JOURNAL OF ENDOVASCULAR THERAPY
INTERNATIONAL SOCIETY OF ENDOVASCULAR SPECIALISTS

*Clinical Investigation*

# Paclitaxel-Coated Balloon Angioplasty for Symptomatic Central Vein Restenosis in Patients With Hemodialysis Fistulas

Journal of Endovascular Therapy
2015, Vol. 22(1) 74–79

DOI: 10.1177/1526602814566907
www.jevt.org
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**Abstract**

**Purpose:** To report a retrospective observational analysis of standard balloon angioplasty (BA) vs. paclitaxel-coated balloon angioplasty (PCBA) for symptomatic central vein restenoses in patients with impaired native hemodialysis fistulas. **Methods:** A retrospective review was conducted of 27 consecutive patients (15 men; mean age 66±13.8 years, range 39–90) with 32 central vein stenoses (CVS; 6 axillary, 11 subclavian, 12 brachiocephalic, and/or 3 superior caval veins) treated successfully using BA. Freedom from reintervention after BA of de novo lesions was 7.4±7.9 months (range 1–24). Twenty-five (92.6%) patients developed symptomatic restenoses and were treated one or more times by BA (n=32) or PCBA (n=20) using custom-made paclitaxel-coated balloons (diameter 6–14 mm). **Results:** Technical (<30% residual stenosis) and clinical (functional fistula) success rates for the initial and secondary angioplasty procedures were 100%. No minor/major procedure-associated complications occurred. Mean follow-up was 18.4±17.5 months. Kaplan-Meier analysis for freedom from target lesion revascularization (TLR) found PCBA superior to BA (p=0.029). Median freedom from TLR after BA was 5 months; after PCBA, >50% of patients were event-free during the observation period (mean freedom from TLR 10 months). Restenosis intervals were prolonged by PCBA (median 9 months) vs. BA (median 4 months; p=0.023). **Conclusion:** Paclitaxel-coated balloon angioplasty of central vein restenosis in patients with hemodialysis shunts yields a statistically significant longer freedom from TLR compared to standard balloon angioplasty.

**Keywords**

endovascular intervention, vein, central venous stenosis, drug-eluting balloon, restenosis, hemodialysis, arteriovenous fistula, target lesion revascularization

## Introduction

Symptomatic central vein stenosis (CVS) is a clinically relevant complication in hemodialysis patients. Stenoses of central veins typically result in dysfunctional dialysis shunts, venous collaterals, edema, ipsilateral extremity tenderness, pain, and cellulitis.[1,2] Further complications include shunt vein thrombosis and excessive bleeding after puncture for dialysis. CVS is commonly associated with central vein catheterization with an incidence of 25% to 50%[3,4] or insertion of pacemaker wires in up to 27%.[5–7] The incidence of CVS without previous central vein catheterization is about 1% to 10%.[8,9] A typical mechanism for the development of CVS is intravasal trauma to the venous endothelium, which results in inflammation of the vessel wall. Microthrombus, intimal hyperplasia, and fibrotic alteration finally lead to CVS.[10,11] The pathophysiological mechanism of CVS in dialysis shunts without a history of central vein catheterization is unclear. A higher venous blood flow and increased pressure after creation of a dialysis fistula are considered the cause.[8,9]

Endovascular treatment with balloon angioplasty is generally accepted as the primary treatment for CVS.[3,12] However, restenosis is frequent. Restenotic lesions are characterized by a significant increase in fibroplastic proliferation within the venous neointima and media as compared to primary stenotic lesions.[13] Several experimental[14,15] and clinical[16–18] studies confirmed the hypothesis of vascular

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remodeling owing to adventitial angiogenesis and scar development. This is the theoretical background for application of antiproliferative therapy at the time of balloon angioplasty within the venous system, as drug-coated balloon angioplasty has been shown to lead to a significant reduction in restenosis in peripheral artery disease.[19,20] Venous smooth muscle cells (SMCs) are more sensitive to the effects of antiproliferative agents as compared with arterial SMCs.[21] Paclitaxel in the perivascular area of hemodialysis grafts resulted in an effective inhibition of neointimal hyperplasia and prevention of restenosis in several animal models.[22,23] A recent randomized controlled clinical trial favored paclitaxel-coated balloon angioplasty (PCBA) for stenoses of hemodialysis access.[24]

Based on these in vitro and clinical results, the purpose of this study was to retrospectively evaluate standard balloon angioplasty (BA) vs. PCBA for the treatment of recurrent symptomatic CVS in patients with hemodialysis fistulas.

## Methods

### Study Design and Patient Cohort

Between 2008 and 2014, 27 consecutive patients (15 men; mean age 66±13.8 years, range 39–90), all with diabetic end-stage renal disease, presented with considerable edematous arm swelling and severely impaired native lower or upper arm hemodialysis fistulas inappropriate for dialysis. Catheter-directed venography depicted 32 de novo nonmalignant CVS (Figure 1) in the axillary (n=6), subclavian (n=11), brachiocephalic (n=12), and/or superior caval vein (n=3). Three patients had 2 venous stenoses and 1 patient had 3. Complete chronic occlusions were not detected. The interval between creation of the hemodialysis fistulas and development of the initial CVS was 39±49 months (range 1–216).

After institutional review board approval and patient informed consent, all 27 patients underwent initial balloon angioplasty. Overall, 52 reinterventions were necessary in 25 (92.6%) of the 27 patients due to clinically symptomatic restenosis and impaired hemodialysis fistula. Fifteen patients underwent 32 reinterventions using standard BA and 10 patients underwent 20 reinterventions using PCBA (Table 1). Selection of patients for BA or PCBA was at the operator's discretion.

### Standard Balloon Angioplasty

Angiography was performed after needle (22-G) puncture of the brachial artery to exclude relevant stenoses in the hemodialysis fistula, arteriovenous anastomosis, and draining shunt veins. CVS was verified by direct phlebography via the shunt vein, into which a standard 0.035-inch hydrophilic guidewire and 7-F sheath (10- or 25-cm long) were inserted. Five thousand units of unfractionated heparin were given through the sheath. Intraluminal crossing of the CVS was always achieved with the 0.035-inch guidewire and 4-F catheter.

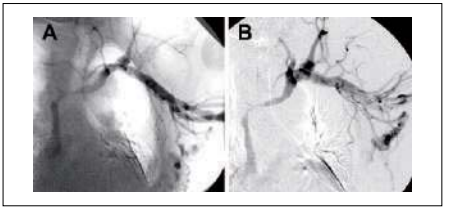


**Figure 1.** (A) Unsubtracted and (B) digital subtraction phlebography via an antecubital vein reveals typical extensive venous collaterals along the chest wall because of high-grade stenosis of the left brachiocephalic vein.

Balloon size was determined according to the diameter of the adjacent normal vein and the length of the stenosis. In most cases, the balloon catheters were typically 40-mm long with diameters ranging from 6 to 12 mm. Inflation pressure was 14 atmospheres for 60 seconds. Additional dilation with larger balloons was performed if recoil with relevant residual stenosis occurred; inflation pressure was also 14 atmospheres for 60 seconds. Pretreatment with 6-mm diameter cutting balloons (Boston Scientific, Natick, MA, USA) and posttreatment high-pressure balloon angioplasty (24 atm for 60 seconds) was also used as necessary for severe recalcitrant recoil. The diameter of the high-pressure balloon was identical to the largest size of the primary balloon. Technical success was defined as residual stenosis <30%. Heparin therapy was maintained for 48 hours. Clinical success was defined as the ability to successfully use the fistula for dialysis after angioplasty.

### Paclitaxel-Coated Balloon Angioplasty Treatment

As drug-coated balloon catheters of appropriate size (diameter >7 to 14 mm) for central veins were not commercially available, all paclitaxel-coated balloons were custom-made using standard over-the-wire balloon catheters (Figure 2) coated with polymer-free microcrystalline paclitaxel at a concentration of 2 μg/mm$^2$ (Elutax-SV; Aachen Resonance, Aachen, Germany).

The PCBA followed the same BA protocol for vascular access, heparin use, sizing of the paclitaxel-coated balloons, and adjuvant procedures for pretreatment and recoil. Balloon catheter length was 40 mm for the 6- to 10-mm diameter balloons and 20 mm for the 10-, 12-, and 14-mm diameter balloons. Inflation pressure was 14 atmospheres for 60 seconds, similar to the BA group.

**Table 1.** Characteristics of Patients Treated for Central Vein Restenosis.[a]

| | Standard Balloon Angioplasty | Paclitaxel-Coated Balloon Angioplasty |
|---|---|---|
| Patients | 15 | 10 |
| Age, y | 66.8±15.0 (39–90) | 64.5±11.2 (50–85) |
| Men | 9 (56) | 6 (60) |
| Diabetes mellitus | 15 | 10 |
| Native arteriovenous fistula | 15 | 10 |
| Dialysis access age, mo | 26.9±22.9 (1–67) | 50.9±62.8 (1–216) |
| Location left arm | 10 | 7 |

[a]Continuous data are presented as the means ± standard deviations (range); categorical data are given as the counts (percentage).

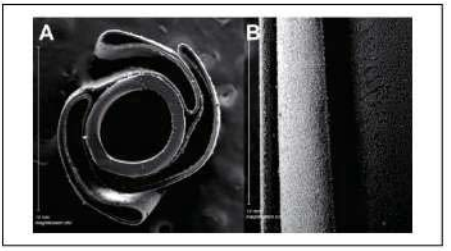


**Figure 2.** Scanning electron microscopy cross-sectional image illustrating (A) special balloon folding and (B) the paclitaxel-coated surface of Elutax SV completely covering the balloon. The drug itself is protected within the folds of the balloon.

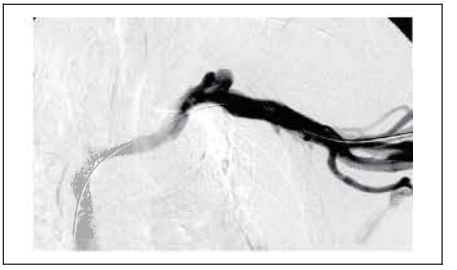

**Figure 3.** Postinterventional venography after dilation with a 10×40-mm paclitaxel-coated balloon depicts a successful reduction in the central venous stenosis. Consequently, there is an obvious improvement in venous inflow and a considerable reduction of venous collaterals.

### *Statistical Analysis*

Continuous data are presented as the means ± standard deviations; categorical data are given as the counts. The differences between groups were evaluated using the unpaired *t* test; differences achieving $p<0.05$ were considered to be statistically significant. Freedom from target lesion revascularization (TLR) was estimated using the Kaplan-Meier method; differences between groups were examined with the log-rank test. Statistical analysis was performed using the Prism software for MacOSX (version 6.0.4, Graphpad, La Jolla, CA, USA).

## Results

Primary technical success (residual stenosis <30%) in the BA and PCBA groups was 100% (Figure 3). Additional dilation with larger balloons was performed in 10 BA patients and 8 PCBA cases because of recoil with relevant residual stenosis. The mean diameters were 8±2 mm for the standard balloons and 10±2 mm (range 6–14) for the coated balloons. Pretreatment with cutting balloons and posttreatment high-pressure balloon angioplasty were necessary in 2 patients in each group. No minor or major procedure-associated complications were observed. There was no relevant bleeding, hematoma, superior vena cava thrombosis, or worsening of hemodialysis fistula function after BA or PCBA. Stent placement was avoided in all patients. Function of the hemodialysis shunts normalized after intervention, which allowed appropriate use for dialysis.

Four patients in the BA group experienced very early restenosis. One patient had 11 reinterventions within 2.7±1.3 months, another patient had 4 reinterventions over 7.8±2.2 months, and 2 patients had recurrences after 1 and 2 months. Although PCBA was under evaluation, the superior results in the PCBA group finally led to crossover of these 4 patients to PCBA for ethical reasons. After crossover to PCBA, the intervention-free time interval markedly increased up to 21 months. One patient died after 6 months without the need for reintervention.

Over a mean follow-up of 18.4±17.5 months, 9 (33%) patients died after 7.2±5.9 months (median survival 6 months, range 1–19); no death was related to the procedure. Failing hemodialysis fistula due to shunt occlusion after BA occurred in 4 patients after 4.0±3.1 months (range 1–9) and after PCBA in 1 patient after 3 months.

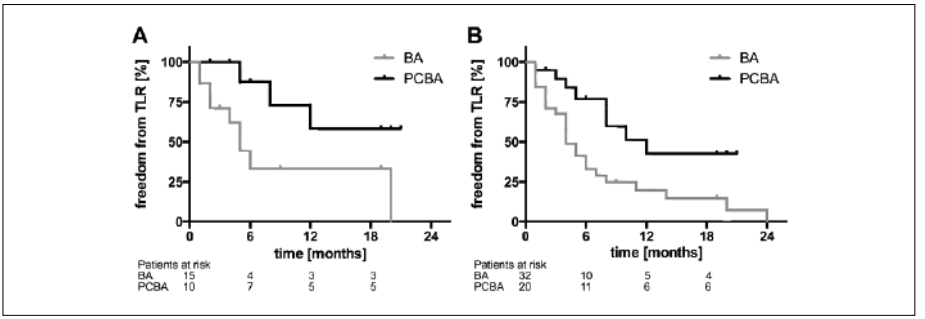


**Figure 4.** Kaplan-Meier plots demonstrate freedom from target lesion revascularization (TLR) after standard balloon angioplasty (BA) and paclitaxel-coated balloon angioplasty (PCBA) of central venous restenosis: (A) initial treatment and (B) pooled data in a crossover design of lesions treated.

### *Comparative Analysis*

Kaplan-Meier analysis of freedom from TLR after first reinterventions revealed PCBA significantly superior to BA (p=0.025; Fig. 4A). The median freedom from TLR after BA was 5 months. For PCBA, 66.7% of patients were event-free during the observation period, resulting in a mean freedom from TLR of 10 months.

A crossover-design analysis in which each patient serves as his or her own control was completed to integrate additional data from recurrent restenosis. Additional statistical analysis of pooled data respecting all consecutive treatments showed a median freedom from TLR after PCBA of 12 months vs. 4 months after BA (p=0.006; Fig. 4B). Time to recurrent restenosis was also significantly prolonged by PCBA (mean 9.5±1.9 months in 4 patients) vs. BA (mean 5±4.9 months in 5 patients, 1 early death). The median time interval to restenosis after PCBA was 9 months vs. 4 months after BA (p=0.021).

## Discussion

Preservation of hemodialysis fistula function in patients with central vein occlusive disease is a relatively common problem. Unfortunately, all available interventional treatment options result in poor midterm patency. As a consequence, several reinterventions are often mandatory. Standard BA is so far the common first-line treatment of choice in CVS. Compared with standard balloons, paclitaxel-coated balloons in endovascular treatment of peripheral artery disease have demonstrated lower restenosis rates and superior clinical outcomes with prolonged time to reintervention. However, due to a limited number of patients and variable designs of existing studies, definitive recommendations for optimal treatment of CVS are lacking. Furthermore, the pathophysiology of atherosclerotic disease is different from the development of CVS. Nonetheless, looking at the histopathology, CVS has similarities to arterial stenosis. In both, hyperproliferation of fibroblasts have been identified as part of the problem.[10,12,13,21,22,24] Neointimal hyperplasia is a local inflammatory process. Local wall delivery of the antiproliferative agent paclitaxel reduces neointimal hyperplasia by inhibition of SMC proliferation and migration. Paclitaxel stabilizes the arrangement of microtubules by binding β-tubulin dimers, inhibiting their depolymerization. The long-lasting disruption of normal microtubule function interferes with a number of cell properties, including division, motility, and shape. Low doses of paclitaxel cause cell-cycle arrest in the G1 phase without causing cellular apoptosis. The resulting cytostatic response with inhibition of SMC proliferation and migration represent the key processes for reduction of neointimal hyperplasia.[25–27] Other studies demonstrated a varying technical success rate for standard balloon dilation of CVS between 70% and 90%. Unsatisfactory initial results and short-term restenosis are often observed.[28] Primary patency rates range from 23% to 55% and 12% to 50% at 6 and 12 months, respectively. A high technical failure rate of 10% to 30% necessitates close surveillance with the need for multiple reinterventions.[29–32]

Bare metal or covered stents have been evaluated with differing results. While bare stents have high primary technical success rates of 82% to 100%, midterm results are as disappointing as they are with BA. Primary patency of self-expanding bare stents range from 42% to 89% at 6 months and 14% to 73% at 12 months.[32–34] Intimal hyperplasia, stent fracture, and migration due to (respiratory) motion and compression lead to early restenosis. Furthermore, bare stents may complicate further endovascular or surgical treatment.[32–34]

The use of covered stents should combine the advantages of mechanical stability and lower in-stent restenosis caused by intima hyperplasia. The primary technical success rate was 100%, but primary patency was only 32% to 67% at 12 months, which makes stenting questionable in vessel segments exposed to high biomechanical stress.[35–37]

Recently, drug-coated balloon angioplasty was used for venous anastomotic stenosis of dialysis fistulas and synthetic grafts. The use of the IN.PACT Amphirion paclitaxel-coated balloon showed a statistically significant improvement in primary patency (70%) compared to BA (25%) after 6 months ($p<0.001$).[24] In failing dialysis fistulas caused by de novo or recurrent juxta-anastomotic stenoses, PCBA achieved a primary patency rate of 92% after 9 months.[38]

In our study, patients with symptomatic CVS initially underwent the well-accepted treatment of choice with BA. As mentioned above, the restenosis rate was high and the intervention-free time interval was relatively short. Even though BA of CVS is a fast and low-risk procedure, patients have to be hospitalized recurrently, and balloon angioplasty itself is uncomfortable and painful. To avoid the disadvantages and complications related to stent implantation, we evaluated the use of PCBA in patients with symptomatic CVS. A technical prerequisite for successful treatment of CVS using PCBA is an appropriate sizing of the drug-coated balloon catheters. Central veins are usually larger in diameter than coronary or peripheral arteries, for which several balloons of different sizes (diameter ≤7 mm) are commercially available. In most of our cases, the diameter of the central veins was too large for commercially available balloon catheters. Consequently, all the PCBA catheters needed to be especially produced, but there was no balloon rupture or disintegration of coating before application. Notably, the treatment with a "double dose" of paclitaxel in 8 patients did not result in any vascular damage, for example, but the patients are too few for subgroup analysis.

Short-term results of a randomized controlled trial of PCBA in the peripheral venous system showed PCBA superior to BA for the treatment of hemodialysis access stenoses.[24] Similar to these results and those of drug-coated balloons in coronary and peripheral artery disease, our patients experienced significantly fewer restenoses of the central veins after PCBA. Furthermore, vessel patency was improved, which resulted in a prolonged freedom from TLR.

### *Limitations*

The study was limited by its small cohort and single-center observational retrospective design. Furthermore, the fact that all patients were diabetics may mean that our results are not reproducible in non-diabetic patients. However, the improved outcome supports the use of PCBA in the management on CVS, at least after inadequate primary BA of de novo lesions.

## Conclusion

Paclitaxel-coated balloon angioplasty of central vein restenosis yields a statistically significant longer freedom from TLR in patients with hemodialysis shunts. A randomized controlled trial for the use of PCBA as first-line strategy is justified.

### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Prof Dr med Arno Buecker was a co-founder of Aachen Resonance.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Cardiovasc Intervent Radiol (2019) 42:835–840
https://doi.org/10.1007/s00270-019-02213-w



# Drug-Eluting Balloon Angioplasty for Juxta-Anastomotic Stenoses in Distal Radiocephalic Hemodialysis Fistulas: Long-Term Patency Results

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Received: 21 November 2018 / Accepted: 26 March 2019 / Published online: 29 March 2019


**Abstract**
*Purpose* To evaluate long-term primary and secondary patency results of drug-eluting balloon angioplasty for the treatment of juxta-anastomotic stenoses in distal radiocephalic arteriovenous fistulas.
*Materials and Methods* Thirty-eight patients with juxta-anastomotic stenotic distal radiocephalic arteriovenous fistulas who underwent endovascular treatment with drug-eluting balloons between January 2014 and August 2016 in our interventional radiology department were included in this retrospective study. Color Doppler examination for follow-up was performed 15 days, 6 months, 12 months, 18 months, 24 months, 36 months, and 48 months after the procedure. Kaplan–Meier analysis was used to estimate primary and secondary patency rates.
*Results* Totally, 42 angioplasty with drug-eluting balloons was performed in 38 patients (20 men and 18 women; mean age 66.42 ± 12.01). Technical and clinical success rate was 100% (42/42). The mean follow-up period was 27.71 months ± 12.98 (range, 1–54 months). The estimated primary patency rates at 6 months were 94.7% (95% CI, 80.9%–99.0%), at 12 months were 81.2% (95% CI, 64.6%–91.4%), at 24 months were 60.7% (95% CI, 43.6%–75.7%), and at 48 months were 53.1% (95% CI, 36.5%–69.1%). The estimated secondary patency rates at 6 months were 97.3% (95% CI, 84.5%–99.8%), at 12 months were 86.5% (95% CI, 70.7%–94.8%), at 24 months were 69.0% (95% CI, 51.8%–82.4%), and at 48 months were 61.7% (95% CI, 44.6%–76.5%).
*Conclusion* Drug-eluting balloon angioplasty is a useful, effective technique in dysfunctional radiocephalic fistulas due to juxta-anastomotic stenoses. We demonstrated remarkably high primary patency rates at 6, 12, 24, and 48 months.

**Keywords** Drug-eluting balloon · Percutaneous transluminal angioplasty · Juxta-anastomotic stenosis

## Introduction

End-stage renal disease (ESRD) is the final stage of chronic kidney disease. It is predicted that the prevalence of ESRD and the need for hemodialysis will grow in the future as the average lifespan increases [1]. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines advise autologous arteriovenous fistula (AVF) for vascular access [2]. Distal radiocephalic AVFs are the first option due to its technical simplicity, lower complication, and higher patency rates [3]. However, in spite of being superior to other accesses, fistulas also have a limited time for appropriate usage. Stenosis, which usually occurs in 3 cm before and after the anastomosis, is the main reason for

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dysfunctional AVFs [4–6]. These types of stenoses are regarded as juxta-anastomotic stenoses (JASs) [7].

Endovascular treatment in AVFs is recommended in K/DOQI guidelines. Several reports have revealed the efficacy of endovascular treatment in AVFs [6, 8–10], but most of the studies have included all types of fistulas such as radiocephalic, radioulnar, or brachial-basilic. Moreover, long-term patency results after percutaneous transluminal angioplasty (PTA) in the most preferred fistula type, radiocephalic fistulas [3], are lacking. Over the past few years, drug-eluting balloons (DEBs) have evolved and taken part in stenotic AVF treatment by inhibiting neointimal hyperplasia [11]. However, it is still needed to be demonstrated how effective is the DEB angioplasty, which has been proven as the primary treatment method [12], in distal radiocephalic fistulas.

The aim of our study was to assess long-term patency results of DEB angioplasty for the treatment of JASs in distal radiocephalic AVFs.

## Materials and Methods

### Patients

Local ethics committee approval was obtained for this retrospective study. Patients who underwent fistulography and endovascular treatment in our department between January 2014 and August 2016 were reviewed. Since we wanted to elucidate long-term outcomes, patients with a minimum follow-up of 2 years were selected for the present study. The interventions performed before the year 2014 were not scanned for the lack of acceptable demographic and clinical data. The inclusion criteria were as follows: autologous distal radiocephalic fistulas with JASs. Arteriovenous grafts, patients without follow-up information, and fistulas that had treated formerly in different hospitals were the exclusion criteria. JASs were described as stenoses occurred in 3 cm before and after the anastomosis. After all, a total of 38 patients (20 men and 18 women; mean age 66.42 $\pm$ 12.01) with sufficient demographic, clinical, and radiologic follow-up data were incorporated in the study.

### Pretreatment Evaluation

Patients in the study were directed to our department with AVF problems from dialysis units. The decrease of the blood flow greater than 20% per month, observing total access blood flow less than 300 mL/min were the conditions that displayed AVF dysfunction. One operator with 15 years of experience performed all the color Doppler examinations and operated all the endovascular treatments (A.G.). Color Doppler examination was used to localize the abnormality, estimate the degree of stenosis, evaluate the outflow vein, figure out the treatment method, and determine the access site. Along with clinical problems, narrowing greater than 50%, peak systolic velocity (PSV) ratio greater than 2:1 compared to the 2-cm proximal from the lesion, and PSV of $\geq$ 500 cm/sec were considered abnormal [13]. Further evaluation with fistulography was performed in these patients.

### Endovascular Treatment

A digital subtraction angiography device (Allura Xper FD10, Philips Healthcare, the Netherlands) was used for fistulography and endovascular procedures. Retrograde outflow vein puncture was performed by ultrasound guidance to minimize hematoma in all procedures. Inflow, fistula, and outflow segments were assessed carefully before the procedure. Blood pressure cuff was used to observe arterial anastomosis better. Initially, we performed a fistulography via 18G cannula. Fistulography images were evaluated, and treatment decision was made by the same experienced interventional radiologist who had performed patients' initial color Doppler examination.

A standard technique was used for the treatment of JASs [14]. If we decided to do angioplasty after fistulography, we placed the sheath using 0.035-inch guidewire through the 18G cannula under local anesthesia. Heparin (5000 IU) was administered intravenously after vascular sheath placement in all cases. Juxta-anastomotic target lesion was passed by manipulation of a 0.035-inch hydrophilic guidewire and a 4F multipurpose vertebral catheter. After advancing the catheter to the arterial side, hand injection was performed for the final decision of balloon size. Then, 0.035- or 0.018-inch guidewire was advanced, and the catheter was removed. After predilatation with plain balloons, DEBs were advanced via guidewire to the lesion. Types of DEBs we used were Elutax SV OTW, ab medica, Dusseldorf, Germany (in 12 procedures), and IN.PACT Admiral Drug-coated balloon, Medtronic, California, USA (in 30 procedures). After the termination of the stenosis, the balloon was held on inflated for 2 min to prevent the elastic recoiling. For refractory lesions, cutting balloons were used. When successful appearance was gained, the procedure was terminated with control of central veins. After sheath removal, hemostasis was gained by manual compression.

### Clinical Outcome and Follow-Up

Technical success, clinical success, primary patency, secondary patency, and minor and major complication rates were considered during clinical outcome analysis.

Technical success was described as the increase in the "thrill" and residual stenosis lower than 30% in both angiographic images and color Doppler examination. The operator performed color Doppler examination and thrill assessment before and after the procedure. During the procedure, the operator evaluated the angiographic images. However, all angiographic images were reviewed retrospectively by 6-year (O.S.) and 5-year (A.P.) experienced radiologists. The radiologists were unaware of the patients' diagnosis and operation findings. The two radiologists assessed the pre- and post-dilatation images and recorded the residual stenoses of $\geq$ 30% if any. Clinical success was defined as the access of the fistula without any problem during dialysis. Total access blood flow of $>$ 300 mL/min was a supportive criterion of the clinical success. Clinical success was evaluated by dialysis unit nephrologists. In the first dialysis session after the procedure, feedback was received via phone call.

Primary patency and secondary patency rates were evaluated based on the instructions of Society of Interventional Radiology Technology Assessment Committee [15]. Primary patency was defined as the time between the first intervention until access thrombosis and repeated endovascular treatment. The interval after the first intervention until the fistula is surgically revised or abandoned was regarded as secondary patency.

Color Doppler examination for follow-up was performed 15 days, 6 months, 12 months, 18 months, 24 months, 36 months, and 48 months after the procedure by an 8-year experienced radiologist (O.A). If a problem was detected by nephrologist, or dialysis unit nurse, patients were directly referred without waiting for the follow-up date. Color Doppler examinations, repeated angiography images, and records of dialysis units were inspected for follow-up data. Follow-up ended in August 2018. Complications were graded according to the CIRSE classification [16].

### Statistical Analysis

Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA). Kaplan–Meier survival analysis was used to estimate primary and secondary patency rates after intervention. Stated patency rate intervals in this study were 95% confidence intervals (CIs). Renal transplantation, exitus because of an independent cause from renal disease with functional AVF, and loss to follow-up were regarded as censored data.

## Results

Characteristics of AVFs and patients' demographic data are demonstrated in Table 1. Forty-two PTA with DEBs was performed in 38 patients. The mean size of the balloons was 5.55 mm $\pm$ 0.67. Cutting balloon was used in one procedure due to refractory stenosis after DEB.

Our technical and clinical success rate was 100% (42/42). Grade 1 complications were experienced in 4 cases. Hematomas at the puncture site that did not affect blood flow were reported after two interventions (2/42, %4.76). Contrast extravasation was observed in two procedures and was managed with balloon inflation (2/42, %4.76).

The mean follow-up period in this study was 27.71 months $\pm$ 12.98 (range, 1–54 months). Eight patients died of an unrelated cause from renal disease with functional fistula during the follow-up period.

At the sixth month, one patient underwent surgical creation of a new fistula; one patient needed reintervention due to stenosis of the same location; one patient died with functional fistula. Thirty-five patients had successfully working AVF at the end of 6 months.

Between the 6th and 12th months, 4 fistulas were thrombosed and abandoned. Repeated endovascular treatment to the same region was performed in one patient.

After 18 months, 4 patients died with functional fistula. 3 fistulas were surgically revised. One patient had recurrent JAS and reintervention was done.

At 24-month follow-up, 3 patients could not continue dialysis with their fistulas and underwent surgical revision.

**Table 1** Demographic features of the patients and characteristics of the AVFs

| | |
|---|---|
| Number of patients | 38 |
| Age (years) | 66.42 $\pm$ 12.01 |
| Female to male ratio | 18/20 |
| Hypertension | 21/38 (55.3%) |
| Hyperlipidemia | 17/38 (44.7%) |
| Diabetes mellitus | |
| Type 1 | 1/38 (2.6%) |
| Type 2 | 20/38 (52.6%) |
| Type of AVF | |
| Radiocephalic | 38/38 (100%) |
| Side of AVF | |
| Right | 13/38 (34.2%) |
| Left | 25/38 (65.8%) |
| Age of AVF at the first intervention (months) | 15.2 $\pm$ 18.3 |
| Stenosis location | |
| Juxta-anastomotic | 38/38 (100%) |

*AVF* arteriovenous fistula

One patient died with functional fistula. At the end of 2 years, there were 18 patients remaining with no necessity for additional intervention.

Between the 24th and 36th months, 2 patients died of heart problems with functional fistula. No endovascular intervention or surgery was performed during this period.

At 48th month, two fistulas were occluded, and surgery was performed to revise. By the end of 48 months, 14 patients did not need any intervention and underwent dialysis successfully. At the end of the follow-up interval, 17 patients (%44.7) had functional AVFs.

At the follow-up, three patients were needed reintervention. At 5 months, one patient had stenosis and the patient was treated by angioplasty with DEB. Two months later, restenosis was detected and the same procedure was performed; 11 months later, restenosis was detected again at the same region and treated with DEB again. No further intervention was needed, and fistula is still patent. The second patient had stenosis at the same site after the intervention, and the patient was treated by angioplasty with DEB. No further stenosis was detected during the follow-up period. The other patient also had recurrent stenosis at 14 months of follow-up; he was treated by angioplasty with DEB. No more stenosis occurred during the follow-up period.

The estimated primary patency rates at 6 months were 94.7% (95% CI, 80.9%–99.0%), at 12 months were 81.2% (95% CI, 64.6%–91.4%), at 18 months were 70.3%, (95% CI, 53.1%–83.4%), at 24 months were 60.7% (95% CI, 43.6%–75.7%), at 36 months were 60.7% (95% CI, 43.6%–75.7%), and at 48 months were 53.1% (95% CI, 36.5%–69.1%).

The estimated secondary patency rates at 6 months were 97.3% (95% CI, 84.5%–99.8%), at 12 months were 86.5% (95% CI, 70.7%–94.8%), at 18 months were 78.4%, (95% CI, 61.6%–89.4%), at 24 months were 69.0% (95% CI, 51.8%–82.4%), at 36 months were 69.0% (95% CI, 51.8%–82.4%), and at 48 months were 61.7% (95% CI, 44.6%–76.5%). Figure 1 summarizes the patency results.

## Discussion

Our study demonstrated that endovascular treatment of JASs in radiocephalic hemodialysis fistulas with DEBs is an effective method. We recorded pretty high primary patency rates even at 48 months with DEBs in this study. Secondary patency rates were greater than primary patency rates as expected.

PTA is an established procedure and is the first option for the management of JASs with its minimally invasive nature [7, 17, 18]. Although surgical creation of a new fistula has lower rates of recurrence [19], secondary patency rates are comparable with surgery and PTA [20]. Despite high recurrence rates, endovascular treatment allows immediate usage of AVF after the procedure and prevents waiting for maturation after the new surgery.

Many studies compared the DEBs and plain balloons in the treatment of stenotic AVFs [12, 21, 22]. All these studies demonstrated that DEBs provide significantly higher primary patency rates and lower recurrence rates. Animal trials displayed the efficacy of paclitaxel on preventing neointimal hyperplasia and reported that local therapy is more useful [23, 24].

Although miscellaneous reports assessed the efficacy of DEBs in AVFs, the sample in these studies included radiocephalic and brachiocephalic fistulas or grafts, juxta-anastomotic, or outflow venous stenoses [6, 8, 9, 25, 26]. As far as we know, minimal number of studies assessed the long-term patency rates after DEB angioplasty in a uniform sample such as autologous radiocephalic AVFs with JASs [7].

We demonstrated better primary patency rates at 6 (94.7%) and 12 (81.2%) months compared to other studies [6, 9, 27, 28]. These results illustrate the efficacy of DEB angioplasty in JAS. Patanè D et al. [7] achieved similar results. The treatment of JASs with DEBs reduces the rate of restenosis and therefore makes the primary patency rates higher. With less repeated interventions, patient comfort and cost-effectiveness get better [22]. After the intervention, two restenoses occurred, and reintervention was performed within 1 year in our study. This number was much better than most of the other studies, except one study had the same number [7].

Patanè D et al. [7] showed a significant decrease in the primary patency rates from the 12th month to the 24th month. Similarly, there was a decline in our study from the 18th (70.3%) month to the 24th (60.7%) month. This decrease may be the consequence of repetitious punctures and vascular damage. However, the results remained the same at the 36th (60.7%) month. These rates are significantly higher than all studies that assessed the management of JASs in radiocephalic fistulas [7, 17, 27, 28].

Manninen et al. [17] assessed the effectiveness of the brachial arterial approach to the failing radiocephalic fistulas. Their primary patency rate was 32.0% at 36 months. This significant lower result compared to our study may be due to the heterogeneous target lesion (JASs or other segments) selection. Moreover, not only DEB angioplasty but also other treatment options such as thromboaspiration or stent deployment were performed in their study. Mortamais et al. [28] evaluated long-term results after endovascular treatment in JASs. They included only radiocephalic AVFs with JASs in their research and reported primary patency rates of 25.5% at 36 and 48 months. We demonstrated significantly greater rates at

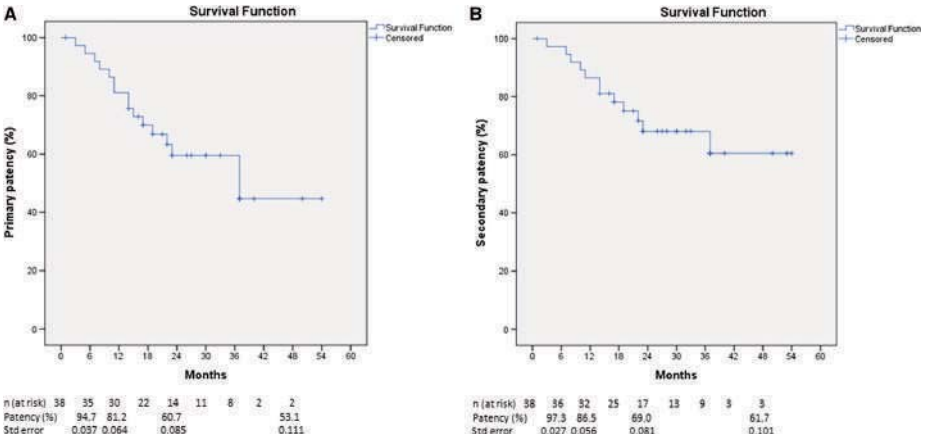


**Fig. 1** Kaplan–Meier survival curves of estimated primary (**A**) and secondary (**B**) patency

48 months (53.1%). These encouraging rates at 6, 12, 18, 24, 36, and 48 months may be the result of DEB selection for the particular lesions in radiocephalic AVFs.

During our follow-up period, recurrent stenosis in the juxta-anastomotic region occurred in only three patients. This promising result may be due to the relatively small sample group. Mortamais et al. [28] reported that residual stenosis after the intervention, stenosis length, and time before the first restenosis significantly increase repeated interventions. On the other hand, Rajan et al. [8] demonstrated that no clinical or anatomic variable affects patency outcome.

The study had some limitations. The retrospective study design was the major limitation of the present study. Second significant limitation was the lack of a control group who were treated by plain balloons. Another limitation was the relatively small sample size of the patient group.

In conclusion, DEB angioplasty is a safe, effective treatment method with high primary patency rates even at long terms. The results we gained in this study demonstrate that JASs in distal radiocephalic AVFs can be effectively treated with DEBs and AVFs can be used safely for years after DEB angioplasty.

**Acknowledgements** This study was carried out in Dokuz Eylul University Faculty of Medicine, Izmir, Turkey.

**Compliance with Ethical Standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical Approval** For this type of study, formal consent is not required. Ethics committee approval was received for this study from the local ethics committee.

**Informed Consent** Informed consent was obtained from all individual participants included in the study.

**Consent for Publication** Consent for publication was obtained for every individual person's data included in the study.

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JVA
ISSN 1129-7298

J Vasc Access 2016; 00 (00): 000-000
DOI: 10.5301/jva.5000508

ORIGINAL ARTICLE

# Systematic review of drug eluting balloon angioplasty for arteriovenous haemodialysis access stenosis

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## ABSTRACT

**Background:** Native or prosthetic arteriovenous (AV) fistulas are preferred for permanent haemodialysis (HD) access. These are marked with circuit steno-occlusive disease leading to dysfunction or even failure. Late failure rates have been reported as high as 50%. Standard angioplasty balloons are an established percutaneous intervention for HD access stenosis. Reported restenosis rates remain high and practice guidelines recommend a wide 6-month primary patency (PP) of at least 50% for any intervention. Neointimal hyperplasia is one of the main causes for access circuit stenosis. Drug eluting balloon (DeB) angioplasty has been proposed as an alternative intervention to reduce restenosis by local drug delivery and possible inhibition of this process.
**Purpose:** To systematically assess the reported efficacy and safety of DeB angioplasty in percutaneous management of prosthetic and autologous HD access stenosis.
**Methods:** Protocol for the review was developed following the PRISMA-P 2015 statement. An electronic database (Medline, EMBASE, Clinical Trials.gov and Cochrane CENTRAL) search was conducted to identify articles reporting on the use of DeB intervention in HD AV access. Backward and forward citation search as well as grey literature search was performed. The MOOSE statement and PRISMA 2009 statement were followed for the reporting of results. Data from the included studies comparing DeBs with non-DeBs were pooled using a random effects meta-analysis model and reported separately on randomised and non-randomised studies.
**Results:** Six studies reported on 254 interventions in 162 participants (mean 27 ± 10 SD). The pooled mean and median duration of follow-up was 12 and 13 months (range 6-24 months). These comprised two randomised control trials (RCTs) and four cohort studies. Participant's mean age was 64 ± 5 years and 61% were male. Target lesions (TLs) ranged from under 2 mm to 5.9 mm and 51 were reported as de novo stenosis. Device failure described as wasting of the DeB was reported in two studies (55% and 92.8%). At 6 months TL PP was reported between 70% to 97% for DeBs in the RCTs and cohort studies, and 0% to 26% for non-DeBs. TLs treated with DeBs were associated with a higher primary patency at 6 months as compared to non-DeB balloons (RCTs: odds ratio [OR] 0.25, 95% CI 0.08 to 0.77 and $I^2$ = 19%, cohort studies: OR 0.10, 95% CI 0.03 to 0.31 and an $I^2$ = 20%). No procedure-related major or minor complications were reported.
**Conclusions:** Current literature reports DeBs as being safe and may convey some benefit in terms of improved rate of restenosis when used to treat AV access disease. However, this body of evidence is small and clinically heterogeneous. A large multicentre RCT may help to clarify the role of DeBs in the percutaneous treatment of AV HD access stenosis.

**Keywords:** Angioplasty, Arteriovenous fistula, Drug coated material, Drug eluting balloon, Meta-analysis, Systematic review

## Introduction

Native or prosthetic arteriovenous (AV) fistulas are preferred for permanent haemodialysis (HD) access as compared to central venous catheters (1-4). These are marked with steno-occlusive disease that leads to access dysfunction and inadequate HD. Late failure rates have been reported as high as 50% (5, 6). Neointimal hyperplasia (NIH) is one of the main causes for access stenosis and resultant failure (7-9). Standard angioplasty balloons are an established percutaneous intervention in access stenosis management. Balloon dilation results in intimal trauma and ensues a cycle of hyperplastic repair and possible further stenosis (10). Reported restenosis rates are high and practice guidelines recommend a wide 6-month access primary patency of at least 50% for any intervention (1-4). Recurrent stenosis and access dysfunction require repeat intervention. This translates in increasing morbidity and healthcare cost (11-13). Access options are limited and further diminish

**Accepted:** November 30, 2015
**Published online:** February 5, 2016

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with each fistula failure. With conventional dilatation and local drug delivery for NIH, drug eluting balloon (DeB) angioplasty has been proposed as an alternative to reduce time to restenosis in AV access intervention (10, 14, 15).

## Objectives

Local delivery of anti-proliferative drugs with coated materials such as balloons and stents have shown promising results in the coronary and peripheral circulation (16-19). Reducing rates of re-intervention may provide benefit of reducing risk from multiple interventions, repeat hospitalizations and perhaps improve long-term patency rates. The safety and efficacy of DeBs in HD access intervention is unclear. The aim of this study is to systematically assess the reported efficacy and safety of DeB angioplasty in percutaneous management of prosthetic and autologous HD access stenosis.

## Methods

### *Study selection*

The review advisory group (RAG) developed a protocol for the review following the PRISMA-P 2015 statement (20). Details of the RAG, including their expertise, were provided to the editors of this Journal. The MOOSE and PRISMA statements were followed for the reporting of results (21, 22). Data extraction tables were predefined prior to literature search. An electronic database search strategy with specific keywords, MeSH terms and text words was developed. This was used to identify landmark papers from relevant electronic databases (Medline, EMBASE and the Cochrane Central register of controlled trials). In conjunction with a research librarian, a final strategy was developed and applied (Appendix with search strategies was provided to editors of this Journal). Search was limited to English language and to time period from 1990 to present. Following duplicate removal, abstracts thus identified were screened online, in duplicate and following pre-set eligibility criteria, using Abstrackr® (23). All disagreements were discussed between the screening authors and the RAG. Full text articles were also reviewed in duplicate. Backward and forward citation search of identified full text articles using Google Scholar® was carried out. Grey literature search was guided by the RAG and included content experts. Pre-set criteria for inclusion and exclusion were based on patient population, target disease and index treatment.

### *Data collection and analysis*

Data were extracted in duplicate for each study and populated predefined tables in Microsoft Excel® for Windows® (Microsoft, Redmond, WA, USA). All disagreements and changes were discussed between screening authors and the RAG. Data collection tables were drafted prior to analysis. Primary outcomes were target lesion revascularisation (TLR) rate comparison and access survival. Data were imported into RevMan (RevMan Version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) for further synthesis and analysis. Analysis of the randomised controlled trials (RCTs) and cohort studies was carried out separately, following practical guidelines for inclusion of non-randomised trials (24, 25). Where there were concerns regarding missing data, contact with article authors was advised by the RAG. Pooled means and medians for continuous outcome variables was carried out and included range and standard deviation. The odds ratio (OR) for each outcome was calculated from individual studies and pooled with the Mantel-Haenszel random-effects method using RevMan. As selection bias can be a feature of cohort studies, this statistical model was decided to be an appropriate measure of outcome. Statistical heterogeneity was assessed with the $Chi^2$ test, with p values <0.10 suggesting significant heterogeneity. Inconsistency across the trials was assessed using $I^2$, where $I^2$<25% suggests mild, $I^2$ between 25% and 50% suggests moderate, and $I^2$>50% suggests extensive statistical inconsistency. Risk of bias assessment was carried out in duplicate using questionnaire assessment provided within RevMan. Results were matched for disagreements and resolved by consensus between authors and the RAG. Publication bias was visual inspection in Deeks' funnel plot. Details of pre-planned subgroup analysis, investigation of heterogeneity and sensitivity analysis were provided to editors of the Journal in following the PRISMA-P statement in the protocol of the study.

## Results

Search results are provided in the PRISMA flow diagram (Fig. 1). After removal of duplicates, 638 abstracts were screened. Abstracts were excluded at this stage if they did not meet the pre-set inclusion and exclusion criteria. In total, nine full text articles were reviewed for eligibility. One was excluded as being a publication from the same group with duplicate data, two were reporting on the wrong target disease and two were in the wrong population. Following backward bibliographic and forward citation search and grey literature search, one further article was included.

### *Description of studies*

The use of DeBs was assessed in a total of six original studies published literature (26-30). These collectively reported on 254 interventions in 162 participants (mean 27 ± 10 SD). The pooled mean and median duration of follow-up was 12 and 13 months (range 6-24 months). There were two single-centre RCTs which compared the use of DeBs for recurrent stenosis with standard angioplasty balloons. The remaining were single-centre prospective or retrospective cohort studies.

### *Randomised controlled trials*

The first trial, the "Drug Eluting Balloon Angioplasty for Dialysis Access Treatment" trial randomised 40 patients with venous outflow stenosis between the intervention and control arms (31). They used an IN.PACT balloon dilation catheter (Invatec-Medtronic, Brescia, Italy) for the intervention arm and Ultra-Thin Diamond and Blue Max PTA (Boston Scientific, Natick, MA, USA), Profiler (Angiodynamics, Latham, NY, USA), or Dorado PTA balloon dilator catheter (Bard Peripheral Vascular, Tempe, AZ, USA) for the control arm patients. The

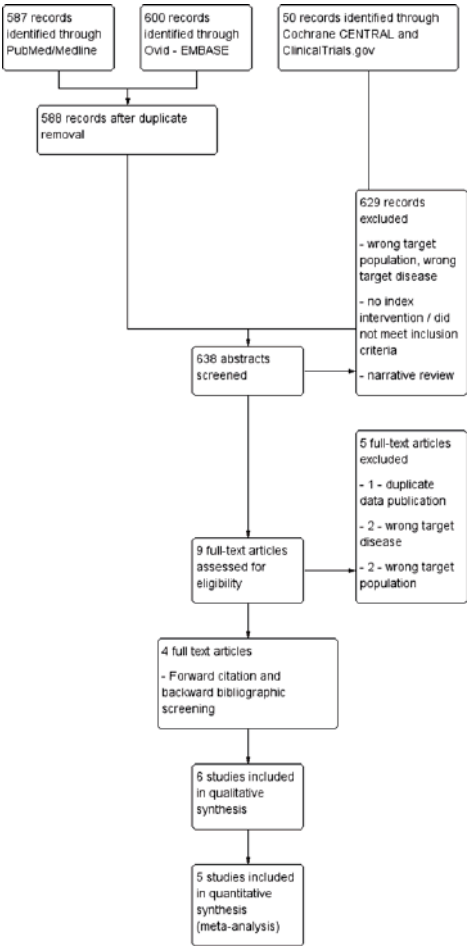


**Fig. 1 -** PRISMA flowchart of study.

authors described device failure as a need for further post-dilation after use of a DeB, because of suboptimal angioplasty. Technical success was a <30% residual stenosis diameter measured immediately after angioplasty regardless of post-dilation. The second trial, the "Prospective Randomized Trial Comparing DEB Versus Conventional PTA for the Treatment of HD AVF or AVG stenoses (DEBAPTA)" trail randomised 30 patients with a recurrent stenosis anywhere along the access circuit (Tab. I). They used the IN.PACT balloon dilation catheters (Invatec-Medtronic, Brescia, Italy) and compared to conventional balloon. The author described anatomical success as <30% diameter measured immediately after angioplasty.

**TABLE I -** Characteristics of randomised controlled trials included in analysis

| | Kitrou et al (29); Katsanos et al (31) | Teo et al (30) |
|---|---|---|
| **Study type** | **RCT[1], single-centre** | **RCT[1], single-centre** |
| Number of patients | 40 | 30 |
| Level of TL | Venous outflow | NS |
| Used for HD | At least 1 session of HD | > 3 months post-formation |
| Recurrent or de novo | NS | Recurrent |
| Inflation time | 1 min at nominal pressure | NS |
| Pre- and post-dilation | No predilation post-dilate if necessary | NS |
| Study device and substance | IN.PACT®[2] FreePac[3] | IN.PACT®[2] FreePac[3] |

RCT = randomized controlled trial; TL = target lesion; SG = stent graft; HD = haemodialysis; NS = not stated.
[1] Detailed study protocol available at clinicaltrials.gov and Cochrane register of clinical trials.
[2] IN.PACT® balloon dilation catheters (Invatec-Medtronic, Brescia, Italy).
[3] FreePac 3 μg/mm² a paclitaxel-eluting formulation that contains hydrophilic urea paclitaxel.

***Cohort studies***

Two prospective studies reported on juxta-anastomotic and venous outflow stenosis intervention; however, one of these studies did not have a comparator arm (28, 32). The results of this non-comparison study reported on survival after radio-cephalic fistulae juxta-anastomotic intervention, and are not included in the meta-analysis (Tab. II). One retrospective cohort reported on the results of a DeB made in-house for non-malignant central venous stenosis (26). The authors reported their experience of using conventional balloons as well as high pressure and cutting angioplasty balloons and compared it to DeBs. The last cohort reported from a prospectively collected database. They reported its use in the case of in-stent stenosis for nitinol stents placed along a vascular access circuit (27). Both functioning and non-maturing fistulas were included in their results (Tab. III).

***Clinical outcomes and risk of bias***

DeBs were not associated with any major or minor complications. Procedural success rates were reported as 100% across the studies. Anatomical success or failure, device failure or success was described in the studies as wasting of the DeB with or without further post-dilation. In the two RCTs, this was 55% (n = 11/20) and 92.8% (n = 13/14). The second RCT also reported on device failure in the comparator group (81.3% n = 13/16). Target lesions (TLs) ranged

**TABLE II -** Cohort study patency and survival, not included in meta-analysis

| | Time period | TL Primary patency | TL Secondary patency | VA Primary patency | VA Secondary patency |
|---|---|---|---|---|---|
| Patanè et al 2014 (28) | 6 months | 96.1 | 100 | 96.1 | NS |
| | 12 months | 90.9 | 100 | 81.8 | 95.41 |
| | 24 months | 57.8 | 94.7 | 57.8 | 94.7 |

TL = target lesion; VA = vascular access; NS = not stated.

**TABLE III -** Characteristics of cohort studies included in analysis

| | Lai et al (32) | Swinnen et al (27) | Massmann et al (26) |
|---|---|---|---|
| **Study type** | **Prospective** | **Retrospective** | **Prospective** |
| No. of patients | 10 | 31 | 25 |
| Level of TL | RC swing | If suitable for DeB | Central venous |
| Used for HD | NS | On HD = 28 non maturing = 3 | All |
| Recurrent or de novo | Recurrent | Recurrent | Recurrent |
| Inflation time | 1 min | NS | 1 min |
| Pre- and post-dilation | Both | Predilated only | Both[1] |
| Study device and substance | SeQuentPlease®[2] PACCOCATH®[3] | IN.PACT®[4] FreePac[5] | Custom-made[6] Elutax-SV®[7] |

RC = radiocephalic; HD = haemodialysis; NS = not stated.
[1] Post dilated if significant wasting of balloon.
[2] SeQuent Please® (B Braun, Berlin, Germany) balloon catheters.
[3] PACCOCATH – (Bayer Shering Pharma AG, Berlin, Germany) coating is a mixture of iopromide and paclitaxel.
[4] IN.PACT® balloon dilation catheters (Invatec-Medtronic, Brescia, Italy).
[5] FreePac 3 µg/mm$^2$ a paclitaxel-eluting formulation that contains hydrophilic urea paclitaxel.
[6] Custom made using standard over-the-wire.
[7] Elutax-SV - paclitaxel 2 µg/mm$^2$ (Aachen Resonance, Aachen, Germany).

from under 2 mm to 5.9 mm and 51 were reported as de novo stenosis. At 6 months, TL primary patency was reported between 70% to 97% for DeBs and 0% to 26% non-DeBs. TLs treated with DeBs were associated with a higher primary patency at 6 months as compared to non-DeB balloons (RCTs: OR 0.25, 95% CI 0.08 to 0.77, p for statistical heterogeneity = 0.27 and $I^2$ = 19%, cohort studies: OR 0.10, 95% CI 0.03 to 0.31, p for statistical heterogeneity = 0.29 and an $I^2$ = 20%), (Fig. 2). A similar trend was observed at 12 months with a proportional increase in number of events lower in the DeB group as compared to the control group. This was with a lower number of patients, as not all of the studies had 12-month follow up data reported (Fig. 3). Despite the overall beneficial effect, a wider confidence interval and possibly a reduction of longer-term benefit was noted for the studies at 12 months. Performance and detection bias was considered as high in the non-RCTs. Reporting bias was considered as high or unclear. Risk of bias assessment of the RCTs was low 57% (n = 8/14 questionnaire assessment) or unclear 43% (n = 6/14). The cohort studies were assessed as having a high selection, performance and detection bias (57%, 12/21) (Figs. 2, 3). Visual assessment of publication bias with Deeks' funnel plot is provided in Figure 4 showing the variable results across the studies.

## Discussion

Neointimal hyperplasia (NIH) in AV dialysis access is one of the main causes of stenosis and circuit dysfunction or failure. Its pathogenesis is well described in literature as being divided into upstream and downstream events (7, 33). The initial upstream events not only refer to the trauma of surgical creation, but also to the ongoing repeated dialysis needle injury, percutaneous intervention, endothelial dysfunction due to uraemia and circuit haemodynamic disturbances. These in turn lead to downstream endothelial injury and migration of smooth muscle cells (SMCs). For an angioplasty balloon to be effective, baric dilation has to tear the intimal or neointimal layer at the level of the stenosis. Part of the internal elastic lamina and tunica media may also be effectively ruptured in order to avoid elastic recoil of the stenosis. This mechanical trauma is followed by a biological cascade of events for repair of the vessel through formation of a neointima (34). Endothelial cells (ECs) regulate further progression by release of nitric oxide. This decreases the recruitment of inflammatory cells and collagen synthesis by vascular SMCs (35). ECs can lose their ability to release nitric oxide as result, and the neointima formed may be hyperplasic, and in turn result in reoccurrence of the stenosis (34, 36). NIH has also been noted in specimens from immature failing AV fistulas (37). DeBs are coated with

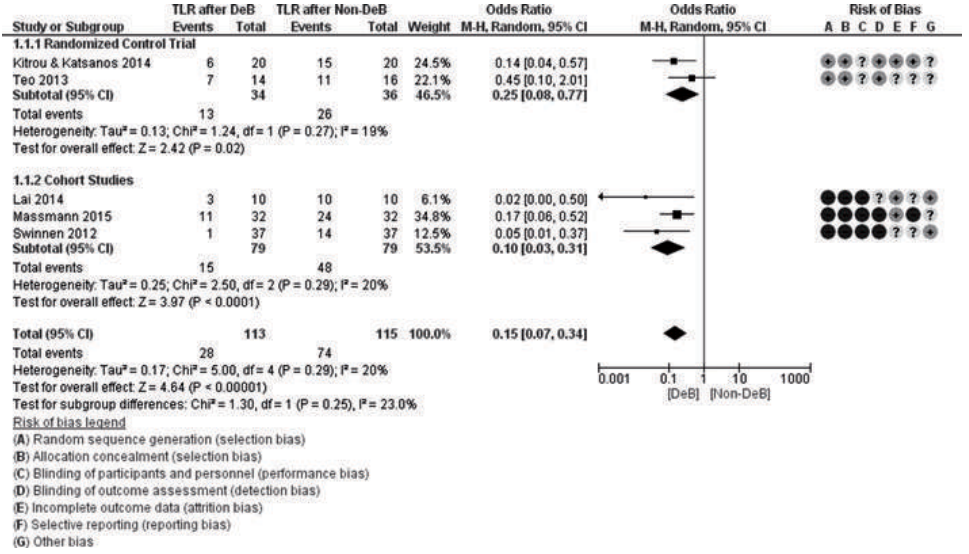


**Fig. 2 -** Analysis of target lesion revascularisation at 6 months using random effect model. Results of the risk of bias assessment for each study meta-analysed is also included with legend. TLR = target lesion revascularisation; M-H = Mantel-Haenszal model; CI = confidence interval.

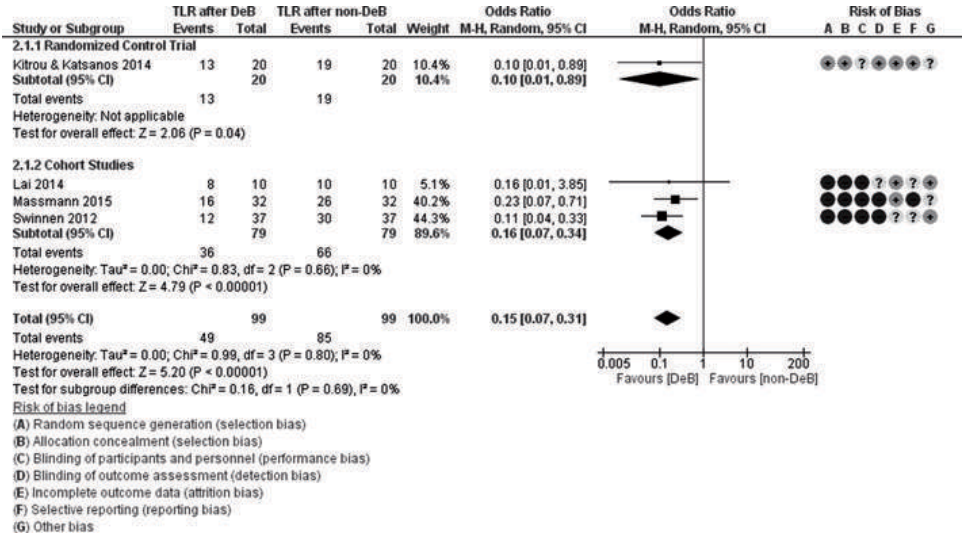


**Fig. 3 -** Analysis of target lesion revascularisation at 12 months using random effect model and risk of bias assessment results.

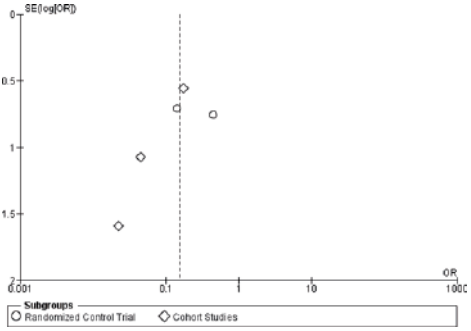


**Fig. 4 -** Deek's funnel plot of all included studies.

lipophilic rapidly absorbing, cytostatic anti-neoplasic substance. Experimental and *in vitro* studies of AV animal models have shown a sustained antiproliferative effect on vascular SMCs (14, 38-40).

Several publications have commented on safety and a possible superior efficacy of using DeBs in the peripheral and coronary circulation (18, 19, 41). Recent trends from these has peaked interest in their use for dialysis access intervention (10, 42). Their use has anecdotally been reserved for lesions that maybe considered difficult to treat due to recurrence. Our study aimed to present the first summation of its use in AV dialysis access to date in literature and perhaps clarify if further cautious exploration could be advocated. Overall, the use of DeB as compared to non-DeB may confer a benefit by reducing time to re-stenosis and subsequent intervention. Greater benefit was noted in the non-randomised studies; however, the risk of selection bias was understandably higher. At 12 months, the confidence interval for interpretation of beneficial results from RCTs was wider than at 6 months. Whether this would implicate an impact on survival of access circuits will require longer-term follow-up data.

Currently available studies had clinical heterogeneity with non-uniform level of intervention. Larger subgroup exploration may help in identifying lesion characteristics most or least responsive to DeBs. Important subgroups that were mentioned in literature include: fistula fashioning - radiocephalic, brachiocephalic, brachiobasilic, etc.; level of stenosis: juxta-anastomotic, outflow, cephalic arch, central veins; pre- and post-dilation of treated lesions; characteristics of fistula and lesion: primary, recurrent, post-thrombosis, multiple level, mature fistula being used, immature fistula not being used; patient clinical diversity derived from past medical history (43-45). Although these were proposed to be undertaken at protocol development stage, data available from studies could not be explored due to small total cohort size. Other confounders that could be argued include use of different surveillance methods for detection of restenosis (46). These can include clinical examination, dialysis parameters, ultrasonography, CT and MR imaging, or even angiography. With each modality, risks versus benefits and accuracy have to be weighed. An example could be contrast administration in a pre-dialysis patient with residual renal function, or even cumulative radiation exposure (47, 48). Utilising the same clinical and imaging inclusion criteria of a target lesion, for both primary and repeat intervention, could aide in translation of trial results. Functional and clinical parameters in association with imaging have been recommended (46). Further studies may consider inclusion of these variables for exploration. In one study design, the comparator intervention was within the same patient access circuit. This may conflict in outcome results as time to thrombosis is an important outcome measure and multiple level disease would carry a higher risk. Our meta-analysis has several limitations. It is at present underpowered to detect differences and there is clinical heterogeneity. A potential signal of benefit does advocate exploration. Further carefully planned studies may gather to form a stronger body of evidence and repeat meta-analysis with planned subgroup and sensitivity analysis would be beneficial.

## Authors' conclusions

Current literature suggests DeBs as safe and may convey some benefit in terms of improved rate of restenosis when compared to standard angioplasty balloons when used to treat AV access disease. However, this body of evidence is small and there is clinical heterogeneity. Interpretation of results from cohort studies is recommended with an appropriate degree of caution. Adequately powered, larger multicentre RCTs may help to clarify the role of DeBs in the percutaneous management of arteriovenous haemodialysis access stenosis.

## Disclosures

Financial support: This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration, under grant agreement no 324487.
Conflicts of interest: The authors have no conflicts of interest to declare in relation to this study.

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# A systematic review and meta-analysis of drug-coated balloon versus conventional balloon angioplasty for dialysis access stenosis

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## ABSTRACT

**Background:** Arteriovenous fistulas for patients undergoing hemodialysis (HD) are at high risk of stenosis. Despite conventional balloon angioplasty (CBA), restenosis rates are high. The use of a drug-coated balloon (DCB) may offer an alternative to reduce restenosis.

**Methods:** This study has been performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. An electronic search on MEDLINE, Embase, and the Cochrane Library was performed to identify articles evaluating DCB angioplasty for patients with HD access stenosis. Risk ratios (RRs) of primary patency were pooled, and relevant subgroup and sensitivity analyses were conducted.

**Results:** There were 17 studies (8 randomized controlled trials [RCTs], 9 cohort studies) included, comprising a total of 1113 stenotic dialysis accesses, of which 54.7% underwent DCB angioplasty and 45.3% underwent CBA. There was a significantly superior 6-month (RR, 0.57; 95% confidence interval [CI], 0.44-0.74; $P < .00001$; $I^2 = 62\%$) and 12-month (RR, 0.73; 95% CI, 0.63-0.84; $P < .0001$; $I^2 = 53\%$) primary patency in the DCB angioplasty group in comparison to the CBA group (71.0% vs 49.2% at 6 months; 44.2% vs 20.6% at 12 months). Subgroup analyses of study design (RCTs, cohort studies) showed similar trends. Sensitivity analyses by excluding one poor-quality RCT and those employing the crossover analysis design also showed similar results. Studies investigating central venous stenosis showed significantly better 6-month (RR, 0.57; 95% CI, 0.41-0.79; $P = .0009$; $I^2 = 67\%$) and 12-month (RR, 0.69; 95% CI, 0.56-0.85; $P = .0004$; $I^2 = 64\%$) primary patency in the DCB angioplasty group in comparison to the CBA group. The pooled rate of minor complications was low in both the DCB (1.1%) and CBA (0.9%) groups.

**Conclusions:** DCB angioplasty appears to be a better and safe alternative to CBA in treating patients with HD stenosis in terms of 6- and 12-month primary patency. However, a larger trial is warranted to establish these findings. (J Vasc Surg 2019;70:970-9.)

**Keywords:** Dialysis access stenosis; Drug-coated balloon; Conventional balloon angioplasty; Central venous stenosis

The clinical practice guidelines for vascular access[1] recommend a fistula-first option in patients who choose hemodialysis (HD) as their mode of renal replacement therapy. However, long-term patency rates at 18 months are dismally low at 51%.[2] A major cause of access dysfunction is the phenomenon of neointimal hyperplasia,[3,4] and risk factors include increasing age, diabetes, smoking, and peripheral vascular disease.[5]

Percutaneous balloon angioplasty has been heralded as the preferred treatment modality for stenosis of HD access. In balloon dilation, the intimal layer, internal elastic lamina, and parts of the tunica media are being forcefully torn during the process to prevent elastic recoil. However, a biologic repair cascade ensues in response to the vascular trauma, leading to remodeling.[6] Unsurprisingly, the 6-month cumulative patency rates after percutaneous balloon angioplasty have been reported to be as low as between 23% and 38%.[7,8]

The need for repeated interventions increases patient morbidity and health care cost,[9] hence warranting the need for an alternative solution. Advancement in the technology of drug-eluting balloon has taken strides. Drug-coated balloons (DCBs) were initially used in coronary and lower limb interventions[10,11] but are now commonly used in arteriovenous fistulas.[12] Earlier experimental studies[13,14] have concluded that paclitaxel exerts an antiproliferative effect on vascular smooth muscle cells, corroborated by results from clinical trials.[15,16] Although a systematic review of the same subject has been published previously,[17] several new studies have now emerged,[18-21] some of which reported contrasting findings. It is the

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Author conflict of interest: none.

Additional material for this article may be found online at www.jvascsurg.org.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214



https://doi.org/10.1016/j.jvs.2019.01.082

aim of this systematic review and meta-analysis to comprehensively appraise the most up-to-date pool of evidence comparing DCB angioplasty against conventional balloon angioplasty (CBA) for both primary and recurrent stenosis in patients undergoing HD.

## METHODS

This systematic review and meta-analysis was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.[22]

**Literature search.** An electronic search was performed on the MEDLINE, Embase, and Cochrane Library databases from date of inception to August 24, 2018, to identify all published and indexed studies evaluating use of DCBs in patients with HD access stenosis. A combination of MeSH and non-MeSH search terms using Boolean operators was used in Medline: (drug eluting balloon.m.p. OR paclitaxel-coated balloon.m.p.) AND (hemodialysis.m.p. OR Renal Dialysis/ OR dialysis access.m.p. OR arteriovenous fistula.m.p. or Arteriovenous Fistula/). A manual search of the reference lists of included studies was performed to identify additional studies. Conference abstracts were considered to reduce the risk of publication bias.

**Study selection.** Two reviewers (I.W., H.Y.) screened the studies independently for potential inclusion, first by abstract and title screening. Thereafter, full texts of studies preliminarily included were obtained and reviewed in their entirety to confirm inclusion. Conflicts were resolved by consensus or by appeal to the senior author.

Any randomized or nonrandomized study that evaluated the use of DCBs in patients with vascular access stenosis was included. Comparative studies, noncomparative studies, and studies investigating HD patients with central venous stenosis were also included. Studies of the following designs were excluded: non-English language, case reports and case series, animal and laboratory studies, literature reviews, and conference abstracts with no extractable data.

**Data extraction.** Primary outcomes of interest included primary patency measured at 6 and 12 months. Secondary outcomes included minor and major complications. Two authors (I.W., H.Y.) independently extracted the following data from each study independently: first author, year, type of publication, mean age, male sex, recurrent or de novo lesion, inflation time, predilation or postdilation, brand of device and paclitaxel, level of target lesion, and primary and secondary outcomes of interest. Conflicts were resolved by consensus or by appeal to the senior author.

**Quality assessment.** The quality of randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias tool, encompassing the following seven domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. For cohort studies, the Newcastle-Ottawa Scale[23] was employed to assess the quality of included studies. It comprises aspects of patient selection, comparability of study groups, and outcome assessment, and studies can be awarded a maximum of 9 points. Noncomparative studies were awarded a maximum of 6 points. Publication bias was

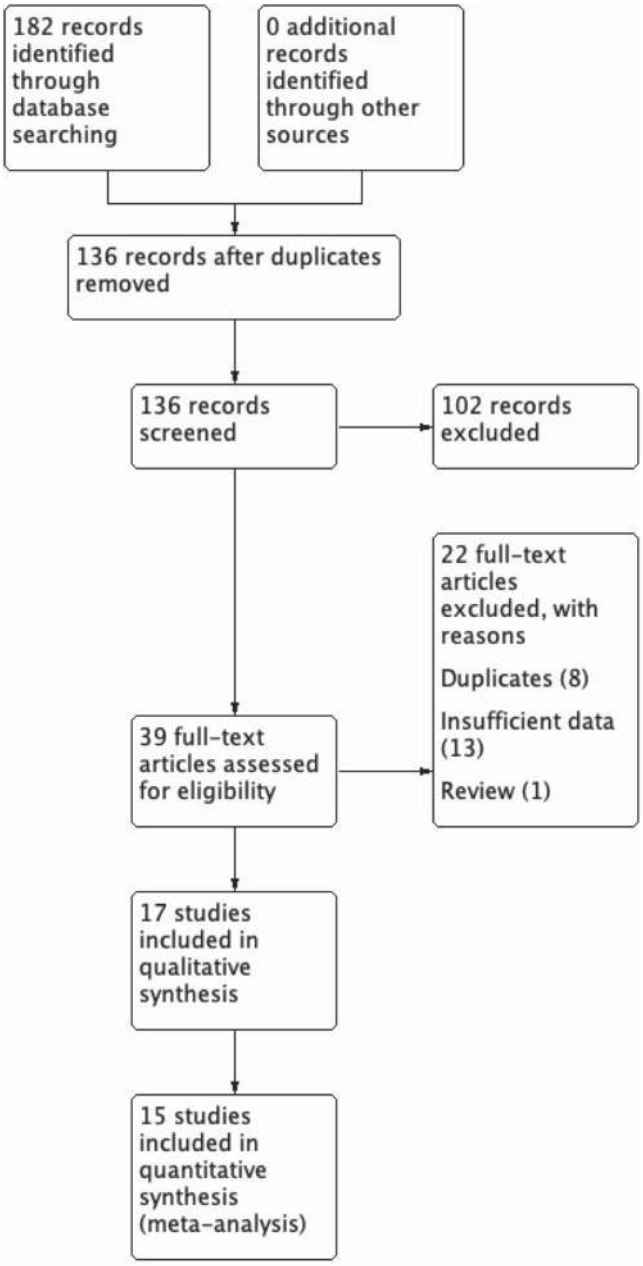


**Fig 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

**Table.** Baseline characteristics of included studies

| First author, year | Study design | Comparison | Total No. of fistulas (PCB/control) | Level of TL | Recurrent/de novo lesion |
|---|---|---|---|---|---|
| Teo, 2013 | RCT | PCB vs CBA | 30 (14/16) | NR | Recurrent |
| Lai, 2014 | PC[a] | PCB vs CBA | 20 (10/10) | RC swing | Recurrent |
| Patane, 2014 | PC | PCB only | 26 | Venous outflow | 7/19 |
| Kitrou, 2015 | RCT | PCB vs CBA | 40 (20/20) | Venous outflow | NR |
| Swinnen, 2015 | RC | PCB vs CBA | 74 (37/37) | NR | Recurrent |
| Verbeeck, 2016 | RC | PCB only | 70 | Venous outflow | Recurrent |
| Roosen, 2017 | RCT | PCB vs CBA | 34 (16/18) | Venous outflow | Recurrent |
| Lucev, 2018 | RC | PCB vs CBA | 62 (31/31) | Venous outflow | De novo |
| Maleux, 2018 | RCT | PCB vs CBA | 64 (33/31) | Venous outflow | 32/32 |
| Qamhawi, 2018 | RC[a] | PCB vs CBA | 52 (26/26) | Venous outflow | 8/44 |
| Trerotola, 2018 | RCT | PCB vs CBA | 285 (141/144) | Venous outflow, RC swing, inflow, cannulation zone, cephalic arch, anastomotic | 203/82 |
| Zheng, 2018 | RC[a] | Combined PCB + CBA | 12 | Venous outflow, access zone | Recurrent |
| Massmann, 2015 | PC | PCB vs CBA | 25 (10/15) | Central venous | Recurrent |
| Kitrou, 2017 | RCT | PCB vs CBA | 40 (20/20) | Central venous | 27/13 |
| Hongsakul, 2018 | RC[a] | PCB vs CBA | 32 (16/16) | Central venous | Recurrent |

*CBA,* Conventional balloon angioplasty; *HD,* hemodialysis; *NR,* not reported; *PC,* prospective cohort; *PCB,* paclitaxel-coated balloon; *RC,* retrospective cohort; *RC swing,* "swing segment" of a distal radial-cephalic native arteriovenous fistula; *RCT,* randomized controlled trial; *TL,* target lesion.
[a]Crossover analysis design.

assessed by judging the degree of symmetry in the funnel plot when 10 or more studies were included in an outcome.

**Statistical analysis.** The risk ratio (RR) for primary patency was calculated from each study and pooled by the Mantel-Haenszel method with 95% confidence intervals (CIs) using Review Manager software (RevMan 5.3; The Cochrane Collaboration, Copenhagen, Denmark). Statistical heterogeneity was assessed using the $I^2$ statistic, whereby a value >50% is deemed to be of substantial heterogeneity. In such instances, a random-effects meta-analysis was conducted to account for interstudy heterogeneity. Otherwise, a fixed-effects model was chosen when the $I^2$ statistic value was ≤50%. A subgroup analysis was performed to differentiate cohort studies from RCTs as well as to segregate studies investigating HD patients with central vein stenosis. To ensure that findings prevail with better-quality data, various sensitivity analyses were performed. For instance, studies deemed to be of poor quality, those including both fistulas and grafts, and those employing a crossover analysis were excluded in sensitivity analysis. Noncomparative studies were not included in the meta-analysis but instead were narratively reviewed.

## RESULTS

**Systematic search.** The systematic search revealed 182 studies, of which 136 remained after duplicate removal. After title and abstract screening, 39 studies remained and were reviewed in their entirety. A total of 17 studies were included after full-text review: 8 RCTs,[12,15,19-21,24-26] 6 retrospective studies,[18,27-31] and 3 prospective cohort studies.[32-34] A total of 15 studies were included in the meta-analysis. The systematic search process is depicted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Fig 1).

**Characteristics and risk of bias of included studies.** Among the cohort studies, two were noncomparative,[31,33] whereas four studies[18,28,30,32] employed a crossover design analysis whereby patients served as their own control. A total of 1113 stenotic dialysis accesses were included, of which 609 (54.7%) underwent DCB angioplasty and 504 (45.3%) underwent CBA. In terms of diagnostic modality, 10 studies employed angiography (>50% stenosis), 4 studies measured inflow rate (<300 mL/min), 2 studies used clinical diagnosis, and 1 study employed catheter-directed venography. All studies looked at interventions for arteriovenous fistulas, except for two studies[15,25] that included both

**Table.** Continued.

| Inflation time, minutes | Predilation or postdilation | Brand of device and paclitaxel | Used for HD | Age, years, PCB/control | Male sex, %, PCB/control |
|---|---|---|---|---|---|
| NR | NR | IN.PACT FreePac | >3 months after formation | NR/NR | NR/NR |
| 1 | Both | SeQuentPlease PACCOCATH | NR | 67.2 ± 9.4 for all | 60 for all |
| >2 | Postdilation | IN.PACT FreePac | NR | 71 ± 13 for all | 80.8 for all |
| 1 | Postdilation | IN.PACT FreePac | >1 session | 64.3 ± 14.5/57.0 ± 14.2 | 60/70 |
| NR | Predilation | IN.PACT FreePac | 28 on HD, 3 nonmatured | 56.1 ± NR | 48.4 for all |
| 1 | Postdilation | IN.PACT FreePac | Yes | 62.5 ± 13.8 | 75.6 for all |
| NR | NR | Invatec, Medtronic | Yes | Median, 80 (71-86)/median, 83 (78-86) | 43.8/77.8 |
| 3 | Predilation | IN.PACT FreePac | Yes | 62.8 ± 17.2/67.0 ± 8.4 | 51.6/48.4 |
| 2 | Predilation | IN.PACT FreePac | Yes | 69.3 ± 14.9/66.9 ± 17.0 | 72.7/58.1 |
| NR | NR | NR | NR | 72.3 ± 14.0/72.3 ± 14.0 | 53.8/53.8 |
| 2 | Predilation | Lutonix | Yes | 64.0 ± 15.0/61.0 ± 13.0 | 61.7/59.0 |
| 2 | NR | Lutonix | Yes | 63.3 ± 2.7/63.3 ± 2.7 | NR/NR |
| 1 | Both | Custom-made Elutax-SV | Yes | 64.5 ± 11.2/66.8 ± 15.0 | 60/60 |
| 2 | Predilation | Lutonix | Yes | 56.7 ± NR (25-81)/57 ± NR (33-81) | 70/75 |
| 3 | Postdilation | IN.PACT FreePac | Yes | 60.0 ± 14.0/60.0 ± 14.0 | 56.3/56.3 |

arteriovenous grafts and fistulas. Among RCTs, the overall risk of bias was low. Most studies (80%) had high risk of detection and performance bias due to limitations associated with blinding of surgeons and operators. Among cohort studies, the overall risk of bias was low as all studies scored a minimum 7/9 as assessed using the Newcastle-Ottawa Scale (Supplementary Figs 1 and 2, online only). The risk of publication bias was low, given symmetry in Deeks funnel plot (Supplementary Figs 3 and 4, online only). A summary of procedural details, mean age, and sex can be found in the Table.

**Six-month primary patency.** The forest plot of 6-month primary patency rates between the DCB angioplasty and CBA groups is depicted in Fig 2. The 6-month cumulative patency in the DCB angioplasty and CBA groups was 71.0% and 49.2%, respectively. Using a random-effects model, there was a significantly superior 6-month primary patency in the DCB angioplasty group (RR, 0.57; 95% CI, 0.44-0.74; $P < .0001$; $I^2 = 62\%$) in comparison to the CBA group. This would mean that the arteriovenous fistulas of patients in the DCB angioplasty group had a 0.57 times reduced risk for development of stenosis compared with the CBA group. A similar observation was noted in subgroup analysis of cohort studies (RR, 0.41; 95%CI, 0.28-0.60; $P < .00001$; $I^2 = 40\%$) and RCTs (RR, 0.71; 95% CI, 0.52-0.98; $P = .03$; $I^2 = 63\%$), in which the cumulative patency in the DCB angioplasty group was higher than in the CBA group (75.6% vs 36.6% for cohort studies; 69.0% vs 54.7% for RCTs). Given the significant risk of performance, detection, and attrition biases in the RCT by Roosen et al,[21] a sensitivity analysis was performed; this showed a significantly superior 6-month primary patency in the DCB angioplasty group (RR, 0.54; 95% CI, 0.46-0.63; $P < .00001$; $I^2 = 40\%$), and the cumulative patency was higher in the DCB angioplasty group (72.6% vs 49.1%). This was similar as well in both subgroup analyses of RCTs and cohort studies. Another sensitivity analysis was performed by removing four studies that employed a crossover design analysis. The 6-month primary patency remained significantly superior in the DCB angioplasty group (72.4%; RR, 0.61; 95% CI, 0.44-0.84; $P = .003$; $I^2 = 67\%$) in comparison to the CBA group (53.7%). Another sensitivity analysis was performed by removing two studies[15,25] that included both arteriovenous fistulas and grafts, and results were again consistently in favor of the DCB angioplasty group, with a higher cumulative patency (70.3%) compared with the CBA group (48.1%; RR, 0.56; 95% CI, 0.41-0.75; $P = .0001$; $I^2 = 66\%$).

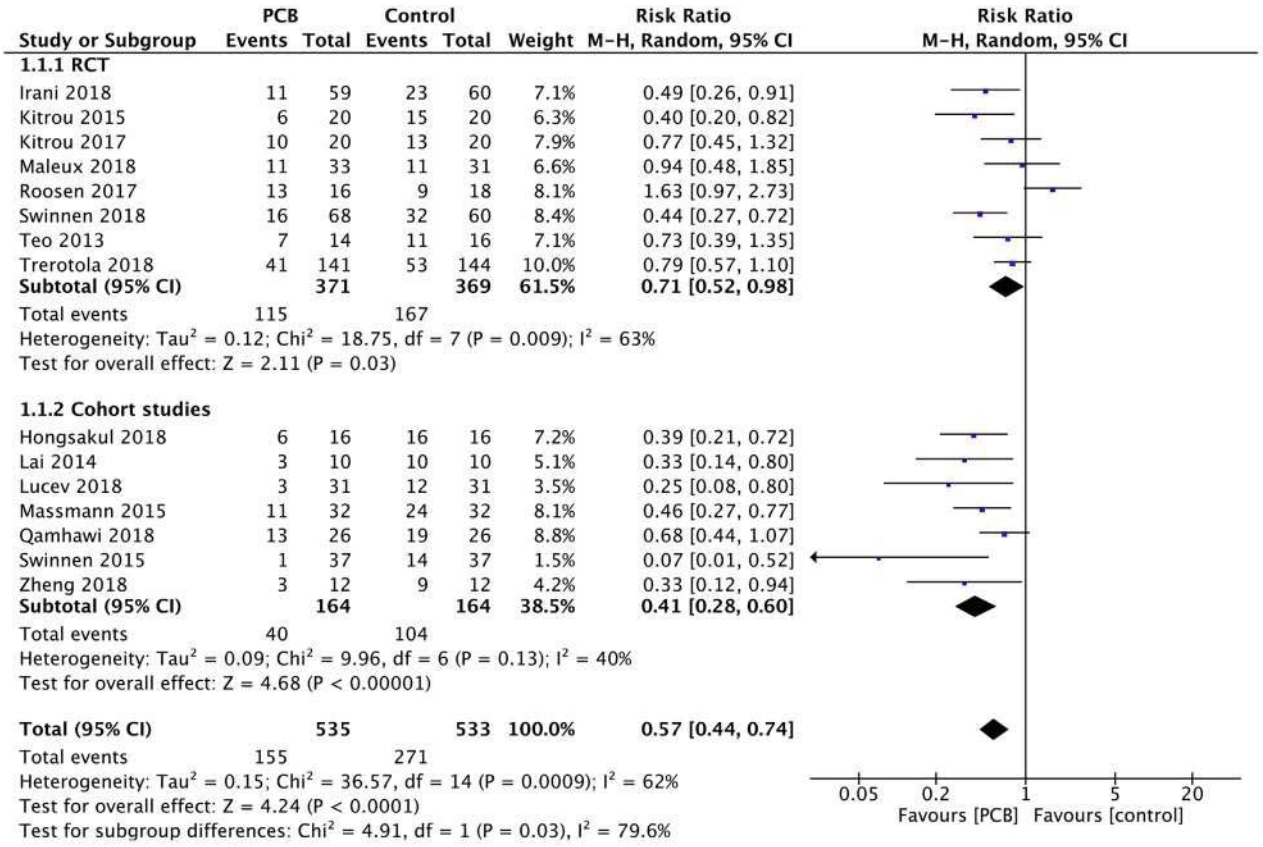


**Fig 2.** Six-month primary patency with subgroup analysis. *CI,* Confidence interval; *M-H,* Mantel-Haenszel; *PCB,* paclitaxel-coated balloon; *RCT,* randomized controlled trial.

**Twelve-month primary patency.** The forest plot of 12-month primary patency rates between the DCB angioplasty and CBA groups is depicted in Fig 3. Similar trends were observed in 12-month primary patency, which was significantly better in the DCB angioplasty group (44.2% vs 20.6%) in comparison to the CBA group (RR, 0.73; 95% CI 0.63-0.84; $P < .0001$; $I^2 = 53\%$). Hence, the use of CBA had a 1.4 times risk for development of stenosis at 12 months compared with DCB angioplasty. Subgroup analysis of RCTs (RR, 0.82; 95% CI, 0.72-0.94; $P = .003$; $I^2 = 10\%$) and cohort studies (RR, 0.62; 95% CI, 0.48-0.84; $P = .0004$; $I^2 = 67\%$) likewise had similar results, hence showing that the DCB angioplasty group had a higher cumulative patency in comparison to the CBA group (38.9% vs 24.4% for RCTs; 51.2% vs 15.9% for cohort studies). A sensitivity analysis was performed by removing the RCT by Roosen et al,[21] and this showed similar results in favor of the DCB angioplasty group, which had a higher cumulative patency rate (45.6% vs 20.8%; RR, 0.69; 95% CI, 0.62-0.76; $P < .00001$; $I^2 = 40\%$). Another sensitivity analysis was performed by removing four studies that employed a crossover design analysis, and the 12-month primary patency remained significantly superior in the DCB angioplasty group (47.2%; RR, 0.71; 95% CI, 0.58-0.86; $P = .0007$; $I^2 = 66\%$) compared with the CBA group (23.6%). An additional sensitivity analysis was performed by removing one study[25] that included both arteriovenous fistulas and grafts, and results were again consistently in favor of the DCB angioplasty group (RR, 0.73; 95% CI, 0.62-0.85; $P < .0001$; $I^2 = 57\%$), in which the cumulative patency rate was higher (43.0% vs 18.2%).

**Central venous stenosis in HD patients.** Given that the maximum diameters of current Food and Drug Administration-approved DCBs, such as the Lutonix (Bard Peripheral Vascular, Tempe, Ariz) and In.PACT Admiral (Medtronic, Santa Rosa, Calif), are too small for central veins, various adjunctive strategies have been described by the authors. In the study by Kitrou et al,[12] predilation was performed with a high-pressure balloon for 2 minutes, followed by the insertion of a 12-mm Lutonix balloon, inflated for 2 minutes. Hongsakul et al[28] performed the angioplasty by using two In.PACT Admiral DCBs (6-7 mm) through the arm and right common femoral vein, inflated at normal pressure (8 atm) for 3 minutes. This was followed by additional dilation with a larger balloon (ATLAS high-pressure balloon; Bard) measuring 12 to 14 mm, inflated at 6 to 10 atm for 2 minutes. Massmann et al[34] employed custom-made DCBs (Elutax-SV; Aachen Resonance, Aachen, Germany), inflated at 14 atm for 1 minute. A random-effects subgroup analysis of studies investigating central venous

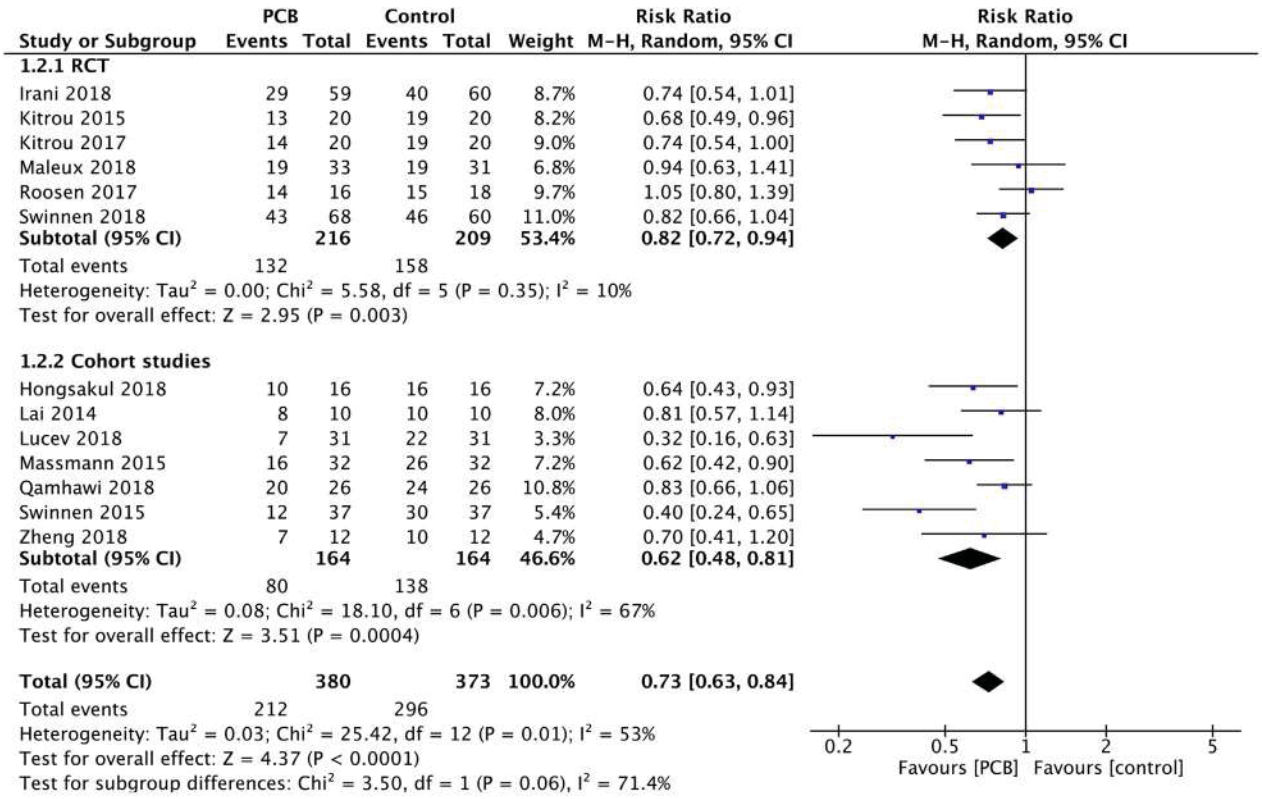


**Fig 3.** Twelve-month primary patency with subgroup analysis. *CI,* Confidence interval; *M-H,* Mantel-Haenszel; *PCB,* paclitaxel-coated balloon; *RCT,* randomized controlled trial.

stenosis also showed significantly superior 6-month primary patency in the DCB angioplasty group (60.3%) in comparison to the CBA group (22.1%; RR, 0.52; 95% CI, 0.35-0.78; $P = .001$; $I^2 = 34\%$; Supplementary Fig 5, online only). Furthermore, the DCB angioplasty group (41.2%) similarly demonstrated superior 12-month primary patency in comparison to the CBA group (10.3%; RR, 0.67; 95% CI, 0.55-0.82; $P = .0001$; $I^2 = 0\%$; Supplementary Fig 6, online only).

**Complications.** With only three studies[20,21,25] reporting complications, the pooled rate of minor complications was low in both the DCB angioplasty (1.1%) and CBA (0.9%) groups. There were no major complications. In one study,[21] there was one case of an allergic reaction to contrast material in the DCB angioplasty group and one case of subtotal fistula occlusion in the control group due to unknown cause. In the study by Irani et al,[25] there was one case of dissection, one case of pseudoaneurysm, and one case of balloon rupture in the DCB angioplasty group, whereas one case of venous rupture was noted in the control group. The cause of complications was not reported in the other study.[20]

**Noncomparative studies.** Two noncomparative studies[31,33] evaluated the efficacy of DCB angioplasty in patients with dialysis access stenosis. Patane et al[33] prospectively evaluated 26 consecutive patients with juxta-anastomotic stenosis of radiocephalic hemodialytic shunt who were treated with DCB angioplasty. Target lesion primary patency rates were 96.1% and 90.0% at 6 and 12 months, respectively. In a more recent retrospective cohort study by Verbeeck et al,[31] the primary patency rates were lower at both 6 months (81.4%) and 12 months (60%).

## DISCUSSION

The conceptual biologic benefit of DCB angioplasty is based on the antiproliferative effects of paclitaxel on vascular smooth muscle cells. Earlier applications of DCB angioplasty occurred in the peripheral and coronary circulation.[35,36] In the context of peripheral artery disease, endothelial injury arises from myriad cardiovascular risk factors, such as smoking, diabetes, and hypertension. This orchestrates platelet and smooth muscle cell activation, resulting in vessel wall thickening and stiffening.[37] A similar concept of neointimal hyperplasia can occur in dialysis access, causing vessel stenosis and consequently fistula or graft failure. Surgery-related trauma, repeated dialysis needling, and other percutaneous interventions potentiate endothelial injury and smooth muscle cell migration, leading to neointimal hyperplasia and ultimately venous stenosis, most commonly at the vein-graft anastomosis or vein-artery anastomosis.[3,38]

Evidently, the use of DCB angioplasty has widened to include several conditions of the peripheral and coronary arteries.[11] For instance, the landmark Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis (LEVANT I) and the drug-eluting balloon in peripheral intervention for the superficial femoral artery (DEBATE-SFA) trials and long-term follow-up studies collectively showed that DCB angioplasty is superior to CBA in peripheral intervention for femoropopliteal artery lesions, with reduced rates of restenosis and improved patency.[10,35,39] Although these findings have heightened interest in the use of DCB angioplasty for dialysis access interventions, its initial use was met with controversy, considering biologic differences between veins and arteries[40] (veins are known to develop stenosis way more quickly than arteries). Some have attributed this difference to two reasons. First, as veins have a less structurally well defined internal elastic lamina, this potentiates smooth muscle cell and myofibroblast migration from the media to the intima. Next, increased venous production of nitric oxide and prostacyclin orchestrates endothelial injury.[3] Hence, the superior patency rates of DCB angioplasty in coronary or lower limb arterial lesions may not directly translate to venous lesions in dialysis access.

To our knowledge, this is the most up-to-date systematic review and meta-analysis comparing DCB angioplasty against CBA in patients undergoing HD. In summary, both 6- and 12-month primary patency rates are significantly better in the DCB angioplasty group in comparison to the CBA group, and this remains consistent in both RCTs and cohort studies. Furthermore, these benefits extended to HD patients with central vein stenosis.

Whereas our study attempted to uniformly summarize the pool of evidence comparing DCB angioplasty against CBA in HD patients, clinical heterogeneity remains unaddressed, including indications for treatment and definition of patency. Although a comprehensive effort was made to perform various subgroup and sensitivity analyses to address heterogeneity in lesion characteristics (central vein stenosis), study designs (RCT, cohort studies), and study quality, other important subgroups, such as fistula fashioning, level of stenosis, recurrent or de novo stenosis, and patient comorbidities, have not been accounted for. Despite our best attempt to collate and stratify these data, these could not be analyzed sufficiently because of the small sample size. Other limitations arise from the inclusion of nonrandomized studies, which are subjected to inherent biases. Selection bias and confounding bias, for instance, are major weaknesses of these studies. Despite conducting a quality assessment and corresponding sensitivity analysis, findings from cohort studies must still be interpreted with caution.

Although Khawaja et al[17] published a systematic review on a similar subject, they included only 6 studies totaling 254 fistula interventions. Despite similar conclusions, the robustness of our methodology makes our findings more recent and credible. Besides the significant increase in sample size (866 vs 254), we have comprehensively performed various subgroup analyses, not just to differentiate study design but also to segregate studies specifically investigating HD patients with central venous stenosis. To our knowledge, as there has been no systematic review evaluating the efficacy of DCB angioplasty in HD patients with central venous stenosis, the study offers the first pooled evidence supporting the use of DCB angioplasty in this select group of patients. Next, various sensitivity analyses have been conducted in our review, as opposed to the study by Khawaja et al.[17] For instance, studies with the crossover analysis design potentiate significant heterogeneity as patients with multiple lesions carry a higher risk of stenosis. To address this major confounder, a sensitivity analysis was performed by excluding these studies. Last, the results of the risk of bias assessment were used to perform a sensitivity analysis of good-quality studies to ensure that our findings prevail.

Nonetheless, knowledge gaps remain that are unaddressed in this review, which future researchers should consider. Cost-effectiveness is an important aspect in clinical decision-making, particularly from repeated interventions for restenosis. For instance, 6-month cumulative patency rates of CBA are low, ranging from 23% to 38%,[7,8] and restenosis results in frequent repeated interventions. Whereas clinicians are primarily concerned about dialysis access type and related complications, patients may worry about the substantial economic burden and downtime associated with repeated hospital admissions for reinterventions,[41] hence underscoring the need to reduce the risk of restenosis. A cost-effectiveness meta-analysis of 40 trials has shown that enhancements to angioplasty, particularly DCB angioplasty, reduced lifetime costs and improved quality of life.[42] Hence, the clinical benefit of DCB angioplasty also translates to the benefit of cost-saving for patients. Whereas DCBs incur a higher initial cost, this may be offset by later cost-savings.[43] Nonetheless, a long-term cost-effectiveness study comparing DCB angioplasty and CBA is needed to conclusively ascertain this.

As the technology of DCB angioplasty continues to evolve, much remains to be seen with a sirolimus-coated balloon.[44] Preliminary, unpublished evidence has reported encouraging safety and efficacy results of a sirolimus-coated balloon (Magic Touch; Envision Scientific PVT, Bhatpore, India) in coronary artery lesions.[45] An in vivo study investigated the use of a porous balloon designed to deliver a nanoencapsulated solution of sirolimus. Whereas clinical benefit cannot be proven from this trial alone, it demonstrates the feasibility of delivering therapeutic doses of sirolimus with balloon angioplasty, a concept previously challenged, given

molecular instability, slow vessel wall uptake, and poor drug retention.[46] More recently, the first in-human trial, SELUTION FIM study (NCT02941224), reported encouraging results of a sirolimus-coated balloon for peripheral artery lesions, with a median late lumen loss of the target lesion of 0.19 mm 6 months postoperatively and a target lesion revascularization rate of 2.3%. Nevertheless, more trials with larger sample sizes are needed to establish these findings.

Next, treatment of central venous stenosis requires balloon diameters of 10 to 14 mm, which are currently available on the market, such as the Lutonix (10-12 mm). However, as some studies employed devices that had smaller diameters, they may not be suited for larger veins. Hence, additional procedures, such as predilation and postdilation, were necessary.[12,28] Although Massmann et al[34] reported the effective use of a custom-made DCB (Elutax-SV), these are not yet approved by the Food and Drug Administration and hence may not be available in the United States. Until newer devices specifically designed for central venous stenoses are commercially available, it is expected that the use of DCBs for these lesions will not be widely adopted worldwide. Furthermore, the use of adjunctive procedures to complement current devices should be validated in future trials.

Last, standardization of surveillance methods can reduce heterogeneity between studies. Regardless of whether ultrasound, computed tomography, or angiography is being employed, future trials should use similar clinical and imaging parameters in their inclusion criteria.[47]

## CONCLUSIONS

In patients with dialysis access stenosis, DCB angioplasty has been shown to be a safe alternative to CBA, offering superior patency rates at both 6 and 12 months. However, given the small sample sizes of included studies, we recommend for future research to consider an adequately powered, well-designed RCT to establish these findings. This should be accompanied with long-term data reported in a homogeneous and standardized manner.

We would like to thank Stephanie Fook Chong from the Health Services Research Unit, Division of Medicine, Singapore General Hospital, for critically reviewing the statistical analysis.

## AUTHOR CONTRIBUTIONS

Conception and design: IW, HY, LT, SQ, CT, TT, TC
Analysis and interpretation: IW, HY, LT, SQ, CT, TT, TC
Data collection: IW, HY, TC
Writing the article: IW, HY, TT, TC
Critical revision of the article: IW, HY, LT, SQ, CT, TT, TC
Final approval of the article: IW, HY, LT, SQ, CT, TT, TC
Statistical analysis: IW
Obtained funding: Not applicable
Overall responsibility: TC

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Submitted Oct 10, 2018; accepted Jan 19, 2019.

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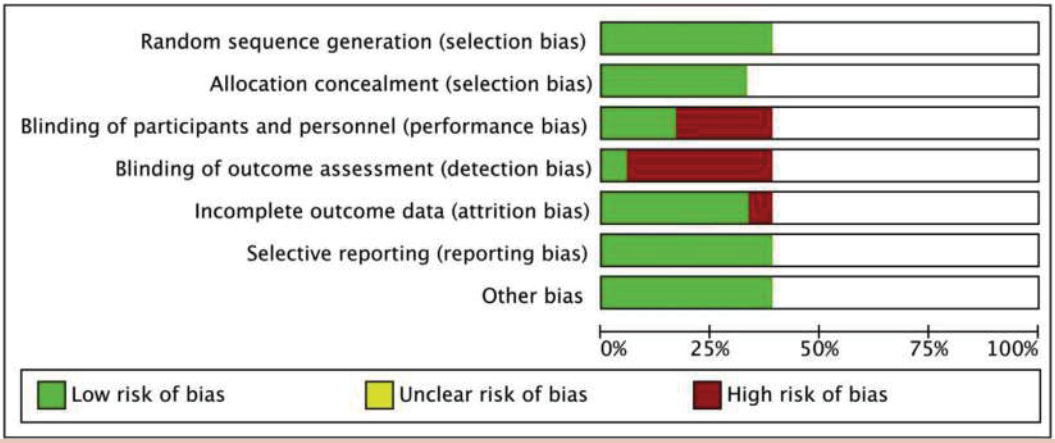
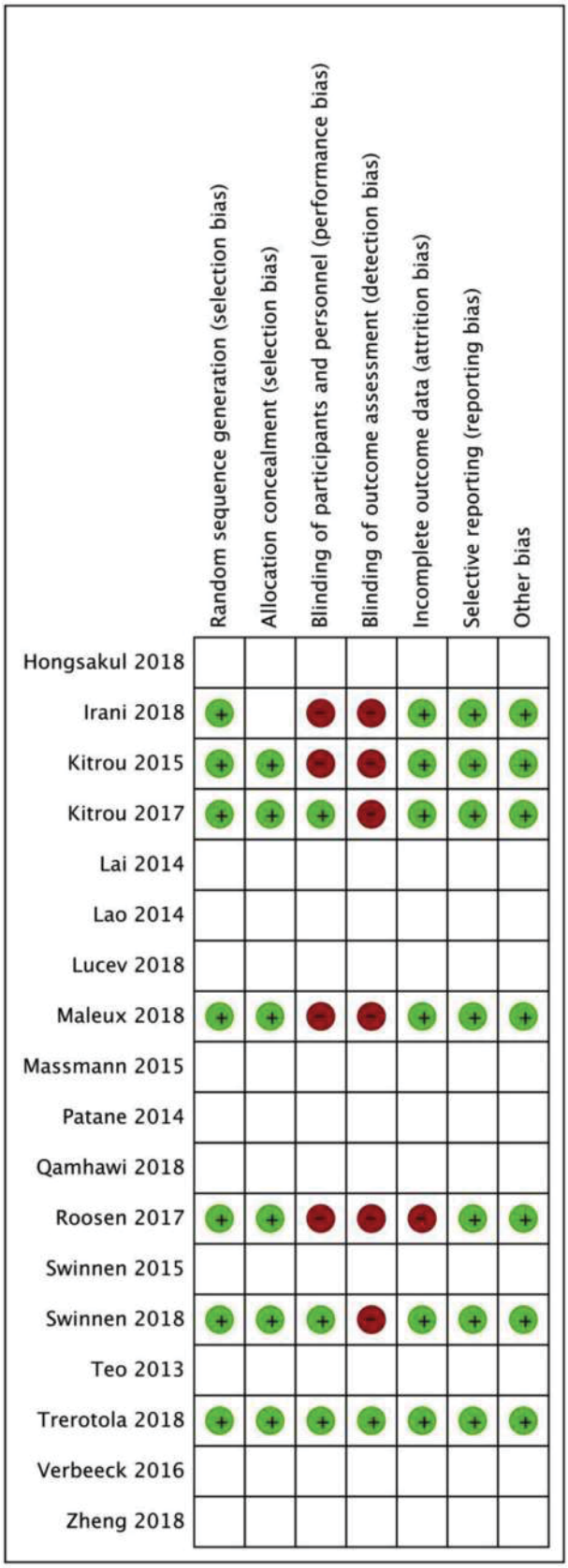
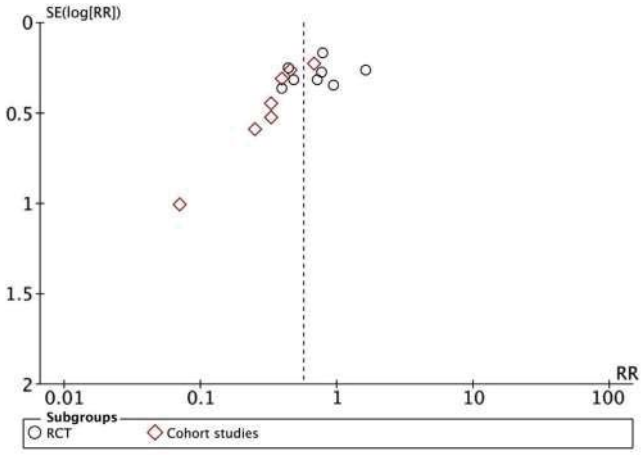


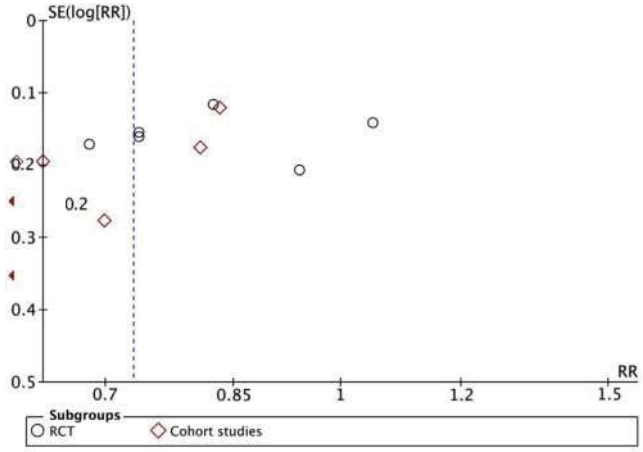

**Supplementary Fig 1 (online only).** Risk of bias graph for randomized controlled trials (RCTs).



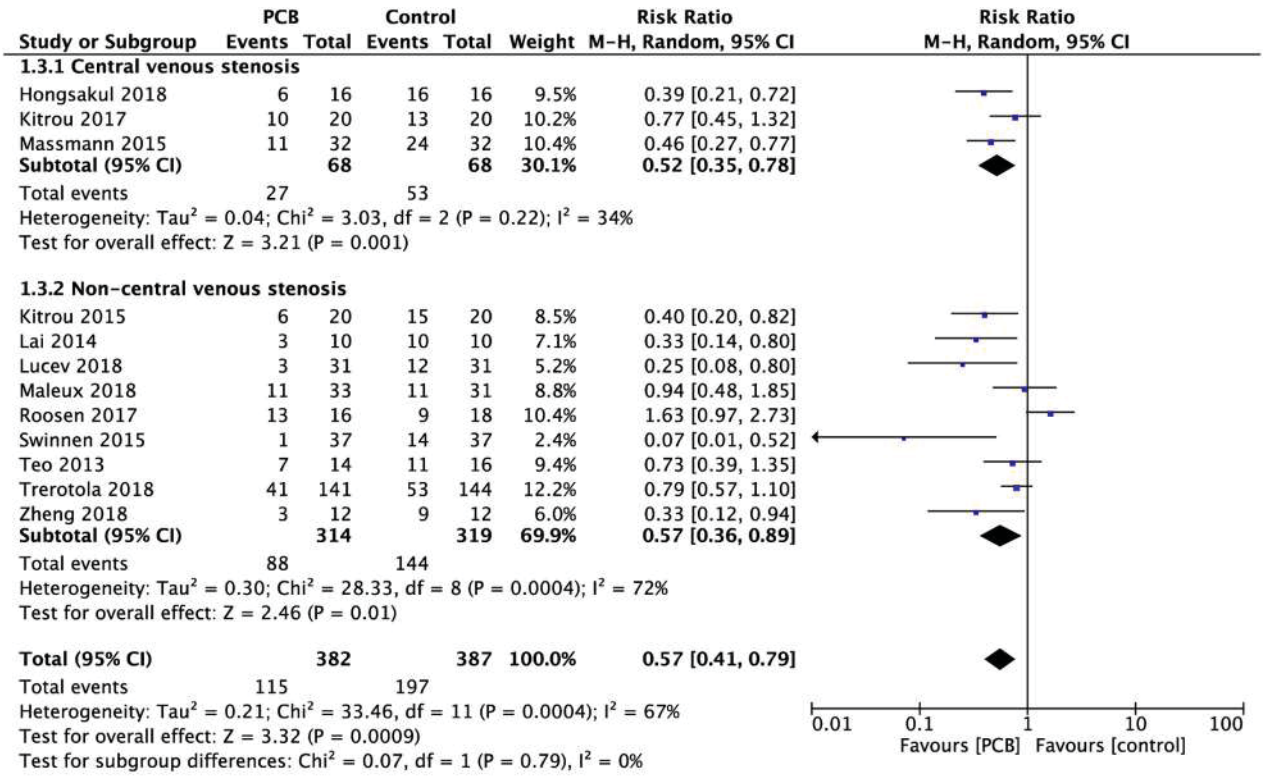

**Supplementary Fig 2 (online only).** Risk of bias summary for randomized controlled trials (RCTs).



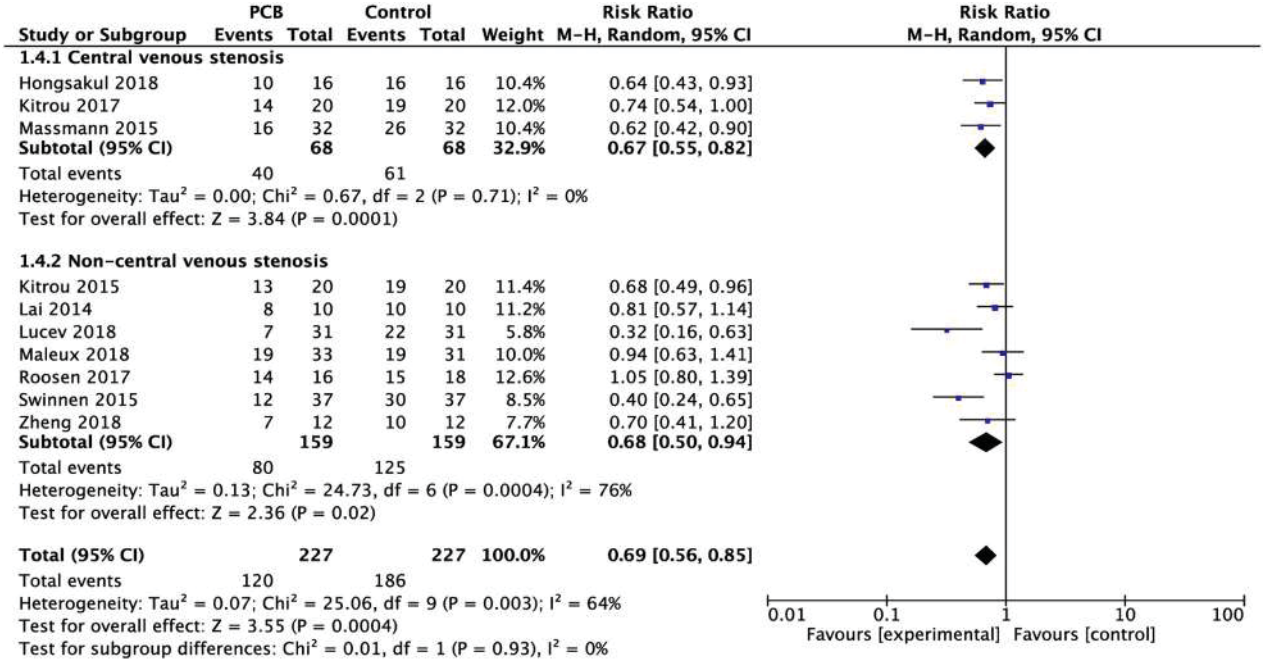

**Supplementary Fig 3 (online only).** Funnel plot assessing publication bias for 6-month primary patency. *RCT,* Randomized controlled trial; *RR,* risk ratio; *SE,* standard error.




**Supplementary Fig 4 (online only).** Funnel plot assessing publication bias for 12-month primary patency. *RCT,* Randomized controlled trial; *RR,* risk ratio; *SE,* standard error.




**Supplementary Fig 5 (online only).** Subgroup analysis of 6-month primary patency of central venous stenosis. *CI,* Confidence interval; *M-H,* Mantel-Haenszel; *PCB,* paclitaxel-coated balloon.




**Supplementary Fig 6 (online only).** Subgroup analysis of 12-month primary patency of central venous stenosis. *CI,* Confidence interval; *M-H,* Mantel-Haenszel; *PCB,* paclitaxel-coated balloon.