Efficiency Of Atorvastatin On In-Hospital Mortality Of Patients With Acute Aortic Dissection (Aad): Study Protocol For A Randomized, Double-Blind, Placebo-Controlled Trial

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Study protocol

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Abstract

Background: Dyslipidemia and local inflammation at sites of lipid deposition on blood vessel walls have been demonstrated to be risk factors for patients with acute aortic dissection (AAD). Statins have anti-inflammatory and lipid-lowering effects, which suggest that statins may play an important role in prevention and treatment of AAD. Some retrospective studies show that statins can protect patients with aortic dissection. However, the effect of statins on survival of AAD patients have been scarcely investigated, especially in randomized trials. In this study, we will perform a randomized controlled trial (RCT) to evaluate the effect of statins on in-hospital mortality of AAD patients.

Methods: A total of 384 subjects diagnosed with AAD in the First Affiliated Hospital of Shantou University Medical College will be recruited. Participants will be randomly divided into atorvastatin-treated or placebo groups. The primary outcome will be the in-hospital mortality.

Discussion: This study is designed to verify the safety and efficacy of atorvastatin in patients with AAD. The aim is to provide a new way to improve survival as a complement to conventional drug therapy.

Trial registration: Registered by Chinese Clinical Trials Registry (Registration number: ChiCTR1900023515, <http://www.chictr.org.cn/edit.aspx?pid=38275&htm=4>). Registered 1 June 2019.

Background

Acute aortic dissection (AAD) is relatively uncommon but is considered a life-threatening, potentially fatal condition[1]. A recent International Registry of Acute Aortic Dissection (IRAD) study shows that 87–90% of AAD is treated surgically, and medical treatment only accounts for 7–8%. Nevertheless, the IRAD study indicates that in-hospital surgical mortality for AAD remains approximately 20%[2], indicating improvement of the long-term outcome of patients with aortic diseases requires further optimization by medical therapy[3]. However, in addition to strict control of blood pressure and heart rate, the effect of other drugs on AAD is still controversial and lacking strong clinical evidence.

Dyslipidemia and atherosclerosis are important risk factors for AAD[4]. Lipid deposition in the vascular wall can lead to local inflammation[5] and promote the release of inflammatory mediators that destroy the vascular wall, leading to aortic dissection (AD)[6]. Atherosclerosis is also strongly correlated with the progression of AD. Statins are classical drugs for lowering low-density lipoprotein cholesterol (LDL-C) levels, and are both anti-inflammatory and anti-atherosclerotic[7], suggesting that statins may delay progression of AAD. In fact, several studies have explored the effects of statin on aortic disease, and evidence suggests that statins may be beneficial for survival of AAD[3, 8–11]. However, due to limited sample size and retrospective study design, the evidence is not strong. Thus, a randomized controlled trial (RCT) with adequate statistical power appears necessary to remove as many biases as possible in order to understand the exact effect of statins on AAD.

Methods

Study design

This is a randomized, prospective, placebo-controlled, single-center trial which will be conducted at the First Affiliated Hospital of Shantou University Medical College. The protocol was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement. For the SPIRIT 2013 checklist, see Additional File 1.

Ethics issues

The present study protocol was approved by the committee of ethics of the First Affiliated Hospital of Shantou University Medical College (Number: 2019038).

Participant recruitment

For the clinical study registered on 1 June 2019, participants were screened after registration. A total of 384 patients will be diagnosed with AAD by means of computed tomography angiography (CTA)[12] in The First Affiliated Hospital of Shantou University Medical College. Those who are willing to take part in the study will be carefully evaluated according to the inclusion and exclusion criteria.

Criteria

Inclusion criteria

1. Patient agrees to cooperate with all study procedures;
2. Age >20 years old;
3. Physical status permits oral medication;
4. Cholesterol < 5.1 mmol/l, triglyceride < 1.7 mmol/l;
5. Provision of written informed consent.

Exclusion criteria

1. Liver dysfunction: alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >3 times the normal value;
2. Breast-feeding or pregnancy (for women of child-bearing age, the human chorionic gonadotropin (HCG) level will also be measured before drug administration);
3. Previous history of coronary atherosclerotic heart disease;
4. Statins used within 6 months before inclusion;
5. Participation in another clinical trial within 6 months;
6. Allergy to statins.

Informed consent

Potentially eligible patients will be invited to take part in our study. Prior to enrollment, trained researchers will introduce the objective and main aspects of the trial to the patients. Patients will also receive information sheets and then be able to have an informed discussion with the participating consultant. Patients will also be informed of the probable benefits and potential risks and assured that participation is entirely voluntary. Patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled after providing written informed consent. The personal information of all participants will always be kept confidential.

Randomization and allocation

The 384 participants will be randomly assigned to either a control or statin-treated group at a ratio of 1:1. The allocation sequence will be generated by using random-number tables, and random numbers will be generated by the random number generator in the SPSS statistical software package (SPSS Inc, Chicago, IL, USA, version 23). Balance in allocation across the study participants will be enhanced through stratification by the type of AAD (two types: type A, type B) and block size four. Based on the allocation sequence, separate staff will package the drug, Participants will receive the corresponding drug package in the order of recruitment. Emergency envelopes containing the random allocation will be prepared individually, and will be unsealed only in the case of serious adverse events.

Blinding

In the study, the participants, trial management team and investigator site teams are blind to treatment allocation throughout the trial. Randomization and drug packaging and identification are performed by a separate staff who do not participate in other procedures of the study. In the event of a medical emergency where revealing the drugs used to treat the patient during hospitalization is necessary for immediate medical treatment decisions, the investigator will un-blind the study.

Interventions

Necessary treatment will be offered to all participants. participants will be randomized into two equal groups: study (atorvastatin) or control (placebo: microcrystalline cellulose (inactive ingredient) in matching capsules) groups as soon as clinical conditions permit. The study group will be required to take atorvastatin 20 mg daily (a safe dose effective in lipid-lowering and anti-inflammatory activity[13, 14] [15]), and the control group will be required to take the placebo daily. The appearance and labeling of the two types of tablets will be identical. Atorvastatin will be provided by Pfizer (New York, USA).

Drugs and placebos covering the whole course of treatment for each participant will be packed uniformly and individually. There is a pharmacist responsible for dispensing the prescription. The scheduled duration of treatment is in the duration of the hospital stay unless a serious adverse event occurs or the participant quits. The detailed study schedule is listed in Fig. 2.

Data handling and record keeping

Once the subjects are formally enrolled, case report forms (CRF) will be established. The CRF will be used to record data for all participants. This task will be completed by the researchers, who will also enter the data into an electronic database.

Follow-up

During hospitalization, staff will be scheduled to follow up every day until participants are discharged or death occurs, and the follow-up results will be recorded in the CRF. Subject survival status (surviving/deceased) and medication status (medication/discontinuation) will be recorded on the CRF after each conversation. Face-to-face adherence reminder sessions will take place at the initial product dispensing and each study visit thereafter. At every visit, participants will receive the drugs scheduled for the next day, and the drugs left from the previous period will be returned. Medication compliance will be recorded accordingly. Follow-up will continue until discharge from the hospital or death.

Withdrawal

Patients may be withdrawn from the study for any of the following reasons:

1. They may choose to withdraw for any reason.
2. They have abnormalities in ALT/AST (≥ 3 times upper limit of normal) after drug administration
3. Based on the investigator's discretion, the patient is no longer eligible for the study for any reason.

Sample size

Preliminary data indicates that acute aortic dissection is associated with an in-hospital mortality of 27.4% [16]. We predict that treatment with atorvastatin will reduce mortality to 12.4%, while no change will be seen in the placebo group, showing a mortality of 27.4%. To obtain 90% power to demonstrate a statistically significant difference (two-sided test, $\alpha=0.05$) between the two treatments, given an estimated dropout rate of approximately 20%, we increased the sample size to 192 per arm for a total of 384 participants. All calculations are done through PASS software (NCSS, America, version 11), using the log-rank test, Freedman method.

Outcome measurements

The primary outcome of this study is the in-hospital mortality. The expected trial target is superiority of atorvastatin treatment in the intervention group compared to the control group.

Data collection management and monitoring

At enrollment, we will collect the demographic information of the participants, including age, gender, blood pressure, heart rate, previous disease history, smoking history, admission blood parameters, including leukocytes, hemoglobin, platelets, cholesterol, triglycerides, creatinine, uric acid, glycosylated

hemoglobin, AST and ALT. During hospitalization, all blood parameters will be collected. At discharge or death of the patient, data will be collected on: patient status, medication in the hospital, diagnosis and comorbidity. All data will be transferred to a database by duplicate entry using EpiData software (Denmark version 3.1) and will be stored in the scientific research platform of the First Affiliated Hospital of Shantou University Medical College, which is a secure server with limited access and supported for anonymity, analysis and review. A data and safety monitoring committee of the First Affiliated Hospital of Shantou University Medical College will review and interpret the data generated from the study in order to ensure the safety of the participants and the integrity of the research data. The committee consists of five independent researchers. Computer-generated and time-stamped audit trails will also be implemented for tracking changes in the electronic source documentation to ensure the integrity of the research data.

Statistical and analytical plans

A comprehensive statistical analysis plan will be prepared before database locking. All analyses will be conducted according to the intention-to-treat (ITT) principles. All statistical analyses will be two-sided, and statistical significance will be set at 0.05. Continuous data will be presented as mean $\pm$ SD, and categorical data will be expressed as frequency and percentage of patients in each category. The Kolmogorov–Smirnov test will be used to confirm the normality of the distribution of continuous data, if $P \geq 0.05$ indicates the data is not normally distributed, advanced data conversion (such as logarithmic conversion) will be performed to see whether the data conform to a normal distribution. If not, the rank sum test will be selected. Otherwise, Student's *t* tests will be used for continuous data. The chi-square test will be used for categorical data. Survival curves will be determined by the Kaplan-Meier method for survival analysis. The difference in changes between the groups will be analyzed using both Student's *t* test and analysis of covariance to adjust for the baseline values. A *p*-value of <0.05 will be used to indicate statistical significance. SPSS statistical software (SPSS Inc, Chicago, IL, USA, version 23) will be used for statistical analysis.

Safety and adverse events

The most common adverse events (AEs) are expected to be liver-enzyme abnormalities, muscle pain, nausea and diarrhea. Participants showing any adverse event will be treated appropriately by doctors, and the project will cover the cost of adverse events. Adverse reactions will be checked at every visit. For any AE that occurs, all details, including the time of occurrence, symptoms and signs, degree, duration, laboratory findings, treatment, outcomes, and causal relationship with the treatment, will be recorded in the CRF. Serious AEs will be reported to the Research Ethics Committee within 24 h, which will decide whether any additional measures should be taken. The total number of patients with AEs related to the study drug (certain, probable, possible) and the total number of patients with AEs leading to discontinuation of study treatment will be summarized.

Patient and public involvement

Patients and public will not be involved in the design of this study or outcome measures, nor will they be involved with the conduct of the study.

Limitations

The limitations of this study should also be considered, including confirming that patients can diet normally before being formally included in the study, which may exclude critically ill patients whose deaths would occur within several hours of onset and would not be reported, thereby reducing the mortality rate reported for AAD. For surgical patients, preoperative fasting is often required, and patients in this group often need to wait until a normal diet is restored after surgery before they can be included in the study, which may also exclude critically ill patients whose deaths would occur before normal dieting is restored and would not be reported, thereby reducing the mortality rate reported for AAD. Considering the safety of atorvastatin, a low dose of 20 mg/day will be used in this study, and any possible effects may not be very significant. This is an exploratory study. If there is no significant positive effect at the end, but the results suggest it is safe and does not increase mortality, effectiveness may be observed by subsequently increasing the dose. We will explore the most appropriate dose in the next study. This study is a single center trial, and the results will need to be [validated](#) in other hospitals.

Discussion

AAD confers poor prognosis if left unmanaged[17]. Currently, although surgical treatment can significantly reduce the mortality, the mortality remains high, which indicates other interventions are needed to further reduce the mortality rate.

The 17-year trends in the presentation, diagnosis, and hospital outcomes of AAD from the IRAD were retrospectively reviewed by Linda et al.[2], who showed that besides the angiotensin receptor blockers and beta-blockers used to treat AAD, statins are being used with increasing frequency. Numerous studies indicate that statins have multiple beneficial actions on the cardiovascular system through improvement of endothelial dysfunction, inflammation, oxidative stress and stabilization of atherosclerotic plaques[18]. Endothelial dysfunction has been recognized as an independent predictor of cardiovascular disease, and statins significantly ameliorate endothelial dysfunction[19]^[20]. Compared with pravastatin, atorvastatin has greater beneficial effects on oxidative stress and endothelial function[21]. Recent reports have demonstrated that statins have anti-inflammatory effects and can decrease morbidity and mortality following aneurysm repair in patients with abdominal aortic aneurysms and aneurysm expansion before operation[22-25]. Several experimental studies demonstrate that the use of statins reduces aortic aneurysm formation, suppresses inflammation in animal models, and can also improve patient survival[26, 27]. A retrospective study showed that patients with AAD who used statins had significantly better prognosis than those who did not[28]. Also, a prospective, and randomized comparative study of patients with uncomplicated acute type B aortic dissection (ABAD) showed that pitavastatin treatment has a suppressive effect on aortic arch dilatation[3]. However, this study included only 50 subjects and did not evaluate patient survival.

In conclusion, there are many related studies suggesting that statins play a positive role in reducing aortic diseases, and initial evidence suggests that improving vascular endothelial function and reducing inflammation can slow down the progress of aortic disease, but strong evidence is lacking. The objective of this trial is to assess the effect of statins on mortality of AAD patients. If the results of our investigation are positive, it will provide evidence regarding the value of statins as an intervention to decrease mortality and delay disease progression in patients with AAD. Also, if the result is negative, it may suggest that a low dose of statins does not clearly improve survival or disease progression in patients with AAD.

Abbreviations

AAD: acute aortic dissection; ABAD: acute type B aortic dissection; AD: aortic dissection; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CONSORT: Consolidated Standards of Reporting Trials; CRF: case report forms; CTA: computed tomography angiography; HCG: human chorionic gonadotropin; IRAD: International Registry of Acute Aortic Dissection; IRB: institutional review board; ITT: intention-to-treat; LDL-C: low-density lipoprotein cholesterol; RCT: randomized controlled trial; TEAE: treatment-emergent adverse events;

Declarations

Trial status: The version of this protocol is 1.0 (date 20190415). Recruitment for the trial started in June 2019 and it expected to end in June 2021.

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Authors' contributors

YC, NX, XW, SY and XT acted as principal investigators and contributed to the concept, drafting, design and revising of the protocol. SW, XH, CC, BW, WL, HL, SY and XT contributed to the concept and critical revision of the protocol. All authors critically reviewed and approved the final version of the manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This clinical trial will be undertaken strictly according to the protocol and good clinical practice regulations. Informed consent will be obtained from all study participants. The study protocol was approved by the committee of ethics of the First Affiliated Hospital of Shantou University Medical College (Number: 2019038).

Consent for publication

Not applicable.

Competing interests None declared.

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Figures

Figure 1

Subject distribution among groups of the study.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT **	<i>T0</i>	0	<i>T0</i>	<i>T24hrs</i>	<i>Discharge</i>	<i>t_x</i>
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
<i>Atorvastatin group</i>
<i>placebo group</i>
ASSESSMENTS:						
<i>Demographic data</i>	X					
<i>History and symptoms</i>	X					
<i>Physical examination</i>	X					
<i>In-hospital mortality</i>			X	X	X	X

Figure 2

Study schedule.

Supplementary Files

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