Drug eluting balloon in fistuloplasty:
Good, bad or ugly?

Advanced Course in Vascular Access 2019

Convenor: Professor Kittipan Rerkasem

2 – 3 May 2019, Chiang Mai, Thailand

Dr John Swinnen

Vascular Surgeon

Dialysis Access Specialist

MSF Trauma Surgeon

Westmead Hospital

University Of Sydney

Disclosures

An independent, clinician driven trial

This study was supported by an

UNCONDITIONAL grant from Medtronic

Chief Researchers

Dr John Swinnen
Dialysis Access Specialist
Westmead Hospital
Sydney

Dr David Burgess
Interventional Cardiologist
Blacktown Hospital
Sydney

Dr Kerry Hitos
Chief Research Officer
Associate Professor Surgery
Westmead Clinical School
University of Sydney

The Native AVF

Western Renal Area Dialysis Service, Sydney, Australia

≈ 1000 patients on Dialysis

- Our philosophy:
  - → **All** fistulas are native (Zero grafts)
    - → Create the fistula,
      - → Mature the fistula,
        - → Survey all fistulas,
          - → Maintain the fistula

For as long as needed, ? For life ?

"Complications"

Problem	Cause	Solution/s	Status
Graft Sepsis	• Fistula Grafts	• Native AVF only	Eliminated
Fistula Occlusion	• Fistula Grafts • No Surveillance	• Native AVF only • Surveillance all AVF • Maintenance of all AVF	Largely Eliminated
Secondary Fistula	• Use of Grafts • No Surveillance	• Native only • Surveillance of all AVF • Maintenance of all AVF	Uncommon
Failure to Mature	• Poor planning • Poor Surgery • No"Force Mature"	• U/S Planning • "Balloon assisted maturation"	Very uncommon (< 10%)
* Central Vein stenosis/occlusion * Sepsis & Death	• Vascaths • Delayed Referral • Poor AVF Management	• Early Referral • PD first policy • "Balloon assisted maturation" • Fistula Surveillance • Fistula Maintenance	**A problem !** *Late referal (WRA 40%) *Part solution No L Vascath!

Biggest Problem: Stenosis!

- Some fistulas never stenose
- Some have a single stenotic episode
- ? 25% of fistulas are “Frequent Fliers”

Fistula Stenosis

- Due to “NIH”, Neo Intimal Hyperplasia
- The “healing process” in the blood vessel
- Initiated at the time of Angioplasty Injury
- Occurs typically between **6 weeks & 6 months**

DEB in AVF at Westmead

- First DEB in AVF in September 2010
- Expensive technology ($2000.00)
- Intervention Criteria for DEB:

→ Recurrent stenoses only

Drug Eluting Balloons in the Native Access Fistula: A Retrospective Study

RACS ASC 2014 Singapore

Vascular Surgery: Friday, 7th May 2014

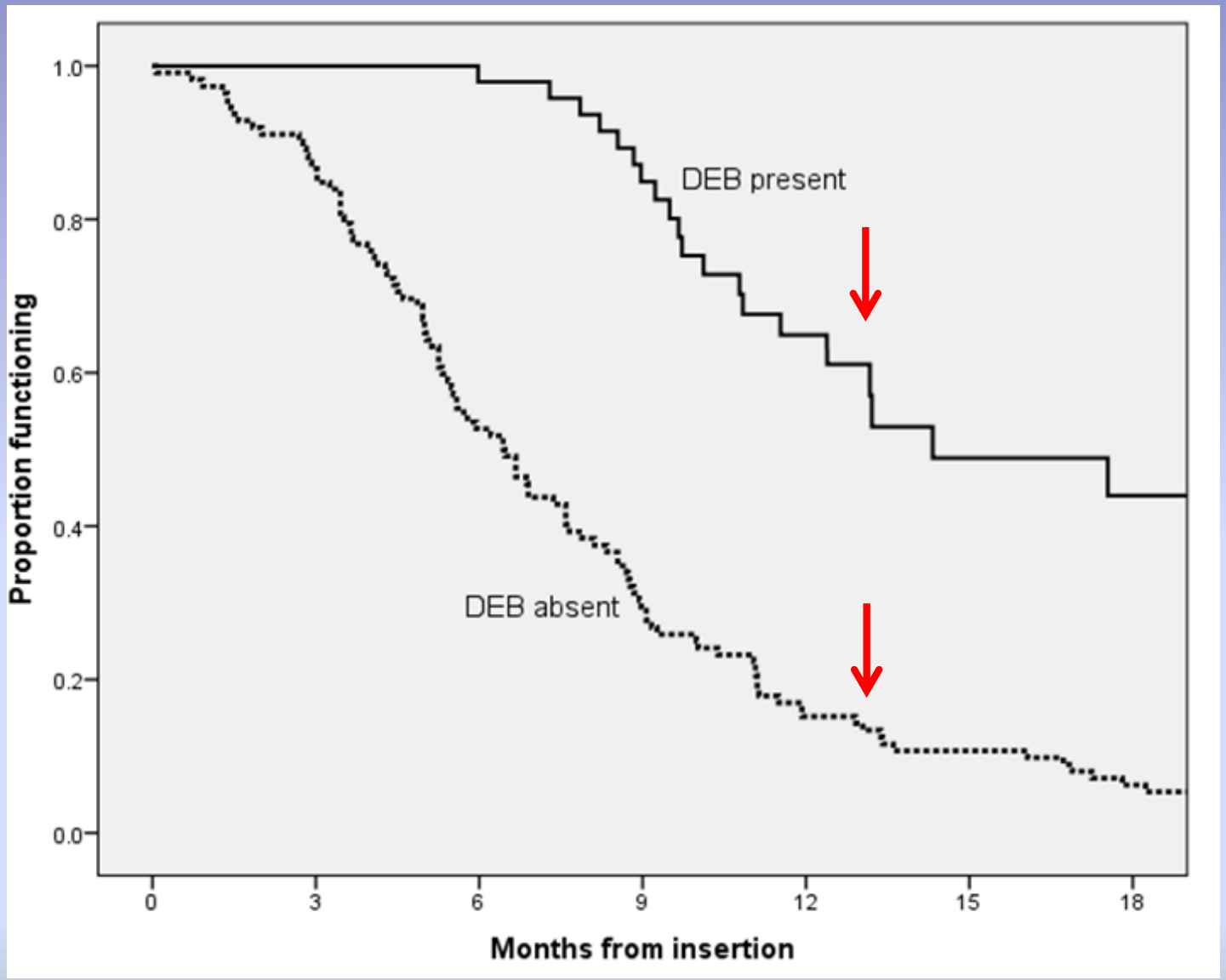
Dr John Swinnen

Access Specialist

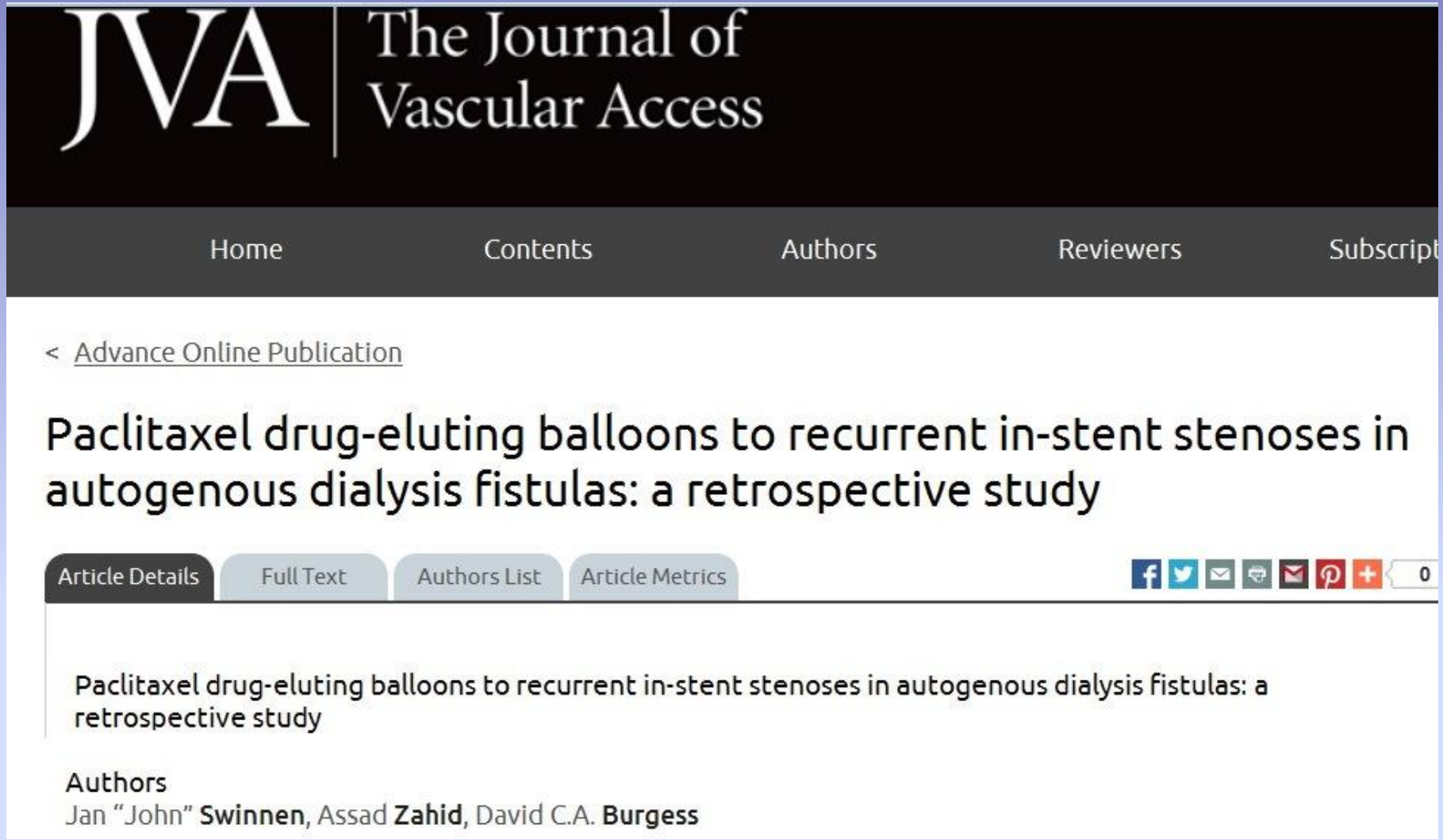
Westmead Hospital

University Of Sydney

RE-INTERVENTION



KM curve for DEB present versus absent. Statistically significant



"Paclitaxel Drug Eluting Balloons to Recurrent Instent Stenoses in Autogenous Dialysis Fistulas: A Retrospective Study"

Multicentre Australian RCT

- DEB vs Sham Balloon in recurrent AVF stenosis.
- From 15th January 2015 – 27th March 2017
- Three centres in New South Wales, Australia:
  - Westmead Hospital, Sydney
  - Blacktown Hospital, Sydney
  - Wollongong Hospital, Wollongong

Methods:

Study Inclusion Criteria

Patient has a Native AVF

AND

The AVF has a Significant Stenosis

AND

The stenosis is Recurrent

AND

The Index Trial Area is visible on U/S

Methods:

Study Inclusion Criteria

<u>Significant Stenosis</u>

Diameter <2.0mm on U/S*

OR

Diameter 2.0mm - 4.0mm +

Other evidence of AVF malfunction

*Fahrtash F, Swinnen J, et al. Defining a significant stenosis in an AVF. *Seminars in Dialysis* 2011

Methods:
Operative Protocol

1. Treat Index Stenosis as normal, including BMS
2. Once GOOD technical result achieved
3. (Stratified) randomisation to DEB or Sham balloon
4. Aspirin + Plavix 1 month and follow-up

Stratified Randomisation

I. Age of Fistula: ≤ 6 months OR >6months

II. Location of Fistula: Forearm OR Other

III. Index Stenosis is an instent stenosis: Yes OR No

IV. Index Stenosis treated with stent placed today: Yes OR No

Methods:
Follow up

Primary Endpoint

Late Lumen Loss of Index Trial Area (ITA)

Secondary Endpoints

1. Qa (Fistula Volume Flow)
2. Re-intervention to ITA

Methods:
Follow up

- Baseline Diameter of ITA:

  Narrowest diameter ITA on U/S > 1day < 1 week post op

  (To eliminate “recoil” & compare f/u U/S with U/S)

- Qa measured in Brachial artery

- Follow up U/S at 6 weeks, 3 months, 6 months, 1 year

Methods:
Follow up

- Sonographers, 8 in all, BLINDED to treatment

- U/S probe 12MHZ or higher

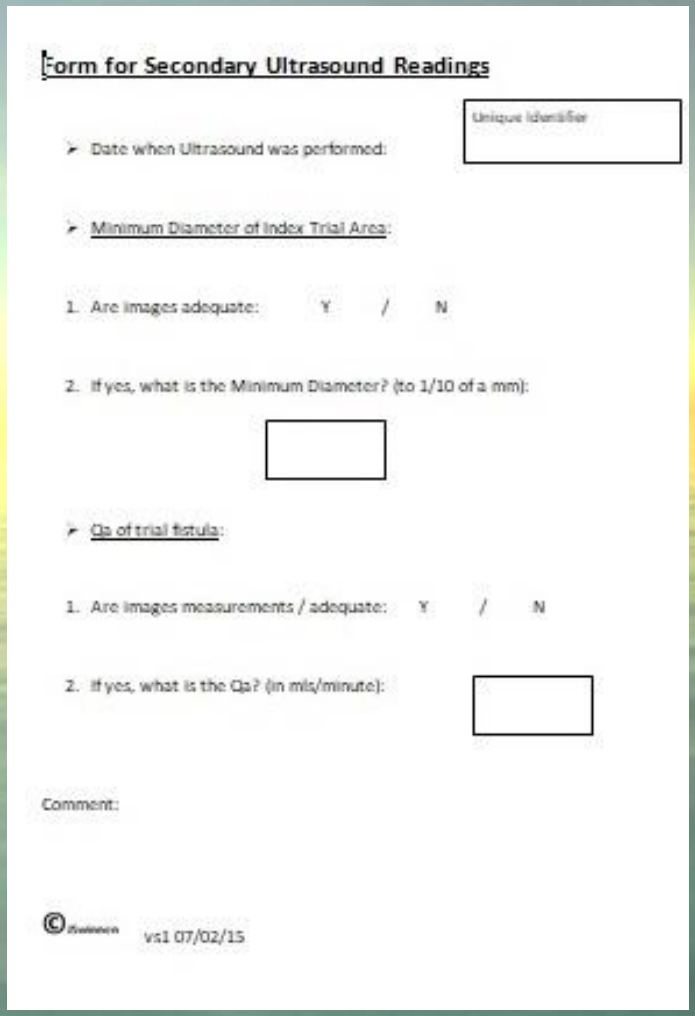
- 13 images required:

  x 2 Brachial a diameter

  x 3 Qa

  x 9 Narrowest area: x3 Grey scale, x6 “color mode)

Secondary Reading of U/S



Form for Secondary Ultrasound Readings

Unique Identifier

- Date when Ultrasound was performed:
- Minimum Diameter of Index Trial Area:

1. Are images adequate: Y / N
2. If yes, what is the Minimum Diameter? (to 1/10 of a mm):

- Qa of trial fistula:

1. Are images measurements / adequate: Y / N
2. If yes, what is the Qa? (in mls/minute):

Comment:

© vs1 07/02/15

- De-identified Images x13 & Sonographer's report sent
- Reviewed by 2 Physicians from Dept NMUS blinded to Rx
- Images judged adequate or not

  Consensus value on Diameter

  Consensus value on Qa

Results

- 3 Centres:

Westmead Hospital, Sydney	71
Blacktown Hospital, Sydney	46
Wollongong, Wollongong	11

- Decision to break trial at 6 months (vs 12 m)
  - → Issue of timeliness
  - → NIH is a phenomenon of 6 weeks – 6 mths

Results

- 144 **recurrent** stenoses entered into trial
- 132 **recurrent** stenoses randomised
- 129 **recurrent** stenoses followed up

Patient Characteristics

No Significant Difference

	Sham	DEB	P Value
	N= 60 (%)	N = 68(%)	
Age (years), mean (± SD)	64.5 (± 13.9)	65.2 (±13.6)	0.780
Male gender	37 (61.7)	42 (61.8)	0.991
Comorbidities			
Diabetes mellitus	39 (65.0)	38 (55.9)	0.293
Current smoker	3 (5.0)	7 (10.3)	0.334
Cause of ESRF			0.540
Diabetes mellitus	29 (18.3)	28 (41.2)	
Glomerulonephritis	7 (11.7)	5 (7.4)	
Hypertension	6 (10.0)	12 (17.6)	
Polycystic	2 (3.3)	6 (8.8)	
Reflux Nephropathy	2 (3.3)	3 (4.4)	
Other	14 (23.3)	14 (20.6)	
Current Renal Replacement Therapy			0.391
CAPD	1 (1.7)	2 (2.9)	
Through Index Fistula	49 (81.7)	62 (91.2)	
Through Other Fistula	2 (3.3)	0 (0.0)	
Predialysis	5 (8.3)	3 (4.4)	
Transplanted	1 (1.7)	0 (0.0)	
Through Vascath	2 (3.3)	1 (1.5)	

Fistula Characteristics

No Significant Difference

Age of fistula			
≤ 6 months	3 (5.0)	2 (2.9)	0.441
> 6 months	57 (92.0)	66 (97.1)	
Location of Index Stenosis for Trial Entry			
In Previously Stented Segment	31 (53.4)	29 (42.6)	0.226
In Previously Unstented Segment	27 (46.6)	39 (57.4)	
AVF Type			0.861
Forearm			
Radio-Cephalic	33 (55.0)	39 (57.4)	
Other Forearm	2 (3.30)	5 (7.4)	
Non Forearm			
Brachio-Cephalic	11 (18.3)	13 (19.1)	
Brachio-Basilic	9 (15.0)	7 (10.3)	
Long Saphenous	3 (5.0)	2 (2.9)	
Other Non-Forearm	2 (3.3)	2 (2.9)	

Recurrent Stenosis Characteristics

No Significant Difference

Anatomical Segment: Site of Index Stenosis			0.342
Artery	9 (15.0)	8 (11.8)	
Anastomosis	9 (15.0)	6 (8.8)	
Swing Vein	23 (38.3)	21 (30.9)	
Useable Segment	10 (16.7)	14 (20.6)	
Outflow Vein	9 (15.0)	19 (27.9)	
Diameter of Index Stenosis (mm), mean (±SD)			
	2.2 ± 2.2	1.9 ± 1.33	0.319
Qa on Study Entry (ml/min), mean (±SD)			
	556.9 ± 350.2	580.3 ± 278.0	0.677
Length of Index Stenosis (mm)			0.487
<5	15 (25.0)	15 (22.1)	
<10	21 (35.0)	19 (27.9)	
≤ 20	14 (23.3)	15 (22.1)	
>20	10 (16.7)	19 (27.9)	
Number of Previous **ITA** Interventions, mean (±SD)			
	2.0 ± 1.3	1.8 ± 1.3	0.567
Number of Previous **Non ITA** Interventions, mean (±SD)			
	2.0 ± 2.2	2.6 ± 3.1	0.422

Primary Endpoint

Late Lumen Loss

Cumulative Percentage Distribution of Late Lumen Loss DEB vs Sham at 6 months and 12 months

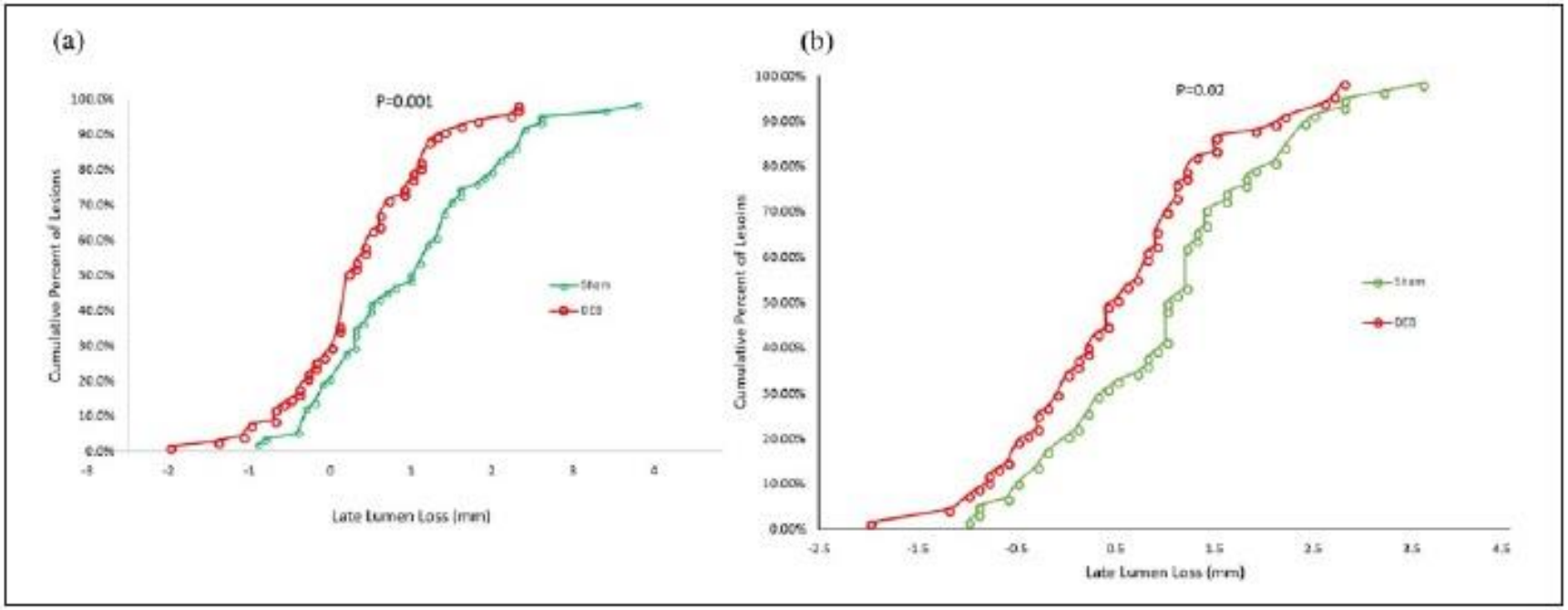
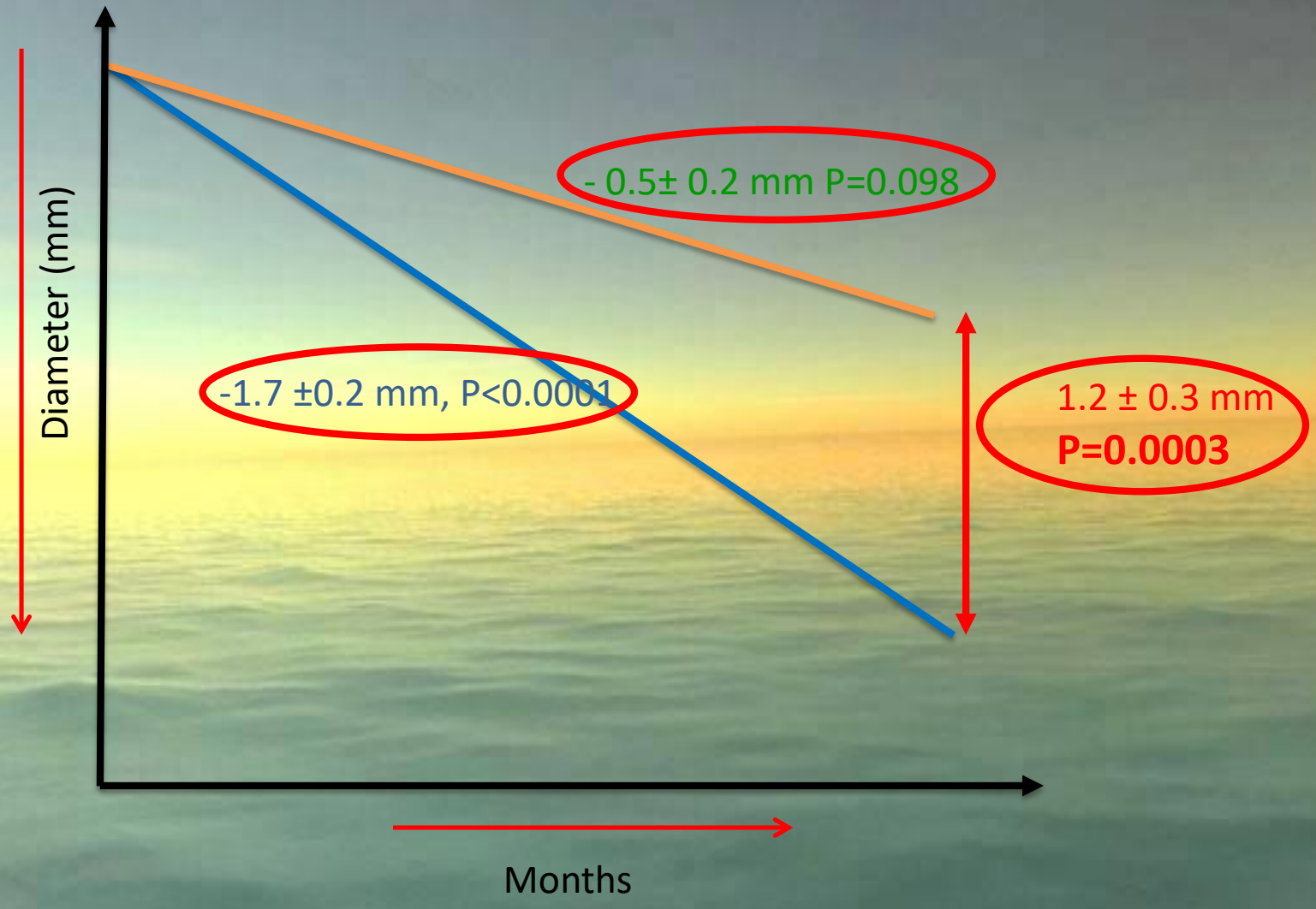


Figure 3. Cumulative percentage distribution for LLL (a) at 6 months and (b) at 12 months.

Rate of Change in Diameter Per Month



© 2015-2017 J.Swinnen – All Rights Reserved

Secondary Endpoint 1

Qa Fistula Volume Flow

Decline in Qa: Fistula Volume Flow

At Six months, using the LMEM:

The rate of Qa decline for the Sham balloon arm was 37 mL/min per month (p = 0.002)

The rate of Qa decline for the DEB balloon arm was 0.40 mL/min per month (p = 0.97)

The difference in decline between the two groups was significant at 37 mL/min (p = 0.02)

At 12 months, using the LMEM:

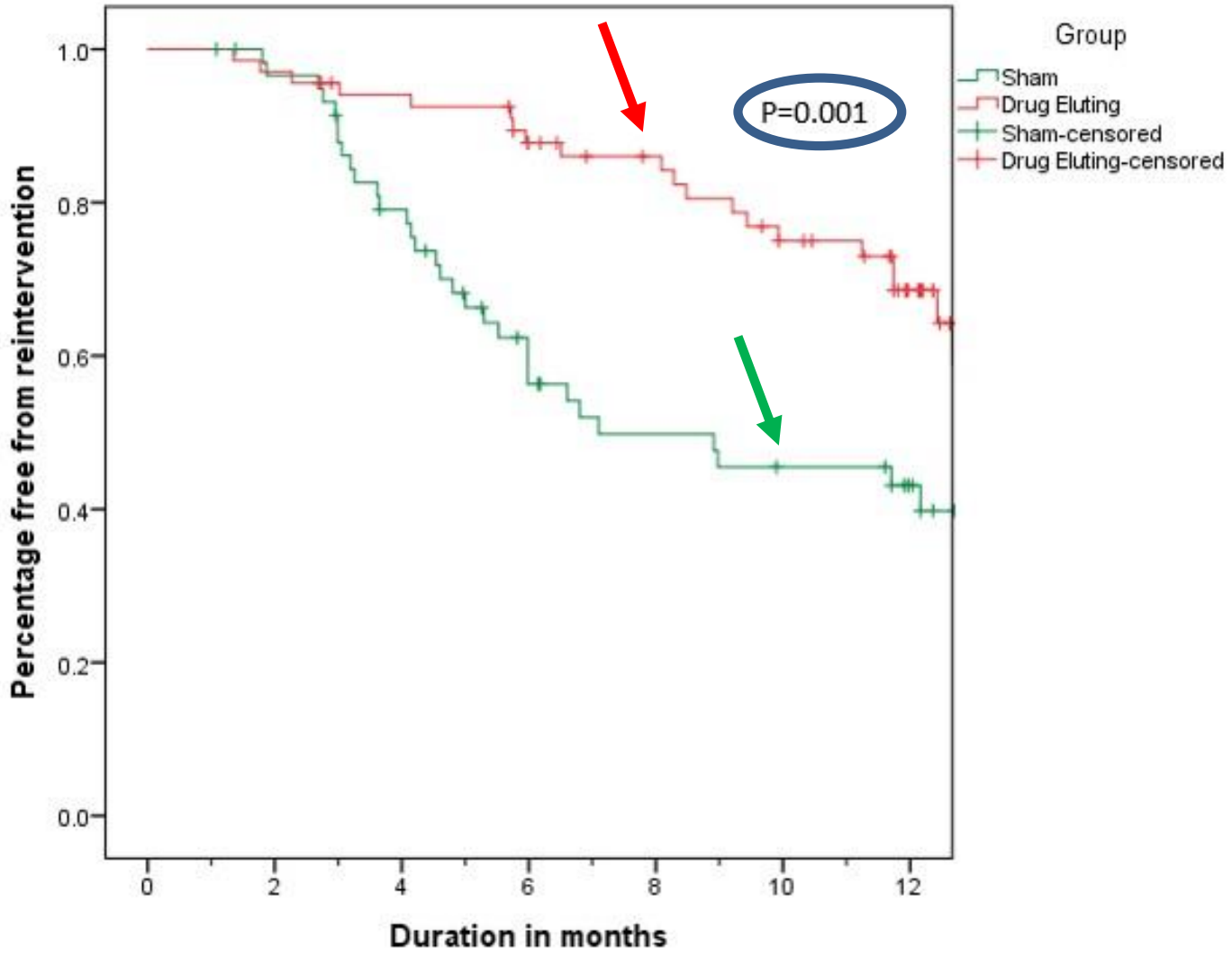
The rate of Qa decline for the Sham balloon arm was 27 mL/min per month (p = 0.001)

The rate of Qa decline for the DEB balloon arm was 18 mL/ min per month (p = 0.003)

The difference in decline between the two groups was 8 mL/min (p = 0.44)

Secondary Endpoint 2

Re-intervention to Index Trial Area

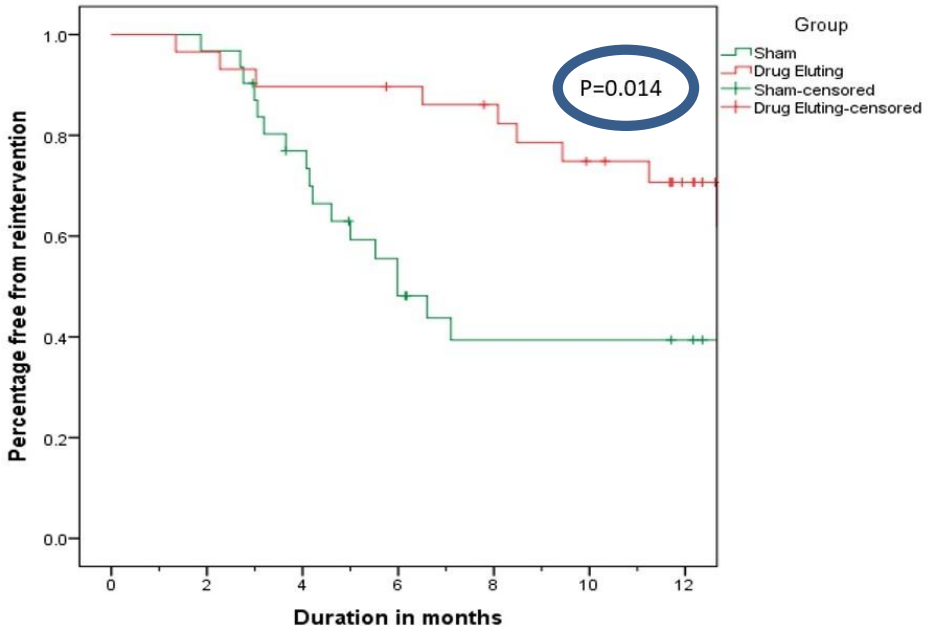


Freedom from Re-Intervention

N at risk

Group							
DEB	68	66	61	52	47	39	25
Sham	60	56	44	28	23	20	14

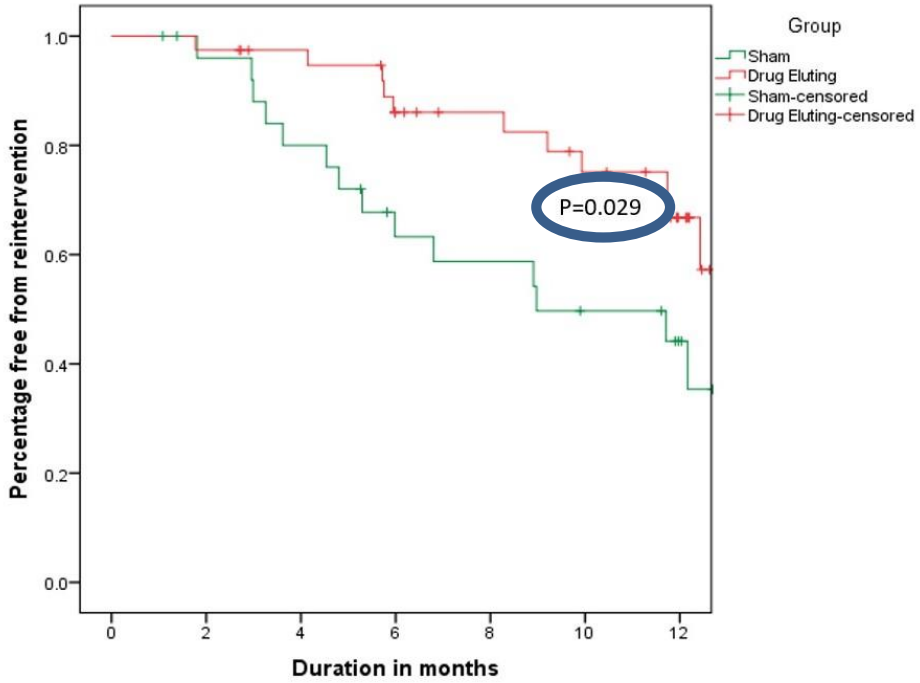
Freedom from Re-Intervention Stented vs Unstented Group



N at risk

Group							
DEB	29	28	26	25	23	19	13
Sham	31	30	22	13	9	9	8

Figure 5a: Kaplan-Meier curve for freedom from reintervention to 12 months follow up in the **stented** group.



Group							
DEB	39	38	35	27	24	20	12
Sham	27	24	20	14	13	10	6

N at risk

Figure 5b: Kaplan-Meier curve for freedom from reintervention to 12 months follow up in the **unstented** group.

Patients Free from Re-Intervention at 12 m

- If patient receives a sham balloon,

  Mean time to re-intervention is **10 months**

- If patient receives a DEB balloon,

  Mean time to re-intervention not measured: **42 m**

Conclusions

Our study demonstrates that the Medtronic DEB:

1. Significantly reduces LLL in the n AVF circuit, in recurrent stenoses
2. Significantly reduces the rate of decline in Volume Flow (Qa)
3. Dramatically prolongs Freedom of Re-intervention from a mean of 10 months to 42 months

Multicentre, randomised, blinded, control trial of Drug Eluting Balloon vs Sham Balloon in Recurrent Native AV Fistula Stenoses

Available online Journal of Vascular Access Surgery

"https://doi.org/10.1177/1129729818801556"

Participants & Recognition

- Dr David Huber, Chief Investigator Wollongong
- Dr Simon Gruenewald, U/S Physician, Westmead H
- Dr George Larcos, U/S Physician, Westmead H
- Dr David Farlow, U/S Physician, Westmead H
- Kirsty Kedacic, Data Base Manager
- Donna Oomens, Sonographer Norwest Private
- Jacqui Spurway, Sonographer Orange Base H
- Kristie Sweeney, Sonographer Bathurst Base H
- Pauline Byrne, Dialysis CNC, Wollongong H
- Wayne Mulligan, Sonographer, Liverpool Private lab
- Kylee Hoskins, Medtronic Rep for Westmead

- MEDTRONIC Australia for its UNCONDITIONAL contribution

Concern of Paclitaxel Devices and Increased Mortality: Does it apply to HD?

DaSy 2019

Singapore 28 – 30 March 2019

Dr John Swinnen

Vascular Surgeon

Dialysis Access Specialist

MSF Trauma Surgeon

Westmead Hospital

University Of Sydney

1 October 2018

Westmead Multi-centre
RCT DEB in recurrent AVF stenosis

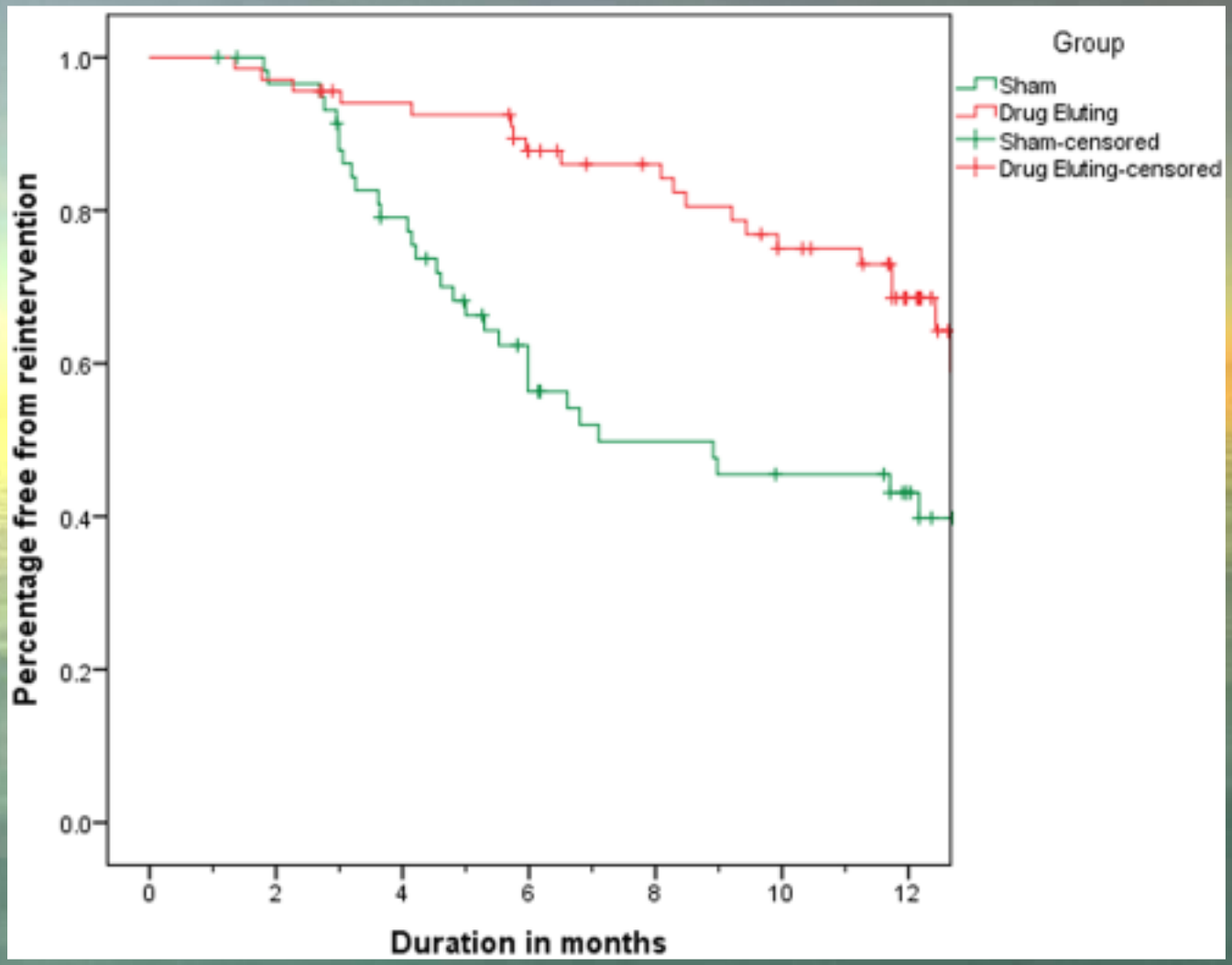
Mean time to re-intervention:

* DEB - 10 Months

* Sham Balloon - 42 Months

"https://doi.org/10.1177/1129729818801556"

Re-intervention Sham vs DEB



Original research article

JVA | The Journal of Vascular Access

Multicentre, randomised, blinded, control trial of drug-eluting balloon vs Sham in recurrent native dialysis fistula stenoses

The Journal of Vascular Access
1–10
© The Author(s) 2018
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1129729818801556
journals.sagepub.com/home/jva
SAGE

Jan "John" Swinnen[1], Kerry Hitos[2], Lukas Kairaitis[3,4], Simon Gruenewald[5], George Larcos[5], David Farlow[5], David Huber[6], Gabriel Cassorla[7], Christopher Leo[8], Laurencia M Villalba[6], Richard Allen[1], Farshid Niknam[6] and David Burgess[9]

Abstract

Background: Endovascular treatment of autogenous arteriovenous haemodialysis fistula stenosis has high reintervention rates. We investigate the effect of drug-eluting balloons in the treatment of recurrent haemodialysis fistula stenosis.

8 December 2018

SYSTEMATIC REVIEW AND META-ANALYSIS

American Heart Association | American Stroke Association

Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitrou, MD, PhD; Miltiadis Krokidis, MD, PhD; Dimitrios Karnabatidis, MD, PhD

Background—Several randomized controlled trials (RCTs) have already shown that paclitaxel-coated balloons and stents significantly reduce the rates of vessel restenosis and target lesion revascularization after lower extremity interventions.

Methods and Results—A systematic review and meta-analysis of RCTs investigating paclitaxel-coated devices in the femoral and/or popliteal arteries was performed. The primary safety measure was all-cause patient death. Risk ratios and risk differences were pooled with a random effects model. In all, 28 RCTs with 4663 patients (89% intermittent claudication) were analyzed. All-cause patient death at 1 year (28 RCTs with 4432 cases) was similar between paclitaxel-coated devices and control arms (2.3% versus 2.3% crude risk of death; risk ratio, 1.08; 95% CI, 0.72–1.61). All-cause death at 2 years (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47; —number-needed-to-harm, 29 patients [95% CI, 19–59]). All-cause death up to 5 years (3 RCTs with 863 cases) increased further in the case of paclitaxel (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93; —number-needed-to-harm, 14 patients [95% CI, 9–32]). Meta-regression showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death (0.4±0.1% excess risk of death per paclitaxel mg-year; $P<0.001$). Trial sequential analysis excluded false-positive findings with 99% certainty (2-sided α, 1.0%).

Conclusions—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted.

Clinical Trial Registration—URL: www.crd.york.ac.uk/PROSPERO. Unique identifier: CRD42018099447. **(*J Am Heart Assoc.* 2018;7:e011245. DOI: 10.1161/JAHA.118.011245.)**

Key Words: balloon angioplasty • paclitaxel • paclitaxel-coated balloon • paclitaxel-eluting stent

Downloaded from htt

The Problem

The meta-analysis on DEB in the femoro-popliteal **arterial** segment has shown:

- 2-fold increase in all-cause mortality at 1 & 2yrs,
- As well as showing a dose response effect

Impact of DEB Mortality Study on Fistula Management WRA

Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Nephrology & Dialysis Consultants Meeting,
Tuesday 18th December 2018
Westmead Hospital

Dr John Swinnen
Vascular Surgeon
Dialysis Access Specialist
MSF Trauma Surgeon

Westmead Hospital

University Of Sydney

Drug Elution Technology

- Paclitaxel to target on angioplasty balloon

- Well established in:

  - Coronary circuit (15 years+)
  - Peripheral Vascular circuit (10 years +)
  - In Fistula circuit (2 years +)

NB: Paclitaxel dose in AVF >>>> Coronary a

Frequent Fliers (≈20% of fistulas)

- Frequent fliers have fewer interventions
  (**decrease** in Morbidity/Mortality)

- Improved fistula flows & better dialysis
  (**decrease** in Morbidity/Mortality)

- Less thromboses / loss of access / new access
  (**decrease** in Morbidity/Mortality)

Meta-analysis: DEB in femoral circuit Doubling of late deaths1 and 2 years.

1. Is this true?

2. If true, does this apply to AVFs

3. Even if true, AND it applies to AVFs

? Does risk outweigh benefit ?

? In Frequent Fliers?

Our Proposal

1. Restrict DEB to frequent fliers

   (≥2 interventions to circuit in 1 year or ≥ 4 overall)

2. Restrict DEB to “precious fistulas”

3. ? Age limit ?

4. Patient consent form for DEB

DEMMAS

Drug **E**luting **M**ortality **M**eta-analysis and **A**VF **S**tudy

Retrospective analysis of Westmead AVF database

- 2000 – 2019:
  2560 Fistuloplasties (JS team) in1200 Patients
- 2000 – 2010: 500 patients, NO DEB (Group 1)
- 2010 – 2019: 300 patients, DEB (Group 2)

Power Calculation

- Hypothesized effect: Doubling 2 year mortality
- Mortality of Study Groups (ANZDATA): 13.3% pa
- Alpha setting at 0.05 and 80% power
- Sample size of 282:141 patients Group 1 and 141 Group 2

Trial Design

- All cause mortality
- Analysis by cause of mortality
- Dose Effect: All patients receiving DEB will have Paclitaxel dose calculated

(Length of balloon x Diameter x Paclitaxel/mm^2)

Result by August 2019

Is Paclitaxel safe in the AVF ?