Drug Eluting Balloon for AVF Angioplasty : Does it work?

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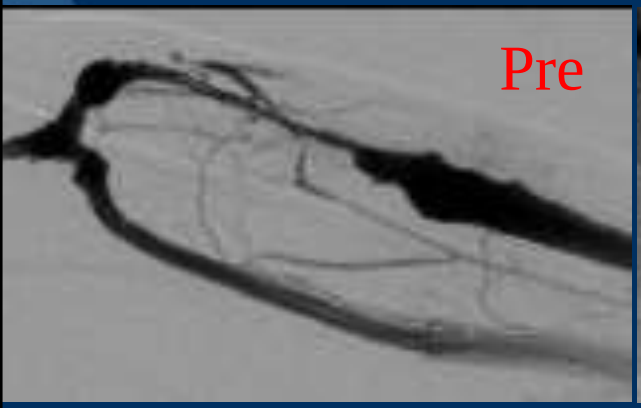
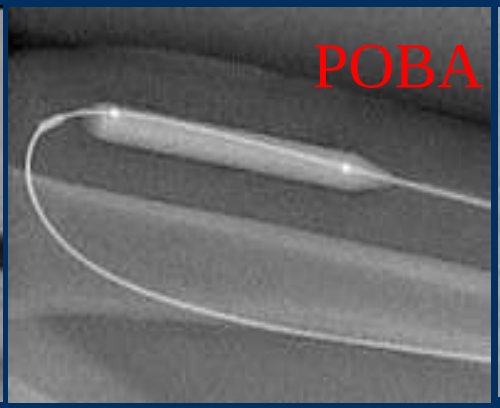
Disclosure

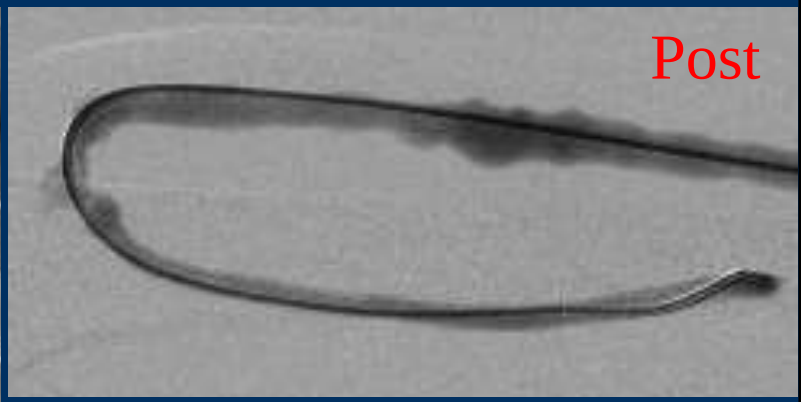
I do not have any potential conflict of interest for this presentation

Kidney Dialysis Outcomes Quality Initiative (K-DOQI) Guidelines

- Stenosis within the dialysis circuit is the main cause of dysfunction / thrombosis of AVF / AVG
- PTA is the standard of care for the treatment of AVF / AVG stenosis
- 6 month primary patency ~ 50%
  - Repeated interventions required to maintain patency and function
  - 12 month secondary patency > 80%







AVF / AVG Stenosis and Patency

- Neo intimal hyperplasia is the main pathologic basis for development of stenosis
- Numerous strategies to increase patency of AVF/AVGs have been explored
  - high pressure balloon angioplasty
  - cutting balloon angioplasty
  - bare metal stenting
  - cryoplasty
  - Stenting with covered stent / stent graft
- Only covered stents have been shown to increase patency in AVGs (Haskal et al, NEJM 2010)

Drug Eluting Balloon (DEB)

- Deposition of an anti proliferative drug onto the vessel wall without leaving a permanent scaffold
- Paclitaxel is the most common drug used in DEBs
  - highly lipophilic, is anti mitotic + anti proliferative
  - promotes tubulin polymerisation resulting in non-functioning microtubules which halts cell division and protein transport, hence inducing apoptosis
  - also inhibits smooth muscle migration into the intima
- DEBs have been shown to be effective in inhibiting neointimal hyperplasia for the treatment of coronary in-stent restenosis and in stenotic femoro-popliteal arterial disease

Scheller et al, NEJM 2006;335:2113-24
Tepe et al, Circulation 2015;3;131(5):495-502

PROSPECTIVE RANDOMISED TRIAL COMPARING DRUG ELUTING BALLOON ANGIOPLASTY VERSUS CONVENTIONAL PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY FOR THE TREATMENT OF DYSFUNCTIONAL HEMODIALYSIS ARTERIO-VENOUS FISTULA OR ARTERIO-VENOUS GRAFT

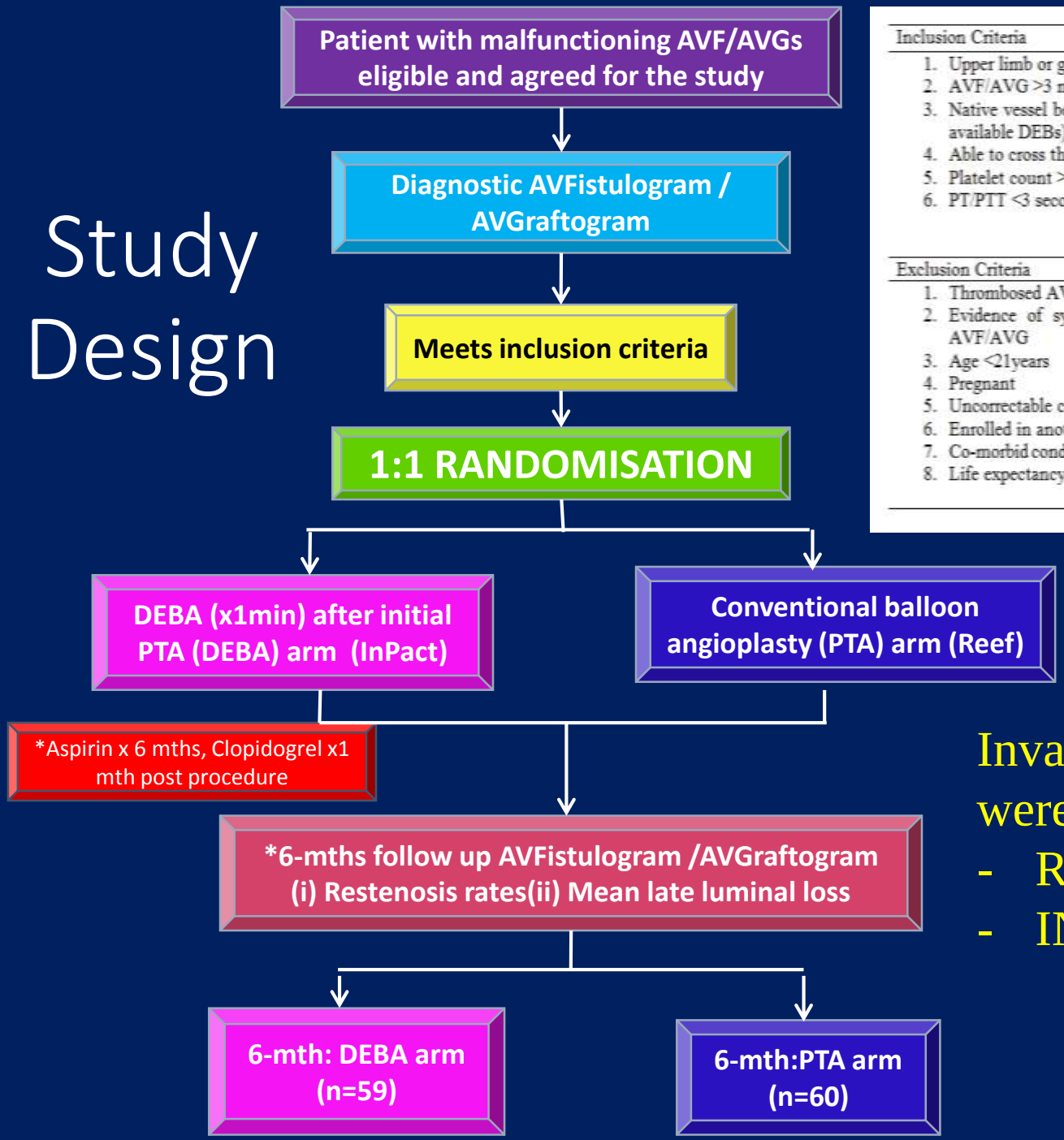
(DEBAPTA Trial)

Investigator Initiated Trial funded by
National Medical Research Council Singapore (NMRC/1296/2011)
Registered on clinicaltrials.gov (NCT01544907)

DEB Angioplasty vs PTA

- Aim
  - To determine the efficacy of DEB angioplasty compared to conventional PTA in AVF and AVG stenoses at 6 months
- Material and Method
  - Prospective RCT (Jan 2012 to Apr 2013)
  - Single centre, un-blinded
  - 119 patients (40 females : 79 males)
  - Mean age of 59.1 years

Study Design



Inclusion Criteria

1. Upper limb or groin malfunctioning AVF/AVG
2. AVF/AVG >3 months old (matured)
3. Native vessel between 4-7mm diameter (corresponding to the sizes of the available DEBs)
4. Able to cross the lesion with guide wire
5. Platelet count $>50x10^9$ / lt
6. PT/PTT <3 seconds above normal

Exclusion Criteria

1. Thrombosed AVF/AVG
2. Evidence of systemic infection or local infection associated with the AVF/AVG
3. Age <21years
4. Pregnant
5. Uncorrectable coagulopathy (despite transfusion) or hypercoagulable state
6. Enrolled in another investigational study
7. Co-morbid conditions limiting ability to comply with follow up requirement
8. Life expectancy <6months

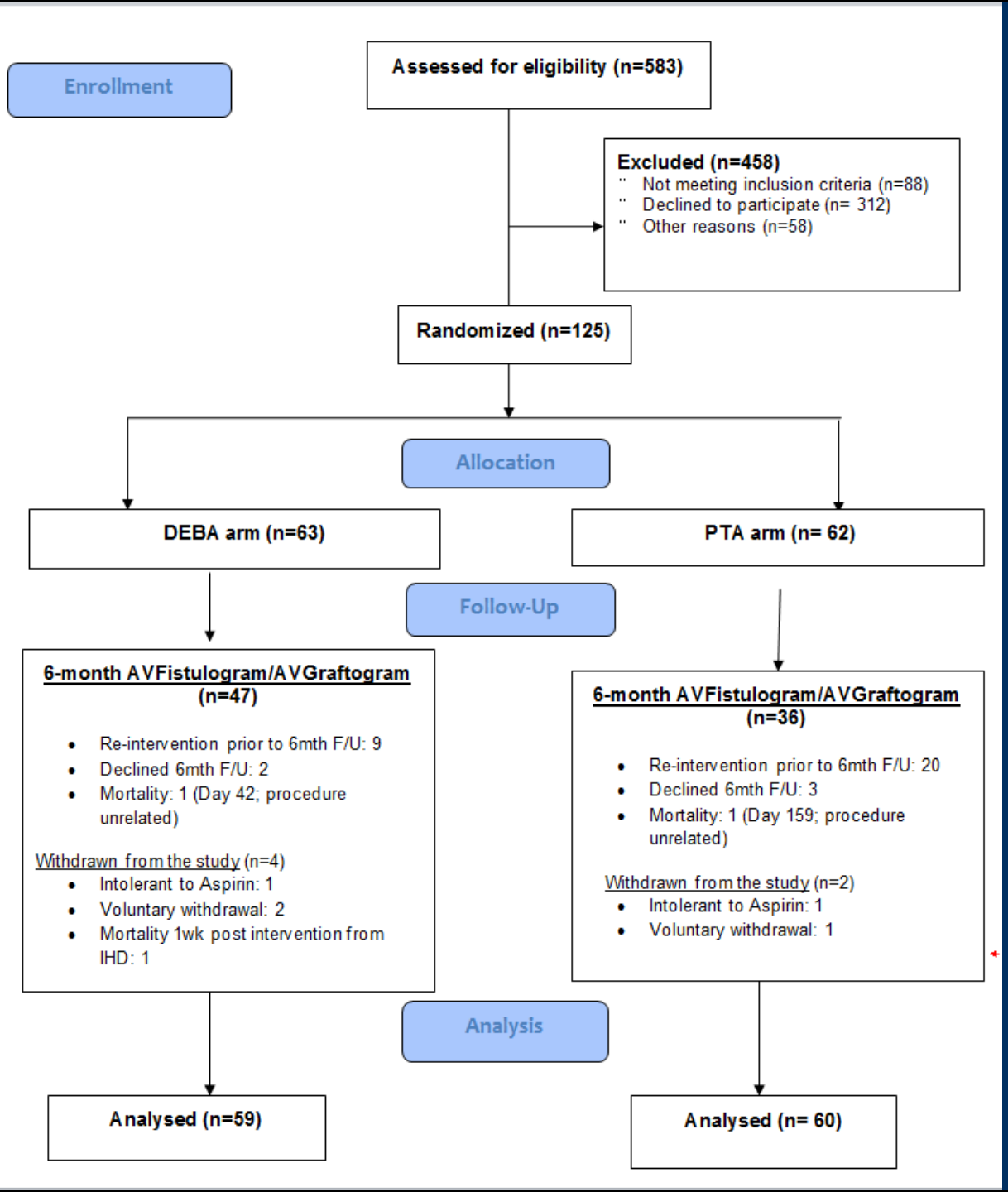
Invatec/Medtronic balloons were used:

- Reef PTA balloon
- IN.PACT Admiral DEB

Study End Points & Definitions

- Primary end point
  - Lesion primary patency at 6 months
  - Restenosis rate at 6month follow up angiogram
- Secondary Endpoints
  - Anatomical and clinical success
  - Lesion primary patency at 12 months
  - Circuit primary patency at 6 and 12 months
- Definitions
  - Lesion primary patency was defined as absence of any repeat intervention (either endovascular or surgical) of the target lesion from the index PTA for the follow-up period.
  - Restenosis rate was defined as the incidence of ≥50% diameter stenosis of the trial lesion at 6-mth follow-up angiogram.
  - Anatomical success was defined as <30% residual diameter stenosis measured immediately after PTA.
  - Clinical success was defined as one successful hemodialysis via the access post-PTA.
  - Circuit primary patency was defined as the time interval from the index PTA to the next access intervention anywhere in the circuit from the arterial inflow to the cavo-atrial junction.

Consort Diagram



Demographic & Clinical Characteristics

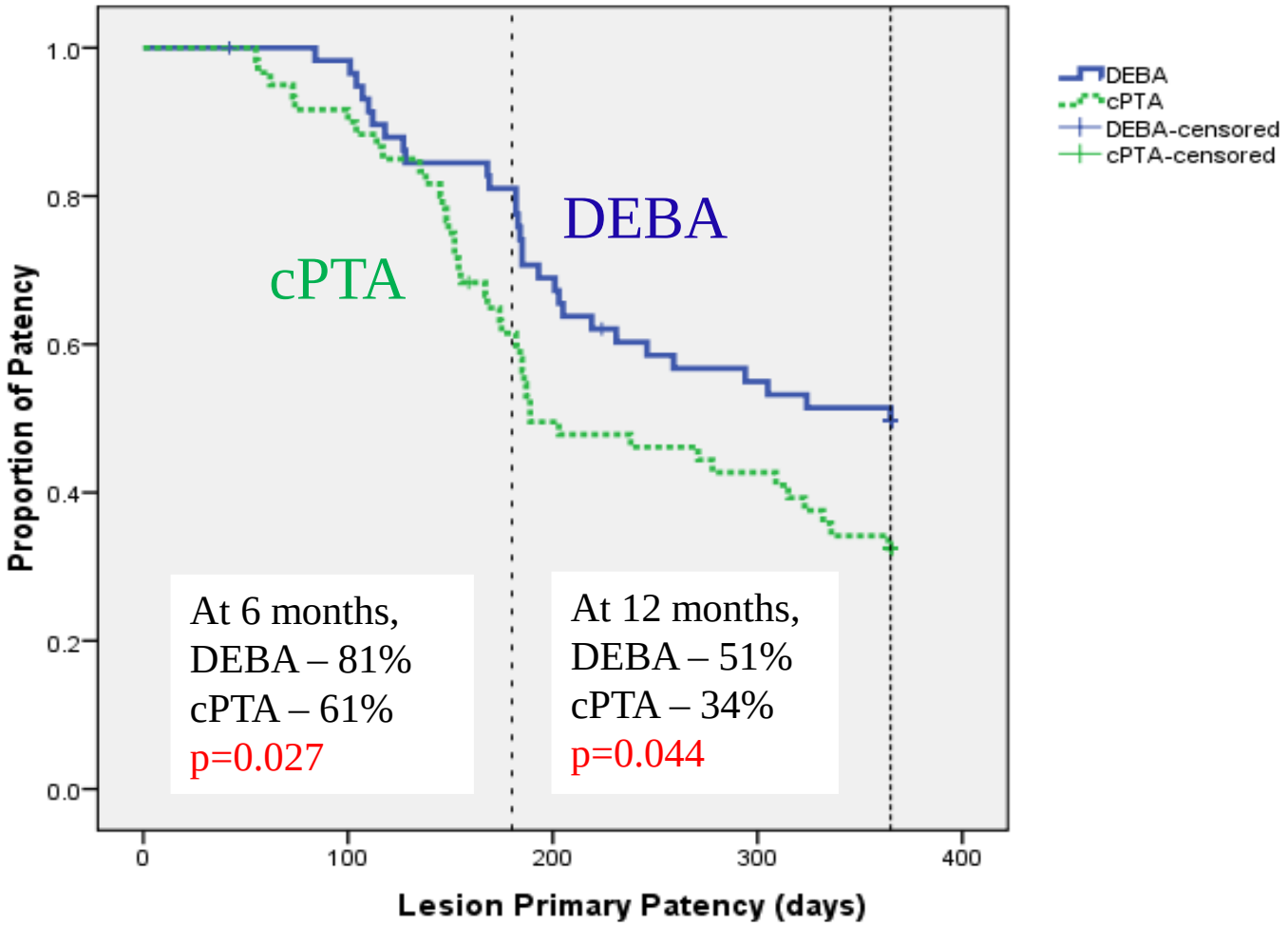
Variable	DEBA (n=59)	PTA (n= 60)	p value
Age (years)			0.838
Mean ± SD	59.0 ± 11.5	59.4 ± 8.80	
Male, no. (%)	39 (66.1)	40 (66.7)	0.948
Smoking, no. (%)	5 (8.5)	6 (10)	0.774
Hyperlipidaemia, no. (%)	40 (67.8)	38 (63.3)	0.608
Hypertension, no. (%)	55 (93.2)	55(91.7)	1.000
Ischaemic Heart Disease, no. (%)	27 (45.8)	23 (38.3)	0.412
Diabetes mellitus, no. (%)	37 (62.7)	34 (56.7)	0.502
Age of Dialysis Access (mos)			0.782
Mean ± SD	44.4 ± 58.6	47.3 ± 54.3	
Range	0–168	3–288	
Side of Dialysis Access, no. (%)			0.791
Left	44 (74.6)	46 (76.7)	
Right	15 (25.4)	14 (23.3)	
Site of Dialysis Access, no. (%)			**0.016** *
Arm	15 (25.4)	28 (46.7)	
Forearm	44 (74.6)	32 (53.3)	
Type of Dialysis Access, no. (%)			0.101
AVF	52 (88.1)	46(76.7)	
AVG	7 (11.9)	14(23.3)	
AVF/AVG Type, no. (%)			0.176
Radio-cephalic (RC)	40 (67.8)	30 (50)	
Brachio-cephalic (BC)	10 (16.9)	18 (30)	
Brachio-basilic (BB)	9 (15.3)	7 (11.7)	
Brachio-brachialis (BBr)	0	2 (3.3)	
Radio-basilic (RB)	0	1 (1.7)	
Brachial-jugular (BJ)	0	1 (1.7)	
Brachial-axillary (BAx)	0	1 (1.7)	
Number of previous angioplasties			0.563
Mean ± SD	1.80 ± 2.32	2.07 ± 2.74	
Range	0-9	0-14	
Length of target lesion (cm)			0.832
Median	2.6	2.5	
Range	0.2–6.3	0.5–8.1	
Anatomic success	53 (89.8)	47 (78.3)	0.087

Results

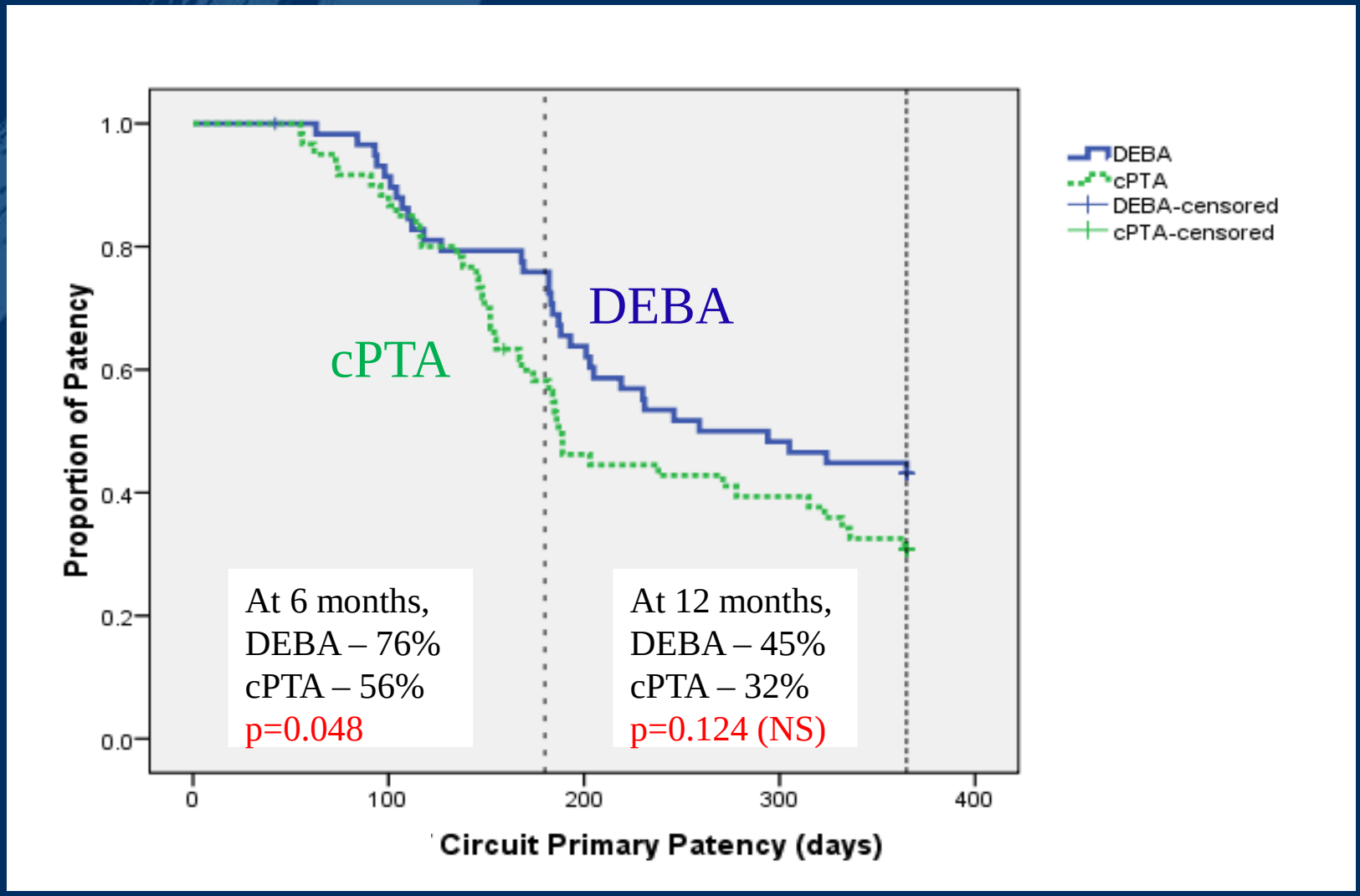
	DEBA	cPTA	p value
Anatomical success	89.9%	78.3%	0.132
Clinical success	100%	100%	-
Restenosis rate (@ 6mths)	34%	62.9%	0.014
Late lumen loss	26.2%	32.5%	0.180

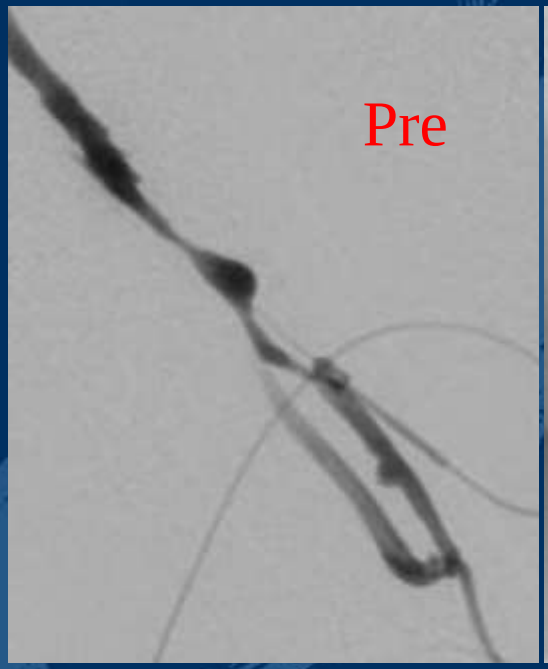
- Anatomical success: <30% residual diameter stenosis measured immediately after PTA
- Clinical success: one successful hemodialysis via the access post-PTA
- Restenosis rate: incidence of ≥50% diameter stenosis of trial lesion at 6mth FU angio
- Late lumen loss: difference between percentage stenosis after angioplasty and at 6 mths

Lesion Primary Patency @ 6 and 12 months



Circuit Primary Patency @ 6 and 12 months





No significant restenosis at 6 month follow up angiogram

Mild restenosis at treated segment with interval development of new adjacent stenosis

Pre

6x60mm DEB

Post DEBA

6 mth angio

Univariate & Multivariate Cox Regression Analysis for Predictors for Lesion Primary Patency

	Variables	DEBA				cPTA			
		Univariate		Multivariate[1]		Univariate		Multivariate[1]	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
	Age (>60 yrs/ <60 yrs)	0.50 (0.23, 1.07)	0.074	0.58 (0.26, 1.26)	0.168	0.98 (0.95, 1.01)	0.219		
	Gender (M/F)	0.67 (0.32, 1.42)	0.293			0.83 (0.43, 1.60)	0.581		
	Smoking (Y/N)	0.79 (0.19, 3.31)	0.744			0.80 (0.28, 2.25)	0.670		
	Types (AVF/AVG)	0.67 (0.23, 1.93)	0.459			0.52 (0.26, 1.02)	0.057	0.55 (0.28, 1.10)	0.090
	Site (Forearm/Arm)	1.15 (0.47, 2.82)	0.767			0.91 (0.49, 1.68)	0.753		
*	Age of dialysis access (>24 mos/ <24 mos)[2]	0.41 (0.19, 0.87)	**0.021**	0.46 (0.21, 0.98)	**0.045**	1.00 (0.99, 1.00)	0.228		
*	No. of previous angioplasties (Y/N)	0.68 (0.33, 1.42)	0.304			2.33 (1.11, 4.91)	**0.026**	2.24 (1.06, 4.73)	**0.035**
	Length of stenosis (cm)	0.87 (0.67, 1.11)	0.253			1.06 (0.88, 1.26)	0.549		

[1] Variables included were significant at $p \leq 0.05$ using forward selection approach.

[2] 24months was the median for the cohort for age of dialysis access

Complications

- No study related mortality
  - 1 death in each arm but not procedure related
- No bleeding complication from dual antiplatelet therapy
- 1 venous rupture at angioplasty site in cPTA arm successfully controlled with balloon tamponade
- 1 balloon rupture in DEBA arm with no sequelae

Summary of Results

- Our study showed that DEBA was significantly superior to cPTA in terms of
  - 6 and 12 month lesion primary patency
  - 6 month circuit primary patency
  - 6 month restenosis rate
- No statistical significance in
  - 12 month circuit primary patency (p = NS)
  - 6 month late lumen loss (p = NS)

DEB Angioplasty for AVF/AVG Stenosis

Author	Year	Type	Study	Group	N	DEB	6m PP	12m PP
Katsanos	2012	AVF, AVG	RCT	DEB PTA	20 20	InPACT	75% 25%	
Lai	2014	AVF	Prospect ive	DEB PTA	10 10	Sequent	70% 0%	20% 0%
Patane	2014	AVF	Retrospe ctive	DEB PTA	26 -	InPACT	96%	91%
Kitrou	2015	AVF, AVG	RCT	DEB PTA	20 20	InPACT		35% 5%
Verbeeck	2016	AVF	Observat ional	DEB PTA	41 -	InPACT	81%	60%
Cildag	2016	AVF	Retrospe ctive	DEB PTA	26 26	Freeway	77% 65%	65% 34%
DEBAPTA Trial at SGH	2017	AVF, AVG	RCT	DEB PTA	59 60	InPACT	81% 61%	51% 34%

Systematic Review of DEB Angioplasty for Dialysis AVF Stenosis

- 6 studies with 254 interventions in 162 patients
  - 2 RCTs and 4 cohort studies
- 6 months Target Lesion Primary Patency
  - 70% to 97% for DEBs
  - 0% to 26% for non-DEBs.
- No procedure-related major or minor complications
- CONCLUSIONS:
  - DEBs are safe with some benefit in terms of improved rate of restenosis. However, this body of evidence is small and clinically heterogeneous.
  - A large multicentre RCT is needed to clarify the role of DEBs in treatment of dialysis access stenosis.

Khawaja et al, J Vasc Access. 2016 Mar-Apr;17(2):103-10

Cost Effectiveness Analysis

- Our study
  - Cost of DEB vs cPTA balloon = SGD 2000 vs SGD 250
  - Mean patency of DEBA vs cPTA = 7.8 months vs 5.7 months
  - 12 month lesion primary patency = 51% vs 34%
- Kitrou et al, Eur J Radiol. 2015 Mar;84(3):418-23.
  - Median patency of DEB vs PTA was 0.64 yrs vs 0.36 yrs
  - 12 month lesion primary patency was 35% vs 5% ($p<0.001$)
  - Incremental Cost Effectiveness ratio (ICER) was 2198€ per primary patency year of dialysis access gained.
  - Incremental Net Benefit (INB) was 1068€ for a willingness-to-pay (WTP) threshold of 5000€ (corresponding acceptability probability >97%).

Conclusions

- DEBA significantly prolonged both 6-month and 12-month lesion primary patency and 6-month circuit primary patency in AVF and AVG stenosis, when compared to cPTA.
- However, the superior circuit primary patency was not sustained at 12 months.
- DEB does work for AVF/AVG stenosis but does the incremental patency of about 2 months justify the high cost of DEB (SGD 2000)? ie Is it cost effective?
- Further large scale trials are needed.

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Thank you for your attention !

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