Trans-Atlantic Debate: Whether Evidence Supports Reducing the Threshold Diameter to 5 cm for Elective Interventions in Women with Abdominal Aortic Aneurysms

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Current practice guidelines recommend the repair of asymptomatic abdominal aortic aneurysms once they reach the 5.5-cm diameter threshold, and are based on information from randomised controlled trials. However, as aneurysms are more common in men, women are under-represented in these trials, and questions persist with regard to whether this repair threshold should apply to them. In addition, women have smaller aortas to begin with and in most aneurysm cohorts are older, have more atherosclerotic risk factors, are less likely to be anatomical candidates for endovascular repair, and do less well after emergent or elective repair of their aneurysm. These are just some of the issues that our discussants address in determining whether the repair threshold should be at a smaller diameter for women.

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Part One: For the Motion. Evidence Supports Reducing the Threshold Diameter to 5 cm for Elective Interventions in Women With Abdominal Aortic Aneurysms

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INTRODUCTION

The decision of when to repair an asymptomatic abdominal aortic aneurysm (AAA) is based on the comparison between the risk of aneurysm rupture and the risk of surgical repair. Although there are multiple clinical risk factors that can influence the risk of rupture, the maximum diameter of the aneurysm has been shown to be the most consistently predictive measure of rupture risk. As women have smaller aortic diameters than men, should the diameter threshold for aneurysm intervention be different for women and men? To address this question, we present the argument that there are sufficient data to support a decrease in the aneurysm diameter threshold for AAA repair for women. There is well-documented evidence that not only do female patients have smaller aortic diameters, but their AAAs also rupture at smaller diameters compared with men, and have an increased risk of fatal aneurysm rupture compared with men.1–3 Furthermore, women experience higher mortality when undergoing repair of an aneurysm rupture. Thus, at the current time, evidence supports a reduction in the diameter threshold for elective AAA interventions in women to 5 cm.

DATA EXIST TO CHANGE THE DIAMETER THRESHOLD

At what aneurysm size is the risk of early intervention outweighed by the risk of rupture and death? This answer is complicated by the difficulty in estimating the rupture risk of aneurysms based on population studies, which vary widely. To address this question, four randomized controlled trials (RCTs) have been performed to determine whether early aneurysm repair is beneficial in patients with small aortic aneurysms. The UK Small Aneurysm and the ADAM
trials randomized patients with small aneurysms (4.0–5.5 cm) to surveillance or early open repair, and the PIVOTAL (4.0–5.0 cm) and CAESAR (4.1–5.4 cm) trials addressed surveillance versus early endovascular repair in this patient population.4–7 All four trials concluded that surveillance was safe in patients with aneurysms <5.5 cm in size and that early repair provided no short- or long-term benefit in reduction of mortality from either aneurysm or aneurysm rupture. As a result of these trials, both the European and American vascular society guidelines have published level one recommendations for repair of asymptomatic AAAs at 5.5 cm or larger if patients are of acceptable operative risk, and continued surveillance for those with aneurysms between 4.0 and 5.4 cm in size.8,9 However, a caveat to this recommendation in both the European and American guidelines is that repair at a maximal diameter of 5.0–5.4 cm may be considered in women. Because none of the randomized trials were powered to detect differences based on sex, both guidelines avoid official recommendation of repair at a lower size threshold in women. Part of the reason that the randomized trials did not include enough women to make recommendations in this patient subgroup is related to the prevalence of the disease, as two-thirds of AAAs occur in men.10 Yet, aneurysms occur in women, particularly those with a family history, and women have smaller arteries than men. A recent analysis of computed tomography scans of normal infrarenal aortic diameters from participants of the Framingham Heart Study revealed that the average diameter for men was 19.3 mm and for women it was 16.7 mm—13% smaller.11 If a 13% reduction in the 5.5-cm diameter threshold was used to determine a new diameter threshold for women, it would be 4.8 cm. Thus, it should be clear that a lack of data from large RCTs does not mean there are not convincing data to support a lower diameter threshold in women.12 As women have smaller aortic diameters at baseline, why would anyone assume that an absolute threshold value should be equally applied to both sexes? Common sense dictates otherwise.

AAAS IN WOMEN RUPTURE AT SMALLER DIAMETERS

There is evidence that women are at higher risk of aneurysm rupture when compared with men and that, when rupture occurs, it does so at smaller diameters in women when compared with men. This has raised concern that early repair at smaller diameters may be beneficial in this patient population. Of the randomized controlled trials for early repair of small AAA, the UK small aneurysm trial included the most women (188; 17% and 18% of the early surgery and surveillance groups, respectively).4 In a follow-up analysis that included both randomized and nonrandomized patients (465 [20.6%] women), the authors reported a threefold increase risk of fatal aneurysm rupture associated with female sex (14% women vs. 5% male; \( p < .01 \)) when adjusted for age, body size and initial AAA diameter.3 Aneurysms in women also ruptured at an average smaller diameter (5.0 cm vs. 6.0 cm for men). Female sex as a risk factor for AAA rupture is supported by other studies.13–15 One cited explanation for increased rupture risk at a smaller aneurysm diameter for women is the smaller overall aortic size (average 3–5 mm smaller than men),11 resulting in a larger relative dilation of the infrarenal aorta in women with AAAs.2 It may also be that absolute aneurysm diameter is less predictive of rupture risk in women. It has been suggested that the most important determinant for rupture of AAA in women is aortic diameter indexed to body size. Thus, the definition of aortic diameter should also include body build.16,17 Lo et al. evaluated 4,045 patients undergoing AAA repair and found that women had smaller-diameter aneurysms and lower body surface area.18 For men, the variable most predictive of rupture was the aortic diameter. However, for women, the variable most predictive of rupture was the aortic size index, which is the aortic diameter divided by the body surface area. Other proposed explanations for increased rupture risk in women include differences in aortic compliance between men and women, a reduced FEV1, smoking status, and hypertension.19 Regardless, even when controlling for comorbidities, female sex is still an independent risk factor for rupture with smaller baseline aortic size as one potential contributing factor.20

WOMEN DO WORSE FOLLOWING AAA INTERVENTION

As with any intervention the benefit to the patient—in this case reduction in rupture risk and mortality—must outweigh the risk of the intervention proposed to reduce that risk. Not only do women have a higher risk of rupture from AAA, but several studies have also demonstrated that they have higher morbidity and mortality after open aneurysm repair when compared with male patients.3,15,21–24 Part of the increased risk of repair for women is that, on average, they present with AAA at a later age than men. However, even when controlling for age and comorbidities, women face increased morbidity and mortality following open repair, with odds ratios for 30-day mortality ranging between 1.3 and 1.7.21 The exact reason for this is unknown and may reflect an absence of the protective effect of estrogen in postmenopausal women or the increased impact or lack of effective medical management of standard cardiovascular risk factors for women.25

With the advent of endovascular repair and the associated decreased 30-day morbidity and mortality when compared with open surgery, one might expect that women may then obtain a benefit from early repair for smaller aneurysms if a minimally invasive approach is used. However, this has not been the case.6,7 Multiple studies have demonstrated inferior results for women following endovascular repair compared with men.15,22,26–28 One explanation for worse outcomes in women may be related to anatomical features. Overall, women less frequently meet anatomical criteria for endovascular aneurysm repair when compared with males and are relegated to open repair.29 As noted previously, women typically have smaller arteries, which may make them prone to a higher risk of rupture in the proximal (infrarenal neck) and distal (iliac) seal zones,
but they also have a higher incidence of neck angulation.\textsuperscript{25,27,30} Increased incidence of endoleaks and late conversion also suggest that endovascular repair may be attempted more frequently in women not meeting the device instructions for use (IFU) than in men.\textsuperscript{21,31} Sweet et al. showed that female sex was independently associated with decreased odds of meeting all device IFU criteria, and this practice has been associated with worse outcomes compared with following IFU criteria.\textsuperscript{21,31,32} Perhaps with the advent of lower profile and smaller-diameter devices, these outcomes will improve but that remains to be seen. Although it could be said that worse outcomes in women following elective repair would argue against repair at a smaller size threshold, outcomes following rupture are even more dismal in women and the risk of rupture at smaller sizes supports consideration of repair in this patient population at a smaller-diameter threshold.

**CONCLUSIONS**

Based on the best evidence currently available, the threshold for elective aneurysm repair in women should be lowered. There is increasing evidence to support that the parameters used to evaluate and recommend treatment for men are not directly applicable to women.\textsuperscript{16} Although there are likely additional factors that contribute to rupture risk in patients with AAA, currently an absolute aneurysmal diameter is the standard by which repair is considered. The normal aortic diameter in women is smaller than in men. If a relative dilation is considered, then an aneurysm diameter of 4.8 cm in women is comparable with a diameter of 5.5 cm in men. Therefore, based on the size differential between men and women at baseline, a threshold of 5.0 cm is reasonable for consideration of repair in women.\textsuperscript{7} Because the RCT data are not powered to support a definitive recommendation for repair at a smaller size threshold in women, both the American and European practice guidelines only recommend it as a consideration in this high-risk population.

An argument against repair at a smaller size threshold would be the increased morbidity and mortality with elective repair in women when compared with men—a problem that is not unique to aneurysmal disease.\textsuperscript{10,33} Increased risk among women is likely due to a combination of decreased detection secondary to lack of uniform screening recommendations for women at risk for aneurysm development, presentation at an older age with more advanced disease, and anatomical factors that appear to contribute to both increased risk of aneurysm rupture and increased morbidity and mortality associated with repair in women. However, the outcomes with repair after rupture are even worse and given that women have a higher rupture rate and at smaller diameters, this would argue for elective repair in this population at a lower size threshold.

**REFERENCES**


Part Two: Against the Motion. Evidence Does Not Support Reducing the Threshold Diameter to 5 cm for Elective Interventions in Women with Abdominal Aortic Aneurysms

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"...and I will do no harm or injustice to [my patients]"

Hippocratic Oath

The management of patients with asymptomatic abdominal aortic aneurysms (AAAs) is focused on the avoidance of rupture, which is associated with very high mortality. Therefore decision-making must balance the risk of rupture against the risk of prophylactic surgery. Therefore, in order to correctly manage patients, it is essential to quantify these risks. Randomised trial evidence has demonstrated that there is no benefit in repairing AAAs <5.5 cm in diameter, either by open or endovascular means. Although these trials were conducted in men and women, as in most other randomised trials in cardiovascular disease, women were under-represented. However, from the trial with the highest proportion of women, women appeared to be at increased risk of aneurysm rupture. Recent evidence synthesis from the RESCAN project has confirmed the increased risk of rupture in women with small (<5.5 cm) AAA compared with men. It is this finding that prompts the question of this debate: “Should women be offered surgery at a lower AAA diameter threshold than men?”. Answering this question requires knowledge of (i) the risk of AAA rupture at specific diameters; (ii) mortality after open and endovascular repair at specific aortic diameters; and (iii) the proportion of women anatomically suitable for endovascular repair and then must be set in the context of the proportion of women who are physiologically fit enough for any repair (Fig. 1).