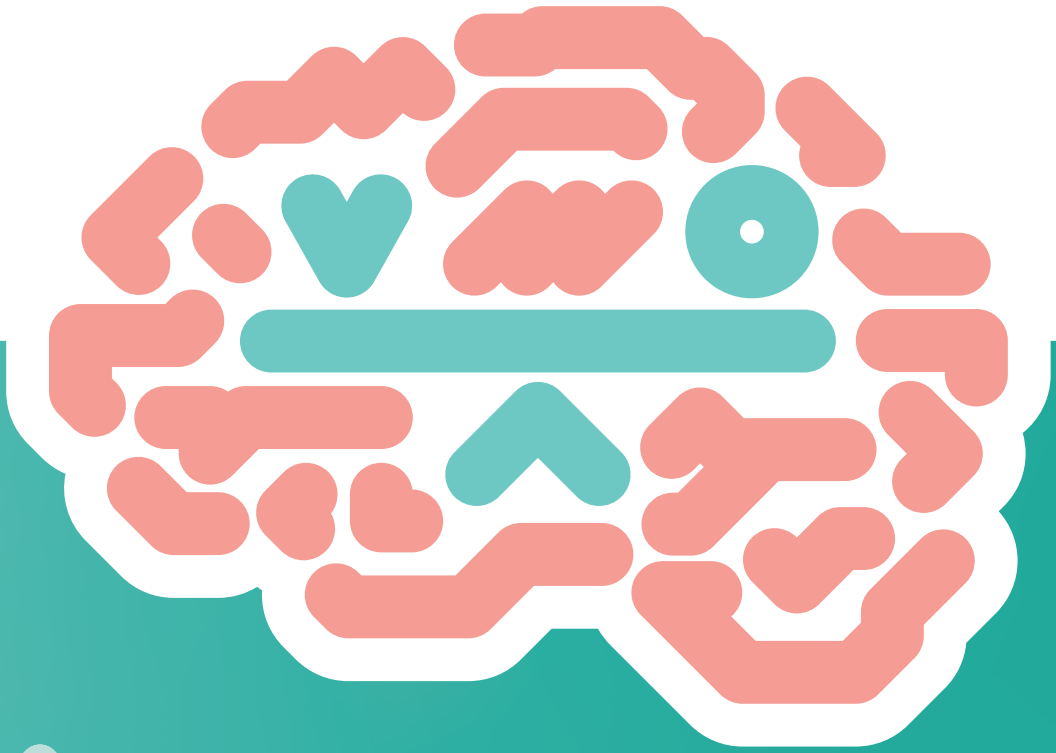
Unruptured intracranial aneurysms: balancing risks and benefits of preventive treatment



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Unruptured intracranial aneurysms: balancing risks and benefits of preventive treatment

Ongeruptureerde intracraniële aneurysma's: een afweging van risico's en baten van preventieve behandeling

(met een samenvatting in het Nederlands)

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Voor mijn familie

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CHAPTER 1

General introduction and outline of thesis

GENERAL INTRODUCTION

Unruptured intracranial aneurysms and subarachnoid haemorrhage

Saccular unruptured intracranial aneurysms are acquired vascular abnormalities that form an outpouching of the arterial wall at major branching brain arteries. The prevalence of unruptured intracranial aneurysms is 3.2% in the general adult population, which means that in Europe alone there are 22 million persons with an intracranial aneurysm.[1-3] Owing to the rising availability and quality of brain imaging, the number of incidentally discovered unruptured intracranial aneurysms is increasing.[4] Many will never rupture, but some do, causing subarachnoid haemorrhage (SAH). Although aneurysmal SAH accounts for only 5% of all strokes, the proportion of life years with high quality-of-life (QoL) lost from SAH is similar to that of ischaemic stroke and intracerebral haemorrhage.[5] This high impact of SAH is explained by the relatively young age at onset (median age 55 years) and the high case-fatality and morbidity.[5, 6] Up to 40% of SAH patients dies, and another 20% remains disabled with loss of independence.

Preventive intracranial aneurysm occlusion

Preventive treatment of unruptured intracranial aneurysms, either by neurosurgical or endovascular treatment, can decrease the risk of aneurysmal SAH and hereby reduce the number of (quality-adjusted) life years lost.[5-7] Microsurgical clipping has been a standard neurosurgical treatment method for patients with intracranial aneurysms for decades. This changed with the introduction of the controlled detachable coils in 1991 and the publication of the International Subarachnoid Aneurysm Trial (ISAT) in 2005.[8,9] This randomized trial compared surgical clipping and endovascular coiling and demonstrated better one-year clinical outcomes for patients treated with coiling as compared to clipping.[9] Although these outcomes are only applicable to patients with ruptured aneurysms considered suitable for both clipping and coiling, it triggered a shift towards endovascular embolization as predominant treatment modality for all intracranial aneurysms.[8-10]

Although procedural complications have declined over time, both preventive treatment options still carry a considerable risk of serious complications.[11-13] Meta-analyses published in 2012 and 2013 reported treatment-related unfavourable outcomes (permanent disability or death) in approximately 7% of patients undergoing microsurgical clipping and 5% of patients undergoing endovascular aneurysm occlusion.[11, 12] Adverse events during hospitalization resulting in less severe or transient morbidity have been reported in up to 15% of patients.[14, 15] In more recent years, endovascular treatment options have expanded even further, with an increasing variety of advanced endovascular methods being used in clinical practice, including balloon and stent-assisted coiling, flow-diverting stents and Woven EndoBridge

(WEB)-devices.[16, 17] However, also for these newer treatments the risk of complications remains considerable, which may partially be explained by the more complex nature of aneurysms treated by such advanced endovascular treatment modalities.[18-22]

Balancing risks and benefits

In management decisions on unruptured intracranial aneurysms, treatment risks have to be carefully balanced against the risk of aneurysm rupture and other factors such as life expectancy and fear for rupture of an untreated aneurysm.[6, 23, 24] Since randomised trials comparing preventive aneurysm occlusion with no occlusion have proven to be difficult, the optimal management of unruptured intracranial aneurysms remains controversial.[23, 25] In such circumstances, prediction modelling and decision analysis are the best evidence-based alternatives to improve the balance between risks and benefits of preventive aneurysm occlusion.[24] For estimations of the rupture risk, the PHASES risk score has been developed to provide absolute 5-year risks of rupture based on six easily retrievable patient and aneurysm characteristics.[26] In daily practice, the 'Neuromind' smartphone app of the PHASES score is increasingly being used to support treatment decisions.[27] In contrast, such risk scores are lacking for the prediction of neurosurgical and endovascular complication risks. Previous risk scores often combined data from patients with ruptured and unruptured aneurysms and the generalizability of the scores that did restrict models to patients with unruptured intracranial aneurysms is limited by selective or outdated study populations.[51-57] Current estimation of treatment risks, as well as decision guidance tools such as the unruptured intracranial aneurysm treatment score (UIATS), are therefore still largely based on expert opinion.[7, 23]

Quality of life outcomes

To enable patients with unruptured intracranial aneurysms to make informed choices during shared decision-making, it is also important to integrate QoL outcomes.[28, 29] Fear of rupture of an untreated aneurysm can have a huge impact on QoL and emotional functioning.[30, 31] In addition, preventive aneurysm occlusion may also reduce QoL, even if no treatment complications occur.[28, 29] Patients may experience restrictions in their family, social and working life during the recovery phase following preventive aneurysm treatment.[32] However, most previous studies on QoL outcomes in patients with unruptured intracranial aneurysms have focused on QoL in patients who did not undergo preventive occlusion or only report on QoL changes after treatment. So far, little data are available on QoL changes over time in patients with and without preventive occlusion and how various individual factors, such as coping style and psychological factors, can influence QoL outcomes in these patients.[28, 29, 33-36]

OUTLINE OF THESIS

The first aim of this thesis was to give an overview of the most up-to-date procedural clinical complication risks, case-fatality risks, and risk factors for endovascular and neurosurgical treatment of unruptured intracranial aneurysms. In **chapter 2** of this thesis, I describe the results of the systematic review and meta-analysis we performed.[37]

The second aim of this thesis was to develop aneurysm treatment risk scores to predict the absolute risks of procedural complications from preventive endovascular (risk score 1) and neurosurgical (risk score 2) aneurysm occlusion. To realize this, we have set up a multicentre cohort study to obtain individual patient data from patients with an unruptured intracranial aneurysm who underwent primary endovascular treatment (standard coiling or an advanced endovascular treatment) or neurosurgical treatment (microsurgical clipping) in one of 10 participating centres in Europe, North America, or Asia between 2000 and 2018. In **chapter 3,** I present the two risk scores we developed.

The third aim of this thesis was to study QoL outcomes in patients with unruptured intracranial aneurysms with and without preventive aneurysm occlusion and to identify predictors of QoL outcome. **Chapter 4** describes the results of a prospective cohort study in two tertiary referral centres for aneurysm care in the Netherlands. By sending eligible participants standardized questionnaires about health-related QoL, anxiety and depression, coping style and restrictions in daily activities shortly after diagnosis and at several moments during follow-up, we were able to accurately describe the time-course and predictors of several QoL outcomes in the first year after aneurysm diagnosis.

In **chapter 5** of this thesis, the most important findings of the research included in this thesis are highlighted, the limitations, strengths and lessons learned are discussed and implications for clinical practice and future research are outlined.

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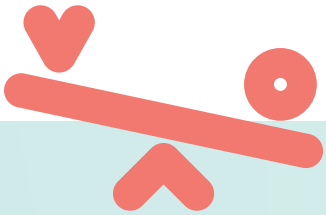
CHAPTER 2

Procedural clinical complications, case-fatality risks, and risk factors in endovascular and neurosurgical treatment of unruptured intracranial aneurysms: A systematic review and meta-analysis



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JAMA Neurology 2019; **76**:282-93.

ABSTRACT

Importance

The risk of procedural clinical complications and the case-fatality rate (CFR) from preventive treatment of unruptured intracranial aneurysms varies between studies and may depend on treatment modality and risk factors.

Objective

To assess current procedural clinical 30-day complications and the CFR from endovascular treatment (EVT) and neurosurgical treatment (NST) of unruptured intracranial aneurysms and risk factors of clinical complications.

Data Sources

We searched PubMed, Excerpta Medica Database, and the Cochrane Database for studies published between January 1, 2011, and January 1, 2017.

Study Selection

Studies reporting on clinical complications, the CFR, and risk factors, including 50 patients or more undergoing EVT or NST for saccular unruptured intracranial aneurysms after January 1, 2000, were eligible.

Data Extraction and Synthesis

Per treatment modality, we analysed clinical complication risk and the CFR with mixed-effects logistic regression models for dichotomous data. For studies reporting data on complication risk factors, we obtained risk ratios (RRs) or odds ratios (ORs) with 95% CIs and pooled risk estimates with weighted random-effects models.

Main Outcomes and Measures

Clinical complications within 30 days and the CFR.

Results

We included 114 studies (106 433 patients with 108 263 aneurysms). For EVT (74 studies), the pooled clinical complication risk was 4.96% (95% CI, 4.00%-6.12%), and the CFR was 0.30% (95% CI, 0.20%-0.40%). Factors associated with complications from EVT were female sex (pooled OR, 1.06 [95% CI, 1.01-1.11]), diabetes (OR, 1.81 [95% CI, 1.05-3.13]), hyperlipidaemia (OR, 1.76 [95% CI, 1.3-2.37]), cardiac comorbidity (OR, 2.27 [95% CI, 1.53-3.37]), wide aneurysm neck (›4 mm or dome-to-neck ratio ›1.5; OR, 1.71 [95% CI, 1.38-2.11]), posterior circulation aneurysm (OR, 1.42 [95% CI, 1.15-1.74]), stent-assisted coiling (OR, 1.82 [95% CI,

1.16-2.85]), and stenting (OR, 3.43 [95% CI, 1.45-8.09]). For NST (54 studies), the pooled complication risk was 8.34% (95% CI, 6.25%-11.10%) and the CFR was 0.10% (95% CI, 0.00%-0.20%). Factors associated with complications from NST were age (OR per year increase, 1.02 [95% CI, 1.01-1.02]), female sex (OR, 0.43 [95% CI, 0.32-0.85]), coagulopathy (OR, 2.14 [95% CI, 1.13-4.06]), use of anticoagulation (OR, 6.36 [95% CI, 2.55-15.85]), smoking (OR, 1.95 [95% CI, 1.36-2.79]), hypertension (OR, 1.45 [95% CI, 1.03-2.03]), diabetes (OR, 2.38 [95% CI, 1.54-3.67]), congestive heart failure (OR, 2.71 [95% CI, 1.57-4.69]), posterior aneurysm location (OR, 7.25 [95% CI, 3.70-14.20]), and aneurysm calcification (OR, 2.89 [95% CI, 1.35-6.18]).

Conclusions and Relevance

This study identifies risk factors for procedural complications. Large data sets with individual patient data are needed to develop and validate prediction scores for absolute complication risks and CFRs from EVT and NST modalities.

KEY POINTS

Question

What is the 30-day clinical complication risk and case-fatality rate of endovascular treatment and neurosurgical treatment of unruptured intracranial aneurysms?

Findings

In this systematic review and meta-analysis of 114 studies and 106 433 patients, among the 74 studies of endovascular treatment, the risk of procedural clinical complications was 4.96% (95% CI, 4.00%-6.12%), and the case-fatality rate was 0.30% (95% CI, 0.20%-0.40%). In 54 studies of neurosurgical treatment, the pooled complication risk was 8.34% (95% CI, 6.25%-11.10%) and the case-fatality rate was 0.10% (95% CI, 0.00%-0.20%).

Meaning

The complication risks were particularly dependent on detailed and standardized recording of complications, method of outcome assessment, and region and varied according to several patient-level, aneurysm-level, and treatment-associated risk factors.

INTRODUCTION

The prevalence of saccular unruptured intracranial aneurysms (UIAs) in the general population is 3%.[1] Owing to the rising availability and quality of brain imaging, the number of incidentally discovered UIAs is increasing.[2,3] Many UIAs remain asymptomatic, but some rupture, causing subarachnoid haemorrhage (SAH). This is a subtype of stroke with a poor prognosis (a case-fatality rate of approximately 35%), often affecting relatively young patients (mean age, 60 years).[4] Preventive treatment of UIAs, either by endovascular treatment (EVT) or neurosurgical treatment (NST), can decrease the risk of SAH, but both treatment modalities carry a risk of serious complications.[5] Currently, the decision to treat UIAs is a balance of risk of rupture, risk of treatment complications, life expectancy, and level of patient anxiety. For estimations of the rupture risk, prediction models are available that provide absolute risks of rupture for the next 5 years based on a few easily available risk factors.[6,7] Such robust data are lacking for the estimation of complication risk from UIA treatment.[5,8] The best available evidence comes from meta-analyses published in 2012 and 2013 on the procedural morbidity and case-fatality risk of EVT and NST.[9,10] However, since the publication of these reviews, there has been a further shift toward EVT as the predominant treatment modality, with an increasing variety of advanced endovascular methods being used, such as stent-assisted or balloon-assisted coiling, flow-diverting stents, and Woven EndoBridge (WEB) Aneurysm Embolization devices. In addition, previous meta-analyses did not focus on risk factors for complications apart from subgroup analyses. Our aim is to provide an overview of the recent literature on EVT and NST, with several new focuses. In addition to assessing the procedural 30-day clinical complication and case-fatality risks of both treatment modalities, we conducted a meta-analysis of the available risk factor data for clinical complications from both EVT and NST, and we separately assess the complication risk of advanced endovascular methods that were increasingly applied in clinical practice over the last few years.

METHODS

Search strategy and selection criteria

We systematically searched PubMed, Excerpta Medica database, and the Cochrane Database between January 1, 2011, and January 1, 2017, to retrieve all relevant articles on procedural clinical complications and case-fatality rates from EVT and NST of UIAs. A detailed query is given in eTable 1 in the Supplement. We checked related articles given on PubMed and reference lists of retrieved articles for further eligible publications and compared the list of articles found with a database of references from one of us (G.J.E.R.). We performed our systematic review and meta-analysis according to the Preferred Reporting Items for Systematic

Reviews and Meta-analyses (PRISMA) recommendations and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[11,12]

Selection of studies and data extraction

Articles were eligible for inclusion if they met the following inclusion criteria: (1) used a longitudinal design documenting procedural clinical complications and/or a case-fatality rate; (2) included at least 50 patients 18 years and older undergoing elective EVT (standard coiling or one of the following advanced endovascular methods: stent-assisted or balloon-assisted coiling, use of stents or flow diverting stents or use of WEB devices) or NST (including only clipping) between January 1, 2000, and January 1, 2017; (3) was written in Spanish, Portuguese, French, Italian, English, German, Dutch, or Scandinavian; (4) included crude or adjusted effect estimates with corresponding 95% CIs for risk factors of clinical complications available or retrievable from the data; and (5) included patients with saccular UIAs. We allowed up to 10% of the aneurysms per study to be fusiform or dissecting; up to 25% of aneurysms to be symptomatic, rather than ruptured; and up to 5% of the aneurysms to be included for retreatment. We excluded (1) animal studies; (2) studies reporting on aneurysms associated with arteriovenous malformations or in populations with specific diseases (such as collagen disorders, Moyamoya disease or syndrome, dwarfism, or autoimmune disorders); (3) studies in which previously ruptured aneurysms could not be distinguished from additional UIAs; and (4) studies in which treatment outcome was not reported separately for ruptured and unruptured aneurysms.

We predefined procedural clinical complications as treatment complications that resulted in transient or permanent morbidity or mortality and occurred during or within 30 days after the procedure. In our primary outcome measure, we included both intracranial clinical ischemic (transient ischemic attack or ischemic stroke) and haemorrhagic (intracerebral haemorrhage, subdural or epidural hematoma, and intraoperative rupture) complications, as well as unspecified complications that resulted in a deterioration in clinical outcome (worsening of modified Rankin Scale or Glasgow Outcome Scale scores or designations as unfavourable or poor, if no standardized outcome scale was used). We defined the case-fatality rate as all deaths that occurred during or within 30 days after the procedure. The assessment of outcome was based on medical records (in the case of single-centre or multicentre studies) or administrative data from databases using International Classification of Diseases, Ninth Edition (ICD-9) and Tenth Edition (ICD-10) records to identify patients. For each study, we extracted details of the exact type of outcome and whether neurological deterioration was assessed with standardized outcome scales (modified Rankin Scale or Glasgow Outcome Scale).

One author (A.M.A.) performed the search and completed data extraction forms for full-text versions of the articles, including a quality assessment (Newcastle Ottawa Scale [NOS]).[13] A second author (A.L.) validated 10% of the extraction forms. Since the level of agreement between these 2 readers was very high (100% for extraction of inclusion and exclusion criteria and 93% for the scoring of NOS forms), we refrained from double reading of the remainder of the studies. In cases of doubt, a consensus meeting was held with 2 other authors (M.D.I.V. and G.J.E.R.). If necessary, we asked authors for additional unpublished data.

For each included study we extracted (1) study characteristics: the enrolment period and midyear of treatment (median of the period during which the study was conducted), size of the study population, follow-up duration, outcome assessment (medical records vs ICD-based administrative databases), and scales used (modified Rankin Scale, Glasgow Outcome Scale, or others); (2) patient and aneurysm characteristics: the mean or median age of the cohort, sex distribution, aneurysm size (maximum dome diameter), and aneurysm location; (3) treatment characteristics: the modality used (EVT or NST; if EVT, standard coiling or advanced endovascular method), and (4) from studies reporting on risk factors, risk estimates per given risk factor and adjustment factors. We assessed the number of patients with clinical complications. If more than 1 category of morbidity was reported and there was no overlap, we extracted complications from both categories. Otherwise, we extracted complication data from the largest category reported. For case-fatality analyses, we assessed the number of patients who died during or within 30 days after the procedure.

Statistical analysis

We performed separate analyses for EVT and NST and analysed complication risk per patient. For each included study, we calculated the proportions of several patient, aneurysm, and treatment characteristics and assessed the occurrence of (1) complications causing any morbidity, including both fatal and nonfatal complications and (2) the occurrence of deaths separately, during or within 30 days after the procedure. We used mixed-effects logistic regression models for dichotomous data for the meta-analysis of proportions. Heterogeneity was classified as moderate ($I^2 = 25\%$-50%), substantial ($I^2 = 50\%$-75%) or considerable ($I^2 \geq 75\%$). Owing to the degree of heterogeneity found, we used random-effect models for all analyses. We performed a sensitivity analysis according to the type of outcome (ischemic or haemorrhagic intracranial clinical complications). To assess potential sources of heterogeneity across studies, we performed predefined subgroup analyses according to methodological quality (high-quality studies defined as ≥7 points on the NOS) and use of advanced endovascular methods. We did additional subgroup analyses according to the method of outcome assessment (medical records vs ICD-based administrative databases, the use of standardized outcome scales [yes or no], region [Europe, North-America, Asia, or other], and midyear of

treatment [periods divided into tertiles]). To further study the influence of time on outcome, we performed meta-regression analyses using the midyear of each study period to express the percentage change of the crude complication risk or case-fatality rate per year. For each of the studies reporting data on risk factors of complications, we obtained risk ratios (RRs) or odds ratios (ORs) with 95% CIs or the raw patient numbers for each risk factor. We used the most adjusted estimate per study. If definitions or cut-off values of risk factors and treatment outcome allowed harmonization in comparable risk factor groups, we subsequently pooled ORs or RRs with a generic inverse variance–weighted, random-effects model.

RESULTS

In total, 5423 articles were screened, of which 114 articles met the eligibility criteria for this review (eFigure 1 and eTables 2-4 in the Supplement).14-127 For EVT, we included 74 studies that included 71,819 patients with 73,066 aneurysms (eTable 3 in the Supplement)16-89 and for NST, we included 54 studies with a total of 34 614 patients with 35,197 aneurysms (eTable 4 in the Supplement).24,30,32,37,38,57,64,65,68,77,87,90-129 Fourteen of 114 studies (12.3%), with a total of 33,676 patients, reported on both EVT and NST.24,30,32,37-39,45,47,57,64,65,68,77,87

Study characteristics

Details of the included studies are given in Table 1 and eTables 3 and 4 in the Supplement. Most of the studies had a retrospective design (68 EVT studies[16-32,34,36-70,72-83,85-87,128] [92%] with 71,098 patients; 53 NST studies[18,24,30,32,37-39,47,57,64,65,68,77,87-117,119-127] [98%] with 34,543 patients) and were single-centre cohorts (52 EVT studies[16,19-23,25,27-29,32,34-36,38,39,41,44-48,50-52,54,56,59-61,63,64,66-68,70,72,74-83,85,86,129] [70%] with 14,444 patients; 40 NST studies[18,32,38,39,47,57,64,65,68,77,87,88,91-95,98-100,102,103,105-114,116-127] [74%] with 9589 patients; Table 1). Of the 114 studies, 15 EVT studies[16,20,31,35,44,45,50,55,62,64,69,71,73,75,84] (20%) with 10,412 patients and 11 NST studies[64,77,95,102,110,112,113,118-120,127] (18%) with 4059 patients were of high methodological quality. Among 74 EVT studies, 59[16,18-20,22,23,25,27-29,31-36,38,40-45,47-51,56,58,60-72,74-84,86,129] (80%) with 16,000 patients reported separately on intracranial ischemic complications and 58[16,18-23,25-29,31-36,38,40-45,47-56,58,60-70,72,74,75,78-80,82-84,86,129] (78%) with 18,520 patients on haemorrhagic complications, and 17[16,18,19,23,31,33,40,43,46,50,54,56,58,59,70,81,129] (23%) with 2248 patients reported on advanced endovascular methods only. Among 54 NST studies, ischemic complications were reported separately in 33 studies[18,32,38,47,64,65,68,77,90,91,93-95,97,101,103-109,111,112,114,115,121-125,127] (61%) with 12,691 patients and haemorrhagic complications in 36 studies[18,32,38,47,64,65,68,88,90,92-94,99,102-110,112-115,119-123,125] (67%) with 10,545 patients. Most studies originated from Asia (38 EVT studies[18-23,25-27,29,35,36,38,39,41,42,45,47,48,54-56,59-63,67,69,70,73-76,78-80] [51%] with 18,942

patients and 29 NST studies[18,38,39,47,88,91-94,99,100,102,105,106,108-114,118-122,125,127] [54%] with 7870 patients) and North America (25 EVT studies[1,4,11,16,22,25-28,33,41,47,48,53,57-59,61-63,130-134] [34%] with 51,296 patients and 15 NST studies[24,30,32,37,57,65,77,87,89,90,96,101,115,117,124] [28%] with 25,247 patients). Data on patient and aneurysm characteristics were available for a subset of studies (Table 1).

Table 1. Baseline characteristics of included studies for endovascular treatment and neurosurgical treatment

	No. (%)	
Characteristic	**EVT**	**NST**
Total		
Included studies[a]	74	54
Patients	71,819	34,614
Aneurysms	73,066	35,197
Procedural clinical complications	4995	6501
Fatalities	379	156
Study characteristics		
Midyear, mean (range)	2008 (2001-2014)	2008 (2001-2014)
Retrospective design	68 (92)	53 (98)
Single-centre, medical records-based	52 (70)	40 (74)
Multicentre, medical records-based	12 (16)	3 (6)
ICD-based administrative database	10 (14)	11 (20)
Methodological quality		
Newcastle Ottawa Scale, points[b]		
≥7	15 (20)	11 (20)
<7	59 (80)	43 (80)
Studies reporting a standardized outcome scale[c]	40 (54)	26 (48)
Region		
Europe	9 (12)	9 (17)
North America	25 (34)	15 (28)
Asia	38 (51)	29 (54)
>1 region	2 (3)	1 (2)
Studies reporting risk factor data	43 (58)	26 (48)
Patient characteristics		
Age, mean, y	57.8	56.1
Female, mean %	74.3	68.9
Aneurysm characteristics	7.2	6.1
Size, mean, mm	84.9	97.1
Anterior circulation, mean %		
Endovascular treatment modality		
Standard coil or mix[d]	57 (77)	NA
Advanced method[e]	17 (23)	NA

a) Numbers of included studies for EVT and clipping do not add up to 114 because 14 studies reported on both treatment modalities. b) Studies were considered high quality if they scored ≥7 points and low quality if they scored <7 points. c) Reporting neurological outcome using the modified Rankin scale, the Glasgow Outcome scale, or another standardized outcome scale. d) Studies did not report which endovascular treatment methods were used. e Studies reported on outcome following advanced endovascular methods (i.e., stent-assisted coiling, balloon-assisted coiling, flow-diverting stents, or Woven EndoBridge devices). EVT=endovascular treatment. ICD=International Classification of Diseases. NA=not applicable. NVT=neurosurgical treatment. WEB=Woven EndoBridge.

Outcomes after EVT

The pooled crude procedural risk from EVT was 4.96% for any clinical complication (95% CI, 4.00%-6.12%; 74 studies[16-87,128,129]; 4995 complications; Table 2), 2.82% for ischemic complications (95% CI, 2.29%-3.47%; 59 studies[16, 18-20,22,23,25,27-29,31-36,38,40-45,47-51,53-56,58,60-72,74-84,86,129]; 437 complications), and 0.90% for haemorrhagic complications (95% CI, 0.64%-1.27%; 58 studies[16,18-23,25-29,31-36,38,40-45,47-56,58,60-70,72,74,75,78-80,82-84,86,129]; 212 complications). The case-fatality rate was 0.30% (95% CI, 0.20%-0.40%; 71 studies[16-56, 58-84,86,87,129]; 379 deaths).

Subgroup analyses

Among 15 high-quality EVT studies,[16,20,31,35,44,45,50,55,62,64,69,71,73,75,84] the complication risk was 4.30% (95% CI, 2.59%-7.07%; 445 complications; Table 2) and the case-fatalityrate was 0.12% (95% CI, 0.02%-0.63%; 27 deaths; 14 studies). Among the 68 studies[16,18-29,31-36,38,39,41-48,50-56,58-64,66-86,129] basing outcome assessment on medical records, the complication risk was 4.42% (95% CI, 3.49%-5.59%; 1005 complications) vs 8.91% (95% CI, 6.38%-12.31%; 3990 complication) among the 10 studies[17,24,30,37,40,49,57,65,87,128] using administrative ICD-coded databases. Complication risks differed according to region but did not change over time (Table 2). In 17 studies[16,18,19,23,31,33,40,43,46,50,54,56,58,59,70,81,129] wherein all patients were treated with advanced endovascular methods, the pooled crude complication risk was 6.13% (95% CI, 4.29%-8.70%; 189 complications; Table 2) and the case-fatality rate was 0.43% (95% CI, 0.17%-1.10%; 14 deaths).

Meta-analyses of risk factor data

Forty-three[16,17,20,21,23-28,31,33-35,37,41,44-46,48-56,60,62,64,67,69,71,74-78,83,86,87,128] of 74 EVT studies (58%) reported on various risk factors for procedural clinical complications. An overview of all risk factors is given in eTable 5 in the Supplement, and pooled risk factors are summarized in Figure 1. Data on age, aneurysm size, and antiplatelet therapy could not be pooled (eFigures 2-4 in the Supplement). For 4809 female patients, the pooled OR for complications from 8 cohorts in 7 studies[20,21,26,28,45,46,62] was 1.06 (95% CI, 1.01-1.11; eFigure 5 in the Supplement). The existence of a coagulopathy and a history of SAH were not associated with an increased complication risk (eFigures 6 and 7 in the Supplement). The associations between cardiovascular risk factors and complications are summarized in eFigures 8-12 in the Supplement. Patients with diabetes (4 cohorts from 3 studies[20,26,55]; pooled OR, 1.81 [95% CI, 1.05-3.13]), hyperlipidaemia (4 cohorts from 3 studies[20,26,49]; pooled OR, 1.76 [95% CI, 1.31-2.37]), and cardiac comorbidity (3 cohorts from 2 studies[20,49]; pooled OR, 2.27 [95% CI, 1.53-3.37]) were at increased risk of complications. A wide aneurysm neck (with a size of ›4mm or a dome-to-neck ratio ‹1.5) was associated with an increased complication risk (5 cohorts from 4 studies[20,26,69,75]; pooled OR, 1.71 [95% CI, 1.38-2.11]; eFigure 13 in the Supplement). Posterior circulation aneurysms were associated with an increased complication risk (6 studies[26,45,55,62,64,69]; pooled OR, 1.42 [95% CI, 1.15-1.74]; eFigure

14 in the Supplement), but aneurysms localized at other locations were not. For aneurysm multiplicity, the pooled OR for complications was 1.08 ([95% CI, 0.65-1.81]; 3 cohorts from 2 studies[20,49]; eFigure 15 in the Supplement). In total, 20 studies[16,20,21,23,26,33,34,44-46,48,50,52,53,55,62,75,78,87] reported on advanced endovascular methods (eFigure 16 in the Supplement). The use of stents was associated with an increased complication risk (compared with no stent use; 2 studies[26,62]; pooled OR, 3.43 [95% CI, 1.45-8.09]), but no data on flow diverters could be meta-analysed (eFigure 16 in the Supplement). Compared with standard coiling, the pooled OR for complications was 1.82 (5 studies[45,46,48,53,55]; 95% CI, 1.16-2.85) in stent-assisted coiling and 1.25 (3 studies[45,55,75]; 95% CI, 0.71-2.20) in balloon-assisted coiling.

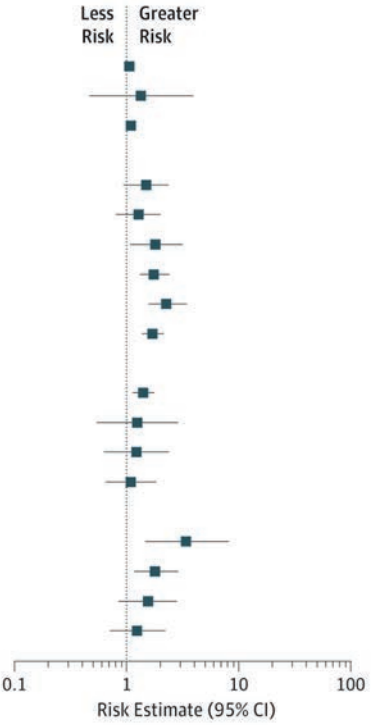
Table 2. Procedural clinical complication and case-fatality rates from endovascular treatment for all included studies and according to several subgroups

Study characteristic	Studies, No.	Events, No.	Patients, No.	Pooled crude risk, % (95%CI)	I^2, %
All studies					
Procedural clinical complications	74	4995	71,819	4.96 (4.00-6.12)	97.8
Ischemic complications	59	437	16,000	2.82 (2.29-3.47)	75.9
Haemorrhagic complications	58	212	18,520	0.90 (0.64-1.27)	76.7
Case-fatality rate	71	379	57,550	0.30 (0.20-0.40)	81.3
High-quality studies					
Procedural clinical complications	15	445	10,412	4.30 (2.59-7.07)	95.6
Case-fatality rate	14	27	9352	0.12 (0.02-0.63)	84.4
Procedural clinical complications					
Method of outcome assessment					
Medical records	64	1005	23,073	4.42 (3.49-5.59)	91.9
ICD-coded databases	10	3990	48,746	8.91 (6.38-12.31)	99.1
Standardized outcome scale[a]					
Yes	40	743	18,104	4.60 (3.50-6.05)	92.1
No	34	4252	53,715	5.39 (3.88-7.45)	98.9
Region					
Europe	9	105	1140	7.16 (4.57-11.10)	75.9
North America	25	4234	51,296	8.26 (6.31-10.70)	98.5
Asia	38	637	18,942	3.31 (2.46-4.44)	91.4
>1 region	2	19	361	1.65 (0.80-2.50)	63.2
Period					
2001-2007	23	2414	29,280	4.81 (3.00-7.62)	98.8
2008-2010	27	1190	20,486	5.13 (4.03-6.51)	90.1
2011-2014	20	1363	21,652	4.64 (2.87-7.43)	97.7
Period, case-fatality data					
2001-2007	23	134	29,280	0.32 (0.20-0.50)	62.6
2008-2010	25	25	7277	0.16 (0.06-0.47)	69.8
2011-2014	19	217	20,592	0.23 (0.09-0.62)	80.9
Advanced endovascular methods[b]					
Procedural clinical complications	17	189	2248	6.13 (4.29-8.70)	78.9
Case fatalities	17	14	2248	0.43 (0.17-1.10)	36.4

a) Reporting neurological outcome using the modified Rankin Scale, the Glasgow Outcome Scale, or another standardized outcome scale. b) Advanced endovascular methods (i.e., stent-assisted coiling, balloon-assisted coiling, flow-diverting stents, or Woven EndoBridge devices). ICD=International Classification of Diseases.

Figure 1. Overview of the association between various patient, aneurysm, and treatment factors and risk of procedural clinical complications from endovascular treatment

Risk Factor	Risk Estimate (95% CI)
Female	1.06 (1.01-1.11)
History of subarachnoid hemorrhage	1.34 (0.46-3.91)
Coagulopathy	1.09 (1.03-1.16)
Cardiovascular comorbidity	
Smoking	1.45 (0.91-2.29)
Hypertension	1.27 (0.91-1.77)
Diabetes	1.81 (1.05-3.13)
Hyperlipidemia	1.76 (1.31-2.37)
Heart comorbidity	2.27 (1.53-3.37)
Wide aneurysm neck	1.71 (1.38-2.11)
Aneurysm location	
Posterior vs ICA	1.42 (1.15-1.74)
MCA vs ICA	1.25 (0.55-2.85)
ACA vs ICA	1.22 (0.63-2.38)
Aneurysm multiplicity	1.08 (0.65-1.81)
Advanced endovascular methods	
Stent vs no stent	3.43 (1.45-8.09)
SAC vs simple coil	1.82 (1.16-2.85)
SAC vs BAC	1.56 (0.86-2.82)
BAC vs simple coil	1.25 (0.71-2.20)



ACA=anterior communicating artery. BAC=balloon-assisted coiling. ICA=internal carotid artery. MCA=middle cerebral artery. SAC=stent-assisted coiling.

Outcomes after NST

The pooled crude procedural risk from NST was 8.34% for any clinical complication (95% CI, 6.25%-11.10%; 54 studies[18,24,30,32,37-39,47,57,64,65,68,77,87-127]; 6501 complications; Table 3), 2.52% for ischemic complications (95% CI, 1.62%-3.91%; 33 studies[18,32,38,47,64,65,68,88,90,91,93-95,97,101,103-109,111,112,114,115,121-125,127]; 509 complications), and 1.23% for haemorrhagic complications (95% CI, 0.71%-2.15%; 36 studies[18,32,38,47,64,65,68,88,90,92-94,99,102-110,112-115,119-123,125]; 292 complications). The case-fatality rate was 0.10% (95% CI, 0.00%-0.20%; 49 studies[18,24,30,32,37-39,47,64,65,68,77,87,88,91-100,102-117,119-127];156 deaths).

Subgroup analyses

In 11 NST studies of high methodological quality, the complication risk was 6.89% (95% CI, 3.80%-12.16%; 303 complications; Table 3) and the case-fatality rate was 0.30% (95% CI, 0.00%-0.94%; 11 studies[64,77,95,102,110,112,113,118-120,127]; 5 deaths). Among the 43 stud-

ies[18,32,38,39,47,64,68,77,88,91-95,97-100,102-114,116-127] basing outcome assessment on medical records, the risk of complications was 6.43% (95% CI, 4.69%-8.75%; 761 complications) vs 20.38% (95% CI, 14.69%-27.56%; 5740 complications) among the 11 studies[30,37,57,65,87,89,90,96,101,115] using *ICD*-coded databases. We found differences in complication risks according to region, with the highest complication risk in North America (15 studies[24,30,32,37,57,65,77,87,89,90,96,101,115,117,124]; pooled crude risk 18.41% [95% CI, 13.85%-24.05%]; 5851 complications; including all 11 *ICD*-based studies[24,30,37,57,65,87,89,90,96,101,115]). Complication risk decreased over time from 11.65% (95% CI, 7.62%-17.41%; 3791 complications; Table 3) in the period 2001 through 2007 (18 studies[24,37,38,64,65,77,87,103,104,107,115,117,120,123-127]) to 5.26% (95% CI, 2.57%-10.44%; 602 complications) in the period 2011 through 2014 (15 studies[18,30,32,39,88,93,97,100,105,110-114,118]). Case-fatality risks did not change over time (Table 3).

Table 3. Procedural clinical complication and case-fatality rates from neurosurgical treatment for all included studies and by subgroup

Study characteristic	Studies, No.	Events, No.	Patients, No.	Pooled crude risk, % (95%CI)	I^2, %
All studies					
Procedural clinical complications	54	6501	34,614	8.34 (6,25-11.10)	99.0
Ischemic complications	33	509	12,691	2.52 (1.62-3.91)	94.3
Haemorrhagic complications	36	292	10,545	1.23 (0.71-2.15)	93.4
Case-fatality rate	49	156	24,901	0.10 (0.00-0.20)	91.4
High-quality studies					
Procedural clinical complications	11	303	4059	6.89 (3.80-12.16)	95.8
Case-fatality rate	11	5	4059	0.30 (0.00-0.94)	73.4
Procedural clinical complications					
Method of outcome assessment					
Medical records	43	761	10,265	6.43 (4.69-8.75)	94.2
ICD-coded databases	11	5740	24,349	20.38 (14.69-27.56)	99.4
Standardized outcome scale[a]					
Yes	26	1906	12,590	8.27 (5.75-11.78)	97.4
No	28	4595	22,024	8.32 (5.29-12.86)	99.4
Region					
Europe	9	231	1314	14.77 (11.07-19.44)	94.2
North America	15	5851	25,247	18.41 (13.85-24.05)	99.1
Asia	29	407	7870	3.34 (2.88-6.50)	93.5
>1 region	1	12	183	6.56 (2.97-10.14)	NA
Period					
2001-2007	18	3791	15,687	11.65 (7.62-17.41)	99.1
2008-2010	20	2091	14,382	8.16 (5.32-12.32)	98.6
2011-2014	15	602	4404	5.26 (2.57-10.44)	96.7
Period, case-fatality data					
2001-2007	17	124	15,587	0.14 (0.03-0.65)	90.8
2008-2010	16	21	4769	0.04 (0.00-0.56)	88.3
2011-2014	15	11	4404	0.06 (0.00-0.80)	61.7

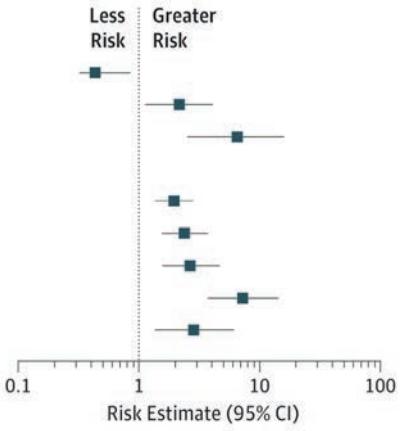
a) Reporting neurological outcome using the modified Rankin Scale, the Glasgow Outcome Scale, or another standardized outcome scale. ICD=International Classification of Diseases. NA=not applicable.

Meta-analyses of risk factor data

Twenty-six[24,37,65,77,87,89,91,95,96,99,101,102,104,106,108,110,112,113,115-120,125-127] of 54 NST studies (48%) reported on various risk factors for procedural clinical complications. A summary of all risk factors is given in eTable 5 in the Supplement, and the pooled risk factors are summarized in Figure 2. We did not pool data for aneurysm size and antiplatelet therapy (eFigures 3 and 4 in the Supplement). Ten studies reported on age: 7[64,95,102,112,113,119,126] reported on age as a continuous variable (OR for complications per year increase, 1.02 [95% CI, 1.01-1.02]; eTable 5 in the Supplement) and 3[91,99,120] reported different age categories (not pooled; eFigure 2 in the Supplement). For 3383 female patients, the pooled OR for complications from 10 studies[91,95,99,102,110,112,113,117,119,120] was 0.43 (95% CI, 0.32-0.85; eFigure 5 in the Supplement). The risk of complications was increased in patients with a coagulopathy (2 studies[101,115]; pooled OR, 2.14 [95% CI, 1.13-4.06]; eFigure 7 in the Supplement) and in those who used anticoagulation therapy (2 studies[110,113]; pooled OR, 6.36 [95% CI, 2.55-15.85]; eFigure 3 in the Supplement). We found several cardiovascular risk factors to be associated with an increased complication risk (eFigures 8-12 in the Supplement): smoking (5 studies[64,91,101,108,119]; pooled OR, 1.95 [95% CI, 1.36-2.79]), hypertension (5 studies[64,91,101,108,119]; pooled OR, 1.45 [95% CI, 1.03-2.03]), diabetes (4 studies[96,101,108,119]; pooled OR, 2.38 [95% CI, 1.54-3.67]), and congestive heart failure (2 studies[115,119]; pooled OR, 2.71 [95% CI, 1.57-4.69]). Posterior circulation aneurysms were associated with an increased complication risk (pooled OR, 7.25 [95% CI, 3.70-14.20]; 3 studies[64,104,112]; eFigure 14 in the Supplement). For aneurysm calcification, the pooled OR for complications was 2.89 (95% CI, 1.35-6.18; 2 studies[77,126]; eFigure 17 in the Supplement).

Figure 2: Overview of the association between various patient, aneurysm, and treatment factors and risk of procedural clinical complications from neurosurgical treatment

Risk Factor	Risk Estimate (95% CI)
Female	0.43 (0.32-0.85)
Coagulopathy	2.14 (1.13-4.06)
Use of oral coagulation	6.36 (2.55-15.85)
Cardiovascular comorbidity	
Smoking	1.95 (1.36-2.79)
Diabetes	1.45 (1.03-2.03)
Heart comorbidity	2.71 (1.57-4.69)
Posterior vs ICA aneurysm location	7.25 (3.70-14.20)
Aneurysm calcification	2.89 (1.35-6.18)



ICA=internal carotid artery.

DISCUSSION

This systematic review and meta-analysis provides risk estimates of clinical complications and case-fatality rates for current preventive EVT and NST of saccular UIAs and identifies several patient-associated, aneurysm-associated, and treatment-associated risk factors for both treatments. We found substantial differences in complication risks according to region and method of outcome assessment. For NST, the complication risks decrease over time, but this is not true for EVT. The use of advanced endovascular methods is associated with an increased risk of clinical complications.

Comparison with previous studies

The pooled crude risks of clinical complications from EVT we found are in line with risks found in previous EVT reviews.[9,130,135] In contrast, the NST complication risks we found were slightly higher than reported in previous reviews.[10,130] A potential explanation for this discrepancy is that, in contrast with previous NST reviews, we did not restrict inclusion criteria to studies reporting on permanent unfavourable outcomes but also included studies with nonpermanent complications and *ICD*-based administrative databases. In our subgroup analysis of studies basing outcome assessment on medical records, the NST complication risk was comparable with the risks found in previous NST reviews.[10,130] The risks reported in ICD-coded databases were 2 to 3 times higher than in studies based on medical records. When interpreting these data, it should be kept in mind that all *ICD*-based studies were performed in North American hospitals, where correct listing of complications leads to higher reimbursement.[136] On the other hand, most of the studies basing their outcome on medical records were single-centre or multicentre studies in which the surgeon or interventionist performed the retrospective analyses themselves, which may result in underestimating complication risks. One previous NST review also found that the complication risk was higher in a subgroup of North American studies.[9] The much lower complication risk in studies originating from Asia has not been reported before. One explanation for this lower risk may be differences in how complications are defined and recorded. Another one is that a higher treatment volume per hospital or surgeon or interventionist leads to more experience with preventive aneurysm treatment, resulting in lower rates of complications.

Previous reviews on EVT and NST included studies published between 1990 and 2011 and reported that complication risks decreased for both EVT and NST over time. Although we did not find significant time trends for EVT and NST for clinical complications and case-fatality rates in the period between 2001 and 2014, we did find that the NST complication risk decreased more than 50% between the periods 2001 to 2007 and 2011 to 2014 and that case-fatality rates were in general lower in the overall period we studied (2001-2014)

compared with earlier periods studied in previous reviews (a decrease from 1.5%-2.0% to <0.5%).[9,10,130,131,137] Unfortunately, we were unable to perform time-trend analyses for standard coiling and advanced endovascular methods separately.

We found that stenting and stent-assisted coiling were associated with an increased complication risk, but balloon-assisted coiling was not. One previous EVT review[9] found that the use of flow diverters was associated with a higher risk of an unfavourable outcome. More recently, several reviews of nonrandomized comparisons have been published on the outcome of various advanced endovascular methods, most of them confirming an increased complication risk for advanced endovascular methods compared with standard coiling.[131-133, 138-140] However, most studies included in these reviews[131-133, 138-140] included a mixture of saccular and nonsaccular aneurysms, making them unsuitable for our current review, which focused on saccular UIAs. For this reason, we also excluded 11 studies on flow diverters at the full-article screening stage (eTable 2 in the Supplement).

Other risk factors studied in previous EVT reviews[9,130,135] are increasing age, sex, aneurysm diameter, aneurysm location, and aneurysm neck size. None of these factors were found to be associated with an increased complication risk in these reviews, but risk factor data could only be studied from a small selection of articles.[9,130,131,135] Separate reviews have been performed for subgroups of anterior and posterior circulation aneurysms.[14,134] Previously identified risk factors for complications from NST are increasing age, aneurysm size, and posterior aneurysm location.[10,132] None of the existing reviews included cardiovascular risk factors as potential determinants for procedural complications for EVT or NST.

Strengths

Our systematic review and meta-analysis has several strengths. To date, this work is the largest overview of UIA treatment outcomes, including data from more than 100,000 patients with treated saccular UIAs. This allowed us to study risk differences according to study design and region. Especially for EVT, we were now able to further explore the association between the use of various advanced endovascular methods and risk of complications. A second strength is that we also studied risk factor data in detail. This enabled us to add several new aneurysm- and treatment-related risk factors to the already known risk factors from the literature. In addition, this is the first joint endovascular and neurosurgical meta-analysis to give a complete overview of the impact of various cardiovascular risk factors on both treatments.

Limitations

Some limitations need to be addressed. First, the complication risks for EVT and NST should not be compared because of the nonrandomized nature of the included studies, which

makes them prone to various sources of bias, such as selection bias. So far, only 1 randomized clinical trial[15] has been published on EVT vs NST in patients with saccular UIAs, which assessed permanent morbidity at 1 year as a secondary outcome. Second, only approximately 20% of the included studies were of high methodological quality. Third, outcome definitions were very heterogeneous across studies, and we were not able to disentangle transient and permanent clinical complications. This heterogeneity underscores the need of cautious interpretation of our meta-analyses of all clinical complications combined. Fourth, a part of the included studies reported very limited data on patient and aneurysm characteristics. As a result, we were limited in our analyses. Fifth, the finding that the complication risk is higher in subgroups of patients treated by NST or advanced endovascular methods may be a reflection of the complex nature of aneurysms treated by such treatment modalities. Finally, in our meta-analysis of risk factors for procedural clinical complications, we relied on the definitions and categorizations of risk factors and reference groups given in the original articles. For several risk factors, such as age and advanced endovascular methods, this meant that studies were noncomparable and could not be pooled or only a subset could be pooled.

CONCLUSIONS

This review provides precise estimates of procedural clinical complications and case-fatality rates from preventive EVT or NST of UIAs. The complication risk varies according to several patient-associated, aneurysm-associated, and treatment-associated risk factors. Most published observational data on preventive UIA treatment remain of poor methodological quality, with sensitivity particularly dependent on detailed and standardized recording of procedural clinical complications, method of outcome assessment and region. For clinical practice, the data from this study can be used to estimate the procedural complication risk from preventive UIA treatment according to patient-associated, aneurysm-associated, and treatment-associated characteristics, which need to be balanced against the risk of rupture when preventive aneurysm treatment is considered.

Through future research, our work can be further extended by meta-analysis of individual patient data from studies of high methodological quality. We underscore the need for detailed and standardized recording of clinical complications and treatment risk factors in a prospective setting to allow for multivariable analyses assessing the independent contribution of the different risk factors. With such data available, scores can be developed to prognosticate individualized procedural complication risks according to each person's risk factor profile.

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SUPPLEMENTARY ONLINE CONTENT

For supplemental tables and figures, please visit:
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CHAPTER 3

Development of the SAFETEA scores for predicting risks of complications of preventive endovascular or micro-neurosurgical intracranial aneurysm occlusion

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ABSTRACT

Objective

Preventive unruptured intracranial aneurysm occlusion can reduce the risk of subarachnoid haemorrhage, but both endovascular and microneurosurgical treatment carry a risk of serious complications. To improve individualized management decisions, we developed risk scores for complications of endovascular and microneurosurgical treatment based on easily retrievable patient, aneurysm, and treatment characteristics.

Methods

For this multicentre cohort study, we combined individual patient data from unruptured intracranial aneurysm patients ≥18 years of age undergoing preventive endovascular treatment (standard coiling, balloon-assisted coiling, stent-assisted coiling, Woven EndoBridge device, or flow-diverting stent) or microneurosurgical clipping at one of 10 participating centres from three continents between 2000 and 2018. The primary outcome was death from any cause or clinical deterioration from neurological complications within 30 days. We selected candidate predictors based on previous knowledge about relevant risk factors and predictor performance and studied the association between predictors and complications with logistic regression. We assessed model performance with calibration plots and concordance (*c*) statistics.

Results

Of 1282 included patients, 94 (7.3%) had neurological symptoms that resolved ‹30 days, 140 (10.9%) had persisting neurological symptoms, and 6 died (0.5%)). At 30 days, 52 patients (4.1%) were dead or dependent. Predictors of procedural complications were: size of aneurysm, aneurysm location, familial subarachnoid haemorrhage, earlier atherosclerotic disease, treatment volume, endovascular modality (for endovascular treatment) or extra aneurysm configuration factors (for microneurosurgical treatment; branching artery from aneurysm neck or unfavourable dome-to-neck ratio), and age (acronym: SAFETEA). For the endovascular model (n=752), the *c*-statistic was 0.72 (95%CI: 0.67-0.77) and the absolute complication risk ranged from 3.2% (95%CI: 1.6%-14.9%; ≤1 point) to 33.1% (95%CI:25.4%-41.5%; ≥6 points). For the microneurosurgical model (n=530), the *c*-statistic was 0.72 (95%CI: 0.67-0.77) and the complication risk ranged from 4.9% (95%CI: 1.5%-14.9%; ≤1 point) to 49.9% (95%CI: 39.4%-60.6%; ≥6 points).

Conclusions

The SAFETEA risk scores for endovascular and microneurosurgical treatment are based on seven easily retrievable risk factors to predict the absolute risk of procedural complications

in patients with unruptured intracranial aneurysms. The scores need external validation before the predicted risks can be properly used to support decision making in clinical practice.

INTRODUCTION

Preventive occlusion of an unruptured intracranial aneurysm can reduce the risk of subarachnoid haemorrhage (SAH) and hereby increase the number of life years with good quality of life.[1,2] However, both endovascular and microneurosurgical treatment carry a risk of serious treatment complications.[3-5] In management decisions on unruptured intracranial aneurysms, these treatment risks have to be carefully balanced against the risk of rupture and other factors such as life expectancy and fear for rupture of an untreated aneurysm.[6] Randomized trials comparing preventive occlusion with no occlusion in patients with unruptured intracranial aneurysms have proven to be difficult. The authors of the trial comparing coiling versus no intervention mention several factors for failure of this trial, including the difficulty to study withhold of a treatment instead of studying a new treatment, the need to include large numbers of patients and long follow up, the huge costs in absence of industry sponsoring, and the administrative hurdles.[7-9] Prediction modelling and decision analysis are currently the best evidence-based alternative to accurately balance the risks and benefits of preventive treatment. For aneurysm rupture, risk scores have been developed to predict the absolute risk of aneurysm rupture based on easily retrievable patient and aneurysm characteristics.[10,11] For the prediction of procedural complications, relevant risk factors have been described in meta-analyses and an expert consensus statement, but risk scores based on individual patient data are limited. Previous grading systems often combined data from patients with ruptured and unruptured aneurysms, making it difficult to distinguish between neurological deterioration due to procedural complications and a complicated clinical course following SAH.[12-18] The generalizability of the scores that did restrict models to unruptured intracranial aneurysm patients is limited by selective study populations or because data were collected before 2000.[16-18] Not only have procedural complication risks changed substantially over time, there has also been a shift towards endovascular treatment as the predominant treatment modality, with an increasing number of studies reporting on advanced endovascular methods, such as stent-assisted coiling, Woven EndoBridge devices, and flow-diverting stents.[3,19-22] The aim of the current study was to establish predictors of treatment complications for endovascular treatment and microneurosurgical treatment separately, and to provide risk prediction scores on the basis of easily retrievable patient, aneurysm, and treatment characteristics.

METHODS

Study design and population

We set up a multicentre registry to obtain individual patient data from unruptured intracranial aneurysm patients who underwent primary endovascular or microneurosurgical treatment in 10 tertiary referral centres from three continents (Europe: The Netherlands (n=4), Germany (n=1), and Finland (n=1); North America: Canada (n=1); and Asia: Hong Kong, China (n=3); eTable 1; Supplemental Material).

We included all consecutive patients ≥18 years of age who had an UIA documented with MR-angiography (MRA), CT-angiography (CTA) or digital subtraction angiography (DSA) and underwent elective endovascular or microneurosurgical treatment at one of the participating centres between January 1st, 2000, and December 31st, 2018. We excluded: (1) patients with non-saccular aneurysm such as fusiform or dissecting aneurysms, extradural aneurysms or aneurysms related to an arteriovenous malformation; (2) patients with imaging of insufficient quality (CTA or MRA slice thickness ›1.0 mm) to assess anatomical risk factors; (3) patients with SAH from another aneurysm ‹30 days before preventive aneurysm treatment; (4) interventions that were a retreatment of a previously treated unruptured intracranial aneurysm; and (5) interventions that were an unsuccessful treatment attempt only. If a patient had more than one aneurysm, we included the first unruptured intracranial aneurysm that was treated in case of separate treatment dates or selected the largest aneurysm if two or more aneurysms were treated in the same session.

Data collection

We extracted the following data from prospectively maintained local unruptured intracranial aneurysm databases and through retrospective data collection from medical records: age at aneurysm treatment, sex, smoking status (current, previous ‹10 years, previous ≥10 years, never), history of SAH, cardiovascular comorbidities (including hypertension, hyperlipidaemia, diabetes, peripheral artery disease, ischemic heart disease or heart failure, large vessel atherosclerosis, prior TIA or stroke), any malignancy, chronic obstructive pulmonary disease (COPD), use of anticoagulation or antiplatelet therapy (prior use versus treatment preloading), family history of SAH or unruptured intracranial aneurysms (›1 affected first degree relative), reason of aneurysm detection, number of intracranial aneurysms, treatment year, endovascular treatment modality, number of aneurysms treated in one session, and treatment volume per centre. We considered patients to have hypertension if this was reported in their medical history, if they used antihypertensive drugs without another indication, or if a systolic blood pressure ›140mmHg or a diastolic blood pressure ›90mmHg was recorded more than once. Carotid artery stenosis was scored as reported by the neuroradiologist and degree of stenosis

was grouped as moderate (50-69%), severe (70-99%) or occluded.[23] We classified reason of aneurysm detection as incidental, symptomatic (symptoms of mass effect such as a cranial nerve palsy or an ischemic event likely to be related to the aneurysm), or screening (familial or polycystic kidney disease). Geometric and morphological aneurysm characteristics were reviewed on pre-treatment MRA, CTA or DSA, depending on the imaging modality available. All investigators performing aneurysm measurements (AMA, KL, JdW and AK) were trained by an experienced interventional neuroradiologist (IvdS). Patients with difficult aneurysm characteristics were double checked the investigator who performed most of the measurements (AMA) and by the interventional radiologist (IvdS). Details on aneurysm measurements are given in eFigure 1 of the Supplemental Material. The aspect ratio (maximum height/neck diameter), dome-to-neck ratio (maximum diameter/neck diameter) and parent-to-neck ratio (parent artery diameter/neck diameter) were calculated.[24-26] Aneurysm morphology was categorized into regular or irregular. An aneurysm was considered irregular if a daughter sac (a protuberance arising from the aneurysm body with a volume less than 25% of the aneurysm volume) was present or if the aneurysm was bi- or multilobulated (a protuberance arising from the aneurysm neck with a volume ≥25% in proportion to the aneurysm).[27] Aneurysms were further evaluated on the presence of branching arteries involving the aneurysm neck. We dichotomized aneurysm location into anterior and posterior circulation aneurysms. We classified the location of anterior circulation aneurysms as internal carotid artery (including posterior communicating artery, anterior choroidal artery, and carotid termination), anterior cerebral arteries (including anterior communicating artery, pericallosal artery) or middle cerebral artery. Posterior circulation aneurysms were identified as those arising from the posterior cerebral artery, basilar artery (including basilar termination, basilar trunk, or sidewall), cerebellar arteries (superior cerebellar artery and posterior inferior cerebellar artery), and vertebral artery. Endovascular treatment modality was categorized into standard coiling and advanced endovascular treatment (balloon-assisted coiling, stent-assisted coiling, Woven EndoBridge devices, or flow-diverting stents). Microneurosurgical treatment consisted of microneurosurgical clipping only. Individual treatment experience cannot easily be translated into a useful predictor for clinical practice, since more experienced surgeons or radiologists often do more complex aneurysms compared to colleagues with less experience. Therefore, we studied the influence of numbers of patients treated per center per year with one treatment modality (either endovascular or microneurosurgical treatment) and dichotomized into less or more than 10 aneurysms treated per center per year.

Outcome events

The primary outcome was death from any cause or any neurological complication resulting in clinical deterioration within 30 days after the procedure. We further subdivided neurological complications into ischemic and haemorrhagic complications, and transient and persisting

neurological complications. Neurological deterioration was scored as transient if clinical symptoms resolved within 30 days. Details of definitions are given in eTable 2. We recorded data on length of hospital stay and clinical outcome at 30 days (categorized as independent or dependent for activities of daily living or deceased). Outcomes were systematically assessed by one investigator (AMA) at seven participating centres. In the other centres outcomes were scored by other investigators (JdW, KL, and AK) under direct supervision (AMA, TK, and AL). All potential neurological complications were discussed with or reviewed by the treating surgeon or interventionalist or team of intracranial aneurysm specialists at each centre.

Statistical analysis

We performed a sample size estimation in which we assumed an average treatment complication rate of 10%. We calculated that if we have 10 patients with complications per predictor and 5 predictors per score, we need 500 patients per risk score. Data were missing on familial SAH in 471 patients (37%) and smoking in 120 patients (9%). For familial SAH we assumed that patients with missing data had a negative family history. We performed sensitivity analyses excluding participants with missing data. Five patients (0.4%) were excluded from the analysis because primary outcome data were missing. For continuous variables (such as age or maximum aneurysm size) we used plots and restricted cubic splines to assess whether variables could be analysed as linear terms or needed transformation. We performed logistic regression analyses to study the association between candidate predictors and endovascular and neurosurgical complication risk separately. In addition, we performed explorative analyses to study combinations of aneurysm configuration factors (such as a wide aneurysm neck, a branching artery involved in the aneurysm neck, or an irregular aneurysm morphology). Inclusion of predictors in the regression models for endovascular treatment and neurosurgical treatment was based on previous knowledge from meta-analyses and expert-based consensus and on predictor performance. We simplified the full models containing all candidate predictors by performing backward selection based on the Akaike Information Criterion.
We assessed discriminatory performance of the models with concordance (*c*) statistics and calibration by visual inspection of graphical calibration slopes and plots. We performed bootstrapping techniques for internal validation. Based on the degree of optimism, shrinkage factors were estimated to shrink the regression coefficients of the models and to correct the *c*-statistics for optimism. We used the regression coefficients in the final multivariable regression models to develop risk scores for endovascular treatment and microneurosurgical treatment for obtaining complication risks for individual patients with a given risk factor profile. We performed the following predefined analyses according to type of outcome: 1) procedural death or persisting neurological complications; 2) any ischemic or haemorrhagic neurological complication; 3) any ischemic neurological complication. In addition to internal validation, we also performed internal-external cross-validation. This means that every centre

in our dataset is left out once and that the entire modelling process is repeated based on the remaining centers.[28]

Standard protocol approvals, registrations, and patient consents
We obtained approval for this study from the Institutional Research Ethics Board of the University Medical Center Utrecht, the Netherlands. No informed consent was required.

RESULTS

We included 1,282 patients with 752 aneurysms treated by endovascular treatment and 530 aneurysms by microneurosurgical clipping (Figure 1). Table 1 shows the baseline characteristics of both treatment cohorts. Centre-specific data are provided in the Supplement (eTable 3). Mean age was 56 years (SD 11) in the endovascular cohort and 55 years (SD 10) in the neurosurgical cohort. In both cohorts, the median treatment year was 2013, most patients were women (endovascular: 77%; microneurosurgical: 65%) and cardiovascular comorbidity was common. In the endovascular cohort, the median aneurysm size prior to treatment was 8 mm (IQR: 6-10), 582 of the unruptured intracranial aneurysms (77%) were in the anterior circulation, and 382 aneurysms (51%) were treated by advanced endovascular methods. Baseline differences between standard coiling and advanced endovascular treatments are specified in eTable 4. Compared to standard coiling, aneurysms treated with advanced endovascular treatments were larger, had a wider neck size and were often located at the basilar termination or ophthalmic region of the internal carotid artery. In the microneurosurgical cohort, the median aneurysm size was 7 mm (IQR 5-9), 523 aneurysms (99%) were in the anterior circulation, and in 84 patients (16%) multiple unruptured intracranial aneurysms were treated in one session.

In the endovascular cohort, procedural complications occurred in 120 of 752 (16.0%) patients (standard coiling: 31/370 (8.4%) and advanced endovascular treatment: 89/382 (23.3%)). Overall, 52 transient (6.9%) and 63 persisting (8.4%) neurological complications occurred, and 5 fatal complications (0.7%)). Twenty patients (2.7%) were dead or dependent at 30 days. The median length of hospital stay was two days (IQR 2-3). Details of the complications are given in eTable 5. In the microneurosurgical cohort, procedural complications occurred in 120 of 530 (22.6%) patients (42 transient (7.9%) and 77 persisting (14.5%) neurological complications, and one fatal complication (0.2%)). At 30 days, 32 patients (6.0%) were dead or dependent (eTable 6). The median length of hospital stay was six days (IQR 4-8).

Table 1. Baseline characteristics for endovascular and neurosurgical treatment cohorts

	Endovascular treatment (n=752)		Neurosurgical treatment (n=530)	
	No complication (n=632)	**Complication** (n=120)	**No complication** (n=410)	**Complication** (n=120)
Patient characteristics				
Women	481 (76)	100 (83)	271 (66)	72 (60)
Age (in years; mean; SD)	55.9 (10.5)	58.0 (11.1)	54.3 (10.3)	58.4 (9.0)
<45	89 (14)	9 (8)	68 (17)	12 (10)
45-59	297 (47)	54 (45)	207 (51)	47 (39)
60-69	194 (31)	41 (34)	112 (27)	53 (44)
70+	52 (8)	16 (13)	23 (6)	8 (7)
Smoking				
Current	243 (38)	40 (33)	184 (45)	41 (34)
Previous	96 (15)	23 (19)	52 (13)	17 (14)
Comorbidity				
Hypertension	334 (53)	75 (63)	238 (58)	76 (63)
Hyperlipidaemia	117 (28)	36 (30)	119 (29)	42 (35)
Diabetes	50 (8)	17 (14)	28 (7)	8 (7)
Carotid disease[a]	17 (3)	5 (4)	19 (5)	16 (13)
Heart disease or PAD[b]	81 (13)	29 (24)	64 (16)	19 (16)
Prior TIA/ischemic stroke	94 (15)	19 (16)	55 (13)	21 (18)
COPD	28 (4)	8 (7)	18 (4)	11 (9)
Prior SAH	86 (14)	8 (7)	72 (18)	17 (14)
Prior use of APT	147 (23)	25 (21)	97 (24)	38 (32)
Prior use of anticoagulation	11 (2)	8 (7)	16 (4)	8 (7)
Symptomatic aneurysm	79 (13)	20 (17)	21 (5)	10 (8)
Aneurysm multiplicity	212 (34)	32 (27)	167 (41)	50 (42)
Family history of SAH	102 (16)	9 (8)	90 (22)	13 (11)
Aneurysm characteristics				
Size of aneurysms (mm; median (IQR))	7.7 (5.5-10.0)	9.1 (6.2-13.7)	6.7 (4.9-8.6)	8.0 (5.2-11.0)
< 3.0	15 (2)	2 (2)	13 (3)	5 (4)
3.0-4.9	106 (17)	15 (13)	93 (23)	18 (15)
5.0-6.9	140 (22)	23 (19)	112 (27)	24 (20)
7.0-9.9	212 (34)	27 (23)	124 (30)	31 (25)
10.0-14.9	116 (18)	30 (25)	59 (14)	32 (27)
15.0-19.9	25 (4)	14 (12)	7 (2)	7 (6)
≥ 20.0	17 (3)	9 (8)	2 (1)	3 (3)
Neck size of aneurysms (mm; median (IQR))	4.0 (3.0-5.2)	5.1 (3.8-6.5)	3.8 (2.9-5.0)	4.0 (2.9-5.6)
<2.5	72 (11)	9 (8)	56 (14)	15 (13)
2.5-4.9	372 (59)	48 (40)	250 (61)	68 (57)
5.0-7.4	153 (24)	47 (39)	89 (22)	30 (25)
≥ 7.5	35 (6)	16 (13)	15 (4)	7 (6)
Parent vessel (mm; median (IQR))	3.0 (2.3-3.6)	3.1 (2.3-3.7)	2.2 (1.9-2.6)	2.3 (2.0-2.8)
< 2.0	83 (13)	13 (11)	123 (30)	25 (21)
2.0-2.9	231 (37)	38 (32)	229 (56)	76 (63)
≥ 3.0	318 (50)	69 (58)	58 (14)	19 (16)

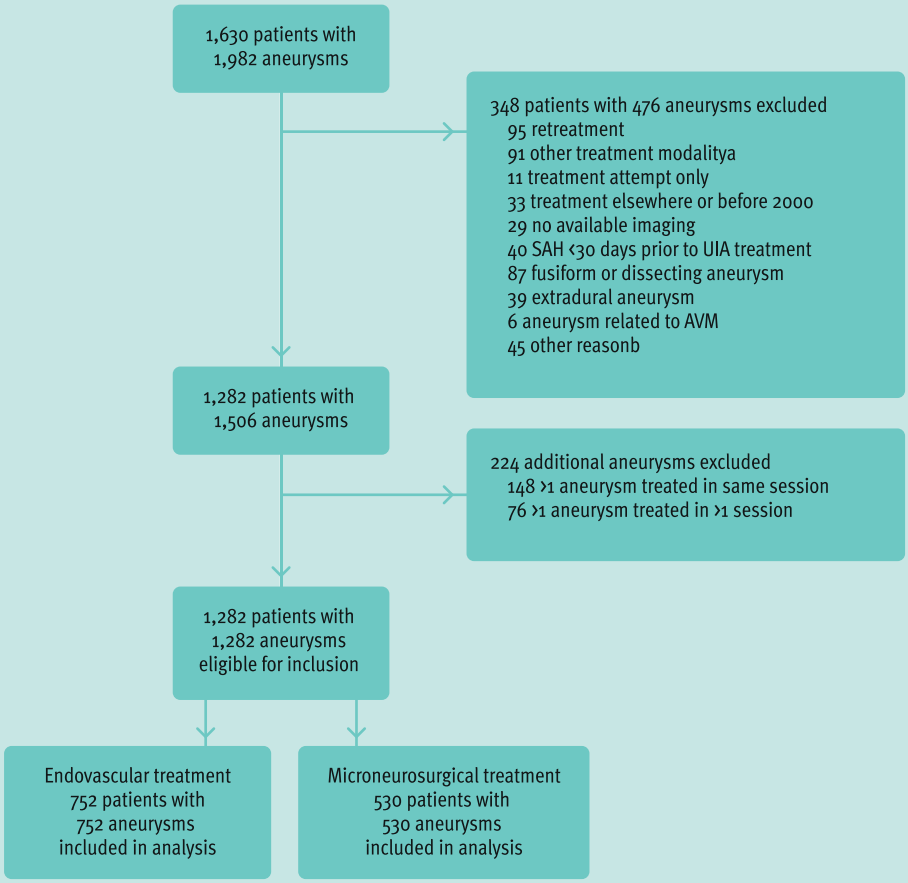
Table 1 continued

Ratios (median (IQR))				
Aspect ratio	1.7 (1.3-2.3)	1.6 (1.2-2.2)	1.5 (1.1-2.0)	1.6 (1.1-2.5)
Dome-to-neck ratio	1.6 (1.3-2.0)	1.6 (1.2-2.1)	1.5 (1.2-2.0)	1.6 (1.2-2.3)
Neck-to-parent ratio	1.4 (1.0-1.9)	1.6 (1.2-2.2)	1.7 (1.3-2.3)	1.7 (1.3-2.3)
Aneurysm location				
Anterior	497 (79)	81 (67)	404 (98)	119 (99)
ACom artery	78 (12)	15 (13)	52 (13)	31 (26)
Pericallosal artery	13 (2)	1 (1)	20 (5)	1 (1)
ICA Carotid termination	58 (9)	3 (3)	15 (4)	6 (5)
ICA PCom/Ant. Choroidal	105 (17)	9 (8)	25 (6)	8 (5)
ICA Ophthalmic region	186 (29)	44 (37)	15 (4)	4 (3)
MCA	57 (9)	9 (8)	277 (68)	69 (58)
Posterior	135 (21)	39 (33)	6 (2)	1 (1)
Basilar termination	95 (15)	33 (28)	0	0
PICA/Vertebral artery	20 (3)	4 (3)	5 (1)	0
Other posterior[c]	20 (3)	2 (2)	1 (0.2)	1 (1)
Aneurysm configuration				
Irregular aneurysm	108 (17)	12 (10)	60 (15)	11 (9)
Branching artery from neck	104 (17)	22 (18)	78 (19)	32 (27)
Treatment characteristics				
Treatment period (range)	2013 (2000-18)	2013 (2000-18)	2013 (2008-2018)	2013 (2000-18)
Endovascular modality				
Standard coil	339 (54)	31 (26)	-	-
Advanced treatment[d]	293 (46)	89 (74)	-	-
Balloon-assisted coil	73 (12)	13 (11)	-	-
Stent-assisted coil	125 (20)	36 (30)	-	-
Woven EndoBridge	21 (3)	5 (4)	-	-
Flow-diverter	74 (12)	35 (29)	-	-
Preloading with APT	392 (62)	91 (76)	-	-
≥1 aneurysm treated/session	38 (6)	9 (8)	62 (15)	22 (18)

a) Carotid disease includes moderate (50-69%) and severe (70-99%) carotid stenosis or carotid occlusion. b) Heart disease includes ischemic heart disease and heart failure. c) Other posterior includes the following aneurysm locations: basilar termination, basilar trunk, basilar sidewall, and superior cerebellar artery. d) Advanced endovascular treatment includes balloon-assisted coil, stentassisted coil, Woven EndoBridge devices, Flow-diverting stents. The following two variables had missing values: 1) smoking (120 patients (9%)) and 2) family history of SAH (471 patients (37%)). A positive family history of SAH indicates >1 affected first degree relative with a SAH or unruptured intracranial aneurysm. n=number. SD=standard deviation. IQR=interquartile range. COPD=chronic obstructive pulmonary disease. TIA=transient ischemic attack. SAH=subarachnoid haemorrhage. APT=antiplatelet therapy. ACom=anterior communicating artery. PCom=posterior communicating artery. ICA=internal carotid artery. MCA=middle cerebral artery. PICA=posterior inferior cerebellar artery.

Table 2 shows the results of the multivariable regression model for endovascular treatment. Size of the aneurysm, aneurysm location, familial SAH, earlier atherosclerotic disease (including coronary, peripheral, and carotid artery disease), treatment volume, endovascular treatment modality and age were independent predictors of complication risk. Due to insufficient predictive power, prior use of anticoagulation, hypertension and aneurysm neck size

Figure 1: Flowchart



a) Other aneurysm treatment modalities included intracranial-extracranial bypass, carotid occlusion or wrapping. b) Other reasons for exclusion included simultaneous treatment of a ruptured aneurysm, retreatment of another aneurysm or another rare combination (such as together with meningioma excision). SAH=subarachnoid haemorrhage. AVM=arterio-venous malformation.

were removed from the final model. Familial SAH was inversely associated with procedural complications. Differences between familial and non-familial aneurysm patients are given in eTable 7. Although we did not find evidence for interaction between familial SAH and patient, aneurysm and treatment characteristics, familial cases were slightly younger, had fewer comorbidities, smaller aneurysms, and were more often treated with standard coiling. After

Table 2: Univariable and multivariable regression analysis of predictors of endovascular treatment risk in patients with unruptured intracranial aneurysms

	Univariable OR (95%CI)	**Multivariable**[a] OR (95%CI)
Female sex	1.57 (0.94-2.62)	-
Age ≥45 years	2.32 (1.14-4.73)	1.85 (0.86-3.98)
Hypertension	1.49 (1.00-2.22)	1.15 (0.72-1.83)
Atherosclerotic disease[b]	2.21 (1.39-3.53)	1.59 (0.90-2.79)
Prior use of oral anticoagulation	4.03 (1.59-10.25)	1.57 (0.50-4.96)
Absence of familial SAH[c]	2.21 (1.39-3.53)	1.61 (0.76-3.41)
Aneurysm size		
<10 mm	Reference	Reference
10-14.9 mm	1.27 (1.22-1.83)	1.21 (0.69-2.12)
≥15 mm	2.11 (1.11-1.79)	1.80 (0.88-3.69)
Aneurysm neck size		
<5 mm	Reference	Reference
5-7.4 mm	2.39 (1.56-3.67)	1.22 (0.74-2.03)
≥7.5 mm	3.56 (1.85-6.84)	1.03 (0.45-2.35)
Aneurysm location		
ACom artery	Reference	Reference
MCA	0.82 (0.34-2.01)	1.15 (0.43-3.06)
ICA Ophthalmic region	1.23 (0.65-2.34)	1.09 (0.52-2.28)
Basilar termination	1.81 (0.92-3.56)	1.17 (0.55-2.51) 0.49
Other locations	0.46 (0.22-0.94)	(0.23-1.05)
Endovascular treatment modality		
Standard coil	Reference	Reference
Balloon-assisted coil	1.95 (0.97-3.90)	1.34 (0.61-2.92)
Stent-assisted coil	5.17 (3.00-8.92)	2.34 (1.21-4.51)
Woven EndoBridge	2.60 (0.92-7.38)	1.11 (0.35-3.53)
Flow-diverter	3.15 (1.87-5.13)	1.85 (0.98-3.47)
Treatment volume <10 cases/year[d]	2.78 (1.64-4.71)	1.66 (0.89-3.11)

a) The initial beta coefficients were adjusted for overfitting. b) Atherosclerotic disease includes coronary, peripheral and carotid artery disease. Carotid disease includes moderate (50-69%) and severe (70-99%) carotid stenosis and carotid occlusion. c) A positive family history of SAH indicates >1 affected first degree relative with a SAH or unruptured intracranial aneurysm. d) Treatment volume <10 cases/year indicates the number of cases treated for each treatment modality separately (standard coil, balloon-assisted coil, stent-assisted coil, Woven EndoBridge devices, Flow-diverting stents) per year per centre. OR=odds ratio. CI=confidence interval. SAH=subarachnoid haemorrhage. ACom=anterior communicating. MCA=middle cerebral artery. ICA=internal carotid artery.

correction for optimism, the *c*-statistic of the endovascular model was 0.72 (95%CI: 0.67-0.77). The calibration of the model was accurate (eFigure 2). In sensitivity analyses according to the type of outcome and internal-external validation, performance of the model was essentially the same, but weaker predictors were dropped from the model depending on the number of outcome events available per analysis (eTables 8 and 9). Similarly, the model remained stable after excluding patients with missing data on familial SAH or including patients with a treatment attempt only (intention-to-treat). The beta coefficients and linear function of the final endovascular model are given in eTable 10, together with a description how to use the score based on clinical examples.

Table 3 shows the results of the multivariable regression model for microneurosurgical treatment. The model containing the size of aneurysm age, aneurysm location, familial SAH, earlier carotid artery disease, treatment volume, extra aneurysm configuration factors (at least one of the following: branching artery involved in the aneurysm neck or dome-to-neck ratio ›2.5) and age best predicted an individual's complication risk. After correction, the *c*-statistic of the microneurosurgical model was 0.72 (95%CI: 0.67-0.77). The calibration plot is given in eFigure 2. The performance of the microneurosurgical model remained stable in sensitivity analysis according to outcome type and internal-external validation (eTables 11 and 12). Intention-to-treat analysis or the exclusion of patients with missing data on familial SAH did not alter the model. Beta coefficients, the linear function, and the applicability of the microneurosurgical model are provided in eTable 13.

Table 3: Univariable and multivariable regression analysis of predictors of neurosurgical treatment risk in patients with unruptured intracranial aneurysms

	Univariable OR (95%CI)	**Multivariable**[a] OR (95%CI)
Female sex	0.77 (0.51-1.17)	-
Age ≥45 years	2.18 (1.15-4.16)	1.68 (0.85-3.34)
Hypertension	1.25 (0.82-1.90)	-
Atherosclerotic carotid disease[b]	3.17 (1.57-6.37)	2.13 (0.98-4.64)
Prior use of oral anticoagulation	1.76 (0.73-4.22)	1.19 (0.46-3.10)
Absence of familial SAH[c]	2.31 (1.24-4.31)	1.65 (0.84-3.23)
Aneurysm size		
‹10 mm	Reference	Reference
10-14.9 mm	2.38 (1.45-3.90)	1.61 (0.92-2.82)
≥15 mm	4.87 (1.92-12.39)	2.69 (0.93-7.79)
Presence of at least one of the following aneurysm configuration factors:		
Branch artery from neck Dome-neck-ratio ›2·5	2.03 (1.33-3.09)	1.58 (0.97-2.57)
Aneurysm location		
MCA	Reference	Reference
ICA PCom and ant. choroidal	1.28 (0.56-2.97)	1.11 (0.45-2.74)
ICA Carotid termination	1.61 (0.60-4.29)	1.91 (0.65-5.60)
ACom artery	2.39 (1.43-4.01)	2.33 (1.33-4.09) 0.47
Other locations	0.59 (0.24-1.44)	(0.17-1.26)
Treatment volume ‹10 cases/year[d]	2.78 (1.81-4.25)	2.31 (1.45-3.68)

a) The initial beta coefficients were adjusted for overfitting. b) Atherosclerotic carotid disease includes moderate (50-69%) and severe (70-99%) carotid stenosis and carotid occlusion. c) A positive family history of SAH indicates ›1 affected first degree relative with a SAH or unruptured intracranial aneurysm. d) Treatment volume ‹10 cases/year indicates the number of cases clipped per year per centre. OR=odds ratio. CI=confidence interval. SAH=subarachnoid haemorrhage. ACom=anterior communicating. MCA=middle cerebral artery. ICA=internal carotid artery. NST=neurosurgical treatment.

Based on the final multivariable regression models for endovascular and microneurosurgical

treatment, we developed two risk scores with the acronym 'SAFETEA', which are presented in Table 4 (endovascular score: panel A; microneurosurgical score: panel B). The corresponding absolute procedural complication risks are illustrated in Figure 2 (endovascular risk score) and Figure 3 (microneurosurgical risk score). For endovascular treatment, the absolute 30-day complication risk increases as the risk score increases. One point on the score is associated with a risk of 3.2% (95%CI: 1.6%-14.9%), whereas the maximum of 6 points is associated with a risk of 33.1% (95%CI: 25.4%-41.5%). For microneurosurgical treatment, the absolute 30-day complication risk ranged from 4.9% (95%CI: 1.5%- 14.9%; 1 point) to 49.9% (95%CI: 39.4%-60.6%; 6 points).

Table 4: Predictors composing the SAFETEA aneurysm treatment risk scores for endovascular treatment (A) and neurosurgical treatment (B)

A. Endovascular risk score		**B. Neurosurgical risk score**	
Predictor	**Points**	**Predictor**	**Points**
(S) Size of aneurysm		(S) Size of aneurysm	
<10 mm (ref.)	0	<10 mm (ref.)	0
10-14.9 mm	1	10-14.9 mm	1
≥15 mm	2	≥15 mm	2
(A) Aneurysm location		(A) Aneurysm location	
ACom (ref.)	0	MCA (ref.)	0
Other	0	Other	0
MCA	1	ICA PCom / Ant. choroidal region	1
ICA Ophthalmic region	1	Carotid termination	1
Basilar termination	1	ACom	1
(F) Familial SAH[a]		(F) Familial SAHa	
Yes (ref.)	0	Yes (ref.)	0
No	1	No	1
(E) Earlier atherosclerotic disease[b]		(E) Earlier carotid diseaseb	
No (ref.)	0	No (ref.)	0
Yes	1	Yes	1
(T) Treatment volume[c]		(T) Treatment volumec	
≥10 cases/year (ref.)	0	≥10 cases/year (ref.)	0
<10 cases/year	1	<10 cases/year	1
(E) Endovascular modality		(E) Extra configuration factors	
Standard coil (ref.)	0	Branch artery from neck or DNR >2.5[d]	0
Balloon-assisted coil	1		1
Stent-assisted coil	2	No (ref.)	2
Woven EndoBridge	1	Yes	1
Flow-diverter	2		2
(A) Age		(A) Age	
<45 year (ref.)	0	<45 year (ref.)	0
≥45 year	1	≥45 year	1

a) A positive family history of SAH indicates >1 affected first degree relative with a SAH or unruptured intracranial aneurysm. b) Atherosclerotic disease includes coronary, peripheral and carotid artery disease. Carotid disease includes moderate (50-69%) and severe (70-99%) carotid stenosis and carotid occlusion. c) Treatment volume <10 cases/year indicates the number of cases treated for each treatment modality separately (standard coil, balloon-assisted coil, stent-assisted coil, Woven EndoBridge devices, Flow-diverting stents or clipping) per year per centre. d) A dome-to-neck ratio of >2.5 indicates that the dome was 2.5 times as large as the neck. SAH=subarachnoid haemorrhage. ACom=anterior communicating. MCA=middle cerebral artery. ICA=internal carotid artery. DNR=dome-to-neck ratio.

Figure 2: Predicted endovascular treatment risk according to the SAFETEA score

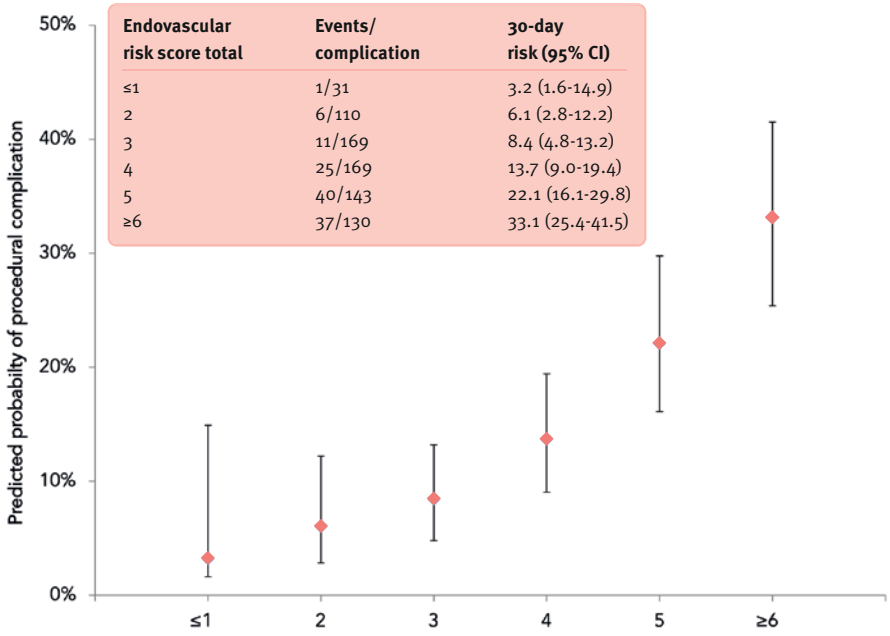
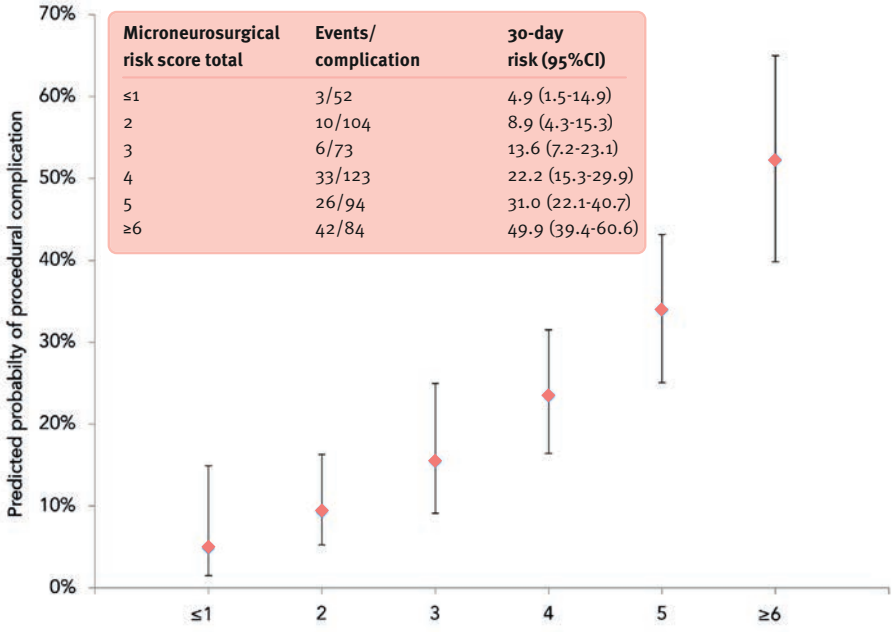


Figure 3: Predicted neurosurgical treatment risk according to the SAFETEA score



CI=confidence interval.

DISCUSSION

We developed prediction models for procedural complications of preventive endovascular and microneurosurgical treatment using data from 10 tertiary aneurysm referral centres from three continents. We found solid discriminatory performance and calibration for both models. Aneurysm treatment risk scores were created for endovascular treatment and microneurosurgical treatment including the following easily retrievable characteristics: size of aneurysm, aneurysm location, familial SAH, earlier atherosclerotic disease, treatment volume, endovascular modality (for endovascular treatment) or extra aneurysm configuration factors (for microneurosurgical treatment; branching artery from aneurysm neck or unfavourable dome-to-neck ratio), and age (acronym: SAFETEA).

The case-fatality rates of less than one percent we found for both endovascular and microneurosurgical treatment are in line with previously reported rates from similar time periods.[3] The risks of non-fatal neurological complications in our study are higher than in previous reviews, but this can be explained by differences in definitions. Earlier studies focused on severe morbidity (modified Ranking Score ≥3), while we also included procedural neurological complications with less severe and transient neurological deterioration.[4,5] We included these non-permanent complications, because they also reduce quality of life. If we restricted complications in our study to death or dependency, the combined risk was less than 3% for endovascular treatment and 6% for microneurosurgical treatment, which is consistent with previous reviews.[4,5] Given the heterogeneity in reported outcome definitions, we performed several sensitivity analyses according to outcome type and found that model performance remained stable across outcomes.

Our finding of an inverse association between familial SAH and procedural risk is most likely explained by differences in age, comorbidities, and aneurysm characteristics between familial and non-familial patients, and not by genetic factors.[15] Compared to standard coiling, advanced endovascular treatments were associated with higher complication risks. Our results illustrate that these higher risks can be partially explained by the morphology of aneurysms treated by such modalities.[26] We found that a wide aneurysm neck was of added value for the prediction of endovascular treatment complications in univariate analyses, but that this was no longer the case when treatment modality was accounted for. Treatment modality remained, however, a strong predictor in the multivariable model, which indicates that either the treatment itself, or other factors not accounted for, contribute to the increased risk of advanced endovascular treatments.

So far, one endovascular risk score has been developed in unruptured intracranial aneurysm

patients only.[16] Risk factors included in that score (cerebral ischemic comorbidity, aneurysm size and location) are consistent with predictors included in our endovascular model, but generalizability is restricted to Chinese patients.[16] For microneurosurgical treatment, two previous models identified age, aneurysm size and location as risk factors.[17,18] Also for those models generalizability is limited, as one score was developed before 2000 and complication risks have decreased over time.[3] In addition, both studies were based on single-centre cohorts and did not restrict analyses to microsurgical clipping.

Limitations

Some limitations need to be addressed. First, since our study is based on retrospectively collected observational data, the recording of data and outcomes varied, which made it impossible to reliably assess outcomes according to standardized outcome scales and meant that we had to make assumptions for patients with missing data on SAH family history. Due to insufficient quality of imaging, inclusion rates were lower before 2008. This may have resulted in less accurate outcome predictions and an underestimation of overall treatment risk if complications were underreported or missed. Second, the assessment of procedural complications was not blinded for treatment allocation, which may have led to diagnostic bias. To minimalize this, all primary outcome events were scored by independent non-treating investigators based on predefined definitions and discussed with or reviewed by intracranial aneurysm experts per participating centre. Third, geometrical or morphological aneurysm details may have been missed or misclassified if no DSA was available or because the scoring was performed by different investigators. Nevertheless, all investigators who performed measurements were trained in a similar way and patients with difficult aneurysm characteristics were double checked by an experienced interventional neuroradiologist. Fourth, because for many aneurysms one of the treatment options is clearly the preferred strategy, we chose to develop separate treatment risk scores for endovascular and microneurosurgical treatment. Our study was however not powered to develop separate models for the different advanced endovascular treatment modalities. Fifth, although centre-specific variation was almost fully accounted for by differences in aneurysm size, treatment volume and treatment modalities used, we cannot rule out that there still existed some variation in case-mix, for example due to differences in patient selection, organization of aneurysm care, and individual treatment experience.[3,29,30] Finally, our models were not externally validated. However, discriminatory performance and calibration of the models were confirmed by internal validation and internal-external validation.

Strengths

Our study also has several strengths. First, all eligible consecutive unruptured intracranial aneurysm patients who underwent preventive aneurysm treatment at one of 10 tertiary aneu-

rysm referral centres from three continents during the two most recent decades were included in our development cohorts, making our findings representative of aneurysm populations that undergo preventive occlusion in similar settings. Second, we systematically collected many predefined outcome events in detail, including transient neurological deficits. This enabled us to perform several sensitivity analyses to confirm the predictive power of our models. Third, the large number of individual patient data allowed us to include several patient, aneurysm, and treatment predictors and to develop unruptured intracranial aneurysm risk scores for endovascular treatment and microneurosurgical treatment separately. Finally, we used the multidisciplinary experience and expertise from our study group, including neurosurgeons, interventional radiologists, neurologists, and clinical epidemiologists, to bring together and discuss both the clinical relevance and predictive performance of key factors involved in the management of unruptured intracranial aneurysms.

CLINICAL IMPLICATIONS AND CONCLUSION

Evidence-based scores for risk prediction can support multidisciplinary team meetings and shared decision-making among aneurysm specialists and patients. However, we would like to stress that the SAFETEA risk scores first need external validation. They should not be used in clinical practice to directly compare absolute complication risks of endovascular treatment with those from neurosurgical treatment, or with rupture risks calculated with the PHASES score. In addition, as the clinical experience with different endovascular treatment modalities grows, further studies are needed to better understand the association between advanced endovascular treatments and outcome. Ideally, such studies should be powered to develop separate risk models for different endovascular treatment modalities, with extension to centres of varying treatment volume and centres in different countries and continents than the ones already included in the current study. Until such studies become available, the risks and predictors described in our study can be used as evidence-based background, alongside existing decision guidance based on expert-opinion, such as the unruptured intracranial aneurysm treatment score (UIATS).[6]

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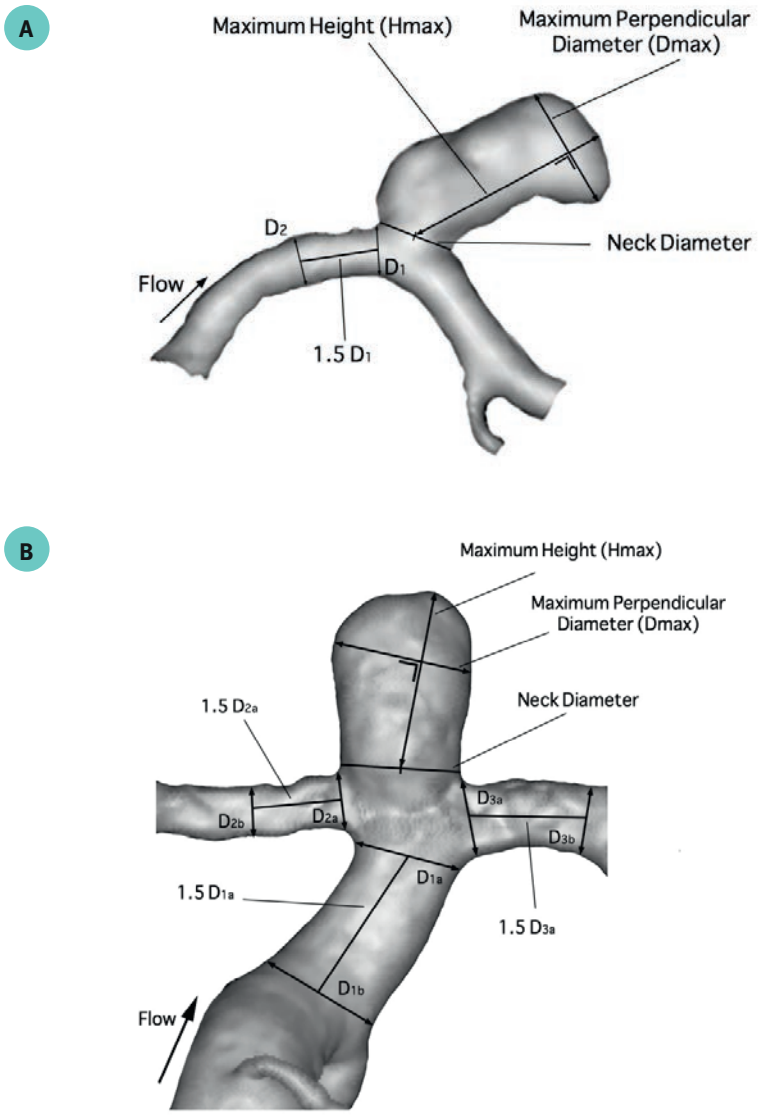
SUPPLEMENTARY CONTENT

eTable 1: Participating centres

Country	Participating center
Netherlands	University Medical Center Utrecht
	University Medical Center Amsterdam
	Erasmus University Medical Center, Rotterdam
	Radboud University Medical Center, Nijmegen
Germany	University Hospital Mannheim
Finland	Kuopio University Hospital
Canada	University of Toronto: Toronto Western Hospital
China	Chinese University of Hong Kong:
	Prince of Wales Hospital
	Kwong Wah Hospital
	Tuen Moon Hospital

eFigure 1: Aneurysm measurements specified



The maximum height is measured from the centre of the neck diameter. The maximum diameter is measured perpendicular to the maximum height. The parent vessel diameter is an average between two measurements (D_1 and D_2) with $1{,}5D_1$ in between the two measurements (**A**). For aneurysms located at an artery termination the diameters of the feeding vessel and all involved branching arteries are measured twice and an average is calculated as parent vessel diameter (**B**).

eTable 2: Outcome definitions specified

Neurological procedural complication	Specification
Ischemic complications[a]	Ischemic stroke
	Ocular ischemia (visual deficit caused by retinal artery occlusion or an anterior ischemic optic neuropathy)
	Transient ischemic attack (neurological deficit lasting <24 hours)
	Venous infarction due to cerebral venous sinus thrombosis
	Unspecified stroke (focal neurological deficit lasting ≥24 hours without imaging confirmation)
Haemorrhagic complications[a]	Subarachnoid haemorrhage
	Intraparenchymal haemorrhage
	Epidural haemorrhage
	Subdural haemorrhage
	Haemorrhage due to cerebral venous sinus thrombosis
Other neurological complications	Cranial nerve palsies
	Hydrocephalus
	Meningitis, (meningo)-encephalitis, ventriculitis and/or cerebritis (neurological deterioration due to neurological infection with compatible findings in cerebrospinal fluid)
	Delirium (transient episode of neuropsychiatric deterioration)
	Other unspecified or rare neurological complications that resulted in a deterioration in clinical outcome (*e.g.*, cortical blindness due to contrast reaction)

a) Stroke subtypes are based on a combination of new neurological deficits and imaging findings relevant to the symptoms, unless otherwise stated.

eTable 3: Centre-specific baseline characteristics

Patient characteristics	Centre 1 n (%)	Centre 2 n (%)	Centre 2 n (%)	Centre 4 n (%)
Number of included patients	264	243	84	50
Women	188 (71)	192 (79)	65 (77)	33 (66)
Age (in years; mean; SD)	56.6; 10.7	56.7; 9.3	56.1; 10.3	54.6; 9.3
<45	33 (13)	20 (8)	7 (8)	9 (18)
45-59	117 (44)	134 (55)	43 (51)	24 (48)
60-69	90 (34)	73 (30)	27 (32)	15 (30)
70+	24 (9)	16 (7)	7 (8)	2 (4)
Smoking				
Current	132 (50)	87 (36)	39 (46)	28 (56)
Previous	75 (28)	54 (22)	16 (19)	7 (14)
Comorbidity				
Hypertension	170 (64)	128 (53)	52 (62)	30 (60)
Hyperlipidaemia	75 (28)	76 (31)	30 (36)	19 (38)
Diabetes	16 (6)	15 (6)	12 (14)	2 (4)
Carotid disease[a]	10 (4)	6 (2)	13 (16)	5 (10)
Heart disease or PAD[b]	52 (20)	28 (11)	13 (16)	12 (24)
Prior TIA/ischemic stroke	48 (18)	36 (15)	20 (24)	4 (8)
COPD	22 (8)	14 (6)	11 (13)	5 (10)
Prior SAH	32 (12)	59 (23)	20 (24)	19 (38)
Prior use of APT	71 (27)	57 (24)	24 (29)	17 (34)
Prior use of anticoagulation	7 (3)	9 (4)	5 (6)	3 (6)
Symptomatic aneurysm	38 (14)	3 (4)	31 (13)	2 (4)
Aneurysm multiplicity	72 (27)	20 (24)	97 (40)	33 (66)
Familial history of SAH[c]	36 (14)	39 (16)	12 (14)	7 (14)
Aneurysm characteristics				
Size of aneurysms (in mm; median (IQR))	8.5 (6.6-11.2)	8.0 (6.5-10.4)	8.0 (5.8-9.7)	6.0 (4.8-8.0)
< 3.0	1 (0.4)	2 (0.8)	0	5 (10)
3.0-4.9	23 (9)	27 (11)	13 (15)	10 (20)
5.0-6.9	53 (20)	54 (22)	22 (26)	17 (34)
7.0-9.9	87 (33)	91 (37)	31 (37)	9 (18)
10.0-14.9	73 (28)	53 (22)	15 (18)	8 (16)
15-19.9	19 (7)	9 (4)	1 (1)	1 (2)
≥ 20.0	8 (3)	7 (3)	2 (2)	0
Neck size of aneurysms (in mm; median (IQR))	4.2 (3.2-5.9)	4.2 (3.3-5.5)	3.9 (2.6-5.2)	3.9 (2.7-5.0)
<2.5	22 (8)	16 (7)	19 (23)	8 (16)
2.5-4.9	148 (56)	142 (58)	40 (48)	28 (56)
5.0-7.4	67 (25)	69 (28)	23 (27)	12 (24)
≥ 7.5	27 (10)	16 (7)	2 (2)	2 (4)
Parent vessel (in mm; median (IQR))	2.6 (2.2-3.3)	2.8 (2.3-3.3)	2.2 (1.8-2.9)	2.2 (2.0-2.5)
< 2.0	34 (13)	18 (7)	27 (32)	12 (24)
2.0-2.9	128 (48)	118 (49)	37 (44)	33 (66)
≥ 3.0	102 (39)	107 (44)	20 (24)	5 (10)

Centre 5 n (%)	Centre 6 n (%)	Centre 7 n (%)	Centre 8 n (%)	Centre 9 n (%)	Centre 10 n (%)
179	82	241	28	65	46
148 (83)	60 (73)	138 (57)	21 (75)	50 (77)	29 (63)
54.3; 10.9	55.0; 10.6	55.1; 10.9	56.0;11.4	56.6; 11.3	57.9; 9.5
34 (19)	16 (19.5)	40 (17)	4 (14)	10 (15)	5 (11)
84 (47)	42 (51)	105 (44)	11 (39)	29 (45)	16 (35)
48 (27)	16 (19.5)	83 (34)	11 (39)	15 (23)	22 (48)
13 (7)	8 (10)	13 (5)	2 (7)	11 (17)	3 (7)
68 (38)	32 (39)	97 (40)	2 (7)	7 (11)	14 (30)
32 (18)	1 (1)	43 (18)	4 (14)	8 (12)	1 (2)
89 (50)	50 (61)	140 (58)	11 (39)	31 (48)	22 (48)
41 (23)	10 (12)	94 (39)	4 (14)	19 (29)	6 (13)
13 (7)	6 (7)	23 (10)	1 (4)	9 (14)	7 (15)
5 (3)	10 (12)	4 (2)	1 (4)	3 (5)	0
28 (16)	16 (19)	32 (13)	3 (11)	6 (9)	3 (6)
11 (6)	11 (13)	33 (14)	5 (18)	11 (17)	10 (22)
5 (3)	4 (5)	4 (2)	0	0	0
12 (7)	20 (24)	6 (3)	2 (7)	4 (6)	9 (19)
31 (17)	18 (22)	59 (25)	6 (21)	14 (21)	9 (19)
2 (1)	5 (6)	10 (4)	0	1 (2)	1 (2)
19 (11)	7 (9)	7 (3)	6 (21)	8 (12)	11 (23)
65 (36)	38 (46)	92 (38)	5 (18)	21 (32)	18 (38)
46 (26)	7 (9)	65 (27)	0	1 (2)	0
7.6 (5.6-9.9)	6.6 (4.4-8.7)	6.2 (4.7-8.7)	9.4 (7.0-17.6)	4.3 (3.4-7.8)	5.5 (4.0-8.4)
2 (1)	5 (6)	7 (3)	1 (4)	10 (15)	2 (4)
27 (15)	22 (27)	63 (26)	1 (4)	30 (46)	16 (35)
45 (25)	15 (18)	74 (31)	3 (11)	5 (8)	11 (24)
61 (34)	22 (27)	57 (24)	11 (39)	17 (26)	8 (17)
39 (22)	11 (13)	28 (12)	3 (11)	3 (5)	4 (9)
4 (2)	6 (7)	7 (3)	4 (14)	0	2 (4)
1 (0.6)	1 (1)	5 (2)	5 (18)	0	2 (4)
4.3 (3.2-5.4)	2.8 (2.5-3.7)	4.0 (3.0-5.0)	5.5 (4.4-7.6)	3.0 (2.5-4.2)	3.8 (3.0-5.0)
18 (10)	20 (24)	24 (10)	2 (7)	16 (25)	7 (15)
102 (57)	55 (67)	150 (62)	9 (32)	38 (58)	26 (57)
50 (28)	7 (9)	61 (25)	9 (32)	9 (14)	12 (26)
9 (5)	0	6 (3)	8 (29)	2 (3)	1 (2)
3.2 (2.1-4.1)	2.1 (1.8-2.4)	2.3 (2.0-2.9)	3.2 (2.9-4.0)	3.2 (2.4-3.9)	3.0 (2.3-3.3)
35 (20)	26 (32)	53 (22)	0	6 (9)	2 (4)
46 (26)	48 (59)	132 (55)	7 (25)	19 (29)	19 (41)
98 (55)	8 (9)	56 (23)	21 (75)	40 (62)	25 (54)

Patient characteristics	Centre 1 n (%)	Centre 2 n (%)	Centre 2 n (%)	Centre 4 n (%)
Ratios (median (IQR))				
Aspect ratio	1.9 (1.4-2.6)	1.7 (1.3-2.2)	1.8 (1.4-2.5)	1.2 (1.0-1.6)
Dome-to-neck ratio	1.7 (1.3-2.2)	1.6 (1.3-2.0)	1.6 (1.2-2.2)	1.4 (1.1-1.9)
Neck-to-parent ratio	1.6 (1.2-2.1)	1.5 (1.2-2.2)	1.6 (1.2-2.0)	1.7 (1.2-2.2)
Aneurysm location				
Anterior	207 (78)	205 (84)	74 (88)	49 (98)
ACom artery	40 (15)	30 (12)	10 (12)	9 (18)
Pericallosal artery	7 (3)	6 (2)	3 (4)	3 (6)
ICA Carotid termination	20 (8)	17 (7)	7 (8)	2 (4)
ICA PCom/Ant. choroidal	31 (12)	39 (16)	7 (8)	0
ICA Ophthalmic region	23 (9)	35 (14)	14 (17)	0
MCA	86 (33)	78 (32)	33 (40)	35 (70)
Posterior	57 (21)	38 (16)	10 (12)	1 (2)
Basilar termination	40 (15)	26 (11)	7 (8)	0
PICA/vertebral artery	9 (3)	6 (2)	2 (2)	0
Other posterior[d]	8 (3)	6 (2)	1 (1)	1 (2)
Aneurysm configuration				
Irregular aneurysm	71 (27)	21 (25)	108 (44)	8 (16)
Branching artery from neck	48 (18)	82 (34)	20 (24)	5 (10)
Treatment characteristics				
Treatment period (range)	2008-2018	2010-2018	2012-2018	2009-2017
Modality				
NST (clip)	121 (46)	49 (20)	37 (44)	50 (100)
EVT (any)	143 (54)	194 (80)	47 (56)	-
Simple coil	60 (42)	173 (89)	32 (68)	-
Advanced EVT[e]	83 (58)	21 (11)	15 (32)	-
BAC	2 (1)	2 (1)	9 (21)	-
SAC	32 (22)	16 (8)	0	-
WEB	18 (13)	0	0	-
FDS	31 (22)	3 (2)	5 (11)	-
EVT preloading with APT	96 (67)	89 (46)	22 (47)	-
≥1 aneurysm treated/session	34 (13)	14 (6)	9 (11)	11 (22)

a) Carotid disease was scored as reported by the neuroradiologist and includes all degrees of stenosis.
b) Heart disease includes ischemic heart disease and heart failure.
c) A positive family history of SAH indicates >1 affected first degree relative with a SAH or UIA.
d) Other posterior includes the following aneurysm locations: basilar termination, basilar trunk, basilar sidewall and superior cerebellar artery.
e) Advanced EVT includes BAC, WEB, FDS and SAC. The following two variables had missing values: 1) smoking: 120 patients (9%) and 2) family history of SAH: 471 patients (37%)). n=number. SD=standard deviation. IQR=interquartile range. COPD=chronic obstructive pulmonary disease. TIA=transient ischemic attack. SAH=subarachnoid haemorrhage. APT=antiplatelet therapy. ACom=anterior communicating artery. PCom=posterior communicating artery. MCA=middle cerebral artery. PICA=posterior inferior cerebellar artery. EVT=endovascular treatment. NST=neurosurgical treatment. BAC=balloon-assisted coiling. SAC=stent-assisted coiling. WEB=Woven EndoBridge Device and FDS=flow-diverting stent.

eTable 3 continued

Centre 5 n (%)	Centre 6 n (%)	Centre 7 n (%)	Centre 8 n (%)	Centre 9 n (%)	Centre 10 n (%)
1.6 (1.3-2.3)	2.1 (1.6-2.5)	1.3 (1.0-1.7)	1.9 (1.3-2.3)	1.3 (1.0-1.7)	1.4 (1.1-1.9)
1.5 (1.2-1.9)	1.9 (1.5-2.6)	1.4 (1.2-1.9)	1.6 (1.3-2.1)	1.3 (1.0-1.7)	1.3 (1.0-1.7)
1.4 (1.0-1.9)	1.4 (1.2-1.7)	1.7 (1.3-2.3)	1.8 (1.2-2.3)	1.0 (0.8-1.4)	1.3 (1.0-1.6)
137 (77)	79 (96)	223 (93)	25 (89)	61 (94)	41 (89)
24 (14)	12 (15)	43 (18)	2 (7)	1 (2)	4 (9)
1 (0.6)	1 (1)	11 (5)	1 (4)	2 (3)	0
17 (9)	4 (5)	12 (5)	0	1 (2)	2 (4)
29 (16)	9 (11)	14 (6)	0	8 (12)	10 (22)
63 (35)	4 (5)	31 (13)	22 (8)	45 (69)	13 (28)
3 (2)	49 (60)	112 (46)	0	4 (6)	12 (26)
42 (23)	3 (4)	18 (7)	3 (11)	4 (6)	5 (11)
35 (20)	0	14 (6)	1 (4)	2 (3)	3 (7)
3 (2)	1 (1)	1 (0.4)	2 (7)	2 (3)	2 (4)
4 (2)	2 (1)	3 (1)	0	0	0
38 (21)	22 (27)	91 (38)	5 (18)	12 (19)	8 (17)
22 (12)	9 (11)	34 (14)	0	4 (6)	12 (26)
2000-2015	2010-2017	2011-2017	2009-2017	2012-2017	2010-2017
-	82 (100)	162 (67)	-	5 (8)	24 (52)
179 (100)	-	79 (33)	28 (100)	60 (92)	22 (48)
88 (49)	-	14 (18)	0	0	3 (14)
91 (51)	-	65 (82)	28 (100)	60 (100)	19 (86)
61 (34	-	12 (15)	0	1 (2)	0
30 (17)	-	22 (28)	0	6 (10)	1 (5)
-	-	8 (10)	0	0	0
-	-	23 (29)	28 (100)	53 (88)	18 (82)
131 (73)	-	37 (47)	28 (100)	59 (98)	21 (96)
9 (5)	7 (9)	30 (12)	1 (4)	11 (17)	6 (11)

eTable 4. Baseline characteristics for standard coiling and advanced EVT separately

	Standard coil (n=370)	**Advanced EVT**[a] (n=382)
Patient characteristics		
Women	283 (77)	298 (78)
Age (in years; mean; SD)	55.7 (10.2)	56.8 (11.0)
<45	46 (12)	52 (14)
45-59	189 (51)	162 (42)
60-69	109 (30)	126 (33)
70+	26 (7)	42 (11)
Smoking		
Current	158 (43)	125 (33)
Previous	67 (18)	52 (14)
Comorbidity		
Hypertension	207 (56)	202 (53)
Hyperlipidaemia	111 (30)	102 (27)
Diabetes	29 (8)	38 (10)
Carotid disease[b]	8 (2)	14 (4)
Heart disease or PAD[c]	54 (15)	56 (15)
Prior TIA/ischemic stroke	57 (15)	56 (15)
COPD	18 (5)	18 (5)
Prior SAH	66 (18)	28 (7)
Prior use of APT	92 (25)	80 (21)
Prior use of anticoagulation	6 (2)	13 (3)
Symptomatic aneurysm	39 (11)	60 (16)
Aneurysm multiplicity	127 (34)	117 (31)
Family history of SAH[d]	68 (18)	43 (11)
Aneurysm characteristics		
Size of aneurysms (mm; median (IQR))	7.6 (5.7-9.7)	8.1 (5.5-11.5)
< 3.0	5 (1)	12 (3)
3.0-4.9	57 (15)	64 (17)
5.0-6.9	94 (25)	69 (18)
7.0-9.9	128 (35)	112 (29)
10.0-14.9	71 (19)	75 (20)
15.0-19.9	8 (2)	31 (8)
≥ 20.0	7 (2)	19 (5)
Neck size of aneurysms (mm; median (IQR))	3.7 (3.0-4.6)	4.7 (3.4-6.4)
<2.5	50 (14)	31 (8)
2.5-4.9	245 (66)	175 (46)
5.0-7.4	72 (19)	128 (33)
≥ 7.5	3 (1)	48 (13)
Parent vessel (mm; median (IQR))	2.8 (2.2-3.4)	3.2 (2.5-3.9)
< 2.0	48 (13)	36 (9)
2.0-2.9	165 (45)	105 (28)
≥ 3.0	157 (42)	241 (63)

eTable 4 continued

Ratios (median (IQR))		
Aspect ratio	1.9 (1.4-2.4)	1.5 (1.2-2.0)
Dome-to-neck ratio	1.7 (1.4-2.2)	1.5 (1.2-1.9)
Neck-to-parent ratio	1.3 (1.0-1.8)	1.5 (1.1-2.1)
Aneurysm location		
Anterior	300 (81)	278 (73)
ACom artery	63 (17)	30 (8)
Pericallosal artery	9 (2)	5 (1)
ICA Carotid termination	38 (10)	23 (6)
ICA PCom/Ant. Choroidal	76 (21)	38 (10)
ICA Ophthalmic region	60 (16)	170 (45)
MCA	54 (15)	12 (3)
Posterior	70 (19)	104 (27)
Basilar termination	48 (13)	80 (21)
PICA/Vertebral artery	13 (4)	9 (2)
Other posterior[e]	9 (2)	15 (4)
Aneurysm configuration		
Irregular aneurysm	137 (37)	109 (29)
Branching artery from neck	68 (18)	58 (15)
Treatment characteristics		
Treatment period (range)	2012 (2001-2018)	2012 (2000-2018)
EVT preloading with APT	165 (45)	318 (83)
≥1 aneurysm treated/session	24 (7)	23 (6)

a) Advanced EVT includes BAC, SAC, WEB and FDS. b) Carotid disease includes moderate (50-69%) and severe (70-99%) carotid stenosis or carotid occlusion. c) Heart disease includes ischemic heart disease and heart failure. d) A positive family history of SAH indicates >1 affected first degree relative with a SAH or UIA. e) Other posterior includes the following aneurysm locations: basilar termination, basilar trunk, basilar sidewall and superior cerebellar artery. The following two variables had missing values: 1) smoking (120 patients (9%)) and 2) family history of SAH (471 patients (37%)). n=number. SD=standard deviation. IQR=interquartile range. COPD=chronic obstructive pulmonary disease. TIA=transient ischemic attack. SAH=subarachnoid haemorrhage. APT=antiplatelet therapy. ACom=anterior communicating artery. PCom=posterior communicating artery. ICA=internal carotid artery. MCA=middle cerebral artery. PICA=posterior inferior cerebellar artery. EVT=endovascular treatment. NST=neurosurgical treatment. BAC=balloon-assisted coiling; SAC=stent-assisted coiling; WEB=Woven EndoBridge Device and FDS=flow-diverting stent.

eTable 5: Specification of procedural (30-day) complications from EVT

	Any EVT n (%)	Standard coil n (%)	Advanced EVT n (%)
Total patients	752	370	382
Transient neurological complication	**52 (6.9)**	**18 (4.9)**	**34 (8.9)**
Ischemic complications	37 (4.9)	13 (3.5)	24 (6.3)
Ischemic stroke	10 (1.3)	3 (0.8)	7 (1.8)
Transient ischemia (≥24 hours)	12 (1.6)	5 (1.4)	7 (1.8)
TIA	15 (2.0)	5 (1.4)	10 (2.6)
Haemorrhagic complications	0	0	0
Other complications	15 (2.0)	5 (1.4)	8 (2.1)
Cranial nerve palsies	5 (0.7)	2 (0.5)	3 (0.8)
Delirium	2 (0.3)	1 (0.3)	1 (0.3)
Deficit not-otherwise-specified[a]	8 (1.1)	2 (0.5)	4 (1.0)
Persisting neurological complication	**63 (8.4)**	**12 (3.2)**	**51 (13.4)**
Ischemic complications	49 (6.5)	11 (3.0)	48 (12.6)
Ischemic stroke	43 (5.7)	11 (3.0)	32 (8.4)
Ocular ischemic syndromes[b]	3 (0.4)	0	3 (0.8)
Unspecified stroke[c]	3 (0.4)	0	3 (0.8)
Haemorrhagic complications	5 (0.7)	0	5 (1.3)
Subarachnoid haemorrhage	4 (0.5)	0	4 (1.0)
Intraparenchymal haemorrhage	1 (0.1)	1 (0.3)	1 (0.3)
Other complications	9 (1.2)	0	9 (2.4)
Cranial nerve palsies	5 (0.7)	0	5 (1.3)
Deficit not-otherwise-specified[a]	4 (0.5)	0	4 (1.0)
Fatal complication	**5 (0.7)**	**1 (0.3)**	**4 (1.0)**
Neurological			
Subarachnoid haemorrhage	4 (0.5)	1 (0.3)	3 (0.8)
Non-neurological			
Retroperitoneal haemorrhage (shock)	1 (0.1)	0 (0.0)	1 (0.3)

a) Unspecified or rare neurological complications resulting in clinical deterioration (e.g., cortical blindness due to contrast reaction). b) Visual deficit caused by retinal artery occlusion or an anterior ischemic optic neuropathy. c) Focal neurological deficit lasting ≥24 hours without imaging confirmation. TIA=transient ischemic stroke.

eTable 6: Specification of procedural (30-day) complications from NST

	n (%)
Total patients	530
Transient neurological complication	**42 (7.9)**
Ischemic complications	16 (3.0)
Ischemic stroke	4 (0.8)
Transient ischemia (>24 hours)	7 (1.3)
TIA	5 (0.9)
Haemorrhagic complications	5 (0.9)
Subdural haemorrhage	2 (0.4)
Epidural haemorrhage	3 (0.6)
Other complications	21 (4.0)
Cranial nerve palsies	1 (0.2)
Meningitis	3 (0.6)
Delirium	7 (1.3)
Deficit not-otherwise-specified[a]	10 (1.9)
Persisting neurological complication	**77 (14.5)**
Ischemic complications	59 (11.1)
Ischemic stroke	50 (9.4)
Ocular ischemic syndromes[b]	3 (0.6)
Unspecified stroke[c]	6 (1.1)
Haemorrhagic complications	8 (1.5)
Intraparenchymal haemorrhage	7 (1.3)
Subdural haemorrhage	1 (0.2)
Other complications	10 (0.2)
Cranial nerve palsies	9 (1.7)
Deficit not-otherwise-specified[a]	1 (0.2)
Fatal complication	**1 (0.2)**
Neurological	
Subarachnoid haemorrhage	1 (0.2)

a) Unspecified or rare neurological complications resulting in clinical deterioration (e.g., cortical blindness due to contrast reaction). b) Visual deficit caused by retinal artery occlusion or an anterior ischemic optic neuropathy. c) Focal neurological deficit lasting ≥24 hours without imaging confirmation. TIA=transient ischemic stroke.

eTable 7: Baseline characteristics stratified for familial and non-familial UIA patients

	No family history of SAH n (%)	Family history of SAH[a] n (%)
Patient characteristics		
Total patients	1068	214
Women	758 (71)	166 (78)
Age (in years; mean; SD)	56.3; 10.2	53.3; 11.0
<45	134 (13)	44 (21)
45-59	502 (47)	103 (48)
60-69	343 (32)	57 (27)
70+	89 (8)	10 (5)
Smoking		
Current	415 (39)	93 (44)
Previous	151 (14)	37 (17)
Comorbidity		
Hypertension	603 (57)	120 (56)
Hyperlipidaemia	315 (30)	59 (28)
Diabetes	92 (9)	11 (5)
Carotid disease[b]	48 (5)	9 (4)
Heart disease or PAD[c]	170 (16)	23 (11)
Prior TIA/ischemic stroke	173 (16)	16 (8)
COPD	55 (5)	10 (5)
Prior SAH	163 (15)	20 (9)
Prior use of APT	269 (25)	38 (18)
Prior use of anticoagulation	40 (4)	3 (1)
Symptomatic aneurysm	122 (11)	8 (4)
Aneurysm multiplicity	374 (35)	87 (41)
Aneurysm characteristics		
Size of aneurysms (mm; median (IQR))	7.7 (5.6-10.1)	6.1 (4.4-8.3)
< 3.0	31 (3)	4 (2)
3.0-4.9	167 (16)	65 (30)
5.0-6.9	238 (22)	62 (29)
7.0-9.9	344 (32)	50 (23)
10.0-14.9	207 (19)	30 (14)
15-19.9	50 (5)	3 (1)
≥ 20.0	31 (3)	0
Neck size of aneurysms (mm; median (IQR))	4.1 (3.0-5.4)	3.9 (2.9-4.5)
<2.5	123 (12)	29 (14)
2.5-4.9	595 (56)	143 (67)
5.0-7.4	285 (27)	34 (16)
≥ 7.5	65 (6)	8 (4)
Parent vessel (mm; median (IQR))	2.6 (2.1-3.3)	2.5 (2.1-3.2)
< 2.0	203 (19)	41 (19)
2.0-2.9	469 (44)	105 (49)
≥ 3.0	396 (37)	68 (32)

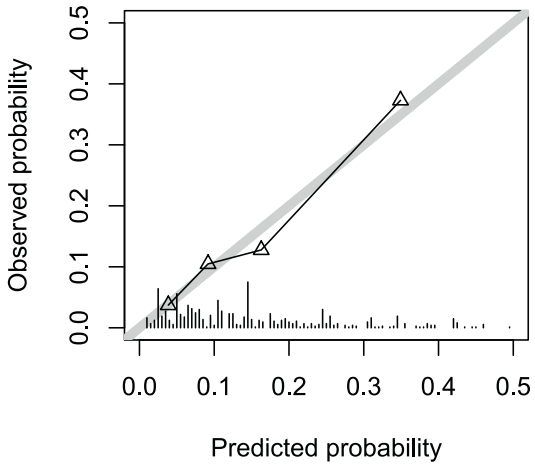
eTable 7 continued

Ratios (median (IQR))		
Aspect ratio	1.7 (1.2-2.3)	1.6 (1.1-1.9)
Dome-to-neck ratio	1.6 (1.3-2.1)	1.6 (1.2-1.8)
Neck-to-parent ratio	1.5 (1.1-2.1)	1.6 (1.0-2.0)
Aneurysm location		
Anterior	907 (85)	194 (91)
ACom artery	149 (14)	27 (13)
Pericallosal artery	31 (3)	4 (2)
ICA Carotid termination	64 (6)	18 (8)
ICA PCom/Ant. choroidal	125 (12)	22 (10)
ICA Ophthalmic region	211 (20)	38 (18)
MCA	327 (31)	85 (40)
Posterior	161 (15)	20 (9)
Basilar termination	111 (10)	17 (8)
PICA/vertebral artery	27 (3)	2 (1)
Other posterior[d]	23 (2)	1 (0.5)
Aneurysm configuration		
Irregular aneurysm	155 (15)	36 (17)
Branching artery from neck	197 (18)	39 (18)
Treatment characteristics		
Treatment period (range)	2000-2018	2000-2018
Modality		
NST (clip)	427 (40)	103 (48)
EVT (any)	641 (60)	111 (52)
Standard coil	302 (28)	68 (32)
Advanced EVT[e]	339 (32)	43 (20)
BAC	66 (6)	20 (9)
SAC	155 (15)	6 (3)
WEB	95 (9)	14 (7)
FDS	23 (2)	3 (1)
EVT preloading with APT	447 (42)	66 (31)
≥1 aneurysm treated/session	105 (10)	26 (12)

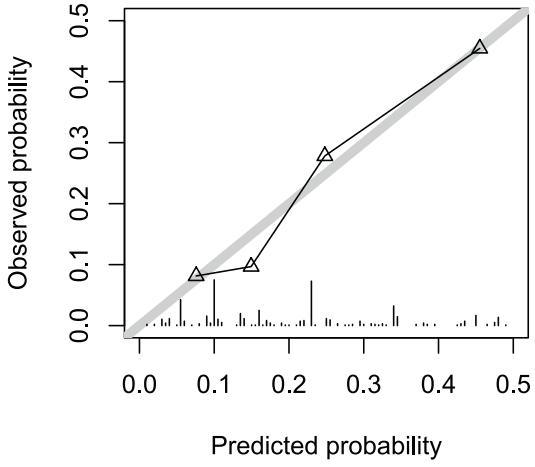
a) A positive family history of SAH indicates >1 affected first degree relative with a SAH or UIA. b) Heart disease includes ischemic heart disease and heart failure. c) Carotid disease was scored as reported by the neuroradiologist and includes all degrees of stenosis. d) Other posterior includes the following aneurysm locations: basilar termination, basilar trunk, basilar sidewall and superior cerebellar artery. e) Advanced EVT includes BAC, WEB, FDS and SAC. Missing values for family history of SAH (471 patients (37%)) were assumed as having a negative family history. Smoking also had missing values: 120 patients (9%). n=number. SD=standard deviation. IQR=interquartile range. COPD=chronic obstructive pulmonary disease. TIA=transient ischemic attack. SAH=subarachnoid haemorrhage. APT=antiplatelet therapy. ACom anterior communicating artery. PCom=posterior communicating artery. MCA=middle cerebral artery. PICA=posterior inferior cerebellar artery. EVT=endovascular treatment. NST=neurosurgical treatment. BAC=balloon-assisted coiling. WEB=Woven EndoBridge Device. FDS=flow-diverting stent. SAC=stent-assisted coiling.

eFigure 2: Calibration plots for procedural risk of EVT (**panel A**) and NST (**panel B**)

Panel A: EVT model



Panel B: NST model



Triangles depict observed and predicted procedural complication risks. The grey 45° line represents ideal agreement between predicted and observed risk.

eTable 8: Sensitivity analysis according to outcome type for the EVT modelling process

Outcome type	Dataset details	Predictors selected	Details final model
EVT SAFETEA model	Total EVT patients: 752	- Size of aneurysm - Aneurysm location	Corrected c-statistic: 0.72 (95%CI: 0.67-0.76)
Procedural death or any neurological complication	Total complications: 120	- Familial SAH - Earlier atherosclerotic disease - Treatment volume	Range absolute risk of complications: 1-67%
Alternative outcome 1	Total EVT patients: 752	- EVT modality - Age	Corrected c-statistic: 0.74 (95%CI: 0.68-0.80)
Procedural death or persisting neurological complications	Total complications: 67	- Size of aneurysm - Aneurysm location - Earlier atherosclerotic disease	Range absolute risk of complications: 1-65%
Alternative outcome 2	Total EVT patients: 752	- Treatment volume - EVT modality	Corrected c-statistic: 0.70 (95%CI: 0.65-0.76)
Any ischemic or haemorrhagic neurological complication	Total complications: 93	- Anticoagulation - Aneurysm location - Familial SAH	Range absolute risk of complications: 1-57%
Alternative outcome 3	Total EVT patients: 752	- EVT modality - Treatment volume - Age	Corrected c-statistic: 0.69 (95%CI: 0.63-0.75)
Any ischemic neurological complication	Total complications: 83	- Anticoagulation - Aneurysm location - Familial SAH	Range absolute risk of complications: 1-45%
		- EVT modality - Treatment volume - Age - Aneurysm neck size	

EVT=endovascular treatment. SAH=subarachnoid haemorrhage. CI=confidence interval.

eTable 9: Internal-external validation for the EVT modelling process

Centre excluded	Details dataset without excluded centre	Predictors selected	Details final model
Centre 1	EVT patients excluded: 143 Total EVT patients: 609 Total complications: 99	- Size of aneurysm - Aneurysm location - Earlier atherosclerotic disease - Treatment volume - Age	Corrected c-statistic: 0.69 (95%CI: 0.63-0.75) Range absolute risk of complications: 1-59%
Centre 2	EVT patients excluded: 194 Total EVT patients: 558 Total complications: 99	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier atherosclerotic disease - Treatment volume - EVT modality	Corrected c-statistic: 0.71 (95%CI: 0.65-0.76) Range absolute risk of complications: 2-69%
Centre 3	EVT patients excluded: 47 Total EVT patients: 705 Total complications: 116	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier atherosclerotic disease - Treatment volume - EVT modality - Age	Corrected c-statistic: 0.72 (95%CI: 0.66-0.76) Range absolute risk of complications: 1-70%
Centre 4	No EVT patients	-	-
Centre 5	EVT patients excluded: 79 Total EVT patients: 673 Total complications: 100	- Size of aneurysm - Aneurysm location - Familial SAH - Treatment volume - EVT modality - Age	Corrected c-statistic: 0.72 (95%CI: 0.67-0.77) Range absolute risk of complications: 1-90%
Centre 6	No EVT patients	-	-
Centre 7	EVT patients excluded: 179 Total EVT patients: 573 Total complications: 94	- Aneurysm location - Familial SAH - Earlier atherosclerotic disease - Treatment volume - EVT modality - Age	Corrected c-statistic: 0.74 (95%CI: 0.68-0.79) Range absolute risk of complications: 1-66%
Centre 8	EVT patients excluded: 28 Total EVT patients: 724 Total complications: 115	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier atherosclerotic disease - Treatment volume - EVT modality - Age	Corrected c-statistic: 0.72 (95%CI: 0.67-0.77) Range absolute risk of complications: 1-71%
Centre 9	EVT patients excluded: 60 Total EVT patients: 730 Total complications: 113	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier atherosclerotic disease - EVT modality - Age	Corrected c-statistic: 0.74 (95%CI: 0.69-0.79) Range absolute risk of complications: 1-74%
Centre 10	EVT patients excluded: 22 Total EVT patients 730 Total complications: 115	- Aneurysm location - Familial SAH - Earlier atherosclerotic disease - Treatment volume - EVT modality - Age - Anticoagulation	Corrected c-statistic: 0.71 (95%CI: 0.65-0.75) Range absolute risk of complications: 1-71%

EVT=endovascular treatment. SAH=subarachnoid haemorrhage. CI=confidence interval.

eTable 10: Beta coefficients from the final EVT regression model

Predictor	Beta coefficient
Intercept	-3.7166
Size of aneurysm	
<10 mm	Reference
10-14.9 mm	0.2719
≥15 mm	0.6832
Aneurysm location	
ACom artery	Reference
Other	-0.7362
MCA	0.2027
ICA Ophthalmic region	0.1001
Basilar termination	0.2355
Familial SAH	
Yes	Reference
No	0.5233
Earlier atherosclerotic disease	
No	Reference
Yes	0.6008
Treatment volume	
≥10 cases/year	Reference
<10 cases/year	0.5448
EVT modality	
Coil	Reference
Balloon-assisted coil	0.3441
WEB-device	0.2383
Flow-diverting stent	0.6799
Stent-assisted coil	0.9673
Age	
<45 year	Reference
≥45 year	0.6970

EVT=endovascular treatment. ACom=anterior communicating. MCA=middle cerebral artery. ICA=internal cerebral artery. SAH=subarachnoid haemorrhage. WEB=Woven EndoBridge.

We used the beta coefficients from our final logistic regression model to calculate a linear function (A).

Linear function

A = -3.7166 (intercept) + 0.2719 (if size 10-14.9 mm) + 0.6832 (if size ≥15 mm) – 0.7362 (if aneurysm location is not ACom, MCA, ICA ophthalmic region or basilar termination) + 0.2027 (if aneurysm location is MCA) + 0.1001 (if aneurysm location is ICA ophthalmic region) + 0.2355 (if aneurysm location is basilar termination) + 0.5233 (if there is no family history of SAH) + 0.6008 (if there is a history of CVD) + 0.5448 (if <10 cases/year are treated at the centre) + 0.3441 (in case of balloon-assisted coiling) + 0.2383 (in case of treatment with a WEB-device) + 0.6799 (in case of treatment with a flow-diverting stent) + 0.9673 (in case of stent-assisted coiling) + 0.6970 (if age ≥45 year)

Example how to use this formula

Consider a 60-year-old patient, no previous cardiovascular disease, no family history of SAH, with an unruptured intracranial aneurysm of the basilar termination of 12 mm. A WEB-device is considered because there is experience with this EVT modality (≥10 cases/year) at the treating centre.

A = -3.7166 (intercept) + 0.6970 (age ≥45 year) + 0.5233 (absence of familial SAH) + 0.2355 (basilar termination) + 0.2719 (size 12 mm) + 0.2383 (WEB-device) = -1.7506

Predicted complication risk = exp(-1.7506)/(1-exp(-1.7506)) = 0.1737/0.8263 = 0.2102 = 21.0%

eTable 11: Sensitivity analysis according to outcome type for the NST modelling process

Outcome type	Dataset details	Predictors selected	Details final model
EVT SAFETEA model Procedural death or any neurological complication	Total EVT patients: 530 Total complications: 120	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier carotid disease - Treatment volume - Extra configuration factors - Age	Corrected c-statistic: 0.72 (95%CI: 0.67-0.77) Range absolute risk of complications: 1-81%
Alternative outcome 1 Procedural death or long-lasting neurological complications	Total EVT patients: 530 Total complications: 78	- Size of aneurysm - Aneurysm location - Earlier carotid disease - Treatment volume - Extra configuration factors - Clip: EVT ratio per centre	Corrected c-statistic: 0.72 (95%CI: 0.66-0.77) Range absolute risk of complications: 4-86%
Alternative outcome 2 Any ischemic or haemorrhagic neurological complication	Total EVT patients: 530 Total complications: 83	- Size of aneurysm - Aneurysm location - Earlier carotid disease - Treatment volume - Extra configuration factors - Clip: EVT ratio per centre	Corrected c-statistic: 0.73 (95%CI: 0.67-0.79) Range absolute risk of complications: 2-90%
Alternative outcome 3 Any ischemic neurological complication	Total NST patients: 530 Total complications: 69	- Size of aneurysm - Aneurysm location - Earlier carotid disease - Clip: EVT ratio per centre	Corrected c-statistic: 0.73 (95%CI: 0.68-0.81) Range absolute risk of complications: 2-90%

NST=neurosurgical treatment. SAH=subarachnoid haemorrhage. CI=confidence interval.

eTable 12: Internal-external validation for the NST modelling process

Centre excluded	Details dataset without excluded centre	Predictors selected	Details final model
Centre 1	NST patients excluded: 131 Total NST patients: 409 Total complications: 99	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier carotid disease - Treatment volume - Extra configuration factors - Age	Corrected c-statistic: 0.72 (95%CI: 0.67-0.77) Range absolute risk of complications: 1-85%
Centre 2	NST patients excluded: 49 Total NST patients: 481 Total complications: 99	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier carotid disease - Treatment volume - Extra configuration factors - Age	Corrected c-statistic: 0.72 (95%CI: 0.67-0.78) Range absolute risk of complications: 1-83%
Centre 3	NST patients excluded: 37 Total NST patients: 493 Total complications: 112	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier carotid disease - Treatment volume - Extra configuration factors - Age	Corrected c-statistic: 0.73 (95%CI: 0.68-0.78) Range absolute risk of complications: 1-79%
Centre 4	NST patients excluded: 50 Total NST patients: 480 Total complications: 107	- Size of aneurysm - Aneurysm location - Familial SAH - Treatment volume - Age	Corrected c-statistic: 0.72 (95%CI: 0.67-0.78) Range absolute risk of complications: 2-84%
Centre 5	No NST patients	-	-
Centre 6	NST patients excluded: 82 Total NST patients: 448 Total complications: 94	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier carotid disease - Treatment volume - Extra configuration factors	Corrected c-statistic: 0.71 (95%CI: 0.65-0.75) Range absolute risk of complications: 2-81%
Centre 7	NST patients excluded: 162 Total NST patients: 368 Total complications: 83	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier carotid disease - Treatment volume - Extra configuration factors - Age	Corrected c-statistic: 0.70 (95%CI: 0.64-0.75) Range absolute risk of complications: 2-85%
Centre 8	No NST patients	-	-
Centre 9	NST patients excluded: 5 Total NST patients: 525 Total complications: 118	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier carotid disease - Treatment volume - Extra configuration factors - Age	Corrected c-statistic: 0.73 (95%CI: 0.67-0.77) Range absolute risk of complications: 1-80%
Centre 10	NST patients excluded: 24 Total NST patients: 506 Total complications: 111	- Size of aneurysm - Aneurysm location - Familial SAH - Earlier carotid disease - Treatment volume - Extra configuration factors - Age	Corrected c-statistic: 0.72 (95%CI: 0.67-0.77) Range absolute risk of complications: 2-81%

EVT=endovascular treatment. SAH=subarachnoid haemorrhage. CI=confidence interval.

eTable 13: Beta coefficients from the final NST regression model

Predictor	Beta coefficient
Intercept	-3.1339
Size of aneurysm	
<10 mm	Reference
10-14.9 mm	0.4970
≥15 mm	1.0167
Aneurysm location	
MCA	Reference
Other	-0.8050
ICA PCom / Ant. choroidal region	0.1045
Carotid termination	0.6766
ACom artery	0.8738
Familial SAH	
Yes	Reference
No	0.5281
Earlier carotid disease	
No	Reference
Yes	0.8140
Treatment volume	
≥10 cases/year	Reference
<10 cases/year	0.8779
Extra configuration factors	
Branch artery from neck or DNR >2.5	
No (ref.)	Reference
Yes	0.4740
Age	
<45 year	Reference
≥45 year	0.5545

NST=neurosurgical treatment. MCA=middle cerebral artery. ICA=internal cerebral artery. PCom=posterior communicating ACom=anterior communicating. SAH=subarachnoid haemorrhage. DNR=dome-to-neck ratio.

We used the beta coefficients from our final logistic regression model to calculate a linear function (A).

Linear function

A= -3.1339 (intercept) + 0.4970 (if size 10-14.9 mm) + 1.0167 (if size ≥15 mm) – 0.8050 (if aneurysm location is not MCA, ICA PCom or anterior choroidal region, carotid termination or ACom) + 0.1045 (if aneurysm location is ICA PCom or anterior choroidal region) + 0.6766 (if aneurysm location is carotid termination) + 0.8738 (if aneurysm location is ACom) + 0.5281 (if there is no family history of SAH) + 0.8140 (if carotid disease is present) + 0.8779 (if <10 cases/year are treated at the centre) + 0.4740 (if there is a branch artery from the aneurysm neck or if the DNR is >2.5) + 0.5545 (if age ≥45 year)

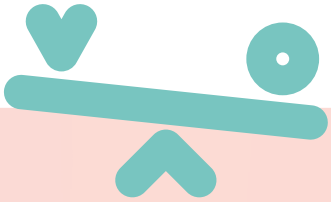
Example how to use this formula

Consider a 39-year-old patient, no carotid disease, no family history of SAH, with an unruptured intracranial aneurysm of the carotid termination of 9 mm, with no branch artery from the aneurysm neck and a dome-neck-ratio <2.5. Clipping is considered because of the young age of the patient. There is experience with clipping (≥10 cases/year) at the treating centre.

A = -3.1339 (intercept) + 0.6766 (carotid termination) + 0.5281 (no family history of SAH) = -1.9292
Predicted complication risk = exp(-1.9292)/(1-exp(-1.9292)) = 0.1453/0.8547= 0.1700 = 17.0%

CHAPTER 4

Quality of life outcomes over time in patients with unruptured intracranial aneurysms with and without preventive occlusion: a prospective cohort study



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ABSTRACT

Objective

In counselling patients with an unruptured intracranial aneurysm (UIA), quality-of-life (QoL) outcomes are important for informed decision-making. We evaluated QoL outcomes in patients with and without preventive aneurysm occlusion at multiple time points during the first year after UIA diagnosis and studied predictors of QoL outcomes.

Methods

We performed a prospective cohort study in patients ≥18 years old with a newly diagnosed UIA in two tertiary referral centres in the Netherlands between 2017 and 2019. Patients were sent QoL questionnaires at 7 (aneurysm occlusion) or 5 (no occlusion) moments during the first year after diagnosis. We collected baseline data on patient and aneurysm characteristics, passive coping style (Utrecht Coping List), occlusion modality, and neurological complications. We assessed health-related QoL (HRQoL) with the EuroQol 5-dimensions (EQ-5D), emotional functioning with the Hospital Anxiety and Depression Scale (HADS), and restrictions in daily activities with the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P). We used a linear mixed effects model to assess the course of QoL over time and to explore predictors of QoL outcomes.

Results

Of 153 eligible patients, 99 (65%) participated, of whom 30/99 (30%) underwent preventive occlusion. Patients undergoing occlusion reported higher baseline levels of passive coping, anxiety and depression, and restrictions than patients without occlusion. During recovery after occlusion, patients reported more restrictions compared to baseline (adjusted USER-P decrease one-month post-occlusion: -12.8 (95%CI:-23.8- -1.9). HRQoL and emotional functioning gradually improved after occlusion (EQ-5D increase at one-year: 8.6 (95%CI:0.1-17.0) and HADS decrease at one-year: -5.4 (95%CI:-9.4- -1.5)). In patients without occlusion, the largest HRQoL improvement occurred directly after visiting the outpatient aneurysm clinic (EQ-5D increase: 9.2 (95%CI:5.5-12.8)). At one-year, QoL outcomes were comparable in patients with and without occlusion. Factors associated with worse QoL outcomes were a passive coping style in all patients, complications in patients with occlusion and higher rupture risks in patients without occlusion.

Conclusions

After UIA diagnosis, QoL improves gradually after preventive occlusion and directly after counselling at the outpatient clinic in patients without occlusion, resulting in comparable one-year QoL outcomes. A passive coping style is an important predictor of poor QoL outcomes in all UIA patients.

INTRODUCTION

In management decisions on saccular unruptured intracranial aneurysms (UIAs), important factors that must be carefully balanced are risk of aneurysm rupture, risk of treatment complications, individual quality of life (QoL) aspects, and life expectancy.[1-4] In patients with an UIA, preventive aneurysm occlusion decreases the risk of aneurysmal subarachnoid haemorrhage (SAH), thereby reducing the number of life years with high QoL lost from SAH.[1,3,4] However, preventive aneurysm repair carries a risk of serious complications and patients who undergo preventive occlusion have to invest a certain amount of time in their recovery period during which they may have a reduced QoL and restrictions in their family, social and work-life.[5,6] On the other hand, in patients without preventive occlusion, fear of aneurysm rupture can have a huge impact on QoL.[7,8] To enable patients to make informed choices about the risks and benefits of preventive occlusion, it is crucial to integrate QoL outcomes during counseling.[2,7] Previous studies have shown that a history of psychiatric disease and a passive coping style can negatively influence QoL in patients diagnosed with intracranial disease.[8-11] Most studies on QoL outcomes in UIA patients so far have focused on QoL in patients who did not undergo aneurysm occlusion or only report on QoL changes after occlusion, with little data available on QoL pre-occlusion, QoL changes over time, or on predictors of QoL in these patients.[12,13] Therefore, we aimed to describe QoL outcomes in UIA patients with and without preventive aneurysm occlusion at several time points during the first year after aneurysm diagnosis and to study which factors influence QoL outcomes.

METHODS

Study population

The study was conducted between January 2017 and October 2019 in two tertiary referral centres for aneurysm care in the Netherlands (University Medical Center Utrecht (UMCU) and Leiden University Medical Center (LUMC)). In both centres, standard clinical practice is to discuss UIA management options in a multidisciplinary team meeting directly after receiving the referral letter and imaging. Thereafter, the patient is invited to the outpatient aneurysm clinic for counselling with a physician experienced in aneurysm care. All adult patients ≥18 years old with a newly detected UIA were eligible for our study. We excluded patients with a medical history of SAH or previously diagnosed UIA, patients with non-saccular (fusiform or dissecting), mycotic or flow-related aneurysms, and patients who were unable to complete questionnaires due to pre-existing cognitive deficits, short life expectancy or language barriers. Eligible patients were sent a letter about the purpose of the study and were contacted by phone before or directly after their initial visit to the outpatient clinic. Informed consent was obtained from all participants. Questionnaires were sent by e-mail. If participants did not have an e-mail address, questionnaires were sent by post. The study was approved by the Institutional Research Ethics Boards of the UMCU and the LUMC.

Data collection

Patient and aneurysm characteristics

We recorded the following patient and aneurysm characteristics: age at aneurysm diagnosis, sex, medical and psychiatric history, reason of aneurysm detection, aneurysm multiplicity, size and location of the aneurysm, and rupture risk according to the PHASES score.[14] PHASES predicts the absolute 5-year risk of aneurysm rupture based on six patient- and aneurysm characteristics: Population, Hypertension, Age, Size of aneurysm, Earlier SAH from another aneurysm, and Site of site of aneurysm. Scores range from 0 to 22 points, with associated risks ranging from 0.4% to 17.8%.[14] In case of preventive occlusion, we also collected data on occlusion modality, in-hospital neurological complications, length of hospital stay and discharge location. Patients were classified as having a psychiatric history if they were under psychological or psychiatric treatment or if the medical record reported the use of medication for depression, an anxiety disorder, or other psychiatric disorders. We assessed coping style at baseline with a subscale of the Utrecht Coping List (UCL-P).[15] The UCL-P consists of 7 items which can be scored on a 4-point scale ranging from 1 (seldom) to 4 (very often), resulting in a sumscore between 7 (low) and 28 (high level of passive coping). High levels are considered unfavourable. We classified reason of aneurysm detection as incidental, symptomatic (symptoms of mass effect such as cranial nerve palsies, seizures, or ischemic event likely to

be related to the aneurysm), or screening (familial or polycystic kidney disease). Occlusion modality was categorized into endovascular treatment (EVT, including coiling, balloon-assisted coiling, stent-assisted coiling, use of Woven-EndoBridge (WEB)-device or use of flow-diverting stent) or neurosurgical treatment (NST; clipping only). We recorded all in-hospital neurological complications resulting in clinical deterioration or death. Complications were scored as transient if clinical symptoms resolved within 30 days and were otherwise classified as persisting.

QoL outcomes

Questionnaires were sent out at referral, after counselling at the outpatient clinic, and at three and six months and one-year follow-up (eFigure 1). Patients who underwent preventive occlusion received additional questionnaires two and four weeks after treatment. We assessed QoL with three measures: health-related QoL (HRQoL), emotional functioning (levels of anxiety and depression), and restrictions in daily activities. HRQoL was measured with the EuroQol EQ-5D (EQ-5D) questionnaire, emotional functioning with the Hospital Anxiety and Depression Scale (HADS) and restrictions in daily activities with the Utrecht Scale for Evaluation of Rehabilitation – Participation (USER-P).[16-18] The EQ-5D evaluates whether mild, moderate, or severe problems exist in one of the following domains: mobility, usual activities, pain or discomfort, self-care and anxiety or depression. Taken together, the scores from all domains provide a descriptive EQ-5D health state that can be converted into a single overall HRQoL score ranging from 0 (worst) to 100 (best health). In addition, patients are asked to value their own HRQoL on a visual-analog scale (EQ-VAS), also ranging from 0 (worst) to 100 (best imaginable health).[16] The HADS is a 14-item questionnaire, with scores ranging between 0 (low levels) and 42 (high levels of anxiety and depression).[17] The USER-P assesses participation in 11 activities, including vocational activities (work, study and housekeeping), transport, leisure, and social activities. All items are scored between 0 (not possible at all) and 3 (no difficulty at all), or as not applicable. Sum scores can be converted to one overall score ranging from 0 (unfavourable) to 100 (favourable participation).[18]

Statistical analysis

At baseline, we calculated median PHASES scores with interquartile ranges (IQR) and mean UCL passive reaction patterns with standard deviations (SD) for patients with and without aneurysm occlusion. The cohorts were compared using x^2 or Student's t test as appropriate. For patients with aneurysm occlusion, we also reported the rate of in-hospital neurological complications. Based on the distribution of data, we calculated mean EQ-5D sumscores, EQ-VAS scores, HADS sumscores and USER-P sumscores at baseline and during follow-up. We also calculated the proportion of patients with restrictions (scores ≤1) per individual USER-P activity at baseline and one-year follow-up. We used a linear mixed effects (LME) model with

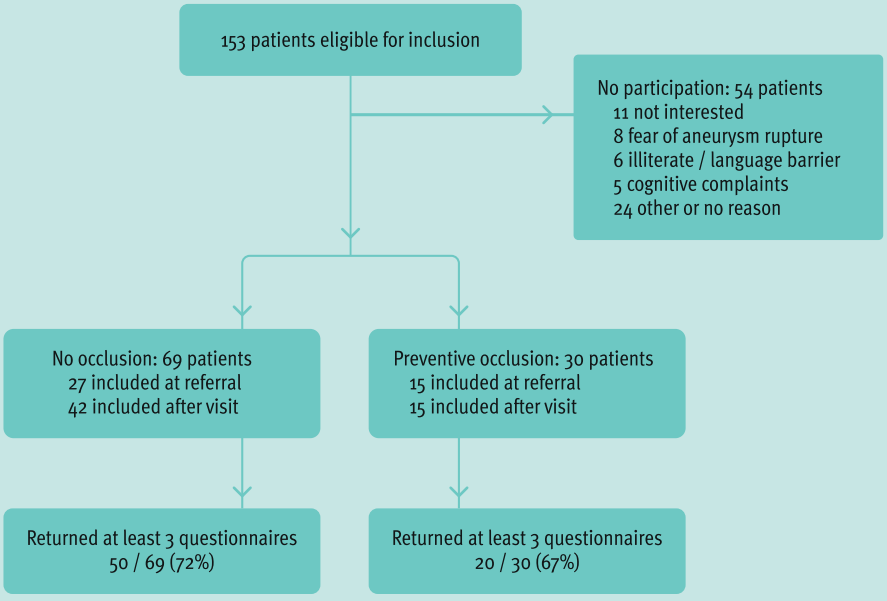
random intercept, random slope, and fixed time effects to assess the course of the EQ-5D, HADS and USER-P sumscores over time in the cohorts with and without aneurysm occlusion and to explore predictors of QoL outcomes. We reported changes as mean differences with corresponding 95% confidence intervals (CI).

RESULTS

Participants

In total, 153 patients who were referred with a newly diagnosed UIA met the inclusion criteria, of whom 99 (65%) participated (Figure 1). The most common reasons to decline participation were no interest (11 patients; 26%) and fear of aneurysm rupture (8 patients; 19%). Forty-two of the participants (42%) were included before their initial visit to the outpatient clinic and 57 participants (58%) directly after their initial clinic visit. During the study, 364/555 (66%) questionnaires were returned, of which 341 (94%) were complete. Three-quarters of the patients (70/99; 71%) returned at least 3 questionnaires. Return rates were comparable among patients with and without preventive aneurysm occlusion (Figure 1), but slightly lower among patients with treatment complications (4/7; 57%).

Figure 1. Flowchart of eligible patients and number of questionnaires sent out and returned



Patient and aneurysm characteristics at baseline

Table 1 shows the baseline characteristics of the participating patients. Of the 99 participants, 30 underwent preventive aneurysm occlusion (11 (38%) underwent NST and 18 (62%) EVT). Patients with and without aneurysm occlusion did not differ in terms of sex or medical history, but patients with occlusion were younger than patients without occlusion (mean: 57 (SD 11) vs. 63 year (SD 9); p<0.01) and had higher mean sumscores for passive coping style (occluded: median: 5/28 points (IQR 3-8) vs. non-occluded: 3/28 (IQR 1-5); p=0.03). In addition, when compared to patients without occlusion, the aneurysms of patients with occlusion were more often symptomatic (5/30 (17%) vs. 1/69 (1%); p<0.01), larger (9 mm (IQR 6-12) vs. 5 mm (IQR 4-7); p<0.01), located in the posterior circulation (9/30 (30%) vs. 9/69 (10%); p<0.01) and they had a higher 5-year rupture risk (median PHASES score: 8 points (IQR 6-9) vs. 4 (IQR 3-5); p<0.01; Table 1). One patient was scheduled for EVT but did not undergo aneurysm occlusion because of difficulties with the intubation procedure. This patient only returned the questionnaires before treatment. Therefore, we left this patient in the preventive occlusion group for analyses of this time point. There were no crossovers in the non-occlusion group. Of the patients who underwent preventive occlusion, 4 patients (14%) had a transient neurological complication and 3 patients (10%) a persisting neurological complication. None of the UIA patients had a SAH during follow-up.

Table 1. Baseline characteristics for included patients

	Aneurysm occlusion	No aneurysm occlusion	p-value
Patient characteristics	**n=30**	**n=69**	
Women, n (%)	19 (63)	49 (71)	0.45
Mean age at diagnosis (SD)	57 (11)	63 (9)	0.01
Medical history, n (%)			
No comorbidity	3 (10)	5 (7)	0.64
TIA or stroke	6 (20)	16 (23)	0.73
Malignancy	1 (3)	7 (10)	0.25
Psychiatric history[a]	4 (13)	5 (7)	0.33
Passive coping style			
Median UCL-P score (IQR)[b]	5 (3-8)	3 (1-5)	0.01
Aneurysm characteristics[c]	**n=30**	**n=89**	
Aneurysm presentation, n (%)			
Incidental	24 (80)	63 (91)	0.05
Symptomatic	5 (17)	1 (1)	<0.01
Familial screening	1 (3)	5 (7)	0.92
Patients with ≥2 aneurysms, n (%)	3 (10)d	13 (19)	0.27
Median size of aneurysms in mm (IQR)	9 (6-12)	5 (4-7)	<0.01
Aneurysm location, n (%)			
Anterior cerebral arteries	9 (30)	17 (19)	0.61
Internal carotid artery	6 (20)	28 (31)	0.23
Posterior communicating artery	2 (7)	6 (7)	0.73
Other internal carotid artery	4 (13)	22 (25)	0.26
Middle cerebral artery	6 (20)	35 (39)	0.08

Table 1 continued

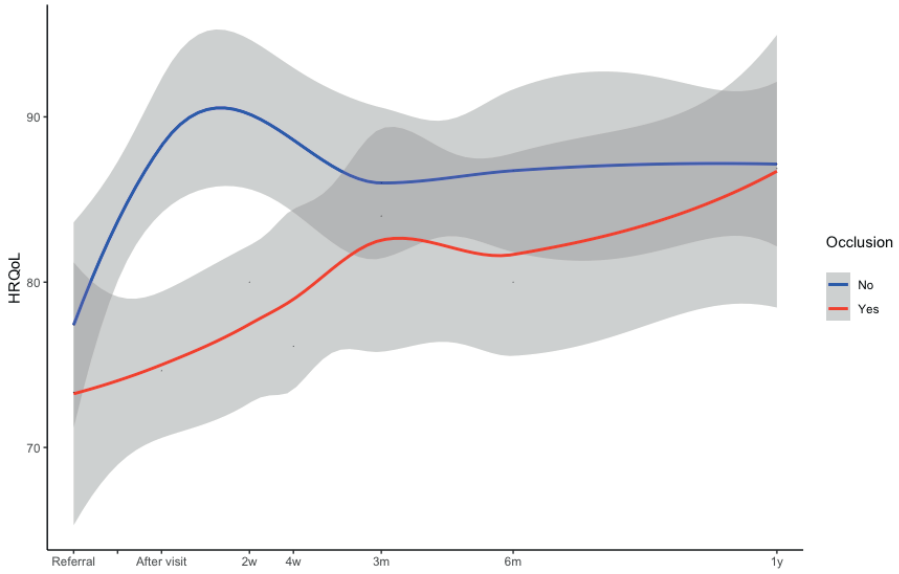
Posterior circulation	9 (30)	9 (10)	<0.01
Median PHASES score (IQR)[e]	8 (6-9)	4 (3-5)	<0.01
Treatment characteristics	**n=29**[a]	-	
Aneurysm occlusion modality, n (%)		-	-
NST	11 (38)		
EVT (any)	18 (62)		
Standard coil	6 (21)		
Advanced EVT[f]	12 (41)		
In-hospital neurological complication, n (%)	7 (24)	-	-
Transient complication[g]	4 (14)		
Persisting complication	3 (10)		
Aneurysms occluded, n (%)	28 (97)	-	-
Days of hospitalization (range)	2 (2-10)	-	-
Transfer location, n (%)		-	-
Home	26 (90)		
Rehabilitation	3 (10)		

a) Patients were classified as having a psychiatric history if they were under psychological or psychiatric treatment or if the medical record reported the use of medication for depression, an anxiety disorder or other psychiatric disorders. b) Passive coping style was assessed at baseline with a subscale of the UCL-P. Sumscores range from 7 (low) to 28 points (high level of passive coping). c) One patient was scheduled for EVT but did not undergo occlusion because of difficulties with the intubation procedure; d) Three patients in the aneurysm occlusion cohort had an additional aneurysm that was followed-up. e) The PHASES risk score assesses the absolute 5-year rupture rate. f) Advanced EVT includes balloon-assisted coiling, stent-assisted coiling, the use of Woven-EndoBridge (WEB)-devices or the use of flow-diverting stents. g) Complications were scored as transient if clinical symptoms resolved within 30 days, and otherwise were considered persisting. conservatively. SD=standard deviation; IQR=interquartile range; UCL-P=Utrecht Coping List–Passive; EVT=endovascular treatment; TIA=transient ischemic attack.

QoL outcomes at baseline

At baseline, HRQoL values were comparable for patients with (mean EQ-5D: 73.3; SD: 16.8) and without (77.4; SD: 17.7) preventive occlusion, as were EQ-VAS scores for both cohorts (Figure 2 and eTable 1) and HRQoL values according to treatment modality (eTable 3 and eFigure 2). In patients with aneurysm occlusion, baseline HADS sumscores were higher (mean: 15.7; SD: 7) than in patients without occlusion (9.4; SD: 6.8; Figure 3 and eTable 1). This was most pronounced among patients undergoing EVT (mean HADS: 19.4; SD: 9; eTable 3 and eFigure 3). USER-P sumscores were comparable for the cohort with aneurysm occlusion (mean USER-P sumscore 78.4; SD: 15.6) and that without (86.5; SD: 15.5) (Figure 4 and eTable 1). Patients with aneurysm occlusion reported more restrictions at baseline than those with no aneurysm occlusion in the subdomains working life (9/12 (75%) *vs.* 4/13 (31%); risk difference: 44%; 95%CI: 5%-69%), going out (9/14 (64%) *vs.* 7/23 (30%); risk difference: 34%; 95%CI: 12%-58%) and activities outside home (11/14 (79%) *vs.* 10/24 (42%); risk difference: 37%; 95%CI: 4%-59%; Figure 5 and eTable 2).

Figure 2. HRQoL of UIA patients with and without preventive aneurysm occlusion over time



The graph illustrates the mean EQ-5D sumscores over time. The grey areas around the lines represent 95% confidence intervals. HRQoL=health-related quality of life. w=week. m=month. y=year.

Figure 3. Levels of anxiety and depression of UIA patients with and without preventive aneurysm occlusion over time

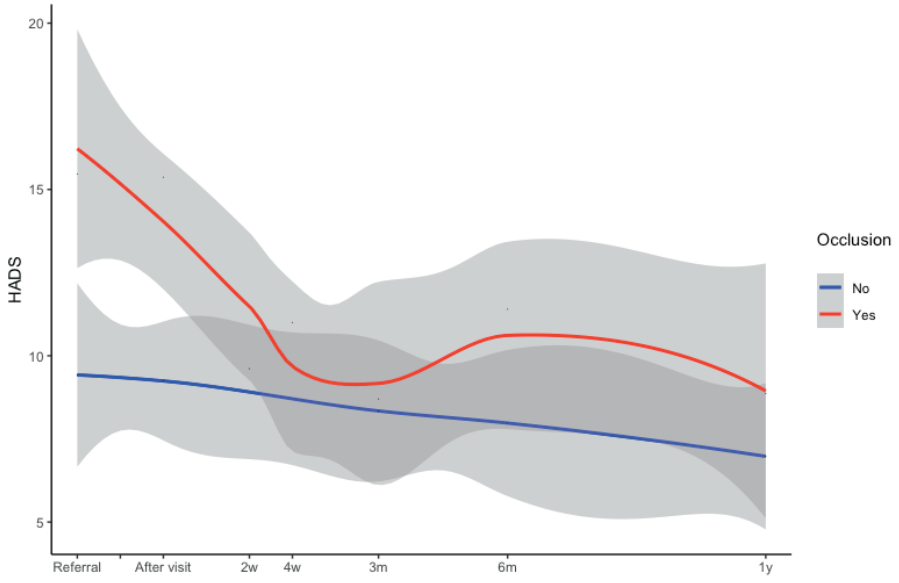
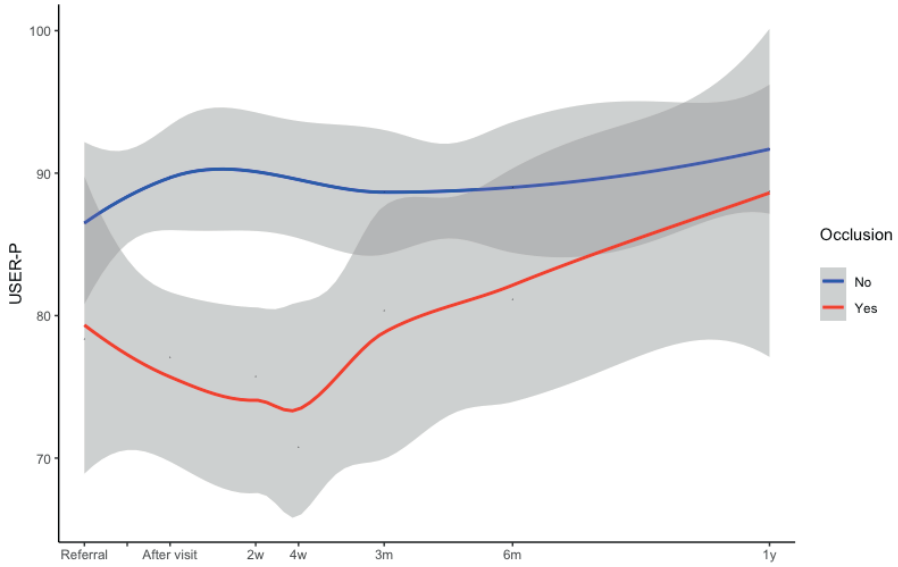


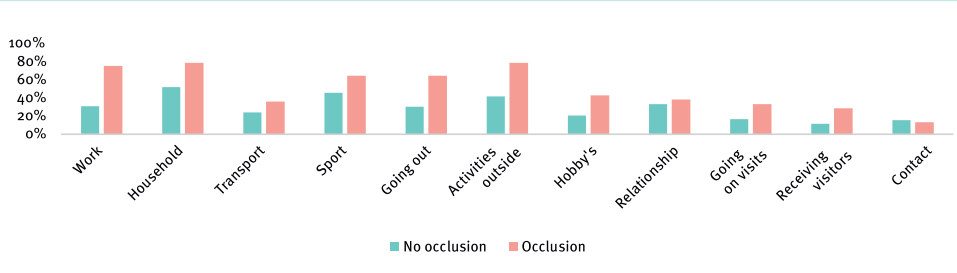
Figure 4. Levels of restrictions in participation of UIA patients with and without preventive aneurysm occlusion over time



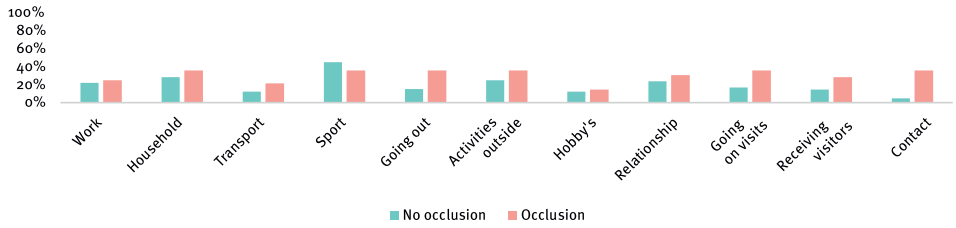
The graphs illustrate the mean HADS (**Figure 3**) and USER-P (**Figure 4**) sumscores over time. The grey areas around the lines represent 95% confidence intervals. HADS=Hospital Anxiety and Depression Scale. USER-P= Utrecht Scale for Evaluation of Rehabilitation–Participation. w=week. m=month. y=year.

Figure 5. Proportion of patients with restrictions for the separate daily activities of the USER-P at baseline (**A**) and one-year follow-up (**B**)

A. Baseline



B. One-year follow-up



QoL course over time

Unadjusted mean EQ-5D, HADS and USER-P sumscores over time are given in eTable 1. The adjusted results from the mixed models on QoL changes over time are given in Table 2, Figures 2-4 (occlusion versus no occlusion) and eFigures 2-4 (according to aneurysm occlusion modality). In patients with preventive aneurysm occlusion, there was no HRQoL change after the initial visit to the outpatient clinic or during the recovery phase, but one-year after UIA diagnosis there was an improvement (mean adjusted EQ-5D sumscore improvement at one-year: 8.6; 95%CI: 0.1-17.0; Table 2 and Figure 2), which was comparable for NST and EVT (eFigure 2). Compared to baseline, an improvement in HADS sumscores was seen at one month, three months, six months and one year after occlusion (Table 2, Figure 3 and eFigure 3). During the recovery phase after aneurysm occlusion more restrictions in daily activities were reported compared to baseline (mean USER-P sumscore change at one month: -12.8; 95%CI: -23.8- -1.9; Table 2 and Figure 4), which was most pronounced among patients undergoing NST (eFigure 4). In patients without preventive aneurysm occlusion, the largest HRQoL improvement occurred directly after their initial visit to the outpatient clinic (EQ-5D sumscore improvement: 9.2; 95%CI:5.5-12.8), with no changes in HADS or USER-P sumscores over time (Table 2 and Figures 2-4). For both cohorts, results for the separate EQ-5D subdomains mobility, self-care, usual activities, pain/discomfort and anxiety/depression are given in eFigure 5. Results from the separate domains were comparable to the EQ-5D sumscore patterns.

Table 2. Results from mixed-model analysis assessing the changes in QoL outcomes of UIA patients with and without preventive aneurysm occlusion over time **(part A)** and according to predictors **(part B)**

	HRQoL (EQ-5D) Coefficient (95% CI)	
Variables	Aneurysm occlusion	No aneurysm occlusion
A. Changes over time		
Time point		
Before outpatient clinic visit	Ref.	Ref.
After outpatient clinic visit	-0.8 (-7.4-5.8)	9.2 (5.5-12.8)
2 weeks after occlusion	1.8 (-5.2-8.8)	-
4 weeks after occlusion	0.7 (-6.6-8.1)	-
3 months	7.3 (-0.1-14.7)	7.4 (3.1-11.6)
6 months	3.7 (-4.0-11.3)	6.9 (2.2-11.5)
One-year	8.6 (0.1-17.0)	6.9 (1.9-11.9)
B. Predictors[a]		
Female sex	2.1 (-6.5-10.7)	0.7 (-6.0-7.3)
Age (continuous)	-0.2 (-0.6-0.2)	-0.1 (-0.4-0.3)
Psychiatric history[b]	15.7 (1.6-30.0)	3.0 (-7.8-13.8)
Passive coping[c]	-2.9 (-4.2- -1.6)	-2.2 (-3.0- -1.3)
(per point increase in UCL-P)		
Aneurysm size (continuous)	-0.4 (-1.7-0.9)	0.6 (-0.5-1.7)
Aneurysm rupture risk	1.6 (-0.8-4.1)	-1.5 (-3.0-0.0)
(per point increase in PHASES)		
Aneurysm occlusion modality		-
NST	Ref.	-
EVT	1.2 (-6.9-9.4)	-
In-hospital neurological complication[d]	-11.5 (-22.8- -0.1)	

a) To estimate for example the HRQoL outcome for female sex at one year follow-up, you first add 8.6 to the reference value (the change in HRQoL over time) and subsequently add 2.1 (the influence of female sex).
b) Patients were classified as having a psychiatric history if they were under psychological or psychiatric treatment or if the medical record reported the use of medication for depression, an anxiety disorder, or other psychiatric disorders. c) Passive coping style was accessed at baseline with a subscale of the UCL-P. Sumscores range from 7 (low) to 28 points (high level of passive coping). d) Complications were scored as transient if clinical symptoms resolved within 30 days, and otherwise were considered persisting. §=No patients with sumscores available. UCL-P=Utrecht Coping List–Passive. PHASES=risk score assessing the absolute 5-year rupture rate. NST=neurosurgical treatment. EVT=endovascular treatment. EQ-5D=EuroQoL 5 dimensions. HRQoL=health-related quality of life. HADS=Hospital Anxiety and Depression Scale. USER-P=Utrecht Scale for Evaluation of Rehabilitation–Participation. 95%CI=95% Confidence Interval. Ref.=Reference.

Emotional functioning (HADS) Coefficient (95% CI)		**Restrictions in daily activities (USER-P)** Coefficient (95% CI)	
Aneurysm occlusion	No aneurysm occlusion	Aneurysm occlusion	No aneurysm occlusion
Ref.	Ref.	Ref.	Ref.
-1.1 (-4.3-2.0)	-0.6 (-2.7-1.4)	-1.7 (-11.8-8.4)	0.3 (-4.4-5.1)
-3.2 (-6.6-0.2)	-	-12.3 (-23.2- -1.4)	-
-4.9 (-8.4- -1.5)	-	-12.8 (-23.8- -1.9)	-
-6.2 (-9.5- -2.9)	-1.2 (-3.4-0.9)	0.9 (-9.8-11.6)	-1.3 (-6.2-3.6)
-4.8 (-8.3- -1.3)	0.7 (-1.6-3.0)	4.6 (-6.6-15.9)	-3.7 (-9.0-1.7)
-5.4 (-9.4- -1.5)	-0.7 (-2.9-1.5)	7.4 (-5.4-20.2)	1.2 (-3.8-6.3)
1.2 (-3.2-5.6)	0.9 (-3.6-5.4)	0.3 (-19.0-19.5)	-6.8 (-16.7-3.1)
-0.1 (-0.3-0.1)	-0.1 (-0.3-0.1)	-0.00 (-0.9-0.9)	0.01 (-0.4-0.4)
§	5.4 (-1.8-12.6)	§	-12.3 (-28.2-3.5)
1.4 (0.6-2.2)	1.5 (0.9-2.0)	-1.0 (-4.4-2.3)	-2.9 (-4.1- -1.8)
-0.3 (-0.9-0.3)	-0.2 (-1.3-0.9)	-2.8 (-5.5- -0.04)	-0.1 (-2.4- 2.3)
0.3 (-1.1-1.7)	1.2 (0.1-2.3)	5.6 (-0.8-12.1)	-2.6 (-5.1- -0.2)
Ref.	-	Ref.	-
1.7 (-2.1-5.4)	-	-0.3 (-16.7-16.1)	-
4.6 (-1.6-10.7)	-	-17.9 (-45.2-9.3)	-

QoL outcomes at one-year follow-up

At one-year follow-up, HRQoL did not differ between patients with (mean EQ-5D: 86.9; SD: 13.0 and EQ-VAS: 76.5; SD: 17.4) and without aneurysm occlusion (EQ-5D: 87.1; SD: 87.1 and EQ-VAS: 81.5; SD: 13.9; eTable 1 and Figure 2). Also emotional functioning did no longer differ between the cohorts at one-year (occluded: mean HADS: 8.9; SD: 5.9 *vs.* non-occluded: 7.0; SD: 6.6; Figure 3). Both patients with and without preventive aneurysm repair reported some restrictions in daily activities at one-year, but no overall differences between the cohorts were seen (occluded: mean USER-P: 88.7; SD: 14.0 *vs.* non-occluded: 91.7; SD: 11.6); Figure 4). The baseline differences between patients with and without aneurysm occlusion in restrictions in working life, going out and activities outside home were no longer seen (eTable 2), but patients with preventive occlusion did report more restrictions in contact with other people as compared to patients without occlusion (2/41 (36%) *vs.* 5/14 (5%); risk difference: 31%; 95%CI: 8%-57%; Figure 5 and eTable 2). We found no differences in HRQoL, emotional functioning and restrictions in daily activities between patients with NST and EVT at one-year (eTable 3 and eFigures 2-4).

Predictors of QoL outcomes

After adjusting for covariates, higher levels of passive coping (specified per additional point on the UCL-P) negatively influenced all QoL outcomes (HRQoL, emotional functioning and participation in daily activities) in patients with and without aneurysm occlusion (Table 2). A history of psychiatric disease was associated with a better HRQoL outcome in patients with preventive occlusion, but not in patients without aneurysm occlusion. Patients with in-hospital neurological complications had a worse HRQoL outcome than patients without complications. We found no differences according to aneurysm occlusion modality (Table 2 and eTable 3). In patients without preventive aneurysm occlusion, a higher absolute aneurysm rupture risk (specified per additional point on the PHASES score) was associated with worse outcomes in emotional functioning and more restrictions in daily activities.

DISCUSSION

In this prospective cohort study, we found several differences between patients with and without preventive aneurysm occlusion at baseline and in their QoL trajectories over time, but showed that QoL outcomes were comparable one-year after UIA diagnosis. Initially, patients with aneurysm occlusion reported more restrictions during their recovery phase, but their HRQoL and emotional functioning gradually improved over time. In patients without aneurysm occlusion, the largest improvement in HRQoL occurred directly after the initial visit to the outpatient aneurysm clinic. Factors associated with worse QoL outcomes were a passive coping style in all patients, in-hospital complications in patients with preventive occlusion and higher rupture risks in patients without occlusion.

Several previous studies reported on QoL aspects in UIA patients, but most had a cross-sectional design and did not assess QoL outcomes at multiple standardized time points during follow-up.[12,13] We found three studies comparing UIA patients with and without preventive aneurysm occlusion.[19-21] One study assessed QoL six months after preventive occlusion or study enrolment and reported a decrease in QoL in patients without preventive occlusion, when compared to patients with occlusion.[19] Two cross-sectional studies reported no differences in QoL outcomes between patients with and without preventive occlusion, but found that overall QoL outcomes in UIA patients were reduced compared with reference populations. In contrast, the QoL outcomes in patients with and without preventive aneurysm occlusion of our study are comparable to EQ-5D measurements and HADS values from general populations in the literature one year after UIA diagnosis.[22,23] The longer time between diagnosis and QoL assessment may have resulted in fewer fully recovered patients participating in previous studies.[20,21]

The baseline differences in emotional functioning and restrictions we found between patients with and without occlusion could, at least partly, be explained by confounding by indication. Larger aneurysms with a higher risk of rupture are more likely to be occluded preventively, which may introduce more fear of rupture and restrictions in daily activities in patients with preventive occlusion than in patients without. These differences in QoL measures may even be present before the formal treatment decision has been made, depending on what the referring physician has already discussed with the patient at the time of UIA diagnosis. Some physicians may have hinted towards the need for preventive occlusion. Alternatively, the higher levels of passive coping and reduced emotional functioning at baseline in patients with preventive aneurysm occlusion may also reflect differences in individual coping style and other psychological characteristics or personality traits. These factors can influence the process and outcome of decision-making in that sense that patients with more fear of rupture

and more perceived restriction in daily life activities may be more inclined to opt for preventive occlusion. These baseline differences in individual coping style and other psychological characteristics or personality traits may then introduce QoL differences at baseline and over time.[8,9,24]

Four previous studies assessed QoL outcomes in UIA patients with preventive aneurysm occlusion with measurements before occlusion and at three months and one year after occlusion.[25-28] The results from these studies are in line with our finding that QoL improved between three months and one-year post-occlusion, with an initial decrease in QoL in the short-term. However, in contrast with our study, QoL outcomes in previous studies did not fully return to pre-occlusion levels at one-year follow-up and in one study it took up to three years for QoL outcomes to normalize post-clipping.[27] One explanation for this discrepancy may be that preventive aneurysm care, including options for aneurysm occlusion and treatment risks, has changed substantially since the previous studies were performed.[5]

Our finding that a substantial proportion of patients with preventive occlusion reported restrictions in daily activities, including working life, prior to occlusion has not been reported before, although one previous study compared employment status pre- and post-occlusion and found that a considerable proportion of UIA patients had a suboptimal employment status before occlusion.[28] This could indicate that a reduced working capability following aneurysm repair is not solely attributable to the aneurysm occlusion itself, but may also be influenced by baseline patient- and aneurysm characteristics and what a physician discusses with the patient.[12,21] Some physicians may advice UIA patients to 'take it easy' during the recovery phase after occlusion.

None of the previous studies in UIA patients compared QoL outcomes before and after the initial visit to an outpatient aneurysm clinic. One previous study in patients with abdominal aortic aneurysms described that patients experience the conservative nature of surveillance as reassuring.[29] A similar mechanism may apply for intracranial aneurysms. Both relief that no invasive treatment is needed as well as reassurance that the aneurysm has a low rupture risk are likely to play a role in a positive counseling effect.

Limitations

Our study has some limitations. First, our study population is relatively small and may represent a selected group, as not all eligible UIA patients participated in our study.
Some patients declined the invitation to participate because of fear for aneurysm rupture or a reduced QoL. This may have biased QoL measurements at baseline and over time and could, at least partly, explain why we found no differences in QoL outcomes between UIA

patients and the general Dutch population at one-year follow-up.[19,20] Second, not all respondents returned all scheduled questionnaires, resulting in variation in group size and distribution during follow-up. However, because we sent out questionnaires at many timepoints, we had detailed and prospective tracking data for most patients and could account for missing data by using robust linear mixed-effects models.

Strengths

The main strength of our study is that it was a prospective cohort study that assessed HRQoL, emotional functioning and restrictions in daily activities simultaneously at several standardized moments during follow-up, in both UIA patients with and without preventive aneurysm occlusion. In addition, this is, to our knowledge, the first study to report QoL outcomes before and after the initial visit to an outpatient aneurysm clinic. This enabled us not only to relate the QoL outcomes over time to differences that exist between UIA patients with and without preventive occlusion, but also to systematically compare QoL outcomes at several time points and to identify factors that influence QoL outcomes.

CONCLUSIONS AND IMPLICATIONS

After UIA diagnosis, QoL improves gradually after preventive occlusion and directly after counselling at an outpatient aneurysm clinic in case of no occlusion. QoL outcomes were eventually comparable in patients with and without preventive aneurysm occlusion at one-year follow-up. Factors associated with worse QoL outcomes were a passive coping style in all patients, complications in patients with preventive occlusion, and higher rupture risks in patients without occlusion. The differences we found in the trajectories of QoL recovery between patients with and without preventive aneurysm occlusion, and the associated amount of time spent with a reduced QoL, should be part of shared decision-making in UIA management. This can be realized by adding QoL data to patient information cards or videos or by using tools that assess the needs and preferences of patients during counselling, such as the time trade-off method to assess how many QALYs a patient is willing to invest in different treatment options.[7, 30] During counselling, patients can be informed that although QoL trajectories differ in the first year between patients undergoing preventive occlusion and patients without preventive aneurysm occlusion, at the end of this year QoL is on group level similar for these two groups. In addition, it is important to identify patients with an unfavourable coping style early following aneurysm diagnosis. By introducing a short intake questionnaire at the outpatient aneurysm clinic, the process of shared decision-making, patient guidance, and education following diagnosis may be further improved.[30, 31] Future studies should assess, ideally in a randomized setting, if such new counselling approaches can improve QoL outcomes.[32]

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SUPPLEMENTARY CONTENT

eFigure 1. Timetable of the questionnaires sent to UIA patients with and without preventive aneurysm occlusion

eTable 1. QoL outcomes of UIA patients with (A) and without (B) preventive aneurysm occlusion over time

eTable 2. Proportion of restrictions in daily activities in patients with and without preventive aneurysm occlusion at baseline (A) and one-year follow-up (B)

eTable 3. QoL outcomes for UIA patient undergoing neurosurgical treatment (A) and endovascular treatment (B)

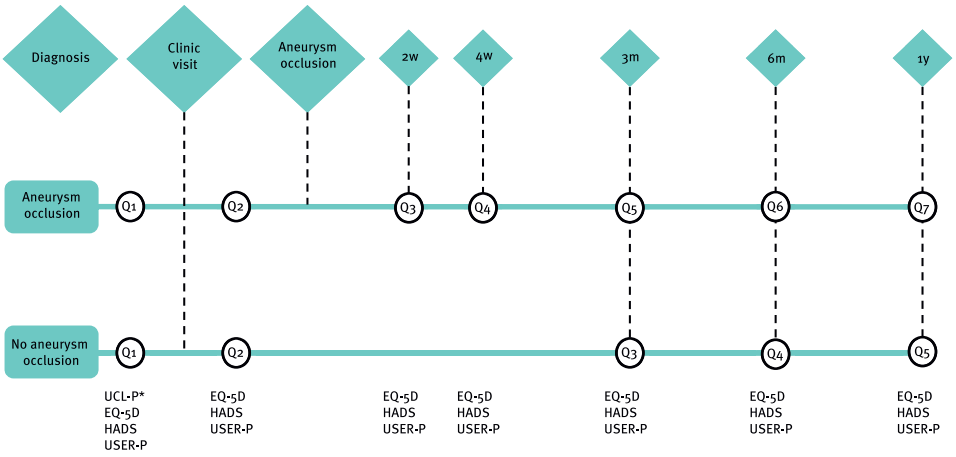
eFigure 2. HRQoL of UIA patients with and without preventive aneurysm occlusion over time, stratified by occlusion modality

eFigure 3. Levels of anxiety and depression of UIA patients with and without preventive aneurysm occlusion over time, stratified by occlusion modality

eFigure 4. Levels of restrictions in participation of UIA patients with and without preventive aneurysm occlusion over time, stratified by occlusion modality

eFigure 5. Subdomains of the EQ-5D in patients with and without preventive aneurysm occlusion at baseline (A) and one-year follow-up (B)

eFigure 1. Timetable of the questionnaires sent to UIA patients with and without preventive aneurysm occlusion



*UCL-P was only assessed at baseline. UCL-P=Utrecht Coping List–Passive. EQ-5D=EuroQoL 5 dimensions. HADS=Hospital Anxiety and Depression Scale. USER-P=Utrecht Scale for Evaluation of Rehabilitation–Participation. w=week. m=month. y=year. q=questionnaire.

eTable 1: QoL outcomes of UIA patients with (A) and without (B) preventive aneurysm occlusion over time

	HRQoL EQ-5D		EQ-VAS	Emotional functioning HADS		Restrictions in daily activities USER-P	
	n	Mean (SD)	Mean (SD)	n	Mean (SD)	n	Mean (SD)
A. Aneurysm occlusion (n=30)[a]							
Before outpatient visit	15	73.3 (16.8)	61.6 (16.2)	15	15.5 (7.7)	15	78.4 (15.6)
After outpatient visit	28	74.6 (17.1)	67.6 (16.7)	27	15.4 (10.1)	27	77.1 (23.7)
2 weeks after occlusion	21	79.5 (15.6)	67.3 (16.3)	19	10.1 (7.3)	18	75.7 (22.5)
4 weeks after occlusion	18	76.1 (20.6)	69.1 (19.4)	17	11.0 (8.7)	17	70.8 (25.7)
3 months after occlusion	20	84.0 (17.0)	76.5 (13.4)	20	8.7 (6.6)	20	80.4 (23.5)
6 months after occlusion	21	80.0 (15.5)	69.3 (20.5)	20	11.4 (7.0)	20	81.1 (21.5)
One-year after occlusion	16	86.9 (13.0)	76.5 (17.4)	15	8.9 (5.9)	14	88.7 (14.0)
B. No aneurysm occlusion (n=69)							
Before outpatient visit	27	77.4 (17.7)	72.6 (17.0)	26	9.4 (6.8)	26	86.5 (15.5)
After outpatient visit	64	88.3 (14.3)	77.8 (16.9)	62	9.2 (7.2)	62	89.7 (15.5)
3 months after outpatient visit	50	86.0 (16.4)	78.5 (19.2)	44	8.3 (6.9)	44	88.7 (15.8)
6 months after outpatient visit	43	86.7 (18.4)	76.0 (23.8)	41	8.0 (7.9)	40	89.0 (14.5)
One-year after outpatient visit	42	87.1 (16.1)	81.5 (13.9)	41	7.0 (6.6)	41	91.7 (11.6)

a) One patient was scheduled for EVT, but did not undergo occlusion because of difficulties with the intubation procedure. EQ-5D=EuroQoL 5 dimensions. HRQoL=health-related quality of life. EQ-VAS=EuroQoL visual-analog scale. HADS=Hospital Anxiety and Depression Scale. USER-P= Utrecht Scale for Evaluation of Rehabilitation–Participation. SD=standard deviation.

eTable 2. Proportion of restrictions in daily activities in patients with and without preventive aneurysm occlusion at baseline (**A**) and one-year follow-up (**B**)

A. Baseline

USER-P activity	No occlusion (%)	Preventive aneurysm occlusion (%)	Absolute difference (%; 95%CI)
1. Work	4/13 (30.8)	9/12 (75.0)	**44.2 (5.3-68.5)**
2. Household	13/25 (52.0)	11/14 (78.6)	26.6 (-5.2-49.7)
3. Transport	6/25 (24.0)	5/14 (35.7)	11.7 (-15.7-40.1)
4. Sport	11/24 (45.8)	9/14 (64.3)	18.5 (-13.4-44.9)
5. Going out	7/23 (30.4)	9/14 (64.3)	**33.9 (11.6-58.3)**
6. Activities outside	10/24 (41.7)	11/14 (78.6)	**36.9 (4.3-59.0)**
7. Hobby's	5/24 (20.8)	6/14 (42.9)	22.0 (-7.1-49.2)
8. Relationship	8/24 (33.3)	5/13 (38.5)	5 (-23.7-35.3)
9. Going on visits	4/24 (16.7)	5/15 (33.3)	16.7 (-9.8-43.5)
10. Receiving visitors	3/26 (11.5)	4/14 (28.6)	17.0 (-7.2-44.2)
11. Contact	4/26 (15.4)	2/15 (13.3)	2.1 (-22.6-24.1)

B. One-year follow-up

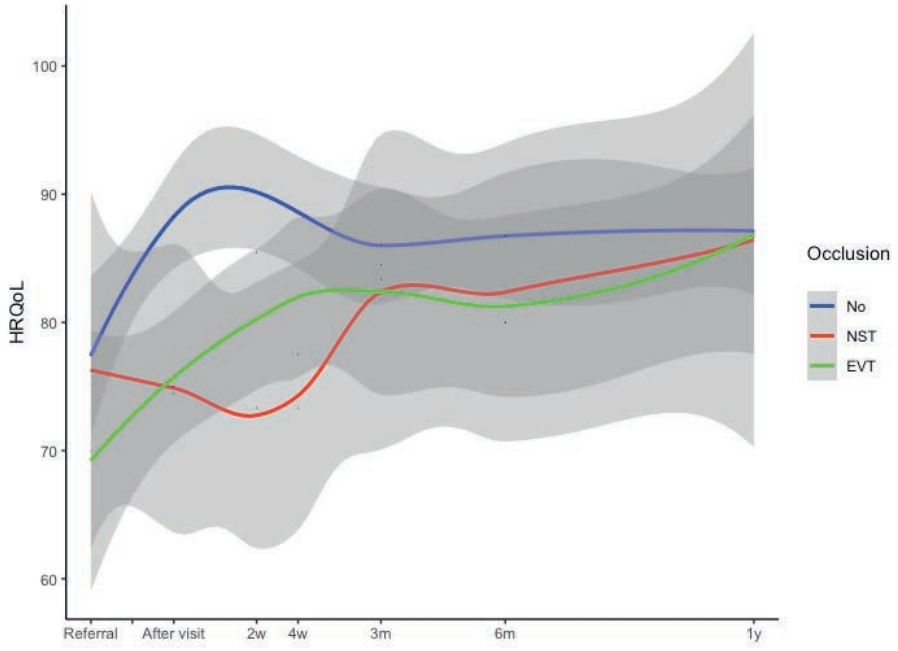
USER-P activity	No occlusion (%)	Preventive aneurysm occlusion (%)	Absolute difference (%; 95%CI)
1. Work	6/27 (22.2)	3/12 (25.0)	2.8 (-22.0-33.3)
2. Household	11/39 (28.2)	5/14 (35.7)	7.5 (-17.3-35.6)
3. Transport	5/40 (13.0)	3/14 (21.4)	8.9 (-10.5-36.0)
4. Sport	18/40 (45.0)	5/14 (35.7)	9.3 (-33.9-20.0)
5. Going out	6/40 (15.0)	5/14 (35.7)	20.7 (-3.2-47.4)
6. Activities outside	10/40 (25.0)	5/14 (35.7)	10.7 (-13.9-38.4)
7. Hobby's	5/40 (12.5)	2/14 (14.3)	17.9 (-15.3-28.4)
8. Relationship	8/34 (23.5)	4/13 (30.8)	7.2 (-17.2-36.3)
9. Going on visits	7/41 (17.0)	5/14 (35.7)	18.6 (-5.4-45.6)
10. Receiving visitors	6/41 (14.6)	4/14 (28.6)	13.9 (-7.9-41.1)
11. Contact	2/41 (4.9)	5/14 (35.7)	**30.8 (8.4-56.6)**

eTable 3. QoL outcomes for patient undergoing neurosurgical treatment (A) and endovascular treatment (B)

	HRQoL EQ-5D		EQ-VAS	Emotional functioning HADS		Restrictions in daily activities USER-P	
	n	Mean (SD)	Mean (SD)	n	Mean (SD)	n	Mean (SD)
A. Neurosurgical treatment (n=11)							
Before outpatient visit	8	76.3 (17.7)	59.9 (19.6)	8	12.3 (5.0)	8	82.2 (15.8)
After outpatient visit	10	75.0 (19.6)	66.7 (18.2)	9	14.3 (10.0)	9	79.6 (26.9)
2 weeks after occlusion	9	73.3 (18.7)	67.2 (12.3)	9	10.3 (6.8)	8	66.0 (29.0)
4 weeks after occlusion	6	73.3 (26.6)	64.2 (25.2)	6	10.8 (9.5)	6	59.1 (29.8)
3 months after occlusion	9	83.3 (21.8)	73.3 (13.5)	9	8.7 (6.0)	9	70.7 (30.9)
6 months after occlusion	8	80.0 (20.0)	71.9 (21.2)	8	10.5 (7.1)	8	76.9 (30.4)
One-year after occlusion	6	86.7 (13.7)	74.8 (22.6)	5	7.4 (5.9)	4	91.7 (16.7)
B. Endovascular treatment (n=19)[a]							
Before outpatient visit	7	70.0 (16.3)	63.6 (13.8)	7	19.1 (9.0)	7	74.0 (15.2)
After outpatient visit	18	74.4 (84.2)	68.1 (16.5)	18	15.9 (7.6)	18	75.8 (22.7)
2 weeks after occlusion	12	84.2 (11.6)	67.3 (19.5)	10	9.8 (8.1)	10	83.6 (12.2)
4 weeks after occlusion	12	77.5 (18.2)	71.8 (16.2)	11	11.1 (8.7)	11	77.1 (22.0)
3 months after occlusion	11	84.6 (12.9)	79.1 (13.4)	11	8.7 (7.2)	11	88.2 (11.5)
6 months after occlusion	13	80.0 (12.9)	67.5 (20.7)	12	12.0 (7.2)	12	83.9 (13.7)
One-year after occlusion	10	87.0 (13.4)	77.5 (14.8)	10	9.6 (6.1)	10	87.6 (13.6)

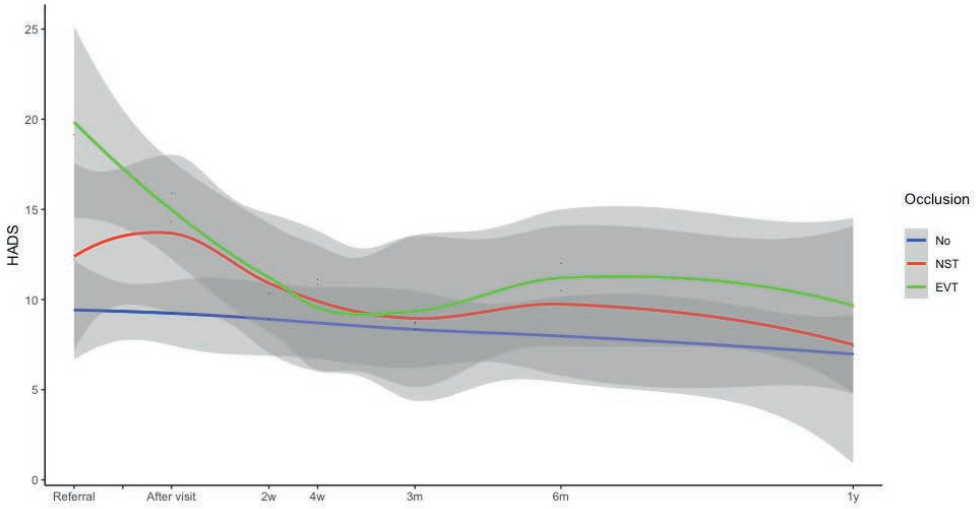
a) One patient was scheduled for EVT, but did not undergo occlusion because of difficulties with the intubation procedure. EQ-5D=EuroQoL 5 dimensions. HRQoL=health-related quality of life. EQ-VAS=EuroQoL visual-analog scale. HADS=Hospital Anxiety and Depression Scale. USER-P= Utrecht Scale for Evaluation of Rehabilitation–Participation. SD=standard deviation.

eFigure 2. HRQoL of UIA patients with and without preventive aneurysm occlusion over time, stratified by occlusion modality



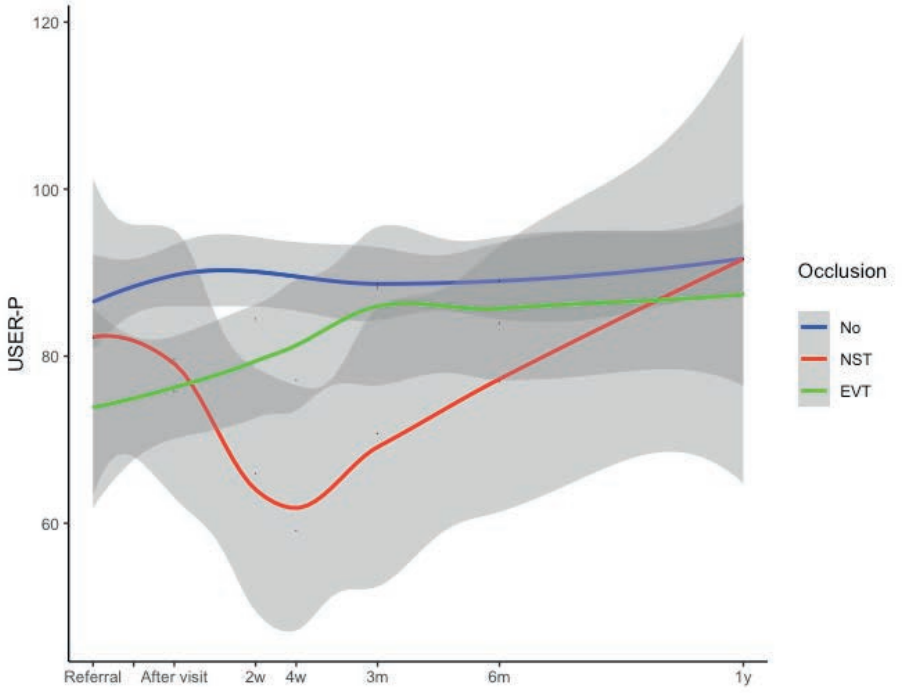
The graph illustrates the mean EQ-5D sumscores over time. The grey areas around the lines represent 95% confidence intervals. HRQoL=health-related quality of life. NST=neurosurgical treatment; EVT=endovascular treatment. w=week. m=month. y=year.

eFigure 3. Levels of anxiety and depression of UIA patients with and without preventive aneurysm occlusion over time



The graph illustrates the mean HADS sumscores over time. The grey areas around the lines represent 95% confidence intervals. HADS= Hospital Anxiety and Depression Scale. NST=neurosurgical treatment. EVT=endovascular treatment. w=week. m=month. y=year.

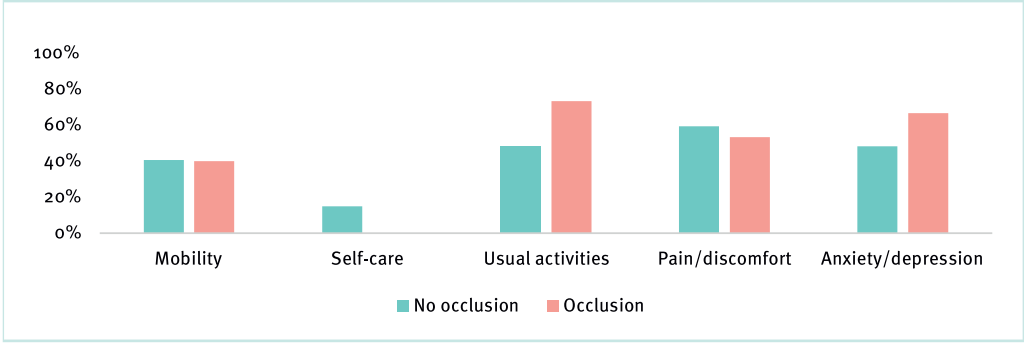
eFigure 4. Levels of restrictions in participation of UIA patients with and without preventive aneurysm occlusion over time



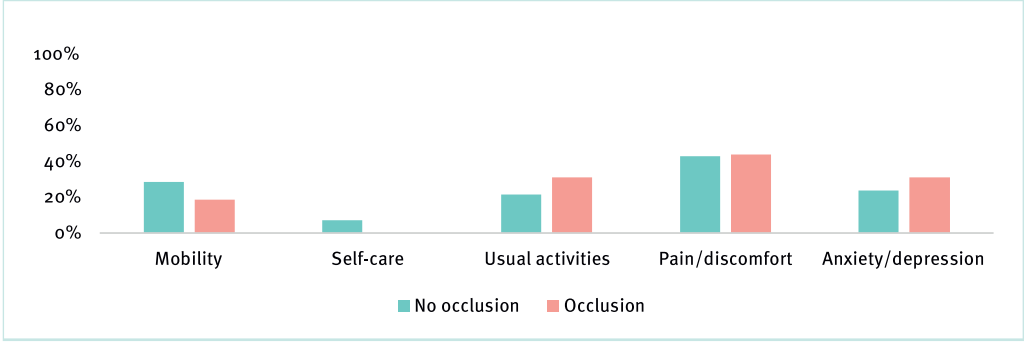
The graph illustrates the mean USER-P sumscores over time. The grey areas around the lines represent 95% confidence intervals. USER-P= Utrecht Scale for Evaluation of Rehabilitation–Participation. NST=neurosurgical treatment. EVT=endovascular treatment. w=week. m=month. y=year.

eFigure 5. Subdomains of the EQ-5D in patients with and without preventive aneurysm occlusion at baseline (**A**) and one-year follow-up (**B**)

A. Baseline



B. One-year follow-up



CHAPTER 5

General discussion

GENERAL DISCUSSION

In this chapter the most important findings of the research included in this thesis are highlighted. In addition to discussing the generated data, I reflect on the limitations, strengths, and lessons learned from the work behind each of these studies. Finally, I make some suggestions for clinical practice and future research.

The prevalence of unruptured intracranial aneurysms is 3%.[1,2,3] Rupture causes subarachnoid haemorrhage (SAH), a subset of stroke with a poor prognosis.[4] Preventive aneurysm occlusion can reduce the risk of aneurysmal SAH but carries a risk of serious complications.[5] Since randomised trials comparing preventive aneurysm occlusion with no occlusion have proven to be difficult,[6] prediction modelling and decision analysis are the best evidence-based alternatives to put risks of aneurysm rupture and treatment complications in proper context.[7,8] Previously, the PHASES and UCAS risk scores have been developed to predict the absolute risk of aneurysm rupture.[9,10] In contrast, estimation of treatment risks is still largely based on expert opinion.[11] Therefore, the first part of this thesis focused on improving the prediction of absolute procedural (30-day) complication risks of preventive endovascular and neurosurgical intracranial aneurysm occlusion. In addition to balancing risks of aneurysm rupture and treatment complications, quality of life (QoL) outcomes should also be considered.[12,13] In patients without preventive aneurysm occlusion, fear of aneurysm rupture can have a huge impact on QoL, but also preventive aneurysm occlusion may reduce QoL, even if no complications occur.[12-14] In the second part of this thesis, I have studied the time-course and predictors of QoL outcomes in patients with and without preventive aneurysm occlusion. The eventual goal of this thesis is to integrate the data generated in these studies into clinical decision-making on unruptured intracranial aneurysms, enabling physicians and patients to use these new results to make a more balanced decision on preventive aneurysm occlusion. This will hopefully increase the number of life years with high QoL in patients with unruptured intracranial aneurysms in the future.[7]

TREATMENT RISKS

Randomized evidence for treatment of ruptured intracranial aneurysms

The first surgical clipping of an intracranial aneurysm was performed by Walter Dandy in 1938.[15] For many years, clipping was regarded as the definite mode of treatment for ruptured aneurysms. This changed with the introduction of an alternative to open surgery: the controlled detachable coils in 1991.[16] As the experience with endovascular coiling increased, the International Subarachnoid Aneurysm Trial (ISAT) was set up in 1994 to compare surgical clipping and endovascular coiling in patients with ruptured intracranial aneurysms.[17] This trial demonstrated better one-year clinical outcomes for patients treated with coiling as compared to clipping.[17] Despite the fact that these findings can only be generalized to patients in good clinical condition with ruptured aneurysms considered suitable for both clipping and coiling, ISAT triggered a paradigm shift towards endovascular treatment as the preferred treatment option for ruptured aneurysms.[18-20]

This change in practice may have also influenced management decisions for patients with *unruptured* intracranial aneurysms. However, there are two reasons why the randomized data from ISAT cannot be extrapolated to patients with unruptured intracranial aneurysms. First, the morbidity and mortality risks for ruptured aneurysm repair reflect a combination of the devastating effects of the SAH itself and the neurological deterioration due to procedural complications and are thus not applicable to an elective, unruptured setting. Second, ruptured aneurysms are occluded with two goals: first to ensure that the patient survives the acute phase of SAH without aneurysm rebleeding and second to reduce the long-term risk of aneurysm rupture. For unruptured aneurysms only the latter goal applies. The early risk of re-rupture is 30-50% following initial bleeding, which is substantially higher than the overall annual rupture risk of approximately 1% for unruptured aneurysms.[2, 3, 8, 21]

Randomized evidence for treatment of unruptured intracranial aneurysms

With many unruptured aneurysms remaining stable over time, the primary question for randomized clinical trials of patients with unruptured intracranial aneurysm is not whether an aneurysm should be clipped or coiled, but whether any preventive invasive treatment outweighs the risks of leaving the aneurysm untreated.[22] This was the rationale behind the Trial on Endovascular Aneurysm Management (TEAM), which was initiated in 2006 to study clinical outcomes with coiling or observation.[23] Due to poor recruitment, the trial was stopped in 2009. At that time, 80 patients had been enrolled and no clinical outcome events had occurred in the endovascular or conservative management arms.[6] The authors of the trial

mention several factors for failure of the TEAM trial, including the difficulty to study withholding a treatment instead of studying a new treatment, the need to include large numbers of patients and long-term follow-up, and the administrative hurdles.[6, 24]

Building on this experience, the same trialists moved away from the 'intervention-no intervention' question and launched the Collaborative UnRuptured Endovascular versus Surgery (CURES) trial in 2010 to compare clipping and endovascular treatment in patients with unruptured intracranial aneurysms suitable for repair with either approach.[25] For this trial, 'treatment failure' was used as a 'pragmatic' composite primary outcome at one year follow-up, comprising angiographic (the occurrence of either failure to accomplish aneurysm occlusion with the initial treatment modality or a major saccular aneurysm remnant or recurrence) and clinical (intracranial haemorrhage within one year following treatment) outcomes. Secondary outcomes included permanent morbidity (modified Rankin Scale of 3 or more) and new perioperative (30-day) neurological deficits.[25] Although the trial is still ongoing, preliminary results of patients enrolled between 2010 and 2016 have been published.[26] One-year treatment failure occurred in 10 of 56 patients (18%) allocated to the endovascular treatment arm and in 5 of 48 patients (10%) allocated to the neurosurgical treatment arm (RR 1.71; 95% CI: 0.63-4.67). Two patients in each treatment arm were dead or dependent at one-year (both 4%; RR 0.86; 95% CI: 0.13-5.86) and new periprocedural neurological deficits occurred more often following clipping (25%) than after endovascular treatment (10%; RR 2.40; 95% CI 0.93-6.18).[26] Continuation of CURES is needed to establish whether these preliminary findings will hold true if sufficient power is reached. However, due to slow recruitment and the declining use of clipping for unruptured aneurysms in clinical practice, it is uncertain whether this trial will be able to establish the supposed superior efficacy of clipping.

Non-randomized evidence for treatment of unruptured intracranial aneurysms

Until recently, the best non-randomized evidence on procedural morbidity and case-fatality of clipping and endovascular treatment came from meta-analyses published in 2012 and 2013.[27, 28] Since the publication of these reviews, the clinical landscape has changed substantially. There has been a shift towards endovascular treatment as the predominant treatment modality, with an increasing variety of advanced endovascular methods being used, such as stent-assisted or balloon-assisted coiling, flow-diverting stents, and Woven EndoBridge (WEB) Aneurysm Embolization devices.[29-34] In addition, previous reviews did not focus on risk factors or complications resulting in non-permanent neurological deficits.[5, 35, 36]

Therefore, in **chapter 2** of this thesis, we performed a systematic review and meta-analysis to summarize all available risk factor data and update the previous literature, also including

studies with non-permanent complications.[5] The pooled risk of clinical complications from any endovascular treatment is approximately 5%, with higher reported risks in patients treated with advanced endovascular methods. Despite the broadening of our definition of treatment complications, the current endovascular risks are comparable with those reported in previous reviews, which could indicate that the risk of permanent morbidity has declined over time, at least for standard coiling.[27, 37] Unfortunately, due to lack of information in most studies included in our meta-analysis, it was not possible to disentangle transient and permanent clinical complications and perform separate time-trend analyses for standard coiling and advanced endovascular methods. For clipping, the overall pooled risk of treatment complications was slightly higher in our current review (8%) than in a previous review (7%).[28] Nevertheless, after restricting our analysis to studies of high methodological quality, this potential difference was no longer present.

Methodological weaknesses

Most discrepancies in outcomes between studies, regions or treatment modalities in our review can be explained by selection bias or case-mix variation, as is the case for many non-randomized comparisons.[38] Cautious interpretation of the data is therefore needed. For example, the finding of an increased complication risk in patients treated by advanced endovascular methods may, at least partially, be explained by confounding by indication: complex aneurysms are treated by advanced treatment modalities because standard coiling is not an option.[39] In a similar way, there are various explanations for the regional differences we found. When interpreting the higher complication risks reported in studies performed in North American hospitals as compared to other continents, it should be kept in mind that in American hospitals the correct listing of complications leads to higher reimbursements.[40] In addition, all American studies were *ICD*-based studies. Such database studies are not very sensitive in identifying complications following interventions.[41] In contrast, the complication risk was substantially lower in studies originating from Asia. This may also be explained by cultural differences in outcome reporting, or because many of the Asian studies were single-centre studies in which the surgeons or interventionalists performed the retrospective analysis themselves.[42-45] However, the lower complication risks may also reflect higher treatment volumes in large Asian hospitals, resulting in more treatment exposure and thus more experience.[46, 47] Unfortunately, without detailed risk factor data, these explanations remain speculations about the variation we found in treatment risk and outcome.

INDIVIDUAL TREATMENT RISK PREDICTION

Given the limitations of the available randomized and non-randomized evidence on treatment complications, we rely on other approaches to improve the prediction of individualized risks and to inform clinical decisions.[7] For aneurysm rupture, the PHASES and UCAS scores have been developed based on individual patient data from prospective cohort studies.[9,10] These cohorts do not reflect 'true' natural history cohorts because of selection bias and preventive treatment during follow-up, they are still considered the best evidence available to estimate the risk of aneurysm rupture.[48-50] Instead of focusing on one arbitrary cut-off point for aneurysm size to distinguish aneurysms with a low rupture risk from those at high rupture risk,[3, 51] the PHASES score now enables clinicians to predict the absolute 5-year risk of aneurysm rupture based on six easily retrievable patient and aneurysm characteristics: Population, Hypertension, Age, Size of the aneurysm, Earlier SAH from another aneurysm and Site of the aneurysm.[9]

In contrast to rupture risk, the estimation of treatment risks is still largely based on opinions of experts and the previously mentioned meta-analyses of observational studies.[8, 11, 27, 28] Existing grading systems often combined data from patients with ruptured and unruptured aneurysms and the generalizability of the risk scores that did restrict models to patients with unruptured intracranial aneurysms is limited by selective or outdated study populations.[52-58] To improve the estimation of treatment risks, we set up a multicentre cohort study with an international and multidisciplinary team of aneurysm experts. The two aneurysm treatment risk scores we developed are presented in **chapter 3** of this thesis. The models provide up-to-date absolute procedural (30-day) complication risks for endovascular treatment and microsurgical clipping separately, based on individual patient data from 10 cohorts from Europa, North America, and Asia. In line with our systematic review and meta-analysis (**chapter 2**), the definition of an unfavourable treatment outcome was not restricted to permanent morbidity.[5] The overall risks of neurological complications were substantially higher in our study (16% overall risk for endovascular treatment and 23% overall risk for microsurgical clipping) as compared with previous reviews.[27, 28, 37] This can be explained by differences in method of ascertainment and outcome definitions, as we also included transient neurological complications. Interestingly, the risks we found are in line with the preliminary safety results reported in the ongoing CURES trial, which also reported high rates of new neurological deficits following endovascular treatment (10%) and clipping (25%).[26] After restricting the complications to permanent morbidity only (death or dependency), the combined risk was less than 3% for endovascular treatment and 6% for neurosurgical treatment, which is consistent with previous reviews.[27, 28, 37] However, because our study is based on retrospectively collected observational data, we were not able to reliably assess outcomes according to standardized outcome scales such as

the modified Rankin Scale. This may have resulted in less accurate outcome predictions and an underestimation of overall treatment risk if complications were underreported or missed. In addition, the scoring of procedural complications was not blinded for treatment modality, which may also have led to bias. To minimalize this and to reach a multidisciplinary consensus, all primary outcome events were first scored by independent non-treating investigators based on predefined definitions and subsequently discussed with or reviewed by intracranial aneurysm experts per participating centre. In contrast to our previous meta-analysis, we found no evidence for regional differences.[5] The centre-specific variation that we did observe was almost fully explained by baseline differences in aneurysm size, treatment volume and modalities used per centre. For advanced endovascular methods, we now illustrate in our risk models that the increased treatment risk is indeed partially explained by confounding by indication.[39] Compared to standard coiling, aneurysms treated with advanced endovascular treatments were larger, had a wider neck size and were often located at the basilar termination or ophthalmic region of the internal carotid artery. Nevertheless, treatment modality remained a strong independent predictor in the multivariable endovascular model, which indicates that either the treatment itself, or factors not accounted for, also contribute to the increased risk of advanced endovascular treatments. We chose to develop separate treatment risk scores for endovascular and neurosurgical treatment, because for many aneurysms one of these treatment options is clearly the preferred or only possible strategy. For both risk scores, we found robust discriminatory performance, calibration, and internal validation based on seven patient, aneurysm, and treatment characteristics. Although we did not yet externally validate the models, we did perform internal-external cross-validation, a process in which every centre in the dataset is left out once and the modelling process is repeated based on the remaining centres. This additional validation showed that the performance of both models was essentially the same. The factors included in the final endovascular and neurosurgical models are Size of aneurysm, Aneurysm location, Familial SAH, Earlier atherosclerotic disease, Treatment volume, Endovascular modality (for endovascular treatment) or extra aneurysm configuration factors (for neurosurgical treatment), and Age (acronym: SAFETEA). The more points a patient scores on the SAFETEA score, the higher the absolute 30-day risk of a complication following preventive aneurysm treatment. For endovascular treatment, one point on the score is associated with a low treatment risk (3%), whereas the maximum of 6 points is associated with a high risk (33%). For neurosurgical treatment, the absolute risks range from 5% (1 point) to 50% (6 points).

Clinical implementation of risk scores

Evidence-based scores for risk prediction such as PHASES and SAFETEA can support multidisciplinary team meetings and shared decision-making among aneurysm specialists and

patients. Since the publication of the PHASES score in 2014, the score is frequently used in clinical practice as a prediction tool in the web application 'Neuromind'. Previously, we have evaluated the effect of the clinical implementation of the PHASES score on the management of unruptured intracranial aneurysms at two Dutch tertiary referral centres for aneurysm care (University Medical Center Utrecht (UMCU) and Leiden University Medical Center (LUMC)).[59] In this implementation study, we found that the decision to treat was made at a higher median PHASES score after implementation, but that the impact of implementation on treatment decisions differed across age subgroups and centres. Despite the fact that age is included as one of the predictors in the PHASES score, we found that especially in younger patients (<50 years) the decision to treat was made less often after the implementation of PHASES.[59] Before implementation, there may have been a strong tendency to treat aneurysms in people of working age more aggressively than aneurysms in elderly people.[60] After implementation, we found no differences in treatment threshold across age groups. Although implementation studies with a 'before-after' design have methodological limitations,[61, 62] this example nicely illustrates how the introduction of an evidence-based risk score can help shift the focus from prior beliefs about individual risk factors to evidence-based weighting of various risk factors. In a similar way, differences in threshold to advise preventive treatment across centres may reflect variation in the weight attributed to the individual factors included in the PHASES score. However, organizational differences may have also played a role. For example, the clinical process is different at the UMCU and the LUMC. In Utrecht, patients are first discussed in a multidisciplinary team, but at the outpatient clinic the patient is first seen by the neurologist. If needed, the patient is referred to a neurosurgeon or interventional radiologist, or they may join during the initial counselling. In Leiden, the initial counselling is not only done by neurologists, but also by neurosurgeons, and interventional radiologists. Clinical context and profession are likely to colour judgement, which can, perhaps even subconsciously, result in differences in interpretation and clinical application of the same score.[22]

With the SAFETEA risk scores ready for implementation, we should be aware of similar biases.[22, 63] As risk factors for aneurysm rupture and procedural complications overlap, the expectation is that there will be a group of patients with high scores on both rupture and complication risk scores. For this group, it may be the case that the absolute 3- or 5-year risk of aneurysm rupture will not outweigh the risk of procedural complications. Notwithstanding the fact that PHASES and SAFETEA risks should not be directly compared and that other QoL factors and lifetime risk of aneurysm rupture should also be considered, this perspective may challenge SAFETEA's implementation.[64] Interventionalists may find it difficult to accept the implications of a high SAFETEA risk score. Furthermore, it could result in an overly critical attitude towards the new aneurysm treatment risk scores. Of course, our models have its shortcomings and they must be externally validated. But should we continue to base our

treatment risk assessment on expert opinion and data from observational reviews, despite the availability of risk scores? I personally do not think we should. Using risk scores will allow physicians to consider several risk factors in a more objective way. Therefore, I think that, until further validation studies become available, the risks and predictors described in our study can already be used as evidence-based background, alongside existing decision guidance.[11] In addition to calculating absolute treatment risks, the use of these risk scores can also create awareness about treatment complications. The acronym SAFETEA not only summarizes the predictors included in the two aneurysm treatment risk scores, but also refers to one of the key principles from the Hippocratic Oath we all took: "first do no harm". Before a treatment decision is made, we should always think: SAFETEA first. Not only to prevent potential harm from a preventive treatment, but also to improve patient safety by being open about the complications that may occur, with or without preventive aneurysm treatment.[65]

QUALITY OF LIFE OUTCOMES

Ultimately, the choice of appropriate management is determined by a strategy that yields the highest number of quality-adjusted life years (QALY).[7] That means that management decisions on unruptured intracranial aneurysms should not and cannot be simplified into a direct PHASES versus SAFETEA comparison. Such an approach would ignore the real-life complexity of the decision-making process in clinical practice.[8, 11] We still need multidisciplinary team meetings and time for shared decision-making at the (outpatient) aneurysm clinic to discuss the risks of rupture and treatment complications in the context of other individual aspects that were not included in the risk scores and QoL outcomes. Fear of aneurysm rupture can exert an important psychological burden, but also recovery from preventive treatment may reduce QoL, even if no complications occur.[12-14] Retrospective data suggest that time to feeling completely recovered or to start working is several months after uncomplicated aneurysm treatment.[66] In addition, from a previous modelling study we know that life expectancy and the awareness of an unruptured intracranial aneurysm are important determinants of cost-effectiveness.[7] However, due to limited data on these factors, modelling outcomes in terms of QALY's remain uncertain.

In **chapter 4** of this thesis, we therefore performed a prospective cohort study at the UMCU and LUMC to study the time-course and predictors of QoL outcomes in patients with and without preventive aneurysm occlusion. Eligible patients were sent standardized questionnaires about health-related QoL, anxiety and depression, coping style and participation in daily activities at several moment in the first year after aneurysm diagnosis. Although not all respondents returned all scheduled questionnaires, we could account for the missing data

by using robust linear mixed-effects models. We showed that although QoL trajectories were different for patients with and without preventive aneurysm occlusion, one-year outcomes were comparable. In fact, in both patient groups, QoL outcomes returned to normal when compared with reference values from general populations.[67, 68] This is a reassuring finding and is not in line with data from previous retrospective and cross-sectional studies suggesting that untreated patients have worse QoL outcomes than treated patients or the general population.[14, 69, 70] However, it may also indicate that our study population represented a selected group, as not all the eligible patients participated in our study and not all participants filled out the questionnaires at one-year follow-up. Some patients declined the invitation to participate because of fear for aneurysm rupture or a reduced QoL and the non-response rate was higher among patients with treatment complications. For patients undergoing preventive aneurysm occlusion we found that they initially experienced more restrictions in daily activities during recovery, but their QoL gradually improved over time. Treatment complications negatively influenced QoL outcome. The largest QoL improvement in patients without preventive treatment was seen directly after their visit to the outpatient aneurysm clinic and an increasing rupture risk negatively influenced QoL outcome. Both relief that no invasive treatment is needed as well as reassurance that the aneurysm has a low rupture risk are likely to play a role in the positive counselling effect we found.[71] Interestingly, even before the treatment decision was made at the outpatient aneurysm clinic, patients undergoing preventive treatment already experienced more restrictions and had higher levels of passive coping and anxiety than patients without preventive occlusion. These baseline differences may, at least partially, be explained by confounding by indication. Patients with larger aneurysms and a higher rupture risk are more likely to be treated. Some referring physicians may have thus already hinted towards the need for preventive occlusion, thereby introducing fear and restrictions in daily activities, including work. Alternatively, the higher levels of passive coping and reduced emotional functioning at baseline in patients with preventive aneurysm occlusion may also reflect differences in individual coping style and other psychological characteristics or personality traits between patients with and without preventive occlusion. Such factors can influence the process of decision-making, thereby introducing QoL differences at baseline and over time.[72-75] However, also after adjustment for baseline differences, we found that in patients with and without preventive aneurysm occlusion, a passive coping style was the most important predictor of a poor QoL outcome. The association between an unfavourable coping style and a poor QoL outcome has previously been described for patients with various illnesses, such as cancer, or following trauma or surgery.[75-77]

LESSONS LEARNED AND BEST PRACTICES

The projects described in chapters 2-4 offer some lessons, which I believe are worth sharing. I have summarized them in two lessons learned, accompanied by two best practices.

1. The bias "to do things as they have always been done" is powerful in medicine

In **chapters 2 and 3** of this thesis, which describe the risks of treatment complications, we decided not only to focus on severe morbidity (a modified Ranking Scale (mRS) of 3 or more) as an outcome measure, as many previous studies had done.[27, 28, 37] Instead, we also included procedural neurological complications with less severe and transient neurological deterioration because these also reduce QoL.[35, 36] In hindsight, I now realize that adopting a 'new' and broader definition for clinical complications comes with challenges. Many clinicians are taught that a score of 0-2 on the mRS, or even 0-3, is considered a "favourable functional outcome".[22, 63] Following SAH, or in the context of some clinical stroke trials, for example trials of surgical decompression in patients with space-occupying hemispheric stroke or endovascular therapy for stroke due to basilar-artery occlusion, this makes sense.[78, 79] Compared with dead or severe disability, an mRS of 2 or 3 can indeed be considered a favourable outcome. But for patients with unruptured intracranial aneurysms, who often receive treatment in an elective setting, it is questionable why an mRS of 0-2, or any new neurological deficit, is called a "favourable" outcome. Without doubt, many interventional and non-interventional aneurysm experts will agree with me that an mRS of 0-2 is not a desired outcome in this preventive context. Therefore I believe it is time to throw this established definition off its pedestal by simply avoiding the term "favourable" for any functional outcome on the mRS, both in research and clinical practice. Another step will be to create more awareness that a considerable number of patients with mRS scores of 0-2 following stroke, or a treatment complication, have unfavourable outcomes in terms of QoL and restrictions in participation.[80] Finally, I have noticed that we can make patient-related outcome measures "top of mind" by simply asking colleagues what their patient would think about this outcome or by instructing them "to think about the patient perspective" during team meetings (**panel Best practice 1**).[81]

Best practice 1 – shifting the focus away from a blame and shame culture

During some of the consensus meetings I hosted for the development of the aneurysm treatment risk scores, there was a strong tendency to search for individual causes to explain the occurrence of complications. This resulted in debates about accountability and whether complications were related to the procedure or not. Arguments such as "this stroke was not caused by the procedure but by atrial fibrillation" or "this is not a complication but an expected risk" were given as reasons not to score a complication. Such a focus on root causes of complications is common in healthcare but makes no sense from a patient's perspective. By introducing the simple instruction "to think about the patient first", I tried to shift the attention away from a blame and shame culture to a more constructive system-based approach.[81-83] Such an approach studies the underlying drivers of complications and has proven to be a more effective approach to achieve sustainable improvements for patients.[82-85]

2. Evidence-based medicine (EBM) is also context-based medicine

For the development of the two aneurysm treatment risk scores (**chapter 3**), I combined prior knowledge from our meta-analysis (**chapter 2**), with expert-based opinion from a team of neurosurgeons, interventional radiologists, neurologists, and clinical epidemiologists. This approach enabled me to bring together and discuss the clinical relevance and predictive performance of key factors involved in the management of unruptured intracranial aneurysms, which I believe is one of the strengths of the project. However, the different views and perspectives of the experts involved also made me realize how strong the influence of prior beliefs, opinions and context are in clinical research. No matter how hard you try to be objective, evidence-based medicine (EBM) is never only "evidence-based".[63] The historical and clinical background of a research field matter. Such a context can help identify knowledge gaps and determine clinically relevant research questions.[63] But it can also colour one's judgement. Choices of outcome definitions and the interpretation and acceptance of data may be influenced by experts who (subconsciously) believe in the benefits (or harms) of the treatments under investigation.[22, 38, 43, 45] For example, at one of the centres participating in the development of the treatment risk scores, I asked the neurosurgeons, interventional radiologists, and neurologists to independently assess all cases with potential treatment complications before I hosted a consensus meeting with the entire team. Neurosurgeons identified more complications among patients undergoing endovascular treatment and interventional radiologists identified more complications among patients undergoing clip-

ping. Neurologists were, as non-interventionalists, more consistent and precise in scoring treatment complications, something that has been described before.[44, 45] Such differences in interpretative judgement between medical specialists underscore the importance of blinded and independent outcome assessment, one of the cornerstones of modern EBM practices.[38, 45, 63] But even randomized trials are not free of subjectivity, as prior beliefs can interfere with the clinical equipoise that is needed to justify recruitment and randomization. Ignoring the context in which a trial is set up, can contribute to its failure, or result in a mismatch between research and practice.[6] Instead, I think we should acknowledge the fact that clinical research is a "complex human business" in which evidence and context are intertwined. To improve EBM's quality and clinical applicability, perhaps we should make the important role of the clinical context more visible by calling it ECBM (evidence- and context-based medicine) from now on.

Best practice 2 – creating a safe and fun learning environment

The pizza intervention

The idea to introduce some fun during the consensus meetings on treatment outcomes was born when one of the master students involved in the project came up with the brilliant suggestion to order pizzas. In a sense, the meetings we were hosting resemble morbidity and mortality (M&M) conferences in clinical practice. From such M&M meetings we know that learning can be improved by creating a physiological safe environment.[85-87] Although free breakfast, snacks and beverages were never formally assessed in a randomized trial, they have been described to facilitate the process of M&M meetings at two hospitals.[86] In hindsight, I think that the "pizza intervention" had a similar effect. It was an easy solution to create a relaxed atmosphere to discuss treatment complications with local experts.

Complication bingo

In addition, I developed bingo charts to score treatment complications to get all team members actively involved in the meetings. I decided to present not only patients with treatment complications, but also patients without complications. By shifting the focus away from a defensive debate about complications towards a broader understanding of how "things usually go right", the bingo game made the discussions not only more interactive, but also much more constructive. When such approaches are implemented in clinical research or practice, it may help multidisciplinary teams to facilitate a safe learning climate, in which teams come up with workable and creative solutions.[82-87]

FUTURE DIRECTIONS

In this thesis we sought to improve the balance between risks and benefits of preventive aneurysm occlusion. The findings described in chapters 2-4 of this thesis did not only reach its goal by generating new data that can be integrated into the process of clinical decision-making on unruptured intracranial aneurysms. Each of the studies also led to new questions and challenges, and thus goals for future research.

But before I discuss these new questions and challenges, there remains one prior question unanswered. Is any preventive aneurysm occlusion justified for patients with unruptured intracranial aneurysms in the first place? When is the evidence sufficient to answer this question?[22, 63] In a world free of prior beliefs, opinions, context, and research bureaucracy, I would probably suggest answering this question according to EBM's golden standards by performing another randomized trial of preventive aneurysm treatments versus no invasive treatment. However, after completing this thesis I doubt whether this is the best way forward. Instead, I have formulated five recommendations for future clinical research to further improve the quality and applicability of the non-randomized evidence in the field of unruptured intracranial aneurysms.

Recommendation 1 – a need for a multidisciplinary approach

First, we need guidelines for detailed and standardized recording of clinical complications and treatment risk factors to enhance the performance, analysis, interpretation, and comparability of observational studies on preventive treatments of unruptured intracranial aneurysms (chapter 2).[5, 38] Such initiatives, which have already been set up for several neurological disorders, including SAH and unruptured intracranial aneurysms, can enable international consortia of aneurysm experts to combine, update and validate individual patient data from new studies.[88-90] A greater coordination of care in multidisciplinary teams not only has the potential to improve methodological standards, but can also create better alignment between various disciplines in the research field of unruptured intracranial aneurysms, as it enables their members to learn from each other's perspectives and expertise.

Recommendation 2 – increasing the clinical impact of treatment risks

Second, our SAFETEA risk scores need external validation (chapter 3). Ideally, such validation efforts should be done in a prospective setting with extension to centres of varying treatment volume and centres in different countries and continents than the ones already included in the development data. In addition, as the clinical experience with different endovascular treatment modalities grows, further studies of high methodological quality are needed to better understand the association between advanced endovascular treatments and outcome. In the meantime, we can already evaluate the clinical impact of the SAFETEA scores on the management of unruptured intracranial aneurysms in a before-after implementation study, as we have previously done for the PHASES score.[59]

Recommendation 3 – integrating QoL in shared decision-making

Third, the differences we found in the trajectories of QoL recovery between patients with and without preventive aneurysm occlusion (chapter 4), should be integrated into clinical decision-making on unruptured intracranial aneurysms. This can be realized by adding QoL data to patient information cards or videos or by using tools that assess the needs and preferences of patients during counselling, such as the time trade-off method to assess how much QALY's a patient is willing to invest in different treatment options.[91,93] In addition, it is important to identify patients with an unfavourable coping style early following aneurysm diagnosis. By introducing a short intake questionnaire at the outpatient aneurysm clinic, the process of shared decision-making, patient guidance, and education following diagnosis may be further improved.[94] For selected patient groups, cognitive behavioural therapy may even be a promising solution.[95] Future studies should assess, ideally with a randomized study design, if such new counselling approaches can further decrease the amount of time spent with a reduced QoL and whether short-term QoL outcomes remain stable over time.[96]

Recommendation 4 – developing a clinical decision tool

Fourth, the newly generated data on treatment complications (chapters 2 and 3) and QoL outcomes (chapter 4) can be used to update and improve a previous cost-effectiveness analysis of preventive treatments of unruptured intracranial aneurysms.[7] The eventual goal will be to translate the individualized outcomes from the different modelling scenarios into a clinical decision-aid, which physicians and patients can use to illustrate how many QALY's a patient will approximately loose or gain per chosen management strategy. Similar approaches are already being used for shared decision-making about the risks and benefits of various medications, such as aspirin and statins, in the primary prevention of cardiovascular disease.[97]

Recommendation 5 – shifting the focus to non-invasive treatments

Fifth, the global incidence of SAH is declining over time and this may well be partially related to the improved targeting of modifiable risk factors such as hypertension and smoking.[98, 99] Currently, we are awaiting the results from the Prospective Randomized Open-label Trial to evaluate risk factor management in patients with Unruptured intracranial aneurysms (PROTECT-U),[100] which studies whether a treatment strategy of aspirin plus intensive blood pressure treatment reduces the risk of aneurysm rupture or growth compared with care as usual in patients who do not qualify for preventive endovascular or neurosurgical intervention. However, in the meantime, further efforts should also be directed at obtaining methodologically rigorous evidence from observational studies on the efficacy of non-invasive treatments to lower the risk of aneurysm rupture.[101]

CONCLUSIONS

Although preventive occlusion of unruptured intracranial aneurysms, either by endovascular treatment or neurosurgical treatment, can decrease the risk of SAH, both treatment modalities still carry a considerable risk of serious complications.[5] With individualized risk scores available to estimate the absolute risks of aneurysm rupture and procedural complications, we can further improve the balance between risks and benefits of preventive aneurysm occlusion.[7] These tools can be used during team meetings and shared decision-making as evidence-based background, alongside decision guidance based on expert-opinion and

patient-related outcome measures, such as QoL outcomes.[11] With the ultimate goal for future clinical practice and research to change the standard for how we approach patients with unruptured intracranial aneurysms in such a way, that the number of quality-adjusted life years for the entire patient group will eventually increase.

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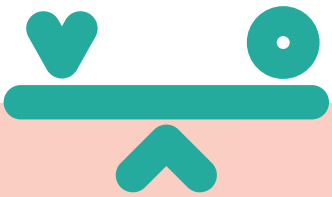
CHAPTER 6

Summary in English
Summary in Dutch (Nederlandse samenvatting)



SUMMARY IN ENGLISH

The prevalence of unruptured intracranial aneurysms is 3% in the general population. Due to the rising availability and quality of brain imaging, the number of incidentally discovered unruptured intracranial aneurysms is increasing. Rupture causes subarachnoid haemorrhage (SAH), a subset of stroke with a poor prognosis. Preventive aneurysm occlusion can reduce SAH risk, but carries a risk of serious complications. Meta-analyses published in 2012 and 2013 reported unfavourable outcomes (permanent disability or death) in approximately 7% of patients undergoing microsurgical clipping and 5% of patients undergoing endovascular aneurysm occlusion. In management decisions on unruptured intracranial aneurysms, these treatment risks need to be carefully balanced against the risk of aneurysm rupture and other individual aspects, such as quality of life (QoL) factors and life expectancy. Fear of aneurysm rupture in untreated patients can have a huge impact on QoL, but also preventive aneurysm occlusion may reduce QoL, even if no complications occur. For aneurysm rupture, the PHASES risk score has been developed to predict the absolute 5-year risk of rupture. In contrast, the estimation of treatment risks is still largely based on expert opinion. In addition, we know little about the risk factors and time-course of QoL outcomes in patients with and without preventive aneurysm occlusion.

The first part of this thesis focuses on improving the prediction of absolute procedural (30-day) complication risks of preventive neurosurgical and endovascular intracranial aneurysm occlusion. The second part of this thesis describes the quality-of-life (QoL) outcomes in patients with unruptured intracranial aneurysms. The overall aim of this thesis is to improve the balance between risks and benefits of preventive aneurysm occlusion and to increase the number of life years with high QoL in patients with unruptured intracranial aneurysms.

Chapter 2 provides the results of a systematic review and meta-analysis we performed to update the previous literature on procedural morbidity and case-fatality of preventive neurosurgical and endovascular aneurysm occlusion and to summarize all available risk factor data. Apart from studies reporting on complications resulting in permanent disability or death, we also included studies with less severe complications. In total, we included 74 studies for endovascular treatment and 54 studies for neurosurgical treatment, with 106,433 patients and 108,263 aneurysms. We found a pooled risk of 5.0% for clinical complications from any endovascular treatment, with a case-fatality rate of 0.3% and higher reported risks in patients treated with advanced endovascular methods (6.1%; 17 studies). For clipping, the overall pooled risk of treatment complications was 8.3% and the case-fatality rate was 0.1%. These risks are largely in line with previous reviews. However, due to the poor methodological quality of most studies included in our meta-analysis, it was not possible to

disentangle transient and permanent clinical complications or to perform formal time-trend analyses. In addition, most of the variation in outcomes we found between studies, regions, and treatment modalities could be explained by selection bias, case-mix variation, and differences in recording of complications. Nevertheless, based on stratified data from 64 studies, we were able to identify several patient, aneurysm, and treatment-associated risk factors, such as various cardiovascular comorbidities and aneurysm location in the posterior circulation.

Given the limitations of the available non-randomized studies on treatment complications and the lack of completed randomized trials comparing preventive aneurysm occlusion with no occlusion, we rely on other approaches to inform clinical treatment decisions. In **chapter 3**, I describe the development of two aneurysm treatment risk scores to predict the absolute risks of procedural complications from preventive endovascular (risk score 1) and neurosurgical (risk score 2) aneurysm occlusion. This study involved individual patient data from 10 participating centres in Europe, North America, and Asia where patients with unruptured intracranial aneurysms underwent primary endovascular treatment (standard coiling or an advanced endovascular treatment) or neurosurgical treatment (microsurgical clipping) between 2000 and 2018. The primary outcome was death from any cause or any neurological complication resulting in clinical deterioration within 30 days after the procedure. The overall complication risks we found in this study were substantially higher (16% for endovascular treatment and 23% for clipping) as compared with previous reviews, including our own recent meta-analysis. This can be explained by differences in outcome definitions: we also included complications that resulted in transient and non-permanent morbidity. If we restrict our analyses to death or dependency only, the risks for endovascular and neurosurgical aneurysm occlusion are comparable with previous reviews. For both the neurosurgical and the endovascular risk score, we found solid discriminatory performance, calibration, and internal validation based on seven patient, aneurysm, and treatment characteristics. The factors included in the final models are Size of aneurysm, Aneurysm location, Familial SAH, Earlier atherosclerotic disease, Treatment volume, Endovascular modality (for endovascular treatment) or Extra aneurysm configuration factors (for neurosurgical treatment), and Age (acronym: SAFETEA). For endovascular treatment the absolute 30-day complication risks range from 3% (1 point on the score) to 33% (≥6 points) and for neurosurgical treatment from 5% (1 point) to 50% (≥6 points). As the clinical experience with different endovascular treatment modalities grows, further studies are needed to better understand the association between advanced endovascular treatments and outcome. In addition, the SAFETEA risk scores need to be externally validated, ideally in centres of varying treatment volume and in different countries and continents than the ones already included in the current study. Until such studies become available, the risks and predictors described in

our study can already be used in clinical practice as evidence-based background, alongside existing decision guidance based on expert-opinion.

In **chapter 4**, the results of a prospective cohort study on the time-course and predictors of QoL outcomes in patients with unruptured intracranial aneurysms are shown. For this study, which was performed at two Dutch tertiary referral centres for aneurysm care, we sent patients standardized questionnaires about health-related QoL, anxiety and depression, coping style and participation in daily activities at several moment in the first year after aneurysm diagnosis and analysed the data with linear mixed-effects models. Of 153 eligible patients, 99 (65%) participated, of whom 30/99 (30%) underwent preventive occlusion. Patients with preventive aneurysm occlusion initially experienced more restrictions in daily activities during recovery, but their QoL gradually improved over time. The largest QoL improvement in patients without preventive occlusion was seen directly after their visit to the outpatient aneurysm clinic. Both relief that no invasive treatment is needed as well as reassurance that the aneurysm has a low rupture risk are likely to play a role in the positive counselling effect we found. Despite the different QoL trajectories for patients with and without preventive aneurysm occlusion, one-year outcomes were comparable. In fact, they returned to normal when compared with reference values from general populations. However, this may also indicate that our study population represents a selected group, as not all the eligible patients participated in our study. Finally, factors associated with worse QoL outcomes were a passive coping style in all patients, complications in patients with occlusion and higher rupture risks in patients without occlusion. These new findings on QoL risk factors and outcome should be integrated into clinical decision-making on unruptured intracranial aneurysms.

In **chapter 5**, the general discussion, I discuss the methodology, strengths, and limitations behind chapters 2, 3 and 4 in more detail. In addition, I reflect upon the projects included in this thesis by sharing two key lessons learned and two best practices. First, I describe why the bias “to do things as they have always been done” is so powerful in medicine and how we can change longstanding definitions or beliefs. Second, I argue why we should make the context of clinical research more visible in evidence-based medicine. Finally, I present five recommendations for future research to improve the quality and applicability of the evidence in the field of unruptured intracranial aneurysms.

SUMMARY IN DUTCH (NEDERLANDSE SAMENVATTING)

Intracraniële aneurysma's zijn uitstulpingen in de slagaders van de hersenen die bij 3% van de bevolking voorkomen. Door toegenomen beschikbaarheid van beeldvorming neemt het aantal bij toeval ontdekte aneurysma's toe. Als een aneurysma barst, ontstaat een subarachnoïdale bloeding (SAB), een bloeding in de ruimte tussen de hersenen en de schedel (de subarachnoïdale ruimte). SAB's treden op jonge leeftijd (gemiddeld 50 jaar) op met een hoge kans op overlijden of blijvende invaliditeit. Om barsten van aneurysma's te voorkomen kunnen ze preventief via de lies (endovasculair) of via een luik in de schedel (neurochirurgisch) worden behandeld. Bij een endovasculaire behandeling wordt een slangetje ('katheter') in de liesslagader ingebracht en opgevoerd tot bij het aneurysma in de hersenen, waarna het aneurysma van binnenuit met platina spiraaltjes ('coils') wordt opgevuld. Soms is er een geavanceerdere behandeling nodig om het aneurysma af te sluiten, dit kan bijvoorbeeld met een stent. Bij een neurochirurgische behandeling wordt het aneurysma van buitenaf met een klemmetje ('clip') afgesloten. Deze behandelingen zijn echter niet zonder risico: overzichtsartikelen uit 2012 en 2013 laten zien dat gemiddeld 7% van de preventief geclipte patiënten een ernstige complicatie krijgt en 5% van de endovasculair behandelde patiënten.

Als een intracranieel aneurysma wordt ontdekt, moeten de voordelen van een preventieve behandeling worden afgewogen tegen het risico op behandelingscomplicaties. Vergelijkende onderzoeken naar de effectiviteit en veiligheid van endovasculaire en neurochirurgische behandelingen zijn tot dusver niet haalbaar gebleken, omdat hiervoor veel patiënten lang gevolgd moeten worden en omdat het moeilijk is (voor behandelaars) om patiënten onbehandeld te laten terwijl preventieve behandelingen al veel worden toegepast in de praktijk. In dergelijke situaties zijn we aangewezen op andere vormen van wetenschappelijk bewijs om behandelbeslissingen te ondersteunen, zoals geïndividualiseerde risicoscores en beslismodellen. De PHASES risicoscore is in 2014 ontwikkeld om de kans op het barsten van een intracranieel aneurysma te voorspellen op basis van zes patiënt- en aneurysmakenmerken. De smartphone app van PHASES wordt in de klinische praktijk vaak gebruikt bij behandelbeslissingen. Zulke risicoscores zijn nog niet beschikbaar om de kans op behandelcomplicaties te voorspellen. Het risico op complicaties wordt nu nog vooral gebaseerd op meningen van deskundigen. Daarnaast is het belangrijk dat artsen en patiënten ook andere patiënt-relevante uitkomsten, zoals kwaliteit van leven, meewegen in de behandelbeslissing. Angst voor het barsten van een onbehandeld aneurysma kan een grote invloed hebben op iemands dagelijks welzijn, maar ook het herstel na een preventieve behandeling kan de kwaliteit van leven van patiënten verminderen, zelfs als er geen behandelcomplicaties zijn opgetreden. Het eerste doel

van mijn proefschrift is om meer inzicht te krijgen in het risico op geringe en ernstige complicaties van een preventieve aneurysmabehandeling, en welke factoren geassocieerd zijn met een verhoogd risico hierop. Het tweede doel van mijn proefschrift is om de kwaliteit van leven bij patiënten met en zonder een preventieve aneurysmabehandeling beter in kaart te brengen in het eerste jaar nadat een intracranieel aneurysma ontdekt is. Deze informatie is noodzakelijk om tot een beter gezamenlijk gewogen behandelbeslissing te komen, met als doel een toename van het aantal jaren in goede gezondheid voor patiënten met ongebarsten intracraniële aneurysma's.

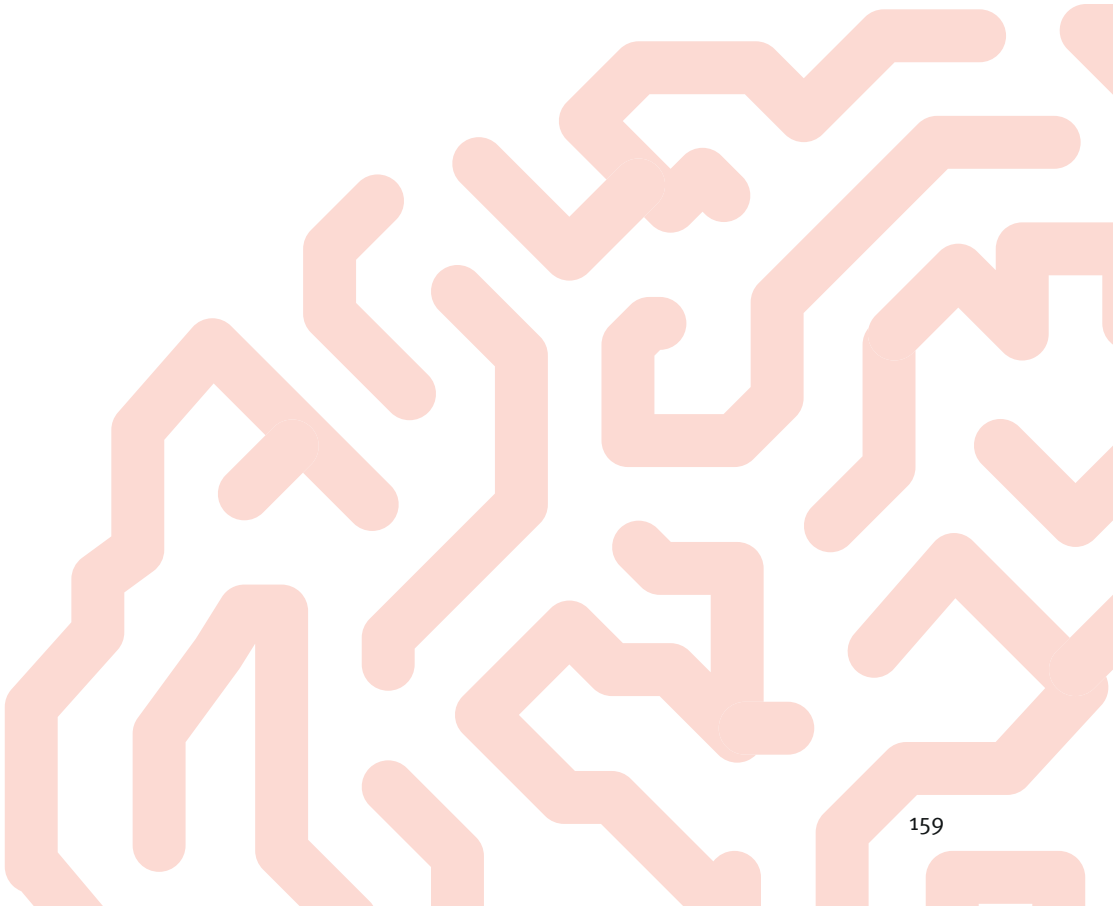
In **hoofdstuk 2** laat ik in een literatuuroverzicht zien wat de huidige behandelrisico's na preventieve endovasculaire en neurochirurgische aneurysmabehandelingen zijn en welke risicofactoren er in de literatuur worden beschreven. In dit overzicht hebben we niet alleen onderzoeken meegenomen die complicaties met zeer ernstige gevolgen (dood of afhankelijkheid van anderen) beschrijven, maar ook onderzoeken met minder ernstige complicaties. We beschrijven de resultaten van ruim honderdduizend behandelde aneurysmapatiënten uit 74 onderzoeken over endovasculaire behandeling en 54 onderzoeken over neurochirurgische behandeling. Het gemiddelde risico op een behandelcomplicatie was 5.0% bij endovasculaire behandeling, met een iets hoger risico (6.1%) na een geavanceerde endovasculaire behandeling (zoals het gebruik van een stent). Het neurochirurgische behandelrisico was 8.3%. Voor zowel endovasculaire als neurochirurgische behandeling was het risico op overlijden iets minder dan een half procent. Deze behandelrisico's komen overeen met de percentages uit eerdere onderzoeken. Helaas konden we geen onderscheid maken tussen tijdelijke en permanente behandelcomplicaties, omdat de methodologische kwaliteit van veel onderzoeken onvoldoende was. Hierdoor konden we ook niet analyseren of het risico op behandelcomplicaties in de loop van de tijd is veranderd. De regionale risicoverschillen die we vonden worden hoogstwaarschijnlijk verklaard door variatie in onderzoekspopulaties en de manier waarop complicaties per onderzoek werden geregistreerd. In sommige landen, zoals de Verenigde Staten bijvoorbeeld, kan er een financiële prikkel zijn om ziekenhuiscomplicaties nauwkeurig te rapporteren. Ook kan er onderrapportage optreden als behandelaars hun eigen complicaties publiceren. Het hogere risico bij patiënten met geavanceerde endovasculaire behandelingen kan mogelijk deels verklaard worden doordat deze patiënten complexere aneurysma's hebben. Tot slot waren er 64 onderzoeken die details over risicofactoren van complicaties rapporteerden. Door de data uit deze onderzoeken samen te nemen konden we diverse nieuwe patiënt-, aneurysma-, en behandeling-gerelateerde risicofactoren identificeren, waaronder verschillende cardiovasculaire risicofactoren en een aneurysmalocatie in de achterste hersencirculatie.

In **hoofdstuk 3** beschrijf ik hoe we met een internationaal team van aneurysma-experts twee risicoscores hebben ontwikkeld voor het voorspellen van de kans op neurologische behandelcomplicaties binnen 30 dagen na preventieve endovasculaire (risicoscore 1) en neurochirurgische (risicoscore 2) behandeling. Voor dit onderzoek hebben we individuele patiëntengegevens verzameld van patiënten met ongebarsten intracraniële aneurysma's die tussen 2000 en 2018 een preventieve endovasculaire behandeling (coiling of een geavanceerde methode) of een neurochirurgische behandeling (clippen) ondergingen in één van 10 deelnemende ziekenhuizen in Europa, Noord-Amerika en Azië. Voor alle patiënten verzamelden we details over hun aneurysma's door op hersenscans aneurysmametingen te verrichten. Voor de risicoscores keken we primair naar alle complicaties die resulteerden in nieuwe neurologische uitvalsverschijnselen of overlijden binnen 30 dagen na de preventieve aneurysmabehandeling. De behandelrisico's die we in dit onderzoek vonden waren een stuk hoger (16% voor endovasculaire behandeling en 23% voor clippen) dan de risico's beschreven in eerdere reviews, inclusief ons eigen overzichtsartikel. Dit kan verklaard worden door een verschil in definities: in hoofdstuk 3 telden we ook complicaties met tijdelijke of niet-permanente neurologische uitval mee. Als we onze analyses beperken tot de eerdere definitie van behandelcomplicaties, dat wil zeggen complicaties met dood of afhankelijkheid als gevolg, dan komen de behandelrisico's wel overeen met de eerdere reviews. Op basis van een combinatie van zeven patiënt-, aneurysma-, en behandelkenmerken kunnen we voor beide behandelingen een individuele inschatting maken van het risico op behandelcomplicaties. Het gaat om de volgende kenmerken: grootte van het aneurysma, plaats van het aneurysma, het familiair voorkomen van SAB's, slagaderverkalking in de medische voorgeschiedenis, het aantal preventieve aneurysmabehandelingen dat een ziekenhuis per jaar verricht, het type endovasculaire behandeling (alleen voor de endovasculaire score), extra aneurysmakenmerken (een bloedvat uit de hals van het aneurysma of de verhouding tussen de grootte van het aneurysma en de aneurysmahals; alleen voor de neurochirurgische score) en leeftijd. Voor endovasculaire behandeling varieert het absolute 30-dagen risico op complicaties tussen 3% (1 punt op de risicoscore) en 33% (≥6 punten). Voor neurochirurgische behandeling ligt het absolute complicatierisico tussen 5% (1 punt) en 50% (≥6 punten). Of de voorspelkracht van de risicoscores robuust blijft buiten onze onderzoekspopulatie zal nog moeten blijken. Hiervoor zijn toekomstige onderzoeken nodig die onze modellen valideren in diverse patiëntengroepen, het liefst ook in andere landen dan degene die al meededen in het huidige onderzoek en in ziekenhuizen met veel en minder ervaring met het behandelen van patiënten met ongeruptureerde intracraniële aneurysma's. In de tussentijd kunnen de absolute behandelrisico's en risicofactoren die wij beschrijven al wel als wetenschappelijke ondersteuning worden gebruikt bij behandelbeslissingen in de klinische praktijk.

Om meer te weten te komen over de kwaliteit van leven bij patiënten met een ongebarsten intracranieel aneurysma hebben we in **hoofdstuk 4** een vragenlijstonderzoek opgezet voor patiënten met en zonder preventieve aneurysmabehandelingen. Via de aneurysmaspreekuren van twee Nederlandse ziekenhuizen hebben we geschikte patiënten benaderd. Deelnemers kregen gedurende het eerste jaar na aneurysmadiagnose op vijf vaste tijdsmomenten vragenlijsten toegestuurd over kwaliteit van leven, gevoelens van angst en depressie, coping stijl (de manier waarop iemand met ziekte omgaat) en beperkingen in dagelijkse activiteiten zoals werk, huishouden en hobby's. Patiënten die een preventieve behandeling ondergingen kregen nog twee extra vragenlijsten toegestuurd in de herstelperiode na behandeling (na twee en vier weken). In totaal hebben we 153 patiënten benaderd en deden er 99 mee (65%). Dertig van de 99 patiënten (30%) onderging een preventieve aneurysmabehandeling (endovasculaire behandeling: 19 patiënten; clippen: 11 patiënten). Voor de patiënten die uiteindelijk behandeld werden gold dat ze kort na de diagnose angstiger en depressiever waren en meer beperkingen ervoeren dan patiënten die geen behandeling ondergingen. Dat kan deels verklaard worden doordat patiënten die geen behandeling ondergingen gemiddeld kleinere aneurysma's hadden met een lagere kans op barsten. Na behandeling namen de vooraf gemelde beperkingen eerst nog toe in de herstelperiode, maar daarna verbeterden alle kwaliteit van leven uitkomsten. Voor patiënten die geen preventieve behandeling ondergingen trad de grootste verbetering in kwaliteit van leven op direct na het bezoek aan het aneurysmaspreekuur, waar ze informatie en uitleg kregen over hun diagnose en samen met de arts een behandelbeslissing namen. Waarschijnlijk spreekt er een enorme geruststelling uit het bericht dat het aneurysma een lage kans heeft op barsten en dat er dus geen preventieve behandeling nodig is. Een jaar na de aneurysmadiagnose vonden we geen verschillen tussen patiënten met en zonder preventieve behandeling en waren de kwaliteit van leven scores zelfs vergelijkbaar met gemiddelden uit de algemene populatie. Een beperking van ons onderzoek is dat niet alle benaderde patiënten wilden deelnemen, soms ook omdat ze de vragenlijsten te confronterend vonden. Toch vonden we duidelijke verschillen in uitkomsten tussen de patiëntengroepen en konden we laten zien dat een ongunstige coping stijl een belangrijke voorspeller is van een verminderde kwaliteit van leven. Daarnaast hadden complicaties bij behandelde patiënten en een hoger risico op barsten bij onbehandelde patiënten ook een negatieve invloed op de uiteindelijke kwaliteit van leven. Deze nieuwe bevindingen over het beloop van kwaliteit van leven en de belangrijke voorspellende waarde van iemands individuele coping stijl moeten worden geïntegreerd in de behandelbeslissing die een arts en patiënt samen nemen op het aneurysmaspreekuur.

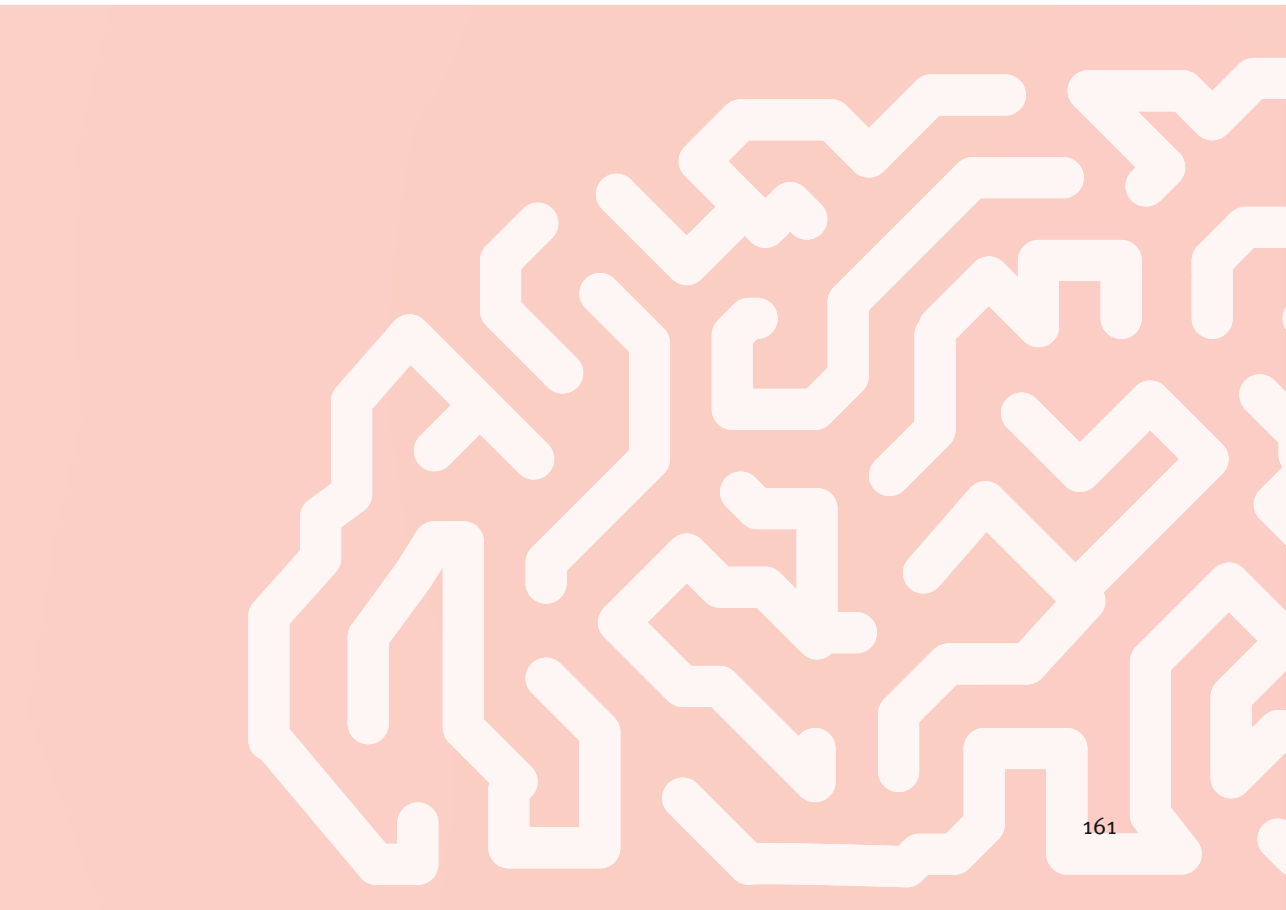
In **hoofdstuk 5**, de discussie van dit proefschrift, bespreek ik de onderzoeksmethoden, de beperkingen en de sterke punten van hoofdstuk 2, 3 en 4. Daarnaast reflecteer ik op

de projecten in dit proefschrift door twee lessen en twee praktijkervaringen te delen. Ten eerste beschrijf ik waarom de gedachte “we doen dingen zoals ze altijd al zijn gegaan” zo krachtig is in de geneeskunde en hoe we diepgewortelde definities en overtuigingen kunnen veranderen. Ten tweede beargumenteer ik waarom het belangrijk is om de klinische context van wetenschappelijk onderzoek zichtbaarder te maken in *evidence-based medicine*. Tot slot geef ik vijf aanbevelingen voor toekomstig onderzoek om de kwaliteit en toepasbaarheid van wetenschappelijk onderzoek op het terrein van ongeruptureerde intracraniële aneurysma’s te verbeteren.



APPENDICE I

Abbreviations



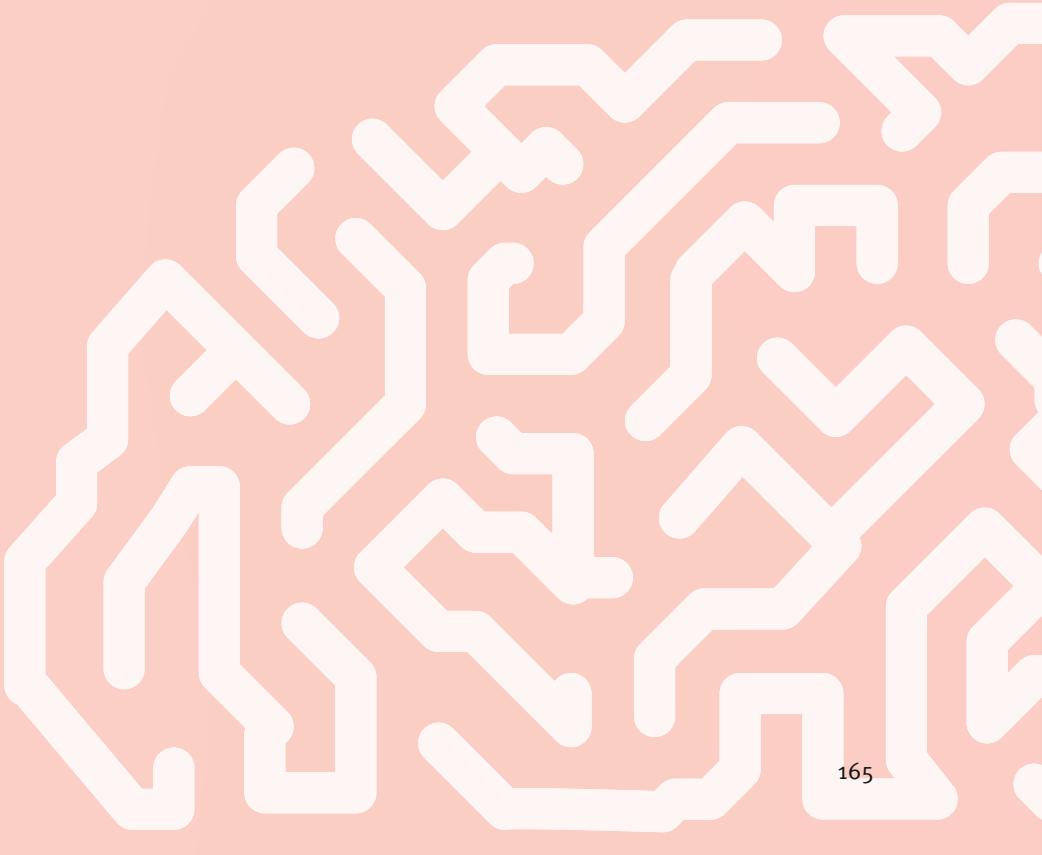
ABBREVIATIONS

ACom	Anterior communicating artery
APT	Antiplatelet therapy
BAC	Balloon-assisted coiling
CFR	Case-fatality rate
CI	Confidence interval
CURES	Collaborative UnRuptured Endovascular versus Surgery (Trail)
COPD	Chronic obstructive pulmonary disease
DNR	Dome-to-neck ratio
ECBM	Evidence- and Context Based medicine
EBM	Evidence Based Medicine
EQ-VAS	EuroQoL visual-analog scale
EQ-5D	EuroQoL 5 dimensions
EVT	Endovascular treatment
FDS	Flow-diverting stent
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related quality of life
ICA	Internal carotid artery
ICD	International Classification of Diseases
IQR	Interquartile range
ISAT	International Subarachnoid Aneurysm Trial
LUMC	Leiden University Medical Center
mRS	Modified Rankin Scale
MCA	Middle cerebral artery
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NA	Not applicable
NOS	Newcastle Ottawa Scale
NST	Neurosurgical treatment
OR	Odds ratio
PAD	Peripheral artery disease
PCom	Posterior communicating artery
PHASES	Acronym for aneurysm rupture risk score (Population, Hypertension, Age, Size of aneurysm, Earlier SAH from another aneurysm, and Site of site of aneurysm)
PICA	Posterior inferior cerebellar artery
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses

PROTECT-U	Prospective Randomized Open-label Trial to evaluate risk factor management in patients with Unruptured intracranial aneurysms
QALY	Quality-adjusted life year
QoL	Quality of life
RR	Risk ratio
SAC	Stent-assisted coiling
SAFETEA	Acronym for aneurysm treatment risk scores (Size of aneurysm, Aneurysm location, Familial subarachnoid haemorrhage, Earlier atherosclerotic disease, Treatment volume, Endovascular modality (for endovascular treatment) or Extra aneurysm configuration factors (for neurosurgical treatment; branching artery from aneurysm neck or unfavourable dome-to-neck ratio), and Age)
SAH	Subarachnoid haemorrhage
TEAM	Trial on Endovascular Aneurysm Management
TIA	Transient ischemic attack
UCAS	Japanese aneurysm rupture risk score (Unruptured Cerebral Aneurysm Study)
UCL-P	Utrecht Coping List (section on passive coping)
UIA	Unruptured intracranial aneurysm
UIATS	Unruptured intracranial aneurysm treatment score
UMCU	University Medical Center Utrecht
USER-P	Utrecht Scale for Evaluation of Rehabilitation-Participation
WEB	Woven EndoBridge

APPENDICE II

Author affiliations



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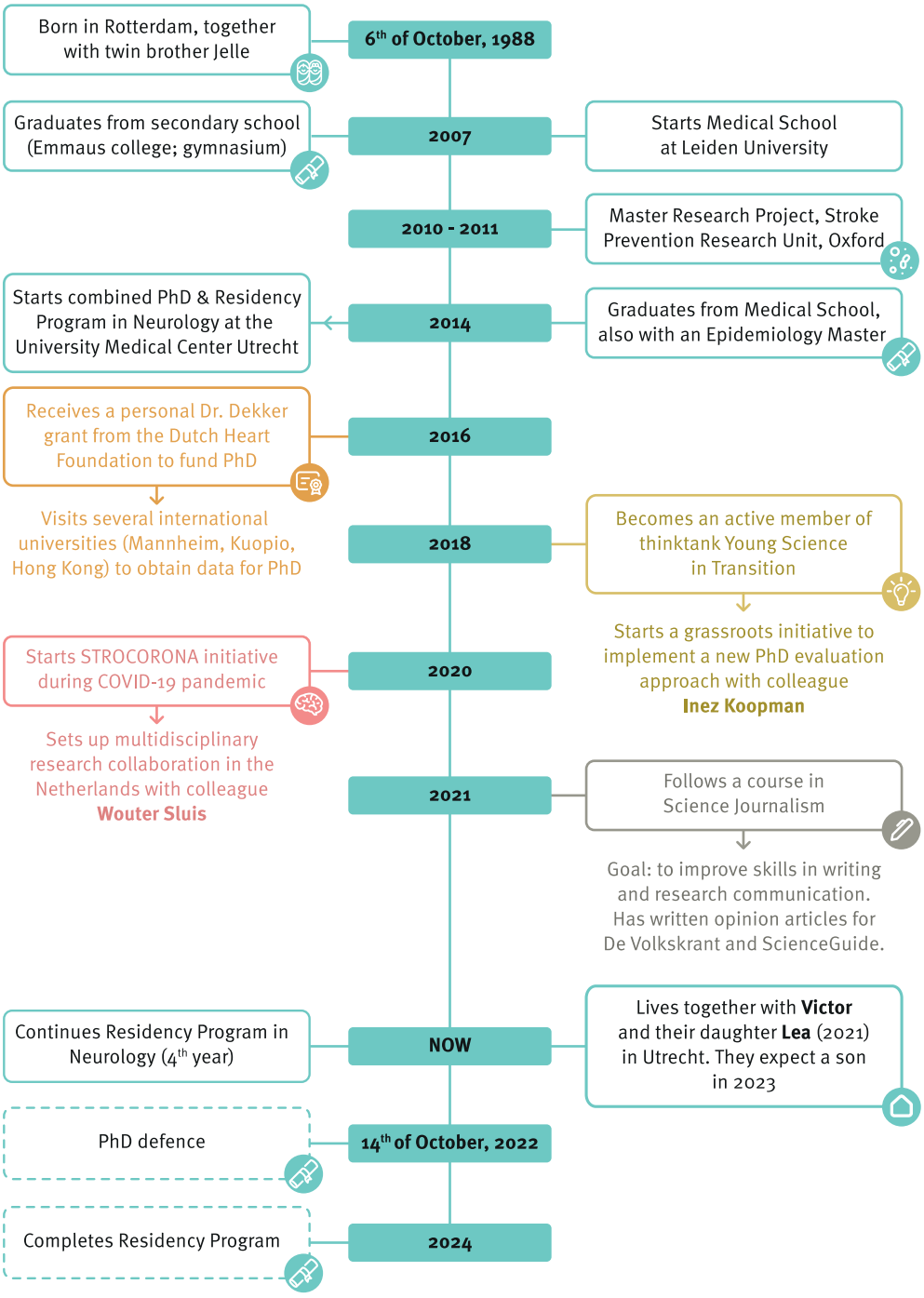
APPENDICE III

Curriculum Vitae

CURRICULUM VITAE



This is me - Annemijn Algra

Future Neurologist

Clinical Epidemiology

Stroke Research

Communication

Innovation

APPENDICE VI

Publications

PUBLICATIONS

This thesis

Quality of life outcomes over time in patients with unruptured intracranial aneurysms with and without preventive occlusion: a prospective cohort study.

Algra AM, Greving JP, Wermer MJH, van Walderveen M, van der Schaaf IC, van der Zwan A, Visser-Meily JMA, Rinkel GJE, Vergouwen MDI.

Neurology 2022; *in press*.

Development of the SAFETEA scores for predicting risks of complications of preventive endovascular or microneurosurgical intracranial aneurysm occlusion.

Algra AM, Greving GP, de Winkel J, Kurtelius A, Laban KG, Verbaan D, van den Berg R, Vandertop WP, Lindgren AE, Krings T, Woo PYM, Wong GKC, Roozenbeek B, van Es A, Dammers R, Etminan N, Boogaarts HD, van der Schaaf IC, van Doormaal TPC, van der Zwan A, Rinkel GJE, Vergouwen MDI.

Neurology 2022; *in press*.

Procedural Clinical Complications, Case-Fatality Risks, and Risk Factors in Endovascular and Neurosurgical Treatment of Unruptured Intracranial Aneurysms: A Systematic Review and Meta-analysis.

Algra AM, Lindgren A, Vergouwen MDI, Greving JP, van der Schaaf IC, van Doormaal TPC, Rinkel GJE.

JAMA Neurology 2019; **76**:282-93.

Other publications

Better science, fewer numbers. If we want to look beyond bibliometrics to evaluate success in academia, we should consider to stop listing all our publications in our CV, thesis or grant applications. To promote responsible use of bibliometrics, I have summarized my top 3 most impactful publications. Still interested in all my publications? Feel free to go to PubMed (don't forget the second initial (M) in my name) or check out my LinkedIn.

How young researchers can re-shape the evaluation of their work. Looking beyond bibliometrics to evaluate success.

Algra AM, Koopman I, Snoek R.

Nature Index. 2020. Available at: www.natureindex.com

IMPACT — Together with Inez Koopman and thinktank Young Science in Transition, I developed and implemented a new evaluation method for PhD candidates. This resulted in local and international impact. Our thinktank is now involved in several early career committees to represent young scientists in the debate how to change recognition and rewards in academia.

Risk, clinical course, and outcome of ischemic stroke in patients hospitalized with COVID-19: a multicenter cohort study.

Sluis WM, Linschoten M, Buijs JE, Biesbroek JM, den Hertog HM, Ribbers T, Nieuwkamp DJ, van Houwelingen RC, Dias A, van Uden IWM, Kerklaan JP, Bienfait HP, Vermeer SE, de Jong SW, Ali M, Wermer MJH, de Graaf MT, Brouwers PJAM, Asselbergs FW, Kappelle LJ, van der Worp HB, **Algra AM**, for the CAPACITY-COVID Collaborative Consortium.

Stroke 2021; **52**: 3978-86.

IMPACT — With the support of the Dutch Heart Foundation and several cardiology networks (including the Dutch CardioVascular Alliance), Wouter Sluis and I managed to set up a study in 16 Dutch hospitals to investigate the association between COVID-19 and ischemic stroke. This multidisciplinary collaboration underscores the importance of *Team-Science* and using the best existing networks (instead of reinventing the wheel) during a pandemic.

Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials.

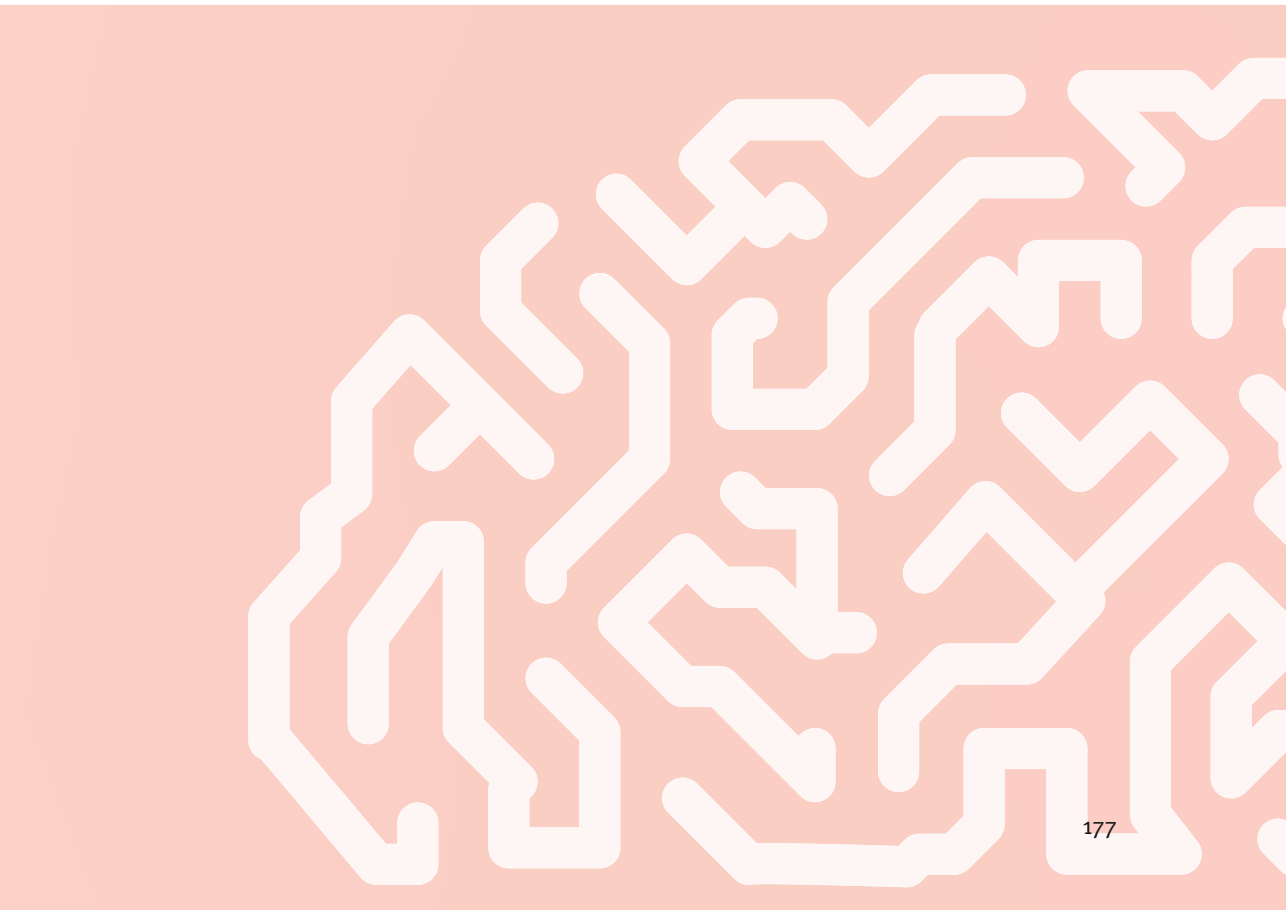
Algra AM, Rothwell PM.

Lancet Oncology 2012; **13**: 518-27.

IMPACT — This publication, which is the result of my Master Research Project in Oxford, shows that results from methodologically rigorous observational studies can be consistent with those obtained from randomised controlled trials. It is highly cited (almost 300 times) and resulted in three research prizes, media attention, changes in guidelines and an ongoing collaboration to update the evidence on this research topic.

APPENDICE V

Acknowledgements (Dankwoord)



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In dit hoofdstuk wil ik een heleboel mensen bedanken. Jullie speelden een cruciale rol bij het tot stand komen van dit proefschrift. Daarnaast zorgden jullie ervoor dat ik me in een divers en warm team tot een zelfstandig klinisch onderzoeker kon ontwikkelen. In dit hoofdstuk blik ik met veel plezier en gepaste trots terug op een leerzame en bewogen promotietijd, vol hoogte- en dieptepunten, avonturen en sterke verhalen.

Allereerst richt ik me tot de **patiënten** die deelnamen aan mijn vragenlijstonderzoek. Aan de 'inclusietelefoon' ging het me eerst vooral om het werven van zoveel mogelijk patiënten voor mijn onderzoek, maar al gauw kwam ik erachter dat *eerst* luisteren veel belangrijker is. Deelnemers die ik zo benaderde bleken veel gemotiveerder om mee te doen. De **vrijwilligers van de Hartstichting** wisten dat al. Na hun advies goed naar de zorgen en vragen van mijn doelgroep te luisteren ben ik de telefoongesprekken anders gaan voeren. Daardoor ben ik gaan inzien hoe belangrijk de context van de patiënt buiten de spreekkamer is. Ik wil alle deelnemers daarom niet alleen bedanken voor hun bijdrage aan mijn onderzoek, maar ook voor de openhartige en leerzame inclusiegesprekken.

Dit promotietraject heb ik kunnen verwezenlijken dankzij een persoonsgebonden subsidie van de **Nederlandse Hartstichting**: een Dekkerbeurs. Daar ben ik heel dankbaar voor. De Hartstichting heeft niet alleen mijn onderzoek gefinancierd, maar mij ook op andere vlakken enorm goed ondersteund. Van cursussen over maatschappelijke impact tot initiatieven om de wetenschap te verbeteren: ik kon altijd aankloppen bij het enthousiaste en warme team van de Hartstichting. Ik ga met veel plezier als referent voor de nieuwe Dekkeraanvragen aan de slag. Ook wil ik de **Koninklijke Nederlandse Akademie van Wetenschappen** van harte bedanken voor de van Leersumbeurs. Hierdoor kon ik tijdens mijn promotie op werkbezoek naar de Chinese Universiteit van Hong Kong.

Geachte **Prof. G.J.E. Rinkel**, beste **Gabriël**. Collega van Kessel schreef in haar dankwoord dat ik iemand ben met nogal wat vecht- en strijdlust die graag buiten de lijntjes kleurt. Ik ben bang dat dat klopt. Ik ben het niet altijd eens met de (on)geschreven regels. Maar mijn drang om dingen op mijn eigen manier te doen en fel te zijn over allerlei wetenschappelijke kwesties komt niet voort uit een gebrek aan bewondering of respect voor jou als promotor. Gelukkig doorzag jij dat en bood je me de ruimte om me te ontwikkelen tot een sterke en zelfstandige onderzoeker. Verder heb je me de weg gewezen in een uitdagend interventielandschap en steunde je me waar nodig. Tot slot waren jouw suggesties op mijn manuscripten altijd haarscherp. "Deze discussie is echt vermoeiend lang," schreef je eens. Inmiddels gaat er in mijn hoofd tijdens het schrijven vanzelf een belletje 'Rinkel-

en', waardoor mijn teksten korter, duidelijker en strakker worden. De Algra-stem geeft dan natuurlijk nog steeds wel een beetje tegengas: "Ik ga er toch nog lekker dit aan toevoegen". Mooi dat daar in de discussie van dit proefschrift ook echt ruimte voor was. Dank Gabriël, ik heb veel van je geleerd en vlieg vol vertrouwen uit, op zoek naar nieuwe uitdagingen in de academie.

Geachte **Dr. M.D.I. Vergouwen**, beste **Mervyn**. Iedere promovendus kent dat heerlijke gevoel nadat je een manuscript naar je promotieteam hebt opgestuurd. Eindelijk, weg ermee. Maar helaas, met jou als copromotor kun je nooit lang genieten van zo'n kleine overwinning. Ping, daar is Ver-*gauw*-en weer. Jouw snelheid van reageren is fantastisch. Daarnaast wil ik je bedanken voor je steun tijdens online vergaderingen waarin we de complicatiegetallen met de behandelaren bespraken. Vooral de besprekingen waar Gabriël niet bij was waren een aantal keer uitdagend. Waar ik mijn professionaliteit af en toe verloor, wist jij je hoofd koel te houden. Na afloop belde je me dan op en liet je me uitrazen, om me daarna nieuwe moed in te spreken. Tot slot wil ik graag een observatie met je delen. In eerste instantie dacht ik namelijk dat jij een beetje *'Old-School'* was, maar je bent eigenlijk best wel hip. Je speelde vroeger in een band, werkt als vader van vier zoons parttime, draagt buiten werk T-shirts, slippers en soms zelfs verkleedoutfits. Wat betreft de Young Sciene in Transtion activiteiten van twee van je promovendi mag je nog wel iets vooruitstrevender zijn. Maar het feit dat je al 'grapjes' maakt over *high-impact* tijdschriften betekent dat de cultuurverandering is begonnen. En dat is best wel cool vind ik.

Geachte **Dr. J.P. Greving**, beste **Jacoba**. Nog zo'n twee-bij-twee tabellen-purist. Ik kan me goed voorstellen dat je van alle principes en hoge h(umor)-index van één Algra al een significant p(unt)-hoofd krijgt. En dan nog één, *what are the odds*? Ik heb veel nieuwe dingen van je geleerd. Van het ontwikkelen van predictiemodellen, tot het doen van een *mixed-model* analyse: je wist me via epidemiologie cursussen, extra lesmateriaal en voorbeeldscripten wegwijs te maken in de materie. Die heerlijke spaghetti-plots die ik nu met R kan maken heb ik voor een groot deel aan jou te danken. Ik heb het verder ook enorm gewaardeerd dat je, ondanks je vertrek naar de huisartsgeneeskunde, toch betrokken bent gebleven als copromotor. Het is ontzettend jammer dat de cerebrovasculaire onderzoeksgroep jou kwijt is als klinisch epidemioloog. Een significant ($p<0.0001$) verlies voor ons. Hopelijk worden de banden met de klinische epidemiologie snel weer aangehaald (ik vermoed dat dat kosteneffectief zal blijken). Dankjewel Jacoba, ik vond onze samenwerking erg plezierig.

Geachte **coauteurs**, hartelijk dank voor jullie bijdragen aan de verschillende hoofdstukken van dit proefschrift. Geachte **Prof. A. van der Zwan**, **Dr. T. P. C. van Doormaal** en **Dr. I. C. van**

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Geachte **Drs. L. H. Hollands**, lieve **Laurie**. Ondanks dat onze publicatie niet in dit proefschrift is opgenomen, wil ik je toch graag uitroepen tot mijn favoriete coauteur. Het was heel leuk om jou te mogen begeleiden en om je steeds beter te leren kennen. Wat ben je toch vrolijk, gevat en lekker recht door zee. Jij eerste auteur, ik laatste, dat hebben we samen mooi voor elkaar gekregen. Leuk dat we contact hebben gehouden en met enige regelmaat kunnen terugblikken op de #prepandemie congressen, neuroborrels en dat ene assistentenweekend (als student smokkelden we je natuurlijk gewoon mee :)).

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Geachte **Prof. J.W.J. Wokke**, beste **John**. Je bent niet meer in ons midden, maar toch wil ik je graag als opleider noemen in mijn dankwoord. Ooit zei je tijdens de overdracht: "Als er nog één e-bike trauma op het ochtendrapport komt, dan schrijf ik een brief aan de krant." Als oudste coassistent hield ik je aan die uitspraak en stuurden we samen een ingezonden brief naar *De Volkskrant* over het gevaar van helmloze ouderen op (te snelle) e-bikes. Het was een cool eerste avontuur. Daarnaast wil ik je bedanken voor je steun tijdens mijn eerste opleidingsjaar, waarin ik, zonder klinische ervaring en met stress over promotiefinanciering, worstelde om mijn hoofd boven water te houden. Je stuurde me naar het St. Antonius, om even afstand te nemen van het academische. Daar ben ik je heel dankbaar voor. Tot slot heb ik genoten van de Barré-dag die ik samen met jou, **Tatjana**, **Celine**, **Annelot** en **Ellen** organiseerde in 2018. In een levendig paneldebat gingen we in discussie over de vraag of alle aios in Utrecht nog wel moeten promoveren en hoe we professionele diversiteit onder aios moeten vormgeven. Inmiddels gaat de modernisering van de opleiding in rap tempo door met Neuron 2.0, kritische beroepsactiviteiten, een nieuw e-portfolio en discipline-overstijgende thema's en profielen. Het is leuk om daar als aios deel van uit te mogen maken.

Geachte **Prof. G.J. Biessels**, beste **Geert Jan**. Inmiddels ken je de *YouTube* video van het mandje van Tichelaar ook. Onder jouw leiding heb ik geleerd om mijn boodschap lekker kort (#mand) te houden tijdens de dienst en overdrachten. In het begin werd ik behoorlijk onzeker van alle onderbrekingen (#IAmSpeaking), maar inmiddels kan ik het aan en heeft het mijn overdrachtsstijl wel strakker en beter gemaakt. Dank daarvoor. Verder vind ik het goed dat je ons als aios aanmoedigt om op tijd na te denken over onze opleidings- en toekomstplannen. Hierbij benadruk je dat het niet de bedoeling is om je promotieonderzoek in je neurologische verdiepingstijd of op een onbetaalde parttime dag af te maken. Helaas is de realiteit weerbarstig en zien velen van ons nog steeds geen andere uitweg. Hopelijk gaat dat in de toekomst echt veranderen. Misschien moeten we binnen onze divisie het nieuwe promotiereglement van de Utrechtse *Graduate School of Life Sciences* (drie publiceerbare

hoofdstukken per proefschrift) nog meer als nieuwe normaal gaan promoten? Ik zou daar erg voor zijn. **Geachte Prof. T. Seute**, beste **Tatjana**. Jij bent een opleider met visie, zeer goed ontwikkelde voelsprieten, naaldhakken, tattoos en uitstekende whisky in de kast (niet in die in het UMC). Aan het begin van de opleiding sparde ik regelmatig met je over allerlei onderwerpen en moedigde je mij aan om me vooral uit te spreken over de zin en onzin van allerlei academische carrière-hoepels. Je bent altijd heel openhartig, zorgzaam en bevlogen tijdens opleidingsgesprekken, dat waardeer ik enorm. Hou dat vast, het is je kracht. Ik hoop dat onze paden elkaar weer vaker gaan kruisen, want ik heb nog genoeg leuke plannen en ideeën voor de opleiding (en voor whiskyproeverijen :)).

Geachte **Dr. M. F. van der Meulen** en **Dr. M. H. Huisman**, beste **Marjon** en **Mark**. De eerste keer dat ik naar het St. Antonius ziekenhuis kwam in 2016 was ik een beetje lamgeslagen na mijn eerste opleidingsjaar. Maar de timide en bleue versie van mezelf verdween in het Antonius als sneeuw voor de zon en sindsdien ben ik jullie #1 Anton-ambassadeur. Bij jullie leerde ik dokter zijn, pragmatisch poli draaien en durfde ik me tijdens de overdracht steeds meer uit te spreken, ook als ik het niet zeker wist. **Marjon**, ik bewonder het enorm hoe jij alle anios en aios onder je hoede neemt, ook als ze afzwaaien naar andere specialismen. Ik twijfel er niet aan dat **Mark** over dezelfde warme en empathische opleider-kwaliteiten beschikt. Geachte **Dr. S. C. Tromp** en **Dr. A.A. Seeber**, beste **Selma** en **Antje**. De KNF-basisstage, die ik in 2021 bij jullie KNF-team deed, verdient het om in het zonnetje gezet te worden. Het bleek niet alleen een hele 'vruchtbare' stage, maar ook wederom een warm Anton-bad. Van het leerdoelengesprek met Selma tot de lol (KNF-bingo) en onderwijsmomenten met alle laboranten: het half jaar vloog voorbij. **Selma**, ik heb veel van je geleerd. Je doorzag mijn leerstijl direct en stimuleerde me op een hele fijne manier. **Antje**, wat zorg je goed voor alle KNF-aios en laboranten en wat ben je een fantastisch persoon. Mijn vriend zei ooit: je hebt het thuis steeds over Antje :). Ik heb veel bewondering voor je, dankjewel voor alle fijne (opleidings)gesprekken.

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Achter al die belangrijke bazen zitten natuurlijk nog belangrijkere mensen. **Ellen**, **Judith**, **Cora**, **Angela**, het team van het **Neurologie Trialbureau** (inclusief topper **Berber**) en alle

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Geachte **Dr. C. J. Frijns**, beste **Rinie**. Jouw passie voor de meest complexe neurologische ziektebeelden (zei iemand vasculitis?) is erg inspirerend, maar tegelijkertijd ook gevaarlijk voor mijn sluimerende *imposter* syndroom. Ik heb de afgelopen jaren veel van je geleerd. Je bent een hele warme, lieve en kundige neurologe, die altijd voor iedereen klaarstaat. Ik vond het dan ook heel terecht dat je laatst een onderwijsprijs won. Mooi dat al je inspanningen worden erkend en gewaardeerd.

Geachte **Prof. L. J. Kappelle**, beste **Jaap**. *"To interpret is to unify the practice and science of medicine."* Deze uitspraak hangt boven de bibliotheek van *The Lancet* in Londen en doet me aan jou denken. Of het nu de anamnese van de TIA-patiënt is, of een hypothese over vrouwelijke hormonen en herseninfarcten, je weet altijd de juiste vragen te stellen. Je hebt me de afgelopen jaren op een hele fijne wijze begeleid en opgeleid. Ooit zei je me dat het in een jonge carrière belangrijk is om weg te blijven van al te veel conflict. Daar heb ik me, zoals je weet, niet altijd aan gehouden. Ik buig niet altijd mee, maar dat brengt denk ik ook mooie kansen en positieve verandering. Dank dat ik altijd op jouw steun en advies heb kunnen rekenen en dat jij mij, samen met Bart, de ruimte hebt gegeven om laatste auteur te worden op het STROCORONA project.

Geachte **Prof. H. B. van der Worp**, beste **Bart**. Kon je eindelijk weer ongestoord p-waarden in baseline tabellen toevoegen, krijg je weer een Algra achter je aan. Samen met **Wouter** klopte ik aan het begin van de pandemie bij je aan met een idee voor een klein 'nevenproject'. We mochten onze gang gaan, maar je adviseerde ons ook om het klein te houden. Dat advies hebben we niet opgevolgd en met alle bescheidenheid: dat heeft ons geen windeieren gelegd. Ik blik met veel plezier terug op dit avontuur. Dankjewel voor je humor en de ruimte die je **Wouter** en mij gaf. We komen binnenkort aankloppen met een nieuw nevenproject

(wees gerust, het gaat niet over corona :)).

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Dear **Prof P. M. Rothwell**, dear **Peter**. Your profile in *The Lancet* says: "Aspirin(g) physician with a little stroke of genius." I can confirm this image, although I would probably cut the word little. But I suppose that was left in there to underscore your modesty. It has been more than a decade ago that I came to Oxford for a year, but it still fuels my enthusiasm for clinical epidemiology and research in general. Despite your busy schedule you always make the time to discuss research findings thoroughly. Your genuine curiosity, sharp observations, and patience with me (and the data), make me want to work even harder. In addition, you are a wonderful mentor, who continues to inspire me. I look forward to continuing our research collaboration and staying in touch with you and **Sarah** (and your bright **girls** :)). Dear **Dr L. Li**, dear **Linxin**. I still remember when you came to Oxford, such a long time ago! Dinners, a ball at Lincoln college, geeky aspirin jokes, Dutch cookies and more: I have plenty of warm memories. It is great to be in the PR Committee together and seeing you at least once a year during the ESOC. Dear **Dr F. Wolters**, dear **Frank**. Although we never spent time together in Oxford, we both know that 'once you come to OXVASC, you will always come back'. It is great to see how well you are doing in Rotterdam and I am sure that our paths will meet again.

Dear **Dr E. C. Sandset,** I am very happy that I got in touch with you during the online ESO-WSO Conference in 2020. Your role as Chair of the Young Stroke Physicians and Researchers committee (and your enthusiasm for #stroke on Twitter) had made me curious to meet

you. During a Zoom meeting, you were very open and supportive to me as an early career researcher and encouraged me to apply for the ESOC Department-to-Department Visit Program. Last June, when the pandemic finally allowed it, I came to visit you in Oslo. As I already wrote in my report for the ESOC: it was a very inspiring trip. From Norwegian best practices to lovely dinners and a long walk along the Oslo Fjord: I came home with a lot of new positive energy and ideas for future collaboration. Tusen tak!

Beste **collega's uit het van Geuns**, nu is het tijd om jullie te bedanken voor al die legendarische onderzoeksjaren. Van de klappie-crashcar en slapende Fransen, tot slechte hitjes, woordgrappen, kerstkaarten en dinertjes: *never a dull moment* in de toren. **Daan en Koen**, dank voor de gezellige start in Utrecht. **Rik en Jeroen**, 'the PRECIOUS-boys', voor jullie maak ik graag 'vlieguurtjes' met die (irritante) strokesemafoon. **Jeroen**, heerlijke koffie maak je; en die afkeurende blikken van jou zijn prachtig. **Rik**, jouw opmerkingen over promoveren zijn erg relativerend. En al die jaren borrelen en karaoke zingen ook. **Wilmar**, het was altijd fijn sparren (en sporten) met je. Het liefst was ik nog aan een project voor de *BMJ Christmas edition* met je begonnen. Als ik weer een gek idee heb, zal ik je zeker consulteren. **Romain**, what would you do after submitting a paper? Mais oui, a votre sante ! Just like Antti, you were an awesome international roommate. Lieve **Liselore**, voordat ik je in 2014 leerde kennen, had jij al een briefje met tips voor mijn oudste coschap achtergelaten. Zo'n warm en attent gebaar (typisch Lies, weet ik nu :)). Niet veel later werden we allebei aangenomen voor de opleiding en konden onze #goudenjaren beginnen. Het is heel leuk om zo samen met jou op te kunnen trekken als aios en SAB-mattie. Ik bewonder de manier waarop je alles altijd gewoon regelt. Je bent zo betrouwbaar, attent, bescheiden en vrolijk (#goudwaard). De tripjes op ESOC-congres en de avonturen in 'autootje 1' naar de Babinski XXL mogen van mij voor altijd doorgaan. Lies, je bent echt een topper! **Anouk**, ik smokkel je hier ook even in de van Genius alinea, dat mag best als vrolijke bijrijder van autootje 1 en fervent bezoeker van de toren. Ga zo door met je creatieve sessies en avontuurlijke *spirit*. Lieve **Emma**, jouw komst in onze toren was niet meer dan logisch. Kamergenoten zijn nu eenmaal essentieel voor een succesvolle promotietijd. Ooit redde je mij op C3-West, waar ik als oudste co net iets te snel in het diepe was geworpen. Een avondje op pad met jou hielp me er weer bovenop. Jouw aanwezigheid op de van Geuns dinertjes, meestal overigens door jou zelf georganiseerd, was niet te missen. De wijnen, de aankleding, het heerlijke eten en de escalatie: *It's totally you, darling*. Maar achter wervelwind Van Kessel schuilt ook een van de liefste, meest georganiseerde, en bevlogen collega's die ik ken. En wat je schreef in jouw dankwoord over mij (iets over rebellie), krijg je bij deze terug. Em, zonder wrijving geen glans, toch?! Lieve **Simone**, a.k.a **Floppy** (generatie "wat is een floppydisk?"). Een keurige naam, een keurig accent, een keurig University College meisje. Of toch niet? Floppy is minder onschuldig dan je denkt. De MR ASAP trial runde je als een baas, geen 'tegenslagje' kreeg jou eronder, stoïcijns

en zelfstandig ging je door. Jouw droogheid heeft je gered. **Remi**, dank voor je uitnodiging om mee te gaan naar Roemenië, samen met Simone en **Gautam**. Het was een schitterend avontuur. Af en toe een reisje, dat houdt de geest scherp. Beste **Wouter**, onze samenwerking valt denk ik het best samen te vatten in vier (ja uiteraard vier) woorden. Bier, poedersneeuw, tellen en (slechte) woordgrappen. Vanaf mijn werkplek keek ik schuin op jouw scherm uit en wist ik je met kleine grapjes of nieuwe plannetjes toch vaak wel even achter je scherm vandaan te lokken. Een van die plannen ('een klein nevenprojectje'), liep een beetje uit de hand. Mooi hoe we het halve land zijn doorgereden in het rode STROCO-autootje om data te verzamelen. Om daarna, mits de pandemie het toeliet, toch ook even op een terras neer te strijken. Jouw snelheid van werken is echt briljant, evenals je chillheid. Ik zie uit naar het volgende nevenproject met je.

Behalve de van Geuns collega's zijn er nog zoveel meer leuke collega's om te noemen. Lieve **Mirthe**, net als Em val jij in de categorie zeer hardwerkende vrouwen met veel stijl. Gaat wat mij betreft uitstekend samen. Het is altijd heerlijk om samen met je in een café te werken: koffiedrinken en daarna laptops open. We kunnen samen goed sparren over onderzoek, maar ook over zoveel meer. En die gevatte opmerkingen van jou, inclusief de alleszeggende Mirthe-blikken: blijf hier alsjeblieft mee door gaan. Lieve **Sanne**, dankjewel voor de kitelessen en gezelligheid op Ameland. Lieve **Laurien**, ooit gingen we samen naar Libanon voor vrijwilligerswerk. Dat werd een hele bijzondere reis. Lieve **Feline**, we delen een passie voor de bergen en voor zeilen. Heel leuk dat ik een weekend mee mocht varen op jouw bootje. Volgend jaar samen toerskiën? **Bart**, a.k.a. tweede jeugd, wat moeten we toch zonder jouw 'mopjes' en reddingsmissies (met schep en touw) op de Babinski. Het waren gouden tijden. **Bram,** er kan maar een koning slechte woordgrappen zijn. Mooi dat je ondanks de vele rode kaarten in de app gewoon doorgaat. Dat kan ik alleen maar toejuichen. **Henk-Jan**, je passie voor R-scripten, het R-getal en veel praten zijn legendarisch. Lieve **Hanna, Janna, Doeschka** en **Sharon**, wat was het gezellig om allemaal tegelijk met verlof te zijn. Heel fijn en dierbaar. **Han**, jij en ik zitten ook nog in een ander gezellig assistentenclubje: de weekend-cie. Met chef-de-cuisine **Sjo**, dj **Maurits** en nu ook **Greg**, **Carmen** en **Crista** inmiddels de best georganiseerde groep ooit. Gelukkig zijn er meestal maar enkele voorbereidende etentjes nodig om alle knopen door te hakken. Aan twijfelen heeft niemand iets. **Camiel**, samen met **Rik** organiseer je al jaren de tweede-vrijdag-van-de-maand borrel. Dat wordt, ondanks dat er af en toe een kleine coup door een paar vrouwelijke aios wordt gepleegd, erg gewaardeerd. Oud-collega's **Celine** en **Mark,** XXL Babinski-gangers van het eerste uur; wat een tripjes waren dat. **Celine**, wat ben je toch een fantastische vrouw. Leuk om elkaar af en toe te blijven spreken, over neurologie en meer. **Mark**, als oudste aios had jij een belangrijke rol in het organiseren van borrels (en iedereen meenemen). Wat een voorbeeldfunctie. Dit heeft zonder enige twijfel bijgedragen aan mijn kwaliteit van (promotie-)leven. **Bart Brouwers**, wat

bofte ik dat wij samen op C3-West werden ingedeeld. Het was bikkelen, maar je hield me overeind met je ervaring en gezelligheid. En wat betreft je suggestie dat **Sanjula** en ik het waarschijnlijk wel goed met elkaar zouden kunnen vinden: goed ingeschat. Het begon op de ESOC in Praag en de rest is geschiedenis.

Verder wil ik graag een aantal 'nevenproject' collega's bedanken. **Marijke**, wat een geluk dat **Wouter** en ik op de rijdende CAPACITY trein mochten stappen. Het bracht ons STROCORONA-project in stroomversnelling en leverde bovendien een mooie samenwerking tussen diverse partijen op. Je hoeft geen hoogleraar te zijn om in te zien dat dat veel slimmer is dan het wiel opnieuw uit te gaan vinden. Aan alle jonge klaren en enthousiaste perifere neurologen: dank voor jullie vertrouwen in ons project. **Mira**, ook jouw rol in deze samenwerking was cruciaal. Het bevestigde wederom wat voor leuk team jullie zijn bij de Hartstichting. **Rinze**, dank dat je Inez en mij in 2018 voor de denktank **Young Science in Transition (SiT)** vroeg. Je kunt het UMC Utrecht natuurlijk niet vergelijken met de Haagse politiek, maar als je dat wel zou doen dan ben jij zonder twijfel de allerbeste Utrechtse spindokter. Door samen actief te zijn in een denktank heb ik veel van je geleerd: van politieke correctheid tot het genereren van positieve (media) aandacht. Jouw geduld, scherpheid en inlevingsvermogen zijn bewonderenswaardig. En voor alle andere **Young SiT-ers** geldt: die gedeelde bevlogenheid geeft veel energie. Met de wind in de rug van ons eigen PhD programma (**Elly Hol** en **Geert Ramakers**), de Utrechtse *Graduate School of Life Sciences* (**Toine Egberts**, **Saskia Ebeling** en de **PhD Council**) en de landelijke "Erkennen en Waarderen" beweging komen we er wel met onze concrete verbeterprojecten. Daar heb ik het volste vertrouwen in. **Sicco**, jouw aanmoediging om gewoon te zeggen waar het op staat heeft me moediger gemaakt. Als ik het YoungSiT interview 'Een promotietraject is meer dan een paar artikelen' voor ScienceGuide teruglees, dan ben ik trots :). Het gaat om kwaliteit, niet kwantiteit. **Anne**, het valt niet te missen dat jij de zus van Emma bent: nog zo'n bevlogen en inspirerende van Kessel. Ik heb veel van je geleerd tijdens de cursus wetenschapsjournalistiek. De deadlines en leuke huiswerkopdrachten dwongen mij om minder genuanceerd en losser te schrijven. Daar ga ik in de toekomst nog veel plezier van hebben.

Lieve **Sanjula**, allerliefste **"bijna-paranimf"** op afstand. Op de ESOC in 2017 in Praag was het direct feest met jou. Ik heb nog nooit iemand ontmoet die zo succesvol en lief tegelijkertijd is. Het maakt niet uit hoe druk je bent of waar je op de wereld uithangt, er is altijd tijd voor familie, vrienden en kleine verzetjes. Ons weekje Oxford was daar het ultieme bewijs van. Verdere anekdotes en sterke verhalen passen hier niet helemaal (daar zou dit dankwoord ook echt onfatsoenlijk lang van worden), maar zijn wel zeer geschikt voor op mijn promotieborrel. Ik hoop stiekem nog steeds dat je er, ondanks je verplichtingen in het buitenland, bij kunt zijn. Dankjewel voor je steun, relativeringsvermogen en altijd

optimistische *mindset*. Waar je straks ook zit, ik kom op bezoek. Had ik trouwens al gezegd hoe trots ik op je ben?

Lieve **Inez**, allerliefste **paranimf**. Waar zal ik beginnen? De #mand versie van onze vriendschap zou alle avonturen echt te kort doen. Het is zo fijn om jou als SAB-mattie te hebben, met onze werkplekken tegenover elkaar (jouw hoofd dat even langs het scherm komt gluren) en onze promotie-overleggen direct na elkaar. Dat vraagt om geouwehoer, ongein en verwondering. Het bleek een hele vruchtbare bodem voor een mooi *grassroots* initiatief. We moderniseerden onze eigen jaarevaluatie, en inmiddels die van vele andere promovendi. Minder #publicatiehijgen en meer waardering voor andere activiteiten. In de van Genius toren vieren we die kleine succesjes allang, maar het is mooi dat daar nu ook officieel aandacht voor komt. Stel je voor, straks is het misschien wel *#evidence-based* dat promovendi blij worden van ons nieuwe evaluatieformulier. Hoe cool is dat? Dankjewel Inez, voor je kameraadschap, vriendschap en de vele gezellige dans-, borrel- en congres-avonturen. Nu je ook aios bent, gaan we daar natuurlijk gewoon nog jarenlang mee door. Dat is overigens onafhankelijk van je aios-status, want we "werken" als aios, maar "zijn" zoveel meer dan dat.

Lieve **vrienden** en **vriendinnen**, ook jullie verdienen natuurlijk een dankbetuiging. Lieve **clubgenoten**, ik vertrok als enige clubgenoot na onze Leidse tijd naar Utrecht. Allemaal kregen we het druk met nieuwe banen. Maar de clubetentjes, lustrumreizen, huwelijken en andere life events gaan vrolijk door. Met tijdens (of dankzij) corona een Boef babyboom. Lieve **Lot**, zo ongeveer vanaf de eerste dag als clubgenoten en geneeskundestudenten werkten we samen aan het nerdy Einthoven Science Project, onder de bezielende leiding van **Kees Swenne**. Al die ecg's die we scoorden en de lekkere Royksöpp hitjes die we daarbij draaiden: mooie tijden waren dat. Evenals onze vakanties naar Australië en Aussois. Lieve **Helena**, wat was het leuk dat we tegelijkertijd een jaar in Oxford zaten en dat we **Josephine** daar tegen het lijf liepen. Hard werken, maar ook genoeg tijd voor pubs, balls, etentjes, inspirerende lezingen en wandelingen door Port Maedow. Het zijn mooie herinneringen. Lieve **P**, dankjewel voor de fijne jaren op de Bankastraat. Lieve **Wen**, onze dagen samen werken (inclusief flauwe grappen tappen en filosoferen over het leven) zijn altijd heerlijk. Lieve **Izzy** en **Lara**, wat gezellig dat we elkaar (samen met de rest van de moedertjesbende) steunen als jonge werkende moeders. Werkt heel relativerend. Lieve **Marit**, we kennen elkaar al uit Leiden, maar onze nerdy vriendschap (#EBMarit) kwam daarna pas echt in stroomversnelling. Heel leuk dat we samen een artikel schreven voor Medisch Contact over professionele diversiteit in de medische opleiding (#aios #candiffer). En de etentjes met Philip en Victor, en inmiddels ook onze kleine meisjes: altijd genieten. Lieve **buren van de Savornin**, wat hebben wij een fantastische straat. We delen van alles met elkaar: van een stoep voor spontane buurtborrels tot een rode kater (onze Sjef) die praktisch bij iedereen

woont: we zijn een hechte straat. Lieve **Ron**, we missen je en hebben je voor altijd in ons Savornin-hart gesloten. **Quirijn**: de cover en vormgeving van dit proefschrift zijn prachtig geworden, dank voor je harde werk. Eerder ontwierp je ook al het geboortekaartje voor onze dochter Lea. Heel leuk om hier samen met je over te kunnen sparren. Cool dat je als buurman bij deze *life-events* betrokken bent. Lieve **Laura**, mijn beste maatje van de middelbare school. We zijn zo verschillend, maar toch ook op heel veel vlakken gelijk. We hebben veel mooie avonturen samen meegemaakt, van wilde studentenjaren tot verdriet en vreugde om een heleboel dingen. Je kent me goed en dat is heel dierbaar.

Lieve **familie**, het laatste woord richt ik tot jullie, want jullie zijn mijn warme en steunende thuisfront, in Utrecht, Rotterdam en Friesland. Lieve **mam**, in jouw proefschrift uit 1983 nam je een stelling op over de achterblijvende arbeidsparticipatie van de vrouw. Hier moest volgens jou verandering in komen. Ik heb deze stelling in dit proefschrift overgenomen. Niet alleen omdat ik super trots ben op zo'n moeder als rolmodel, maar ook omdat het helaas nog steeds een actueel probleem is. Dat jij dit in 1983 al op de agenda zette (toen aios nog ontslagen werden als ze zwanger raakten en chirurgie "echt geen beroep voor meisjes" was) is best wel gaaf. Ik realiseer me nu pas hoe knap het is wat je allemaal tegelijkertijd deed. Hoe hard en liefdevol je altijd werkte, je volledig inzette voor je patiënten en je aios, maar er ook altijd 'gewoon' was voor Jelle, pap en mij. Altijd vrolijk en met open vizier. Zonder poespas, maar met een grote Margriet-we-fixen-dit-wel-even-lach. Tenzij er onrecht is. Dat raakt je, en dat begrijp ik heel goed. Op mijn promotie heffen we samen het glas om stil te staan bij jouw prachtige carrière in de reumatologie en mijn toekomst in de neurologie, waar dat ook mag zijn. Lieve **pap**, na vele jaren blootstelling aan twee-bij-twee tabellen, verhalen over aspirientjes en dansmoves op congressen, kan ik bevestigen dat je opvoeding geslaagd is. De woordgrappen kreeg ik er als genetisch cadeautje bij :). Als 'dochter van' zijn er natuurlijk momenten van onzekerheid geweest, zeker als mensen allerlei dingen voor mij invulden. Maar als ik zie hoe geliefd jij bent in de Stroke onderzoekswereld (in je rode congresjasje), dan kan ik alleen maar ongelofelijk trots zijn. Ik heb inmiddels mijn eigen paarse en groene congresjasjes en ontwikkelde in de afgelopen jaren mijn eigen academische stijl (een beetje ongehoorzaam, maar altijd te motiveren voor een nieuw wetenschappelijk avontuur). Ik beloof je dat ik altijd mee uit dansen zal gaan met de promovendi op congres, ook als staflid. "KISS" van je dochter :). Lieve **tante Mijna**, jouw doorzettingsvermogen en passie voor de ontwikkelingsneurologie zijn een grote inspiratie voor mij. Ik bof maar met de combinatie van *nature and nurture* die mij is toebedeeld. En het AEB (Algra-Editorial-Board) gaat nog lang niet met pensioen!

Lieve **Jeannette**, ik bof met zo'n relaxte schoonmoeder en lieve beppe voor Lea. Jij bent altijd geïnteresseerd in de verhalen uit de academie en regelmatig ook 'een tikkeltje verbaasd'

over wat zich daar allemaal afspeelt. Jouw steun en nuchterheid zijn goud waard. Evenals die heerlijke tuinweekenden in Friesland. Ik voel me er helemaal thuis. Dikke tut! Lieve **Cathelijne**, we werken allebei in een wereld van modellen, alleen zijn mijn 'topmodellen' net niet strak genoeg voor de *cover* van de *Vogue*. Behalve dat je een hele knappe schoonzus bent, ben je ook heel slim, lief en chill en maak je, samen met Ritsert, heerlijke pasta (duurt wel lang). Tot slot vind ik het heel bijzonder dat je Lea's voogd bent.

Lieve **Jelle**, **tweelingbroer** en **paranimf**. Ik schreef dit dankwoord grotendeels vanuit Aussois, het bergdorp waar wij vele zomers en winters kwamen als kinderen. Ons 30-jarige tweelinglustrum vierden we dan ook daar met een week toerskiën met onze vaste berggids Simon. Veel poedersneeuw en gave beklimmingen. De Mont Blanc op toerski's staat nog steeds op mijn *bucketlist*, maar nu ik moeder van Lea ben geworden weet ik niet helemaal zeker of ik dat nog durf. Al weten Simon en jij me wel altijd door spannende etappes heen te loodsen. Heel dierbaar dat je ook tijdens mijn promotie weer aan mijn zijde staat als tweelingbroer.

Lieve **Victor**, het is eindelijk zover. Mijn proefschrift is af. Nu hoef je nooit meer te luisteren naar al mijn onderzoeksverhalen. Geintje, ik ga natuurlijk gewoon vrolijk door :). Dankjewel voor je aandacht, rust, liefde en heldere observaties. Wat is het fijn om met iemand te zijn die me altijd steunt bij tegenwind ('tegenwind doet de vlieger stijgen'), maar die me tegelijkertijd ook een spiegel voorhoudt. Ik bewonder je zelfstandigheid en doorzettingsvermogen als advocaat-ondernemer. De overstap die je recent maakte laat zien dat je weet waar je voor staat. Carrière maken met de handrem erop? Nee, bedankt. Vic, ik ben ongelofelijk trots op je. Ga zo door, ik zal je altijd steunen. En wat betreft de stelling uit het proefschrift van mijn moeder over mannen die een grotere taak in huishouding en/of gezin op zich willen nemen? Wat bof ik toch met jou. Je bent zo'n lieve, vrolijke en relaxte vader voor onze dochter **Lea**. Als ik naar jullie kijk, vergeet ik de rest van de wereld. Ik ben dol op onderzoek doen, maar nog veel doller op jullie.

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