Neurymal subarachnoid hemorrhage (aSAH) accounts for 5% of all strokes, with an incidence of 2 to 16 per 100,000 and has a worse prognosis when compared with other types of stroke. Morbidity and mortality is high and survivors are often severely disabled. Because of the relatively young age at which aSAH usually occurs, the loss of productive life years from aSAH is comparable with that of ischemic stroke, even though the latter has a much higher incidence. If the patient survives the initial aSAH, the major early complication is a rebleeding from the ruptured aneurysm with reported incidences of 8% to 23% in the first 72 hours after the ictus. The consequences of a rebleeding are severe, with reported mortality rates ≤60%. Urgent repair of the ruptured aneurysm by endovascular coiling or neurosurgical clipping is thus of utmost importance; as soon as the aneurysm is successfully repaired, the chance of a rebleeding is negligible.

Background and Purpose—Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating type of stroke associated with high morbidity and mortality. One of the most feared complications is an early rebleeding before aneurysm repair. Predictors for such an often fatal rebleeding are largely unknown. We therefore aimed to determine predictors for an early rebleeding after aSAH in relation with time after ictus.

Methods—This observational prospective cohort study included all consecutive patients admitted with aSAH between January 1998 and December 2014 (n=1337) at our University Neurovascular Center. Clinical predictors for rebleeding ≤24 hours were identified using multivariable Cox regression analyses. Kaplan–Meier analyses were applied to evaluate the time of rebleeding ≤72 hours after aSAH.

Results—A modified Fisher grade of 3 to 4 was a predictor for an in-hospital rebleeding ≤24 hours after ictus (adjusted hazard ratio, 4.4; 95% confidence interval, 2.1–10.6; P<0.001). The numbers needed to treat to prevent 1 rebleeding ≤24 hours was calculated 15 (95% confidence interval, 10–25). Also, the initiation of external cerebrospinal fluid-drainage (adjusted hazard ratio, 1.9; 95% confidence interval, 1.4–2.5; P<0.001) was independently associated with a rebleeding ≤24 hours. Cumulative in-hospital rebleeding rates were 5.8% ≤24 hours, and 1.2% in the time frame 24–72 hours after ictus.

Conclusions—In our opinion, timing of treatment of aSAH patients, especially those with a modified Fisher grade of 3 or 4 in a good clinical condition, should be reconsidered. These aSAH patients might be regarded a medical emergency, requiring aneurysm repair as soon as possible. In this respect, our findings should provoke the debate on timing of aneurysm repair, especially in patients considered to be at high risk for rebleeding. (Stroke. 2015;46:2100-2106. DOI: 10.1161/STROKEAHA.115.010037.)

Key Words: aneurysm ■ rebleeding ■ regression analysis ■ stroke ■ subarachnoid hemorrhage
aneurysm repair is set at <72 hours after ictus, unless the patient is in a moribund condition.\textsuperscript{5,6}

Recent studies have already extensively focused on the incidence of a rebleeding after aneurysm repair, especially related to the type of treatment.\textsuperscript{4,7} Although studies in the past have already showed that a rebleeding most frequently occurs in the first 24 hours after ictus,\textsuperscript{8-10} exact rebleeding rates in relation to time after ictus have never been undisputedly established.\textsuperscript{3} Moreover, although several risk factors have been linked to an early rebleeding in retrospective analyses of rather small series of patients,\textsuperscript{11-14} firm evidence about risk factors is lacking. In clinical practice, it is therefore still unknown which patients are at an increased risk for a rebleeding and thus require immediate aneurysm repair. In view of the aforementioned, it was our aim to identify risk factors for early rebleeding in relation to the exact time after ictus.

**Methods**

**Patients**

Between January 1998 and December 2014, 1620 consecutive patients with a subarachnoid hemorrhage (SAH) were admitted to our university neurovascular center. All clinical relevant data of these patients were prospectively collected. Given the observational design of the study and the fact that treatment of patients was according to standard clinical care, our institutional review board decided, according to Dutch regulations, that informed consent was not required. The study was registered in our local trial register (UTOPIA 1500132).

**Treatment Protocol**

A standardized multidisciplinary protocol is applied to all SAH patients admitted to our center. Before 2002, SAH patients were subject to digital subtraction angiography <12 hours after admission. Since 2002, all patients undergo immediate computed tomography (CT) angiography after established diagnosis of SAH, followed by digital subtraction angiography <48 hours in case of a negative CT angiography. All imaging is immediately evaluated by an interventional neuroradiologist and a vascular neurosurgeon. If an underlying intracranial aneurysm is detected, treatment (either endovascular coiling or neurosurgical clipping) is instigated as soon as technically and logistically feasible, also dependent on the patients' clinical condition. In case of a concomitant space-occupying hematoma, emergency craniotomy with evacuation of the hematoma and concomitant clipping of the aneurysm is performed. Antifibrinolytic therapy has not been used during the study time frame.

**Study Inclusion**

From the total of 1620 SAH patients, 1337 were aneurysmal, of whom 132 were excluded for this study: 101 patients with a fusiform or dissecting intracranial aneurysm, as well as 31 patients with a treated intracranial aneurysm in the past. As such, 1205 patients with a ruptured saccular intracranial aneurysm were considered eligible for this study (Figure 1).

**Imaging**

All available imaging of the included patients was reanalyzed by 2 reviewers (N.A.B. and C.E.D.) to agree on the amount of blood on the initial CT scan according to the modified Fisher (mFisher) scale\textsuperscript{15} (Table 1) and maximum diameter of the aneurysm. In patients harboring multiple intracranial aneurysms in whom it was not possible to identify the symptomatic aneurysm (n=43), the aneurysm location was designated as unknown. Imaging of patients admitted before 2000 was not available for reevaluation. Although the radiological reports of these patients were available, mFisher grade and maximum aneurysm diameter were considered unknown because these factors were frequently not taken into account.

**Data Analysis**

The following data were prospectively collected: age at time of aSAH, sex, history of SAH, presence of hypertension (defined as a systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg during multiple recent measurements or controlled using antihypertensive drugs), use of platelet inhibitors or vitamin-K antagonist, date and time of ictus, the World Federation of Neurosurgeons (WFNS) score \textsuperscript{16} on initial in-hospital assessment, aneurysm location and type, hydrocephalus, the timing of placement of a ventricular or lumbar drainage system for external CSF drainage, and time to aneurysm repair, rebleeding, or death because of any cause.

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**Figure 1.** Patient flowchart. SAH includes subarachnoid hemorrhage.
For this study, the location of the aneurysm was classified into: (1) the anterior cerebral arteries (including the anterior cerebral artery, anterior communicating artery, and pericallosal artery), (2) the middle cerebral artery, (3) posterior communicating artery, (4) other internal carotid artery aneurysms, (5) the basilar artery, and (6) other arteries in the posterior circulation (including the vertebral artery, cerebellar arteries, and posterior cerebral artery). Aneurysm size and age were both categorized into 5 consecutive groups, similar to the recent paper by Greving et al., whereas the amount of blood on the initial CT scan was classified according to the mFisher scale.

Outcome

The primary end point of this study was an in-hospital rebleeding ≤24 hours after the ictus. Rebleedings ≤72 hours were also analyzed. A rebleeding of the ruptured intracranial aneurysm was defined as a sudden clinical deterioration with a concomitant increase of subarachnoid, intracerebral, or intraventricular blood on the subsequent CT scan (performed <1 hour after onset of symptoms; n=65, 80%). A clinical deterioration was defined as a decrease in Glasgow Coma Scale (GCS) in awake patients. Patients in an already poor clinical condition are intubated and sedated and closely monitored on the intensive care unit (ICU) with the large majority already having an external ventricular catheter. In case of a sudden change of blood pressure, pupil size or fresh blood coming out the CSF drainage system, a CT is performed to confirm a rebleeding. Patients who suddenly died without CT confirmation of a rebleeding (n=16, 20%) were classified as a rebleeding if similar signs and symptoms occurred or if the external CSF drainage system produced fresh blood. The time of rebleeding after ictus was determined at time of onset of symptoms or by the time of the confirmatory CT scan.

Statistical Analysis

Events (rebleedings) ≤24 hours were measured from time of ictus until time of rebleeding in hours. Patients without a rebleeding (controls) were censored at the time of aneurysm repair or death because of any cause. One minus survival curves were depicted by the method of Kaplan–Meier. Log-rank tests were applied when deemed necessary. Categorical data are presented as counts and percentages. Continuous variables are presented as mean with SD or medians with interquartile ranges, depending on normality of data. Hazard ratios (HRs) for a rebleeding were obtained using multivariable Cox proportional hazard survival analysis. After univariate analysis of all clinically relevant covariates, those with a P value <0.15 were included in the initial multivariable model. A backward elimination strategy was used to achieve the most suitable model to estimate the adjusted hazard ratios with the final multivariable model only including covariates associated with a rebleeding at a level of P<0.10. Numbers needed to treat and 95% confidence intervals (CIs) of patients with a high mFisher grade (3–4) to prevent 1 rebleeding ≤24 hours with an ultraearly treatment strategy were calculated as the reciprocal of the absolute risk reduction. A rebleeding ≤3 hours after ictus was considered nonpreventable. A 2-tailed P value of 0.05 was considered to indicate statistical significance. All analyses were performed using SPSS software (version 22.0, SPSS Inc.).

Results

Baseline Patient Characteristics

Patient characteristics are shown in Table 2. Of all patients, a female predominance was observed (67%), and median age was 55 years (interquartile range, 46–64 years). A group of 374 patients (31%) was in a poor clinical condition (WFNS 4/5) at time of admission. Aneurysms of the anterior cerebral arteries followed by the middle cerebral artery were most frequently observed. A total of 286 patients (21%) required external CSF drainage before aneurysm repair because of acute hydrocephalus ≤24 hours after the ictus.

Cumulative Incidence of Early Rebleeding After aSAH and Treatment

Rebleeding ≤24 hours was confirmed in 70 of 1205 patients (5.8%); an additional 11 of 906 patients (1.2%) had a rebleeding between 24 and 72 hours after the ictus; 299 patients had already been censored during the first 24 hours. Of all patients with a rebleeding, 46 patients (57%) died as a result of the rebleeding. The mortality attributed to a rebleeding was not associated with time of rebleeding after ictus (data not shown). The incidence of an early rebleeding in relation to the exact time after ictus is depicted by the Kaplan–Meier analyses as shown in Figure 2A with censoring of cases at time of aneurysm repair or death because of any cause. Median time of aneurysm repair in all patients treated <72 hours after ictus (n=648) was 31 hours (interquartile range, 21–47 hours).

Risk Factors for a Rebleeding ≤24 hours

After univariate Cox regression analysis, the following covariates were associated (P<0.15) with a rebleeding ≤24 hours (Table 3): hypertension, WFNS score at admission, larger aneurysm size, presence of an intracerebral hematoma, a higher mFisher grade, and external CSF drainage before aneurysm repair. Because of the observed strong dichotomization between mFisher grade of 0 to 2 and 3 to 4, the mFisher scale was dichotomized accordingly for further analysis. After multivariable analysis, an mFisher grade of 3 to 4 was associated with the occurrence of an early rebleeding (adjusted HR [aHR], 4.7; 95% CI, 2.1–10.6; P<0.001). Also initiation of external CSF drainage was statistically associated with a rebleeding (aHR, 1.7; 95% CI, 1.4–2.5; P<0.001). The rebleeding occurred with a median of 1 hour after initiation of CSF drainage (interquartile range, 0–2 hours). If the mFisher scale was not dichotomized but included as a categorical covariate in the initial multivariable model, it remained significantly associated with a rebleeding (data not shown). Overall,
Table 2. Baseline Patient Characteristics

<table>
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<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
</tr>
<tr>
<td>Total</td>
<td>1205 (100)</td>
<td>70 (6)</td>
<td>1135 (94)</td>
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<td>1 (&lt;1)</td>
<td>266 (99)</td>
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<td>226 (100)</td>
<td>5 (2)</td>
<td>221 (98)</td>
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<tr>
<td>3</td>
<td>177 (100)</td>
<td>10 (6)</td>
<td>167 (94)</td>
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<tr>
<td>4</td>
<td>406 (100)</td>
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<tr>
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<td>91 (100)</td>
<td>5 (5)</td>
<td>86 (95)</td>
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<tr>
<td>Intracerebral hematoma</td>
<td>187 (100)</td>
<td>19 (10)</td>
<td>168 (90)</td>
</tr>
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<td>Subdural hematoma</td>
<td>19 (100)</td>
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<td>17 (89)</td>
</tr>
<tr>
<td>External CSF drainage*</td>
<td>286 (100)</td>
<td>22 (8)</td>
<td>264 (92)</td>
</tr>
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</table>

WFNS indicates World Federation of Neurosurgeons Scale.
*Cerebrospinal fluid drainage ≤24 h, before treatment

The size of the aneurysm in relation with the risk of a rebleed ≤24 hours showed a trend (P=0.07), with a larger aneurysm being at a greater risk for a rebleeding, especially those with a diameter ≥20 mm (aHR, 4.4; 1.6–13.2; P=0.007).

The numbers needed to treat using an ultraearly treatment strategy in patients with a high mFisher grade (n=583) to prevent 1 rebleeding ≤24 hours was calculated 15 (95% CI, 10–32). As the mortality rate of patients having rebleeding ≤24 hours was 60%, the numbers needed to treat to prevent 1 death was 25 (95% CI, 15–75). The association between a rebleeding with the mFisher grade is illustrated in Figure 2B, in which the dichotomized mFisher scale in relation with the occurrence of a rebleeding as a function of time is graphically presented (log-rank, P<0.001).

Discussion

This study revealed some novel issues about the first 24 hours after aSAH. First, most importantly, a high mFisher grade (3 or 4) on the initial CT scan, that is, thick SAH with or without blood in both lateral ventricles, was identified as a strong independent predictor for rebleeding ≤24 hours. Second, initiation of external CSF drainage, either lumbar or ventricular, was found independently associated with a rebleeding ≤24 hours.

In our study, an mFisher grade of 3 or 4 was by far the strongest risk factor associated with a rebleeding ≤24 hours, also independent of the patient’s clinical condition as assessed by the WFNS score at admission. This is remarkable, as this observation illustrates that not only the clinical condition on admission (either measured by the Hunt and Hess or WFNS score) is predictive for a rebleeding, as suggested by others, but rather the amount of blood as measured by the mFisher scale. We speculate that the amount of blood is a surrogate marker of the defect size and stability of the ruptured aneurysm wall, irrespective of the patient’s clinical condition.

Our results also suggest that patients might be at an increased risk of rebleeding in case of external CSF drainage before aneurysm repair. This observation confirms previous reports in the literature already suggesting the association between external CSF drainage and a rebleeding. Although the majority of rebleedings occurred almost immediately after initiation of CSF drainage, a causal relation is still difficult to prove. In this respect is would be of interest to know whether the amount of CSF drainage also plays a role. A rebleeding after initiation of CSF drainage might be explained by the sudden change of the transluminal pressure over the already damaged and vulnerable aneurysm wall. This, in turn, interferes with the critically stable local anatomic situation after aSAH. Apart from larger aneurysm size, additional risk factors as identified in the past could not be confirmed. This is probably explained by the methodological design and small sample size of these previous studies.

Both the European Stroke Organization (ESO) and the American Stroke Association (ASA) have issued a guideline in which it is recommended that treatment of a ruptured intracranial aneurysm should be instigated as soon as logistically feasible to reduce the risk of a rebleeding, preferably <72 hours after the ictus. In clinical practice, interpretation of this recommendation is highly heterogeneous; some
neurovascular centers treat aSAH patients on an emergency basis, but a significant proportion of centers consider the treat-
ment of a ruptured intracranial aneurysm a daylight job, both
diagnostically and surgically. Some authors advocate the use
of antifibrinolytic therapy in the time frame between ictus and
aneurysm repair to avoid a rebleeding. Although this seems to
be the case, the incidence of delayed cerebral ischemia is also
significantly increased. It is therefore still unknown whether
the application of antifibrinolytic therapy is really useful.23
Currently, a prospective trial investigates whether ultraearly
administration of tranexamic acid prevents rebleeding and
subsequently also leads to a better outcome.24

It is clear that emergency aneurysm repair avoids the pos-
sible use of antifibrinolytic therapy. Such an early treatment
strategy was already advocated by Phillips et al25, reporting
that treatment of ruptured intracranial aneurysms ≤24 hours
was associated with improved clinical outcomes compared
with delayed treatment. The same conclusion was drawn
by Wong et al26 in their sub analysis of the Intravenous
Magnesium after Aneurysmal Subarachnoid Hemorrhage trial
as well as by Sandström et al.27 Oudshoorn et al28 made a plea
for a delayed treatment strategy, as outcome in their series did
not depend on aneurysm repair ≤24 hours instead of 24 to
72 hours. Their study, however, was based on a retrospective
chart review of a highly heterogeneous cohort. Moreover, the
24-hour cutoff point used in their study is highly question-
able because the large majority of rebleedings occurred much
earlier.

Of interest, in a recently published large retrospec-
tive comparative cohort study (n=1224), Park et al29 clearly
showed that emergency treatment (median time from admis-
sion to start of aneurysm repair 3 hours) was not only associ-
ated with a significantly lower rebleeding rate but also with an
improved clinical outcome.

Our study identified strong independent clinical predictors
for a rebleeding ≤24 hours after ictus in a large prospectively
kept cohort of aSAH patients. In our opinion, these results
should lead to reconsideration of current clinical practice;
patients with a high mFisher grade (3 or 4) might benefit from
immediate aneurysm repair 24/7, particularly if they are in a
relatively good clinical condition (WFNS I–III). This change
in treatment paradigm would be in line with recent changes
in the treatment of ischemic stroke, in which it has become
apparent that immediate endovascular intervention (<6 hours)
is beneficial in a subgroup of patients.30

Obviously, our findings provoke the question whether
ultraearly treatment with the inevitable avoidance of rebleed-
ings is also associated with improved clinical outcome.
Theoretically, a possible disadvantage of an ultraearly treat-
ment strategy, especially when performed at night, might be
an increase in treatment-related complications. Although Park
et al recently showed that this is not likely,28 a randomized
controlled trial comparing ultraearly treatment versus conven-
tional treatment would be needed to unequivocally answer this
question. Apart from the highly questionable ethical feasibil-
ity of such a trial, it is to be expected that prevention of a
rebleeding at least improves survival.

Some limitations of our study need to be addressed. The
analyses of our prospectively kept cohort were retrospectively
performed. As a result, not all previously reported predic-
tors for a rebleeding could be assessed. Although premorbid
hypertension was assessed, hypertension on admission, espe-
cially elevated systolic blood pressure, was not included in
our model. This might have influenced our results because this
variable has been associated with a rebleeding in previous stud-
ies. Also, missing imaging at the reevaluation of the mFisher
scale and aneurysm size may theoretically have influenced
our results. Although from a clinical point of view, there is no
reason to think that cases with an unknown mFisher scale and
aneurysm size differ in any other way from the fully observed
data set. About the generalizability of our conclusions and
recommendations, a remark has to be made about nondensely
populated areas and countries with fewer resources; in such
areas, it obviously will be difficult to achieve an ultraearly
treatment strategy as proposed. Finally, an underestimation
of the incidence of an early rebleeding after aSAH is likely
because unmistakably a group of patients may already have
rebleeding before admission. Also, theoretically, patients on

Figure 2. A and B, Kaplan–Meier one minus survival analyses of patients with a rebleeding <72 hours after ictus (A) and dichotomized
according to the mFisher scale (grade 0–2 versus 3–4; B). SAH includes subarachnoid hemorrhage.
the ICU in an already poor clinical condition might have a rebleeding without clear signs of it because they are intubated and sedated. However, as these patients are closely monitored on the ICU, with the large majority of these patients also having an external ventricular catheter, it is unlikely that this has actually happened.
In our opinion, timing of treatment of aSAH patients, especially those with an mFisher grade of 3 or 4 in a good clinical condition, should be reconsidered. This category of aSAH patients might be regarded a medical emergency, requiring aneurysm repair as soon as possible, preferably 24/7. In this respect, our findings should provoke the debate on the best timing of aneurysm repair, especially in patients considered at risk for rebleeding.

Acknowledgments

C.E. Van Donkelaar built the database, coanalyzed data, and revised the article. Dr Bakker built the database, drafted the manuscript, and performed all analyses. Dr Veeger performed all analyses and revised the article. Dr Uyttenboogaart performed endovascular treatment and revised the article. Dr Metzemaekers has treated the majority of aneurysm patients and revised the article. Dr Groen facilitated the study and revised the article. Dr Luijckx is involved in treatment and revised the article. Dr Bakker built the database, drafted the manuscript, and revised the article. Dr Groen facilitated the study and revised the article. Dr Van Dijk created and supervised the study and codrafted the article.

Disclosures

None.

References

Predictive Factors for Rebleeding After Aneurysmal Subarachnoid Hemorrhage: Rebleeding Aneurysmal Subarachnoid Hemorrhage Study
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