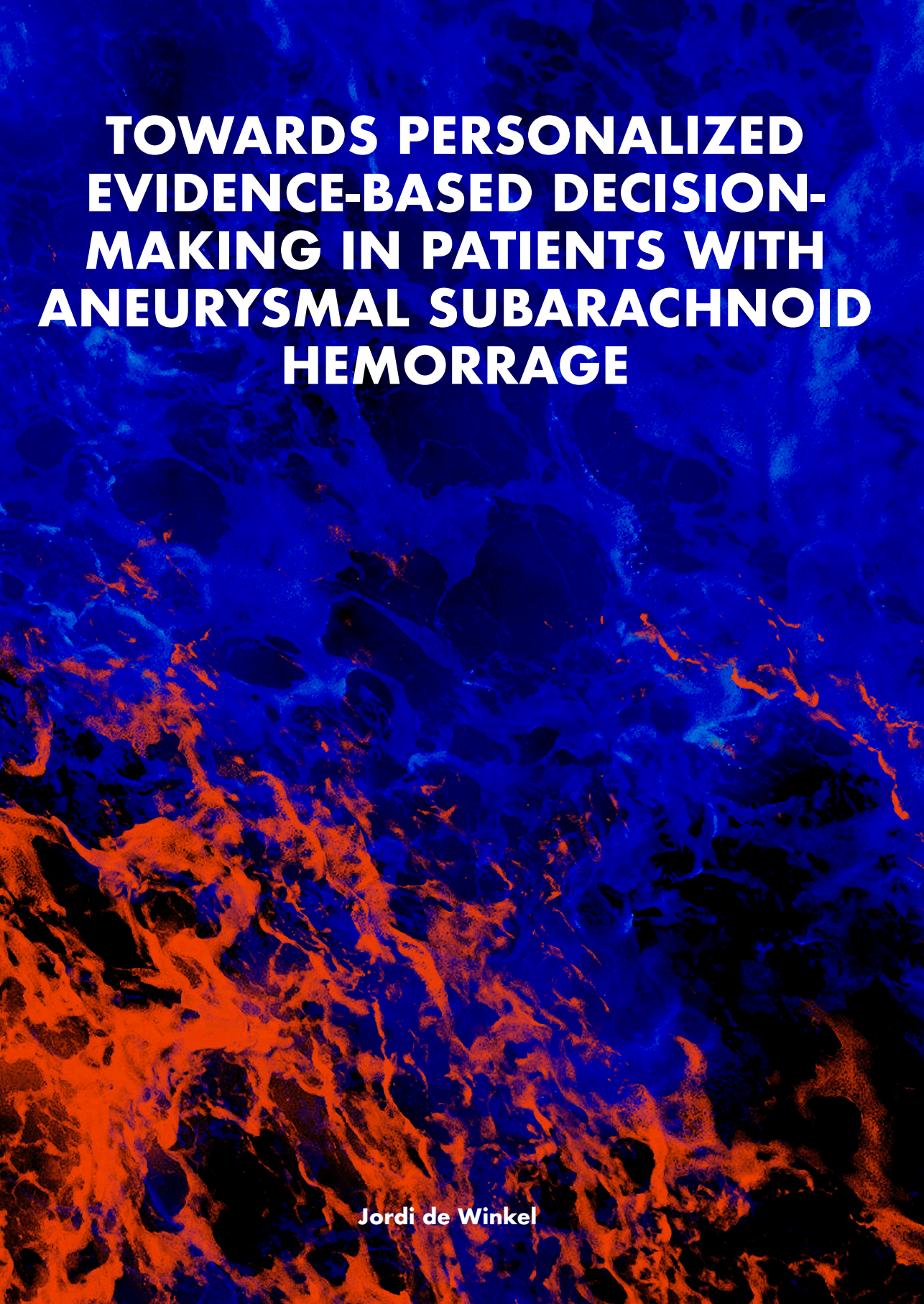
TOWARDS PERSONALIZED EVIDENCE-BASED DECISION-MAKING IN PATIENTS WITH ANEURYSMAL SUBARACHNOID HEMORRAGE



Jordi de Winkel

Towards Personalized Evidence-Based Decision-Making in Patients with Aneurysmal Subarachnoid Hemorrhage

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Richting gepersonaliseerde op wetenschappelijk bewijs berustende besluitvorming voor patiënten met een aneurysmatische subarachnoïdale bloeding

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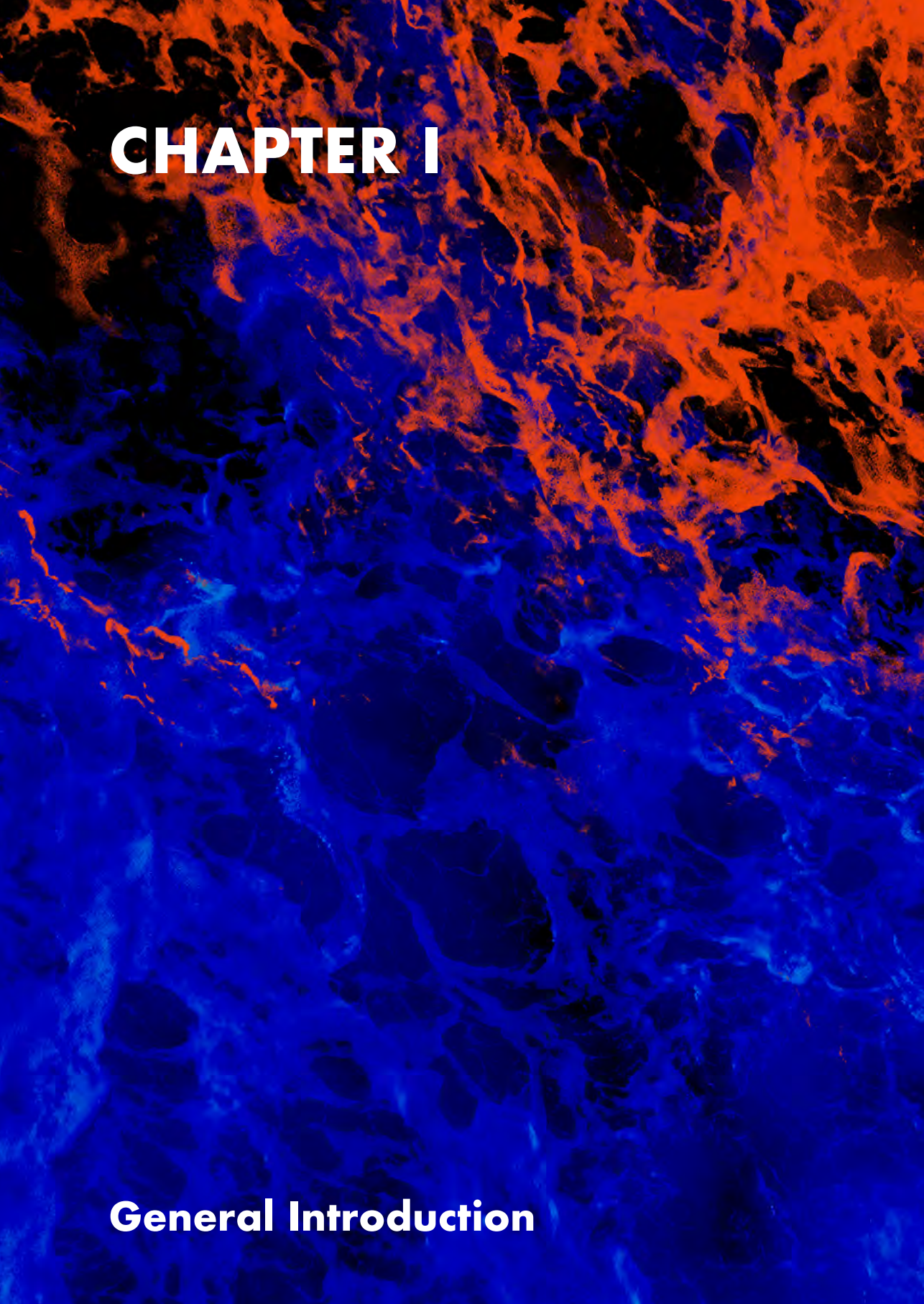
Foreword

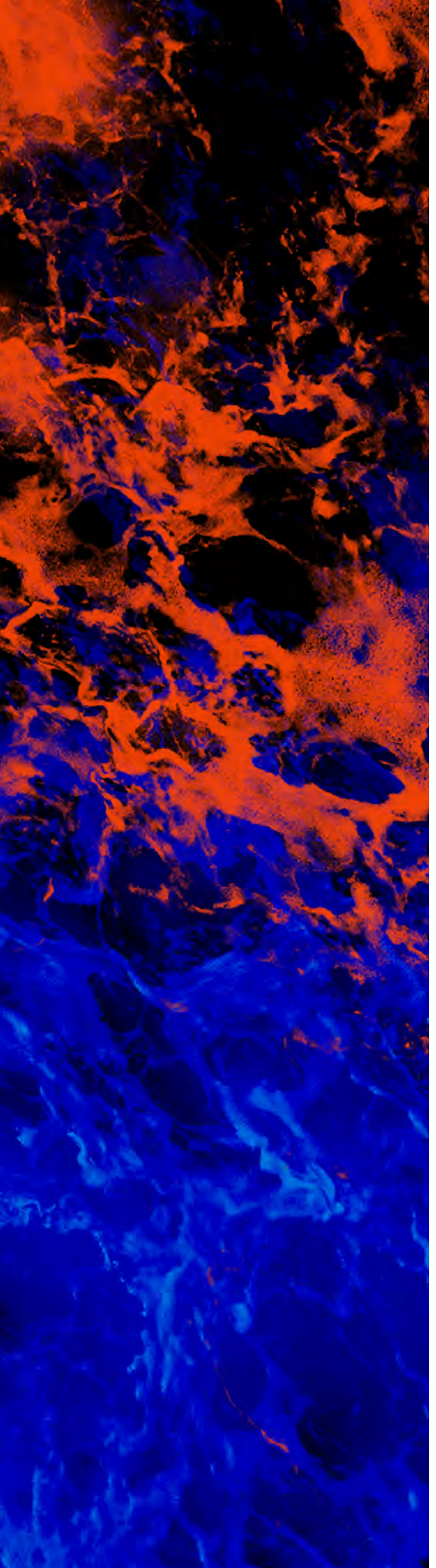
Recently, in a leading Dutch newspaper I read about the "birth month effect" (*"Wel voetbaltalent, maar in december geboren? Das pech hebben", NRC,* March 10, 2023). In short, kids born in the last quarter of the year, are less often scouted for professional soccer teams than their peers born in the first quarter. Junior soccer teams are divided by age and the "reference date" is set on January 1st. As a result, children born in December face a significant disadvantage competing with peers born in January, who are approximately one year older. Even though the birth month effect has been known since 1985 (Barnsley and Thompson, Canadian Journal of Behavioral Science) and the enormous amount of money involved in professional soccer, the effect still exists to date. The numbers speak for themselves: of the Dutch boys between 8-11 years old selected for elite squads approximately 33% were born in the first quarter of the year versus 18% in the last quarter. This remarkable difference persists. Thirty-four percent of professional players in the Eredivisie (Dutch Premier League) were born in the first quarter versus and 16% in the last quarter.

In this example, age acts as a confounder in the association of agility, height, strength, speed, et cetera with the outcome "skill". The example illustrates the need for multivariable decision-making. For humans, it is difficult to weigh each factor simultaneously and consider (potential) non-linear and additive effects. Consequently, it leads to flawed decision-making and loss of potential talent. There is a parallel with medical decision-making. Most medical decisions are also based on "expert opinion" and might be made more effectively. On the other hand, practice is usually more difficult than theory. In this thesis, I will explore personalized (multivariable) medical decision-making from root to stem and illustrate the potential benefits and the practical difficulties.



CHAPTER I

General Introduction



Subarachnoid hemorrhage

A brief introduction of terminology

Subarachnoid hemorrhage (SAH) is a bleed into the subarachnoid space that surrounds the brain. The causes of SAH can be classified as either primary or secondary. The primary variant (also referred to as spontaneous or non-traumatic SAH) is most often caused by the rupture of an intracranial aneurysm (IA). Approximately 80% of primary SAH is of aneurysmal origin, 5% is non-aneurysmal, and 10% is classified as cryptogenic, as there is no identifiable origin of the bleeding.[1,2] Non-aneurysmal SAH can be caused by other vascular malformations such as an arteriovenous malformation. In some cases, the bleeding pattern is distinctly perimesencephalic, which is a relatively benign variant of SAH. In secondary SAH, the hemorrhage is consequential to another disease, or caused by trauma. This thesis will focus on primary aSAH caused by aneurysms with a saccular configuration. Less common types of IAs, such as mycotic aneurysms, pseudo-aneurysms, fusiform aneurysms, and dissecting aneurysms, will not be discussed.

Aneurysmal subarachnoid hemorrhage in perspective

The incidence of aneurysmal subarachnoid hemorrhage (aSAH) varies geographically. For example, it is more common in Finland and Japan. The cause of this higher prevalence is still not understood.[3,4] aSAH affects women more often than men,[5] and Black people more often than Caucasian people.[6] The incidence of aSAH is 6.1-10.5 cases per 100,000 person-years,[1,7] and occurs most often in the fifth decade of life.[8,9]

Patients with SAH typically present with a sudden-onset, worst-headache-of-my-life (also called thunderclap) headache, nausea, loss of consciousness, and signs of meningeal irritation. SAH is a severe disease. Approximately one in three patients do not survive the initial bleeding and, of those that do survive, about one in five will not regain functional independence.[10] Because of this, even though aSAH is a relatively uncommon disease (approximately 1-6% of all strokes), it contributes greatly to stroke-related lost life-years.[11,12]

Diagnosis and treatment

Suspected SAH is diagnosed using computed tomography (CT) imaging or lumbar puncture with subsequent cerebrospinal fluid (CSF) analysis. In order to identify the origin of the SAH, CT angiography, digital subtraction angiography (DSA), or magnetic resonance imaging angiography (MRA) is performed.

Ideally, the care for patients with aSAH is organized in high-volume specialized stroke centers.[8] The current standard of care consists of the management of pain, blood pressure, fluids, and electrolytes, as well as the administration of nimodipine, and prophylaxis against deep venous thrombosis and seizures. Crucially, the cornerstone of aSAH management is to prevent the aneurysm from rebleeding (or rerupturing) as this is associated with high morbidity and mortality.[13] Rebleeds most frequently occur in the hours shortly after the ictus, especially within 2 to 12 hours.[14] A lot of research has focused on the optimal timing of aneurysm treatment. However, the currently available evidence is conflicting. Some studies have shown that ultra-early aneurysm treatment (within 24 hours) compared to delayed aneurysm treatment (within 1-3 days) can prevent rebleeding, but a beneficial effect on patient outcomes has not been established.[15,16] Two explanations for the lack of benefit of emergency aneurysm treatment on patient outcomes have been proposed. Firstly, the number of preventable rebleeds may be limited. Secondly, the benefit of earlier aneurysm treatment may be offset by decreased recovery of the vulnerable post-SAH brain.[17]

There are two approaches to aneurysm treatment: the endovascular and the neurosurgical aneurysm approach. Historically, patients were treated with micro-neurosurgery: a clip is placed across the neck of the aneurysm, occluding the dome. In the early 1990s, an endovascular approach to aneurysm treatment emerged.[18] In this technique, platinum coils are placed inside the dome of the aneurysm, occluding the dome by causing a thrombus to form inside of it. Currently, additional endovascular aneurysm treatment strategies exist, such as stent or balloon-assisted coiling, (intra-luminal) flow diverters, and woven-endobridge devices. However, the use of these techniques is not recommended as a first approach and varies depending on local preferences.

On an individual level, there is no consensus whether endovascular or neurosurgical aneurysm treatment leads to better patient outcomes. Several trials have investigated the safety and efficacy of endovascular versus neurosurgical aneurysm treatment.[19-22] These trials showed that, in patients who are technically and logistically amenable to endovascular and neurosurgical aneurysm treatment, endovascular treatment is preferred because of better expected functional and cognitive outcomes.[19,23] However, long-term follow-up showed that patients who were treated endovascularly had complete aneurysm occlusion less often, leading to more retreatment and rebleeding after initial aneurysm treatment.[24,25] It is not clear to what extent this affects functional outcome in the long term.[26]

International guidelines recommend discussing each aneurysm with

a multidisciplinary team and weighing factors favoring neurosurgical aneurysm treatment and endovascular aneurysm treatment on a per patient basis.[27,28] Patient characteristics favoring neurosurgical aneurysm treatment are young age, the presence of concomitant intracerebral hemorrhage, wide-necked aneurysms, giant or very small aneurysms, and middle cerebral artery aneurysms. Patients in worse clinical condition, who have vasospasm at presentation or an aneurysm located in the posterior circulation, are better suited for endovascular aneurysm treatment.[27,28]

Besides studies that focused on neurosurgical and endovascular aneurysm treatment, numerous trials were conducted on the medical management of aSAH.[29-39] These trials aimed to examine the treatment of cerebral vasospasm or pathophysiological pathways that are (thought to be) associated with delayed cerebral ischemia (DCI). DCI is a complex multifactorial process and an important predictor of poor outcome after aSAH. However, of all these trials, only the decades-old British Nimodipine Trial found that administrating nimodipine to aSAH patients effectively reduced death and disability.[31]

Practice variability

Due to the absence of high-quality evidence-based therapies, treatment decision-making is often subjective and dependent on local preferences and expertise. This has led to widespread practice variability. The existence of practice variability implies that some patients will not receive optimal treatment, although it is unclear who does and who does not.[41,42] However, practice variability also creates the potential to utilize varying center-specific treatment algorithms as an instrumental variable in comparative effectiveness research. Differences in outcome attributable to variability in treatment algorithms can serve as a stepping-stone for future randomized controlled trial development.

Individualized outcome prediction

Another strategy for improving patient outcomes is the individualization of care pathways or treatment strategies. From the moment the patient arrives at the emergency department to aneurysm treatment in the operating room or neuro-interventional angio-suite, numerous medical decisions are made. If these decisions depend on individualized estimates of outcome, they could be made more effectively. Using mathematical modeling, it is possible to predict patient outcome conditional on risk factors (also predictors, determinants, or patient characteristics). Examples of such clinical prediction models are the PHASES and the SAFETEA scores[43,44].

These scores are used to weigh the individualized estimated 5-year rupture risk against the procedural complication risk before deciding on preventive aneurysm treatment in patients with an unruptured intracranial aneurysm.

Many patient, aneurysm, and bleeding characteristics have been established that were found to be associated with functional outcome[45]. Using these variables, clinical prediction models have been developed to predict outcome in patients with aSAH.[46,47] However, at present no clear guidance exists to what extent these prognostic estimates should impact medical decision-making. Even among patients presenting in the poorest clinical condition, approximately half recover to functional independence when implementing maximum therapies.[15] This is also true for a recently developed model predicting aneurysmal rebleeding in aSAH patients.[46] It has been suggested that this model could be used to improve the selection of patients that require emergency aneurysm treatment to avoid potential rebleeding, but no formal treat-no treat threshold was defined.

Because clinical prediction models are meant to facilitate (shared) clinical decision-making, it is paramount that the prognostic estimates are valid and precise. To assess the validity and precision of the predictions of a clinical prediction model, a model needs to be externally validated. External validation is used to assess the generalizability (performance in a similar dataset) and transportability (performance in a different but related dataset) of the model. While clinical prediction models undoubtedly have great value for improving medical decision-making, this field of research is also tormented by poorly conducted research. Lacking external validation, inadequate modeling strategies, newly developed models in cases where a similar model already existed, models that do not fit the intended purpose, or models lacking software to enable clinical application are some of the contributors to research waste in prediction modeling research. Throughout this thesis, I will touch upon several of these issues.

Personalized decision-making

There is growing recognition that averaged treatment effects found in RCTs apply to the population as a whole, but are not tailored to the individual. For some study treatments, depending on individual patient characteristics, the treatment effect may be more beneficial, less beneficial, or even harmful. This principle is called heterogeneity of treatment effect (HTE). HTE is defined as *"the nonrandom variation in the magnitude or direction of a treatment effect across levels of a covariate against a clinical outcome"*.[48] Traditionally, this is investigated with subgroup analysis. The treatment effect is stratified for age, sex, or severity of disease to investigate

differences between patient groups. However, there are two downsides to this approach: by design, RCTs are underpowered to show these differences and conventional subgroup analysis investigate heterogeneity of treatment effect one variable at a time instead of multivariably.

The concept of HTE is important in the context of personalized medicine (or precision medicine). Personalized medicine refers to tailoring treatment to individual patients based on patient-specific information such as genetic information, clinical data, patient environment, and risk or prognosis. If we take into account that the average treatment effect does not hold patients with certain characteristics, how does this impact medical decision-making? A recent example of modeling for HTE is the MR PREDICTS decision tool.[49,50] This tool aimed to improve the selection of patients with acute ischemic stroke for intra-arterial treatment by predicting individual treatment benefit and avoiding futile treatments. For patients with aSAH, (evidence-based) personalized decision-making based on HTE is still unknown territory.

Hypothesis

This thesis is built on the hypothesis that to improve outcome in aSAH patients, we must shift from one-size fits all policies to individualized, evidence-based, treatment decision-making. I will examine three opportunities to help achieve this: understanding and evaluating practice variability, predicting individualized outcomes, and using individualized estimates of treatment effect. It is possible that the sparsity of evidence-based therapies has added to practice variability in the treatment of aSAH. Consequently, it is unavoidable that some patients currently receive suboptimal care. There is an opportunity to conduct comparative effectiveness research to utilize this variation, however, a contemporary overview of practice variability should be conducted first.

Secondly, in order to conduct personalized medicine it is important to know what factors determine patient outcome. After establishing this, clinical prediction models can be developed to predict outcome and guide treatment decisions on individual basis. However, if they are not developed and validated properly, using clinical prediction models can be harmful. Additionally, what to do with the risk estimates calculated with these models is usually much more opaque. What outcomes can ultimately be avoided and are thus meaningful to predict? What changes in treatment algorithms are required, and to whom do they apply?

Thirdly, in addition to predicting individualized outcomes, personalized decision-making can be further improved by modeling individualized

estimates of treatment effect. In terms of aneurysm treatment, there is a trade-off between functional outcome and durability of treatment. Is it possible to use HTE to determine the optimal strategy for individual patients? Next, how do we integrate these outcomes to overall quality-adjusted life expectancy in order to make them comparable?

Aims of this thesis

This thesis has three specific aims:

1. **To characterize international variations in treatment and organizational aspects of care that could impact outcomes in patients with aSAH.**

2. **To optimize and individualize outcome prediction for patients with aSAH.**
   - To systematically review and meta-analyze early predictors of functional outcome in poor-grade aSAH patients.
   - To externally validate the ARISE prediction models for predicting pre-interventional aneurysmal rerupture within 24 and 72 hours.
   - To illustrate the pitfalls of single-study external validation by conducting a large number of external validations of a prediction model for functional outcome in aSAH patients.

3. **To optimize and individualize treatment in patients with aneurysmal subarachnoid hemorrhage.**
   - To develop and internal-externally validate a prediction tool to predict benefit of endovascular coiling compared to neurosurgical clip-reconstruction.
   - To develop a decision model to investigate the optimal aneurysm treatment strategy for individual aSAH patients.

Data used in this thesis

- The *International Subarachnoid Aneurysm Trial* (ISAT) was an international multi-center randomized controlled trial including 2143 patients conducted from 1994-2004.[21] ISAT aimed to investigate the safety and efficacy of neurosurgical clip-reconstruction versus endovascular aneurysm coiling for patients with aSAH. Patient eligibility was based on the principle that patients had to be amenable to both endovascular coiling and neurosurgical clip-reconstruction. Patients were randomly allocated to one of the treatment strategies in a 1:1 ratio. The primary outcome was functional outcome at 12 months.

- The *SAHIT data repository* is an international registry containing individual patient data from patients with aSAH from 11 randomized controlled trials[21,30-35,51-54] and 8 observational data sources.[55-58] The repository contains data on 14000 individual patients with aSAH from North America, Europe, Asia, and Australia. The RCTs included are the Albumin in Subarachnoid Hemorrhage Trial (ALISAH), the British Aneurysm Nimodipine trial (BRANT), the Clazosentan to Overcome Neurological Ischemia and Infarction occurring after SAH trial (CONSCIOUS-I), the Acute Systemic Erythropoietin Therapy to Reduce Delayed Ischemic Deficits following SAH and the Effects of Acute Treatment with Statins on Cerebral Autoregulation in patients after SAH trials (EPO/Statin), the Heinrich Heine University Concomitant Intraventricular Fibrinolysis and Low-Frequency Rotation After Severe Subarachnoid Haemorrhage trial (HHU), the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST), the Intravenous Magnesium Sulphate for Aneurysmal Subarachnoid Haemorrhage trial (I-MASH), ISAT, the Matrix and platinum science trials (MAPS), the Tirilazad trials, the Magnesium Sulphate in Aneurysmal Subarachnoid Haemorrhage trials (MASH-I). The observational registries are the Cerebral aneurysm re-rupture after treatment (CARAT), the SAH registry of the University of Chicago, the Observational Neurocognitive Study from the University of Durham, the Hospital registry from Kurashiki Central Hospital, the University of Leeds Neurocognitive observation, the subarachnoid hemorrhage outcomes project of Columbia University (SHOP), the St Michael's Hospital registry, the Swiss study on SAH (SWISS), the University Medical Centre Utrecht SAH Registry, the dataset of subarachnoid treatment of the University of Washington.
- The *Erasmus MC Aneurysmal Subarachnoid Hemorrhage Registry* (n = 634) and *Oslo University Aneurysmal Subarachnoid Hemorrhage Registry* (n = 833) are retrospective observational cohorts with aSAH patients from the Erasmus MC University Medical Center Rotterdam from 2014 to 2020 and the Oslo University Hospital from 2013-2020.

Outline of this thesis

In **PART I**, I start by describing international practice variability in the treatment of aneurysmal subarachnoid hemorrhage (**Chapter 2**). The absence of high-quality evidence-based medicine can lead to regional and international differences in treatment algorithms and potentially less favorable patient outcomes. However, practice variability also creates possibilities to conduct comparative effectiveness research on observational

data. Secondly, I discuss a recently completed RCT investigating Flow Diverter treatment and illustrate how practice variability might have been utilized to conduct comparative effectiveness research for improving the design of this RCT.

In **PART II**, I continue with a systematic review and meta-analysis investigating early predictors of functional outcome in poor-grade aneurysmal subarachnoid hemorrhage patients (**Chapter 3**). Establishing predictors of outcome helps with accurately estimating individual patient prognosis. This can be a starting point for individualized outcome prediction. Next, I externally validate and update models predicting aneurysmal rebleeding in patients with aSAH **(Chapter 4)**, and study the pitfalls of single-study external validation **(Chapter 5)**. I also respond to a paper evaluating a neutrophil count as a risk factor for in-hospital mortality in patients with aSAH through a letter to the editor. Lastly, I wrote a reply to an opinion piece discussing a suggested paradox that clinical prediction models are rarely used in clinical practice while so many of them are developed.

In **Part III**, I develop two models: one model predicting functional outcome and one model predicting durability of treatment in patients with aSAH. These models are the basis of a web-based prediction tool to estimate the individualized treatment benefit of endovascular coiling versus neurosurgical clip-reconstruction (**Chapter 7 and Chapter 8**). Next, I develop a decision model to maximize the quality-adjusted life expectancy when choosing between endovascular coiling and neurosurgical clip-reconstruction. (**Chapter 9**). In the last chapter, I discuss the results of this thesis, provide perspective, and address possible future directions (**Chapter 10**).

References

1. Chou SH. Subarachnoid Hemorrhage. *Continuum (Minneap Minn)*. Oct 1 2021;27(5):1201-1245. doi:10.1212/CON.0000000000001052
2. van Gijn J, Rinkel GJ. Subarachnoid haemorrhage: diagnosis, causes and management. *Brain*. Feb 2001;124(Pt 2):249-78. doi:10.1093/brain/124.2.249
3. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. Jan 21 2014;129(3):e28-e292. doi:10.1161/01.cir.0000441139.02102.80
4. Linn FH, Rinkel GJ, Algra A, van Gijn J. Incidence of subarachnoid hemorrhage: role of region, year, and rate of computed tomography: a meta-analysis. *Stroke*. Apr 1996;27(4):625-9. doi:10.1161/01.str.27.4.625
5. Lindsay KW, Teasdale GM, Knill-Jones RP. Observer variability in assessing the clinical features of subarachnoid hemorrhage. *J Neurosurg*. Jan 1983;58(1):57-62. doi:10.3171/jns.1983.58.1.0057
6. Broderick JP, Brott T, Tomsick T, Huster G, Miller R. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. *N Engl J Med*. Mar 12 1992;326(11):733-6. doi:10.1056/NEJM199203123261103
7. Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. *N Engl J Med*. Jan 26 2006;354(4):387-96. doi:10.1056/NEJMra052732
8. Shea AM, Reed SD, Curtis LH, Alexander MJ, Villani JJ, Schulman KA. Characteristics of nontraumatic subarachnoid hemorrhage in the United States in 2003. *Neurosurgery*. Dec 2007;61(6):1131-7; discussion 1137-8. doi:10.1227/01.neu.0000306090.30517.ae
9. Etminan N, Chang HS, Hackenberg K, et al. Worldwide Incidence of Aneurysmal Subarachnoid Hemorrhage According to Region, Time Period, Blood Pressure, and Smoking Prevalence in the Population: A Systematic Review and Meta-analysis. *JAMA Neurol*. May 1 2019;76(5):588-597. doi:10.1001/jamaneurol.2019.0006
10. Hop JW, Rinkel GJ, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. *Stroke*. Mar 1997;28(3):660-4. doi:10.1161/01.str.28.3.660
11. Roos YB, Dijkgraaf MG, Albrecht KW, et al. Direct costs of modern treatment of aneurysmal subarachnoid hemorrhage in the first year after diagnosis. *Stroke*. Jun 2002;33(6):1595-9. doi:10.1161/01.str.0000016401.49688.2f
12. Mayberg MR, Batjer HH, Dacey R, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. Nov 1994;25(11):2315-28. doi:10.1161/01.str.25.11.2315

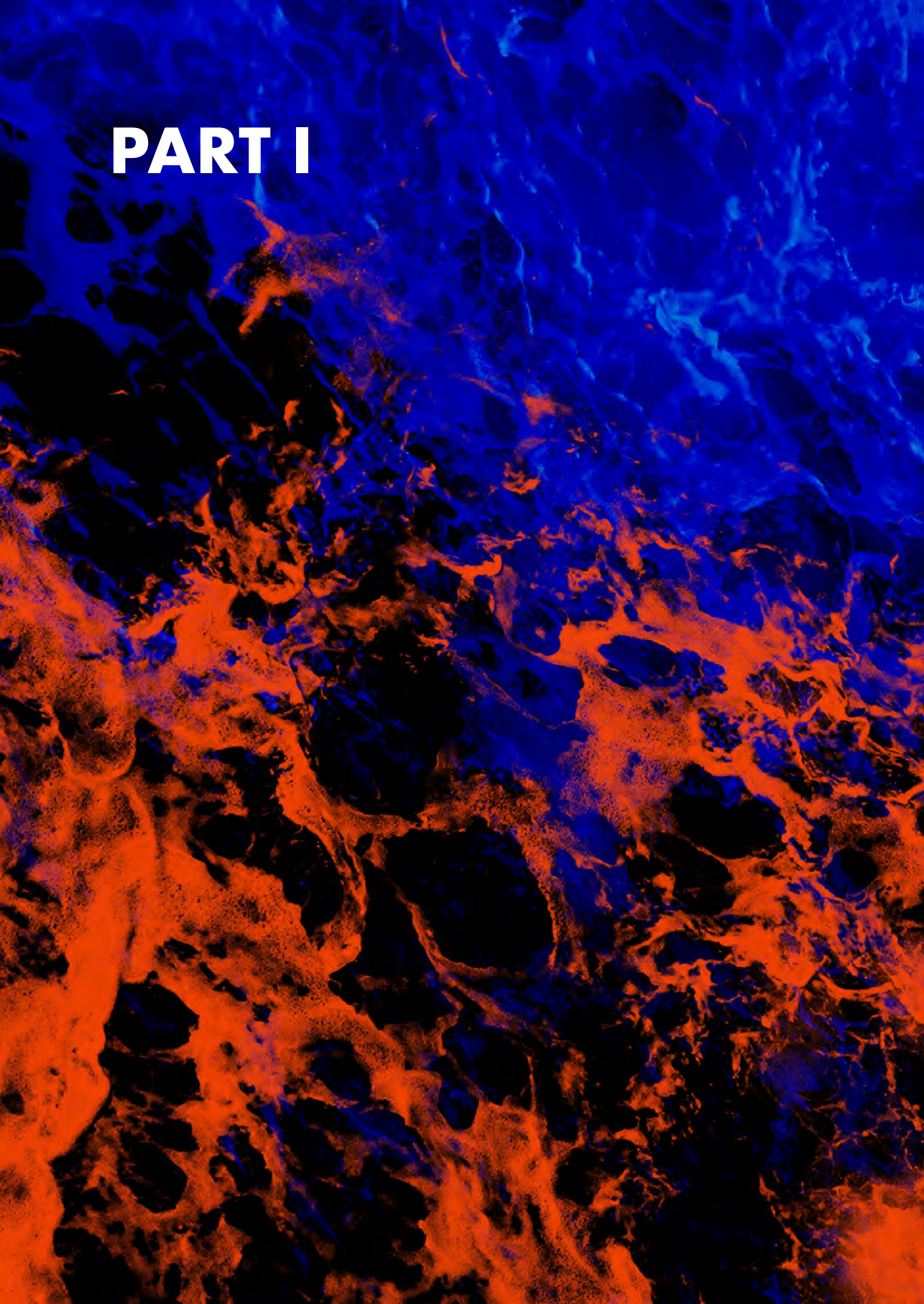
13. Lord AS, Fernandez L, Schmidt JM, et al. Effect of rebleeding on the course and incidence of vasospasm after subarachnoid hemorrhage. *Neurology*. Jan 3 2012;78(1):31-7. doi:10.1212/WNL.0b013e31823ed0a4
14. Germans MR, Coert BA, Vandertop WP, Verbaan D. Time intervals from subarachnoid hemorrhage to rebleed. *J Neurol*. Jul 2014;261(7):1425-31. doi:10.1007/s00415-014-7365-0
15. Han Y, Ye F, Long X, et al. Ultra-Early Treatment for Poor-Grade Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis. *World Neurosurg*. Jul 2018;115:e160-e171. doi:S1878-8750(18)30712-5 [pii]10.1016/j.wneu.2018.03.219
16. Rawal S, Alcaide-Leon P, Macdonald RL, et al. Meta-analysis of timing of endovascular aneurysm treatment in subarachnoid haemorrhage: inconsistent results of early treatment within 1 day. *J Neurol Neurosurg Psychiatry*. Mar 2017;88(3):241-248. doi:10.1136/jnnp-2016-314596
17. Oudshoorn SC, Rinkel GJ, Molyneux AJ, et al. Aneurysm treatment <24 versus 24-72 h after subarachnoid hemorrhage. *Neurocrit Care*. Aug 2014;21(1):4-13. doi:10.1007/s12028-014-9969-8
18. Guglielmi G, Vinuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: Preliminary clinical experience. *J Neurosurg*. Jul 1991;75(1):8-14. doi:10.3171/jns.1991.75.1.0008
19. Darsaut TE, Raymond J. Barrow ruptured aneurysm trial. *J Neurosurg*. Aug 2012;117(2):378-9; author reply 379-80. doi:10.3171/2011.12.JNS112279
20. Koivisto T, Vanninen R, Hurskainen H, Saari T, Hernesniemi J, Vapalahti M. Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms. A prospective randomized study. *Stroke*. Oct 2000;31(10):2369-77. doi:10.1161/01.str.31.10.2369
21. Molyneux A, Kerr R, International Subarachnoid Aneurysm Trial Collaborative G, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized trial. *J Stroke Cerebrovasc Dis*. Nov-Dec 2002;11(6):304-14. doi:10.1053/jscd.2002.130390
22. Vanninen R, Koivisto T, Saari T, Hernesniemi J, Vapalahti M. Ruptured intracranial aneurysms: acute endovascular treatment with electrolytically detachable coils--a prospective randomized study. *Radiology*. May 1999;211(2):325-36. doi:10.1148/radiology.211.2.r99ap06325
23. Molyneux AJ, Kerr RS, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet*. Sep 3-9 2005;366(9488):809-17. doi:10.1016/S0140-6736(05)67214-5

24. Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RS. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). *Lancet*. Feb 21 2015;385(9969):691-7. doi:10.1016/S0140-6736(14)60975-2
25. Spetzler RF, McDougall CG, Zabramski JM, et al. Ten-year analysis of saccular aneurysms in the Barrow Ruptured Aneurysm Trial. *J Neurosurg*. Mar 8 2019;132(3):771-776. doi:10.3171/2018.8.JNS181846
26. Campi A, Ramzi N, Molyneux AJ, et al. Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in the International Subarachnoid Aneurysm Trial (ISAT). *Stroke*. May 2007;38(5):1538-44. doi:10.1161/STROKEAHA.106.466987
27. Connolly ES, Jr., Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. *Stroke*. Jun 2012;43(6):1711-37. doi:10.1161/STR.0b013e3182587839
28. Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis*. 2013;35(2):93-112. doi:10.1159/000346087
29. Jang YG, Ilodigwe D, Macdonald RL. Metaanalysis of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2009;10(1):141-7. doi:10.1007/s12028-008-9147-y
30. Macdonald RL, Kassell NF, Mayer S, et al. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. *Stroke*. Nov 2008;39(11):3015-21. doi:10.1161/STROKEAHA.108.519942
31. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *BMJ*. Mar 11 1989;298(6674):636-42. doi:10.1136/bmj.298.6674.636
32. Tseng MY, Hutchinson PJ, Richards HK, et al. Acute systemic erythropoietin therapy to reduce delayed ischemic deficits following aneurysmal subarachnoid hemorrhage: a Phase II randomized, double-blind, placebo-controlled trial. Clinical article. *J Neurosurg*. Jul 2009;111(1):171-80. doi:10.3171/2009.3.JNS081332
33. Tseng MY, Hutchinson PJ, Turner CL, et al. Biological effects of acute pravastatin treatment in patients after aneurysmal subarachnoid hemorrhage: a double-blind, placebo-controlled trial. *J Neurosurg*. Dec 2007;107(6):1092-100. doi:10.3171/JNS-07/12/1092

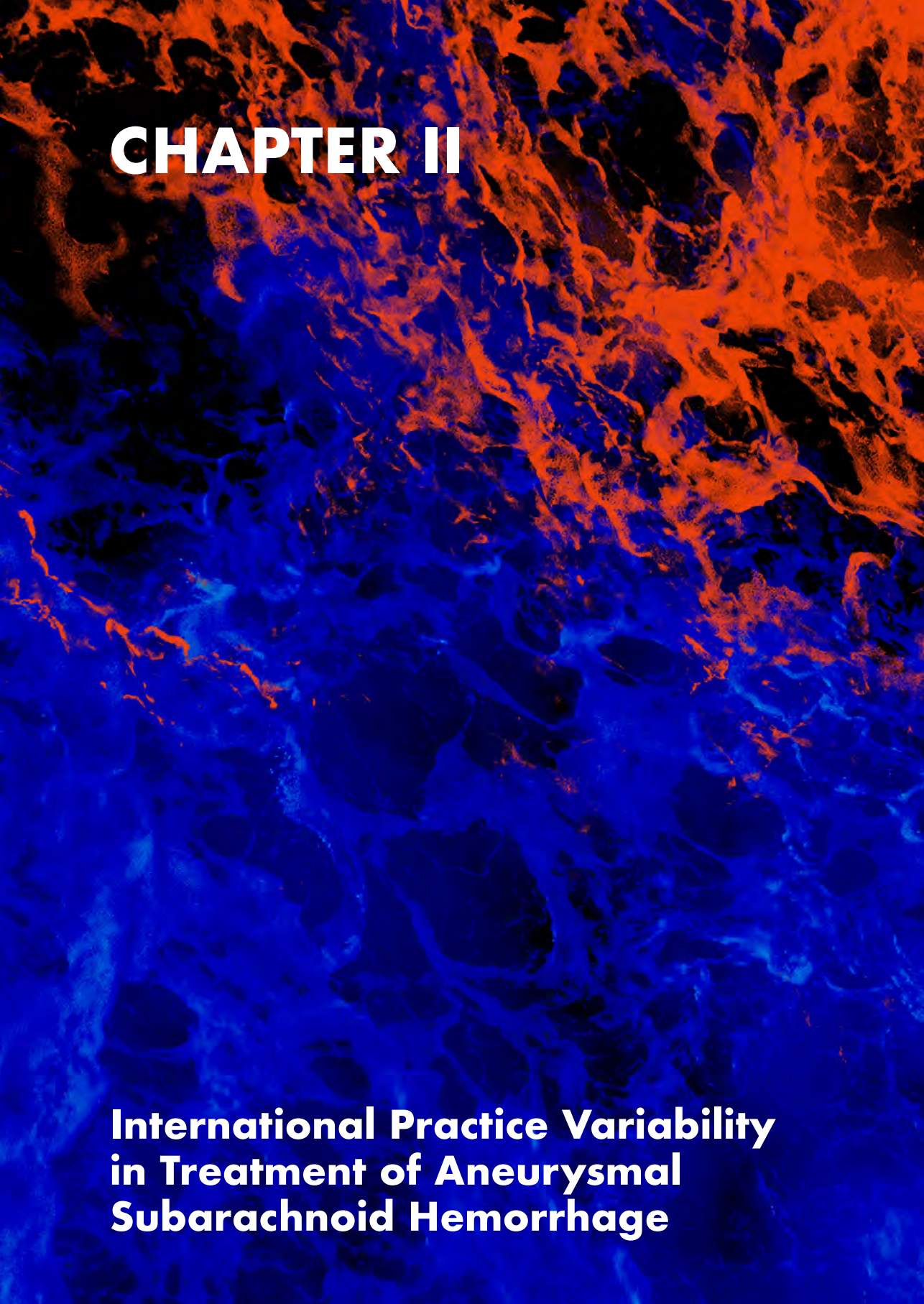
34. van den Bergh WM, Algra A, van Kooten F, et al. Magnesium sulfate in aneurysmal subarachnoid hemorrhage: a randomized controlled trial. *Stroke*. May 2005;36(5):1011-5. doi:10.1161/01.STR.0000160801.96998.57
35. Wong GK, Poon WS, Chan MT, et al. Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage (IMASH): a randomized, double-blinded, placebo-controlled, multicenter phase III trial. *Stroke*. May 2010;41(5):921-6. doi:10.1161/STROKEAHA.109.571125
36. Dorhout Mees SM, Algra A, Vandertop WP, et al. Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. *Lancet*. Jul 7 2012;380(9836):44-9. doi:10.1016/S0140-6736(12)60724-7
37. Haley EC, Jr., Kassell NF, Torner JC. A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. *J Neurosurg*. Apr 1993;78(4):537-47. doi:10.3171/jns.1993.78.4.0537
38. Haley EC, Jr., Kassell NF, Torner JC. A randomized trial of nicardipine in subarachnoid hemorrhage: angiographic and transcranial Doppler ultrasound results. A report of the Cooperative Aneurysm Study. *J Neurosurg*. Apr 1993;78(4):548-53. doi:10.3171/jns.1993.78.4.0548
39. Macdonald RL, Hanggi D, Ko NU, et al. NEWTON-2 Cisternal (Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage): A Phase 2, Multicenter, Randomized, Open-Label Safety Study of Intracisternal EG-1962 in Aneurysmal Subarachnoid Hemorrhage. *Neurosurgery*. Dec 15 2020;88(1):E13-E26. doi:10.1093/neuros/nyaa430
40. Wolf S, Mielke D, Barner C, et al. Effectiveness of Lumbar Cerebrospinal Fluid Drain Among Patients With Aneurysmal Subarachnoid Hemorrhage: A Randomized Clinical Trial. *JAMA Neurol*. Jun 18 2023;doi:2806583 [pii]noi230038 [pii]10.1001/jamaneurol.2023.1792
41. Sakowitz OW, Raabe A, Vucak D, Kiening KL, Unterberg AW. Contemporary management of aneurysmal subarachnoid hemorrhage in germany: results of a survey among 100 neurosurgical departments. *Neurosurgery*. Jan 2006;58(1):137-45; discussion 137-45. doi:00006123-200601000-00015 [pii]10.1227/01.neu.0000194532.47239.7c
42. Velly LJ, Bilotta F, Fabregas N, et al. Anaesthetic and ICU management of aneurysmal subarachnoid haemorrhage: a survey of European practice. *Eur J Anaesthesiol*. Mar 2015;32(3):168-76. doi:10.1097/EJA.0000000000000163
43. Algra AM, Greving JP, de Winkel J, et al. Development of the SAFETEA Scores for Predicting Risks of Complications of Preventive Endovascular or Microneurosurgical Intracranial Aneurysm Occlusion. *Neurology*. Sep 2 2022;doi:10.1212/WNL.0000000000200978

44. Greving JP, Wermer MJ, Brown RD, Jr., et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol*. Jan 2014;13(1):59-66. doi:10.1016/S1474-4422(13)70263-1
45. Jaja BN, Cusimano MD, Etminan N, et al. Clinical prediction models for aneurysmal subarachnoid hemorrhage: a systematic review. *Neurocrit Care*. Feb 2013;18(1):143-53. doi:10.1007/s12028-012-9792-z
46. van Lieshout JH, Mijderwijk HJ, Nieboer D, et al. Development and Internal Validation of the ARISE Prediction Models for Rebleeding After Aneurysmal Subarachnoid Hemorrhage. *Neurosurgery*. Sep 1 2022;91(3):450-458. doi:00006123-202209000-00011 [pii]10.1227/neu.0000000000002045
47. Jaja BNR, Saposnik G, Lingsma HF, et al. Development and validation of outcome prediction models for aneurysmal subarachnoid haemorrhage: the SAHIT multinational cohort study. *BMJ*. Jan 18 2018;360:j5745. doi:10.1136/bmj.j5745
48. Kent DM, Paulus JK, van Klaveren D, et al. The Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement. *Ann Intern Med*. Jan 7 2020;172(1):35-45. doi:10.7326/M18-3667
49. Venema E, Mulder M, Roozenbeek B, et al. Selection of patients for intra-arterial treatment for acute ischaemic stroke: development and validation of a clinical decision tool in two randomised trials. *BMJ*. May 3 2017;357:j1710. doi:10.1136/bmj.j1710
50. Venema E, Roozenbeek B, Mulder M, et al. Prediction of Outcome and Endovascular Treatment Benefit: Validation and Update of the MR PREDICTS Decision Tool. *Stroke*. Aug 2021;52(9):2764-2772. doi:10.1161/STROKEAHA.120.032935
51. Etminan N, Beseoglu K, Eicker SO, Turowski B, Steiger HJ, Hanggi D. Prospective, randomized, open-label phase II trial on concomitant intraventricular fibrinolysis and low-frequency rotation after severe subarachnoid hemorrhage. *Stroke*. Aug 2013;44(8):2162-8. doi:10.1161/STROKEAHA.113.001790
52. McDougall CG, Johnston SC, Gholkar A, et al. Bioactive versus bare platinum coils in the treatment of intracranial aneurysms: the MAPS (Matrix and Platinum Science) trial. *AJNR Am J Neuroradiol*. May 2014;35(5):935-42. doi:10.3174/ajnr.A3857
53. Suarez JI, Martin RH, Calvillo E, et al. The Albumin in Subarachnoid Hemorrhage (ALISAH) multicenter pilot clinical trial: safety and neurologic outcomes. *Stroke*. Mar 2012;43(3):683-90. doi:10.1161/STROKEAHA.111.633958
54. Todd MM, Hindman BJ, Clarke WR, Torner JC, Intraoperative Hypothermia for Aneurysm Surgery Trial I. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med*. Jan 13 2005;352(2):135-45. doi:10.1056/NEJMoa040975

55. Helbok R, Kurtz P, Vibbert M, et al. Early neurological deterioration after subarachnoid haemorrhage: risk factors and impact on outcome. *J Neurol Neurosurg Psychiatry*. Mar 2013;84(3):266-70. doi:10.1136/jnnp-2012-302804
56. Johnston SC, Dowd CF, Higashida RT, et al. Predictors of rehemorrhage after treatment of ruptured intracranial aneurysms: the Cerebral Aneurysm Rerupture After Treatment (CARAT) study. *Stroke*. Jan 2008;39(1):120-5. doi:10.1161/STROKEAHA.107.495747
57. Reilly C, Amidei C, Tolentino J, Jahromi BS, Macdonald RL. Clot volume and clearance rate as independent predictors of vasospasm after aneurysmal subarachnoid hemorrhage. *J Neurosurg*. Aug 2004;101(2):255-61. doi:10.3171/jns.2004.101.2.0255
58. Schatlo B, Fung C, Fathi AR, et al. Introducing a nationwide registry: the Swiss study on aneurysmal subarachnoid haemorrhage (Swiss SOS). *Acta Neurochir (Wien)*. Dec 2012;154(12):2173-8; discussion 2178. doi:10.1007/s00701-012-1500-4

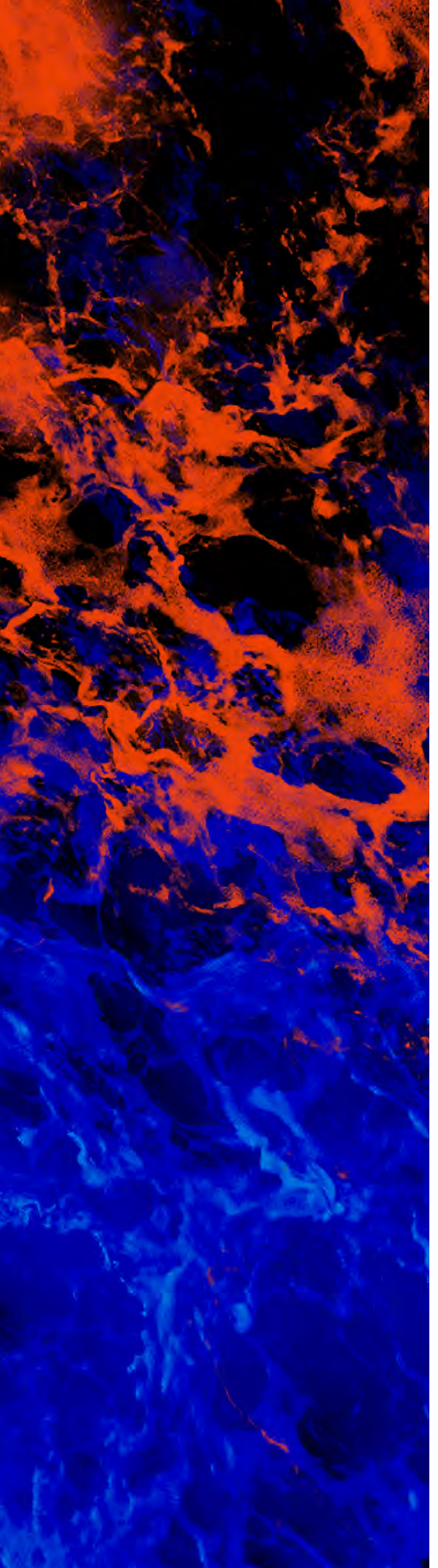

PART I


Characterizing
Practice Variability



CHAPTER II

International Practice Variability in Treatment of Aneurysmal Subarachnoid Hemorrhage



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Jordi de Winkel, Mathieu van der Jagt, Hester F Lingsma, Bob Roozenbeek, Eusebia Calvillo, Sherry H-Y Chuo, Peter H Dziedzic, Nima Etminan, Judy Huang, Nerissa U Ko, Robert Loch Macdonald, Renee L Martin, Niteesh R Potu, Chetan P Venkatasubba Rao, Mervyn DI Vergouwen, and Jose I Suarez.

Abstract

Introduction: Prior research suggests substantial between-center differences in functional outcome following aneurysmal subarachnoid hemorrhage (aSAH). One hypothesis is that these differences are due to practice variability.

Methods and analysis: To characterize practice variability, we sent a survey to 230 centers, of which 145 (63%) responded. Survey respondents indicated that an estimated 65% of ruptured aneurysms were treated endovascularly. Sixty-five percent of aneurysms were treated within 24 h of symptom onset, 18% within 24–48 h, and eight percent within 48–72 h. Centers in the United States (US) and Europe (EU) treat aneurysms more often endovascularly (72% and 70% vs. 51%, respectively, US vs. other $p < 0.001$, and EU vs. other $p < 0.01$) and more often within 24 h (77% and 64% vs. 46%, respectively, US vs. other $p < 0.001$, EU vs. other $p < 0.01$) compared to other centers. Most centers aim for euvolemia (96%) by administrating intravenous fluids to 0 (53%) or +500 mL/day (41%) net fluid balance. Induced hypertension is more often used in US centers (100%) than in EU (87%, $p < 0.05$) and other centers (81%, $p < 0.05$), and endovascular therapies for cerebral vasospasm are used more often in US centers than in other centers (91% and 60%, respectively, $p < 0.05$).

Conclusions: We observed significant practice variability in aSAH treatment worldwide. Future comparative effectiveness research studies are needed to investigate how practice variation leads to differences in functional outcome.

Introduction

Spontaneous aneurysmal subarachnoid hemorrhage (aSAH) is a neurological emergency that continues to cause high morbidity and case-fatality, leading to over 27% of all stroke-related years of potential life lost before the age of 65 and a very high cost to society.[1-8] Approximately one in three aSAH survivors are left dependent.[9-10] The most dreaded complications after aSAH include rebleeding, early brain injury (EBI), and delayed cerebral ischemia (DCI), which are the main causes of neurological deterioration and disability.[11-12] Despite advances in diagnosis, prevention, and treatment of complications of aSAH, only a modest improvement in outcome has been observed.[5,9,11] The main therapies that improve long-term clinical outcomes and that are supported by evidence from randomized controlled trials are endovascular repair of the ruptured cerebral aneurysm in cases where the aneurysm is amenable to either coiling or surgical clipping, and administration of oral nimodipine to decrease the risk of DCI.[13] Most other management is based on weak evidence. Prior retrospective observational and registry studies have suggested that there are substantial between-center differences in functional outcome following aSAH that are most likely explained by case volume and variabilities in care.[14] Understanding which variabilities in care have an impact on aSAH outcome represents an important and dire unmet need. In this survey study, we aimed to characterize variations in treatment and organizational aspects of care that may impact patient outcomes.

Materials and Methods

Survey Development

In 2019 a "Provider Profiling Questionnaire" was sent to 230 Neurocritical Care Research Network (NCRN)-affiliated sites worldwide to recruit participants for the International Subarachnoid Hemorrhage Comparative Effectiveness Research Alliance (INSIDER) study (Please see Electronic Supplementary File S1, available via: https://www.mdpi.com/2077-0383/10/4/762/s1). INSIDER is a planned seven-year prospective observational study to determine practice variability in aSAH and its effect on outcome. The survey was developed based on the clinical expertise of the principal investigators. Various disciplines (neurologists, neurosurgeons, neuro-intensivists, and epidemiologists) participated in its development. The survey consisted of several topics covering elements of aSAH treatment, which have been the subject of debate in recent decades, such as the type

and timing of aneurysm treatment, fluid management, and treatment of DCI. Both open-answer and multiple-choice questions were used. In the present survey study, we focus on the Questions 1, 5, 7, 9–12, 17–22, 24–25, 27–34, and 36. The Institutional Review Board (IRB) at the Johns Hopkins University School of Medicine approved the study protocol under the exemption category and waived the need for written, informed consent.

Statistical Analyses

Descriptive statistics were used to describe aSAH practice variability and displayed in tables or figures. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as medians with interquartile ranges or means with standard deviations. A geographical map was used to represent participating centers and their countries of origin. For further analyses, centers were geographically categorized as European, United States (US), or non-European or non-US, henceforth called "other". Chi-squared test and ANOVA were used to compare regional differences. Post-hoc multiple comparison was performed with Bonferroni test. Analyses were performed with IBM SPSS Statistics, Version 25, for Windows (IBM, Chicago, IL, USA) and open-source software RStudio, Version 3.6.3, for macOS (R Foundation for Statistical Computing, Vienna, Austria).

Results

Center Characteristics

A total of 145 centers across five continents responded (response rate 63%). Of the survey respondents, 64 (44%) were located in the US (Figure 1 and Table 1), 37 (26%) were European, and 44 (30%) were from other areas.

The majority of centers were academic (n = 121, 84%). The number of beds varied greatly between centers. Most centers had 0–100 intensive care unit (ICU) beds (n = 112, 76%). The median number of neurological ICU beds was 15 (IQR 8–24).

On average, 47% (SD 27) of patients with aSAH presented primarily to the survey respondents' center. Most of the participating centers treated at least 200 aSAH patients per year (n = 73, 49%). aSAH patients were in most cases admitted to a dedicated neurological ICU (n = 96, 66%) or at a medical-surgical ICU (n = 38, 25%).

Completion rate of the survey's questions varied from 48% (n = 69) to 100% (n = 145).

Some proportions exceeded 100% because multiple answers were allowed.

Figure 1. Geographical map representing the countries of origin of participating centers.

Table 1. Overview of center characteristics.

Center Characteristic	*n* Completed	*n* (%), Mean (SD), or Median (IQR) — Range
Centers per region	145	
United States		64 (44)
Europe		37 (26)
Other		44 (30)
Type of institution	145	
Academic		121 (84)
Private non-academic		11 (8)
Public non-academic		8 (6)
Other		5 (4)
No. of hospital beds		144
<250		11 (8)
250–500		24 (17)
500–750		32 (22)
750–1000		41 (28)

>1000		36 (25)
No. of intensive care unit (ICU) beds	144	60 (33–100)—380
0–100		109 (76)
101–200		32 (22)
201–300		1 (1)
301–400		2 (1)
No. of neurological ICU beds	139	15 (8–24)—48
0–10		56 (39)
11–20		39 (27)
21–30		33 (23)
31–40		6 (4)
40>		4 (3)
How many patients per year do you see with aneurysmal subarachnoid hemorrhage (aSAH) at your center?	145	
0–40		5 (3)
40–60		25 (17)
60–100		17 (12)
100–150		12 (8)
150–200		14 (10)
>200		72 (50)
What percentage of patients with aSAH present primarily to your hospital—as opposed to referred patients?	142	47 (27)
0–25%		39 (27)
26–50%		50 (35)
51–75%		24 (17)
76–100%		29 (20)
Where are aSAH patients admitted?*	145	
Dedicated Neurological ICU		96 (66)
Surgical ICU		15 (10)
Medical ICU		9 (6)
Medical-Surgical ICU		36 (25)
Intermediate Care Unit		18 (12)
Other		11 (8)

Abbreviations: SD = standard deviation; IQR = interquartile range.
* Multiple answers possible. Proportions can exceed 100%.

Aneurysm Treatment

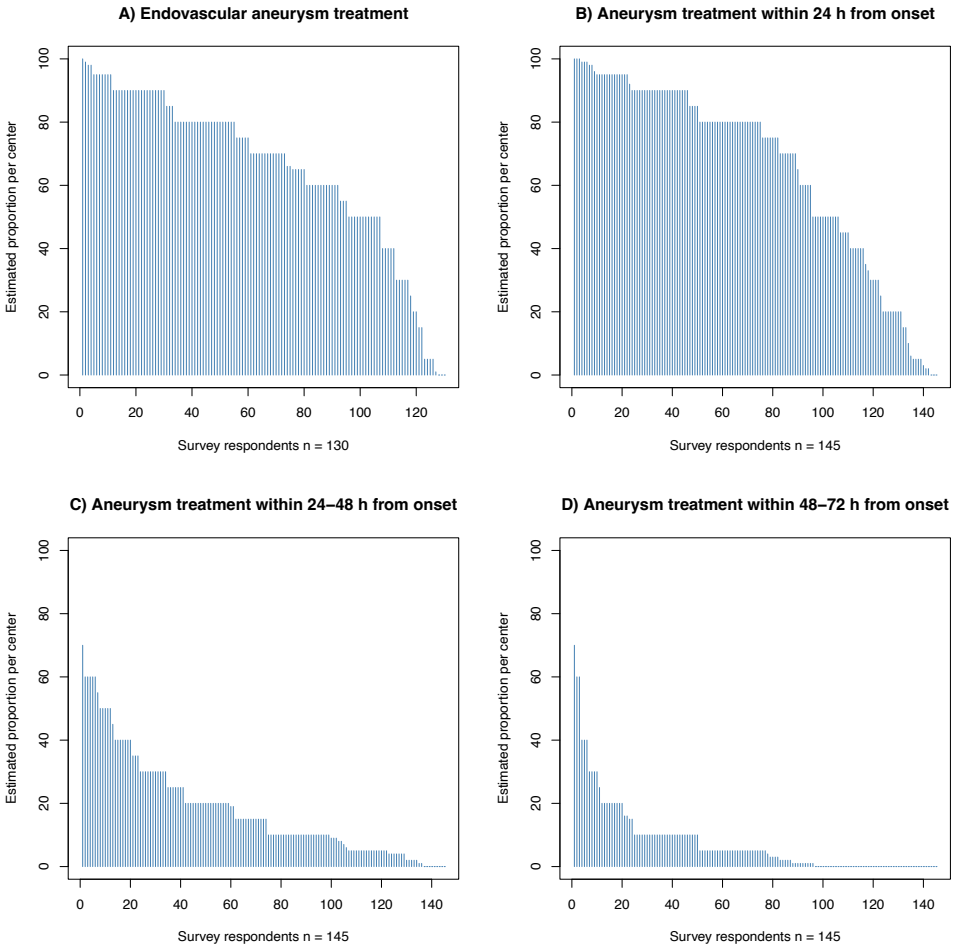
Overall, survey respondents indicated that a mean estimated 65% of all treated ruptured aneurysms were treated endovascularly. In addition, a mean estimated 65% of treated aneurysms were treated within 24 h of symptom onset, whereas a mean estimated 18% were treated within 24–48 h, a mean estimated 8% were treated within 48–72 h, and a mean estimated 9% of aneurysms were unaccounted for (Table 2, Figure 2A–D). It is unknown if the latter 9% accounts for aneurysms treated later than 72 h, not treated at all, or a combination of both.

Table 2. Type and timing of aneurysm treatment.

Aneurysm Treatment Characteristic	*n* Completed	Mean estimate (SD), *n* (%)
Proportion of aneurysms treated by endovascular coiling	130	65% (26)
Timing of aneurysm treatment*		
Proportion of aneurysm treatment <24 h from symptom onset	145	65 (30)
Proportion of aneurysm treatment 24–48 h from symptom onset	145	18 (16)
Proportion of aneurysm treatment >48 h from symptom onset	145	8 (12)
Number of centers that treat the majority (>50%) of aneurysms in particular time window from symptom onset†	145	
Within 24 h from symptom onset		96 (66)
Within 24–48 h from symptom onset		7 (5)
Within 48–72 h from symptom onset		3 (2)

Abbreviations: SD = standard deviation.
* Percentages do not add up to 100%. Not all centers treat a majority of aneurysms in a particular time window.
† Estimated mean percentages do not add up to 100%. Nine percent is unaccounted for.

Figure 2. Type and timing of aneurysm treatment: **(A)** per center estimated proportion of patients with aneurysmal subarachnoid hemorrhage (aSAH) who have their aneurysm treated by endovascular means, **(B)** per center estimated proportion of patients with aSAH who have their aneurysm treated within 24 h from symptom onset, **(C)** per center estimated proportion of patients with aSAH who have their aneurysm treated within 24–48 h from symptom onset, and **(D)** per center estimated proportion of patients with aSAH who have their aneurysm treated within 48–72 h from symptom onset.



Ninety-six centers (66%) reported treating the majority (e.g., >50%) of aneurysms within 24 h (Figure 2B). Seven centers (5%) treat the majority of aneurysms between 24–48 h (Figure 2C), and only three (2%) 48–72 h after onset (Figure 2D). Thirty-nine centers (27%) do not treat the majority of aneurysms in any particular time window.

In US and European centers, aneurysms were more often treated by endovascular techniques than in other centers (Table 3, mean estimates

72%, 70%, and 51%, respectively; European vs. other p < 0.01; and US vs. other p < 0.001). The estimated proportion of aneurysms being treated within 24 h was equal in US and European centers but higher than in other centers (mean estimate 77%, 67%, 46%, respectively, European vs. other p < 0.01 and US vs. other p < 0.001).

Table 3. Type and timing of aneurysm treatment per geographical region.

Aneurysm Treatment Characteristic	Europe (EU) Mean % (SD)	United States (US) Mean % (SD)	Other* Mean % (SD)	*p*-Value
Aneurysms treated endovascular	70 (18)	72 (19)	51 (33)	EU vs. other $p < 0.01$; US vs. other $p < 0.001$
Aneurysms treated <24 h†	67 (24)	77 (23)	46 (34)	EU vs. other $p < 0.01$; US vs. other $p < 0.001$
Aneurysms treated ≥24 h†	30 (21)	22 (22)	30 (24)	0.109

Abbreviations: SD = standard deviation.
* All non-US and non-EU centers are categorized as "other".
† Estimated mean percentages do not add up to 100%. *p*-values are calculated with ANOVA, and in case of a significant result they are calculated with a post-hoc multiple comparison Bonferroni test. Only significant *p*-values are reported.

Fluid Management

Nearly all centers aimed for a euvolemic state in aSAH patients in their hospital (*n* = 136, 96%, Table 4). Furthermore, 66 (53%) of survey respondents targeted for 0 mL/day net fluid balance and 51 (41%) for +500 mL/day, adjusting for insensible losses. None aimed for a negative net fluid balance. To reach the preferred volemic state, 66 (54%) respondents administered 2 L fluid daily, and 19 (16%) balanced this with output. The most commonly used maintenance fluid was 0.9% saline (*n* = 101, 86%) or, alternatively, balanced solutions (*n* = 59, 50.0%). Again, some proportions exceeded 100% as multiple answers were allowed.

In centers where fluid management was guided by clinical blood testing (*n* = 69, 49%), the most common compounds measured were lactate (*n* = 56, 81%), B-type natriuretic peptide (*n* = 31, 45%), and troponin (*n* = 30, 44%). They were often assessed in some sort of combination (*n* = 37, 54%). When fluid management was guided by advanced hemodynamic monitoring

in the ICU (n = 108, 84%), this was performed with echocardiography of inferior vena cava (n = 85, 77%), pulmonary artery catheter (n = 11, 10%), transpulmonary thermodilution (n = 53, 48%), or by other means (n = 29, 26%). Eighteen survey respondents (17%) estimated using advanced hemodynamic monitoring in less than 10% of aSAH patients, 40 (38%) in 10–25%, and 47 (45%) in more than 25%.

Table 4. Fluid management in aSAH.

Fluid Management Characteristic	*n* Completed	*n* (%)
What is the goal of maintenance intravenous fluids in aneurysmal subarachnoid hemorrhage (aSAH) in your hospital?	142	
Euvolemia		136 (96)
Hypervolemia		5 (3)
Other		1 (1)
What goal of net fluid balance for aSAH patients do you use at your institution?	124	
−500 mL/day		0
0 mL/day		66 (53)
+500 mL/day		51 (41)
+1 L/day		2 (2)
Other		5 (4)
What goal of fluid intake for aSAH patients do you use at your institution?	122	
1 L/day		11 (9)
2 L/day		66 (54)
3 L/day		0
>3.5 L/day		2 (2)
Other		43 (35)
Does your center use clinical blood tests to guide fluid management of aSAH patients?	141	
Yes		69 (49)
No		72 (51)
Which?*	69	
Troponin		30 (44)
B-type (or brain) natriuretic peptide		31 (45)
Neuron-specific enolase		3 (4)
Interleukin 6		2 (3)

Lactate		56 (81)
Others		9 (13)
Which maintenance fluids do you use for aSAH patients in your hospital?*	118	
0.9% saline		101 (86)
3% saline		1 (1)
5% human albumin		11 (9)
20% human albumin		3 (3)
25% human albumin		4 (3)
Synthetic colloid		1 (1)
Balanced solutions		59 (50)
Other		2 (2)
Do you use advanced hemodynamic monitoring to guide fluid management at the intensive care unit?	128	
Yes		108 (84)
No		20 (16)
How often?	105	
<10% of patients		18 (17)
10–25% of patients		40 (38)
>25% of patients		47 (45)
With what device?*	110	
Echocardiography/Inferior vena cava		85 (77)
Pulmonary artery catheter		11 (10)
Transpulmonary thermodilution		53 (48)
Other		29 (26)

* Multiple answers possible. The sample total can exceed $n = 145$.

Cerebral Vasospasm and Delayed Cerebral Ischemia

Almost all centers routinely administer nimodipine in patients with aSAH ($n = 136$, 98%, Figure 3). Similarly, most centers induce hypertension if the patients develop DCI ($n = 128$, 91%). However, induced hypertension was more often used in US centers than European or other centers (Table 5, 100%, 87%, and 81%, respectively, US vs. other $p < 0.05$ and US vs. European $p < 0.05$). Less often, survey respondents indicated to use hypervolemia ($n = 37$, 26%) or hemodilution ($n = 14$, 11%) for treatment of DCI. About a quarter of survey respondents stated that they use biomarkers or laboratory

testing to guide DCI management (n = 28, 23%). Endovascular treatment of angiographic vasospasm is commonly performed (n = 95, 77%), although significantly more in US centers than in European and other centers (91% vs. 74% and 60%, respectively; US vs. other $p < 0.05$).

Figure 3. Management of delayed cerebral ischemia (DCI) in survey respondents' hospitals.

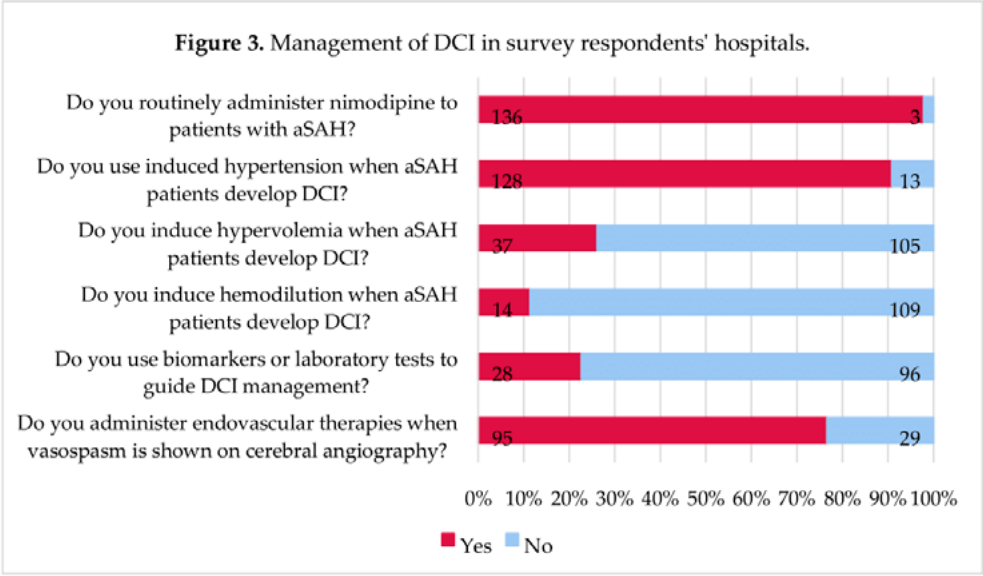


Table 5. Regional differences in vasospasm and DCI management.

DCI management characteristic	*n* Completed	Europe (EU) *n*, (%)	United States (US) *n*, (%)	Other* *n*, (%)	*p*-Value
Do you routinely administer nimodipine to patients with aneurysmal subarachnoid hemorrhage (aSAH)?	139	35 (97)	62 (100)	39 (95)	0.238
Do you use induced hypertension when aSAH patients develop delayed cerebral ischemia (DCI)?	141	32 (87)	62 (100)	34 (81)	US vs. other $p < 0.05$; US vs. EU $p < 0.05$

Do you induce hypervolemia when aSAH patients develop DCI?	142	6 (16)	19 (30)	12 (29)	0.280
Do you induce hemodilution when aSAH patients develop DCI?	123	2 (6)	6 (12)	6 (16)	0.391
Does your center use biomarkers or laboratory tests to guide DCI management?	124	9 (26)	14 (26)	5 (14)	0.289
Do you perform endovascular therapies when vasospasm is shown on cerebral angiography?	124	25 (74)	48 (91)	22 (60)	US vs. other $p < 0.05$

* All non-US and non-EU centers are categorized as "other". *p*-values are calculated with chi-squared test, and in case of a significant result, a post-hoc multiple comparison Bonferroni test. Only significant *p*-values are reported.

Discussion

We performed an international and multi-center survey of hospital characteristics and treatment variation of aSAH patients. We observed significant variability of care of aSAH patients between individual centers as well as remarkable regional differences. Marked variability in treatment was observed in timing of aneurysm treatment, fluid management, and endovascular therapy of DCI.

Our findings reaffirm a shift from neurosurgical clipping of ruptured aneurysms to endovascular aneurysm treatment. In our study, survey respondents estimated that 65% of patients were treated endovascularly. Contrarily, an earlier survey study reported only an estimated 37% of patients were treated endovascularly; however, this study was conducted more than a decade ago.[15] More recently, Velly et al. reported that 66% of survey respondents treated more than 60% of aneurysms by endovascular techniques.[16] Further analyses show that European and US centers treat aneurysms endovascularly equally as often, but significantly more often

than centers in other parts of the world. Even though we did not collect data on factors that led to this shift in practice, it is important to point out that it may have been driven by results from important clinical trials.[17,18] The International Subarachnoid Hemorrhage Trial (ISAT) showed that when there is equipoise, the probability of disability-free survival is greater with endovascular coiling than with surgical clipping up to 10 years after treatment. The Barrow Ruptured Aneurysm Trial (BRAT) reported that outcome differences between these two treatment modalities may differ depending on aneurysm location, with better outcomes found in patients with posterior circulation aneurysms treated with endovascular coiling.

We found a strong preference for aneurysm repair within 24 h of the ictus. An estimated 65% of aneurysms were treated within 24 h from symptom onset. Additionally, we found that in European and US centers, aneurysms were equally as often treated within 24 h but significantly more often in comparison to centers in other geographic regions. Previous survey research found even greater proportions of aneurysm treatment within 24 h ranging from an estimated 79–81%.[16,19] However, both of these studies only included European respondents.

The American Stroke Association (ASA) guidelines recommend aneurysm treatment as early as feasible, and the European Stroke Organization (ESO) guidelines recommend repair as early as technically and logistically possible within 72 h after aSAH.[1,20] More recently, some experts advocated for aneurysm treatment on an emergency basis,[21,22] primarily because rebleeding occurs most often in the hours following ictus.[23–27] Others found that aneurysm treatment within 24 h as opposed to 24–72 h was associated with worse outcome.[28,29] We were unable to investigate the relationship between timing of aneurysm treatment and outcome because our survey study did not collect individual patients' outcomes.

One of the cornerstones of aSAH management is maintenance of euvolemia. We found that nearly all survey respondents (96%) aim for euvolemia as the goal of maintenance IV fluids. Euvolemia has been predicated on the observation that hypovolemia is associated with DCI.[30] As a result, current recommendations state that a negative fluid balance should be avoided in aSAH. In addition, more recent evidence indicates that hypervolemia may also be harmful.[31,32]

To reach euvolemia, in many cases, survey respondents aim for a 0 mL/day (53%) or slight positive net fluid balance +500 mL/day (41%), adjusting for insensible losses. However, we observed significant variability in methods used to reach euvolemia: onethird of survey respondents did not clearly state a daily fluid intake goal (e.g., 1 L/day to >3.5 L/day) and about half of the

respondents used clinical blood testing to guide fluid management despite questionable validity of such laboratory tests. Moreover, a great variety of clinical blood tests were used. Additionally, advanced hemodynamic monitoring was indicated to be widely used (84%), but it is unclear how this impacts fluid management. It is possible that this variation is explained by the less well-defined triggers to stop administering fluids. Optimizing fluid management strategies could potentially be an easy and affordable treatment target if supported by good quality evidence.

DCI is an important and much studied complication after aSAH, occurring in approximately 30% of patients.[33] Treatment of DCI includes hemodynamic and mechanical endovascular therapy or direct infusion of vasodilating drugs to reverse vasospasm. Despite a lack of evidence from randomized controlled trials to support use of any of these treatments and evidence for an increased risk of complications, our survey study showed that induced hypertension (91%), induced hypervolemia (26%), and induced hemodilution (11%) were frequently used. Interestingly, we observed an increased preference for using induced hypertension alone compared to previous survey research, which has found up to half of respondents use induced hypertension, hypervolemia, and hemodilution combined as treatment of DCI.[15,19,34] Our survey study underscores the variability in the management of DCI in patients with aSAH.

In the US, almost all aSAH patients (91%) are treated with endovascular techniques when vasospasm is shown on cerebral angiography, while this is significantly less used in other, non-European, parts of the world. Our results are in agreement with prior survey research that found comparable use of endovascular techniques among European survey respondents (78%).[16] As expected, prevention of DCI with nimodipine (98%) was most widely accepted among our survey respondents.

An important strength of this survey study is that it offers insight into contemporary treatment variation. aSAH is a rapidly evolving field of medicine with notable improvements in intensive care management and aneurysm obliteration techniques. In addition to previous survey research, our study serves as a new worldwide benchmark for practice variability in aSAH and adds to other important prospective observational studies investigating the practice of treatment of neurocritically-ill patients in general.[35,36]

Several limitations must be taken into account when interpreting this survey study. We included 145 centers with good worldwide representation, except the African continent, and an adequate response-rate of 65%. Nevertheless, there was an overrepresentation of US centers (44%),

academic centers (84%), and centers located in high-income countries or areas (81%). Therefore, the results of this survey study might not be generalizable to centers located in low- and middle-income countries or non-academic centers. However, it is important to mention that aSAH patients are generally treated in specialized centers.

In our survey, we have asked to estimate the proportions of patients treated within 24 h, 24–48 h, and 48–72 h. We could not differentiate between aneurysms not treated at all and aneurysms treated later than 72 h (9% in total). A similar ambiguity is present in the question regarding proportions of aneurysms treated by endovascular or neurosurgical means. Although the question did not specifically ask for proportions of treated aneurysms, instead of all aSAH patients, we have interpreted the results as such. As mentioned above, some aneurysms remain untreated.

As in all survey-related research, this study is vulnerable to recall and responder bias. More specifically, the results of our survey study are based on the perception of aSAH center practice, not actual clinical practice. The latter will be most present in a minority of questions asking for estimated proportions. Other simple yes-or-no questions regarding clinical practice or specific center characteristics will most likely be less or unaffected by recall bias. However, we have not verified the accuracy of reported survey data. Additionally, possible bias may have been introduced because of incomplete responses to survey questions.

Furthermore, our survey participants included bedside clinicians, such as intensivists and neurosurgeons, and did not include neuroradiologists or neuro-interventionalists that do not participate in the daily care of aSAH patients. The addition of these practitioners' perspectives in future surveys and studies would be valuable.

As randomized controlled trials are expensive, impractical, and sometimes ethically unjustifiable in the field of aSAH, there is an urgent call for other means to evaluate treatment outcomes in aSAH. Previous research suggests that significant between-center practice variability is associated with variation in clinical outcome.[14] We hypothesize that large practice variability can primarily occur in the absence of treatment strategies supported by high-quality evidence. This void leaves room for interpretation or personal preferences translating to practice variability. Future comparative effectiveness research (CER) should utilize this variability in aSAH care to determine whether it is associated with a clinical outcome.

In conclusion, we identified significant treatment variation in the type and timing of aneurysm treatment, fluid management, and endovascular

therapies of DCI. We propose that future research focusses on these topics in relation to patient outcome as opportunities for CER.

References

1. Connolly, E.S., Jr.; Rabinstein, A.A.; Carhuapoma, J.R.; Derdeyn, C.P.; Dion, J.; Higashida, R.T.; Hoh, B.L.; Kirkness, C.J.; Naidech, A.M.; Ogilvy, C.S.; et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the American Heart Association/ american Stroke Association. Stroke 2012, 43, 1711–1737.
2. Etminan, N.; Chang, H.S.; Hackenberg, K.; de Rooij, N.K.; Vergouwen, M.D.I.; Rinkel, G.J.E.; Algra, A. Worldwide Incidence of Aneurysmal Subarachnoid Hemorrhage According to Region, Time Period, Blood Pressure, and Smoking Prevalence in the Population: A Systematic Review and Meta-analysis. JAMA Neurol. 2019, 76, 588–597.
3. Sudlow, C.L.; Warlow, C.P. Comparable studies of the incidence of stroke and its pathological types: Results from an international collaboration. International Stroke Incidence Collaboration. Stroke 1997, 28, 491–499.
4. Go, A.S.; Mozaffarian, D.; Roger, V.L.; Benjamin, E.J.; Berry, J.D.; Blaha, M.J.; Dai, S.; Ford, E.S.; Fox, C.S.; Franco, S.; et al. Heart Disease and Stroke Statistics–2014 Update: A Report From the American Heart Association. Circulation 2013, 129, e28–e292.
5. van Gijn, J.; Rinkel, G.J. Subarachnoid haemorrhage: Diagnosis, causes and management. Brain 2001, 124, 249–278.
6. Rinkel, G.J.; Djibuti, M.; Algra, A.; van Gijn, J. Prevalence and risk of rupture of intracranial aneurysms: A systematic review. Stroke 1998, 29, 251–256.
7. Turan, N.; Heider, R.A.; Zaharieva, D.; Ahmad, F.U.; Barrow, D.L.; Pradilla, G. Sex Differences in the Formation of Intracranial Aneurysms and Incidence and Outcome of Subarachnoid Hemorrhage: Review of Experimental and Human Studies. Transl. Stroke Res. 2016, 7, 12–19.
8. Roos, Y.; Dijkgraaf, M.; Albrecht, K.; Beenen, L.; Groen, R.; De Haan, R.; Vermeulen, M. Direct costs of modern treatment of aneurysmal subarachnoid hemorrhage in the first year after diagnosis. Stroke 2002, 33, 1595–1599.
9. Hop, J.W.; Rinkel, G.J.; Algra, A.; van Gijn, J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: A systematic review. Stroke 1997, 28, 660–664.
10. Johnston, S.C.; Selvin, S.; Gress, D.R. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. Neurology 1998, 50, 1413–1418. [CrossRef] [PubMed]
11. Suarez, J.I.; Tarr, R.W.; Selman, W.R. Aneurysmal subarachnoid hemorrhage. N. Engl. J. Med. 2006, 354, 387–396.
12. Sabri, M.; Lass, E.; Macdonald, R.L. Early brain injury: A common mechanism in subarachnoid hemorrhage and global cerebral ischemia. Stroke Res. Treat. 2013, 2013, 394036.

13. Diringer, M.N.; Bleck, T.P.; Claude Hemphill, J., 3rd; Menon, D.; Shutter, L.; Vespa, P.; Bruder, N.; Sander Connolly, E., Jr.; Citero, G.; Gress, D.; et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit. Care 2011, 15, 211–240.
14. Dijkland, S.A.; Jaja, B.N.R.; van der Jagt, M.; Roozenbeek, B.; Vergouwen, M.D.I.; Suarez, J.I.; Torner, J.C.; Todd, M.M.; van den Bergh, W.M.; Saposnik, G.; et al. Between-center and between-country differences in outcome after aneurysmal subarachnoid hemorrhage in the Subarachnoid Hemorrhage International Trialists (SAHIT) repository. J. Neurosurg. 2019, 133, 1132–1140.
15. Sakowitz, O.W.; Raabe, A.; Vucak, D.; Kiening, K.L.; Unterberg, A.W. Contemporary management of aneurysmal subarachnoid hemorrhage in germany: Results of a survey among 100 neurosurgical departments. Neurosurgery 2006, 58, 137–145. [CrossRef]
16. Velly, L.J.; Bilotta, F.; Fabregas, N.; Soehle, M.; Bruder, N.J.; Nathanson, M.H.; European Neoruanaesthesia and Crisital Care Interest Group (ENIG). Anaesthetic and ICU management of aneurysmal subarachnoid haemorrhage: A survey of European practice. Eur. J. Anaesthesiol. 2015, 32, 168–176.
17. Molyneux, A.J.; Birks, J.; Clarke, A.; Sneade, M.; Kerr, R.S. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). Lancet 2015, 385, 691–697.
18. Spetzler, R.F.; McDougall, C.G.; Zabramski, J.M.; Albuquerque, F.C.; Hills, N.K.; Russin, J.J.; Partovi, S.; Nakaji, P.; Wallace, R.C. The Barrow Ruptured Aneurysm Trial: 6-year results. J. Neurosurg. 2015, 123, 609–617.
19. Hofman, M.; Hajder, N.; Duda, I.; Krzych, L.J. A Questionnaire Survey of Management of Patients with Aneurysmal Subarachnoid Haemorrhage in Poland. Int. J. Environ. Res. Public Health 2020, 17, 4161.
20. Steiner, T.; Salman, R.A.-S.; Beer, R.; Christensen, H.; Cordonnier, C.; Csiba, L.; Forsting, M.; Harnof, S.; Klijn, C.J.M.; Krieger, D.; et al. European Stroke Organisation (ESO) Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. Int. J. Stroke 2014, 9, 840–855.
21. Phillips, T.J.; Dowling, R.J.; Yan, B.; Laidlaw, J.D.; Mitchell, P.J. Does Treatment of Ruptured Intracranial Aneurysms Within 24 Hours Improve Clinical Outcome? Stroke 2011, 42, 1936–1945.
22. Laidlaw, J.D.; Siu, K.H. Ultra-early surgery for aneurysmal subarachnoid hemorrhage: Outcomes for a consecutive series of 391 patients not selected by grade or age. J. Neurosurg. 2002, 97, 250–258.
23. Naidech, A.M.; Janjua, N.; Kreiter, K.T.; Ostapkovich, N.D.; Fitzsimmons, B.F.; Parra, A.; Comminchau, C.; Sander Connolly, E.; Mayer, S.A. Predictors and

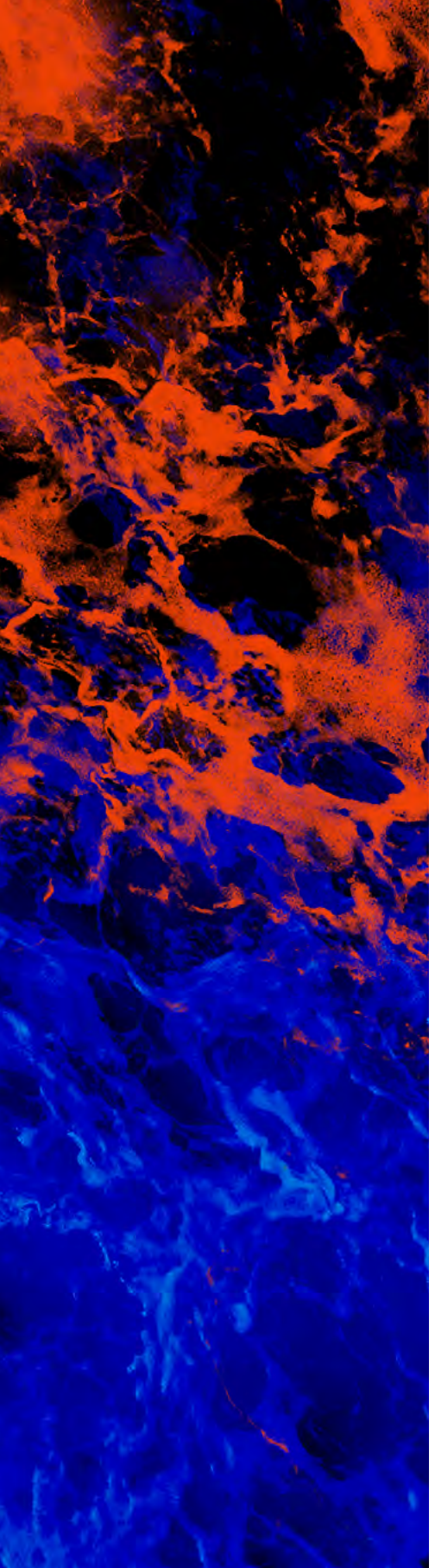
impact of aneurysm rebleeding after subarachnoid hemorrhage. Arch. Neurol. 2005, 62, 410–416.
24. van Donkelaar, C.E.; Bakker, N.A.; Veeger, N.J.; Uyttenboogaart, M.; Metzemaekers, J.D.; Luijckx, G.J.; Groen, R.J.M.; van Dijk, J.M.C. Predictive Factors for Rebleeding After Aneurysmal Subarachnoid Hemorrhage: Rebleeding Aneurysmal Subarachnoid Hemorrhage Study. Stroke 2015, 46, 2100–2106.
25. Fujii, Y.; Takeuchi, S.; Sasaki, O.; Minakawa, T.; Koike, T.; Tanaka, R. Ultra-early rebleeding in spontaneous subarachnoid hemorrhage. J. Neurosurg. 1996, 84, 35–42.
26. Koopman, I.; Greving, J.P.; van der Schaaf, I.C.; van der Zwan, A.; Rinkel, G.J.; Vergouwen, M.D. Aneurysm characteristics and risk of rebleeding after subarachnoid haemorrhage. Eur. Stroke J. 2019, 4, 153–159.
27. Inagawa, T.; Kamiya, K.; Ogasawara, H.; Yano, T. Rebleeding of ruptured intracranial aneurysms in the acute stage. Surg. Neurol. 1987, 28, 93–99.
28. Brilstra, E.H.; Rinkel, G.J.; Algra, A.; van Gijn, J. Rebleeding, secondary ischemia, and timing of operation in patients with subarachnoid hemorrhage. Neurology 2000, 55, 1656–1660.
29. Oudshoorn, S.C.; Rinkel, G.J.E.; Molyneux, A.J.; Kerr, R.S.; Mees, S.M.D.; Backes, D.; Algra, A.; Vergouwen, M.D.I. Aneurysm treatment <24 versus 24–72 h after subarachnoid hemorrhage. Neurocrit. Care 2014, 21, 4–13.
30. Wijdicks, E.F.; Vermeulen, M.; Hijdra, A.; van Gijn, J. Hyponatremia and cerebral infarction in patients with ruptured intracranial aneurysms: Is fluid restriction harmful? Ann. Neurol. 1985, 17, 137–140.
31. van der Jagt, M. Fluid management of the neurological patient: A concise review. Crit. Care 2016, 20, 126.
32. Rass, V.; Gaasch, M.; Kofler, M.; Schiefecker, A.J.; Ianosi, B.A.; Steinkohl, F.; Beer, R.; Pfausler, B.; Gizewski, E.R.; Thome, C.; et al. Fluid Intake But Not Fluid Balance Is Associated With Poor Outcome in Nontraumatic Subarachnoid Hemorrhage Patients. Crit. Care Med. 2019, 47, e555–e562.
33. Roos, Y.B.; de Haan, R.J.; Beenen, L.F.; Groen, R.J.; Albrecht, K.W.; Vermeulen, M. Complications and outcome in patients with aneurysmal subarachnoid haemorrhage: A prospective hospital based cohort study in the Netherlands. J. Neurol. Neurosurg. Psychiatry 2000, 68, 337–341.
34. Stevens, R.D.; Naval, N.S.; Mirski, M.A.; Citerio, G.; Andrews, P.J. Intensive care of aneurysmal subarachnoid hemorrhage: An international survey. Intensive Care Med. 2009, 35, 1556–1566.
35. Rao, C.P.V.; Suarez, J.I.; Martin, R.H.; Bauza, C.; Georgiadis, A.; Calvillo, E.; Hemphill, J.C.; Sung, G.; Oddo, M.; et al.; PRINCE Study Investigators. Global Survey of Outcomes of Neurocritical Care Patients: Analysis of the PRINCE Study Part 2. Neurocrit. Care 2019, 32, 88–103.

36. Suarez, J.I.; Martin, R.H.; Bauza, C.; Georgiadis, A.; Rao, C.P.V.; Calvillo, E.; Hemphill, J.C.; Sung, G.; Oddo, M.; Taccone, F.S.; et al. Worldwide Organization of Neurocritical Care: Results from the PRINCE Study Part 1. Neurocrit. Care 2019, 32, 172–179

Supplemental material

The Provider Profiling Questionnaire is available online at https://www.mdpi.com/2077-0383/10/4/762. File S1: Insider study.

Response to: “Flow Diversion in the Treatment of Intracranial Aneurysms: A Pragmatic Randomized Care Trial”



American Journal of Neuroradiology, 2022.
Jordi de Winkel and Bob Roozenbeek.

With great interest, we read the article by Raymond et al,[1] which described the results of the Flow Diversion in the Treatment of Intracranial Aneurysms Trial. This parallel-group, pre-randomized, controlled, open-label, all-inclusive, pragmatic care trial included 278 patients from 3 centers in Canada during 10 years (2011–2020). In this study, patients who underwent flow diversion (FD) had significantly fewer poor outcomes than patients receiving alternative standard management options (ASMO; relative risk, 0.68; 95% CI, 0.50–0.92). The authors concluded, "For patients with mostly unruptured, large, anterior circulation (carotid) aneurysms, FD was more effective than the alternative standard management option in terms of angiographic outcome." The authors conducted an all-inclusive care trial because previous trials lacked comparison with routine clinical practice and compared FD only with a specific alternative strategy. This all-inclusive policy is convenient because there is no widely supported consensus on which patients are suitable for FD, and stringent selection criteria may have limited center participation. Nevertheless, there is also a significant downside to this approach.

In this study, patients were eligible for inclusion if they had "an aneurysm for which FD was considered a promising treatment." Because of lacking clinical consensus, the study population was dependent on local practice and preferences. In such cases, it is too early to perform a randomized controlled trial (RCT) that will generate conclusions that will be supported by the community and implemented in routine practice. However, varying local treatment algorithms also have great potential to evaluate safety and efficacy outside the scope of an RCT. In comparative effectiveness research (CER), one uses varying center-specific treatment algorithms as an instrumental variable to evaluate clinical interventions on observational data.[2] Such research will facilitate clinical consensus on patient eligibility for FD treatment and works as a stepping stone for future RCTs.[3,4] For now, without a clearly defined target population, it is difficult to assess the generalizability of the results of this study.

Furthermore, in the primary analysis, the authors found a significant difference in good outcome (a composite outcome of mRS<3 and complete or near-angiographic occlusion) between FD and ASMO therapies. This difference was driven by a higher rate of complete angiographic occlusion in the FD group. This is problematic because the patients in the ASMO group were allowed to be treated conservatively and were consequently scored with "incomplete occlusion." This feature has created an imbalance between study groups and complicates the interpretation of the results. Alternatively, it would have been more informative to limit inclusion to

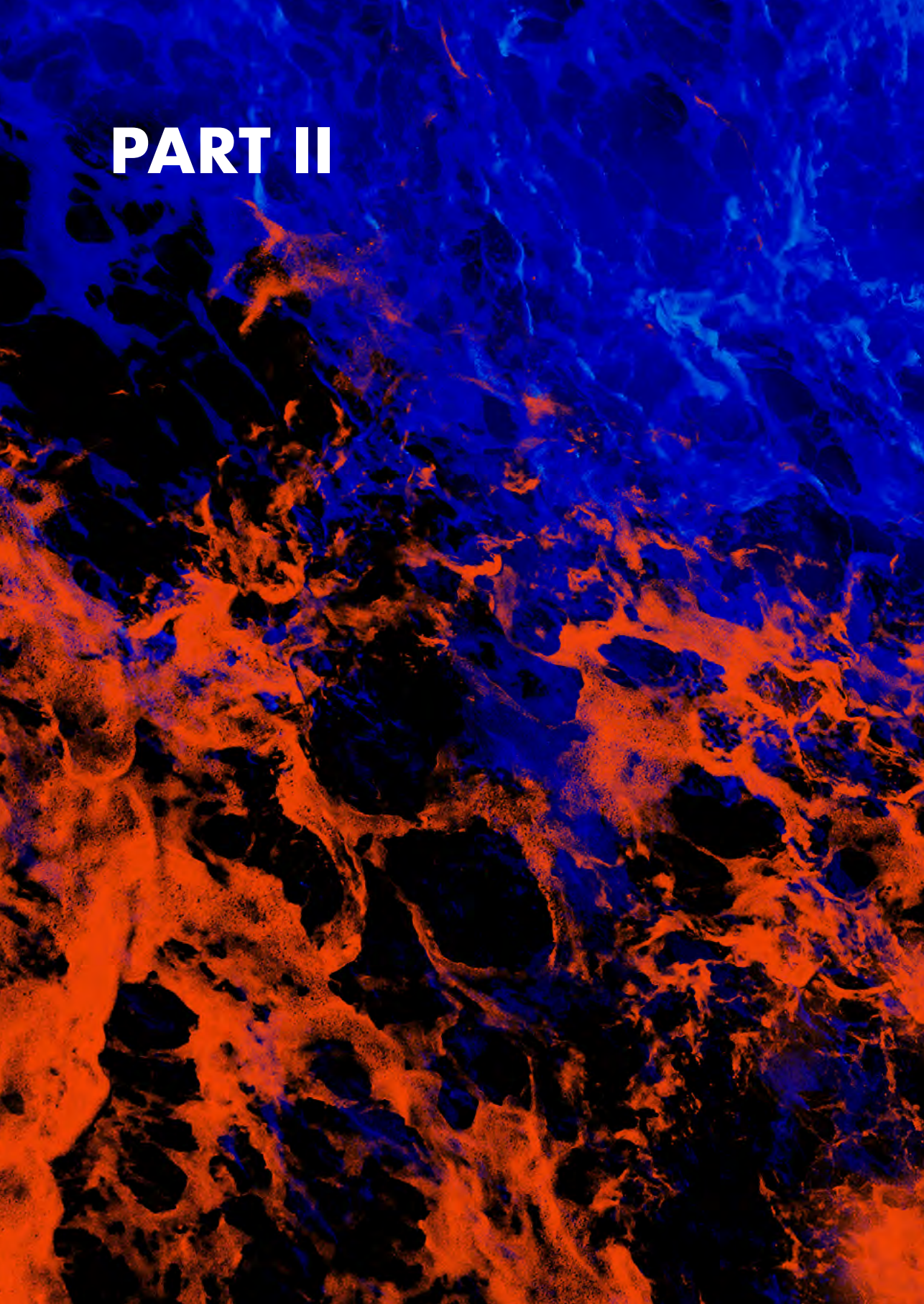
patients who actually received aneurysm treatment.

Last, to investigate the heterogeneity of the treatment effect, the authors conducted a subgroup analysis by adding interactions to the model between baseline characteristics and treatment assignment. This approach requires a much larger sample size, and interactions are usually selected parsimoniously. The authors also conducted a conventional subgroup analysis by reporting the treatment effects stratified per subgroup. On the basis of these results, they concluded that FD was more effective than ASMO for each subgroup with a significantly different treatment effect. However, the study was underpowered to draw such specific conclusions. At best, these results can be interpreted as a motivation for future research.

In conclusion, the authors have conducted a challenging and ambitious trial, and even with its limitations, the higher rate of aneurysm occlusion is promising and mandates future research. We recommend first conducting a survey study to examine FD practice variability and afterward conducting CER as a stepping stone for future RCT development. This approach has the highest probability to generate conclusions that could lead to adoption of FD therapy in routine practice and thus aid in minimizing research waste.

References

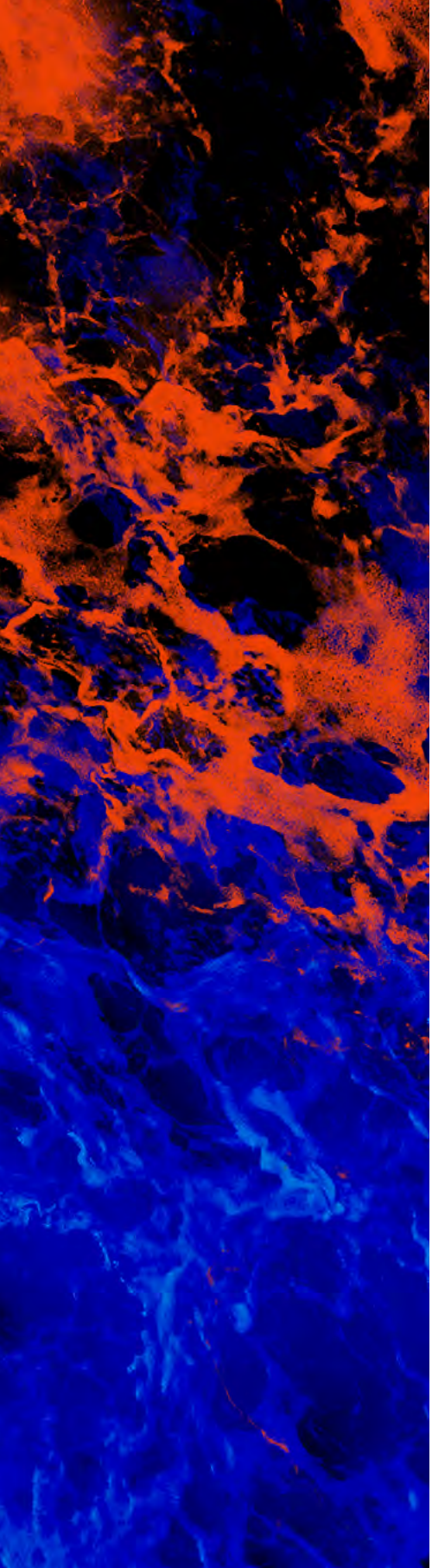
1. Raymond J, Iancu D, Boisseau W, et al. Flow diversion in the treatment of intracranial aneurysms: a pragmatic randomized care trial. AJNR Am J Neuroradiol 2022;43:1244–51
2. Ceyisakar IE, van Leeuwen N, Steyerberg EW, et al. Instrumental variable analysis to estimate treatment effects: a simulation study showing potential benefits of conditioning on hospital. BMC Med Res Methodol http://dx.doi.org/10.3174/ajnr.A7718 2022;22:121
3. van Essen TA, Lingsma HF, Pisica D, et al; CENTER-TBI Collaboration Group. Surgery versus conservative treatment for traumatic acute subdural haematoma: a prospective, multicentre, observational, comparative effectiveness study. Lancet Neurol 2022;21:620–31
4. Wiegers EJA, Lingsma HF, Huijben JA, et al; OzENTER-TBI Collaboration Groups. Fluid balance and outcome in critically ill patients with traumatic brain injury (CENTER-TBI and OzENTER-TBI): a prospective, multicentre, comparative effectiveness study. Lancet Neurol 2021;20:627–38


PART II


Individualized
Outcome Predictions

CHAPTER III

Early Predictors of Functional Outcome in Poor-Grade Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis



BMC Neurology, 2022.
Jordi de Winkel, Tim Y Cras, Ruben Dammers, Pieter-Jan van Doormaal, Mathieu van der Jagt, Diederik WJ Dippel, Hester F Lingsma, and Bob Roozenbeek.

Abstract

Background: Patients with poor-grade aneurysmal subarachnoid hemorrhage (aSAH) often receive delayed or no aneurysm treatment, although recent studies suggest that functional outcome following early aneurysm treatment has improved. We aimed to systematically review and meta-analyze early predictors of functional outcome in poor-grade aSAH patients.

Methods: We included studies investigating the association of early predictors and functional outcome in adult patients with confirmed poor-grade aSAH, defined as World Federation of Neurological Surgeons (WFNS) grade or Hunt and Hess (H-H) grade IV-V. Studies had to use multivariable regression analysis to estimate independent predictor effects of favorable functional outcome measured with the Glasgow Outcome Scale or modified Rankin Scale. We calculated pooled adjusted odds ratios (aOR) and 95% confidence intervals (CI) with random effects models.

Results: We included 27 studies with 3287 patients. The likelihood of favorable outcome increased with WFNS grade or H-H grade IV versus V (aOR 2.9, 95% CI 1.9-4.3), presence of clinical improvement before aneurysm treatment (aOR 3.3, 95% CI 2.0-5.3), and intact pupillary light reflex (aOR 2.9, 95% CI 1.6-5.1), and decreased with older age (aOR 0.7, 95% CI 0.5-1.0, per decade), increasing modified Fisher grade (aOR 0.4, 95% CI 0.3-0.5, per grade), and presence of intracerebral hematoma on admission imaging (aOR 0.4, 95% CI 0.2-0.8).

Conclusions: We present a summary of early predictors of functional outcome in poor-grade aSAH patients that can help to discriminate between patients with favorable and with unfavorable prognosis and may aid in selecting patients for early aneurysm treatment.

Background

Aneurysmal subarachnoid hemorrhage (aSAH) is a severe type of stroke that is associated with high morbidity and mortality.[1,2] The clinical severity of aSAH is classified with the World Federation of Neurological Surgeons grade (WFNS) or Hunt and Hess grade (H-H), with a higher clinical grade indicating poorer prognosis. Patients with WFNS grade IV-V or H-H grade IV-V account for 18-24% of the SAH population and are referred to as "poor-grade patients".[3]

In agreement with current guidelines[4,5], the majority of aSAH patients are being treated within 24 hours.[6] Aneurysm treatment in poor-grade patients is often delayed until signs of neurological recovery to avoid providing futile therapies to moribund patients or adding to a high proportion of patients ending up in vegetative or functionally dependent state. However, subjecting poor-grade patients to delayed aneurysm treatment may result in rebleeding and potential loss of life. Especially, because rebleeding occurs most often in the hours following the ictus.[7]

There is evidence that outcome following poor-grade aSAH is better than historically assumed. A recent meta-analysis investigating poor-grade patients has indicated that 76% of poor-grade patients may survive and 47% may experience favorable functional outcome.[3] In addition, some studies reported that emergency aneurysm treatment reduced the risk of rebleeding[3,8] and improved functional outcome.[8] Other studies did not find improved functional outcome with aneurysm treatment within 24 hours.[3,9,10]

In conclusion, there is a need to identify early predictors of functional outcome to improve patient selection for (early) aneurysm treatment to avoid unnecessary rebleeding. Many predictors of functional outcome have been identified, but these have not been confirmed in a poor-grade population. In this systematic review and meta-analysis, we aimed to investigate early predictors of functional outcome in poor-grade aSAH patients.

Methods

We conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (Supplemental Table 1).[11] The study protocol was registered with the International Prospective Register of Systematic Reviews prior to study eligibility selection and was published on 08/13/2020 (available via: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020198603).

We developed a comprehensive search strategy with the aid of a medical information specialist to systematically search Embase, Medline, Google Scholar, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials (Supplemental Methods 1). We searched from inception to present date and limited our search to peer-reviewed articles written in English. We conducted our primary search on 05/25/2020 and performed a re-run on 11/30/2020. Potentially eligible articles after title and abstract screening underwent full-text review (Supplemental Methods 2). We evaluated the bibliography of eligible studies for additional references. The selection process was recorded using Endnote X9 software.

We performed data extraction with a data extraction form (available upon request). We contacted the corresponding authors in case of missing data. We performed quality assessment with the Quality In Prognosis Studies (QUIPS) tool for quality assessment.[12] Risk of bias (ROB) plots were created with the robvis ROB visualization tool.[13] A detailed description of the criteria to reach the final verdict on ROB is given elsewhere (Supplemental Methods 3). We performed the process of study selection, data extraction and quality assessment blinded and independently (J.W.,T.Y.C.). Any disagreements were solved by consulting a third reviewer (B.R. or H.F.L.).

The primary outcome was favorable functional outcome measured with the Glasgow Outcome Scale (GOS) or the modified Rankin Scale (mRS). We did not define favorable outcome or the time of outcome measurement (i.e., some studies defined favorable outcome as a mRS of 0-2 at 6 months, while others defined favorable outcome as a mRS of 0-3 at 1 year).

We summarized study characteristics and reported them as means with standard deviations or medians with interquartile ranges. We performed a systematic review of early predictors of functional outcome. Furthermore, for predictors which were adequately reported and uniformly defined in multiple studies, we performed a meta-analysis and calculated pooled adjusted odds ratios (aOR) and 95% confidence intervals (CI) with random effects models. The results of the meta-analysis were described with Forest plots. When multiple studies reported results based on the same study population, we included the study with the largest sample size.[14-20] We accounted for heterogeneity in the study design by performing post-hoc subgroup analyses stratifying for length of follow-up, for studies with a favorable outcome definition mRS 0-2 or GOS 4-5, and for studies including patients who have received aneurysm treatment and studies including patients who have not received aneurysm treatment. We defined early follow-up as follow-up up to six months and late follow-up as beyond six months after SAH. We assessed between-study heterogeneity with Higgin's

& Thompson's I^2 and influence plots, and publication bias by analyzing funnel plots and Eggers' regression test for funnel plot asymmetry. We adjusted for publication bias with the trim-and-fill method.[21] We did not assess publication bias in meta-analyses including less than five studies. To offer a complete overview of available prognostic research, any study that was not eligible for meta-analysis is summarized separately in a descriptive manner. We performed analysis with R software (version 3.6.3, meta package version 5.1.1, metafor package version 3.0.2).

Results

We included 27 studies (n = 3287) that met our selection criteria in our review (Supplemental Figure 1).[14-20,22-41] Year of publication ranged from 1996 to 2020 (Supplemental Table 2). We did not identify additional studies through bibliographical review.

The median duration of follow up was 6 months (IQR 3-12, Table 1), the median sample size of the multivariable analysis was 104 (IQR 80-154), and 76% of patients received aneurysm treatment. One study did not report on how many patients were provided aneurysm treatment and in one study aneurysm treatment was not provided at all. Most studies had a single center (n = 17, 63%) and retrospective (n = 24, 89%) design.

Table 1. Summary of study characteristics.

Study characteristic	
Patients in multivariable analysis – median (IQR)	104 (80-154)
Study design – n (%)	
Single-center	17 (63)
Multi-center	7 (26)
Retrospective	24 (89)
Prospective	3 (11)
Cohort	26 (96)
Case-control	1 (3)
Length of follow up – n (%)	
median (IQR)	6 (3-12)
<6 months	15 (56)
>6 months	11 (41)
Not reported	1 (3)

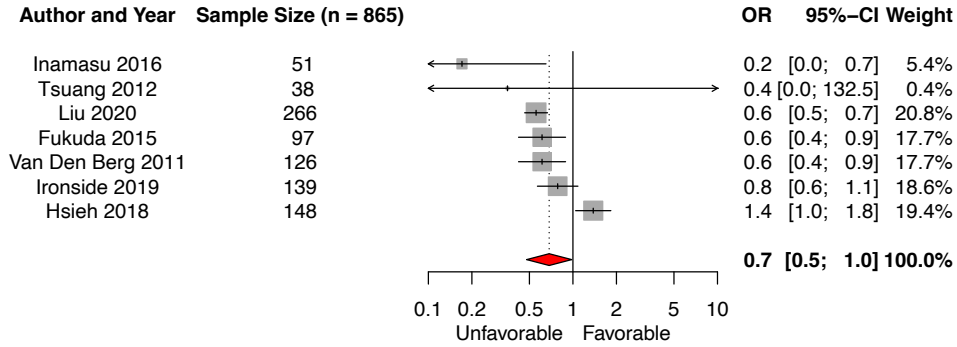
Definition of favorable outcome by mRS – n (%)	19 (70)
mRS 0-1	1 (4)
mRS 0-2	9 (33)
mRS 0-3	8 (30)
mRS 0-4	1 (4)
Definition of favorable outcome by GOS – n (%)	7 (26)
GOS 4-5	8 (30)
No definition of favorable outcome reported – n (%)	1 (4)
Studies that have exclusively included patients that were WFNS or H-H grade V – n (%)	5 (19)
Mean percentage of patients that received aneurysm treatment* – (%)	76
Studies that included only patients that received aneurysm treatment* – n (%)	16 (60)

Abbreviations: IQR = interquartile range; mRS = modified Rankin Scale; GOS = Glasgow Outcome Scale, WFNS = World Federation of Neurological Surgeons, H-H = Hunt and Hess.
* One study did not report the number of patients that received aneurysm treatment.

The studies investigated 82 early predictors of functional outcome with multivariable regression analysis. Taking into account predictor definition, reporting quality, and, if present, categorization we were able to conduct a systematic review of sixteen and meta-analysis of nine early predictors. We meta-analyzed age per decade increase, sex, clinical grade, pupillary light reflex, clinical improvement before aneurysm treatment, modified Fisher grade, and presence of hydrocephalus, intraventricular hemorrhage (IVH), and intracerebral hematoma (ICH) on admission imaging (Supplemental Table 3). Aneurysm size, aneurysm location, Glasgow Coma Scale (GCS), Fisher grade, other concomitant bleeding, brain infarction on admission imaging, and leukocytosis were suitable for systematic review (Supplemental Table 4).

We included fifteen studies in the systematic review of the early predictor age. Seven studies were eligible for meta-analysis (n = 865). The likelihood of favorable functional outcome decreased with older age (per decade, pooled aOR 0.7, 95% CI 0.5-1.0, Figure 1).[24-27,31,38,39] We observed moderate funnel plot asymmetry, and after adjusting for publication bias the effect of age was no longer significant (p = 0.10, Supplemental Figure 2A-B). In the eight studies not eligible for meta-analysis older age was often associated with worse functional outcome.[14,15,19,29,35-37]

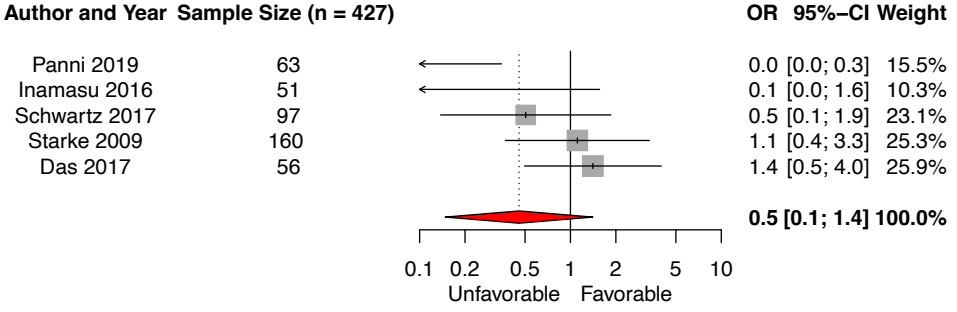
Figure 1. Forest plot of the effect of age (per decade increase) on functional outcome.



Abbreviations: OR = adjusted odds ratio; CI = confidence interval

We included six studies in the systematic review investigating the effect of sex on functional outcome. Five studies (*n* = 427) were eligible for meta-analysis.[15,23,26,32,35] We did not observe an association between sex and the likelihood of favorable functional outcome (pooled aOR 0.5, 95% CI 0.1-1.4, Figure 2). One study was not eligible for meta-analysis and found no association between age and functional outcome.[41]

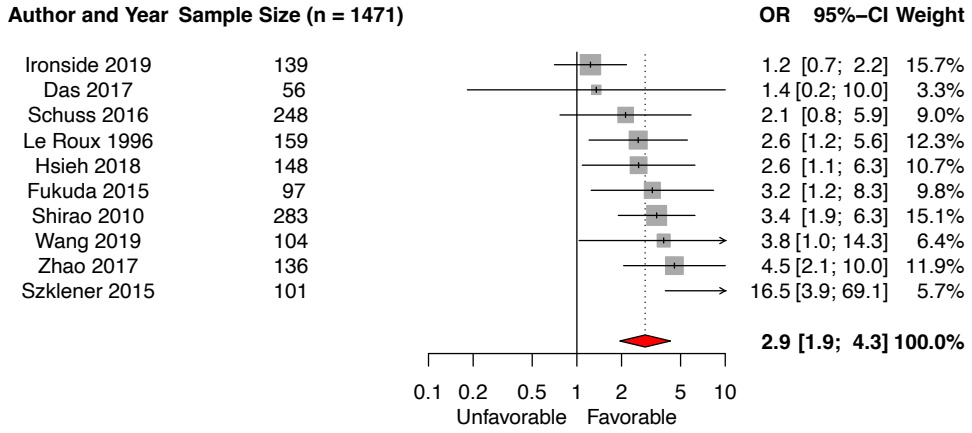
Figure 2. Forest plot of the effect male sex on functional outcome.



Abbreviations: OR = adjusted odds ratio; CI = confidence interval

We included thirteen studies in the systematic review of clinical grade on the likelihood of favorable functional outcome. Ten studies (*n* = 1471) were eligible for meta-analysis. The pooled aOR of WFNS grade IV versus V and H-H grade IV versus V was 2.9 (95% CI 1.9-4.3, Figure 3). [17,23-25,27,30,34,36,37,40] The effect estimate for clinical grade was similar when including only studies investigating WFNS grade and not H-H grade.[17,24,34,36,40] In three studies not included in the meta-analysis higher clinical grade was associated with poorer outcome.[14,16,18]

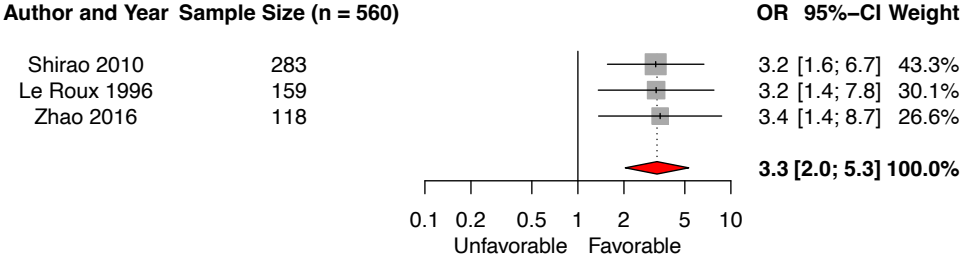
Figure 3. Forest plot of the effect of admission WFNS gradeand H-H grade IV versus V on functional outcome.



Abbreviations: OR = adjusted odds ratio; CI = confidence interval

We included three studies (*n* = 560, (11%)) investigating the effect of clinical improvement before aneurysm treatment on the likelihood of favorable functional outcome.[17,30,36] The pooled aOR was 3.3 (95% CI 2.0-5.3, Figure 4). Further, we reviewed GCS on admission as an early predictor. Three studies included in the systematic review reported an increased likelihood of favorable functional outcome with increasing GCS.[15,20,31,41]

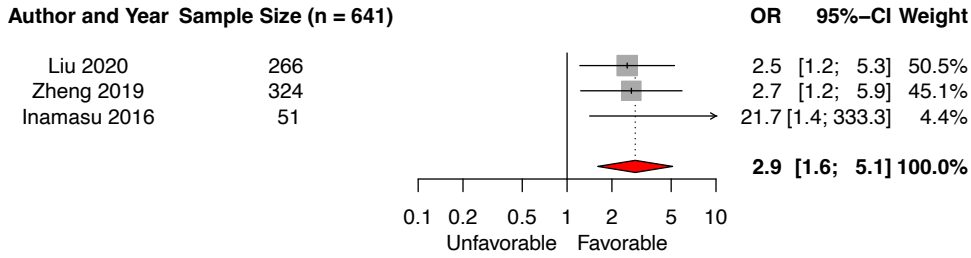
Figure 4. Forest plot of the effect of presence of clinical improvement before aneurysm treatment on functional outcome.



Abbreviations: OR = adjusted odds ratio; CI = confidence interval

We included three studies (*n* = 641) in the systematic review and meta-analysis of the effect of intact pupillary light reflex on admission.[20,26,31] The pooled aOR was 2.9 (95% CI 1.6-5.1, Figure 5).

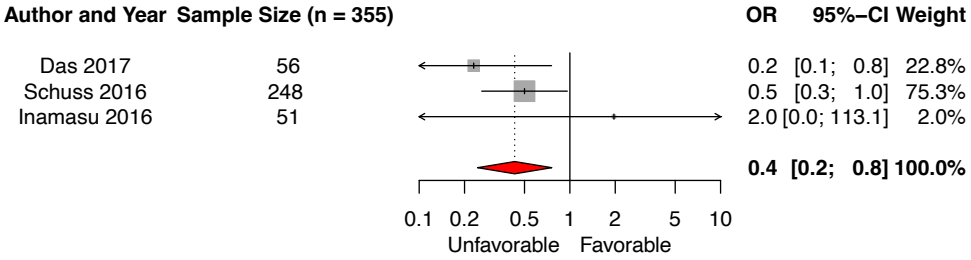
Figure 5. Forest plot of the effect of intact pupillary light reflex on admission on functional outcome.



Abbreviations: OR = adjusted odds ratio; CI = confidence interval

We included seven studies in the systematic review of the effect of presence of ICH on admission imaging on the likelihood of favorable functional outcome. Three studies (*n* = 355) were eligible for meta-analysis.[23,26,34] The pooled aOR was 0.4 (95% CI 0.2-0.8, Figure 6). The remaining four studies did not report a significant effect of ICH on functional outcome.[25,28,32,41]

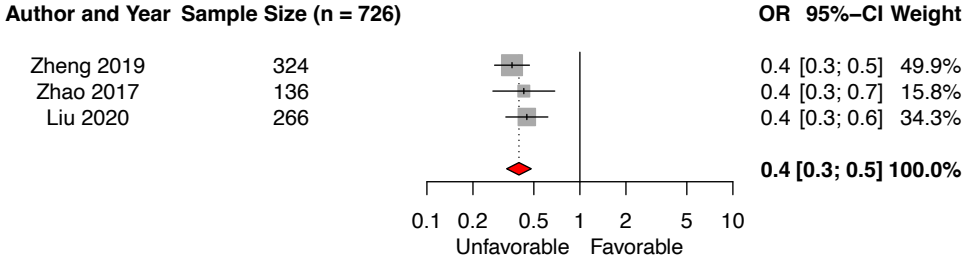
Figure 6. Forest plot of the effect of presence of intracerebral hematoma on functional outcome.



Abbreviations: OR = adjusted odds ratio; CI = confidence interval

We included three studies (*n* = 726) in the meta-analysis of the effect of modified Fisher grade per grade on the likelihood of favorable functional outcome.[18,20,31] We found a pooled aOR of 0.4 (95% CI 0.3-0.5, Figure 7). We included six studies in the systematic review investigating the effect of Fisher grade on functional outcome.[19,23,25,36,37,40,41] Three studies reported a significant association of higher Fisher grade with functional outcome.

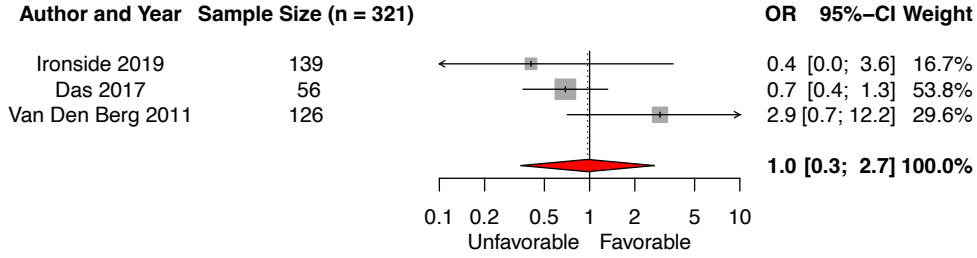
Figure 7. Forest plot of the effect of modified Fisher grade (per grade increase) on functional outcome.



Abbreviations: OR = adjusted odds ratio; CI = confidence interval

We included five studies in the systematic review of the effect of presence of hydrocephalus before aneurysm treatment on functional outcome. Three studies (n = 321) were eligible for meta-analysis.[23,27,39] The pooled aOR was 1.0 (95% CI 0.3-2.7, Figure 8). Two studies were not eligible for meta-analysis. Neither found a significant association with functional outcome.[29,40]

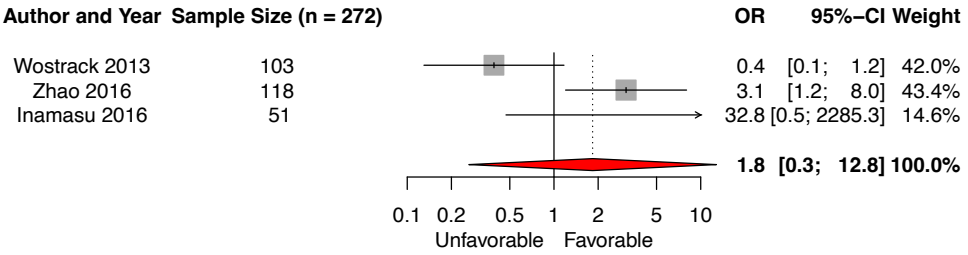
Figure 8. Forest plot of the effect of hydrocephalus on functional outcome.



Abbreviations: OR = adjusted odds ratio; CI = confidence interval

We included seven studies in the systematic review of the effect of presence of IVH on admission imaging on the likelihood of favorable functional outcome. Three studies were eligible for meta-analysis (n = 272).[16,26,41] The pooled aOR was 1.8 (95% CI 0.3-12.8, Figure 9). Four studies were not eligible for meta-analysis and analyzed in with systematic review. Two found an association of IVH with functional outcome.[30,32,40,41]

Figure 9. Forest plot of the effect of intraventricular hemorrhage on functional outcome.

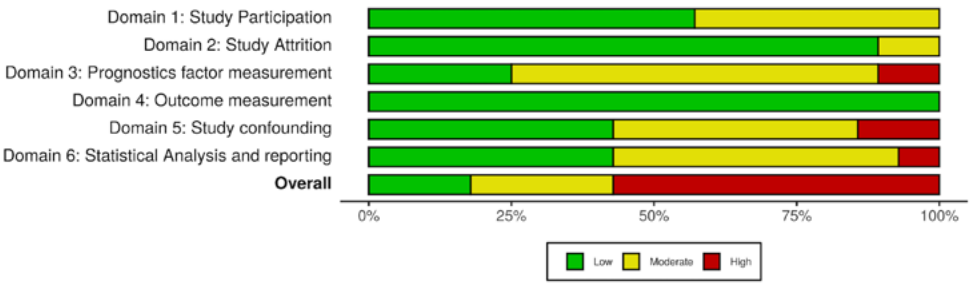


Abbreviations: OR = adjusted odds ratio; CI = confidence interval

Additionally, we conducted a systematic review of aneurysm size, aneurysm location, presence of brain infarction on admission imaging, leukocytosis, and other concomitant bleeding in relation to function outcome (Supplemental Table 4).

We performed subgroup analyses for length of follow-up, for favorable outcome definition, and for studies including only patients that received aneurysm treatment for the predictors age, sex, and clinical grade, which showed similar results as the main analysis. The overall risk of bias as assessed with the QUIPS ROB tool for prognostic studies was high (Figure 10, and Supplemental Figure 3).

Figure 10. Risk of bias summary plot.



Discussion

We systematically reviewed and meta-analyzed early predictors of functional outcome in poor-grade aSAH patients. In agreement with previous research, we confirmed that age, clinical grade, pupillary light reflex, presence of ICH, and modified Fisher grade were predictors of functional outcome.[42-48] In addition, we summarized available prognostic research of less well-known early predictors. In contrast to previous research, we did not find an association of functional outcome and sex,

hydrocephalus, and IVH, and found little evidence of aneurysm size as an early predictor in this population.[42-45,47]

Overall, we found that higher level of consciousness and clinical improvement indicated better patient prognosis. Reassessing clinical condition after initial neurological resuscitation obtains more reliable prognostic estimates and may mandate re-evaluation of clinical management.[49]

Not surprisingly, aSAH patients with intact pupillary light reflexes on admission had a greater likelihood of favorable functional outcome. However, seven of the included studies in the present systematic review excluded patients with absent brainstem reflexes.[18,24,26,30,33,38,41] A previous study advocated to add signs of brain stem herniation such as absent brainstem reflexes to the WFNS grade to improve prognosis prediction among grade V patients.[50]

Many studies considered imaging-characteristics as predictors of functional outcome, with one-third of predictors evaluated being imaging-based. The widespread availability of imaging at baseline makes imaging-characteristics interesting for predicting prognosis. We observed that many studies used categorization and dichotomization, and applied different definitions for equal predictors. This has made the results of these studies unsuited for further meta-analysis. We advocate to adhere to the common data elements for SAH and unruptured intracranial aneurysms[51], and to limit categorization and dichotomization to enhance reproducibility and avoid losing valuable information within the data.

Nonetheless, we found that presence of ICH and modified Fisher grade were significantly associated with functional outcome. Presence of ICH was previously reported as a predictor of unfavorable outcome.[52] Prognosis of these patients may be intertwined with rapid hematoma evacuation. Denying surgical treatment because of poor expected outcome could lead to a self-fulfilling prophecy. Although, we found no association of other imaging-characteristics with functional outcome, due to lacking high-quality evidence, their prognostic value remains undetermined.

This study is strengthened by the comprehensive summary of prognostic research of early predictors of functional outcome in a poor-grade aSAH population. We confirmed predictors of outcome in a poor-grade population, and showed that there is an absence of high-quality prognostic evidence. Another strength is to limit study eligibility to those that performed multivariable analyses. This has added to the validity of the results.

Several limitations must be considered while interpreting this study. Methodological variation between the included studies led to considerable

heterogeneity. For example, there was no uniform definition of favorable outcome in the included studies. This has made interpretation of the results of the meta-analysis more complicated and could have led to biased results.

Also, specific patient-characteristics may have guided the decision whether or not to pursue aggressive management. This may affect functional outcome and could have affected estimated predictor effects. However, most studies applied an aggressive treatment policy. This is illustrated by the high percentage of patients (76%) that received aneurysm treatment. Subgroup analysis for studies with a favorable outcome definition of mRS 0-2 and GOS 4-5, and for studies including exclusively patients who received aneurysm treatment did not indicate different findings than in the main analysis.

The results of our study could be affected by publication and reporting bias. When present, we aimed to adjust for publication bias. Not all studies reported non-significant aORs and CIs leading to a possible overestimation of the effect size estimates. Attempts to request the authors to provide this information were not successful.

Ultimately, the quality of the included studies determine the reliability of the results. Most studies had a small sample size and a high ROB. Because of this, the results have to be interpreted with caution.

Nevertheless, in this study, we obtained more valid and more precise estimates of predictors of functional outcome in a poor-grade aSAH population and summarized prognostic research for future prospective research. To date, no other intervention than aneurysm treatment can effectively minimize the risk of aneurysmal rebleeding. Poor-grade patients often receive delayed aneurysm treatment. Poor-grade patients that are most likely to achieve favorable outcome may be candidates for early aneurysm treatment. We argue that the early predictors of functional outcome that we present in this study could aid patient selection to avoid unnecessary rebleeding. Improving patient selection for early aneurysm treatment can both benefit patient outcome and ensure optimal allocation of limited health care resources.

Nonetheless, it should be noted that average improved functional outcome does not equal individual patient benefit. Individual treatment (strategy) effects can vary within the population. To provide absolute estimates of individual treatment benefit we have to model for heterogeneity of treatment effects which can only be performed using randomized data.[53] First, larger prospective observational research is needed to confirm these predictors of functional outcome in a poor-grade aSAH population. Next steps would be to implement these predictors of outcome in a prediction

rule for clinical practice to provide estimates of expected benefit of early versus delayed aneurysm treatment in terms of functional outcome.

Conclusions

We found that WFNS and H-H grade IV as opposed to V on admission, lower modified Fisher grade, the absence of intracerebral hematoma, intact pupillary light reflexes, and clinical improvement before aneurysm treatment were predictors of favorable functional outcome in poor-grade aSAH patients. These predictors can help discriminate between poor-grade aSAH patients with favorable and with unfavorable prognosis and may aid in selecting patients for early aneurysm treatment. The present study can serve as a stepping-stone for future decision modeling research focusing on selecting poor-grade aSAH patients for early aneurysm treatment.

References

1. Rinkel GJ, Algra A. Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. *Lancet Neurol. 2011;10(4):349–56.*
2. Rinkel GJ, Gijn J. Subarachnoid hemorrhage. *Neurology*. 1994;44(1):191–2.
3. Han Y, Ye F, Long X, Li A, Xu H, Zou L, et al. Ultra-Early Treatment for Poor-Grade Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis. *World Neurosurg*. 2018;115:e160–71.
4. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/ american Stroke Association. *Stroke*. 2012;43(6):1711–37.
5. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G, et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis. 2013;35(2):93–112.*
6. de Winkel J, van der Jagt M, Lingsma HF, Roozenbeek B, Calvillo E, Chou SH, et al. International Practice Variability in Treatment of Aneurysmal Subarachnoid Hemorrhage. *J Clin Med*. 2021;10(4):762.
7. Germans MR, Coert BA, Vandertop WP, Verbaan D. Time intervals from subarachnoid hemorrhage to rebleed. *J Neurol*. 2014;261(7):1425–31.
8. Park J, Woo H, Kang DH, Kim YS, Kim MY, Shin IH, et al. Formal protocol for emergency treatment of ruptured intracranial aneurysms to reduce in-hospital rebleeding and improve clinical outcomes. *J Neurosurg*. 2015;122(2):383–91.
9. Rawal S, Alcaide-Leon P, Macdonald RL, Rinkel GJ, Victor JC, Krings T, et al. Meta-analysis of timing of endovascular aneurysm treatment in subarachnoid haemorrhage: inconsistent results of early treatment within 1 day. *J Neurol Neurosurg Psychiatry*. 2017;88(3):241–8.
10. Oudshoorn SC, Rinkel GJ, Molyneux AJ, Kerr RS, Dorhout Mees SM, Backes D, et al. Aneurysm treatment <24 versus 24–72 h after subarachnoid hemorrhage. *Neurocrit Care*. 2014;21(1):4–13.
11. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006–12.
12. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med. 2013;158(4):280–6.*
13. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods. 2021;12(1):55–61.*
14. Mocco J, Ransom ER, Komotar RJ, Schmidt JM, Sciacca RR, Mayer SA, et al. Preoperative prediction of long-term outcome in poor-grade aneurysmal

subarachnoid hemorrhage. *Neurosurgery*. 2006;59(3):529–38 discussion-38.
15. Starke RM, Komotar RJ, Kim GH, Kellner CP, Otten ML, Hahn DK, et al. Evaluation of a revised Glasgow Coma Score scale in predicting longterm outcome of poor grade aneurysmal subarachnoid hemorrhagepatients. *J Clin Neurosci. 2009;16(7):894–9.*
16. Zhao B, Tan X, Zhao Y, Cao Y, Wu J, Zhong M, et al. Variation in Patient Characteristics and Outcomes Between Early and Delayed Surgery in Poor-Grade Aneurysmal Subarachnoid Hemorrhage. *Neurosurgery*. 2016;78(2):224–31.
17. Zhao B, Yang H, Zheng K, Li Z, Xiong Y, Tan X, et al. Preoperative and postoperative predictors of long-Term outcome after endovascular treatment of poor-grade aneurysmal subarachnoid hemorrhage. *J Neurosurg. 2017;126(6):1764–71.*
18. Zhao B, Zhao Y, Tan X, Cao Y, Wu J, Zhong M, et al. Factors and outcomes associated with ultra-early surgery for poor-grade aneurysmal subarachnoid haemorrhage: A multicentre retrospective analysis. *BMJ Open. 2015;5(4):e007410.*
19. Zheng K, Zhao B, Tan XX, Li ZQ, Xiong Y, Zhong M, et al. Comparison of Aggressive Surgical Treatment and Palliative Treatment in Elderly Patients with Poor-Grade Intracranial Aneurysmal Subarachnoid Hemorrhage. *BioMed Res Int. 2018;2018:5818937.*
20. Zheng K, Zhong M, Zhao B, Chen SY, Tan XX, Li ZQ, et al. Poor-grade aneurysmal subarachnoid hemorrhage: Risk factors affecting clinical outcomes in intracranial aneurysm patients in a multi-center study. *Front Neurol*. 2019;10:123.
21. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455–63.
22. Anqi X, Ruiqi C, Yanming R, Chao Y. Elevated hemoglobin is associated with poor prognosis in Tibetans with poor-grade aneurysmal subarachnoid hemorrhage after clipping: A Retrospective Case-Control Study. *Neurochirurgie*. 2019;65(6):365–9.
23. Das KK, Singh S, Sharma P, Mehrotra A, Bhaisora K, Sardhara J, et al. Results of Proactive Surgical Clipping in Poor-Grade Aneurysmal Subarachnoid Hemorrhage: Pattern of Recovery and Predictors of Outcome. *World Neurosurg*. 2017;102:561–70.
24. Fukuda H, Hayashi K, Moriya T, Nakashita S, Lo BW, Yamagata S. Intrasylvian hematoma caused by ruptured middle cerebral artery aneurysms predicts recovery from poor-grade subarachnoid hemorrhage. *J Neurosurg*. 2015;123(3):686–92.
25. Hsieh PC, Wu YM, Wang AY, Chen CC, Chang CH, Chin SC, et al. The venous delay phenomenon in computed tomography angiography: a novel imaging outcome

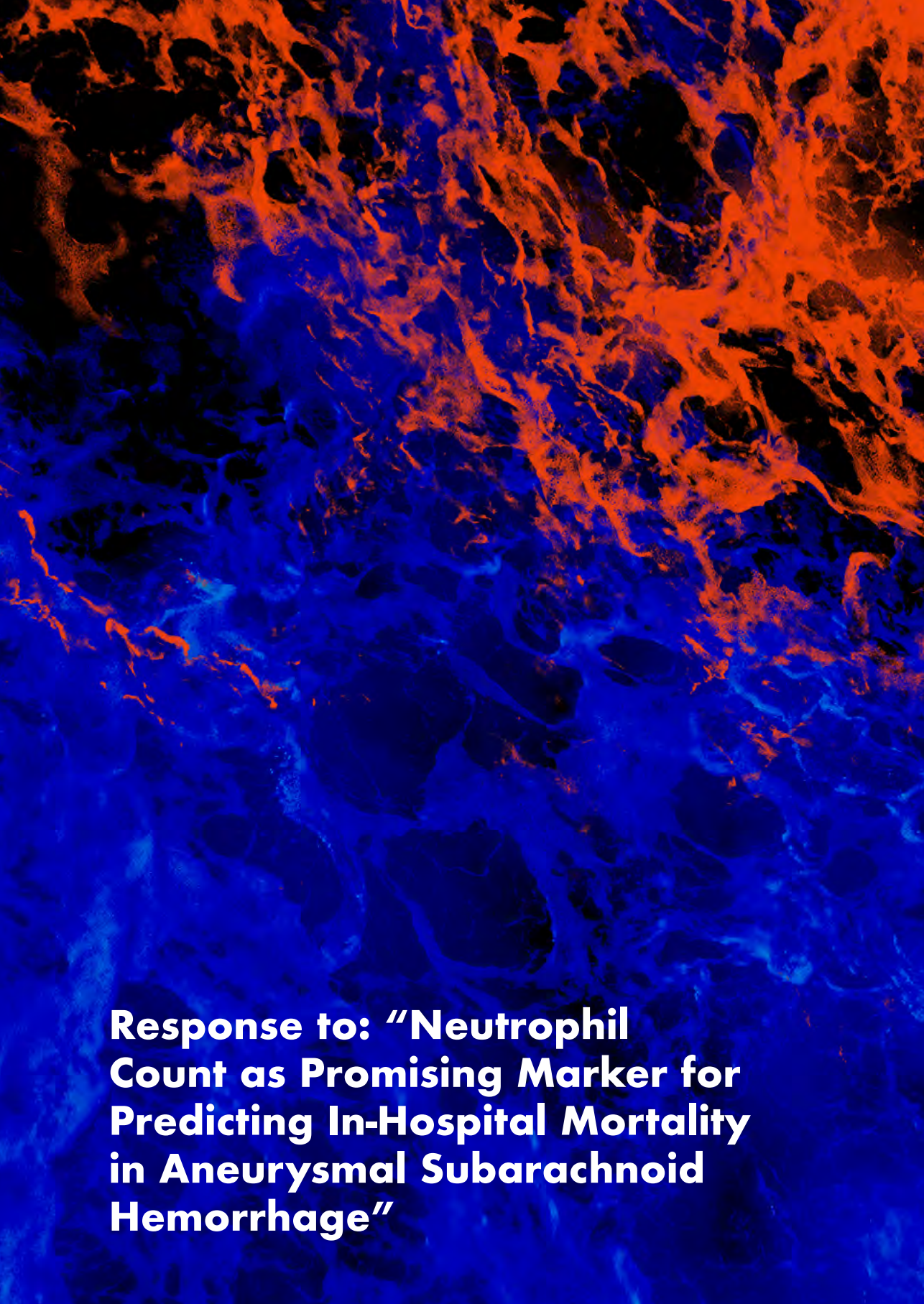
predictor for poor cerebral perfusion after severe aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2018;129(4):876–82.
26. Inamasu J, Nakae S, Ohmi T, Kogame H, Kawazoe Y, Kumai T, et al. The outcomes of early aneurysm repair in World Federation of Neurosurgical Societies grade V subarachnoid haemorrhage patients with emphasis on those presenting with a Glasgow Coma Scale score of 3. *J Clin Neurosci*. 2016;33:142–7.
27. Ironside N, Buell TJ, Chen CJ, Kumar JS, Paisan GM, Sokolowski JD, et al. High-Grade Aneurysmal Subarachnoid Hemorrhage: Predictors of Functional Outcome. *World Neurosurg*. 2019;125:e723–8.
28. Kaneko J, Tagami T, Unemoto K, Tanaka C, Kuwamoto K, Sato S, et al. Functional Outcome Following Ultra-Early Treatment for Ruptured Aneurysms in Patients with Poor-Grade Subarachnoid Hemorrhage. *J Nippon Med Sch*. 2019;86(2):81–90.
29. Konczalla J, Seifert V, Beck J, Guresir E, Vatter H, Raabe A, et al. Outcome after Hunt and Hess Grade V subarachnoid hemorrhage: a comparison of pre-coiling era (1980–1995) versus post-ISAT era (2005–2014). *J Neurosurg*. 2018;128(1):100–10.
30. Le Roux PD, Elliott JP, Newell DW, Grady MS, Winn HR. Predicting outcome in poor-grade patients with subarachnoid hemorrhage: a retrospective review of 159 aggressively managed cases. *J Neurosurg*. 1996;85(1):39–49.
31. Liu J, Xiong Y, Zhong M, Yang Y, Guo X, Tan X, et al. Predicting Long-Term Outcomes After Poor-Grade Aneurysmal Subarachnoid Hemorrhage Using Decision Tree Modeling. *Neurosurgery*. 2020;87(3):523–9.
32. Panni P, Colombo E, Donofrio CA, Barzaghi LR, Albano L, Righi C, et al. Hemorrhagic burden in poor-grade aneurysmal subarachnoid hemorrhage: a volumetric analysis of different bleeding distributions. *Acta Neurochir (Wien)*. 2019;161(4):791–7.
33. Ridwan S, Kristof R. Cardiac Arrest in Patients with Poor-Grade Aneurysmal Subarachnoid Hemorrhage: A Single-Center Experience. *J Neurol Surg A Cent Eur Neurosurg*. 2019;80(6):409–12.
34. Schuss P, Hadjiathanasiou A, Borger V, Wispel C. Poor-grade aneurysmal subarachnoid hemorrhage: factors influencing functional outcome—a single-center series. *World neurosurgery*. 2016;85:125–9.
35. Schwartz C, Pfefferkorn T, Ebrahimi C, Ottomeyer C, Fesl G, Bender A, et al. Long-term Neurological Outcome and Quality of Life after World Federation of Neurosurgical Societies Grades IV and V Aneurysmal Subarachnoid Hemorrhage in an Interdisciplinary Treatment Concept. *Neurosurgery*.2017;80(6):967–74.
36. Shirao S, Yoneda H, Kunitsugu I, Ishihara H, Koizumi H, Suehiro E, et al. Preoperative prediction of outcome in 283 poor-grade patients with subarachnoid hemorrhage: a project of the Chugoku-Shikoku Division of the

Japan Neurosurgical Society. *Cerebrovasc Dis*. 2010;30(2):105–13.
37. Szklener S, Melges A, Korchut A, Zaluska W, Trojanowski T, Rejdak R, et al. Predictive model for patients with poor-grade subarachnoid haemorrhage in 30-day observation: a 9-year cohort study. *BMJ Open. 2015;5(6):e007795.*
38. Tsuang FY, Chen JY, Lee CW, Li CH, Lee JE, Lai DM, et al. Risk profile of patients with poor-grade aneurysmal subarachnoid hemorrhage using early perfusion computed tomography. *World Neurosurg. 2012;78(5):455–61.*
39. van den Berg R, Foumani M, Schroder RD, Peerdeman SM, Horn J, Bipat S, et al. Predictors of outcome in World Federation of Neurologic Surgeons grade V aneurysmal subarachnoid hemorrhage patients. *Crit Care Med*. 2011;39(12):2722–7.
40. Wang X, Han C, Xing D, Wang C, Ding X. Early management of poor-grade aneurysmal subarachnoid hemorrhage: A prognostic analysis of 104 patients. *Clin Neurol Neurosurg*. 2019;179:4–8.
41. Wostrack M, Sandow N, Vajkoczy P, Schatlo B, Bijlenga P, Schaller K, et al. Subarachnoid haemorrhage WFNS grade V: is maximal treatment worthwhile? *Acta Neurochir (Wien)*. 2013;155(4):579–86.
42. Jaja BN, Cusimano MD, Etminan N, Hanggi D, Hasan D, Ilodigwe D, et al. Clinical prediction models for aneurysmal subarachnoid hemorrhage: a systematic review. *Neurocrit Care*. 2013;18(1):143–53.
43. Jaja BNR, Saposnik G, Lingsma HF, Macdonald E, Thorpe KE, Mamdani M, et al. Development and validation of outcome prediction models for aneurysmal subarachnoid haemorrhage: the SAHIT multinational cohort study. *BMJ*. 2018;360:j5745.
44. Lo BW, Fukuda H, Nishimura Y, Farrokhyar F, Thabane L, Levine MA. Systematic review of clinical prediction tools and prognostic factors in aneurysmal subarachnoid hemorrhage. *Surg Neurol Int*. 2015;6:135.
45. Risselada R, Lingsma HF, Bauer-Mehren A, Friedrich CM, Molyneux AJ, Kerr RS, et al. Prediction of 60 day case-fatality after aneurysmal subarachnoid haemorrhage: results from the International Subarachnoid Aneurysm Trial (ISAT). *Eur J Epidemiol*. 2010;25(4):261–6.
46. Risselada R, Lingsma HF, Molyneux AJ, Kerr RS, Yarnold J, Sneade M, et al. Prediction of two month modified Rankin Scale with an ordinal prediction model in patients with aneurysmal subarachnoid haemorrhage. *BMC Med Res Methodol*. 2010;10:86.
47. Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke*. 2007;38(8):2315–21.
48. Stienen MN, Germans M, Burkhardt JK, Neidert MC, Fung C, Bervini D, et al. Predictors of In-Hospital Death After Aneurysmal Subarachnoid Hemorrhage:

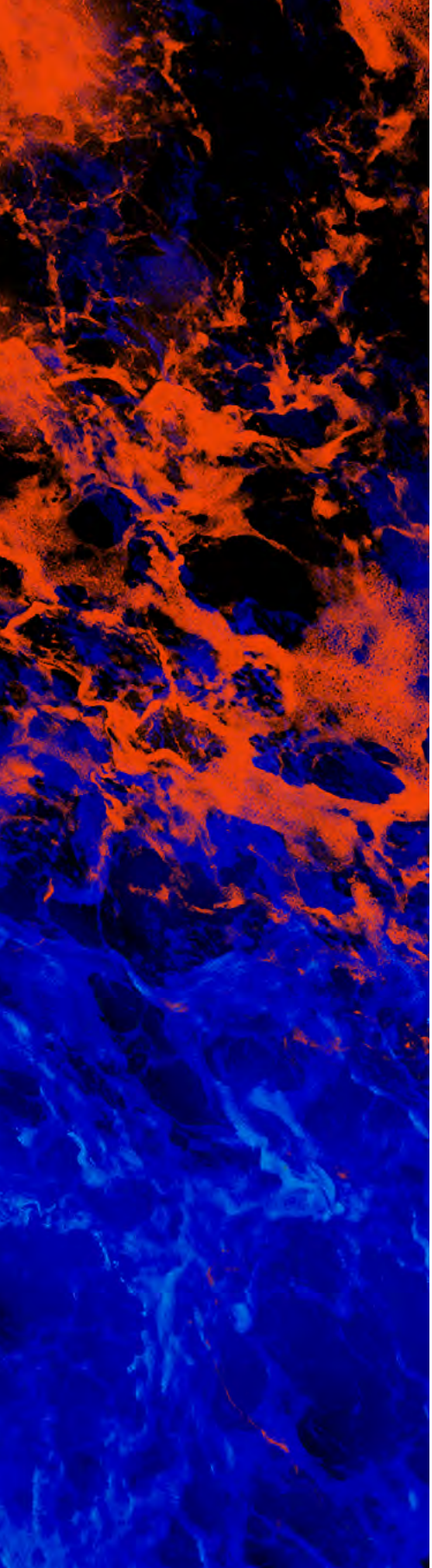
Analysis of a Nationwide Database (Swiss SOS [Swiss Study on Aneurysmal Subarachnoid Hemorrhage]). *Stroke*. 2018;49(2):333–40.
49. Giraldo EA, Mandrekar JN, Rubin MN, Dupont SA, Zhang Y, Lanzino G, et al. Timing of clinical grade assessment and poor outcome in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2012;117(1):15–9.
50. Raabe A, Beck J, Goldberg J, Z Graggen WJ, Branca M, Marbacher S, et al. Herniation world federation of neurosurgical societies scale improves prediction of outcome in patients with poor-grade aneurysmal subarachnoid hemorrhage. *Stroke*. 2022. https:// doi. org/ 10. 1161/ STROKEAHA. 121. 036699.
51. Bijlenga P, Morita A, Ko NU, Mocco J, Morel S, Murayama Y, et al. Common Data Elements for Subarachnoid Hemorrhage and Unruptured Intracranial Aneurysms: Recommendations from the Working Group on Subject Characteristics. *Neurocrit Care*. 2019;30(Suppl 1):20–7.
52. Guresir E, Beck J, Vatter H, Setzer M, Gerlach R, Seifert V, et al. Subarachnoid hemorrhage and intracerebral hematoma: incidence, prognostic factors, and outcome. *Neurosurgery. 2008;63(6):1088–93 discussion 93–4.*
53. Kent DM, van Klaveren D, Paulus JK, D'Agostino R, Goodman S, Hayward R, et al. The Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement: Explanation and Elaboration. *Ann Intern Med*. 2020;172(1):W1–25.

Supplemental Material

Supplemental material available via: https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-022-02734-x



Response to: “Neutrophil Count as Promising Marker for Predicting In-Hospital Mortality in Aneurysmal Subarachnoid Hemorrhage”



Posted to Stroke's Online Comment System, 2021. No Peer-Review.
Jordi de Winkel and Diederik WJ Dippel.

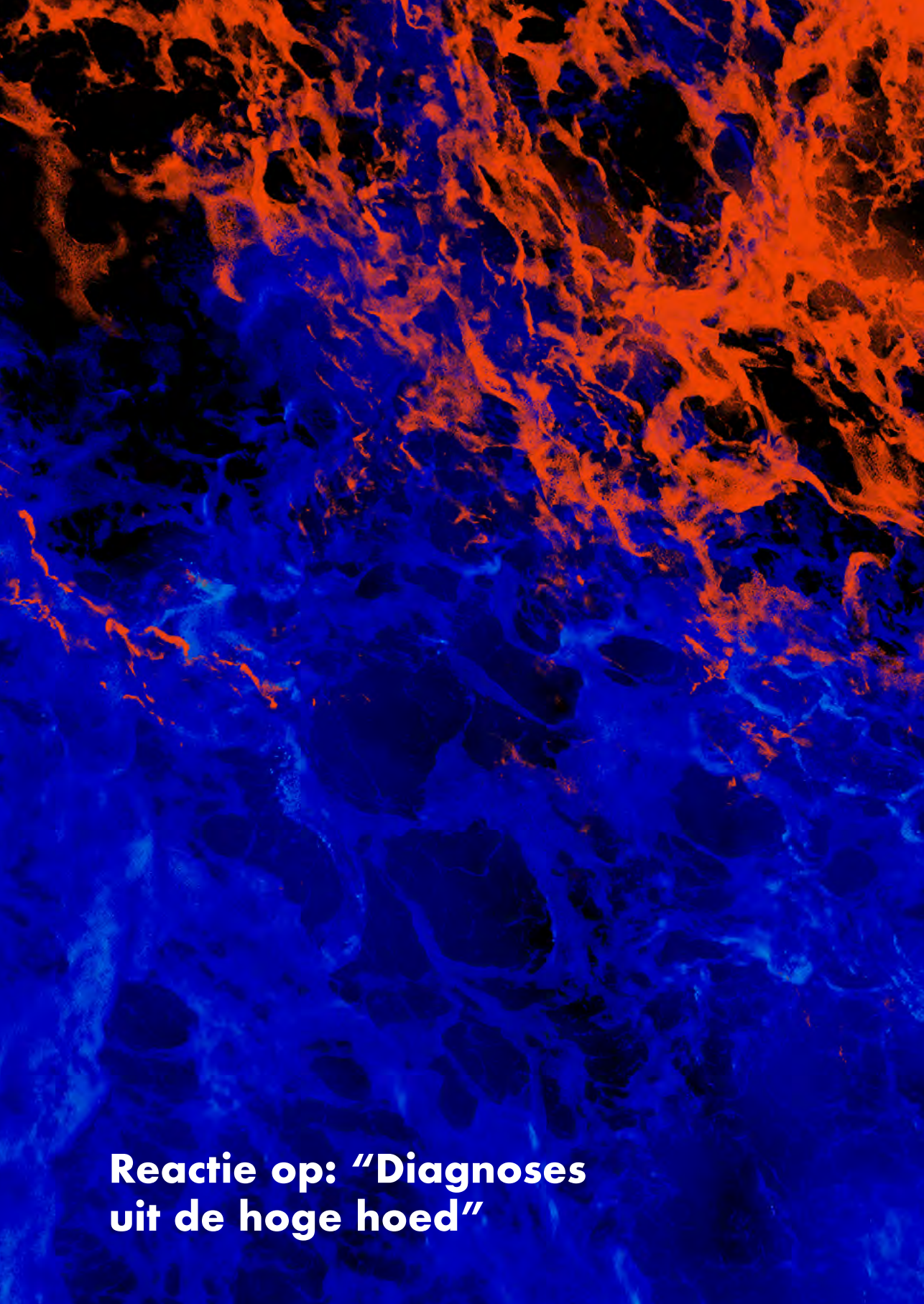
With great interested we read the article by Zhang et al[1], who studied the association between admission blood neutrophil counts with in-hospital mortality (IHM) and hospital acquired infections (HAI), in a retrospective observational study including 6041 patients with aneurysmal subarachnoid hemorrhage. They used propensity score matching (PSM) and multivariable logistic regression modeling (LRM) to investigate differences in IHM and HAI in patients with high and with low admission blood neutrophil counts, dichotomized at the median. They included age, sex, hypertension, diabetes, chronic renal failure, coronary heart disease, smoking, alcohol use, Hunt & Hess grade, and Fisher grade as confounders for PSM, and additionally, added time from onset to admission, external ventricular drain, and aneurysm treatment as confounders in the LRM.

They found that high admission neutrophil counts were associated with increased risk of IHM (OR 1.53 [95% CI, 1.14-2.06]) and HAI (OR 1.61 [95% CI, 1.38-1.79]). They conclude that quantification of admission neutrophil counts may help physicians to design more effective management, and they suggest a role for prophylactic antibiotic treatment.

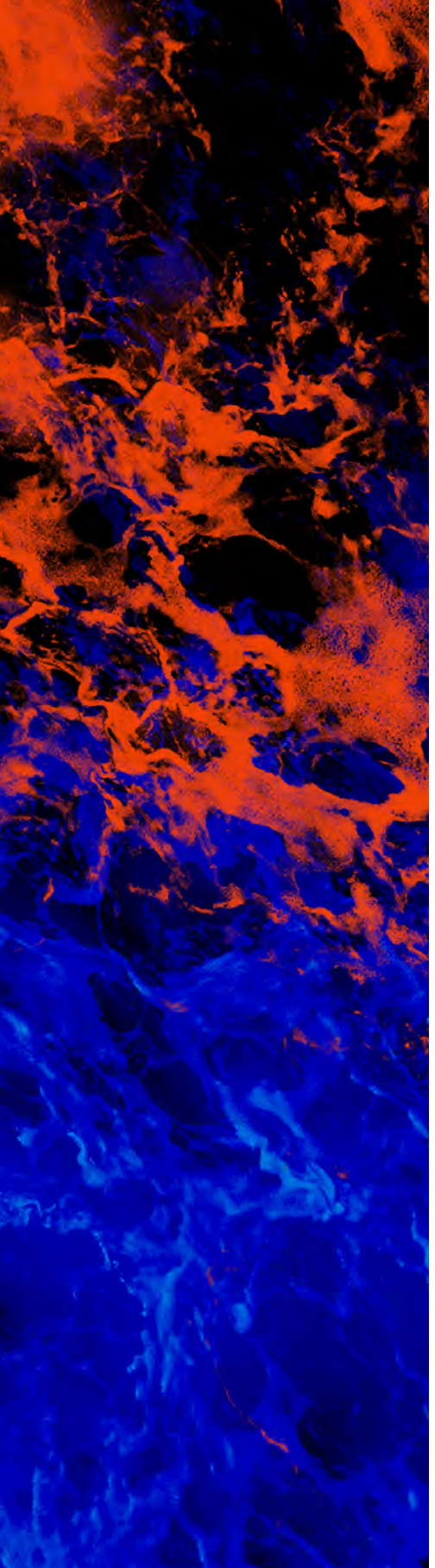
The authors excluded 22% (1708/7749) of patients because the admission blood neutrophil counts were not available. While the authors do mention in the discussion that this could have led to ascertainment bias, we believe that this aspect was underappreciated. It is of paramount importance to demonstrate that missing admission neutrophil counts were not related with treatment or with the outcome to obtain unbiased results[2]. It is possible that patients with poor prognosis were not subjected to laboratory investigation, and not considered for further treatment. While the authors do perform multiple imputation, they only do so after excluding patients with incomplete admission neutrophil counts, which in fact makes this a complete case analysis. Although the authors thoroughly demonstrate that there is little difference between the results of the PSM and LRM analysis, possibly, they are equally biased. In conclusion, we thank the authors for drawing our attention to the suggested association of admission neutrophil count and outcome. Admission neutrophil count can be considered as a factor in future prediction modeling studies.

References

1. Zhang, Y.; Li, L.; Jia, L.; Li, T.; Di, Y.; Wang, P., et al. Neutrophil Counts as Promising Marker for Predicting In-Hospital Mortality in Aneurysmal Subarachnoid Hemorrhage. *Stroke* **2021**, 52, 3266-75.
2. van der Heijden, G.J.; Donders, A.R.; Stijnen, T.; Moons, K.G. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. *J Clin Epidemiol* **2006**, 59, 1102-9.



Reactie op: “Diagnoses uit de hoge hoed”



Medisch Contact 2022;77:39.
No Peer Review.
Jordi de Winkel

In het Medisch Contact van 15 juni 2022 neemt dr. Miquel Ekkelenkamp, arts-microbioloog in het UMC Utrecht, commerciële algoritmen en medische predictiemodellen onder de loep. Met een geestige kwinkslag stelt Ekkelenkamp dat grote Tech bedrijven angstvallig hun intellectueel eigendom beschermen terwijl de algoritmen meestal teleurstellen. Ekkelenkamp trekt een parallel met medische predictiemodellen. Zijn Pubmed search levert een grote hoeveelheid aan ontwikkelde modellen op terwijl er weinig in de klinische praktijk worden geïmplementeerd. Hij concludeert: *"Kennelijk vertrouwen de meeste artsen een voorspelling uit een computer pas als ze tot in detail kunnen nagaan waar die op is gebaseerd – en dan kunnen ze ook wel zonder al die ICT. Dat lijkt me terecht."*.

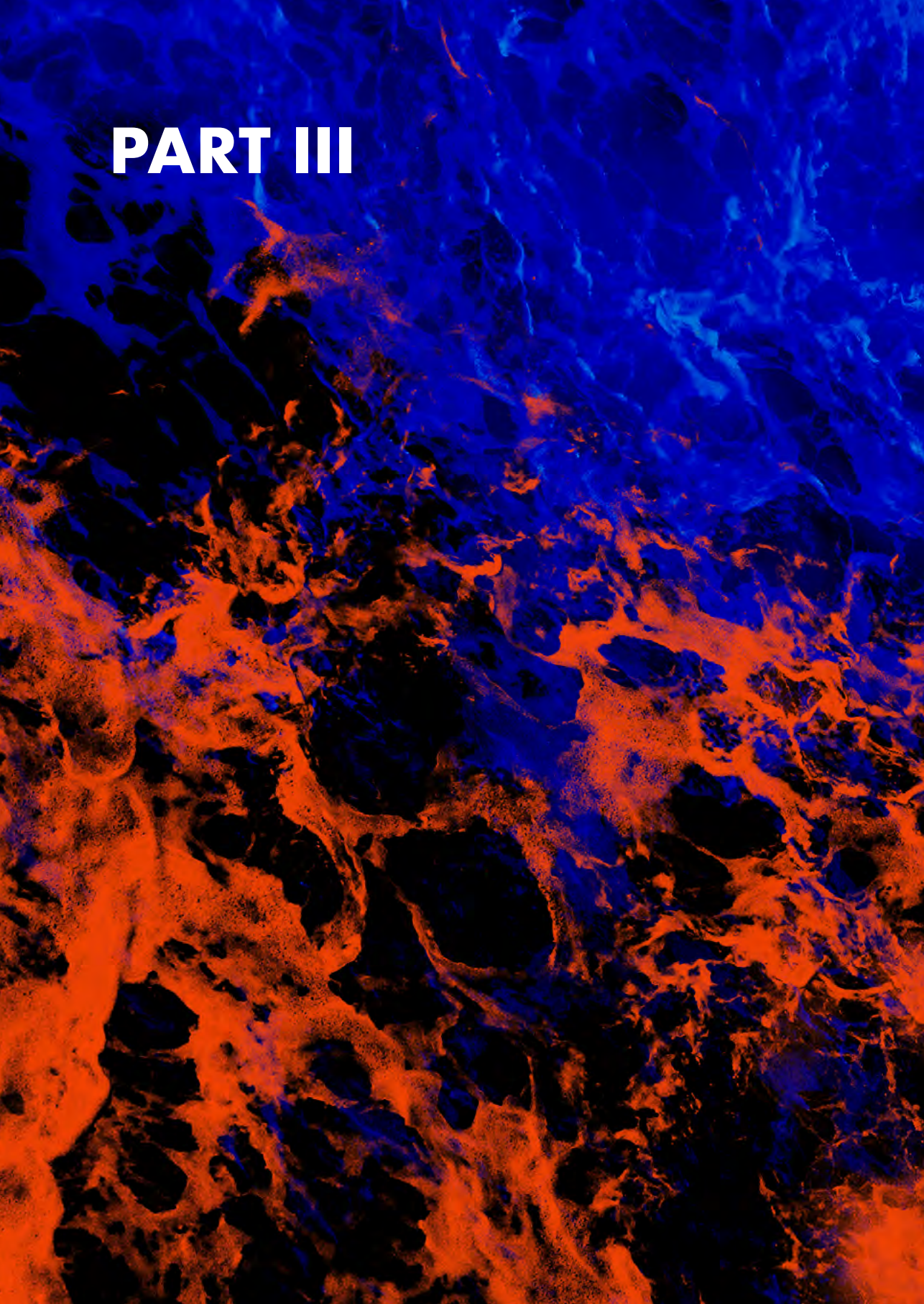
In deze laatste bewering is er sprake van een denkfout. Er is inderdaad een discrepantie in het aantal ontwikkelde modellen en het aantal dat is geïmplementeerd in de klinisch praktijk.[1] Het is ook aannemelijk dat een intuïtiever model een grotere kans maakt om geïmplementeerd te worden. Dit betekent echter niet dat een clinicus altijd even goed is in het maken van complexe multivariabele voorspellingen als een predictiemodel.[2,3] Het is voor het menselijke brein lastig om meerdere variabelen die van elkaar afhankelijke zijn te wegen en op basis daarvan tot een betrouwbare schatting te komen. Hou hierbij ook rekening met het feit dat niet elke variabele een lineair verband heeft met de uitkomst, en dat sommige variabelen elkaars invloed op de uitkomst kunnen beïnvloeden.

Er zijn nog meer redenen waarom een predictiemodel niet wordt geïmplementeerd in de klinisch praktijk. Bijvoorbeeld omdat de variabelen slecht gedefinieerd of niet beschikbaar zijn, omdat het model slecht presteert of een externe validatie hiervan ontbreekt, of doordat, zoals Ekkelenkamp terecht stelt, de voorspellingen op een ondoorzichtige manier tot stand komen.[4,5] Dit laatste geldt met name voor machine learning modellen.[6] Het over één kam scheren van gecompliceerde "black-box" machine learning modellen en eenvoudige intuïtieve prognostische of diagnostisch modellen is niet correct.

De suggestie dat medici die gebruikmaken van dit soort modellen "*blind varen*" doet geen recht aan de expertise die over de jaren heen is opgebouwd. Van degene die hierna tóch besluiten geen gebruik te maken van predictiemodellen, moeten we vooral hopen dat zij durven inconsequent te zijn. Beter ten halve gekeerd dan ten hele gedwaald.

Referenties

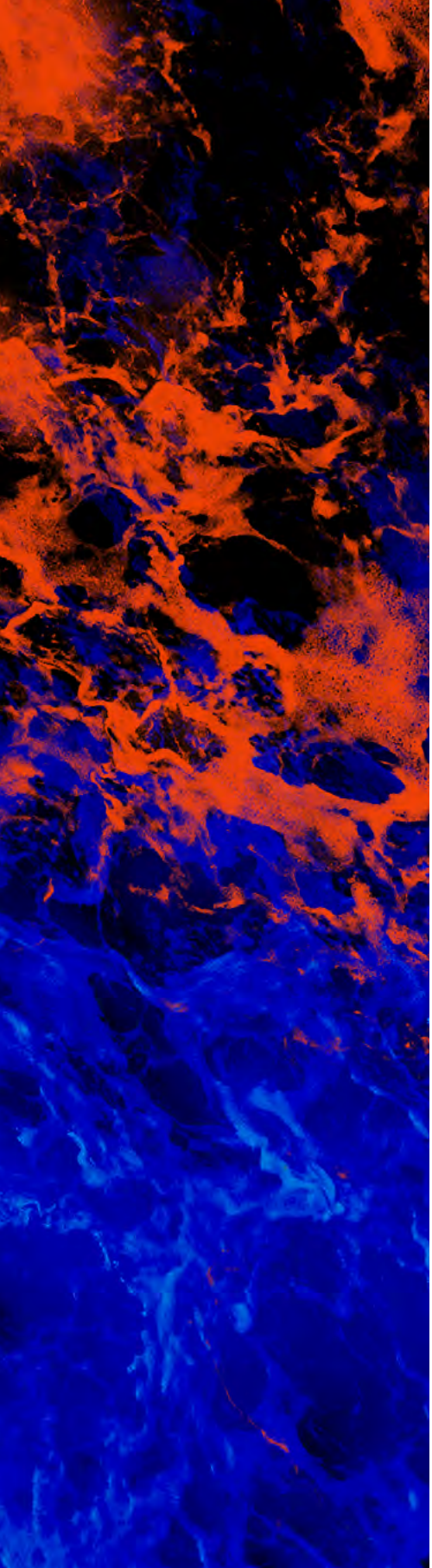
1. Damen JA, Hooft L, Schuit E, Debray TP, Collins GS, Tzoulaki I, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. BMJ. 2016;353:i2416.
2. Stiell I, Wells G, Laupacis A, Brison R, Verbeek R, Vandemheen K, et al. Multicentre trial to introduce the Ottawa ankle rules for use of radiography in acute ankle injuries. Multicentre Ankle Rule Study Group. BMJ. 1995;311(7005):594-7.
3. Spanos A, Harrell FE, Jr., Durack DT. Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations. JAMA. 1989;262(19):2700-7.
4. Toll DB, Janssen KJ, Vergouwe Y, Moons KG. Validation, updating and impact of clinical prediction rules: a review. J Clin Epidemiol. 2008;61(11):1085-94.
5. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ. 2009;338:b606.
6. Wilkinson J, Arnold KF, Murray EJ, van Smeden M, Carr K, Sippy R, et al. Time to reality check the promises of machine learning-powered precision medicine. Lancet Digit Health. 2020;2(12):e677-e80.


PART III


Personalized
Decision-Making

CHAPTER VI

Endovascular Versus Neurosurgical Aneurysm Treatment: A Study Protocol for Derivation and Validation of a Clinical Prediction-Tool for Individualized Decision-Making



BMJ Open, 2022.
Jordi de Winkel, Bob Roozenbeek,
Simone A Dijkland, Ruben Dammers,
Pieter-Jan van Doormaal, Matieu van der Jagt,
David van Klaveren, Diederik WJ Dippel,
Hester F Lingsma.

Abstract

Introduction: Treatment decisions for aneurysmal subarachnoid haemorrhage patients should be supported by individualised predictions of the effects of aneurysm treatment. We present a study protocol and analysis plan for the development and external validation of models to predict benefit of neurosurgical versus endovascular aneurysm treatment on functional outcome and durability of treatment.

Methods and analysis: We will use data from the International Subarachnoid Aneurysm Trial for model development. The outcomes are functional outcome, measured with modified Rankin Scale at 12 months, and any retreatment or rebleed of the target aneurysm during follow-up. We will develop an ordinal logistic regression model and Cox regression model, considering age, World Federation of Neurological Surgeons grade, Fisher grade, vasospasm at presentation, aneurysm lumen size, aneurysm neck size, aneurysm location and time-to-aneurysm-treatment as predictors. We will test for interactions with treatment and with baseline risk and derive individualised predicted probabilities of treatment benefit. A benefit of ≥5%will be considered clinically relevant. Discriminative performance of the outcome predictions will be assessed with the *c*-statistic. Calibration will be assessed with calibration plots. Discriminative performance of the benefit predictions will be assessed with the *c*-for benefit. We will assess internal validity with bootstrapping and external validity with leave-one-out internal-external cross-validation.

Ethics and dissemination: The medical ethical research committee of the Erasmus MC University Medical Center Rotterdam approved the study protocol under the exemption category and waived the need for written informed consent (MEC-2020-0810). We will disseminate our results through an open-access peer-reviewed scientific publication and with a web-based clinical prediction tool.

Introduction

In the past decade, trial evidence showed that, in patients with aneurysmal subarachnoid haemorrhage (aSAH), endovascular aneurysm treatment leads to improved functional outcome in comparison to neurosurgical aneurysm treatment.[1–4] Because of this, it is customary to provide endovascular aneurysm treatment when patients are, in the perception of the clinicians, equally eligible for both treatment approaches.[5–7] This principle is referred to as 'treatment equipoise'. However, long-term follow-up revealed that patients who underwent neurosurgical aneurysm treatment had a higher degree of aneurysm occlusion, and lower rates of rebleeding and retreatment of the target aneurysm.[2,8] There is a trade-off between shortterm to medium-term expected functional outcome and the long-term risk of complications related to rebleeding and retreatment. In the International Subarachnoid Aneurysm Trial (ISAT), on average, the excess retreatment and rebleeding following endovascular treatment did not lead to a worse functional outcome at longest follow-up.[9] However, evidence from randomised controlled trials (RCTs) applies to the population as a whole. Ideally, treatment effects are estimated for the individual patient. To assess individual patient treatment benefit it is necessary to model for heterogeneity of treatment effect. This means that the direction and magnitude of the treatment effect can vary depending on patient characteristics.[10] Clinical prediction models accounting for this heterogeneity can enable personalised decision making and lead to improved patient outcome. For aSAH patients this could mean, weighing the individualised risk of rebleeding and retreatment against the individualised probability of favourable functional outcome. We present a study protocol for a study aiming to develop a clinical prediction tool to predict benefit of endovascular and neurosurgical aneurysm treatment in terms of functional outcome and durability of aneurysm treatment in individual patients with aSAH.

Methods and Analysis

Development Cohort

We will use data from the ISAT trial for model development. The ISAT trial was an international multicentre RCT that included 2143 patients with aSAH.[11] The ISAT trial aimed to investigate the safety and efficacy of neurosurgical versus endovascular aneurysm treatment for patients with

aSAH. Patient eligibility was based on the treatment equipoise policy. Patients were randomly assigned to neurosurgical aneurysm treatment or endovascular aneurysm treatment in a 1:1 ratio with a 24-hour telephone randomisation service. Detailed information about the study protocol can be found elsewhere.[12] An advantage of using trial data for development of a prediction model is that the data are carefully and prospectively collected with a generally well-defined study population. Too stringent selection criteria may, however, limit generalisability.[13] Since ISAT was published there has been extensive debate regarding the generalisability of the study population.[14,15] Because of the treatment equipoise policy in the ISAT study, 80% of the initially screened patients were excluded.[14] However, in this study, we specifically target the remaining 20%. Ultimately, in ISAT, there was an underrepresentation of elderly and poor-grade patients, as well as aneurysms located at the middle cerebral artery or in the posterior circulation. Also, aneurysms in the ISAT study population were smaller. This could lead to increased uncertainty on the effect of a predictor with fewer observations.

Outcomes of Interest

The outcomes of interest are the modified Rankin Scale (mRS) score at 12 months and any rebleed or retreatment of the target aneurysm after aneurysm treatment during follow-up. The mRS is a seven-point scale ranging from 0—no symptoms to 6—death.[16] In ISAT the mRs scores were collected with a standardized postal questionnaire.[17] For presentation purposes, favourable functional outcome will be defined as mRS 0–2. The total duration of follow-up of the ISAT trial was 18 years. We will define rebleed as any clinically or radiologically confirmed SAH after the first (partial) occlusion of the aneurysm. Retreatment will be defined as any endovascular or neurosurgical reintervention of the target aneurysm. The target aneurysm will be defined as the aneurysm which was identified as the origin of SAH and subsequently treated. If a patient was retreated because of a rebleed we will consider this a 'rebleed'. Cross-over or a second treatment attempt after initial failed treatment without (partial) occlusion will not be considered retreatment. All patients in the development cohort are eligible for inclusion in the model predicting functional outcome. In the model predicting any rebleed or retreatment during follow-up, we will exclude patients that have not had aneurysm treatment.

Potential Predictors

Potential predictors are selected based on clinical expertise and literature review. To fit the purpose of guiding aneurysm treatment decision making, we will only consider predictors that are available during early admission in a standard clinical setting. For both models, we consider age, World Federation of Neurological Surgeons (WFNS) grade, Fisher grade, vasospasm at presentation, aneurysm lumen size, aneurysm neck size, aneurysm location, aneurysm treatment and time-to-aneurysm treatment. Aneurysm lumen size will be defined as the maximum lumen size of the aneurysm dome. Aneurysm location will be categorised as anterior cerebral artery, anterior communicating artery, middle cerebral artery, posterior communicating artery, internal carotid artery and other posterior circulation aneurysms. Aneurysm treatment will be entered into the model as the allocated or assigned treatment. Vasospasm at presentation will be dichotomised into present or absent.

Missing Data

We will use multiple imputation to account for missing data (Table 1). The proportion of missing data in ISAT was negligible. We assume that data are missing at random. The imputation model will contain the predictors and the outcomes, with the addition of sex. We will inspect patterns of missingness and assess the imputed data for adequacy. Possibly, patients that did not receive aneurysm treatment may have had an unfavourable prognosis (not justifying further treatment) or died beforehand. Because of this, we anticipate missing values for the time-toaneurysm-treatment variable. In the model predicting durability of treatment, we will exclude patients without time-to-aneurysm-treatment because the model will only be used for patients that will receive aneurysm treatment. However, in the model predicting functional outcome, this will lead to selection bias. Additionally, we cannot perform multiple imputation because time-to-aneurysm treatment is missing-not-at-random (i.e., missingness is related to the outcome). To account for this, we will truncate time-to-aneurysm treatment at the 95th percentile. We will assign the value of the 95th percentile to patients that for whatever reason did not receive aneurysm treatment. This approach may lead to a (slight) overestimation of the effect size of time-to-aneurysm-treatment.

Table 1. Baseline characteristics of the derivation cohort and availability of predictors and outcomes.

Variable	*n* Completed (%)	Derivation cohort
Age (years) – mean (SD)	2143 (100)	52 (11.6)
Sex (female) – n (%)	2143 (100)	1345 (63)
WFNS grade – n (%)	2112 (99)	
I		1335 (62)
II		549 (26)
III		134 (6)
IV		74 (3)
V		20 (1)
Fisher grade – n (%)	2129 (99)	
1		114 (5)
2		360 (17)
3		902 (42)
4		753 (35)
Severity of vasospasm at presentation – n (%)	2143 (100)	
Absent		1694 (79)
Present		449 (21)
Aneurysm lumen size (mm) – median (range)	2143 (100)	5 (4-7)
Aneurysm neck size >4mm – n (%)	2138 (100)	580 (27)
Aneurysm location – n (%)	2143 (100)	
Internal carotid artery		490 (23)
Anterior cerebral artery		528 (25)
Middle cerebral artery		303 (14)
Anterior communicating artery		556 (26)
Posterior communicating artery		207 (10)
Other posterior circulation aneurysms*		59 (3)
Allocated treatment – n (%)	2143 (100)	
Endovascular		1073 (50)
Neurosurgical		1070 (50)
Time-to-aneurysm-treatment (days) – median (range)†	2108 (98)	3 (2-6)
12-month mRS – n (%)	2134 (100)	

0		462 (22)
1		595 (28)
2		501 (24)
Favorable (0-2)		1558 (73)
3		247 (12)
4		73 (3)
5		66 (3)
Died		190 (9)
Unfavorable (3-6)		576 (27)
Retreatment of target aneurysm – n (%)	2108 (98)	134 (6)
Rebleed of target aneurysm – n (%)	2108 (98)	74 (4)

Abbreviations: mm = millimeter; mRS = modified Rankin Score; SD = standard deviation; WFNS grade = World Federation of Neurological Surgeons grade.
* Other posterior circulating aneurysms locations are vertebral artery, basilar artery, anterior inferior cerebellar artery, posterior inferior cerebellar artery, and superior cerebellar artery.
† Time-to-aneurysm-treatment is truncated at 14 days. In the ordinal model, missing time-to-aneurysm-treatment will be imputed with the mean. In the Cox model, any patient that has not received aneurysm treatment will be imputed with 14 days.

Model Specification and Estimation

We will use ordinal logistic regression to develop a model for the mRS. Effect size estimates will be expressed as common ORs with 95% CIs. We will use Cox regression to develop a model for the time-to-event outcomes. Censoring occurs when patients are lost to follow-up or in case of death. Effect size estimates will be expressed as hazard ratios with 95% CIs. To reduce the full model to the preliminary main effects model we will eliminate all predictors with a significance level above the threshold of $p>0.20$, and assess the changes in the remaining coefficients. The potential nonlinearity of continuous predictors will be assessed by likelihood ratio tests (LRTs) of restricted cubic splines. We will also use LRTs to assess interaction with treatment of predictors and of baseline risk. We will consider interaction with treatment for: age, vasospasm at presentation, aneurysm lumen size, aneurysm location, aneurysm neck size and time-to-aneurysm treatment. If the omnibus LRT indicates additivity, the individual predictors will be tested one by one with a more stringent $p<0.05$ for non-linearity. We will take several other measures to prevent overfitting. First, all predictors are preselected based on clinical knowledge and expertise. Next, we apply lenient p value to select predictors for the preliminary main effects models. Last, we will be parsimonious and test only those for interaction with treatment of predictors that are clinically plausible. We will comply with

the PATH statement in modelling for heterogeneity in treatment effect.[10,18] All statistical analyses will be performed with R software (Version 4.1.1, R Foundation for Statistical Computing) using the rms (Version 6.2.0), Hmisc (Version 4.5.0), survival (Version 3.3.1) and mice (Version 3.13.0) packages.

Benefit of Treatment

We will derive predicted probabilities of favourable outcome at 12 months and of any retreatment or rebleed within 10 years follow-up for patients with aneurysms treated endovascular and neurosurgical. Treatment benefit will be defined as the absolute difference between the predicted probability of favourable functional outcome, and the predicted probability of retreatment or rebleed, with endovascular and neurosurgical aneurysm treatment. A benefit of ≥5% will be considered clinically relevant.

Model Performance

We will assess model performance in terms of discrimination and calibration. Prediction models need to discriminate between patients who experience the event and patients who do not. Furthermore, the model must have accurate risk estimates—the ratio between the predicted and the observed events for an ordinal outcome, or time to event for survival data.[19,20] We will assess performance of the outcome predictions with the *c*-statistic and with calibration plots.[19] To assess the performance of the benefit predictions we will use the *c*-for-benefit.[21,22] We consider rebleed and retreatment as markers of revascularisation of the aneurysm and assume that predictors of rebleed and retreatment are equal. We will test this assumption by performing a sensitivity analysis. We will rerun the model with separate outcomes and evaluate the discriminative performance.

Validation

To assess internal validity, we will use bootstrapping.[23] We will draw 200 random samples from the study population and analyse them as if they were an original sample. By subtracting the difference in performance, or mean optimism estimate, between the bootstrap and original sample, we obtain the optimism-corrected performance estimates.[24] The final coefficients will be shrunk with penalised regression. External validation is an underappreciated step in prediction modelling, and it has led to a sprawl of prediction models that are of low quality and sparsely used in the clinical context. Ideally, external validation of a model predicting treatment benefit is performed with randomised data.[10] Besides the ISAT trial, at present, three trials investigated the safety and efficacy of endovascular versus

neurosurgical aneurysm treatment.[1,3,4] Taking into account the sample size and the need for longterm follow-up only the BRAT trial is eligible. At present, we do not have access to these data. Therefore, we will use leave-one-out internal-external cross-validation to assess external validity. Generalisability may be affected due to technological improvement or increased experience in endovascular techniques, and other supportive treatments. Possibly due to these improvements, since the publication of ISAT, the rates of retreatment and rebleeding of the target aneurysm have decreased.[25] Sample size calculation Many prediction models are underpowered for the number of parameters in the model.[26] We used the pmsampsize package (V.1.1.12) to calculate the required sample size for the Cox model.[27,28] Based on the number of considered parameters,[20] the event rate of rebleed or retreatment (estimated at 0.05 per year), and the estimated r2 value based on previous models (30%), the total required sample size is 494 patients. In the development cohort, we have 2143 patients, meaning that our sample size is sufficient for reliable modelling. Because no similar tool exists for a model with an ordinal outcome, we apply the rule of thumb of a minimum of 10 events per variable,[29–32] which would theoretically allow us to test for ≈ 200 parameters. For external validation, a minimum sample size of at least 100 events and non-events is proposed.[33]

Patient and Public Involvement
None.

Ethics and dissemination

The medical ethical research committee of the Erasmus MC University Medical Center Rotterdam approved the study protocol under the exemption category and waived the need for written informed consent (MEC-2020-0810). We plan to disseminate our results through an open-access publication in a peer-reviewed scientific journal and conference presentations. We will adhere to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement, a 22-item reporting checklist for prediction modelling studies.[34] The R code of the models will be made publicly available for transparency and to enhance future external validation and model updating efforts. The R code will be accessible via: https://github.com/WinkelJordi/SHARP. The data needed to conduct this study has been received and is prepared for analysis. We anticipate finishing the analysis and ready the manuscript for submission

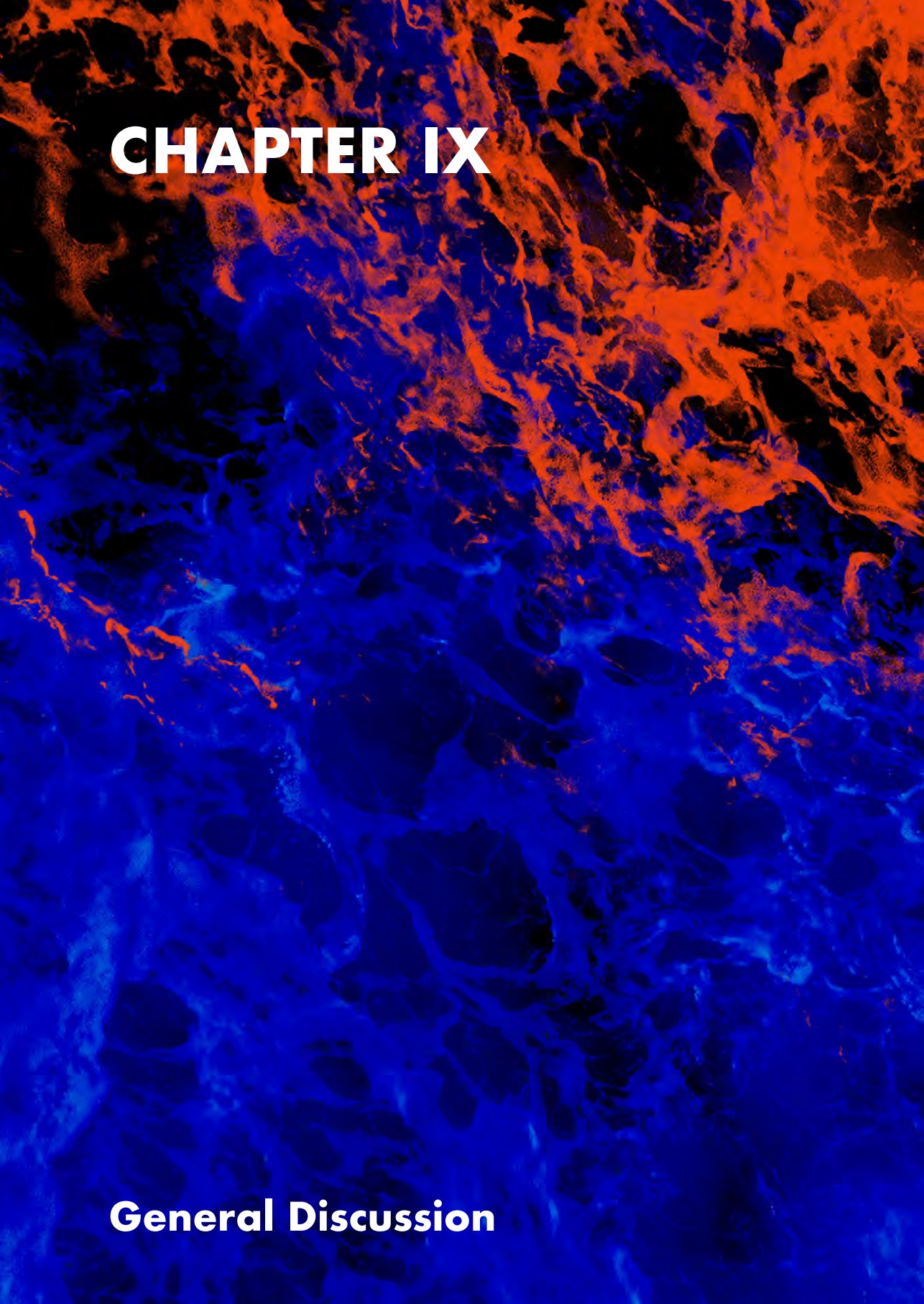
no later than 1 August 2023. The developed models will be integrated into a webbased clinical prediction tool. The web-based clinical prediction tool will be developed using the Shiny package (V.1.7.0). This tool will provide absolute estimates, based on baseline patient characteristics, of benefit of treatment in terms of functional outcome and durability of treatment. In the future, this tool could potentially be used to choose the optimal treatment strategy, maximising favourable functional outcome and durability of treatment. Previously, a similar tool has been proposed for intra-arterial treatment for acute ischaemic stroke.[35] The proposed study will provide much-needed individually tailored evidence in the long-lasting discussion of neurosurgical versus endovascular aneurysm treatment. We believe that this study will prove to be an important addition to personalised medicine in the field of aSAH.

References

1. McDougall CG, Spetzler RF, Zabramski JM, et al. The Barrow ruptured aneurysm trial. J Neurosurg 2012;116:135–44.
2. Molyneux AJ, Birks J, Clarke A, et al. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International subarachnoid aneurysm trial (ISAT). Lancet 2015;385:691–7.
3. Vanninen R, Koivisto T, Saari T, et al. Ruptured intracranial aneurysms: acute endovascular treatment with electrolytically detachable coils--a prospective randomized study. Radiology1999;211:325–36.
4. Koivisto T, Vanninen R, Hurskainen H, et al. Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms. A prospective randomized study. Stroke 2000;31:2369–77.
5. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American heart association/american stroke association. Stroke 2012;43:1711–37.
6. de Winkel J, van der Jagt M, Lingsma HF, et al. International practice variability in treatment of aneurysmal subarachnoid hemorrhage. J Clin Med 2021;10. doi:10.3390/jcm10040762. [Epub ahead of print: 14 02 2021].
7. Steiner T, Juvela S, Unterberg A, et al. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis 2013;35:93–112.
8. Spetzler RF, McDougall CG, Zabramski JM, et al. Ten-year analysis of saccular aneurysms in the Barrow ruptured aneurysm trial. J Neurosurg 2019;132:771–6.
9. Campi A, Ramzi N, Molyneux AJ, et al. Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in the International subarachnoid aneurysm trial (ISAT). Stroke 2007;38:1538–44.
10. Kent DM, Paulus JK, van Klaveren D, et al. The predictive approaches to treatment effect heterogeneity (PATH) statement. Ann Intern Med 2020;172:35–45.
11. Molyneux AJ, Kerr RSC, Yu L-M, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet 2005;366:809–17.
12. Molyneux A, Kerr R, et al, International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized trial. J Stroke Cerebrovasc Dis 2002;11:304–14.

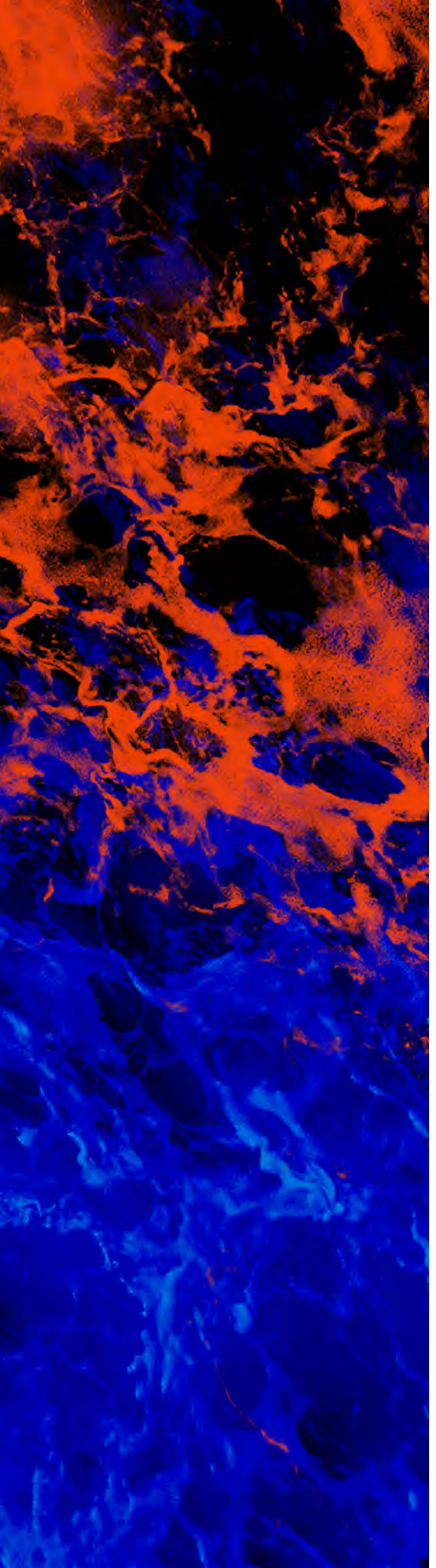
13. Steyerberg EW. Clinical Prediction Models. In: A practical approach to development, validation, and updating. Springer, 2019.
14. Ausman JI. ISAT study: is coiling better than clipping? Surg Neurol 2003;59:discussion 5-73; author reply 73-5:162–5.
15. Britz GW. ISAT trial: coiling or clipping for intracranial aneurysms? Lancet 2005;366:783–5.
16. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–7.
17. Lindley RI, Waddell F, Livingstone M, et al. Can simple questions assess outcome after stroke? Cerebrovasc Dis 1994;4:314–24.
18. Kent DM, van Klaveren D, Paulus JK, et al. The predictive approaches to treatment effect heterogeneity (path) statement: explanation and elaboration. Ann Intern Med 2020;172:W1–25.
19. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21:128–38.
20. Van Calster B, Nieboer D, Vergouwe Y, et al. A calibration hierarchy for risk models was defined: from utopia to empirical data. J Clin Epidemiol 2016;74:167–76.
21. van Klaveren D, Steyerberg EW, Serruys PW, et al. The proposed 'concordance-statistic for benefit' provided a useful metric when modeling heterogeneous treatment effects. J Clin Epidemiol2018;94:59–68.
22. Takahashi K, Serruys PW, Fuster V, et al. Redevelopment and validation of the SYNTAX score II to individualise decision making between percutaneous and surgical revascularisation in patients with complex coronary artery disease: secondary analysis of the multicentre randomised controlled SYNTAXES trial with external cohort validation. Lancet 2020;396:1399–412.
23. Efron B, Tibshirani RJ. An introduction to the bootstrap. 1st ed. Chapman & Hall/CRC, 1994.
24. Harrell FE. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. New York: Springer, 2015.
25. Catapano JS, Labib MA, Srinivasan VM, et al. Saccular aneurysms in the post-Barrow ruptured aneurysm trial era. J Neurosurg 2021:1–8.
26. Wessler BS, Lai Yh L, Kramer W, et al. Clinical prediction models for cardiovascular disease: Tufts predictive analytics and comparative effectiveness clinical prediction model database. Circ Cardiovasc Qual Outcomes 2015;8:368–75.
27. Riley RD, Snell KI, Ensor J, et al. Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. Stat Med 2019;38:1276–96.
28. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for

developing a clinical prediction model. BMJ 2020;368:m441.
29. Harrell FE, Lee KL, Califf RM, et al. Regression modelling strategies for improved prognostic prediction. Stat Med 1984;3:143–52.
30. Peduzzi P, Concato J, Feinstein AR, et al. Importance of events per independent variable in proportional hazards regression analysis. II. accuracy and precision of regression estimates. J Clin Epidemiol 1995;48:1503–10.
31. Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373–9.
32. Steyerberg EW, Eijkemans MJ, Harrell FE, et al. Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. Med Decis Making 2001;21:45–56.
33. Vergouwe Y, Steyerberg EW, Eijkemans MJC, et al. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. J Clin Epidemiol 2005;58:475–83.
34. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. Br J Surg 2015;102:148–58.
35. Venema E, Mulder MJHL, Roozenbeek B, et al. Selection of patients for intra-arterial treatment for acute ischaemic stroke: development and validation of a clinical decision tool in two randomised trials. BMJ 2017;357:j1710.



CHAPTER IX

General Discussion



This thesis is built on the hypothesis that to improve outcome in aSAH patients, we must shift from one-size fits all policies to individualized treatment decision-making. I examined three possibilities to do so: (1) understanding and identifying practice variability that enables conducting comparative effectiveness research (CER) on observational data and (2) acquiring individualized estimates of outcome, and of (3) treatment effect to tailor treatment to the individual patient.

Textbox 1. Aims of this thesis.

1. **To characterize international variations in treatment and organizational aspects of care that could impact outcomes in patients with aSAH.**

2. **To optimize and individualize outcome prediction for patients with aSAH.**
   - To systematically review and meta-analyze early predictors of functional outcome in poor-grade aSAH patients.
   - To externally validate the ARISE prediction models for predicting pre-interventional aneurysmal rerupture within 24 and 72 hours.
   - To illustrate the pitfalls of single-study external validation by conducting a large number of external validations of a prediction model for functional outcome in aSAH patients.

3. **To optimize and individualize treatment in patients with aneurysmal subarachnoid hemorrhage.**
   - To develop and internal-externally validate a prediction tool to predict benefit of endovascular coiling compared to neurosurgical clip-reconstruction.
   - To develop a decision model to investigate the optimal aneurysm treatment strategy for individual aSAH patients.

PART I: Characterizing Practice Variation

The Choice and Timing of Aneurysm Treatment

The choice of aneurysm treatment in the American and European SAH guidelines is supported by level 1 evidence.[1,2] In 2006, the randomized International Subarachnoid Aneurysm Trial (ISAT) compared endovascular coiling with (conventional) neurosurgical clip-reconstruction and found that, on average, coiling led to better functional outcome compared to

neurosurgical clip-reconstruction in patients amenable to both strategies.[3] This effect persisted for more than a decade after the initial treatment.[4] The benefit of endovascular coiling over neurosurgical clip-reconstruction was later confirmed in the (pseudo)-randomized Barrow Ruptured Aneurysm Trial (BRAT).[5]

Despite the existence of the abovementioned guidelines, we found evidence of large practice variability in the choice of aneurysm treatment in our survey study **(Chapter 2)**. The reported proportion of patients who underwent endovascular treatment per center ranged from 0-100% (mean 65%). Twenty-five percent of centers reported to treat more than 90% of patients endovascularly, while another 25% of centers reported to treat less than 50% of patients endovascularly. This variability cannot be explained by centers that treat aneurysms exclusively neurosurgically or endovascularly – since only 4 centers (3%) exclusively employed one specific intervention.

While it is widely understood that aneurysms must be secured, the timing of aneurysm treatment is still being debated. It may seem logical to do so as soon as possible to avoid potential rebleeds, however the high-quality evidence on the timing of aneurysm treatment is both limited and conflicting. A 2017 meta-analysis found that early aneurysm treatment (<24 hours versus 24 to 72 hours) showed a reduction in the incidence of rebleeds but did not effectively improve outcome, which was assessed at varying time points.[6] Subsequently, guidelines state that aneurysm occlusion should be performed as early as logistically and technically feasible and no later than 72 hours after the ictus.[1,2] There have been no substantial changes in this recommendation in the latest update of the American Heart Association/ American Stroke Association guideline.[7]

Similar to the choice of type of aneurysm treatment, we observed a large degree of practice variability in the timing of aneurysm treatment. Sixty-five percent of respondents reported treating the majority (>50%) of aneurysms within 24 hours, 18% reported treating the majority between 24 and 48 hours, and 8% reported treating the majority between 48-72 hours. It is important to note that, as with all survey studies, these results may have been affected by recall bias.

One particular concern that must be investigated is whether these differences are caused by health disparities such as (timely) access to endovascular treatment. We observed geographical differences in the proportion of aneurysms that are treated endovascularly. In the centers located in the United States the mean proportion was 72% and in European centers 70%. In "other participating centers" this proportion was 51%. These regional differences were statistically significant (United States

versus "other" $p<0.001$ and Europe versus "other" $p<0.01$). The timing of aneurysm treatment also varied geographically. In the centers located in the United States the majority of patients were estimated to be treated within 24 hours (77%). This was also observed for European centers (67%). Again, we found a statistically significant difference between the centers located in the United States and other participating centers ($p<0.001$) and between European centers and other participating centers ($p<0.01$). If health disparities (partially) explain the non-adherence to guideline recommendations, a possible target for improving outcomes could be identifying factors that contribute to delay of aneurysm treatment. Increasing access to endovascular aneurysm treatment is another potential target for improvement. It must be noted that due to a lack of representation in the developing world, our survey study does not accurately display SAH care in such areas.

Another possibility is that practice variation is caused by uncertainty in the available evidence. For example, there have been serious concerns about the generalizability of the ISAT due to its pragmatic trial design.[8] By including only aSAH patients amenable to both strategies, the study population became heavily selected. Ninety percent of initially screened patients were excluded.[9] As a consequence, certain aneurysm locations as well as poor-grade aSAH patients were underrepresented in ISAT. To address this, BRAT was conducted with a liberal all-inclusive policy and confirmed the beneficial effect of endovascular coiling on functional outcome compared to neurosurgical clip-reconstruction. Nevertheless, due to the introduction of new endovascular devices, neurosurgical techniques, and the increasing experience of interventionalists, there are currently no formal criteria for when to treat either endovascularly or neurosurgically. The decision is made multidisciplinary and depends on local preferences and experience rather than evidence. This uncertainty most likely contributes to practice variation.

A similar issue concerning generalizability was observed in the Flow Diversion in the Treatment of Intracranial Aneurysms Trial (FIAT, **PART I**).[10] This Canadian pragmatic care trial of patients who underwent flow diversion versus any alternative standard management options was published in the *American Journal of Neuroradiology*. Patients were included if they had an aneurysm for which flow diversion was deemed a promising treatment. The study showed that flow diversion was associated with fewer poor outcomes (relative risk, 0.68; 95% CI, 0.50–0.92).

Both FIAT and ISAT perfectly exemplify the field of tension between local treatment preferences and generalizability. Stringent selection

criteria and standardized treatment protocols will make trials more easily generalizable. However, specialists elsewhere may not agree on the exact population in which there is clinical equipoise. Additionally, there may be local differences in treatment preference, practitioner experience, how the intervention is performed. This may hamper center participation and patient inclusion. FIAT and ISAT used liberal selection criteria. Patient eligibility depended on local assessment. Since the exact motivation for the determination of eligibility is unknown, it is difficult (if not impossible) to determine to which patient population the results of the trial can be applied. It can be argued that, even if FIAT convincingly showed that certain patients should be treated with flow diversion, we still do not know exactly who these patients are. It is questionable whether you can simply extrapolate the averaged treatment effect from an unknown population.

Practice Variation in ICU Management and DCI Prevention

Many randomized controlled trials (RCTs) have been conducted to examine optimal medical management for patients with aSAH. Most of these trials targeted cerebral vasospasm or pathophysiological pathways associated with delayed cerebral ischemia (DCI). However, the vast majority of these trials failed to significantly reduce death or disability in the population of patients exposed to the experimental intervention. Because of the sparsity of high-quality randomized evidence, a myriad of fluid management, DCI prevention strategies and rescue therapies for cerebral vasospasm exist. In **Chapter 2** practice variability in these policies was investigated.

Firstly, 97% of participating centers adhere to the recommendation to administer nimodipine to aSAH patients to prevent DCI. This recommendation is supported by the British Nimodipine Trial.[11] It supports the idea that, when evidence is unequivocal, there is little room for practice variability. Next, it was found that a substantial proportion of centers still use apply triple-H-therapy. Triple-H therapy aims to increase cerebral perfusion by inducing hypertension, hemodilution, and hypervolemia in patients suspected of DCI. Previous research showed that triple-H therapy is associated with more complications and higher costs, however there is no high-quality evidence proving or disproving its efficacy.[12] The current standard of practice is maintaining euvolemia and using induced hypertension only in patients with established DCI. Nevertheless, 26% of centers still induce hypervolemia and 11% apply hemodilution. In summary, the high degree of practice variation indicates that further research in order to provide evidence-based therapies is urgently needed for aSAH patients. RCTs have yielded little progress in the last decades. Comparative

effectiveness research (CER) on observational data may serve as an alternative strategy for evidence generation. I found that possible targets for such CER could be timing of aneurysm treatment, rescue therapies for DCI, and fluid management in aSAH patients. CER in the field of traumatic brain injury has proven that investigating the latter has led to specific therapeutic recommendations.[13]

PART II: Optimizing and Individualizing Outcome Prediction

Outcome Prediction and Treatment Decision-Making

Most therapies aim to have a beneficial effect on patient outcome. However, perceived or predicted patient outcome also affects treatment decisions. In **Chapter 3**, this was illustrated with an example. In aSAH patients with a WFNS grade or Hunt and Hess grade IV-V, aneurysm treatment is often delayed until neurological recovery to avoid providing futile therapies to moribund patients and to prevent adding to a high proportion of patients ending up in a functionally dependent or vegetative state. However, delaying aneurysm treatment in poor-grade patients may result in rebleeding.

The influence of perceived (poor) prognosis and treatment is often based on expert opinion and not supported by evidence. Treatment choices can be made more effectively by assessing prognosis on an individual level. This allows for treatment to shift from a one-size-fits-all policy to individually tailored decision-making. Clinical prediction models can be used to predict the probability of a disease, or an outcome conditional on a set of patient characteristics.

In **Chapter 3,** patient characteristics that can be considered in the development of such a clinical prediction model are identified. This chapter contains a systematic review and meta-analysis of early predictors of functional outcome in poor-grade aSAH patients. The likelihood of favorable functional outcome in patients with poor-grade aSAH increased with WFNS grade IV and Hunt and Hess grade IV versus V, the presence of clinical improvement before aneurysm treatment, and intact pupillary light reflex, and decreased with older age, increasing modified Fisher grade, and presence of intracerebral hematoma on admission imaging.

This study raises several valuable points. Firstly, it did not identify any novel predictors for the poor-grade patients that have not been previously suggested for the all-grade aSAH population.[12,14-16] There is no

evidence that the predictors of functional outcomes differ in poor-grade aSAH patients from all-grade aSAH patients. As such, the SAHIT model remains the most reliable prediction model to predict functional outcome in all aSAH patients.[14] In the future, the SAHIT model could be extended to include pupillary reflex status, intracerebral hemorrhage, and clinical improvement before aneurysm treatment to better fit the poor-grade population. Furthermore, interactions between other predictors and WFNS grade can be considered, but only when clinically plausible. Second, despite presentation in poor neurological condition, 76% of patients may survive and 47% may still achieve a favorable functional outcome.[17] As such, an univariable approach to decision-making (i.e., delaying treatment solely based on neurological status at admission) is no longer justifiable. Poor-grade presentation should not preclude timely aneurysm treatment, and the SAHIT model (both the original and a potential extended model) can be used to obtain an estimate of patient prognosis. Lastly, there was extensive methodological heterogeneity between the included studies. As previously proposed, all prediction modeling studies should use appropriate statistical methodology, adhere to the TRIPOD reporting guidelines, and follow the Common Data Elements for SAH and unruptured intracranial aneurysms.[18-20]

PART 2 contains a response to "Neutrophil Counts as Promising Marker for Predicting In-Hospital Mortality in Aneurysmal Subarachnoid Hemorrhage".[21] This study was published in *Stroke*. The authors aimed to study the association between admission blood neutrophil counts with in-hospital mortality (IHM) and hospital-acquired infections (HAI), with a retrospective observational study including 6041 patients with aSAH. They found an increased risk of IHM (OR 1.53, 95% CI: 1.14-2.06) and HAI (OR 1.61, 95% CI: 1.38-1.79) with increasing neutrophil count on admission. However, the authors excluded 22% (1708/7749) of patients because the admission blood neutrophil counts were not available. They did not investigate whether this missingness may have been related to IHM or HAI. Furthermore, they applied multiple imputation but did so only after excluding the patients without a neutrophil count. Due to this, the analysis should be classified as a complete case analysis. A better strategy would have been to apply multiple imputation to the outcome as well.[22] This study was explorative in nature and should not have direct harmful clinical consequences. However, conducting a study without the appropriate data or methodology does constitute research waste and should be avoided.

Accuracy and Validity of Outcome Predictions

Clinical prediction models can influence treatment decision-making on

multiple levels. Prognostic estimates can be discussed with patients (or relatives) at the bedside to facilitate shared decision-making, but also to allocate resources more effectively (e.g., in case of scarcity, potentially harmful interventions, or to avoid futile interventions). Hence, it is paramount that the prognostic estimates are valid and precise. Unreliable prognostic estimates could give rise to faulty decision-making and thereby patient harm.

In **Chapter 4**, the external validity of existing prognostic models was assessed. As mentioned previously, the evidence regarding early (within 24 hours) aneurysm treatment as opposed to treatment standard (within 72 hours) is conflicting.[6] The Aneurysmal RebleedIng after Subarachnoid hEmorrhage (ARISE) prediction models have been developed to predict the risk of pre-interventional rebleeding in patients with aneurysmal subarachnoid hemorrhage.[23] The research question was whether a prediction model could accurately distinguish patients with a high risk of pre-interventional rebleeding from those with a low risk. Possibly, these models could be used to study the effect of earlier aneurysm treatment in a high-risk subpopulation. The base model included age, sex, hypertension, World Federation of Neurological Surgeons (WFNS) grade, Fisher grade, aneurysm size, and cerebrospinal fluid (CSF) diversion. Aneurysm morphology (complex versus simple) was added to the extended model. The models showed promising discrimination at development (base model *c*-statistic was 0.77 and extended model *c*-statistic was 0.79).

In my study, an external validation of the ARISE prediction models was performed with multicenter international retrospective cohort data. The base model discriminated moderately well (*c*-statistic of 0.70 in the Rotterdam cohort and 0.75 in the Oslo cohort). The extended model showed poorer discrimination (*c*-statistic of 0.64 in the Rotterdam cohort and 0.71 in the Oslo cohort). This was explained by contradictory predictor effects and case-mix variation. Both models required recalibration, however, taking into account that the extended model discriminated worse than the base model, it was chosen to only update the base model. After updating the baseline hazard the model calibrated well over the range of clinically relevant and most prevalent predicted risks.

Since local updating is required to obtain accurate and valid prognostic estimates, it is not currently advisable to implement the prediction model in clinical practice. At present the updated ARISE base model can be considered for a prospective impact analysis in the centers participating in development and validation. However, it can be argued that a better approach would be to re-estimate the model with pooled data (from the development and validation studies). Firstly, the model can be improved

by redefining and re-measuring aneurysm morphology. The incidence of aneurysm irregularity was highly variable between cohorts and this might be explained by measurement error. Secondly, CSF diversion should be omitted. CSF diversion is not truly a baseline variable and seems to have different clinical consequences across participating centers. Both aneurysm morphology and CSF diversion had contradictory predictor effects that impaired model performance and transportability of the model. Lastly, the model can be improved by censoring for mortality in all cohorts. The re-estimated model can be validated using internal-external leave-one-cluster-out cross-validation. Because a pooled development and validation ARISE cohort has data from multiple sources with slightly different patient populations from different geographical areas, this clustering can be utilized to benefit the interpretation of the model performance.

In **Chapter 5**, the potential benefits of such a method compared to the default "single-study external validation" method were discussed. Two potential pitfalls of single-study external validation were identified. (1) Model performance with single-study external validation can depend heavily on the choice of validation data and can thus lead to a false appreciation of a clinical prediction model. (2) To accurately appreciate generalizability and transportability it is necessary to investigate heterogeneity between the derivation and validation data and the representativeness to the intended population. Examining model performance within clustered data allows for a better appreciation of transportability across geographical and temporal dimensions. It was concluded that a *single* single-study external validation cannot be interpreted as decisive proof of model performance. Internal-external leave-one-cluster-out cross-validation is better equipped to address the pitfalls of single-study external validation. As a minimum, I advised evaluating selection criteria, recruitment dates, geographical location, and study design of the development and the validation data, to obtain a gross estimate of between-cluster heterogeneity. If clustered data is not available, a reasonable alternative strategy is conducting multiple (smaller) single-study external validations each exploring another dimension.

Last, in **PART 2**, an article published in *Medisch Contact*: "Diagnoses uit de Hoge Hoed" was discussed. In this opinion piece, the author discusses clinical prediction models. It is argued that clinical prediction models are barely used in clinical practice because they are considered a "black box". The physicians intended to use them do not understand the calculations that produce the predictions, and if they did, they wouldn't need the models. However, many clinical prediction models are used in clinical practice.

This article (rather eloquently) portrays a common misconception about prediction. The effects of a single predictor on a certain outcome of interest have to be valued in the context of many other variables. Additionally, this variable might have a non-linear association with the outcome or interact with other predictors. Such calculations are usually too complex to perform without the use of statistical software. Indeed, the field of clinical prediction models (like many other fields) currently has to cope with poorly conducted research. However, simply discarding them all together does not do justice to the work that has been done, nor does it do a service to patients that benefit from reliable risk estimation.

In summary, this opinion piece shows that (1) developing ever more complicated modeling techniques may hamper use or adherence in clinical practice, (2) an imbalance in the number of developed models versus models applied in clinical practice may undermine the belief in models as a whole, and (3) models should be accompanied by software that makes application easy and accessible.

PART III: Optimizing and Individualizing Treatment

There is a growing understanding that average treatment effects as found in RCTs do not necessarily apply to individual patients. Not all patients are alike and so treatment effects can vary depending on patient characteristics such as sex, age, or severity of the disease. Hypothetically, in some patients, the treatment may even be harmful, while the overall treatment effect was found to be beneficial. In **Chapter 6** and **Chapter 7**, the concept of heterogeneity of treatment effect in aSAH patients treated with endovascular coiling or with neurosurgical clip-reconstruction was investigated. The ISAT data was used for the analysis. It was hypothesized that, even though endovascular coiling *on average* leads to better functional outcome, some subgroups may benefit more from neurosurgical clip-reconstruction. Additionally, that the decision-making process could be improved by also taking into account the durability of treatment. Revascularization of the aneurysm can lead to the need for retreatment in the future or rebleeding and subsequent adverse outcomes. It has been shown that *on average* endovascular coiling leads to more rebleeding and need for retreatment during follow-up than neurosurgical clip-reconstruction. Currently, durability of treatment is not a decisive factor in in the decision-making process.

A clinical prediction tool was developed to predict benefit of endovascular coiling versus neurosurgical clip-reconstruction. Heterogeneity of treatment effect was investigated with an "effect modeling" approach.[24] Interaction terms were added to the model between treatment and predefined, parsimoniously selected predictors of functional outcome and durability of treatment. It was discovered that there was a substantial variation in treatment benefit in both outcomes, but there was no evidence for significant interaction. The variation in treatment benefit was not attributable to a relative difference in treatment effect for. Every patient in ISAT benefited to some degree from endovascular coiling over neurosurgical clip-reconstruction in terms of functional outcome and durability of treatment. The variation in treatment benefit was therefore purely (baseline) risk-based.

On average the predicted probability of favorable functional outcome (mRS 0-2) was 6% (95% CI 3-10) in favor of endovascular coiling and the predicted probability of no retreatment or rebleed during 10 years of follow-up was 11% (95% CI 9-13) in favor of neurosurgical clip-reconstruction. Patients who had a very high probability of independent survival had less benefit from being treated with endovascular coiling as opposed to neurosurgical clip-reconstruction since they were likely to survive independently regardless. When applying a 5% clinically relevant benefit threshold, it was found that 134 patients (6%) may be better off with neurosurgical clip-reconstruction, as opposed to current guideline recommendations. These patients had no relevant benefit in terms of functional outcome from endovascular coiling over neurosurgical clip-reconstruction, but did have benefit of neurosurgical clip-reconstruction over endovascular coiling because of lower retreatment and rebleed rates. These patients were young, in a more favorable clinical condition, and without extensive SAH or vasospasm on admission imaging. The SHARP prediction tool (https://sharpmodels.shinyapps.io/sharpmodels/) enables estimating this individualized treatment benefit for each patient. Interpretation of these findings was limited by: (1) functional outcome and durability of treatment are weighed differently and (2) post-interventional rebleeding and retreatment have different clinical consequences.

In **Chapter 8**, a decision model was developed to integrate both outcomes to predict the optimal strategy in terms of quality-adjusted life expectancy. A Markov state-transition model was developed and a microsimulation was conducted to stochastically model each patient in ISAT. The SHARP prediction models were used to calculate the individualized initial health state distribution and cycle-dependent event probability and found that on

average endovascular coiling led to higher predicted quality-adjusted life expectancy (0.83, 95% CI 0.82-0.85). However, it was also reaffirmed that there is a subpopulation (*n* = 13, 0.6%) that may benefit from neurosurgical clip-reconstruction over endovascular coiling. This subpopulation had similar characteristics as observed in **Chapter 7**. The average predicted benefit in this subpopulation was 0.11 (95% CI 0.11-0.12, range 0.00-0.32) or ~6 weeks in full health. The proportion of patients that had clinically relevant benefit (threshold >0.02 Δ quality-adjusted life expectancy (QALE)) was negligible (0.6%, *n* = 12). Because of this, a SHARP decision tool will have limited clinical consequences and was not developed.

Two limitations have to be taken into account when interpreting these results. Firstly, both the prediction tool and the decision model were not externally validated. To validate these studies, we needed to have access to trial data (randomly allocated to endovascular coiling versus neurosurgical clip-reconstruction) assessing functional outcome and durability of treatment with a very long follow-up. This meant that only the pseudo-randomized BRAT (*n* = 356) would be eligible, however the investigators declined our invitation to participate.[5,25-28] Therefore, it was not possible to confirm model performance and transportability in independent data. Secondly, as stated before, there have been concerns about the generalizability of ISAT due to the selected patient population and progress in aneurysm treatment. When considering patients equally amenable to endovascular coiling as to neurosurgical clip-reconstruction – the decision problem – this has little influence on generalizability. However, presently, more patients will probably fulfill this criterion and there is reason to believe that current retreatment and rebleed rates may be less than observed in ISAT.[29] Because the BRAT trial included more recently treated American aSAH patients and applied an all-inclusive policy this cohort is suited to explore validity in the geographical, temporal, and methodological dimensions.[27]

The studies in **PART III**, are based on state-of-the-art modeling techniques and aimed at improving decision-making with the best data available. The next best alternative was used to full independent external validation – leave-one-cluster-out internal-external cross-validation – and assessed model performance of the risk predictions over multiple dimensions (center, study period, and geographical area). These results can support and incentivize the multidisciplinary discussion about optimal aneurysm treatment. They have provided some evidence-based nuance to the one-size-fits-all policy advised by current guidelines. This policy may have resulted in suboptimal decision-making in the years following the publication of ISAT, but future research is necessary to confirm whether this is still the case.

Future Directions

A New Era, A New Randomized Trial?

The ISAT trial selected patients based on *"having an intracranial aneurysm that was judged by both the neurosurgeon and the interventional neuroradiologist to be suitable for either technique based on its angiographic anatomy"*. ISAT was designed to overcome an enrollment issue often observed in trials investigating surgical interventions. There is no consensus as to what patients are good candidates for experimental interventions. In ISAT, this issue was avoided by making this decision locally and not specifying universal criteria for enrollment.

There is, of course, a downside to this liberal approach. Although the superiority claim of coiling over clipping of ISAT was limited to the specific ISAT population it was still unclear "to whom the results of the trial applied".[30] If local preferences determine who was eligible at the time, local preferences will determine to whom the results can be generalized. Additionally, the decrease in dependent survival was driven by the greater incidence of technical complications and the longer time needed to secure the aneurysm in the clipping group.[31] As such, the generalizability of the treatment effects in current times is highly uncertain. This problem has been acknowledged in the community and has led to worldwide practice variability. If one would ask 100 multidisciplinary teams to define patients that are *"from a technical and logistical perspective equally eligible for both treatments"*, the answers would most likely vary greatly.

Contrarily to the field of ischemic stroke, where the boundaries of endovascular thrombectomy are constantly explored, the body of evidence for the choice of aneurysm treatment has been more or less stagnant for over a decade. This can be explained by the fact that there currently is no awareness of what the boundaries could be to begin with, and consequently, we do not know if, or in what direction, we can stretch them further. This impairs future innovation. I advocate for conducting a novel RCT to re-investigate the safety and efficacy of endovascular versus neurosurgical aneurysm treatment. Such a trial should consist of patients that are not limited by the initial severity of disease but by strict boundaries regarding aneurysm location, aneurysm morphology, and presence of concomitant intraparenchymal hemorrhage or intraventricular hemorrhage that would render coiling or clipping unfeasible. This strictly defined population limits the degree of cross-overs and sets clear therapeutic boundaries that, in the future, may be challenged again. Centers' participation should depend on their willingness to adhere to strict inclusion and exclusion criteria. The

trial should include all endovascular and neurosurgical aneurysm treatment options, as long as there is uncertainty about whether the endovascular or neurosurgical counterpart is more beneficial. The primary endpoint should be functional outcome. The secondary endpoints should include pretreatment rebleeding, treatment failure, intra-operative complications, post-treatment angiographic success, long-term durability of treatment, and quality of life. This trial should aim to include a large sample to enable investigation of future individualized treatment effects.

Textbox 2. Recommendations for future research (I).

1. **A novel randomized controlled trial to investigate the safety and efficacy of endovascular aneurysm treatment versus neurosurgical aneurysm treatment.**
   - Evaluate the relative treatment effect of endovascular versus neurosurgical aneurysm treatment using modern techniques and devices.
   - Evaluate the differences in time-to-treatment between endovascular and neurosurgical aneurysm treatment and their contribution to pre-treatment rebleeding.
   - Evaluate the differences in intra-operative complications of endovascular versus neurosurgical aneurysm treatment and its effects on functional outcome.
   - Evaluate differences in the long-term durability of treatment of endovascular versus neurosurgical aneurysm treatment.

2. **Implement a trial design that allows for the formulation of clear therapeutic recommendations and future studies exploring new frontiers.**

3. **This trial could be used for external validation of the SHARP prediction models and for validating and updating the SHARP decision tool to enhance personalized treatment decision-making for this patient population.**

Comparative Effectiveness Research

There is a scarcity of evidence-based pharmacological and hemodynamic therapies to improve the outcome of aSAH patients. Lacking evidence on these matters (either proving or disproving suggested therapies) has added to uncertainty in the treatment of patients with aSAH, leading to worldwide practice variability.

This phenomenon is not unique to aSAH-related care. Much like in the field of aSAH research, the field of TBI research was also rife with small and fragmented studies, that often used varying treatment protocols and varying definitions of exposures and outcomes.[32] Subsequently, large collaborative efforts, such as TRACK-TBI (United States) and CENTER-TBI (Europe), were developed to evaluate the effect of practice variability on outcome in patients with traumatic brain injury (TBI).[33,34] The concept of CER is to investigate interventions on observational data using real-world heterogeneity in treatment regimens that serve as an instrumental variable. It can be considered as the observational counterpart of to the RCT. CER can be of value when RCTs are difficult to conduct because of lacking clinical equipoise, have unsatisfactory results, or have generalizability issues. CER can generate hypotheses that can then serve as a stepping-stone for future RCT development.

Before implementing this method, two prerequisites have to be met. Firstly, to effectively harmonize data collection, there must be uniform definitions of variables, outcomes, complications, et cetera. For TBI, this prerequisite was met by the publication of National Institutes of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDEs).[35,36] Recently, the NINDS has also formulated CDEs to harmonize data collection for unruptured intracranial aneurysms and SAH.[20] Secondly, there must be a comprehensive overview of practice variability to determine what the possible targets are for CER. Presently, with the publication of our practice variability survey study, both prerequisites are met.

As an alternative to conducting RCTs, a large international collaborative CER effort could be undertaken. The upside of such an approach is the opportunity to investigate a broader scope of treatments than, for example, just the optimal intervention for ruptured aneurysms. The research focus of this collaboration should be to investigate treatments and generate hypotheses for RCTs on the topics of timing of aneurysm treatment, fluid management, induced hypertension, and rescue therapies for cerebral vasospasm. With CER we can also identify interventions that have the largest health benefit and so help to prioritize RCT development. For example, it would also be interesting to see whether prophylactic lumbar cerebrospinal fluid drain insertion is adopted in clinical practice in the coming years because of its recently found beneficial effect on 6-month functional outcome.[37] Especially because this trial contradicts the earlier LUMAS trial that failed to show such an effect.[38] Another benefit of CER could be the identification and investigation of therapies that do not improve patient outcome but are associated with harm or increased costs without beneficial outcomes. A practice that could be considered unethical in an RCT format.

Textbox 3. Recommendations for future research (II).

1. **A large collaborative comparative effectiveness research initiative to identify effective (and ineffective) strategies could improve outcomes in patients with aneurysmal subarachnoid hemorrhage.**

2. **The main focus should include currently debated therapies, including timing of aneurysm treatment, fluid management, induced hypertension, rescue therapies for cerebral vasospasm, and prophylactic lumbar cerebrospinal fluid drain insertion.**

Closing Message

This thesis aimed to provide evidence for the improvement of outcomes in patients with aSAH, by characterizing practice variability in the treatment strategies, individualized outcome prediction, and optimizing treatment based on individualized estimates of treatment effect. Firstly, I found that there was large practice variability in a wide variety of treatment strategies which implies that, currently, not all patients receive optimal treatment. I identified possible targets to investigate using CER that could impact outcome in patients with aSAH. Secondly, I identified predictors of outcome, validated an existing prediction model, and evaluated methods for external validation. These studies aid in optimizing and individualizing outcome prediction for patients with aSAH. Lastly, I established that in the post-ISAT era, some patients may have had suboptimal treatment in terms of quality-adjusted life expectancy when modeling for initial predicted functional outcome and long-term durability of treatment. I showed that using sophisticated modeling techniques has the potential to tilt longlasting treatment paradigms. However, we need contemporary high-quality randomized data to improve the SHARP models and truly enable personalized treatment decision-making.

References

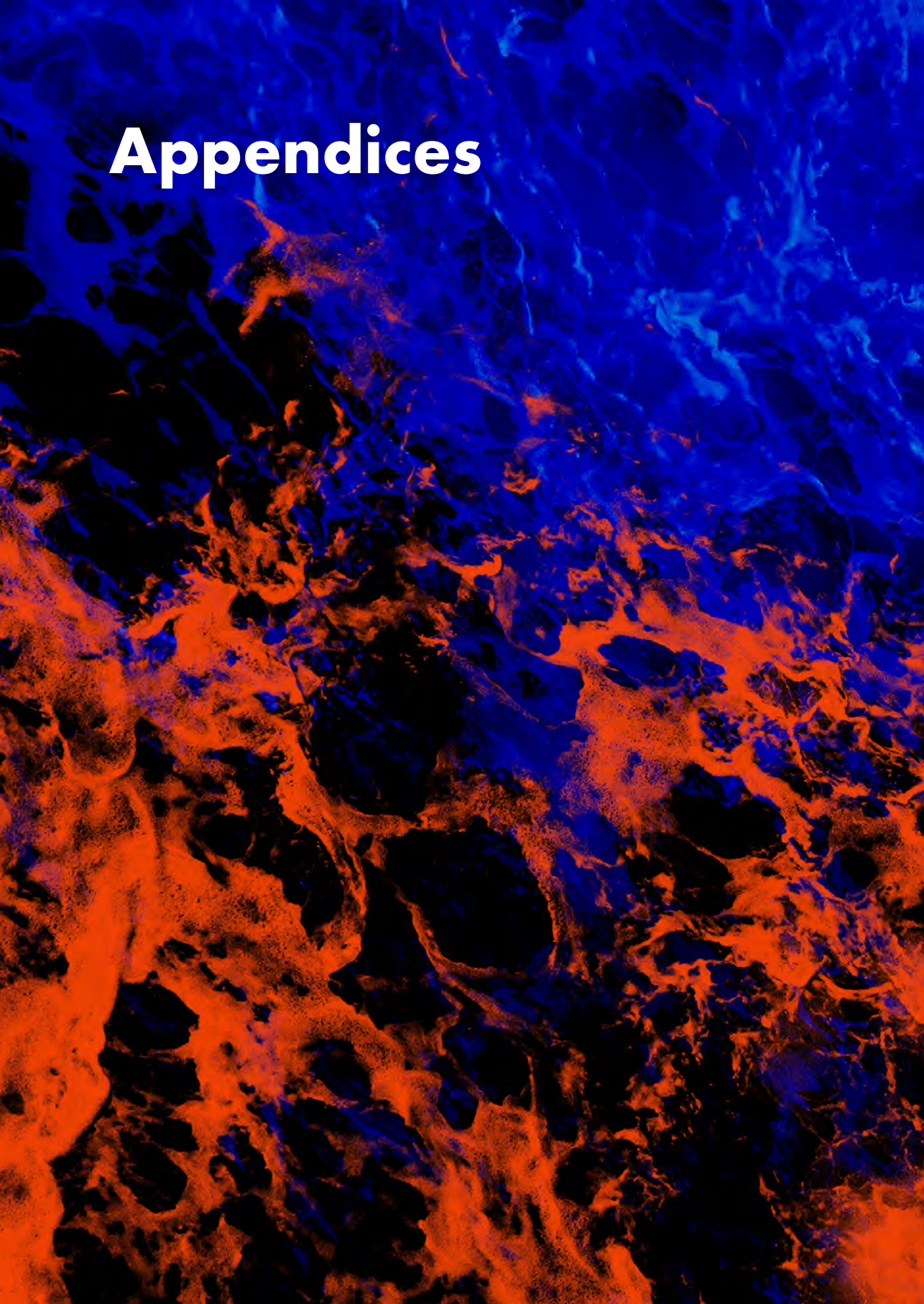
1. Connolly ES, Jr., Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. *Stroke*. Jun 2012;43(6):1711-37. doi:10.1161/STR.0b013e3182587839
2. Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis*. 2013;35(2):93-112. doi:10.1159/000346087
3. Molyneux AJ, Kerr RS, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet*. Sep 3-9 2005;366(9488):809-17. doi:10.1016/S0140-6736(05)67214-5
4. Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RS. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). *Lancet*. Feb 21 2015;385(9969):691-7. doi:10.1016/S0140-6736(14)60975-2
5. McDougall CG, Spetzler RF, Zabramski JM, et al. The Barrow Ruptured Aneurysm Trial. *J Neurosurg*. Jan 2012;116(1):135-44. doi:10.3171/2011.8.JNS101767
6. Rawal S, Alcaide-Leon P, Macdonald RL, et al. Meta-analysis of timing of endovascular aneurysm treatment in subarachnoid haemorrhage: inconsistent results of early treatment within 1 day. *J Neurol Neurosurg Psychiatry*. Mar 2017;88(3):241-248. doi:10.1136/jnnp-2016-314596
7. Hoh BL, Ko NU, Amin-Hanjani S, et al. 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. *Stroke*. Jul 2023;54(7):e314-e370. doi:10.1161/STR.0000000000000436
8. Raymond J, Kotowski M, Darsaut TE, Molyneux AJ, Kerr RS. Ruptured aneurysms and the International Subarachnoid Aneurysm Trial (ISAT): What is known and what remains to be questioned. *Neurochirurgie*. Apr-Jun 2012;58(2-3):103-14. doi:10.1016/j.neuchi.2012.02.020
9. Ausman JI. ISAT study: is coiling better than clipping? *Surg Neurol*. Mar 2003;59(3):162-5; discussion 165-73; author reply 173-5. doi:10.1016/s0090-3019(03)00074-0
10. Raymond J, Iancu D, Boisseau W, et al. Flow Diversion in the Treatment of Intracranial Aneurysms: A Pragmatic Randomized Care Trial. *AJNR Am J Neuroradiol*. Sep 2022;43(9):1244-1251. doi:10.3174/ajnr.A7597
11. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British

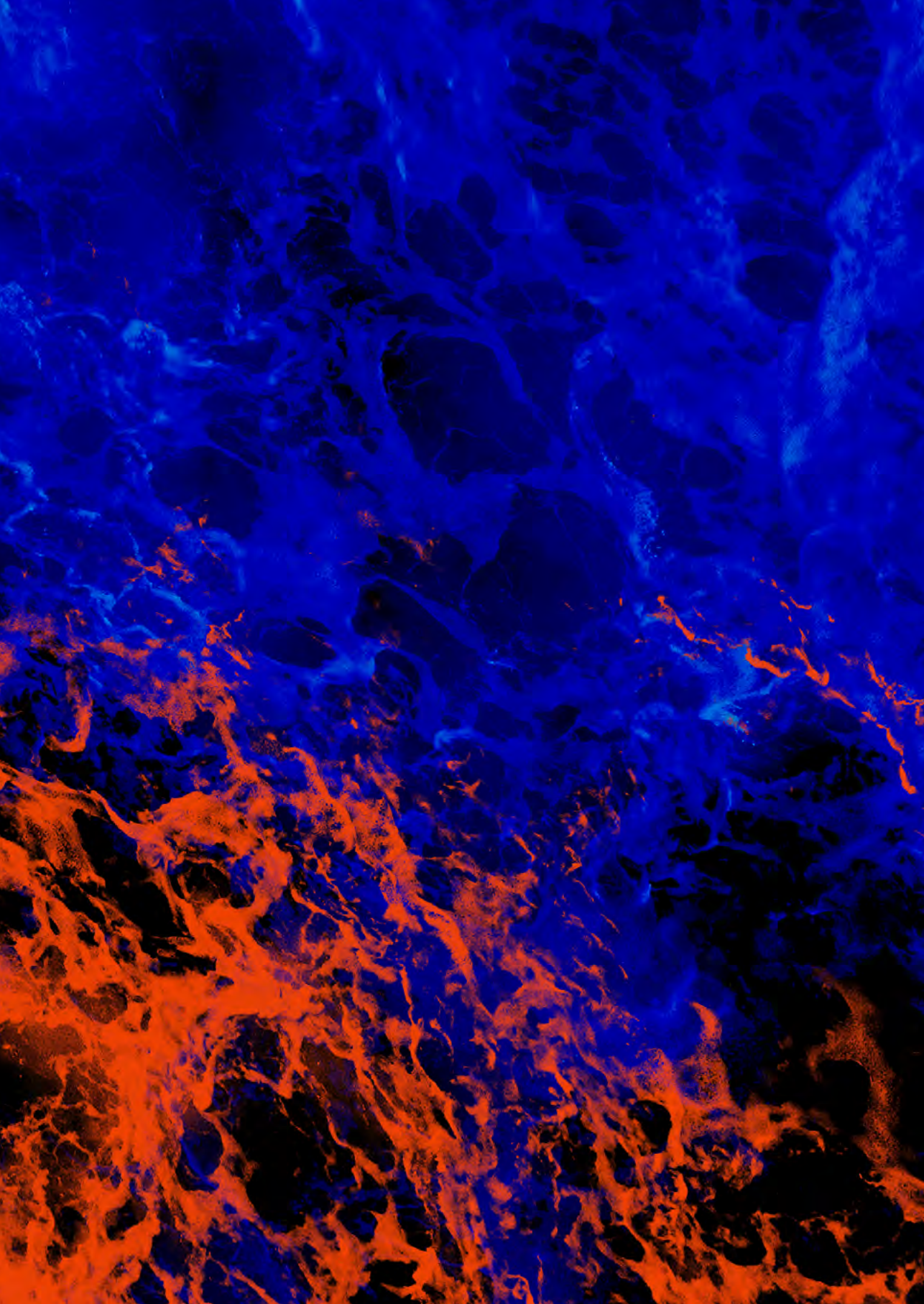
aneurysm nimodipine trial. *BMJ*. Mar 11 1989;298(6674):636-42. doi:10.1136/bmj.298.6674.636
12. Jaja BN, Cusimano MD, Etminan N, et al. Clinical prediction models for aneurysmal subarachnoid hemorrhage: a systematic review. *Neurocrit Care*. Feb 2013;18(1):143-53. doi:10.1007/s12028-012-9792-z
13. Maas AIR, Menon DK, Manley GT, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. *Lancet Neurol*. Nov 2022;21(11):1004-1060. doi:10.1016/S1474-4422(22)00309-X
14. Jaja BNR, Saposnik G, Lingsma HF, et al. Development and validation of outcome prediction models for aneurysmal subarachnoid haemorrhage: the SAHIT multinational cohort study. *BMJ*. Jan 18 2018;360:j5745. doi:10.1136/bmj.j5745
15. Risselada R, Lingsma HF, Bauer-Mehren A, et al. Prediction of 60 day case-fatality after aneurysmal subarachnoid haemorrhage: results from the International Subarachnoid Aneurysm Trial (ISAT). *Eur J Epidemiol*. Apr 2010;25(4):261-6. doi:10.1007/s10654-010-9432-x
16. Risselada R, Lingsma HF, Molyneux AJ, et al. Prediction of two month modified Rankin Scale with an ordinal prediction model in patients with aneurysmal subarachnoid haemorrhage. *BMC Med Res Methodol*. Sep 29 2010;10:86. doi:10.1186/1471-2288-10-86
17. Han Y, Ye F, Long X, et al. Ultra-Early Treatment for Poor-Grade Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis. *World Neurosurg*. Jul 2018;115:e160-e171. doi:10.1016/j.wneu.2018.03.219
18. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD). *Ann Intern Med*. May 19 2015;162(10):735-6. doi:10.7326/L15-5093-2
19. Steyerberg EW. *Clinical prediction models : a practical approach to development, validation, and updating*. Statistics for biology and health. Springer; 2009:xxviii, 497 p.
20. Suarez JI, Sheikh MK, Macdonald RL, et al. Common Data Elements for Unruptured Intracranial Aneurysms and Subarachnoid Hemorrhage Clinical Research: A National Institute for Neurological Disorders and Stroke and National Library of Medicine Project. *Neurocrit Care*. Jun 2019;30(Suppl 1):4-19. doi:10.1007/s12028-019-00723-6
21. Zhang Y, Li L, Jia L, et al. Neutrophil Counts as Promising Marker for Predicting In-Hospital Mortality in Aneurysmal Subarachnoid Hemorrhage. *Stroke*. Oct 2021;52(10):3266-3275. doi:10.1161/STROKEAHA.120.034024
22. van Ginkel JR, Linting M, Rippe RCA, van der Voort A. Rebutting Existing Misconceptions About Multiple Imputation as a Method for Handling Missing Data. *J Pers Assess*. May-Jun 2020;102(3):297-308. doi:10.1080/00223891.2018.1530680

23. van Lieshout JH, Mijderwijk HJ, Nieboer D, et al. Development and Internal Validation of the ARISE Prediction Models for Rebleeding After Aneurysmal Subarachnoid Hemorrhage. *Neurosurgery*. Sep 1 2022;91(3):450-458. doi:10.1227/neu.0000000000002045
24. Kent DM, van Klaveren D, Paulus JK, et al. The Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement: Explanation and Elaboration. *Ann Intern Med*. Jan 7 2020;172(1):W1-W25. doi:10.7326/M18-3668
25. Darsaut TE, Raymond J. Barrow ruptured aneurysm trial. *J Neurosurg*. Aug 2012;117(2):378-9; author reply 379-80. doi:10.3171/2011.12.JNS112279
26. Spetzler RF, McDougall CG, Albuquerque FC, et al. The Barrow Ruptured Aneurysm Trial: 3-year results. *J Neurosurg*. Jul 2013;119(1):146-57. doi:10.3171/2013.3.JNS12683
27. Spetzler RF, McDougall CG, Zabramski JM, et al. Ten-year analysis of saccular aneurysms in the Barrow Ruptured Aneurysm Trial. *J Neurosurg*. Mar 8 2019;132(3):771-776. doi:10.3171/2018.8.JNS181846
28. Spetzler RF, McDougall CG, Zabramski JM, et al. The Barrow Ruptured Aneurysm Trial: 6-year results. *J Neurosurg*. Sep 2015;123(3):609-17. doi:10.3171/2014.9.JNS141749
29. Catapano JS, Labib MA, Srinivasan VM, et al. Saccular aneurysms in the post-Barrow Ruptured Aneurysm Trial era. *J Neurosurg*. Nov 26 2021:1-8. doi:10.3171/2021.8.JNS211060
30. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet*. Jan 1-7 2005;365(9453):82-93. doi:10.1016/S0140-6736(04)17670-8
31. Bakker NA, Metzemaekers JD, Groen RJ, Mooij JJ, Van Dijk JM. International subarachnoid aneurysm trial 2009: endovascular coiling of ruptured intracranial aneurysms has no significant advantage over neurosurgical clipping. *Neurosurgery*. May 2010;66(5):961-2. doi:10.1227/01.NEU.0000368152.67151.73
32. Huijben JA, Wiegers EJA, Lingsma HF, et al. Changing care pathways and between-center practice variations in intensive care for traumatic brain injury across Europe: a CENTER-TBI analysis. *Intensive Care Med*. May 2020;46(5):995-1004. doi:10.1007/s00134-020-05965-z
33. Maas AI, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery*. Jan 2015;76(1):67-80. doi:10.1227/NEU.0000000000000575
34. Yue JK, Vassar MJ, Lingsma HF, et al. Transforming research and clinical knowledge in traumatic brain injury pilot: multicenter implementation of the common data elements for traumatic brain injury. *J Neurotrauma*. Nov 15 2013;30(22):1831-44. doi:10.1089/neu.2013.2970

35. Maas AI, Harrison-Felix CL, Menon D, et al. Common data elements for traumatic brain injury: recommendations from the interagency working group on demographics and clinical assessment. *Arch Phys Med Rehabil*. Nov 2010;91(11):1641-9. doi:10.1016/j.apmr.2010.07.232
36. Maas AIR, Ercole A, De Keyser V, Menon DK, Steyerberg EW. Opportunities and Challenges in High-Quality Contemporary Data Collection in Traumatic Brain Injury: The CENTER-TBI Experience. *Neurocrit Care*. Aug 2022;37(Suppl 2):192-201. doi:10.1007/s12028-022-01471-w
37. Wolf S, Mielke D, Barner C, et al. Effectiveness of Lumbar Cerebrospinal Fluid Drain Among Patients With Aneurysmal Subarachnoid Hemorrhage: A Randomized Clinical Trial. *JAMA Neurol*. Aug 1 2023;80(8):833-842. doi:10.1001/jamaneurol.2023.1792

Appendices





Summary

Despite improvements in the outcomes of patients with aneurysmal subarachnoid hemorrhage (aSAH) about half of aSAH patient do not recover to functional independence. Much research has focused on finding effective therapies for all SAH patients, but less interest has been taken into personalizing treatment. There is a growing understanding that averaged expected outcomes or treatment effects do not apply to the individual patient. The overall hypothesis of this thesis was that we can improve outcomes of aSAH patients by understanding practice variability and using individualized estimates of outcome and treatment effect to shift from one-size-fits-all all policy to individualized decision-making. The specific aims were:

1. **To characterize international variations in treatment and organizational aspects of care that could impact outcomes in patients with aSAH.**

2. **To optimize and individualize outcome prediction for patients with aSAH.**
   - To systematically review and meta-analyze early predictors of functional outcome in poor-grade aSAH patients.
   - To externally validate the ARISE prediction models for predicting pre-interventional aneurysmal rerupture within 24 and 72 hours.
   - To illustrate the pitfalls of single-study external validation by conducting a large number of external validations of a prediction model for functional outcome in aSAH patients.

3. **To optimize and individualize treatment in patients with aneurysmal subarachnoid hemorrhage.**
   - To develop and internal-externally validate a prediction tool to predict benefit of endovascular coiling compared to neurosurgical clip-reconstruction.
   - To develop a decision model to investigate the optimal aneurysm treatment strategy for individual aSAH patients.

PART I: Characterizing Practice Variation

In **PART I** of this thesis, I investigated and characterized practice variability in treatment and the organizational aspects of care of aSAH patients. In **Chapter 2**, I found that there was large practice variation in terms of type and timing of aneurysm treatment, fluid management, and prevention and rescue therapies in case of delayed cerebral ischemia. This practice variation may be preceded by uncertainty or disbelief in the available evidence. Specifically for the choice of aneurysm treatment, the evidence is decades old and heavily contested. The concerns about the generalizability of ISAT may add to worldwide practice variability. Concerning the optimal timing of aneurysm treatment, fluid management, and rescue therapies for delayed cerebral ischemia there is a dearth of high-quality evidence. Inevitably practice variability will lead to some patients receiving suboptimal treatment.

PART II: Optimizing and Individualizing Outcome Prediction

In the second part of this thesis, I evaluated multiple aspects of optimizing and individualizing outcome prediction in patients with aSAH. Naturally treatment is aimed to influence outcome, but outcome can also shape treatment decision-making. For example, a low expected survival probability may lead to withholding further invasive treatments and abstaining. In other words, there is a reciprocity between perceived outcome and treatment. A physcians' opinion about the expected outcome is usually based on clinical expertise and past experiences (so called expert opinion). However, decision-making based can be improved by obtaining individualized outcome estimates. In short, first, patient characteristics (or predictors) have to be identified that are associated with the outcome of interest. Second, a prediction model should be developed that allows for individualized outcome prediction. Third, such a model needs to be assessed with external validation (and impact analysis).

In **Chapter 3**, I presented a summary of early predictors of functional outcome in poor-grade aSAH patients. I found that the likelihood of favorable functional outcome in patients with poor-grade aSAH increased with WFNS grade IV and Hunt and Hess grade IV versus V, the presence of clinical improvement before aneurysm treatment, and intact pupillary light

reflex, and decreased with older age, increasing modified Fisher grade, and presence of intracerebral hematoma on admission imaging. These predictors can help to discriminate between patients with favorable and unfavorable prognoses and may aid in selecting patients for early aneurysm treatment. In the future, the SAHIT model could be extended with these predictors to improve risk prediction in poor-grade patients.

In **Chapter 4**, I externally validated the ARISE prediction models used for predicting pre-interventional rebleed in patients with aSAH. I found that the ARISE base model had a good discriminative ability for the prediction of pre-interventional rebleeding, although updating the baseline hazard for each center was needed to improve calibration. The ARISE extended model showed poorer discrimination than the base model and also lacked adequate calibration. Because of this, we did not perform an update of the extended model. Because of the large heterogeneity between cohorts, a local revision is required and implementation without it is discouraged. The local baseline hazard has been obtained for 5 development and 2 validation centers. In these centers, the next step should be conducting a formal impact analysis of the ARISE base model with a cluster randomized trial or a before-after study. Alternatively, the ARISE prediction models can be improved by redefining and remeasuring predictors and apply censoring for mortality in each cohort (as opposed to only in the Rotterdam cohort). The model can be refitted on a pooled development and validation dataset and validity could be assessed with internal-external leave-one-cluster-out cross-validation.

In **Chapter 5**, I focused on methods for external validation. I conducted a leave-one-cluster-out internal-external cross-validation of the SAHIT model developed on the SAHIT data repository. Because this repository included many different patient cohort it mimics the process of conducting a large number of single-study external validations. The SAHIT model is used for predicting functional outcome in patients with aSAH. I demonstrated two potential pitfalls in the interpretation of model performance with single-study external validation. (1) With single-study external validation model performance is highly variable and depends on the choice of validation data, (2) no insight is provided into the generalizability or transportability of the model that is needed to guide local implementation. As such, a single single-study external validation can easily be misinterpreted and lead to a false appreciation of the clinical prediction model. Internal-external leave-one-cluster-out cross-validation is better equipped to address these pitfalls.

PART III: Optimizing and Individualizing Treatment

Not all patients are alike and so treatment effects can vary depending on patient characteristics such as sex, age, or severity of the disease. **Part III** was focused on individualizing the choice of aneurysm treatment based on such characteristics. First, in **Chapters 6 and 7**, I developed two prediction models that predict the 2-month favorable functional outcome and the within 10-year probability of no retreatment or rebleed after endovascular coiling and neurosurgical clip-reconstruction. Next, I used these models to calculate the individualized treatment benefit. I identified patients may benefit from neurosurgical clip-reconstruction over endovascular coiling despite guideline recommendations. These patients had no clinically relevant benefit of coiling over clipping in terms of functional outcome but did have a clinically relevant lower probability of no retreatment or rebleed with clipping over coiling. This individualized treatment benefit can be easily calculated with the SHARP web-based prediction tool: https://sharpmodels.shinyapps.io/sharpmodels/. However, the interpretation of these results was complicated. Functional outcome and durability of treatment are incomparable and rebleeding and retreatment have different clinical consequences. Therefore, in **Chapter 8**, we developed a Markov state-transition model to express individualized treatment benefit in terms of quality-adjusted life expectancy. Again, we found that some patients may have clinically relevant benefit of neurosurgical clip-reconstruction over endovascular coiling, but the proportion of patients that had this benefit was negligible. The generalizability of these results is not fully understood. Rebleed and retreatment rates may have declined over the past years due to increased experience and the introduction of new techniques and devices. Given that the cycle-dependent rebleed and retreatment rates were highly influential on the preferred aneurysm treatment external validation and model updating are necessary before developing a web-based decision tool.

I conclude that there are two major directions to move forward. First, practice variation can be utilized to investigate effective therapies based on observational data using comparative effectiveness research. Second, a contemporary randomized controlled trial can be conducted to investigate the safety and efficacy of endovascular versus neurosurgical aneurysm treatment strategies in this day and age. This trial should have a clearly defined patient population and can be used to validate the SHARP prediction

tool and decision model. The sample size of such a trial should be large enough the investigate future individualized treatment effects. This study will serve as a benchmark for future trials.

Samenvatting

Ondanks verbetering van de uitkomsten van patiënten met een aneurysmatische subarachnoïdale bloeding (aSAB) herstelt slechts de helft tot volledige functionele onafhankelijkheid. Veel onderzoek heeft zich gefocust op het vinden van effectieve behandelingen voor aSAB patiënten, maar slechts weinig studies hebben gekeken naar het personaliseren van de behandeling in deze patiëntengroep. In toenemende mate wordt duidelijk dat een gemiddelde behandeleffect niet toepasbaar is op de individuele patiënt. De overkoepelende hypothese van deze dissertatie was dat we patiëntuitkomsten van aSAB patiënten kunnen verbeteren door: (1) praktijkvariatie te begrijpen en te identificeren en (2) door geïndividualiseerde schattingen van patiëntuitkomsten en (3) behandeleffect te gebruiken om van "one-size-fits-all" besluitvorming naar gepersonaliseerde besluitvorming te bewegen. De specifieke doelen waren:

1. **Het karakteriseren van internationale variatie in de behandeling en de organisatorische aspecten van de zorg voor aSAB patiënten die een impact kunnen hebben op patiëntuitkomsten.**

2. **Het optimaliseren en individualiseren van het voorspellen van patiëntuitkomsten in patiënten met een aSAB.**
   - Het systematisch en meta-analytisch onderzoeken wat de vroege voorspellers zijn van functionele uitkomst in patiënten met een hooggradige aSAB.
   - Het uitvoeren van een externe validatie van de ARISE-predictiemodellen welke de kans voorspellen op een pre-interventie recidief bloeding binnen 24 of 72 uur na SAB.
   - Het illustreren wat de valkuilen zijn van een "één-enkele-studie externe validatie" door het uitvoeren van een groot aantal externe validaties van een predictiemodel dat de functionele uitkomst voorspeld in patiënten met een aSAB.

3. **Het optimaliseren en individualiseren van de behandeling van patiënten met een aSAB.**
   - Het ontwikkelen en valideren van predictiemodellen die het behandelvoordeel van endovasculaire coiling versus neurochirurgische clip-reconstructie voorspellen.
   - Het ontwikkelen van een beslismodel om de optimale aneurysma behandelingsstrategie te bepalen voor een individu met een aSAB.

Deel I: Het Karakteriseren van Praktijkvariatie

In **Deel I** van deze dissertatie heb ik praktijkvariatie in de behandeling en organisatorische aspecten van de zorg voor van patiënten met een aSAB onderzocht. In **Hoofdstuk 2** vond ik dat er wereldwijd sprake was van veel variatie in de mate van gebruik van een endovasculaire en de neurochirurgische aneurysmabehandeling. Ook vond ik dat er veel variatie was in de tijd tot aneurysmabehandeling, het vochtbeleid en de preventie en noodbehandelingen van uitgestelde cerebrale ischemie. Deze praktijkvariatie wordt mogelijk veroorzaakt door twijfel en onzekerheid rondom het bestaande bewijs. De trial die de welke de voorkeur voor een endovasculaire boven een neurochirurgische aneurysmabehandeling ondersteund is oud en wordt betwist. Een van de zorgen is de generaliseerbaarheid van deze trial. Met betrekking tot de optimale tijd tot aneurysmabehandeling, vochtbeleid en noodbehandelingen van uitgestelde cerebrale ischemie wordt de praktijkvariatie mogelijk veroorzaakt door het ontbreken van hoge kwaliteit bewijs. Voor sommige patiënten met een aSAB betekent dit onvermijdelijk dat zij een suboptimale behandeling ontvangen.

Deel II: Het Optimaliseren en Individualiseren van Het Voorspellen van Uitkomsten

In **Deel II** van deze dissertatie heb ik enkele aspecten van de optimalisering en individualisering van het voorspellen van patiëntuitkomsten onderzocht. Er bestaat een zekere mate van wederkerigheid tussen de behandeling en de verwachte uitkomst. Bijvoorbeeld: het behandelen van ziekte heeft invloed op de overleving, maar de verwachte overleving kan ook de keuze voor de behandeling beïnvloeden. Bijvoorbeeld een agressiever behandeling bij en hoge kans op overleving versus afzien van behandeling bij een

infauste prognose. De prognose van de individuele patiënt wordt meestal bepaald aan de hand van klinisch ervaring en expertise. Deze vorm van anekdotisch bewijs is echter niet voldoende om behandelbeslissingen op te baseren. Zulke beslisvorming kan verbeterd worden met behulp van geïndividualiseerde patiëntuitkomsten. Eerst zullen patiëntkarakteristieken worden geïdentificeerd die geassocieerd zijn met de uitkomst waarin we geïnteresseerd zijn. Dan moet er een predictiemodel ontwikkeld worden dat geïndividualiseerde uitkomstpredictie mogelijk maakt. Tot slot moet zo'n model worden gevalideerd en moet er een impact analyse gedaan worden.

In **Hoofdstuk 3** heb ik middels een systematisch review en meta-analyse onderzocht wat de vroege predictoren van een gunstige functionele uitkomst zijn in patiënten met een hooggradige aSAB. Ik vond dat de kans op een gunstige functionele uitkomst bij patiënten met een hooggradige aSAB toeneemt bij: een WFNS-graad I-III of een Hunt-Hess graad I-III en de aanwezigheid van klinische verbetering voor de aneurysmabehandeling en intacte pupilreflexen. De kans op een gunstige functionele uitkomsten bij patiënten met een hooggradig aSAB neemt af met: hogere leeftijd, de aanwezigheid van een intracerebraal hematoom op de opnamebeeldvorming en een hogere modified Fisher graad. Deze predictoren kunnen helpen in het discrimineren tussen patiënten met een gunstige en ongunstige prognose en kunnen helpen in het selecteren van patiënten die aanmerking zouden moeten komen voor een vroege aneurysmabehandeling. Daarnaast zou SAHIT-model kunnen worden uitgebreid met deze vroege predictoren om de risicovoorspellingen van patiënten met een hooggradige aSAB te verbeteren.

In **Hoofdstuk 4** heb ik de ARISE-predictiemodellen extern gevalideerd. De ARISE-predictiemodellen worden gebruikt voor het voorspellen van een pre-interventie recidief bloeding in patiënten met een aSAB. Het basis ARISE-model discrimineerde goed, maar was onvoldoende gekalibreerd. Er was een update nodig van de *baseline hazard* voor elk individueel centrum dat onderdeel was van de dataset om de kalibratie van het model te verbeteren. Het verlengde ARISE-model toonde een slechtere discriminatie dan het basismodel en was eveneens matig gekalibreerd. Om deze reden werd er voor dit model geen update uitgevoerd. Ik concludeerde dat de noodzaak tot lokale revisie werd veroorzaakt door de hoge mate van heterogeniteit tussen de cohorten. Hierom ontraad ik implementatie van het model in de huidige vorm in nieuwe datasets. In de dataset die gebruikt zijn voor ontwikkeling en validatie van het model is nu echter een lokale waarde voor de *baseline hazard* is beschikbaar. In deze 7 is het mogelijk om een impact analyse te verrichten van het basis ARISE-model door middel van

een cluster-gerandomiseerde studie of een voor-na studie (Engels: before-after study). Als alternatief adviseer ik om het model te verbeteren door enkele voorspellers te herdefiniëren en opnieuw te bepalen. Daarnaast is het belangrijk om in alle cohort te censureren in het geval dat de patiënt overleden is, iets wat nu niet in alle cohorten is gebeurd. Daarna zou het model opnieuw geschat kunnen worden op een gecombineerde dataset (i.e., de ontwikkelings- en de validatiedataset) en door middel van interne-externe kruisvalidatie worden gevalideerd.

In **Hoofdstuk 5** heb ik gefocust op de methodiek van het extern valideren van predictiemodellen. Hierbij heb ik interne-externe kruisvalidatie en externe validatie middels een enkel studie (Engels: single-study external validation) vergeleken. Door een interne-externe kruisvalidatie uit te voeren op een cohort met een groot aantal studies heb ik het proces van een multipele "externe validaties middels een enkele studies" nagebootst. Ik heb dit gedaan voor het SAHIT-model. Dit model voorspelt functionele uitkomst op 12 maanden voor patiënten met een aSAB. Ik vond twee potentiële valkuilen: (1) met "externe validatie middels een enkele studie" zijn de modelprestaties uiterst variabel en afhankelijk van de keuze van de validatiedataset en (2) er wordt geen inzicht geboden in generaliseerbaarheid en transporteerbaarheid van het model. Inzicht in generaliseerbaarheid en transporteerbaarheid zijn noodzakelijk om lokale implementatie te sturen. Het uitvoeren van één enkele "externe validatie middels een enkele studie" kan hierom leiden tot misinterpretatie en valse waardering van een klinisch predictiemodel. Interne-externe kruisvalidatie is beter toegerust om met deze valkuilen om te gaan.

Deel III: Het Optimaliseren en Individualiseren van Behandeling

Niet alle patiënten zijn hetzelfde. Hierom kunnen gemiddelde behandeleffecten kunnen variëren op basis van individuele patiëntkarakteristieken. In **Deel III** onderzoek ik het individualiseren van de aneurysmabehandelingskeuze op basis van dit soort karakteristieken. In de **Hoofdstukken 6 en 7** heb ik twee predictiemodellen ontwikkeld die de kans op een goede functionele uitkomst op 2 maanden en de kans op het niet hebben van een recidief bloeding of herbehandeling gedurende 10 jaar voorspellen na endovasculaire coiling en neurochirurgische clip-reconstructie. Vervolgens heb ik deze modellen gebruikt om het

geïndividualiseerde behandelvoordeel te berekenen. Dit geïndividualiseerde behandelvoordeel is gedefinieerd als het absolute risico verschil op de uitkomst na een endovasculaire coiling en na een neurochirurgische clip-reconstructie. Ik identificeerde een substantiële groep aSAB patiënten die mogelijk behandelvoordeel hebben als zij neurochirurgische zouden worden behandeld in plaats vinden endovasculair. In deze patiënten is een endovasculaire behandeling de huidige standaard.

Deze groep had namelijk geen klinisch relevant voordeel van endovasculaire coiling versus neurochirurgische clip-reconstructie op gebied van functionele uitkomst, maar wel voordeel van clip-reconstructie versus endovasculaire coiling vanwege een klinisch relevante lagere kans op het hebben van een recidief bloeding of herbehandeling. Het geïndividualiseerde behandelvoordeel kan worden berekend met de SHARP webapplicatie: https://sharpmodels.shinyapps.io/sharpmodels. Er waren meerdere factoren die de interpretatie van deze bevindingen compliceerden. Ten eerste omdat functionele uitkomst en duurzaamheid van behandeling twee onvergelijkbaar begrippen zijn. Ook hebben een herbehandeling en een recidief bloeding hebben beide totaal verschillende klinische consequenties. Hierom hebben we in **Hoofdstuk 8** een Markov transtitie-in-toestand beslismodel ontwikkeld om het geïndividualiseerde behandelvoordeel uit te drukken in voor kwaliteit geadjusteerde levensverwachting. Met deze studie herbevestigde ik dat sommige patiënten, ditmaal uitdrukt in voor kwaliteit geadjusteerde levensverwachting, mogelijk behandelvoordeel hebben van neurochirurgische clip-reconstructie ten opzichte van endovasculaire coiling. Echter was de proportie van patiënten met dit voordeel verwaarloosbaar. Ook was er onduidelijkheid over de generaliseerbaarheid van de resultaten. Het aantal recidief bloedingen en herbehandelingen na een aneurysmabehandeling is afgenomen door de jaren vanwege toegenomen ervaring van interventionisten en de introductie van nieuwe technieken en materialen. De cyclusafhankelijke recidief bloeding- en herbehandelingskansen hadden de meeste impact op het behandelvoordeel. Hierom is een externe validatie en update van het model nodig voordat het zinvol is om een webapplicatie te maken van het SHARP-beslismodel.

Ik concludeer dat er twee richtingen zijn voor vervolgonderzoek. Ten eerste, het onderzoeken van effectieve behandelingen op observationele data door middel van het gebruiken van praktijkvariatie middels vergelijkend effectiviteitsonderzoek. Ten tweede, het verrichten van een hedendaagse gerandomiseerde studie naar de effectiviteit van moderne neurochirurgische versus endovasculaire aneurysmabehandelingen. Deze studie zou een scherp gedefinieerde patiëntpopulatie moeten hebben en

kan worden gebruikt om de SHARP-predictiemodellen en het beslismodel te valideren. De onderzoekspopulatie moet groot genoeg zijn om later het geïndividualiseerd behandeling effect mee te onderzoek en de follow-up moet lang genoeg zijn om recidief bloedingen en herbehandelingen te vervolgen. Deze studie kan als een maatstaaf dienen voor toekomstig gerandomiseerd onderzoek.

Dankwoord

Ten eerste wil ik mijn promotoren Professor Lingsma en Professor Dippel, en mijn co-promotor Dr. Roozenbeek bedanken. Ik voel me gezegend dat ik van jullie heb mogen leren en gebruik heb mogen maken van de schat aan kennis en kunde die jullie tot jullie beschikking hebben. We hebben jarenlang uitstekend samengewerkt. Deze samenwerking vormt de basis van mijn proefschrift waar ik erg trots op ben. Jullie hebben mij de gelegenheid geboden om mij te ontwikkelen als onderzoeker, maar ook als mens. Ik heb me altijd vrij gevoeld om de uitdagingen aan te gaan die ik relevant vond voor mijn ontwikkeling.

Naar aanleiding van mijn werk als masteronderzoeker aan de afdeling Neurologie met Bob werd ik in de zomer van 2019 uitgenodigd voor een gesprek met Hester en Bob. Het doel van dit gesprek was om kennis te maken en te bespreken of het doen van onderzoek eventueel bij mij zou passen. Ik verliet het kantoor Na-2315 enigszins verbaasd. Blijkbaar had ik zojuist ingestemd met een driejarig promotietraject, maar ik had ook net afgesproken om minimaal de komende 12 maanden te werken als ANIOS in het Franciscus Gasthuis en Vlietland. Met hangende pootjes ben ik het gesprek aangegaan met Stef Bakker, die mij gelukkig deze kans gunde. We spraken af dat ik 9 maanden zou blijven en in april 2020 zou beginnen met het onderzoek. Ik heb geen moment spijt gehad van deze beslissing.

Beste Hester, ik ben heel dankbaar voor jouw hulp als methodologisch zwaargewicht en promotor de afgelopen jaren. Maar nog belangrijker is dat ik je ook als persoon erg waardeer. Ik heb me altijd op mijn gemak gevoeld bij je en heb nooit getwijfeld of ik je iets wel of niet kon vragen. Ik bewonder hoe jij leiding geeft aan de CMB-sectie. Je bent benaderbaar, vriendelijk, empathisch, gezellig en ontzettend deskundig. Als ik ooit in de situatie kom waarin ik een team moet leiden, dan ben jij degene aan wie ik mij zou spiegelen. Ik hoop dat we in de toekomst onze gesprekken over werk (en vooral ook níet over werk) kunnen voortzetten.

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al snel stond ik weer op het verkeerde been na een paar kritische vragen van jouw kant. We hebben samen eindeloze lappen tekst doorgespit op zoek naar de beste formuleringen. Bedankt dat je er de afgelopen jaren voor me bent geweest en ik hoop dat ik je de komende tijd in de kliniek nog af en toe lastig mag vallen met slimme (en minder slimme) vragen.

Beste Diederik, ik ben er trots op dat ik heb mogen samenwerken met een van de giganten van het Nederlandse neurovasculaire onderzoeksgilde. Omdat we elkaar maar eens in de twee maanden spraken, keek jij met een frisse blik naar mijn projecten. Vaak wees je me op verbeterpunten en liet je me zien waar ik nog vooruitgang kon boeken. Bedankt voor je vriendelijke en directe manier van leidinggeven aan onze onderzoeksgroep. Het is er tot nu toe nog niet van gekomen, maar ik hoop dat we samen met de neurovasculaire groep nog eens op de fiets de bergen kunnen trotseren.

Professor Wermer, Professor Ikram, Professor Dirven, leden van de kleine commissie, hartelijk dank dat jullie dit proefschrift hebben willen beoordelen en plaats hebben willen nemen in de oppositiecommissie.

Beste Daan, David, Mathieu, Pieter-Jan en Ruben, dank jullie wel voor alle klinische, methodologische en statistische ondersteuning die jullie hebben geleverd voor de manuscripten in dit proefschrift. Ik neem alles wat ik de afgelopen jaren van jullie heb geleerd mee in mijn carrière. Ik weet zeker dat ik er veel profijt van zal hebben en ik hoop van harte dat we in de toekomst nog vaker kunnen samenwerken.

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paden elkaar nog eens zullen kruisen, jij als kersverse neurochirurg en ik als assistent. Carolien, je bent vaak een redder in nood voor me geweest tijdens mijn promotie. Jij bent een spil in het CMB-juniorenteam en ik weet zeker dat je een gouden toekomst tegemoet gaat. Annemijn, ons onderzoek heeft geen onderdeel uitgemaakt van dit proefschrift. Desalniettemin ben jij met jouw bevlogen en eigenzinnige karakter een voorbeeld voor me geweest. Ik hop dat we elkaar nog vaak zullen tegenkomen.

Beste neurovasculaire onderzoeksgroep, beste Bridget, Daniël, Femke, Jasper, Martijne, Nadia, Nadinda, Nikki, Noor, Peter, Rob, Ruben, Sanne en Wouter, ik wil jullie bedanken voor alle leerzame besprekingen en discussies die we hebben gehad. Maar bovenal wil ik jullie bedanken voor de gezelligheid. Onze borrels, feestjes en nachten in München en na Hester's oratie hebben ervoor gezorgd dat we naar elkaar toe zijn gegroeid. Ik kijk ernaar uit om straks allemaal samen in de kliniek te werken. Zullen we het dan nog eens dunnetjes overdoen?

Beste collega's van de CMB-sectie en van de afdeling Maatschappelijke Gezondheidszorg, beste leden van het Twitter Team en leden van de JRC, beste Judith, jullie zijn de kers op de taart van mijn promotie. Ik heb enorm geprofiteerd van de diverse achtergronden en expertise die jullie hebben. Binnen MGZ heb ik me, samen met jullie, ten volle kunnen ontwikkelen. Na de solitaire onderzoekstijd vanwege de coronapandemie ben ik door jullie in de groep opgenomen en hebben jullie me wegwijs gemaakt op de afdeling. Bedankt voor alle gezellige momenten en vergeet me niet te bellen voor de volgende ronde Soju-shots.

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Beste vrienden en familie, ook jullie wil ik bedanken voor jullie steun in de afgelopen jaren. Bedankt dat jullie naar mijn eindeloze verhalen over clippen en coilen wilden luisteren. Beste moeders, met de voltooiing van dit proefschrift kan ik eindelijk zeggen: "Ja, ik ben nu eindelijk *afgestudeerd*". Lieve Ruul en Tim, bedankt dat ik op woensdag en zaterdag mijn hart kon luchten als mijn onderzoeksprojecten weer eens niet wilden vlotten. Tim, mijn grote broer en paranimf, jij bent altijd al mijn grote voorbeeld geweest.

Kirsten, we hebben de afgelopen 3 jaar ontzettend veel meegemaakt. We zijn "getrouwd", op schitterende vakanties geweest en we hebben samen een huis gekocht en verbouwd. Hoewel je na drie jaar nog steeds niet weet waar mijn onderzoek over gaat, kon ik altijd bij jou terecht met mijn verhalen na een lange werkdag, hoe saai die soms ook waren. Juíst omdat we totaal andere dingen doen, kan ik na een werkdag alles achter me laten en met jou praten over de dingen die echt belangrijk zijn in het leven. Ik kan niet wachten om binnenkort ons vierde familielid in Charlois te verwelkomen.

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I wish to thank Daan Nieboer from the Erasmus MC University Medical Center Rotterdam for his help with developing the Gaussian copula function for the paper: "Personalized Decision-Making for Aneurysm Treatment of Aneurysmal Subarachnoid Hemorrhage: Development and Validation of a Clinical Prediction Tool".

I wish to thank to the authors of the International Subarachnoid Aneurysm Trial and the SAHIT Collaboration for supplying the data necessary to conduct this research. I used this data to do the analysis for the paper: "Pitfalls of Single-Study External Validation Illustrated with A Model Predicting Functional Outcome after Aneurysmal Subarachnoid Hemmorrhage".

I wish to thank Bridget Schoon for her work on the language editing of the introduction and discussion of this thesis.

Last, I wish to thank Esmee Venema from the Erasmus MC University Medical Center Rotterdam for her help with the R Coding necessary to develop the Shiny app. With this knowledge I was able to analyze and write the paper: "Personalized Decision-Making for Aneurysm Treatment of Aneurysmal Subarachnoid Hemorrhage: Development and Validation of a Clinical Prediction Tool".

List of Publications

1 Looman KIM., **de Winkel J.**, Dalm VASH. Tyrosine Kinase Inhibitors in the Treatment of Systemic Sclerosis: A Systematic Review. *Erasmus Journal of Medicine*. 2014;4:19-24.

2 **de Winkel J.**, van der Jagt M., Lingsma HF., et al. International Practice Variability in Treatment of Aneurysmal Subarachnoid Hemorrhage. *Journal of Clinical Medicine*. 2021;10(4):762. doi: 10.3390/jcm10040762

3 **de Winkel J.**, Cras TY., Dammers R., et al. Early Predictors of Functional Outcome in Poor-Grade Aneurysmal Subarachnoid Hemorrhage: a Systematic Review and Meta-Analysis. *BMC Neurology*. 2022;22:239. doi: 10.1186/s12883-022-02734-x

4 **de Winkel J.**, Dippel DWJ. Letter by De Winkel et al. regarding article: "Neutrophil Count as Promising Marker for Predicting In-Hospital Mortality in Aneurysmal Subarachnoid Hemorrhage". *Stroke*. *No peer review*.

5 **de Winkel J.** Reactie op: "Diagnoses uit de hoge hoed". *Medisch Contact*. 2022;77:39. *No peer review*.

6 Algra AM., Greving JP., **de Winkel J.**, et al. Development of the SAFETEA Scores for Predicting Risks of Complications of Preventive Endovascular or Microneurosurgical Intracranial Aneurysm Occlusion. *Neurology*. 2022;99(16):1725-37. doi: 10.1212/WNL.0000000000200978

7 **de Winkel J.**, Roozenbeek B. Response to: "Flow Diversion in the Treatment of Intracranial Aneurysms: A Pragmatic Randomized Care Trial". *American Journal of Neuroradiology*. 2022;44(1):e7-8. doi: 10.3174/ajnr.A7718

8 **de Winkel J.**, Roozenbeek B., Dijkland SA., et al. Endovascular Versus Neurosurgical Aneurysm Treatment: A Study Protocol for Derivation and Validation of a Clinical Prediction Tool for Individualized Decision Making. *BMJ Open*. 2022;12:e065903. doi:10.1135/bmjopen-2022-065903

9 **de Winkel J.**, Roozenbeek B., Dijkland SA., et al. Personalized Decision-Making for Aneurysm Treatment of Aneurysmal Subarachnoid Hemorrhage: Derivation and Validation of a Clinical Prediction Tool. Submitted to *BMC Neurology*.

10 Mijderwijk H-J., **de Winkel J.**, Nieboer D., et al. External Validation and Update of The ARISE Prediction Models for Aneurysmal Rerupture after Aneurysmal Subarachnoid Hemorrhage. Submitted to *Neurosurgery*.

11 **de Winkel J.**, Cras TY., Roozenbeek B., et al. Endovascular Coiling Versus Neurosurgical Clip-Reconstruction after Subarachnoid Hemorrhage: A Decision Model to Estimate Individualized Treatment Benefit. Submitted to *Neurology*.

12 **de Winkel J.**, Maas CCHM., Roozenbeek B., et al. Pitfalls of Single-Study External Validation Illustrated with A Model Predicting Functional Outcome after Aneurysmal Subarachnoid Hemmorrhage. Submitted to *BMC Medical Research Methodology*.

PhD Portfolio

Name PhD student: Jordi de Winkel
PhD period: April 2020-June 2023
Erasmus MC Department: Public Health and Neurology

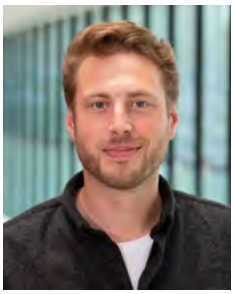
Promotor(s): Prof. dr. Hester F. Lingsma and Prof. dr. Diederik W.J. Dippel
Supervisor: Prof. dr. Hester F. Lingsma and dr. Bob Roozenbeek

Activity	Year	Workload (Hours/ECTS)
1. PhD Training		
NIHES Courses		
CC02 – Biostatistics I: Basic Principles	2020	5,7
EP03 – Biostatistics II: Classical Regression Models	2020	4,3
ESP70 – Fundamentals of Medical Decision Making	2021	0,7
ESP66 – Logistic Regression	2021	1,4
ESP65 – The Practice of Epidemiology	2021	0,7
ESP80 – Data Science in Epidemiology	2021	0,7
EL004 – Topics in Medical Decision Making	2022	1,4
Subtotal		13,5
Graduate School Courses		
Scientific Integrity	2020	0,3
Biomedical Writing Course	2021	2,0
Subtotal		2,3
Other courses or lectures		
eBROK	2021	1,5
CTa cursus 2021	2021	0,3
CEPHIR Seminar 2021	2021	0,2
Masterclass Mayank Goyal	2021	0,2
Lecture Claire Miller	2021	0,2
Lecture Denis Vivien	2021	0,2
Nascholing Dutch Society of Neurology	2021	0,3
Department of Public Health Writing Course by prof. Hester Lingsma	2021	0,2
Career Day 2022	2022	0,2
Department of Public Health How Editor's Handle Manuscripts by prof. Lex Burdorf and prof. Frank van Lenthe	2022	0,2

JRC workshop: Unlock Your true Powerpoint Potential Course	2023	0,1
JRC workshop: Systematic Reviews by Lex Burdorf		0,1
Pizza, Drinks, Science, afdeling Neurologie	2023	0,1
Regionale Neurologenavond (Big data: toekomst of hype?)	2023	0,1
European Stroke Organisation Stroke Webinar	2023	0,1
Weekly Department of Public Health Monday Meeting	2020-2023	4,5
Biweekly Neurovascular Research Meeting	2020-2023	2,25
Weekly Department of Neurology Referaat	2020-2023	4,5
Weekly Department of Neurology Patient demonstration	2020-2023	3
Monthly Department of Public Health Medical Decision Making Section Research Meeting	2020-2023	1
Subtotal		19,25
2. Presentations at National and International Conferences		
European Stroke Organisation Conference 2020 – participation only	2020	0,7
European Stroke Organisation Conference 2021 – oral presentation	2021	1,5
European Stroke Organisation Conference 2022 – poster presentation	2022	1,5
Wetenschappelijke Vergadering NNW & NNG 2022 – oral presentation	2022	0,3
Smarter Medical Decision Making Conference 2022 – oral presentation	2022	3,2
Smarter Medical Decision Making Conference 2022 – Social Media Reporter	2022	0,6
European Stroke Organisation Conference 2023 – poster	2023	1,5
Subtotal		9,3
3. Teaching Activities		
Supervising Master Thesis – Assisted dr. Bob Roozenbeek with supervising Master student Merel Huijg from the Erasmus University Rotterdam. Topic: Aneurysmal Subarachnoid Hemorrhage.	2020-2021	1,5
Supervising Community Project – Supervising a group of Bachelor Students from the Erasmus University Rotterdam. Topic: Evaluatie van Aneurysmatische Subarachnoidale Bloeding Richtlijnen en Implementatie Ervan.	2020-2021	1,0
Master Consultancy Program	2020-2023	0,3
Nascholing Verpleegkundigen Neurologie & Neurochirurgie	2021	0,3
PKV Onderwijs	2021-2022	0,6
Subtotal		3,7

4. Other Activities		
Department of Public Health Twitter Team – Editor	2021-2023	2,0
PROTECT-U Investigator	2021-2023	0,3
Junior Vertegenwoordigers Overleg/Junior Researchers Committee – Secretary	2022-2023	2,0
Publication Prizes Committee – Jury member	2022-2023	0,3
Peer Review *Clinical Neurology and Neurosurgery*	2023	0,1
Subtotal		4,7
Total		52,75

About the Author



Jordi de Winkel, 4th of March 1992, was born and raised in Rotterdam, Zuid-Holland, The Netherlands. His passion for debate and politics was visible at an early age as he was one of the Emmauscollege Rotterdam representatives at the Erasmian European Youth Parliament (2008) and the Model European Parliament (2009) and a member of the student and representatives' committee of Emmauscollege Rotterdam (2014-2015).

After finishing secondary school (2010) he did a poor attempt to obtain a Bachelor in Dutch Language and Culture at Utrecht University (2011) and afterward a successful attempt at obtaining a Bachelor (2015) and Master degree (2019) in Medicine at the Erasmus University Rotterdam. During his Bachelor, he did electives in Immunology and Psychiatry (2014-2015). He did his Master's research project at the Department of Neurology of the Erasmus MC collecting data for a large international prospective observational cohort study led by Dr. Annemijn Algra aiming to develop risk scores for treatment-related complications of preventive treatment of unruptured intracranial aneurysms (2018). Jordi did a 6-week Neurology and Radiology elective program at the esteemed Keio University Hospital in Tokyo, Japan (2019). During his studies he worked at Stichting Lanteren Venster (2015-2018) an art-house movie theater in Rotterdam, Stichting Pameijer in Capelle aan den Ijssel a facility for people with a developmental disability (2018), and as a student assistant at Gezondheidscentrum De Akkers in Spijkenisse (2018).

After his studies, he worked for nine months at the Department of Neurology in the Franciscus Gasthuis and Vlietland as a resident-not-in-training (2019). In April 2020 he started a Ph.D. project at the Department of Neurology and Department of Public Health of the Erasmus MC supervised by Dr. Bob Roozenbeek, Prof. Dr. Diederik Dippel, and Prof. Dr. Hester Lingsma that has resulted in the present thesis.

Jordi recently moved into his dreamhouse living his happily ever after in Charlois, Rotterdam, with his lovely partner Kirsten and cat Tico. He is a track and field and movie enthusiast and news junkie, with a habit of getting into heated discussions with whoever dares to disagree. Last but not least during the weekends he is a fierce non-violent hooligan supporting his favorite football team Feyenoord Rotterdam.