Dual Antiplatelet Therapy vs Alteplase for Patients with Minor Nondisabling Acute Ischemic Stroke: The ARAMIS Randomized Clinical Trial

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Key Points

Question Is dual antiplatelet therapy noninferior to intravenous thrombolysis in patients with minor nondisabling acute ischemic stroke?

Findings In this noninferiority randomized clinical trial that included 760 participants, excellent neurologic function at 90 days (modified Rankin Scale score of 0 or 1) occurred in 93.8% of those randomized to dual antiplatelet therapy and 91.4% of those randomized to receive intravenous alteplase, a difference that met the prespecified noninferiority margin of -4.5 percentage points.

Meaning Among patients with minor nondisabling acute ischemic stroke, dual antiplatelet therapy, compared with intravenous alteplase, met the criteria for noninferiority with regard to excellent functional outcome at 90 days.

Abstract

IMPORTANCE Intravenous thrombolysis is increasingly used in minor stroke patients, but its benefit in patients with minor nondisabling stroke is unknown.

OBJECTIVE To investigate whether dual antiplatelet therapy (DAPT) is noninferior to intravenous thrombolysis among patients with minor nondisabling acute ischemic stroke.

DESIGN, SETTING, PARTICIPANTS This multicenter, open-label, blinded-endpoint, noninferiority randomized clinical trial included 760 patients with acute minor nondisabling stroke (National Institute of Health stroke scale (NIHSS) ≤ 5, with ≤ 1 point on the NIHSS in several key single item scores). The trial was conducted at 38 hospitals in China from October 2018, through April 2022. The final follow-up was July 18, 2022.

INTERVENTIONS Eligible patients were randomly assigned within 4.5 hours of onset into DAPT group (n=393): clopidogrel: 300 mg on the first day, followed by 75 mg daily for 12±2 days, aspirin: 100 mg on the first day, followed by 100 mg daily for 12±2 days, afterwards, guideline-based antiplatelet treatment until 90 days, or alteplase group (n=367): intravenous alteplase (0.9 mg/kg; maximum dose 90 mg) followed by guideline-based antiplatelet treatment beginning 24 hours after alteplase.

MAIN OUTCOMES AND MEASURES The primary endpoint was excellent functional outcome, defined as a modified Rankin scale score of 0 or 1 at 90 days. The noninferiority of DAPT to alteplase was defined on the basis of a lower boundary of the one-sided 97.5% confidence interval of the risk difference equal to or larger than -4.5 percentage points (noninferiority margin), based on a full analysis set, which included all randomized participants with at least one efficacy evaluation regardless of treatment allocation. The 90-day endpoints were assessed in a blinded manner. A safety endpoint was symptomatic intracerebral hemorrhage up to 90 days.

RESULTS Among 760 eligible randomized patients (median [IQR] age, 64 [57-71] years; 223 women [31.0%]; median [IQR] NIHSS score, 2 [1-3]), 719 (94.6%) completed the trial. At 90 days, 93.8% (346/369) in the DAPT group and 91.4% (320/350) in the alteplase group had an excellent functional outcome (risk difference, 2.4% [95% CI, -1.5%-6.2%]; crude relative risk, 1.38 [95% CI, 0.81-2.32]. The unadjusted lower limit of the one-sided 97.5% confidence interval was -1.5%, larger than the -4.5% noninferiority margin (*P*=.0002 for noninferiority test). Symptomatic intracerebral hemorrhage at 90

days occurred in 0.3% (1/371) in the DAPT group and 0.9% (3/351) in the alteplase group.

CONCLUSIONS AND RELEVANCE Among patients with minor nondisabling stroke presenting within 4.5 hours of symptom onset, dual antiplatelet treatment was noninferior to intravenous alteplase with regard to excellent functional outcome at 90 days.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03661411.

Introduction

Current guidelines recommend intravenous alteplase for patients with acute ischemic stroke (AIS) presenting within 4.5 hours of symptom onset.[1-3] Minor stroke, defined as a National Institutes of Health Stroke Scale (NIHSS) score ≤ 5, accounted for about half of AIS patients in 2016 (50.0%)[4] and 2019 (46.9%),[5] but the evidence in support of intravenous thrombolysis for these patients has remained inconclusive.[6,7] The Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits (PRISMS) study compared intravenous alteplase versus aspirin alone in patients with minor nondisabling deficits.[7] The results showed no significant difference in the 90-day functional outcomes between groups, but a higher rate of symptomatic intracerebral hemorrhage (sICH) in the alteplase group.

The Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA (POINT) and Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) studies confirmed the efficacy and safety of dual antiplatelet treatment (DAPT) in patients presenting with minor stroke within 12 or 24 hours of symptom onset, respectively.[8,9] The CHANCE study indicated that the benefit of reducing recurrent stroke with DAPT would be most effective within the first 2 weeks.[10]

In this context, it is possible that a 2-week course of DAPT could have a similar efficacy to intravenous alteplase on 90-day functional outcomes in patients presenting with minor nondisabling stroke. We conducted the Antiplatelet vs. R-tPA for Acute Mild Ischemic Stroke (ARAMIS) study to determine whether DAPT would be noninferior to intravenous alteplase with respect to efficacy and have less hemorrhagic events in AIS patients presenting with nondisabling deficits within 4.5 hours of symptom onset.

Methods

Study Design

We conducted a multicenter, randomized, open-label, blinded-endpoint assessment, noninferiority trial to assess the efficacy and safety of DAPT compared with intravenous alteplase in patients presenting with minor stroke and nondisabling deficits within 4.5 hours of symptom onset.

The protocol, which has been published[11] and available in the Supplement 1, was approved by the ethics committees of all participating sites. Both the final protocol and statistical analysis plan

(Supplement 2) were completed on May 6, 2020. Signed informed consent was obtained from patients or their authorized representatives. The investigators vouch for the completeness and accuracy of the data, for the adherence to the trial protocol, and for the accurate reporting of adverse events.

The trial was conducted at 38 hospitals (Supplement 3 eAppendix 1) in China. On-site and online training were provided before and during the study to ensure protocol compliance. A Steering Committee met monthly to oversee the trial. An independent Data Monitoring Committee (DMC) regularly reviewed safety data (Supplement 3 eAppendix 2). An independent clinical research organization (Liaoning Zhongshuang Medical Technology Co., Ltd.) monitored the trial for quality control.

Participants

Patients were eligible if they were 18 years of age or older; had an acute ischemic stroke with a NIHSS (range 0 to 42, with higher scores indicating greater stroke severity) ≤ 5, with ≤ 1 point on the NIHSS in single item scores such as vision, language, neglect, or single limb weakness and a score of 0 in the consciousness item at the time of randomization; computed tomography or magnetic resonance imaging was performed on admission to identify patients with ischemic stroke; study treatment could be started within 4.5 hours of stroke symptoms. Exclusion criteria were pre-stroke disability (modified Rankin Scale [mRS] scores ≥ 2; range 0 [no symptoms] to 6 [death]), history of intracerebral hemorrhage, or definite indication for anticoagulation. All investigators were trained with regards to adjudicating a pre-stroke deficit as non-disabling by consultation with patients and their available family members based on the patient's career and hobbies, to adjudicate whether the neurologic deficit would affect his/her activities of daily living and work. Detailed inclusion and exclusion criteria are in Supplement 3 eMethods.

Randomization and Masking

Eligible patients were randomly assigned in a 1:1 ratio to receive DAPT or intravenous alteplase, with the simple randomization method without blocking schema through a computer-generated random sequence via a central web-based program at http://aramis.medsci.cn (Shanghai Meisi Medical Technology Co., Ltd.). The study team members were unblinded to the treatment allocation. Trained assessors, who determined 90-day outcomes, were unaware of the treatment group assignments.

Procedures

Patients were randomly assigned to the alteplase group (according to guidelines[1-3]: 0.9 mg/kg [10% as a bolus, 90% infused over 1 hour] to a maximum of 90 mg, followed by guideline-based antiplatelet treatment beginning 24 hours after intravenous thrombolysis) or DAPT group (clopidogrel: a loading dose of 300 mg on the first day, followed by 75 mg per day for 12±2 days; aspirin: 100 mg on the first day, followed by 100 mg daily for 12±2 days; afterwards, single or dual antiplatelet based on guidelines until 90 days).

Outcomes

The primary outcome was an excellent functional outcome at 90 days, defined as mRS score of 0 to 1. The secondary outcomes were favorable functional outcome (mRS 0 to 2) at 90 days, change in NIHSS at 24 hours, early neurological improvement at 24 hours defined as a decrease of 2 or more points in NIHSS, early neurological deterioration at 24 hours defined as an increase of 2 or more points in the NIHSS but not as a result of cerebral hemorrhage, new stroke or other vascular events at 90 days, 90-day all-cause mortality, and ordinal shift of the mRS score at 90 days.

The safety outcomes were sICH and any bleeding event during the study. sICH was defined as evidence of bleeding on head CT associated with neurological deterioration (NIHSS $\geq$ 4 point increase).

Clinical assessments were performed at baseline, 24 hours, 7 days, 12 days (or hospital discharge if earlier), and at 90 days after randomization. The baseline and follow-up NIHSS were evaluated by the same neurologist. Follow-up at 90 days was done in person or by telephone (if in person was not possible), by a certified staff member in each center who was unaware of the treatment assignment. To ensure validity and reproducibility of the evaluation, a training course was held for all investigators. Central adjudication of clinical outcomes and adverse events was done by trained physicians unaware of patient treatment assignment (Supplement 3 eMethods).

Sample Size Calculation

Power calculations were based on the estimated treatment effects of a binary assessment of excellent functional outcomes at 90 days. Sample size assumptions were amended in May 2020 based on new registry information regarding the expected excellent functional outcome rate in the thrombolytic group and on recognition that the initial sample size calculations had inadvertently been based on a superiority design. In the Intravenous Thrombolysis Registry for Chinese Ischemic Stroke within 4.5

hours of Onset (INTRECIS) study,[12] the proportion of patients with excellent functional outcomes in minor acute stroke treated with alteplase was estimated to be 87%. Based on the PRISMS trial,[7] we assumed that the proportion of patients with excellent functional outcomes was 89.5% in the DAPT group. We estimated that a sample size of 666 would provide 80% power (at a one-sided alpha level of 0.025) to test the hypothesis that the proportion of patients with excellent functional outcomes in the DAPT group would be noninferior to the alteplase group with a lower boundary of the one-sided 97.5% confidence interval of the risk difference equal to or larger than -4.5 percentage points. The choice of the noninferiority margin of -4.5 percentage points was based on the Third International Stroke Trial (IST-3), where subgroup analysis showed a 9% absolute difference in the proportion of favorable outcome in patients with minor stroke who were treated with intravenous alteplase compared to standard medical treatment.[13] We contended that preserving at least 50% of the alteplase treatment effect observed in the IST-3 trial would be clinically meaningful considering the convenience, cost and safety of DAPT vs alteplase. Therefore, -4.5 percentage points was used as noninferiority margin in this trial. Assuming a 12% attrition rate, the sample size was 757, and rounded to 760 participants.

Statistical analysis

Statistical analyses were performed on a full analysis set, which included all randomized participants with at least one efficacy evaluation according to the group they were originally assigned. A generalized linear model (GLM) with binomial distribution and identity link function was performed for the primary outcome, generating a risk difference between DAPT or intravenous alteplase treatment with the two-sided 95% CI (equivalent to the one-sided 97.5% CI). A risk ratio with their 95% CI was also calculated using GLMs. In sensitivity analyses, missing values in the primary outcome were imputed using the last observation carried forward, the worst-case scenario, and best-case scenario approaches. An interim analysis was planned after 50% of patients had completed follow-up, but was not performed due to no safety concerns after discussion of the steering committee with the DMC (Supplement 2). Other secondary outcomes were analyzed similarly.

The 90-day mRS score was compared using ordinal logistic regression via GLM with treatment effect presented as OR with 95% CI. A GLM was also used to compare changes in log (NIHSS score+1) between admission and 24 hours, and a geometric mean ratio with 95% CI was calculated between the DAPT and alteplase groups. Time-to-event outcomes of stroke and other vascular events were

compared using Cox regression models, and the corresponding treatment effects are presented as hazard ratios (HR) with 95% CI. The proportionality assumption was tested by including a time-treatment interaction in the Cox model.

The primary analyses of the primary and secondary outcomes were unadjusted. A death event was equivalent to a mRS score of 6. Covariate adjusted GLM analyses were performed for all outcomes, adjusting for seven prespecified factors: age, sex, diabetes, baseline NIHSS, time from symptom onset to treatment, location of responsible vessel, and stroke etiology. The degree of vascular stenosis was not included as an adjustment covariate as originally prespecified because missingness exceeded 30%. In addition, for sensitivity analysis of the primary outcome, prespecified factors plus crossover as a post hoc covariate adjusted analysis was performed with the same method.

Subgroup analysis of the primary outcome was performed using GLM with identity link function on eight prespecified subgroups (age [<65 years or ≥65 years], history of diabetes [present or not present], time from symptom onset to treatment [≤ 2 hours or > 2 hours], location of index vessel [anterior circulation or posterior circulation], sex [female or male], NIHSS score at randomization [0 to 3 or 4 to 5], and stroke etiology (large-artery atherosclerosis, cardioembolic, small-artery occlusion, other determined cause, and undetermined cause) and degree of vascular stenosis (<50% vs. ≥50%). Detailed statistical analyses are described in the statistical analysis plan (Supplement 2). In addition, large artery occlusion [yes or no]) as a post hoc subgroup analysis was also performed with the same method. Assessment of the homogeneity of treatment effect by a subgroup variable was conducted by a GLM model with the treatment, subgroup variable, and their interaction term as independent variables, and the *P* value was presented for the interaction term.

The primary analysis was based on a full analysis set population, defined as all patients with valid informed consent regardless of whether they prematurely discontinue treatment or are otherwise protocol violators, which did not include patients lost to follow-up or withdrawn. Per-protocol (PP) and as treated (AT) analyses for the primary and secondary outcomes were performed with same methods. The safety population, which consisted of all randomized patients who received at least one dose of the study drug and didn't withdraw consents was used for the analysis of adverse events. Complete definitions of all analytic populations are shown in Supplement 2. For the secondary outcomes, a 2-sided *P* value of less than .05 was considered statistically significant. Because of the potential for

inflating the type I error due to multiple comparisons, the findings from subgroup and secondary outcome analyses should be interpreted as exploratory. SAS (version 9.4; SAS Institute), SPSS (version 23; IBM Corporation), and R (version 4.1.0; R Development Core Team, www.r-project.org) software were used for the statistical analyses.

Results

Trial Population

Between October 1, 2018, and April 18, 2022, 835 patients were screened, and 760 were randomly assigned to the DAPT (393 patients) or alteplase (367 patients) group after excluding 75 patients (60 ineligible by inclusion criteria and 15 excluded due to no randomization outcome). After 37 (5.0%) patients were further excluded (20 withdrew consent due to patient decision, and 17 patients were withdrawn due to clinical reasons), the full analysis set population included 719 patients (369 in the DAPT group, 350 in the alteplase group, Figure 1). Due to a total of 147 patients who had a protocol violation, which involved 87 patients in the DAPT group crossing over to the alteplase group, and 60 patients in the alteplase group crossing over to the DAPT group, 574 patients in the PP population (283 in DAPT group, 291 in alteplase group) and 723 in the AT population (344 in DAPT group, 379 in alteplase group) were included (Figure 1 and Supplement 3 eFigure 1). The trial was completed in July 2022.

The treatment groups were well balanced with respect to baseline patient characteristics in the full analysis set (Table 1), PP (Supplement 3 eTable 1) and AT (Supplement 3 eTable 2) populations. The median age of the patients was 64 years (interquartile range, IQR, 57 to 71), and 223 patients (31.0%) were women. The median NIHSS (IQR) was 2 (1 to 3). The median time (IQR) from stroke onset to treatment was 182 minutes (133 to 230) in the DAPT group and 180 minutes (126 to 225) in the alteplase group. There were 241 (33.7%) patients with missing vessel imaging data. The detailed antiplatelet treatment after hospital discharge was shown in eTable 3 in Supplement 3.

Primary Outcome

For the primary outcome, the proportion of patients with mRS scores of 0 or 1 at 90 days was 93.8% (346/369) in the DAPT group and 91.4% (320/350) in the alteplase group. In the full analysis set, the risk difference of having an excellent outcome at 90 days was 2.3% (unadjusted 95% CI -1.5% to 6.2%;

P=0.0002 for noninferiority; adjusted 95% CI -1.6% to 6.1%; Table 2, Figure 2). The PP analysis (Supplement 3 eFigure 2 and eTable 4) and AT analysis (Supplement 3 eFigure 3 and eTable 5) yielded similar results. Similar RD results were observed in the last observation carried forward, worst-case scenario, and best-case scenario sensitivity analyses (Supplement 3 eTable 6). DAPT was shown noninferior to intravenous alteplase because the lower boundary of the two-sided 95% (one-sided 97.5%) confidence interval was greater than the prespecified value of -4.5% (Supplement 3 eTable 7). Furthermore, there was no effect of crossovers on the noninferiority result in the primary outcome (Supplement 3 eTable 8). Subgroup analysis in the full analysis set, PP, and AT analysis are presented in Figure 3 and Supplement 3 eFigure 4 and eFigure 5, respectively. There was no treatment heterogeneity in the absolute risk of having a primary outcome across these subgroups.

Secondary Outcomes

For secondary outcomes, the results in both the unadjusted and adjusted full analysis set populations are shown in Table 2. In the full analysis set, no significant differences between groups were found in secondary outcomes, except that less patients had early neurological deterioration at 24 hours in the DAPT group (unadjusted RD -4.5%, 95% CI -8.2% to -0.8%; adjusted RD -4.6%, 95% CI -8.3% to -0.9%; Table 2). In the PP and AT analysis, similar results were obtained, but a lower risk of early neurological improvement was observed in the DAPT group (Supplement 3 eTable 4 and eTable 5).

Adverse Events

Analyses of adverse events were based on the safety population. One patient experienced sICH and six patients experienced other bleeding events in the DAPT group, while three patients experienced sICH and nineteen patients experienced other bleeding events in the alteplase group (Table 2, Supplement 3 eTable 4 and eTable 5). The detailed intracerebral hemorrhage data were shown in eTable 9 in Supplement3.

Discussion

This randomized trial showed that among patients with nondisabling minor acute ischemic stroke, DAPT was noninferior to intravenous alteplase when administered within 4.5 hours of stroke onset for the primary outcome of excellent functional outcome at 90 days. More early neurological deterioration and bleeding events occurred in the alteplase group. There were no significant differences between the

two groups regarding other secondary outcomes and subgroup analysis.

The PRISMS study was the first randomized, multicenter trial to investigate the effect of intravenous alteplase versus single antiplatelet in patients presenting with acute minor ischemic stroke,[7] but the trial was inconclusive due to early study termination. Based on this result, intravenous alteplase is not recommended for minor nondisabling stroke according to current guidelines.[1,2] However, subgroup analysis of patients with minor ischemic stroke showed the superiority of intravenous alteplase compared to standard medical treatment in the IST-3 randomized trial.[13] Furthermore, there was an increasing proportion of these patients receiving thrombolytic therapy in routine clinical practice,[14,15] although the ratio of minor nondisabling vs disabling stroke was uncertain. As it can be challenging for stroke physicians to decide whether to give intravenous alteplase in patients with minor nondisabling stroke, it was important to investigate whether intravenous alteplase should be administered for minor nondisabling stroke.

The ARAMIS study was the first study to attempt to address this issue with a strategy different from PRISMS.[7] A combination of aspirin plus clopidogrel (a loading dose of 300 mg) was administered for 12 ± 2 days, followed by guideline-based antiplatelet treatment until 90 days in our trial, whereas aspirin 325 mg alone was used for 90 days in the PRISMS study. The choice of DAPT was based on the CHANCE[8] and POINT[9] studies, which demonstrated the superiority of DAPT to aspirin alone in acute minor stroke. The 12 ± 2 days of DAPT was based on the CHANCE trial suggesting that the benefit of DAPT was offset by the potential risk of bleeding events approximately at the 10th day.[10] Collectively, this trial demonstrated that short-term DAPT (12 ± 2 days) initiated in patients presenting within 4.5 hours of a nondisabling minor stroke, had noninferior efficacy to intravenous alteplase on 90-day functional outcomes with less bleeding risk. In this trial, the proportion of patients with excellent functional outcome (91.5% vs 93.7%) was higher than that achieved in PRISMS (78.2% vs 81.5%),[7] which may partially be attributed to the different proportion of Asian patients (100% vs 0.3%, respectively), differing comorbidities or vascular risk factor profile. Moreover, two studies reported a comparable proportion of excellent outcome among Chinese patients with minor stroke (87%-89.4%).[12,16] In addition, in the subgroup with NIHSS >3, the point estimate for the primary outcome excellent functional outcome favored the alteplase group over the DAPT group, although this was not statistically significant. The potential benefit of alteplase in this population warrants further

investigation.

In the secondary outcomes, compared with DAPT, there was more early neurological deterioration (9.1%) in patients receiving alteplase, which was comparable to a recent study that reported 13.3% early neurological deterioration in Chinese patients with mild stroke after intravenous alteplase.[17] This could be related to thrombus progression or stroke reoccurrence due to the lack of an antithrombotic treatment effect within 24 hours after alteplase, considering its short half-life. In contrast, greater early neurologic recovery was found in the alteplase vs DAPT group in the per-protocol analysis and as treated analyses, but this effect was lost in the full analysis set. The lost effect may be due to more DAPT crossover patients in the alteplase group vs alteplase crossover patients to the DAPT group in the full analysis set, which may have weakened the potential benefit of alteplase on early neurological improvement. Collectively, these results may suggest the possible benefit of alteplase on early neurological improvement. There were no significant differences between groups in the other secondary outcomes such as recurrent stroke. Given the benefit of DAPT in minor stroke, [8,9] we contend that the lack of effect on recurrent stroke may be attributed to the relatively small sample and low rate of recurrent stroke in this population. The lack of an a priori plan for multiple comparisons of secondary outcomes precludes firm conclusions and these findings should be interpreted with caution.

For the safety outcomes, compared with the DAPT group, there were numerically more sICH and significantly more bleeding events in the alteplase group, which was expected given the known higher rate of hemorrhage with alteplase. The 0.9% rate of sICH with alteplase in this study was comparable to other studies of Chinese patients with minor stroke who were treated with alteplase (0-1.0%).[18,19]

The strengths of this randomized trial were its large sample size, multicenter recruitment, and dual antiplatelet strategy, which enhances the generalizability of the results. Age, sex, medical history, onset of symptom to treatment time and presumed stroke cause in the trial were similar to routine clinical practice.[12] The results were confirmed in various sensitivity analyses. This finding, along with better safety outcomes, provides robust evidence for the effectiveness of DAPT being noninferior to intravenous alteplase in patients with minor nondisabling acute ischemic stroke.

Limitations

This study had several limitations. First, the non-inferiority design of the trial may be a main limitation due to DAPT as a standard treatment in this target population according to the current

guidelines[1,2] which were published after patient enrollment began for this trial. The 2018 AHA/ASA guideline and the 2020 Chinese Stroke Association Guidelines stated that in patients with mild non-disabling AIS within 3 hours of symptom onset, intravenous alteplase may be considered.[3,20] However, in this target population of patients with minor non-disabling stroke, the uncertain benefit of DAPT on 90-day mRS,[8,9] inconclusive evidence of intravenous alteplase[7] and increasing proportion of patients receiving alteplase[14,15] render the current non-inferiority design important to inform the best treatment. Second, there was a high crossover rate (20.4%) in this trial, which may have compromised the integrity of the recruitment and consent process, and clinical equipoise. However, the demonstration of the noninferiority of DAPT to intravenous alteplase was robust given the concordance of findings by the full analysis set, PP and AT analyses, and various sensitivity analyses. Third, the lack of vessel imaging data in some patients makes the subgroup analysis of etiology (large artery atherosclerosis vs small artery occlusion) and large artery occlusion (yes vs no) less powerful, because prior studies showed the possible benefit of alteplase or tenecteplase in mild stroke patients with large artery atherosclerosis or large artery occlusion,[21-23] which will be further assessed in the TEMPO-2 trial (NCT02398656) comparing tenecteplase vs standard of care in minor stroke patients with a confirmed large vessel occlusion. Fourth, this trial was an open-label design; blinded endpoint evaluations were used to reduce bias in the assessment of the primary endpoint. For secondary endpoints, the neurologist who was unblinded to the treatment assessment conducted the early neurological assessment, which may have led to assessment bias for the early neurological outcomes. Fifth, patients with possible cardioembolism were excluded and a lower proportion of women were enrolled in this trial, which may affect the generalizability of the findings from this study. Sixth, high rates of the primary endpoint in the DAPT and alteplase groups may have created a ceiling effect that limited the opportunity for either agent to show superiority to the other one. Seventh, further confirmation of the findings outside China may be needed, given the differences in etiology of ischemic stroke in other populations.

Conclusions

Among patients presenting with minor nondisabling acute ischemic stroke within 4.5 hours of symptom onset, dual antiplatelet treatment was noninferior to intravenous alteplase with regard to excellent functional outcome at 90 days.

Author Contributions

HSC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: HSC.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: HSC.

Statistical analysis: YC and DLW.

Administrative, technical, or material support: All authors.

Supervision: HSC.

Conflict of Interest Disclosures

We declared no competing interests.

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Role of the Funder/Sponsor

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from the national insurance system. The funders of the study had no role in the study design and conduct of the study; collection; management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The corresponding author had access to all data in the study and had overall responsibility for the decision to submit for publication.

Group Information

The ARAMIS Trial members from each participating center are listed in eAppendix 3 in Supplement 3 and the principal investigators are listed in Supplement 4.

Data Sharing

See Supplement 5.

Acknowledgments

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Figure Legends

Figure 1 Recruitment, Randomization, and Patient Flow in the ARAMIS Randomized Clinical Trial

This figure shows the overall patient flow in the trial, including the full analysis set population, the per-protocol population, and as-treated population. APTT = Abnormal activated partial thromboplastin time; MRI = Magnetic Resonance Imaging; NIHSS = National Institutes of Health Stroke Scale; SBP = Systolic blood pressure.

[a] Eligibility was assessed according to inclusion criteria by local trained neurologists. [b] The high crossover rate was attributed to consent misunderstanding or fluctuation of neurological deficit, which resulted in the crossover requested by patients or their authorized representatives, or as decided by investigators. The baseline characteristics in patients with crossover are shown in Supplement 3 eTable 10.

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

The raw distribution of scores is shown. Scores ranged from 0 to 6. 0 = no symptoms, 1 = symptoms without clinically significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death. DAPT = dual antiplatelet.

Figure 3 Primary Outcome by Prespecified Subgroups in the Full Analysis Set

The primary outcome was a modified Rankin Scale score of 0 to 1 at 90 days. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events) and horizontal lines represent the 95% CI. NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficits. CI = confidence interval; DAPT = dual antiplatelet; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale.

524 **Table 1. Baseline Characteristics in the Full Analysis Set.**

Baseline characteristics	**Dual Antiplatelet Treatment (N=369)**	**Alteplase (N=350)**
Age, years	65 (57-71)	64 (56-71)
Sex		
Male	256 (69.5%)	240 (68.6%)
Female	113 (30.6%)	110 (31.4%)
Current smoker [a]	122 (33.1%)	118 (33.7%)
Current drinker [a]	59 (16.0%)	56 (16.0%)
Medical history		
Hypertension	211 (57.2%)	169 (48.3%)
Diabetes mellitus	101 (27.4%)	86 (24.6%)
Prior ischemic stroke [b]	82 (22.2%)	77 (22.0%)
Prior transient ischemic attack	4 (1.1%)	2 (0.6%)
Time from onset of symptom to assigned treatment, min	182 (134-230)	180 (127-225)
Time from onset to hospital discharge, day	8 (6-11)	8 (6-10)
Median INR at randomization	1.00 (0.94-1.05)	0.98 (0.93-1.04)
>1.2	5/358 (1.4)	4/344 (1.2)
Median APTT at randomization, second	31.8 (27.2-36.3)	31.9 (27.4-35.7)
>43.5	15 (4.1)	13 (3.7)
Median systolic blood pressure at randomization, mm Hg	150 (137-166)	151 (139-162)
>140	245 (66.4)	242 (69.1)
Median diastolic blood pressure at randomization, mm Hg	88 (81-95)	88 (80-95)
>90	142 (38.5)	132 (37.7)
Median blood glucose level at randomization, mmol/liter	6.3 (5.4-8.3)	6.4 (5.4-8.1)
>7.0	112/316 (35.4)	121/314 (38.5)
NIHSS score at randomization [c]	2 (1-3)	2 (1-3)

NIHSS score of 0 at randomization	27 (7%)	29 (8%)
Estimated pre-stroke function (mRS)		
No symptoms (score 0)	275 (74.5%)	256 (73.1%)
Symptoms without any disability (score 1)	94 (25.5%)	94 (26.9%)
Presumed stroke cause [d]		
Undetermined cause	225 (61.0%)	221 (63.1%)
Small-artery occlusion	87 (23.6%)	79 (22.6%)
Large-artery atherosclerosis	54 (14.6%)	46 (13.1%)
Other determined cause	2 (0.5%)	3 (0.9%)
Cardioembolic	1 (0.3%)	1 (0.3%)
Location of responsible vessel [e]		
Anterior circulation	283 (76.7%)	279 (79.7%)
Posterior circulation	83 (22.5%)	70 (20.0%)
Anterior and posterior circulation	3 (0.8%)	1 (0.3%)
Degree of responsible vessel stenosis [f]		
Mild (< 50%)	191/246 (77.6%)	185/232 (79.7%)
Moderate (50%-69%)	21/246 (8.5%)	15/232 (6.5%)
Severe (70%-99%)	14/246 (5.7%)	16/232 (6.9%)
Occlusion (100%)	20/246 (8.1%)	16/232 (6.9%)

Data are n/N (%) or median (IQR). APTT = activated partial thromboplastin time. DAPT = dual antiplatelet treatment. INR = international normalized ratio. IQR = interquartile range. NIHSS = National Institutes of Health Stroke Scale. mRS = modified Rankin Scale.

[a] Current smokers smoke at least 1 cigarette per day within one year before the onset of the disease. Current drinkers consume alcohol at least once a week within one year before the onset of the disease and consume alcohol continuously for more than one year.

[b] Referring only to patients with premorbid mRS ≤ 1.

[c] Patients with NIHSS scores less than or equal to 5 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficit.

[d] The presumed stroke cause was classified according to the "Trial of Org 10172 in the Acute Stroke

Treatment (TOAST)" classification system.

[e] The classification was defined according to the anatomical location of responsible vessel based on the patient's clinical presentation and neuroimaging, which refers to the clinical features of the "Oxfordshire Community Stroke Project (OCSP)" classification system.

[f] The degree of stenosis was determined by cerebral vessel examination. The diagnosis was based on the clinician's interpretation of the clinical presentation and results of the investigations at the time of hospital discharge.

542 **Table 2. Trial Outcomes in the Full Analysis Set and Safety Population.**

Outcome	Dual Antiplatelet Treatment (N=369)	Alteplase (N=350)	Treatment Effect Metric	Unadjusted		Adjusted [a]	
				Treatment Difference (95% CI)	P Value	Treatment Difference (95% CI)	P Value
Primary outcome (full analysis set)							
mRS [b] score 0-1 within 90 days	346 (93.8%)	320 (91.4%)	RD [c,d]	2.3% (-1.5% to 6.2%)	<.001	2.3% (-1.6% to 6.1%)	<.001
			RR [c]	1.38 (0.81 to 2.32)	.23	1.36 (0.80 to 2.30)	.22
Secondary outcomes (full analysis set)							
mRS [b] score 0-2 within 90 days	354 (95.9%)	334 (95.4%)	RD [c]	0.5% (-2.5% to 3.5%)	.74	0.5% (-3.5% to 2.5%)	.83
			RR [c]	1.12 (0.56 to 2.24)	.74	1.12 (0.56 to 2.25)	.64
mRS [b] score distribution within 90 days			OR [c]	1.16 (0.83 to 1.61)	.39	1.11 (0.80 to 1.55)	.51
Early neurological improvement within 24 hours [e]	62 (16.8%)	74 (21.1%)	RD [c]	-4.1% (-9.8% to 1.7%)	.16	-3.1% (-8.7% to 2.4%)	.27
			RR [c]	0.95 (0.89 to 1.02)	.17	0.84 (0.62 to 1.14)	.27
Early neurological deterioration within 24	17 (4.6%)	32 (9.1%)	RD [c]	-4.5% (-8.2% to -0.8%)	.02	-4.6% (-8.3% to -0.9%)	.02
			RR [c]	0.50 (0.29 to 0.89)	.02	0.50 (0.28 to 0.89)	.02

hours [f]							
Median change in NIHSS score at 24 hours from baseline [g]	0 (-0.41 to 0)	0 (-0.69 to 0)	GMR [c]	0.03 (-0.05 to 0.11)	.51	0.01 (-0.07 to 0.09)	.68
Stroke or other vascular events within 90 days	1 (0.3%)	2 (0.6%)	HR [h]	0.47 (0.04 to 5.20)	.54	0.46 (0.04 to 5.17)	.45
Death at 90 days	2 (0.5%)	3 (0.9%)	RD [c]	-0.3% (-1.5% to 0.9%)	.61	-0.3% (-1.5% to 0.9%)	.49
			RR [c]	0.63 (0.11 to 3.76)	.61	0.58 (0.10 to 3.51)	.49
Safety outcomes (safety population)							
Symptomatic intracerebral hemorrhage [i]	1/371 (0.3%)	3/352 (0.9%)	RD [c]	-0.6 % (-1.7% to 0.5%)	.30	-2.4 % (-12.1% to 7.3%)	.63
			RR [c]	0.32 (0.03 to 3.02)	.32	0.31 (0.03 to 2.99)	.36
Any bleeding events [j]	6/371 (1.6%)	19/352 (5.4%)	RD [c]	-3.8% (-6.5% to -1.1%)	.006	-3.6% (-6.4% to -0.7%)	.01
			RR [c]	0.30 (0.12 to 0.74)	.009	0.31 (0.12 to 0.76)	.01

Data are n/N (%) or median (IQR). CI = confidence interval; DAPT = dual antiplatelet treatment; GMR = geometric mean ratio; RR = risk ratio; RD = risk difference; OR = odds ratio; HR= hazard ratio; mRS = modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IQR = interquartile range.

[a] Adjusted for pre-specified prognostic variables (age, sex, history of diabetes mellitus, NIHSS score at randomization, time from symptom onset to receive assigned treatment, location of responsible vessel, and stroke etiology). The degree of vascular stenosis was planned in the covariate adjusted analyses but was excluded due to a large

proportion of missing values (see the Supplement 2).

[b] mRS scores range from 0 to 6: 0, no symptoms, 1 = symptoms without clinically significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability; and 6 = death.

[c] Calculated using a generalized linear model.

[d] Non-inferiority will be claimed if the lower limit of the one-sided 97.5% (two-sided 95%) confidence interval for the risk difference is above -4·5%. P values for noninferiority of the crude and adjusted analysis were presented, respectively.

[e] Early neurological improvement was defined as a decrease between baseline and 24 hours score of ≥ 2 on the NIHSS.

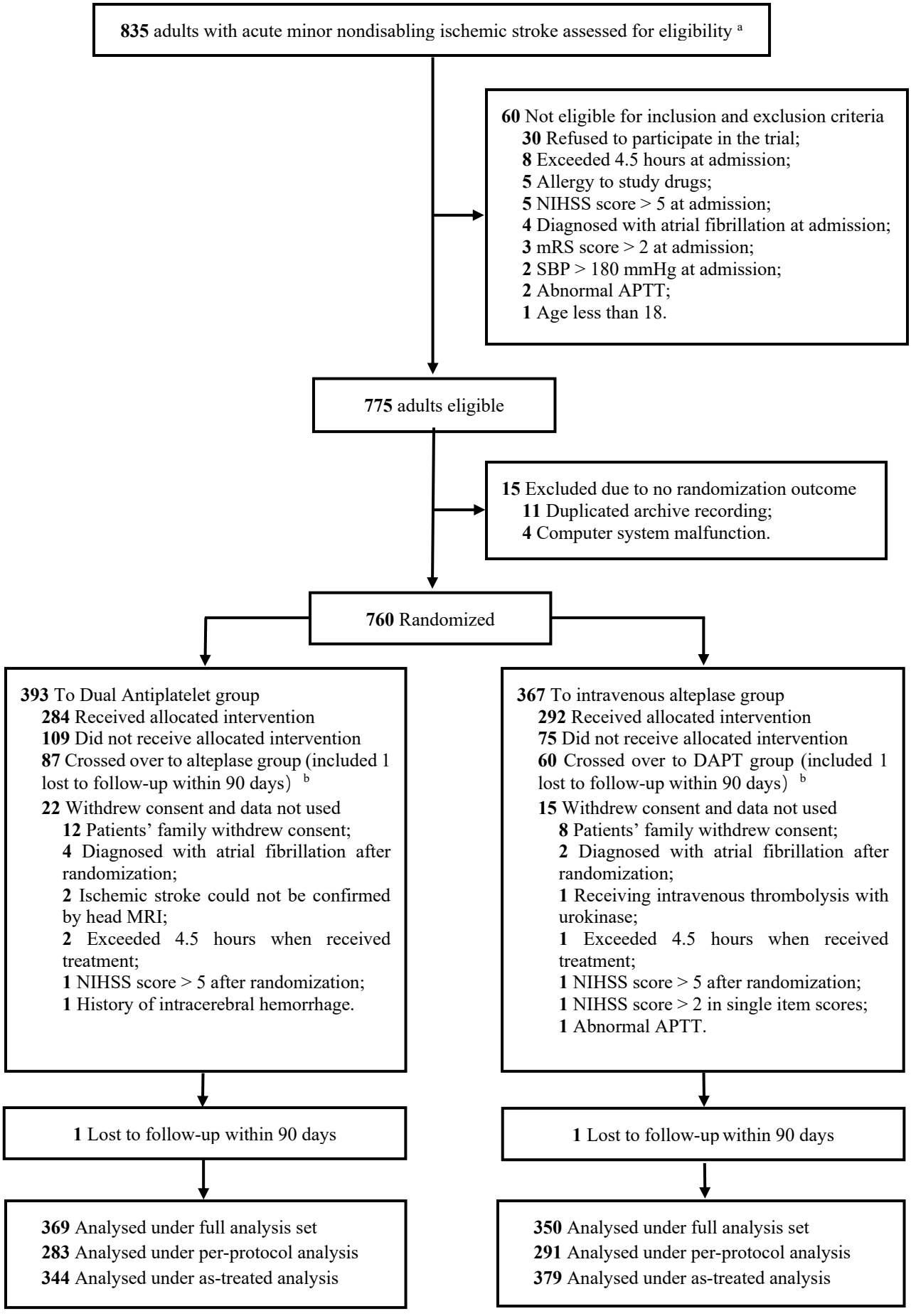
[f] Early neurological deterioration was defined as an increase between baseline and 24 hours of ≥ 2 on the NIHSS, but not as a result of cerebral hemorrhage.

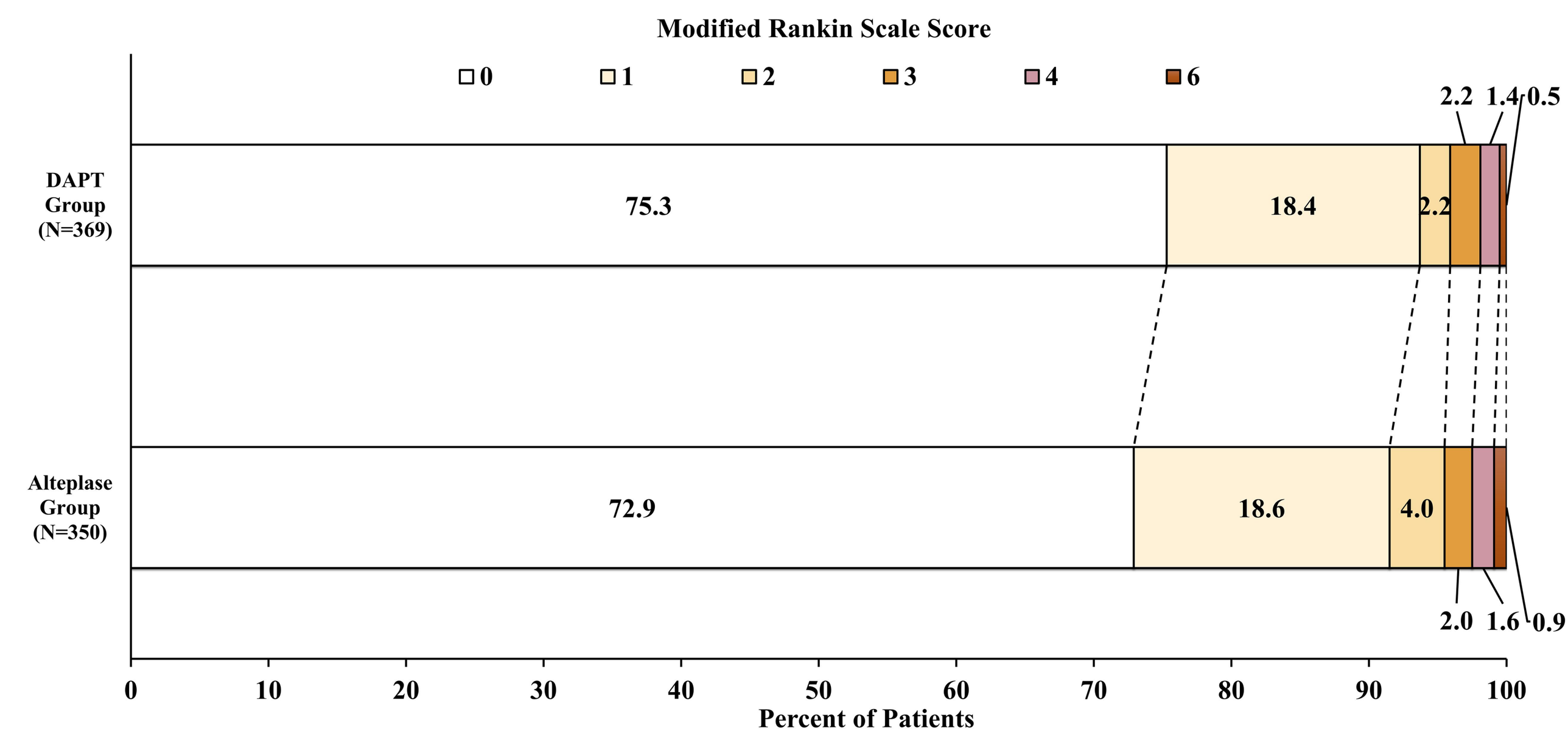
[g] NIHSS scores range 0–42, with higher scores indicating greater stroke severity. The log (NIHSS+1) was analyzed using a generalized linear model.

[h] Calculated using Cox regression model. No violation of hazard proportionality assumption was found and the P value for the interaction was 0.36.

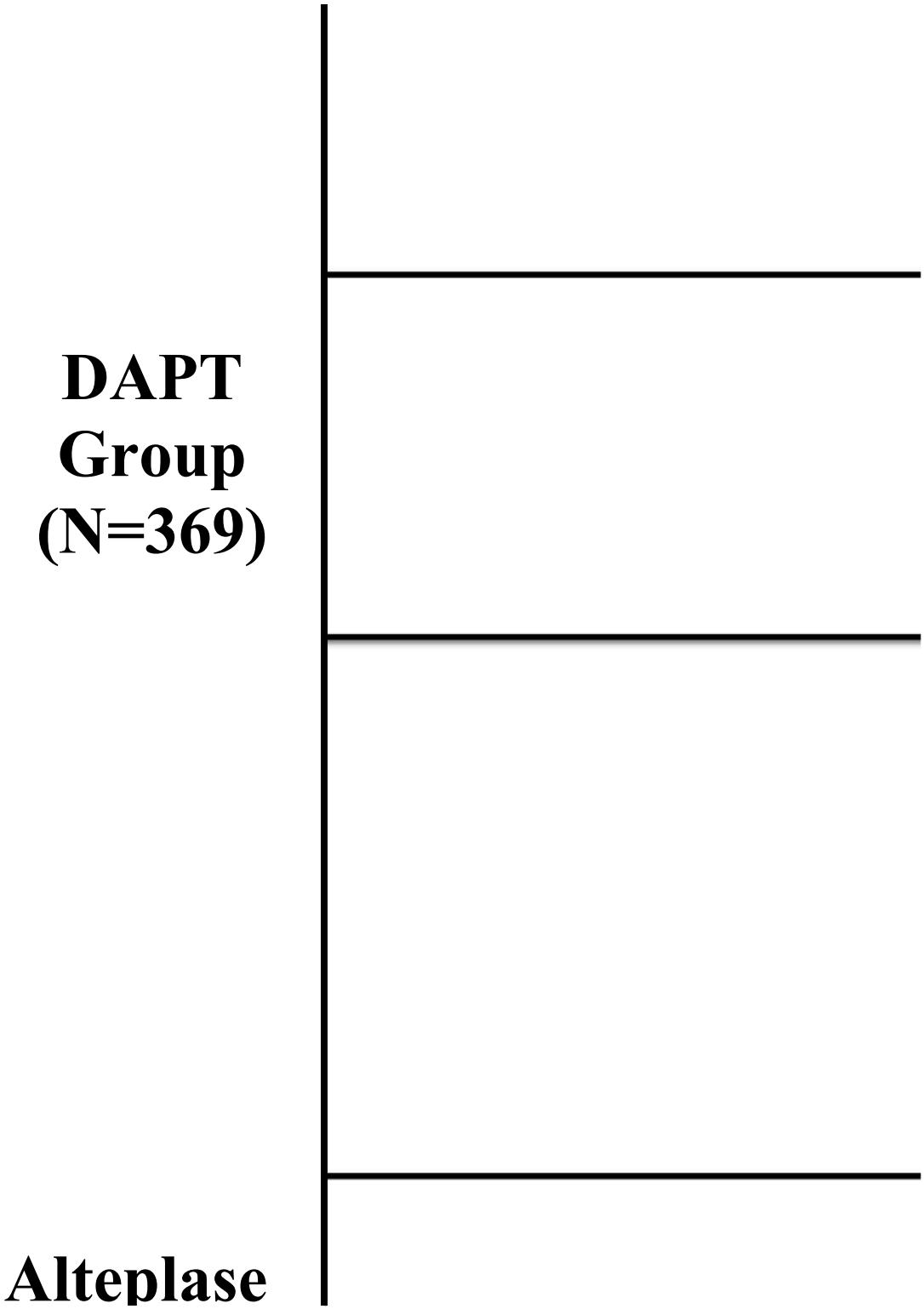
[i] Symptomatic intracerebral hemorrhage was defined as any evidence of bleeding on the head CT scan associated with clinically significant neurological deterioration (NIHSS score ≥ 4 points increase).

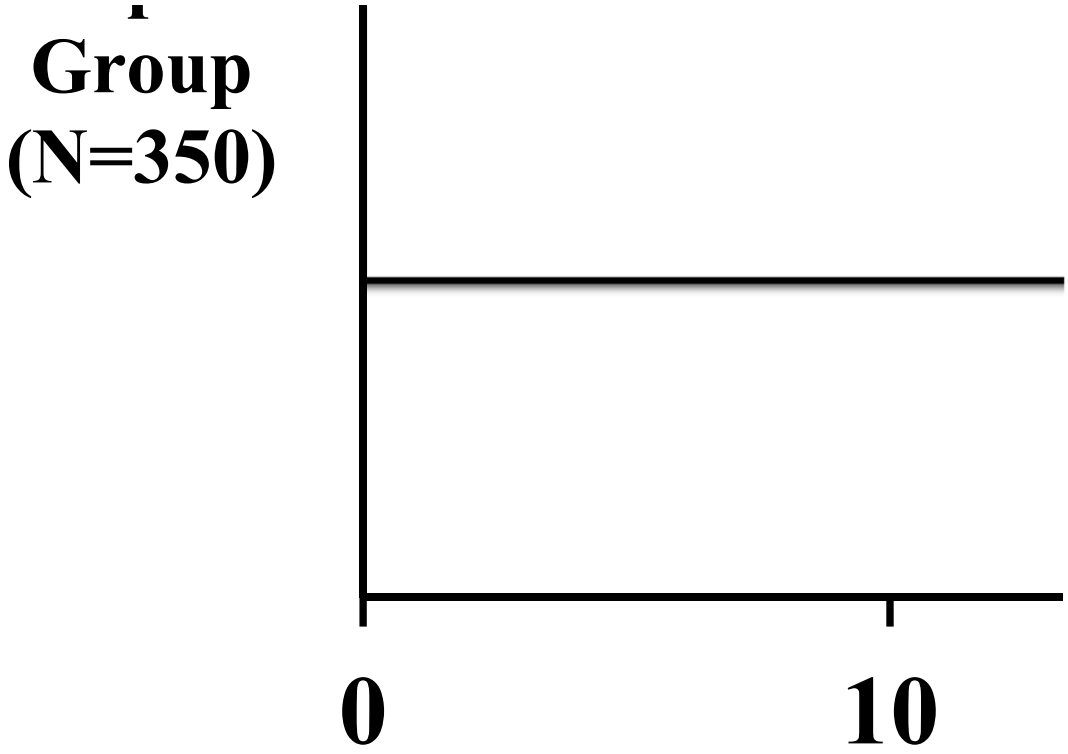
[j] There were 1 patient with symptomatic intracerebral hemorrhage and 5 patients with gingival bleeding in the DAPT group. There were 1 patient with epistaxis, 1 patient with asymptomatic intracerebral hemorrhage, 3 patients with symptomatic intracerebral hemorrhage and 14 patients with gingival bleeding in the alteplase group.


835 adults with acute minor nondisabling ischemic stroke assessed for eligibility [a]
60 Not eligible for inclusion and exclusion criteria
30 Refused to participate in the trial;
8 Exceeded 4.5 hours at admission;
5 Allergy to study drugs;
5 NIHSS score > 5 at admission;
4 Diagnosed with atrial fibrillation at admission;
3 mRS score > 2 at admission;
2 SBP > 180 mmHg at admission;
2 Abnormal APTT;
1 Age less than 18.
775 adults eligible
15 Excluded due to no randomization outcome
11 Duplicated archive recording;
4 Computer system malfunction.
760 Randomized
393 To Dual Antiplatelet group
284 Received allocated intervention
109 Did not receive allocated intervention
87 Crossed over to alteplase group (included 1 lost to follow-up within 90 days) [b]
22 Withdrew consent and data not used
12 Patients' family withdrew consent;
4 Diagnosed with atrial fibrillation after randomization;
2 Ischemic stroke could not be confirmed by head MRI;
2 Exceeded 4.5 hours when received treatment;
1 NIHSS score > 5 after randomization;
1 History of intracerebral hemorrhage.
367 To intravenous alteplase group
292 Received allocated intervention
75 Did not receive allocated intervention
60 Crossed over to DAPT group (included 1 lost to follow-up within 90 days) [b]
15 Withdrew consent and data not used
8 Patients' family withdrew consent;
2 Diagnosed with atrial fibrillation after randomization;
1 Receiving intravenous thrombolysis with urokinase;
1 Exceeded 4.5 hours when received treatment;
1 NIHSS score > 5 after randomization;
1 NIHSS score > 2 in single item scores;
1 Abnormal APTT.
1 Lost to follow-up within 90 days
1 Lost to follow-up within 90 days
369 Analysed under full analysis set
283 Analysed under per-protocol analysis
344 Analysed under as-treated analysis
350 Analysed under full analysis set
291 Analysed under per-protocol analysis
379 Analysed under as-treated analysis


Modified Rankin Scale Score
0
1
2
3
4
6
DAPT Group (N=369)
75.3
18.4
2.2
2.2
1.4
0.5
Alteplase Group (N=350)
72.9
18.6
4.0
2.0
1.6
0.9
0
10
20
30
40
50
60
70
80
90
100
Percent of Patients

Alteplase Group (N=350)	72.9	18.6	4.0	2.0	1.6	0.9
DAPT Group (N=369)	75.3	18.4	2.2	2.2	1.4	0.5
	0	1	2	3	4	6


DAPT
Group
(N=369)
Alteplase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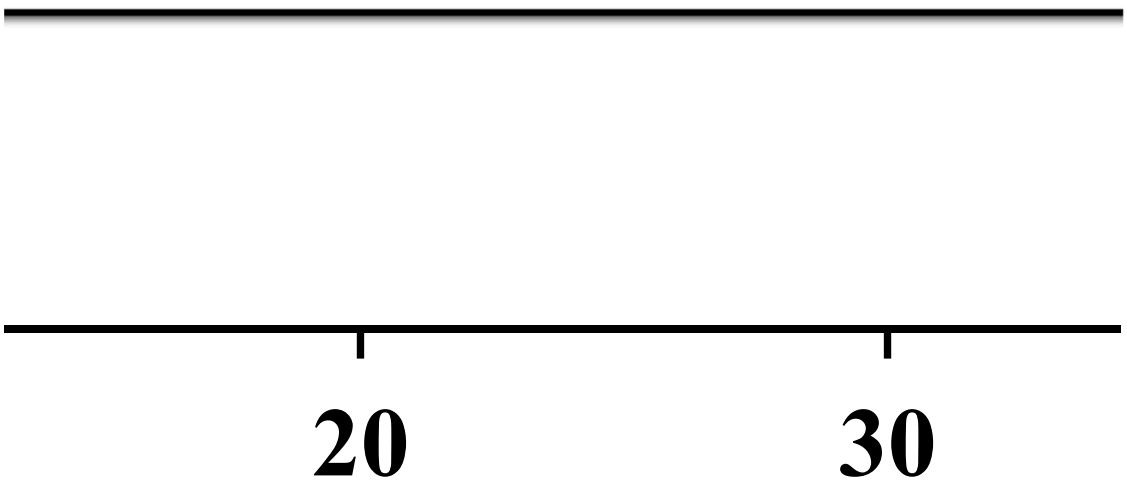
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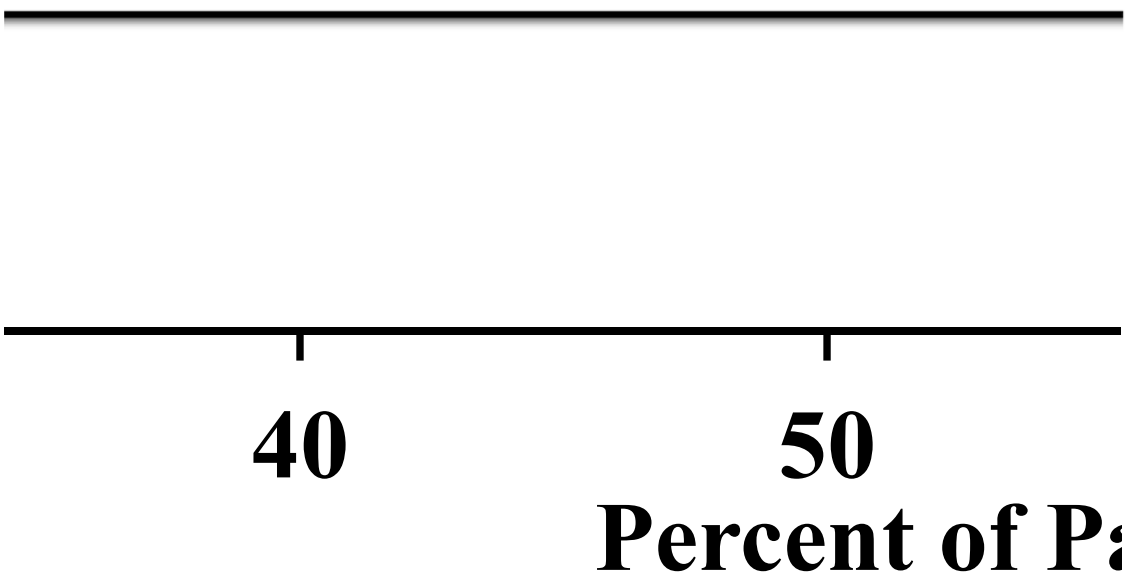
Modified Rankin Sca

75.3


72.9
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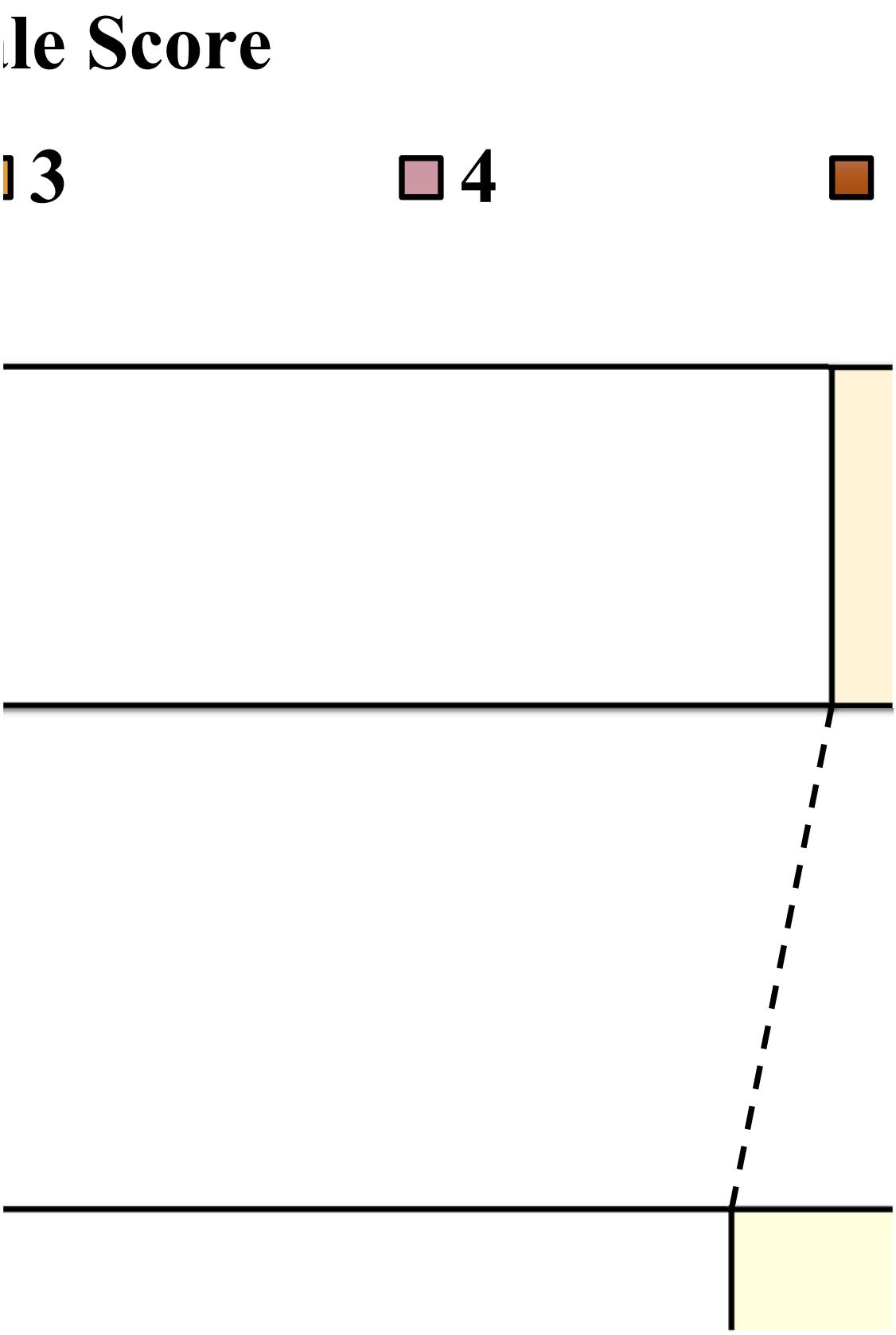
50
Percent of Pa


le Score
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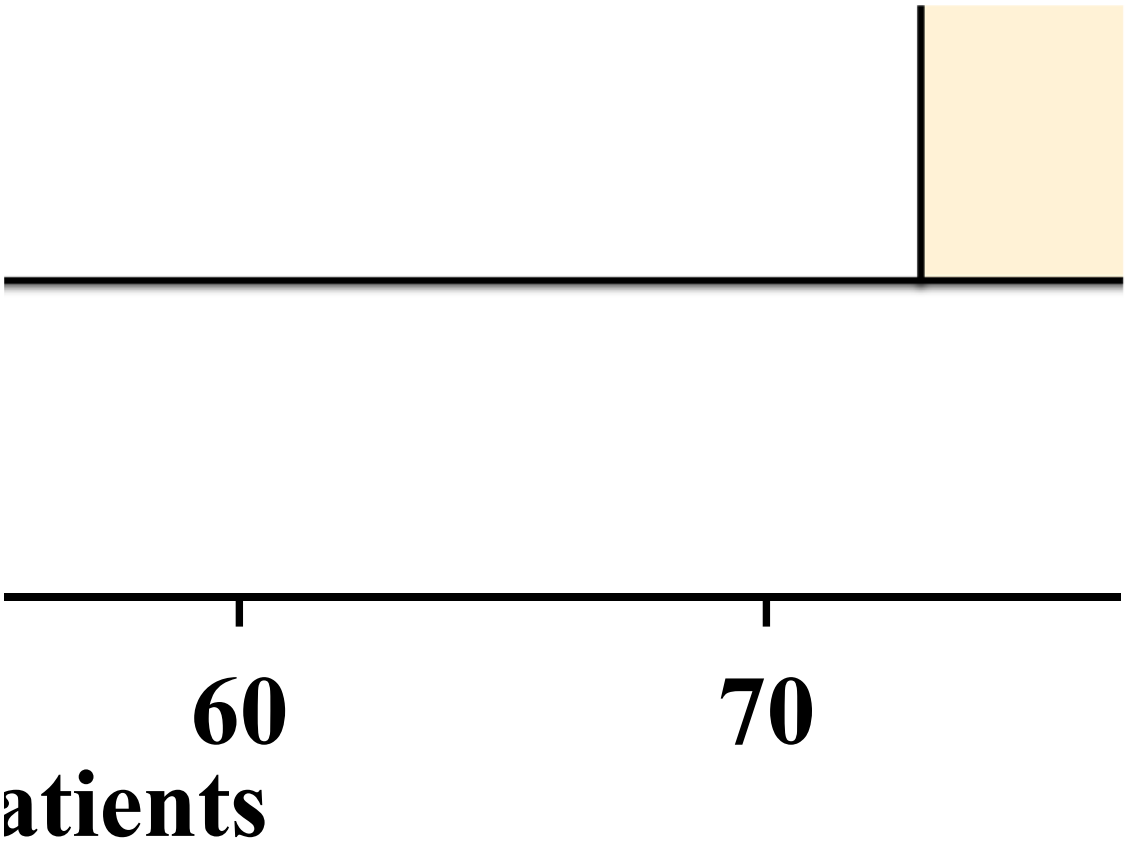
4


60
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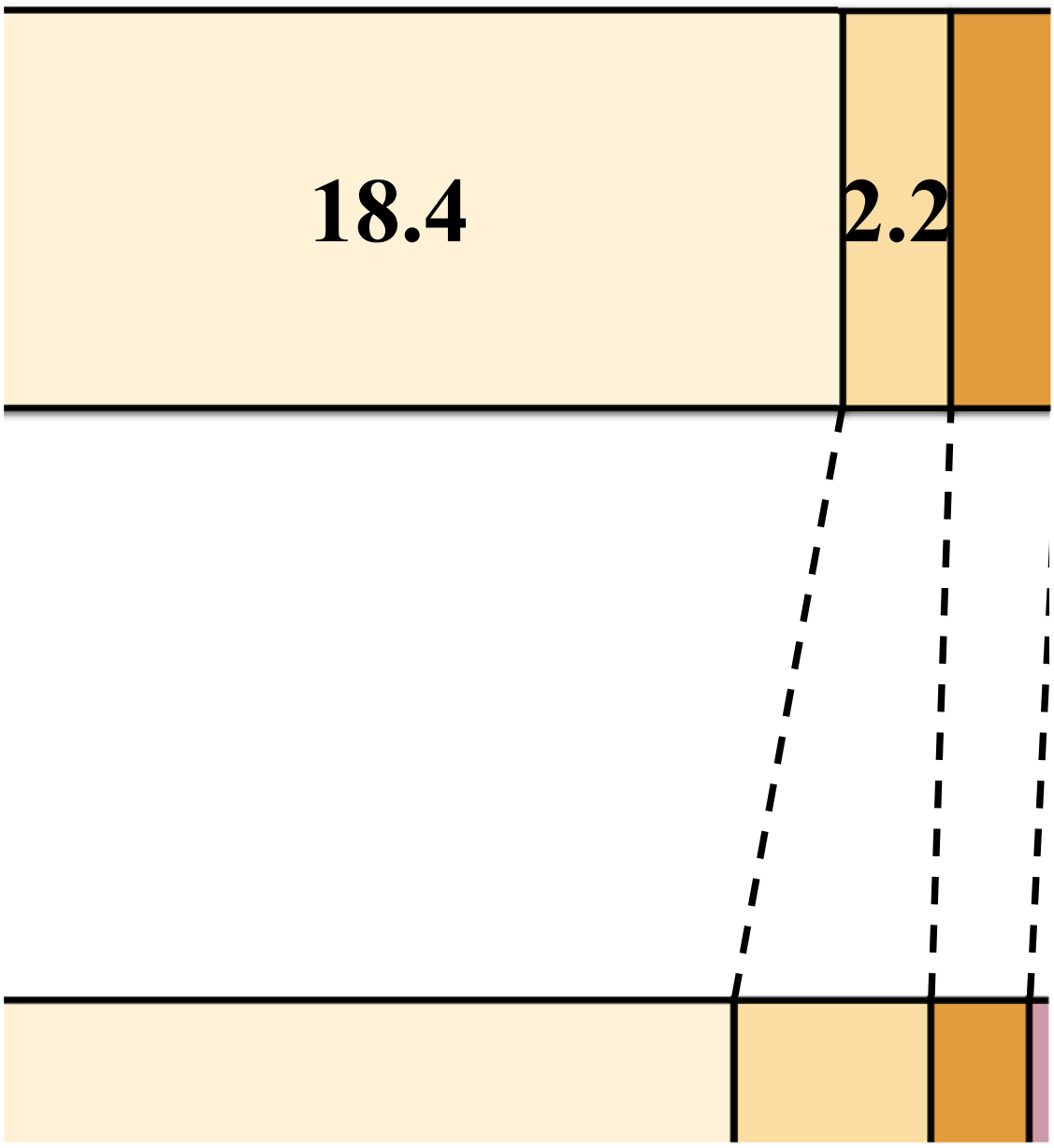
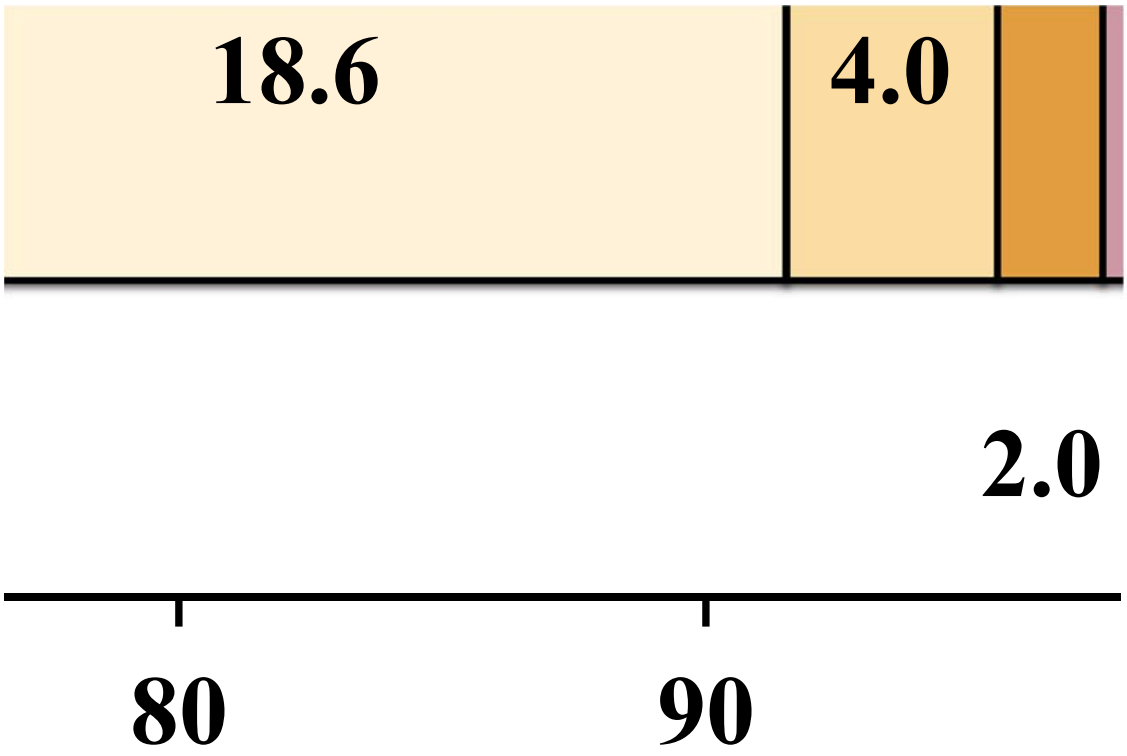
atients

6

2.2




18.6
4.0
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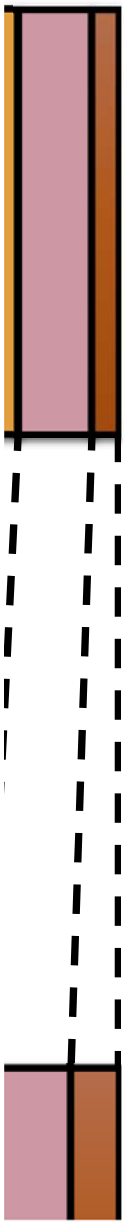
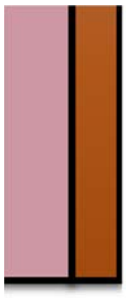
90

1.4 0.5

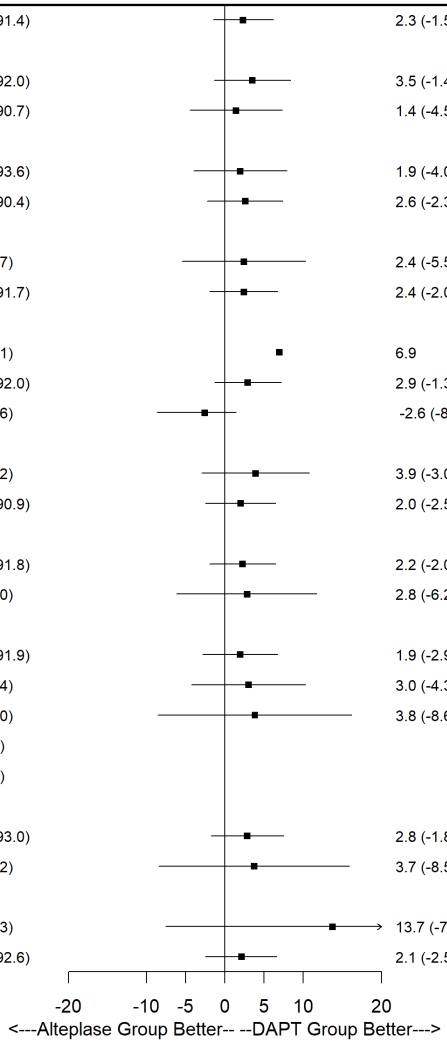




1.6 0.9

100

Subgroup	No. of Patients	DAPT Group Events, n/N (%)	Alteplase Group Events, n/N (%)	Risk Difference (95% Confidence Interval)	P Value for Interaction
Overall	719	346/369 (93.8)	320/350 (91.4)	2.3 (-1.5 to 6.2)	
Age (years)					**.60**
<65	366	170/178 (95.5)	173/188 (92.0)	3.5 (-1.4 to 8.4)	
≥65	353	176/191 (92.1)	147/162 (90.7)	1.4 (-4.5 to 7.3)	
Sex					**.88**
Female	223	108/113 (95.6)	103/110 (93.6)	1.9 (-4.0 to 7.9)	
Male	496	238/256 (93.0)	217/240 (90.4)	2.6 (-2.3 to 7.4)	
History of diabetes mellitus					**.99**
Yes	187	94/101 (93.1)	78/86 (90.7)	2.4 (-5.5 to 10.3)	
No	532	252/268 (94.0)	242/264 (91.7)	2.4 (-2.0 to 6.7)	
NIHSS score at admission					**.33**
0	56	27/27 (100.0)	27/29 (93.1)	6.9	
1-3	529	264/278 (95.0)	231/251 (92.0)	2.9 (-1.3 to 7.2)	
4-5	134	55/64 (85.9)	62/70 (88.6)	-2.6 (-8.7 to 1.4)	
Time from the onset of symptom to treatment (hours)					**.65**
≤2	145	69/71 (97.2)	69/74 (93.2)	3.9 (-3.0 to 10.8)	
>2	574	277/298 (93.0)	251/276 (90.9)	2.0 (-2.5 to 6.5)	
Location of responsible vessel					**.92**
Anterior circulation stroke	562	266/283 (94.0)	256/279 (91.8)	2.2 (-2.0 to 6.5)	
Posterior circulation stroke	153	77/83 (92.8)	63/70 (90.0)	2.8 (-6.2 to 11.7)	
Stroke etiology					**.76**
Undetermined cause	446	221/225 (93.8)	203/221 (91.9)	1.9 (-2.9 to 6.7)	
Small artery occlusion	166	83/87 (95.4)	73/79 (92.4)	3.0 (-4.3 to 10.3)	
Large artery arteriosclerosis	100	49/54 (90.7)	40/46 (87.0)	3.8 (-8.6 to 16.2)	
Other determined cause	5	2/2 (100.0)	3/3 (100.0)		
Cardioembolic	2	1/1 (100.0)	1/1 (100.0)		
Degree of reponsible vessel stenosis					**.90**
≤50%	375	182/190 (95.8)	172/185 (93.0)	2.8 (-1.8 to 7.5)	
>50%	102	50/55 (90.9)	41/47 (87.2)	3.7 (-8.5 to 15.9)	
Large artery occlusion					**.30**
Yes	36	19/20 (95.0)	13/16 (81.3)	13.7 (-7.6 to 35.1)	
No	441	213/225 (94.7)	200/216 (92.6)	2.1 (-2.5 to 6.6)	



Subgroup	No. of Patients	DAPT Group Events, n/N (%)	Alteplase Group Events, n/N (%)	Risk Difference (95% Confidence Interval)	P Value for Interaction
Overall	719	346/369 (93.8)	320/350 (91.4)	2.3 (–1.5 to 6.2)	
Age (years)					**.60**
<65	366	170/178 (95.5)	173/188 (92.0)	3.5 (–1.4 to 8.4)	
=65	353	176/191 (92.1)	147/162 (90.7)	1.4 (–4.5 to 7.3)	
Sex					**.88**
Female	223	108/113 (95.6)	103/110 (93.6)	1.9 (–4.0 to 7.9)	
Male	496	238/256 (93.0)	217/240 (90.4)	2.6 (–2.3 to 7.4)	
History of diabetes mellitus					**.99**
Yes	187	94/101 (93.1)	78/86 (90.7)	2.4 (–5.5 to 10.3)	
No	532	252/268 (94.0)	242/264 (91.7)	2.4 (–2.0 to 6.7)	
NIHSS score at admission					**.33**
0	56	27/27 (100.0)	27/29 (93.1)	6.9	
1–3	529	264/278 (95.0)	231/251 (92.0)	2.9 (–1.3 to 7.2)	
4–5	134	55/64 (85.9)	62/70 (88.6)	–2.6 (–8.7 to 1.4)	
Time from the onset of symptom to treatment (hours)					**.65**
=2	145	69/71 (97.2)	69/74 (93.2)	3.9 (–3.0 to 10.8)	
>2	574	277/298 (93.0)	251/276 (90.9)	2.0 (–2.5 to 6.5)	
Location of responsible vessel					**.92**
Anterior circulation stroke	562	266/283 (94.0)	256/279 (91.8)	2.2 (–2.0 to 6.5)	
Posterior circulation stroke	153	77/83 (92.8)	63/70 (90.0)	2.8 (–6.2 to 11.7)	
Stroke etiology					**.76**
Undetermined cause	446	221/225 (93.8)	203/221 (91.9)	1.9 (–2.9 to 6.7)	
Small artery occlusion	166	83/87 (95.4)	73/79 (92.4)	3.0 (–4.3 to 10.3)	
Large artery arteriosclerosis	100	49/54 (90.7)	40/46 (87.0)	3.8 (–8.6 to 16.2)	
Other determined cause	5	2/2 (100.0)	3/3 (100.0)		
Cardioembolic	2	1/1 (100.0)	1/1 (100.0)		
Degree of reponsible vessel stenosis					**.90**
=50%	375	182/190 (95.8)	172/185 (93.0)	2.8 (–1.8 to 7.5)	
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Large artery occlusion					**.30**
Yes	36	19/20 (95.0)	13/16 (81.3)	13.7 (–7.6 to 35.1)	
No	441	213/225 (94.7)	200/216 (92.6)	2.1 (–2.5 to 6.6)