Hemodialysis Arteriovenous Fistula and Graft Stenoses: Randomized Trial Comparing Drug-eluting Balloon Angioplasty with Conventional Angioplasty

Journal Club
8 July 2019

TENGKU AZRAN BIN RAJA MAMAT

SUPERVISOR: AP DR MOHD SHAFIE ABDULLAH

Hemodialysis Arteriovenous Fistula and Graft Stenoses: Randomized Trial Comparing Drug-eluting Balloon Angioplasty with Conventional Angioplasty

Farah Gillan Irani, MBBS, FRCR • *Terence Kiat Beng Teo, MBBS, FRCR* • *Kiang Hiong Tay, MBBS, FRCR, FAMS* •
Win Htet Yin, MBBS, BSc (Hons)† • *Hlaing Hlaing Win, MBBS, MSc* • *Apoorva Gogna, MBBS, FRCR, FAMS* •
Ankur Patel, MBBS, MRCS, FRCR • *Chow Wei Too, MBBS, FRCR* • *Shaun Xavier Ju Min Chan, MBBS, FRCR* •
Richard Hoau Gong Lo, MBBS, FRCR, FAMS • *Luke Han Wei Toh, MBBS, FRCR, FAMS* •
Siew Ping Chng, MBBS, MRCS, FAMS • *Hui Lin Choong, MBBS, MMed, FAMS* • *Bien Soo Tan, MBBS, FRCR, FAMS*

From the Departments of Vascular and Interventional Radiology (F.G.I., K.H.T., W.H.Y., H.H.W., A.G., A.P., C.W.T., S.X.J.M.C., R.H.G.L., L.H.W.T., B.S.T.), Vascular Surgery (S.P.C.), and Renal Medicine (H.L.C.), Block 2 Level 1, Singapore General Hospital, Outram Rd, Singapore 169608; and Department of Radiology, Mount Elizabeth Hospital, Singapore (T.K.B.T.). Received April 16, 2017; revision requested June 27; revision received May 10, 2018; accepted May 21. **Address correspondence to** F.G.I. (e-mail: *farah.gillan.irani@singhealth.com.sg*).

Introduction

- Hemodialysis failure constitutes substantial morbidity and cost to patients (1 billion per annum in the US)

- Kidney Dialysis Outcomes Quality Initiative guideline

  - Recommend treating stenosis >50% associated with flow rate reduction and elevated venous pressure.

- Percutaneous transluminal angioplasty (PTA) is the standard of care.

- However

  - 12-month patency rate is only 46%.

  - Repeated PTA: >70% patency rate at 2 years.

- PTA is a traumatic event
  - Inflammatory and proliferative response.
  - Increased vascular smooth muscle cell proliferation.
- Strategies to increase patency:
  - Bare metal stent placement
  - Cryoplasty
  - Cutting balloon angioplasty
  - Covered stent

- Paclitaxel
  - Prevent neointimal hyperplasia by causing cellular apoptosis and inhibition of vascular smooth muscle cell migration to the intima.
  - Most commonly used drug in drug-eluting balloons (DEB).
  - Highly lipophilic – rapidly absorbed and retained in the endothelial cells.
  - The balloon acts as the vehicle to deposit the drug into the wall, no permanent scaffold is left.
- DEB PTA has been shown to be effective in coronary and femoropopliteal arterial diseases.
- Minimal data in dialysis circuit.

Materials and Methods

- Prospective randomised single centre clinical trial.
- Independently funded by national research grant.

Enrolment between January 2012 and May 2013

Inclusion criteria
Upper limb or groin malfunctioning AVF or AVG
AVF or AVG >3 months old (matured)
Native vessel 4–7 mm in diameter (corresponding to the sizes of the available DEBs)
Able to cross the lesion with a guidewire
Platelet count >50 × 10^9/L
PT/PTT <3 seconds above normal
Exclusion criteria
Thrombosed AVF or AVG
Evidence of systemic infection or local infection associated with the AVF or AVG
Age <21 years
Pregnancy
Uncorrectable coagulopathy (despite transfusion) or hypercoagulable state
Enrolled in another investigational study
Comorbid conditions limiting ability to comply with follow-up requirement
Life expectancy <6 months

Figure 1: Inclusion and exclusion criteria used in this study. *AVF* = arteriovenous fistula, *AVG* = arteriovenous graft, *DEB* = drug-eluting balloon, *PT* = prothrombin time, *PTT* = partial thromboplastin time.
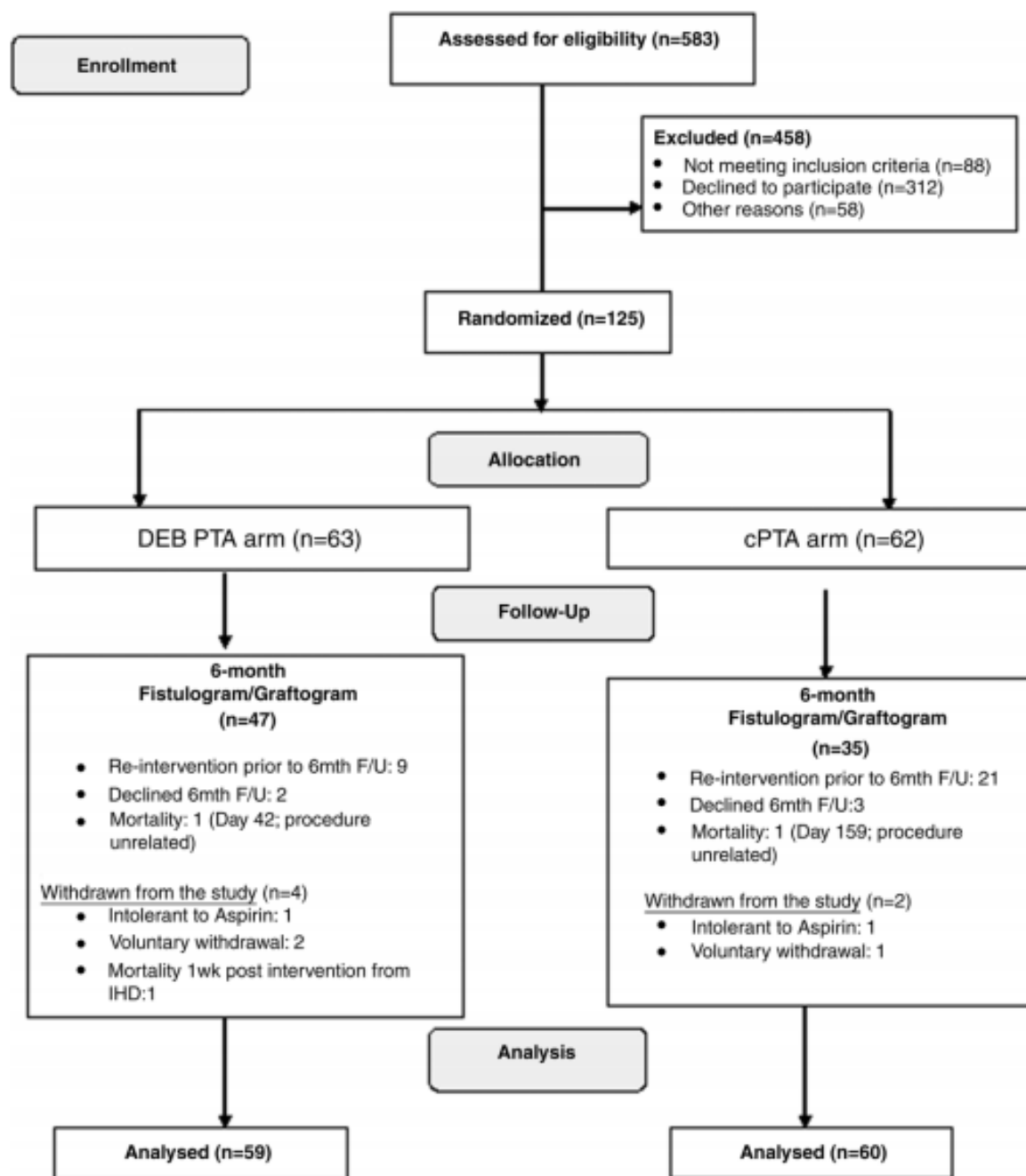
Figure 4: Consort flow diagram. *cPTA* = conventional balloon angioplasty, *DEB* = drug-eluting balloon, *F/U* = follow-up, *IHD* = ischemic heart disease, *PTA* = percutaneous transluminal angioplasty.

Outcomes

- Primary end point
  - lesion primary patency and restenosis rate at 6 months.
- Secondary end points
  - Anatomic and clinical success after PTA
  - Circuit primary patency at 6 months
  - Lesion and circuit primary patency at 1 year

- Lesion primary patency: absence of repeat intervention in the target lesion during follow up.

- Restenosis: incidence of at least 50% diameter narrowing

- Anatomic success: <30% residual diameter stenosis at target lesion measured immediately after PTA

- Clinical success: one successful HD via the access after PTA

- Circuit primary patency: interval from index PTA to the next access intervention anywhere in the dialysis circuit

Procedures

- Treatment was performed by procedurists with 2-20 years of experience.

- Diagnostic fistulogram or graftogram was obtained using standard techniques.

- All stenotic lesions were assessed with one view in single plane angiography.

- In multiple stenoses → most severe stenosis was chosen to be the target lesion.

- Site, degree and length of the target lesion were documented and measured by using digital measuring software (Artis Zeego or Artis dMP)

- The AVF or AVG was accessed in either ante or retrograde fashion.

- Appropriate-size vascular sheath (5-7F) was inserted.

- If the target lesion was more peripheral, the central lesions were treated first.

- 4F angled tip catheter (Berenstein) and 0.035-in glidewire (Terumo) were used to cross the target lesion, manipulated into the non stenotic central vein or feeding artery depending on the location of the stenosis.

- The glidewire was exchanged with 0.035-in Teflon guidewire (Started guideweire, Boston Scientific)

- Heparin 2000IU was administered prior to first PTA.

- 1:1 randomisation was performed using sealed envelope technique.
- The procedure was performed according to protocols.
- Final angiogram was obtained.
- Diameter, length of the balloon, number of inflation, degree of residual stenosis were recorded.

Protocols for cTPA

- Appropriate-sized (same size or 1mm larger) semicompliant high-pressure balloon (Reef HP) was used.

- The balloon was inflated up to rated burst pressure (20-22 atm) using inflation device.

- The pressure was maintained for 2 minutes.

- Post-PTA angiogram was obtained immediately.

- If persistent waist on the balloon → further PTA using balloon of the same size with pressure up to 30 atm.

- If residual stenosis >30%, repeat PTA using same balloon or oversized by 1mm was performed .

Protocols for DEB PTA
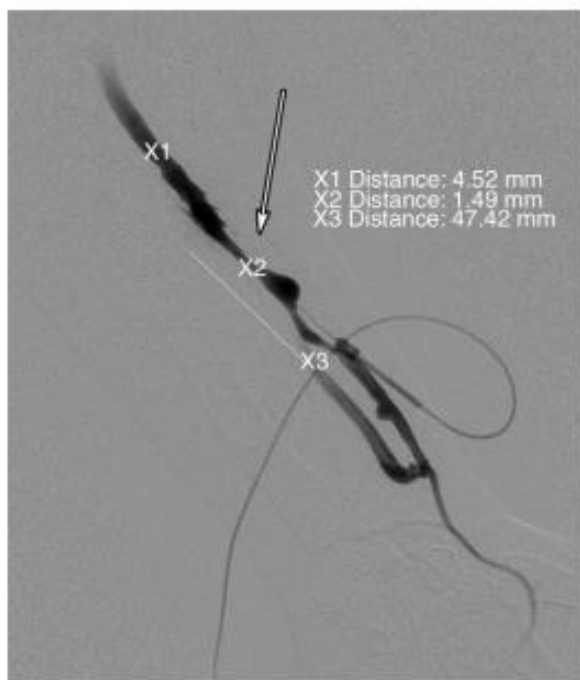
- Over-the-wire INPACT Admiral DEB.

- Shaft length of 80cm, diameter 4 to 7mm, length 40 to 80mm.

- The balloons were uniformly coated with paclitaxel (3microg/mm2), with urea as excipient and patented coating technology.

- DEB diameter was either the same or 1mm larger than the conventional balloon.

- The balloon length was the same or one length longer than conventional balloon.
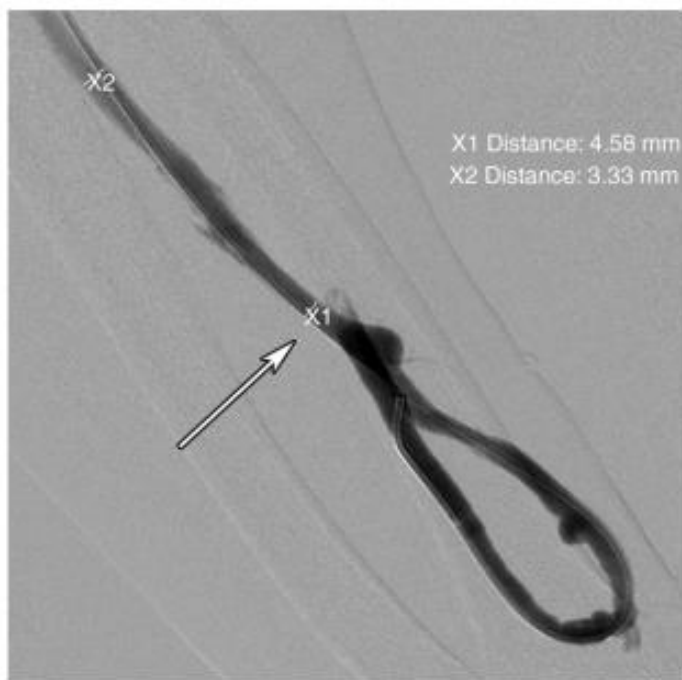
- cPTA was performed first exactly the same to cPTA arm to dilate the stenosis.

- After post-PTA angiography, appropriate-sized DEB was inflated across the target lesion → maintained for 1 minute to allow complete drug elution into the vessel wall.

- DEB PTA is a process to apply the drug to the vessel wall rather than conventional dilatation of the stenosis.

Post procedure

► All received 100mg acetylsalicylic acid (Aspirin) and 75mg clopidogrel (Ranbaxy Malaysia) daily for a month, then continue to take aspirin for another 5 months.

► Regular dialysis was resumed.

► If the participant experienced episode of suboptimal dialysis → referred back for assessment by clinicians (15 year experience) → reintervention if necessary.

► If the intervention involved the target lesion → participation was terminated (target lesion primary patency ended)

► If the intervention did not include the target lesion → continue with 6 month follow up.

a.

X1 Distance: 4.52 mm
X2 Distance: 1.49 mm
X3 Distance: 47.42 mm

b.

X1 Distance: 4.58 mm
X2 Distance: 3.33 mm

X2 Distance: 4.76 mm
X3 Distance: 4.58 mm

X3 Distance: 6.22 mm

X1 Distance: 6.24 mm
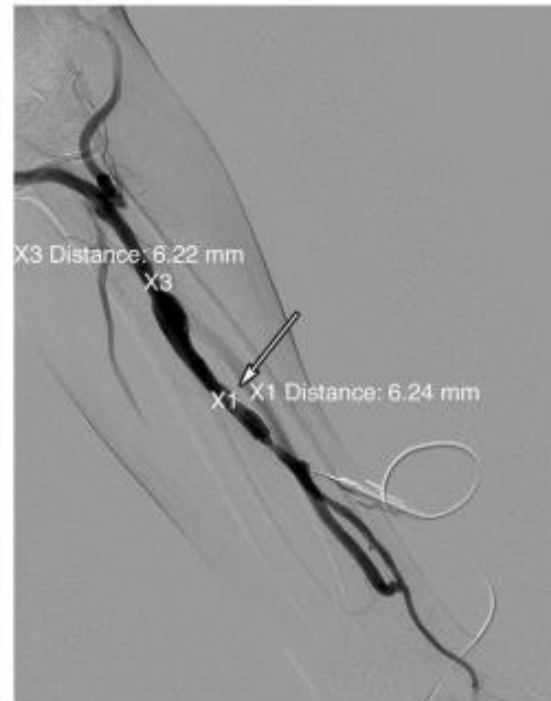
- Follow up at 6 months.
  - Follow up angiography in the same projection.
  - The target lesion was measured to assess for restenosis.
  - Dialysis circuit was also assessed for patency and stenotic lesion.
  - If no flow problem → no treatment was offered.
- Follow up after 6 months.
  - Observed for 1 year.
  - Look for 1 year lesion and circuit primary patency rate.
  - Periodical access to the national electronic medical record system.
  - If lack of patency of the target lesion was discovered at any point, the participation was terminated.

Statistical analysis

- Sample size of 60 participants per treatment group to detect significant difference.

- 80% power.

- 6 month and 1 year patency rates: Kaplan-Meier product-limit estimator.

- Primary patency curves were compared using log-rank test.

- Hazard ratios for both groups were estimated using Cox proportional hazards regression.

- Restenosis rates and anatomic success rates were compared using Fischer exact test.

- Cox proportional hazards regression analyses were performed to identify variables.

- Statistical analyses were performed using SPSS software.

Results

- 583 participants were screened → 125 were enrolled → 119 were included in the final analysis.

- 84 (67.2%) male, 41 (32.8%) female.

- Mean age: 59.2 years (25-83 years)

- More forearm access in DEB PTA group → smaller-diameter conventional balloon in DEB PTA group (6 and 5mm) compared to cPTA (7 and 6mm)

- Otherwise, no significant differences between DEB PTA and cPTA.

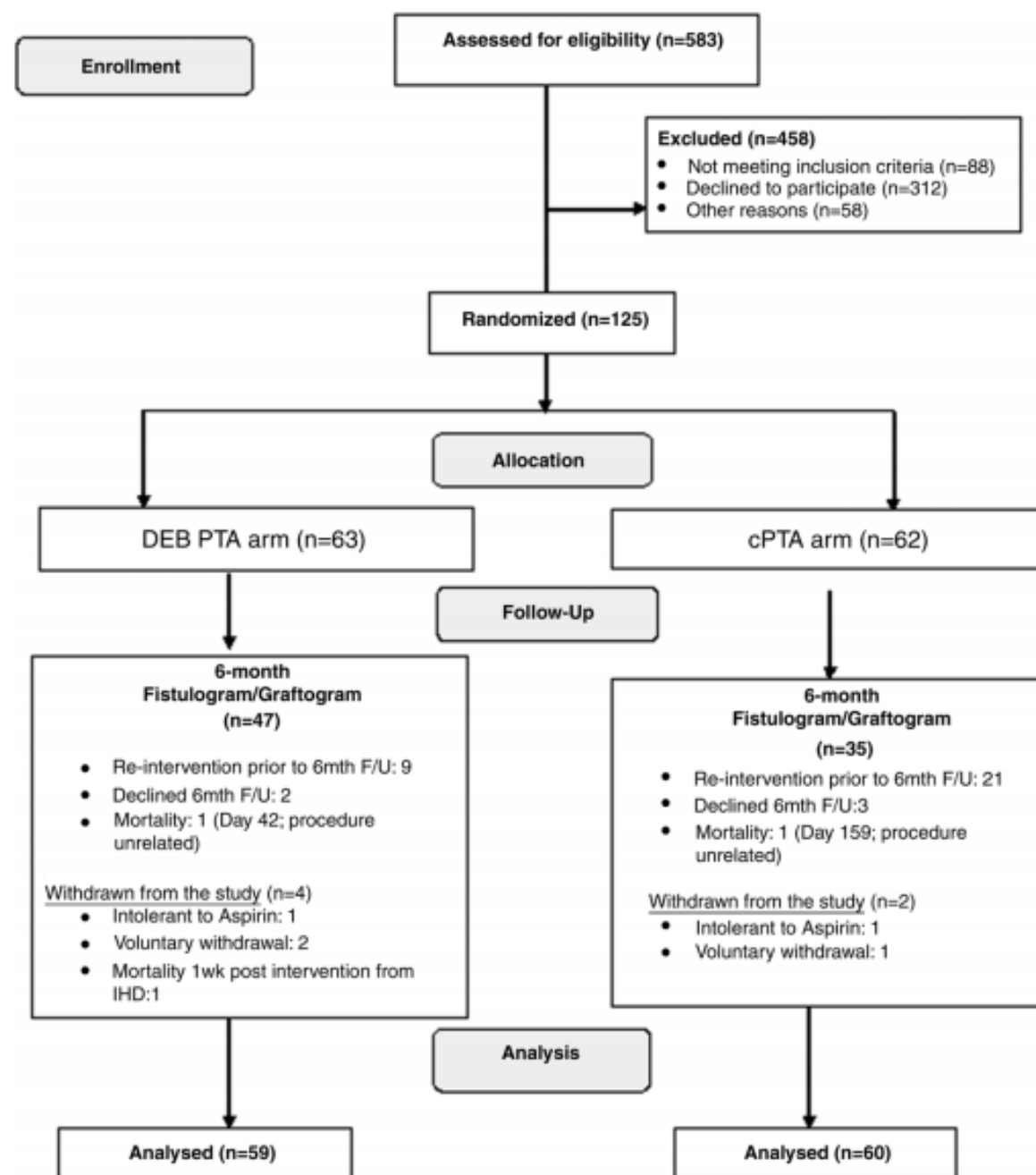- Most common balloon length was 40mm followed by 60mm (in both groups).

Figure 4: Consort flow diagram. *cPTA* = conventional balloon angioplasty, *DEB* = drug-eluting balloon, *F/U* = follow-up, *IHD* = ischemic heart disease, *PTA* = percutaneous transluminal angioplasty.

Table 1: Demographic and Clinical Characteristics of Hemodialysis Access for 119 Participants in DEB PTA and cPTA Trial

Variable	DEB PTA (n = 59)	cPTA (n = 60)	P Value
Age (y)	59.0 ± 11.5	59.4 ± 8.80	.84
Sex	...	...	.95
Male	39 (66.1)	40 (66.7)	...
Female	20 (33.9)	20 (33.3)	...
Smoking history	5 (8.5)	6 (10)	.77
Hyperlipidemia	40 (67.8)	38 (63.3)	.61
Hypertension	55 (93.2)	55 (91.7)	>.99
Ischemic heart disease	27 (45.8)	23 (38.3)	.41
Diabetes mellitus	37 (62.7)	34 (56.7)	.50
Age of dialysis access (mo)	...	...	.78
Mean ± SD	44.4 ± 58.6	47.3 ± 54.3	...
Range	0–168	3–288	...
Side of dialysis access	...	...	.79
Left	44 (74.6)	46 (76.7)	...
Right	15 (25.4)	14 (23.3)	...
Site of dialysis access	...	...	.02
Arm	15 (25.4)	28 (46.7)	...
Forearm	44 (74.6)	32 (53.3)	...
Type of dialysis access	...	...	.10
AVF	52 (88.1)	46 (76.7)	...
AVG	7 (11.9)	14 (23.3)	...
AVF or AVG type	...	...	.18
Radiocephalic	40 (67.8)	30 (50)	...
Brachiocephalic	10 (16.9)	18 (30)	...
Brachiobasilic	9 (15.3)	7 (11.7)	...
Brachio-brachialis	0	2 (3.3)	...
Radiobasilic	0	1 (1.7)	...
Brachial-jugular	0	1 (1.7)	...
Brachial axillary	0	1 (1.7)	...
No. of previous angioplasties	...	...	.56
Mean ± SD	1.80 ± 2.32	2.07 ± 2.74	...
Range	0–9	0–14	...
No. of lesions	...	...	.41
Single	27 (45.8)	32 (53.3)	...
Multiple	32 (54.2)	28 (46.7)	...
Central vein stenosis	10 (16.9)	4 (6.7)	.07
Target lesion location	...	...	.56
Juxta- and arteriovenous anastomosis	27 (45.8)	27 (45.8)	...
Cannulation zone	15 (25.4)	15 (25.4)	...
Venous outflow	11 (18.6)	11 (18.6)	...
Intragraft	1 (1.7)	1 (1.7)	...
Venous graft anastomosis	5 (8.5)	5 (8.5)	...
Target lesion percentage stenosis (%)	62.7 ± 12.5	67.8 ± 12.7	.03
Target lesion length (cm)	...	...	.83
Median	2.6	2.5	...
Range	0.2–6.3	0.5–8.1	...
No. of inflations	...	...	.11
Median	2	2	...
Mean	2.15	2.2	...
Median inflation pressure (atm)	16 ± 4.88	20 ± 4.889	.39
Anatomic success	53 (89.8)	47 (78.3)	.132

Note.—Unless otherwise indicated, data are mean ± standard deviation, and data in parentheses are percentages. AVF = arteriovenous fistula, AVG = arteriovenous graft, DEB PTA = drug-eluting balloon angioplasty, cPTA = conventional balloon angioplasty, SD = standard deviation.

- High pressure PTA: 1 in DEB; 2 in cPTA.

- Additional larger balloon: 1 in DEB; 4 in cPTA.

- Target lesion percentage stenosis: more severe in cPTA (67.8% vs 62.7%)

- Anatomic success rate: no significant difference (DEB: 89.9%, cPTA: 78.3%).

- Clinical success rates: both 100%.

- Reintervention prior to 6-month follow up: DEB: 15.3%; cPTA: 35.0%.

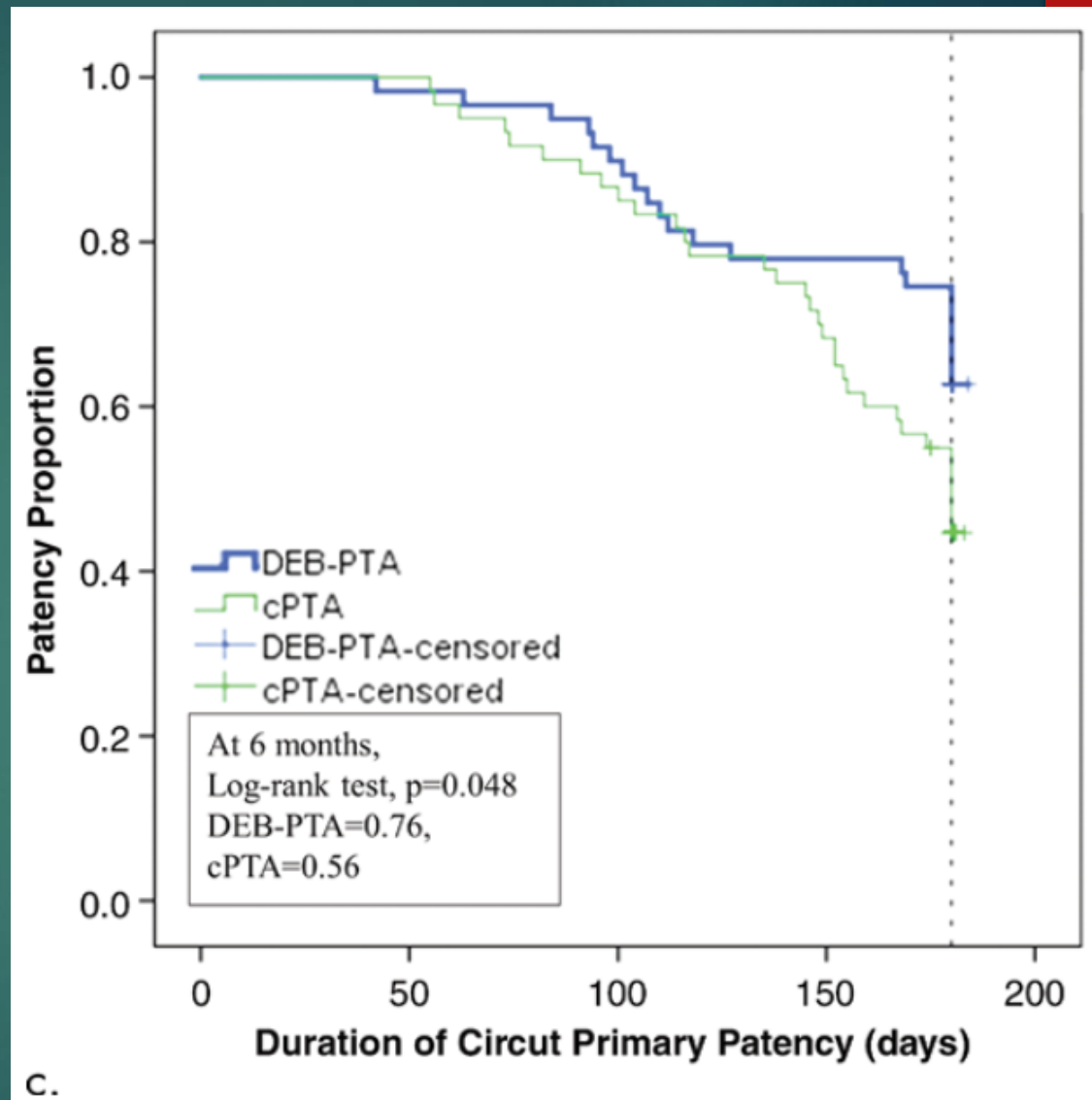- Restenosis rate at 6 months: DEB: 34% (16 of 47); cPTA: 62.9% (22 of 35)

Lesion primary patency at 6 months (Kaplan-Meier)

- DEB PTA: 81%

- cPTA: 61%

- P= 0.03

- Hazard ratio for DEB/cPTA: 0.530 (95% confidence interval: 0.295, 0.952)(P= 0.03)
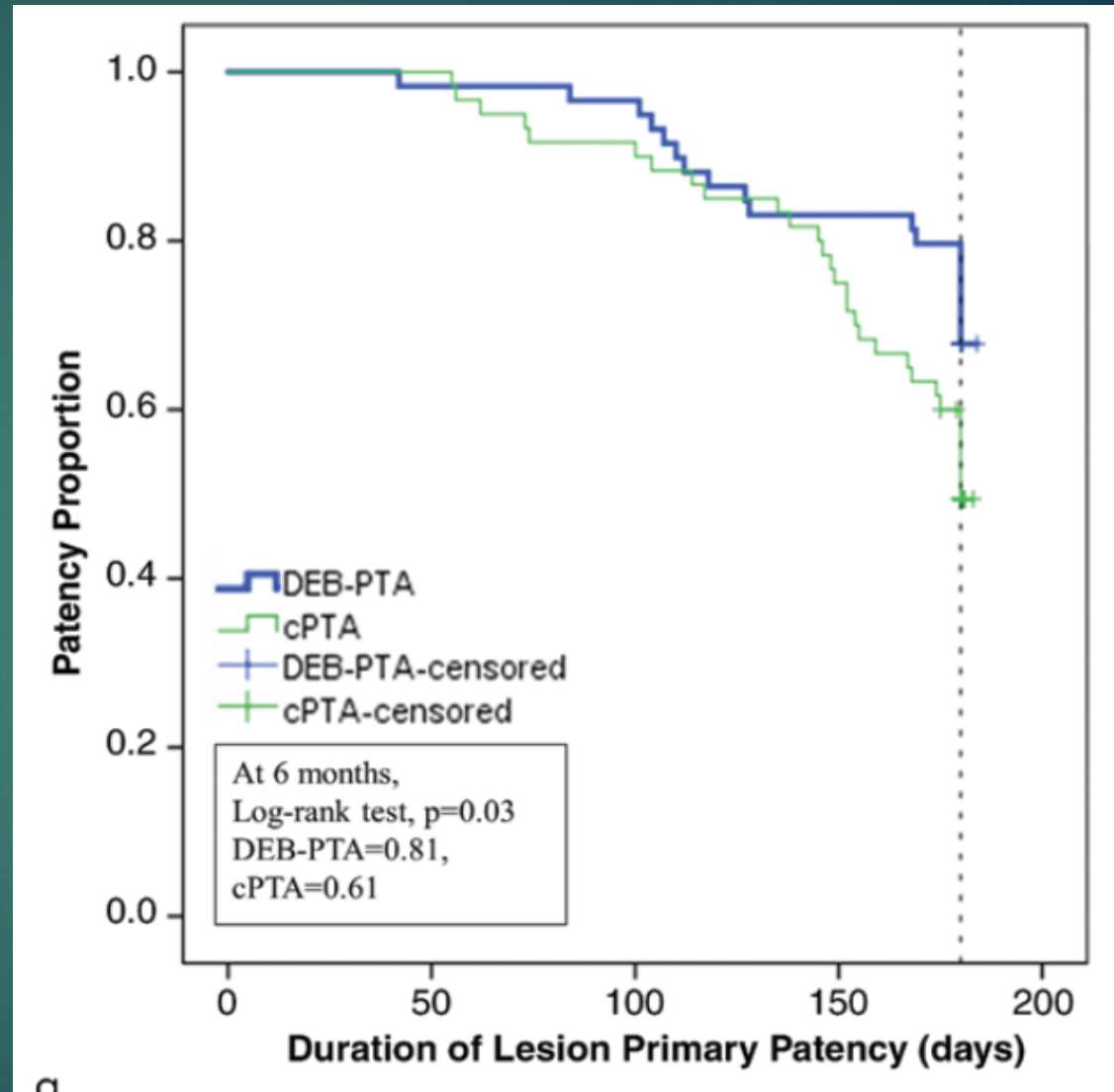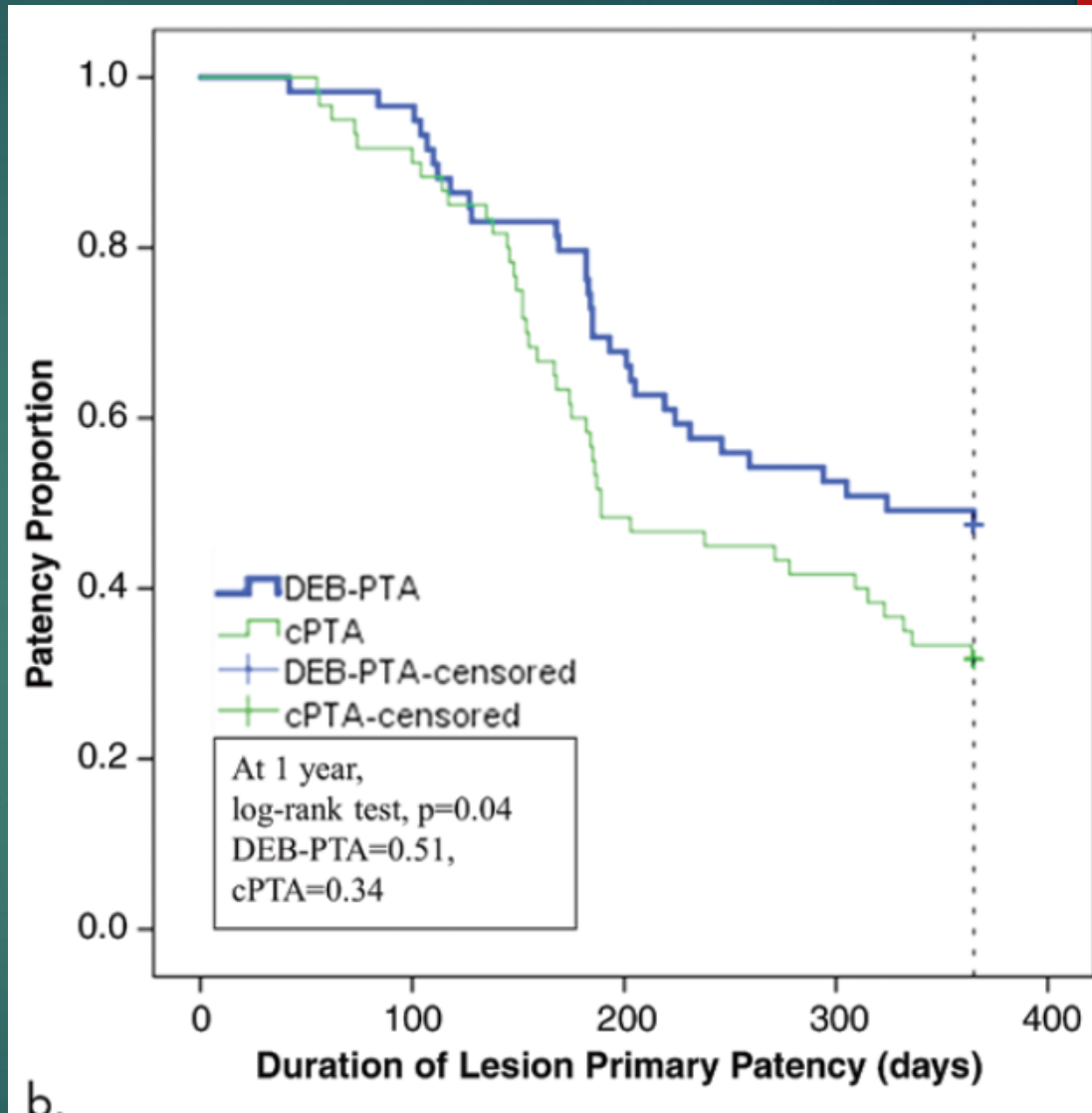
Circuit primary patency at 6 months (Kaplan-Meier)

- DEB PTA: 76%

- cPTA: 56%

- P= 0.048

- Hazard ratio for DEB/cPTA: 0.583 (95% confidence interval: 0.336, 1.012) (P= 0.55)

Lesion primary patency at 1 year (Kaplan-Meier)

- DEB PTA: 51%

- cPTA: 34%

- P= 0.04

- Hazard ratio for DEB/cPTA: 0.615 (95% confidence interval: 0.381, 0993)(P= 0.047)

Circuit primary patency at 1 year (Kaplan-Meier)

- DEB PTA: 45%

- cPTA: 32%

- P= 0.16

- Hazard ratio for DEB/cPTA: 0.699 (95% confidence interval: 0.442, 1.107)(P= 0.13)
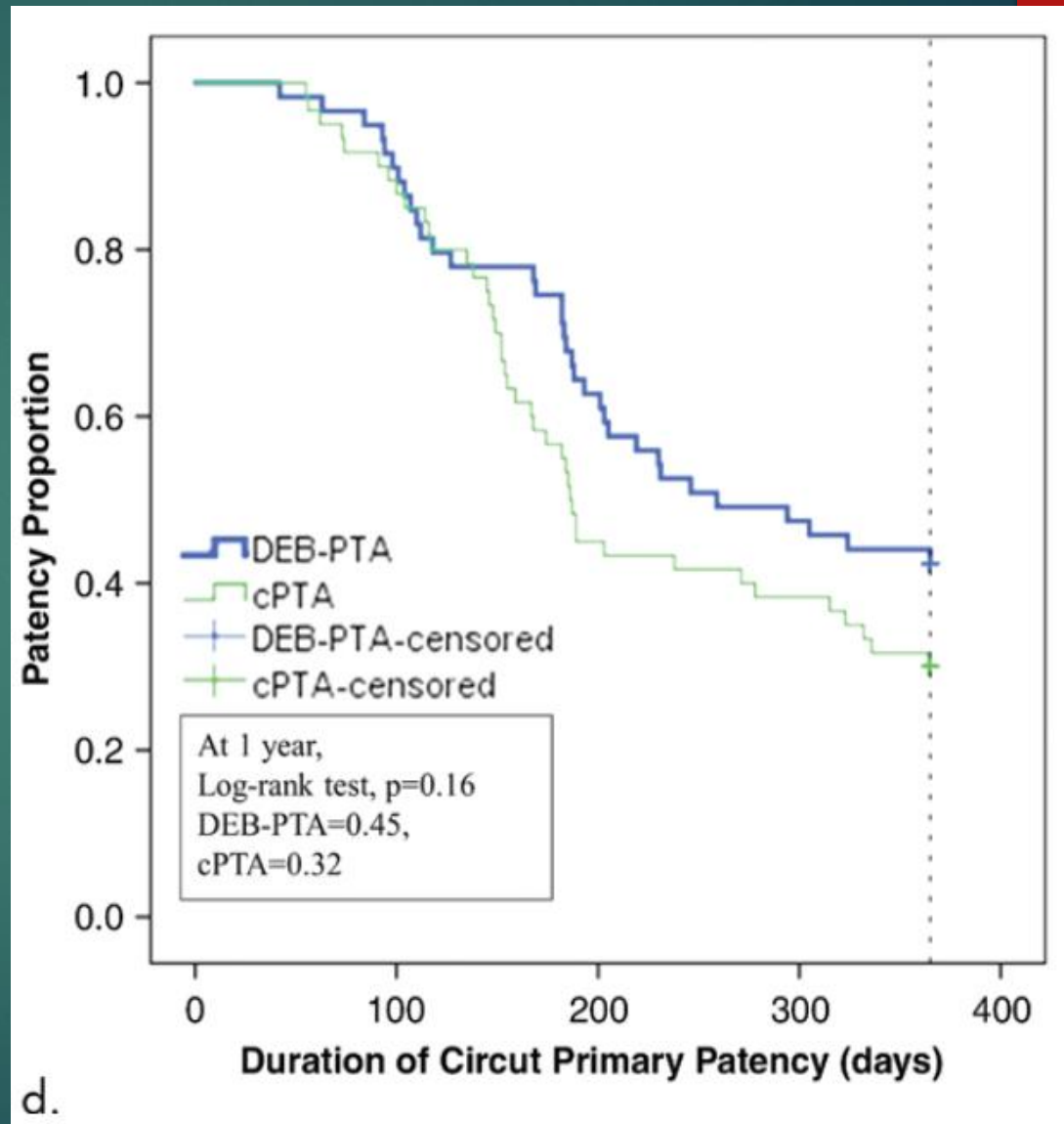
Table 2: Uni- and Multivariable Cox Regression Analyses to Identify the Predictors for Lesion Primary Patency End

| | DEB PTA | | | | cPTA | | | |
| | Univariable | | Stepwise Multivariable* | | Univariable | | Stepwise Multivariable* | |
Variable	Hazard Ratio	P Value	Hazard Ratio	P Value	Hazard Ratio	P Value	Hazard Ratio	P Value
Age (>60 y vs <60 y)	0.50 (0.23, 1.07)	.07	0.58 (0.26, 1.26)	.17	0.98 (0.95, 1.01)	.22	...	...
Sex (male/female)	0.67 (0.32, 1.42)	.29	...	...	0.83 (0.43, 1.60)	.58	...	...
Smoking (yes/no)	0.79 (0.19, 3.31)	.74	...	...	0.80 (0.28, 2.25)	.67	...	...
Types (AVF vs AVG)	0.67 (0.23, 1.93)	.46	...	...	0.52 (0.26, 1.02)	.06	0.55 (0.28, 1.10)	.09
Site (forearm vs arm)	1.15 (0.47, 2.82)	.77	...	...	0.91 (0.49, 1.68)	.75	...	...
Age of dialysis access (>24 mo vs <24 mo)†	0.41 (0.19, 0.87)	.02	0.46 (0.21, 0.98)	.045	1.00 (0.99, 1.00)	.23	...	...
Previous angioplasty (yes/no)	0.68 (0.33, 1.42)	.30	...	...	2.33 (1.11, 4.91)	.03	2.24 (1.06, 4.73)	.04
Target lesion length (cm)	0.87 (0.67, 1.11)	.25	...	...	1.06 (0.88, 1.26)	.55	...	...
Target lesion percentage stenosis (%)	1.01 (0.98, 1.04)	.56	...	...	1.02 (1.00, 1.05)	.09	...	...

Note.—Data in parentheses are 95% confidence intervals. AVF = arteriovenous fistula, AVG = arteriovenous graft, cPTA = conventional PTA, DEB = drug eluting balloon, PTA = percutaneous transluminal angioplasty.

* Variables significant ($P < .20$) at univariable analysis were included in the stepwise multivariable analysis. Significance levels to enter and stay in stepwise multivariable analysis were $P < .20$ and $P < .25$, respectively.

† The median age was 24 months for the cohort for age of dialysis access.

Table 3: Uni- and Multivariable Cox Regression Analyses to Identify the Predictors for Circuit Primary Patency End

| | DEB PTA | | | | cPTA | | | |
| | Univariable | | Stepwise Multivariable* | | Univariable | | Stepwise Multivariable* | |
Variable	Hazard Ratio	P Value	Hazard Ratio	P Value	Hazard Ratio	P Value	Hazard Ratio	P Value
Age (>60 y vs <60 y)	0.65 (0.32, 1.31)	.23	...	...	0.98 (0.95, 1.02)	.30	...	...
Sex (male/female)	0.74 (0.36, 1.50)	.40	...	...	0.90 (0.47, 1.72)	.75	...	...
Smoking (yes/no)	0.63 (0.15, 2.63)	.53	...	...	0.75 (0.27, 2.10)	.58	...	...
Types (AVF vs AVG)	0.48 (0.19, 1.25)	.14	0.38 (0.14, 1.04)	.06	0.58 (0.30, 1.14)	.12	...	...
Site (forearm vs arm)	0.68 (0.32, 1.47)	.33	...	...	0.80 (0.43, 1.48)	.48	...	...
Age of dialysis access (>24 mo vs <24 mo)[†]	0.44 (0.22, 0.89)	.02	0.47 (0.23, 0.96)	.04	0.90 (0.48, 1.70)	.75	...	...
No. of previous angioplasties (yes/no)	0.57 (0.29, 1.13)	.11	0.58 (0.28, 1.19)	.14	2.6 (1.23, 5.46)	.01	2.60 (1.23, 5.46)	.01
Length of stenosis (cm)	0.94 (0.74, 1.18)	.58	...	...	1.08 (0.91, 1.28)	.36	...	...
No. of lesions (single vs multiple)	0.64 (0.31, 1.29)	.21	...	...	0.63 (0.34, 1.17)	.14	...	...
Target lesion percentage stenosis (%)	1.01 (0.98,1.04)	.49	...	...	1.01 (0.99,1.04)	.29	...	...

Note.—Data in parentheses are 95% confidence intervals. AVF = arteriovenous fistula, AVG = arteriovenous graft, cPTA = conventional PTA, DEB = drug eluting balloon, PTA = percutaneous transluminal angioplasty.

* Variables significant (P < .20) at univariable analysis were included in the stepwise multivariable analysis. Significance levels to enter and stay in stepwise multivariable analysis were P < .20 and P < .25, respectively.

[†] The median age was 24 months for the cohort for age of dialysis access.

- Age of dialysis access
  - Significant factor and protective for both lesion and circuit patency in DEB PTA group
  - Not significant in cPTA group
- Number of previous PTAs
  - Associated with loss of primary patency of both lesion and circuit in cPTA group
  - Not significant for DEB PTA group

- Complications
  - All were classified as minor.
  - No major haemorrhagic complication.
  - 2 deaths (1 in each group) from unrelated causes.
  - DEB PTA
    - Dissection (1) and small pseudoaneurysm (1) from conventional balloon rupture (1).
    - Resolved with balloon tamponade.
    - No long term sequalae.
  - cPTA
    - Venous rupture (1).
    - Successfully controlled with balloon tamponade.

Discussion

- DEB PTA is superior in maintaining lesion and circuit primary patency at 6 months.
    - Similar to previous studies: Patane et al (retrospective), Kitrou et al (retrospective), Lai et al (observational) and Katsanos et al (prospective).
    - Katsanos and Kitrou: high proportion of AVGs.
    - Patane and Lai: the lesions were only within juxta-anastomotic segment.
- At 1 year
    - Improved lesion patency
    - No difference in circuit patency
    - Contrary to Kitrou et al (prospective RCT): improvement of circuit patency at 1 year.
        - Kitrou only included patients with 1 lesion.
        - In this study: multiple lesion, and only the most severe is treated with DEB PTA.
        - Can be resolved by performing trials where all the lesions in the circuit are treated with DEB PTA.

- DEB PTA group had more forearm AVFs → smaller balloon.
  - In spite of this, superior target and circuit patency at 6 months.
- Target lesion percentage stenosis was more severe in cPTA group.
  - Not a confounder based on Cox regression analyses.
  - Could be due to no significant difference in anatomic success rates.
- Age of dialysis is protective for lesion and circuit patency (risk of patency loss decreases with age).
  - DEB PTA would be more useful in older, more mature AVFs and AVG.

- History of previous PTA
  - Significantly greater risk of loss of lesion and circuit patency in cPTA group.
  - Not significant in DEB PTA group.
  - This suggests that DEB PTA might offer greater benefit in patients who have undergone previous PTA.
  - It may be that lesions with previous PTA have greater tendency for intimal hyperplasia – reduced by DEB PTA.
- No bleeding complication was encountered.
  - Even in patients on dual antiplatelet therapy.
  - DEB PTA is safe in patients with multiple comorbidities.

- Unblinded nature of the study
  - Could have introduced measurement bias favouring the DEB PTA.
- Randomisation after lesion crossing (instead of intention to treat randomisation)
  - Could have introduced some bias.
  - Allowed to get equivalence in each arm for meaningful result.
- Treatment of only the most severe stenosis in DEB PTA group
  - Could have diluted the effect of DEB PTA in prolonging circuit primary patency.
  - However, Cox regression analyses showed the number of lesions was not significant for circuit patency.
  - Inclusion of only solitary lesion would have led to very prolonged recruitment (Asians are known to have multiple lesions compared to Western patients)
- 1 year follow up was conducted through record review, not through clinical assessment with strict protocols.

Conclusion

▶ DEB PTA is able to significantly prolong 6-month and 1-year lesion primary patency, and 6-month circuit primary patency in participants with AVF or AVG stenosis when compared with cPTA.

▶ Further prospective trials investigating the use of DEB PTA in selected groups and in treating all significant stenoses within dialysis circuit is required.