

Screening women aged 65 years or over for abdominal aortic aneurysm: a modelling study and health economic evaluation

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Scientific summary

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Background

The NHS Abdominal Aortic Aneurysm Screening Programme (NAAASP) was initiated for men in England and later extended to all of the UK following the large Multicentre Aneurysm Screening Study (MASS) randomised trial in men and subsequent health economic modelling. For women, there has been only one small randomised trial of abdominal aortic aneurysm (AAA) screening. AAA screening in women has not been considered worthwhile because the prevalence of AAAs (aortic diameter of ≥ 3.0 cm) in women is substantially lower than in men. However, modelling suggests that NAAASP would still be cost-effective for women at a threshold of £20,000 per quality-adjusted life-year (QALY) even down to an AAA prevalence of 0.35%. Moreover, one-third of deaths from AAA in the UK are now in women. Hence, the cost-effectiveness of AAA screening in women needs to be formally assessed.

Objectives

The scientific objectives of this project were to:

1. adapt a previous multistate model of AAA screening in men to create a more flexible discrete event simulation (DES) model
2. obtain information from published literature, where possible, on input parameters for this model relevant to women rather than men
3. seek other information or data sources on input parameters for women that are not available in the published literature
4. run the model for women to estimate life-years gained, incremental costs and incremental cost-effectiveness for a population-based AAA ultrasound screening programme in women, and assess the impact of parameter uncertainty on the conclusions using probabilistic and deterministic sensitivity analyses
5. assess modifications that might make a screening programme more appropriate and cost-effective for women.

Methods

A DES model was developed using the R programming language (The R Foundation for Statistical Computing, Vienna, Austria) to provide a clinically realistic model of screening, surveillance, AAA growth and rupture, elective and emergency AAA repair operations, and deaths from AAAs and non-AAA causes. This was validated for men against the MASS trial. Input parameters specifically for women were then employed. To obtain sufficient precision, the model was run for 10 million women. Parameter uncertainty was addressed by sensitivity analyses, both probabilistic (1000 runs of 500,000 women) and deterministic (runs of 10 million women).

Systematic reviews were undertaken, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, for key parameters in women. These included AAA prevalence at different ages and parameters related to elective surgery [proportion suitable for endovascular aneurysm repair (EVAR), non-intervention rate and operative mortality following endovascular and open AAA repair]. We also carried out literature reviews of attendance rates following invitation to attend screening, of non-intervention rates and of outcomes for emergency surgery for ruptured AAAs.

Rates of aortic diameter expansion and AAA rupture were estimated using individual data from an international collaboration of AAA surveillance, using multilevel and joint modelling, respectively.

Anonymised individual data from the UK National Vascular Registry (NVR) were analysed to estimate parameters related to elective and emergency AAA operations in women (proportion receiving endovascular repair and operative mortality rates) and how these depended on age and AAA diameter. Summarised tabular data from the English Hospital Episode Statistics (HES) database were used to cross-check estimates from the NVR, and provide up-to-date information on hospital length of stay (LOS) for AAA operations. Data from the endovascular aneurysm repair trial 1 (EVAR-1) and Immediate Management of Patients with Ruptured aneurysm: Open versus Endovascular Repair (IMPROVE) trial were used to provide estimates of long-term AAA mortality and reintervention rates after AAA surgery.

Costs were considered from a NHS perspective. Those related to screening and surveillance were obtained from NAAASP. Costs related to surgery and reinterventions were derived from the individual patient data in the EVAR-1 and IMPROVE trials, supplemented by hospital LOS data from HES. Costs were adjusted to 2014–15 prices. Utility adjustments for quality of life (QoL) were based on age alone.

Models were run for women aged ≥ 65 years, up to age 95 years. Discounting at 3.5% per year was applied to costs and life-years. The base-case model adopted the same age at screening (65 years), definition of AAA (diameter of ≥ 3.0 cm), surveillance intervals (1 year for AAAs with a diameter of 3.0–4.4 cm, 3 months for AAAs with a diameter of 4.5–5.4 cm) and AAA diameter for consideration of surgery (5.5 cm) as in NAAASP for men, and used surgical parameters based on the overall estimates from the NVR. Other options for a screening programme were also investigated to try to improve cost-effectiveness.

Results

The DES model had a similar structure to a previous multistate Markov model for AAA screening based on the MASS trial, but was much more sophisticated. It modelled individuals in continuous time, aortic size was considered as a continuous variable and the model allowed the flexibility to change screening options such as the intervention threshold. The model validated as well against the MASS data as the original Markov model in terms of numbers of key events and yielded an incremental cost-effectiveness ratio (ICER) estimate for men in NAAASP of £6400 per QALY gained as compared with £7400 from the Markov model.

The prevalence of AAAs (aortic diameter of ≥ 3.0 cm) was estimated from the first systematic review as 0.43% [95% confidence interval (CI) 0.23% to 0.80%] in women aged 65 years and 1.15% (95% CI 0.59% to 2.24%) at age 75 years. The corresponding attendance rates following invitation to screening were estimated as 73% and 62%, respectively. In the systematic reviews for elective operations, women were shown to fare worse than men in all respects: the proportion suitable for EVAR was 34% (95% CI 25% to 44%), lower than in men (54%); the non-intervention rate was 34% (95% CI 28% to 40%), higher than in men (19%); and 30-day mortality was 2.2% (95% CI 1.9% to 2.7%) following EVAR and 5.4% (95% CI 4.2% to 6.9%) following open AAA repair, both of which are higher than in men (1.3% and 2.8%, respectively).

Based on the international AAA surveillance data, aortic diameters in women were estimated to increase on average by 5.3% per year, with a standard deviation (SD) between individuals of 3.8%. Rupture rates were 4.3 times higher in women than in men, and increased by 31% for each 5% increase in AAA diameter, being 0.17 and 4.6 per 100 woman-years at 3.0 cm and 5.5 cm, respectively.

Based on women in the NVR, for elective operations, the proportion receiving EVAR increased greatly with age but decreased somewhat with AAA diameter, and open AAA repair mortality increased with age. For emergency operations of ruptured AAAs, operative mortality increased with age for both endovascular and open repair. The cost of elective operations was higher in women than men owing to a longer hospital LOS.

For the base-case model, invitation to screening increased elective operations by 21%, lowered emergency operations by 4% and decreased AAA deaths by 3%. Per one woman invited to screening, the estimated gain in life-years was 0.00285, the gain in discounted QALYs was 0.00110 and the discounted incremental cost was £33.99. This gave an ICER of £31,000 per QALY gained. The corresponding incremental net monetary benefit (INMB) at a threshold of £20,000 per QALY was –£12.03 (95% uncertainty interval –£27.88 to £22.12).

The deterministic sensitivity analyses halved or doubled the AAA prevalence, halved or doubled the rates of dropout from surveillance and incidental AAA detection, included the dependence of surgical parameters on age and AAA diameter, based surgical parameters on the literature reviews, and altered the unit costs of screening and operations downwards by 20% or upwards by 25%. None of these analyses brought the ICER below £20,000 per QALY gained, except when modifying the distribution of aortic diameters at screening; for example, doubling the AAA prevalence to 0.86% gave an ICER of £13,000.

In the investigation of alternative screening options, increasing the age at screening to 70 years gave an ICER of £24,000 per QALY gained. Lowering the threshold for considering surgery to a diameter of 5.0 cm or 4.5 cm gave ICERs of £28,000 and £27,000 per QALY gained, respectively. Lowering the diameter defining an AAA in women to 2.5 cm, together with 5-year surveillance intervals for the 2.5- to 2.9-cm group, gave an ICER of £25,000 per QALY gained. Putting together the options of screening at age 70 years, considering surgery at a diameter of 5.0 cm, and including the 2.5- to 2.9-cm group in surveillance, gave an ICER of £23,000 per QALY gained. The corresponding INMB at a threshold of £20,000 per QALY was –£5.08 (95% uncertainty interval –£31.53 to £69.98).

Conclusions

The conclusion of our analyses is that the accepted criteria for a cost-effective AAA screening programme in women are not currently met. We did not find any combination of screening options for women that would make population AAA screening cost-effective at a willingness-to-pay threshold of £20,000 per QALY. This is in marked contrast to previous findings in men.

The DES model developed for this project was novel in a number of respects. First, because it considered individuals rather than groups, aortic diameter expansion could be more precisely represented, allowing for the substantial heterogeneity between people in growth rates. Moreover, and importantly in the context of investigating AAA screening for women, it allowed the modelling of different screening options, which would not be feasible in a single multistate model. The downside of individual modelling is the computational requirements, as millions of individuals have to be modelled to ensure that the results obtained are reliable.

The systematic review of AAA prevalence was of key importance to this project. However, the available data in women were rather limited and complicated by studies having been undertaken in different calendar years that used different screening approaches and ultrasound measurement techniques. In addition, individual data on aortic size distribution were available from only two modestly sized studies: (1) a Swedish study of 5140 women aged 70 years and (2) a Danish study of 570 women aged 67 years; this limited the exact description of the aortic diameter distribution in women. As revealed by a sensitivity analysis using the Swedish data, this may have a considerable impact on the cost-effectiveness estimates.

Based on the international AAA surveillance data, the AAA rupture rate in women increased by about 30-fold when the AAA diameter increased from 3.0 cm to 5.5 cm, and the AAA rupture risk in women was about fourfold that of men at the same AAA diameter. This might lead one to propose that the threshold for surgery for women should be lowered to a diameter of 4.5 cm, as this might give a similar balance of risk and benefit as the 5.5-cm diameter threshold for men. However, because of the worse elective surgery outcomes in women, the cost-effectiveness based on 4.5-, 5.0- or 5.5-cm diameter thresholds for women were very similar.

The analysis of the individual data for women in the NVR was important in a number of respects. First, it substantiated in recent UK data the overall higher mortalities in women than men for elective operations, as found in the systematic review. Second, it showed that the proportion of patients actually receiving elective EVAR was lower in women than men, which paralleled the difference in the proportion suitable for EVAR found in the systematic review. Third, it provided reliable estimates of these parameters for emergency surgery for ruptured AAAs, while the literature review undertaken for emergency surgery was less detailed. Fourth, it allowed the modelling to include dependence of these parameters on age and AAA diameter for elective operations, and on age for emergency operations.

The base-case cost-effectiveness analysis showed that the average number of life-years gained per woman invited was very small: 0.00285 life-years or 1.04 life-days. A small average life-years gain is expected in population screening as the vast majority of those screened have normal aortic diameter and no change in life expectancy. Nevertheless, this very small gain in life-years is the main reason for the unfavourable cost-effectiveness results. Using National Institute for Health and Care Excellence (NICE) recommended discounting for costs and life-years, the ICER per QALY gained was estimated as £31,000. This is above the threshold of £20,000 generally used by NICE as a basis for approving health interventions for use in the NHS. The sensitivity analyses did not change this conclusion, but also underlined the pivotal role of AAA prevalence in determining the ICER. When the AAA prevalence was doubled, from 0.43% to 0.86%, the ICER fell below £20,000 per QALY gained. Moreover, the uncertainty indicated by the probabilistic sensitivity analysis was considerable.

Screening women for AAA might become more cost-effective if one moved away from the options adopted in NAAASP for men. Screening became more cost-effective if offered at age 70 years. Lowering the threshold for defining an AAA to a diameter of 2.5 cm, lengthening surveillance intervals somewhat for the smallest AAAs, or lowering the threshold for considering elective surgery made AAA screening for women slightly more cost-effective, but these changes considered individually did not bring the ICER down below £20,000 per QALY gained. Even when the best options were combined, the estimated ICER was £23,000 per QALY gained.

The study undertaken had a number of strengths:

- the use of individual simulation modelling, which allowed evaluation of multiple screening options
- modelling aortic diameter as a continuous variable
- the use of women-specific parameters wherever possible
- systematic reviews undertaken for key parameters
- extensive re-analysis of data sources.

The study also had some limitations:

- lack of validation of the model against empirical data for women
- the problem that some parameters were poorly estimated or not specifically available for women
- the relevance of some parameter values to current women in the UK was uncertain.

Our main recommendations for future research are:

1. Undertake a large-scale empirical study of the current attendance rate at screening, AAA prevalence and exact aortic size distribution for women screened at relevant ages. This could include the investigation of whether or not AAA screening, and positive or negative results, influence QoL.
2. Capitalise on the development of the DES model by evaluating screening options in men, to assess whether or not NAAASP could be improved.

Study registration

This study is registered as PROSPERO CRD42015020444 and CRD42016043227.

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