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Protocol for Guo's aortIc Arch recoNstrucTion: a prospective, multicentre and single-arm study to evaluate the safety and efficacy of the WeFlow-Arch modular inner branch stent-graft system for aortic arch lesions (GIANT study)

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ABSTRACT

Introduction Endovascular repair of the entire aortic arch provides treatment opportunities for patients with aortic arch lesions who are intolerant to open surgery. However, the complex anatomical configuration, high-speed blood flow and long access from the femoral artery increase the difficulty of endovascular aortic arch repair. On the basis of our earlier studies, a new modular inner branch stent-graft system was developed specifically for lesions located in the aortic arch and part of the ascending aorta. This study aims to evaluate the safety and efficacy of the novel modular branch stent-graft system in patients with aortic arch lesions who are unsuitable for open aortic arch replacement.

Methods and analysis This prospective, multicentre, single-arm, clinical trial will enrol 80 patients with aortic arch lesions requiring intervention, namely, true aortic arch aneurysms, pseudo-aortic arch aneurysms and penetrating ulcers involving the aortic arch. Clinical information and CT angiography (CTA) images will be collected and analysed to investigate the safety and efficacy of the novel modular branch stent-graft system. Patients will be followed up for 5 years. The primary outcome will be all-cause mortality and severe stroke within 12 months after the procedure. In addition, this trial will evaluate mid-term to long-term clinical and imaging outcomes through the annual clinical and CTA follow-up for 2–5 years postoperatively.

Ethics and dissemination We have registered the study on a registry website (https://clinicaltrials.gov/ct2/home). The study findings will be disseminated through peer-reviewed journals, physician newsletters, conferences and the mass media.

Trial registration number NCT04765592.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a prospective, multicentre, single-arm study with a 60-month follow-up, and the participating centres are from different geographical climate regions of China.
⇒ This is the first study focusing on our novel modular branch stent-graft system, which is dedicated for endovascular repair of the entire aortic arch.
⇒ This is a single-arm prospective study, and there is no control group for comparison with other treatment modalities.
⇒ This is an open-label study, which has the potential to introduce bias.
⇒ This study will be performed in an East Asian population, resulting in limitations associated with ethnicities and geographical regions.

INTRODUCTION

The supra-aortic branches provide the blood supply to the brain, and the revascularisation of these branches is part and parcel of aortic arch repair. Endovascular repair of the aortic arch, which avoids a long hypothermic cardiopulmonary bypass, circulatory arrest, and antegrade or retrograde cerebral perfusion, provides a curative chance for patients with aortic arch pathology who cannot tolerate open surgical repair.[1–3] Combined with surgical debranching of the supra-aortic branches, the use of endovascular-based approaches, including parallel stent-grafts, scallop or fenestrated stent-grafts, in situ fenestrations and branched stent-grafts, has recently expanded rapidly.[4]

With technological advancements, endovascular repair of the entire aortic arch (proximal landing located in zone 0, distal landing in zone 3) in accordance with Ishimaru[5] has become attractive. However, endovascular repair remains very difficult when the ascending aorta or aortic arch is involved. The main technical challenge is to maintain sustained blood flow to the supra-aortic branches to avoid prolonged cerebral and

upper extremity ischaemia during the procedure. In addition, arch curvature and a long access from the femoral artery increase concerns about precise alignment and deployment of a stent-graft. Furthermore, owing to the proximity of the landing zone to the left ventricle, with great pulsatility and large blood flow, a windsock effect of the stent-graft before complete deployment could lead to stent-graft migration or kinking.[6–8] The current clinical evidence indicates that procedural complications, namely, cerebral ischaemia, endoleak and retrograde dissection, are associated with endograft design and a complicated procedure.[9–12]

To address the stated challenges, several innovative dedicated stent-grafts for total endovascular aortic arch repair have been developed, namely, the Inoue outer branched stent-graft,[9 13] Najuta fenestrated stent-graft,[14 15] Cook two-inner branch endograft,[16 17] Bolton inner double-branch endoprosthesis[18 19] and Endospan NEXUS stent-graft.[20 21] However, there is no ideal endovascular solution to the ascending aorta/aortic arch challenge that can completely exclude the aortic arch pathology, avoid embolic stroke and preserve perfusion of the supra-aortic multi-branches without surgical debranching of the supra-aortic branches or a complex endovascular procedure.

On the basis of our earlier studies,[22–24] we developed a new modular inner branch stent-graft system (WeFlow-Arch; Hangzhou Endonom Medtech Co., Ltd., Hangzhou, China) specifically for lesions located in the aortic arch and part of the ascending aorta. The stent-graft system is under review by the National Medical Products Administration. In our centre, the preliminary results of eight cases from June 2019 to October 2021 showed a technical success rate of 100%, and no patients suffered symptomatic cerebral ischaemia. The Guo's aortIc Arch recoNstrucTion (GIANT) study is a prospective, multicentre, single-arm study. The aim is to investigate the clinical results after endovascular aortic arch repair using this stent-graft system in patients with aortic arch lesions who are unsuitable for open aortic arch replacement.

OBJECTIVE

The objective of the study is to evaluate the safety and efficacy of the modular branch stent-graft system (WeFlow-Arch) in endovascular repair of the aortic arch.

The primary outcome will be all-cause mortality and severe stroke within 12 months after the procedure. All-cause mortality will comprise cardiac mortality, non-cardiac mortality and mortality from unknown causes. Severe stroke is defined as a modified Rankin scale score ≥2 at 90 days following stroke onset.[25]

The secondary outcomes are as follows:

1. Technical success, defined by the composite of successful stent-graft deployment, all branching stents patency, and the absence of type I/III endoleaks, migration and rupture at the final angiography;
2. Twelve-month clinical success, defined as aortic aneurysm diameter growth ≤5 mm compared with the preoperative aortic aneurysm size;
3. The maximum diameter of aortic aneurysm at 1 month, 6 months, 12 months and 2–5 years after the surgery;
4. Incidence of endoleak (type I/II/III/ IV) immediately after the surgery, and 1 month, 6 months, 12 months and 2–5 years after the surgery;
5. Incidence of stent-graft migration 1 month, 6 months, 12 months and 2–5 years after the surgery, with migration defined as aortic or branching stent-graft migration of>10 mm;
6. Supra-aortic branch patency rate 1 month, 6 months, 12 months and 2–5 years after the surgery;
7. Incidence of stent-graft-induced aortic dissection leading to conversion to open surgery or secondary intervention 1 month, 6 months, 12 months and 2–5 years after the surgery;
8. Incidence of 30-day major adverse events, namely, all-cause mortality, myocardial infarction, ischaemic stroke, or respiratory failure;
9. Twelve-month aortic aneurysm-related mortality;
10. Incidence of severe adverse events 1 month, 6 months, 12 months and 2–5 years after the surgery, including death, serious deterioration in patient health and any adverse event requiring interventional therapy or open surgery;
11. Incidence of device-related adverse events (as determined by the clinical investigators) 1 month, 6 months, 12 months and 2–5 years after the surgery.

METHODS

Study design

This is a prospective, multicentre, single-arm study. All enrolled patients will undergo CT angiography (CTA) and clinical evaluation 30 days, 3 months, 6 months and 12 months in the first year postoperatively, and annuals in 2–5 years after the surgery. Clinical information will be acquired through the patients' electronic medical records and the CTA Digital Imaging and Communication in Medicine files from the radiology department databases.

The clinical study was conceived, designed and initiated, and will be performed by the Department of Vascular Surgery, Chinese PLA General Hospital. Twenty-three additional medical centres with high annual surgery volume (thoracic endovascular aortic repair >30 cases per year) in different geographical climate regions of China were invited to participate in this study. The geographical distribution of all participating centres at the start of the trial comprises the following: Northeast China (n=2), North China (n=6), East China (n=11), Central China (n=2), South China (n=1) and Southwest China (n=3) (table 1). All participants received specific training and passed a training test prior to performing the formal procedure.

Table 1 Participating trial centres

Clinical trial institution	Geographical region
Chinese PLA General Hospital	North China
Peking University People's Hospital	North China
Beijing Anzhen Hospital, Capital Medical University	North China
Tianjin Medical University General Hospital	North China
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences	North China
The First Affiliated Hospital of PLA Air Force Military Medical University	North China
The Second Affiliated Hospital of Harbin Medical University	Northeast China
The First Affiliated Hospital of China Medical University	Northeast China
Zhongshan Hospital, Fudan University	East China
Nanjing First Hospital	East China
Nanjing Drum Tower Hospital	East China
The Affiliated Hospital of Qingdao University	East China
The Ninth People's Hospital, Shanghai Jiaotong University School of Medicine	East China
Renji Hospital, Shanghai Jiaotong University School of Medicine	East China
Shandong Provincial Hospital	East China
The First Affiliated Hospital of Soochow University	East China
First Affiliated Hospital of Zhejiang University School of Medicine	East China
Second Affiliated Hospital of Zhejiang University School of Medicine	East China
The Second Affiliated Hospital of Nanchang University	East China
Xiangya Hospital of Central South University	Central China
First Affiliated Hospital of Zhengzhou University	Central China
The First Affiliated Hospital, Sun Yat-sen University	South China
West China Hospital of Sichuan University	Southwest China
The First People's Hospital of Yunnan Province	Southwest China

The centres listed in the table are the originally participating hospitals at the start of the trial.

PLA, People's Liberation Army.

Participants

This study uses competitive enrolment. We plan to recruit 80 patients who meet the inclusion criteria to participate in this study from June 2021 to December 2022. All patients will be followed up until death or the end of follow-up (5 years after surgery). The endpoint of the study is defined as the date of the last follow-up visit of the last participant. The estimated end date is December 2027.

Criteria

Inclusion criteria:

1. Patients aged 18–80 years;
2. Patients who are diagnosed with aortic arch lesions requiring intervention, namely, true aortic arch aneurysms, pseudo-aortic arch aneurysms and penetrating ulcers involving the aortic arch;
3. Patients with surgical contraindications or high surgical risk;
4. Patients with a suitable vascular condition, namely, ascending aorta length ≥50 mm (from the sinotubular junction to the proximal margin of the innominate artery (IA))
   a. Ascending aorta diameter ≥24 mm and ≤48 mm;
   b. Proximal anchoring zone length ≥30 mm;
   c. IA diameter ≤24 mm and ≥7 mm, length ≥20 mm;
   d. Left common carotid artery (LCCA) or left subclavian artery (LSA) diameter ≤24 mm and ≥7 mm, length≥20 mm;
   e. Suitable arterial access for endovascular treatment (such as diameter, tortuosity and calcification);
5. Patients who understand the purpose of the trial, have good compliance and are able to complete the follow-up.

Exclusion criteria:

1. Patients who experienced systemic infection within the previous 3 months;
2. Patients who underwent surgeries in the neck within 3 months of the endovascular procedure;
3. Patients who underwent endovascular interventional treatment involving the aortic arch;

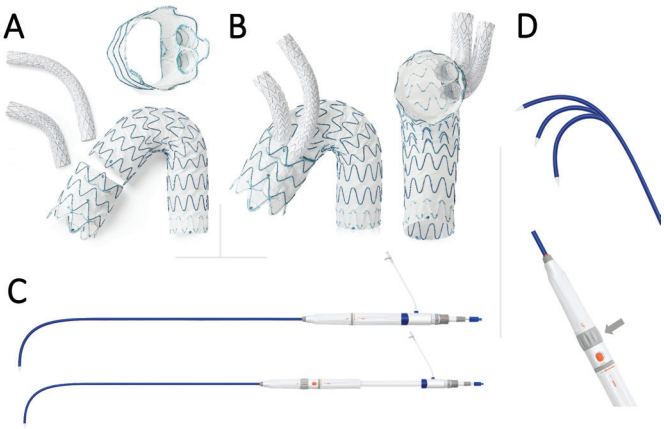

Figure 1 Design of the new modular inner branch stent-graft and delivery system. The modular stent-graft before (A) and after (B) assembly. The dedicated delivery systems are shown for ascending aorta stent-grafting (upper image in panel C; pre-curved design) and aortic arch stent-grafting (lower image in panel C; pre-curved plus steerable design). Schematic diagram of the steering operation of the pre-curved plus steerable delivery system (D). First, ascending aorta stent-graft; second, bridging cover-stents; third, aortic arch stent-graft. The arrow indicates the control dial that is used to steer the direction of the tip.

4. Patients with infectious aortic disease, Takayasu arteritis, or Marfan syndrome (or other connective tissue diseases);
5. Severe stenosis, calcification, thrombosis, or tortuosity of the carotid or subclavian artery;
6. Patients who underwent heart transplantation;
7. Patients who suffered myocardial infarction or stroke within 3 months of the endovascular procedure;
8. Patients with New York Heart Association class IV heart function;
9. Patients with an active peptic ulcer or upper gastrointestinal bleeding within 3 months of the endovascular procedure;
10. Patients with haematological abnormalities, namely, leucopenia (white blood cell count $<3\times10^9$/L), acute anaemia (haemoglobin <90 g/L), thrombocytopenia (platelet count $<50\times10^9$/L), or a history of bleeding diathesis or coagulopathy;
11. Patients with renal insufficiency (creatinine >265 µmol/L) or end-stage renal disease;
12. Patients who are pregnant or breast feeding;
13. Patients with allergies to contrast agents;
14. Patients with a life expectancy of less than 12 months;
15. Patients participating in another drug or device study;
16. Any other disease or abnormality that the investigators believe may hinder endovascular treatment.

Design of the device

The concept of Guo's aortic arch reconstruction is to use different dedicated stent-graft modules to achieve the goals of covering aortic arch lesions and reconstructing supra-aortic arteries, respectively. Segmental deployment simplifies procedures associated with complicated anatomical matching and avoids extended interruption of the supra-aortic blood supply. The endografts of the modular inner branch stent-graft system consist of three modules: one ascending aorta stent-graft with two inner branches, bridging cover-stents and one tubular aortic arch stent-graft (figure 1A and B).

Module 1, the ascending aorta stent-graft (proximal non-bare stent), ranges in size from 28 mm to 52 mm in proximal diameter and from 30 mm to 70 mm in length. The distinguishing feature of this module is the two inner branches of equal diameter in the anterior aspect of the endograft, which are designed to connect to the IA by the anterior inner branch and to the LCCA or LSA by the posterior inner branch. In addition, integral suturing of the connection sites seals the gutter around the inner branches to avoid potential endoleaks. The module's delivery system has a self-aligning design. The module is mounted in the pre-curved delivery system (size range from 22 Fr to 24 Fr) (figure 1C, upper image), and the two inner branches align with the anterior aspect of the ascending aorta. Radiopaque marker rings are attached at both ends of the inner branches for imaging identification during reconstruction of the supra-aortic arteries.

Module 2 is a self-expandable tapered cover-stent that is mounted in a delivery system with a diameter of 12 Fr and which is used to bridge the inner branches of module 1 to the supra-aortic arteries via the right brachial or LCCA access. The tapered design allows the distal and proximal segments of module 2 to match the diameters of the inner branch and the supra-aortic arteries, respectively. Module 3, which is a tubular aortic arch stent-graft, is mounted in a pre-curved delivery system (size range from 20 Fr to 22 Fr) with the steerable device (figure 1C (lower image) and D), which is designed to avoid iatrogenic displacement of module 1 during introducing manipulations.

Endovascular aortic procedures

The procedures are performed under general anaesthesia in a hybrid operating room.

Operation step one: approach preparation

Bypass between the LCCA and LSA is performed before the endovascular procedure. After the LCCA and LSA are exposed surgically through a neck incision, intravenous heparin is administered to achieve an activated clotting time of at least 250 s. After the bypass is performed, the LCCA is directly punctured, and a 6 Fr sheath is inserted to establish vascular access. The approach to the right brachial artery or axillary artery is surgically exposed according to the diameter of the IA to meet the delivery system size, and the artery is directly punctured. Left radial artery catheterisation is performed with a 5/6 Fr sheath. One of the femoral arteries is cannulated percutaneously with a 6 Fr sheath, and two Perclose ProGlide (Abbott Vascular, Redwood City, CA, USA) sutures are prepositioned. Intraoperative use of a temporary pacemaker to reduce cardiac output is at the discretion of

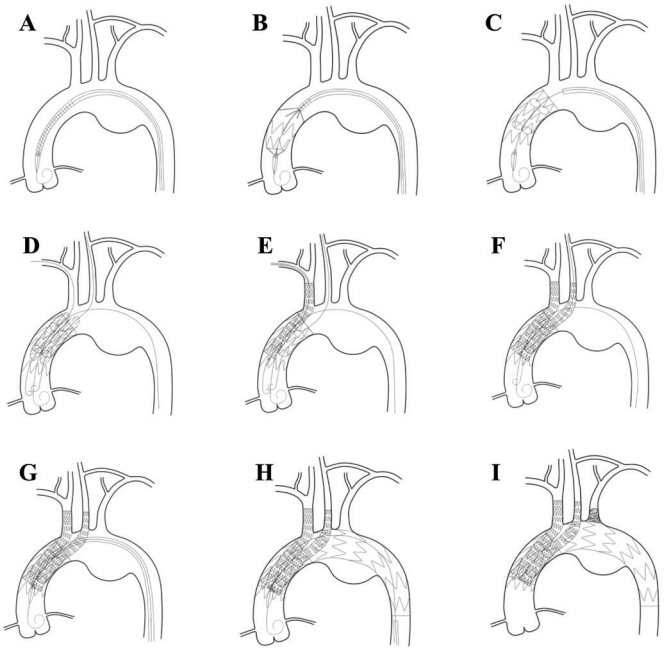

Figure 2 Schematic diagram of the endovascular procedure. A–C, Module 1 is deployed in the ascending aorta, and the two inner branches of the endograft self-align with the anterior aspect of the ascending aorta. D–F, Module 2 is deployed to bridge the inner branches of module 1 to the supra-aortic arteries via the right brachial and left common carotid artery accesses, respectively. G–I, Module 1 is deployed to overlap the lumen of module 1 via a steerable pre-curved delivery system, and the proximal portion of the left subclavian artery is embolised using coils.

the operator. The contralateral femoral vein is used to implant a temporary pacemaker.

Operation step two: ascending aorta stent-grafting

A Lunderquist wire (Cook Medical, Bloomington, IN, USA) is prepositioned in the aortic sinus or left ventricle, and module 1 is advanced beyond the IA ostium and deployed in zone 0 (under rapid pacing if necessary). Device rotation is automatically controlled by the pre-curved delivery system (figure 2A–C).

Operation step three: bridging cover-stents and aortic arch stent-grafting

Two expanded balloons that are used to verify the wires from the right brachial artery and the LCCA are positioned in the anterior and posterior inner branches, respectively. Module 2 is then introduced over the guidewire and bridges the IA or LCCA with the inner branches, respectively (figure 2D–F). The module 3 aortic arch stent-graft is introduced over the Lunderquist wire to overlap the lumen of module 1 via a steerable pre-curved delivery system.

Operation step four: balloon dilation and LSA occlusion

After the modules are dilated to the arterial wall by balloon inflation to ensure an adequate seal, embolisation of the proximal portion of the LSA from the LSA orifice to the vertebral artery origin is performed using coils through the left radial or brachial artery access (figure 2G–I).

The preventive management of spinal cord ischaemia:

1. One-stage left subclavian artery revascularisation using LSA–LCCA bypass
2. Stable blood pressures and haemoglobin levels in perioperative period (mean arterial pressure ≥80 mmHg; central venous pressure ≤12 mmHg; haemoglobin level ≥10 g/dL).
3. Antiplatelet and anticoagulant therapy
4. Postoperative neurological assessments on a one to two hourly before awakening from anaesthesia.
5. Prompt cerebrospinal drainage catheter insertion and maintenance when spinal cord ischaemia is confirmed.

Data collection

Table 2 summarises the schedule for the study visits and data collection. We developed a standardised case report form for use in data collection, which will comprise medical record data, CTA imaging data and follow-up data. Demographics, comorbidities, surgical details and perioperative data will be collected during hospitalisation. Preoperative and follow-up CTA images 1, 6 and 12 months in the first year postoperatively, and annuals in 2–5 years after the surgery will be submitted to an imaging core laboratory in the Digital Images and Communication in Medicine format and will be assessed by experienced vascular surgeons who are blinded to the clinical results. Double data entry and cross-validation methods will be used to ensure the quality of the data. A monitoring team comprising clinical research associates who are independent from the investigators and sponsors will constantly review all clinical study data in accordance with regulatory requirements.

Statistical methods

Sample size calculation

A sample size calculation was performed on the basis of the objective performance of the primary endpoint of the study. Combined with our preliminary single-centre data pertaining to endovascular repair of the aortic arch (unpublished, 2022) and previous studies,[26–28] we estimated that the incidence rate of the composite primary endpoint of all-cause mortality and severe stroke within 12 months was 35% (objective performance), and the expected incidence rate of the modular branch stent-graft system was 20%. The level of statistical significance was set at 2.5% for one-sided tests, and the overall power was set at 80%. The calculated sample size was 72 subjects. Considering a dropout rate of 10%, the required sample size was increased to 80 subjects. Therefore, the aim is to enrol at least 80 patients in the clinical trial.

Statistical analysis

An interim analysis is performed on the primary endpoint when all patients have completed the 12-month follow-up. The interim analysis is performed by an independent statistician. Three analysis subject sets will be distinguished:

Table 2 Schedule for the study visits and data collection

	Baseline (−15 days~1 day)	Operation day	Discharge day	Post-30 days (±7 days)	Post-6 months (±30 days)	Post-12 months (±30 days)	Post-24 months (±30 days)	Post-36 months (±30 days)	Post-48 months (±30 days)	Post-60 months (±30 days)
Informed consent	×									
Eligibility screen	×									
Medical history/ demographics	×									
Pregnancy test	×									
Physical examination	×	×	×							
Blood routine	×		×							
Urine routine	×		×							
Coagulation function	×		×							
Liver/renal function	×		×							
Modified Rankin score	×		×							
Electrocardiography	×		×							
Echocardiography	×									
Thoracic X-ray	×									
CTA	×				×	×	×	×	×	×
DSA		×								
Operation record		×								
Medication record	×	×	×	×	×	×	×	×	×	×
Adverse events record	×	×	×	×	×	×	×	×	×	×

CTA, CT angiography; DSA, digital subtraction angiography; Post, post-procedure.

a full analysis set, a per-protocol set and a safety set. The primary and secondary endpoints will be evaluated using both the full analysis set (using the intention-to-treat principle; all enrolled patients) and the per-protocol set (patients who complete the trial in accordance with the protocol without major violations). All safety analyses will be performed using the safety set (all enrolled patients treated by the device).

Continuous variables will be expressed as mean±SD, or median (IQR) if distributions were skewed. Categorical and ranked variables will be expressed as number and percentage. The Kaplan-Meier method will be used to estimate the cumulative rate of each endpoint, and Kaplan-Meier curves will be created. Statistical calculations will be performed using SAS software (V.9.4 or above; SAS Institute Inc., Cary, NC, USA).

Ethics and dissemination

The study will be conducted in accordance with the tenets of the Declaration of Helsinki. Any significant protocol modifications will be forwarded to the ethics committee for approval.

The patient and his/her family members will be given information about the study, namely, the potential advantages and risks of the modular inner branch stent-graft system, and any alternative treatments that are available. Written informed consent will be provided by the patients or their immediate family members during standard clinical visits required for the endovascular procedure. The example of informed consent form is provided in online supplemental material.

The patients' information will be maintained in accordance with international good clinical practice standards. Data for all enrolled patients will be anonymised and allocated a unique code as a study identification. Only direct members of the study team will have access to the data linked to a participant's identity. Paper-based materials (eg, the case report form) will be stored in locked file cabinets, while electronic data files that are identifiable will be stored in a password-secured separate server behind a firewall to guard against inappropriate use or malicious or accidental loss or destruction. We anticipate that the study results may provide a novel solution for endovascular repair of the entire aortic arch and a novel therapeutic option for aortic arch lesions.

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Contributors FL and HZ contributed equally to this manuscript. WG initiated the conception and design of the study, while FL, YG, DR, XJ, JX, XM, LW and TF helped with the implementation of the study. FL, HZ and WG prepared the first draft of the manuscript. All authors contributed to the study protocol and approved the submitted version.

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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 applicable.

Ethics approval The study protocol involves human participants and has been reviewed and approved by the ethics committee of the Chinese PLA General Hospital (2020-034) and each participating centre. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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Informed Consent Form

Trial product name: WeFlow-Arch modular inner branch stent-graft system

Model specification: All specifications

Sponsor: Hangzhou Endonom Medtech Co., Ltd.

Protocol name: A prospective, multicenter and single-arm study to evaluate the safety and efficacy of the WeFlow-Arch modular inner branch stent-graft system for aortic arch lesions

Version number and date of informed consent form: V1.0/December 7, 2020

Clinical trial institution:_____

Investigator:_____

Informed Consent Version Number: V1.0 / Version date: 20201207

STUDY PARTICIPANT INFORMATION SHEET

Dear participant:

You will be invited to participate in "A prospective, multicenter and single-arm study to evaluate the safety and efficacy of the WeFlow-Arch modular inner branch stent-graft system for aortic arch lesions". The following describes the trial background, purpose, methods, benefits and potential risks or inconveniences that this trial's medical device may cause you during the trial, as well as your rights. Please read it carefully before participating in the clinical trial. The information provided in this informed consent form can help you decide whether to participate in this clinical trial. If you have any questions, please ask the investigator in charge of the trial to ensure that you fully understand the relevant content. Your participation in this trial is voluntary. If you agree to participate in the clinical trial, please sign the statement of informed consent.

1. Background of the trial

Severe aortic dilation, such as aortic aneurysm, would seriously affect patients living quality and even cause patients death. Based on the location of the lesion, the condition may be classified as ascending aortic aneurysm, arch aneurysm, descending aortic aneurysm, abdominal aortic aneurysm, etc. More than 70% of patients with untreated thoracic aortic aneurysm eventually progress to aneurysm rupture, and more than 90% of such ruptures are fatal. Current consensus opinion states that symptomatic or large true aneurysms, penetrating ulcers and pseudoaneurysms, should be considered for operative and interventional procedures. Recent developments in the field, combined with both domestic and overseas experience suggest that open operation is typically required for aortic aneurysms involving the ascending aorta or the aortic arch due to the lack of an adequate anchoring zone. Surgical repair of aneurysms in the ascending aorta and aortic arch requires the use of deep hypothermic circulatory arrest, with mortality rates of 2%-16.5% and stroke rates of 2%-18% reported. Arch hybrid operation generally provides adequate proximal anchoring zone for endovascular repair and avoids the use of deep hypothermic circulatory arrest, but mortality and stroke rates remain high, with 0%-15% mortality and 0%-11% stroke rates reported.

In recent years, the development of fenestrated and branch stent-graft has provided new devices and methods for the treatment of complex aortic lesions, greatly reducing the high mortality rate (14% vs 8%) associated with open operation and endovascular intervention, with less injury, fewer complications, lower mortality, and faster recovery. This has allowed even elderly patients or patients with associated cardiac, pulmonary, hepatic, and renal insufficiency to be treated aggressively, who were previously deemed

unsuitable for open operation.

Parallel stenting and fenestration are currently used techniques in the procedure of endovascular aortic arch repair. The parallel stenting technique, also known as chimney stenting, preserves the branch vessels and expands the landing zone by releasing small stents along the outside of the aortic stent-graft. The technique relies on the close conformation of the aortic stent-graft and the aortic wall around the chimney stent, and the gutter between the small stent and aortic stent graft is considered one of the main sources of endoleak.

Fenestration technique can be either *ex vitro* or *in situ*. One of the main disadvantages of *ex vitro* fenestration is inaccurate alignment during the procedure. *In situ* fenestration prevents the risk of inaccurate alignment, but the technique still suffers from some drawbacks, including the risk of fenestration debris-related embolism as well as unsuitability for use in the treatment of torturous aortic lesion. Branch stent-graft technology, especially multi-branch stent-graft for aortic arch reconstruction, represents a major development direction for multivessel aortic arch reconstruction as it more closely conforms to normal anatomical structure and blood flow in the human body.

Global research on multi-branched stent-grafts remains in the preliminary stages, and the present study seeks to develop and design a modular inner branch stent-graft system to address the problems of current clinical endovascular repair techniques and products for the aortic arch.

The endografts of the modular inner branch stent-graft system consist of three modules: one ascending aorta stent-graft with two inner branches, bridging cover-stents, and one tubular aortic arch stent-graft. The ascending aorta stent-graft has two inner branches that can be combined with bridging cover-stents for endovascular reconstruction of the innominate artery, left common carotid artery or left subclavian artery. The aortic arch stent graft is combined with the ascending aortic stent-graft to address lesions present in the arch and descending aorta.

The clinical trial has been approved by the ethics committee of the Chinese PLA General Hospital (2020-034) and each participating hospital (institution:_____, approval code:_____)

2. Trial objective

The goal of the study is to evaluate the safety and efficacy of WeFlow-Arch modular inner branch stent-graft system in the endovascular interventional treatment of patients with aneurysmal lesions of the aortic arch.

3. Trial content and methods

This is a prospective, multicenter and single-arm study to evaluate the safety and efficacy of the WeFlow-Arch modular inner branch stent-graft system for aortic arch lesions, including: true aortic arch aneurysms, pseudo-aortic arch aneurysms and aortic arch ulcers. Duration of the participation, the trial

device will be implanted during the procedure and will be follow up for a period of 5 years, respectively, at 30 days, 6 months, 12 months, 2 years, 3 years, 4 years, and 5 years after stent implantation. Therein, CTA (CT angiography) examinations were performed at 30 days, 6 months, and 12 months after the procedure.

4. The trial process

The clinical trial you participate in will be divided into three phases:

1). Screening period:

If you are willing to participate in this study, the doctor will ask for and record your medical history before you are selected for the study, and you will be required to undergo a series of medical examinations to help the doctor determine whether you are eligible to participate in this clinical study. (Refer to: Trial flow chart)

2). Treatment period:

If you meet the inclusion criteria and do not meet any exclusion criteria, your doctor will perform endovascular repair of the aortic arch on the first day of the treatment period. The main procedure is as follows:

The procedures are not at all painful and performed under general anesthesia in a hybrid operating room. Before the endovascular procedure, bypass between the left common carotid artery and left subclavian artery is performed through a neck incision. The vascular accesses for endovascular procedure are established through the left common carotid artery, the right brachial artery or axillary artery, left radial artery, and the femoral artery on one limb by percutaneous puncture or direct vision puncture. After evaluating the conditions of your aortic arch lesion, the stent-graft will be implanted into the correct position of aorta using standard interventional protocol. In this process, the doctor will use X-rays and a contrast agent to observe the conditions of your aorta. And generally, the doses of X-rays and a contrast agent you receive will be no more than those used in routine procedures on other complex aortic diseases.

After the procedure, you will be transferred to the post-anesthesia care unit or intensive care medicine, and then to general wards when the condition is stable.

3). Follow-up period:

According to the study protocol, you need to undergo vital signs, blood routine, urine routine, coagulation function, liver and kidney function tests, and other examinations before leaving the hospital. And at 30 days, 6 months, and 12 months after the operation, you will receive regular telephone follow-up or outpatient review and reexaminations, including CTA. At the 2, 3, 4, and 5 years after the operation, you will be followed up by regularly telephone to assess your health statuses

See the **Trial flow chart** below for details:

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Trial flow chart

Trial Procedure	**Screening period**	**Operation**	**Follow-Up**				
Visit	V1	V2	V3	V4	V5	V6	V7-10
Days	Day -15 ~ -1	0	Before discharge	30 days after operation ± 7 days	6 months after operation ± 30 days	12 months after operation ± 30 days	2-5 years after operation ± 30 days
Signing of Informed Consent Form	X						
Inclusion/Exclusion Criteria	X						
Medical History/Demographic Data	X						
Pregnancy Test	X						
Physical Examination	X	X	X				
Blood routine examination	X		X				
Urine routine examination	X		X				
Coagulation Function test	X		X				
Liver and Kidney Function	X		X				
Evaluation of Clinical Symptoms (Modified Rankin Score)	X		X	X	X	X	
12-lead ECG	X		X				
Echocardiography	X						
Chest X-ray	X						
CTA	X			X	X	X	
DSA		X					
Operation Records		X					
Medication Record	X	X	X	X	X	X	X
Adverse Event Record	X	X	X	X	X	X	X

Notes:

- Pregnancy test: Women of childbearing age during screening as well as women who are suspected of being pregnant during the course of screening will be subject to this test (urine or blood pregnancy test);
- Physical examination: Heart rate, respiration, blood pressure, body temperature and arterial pulsation in the upper and lower extremities;
- Blood routine examination: Erythrocytes, leukocytes, platelet count and hemoglobin;
- Urine routine examination: pH, leukocytes, erythrocytes and proteins;
- Liver and kidney function: Creatinine (Cr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL);
- Coagulation function testing: Activated partial thromboplastin time (APTT), prothrombin time (PT), international standard ratio (INR), fibrinogen (FIB), thrombin time (TT), D dimer D-dimer:
- Data pertaining to past medication and past medical history for the 3 months preceding the date on which informed consent is obtained will be collected;
- CTA measurement data during the screening period needs to be reviewed and confirmed by the team leader, and enrollment can proceed after confirmation;
- Before discharge (visit 3): refers to a visit from before the operation to a day before discharge, and the results of the last laboratory test before discharge are collected;
- CTA data obtained prior to the operation and at 30 days ± 7 days after the operation, 6 months ± 30 days after the operation and 12 months ± 30 days after the operation will be collected;
- Medication records created prior to the operation, during the operation, prior to discharge and at 30 days ± 7 days after the operation, 6 months ± 30 days after the operation and 12 months ± 30 days after the operation as well as adverse event records created after informed consent is obtained, during the operation, prior to discharge and at 30 days ± 7 days after the operation, 6 months ± 30 days after the operation and 12 months ± 30 days after the operation will be collected;
- Participants' modified Rankin scores obtained 90 days after stroke onset will be collected;
- Where feasible, laboratory test data obtained 15 days prior to participant enrollment (prior to signing of informed consent) as well as CTA and ultrasound, 12-lead ECG data, and chest radiography obtained 30 days prior to enrollment (prior to signing of informed consent) may be used as baseline assessment data without any need for re-examination.
- Participants were followed up for 2, 3, 4, and 5 years (± 30 days) by telephone follow-up, and adverse events and medications related to adverse events were recorded.

5.Trial funding

Hangzhou Endonom Medtech Co., Ltd. will be responsible for relevant testing expenses possibly required for device implantation or the study.

6. No-cost diagnosis and treatment and other subsidies that may be obtained during the trial

1). By participating in this trial, you can receive a free WeFlow-Arch modular inner branch stent-graft system.

2). By participating in this trial, you can be provided with international clinical trial insurance. (Insurance company name:_____, insurance code:_____)

3). During the study, blood routine examination, urine routine examination, liver and kidney function, coagulation function, electrocardiogram, echocardiography, chest X-ray examination, CTA examination, and a pregnancy test (urinary/blood pregnancy) can be performed for free before the operation. A free blood routine examination, urine routine examination, liver and kidney function, coagulation function, and electrocardiogram examination will be performed at the time of discharge, and a free CTA examination will

be performed at 30 days, 6 months, and 12 months after the operation. You will not be able to participate in this study if you are pregnant and/or breastfeeding.

4). You will not receive remuneration for taking part in this study.

7. Potential benefits of participating in this study

Your potential benefits, following endovascular repair, primarily include alleviation of swelling and pain symptoms caused by the aortic aneurysm, prevention of local tissue ischemia and tissue or organ compression, recovery of normal blood circulation, and even saving your life. However, it is not possible to ensure that you will obtain the benefits herein. The possible benefits you may get from participating in this study also include good medical care by medical staff and attention to your condition. You may not receive benefits other than these, but the medical data provided by your participation in this study may help other patients with the same disease in the future.

8. Possible risks and discomfort

Over the course of many years of clinical applications, endovascular repairs have been proven safe and effective. However, it is an interventional procedure, and, as in other interventional procedures, there are intraoperative and postoperative possibilities of some adverse events, including but not limited to intraoperative respiratory/circulatory failure-induced cardiac arrest, sudden death, malignant arrhythmia, acute heart failure, acute myocardial infarction, cerebrovascular accident, bleeding risk, anesthesia risk, allergies, systemic inflammatory response, rupture of aneurysm, hemorrhagic shock, and cardiac tamponade; device-related complications, including stent-graft migration or collapse, kinking , endoleak due to inadequate seal at the site of the graft attachment, stent-graft fracture, and graft-related infection; and postoperative new-onset lung infection, pleural effusion, hypostatic pneumonia, acute kidney injury, acute upper limb ischemia, visceral ischemia, aortic dissection or rupture, retrograde type A dissection, paraplegia, cerebral stroke, spinal ischemia, access-related complication, coagulation disorder, pain, etc.

If you experience any discomfort during the study period, or if there is a new change in your condition, or any unexpected situation, regardless of whether it is related to the study, you should notify your doctor promptly, and the doctor will make a judgment and give appropriate medical treatment.

9. Treatment and financial compensation for trial-related injury

If there is a need for treatment during the study period, if your injury was caused by study equipment or study procedures, the sponsor will provide free treatment and provide reasonable compensation; inspection and treatment costs caused by non-study devices or study procedures will be borne by you or your medical insurance.

10. Alternative diagnosis and treatment methods other than this trial

If you decide not to participate in this clinical trial, your doctor will choose a suitable alternative

treatment, such as medication or surgical treatment, based on your physical condition.

11. Confidentiality of medical records

Your medical records (including research medical records and physical and chemical test reports, etc.) will be kept in the hospital as required. Except for investigators, ethics committees, inspections, audits, competent authorities, and other relevant personnel that are allowed to view your medical records, other personnel not related to the trial will not have the right to view your medical records without permission. In addition, if you consent, your private doctor will be informed of your participation in the study. The public report of the results of this trial will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data within the permitted scope.

12. Loss to follow-up

If, after the clinical trial is approved, a participant is unable to complete the follow-up for a participant-related reason, the investigators should use all available avenues to contact the participant in order to inquire after the reason, including investigating the whereabouts of the participant by looking up civil registration information; if the participant drops out due to an adverse event, and the follow-up ultimately determines that there is a causal relationship with the trial device, the event must be recorded in the eCRF and the sponsor should be notified accordingly.

13. Voluntary participation and withdrawal from the trial

You can choose not to participate in this trial, or you can withdraw from the trial after informing the investigator at any time without being discriminated or retaliated against. None of your medical treatment and rights will be affected by this.

If you need other diagnosis/treatment, or you did not follow the trial plan, or for any other reasonable reasons, the investigator can terminate your continued participation in this trial.

14. Relevant contact information for new information

If there is any important new information during the study that may affect your willingness to continue participating in the study, your doctor will notify you promptly. If you are interested in your own study data, or after the trial is over, you want to know the findings of this trial, you can ask any questions about this trial at any time and get corresponding answers. Please call and (investigator or related personnel).

The Ethics Committee has reviewed and approved the trial. If you have any questions related to your rights/interests, or if you want to report difficulties, dissatisfaction, or concerns encountered in the process of participating in this trial, please contact:_____ , the Ethics Committee, tele:_____ .

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Participant's signature sheet

15. Participant statement

I have read this informed consent form carefully. I have had the opportunity to ask questions and all questions have been answered. I understand that participation in this trial is voluntary. I can choose not to participate in this trial, or I can withdraw after informing the researcher at any time without being discriminated or retaliated against. None of my medical treatment or rights will be affected by these.

If I need other diagnosis/treatment, or I did not follow the trial plan, or there are other reasonable reasons, the investigator can terminate my continued participation in this clinical trial.

I permit the competent authorities, the sponsor, and the insurer to review my files. Since the study will be conducted in several countries, I likewise consent to the review of my personal study data by the competent authorities of the relevant countries.

I also consent to the scientific publication of the study results so long as data protection regulations are observed.

I agree to having my primary care physician notified regarding my participation in this study.

I voluntarily agree to participate in this clinical trial, and I will receive a signed copy of the "Informed Consent Form."

Participant's signature: _____ Date:_____Year _____ Month _____ Day

Participant's contact phone number: _____

※If the participant is unable to sign informed consent due to incapacity or other reasons, it shall be signed by a legal guardian or authorized person.

Guardian or authorized person's signature: _____ Date:_____Year ____ Month ___ Day

Relationship with the participant: _____

Reason why the participant cannot sign the informed consent form: _____

_____

Guardian's contact phone number: _____

※If the participant or their guardian is not able to read, a witness should be present during the informational process (if involved):

Witness signature: _____ Date:_____Year _____ Month _____ Day

16. Investigator's Statement

I have accurately informed the participant of the contents of the informed consent form and answered their questions. The participant voluntarily participates in this clinical trial.

Investigator's Signature: _____ Date:_____Year _____ Month _____ Day