

Outcomes of Clazosentan Versus Fasudil in Aneurysmal Subarachnoid Hemorrhage Outside Japanese Pivotal Trial Criteria: An Exploratory RECOVER Subgroup Analysis

Yosuke Sakai

Nagoya University Graduate School of Medicine

Shinsuke Muraoka

`neuro-smuraoka@umin.ac.jp`

Nagoya University Graduate School of Medicine

Takashi Izumi

Nagoya University Graduate School of Medicine

Issei Takeuchi

Nagoya University Graduate School of Medicine

Shunsaku Goto

Nagoya University Graduate School of Medicine

Masahiro Nishihori

Nagoya University Graduate School of Medicine

Yusuke Sakamoto

Aichi Medical University

Satoshi Maesawa

National Hospital Organization Nagoya Medical Center

Shinji Ota

Chitahanto Medical Center

Takeshi Kinkori

Okazaki City Hospital

Takumi Asai

Kariya Toyota General Hospital

Osamu Suzuki

Nagoya Ekisaikai Hospital

Kazuki Nishida

Nagoya University Graduate School of Medicine

Basile Chretien

Nagoya University Graduate School of Medicine

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Abstract

Objective

Japanese phase 3 clazosentan trials excluded patients aged ≥ 76 years, WFNS grade V, and Fisher groups other than 3. Using RECOVER, we compared clazosentan with fasudil in these post-approval populations.

Methods

After excluding patients who received both agents, this prespecified subgroup analysis included 398 patients (clazosentan 161; fasudil 237). The primary endpoint was favorable discharge outcome (modified Rankin Scale 0–2). Subgroups were age ≥ 76 years, WFNS grade V, Fisher group 1, 2, or 4, and Fisher group 4. Adjusted logistic and interaction analyses were exploratory.

Results

The subgroup sizes were 75 patients aged ≥ 76 years, 71 with WFNS grade V, 173 with Fisher group 1, 2, or 4, and 96 with Fisher group 4, respectively. Estimated associations for favorable outcome favored clazosentan in patients aged ≥ 76 years (40.0% vs 24.0%; adjusted OR 3.52), those with WFNS grade V (21.7% vs 12.5%; adjusted OR 1.59), those with Fisher group 1, 2, or 4 (67.1% vs 43.7%; adjusted OR 3.17, 95% CI 1.31–8.12), and those with Fisher group 4 (45.5% vs 22.2%; adjusted OR 3.12). Vasospasm-related delayed cerebral ischemia was absent in the clazosentan group in both Fisher-defined subgroups. No consistent excess of major adverse events was identified.

Conclusions

Trial exclusion criteria did not identify subgroups with loss of favorable association or clear safety penalty. Age ≥ 76 years, WFNS grade V, or non-Fisher group 3 status reflect trial ineligibility rather than contraindication, and they should prompt individualized benefit-risk assessment rather than automatic avoidance.

Introduction

Cerebral vasospasm and delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage (aSAH) remain important determinants of functional outcome even when the ruptured aneurysm is secured early. International guidelines recommend nimodipine after aSAH [7], but nimodipine has not been approved for this indication in Japan. Consequently, fasudil, a Rho kinase inhibitor, has been widely used as standard pharmacological prophylaxis against cerebral vasospasm in Japanese clinical practice [8]. Clazosentan, a selective endothelin A receptor antagonist, has emerged as a targeted

pharmacological option for reducing vasospasm-related morbidity and mortality. In CONSCIOUS-2, CONSCIOUS-3, and REACT, clazosentan reduced angiographic vasospasm and vasospasm-related morbidity, but did not improve functional outcome [9–11]. In contrast, the Japanese phase 3 clinical trial demonstrated significant reductions in vasospasm-related morbidity and all-cause mortality after both coiling and clipping, thereby providing the evidence base for the approved clinical use of clazosentan in Japan [5].

The patients for whom clinicians most need guidance are not necessarily the patients best represented in pivotal trials. The Japanese phase 3 trial was restricted to patients aged 20–75 years, those with World Federation of Neurosurgical Societies (WFNS) grade I–IV, and those with Fisher group 3 [5]. Consequently, uncertainty remains regarding the use of clazosentan in patients aged ≥ 76 years, those presenting with WFNS grade V, and those with Fisher groups other than 3. These groups are frequently encountered in routine neurosurgical practice and represent precisely the populations in whom clinicians may hesitate to use clazosentan because of reduced cardiopulmonary reserve, severe early brain injury, hydrocephalus, intraventricular hemorrhage, intracerebral hemorrhage, or concern for brain edema.

The RECOVER study directly compared clazosentan and fasudil in a multicenter retrospective Japanese cohort and suggested a potential clinical advantage of clazosentan [13]. Because fasudil remains the conventional Japanese comparator, RECOVER provides a pragmatic opportunity to examine whether the post-approval advantage of clazosentan extends beyond the population selected for the domestic phase 3 trials. Therefore, the present analysis constructed a comparative cohort from RECOVER by excluding patients who received both agents and compared efficacy and safety in four clinically relevant subgroups: patients aged ≥ 76 years, those with WFNS grade V, those with Fisher group 1, 2, or 4, and those with Fisher group 4 alone.

Whereas the RECOVER primary analysis and a previous stratified report evaluated the overall treated cohort, the present study was specifically designed to address the trial-ineligible populations that most often prompt clinical hesitation, and to test whether exclusion-criteria status modifies the treatment-associated outcome. We hypothesized that, in these underrepresented subgroups, clazosentan would retain the favorable direction of association with vasospasm-related morbidity and discharge outcome observed in the overall cohort, supporting that trial exclusion criteria need not preclude its use; we did not, however, design the study to demonstrate non-inferiority, and we anticipated that any safety signals related to cardiopulmonary reserve, edema, or hemorrhage would require cautious interpretation given the limited statistical power.

Materials and Methods

Study Design and Ethics

This study was a prespecified subgroup analysis of RECOVER (REtrospective study of Clazosentan and fasudil in subarachnOid hemorrhage: Vasospasm prEvention and patient pRognosis), a multicenter

retrospective observational study of patients with aSAH [13]. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Nagoya University Hospital (approval number: 2022 – 0476). The requirement for individual informed consent was waived, and an opt-out approach was used because only anonymized retrospective clinical data were analyzed. This study was reported in accordance with the STROBE statement [28].

Study Population

RECOVER enrolled patients with aSAH who had a premorbid modified Rankin Scale (mRS) score of 0–2 [25], underwent microsurgical clipping or endovascular coiling within 48 hours of onset, and received perioperative fasudil or clazosentan between April 2021 and March 2024. The diagnosis of aSAH was established using head CT, CT angiography, or digital subtraction angiography (DSA). Because clazosentan became clinically available in Japan in May 2022, the comparative cohort was constructed to contrast a pre-availability period in which fasudil was the standard agent (April 2021–March 2022) with a subsequent period of established clazosentan use (April 2023–March 2024). The intervening transition year (April 2022–March 2023) was not used for the primary comparison, so that the initial period of familiarization with clazosentan-specific perioperative management—particularly the prevention and treatment of fluid retention—would not dominate the comparison; this sequential framework is consistent with the design of the RECOVER primary analysis. For the present analysis, patients who received both agents were excluded to avoid mixed pharmacological exposure. Patients with missing discharge mRS or perioperative complication data were also excluded.

Treatment Protocol

Treatment Protocol

Perioperative care basically followed the recommended perioperative clinical management protocol. Clazosentan was administered as a continuous intravenous infusion at 10 mg/h after aneurysm repair, generally from postoperative day 1 through day 14. Fasudil was administered at 30 mg three times daily during the same vasospasm-prone period. Concomitant cilostazol, statins, levetiracetam, and perampanel were sometimes used at the discretion of the treating physicians. Clazosentan was discontinued when severe or progressive adverse events, such as pulmonary complications, refractory hypotension, or symptomatic cerebral edema, were judged to have occurred.

Subgroup Definitions

Four prespecified subgroups were analyzed because they represent patients who were underrepresented in pivotal trials and in whom clazosentan use is often approached cautiously; patients aged ≥ 76 years, those with WFNS grade V, those with Fisher group 1, 2, or 4, and those with Fisher group 4 alone. WFNS grade was defined at initial presentation or before aneurysm treatment [21]. Fisher group was assigned from initial CT findings [6]. Fisher group 1, 2, or 4 was used to evaluate patients outside Fisher group 3,

and Fisher group 4 was analyzed separately because intraventricular or intracerebral blood may simultaneously increase DCI risk and raise concern for brain edema.

Data Collection

In RECOVER, clinical information was collected retrospectively at each participating institution using anonymized electronic data registration forms. In the present study, patient characteristics, treatment details, imaging findings, clinical outcomes, and perioperative complications were extracted from the RECOVER registry database. Baseline characteristics assessed included age, sex, WFNS grade, Fisher group, location of ruptured aneurysm, treatment modality, presence of cerebrospinal fluid drainage, and concomitant medications.

Outcomes

The primary endpoint was favorable outcome at discharge, defined as an mRS score of 0–2. Efficacy outcomes were angiographic vasospasm and vasospasm-related DCI. Angiographic cerebral vasospasm was defined as a reduction in arterial diameter of $\geq 25\%$ compared with the initial preoperative computed tomography angiography (CTA). Postoperative vasospasm was evaluated by comparing preoperative CTA with postoperative non-contrast magnetic resonance angiography (MRA). MRA was routinely performed and was additionally indicated when new neurological deficits occurred. A specialized sequence was used to reduce metallic artifacts adjacent to coils or clips, and DSA was reserved for patients with clinically significant vasospasm requiring intervention, such as balloon angioplasty. Vasospasm-related DCI was defined as a new cerebral infarction or neurological deterioration occurring between days 4 and 20 after aSAH that was consistent with vasospasm and was absent on initial or immediate postoperative imaging [27]. Other potential contributors, including hypoxia, electrolyte imbalance, infection, hydrocephalus, seizures, and treatment-related injury, were systematically excluded. When patients could be clinically assessed, neurological deterioration required a decrease of at least 2 points on the Glasgow Coma Scale. Safety outcomes included brain edema, pulmonary complication, hypotension, and de novo intracranial hemorrhage (ICH). All outcomes were evaluated in the overall sequential comparative cohort and in each prespecified subgroup.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation or median [interquartile range], and categorical variables as number (%). Between-group comparisons were performed using Student's t-test or Wilcoxon rank-sum test for continuous variables and chi-square test or Fisher's exact test for categorical variables. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Multivariable logistic regression analysis was used to compare the clazosentan and fasudil groups within each prespecified subgroup, yielding adjusted ORs with 95% CIs. The outcomes analyzed were favorable outcome, vasospasm-related DCI, angiographic vasospasm $> 25\%$, brain edema, pulmonary complication, hypotension, and de novo ICH. Treatment group was entered as the primary explanatory

variable. Because of limited subgroup sample sizes, covariates were deliberately restricted and included a priori as follows: WFNS grade, Fisher group, treatment modality, and cerebrospinal fluid (CSF) drainage for the age ≥ 76 years subgroup; age, Fisher group, treatment modality, and CSF drainage for the WFNS grade V subgroup; age, WFNS grade, treatment modality, and CSF drainage for the Fisher group 1, 2, or 4 subgroup; and age, WFNS grade, treatment modality, and cilostazol use for the Fisher group 4 subgroup.

In addition to subgroup analyses, stratified analyses were performed using the overall sequential comparative cohort. Whereas subgroup analyses estimate adjusted ORs from data restricted to the relevant subgroup, stratified analyses estimate ORs for each stratum from the overall cohort data; accordingly, the two sets of values may differ. The stratification factors for the stratified analysis of favorable outcome were age (< 76 vs ≥ 76 years), WFNS grade (I–IV vs V), and Fisher group (3 vs 1, 2, or 4). Similar stratified analyses were also performed for other major outcomes including Fisher group 4 (non-4 vs 4). Adjusted odds ratios (ORs) for clazosentan use in each stratum were calculated with adjustment for sex, treatment modality, and CSF drainage. To explore whether treatment effects differed by stratification factor, p-values for interaction were calculated using logistic regression models including interaction terms between treatment group and each stratification factor.

Cases with unstable estimates were reported as not estimable (NE). Firth penalized logistic regression was used in cases of complete or quasi-complete separation, or when estimates were otherwise unstable. No correction for multiple comparisons was performed, and all subgroup and stratified analyses were interpreted as exploratory. All statistical analyses were performed using R software.

Results

Patient Selection and Baseline Characteristics

Among 466 patients enrolled in RECOVER, 4 with aneurysm re-rupture, 30 with incomplete data, and 34 who received both agents were excluded. The final sequential comparative cohort comprised 398 patients, including 161 treated with clazosentan and 237 treated with fasudil (Fig. 1). The prespecified subgroups included 75 patients aged ≥ 76 years (clazosentan, $n = 25$; fasudil, $n = 50$), 71 with WFNS grade V (clazosentan, $n = 23$; fasudil, $n = 48$), 173 with Fisher group 1, 2, or 4 (clazosentan, $n = 70$; fasudil, $n = 103$), and 96 with Fisher group 4 alone (clazosentan, $n = 33$; fasudil, $n = 63$). Baseline characteristics of the overall cohort were generally comparable between groups (Table 1), and subgroup characteristics are shown in Online Resources 1–4. Baseline characteristics and outcomes of the 34 patients who received both agents are described in Online Resource 5.

Among 466 patients with aneurysmal subarachnoid hemorrhage in RECOVER, 4 with aneurysm re-rupture, 30 with incomplete data, and 34 treated with both fasudil and clazosentan were excluded. The sequential comparative cohort comprised 237 fasudil-treated and 161 clazosentan-treated patients. Prespecified subgroups were age ≥ 76 years ($n = 75$), WFNS grade V ($n = 71$), Fisher group 1, 2, or 4 ($n = 173$), and Fisher group 4 ($n = 96$).

Table 1
Baseline characteristics of the overall comparative cohort

Women, n (%)	Clazosentan (n = 161)	Fasudil (n = 237)	P value
	110 (68.3%)	153 (64.6%)	0.452
Age, mean $\pm$ SD, years	61.6 $\pm$ 12.7	63.5 $\pm$ 13.6	0.153
$\geq$ 76 years, n (%)	25 (15.5%)	50 (21.1%)	0.192
WFNS classification			
Median [IQR]	2.0 [2.0–4.0]	3.0 [2.0–4.0]	0.059
Grade V, n (%)	23 (14.3%)	48 (20.3%)	0.143
Fisher classification			
Median [IQR]	3.0 [3.0–3.0]	3.0 [3.0–4.0]	0.057
Fisher group 1,2,4, n (%)	70 (43.5%)	103 (43.5%)	> 0.999
Fisher group 4, n (%)	33 (20.5%)	63 (26.6%)	0.189
Anterior aneurysm site, n (%)	132 (82.0%)	195 (82.3%)	> 0.999
Intervention			
EVT, n (%)	63 (39.1%)	92 (38.8%)	0.834
CSF drainage, n (%)	84 (52.2%)	119 (50.2%)	0.681
Length of stay, median [IQR], days	28.0 [21.0–41.0]	34.0 [22.0–49.0]	0.015
Concomitant medications			
Cilostazol, n (%)	94 (58.4%)	152 (64.1%)	0.250
Statin, n (%)	85 (52.8%)	122 (51.5%)	0.758

EVT=endovascular treatment.

Efficacy Outcomes

Favorable outcome was compared between the clazosentan and fasudil groups in each prespecified subgroup (Online Resource 8). Outcomes in the overall cohort are summarized in Online Resource 6.

In the age $\geq$ 76 years subgroup, favorable outcome was achieved in 40.0% of patients in the clazosentan group and 24.0% in the fasudil group (10/25 vs 12/50; adjusted OR 3.52, 95% CI 0.89–16.53; adjusted p = 0.085) (Table 2). In the WFNS grade V subgroup, favorable outcome was achieved in 21.7% and 12.5% of patients, respectively (5/23 vs 6/48; adjusted OR 1.59, 95% CI 0.32–7.42; adjusted p = 0.557)

(Table 3). As an exploratory finding, favorable outcome was significantly more frequent with clazosentan in the broader Fisher group 1, 2, or 4 composite subgroup (67.1% [47/70] vs 43.7% [45/103]; adjusted OR 3.17, 95% CI 1.31–8.12; adjusted $p = 0.012$) (Table 4). In Fisher group 4 subgroup, favorable outcome was achieved in 45.5% of patients in the clazosentan group and 22.2% in the fasudil group (15/33 vs 14/63; adjusted OR 3.12, 95% CI 0.97–10.75; adjusted $p = 0.061$) (Table 5).

In the stratified analysis of the overall cohort, the adjusted ORs for the association between clazosentan use and favorable outcome were in a favorable direction for clazosentan across all strata: age < 76 years (OR 2.17, 95% CI 1.34–3.58), age $\geq$ 76 years (OR 2.03, 95% CI 0.69–6.04), WFNS grade I–IV (OR 2.09, 95% CI 1.29–3.44), WFNS grade V (OR 2.41, 95% CI 0.58–10.13), Fisher group 3 (OR 1.78, 95% CI 1.01–3.15), Fisher group 1, 2, or 4 (OR 2.88, 95% CI 1.49–5.73), non-Fisher group 4 (OR 1.91, 95% CI 1.04–3.51), and Fisher group 4 (OR 3.00, 95% CI 0.99–9.11) (Fig. 2). No statistically significant interaction was detected by age, WFNS grade, Fisher group, or Fisher group 4 status (age: $p = 0.885$; WFNS grade: $p = 0.838$; Fisher group: $p = 0.294$; Fisher group 4: $p = 0.489$). However, these interaction analyses were underpowered, and the absence of significant interaction should not be interpreted as evidence that treatment-associated differences were identical across strata.

Table 2
Outcomes in the age $\geq$ 76 years subgroup

Favorable outcome (mRS 0–2)	Clazosentan (n = 25)	Fasudil (n = 50)	P value	Adjusted OR (95% CI)	Adjusted P value
	10 (40.0%)	12 (24.0%)	0.183	3.52 (0.89–16.53)	0.085
Mortality at discharge	2 (8.0%)	4 (8.0%)	> 0.999	3.37 (0.31–47.84)	0.312
Vasospasm-related DCI	3 (12.0%)	10 (20.0%)	0.524	0.38 (0.05–2.09)	0.295
Angiographic vasospasm > 25%	7 (28.0%)	19 (38.0%)	0.449	0.65 (0.20–1.94)	0.444
Brain edema	0 (0.0%)	4 (8.2%)	0.293	NE	0.125
Pulmonary complication	3 (12.0%)	6 (12.0%)	> 0.999	1.22 (0.23–5.71)	0.807
Hypotension	1 (4.0%)	2 (4.0%)	> 0.999	1.01 (0.05–11.27)	0.993
De novo ICH	2 (8.0%)	0 (0.0%)	0.108	NE	0.089

CI=confidence interval; DCI=delayed cerebral ischemia; ICH=intracranial hemorrhage.

Adjusted models included age, WFNS grade, Fisher group, endovascular treatment, and CSF drainage.

NE = not estimable; because of zero events in one arm (complete separation), the adjusted odds ratios for de novo ICH

and brain edema was unstable and reported as NE rather than as point estimates with implausibly wide confidence intervals.

MLE: Favorable outcome (mRS 0–2), Mortality at discharge, Vasospasm-related DCI, Angiographic vasospasm > 25,

Pulmonary complication, Hypotension, De novo ICH.

Firth: Brain edema.

Table 3
Outcomes in the WFNS grade V subgroup

Favorable outcome (mRS 0–2)	Clazosentan (n = 23)	Fasudil (n = 48)	P value	Adjusted OR (95% CI)	Adjusted P value
	5 (21.7%)	6 (12.5%)	0.319	1.59 (0.32–7.42)	0.557
Mortality at discharge	1 (4.3%)	3 (6.2%)	> 0.999	0.71 (0.03–6.47)	0.777
Vasospasm-related DCI	2 (8.7%)	6 (12.5%)	> 0.999	0.61 (0.07–3.55)	0.603
Angiographic vasospasm > 25%	5 (21.7%)	13 (27.1%)	0.774	0.64 (0.15–2.37)	0.522
Brain edema	4 (17.4%)	12 (25.0%)	0.556	0.37 (0.06–1.88)	0.257
Pulmonary complication	3 (13.0%)	4 (8.3%)	0.674	3.11 (0.46–23.61)	0.240
Hypotension	3 (13.0%)	1 (2.1%)	0.100	4.16 (0.32–101.82)	0.285
De novo ICH	0 (0.0%)	1 (2.1%)	> 0.999	NE	0.680

CI=confidence interval; DCI=delayed cerebral ischemia; ICH=intracranial hemorrhage.

Adjusted models included age, Fisher group, endovascular treatment, and CSF drainage.

NE = not estimable; because of zero events in one arm (complete separation), the adjusted odds ratio for de novo

ICH was unstable and is reported as NE rather than as a point estimate with an implausibly wide confidence interval.

MLE: Favorable outcome (mRS 0–2), Mortality at discharge, Vasospasm-related DCI, Angiographic vasospasm > 25%,

Brain edema, Pulmonary complication, Hypotension, De novo ICH.

Table 4
Outcomes in the Fisher group 1,2,4 subgroup

Favorable outcome (mRS 0–2)	Clazosentan (n = 70)	Fasudil (n = 103)	P value	Adjusted OR (95% CI)	Adjusted P value
	47 (67.1%)	45 (43.7%)	0.003	3.17 (1.31–8.12)	0.012
Mortality at discharge	2 (2.9%)	4 (3.9%)	> 0.999	1.58 (0.24–9.40)	0.608
Vasospasm-related DCI	0 (0.0%)	12 (11.7%)	0.002	NE	0.002
Angiographic vasospasm > 25%	7 (10.0%)	33 (32.0%)	< 0.001	0.24 (0.09–0.57)	0.002
Brain edema	8 (11.4%)	18 (17.8%)	0.286	0.45 (0.13–1.43)	0.189
Pulmonary complication	4 (5.7%)	4 (3.9%)	0.716	1.42 (0.26–7.02)	0.662
Hypotension	2 (2.9%)	2 (2.0%)	> 0.999	0.96 (0.04–12.07)	0.976
De novo ICH	3 (4.3%)	4 (3.9%)	> 0.999	0.78 (0.10–4.26)	0.782

CI=confidence interval; DCI=delayed cerebral ischemia; ICH=intracranial hemorrhage.

Adjusted models included age, WFNS grade, endovascular treatment, and CSF drainage.

NE = not estimable; vasospasm-related DCI occurred in no clazosentan-treated patient (0/70), producing complete separation, so the adjusted odds ratio is reported as NE; the unadjusted between-group difference (0.0% vs 11.7%) remained significant (p = 0.002).

MLE: Favorable outcome (mRS 0–2), Angiographic vasospasm > 25%, Brain edema, Pulmonary complication.

Firth: Mortality at discharge, Vasospasm-related DCI, Hypotension, De novo ICH.

Table 5
Outcomes in the Fisher group 4 subgroup

Favorable outcome (mRS 0–2)	Clazosentan (n = 33)	Fasudil (n = 63)	P value	Adjusted OR (95% CI)	Adjusted P value
	15 (45.5%)	14 (22.2%)	0.034	3.12 (0.97– 10.75)	0.061
Mortality at discharge	2 (6.1%)	2 (3.2%)	0.606	1.47 (0.20– 10.86)	0.690
Vasospasm-related DCI	0 (0.0%)	10 (15.9%)	0.014	NE	0.014
Angiographic vasospasm > 25%	4 (12.1%)	23 (36.5%)	0.016	0.20 (0.05– 0.63)	0.011
Brain edema	7 (21.2%)	18 (29.5%)	0.468	0.48 (0.12– 1.69)	0.267
Pulmonary complication	2 (6.1%)	1 (1.6%)	0.271	3.02 (0.37– 35.43)	0.297
Hypotension	2 (6.1%)	1 (1.6%)	0.276	1.51 (0.12– 19.81)	0.731
De novo ICH	1 (3.0%)	3 (4.8%)	> 0.999	0.72 (0.07– 4.98)	0.746

CI=confidence interval; DCI=delayed cerebral ischemia; ICH=intracranial hemorrhage.

Adjusted models included age, WFNS grade, endovascular treatment, and cilostazol.

NE = not estimable; vasospasm-related DCI occurred in no clazosentan-treated patient (0/33), producing complete separation, so the adjusted odds ratio is reported as NE; the unadjusted between-group difference (0.0% vs 15.9%) remained significant (p = 0.014).

MLE: Favorable outcome (mRS 0–2), Angiographic vasospasm > 25%, Brain edema.

Firth: Mortality at discharge, Vasospasm-related DCI, Pulmonary complication, Hypotension, De novo ICH.

Adjusted ORs and 95% CIs for the association between clazosentan and favorable discharge outcome are shown across age, WFNS grade, Fisher group, and Fisher group 4 strata in the overall cohort. Models were adjusted for sex, treatment modality, and CSF drainage. Interaction tests were underpowered; no statistically significant treatment-by-subgroup interaction was identified.

Secondary Efficacy and Safety Outcomes

Vasospasm-related DCI and angiographic vasospasm were numerically less frequent with clazosentan in the age ≥ 76 years and WFNS grade V subgroups, but the adjusted differences were not statistically significant (Tables 2 and 3). In Fisher group 1, 2, or 4 subgroup, vasospasm-related DCI occurred in none of 70 clazosentan-treated patients and 12 of 103 fasudil-treated patients (0.0% vs 11.7%; $p = 0.002$). Angiographic vasospasm occurred in 7 of 70 patients (10.0%) and 33 of 103 patients (32.0%), respectively (adjusted OR 0.24, 95% CI 0.09–0.57; adjusted $p = 0.002$) (Table 4). In Fisher group 4 subgroup, vasospasm-related DCI occurred in none of the 33 clazosentan-treated patients and in 10 of the 63 fasudil-treated patients (0.0% vs 15.9%; $p = 0.014$). Angiographic vasospasm occurred in 4 of 33 patients (12.1%) and 23 of 63 patients (36.5%), respectively (adjusted OR 0.20, 95% CI 0.05–0.63; adjusted $p = 0.011$) (Table 5).

No consistent excess risk of brain edema, pulmonary complication, hypotension, or de novo ICH was observed with clazosentan in any subgroup (Tables 2–5). In the age ≥ 76 years subgroup, de novo ICH occurred in 2 of 25 clazosentan-treated and 0 of 50 fasudil-treated patients (8.0% vs 0.0%; unadjusted $p = 0.108$); because of the zero events count in the fasudil arm, the adjusted odds ratio was not estimable, and this numerical imbalance should be regarded as a hypothesis-generating safety signal warranting surveillance rather than a quantified risk.

To assess whether exclusion of 34 patients who received both agents biased the overall favorable-outcome result, a tipping-point sensitivity analysis was performed in which all combined-use patients were assigned to either the clazosentan arm or the fasudil arm. Under both extreme scenarios, the overall association between clazosentan and favorable outcome remained statistically significant and favored clazosentan: adjusted OR 2.20 (95% CI 1.36–3.62; $p = 0.002$) when all combined-use patients were assigned to the clazosentan arm, and adjusted OR, 1.80 (95% CI 1.09–3.00; $p = 0.023$) when they were assigned to the fasudil arm (Online Resource 7). This analysis bounds the potential exclusion bias for the overall favorable-outcome result only and does not extend to the subgroup findings.

Discussion

Principal Findings

This multicenter sequential cohort analysis evaluated clazosentan and fasudil in patients with aSAH who are frequently encountered in clinical practice but were incompletely represented in pivotal clazosentan trials. The principal finding is not that these subgroup factors are clinically unimportant. Older age, WFNS grade V, and Fisher group 4 each identify patients with substantial competing risks for poor outcome. Rather, clazosentan was not associated with a reversal of the favorable association or with a clear safety penalty in any prespecified subgroup. In the age ≥ 76 years, WFNS grade V, and Fisher group 4 subgroups, the estimates were directionally favorable but statistically uncertain. As an exploratory finding, favorable outcome was significantly more frequent with clazosentan in the broader Fisher group 1, 2, or 4 composite subgroup.

These results address a practical clinical question: whether trial exclusion criteria should be treated as clinical contraindications. Our data do not support automatic avoidance of clazosentan based solely on age ≥ 76 years, WFNS grade V, or non-Fisher group 3 status. Instead, they support a more individualized approach in which expected DCI risk, competing causes of poor outcome, cardiopulmonary reserve, brain edema risk, and the feasibility for early intensive monitoring are considered together.

The most robust evidence in this study is not the magnitude of any individual subgroup odds ratio but the consistency of the treatment-associated effect across strata. In the overall cohort, the adjusted odds ratios for favorable outcome favored clazosentan in every stratum of age, WFNS grade, and Fisher group, and no treatment-by-subgroup interaction reached statistical significance. Interpreted together, these analyses indicate that the favorable association demonstrated in the RECOVER primary cohort is not lost in the trial-ineligible populations, which is the central question addressed here. The within-subgroup odds ratios, although directionally concordant, were derived from small strata with wide confidence intervals and are therefore best regarded as supportive rather than independently confirmatory. We accordingly frame the following discussion around this hierarchy—consistency of effect across strata as the primary signal, and individual subgroup estimates as secondary—which underlies our conclusion that exclusion-criteria status should not, by itself, preclude clazosentan.

Efficacy Outcomes by Subgroup

The lack of statistical significance in the age ≥ 76 years and WFNS grade V subgroups likely reflects the multifactorial determinants of outcome in these populations. In elderly patients, the frequency of angiographic vasospasm decreases with age, whereas in-hospital mortality and morbidity are worse than in younger patients, and the relationship between vasospasm and DCI appears to be modified by age [2]. In patients with WFNS grade V, early brain injury occurring immediately after the hemorrhage substantially contributes to prognosis. Neurological injury mediated by elevated intracranial pressure and microcirculatory dysfunction cannot be mitigated by DCI prevention alone [18, 20, 23]. In addition, age-related decline in endothelin B receptor-mediated vasodilatory function may attenuate the vasosuppressive effect of clazosentan [29]. Consequently, the absence of significant differences in these two subgroups should not be interpreted as evidence that clazosentan is ineffective. Rather, any DCI-suppressive effect may not be fully reflected in discharge modified Rankin Scale (mRS) scores when competing determinants of outcome are dominant. This interpretation is consistent with previous real-world comparative data [12], and larger studies are required to clarify the efficacy of clazosentan in these specific populations.

The Fisher group findings are clinically important because the domestic phase 3 evidence was strongest in Fisher group 3. Fisher group 4 is associated with early brain injury, acute hydrocephalus, elevated intracranial pressure, and increased DCI risk; thick cisternal clot and intraventricular blood are independent risk factors for DCI, with additive effects [3]. In the present analysis, clazosentan was still associated with higher odds of favorable outcome and lower frequencies of vasospasm-related endpoints in Fisher group 4. The broader Fisher group 1, 2, or 4 composite subgroup also showed a significant favorable association. Because this composite includes lower-risk Fisher group 1 and 2

patients, prognostic heterogeneity should be considered. Nevertheless, this result is directionally consistent with the Fisher group 4 analysis and argues against automatic exclusion of non-Fisher group 3 patients from consideration of clazosentan.

The stratified analyses support this interpretation. Adjusted ORs for favorable outcome favored clazosentan across all examined strata, and the underpowered interaction analyses provided no evidence that the favorable association was confined to younger patients, patients with less severe WFNS grades, or those with Fisher group 3. This finding is directionally consistent with recent multicenter data suggesting that clazosentan may have effects across age, severity, and clot-volume strata [22].

These findings remain hypothesis-generating. In the present dataset, WFNS grade V was imbalanced within the Fisher group 1, 2, or 4 subgroup, and cilostazol use differed in the Fisher group 4 subgroup. Because combined cilostazol and clazosentan therapy has been associated with reduced vasospasm-related DCI [24], this imbalance may have contributed to the Fisher group 4 findings. The cilostazol-adjusted OR of 3.12 (95% CI 0.97–10.75; $p = 0.061$) remained favorable to clazosentan but did not reach statistical significance, consistent with a directional signal in the context of a small and potentially confounded subgroup.

Safety Considerations

Safety is the central practical barrier to clazosentan use in underrepresented patients. Selective endothelin A receptor blockade may promote fluid retention and vascular permeability, which can manifest as pulmonary edema or brain edema [26]. Fluid retention has been reported early after clazosentan initiation and appears more common in elderly patients [1]. In RECOVER, early positive fluid balance was associated with clazosentan discontinuation and worse outcome, emphasizing that the treatment question is not simply whether clazosentan should be used, but whether the patient can be monitored and managed through the high-risk early period [14]. Decreased intraday variation in urine output may also serve as an early warning sign in elderly patients receiving clazosentan [16, 17]. In Fisher group 4, brain edema and intracranial pressure require particular attention because hematoma, intraventricular blood, hydrocephalus, and surgery may disrupt the blood-brain barrier [4, 19].

In the present analysis, clazosentan was not associated with a consistent excess of pulmonary complications, hypotension, brain edema, or de novo ICH. However, this finding should not be interpreted as proof of safety. Event counts were small, and CIs for rare events were wide. The numerical signal for de novo ICH in older patients, although not statistically significant, illustrates the need for careful surveillance rather than reassurance based on underpowered safety comparisons. Because these underrepresented subgroups are precisely the populations in which safety concerns motivate exclusion, and because each subgroup contained only 23 to 33 patients per arm, the absence of a detected safety signal should be regarded as hypothesis-generating rather than as evidence that clazosentan is safe in these patients. Accordingly, our data support reconsidering automatic avoidance, not relaxation of vigilance.

Clinical Implications

The clinically actionable message is not that every trial-ineligible patient should receive clazosentan. Rather, trial ineligibility should be distinguished from contraindication. Patients with Fisher group 4 or other high DCI-risk features may be considered for clazosentan when cardiopulmonary reserve, fluid balance, brain edema risk, liver function, and early monitoring capacity are acceptable. Conversely, fasudil remains a reasonable option when the risk of treatment intolerance predominates or close monitoring cannot be ensured. This framework may support bedside decision-making while preserving the exploratory nature of the evidence.

Limitations

This study has several limitations. First, treatment was not randomized, and treatment selection bias and unmeasured confounding cannot be completely eliminated. The sequential before-and-after design also leaves room for changes in background care, case mix, and discharge practice, because fasudil-treated patients were enrolled from April 2021 to March 2022 and clazosentan-treated patients from April 2023 to March 2024. Because this design deliberately compared a pre-availability period with a later period of established clazosentan use, the two periods differed mainly in the perioperative management of clazosentan-specific adverse effects—particularly fluid retention, which can offset the antivasospastic benefit of the drug—rather than in generic standards of aSAH care. The more favorable outcomes in the clazosentan period may therefore reflect that an optimized perioperative protocol minimized these intolerance-related complications and thereby allowed the strong vasospasm-prevention effect of clazosentan to translate into clinical benefit. Nevertheless, as a sequential observational comparison, residual temporal confounding cannot be excluded, and the principal interpretation of this study remains the more conservative one that trial exclusion criteria should not be treated as contraindications. Second, subgroup sample sizes were limited, confidence intervals were wide, interaction tests were underpowered, and rare safety events were particularly difficult to evaluate. Third, no correction for multiple comparisons was performed; therefore all subgroup findings should be interpreted as exploratory. Fourth, background imbalances were noted in some subgroups, including higher proportions of WFNS grade V (29.1% vs 15.7%; $p = 0.046$) and higher median Fisher group (4 vs 2; $p = 0.032$) in the fasudil arm of the Fisher group 1, 2, or 4 subgroup, as well as higher cilostazol use in the Fisher group 4 subgroup. Fifth, detailed safety-relevant information, including fluid balance, diuretic use, liver function changes, and intracranial pressure management, could not be adequately incorporated into the present analysis. Sixth, the primary endpoint was favorable outcome at discharge. The shorter median length of stay in the clazosentan cohort (28 vs 34 days overall; $p = 0.015$; 27 vs 33 days in the Fisher group 1, 2, or 4 subgroup; $p = 0.029$) may have influenced discharge mRS independently of treatment and limits comparison with studies evaluating 90-day outcomes. Seventh, the order of drug exposure in the 34 patients who received both agents was not captured, so the direction of potential exclusion bias could not be determined, although the tipping-point analysis bounded the overall favorable-outcome association. Eighth, angiographic vasospasm was assessed by comparing preoperative CTA with postoperative MRA, which may have introduced measurement variability. Finally, this study reflects

Japanese practice, in which fasudil has been the standard comparator; generalizability to settings where nimodipine is standard requires caution. Prospective randomized trials evaluating clazosentan are ongoing, and their results are awaited to provide more definitive evidence [15].

Conclusions

In this exploratory subgroup analysis of the RECOVER sequential cohort, clazosentan showed directionally favorable associations in patients aged ≥ 76 years, those with WFNS grade V, and those with Fisher group 4, and the broader Fisher group 1, 2, or 4 composite subgroup showed a significant favorable association. No consistent excess of major adverse events was observed, although safety events were sparse. These results suggest that age ≥ 76 years, WFNS grade V, or non-Fisher group 3 status alone should not mandate uniform avoidance of clazosentan. In other words, ineligibility for the pivotal trials should be interpreted as absence of trial evidence rather than as a contraindication. Individual benefit-risk assessment that considers the expected benefit of DCI prevention alongside treatment-intolerance risk may help identify patients in whom clazosentan can be attempted with close early monitoring versus those in whom fasudil may be the safer initial strategy.

Declarations

Competing Interests

The last author, Professor Ryuta Saito, received research funding from Nxera Pharma Japan, the distributor of clazosentan. However, Professor Saito was not involved in the planning or analysis of this study and contributed solely in a supervisory capacity. The other authors declare no competing interests related to this study.

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Competing interests: The last author, Professor Ryuta Saito, received research funding from Nxera Pharma Japan, the distributor of clazosentan. However, Professor Saito was not involved in the planning or analysis of this study and contributed solely in a supervisory capacity. The other authors declare no competing interests related to this study.

Ethics approval: This study was approved by the Institutional Review Board of Nagoya University Hospital (approval number: 2022 – 0476).

Consent to participate: The requirement for individual informed consent was waived, and an opt-out approach was used because only anonymized retrospective clinical data were analyzed.

Consent for publication: All authors have read and approved the final manuscript and consent to its publication.

Data availability: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contribution

YS and SM made substantial contributions to the conception and design of the study, analyzed and interpreted the data, and drafted a significant portion of the manuscript or figures. TI and IT made substantial contributions to the conception and design of the study and critically reviewed the manuscript. SG, MN, YS, SM, SO, TK, TA, OS, and the RECOVER Study Collaborators acquired clinical data and critically reviewed the manuscript. KN and BC analyzed and interpreted the data statistically and critically reviewed the manuscript. RS critically reviewed the manuscript and supervised the study.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

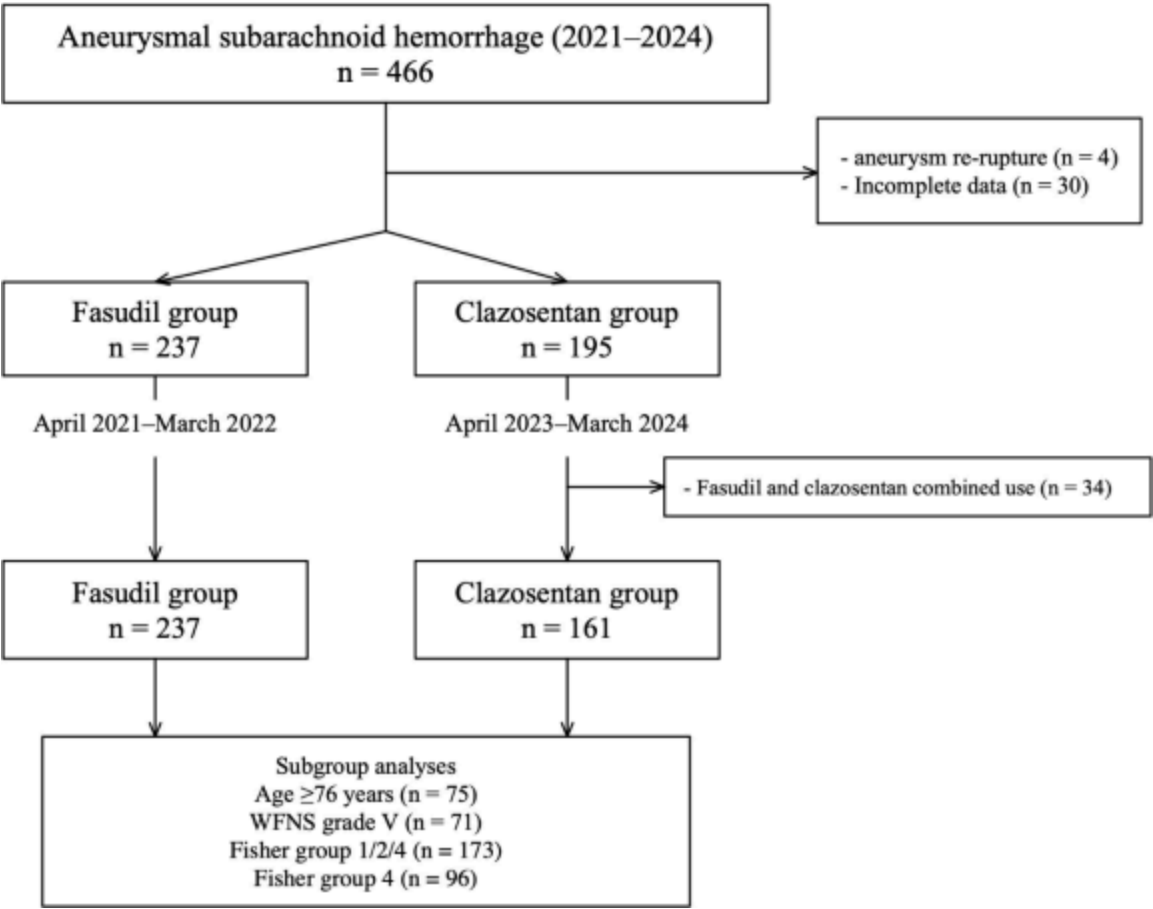


Figure 1

Study flow diagram. Among 466 patients with aneurysmal subarachnoid hemorrhage in RECOVER, 4 with aneurysm re-rupture, 30 with incomplete data, and 34 treated with both fasudil and clazosentan were excluded. The sequential comparative cohort comprised 237 fasudil-treated and 161 clazosentan-treated patients. Prespecified subgroups were age ≥ 76 years (n = 75), WFNS grade V (n = 71), Fisher group 1, 2, or 4 (n = 173), and Fisher group 4 (n = 96).

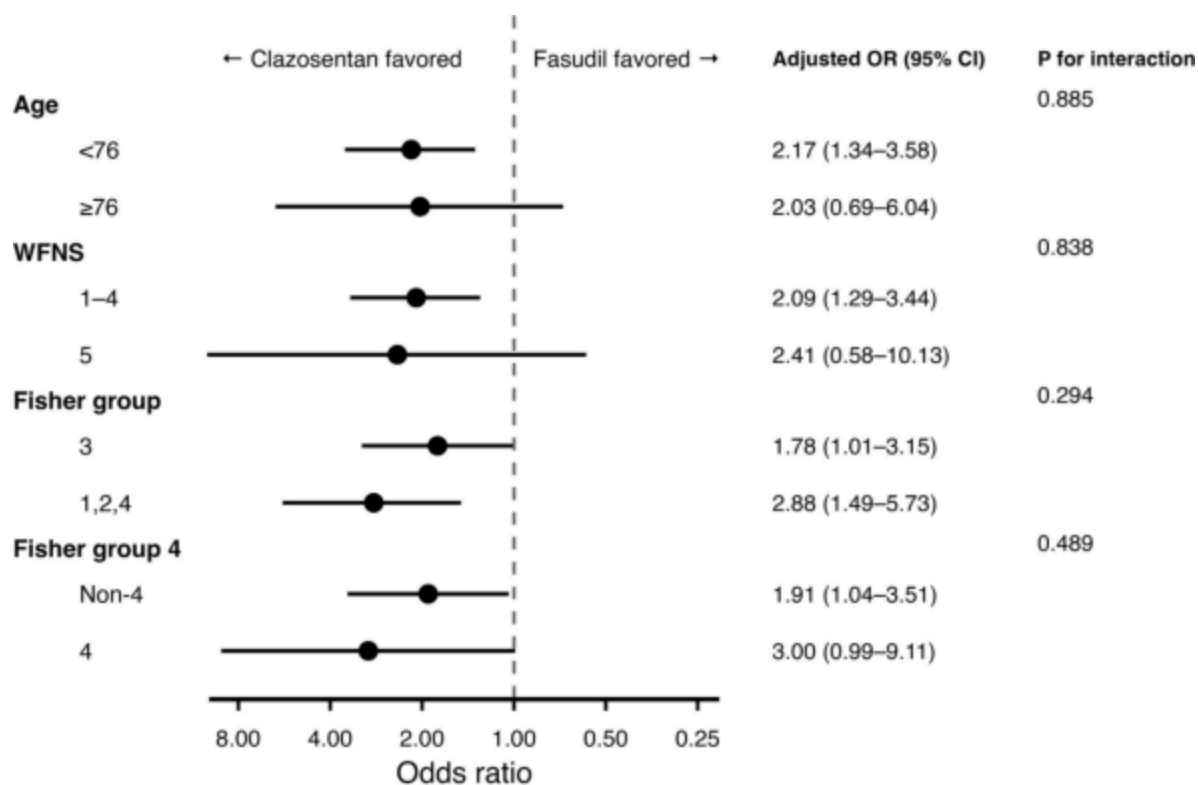


Figure 2

Stratified assessment of favorable outcome. Adjusted ORs and 95% CIs for the association between clazosentan and favorable discharge outcome are shown across age, WFNS grade, Fisher group, and Fisher group 4 strata in the overall cohort. Models were adjusted for sex, treatment modality, and CSF drainage. Interaction tests were underpowered; no statistically significant treatment-by-subgroup interaction was identified.

Supplementary Files

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