Safety and Efficacy of Atorvastatin for Chronic Subdural Hematoma in Chinese Patients
A Randomized ClinicalTrial

Rongcai Jiang, MD, PhD; Shiguang Zhao, MD, PhD; Renzhi Wang, MD, PhD; Hua Feng, MD, PhD; Jianmin Zhang, MD, PhD; Xingang Li, MD, PhD; Ying Mao, MD, PhD; Xianrui Yuan, MD, PhD; Zhou Fei, MD, PhD; Yuanli Zhao, MD, PhD; Xinguang Yu, MD, PhD; Wai Sang Poon, MBCHB, FRCSEd, FHKAM; Xide Zhu, MD; Ning Liu, MD; Dezhi Kang, MD, PhD; Tao Sun, MD; Baohua Jiao, MD, PhD; Xianzhi Liu, MD; Rutong Yu, MD, PhD; Junyi Zhang, MD; Guodong Gao, MD, PhD; Jiehe Hao, MD; Ning Su, MD; Gangfeng Yin, MD; Xingen Zhu, MD; Yicheng Lu, MD; Junji Wei, MD, PhD; Jin Hu, MD, PhD; Rong Hu, MD, PhD; Jianrong Li, MD; Dong Wang, MD, PhD; Huijie Wei, MD, PhD; Ye Tian, MD, PhD; Ping Lei, MD, PhD; Jing-fei Dong, MD, PhD; Jianning Zhang, MD, PhD

+ **Supplemental content**

IMPORTANCE Chronic subdural hematoma (CSDH) is a trauma-associated condition commonly found in elderly patients. Surgery is currently the treatment of choice, but it carries a significant risk of recurrence and death. Nonsurgical treatments remain limited and ineffective. Our recent studies suggest that atorvastatin reduces hematomas and improves the clinical outcomes of patients with CSDH.

OBJECTIVE To investigate the safety and therapeutic efficacy of atorvastatin to nonsurgically treat patients with CSDH.

DESIGN, SETTING, AND PARTICIPANTS The Effect of Atorvastatin on Chronic Subdural Hematoma (ATOCH) randomized, placebo-controlled, double-blind phase II clinical trial was conducted in multiple centers in China from February 2014 to November 2015. For this trial, we approached 254 patients with CSDH who received a diagnosis via a computed tomography scan; of these, 200 (78.7%) were enrolled because 23 patients (9.1%) refused to participate and 31 (12.2%) were disqualified.

INTERVENTIONS Patients were randomly assigned to receive either 20 mg of atorvastatin or placebo daily for 8 weeks and were followed up for an additional 16 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was change in hematoma volume (HV) by computed tomography after 8 weeks of treatment. The secondary outcomes included HV measured at the 4th, 12th, and 24th weeks and neurological function that was evaluated using the Markwalder grading scale/Glasgow Coma Scale and the Barthel Index at the 8th week.

RESULTS One hundred ninety-six patients received treatment (169 men [86.2%]; median [SD] age, 63.6 [14.2] years). The baseline HV and clinical presentations were similar between patients who were taking atorvastatin (98 [50%]) and the placebo (98 [50%]). After 8 weeks, the HV reduction in patients who were taking atorvastatin was 12.55 mL more than those taking the placebo (95% CI, 0.9-23.9 mL; P = .003). Forty-five patients (45.9%) who were taking atorvastatin significantly improved their neurological function, but only 28 (28.6%) who were taking the placebo did, resulting in an adjusted odds ratio of 1.957 for clinical improvements (95% CI, 1.07-3.58; P = .03). Eleven patients (11.2%) who were taking atorvastatin and 23 (23.5%) who were taking the placebo underwent surgery during the trial for an enlarging hematoma and/or a deteriorating clinical condition (hazard ratio, 0.47; 95% CI, 0.24-0.92; P = .03). No significant adverse events were reported.

CONCLUSIONS AND RELEVANCE Atorvastatin may be a safe and efficacious nonsurgical alternative for treating patients with CSDH.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCTO2024373.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jianning Zhang, MD, PhD, Department of Neurosurgery, Tianjin Medical University General Hospital, Tianjin Neurological Institute, 154 Anshan Rd, Heping District, Tianjin, People's Republic of China 300052 (jianningzhang@hotmail.com).

C hronic subdural hematoma (CSDH) is increasingly common because of the aging population.[1] Its incidence increases from 1 to 13 of 100 000 in the general population to 127.1 of 100 000 among patients 80 years or older.[2] More than 80% of patients with CSDH have a history of traumatic brain injury.[3] The current treatment for CSDH is surgery to remove the hematoma,[4] but the surgery carries a recurrence rate of approximately 25.6% in high-risk patients[5] and a mortality rate of 24% to 32% in elderly patients.[6] An overall mortality rate of 38.4% is reported for patients 90 years or older, independent of treatments.[7] Safer and more effective nonsurgical treatments are therefore highly desirable. Dexamethasone, perindopril, and tranexamic acid have been investigated for nonsurgically treating patients with CSDH, but, to our knowledge, they have failed to show significant efficacy in controlled clinical trials.[8,9]

We report the results of a double-blind, randomized, placebo-controlled phase II clinical trial that was designed to test the efficacy of atorvastatin for nonsurgically treating patients with mild to moderate CSDH. This trial was developed based on several lines of supporting evidence. First, the development and recurrence of CSDH is associated with localized inflammation and the overexpression of vascular endothelial growth factor, which leads to the development of immature "leaky" vessels and a subsequent hematoma.[10-12] Our study in a rat model of subdural hematoma supported this mechanism[12] and further demonstrated that blocking inflammation and immature angiogenesis promoted rapid hematoma absorption.[13,14] Second, statins (β-hydroxy β-methylglutaryl-CoA reductase inhibitors), which were originally developed for reducing low-density lipoprotein cholesterol levels in patients with hyperlipidemia,[15] have been shown to reduce inflammation in the vessel wall[16] and mobilize endothelial progenitor cells for vascular repairs.[17-20] Third, our pilot and uncontrolled study of 23 patients with CSDH found that oral atorvastatin (20 mg daily for 1-8 months) significantly reduced hematomas and improved clinical outcomes in 96% of participants,[21] which was consistent with a systematic literature review.[22]

Methods

Patients

Patients who received a diagnosis of mild or moderate subdural hematoma and were treated in outpatient clinics were recruited from February 5, 2014, to November 7, 2015, from 25 neurosurgical departments, all of them members of the Oriental Neurosurgical Evidence-Based Study Team (ONET). ONET was established to foster clinical and research collaborations in neurosurgery between mainland China and Hong Kong. The inclusion criteria included symptomatic patients who were age 18 to 90 years, a diagnosis of unilateral or bilateral supratentorial CSDH by computed tomography (CT), no previous CSDH surgery, and no statin treatment in the previous 6 months. The clinical presentations of the patients were nonfocal, including headache, weakness of limbs, and mental decline. Patients who had a high risk of cerebral hernia, re-

Key Points

Question Can atorvastatin treat chronic subdural hematoma?

Findings In this randomized clinical trial, administering atorvastatin reduced chornic subdural hematomas by 29 mL vs 17 mL for placebo in 8 weeks.

Meaning Atorvastatin is an effective conservative therapy of chronic subdural hematomas.

quired emergency surgery, were allergic to statins, received a diagnosis of cancer, had historical and current bleeding or thrombosis with or without treatment (or were taking prophylactic antiplatelet medications), or had developed multiple organ failure were excluded. The inclusion and exclusion criteria are specified in the original report on the trial design[23] and registration (https://clinicaltrials.gov/ct2/show/NCT02024373).

Study Design and Oversight

This trial was conducted in accordance with the International Conference on Harmonization guidelines for good clinical practice. Its study design was difference-in-difference. The data were collected by the contract research organization Beijing Stemexcel Technology Co. The trial protocol (Supplement 2) was approved by the ethics committees of the participating hospitals and is schematically described in **Figure 1**. During the initial screening, patients were provided with detailed information about the trial and eligible patients were recruited after providing written consent. The patients were centrally randomized using the Data Acquisition System for Electronic Data Capture, version 5.0 (Beijing Stemexcel Technology Co). The demographic information of patients who were enrolled at each study site was imported into the central randomization system, which then generated a random number that determined whether a patient received atorvastatin or placebo at a randomization ratio of 1:1. There was no stratification during the randomization. Atorvastatin (Pfizer) and the placebo were stored at individual participating hospitals (at 20°-30°C and while avoiding direct light), with access restricted to research nurses who were responsible for the storage, distribution, and inventory of the medications. The placebo pills were made of dextrin and had the same weight and appearance as the atorvastatin (Shandong ARURA Pharmaceutical Research & Development Co). All the patients were treated in an outpatient setting and received 7-day supplies of the medication in 7 individual packages. They returned the empty packages at the end of each week to exchange them for the next week's supply until the treatment ended.

For recruitment, each patient or guardian, assisted by a nurse coordinator who was assigned to the study, completed a short questionnaire about his or her condition, underwent physical examinations that were conducted by an attending neurosurgeon who was masked to the treatment, and received a CT scan. All data were collected onsite by nurse coordinators and submitted electronically to the data acquisition system, which also randomized the patients. All data

Figure 1. Schematic Illustration of the Trial Protocol
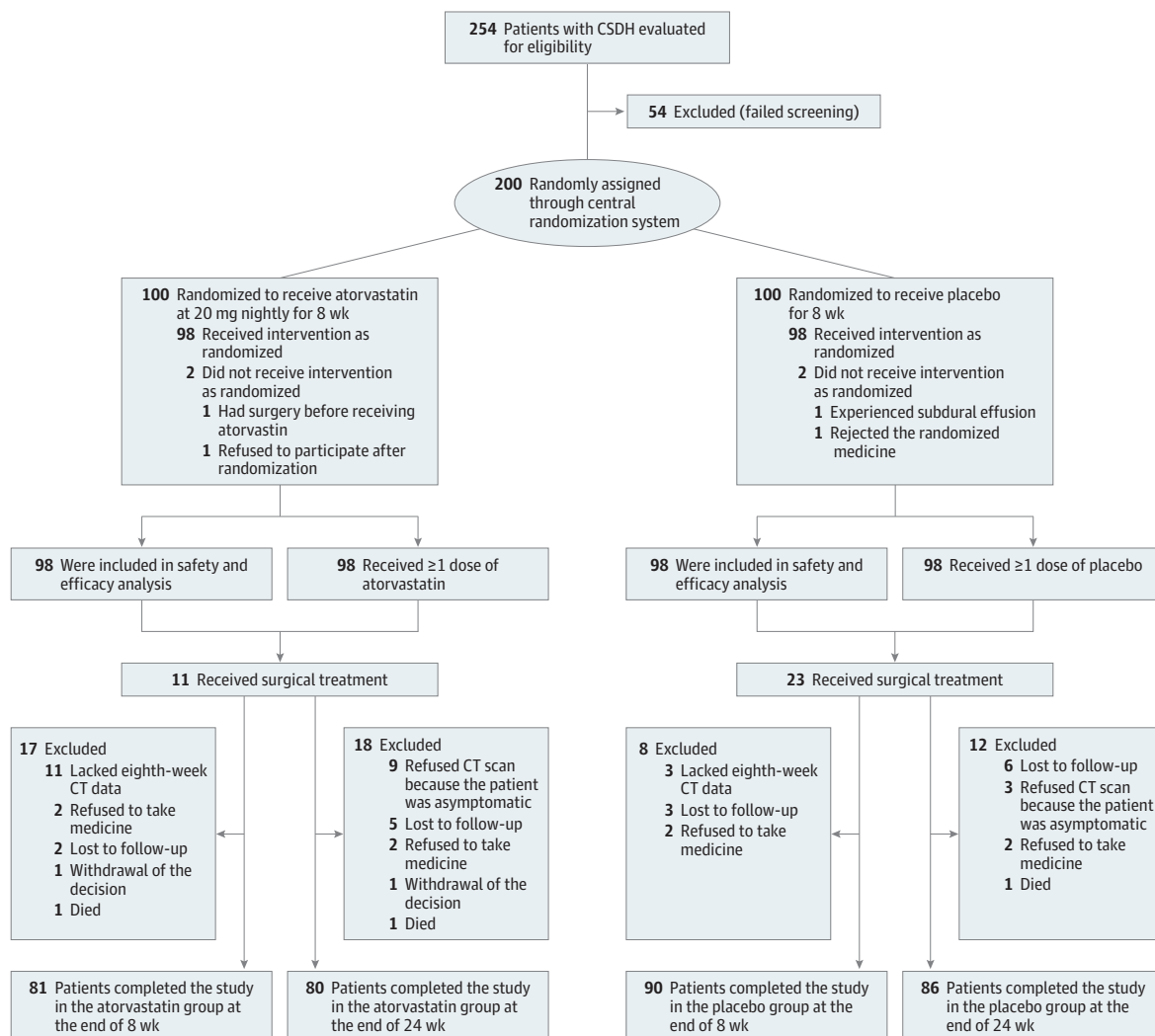
CSDH indicates chronic subdural hematoma; CT, computed tomography.

entries were validated by a second nurse before submission. The trial was overseen by a data monitoring board that was independent of the study investigators. This board was composed of clinicians, neurosurgeons, clinical trial experts, epidemiologists, and biostatisticians from university hospitals and the contracted trial design organization.

Atorvastatin was administered at 20 mg per night for 8 weeks. This dosage was chosen because it is used for patients with hyperlipidemia with minimal adverse effects[24,25] and because atorvastatin at a higher dose (80 mg) was reported to increase the risk of bleeding in patients with a low body weight and uncontrolled hypertension in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial.[26] Treatment compliance was monitored by regular contact with the patients and by pill counting during patients' weekly visits to their outpatient clinics. Patients were also evaluated by plasma levels of low-density lipoprotein cholesterol on the eighth week of treatment, when the primary study variable was recorded,

as an indicator of atorvastatin ingestion (compliance). After 8 weeks of treatment, the patients were followed up for another 16 weeks. During the trial, patients would undergo surgery to remove a hematoma when their neurological dysfunction deteriorated (worsened headache, progressive limb paralysis, or changes in levels of consciousness) or CT scan results showed a hematoma enlargement and/or a midline shift of more than 1 cm. The decision to undergo surgery was masked to the treatment assignments.

The primary outcome of the trial was changes in HV (in milliliters) from the pretreatment baseline after 8 weeks of treatments. Hematoma volume measured in the 4th, 12th, and 24th weeks after enrollment served as secondary outcomes. Hematoma volume was measured using the Tada formula on the CT scan: maximal length × maximal width × maximal thickness of a hematoma, then divided by 2.[27] The location, density, and compartmentalization of the hematoma, and the presence of basal ganglia suppression and midline shift, were also

recorded. To standardize the measurements and reduce interhospital variation, CT scan images from patients who were enrolled at each study site were electronically sent to the medical imaging center of Tianjin Medical University General Hospital and analyzed by 3 neuroradiologists who were masked to the treatment. If the coefficient of variation among HV measurements by the 3 neuroradiologists was more than 25%, a fourth neuroradiologist was called in to perform an additional analysis.

The secondary outcome also included the assessment of neurological function after 8 weeks of treatment, which was evaluated at each study site by 2 attending neurosurgeons who were masked to the treatment. Neurological function was evaluated using the Markwalder grading scale/Glasgow Coma Scale (eTable 1 in Supplement 1), which provides a combined score of the activities of daily living (ADL) and the Barthel Index (which measures the daily living activities of patients with neurological diseases[8,28,29]), and the Glasgow Outcome Scale (GOS). The GOS was originally developed to evaluate the recovery of patients with traumatic brain injury, who are much younger than patients with CSDH. A potential cofounding factor is that aging patients may require living assistance independent of CSDH, which potentially exaggerates the GOS score. For patients who underwent surgery during the trial, the HV measurements that were made immediately before surgery were recorded as the primary outcome and were compared with the baseline. Complete blood cell counts, and serum levels of alanine aminotransferase, aspartate transaminase, gamma glutamyl transpeptidase, urea nitrogen, and creatinine were measured at the baseline and at the 4th, 8th, and 24th weeks of the trial to evaluate hematological, liver, and kidney function.

Statistical Analysis

The data were analyzed by Beijing Stemexcel Technology Co independently of the study investigators. The results from our pilot study[21] indicated that an estimated 80% of patients in the atorvastatin group would achieve hematoma reduction and neurological improvement, but only 50% of placebo patients would have the same outcome. With 90% power and a type I error probability of .05, we needed to recruit a minimum of 51 patients in each group to reach statistical significance, as previously described in the trial design.[23] We also included a 40% dropout to calculate the sample size.

The trial data were analyzed according to the modified intention-to-treat principle and based on the full analysis set (FAS) and the per protocol set (PPS). The FAS included the patients who took the drug at least once and underwent the primary therapeutic evaluation data at baseline. In the FAS, missing data from the 8 weeks of treatment were replaced with the last available data according to the last observation carried forward (LOCF) principle. The quantitative results of the study were not altered by the choice of methods that were used to address missing data (baseline observation carried forward, average observation carried forward, and multiple imputation). Unlike the FAS, the PPS included patients who finished the 8 weeks of treatment without undergoing surgery. Changes in HV were initially analyzed using an analysis of covariance

as a linear model, as specified in the trial registration. However, the data on HV changes were found to be asymmetrical (a skewed distribution) during the initial analysis. Therefore, they were presented by median values and analyzed using the Wilcoxon test.

Table. Baseline Characteristics of Patients With CSDH Enrolled in the Study

Characteristic	No. (%)	
	Atorvastatin (n = 98)	Placebo (n = 98)
Age, median (IQR), y[a]	63.0 (24.0-88.0)	67.0 (26.0-89.0)
Male sex[b]	81 (83)	88 (90)
Body height, median (IQR), cm[a]	170.0 (145.0-180.0)	170.0 (153.0-180.0)
Weight, median (IQR), kg[a]	67.0 (44.0-91.5)	65.0 (40.0-100.0)
CSDH with TBI history[b]	89 (91)	88 (90)
Hypertension[b]	15 (15.3)	17 (17.3)
Diabetes[b]	3 (3.1)	9 (9.2)
Hyperlipidaemia[b]	9 (9.2)	14 (14.3)
MGS-GCS score[a]		
0	3 (3)	1 (1)
1	89 (91)	86 (88)
2	6 (6)	11 (11)
ADL-BI score[b]		
<85	18 (18.4)	26 (26.5)
≥85	80 (81.6)	72 (73.5)
Baseline hematoma volume, median (IQR), mL[a]	62.9 (40.7-90.9)	62.3 (39-104.3)
Bilateral hematomas, No.	21 (21.4)	37 (37.8)
Baseline HV in bilateral hematoma, median (IQR)[a]	82.3 (45.2-125.3)	74 (43.2-119.0)

Abbreviations: ADL-BI, activities of daily living–Barthel Index; CSDH, chronic subdural hematoma; HV, hematoma volume; IQR, interquartile range; MGS-GCS, Markwalder grading scale–Glasgow Coma Scale; TBI, traumatic brain injury.
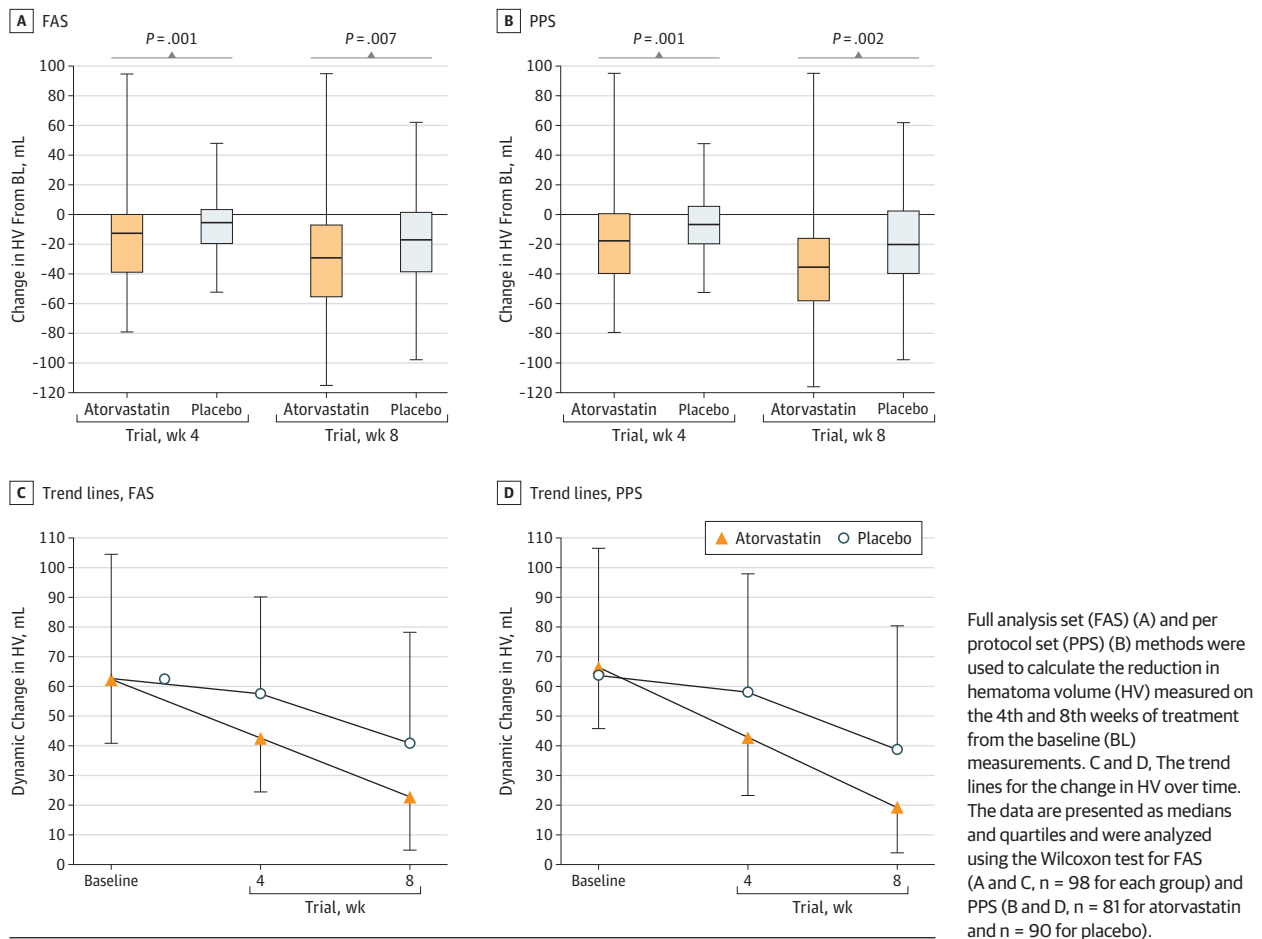
[a] Analysis by Wilcoxon test.

[b] Analysis by χ² test.

Results

A total of 254 patients with CSDH were screened and 200 (78.7%) were enrolled. The regions where these patients were recruited from are listed in eTable 2 in Supplement 1. Among the 54 patients who were excluded from the trial, 6 (11.1%) were currently taking statins, 25 (46.3%) had existing conditions, and 23 (42.6%) refused to participate. Two patients from the atorvastatin group were excluded after randomization but before treatment began because they were switched to surgery for a worsened neurological condition. Two patients from the placebo group were also excluded, 1 because of misdiagnosis and the other because of refusal of treatment (eResults in Supplement 1). A total of 196 patients (98 in each group) received the treatments. There was no significant difference in baseline condition between the 2 groups of patients except for the number of patients with a bilateral hematoma (**Table**). The baseline HV of patients with a bilateral hematoma showed no

Figure 2. Changes in Hematoma Volume

Full analysis set (FAS) (A) and per protocol set (PPS) (B) methods were used to calculate the reduction in hematoma volume (HV) measured on the 4th and 8th weeks of treatment from the baseline (BL) measurements. C and D, The trend lines for the change in HV over time. The data are presented as medians and quartiles and were analyzed using the Wilcoxon test for FAS (A and C, n = 98 for each group) and PPS (B and D, n = 81 for atorvastatin and n = 90 for placebo).

statistical difference between patients taking atorvastatin and patients taking the placebo. The concurrent use of prescription medications among the patients is listed in eTable 3 in Supplement 1 and was found to be randomly distributed between the 2 groups. An extensive literature search found that none of these concurrent medications affected CSDH development or the effects of atorvastatin.

Efficacy of Atorvastatin

The reduction in HV measured after 8 weeks of treatment (the primary outcome) was significantly greater for patients who received atorvastatin (29.40 mL) compared with those who received the placebo (16.85 mL) in the FAS analyses ($z = 7.397$; $P = .01$) (Figure 2A). Patients taking atorvastatin were found to have a reduced HV by 12.55 mL more than patients taking the placebo (95% CI, 0.9-23.9 mL; $P = .003$). The data were also analyzed after adjusting for the confounding variables of age, clinical severity, and the presence of a bilateral hematoma. The adjusted results showed that HV was reduced more in patients who were taking atorvastatin than those taking the placebo (95% CI, 1.187-20.275 mL; $P = .03$). For the FAS analysis, the missing data from the eighth week for patients who were switched to surgery were replaced with the last available data using LOCF. The PPS analysis, which also included patients who

completed 8 weeks of treatment whether or not they underwent surgery, yielded a similar result after adjustingt for the confounding variables (Figure 2B). Hematoma volume was reduced by 15.35 mL more in patients who were taking atorvastatin than patients who were taking the placebo (95% CI, 2.2-26.55 mL; $P = .002$). When plotted as continuous variables, HV reduced gradually in patients of both groups, but the reduction was significantly greater for patients who received atorvastatin (Figures 2C and D), suggesting an accumulative dosing effect of atorvastatin. The HV measured at the 4th, 12th, and 24th weeks after enrollment (secondary outcomes) also showed a significantly greater reduction in patients taking atorvastatin than in those taking the placebo (eTable 4 in Supplement 1). The plasma levels of low-density lipoprotein cholesterol were significantly lower in patients who were taking atorvastatin than in those taking the placebo (eTable 5 in Supplement 1), indicating the patients' compliance in atorvastatin treatment. Together, these data suggest that atorvastatin reduced the volume of CSDH.

Consistent with the HV reduction, 45 patients (45.9%) taking atorvastatin showed significant improvements in neurological function after 8 weeks of treatment (secondary outcome), as compared with only 28 (28.6%) taking the placebo, resulting in an adjusted odds ratio of 1.96 for clinical improve-

Figure 3. Neurological Function and Rate of Surgery
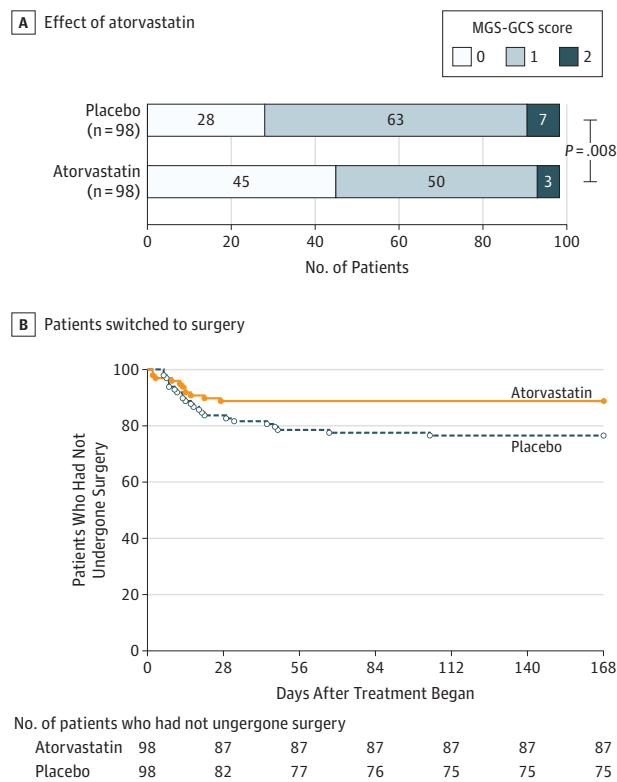
A, The Markwalder grading scale/Glasgow Coma Scale (MGS-GCS) was used to evaluate the effect of atorvastatin on improving the neurological function of patients with chronic subdural hematoma (scores were measured on the eighth week of treatment) (Wilcoxon test, n = 98). B, Patients were switched to surgery because of increasing hematoma volume and/or deteriorating neurological symptoms (log-rank test, n = 196; hazard ratio, 0.47; 95% CI, 0.24-0.92; P = .03).

ments by atorvastatin (95% CI, 1.07-3.58; P = .03) (**Figure 3**A). When patients were ranked by ADL-BI scores as dependent living (ADL < 85) and independent living (ADL ≥ 85),[30] more patients who taking atorvastatin than taking the placebo were found to be independent (eTable 6 in Supplement 1). The GOS score measured at the eighth week was trending for atorvastatin but did not reach statistical significance between the 2 groups (eTable 7 in Supplement 1). These results suggest that atorvastatin could improve neurological function in patients with CSDH.

Patients Switched to Surgery
Thirty-four patients (17.3%) were switched to surgery during the trial because of increased HV and/or exacerbated neurological dysfunction (11 [11.2%] from the atorvastatin group and significantly fewer than 23 [23.5%] from the placebo group) (log-rank test, P = .03) (Figure 3B). The treatment switches were made at various times during the trial (eTable 8 in Supplement 1), but most of the patients who were taking atorvastatin were switched early during the trial. Three of the 11 patients (27.35%) who were taking atorvastatin were switched to surgery during the first 72 hours of treatment before atorvastatin had

reached the therapeutic dosage as defined by its pharmacokinetics.[25] Together, these results suggest that atorvastatin reduces the need for surgery in patients with CSDH.

Subgroup Analyses
In addition to the prespecified primary and secondary outcomes, we also performed post hoc subgroup analyses. When the patients were divided into 2 age groups, those age 65 years or older were found to have had a significantly greater reduction in HV after 8 weeks of treatment than those age 18 to 64 years (eFigure in Supplement 1). When patients were grouped by baseline HV, those with a hematoma of more than 30 mL were found to have experienced a greater relative reduction in HV while taking atorvastatin than those with a hematoma of 30 mL or less (eFigure in Supplement 1). We used an HV of 30 mL to group patients because this volume has been widely used as an indication for surgery in patients with an intracranial hematoma. These results indicate that atorvastatin may be more effective for older patients and patients with larger CSDH.

Safety
Two patients died during the trial, 1 of whom was age 61 years and receiving atorvastatin and died of pulmonary embolism caused by multiple limb fractures on day 172 after randomization. The other was 73 years old receiving placebo and died of myocardial infarction on day 25 after randomization. Their deaths were determined to be unrelated to the trial treatment by the monitoring board.

The results of routine blood and coagulation tests conducted during the trial are listed in eTable 9 in Supplement 1. The laboratory measurements of liver and kidney function are listed in eTable 10 in Supplement 1. Fifteen patients (24%) presented with mild liver abnormalities and 8 (13%) with mild kidney abnormalities, but none required treatment. Two patients (2%) were considered to have had treatment-related adverse events. One female patient developed diplopia and right-abduction nerve palsy 3 weeks after receiving atorvastatin treatment. Her palsy disappeared and the hematoma was absorbed during the follow-up period. The other developed pruritus after 6 weeks of participating in the trial, but the symptom remitted after 4 days and the patient completed the trial.

Discussion
With the continuous increase in life expectancy and the therapeutic or prophylactic use of anticoagulation and antiplatelet medications, the incidence of CSDH is expected to increase significantly worldwide. Surgery has long been the first choice for treating CSDH, but it carries a considerable risk of complications and could be contradicted for patients who have mild symptoms, are at an advanced age, are taking long-term anticoagulation and/or antiplatelet medications, or are in poor physical health. Reports on the self-absorption of CSDH remain sporadic.[31-33] Effective and low-cost nonsurgical treatments could significantly improve the outcomes of CSDH. This trial was designed to investigate atorvastatin as a nonsurgical

alternative for treating CSDH. We made several novel observations. First, atorvastatin reduced hematomas, improved neurological function and quality of life, and reduced the need for surgery in patients with CSDH. Second, the effect of atorvastatin was not only observed during the treatment, but also persisted during a follow-up period of 16 weeks. Third, atorvastatin appears to be more effective for older patients with relatively larger hematomas, but this finding requires validation in larger cohorts because this study was not powered to conduct subgroup analyses. Further studies could determine the effectiveness of other statins in reducing CSDH and improving its clinical outcomes.

The findings of this trial support our early observations in animal models that atorvastatin reduces hematomas, primarily by suppressing local inflammation.[12-14] Inflammation at the site of the hematoma has been widely reported to disrupt the endothelial cell barrier, leading to the formation of "leaky vessels."[13,14] Atorvastatin has been reported to promote angiogenesis in models of stroke and brain injury.[16,34,35] By reducing inflammation-induced vascular leakage and promoting angiogenesis, atorvastatin prevents the formation and accelerates the absorption of the hematoma to improve the neurological function of patients with CSDH.

The findings also raise the important question as to whether statins in general or atorvastatin in particular prevent the development of CSDH. Statins have been widely used in developed countries and by 23.2% of patients in the United States,[36] but, to our knowledge, the number of Chinese patients taking statins has not been reported. More importantly, there are no reported epidemiological data on the incidence of CSDH in patients who are taking statins in any population. Answering these questions is important for public health and disease prevention, but it will require a properly designed epidemiological study that goes beyond the scope of this trial. Nevertheless, the information we obtained during the recruitment period of this trial may provide a clue. We screened 254 patients with CSDH, and 6 (2.4%) were taking statins, which was significantly lower than the expected rate of statin use in the general Chinese population.

Limitations

The study has several limitations. First, the trial was conducted exclusively among Chinese patients in China. Whether its findings are reproducible in other races/ethnicities or countries remains to be investigated. Second, the numbers of patients who were recruited from participating centers differed significantly, potentially resulting in regional biases. Third, the post hoc method was used to conduct subgroup analyses that may not be sufficiently powered. Finally, the data from patients who underwent surgery during the trial were analyzed using the LOCF method, which could create bias against patients with a large hematoma, as they were more likely to be switched to surgery during the trial. However, this bias should not affect the outcome of this trial because more patients who were taking the placebo were switched to surgery, suggesting that placebo patients are more likely to experience deteriorating clinical conditions or an enlarged hematoma.

Conclusions

This double-blind, randomized, placebo-controlled phase II clinical trial finds atorvastatin at 20 mg daily to be safe and effective for nonsurgically treating CSDH. It is also cost-effective in comparison with surgery.[23] Atorvastatin may be more effective in patients 65 years and older and/or with a hematoma of 30 mL or more. Our findings laid the foundation for a phase III trial to determine the efficacy of atorvastatin for treating patients with CSDH. The findings also call for the study of other statins for preventing and treating CSDH.

Author Affiliations: Key Laboratory of Post-Neurotrauma Neurorepair and Regeneration in Central Nervous System, Ministry of Education in China and Tianjin, Tianjin Neurological Institute, Tianjin, China (Jiang, D. Wang, H. Wei, Tian, Jianning Zhang); Department of Neurosurgery, First Affiliated Hospital of Harbin Medical University, Harbin, China (S. Zhao); Department of Neurosurgery, Peking Union Medical College Hospital, Beijing, China (R. Wang, J. Wei); Department of Neurosurgery, Southwest Hospital, Chongqing, China (Feng, R. Hu); Department of Neurosurgery, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China (Jianmin Zhang); Department of Neurosurgery, Qilu Hospital of Shandong University, Jinan, China (X. Li); Department of Neurosurgery, Huashan Hospital Fudan University, Shanghai, China (Mao, J. Hu); Department of Neurosurgery, Xiangya Hospital of Central South University, Changsha, China (Yuan); Department of Neurosurgery, Xijing Hospital, Xian, China (Fei); Department of

Neurosurgery, Beijing TianTan Hospital, the Capital Medical University, Beijing, China (Y. Zhao); Department of Neurosurgery, General Hospital of Chinese People's Liberation Army, Beijing, China (X. Yu); Division of Neurosurgery, Department of Surgery, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong (Poon); Department of Neurosurgery, Linyi People's Hospital, Linyi, China (Xide Zhu); Department of Neurosurgery, Jiangsu Provincial Hospital, Nanjing Medical University First Affiliated Hospital, Nanjing, China (N. Liu); Department of Neurosurgery, First Affiliated Hospital of Fujian Medical University, Fuzhou, China (Kang); Department of Neurosurgery, General Hospital of Ningxia Medical University, Yinchuan, China (Sun); Department of Neurosurgery, Second Affiliated Hospital of Hebei Medical University, Shijiazhuang, China (Jiao); Department of Neurosurgery, First Affiliated Hospital of Zhengzhou University, Zhengzhou, China (X. Liu); Department of Neurosurgery, Affiliated Hospital of Xuzhou Medical College, Xuzhou, China (R. Yu); Department of Neurosurgery, Central Hospital of Erdos, Erdos, China (Junyi Zhang); Department of Neurosurgery, Xi'an Tangdu Hospital of the fourth Military Medical University, Xian, China (Gao); Department of

Neurosurgery, First Affiliated Hospital of Shanxi Medical University, Taiyuan, China (Hao); Department of Neurosurgery, Provincial People's Hospital of Inner Mongolia, Huhehot, China (Su); Department of Neurosurgery, Cangzhou Central Hospital, Cangzhou, China (Yin); Department of Neurosurgery, Second Affiliated Hospital of Nanchang University, Nanchang, China (Xingen Zhu); Department of Neurosurgery, Shanghai Changzheng Hospital, Shanghai, China (Lu); Department of Neurosurgery, 117th Hospital of Chinese People's Liberation Army, Hangzhou, China (J. Li); Laboratory of Neuro-Trauma and Neurodegenerative Disorders, Tianjin Geriatrics Institute, Tianjin Medical University General Hospital, Tianjin, China (Lei); Department of Geriatrics, Tianjin Medical University General Hospital, Tianjin, China (Lei); Bloodworks Research Institute, Division of Hematology, Department of Medicine, University of Washington School of Medicine, Seattle (Dong).

Author Contributions: Drs Jiang and Zhang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Jiang, R. Wang, Mao, Fei, Y. Zhao, X. Yu, Xide Zhu, N. Liu, Sun, R. Yu, Su, Xingen

REFERENCE

1. Liu W, Bakker NA, Groen RJ. Chronic subdural
hematoma: a systematic review and meta-analysis
of surgical procedures. *J Neurosurg*. 2014;121(3):
665-673. doi:10.3171/2014.5.JNS132715

2. Karibe H, Kameyama M, Kawase M, Hirano T,
Kawaguchi T, Tominaga T. Epidemiology of chronic
subdural hematomas [article in Japanese]. *No
Shinkei Geka*. 2011;39(12):1149-1153.

3. Tseng JH, Tseng MY, Liu AJ, Lin WH, Hu HY,
Hsiao SH. Risk factors for chronic subdural
hematoma after a minor head injury in the elderly:
a population-based study. *Biomed Res Int*. 2014;
2014:218646. doi:10.1155/2014/218646

4. Brennan PM, Kolias AG, Joannides AJ, et al. The
management and outcome for patients with
chronic subdural hematoma: a prospective,
multicenter, observational cohort study in the
United Kingdom. *J Neurosurg*. 2017;127(4):732-739.
doi:10.3171/2016.8.JNS16134

5. Shimamura N, Ogasawara Y, Naraoka M,
Ohnkuma H. Irrigation with thrombin solution
reduces recurrence of chronic subdural hematoma
in high-risk patients: preliminary report.
J Neurotrauma. 2009;26(11):1929-1933. doi:10.1089
/neu.2009.0879

6. Miranda LB, Braxton E, Hobbs J, Quigley MR.
Chronic subdural hematoma in the elderly: not a
benign disease. *J Neurosurg*. 2011;114(1):72-76. doi:
10.3171/2010.8.JNS10298

7. Lee L, Ker J, Ng HY, et al. Outcomes of chronic
subdural hematoma drainage in nonagenarians and
centenarians: a multicenter study. *J Neurosurg*.
2016;124(2):546-551. doi:10.3171/2014.12.JNS142053

8. Sun TF, Boet R, Poon WS. Non-surgical primary
treatment of chronic subdural haematoma:
preliminary results of using dexamethasone. *Br J
Neurosurg*. 2005;19(4):327-333. doi:10.1080
/02688690500305332

9. Iorio-Morin C, Blanchard J, Richer M, Mathieu D.
Tranexamic Acid in Chronic Subdural Hematomas
(TRACS): study protocol for a randomized
controlled trial. *Trials*. 2016;17(1):235. doi:10.1186
/s13063-016-1358-5

10. Hohenstein A, Erber R, Schilling L, Weigel R.
Increased mRNA expression of VEGF within the
hematoma and imbalance of angiopoietin-1 and -2
mRNA within the neomembranes of chronic
subdural hematoma. *J Neurotrauma*. 2005;22(5):
518-528. doi:10.1089/neu.2005.22.518

11. Nagy JA, Vasile E, Feng D, et al. VEGF-A induces
angiogenesis, arteriogenesis, lymphangiogenesis,
and vascular malformations. *Cold Spring Harb Symp
Quant Biol*. 2002;67:227-237. doi:10.1101/sqb
.2002.67.227

12. Wang D, Jiang R, Liu L, Dong JF, Zhang JN.
Membrane neovascularization and drainage of
subdural hematoma in a rat model. *J Neurotrauma*.
2010;27(8):1489-1498. doi:10.1089/neu.2009.1057

13. Wang D, Li T, Wei H, et al. Atorvastatin
enhances angiogenesis to reduce subdural
hematoma in a rat model. *J Neurol Sci*. 2016;362:91-
99. doi:10.1016/j.jns.2016.01.017

14. Li T, Wang D, Tian Y, et al. Effects of atorvastatin
on the inflammation regulation and elimination of
subdural hematoma in rats. *J Neurol Sci*. 2014;341
(1-2):88-96. doi:10.1016/j.jns.2014.04.009

15. Nawrocki JW, Weiss SR, Davidson MH, et al.
Reduction of LDL cholesterol by 25% to 60% in
patients with primary hypercholesterolemia by
atorvastatin, a new HMG-CoA reductase inhibitor.
Arterioscler Thromb Vasc Biol. 1995;15(5):678-682.
doi:10.1161/01.ATV.15.5.678

16. Potey C, Ouk T, Petrault O, et al. Early treatment
with atorvastatin exerts parenchymal and vascular
protective effects in experimental cerebral
ischaemia. *Br J Pharmacol*. 2015;172(21):5188-5198.
doi:10.1111/bph.13285

17. Araújo FA, Rocha MA, Mendes JB, Andrade SP.
Atorvastatin inhibits inflammatory angiogenesis in
mice through down regulation of VEGF, TNF-alpha
and TGF-beta1. *Biomed Pharmacother*. 2010;64(1):
29-34. doi:10.1016/j.biopha.2009.03.003

18. Sobrino T, Blanco M, Pérez-Mato M,
Rodríguez-Yáñez M, Castillo J. Increased levels of
circulating endothelial progenitor cells in patients
with ischaemic stroke treated with statins during
acute phase. *Eur J Neurol*. 2012;19(12):1539-1546.
doi:10.1111/j.1468-1331.2012.03770.x

19. Buttmann M, Lorenz A, Weishaupt A,
Rieckmann P. Atorvastatin partially prevents an
inflammatory barrier breakdown of cultured human
brain endothelial cells at a pharmacologically
relevant concentration. *J Neurochem*. 2007;102(4):
1001-1008. doi:10.1111/j.1471-4159.2007.04563.x

20. Liu Y, Wei J, Hu S, Hu L. Beneficial effects of
statins on endothelial progenitor cells. *Am J Med Sci*.
2012;344(3):220-226. doi:10.1097/MAJ
.0b013e31824998f9

21. Wang D, Li T, Tian Y, et al. Effects of atorvastatin
on chronic subdural hematoma: a preliminary
report from three medical centers. *J Neurol Sci*.
2014;336(1-2):237-242. doi:10.1016/j.jns.2013.11.005

22. Qiu S, Zhuo W, Sun C, Su Z, Yan A, Shen L.
Effects of atorvastatin on chronic subdural
hematoma: a systematic review. *Medicine (Baltimore)*.
2017;96(26):e7290. doi:10.1097/MD
.0000000000007290

23. Jiang R, Wang D, Poon WS, et al. Effect of
ATorvastatin On Chronic subdural Hematoma
(ATOCH): a study protocol for a randomized
controlled trial. *Trials*. 2015;16:528. doi:10.1186
/s13063-015-1045-y

24. Bakker-Arkema RG, Davidson MH, Goldstein
RJ, et al. Efficacy and safety of a new HMG-CoA
reductase inhibitor, atorvastatin, in patients with
hypertriglyceridemia. *JAMA*. 1996;275(2):128-133.
doi:10.1001/jama.1996.03530260042029

25. Cilla DD Jr, Whitfield LR, Gibson DM, Sedman
AJ, Posvar EL. Multiple-dose pharmacokinetics,
pharmacodynamics, and safety of atorvastatin, an
inhibitor of HMG-CoA reductase, in healthy
subjects. *Clin Pharmacol Ther*. 1996;60(6):687-695.
doi:10.1016/S0009-9236(96)90218-0

26. Amarenco P, Bogousslavsky J, Callahan A III,
et al; Stroke Prevention by Aggressive Reduction in
Cholesterol Levels (SPARCL) Investigators.
High-dose atorvastatin after stroke or transient
ischemic attack. *N Engl J Med*. 2006;355(6):549-559.
doi:10.1056/NEJMoa061894

27. Kothari RU, Brott T, Broderick JP, et al. The
ABCs of measuring intracerebral hemorrhage
volumes. *Stroke*. 1996;27(8):1304-1305. doi:10.1161
/01.STR.27.8.1304

28. Markwalder TM, Steinsiepe KF, Rohner M,
Reichenbach W, Markwalder H. The course of
chronic subdural hematomas after burr-hole
craniostomy and closed-system drainage.
J Neurosurg. 1981;55(3):390-396. doi:10.3171/jns.1981
.55.3.0390

29. Chari A, Hocking KC, Edlmann E, et al. Core
outcomes and common data elements in chronic

subdural hematoma: a systematic review of the literature focusing on baseline and peri-operative care data elements. *J Neurotrauma*. 2016;33(17): 1569-1575. doi:10.1089/neu.2015.4248

30. Wong GK, Poon WS, Chan MT, et al; IMASH Investigators. Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage (IMASH): a randomized, double-blinded, placebo-controlled, multicenter phase III trial. *Stroke*. 2010;41(5):921-926. doi:10.1161/STROKEAHA.109.571125

31. Ratre S, Yadav Y, Choudhary S, Parihar V. Spontaneous resolution of chronic subdural haematoma in a patient receiving anticoagulant therapy. *J Assoc Physicians India*. 2015;63(8):79-80.

32. Lee GS, Park YS, Min KS, Lee MS. Spontaneous resolution of a large chronic subdural hematoma which required surgical decompression. *J Korean Neurosurg Soc*. 2015;58(3):301-303. doi:10.3340/jkns.2015.58.3.301

33. Tiwari AR, Maheshwari S, Balasubramaniam S, Devendra T, Savant H. Spontaneous resolution of non traumatic chronic subdural haematoma despite continued antiplatelet therapy: a case report. *J Clin Diagn Res*. 2015;9(6):PD01-PD02.

34. Rodríguez-Perea AL, Gutierrez-Vargas J, Cardona-Gómez GP, Guarin CJ, Rojas M, Hernández PA. Atorvastatin modulates regulatory T cells and attenuates cerebral damage in a model of transient middle cerebral artery occlusion in rats. *J Neuroimmune Pharmacol*. 2017;12(1):152-162. doi:10.1007/s11481-016-9706-5

35. Chen J, Zacharek A, Li A, et al. Atorvastatin promotes presenilin-1 expression and Notch1 activity and increases neural progenitor cell proliferation after stroke. *Stroke*. 2008;39(1): 220-226. doi:10.1161/STROKEAHA.107.490946

36. Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003-2012. *NCHS Data Brief*. 2014;(177):1-8.