



OPEN ACCESS

EDITED BY

Camillo Sherif,
St. Pölten University Hospital, Karl Landsteiner
University of Health Sciences, Austria

REVIEWED BY

Qazi Zeeshan,
University of Pittsburgh Medical Center,
United States
Stefan Yu Bögli,
Cambridge University
Hospitals NHS Foundation Trust,
United Kingdom

*CORRESPONDENCE

Axel Neulen

✉ axel.neulen@unimedizin-mainz.de

Carolin Brockmann

✉ carolin.brockmann@unimedizin-mainz.de

RECEIVED 27 May 2025

ACCEPTED 17 October 2025

PUBLISHED 03 December 2025

CITATION

Neulen A, Fassl V, Kurz E, Kramer A,
Nedwed AS, Brockmann MA, Ringel F and
Brockmann C (2025) Clinical outcomes in
spontaneous subarachnoid hemorrhage after
introduction of continuous intra-arterial
vasospasmolysis for treatment of refractory
delayed cerebral ischemia.
Front. Neurol. 16:1636083.
doi: 10.3389/fneur.2025.1636083

COPYRIGHT

© 2025 Neulen, Fassl, Kurz, Kramer, Nedwed,
Brockmann, Ringel and Brockmann. This is an
open-access article distributed under the
terms of the [Creative Commons Attribution
License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or
reproduction in other forums is permitted,
provided the original author(s) and the
copyright owner(s) are credited and that the
original publication in this journal is cited, in
accordance with accepted academic
practice. No use, distribution or reproduction
is permitted which does not comply with
these terms.

Clinical outcomes in spontaneous subarachnoid hemorrhage after introduction of continuous intra-arterial vasospasmolysis for treatment of refractory delayed cerebral ischemia

Axel Neulen^{1*}, Verena Fassl¹, Elena Kurz¹, Andreas Kramer^{1,2},
Annekathrin Silvia Nedwed³, Marc A. Brockmann⁴,
Florian Ringel^{1,2} and Carolin Brockmann^{4*}

¹Department of Neurosurgery, University Medical Center of the Johannes Gutenberg-University of Mainz, Mainz, Germany, ²Department of Neurosurgery, LMU University Hospital, LMU Munich, Munich, Germany, ³Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Center of the Johannes Gutenberg-University of Mainz, Mainz, Germany, ⁴Department of Neuroradiology, University Medical Center of the Johannes Gutenberg-University of Mainz, Mainz, Germany

Background: In patients with refractory delayed cerebral ischemia (DCI) after spontaneous subarachnoid hemorrhage (SAH), endovascular therapy of cerebral vasospasms is a treatment option. In our center, continuous intra-arterial vasospasmolysis with nimodipine (ciaN) has been introduced as the standard endovascular therapy for cerebral vasospasms since 2016. This study investigated the outcomes of SAH patients before and after introduction of ciaN.

Methods: Data pertaining to all patients treated for SAH in our center between 2011 and 2021 were retrospectively recorded.

Results: 145 patients before (pre-ciaN group) and 147 after (ciaN group) introduction of ciaN met the inclusion criteria. 36 patients in the pre-ciaN group and 51 in the ciaN group received endovascular vasospasm treatment. At discharge, outcomes tended to improve in the ciaN group. After 6 months, there was a significantly improved outcome in the ciaN group (mRS 0–2, Fisher's exact test). After propensity score matching, there were no significant differences between the pre-ciaN and ciaN groups in the subgroups of patients without endovascular vasospasm treatments. Conversely, in the subgroups of patients who had received endovascular vasospasm treatments, there was a significantly improved outcome at discharge and after 6 months, and a significant reduction of DCI-associated infarctions.

Conclusion: Outcome after spontaneous subarachnoid hemorrhage has improved since the introduction of ciaN in our center. Our data indicate a contribution of the changes in treatment standard for endovascular vasospasm therapies from angioplasties to ciaN. Prospective studies are needed to compare the effect of ciaN in DCI with standard medical therapy.

KEYWORDS

subarachnoid hemorrhage, cerebral perfusion, delayed cerebral ischemia, nimodipine, vasospasm, endovascular

Introduction

Spontaneous subarachnoid hemorrhage (SAH), which is caused by rupture of an intracranial aneurysm in most cases, is a type of hemorrhagic stroke (1, 2). It accounts for approximately 5% of all strokes in most western countries (3). Compared with other forms of stroke, patients with SAH are younger with a mean age of approximately 55 years, as reported in most studies (4). Brain injury after SAH develops in two phases: Early brain injury occurs as the direct consequence of bleeding and the associated transient global cerebral ischemia (5, 6). In contrast, delayed cerebral ischemia (DCI) occurs within the first weeks after SAH onset (5). The pathophysiology of DCI is complex. In addition to vasospasms of large intracranial arteries, microvasospasms, microthrombosis, cortical spreading depressions, and inflammation have been described as contributing factors (5). It leads to cerebral hypoperfusion and, in some cases, to cerebral infarctions (DCI-associated infarctions) and is a central factor influencing neurological outcomes (5).

Oral nimodipine in the first weeks after SAH is the only evidence-based therapy that reduces the rates of delayed infarctions and improves outcomes (7). If DCI still occurs, current guidelines recommend inducing hypertension (8), despite a lack of prospective studies showing its effects on outcomes. In case of DCI that does not respond to induced hypertension, endovascular therapies targeting cerebral vasospasms can be applied (8). These endovascular approaches aim to improve brain perfusion by mitigating vasospasms either by angioplasty of large vasospastic arteries or by intra-arterial infusion of vasodilating drugs into vasospastic arteries.

Intra-arterial infusion of vasodilating drugs can be performed either as “single-shot” application—that is, the intra-arterial infusion is terminated after angiography—or as continuous intra-arterial infusion (9–14). For continuous intra-arterial infusion, a catheter is commonly left behind in an internal carotid or vertebral artery, depending on the location of the vasospasms. To prevent embolism from the intra-arterial catheters, anticoagulation or antiplatelet therapy is necessary until the catheter is removed. Previous studies have found that continuous intra-arterial infusion into vessels affected by vasospasms is a secure method that significantly reduces cerebral angiographic vasospasms and leads to a low complication rate (9–14). However, it remains unclear whether the intra-arterial infusion of nimodipine in case of refractory DCI in patients with SAH improves outcomes.

At our center, the endovascular treatment of vasospasms is offered to patients with SAH and refractory DCI as rescue treatment. Until 2015, endovascular treatment comprised a single-shot intra-arterial infusion of nimodipine and/or angioplasty of vasospastic arteries. In 2016, the standard was changed to single-shot intra-arterial infusion of nimodipine or continuous intra-arterial infusion of nimodipine (ciaN). Angioplasty was no longer routinely performed because we considered ciaN to be similarly effective and associated with less complications. This study aimed to analyze the effects of the change in the treatment standard by comparing the outcomes before and after the switch in the method for endovascular vasospasm treatment in two cohorts of patients with SAH.

Methods

Ethics approval

The study was approved by the local Ethics Committee (Ethikkommission der Landesärztekammer Rheinland Pfalz). Because of the retrospective nature of the study, the requirement for informed consent was waived.

Patients and study design

We retrospectively identified all patients aged ≥ 18 years, treated at the neurosurgical intensive care unit of the Medical Center of the Johannes Gutenberg-University of Mainz, Germany, with the diagnosis of spontaneous SAH between January 01, 2011, and June 30, 2021. The patients were assigned to the cohorts before (January 01, 2011, to December 31, 2015) and after (July 01, 2016, to June 30, 2021) the introduction of ciaN, which replaced angioplasty as the standard endovascular therapy for refractory DCI. During the period from January 2016 to June 2016, both methods (ciaN and angioplasty) were used. Therefore, patients treated during this period were excluded.

Furthermore, patients with available imaging data (either cranial computed tomography or cranial magnetic resonance imaging) acquired between 14 and 28 days after SAH onset to be analyzed for DCI-associated infarctions and available clinical outcome data at hospital discharge were included.

Data analysis and study endpoints

Data were collected in anonymized data tables.

Data on the patients (age, sex, smoking, and arterial hypertension), bleeding events (presence of an aneurysm as bleeding source, Hunt and Hess [H&H] and Fisher scores), and whether an endovascular treatment of refractory DCI was performed were extracted from the patient charts. Data on the clinical outcomes (favorable and unfavorable outcomes) were extracted from the patient charts. A favorable outcome was defined as an mRS score of 0–2; an unfavorable outcome was defined as an mRS score of 3–6. The outcomes were evaluated at hospital discharge and at clinical follow-up after 6 months. In cases of missing data 6 months after SAH, outcome data at 3–12 months after SAH were evaluated, if available.

As an additional outcome parameter, we analyzed the presence of DCI-associated infarctions. To analyze DCI-associated infarctions, imaging data (cranial computed tomography [CT] or magnetic resonance imaging [MRI]) acquired 14–28 days after SAH onset were analyzed by a neuroradiologist blinded to the other data. In case of the presence of cerebral infarctions, the complete history of cranial imaging starting from SAH onset was analyzed, and infarctions were identified as DCI-related if no other causes were present.

Clinical management of SAH and DCI

Clinical management was performed according to our institutional protocols as described (9, 15–19). In brief, SAH was

diagnosed using cranial CT scans. CT angiography (CTA) and digital subtraction angiography were performed to identify the source of the bleeding. If an aneurysm was present, the case was discussed between the endovascular and surgical specialists, and the aneurysm was treated after interdisciplinary consensus by either surgical clipping or endovascular coiling within 24 h. If necessary, external ventricular or lumbar drains were used to treat hydrocephalus. Patients were closely monitored neurologically. All patients were admitted to the intensive care. After securing the bleeding source and if deemed appropriate by the attending neurointensivists, some patients were transferred to the intermediate care unit and, in some cases, to the neurosurgical ward. Here, too, the patients were closely monitored neurologically. In unconscious patients, if indicated, intraparenchymal probes placed in the frontal region were used for ICP and ptiO_2 (brain tissue oxygenation) monitoring.

All patients received oral nimodipine at a dose of 60 mg every 4 h for 3 weeks after SAH onset. DCI was suspected in cases of global or focal neurological deterioration or, in unconscious patients, in cases of increasing Doppler sonographic flow velocities of the intracranial arteries or a decrease in ptiO_2 to <15 mmHg. In these cases, hypertension was induced, and CT perfusion imaging and CTA were performed. In cases with refractory DCI that are not responsive to induced hypertension, cerebral hypoperfusion, and severe angiographic vasospasms, digital subtraction angiography and endovascular vasospasm therapies were indicated after interdisciplinary consensus between neurointensivists and endovascular specialists (9).

In addition to the switch from angioplasties to *ciaN*, routine administration of magnesium and simvastatin was discontinued during the study period following the publication of the MASH-2 trial (20) and the STASH trial (21). Otherwise, the relevant treatment standards remained constant throughout the observation period.

Endovascular vasospasm therapy

ciaN

For *ciaN*, the common femoral artery was routinely used to obtain subpetrous vascular access using a 6-Fr guiding catheter. Furthermore, 1–2 microcatheters were placed in the extracranial internal carotid artery (ICA) or vertebral artery (VA) according to the site of impending infarction. Nimodipine (Nimotop® S, 10 mg/50 mL, Bayer Vital GmbH GB Pharma) was initially administered at a rate of 2 mg/h (10 mL/h) in combination with 10 mL/h of heparin (Ratiopharm, Ulm, Germany), 1 IU/mL resulting in an infusion rate of 20 mL/h to prevent catheter obstruction or thrombus apposition. Depending on the clinical and radiographic course of the individual patient, the nimodipine administration rate was then reduced successively. Platelet inhibition with Tirofiban (Advanz Pharma Corp., London, United Kingdom) at a body weight-adapted dose was performed to prevent thromboembolic complications.

Single-shot intra-arterial vasospasmolysis with nimodipine

Single-shot intra-arterial vasospasmolysis with nimodipine was performed using the same approach used for *ciaN*. One milligram of

nimodipine was administered through the guiding catheter positioned in either the ICA or VA for 30 min.

Angioplasty

Using a 6-Fr guiding catheter in the desired ICA or VA extracranially, a microcatheter was advanced over a 0.014-inch microwire. Noncompliant balloons were selected based on vessel diameter and were positioned at the desired stenosis to perform PTA.

Statistical analysis

The aim of the statistical analysis was to determine whether the change in the standard therapy for refractory DCI had an influence on the outcomes (DCI-associated infarctions and favorable outcome at discharge and at 6 months). For this purpose, contingency tables were created, and Fisher's exact tests were performed.¹ Two-sided *p*-values <0.05 were used to denote statistical significance.

Propensity score matching adjusting for the categories age, sex, H&H and Fisher scores, hypertension, active nicotine use, and detection of an aneurysm as bleeding source was used to isolate the treatment effect. We estimated inverse probability weights (using the R package *WeightIt*, v. 1.4.0) and created an integer-weighted pseudo-population by normalizing weights to mean 1 and replicating rows accordingly. Counts shown in consistency tables therefore reflect the weighted pseudo-sample and do not equal raw patient counts. The effective sample size (ESS) of 136 was reported to contextualize precision.

Results

Patients

A total of 479 consecutive patients treated at our department between January 01, 2011, and June 30, 2021, with the diagnosis of spontaneous SAH were screened. Of them, 20 were treated between January 01, 2016, and June 30, 2016 and were thus excluded. Of the remaining 459 patients, clinical outcome data and cranial CT or MRI acquired 14–28 days after SAH onset were available for 292 patients, who were included in our study. Of the 292 patients, 145 were treated before the introduction of *ciaN* (2011–2015), and 147 were treated after the introduction of *ciaN* (2016–2021). Figure 1 presents a detailed overview of the included patients.

An aneurysm as bleeding source was detected in 92% (pre-*ciaN* group) and 91% (*ciaN* group). No significant differences in patient sex, age were observed between the two groups. Regarding the H&H scores and Fisher scores at hospital admission, the proportion of patients with H&H scores of 4 and 5 and Fisher 4 were higher in the *ciaN* group than in the pre-*ciaN* group. Further heterogeneities were observed concerning arterial hypertension and active nicotine use. Figure 2 presents detailed data on the patients and the severity of the bleeding event.

¹ <https://www.graphpad.com/quickcalcs/contingency1/>

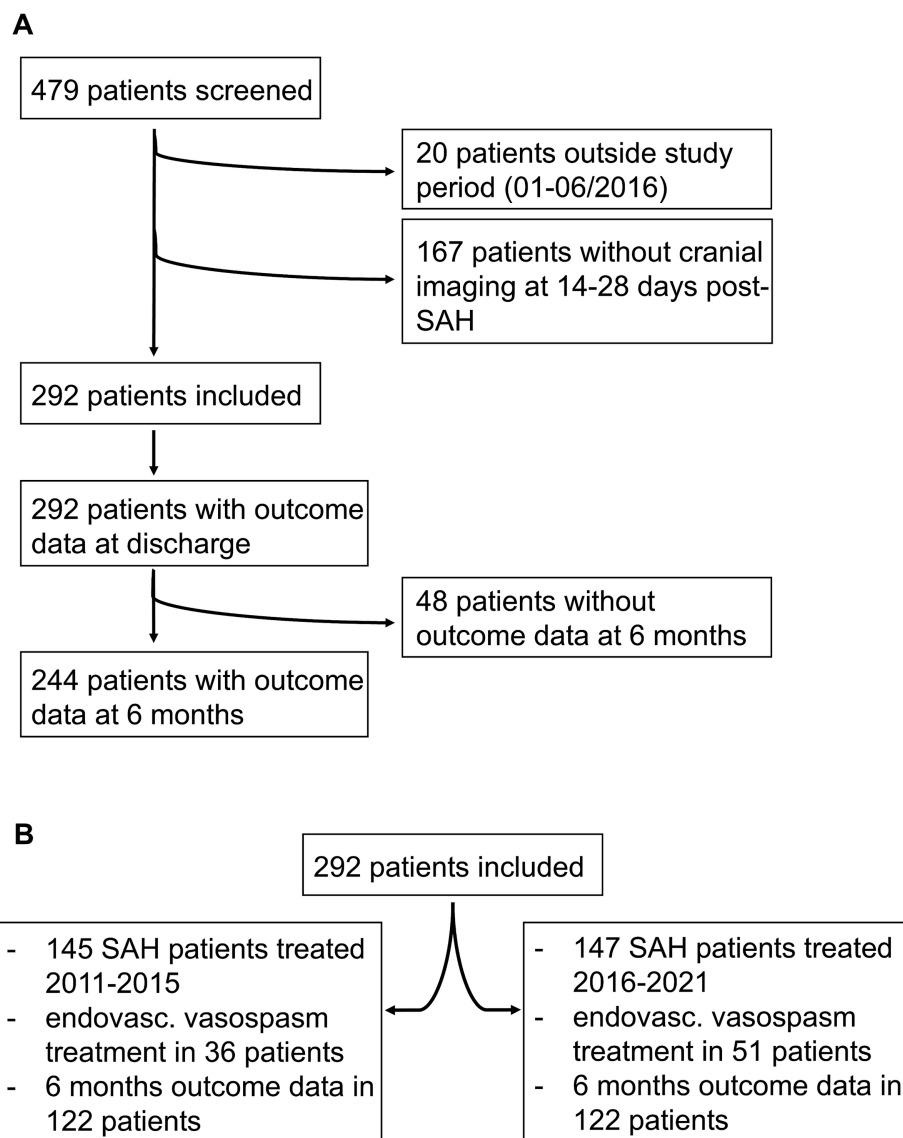


FIGURE 1

Patients. (A) Identification and exclusion of patients included in the evaluation. (B) Shows patients included in the cohorts before and after the introduction of ciaN.

Endovascular interventions for treating severe vasospasms

Of the 292 patients included in our study, endovascular vasospasm treatment for refractory DCI was performed in 87 patients (29.8%): 36 patients in the pre-ciaN group (24.8%) and 51 patients in the ciaN group (34.7%).

The treatments performed in the 36 patients in the pre-ciaN group were balloon angioplasty of the vasospastic cerebral arteries in 19 patients, together with intra-arterial single-shot application of nimodipine. Only one patient received a continuous intra-arterial nimodipine infusion. The other patients received intra-arterial single-shot applications of nimodipine only. Of the 36 patients, 27 underwent more than one endovascular intervention.

Of the 51 patients in the ciaN cohort, only three underwent balloon angioplasty of the vasospastic cerebral arteries. In total, 21

patients received continuous intra-arterial nimodipine infusions. The remaining 27 patients received single-shot applications of nimodipine only. Thirty-seven patients underwent more than one endovascular intervention.

Of the patients admitted with high H&H scores, a similar proportion received endovascular vasospasm treatments in the ciaN and pre-ciaN groups, whereas, in patients with low H&H scores, the rate of endovascular treatments tended to be higher in the ciaN group: Of the 92 patients admitted with H&H scores of 4 or 5, 31 (33.7%) obtained endovascular vasospasm treatments (pre-ciaN cohort: 30.8% vs. ciaN cohort: 35.8%, *n.s.*) compared with 56 (28.0%) of the 200 patients admitted with H&H scores of 1–3 (pre-ciaN cohort: 22.6% vs. ciaN cohort: 34.0%, *n.s.*).

The average duration of ciaN was 5 days, up to 15 days in 1 case. Regarding ciaN, there were some minor complications. Microcatheter obstruction occurred in some cases, resulting in

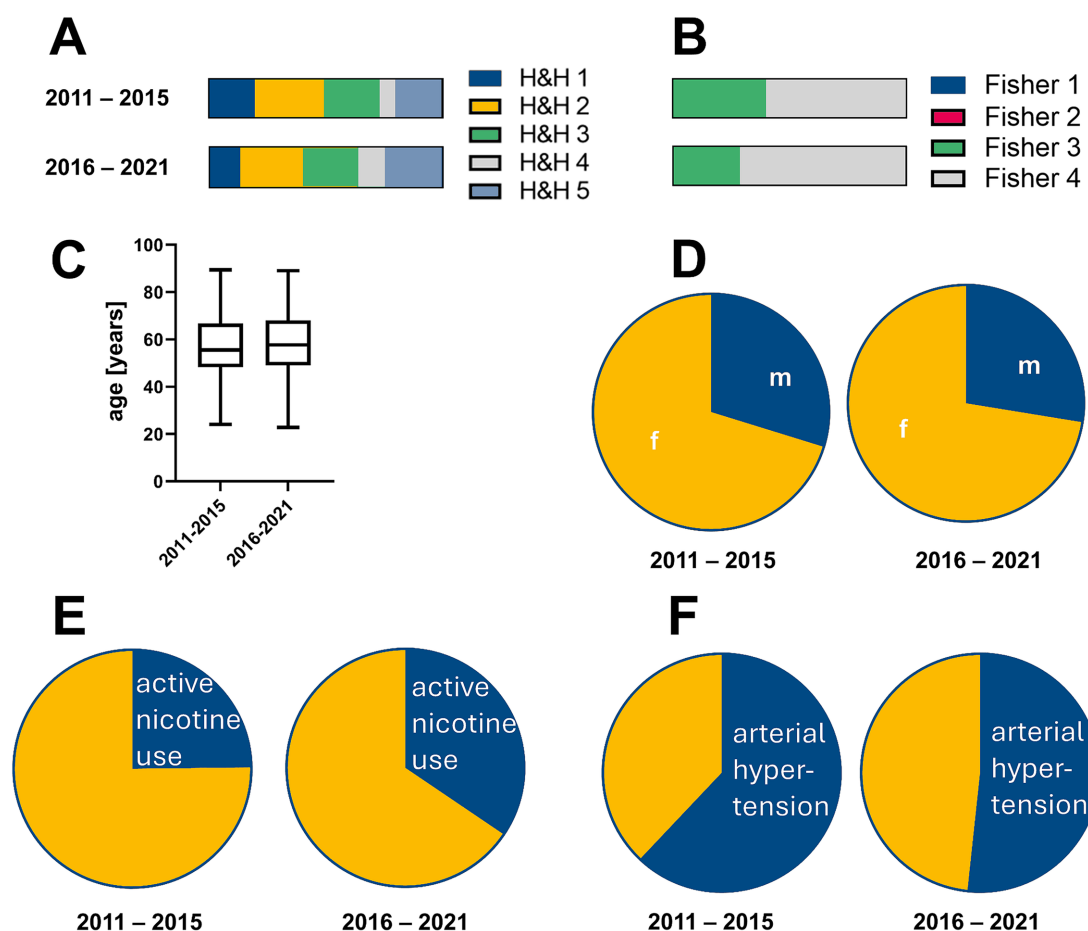


FIGURE 2
Patient characteristics. (A–F) Show the characteristics of the patients included in the cohorts before and after the introduction of ciaN.

pressure alarms from the infusion pumps. Dislocation of a microcatheter also occurred. In these cases, the affected microcatheter was removed or replaced if necessary. Furthermore, a vessel dissection at the arterial access sheath occurred in two cases, which did not require specific treatment. In one case, follow-up imaging showed cerebral hyperperfusion, which resolved after ciaN was discontinued. However, no complications of ciaN affecting long term outcome were detected. ICP elevations or relevant cerebral edema associated with intraarterial Nimodipine infusion or infections induced by ciaN were not observed.

DCI-associated cerebral infarctions

Overall, among the 292 included patients, 39 DCI-associated cerebral infarctions (13.4%) were noted. Overall, no significant differences in the rates of DCI-associated infarctions were observed between the pre-ciaN and ciaN groups (13.8% vs. 12.9%, *n.s.*). Patients who received endovascular vasospasm treatments after the introduction of ciaN tended to experience less DCI-associated infarctions (pre-ciaN vs. ciaN: 36.1% vs. 23.5%, *n.s.*). Figure 3 summarizes the data on the occurrence of DCI-associated infarctions in more detail.

After propensity score matching, there were still no significant differences in the rates of DCI-associated infarctions between the pre-ciaN and ciaN groups. However, when considering the subgroups of patients who received endovascular vasospasm treatment, there were significantly less DCI-associated infarctions in the ciaN group (18.9% vs. 33.0%, $p < 0.05$), while there was no significant difference for those patients who did not receive endovascular vasospasm treatments. Figure 4 summarizes the data on the occurrence of DCI-associated infarctions in the weighted pseudo-sample after propensity score matching in more detail.

Clinical outcome

Overall, of the 292 included patients, 98 (33.6%) were discharged with mRS scores of 0–2, and 194 (66.4%) were discharged with mRS scores of 3–6. There was a higher rate of patients discharged with favorable mRS scores in the ciaN group, which did not reach statistical significance (mRS 0–2, pre-ciaN vs. ciaN groups: 30.3% vs. 36.7%, *n.s.*). This was more pronounced in the subgroup of patients who received endovascular vasospasm treatments (mRS 0–2, endovascular treatment, pre-ciaN vs. ciaN groups: 11.1% vs. 23.5%, *n.s.*; mRS 0–2, no endovascular treatment, pre-ciaN vs. ciaN groups: 34.9% vs. 43.8%, *n.s.*).

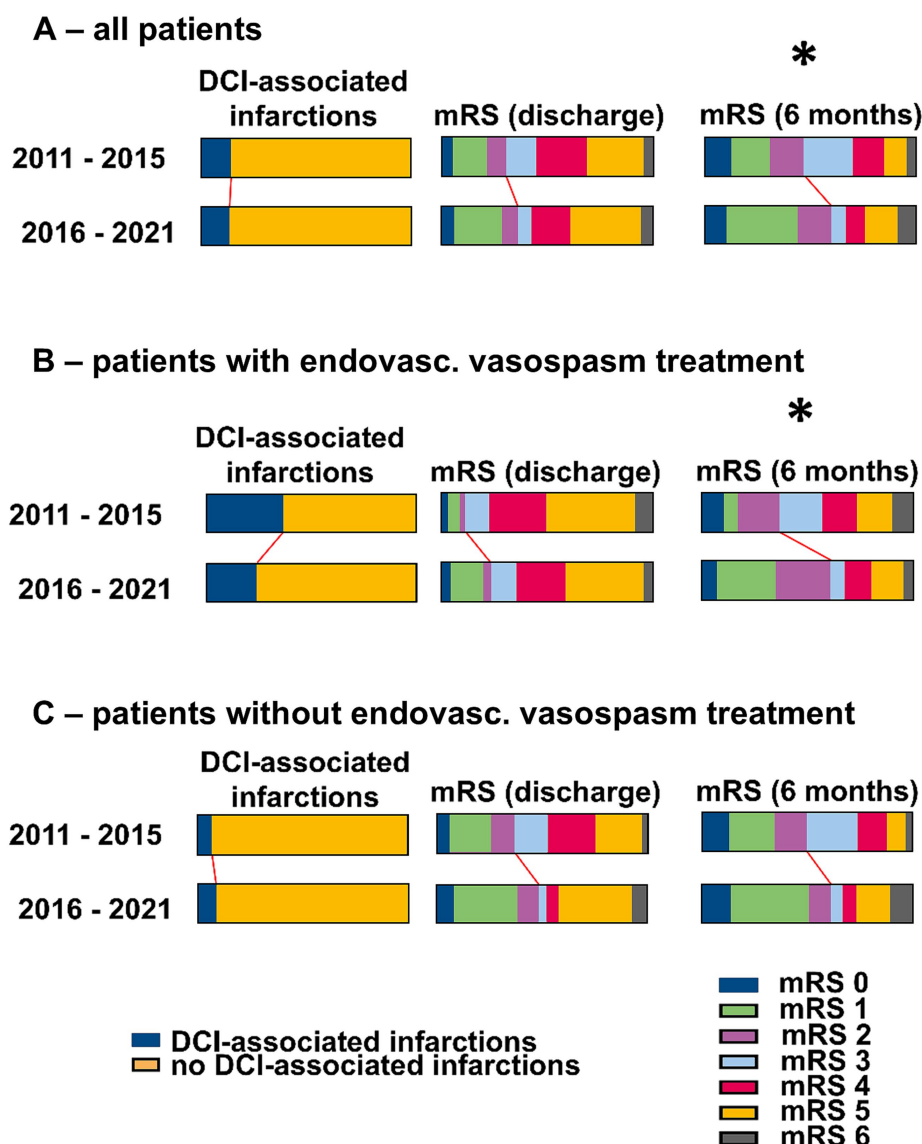


FIGURE 3

Outcomes in the cohorts before and after the introduction of ciaN. (A) All patients. (B) Patients with endovascular vasospasm treatments. (C) Patients without endovascular vasospasm treatments. * $p < 0.05$ (Fisher's exact test).

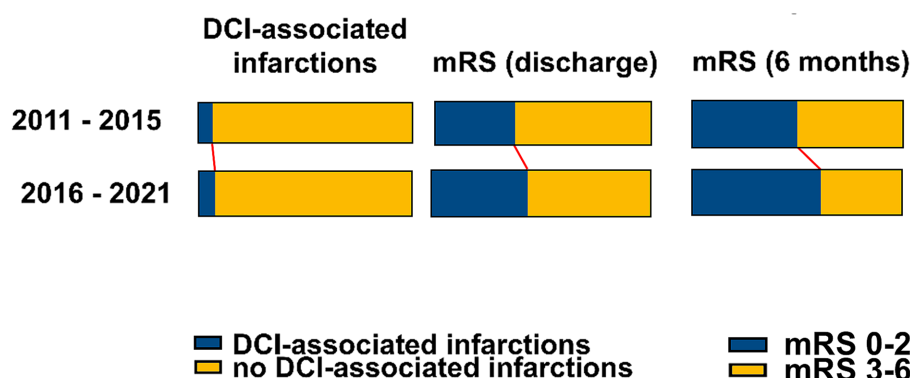
Six-month follow-up data were available for 244 patients (83.6%, pre-ciaN cohort: 84.1%, ciaN cohort: 83.0%), of whom 131 (53.7%) achieved favorable outcomes with mRS scores of 0–2. There were significantly more patients with favorable outcomes at 6 months in the ciaN group (mRS 0–2, pre-ciaN vs. ciaN groups: 46.7% vs. 60.7%, $p < 0.05$). This difference between the pre-ciaN and ciaN groups was most pronounced in patients who received endovascular vasospasm treatments (mRS 0–2, endovascular treatment, pre-ciaN vs. ciaN groups: 36.7% vs. 63.0%, $p < 0.05$; mRS 0–2, no endovascular treatment, pre-ciaN vs. ciaN groups: 50.0% vs. 60.5%, *n.s.*), and in patients with H&H scores 1–3 (mRS 0–2, H&H 1–3, pre-ciaN vs. post-ciaN: 56.0% vs. 78.2%, $p < 0.01$). Figure 3 summarizes neurological outcomes in more detail.

After propensity score matching, outcomes at discharge and at 6 months were significantly better in the ciaN group (at discharge, mRS 0–2, pre-ciaN vs. ciaN groups: 23.2% vs. 34.0%, $p < 0.05$; at 6 months,

mRS 0–2, pre-ciaN vs. ciaN groups: 44.8% vs. 59.6%, $p < 0.01$). When considering the subgroups of patients who received endovascular vasospasm treatment, the difference was markedly larger (endovasc. Vasospasm therapy, at discharge, mRS 0–2, pre-ciaN vs. ciaN groups: 7.2% vs. 24.2%, $p < 0.05$; at 6 months, mRS 0–2, pre-ciaN vs. ciaN groups: 38.0% vs. 58.1%, $p < 0.01$). Conversely, in the subgroup of patients who did not receive endovascular vasospasm therapies, there were no statistical differences in outcome at discharge or at 6 months. This indicates a contribution of the change in treatment standard for endovascular vasospasm therapies from angioplasties to ciaN.

Discussion

In our clinical center, the standard of endovascular vasospasm therapy for patients with SAH and refractory DCI was changed in

A – all patients**B – patients with endovasc. vasospasm treatment****C – patients without endovasc. vasospasm treatment****FIGURE 4**

Weighted pseudopopulation—outcomes in the cohorts before and after the introduction of ciaN. The Figure shows the results from evaluation of the weighted pseudopopulation after propensity score matching. (A) All patients. (B) Patients with endovascular vasospasm treatments. (C) Patients without endovascular vasospasm treatments. * $p < 0.05$ (Fisher's exact test).

2016. In previous years, angioplasty of vasospastic vessel segments was performed in cases of DCI refractory to induced hypertension. Since 2016, angioplasty has been performed only in exceptional cases, whereas ciaN has been performed as the standard endovascular vasospasm therapy. For ciaN, an intra-arterial catheter is inserted into the internal carotid or VA, and nimodipine is continuously infused over several days. Antiplatelet therapy with tirofiban or anticoagulation is necessary during ciaN to prevent thromboembolic complications. In this study, patients treated after SAH in our center were retrospectively recorded over 10 years. The outcomes in the years before and in the years after the change in standard endovascular vasospasm therapy were then compared.

The most important finding was that the clinical outcomes at 6 months after SAH significantly improved after switching to ciaN. After propensity score matching, there was a significantly improved outcome at discharge and after 6 months as well as a reduced rate of DCI-associated infarctions in the ciaN cohort only in

the subgroup of patients with endovascular vasospasm treatment. This indicates a contribution of the changes in treatment standard from angioplasties to ciaN to the improved outcomes.

Interestingly, we observed that in patients who were admitted with H&H scores of 1–3, 6-month outcomes improved by a markedly smaller, however, significant extent since 2016 also in patients who were not treated endovascularly for vasospasms (Supplementary tables), indicating that other factors may have also contributed to the improved outcomes. The improvement is most likely due to general improvements, particularly of endovascular and surgical aneurysm occlusion and intensive care therapy (22). The detailed cause cannot be determined by the current evaluation approach.

During angioplasty, a balloon is inserted into the vasospastic vascular segment and expanded under a defined pressure (23, 24). This approach results in the elimination of vasospasm. The structure of the vessel wall is initially impaired by angioplasty, so that subsequent vasospasm does not immediately reoccur in the angioplasty segment.

During ciaN, a microcatheter is inserted into the ICA or VA. This is used to continuously infuse nimodipine into the vasospastic vascular bed. Therefore, not only the vasospasm of the large vessels but also microvasospasms are targeted, which play an important role (5). In line with this pathophysiological concept, our group has shown that by infusing nimodipine directly into the vasospastic vascular bed, a reduction in vasospasm of the large vessels and a significant increase in cerebral perfusion can be achieved (25). The better outcomes in patients treated with ciaN could therefore be explained by the fact that ciaN not only reduces angiographic vasospasm of the large cerebral vessels but also has an effect on the small vessels, which is crucial for cerebral perfusion. We and others have further reported that ciaN is a safe procedure and that complications are rare (9–14).

In a prospective, randomized study by Vatter et al. (26), the effects of endovascular vasospasm therapy (angioplasty or single-stage intra-arterial pharmacological vasospasmolysis) were compared with those of the best medical management (induced hypertension). The authors found that endovascular therapy resulted in worse neurological outcomes. In our study, no statement can be made about the effects of the best medical management because all patients with refractory DCI were offered endovascular treatment. It is therefore not possible to make a statement regarding whether ciaN is superior to the best medical management. We cannot rule out that the observed improvement in outcomes is solely due to the avoidance of angioplasty and that ciaN is not better than the best medical management. In our opinion, a prospective clinical study comparing ciaN with the best medical management for treating DCI after SAH refractory to induced hypertension is warranted.

The neurological outcomes significantly improved after the introduction of ciaN. In contrast, no significant reduction in the number of DCI-associated infarctions was observed. In both groups, before and after the introduction of ciaN, DCI-associated infarctions were in most cases not territorial infarctions, but rather small subterritorial lesions, with presumably often a lack of functional relevance. This implies that the observed improvement in outcomes is not because of the prevention of infarctions, but rather due to the neuroprotective effects of ciaN through improved cerebral perfusion compared with angioplasty. Interestingly, a study by Vatter et al. (26) also reported no difference in the frequency of DCI-associated infarctions, despite a significant difference in neurological outcomes.

Conclusion

Our analysis revealed that switching from angioplasty to continuous intra-arterial vasospasmolysis as the standard endovascular treatment for refractory DCI after SAH significantly improved clinical outcomes. It remains unclear whether the improvement in outcomes is due only to the avoidance of angioplasty or whether ciaN also improves outcomes compared with the best medical management. A prospective clinical study comparing ciaN with the best medical management for treating DCI after SAH refractory to induced hypertension is therefore warranted.

Limitations

Our study is a retrospective single-center evaluation. The retrospective character can cause selection and information bias.

Furthermore, it limits the generalizability of the results. Additionally, there were heterogeneities in the patient cohorts; propensity score matching was used, however, it is not possible to control for all relevant confounders.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethikkommission der Landesärztekammer Rheinland Pfalz. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

AN: Conceptualization, Methodology, Supervision, Writing – review & editing, Writing – original draft. VF: Investigation, Writing – review & editing, Formal analysis. EK: Writing – review & editing. AK: Writing – review & editing. AN: Writing – review & editing, Formal analysis, Methodology. MB: Writing – review & editing. FR: Writing – review & editing. CB: Writing – review & editing, Supervision.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

Parts of this study are part of the doctoral thesis of V. Fassl, presented to the Medical Faculty of the Johannes Gutenberg-University of Mainz.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2025.1636083/full#supplementary-material>

References

- Lawton MT, Vates GE. Subarachnoid hemorrhage. *N Engl J Med.* (2017) 377:257–66. doi: 10.1056/NEJMc1605827
- Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. *Lancet (London, England).* (2017) 389:655–66. doi: 10.1016/S0140-6736(16)30668-7
- GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2021: a systematic analysis for the global burden of disease study 2021. *Lancet Neurol.* (2024) 23:973–1003. doi: 10.1016/S1474-4422(21)00252-0
- Etminan N, Chang HS, Hackenberg K, de Rooij NK, Vergouwen MDI, Rinkel GJE, 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.* (2019) 76:588–97. doi: 10.1001/jamaneurol.2019.0006
- Macdonald RL. Delayed neurological deterioration after subarachnoid haemorrhage. *Nat Rev Neurol.* (2014) 10:44–58. doi: 10.1038/nrneurol.2013.246
- Sabri M, Lass E, Macdonald RL. Early brain injury: a common mechanism in subarachnoid hemorrhage and global cerebral ischemia. *Stroke Res Treatment.* (2013) 2013:394036. doi: 10.1155/2013/394036
- Neifert SN, Chapman EK, Martini ML, Shuman WH, Schupper AJ, Oermann EK, et al. Aneurysmal subarachnoid hemorrhage: the last decade. *Transl Stroke Res.* (2021) 12:428–46. doi: 10.1007/s12975-020-00867-0
- Hoh BL, Ko NU, Amin-Hanjani S, Chou SHY, Cruz-Flores S, Dangayach NS, et al. 2023 guideline for the Management of Patients with Aneurysmal Subarachnoid Hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke.* (2023) 54:e314–70. doi: 10.1161/STR.0000000000000436
- Kramer A, Selbach M, Kerz T, Neulen A, Brockmann MA, Ringel F, et al. Continuous intraarterial nimodipine infusion for the treatment of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: a retrospective, single-center cohort trial. *Front Neurol.* (2022) 13:829938. doi: 10.3389/fneur.2022.829938
- Mayer TE, Dichgans M, Straube A, Birnbaum T, Müller-Schunk S, Hamann GF, et al. Continuous intra-arterial nimodipine for the treatment of cerebral vasospasm. *Cardiovasc Intervent Radiol.* (2008) 31:1200–4. doi: 10.1007/s00270-008-9346-0
- Bele S, Proescholdt MA, Hochreiter A, Schuierer G, Scheitzach J, Wendl C, et al. Continuous intra-arterial nimodipine infusion in patients with severe refractory cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a feasibility study and outcome results. *Acta Neurochir.* (2015) 157:2041–50. doi: 10.1007/s00701-015-2597-z
- Hockel K, Diedler J, Steiner J, Birkenhauer U, Danz S, Ernemann U, et al. Long-term, continuous intra-arterial Nimodipine treatment of severe vasospasm after aneurysmal subarachnoid hemorrhage. *World Neurosurg.* (2016) 88:104–12. doi: 10.1016/j.wneu.2015.11.081
- Ott S, Jedlicka S, Wolf S, Peter M, Pudenz C, Merker P, et al. Continuous selective intra-arterial application of Nimodipine in refractory cerebral vasospasm due to aneurysmal subarachnoid hemorrhage. *Biomed Res Int.* (2014) 2014:1–11. doi: 10.1155/2014/970741
- Weiss M, Albanna W, Conzen-Dilger C, Kastenholz N, Seyfried K, Ridwan H, et al. Intraarterial Nimodipine versus induced hypertension for delayed cerebral ischemia: a modified treatment protocol. *Stroke.* (2022) 53:2607–16. doi: 10.1161/STROKEAHA.121.038216
- Pantel T, Neulen A, Mader MMD, Kurz E, Piffko A, Fassl V, et al. Impact of pre-hospital handling and initial time to cranial computed tomography on outcome in aneurysmal subarachnoid hemorrhage patients with out-of-hospital sudden cardiac arrest—a retrospective bi-centric study. *Front Cardiovascular Med.* (2023) 10:1209939. doi: 10.3389/fcvm.2023.1209939
- Neulen A, Pantel T, König J, Brockmann MA, Ringel F, Kantelhardt SR. Comparison of Unruptured intracranial aneurysm treatment score and PHASES score in subarachnoid hemorrhage patients with multiple intracranial aneurysms. *Front Neurol.* (2021) 12:616497. doi: 10.3389/fneur.2021.616497
- Neulen A, Kunzelmann S, Kosterhon M, Pantel T, Stein M, Berres M, et al. Automated grading of cerebral vasospasm to standardize computed tomography angiography examinations after subarachnoid hemorrhage. *Front Neurol.* (2020) 11:13. doi: 10.3389/fneur.2020.00013
- Neulen A, Stein M, Pantel T, Berres M, Brockmann C, Giese A, et al. Image-guided transcranial Doppler ultrasound for monitoring Posthemorrhagic vasospasms of Infratentorial arteries: a feasibility study. *World Neurosurg.* (2020) 134:284–91. doi: 10.1016/j.wneu.2019.10.144
- Neulen A, Prokesh E, Stein M, König J, Giese A. Image-guided transcranial Doppler sonography for monitoring of vasospasm after subarachnoid hemorrhage. *Clin Neurol Neurosurg.* (2016) 145:14–8. doi: 10.1016/j.clineuro.2016.03.012
- Dorhout Mees SM, Mees SMD, Algra A, Vandertop WP, van Kooten F, Kuijsten HAJM, et al. Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. *Lancet.* (2012) 380:44–9. doi: 10.1016/S0140-6736(12)60724-7
- Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. *Lancet Neurol.* (2014) 13:666–75. doi: 10.1016/S1474-4422(14)70084-5
- Mackey J, Khoury JC, Alwell K, Moomaw CJ, Kissela BM, Flaherty ML, et al. Stable incidence but declining case-fatality rates of subarachnoid hemorrhage in a population. *Neurology.* (2016) 87:2192–7. doi: 10.1212/WNL.0000000000003353
- Neumann A, Schacht H, Schramm P. Neuroradiological diagnosis and therapy of cerebral vasospasm after subarachnoid hemorrhage. *RoFo.* (2024) 196:1125–33. doi: 10.1055/a-2266-3117
- Francoeur CL, Mayer SA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. *Crit Care.* (2016) 20:277. doi: 10.1186/s13054-016-1447-6
- Reder SR, Lückerrath S, Neulen A, Beiser KU, Grauhan NF, Othman AE, et al. DSA-based 2D perfusion measurements in delayed cerebral ischemia to estimate the clinical outcome in patients with aneurysmal subarachnoid hemorrhage: a technical feasibility study. *J Clin Med.* (2023) 12:4135. doi: 10.3390/jcm12124135
- Vatter H, Güresir E, König R, Durner G, Kalff R, Schuss P, et al. Invasive diagnostic and therapeutic Management of Cerebral VasoSpasm after aneurysmal subarachnoid hemorrhage (IMCVS)—a phase 2 randomized controlled trial. *J Clin Med.* (2022) 11:6197. doi: 10.3390/jcm111206197