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# Atorvastatin for unruptured intracranial vertebrobasilar dissecting aneurysm (ATREAT-VBD): protocol for a randomised, double-blind, blank-controlled trial

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## ABSTRACT

**Introduction** Vertebrobasilar dissecting aneurysms (VBDAs) are associated with serious complications and a poor prognosis. It is believed that inflammation of the aneurysm wall may be the main cause of rupture or deterioration. Atorvastatin has been shown to inhibit inflammation and may be a suitable drug candidate. Here, we report a clinical research study protocol to investigate whether atorvastatin inhibits inflammation of the aneurysm wall, as measured by signal index enhancement.

**Methods and analysis** We have designed a single-centre, randomised, double-blind, blank-controlled clinical trial. 40 patients with non-ruptured VBDAs with enhancement aneurysm walls will be enrolled in Beijing Tiantan Hospital. Eligible patients will be randomly divided into two treatment groups, at a ratio of 1:1, to receive atorvastatin 20 mg orally for 6 months or no treatment. The primary assessment outcome will be the change in aneurysm wall enhancement, as measured by the signal index during the 6-month treatment period. The secondary assessment outcomes will be the aneurysm morphology (intramural haematoma, dissection valve and false lumen) and changes in the concentrations of inflammatory factors, including C reactive protein, tumour necrosis factor-α, interleukin (IL)-1β and IL-6.

**Ethics and dissemination** The protocol has been approved by the medical ethics committee of the Beijing Tiantan Hospital at which the work will be conducted (Approval No. KY 2019-024-02). Written informed consent will be obtained from all participants. Findings from the study will be submitted for publication in a peer-reviewed journal.

**Trial registration number** NCT04943783.

## Strengths and limitations of this study

- This is the first randomised controlled trial to investigate the feasibility of atorvastatin in the prevention and treatment of unruptured vertebrobasilar dissecting aneurysms.
- This study will test the methodology for providing atorvastatin intervention in two distinct periods (entry and 6 months).
- There is no absolute placebo control.
- The study will lack histological verification of inflammatory changes in aneurysm wall.

## INTRODUCTION

Unruptured intracranial vertebrobasilar dissecting aneurysms (UIVBDAs) are a serious health problem and a leading cause of stroke in adults aged <50 years.[1 2] The mortality rate of patients with UIVBDAs ranges between 19% and 50%.[3] However, in recent years, an increasing number of patients with UIVBDA have received medical treatment, including acute stroke treatment and long-term prevention of ischaemic stroke.[4 5] However, no drug treatments to arrest dissecting aneurysm progression and subsequent rupture or occlusion have been established.

With regard to the anatomy of intracranial dissecting aneurysms, the intradural artery is characterised by a well-developed elastic plate, absence of elastic fibres in the media, and few adventitia tissues or absence of an elastic plate in the adventitia.[6 7] In addition, dissecting aneurysms are processed further before the equilibrium between vessel wall repair and extracellular matrix breakdown is reached, and inflammatory cells promote matrix breakdown.[1] As is commonly accepted, inflammatory cell infiltration is one of its characteristics.

High-resolution MRI (HR-MRI) of the vessel wall (HR-VW-MRI) is increasingly used in clinical practice as the only non-invasive imaging method to examine the structure of the vessel wall.[8 9] Aneurysm wall augmentation is a sign of inflammation on HR-MRI and can predict the unstable state of intracranial aneurysms (IAs).[10 11] Studies have shown that

HR-MRI can provide information for the diagnosis and follow-up of UIVBDAs, such as intramural haematomas, double-lumen and endometrial flaps.[12 13]

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are often used as cholesterol-lowering drugs.[14 15] In addition to their lipid-lowering effects, statins also protect the vascular system by exerting anti-inflammatory effects, stimulating the production of extracellular matrix, and promoting chemotaxis and migration of mesenchymal progenitor cells.[16] Statins also inhibit the expression of several matrix metalloproteinases in smooth muscle cells and macrophages.[17] Researchers believe that statins may also reduce the rate of growth and risk of rupture of abdominal aortic aneurysm and dissection through their pleiotropic effects.[18] In addition, studies have shown that statins and aspirin, through their anti-inflammatory effects, can reduce the rate of growth and the risk of rupture of intracranial cystic aneurysms.[13 19]

We, therefore, hypothesised that atorvastatin could reduce the inflammatory response of the UIVBDAs, mobilise endothelial progenitor cells for vascular repair, and thus inhibit the growth and rupture of aneurysms.

**Box 1 Participant inclusion and exclusion criteria**

**Inclusion criteria**

1. Patient has a UIVBDA identified on imaging (CTA, MRA, DSA).
2. Verification of UIVBDA diagnosis by HR-MRI technique.
3. Written informed consent by the patient.
4. Age >18 years by the time of inclusion.

**Exclusion criteria**

1. The aneurysm types of non-dissecting aneurysms, such as saccular aneurysms, fusiform aneurysms, traumatic aneurysms, etc.
2. Patients with MRI contraindications: metallic implant, contrast allergy, claustrophobia, etc.
3. Planned treatments of the aneurysm within 6 months.
4. Several impaired liver or renal functions.
5. Retreatment of recurrent aneurysm.
6. Pregnant or lactating women.
7. Patients with malignant diseases and significant cardiovascular risk diseases, such as liver disease, kidney diseases, congestive heart failure, malignant tumours, etc.
8. Poor compliance patients.
9. Patient is taking other vasoactive medicines, such as ACE.

CTA, CT angiography; DSA, digital subtraction angiography; HR-MRI, high-resolution MRI; MRA, magnetic resonance angiography; UIVBDA, unruptured intracranial vertebrobasilar dissecting aneurysm.

## METHODS AND ANALYSIS

### Trial design and setting

This study is a single-centre, prospective, double-blind, randomised, blank-controlled trial. This study will enrol 40 eligible patients with UIVBDAs showing aneurysm wall enhancement in Beijing Tiantan Hospital. Eligible patients will be randomly divided into two treatment groups at a ratio of 1:1. The case group will receive 20 mg atorvastatin per day and the control group will not take atorvastatin. The treatment duration will be 6 months. Recruitment for the study began in July 2021 with an expected completion date in January 2022.

### Study objective

The main purpose of this study is to compare the effect of atorvastatin on UIVBDA wall augmentation between patients who undergo treatment with atorvastatin for 6 months and those who do not. The secondary purpose is to assess the aneurysm morphology (intramural haematoma, dissection valve and false lumen) and changes in the concentrations of inflammatory factors, including C reactive protein (CRP), tumour necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6.

### Study population and sample size

The inclusion and exclusion criteria of the trial are shown in box 1. Written consent from participants will be required before enrolment. The wall reinforcement index of unstable aneurysms is higher than that of stable aneurysms (1.70±1.06 vs 0.89±0.88, respectively).[20] We suspect that atorvastatin will reduce the UIVBDA wall enhancement index (WEI). We estimate that each group will need at least 16 patients to observe any effect of atorvastatin on the aneurysm WEI (≥5%) with an α of 5% and a β of 20%. In addition, we have assumed a drop-out rate of 10%–20%; thus, a maximum of 20 patients will be recruited into each group.

### Randomisation

Random numbers will be generated by an independent third party using SPSS software (V.26.0, IBM) to generate a random sequence for blinding and to maintain the integrity of the study. The treatment allocation will be sealed in an envelope. These envelopes will only be opened by field researchers who are not involved in the clinical management or recruitment of participants. The clinical team and the participants will not be aware of the treatment allocation.

### HR-VW-MRI protocol

All examinations will be performed using a 3.0 T MRI system (Prisma, Siemens Healthineers; Erlangen, Germany) with a 32-channel head coil. Three-dimensional (3D) time-of-flight magnetic resonance angiography will be used for localisation. VW-MRI will be acquired in the sagittal plane with whole-head coverage and an isotropic resolution of 0.7 mm before and after intravenous gadolinium contrast injection. Multiplanar reformats will be reconstructed for VW-MRI sequences for review. The protocol will include 3D T1-weighted imaging (T1WI; sampling perfection with application-optimised contrasts using different flip angle evolutions) and contrast-enhanced 3D T1WI. Post-contrast T1WI will be performed 3 min after gadolinium injection (0.1 mmol/kg gadopentetate dimeglumine, Magnevist, Bayer Schering Pharma) using parameters identical to those of pre-contrast T1WI. The voxel size for 3D T1W sequences will be 0.7×0.7×0.7 mm. The other

Table 1 Imaging parameters of HR-VW-MRI

| | 3D TOF MRA | 3D T1WI SPACE |
|---|---|---|
| TR/TE (ms) | 22/3.86 | 800/22 |
| Flip angle (°) | 25 | 180 |
| Slice thickness (mm) | 0.9 | 0.7 |
| Number of slices | 52 | 48 |
| Field of view (mm) | 160×160 | 240×160 |
| Matrix | 256×256 | 320×240 |
| Scanning time | 3'03" | 4'17" |
| In-plane resolution | 0.75×1.07 | 0.70×0.70 |

3D, three-dimensional; HR-VW-MRI, high-resolution vessel wall MRI; MRA, magnetic resonance angiography; SPACE, sampling perfection with application-optimised contrasts using different flip angle evolutions; TE, echo time; TOF, time-of-flight; TR, repetition time; T1W, T1-weighted imaging.

parameters will be as follows: echo train length: 52, slices: 224, integrated parallel acquisition techniques (IPAT): 2. The parameters of the imaging sequences are listed in table 1.

## Image analysis

The image quality will be assessed using a previously described method. Each slice will be graded on a 4-point scale (1=poor; 2=adequate; 3=good; 4=excellent) based on the overall signal-to-noise ratio and the contrast between the vessel wall and the surrounding tissues.[21–23] Imaging data sets with an image quality score of 1 will be excluded. Quantitative analysis of the aneurysm wall on VW-MRIs will be performed using VesselMASS software (V.2014-EXP, MEDIS, Leiden University Medical Center; Leiden, the Netherlands) at a dedicated post-processing workstation. The wall enhancement volume rate (WEVR) analysis of the VW-MRIs will be performed using the latest version of 3D Slicer. We will perform a 3D reconstruction of the aneurysms in 3D Slicer with post-contrast T1W sequences. All VW-MRI data will be analysed independently by two experienced neuroradiologists who are blinded to patients' clinical data and treatment. One neuroradiologist will repeat the image analysis after a 2-week interval. The collected results will be analysed to assess interobserver and intraobserver reliability. The three slices with the most significant enhancement on post-contrast VW-MRI will be selected by the raters who will then trace the lumen and outer boundaries of the aneurysm wall through the optimally displayed angle (coronal, sagittal or axial based on the specific geometry of the aneurysm). The software will be used to automatically match the slice locations of the corresponding pre-contrast images. The inner lumen and outer wall contours of the aneurysm will be automatically segmented by the software, with manual adjustment of the contours if the neuroradiologist considers the tracings to be unsatisfactory. Subsequently, all obtained contours of each layer of the aneurysm will be automatically segmented into four quarters, and the mean enhancement signal intensity (SI) of each quarter (defined as quarter SI) will be calculated automatically. The quarter with the highest mean SI will be selected for each slice, and the average value of the three quarters from the corresponding three slices will be used to represent the SI of the aneurysm wall. This method will permit the evaluation of the most intensely enhanced segments of the aneurysm wall. The average SI of the aneurysm wall at the corresponding position on pre-contrast vessel wall imaging will be obtained using similar methods. To normalise the SI, similar methods will be used to measure the average SI of regions of interest in the adjacent white matter on pre-contrast and post-contrast vessel wall images.[24]

For the 3D aneurysm WEVR analysis, in 3D Slicer, we will manually delineate the outline of each layer of the aneurysm on post-contrast VW-MRI and then reconstruct the entire aneurysm wall volume. After rendering the 3D aneurysm model, the normal vasculature will be isolated by modifying the threshold tool. The threshold level will be adjusted until the major cerebral blood vessels show clear and distinct margins on axial, sagittal and coronal images. According to this threshold setting, the aneurysm volume of the enhanced part will be segmented and reconstructed.

## Central imaging analysis

All baseline and follow-up HR-VW-MRIs from the study participants will be collected at a centre of excellence for neuroimaging, where intensive image analysis will be performed. This will include a review of the UIVBDA diagnosis through a consensus reading by two experienced researchers and a central analysis of the initial and follow-up MRIs of the brain by the independent core imaging laboratory. The latter will consist of two experienced neuroradiologists who will evaluate the imaging component of the comprehensive result measurement. The reviewers from the core imaging laboratory will not know about treatment allocation or the clinical results.

## Follow-up

After participating in the study, the participants will be scheduled for the first clinical and imaging (HR-VW-MRI) follow-up examinations. The second clinical and imaging examinations will be performed 180±30 days after registration.

## Outcome events

### Primary outcome measures

The primary outcome measure will be the change in aneurysm wall inflammation, as measured by HR-VW-MRI. The quantitative WEI and WEVR from HR-VW-MRI will be compared between the treatment and control groups at the end of the 6-month treatment period. The WEVR will be calculated as follows[21]:

$$\text{WEVR} = \frac{\text{aneurysm enhancement volume}}{\text{whole aneurysm volume}} \times 100\%$$

Each voxel will be defined as enhanced when its SI is higher than the SI of the adjacent normal vessel wall.

The quantitative WEI will be calculated as follows (where SI denotes the signal intensity)[25]:

$$WEI = \frac{\frac{SI\_Wallpostcontrast}{SI\_White\ matterpostcontrast} - \frac{SI\_Wallprecontrast}{SI\_White\ matterprecontrast}}{\frac{SI\_Wallprecontrast}{SI\_White\ matterprecontrast}}$$

### Secondary outcome measures

The secondary outcome measures will be:

1. The change in aneurysmal morphology from before treatment to the 6-month follow-up (a maximum diameter increase of ≥1 mm or the appearance of a daughter sac will be defined as a change in aneurysmal morphology).
2. The change in aneurysmal wall features from before treatment to the 6-month follow-up (an intramural haematoma decrease of ≥1 mm or disappearance of the false lumen will be defined as a change in aneurysmal wall features).
3. The changes in CRP, TNF-α, IL-1β and IL-6 concentrations in patients with unruptured IAs from before treatment to the 6-month follow-up. CRP, TNF-α, IL-1β and IL-6 concentrations will be measured twice (before treatment and at the 6-month follow-up). A turbidimetric immunoassay will be performed to measure the CRP concentration, and an ELISA will be performed to measure TNF-α, IL-1β and IL-6 concentrations. A blood sample will be drawn from the brachial vein of each participant at a fixed time in the morning before breakfast.

### Data management

The final data collection and storage will be done through the electronic case report form using an electronic database that is fully compliant with data protection legislation (Health Insurance Portability and Accountability Act/Personal Information Protection and Electronic Documents Act). In addition to the electronic case report form, the data will be stored along with associated supporting documents, such as scans, medical records, care reports and blood tests. All research papers and documents will be kept at all test centres that participate in the research for at least 10 years. Upon completion of the research, the data will be reviewed by the research ethics committee, the quality assurance committee and other regulatory agencies. Research documents in paper form (consent forms, questionnaires and source data set from the diagram coordinator) will be properly stored at the Department of Neurosurgery. All computerised files will be password protected.

### Safety considerations

Serious adverse drug reactions/events are related to the following conditions: death, disability and hospitalisation for emergencies. Although drug-related morbidities are rare, once the series of adverse drug events are confirmed in a patient, the patient will be removed from the study and a report should be completed within 24 hours.

### Statistical analysis

The association between independent parameters will be evaluated using the $X^2$ test or Fisher's exact test for categorical variables and the non-parametric Mann-Whitney U test for continuous variables. The Wilcoxon signed-rank test will be used to compare the pretreatment and post-treatment variables. The bivariate non-parametric correlation between HR-VW-MRI wall enhancement and blood inflammatory markers will be tested using Spearman's r coefficient. The intraclass correlation coefficient will be calculated to measure the interobserver and intraobserver reproducibility in the measurements of WEI, WEVR and aneurysm size. All statistical analyses will be performed by a statistician using SPSS software (V.26.0, IBM).

### Patient and public involvement

There was no patient or public involvement in the study. Study results will not be disseminated to participants specifically. However, if participants are interested in the results of the research, they will receive any information, the manuscript and published research on this topic in the future.

### Ethics and dissemination

The study has been approved by the Ethics Committee of Beijing Tiantan Hospital (Approval No. KY 2019-024-02). This clinical trial will be conducted following the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the International Conference on Harmonization Guidelines for Good Clinical Practice. Written informed consent will be obtained from all participants (online supplemental material). Findings from the study will be submitted for publication in a peer-reviewed journal.

## DISCUSSION

ATREAT-VBD is a clinical study based on atorvastatin for the treatment of UIVBDAs. To our knowledge, this is the first conservative treatment study to completely exclude the effects of intervention, while previous studies have focused on reducing the recurrence of UIVBDAs after the intervention. This study is based on our previous research[26 27] and the known effects of statins in regulating inflammation and promoting angiogenesis in chronic subdural haematoma.[15]

At present, there is a lack of effective prevention and treatment measures for the causes and risk factors of UIVBDAs. There have been reports of bypass grafting and decompression surgery for vertebrobasilar artery extension and compression of the brain stem, as well as case reports on the effectiveness of endovascular therapy when drug therapy fails.[28 29] However, no drugs, endovascular therapies or surgical approaches have been systematically studied on a large scale.

We, therefore, believe that this study is necessary because conservative treatment options for UIVBDAs are very limited. Although some studies have shown that anti-thrombotic or platelet-inhibiting drugs are effective, they often result in a high rate of complications.[3 4] These complications include gastric ulcer and bleeding, intracranial haematoma and worsening of UIVBDAs.[30] In contrast, studies have shown that atorvastatin has a high curative effect in the treatment of unruptured IAs with few side effects. The most common side effect with atorvastatin is myopathy, which is considered dose related and is self-relieving when atorvastatin therapy is terminated.[31] Therefore, atorvastatin is considered to be safer than currently available conservative treatments. In addition, several studies have shown that a 20 mg dose of atorvastatin can have anti-inflammatory effects and reduce the biomarkers of inflammation in the vessel wall and the abundance of inflammatory cells. If the ATREAT-VBD Study proves the effectiveness of atorvastatin, we believe that atorvastatin could be a useful complementary treatment option to traditional interventions that are independent of drug intervention. However, the study considers a variety of clinical control factors, and research progress may be reduced as a result.

We recognise that the trial has some potential limitations. According to modern practice, early surgery may be the preferred option for patients with high risk of bleeding or ischaemic stroke, so this study included only patients with mild to moderate aneurysms and mild symptoms. Additionally, the trial does not include a placebo in the control group and the study will be conducted at a single centre in China, potentially limiting generalisability.

## Trial status

Recruitment started in July 2021 and ended in January 2022. Follow-up is ongoing at the time of preparation of this manuscript.

**Contributors** MT performed the manuscript writing. XY and YisenZ made a critical revision to the manuscript for important intellectual content. HK, JH, ML, JL, YingZ and KW participated in the final design of the study. XY and YisenZ conceived and designed the research, and handled funding and supervision. All authors read and approved the final manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

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