A Randomized Trial Comparing Drug-coated Balloon and Regular Balloon for Dialysis Access Stent Graft Restenosis

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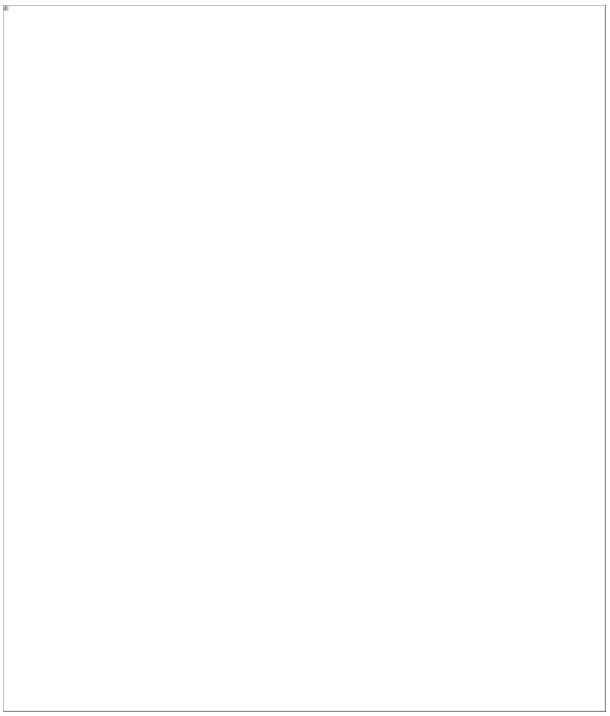
2 Abstract

Background

Prosthetic arteriovenous hemodialysis access graft (AVG) has high incidences of venous anastomotic stenosis and access failure. We can use stent graft in AVG with re- current venous anastomotic stenosis to improve long-term patency rate. However, after stent graft implementation, the effective treatment for restenosis of stent graft is still unknown. We thus design this study to investigate the efficacy and safety of drug- coated balloon versus regular balloon angioplasty in stent graft restenosis.



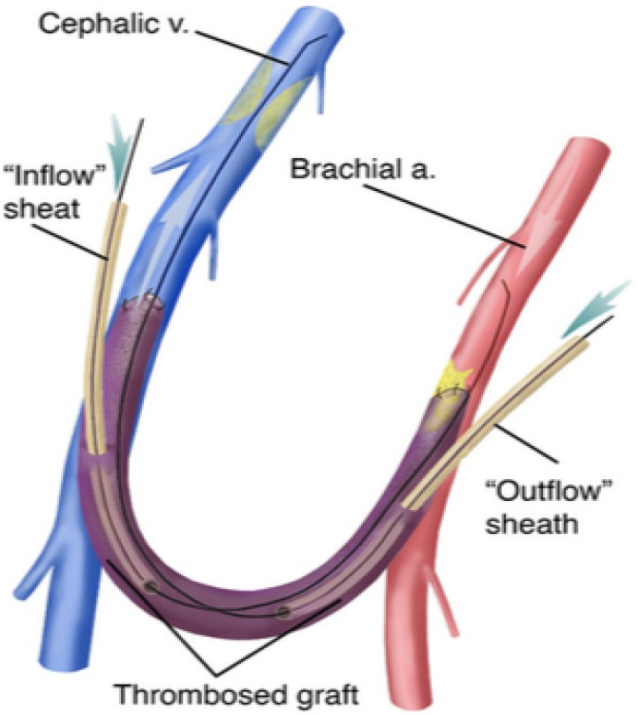


Figure 1: Dialysis access: AV graft.

Methods

We designed a randomized trial to evaluate the efficacy and safety of drug-coated balloon versus regular balloon for in-stent restenosis in stent graft. We plan to enroll 40 patients who presented with prosthetic AVG in-stent restenosis, and then to evaluate the restenosis lesions with intravascular ultrasound. Patients will be randomized into two groups of treatment: drug-coated balloon angioplasty or regular balloon angioplasty.

3 Background

Recurrent arteriovenous graft (AVG) thrombosis decreases quality of life in end-stage renal disease patients and increases medical expenditure significantly. For recurrent venous anastomosis site restenosis, there was established evidence to use stent graft to improve long-term patency rate.[1] For hemodialysis access stenosis, regular balloon, cutting balloon, and drug-eluting balloon have been proved to be safe in treatment of various morphology of stenosis.

In regard of regular balloon angioplasty to AVG, the 1-year primary patency rate is around 5%. Currently some data suggested that drug-coated balloon (paclitaxel coated balloon) can lead to higher primary patency rate around 35%. However, there is no established evidence to support use of drug-coated balloon for AVG stent graft restenosis.[2]

Purpose (for clinicaltrials.gov registration)

The purpose of this study is to determine whether drug-coated balloon is more effective than regular or common PTA balloon in graft stent patency. The condition is for hemodialysis access intervention. The focused graft stent is that implanted for hemodialysis access. The intervention included drug-coated balloon (paclitaxel-coated balloon) versus regular or common balloon.

- Study type: interventional
- Study Design:
  - Allocation: randomized
  - Endpoint classification: efficacy study
  - Intervention model: parallel
  - Masking: single blind (outcomes assessor)
  - Primary purpose: treatment
- Official title: as the study project title

Literature Review

3.1 Studies utilizing paclitaxel-coated balloon for dialysis access

Author, year	Study population	Method	Results
Konstantinos, 2012	N = 40, failing native AVF	Randomized, DCB versus plain balloon angioplasty	6-month primary patency rate (DCB versus PB): 70% versus 25%.
Pantane, 2014	N = 26, AVF, radiocephalfc, junta-anastomotic site	Observational single arm	Technical success 100%, 1-year target lesion primary patency rate 90.9%
Lai, 2014	N = 20, AVF with inflow lesions	Randomized, DCB versus plain balloon angioplasty	6-month patency rate: 70% versus 0%, 1-year patency rate: 20% versus 0%.
Kitrou, 2015	N = 40, AVG and AVF included	Randomized, DCB versus plain balloon angioplasty	1-year cumulative target lesion primary patency rate: 35% versus 5%.

Figure 2: Summary table of paclitaxel-coated balloon for dialysis access.

In 3 studies, the study populations were patients with AV fistulae.[Katsanos2012, Patane2014, Lai2014]. Only 1 study focused on AV grafts.[Kitrou2015]

In 3 studies, the study design involved randomization with comparison to plain balloon angioplasty, while one study had single arm in design.[Patane2014]

3.2 Evidences suggested that DCB may be useful for dialysis access in-stent restenosis.

This clinical implication mainly come from studies focusing on AVF (dialysis access) and SFA in-stent restenosis studies.

3.3 Mechanisms of in-stent restenosis of AV grafts

3.4 Mechanisms of balloon angioplasty- artery

3.5 Mechanisms of balloon angioplasty- arterialized vein

- Vessel wall and stent expansion.[Higuchi2001]

3.6 Mechanisms of luminal gain after balloon angioplasty for coronary in-stent restenosis

- Neointimal tissue compression or extrusion out of the stent.[Gordon1993, Mehran1996]
- Vessel wall and stent expansion.[Mehran1996]
- Plaque redistribution.[Mehran1996]
- Plaque fracture.

3.6.1 Intravascular Ultrasound

There are literatures discuss the IVUS use and stent graft use in hemodialysis access.[Higuchi2001, Arbab-Z]

3.6.2 Mechanisms of vessel dilatation after angioplasty to AV fistulae

Intravascular ultrasound imaging before and after angioplasty for stenosis of arteriovenous fistulae in haemodialysis patients. Dr. Higuchi demonstrated that IVUS can perform qualitative and quantitative studies of AVF after balloon angioplasty. They found that both stretching of vessel wall and plaque fractures contributed to luminal dilatation after balloon angiplasty.[Higuchi2001]

3.6.3 Intravascular ultrasound (IVUS) as a sensitive study tool

Hemodialysis access assessment with intravascular ultrasound. Dr. Arbab-Zadeh reported that IVUS identified more lesions that angiography. And IVUS is a safe and feasible study tool for AVG lesions.[Arbab-Zadeh2002]

The use of intravascular ultrasound to assist angiography in diagnosis and management of hemodialysis access. Dr. Maursetter reported case experience in using IVUS to provide treatment guidance.[Maursetter2011]

Intravascular ultrasound-guided angioplasty of hemodialysis loop graft in a patient with contrast allergy. Dr. Casey reported that using IVUS can avoid contrast use in patient with contrast allergy.[Casey2014]

3.6.4 Limitations of prior studies

- No IVUS data: not able to differentiate between intimal hyperplasia versus in-situ thrombosis
- Not aimed to AVG lesions. However, the AVG has the worst thrombosis and restenosis rates in comparison to AVF.
- No solution to stent graft stenosis available yet. However, the stent graft is the current treatment standard.
- Case numbers

4 Purpose and goals

1. To evaluate the treatment efficacy of regular balloon versus drug-coated balloon in-stent restenosis in AVG.
2. To evaluate the primary patency rate and secondary patency rate.
3. To evaluate the changes in luminal parameters by IVUS.
4. To establish a research database.
5. To describe the anatomical distribution of in-stent restenosis of stent graft in AV graft.

5 Materials and Methods

Investigational Plan

Table 2: Investigational Plan for Graft Stent Stenosis Study

IRB Number	
Principal Investigator	Mu-Yang Hsieh
Co-Principal Investigator	Chih-Cheng Wu
Angiography Core Laboratory	
IVUS Core Laboratory	
Biomarker Core Laboratory	
Clinical Events Follo-wup	

Study Design

This is a prospective, single-blind, single-center, randomized trial designed to assess the efficacy of drug-coated balloon angioplasty in comparison to regular balloon angioplasty in maintaining primary patency in patients with in-stent restenosis of stent graft placed for dialysis access dysfunction. The institutional review board in our hospital approved the study.

Background and Rationale

Null Hypothesis

The post-angioplasty primary patency rate is the same between drug-coated balloon angioplasty to regular balloon angioplasty in hemodialysis access stent graft restenosis.

Description of Devices

Study Population

The patients were eligible if they had end-stage renal disease and had graft stent at dial- ysis vascular access. Details of the inclusion and exclusion criteria are provided in table

1. The study flow chart was presented in Figure 3. The patients or legal representative provided written informed consent.

Eligibility

Patients visited our catheterization lab for shunt dysfunction. Patients age between 20 years to 90 years. We do not accept healthy volunteers.

Inclusion Criteria

The patients will be enrolled if they meet the following criteria: 1. Age of 20 to 90 years on regular hemodialysis at least 3 months, 2. had stent graft implemented at dialysis vascular access, 3. Angiographic evidence of stenosis within the stent graft or less then
2 cm from the stent graft edge, 4. clinical evidence of a hemodynamically significant stenosis or thrombosis, 5. patients ability to provide written informed consent.

Exclusion Criteria

The patient will be excluded from the study by the following criteria: Elbow fracture or any disease involve the elbow joint that prohibit the flexion maneuver. Target lesion cannot be cross by the guide wire. Known hypersensitivity to heparin or contrast medium. Patients have bleeding diathesis. Patients participating in another clinical tri- als with interfere with this trial in the past three months. Untreatable bleeding diathe- sis. Other diseases, such as cancer, liver disease, or cardiac insufficiency, which may lead to protocol violations or markedly shorten a patient's life expectancy (less than three months). Patients unable or unwilling to participate this trial. Pregnancy, lac- tating woman, non-adult, criminals in sentence, psychiatric patients, research staffs or colleagues are prohibited from joining this study.

Sample Size Estimation

The required sample for analysis of covariance of change in patency rate of AVG to detect a 45% difference, controlling for baseline values with 80% power and type I error of 0.05 is 19 participants per group. Allowing for a 15% drop-out rate, we aimed to recruit 21 participants per group.[3]

The sample size was estimated according to the following parameters: for a alpha of 0.05 and power of 0.90, the restenosis rate of AVG venous anastomosis site 49% versus
77% at 6 months in groups treated with stent graft versus standard balloon angioplasty, the sample size was calculated to be 114 patients.[4]

Because the estimated sample size number 114 patients will require 3 years to complete

the enrollment number, we plan to do a pilot study first, and the intended enrollment number in pilot study is 20 patients.

The study flow chart is presented in Figure 3.

5.1 Randomization Process

5.1.1 Informed consent

The patient or family has to sign all the investigational documents before enrollment.

5.1.2 Randomization

At the time of enrollment, the research assistant will use computer to generate randomization allocation table with computer-based program (REDCap). REDCap (Research Electronic Data Capture) system is a validated and mature databank developed by Vanderbilt University. It is also extensively used in Stanford University. The randomization module in REDCap is computer-based and excluded any manipulation process that can alter randomization result.

The patient will be randomized into drug-coated balloon group or into regular balloon group.

Biomarkers

Patients will also receive blood sampling with target biomarkers measurements. The biomarkers to be focused in our study: uremic toxins and miRNAs, or other novel markers, which are found to be associated with vascular access restenosis.

5.2 Intravascular Ultrasound Evaluation

5.2.1 Imaging Before and After Endovascuar Intervention

After obtaining vascular access, a 0.035-inch wire was used to traverse the occlusion or stenosis in the stent graft. The wire was then exchanged to a 0.014-inch wire by a bal- loon catheter. Intravascular ultrasound was then performed across the whole length of the stent graft (25 mm within the stent edge) and the lesion (5 mm of the lesion margin). The parameters were collected as Table 6. Both angiography and IVUS parameters are to be collected.[Stone2011]

An additional measurement of luminal area with elbow in extension or flexion was done to obtain another parameter regarding mechanical stress to the venous anastomosis junction.

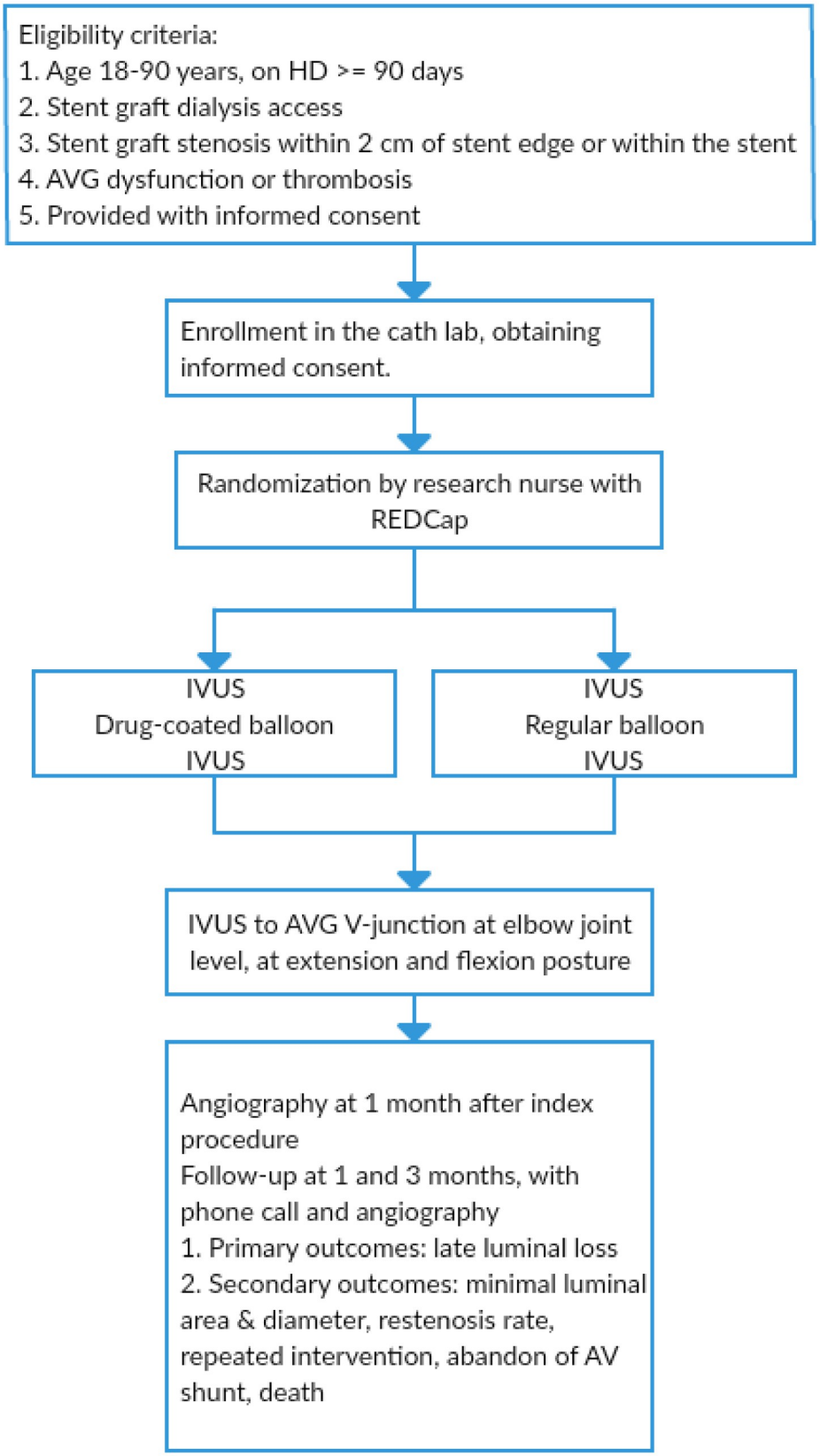


Figure 3: The study flow chart.

Table 4: Study Protocol Checklist

	Content	Confirmation
Enrollment	Evaluation	Cath room team
Randomization		By REDCap
Device and Equipment	IVUS	
Angiography IVUS set-up	QCA with track	before and after angioplasty
IVUS	before and after lesion: 5 mm, before and after stent edge: 25 mm	

Intravascular Ultrasound (IVUS) The interpretation of IVUS is performed by physician unaware of the group assignment. The minimal luminal area (MLA) has to be documented.[5,6]

IVUS procedures

1. A track use is mandatory. The IVUS pull-back speed is set to 1 mm/sec.
2. IVUS evaluation must include 2.5 cm beyond the stent edge. If the lesion extends beyond the stent edge, IVUS has to evaluate distal 0.5 cm further.
3. IVUS maximal depth: 8 mm.
4. IVUS must be performed before and after angioplasty in the index procedure.

Endovascular Intervention

Balloon used: Drug-coated balloon (Boston-Scientific), Regular balloon (Wanda). The size of balloon is determined by the operator.

Drug-coated balloon: inflation time 1 minute. Regular balloon: inflation determined by the operator.

1. Sequence of balloon angioplasty: DCB first, then cutting or high-pressure as indicated.
2. If DCB not enough in length, treat at least one lesion of in-stent restenosis. Note it within the study report.

Table 6: Study Protocol Case Report Form[Stone2011]

Category	Parameters	Result
Angiography	Reference vessel diameter (mm) Minimal luminal diameter (mm) Diameter stenosis (%) Lesion length (mm)	
IVUS (gray scale)	lesion: 5 mm; stent edge: 25 mm Minimal lumen area (mm2) Minimal lumen area ≤4.0mm External elastic membrane area (mm2) Plaque and media cross sectional area (mm2) Plaque burden (%) Lesion length (mm) Remodeling index (median [IQR]) Distance to the minimal lumen area (mm)	
IVUS (radiofrequency)	Tissue composition (%, median [IQR]): • fibrous tissue • fibrofatty • dense calcium • necrotic core Lesion classification: • pathological intimal thickening • thick-cap fibroatheroma • thin-cap fibroatheroma • fibrotic plaque • fibrocalcific plaque	

For patients presented with acute shunt thrombolysis

This study will not use urokinase for acute thrombosis patient. Please arrange follow-up of patient after acute thrombosis treatment.

Outcomes measurement (for clinicaltrials.gov registration)

- Primary outcome measures
  - target lesion late luminal loss [time frame: 1 and 3 months] [designated as safety issue: no]
    measure the difference of the MLD (minimal luminal diameter) by IVUS at 0 time and at 1, 3, and 6 months
- Secondary outcome measures
  - minimal luminal area and diameter (MLA and MLD) [time frame: 1 and 3 months] [designated as safety issue: no]
    measured MLA and MLD of target lesion at 1 and 3months
  - Restenosis rate of target lesion [time frame: 1 and 3] [designated as safety issue: no]
    >50% stenosis is designated as restenosis
  - repeated intervention for AV shunt
  - abandon of AV shunt
    because of repeated non-salvageable occlusion, the arteriovenous shunt (including both fistula or grafts) was abandoned
  - death
    death of any cause

The other secondary end points were: the primary patency rate, which was a composite of recurrent in-stent restenosis and shunt dysfunction requiring endovascular treatment and acute thrombosis. Shunt acute thrombosis was defined as no thrills or pulsations and confirmation made by angiography, the luminal area documented by intra-vascular ultrasound study; the secondary patency rate; the rate of repeated endovascular intervention.

Safety assessments included the incidence of hematoma, vessel rupture, infection, and the pain scale rated by patients after recovering from treatment.

The patient will be followed at 30 days with angiography in the cath lab.

Statistical Analysis

We plan to enroll 20 patients as a pilot study.

Participants will be randomly assigned into two groups according to the use of drug-coated or regular balloons. These two groups will be compared in the following parameters: clinical data, laboratory data, intravascular ultrasound parameters before and after balloon angioplasty, post-interventional lesion primary and secondary patency (PLP and PLS).

For patient with very long graft stent longer than the coverage of drug-coated balloon, there will be additional comparison of the lesion treated with drug-coated balloon and regular balloon in the same vessel.

Two-sample student ' s t tests will be used for the comparisons of continuous variables. Chi-square test will be used to detect difference between categorical variables. For patients with recurrent thrombosis or stent graft stenosis, univariate correlation will be analyzed by the Spearman rank correlation test. Difference is considered statistically significant if $P < 0.05$. All statistics works were analyzed using the SPSS 17.0 software (Chicago, IL, USA), R software (Gimc packages).

6 Anticipated results

1. To provide results to support the use of DCB in AVG in-stent restenosis.
2. To decrease medical expenditure.

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