Lutonix AV Clinical Trial

24 Month Results- Safety

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Disclosure

Speaker name:

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I have the following potential conflicts of interest to report:

- ■ Consulting
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ■ Other(s)

☐ I do not have any potential conflict of interest

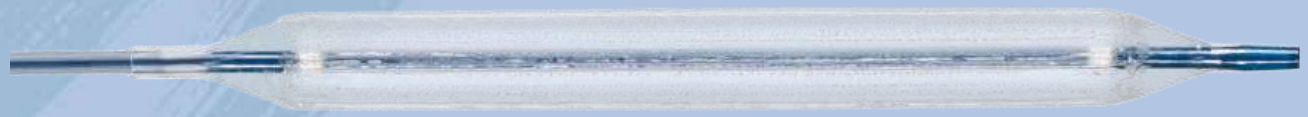
Lutonix AV IDE Clinical Trial

Study Design

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

- ✓ Prospective
- ✓ Multi-Center
- ✓ Randomized (1:1)
- ✓ Core Lab Adjudicated
- ✓ Clinical Events Committee (CEC)
- ✓ Data & Safety Monitoring Board (DSMB)

Lutonix AV IDE Clinical Trial



Study Device: LUTONIX® 035 DCB

- 2 µg/mm^2 paclitaxel + polysorbate and sorbitol excipients
- 4-12 mm diameters, 40-100 mm lengths
- .035” guidewire compatible, nylon, semi-compliant balloon
- Over the wire, co-axial shaft
- Nominal 6atm, RBP up to 12atm

Photo courtesy of BD

Lutonix AV IDE Clinical Trial

Primary Endpoint- 6 Month Results

CJASN ePress. Published on July 24, 2018 as doi: 10.2215/CJN.14231217

Article

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

Scott O. Trerotola,[1] Jeffrey Lawson,[2,3] Pabli 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 205 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 nonmaturation or dysfunction. After successful angioplasty (≤30% residual stenosis), lesions were treated with either a paclitaxel-coated balloon or an uncoated control balloon of similar design in the drug-coated balloon. Access function during follow-up was determined per current 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 0.46 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 NCT01840022).

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

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 Health Insurance Portability and Accountability Act and the Declaration of Helsinki, and each site obtained

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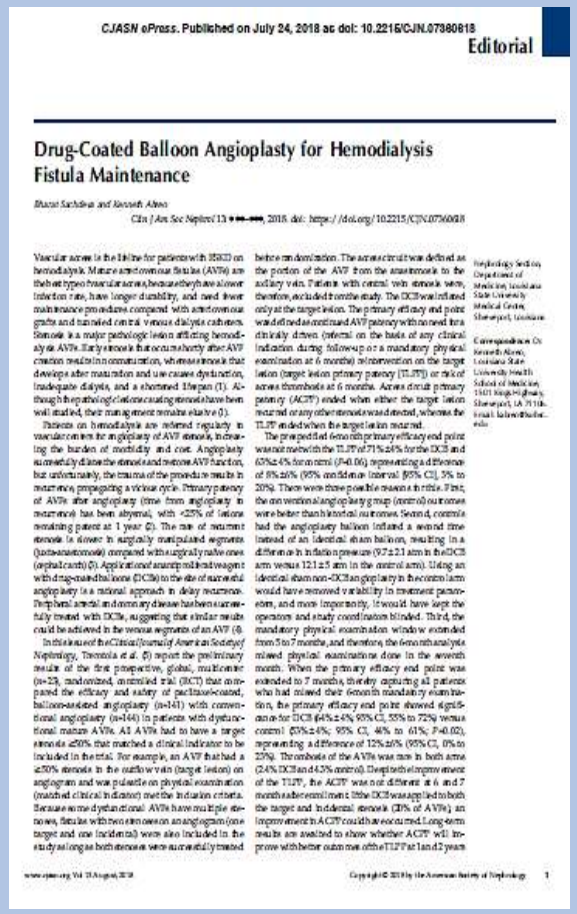

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Editorial

Drug-Coated Balloon Angioplasty for Hemodialysis Fistula Maintenance

Bharat Sachdeva and Kenneth Abreo

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Vascular access is the lifeline for patients with ESRD 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 pathophysiology of stenosis and restenosis have been well studied, their management remains elusive (1).

Patients on hemodialysis are referred regularly in 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 neointimal proliferation, perpetuating a vicious cycle. Primary patency of AVFs after angioplasty (time from angioplasty to restenosis) has been abysmal, with <25% of lesions remaining patent at 1 year (2). The rate of restenosis stenosis is slower in surgically manipulated segments (juxta-anastomotic) compared with surgically native ones (cephalic arch) (3). Application of an antiproliferative agent with drug-coated balloons (DCBs) to the site of successful angioplasty is a rational approach in delay restenosis. 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 cephalic vein (target lesion) on angiogram and was palpable 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 (elective) 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 restenosed or any other stenosis was detected, whereas the TLPP ended when the target lesion restenosed.

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 in this. First, the conventional angioplasty group (control) outcomes were better than historical outcomes. Second, control 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 was 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 (50%±4%; 95% CI, 46% 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 (28% 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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Trerotola et al. Clin J Am Soc Nephrol 2018 Aug 7;13(8):1215-1224

Sachdeva et al. Clin J Am Soc Nephrol 2018 Aug 7;13(8):1140-1141

AV-DCB Published Trials

Title	Device	DCB	Control	RCT	Follow Up (mo.)
Trerotola 2018	Lutonix®	N=141	N=144	✓	24
Lucev 2018	In.Pact™	N=31	N=31	✓	24
Patane 2018	Lutonix®, In.Pact™	N=60	N=86		12
Zheng 2018	Lutonix®	N=23			
Bjorkman 2018	In.Pact™	N=19	N=20	✓	12
Swinnen 2018	In.Pact™	N=70	N=62	✓	12
Irani 2018	In.Pact™	N=59	N=60	✓	12
Maleux 2018	In.Pact™	N=33	N=31	✓	12
Kitrou 2017	Lutonix®	N=20	N=20	✓	12
Troisi 2017	Freeway™, In.Pact™	N=38			
Kitrou 2016	Lutonix®	N=39			
Verbeek 2016	In.Pact™	N=41			
Swinnen 2015	In.Pact™	N=37			
Massmann 2015	Elutax	N=15			
Lai 2014	Sequent®	N=10	N=10	✓	12
Patane 2014	In.Pact™	N=26			
Kitrou 2014	In.Pact™	N=20	N=20	✓	12
Katsanos 2012	In.Pact™	N=20	N=20	✓	6

Lutonix AV IDE Clinical Trial

Key Demographics

Variable	Lutonix (N=141)	Control (N=144)
Mean age	63.6	61.0
Male, n (%)	61.7%	59.0%
Hypertension, n (%)	94.3%	98.6%
Diabetes mellitus, n (%)	58.2%	65.3%
Dyslipidemia, n (%)	60.3%	58.3%
Current smoking, n (%)	13.5%	14.6%
Peripheral arterial disease, n (%)	9.9%	18.1%
Coronary heart disease, n (%)	30.5%	27.8%

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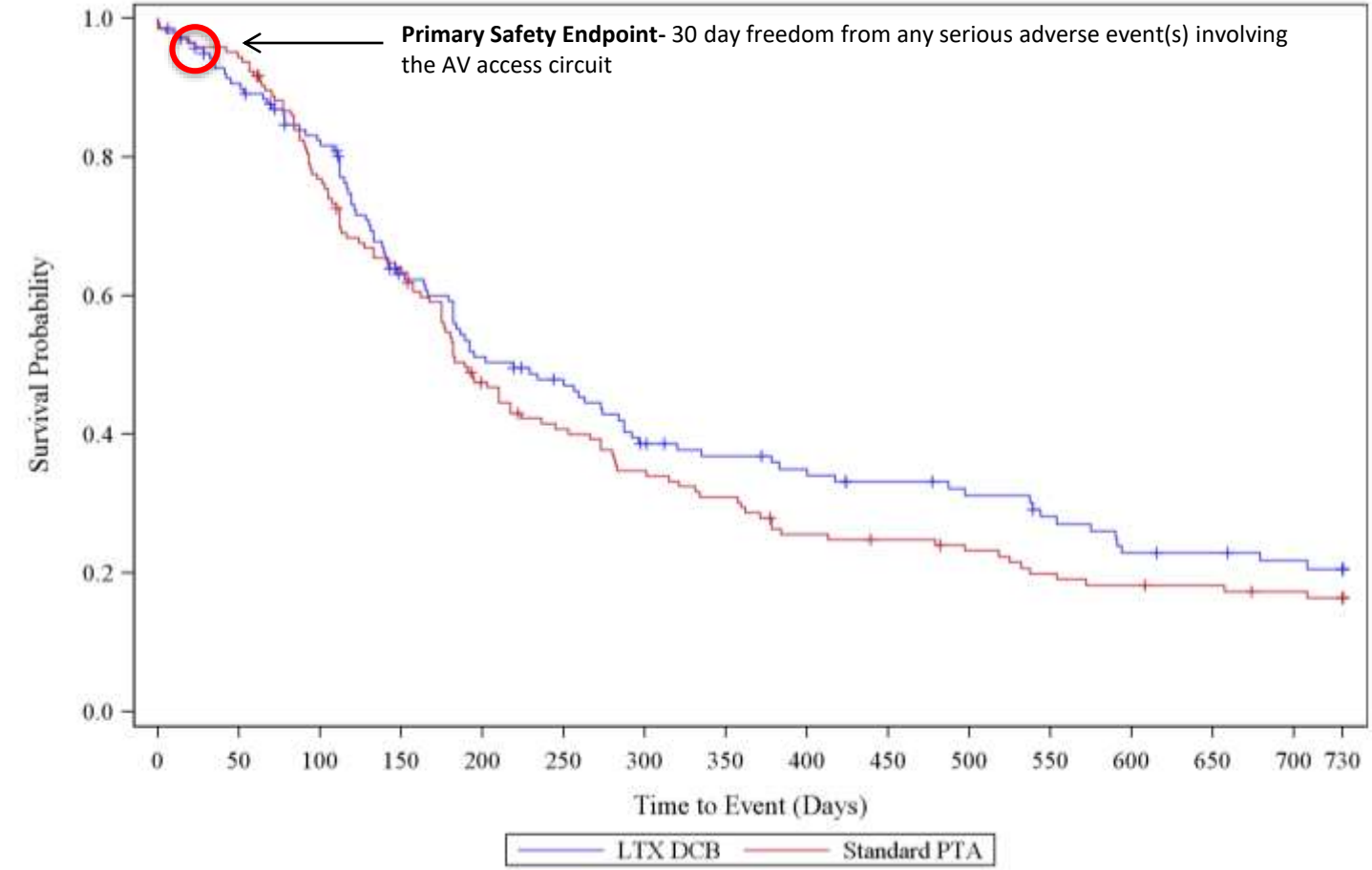
Safety – Non-Inferior to PTA



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Freedom from Safety Events

	Lutonix IDE	Difference	P value
12 Months	**36.9% Lutonix** 28.7% Control	**+8.2%**	0.0009
24 Months	**20.6% Lutonix** 16.5% Control	**+4.2%**	0.0028

Safety: Freedom from serious adverse event(s) involving the AV access circuit

Lutonix AV IDE Clinical Trial

Deaths - 24 Months

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

US 2 year mortality on hemodialysis-33.2%[1]

1. USRDS 2018 Chapter 5: Mortality, Table 5.3

Lutonix AV IDE Clinical Trial

Comparable Safety to PTA

- Only FDA approved DCB for AV fistulae in U.S.
  - Safety outcomes non-inferior to PTA
  - Mortality rate non-inferior to PTA
  - Mortality rate lower than expected (USRDS)
  - Only DCB with multi-center RCT 2 year results
- Next step: Post-approval study, now enrolling (n=213)

Lutonix AV Clinical Trial Sites

Investigator	Site Name	State	Investigator	Site Name	State
Balamuthusamy, Saravanan	Tarrant Vascular Clinic	TX	Nadolski, Greg	Hospital of the University of PA	PA
Waheed, Umar	Southwest Vascular Center	AZ	Atray, Naveen	Capital Nephrology Medical	CA
Lipkowitz, George	Renal &Transplant Assoc of NE	MA	Bratton, Charles	Medical University of SC	SC
Saad, Theodore	Nephrology Associates	DE	Pflederer, Timothy	Renal Care Associates, S.C.	IL
Hoggard, Jeffrey	Capital Nephrology Assoc	NC	Kamel, Ahmed	University of Alabama at Birmingham	AL
Peeler, David	University Vascular Access	TN	Schultz, Scott	Minnesota Vascular Surgery Center	MN
Neyra, Roxana	Arizona Kidney Disease and Hypertension Center	AZ	Wilkins, Luke	University of Virginia	VA
Lawless, Mike	Life Access Center	OK	Irani, Zubin	Massachusetts General Hospital	MA
Licht, Jonah	Providence Interventional	RI	Tasse, Jordan	Rush University	IL
Makris, Angelo	Chicago Access Care	IL	Davanzo, William	Phoebe Putney Memorial Hospital	GA
Molnar, Robert	San Antonio Kidney Disease Center	TX	Resnick, Scott	Northwestern	IL
Kramer, Ari	Michigan Vascular Access	MI	Ross, John	Access Connections	SC
Chan, Micah	Spartanburg Regional Hospital	SC			

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