**Title:** Atorvastatin combined with or without dexamethasone for the treatment of chronic subdural hematoma in super-aged patients

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The authors confirm that the PI for this paper is Rongcai Jiang. and that he had direct clinical responsibility for patients.

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## What is already known about this subject

- Chronic subdural hematoma (CSDH) is common in aged people.
- Burr-hole-drainage and twist-drill craniotomy are the first-line therapies for CSDH whose mortality rate among super-aged patients (over 90 years) is 38.4%.
- Atorvastatin or combined with dexamethasone has been proven to be effective in eliminating CSDH with a median age of 63 years.

## What this study adds

- Atorvastatin or atorvastatin combined with low-dose dexamethasone benefits the hematoma elimination and symptom remission within 6 to 24 weeks for super-aged CSDH patients.
- The patients over 90 years obtain complete recovery after 1~4 years' follow-up.
- Atorvastatin with or without dexamethasone is safe and effective for the treatment for super-aged CSDH patients.

## ABSTRACT

**Aim：** Chronic subdural hematoma (CSDH) is common in aged people, and minimally invasive surgical interventions such as burr-hole-drainage and twist-drill craniostomy are the first-line therapeutic options for this condition. However, the mortality rate among super-aged patients (over 90 years of age) with CSDH is as high as 38.4% after these surgical procedures. Atorvastatin alone or in combination with dexamethasone has been proven to be effective in eliminating CSDH. In the current study, the researchers evaluated the therapeutic efficacy of atorvastatin with or without dexamethasone on the CSDH patients over 90 years.

**Methods：** The study attempted to treat 12 super-aged patients with primary or post-operative relapsed CSDH by using atorvastatin alone or in combination with dexamethasone. The changes in hematoma volume measured with computed tomography (CT) or magnetic resonance imaging (MRI) and the patients' neurological improvement were monitored by activities of daily living (ADL) and modified Rankin scale (MRS) scores.

**Results：** Treatment with atorvastatin or atorvastatin combined with low-dose dexamethasone had beneficial effects on hematoma elimination and/or symptom remission within 6 to 24 weeks in 12 super-aged patients. All of them showed complete recovery after 1~4 years of follow-up.

**Conclusion：** The findings in this study indicate that atorvastatin with or without dexamethasone is safe and effective for the treatment for CSDH in super-aged patients.

## Introduction

Chronic subdural hematoma (CSDH) is an imperceptible collection of cerebrospinal fluid mixed with old hemocytes and their degraded products within the subdural space. It is a common disorder evoking neurological deficits and cerebral injury, especially in the elderly population[1, 2]. Brain trauma, a prolonged history of taking oral anticoagulants and antiplatelet drugs, and advanced age are the main risk

factors for CSDH[2, 3]. Burr-hole drainage and twist-drill craniostomy are the first-line therapeutic options for CSDH, while some hospitals also practice “cookie” craniotomy. However, despite advancements in neurosurgical techniques and operative instruments, management of CSDH remains extremely challenging due to the high rate of relapse and the higher susceptibility to complications among aged patients.

To address the limitations of operative procedures, several drugs, including dexamethasone, tranexamic acid, angiotensin converting enzyme inhibitors, and even traditional Chinese medicines, have been used to treat CSDH. However, none of them have been proven to be effective in randomized controlled trials (RCTs). Despite the low effectiveness of the current treatment approaches, single atorvastatin administration has been proved to be effective and safe in preventing CSDH relapse[4, 5]. In fact, the combination of atorvastatin and dexamethasone could further improve the therapeutic effects on CSDH in our proof-of-concept study (data not shown here). In 2018, atorvastatin treatment was confirmed to effectively eliminate CSDH in comparison with a placebo without causing any significant side effects[6]. In addition, the combination of atorvastatin and low-dose dexamethasone was shown to cure relapsed CSDH in four pediatric patients[7].

Age has a significant impact on the prognosis of CSDH, with the CSDH-related mortality rates among super-aged patients being as high as 32% to 40%[8, 9]. Therefore, it is reasonable to consider the use of the atorvastatin/dexamethasone drug regimen to treat CSDH in super-aged patients, since most of these patients tend to reject surgical interventions because of their poor health condition or surgical contraindications. Although there are no data indicating a higher relapse ratio in super-aged patients with CSDH, these patients may prefer conservative therapy and are more prone to decline further surgical therapy if conservative medication could achieve similar outcomes[10, 11]. Therefore, in the present study, we report the findings for 12 super-aged patients with CSDH who received atorvastatin alone or in combination with dexamethasone from 2016.

## Methods

This study recruited a total of 12 super-aged patients (age greater than 90 years, 2 were excluded according the criteria) who were diagnosed as having CSDH and received atorvastatin or dual atorvastatin and dexamethasone therapy at the outpatient and inpatient neurosurgical departments of General Hospital of Tianjin Medical University, the largest and most advanced medical center in Tianjin, between January 2016 and December 2019.

The inclusion criteria were as follows: (1) age ≥ 90 years; (2) definite diagnosis of CSDH by CT or MRI scan; (3) absence of severe cerebral edema, cerebral herniation, or any indications for immediate surgery; (4) complete comprehension of the nature of the study and provision of informed consent.

Patients who met the following criteria were excluded: (1) allergy to or side-effects of statins or their ingredients; (2) cerebral herniation; (3) severe comorbidities such as hepatic and renal insufficiency, diabetes, severe dyslipidemia, or organ failure; (4) oral atorvastatin or dexamethasone medication for more than 1 week before recruitment; (5) refusal to receive oral administration of atorvastatin and dexamethasone; (6) severe neurological impairment, including coma, vomiting, or headache related to the expansion of CSDH, indicating brain hernia and an emergency surgical operation; (7) other conditions that caused discomfort to the patients or led to a critical condition during the study period, as determined by neurosurgeons.

All of the patients accepted oral atorvastatin at a daily dose of 20 mg for more than 8 weeks, and dual atorvastatin and dexamethasone (total 4 weeks, 0.75 mg/each dose, three times a day for 2 weeks, twice a day for 1 week, and once a day for 1 week) administration was performed if the single drug showed no efficacy at 2 weeks with no obvious reduction in the symptoms or intracranial hematoma. Head computed tomography (CT) or magnetic resonance imaging (MRI) was performed at the beginning of therapy, at follow-up assessments during the course of treatment, and at six months after the treatment. The levels of liver and kidney function markers, serum lipid markers, and blood glucose were tested before treatment, at 2- and 4-week follow-up assessments, and within one month of drug withdrawal. Blood platelet levels and coagulation function were tested for patients with hemorrhagic

tendencies such as hematopathy, those receiving long-term administration of drugs such as warfarin, aspirin, and clopidogrel, and those showing recurrence when the CSDH diagnosis was made by CT or MRI scans. The clinical outcomes were evaluated using the activities of daily living (ADL) and modified Rankin scale (MRS) scores. Baseline data and information regarding clinical characteristics, including pharmacological or surgical interventions, were collected and organized when the patient began his/her treatment. (Fig.1)

**Results**

A total of 14 patients were screened and 2 were excluded. One of the two excluded patients, one had been diagnosed as having severe leukemia, and it was unclear whether the CSDH was associated with the tumor even though he had experienced mild head trauma. The other excluded patient had severe COPD (chronic obstructive pulmonary disease) and was unable to lie still; therefore, he rejected hematoma-targeted therapy. Finally, a total of 12 CSDH patients aged over 90 years agreed to receive treatment with atorvastatin, both atorvastatin and dexamethasone, and surgical drainage. The CSDH appeared on the left side in most of the patients (9/12), and their initial symptoms included headache, nausea, dizziness, alalia, weakness of limbs, and dizziness. Two patients also received warfarin or clopidogrel (Table 1). Five patients (41.67%) were treated with atorvastatin alone while 7 (58.33%) received dual administration of atorvastatin and dexamethasone, and both groups showed absorption of CSDH and improvement in the neurological condition. One patient underwent surgical drainage initially but showed rapid enlargement of the hematoma and worsened neurological condition over a 24-h hospitalization period; he was subsequently treated with atorvastatin and dexamethasone and showed improved absorption despite presenting with postoperative recurrence. Only one patient (8.33%) required a surgical operation after receiving atorvastatin therapy; the patient experienced severe symptoms of increased intracranial pressure, including serious headache, nausea, and loss of consciousness, on the third day of atorvastatin therapy. He subsequently accepted atorvastatin therapy to obtain relief from significant headache post-operation. The duration and dose of atorvastatin and

dexamethasone, the degree of reduction in CSDH, and the improvement in the neurological function of the patients are listed in Table 2.

Atorvastatin and dexamethasone did not induce any obvious changes in the levels of alanine transaminase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), urea, and creatinine, indicating that the drugs did not affect liver and kidney function. Moreover, during atorvastatin treatment, all patients achieved improvement in CSDH absorption, but none of them showed a decrease in total cholesterol (TC) and triglyceride (TG) levels, which are the primary targets for atorvastatin while treating hyperlipidemia. Moreover, blood glucose levels were not influenced by dexamethasone administration, except in one patient with diabetes (Tables 2 & 3).

The patients who take the received warfarin (Case 8) or clopidogrel (Case 1) and the patient who experienced recurrence after surgical drainage (Case 11) showed normal values for platelet count (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) during the treatment. One patient with myelodysplastic syndrome (MDS) (Case 11) and one patient who showed recurrence of head injury during the course of atorvastatin and dexamethasone treatment (Case 7) showed reductions in PLT (Table 4).

Comparison of the MRI and CT findings obtained before and after treatment with atorvastatin showed that the medication reduced hematoma volume and modified the neurological condition in 100% of the patients (4/4), and it caused a medial CSDH volume reduction of 72% in these patients. The symptoms caused by CSDH, such as headache, dizziness, limb weakness, and bradylalia, improved or disappeared with the administration of atorvastatin for 12 to 24 weeks, and the ADL and MRS scores showed that atorvastatin was safe for the patients and increased their living ability and quality of life while simultaneously promoting absorption of intercranial hematoma. These initial results suggest that atorvastatin can safely improve neurological function at a dose of 20 mg/day in most super-aged patients with CSDH（Fig 2）.

Seven patients did not show obvious absorption of CSDH after receiving conservative atorvastatin treatment in the initial stage, and their hematoma reduced after dual-agent treatment for an average period of 12 weeks, with dexamethasone being initiated from the 3rd to 6th week. The maximum width in these patients diminished from 19.91 mm to 3.80 mm. After the original treatment with single atorvastatin, some of these patients still experienced headache, dizziness, unilateral limb weakness, or bradyarthria, and the hematoma did not show an obvious reduction in size. All of them achieved remission of symptoms after receiving additional treatment with dexamethasone for 4 weeks, and their follow-up CT and MRI findings showed significant absorption of the hematoma and a substantial improvement in the symptoms; all seven patients achieved total or subtotal diminution of hematoma volume, indicating that dexamethasone plays an auxiliary role in atorvastatin via its anti-inflammatory and anti-edema activities（Fig 3）.

Two CSDH patients with recurrence were finally cured with atorvastatin and dexamethasone. One patient was switched to surgical drainage because of rapid enlargement of the hematoma volume and symptomatic deterioration after only one day of hospitalization, and the hematoma appeared again at one week after the operation. Subsequently, he showed nearly absolute absorption of hematoma after treatment with atorvastatin and dexamethasone (Fig. 4G). The other patient showed recurrence after an accidental fall and head injury despite showing initial absorption of hematoma as a result of atorvastatin and dexamethasone therapy. Her lesion had reduced after administration of the dual-drug regimen for 2 weeks, but it became larger than the primary volume after the fall and injury. The recurrent hematoma diminished in size after 2 weeks of additional oral therapy (Fig. 4H). Thus, the dual-drug regimen could facilitate CSDH absorption and reduce the hematoma width in cases of postoperative recurrence.

**Discussion**

This study assessed the therapeutic effect of atorvastatin with or without

dexamethasone in super-aged CSDH patients who refused or were incapable of tolerating operative treatment. The study yielded several novel observations. First, atorvastatin reduced the volume of the CSDH hematoma and modified neurological disorders. Second, dexamethasone strengthened the hematoma-reducing effects of atorvastatin, and was beneficial in the treatment of recurrent CSDH without significant adverse effects in super-aged patients. Third, both single atorvastatin and dual-drug therapy were safe for the aging patients, even in those receiving aspirin or clopidogrel and in a patient with MDS, but the findings need to be validated a larger randomized controlled trial because it is of the lack of a control group of super-aged patients who underwent operative therapy. More intensive studies could provide conclusive findings regarding the effectiveness and safety of the two drugs in decreasing CSDH in super-aged patients under all conditions.

With the gradual aging of the worldwide population, super-aged patients have become the primary susceptible population for CSDH. Patients over 90 years of age usually reject surgical options because of their multiple complications, the risk of mortality, pain, and fear of awake anesthesia during the operation. Although various drugs, including corticosteroids, angiotensin-converting enzyme inhibitors, and tranexamic acid, have been assessed for nonsurgical treatment of CSDH to accelerate the resolution of this condition in elderly patients, most of these efforts were unsuccessful due to the lack of safety or efficacy or the enrolment of patients of an advanced age[12-16]. These therapies primarily aim to replace burr-hole drainage and craniostomy in such aged patients, especially extremely old patients aged over 80 and 90 years. Elderly patients usually suffer from multiple chronic complications like type 2 diabetes, hyperlipemia, high platelet aggregation, and atrial fibrillation, whose target organs are mainly microvascular; thus, treatments depending on anti-coagulant and anti-platelet effects potentially increase the risk of continuous hemorrhage[17, 18].

Unfortunately, most of these drugs fail to stably promote CSDH absorption or improve patients' symptoms; in some cases, single dexamethasone and mannitol can aggravate the symptoms, cause encephaledema, and result in deterioration of the disorder. Atorvastatin significantly reduced the volume of CSDH and improved clinical outcomes in 96% of participants in the ATOCH trial, a double-blind,

randomized, placebo-controlled phase II clinical trial in which conservative treatment of CSDH with a 20-mg daily dose of atorvastatin was found to be more safe and effective than surgical drainage for older patients with a median age of 63 years. However, no previous report has clarified whether atorvastatin could benefit super-aged CSDH patients over 90 years; therefore, we have summarized the safety and efficacy of oral administration of atorvastatin in super-aged CSDH patients. In the present study, atorvastatin showed obvious promotion of hematoma absorption in most patients aged over 90 years.

The first probable mechanism underlying the beneficial effects of atorvastatin is the activation of anti-inflammatory factors and alteration of the inflammatory environment in the hematoma capsule. The local inflammatory activity in CSDH plays a critical role in recurrence of the disease, and selective elevation of anti-inflammatory cytokines in the hematoma fluid could decrease the probability of recurrence[19, 20]. Atorvastatin may accelerate CSDH absorption and improve neurological functional recovery and cognitive outcome by increasing the levels of $FoxP3^{+}CD4^{+}CD25^{+}$ regulated T cells (Tregs) in the brain tissue surrounding the hematoma and in blood circulation, which decreases the levels of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α and increases the levels of anti-inflammatory cytokines such as IL-10 and IL-13 to suppress intracranial inflammation[21]. As one of the immune cells, Tregs originate in the bone marrow and are activated in peripheral circulation, after which they migrate to the intracranial lesion site by chemotactic movement via the concentration gradient of SDF-1a, whose specific receptor CXCR4 is stimulated on the surface of Tregs[22] .

Additionally, the roles of both inflammation and angiogenesis in CSDH development have gained interest. Two primary mechanisms have been well-documented in the process of hematoma formation. Angiogenesis is active during initiation and leads to the formation of a primitive vascular network, which also plays a role in the continuous leakage of immature microvascular elements in CSDH[23]. With the stimulation of pro-angiogenesis factors, the immature and dysfunctional microvessels show large gaps between the endothelial cells, resulting in the exudation and leakage of inflammatory cytokines and cells. In addition to inflammation and

angiogenesis, lesions of the intracranial lymphatic drainage are a probable mechanism underlying the formation of CSDH[24]. Atorvastatin promotes maturation of neovascularization and corrects dysfunction of the tubes by regulating the secretion of VEGF, angiopoietin 1/2, etc., and the endothelial progenitor cells are involved in the processes regulated by atorvastatin[25].

Single atorvastatin therapy promoted obvious absorption of CSDH and improved the symptoms in 5 of 12 patients, which is consistent with the results of the ATOCH trial[6], which demonstrated a 45.9% rate of neurological function improvement after atorvastatin administration in patients with CSDH. In addition to its lipid-lowering effects, atorvastatin plays an important role in the regulation of vascular function in brain injury and reduces cell death in peri-hematomal brain tissue after intracerebral hemorrhage (ICH) via anti-inflammation[26, 27]. The effects of atorvastatin in promoting CSDH absorption are probably associated with these mechanisms. In one patient who showed only a mild and incomplete reduction in hematoma size, the symptoms of dizziness and weakness of the limbs disappeared after the therapy without any significant complications, and the hematoma surrounded by fibrous membrane was shown to have undergone organization in 4-year follow-up CT scan(Case 2). Thus, the aim of treatment for aging CSDH patients should not necessarily be reduction in the size of the hematoma but can simply be alleviation of the patients' symptoms and discomfort.

The findings also indicate that atorvastatin can promote absorption of the liquid element and local repair around the hematoma. Atorvastatin has a limited role in the treatment of CSDH in some patients since it does not significantly reduce the hematoma volume and symptoms, and dexamethasone strengthens the curative effect of atorvastatin by promoting the elimination of the intracranial hematoma. In our study, six patients who underwent the combination treatment with atorvastatin and dexamethasone all achieved satisfactory results. Previous animal studies have shown that dexamethasone blocks the formation of neocapillaries in the hematoma membrane and interferes with fibrinolytic activity within the accumulated blood[28, 29]. The mechanism underlying the effects of dexamethasone probably involves reduction of edema and anti-inflammatory activity in the dura mater and drainage channels,

such as the venous sinus and the lymphatic vessels on the dura. Although the previous study suggested that dexamethasone treatment for 3 weeks could only yield a transient reduction in hematoma thickness in CSDH without subjective improvement and also contribute to more severe side effects[13], in our study, the 6 patients were cured with a shorter period of dexamethasone treatment combined with atorvastatin. Dexamethasone facilitated the effect of atorvastatin in CSDH absorption and played an auxiliary role in the regulation of inflammation and edema in the initial stage of therapy and did not induce serious adverse events subsequently. Furthermore, the dual-agent therapy had beneficial effects in patients with various CT or MRI characteristics, which suggests that this therapeutic regimen could promote the absorption of hematoma with different compositions.

Nevertheless, one patient required craniotomy because of rapid progression of hematoma volume and symptomatic deterioration just one day after admission. Thus, single atorvastatin or combination treatment for aging patients should be effective mainly in patients with slowly developing hematomas and mild symptoms that provide sufficient time for the incremental effects of the medication to appear. This finding also indicates that when patients with large CSDH receive conservative treatment, critical care monitoring is essential till an effective reduction in the size of the hematoma is observed. An emergency surgical procedure should be the final alternative option for patients showing further neurological impairment during conservative treatment.

## Conclusion

Level II evidence showed that CSDH in super-aged patients could be conservatively treated by atorvastatin with safety and efficiency. Despite the limitations, our study suggests that most super-aged CSDH patients could be cured by atorvastatin or its combination with dexamethasone via absorption of hematoma and alleviation of symptoms. Although surgical interventions are still the primary method for CSDH at present, more effective and noninvasive therapies are evolving and merit further studies based on a large number of cases, collective experience, and rational indications.

## Declaration of financial and conflicting interests

The staff in the research study received salary support through the General Hospital of Tianjin Medical University and The Neurological Institute of Tianjin. The authors have no personal financial interest in any of the medications or devices and no conflicts of interest with respect to the research, authorship, publication of the article.


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## Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Table 1. Baseline and clinical characteristic of the 12 CSDH patients aged over 90 years

| Case | Gender | Age (year) | History of Trauma (Y/N) | Hematoma Side | Initial Symptoms | Duration of Symptoms | Anamnesis | Use of antiplatelet drugs or anticoagulants (Y/N) |
|---|---|---|---|---|---|---|---|---|
| 1 | F | 95 | N | right | headache、left-sided weakness | 8 w | hypertension、DM、OCI、CAD | Y (clopidogrel) |
| 2 | F | 94 | Y | left | headache、unconsciousness、dilirium | 4 w | hypertension、TIA、CAD | N |
| 3 | F | 90 | N | left | dizziness、headache | 4 w | hypertension | N |
| 4 | M | 91 | N | left | - | - | DM、CAD | N |
| 5 | M | 92 | N | bilateral | headache | 4 w | hypertension | N |
| 6 | M | 90 | Y | left | unconsciousness、alalia、weakness of legs | 24 w | hypertension、DM、OCI、CAD | N |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 7 | M | 98 | N | left | headache、hypaesthesia of left-sides | 4 w | hypertension | N |
| 8 | M | 91 | N | left | weakness of right leg | 4 w | aortic valve stenosis、valve replacement | Y (warfarin) |
| 9 | M | 90 | N | left | right-sided weakness | 1 d | hypertension | N |
| 10 | M | 90 | N | bilateral | alalia | 3 w | OCI、atrial fibrillation | N |
| 11 | F | 91 | N | left | alalia、 weakness of right arm | 3 d | MDS | N |
| 12 | M | 90 | N | left | unconsciousness、right-sided weakness、headache | 5 d | hypertension | N |

DM: Diabetes Mellitus 、OCI：Old Cerebral Infarction、CAD: Coronary Artery Disease、MDS: Myelodysplastic Syndromes、TIA: Transient Ischemic Attacks

## Table 2. Efficacy of atorvastatin & dexamethasone in CSDH for aging patients

| Case | Treatment Method | Time of Treatment | Initial Thickness of Hematoma (mm) | Final Thickness of Hematoma (mm) | Hematoma Clearance Ration | Outcome of Symptoms | mRS | ADL | Recurrence or Increase ( Y/N ) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | A | A: 12w | 25.3 | 0 | 100% | symptoms disappeared completely | 0 | 90 | N |
| 2 | A | A: 24w | 26.5 | 20.1 | 24% | symptoms disappeared completely | 0 | 100 | N |
| 3 | A | A: 12w | 17.6 | 0 | 100% | symptoms disappeared completely | 0 | 100 | N |
| 4 | A | A: 12w | 11.1 | 4 | 64% | symptoms disappeared completely | 0 | 100 | N |
| 5 | # A | A: 12w | 17.6 | 0 | 100% | symptoms disappeared completely | 0 | 100 | N |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 6 | A&D | A: 16w ; D: 3d | 22.1 | 0 | 100% | disappearance of unconsciousness、alalia | 0 | 80 | N |
| 7 | A&D | A: 6w ; D: 4w | 13.4 | 5.1 | 62% | symptoms disappeared completely | 0 | 90 | Y |
| 8 | A&D | A: 12w ; D: 4w | 27.7 | 9.2 | 67% | symptoms disappeared completely | 0 | 100 | N |
| 9 | A&D | A: 24w ; D: 4w | 20.6 | 0 | 100% | symptoms disappeared completely | 0 | 100 | N |
| 10 | A&D | A: 8w ; D: 4w | 20 | 5.8 | 71% | symptoms disappeared completely | 1 | 90 | N |
| 11 | A&D | A: 12w ; D: 4w | 16.2 | 0 | 100% | symptoms aggravated | 0 | 100 | N |
| 12 | # A&D | A: 8w; D: 4w | 29.4 | 6.5 | 78% | symptoms disappeared completely | 0 | 100 | Y |

A:Atorvastatin、 D:Dexamethsone、 #：Postsurgery

**Table 3. Liver and kidney function in CSDH patients receiving atorvastatin & dexamethasone**

| | Atorvastatin | | | | Atorvastatin+Dexamethasone | | | |
|---|---|---|---|---|---|---|---|---|
| Biochemical indexes | Pretreatment | 2-week follow-up | 1-month follow-up | Drug withdrawal for 1 month | Pretreatment | 2-week follow-up | 1-month follow-up | Drug withdrawal for 1 month |
| ALT | 16.40±7.09 | 19.20±6.43 | 18.20±7.30 | 27.00±10.49 | 16.86±5.96 | 26.57±9.21 | 28.57±6.76 | 24.43±5.04 |
| AST | 19.20±6.50 | 23.20±6.40 | 18.60±5.00 | 22.60±6.07 | 19.43±6.11 | 25.57±7.58 | 24.29±3.99 | 24.43±3.70 |
| GGT | 26.20±12.84 | 32.20±21.08 | 23.20±8.30 | 23.00±8.10 | 22.86±11.18 | 29.14±12.71 | 24.29±8.28 | 26.57±7.44 |
| UREA | 6.94±0.55 | 5.94±0.46 | 6.06±1.88 | 6.48±0.83 | 5.20±1.72 | 6.79±1.80 | 7.57±1.60 | 6.00±1.21 |
| CREA | 83.40±18.91 | 78.60±17.18 | 73.20±8.66 | 77.20±12.29 | 81.57±23.16 | 79.14±18.25 | 87.71±26.17 | 84.86±18.51 |
| GLU | 5.76±0.69 | 6.06±1.11 | 5.54±0.82 | 5.52±0.90 | 5.44±1.08 | 5.39±0.36 | 5.37±0.47 | 5.26±0.33 |
| TC | 3.71±0.72 | 3.49±0.66 | 3.33±0.39 | 3.29±0.57 | 3.83±0.86 | 3.22±0.81 | 3.49±0.77 | 3.45±0.76 |
| TG | 0.94±0.19 | 0.84±0.16 | 0.81±0.18 | 0.76±0.16 | 0.83±0.15 | 0.92±0.15 | 0.85±0.29 | 0.87±0.13 |
| ALT: 5-40 U/L AST: 8-40 U/L GGT: 7-49 U/L UREA:1.7-8.3 mmol/L CREA: 44-115umol/L GLU:3.9-6.1 mmol/L TC:2.8-5.17mmol/L TG:0.56-1.71 mmol/L | | | | | | | | |

**Table 4. Coagulation function parameters in the five patients with potential hemorrhagic tendency**

| Case. | Reason for coagulation examinations | PLT ( $*10^9$) | PT | APTT | TT |
|---|---|---|---|---|---|
| 1 | Clopidogrel antiplatelet therapy | 161 | 10.9 | 31.8 | 20 |
| 7 | Recurrence | 105 | 11.3 | 24.7 | 19.5 |
| 8 | Warfarin anticoagulation therapy | 245 | 22.6 | 35.5 | 18.7 |
| 11 | MDS | 6 | 12.5 | 36 | 21.7 |
| 12 | Increased hematoma postsurgery | 166 | 13.4 | 28.5 | 20.2 |
| PLT：125-350 *109 /L PT:9.5-15sec APTT:20-40sec TT:13-25sec | | | | | |

**Figure legends**

**Fig. 1 Schematic illustration of the study procedure**

**Fig2.Patients receiving single atorvastatin treatment**

**Fig. 2 A-Case 3**: MRI in a 90-year-old man with spontaneous CSDH who experienced headache and dizziness for about one month and was treated with only atorvastatin without surgical operation. A1: Pre-treatment axial T2 image shows meniscoid chronic hematoma in the left frontotemporoparietal area (maximum hematoma width, 17.6 mm); A2: axial T2 image obtained after treatment for one month shows a decrease in maximum width (16.5 mm), and the patient's uncomfortable symptoms disappeared completely; A3: axial T2 image obtained at the five-month follow-up shows complete resolution of hematoma. **B-Case 4**: Images from a 91-year-old man with asymptomatic CSDH that was incidentally identified in a CT scan during a health examination and treated by single atorvastatin without surgical therapy. B1: Pre-treatment axial CT scan shows meniscoid chronic hematoma in the left frontotemporoparietal lobe (maximum hematoma width, 11.1 mm); B2: axial CT scan obtained after two months of atorvastatin treatment shows a decrease in maximum width (9.8 mm); B3: three-month follow-up axial CT scan shows subtotal absorption of hematoma. **C-Case 2**: Images from a 94-year-old female CSDH patient with a history of traumatic brain injury. She experienced headache and mild dizziness for one month and was treated by single atorvastatin without surgical operation. C1: Pre-treatment axial CT scan shows chronic hematoma in the left frontal, temporal, and parietal lobes (maximum hematoma width, 26.5 mm). C2:

Axial CT scan obtained at two years' follow-up shows only a slight decrease in the maximum width of the hematoma (22.2 mm); however, the subdural hematoma showed changes in organization and calcification, and the patient's symptoms disappeared completely. C3: Four-year follow-up axial CT scan shows completely calcified hematoma on the left side of the brain.

**Fig3.Auxiliary function of dexamethasone in CSDH absorption**

**Fig. 3 D-Case 9**: Images from a 90-year-old man with spontaneous CSDH who experienced right-sided weakness for one day and was treated with atorvastatin and dexamethasone without surgical operation. D1: Pre-treatment axial CT scan shows mixed density in the hematoma of the left frontal, temporal, and parietal lobes (maximum hematoma width, 20.6 mm); D2: axial CT scan after one month of treatment shows a decrease in the maximum width (13.9 mm) and mass effect of hematoma; D3: at the end of the six-month treatment period, axial CT scan shows total resolution of hematoma on the left side. **E-Case 10**: Images in a 90-year-old man with spontaneous bilateral CSDH, causes alalia for about three weeks, treated by atorvastatin and dexamethasone without surgical operation. E1: Pre-treatment Axial T1 image shows bilateral enormous hematomas occupying the intracranial area compress he brain parenchyma and cause a midline shift (maximum hematoma width, 20mm); E2: Axial CT scan after one month treatment shows decrease in maximum width (8.7mm) and the hematoma of the right side is absorbed completely; E3: At 8 weeks treatment, axial CT scan shows the hematoma of left side is almost completely absorbed (maximum hematoma width, 5.8mm). **F-Case 11**: Images from

a female 91-year-old myelodysplastic syndrome (MDS) patient with spontaneous CSDH who experienced right-arm weakness and alalia for three days and was treated with atorvastatin and dexamethasone without surgical operation. F1: Pre-treatment axial CT scan shows mixed density in the hematoma of the left frontal, temporal, and parietal lobes (maximum hematoma width, 16.2 mm); F2: axial CT scan obtained after two weeks of treatment shows no change in the width of the hematoma, whereas the density of the hematoma is decreased; F3: at the end of the six-month follow-up, axial CT scan shows total resolution of the hematoma on the left side, and the patient's symptoms disappeared completely.

**Fig4.Patients who had undergone craniotomy or showed recurrence and were treated with atorvastatin and dexamethasone**

**Fig. 4 G-Case 7**: A 98-year-old female patient presenting with headache and hypoesthesia of the left sides for half a year. G1: Pre-treatment axial T2 image shows a chronic subdural hematoma on the brain with a mild midline shift (maximum hematoma width, 13.4 mm); G2: head CT scan obtained after 2 weeks of dual-drug treatment indicated a reduction in the amount of hematoma (maximum hematoma width, 9.7 mm); G3: the patient injured her head in an accidental fall in the fourth week of therapy, and CT showed recurrence of hematoma after the head injury (maximum hematoma width, 13.7 mm); G4: the patient continued receiving atorvastatin and dexamethasone for 6 weeks, and the CT showed 62% (maximum hematoma width, 5.1 mm) absorption of the hematoma, and her symptoms had disappeared. **H-Case 12**: A 90-year-old male presenting with left-sided hemiparesis and unconsciousness. H1: Pre-treatment axial T2 image showed that a mixed

subacute and chronic subdural hematoma compressing the brain parenchyma and causing a midline shift (maximum hematoma width, 29.4 mm); H2: Follow-up head CT scan obtained after twist drill craniostomy revealed a reduction in the amount of hematoma (maximum hematoma width, 12.4 mm). H3: Axial CT scan obtained one week after the operation showed an increase in hematoma volume (maximum hematoma width, 14.9 mm), after which the patient agreed to receive oral administration of atorvastatin and dexamethasone. H4: Axial CT scan two months after the operation showed almost complete absorption of the hematoma, and the patient's symptoms disappeared completely.