

ANEURYSM OCCLUSION IN ELDERLY PATIENTS WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE: A COST-UTILITY ANALYSIS

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ABSTRACT

Background: Aneurysm occlusion after subarachnoid hemorrhage (SAH) aims to improve outcome by reducing the rebleeding risk. With increasing age overall prognosis decreases and the complications of aneurysm occlusion increase. The balance of risks for aneurysm occlusion in elderly SAH patients in different age categories and clinical conditions is unknown.

Methods: A Markov model was used to evaluate quality-adjusted life years (QALY), additional costs, and incremental cost-effectiveness ratios (ICER) of aneurysm occlusion in 192 patient subgroups, based on age, gender, neurological condition at admission, time since SAH, and aneurysm size and location. Probabilistic sensitivity analyses were performed.

Results: For patients admitted in poor condition ≥ 10 days after SAH, and patients older than 80 year, admitted in poor condition admitted ≥ 4 days after SAH, occlusion implied QALY loss and increased costs. Only for women younger than 79 and men younger than 74 years admitted in good condition within 4 days the ICER of occlusion fell below € 50,000 per QALY. Occlusion was beneficial and cost-saving in women aged 74 years or younger admitted in good condition within 4 days and a small posterior circulation aneurysm.

Conclusions: Aneurysm occlusion is harmful in some subgroups of elderly patients and beneficial in others. It is cost-effective only in specific subgroups that comprise a large part of the patients encountered in clinical practice. Beyond the age of 80 years the balance between risks and benefits is often no longer positive for occlusion, and it should only be considered if the predicted life expectancy leaves margin for benefit.

INTRODUCTION

Almost half the patients with aneurysmal subarachnoid hemorrhage (SAH) die within the first months, whereas 10-20% remain dependent on help for activities of daily life.[1] In patients surviving the initial hours after SAH, rebleeding is an important complication. The risk is particularly high immediately after SAH, and decreases steadily over time after the first 24 hours.[2] Untreated aneurysms have a cumulative risk of rebleeding within the first month after SAH of approximately 40%.[3] If no rebleeding occurs before day 10, the remaining risk within the first month decreases to 25%. At day 15 this risk is 15% and at day 20 only 5%.[3]

Although generally SAH occurs in relatively young patients, currently 15-20% of the patients with SAH are over 70 years old.[4,5] Aneurysm occlusion reduces the risk of poor outcome (death or dependence).[2] However, the evidence is limited to the typical patient population, and may not apply to the elderly. The risk of complications of aneurysm treatment increases with age,[2,6] as does the prevalence of co-morbidity.[7] For unruptured aneurysms the risk of poor outcome from preventive aneurysm occlusion can be higher than 30% for patients older than 70 years, depending on the size and site of the aneurysm.[8] In patients with SAH, the risks associated with aneurysm treatment are likely to be higher. Moreover as life expectancy decreases, aneurysm occlusion to prevent recurrent SAH in the long term loses relevance. Thus, occlusion in elderly patients probably has worse cost-effectiveness compared to younger patients, and may even decrease the risk of good outcome, for example in patients in a poor clinical condition, especially if already several days have elapsed after the SAH. The (cost-) effectiveness does not depend on patient age only, but also on gender, clinical condition on admission, time since onset, type of treatment, and aneurysm site and size. We used Markov model Monte Carlo simulation to assess health effects and costs of aneurysm occlusion in elderly patients with SAH according to age, clinical condition, days since onset, and site and size of the aneurysm.[9,10]

METHODS

Model structure

A Markov model was developed to reflect patients over 70 years of age admitted to the hospital with SAH, using data from the literature. Supportive medical treatment only was compared with aneurysm occlusion (i.e. coiling as preferred treatment and clipping if coiling is not feasible). Figure 1 depicts the occlusion strategy. Outcomes were assessed for 5 year age categories (70-74, 75-79, 80-84, 85+), gender, neurological condition at admission (poor-grade or good-grade), day of treatment since onset (<4, 4-10, 11-21), aneurysm size (<10 or ≥ 10 mm) and aneurysm location (anterior or posterior). Ultimately, outcomes in terms of costs (Euros, € 1 = \$1.20 as of November 2008) and effects (quality-adjusted life-years (QALYs)) were estimated for 192 subgroups.

The model used time cycles of one month and a lifetime horizon. Two entry health states were defined through which patients enter the model: good or poor clinical condition at admission. Three outcome health states were distinguished for the conservative treatment strategy: good or poor clinical condition, and dead. The aneurysm occlusion strategy comprised five outcome health states: good or poor clinical condition after coiling, good or poor clinical condition after clipping, and dead. Separate health states for coiled and clipped patients were required, as these treatments imply different risks of recurrent SAH. Poor clinical condition on admission was defined as Hunt and Hess Scale IV-V, World Federation of Neurological Surgeons Scale grade IV-V, or Hunt and Kosnik Scale grade IV-V. Poor outcome was defined as modified Rankin Scale grade 4-5, or Glasgow Outcome Scale grade 2-3. In all outcome health states, except dead, a distinction was made between the first month after the SAH, the second to eighteenth month after the SAH, and subsequent months. In the first month a patient is at high risk of rebleeding and may be treated with aneurysm occlusion or not. Patients may be admitted early after onset of SAH, but also later due to patient or doctor delay. Since treatment effects decrease with time lapsed, and the risk of treatment varies over time, different time frames were considered. Patients eligible for treatment <4 days were assumed to be treated the day after admission. Patients eligible for treatment between days 4-10 were assumed to be treated on day 10, whereas patients eligible ≥ 10 days after SAH were assumed to be treated the day after treatment became viable.

Rebleeding may be fatal, or cause neurological deterioration (i.e. patients may move from good to poor health states). We assumed conservatively managed patients may rebleed during the entire first month, whereas patients with occluded aneurysms can rebleed only up to occlusion. After the first month treatment is assumed to have ended.

In the second to eighteenth month after SAH, patients may die from unrelated causes, experience recurrent SAH, or recover (i.e. they may move from poor to good health states). Patients in poor health states were assumed to have a high age-dependent risk of dying from unrelated causes. Patients in good health states were assumed to be healthy but still experiencing excess mortality compared with the general population.[11] After eighteen months patients may still die from unrelated causes, or have recurrent SAH. Recovery from the initial SAH, however, was no longer considered possible.

Model parameters

Table 1 shows the model parameters. The utilities in Table 1 were derived from the literature, and are allocated to the similarly named health states depicted in Figure 1. The costs of aneurysm coiling and clipping from Table 1 are event costs associated with treatment options at the start of subtree (D) in Figure 1. Note that the cost of medical management is incurred for both healthy and disabled patients in the conservative treatment strategy, which is not shown in Figure 1. Moreover, regardless of treatment strategy the annual costs of a nursing home are accounted for in patients remaining in a disabled state. The cost associated with death is incurred once for each patient at the time of death. For both treatment strategies, recurrent SAH may occur from 18 months onwards after the initial episode of SAH, in both healthy and disabled patients. A cost equal to the cost of conservative treatment is assumed. Transition probabilities and relative effects dependent on subgroup characteristics are shown in Table 2. Briefly, beta distributions were used for binomial data and Dirichlet distributions for multinomial data whenever possible, i.e. when event counts and non-event counts were available. In case actual (count) data were not available uniform distributions were used, with ranges based on expert opinion. Finally, triangular distributions were used for recalculated estimates from systematic review studies, and in case the range of uncertainty was not completely contained in the interval [0, 1].

Only actual medical costs were taken into account. Age and gender-specific mortality risks were used to model survival unrelated to SAH.

TABLE 1.

Model parameter	Value*	Range	Distribution	Source
Probabilities				
P(recovery to good state in month 1-18 after SAH)	0.281	0.121-0.494	Beta	[12]
P(recurrent SAH per year) after coiling, year 1	0.026	0.017-0.038	Beta	[13]
P(recurrent SAH per year) after coiling, year 2+	0.002	0.001-0.005	Beta	[13]
P(recurrent SAH per year) after clipping, year 1	0.010	0.005-0.018	Beta	[13]
P(recurrent SAH per year) after clipping, year 2+	0.0006	0.00008-0.0024	Beta	[13]
P(recurrent SAH per year) after cons. tr., year 1	0.113	0.09-0.139	Beta	[14]
P(recurrent SAH per year) after cons.tr., year 2+	0.142	0.106-0.185	Beta	[14]
P(poor outcome) due to coiling complications	0.033	0.009-0.083	Beta	[15], [16],†
P(death) due to coiling complications	0.025	0.005-0.071	Beta	[15],[16],‡
Costs in Euros				
Coiling ruptured aneurysm	26,785	25,259-28,388	Log-normal	[17],‡,#
Clipping ruptured aneurysm	29,313	27,247-31,522	Log-normal	[17], ‡,#
Conservative treatment	17,080	-	-	[18],‡,\$
Cost recurrent SAH (conservative treatment)	17,080	-	-	[18],‡,%
Cost nursing home for poor patients (per year)	77,490	-	-	[19],‡
Cost of patient death – not directly related to aneurysm treatment	2,579	-	-	[20],‡
Utilities				
Death	0	-	-	-
Disabled (poor clinical state, in nursing home)	0.44	0.11-0.71	Triangular	[21],\$
Healthy (good clinical state)	0.87	0.77-0.95	Beta	[22]
Discounting				
Cost discount per year	4%	-	-	-
Benefits (effects) discount per year	4%	-	-	-

* Values are recalculated from the referenced studies. P (X) denotes the probability of the event X occurring.

† Data from these two studies were combined in order to get a more robust estimate. The probability of the outcomes poor and death for conservative treatment were set to the respective probabilities of these outcomes for coiling with the risk of perioperative complications resulting in poor outcome or death subtracted.

‡ Costs are updated to 2005 with Dutch inflation indices, and converted to Euros (€1 = \$1.27; December 2007)

Cost of treatment is assumed to include costs due to possible rebleeding before or during the treatment.

\$ Costs were obtained by summing up the medical and hospital stay components of the cost of aneurysm coiling.

% Recurrent SAH is assumed to be treated conservatively (due to the expected age and condition at recurrence).

\$ Estimates of the utility of patients after major stroke vary widely,[23] thus a large range was used.

TABLE 2.

Model parameters dependent on subgroup characteristics	Value*	Range	Distri- bution	Age	Gender	Day adm.	Clinical state	Aneurysm size	Aneurysm location	Source
<i>Probabilities</i>										
P(aneurysm coiling is possible)	0.729	0.609-0.828	Beta						Anterior	[24]
	0.950	0.751-0.999	Beta						Posterior	[24]
P(death in nursing home per year),	0.222	0.200-0.244	Uniform	70-74	Female					[25],†
	0.265	0.238-0.291	Uniform	75-79						[25],†
	0.315	0.284-0.347	Uniform	80-84						[25],†
	0.447	0.403-0.492	Uniform	85+						[25],†
P(death in nursing home per year),	0.264	0.237-0.290	Uniform	70-74	Male					[25],†
	0.314	0.283-0.346	Uniform	75-79						[25],†
	0.374	0.337-0.412	Uniform	80-84						[25],†
	0.531	0.478-0.584	Uniform	85+						[25],†
P(death after rebleeding before treatment)	0.558	0.407-0.754	Dirichlet ¹				Good			[26]
	0.882	0.726-0.967	Dirichlet ²				Poor			[26]
P(poor outcome after rebleeding before trm.)	0.294	0.151-0.475	Dirichlet ¹				Good			[26]
	0.133	0.039-0.307	Dirichlet ²				Poor			[26]
P(good outcome after rebleeding before treatment)	0.118	0.033-0.275	Dirichlet ¹				Good			[26]
	0	-	-				Poor			‡
P(favourable outcome) after aneurysm clipping)%	0.639	0.585-0.691	Beta	70-79			Good			[5]
	0.235	0.162-0.322	Beta	70-79			Poor			[5]
	0.606	0.483-0.720	Beta	80+			Good			[5]
	0.111	0.014-0.347	Beta	80+			Poor			[5]
P(unfavourable outcome after clipping is poor clinical condition and not death)	0.389	0.173-0.643	Beta				Good			[27]
	0.107	0.023-0.282	Beta				Poor			[27]

TABLE 2. CONTINUED

Model parameters dependent on subgroup characteristics	Value*	Range	Distribution	Age	Gender	Day adm.	Clinical state	Aneurysm size	Aneurysm location	Source.
<i>Probabilities</i>										
P(death) after coiling	0.043	0.022-0.074	Dirichlet ³				Good			[28]
	0.121	0.034-0.282	Dirichlet ⁴				Poor			[28]
P(poor outcome) after coiling	0.104	0.071-0.145	Dirichlet ³				Good			[28]
	0.394	0.229-0.579	Dirichlet ⁴				Poor			[28]
P(rebleeding before treatment)	0.089	0.058-0.129	Beta			< 4		< 10 mm		[29]
	0.192	0.109-0.301	Beta			< 4		≥ 10 mm		[29]
	0.24	0.192-0.288	Uniform			4-10				[3],&
	0.41	0.328-0.492	Uniform			> 10				[3],&
<i>Relative effects on model parameters</i>										
Standardized mortality ratio death other causes	1.565	1.422-1.751	Beta	70-79						#
	1.282	1.186-1.418	Beta	80+						#
RR of good outcome after aneurysm occlusion	1	-	-					< 10 mm		[30],§
	0.592	0.200-1.389	Triangular					≥ 10 mm		[30],§
Relative effect on cost of treatment, based on length-of-stay hospital data	0.85	0.70-1.00	Uniform				Good			[31]
	1.15	1.00-1.30	Uniform				Poor			[31]

* Values are recalculated from the referenced studies. P (X) denotes the probability of the event X occurring.

† We assumed a 10% uncertainty in the estimates, standard analyses resulted in just 1% uncertainty as 43,510 patients were assessed in the reference study (with 10% age categories overlap slightly).

‡ Probability is zero by definition: A rebleeding may cause a degradation of health condition (e.g. from good condition to poor condition), but never an improvement.

Unpublished data obtained from Swedish registries [32]. This is the standardized mortality ratio (SMR) for patients in good clinical condition after treatment, compared with the general population.

§ The relative effect calculated from the referenced study, containing patients in poor clinical condition, was also applied to patients in good clinical condition.

% Here favourable outcome is defined as 'good clinical condition', unfavourable is defined as 'poor clinical condition' or 'dead'.

& The uncertainty in these estimates was not given or estimable directly. Therefore, a 20% degree of uncertainty was assumed and a uniform distribution was used.

Dirichlet¹ Parameters denoted by d(i) follow a combined Dirichlet distribution, i.e. the uncertainty in the combined parameter set is evaluated simultaneously.

Model assumptions

The complication rate of clipping was assumed to depend on patient age.[5] However, this was not assumed for the less invasive coiling procedure. The likelihood of recovery from the initial SAH was assumed to be equal for the treatment modalities. Patients with recurrent SAH were assumed to always be treated conservatively due to advanced age and presumed very poor condition after subsequent SAH. As the model focused on elderly patients eligible for occlusion, it was assumed that in the occlusion strategy all patients would be coiled or clipped. The model did not account for costs of follow-up after occlusion. It was assumed that follow up angiograms would not be performed in elderly patients. Severe complications (rebleeding, treatment complications or recurrent SAH) occurring in patients in poor health states were presumed to be fatal. Likewise, patients in good health states experiencing complications were assumed to (temporarily) move to poor health states. The utility of patients in poor health states was set equal to the health-related quality of life of survivors of a major stroke. Furthermore, these patients were assumed to move to nursing homes after hospital discharge.

Model simulation

The Markov model was constructed using TreeAge (2009, TreeAge Software, Williamstown, MA). For each subgroup a Monte Carlo simulation was performed comprising 1,000 hypothetical cohorts of 10,000 elderly patients. The clinical course of the patients over time was evaluated.

Model outcomes

For each subgroup the expected number of patients with one or more recurrent haemorrhages, expected costs and quality-adjusted life expectancy (QALE) were calculated. Also, the management outcome of patients at discharge, one month after SAH, was determined (i.e. the health state occupied by patients). The expected incremental costs and health benefits, and incremental cost-effectiveness ratios (ICER) for occlusion were calculated for each subgroup. In addition, cost-effectiveness acceptability curves (CEAC) were constructed.[33] Our base group consisted of 70-74 year old women admitted in good clinical condition <4 days after SAH, with an anterior aneurysm <10mm. This group represents the largest

proportion of elderly with SAH, and may expect the highest benefit from occlusion. Probabilistic sensitivity analyses were performed.[34,35] Also, the effects of a 1.5% discount rate instead of 4%, and a doubled mortality risk were assessed.

RESULTS

Table 3 shows the expected outcomes per strategy. The number of patients with good outcome at one month increased rapidly with time since onset for the conservative treatment strategy, but not for the occlusion strategy. The QALEs in Table 3 reflect the balance between the (remaining) risk of rebleeding, the risk of treatment complications, and the risk of recurrent SAH, i.e., summarize the overall health benefits.

Figure 2 shows a nomogram with the absolute change in QALE for the occlusion strategy. Occlusion did not provide health benefits in patients admitted in poor condition ≥ 10 days after SAH. It provided minimal or no health benefits in patients older than 80 years admitted in poor condition ≥ 4 days after SAH. For most other subgroups of elderly, occlusion resulted in health benefits.

In Figure 3 the uncertainty with respect to the incremental costs and effects of aneurysm occlusion compared with conservative treatment is shown. This is the uncertainty in model outcomes that is due to parameter uncertainty caused by sampling values for the model parameters for which distributions were defined in Tables 1 and 2. Figure 3 indicates that there is relatively little uncertainty with respect to the difference in health effects: the incremental health effect is positive for all subgroups of men and women shown, except for men or women admitted in poor condition > 10 days after SAH where it is clearly negative. Furthermore, for all subgroups of men the incremental costs are highly likely to be positive. For women incremental costs are likely to be positive for women admitted in poor condition < 4 days after SAH and women admitted in good condition > 10 days after SAH. Incremental costs for women admitted in good condition < 4 days after SAH may be positive or negative, as well as the incremental costs for women admitted in poor condition > 10 days after SAH.

Figure 4 shows the estimated health gains and additional costs of occlusion, for selected subgroups. It is apparent that incremental costs are larger for patients admitted in poor condition than for patients admitted

in good condition. Incremental costs are similar for men and women, whereas incremental effects are higher for women and in patients admitted <4 days.

Applying a willingness-to-pay threshold of € 50,000/QALY the probability that aneurysm occlusion is cost-effective varied from 0% to 90%. Thus, occlusion is likely to be cost-effective only in some subgroups of elderly. The estimated ICER of occlusion fell below € 50,000/QALY only for women aged 70-79 year, and men aged 70-74 years admitted in good condition <4 days.

In all subgroups except in women aged 70-74 years, admitted in good condition <4 days after onset, with a small posterior aneurysm, occlusion was more costly than conservative treatment. In this subgroup occlusion saved € 1,409 and resulted in 0.36 QALY gain, i.e. the occlusion strategy dominated the conservative strategy.

Figure 5 presents cost-effectiveness acceptability curves for subgroups in which occlusion may be cost-effective. For all other subgroups it appeared unlikely that occlusion will ever become cost-effective.

Cost-effectiveness of occlusion was slightly worse in patients with large aneurysms than in patients with small aneurysms, and slightly better when the aneurysm is located in the posterior circulation compared with the anterior circulation (not shown).

In our base group the preferred treatment would be aneurysm occlusion, resulting in 0.29 QALY gain, at an additional cost of € 72 (ICER € 247/QALY). Probabilistic sensitivity analysis in this subgroup demonstrated results were sensitive to the parameter relating treatment costs to clinical condition of the patient, for both strategies. Also, results for conservative treatment were sensitive to the probability of poor or good outcome after rebleed and to risk of recurrent SAH after conservative treatment. Results for occlusion were sensitive to the probability of poor or good outcome after coiling.

With a 1.5% discount rate for costs and effects instead of 4% the ICER of occlusion in the base group improved from € 247 to € 118/QALY. Doubling the mortality rate due other causes, e.g. due to additional cardiovascular events, resulted in a worse ICER (€ 26054/QALY).

TABLE 3.

Gender	Age cat.	Clinical cond.	Day of adm.	Poor outcome at 1 month		Good outcome at 1 month		Patients with recurrent SAH		Quality-adjusted life expectancy					
				Conservative	Occlusion	Conservative	Occlusion	Conservative	Occlusion	Conservative	Occlusion				
Men															
70-74 years	Poor	< 4	2,877 (1,910-3,970)	3,039 (1,697-4,610)	3,266 (2,093-4,413)	4,108 (2,663-5,833)	474 (343-610)	117 (63-187)	0.46 (0.33-0.58)	0.56 (0.45-0.70)					
		4-10	3,240 (2,063-4,503)	2,994 (1,687-4,540)	3,833 (2,757-5,027)	3,939 (2,520-5,670)	538 (357-720)	115 (57-190)	0.52 (0.41-0.65)	0.54 (0.43-0.66)					
		> 10	3,547 (1,980-5,023)	3,019 (1,510-4,573)	4,607 (3,343-6,317)	4,147 (2,673-5,887)	640 (473-823)	118 (73-180)	0.60 (0.47-0.75)	0.56 (0.44-0.68)					
	Good	< 4	1,694 (1,157-2,287)	1,152 (660-1,807)	5,984 (5,083-6,930)	7,819 (6,370-9,283)	594 (433-770)	135 (83-197)	0.67 (0.56-0.78)	0.83 (0.74-0.93)					
		4-10	1,468 (1,017-2,033)	1,120 (637-1,723)	6,901 (5,967-7,650)	7,630 (6,027-9,283)	639 (493-800)	130 (80-197)	0.74 (0.63-0.84)	0.82 (0.73-0.90)					
		> 10	1,178 (827-1,580)	1,146 (680-1,723)	7,895 (7,297-8,357)	7,840 (6,370-9,313)	693 (540-863)	132 (80-207)	0.81 (0.73-0.90)	0.83 (0.75-0.93)					
	80-84 years	< 4	2,954 (2,053-3,920)	3,108 (1,843-4,513)	3,255 (2,270-4,657)	3,736 (2,270-5,720)	319 (210-423)	73 (33-120)	0.23 (0.16-0.30)	0.26 (0.19-0.33)					
		4-10	3,212 (2,157-4,537)	2,977 (1,643-4,720)	3,848 (2,463-5,280)	3,661 (2,197-5,323)	356 (240-470)	73 (37-113)	0.27 (0.18-0.34)	0.26 (0.18-0.33)					
		> 10	3,634 (2,290-5,093)	3,135 (1,853-4,763)	4,545 (3,033-5,833)	3,776 (2,433-5,297)	408 (290-577)	78 (40-123)	0.30 (0.22-0.38)	0.27 (0.20-0.34)					
	< 4	1,690 (1,197-2,437)	1,156 (670-1,887)	6,022 (5,123-6,893)	7,727 (6,083-9,453)	388 (287-520)	91 (50-133)	0.36 (0.32-0.42)	0.43 (0.39-0.47)						
	4-10	1,432 (980-1,893)	1,162 (670-1,783)	6,957 (6,227-7,753)	7,561 (6,180-9,113)	424 (307-530)	89 (50-140)	0.39 (0.35-0.44)	0.42 (0.38-0.46)						
	> 10	1,157 (783-1,583)	1,137 (647-1,843)	7,921 (7,353-8,440)	7,801 (6,120-9,523)	462 (350-587)	91 (47-137)	0.43 (0.39-0.47)	0.43 (0.39-0.47)						
Women															
70-74 years	Poor	< 4	2,907 (1,823-4,010)	3,097 (1,623-4,753)	3,236 (1,953-4,433)	4,059 (2,463-5,740)	608 (440-797)	149 (97-210)	0.82 (0.60-1.00)	1.02 (0.76-1.23)					
		4-10	3,246 (2,053-4,590)	2,982 (1,677-4,650)	3,804 (2,480-5,537)	3,921 (2,393-5,607)	696 (513-890)	140 (87-203)	0.96 (0.72-1.21)	1.00 (0.77-1.19)					
		> 10	3,568 (2,267-4,950)	3,033 (1,747-4,493)	4,526 (3,237-5,873)	4,091 (2,633-5,750)	799 (607-970)	147 (87-220)	1.11 (0.85-1.36)	1.04 (0.80-1.26)					
	Good	< 4	1,692 (1,173-2,423)	1,132 (610-1,750)	6,003 (5,083-6,860)	7,815 (6,073-9,623)	763 (590-993)	174 (113-240)	1.18 (1.00-1.38)	1.49 (1.33-1.64)					
		4-10	1,451 (1,057-2,047)	1,130 (663-1,717)	6,898 (5,987-7,617)	7,622 (6,127-9,223)	830 (633-1,043)	170 (107-250)	1.30 (1.13-1.49)	1.46 (1.33-1.61)					
		> 10	1,168 (843-1,620)	1,122 (637-1,707)	7,922 (7,433-8,437)	7,884 (6,297-9,453)	897 (717-1,080)	175 (117-247)	1.45 (1.28-1.60)	1.51 (1.36-1.65)					
	80-84 years	< 4	2,924 (1,893-4,230)	3,124 (1,847-4,763)	3,263 (2,187-4,447)	3,747 (2,437-5,443)	417 (273-567)	101 (53-167)	0.36 (0.26-0.46)	0.41 (0.30-0.52)					
		4-10	3,146 (1,773-4,477)	2,899 (1,590-4,520)	3,919 (2,453-5,397)	3,657 (2,073-5,457)	484 (337-653)	98 (50-157)	0.41 (0.30-0.51)	0.40 (0.30-0.49)					
		> 10	3,691 (2,390-5,137)	3,173 (1,810-4,747)	4,478 (2,870-6,223)	3,739 (2,113-5,580)	556 (380-733)	99 (57-153)	0.46 (0.34-0.58)	0.41 (0.30-0.52)					
	< 4	1,678 (1,130-2,407)	1,169 (697-1,800)	6,011 (5,060-6,860)	7,717 (6,183-9,340)	523 (390-680)	120 (63-187)	0.53 (0.47-0.59)	0.64 (0.59-0.70)						
	4-10	1,445 (970-2,033)	1,180 (670-1,870)	6,920 (6,147-7,667)	7,502 (5,983-9,063)	566 (443-703)	118 (67-180)	0.58 (0.52-0.65)	0.63 (0.56-0.69)						
	> 10	1,170 (833-1,473)	1,158 (663-1,730)	7,928 (7,430-8,417)	7,754 (6,087-9,400)	618 (493-787)	119 (70-177)	0.64 (0.58-0.70)	0.65 (0.59-0.71)						

DISCUSSION

Occlusion of ruptured intracranial aneurysms instead of conservative treatment improves outcome only in some subgroups of elderly patients. Moreover, even if the outcome is (slightly) improved the costs may be prohibitive. Therefore, no single optimal strategy for all elderly patients with SAH exists. In patients admitted in poor condition and >10 days after SAH occlusion will even decrease the QALE. From our nomogram it is apparent that the health benefits provided by occlusion decrease with patient age and with time elapsed after SAH onset (Figure 2). In addition, these health benefits are lower for men than for women, are lower for small compared to large aneurysms, and are lower for aneurysms in the posterior rather than the anterior circulation. The particular nomogram format chosen facilitates rapid inspection in clinical practice of the estimated health benefits of occlusion, given the specific characteristics of an individual patient and the ruptured aneurysm. In subgroups of patients in which occlusion results in health benefits, the cost-effectiveness varied considerably and depended foremost on the clinical condition of the patient and time elapsed since onset of SAH. In addition, cost-effectiveness decreased with increasing age and was worse for men than for women. Occlusion was cost-effective in women aged 70-79 years, and men aged 70-74 years, admitted in good condition <4 days after SAH. Although the limited data available in the literature on elderly patients with SAH resulted in uncertainty surrounding estimates of cost-effectiveness, this uncertainty has little impact on our conclusions. The ICER of occlusion was less than € 50,000/QALY for only 7 of the 192 subgroups of elderly. However, these subgroups consist of the youngest elderly, admitted to the hospital early, and therefore contain the most patients.

Our study provides new insight for indications where as yet no randomized controlled trial has been conducted, and very likely never will be. For many elderly conservative treatment appears to be the preferred option. Our model-based findings are in fact quite similar to evidence obtained in an actual RCT in patients with abdominal aorta aneurysms (AAA).[36]

Our study has certain limitations. Firstly, we could not include in the model all patient and aneurysm characteristics (risk factors) that may affect the risk of rebleeding, treatment outcome, and the risk of recurrent SAH. Accurate estimates of the effect of characteristics such as smoking, hypertension and aneurysm shape, are not available from the literature. Therefore, our model provides estimates for ‘average’ values of these characteristics.

Secondly, co-morbidities and disease histories were not explicitly accounted for. Elderly patients may already have a reduced life expectancy (e.g. due to a cardiovascular event preceding the SAH). In the model patients surviving SAH in good condition experience only excess mortality due to SAH. Thus, the predicted health benefits of occlusion are probably overestimated.

Thirdly, we did not include uncertainty regarding the cost estimates used in our model, due to lack of detailed data on these costs. Consequently, the already considerable uncertainty in our model results still is an underestimation of the total uncertainty.

Finally, the assumptions underlying our analysis may have influenced our results. Most notably, the assumption that no angio or MRA follow-up would be performed after coiling will result in overly optimistic cost-effectiveness estimates for the occlusion strategy when in actual practice follow-up would be performed. Similarly, the assumption that recurrent SAH in patients in poor health states will be fatal, and in patients in good health states will cause them to (temporarily) move to poor health states, may also lead to overly optimistic cost-effectiveness estimates for the occlusion strategy when in fact the consequences of recurrent SAH might be less severe, e.g. due to improved medical care.

A low risk of perioperative complication of occlusion was used, and a high risk of recurrent SAH following the index SAH (Table 1). Actual perioperative complication risks in elderly patients may be higher (e.g. the mortality risk from coiling may be 5%)[37] and the risk of recurrent SAH may be lower (e.g. 3.5% per year)[38]. Consequently, health benefits may again be overestimated.

With an ageing population the number of elderly patients with SAH increases. How to provide optimal treatment to these patients is a multi-faceted problem. Studies concluding that age alone should not preclude aneurysm treatment often performed coiling or clipping in all (treatable) elderly patients with

SAH.[4,5] However, the favourable outcomes found in some patients with occluded aneurysms were never compared directly with outcomes of patients in a condition suitable for occlusion but offered conservative treatment. Since a very poor clinical condition of patients is a major reason for not performing aneurysm treatment, the fatality and morbidity rates reported for these patients are high indeed. This may simply be explained by the poor prognosis from the outset, and not from withholding aneurysm treatment.

From our direct (model-based) comparison of no aneurysm treatment and occlusion we conclude that occlusion is harmful in some subgroups of patients and beneficial in others. It is cost-effective only in specific subgroups that comprise a large part of the patients encountered in clinical practice. Beyond the age of 80 years the balance between risks and benefits is often no longer positive for occlusion, and it should only be viewed as option in patients with a prolonged life expectancy. A final important finding is that if aneurysm occlusion is considered, it should be done as soon as possible, because postponing will render occlusion ineffective and inefficient.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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Table legends

Table 1. Value, range, and distribution for model parameters independent of the subgroup under consideration.

Table 2. Value, range, and distribution for model parameters that depend on the subgroup under consideration.

Table 3. The expected number of patients (95% CI) surviving the first month after treatment, in poor condition and good condition, in a hypothetical cohort of 10,000 women with SAH from an anterior aneurysm <10mm. Also, the expected number of patients with recurrent SAH and the estimated QALE per patient are shown.

Figure legends

Figure 1. Illustration of the aneurysm occlusion strategy part of the Markov model. Copies of the subtrees (A)-(D) are used at several locations in the model.

Figure 2. Nomogram of the expected effect of aneurysm occlusion, in months of changes to the quality-adjusted life expectancy of patients.

Figure 3. The cost-effectiveness plane showing the uncertainty in incremental costs and effects of aneurysm occlusion for selected subgroups of elderly men [A] and women [B]. All subgroups concern 70-74 years old patients with ruptured aneurysms <10mm of the anterior circulation.

Figure 4. The cost-effectiveness of aneurysm occlusion for selected subgroups of elderly men [A] and women [B]. Subgroups differ with respect to age category, day of admission, and clinical status at admission. All subgroups concern patients with ruptured aneurysms <10mm of the anterior circulation. Lines connect the age categories 70-74, 75-79, 80-84, and 85+ years. In general, the health gain due to occlusion decreases with age, therefore age increases along the lines, from the *right* to the *left*.

Figure 5. Cost-effectiveness acceptability curves for all subgroups of elderly men [A], and women [B], in which the probability that occlusion was cost-effective, compared with conservative treatment, exceeded 20% for a willingness-to-pay of € 100,000/QALY.

Figure 1.

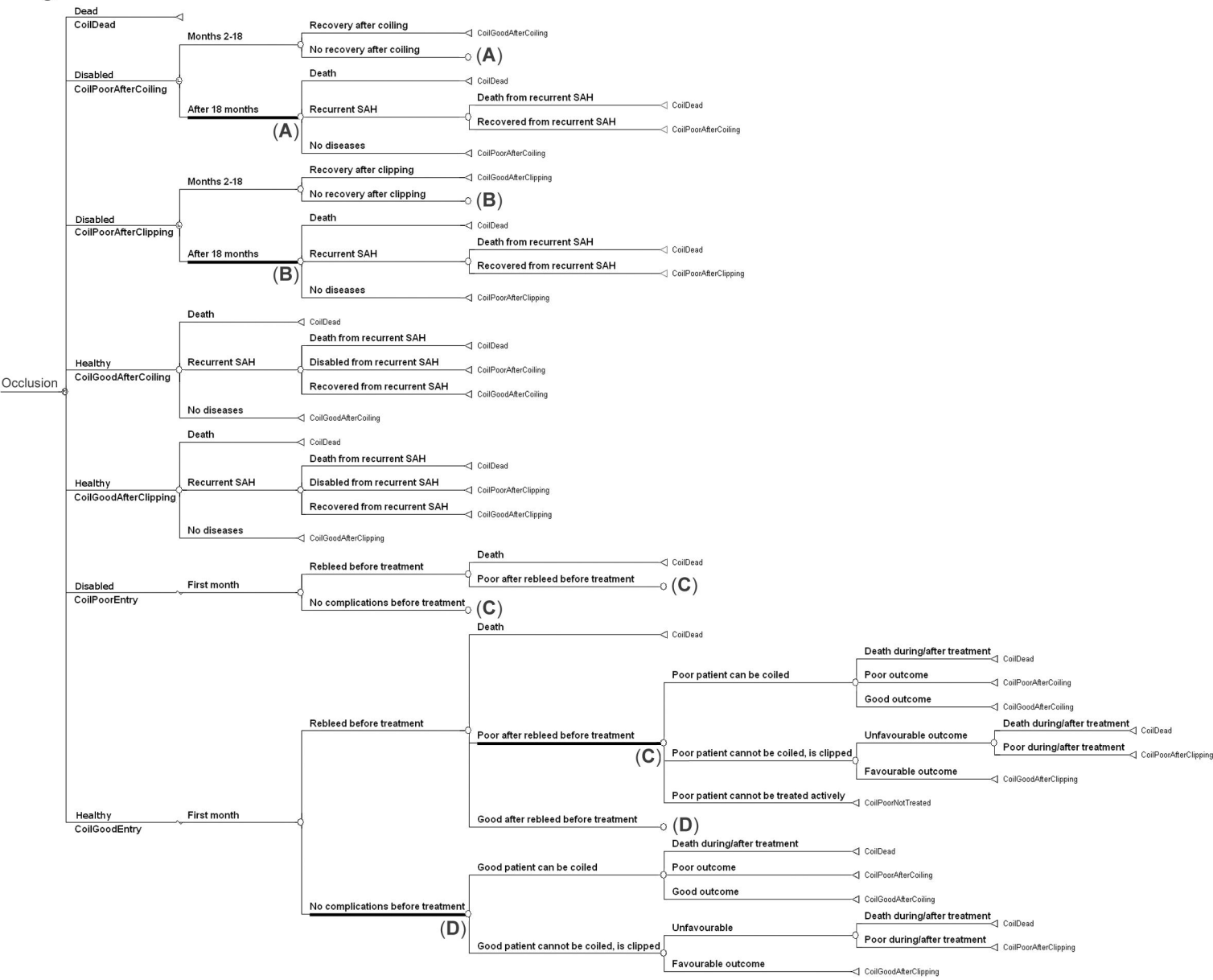
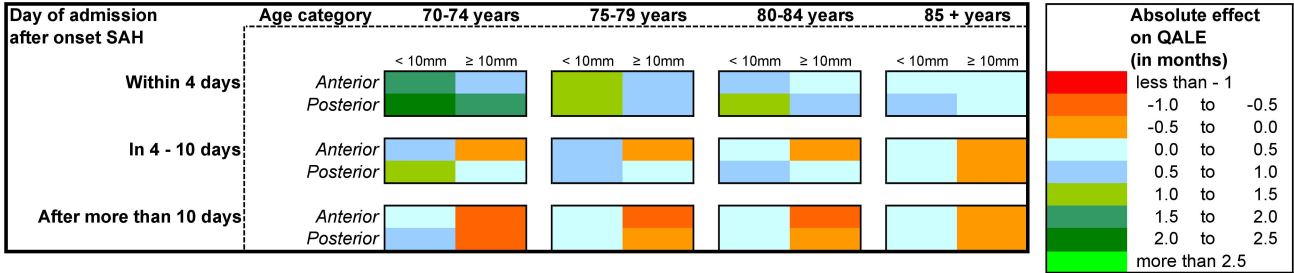
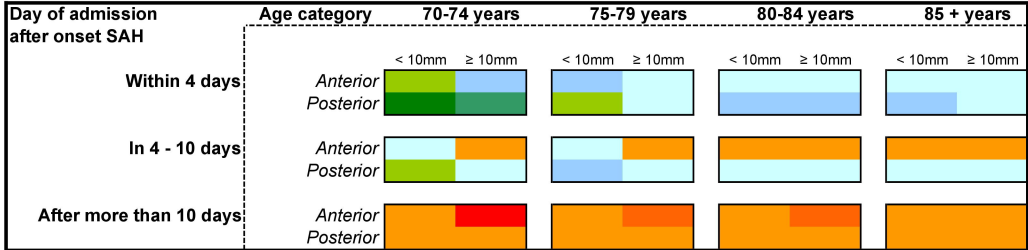


Figure 2.

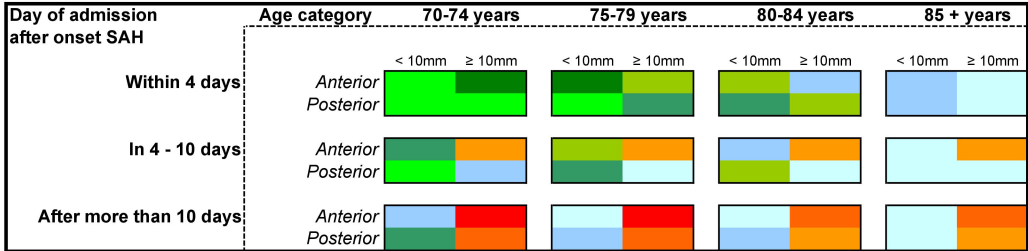
Elderly men with SAH - Admitted in good clinical condition



Elderly men with SAH - Admitted in poor clinical condition



Elderly women with SAH - Admitted in good clinical condition



Elderly women with SAH - Admitted in poor clinical condition

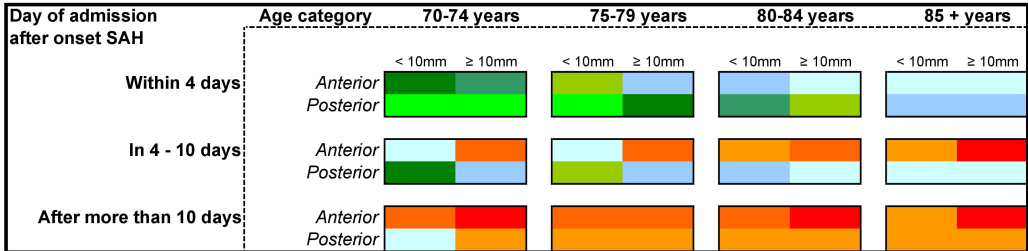


Figure 3.

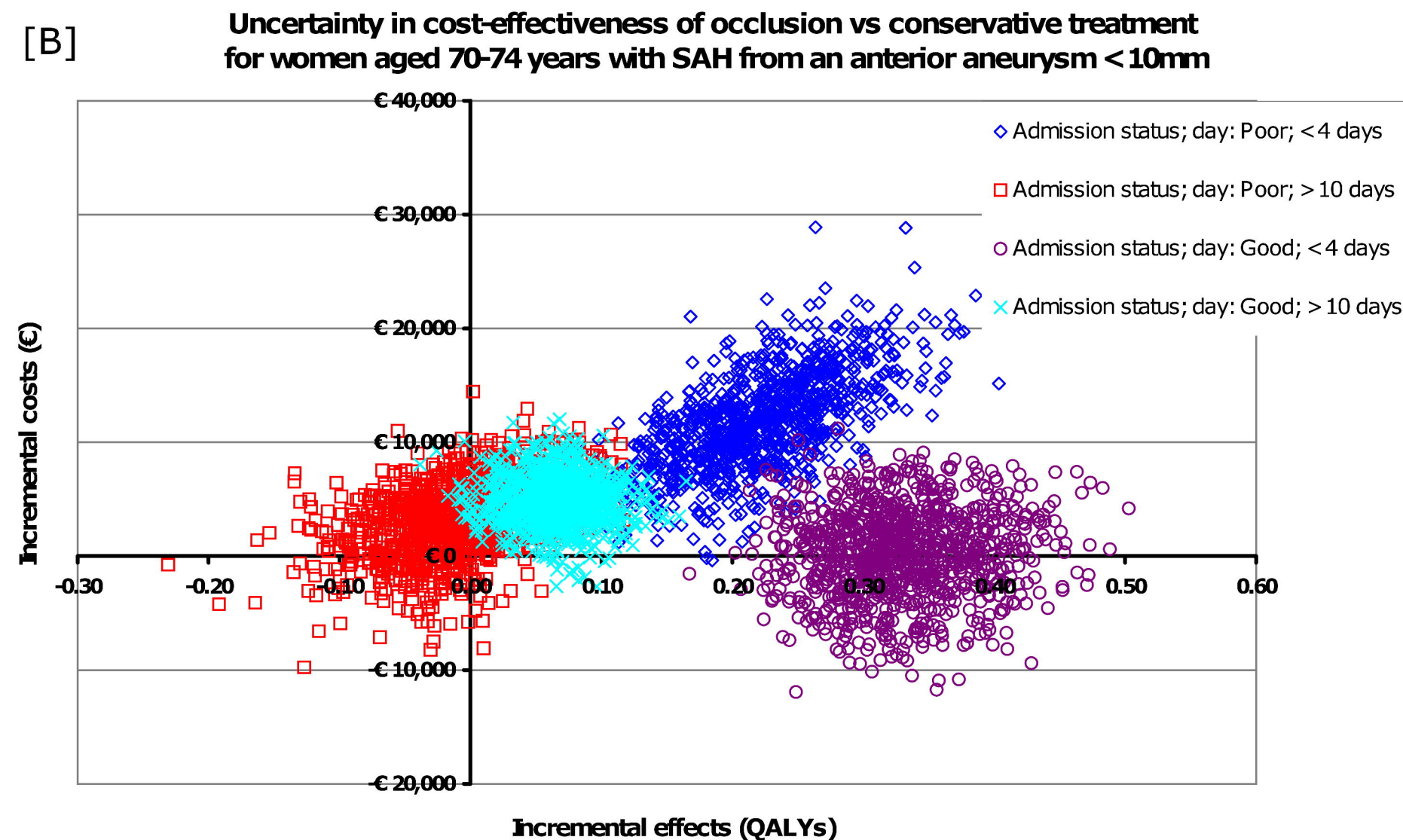
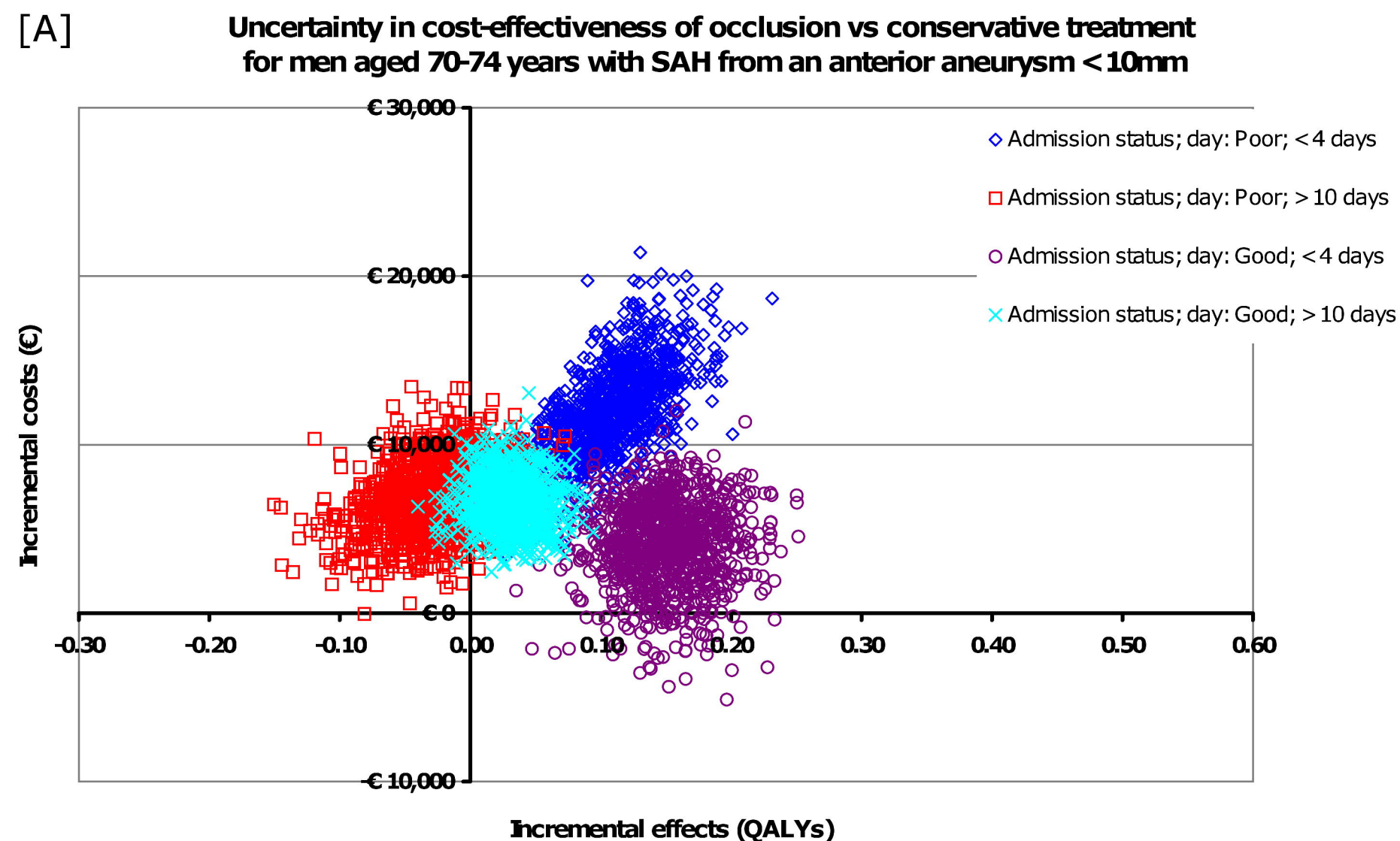
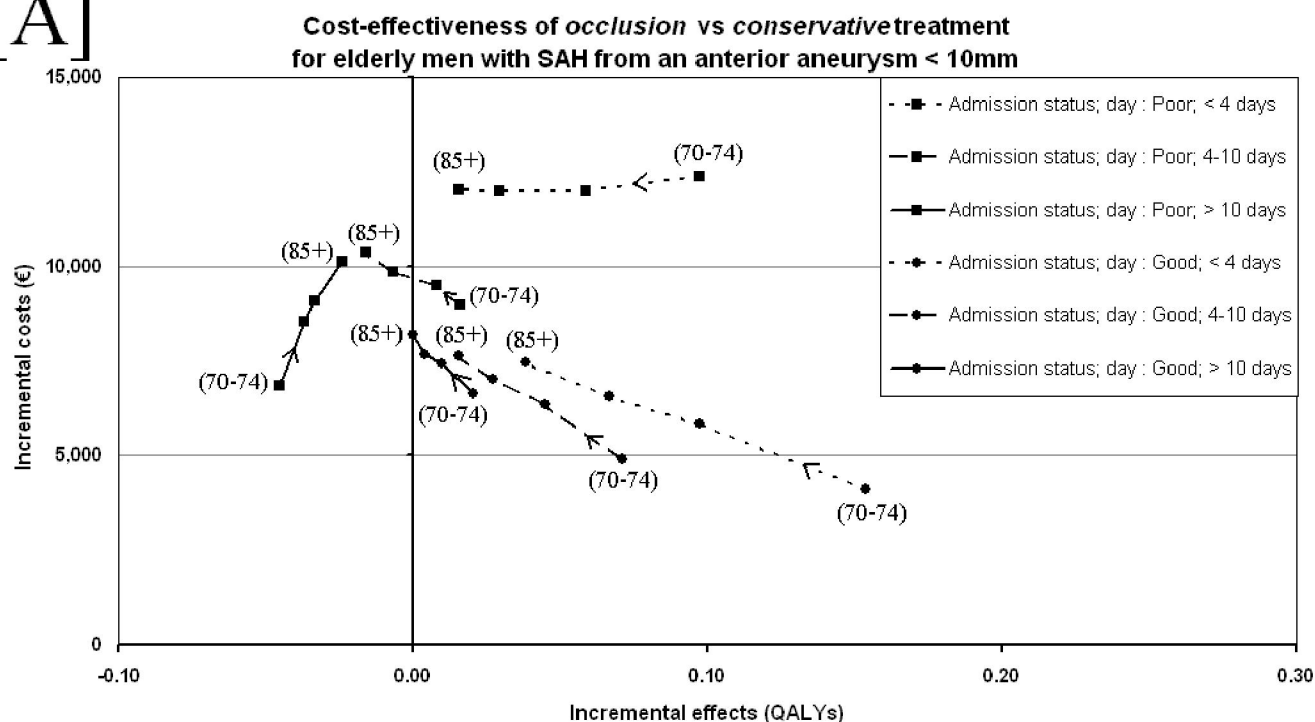


Figure 4.

[A]



[B]

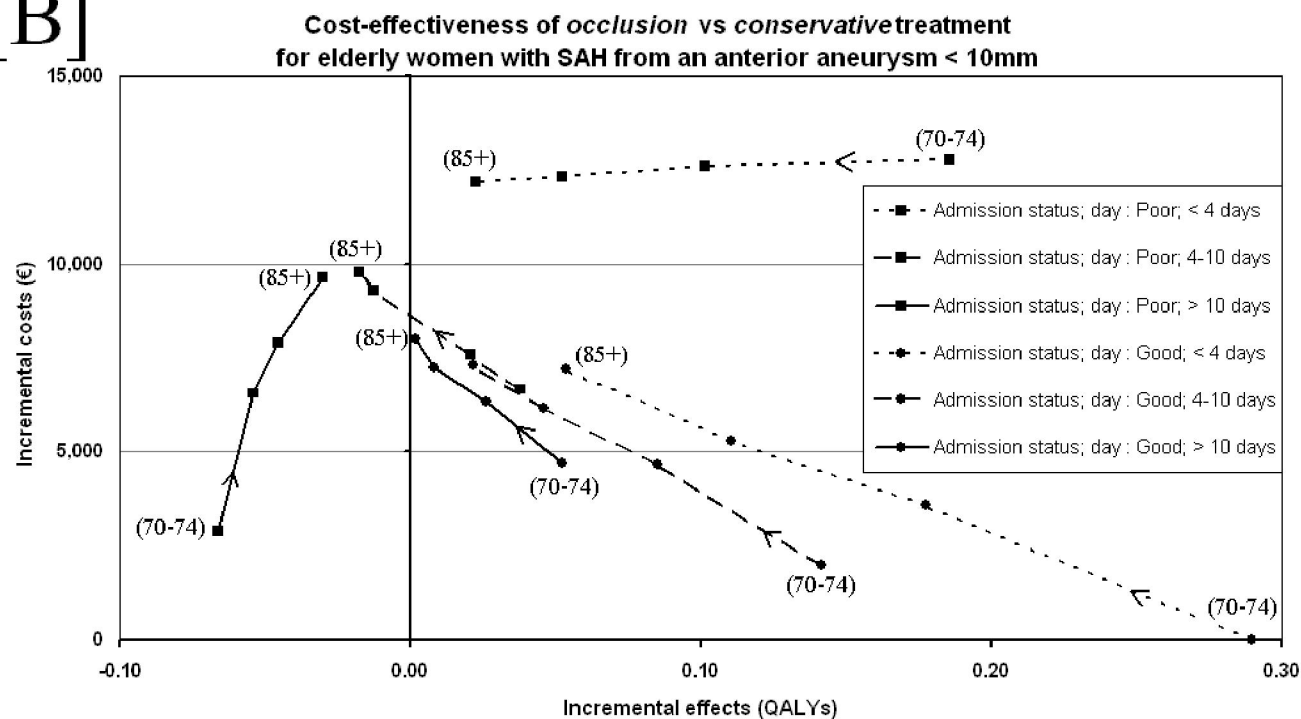
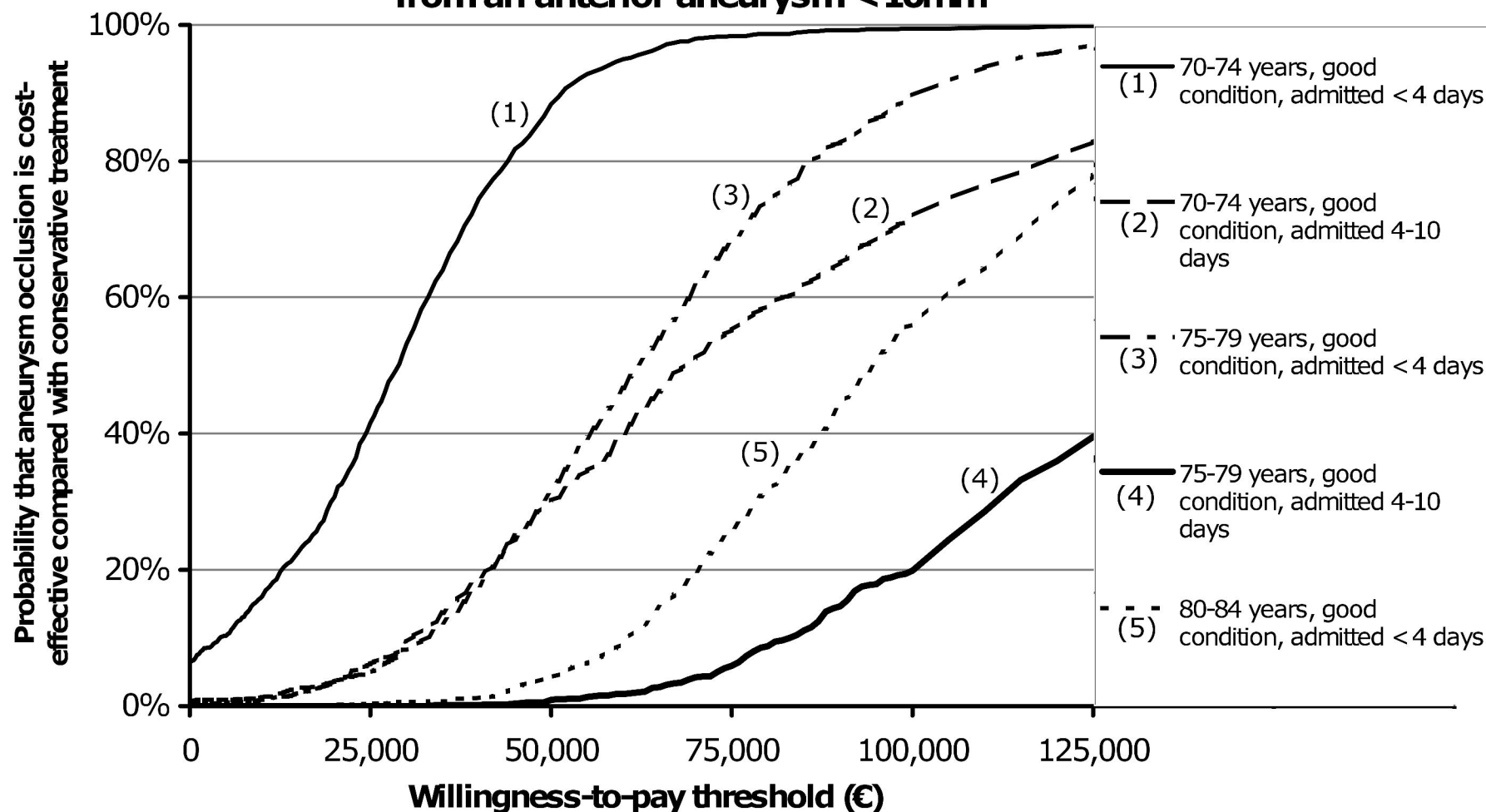


Figure 5.

[A]

**Cost-effectiveness acceptability curve for elderly men with SAH
from an anterior aneurysm < 10mm**



[B]

**Cost-effectiveness acceptability curve for elderly women with SAH
from an anterior aneurysm < 10mm**

