Time trends in the risk of delayed cerebral ischemia after subarachnoid hemorrhage: a meta-analysis of randomized controlled trials

Luigi Rigante, MD,¹ Jasper Hans van Lieshout, MD, PhD,² Mervyn D. I. Vergouwen, PhD,³ Carlijn H. S. van Griensven, MD,⁴ Priya Vart, PhD,⁵ Lars van der Loo, MD,⁶ Joost de Vries, PhD,¹ Ruben Saman Vinke, MD,¹ Nima Etminan, PhD,⁷ Rene Aquarius, PhD,¹ Andreas Gruber, PhD,⁸ J Mocco, MD,⁹ Babu G. Welch, MD,¹⁰ Tomas Menovsky, PhD,¹¹ Catharina J. M. Klijn, PhD,¹² Ronald H. M. A. Bartels, PhD,¹ Menno R. Germans, PhD,¹³ Daniel Hänggi, PhD,² and Hieronymus D. Boogaarts, PhD¹

¹Department of Neurosurgery, Radboud University Medical Centre, Nijmegen, The Netherlands; ²Department of Neurosurgery, Henrich-Heine-University Düsseldorf, Germany; ³Department of Neurology and Neurosurgery, UMC Utrecht Brain Center, Utrecht University, Utrecht, The Netherlands; ⁴Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands; ⁵Department for Health Evidence, Radboud University Medical Centre, Nijmegen, The Netherlands; ⁶Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands; ⁷Department of Neurosurgery, Universitätsmedizin Mannheim, Germany; ⁸Department of Neurosurgery, Kepler University Hospital, Linz, Austria; ⁹Department of Neurosurgery, Mount Sinai Health System, New York, New York; ¹⁰Department of Neurosurgery, University of Texas Southwestern, Dallas, Texas; ¹¹Department of Neurosurgery, Antwerp University Hospital, Edegem, Belgium; ¹²Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Centre, Nijmegen, The Netherlands; and ¹³Department of Neurosurgery, University Hospital Zurich and Clinical Neuroscience Center, Zurich, Switzerland

OBJECTIVE Delayed cerebral ischemia (DCI) contributes to morbidity and mortality after aneurysmal subarachnoid hemorrhage (aSAH). Continuous improvement in the management of these patients, such as neurocritical care and aneurysm repair, may decrease the prevalence of DCI. In this study, the authors aimed to investigate potential time trends in the prevalence of DCI in clinical studies of DCI within the last 20 years.

METHODS PubMed, Embase, and the Cochrane library were searched from 2000 to 2020. Randomized controlled trials that reported clinical (and radiological) DCI in patients with aSAH who were randomized to a control group receiving standard care were included. DCI prevalence was estimated by means of random-effects meta-analysis, and subgroup analyses were performed for the DCI sum score, Fisher grade, clinical grade on admission, and aneurysm treatment method. Time trends were evaluated by meta-regression.

RESULTS The search strategy yielded 5931 records, of which 58 randomized controlled trials were included. A total of 4424 patients in the control arm were included. The overall prevalence of DCI was 0.29 (95% CI 0.26–0.32). The event rate for prevalence of DCI among the high-quality studies was 0.30 (95% CI 0.25–0.34) and did not decrease over time (0.25% decline per year; 95% CI –2.49% to 1.99%, $p = 0.819$). DCI prevalence was higher in studies that included only higher clinical or Fisher grades, and in studies that included only clipping as the treatment modality.

CONCLUSIONS Overall DCI prevalence in patients with aSAH was 0.29 (95% CI 0.26–0.32) and did not decrease over time in the control groups of the included randomized controlled trials.

<https://thejns.org/doi/abs/10.3171/2021.12.FOCUS21473>

KEYWORDS aneurysmal subarachnoid hemorrhage; cerebral vasospasm; delayed cerebral ischemia; delayed ischemic neurologic deficit; meta-analysis

ABBREVIATIONS aSAH = aneurysmal subarachnoid hemorrhage; DCI = delayed cerebral ischemia; ER = event rate; RCT = randomized controlled trial.

SUBMITTED August 8, 2021. **ACCEPTED** December 21, 2021.

INCLUDE WHEN CITING DOI: 10.3171/2021.12.FOCUS21473.

DELAYED cerebral ischemia (DCI) is an important contributor to morbidity and mortality after aneurysmal subarachnoid hemorrhage (aSAH).^{1,2} A decrease in the case-fatality rate of aSAH, most likely due to reduction in aneurysm rebleeding resulting from earlier treatment, has been described.³

Despite improvements in neurocritical care and endovascular and surgical aneurysmal repair, it is unclear whether this has led to a decrease in DCI prevalence and its consequences over time. In fact, no data on time trends in the prevalence of DCI have been reported.^{4,5} The aim of this study was to investigate potential time trends in the prevalence of DCI in clinical studies of DCI within the last 20 years.

Methods

Search Strategy and Selection Criteria

This study was performed according to the PRISMA statement.⁶ Search strategies were developed in consultation with a research librarian with systematic review expertise. Literature was reviewed through the PubMed, Embase, and Cochrane Central Register of Controlled Trials from 2000 to March 31, 2020, using keywords specific to aSAH, cerebral vasospasm, and DCI. Complete search syntaxes for the PubMed, Embase, and Cochrane databases are included in the Supplemental Appendix. Citations used in articles that were included in the present review were hand searched.

We included randomized controlled trials (RCTs) that investigated patients with aSAH in a control group that underwent standard preventive therapy for DCI, which consisted of administration of nimodipine and/or maintaining normovolemia.

Patients randomized to the intervention arms were excluded from the analysis to avoid bias due to the possible effect on DCI prevalence. We included only RCTs that reported clinical signs of DCI, or any other synonym of DCI, as an outcome measure and included more than 10 patients in the control group. In the full-text screening, we used the following exclusion criteria: 1) studies not reporting on DCI; 2) articles for which the full text was not available; 3) animal studies; 4) non-RCTs; 5) articles written in languages other than English and Dutch; and 6) studies reporting only on angiographic vasospasm as a measure of DCI. If several articles used the same or overlapping patient populations, we included only the report with the largest population or with the most relevant information.

Two authors (L.R. and C.H.S.V.G.) independently assessed titles and abstracts according to the predefined inclusion criteria. If an abstract was judged by both authors to meet the requirements, the full article was reviewed; discrepancies were solved with a third author (H.D.B.).

Outcome Measures and Quality Assessment

The primary outcome was the prevalence of DCI. Because heterogeneous definitions of DCI were expected, the quality of the DCI definition was graded. We designed a DCI definition sum score based on the separate entities used in the definition of DCI formulated by Vergouwen et al.: “the occurrence of focal neurological impairment

(such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies” (Supplemental Table 1).⁴ Additionally, the quality of the trials was assessed using the Jadad score.⁷

Data Extraction

Titles, abstracts, and keywords of the obtained reports were screened by two authors (C.H.S.V.G. and L.R.), and duplicates were eliminated. The included articles were assessed for eligibility in full text. Endnote (X9, Clarivate) was used as the citation manager. Control groups of included studies were used to extract data on the prevalence of DCI. Data extracted for each study were: authors and publication year; median year of data collection, study population/control group size, sex, clinical grade of aSAH; Fisher grade and type of treatment (clipping or coiling); and DCI definition and occurrences.

Statistical Analysis

Stata software version 14 (StataCorp LLC) was used for statistical analysis. Results are presented as the event rate (ER) with 95% CI. The I^2 value was used to present between-study heterogeneity.

Random-effects model meta-regression was used to determine the overall DCI prevalence over time. The median year of each data collection period was used. When not mentioned in the studies, the data collection year was considered the mean of the difference between the median data collection year and the year of publication of all other trials. Only studies with a high-quality definition (DCI sum score ≥ 3) and high quality (Jadad score ≥ 3) were included for the quantitative meta-analysis.

In accordance with known risk factors for DCI, subgroup analyses for the DCI sum score, clinical grade, Fisher grade, and aneurysm repair modality were performed whenever possible.^{8,9} To assess the linear trend in incidence rate across subgroups, univariable meta-regression analysis was performed separately for each variable.

Results

Included Studies

The search results are presented in the PRISMA flow diagram (Fig. 1). Our search strategy identified 5931 articles after removing duplicates. Two articles were identified after a hand search of the references and were evaluated in full text.^{10,11} Discrepancies were resolved in accordance. Of the 227 articles selected for full-text review, 169 were excluded for not meeting the inclusion criteria. Fifty-eight RCTs were included, describing a total of 4424 patients in the control arm. These references can be found at the end of the Supplemental Data.

The characteristics and quality assessment of the included studies are listed in Supplemental Table 2. The attribution of the DCI sum score is described in Supplemen-

FIG. 1. Flowchart of the study search results.

tal Table 3, and the quality assessment of the studies by the mean Jadad score is described in Supplemental Table 4.

Analysis of Overall DCI Prevalence

The overall DCI prevalence was 0.29 (95% CI 0.26–0.32). Heterogeneity between trials (I^2) was 72% ($p < 0.001$) (Supplemental Fig. 1). The DCI prevalence among high-quality studies was 0.30 (95% CI 0.25–0.34). Heterogeneity between trials (I^2) was 78% ($p < 0.001$) (Supplemental Fig. 2). Moreover, the prevalence of DCI among high-quality studies did not significantly decrease over time (0.25% decline per year; 95% CI –2.49% to 1.99%, $p = 0.819$) (Fig. 2).

Subgroup Analyses

No trend in change in DCI prevalence was found among studies with different DCI sum scores (Table 1). DCI prevalence was not significantly higher in studies that included only higher clinical grades (ER 0.40, 95% CI 0.24–0.56) compared with studies including all grades (ER 0.28, 95% CI 0.25–0.31) and in studies including only higher Fisher grades (ER 0.31, 95% CI 0.26–0.37) compared with studies including all Fisher grades (ER 0.26, 95% CI 0.22–0.29). Regarding treatment modality, there was no significantly higher prevalence of DCI in studies that included only clipping (ER 0.28, 95% CI 0.22–0.33) compared with studies that included only coiling (ER 0.23, 95% CI 0.17–0.28).

FIG. 2. Meta-regression scatterplot showing DCI prevalence over time in high-quality studies (Jadad score ≥ 3 and DCI definition score ≥ 3).

Discussion

The aim of this systematic review was to determine time trends in the prevalence of DCI in patients with aSAH. Only control groups of RCTs were considered in order to obtain the most reliable comparison among studies over time and to have a valid estimate of DCI prevalence for future research. The overall DCI prevalence in our review was 0.29 (95% CI 0.26–0.32), and DCI prevalence among high-quality studies was 0.30 (95% CI 0.25–0.34). Our meta-regression analysis showed no significant change in DCI prevalence over time among high-quality studies.^{12–14}

The population analyzed in our study was the control group undergoing standard treatment for DCI (nimodipine and/or normovolemia) irrespective of the treatment modality, to eliminate any influence on DCI prevalence due to non-evidence-based preventive treatments. A previous meta-analysis on treatment modality that compared coiling versus clipping showed a lower prevalence of DCI in the endovascular (0.32) versus the surgical group (0.38) (risk ratio 0.84, 95% CI 0.74–0.96). We also found a lower prevalence in studies that included patients who underwent only coiling (ER 0.23, 95% CI 0.17–0.28) compared with studies that included patients who underwent only clipping (ER 0.28, 95% CI 0.22–0.33). However, the confidence intervals were overlapping, and the number of studies included in each subgroup was limited; therefore, we were unable to draw any conclusion.¹⁵

The case-fatality rate of SAH in population-based studies has declined over past decades, most likely due to a pronounced reduction in aneurysmal rebleeding resulting from earlier treatment and endovascular treatment.^{1–3,16} Additionally, such decline cannot be attributed to the constant prevalence of DCI over time estimated by our meta-analysis, although we included only RCTs and not population-based studies.

Several terms and definitions are used for DCI, which makes it difficult to pool data from various studies. Uniform definitions for SAH-related variables (including DCI) are published by the NIH Common Data Elements

TABLE 1. Subgroup analysis by DCI sum score, Fisher grade, clinical grade, and aneurysm treatment method

	Pooled ER (95% CI)	% Heterogeneity (I ²)	p Value for Trend
DCI sum score			0.66
0 (n = 5)	0.31 (0.23–0.39)	00.0	
1 (n = 1)	0.25 (0.20–0.31)		
2 (n = 20)	0.30 (0.25–0.35)	73.4	
3 (n = 18)	0.27 (0.22–0.32)	78.5	
4 (n = 10)	0.30 (0.23–0.37)	69.0	
5 (n = 4)	0.32 (0.23–0.42)	73.5	
Fisher grade			0.11
NA (n = 17)	0.28 (0.23–0.33)	83.1	
1–4 (n = 19)	0.26 (0.22–0.29)	51.6	
≥2 (n = 16)	0.31 (0.26–0.37)	58.9	
mF 1–4 (n = 6)	0.36 (0.25–0.47)	77.8	
Clinical grade			0.13
NA (n = 3)	0.38 (0.24–0.52)		
All clinical grades (n = 50)	0.28 (0.25–0.31)	71.6	
Only high clinical grades (n = 5)	0.40 (0.24–0.56)	45.0	
Aneurysm treatment method			0.12
NA (n = 10)	0.33 (0.25–0.41)	82.0	
Clipping only (n = 15)	0.28 (0.22–0.33)	59.6	
Clipping & coiling (n = 31)	0.29 (0.25–0.32)	70.0	
Coiling only (n = 2)	0.23 (0.17–0.28)		

mF = modified Fisher; n = number of studies included; NA = not available.

Repository.^{17,18} We tried to reduce the bias and heterogeneity between studies, to correct for the various DCI definitions among them, by developing a DCI sum score. Despite this correction, analysis of high-quality studies showed the same results as low-quality studies, indicating that the DCI definition did not influence the prevalence of DCI. Nevertheless, despite the development of the DCI sum score, a changing definition over time might have influenced the results in any given study.

We could not find a significant association between the clinical and Fisher grades and DCI; the subgroups were not suitable to make a distinction between high and low grades due to overlap. In the literature, however, an association between higher clinical grades and high modified Fisher grades and DCI has been reported and used for prediction models such as the VASOGRADE scale.¹⁹

Study Limitations

Heterogeneity between studies is a limitation of our study that must not be overlooked. It was caused by methodological differences between the studies and biological or social differences between the populations studied. By only selecting studies with control groups undergoing standard preventive therapy for DCI and, nevertheless, reaching a large number of patients, heterogeneity between studies was reduced. Additionally, as mentioned, the low number of studies that included only coiling as the treatment modality was a limiting factor for data interpretation.

Conclusions

In our systematic review, the overall DCI prevalence in high-quality studies did not change over time within the last 2 decades. Despite many attempts to improve the diagnosis and prevention of DCI, no reduction in prevalence was achieved. Given the large heterogeneity of the definition of DCI among studies, we advocate for a uniform definition in future studies to reduce interobservational bias. This is particularly relevant given the critical importance of DCI in determining the outcome of aSAH, and as a target for clinical trials.

Acknowledgments

We would like to thank OnYing Chan for her assistance with the literature search.

References

1. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. *Lancet Neurol*. 2009;8(7):635–642.
2. Lovelock CE, Rinkel GJ, Rothwell PM. Time trends in outcome of subarachnoid hemorrhage: population-based study and systematic review. *Neurology*. 2010;74(19):1494–1501.
3. Vergouwen MD, Jong-Tjien-Fa AV, Algra A, Rinkel GJ. Time trends in causes of death after aneurysmal subarachnoid hemorrhage: A hospital-based study. *Neurology*. 2016;86(1):59–63.
4. Vergouwen MD, Vermeulen M, van Gijn J, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid

- hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke*. 2010;41(10):2391-2395.
5. Velat GJ, Kimball MM, Mocco JD, Hoh BL. Vasospasm after aneurysmal subarachnoid hemorrhage: review of randomized controlled trials and meta-analyses in the literature. *World Neurosurg*. 2011;76(5):446-454.
 6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100.
 7. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
 8. de Rooij NK, Rinkel GJ, Dankbaar JW, Frijns CJ. Delayed cerebral ischemia after subarachnoid hemorrhage: a systematic review of clinical, laboratory, and radiological predictors. *Stroke*. 2013;44(1):43-54.
 9. Dorhout Mees SM, Kerr RS, Rinkel GJ, Algra A, Molyneux AJ. Occurrence and impact of delayed cerebral ischemia after coiling and after clipping in the International Subarachnoid Aneurysm Trial (ISAT). *J Neurol*. 2012;259(4):679-683.
 10. Hillman J, Fridriksson S, Nilsson O, Yu Z, Säveland H, Jakobsson KE. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. *J Neurosurg*. 2002;97(4):771-778.
 11. Sillberg VA, Wells GA, Perry JJ. Do statins improve outcomes and reduce the incidence of vasospasm after aneurysmal subarachnoid hemorrhage: a meta-analysis. *Stroke*. 2008;39(9):2622-2626.
 12. Roos YBWEM, de Haan RJ, Beenen LFM, Groen RJM, Albrecht KW, 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(3):337-341.
 13. Hijdra A, Van Gijn J, Stefanko S, Van Dongen KJ, Vermeulen M, Van Crevel H. Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: clinicoanatomic correlations. *Neurology*. 1986;36(3):329-333.
 14. Findlay JM, Kassell NF, Weir BK, et al. A randomized trial of intraoperative, intracisternal tissue plasminogen activator for the prevention of vasospasm. *Neurosurgery*. 1995;37(1):168-178.
 15. Lindgren A, Vergouwen MD, van der Schaaf I, et al. Endovascular coiling versus neurosurgical clipping for people with aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2018;8:CD003085.
 16. Mukhtar TK, Molyneux AJ, Hall N, et al. The falling rates of hospital admission, case fatality, and population-based mortality for subarachnoid hemorrhage in England, 1999-2010. *J Neurosurg*. 2016;125(3):698-704.
 17. de Oliveira Manoel AL, van der Jagt M, Amin-Hanjani S, et al. Common data elements for unruptured intracranial aneurysms and aneurysmal subarachnoid hemorrhage: recommendations from the working group on hospital course and acute therapies-proposal of a multidisciplinary research group. *Neurocrit Care*. 2019;30(suppl 1):36-45.
 18. Suarez JJ, 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*. 2019;30(suppl 1):4-19.
 19. de Oliveira Manoel AL, Jaja BN, Germans MR, et al. The VASOGRADE. A simple grading scale for prediction of delayed cerebral ischemia after subarachnoid hemorrhage. *Stroke*. 2015;46(7):1826-1831.

Disclosures

Dr. de Vries: consultant for Stryker Neurovascular and Evasec Ltd. Dr. Mocco: direct stock ownership in Imperative, Endostream, Synchron, Viseon, Vastrax, Viz.ai, and Q-Apel; and principal investigator of grant funded by MicroVention, Penumbra, and Stryker. Dr. Welch: consultant for Stryker Neurovascular, Medtronic, MicroVention, and Balt; and royalties from Peter Lazic.

Author Contributions

Conception and design: Rigante, van Griensven, Boogaarts. Acquisition of data: Rigante, van Griensven, Boogaarts. Analysis and interpretation of data: Rigante, Vart, Aquarius, Germans, Boogaarts. Drafting the article: Rigante, van Griensven. Critically revising the article: Rigante, van Lieshout, Vergouwen, van der Loo, de Vries, Vinke, Etminan, Aquarius, Gruber, Mocco, Welch, Menovsky, Klijn, Bartels, Germans, Hänggi, Boogaarts. Reviewed submitted version of manuscript: Rigante, Germans, Boogaarts. Approved the final version of the manuscript on behalf of all authors: Rigante. Statistical analysis: Rigante, Vart, Boogaarts. Administrative/technical/material support: Rigante, de Vries, Bartels, Boogaarts. Study supervision: Rigante, Bartels, Boogaarts.

Supplemental Information

Online-Only Content

Supplemental material is available online.

Supplemental Figs., Tables, and Appendix. <https://thejns.org/doi/suppl/10.3171/2021.12.FOCUS21473>.

Correspondence

Luigi Rigante: Radboud University Medical Centre, Nijmegen, The Netherlands. luigirigante@gmail.com.