Title

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

Running title: Clazosentan outside Japanese pivotal criteria

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Online Resource Legends

Online Resource 1. Baseline characteristics in the age ≥76 years subgroup.

Online Resource 1. Baseline characteristics in the age ≥76 subgroup

	Clazosentan (n=25)	Fasudil (n=50)	P value
Women, n (%)	20 (80.0%)	43 (86.0%)	0.519
Age, mean ± SD, years	79.4 ± 3.1	81.1 ± 4.2	0.051
≥76 years, n (%)	25 (100.0%)	50 (100.0%)	
WFNS classification			
Median [IQR]	3.0 [3.0–4.0]	4.0 [2.0–4.0]	0.852
Grade V, n (%)	2 (8.0%)	10 (20.0%)	0.316
Fisher classification			
Median [IQR]	3.0 [3.0–4.0]	3.0 [3.0–3.0]	0.462
Fisher group 1,2,4, n (%)	10 (40.0%)	15 (30.0%)	0.441
Fisher group 4, n (%)	7 (28.0%)	9 (18.0%)	0.375
Anterior aneurysm site, n (%)	22 (88.0%)	45 (90.0%)	>0.999
Intervention			
EVT, n (%)	11 (44.0%)	17 (34.0%)	0.453
CSF drainage, n (%)	14 (56.0%)	26 (52.0%)	>0.999
Length of stay, median [IQR], days	32.0 [26.8–44.0]	42.0 [29.0–55.0]	0.196
Concomitant medications			
Cilostazol, n (%)	13 (52.0%)	28 (56.0%)	0.808
Statin, n (%)	13 (52.0%)	26 (52.0%)	>0.999

EVT=endovascular treatment.

Online Resource 2. Baseline characteristics in the WFNS grade V subgroup.

Online Resource 2. Baseline characteristics in the WFNS grade V subgroup

	Clazosentan (n=23)	Fasudil (n=48)	P value
Women, n (%)	17 (73.9%)	31 (64.6%)	0.589
Age, mean ± SD, years	62.5 ± 12.7	65.7 ± 11.6	0.309
≥76 years, n (%)	2 (8.7%)	10 (20.8%)	0.313
WFNS classification			
Median [IQR]	5.0 [5.0–5.0]	5.0 [5.0–5.0]	
Grade V, n (%)	23 (100.0%)	48 (100.0%)	
Fisher classification			
Median [IQR]	3.0 [3.0–4.0]	4.0 [3.0–4.0]	0.695
Fisher group 1,2,4, n (%)	11 (47.8%)	30 (62.5%)	0.307
Fisher group 4, n (%)	11 (47.8%)	27 (56.2%)	0.613
Anterior aneurysm site, n (%)	14 (60.9%)	33 (68.8%)	0.595
Intervention			
EVT, n (%)	7 (30.4%)	20 (41.7%)	0.598
CSF drainage, n (%)	19 (82.6%)	31 (64.6%)	0.172
Length of stay, median [IQR], days	39.0 [33.0–57.5]	45.0 [31.0–58.0]	0.746
Concomitant medications			
Cilostazol, n (%)	17 (73.9%)	27 (56.2%)	0.195
Statin, n (%)	12 (52.2%)	25 (52.1%)	>0.999

EVT=endovascular treatment.

Online Resource 3. Baseline characteristics in the Fisher group 1, 2, 4 subgroup.

Online Resource 3. Baseline characteristics in the Fisher group 1,2,4 subgroup

	Clazosentan (n=70)	Fasudil (n=103)	P value
Women, n (%)	48 (68.6%)	58 (56.3%)	0.114
Age, mean ± SD, years	61.1 ± 12.4	63.2 ± 12.9	0.288
≥76 years, n (%)	10 (14.3%)	15 (14.6%)	>0.999
WFNS classification			
Median [IQR]	2.0 [1.0–4.0]	3.0 [1.5–5.0]	0.061
Grade V, n (%)	11 (15.7%)	30 (29.1%)	0.046
Fisher classification			
Median [IQR]	2.0 [2.0–4.0]	4.0 [2.0–4.0]	0.032
Fisher group 1,2,4, n (%)	70 (100.0%)	103 (100.0%)	
Fisher group 4, n (%)	33 (47.1%)	63 (61.2%)	0.086
Anterior aneurysm site, n (%)	53 (75.7%)	83 (80.6%)	0.456
Intervention			
EVT, n (%)	23 (32.9%)	34 (33.0%)	>0.999
CSF drainage, n (%)	31 (44.3%)	49 (47.6%)	0.876
Length of stay, median [IQR], days	27.0 [20.0–38.0]	33.0 [21.5–48.0]	0.029
Concomitant medications			
Cilostazol, n (%)	41 (58.6%)	60 (58.3%)	>0.999
Statin, n (%)	39 (55.7%)	53 (51.5%)	0.644

EVT=endovascular treatment.

Online Resource 4. Baseline characteristics in the Fisher group 4 subgroup.

Online Resource 4. Baseline characteristics in the Fisher group 4 subgroup

	Clazosentan (n=33)	Fasudil (n=63)	P value
Women, n (%)	22 (66.7%)	34 (54.0%)	0.279
Age, mean ± SD, years	64.3 ± 13.0	65.8 ± 11.6	0.585
≥76 years, n (%)	7 (21.2%)	9 (14.3%)	0.401
WFNS classification			
Median [IQR]	4.0 [3.0–5.0]	4.0 [3.0–5.0]	0.507
Grade V, n (%)	11 (33.3%)	27 (42.9%)	0.389
Fisher classification			
Median [IQR]	4.0 [4.0–4.0]	4.0 [4.0–4.0]	
Fisher group 1,2,4, n (%)	33 (100.0%)	63 (100.0%)	
Fisher group 4, n (%)	33 (100.0%)	63 (100.0%)	
Anterior aneurysm site, n (%)	24 (72.7%)	49 (77.8%)	0.620
Intervention			
EVT, n (%)	9 (27.3%)	13 (20.6%)	0.447
CSF drainage, n (%)	18 (54.5%)	36 (57.1%)	>0.999
Length of stay, median [IQR], days	36.0 [29.2–52.5]	43.0 [31.5–56.5]	0.185
Concomitant medications			
Cilostazol, n (%)	25 (75.8%)	29 (46.0%)	0.009
Statin, n (%)	19 (57.6%)	28 (44.4%)	0.286

EVT=endovascular treatment.

Online Resource 5. Characteristics and outcomes of the 34 combined-use patients.

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	Combined-use patients (n=34)
Baseline characteristics	
Women, n (%)	27 (79.4%)
Age, mean ± SD, years	62.5 ± 14.1
≥76 years, n (%)	6 (17.6%)
WFNS Grade V, n (%)	6 (17.6%)
Fisher group 4, n (%)	9 (26.5%)
Anterior aneurysm site, n (%)	29 (85.3%)
Intervention	
EVT, n (%)	11 (32.4%)
CSF drainage, n (%)	22 (64.7%)
Length of stay, median [IQR], days	34 [28–50]
Cilostazol use, n (%)	32 (94.1%)
Outcomes	
Favorable outcome (mRS 0–2), n (%)	23 (67.6%)
Mortality at discharge, n (%)	0 (0.0%)
Vasospasm-related DCI, n (%)	3 (8.8%)
Angiographic vasospasm >25%, n (%)	12 (35.3%)
Brain edema, n (%)	7 (20.6%)
Pulmonary complication, n (%)	6 (17.6%)
Hypotension, n (%)	1 (2.9%)
De novo ICH, n (%)	2 (5.9%)

EVT=endovascular treatment; DCI=delayed cerebral ischemia; ICH=intracranial hemorrhage.

Online Resource 6. Outcomes in the overall comparative cohort.

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	Clazosentan (n=161)	Fasudil (n=237)	P value	Adjusted OR (95% CI)	Adjusted P value
Favorable outcome (mRS 0–2)	107 (66.5%)	115 (48.5%)	<0.001	2.08 (1.23–3.57)	0.007
Mortality at discharge	4 (2.5%)	11 (4.6%)	0.299	0.69 (0.18–2.15)	0.541
Vasospasm-related DCI	5 (3.1%)	25 (10.6%)	0.006	0.28 (0.09–0.73)	0.016
Angiographic vasospasm >25%	22 (13.7%)	79 (33.3%)	<0.001	0.31 (0.17–0.52)	<0.001
Brain edema	11 (6.8%)	26 (11.1%)	0.164	0.64 (0.26–1.48)	0.306
Pulmonary complication	9 (5.6%)	12 (5.1%)	0.823	1.36 (0.49–3.62)	0.542
Hypotension	4 (2.5%)	3 (1.3%)	0.448	1.75 (0.31–9.92)	0.506
De novo ICH	5 (3.1%)	6 (2.5%)	0.762	1.07 (0.26–3.89)	0.922

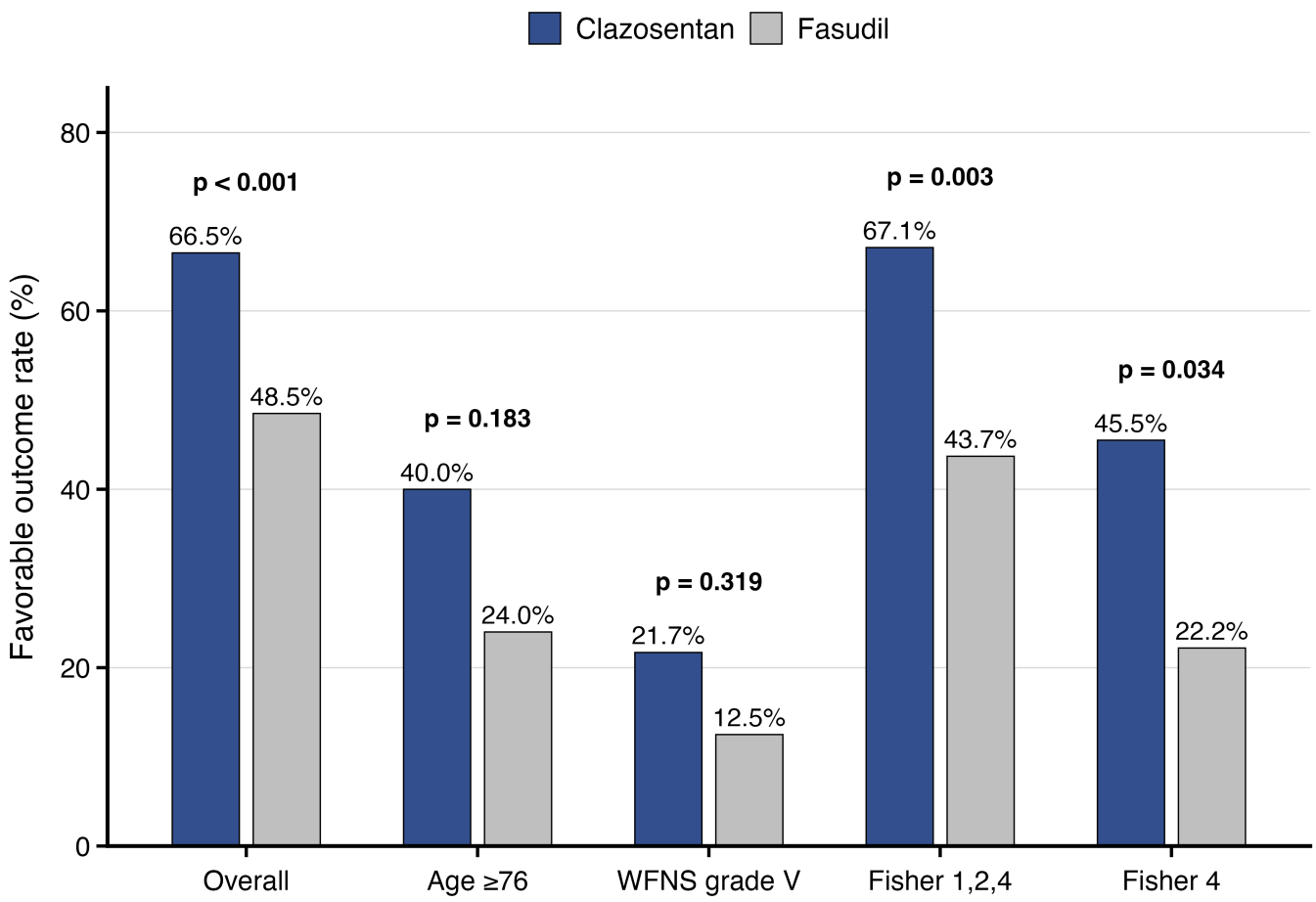
CI=confidence interval; DCI=delayed cerebral ischemia; ICH=intracranial hemorrhage.
Adjusted models included age, WFNS grade, Fisher group, endovascular treatment, and CSF drainage.
MLE: Favorable outcome (mRS 0–2), Mortality at discharge, Vasospasm-related DCI, Angiographic vasospasm >25%, Brain edema, Pulmonary complication, Hypotension, De novo ICH.

Online Resource 7. Tipping-point sensitivity analysis for favorable outcome.

Online Resource 7. Tipping-point sensitivity analysis for favorable outcome

	Unadjusted OR (95% CI)	Unadjusted P value	Adjusted OR (95% CI)	Adjusted P value
All 34 combined-use patients assigned to clazosentan	2.12 (1.44–3.15)	<0.001	2.20 (1.36–3.62)	0.002
All 34 combined-use patients assigned to fasudil	1.91 (1.28–2.87)	0.002	1.80 (1.09–3.00)	0.023

Online Resource 8. Favorable outcome by subgroup.



Bar graph showing the proportion of patients with favorable outcome, defined as a discharge modified Rankin Scale score of 0–2, in the clazosentan and fasudil groups across the overall cohort and prespecified subgroups. Favorable outcome was more frequent in the clazosentan group than in the fasudil group in the overall cohort (66.5% vs 48.5%, $p < 0.001$), the Fisher group 1/2/4 subgroup (67.1% vs 43.7%, $p = 0.003$), and the Fisher group 4 subgroup (45.5% vs 22.2%, $p = 0.034$). In the age ≥76 years and WFNS grade V subgroups, the favorable outcome rate was numerically higher in the clazosentan group, but the differences were not statistically significant. WFNS = World Federation of Neurosurgical Societies.