Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness

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Scientific summary

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Background

Small abdominal aortic aneurysms (AAAs; 3.0–5.4 cm in diameter) are usually asymptomatic and managed by regular ultrasound surveillance until they grow to a diameter threshold (commonly 5.5 cm) at which surgical intervention is considered. The choice of appropriate intervals for surveillance is governed by the growth and rupture rates of small AAAs. Growth rates increase with AAA diameter, vary between people and may depend to an extent on patient characteristics. Rupture rates for small AAAs are considered to be low, but there is little evidence to quantify this and how they depend on AAA diameter and patient characteristics. The intervals between surveillance scans should be chosen to control to acceptable levels both the risk of rupture and the risk of growth to a size where surgery is indicated.

Various rescanning intervals are used in different surveillance programmes. Currently, in the NHS Abdominal Aortic Aneurysm Screening Programme (NAAASP) for men aged 65 years, yearly intervals are employed for 3.0–4.4-cm AAAs and 3-month intervals for 4.5–5.4-cm AAAs. These choices were based on the intervals used in the large UK Multicentre Aneurysm Screening Study (MASS) randomised trial of men aged 65–74 years, which showed that AAA screening reduced AAA-related mortality by about a half and was very cost-effective. Whether or not these intervals are optimal is not known, as there are no direct comparisons of different surveillance policies. However, changing these intervals would influence both effectiveness and costs. For example, lengthening the intervals would reduce surveillance costs, but would slightly increase AAA ruptures leading to both greater mortality and increased costs through emergency surgery. The best choice of surveillance intervals needs to take this balance into account.

Objectives

The aim of this series of studies was to inform the evidence base for choice of appropriate surveillance intervals for small AAAs. This was first attempted by (i) a systematic literature review of published small AAA growth rates and (ii) a systematic literature review of published small AAA rupture rates. Since published information proved insufficient for detailed modelling of small AAA growth and rupture rates, the project proceeded with (iii) analysis of individual patient data (IPD) from existing surveillance programmes, (iv) use of these IPD to investigate individual characteristics associated with growth and rupture rates, and to provide inputs for health economic modelling, and (v) development of a cost-effectiveness modelling framework to assess the impact of different surveillance intervals on costs, life expectancy and costs per quality-adjusted life-year (QALY) gained.

Methods

The databases MEDLINE, EMBASE on OvidSP, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov and controlled-trials.com were searched from inception up until to the end of 2009. A systematic review of small AAA growth rates in published studies identified 61 potentially eligible reports. Detailed review yielded 15 studies providing growth rates for aneurysms of 3.0–5.5 cm in diameter (14 expressed as mm/year, one as percentage change/year). Additional studies published up to September 2012 were also reviewed.

Similarly, a systematic review of small AAA rupture rates in published studies identified 54 potentially eligible reports. There were only 14 studies from which rupture rates (as ruptures per 100 person-years) were available. Additional studies published up to September 2012 were also reviewed.

We obtained IPD on 15,475 patients under surveillance for small AAA from 18 studies, harmonised the data sets and developed novel statistical methods for their analysis. Individual AAA diameters in each study were analysed using a random-effects model that allowed for between-patient variability in size and growth rates. Rupture rates were analysed by joint proportional hazards regression to incorporate the modelled AAA diameter as a time-varying covariate. Predictions of the risks of exceeding 5.5 cm in diameter, and of rupture, within given time intervals were estimated, and pooled across studies in a second stage using random-effects meta-analysis. Acceptable risks were informed by the views of a focus group.

The influence of covariates (including demographics, medical and drug history) on aneurysm growth and rupture rates was investigated in each IPD surveillance data set. Growth rates were analysed using longitudinal random-effects modelling and rupture rates by Cox proportional hazards regression with adjustment for aneurysm diameter. The effects of covariates were combined across studies in a second stage using random-effects meta-analysis.

To perform the cost-effectiveness analyses, we first updated the original health economic model of AAA screening based on 4-year follow-up data in the MASS trial to employ the 10-year follow-up data now available, undertaking internal validation and parameter recalibration. We then modified the modelling framework to incorporate unobserved 'tunnel' states to allow the investigation of different surveillance intervals. Up-to-date (2010–11) unit costs were estimated for screening, surveillance, and elective and emergency surgery, drawing on data from various sources. We also incorporated data from NAAASP on the prevalence, attendance rate and distribution of AAA sizes at screening. Finally, we derived transition rates for AAA growth and rupture applicable to modelling different surveillance intervals from bespoke analyses of the 18 IPD surveillance data sets. We used a threshold value of £20,000 per QALY gained to calculate net benefit.

Results

In the systematic literature review of growth rates, the 15 studies included 7630 persons (predominantly male) enrolled during 1976–2005. The pooled mean growth rate was 2.32 mm/year [95% confidence interval (CI) 1.95 to 2.70 mm/year] but there was very high heterogeneity between studies, with average growth rates ranging from –0.33 to +3.95 mm/year. Six studies reported growth rates by 5-mm-diameter bands, which showed the trend for growth rate to increase with aneurysm diameter. Naive methods to estimate linear growth rates (such as last measurement minus first measurement/time interval) were associated with higher growth rate estimates. Meta-regression analysis showed that a 1-cm increase in aneurysm diameter was associated with a 1.62 mm/year [standard error (SE) = 0.20] increase in growth rate. Neither mean age nor percentage of women in each study had a significant effect. On average, a 3.5-cm aneurysm would take 6.2 years to reach 5.5 cm, whereas a 4.5-cm aneurysm would take only 2.3 years.

Detailed review of the 54 studies identified in the systematic literature review of rupture rates showed that ascertainment of rupture, patient follow-up and causes of death were poorly reported. Diagnostic criteria for rupture were never reported. The 14 studies in which rupture rates were available included 9779 patients (89% male) over the time period 1976–2006, but only seven of these studies provided rupture rates specifically for the AAA diameter range 3.0–5.5 cm. These ranged from 0 to 1.61 ruptures per 100 person-years.

In the analysis of IPD data sets, growth and rupture rates varied considerably between studies. For each 0.5-cm increase in AAA diameter, growth rates increased on average by about 0.5 mm/year and rupture rates doubled. For a 3.0-cm AAA the average growth rate in men was 1.3 mm/year (95% CI 1.0 to 1.5 mm/year), and for a 5.0-cm AAA it was 3.6 mm/year (95% CI 3.3 to 3.9 mm/year); the corresponding average rupture rates were 0.05 per 100 person-years (95% CI 0.03 to 0.07) and 0.64 (95% CI 0.43 to 0.95). To control the risk of exceeding 5.5 cm to below 10% in men, on average a 7-year surveillance interval

is sufficient for a 3.0-cm aneurysm, whereas an 8-month interval is necessary for a 5.0-cm aneurysm. To control the risk of rupture to below 1%, the corresponding estimated surveillance intervals are 9 years and 17 months.

Aneurysm growth rates were independent of age and sex. Average growth rates were higher in smokers (by 0.35 mm/year; $p < 0.001$) and lower in patients with diabetes (by 0.51 mm/year; $p < 0.001$). Mean arterial pressure had no effect and antihypertensive or other cardioprotective medications had only small, non-significant effects on aneurysm growth, consistent with the observation that calendar year of enrolment was not associated with growth rates. Rupture rates were almost fourfold higher in women than men ($p < 0.001$), doubled in current smokers ($p = 0.001$) and increased with higher blood pressure ($p = 0.001$), with some evidence that the aneurysm size had decreased over calendar time ($p = 0.03$).

Compared with the current surveillance policy in NAAASP, increasing the surveillance interval for the smallest aneurysms (3.0–4.4 cm) decreased costs and led to a positive net monetary benefit. For example, increasing the current 1-year interval to 2 years reduced costs by £2.57 and increased net monetary benefit by £1.33 per man invited to screening. Decreasing the interval from 1 year for these smallest aneurysms led to higher costs and a negative net benefit. For the larger aneurysms (4.5–5.4 cm), it was not similarly cost-effective to increase surveillance intervals from the current 3 months. For example, an increase to 6 months decreased costs by £1.51 but this was offset by a decrease in life expectancy so that the net benefit was only £0.10 per man invited to screening.

Conclusions

From the systematic reviews, we conclude that there is considerable variation between studies in the reported growth rates of small aneurysms beyond that explained by aneurysm diameter. Fuller evidence on which to base surveillance intervals for patients in screening programmes requires an IPD meta-analysis. We also conclude that rupture rates of small AAAs would appear to be low. However, most studies on rupture have been poorly reported and did not have clear ascertainment and diagnostic criteria for aneurysm rupture.

From the analysis of the IPD surveillance data sets, we conclude that surveillance intervals of several years are clinically acceptable for men with AAA diameters in the range of 3.0 to 4.0 cm. Intervals of around 1 year are suitable for 4.0–4.9-cm AAAs, whereas intervals of 6 months are appropriate for 5.0–5.4-cm AAAs. These intervals are longer than those currently employed in the UK AAA screening programmes. Recommendations for frequency of surveillance of individual patients could also consider diabetes and smoking, in addition to aneurysm diameter, but this would be difficult to organise in practice. Nevertheless, information given to patients who continued smoking is likely to increase both growth and rupture rates may be helpful in persuading them to quit. Our data also indicate differing risk factors for growth and rupture and suggest that a lower threshold for surgical intervention in women than men may be justified. No single class of drug used for cardiovascular risk reduction, including statins, was shown to have a major effect on the growth or rupture rate of small aneurysms.

Our cost-effectiveness investigations showed that lengthening the surveillance intervals from 1 year for 3.0–4.4-cm AAAs was cost-effective. However, the differences in costs were small, up to about £4 within an overall cost of £300 per man invited to AAA screening. Lengthening the 3-month interval for 4.5–5.4-cm AAAs to 6 months was neutral in terms of cost-effectiveness. Our results may be susceptible to the detailed modelling assumptions made and parameter estimates used, and the fact that our updated health economic model did not validate very well on the 10-year MASS trial data. Nevertheless, the cost-effectiveness analyses support some lengthening of surveillance intervals for the smallest aneurysms, in line with the clinical conclusions above.

Research implications

We draw the following conclusions about future research priorities:

- We identified that the definition and diagnostic criteria of AAA rupture were poorly reported in published studies. There is a need for standardised definitions and reporting, so that rupture rates can be more reliably estimated.
- We observed large variation in growth rates between studies, which was largely unexplained. The identification of both methodological reasons, for example how AAA diameters are measured, and biological causes for this variation are important. The latter could lead to the identification of factors and biological pathways related to increased growth rates or rupture rates that were amenable to intervention. Such interventions should then be assessed in randomised trials.
- We have shown that the clinical progression of AAA is different in women compared with men, with women at substantially higher risk of rupture. Currently, women are not screened for AAA in the UK and those with opportunistically detected AAA are usually entered into generic rather than sex-specific surveillance programmes. In addition to obtaining evidence to investigate the efficacy and cost-effectiveness of AAA screening in women, surveillance programmes and criteria for considering surgery need to be tailored for women.
- Although we have provided evidence about appropriate surveillance intervals for small AAAs, we have always used the currently accepted diameter of 5.5 cm for considering elective surgery. Related research could aim to determine whether or not it is possible to develop personalised criteria or patient-specific thresholds for elective surgery.
- Comparable studies with data sets of substantial size are required for the kind of research undertaken here. Future research should focus on the collection and use of large, well-structured and internationally compatible data sets, along with statistical and epidemiological methods needed for their harmonisation and analysis. The recent inception of national AAA screening programmes in several countries may facilitate such research.

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