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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 repair of asymptomatic abdominal aortic aneurysms once they reach the 5.5-cm-diameter threshold and are based on information from randomized controlled trials. However, because aneurysms are more common in men, women are under-represented in these trials, and questions persist about 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 anatomic candidates for endovascular repair, and do poorer after emergency 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. (J Vasc Surg 2014;60:1695-702.)

PART I: EVIDENCE SUPPORTS REDUCING THE THRESHOLD DIAMETER TO 5 CM FOR ELECTIVE INTERVENTIONS IN WOMEN WITH ABDOMINAL AORTIC ANEURYSMS

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The decision of when to repair an asymptomatic abdominal aortic aneurysm (AAA) is based on the risk of aneurysm rupture compared with the risk of surgical repair. Although multiple clinical risk factors 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. Because 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 female patients. There is well-documented evidence that female patients not only have smaller aortic diameters but that their AAAs also rupture at smaller diameters compared with male patients and they 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 reducing 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 have been performed to determine whether early aneurysm repair is beneficial in patients with small aortic aneurysms. The UK Small Aneurysm and the Aneurysm Detection and Management (ADAM) trials randomized patients with small aneurysms (range, 4.0-5.5 cm) to surveillance or early open repair, and the Positive Impact of EndoVascular Options for Treating Aneurysms Early (PIVOTAL; range, 4.0-5.0 cm) and Comparison of Surveillance vs Aortic Endografting for Small Aneurysm Repair (CAESAR; range, 4.1-5.4 cm) trials addressed surveillance vs early endovascular repair in this patient population.[3-7]

All four trials concluded that surveillance was safe in patients with aneurysms <5.5 cm in size and that early repair provided no short-term or long-term benefit in the reduction of mortality from all causes or aneurysm rupture. As a

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result of these trials, the European and American vascular society guidelines have both published level one recommendations for repair of asymptomatic AAAs at ≥5.5 cm if patients are of acceptable operative risk and for continued surveillance for those with aneurysms sized between 4.0 and 5.4 cm.[8,9] However, a caveat to this recommendation in the European and American guidelines is that repair at a maximal diameter of 5.0 to 5.4 cm may be considered in female patients. Because none of the randomized trials were powered to detect differences based on sex, both guidelines avoid an official recommendation of repair at a lower size threshold in female patients.

Part of the reason that the randomized trials did not include enough female patients to make recommendations in this patient subgroup is related to the prevalence of the disease, because two-thirds of AAAs occur in men.[10] Yet, aneurysms do 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 was 19.3 mm for men and 16.7 mm for women, 13% smaller.[11] If a 13% reduction in the 5.5 cm diameter threshold were 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 randomized controlled trials does not mean there are not convincing data to support a lower diameter threshold in female patients.[12] Because women have smaller aortic diameters at baseline, why would anyone assume that an absolute threshold value should be equally applied to both genders? Common sense dictates otherwise.

FEMALE PATIENTS RUPTURE AT SMALLER ANEURYSM DIAMETER

There is evidence that female patients are at higher risk for aneurysm rupture compared with male patients and that when rupture occurs, it does so at smaller diameters in women 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 AAAs, the UK Small Aneurysm Trial included the most female patients, at 188 (17% of the early surgery group and 18% of the surveillance group).[4] In a follow-up analysis that included randomized and nonrandomized patients (465 female patients [20.6%]), the authors reported a threefold increased risk of fatal aneurysm rupture associated with female sex (14% female vs 5% male; $P = .001$) when adjusted for age, body size, and initial AAA diameter.[3] Women also ruptured at an average smaller aneurysm diameter of 5.0 cm vs 6.0 cm for men.

Other studies support female sex as a risk factor for AAA rupture.[13-15] One cited explanation for an 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] Absolute aneurysm diameter may also be less predictive of rupture risk in female patients.

Some have suggested that the most important determinate for rupture of an 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[18] evaluated 4045 patients undergoing AAA repair and found that women had smaller-diameter aneurysms and smaller body surface area. The variable most predictive of rupture for men was the aortic diameter; however, the variable most predictive of rupture for women was the aortic size index, which is the aortic diameter divided by the body surface area. Other proposed explanations for the increased rupture risk in female patients include differences in aortic compliance between male and female patients, a reduced forced expiratory volume in 1 second, 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]

FEMALE PATIENTS DO WORSE AFTER 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. Female patients not only have a higher risk of rupture from the AAA, but several studies have demonstrated that female patients also have higher morbidity and mortality after open aneurysm repair 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 after 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 effect of—or lack of effective medical management of—standard cardiovascular risk factors for female patients.[25]

With the advent of endovascular repair and the associated decreased 30-day morbidity and mortality compared with open surgery, one might expect that female patients may then obtain a benefit from early repair for smaller aneurysms if a minimally invasive approach is used. This has not been the case, however.[6,7] Multiple studies have demonstrated inferior results for women after endovascular repair compared with male patients.[15,22,26-28] One explanation for worse outcomes in female patients may be related to anatomic features. Overall, women less frequently meet anatomic criteria for endovascular repair compared with men and are relegated to open repair.[29]

As noted previously, female patients typically have smaller arteries that 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.[26,27,30] An increased incidence of endoleaks and late conversion also suggests that endovascular repair may be attempted more frequently in female patients who do not meet the device instructions for use (IFU) than in male patients.[21,31] Sweet et al[32] showed that female sex