JOURNAL CLUB : RETEPLASE VERSUS ALTEPLASE FOR ACUTE ISCHEMIC STROKE

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INTRODUCTION

- Reperfusion therapy is an evidence based intervention for ischemic stroke.
- Intravenous alteplase is the internationally approved standard thrombolytic agent for acute ischemic stroke within 4.5 hours after symptom onset.
- Recent studies have shown that Tenecteplase, a genetically modified form of alteplase given as a single bolus, delivers clinical benefits similar to those of alteplase.
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- The demand for intravenous thrombolysis in acute ischemic stroke has increased substantially with the continuous improvement in the quality of stroke care. From 2015 to 2019, the use of intravenous thrombolysis grew by 60.3%, reaching 22.9% among patients treated within 4.5 hours after symptom onset.

- Reteplase is a rPA characterized by a double-bolus approach (the boluses are separated by 30 minutes) with a fixed dose regimen. Reteplase was approved for the treatment of acute MI in many countries.

- A metanalysis of reteplase with alteplase in patients of acute MI showed no differences between the two in terms of mortality or the incidence of disabling stroke.

- In a phase 2, randomized, controlled trial, the proportion of patients with an excellent functional outcome was higher with two 18-mg doses of reteplase than with two 12-mg doses or with alteplase at a dose of 0.9 mg per kilogram of body weight, and the higher dose of reteplase was not associated with an increased risk of fatal bleeding.

- In these study Reteplase versus Alteplase for Acute Ischemic Stroke (RAISE) trial to compare reteplase at a double-bolus dose of 18 mg plus 18 mg (with a 30-minute interval) and standard alteplase with respect to the functional outcome in patients with acute ischemic stroke who were eligible for intravenous thrombolysis .

- The RAISE trial was a phase 3, multicenter, prospective, open-label, noninferiority, randomized trial with blinded end-point assessment; the trial was conducted at 62 sites in China.

- The open-label design was implemented because of the unavailability of placebo and to avoid potential delay in the administration of thrombolytic agents.

- Intracranial hemorrhage, other clinically significant hemorrhage events, and death from any cause were evaluated by an independent clinical event committee whose members were unaware of the trial-group assignments. Local investigators vouched for the accuracy and completeness of the other serious adverse events.

- Trial patient :

- Patients eligible were 18 to 80 years of age, could receive intravenous thrombolysis within 4.5 hours after the time that they had last been known to be well, had excellent functional status before the onset of their stroke (defined by a score of ≤1 on the modified Rankin scale, with scores ranging from 0 [no neurologic deficit, no symptoms, or completely recovered] to 6 [death]).

- Ischemic stroke is typically diagnosed by means of non contrast computed tomography or magnetic resonance imaging in patients with symptoms of neurologic impairment. Patients were excluded from participation if they had previously undergone or were planned to undergo endovascular thrombectomy.

- Eligible patients were randomly assigned in a 1:1 ratio to receive intravenous reteplase or intravenous alteplase.

- The intravenous thrombolytic treatment was conducted in an open-label manner. Reteplase was given as two intravenous 18-mg bolus doses, each administered over a period of 2 minutes; the first dose was administered immediately after randomization and the second 30 minutes later.
- Alteplase was administered at a dose of 0.9 mg per kilogram (maximum dose, 90 mg), with 10% of the dose delivered as a bolus within 1 minute; the remaining dose was infused intravenously during the subsequent 60 minutes.
- All other treatments followed standard practice for the management of ischemic stroke.

- The primary efficacy outcome was an excellent functional outcome, defined as a modified Rankin scale score of 0 or 1 at 90 days. The secondary efficacy outcomes included a good functional outcome defined as a modified Rankin scale score of 0 to 2 at 90 days .

- National Institutes of Health Stroke Scale (NIHSS) score of 4 to 25 (range, 0 [no neurologic deficit] to 42 [death]). Early dramatic recovery with respect to the NIHSS score (defined as a decrease of ≥4 points or a score of ≤1 at 24 hours and at 7 days) .

- And a Barthel Index score of at least 95 (range, 0 to 100, with higher scores indicating better independent function) at 90 days.

- The clinical assessments were conducted at 30 days and 90 days by neurologists who were unaware of the trial-group assignments and who had received specialized training and certification.

- The modified Rankin scale score at 90 days was obtained either through face-to-face interviews or telephone conversations.

- The clinical event committee adjudicated the end-point events on the basis of clinical symptoms, laboratory tests, and imaging data. Adverse events and serious adverse events were classified according to standardized terminology

Table 1. Baseline Characteristics of the Patients in the Intention-to-Treat Population.*

Characteristic	Reteplase (N = 707)	Alteplase (N = 705)
Age		
Median (IQR) — yr	63 (56–70)	63 (56–70)
Distribution — no. (%)		
18–60 yr	294 (41.6)	299 (42.4)
>60 yr	413 (58.4)	406 (57.6)
Sex — no. (%)		
Female	199 (28.1)	217 (30.8)
Male	508 (71.9)	488 (69.2)
Asian race — no. (%)†	707 (100)	705 (100)
Median weight (IQR) — kg	68.7 (60.0–75.0)	67.5 (60.0–75.0)
Coexisting conditions — no. (%)		
Hypertension	531 (75.1)	525 (74.5)
Diabetes	188 (26.6)	167 (23.7)
Hyperlipidemia	279 (39.5)	294 (41.7)
Coronary heart disease	176 (24.9)	183 (26.0)
Arrhythmia‡	94 (13.3)	111 (15.7)

NIHSS score at admission§		
Median (IQR)	6 (5–8)	6 (5–8)
Distribution — no. (%)§		
4–7	462 (65.3)	471 (66.8)
>7	245 (34.7)	234 (33.2)
Modified Rankin scale score before indexed stroke — no. (%)¶		
0	660 (93.4)	640 (90.8)
1 or 2‖	47 (6.6)	65 (9.2)
Time from symptom onset to administration of reteplase or alteplase**		
Median (IQR) — min	180 (131–221)	183 (139–222)
Distribution — no./total no. (%)		
<3 hr	330/700 (47.1)	329/699 (47.1)
≥3 hr	370/700 (52.9)	370/699 (52.9)
Median time from arrival in emergency department to administration of reteplase or alteplase (IQR) — min**	59 (37–82)	60 (39–85)

Table 2. Primary and Secondary Efficacy Outcomes.*

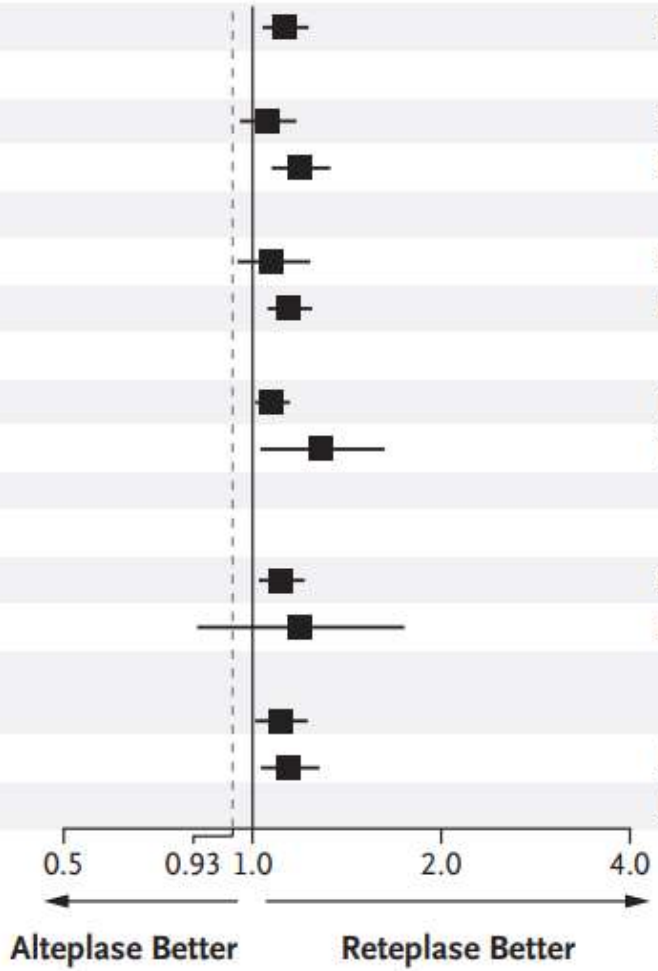
Outcome	Reteplase (N=707)	Alteplase (N=705)	Risk Ratio or Common Odds Ratio (95% CI)	Risk Difference (95% CI)
				percentage points
Primary outcome				
Modified Rankin scale score of 0 or 1 at 90 days — no. (%)	562 (79.5)	496 (70.4)	1.13 (1.05–1.21)	9.4 (3.3–15.4)
Secondary outcomes				
Modified Rankin scale score of 0–2 at 90 days — no. (%)	603 (85.3)	563 (79.8)	1.07 (1.02–1.12)	5.8 (1.8–9.8)
Median modified Rankin scale score at 90 days (IQR)	0 (0–1)	1 (0–2)	0.61 (0.27–0.95)†	
Ordinal distribution of the modified Rankin scale score at 90 days — no. (%)				
0	381 (53.9)	292 (41.4)		
1	181 (25.6)	204 (29.0)		
2	41 (5.8)	67 (9.4)		
3	38 (5.3)	63 (9.0)		
4	26 (3.7)	43 (6.1)		
5	7 (0.9)	9 (1.2)		
6	34 (4.7)	27 (3.8)		
Early dramatic recovery at 24 hr — no. (%)‡	411 (58.1)	340 (48.2)	1.21 (1.05–1.36)	10.0 (1.9–18.2)
Early dramatic recovery at 7 days — no. (%)‡	519 (73.5)	469 (66.5)	1.10 (1.02–1.19)	7.0 (1.2–12.8)
Barthel Index score of ≥95 at 90 days — no. (%)§	580 (82.0)	537 (76.2)	1.08 (1.02–1.13)	6.3 (2.0–10.5)

DISCUSSION

- The RAISE trial showed that intravenous reteplase was noninferior to intravenous alteplase in achieving an excellent functional outcome.
- The percentage of patients with an excellent functional outcome at 90 days was higher by 9.4 percentage points with reteplase than with alteplase.
- No significant between-group difference was observed regarding the incidence of symptomatic intracranial hemorrhage, and mortality did not differ substantially between the two groups.
- We observed a higher incidence of any intracranial hemorrhage and adverse events at 90 days in the reteplase group than in the alteplase group.

DISCUSSION

Subgroup	No. of Patients	Reteplase	Alteplase	Risk Ratio (95% CI)
		no. of patients with event/no. of patients (%)		
Overall	1412	562/707 (79.5)	496/705 (70.4)	1.13 (1.05–1.21)
Age				
18–60 yr	593	248/294 (84.2)	238/299 (79.5)	1.06 (0.97–1.15)
>60 yr	819	315/413 (76.2)	259/406 (63.7)	1.20 (1.10–1.29)
Sex				
Female	416	148/199 (74.5)	150/217 (69.0)	1.08 (0.94–1.22)
Male	996	414/508 (81.5)	347/488 (71.0)	1.15 (1.07–1.22)
NIHSS score at admission				
4–7	933	390/462 (84.5)	370/471 (78.5)	1.08 (1.02–1.13)
>7	479	172/245 (70.1)	127/234 (54.2)	1.29 (1.07–1.51)
Score on modified Rankin scale before indexed stroke				
0	1300	538/660 (81.6)	469/640 (73.3)	1.11 (1.04–1.19)
1 or 2	112	24/47 (50.5)	27/65 (42.2)	1.20 (0.82–1.58)
Time from symptom onset to administration of reteplase or alteplase				
<3 hr	665	268/334 (80.4)	240/331 (72.4)	1.11 (1.03–1.20)
≥3 hr	747	294/373 (78.8)	257/374 (68.6)	1.15 (1.05–1.25)



DISCUSSION

- The potential advantages inherent in reteplase lie in its favorable trade-off between efficacy and the risk of fatal bleeding.

- The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) trial18 and the Reteplase versus Alteplase Patency Investigation during Acute Myocardial Infarction (RAPID II) trial16 showed that reteplase had an efficacy similar to that of alteplase among patients with acute myocardial infarction, with no significant differences in outcomes with respect to death or hemorrhagic stroke.

- these trial showed that reteplase was superior to alteplase in improving patients’ functional outcomes without increasing the incidence of symptomatic intracranial hemorrhage and death among eligible patients with acute ischemic stroke.

- In addition, the percentage of patients who had an early dramatic recovery with respect to the NIHSS score at 24 hours was higher by 10 percentage points with reteplase than with alteplase.

- The mechanism underlying the benefits of reteplase may involve a higher incidence of recanalization. There were safety concerns for reteplase in terms of any intracranial hemorrhage, clinically relevant non massive hemorrhage, and overall adverse events.

- In the current trial, we observed a higher percentage of patients with an excellent functional outcome in both the reteplase and alteplase groups than in previous trials, including the Tenecteplase .

- This difference may be attributed to a higher prevalence of atherothrombosis than embolus among Asian patients along with the relatively younger age and lower NIHSS scores (reflecting mostly mild strokes) at admission in our trial — all factors that strongly predict better functional outcomes for the patients.

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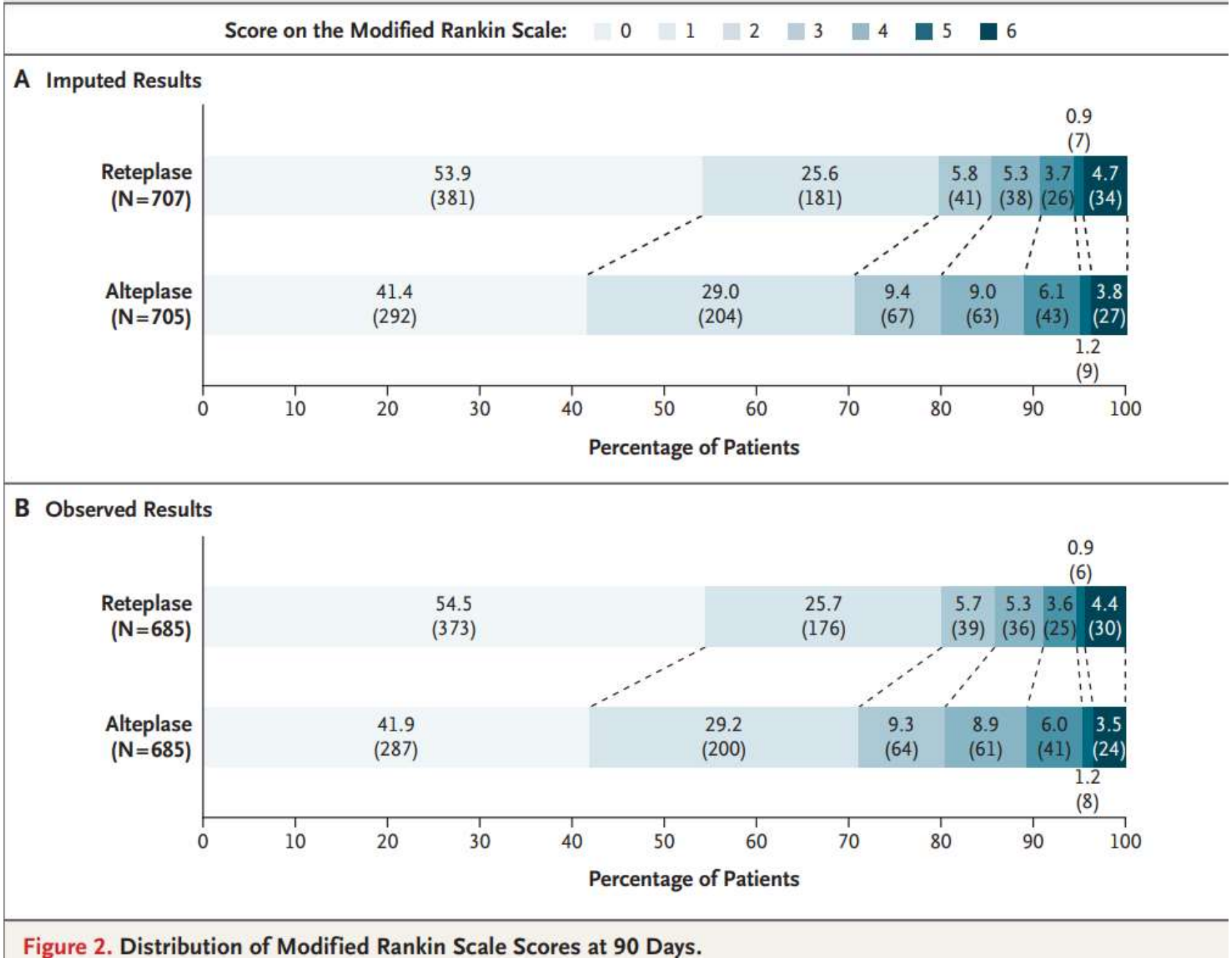

Figure 2. Distribution of Modified Rankin Scale Scores at 90 Days.

◦ **Safety outcome :**

Table 3. Safety Outcomes.*

Outcome	Reteplase (N=700)	Alteplase (N=699)	Risk Ratio (95% CI)
	no. of patients (%)		
Primary safety outcome			
Symptomatic intracranial hemorrhage within 36 hr†	17 (2.4)	14 (2.0)	1.21 (0.54–2.75)
Secondary safety outcomes			
Symptomatic intracranial hemorrhage within 7 days†	17 (2.4)	15 (2.1)	1.13 (0.52–2.44)
Parenchymal hemorrhage type 2 within 36 hr‡	12 (1.7)	10 (1.4)	1.20 (0.36–4.03)
Any intracranial hemorrhage within 90 days§	54 (7.7)	34 (4.9)	1.59 (1.00–2.51)
Major hemorrhage within 90 days§	23 (3.3)	21 (3.0)	1.09 (0.65–1.85)
Clinically relevant nonmassive hemorrhage within 90 days§	38 (5.4)	17 (2.4)	2.23 (1.03–4.84)
Death within 90 days	30 (4.3)	24 (3.4)	1.25 (0.66–2.35)
Death within 7 days	11 (1.6)	11 (1.6)	1.00 (0.35–2.83)
Any adverse event	641 (91.6)	576 (82.4)	1.11 (1.03–1.20)
Serious adverse event	105 (15.0)	83 (11.9)	1.26 (0.99–1.61)

- Previous studies have investigated the bolus administration regimens of reteplase in patients with acute myocardial infarction. By the integration of pharmacokinetic–pharmacodynamic analysis with clinical findings, double-bolus administration has been shown to increase the incidence of successful reperfusion and reduce the incidence of early re-thrombosis as compared with single bolus .

- The safety profile of single-bolus and double-bolus administration regimens remains consistent .

- Women were less represented than men in this trial. Therefore, the findings may not be generalizable to other patient populations.

THANK YOU