Expanded Methods

Calibration of UIA formation and rupture risk

We calibrated the probability of UIA formation and rupture risk in our model to ensure that prevalence and incidence figures from the model were similar to those reported in the literature. For this calibration the following data from the literature were used: a prevalence of UIA in the general population of 3.2% (95% confidence interval (CI) 1.9-5.2) and of 4.0% (95% CI 1.9-5.2) for the population with one affected FDR, aSAH incidence of 9/100,000 per year (95% CI 8.8-9.5) in the general population and 20.7/100,000 per year in persons with one affected FDR based on an incidence ratio of 2.3 calculated by dividing the observed incidence rate of aSAH in persons with one affected FDR by the expected incidence for the general population (2.3 * 9/100,000 = 20.7/100,000), a rupture risk for UIA in the general population of 1.4% per year (95% CI 1.1-1.6%) and the odds ratio of aSAH in persons with one affected FDR of 2.15 (95% CI 1.77-2.59).

We considered the 3% lifetime risk of aSAH realistic given the estimated lifetime risk of aSAH of 0.7-1.5% in the general population and an incidence ratio for aSAH in persons with one affected FDR which is approximately two times higher as compared to the general population. We also considered the lifetime risk of approximately 10% of developing an UIA realistic given the UIA prevalence of 4% in a single screening of persons with one affected FDR combined with the knowledge that the prevalence of UIA increases with age and recurrent UIA can be found during repeated screening of persons with familial aSAH.

Utilities

We converted the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) scores to utilities using the method as described by Nichol or used available EuroQol (EQ5D) scores. We assumed that the effect of screening on utility lasted one year and that utility changed each time screening was performed.

Assumptions

We made the following assumptions: the risk of UIA development and growth are constant throughout life and the risk of rupture is constant over time. There is a linear increase in rupture risk with the number of UIAs per individual. When UIAs are treated we considered all UIA present to be treated during one intervention. We assumed treated UIA never to reopen again and the risk of regrowth to be incorporated in the lifetime risk of UIA development. We considered MRA to be performed without any complications, because no contrast enhancement is needed for UIA screening and complications of MRA are mainly attributable to contrast use. There is a small risk of 5% on false positive MRA results, meaning that a limited number of persons without an UIA may be misclassified as having a small UIA (<5mm). These persons will have the usual follow up for small known UIA, but we assumed that after the first follow-up 50% of the false positive results will be correctly converted to negative results, and that after the second follow up all false positives will be classified as negative results. It is likely that there is a
lower chance of false positive MRA with repeated screening as radiologists can compare images and look specifically at sites where abnormalities were previously suspected. Since there is no literature available on these probabilities we estimated the chance to have a false positive MRA at repeated screening (i.e. after the first screening) to be 1-2%. 
Additional figures

Figure I Conceptual representation of the no screening arm of the Markov model

Legend

On the left the different health states (death, disabled, healthy with small aneurysm, healthy with aneurysm, healthy) are displayed. The tree emerging from each health state composes the possible transitions (at each ○) and subsequent health state (Δ). In time steps of one year persons progress through the decision model and can move from one health state to another based on transition probabilities. Costs and utility values are linked to the health states and interventions during each cycle and aggregated until persons reach the death state. Clone 1 refers to different parts of the model which should be copied at that point.
Figure II Incremental cost effectiveness plane showing incremental costs and incremental effects for all screening strategies compared to no screening, and a cost-effectiveness threshold of €20.000 per QALY.
Figure III Probability of cost effectiveness per screening strategy when compared to no screening for three cost-effectiveness threshold values
Figure IV Cost effectiveness acceptability frontier

Legend

For a range of values for the cost-effectiveness threshold (x-axis) it can be estimated a) what the probability is that a specific screening strategy is cost-effective; and b) which screening strategy has the highest expected net health benefit of all strategies considered. The selected best screening strategies based on the net health benefit are shown, along with the probability that each visualized strategy is cost-effective. First, it should be noted that a strategy can be optimal even if it does not have the highest probability of being cost-effective (for example, strategy 30-70-5 is selected for thresholds of €30,000-40,000 per QALY because its expected net health benefit exceeds that of strategy 20-70-5). Second, it should be recognized that the probabilities of being cost-effective of all 24 strategies considered necessarily add up to one. This results in relatively low probabilities of strategies being optimal (for example, a probability of less than 15% for strategy 20-70-5 for thresholds in excess of €45,000 per QALY).
Figure V: The value of collecting additional evidence on one or more model parameters

Legend

Barplot indicating the maximum value of collecting evidence on sets of model parameters (top 4 rows) or on single model parameters (remaining rows), expressed in Euros per person screened. Here the maximum value relates to the hypothetical situation that additional evidence would resolve all uncertainty in the considered parameter(s).
### Table 1 Probabilities and distributions used in our Markov model

<table>
<thead>
<tr>
<th>Event</th>
<th>Probability</th>
<th>Type of distribution</th>
<th>95% CI/range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm development (de novo) (per year) *</td>
<td>0.00165</td>
<td>normal</td>
<td>0.001649-0.001651</td>
<td>‡</td>
</tr>
<tr>
<td>Aneurysm growth (from &lt;5 mm to &gt;5 mm, per year) *</td>
<td>0.033</td>
<td>triangular</td>
<td>0.03 -0.081</td>
<td>14-17</td>
</tr>
<tr>
<td>Risk of aneurysm being small (&lt;5mm) (per event) *</td>
<td>0.583</td>
<td>beta</td>
<td>0.424-0.738</td>
<td>1,3</td>
</tr>
<tr>
<td>Rupture risk for large aneurysms (&gt;5mm) (per year) *</td>
<td>0.014</td>
<td>uniform</td>
<td>0.011-0.016</td>
<td>6</td>
</tr>
<tr>
<td>Rupture risk for small aneurysms (per year)*</td>
<td>0.0075</td>
<td>uniform</td>
<td>0.005-0.010</td>
<td>6,18</td>
</tr>
<tr>
<td>Risk of mortality in nursing home during first year *</td>
<td>0.228</td>
<td>beta</td>
<td>0.149-0.321</td>
<td>19</td>
</tr>
<tr>
<td>Risk of mortality in nursing home after first year (per year)*</td>
<td>0.152</td>
<td>beta</td>
<td>0.033-0.271</td>
<td>19</td>
</tr>
<tr>
<td>Probability leave nursing home/rehabilitation centre in good condition (per year)*</td>
<td>0.261</td>
<td>beta</td>
<td>0.177-0.357</td>
<td>19</td>
</tr>
<tr>
<td>Risk death other causes (per year)*</td>
<td>age dependent</td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Risk death aSAH (per event)</td>
<td>0.261</td>
<td></td>
<td>0.242-0.274</td>
<td>21</td>
</tr>
<tr>
<td>- 20-50 y *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk death aSAH (per event)</td>
<td>0.295</td>
<td></td>
<td>0.279-0.310</td>
<td>21</td>
</tr>
<tr>
<td>- 50-65 y *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk disability aSAH (per event)*</td>
<td>0.471</td>
<td></td>
<td>0.453-0.489</td>
<td>21</td>
</tr>
<tr>
<td>Risk death preventive coiling (per event)†</td>
<td>0.090</td>
<td>beta</td>
<td>0.065-0.097</td>
<td>19,22</td>
</tr>
<tr>
<td>Risk disability preventive coiling (per event)†</td>
<td>0.008</td>
<td>beta</td>
<td>0.0057-0.0105</td>
<td>25-26</td>
</tr>
<tr>
<td>Risk death preventive clipping (per event)†</td>
<td>0.014</td>
<td>beta</td>
<td>0.0063-0.0254</td>
<td>18,26,27</td>
</tr>
<tr>
<td>Risk disability preventive clipping (per event)†</td>
<td>0.012</td>
<td>beta</td>
<td>0.0093-0.0153</td>
<td>18,25,24,28</td>
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<tr>
<td>Risk MRA false positive (only &lt;5mm), 1st scan (per event)†</td>
<td>0.025</td>
<td>beta</td>
<td>0.0029-0.0585</td>
<td>18,25,28</td>
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<tr>
<td>Risk death preventive clipping (per event)†</td>
<td>0.056</td>
<td>beta</td>
<td>0.0231-0.1014</td>
<td>29</td>
</tr>
<tr>
<td>Risk MRA false positive next scans (per event) †</td>
<td>0.015</td>
<td>range</td>
<td>0.01-0.02</td>
<td>§</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Risk MRA false negative (per event) †</td>
<td>0.073</td>
<td>beta</td>
<td>0.0356-0.122</td>
<td>28-31</td>
</tr>
<tr>
<td>SMR after aSAH (per year)*</td>
<td>2.200</td>
<td>normal</td>
<td>2.100-2.300</td>
<td>21</td>
</tr>
<tr>
<td>Probability coiling as treatment for unruptured aneurysm (per event) †</td>
<td>0.384</td>
<td>beta</td>
<td>0.332-0.438</td>
<td>32-34, local data</td>
</tr>
</tbody>
</table>

**Utilities**

<table>
<thead>
<tr>
<th>Utilities</th>
<th>utility</th>
<th>distribution</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utility unscreened population (healthy) *</td>
<td>0.839</td>
<td>normal</td>
<td>0.832-0.847</td>
</tr>
<tr>
<td>Utility screen negatives (reassured persons) †</td>
<td>0.846</td>
<td>triangular</td>
<td>0.839-0.854</td>
</tr>
<tr>
<td>Utility screen positive (anxious persons) †</td>
<td>0.805</td>
<td>triangular</td>
<td>0.798-0.813</td>
</tr>
<tr>
<td>Utility recovered after SAH/rehabilitation *</td>
<td>0.819</td>
<td>triangular</td>
<td>0.812-0.827</td>
</tr>
<tr>
<td>Utility disabled (living in nursing home/rehabilitation centre) *</td>
<td>0.4</td>
<td>triangular</td>
<td>0.393-0.408</td>
</tr>
<tr>
<td>Death *</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Costs**

<table>
<thead>
<tr>
<th>Costs</th>
<th>costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost screening (per event) †</td>
<td>€492</td>
</tr>
<tr>
<td>Cost disabled (in nursing home) (per year)*</td>
<td>€ 92082</td>
</tr>
<tr>
<td>Cost death (per event)*</td>
<td>€ -</td>
</tr>
<tr>
<td>Cost SAH treatment (per event) *</td>
<td>€ 30555</td>
</tr>
<tr>
<td>Cost preventive clipping (per event) †</td>
<td>€ 9744</td>
</tr>
<tr>
<td>Cost preventive coiling (per event) †</td>
<td>€11368</td>
</tr>
</tbody>
</table>

aSAH = aneurysmal subarachnoid haemorrhage; MRA = magnetic resonance angiography; SMR = standardized mortality ratio

**Comments**

* = parameter used in both arms
† = parameter used in screening arm
‡ = described in methods: estimate based on literature
§ = described in methods: assumption based on expert opinion
|| = difference between mentioned utility and the utility of an unscreened population
REFERENCES


