E   A   b P I   A   l   A
A   N   F   P   W A I   S

The ARAIS Randomized Clinical Trial

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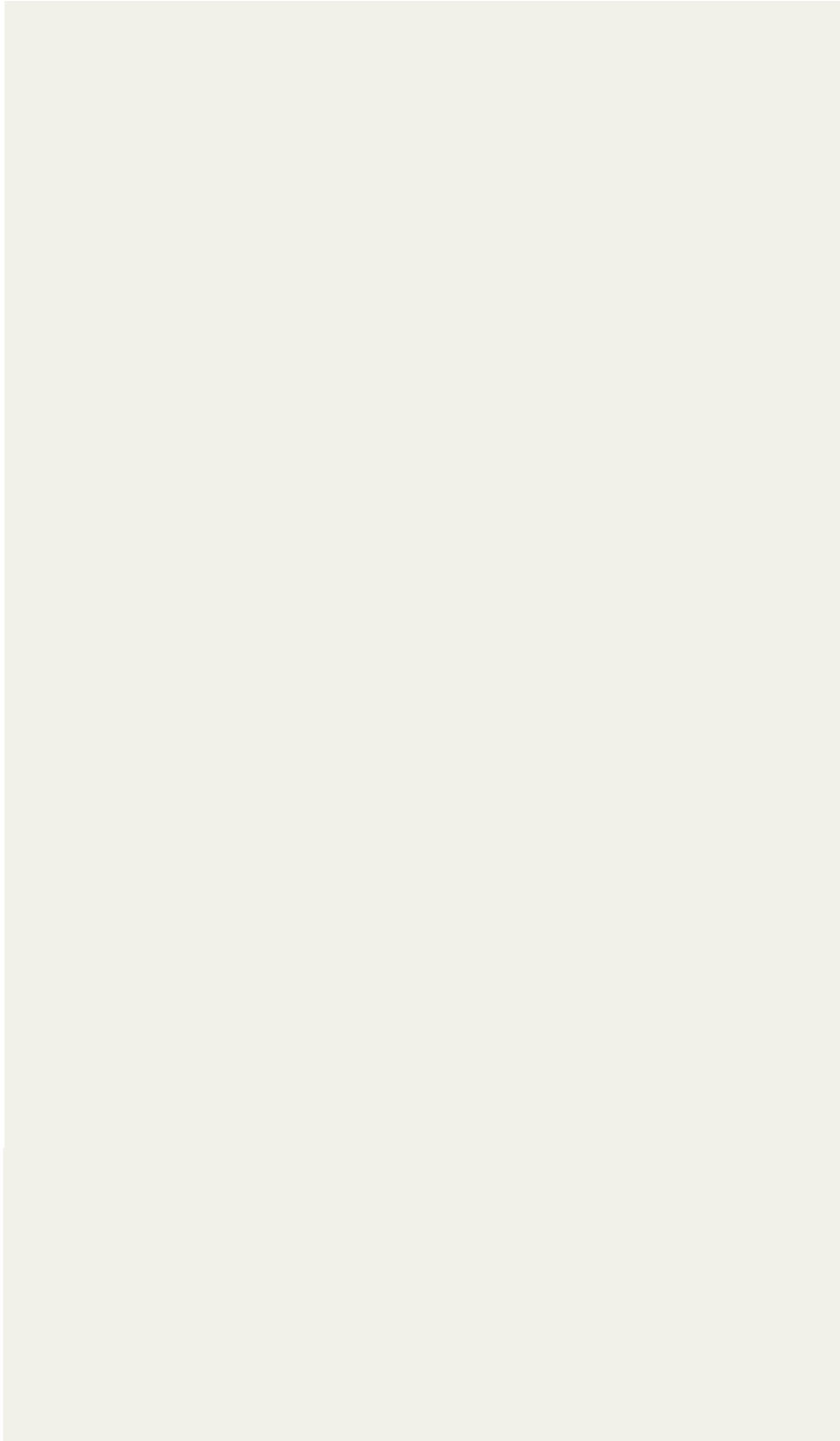
Current guidelines recommend reperfusion therapies, such as intravenous thrombolysis and endovascular thrombectomy, as the most effective strategies for management of acute ischemic stroke (AIS). Vessel recanalization was strongly associated with lower mortality and improved functional outcome of reperfusion therapies in patients with AIS. However, only   % of patients achieved complete recanalization through intravenous thrombolysis, while approximately   % of patients with large artery occlusion did not achieve successful reperfusion after endovascular thrombectomy. Although endovascular therapy has been shown to be effective in AIS with large artery occlusion, its use in clinical practice was limited due to a reliance on device availability and experienced clinicians. In addition,   % to   % of the population with initial recanalization underwent reocclusion after alteplase (recombinant tissue-type plasminogen activator) thrombolysis and had clinical deterioration and poor outcomes. · Thus, an effective and simple method is needed to improve vessel recanalization, prevent reocclusion, and reduce AIS disability.

Argatroban, a selective thrombin inhibitor, directly inhibits free and clot-associated thrombin as well as thrombin-induced events and has been widely used to treat AIS, particularly in Asian countries such as China and Japan. · Growing evidence from preclinical studies demonstrated the effect of argatroban plus alteplase in ischemic stroke by enhancing and sustaining arterial recanalization. ·
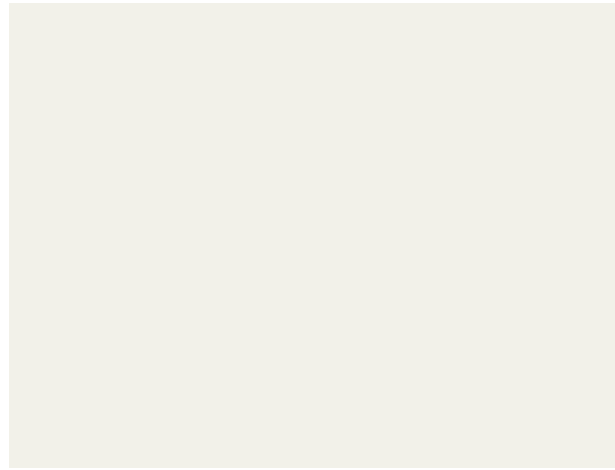
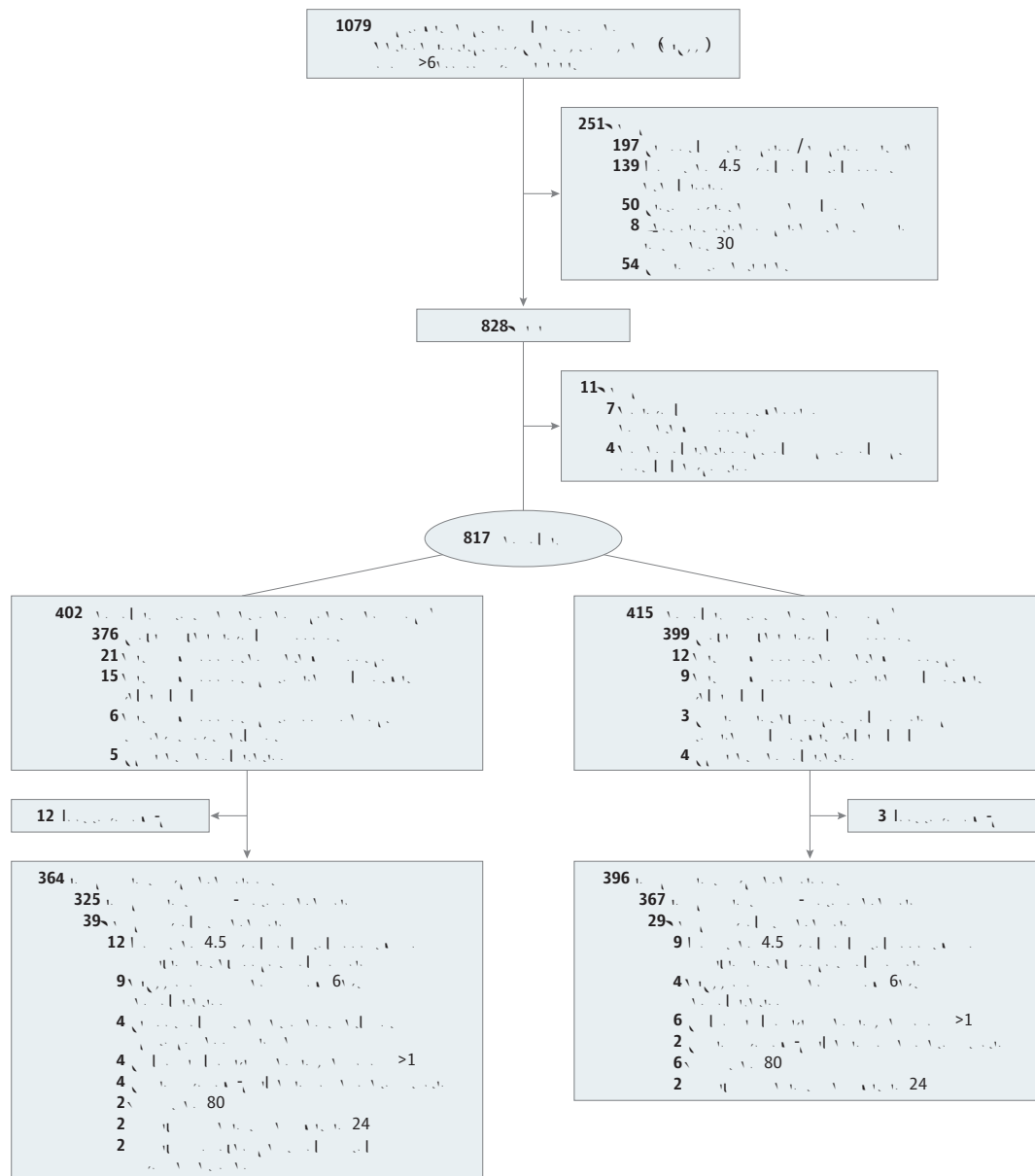based on current guidelines were also received by the patients in both groups.

Argatroban infusion rates were adjusted to achieve a target activated partial thromboplastin time (APTT) of . × baseline (± %). A dosing algorithm was developed so that standardized increments or decrements of argatroban infusion rate took place in response to the APTT. APTT was monitored at baseline and at , , , , and hours after initiation of argatroban; within to hours of any argatroban infusion adjustment; and in the event of major systemic bleeding. Argatroban infusion was terminated immediately if major systemic bleeding or symptomatic intracranial hemorrhage was suspected.

The NIHSS was used to assess neurologic status at baseline, hours, hours, days, and days after randomization. A detailed flowchart of the assessment schedule is provided in the study protocol (Supplement). Data on demographic and clinical characteristics were obtained at randomization. Follow-up data were collected at days, days (or at

alteplase and alteplase alone groups. The time-to-event outcomes of stroke or other vascular events were compared using Cox regression models, and the corresponding treatment effects were presented as hazard ratios with   % CIs. The hazard proportionality assumption was tested by introducing an interaction between time and treatment in the Cox model.

The primary analyses of the primary and secondary outcomes were unadjusted. Covariate-adjusted GLM analyses were also performed for all outcomes, adjusting for   pre-specified prognostic factors: age, sex, NIHSS score at randomization, time from symptom onset to thrombolysis, pre-morbid function (mRS score of   or   ), and history of stroke or transient ischemic attack. Endovascular therapy and large artery occlusion were planned in the covariate-adjusted analyses but were excluded due to skewed distribution or large peru.2(pec [(Co)24.ec [(Co8sl24.ec [(Co8sl24.ec [(o8sl24.ec [(o8sd9(varia)98sd9(varibo280.1(th8sdessio68sdessio6b..Salu(and)o6b..)-pec ..

Figure 1. P   F   ARAIS R   C   T

1079

251
197
139   4.5
50
8
30
54

828

11
7
4

817

402
376
21
15
6
5

415
399
12
9
3
4

12

3

364
325
39
12   4.5
9   6
4
4   >1
4
2   80
2   24
2

396
367
29
9   4.5
4   6
6   >1
2
6   80
2   24

[a] A total of 383 patients in the argatroban plus alteplase group and 397 patients in the alteplase group were included in the safety population.

[b] Patients lost to follow-up due to missing any follow-up assessments after treatment.

[c] Baseline characteristics in patients missing primary outcome data are shown in eTable 4 in Supplement 3.

per-protocol analyses (eTable in Supplement). A post hoc ordinal logistic regression analysis showed no significant differences in the mRS score improvement at days, in which the proportional odds assumption was met ($P = .$; Table and eTable in Supplement).

A prespecified subgroup analysis showed no evidence of effect modification in the risks of having a primary outcome between the argatroban plus alteplase and alteplase alone groups by age, sex, NIHSS score at randomization, endovascular therapy, large artery occlusion, time from the onset of symptoms to treatment, mRS score at admission, and history of stroke or transient ischemic attack (eFigure in Supplement). The results of the per-protocol analysis were similar to those of the full analysis set population for the primary outcome (eFigure in Supplement).

A   B

The occurrence of adverse events was similar across the groups, including symptomatic intracranial hemorrhage, other intracranial bleeding events, major bleeding events, other

Table 1.B. C... P... S... E... A... b... P... A... A... N... F... A... A... I... S...

Characteristic	No. (%)			
	Full analysis set		Randomization set	
	Argatroban plus alteplase (n = 364)	Alteplase alone (n = 396)	Argatroban plus alteplase (n = 402)	Alteplase alone (n = 415)
...	66 (58-72)	64 (56-71)	66 (58-72)	64 (56-71)
...				
...	249 (68.4)	289 (73.0)	271/397 (68.3)	299/411 (72.7)
...	115 (31.6)	107 (27.0)	126/397 (31.7)	112/411 (27.3)
...	131 (36.0)	141 (35.6)	141/396 (35.6)	143/411 (34.8)
...	69/354 (19.5)	69/389 (17.7)	73/386 (18.9)	69/404 (17.1)
...				
...	203 (55.8)	223 (56.3)	216/397 (54.4)	232/411 (56.4)
...	91 (25.0)	81 (20.5)	100/397 (25.2)	87/410 (21.2)
...	74 (20.3)	68 (17.2)	82/397 (20.7)	74/411 (18.0)
...	18/346 (5.2)	21/378 (5.6)	19/365 (5.2)	22/388 (5.7)
...	3 (0.8)	3 (0.8)	3/397 (0.8)	4/411 (1.0)
...	3 (0.8)	4 (1.0)	3/397 (0.8)	5/411 (1.2)
...	22.9 (21.0-24.0)	23.7 (21.0-24.0)	22.7 (20.1-24.0)	23.5 (21.0-24.0)
...				
...				
...	154 (139-170)	150 (136-166)	152 (138-170)	150 (136-165)
>140 ...	242 (66.5)	250 (63.1)	257/397 (64.7)	250/411 (60.8)
...				
...	90 (80-98)	88 (80-97)	90 (80-98)	88 (80-97)
>90 ...	142 (39.0)	142 (35.9)	151/397 (38.0)	145/411 (35.3)
...				
...	118.8 (102.8-164.0)	121.0 (102.6-160.7)	120.8 (102.6-162.2)	120.6 (102.6-163.8)
>126 ...	128/293 (43.7)	143/324 (44.1)	144/321 (44.9)	150/335 (44.8)
...	9 (7-12)	8 (6-12)	9 (7-12)	9 (6-12)
...	75 (71-79)	74 (70-78)	75 (71-79)	74 (70-78)
... 8152				

bleeding events, and other most common adverse events be-
tween the   groups (**Table 3**

Figure 2. Distribution of Modified Rankin Scale Scores at 90 Days in the Full Analysis Set

at hours, or change in NIHSS score compared with randomization at days. The lack of a significant effect on early outcomes correlated well with the negative primary outcome because the changes in these early outcomes, such as an increase in early neurologic improvement and a decrease in early neurologic deterioration, will result in the high risk of excellent functional outcome at days. Furthermore, no significant difference in risk of having other secondary outcomes, such as stroke or other vascular events within days, was found between the groups.

For the adverse events, similar rates of bleeding events were observed between the argatroban plus alteplase group and the alteplase alone group, which was consistent with previous studies. In this trial, the symptomatic intracranial

hemorrhage rate was .% to .%, which was lower than in previous studies.· This phenomenon could be due to the lower median NIHSS score at risk in the present study, which was comparable to recent studies involving a similar population: Chinese population with moderate neurologic function (median NIHSS score of to) and similar definition of symptomatic intercranial hemorrhage.· Despite the neutral results in this trial, the finding that no harmful profile of argatroban was observed in patients who received intravenous alteplase suggests the possible safety and feasibility of anticoagulants immediately after thrombolysis, which was prohibited by the current guidelines.

L   .

This study has several limitations. First, more patients dropped out in the argatroban plus alteplase group than the alteplase alone group due to less willingness to adhere to the study protocol among patients and their families randomized to the argatroban plus alteplase group. As a result, the number of patients in the argatroban plus alteplase group (n =   ) did not meet the minimum sample size (n =   ) that was required according to the power calculation; thus, the lower statistical power and imbalanced sample sizes between the groups cannot be ignored. In addition, there was a large difference in the percentage of patients with excellent functional outcome between the assumed values in the sample size calculation (%) and observed values in this trial (%). The difference might be attributed to the enrolled population with milder neurologic deficit (a median NIHSS score of   vs a median NIHSS score of   - . in previous studies ·) as well as the improvement in

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and try to ensure that the primary end point was measured objectively. Third, a lower proportion of patients with large artery occlusion was enrolled in the trial than in previous studies, which may be the main cause of the negative results of this trial. Thus, the effect of alteplase plus argatroban in patients with large artery occlusion warrants investigation in future trials. In addition, endovascular thrombectomy was used infrequently because most participating sites did not have endovascular thrombectomy capability. This limits generalizability to sites with readily available endovascular thrombectomy. Fourth, argatroban (- g/kg bolus followed by g/kg per minute) was used in our trial based on previous studies, while high-dose argatroban (- g/kg bolus followed by g/kg per minute) was used in previous studies. In addition, only . % patients met target APTT at hours, and it took approximately hours to reach target APTT (eTable and eFigure in Supplement). The low dose of argatroban and low target APTT

rate may partially contribute to the neutral results, because high doses of argatroban and good target APTT theoretically may produce a better improvement of clinical outcome if symptomatic intracranial hemorrhage did not increase. Fifth, the dropout rate in this trial may have introduced attrition bias or possible confounding. Sixth, further confirmation of these conclusions in non-Chinese populations would be welcome, given the differences in body mass index, comorbidities, and etiology of patients with AIS.

Conclusions

Among patients with AIS, treatment with argatroban plus intravenous alteplase compared with alteplase alone did not result in a significantly greater likelihood of excellent functional outcome at days.

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