**International Journal of Technology Assessment in Health Care, 16:1** (2000), 22–34.


# COST-EFFECTIVENESS OF TARGETED SCREENING FOR ABDOMINAL AORTIC ANEURYSM

## *Monte Carlo–based Estimates*

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Abstract

**Objectives:** This article reports a cost-effectiveness analysis of targeted screening for abdominal aortic aneurysm (AAA). A major emphasis was on the estimation of distributions of costs and effectiveness.
**Methods:** We performed a Monte Carlo simulation using C programming language in a PC environment. Data on survival and costs, and a majority of screening probabilities, were from our own empirical studies. Natural history data were based on the literature.
**Results:** Each screened male gained 0.07 life-years at an incremental cost of FIM 3,300. The expected values differed from zero very significantly. For females, expected gains were 0.02 life-years at an incremental cost of FIM 1,100, which was not statistically significant. Cost-effectiveness ratios and their 95% confidence intervals were FIM 48,000 (27,000–121,000) and 54,000 (22,000–∞) for males and females, respectively. Sensitivity analysis revealed that the results for males were stable. Individual variation in life-year gains was high.
**Conclusions:** Males seemed to benefit from targeted AAA screening, and the results were stable. As far as the cost-effectiveness ratio is considered acceptable, screening for males seemed to be justified. However, our assumptions about growth and rupture behavior of AAAs might be improved with further clinical and epidemiological studies. As a point estimate, females benefited in a similar manner, but the results were not statistically significant. The evidence of this study did not justify screening of females.

**Keywords:** Screening, Monte Carlo simulation, Abdominal aortic aneurysm, Cost-effectiveness analysis, Life-years gained

This article was finished at the German Cancer Research Center, Division of Epidemiology, at Heidelberg in June 1998. The division and our colleagues there are acknowledged for providing facilities and for constructive feedback. Especially, we want to thank Professor Matti Hakama. An earlier draft of this article was presened at the Nordic Health Economists' study group meeting in Oslo in August 1998. The opponent and the audience there are acknowledged for engaging us in productive discussion that improved the paper substantially. We also want to thank an anonymous referee.

The incidence of ruptured abdominal aortic aneurysms (AAAs) has increased in all Western countries, and varies between 2.9 and 14.1 per 100,000 inhabitants (7). From 1987 to 1995 in Finland, the total number of annual deaths due to ruptured AAAs increased by more than 60% from 171 to 274 (17). The mortality of patients with a ruptured AAA is high; approximately two-thirds of such patients die before reaching the hospital (3), and the operative mortality of emergency patients has been around 50% in most studies (3;7). The total mortality rate of patients with ruptured AAA is as high as 85% to 95% when subjects both operated on and those who die before reaching the hospital are included (1). On the other hand, the operative mortality of elective AAA patients is generally less than 5% (1;20). Thus, AAA seems to be a potential candidate for screening if an acceptable screening strategy can be found and as far as the negative side effects of the screening remain acceptable when compared to its benefits.

Ultrasonography is a potentially attractive screening method because it is virtually 100% sensitive, noninvasive, riskless, and relatively inexpensive (3;20). Population-based screening for AAA has been suggested for all males over 50 years of age (11), but this approach has not received support from system-theoretical cost-effectiveness analyses (5;10). Targeted screening of high-risk groups, particularly screening of first-degree relatives (probably only males) of patients with AAA, has been an alternative suggestion (2). In this paper we report the results of a simulation model of the cost-effectiveness of targeted AAA screening.

## STUDY OBJECTIVES

The purpose of this study was to estimate the cost-effectiveness of targeted screening for AAA. In particular, we tried to answer the three following questions:

1. Would screening of first-degree male relatives over 50 years of age (father, children, or brothers) of patients with AAA lead to a positive health effect, i.e., an increase in life expectancy? Furthermore, what would be the distribution of life-years gained or lost due to screening? (strategy 1)
2. If screening for males appears to be effective, should first-degree female relatives also be included in the screening program? (strategy 2)
3. What is the incremental cost-effectiveness of each screening strategy?

To our knowledge, there are no randomized controlled trials of the long-term effects of AAA screening on mortality, or any empirical cost-effectiveness studies with sufficiently long follow-up. Our study questions are difficult and very time-consuming to study in a randomized, controlled setting. Thus, and because uncertainty and stochasticity are prevalent in our study problem, we decided to perform a Monte Carlo simulation of the cost-effectiveness of AAA screening.

In our model, we first estimated the expected incremental outcomes of screening, i.e., we wanted to know what the average gain (or loss) of life-years would be when comparing a scenario with screening to the current situation where there is no systematic screening. In a similar manner, we estimated the expected incremental costs. Second, we simulated the distributions of both life-years gained (lost) and incremental costs, and calculated their 95% confidence limits. Third, we calculated cost-effectiveness ratios (C/E ratios) and their 95% confidence limits.

## METHODS

The simulation model was constructed in cooperation with economists and vascular surgeons, and it was programmed in C programming language in a PC environment.

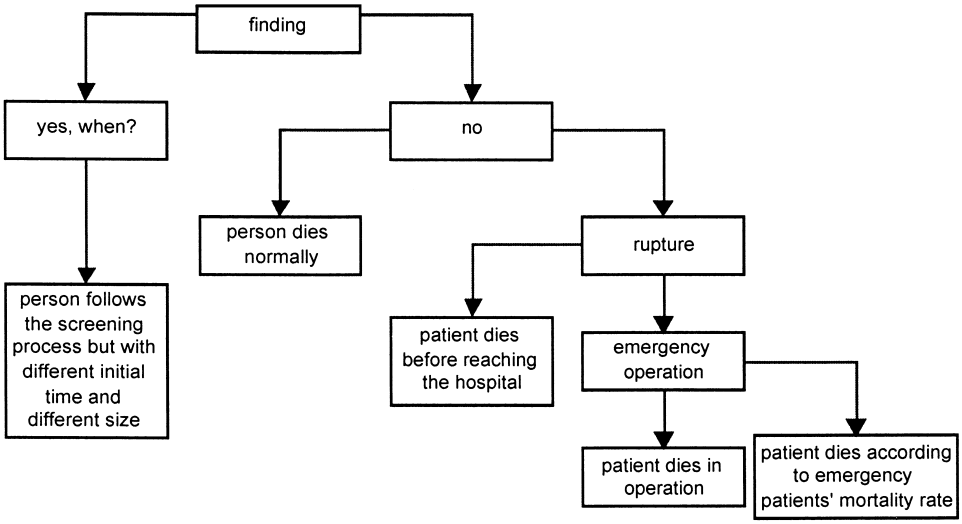


**Figure 1.** Flow diagram of the current practice.

In the model, we simulated for each person a time of death based on the current-practice model. Similarly, we simulated all AAA-specific diagnosis and treatment costs and the times when they occurred. The current practice is schematically presented in Figure 1.

Second, we considered the case where individuals were screened. For each person we simulated time of death, AAA-specific costs, and their timing. The screening model is presented in Figure 2. The incremental effectiveness was calculated as the difference between life-years gained under the current-practice model and under the screening model. Similarly, incremental cost was the difference between the net present values of costs of the two scenarios.

There were two connections between the current-practice model and the screening model that should be emphasized. First, all the incidental findings under the current practice were assumed to behave in the same manner they would have if they had been found in screening. Particularly, AAAs found incidentally or detected by screening were assumed to grow and cause costs in the same manner. The only difference was that incidental findings occurred at a later random time than findings due to screening. Due to the later detection, incidental findings tended to be larger than screening-detected AAAs. Second, all the persons that refused to be screened were assumed to follow the current-practice scenario, i.e., refusal of screening was assumed to be independent of AAA status. The main features of the model are described below in detail.

### Arrival Process

In the model, an arbitrary (but deterministic) number of people were invited to participate in screening at a deterministic time $t_0$. Each person had a random age in the range of 50 to 85 years. The gender-specific probability density of age was based on that of the 50- to 85-year old general Finnish population (18).

### Screening Probabilities and the Growth Model

Screening detects AAAs of different diameters. Screening probabilities and the size distribution of detected AAAs of males were based on empirical data from



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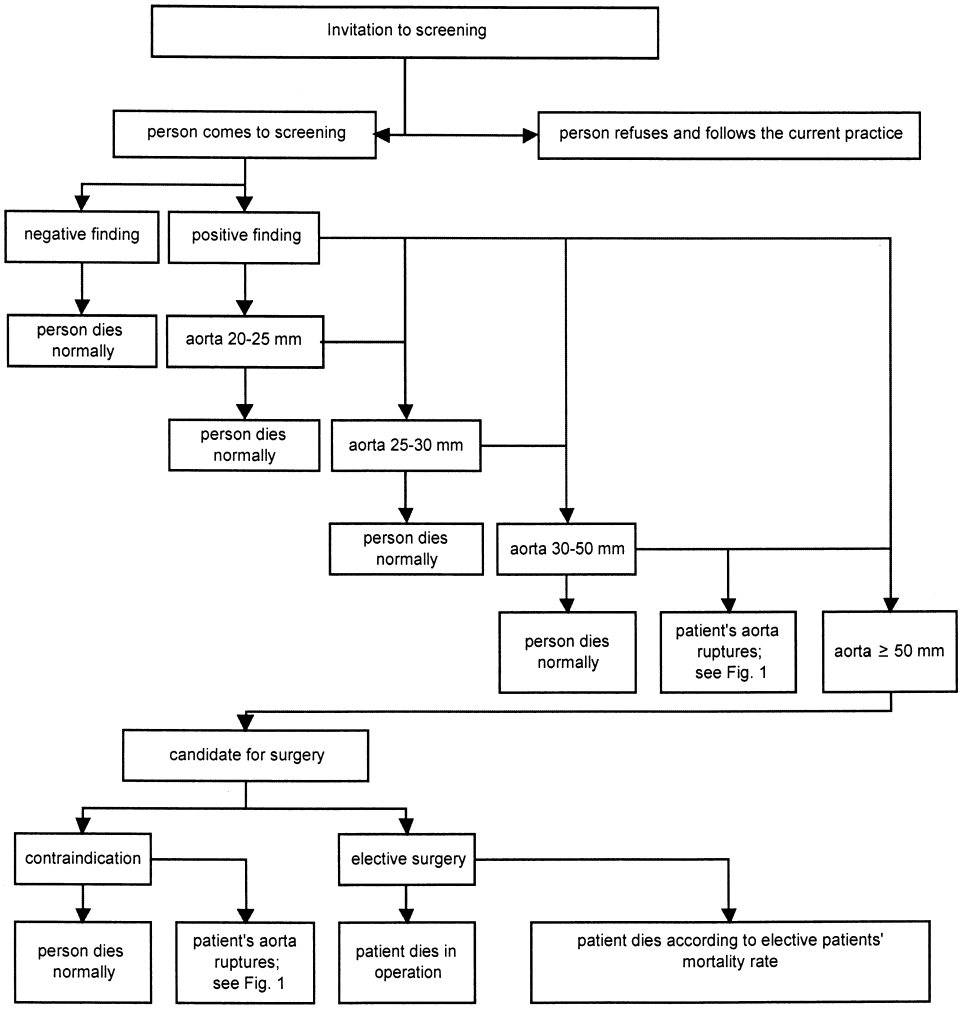


**Figure 2.** The screening model.

the Helsinki University Central Hospital (HUCH), collected during the 1992–94 period (n = 238, of which 38 were positive findings). The data have been described and discussed in detail by Salo et al. (15) and Soisalon-Soininen (16). In the data there were only a few observations of AAA in females, so we were forced to assume the AAA prevalences and rupture incidences among females to be one-fourth those among males. This assumption was based on the literature (1;3;7;14;20).

Seventy-four percent of invited persons participated in screening, and 24% of males and 6% of females had a positive screening result. Of the patients with positive findings, approximately 30% had an AAA larger than 50 mm in diameter, and were thus candidates for surgery. The remaining 70% of persons with positive findings were distributed in size intervals of 20 to 25 mm, 25 to 30 mm, and 30 to 50 mm. Distributions within the intervals were assumed to be uniform, whereas initial allocation between intervals was assumed to follow the empirically verified ratio of 8:1:1 (16).



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In the interval of 20 to 25 mm, 80% of aortas were assumed to be exceptionally large but normal and were not expected to grow over time. The remaining 20% of this interval's aortas and all cases in other intervals were assumed to grow exponentially at a constant annual rate of 5%. AAAs were assumed to have a rupture risk that was an increasing function of the aorta's diameter. We used a quadratic increasing risk function that gave a 5% annual rupture risk at an aortic diameter of 50 mm, an annual risk of 100% at 100 mm, and that had a vertical intercept (zero probability of rupture) at 40 mm.

### Follow-up and Treatment

We used a threshold size of 50 mm for elective surgery, i.e., all aortas for which the largest diameter was 50 mm or more in the first screening or which reached this threshold later on during the follow-up were operated on, unless there was contraindication for the operation. The contraindication rate was assumed to be 20%.

All aortas in the 20- to 30-mm size range were examined annually, and all aortas for which the largest diameter was more than 30 mm were examined at 6-month intervals.

### Possible Causes of Death and Their Timing

Simulation was continued for each person until his or her death, which occurred at a stochastic time $t_1$. There were three possible causes of death in the model. First, death might occur due to some cause other than AAA. In our analysis, screening was assumed to be 100% sensitive and specific. In the light of clinical research this assumption seems to be realistic (3). It also was assumed that a person who had once got a negative screening result would not at a higher age be found to have an AAA. Thus, normal mortality was the only possible cause of death for persons with a negative screening result. Furthermore, even a person with a positive screening result might die of non-AAA causes before his or her AAA reached the threshold size for operation or before it ruptured. Normal mortality was assumed to follow the annual gender- and age-specific hazard probabilities of the general Finnish population (17).

Second, there was a positive operative mortality for both emergency and elective surgery patients (38% and 4%, respectively). Furthermore, a majority of the emergency patients (60%) died before reaching the hospital. These mortality probabilities were used in the model as deterministic parameters. Estimates of operative mortality were based on the analysis of data on all patients with AAA in Finland during the 1987–89 period (512 elective and 182 emergency patients) (16).

Third, persons who survived an elective or an emergency operation had higher annual mortality rates than the general population. We performed a survival analysis for 576 elective (486 males, 90 females) and 277 emergency (239 males, 38 females) patients who survived at least 30 days after the surgery. In the analysis, we included all AAA patients operated on at the HUCH between 1968 and 1992, and we estimated 15-year annual survival rates using the actuarial method (13). For females, we calculated survival rates by pooling men and women together because the small number of women produced unstable results, particularly in the end of the follow-up. As a result, we obtained for each gender, and for elective and emergency patients, a 15-year series of annual relative mortality rates, which were used as annual excess risks of death. After the first 15 years after the operation, the patients

were assumed to have the normal population mortality rates, i.e., no excess risk of death.

### Costs and Discounting

In the model, we considered direct costs of screening, incremental costs of treatment, and incremental postoperative costs during the first 5 years after the operation. Direct costs of screening were deterministic, and they were based on the empirical HUCH screening data (16). Treatment costs were based on a small sample of the HUCH operations (emergency, n = 29; elective, n = 35), and the sample included costs of operation, intensive care, hospital stay, hospital medications, blood products, laboratory and radiography examinations, and equipment overheads. Because the sample was small, we did not want to use empirical cost distributions. Instead we assumed that costs were distributed normally with an empirical mean and variance.

The 5-year postoperative costs (excluding the first admission that was included in the treatment costs) were estimated by calculating costs according to the diagnosis-related groups (DRG) for all AAA surgery patients in Finland during the 1987–89 period (total, n = 596, both genders combined). In this case, the data source was the Finnish National Discharge Register. We again assumed normality of costs with an empirical mean and variance. All costs and life-year gains (losses) were discounted at a rate of 5%.

### Sensitivity Analysis

We performed a one-way sensitivity analysis where we allowed the key uncertain parameters to vary within a feasible range. There is clinical contradiction about the optimal timing of an elective operation for AAA (8). In addition to the baseline assumption of 50 mm, we allowed for threshold sizes of 40 mm and 45 mm.

The real growth rate of AAA is another uncertain feature. In the literature, the growth rate has typically been reported to be linear (4;6), even though data seem to support exponential growth models. In the sensitivity analysis we allowed for two alternative growth intensities, 2% and 10% per annum, which, in the light of clinical studies (4;6), must be seen as extreme minimum and extreme maximum scenarios.

The rupture model is a key uncertain feature of our analysis. Typically, piecewise linear rupture models have been assumed, even though they do not fit the existing data well (5;10). In our sensitivity analysis we kept the assumption of a quadratic rupture probability, but we analyzed two alternative scenarios where we set the maximum size of the AAA (i.e., the size above which the annual rupture probability was 1) to be alternatively 75 mm or 150 mm.

It is complicated to make an assumption of the growing tendency of the small dilatations. There are no studies of the natural history of aortas having diameters in the range of 20 to 25 mm, but it seems obvious that the majority of these small dilatations will never become AAAs (9). Our 20% assumption was in line with the findings of Lucarotti et al. (9), and in the sensitivity analysis we allowed for two other feasible proportions (10% and 30%).

Attendance rate, the probability of a positive finding, the proportion of AAAs 50 mm or larger in diameter, operative mortality rates, and emergency patients' preoperative mortality rates were based on our own empirical data. Baseline values were the respective observed proportions, and alternative values were the lower and upper limits of the 95% confidence intervals (CIs) of the proportions. The

uncertain parameters, their baseline values, and alternative values are presented in Table 1.

## RESULTS

We ran the simulation for 10,000 males and 10,000 females. For males, the expected values for both effectiveness and costs were positive (0.07 life-years gained at an incremental cost in Finnish currency of FIM 3,300 per each screened man), indicating that screening resulted in an expected gain in life-years at a positive cost. The expected values of incremental life-years and costs differed from zero very significantly ($p < .0001$). For women, the results of screening were qualitatively similar, but the expected values were lower (0.02 life-years, FIM 1,100). For females, the expected life-year gain was positive only at the 5% significance level.

For the vast majority of screened persons, quite naturally, screening had no effect on their life expectancy. Only 6% of males and 2% of females either benefited or lost lifetime due to screening. For males the standard deviation of incremental life-years gained was 1.7, and 95% of simulated observations fell within the range of 0.0 to 1.6 years. For females the standard deviation was 1.3 years, and more than 98% of women neither gained nor lost life-years because of screening. Figure 3 presents the distributions of life-years gained or lost due to screening (the y-axis shows the logarithmic frequency).

Persons who had only very minor incremental costs of FIM 0 to FIM 1,000 dominated cost distributions, at the individual level, with 71% of males and 87% of females in this range. These persons were mainly those who had a negative screening result and who correspondingly had only the incremental direct costs of screening, or those persons who refused screening and who did not have an AAA, for whom the incremental costs were zero. The standard deviations of incremental costs were FIM 19,000 and FIM 9,000, and 95% of simulated costs were in the ranges of FIM −14,000 to FIM 65,000 for males and FIM −1,000 to FIM 9,000 for females. Figure 4 presents the distribution of the incremental costs of screening (the y-axis shows the logarithmic frequency).

The C/E ratios and their 95% CIs were FIM 48,000 (27,000–121,000) and FIM 54,000 (22,000–∞) per life-year gained for males and for females, respectively (for calculation of CIs, see Appendix 1). Females' wide CI came from the fact that their expected life-year gain was more uncertain than males', and the lower limit of their 97.5% CI was 0.0.

According to the sensitivity analysis, the model produced stable results. No alternative caused a substantial change in expected costs or effectiveness. Particularly, all parameter alternatives resulted in a positive expected life-year gain at a positive incremental cost (Figure 5). Furthermore, in all tested alternatives both expected life-year gains and incremental costs differed from zero at least at the 5% significance level and in most alternatives at the 1% or 0.1% significance levels. For females the results were qualitatively similar, but the significance was lower than for males.

Altogether, incremental life-years gained for males in the screening group varied in different scenarios from 0.04 to 0.12 life-years per each man, and the incremental costs from FIM 2,500 to FIM 4,100 per each man. The C/E ratios varied in the range of FIM 22,000 to FIM 85,000 per life-year gained.

The results were sensitive to three assumed parameters. The annual growth of aneurysms was a major uncertain parameter. A low annual growth rate reduced

**Table 1.** Sensitivity Analysis

| Uncertain parameter | Baseline value | First alternative value | Second alternative value |
|---|---|---|---|
| Discount rate | 5% | 0%<br>A | 7%<br>B |
| Annual rupture risk | Quadratic: 0% annual risk at 40 mm; 5% at 50 mm; 100% at 100 mm | Quadratic: 0% annual risk at 40 mm; 5% at 50 mm; 100% at 75 mm<br>C | Quadratic: 0% annual risk at 40 mm; 5% at 50 mm; 100% at 150 mm<br>D |
| Attendance rate | 74% | 69%<br>E | 79%<br>F |
| Proportion of positive findings in the first screening | 27% | 18%<br>G | 35%<br>H |
| Proportion of AAAs ⩾ 50 mm in the first screening | 8% | 3%<br>I | 14%<br>J |
| Proportion of contraindications | 20% | 10%<br>K | 30%<br>L |
| Proportion of growing dilatations in range of 20–25 mm | 20% | 10%<br>M | 30%<br>N |
| Annual growth rate | 5% | 2%<br>O | 10%<br>P |
| Threshold for surgery | 50 mm | 40 mm<br>Q | 45 mm<br>R |
| Preoperative rupture mortality | 60% | 54%<br>S | 66%<br>T |
| Emergency patients' operational mortality | 38% | 31%<br>U | 45%<br>V |
| Elective operational mortality | 4% | 3%<br>W | 7%<br>X |
| Total cost of screening | | baseline − 20%<br>Y | baseline + 20%<br>Z |

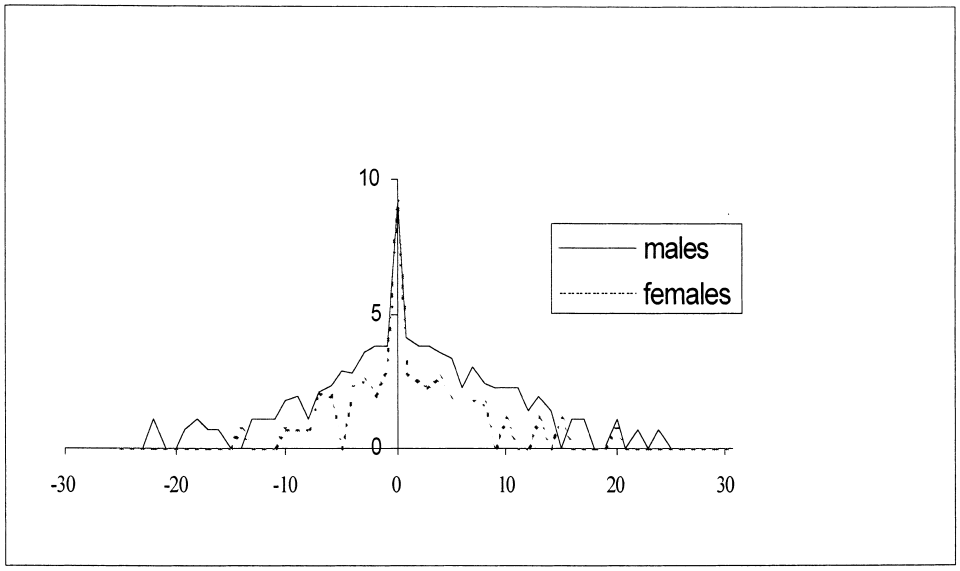


**Figure 3.** Distribution of incremental loss or gain in life-years due to screening for males and females; y-axis shows the logarithmic frequency, and x-axis shows life-year gain or loss.

the incremental effectiveness of screening because normal mortality became a more important cause of death and incremental life-year gains became smaller. Similarly, preoperative rupture mortality was a key uncertain parameter, and smaller parameter estimates rapidly decreased the effectiveness of the screening program. Thirdly,

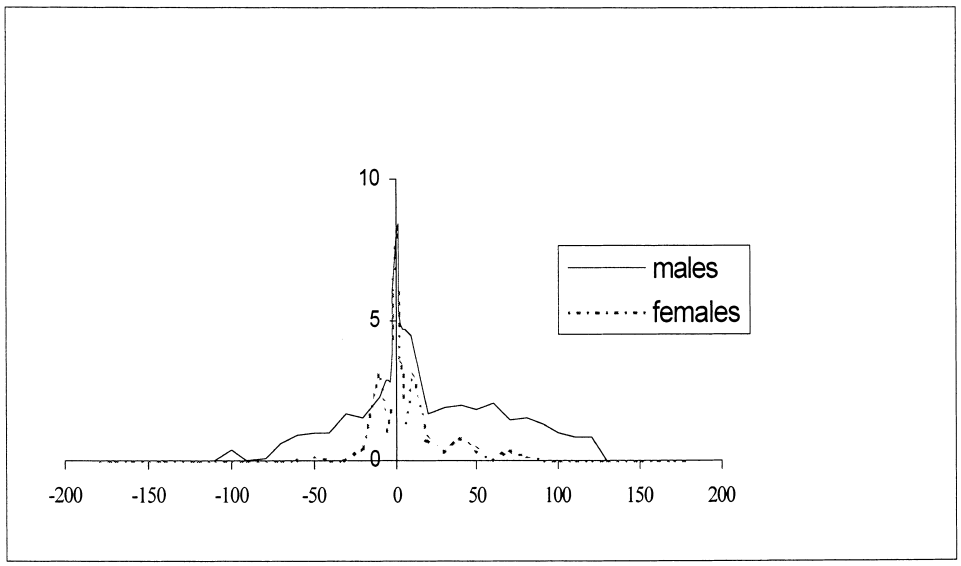


**Figure 4.** Distribution of incremental costs for males and females; y-axis shows the logarithmic frequency, and x-axis shows incremental cost in FIM 1,000.

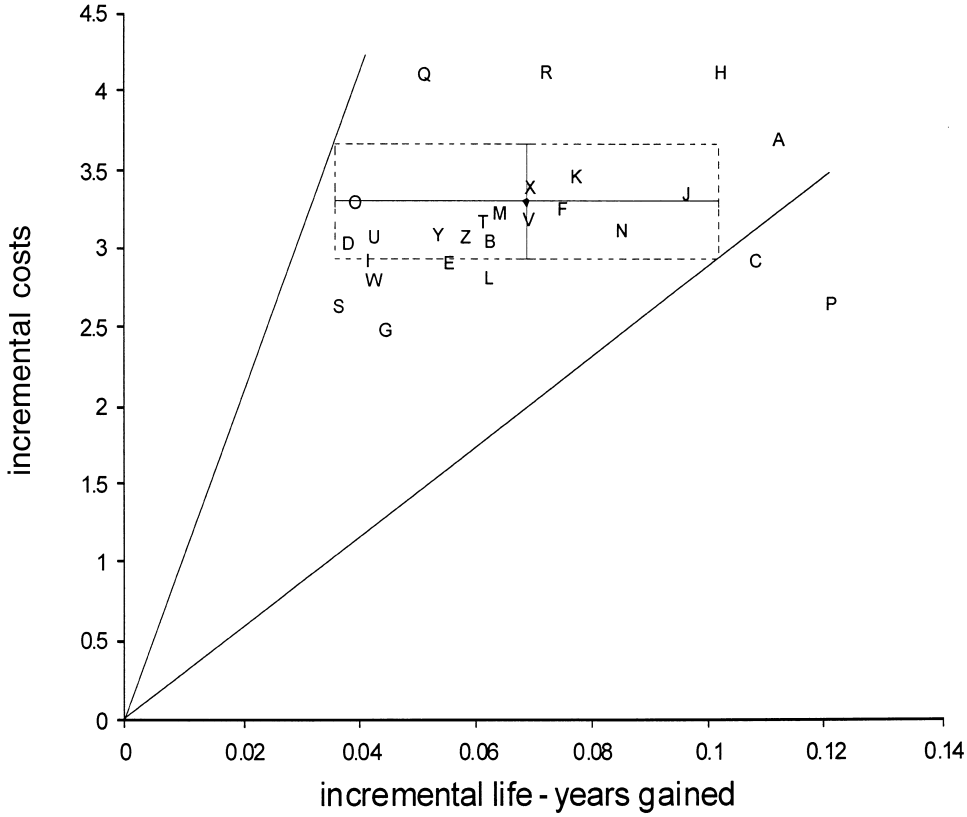


**Figure 5.** Results of the sensitivity analysis. Each letter presents one simulated cost-effectiveness pair. Letters denote corresponding parameter values in Table 1. The baseline cost-effectiveness pair is denoted by a point, and vertical and horizontal lines represent the 95% CI for the baseline costs and effectiveness. The slopes of the two ascending lines are the limits of the 95% CI of the baseline C/E ratio.

the annual rupture risk of AAAs had a large impact on the estimates of life-years gained.

The proportions of positive findings and of large AAAs among the findings had remarkable impacts on results. The discount rate had a large impact on life-year gain estimates, but only a surprisingly small impact on cost estimates. On the other hand, threshold size, emergency patients' operational mortality, attendance rate, the proportion of growing dilatations, the proportion of contraindications, and total costs of screening did not have a large impact on results.

A graphic presentation of the results of the sensitivity analysis appears in Figure 5. Each letter stands for a simulated cost-effectiveness pair as described in Table 1. The black point in the middle and the horizontal and vertical lines that go through the point denote the baseline estimates for costs and effectiveness and their 95% CIs. The two upward sloping lines denote the upper and lower limits of the 95% CI of the C/E ratio of the baseline analysis (for details see Appendix 1). It can be clearly seen that nearly all parameter alternatives produced C/E ratios that did not differ significantly from the baseline estimate.



https://doi.org/10.1017/S0266462300016135 Published online by Cambridge University Press

## DISCUSSION

Our simulation showed that targeted screening of males for AAAs resulted in a positive expected gain in life-years at a moderate positive expected cost. Both costs and effectiveness differed from zero very significantly. The incremental C/E ratio of FIM 48,000 was favorable for screening when comparing targeted AAA screening of males to other existing screening practices, and it was much better than the reported C/E ratios for population-based screening (5;10). As a point estimate, the incremental cost-effectiveness of screening for females was worse than that of screening for males only, but the difference was small, and it was not statistically significant. However, in our model females' life-year gain did not significantly differ from zero. As a corollary, females' C/E ratio had a very wide CI. Furthermore, it should be kept in mind that because of a lack of data many parameters for females were based on speculative assumptions.

The sensitivity analysis showed that the results for males were stable. Screening had favorable expected C/E ratios with all considered parameter values. Particularly, no parameter value resulted in an expected loss in life expectancy. The hypothesis that expected incremental life-year gain or incremental cost would be zero could be rejected at least at the 5% confidence level in all scenarios. Females' sensitivity analysis was not reported, because even the base-case analysis revealed the underlying uncertainty. We concluded that screening of males seemed to result in a significantly positive and stable expected life-year gain at a C/E ratio that usually is considered acceptable. On the other hand, results for females seemed to be too uncertain to let us recommend targeted screening for females.

In the sensitivity analysis, assumptions on growth and rupture rates had a large impact on results. These assumptions could not be properly verified because of a lack of data. Collin et al. (4) and Guirguis and Barber (6) reported growth rates for AAAs, and their results supported our exponential growth model. However, two comments should be made. First, in light of their results, our model might somewhat overestimate the growth rate of small AAAs and underestimate the growth rate of large AAAs. Second, the variability of growth rates seems to be high; for example, Collin et al. (4) reported that some persons had even higher than 40% annual growth rates, and Guirguis and Barber (6) reported substantial annual decreases in aortic diameters in some cases. Clearly, further clinical research is required in this field, particularly concerning the behavior of small ($< 25$ mm) dilatations and large ($> 50$ mm) aneurysms.

Our exponential rupture model is supported by clinical studies. For example, Nevitt et al. (12) and Guirguis and Barber (6) reported rupture probabilities that increased rapidly as functions of aortic diameter. However, we were forced to assume the functional form of the hazard function, because we were not aware of any appropriate data from which an empirical hazard function could have been derived.

The estimate of 60% preoperative rupture mortality and its 95% CI (54% to 66%) were based on our empirical data. Even though the CI was relatively narrow, the results were sensitive to this parameter. A more accurate parameter estimate would be welcome. Results were also sensitive to proportions of positive findings and of large aneurysms in screening.

We assumed that persons who were not detected to have an AAA in the first screening would not develop one at a later age. This simplification was done because we did not know whether these persons would systematically differ from the persons with AAA detected in the first screening round, and because these persons would

be candidates for surgery in any case at a relatively old age (with the current growth model, the first undetected AAAs would reach the 50-mm operation threshold at earliest 19 years after the first screening). However, the incremental cost-effectiveness of rescreening might be a very interesting topic for later studies. Even other dynamic aspects of the model might be improved; for instance, the contraindication probability or operational mortality rates might well be dependent on patients' ages. However, suitable data on these aspects seem to be very limited.

Our study raised one important issue that is hardly discussed in the literature, which is that even though average expected effectiveness was significantly positive, individual variations were high. The distributions of incremental life-years gained or lost had thick tails, and an individual might gain or lose up to 20 years in life expectancy. Risk-averse decision makers should be interested not only in expected values but also in the variances of outcome variables.

In later studies, a further step is to improve cost estimation so that the assumptions of normality of costs can be either empirically justified or replaced by more appropriate distributions. Furthermore, analysis of the distribution of C/E ratios, particularly when they are simulation-based, still remains a topical research area.

## POLICY IMPLICATIONS

We modeled the cost-effectiveness of screening for AAAs among first-degree relatives of patients with AAA. Screening of males for AAAs was cost-effective as far as the expected cost-effectiveness ratio was considered. However, individual variation of the screening's impact on life expectancy was high, which may be a counterargument against screening. Evidence did not justify screening of females.

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## APPENDIX 1

### Calculation of Confidence Intervals for Cost-effectiveness Ratios

Because cost-effectiveness ratios are ratios of random variables, it is complicated to analyze their distributions. Therefore, we used the approach introduced by Wakker and Klaassen (19) to derive 95% CIs for incremental cost-effectiveness ratios. We also calculated lower limits of the CIs using the same method.

It should be kept in mind, as Wakker and Klaassen clearly discussed, that this method gives very conservative results, i.e., wide CIs. This is because the covariance information of costs and effectiveness is not utilized.

We first took the 97.5% CIs for expected life-year gains and for expected costs for males. Because the simulation runs were independent of each other, we could use the central limit theorem to state that both of these distributions were approximately normal. The 97.5% CI of expected life-years gained per each screened man was 0.04 to 0.10. Expected incremental costs had a 97.5% CI of FIM 2,900 to FIM 3,700. For females the corresponding CIs were 0.00 to 0.04 life-years gained and FIM 900 to FIM 1,300.

The lower limit of the 95% CI of the cost-effectiveness ratio was simply calculated by dividing the lower limit of costs by the upper limit of effectiveness, and the upper limit was calculated by dividing the upper limit of costs by the lower limit of effectiveness. Thus, for males and females the 95% CIs of cost-effectiveness ratios were: (FIM 2,900/0.10–3,700/0.04) = (FIM 27,000–121,000), and (FIM 900/0.04–1,800/0.00) = (FIM 22,000–∞) per life-year gained for males and females, respectively.