Disclosure

Consultant –Teleflex, MedComp, Cook, BD Bard, WL Gore, Lutonix, Adrenas

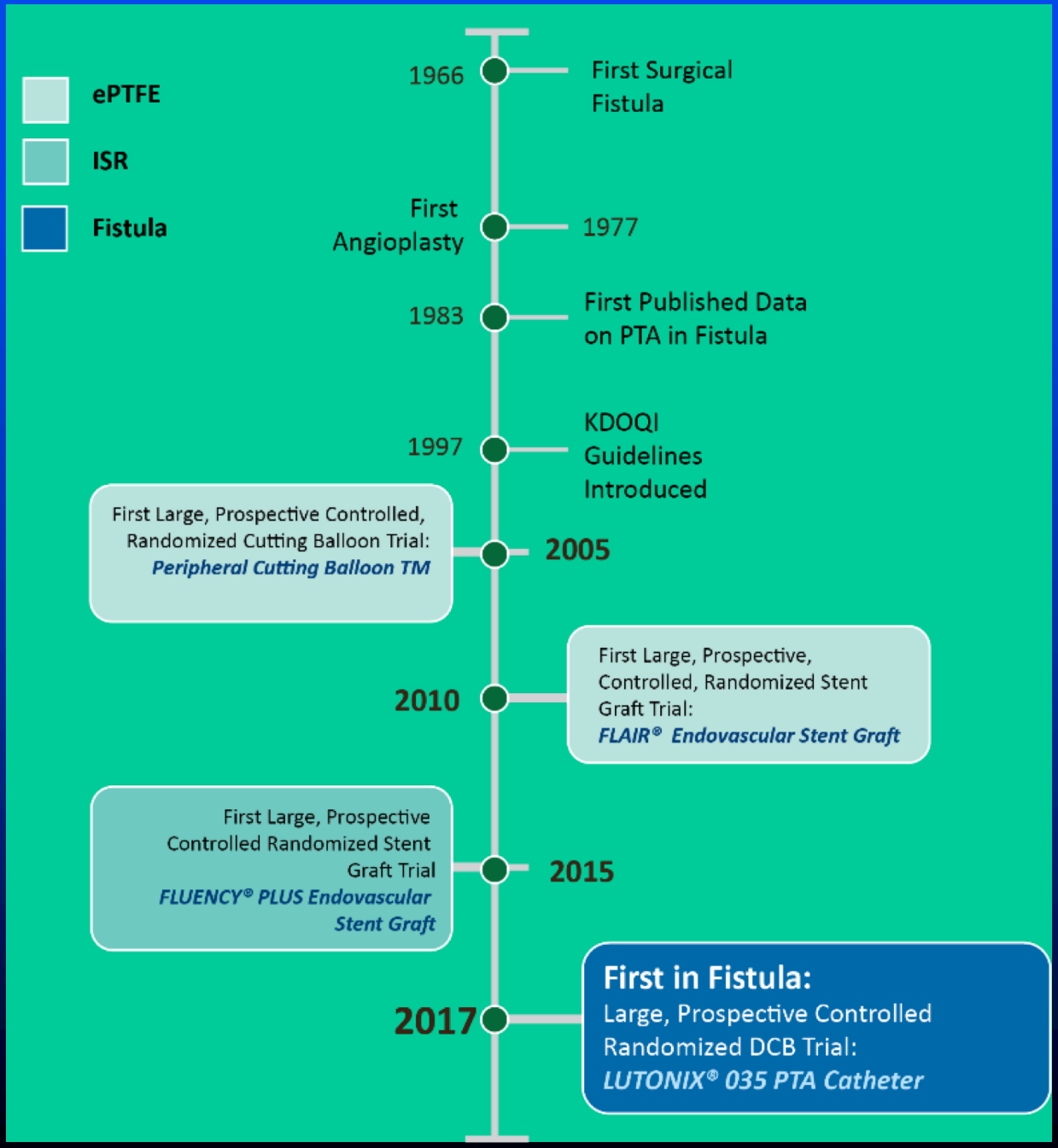
Other Financial or Material Support – National PI, Lutonix AV trial

Royalty, Cook and Teleflex

Penn IR

DCB in Failing AVF

Penn IR


ePTFE
ISR
Fistula
1966
First Surgical Fistula
First Angioplasty
1977
1983
First Published Data on PTA in Fistula
1997
KDOQI Guidelines Introduced
First Large, Prospective Controlled, Randomized Cutting Balloon Trial:
Peripheral Cutting Balloon TM
2005
2010
First Large, Prospective, Controlled, Randomized Stent Graft Trial:
FLAIR® Endovascular Stent Graft
First Large, Prospective Controlled Randomized Stent Graft Trial
FLUENCY® PLUS Endovascular Stent Graft
2015
2017
First in Fistula:
Large, Prospective Controlled Randomized DCB Trial:
LUTONIX® 035 PTA Catheter

Penn IR

Evidence in DCB-refreshing

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Author	Type	Results
Percutaneous Angioplasty Using a Paclitaxel-Coated Balloon Improves Target Lesion Restenosis on Inflow Lesions of Autogenous Radiocephalic Fistulas: A Pilot Study Lai et al. JVIR 2014: 25:535-541	Cohort N=10 (20 lesions) AVF	TLR 251 days DCB 103 days POBA TLPP at 6 ($p<0.01$) and 12 months (P=NS) 70%, 20% DCB 0%, 0% POBA
Paclitaxel-Coated vs. Plain Balloon Angioplasty for Dysfunctional Arteriovenous Fistulae: One-Year Results of a Prospective Randomized Controlled Trial Kitrou et al. JVIR 2015;26:348-354	RCT n=40 AVF	TLR-free survival 308 days DCB vs 161 days POBA ($p=0.03$) ACPP 270 days DCB vs 161 ($p=0.04$)
Paclitaxel-Coated Balloon Angioplasty vs. Plain Balloon Dilation for the Treatment of Failing Dialysis Access: 6-Month Interim Results from a Prospective Randomized Controlled Trial Katsanos et al. J Endovasc Ther 2012;19:263-272	RCT n=40 Grafts+AVF	70% TLPP at 6 months DCB 25% TLPP at 6 Months POBA ($P<0.001$)
Drug-eluting versus plain balloon angioplasty for the treatment of failing dialysis access: Final results and cost-effectiveness analysis from a prospective randomized controlled trial Kitrou et al, Eur J Radiol 2015;84:418-423	RCT n=40 Grafts+AVF	35% TLPP at 12 months DCB 5% TLPP at 12 months POBA ($P<0.001$)

Author	Type	Results
Paclitaxel-coated balloons for the treatment of symptomatic central venous stenosis in dialysis access: Results from a randomized controlled trial Kitrou et al, JVIR 2017;28:811-817	RCT n=40 19 AVF/21G	Median intervention free patency better for DCB 179 vs 125 days P=0.026
Multicenter, Randomized Trial of Conventional Balloon Angioplasty versus Paclitaxel-Coated Balloon Angioplasty for the Treatment of Dysfunctioning Autologous Dialysis Fistulae Maleux et al, JVIR 2018;29:470-475	RCT N=64 AVF	3,6,12 month primary patency for DCB angioplasty and PTA 88% vs 80% (P=.43), 67% vs 65% (P=.76), and 42% vs 39% (P =.95), respectively
Drug Coated Balloon Angioplasty in Failing AV Fistulas: A Randomized Controlled Trial Trerotola et al, CJASN 2018;13:1215-1224	RCT N=285 AVF	180 day TLPP 71% DCB vs 63% PTA, P=0.06 6 month TLPP 64% DCB vs 53% PTA, P=0.02
Hemodialysis Arteriovenous Fistula and Graft Stenoses: Randomized Trial Comparing Drug-eluting Balloon Angioplasty with Conventional Angioplasty Irani et al, Radiology 2018;289:238-247	RCT N=119 AVF and AVG	6 month TLPP 81% DCB vs 61% PTA, P=0.03 12 month TLPP 51% DCB vs 34% PTA, P=0.04 6 month ACPP 76% DCB vs 56% PTA, P=0.048
Drug-Coated Versus Plain Balloon Angioplasty In Arteriovenous Fistulas: A Randomized, Controlled Study With 1-Year Follow-Up (The Drecorest II-Study) Bjorkman et al, Scand J Surgery 2018;__:1-6	RCT N=39 AVF	12 month TLR 88.9 DCB vs 22.2% PTA, P=0.001 RR 7.09, 95% CI 0.01-10.3

More to come!

- PAVE (RCT-UK, M. Robson)
- DCB in cephalic arch restenosis (RCT-Israel, A. Verstandig, NCT02368197)
- APERTO (RCT-Netherlands, P. Pattynama, NCT02558153)
- DEBEFF (RCT-Saudi Arabia, N. Haq, NCT02632955)
- FISBAL (RCT-Spain, M. Vargas, NCT02565953)
- ABISS (RCT-France, R. Coscas, NCT02753998)
- FAVABED (RCT-France, J-F Heautot, NCT02913274)
- DEB (RCT-Canada, E. Therasse, NCT01928498)
- IN.Pact AV access trial (RCT, A Holden, R Lookstein)

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Lutonix AV Clinical Trial

A Prospective, Global, Multicenter, Randomized, Controlled Study Comparing LUTONIX® 035 AV Drug Coated Balloon PTA Catheter vs. Standard Balloon PTA Catheter for the Treatment of Dysfunctional AV Fistulae

Trerotola et al, CJASN 2018;13:1215-1224

Penn IR

Drug Coated Balloon Angioplasty in Failing AV Fistulas
A Randomized Controlled Trial

Scott O. Trerotola,[1] Jeffrey Lawson,[2,3] Prabir Roy-Chaudhury,[4] and Theodore F. Saad,[5] for the Lutonix AV Clinical Trial Investigators

Abstract

Background Restenosis remains a problem in hemodialysis access interventions. Paclitaxel-coated balloons have shown promise in reducing access-related restenosis in small trials. The primary hypotheses for our multicenter trial were superior effectiveness at 180 days and noninferior safety at 30 days of a drug-coated balloon compared with conventional angioplasty for treatment of dysfunctional arteriovenous fistulas.

Design, setting, participants, & measurements This randomized trial enrolled 285 patients with dysfunctional arteriovenous fistulas at 23 centers. Grafts, central venous stenoses, thrombosed fistulas, and immature fistulas were excluded. All patients received angioplasty of the lesion responsible for access dysfunction. After successful angioplasty (≤30% residual stenosis), lesions were treated with either a paclitaxel-coated balloon or an uncoated control balloon of similar design to the drug-coated balloon. Access function during follow-up was determined per centers' usual protocols; reintervention was clinically driven. The primary efficacy outcome assessment was done at 6 months, and the safety assessment was done within 30 days of the procedure. Prespecified secondary end points included assessment of postintervention target lesion primary patency and access circuit primary patency at 6 months.

Results The 180-day end point was not met with target lesion primary patency (71%±4% for the drug-coated balloon and 63%±4% for control; P=0.06), representing a difference of 8%±6% (95% confidence interval, −3% to 20%). Access circuit primary patency did not differ between groups. Interventions to maintain target lesion patency were fewer for the drug-coated balloon at 6 months (0.31 versus 0.44 per patient; P=0.03). The primary safety noninferiority end point was met and did not differ between groups (P=0.002).

Conclusions Paclitaxel-coated balloon–assisted angioplasty did not meet the primary effectiveness end point at 180 days compared with conventional angioplasty. Both arms showed equivalent safety (ClinicalTrials.gov number NCT02440022).

Clin J Am Soc Nephrol 13: 1215–1224, 2018. doi: https://doi.org/10.2215/CJN.14231217

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Introduction

It has been 51 years since the original description of hemodialysis fistulas (1), and the superiority of fistulas over other forms of hemodialysis access remains widely accepted (2). However, failure of fistulas remains as pervasive a problem today as it was half a century ago. Access failure results in missed or inadequate treatments, hospitalization, and catheter use, costing the United States health care system approximately $2 billion annually (3). In spite of substantial advances in our understanding of the pathophysiology of access stenosis and restenosis, there have been no large-scale studies showing superiority of any intervention for treating fistula-related stenosis. Among the most promising candidates for preventing *de novo* stenosis or restenosis after intervention is paclitaxel, which has proven to be beneficial in preventing restenosis in large studies in other vascular beds (4–6) and several small, randomized, single-center studies in hemodialysis access (both grafts and fistulas) (7–11). These studies have used specialized angioplasty balloons that have the ability to deliver the drug to the vessel wall, where it is rapidly taken up and remains in the vessel wall. The purpose of this study was to investigate the hypothesis that paclitaxel-coated balloon treatment after successful angioplasty of stenosis in hemodialysis fistulas would improve outcomes compared with angioplasty alone.

Materials and Methods

Study Design

This multicenter (n=23), prospective, randomized, controlled trial was carried out under an investigational device exemption from the US Food and Drug Administration, and it was designed to test the safety and effectiveness of a drug-coated balloon in hemodialysis fistula–related venous stenosis. The study was carried out in full compliance with the Heath Insurance Portability and Accountability Act and the Declaration of Helsinki, and each site obtained

Drug-Coated Balloon Angioplasty for Hemodialysis Fistula Maintenance

Bharat Sachdeva and Kenneth Abreo

Clin J Am Soc Nephrol 13: 1140–1141, 2018. doi: https://doi.org/10.2215/CJN.07360618

Vascular access is the lifeline for patients with ESKD on hemodialysis. Mature arteriovenous fistulas (AVFs) are the best type of vascular access, because they have a lower infection rate, have longer durability, and need fewer maintenance procedures compared with arteriovenous grafts and tunneled central venous dialysis catheters. Stenosis is a major pathologic lesion afflicting hemodialysis AVFs. Early stenosis that occurs shortly after AVF creation results in nonmaturation, whereas stenosis that develops after maturation and use causes dysfunction, inadequate dialysis, and a shortened lifespan (1). Although the pathologic lesions causing stenosis have been well studied, their management remains elusive (1).

Patients on hemodialysis are referred regularly to vascular centers for angioplasty of AVF stenosis, increasing the burden of morbidity and cost. Angioplasty successfully dilates the stenosis and restores AVF function, but unfortunately, the trauma of the procedure results in recurrence, propagating a vicious cycle. Primary patency of AVFs after angioplasty (time from angioplasty to recurrence) has been abysmal, with <25% of lesions remaining patent at 1 year (2). The rate of recurrent stenosis is slower in surgically manipulated segments (juxta-anastomosis) compared with surgically naïve ones (cephalic arch) (3). Application of an antiproliferative agent with drug-coated balloons (DCBs) to the site of successful angioplasty is a rational approach to delay recurrence. Peripheral arterial and coronary disease has been successfully treated with DCBs, suggesting that similar results could be achieved in the venous segments of an AVF (4).

In this issue of the *Clinical Journal of American Society of Nephrology*, Trerotola *et al.* (5) report the preliminary results of the first prospective, global, multicenter (n=23), randomized, controlled trial (RCT) that compared the efficacy and safety of paclitaxel-coated, balloon-assisted angioplasty (n=141) with conventional angioplasty (n=144) in patients with dysfunctional mature AVFs. All AVFs had to have a target stenosis ≥50% that matched a clinical indicator to be included in the trial. For example, an AVF that had a ≥50% stenosis in the outflow vein (target lesion) on angiogram and was pulsatile on physical examination (matched clinical indicator) met the inclusion criteria. Because some dysfunctional AVFs have multiple stenoses, fistulas with two stenoses on an angiogram (one target and one incidental) were also included in the study as long as both stenoses were successfully treated before randomization. The access circuit was defined as the portion of the AVF from the anastomosis to the axillary vein. Patients with central vein stenosis were, therefore, excluded from the study. The DCB was inflated only at the target lesion. The primary efficacy end point was defined as continued AVF patency with no need for a clinically driven (referral on the basis of any clinical indication during follow-up or a mandatory physical examination at 6 months) reintervention on the target lesion (target lesion primary patency [TLPP]) or risk of access thrombosis at 6 months. Access circuit primary patency (ACPP) ended when either the target lesion recurred or any other stenosis was detected, whereas the TLPP ended when the target lesion recurred.

The prespecified 6-month primary efficacy end point was not met with the TLPP of 71%±4% for the DCB and 63%±4% for control (P=0.06), representing a difference of 8%±6% (95% confidence interval [95% CI], 3% to 20%). There were three possible reasons for this. First, the conventional angioplasty group (control) outcomes were better than historical outcomes. Second, controls had the angioplasty balloon inflated a second time instead of an identical sham balloon, resulting in a difference in inflation pressure (9.7±2.1 atm in the DCB arm versus 12.1±5 atm in the control arm). Using an identical sham non-DCB angioplasty in the control arm would have removed variability in treatment parameters, and more importantly, it would have kept the operators and study coordinators blinded. Third, the mandatory physical examination window extended from 5 to 7 months, and therefore, the 6-month analysis missed physical examinations done in the seventh month. When the primary efficacy end point was extended to 7 months, thereby capturing all patients who had missed their 6-month mandatory examination, the primary efficacy end point showed significance for DCB (64%±4%; 95% CI, 55% to 72%) versus control (53%±4%; 95% CI, 44% to 61%; P=0.02), representing a difference of 12%±6% (95% CI, 0% to 23%). Thrombosis of the AVFs was rare in both arms (2.4% DCB and 4.3% control). Despite the improvement of the TLPP, the ACPP was not different at 6 and 7 months after enrollment. If the DCB was applied to both the target and incidental stenosis (20% of AVFs), an improvement in ACPP could have occurred. Long-term results are awaited to show whether ACPP will improve with better outcomes of the TLPP at 1 and 2 years

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Lutonix AV Clinical Trial

Study Design	Prospective, Global, Multicenter, Randomized, Core lab Blinded, Safety and Effectiveness
Objective	To assess the safety and effectiveness of the LUTONIX® 035 AV Drug Coated Balloon PTA Catheter in the treatment of dysfunctional AV fistulae
Number of Patients/Sites	285 randomized subjects at 23 clinical sites
Primary Effectiveness Endpoint	Target Lesion Primary Patency (TLPP) - 6 months
Primary Safety Endpoint	Freedom from any serious adverse event(s) involving the AV access circuit through 30 days
Follow Up	1, 3, 6, 9, 12, 18, 24 month visits
Status	First Subject: June 2015 Enrollment Completion: March 2016

Trerotola et al, CJASN 2018;13:1215-1224

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Lutonix AV Clinical Trial

Key Inclusion Criteria

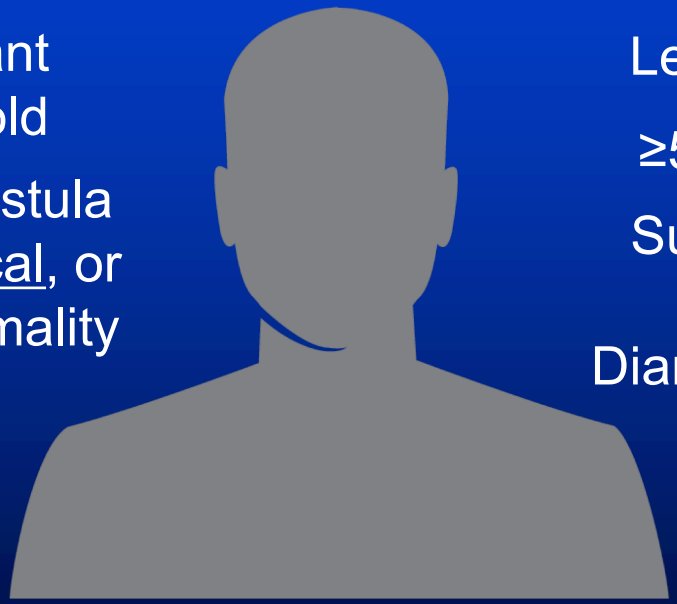
CLINICAL

Male or non-pregnant female ≥21 years old

Upper extremity AV fistula w/clinical, physiological, or hemodynamic abnormality

Fistula created ≥30 days

- 1+ hemodialysis session
- 2 needles
- catheter removed ≥ 30 days



ANGIOGRAPHIC

Length ≤10 cm

≥50% stenosis

Successful pre-dilation

Diameter 4-12 mm

Trerotola et al, CJASN 2018;13:1215-1224

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Lutonix AV Clinical Trial

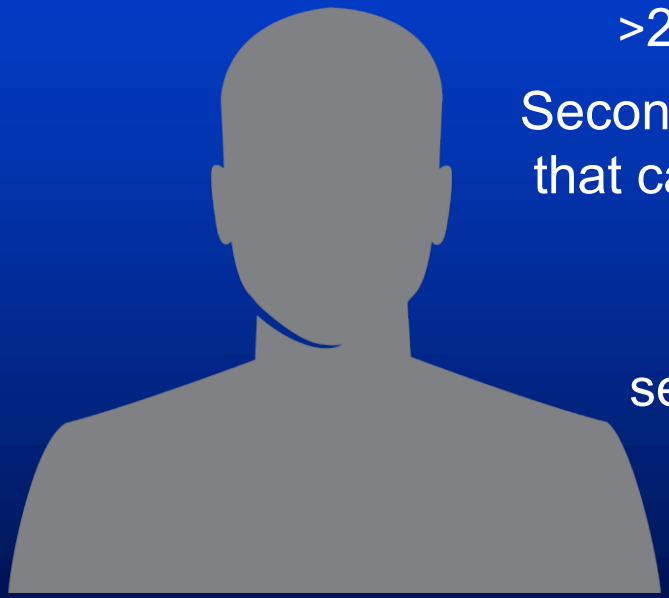
Key Exclusion Criteria

CLINICAL

Leg access

Central veins

Thrombosed access



ANGIOGRAPHIC

>2 lesions in circuit

Secondary non-target lesion that cannot be successfully treated

Central veins as a secondary lesion, which is clinically significant

Bare or covered stent in target or secondary non-target lesions

Trerotola et al, CJASN 2018;13:1215-1224

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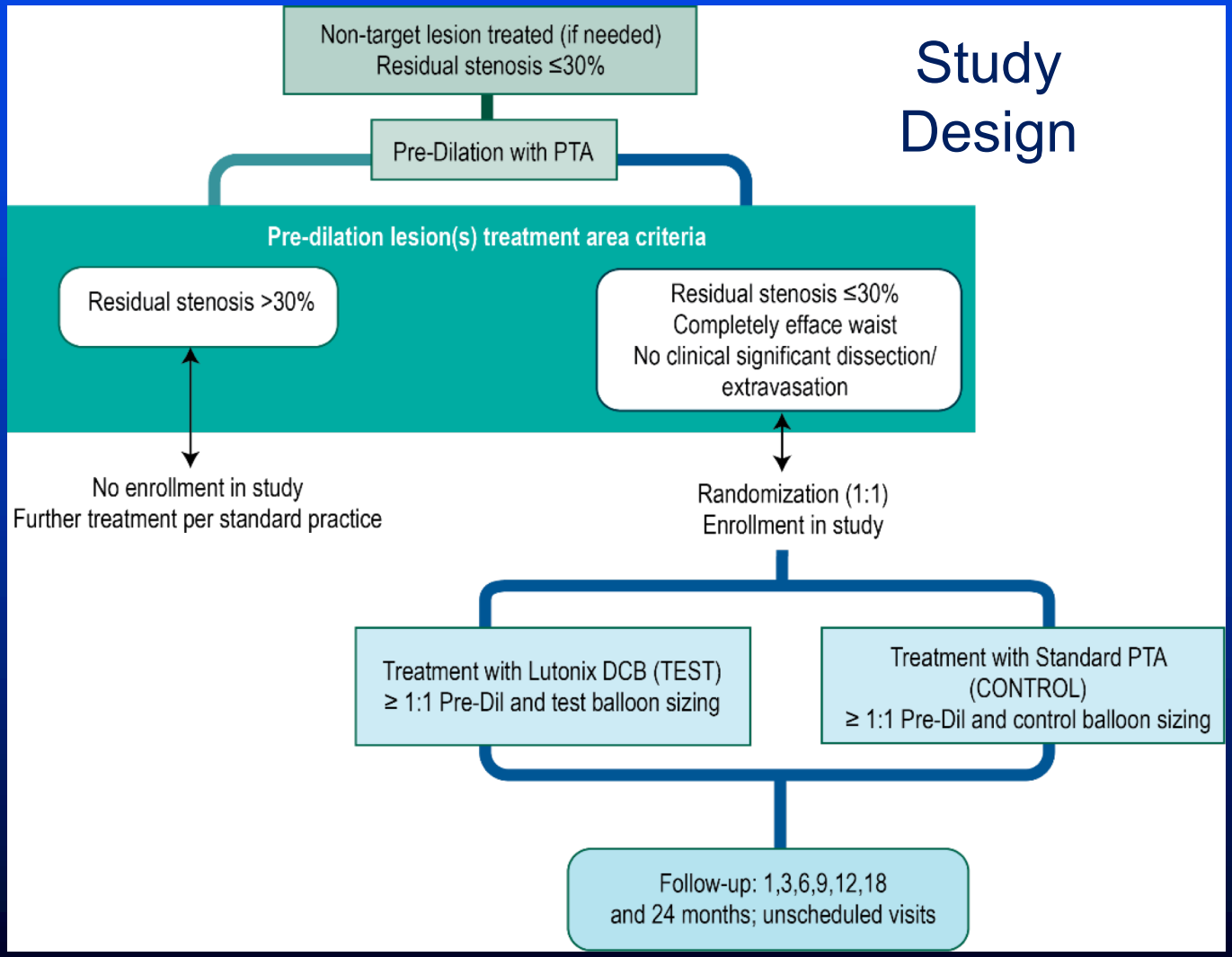
Lutonix AV Clinical Trial



Study Design

Trerotola et al, CJASN 2018;13:1215-1224

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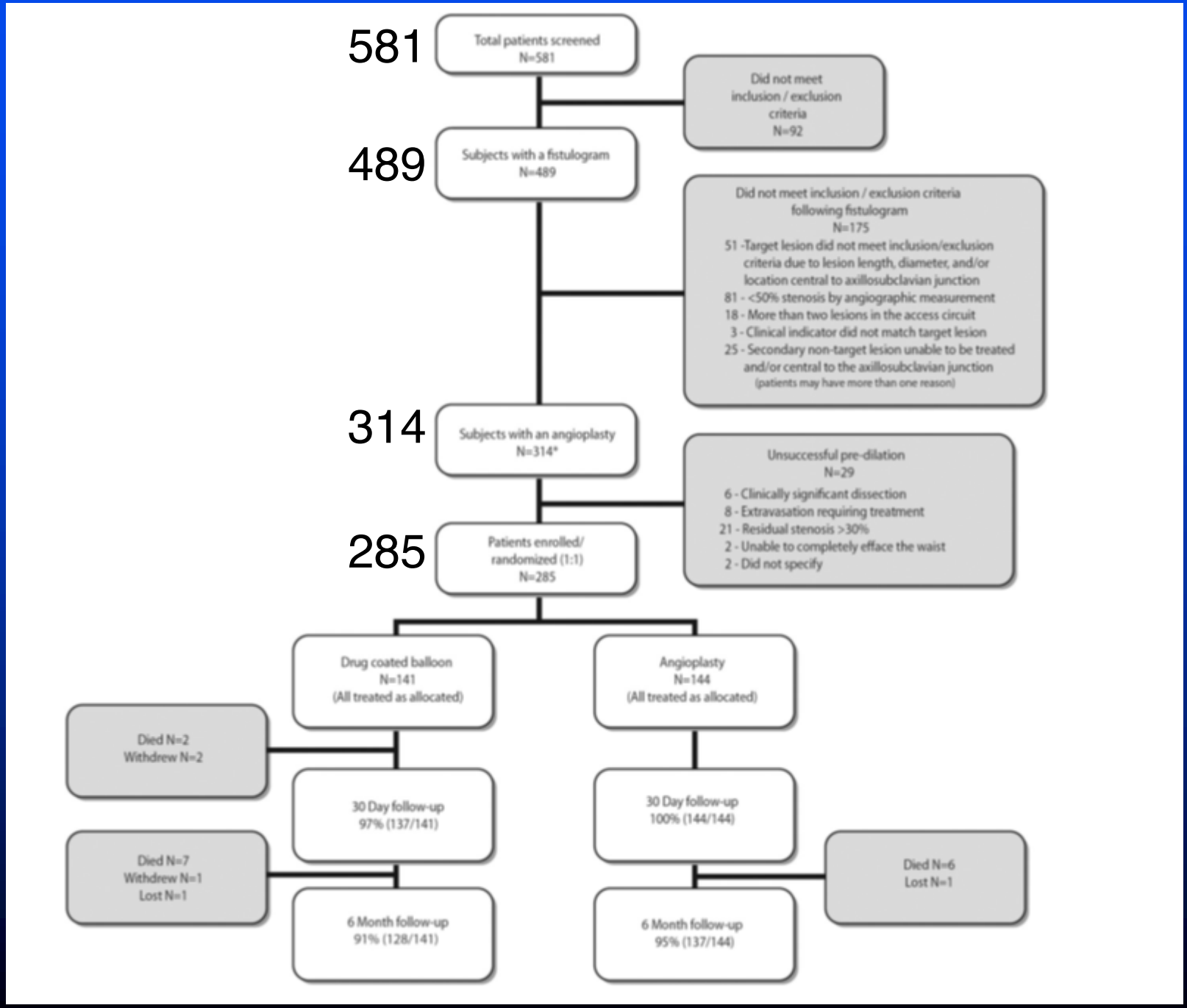

Trerotola et al, CJASN 2018;13:1215-1224

Lutonix AV Clinical Trial

Target Lesion Locations

	DCB (n=141)	PTA (n=144)
Anastomotic (%)	4.3%	3.5%
Cephalic arch (%)	18.7%	22.5%
Cannulation zone (%)	4.3%	9.9%
Inflow (%)	33.8%	29.6%
Outflow (%)	24.5%	22.5%
Swing point (%)	14.4%	12.0%

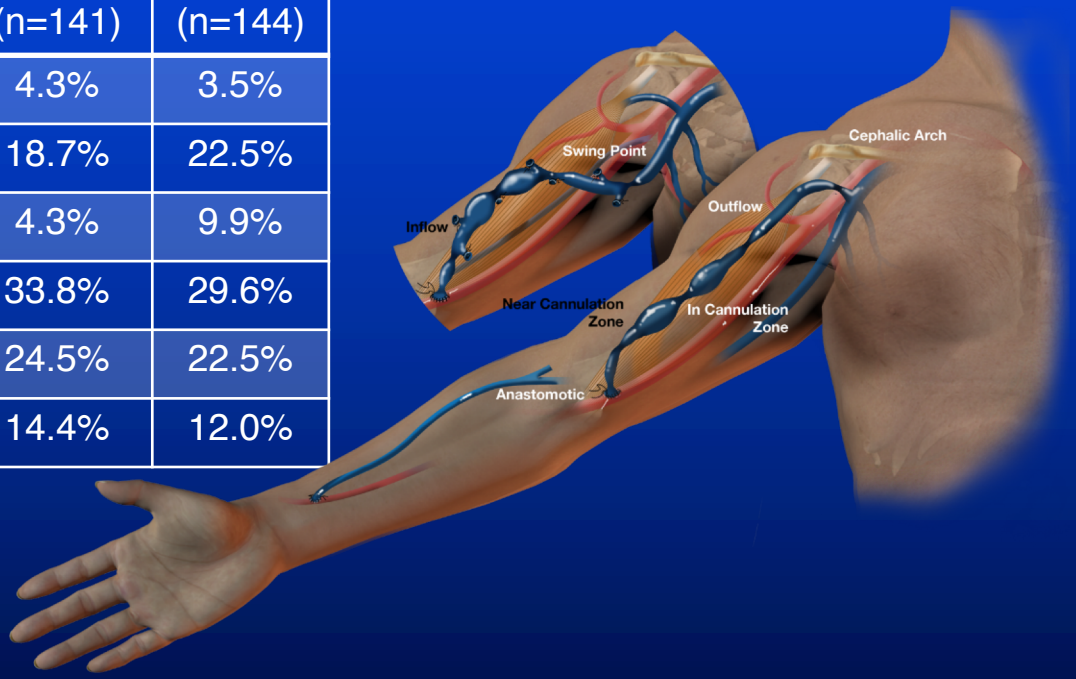

Image courtesy of Bard: illustration by Paul Schiffmacher

Trerotola et al, CJASN 2018;13:1215-1224

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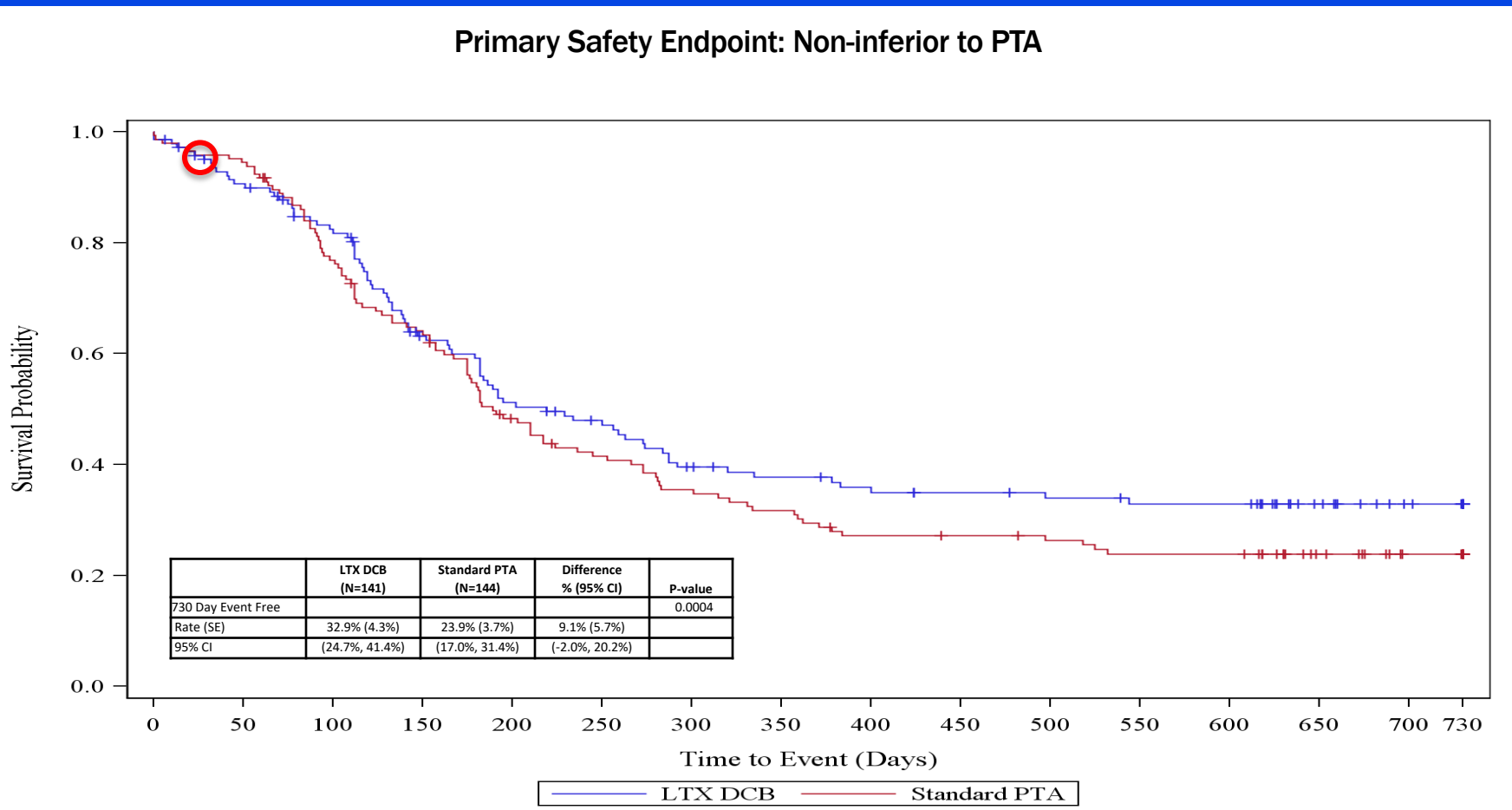
Lutonix AV Clinical Trial



	LTX DCB (N=141)	Standard PTA (N=144)	Difference % (95% CI)	P-value
730 Day Event Free				0.0004
Rate (SE)	32.9% (4.3%)	23.9% (3.7%)	9.1% (5.7%)	
95% CI	(24.7%, 41.4%)	(17.0%, 31.4%)	(-2.0%, 20.2%)	

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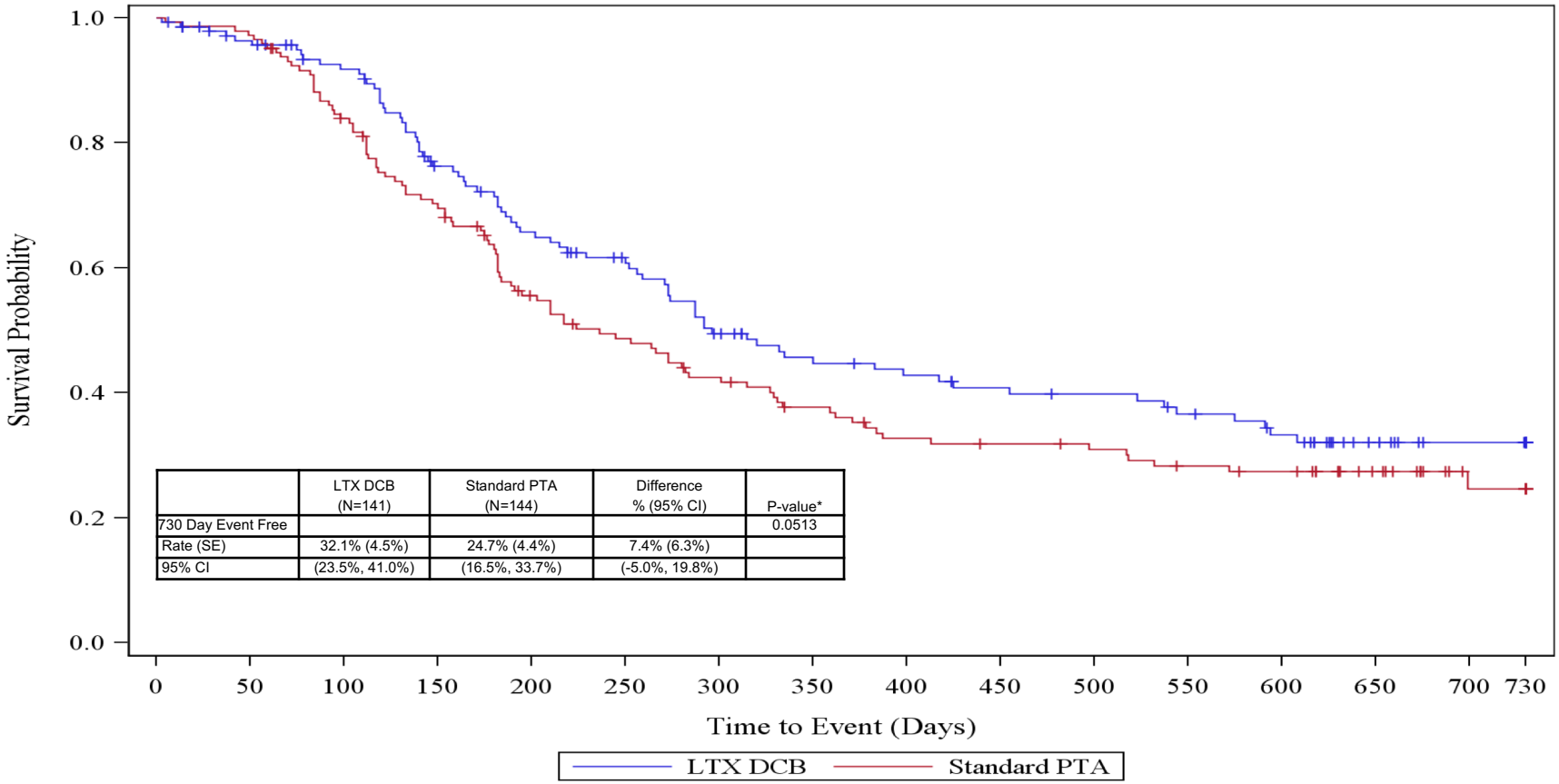
Lutonix AV Clinical Trial

TLPP Interim 24 month Results



	LTX DCB (N=141)	Standard PTA (N=144)	Difference % (95% CI)	P-value*
730 Day Event Free				0.0513
Rate (SE)	32.1% (4.5%)	24.7% (4.4%)	7.4% (6.3%)	
95% CI	(23.5%, 41.0%)	(16.5%, 33.7%)	(-5.0%, 19.8%)	

Trerotola et al, CJASN 2018;13:1215-1224

Number of Interventions to Maintain TLP

	LTX DCB (n=141)	Standard PTA (n=144)	P-value*	% Fewer Interventions than PTA
Number of interventions, 6 Months	44	64	0.034	**31.3% Fewer**
Number of interventions, 9 Months	76	103	0.023	26.2% Fewer
Number of interventions, 12 Months	114	138	0.086	17.4% Fewer
Number of interventions, 18 Months	161	185	0.106	13.0% Fewer
Number of interventions, 24 Months	195	211	0.131	7.6% Fewer

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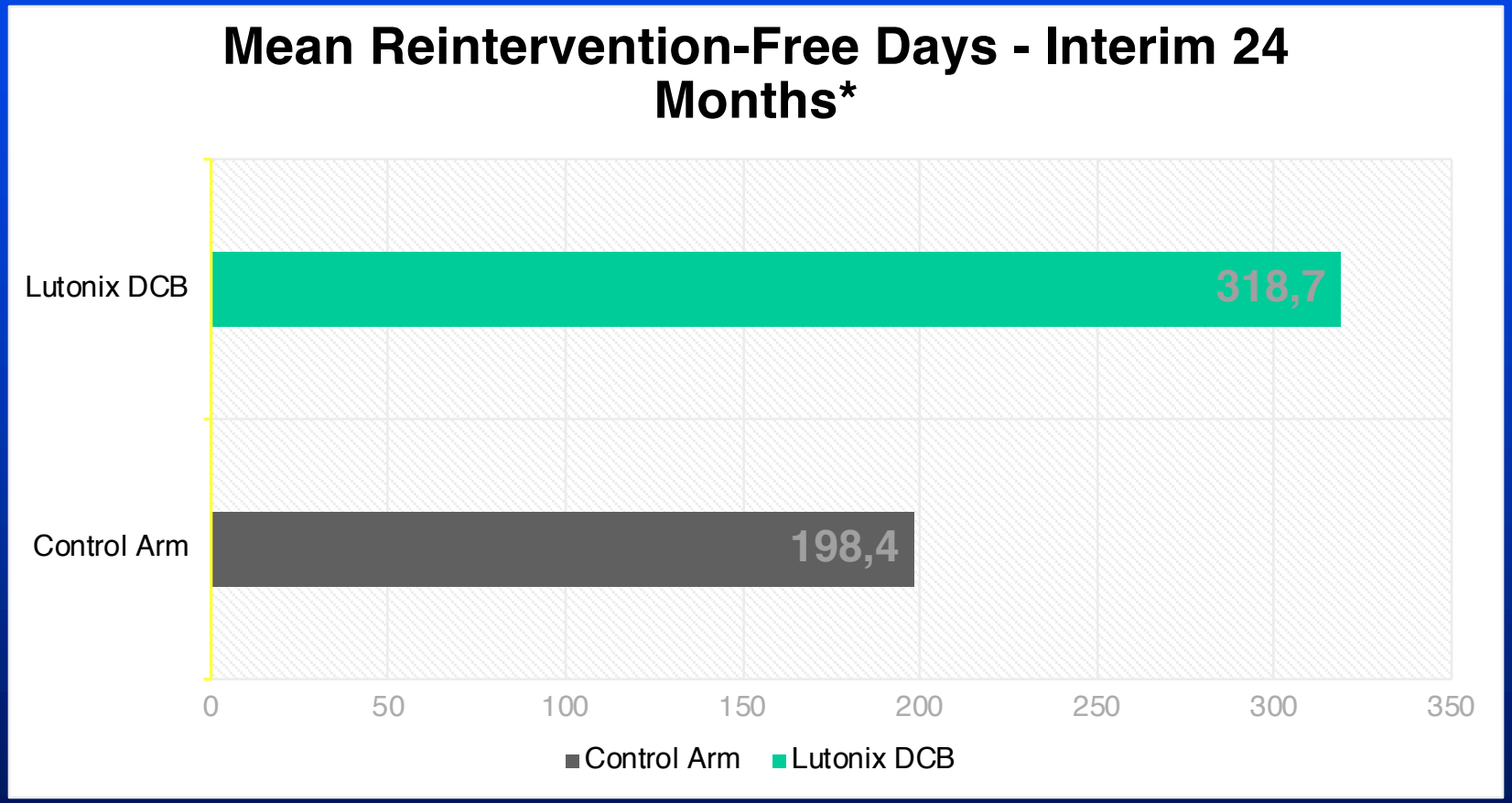

*for those experiencing an event; p<0.001

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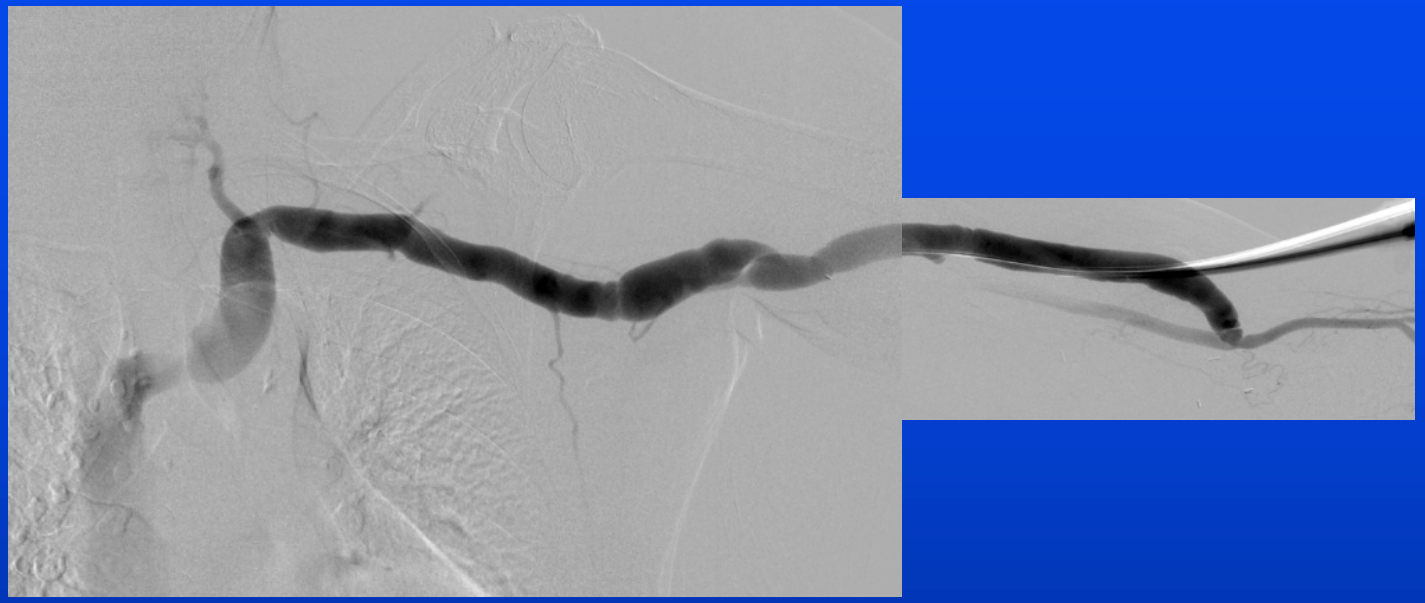
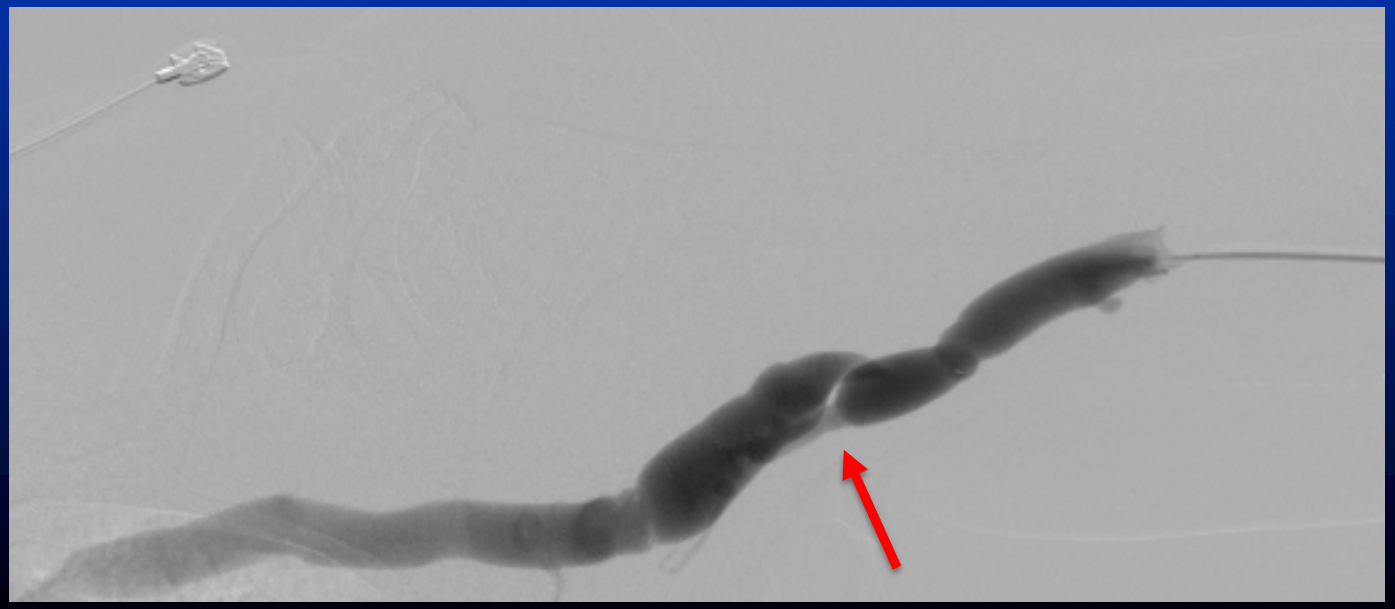


LUA BVT with abnormal exam (pulsatile)



>50%

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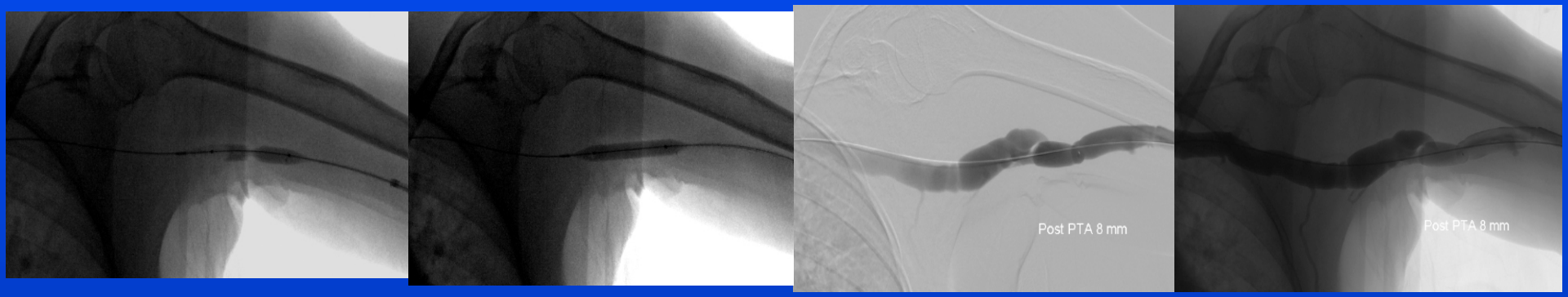
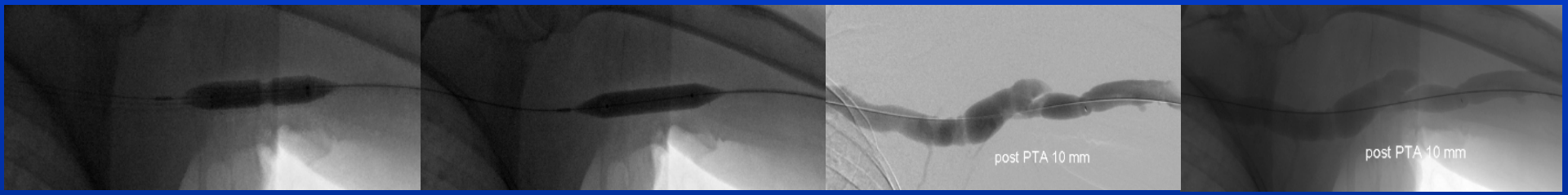
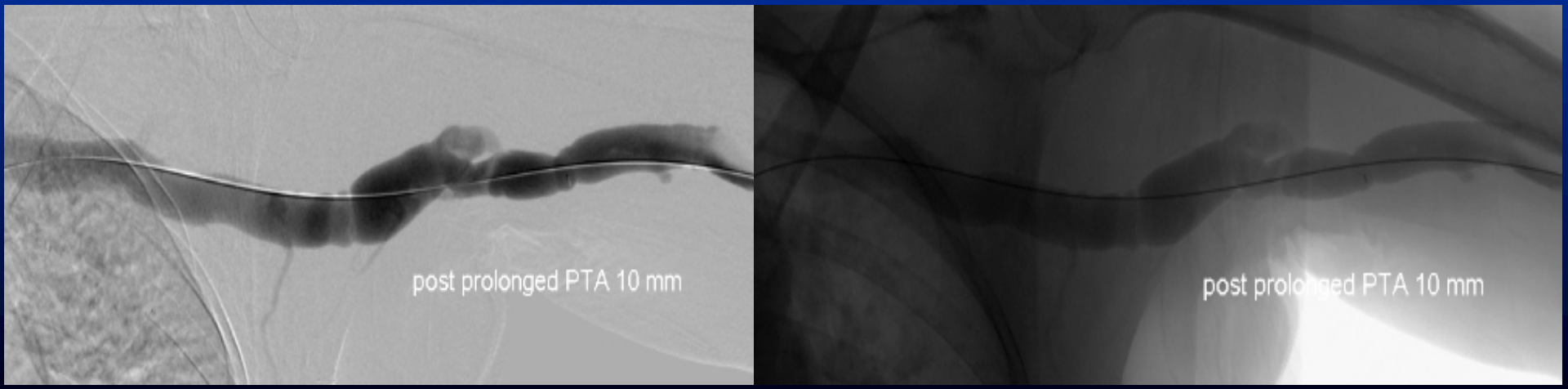
Vessel preparation



Conquest 8 mm x 4 cm @ >30 atm

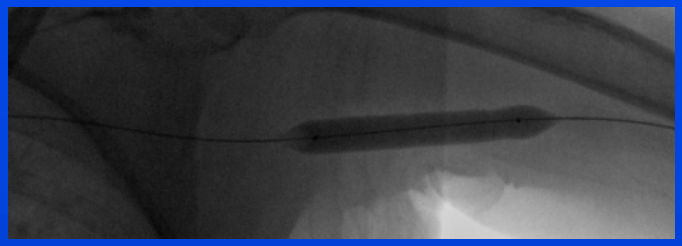


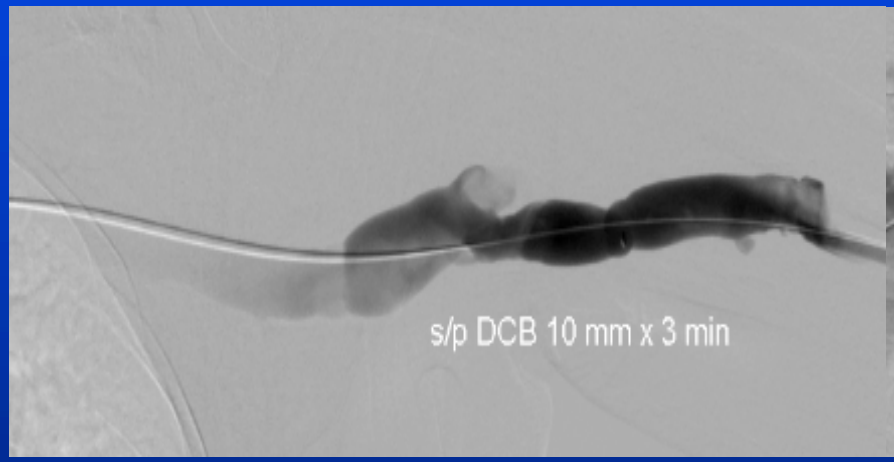
Conquest 10 mm x 4 cm @ >30 atm (56% residual stenosis)

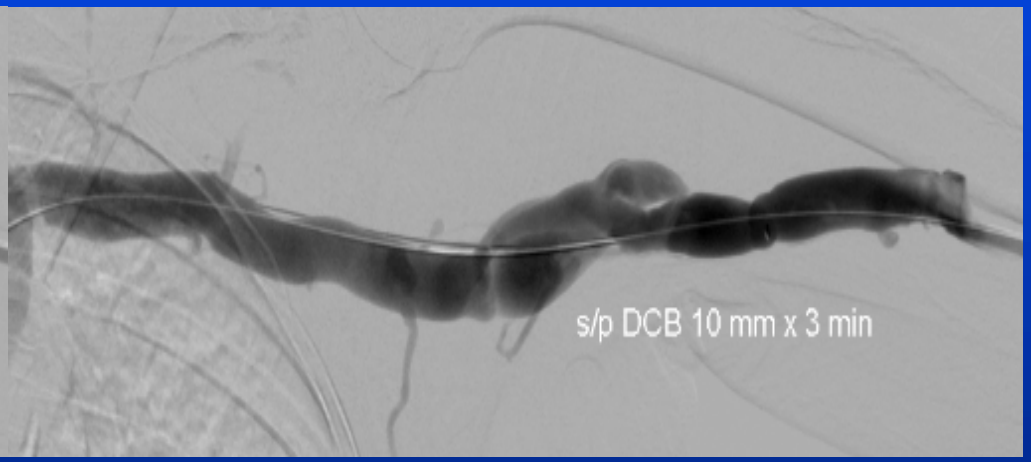


5 minute inflation w/10 mm Conquest (25% residual stenosis)

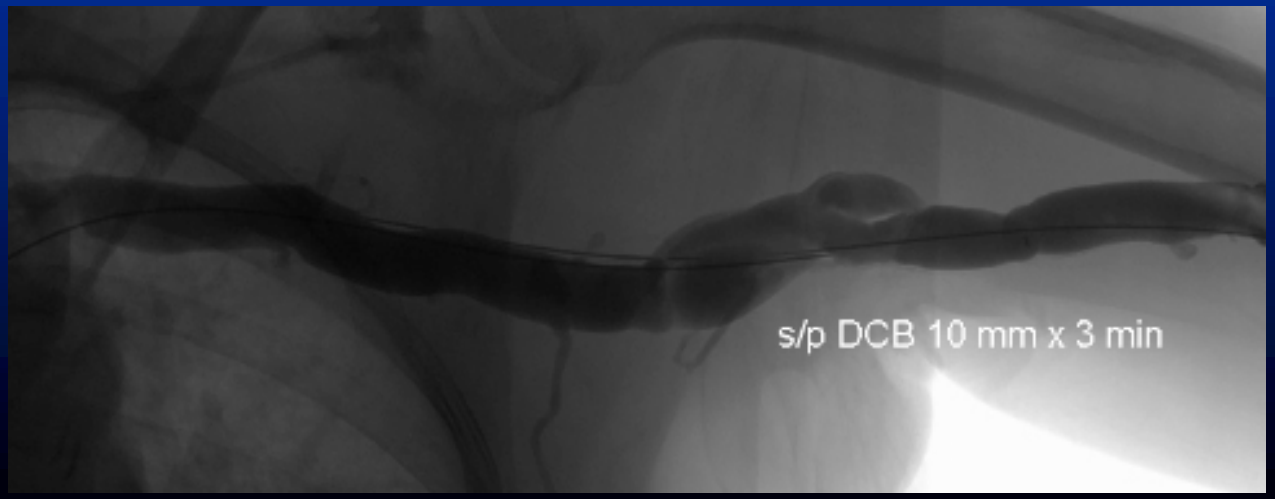
Drug delivery w/DCB (10 mm x 6 cm) inflated to 12 atm (thus ~10.8 mm)







Good thrill restored



Some new things to learn

- Geographic miss
  - Longer is better
- Contact time
  - Longer is better
- Transit time
  - Shorter is better
- Compliant balloons (old new)
  - Goldilocks inflation

Penn IR

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

So what about AVF?

Description	Lutonix (n=141)	Control (n=144)	P value
Number of deaths at 24 months	33 (23.4%)	26 (18.1%)	**P=0.265**

N= 4 voluntarily withdrew from dialysis- Lutonix
N=1 voluntarily withdrew from dialysis- control

Expected 2 year mortality on hemodialysis (US) 33.2%[1]

[1]USRDS Table 5.3 Adjusted survival percentage v2 Mortality 18, 66.8% survival at 24 months

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DCB in AVF

- New approach to restenosis in HD
- Evidence mounting
- More yet to come
  - Ongoing trials
  - Global registry n=324 enrolled
  - Postmarket study n=213
  - IN.Pact 100% enrolled (n=330)
  - Specific lesion locations
  - Different vessel preparation

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