

Patients with acute ischemic stroke or transient ischemic attack (TIA) are at high risk of recurrent stroke and poor functional outcomes within months.¹⁻³ High levels of low-density lipoprotein cholesterol (LDL-C) and other atherogenic lipoproteins may contribute to this risk. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) and the Treat Stroke to Target (TST) trials indicated that administering intensive statin therapy to lower LDL-C levels in patients with stroke or TIA is effective in reducing the risk of stroke recurrence. Based on previous studies that focused on the nonacute phase, current guidelines recommend high-intensity statin therapy for secondary prevention in patients with atherosclerotic ischemic stroke.⁴ However, guidelines lack clear recommendations for the timing of statin administration in the acute phase, which had been discussed in acute coronary syndromes.⁵ Results from the Fast Assessment of Stroke and TIA to Prevent Early Recurrence (FASTER) study with small sample size (N = 100) showed no superiority of simvastatin initiated acutely to placebo. The use of immediate or delayed high-intensity statins within 24 hours of stroke remains controversial, particularly for those patients with acute mild stroke or high-risk TIA of presumed atherosclerotic cause.⁶⁻⁸ Thus, the safety and efficacy of immediate high-intensity statin therapy for reducing early recurrence are still uncertain.

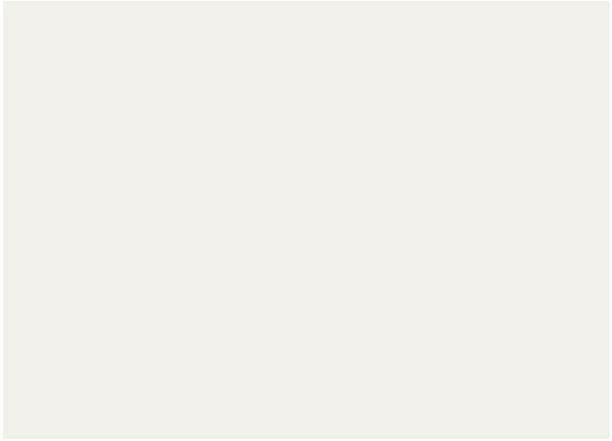
In addition to their LDL-lowering effects, statins have been found to possess various cytoprotective benefits, including protection of endothelial function, antioxidant properties, and anti-inflammatory effects.⁹⁻¹¹ Preclinical studies have shown that administering statins immediately after a stroke can reduce the size of the infarct and improve neurological outcomes.¹² In humans, the SPARCL trial suggests that atorvastatin, 80 mg per day, may improve functional outcome at 5 years as compared with placebo in patients with recurrent stroke. Meta-analysis and observational studies have further indicated that early statin treatment is associated with good functional outcome and lower mortality.¹³⁻¹⁵ Conversely, discontinuation of statin treatment after admission has been linked to poorer functional outcomes, increased mortality, and dependence.¹⁶ However, there is a lack of high-quality RCTs providing evidence for the neuroprotective effects or for the effective improvement of functional outcomes in patients receiving acute statin treatment.

We conducted the Intensive Statin and Antiplatelet Therapy for High-Risk Intracranial or Extracranial Atherosclerosis (INSPIRES) trial. This study aimed to determine (1) whether immediate-intensive statin therapy initiated within 24 hours of symptom onset is safe and can lower the risk of recurrent stroke compared with delayed therapy in patients with mild ischemic stroke or high-risk TIA and atherosclerosis and (2) whether immediate-intensive statin therapy improves functional outcomes in these patients.

Methods

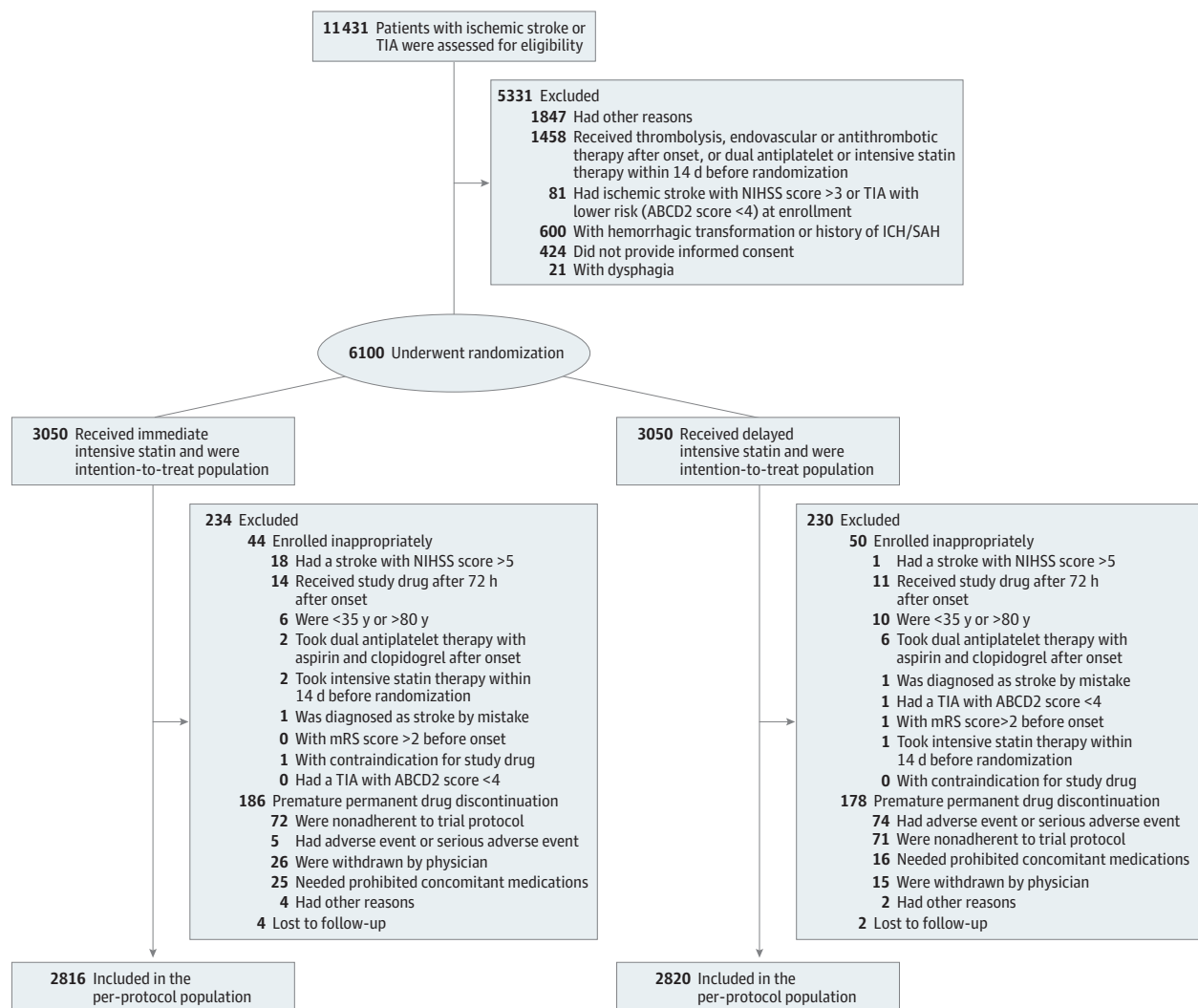
Study Design

The INSPIRES study was a multicenter, double-blind, placebo-controlled, 2 × 2 factorial, randomized clinical trial in which



patients at 10 centers in China underwent randomization from September 2013 to October 2014. Results of the intensive statin arm are presented here whereas results of an arm comparing the combination of clopidogrel with aspirin vs aspirin alone will be published elsewhere. Details of the rationale and design of the INSPIRES study have been described previously. The protocol, statistical analysis plan, and information on committees, sites, and investigators are available in [Supplement 1](#), [Supplement 2](#), and the eAppendix in [Supplement 3](#), respectively. The trial was approved by the ethics committee at Bptembijg

Figure 1. Enrollment and Randomization of Patients



Patients who were enrolled inappropriately or discontinued trial drug were included in the intention-to-treat analysis, as were patients who died of a cause other than stroke or were lost to follow-up. The ABCD2 score assess the risk of stroke on the basis of age, blood pressure, clinical features, duration of transient

ischemic attack (TIA), and presence of diabetes (range, 0-7, higher scores indicating higher risk of stroke) ICH indicates intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SAH, subarachnoid hemorrhage.

anticoagulation therapy, or antiplatelet therapy except for clopidogrel and aspirin after onset; if they received dual antiplatelet therapy with aspirin and clopidogrel or intensive statin therapy within weeks before randomization; or if they had severe hepatic or kidney dysfunction. A complete description of the inclusion and exclusion criteria for the trial is available in the eAppendix of Supplement .

Randomization and Masking

Eligible participants were randomly assigned in a 1:1:1 ratio into groups as follows: () intensive antiplatelet therapy plus immediate-intensive statin therapy, () intensive antiplatelet therapy plus delayed-intensive statin therapy, () standard antiplatelet therapy plus immediate-intensive statin therapy, and () standard antiplatelet therapy plus delayed-intensive statin

therapy. A randomization sequence was computer generated centrally and stratified by participating centers via block randomization, with a block size of with stratification for study sites, at the Statistics and Data Centre at the China National Clinical Research Center for Neurological Diseases (Beijing, China). All the participants and their representatives, investigators, the independent clinical event adjudication committee, and the data safety and monitoring board were masked to treatment allocation. Participants were assigned a random number corresponding to a medication package that was administered to the patient.

Procedures

Participants in the immediate-intensive statin therapy group received atorvastatin, mg daily, for days to , followed

Table 1. Baseline Characteristics of the Patients

Characteristic	Immediate-intensive statin (n = 3050)	Delayed-intensive statin (n = 3050)
Age, median (IQR), y	65 (57-71)	65 (57-71)
Sex, No. (%)		
Women	1056 (34.6)	1129 (37.0)
Men	1994 (65.4)	1921 (63.0)
Body mass index, median (IQR) ^a	24.5 (22.6-26.7)	24.4 (22.6-26.6)
Medical history, No. (%)		
Hypertension	2044 (67.0)	2039 (66.9)
Diabetes	813 (26.7)	845 (27.7)
Dyslipidemia	115 (3.8)	111 (3.6)
Previous ischemic stroke	927 (30.4)	882 (28.9)
Previous TIA	47 (1.5)	50 (1.6)
Previous myocardial infarction	53 (1.7)	60 (2.0)
Current smoker, No. (%)	876 (28.7)	907 (29.7)
Application of agents before events, No. (%) ^b		
Lipid-lowering agents	302 (9.9)	285 (9.3)
Aspirin	403 (13.2)	390 (12.8)
Clopidogrel	22 (0.7)	21 (0.7)
Qualifying event, No. (%)		
TIA	429 (14.1)	372 (12.2)
Acute single ischemic infarction	583 (19.1)	591 (19.4)
Acute multiple ischemic infarctions	2038 (66.8)	2087 (68.4)
With ≥50% symptomatic stenosis, No./total No. (%) ^c		
Yes	2446/2979 (82.1)	2469/2989 (82.6)
No	533/2979 (17.9)	520/2989 (17.4)
NIHSS in qualifying ischemic stroke, No./total No. (%) ^d		
≤3	2000/2621 (76.3)	2033/2678 (75.9)
>3	621/2621 (23.7)	645/2678 (24.1)
ABCD2 score among patients with TIA, No./total No. (%) ^e		
≤5	339/429 (79.0)	302/372 (81.2)
>5	90/429 (21.0)	70/372 (18.8)
LDL-C level at baseline, mean (SD), mmol/L	2.56 (0.78)	2.67 (0.79)
LDL-C level at 90 d, mean (SD), mmol/L	1.98 (0.66)	1.99 (0.70)
Clopidogrel-aspirin assignment, No. (%)	1525 (50)	1525 (50)

Abbreviations: LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

SI conversion factor: To convert LDL-C to milligrams per deciliter, divide by 0.0259.

^a Calculated as weight in kilograms divided by height in meters squared.

^b Patients received medication within 1 month before symptom onset.

^c Data were missing in 132 cases due to the absence of both intracranial and extracranial arterial vascular assessments, or participants did not have more than 50% stenosis in intracranial (or extracranial) arteries but were missing in extracranial (or intracranial) vascular assessments.

^d Scores on the NIHSS range from 0 to 42 for patients with ischemic stroke, with higher scores indicating more severe stroke.

^e The ABCD2 score assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and the presence or absence of diabetes mellitus for patients with transient ischemic attack, with scores ranging from 0 to 7 and higher scores indicating greater risk.

by mg daily for days to . Participants in the delayed-intensive statin therapy group received an atorvastatin placebo for days to , followed by atorvastatin placebo and atorvastatin, mg daily, for days to , and then mg daily for days to . After the -month study therapy, participants received standard care based on the latest guidelines at the discretion of the local investigator, and outcomes were followed up for an additional months with continued information collection, which has yet to undergo analysis. A detailed flowchart of the assessment schedule is provided in the protocol (Supplement).

Outcomes

The primary efficacy outcome was any new stroke (ischemic or hemorrhagic) at days. Secondary efficacy outcomes included composite vascular event (stroke, myocardial infarction [MI], or vascular death), ischemic stroke, TIA, MI, vascular death, and poor functional outcome (mRS score of -) within months. The new stroke or TIA was also measured using a -level ordered category scale that incorporated vascular events with mRS score: = death, = fatal stroke (stroke with subsequent death), = severe stroke (stroke followed by mRS score of or), = moderate stroke (stroke followed by mRS score of or), = mild stroke (stroke followed by mRS score of or), = TIA, and = neither stroke nor TIA at months. Definitions for efficacy outcomes can be found in Supplement .

The primary safety outcome was moderate to severe bleeding defined by the standards from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria. The secondary safety outcomes included hepatotoxicity (alkaline phosphatase or aspartate aminotransferase level more than times the upper limit of normal range), muscle toxicity (creatinine kinase level more than times the upper limit of normal range, presence of muscle pain, myopathy, or rhabdomyolysis), all-cause mortality, intracranial hemorrhage, any bleeding, and additional adverse or severe adverse events within days.

All efficacy and safety outcome events were confirmed by an independent clinical event adjudication committee whose members were unaware of the study group assignments. The committee physicians adjudicated ischemic stroke subtypes, MI, and death according to available medical records, including imaging examinations.

Sample Size Calculation

The minimal sample size for the trial is determined by the necessity that a clinically meaningful difference in effectiveness between treatment and control groups has to be detected. Based on previous studies, the risk of new stroke during days is presumed to be . % in the group with aspirin (with half delayed-intensive statin therapy and half immediate-intensive statin therapy) and . % in the delayed-intensive statin therapy group (with half aspirin and half dual antiplatelet therapy), and % in the group with aspirin plus delayed-intensive statin therapy, dual antiplatelet therapy, and immediate-intensive statin therapy can reduce this risk by %. The effects of dual antiplatelet and immediate-intensive statin therapy will be similar and additive. We determined that

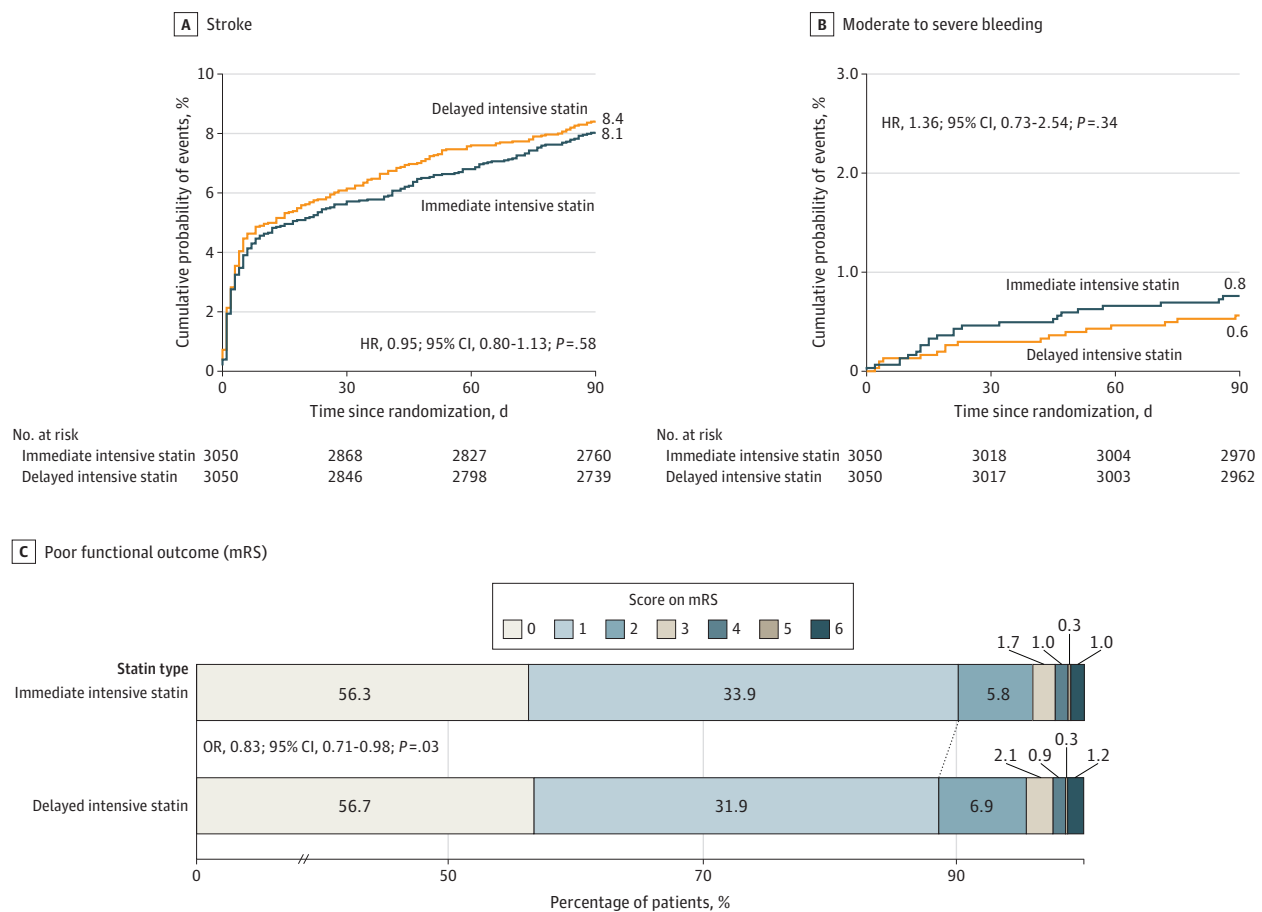
a total of participants would provide % power to detect a relative risk reduction of % in the risk of stroke in the immediate intensive statin group, with a final -sided significance level of . , assuming % overall rate of dropouts. The type I error level of the statistical significance was set at a -sided of . in the final analysis.

Statistical Analysis

The main efficacy and safety analyses were based on the intention-to-treat analysis principle. The cumulative risks of the primary outcome of stroke events during the -day period were assessed with Kaplan-Meier analyses and the log-rank test. Unadjusted differences between the groups in incidences of stroke within days were estimated by using a Cox proportional-hazards method, with pooled study centers (those with < enrolled participants were pooled together) set as a random effect, and hazard ratio (HR) and % CI were reported. Assessment of the interaction between the trial group and a logarithmic function of survival time and proportionality was conducted to verify that no evidence against the proportional hazards assumption was found. Participants were reviewed at their last follow-up evaluation when they experienced a clinical event, at the end of the trial, at the time of withdrawal from the trial, or at the last visit if primary outcome data were missing. If there were multiple events of the same type, the time to the first event was used. Similar methods were applied to compare the secondary efficacy outcomes of composite vascular events, ischemic stroke, hemorrhagic stroke, myocardial infarction, TIA, bleeding, and mortality. Shift analysis was conducted for comparison of the secondary outcomes of ordinal stroke or TIA combined with the mRS outcome between treatment groups using ordinal logistic regression, with the proportionality assumption met, and the common odds ratio (OR) and its % CI were calculated. Poor functional outcome, hepatotoxicity, and muscle toxicity were compared using binary logistic regression with pooled study centers set as a random effect, and the OR and its % CI were calculated. Because of the low rates of mortality in each trial group, we did not conduct a competing risk analysis. Other adverse events and serious adverse events were compared using the test or Fisher exact test. Interactions between treatment assignment and prespecified subgroups for the primary outcome were estimated by including terms for treatment, subgroup, and treatment-by-subgroup interaction in the Cox model.

The statistical analysis plan did not include a provision for correcting for multiplicity when performing tests for secondary or other outcomes; results are reported as point estimates and % CIs. The widths of the CIs have not been adjusted for multiplicity; therefore, the intervals should not be used to infer definitive treatment effects for secondary outcomes. All statistical analyses were performed with SAS software, version . (SAS Institute Inc).

Figure 2. Cumulative Probability of Stroke (Primary Efficacy Outcome) and Moderate to Severe Bleeding and Distribution of Modified Rankin Scale (mRS) Score



A, The probability of ischemic or hemorrhagic stroke. B, The probability of moderate to severe bleeding. C, The distribution of mRS score. HR indicates hazard ratio.

poor functional outcome, there were significant interaction effects with statin treatment \times diabetes (P value for interaction = . . .), indicating possible treatment effect in participants without diabetes (eFigure in Supplement).

Adverse Events

The primary safety outcome, moderate to severe bleeding defined by the GUSTO criteria, occurred in participants (. . %) in the immediate-intensive statin group and participants (. . %) in delayed-intensive statin group (HR, . . ; % CI, . . - . . ; $P = . .$) (Figure B and Table). The rate of secondary safety outcomes was similar across the groups, including hepatotoxicity, muscle toxicity, all-cause mortality (Table), other adverse events (eTable in Supplement), and severe adverse events (eTables and in Supplement). The overall adverse event occurred in participants (. . %) in the immediate-intensive statin group and participants (. . %) in the delayed-intensive statin group ($P = . .$) (eTable in Supplement). The results of the per-protocol analysis of safety were consistent with those of the primary intention-to-treat analysis (eTable in Supplement).

Discussion

In this doubled-blind, placebo-controlled, randomized clinical trial in Chinese patients with mild ischemic stroke or high-risk TIA presumed to be caused by atherosclerosis, immediate-intensive statin therapy showed no significant difference compared with delayed-intensive statin therapy in reducing the risk of stroke. However, secondary analysis suggested that immediate treatment may be associated with reduced risk of poor functional outcome at days, compared with delayed-intensive statin therapy. There were no substantial differences observed in the incidence of adverse events, such as bleeding, hepatotoxicity, or muscle toxicity, between the groups.

Currently, guidelines recommend high-intensity statins for secondary prevention for patients with ischemic stroke. The mechanisms of improving outcomes by statins after ischemic events may include LDL-C lowering, neuroprotective effects, and enhancing endothelial function. However, evidence for the effect of statins in reducing stroke recurrence after immediate administration in patients with acute ischemic stroke remains unclear, particularly in the acute phase (within hours). Pre-

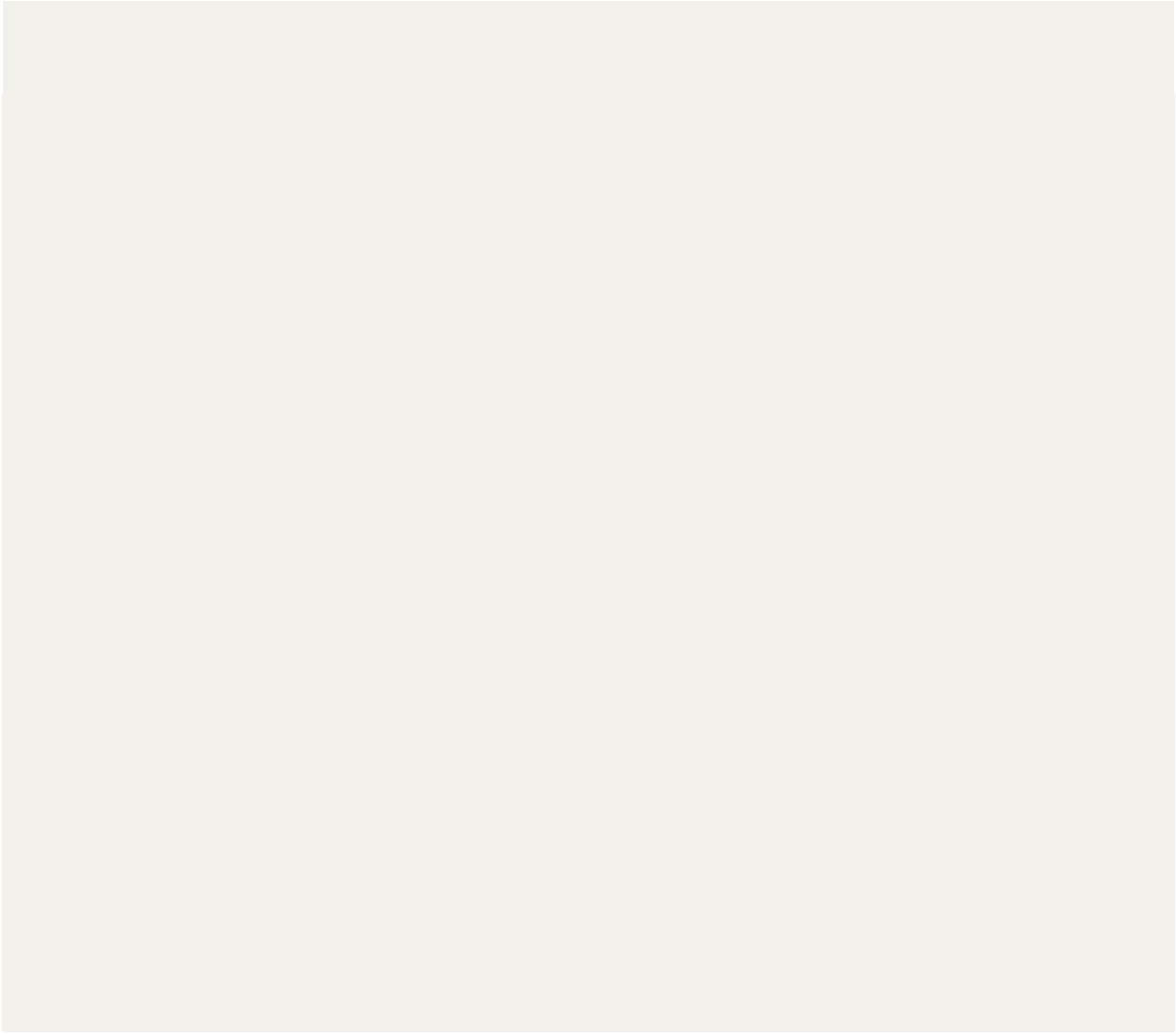
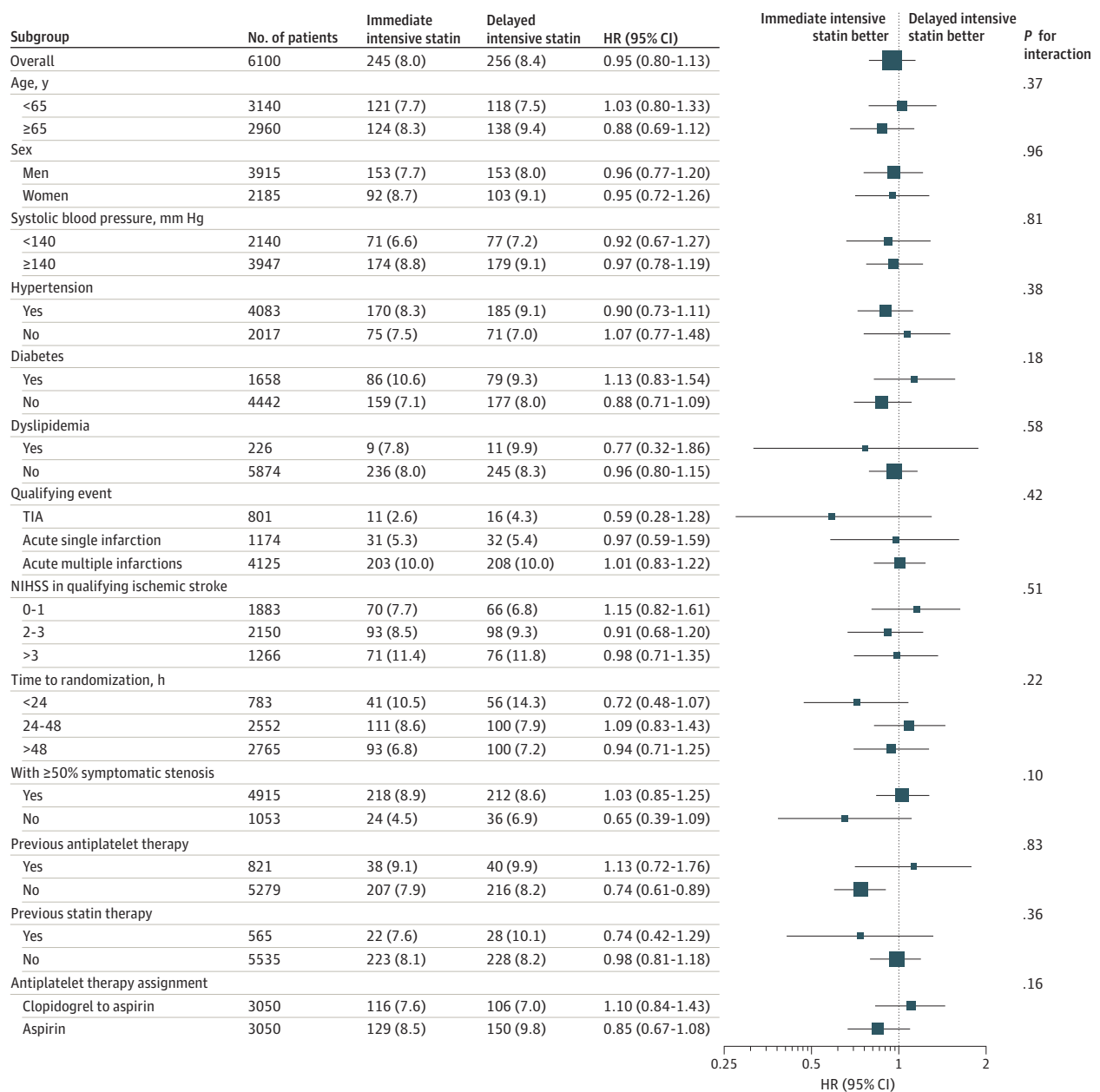


Figure 3. Hazard Ratio (HR) for the Stroke According to Prespecified Subgroups



The trial was not powered to allow definite conclusions based on the results of the subgroup analyses. Systolic blood pressure data were missing in 8 patients in the immediate statin group and 5 patients in the delayed statin group. Data

on 50% or greater symptomatic stenosis were missing in 71 patients in the immediate statin group and 61 patients in the delayed statin group. NIHSS indicates National Institutes of Health Stroke Scale.

stroke. Our study demonstrated that immediate-intensive statin therapy was marginally associated with improved functional outcomes at 90 days, different from the results of the Stroke Treatment With Acute Reperfusion and Simvastatin (STARS) and Administration of Statin on Acute Ischemic Stroke Patient (ASSORT) trials. Moreover, patients without a history of diabetes or dyslipidemia might receive the pronounced clinical benefit from immediate-intensive statin with better functional outcome. The discrepant results may be attributed to the

differences in sample sizes of each trial, stroke etiology differences, and inadequate doses of statins in previous studies. Our study provides some evidence of the benefits of early intensive statin therapy for patients with acute ischemic stroke, but results will need to be repeated in a trial focused on functional outcome as a primary outcome.

Concerns have been raised about whether statins increase the risk of bleeding, especially in patients with prior intracerebral hemorrhage. Previous studies have produced

conflicting results on this matter. The SPARCL trial and the Heart Prevention Study reported an increased risk of bleeding with statin treatment in patients with prior stroke, whereas other studies have found no evidence of such risk. We found that immediate-intensive statin therapy did not increase the risk of bleeding within 7 days and appeared to be safe in the short term. This study did not provide evidence of increased risk of bleeding within 7 days in immediate-intensive statin therapy group.

Limitations

One of the major limitations was that the population studied (mainly Han Chinese patients) may imply differences in prior and concurrent exposures and ethnocultural practices as compared with other populations, with low statin use at baseline. There may be limitation of potential underpower for interaction within the 2×2 design. Thus, we might necessarily assume no interaction here between antiplatelet therapy and lipid-lowering therapy. The large number of statistical tests in this study, lack of control for multiple hypothesis tests, small

sample size in subgroups, lack of generalizability, low proportion (10%) of women enrolled, and site-to-site variability also need to be considered as potential limitations. Furthermore, we did not have enough power for the secondary outcome of functional outcome. With a negative primary outcome, the results of the secondary outcome (functional outcome) must be evaluated as hypothesis generating.

Conclusions

In conclusion, this randomized clinical trial in Chinese patients with acute mild ischemic stroke or high-risk TIA from atherosclerosis revealed that immediate-intensive statin therapy administered within 7 hours after symptom onset did not significantly reduce the risk of subsequent stroke as compared with delayed-intensive statin therapy within 7 days. However, immediate-intensive statin therapy may be related to improved functional outcomes with no increase in risk of bleeding at 7 days as compared with delayed therapy.

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