A novel ultrasound controlled paclitaxel releasing balloon catheter versus plain balloon catheter in the treatment of small coronary vessel stenosis: study protocol of a randomized controlled clinical trial (Vasoguard I Trial)

Yueyi Pan

Department of Cardiology, Zhongshan Hospital,Fudan University;Shanghai Institute of Cardiovascular diseases.

Feng Zhang

Department of Cardiology, Zhongshan Hospital, Fudan University;Shanghai Institute of Cardiovascular diseases.

Jingpu Wang

Department of Cardiology, Zhongshan Hospital, Fudan University;Shanghai Institute of Cardiovascular Diseases.

Ji'e Yang

Department of Cardiology, Zhongshan Hospital, Fudan University;Shanghai Institute of Cardiovascular Diseases.

Li Shen

Department of Cardiology, Zhongshan Hospital, Fudan University;Shanghai Institute of Cardiovascular Diseases.

Juying Qian

Department of Cardiology, Zhongshan Hospital, Fudan University;Shanghai Institute of Cardiovascular diseases.

Haijun Zhang

National United Engineering Laboratory for Biomedical Material Modification, Branden Biomedical Park.

Junbo Ge (✉ jbge@zs-hospital.sh.cn)

Zhongshan Hospital Fudan University   https://orcid.org/0000-0002-9360-7332

Study protocol

Abstract

Background The optimal intervention strategy remains controversial in small vessel disease which is a very common kind of coronary artery lesions. For now, balloon-only percutaneous coronary intervention is the major percutaneous revascularization method in these patients, but the restenosis rate is still at a high level. Drug coated balloon is designed to deliver paclitaxel to target vessel to inhibit the proliferation of vascular endothelial cells, it aims at restraining the stenosis process after intervention so as to reduce the rate of restenosis. Ultrasound controlled paclitaxel releasing balloon catheter (Vasoguard TM) is a newly designed drug coated balloon, expected to promote the drug release process via external ultrasound intervention so as to improve drug bioavailability. The current trial was designed to assess the efficacy and safety of Vasoguard in the treatment of small vessel coronary disease.

Methods A prospective, multicenter, randomized, controlled clinical trial has been designed to compare the safety and efficacy of Vasoguard with plain balloon angioplasty in the treatment of small vessel coronary disease. 230 patients will be included in this trial, the primary endpoint is late lumen loss of target lesion at 9 months post operation measured by quantitative coronary angiography. Secondary endpoints include angiographic findings such as device success rate, operation success rate, in-segment restenosis, clinical outcomes such as target lesion revascularization, target vessel revascularization, device oriented composite endpoint and thrombotic events.

Discussion This trial will evaluate the efficacy and safety of Vasoguard in the treatment of small vessel coronary disease by comparing to plain balloon angioplasty. It will clarify the practicability of the newly designed balloon and may lend more credence to the role of drug coated balloon in the treatment of small vessel disease.

Background

Percutaneous coronary intervention (PCI) is one of the most effective treatments of coronary heart disease, which has significantly reduced the risk of acute myocardial infarction (AMI) and unstable angina[1, 2]. Clinical studies have shown that for large coronary vessel (3 mm in diameter or higher) lesions, rate of restenosis (RS) and the incidence of major adverse cardiovascular events (MACE) have decreased significantly since the emergence of PCI[3]. The intervention of small coronary vessels accounts for 20%-30% of all PCI performed, but the incidence of restenosis after operation is still at a high level[4–6]. Balloon only PCI is more commonly used in small vessel disease (SVD) relative to large vessels, and for the lesions show optimal efficacy after balloon angioplasty, balloon only PCI has similar long-term results to stents implantation [7, 8]. Cutting balloon is a kind of effective treatment for small vessel disease, it could vertically cut the plaque, lessen the elastic and fibrotic continuity of the internal fibrous layer, make the tissue more amenable to being pushed outward the balloon. It can avoid extruding and tearing to plaques during dilatation, so its curative effect is superior to the plain balloon dilatation. But cutting balloon also has some defects, it is easy to induce coronary dissection and perforation, meanwhile, the plaque shed off could lead to stent thrombosis, so cutting balloon is mainly used for non-

calcified centripetal stenosis lesions, in-stent restenosis and bifurcation lesions[9–12]. Drug coated balloon (DCB) is a plain balloon coating with anti-proliferative drugs, it can extrude the drug into the vessel during balloon expansion process, to ensure adequate drug dissolved and permeate to the vessel walls, so as to realize the early anti-proliferation effect to the vascular. That is, DCB could release the coated drug immediately in a very short time without the plant of polymers, so it induces less chronic inflammatory reactions compared with drug eluting stents (DES)[13–16]. Bello study reported long-term follow-up outcomes after treatment with DCB or DES for de novo small vessel disease, in this study, DCB showed lower late lumen lose in the angiographic follow up as well as lower incidence of MACE[17]. A recent study suggest that paclitaxel-coated balloon showed low target vessel revascularization (TVR) and MACE in the treatment of small coronary vessels 2.0-2.75 mm in diameter[18].

Despite its impressive effectiveness, DCB has certain technical restrictions in the process of clinical treatment, a large percent of the drug is washed out during the delivery of the balloon in the artery, and the process that the drug diffusing to the target vessel is uncontrollable in the short period of time (30 to 60 seconds) when the balloon is dilated. For these reasons, the bioavailability of the coated drug on the balloon is low, it's reported that only about 5% is absorbed by the vessel wall[19]. In considering of this, we designed a novel drug coated balloon which is ultrasound-controlled paclitaxel release balloon.

The novel balloon use paclitaxel-loaded poly(lactide-co-glycolide) (PLGA) microspheres as new coating technique. PLGA microspheres have the ultrasound characteristic that can release the drug contained only under ultrasound which could broke the microspheres, so the ultrasound system will be turned off during the delivery of the balloon in the vessel so as to reduce the wash-out of the drug and will be turned on when the balloon is dilated in the target vessel to promote the release of the paclitaxel contained. In our previous study, the novel balloon catheter improved the drug content in the target vessel and reduced the drug concentration in the plasma, thus increased the bioavailability of the balloon. It effectively inhibited restenosis after stent implantation in the porcine model[20].

Study Objectives

The primary objective of the study is to evaluate the safety and efficacy of ultrasound controlled paclitaxel releasing balloon catheter in treatment of small vessel coronary disease.

Methods

Study design

This trial will be a multicenter, prospective and randomized controlled clinical study that comparing the safety and efficacy of the novel DCB Vasoguard with plain balloon catheter Maverick2 in the treatment of small vessel coronary disease.

A brief flowchart of the entire study is summarized in Fig. 1. The schedule of events for this trial is described in Fig. 2.

Patient population

Male or non-pregnant female aged 18 to 80 years, who has stable angina pectoris, unstable angina pectoris, old myocardial infarction, or asymptomatic myocardial ischemia will be included in this study, patients are eligible for inclusion if target vessel is 1.5–2.5 mm in diameter, 40 mm or less in length with a stenosis of ≥ 70% by coronary angiogram or ≥ 50% with evidence of ischemia. Patients will be excluded if they present with the followings: female patients during pregnancy and lactation, severe congestive heart failure or NYHA IV heart failure, patients suffered acute myocardial infarction within a week, patients who suffered stroke within six months, or patients with the following angiographic conditions: thrombosis evidence in target vessel, distorted or severe calcified lesions. All the inclusion criteria and exclusion criteria are respectively summarized in Table 1.

Randomization

Patient meets all of the inclusion criteria and none of the exclusion criteria will sign the informed consent and be randomized 1: 1 to either Vasoguard group or Maverick group with a sealed envelope method. The random allocation sequence will be generated by using a computer-based system before recruitment started and then a copy of the randomization list will be securely stored in an sealed envelope which will be opened after patient enrollment in the study.

Endpoints

The primary endpoint of the study is late lumen loss (LLL) in segment measured by quantitative coronary angiography (QCA) at 9 months post procedure. Secondary endpoints can be divided into angiographic findings such as success rate of device and operation, in-segment restenosis at 9 months and clinical outcomes such as target lesion revascularization (TLR) and TVR, device oriented composite endpoint (DOCE, include cardiac death, myocardial infarction due to TLR), thrombotic events.

Conduct of the study

The following procedures will be operated when the patient is enrolled. The detailed treatment strategy will be determined by the interventional operator. Figure 2 shows the schedule of events of the present study. Operators should refer to the updated instructions for use, evaluate the indication and contraindication, also the precaution and management of complications.

Coronary angiography and percutaneous coronary intervention

In the angiography procedure we should concentrate on achieving optimal angiographic images and to minimize the risk of complications induced by procedure. PCI should be performed according to current international guidelines by either the radial or the femoral approach. A loading dose of 300 mg aspirin and 300 mg clopidogrel will be given to each patient enrolled before the procedure while heparin will be injected to retain the activated clotting time > 250 seconds during the procedure. Application of

intravascular ultrasound and glycoprotein IIb/IIIa inhibitors will be left to the operators' discretion. All of the target lesions will be pre-dilated with regular balloon after obtaining coronary angiograms. The patient will be randomly allocated to either the Vasoguard group or the Maverick group if optimal predilation is operated.

In the Vasoguard group, the instruction of device should be preoperatively refered by the operator and appropriate specifications of the balloon should be selected according to the target vessel to keep the balloon at least 2 to 3 mm longer than the target lesion so as to cover the entire plaque. The Vasoguard balloon will be dilated and last for 60 seconds after being delivered to the target vessel. At the same time, the external ultrasound will be given to promote the drug release process via an ultrasound probe which aims at the projection site of the balloon on the surface of the body. The success of the procedure is defined to be a residual stenosis ≦ 50% and TIMI flow grade 3 without any flow-limiting coronary dissection or stent thrombosis.

Quantitative coronary angiography

QCA will be conducted according to the coronary angiograms at baseline, immediately post-procedure and at the 9-month follow-up. Minimal lumen diameter (MLD) and reference vessel diameter will be measured via QCA, target lesion LLL will be defined as the difference between the MLD post-procedure and at 9 months.

Pharmacological therapy post-procedure

Treatment of all the patients included in this study will be consistent with the new clinical practice guidelines. Dual antiplatelet therapy (DAPT) with 100 mg of aspirin and 75 mg of clopidogrel daily should be performed till 3 months post-procedure, aspirin then should be taken over a long period. If the patient is taking two or more kinds of anticoagulants or antiplatelet agents before operation according to the condition of diseases and the duration will be longer than 3 months post-procedure, the anticoagulants or antiplatelet agents could be taken according to the diseases.

Follow-up

Clinical follow-up will be conducted at 1, 6, 9 and 12-months post-procedure by outpatient or telephone. During the follow-up, information include angina class and ischemic events, cerebrovascular accidents and bleeding events should be collected, such as death, MI, ischemia-driven TVR, rehospitalization and other adverse events, and the adjustment of drugs should also be recorded. Investigators should submit original date and documents of the clinical events. Endeavor should be made to acquire the original date if the patient is readmitted to another hospital.

Angiographic follow-up will be conducted at 9 months post-procedure. Coronary angiography conducted earlier than that will be regarded as an endpoint angiogram if it shows restenosis (diameter stenosis > 50%) or thrombosis. Similarly, unscheduled angiogram will be considered as the 9-month follow-up angiogram if it is conducted > 6 months post-procedure. On the contrary, if an angiogram is performed before 6 months post-procedure and present neither restenosis nor thrombosis in target lesion, then the 9-

month angiographic follow-up still should be performed. Copies of angiogram must be submitted to the angiographic core laboratory of the study, include the baseline angiogram from all randomized patients, the 9-month follow-up angiogram and all of the unscheduled angiograms within 12 months post-procedure.

Table 1
Inclusion and exclusion criteria of Vasoguard I trial.

Inclusion criteria	Exclusion criteria
8 to 80 years aged.	In pregnancy or lactation.
Stable angina pectoris, unstable angina pectoris, old myocardial infarction or asymptomatic myocardial ischemia.	NYHA class IV heart failure or left ventricular ejection fraction < 30%.
With a life expectancy of more than 2 years.	With a life expectancy of less than 2 years.
With a target vessel of 1.5–2.5 mm in diameter, 40 mm or less in length.	Acute myocardial infarction within a week or stroke in six months.
With a lesion of ≥ 70% stenosed revealed by coronary angiogram, or ≥ 50% stenosed with objective evidence of myocardial ischemia.	With bleeding tendency and have contraindications for anticoagulation and antiplatelet drugs.
Single coronary small vessel or two branches of small vessel disease.	Severe renal failure (GFR ≤ 30 ml/min).
Be able to understand the purpose of the trial, be willing to sign informed consent voluntarily and to accept the clinical telephone follow-up and angiographic follow-up.	With peptic ulcer or gastrointestinal bleeding 6 months prior to study enrolment.
With a target lesion which can be predilated successfully (defined as a residual stenosis ≤ 50% after pre-dilatation without flow limiting dissection or thrombosis).	Participating in another clinical trial and the primary endpoint follow-up has not been completed.
	Cannot comply with 3-month dual antiplatelet therapy.
	Being allergic to paclitaxel, PLGA or contrast agent.
	Triple vessel coronary artery disease.
	Evidence of thrombosis in target vessel.
	Stenosis of vein graft after coronary artery bypass grafting.

Statistical Analysis

Sample size

The primary endpoint of this clinical trial was LLL within the target lesion segment at 9 months post procedure, and the objective is to determine whether the ultrasound controlled paclitaxel releasing balloon catheter is superior than plain coronary balloon catheter for treatment of small vessel coronary disease. According to the literature and clinical judgment, the LLL of plain coronary balloon group was expected to be 0.7 ± 0.6 mm, then we postulated LLL of test group would be 0.3 mm, assumed a superiority margin of 0.15 mm as the acceptable difference for the superior test, set an alpha-level of 0.025, a statistical power of 80% and an estimated expulsion rate of 20% at 9-month angiographic follow-up. Therefor, the required sample size is 230 in all, 115 patients in the Vasoguard arm and 115 patients in the Maverick arm.

Statistical analysis

In descriptive analysis, enumeration data will be described with frequency and constituent ratio, while measurement data with mean, standard deviation, maximum, minimum, medians and percentile. In the analysis of baseline characteristics, intergroup comparison of enumeration data will be analysed by chi-square test or Fisher's exact test. Measurement data obey normal distribution can be compared by group t-test, but Wilcoxon rank sum test will be adopted if measurement data obey non-normal distribution. For the primary efficacy endpoint, analysis of covariance will be used for the intergroup comparison. In addition to estimating LLL in segment 9 months post-procedure, the difference of LLL between the two groups and its 95% confidence interval will also be assessed. For the analysis of other efficacy endpoints, paired t-test can be conducted for intragroup comparison of measurement data obey normal distribution while Wilcoxon sign rank test for measurement data obey non-normal distribution. Comparison between groups is similar to the analysis of baseline characteristics. Adverse events will be described by number of cases and the incidence, and then will be compared by chi-square or Fisher's exact test.

Study monitoring and data management

The clinical research associate (CRA) will do the monitoring of the process conducted by each clinical center according to the approved monitoring plan to ensure the process in accordance with the requirements of the protocol. They will provide image records in the study as required and timely submit these records to imaging measurement laboratories and data statistics center. The CRA will be responsible for communicating with researchers and clinical centers to obtain or submit the data needed for ethical and regulatory approval in time. They will also confirm the documents of informed consent procedure, the follow-up status and the reasons for withdrawal. The case report form (CRF) will be completed by the investigator for each included case and should be reviewed by the CRA. The first copy of the CRF will be handed over to the data manager for data entry or management, and the contents of the CRF should not be modified after that.

Discussion

PTCA of small vessel disease with plain balloon angioplasty

For the lesions in coronary arteries ≧ 3 mm in diameter, stenting has been proved to be superior to plain old balloon angioplasty (POBA) with 25–30% reduction of restenosis[21, 22]. Studies have shown that in large vessels, comparing to the patients accepted POBA, those who accept stenting could obtain a larger MLD immediately after procedure, but, also a greater LLL at angiography follow up, that is because the metal struts of the stents could induce stronger response of neointimal proliferation[23]. For large vessels treated by stents, the initial acute gain post-procedure is greater than the absolute LLL. But for small vessel disease, acute gain post-procedure is much lower than that in large vessels because of smaller diameter of the vessel. In this condition, though the LLL in small vessels is similar to that in large vessels, the benefits shown in the follow-up is much lower[24]. Consistent with the analysis above, some studies have shown that, for small vessel disease, optimal POBA may not be inferior to stenting. Kastrati conducted a randomized trial included 404 patients with symptomatic coronary artery disease, compared bare metal stent (BMS) with POBA in the intervention of small vessels disease, it showed no significant differences of the restenosis rate at 6 month, also the adverse events at 7 month post-procedure between the two groups[25]. A meta-analysis included 4383 patients showed stenting group has similar MACE rate to POBA group with the percentage 18% versus 21%[26]. Thus, balloon angioplasty has been regarded as one of the major interventions in patients with small vessel coronary disease in clinical practice.

DCB and DES for PCI of small vessel disease

DES could significantly reduce the restenosis rate after PCI compared to BMS[27–29], nevertheless, the restenosis rate could still up to 30% after DES planting for small vessel coronary lesions because of the histological and anatomic features [24, 29–31].

DCB is designed to delivery anti-proliferative drugs to target lesion without introduction of a foreign body, it could provide a larger area for the contact of the drug with vessel wall compared to DES. Therefor, DCB has been proved to shorten the duration of DAPT and reduce the risk of late stent thrombosis compared to DES[15, 32]. Promising results have been shown of DCB in the intervention of SVD, in-stent restenosis (ISR), and some other special coronary lesions. The PEPCAD I study[13, 33] was the first trial to assess the performance of a DCB in a high risk patient population with small coronary vessel disease, one hundred and eighteen patients with a target vessel diameter of 2.25–2.8 mm were treated by paclitaxel coated balloons (PCB), LLL in the 6 month angiographic follow-up and MACE rate in the 12 month clinical follow-up are both promising and are not inferior to the results of DES for SVD reported by other studies[34–38]. In BELLO study[17], which is the first long-term follow-up RCT comparing PCB with paclitaxel eluting stent for SVD, PCB showed significant lower LLL in the 6 month angiographic follow-up and a tendency towards lower incidence of MACE during 2 year clinical follow-up compared to DES. Similarly, the efficacy and safety of DCB were verified in SeQuent Please World Wide Registry[39], the real world study include 2095 patients from 75 centers demonstrated that TLR and MACE were both low and promising. Additionally, DCB could reduce the incidence of late and very late stent thrombosis compared to DES by means of avoiding the implantation of polymer[40]. These results indicated that DCB is significant in the intervention of SVD and has an important role to play in the DES area.

The limitation of current DCB and innovation of Vasoguard

The function of DCB depends on the antiproliferative drug coated on the surface of the balloon. Bettina Kelsch studied the dose response relationship between the drug coated and anti-proliferation effect in porcine coronary artery, demonstrated the fact that, drug loss could be as high as 30% when the balloon was delivering to target lesion through the guiding catheter and blood while over 40% was washed away during the balloon dilation, only 20–30% of the left drug was taken up into the target vessel wall eventually[19]. As to the relation between the dose and effects, researchers find that neointimal area on cross sections decreased with the increasement of the dosage of drug within limits. The drug began to take effect at a dose of 1 μg/mm^2 and the maximum anti-proliferation effect was reached when the dose was 3 μg/mm^2, with no further increase at higher doses[19, 41]. Through these studies, it's definite that the utilization of the drug coated on the balloon is still at a low level, and it is hard to improve the effect of DCB by simply increasing the concentration of the drug coated as it's up to 3 μg/mm2. Therefore, upgrading of the drug utilization is the direction to improve the curative effect of DCB.

Vasoguard is a novel DCB which use a new drug delivery system based on ultrasound to improve the utilization of the drug. Paclitaxel is encapsulated in PLGA microspheres which have the ultrasound characteristic that can release the drug only under ultrasound, that is, the ultrasound will be turned off when the balloon is delivered in the vessel and turned on when the balloon is dilated in the target vessel so as to reduce the wash-out of the drug and promote the release of the drug. Overall, Vasoguard is designed to overcome the disadvantage of low antiproliferative drug utilization of DCB and to improve utilization without need to increase the concentration of the drug coated. In addition, Vasoguard has been shown to be safe and effective in animal and is expected to improve the result of intervention of SVD.

Trial status

The protocol version number is 2016-R-1, V1.2 dated 2 June 2017. Recruitment started in 15 september 2017 and is scheduled to end in August 2020.

Abbreviations

BMS
bare metal stent
CRA
clinical research associate
CRF
case report form
DAPT
dual antiplatelet therapy
DCB
drug coated balloon
DES
drug eluting stents

DOCE

device oriented composite endpoint

ISR

in-stent restenosis

LLL

late lumen loss

MACE

major adverse cardiovascular events

MI

myocardial infarction

MLD

minimal lumen diameter

PCI

percutaneous coronary intervention

PLGA

poly(lactide-co-glycolide)

POBA

plain old balloon angioplasty

PVB

paclitaxel coated balloons

QCA

quantitative coronary angiography

SVD

small vessel coronary disease

TLR

target lesion revascularization

TVR

target vessel revascularization

Declarations

Ethical approval and consent to participate

This study has been approved by ethics committee of Zhongshan Hospital, Fudan University. Informed consent will be obtained from all study participants. The patients can withdraw from the trial at any time.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YP and FZ are joint first authors. JG, as a corresponding author, conceived the idea and designed the study. YP and FZ developed the study protocol and drafted the manuscript. The patient consent form and CRF were prepared by YP, JW and JY. LS, JQ and HZ reviewed the protocol and manuscript and contributed ideas and information that are helpful to the overall trial design. All authors read and approved the final manuscript.

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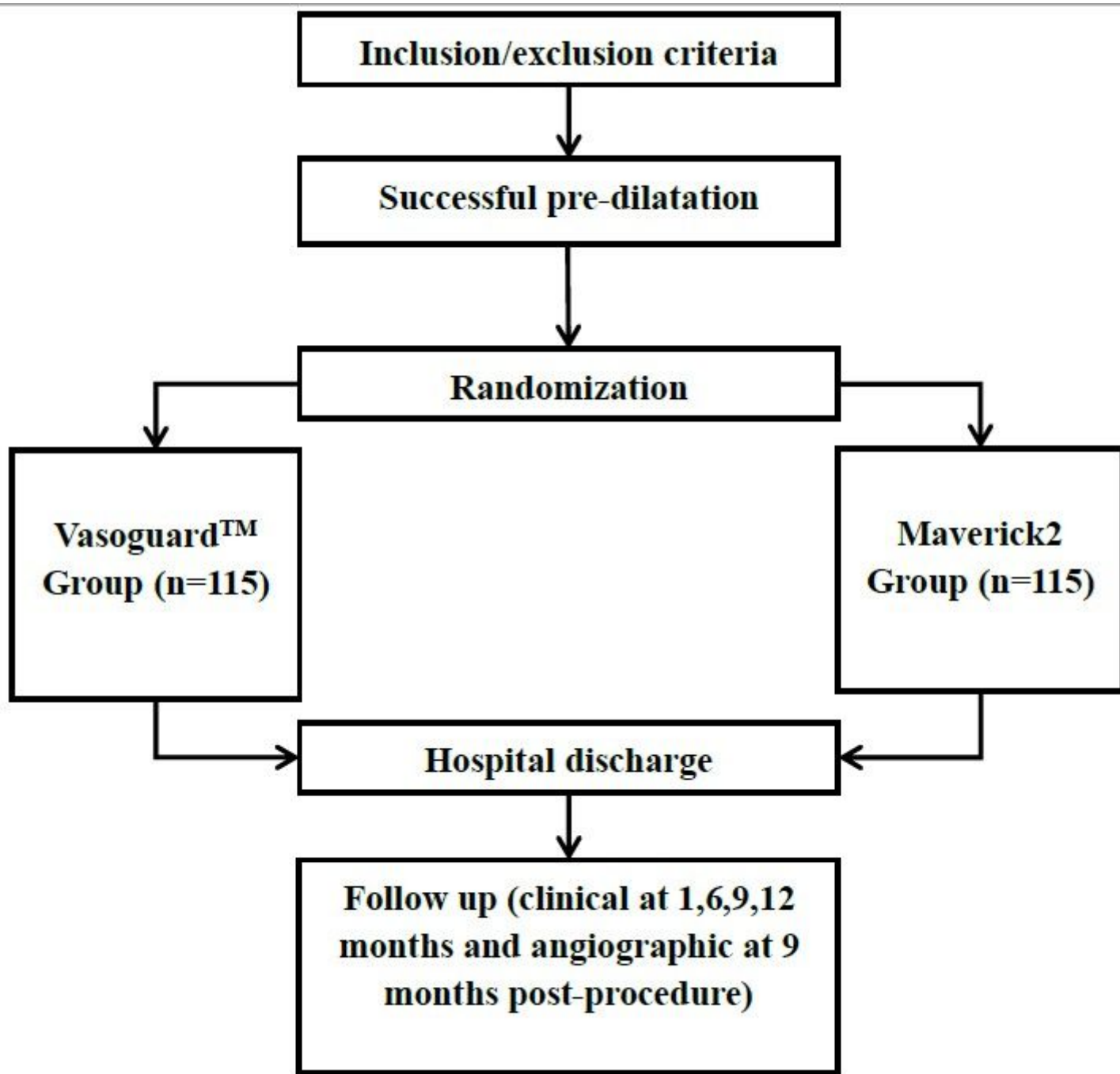
Figures

Figure 1

Flowchart of Vasoguard I Trial

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					
TIMEPOINT		0	24-48h	discharge	1m	6m	9m	12m
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Inclusion/exclusion criteria	X							
Medical/clinical history	X							
Pregnancy test[1]	X							
Vital signs[2]		X						
Blood-rt, urine-rt, stool-rt	X							
Blood biochemical test[3]	X							
CK, CK-MB[4]	X		X					
TNT/TNI[4]	X		X					
Twelve-lead ECG	X		X	X				
UCG	X							
CCS grading of angina	X			X	X	X	X	X
Anticoagulant/antiplatelet	X	X	X	X	X	X	X	X
Other medications	X	X	X	X	X	X	X	X
Withdrawal Criteria		X	X	X	X	X	X	X
Allocation		X						
INTERVENTIONS:								
Angiogram		X					X	
Pre-dilatation		X						
Vasoguard		X						
Maverick		X						
ASSESSMENTS:								
Demographic data	X							
QCA		X					X	
Events		X	X	X	X	X	X	X

Figure 2

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) diagram for this protocol. 1. Pregnancy test is only for women at childbearing age. 2. Vital signs: temperature, respiratory rate, heart rate (pulse) and blood pressure. 3. Blood biochemical test: total cholesterol, triglyceride, low density lipoprotein, high density lipoprotein, creatinine, fasting blood glucose, alanine aminotransferase,

aspartate aminotransferase. 4. CK, CK-MB, TNT or TNI should be measured 12-24 hours post procedure. If the result is abnormal, it should be reexamined within 48 hours.

Supplementary Files

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

- FundingDocumentation.PDF
- SPIRITchecklistforVasoguardI.pdf
- EthicalApprovalDocument.pdf