Research Square

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Comparison of BARD®LIFESTREAM™ Covered Balloon-Expandable Stent Versus GORE® VIABAHN™ Covered Self-Expandable Stent in Treatment of Aortoiliac Obstructive Disease: Study Protocol for a Prospective Randomized Controlled Trial(NEONATAL Trial)

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Research Article

Keywords: Randomized controlled trial, Covered balloon-expandable stent, Covered self-expanding stent, Aortoiliac obstructive disease

Posted Date: December 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1016806/v1

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Abstract

Background

Covered stent has become one of the mainstream therapies for aortoiliac obstructive disease (AIOD), with higher patency rate compared to bare metal stent. Covered balloon-expandable (CBE) stent can be placed more accurately with higher radial support force, while covered self-expanding (CSE) stent has greater elasticity and higher trackability. However, there is no level I evidence regarding the comparison safety and efficacy between the CSE stent and CBE stent in AIOD up to date. Therefore, this study aims to compare the efficacy and safety of CBE stent (BARD®LIFESTR`EAM™) and CSE stent (GORE® VIABAHN™) in AIOD.

Methods

This trial is a prospective, single center, paralleled, non-inferiority, randomized controlled trial. A total of 106 patients will be enrolled and these patients will be randomized to either the CBE stent group or CSE stent group. The primary end point of the study is occurrence of Target Lesion Revascularization (TLR) at 12 months after the intervention.

Discussion

To our knowledge, the NEONATAL trial is the first RCT to compare CBE and CSE stent in AIOD patients. The results of clinical trials may contribute to establishing a strategic guideline for choosing the optimal type of covered stent in treatment of AIOD patients.

Trial registration:

ChiCTR2100046734; Registered on 27 May, 2021 in Chinese Clinical Trials Registry.

Introduction

Aortoiliac obstructive disease (AIOD) is a common chronic atherosclerotic arterial occlusive disease involving infrarenal aorta or iliac arteries, which accounts for approximately one-third of all peripheral artery disease cases with high economic burden in treatment [1]. Trans-Atlantic Inter-Society Consensus (TASC) recommended the endovascular approach as the preferred treatment for TASCII A and B aortoiliac lesions instead of open surgery [2]. A related systematic review showed that endovascular treatment was considered as valid as open surgical revascularization due to shorter hospitalization and a similar long term patency rate in TASCII C and D lesions [3; 4]. Furthermore, the recent guideline from European Society of Vascular Surgery suggested that endovascular-first strategy may be considered for aorto-iliac occlusive lesions if done by an experienced team [5]. Regarding the device selection in aortoiliac artery

interventions, covered stents have higher class of recommendation in moderate to severe calcified and diffuse lesions compared to bare metal stents with superior patency rate [6; 7; 8].

Covered stents are classified as self-expandable or balloon-expandable, according to the mechanics of stent deployment. Technically, self-expandable stents have greater elasticity, allowing them to maintain their shape after post-dilation and continue to expand as the vessel remodels until they reach the appropriate size. Besides, self-expandable stents are more flexible and trackable, thus they are easier to pass through tortuous vessels. By comparison, balloon-expandable stents have much greater radial support strength, which is especially vital in diffuse, heavily calcified lesions. In addition, balloon-expandable stents can be deployed more precisely with minimal geographic displacement, hence they are adopted widely in lesions involving aortic bifurcations.

Current evidence has showed that the 1-year restenosis rate and target lesion revascularization rate of self-expandable bare stents are higher than those of balloon- expandable bare stents in AIOD patients [9]. However, the efficacy and safety of covered balloon-expandable (CBE) stents versus covered self-expanding (CSE) stents in treatment of Aortoiliac obstructive disease remains unknown.

Current evidence regarding CBE and CSE stent in AIOD mainly focus on the comparison with bare metal stents (BMS). Several studies suggested that patients who received CBE stents had an enduring patency advantage, a lower rate of revascularization, and similar limb amputations rate compared with those who received BMS [6; 8]. Additionally, another study shows that CBE stents were found to be superior to bare metal balloon-expandable stents for the treatment of common iliac artery (CIA) disease at 3 years regarding primary patency, assisted patency, and secondary patency [10]. However, another study demonstrated that the use of CSE stents has similar early and midterm outcomes compared with BMS in severe iliac lesions, while CSE seemed to have higher midterm patency than BMS only in TASC D subjects[11]. As there is no direct comparison between CSE and CBE stent in AIOD patients, no certain conclusion can be drawn regarding which type of stent is superior.

The Gore Viabahn endoprosthesis (W. L. Gore and Associates, Flagstaff, Ariz) and LifeStream covered iliac stent (Bard Peripheral Vascular, Inc, Tempe, Ariz) represents one of the most widely used CSE and CBE stent, respectively. This prospective, single center, paralleled, non-inferiority, randomized controlled trial aims to compare the safety and efficacy between CSE stent and CBE stent in AIOD patients, with special focus on midterm and long-term freedom from target lesion revascularization (TLR).

Methods/design

Study setting

Our trial is planned to be conducted in West China Hospital, Chengdu, China. This study was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University (approval number: 2021-212) on 11 March 2021. The trial was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2100046734) on 27 May, 2021. NEONATAL trial is a prospective, single

center, paralleled, non-inferiority, single-blind trial, randomized controlled trial (allocation ratio 1:1). The present protocol was written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement for study protocols of clinical trials [12]. The SPIRIT flow Diagram is shown as Figure 1, and the SPIRIT Checklist is added in Additional file 1. Table 1 shows the schedule of enrollment, interventions, and assessments.

Eligibility criteria

Patients at least 18 years old who are diagnosed with AIOD (Rutherford classification from 2 to 6) will be screened for study recruitment. The inclusion and exclusion criteria are showing in Table 2.

Assignment of interventions

In our trial, the included patients were randomly allocated at 1:1 ratio to CBE stenting group or CSE stenting group. The allocation sequence was computer generated by a biostatistician within sex and 5-year age groups in blocks of ten, and stratification was performed by numbers of treatable legs. As for patients who required intervention in bilateral iliac arteries, the randomization was performed according to the treated arteries. The study nurse in the operating room will prepare the sealed, opaque, consecutively numbered envelopes, and informed the surgeon of the allocation results before intervention. Both study nurse and biostatistician were not involved in the perioperative management of patients. The outcome assessors and data analysts will be blinded to the interventions.

Details of intervention

Prior to the endovascular intervention, informed consent (see Additional file 2) will be obtained from all participants by investigators. The included patients will receive the same perioperative management, including antiplatelet drugs, statin usage, and blood controls. Both common femoral arteries and sometimes left brachial artery will be used for access. Whether to adopt percutaneous or cutdown access route will be determined by the surgeons. After obtaining the arterial access, 0.5mg/kg of unfractionated heparin will be administered. Fluro-opaque ruler will be used to record location and extent of the lesion. Both intraluminal and subintimal recanalization of iliac lesions will be allowed. After the successful passage of the guidewire, the target lesion will be predilated with downsized balloon in CBE group, and with equal-sized balloon in CSE group. During actual intervention, the allocated choice of covered stents may be modified according to intraoperative findings, for instance, the length of lesions did not match the stents. Multiple stents are required when needed and multiple stents edges should overlap by at least 10mm. Furthermore, additional bare metal stents can be added in both groups, according the discretion of surgeons. Post dilation balloon will be performed within the stented segment, with less than 10 % oversizing. A final angiography will be performed after the intervention in both groups, with the use of the same angles and magnifications used at the baseline angiograms.

Postoperative management include a dual antiplatelet regimen for three months, involving 100 mg of aspirin once a day plus 75 mg of clopidogrel once a day. Clopidogrel is not required if a participant is taking warfarin, other direct thrombin inhibitors, factor Xa inhibitors) or low molecular weight heparin will

be used according to physician's recommendation. anticoagulants therapy will be discontinued when other surgical procedure is required and then the participant is to resume anticoagulants therapy as soon as possible after the surgery. Drug side effects will be checked and monitored at outpatient visit or telephone follow up. According to comprehensive surgeon's recommendation, drug therapy will be discontinued. Clinical follow-up will be planned at 1, 6, 12, 24 and 36 months to evaluate clinical outcomes.

CBE and CSE Stent

The CBE stent used in our trial is BARD® LIFESTREAM™ Covered Stent, a permanently stent used to maintain patency of common or external iliac artery. The stent is a balloon-expandable stent with expanded polytetrafluoroethylene (ePTFE) encapsulated between two layers (inner and outer). The implant is pre-mounted on an over-the-wire balloon catheter that acts as the delivery system. The configurations of BARD® LIFESTREAM™ Covered Stent offered 16, 26, 37, 38 and 58 mm in length and 5 to 12 mm in diameter. The stents can be overlapped if the target lesion exceeds the longest available length of stent.

GORE® VIABAHN™ self-expandable covered stent is the only CSE stent adopted in our trial, it consists of two main components: intravascular covered stent and catheter-based delivery system. The stent consists of self-expanding nickel-titanium alloy stent combined with ePTFE intracavity coated, which is offered in lengths of 25, 50 and 100 mm and in diameters of 5 to 11,12 mm in the configurations.

Follow up and outcomes of interest

All included patients will be followed up in outpatient clinics at 1 month, 6months, 12-months, 24-months, and 36-months after initial intervention. Patients who fail to come back will be followed up on telephone. Trained researcher will collect the outcomes of interest, blinded to the intervention groups. All participants have the right to withdraw from the study at any time for any reason. The principal investigators also have the right to withdraw patients from the study if subjects break the protocol.

Primary outcome

The primary end point of this study is target lesion revascularization (TLR) (TLR is defined as the first revascularization procedure (e.g. PTA, atherectomy, etc.) of the target lesion(s)) assessed at 12months after the intervention.

Secondary outcomes

The following secondary end points of this study are collected at 1-, 6-, 12-, 24- and 36 months post-index procedure:

(1) stent and/or surgical related mortality; (2) all-cause mortality; (3) amputation-free survival; (4) acute limb ischemia rate;(5) major adverse cardiovascular and cerebrovascular events (MACCE); (6) target vessel revascularization (TVR), (TVR is defined as the first revascularization procedure (e.g. PTA, stenting, surgical bypass, etc.) in the target vessel(s)); (7) primary patency (the loss of primary patency is defined

as target lesion(s) is determined to be > 50% stenosis or TLR/TLR needed in follow up); (8) primary assisted patency (the loss of primary assisted patency is defined as target lesion(s) is determined to be > 50% stenosis after TLR); (9) secondary patency (the loss of secondary patency is defined as target lesion(s) is determined to be > 50% stenosis after endovascular procedure or surgical bypass TVR).

Data collection and management

Importantly, the investigators will be urged to follow up on patients by telephone contacts. Data will be collected as detailed as possible. Collected data lists will be stored in Monitoring committee and will be made available to the third-party regulatory body upon request.

Sample size calculation

We calculated the sample size for this study based on the results of previous studies[4; 13]. As is reported previously in AIOD patients, the 9-month primary patency of CBE stent (BARD®LIFESTREAM™ Stent) was 89.1%, while the 9-month primary patency of the CSE stent (GORE® VIABAHN™ stent) was estimated to be 82.2% based on VIASTAR Trial [14; 15]. In the present study, we hypothesized that the primary patency of CBE stent is not inferior to that of CSE stent, the predetermined noninferiority margin on risk difference scale (δ) is set as 10 % between treatment groups. There was clinical consensus that this non-inferiority margin would be acceptable if safety is maintained and patients are treated more easily, regardless of stent classification [16]. The power analysis is based on a Choi et al. Trials (2016) 17: 302 Page 5 of 10 non-inferiority principle. The type I error rate is 0.05, the power of the test is set as 80%, and the randomization ratio is set as 1:1. After accounting for a 15 % dropout rate. it was calculated that 53 lesions per group are needed for a total of 106 lesions.

In order to achieve adequate participant enrolment, we recruit patients by putting up posters or advertising on the Internet, furthermore, we actively recruit patients from outpatient department and emergency department.

Data collection and management

Two investigators use a pre-identified and unified case report form (CRF) to record the data of included patients independently. Both received training for data collection. Demographics, comorbidities, and prescriptions of cardiovascular drugs were recorded from patient chart. Imaging anatomic parameters were measured from picture archiving and communication system (PACS). Laboratory results were collected from laboratory information system (LIS).

As for data management, two investigators retrieved data from CRF and recorded in two identical electronic form, and cross check is performed to ascertain the accuracy of data. We also set range checks for data values.

Statistical analysis

R studio Version 1.2.1335 (http://www.R-project.org) and Empower (www.empowerstats.com, X&Y solutions, Inc., Boston, MA) were utilized for statistical analysis. Categorical data are expressed as

numbers and rate, while continuous data are expressed as means ± standard deviation (SD) if they are normally distributed, or median (interquartile range [IQR]) vice versa. Student's *t* test or Mann-Whitney *U* test is used for univariate analysis of continuous data, and the $\chi 2$ test or Fischer's exact test is used for categorical data. For primary analyses, multivariate logistic regression is adopted to calculate adjusted odds ratios (OR) and 95% confidence interval (95% CI) for short-term outcomes. Cox proportional hazard regression analysis is used to generate adjusted hazard ratio (HR) and corresponding 95% CI for long-term outcomes. The primary and secondary end points will be analyzed in the modified intention-to-treat analysis, which includes all subjects undergo randomization and subsequent interventions. Sensitivity analyses of primary and secondary endpoints are performed in the per-protocol population, based on the treatment actually received. The noninferiority margin was set at 10 percentage points for the absolute difference between groups. If the standard of noninferiority was reached, the primary and secondary outcomes were subsequently tested for superiority ($P<0.05$). Noninferiority will be considered proven if conclusions drawn from the intention-to-treat and per protocol analyses are consistent.

Further pre-specified subgroup analyses will be carried out in the following subgroups: TASC II C-D lesions versus A-B lesions, occlusion versus stenosis. Adjustment analyses for primary and secondary endpoints were performed based on the Hochberg method [17]. Multiple imputation was used to handle missing data.

Monitoring

Monitoring committee consists of biostatisticians, surgeons, investigators, and nurses who neither be involved in the conduct of this study, nor financial and professional interests. Annual monitoring will be conducted by Monitoring committee. Monitoring committee will provide feedback to investigators and vascular surgeon as soon as there are any problems. Ethics committee and monitoring committee will have access to check the collected data and question the rationality of the study protocol before, during, and after the trial. Classical interim analyses are performed by an independent statistician who will be a person other than the regular study statistician. The trial will be terminated when one treatment group is significantly superior or inferior to the other treatment group. The final decisions regarding study modifications or stop rest with both ethics committee and monitoring committee. All serious adverse events (SAEs) must be reported as soon as possible. The SAE form contains the following information: identification of the subject, attending surgeon, description of the SAE (event, beginning and duration, severity, outcome, treatment, or interventions taken). To maintain the quality and safety of trial, unblinding occur only in exceptional circumstances when knowledge of the actual treatment is essential for further management of the subject.

Amendments

All substantial amendments will be notified to the Ethics Committee on Biomedical Research, monitoring committee and the upstream authorities. Non-substantial amendments will not be notified to the monitoring committee and the upstream authorities, but will be recorded and filed by the sponsor. Update informed Consent forms will be sent to new patients after amendments.

Discussion

The past three decades has witnessed open surgery shift to endovascular strategies as the preferred treatment for mild-to-moderate-to-severe AIOD. Endovascular therapy is increasingly preferred as the first-line treatment in most AIOD patients. Different stents have different designs (covered stents, bare metal stents, self-expanding stents and balloon-expandable stents) but which type is the best for AIOD patients have yet to be fully elucidated [18].

Previous studies showed that covered stents can create a smooth hemodynamically favorable lumen and resist hyperplastic ingrowth through BMS interstices, in addition, covered stents also can protect against iliac artery rupture when post-dilation [8; 10; 19]. Self-expandable stents have high elasticity and small radial force, which helped to prevent circumferential stress and a subsequently enhanced neointimal proliferation. It may is the reason why self-expandable bare metal stents led to a decreased incidence of restenosis at 12 months than the treatment with balloon-expandable bare metal stents[9]. However, the best choice between CBE stent and CSE stent is left to the interventionalist's preference and lack of RCT data now, leading to there is no consensus or relevant guidelines on which stents in AIOD.

The Viabahn stent and LifeStream stent represents one of the most widely used CSE and CBE stents, respectively. Previous study shows that Viabahn covered stent can be considered an acceptable patency with low complications during the long-term period in low-risk young AIOD patients [4], especially for complex aortoiliac occlusion lesions [20]. Another one study indicated LifeStream stent provided satisfactory 9-month clinical outcomes, including a low rate of TLR for the treatment of stenotic and occlusive lesions of the iliac arteries [15]. However, there is no long-term period patency and TLR of LifeStream stent. Furthermore, there is no cohort or RCT study to compare the efficacy or effect between Viabahn stent and LifeStream stent.

In conclusion, this trial was designed to compare the efficacy and safety between CBE stent (BARD®LIFESTREAM™) versus SBE stent (GORE® VIABAHN™) in AIOD patients, hoping to provide level 1 evidence for stent selection in aortoiliac occlusive lesions.

Trial status

Ethics approval has been granted before submission. The trial is currently in the recruitment phase. Study enrollment began on 1 June 2020. It is estimated that recruitment will be completed by 1 June 2022, with a study completion date of 1 June 2024.Any protocol amendments will be updated in Chinese Clinical Trials Registry.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University (approval number: 2021-212) on 3 March 2021. Informed consent will be obtained from each participant or from each of the participant's legally responsible relative (Additional file 3).

Consent for publication

Not applicable

Confidentiality and Access to data

All members have signed a confidentiality agreement with the investigator. In addition, members will treat the reports, meeting discussions, and minutes as confidential. Participants' identity information is encrypted to prevent leakage during the whole study. The investigator is required to maintain adequate records to enable the conduct of the study to be fully documented. Documents used for the conduct of the study (e.g., patient files and originals of test results) must be kept by the investigator for a period of 15 years. Ethics committee and monitoring committee will have access to the final trial dataset. Independent institution will be contacted for monitoring and quality assurance during the conduct of the study.

Consent for publication

Upon trial completion, the main manuscript with results, whether positive, negative, or neutral, will be submitted to a major clinical journal for peer review and publication.

Competing interests

The authors declare that they have no competing interests.

Funding

This trial was conducted with no external funding, internal funding, grants

nor individual funding.

Authors' contributions

YD: Conception and Design, Critical Revision, Approval of the Manuscript, Agreement to be Accountable, Statistical Analysis, Obtaining Funding;

WTH: Conception and Design, Critical Revision, Approval of the Manuscript, Agreement to be Accountable, Statistical Analysis, Obtaining Funding;

QYH: Conception and Design, Writing the Manuscript, Approval of the Manuscript, Agreement to be Accountable, Statistical Analysis;

WJR: Conception and Design, Writing the Manuscript, Approval of the Manuscript, Agreement to be Accountable, Statistical Analysis;

ZJC: Conception and Design, Writing the Manuscript, Approval of the Manuscript, Agreement to be Accountable;

HB: Conception and Design, Writing the Manuscript, Approval of the Manuscript, Agreement to be Accountable;

XF: Conception and Design, Writing the Manuscript, Approval of the Manuscript, Agreement to be Accountable.

DXJ: Conception and Design, Writing the Manuscript, Approval of the Manuscript, Agreement to be Accountable.

CXY: Conception and Design, Writing the Manuscript, Approval of the Manuscript, Agreement to be Accountable.

GQ: Conception and Design, Writing the Manuscript, Approval of the Manuscript, Agreement to be Accountable.

Acknowledgements

Not applicable

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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Table 2
Inclusion criteria and Exclusion criteria

Inclusion criteria	Exclusion criteria
The participants meeting the following criteria will be included: (1) The subject is a male or non-pregnant (or no plan to become pregnant during study) female ≥ 18 years old with an expected lifespan sufficient to allow for completion of all study procedures. (2) Symptomatic peripheral artery disease with moderate to severe claudication (Rutherford score of 2 to 3); Chronic CLI with resting ischemic pain (Rutherford score of 4); Chronic CLI with ischemic ulcers (Rutherford score of 5 to 6). (3) Subjects diagnosed with aortoiliac obstructive disease (Trans-Atlantic Inter-Society Consensus, TASC II, TASC II A-D). (4) The target lesion(s) can be successfully crossed with a guide wire and pre-dilated with an appropriately sized Percutaneous endovascular angioplasty (PTA) balloon. (5) The subject provides informed consent using an Informed Consent Form (ICF) that is reviewed and approved by the Ethics Committee (EC).	The participants meeting the following criteria will be excluded: (1) The subject is asymptomatic, has mild claudication described as Rutherford Category 0 (asymptomatic) or 1 (mild claudication). (2) The subject has a vascular graft previously implanted in the native iliac vessel. (3) The subject has an abdominal aortic aneurysm (AAA) contiguous to the iliac artery target lesion(s) or subject has a pre-existing target iliac artery aneurysm or perforation or dissection of the target iliac artery. (4) The subject has a serum creatinine ≥ 2.5 mg/dl or is currently on dialysis. (5) The subject has a known uncorrectable bleeding diathesis or active coagulopathy (platelet count< 80,000/μL). (6) The subject has intolerance to the antiplatelet, anticoagulant, or thrombolytic medications. (7) The subject has a known allergy or sensitivity to stainless steel (i.e., Nickel), ePTFE or contrast media. (8) The subject suffered a stroke, or transient ischemic attack (TIA) within 3 months prior to the procedure.

Figures

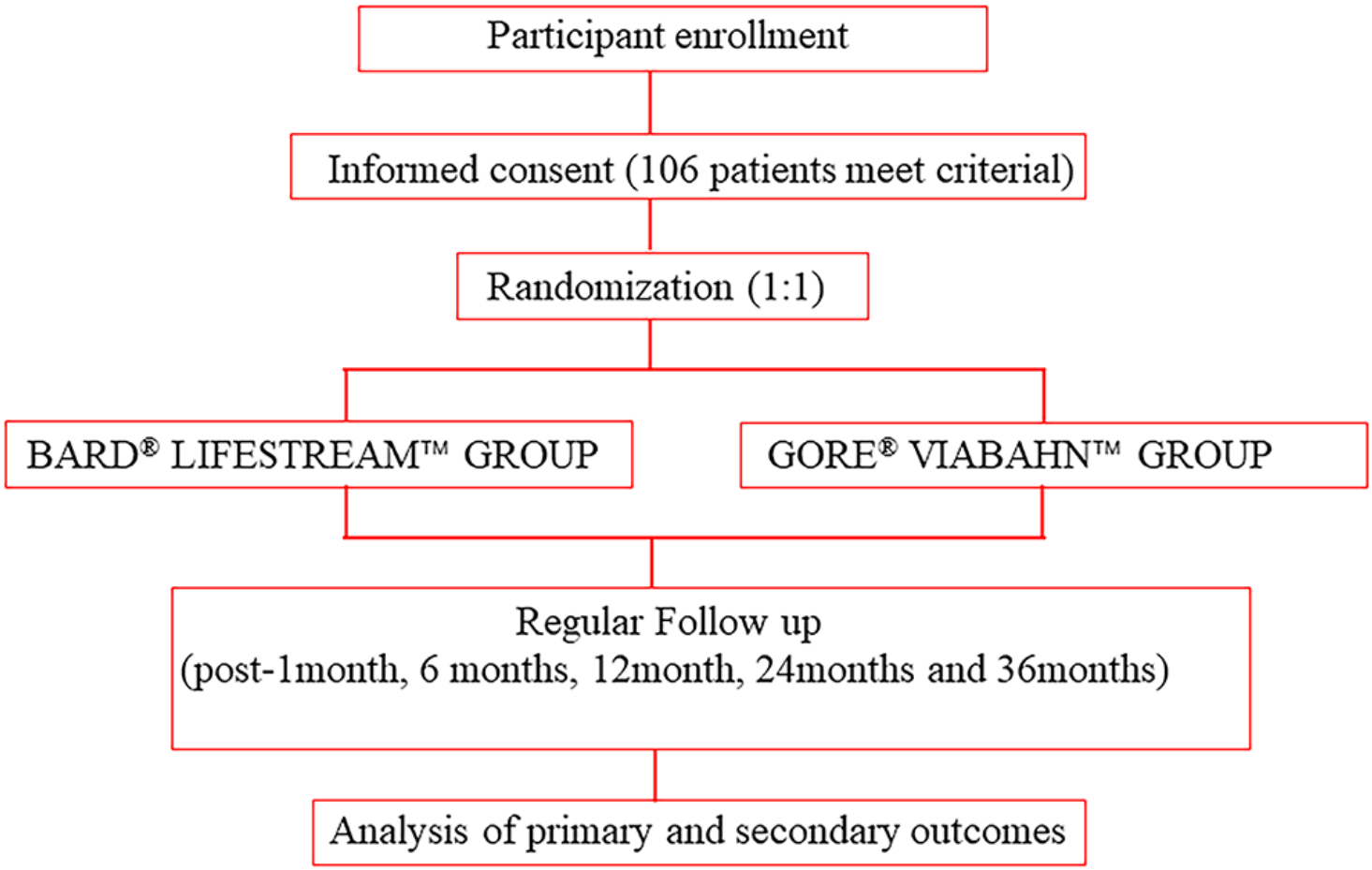

Figure 1

The procedure of screening, randomization, and follow-up of patients in the trial.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.jpg
- SPIRITchecklistAdditionalfile1.docx