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Medical Decision Making

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Do Intraindividual Variation in Disease Progression and the Ensuing Tight Window of Opportunity Affect Estimation of Screening Benefits?

Hendrik Koffijberg, PhD, Gabriel Rinkel, MD, Erik Buskens, PhD, MD

Background. *The effects of variation in disease progression between individuals on the effectiveness of screening have been assessed extensively in the literature. For several diseases, progression may also vary within individuals over time. The authors study the effects of intraindividual variation and the combined effects of inter- and intraindividual variation in disease progression on the effectiveness of screening.* ***Methods***. *The authors investigated the risk reduction of aneurysmal subarachnoid hemorrhage (SAH) achieved by screening for intracranial aneurysms in a simulation study as a function of the inter- and intraindividual variation in the risk of aneurysm rupture. They also extended a previously constructed Markov model for the cost-effectiveness analysis of screening for new aneurysms in patients with clipped aneurysms after SAH. A time-varying risk of aneurysm rupture was introduced, and the influence of this variation on cost-effectiveness was assessed.* ***Results***. *The risk reduction provided by screening decreased with increasing intraindividual variation in disease progression. The expected number of prevented instances of SAH was overestimated by 58% in this simulation study when high degrees of inter- and intraindividual variation were present. Interindividual variation alone resulted in up to 33% overestimation and intraindividual variation in up to 43% overestimation. In the extended Markov model, screening benefits were overestimated by 24% when a high degree of intraindividual variation was present but ignored.* ***Conclusions***. *If intraindividual variation in disease progression is ignored in decision models, subsequent cost-effectiveness analyses of screening strategies will overestimate the benefits provided by screening. This bias is comparable to, but partially independent of, the bias caused by ignoring interindividual heterogeneity.* ***Key words:*** *disease progression; heterogeneity; cost-effectiveness analysis; simulation.* **(Med Decis Making 2009;29:82–90)**

Modern diagnostic tools allow accurate assessment of the stage of a disease at a particular moment in time. In modeling studies on the effects of screening and intervention after detection of disease, often an overall steady or linear disease progression is assumed. Models are generally based on an average rate of transition between different stages of the disease.[1,2] However, diseases may progress at different speeds in different individuals. This difference in disease progression between individuals (interindividual variation) leads to a heterogeneous population. Not taking into account this heterogeneity may affect the validity of the results of regression models and decision analytical models on the effectiveness of screening[3–6] and may even affect the results of trials when benefits from treatment depend on disease progression rates.[7]

In addition to differences in disease progression *between* individuals, disease progression *within* individuals may vary over time. Examples of intraindividual variation in progression over time are the

staccato growth of abdominal aortic aneurysms and intracranial aneurysms,[8,9] sudden changes in progression of atherosclerosis,[10] and heterogeneity in metastatic prostate carcinoma.[11] This intraindividual variation in disease progression over time may affect the results of decision models. Decision models generally assume constant progression or risks. Simple calculations are used to transform the long-term rates observed to yearly risks. Clearly, such recalculated annual risks ignore any variability in disease progression between and within individuals over time. As a result, in reality, fewer events may be prevented than predicted using a constant risk assumption. We hypothesize that not only interindividual variability but also intraindividual variation in risk over time may negatively affect the model-based estimations of health gains. We study the effects of inter- and intraindividual variation in disease progression over time in a simulation study on the effectiveness of screening and preventive treatment for intracranial aneurysms in terms of reducing instances of aneurysmal subarachnoid hemorrhage (SAH) due to aneurysmal rupture. Also, we incorporate inter- and intraindividual variation in disease progression in a previously developed Markov model to reassess the cost-effectiveness of screening for new aneurysms in patients who had an intracranial aneurysm clipped after SAH.[12] Originally, for this Markov model, a constant risk of aneurysm growth and aneurysm rupture had been assumed.[9,13,14]

METHODS

Simulation Study

In a simulation study on intracranial aneurysm growth and rupture, we investigated the effect of variation in risk of rupture within and between individuals on the efficacy of screening (i.e., the reduction in instances of SAH) for 8 different screening strategies. A time horizon of 25 years was used, and a hypothetical cohort of 100,000 women, aged 50 at entry in the model and all having survived a previous episode of SAH, was simulated. This starting age was similar to the age at entry in the previously developed ASTRA decision model.[12] Women have a higher risk of SAH than do men, and the risk of SAH is higher for individuals older than 60 than for individuals younger than that age.[15,16] In addition, the risk of SAH is increased in patients with previous SAH.[17] Within our time horizon, women aged 50 at entry in the model thus constitute a relevant

high-risk group because they are at risk of developing new aneurysms that may rupture later in life (e.g., when the patients are older than 60 years of age). The assumed combined annual risks of aneurysm formation and aneurysm rupture resulted in an estimated cumulative risk of SAH of 10.2% for an individual after 25 years. Competing mortality was taken into account in this risk estimation. Without any screening, the expected number of SAH instances in our hypothetical cohort would therefore be 10,200. An individual's risk of rupture was determined by constructing a risk profile describing the risk of rupture for each subsequent day of the 25-year period covered. These risk profiles were constructed based on 2 parameters: the *within*-individual variation of risk over time (WIV, or intraindividual variation) and the *between*-individual variation of risk (BIV, or interindividual variation). Increasing values of WIV result in more irregular, chaotic risk profiles, and increasing values of BIV result in more individuals at high risk and at low risk of disease.

We investigated 3 categories of values for WIV and BIV separately: no variation, low variation, and high variation. The overall risk of aneurysm rupture was dependent on a risk based on aneurysm growth and a risk based on aneurysm size; each factor was set to account for 50% of the total risk. The average 25-year risk of aneurysm rupture in our hypothetical cohort was fixed (i.e., standardized to 10.2%) and therefore the same for all combinations of BIV and WIV values. The profile of rupture risk based on size was determined by the rate and duration of aneurysm growth, and thus it was the cumulative of the growth-related risk profile. Details of the compilation of risk profiles are given in the appendix.

For each screening strategy, we defined a screening interval in years, a detection threshold comprising the cumulative risk of rupture individuals must have experienced before an aneurysm can be detected, and a risk-free period after treatment in years. The detection threshold in reality is largely determined by aneurysm size.[18] Because no detailed information is available on aneurysm growth rates, modeling of changes over time in the distribution of aneurysm sizes in a study population is infeasible. Therefore, our model does not account for actual aneurysm size but instead is based on risk of aneurysm rupture. We therefore defined the detection threshold as the minimum amount of absolute risk of rupture experienced by an individual that would allow the aneurysm to be detected. We assumed that aneurysms exceeding the detection threshold would always be detected and that detected aneurysms would always be treated.
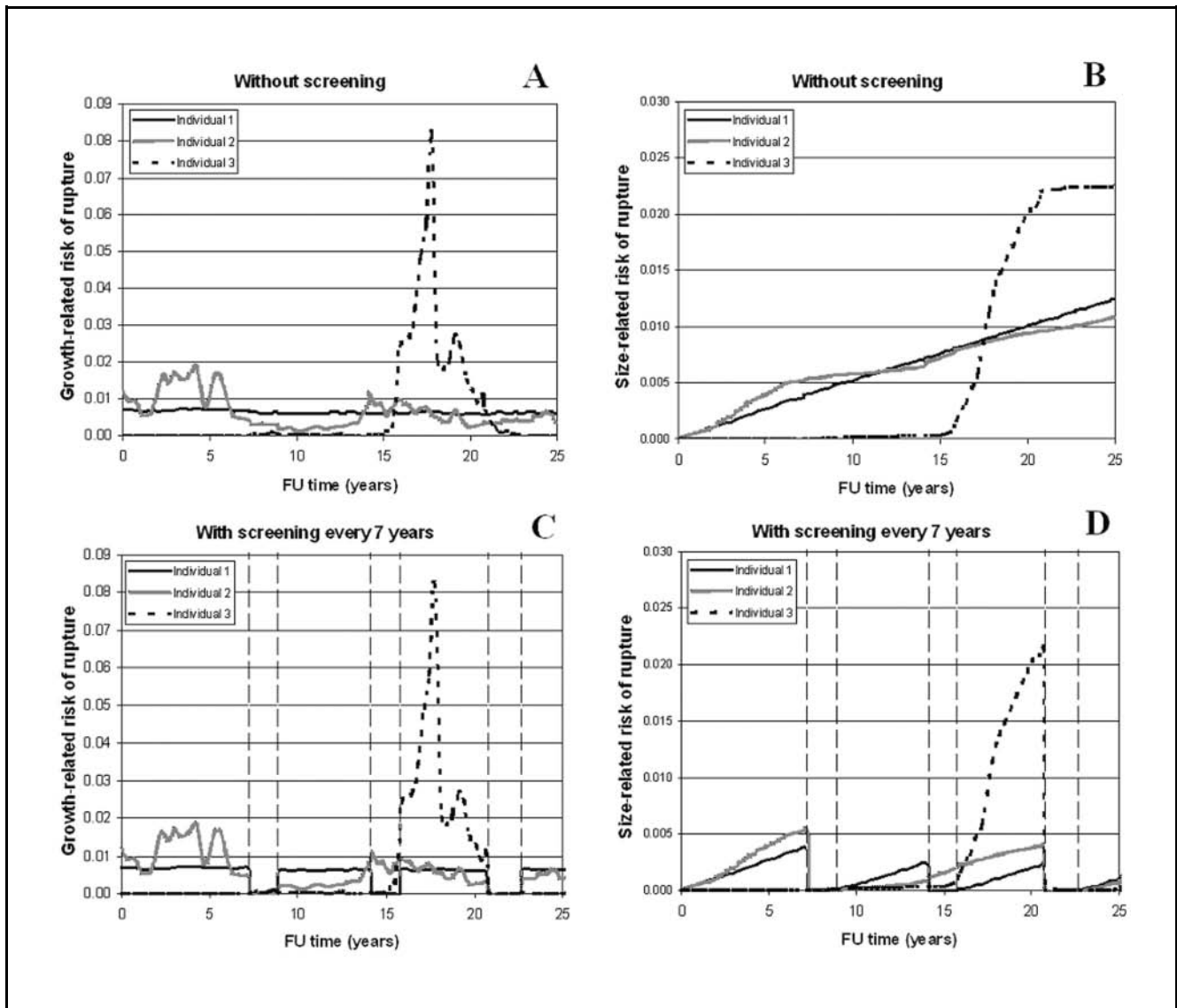
Figure 1   Exemplary risk profiles of aneurysm rupture with the corresponding risk reduction offered by screening. Three examples of risk profiles for individuals. The original growth-related and size-related risk profiles are shown in A and B, and the corresponding risk profiles after screening are shown in C and D. The vertical lines in C and D show the screening moments and the end of the risk-free period after each screening moment. Here the screening interval was 7 years, the detection threshold was 1%, and the risk-free period was 2 years. The 3 individuals experience the same total risk of subarachnoid hemorrhage before screening (i.e., there is no interindividual variation). No variation of risk over time is assumed for individual 1, a small variation is assumed for individual 2, and a high variation over time is assumed for individual 3. In this example, the relative risk reduction provided by screening and preventive treatment is 54.4% for individual 1, 41.8% for individual 2, and 29.2% for individual 3. FU, follow-up.

The risk-free period was defined as the period after aneurysm treatment in which the risk of formation and rupture was zero. Eight screening strategies were defined, with screening intervals of 2 years or 5 years, detection thresholds of 1% or 3% absolute risk, and a risk-free period of 1 year or 2 years. Random draws from the possible characteristics yielded a specific

risk profile for each hypothetical individual in the cohort. The expected health benefit of the screening strategies was calculated as the sum of the expected risk reductions for all individuals. A visualization of the screening process, for 3 hypothetical individuals, is given in Figure 1. During the first screening examination, no aneurysm was detected for individual 3

because the detection threshold of 1% was not exceeded. Similarly, in the second screening examination, no aneurysm was detected for individuals 2 and 3.

Extended Markov Model

In the ASTRA project, we constructed a Markov decision model to determine the cost-effectiveness of screening for (new) aneurysms in patients with clipped aneurysms after subarachnoid hemorrhage.[12] The decision model was used to estimate long-term costs and effects of a screening strategy in which patients were screened every 5 years for new aneurysms, up to the age of 70 years. The cost-effectiveness analyses showed that screening in general is not cost-effective but that screening in patients with additional risk factors may be beneficial and cost-effective. In particular, screening was estimated to be cost-saving and provided additional quality-adjusted life years (QALYs) for patients with at least a 4.5 times increased risk of aneurysm formation and a 4.5 times increased risk of rupture. Within this model, the annual risk of aneurysm formation and aneurysm rupture was considered constant. To assess whether variation in risks between and within individuals over time affects the results of this model, we extended the original Markov model with these 2 variations in risks, defined and categorized alike in the simulation study (see appendix). In addition, the extended model reflected 2 new assumptions. (1) On average, an aneurysm can be detected only using computed tomographic angiography (CTA) 2 years and onward after formation. The original model used a probability of false-negative CTA that was independent of aneurysm size. However, in practice, aneurysms smaller than 3 mm may easily be missed, whereas it is unlikely that aneurysms over 5 mm will be missed at all.[18] We again used the cumulative risk of rupture experienced by individuals as a proxy of the corresponding aneurysm sizes. In the resulting model, risk of aneurysm rupture may vary over time and between individuals. Consequently, an aneurysm will be detected once an individual has experienced a cumulative risk of rupture equaling twice the annual risk of rupture used in the original model. Thus, on average, the risk threshold will be exceeded after 2 years, but individuals (temporarily) at high risk may surpass the detection threshold in less than 2 years. Conversely, for individuals at low risk, the threshold may not be surpassed until many years have passed. The probability of a false-negative CTA equals 1 for aneurysms considered small and not detectable and

equals 0 for aneurysms considered large and detectable. In the model, both small and large aneurysms may rupture. (2) In the year following treatment, by definition, aneurysm formation is precluded, as well as rupture.

We used the extended Markov model to simulate a hypothetical cohort of 50,000 individuals. Both the extended Markov model and the simulation study were implemented using Mathematica (v5.2, Wolfram Research, Inc., Champaign, Illinois).

RESULTS

Simulation Study

The expected number of instances of SAH that may be prevented by screening is shown in Figure 2, where the screening strategies are ranked by effectiveness. All screening strategies result in a substantial reduction of the number of SAHs, regardless of the degree of within- and between-individual variation. However, for all strategies and regardless of the degree of interindividual variation, the expected number of prevented SAH instances drops with an increasing degree of intraindividual variation. In Figure 2A, for example, this reduction is 16% for strategy 1 when low intraindividual variation is present (no WIV: 5934 SAHs prevented, low WIV: 5004 SAHs prevented, a difference of 930 instances [16%]). With high intraindividual variation, again a 16% reduction is found (low WIV: 5004 SAHs prevented, high WIV: 4215 SAHs prevented, a difference of 789 instances [16%]). Although for strategies less effective than strategy 1, such as strategy 8, the reduction in absolute numbers of instances prevented may be smaller (Table 1), the relative reduction in instances prevented is still substantial. The reduction in efficiency of screening caused by both types of variation appears partially independent and additive (Table 1). In other words, any intraindividual variation will add to the effects caused by interindividual variation and vice versa. If there is a high degree of both types of variation, the reduction in efficiency may be as high as 58% (strategy 2 in Table 1).

Extended Markov Model

After extending the Markov model with the 2 new assumptions, the predictions were similar to those from the original model if WIV and BIV were set to 0, which shows that the 2 additions hardly affect the outcome. Table 2 shows the results of

Table 1 Fraction of the Expected 10,200 SAH Instances That May Be Prevented by Screening

		Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5	Strategy 6	Strategy 7	Strategy 8
Screening interval, years		2	5	2	2	5	5	2	5
Detection threshold, % risk		1	1	3	1	3	1	3	3
Period of zero risk, years		2	2	2	1	2	1	1	1
WIV	BIV								
No	No	58 (NA)	49 (NA)	48 (NA)	44 (NA)	39 (NA)	37 (NA)	31 (NA)	28 (NA)
No	Low	52 (11)	39 (19)	46 (4)	40 (8)	38 (3)	34 (7)	29 (7)	26 (8)
No	High	45 (22)	32 (33)	41 (14)	38 (13)	36 (8)	32 (11)	28 (9)	24 (14)
Low	No	49 (16)	32 (35)	46 (5)	34 (23)	35 (10)	33 (9)	29 (8)	26 (7)
Low	Low	46 (21)	31 (37)	45 (7)	32 (28)	33 (17)	32 (12)	28 (11)	25 (10)
Low	High	42 (29)	26 (46)	38 (20)	29 (34)	32 (19)	29 (20)	25 (18)	23 (16)
High	No	41 (29)	28 (43)	40 (16)	28 (35)	32 (17)	31 (15)	26 (16)	23 (19)
High	Low	37 (36)	24 (51)	33 (31)	24 (44)	28 (27)	28 (24)	22 (30)	21 (23)
High	High	32 (44)	21 (58)	31 (36)	22 (51)	28 (28)	27 (26)	20 (36)	19 (33)

Values are in percentages. Values in parentheses are the relative reductions in the number of subarachnoid hemorrhage instances prevented compared with the first category, in which no inter- and intraindividual variation is assumed. WIV, within-individual variation; BIV, between-individual variation; NA, not applicable.

simulating cohorts of individuals in the extended Markov model. For each category of relative risk of rupture and formation, 9 rows show the results for the 9 combinations of categories of BIV and WIV. Within similar categories of BIV and increasing WIV, the expected number of SAHs that can be prevented by screening decreased, and the costs per individual increased. Within similar categories of WIV and increasing BIV, effectiveness of screening decreased only in the 5-fold increased risk category.

At a cost-effectiveness threshold of €20,000 per QALY, the original and extended models lead to the same conclusion—that is, in this case, the results appeared robust. Screening appeared cost-effective for individuals with at least a 2-fold increased risk (i.e., regardless of any variation between or within individuals). However, the number of instances of SAH prevented in this group of patients may be overestimated substantially when inter- and intraindividual variation is not taken into account. If no variation is assumed, the expected number of prevented SAHs is 5685, whereas in the presence of a high degree of intraindividual variation, this number decreases to 4576. Thus, without taking into account intraindividual variation in risks, the number of SAH instances prevented by screening will be overestimated by 24%. Similarly, if interindividual variation is not taken into account (in the absence of intraindividual variation), the number of SAHs prevented by screening will be overestimated by 2%. If a high degree of both types of variation is present but not accounted for, the number of prevented SAHs will be overestimated by 29%.

DISCUSSION

Variation of disease progression within individuals over time reduces the efficacy of screening to a considerable extent and decreases cost-effectiveness. Although the effects of inter- and intraindividual variation are not completely independent (i.e., they do not add up), taking into account only one type of variation still results in overestimating the yield of screening when variation of the other type is also present. Furthermore, the overestimation from intraindividual variation may be similar to or even greater than the overestimation due to interindividual variation, as in our examples.

The decreased (cost-)effectiveness of screening strategies due to intraindividual variation in disease progression can be explained easily. For efficiency reasons, individuals with short periods of rapidly growing disease should be screened often to ensure timely detection, whereas those with (short periods of) slowly progressing disease can be screened at longer intervals. When no intraindividual variation in disease progression is assumed, it is possible to determine an optimal screening interval—that is, a screening strategy resulting in the lowest cost-effectiveness ratio for low- and high-risk individuals separately. However, if the optimal screening interval is determined using an average progression speed in the presence of intraindividual variation in disease progression, screening procedures will be performed at suboptimal points in time. Individuals will be screened unnecessarily often during periods of stable disease and too infrequently during periods with
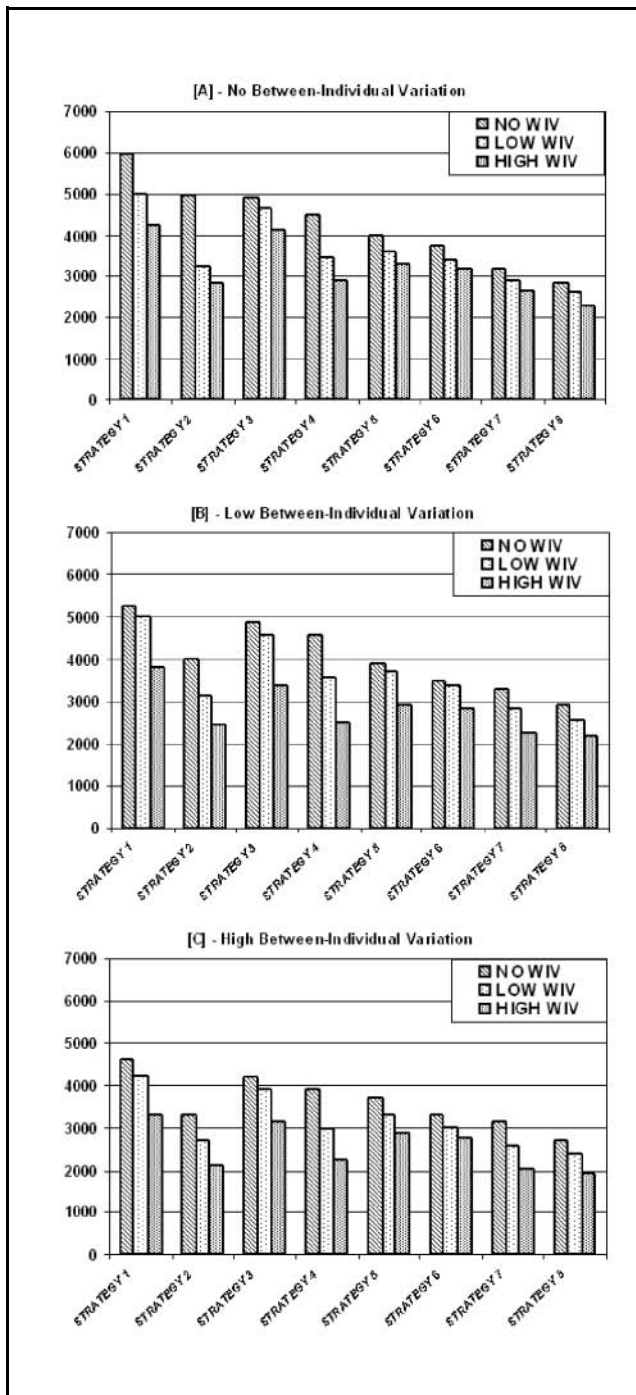
Figure 2 The expected number of instances of subarachnoid hemorrhage (SAH) that may be prevented by each screening strategy, when the total number of expected instances of SAH is 10,200. The interindividual variation is set to (A) no, (B) low, and (C) high for 3 degrees of intraindividual variation. Definition of the 8 screening strategies, in terms of the screening interval, detection threshold, and period of zero risk, is given at the top of Table 1. WIV, within-individual variation.

rapid disease progressing. The number of suboptimal screening procedures will increase with increasing intraindividual variation in progression, and as a consequence, screening efficacy and cost-effectiveness will decrease.

In our example of the extended Markov model, incorporating inter- and intraindividual variation in disease progression resulted in the same overall conclusion compared with the original model regarding the cost-effectiveness of screening for intracranial aneurysms. However, in other situations, ignoring intraindividual variation in disease progression may lead to different overall conclusions with respect to the benefits of screening than accounting for intraindividual variation in disease progression. This can be illustrated by applying a hypothetical cost-effectiveness threshold of €5000 per QALY in our example. Apparent from Table 2, screening would be deemed cost-effective for individuals with a 2-fold increased risk if variation in risk is not taken into account (i.e., BIV = no, WIV = no, incremental cost-effectiveness ratio [ICER] = €3336/QALY) but would no longer be deemed cost-effective if some variation in risk is taken into account. This illustrates that in some cases the issue may be nontrivial. Thus, models that do not account for intraindividual heterogeneity may provide unrealistic results.

Although currently the supporting evidence is limited, we feel that our results are not unique for intracranial aneurysm development or characteristics of aneurysm screening procedures. It is known, for example, that biological variation may cause intraindividual changes in factors such as lipid levels, cell-mediated immunity, and blood flow velocities. However, these changes have not been related to screening efficiency.[19–21] Instead of accounting for intraindividual changes in risk, it is advocated to perform repeated measurements to determine a robust, average risk for each individual. In addition, intraindividual variation previously has been classified as a risk factor itself for schizophrenia,[22] and variation in risk over time in individuals surviving coronary artery bypass graft surgery has been assessed.[23] Assuming constant risk in these patients during the postoperative period may substantially overestimate or underestimate risk at some times.

Our study has certain limitations. The values for the parameters WIV and BIV were chosen somewhat arbitrarily, to represent no variation and low and high degrees of variation. This was done because no clinical data on the variation of aneurysm growth rates in individuals were available from the literature. Thus, in reality, the extent of the

Table 2 Comparison of the Screening Strategy with the No-Screening Strategy

Relative Risk of Aneurysm Formation and Rupture	BIV	WIV	Additional Costs per Individual, in €	Additional QALYs per Individual	ICER, in € per QALY	Subarachnoid Hemorrhage Cases Prevented
1.0	No	No	576	−0.01	NA	1878
	No	Low	590	−0.02	NA	1820
	No	High	617	−0.02	NA	1621
	Low	No	627	−0.04	NA	1733
	Low	Low	863	−0.06	NA	1646
	Low	High	916	−0.06	NA	1602
	High	No	718	−0.02	NA	1711
	High	Low	779	−0.04	NA	1699
	High	High	881	−0.04	NA	1621
2.0	No	No	−300	−0.09	3336	5685
	No	Low	−293	−0.09	3259	5530
	No	High	−262	−0.11	2383	4576
	Low	No	−706	−0.10	7060	5670
	Low	Low	−692	−0.09	7689	5453
	Low	High	−650	−0.10	6496	4613
	High	No	−774	−0.08	9671	5573
	High	Low	−754	−0.08	9422	5338
	High	High	−739	−0.10	7387	4406
5.0	No	No	−5711	0.04	−136,426	15,209
	No	Low	−5458	0.04	−131,954	14,868
	No	High	−5089	0.05	−100,964	13,011
	Low	No	−4717	0.05	−101,630	14,898
	Low	Low	−3677	0.04	−94,634	14,458
	Low	High	−3365	0.04	−88,363	12,344
	High	No	−4504	0.04	−112,337	14,114
	High	Low	−3423	0.03	−103,005	13,454
	High	High	−3046	0.03	−95,739	11,231

For each subgroup, results are shown for 9 combinations of inter- and intraindividual variation. For each combination, the additional costs and quality-adjusted life years (QALYs) per individual are shown. In addition, the incremental cost-effectiveness ratio (ICER) of screening compared with no screening is shown. WIV, within-individual variation; BIV, between-individual variation; NA, not applicable.

reduction in screening efficacy from intraindividual variation in aneurysm growth rates may differ from the results presented here. However, regardless of the actual degree of variation, the benefits provided by screening will be overestimated if this variation is not taken into account.

In addition to the degree of inter- and intraindividual variation, the distribution of the intraindividual risk over time and the fraction of individuals having a risk that is markedly lower or higher than average influence the impact of variation on cost-effectiveness. The impact of intraindividual variation on (cost-)effectiveness will be highest if the variation is caused by individuals experiencing all their risk in a very short time period. Similarly, the impact of interindividual variation will be highest if it is caused by a very small fraction of all individuals who, together, experience all of the total population risk.

Although the effects of heterogeneity among individuals in their susceptibility to disease have

been assessed in many studies,[3–6] the effects of intraindividual variation in disease progression over time rarely have been investigated. Our results show that information on the distribution of inter- and intraindividual variation in disease progression should be taken into account when developing cost-effectiveness models. Unless evidence supports a constant rate of progression in all individuals, simplications with respect to intraindividual heterogeneity result in overly optimistic conclusions regarding (cost-)effectiveness of screening programs. This bias is similar to, but partially independent of, the bias caused by ignoring interindividual heterogeneity.

APPENDIX

In the simulation model, random risk profiles were generated, with each risk profile consisting of a risk profile

due to aneurysm growth and a risk profile due to aneurysm size. Together, these 2 profiles made up the overall risk profile for an individual, and both profiles accounted for 50% of the overall risk of SAH. The profile of rupture risk due to size was determined by the rate and duration of aneurysm growth, and thus it was the cumulative of the growth-related risk profile. The variation in risk was introduced using 2 parameters: BIV (between-individual variation) and WIV (within-individual variation). Values of WIV greater than 0 cause risks to vary over time within individuals, and values of BIV greater than 0 cause heterogeneity in the absolute risk experienced by different individuals. We investigated 3 categories of values for WIV: no variation (value 0), low variation (value 0.15), and high variation (value 0.5). The categories of no, low, and high variation were also investigated for BIV with corresponding values 0, 0.5, and 2. Because the effects of WIV and BIV are not implemented similarly, the categories of no, low, and high variation are not based on the same values for both types of variations. The value of WIV determines the variation in risks that individuals experience from day to day, over the 25-year time horizon. The value of BIV, on the other hand, determines the total variation in relative risk that is present in the hypothetical cohort of individuals. The total risk of aneurysm rupture in our hypothetical cohort was standardized to be the same for all combinations of values of BIV and WIV.

For both risk profiles, values were determined for each day, over the 25-year time horizon, according to the pseudo-code routine presented below. Note that parameter WIV is used only in line 09, when the change in risk is determined per day, using a random value and the risk of the preceding day. When WIV is near 0, the risk of each day will approximately equal the risk of the preceding day, and there will be very low variation in risks within individuals over time. Similarly, parameter BIV is used only in line 02, when the relative risks over the complete period are determined for all individuals. When BIV is near 0, the sum of these relative risks, divided by the number of individuals, will equal 1—that is, the total risk experienced will be approximately equal for all individuals (regardless of any variation in risks over the days that individuals may experience). In this way, the parameters BIV and WIV independently control the degree of inter- and intraindividual variation, whereas the total risk of SAH over the entire hypothetical cohort of individuals remains unchanged. Thus, when individuals are not screened to prevent SAH instances, the expected number of events for arbitrary values of the parameters WIV and BIV is equal to the expected number of events when the same, constant, (annual) risks are used for all individuals.

The original Markov decision model was similarly extended to incorporate inter- and intraindividual variation. Similar to the original model, the extended model used time cycles of 1 year.

Pseudocode for the Determination of the Daily Risk of SAH, Separately for All Hypothetical Individuals, Based on Variation between and within Individuals

```
01. For i = 1 To NumInd do:                                          // Perform for all individuals
02.     IndTotalRR [i] = Exp(Random(NormalDistribution
        (mean = 0, sd = BIV)))                                       // Determine the target risk per individual
03.     SumTotalRR = SumTotalRR + IndTotalRR [i]/NumInd              // Determine average, overall relative risk
04. End for i.
05. For i = 1 To NumInd do:                                          // Perform for all individuals
06.     RiskGrowth [i,1] = OverallCumRisk / (25*365)                 // Set risk due to growth for day 1
07.     CumRiskGrowth [i,1] = RiskGrowth [i,1]                       // Set cumulative risk due to growth for day 1
08.     For j = 2 To 25*365 do:                                      // Set the growth profile for day 2 and onward
09.         RiskGrowth [i,j] = RiskGrowth [i, j-1]*
            Exp(Random(NormalDistribution(mean = 0, sd = WIV)))      // Model the risk per day
10.         CumRiskGrowth [i,j] = CumRiskGrowth [i,j] +
            RiskGrowth [i,j]                                         // Determine the cumulative risk
11.     End for j.
12.     TotRiskGrowth = CumRiskGrowth [i, 25*365]                    // Determine the total risk due to growth
13.     For j = 1 To 25*365 do:                                      // Normalize and scale the profiles
14.         RiskGrowth [i,j] = (RiskGrowth [i,j]/TotRiskGrowth )* 0.5 * OverallCumRisk * (IndTotalRR [i] / SumTotalRR)
15.         RiskSize [i,j] = (CumRiskGrowth [i,j]/TotRiskGrowth) * 0.5 * OverallCumRisk * (IndTotalRR [i] / SumTotalRR)
16.         RiskRupture [i,j] = RiskGrowth [i,j] + RiskSize [i,j]
17.     End for j.
18. End for i.
```

PATIENT HETEROGENEITY

89

With the parameters defined as follows:

WIV:	Within-individual variation or intraindividual heterogeneity
BIV:	Between-individual variation or interindividual heterogeneity
NumInd:	The number of individuals in the hypothetical cohort
IndTotalRR [i]:	The relative risk of aneurysm formation and rupture for individual i
SumTotalRR:	The average relative risks over all individuals (used for scaling)
OverallCumRisk:	The cumulative overall (total) risk of aneurysm formation and rupture per patient: 0.102
RiskGrowth [i,j]:	The risk of aneurysm rupture due to aneurysm growth, for individual i on day j
CumRiskGrowth [i,j]:	The cumulative risk of aneurysm rupture due to aneurysm growth, for individual i on day j
TotRiskGrowth:	The total risk of rupture due to aneurysm growth for a specific individual
RiskSize [i,j]:	The risk of aneurysm rupture due to aneurysm size, for individual i on day j
RiskRupture [i,j]:	The total risk of rupture, due to aneurysm growth and aneurysm size, for individual i on day j

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