of smoking among women in our geographically restricted population, in an insular area in the east Mediterranean Sea, in the island of Crete may provide a possible explanation. Smoking has been proven to be a significant risk factor for AAA development and reduced smoking rates have been hypothesized to be the most important reason for the observed progressively decreasing AAA incidence in the developed world.<sup>1-4</sup> Since there are no official smoking rates in our target population we cannot prove a causal relationship between low rates of tobacco consumption and AAA in female patients but until recently fixed cultural and habitual perceptions kept very low rates of smoking among women. These data indicate that in specific populations the rate of clinically relevant AAAs in female patients may be far lower compared to the typical values reported in the published literature. Currently, an increase of women smokers on the isle of Crete has been observed and it will be of interest to see if this will be accompanied by an increase in AAA disease in females.

Another observation that should be emphasized is that women in our study population very commonly presented with complex AAAs, involving the renal arteries. Specifically,

3/7 women presented supra- or para-renal extension of the aneurysm which is a remarkable difference with the 4% rate of complex AAAs among men in our study cohort. The 3 female patients with proximal AAAs were treated electively, 2 with open repair and 1 with double chimney EVAR. This rate of proximal AAA extension is remarkably higher compared to the typical values reported in the literature which approximate 8%.<sup>20</sup> Previous reports assessing the eligibility for EVAR, have recorded 63% of women presenting aortic necks shorter than 15mm but this fact alone may not provide an adequate explanation for our finding.<sup>21</sup> Therefore the reason for this large discrepancy is largely unknown, but we hypothesize that a genetic predisposition for aneurysmal degeneration may have played a role, taking into account that one of the female patients with pararenal involvement presented with bilateral popliteal aneurysms and another one with innominate artery aneurysm.

There may be several implications of these observations, regarding clinical practice. At the same time that population screening for AAA in women is not recommended, specific categories of female patients may benefit from screening such as those who smoke or those with first degree relatives having a known AAA.<sup>18,22</sup> If a very low prevalence of AAA exists in a specific population, which we believe is the case in our region, it is very unlikely that any kind of screening protocol even in specific groups of patients may be cost-effective. Instead of a screening protocol, we have worked with medical staff in primary care in an effort to inform them on the diagnosis and initial management of patients with aneurysmal disease. This was done via a series of informative meetings performed in all four prefectures covered within our Hospital's catchment area. Furthermore, referral of patients with an aneurysm, both small and large, are given priority booking in our outpatient clinic for evaluation and are regularly followed-up thereafter.

Moreover, since women have been proven to be more susceptible to rupture at smaller diameters, at the same time presenting a higher operative risk compared to male patients in both elective and emergent settings a lower size threshold of 50mm is currently recommended as the indication for elective repair in female patients but with a weak recommendation in guidelines.<sup>18,22,23</sup> We believe that inside populations with a low prevalence of AAA among women this lower threshold may be particularly indicated since reduced awareness of patients and physicians may lead to inadequate diagnostic and surveillance protocols and an increase in the dimensions of lesions may progress unnoticed with a considerable risk for rupture. At the same time, repair at these dimensions may increase EVAR suitability, which generally is lower among women.<sup>23</sup> The RESCAN meta-analysis indicated that for female patients the rupture risk for AAAs measuring 45mm is equivalent to that of 55mm AAAs in male patients.<sup>24</sup> In our center we have taken into account a 50mm threshold for AAA repair according to international recommendations, whereas the maximum dimensions for female patients treated electively ranged from 52mm to 63mm.<sup>22</sup> Regarding the secondary objectives of this study, we believe that with the exception of

the gender distribution, the remaining characteristics of the study population is that of a typical cohort of patients with AAA, with a high prevalence of smoking and hypertension and a low prevalence of diabetes.<sup>15</sup> The outcomes of AAA repair are similar to those reported in the literature for both elective and non-elective procedures.<sup>12,15</sup> We should clarify that the absence of endovascular treatment for ruptured AAAs is a result of management economic policy of our institution which does not allow to stock endografts of all sizes onsite while at the same time the geographic isolation of our region from the endograft companies on mainland Greece results in a delayed acquisition of the endograft of 8 to 20 hours, depending on the time of day of patient admission. This practice is now about to change according to the international guidelines.

## CONCLUSION

Rate of female patients among subjects receiving AAA treatment is considerably low in the population of Crete, an island in the east Mediterranean Sea. Low smoking rates among women during the past decades may explain the remarkable difference between our study population and rate of women undergoing AAA treatment reported in most current series.

**Conflict of interest:** None

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