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Abdominal Aortic Aneurysm
The Prognosis in Women Is Worse Than in Men

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Most manifestations of cardiovascular disease are more common in men than in women. However, cardiovascular disease is the most common cause of death in women worldwide. Coronary heart disease in women has a worse outcome than in men, and this has attracted considerable attention in recent years, with calls for more gender-specific research. Abdominal aortic aneurysms (AAAs) also are less common in women than in men, and, as with coronary heart disease, there is evidence that women with AAA also have a worse prognosis. The present review addresses the epidemiology, development, natural history, management, and outcomes of AAA in women.

Prevalence and Incidence
When the definition of a maximum external diameter $\geq 3$ cm is used, the prevalence of AAA is up to 6 times greater in men than in women. In a community-based screening study of the older population, the prevalence of AAA was 1.3% in women compared with 7.6% in men. Similarly, the ratio of men to women in surgical series is $\sim 5:1$. Because of the relatively low prevalence, women were excluded from the large trials of screening for AAA. The prevalence in women from families with a strong history of AAA may be as high as 8.3%, and these women should be offered screening. Modeling studies have indicated that screening for AAA in women could be cost-effective because the rupture rate appears to be much higher in women than in men.

The incidence of AAA has continued to rise over the last 4 decades. Initially, a similar pattern was seen in both genders, although the increase in mortality and admission rate has been more marked in women. Inspection of data derived from national (England and Wales) statistics shows that the annual number of hospital admissions for aneurysm rupture between 1997 and 2005 has declined by 2% to 3% per annum in men. In women, although the total number of admissions for ruptured AAA is $\sim 40\%$ of male admissions, there has been an increase of $\sim 0.5\%$ per annum since 2005. The reasons for this are unknown. Population screening for AAA in men is not yet widespread in England and Wales and is unlikely to have made a major contribution to these trends. However, AAA appears to be a late event after smoking exposure, and these trends may reflect temporal changes in smoking prevalence. The rise of smoking in women occurred over the period 1950 to 1970, several decades after the widespread uptake of smoking by men. Since then, rates of cessation have been greater in men than in women.

The presence of an AAA is associated with aneurysms of the iliac, femoral, and popliteal arteries, but, compared with AAA, all of these have a higher incidence ratio in men versus women. However, some aneurysms are found predominantly or equally in women, with splenic and cerebral artery aneurysms being respective examples.

Natural History: Expansion and Rupture
There is no good evidence to suggest that aneurysm growth rate is different in men and women. Although a single small study suggested that female gender was an independent predictor of growth rate, the magnitude of the difference was only 0.7 mm per annum. For a given diameter, the time to rupture is less in women than in men. In the UK Small Aneurysm Trial, the risk of rupture in women was 4-fold that of men (hazard ratio, 4.0; 95% CI, 2.0 to 7.9). This pattern was also seen in a retrospective study of 476 patients (99 women) deemed unfit for elective surgery; the annual risk of rupture of 5- to 5.9-cm aneurysms was 1% in men and 3.9% in women. For AAAs kept under surveillance, rupture appears to occur at smaller diameters in women (mean, 5 cm) than in men (mean, 6 cm). A population-based study from Finland found that aneurysm diameter was $< 5.5$ cm in 24% of cases of ruptured AAA in women compared with only 5% in men ($P < 0.01$, $\chi^2$ test).

In a single-center series, it has been demonstrated that the ratio of infrarenal to suprarenal aortic diameters was greater in women than in men, and from regression analysis the ratio in a 5.5-cm AAA in men was similar to a 5.2-cm AAA in women. Moreover, the difference widened exponentially with increasing aneurysm diameter.

A systematic review of studies of the natural history, progressing to rupture, of AAA $> 5$ cm (usually in patients unfit for open AAA repair) identified only 4 studies examining the role of gender. Even in the absence of adjustment for AAA diameter, a meta-analysis showed that the annual risk of rupture of large AAA ($\geq 5$ cm in diameter)
was 18% (95% CI, 8% to 26%) in women versus 12% (95% CI, 5% to 20%) in men. For patients with an AAA ≥5.5 cm in diameter and suitable for endovascular repair in the Endovascular Aneurysm Repair (EVAR)-2 trial, the rate of rupture in the no-intervention group was 2-fold higher in women despite the fact that morphological suitability for EVAR appeared to lower the overall rupture risk (EVAR Trial Participants, unpublished data, 2007).

In a population-based study, Katz et al were the first to report that in the event of rupture, men were more likely to be treated with surgery than women (odds ratio, 1.4; 95% CI, 1.14 to 1.9). This has been confirmed in other studies. Female gender is also an independent predictor (hazard ratio, 1.69; 95% CI, 1.28 to 2.22) of in-hospital death after surgery for ruptured AAA. Although women presenting with ruptured AAA are on average 5 years older than men (~80 versus ~75 years), most of these adverse outcomes are independent of age. In summary, the risk of rupture and the likelihood of a poor outcome after rupture are greater in women than in men.

### Biological and Anatomic Factors Influencing AAA Development

The ability of the aorta to resist hemodynamic strain and conduct the pulse pressure depends on its underlying molecular and anatomic architecture. Differences between men and women start before birth, with birth weights being greater in boys than in girls. The risk of cardiovascular disease in later life is inversely related to birth weight, a finding that might be attributable to nutrition in utero. Those with intrauterine growth restriction and premature births appear to have a particularly high risk of cardiovascular disease in later life. Aortic wall thickness, a potential marker for the susceptibility to atherosclerosis, has been shown to be increased in neonates with growth restriction (mean, 300 m/kg versus 199 m/kg in controls). Premature births appear to have a long-lasting effect on aortic stiffness because postpubertal teenagers have aortas that are 15% more compliant than a normal birth cohort. The impact of gender on these developmental factors and their role in the etiology of AAA remain to be elucidated.

In later life, there are differences in aortic diameter and stiffness between healthy men and women. At any age, men have larger-diameter aortas than women, although the absolute difference in infrarenal aortic diameter is only ∼1.4 mm. There also is a more marked age-dependent increase in diameter observed after 45 to 54 years in men than in women. Hence, if a diameter of 3 cm is used as a definition of AAA, the prevalence between the age groups 45 to 54 years and 75 to 84 years increased from 2.6% to 19.8% in men compared with 0.5% to 5.2% in women. This age-dependent increase in aortic diameter is accompanied by a compensatory increase in wall thickness to minimize the increase in circumferential wall stress, but the compensatory response is greater in women than in men. Other arteries, including the common femoral artery, are smaller in women, which may affect suitability for endovascular repair in the presence of an AAA (see below). At any age, healthy men also have stiffer aortas than women, but this may not be independent of the lower aortic diameters in women. However, it has been suggested that smoking causes much greater aortic stiffening in women than in men.

With stiffer, larger-diameter aortas that are more prone to age-dependent increases in diameter without sufficient compensatory aortic thickening, it is not surprising that AAA is more common in men than in women. However, in part because of their smaller stature, the morphology of AAA in women may differ from that in men; for example, women have shorter and more angulated AAA necks than men.

### Risk Factors for AAA: Role of Estrogens

Endogenous estrogen appears to confer protection against cardiovascular disease in premenopausal women. Unfortunately, postponing menopause with hormone treatment does not reduce the risk of coronary heart disease. The delayed onset of AAA in women suggests that estrogens also may play a role in reducing the prevalence of AAA in women.

In rats, estrogens have been shown to lower the aortic collagen:elastic ratio, whereas testosterone increases the proportion of collagen. This is likely to contribute to the lower aortic stiffness seen in women. A number of recent animal model studies support a possible role for estrogen in protection against AAA, irrespective of whether the elastic tissue destruction associated with experimental aneurysm formation was generated by elastase infusion or angiotensin II administration. Compared with female rats, males have shorter and more angulated AAA necks than men. The role of nitric oxide (which has the potential to lower aortic stiffness seen in women with AAA) has been suggested to be involved in the development of AAA, and the potential for nitric oxide synthase inhibitors to reduce the prevalence of AAA in women has been studied. In a mouse model of AAA, nitric oxide synthase inhibitors have been shown to reduce the prevalence of AAA in female mice.

### Angiotensin II and Estrogen in AAA

Angiotensin II has been implicated in the formation of aneurysms in mouse models of AAA. Chronic infusion of angiotensin II in apolipoprotein E–deficient mice causes degeneration of the aortic elastic lamina, resulting in experimental aneurysm formation. These aneurysms are more common in male mice, and their formation is attenuated by estradiol in male mice. Even in the absence of hormones, it is possible that gender influences the phenotype of aortic smooth muscle cells. In response to interleukin-1, cells cultured from rat male aortas synthesize much more matrix metalloproteinase-9 than corresponding cells harvested from female aortas. Furthermore, pretreating male rats with estradiol-17β reduced matrix metalloproteinase-9 activity in aorticas explants by 60%. Recently, it has been shown that treatment with tamoxifen (a selective estrogen receptor modulator) resulted in smaller aneurysms and lower matrix metalloproteinase-9 activity in a rat elastase perfusion model. The role of nitric oxide (which has the potential to promote tissue damage) has been studied in a mouse model of AAA. In a study of the elastase perfusion model in mice lacking inducible nitric oxide synthase, and in contrast to other mouse models, an unexpected increase in aneurysm
formation was seen in female but not male mice. This effect was partly attenuated by oophorectomy.

Other Risk Factors
In men, the dominant risk factors for AAA are age, smoking, and familial history of AAA. There are weaker and inconsistent associations with other manifestations of cardiovascular disease and risk factors such as hypertension and dyslipidemia. Most studies comparing men and women with AAA report similar risk factor profiles. At the time of presentation, women tend to be 3 to 5 years older than men with AAAs. Apart from older age, the only consistent difference is a greater likelihood of previous history of cerebrovascular disease in women. One study found the negative association with diabetes to be stronger, and another study found hypertension to be a significant risk factor in women but not in men.

These studies do not necessarily tell us why AAA is more common in men than in women. Smoking is the key modifiable risk factor for AAA, and, at least until recently, men have smoked more than women. Moreover, a recent population-based study has highlighted the possibility that, in the United States, smoking is a more potent risk factor for AAA in women than in men, whereas hypertension is a risk factor in men only. This latter observation contrasts with the findings from a Scandinavian study. The existence of familial aggregation of AAA implicates genetic factors in the etiology of AAA. Women with AAA are more likely to have a positive family history of this disorder. Female relatives of affected patients are at increased risk of AAA, although male relatives remain at greatest risk.

Gender and Treatment
The early and long-term results of surgery for AAA are worse in women than in men. Women undergoing elective surgery for AAA are, on average, 2 years older than men. Some population-based studies have found that the case fatality after elective surgery is 35% to 50% higher in women than in men, although other studies have found no difference. In a population-based study, the relative survival at 5 years after elective surgery is worse for women than men. Twelve-year follow-up of patients in the UK Small Aneurysm Trial confirms that the standardized mortality of these patients compared with the general population was 1.53 (95% CI, 1.41 to 1.66) in men versus 2.44 (95% CI, 2.06 to 2.90) in women. This may be because women with AAA have greater cardiovascular comorbidity than men and highlights the importance of adequate management of atherosclerotic risk factors in these patients. The role of statins on the long-term survival of patients with AAA is topical, and statins also may reduce AAA growth rates. It is not known whether increased statin use will improve long-term survival in women with AAA. Women have been underrepresented in the statin trials for cardiovascular disease, and prescription of statins to women appears lower than for men. Therefore, treatment practices may favor men over women.

Endovascular repair of AAA is proving to be technically more difficult in women than in men. The proportion of cases deemed unsuitable because of adverse anatomic features is greater in women. The risk of a failed procedure and the need for additional reconstructive procedures are greater in women. In a study of 704 cases (98 women) from the Cleveland Clinic, graft limb occlusions were significantly more common in women (11% versus 3.3%; P=0.022). The problems relate not only to smaller access vessels but also to shorter, wider, and more angulated aneurysm necks and possibly a greater likelihood of suprarenal involvement. Nevertheless, the case fatality, endoleak, and late reintervention rates are similar for men and women.

Conclusion: Aortic Diameter Threshold for Intervention in Women
It is now generally accepted that coronary heart disease is underdiagnosed and undertreated in women. A similar situation exists for women with AAA. All clinicians need to be aware that although women are inherently less likely than men to develop an AAA, those who develop an AAA fare worse than men.

Two randomized controlled trials concluded that survival is not improved by elective surgery for AAAs <5.5 cm. On the basis of these trials, the current American College of Cardiology/American Heart Association guidelines make the following class I recommendation: “Patients with infrarenal or juxtarenal AAAs measuring 4.0 to 5.4 cm in diameter should be monitored by ultrasound or CT scans every 6 to 12 months to detect expansion.” However, the vast majority of trial participants were men: 83% in the UK Small Aneurysm Trial and 99% in the Aneurysm Detection and Management Trial. Applying criteria for treatment that are suitable for men with AAA may not be appropriate for women. In particular, a threshold of 5.5 cm for intervention would seem too high in women, and recent data suggest that a 5.5-cm AAA in men might carry a rupture risk similar to that of a 5.2-cm AAA in women. The Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery have recommended elective repair at 4.5 to 5 cm in women, although the published guidelines contained no caveat concerning the level of evidence for this recommendation. Relevant evidence for women from randomized controlled trials is unlikely to become available in the foreseeable future. The weight of existing evidence suggests that women carry higher risks than men; therefore, it would seem prudent to advocate a conservative aneurysm diameter threshold of 5 cm for elective intervention in women.

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