Clinical factors associated with delayed ischemic and non-ischemic adverse events in clazosentan therapy after aneurysmal subarachnoid hemorrhage: Early insights from a multicenter prospective registry

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Abstract

Clazosentan (CLZ) therapy prevents delayed ischemia following aneurysmal subarachnoid hemorrhage (aSAH), but non-ischemic adverse events necessitate optimized protocols. This study presents outcomes of contemporary CLZ therapy under a unified protocol and identifies factors influencing delayed ischemic and non-ischemic adverse events following aSAH. This multicenter prospective registry analyzed data from 80 aSAH patients receiving CLZ therapy (April 2023 - October 2024). Primary endpoints were delayed ischemic events and non-ischemic adverse events; secondary endpoint was favorable outcome (modified Rankin Scale 0-2) at discharge or six weeks post-onset. Delayed ischemic events occurred in 19 patients (23.8%), including delayed ischemic neurological deterioration (8.8%), moderate-to-severe cerebral vasospasm (20.0%), and symptomatic delayed cerebral infarction (7.5%). Non-ischemic adverse events were observed in 22 patients (27.5%). Favorable outcomes were achieved in 52 patients (65.0%). Delayed ischemic events were associated with female sex, poor severity grades, higher Fischer scale scores, and elevated neutrophil-to-lymphocyte ratios. Non-ischemic adverse events were associated with older age, anemia, hypoproteinemia, and elevated cardiothoracic ratios. Multivariate analysis identified non-ischemic adverse events as significant for unfavorable outcomes (FDR $p<.001$), whereas delayed ischemic events were not (FDR $p=.705$). Among non-ischemic adverse events, pulmonary edema was the strongest factor associated with unfavorable outcomes. In conclusion, CLZ therapy with appropriate candidate selection and management protocol appears promising as a treatment option to prevent delayed ischemia after aSAH, though potential confounders warrant careful consideration. Addressing clinical risk factors for non-ischemic adverse events may further enhance treatment outcomes.

Keywords: DCI, endothelin, fluid retention, vasodilator, vasospasm, pulmonary complication

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a major subtype of hemorrhagic stroke that severely affects the patient's quality of life. More than 20% of patients with aSAH die within days to weeks after onset, and nearly half of the survivors experience long-term disability and/or cognitive impairment [8, 27]. Despite this, outcomes of aSAH have not shown clear improvement over the past 20 years (from 2000 to 2019) [33]. Although various factors, including primary brain damage, affect the prognosis of patients with aSAH, delayed cerebral ischemic events—cerebral vasospasm (CVS), delayed ischemic neurological deterioration (DIND), or delayed cerebral ischemia (DCI)—remain critical determinants of patient outcome. Triple-H therapy (hypervolemia, hemodilution, and hypertension) and pharmacological treatments, including nimodipine, nicardipine, cilostazol, magnesium, fasudil hydrochloride, and sodium ozagrel, are employed during the first two weeks post-onset to reduce DCI [2, 12]. However, robust clinical evidence supporting their efficacy in preventing DCI after aSAH has been limited [31].

Clazosentan (CLZ), a selective endothelin receptor subtype A antagonist, has been studied for its potential to prevent CVS following aSAH [28, 29]. Some studies have demonstrated the effectiveness of CLZ in reducing vasospasm-related mortality/morbidity [3, 5, 17, 18, 34], while other studies suggest that CLZ may provide limited benefits [16, 21]. These mixed findings highlight the dual nature of CLZ: a lower incidence of delayed ischemic events due to its strong vasodilating action but a higher risk of non-ischemic adverse events such as pulmonary edema/pleural effusion, hypotension, and anemia [7, 13, 29].

Based on the results of a randomized controlled trial in Japan [3], CLZ (administered at 10 mg/h from the postoperative period to day 15 after the onset of aSAH) was approved by the Pharmaceuticals and Medical Devices Agency (PMDA) in January 2022 for the prevention of CVS [15]. Since then, CLZ therapy has become a major treatment option in Japan [12, 19, 22], with real-world clinical data being accumulated. Recent retrospective comparative studies in Japan have

evaluated the outcomes of CLZ therapy compared with conventional treatments, such as fasudil hydrochloride and sodium ozagrel combined with hyperdynamic therapy [10, 20, 23, 30]. These studies consistently reported a significantly lower incidence of vasospasm-related ischemic events in the CLZ group than in the conventional treatment group. In contrast, the incidence of non-ischemic adverse events (e.g. fluid retention) was consistently higher in the CLZ group. During the first year after PMDA approval, difficulties in fluid management during CLZ therapy were frequently reported and discussed in Japan, with the majority being due to fluid overload and the use of concomitant medications [1, 9, 11, 20, 25, 26, 32]. These findings emphasize the need for a more refined CLZ therapy protocol, including appropriate fluid management and use of concomitant medications, as well as careful candidate selection for CLZ therapy.

Based on the initial experiences, our group established a recommended management protocol and launched a prospective registry study in April 2023 (one year after PMDA approval). This study presents an initial analysis of registry data, aiming to identify the real-world outcomes of CLZ therapy and clinical factors influencing delayed ischemic and non-ischemic adverse events following aSAH in recent years.

Methods

Ethical considerations

This study adhered to the STROBE statement, Good Clinical Practice guidelines, and Declaration of Helsinki. This study was approved by the central Institutional Review Board (IRB) of Hokkaido University Hospital (No. 022-0137) and the IRBs of each participating institute. All participants provided written informed consent upon enrollment in the registry.

Study design

This multicenter prospective registry recruited participants from nine hospitals in Hokkaido Prefecture,

Japan (Hokkaido University Hospital, Teine Keijinkai Hospital, Otaru General Hospital, Sapporo Azabu Neurosurgical Hospital, Sapporo Hakuyokai Hospital, Kushiro Rosai Hospital, Tomakomai City Hospital, Sapporo Shuyukai Hospital, and Hokkaido Medical Center). Since April 2023, patients meeting all the following criteria have been enrolled in the registry: (1) age 20 years or older; (2) pre-onset modified Rankin Scale (mRS) of 0-3; (3) spontaneous aSAH; (4) a ruptured aneurysm treated by surgical clipping, endovascular coiling, or aneurysm trapping; and (5) written consent to participate in the study.

In this study, the data registered and validated between April 2023 and October 2024 were used. To clarify the clinical effects of CLZ therapy, the following patients were excluded from the analysis: (1) patients with significant disability following aneurysm surgery that made subsequent CVS treatment infeasible and (2) those who received CVS treatments other than CLZ therapy.

Recommended management protocol

In our unified protocol for CVS management, CLZ therapy was primarily recommended. However, alternative CVS therapies were considered if patients had multiple risk factors, including advanced age (> 75 years); delayed admission from onset (> 3 days); World Federation of Neurosurgical Societies (WFNS) grade V; and the presence of massive hematoma, neurogenic lung, Takotsubo cardiomyopathy, or other cardiopulmonary or systemic inflammatory diseases. The choice of surgical intervention for the culprit aneurysm (microsurgical clipping or endovascular coiling), performance of decompressive craniotomy, and use of cerebrospinal fluid (CSF) drainage were determined at the discretion of the attending physician.

When CLZ therapy was selected, continuous intravenous infusion of CLZ (10 mg/h) was administered from postoperative days 1 to 15 after the onset of SAH. The use of cilostazol as a concomitant medication was permitted; however, fasudil hydrochloride and ozagrel sodium were not recommended under our protocol [24]. To prevent fluid retention, fluid management was

recommended to start at 1.0 mL/kg/h. If abnormal body weight gain (> 1 kg/day) or an increase in fluid balance exceeding 1000 mL was observed, furosemide administration was recommended. Enteral feeding or oral intake was initiated the day after the aneurysm surgery. A detailed patient management protocol is also provided in the **Supplementary material**.

The imaging protocol is illustrated in **Figure 1**. Following the diagnosis of SAH, computed tomography angiography (CTA) or digital subtraction angiography (DSA) was performed to identify the cerebral aneurysm responsible. After the aneurysm surgery, magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI) and MR angiography (MRA), was performed before the initiation of CVS therapy to detect surgery-related complications (e.g., cerebral infarction). Imaging studies conducted before the initiation of CVS therapy were also used as baseline angiographic data.

Routine CTA or DSA was performed 7 (± 2) days post-aSAH to assess obliteration of aneurysm and CVS. MRI, including DWI and MRA, was repeated at 7 (± 2) and 14 (± 2) days post-aSAH. Additionally, perfusion studies such as single-photon emission computed tomography or arterial spin labeling MRI were conducted 7 (± 2) days post-aSAH.

If a patient exhibited neurological deterioration or consciousness disturbances at any point, MRI and blood tests were performed immediately to diagnose DIND. When neurological deterioration or consciousness disturbances were suspected to be related to CVS, rescue therapy, including hyperdynamic therapy, intravenous administration of fasudil hydrochloride, or endovascular therapy (intra-arterial administration of fasudil hydrochloride and/or percutaneous balloon angioplasty), was initiated, as necessary.

Protocol adherence was regularly monitored throughout the study period. Clinical management variations, such as the use of fasudil hydrochloride and ozagrel sodium, were systematically recorded.

Clinical data collection and assessments

A data collection sheet was used to collect clinical data from all participating hospitals. The data sheet

included the following information: age, sex, height, body weight, WFNS grade, Fischer scale, aneurysm location and size, comorbidity, risk factors for stroke (hypertension, dyslipidemia, diabetes mellitus, smoking history), laboratory tests, surgical procedure, use of CSF drainage, surgery-related complications, medications for baseline CVS therapy, the use of rescue therapy, fluid balance data (infusion and urine volume), occurrence of any delayed ischemic events and adverse events, the need for CSF shunt surgery, and the mRS at discharge or six weeks after the onset.

Imaging data including CT, CTA, DSA, MRI, MRA, and chest radiography were collected centrally at the Research Management Center (Hokkaido University Hospital). The Imaging Review Committee, consisting of three independent members (TS, DS, and HU), assessed the presence, absence, and severity of CVS as well as the incidence of delayed cerebral infarcts, by comparing baseline and follow-up imaging studies. Committee members were blinded to clinical outcomes and all other clinical information during the imaging assessment process. All committee members participated in consensus discussions, and final decisions regarding the status of CVS and the presence of delayed cerebral infarcts were reached by unanimous agreement.

Endpoints and definitions

The primary endpoints included delayed ischemic events and non-ischemic adverse events.

The delayed ischemic events included DIND, CVS, and delayed cerebral infarction. DIND was defined as the occurrence of focal neurological impairment (an increase of 2 or more points on the National Institute of Health Stroke Scale) or a decrease of at least 2 points on the Glasgow Coma Scale, lasting for ≥ 2 h [3]. Symptoms caused by factors other than delayed ischemia (e.g., surgery-related symptoms, seizures, or metabolic disorders) were excluded from DIND based on clinical assessment, brain CT or MRI scans, and appropriate laboratory studies. CVS was defined using baseline and follow-up imaging data as follows [5, 34]: (1) a > 33% reduction in the diameter of intracranial arteries on DSA or CTA or a > 50% reduction on MRA was classified as moderate CVS, and (2) a > 67%

diameter reduction on DSA or CTA or disruption of peripheral vessels on MRA was classified as severe CVS. Delayed cerebral infarction was rigorously evaluated using imaging studies, typically DWI-MRI. Patients with cerebral infarctions related to surgical procedures (microsurgical and endovascular) were excluded.

Non-ischemic adverse events were defined as adverse events potentially related to CVS management that required additional treatment (grade ≥2 based on the Common Terminology Criteria for Adverse Events, version 5.0). The priority events investigated included pulmonary edema, pleural effusion, brain edema, hypotension, anemia, electrolyte imbalance, arrhythmias, and hepatobiliary and renal dysfunction [4].

The secondary endpoint was defined as the outcome at six weeks after onset or at the time of discharge. A favorable outcome was defined as an mRS score of 0–2.

Statistical analysis

Missing data were minimal (<5%), and no imputation methods were employed in this analysis. Patients with incomplete essential data were excluded from relevant statistical analyses.

Continuous data were presented as mean values and standard deviations, while dichotomous or categorical variables were expressed as ratios or frequencies. Continuous data were compared between the two groups using Welch's *t* test, and dichotomous variables were compared using Fisher's exact test. Ordinal variables (e.g., WFNS grade or Fischer scale) were evaluated using the Cochran–Armitage trend test.

To assess the predictive performance of identified risk factors for non-ischemic adverse events, we performed receiver operating characteristic (ROC) curve analyses. The predictive accuracy was evaluated by calculating the area under the curve (AUC). Optimal cutoff values for each variable were determined based on the maximum sum of sensitivity and specificity.

Multivariate logistic regression analysis for outcome was conducted using variables selected

based on the following criteria: (1) factors previously demonstrated to be associated with outcomes in aSAH patients (age, WFNS grade, Fischer scale) and (2) factors selected based on biological plausibility and clinical relevance (surgical complications, CSF shunt dependence, delayed ischemic events, and non-ischemic adverse events). False Discovery Rate (FDR) LogWorth analysis was used to determine the strength and order of associations between all variables and unfavorable outcomes. In addition, multivariate logistic regression analysis for outcome was conducted using non-ischemic adverse events that showed significant correlations in the univariate analysis, to clarify their relative associations with unfavorable outcomes.

Statistical analyses were performed using JMP Pro (version 17.0.0, SAS Institute Inc., Cary, North Carolina, USA). Statistical significance was defined as $p < .05$.

Results

Patients

The patients included in this study are summarized in **Figure 2**. Data from 104 patients were registered and confirmed across nine participating hospitals during the study period (between April 2023 and October 2024). Of these, one patient who died early after aneurysm surgery and could not receive any CVS treatment was excluded. Additionally, 23 patients (22.1%) who did not receive CLZ therapy were excluded. Majority of these patients had multiple risk factors, including older age (n = 10), admission > 3 days after onset (n = 2), WFNS grade V (n = 9), presence of massive intracranial hematoma (n = 6), systemic complications (n = 8), neurogenic lung (n = 4), and Takotsubo cardiomyopathy (n = 3).

The remaining 80 patients (76.9%) who received CLZ therapy were included in the subsequent analyses. Baseline patient data are summarized in **Table 1**.

Treatments for CVS

The details of CVS treatment are summarized in **Table 2**. For baseline CVS treatment, CLZ therapy

was initiated at 44.9 ± 16.9 h (range: 12 to 101) after the onset of aSAH, with a treatment duration of 12.3 ± 1.7 days. CLZ therapy was discontinued in 3 patients (3.8%) for the following reasons: pulmonary complications (n = 1), hypotension (n = 1), and systemic inflammatory disease (n = 1). For concomitant medications, cilostazol was added in 71 patients (89.8%) as part of the baseline CVS treatment. Although fasudil hydrochloride was also used in 4 patients (5.0%) for baseline CVS treatment, one patient received it only on days 2-4 after aSAH onset and before CLZ initiation, while the remaining 3 patients received it after CLZ discontinuation. Therefore, these 4 cases were not regarded as protocol violations.

During the CVS treatment, the mean infusion volume was 1570.5 ± 601.4 mL/day, and the mean urine volume was 1806.8 ± 509.7 mL/day. Rescue therapy was administered to 7 patients (8.8%), of whom 3 (3.8%) underwent endovascular intervention (intra-arterial administration of fasudil, n = 3; percutaneous balloon angioplasty, n = 1).

Overall results

The overall results are summarized in **Table 3**.

Surgical complications were observed in 10 patients (12.5%), and symptomatic cerebral infarction was detected in 7 patients (8.8%). Delayed ischemic events occurred in 19 patients (23.8%). The incidence of DIND, moderate CVS, severe CVS, and delayed cerebral infarction was 7 (8.8%), 12 (15.0%), 4 (5.0%), and 10 (12.5%), respectively. Symptomatic cerebral infarction was observed in 6 patients (7.5%).

Non-ischemic adverse events were observed in 22 patients (27.5%). The non-ischemic adverse events were as follows: pulmonary edema in 7 (8.8%), pleural effusion in 10 (12.5%), brain edema in 4 (5.0%), hypotension in 4 (5.0%), anemia in 6 (7.5%), hepatobiliary disorder in 6 (7.5%), renal disorder in 2 (2.5%), electrolyte imbalance in 4 (5.0%), and infection in 4 patients (5.0%).

A total of 21 patients (26.3%) required CSF shunt surgery, and favorable outcomes were

observed in 52 patients (65.0%).

Clinical factors correlated with delayed ischemic events and non-ischemic adverse events

The results of the univariate analyses for delayed ischemic and non-ischemic adverse events after aSAH onset are summarized in **Table 4**.

The occurrence of delayed ischemic events significantly correlated with female sex ($p = .045$), a higher WFNS grade ($p = .008$), higher Fischer scale score ($p = .010$) , and higher neutrophil-to-lymphocyte ratio at admission ($p = .040$).

In contrast, the occurrence of non-ischemic adverse events was significantly correlated with age ≥ 75 years ($p = .016$), lower hemoglobin levels at admission ($p = .003$), lower hematocrit levels ($p = .003$), lower total protein levels ($p = .050$), and lower albumin levels at admission ($p = .003$) and higher cardiothoracic ratios on chest radiography before the initiation of CVS therapy ($p = .005$). The results of ROC curve analysis including AUC, optimal cutoff values, sensitivity, and specificity are summarized in **Figure 3** and **Table 5**.

Clinical factors correlated with unfavorable outcome

The results of univariate and multivariate analyses for unfavorable outcomes (mRS ≥ 3) are summarized in **Table 6**.

Unfavorable outcomes were significantly correlated with age ≥ 75 years ($p = .020$), WFNS grades IV–V ($p < .001$), a Fischer scale score of 4 ($p = .003$), and CSF shunt dependence ($p = .001$). Delayed ischemic events ($p < .001$) and non-ischemic adverse events ($p < .001$) were also associated with unfavorable outcomes.

In the multivariate logistic regression analysis, WFNS grades IV–V (FDR LogWorth = 7.60, FDP $p < .001$) and non-ischemic adverse events (FDR LogWorth = 4.54, FDP $p < .001$) were the strongest factors associated with unfavorable outcomes, whereas delayed ischemic events were not

(FDR LogWorth=0.15, FDP p = .705). Among non-ischemic adverse events, pulmonary edema was the strongest factor associated with unfavorable outcomes (**Table 7**, FDR LogWorth = 1.89, FDP p = .013).

Discussion

This multicenter prospective cohort study provides real-world data on the clinical outcomes of CLZ therapy after one year of experience and protocol adjustments in Japan. It also identified the clinical factors associated with delayed ischemic and non-ischemic adverse events during CLZ therapy following the onset of aSAH. Notably, multivariate analysis indicated that non-ischemic adverse events, rather than delayed ischemic events, were a strong determinant of unfavorable outcomes. These findings suggest that preventing non-ischemic adverse events is a critical factor in optimizing CLZ therapy for aSAH patients.

The latest guidelines from the American Heart Association/American Stroke Association emphasize the prevention of DCI as a critical treatment objective after aSAH [8]. Specifically, the early initiation of nimodipine and appropriate blood pressure management are recommended as strategies for preventing delayed ischemic events. However, these guidelines do not specifically mention endothelin receptor antagonists, such as CLZ. Therefore, the present findings provide valuable insights into the potential role and management considerations of CLZ therapy, highlighting the importance of individualized therapeutic strategies and risk stratification.

Comparison with previous studies

According to a recent meta-analysis [29], which included six randomized controlled trials [3, 5, 16–18, 21, 34], the incidence rates of DIND, symptomatic delayed cerebral infarction, and the need for rescue therapy were 14.4%, 10.7%, and 12.4%, respectively. Recent studies conducted after the PMDA approval of CLZ in Japan reported rates of 5.6%–15.6%, 4.7%–10.0%, and 6.3%–16.1%, respectively

[9, 20, 23, 30]. Because our rates were 8.8%, 7.5%, and 8.8%, respectively, the results of this cohort appear to be comparable to those of recent studies in Japan.

In studies conducted after the PMDA approval of CLZ in Japan, the incidence of non-ischemic adverse events, represented by pulmonary edema and pleural effusion, ranged from 19.8% to 56.3% [9, 20, 23, 30]. In contrast, the incidences of pulmonary edema and pleural effusion in the present study were 8.8% and 12.5%, respectively, which were lower than those reported in previous studies. This strongly suggests improved candidate selection for CLZ therapy and better fluid management during CLZ therapy in the first year after PMDA approval in Japan. During the first year after approval, multiple researchers highlighted the importance of avoiding hypervolemia and recommended the use of furosemide to prevent fluid retention complications [1, 9, 10]. In fact, the infusion volumes in this study (approximately 1500 mL/day) were lower than those reported in previous studies, indicating a fluid intake of 2000–4000 mL/day [1, 9, 23, 26, 32]. The interim analysis of a post-marketing survey demonstrated a nationwide reduction in non-ischemic complications from 38.3% between January 2022 and March 2023 to 25.2% after April 2023 [4].

Surprisingly, infusion and urine volume were no longer associated with non-ischemic adverse events in this study (**Table 4**). This finding suggests that the fluid management protocol implemented during CLZ therapy in this study effectively prevented non-ischemic adverse events during CLZ therapy. Future research should focus on identifying optimal fluid management protocols in categorized patient subgroups (e.g., patients aged ≥ 75 years).

In combination with CLZ, cilostazol was administered to most patients (89.8%). Although the combined effects require further investigation, cilostazol did not appear to increase the risk of non-ischemic adverse events.

Practical implications on clinical factors correlated with endpoints

In our study, the occurrence of delayed ischemic events was correlated with female sex, a higher WFNS

grade, Fischer scale score, and neutrophil-to-lymphocyte ratio at admission. However, this was not surprising, as these are the most well-known factors [6, 14, 35]. A key finding of the present study was that non-ischemic adverse events during CLZ therapy were associated with older age (≥ 75 years), anemia (lower hemoglobin and hematocrit levels), hypoproteinemia (lower total protein and albumin levels), and a higher cardiothoracic ratio on radiography before the initiation of CLZ therapy. These factors have the potential to help predict adverse events, enabling appropriate candidate selection for CLZ therapy or early interventions such as blood transfusion or albumin supplementation, prior to the initiation of CLZ therapy. Our ROC curve analyses (**Figure 3** and **Table 5**) provided objective evidence supporting the utility of age, the neutrophil-to-lymphocyte ratio, serum albumin, and the cardiothoracic ratio as predictive indicators. The identified optimal cutoff values may assist clinicians in early identification of patients at risk, potentially enabling individualized preventive measures and treatment adjustments.

For patients presenting with these factors, whether avoiding CLZ therapy or implementing early interventions alongside it would be a better choice should be explored in future studies. Because our multivariate analysis indicated that non-ischemic adverse events, rather than delayed ischemic events, had a stronger influence on aSAH outcomes, minimizing such events appears to be more crucial for improving contemporary aSAH outcomes.

To clarify the relative contributions of priority non-ischemic adverse events to unfavorable clinical outcomes, we performed an additional multivariate logistic regression analysis (**Table 7**). This analysis demonstrated that pulmonary edema was the strongest non-ischemic adverse event significantly associated with unfavorable outcomes (FDR $p = .013$). Although other events such as pleural effusion, hypotension, anemia, and hepatobiliary disorders showed associations in univariate analysis, their independent impacts were less pronounced in multivariate settings. These results highlight the particular clinical relevance of pulmonary edema, underscoring the necessity for careful fluid management to prevent severe respiratory complications during CLZ therapy.

Limitations

This study had several limitations. First, because this prospective study had a single-arm design, it did not allow for comparative efficacy assessments of CLZ therapy. Specifically, older patients and those with more severe or systemic complications were intentionally excluded from the CLZ therapy, making comparisons with other treatment modalities infeasible under the study protocol. Furthermore, this exclusion may have influenced the positive effects of CLZ therapy observed in this study.

Second, the sample size was limited. Although our sample size was sufficient to detect initial signals and main associations, it was relatively modest, limiting the statistical power for detailed subgroup analyses. Consequently, the associations identified in this study should be interpreted cautiously, as these relationships may differ in larger cohorts or with longer follow-up durations. Further accumulation of participants will enable more rigorous multivariate analyses to identify the clinical factors influencing key endpoints and allow for stratified analyses in categorized patient subgroups (e.g., patients aged ≥ 75 years).

Third, the observation period was relatively short. Longer-term results with a detailed assessment of cognitive function are necessary to better understand the long-term outcomes in patients with aSAH.

Fourth, although a unified recommended protocol was provided to all the participating hospitals, the surgical procedures and drainage techniques were left to the discretion of the attending physicians, which may have significantly influenced the study endpoints.

Conclusions

CLZ therapy with appropriate candidate selection and management protocols appears to be a feasible option for reducing the incidence of delayed ischemia following aSAH. However, given the observational nature of this study, the influence of potential confounding factors must be considered.

Additionally, addressing clinical risk factors associated with non-ischemic adverse events may further improve overall treatment outcomes.

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Declarations

Ethical approval: This study was approved by the central Institutional Review Board (IRB) of Hokkaido University Hospital (No. 022-0137) and the IRBs of each participating institute.

Clinical trial number: not applicable.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Authors' contributions: Taku Sugiyama and Miki Fujimura contributed to the study conception and design. Data collection was performed by Masaaki Hokari, Daisuke Shimbo, Haruto Uchino, Yusuke Shimoda, Michinari Okamoto, Yasuhiro Ito, Masayuki Gekka, Hisayasu Saito, Taiji Yamamoto, Yusuke Fujiwara, and Taku Sugiyama. Data analysis was performed by Taku Sugiyama, Masaaki Hokari, Daisuke Shimbo, and Haruto Uchino. The draft of the manuscript was written by Taku Sugiyama, and all authors read and approved the final manuscript.

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Figure Legends

Fig. 1 Imaging protocol

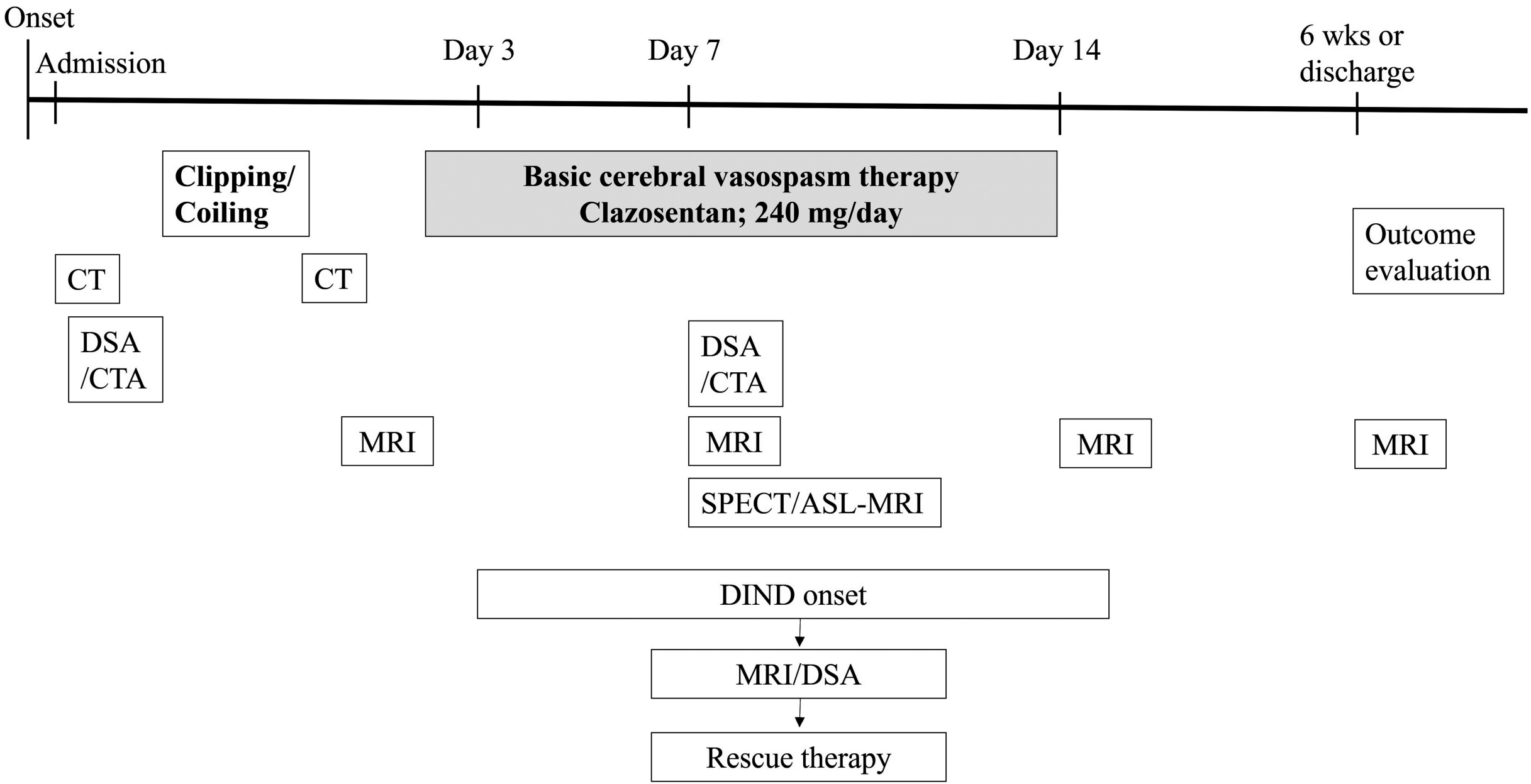
Abbreviations: wks, weeks; CT, computed tomography; DSA, digital subtraction angiography; CTA, CT angiography; MRI, magnetic resonance imaging; SPECT, single photon emission CT; ASL, arterial spin labeling; DIND, delayed ischemic neurological deterioration

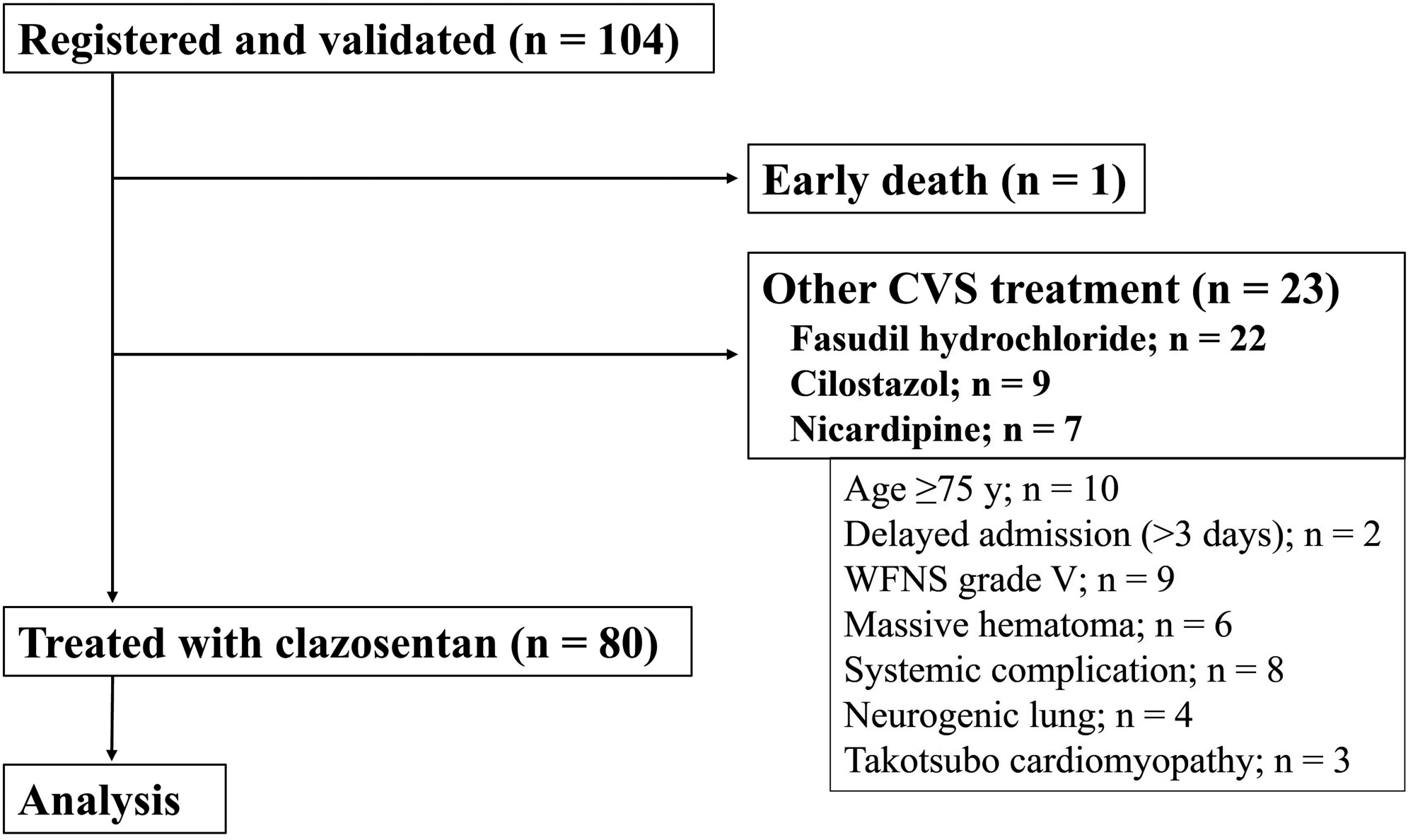
Fig. 2 Flow chart showing the patient selection process in this study

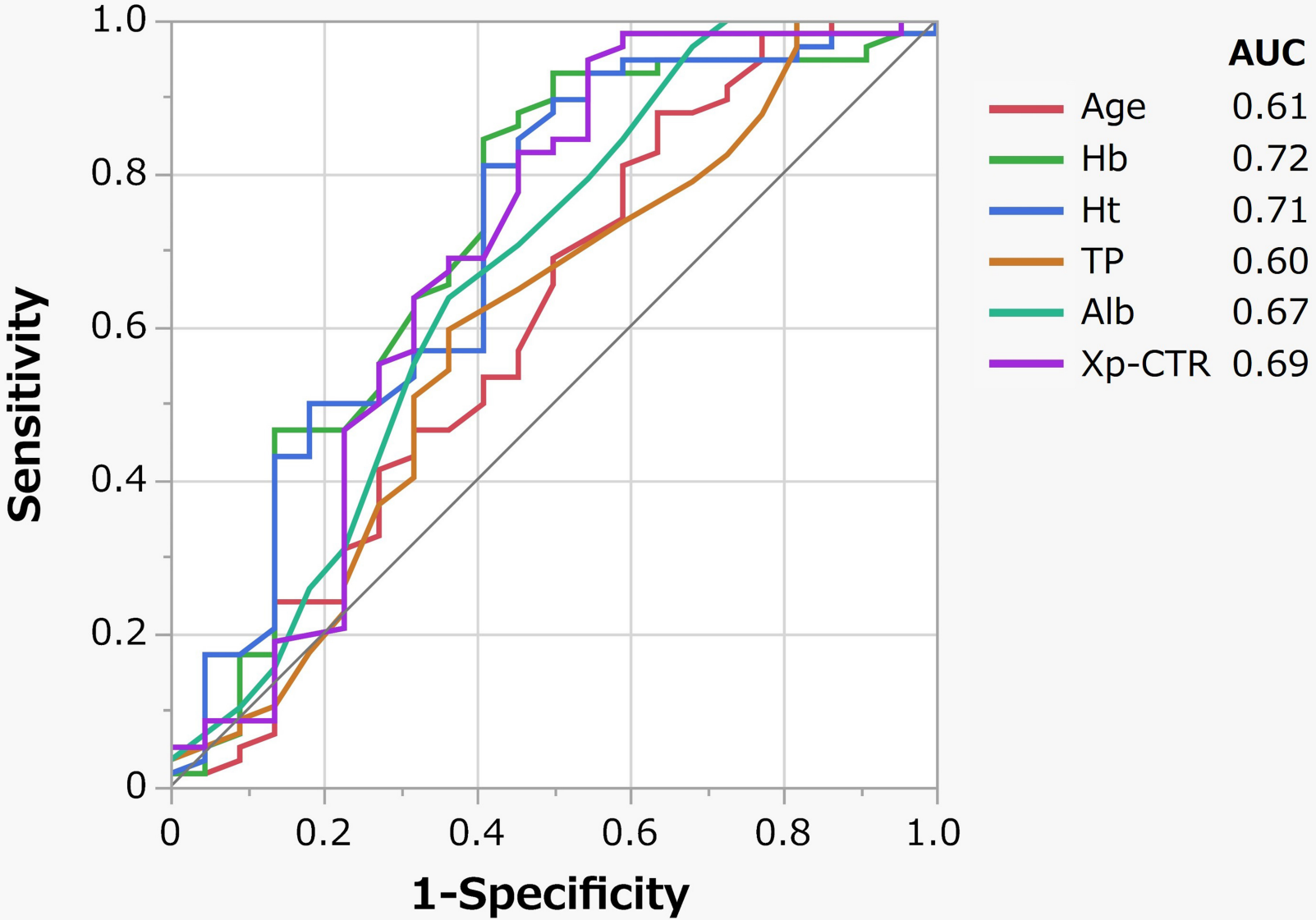
Abbreviations: n, number; CVS, cerebral vasospasm; WFNS, World Federation of Neurosurgical Societies

Fig. 3 Receiver operating characteristic curves for identified factors to predict non-ischemic adverse events.

Abbreviations: AUC, area under the curve; Hb, hemoglobin; Ht, hematocrit; TP, total protein; Alb, albumin; Xp, X-ray photograph; CTR, cardiothoracic ratio


Onset
Admission
Day 3
Day 7
Day 14
6 wks or discharge
Clipping/ Coiling
Basic cerebral vasospasm therapy
Clazosentan; 240 mg/day
Outcome evaluation
CT
CT
DSA /CTA
DSA /CTA
MRI
MRI
MRI
MRI
SPECT/ASL-MRI
DIND onset
MRI/DSA
Rescue therapy


Registered and validated (n = 104)
Early death (n = 1)
Other CVS treatment (n = 23)
Fasudil hydrochloride; n = 22
Cilostazol; n = 9
Nicardipine; n = 7
Age ≥75 y; n = 10
Delayed admission (>3 days); n = 2
WFNS grade V; n = 9
Massive hematoma; n = 6
Systemic complication; n = 8
Neurogenic lung; n = 4
Takotsubo cardiomyopathy; n = 3
Treated with clazosentan (n = 80)
Analysis


1.0
0.8
0.6
0.4
0.2
0
Sensitivity
0
0.2
0.4
0.6
0.8
1.0
1-Specificity
AUC
Age 0.61
Hb 0.72
Ht 0.71
TP 0.60
Alb 0.67
Xp-CTR 0.69

Age (y)	59.1 ± 13.0 (range: 33-90)
Female sex	56 (70.0%)
Body weight (kg)	58.1 ± 13.3 (33.4-105.5)
BMI	22.8 ± 4.8 (14.3-42.5)
Onset to Admission time (h)	7.8 ± 19.5 (0-129)
WFNS grade	
I	30 (37.5%)
II	17 (21.3%)
III	2 (2.5%)
IV	20 (25.0%)
V	11 (13.8%)
Fischer scale	
2	17 (21.3%)
3	50 (62.5%)
4	13 (16.3%)
Aneurysm location	
ICA	21 (25.9%)
ACA	24 (30.0%)
MCA	21 (25.9%)
VA-PICA	11 (13.8%)
BA	2 (2.5%)
PCA	1 (1.3%)
Aneurysm size (mm)	5.6 ± 3.2 (2.0-23.1)

Risk factor/comorbidities	
Hypertension	35 (43.8%)
Dyslipidemia	19 (23.8%)
Diabetes	3 (3.8%)
Smoking	26 (32.5%)
Neurogenic lung	2 (2.6%)
Takotsubo cardiomyopathy	4 (5.0%)
Other systemic diseases	8 (10.0%)

Table 1. Baseline patient characteristics

BMI, body mass index; WFNS, World Federation of Neurosurgical Society; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; VA, vertebral artery; PICA, posterior inferior cerebellar artery; BA, basilar artery; PCA, posterior cerebral artery

Surgical procedure	
Clipping	53 (66.3%)
Coiling	21 (26.3%)
Parent artery occlusion	6 (7.5%)
Decompressive craniotomy	8 (10.0%)
Cerebrospinal fluid drainage	57 (71.3%)
Ventricular	28 (35.0%)
Cisternal	24 (30.0%)
Lumbar	39 (48.8%)
Duration (days)	8.4 ± 9.0 (1-57)
Clazosentan therapy	
Onset to administration (h)	44.9 ± 16.1 (12-101)
Dosage (mg/day)	240
Duration (day)	12.3 ± 1.7
Discontinuation	3 (3.8%)
Concomitant medications	
Cilostazol	71 (89.8%)
Fasudil	4 (5.0%)
Albumin	2 (2.5%)
Statins	16 (20.0%)
Anti-epileptics	40 (50.0%)
Fluid management	
Post-op. day 1 to post-onset day 7	
Mean infusion volume/day (mL)	1704.6 ± 454.5

Mean urine volume/day (mL)	1735.6 ± 535.5
Post-onset day 8 to 15	
Mean infusion volume/day (mL)	1461.8 ± 760.0
Mean urine volume/day (mL)	1896.6 ± 615.6
Rescue therapy	7 (8.8%)
Intra-venous administration of fasudil	5 (5.3%)
Endovascular intervention	3 (3.8%)
Intra-arterial administration of fasudil	3 (3.8%)
Percutaneous balloon angioplasty	2 (2.5%)

Table2. Treatment for cerebral vasospasm

Surgical complication	10 (12.5%)
Intraoperative rupture	3 (3.8%)
Intraoperative cerebral infarction	7 (8.8%)
Re-rupture after aneurysm surgery	0
Delayed ischemic event	19 (23.8%)
Delayed ischemic neurological deterioration	7 (8.8%)
Cerebral vasospasm	16 (20.0%)
Moderate	12 (15.0%)
Severe	4 (5.0%)
Cerebral infarction	10 (12.5%)
Symptomatic infarction	6 (7.5%)
Non-ischemic adverse event	22 (27.5%)
Pulmonary edema	7 (8.8%)
Pleural effusion	10 (12.5%)
Brain edema	4 (5.0%)
Hypotension	4 (5.0%)
Anemia	6 (7.5%)
Hepatobiliary disorder	6 (7.5%)
Renal disorder	2 (2.5%)
Electrolyte imbalance	4 (5.0%)
Infection	4 (5.0%)
Shunt dependence	21 (26.3%)
Outcome (modified Rankin Scale)	

0	25 (31.3%)
1	19 (23.8%)
2	8 (10.0%)
3	10 (12.5%)
4	13 (16.3%)
5	5 (6.3%)
6	0 (0.0%)

Table3. Overall results

	Delayed ischemic event			Non-ischemic adverse event		
	Yes	No		Yes	No	
N	19	61	p-value	22	58	p-value
Age ≥75 y	4 (21.1%)	8 (13.1%)	.465	7 (31.8%)	5 (8.6%)	.016*
Female sex	17 (89.5%)	39 (63.9%)	.045*	15 (68.2%)	41 (70.7%)	1.00
BMI	24.5 ± 7.6	22.3 ± 3.5	.137	23.6 ± 7.5	22.5 ± 3.2	.434
WFNS grade			.008**			.551
I	2 (10.5%)	28 (45.9%)		6 (27.3%)	24 (41.4%)	
II	5 (26.3%)	12 (19.7%)		5 (22.7%)	12 (20.7%)	
III	0 (0.0%)	2 (3.3%)		0 (0.0%)	2 (3.5%)	
IV	8 (42.1%)	12 (19.7%)		11 (50.0%)	9 (15.5%)	
V	4 (21.1%)	7 (11.5%)		0 (0.0%)	11 (19.0%)	
Fischer scale			.010*			.712
2	2 (10.5%)	15 (24.6%)		4 (18.2%)	13 (22.4%)	
3	10 (52.6%)	40 (65.6%)		16 (72.7%)	34 (58.6%)	
4	7 (36.8%)	6 (9.8%)		2 (9.1%)	11 (19.0%)	
Aneurysm location			1.00			1.00
Anterior circulation	16 (84.2%)	50 (82.0%)		18 (81.8%)	48 (82.8%)	
Aneurysm size	5.9 ± 3.5	5.5 ± 3.2	.642	6.0 ± 3.0	5.5 ± 3.3	.576
Past medical history						
Hypertension	10 (52.6%)	25(41.0%)	.433	8 (36.4%)	27 (46.6%)	.459
Dyslipidemia	5 (26.3%)	14 (23.0%)	.764	6 (27.3%)	13 (22.4%)	.770

Diabetes	2 (10.5%)	1 (1.6%)	.125	2 (9.1%)	1 (1.7%)	.182
Current smoker	4 (21.1%)	22 (36.1%)	.272	9 (40.9%)	17 (29.3%)	.423
Other systemic disease	0 (0.0%)	8 (13.1%)	.188	4 (18.2%)	4 (6.9%)	.205
Surgical procedure			.173			1.00
Clipping	10 (52.6%)	43 (70.5%)		15 (68.2%)	38 (65.5%)	
Coiling	9 (47.4%)	18 (29.5%)		6 (27.3%)	15 (25.9%)	
Decompressive craniotomy	4 (21.1%)	4 (6.6%)	.086	4 (18.2%)	4 (6.9%)	.205
Cerebrospinal fluid drainage	17 (89.5%)	40 (65.6%)	.079	19 (86.4%)	38 (65.5%)	.097
Surgical complication	4 (21.1%)	6 (9.8%)	.237	2 (9.1%)	8 (13.8%)	.719
Serum test						
WBC ($x10^6/\mu L$)	12.6 ± 4.7	10.4 ± 3.7	.050	11.4 ± 3.8	10.6 ± 4.1	.468
NLR	11.3 ± 14.4	6.4 ± 5.3	.040*	8.7 ± 12.5	6.9 ± 6.8	.457
Hb (g/dL)	13.2 ± 1.4	13.4 ± 1.4	.566	12.7 ± 1.5	13.6 ± 1.2	.003**
Ht	40.1 ± 3.7	40.6 ± 3.7	.664	38.5 ± 4.0	41.2 ± 3.3	.003**
Plt ($x10^4/\mu L$)	24.7 ± 7.5	25.4 ± 7.3	.731	24.8 ± 9.5	25.4 ± 6.4	.779
TP (g/dL)	7.3 ± 0.6	7.0 ± 0.6	.075	6.8 ± 0.8	7.1 ± 0.5	.050*
Alb (g/dL)	4.2 ± 0.5	4.2 ± 0.4	.736	4.0 ± 0.6	4.3 ± 0.3	.003**
eGFR ($mL/min/1.73m^2$)	86.7 ± 19.8	83.7 ± 21.0	.581	89.5 ± 23.2	82.5 ± 19.4	.190
Na (mmol/L)	139.8 ± 2.7	139.5 ± 2.2	.651	139.3 ± 2.1	139.7 ± 2.4	.482
CRP (mg/dL)	0.9 ± 2.8	0.2 ± 0.5	.083	0.7 ± 2.6	0.3 ± 0.5	.207
Stress index (Glu/K)	52.0 ± 13.5	45.8 ± 17.0	.149	47.2 ± 15.6	47.3 ± 16.8	.964
Xp-CTR	56.4 ± 8.8	54.5 ± 5.7	.269	58.2 ± 8.0	53.7 ± 5.5	.005**

Concomitant medications						
Cilostazol	16 (84.2%)	55 (90.2%)	.437	17 (81.0%)	53 (93.0%)	.201
Fasudil	1 (5.3%)	3 (4.9%)	1.00	1 (4.8%)	2 (3.5%)	1.00
Statin	6 (31.6%)	10 (16.4%)	.190	6 (28.6%)	10 (17.5%)	.346
Anti-epileutics	11 (57.9%)	29 (47.5%)	.600	13 (61.9%)	25 (43.9%)	.204
Fluid management						
Post-op. day 1 to post-onset day 7						
Mean infusion volume/day	1761.1 ± 344.9	1684.2 ± 489.4	.542	1710.5 ± 494.3	1702.2 ± 443.4	.947
Mean urine volume/day	1724.7 ± 356.7	1739.5 ± 589.9	.921	1918.2 ± 738.6	1664.8 ± 421.2	.080
Post-onset day 8 to 15						
Mean infusion volume/day	1655.4 ± 561.5	1392.1 ± 813.4	.210	1598.5 ± 1007.7	1408.8 ± 644.3	.360
Mean urine volume/day	1729.0 ± 436.9	1956.9 ± 661.8	.180	1788.0 ± 563.5	1938.7 ± 635.2	.369

Table 4. Correlation of delayed ischemic and non-ischemic adverse events with multiple variables for clazosentan therapy

* p<.05, ** p<.01

N, number; BMI, body mass index; WFNS, World Federation of Neurosurgical Societies; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; Hb, hemoglobin; Ht, hematocrit; Plt, platelet; TP, total protein; Alb, albumin; eGFR, estimated glomerular filtration rate; Na, sodium; CRP, C-reactive protein; Glu, glucose, K, potassium; Xp, X-ray photograph; CTR, cardiothoracic ratio; post-op., post-operative

Factors	AUC (95%CI)	Optimal cutoff	Sensitivity	Specificity
Age	0.61 (0.45-0.75)	71 y	0.88	0.36
Hb	0.72 (0.56-0.84)	12.8 g/dL	0.84	0.59
Ht	0.71 (0.55-0.83)	38.8 %	0.81	0.59
TP	0.60 (0.44-0.74)	7.0 g/dL	0.60	0.64
Alb	0.67 (0.50-0.80)	3.8 g/dL	0.97	0.32
Xp-CTR	0.69 (0.52-0.82)	60.9 %	0.95	0.45

Table 5. Receiver operating characteristic curve analysis for non-ischemic adverse events

AUC, area under the curve; CI, confidence interval; Hb, hemoglobin; Ht, hematocrit; TP, total protein; Alb, albumin; Xp, X-ray photograph; CTR, cardiothoracic ratio

	Unfavorable outcome					
	Yes	No	Univariate analysis		Multivariate analysis	
N	28	52	OR (95%CI)	p-value	FDR LogWorth	FDR p-value
Age ≥75 y	8 (28.6%)	4 (7.7%)	4.80 (1.30 – 17.8)	.020*	1.42	.038*
WFNS grade IV-V	24 (85.7%)	7 (13.5%)	38.57 (10.26 – 145.06)	<.001***	7.60	<.001***
Fischer scale 4	10 (35.7%)	3 (5.8%)	9.07 (2.24 – 36.75)	.003**	0.28	.520
Surgical complication	6 (21.4%)	4 (7.7%)	3.27 (0.84 – 12.78)	.090	1.48	.033*
CSF shunt dependence	14 (50.0%)	7 (13.5%)	6.43 (2.17 – 19.07)	.001**	0.57	.269
Delayed ischemic event	13 (46.4%)	6 (11.5%)	6.64 (2.15 – 20.55)	<.001***	0.15	.705
Non-ischemic adverse event	15 (53.6%)	7 (13.5%)	7.42 (2.50 – 22.04)	<.001***	4.54	<.001***

Table 6. Factors associated with unfavorable outcomes

* p<.05, ** p<.01, *** p<.001

OR, odds ratio; CI, confidence interval; FDR, False Discovery Rate

	Unfavorable outcome					
	Yes	No	Univariate analysis		Multivariate analysis	
N	28	52	OR (95%CI)	p-value	FDR LogWorth	FDR p-value
Pulmonary edema	7 (25.0%)	0 (0.0%)	NA	<.001***	1.89	.013*
Pleural effusion	8 (28.6%)	2 (3.9%)	10.00 (1.95 – 51.24)	.003**	0.33	.463
Brain edema	1 (3.6%)	3 (5.8%)	0.60 (0.06 – 6.10)	1.00		
Hypotension	4 (14.3%)	0 (0.0%)	NA	.013*	1.02	.096
Anemia	5 (17.9%)	1 (1.9%)	11.09 (1.22 – 100.33)	.018*	0.19	.640
Hepatobiliary disorder	5 (17.9%)	1 (1.9%)	11.09 (1.22 – 100.33)	.018*	0.19	.640
Renal disorder	2 (7.1%)	0 (0.0%)	NA	.120		
Electrolyte imbalance	2 (7.1%)	2 (3.9%)	1.92 (0.26 – 14.45)	.609		
Infection	4 (14.3%)	0 (0.0%)	NA	.013*	1.16	.069

Table 7. Association between non-ischemic adverse events and unfavorable outcomes

* p<.05, ** p<.01, *** p<.001

OR, odds ratio; CI, confidence interval; FDR, False Discovery Rate; NA, not applicable