uality of care for aneurysmal subarachnoid hemorrhage

From theoretical considerations to practical implementations

H.D. Boogaarts

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Dedicated to all patients suffering from aneurysmal subarachnoid hemorrhage

Contents

Chapter 1

General introduction

HISTORICAL PERSPECTIVE

It is thought that Bonet in 1679 and Wiseman in 1696 were the first to identify that intracranial aneurysms are causative of subarachnoid hemorrhage (SAH).[3] The earliest verified case-report of a ruptured intracranial aneurysm (basilar artery) is probably that of Blackall in 1814.[1,2] Initial reports on the surgical management of ruptured aneurysms concerned craniotomies that were conducted to treat suspected brain tumors, with intracranial aneurysms subsequently being discovered during this surgery.[8] In 1885, Victor Horsely was the first to carry out a ligation of both carotid arteries for the treatment of an intracranial aneurysm.[13] Norman Dott then performed a successful wrapping of an aneurysm in 1931.[7] A major step forward in aneurysm treatment was achieved by Walter Dandy in 1937, who was the first to use a metal clip to obliterate an aneurysm.[4] Simultaneously, the advent of the cerebral angiography as a result of the work by Egas Moniz in the early 1930s made the imaging of the aneurysms possible.[17] The introduction of the operation microscope by Yasargil and the use of associated micro-instrumentation in the 1960s led to a dramatic improvement in results.[14] Further advancements were made in using the calcium antagonist nimodipine and maintaining a high fluid intake to reduce the risk of delayed cerebral ischaemia.[21] Surgical clipping remained the only treatment option for treating aneurysms for decades. However, the development of the Guglielmi detachable coil (GDC) in 1990 made endovascular treatment possible.[9,10] Increased experience of this technique finally led to the International Subarachnoid Aneurysm Trial (ISAT), where open surgical clipping was compared to endovascular coiling for the treatment of ruptured aneurysms.[16] The outcome of this trial, which was interrupted following an intermediate analysis, revealed that endovascular coiling produced significantly better results in terms of survival free of disability at 1 year.[16] Despite the possible, slightly increased, long-term risks of aneurysmal regrowth and re-bleeding that are associated with endovascular treatment, a shift occurred towards coiling as the preferential treatment modality. Surgical clipping does, however, remain the treatment of first choice for a small subset of aneurysms, for example, those that are broad-based or when simultaneous hematoma evacuation must be performed. New developments of catheters and devices like stents, intrasaccular flow disruptors, and flowdiverters will probably further increase the number of patients treated endovascularly.

EPIDEMIOLOGY

The incidence of aneurysmal subarachnoid hemorrhage (aSAH) is about 9 per 100,000 per year, and is a major cause of death and disability.[15,18] The mean age at presentation is between 50 and 60 years.[27] The incidence rate of rebleeding after an SAH has been estimated to be about 15% during the first 24 hours, and has a high associated mortality rate of up to 50%.[19] Closure of the aneurysm after initial SAH is the primary goal to prevent aneurysmal rebleeding. Common associated problems like intra cerebral hematoma or hydrocephalus require emergency neurosurgical treatment. Although the case fatality rate has declined over the years, it still remains substantial at about 30 to 40%.[18] Outcomes are mainly determined by the clinical grade at admission, and are further influenced by age and the extent of the bleeding.[12] Additionally, treatment complications and secondary complications like hydrocephalus and delayed cerebral ischemia further determine the course of the disease.[20] Rehabilitation is an essential part of treatment after the initial hospital stay. Recovery after an SAH can be a long-term process, and may take up to several years.[26] Independence in terms of daily life activities is achieved in 36–51% of the patients. Cognitive dysfunction is a major cause of difficulties in returning to work, mood disturbances, and a reduced quality of life.[23]

QUALITY OF CARE

Pioneering work with respect to quality evaluation in healthcare has been conducted by Avedis Donabedian, who described quality design in relation to the three-part classification of a structure, process, and outcome model. Structure refers to the conditions under which care is provided, and it includes material and human resources as well as organizational characteristics.[5,6] The activities that constitute healthcare are assessed by process measures i.e. the actual process of healthcare, including diagnosis, treatment, rehabilitation, prevention, and patient education by professionals. Additionally, patients themselves, as well as their families, are also considered to be contributors to healthcare delivery. Outcome, meanwhile, measures the results of healthcare, which are also related to factors of a disease itself.

More recently, the theme of quality has been redefined by Porter.[22] Central in his view of quality is the concept of value which is characterized as the health outcomes achieved per dollar spent. This is defined around patients and unites all the interests of the actors in the system. Improving performance and accountability depends on having this shared goal. The result of care is not represented in a single outcome, although multiple, sometimes competing, outcomes do define success. In order to determine relevant outcomes, they can generally be divided into three 2-level tiers: The first tier contains the health status achieved or retained (survival is the most important level and the degree of recovery the second level). The second tier incorporates the time to recovery, the time to return to normal activities at level one, and the disutility of care-like complications on another level. The third tier is the sustainability of health, and is divided into a level of sustainability of health or recovery and the nature of recurrences, and another level of the long-term consequences of therapy. The precise definition of these outcomes is disease specific. An SAH specific outcome in tiers is provided in Table 1.1. The measurement of outcomes should be performed with at least one outcome dimension in each tier. These outcomes, weighted with the costs associated with an entire care cycle, define value.

Quality measurement will contribute to quality improvement. Improvements in healthcare are generally seen as a continuous process. Several strategies or combinations thereof are in use, such as plan-do-study-act, six-sigma, and lean.[25] Key in these improvement strategies is the cycle of measurement and the feedback of changes implemented to the system.

Table 1.1 Outcome Tier in aSAH

	General description	Aneurysmal SAH
Tier 1 Health status achieved or retained	Survival Degree of health or recovery	Mortality rate mRS, GOS
Tier 2 Process of recovery	Time to recovery and time to return to normal activities	(Time to) return to work
	Disutility of care or treatment process (e.g. diagnostic errors, ineffective care, treatment-related discomfort, complications, adverse effects)	Rebleed Complications
Tier 3 Sustainability of health	Sustainability of health or recovery and nature of recurrences	Residual aneurysm Rebleed after treatment Re-treatment
	Long-term consequences of therapy (e.g. care-induced illnesses)	Coping problems due to insufficient aftercare

The outcome measures hierarchy after Porter adopted for aneurysmal subarachnoid hemorrhage.[22] mRS: Modified Rankin Scale, GOS: Glasgow Outcome Scale.

SUBARACHNOID HEMORRHAGE AND QUALITY OF CARE

This thesis evaluates several aspects of the quality of care for patients with an aSAH. Structure measures have been used as a set of minimum standards for healthcare. Often, minimum volume standards are used for complex diseases and, as indicators of quality.[11,24] In the second chapter of this thesis, the relationship between hospital volume and outcomes for aSAH in the published literature is investigated.

Outcomes in the treatment of subarachnoid hemorrhage are strongly related to the clinical condition at presentation. In comparing outcomes, case-mix correction is essential. However, it is questionable whether co-morbid conditions have a significant impact on outcomes and should be accounted for. The Charlson co-morbidity index is a tool used to weight co-morbid conditions in predicting mortality. In the third chapter, the association between outcomes and this index is evaluated.

Preventing a rebleed is paramount in the treatment of patients with a ruptured aneurysm, since this symptom is associated with high morbidity and mortality. Currently, ultra-early (within 24 hours) treatment is advised for patients in a good clinical condition. Non-modifiable factors like a delayed diagnosis or a transfer from another hospital might delay treatment. On the other hand, suboptimal hospital logistics can be causative. In Chapter 4 aneurysm size as a risk factor for aneurysmal rebleeding is investigated in the literature to identify the patients who might benefit from ultra-early treatment.

In Chapter 5, procedure-related complications are investigated. Procedural complications can have devastating consequences for outcomes. The special focus of the evaluation concerns whether dual trained (open and endovascular) neurosurgeons have comparable results to open vascular neurosurgeons and interventional neuroradiologists. Having insight into the treatment-related complications of one's own results, and not just of those published in the literature, provides a starting point for the improvement cycle.

Care delivery should both be centered on the patient and investigate patients' needs. In Chapter 6, an online health community for patients with aSAH is described and evaluated from a patient's perspective.

The follow-up of patients treated with endovascular coiling after aneurysm rupture is required because recurrences occur in approximately 20% of those treated, leading to a need for retreatment in about 9% of cases. Digital substraction angiography (DSA) is considered to be the reference standard for evaluating aneurysms after coiling, although it has associated risks like cerebral thromboembolism and contrast nephrotoxicity, and utilizes ionizing radiation. Magnetic Resonance Angiography (MRA) is also used, and is more commonly available, and eliminates the previously-mentioned risks. However, it remains questionable whether MRA techniques, especially in terms of time of flight or contrast-enhanced MRA, can be used for follow up imaging. In Chapter 7, the accuracy of TOF-MRA and CE-MRA is evaluated in terms of detecting residual flow in the follow-up of coiled intracranial aneurysms.

A quality registry has been developed (Quality Registry NeuroSurgery: QRNS) to compare outcomes with respect to the most important parameters between centers in the Netherlands. The development and structure of this registry are outlined in Chapter 8.

The different parts of this thesis are then discussed in Chapter 10, while recommendations are made for further improvements in the quality of care registration for patients with aSAH.

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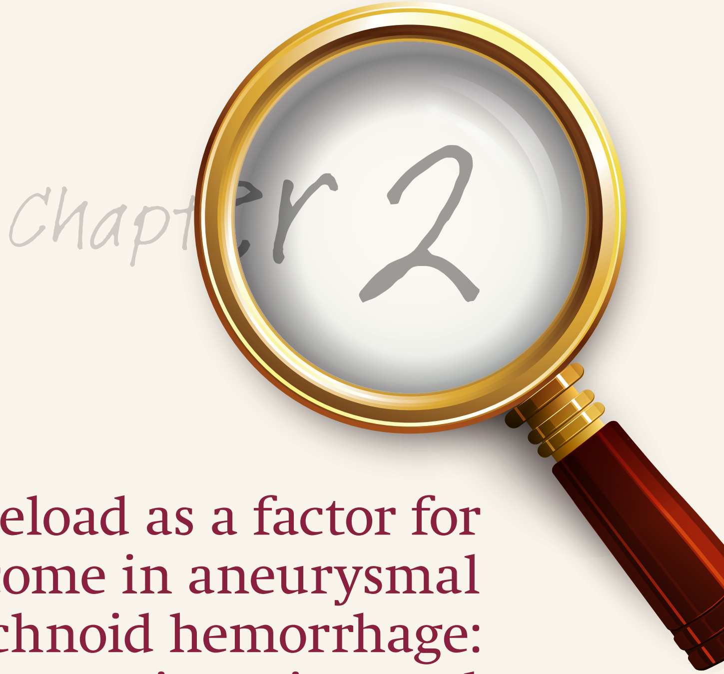

Caseload as a factor for outcome in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis

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ABSTRACT

Object Increasing evidence exists that treatment of complex medical conditions in high-volume centers is found to improve outcome. Patients with subarachnoid hemorrhage (SAH), a complex disease, probably also benefit from treatment at a high-volume center. The authors aimed to determine, based on published literature, whether a higher hospital caseload is associated with improved outcomes of patients undergoing treatment after aneurysmal subarachnoid hemorrhage.

Methods The authors identified studies from MEDLINE, Embase, and the Cochrane Library up to September 28, 2012, that evaluated outcome in high-volume versus low-volume centers in patients with SAH who were treated by either clipping or endovascular coiling. No language restrictions were set. The compared outcome measure was in-hospital mortality. Mortality in studies was pooled in a random effects meta-analysis. Study quality was reported according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria.

Results Four articles were included in this analysis, representing 36,600 patients. The quality of studies was graded low in 3 and very low in 1. Meta-analysis using a random effects model showed a decrease in hospital mortality (OR 0.77 [95% CI 0.60–0.97]; $p = 0.00$; $I^2 = 91\%$) in high-volume hospitals treating SAH patients. Sensitivity analysis revealed the relative weight of the 1 low-quality study. Removal of the study with very low quality increased the effect size of the meta-analysis to an OR of 0.68 (95% CI 0.56–0.84; $p = 0.00$; $I^2 = 86\%$). The definition of hospital volume differed among studies. Cutoffs and dichotomizations were used as well as division in quartiles. In 1 study, low volume was defined as 9 or fewer patients yearly, whereas in another it was defined as fewer than 30 patients yearly. Similarly, 1 study defined high volume as more than 20 patients annually, and another defined it as more than 50 patients a year. For comparability between studies, recalculation was done with dichotomized data if available. Cross et al., 2003 (low volume ≤ 18, high volume ≥ 19) and Johnston, 2000 (low volume ≤ 31, high volume ≥ 32) provided core data for recalculation. The overall results of this analysis revealed an OR of 0.85 (95% CI 0.72–0.99; $p = 0.00$; $I^2 = 87\%$).

Conclusions Despite the shortcomings of this study, the mortality rate was lower in hospitals with a larger caseload. Limitations of the meta-analysis are the not uniform cutoff values and uncertainty about case mix.

INTRODUCTION

Caseload in relation to outcome has been a topic of an increasing number of publications in the medical literature. Hospital volume and outcome are generally more strongly associated for medical conditions that require more complex management.[15,35] Regulations for centralization of specialized care are emerging from the medical field, government, and health insurance companies. For treatment of patients with ruptured cerebral aneurysms, a complex disease, several studies with contrasting results have appeared.[6,7,16] The purpose of this study was to perform a meta-analysis to investigate the relationship between caseload and outcome in series of patients undergoing treatment of aneurysms after subarachnoid hemorrhage (SAH). The treatment modality could be either clipping or coiling. Hospital mortality was chosen as the outcome measure.

METHODS

The meta-analysis was constructed according to the MOOSE (meta-analysis of observational studies in epidemiology) guidelines.[37] An independent experienced librarian searched the literature published in MEDLINE, Embase, and the Cochrane Library through September 28, 2012, using the following key words: SAH, case load, outcome, aneurysm. No language restrictions were used. For a detailed search string please see Table 2.1. Studies were eligible for inclusion if they met the following criteria: 1) evaluated in-hospital mortality after open and/or endovascular treatment in patients with ruptured intracranial aneurysms, 2) compared low-volume with high-volume hospitals, and 3) provided an odds ratio or core data to calculate an odds ratio. If the same data were used in more than one article, the most recent or largest data set was included. Duplicate papers were removed. Conference abstracts, reviews, editorials, meta-analyses, and animal studies were also excluded. Studies were excluded if they did not provide postoperative mortality rates in patients treated for ruptured aneurysms with endovascular coiling or surgical clipping in relation to volume. Two researchers (M.v.A. and H.D.B.) independently reviewed the titles and abstracts of the articles. In the case of disagreement during this process, a third reviewer (J.d.V.) was asked. From the remaining articles, full-text versions were obtained and were independently evaluated by the same researchers. From the full-text versions, reference screening was performed to evaluate other possible studies. A data recording form, developed for this purpose, was used by 2 authors (M.v.A. and R.B.) for independent data extraction from each study. After extraction, data were reviewed and were compared by the first author. Disagreement was

Table 2.1 Search strategy and results of MEDLINE, Embase, and Cochrane Library searches*

Step	Search	Results		
		Pubmed	Cochrane	Embase
1	subarachnoid hemorrhage[Mesh:noexp]	14,980	375	26,035
2	subarachnoid haemorrhage[tiab] OR (subarachnoid[tiab] AND hemorrhage[tiab]) OR subarachnoid hemorrhage[tiab] OR subarachnoid haemorrhages[tiab] OR subarachnoid hemorrhages[tiab] OR SAH[tiab] OR SAHs[tiab] OR subarachnoid hematoma[tiab] OR subarachnoid bleeding[tiab]	17,916	930	22,474
3	Step 1 OR Step 2	22,212	1,214	31,404
4	intracranial aneurysm[Mesh]	19,901	333	23,962
5	(brain aneurysm[tiab] OR brain aneurysms[tiab] OR cerebral aneurysm[tiab] OR cerebral aneurysms[tiab])	4,006	372	5,034
6	Step 4 OR Step 5	20,790	492	30,331
7	rupture*[tiab]†	86,436	2,304	102,580
8	Step 6 AND Step 7	5,423	193	4,981
9	Step 3 OR Step 8	24,675	985	33,626
10	"neurosurgery/statistics and numerical data"[mesh]‡	1,923	13	964
11	workload[Mesh]	13,778	487	24,873
12	high volume[tiab] OR high volumes[tiab] OR high-volume[tiab] OR higher volume[tiab] OR higher volumes[tiab] OR low volumes[tiab] OR lower volumes[tiab] OR low-volume[tiab] OR lower-volume[tiab] OR workload[tiab] OR (work[tiab] AND load[tiab]) OR caseload[tiab] OR caseloads[tiab] OR surgeon volume[tiab] OR workloads[tiab] OR surgical volume[tiab] OR operative volume[tiab] OR surgical volumes[tiab] OR operative volumes[tiab] OR (case[tiab] AND load[tiab]) OR case volume[tiab] OR case volumes[tiab] OR operation rate[tiab] OR operation rates[tiab] OR hospital volume[tiab] OR hospital volumes[tiab] OR highest-volume[tiab] OR highest-volumes[tiab]	42,833	24,767	56,421
13	Step 10 OR Step 11 OR Step 12	54,269	24,778	71,050
14	Step 9 AND Step 13	76	35	152

* MeSH = Medical Subject Headings; noexp = no explosion of MeSH heading; tiab = title/abstract.
† The asterisk in this field indicates that rupture was a major topic of these articles.
‡ Quotation marks indicate that the entire phrase was searched.

solved by consensus. Assessment of the methodological quality of the studies included in the review was done according to the GRADE guidelines.[14] The studies were independently assessed by the 2 researchers (R.B. and J.d.V.) for limitations, indirectness, inconsistency, imprecision, and publication bias. Overall in-hospital mortality after open surgical and/or endovascular treatment in patients with SAH was defined as the primary end point.

Statistical analysis

To identify potential associations between hospital volume and mortality, a pooled odds ratio with 95% confidence intervals was constructed. The significance of the overall odds ratio was determined by the z-test. The Type I error was set at 0.05. The tests were 2-tailed. The random effects model was used as the preferable approach to manage potential between-study heterogeneity. Statistical heterogeneity across studies was quantified using the I^2 statistic. This statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[19] The I^2 statistic was calculated from Q (the Cochran heterogeneity statistic) as follows: $I^2 = 100\% \times (Q - df)/Q$. For sensitivity analysis, each study was removed in turn from the total, and the remaining studies were reanalyzed to identify the impact of each study on the overall result. Publication bias was graphically assessed using a funnel plot. In addition, Egger's test was used for quantitative assessment. Comprehensive Meta-Analysis software (version 2.2.046, BIOSTAT) was used for statistical analysis.

RESULTS

Included studies

The initial search revealed 263 studies (Table 2.1). After removing duplicate studies, abstracts from 211 studies, including one found by reference screening,[36] were evaluated. One hundred seventy-nine studies were excluded because they did not meet inclusion criteria. Thirty-two studies were considered for full-text evaluation.[1–13,16–18,20–23,25–27,30–34,36,38–40] Twenty-eight studies were excluded for the following reasons: 2 were review studies,[34,40] 5 had insufficient data,[5,8,10,36,39] 3 included treatment of unruptured aneurysms,[3,21,33] 8 contained single-center data,[4,6,11–13,22,30,31] 3 had no caseload comparison,[18,25,26] 2 did not have mortality as an outcome,[1,20] 1 was an editorial,[17] 3 had overlapping source data,[2,7,32] and 1 included only patients older than 65 years.[38] Therefore, 4 studies were included for final analysis (Figure 2.1).[9,16,23,27] The selected studies involved a total of 36,600 patients. Retrospective data from databases were used in 3 studies, and 1 evaluated data from a survey (Table 2.2). The treatment modality was clipping or endovascular coiling in 3 studies, and 1 study only evaluated open surgical results. Hospital volume definitions differed between studies. Cutoffs and dichotomizations were used as well as division in quartiles. Low volume was defined as 9 or fewer patients yearly in 1 study and as fewer than 30 in another. Similarly, high volume was defined as more than 20 patients annually in 1 study and as more than

50 patients annually in another. The definitions used in the articles were used for primary analysis. The methodological quality of 3 articles was graded as low and 1 as very low. Uprating was not performed (Table 2.3).

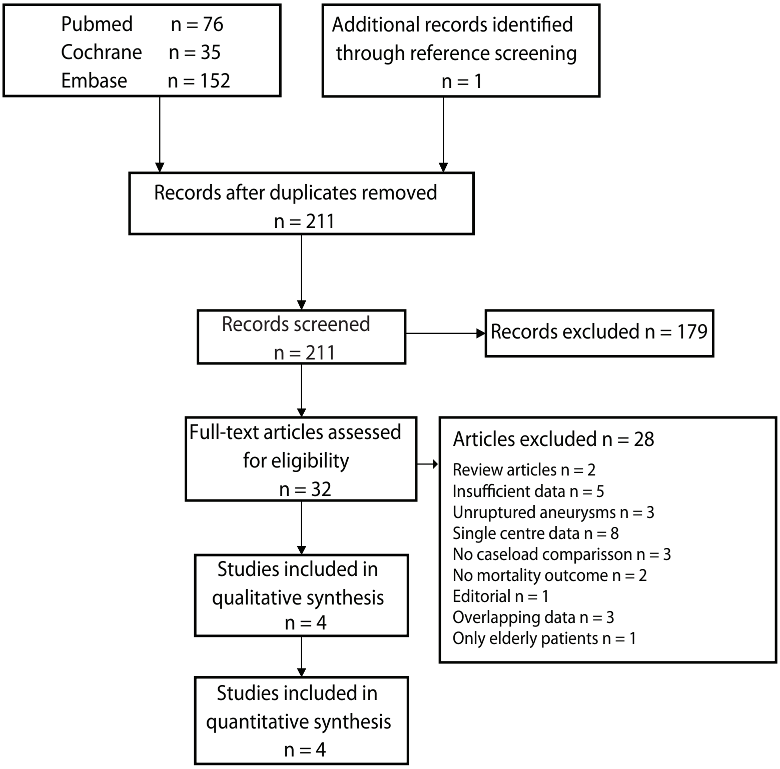


Figure 2.1 Chart showing the results of the literature search.

Table 2.2 Characteristics of the studies

			Definition of Vol	
Authors & Year	Source, Years	Treatment modality	Low	High
Johnston, 2000	University Health Systems Consortium, 1994–1997	Clipping & coiling	0–16 (1th quartile)	> 45 (4th quartile)
Cross et al., 2003	Database (California & Florida), 1998–2000	Clipping & coiling	0–9 (1th quartile)	36–158 (4th quartile)
Hattori et al., 2007	Survey Japan, 2003	Clipping	< 30 (1th group)	≥ 50 (3rd group)
Leake et al., 2011	Nationwide Inpatient Sample (NIS) database, 2001–2008	Clipping & coiling	≤ 20	> 20

Table 2.3 GRADE evidence profile

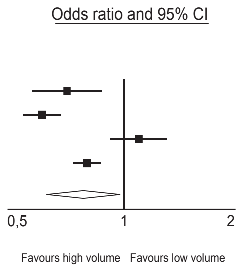
Authors & Year	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Pubication bias	Magnitude of effect	Quality
Johnston, 2000	Observational	None	None	None	None	None	None	Low
Cross et al., 2003	Observational	None	None	None	None	None	None	Low
Hattori et al., 2007	Observational	Serious	None	None	None	None	None	Very low
Leake et al., 2011	Observational	None	None	None	None	None	None	Low

Meta-analysis

The overall meta-analysis suggested a significant relationship for in-hospital mortality for SAH patients in favor of high-volume hospitals (OR 0.77 [95% CI 0.60–0.97] random model) (Figure 2.2A). The Q value for the test of heterogeneity was 33.2 (p = 0.0001), indicating heterogeneity and justifying the use of the random effects analysis. The sensitivity analysis revealed a relative weight of the study by Hattori et al.[16] Including this study and subsequently removing others by alternation lifted the point estimate slightly upward. The result was not statistically significant. However, removal of this study with very low quality (see Table 2.3) increased the effect size to an OR 0.68 (95% CI 0.56–84) (Figure 2.2B).[7] The funnel plot suggested publication bias; however, the Egger's test (intercept 1.21, p = 0.86 [2-tailed]) did not (Figure 2.3). This result should be interpreted with great caution, because of the very limited number of studies. For comparability between studies, recalculation was done with dichotomized data if available (Table 2.4). Cross et al. (low volume ≤ 18 patients, high volume ≥ 19 patients) and Johnston (low volume ≤ 31 patients, high volume ≥ 32 patients)

A: Meta-analysis high versus low volume hospitals

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Johnston, 2000	0,690	0,550	0,865	-3,209	0,001
Cross et al., 2003	0,586	0,517	0,664	-8,381	0,000
Hattori et al., 2007	1,100	0,915	1,322	1,016	0,310
Leake et al., 2011	0,786	0,719	0,859	-5,323	0,000
Overall	0,767	0,604	0,972	-2,190	0,029



B: Sensitivity analysis

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Johnston, 2000	0,791	0,588	1,065	-1,546	0,122
Cross et al., 2003	0,843	0,665	1,070	-1,401	0,161
Hattori et al., 2007	0,684	0,555	0,842	-3,574	0,000
Leake et al., 2011	0,762	0,512	1,133	-1,345	0,179
Overall	0,767	0,604	0,972	-2,190	0,029

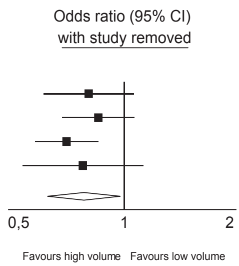


Figure 2.2 Forest plots showing results of the meta-analysis of high versus low volume hospitals (A) and sensitivity analysis (B).
The squares indicate the mean, the whiskers indicate the 95% CI, and the diamonds indicate the pooled estimate (the width of the diamond represents the 95% CI).

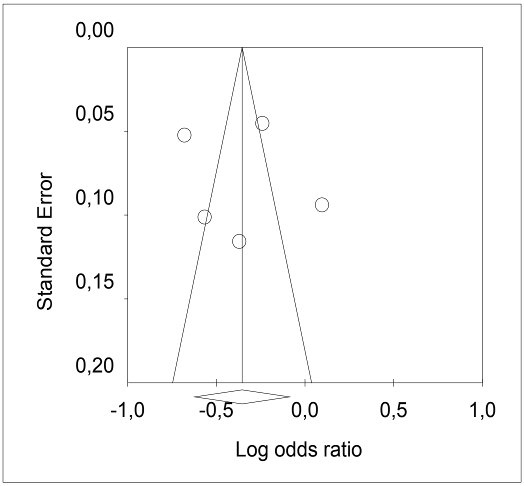


Figure 2.3 Funnel plot.
The *points* correspond to the treatment effects from individual studies, the *diagonal lines* show the expected 95% confidence intervals around the summary estimate. Odds ratios are plotted on a logarithmic scale.

provided core data for recalculation.[9,23] The overall results of this analysis of the 4 studies revealed an OR of 0.85 (95% CI 0.72–0.99).

DISCUSSION

This meta-analysis demonstrates that treatment of patients with ruptured intracranial aneurysms in high-volume centers is associated with lower in-hospital mortality compared with low-volume centers. The positive correlation between a high-volume center and outcome could be attributed to several factors. First of all, high-volume centers more likely have a subspecialized team working in a multidisciplinary setting. A well-functioning and experienced team consisting of neurologists, neurosurgeons, neuroradiologists, neurointerventionalists, neurorehabilitation specialists, neurointensivists, and a dedicated nursing team will certainly contribute to a better outcome.[5,8,24] A potential drawback of centralization would be the risk of rehemorrhage and death during transfer; however, as investigated by Bardach et al., the organization of SAH care in high-volume hospitals is justified not only for costeffectiveness but also for patient outcome.[1]

Several limitations of this study should be mentioned. First, the study data mainly rely on retrospective data based on hospital coding and can therefore be biased. Second, the patients within the studies were a selection of a population mainly from northern US

Table 2.4 Study core data*

	High-Vol Hospitals				Low-Vol Hospitals			
Authors & Year	Total	Deaths	Alive	Mortality	Total	Deaths	Alive	Mortality
Johnston, 2000	4,693 (7,573)	1,000 (1,730)	3,693 (5,843)	21.3% (22.8%)	408 (1,961)	115 (489)	293 (1,472)	28.2% (24.9%)
Cross et al., 2003	2,305 (4,787)	622 (1,387)	1,683 (3,400)	27.0% (29.0%)	2,268 (4,503)	877 (1,652)	1,391 (2,851)	38.7% (36.7%)
Hattori et al., 2007	2,522	257	2,265	10.2%	2,631	246	2,385	9.4%
Leake et al., 2011	8,247	1,004	7,243	10.6%	8,556	1,283	7,273	14.2%

* Values are the number of patients unless specified otherwise. Numbers in parentheses indicate the number of patients if dichotomization was used (see text).

databases. Infrastructural and geological characteristics might not be applicable to other countries. Third, the treatment modality might be associated with outcome and with hospital volume; centers also providing endovascular treatment have better results because of the lower associated morbidity and mortality rates as found in the International Subarachnoid Aneurysm Trial (ISAT) and recently the Barrow Ruptured Aneurysm Trial (BRAT).[28,29] High-volume centers are more likely to have an endovascular treatment modality and thus will probably have better results.[9,13] Fourth, we used unadjusted core data from the studies to attain comparability, since adjustment for case mix was not done or it was done in different ways. Hattori et al. corrected for initial clinical grade, but not for comorbidities and did not find a significant difference in the distribution of the World Federation of Neurosurgical Societies grade on admission between the different volume groups.[16] Cross et al. corrected for comorbidities but not for initial grade.[9] Leake et al. did not correct for comorbid conditions nor initial grade.[27] Johnston corrected for age but not for comorbidities or initial grade.[23] Fifth, the distinction between low volume and high volume is artificial. As shown, a uniform cutoff is not provided. At best, an approximate cutoff could be estimated. However, recalculation with dichotomized data revealed comparable results, centering the possible distinction between high volume and low volume around 20–30 patients yearly. Sixth, in-hospital mortality was chosen as the primary outcome measure; although commonly used as a measure of quality of care, it can be influenced by discharge policies. Better would be a more detailed outcome measure such as the modified Rankin Scale score; unfortunately, only the study by Hattori et al. provided these data.[16] Finally, transfer of patients might cause bias. Patients who were likely to die were not transferred to a high-volume center for treatment; conversely, transferred patients tended to do better than patients in community hospitals.[13,41]

This study does not answer the question of how much patients should be treated by a single surgeon or neurointerventionalist to obtain the best result.[3,26,39] As previously stated, the results of treatment are not merely the merits of one specialist but the chain of care. In the scope of quality of care and the increasing demand for centralization, volume number alone is not sufficient as a parameter to guide these developments. Caseload should be seen as one of the cofactors related to outcome.

CONCLUSIONS

Despite shortcomings of the included studies but based on the best available data at this moment, mortality is lower in hospitals that treat a high volume of patients with SAH.

Although a true cutoff value to distinguish between high- and low-volume centers could not be given, it probably can be centered between 20 and 30 patients annually. An explanation for the relationship between outcome and caseload could be a multidisciplinary approach resulting in a team dedicated to the care of patients with SAH. As such, the number of treated patients yearly cannot be used as a sole measure for quality of care.

Acknowledgment

We would like to thank Alice Tillema for the literature search.

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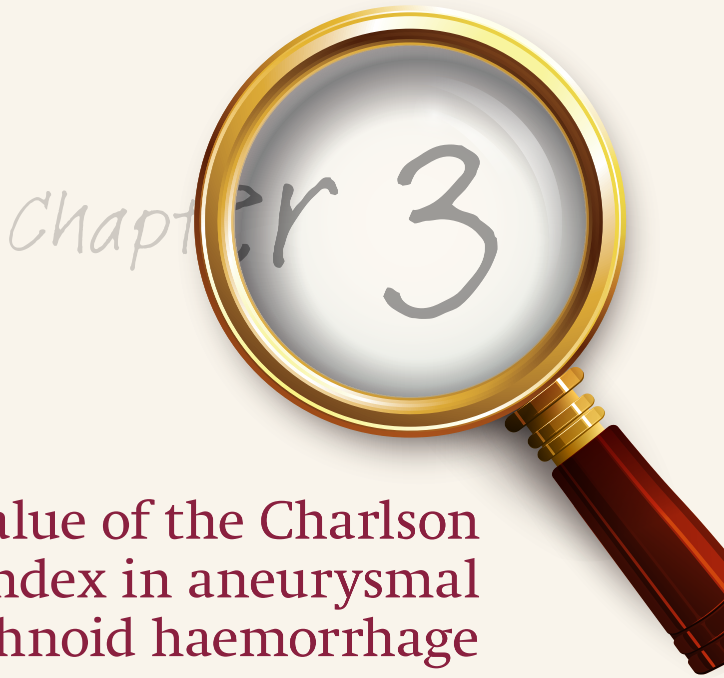

The value of the Charlson Co-morbidity Index in aneurysmal subarachnoid haemorrhage

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ABSTRACT

Background Several studies have included different comorbid conditions in prediction models for stroke patients. For subarachnoid haemorrhage (SAH), it is not known whether the Charlson Co-morbidity Index (CCI) is associated with outcome. We evaluated if this index was associated with outcome in patients with ruptured intracerebral aneurysms.

Methods The data of all consecutive aneurysmal SAH (aSAH) patients treated at the Radboudumc, Nijmegen, The Netherlands and entered in the database were retrospectively analysed. Clinical condition at admission was recorded using the WFNS (World Federation of Neurological Surgeons Grading System) grade was collected, as were the age and treatment modality. The burden of co-morbidity was retrospectively registered using the CCI. Outcome was dichotomised on the modified Rankin Scale (mRS; 0–2, favourable outcome; 3–6, unfavourable outcome). A binary logistic regression analysis was performed.

Results Between 6th May 2008 and 31st July 2013, 457 patients were admitted because of non-traumatic SAH (aSAH). Seventy-seven (16.8%) patients had no aneurysm. Of the 380 patients with aSAH, information on co-morbid conditions was available for 371 patients. Thirty-six of those 371 had no treatment because of: bad clinical condition in 34 (9.2%), a non-treatable dissecting aneurysm in 1 (0.3%) and the explicit wishes of another. Co-morbidity was present in 113 (31.5%) patients. Binary logistic regression analysis revealed no added value of using the CCI in predicting the outcome ($p = 0.91$).

Conclusions This study reports that the CCI is not associated with the outcome classified on the mRS at 6 months in patients after aSAH. The CCI has no added value in case-mix correction.

INTRODUCTION

The Charlson Co-morbidity Index (CCI) is an index used to weight co-morbid conditions in predicting mortality.[3] Depending on the strength of the relationship with mortality, between 1 and 6 points are assigned to a set of co-morbidities.[8] The CCI has been evaluated for use in cases of intracerebral haemorrhage and ischaemic stroke, but not for aneurysmal subarachnoid haemorrhage (aSAH).[1,8] Co-morbid conditions can, however, influence the outcome in SAH.[4–6,9,11,13,15,19] Aneurysmal SAH is a distinct group of stroke patients, in which perhaps other co-variables should be taken in to account when assessing the weight of the CCI. A recent review of prediction models in aSAH revealed the most commonly identified and valuable patient factors that are associated with outcome; namely, age and initial condition at presentation.[10] Treatment modality (endovascular coiling or clipping) is also known to influence outcomes.[12,14] The purpose of this study was to evaluate whether the CCI is associated with a 6-month functional outcome in aSAH.

METHODS

Retrospectively, the data of all consecutive aSAH patients treated in the Radboudumc, Nijmegen, The Netherlands from May 6th 2008 to July 31st 2013 were analysed. Clinical condition at admission as recorded by the WFNS (World Federation of Neurological Surgeons Grading System) scale was used in analysis, as were treatment modality and age.[7,21] The primary outcome was recorded using the modified Rankin Scale (mRS) after 6 months, because of protocolised combined imaging and clinical follow-up after the same period. The co-morbidities were extracted from the electronic patient files. The total CCI score for each patient was computed and four categories of co-morbidity were defined as previously used by others: 0 (none), 1 (moderate), 2 (severe) and 3 or higher (very severe).[1,20] The study was approved by the institutional review board. The results are reported according to the STROBE statement guidelines.[22]

Statistical analysis

A binary logistic regression analysis was performed using the mRS score as a dichotomised variable (0–2, favourable outcome; 3–6, unfavourable outcome). SPSS (version 20; SPSS, Chicago, IL, USA) was used for the statistical analysis and the significance was considered to be $p < 0.05$.

RESULTS

Between 6th May 2008 and 31st July 2013, 457 patients were admitted because of a non-traumatic SAH (aSAH). Seventy-seven (16.8%) patients had no aneurysm. Of the 380 patients with aSAH, eight (2.1%) did not have a follow-up because they returned to their home country. One (0.3%) patient had no information on his co-morbid condition, meaning that analysis was possible for 371 patients. Thirty-six of those 371 had no treatment (Figure 3.1). Treatment was preferentially endovascular in patients with aneurysms equally suitable for clipping or coiling. The last follow-up was 1st February 2014. The characteristics of the patients are set out in Table 3.1, while the frequency of each co-morbidity is provided in Table 3.2. The distribution of the CCI sum-scores is given in Figure 3.2, and is categorised according to severity within each outcome group in Table 3.3. Co-morbidity was present in 113 (31.5%) patients. There were no differences in CCI frequency distribution within the two outcome (mRS) categories (Pearson chi-squared test $p = 0.084$). A binary logistic regression analysis revealed no beneficial use of the CCI in predicting outcome (odds ratio, 1.020; $p = 0.91$) (Table 3.4). In this model, strong predictors of outcome were initial grade (WFNS), age and treatment modality (area under the receiver operating characteristic curve, 0.86; SE, 0.02). In a sub-analysis using no versus any co-morbidity, no added value was found ($p = 0.95$). An ordinal regression analysis using non-dichotomised mRS outcomes did not change the previous findings.

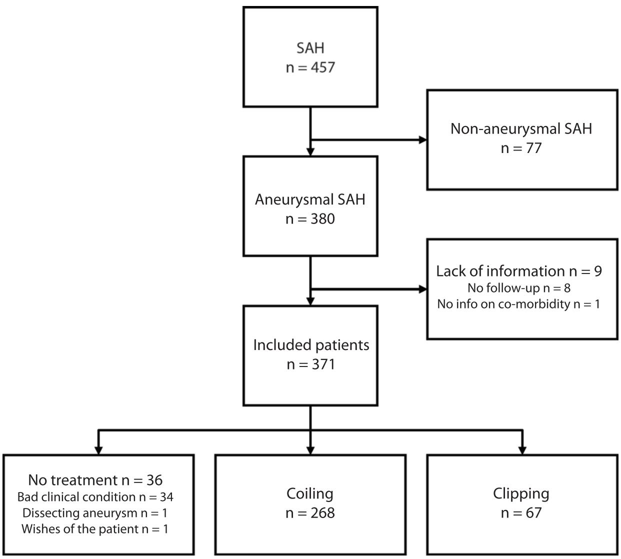

Figure 3.1 Flowchart for the progression of 457 patients admitted because of non-traumatic subarachnoid haemorrhage (SAH).

Table 3.1 Patient characteristics

Variable	n (%)
Sex	
Male	115 (31.0)
Female	256 (69.0)
Age, mean [SD]	55.4 [13.2]
WFNS	
I	133 (35.8)
II	82 (22.1)
III	15 (4.0)
IV	80 (21.6)
V	61 (16.4)
Treatment modality	
Clip	67 (18.1)
Coil	268 (72.2)
Not treated	36 (9.7)

n = number of patients; SD = standard deviation; WFNS = World Federation of Neurological Surgeons Grading System for SAH.

Table 3.2 Charlson Co-morbidity Index (CCI) categories in aneurysmal subarachnoid haemorrhage

Condition	CCI weight	Total frequency, n (%)
Myocardial infarct	1	11 (3.0)
Congestive heart failure	1	0 (0.0)
Peripheral vascular disease	1	15 (4.0)
Cerebrovascular disease	1	28 (7.5)
Dementia	1	0 (0.0)
Chronic pulmonary disease	1	30 (8.1)
Connective tissue disease	1	12 (3.2)
Ulcer disease	1	0 (0.0)
Mild liver disease	1	2 (0.5)
Diabetes	1	18 (4.9)
Diabetes with end-organ damage	2	0 (0.0)
Hemiplegia	2	2 (0.5)
Moderate or severe renal disease	2	6 (1.6)
Any tumour	2	21 (5.7)
Leukaemia	2	2 (0.5)
Lymphoma	2	0 (0.0)
Moderate or severe liver disease	3	0 (0.0)
Metastatic solid tumor	6	1 (0.3)
AIDS/HIV	6	0 (0.0)

AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus.

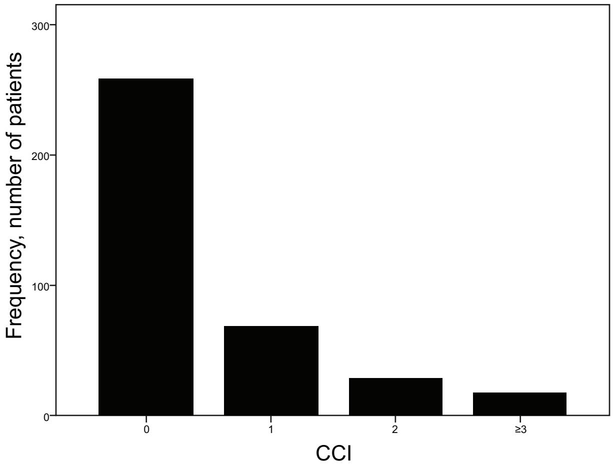

Figure 3.2 Distribution of the Charlson Co-morbidity Index (CCI) sum-scores.

Table 3.3 Cross-tabulation Charlson Co-morbidity Index (CCI) categories by dichotomised modified Rankin Scale (mRS)

	mRS		
CCI	0–2	3–6	Total
0	167 (72.6%)	91 (64.5%)	258 (69.5%)
1	39 (17.0%)	29 (20.6%)	68 (18.3%)
2	18 (7.8%)	10 (7.1%)	28 (7.5%)
≥ 3	6 (2.6%)	11 (7.8%)	17 (4.6%)
Total	230 (100%)	141 (100%)	371 (100%)

Percentages are given within mRS group.

Table 3.4 Odds ratios for variables in outcome analysis using binary logistic regression analysis. Higher odds ratio is related to worse outcome in dichotomised mRS

Variable	Odds ratio	Level of sign (p value)
Aage	1.052	0.00
WFNS*	2.067	0.00
CCI	1.020	0.91
Treatment (coil)	1.000	0.00
Treatment (clip)	2.205	0.02
Treatment (none)	47.544	0.00

Treatment reference group is coiling.
WFNS = World Federation of Neurological Surgeons grading system for SAH; CCI = Charlson Co-morbidity Index sum score.

DISCUSSION

The CCI for co-morbid conditions is not associated with the outcome at 6 months in aSAH in these data. The value of the CCI for acute ischaemic stroke and non-traumatic (non-aneurysmal) intracerebral haemorrhage (ICH) is often reported.[1,8,20] Stroke patients are generally much older, with a mean age of over 70 years, compared with aSAH patients in general and this cohort in particular (mean age, 55.4)[20,25] (Table 3.1). Increased age is associated with the increased prevalence of co-morbidities, and strokes share risk factors with many chronic diseases (e.g. myocardial infarction, diabetes).[20] Several limitations of this study have to be noted. First, the chart review was conducted retrospectively. However, studies including co-morbidity frequently rely on administrative hospital (coding) data that are retrospectively gathered.[4,6] Secondly, the analysis was carried out on 371 patients. If the investigated group of patients were larger, it is possible that there would have been a small significant result. Thirdly, the CCI was developed to predict 1-year mortality, but in our series we evaluated outcome at 6 months because of protocolised imaging and clinical follow-up. Recent studies have revealed that a minority of patients improve between 6 and 12 months.[23]

Contrasting reports have appeared for co-morbid conditions in aSAH.[1,4–6,8,13,18,19,24] Using administrative databases, O'Kelly et al.[16] found a significant increase in the hazards of death and re-admission for SAH per unit increase on the Deyo adaptation of the CCI (HR, 1.14 [1.08–1.21]; $p < 0.001$) in a retrospective cohort of 3,120 patients. Other reports evaluated several individual co-morbid conditions in relation to outcome for aSAH with predominantly negative or contrasting results (see Supplemental Table S3.1, which illustrates the value of co-morbidity in aneurysmal SAH reported in the literature). Meanwhile, Langham et al.[11] found a significant contribution of any co-morbid condition to outcome, which was defined as death or severe disability at 6 months, in a cohort of 2,397 patients (univariate, 1.87 [1.56–2.25], $p < 0.001$; multivariate, 1.46 (1.20–1.78), $p = 0.0003$). In the Langham report, the CCI itself was not used, and other co-morbid conditions like hypertension (not part of the CCI) were included. Finally, in their retrospective study of the treatment of ruptured and unruptured aneurysms, Cowan et al.[4] found that co-morbid conditions (not specifically in the form of CCI) were significant predictors of death (OR, 1.08 [1.04–1.12], $p < 0.001$, for each condition increase).

For a comparison of outcome in the treatment of aSAH, case-mix correction is essential. A major clinical variable is initial grade as evaluated by the WFNS scale. The odds ratio associated with WFNS is reported to be between 2.14 and 13.51 depending on the grade.[17,18]

De Toledo found a relative risk for poor outcome (Expβ) dependent on the WFNS scale of 3.43–78.1. An often reported co-morbid condition associated with bad outcome is hypertension, but this is not included in the CCI.[5,13,18,19]

Due to the evolving interest in healthcare outcomes overall, the registration burden is growing enormously. To increase data entry by healthcare providers, focusing on items of significant interest is of utmost importance. This study will contribute to the selection of items that are relevant for outcome measurement of SAH; strong predictors of outcome were initial grade, age and treatment modality. Regarding treatment modality, we had a relatively high ratio of endovascular treated patients. According to a European internet survey, high-volume centres have a significantly higher proportion of coiled ruptured aneurysms in comparison with low-volume centres.[2] Within these high volume centres, we are at the high end of the spectrum of proportion coiled aneurysms. We showed that the CCI as a whole set of co-morbidity parameters is not associated with clinical outcome.

CONCLUSIONS

This study reports that the CCI is not associated with the outcome classified on the mRS at 6 months in patients after aSAH. The CCI has no added value in case-mix correction.

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SUPPLEMENT

Supplemental Table S3.1 Reported value of co-morbidity in aneurysmal SAH in literature

Condition \ Author, year	Cowan et al., 2003[1]	Cross et al., 2003[2]	Crowley et al., 2009[3]	Mocco et al., 2006[4]	Rosen et al., 2004[5]	Rosengart et al., 2007[6]	Zacharia et al., 2009[7]
Myocardial infarct	NS	Sign	-	NS	-	NS	-
Congestive heart failure	NS	Sign	NS	NS	-	-	-
Peripheral vascular disease	NS	-	-	-	-	-	-
Cerebrovascular disease	NS	-	-	NS	-	-	-
Dementia	NS	-	-	-	-	-	-
Chronic pulmonary disease	Sign	NS	NS	-	-	-	-
Connective tissue disease	NS	-	-	-	-	-	-
Ulcer disease	NS	-	-	-	-	-	-
Mild liver disease	NS	-	Sign	-	NS	NS	-
Diabetes	NS	NS	NS	NS	NS	NS	Sign
Diabetes with end-organ damage	NS	NS	NS	NS	NS	NS	-
Hemiplegia	NS	-	-	-	-	-	-
Moderate or severe renal disease	Sign	-	NS	NS	-	-	-
Any tumor	NS	-	-	-	-	-	-
Leukemia	NS	-	-	-	-	-	-
Lymphoma	NS	-	Sign	-	-	-	-
Moderate or severe liver disease	NS	-	-	-	NS	NS	-
Metastatic solid tumor	NS	NS	NS	-	-	-	-
AIDS/HIV	NS	-	NS	-	-	-	-

Sign = statistically significant; NS = statistically not significant; - = not evaluated; AIDS = Acquired Immune Deficiency Syndrome; HIV = Human Immunodeficiency Virus.

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Chapter 4

Aneurysm diameter as a risk factor for pretreatment rebleeding: a meta-analysis

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ABSTRACT

Object Aneurysmal rerupture prior to treatment is a major cause of death and morbidity in aneurysmal subarachnoid hemorrhage. Recognizing risk factors for aneurysmal rebleeding is particularly relevant and might help to identify the aneurysms that benefit from acute treatment. It is uncertain if the size of the aneurysm is related to rebleeding. This meta-analysis was performed to evaluate whether an association could be determined between aneurysm diameter and the rebleeding rate before treatment. Potentially confounding factors such age, aneurysm location, and the presence of hypertension were also evaluated.

Methods The authors systematically searched the PubMed, Embase, and Cochrane databases up to April 3, 2013, for studies of patients with aneurysmal subarachnoid hemorrhage that reported the association between aneurysm diameter and pretreatment aneurysmal rebleeding. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria were used to evaluate study quality.

Results Seven studies, representing 2,121 patients, were included in the quantitative analysis. The quality of the studies was low in 2 and very low in 5. Almost all of the studies used 10 mm as the cutoff point for size among other classes, and only one used 7 mm. An analysis was performed with this best unifiable cutoff point. Overall rebleeding occurred in 360 (17.0%) of 2,121 patients (incidence range, from study to study, 8.7%–28.4%). The rate of rebleeding in small and large aneurysms was 14.0% and 23.6%, respectively. The meta-analysis of the 7 studies revealed that larger size aneurysms were at a higher risk for rebleeding (OR 2.56 [95% CI 1.62–4.06]; $p = 0.00$; $I^2 = 60\%$). The sensitivity analysis did not alter the results. Five of the 7 studies reported data regarding age; 4 studies provided age-adjusted results and identified a persistent relationship between lesion size and the risk of rebleeding. The presence of hypertension was reported in two studies and was more prevalent in patients with rebleeding in one of these. Location (anterior vs posterior circulation) was reported in 5 studies, while in 4 there was no difference in the rebleeding rate. One study identified a lower risk of rebleeding associated with posterior location aneurysms.

Conclusions This meta-analysis showed that aneurysm size is an important risk factor for aneurysmal rebleeding and should be used in the clinical risk assessment of individual patients. The authors' results confirmed the current guidelines and underscored the importance of acute treatment for large ruptured aneurysms.

INTRODUCTION

The incidence of aneurysmal subarachnoid hemorrhage (SAH) is about 5–10 cases per 100,000.[21,26] Closure of the aneurysm after initial SAH is the primary goal to prevent aneurysmal rebleeding, which has an associated mortality rate of up to 50%.[32] The incidence of rebleeding after an SAH has been estimated to be 14%–17% during the first 24 hours, and studies have shown that 87%–92% of all rebleeding occurs within the first 6 hours after the initial bleed.[9,32] Endovascular coiling or clipping to secure the aneurysm is advised as early after rupture as is feasible to reduce the rate of rebleeding.[8] Currently, ultra-early treatment, considered to be within 24 hours, is advised for patients in good clinical condition.[34] Although nonmodifiable causes, such as transfer from other hospitals and late diagnosis, might delay treatment, ultra-early treatment can also be difficult due to internal logistics issues like limited 24/7 surgical coverage and access to operating theaters and anesthetic and nursing staff.[34]

Recognizing risk factors for aneurysmal rebleeding is particularly relevant and might help to identify the aneurysms that benefit from acute treatment. In recent years, several risk factors, such as hypertension and the location and size of the aneurysm, have been shown to be associated with rebleeding.[9,10,19,28,37] Biomechanical studies have indicated that cerebral aneurysmal rupture occurs when there is a decrease in the ratio of the artery wall thickness to the radius of the aneurysm.[7] This concept might explain the possible relationship between aneurysm diameter and the risk of rebleeding. However, the association between the risk of rebleeding and aneurysm size might be confounded by age.[28] In particular, older patients may have larger aneurysms, and their general condition makes it more likely that treatment is postponed, leaving these individuals more prone to rebleeding. This meta-analysis was performed to evaluate whether an association could be established between aneurysm diameter and rebleeding rate before treatment. Potentially confounding factors like age, aneurysm location, and the presence of hypertension were also evaluated.

METHODS

Search strategy and selection criteria

The meta-analysis was constructed using the MOOSE guidelines.[38] In particular, an independent, experienced librarian systematically searched the PubMed, Embase, and Cochrane databases up to April 3, 2013, for studies of patients with aneurysmal SAH that reported the association between aneurysm diameter and pretreatment aneurysmal rebleeding. The search strategy is set out in Table 4.1.

Data extraction

Two authors (J.V.L. and H.B.) independently read all titles and abstracts and selected those that appeared to be relevant for a full text review without language restrictions. Conference abstracts, reviews, meta-analyses, editorials, and animal studies were excluded. From the remaining studies, full-text articles were obtained and independently evaluated by two of the authors (J.V.L. and H.B.). Studies were deemed to be eligible if they included: 1) patients with SAH in either a prospective or retrospective population-based design; 2) the association between aneurysm diameter and the rebleeding rate; and 3) results that included or enabled the calculation of an odds ratio. A third author (R.B.) was consulted to resolve any disagreements. Reference screening was conducted to identify additional studies from the full-text articles that were evaluated. Included studies were selected for a quality review. The

Table 4.1 Search strategy and results in Pubmed, EMBASE and Cochrane databases

		No. of studies		
Step	Search terms	Pubmed	Embase	Cochrane
1	subarachnoid haemorrhage.ti,ab. OR Subarachnoid Hemorrhage[Mesh:noexp] OR (subarachnoid.ti,ab. AND hemorrhage.ti,ab.) OR subarachnoid hemorrhage.ti,ab. OR subarachnoid haemorrhages.ti,ab. OR subarachnoid hemorrhages.ti,ab. OR SAH.ti,ab. OR SAHs.ti,ab. OR subarachnoid hematoma.ti,ab. OR subarachnoid bleeding.ti,ab. OR ((Brain Aneurysm.ti,ab. OR brain aneurysms.ti,ab. OR Cerebral Aneurysm.ti,ab. OR cerebral Aneurysms.ti,ab. OR "Intracranial Aneurysm"[Mesh]) AND (rupture*.ti,ab.)))))†‡	25,423	35,627	998
2	("Recurrence"[Mesh] OR Recurrence.ti,ab. OR Recurrences.ti,ab. OR Rebleed*.ti,ab.)	306,816	339,678	21,206
3	Step 1 AND Step 2	1,844	2,151	75
4	("Risk"[Mesh] OR Risk.ti,ab. OR sized.ti,ab. OR sizes.ti,ab. OR 10 mm.ti,ab. OR 7 mm.ti,ab. OR 5 mm.ti,ab. OR 6 mm.ti,ab. OR 8 mm.ti,ab. OR 9 mm.ti,ab. OR diameter.ti,ab.)	1,849,179	2,355,608	111,279
5	Step 3 AND Step 4	610	773	25
6	Limits: none	610	773	25

MeSH = Medical Subject Headings; mm = millimeter; noexp = no explosion of MeSH heading; ti,ab = title/abstract.
† The asterisk in this field indicates that rupture was a major topic of these articles.
‡ Quotation marks indicate that the entire phrase was searched.

methods recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for rating the quality of evidence were applied.[2,11–17] The ORs and 95% CIs between small and large intracranial aneurysms were extracted or calculated. Size categories were then registered. The cutoff between small and large size had to be established according to the published data. In cases of overlapping cohorts, we excluded the one with the lesser-quality data or, if equal in quality, the one with the fewest patients to prevent an artificial increase in effect size.

Statistical analysis

Comprehensive Meta-Analysis software (Version 2.2.046, 2007, Biostat, Inc.) was used to perform statistical analysis. The odds ratio for the risk of the rebleeding of small compared with large intracranial aneurysms was used as the effect size. Size cutoff was determined based on the presence of a (close to) common value across the studies. Both fixed- and random-effect models were used to calculate the summary ORs and 95% CIs. The significance of the overall OR was determined using a Z-test. For the sensitivity analysis, each study was removed from the total and the remaining studies were reanalyzed. The Type I error was set at 0.05 and the tests were 2-tailed. We assessed the heterogeneity between the study estimates using the I^2 statistic, with thresholds for a low degree of heterogeneity set at 40%.[13] The funnel plots were inspected, and the Egger test was used to look for evidence of publication bias.

RESULTS

Included studies

The literature search revealed a total of 1,408 records: 610 in PubMed, 773 in Embase, and 25 in the Cochrane database (Figure 4.1, Table 4.1). An additional study was found by screening the references. After the removal of duplicates, we were able to identify 867 studies. Review of the abstracts left us with 26 studies for the full-text evaluation.[3–6,9,10,18–20,22–25,27–31,33,35–37,39,41] Ten studies were excluded because they did not evaluate aneurysm diameter as a risk factor for rehemorrhage rate.[4,6,9,18,22,24,29,36,39,41] Two other articles were excluded because one was a review and the other was an editorial.[25,36] One study was written in Japanese and was thus also excluded.[31] Four studies used an overlapping cohort, and the one with most appropriate data was selected.[5,19,20,27,28,30,35] In total we identified 9 studies that met our inclusion criteria.[3,10,19,23,27,28,33,37,41] Clinical and/or radiological definitions of rebleeding were

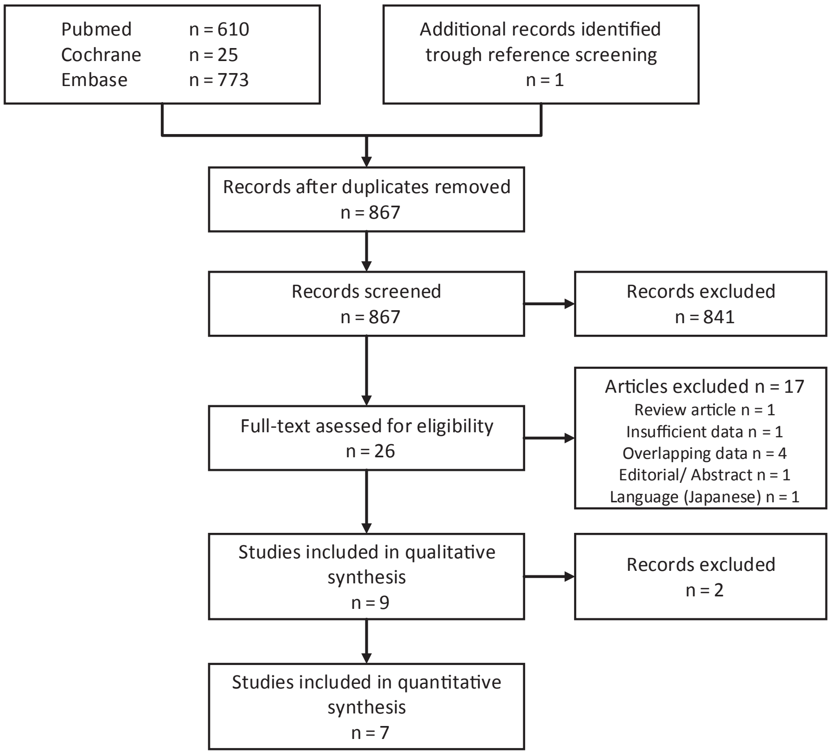


Figure 4.1 Chart showing the results of the literature search.

given in 8 studies and these are listed in Table 4.2. Only 1 study reported the median time to rebleeding and the median time to aneurysm repair.[3] Aneurysm size categories were given in 7 studies, while 2 others reported the mean size for the lesions in the non-rebleeding group compared with the rebleeding group (Table 4.2). Four studies reported on time to treatment or time to rebleeding (Table 4.2).

Quality assessment

The methodological quality of the 9 included studies was assessed. Of a total of 45 scores, there was no disagreement (Table 4.3). As a consequence of their observational design, all of the studies started with a maximal quality score of low. None of the studies were rated down based on serious inconsistency, indirectness, imprecision, or publication bias. In 5 studies, however, the quality was rated down because of serious limitations: Adjustment of the rebleeding rate for the time after the initial hemorrhage was not performed, or consecutive series were not reported.[10,19,23,33,37]

Table 4.2 Definitions of aneurysmal rebleeding, time to treatment, and aneurysm size categories

Authors & Year	No. of centers	Definition of rebleeding: Clinical	Radiological	Max follow-up (time to last rebleed)	Aneurysm size categories
Kassell & Torner, 1983	12	NR	NR	NR	0–4.9, 5–9.9, 10–14.9, 15–19.9, 20–30 mm
Paré et al., 1992	1	Rebleeding confirmed by bloody ventricular drainage, cataclysmic clinical deterioration, or intraoperatively	Rebleeding confirmed on CT	NR	< 1.0 cm, ≥ 1.0 cm
Beck et al., 2006	1	Any deterioration; new neurological deficit; a decrease in the level of consciousness; or severe headache. In comatose patients, any suspicious event like bradycardia & sudden rise in blood pressure or appearance of new blood on ventricular drainage	NR	Mean time at risk for nonrebleeding & rebleeding group: 80 ± 157 vs 97 ± 139 hrs ($p = 0.91$)	NR: reported mean size in non-rebleeding & rebleeding group: 6.9 ± 4.7 vs 11.2 ± 9.2 mm ($p = 0.002$)
Machiel Plezier et al., 2006	1	Sudden decrease in consciousness or a sudden increase in headache	Any increase of hemorrhage on CT	Max 30 days	≤ 10 mm, > 10 mm
Inagawa, 2010	1	Definite clinical deterioration	Fresh blood on CT	Max 14 days	< 5, ≥ 5–10, ≥ 10 mm
Guo et al., 2011	1	Sudden deterioration in consciousness or sudden increase in headache	Any increase of hemorrhage on CT	Max 72 hours	≤ 5, > 5 to ≤ 10, > 10 to ≤ 15, > 15 to ≤ 20, > 20 mm
Shiue et al., 2011	4	NR	Fresh hemorrhage found on repeat neuroimaging	NR	< 5, 5–9, ≥ 10 mm
Lord et al., 2012	1	Acute deterioration in neurological status in conjunction w/ CT changes	New hemorrhage or increase in hemorrhage burden on repeat CT	NR	NR: reported mean size in non-rebleeding & rebleeding group: 7 mm (5–10) vs 8 mm (6–15) ($p = 0.001$)
Tsui et al., 2012	1	NR	Active bleeding w/ contrast extravasation during CTA or hematoma vol difference (max diameter difference, > 3 mm) or new hematoma location between 2 consecutive CT scans	NR	< 7 mm, ≥ 7 mm

CTA = CT angiography; NR = not reported.

Table 4.3 GRADE quality assessment

Authors & Year	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality
Kassell & Torner, 1983	Observational	Serious	None	None	None	None	Very low
Paré et al., 1992	Observational	Serious	None	None	None	None	Very low
Beck et al., 2006	Observational	None	None	None	None	None	Low
Machiel Plezier et al., 2006	Observational	None	None	None	None	None	Low
Inagawa, 2010	Observational	Serious	None	None	None	None	Very low
Guo et al., 2011	Observational	Serious	None	None	None	None	Very low
Shiue et al., 2011	Observational	Serious	None	None	None	None	Very low
Lord et al., 2012	Nested case-control study	None	None	None	None	None	Low
Tsui et al., 2012	Observational	None	None	None	None	None	Low

Data analysis

Seven of 9 studies provided core data, making calculation of the OR possible.[10,19,23,28,33,37,41] Almost all of the studies used 10 mm as the cutoff point for aneurysm size among others classes, with only 1 study using 7 mm (Table 4.4). An analysis was performed with this best unifiable cutoff point. Overall rebleeding occurred in 360 (17.0%) of 2,121 patients (incidence range, from study to study, 8.7%–28.4%). The rate of rebleeding in small and large aneurysms was 14.0% and 23.6%, respectively (absolute risk difference 9.6%). The meta-analysis of the 7 studies revealed that larger size aneurysms had an overall OR for rebleeding of 2.32 (95% CI 1.77–3.04; p = 0.00) and an OR of 2.56 (95% CI 1.62–4.06; p = 0.00) for a fixed- and a random-effect model, respectively (Figure 4.2 upper). The results were subject to heterogeneity, which was determined by the I^2 statistic to be 60%, indicating that the random-effect the results (Figure 4.2 lower). The funnel plot gave no indication of publication bias, but the findings are of limited value because of the small number of studies

Table 4.4 Rebleeding rates

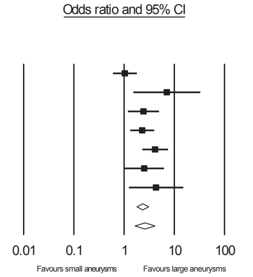
	Aneurysm size used for analysis		Rebleeding rate (%)*		
Authors & Year	Small	Large	Small	Large	Total rebleeding
Kassell & Torner, 1983	< 10 mm	≥ 10 mm	49/469 (10.4)	21/195 (10.7)	70/664 (10.5)
Paré et al., 1992	< 10 mm	≥ 10 mm	2/61 (3.3)	13/67 (19.4)	15/128 (11.7)
Beck et al., 2006	NA: reported mean size in non-rebleeding & rebleeding group; 6.9 ± 4.7 vs 11.2 ± 9.2 mm (p = 0.002)		NR	NR	NA
Plezier et al., 2006	≤ 10 mm	> 10 mm	68/281 (24.2)	22/73 (30.1)	90/354 (25.4)
Inagawa, 2010	< 10 mm	≥ 10 mm	48/205 (23.4)	33/80 (41.3)	81/285 (28.4)
Guo et al., 2011	≤ 10 mm	> 10 mm	18/169 (10.7)	52/157 (33.1)	70/326 (21.5)
Shiue et al., 2011	< 10 mm	≥ 10 mm	13/195 (6.7)	9/59 (15.3)	22/254 (8.7)
Lord et al., 2012	NA: reported mean size in non-rebleeding & rebleeding group; 7 mm (5–10) vs 8 mm (6–15) (p = 0.001)		NR	NR	NA (case-control study)
Tsui et al., 2012	< 7 mm	≥ 7 mm	5/75 (6.7)	7/35 (20.0)	12/110 (10.9)
Total	NA	NA	203/1455 (14.0)	157/666 (23.6)	360/2121 (17.0)

NA = not applicable; NR = not reported.
* The rebleeding rate is the percentage derived by dividing the number of patients with a rebleed by the total number of patients.

A Meta-Analysis: rebleed risk in large vs small aneurysms

Model	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Kassel & Torner, 1983	1.039	0.603	1.792	0.138	0.890
	Pare et al., 1992	7.102	1.532	32.922	2.505	0.012
	Machiel Plezier et al., 2006	2.430	1.191	4.956	2.441	0.015
	Inagawa, 2010	2.297	1.325	3.981	2.962	0.003
	Guo et al., 2011	4.154	2.301	7.502	4.723	0.000
	Shiue et al., 2011	2.520	1.019	6.234	2.000	0.045
	Wu et al., 2012	4.333	1.243	15.104	2.302	0.021
Fixed		2.319	1.772	3.036	6.123	0.000
Random		2.562	1.619	4.056	4.015	0.000

(Statistics for each study)



B Sensitivity-Analysis: rebleed risk in large vs small aneurysms

Model	Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
	Kassel & Torner, 1983	1.039	0.603	1.792	0.138	0.890
	Pare et al., 1992	2.364	0.367	15.237	0.905	0.366
	Machiel Plezier et al., 2006	2.130	0.849	5.342	1.612	0.107
	Inagawa, 2010	2.069	1.130	3.790	2.354	0.019
	Guo et al., 2011	2.457	1.380	4.376	3.054	0.002
	Shiue et al., 2011	2.441	1.493	3.992	3.558	0.000
	Wu et al., 2012	2.562	1.619	4.056	4.015	0.000
Random		2.562	1.619	4.056	4.015	0.000

(Cumulative statistics)

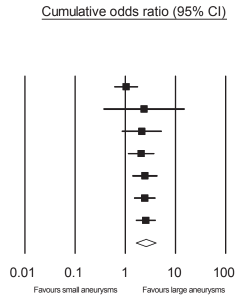


Figure 4.2 Forest plots showing results of the meta-analysis of studies reporting rebleeding risk of large versus small aneurysms (upper) and sensitivity analysis (lower).
The *squares* indicate the mean, the *whiskers* indicate the 95% CI, and the *diamonds* indicate the pooled estimate (the width of the *diamond* represents the 95% CI).

considered (Figure 4.3). The Egger regression test revealed an intercept of 2.3 with a 2-tailed p value of 0.22, and it was accordingly not statistically significant. Five of the 7 studies reported data on age; 4 studies provided age-adjusted results and identified a persistent relationship between size and the risk of rebleeding.[10,19,28,37] The presence of hypertension was reported in 2 studies and was more prevalent in patients with rebleeding in 1 of these studies.[10,19] Location (anterior vs posterior circulation) was reported in 5 studies, while in 4 there was no difference in the rebleeding rate.[10,19,33,37,41] One study identified a lower risk of rebleeding associated with posterior circulation aneurysms.[37] These findings provide insufficient evidence to relate hypertension and/or location of the aneurysm with the rebleeding rate.

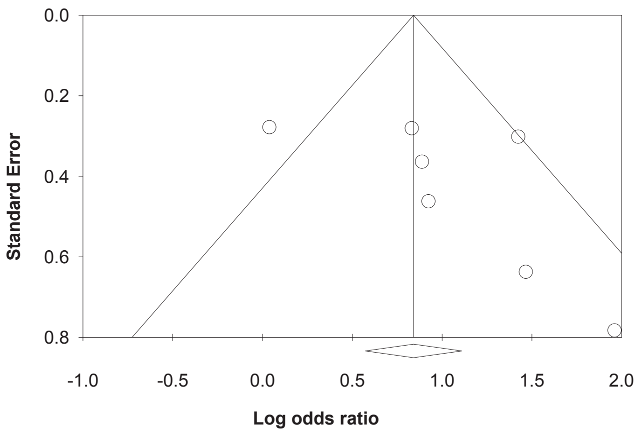


Figure 4.3 Funnel plot.
The *points* correspond to the treatment effects from individual studies, the *diagonal lines* show the expected 95% confidence intervals around the summary estimate. Odds ratios are plotted on a logarithmic scale.

Only a single study evaluated the risk of rebleeding over time dichotomized for size; the authors found a difference of rebleeding rate within 24 hours that persisted for 3 days after the initial hemorrhage.[28] They reported a hazard ratio for large aneurysm of 2.4 (95% CI 1.2–4.5). In another study, median time to aneurysm obliteration did not differ between rebleeding and non-rebleeding groups but was not stratified according to lesion size.[3]

The use of antifibrinolytic agents was reported only by 1 study; the investigators included patients from 1996 to 2011, and from 2003 on, they used, on a routine basis, aminocaproic acid for all patients before aneurysm clipping or coiling.[27]

Conflicting results have been reported regarding the effect of clinical grade on the risk of rebleeding. Six studies evaluated Hunt and Hess grade as a factor in relation to rebleeding. One study matched for Hunt and Hess grade found a significant difference in aneurysm size in those with rebleeding versus those without rebleeding.[27] Two studies reported no significant association between Hunt and Hess grade and rebleeding risk.[32,40] The authors of one study concluded that the larger the aneurysm, the worse was the World Federation of Neurosurgical Societies grade, but did not report it as a independent risk factor.[14] Two studies found Hunt and Hess grade to be a statistically significant independent risk factor for rebleeding (ORs 2.5 and 4.9).[5,7] Clinical grade at admission is a possible independent risk factor for rebleeding.

DISCUSSION

The findings of this meta-analysis show that aneurysm size is an important determinant of aneurysmal rebleeding. Age and location are unlikely to be confounding factors. The presence of hypertension was insufficiently registered to determine the role of possible confounding effects. To reduce rebleeding rates, patients with large aneurysms should, when feasible, undergo acute treatment rather than ultra-early treatment, despite possible logistical issues. Additionally, if patients are referred from other centers, or if the diagnosis is delayed, those with large aneurysms still require urgent treatment because it has been shown that the effect size of this association might persist for up to 72 hours after the initial bleed.[28] An increased risk is seen even within 24 or 48 hours, the time window in which most aneurysm are currently treated.[25]

The results of this analysis for ruptured aneurysms correspond with those of the ISUIA study, in which the primary bleeding risk was greater for individuals with larger unruptured aneurysms.[40]

The present research has several limitations. First, there is a potential for publication bias; studies showing no association between aneurysm diameter and rebleeding rate are less likely to be published. The estimated effect size in this meta-analysis could therefore be overestimated. Second, the studies considered did not include data from patients who had died before hospital admission, and this rate would be estimated to be as high as 15%.[26] Rebleeding rates during transfer to the hospital were also included and may be as high as 24%.[10] Moreover, the average time to hospital admission varied considerably after the initial SAH. Only one study reported median time to aneurysm repair and aneurysm rebleeding.[10] The research by Machiel Pleizier et al. revealed that there is no significant difference between small and large aneurysms when it comes to the risk of rebleeding 72 hours after the initial SAH.[28] Third, only one study reported the use of aminocaproic acid.[27] Although antifibrinolytic therapy does not improve survival or the chance of being independent in activities of daily living, it does reduce the risk of rebleeding by approximately 35%, as indicated in a recent Cochrane review.[1] Therefore, it is an important factor in rebleeding rate; unfortunately, the published studies did not provide data with which to evaluate the effects of both size and antifibrinolytic therapy together. Fourth, the cutoff for aneurysm size at 10 mm is artificial and chosen based on the categories set out in the published literature. Fifth, even if rebleeding is prevented in patients with large aneurysms, there is still a substantial rate of rebleeding events (14.0%) in cases involving small aneurysms. Only the acute treatment of all patients is optimal for prevention of rebleeding.[28]

Hypothetically, acute treatment could be associated with additional treatment risks like increased intraoperative rupture due to the newly formed instable thrombus. However, for treatment within 24 hours, it has been shown that this timeframe was associated with improved clinical outcomes, although the benefit was more pronounced for coiling than clipping.[34] Moreover, it is unlikely that the risks of acute treatment will accrue in such a way that they outweigh the very high morbidity and mortality rates associated with rebleeding.

CONCLUSIONS

This meta-analysis showed that aneurysm size is an important risk factor for aneurysmal rebleeding and should be used in the clinical risk assessment of individual patients. Our results confirmed the current guidelines and stressed the importance of acute treatment for large ruptured aneurysms.

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Chapter 5

Treatment of patients with ruptured aneurysm by neurosurgeons that perform both open surgical and endovascular techniques is safe and effective: results of a single centre in Europe

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ABSTRACT

In Europe only few neurosurgeons are trained in both open surgical clipping as well as in endovascular techniques for treatment of intracranial aneurysms. To investigate the safety and efficacy of performing both techniques we, two dual trained neurosurgeons, analyzed our results in repairing ruptured intracranial aneurysms. Prospectively collected data from 356 patients that underwent open surgical or endovascular repair of a ruptured intracranial aneurysm at the Neurosurgical Centre Nijmegen from 2006 to 2012 by two dual trained neurosurgeons were retrospectively analyzed. Complication rates, occlusion rates, and retreatment rates were obtained. Combined procedural persistent neurological morbidity and mortality after endovascular treatment and open surgical clippingwere 2.1%and 1.4%, respectively. Overall procedure-related clinical complication rate for endovascular treatment was 5.9% in 285 procedures for 295 aneurysms. Overall procedure-related clinical complication rate for open treatment was 9.9% in 71 procedures for 72 aneurysms. Follow-up was available for 255 out of 295 coiled aneurysms, 48 aneurysms recurred and 34 needed retreatment. For clipping 54 out of 72 treated aneurysms had follow-up; four aneurysms were incompletely clipped. One aneurysm was retreated. Treatment of ruptured intracranial aneurysms by neurosurgeons that perform both open surgical clipping as well as endovascular techniques is safe and effective. Developing training programs in Europe for hybrid neurosurgeons that can provide comprehensive patient care should be considered.

INTRODUCTION

Background

In many countries neurosurgeons have both open surgical as well as endovascular techniques in their armamentarium to treat patients with subarachnoid hemorrhage. In Europe neurosurgeons perform open surgical vascular procedures, however, only very few of them are trained in endovascular treatment. It is often questioned if one physician would be able to conduct both open and endovascular techniques successfully and safely. To answer that question, we, two neurosurgeons that perform both open neurosurgical clipping and endovascular coiling, evaluated our results of 356 patients treated at our centre for ruptured intracranial aneurysms. In this report we focus on safety and efficacy of the procedure.

MATERIALS AND METHODS

Data of all patients that underwent open surgical or endovascular repair of a ruptured intracranial aneurysm at the Neurosurgical Centre Nijmegen (Radboud University Nijmegen Medical Centre and Canisius Wilhelmina Hospital Nijmegen) from 2006 to 2012 by two neurosurgeons (HDB & JDV) were prospectively entered in a database by a dedicated physician's assistant. Complications were registered by the same physician's assistant. Complications were cross-checked using the neurosurgery department complications registry.

Complications were recorded as being radiological / intraprocedural with no clinical neurological consequences, complications with transient neurological deficit, and with permanent neurological morbidity or dead. Also non-neurological procedural complications were registered. Complications were analyzed as of a primary treatment modality and on a per patient basis.

Recurrence rates and retreatment rates were analyzed as well.

Decision-making process

The majority of patients were coiled. The reasons not to treat a patient with coiling were the following: middle cerebral artery aneurysmswith a space-occupying hematoma; aneurysms that both had an unfavorable dome-to-neck ratio for coiling and that were expected to be amenable for clipping as well; and patients with vascular anatomy unfavorable for endovascular navigaton (for example severe tortuosity of proximal vessels, carotid stenosis).

Training

The senior author (JDV) had his open surgical and the first part of his endovascular training at the Department of Neurosurgery, University of Freiburg, Freiburg, Germany. His further endovascular training was done at the Department of Radiology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands and the last part at the Department of Neuroradiology, Karolinska Institute, Stockholm, Sweden. The other author (HDB) had his open surgical and endovascular fellowship at the Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands. For theoretical sub specialization both attended and successfully completed the Master in NeuroVascular Diseases (Université Paris Sud-Faculté de Médecine de Bicêtre & Mahidol University, Ramathibodi and Siriraj Medical Schools), and the Pierre Lasjaunias European Course of Diagnostic and Interventional Neuroradiology (ECNR-course).

RESULTS

Included studies

From July 28th 2006 to January 1th 2013, all patients with aneurysmal subarachnoid hemorrhage (SAH) were prospectively entered in a database by a physician's assistant. Threehundred-fifty-six patients with 367 aneurysms were treated, 239 (67.1%) were female, 117 (32.9%) male. Nine moribund patients were not treated and died shortly after admission. Mean age was 54.6 years (Table 5.1). Clinical presentation as reported by a Hunt & Hess grade is given in Table 5.1. Seventy-one patients with 72 aneurysms were treated by surgical clipping (one patient had two aneurysms treated in the same procedure), 285 patients with 295 aneurysms were treated endovascular (285 coiling procedures). In 11 patients with two aneurysms, treatment was done for both aneurysms if either could be the cause of the SAH. Open surgical treatment was most frequently done for middle cerebral artery (MCA) aneurysms. Anterior communication aneurysms were most frequent in the endovascular treatment group, for detailed information see Table 5.2.

In five patients the intended endovascular coiling was converted into open surgical clipping as the aneurysms in these patients appeared to have a very wide-neck and could not be

Table 5.1 Demographic data SAH patients

	Open (%)	Endovascular (%)	Overall
Number of patients	71 (19.9)	285 (80.1)	356 (100.0)
Male	18 (25.4)	99 (34.7)	117 (32.9)
Female	53 (74.6)	186 (65.3)	239 (67.1)
Number of aneurysms	72 (19.6)	295 (80.4)	367 (100.0)
Age, mean [SD]	53.1 [10.7]	55.0 [13.2]	54.6 [12.8]
Hunt & Hess			
1	12 (16.9)	44 (15.4)	56 (15.7)
2	17 (23.9)	93 (32.6)	110 (30.9)
3	11 (15.5)	61 (21.4)	72 (20.3)
4	18 (25.4)	50 (17.5)	68 (20.2)
5	13 (18.3)	37 (13.0)	50 (14.0)

Table 5.2 Aneurysm location

Aneurysm location	Open; number of aneurysms n, (%)*	Endovascular; number of aneurysms n, (%)*
Anterior circulation	62 (86.1)	186 (63.0)
Internal carotid	2 (2.8)	4 (1.4)
Ophthalmic	-	3 (1.0)
Paraophthalmic	-	7 (2.4)
Anterior choroidal	-	3 (1.0)
Carotid terminus	1 (1.4)	7 (2.4)
Anterior communicating	12 (16.7)	132 (44.7)
A1 or A2	-	3 (1.0)
Pericallosa	-	7 (2.4)
Middle cerebral	47 (65.3)	20 (6.8)
Posteroir circulation	10 (13.9)	109 (36.9)
Vertebral	-	6 (2.0)¶
Posterior inferior cerebellar	-	10 (3.4)
Superior cerebellar	1 (1.4)	8 (2.7)
Basilar terminus	-	28 (10.6)
Posterior cerebral	-	3 (1.0)
Posterior communicating	9 (12.5)	52 (17.6)
Mid-basilar	-	2 (0.7)
Total	72 (100)	295 (100)

¶ In 4 patients parent vessel occlusion because of a dissecting aneurysm.
* Data in parentheses are percentages of aneurysms of total within each group (open or endovascular).

treated by endovascular means even with the use of a balloon or double catheter technique. Stent-assisted coiling was considered to be the most appropriate treatment modality in 11 patients.

Complications

Endovascular treatment of ruptured aneurysms was associated with 2.8% neurological morbidity and 1.1% mortality in our series. Neurological morbidity was transient in 1.8%, permanent in 1.1% and non-neurological complication occurred in 2.1% of the cases.

Overall procedure-related clinical complication rate for endovascular treatment was 5.9% in 285 procedures for 295 aneurysms. Radiological complications without clinical consequences were present in 7.7%. Coil perforation was present in 1.4% of the cases and remained without clinical sequelae. Combined procedural persistent neurological morbidity and mortality after endovascular treatment was 2.1% (Table 5.3).

Open surgical clipping (71 procedures) was associated with 8.4% neurological complications. There was no surgery related mortality. Neurological deficit was transient in 7.0% and

Table 5.3 Complications in endovascular procedures

Complications	Radiological without clinical consequences n, (%)	Transient complications n, (%)	Permanent complications n, (%)	Mortality n, (%)	Non-neurological n, (%)
Aneurysm perforation	4 (1.4)	0	0	0	0
Coil protrusion	3 (1.1)	0	0	0	0
Vasospasm	4 (1.4)	0	0	0	0
Thromboembolism	4 (1.4)	5 (1.8)	3 (1.1)	3 (1.1)	0
Dissection	1 (0.4)	0	0	0	0
Acces not possible via groin next day via brachial artery	1 (0.4)	0	0	0	0
Anerysm spurium	0	0	0	0	4 (1.4)
Retroperitoneal hemorrhage	0	0	0	0	1 (0.4)
Myocardial infarction	0	0	0	0	1 (0.4)
Attempted coiling not possible: clipping	5 (1.8)	0	0	0	0
Total	22 (7.7)	5 (1.8)	3 (1.1)	3 (1.1)	6(2.1)

permanent in 1.4% of the cases. Non-neurological complications were present in 1.4%, not including meningitis. Meningitis was diagnosed in all cases with external drainage and considered to be related to the external drainage rather than the operation *per se*. Overall procedure-related clinical complication rate for open treatment was 9.9%. There were no patients with new postoperative seizures.

Combined procedural persistent neurological morbidity and mortality after open surgical clipping was 1.4% (Table 5.4).

Table 5.4 Complications in open surgical procedures

Complications	Procedural, without clinical consequences n, (%)	Transient complications n, (%)	Permanent complications n, (%)	Mortality n, (%)	Non-neurological n, (%)
Intra operative aneurysm rupture	3 (4.2)	0	0	0	0
Hypodensity / infarction	2 (2.8)	0	0	0	0
Epidural / subdural hematoma	0	2 (2.8)	0	0	0
Neurological deficit	NA	3 (4.2)	1 (1.4)	0	NA
Skull fracture	0	0	0	0	1 (1.4)
Additional coiling needed	2 (2.8)	0	0	0	0
Total	5 (7.0)	5 (7.0)	1 (1.4)	0	1 (1.4)

NA = not applicable.

Recurrence and retreatment

There were 255 out of 295 aneurysms that had follow-up imaging, 48 (18.8%) had a recurrence, of these 34 (13.3%) required retreatment with a mean follow-up of 13.8 months (range: fu at discharge – 83 months).

Fifty-four out of 72 clipped aneurysms had follow-up imaging. Four (7.4%) neck rests were found, one aneurysm was retreated (1.9%) with a mean follow-up of 6.5 months (range: fu at discharge – 56 months).

DISCUSSION

This series demonstrate that treatment of patients with ruptured aneurysms by neurosurgeons that perform both clipping and coiling is safe and effective.

Endovascular treatment

In the present series overall procedural neurological permanent morbidity and mortality rates for endovascular procedures were 1.1% and 1.1%, respectively. Transient neurological deficit was present in 1.8%. Compared to data in the literature, our complication rates are low. Permanent complications are present in 2.4% according to a large study of Brilstra reviewing 509 aneurysms in 14 studies.[3] In other case series the rate for procedural permanent morbidity ranges from 3.2% to 5.9%.[7,10,15,27] Transient morbidity ranges from 0.8% to 3.4%.[10,15] Mortality in the aforementioned review was 1.1%.[3] Indivudual case series had somewhat higher rates ranging from 1.5% to even 7.5%.[7,10,15,27] Reported rate of perforation in the review of Brilstra was 2.8%.[3] Cloft reported on perforations in their meta-analysis of 12 studies in 1,248 SAH patients in 4.1%.[6] Other case series had rates from aneurysm perforation in 2.5% to 7.6%.[7,10,15,22,27] Rupture due to perforations can be without clinical consequences in 73–83%.[4,20,27] Thromboembolism is the main cause of morbidity and mortality in our series, accounting for totally 2.2% of combined morbidity and mortality. In 15 patients thromboembolic (TE) complications were encountered, in four of these patients only small thrombus formation was noted and remained clinically silent. Ross reported clinically significant thromboembolism in 6% of the case series with 70% ruptured aneurysms. Dinc in his series of 481 SAH patients reported 5.0% TE complications with clinical sequelae. Van Rooij et al., reported TE events to account for 4.7% of combined morbidity and mortality. Inability to treat the aneurysm endovascular accounts probably for 4–37% of the cases.[13,14,28] In conclusion, concerning endovascular treatment of ruptured intracranial aneurysms, the results of present series are in the lower range of complication rates reported in the literature.

In this series recurrence rate after coiling was 18.8%. Retreatment rate was 13.3%. A recent systematic review of 8,040 aneurysms showed a recurrence rate after coiling of 20.8% and retreatment rate of 10.3%.[8] Our results are in line with this systematic review.

Open surgical treatment

In open surgical treatment procedure-related permanent neurological morbidity was present in 1.4%. There was no surgery related mortality. In SAH it might be difficult to discern between disease and procedure related adverse events, also in patients with very bad clinical condition additional neurological deficit might be difficult to notice. In the context of these restrictions results should be interpreted. Mortality from unruptured aneurysm series ranges from 1% to 3%.[28] Wong et al., performed a review of complications related to open surgery for which the main preoperative complications can be listed; intraoperative rupture 19–35%, major vessel occlusion 3–12%, medical adverse events 2–17%, seizures 4–42% failure to secure rupture site 1–6%.[28] In a recent study data fromthe Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) were analyzed for occurrence of a postoperative neurological deterioration.[12] Acute postoperative neurological deterioration was observed in 42.6%. Compared to the abovementioned data the procedure-related persistent neurological morbidity and mortality after surgical clipping in our series are low. The open surgical group had a higher overall procedure-related clinical complication rate than the endovascular group (9.9% vs 5.9%). Although the present series is not a randomized study, our results could reflect to the more invasiveness of open surgery. This was well documented in randomized studies, although these studies focused on six month and one year follow-up.[13,14] Interestingly the Barrow Ruptured Aneurysm Trial showed similar outcomes based on mRS score between coiled and clipped aneurysms of the anterior circulation at three year follow-up.[25] In this study patients in the clip group had a significantly higher degree of aneurysm obliteration and a significantly lower rate of recurrence and retreatment. A recent case series in which treatment results of dual trained neurosurgeons were analyzed also demonstrated a higher permanent procedure-related neurological morbidity in clipped patients than in coiled patients (8.3% versus 3.7%).[5] Another case series of a single dual trained neurosurgeon disclosed almost equal rates of combined procedure-related persistent neurological morbidity and mortality (2.8% for coiled patients and 3.5% for clipped patient).[1] Persistent procedure-related neurological morbidity and mortality after surgical clipping and endovascular treatment were similar in our series as well.

In this series incomplete clipping rates were 7.4%. There was one patient who had retreatment after clipping. In the literature, rates of incomplete clipping vary between 5% and 30% as was demonstrated in a recent meta-analysis.[26] Incomplete clipping had occurred in 20% of the patients included in the International Subarachnoid Aneurysm Trial (ISAT).[14] In conclusion, our rates of incomplete clipping are in line with the literature.

Historical background and a changing neurovascular world

Neurosurgery focuses on invasive treatment of neurological diseases. An important part of neurosurgical care includes the treatment of neurological emergencies among which cerebrovascular diseases form the main group. Patients with ruptured aneurysms will stay at neurosurgical wards for several weeks. Thus, both neurosurgeons as well as their neurosurgical residents have build up extensive knowledge in treating patients with cerebrovascular disease. So typically neurosurgeons have been responsible for comprehensive care of patients harboring aneuryms.

Today the neurovascular realm has changed and the vast majority of patients with ruptured aneurysms is being treated with endovascular techniques. In our series 80% of the patients were coiled. In the vast majority of European centres coilings are performed by radiologists. This means that the extensive knowledge which is available in the neurosurgical community is not being transferred into an invasive therapy performed by a neurosurgeon. This is an interesting contradiction as the core task of neurosurgery is treating neurological diseases by invasive techniques.

There are numerous reports on training neurosurgical residents in endovascular neurosurgery and outside Europe the realm of endovascular treatment has been entered by many neurosurgeons.[9,11,16,18,21] In these reports it is concluded that there is a benefit in extending the armamentarium of the neurosurgeon with endovascular techniques. Neurosurgeons that perform diagnostic and therapeutic angiography increase their knowledge of neurovascular anatomy.[21] The experience and knowledge obtained in one technique (endovascular or open) is useful for the other. By performing both open as well as endovascular techniques there is an unbiased and well-considered assessment of which therapy would be indicated in a given patient.[21] A recent study showed good treatment results of a single dual trained neurosurgeon with low complication rates for both coiled and clipped patients (respectively 2.8% and 3.8%).[1] The results of our series suggest as well that dual trained neurosurgeons can perform both coiling and clipping with very low complication rates.

The hybrid neurosurgeon can carefully weigh the benefits of either treatment modality and, therefore, is able to offer a comprehensive patient care. There are many factors that have to be weighed in order to choose between open or endovascular therapy. Clinical factors that have an impact on choice of treatment modality are clinical grade, age, and comorbidity (cardiac/pulmonary, hematological, or kidney disease, and contrast allergy). Radiological factors are: presence of a spaceoccupying hematoma and brain edema. Angiographic factors are: aneurysm location, aneurysm architecture, and condition of proximal arteries (starting with the femoral artery up to the parent artery from which the aneurysm arises) that need to be catheterized. This gives the hybrid neurosurgeon the possibility to evaluate each aneurysm on a case-by-case basis.[1] Decision-making can be refined. For example: the dogma that "MCA aneurysms should be clipped" can be modified as small MCA aneurysms with a favorable dome-to-neck ratio are good candidates for coiling. This paper has not proven that a hybrid neurosurgeon has better results than a collegial team. This could only be proven in randomized trials. But the question is: are such trials needed? We feel that are several ways to offer optimal comprehensive patient care at a given institution.

It may be discussed that a hybrid neurosurgeon will have a preference for one of the both techniques. This might influence his/her decision whether to clip or to coil. The question is: does that matter as long as his/her results are good?

During our endovascular training program, there was a high enough case-load to be trained in special endovascular techniques like balloon-remodeling and stent-assisted coiling. For open neurovascular training the range of clipping techniques as well as skull base approaches could be trained. As indications for bypass surgery had dramatically dropped over the last years, training for this type of surgerywas not included in the open surgical program. We have started to cooperate with a high-volume-bypass neurosurgical centre as both authors of the manuscript do not perform bypass surgery.

If the number of clippings will further decrease, the aforementioned positive interaction of the two techniques might become more and more important. If clippings become rare, neurosurgeons that perform open techniques should be as much as possible involved in treating cerebrovascular diseases. Today, most European centres still have senior neurosurgeons that were trained in the years that most patients were clipped. For younger neurosurgeons it will take many years to finish a proper training because of the decreasing case-load. There are several ways to solve this issue, like further centralization of this low-volume, high-complex disease. Neurosurgeons performing both techniques, however, might be a more appropriate solution. Apart from the positive interaction between both techniques there are relevant patient-care logistic issues to mention. By having divided the invasive treatment of patients with ruptured aneurysms between two specialties (neuroradiology and neurosurgery), there is need for a double 24/7 emergency service,which makes this service more complex and more expensive. Apart from complexity and costs, the efficiency of a neurosurgeon being on call just for clipping is very low considering the frequency in which a clipping is necessary. This might discourage young neurosurgeons to sub-specialize in open cerebrovascular treatment only.

An alternative for a dual trained neurosurgeon would be to train neuroradiologists in both open and endovascular techniques. Such training programs have not yet been developed.

Endovascular training in Europe

Recently the European Society of Neuroradiology (ESNR), the European Board of Neuroradiology (EBNR), the European Union of Medical Specialists (UEMS) Section of Neurosurgery, and the European Association of Neurological Surgeons (EANS) approved guidelines for Standards of training in endovascular neurointerventional therapy.[18] Thanks to this regulation we were able to start an endovascular fellowship program in our centre.

In Europe still there are only few neurosurgeons trained in endovascular techniques and training programs are mostly dependent on local initiatives. Hybrid neurosurgeons are even rarer.

This while neurosurgeons contributed significantly to the initiation of neuroendovascular techniques.[17] In the last two decades, however, interventional neuroradiologists were the most active in this field. Therefore, neurosurgeons entering the endovascular field should work in close collaboration with interventional neuroradiologists, creating a positive interaction between the both groups. Neurologists as well have shown great interest in this field, and it is expected that the lines between neurology, neurosurgery, and radiology will blur.[24]

Outside Europe, numerous hybrid training programs for neurosurgeons have been developed.

Typically these programs incorporate the endovascular training into the neurosurgical residency.[24] A recent study could document the safety and efficacy of training a senior neurosurgical resident in diagnostic transfemoral catheter angiography.[23]

A recently published document mentions the aimto acquire “particular qualification” in “interventional neuroradiology” (INR).[19] Like Non-European Neurosurgeons, we feel it would be very effective for European Neurosurgeons as well to have the opportunity to perform the clinical neurosciences as well as the diagnostic neuroradiology part during their neurosurgical residency.

From the perspective of INR, European training standards are very well defined. In these documents, however, only the endovascular treatment part is considered. For optimizing patient care a comprehensive approach is warranted. We feel that there is an essential and urgent task for the European neurosurgical community to take up the responsibility to develop European training standards, and to organize and support training programs for both open vascular neurosurgery, and hybrid vascular neurosurgery in order to guarantee a comprehensive neurovascular patient care.

In a recent comment it was pointed out that even current training standards are incomplete.[2] In this commentary it was stated that current programs do not provide basic sciences needed for endovascular surgery, such as vascular biology, vascular physiology expertise in the coagulation cascade, and study of the endothelium. Updating of training programs is essential.

This series shows that both the endovascular and the open training program were safe as complications of both clipping and coiling were low. Thus, the standards of training as approved by the abovementioned societies have worked for our centre. There were no differences in complication rate between the senior and the junior author. Thus, under controlled supervising, patients do not suffer from the learning curve of the trainee. We feel there is no essential difference between training an open neurosurgical or endovascular procedure. From the early beginning of their residency, neurosurgical residents typically are trained in numerous percutaneous surgical procedures. The specific eye-hand-coordination needed for those procedures resembles very much the coordination that is needed for endovascular procedures. As the number of clippings is significantly lower than the number of coilings it will take much longer for a cerebrovascular neurosurgeon to develop skills in clipping.

CONCLUSIONS

This series demonstrate that neurosurgeons that perform both endovascular and open treatment for ruptured cerebral aneurysms can do this with low morbidity and mortality and high efficacy. We encourage other European neurosurgeons to start up endovascular treatment together with interventional neuroradiology. Current European regulations for training provide a framework to develop this subspecialty of endovascular neurosurgery.

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Chapter 6

An online health community for aneurysmal subarachnoid hemorrhage patients: a pilot study

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ABSTRACT

Background Aneurysmal subarachnoid hemorrhage (aSAH) is a condition affecting relatively young patients and has high rates of morbidity and mortality. Online health communities have emerged to fill the void for patient advocacy and information, allowing individuals with shared experiences and chronic disorders to connect.

Objective We have developed an online health community for aSAH patients, and this pilot study was conducted to evaluate it from a patient's perspective.

Methods We implemented an online, members-only, health community (MijnSAB, translation: MySAH) in addition to the usual aSAH care at Radboudumc, Nijmegen, the Netherlands. A questionnaire that was sent to consecutive aSAH patients was used to evaluate the usability and utility of MySAH. Answers were provided using a 5-point Likert scale. There was also one open-ended question asking about what was missing from the MySAH tool.

Results In total, 66 consecutive patients with aneurysmal subarachnoid hemorrhage were informed about the online health community. Of 64 potential MySAH users, 26 patients gained access to MySAH, 20 of whom were willing to participate in the evaluation. Those who used the community were younger ($p = 0.03$) and in a better condition at discharge ($p = 0.03$). The patients were positive about MySAH's contribution to the quality of their care, but not to their quality of life. Most patients (18/20, 90%) reported that they would recommend the community to others in their position. Open suggestions on how to improve the tool included more frequent blogs, including by a rehabilitation specialist.

Conclusions This pilot study showed that the online health community, MySAH, has a beneficial effect on the aftercare of patients suffering from aSAH because it gives easy access to relevant information provided by peers or caregivers. Due to the variable clinical outcomes after aSAH, the tool will mainly be useful for a select group of patients (with a better clinical outcome).

INTRODUCTION

The incidence of aneurysmal subarachnoid hemorrhage (aSAH) is approximately nine cases per 100,000.[5] The condition affects relatively young patients, with an average age at first onset of 55 years, and has significant rates of morbidity and mortality.[5] Health-related quality of life is also significantly reduced compared to the normal population.[8,9,11] Online health communities are increasingly being used to assist these patients and can be a valuable addition to the standard clinical and outpatient care.[1,12,18] Such communities give patients the opportunity to communicate with professionals and peers and to learn more about their disease and future expectations.[10]

We have developed an online health community for aSAH-patients, and this pilot study was conducted to evaluate it from a patient's perspective.

METHODS

Implementation

We implemented an online, members-only health community (MijnSAB, translation: MySAH) as an addition to the usual aSAH care provided at Radboudumc. The tool has three main functionalities, which are in line with those described for other online communities.[1] First, information on relevant news can be provided in blogs. Second, the resource is an interactive forum whereby patients can contact others with the disease or put questions to the medical team. Third, general information concerning several aspects of the disease is provided. An example of the access page in the form of a poster used for promotion purposes among patients is shown in Figure 6.1. Examples of the translated content ("Can I?") are set out in Multimedia Appendix 6.1.

The community tool has been used by Radboudumc to improve patient-centered care in a number of different medical specialties, with ParkinsonNet being an example.[18] The technical maintenance costs are € 5000 per annum.

In our MySAH community, patients logged in to the site using a personal digital identification code. Attention was drawn to new messages by pop-ups in a patient's mailbox. Two physician assistants and a nurse practitioner were responsible for daily communication with the community. Weekly checks on the Web-blogs were made by two neurosurgeons. General questions without the need for the intervention of a neurosurgeon were answered by the

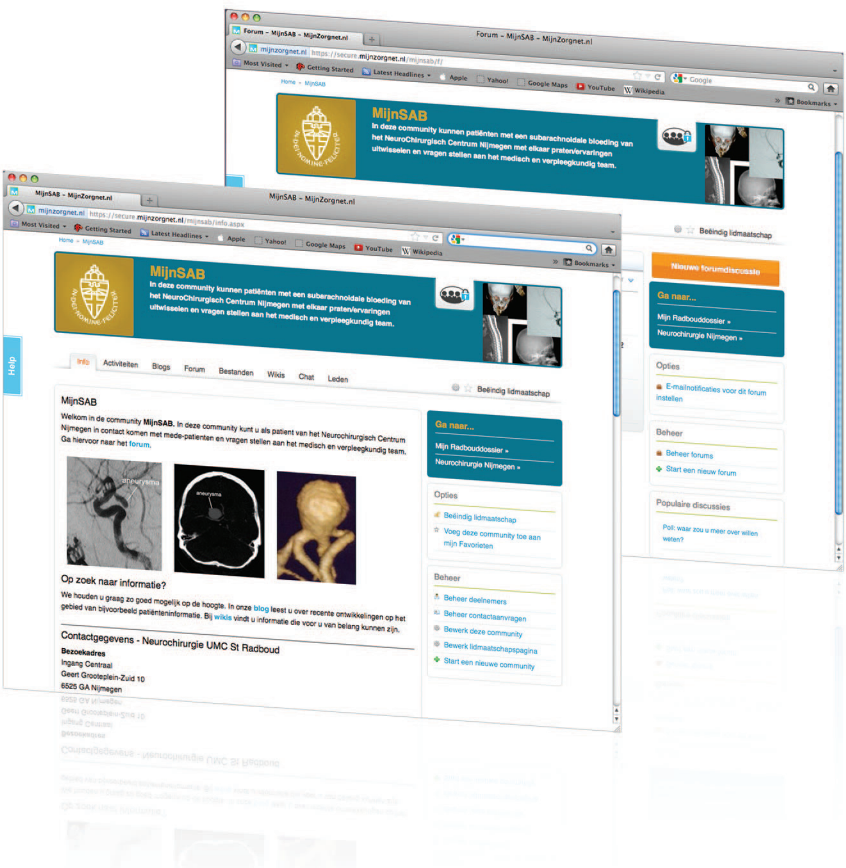

Figure 6.1 **Poster of access page.**

physician assistants or nurse practitioner. If the answers to questions required more specialist knowledge, responses were provided by one of the two neurosurgeons.

We used a questionnaire, which was sent to consecutive aSAH patients, to evaluate the usability and utility of MySAH. If patients were unable to complete the questionnaire, their caregivers were asked to do it for them. Those who did not return a completed questionnaire within 3 weeks were contacted by telephone and asked why. An eventual telephone evaluation was conducted by a physician assistant who was not involved in the treatment of the patients.

All of the aSAH patients referred to Radboudumc between November 1, 2012, and September 30, 2013, were candidates for participation, and all survivors were invited to take part in the research. The demographics of all of the referred patients were registered, as were the modified Rankin scale (mRS) at discharge and the type of post-hospital care (home, rehabilitation, or nursing home). The mRS is frequently used in aSAH patients to score outcomes and is an ordinal scale varying from 0 to 6 (0 = No symptoms; 1 = No significant disability. Able to carry out all usual activities, despite some symptoms; 2 = Slight disability. Able to look after own affairs without assistance but unable to carry out all previous activities; 3 = Moderate disability. Requires some help but able to walk unassisted; 4 = Moderately severe disability. Unable to attend to own bodily needs without assistance and unable to walk unassisted; 5 = Severe disability. Requires constant nursing care and attention, bedridden, and incontinent; and 6 = Dead). The mRS scores have been dichotomized as ≤ 3 and ≥ 4 because it was assumed that patients with a score of more than 3 would use the Internet less often. Approval for the study was obtained from the local medical ethics committee (CMO Arnhem-Nijmegen).

Questionnaire

We developed a questionnaire that had two parts. The first of these contained general questions on perceived care, while the second asked questions on the usability and usefulness of the MySAH community. The questions were adapted from a previously published patient agreement questionnaire containing usability-related and usefulness-related statements and were expanded for use with MySAH.[15] Answers were given using a 5-point Likert scale, the data were summarized by a median, and for the analysis, the results were collapsed in two categories, with the neutral score counted on the negative side (agree/disagree). The results are presented graphically with median and interquartile ranges.[7] There was one open-ended question about what was missing from the MySAH tool. If possible, the responses were classified according to the three components of the community and with respect to suggested technical alterations.

RESULTS

Included patients

In total, 66 patients with aneurysmal subarachnoid hemorrhage were informed about the online health community. Two patients died in the post-discharge period. Of the 64 remaining potential MySAH users, 38 did not log in, 4 could not be contacted in the post-operative period, 3 were willing to log in after a rehabilitation period, 2 did not log in because of their clinical condition, 5 had technical difficulties logging in, 5 did not have a computer, and 19 did not provide a reason for their non-participation. Finally, 26 patients did gain access to MySAH, 20 of whom were willing to participate in the study (Figure 6.2). The demographics of the patients, stratified by their participation, are shown in Table 6.1.

The participants who evaluated MySAH were not significantly different in terms of their gender or discharge location ($p = 0.33$). However, those who did participate were younger ($p = 0.03$) and were in a better clinical condition (mRS) at discharge ($p = 0.03$).

Patient satisfaction and the use and usability of MySAH

The MySAH community was used for a mean period of 7.2 months, mainly bi-monthly (9/20, 45%) or monthly (7/20, 35%). A minority used the tool weekly (3/20, 15%) or daily (1/20, 5%). In most cases (16/20, 80%), the patient was the main user of MySAH, while the other responders were proxies. No specific part of the MySAH community was used

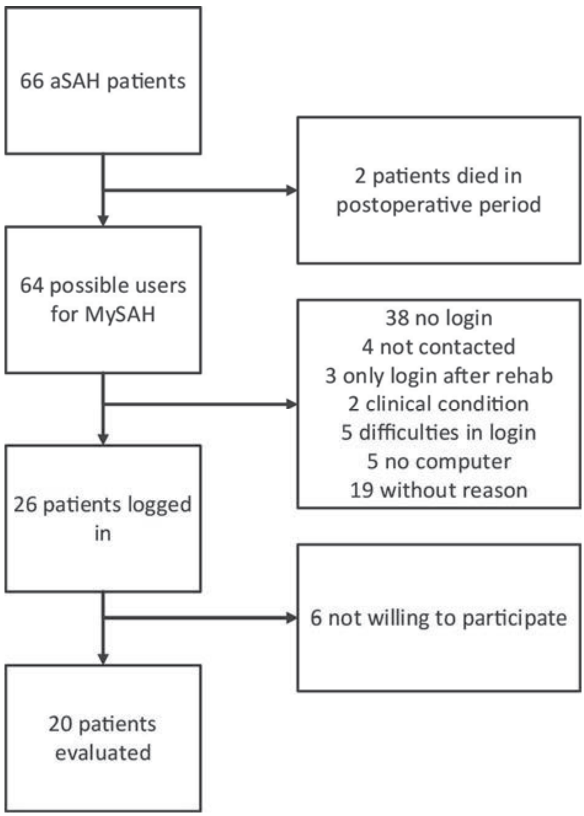

Figure 6.2 **Flow chart of patients included in study.**

Table 6.1 Patient characteristics

	Participant	Non-participant	Total	P value for calculated difference between groups[a]
Number of patients, n (%)	20 (30)	46 (70)	66 (100)	Not applicable
Male/female, n/n	6/14	17/29	23/43	0.78[b]
Age in years, median (SD)	48.5 (11.7)	56.0 (11.9)	54.0 (12.2)	0.03[c]
mRS at discharge, n				
≤ 3	19	31	50	0.03[b]
≥ 4	1	15	16	
Discharge, n				
Home	14	22	36	0.33[b]
Rehabilitation	5	18	23	
Nursing home	1	6	7	

[a] Values are considered to be significant if $p < 0.05$.
[b] Fisher's Exact test (2-sided).
[c] Mann-Whitney U test (2-tailed).

preferentially by either the patients (wiki: 4/20, 20%; forum: 10/20, 50%; blogs: 2/20, 10%; not answered: 2/20, 10%) or their proxies (wiki: 3/20, 15%; forum: 2/20, 10%; blogs: 2/20, 10%; and not answered: 12/20, 65%).

The questionnaires were mainly completed by the patients and in a minority of cases by their caregivers. Patient satisfaction with treatment, post-treatment care, and communication with caregivers was generally rated positively (see Figure 6.3).

The information was easy to use (4.0) and find (4.0) and was also clear (5.0). However, it was not beneficial for managing health, making important decisions regarding health (2.5), or making contact with caregivers (3.0). Patients were positive about MySAH's contribution to the quality of their care, but not to their quality of life. No specific component (blog, forum, or wiki) was preferentially rated, nor did the patients discard one aspect in particular. Most patients (18/20, 90%) would recommend the community to others in their position.

Open remarks

In total, 16 patients made 21 suggestions for future improvements to the community (Table 6.2). These responses were classified according to the three components of the community and with respect to suggested technical alterations. More frequent blogs, including by a rehabilitation specialist, was one suggestion. The forum could apparently also benefit

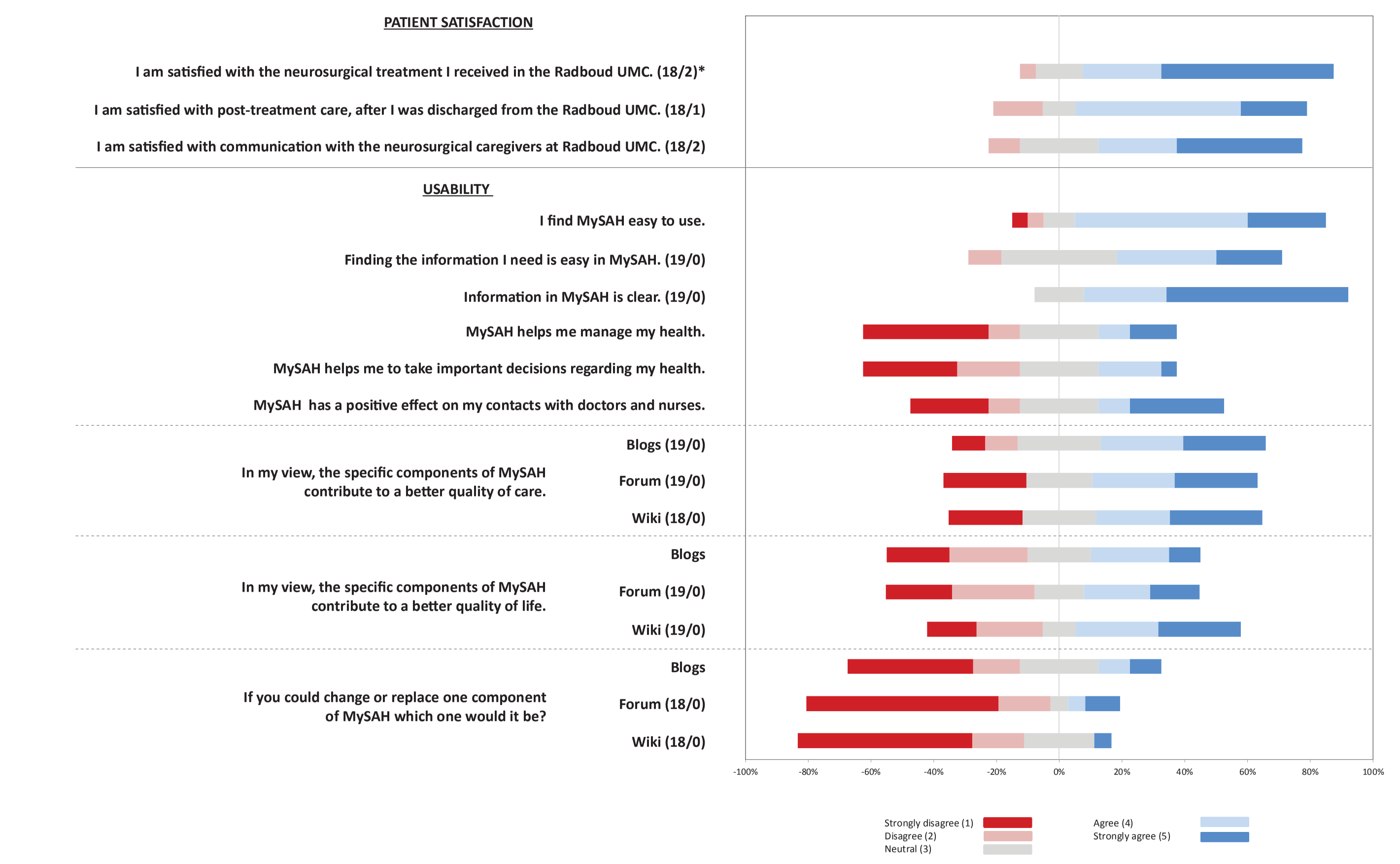

Figure 6.3 Patient satisfaction and usability (results of the questionnaire are depicted as a set of diverging stacked bar charts.
Each stacked bar is 100% wide and partitioned by the percent of that group who have selected the agreement level indicated in the legend below the body of the plot. The legend is ordered by the values of the labels. Asterisk = answer by number of patients/caregivers).

Table 6.2 Items for improvement[a]

Item	Suggestion
Blogs	More blogs (1), in combination with rehabilitation specialist (2)
Forum	More patient contact (1), also positive experiences (1)
Wiki / information	More information on aftercare (2), psychological consequences at home (3), pregnancy after aSAH (1), current news (2), and general information (3)
Technical	Login (1), navigation (1), layout (3)

[a] Numbers in parentheses = number of patients who suggested this improvement.

from use by a larger number of patients overall and by patients with more positive disease experiences. The wiki section should contain more information about aftercare, psychological consequences when at home, pregnancy after aSAH, current news, and more general factors. Other suggestions were related to login and layout and navigation on the site.

DISCUSSION

Principal findings

The conceptual framework of the online community, MySAH, is to improve patient care and obtain better clinical outcomes through optimizing engagement of the patient with the treatment. This is accomplished by an exchange of information between patient and caregiver and vice versa. Such a concept is comparable with sociological studies in other fields.[17]

This online health community has promising features. Although the number of responses to the questionnaire was not high (30% responders), the majority graded the items concerning usability as good. The response rate is probably related to the clinical outcome after aSAH; the patients using the community were generally in better health, which means that it may not be valuable for those in a worse condition. The users of the community were also younger, which is generally the case with health-related Internet use.[19]

At our center, the treatment of aSAH patients is carried out by a subspecialist team working in a multidisciplinary setting. This team consists of neurologists, neurosurgeons, neuroradiologists, neurorehabiliation specialists, neurointensivists, and a dedicated nursing team using a protocolized aftercare program. This probably contributes to patient satisfaction with treatment, post-treatment care, and communication with caregivers. As important decisions are already taken within this framework, it is likely that no additional benefit of the online health community was identified with respect to managing health, making decisions regarding health, or making contact with caregivers. Moreover, a recent study investigating the use of an online forum identified a participant's motivation to seek out information as one of the factors related to participation in an online community.[4]

However, the patients were positive about MySAH's contribution to their quality of care. Indeed, with the increasing centralization of subspecialized care, this online health community can provide additional, easy access (after-) care at a distance without the need to travel.[3] This was also emphasized in the open suggestions made by the patients concerning how to improve communication with the specialists (rehabilitation specialist) involved with health care after aSAH, and could be valuable in a future online health community. Such a tool would enable answers to be provided quickly on apparently less important, but for the patient at their stage of rehabilitation, very relevant issues (eg, washing hair, biking, sex). MySAH might also serve as a tool for self-management whereby patients are helped to gain control over their lives.[18] Additionally by implementing and evaluating this online community, patient engagement has led to advancements in the aftercare, especially by improved and tailored information. A lesson learned: for future caregivers starting a community, careful selection of the possible participants and their needs is paramount.

As indicated in other publications, household Internet access in the Netherlands is about 92% and should therefore be a minor limitation with respect to access to an online health tool.[16,18] Indeed, this is in line with our data in which only five of 66 patients (7.6%) did not have a computer. However, in some other states in the European Union, Internet access is less, down to 45%, and might therefore be a restricting factor in the success of such an online community.[16,18]

Health-related quality of life is significantly reduced in patients with aneurysmal sub-arachnoid hemorrhage.[6,8,9] Important factors associated with this are physical health issues, depression, cognitive impairment, anxiety, and fatigue,[2,8,9,13,20] and standard aftercare and rehabilitation focuses on these problems. These impairments may, however, have been barriers to the use of the community by those who might potentially benefit from it. Those who did participate evaluated the tool neutrally, regarding their quality of life as neutral.

Limitations

This research has several limitations. First, the number of patients evaluated was only 20, as some of those approached were unwilling or unable to use the MySAH tool. However, within this pilot study, this outcome highlighted the limitations of the community in this patient category. Moreover, for evaluation purposes, having 20 participants is considered to be adequate.[15] Second, usability was self-reported, although from a quality of life perspective the use of subjective experiences is important.[20] Third, the online health community was used as an additional aftercare program and might have experienced some redundancy.

Future studies should assess the value of this online health community when fully integrated in, and as an adjunct to, face-to-face interactions. This could tailor aftercare to the wishes of the patient, enabling more patient-centered care. In our view, it should be emphasized that face-to-face contact continues to be essential in order to precisely determine outcomes and identify possible neurological deficits. Moreover, we envisage a broader use for the MySAH community in other centers involved in aSAH care in the Netherlands. Certainly, the general sections of the site could productively be used by patients from other centers, and the experiences of other caregivers would probably also be beneficial. Furthermore, a larger group of active members may possibly facilitate community sustainability.[14,21] Indeed, organizational commitment and financial and human resources are essential to maintain a community, and these efforts can be supported by the involvement of a larger group of people who provide care to aSAH patients.[21] As a result of the responses to the open questionnaire used in this pilot study, information will be added to the wiki section and rehabilitation specialists will become engaged in the MySAH community.

CONCLUSIONS

In this pilot study, the online health community MySAH contributed to the aftercare of patients suffering from aSAH. There was easy access to information that was relevant for patients and families, which could be obtained from peers or caregivers. The MySAH community will, however, mainly be useful for a select group of patients because of differences in clinical outcomes.

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MULTIMEDIA APPENDIX 6.1

English translation of frequently asked questions in category "Can I…?" (In Dutch; Mag ik…?).

"Can I…?"

…. Fly? Yes you can!

After a subarachnoid hemorrhage, many people wonder if they are allowed to fly. They are afraid that the changed air pressure on the plane may cause a new bleed. Medically speaking, though, there is no reason not to fly.

…. Have sexual intercourse again?

Having sexual intercourse after a subarachnoid hemorrhage… No problem.

After a subarachnoid hemorrhage, many people wonder if they can have sexual intercourse again. They are anxious that a new bleed may occur. It is, however, safe to do so and there is no increased risk of a new hemorrhage.

It often happens that the physical effects of the hemorrhage (fatigue, headache) or feelings of anxiety or apathy affect your relationship and sex life. We recommend that you discuss this with your partner. It is also possible to speak about this with one of your healthcare professionals.

…. Drive my car?

Driving my car after an aneurysm or subarachnoid hemorrhage: is it permitted?

The answer to this question depends on a number of factors. You can read more about government regulations in this blog.

If you have a disease or a condition in which fitness to drive is an issue, as a license holder you are obliged to report this to the Central Bureau for Driver Licences (Dutch: CBR) by way of a "self-declaration".

There are stricter regulations for people who use their license for professional purposes.

The conditions in which this applies are described in the 2000 Ministry of Transport and Water regulation: 'Suitability Requirements'. This regulation was last revised in 2008. Subarachnoid hemorrhage and cerebral aneurysms are both discussed in this regulation.

In summary, the following applies:

People with an accidentally-discovered aneurysm that has not bled, and is not being treated, are generally considered by the CBR to be appropriate to hold a driving license without any time limitations.

People with bleeding from an aneurysm should not drive until six months after the hemorrhage. After this period, when fitness to drive is not an issue, a person can be considered by the CBR to be suitable to hold a driving license. When there is doubt about a dysfunction that may bring the issue of safety into question, the individual's driving must be assessed. In particular, a test drive with an expert from the CBR is required. The CBR has a comprehensive protocol for the test drive procedure. When the driving is assessed as being good, a license is approved for a term of three years.

If you have any questions about your situation and resuming driving, please discuss these with your healthcare professionals.

…. Drink alcohol?

A nice glass of wine? You can!

When you are treated for a ruptured aneurysm, you might wonder whether you can drink alcohol. There is no harm in doing so, as long as it's in moderation. Keep in mind the medication that you are taking and always read the warnings in the leaflet that comes with the drugs.

…. Practice sport?

When you are diagnosed with a subarachnoid hemorrhage due to an aneurysm, you might wonder whether you can take part in sport. There is no harm in doing so. In fact, once you're ready, it is good for your health to participate in sports again.

Please do be aware that you need to build up your physical endurance. However, we recommend gradually increasing the duration, intensity and frequency of your exercise.

…. Go to the sauna?

It is often asked whether a visit to the sauna is possible after a subarachnoid hemorrhage. The answer to this question is 'Yes'.

A visit to the sauna can be relaxing and is therefore for good for you. Once there, like for everyone else, it is important that you drink enough. If you have high blood pressure, it is even more important that you adhere to the sauna regulations. In the sauna, your blood pressure goes down because the blood vessels expand. When cooling off, the opposite occurs. In people with high blood pressure, these fluctuations are greater, meaning that you should stick closely to the requirements of the establishment.

Chapter 7

MRA versus DSA for follow-up of coiled intracranial aneurysms: a meta-analysis

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ABSTRACT

MR angiography is proposed as a safer and less expensive alternative to the reference standard, DSA, in the follow-up of intracranial aneurysms treated with endovascular coil occlusion. We performed a systematic review and meta-analysis to evaluate the accuracy of TOF-MRA and contrast-enhanced MRA in detecting residual flow in the follow-up of coiled intracranial aneurysms. Literature was reviewed through the PubMed, Cochrane, and EMBASE data bases. In comparison with DSA, the sensitivity of TOF-MRA was 86% (95% CI: 82–89%), with a specificity of 84% (95% CI: 81–88%), for the detection of any recurrent flow. For contrast-enhanced MRA, the sensitivity and specificity were 86% (95% CI: 82–89%) and 89% (95% CI: 85–92%), respectively. Both TOF-MRA and contrast-enhanced MRA are shown to be highly accurate for detection of any recanalization in intracranial aneurysms treated with endovascular coil occlusion.

INTRODUCTION

The prevalence of unruptured intracranial aneurysms in the world population is approximately 2–3%.[58,71] The current standard treatment to eliminate the risk of (re)bleeding is exclusion of the aneurysm from the intracranial circulation by use of endovascular detachable coil occlusion.[47] However, recurrences occur in approximately 20% of treated patients, leading to a need for retreatment in approximately 9% of all cases.[49]

DSA is the reference standard for evaluating aneurysms after coiling. However, this technique exposes patients to risks such as cerebral thromboembolism, contrast nephrotoxicity, and ionizing radiation. The transient neurologic complication rate after DSA has been reported to be in the range of 0.34–1.3%, with a risk for permanent neurologic complications of 0.5%. This risk accumulates because repeated follow-ups are necessary.[15,69,77]

MRA can be used for follow-up of coiled intracranial aneurysms, with TOF and contrast-enhanced (CE) MRA being the most commonly used techniques currently available. MRA eliminates the risks of cerebral thromboembolism and ionizing radiation. There is, however, a continuing debate about which of these 2 MRA techniques is best suited for aneurysm follow-up. The systematic review and meta-analysis performed by Kwee et al. in 2007 compared TOF-MRA and CE-MRA with DSA for follow-up of coiled aneurysms.[41] The analysis revealed a moderate to high diagnostic performance of bothMRAtechniques. Because the moderate methodologic quality of the studies available at the time, Kwee and Kwee could not conclude whether MRA can replace DSA as the standard method of reference.[41] Since then, the number of studies on this subject has more than doubled, and study setup and statistical methodology have substantially improved.

The goal of the current study is to systematically review the medical literature to establish whether TOF-MRA and CE-MRA can now be considered good enough for follow-up of patients with coiled intracranial aneurysms.

MATERIALS AND METHODS

Data sources

The medical literature comparing MRA and DSA for evaluating intracranial aneurysms after coiling was reviewed through the use of a variety of data bases—PubMed, EMBASE, and the Cochrane Library—and was updated until March 2012 (Supplemental Table S7.1).

Study selection

After an initial search of the literature by an experienced librarian, duplicate publications were removed. From the pooled list of publications, 2 researchers (M.J.v.A. and H.D.B.) independently reviewed the titles and abstracts of the articles. Studies were excluded if they did not compare MRA with DSA for follow-up of patients with intracranial aneurysms treated with endovascular coil occlusion. Conference abstracts, reviews, editorials, meta-analyses, and animal studies were also excluded. Only articles in English were screened. From the remaining articles, full-text versions were obtained and were independently evaluated by the same researchers (M.J.v.A. and H.D.B.). Studies were eligible for inclusion if they 1) evaluated MRA and DSA for follow-up of patients with intracranial aneurysms treated with endovascular coil occlusion; 2) contained data for 2×2 contingency tables; 3) used the Raymond et al. classification or other compatible scales to grade recurrent flow in intracranial aneurysms;[57,59,60] 4) analyzed TOF and CE MRA separately; and 5) provided data that excluded stent-assisted coiling of intracranial aneurysms. If the same data were used in more than 1 article, the most recent version was included. If the 2 researchers disagreed about selection of articles, an independent third reviewer (R.H.M.A.B.) decided the outcome.

Study quality

The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) method was used to assess the methodologic quality of the studies included in this review.[5,27-35,63] The studies were independently assessed by the 2 researchers (M.J.v.A. and H.D.B.) for limitations, indirectness, inconsistency, imprecision, and publication bias. Agreement between the researchers was quantified by use of Cohen κ.[9] In the case of disagreement, a third reviewer (R.H.M.A.B.) made the final decision.

Data analysis

The *Meta-DiSc* software (http://www.hrc.es/investigacion/metadisc_en.htm) and SPSS statistical package (version 19.0.0; IBM, Armonk, New York) were used for statistical analysis.[80] To evaluate effect size, 2×2 contingency tables were constructed from the articles comparing MRA and DSA. If the true-positive rate, false-positive rate, true-negative rate, or false-negative rate was zero, a standard correction of 0.5 was added to all of the cells of the contingency table. Pooled sensitivity and specificity with 95% confidence intervals were constructed. Data about the accuracy of MRA for grading recurrent flow, as defined by Raymond et al.,[57,59,60] were extracted if available. Classification scales that were compatible with Raymond et al. were also utilized, meaning that the findings could be assigned to 1 of the following categories: complete occlusion; residual neck (1–3 mm); and residual aneurysm (> 3 mm). Results were depicted in a Forest plot and a summary receiver operating characteristic (SROC) curve. An SROC curve plots the positive rate against the false-positive rate of a diagnostic test at the different possible cutpoints. Heterogeneity between the studies was examined by use of the I^2 test. As an indicator of low heterogeneity, a percentage < 40% was taken.[31]

RESULTS

Included studies

Our search string found 424 studies in PubMed, 12 in Cochrane, and 580 articles in EMBASE (Supplemental Table S7.1). A total of 681 studies remained after removal of duplicates. After screening titles and abstracts, 51 articles were deemed fit for full-text evaluation.[1,3,4,8,10-14,16-26,36-40,42-46,48,50-56,61,62,64,66,68,70,72-75,78,79,81] No new articles were found by screening their references. After evaluation of the full-text versions, 3 articles were excluded because they were review papers.[40,72,81] Another 5 studies were omitted because they did not provide enough data for the 2×2 contingency tables.[1,54,55,61,73] Four further studies were left out because they did not compare MRA with DSA,[22,53,64,68] while another 4 were not studying intracranial aneurysms treated with endovascular coil occlusion.[16,36,44,48] Two articles were excluded because information about TOF-MRA and CE-MRA could not be separated.[17,62] One article was excluded because it used CE–TOFMRA.[8] Another 3 articles were excluded because their data were used in earlier studies.[13,24,25] Three studies included patients who had been treated with a secondary Neuroform stent (Stryker Neurovascular, Fremont, California) and were thus omitted (Figure 7.1).[11,12,78] This left 26 studies that were eligible for inclusion (Figure 7.1; Supplemental Table S7.2).[3,4,10,14,18-21,23,26,37-39,42,43,45,46,50-52,56,66,70,74,75,79] Of these articles, 24 researched TOF-MRA[3,4,10,14,18-21,26,37-39,42,43,46,50-52,56,66,70,74,75,79] and 14 researched CE-MRA.[3,14,20,23,38,39,42,43,45,46,50,56,66,75] Twelve studies assessed both TOF-MRA and CE-MRA for the detection of recanalization in coiled intracranial aneurysms in the same subjects.[3,14,20,38,39,42,43,46,50,56,66,75]

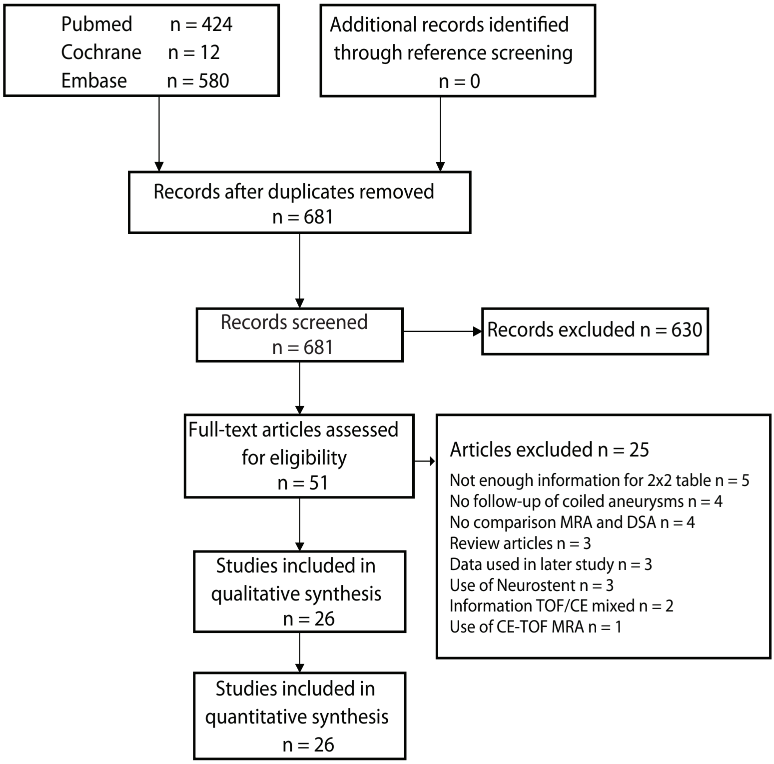

Figure 7.1 Search results.

Study quality assessment

We analyzed the methodologic quality of the 26 articles included in our review according to the GRADE criteria (Supplemental Table S7.3).[5,27-35,63] There was disagreement between the assessments by the 2 researchers with respect to 5 of 104 GRADE scores, resulting in a Cohen κ of 0.81. All of the articles comprised valid studies comparing MRA with the reference standard (DSA). Because of this validity, all of the studies started with a maximal quality score of 4.[63] None of the articles gave any indication that they contained serious inconsistencies or were imprecise.[5,27-35,63] Two studies were rated down because of indirectness; they did not provide enough information concerning their MRA techniques or only included anterior communicating artery aneurysms.[37,43] Quality was rated down in 14 studies because of the following major limitations: the studies did not include consecutive patients, the studies were not prospective, or there was no blinding of the researchers.[3,14,19,20,26,39,45,51,52,56,66,74,75,79]

Data analysis

The pooled results for the sensitivity and specificity of TOF-MRA and CE-MRA are presented in Table 7.1. The sensitivity and specificity for the detection of any recanalization, meaning residual neck or residual aneurysm, are shown in Figure 7.2A–D. TOF-MRA had both a pooled sensitivity and specificity of 86% (95% CI: 83–89%). Pooled sensitivity and specificity of CE-MRA were 85% (95% CI: 81–89%) and 88% (95% CI: 84–91%), respectively. SROC curves are displayed in Figure 7.3A–B for TOF-MRA and CE-MRA. As shown in Figure 7.2A–D, the results were subject to heterogeneity, with I^2 values ranging between 66–80%. For subanalysis, different study variables were distinguished: retrospective versus prospective studies, 2D versus 3D DSA, different MR field strengths, GRADE criteria, and weighted results according to GRADE (Supplemental Table S7.2).

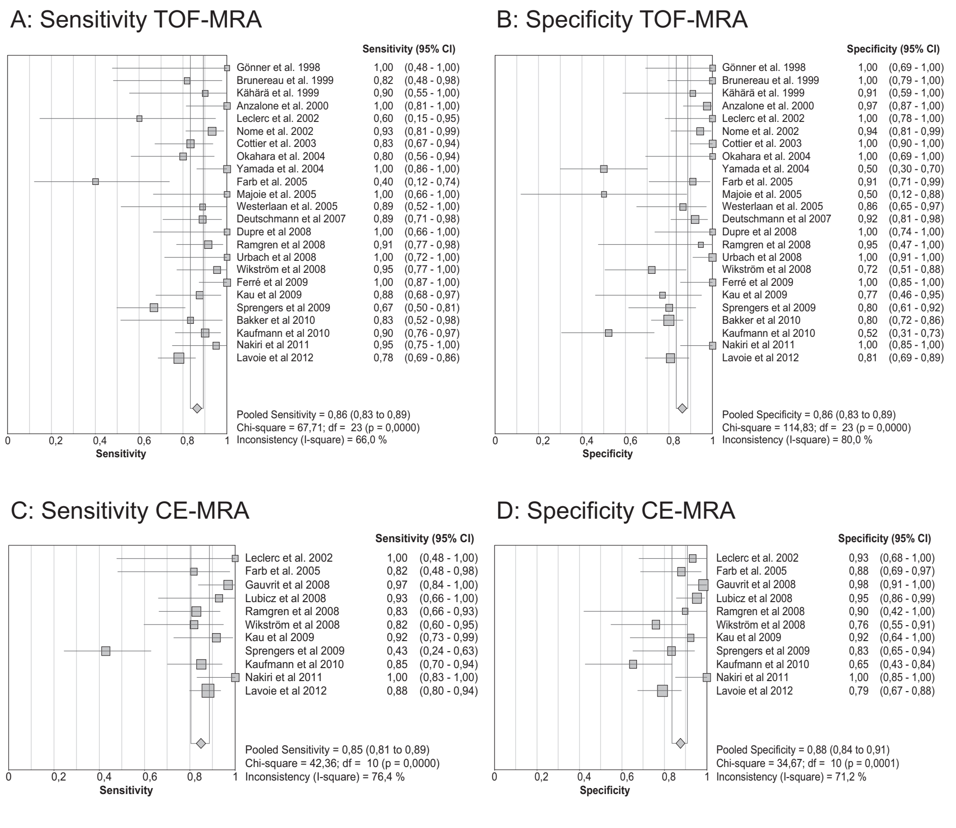

Figure 7.2 Pooled sensitivity/specificity in detecting any recurrent flow.
A = Sensitivity for TOF-MRA. B = Specificity for TOF-MRA. C = Sensitivity for CE-MRA. D = Specificity for CE-MRA.

Table 7.1 Pooled sensitivity and specificity for MRA versus DSA

	TOF-MRA				CE-MRA			
	Sensitivity	Specificity	Positive LR	Negative LR	Sensitivity	Specificity	Positive LR	Negative LR
Any recanalization	86% (83–89%)	86% (83–89%)	6.3 (4.1-9.8)	0.17 (0.11–0.25)	85% (81–89%)	88% (84–91%)	6.2 (3.6–10.6)	0.16 (0.08–0.33)
Residual neck	78% (71–84%)	93% (90–95%)	9.6 (4.5–20.6)	0.29 (0.19–0.46)	56% (41–70%)	91% (84–95%)	6.3 (1.8–22.5)	0.40 (0.15–1.08)
Residual aneurysm	83% (77–88%)	96% (94–97%)	21.4 (10.5–43.7)	0.21 (0.13–0.35)	77% (68–85%)	90% (86–94%)	7.5 (3.8–14.7)	0.29 (0.18–0.48)

Percentages are shown with 95% confidence intervals in parentheses; LR indicates likelihood ratio.
DSA = digital subtraction angiography; MRA = magnetic resonance angiography; TOF = time-of-flight; CE = contrast-enhanced.

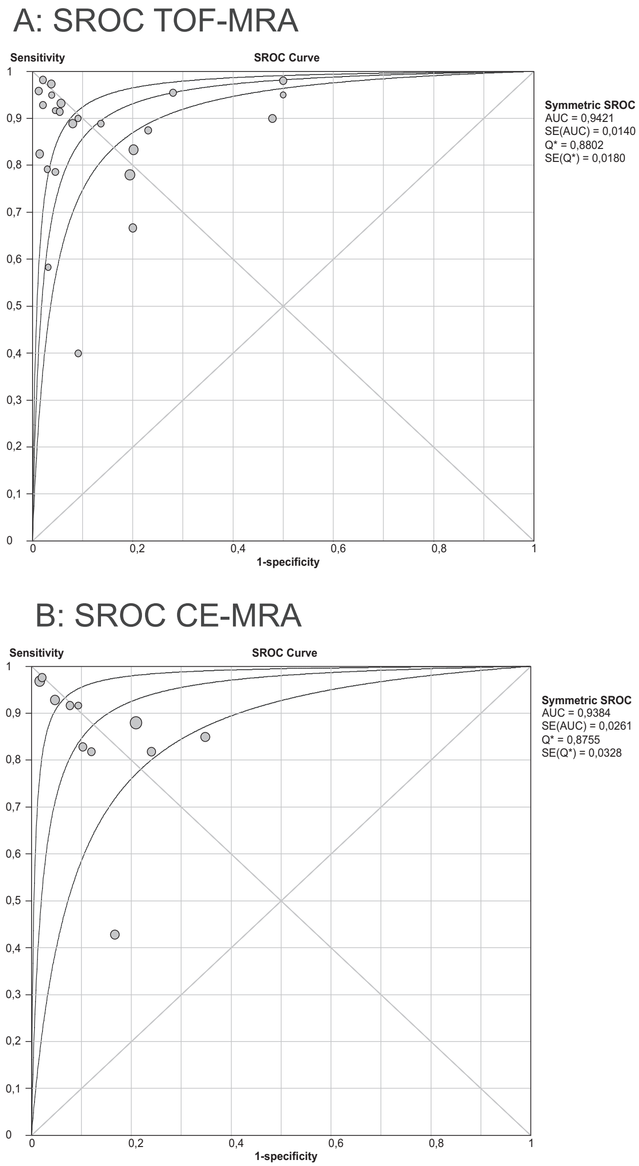

Figure 7.3 A, Summary receiver operating characteristic for TOF-MRA. B, Summary receiver operating characteristic for CE-MRA.

DISCUSSION

The results of our meta-analysis reveal that MRA now has a high degree of sensitivity and specificity in detecting any recanalization during the follow-up of coiled intracranial aneurysms. However, a subanalysis for residual neck or residual aneurysm (Raymond scale

2 or 3, respectively) revealed lower sensitivity and specificity of both MRA techniques compared with DSA as the reference standard (Table 7.1). A possible explanation is the small number of studies and patients included therein, which is reflected in the large 95% confidence intervals. Another potential explanation is false-positive findings seen on DSA possibly caused by pulsation artifacts.[18] However, this comparison makes MRA the reference standard compared with DSA. Because our study compared MRA with the reference standard, DSA, these cases also were judged in favor of DSA. This results in false-negative values for the MRA and a lower sensitivity.

This subanalysis also showed lower sensitivities of the CE-MRA compared with the TOF-MRA for the detection of residual neck or residual aneurysm. The contrast timing together with the narrow interval of scanning in CE-MRA might be the cause of this lower sensitivity. The short time window between the arterial and venous phase of contrast enhancement to avoid venous enhancement and vessel overlap lowers the spatial resolution.[56] Additionally, the acquisition time for TOF-MRA is much longer compared with CE images, leading to improved resolution. The disadvantage of TOF-MRA is its limited coverage; however, TOF is adequate for the evaluation of intracranial vessels. Suboptimal imaging in CE-MRA may therefore lead to more false-negative values, especially in small remnants, lowering the sensitivity.

Significant sources of heterogeneity in this meta-analysis are variations in study design and reporting of data. Evaluation of the studies revealed 5 possible explanations for this heterogeneity: 1) Publication bias remains a potential cause of heterogeneity, because articles with better results are more likely to be published than studies with insignificant or negative findings. 2) Not all of the studies had a prospective design and enrolled patients consecutively, which can be a cause of bias.[6] Sixteen of the 26 were prospective;[4,10,14,19,21,37,39,42,43,46,50,52,56,66,70,75] only 12 studies included consecutive patients.[4,18,21,23,37,38,42,43,46,50,56,70] Retrospective studies tended to be better, with low heterogeneity, compared with the results of the prospective studies, though these findings were not statistically significant (Table 7.2). 3) For the reference standard, 8 reference studies used 3D (rotational) DSA for comparison to MRA,[4,23,38,39,45,50,52,79] whereas the other studies used 2D DSA. Because 3D DSA is better at evaluating recurrent flow in intracranial aneurysms,[65,67] the use of the 2D DSA may reduce calculated specificity but also increase calculated sensitivity of MRA if a true recanalization is missed by DSA. The use of DSA as the reference standard will potentially cause DSA false-negative values to count as MRA false-positive values. In general, MRA tends to perform better when compared with 3D DSA than when compared with 2D DSA (Table 7.2). 4) Heterogeneity may also be

Table 7.2 Subclasses of sensitivity and specificity in TOF-MRA and CE-MRA

	TOF-MRA		CE-MRA	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Retrospective	90% (85–94%)	87% (82–91%)	93% (85–97%)	95% (90–98%)
Prospective	85% (81–88%)	86% (82–89%)	82% (77–87%)	82% (75–87%)
2D-DSA	85% (82–89%)	91% (88–93%)	80% (74–85%)	82% (76–88%)
3D-DSA	90% (84–95%)	76% (70–82%)	92% (86–96%)	93% (88–96%)
1.0–1.5T	86% (83–89%)	85% (81–88%)	89% (84–92%)	87% (83–91%)
3T	88% (82–92%)	87% (80–92%)	79% (71–86%)	83% (74–91%)
GRADE 2–3	87% (82–90%)	86% (81–89%)	77% (70–84%)	85% (79–90%)
GRADE 4	86% (81–90%)	87% (83–90%)	92% (86–95%)	90% (85–94%)
Weighted results	86% (85–88%)	86% (85–88%)	87% (85–89%)	88% (86–90%)

Percentages are shown with 95% confidence intervals in parentheses.
DSA = digital subtraction angiography; MRA = magnetic resonance angiography; TOF = time-of-flight; CE = contrast-enhanced; GRADE = grades of recommendation, assessment, development, and evaluation; SROC = summary receiver operating characteristic.

caused by different field strengths used in the various studies.[2,7] Five studies only researched 3T MRA,[21,46,50,66,70] whereas 2 articles studied both 3T and 1.5T MRA techniques.[39,56] Two studies were performed with a 1T scanner.[10,51] The rest of the articles evaluated MRA by use of 1.5T units. There is a trend toward higher pooled sensitivity and specificity of TOF-MRA with 3T units compared with 1.5T scanners, though the 95% confidence intervals overlap (Table 7.2). This trend might be caused by the higher resolution of images created with a 3T MR imaging compared with 1.5T scanners.[76] However, the sensitivity and specificity of 3T CE-MRA is lower than that at 1.5T, though this difference is not statistically significant. Again, the small number of studies researching CE-MRA at 3T limits the interpretation of results and might be the cause of this nonsignificant difference without reflecting any underlying inferiority.[39,46,50,56,66] 5) A final cause of heterogeneity might be the difference in study quality as judged by the GRADE criteria.[5,27-35,63] GRADE 4 quality studies tend to have higher sensitivity and specificity. This difference reaches significance in sensitivity for CE-MRA (Table 7.2). Weighted by GRADE, overall comparisons between TOF-MRA and CE-MRA revealed results that were similar to the overall pooled results.

Our results provide a more detailed and updated evaluation of the accuracy of MRA for follow-up of coiled intracranial aneurysms than earlier work by Kwee and Kwee.[41] Our detailed subanalysis of results reveals consistently good performance of MRA techniques with pooled sensitivities and specificities well above 80%. For the important question of residual aneurysms (Raymond grade 4), CE-MRA even provides a pooled sensitivity and specificity > 90%, with a lower 95% confidence interval of ≥ 85%.

CONCLUSIONS

This meta-analysis has revealed that MRA has a high diagnostic performance when it comes to the detection of residual flow in the follow-up of intracranial aneurysms treated with endovascular coil occlusion and therefore should be routinely used for follow-up. CE-MRA did not perform significantly better than TOF-MRA, indicating that follow-up with the latter should be adequate.

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SUPPLEMENT

Supplemental Table S7.1 Search strategy and results of MEDLINE, Embase, and Cochrane Library searches*

Step	Search	Results		
		Pubmed	Cochrane	Embase
1	Subarachnoid Hemorrhage[Mesh]	14,698	811	24,338
2	((Subarachnoid[tiab] OR Subarachnoidal[tiab]) AND (Haemorrhage[tiab] OR Hemorrhage[tiab] OR Haemorrhages[tiab] OR Hemorrhages[tiab] OR Hematoma[tiab] OR Bleeding[tiab] OR Blood[tiab])) OR SAH[tiab] OR SAHs[tiab]	18,856	1,026	22,994
3	#1 OR #2	22,949	1,026	30,916
4	Intracranial Aneurysm[Mesh]	19,390	441	22,471
5	((Aneurysm[tiab] OR Aneurysms[tiab]) AND (Brain[tiab] OR Cerebral[tiab] OR Intracranial[tiab] OR Intra-cranial[tiab] OR Basilar Artery[tiab] OR Anterior Communicating Artery[tiab] OR Middle Cerebral Artery[tiab] OR Posterior Cerebral Artery[tiab] OR Anterior Cerebral Artery[tiab] OR Posterior Communicating Artery[tiab]))	18,364	555	22,051
6	#4 OR #5	25,687	555	30,331
7	#3 OR #6	40,494	1,307	50,984
8	Magnetic Resonance Angiography[Mesh]	14,084	487	18,939
9	((Angiography[tiab] OR Angiographies[tiab]) AND (MRI[tiab] OR Magnetic Resonance[tiab] OR MR[tiab])) OR ((Angiogram[tiab] OR Angiograms[tiab]) AND (MR[tiab] OR MRI[tiab])) OR Perfusion Magnetic Resonance Imaging[tiab] OR Perfusion Weighted MRI[tiab] OR MRA[tiab] OR MRAs[tiab] OR MR angiographic[tiab] OR MRI angiographic[tiab]	18,497	681	23,394
10	#8 OR #9	25,439	681	32,287
11	Angiography, Digital Subtraction[Mesh]	6,783	357	11,616
12	((Angiography[tiab] OR Angiographies[tiab] OR Angiographic[tiab]) AND (Digital Subtraction[tiab] OR Digital[tiab] OR Catheter[tiab])) OR DSA[tiab] OR DSAs[tiab] OR IDSA[tiab] OR Catheter-angiography[tiab]	14,362	632	13,488
13	#11 OR #12	18,002	703	18,709
14	#7 AND #10 AND #13	561	13	744
15	Limits: English	424	12	580

* MeSH = Medical Subject Headings; tiab = title/abstract.

Supplemental Table S7.2 Study characteristics of the included articles

Ref.	Author	Year	Prospective?	Consecutive?	No. of patients	Mean age	Evaluated aneurysms	Type MRA	Field strength	DSA	Interpreters
26	Gonner et al.	1998	Not stated	Not stated	14	50	18	TOF	1.5T	2D	2 interpreters
10	Brunereau et al.	1999	Yes	Not stated	26	52	27	TOF	1.0T	2D	2 interpreters
37	Kahara et al.	1999	Yes	Yes	20	49	21	TOF	Not stated	2D	2 interpreters
3	Anzalone et al.	2000	Not stated	Not stated	49	53	64	TOF, CE	1.5T	2D	1 interpreter
43	Leclerc et al.	2002	Yes	Yes	20	49	20	TOF, CE	1.5T	2D	Not stated
51	Nome et al.	2002	Not stated	Not stated	51	Not stated	79	TOF	1.0T	2D	3 interpreters
14	Cottier et al.	2003	Yes	Not stated	58	52	71	TOF, CE	1.5T	2D	2 interpreters
52	Okahara et al.	2004	Yes	Not stated	33	63	33	TOF	1.5T	3D	2 interpreters
79	Yamada et al.	2004	Not stated	Not stated	39	59	51	TOF	1.5T	3D	1 interpreter
20	Farb et al.	2005	Not stated	Not stated	28	47	36	TOF, CE	1.5T	2D	3 interpreters
46	Majoie et al.	2005	Yes	Yes	20	49	21	TOF, CE	3T	2D	Not stated
74	Westerlaan et al.	2005	Not stated	Not stated	31	52	31	TOF	1.5	2D	1 interpreter
18	Deutschmann et al.	2007	Not stated	Yes	127	49.6	188	TOF	1.5T	2D	3 interpreters

Supplemental Table S7.2 continues on next page

Supplemental Table S7.2 *Continued*

Ref.	Author	Year	Prospective?	Consecutive?	No. of patients	Mean age	Evaluated aneurysms	Type MRA	Field strength	DSA	Interpreters
19	Dupre et al.	2008	Yes	Not stated	15	47.7	17	TOF	1.5T	2D	2 interpreters
23	Gauvrit et al.	2008	Not stated	Yes	170	46	92	CE	1.5T	3D	3 interpreters
45	Lubicz et al.	2008	No	Not stated	55	46	67	CE	1.5T	3D	2 interpreters
56	Ramgren et al.	2008	Yes	Yes	37	51	41	TOF, CE	1.5T, 3T	2D	3 interpreters
70	Urbach et al.	2008	Yes	Yes	50	47	50	TOF	3T	2D	3 interpreters
75	Wikström et al.	2008	Yes	No	38	Not stated	47	TOF, CE	1.5T	2D	4 interpreters
21	Ferré et al.	2009	Yes	Yes	51	51	50	TOF	3T	2D	2 interpreters
38	Kau et al.	2009	No	Yes	32	52.2	37	TOF, CE	1.5T	3D	3 interpreters
66	Sprengers et al.	2009	Yes	Not stated	67	49	69	TOF, CE	3T	2D	2 interpreters
4	Bakker et al.	2010	Yes	Yes	190	54	141	TOF	1.5T	3D	MDP
39	Kaufmann et al.	2010	Yes	Not stated	58	59.3	63	TOF, CE	1.5T, 3T	3D	2 interpreters
50	Nakiri et al.	2011	Yes	Yes	30	54.5	43	TOF, CE	3T	3D	2 interpreters
42	Lavoie et al.	2012	Yes	Yes	157	53	167	TOF, CE	1.5T	2D	3 interpreters

MDP = Multidisciplanary panel.

Supplemental Table S7.3 GRADE analysis

Ref.	Comparison with DSA?	Limitations	Inconsistency	Indirectness	Imprecision	Pub. bias	Quality
26	Yes	+	-	-	-	-	3 / 4
10	Yes	-	-	-	-	-	4 / 4
37	Yes	-	-	+	-	-	3 / 4
3	Yes	+	-	-	-	-	3 / 4
43	Yes	+	-	+	-	-	2 / 4
51	Yes	+	-	-	-	-	3 / 4
14	Yes	+	-	-	-	-	3 / 4
52	Yes	+	-	-	-	-	3 / 4
79	Yes	+	-	-	-	-	3 / 4
20	Yes	+	-	-	-	-	3 / 4
46	Yes	-	-	-	-	-	4 / 4
74	Yes	+	-	-	-	-	3 / 4
18	Yes	-	-	-	-	-	4 / 4
19	Yes	+	-	-	-	-	3 / 4
23	Yes	-	-	-	-	-	4 / 4
45	Yes	+	-	-	-	-	3 / 4
56	Yes	+	-	-	-	-	3 / 4
70	Yes	-	-	-	-	-	4 / 4
75	Yes	+	-	-	-	-	3 / 4
21	Yes	-	-	-	-	-	4 / 4
38	Yes	-	-	-	-	-	4 / 4
66	Yes	+	-	-	-	-	3 / 4
4	Yes	-	-	-	-	-	4 / 4
39	Yes	+	-	-	-	-	3 / 4
50	Yes	-	-	-	-	-	4 / 4
42	Yes	-	-	-	-	-	4 / 4

Chapter 8

Quality registration of complex care: a national approach for neurosurgical procedures

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Submitted for publication

ABSTRACT

In the Netherlands, the National Neurosurgical Society has initiated a physician-driven, national outcome register for four highly-complex/low-volume disorders: high-grade gliomas, pituitary tumors, hydrocephalus in children under the age of two, and aneurysmal subarachnoid hemorrhages. The main purpose of the quality register is to ensure that each surgeon improves the quality of his/her care. The primary way of achieving this is by providing outcome data in a dashboard for each center that is updated two-weekly and compared to the center's historical figures and the national average. Information on the number of registered patients per hospital is made public. Initial experiences with registration up to 6,000 patients are discussed.

INTRODUCTION

Healthcare is at a turning point. Continuously rising costs, despite attempted savings, means there is a need to redefine the ultimate goal.[8] Reforms aim to achieve the best outcomes for the lowest price.[2] However, until recently outcomes were not systematically recorded and, when they were measured, were hard to compare. Systematic neurosurgical outcome registers have emerged in the last few decades, e.g. the Swedish spine registry (Swespine), the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), and more recently the neurosurgical specific National Neurosurgery Quality and Outcome Database (N2QOD), among others.[2,3,10,15] Typically, these outcome registries focus on spinal procedures, while those for more complex neurosurgical conditions are still being developed.[10,12]

There is an increasing need to also monitor outcomes for these highly-complex/low-volume interventions, because they are often associated with significant morbidity and mortality, as well as a high cost per patient. Registers based on hospital coding, typically only provide general data, and not the information needed to produce meaningful, casemix-corrected, disease-specific outcomes. In the Netherlands, the National Neurosurgical Society has initiated a physician-driven, national outcome register for four highly-complex/low-volume disorders. This initiative has been embraced and financed by the government organization responsible for healthcare inspection and a number of the larger insurance companies. After four years of data collection, meaningful information has started to emerge. Patient participation in the data-analysis and publication of some of the results will be the next phase. This paper describes our experiences with our national outcome register and we hope it will provide a framework for other neurosurgical communities.

NEUROSURGERY IN THE NETHERLANDS

The healthcare system in the Netherlands (17 million inhabitants) can be described as a well-regulated, socialized medicine. Right from the start of neurosurgery in the country, the discipline has been covered by national laws. Government regulations mean that intracranial neurosurgery, as well as complex spine and nerve surgery, can only performed in centers with appropriate government permission. Complex neurosurgery is thus currently performed in 18 hospitals; eight of these are also academic establishments and 10 are major regional general hospitals with a recognized top-clinical and training status. Ninety-two percent of the 120 neurosurgeons in the Netherlands are members of the Neurosurgical National Society (Nederlandse Vereniging voor Neurochirurgie, NVvN), which is the only such body in the country. The maintenance and improvement of the quality of care has always been the primary focus of the NVvN, which is why it put in place the national outcome register.

REGISTERED DISORDERS

Four intracranial disorders are subject to registration: high-grade gliomas, pituitary tumors, hydrocephalus in children under the age of two, and aneurysmal subarachnoid hemorrhages. These specific diseases were chosen because they have a relatively high incidence rate, require a complex multidisciplinary treatment, and cause significant mortality and morbidity and/or have a lifelong impact. The initial basis of this outcome register was a set of quality indicators that were determined by a consensus of the society's members in 2007 (Table 8.1).

Table 8.1 Quality indicators per disease classified by structure, process and outcome

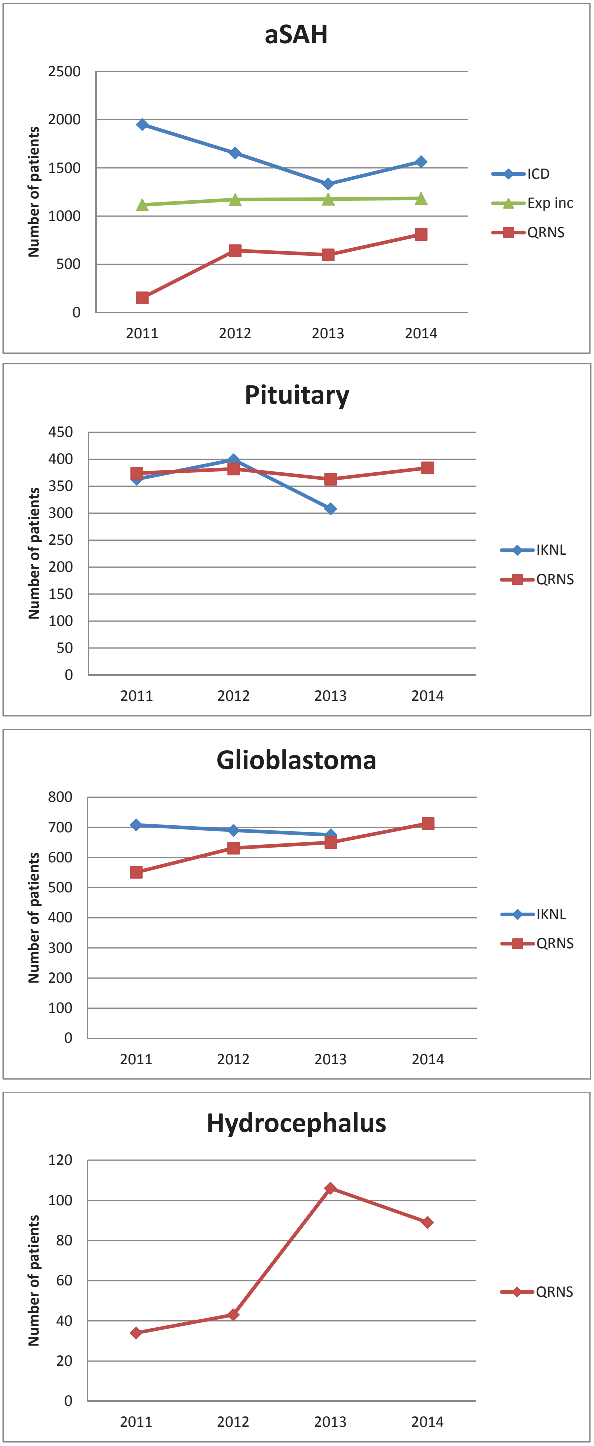
	Aneurysmal subarachnoid hemorrhage	High grade glioma	Pituitary tumors	Hydrocephalus under the age of 2
Structure	Number of patients	Number of patients, total number of tumor related craniotomies	Number of patients	Number of patients, implant registry system, protocols for secondary treatment (physiotherapy)
Process	Complications, time of bleeding, hospitalization, and treatment, treatment modality Number of patients transferred or not accepted for treatment	Complications, proportion of patients operated ≤ 4 weeks from diagnosis (MR), proportion of patients started with radiotherapy ≤ 8 weeks	Complications, time from diagnosis to treatment	Complications, cause of hydrocephalus
Outcome	6 months outcome (mRS)	30 days mortality, and Survival status 6, 12, 18, and 24 months postoperative, Karnovsky performance score pre, and 6 weeks postoperative	30 days mortality, proportion of cure in hormone active tumors (Cushing & acromegaly), proportion of visual improvement (if applicable)	Percentage of 1 year "shunt survival", percentage of shunt infections 1 year after placement

ORGANIZATION OF REGISTER

The quality register, which has a number of sub-registers, is embedded in the NVvN in the form of a special register committee, but is ultimately the responsibility of the organization's board of directors. Each sub-register has its own group of experts, with one delegate per center. The main purpose of the quality register is to ensure that each surgeon improves the quality of his/her care. The primary way of achieving this is by providing outcome data for each center that is updated two-weekly and compared to the center's historical figures and the national average. The data are corrected for case-mix, statistically analyzed, and discussed by expert groups. During national meetings of the NVvN, outcome data per center are presented, without naming the particular source establishment. Specific items per register are also evaluated, and the register is modified where necessary. The results are not surgeon based, as complex diseases, that often require treatment in a multidisciplinary setting are evaluated. The outcomes are considered to be results arising from the complete chain of care. A quality of care control cycle is effectively created in this way for the whole team. It is not the NVvN's intention to criticize any colleague or practice. However, a responsibility has been imposed to raise an alert about significant outliers. A system to achieve this in a professional manner has been established. Although the system is partly financed by healthcare insurance, these companies are not given the data. Quality improvements by auto-regulation, which are accomplished by reducing any undesirable variability, with subsequent improvements in the mean, are the goal of every stakeholder in the care process. Several methods are used to achieve internal data validity: data verification with a random sample; data entry by independent data typists; and cross-checks with other registers, e.g. a nationwide pathology database. Automated coupling with electronic patient files also minimizes drop-outs. The automated coupling transfers primary patient data like date of birth and sex, which are encrypted by a trusted third party (ZorgTTP) to guarantee the privacy of all patients.

INITIAL EXPERIENCES

Initial registration was slow due to a cumbersome registration process and a lack of direct feedback about the entered data. This process has now been improved, and up to 6,000 patients are registered. Information on the number of registered patients per hospital is made public at http://www.qrns.nl/stand-van-zaken. Yearly totals per disease are set out in Figure 8.1. A benchmark for the total numbers is also provided, if available to estimate the



A: Aneurysmal subarachnoid hemorrhage (aSAH)
ICD (International Classification of Diseases), QRNS: Quality Registry Neurosurgery, Exp inc: expected incidence based on published literature of 7 per 100,000.[16] Number of inhabitants based on *eurostat*.[17]

B: Glioblastoma multiforme
IKNL: Database of the Netherlands Cancer Registry (2014 number of patients from IKNL not yet available), QRNS: Quality Registry Neurosurgery.

C: Pituitary surgery
IKNL: Database of the Netherlands Cancer Registry (2014 number of patients from IKNL not yet available), QRNS: Quality Registry Neurosurgery. Larger number of cases in QRNS explained by the registration of also non-tumorous diseases.

D: Hydrocephalus under the age of 2
QRNS: Quality Registry Neurosurgery. No benchmark available.

Figure 8.1 Numbers of patients registered in the QRNS system compared to other registers.

number of missing cases. Possible benchmarks for the total number of patients are: ICD coding, calculated incidence, or the database of the Netherlands Cancer Registry (NCR) hosted by the Netherlands Comprehensive Cancer Organization (IKNL).[1,14] A growing number of patients have been registered, although further improvement in this regard is one of the most important goals in the near future. The combination of the quality register and a scientific interest in nationwide data will provide additional incentives to complete the data recording process. Additionally, involving other associated specialists like endocrinologists for a pituitary register, neurologists and neurointerventionalists for an aSAH register, and neurologists for a glioblastoma register helps in gaining support and motivation for the data entry process. Finally, a new interface for the quality register system has been realized by automated coupling with electronic patient files as discussed above.

The new register system produces a two-weekly-updated dashboard. The outcome results of each center can thus be visualized and compared to anonymized nationwide data using a "statistical mirror". Deviations from the mean can be detected early by users themselves and allows care to be evaluated by, e.g., easy to read funnel plots (Figure 8.2). Detailed descriptions per disease will be the subject of forthcoming publications. Although the register is used primarily for quality purposes, the scientific publication of nationwide results will provide a valuable benchmark for other centers worldwide. Publication of the results will be in accordance with each local representative, and the data are submitted to the QRNS committee for approval.

DISCUSSION

The QRNS system and organization has two primary goals: registering nationwide (risk-adjusted) outcomes for complex neurosurgical diseases to provide a benchmark for primary outcome measures; and identifying hospital outliers and initiating a quality improvement process if required. The success of this quality initiative is achieved by institutional embedding nationally with local (hospital) representatives and, by providing real time-feedback.

Pioneering work on quality measurement has been conducted by Donabedian who outlined a conceptual framework for providing insight into healthcare delivery.[4,5] This framework distinguishes structure, process, and outcome measures. More recently, the topic of quality has focused more on value, as raised by Porter.[13] Value is defined as health outcomes achieved per dollar spent, and is centered on the patient, encompassing the entire cycle of care.[13] Outcomes are condition specific and have multiple hierarchal layers according to this view.

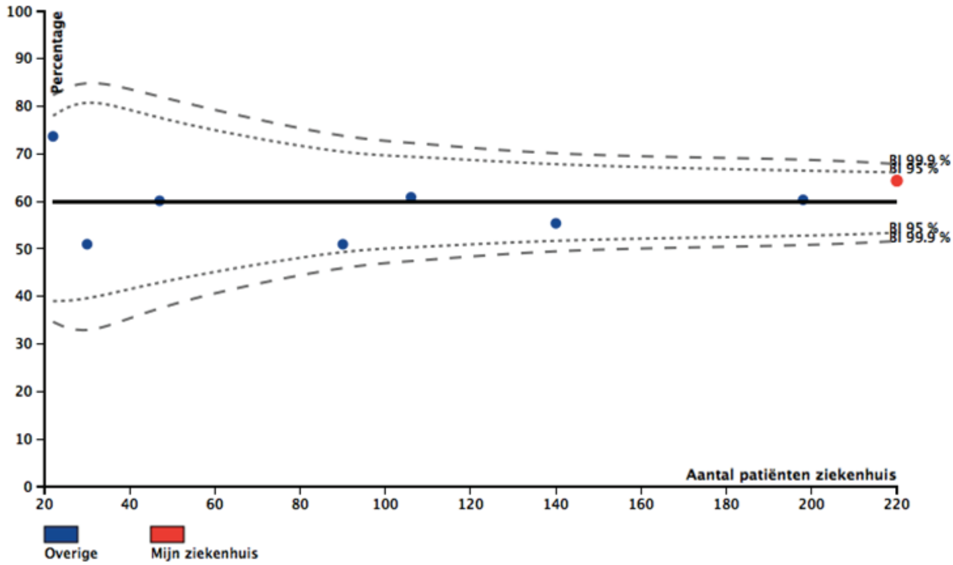


Figure 8.2 Screenshot from online dashboard for aneurysmal subarachnoid hemorrhage: Funnel plot for case mix corrected 6 months outcome (percentage of patients with mRS≤2) as a function of total number of treated patients per hospital.
The horizontal line indicates nationwide mean percentage of patients with mRS≤2 after 6 months. Dotted and interrupted lines of funnel indicate 95% and 99.9% confidence intervals respectively. Anonymized other hospitals indicated by blue dots, own hospital depicted in red. Translation of text in figure: Mijn ziekenhuis: My hospital, Overige: Other hospitals, Aantal patienten ziekenhuis: Number of patients per hospital, Percentage: percentage.

Quality evaluation should indeed have outcome measurement as its ultimate goal, although, the current healthcare system has barriers when evaluating complex heterogeneous conditions using almost all levels of care. Additionally, from a quality improvement point of view, it is essential to not only focus on outcomes but also on the process of healthcare delivery.[11,16] Several approaches to healthcare improvement focus on tools like plan-do-study-act, six-sigma, lean strategies or combinations of thereof.[16] These strategies can be applied to different elements of the process of healthcare delivery, and provide tools for rapid improvements.[9] The QRNS contains outcome as well as structure and process indicators for this reason. Moreover, in very complex diseases, natural variabilities in outcomes may be high, which could potentially mask a small, but relevant, effect of structure or process elements, especially if the number of patients is low.

Health-related quality of life measures are not yet included, but the glioblastoma dataset will be extended in the near future with such questionnaires (QLQ-C30, QLQ-BN20).[6,7]

The costs of care, which are the denominator of the value equation, are not directly evaluated by this system.[13] Healthcare insurance provides more or less similar payments for each disease to different hospitals in the Netherlands. Future benchmarks with other centers in Europe or around the world will enable comparisons to be made of the value achieved in healthcare.

The system evaluates aggregated hospital-based rather than individual patient results. However improvements in overall results eventually lead to in improvements for the individual patients. Based on the nationwide results on the outcomes achieved, prediction models will be constructed that can identify possible discrepancies at the individual patient level.

CONCLUSION

The QRNS is a nationwide quality register system for complex neurosurgical diseases. The register is embedded in the Dutch neurosurgical society. An online up-to-date dashboard provides insight into the performance of each hospital and can be a starting point for quality improvement processes.

Disclosure

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Chapter 9

Summary and conclusion

Quality of care measurement for patients with aneurysmal subarachnoid hemorrhage (aSAH) is challenging. The multiplicity of factors that affect the outcome make a transparent determination of such a measurement and comparison between measurements difficult. This thesis evaluated several aspects of quality of care for patients with aSAH.

In many complex diseases hospital volume is used as a structure indicator to differentiate between hospitals. For aSAH, provider volume is also related to in-hospital mortality in reported literature. This finding was discussed in **Chapter 2**. The meta-analysis of four studies representing 36,600 patients revealed a significant relationship that became even stronger when one low-quality study was removed. It should be noted that there was no uniform cut-off between high and low volume hospitals. To attain comparable results between studies, recalculation with dichotomized data centering around 20–30 patients per year was performed. This also revealed a significant relationship. It should be noted that the data mainly rely on retrospectively coded US hospital databases. Furthermore, treatment modality was not evaluated and case-mix correction was not performed, even though both are known to be influential for outcome. This meta-analysis does not provide a number of patients to be treated by a single neurosurgeon or neurointerventionalist. The results of treatment are not the merits of one specialist but the outcome of the chain of care. In the scope of quality of care and the increasing demand for centralization, volume number alone is not sufficient as a parameter to guide these developments. Hospital volume should be seen as one of the cofactors related to outcome.

Outcomes in aSAH are mainly determined by clinical condition at admission. Comorbidity on the other hand also influences outcome. The Charlson Comorbidity Index (CCI), an index used to weight several co-morbid conditions, is used for case-mix correction in ischemic cerebrovascular disease. In **Chapter 3**, we evaluated this index for case-mix correction in aSAH. We retrospectively analyzed a consecutive series of aSAH patients treated at Radboud university medical center (Radboudumc), Nijmegen. A binary logistic regression analysis revealed no beneficial use of the CCI in predicting 6-months outcome after aSAH. In this model strong predictors of outcome were initial grade (WFNS: World Federation of Neurological Surgeons Grading System), age and treatment modality. A larger number of patients could elucidate a small but relevant relationship. Hypertension is not included in the CCI but is a frequently reported comorbid condition associated with bad outcome. The growing interest in outcome registration and associated parameters relevant to outcome places an increasing burden on healthcare providers. Focus on items of significant interest is therefore important. The CCI as a whole set of comorbidity parameters has no association with outcome.

For patients with aSAH, rerupture of the aneurysm prior to treatment is a major cause of morbidity and mortality. It is important to recognize risk factors for aneurysmal rebleeding and these might help to identify aneurysms that benefit from acute treatment. In **Chapter 4** we investigated whether aneurysm size is related to rebleeding by performing a meta-analysis of the published literature. The results of this analysis of 7 studies and 2,121 patients show that aneurysm size is an important determinant of aneurysmal rebleeding. It is unlikely that age and location are confounding factors. Hypertension was insufficiently registered to determine the role of possible confounding effects. Patients with large aneurysms should undergo acute treatment rather than ultra-early treatment when feasible. Since the effect size of this association might persist for up to 72 hours after the initial bleed, referred patients or patients with delayed diagnosis still require urgent treatment. It is important to note that there is a potential for publication bias; studies showing no association between aneurysm diameter and rebleeding rate are less likely to be published. Also patients who died before hospital admission were not included. Confounding factors like time to hospital admission, time to aneurysm repair and the effect of aminocaproic acid were insufficiently registered to assess their effect on the results.

Analysis of complications and durability of the treatment of aSAH patients, as part of the second and third tiers respectively in the outcome hierarchy, is important. Knowledge of these, especially one's own results, provides a starting point of the improvement cycle. The results are presented in **Chapter 5** and placed in the context of dual trained neurosurgeons. Prospectively collected data from 356 patients treated at the Neurosurgical Centre Nijmegen revealed a combined procedural persistent neurological morbidity and mortality after endovascular and/or surgical treatment of 2.1% and 1.4% respectively. Overall procedure-related clinical complication rate was 5.9% and 9.9% respectively. Regarding durability of the endovascular treatment recurrence rate was 18.8% and retreatment rate 13.3% (mean follow-up of 13.8 months). Open surgical treatment revealed 7.4% neck rests with retreatment of 1.9% (mean follow-up of 6.5 months). These results are comparable with those published in the literature. Treatment of aSAH by dual trained neurosurgeons is safe and effective.

Healthcare delivery should be centered on the patients and investigate patients' needs. This can be accomplished by an exchange of information between patient and caregiver and between patients. An online health community might contribute to this. The value of such a community for aSAH patients is reported in **Chapter 6**. An online, members only, health community (mijn SAB, translation: MySAH) was implemented in addition to the usual aSAH care at Radboudumc, Nijmegen. The use and usability of the MySAH community were evaluated using a questionnaire. Of the 66 consecutive aSAH patients informed about the community, 26 gained access to MySAH and 20 were willing to participate. Participants were younger and in a better clinical condition at discharge than non-participants. The patients were positive about the contribution to the quality of care but not about the contribution to their quality of life. This pilot study indicated a beneficial effect of the online health community (MySAH) on the aftercare of aSAH patients, because it provides in easy access to relevant information provided by peers or caregivers. The community will mainly be useful for patients with a better clinical outcome.

The possibility of aneurysm recurrence among patients treated endovascularly (coiled) necessitates imaging control. Both digital subtraction angiography (DSA) and MR angiography (MRA) are suitable, although the latter is a safer and less expensive. Two MRA techniques, time of flight (TOF) and contrast enhanced (CE) are the most commonly used techniques available. In **Chapter 7** the medical literature is systematically reviewed to evaluate the accuracy of TOF-MRA and CE-MRA in detecting residual flow in coiled aneurysms. Of the 26 studies eligible for inclusion, 24 investigated TOF-MRA, 14 CE-MRA and 12 studies assessed both TOF-MRA and CE-MRA. The analysis revealed that MRA (both TOF and CE) has a high degree of sensitivity in detecting any recanalization. A subanalysis, however, for residual neck or residual aneurysm revealed lower sensitivity and specificity of both MRA techniques compared with DSA. This might be explained by the small number of studies and the low number of patients these included. False-positive findings seen on DSA that might have been caused by pulsation artifacts are another explanation. Since the reference standard is DSA, these cases were judged in favor of DSA. This results in false-negative values for the MRA and lower sensitivity. Further findings of the subanalysis were lower sensitivities of the CE-MRA compared with the TOF-MRA, which were probably related to contrast timing in CE-MRA, and longer acquisition time for TOF-MRA. This meta-analysis could be subject to several sources of heterogeneity: publication bias, retrospective analysis of studies, the use of 2D or 3D (rotational) DSA as a reference, different field strength of MR (1, 1.5 or 3T) and finally difference in study quality.

To improve quality measurement is the first step. **Chapter 8** outlines the Dutch neurosurgical quality register for aSAH and three other highly-complex/low-volume disorders. The register is embedded in the Netherlands Society for Neurosurgery (Nederlandse Vereniging voor Neurochirurgie, NVvN). The main goal of the quality register is to provide a benchmark for primary outcome measures. Secondly it aims to identify hospital outliers and initiate a quality improvement process. This is achieved by providing outcome data for each center in an online dashboard, which is updated once every two weeks and compared to the center's historical figures and national average. The outcome measures are hospital based because it evaluates a complex disease requiring treatment in a multidisciplinary setting. The results therefore arise from the complete chain of care. A growing proportion of the expected number of patients nationwide are registered compared with ICD coding or calculated incidence. However, further improvement in registration is needed in the near future. To facilitate this an automated coupling with the electronic patient file is being realized. Secondly involvement of neurologist and neurointerventionalists in the registration can contribute to this. Thirdly combining a quality register with a scientific interest in nationwide data will probably provide additional incentives for data entry.

FUTURE PERSPECTIVES

The measurement of quality of care in aSAH requires standardized, clear outcome measures. Mortality and the modified Rankin scale are used as primary outcome measures in multiple clinical trials and the Dutch neurosurgical quality register (QRNS).[2-4] Although changes in case fatality over the years indicate that these are still relevant outcome measures, more refined standardized outcome measures including neuropsychological assessment and health-related quality of life should be developed and validated.[5,9] This should also include a disease- specific, patient-reported, outcome measurement (PROM). Ideally a composite score of outcome should be reached that encompasses all relevant items defined in the different outcome tiers.[6]

Outcomes of care for aSAH are measured on an aggregate level of the hospital. Clearly it is considered to be the result of the entire chain of care. From a quality improvement point of view, however, these composite results need to be disentangled to identify the differences causing the outcomes achieved. Future analysis will elucidate if the registered items are distinctive and provide tools for quality improvement. The results should also be applied to construct a prediction model. Outcomes can then be evaluated on an individual patient level. Discrepancies between attained and predicted outcome warrants evaluation of the course of treatment and can highlight possible causes of underperformance. This will be an additional stimulus for the improvement of care.

Although preliminary results of the Dutch neurosurgical quality register (QRNS) are promising, the amount of missing values is substantial. Meaningful conclusions cannot be drawn at present. High compliance with the quality register is therefore of paramount importance. A highly automated data entry via couplings with the electronic patient file, like the UK nephrology register, is the ultimate goal.[8] Couplings to import basic patient data are a practical first step. A multidisciplinary registration, by all specialists involved would probably also decrease the percentage of missing data. After nationwide results become reliable, a benchmark with other centers in other countries will place the results in a broader perspective. Future clinical trials can use the register as a platform to implement an electronic case report form.

The preliminary results of the quality register (QRNS) in the funnel plot for the treatment of aSAH do not indicate any significant difference in hospital performance.[1] If these findings are confirmed in the near future, once reliable results are available, then it can be questioned if the continuation of the register is still justified. Besides the value of such a register from a patient counseling perspective and a scientific research perspective, the goal in the future should be to improve the mean outcome. Even the slightest improvement in care for this disease with major socioeconomic impact justifies the effort and costs associated with the register.[7] It will be an endeavor to distribute the economic gain to caregivers for the coverage of the register for which registration is a non-negligible burden.

CONCLUSION

In this thesis we have evaluated several aspects of quality of care for patients with aneurysmal subarachnoid hemorrhage. There is a relationship between hospital volume and in-hospital mortality. However volume number alone is not sufficient as a parameter to assess outcome. Systematic outcome measurement is the starting point of quality measurement and a quality improvement cycle. Although case-mix correction is important, the Charlson Comorbidity Index as a whole has no additional value for this. Patients with large aneurysms should be treated acutely, since they have an increased rebleeding risk with high associated morbidity and mortality. Analysis of treatment risks and durability of treatment are important secondary and tertiary outcome measures. Dual-trained (open and endovascular) neurosurgeons have similar results compared to the published literature. Patient involvement by means of an online health community in aftercare is beneficial because it provides an easy access to relevant information provided by peers or caregivers. It is probably useful for only a subset of patients, however. For the follow-up of coiled aneurysms, MRA has a high degree of sensitivity compared to DSA in detecting any recanalization and should be used in preference to DSA because it has no associated risks. The Dutch neurosurgical quality register (QRNS) provides a visualization of outcome data for aSAH patients, but increased compliance with the system is need for reliable results to be achieved.

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Samenvatting en conclusie

Het is een uitdaging om de kwaliteit van zorg voor patiënten met een aneurysmatische subarachnoïdaalbloeding (SAB) te meten. Een hoeveelheid van factoren die invloed hebben op de uitkomst maakt het dat het meten en vergelijken hiervan moeilijk is. In dit proefschrift zijn verschillende aspecten van de kwaliteit van zorg voor patiënten met een SAB geëvalueerd.

Voor veel complexe ziektebeelden is aantallen per ziekenhuis een gebruikte structuurindicator om tussen ziekenhuizen te differentiëren. Bij patiënten met een SAB is er in de literatuur ook een relatie tussen in-ziekenhuis mortaliteit en ziekenhuisvolume. Deze bevinding is het onderwerp van **hoofdstuk 2**. In de meta-analyse van vier studies met in het totaal 36.600 patiënten werd een statistisch significante relatie aangetoond tussen uitkomst en ziekenhuisvolume. Het effect werd zelfs sterker als een studie van lage kwaliteit werd verwijderd. Belangrijk is het dat er geen uniforme grens is tussen hoog en laag volume ziekenhuizen. Om vergelijkbare groepen te krijgen werd een herberekening verricht met gedichotomizeerde data met als grens 20 tot 30 patiënten per jaar per ziekenhuis. Ook dit liet een statistisch significante relatie zien. De studies maken wel gebruik van retrospectief gecodeerde databases in de Verenigde Staten. Twee elementen die van invloed zijn op de uitkomst zijn niet mee genomen: case-mix correctie en behandelingsmodaliteit. Deze meta-analyse geeft niet weer hoeveel patiënten door een enkele neurochirurg of neurointerventionalist behandeld moeten worden. De resultaten zijn niet de verdienste van slechts één specialist, echter van de gehele zorgketen. In het licht van kwaliteit van zorg en de toenemende vraag om centralisatie zijn ziekenhuisaantallen alleen onvoldoende om hier richting aan te geven. Ziekenhuisvolume moet als een van de cofactoren gezien worden gerelateerd aan uitkomst.

De belangrijkste factor die de uitkomst bepaalt bij patiënten met een SAB is de klinische conditie bij presentatie in het ziekenhuis. Daarnaast kan comorbiditeit ook de uitkomst beïnvloeden. De Charlson Comorbidity Index (CCI) is een index om verschillende comorbiditeiten te wegen, en kan gebruikt worden in ischemische beroerte. In **hoofdstuk 3** evalueren we de waarde van de CCI voor patiënten met een SAB. Alle opeenvolgende SAB-patiënten behandeld in het Radboudumc zijn retrospectief geanalyseerd. Analyse liet geen toegevoegde waarde zien van de CCI in het voorspellen van de uitkomst na 6 maanden. In de analyse kwamen initiële klinische conditie (WFNS: World Federation of Neurological Surgeons Grading System), leeftijd en behandelingsmodaliteit als sterke voorspellers voor de uitkomst naar voren. Mogelijk is het aantal patiënten te klein om een onderliggende significante relatie aan te tonen. Daarnaast is hypertensie gerelateerd aan een slechte uitkomst en die niet in de CCI opgenomen is. De toenemende interesse in uitkomstregistratie en daarmee gepaard gaande registratie van parameters relevant voor de uitkomst wordt veelal als een last ervaren door zorgverleners. Het is derhalve noodzakelijk om parameters te registreren die van belang zijn voor een gewogen uitkomstmeting. De CCI heeft geen toegevoegde waarde voor het wegen van comorbiditeit in de uitkomst bij SAB-patiënten.

Het krijgen van een hernieuwde bloeding voor aanvang van de behandeling is een belangrijke oorzaak van morbiditeit en overlijden bij patiënten met een SAB. Daarom is het van belang om risicofactoren voor hernieuwde bloeding te herkennen en om patiënten te selecteren die baat hebben bij acute behandeling. In **hoofdstuk 4** wordt de relatie tussen aneurysmagrootte en de kans op hernieuwde bloeding voor behandeling onderzocht door middel van een meta-analyse van de literatuur. Het resultaat van deze analyse van 7 studies met in het totaal 2.121 patiënten laat zien dat aneurysmagrootte een belangrijke factor is gerelateerd aan hernieuwde bloeding. Het is onwaarschijnlijk dat de resultaten beïnvloed worden door de leeftijd van de patiënt en de plaats van het aneurysma. Over hypertensie kan geen uitspraak gedaan worden omdat hiervoor de gegevens onvoldoende waren. Patiënten met een groot intracranieel aneurysma moeten indien mogelijk eerder een acute dan een vroege (binnen 24 uur) behandeling ondergaan. Omdat de relatie tussen grootte en risico op hernieuwde bloeding de eerste 72 uur aan lijkt te houden na de eerste bloeding, geldt de noodzaak tot acute behandeling ook voor patiënten die verwezen zijn vanuit andere centra of patiënten waarbij de diagnose vertraagd gesteld is. Deze studie kan beïnvloed zijn door publicatiebias omdat studies die geen relatie zouden laten zien mogelijk minder makkelijk gepubliceerd worden. Tevens is het zo dat patiënten die overleden zijn voor ziekenhuisopname niet in deze studies zijn opgenomen. Andere zogenaamde confounders zoals tijd tot ziekenhuisopname, tijd tot operatie en het effect van aminocapronzuur, zijn onvoldoende gedocumenteerd om de invloed op de uitkomst te beoordelen.

Analyse van complicaties en duurzaamheid van de behandeling, als onderdeel van de tweede en de derde rij in de uitkomsthiërarchie, is belangrijk. De analyse van resultaten van de behandeling bieden een startpunt voor de verbeteringscyclus. De eigen resultaten zijn onderwerp van **hoofdstuk 5** en worden bediscussieerd met specifieke aandacht voor open en endovasculair werkende ("hybride") neurochirurgen. Hiertoe zijn de prospectief geregistreerde gegevens van 356 SAB-patiënten, behandeld op de afdeling neurochirurgie van het Radboudumc te Nijmegen, geanalyseerd. Er is een gecombineerde blijvende morbiditeit en mortaliteit van endovasculaire of open chirurgische behandeling van 2,1%, respectievelijk 1,4%. Het procedurele complicatierisico was 5,9%, respectievelijk 9,9%. Wat betreft de duurzaamheid werd er een nekrest van het aneurysma gezien bij endovasculaire behandeling in 18,8% en was er noodzaak tot herbehandeling in 13,3% (gemiddelde follow-up van 13,8 maanden). Bij de open chirurgische behandeling waren er nekresten in 7,4% met herbehandeling in 1,9% (gemiddelde follow-up van 6,5 maanden). De resultaten zijn hiermee in lijn met de gepubliceerde. De behandeling van SAB-patiënten door neurochirurgen die zowel endovasculaire als open chirurgische behandeling bieden is veilig en effectief.

Zorg moet gecentreerd zijn rondom de patiënt. De behoeften van de patiënt moeten continu geëvalueerd worden. Dit kan bereikt worden door het uitwisselen van informatie tussen patiënt en zorgverlener en tussen patiënten onderling. Een *online health community* kan hieraan bijdragen. De waarde van een dergelijke *community* voor SAB-patiënten wordt besproken in **hoofdstuk 6**. Een *online health community*, genoemd Mijn SAB, voor SAB-patiënten is geïmplementeerd in aanvulling op de gebruikelijke SAB-zorg in het Radboudumc, Nijmegen. Het gebruik en de bruikbaarheid van deze community werden geëvalueerd met behulp van een enquête. Zesenzestig opeenvolgende SAB-patiënten werden geïnformeerd over de *community*, waarvan er 26 toegang verkregen tot Mijn SAB en 20 participeerden in het onderzoek. De patiënten beoordeelden de bijdrage van de *community* aan de kwaliteit van zorg als positief, maar niet aan de kwaliteit van leven. Deze pilotstudie liet de aanvullende waarde van de *online health community* (Mijn SAB) zien op de nazorg voor SAB-patiënten. Mijn SAB voorzag in laagdrempelige toegang tot belangrijke informatie van medepatiënten of zorgverleners. Vooral patiënten in een betere klinische conditie hebben hier voordeel bij.

Voor endovasculair behandelde (gecoilde) aneurysmata is controle nodig gezien de kans op rekanalisatie van het aneurysma. Zowel digitale subtractie angiografie (DSA) als magnetische resonantie angiografie (MRA) kunnen hiervoor gebruikt worden, hoewel de laatst genoemde veiliger en minder duur is. Twee MRA-technieken, te weten *time of flight* (TOF) en met contrast (*contrast enhanced*: CE), zijn de meest beschikbare technieken. In **hoofdstuk 7** is de medische literatuur systematisch geëvalueerd om de nauwkeurigheid van TOF-MRA en CE-MRA in het detecteren van aneurysmarekanalisatie te bepalen. Van de 26 studies die voldeden aan de inclusiecriteria, evalueerden er 24 TOF-MRA, 14 CE-MRA en 12 zowel TOF- als CE-MRA. De analyse liet zien dat MRA (TOF en CE) een hoge sensitiviteit heeft in het detecteren van elke vorm van rekanalisatie. Een subanalyse naar of nekrest, of restaneurysma, liet echter zien dat beide MRA-technieken een lagere sensitiviteit en specificiteit hebben dan DSA. Een verklaring hiervoor is mogelijk het geringe aantal studies en het lage aantal patiënten dat hierin geïncludeerd is. Een andere verklaring is dat fout-positieve bevindingen op de DSA het gevolg zijn van pulsatie-artefacten. Omdat DSA de gouden standaard is, worden deze gerekend in het voordeel van DSA. Dit leidt tot fout-negatieve waarden voor de MRA met een lagere sensitiviteit. Andere bevindingen van de subanalyse waren de lagere sensitiviteit van CE-MRA vergeleken met TOF-MRA, wat waarschijnlijk gerelateerd is aan de contrasttiming in CE-MRA, en de langere acquisitietijd voor TOF-MRA. In deze meta-analyse kan er heterogeniteit tussen de geïncludeerde studies bestaan. Dit kan komen door publicatiebias, retrospectieve analyses van studies, het wisselend gebruik van 2D of 3D (rotatie) DSA als referentie, verschillende veldsterkten voor de MRI (1, 1,5 of 3T) en ten slotte verschil in kwaliteit van de studies.

Kwaliteitsverbetering begint met het meten van de huidige stand van zaken. In **hoofdstuk 8** wordt het Nederlands kwaliteitsregistratiesysteem (QRNS: *Quality Registry NeuroSurgery*) voor SAB-patiënten en drie andere hoog complex / laag volume ziektebeelden beschreven. Het registratiesysteem is ingebed in de Nederlandse Vereniging voor Neurochirurgie (NVvN) met als belangrijkste doel een ijkpunt te geven voor primaire uitkomsten bij de ziektebeelden. Daarnaast heeft het tot doel om uitschieters te signaleren en een verbeteringsproces in te kunnen zetten. Het direct inzichtelijk maken van de uitkomstgegevens in een online dashboard, dat elke 2 weken geactualiseerd wordt, draagt hiertoe bij. De uitkomst van het eigen ziekenhuis wordt afgezet tegen het landelijk gemiddelde. Er is gekozen voor uitkomstmaten op ziekenhuisniveau omdat er complexe ziektebeelden geëvalueerd worden die multidisciplinaire zorg vragen. De resultaten van behandeling zijn dus het product van de gehele zorgketen. Er is een groeiend percentage patiënten dat geregistreerd wordt, uitgaande van totalen door ICD-coderingen of een berekende incidentie. De registratie zal moeten verbeteren in de nabije toekomst. Hiervoor wordt een automatische koppeling met het elektronische patiëntendossier gerealiseerd. Tevens kan de betrokkenheid van neurologen en neurointerventionalisten bij de registratie tot een verbetering leiden. Ten slotte kan het combineren van het kwaliteitsregistratiesysteem met wetenschappelijke interesse in landelijke uitkomstgegevens leiden tot een verbetering in de invoer van data.

TOEKOMSTBLIK

Om kwaliteit van zorg voor SAB-patiënten te meten is het van belang gestandaardiseerde heldere uitkomstmaten te hebben. Mortaliteit en de modified Rankin scale zijn primaire uitkomstmaten die in veel trials en het Nederlands kwaliteitsregistratiesysteem (QNRS) gebruikt worden.[2-4] Hoewel het zo is dat veranderingen in deze uitkomstmaten over de jaren aangeeft dat dit enkele nog steeds relevante parameters zijn, is er ook een noodzaak tot meer verfijnde uitkomstmaten, zoals neuropsychologische testen en gezondheidsgerelateerde kwaliteit van leven uitkomsten, welke ontwikkeld en gevalideerd moeten worden.[5,9] Dit zou ook een ziektespecifieke patiëntgerapporteerde uitkomstmaat (een zogenaamde PROM) moeten bevatten. Idealiter zou een samengestelde score gemaakt moeten worden die alle relevante uitkomsten van de verschillende uitkomstlagen bevat.[6]

De uitkomsten van zorg voor patiënten met een SAB worden gemeten op het niveau van het ziekenhuis. Dit is een logische keuze aangezien de uitkomst het resultaat is van het functioneren van de gehele zorgketen. Vanuit het oogpunt van kwaliteitsverbetering is het nodig deze samengestelde uitkomst te ontwarren om oorzaken van verschillen te kunnen identificeren. Toekomstige analyses zullen laten zien of de geregistreerde items onderscheidend zijn en een handvat bieden voor kwaliteitsverbetering. De resultaten kunnen ook gebruikt gaan worden voor het maken van een predictiemodel. Dan is het mogelijk om op individueel patiëntniveau uitkomsten te voorspellen. Discrepanties in bereikte en voorspelde uitkomst nopen tot evaluatie van de behandeling en kunnen eventuele problemen aan het licht brengen. Dit zal een toegevoegde stimulus zijn voor de verbetering van zorg.

Hoewel de eerste resultaten van het Nederlands kwaliteitsregistratiesysteem (QRNS) veelbelovend zijn, is het aantal missende items nog aanzienlijk. Tot op heden kunnen betekenisvolle conclusies nog niet getrokken worden. Het volledig invullen van het kwaliteitsregistratiesysteem is daarom van kardinaal belang. Het uiteindelijke doel is een volledig automatische gegevensinvoer met behulp van koppelingen met het elektronisch patiëntendossier zoals het geval is bij het nefrologieregister in het Verenigd Koninkrijk.[8] Koppelingen om basale patiëntgegevens over te brengen is een eerste praktische stap. Ook kan een multidisciplinaire registratie door alle betrokken specialisten bijdragen aan een afname van missende gegevens. Nadat landelijke data betrouwbaar zijn, kan een vergelijk met andere centra in andere landen de resultaten in een breder perspectief zetten. Toekomstige klinische trials kunnen het registratiesysteem als een platform gebruiken om daar het casusformulier onder te brengen.

De eerste resultaten van het kwaliteitsregistratiesysteem (QRNS) laten in de funnelplot voor de behandeling van SAB-patiënten geen significante verschillen zien in ziekenhuisuitkomsten.[1] Indien deze bevindingen in de nabije toekomst bevestigd worden, als betrouwbare resultaten beschikbaar worden, dan kan men zich afvragen of het continueren van een dergelijk registratiesysteem nog gerechtvaardigd is. Naast de waarde van een dergelijk registratiesysteem om patiënten te kunnen voorlichten en intrinsieke wetenschappelijke waarde, moet het uiteindelijke doel zijn de gemiddelde uitkomst te verbeteren. Zelfs de geringste verbetering in zorg voor deze ziekte met grote socio-economische gevolgen rechtvaardigt de inspanningen en kosten gepaard gaande met deze kwaliteitsregistratie.[7] Het zal een uitdaging worden om de economische winst die behaald gaat worden ook te verdelen onder zorgverleners voor de dekking van het registratiesysteem, wat een niet onaanzienlijke inspanning vergt.

CONCLUSIE

In dit proefschrift zijn er verschillende aspecten van de kwaliteit van zorg voor patiënten met een aneurysmatische subarachnoïdaalbloeding geëvalueerd. Er is een relatie tussen ziekenhuisaantallen en ziekenhuissterfte. Echter het afmeten van de uitkomst aan de aantallen is onvoldoende. Het systematisch meten van de uitkomst is het startpunt van kwaliteitsmeting en de kwaliteitsverbeteringcyclus. Hoewel case-mix correctie belangrijk is, heeft de Charlson Comorbidity Index daarvoor geen toegevoegde waarde. Patiënten met grote aneurysmata's dienen acuut behandeld te worden omdat hierbij een verhoogd hernieuwd bloedinggevaar is met vaak hoge morbiditeit en mortaliteit. Analyse van behandelingsrisico's en duurzaamheid van behandeling zijn relevante secundaire en tertiaire uitkomstmaten. Neurochirurgen die zowel open als endovasculaire behandeling uitvoeren hebben vergelijkbare resultaten met gepubliceerde series. De betrokkenheid van de patiënt in de nazorg door middel van een *online health community* wordt als een winst beschouwd, omdat het laagdrempelig toegang geeft tot informatie van medepatiënten of zorgverleners. Wel is het zo dat het waarschijnlijk waardevol is voor een deel van de patiënten. Voor de controle van gecoilde aneurysmata heeft MRA een hoge sensitiviteit in vergelijk met DSA in het detecteren van rekanalisatie, en moet daarom bij voorkeur gebruikt worden omdat het geen risico's heeft zoals die aan een DSA verbonden zijn. Het Nederlands neurochirurgisch kwaliteitsregistratiesysteem (QRNS) voorziet in het inzichtelijk maken van de uitkomsten van SAB-patiënten, echter volledige informatie is noodzakelijk om betrouwbare gegevens te verkrijgen.

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About the author

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Hieronymus Damianus (Jeroen) Boogaarts was born on 27 September 1973 in Duiven, the Netherlands. In 1993, he finished secondary school at Liemers College in Zevenaar and began a degree in musicology at Utrecht University. The following year, he also began studying medicine at the same university. In 1998, he graduated with a university degree in medicine (he earned his degree in musicology three years later). He passed his medical exams and qualified as a doctor in 2000. He then worked for several months as a resident in internal medicine and cardiology at the Lorentz Ziekenhuis Zeist before beginning his residency in neurosurgery at Radboud University Nijmegen in 2001 (under Prof J.A. Grotenhuis). He started training to become a neurosurgeon in 2003. In 2008, he earned a Master's degree in clinical epidemiology (under the supervision of Prof A. Hofman) from the Netherlands Institute for Health Sciences (NIHES) in Rotterdam. In 2009, he earned a Master's degree in neurovascular diseases from Paris-Sud University (under the supervision of Prof P. Lasjaunias). In 2009, he began a fellowship in endovascular and open vascular neurosurgery at Radboud University Nijmegen (under the supervision of Dr J. de Vries). Since 2010, he has been a neurosurgeon on the staff of the department of neurosurgery at Radboud university medical center. His areas of expertise include open vascular, endovascular neurosurgery and endoscopic neurosurgery.

Jeroen is married to Simone de Bruin. They have four children; Clemens, Pia, David and Frans.

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Hieronymus Damianus Boogaarts (Jeroen) is geboren op 27 september 1973 te Duiven. Hij behaalde in 1993 zijn VWO-diploma aan het Liemers College te Zevenaar en startte zijn opleiding musicologie aan de Universiteit Utrecht. De studie geneeskunde werd in 1994 begonnen aan dezelfde universiteit. In 1998 werd het doctoraal geneeskunde en in 2000 het artsexamen met goed gevolg afgelegd. Zijn doctoraal voor musicologie werd behaald in 2001. Na enkele maanden als arts-assistent interne geneeskunde en cardiologie in het Lorentz Ziekenhuis te Zeist gewerkt te hebben begon hij zijn arts-assistentschap neurochirurgie bij de afdeling neurochirurgie van het St. Radboud ziekenhuis, Nijmegen (Prof. dr. J.A. Grotenhuis). De opleiding tot neurochirurg werd in 2003 gestart. In 2008 behaalde hij zijn master in klinische epidemiologie aan het Netherlands Institute for Health Sciences (NIHES) (Prof. dr. A. Hofman), Rotterdam. In 2009 verkreeg hij zijn master in *neurovascular diseases* aan de Université Paris XI (Prof. P. Lasjaunias). Na het voltooien van de opleiding tot neurochirurg in 2008 werd in 2009 gestart met een open en endovasculair fellowship aan de afdeling neurochirurgie van het St. Radboud ziekenhuis, Nijmegen (Dr. J. de Vries). Vanaf 2010 tot heden is hij werkzaam als staflid van de afdeling Neurochirurgie van het Radboudumc met als expertise open en endovasculaire neurochirurgie alsmede endoscopische neurochirurgie.

Jeroen is getrouwd met Simone de Bruin en zij hebben 4 kinderen: Clemens, Pia, David en Frans.

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