Clinical Application of New Technique of Thoracoabdominal Aortic Stent Graft System

Protocol

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1. Study Background

Thoracic abdominal aortic aneurysm (thoracoabdominal aortic aneurysm, TAAA) is an aneurysm-like lesion involving the descending and abdominal aorta. Thoracic abdominal aortic aneurysm incidence rate accounts for approximately 7-15% of all aortic aneurysm-like dilated lesions. One epidemiological investigation result showed an incidence rate of approximately 6-10/100,000 patients per year for thoracic and abdominal aortic aneurysms and an annual rupture rate of 3.5/100,000 patients[1]. With the increasing surgical treatment of abdominal aortic aneurysms, reports of perirenal abdominal aortic aneurysms are also growing over the years, accounting for roughly 8 -20% of abdominal aortic aneurysms.

Thoracic abdominal aortic aneurysms and perirenal abdominal aortic aneurysms currently face difficulties in clinical treatment methods due to the involvement of multiple veisceral branching vessels. Traditional treatments include open and hybrid surgery. Open surgery includes the Etheredge, Debakey, and Debakey-Schumacker methods,have risks of peroperative bleeding, shock, multiple organ failure etc. due to its thoraco-abdorminal combined incision, sizabale wound, and complex reconstraction of visceral artery.The prognoss of patients undergoing open surgeries is heavily dependent on the proficiency of surgical technique among operating surgeons.In order to prevent the potential risks of open surgery and reduce the size of the incision wound caused by traditional thoracotomy and laparotomy procedures, many scholars have made corresponding attempts. In 1999, Quiñones-Baldrich et al[3] first used hybrid surgery for the treatment of TAAA[3]. Even though hybrid surgery generates less surgical trauma than open surgery, the issues of high mortality and complications remain unsolved. Simultaneously, due to the increased exposure of complicated anatomical posterior peritoneal regions, hybridization techniques need to be performed by experienced vascular surgeons and high level treatment center, further limiting its clinical application.

In recent years, with the rapid development of endovascular therapy technology, current major endovaslcular treatments include fenestrated endograft, branched

endograft, and octopus stents[4-8]. The results of a crossestional study of 2,607 patients showed perioperative mortality rate of 23.9%, 30.9%, and 10.6%, respectively, and found that postoperative complications of endovascular therapy (10.5%) were significantly lower than those of open surgery (33.5%) and hybrid surgery (31.6%). In Comparison with open surgery and hybrid surgery, endovascular therapy has the following advantages: (1) minimally invasive surgery, no chest or abdominal incision; (2) There is no need to block aorta during operation, therefore reduce the occurrence of complications of visceral ischemia; (3) Reduce blood loss and hospitalization time; (4) Reduce spinal cord complications and the mid-stent patency rate is good. Endovascular therapy is being used in the treatment of thoracic abdominal aortic aneurysms due to its advantages such as small incision wound and low complication rate. However, the technique of interventional operation and the design of standardized branch stents are still the focus of the research, and further research is needed.

2. Study Design

2.1 Study Purpose

To evaluate the feasibility of the thoracic-abdominal aortic stent-graft system for endovascular treatment of thoracic-abdominal aortic aneurysms and pararenal abdominal aortic aneurysm.

2.2. Method Selection and Reasons

There are no commercially available stent-graft systems for the effective endovascular treatment for thoracoabdominal aortic aneurysms and pararenal abdominal aortic aneurysm in China, so a prospective, single-group feasibility study is proposed for this study.

2.3 Inclusion and Exclusion Criteria

2.3.1 Inclusion criteria

(1) Age ≥18 and ≤80 years;

(2) Patients diagnosed with type Crawford I-V thoracoabdominal aortic aneurysmsa and pararenal abdominal aortic aneurysm, and should meet at least one of the following conditions:

a） The maximum diameter of thoracoabdominal aortic aneurysms and

pararenal abdorminal aortic aneurysm > 50 mm;

b） Rapid growth of sac >5 mm in diameter in the most recent 6 months;

c） Definite symptoms of abdominal pain and low back pain associated with thoracicabdominal aortic aneurysms.

(3) Patients with four indispensable reno-visceral arteries including superior mesenteric artery, celiac trunk and bilaterial renal arteries.
(4) Proximal landing zone 20－36 mm in diameter;
(5) Proximal landing zone ≥25 mm in length;
(6) If distal landing zone in abdominal aorta, distal landing zone should be 12-36mm in diameter and ≥15 mm in length.
(7) The visceral vascular branches landing zone 6~13 mm in diameter and ≥15 mm in length;
(8) The renal artery landing zone 4.5~9 mm in diameter and ≥15 mm in length;
(9) Patients who using the abdominal aortic bifurcation stent graft system should also meet the following criteria:

a. The iliac artery landing zone 7 ~25 mm in diameter;

b. The iliac artery landing zone ≥15 mm in length;

(10) Patients with appropriate iliacofemoral access and at least one patent upper extremity access;
(11) Patients who can understand the purpose of the trial, volunntarily participate and sign the informed consent form, and are willing to complete the follow-up according to the requirements of the protocol;

2.3.2 Exclusion criteria

(1) Ruptured aortic aneurysm in unstable haemodynamic condition;
(2) Aneurysmal aortic dissection;
(3) Infected or mycotic aortic aneurysm;
(4) Requiring simultaneous coverage or embolisation for bilateral internal iliac arteries;
(5) Severe stenosis, calcification, or mural thrombus at stent-graft landing zone;
(6) Diagnosis of acute coronary syndrome within 6 months;
(7) Patients with any transient ischemic attack (TIA) or ischemic stroke within 3 months;
(8) An allergic history for contrast agents, anticoagulants, antiplatelet drugs, stent graft or materials of delivery system#
(9) Patients with connective tissue diseases;

(10) Patients with takayasu arteritis;

(11) Patients with serious vital organ dysfunction or other serious disease;

(12) Preoperative liver renal function abnormalities (ALT or AST ≥ 5 times the upper limit of normal value), or serum creatinine ≥ 150 μmol/L;

(13) Severe pulmonary insufficiency who cannot tolerate general anaesthesia;

(14) Severe coagulation dysfunction;

(15) Undergone major surgical or interventionic surgery within 30 days before surgery;

(16) Patients whose systemic or local infection may increase the risk of intravascular graft infection;

(17) Planning pregnancy, pregnancy, or breastfeeding;

(18) The patient participated in other clinical trials or not completed or withdrawn from other clinical trials within the last 3 months at the time of screening period ;

(19) Life expectancy less than 1 year;

(20) Patients not appropriate for endovascular repair based on the investigators' clinical judgement.

2.3.3 Exit criteria

All patients should participate in the study voluntarily, and may withdraw from the study at any time without penalty, and the rights and interests will not be affected thereby, and the reasons for discontinuing the study may include, but are not limited to:

- Patient voluntary withdrawal
- For therapeutic reasons, the investigator may allow the patient to withdraw from the study without patient's consent
- Patient lost to follow-up
- Study Terminated

If the patient meets the above criteria and discontinues participation in the study, the study completion page of the patient's case report form should be completed.

2.3 Study Endpoints

2.4.1 Primary Endpoint

Incidence rates of Major Adverse Events (MAE) within 30 days postoperative

Evaluation time: Within 30 days postoperative

Precautions: Major adverse events are defined as all-cause death, liver failure, intestinal necrosis, splenic infarction, renal infarction, renal failure, cerebral infarction, paraplegia, myocardial infarction, and respiratory failure within 30 Days Postoperative. Among them, liver failure is defined as severe liver damage, leading to serious dysfunction or decompensation of its synthesis, detoxification, excretion and biotransformation. Renal failure is defined as prolonged dialysis, kidney transplantation, or other fatal outcome. Guidance for respiratory failure significantly prolongs intubation, tracheotomy, worsening lung function, oxygen dependence, or other fatal outcome.

2.4.2 Secondary Endpoint

（1） **Immediate intraoperative success rate [Intraoperative]**

Definitions of Immediate Technical Success: The delivery system is successfully delivered to the intended location, the thoracoabdominal aortic stent graft system is successfully deployed, the branch vessels are successfully reconstructed, and the delivery system can safely withdraw from the body; No type I or III endoleaks requiring intervention; No conversion surgery.

（2） **Perioperative delivery-related complication rate [intraoperative and pre-discharge]**

Delivery-related complications refer to intraoperative conveyor-related conversion to laparotomy, bleeding, hematoma, and pseudoaneurysm in the delivery approach

（3） **Aneurysm-related mortality rate [6, 12 months postoperation]**

Aneurysm-related death is defined as death caused by a ruptured aneurysm or by surgery to treat thoracic and abdominal aortic aneurysm, pararenal abdominal aortic aneurysm.

（4） Incidence rate of Serious Adverse Events (SAEs) [6, 12 months postoperation]

Serious adverse events refers to death or serious deterioration of patient health condition during the clinical trial, including fatal illness or injury, permanent impairment of body structure or function,hospitalization or prolonged hospital stay, and medical or surgical intervention to avoid permanent impairment of body structure or function; Events that cause to fetal distress, fetal death, or congenital abnormalities, congenital defects, etc.

（5） Incidence rate of device-related adverse events [6, 12 months postoperation]

Adverse events refers to adverse medical events that occur during clinical trial, whether or not related to the investigational medical device. However,postoperative stress responses, such as fever,constipation, etc., should be distinguished by the investigator judgment as normal postoperative stress responses and therefore do not need to be recorded as adverse events. Device-related adverse events refers to those that are judged by the investigator to be positively related, possibly related, or undeterminable to the investigational medical device.

（6） Incidence rate of Type I or Type III endoleaks [6 and 12 months postoperation]

Type I endoleaks, also known as peri-graft endoleaks or graft-related endoleaks, refers to endoleaks formed by the inability of tight-fitting between the stent blood vessels and autologous blood vessels, resulting in continuous blood flowinto the aneurysm lumen, including proximal Type I endoleaks and distal Type I endoleaks. Type III endoleaks refers to the continuous flow of blood into the aneurysm cavity caused by the inablitiy of the stent blood vessel to seal its own interface or the rupture of the artificial vessel.

（7） Incidence rate of Thoracic Abdominal Aortic Stent Graft System Displacement [6, 12 months postoperation]

Stent migration requiring intervention.

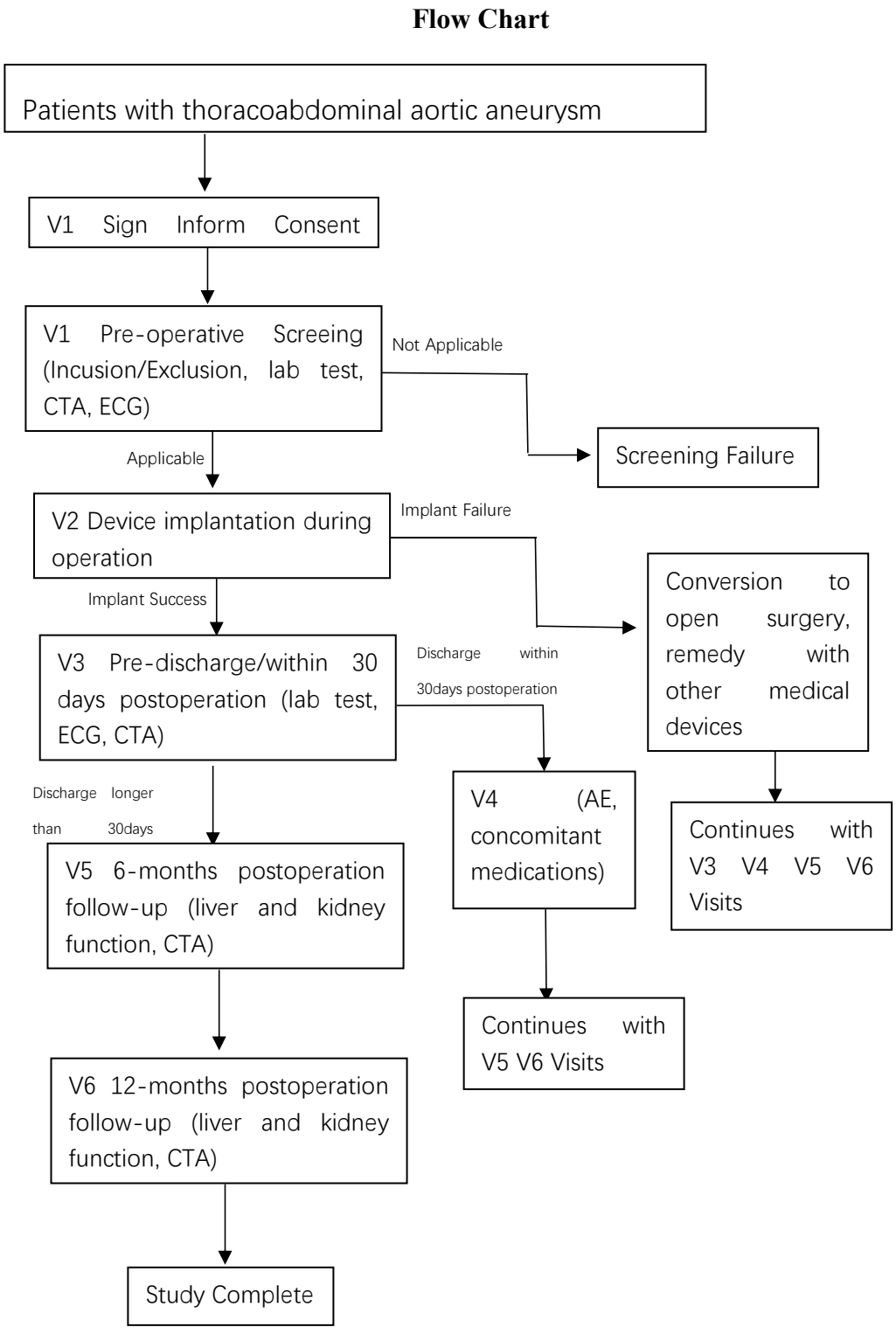
（8） Incidence rate of branch stent occlusion [6, 12 months postoperation]

The main stent and branch stent were structurally intact, the blood flow in branch stent was unobstructed, and there was no branch stent occlusion caused by thrombus.

（9） Incidence rate of conversion of thoracic and abdominal aortic aneurysms to open surgery or secondary interventional surgery [6, 12 months postoperation]

2.5 Study process

2.5.1 Flow chart



2.5.2 Summary of Trial Data Collection

Summary of Trial Data Collection

Visit Time / Visit / Items	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit6
	Pre-operation[1] (-30~0d)	Intra-operative (0d)	Before discharge[2]	30d Post-operation[2,3] (±3d)	6M±30d Post-operation[2]	12M±30d Post-operation[2]
Informed Consent	▲					
Inclusion Exclusion Criteria	▲					
Demographic Data	▲					
Vital Signs	▲	▲	▲			
Current Medical History	▲					
Past Medical History	▲					
Family Medical History	▲					
Chest and abdomen Examination	▲					
Blood routine[4]	▲		▲			
Urine routine[5]	▲		▲			
Liver and kidney function[6]	▲		▲		▲	▲
Enzyme tests[7]	▲		▲			
Pregnancy test[8]	▲					
12-lead ECG	▲		▲			
CTA/MRI[9]	▲		▲		▲	▲
DSA		▲				
Surgical Record		▲				
Adverse Events	▲	▲	▲	▲	▲	▲
Concomitant Medications[10]	▲	▲	▲	▲	▲	▲
Device Defect	▲	▲	▲		▲	▲

1. Preoperative (Visit 1): Preoperative laboratory or imaging studies have been performed prior to the informed consent form and can be used as baseline data

2. Patients requiring staged surgery: 1) Only follow-up visit 3 at the last surgery; 2) Visit 4,5,6 follow-up date calculated from the date of last procedure

3. If discharged within 30 days after surgery, Visit 4 (telephone follow-up) should be completed within 30 days after surgery;

Blood routine test: Hemoglobin content (Hgb), red blood cell count (RBC), white blood cell count (WBC), neutrophil count (NEUT), platelet count (PLT)

Urine routine test: Urine glucose (GLU), urine protein (PRO), urine red blood cell count (ERY), urine white blood cell count (LEU)

6.Liver and kidney function: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (STB), albumin (ALB), creatinine (SCR), urea (Urea), glucose (GLU) (if glucose values are not included in the liver and kidney function test sheet, the investigator needs to issue a separate test sheet to meet the glucose data collection)

7.Enzymatic tests: Lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase isoenzyme (CK-MB)

8. Pregnancy test: Only for unmenopausal women

9.1) Patients with abnormal renal function before discharge, 6 months after operation and 12 months after operation were examined by MRI; 2) When collecting the image data of this center, the electronic format is required to be DICOM format, and the distance between each plain scan is recommended to be less than 2 mm.

10. Concomitant medications: Anticoagulants, antiplatelet drugs, antihypertensive drugs, lipid-lowering drugs, glucose-lowering drugs, antibiotics

3. Statistical analysis

3.1 Sample size calculation

This study is a feasibility study and the total sample size expected to be 15.

3.2 Statistical analysis plan

3.2.1 Enrollment Analysis

(1) Calculate the number of enrolled and completed cases.

(2) List cases and causes of protocol violations.

3.2.2 Baseline data analysis

Descriptive statistics demography and other baseline data.

3.2.3 Primary endpoint analysis

Incidence rate of major adverse events within 30 days postoperative

3.2.4 Secondary endpoint analysis

Immediate intraoperative success rate, incidence rate of perioperative delivery-related complications, aneurysm-related mortality rate, incidence rate of device-related AEs, SAEs, incidence rate of type I or III endoleaks, incidence rate of stent migration, incidence rate of branch stent occlusion, and incidence rate of open or secondary interventional procedures were calculated, and trial discontinued due to adverse events and cases of SAEs were specifically noted.

4. Ethical issues and informed consent of clinical trial

Prior to the clinical trial, the investigator needs to submit the study protocol, informed consent form and other relevant documents to the Medical Ethics Committee. Clinical trials may not be started until Ethics Committee approval has been obtained. Any changes to the protocol must be approved by the Ethics Committee before they can be implemented.

Before each subject is enrolled in this study, it is the responsibility of the investigator to provide a complete and comprehensive description of the informed consent form in writing to the subject or the subject's guardian. The investigator should give sufficient time for the subjects to understand the details of the study before signing. The informed consent form was signed by the investigator and the subject or the subject's legal representative. The informed consent form is made in duplicate, and each party keeps one copy.

Subjects participating in this study will have free access to the Thoracic and Abdominal Aortic Stent Graft System and study-related examinations during postoperative follow-up, as well as medical guidance from physicians and device-related insurance coverage during follow-up.