Alternative concepts for drug delivery in BTK arteries – the LIMBO project

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Disclosure

Speaker's name: Dierk Scheinert

I have the following potential conflicts of interest to report:

Advisory Board /Consultant:

Abbott, Biotronik, Boston Scientific, Cook Medical, Cordis, CR Bard, Gardia Medical/Allium, Medtronic, TriReme Medical, Trivascular, Upstream Peripheral Technologies

Targeted Drug Delivery – The Next Generation for PAD

- Local intimal drug therapy with paclitaxel has shown some limitations
  - DES has shown improvements only in short-segment BTK disease
  - Well-controlled clinical trials of DCB in BTK arteries have been inconsistent or disappointing
  - Flaking of drug from balloons may have negative outflow consequences

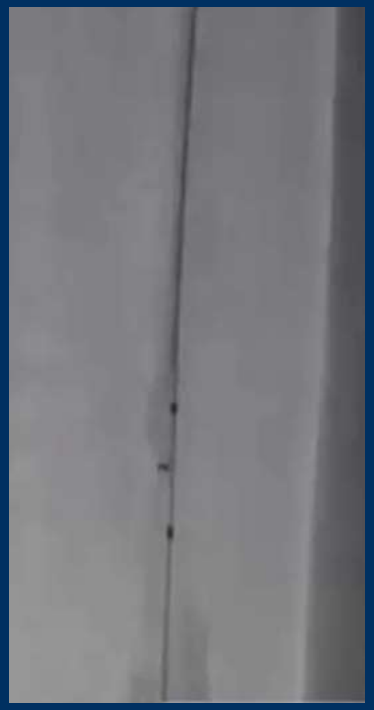
- Eliminating the constraint of *"what drugs can be coated onto a balloon"* allows the exploration of many other medicines to treat the variety of patients we see each day

- Efficient delivery of liquid therapeutics beyond the vessel wall
  - Target the root of the disease: inflammation
  - Bypasses medial calcification regardless of diffusion kinetics
  - Independent of balloon sizing, surface area and full contact to deliver an effective dose

Bullfrog Micro-Infusion Device Features

- Needle (34 Gauge) is constantly sheathed during manipulation to prevent vessel injury
- Balloon self-adjusts to a range of vessel diameters (2-4 mm, 3-6 mm or 4-8 mm)
- Balloon inflation limited to 2 atm to prevent barotrauma

- Contrast co-delivered with drug confirms real-time procedural success



- Each injection starts on one side and then spreads up, down and around the artery
- Diffusion continues over time to fill any visual “gaps”

Visualizing the Therapy

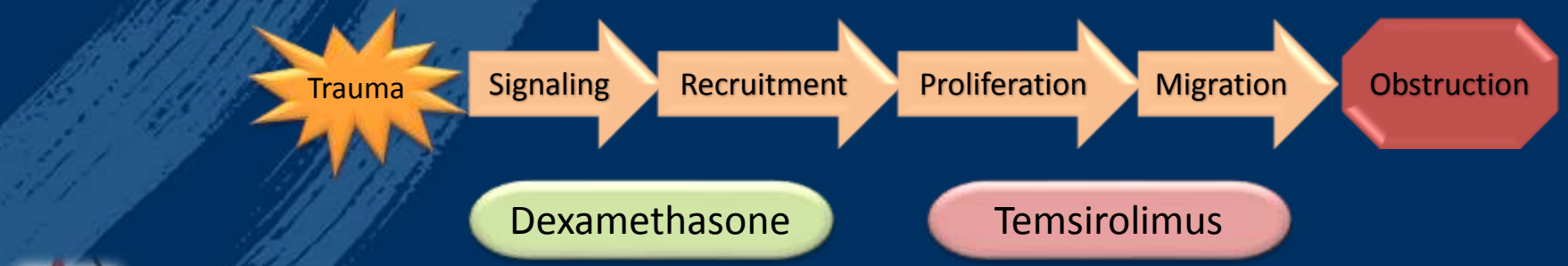
20% contrast : 80% drug is mixed and co-administered to provide immediate feedback

“Painting” the vessel

Above the knee

Below the knee

Exploring the Alternatives in Targeted Drug Therapy



SFA

Popliteal

Infrapop

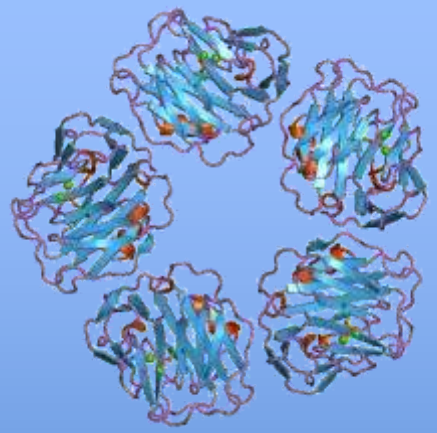
DANCE
281 subjects
Open-label

LIMBO-PTA &
LIMBO-ATX
240 total subjects
1:1 RCT

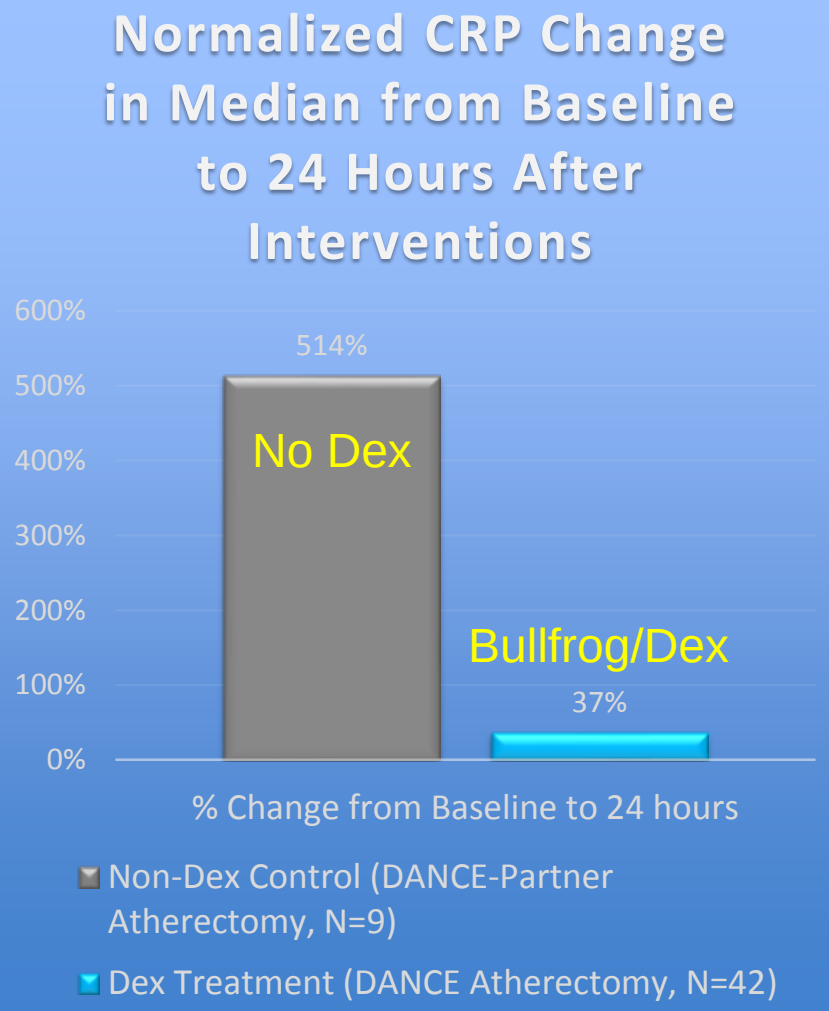
TANGO
60 total subjects
Dose-escalation
RCT

Biomarkers: CRP

C-Reactive Protein (CRP)

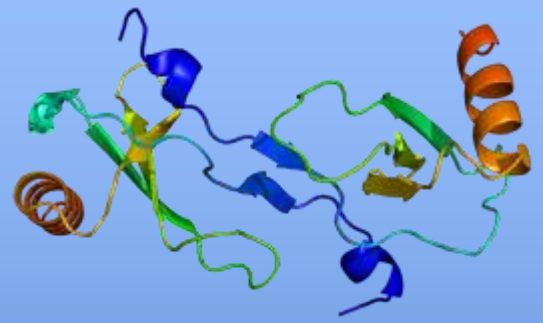


- Circulating levels rise in response to inflammatory cytokines (e.g. IL-6) expressed in response to local triggers (e.g. inflammation)
- Physiologic role: bind to dead or dying cells to activate the complement system via C1Q complex
- Elevations tied to restenosis [Schillinger et al. Radiology 2002; 225:21-26.]

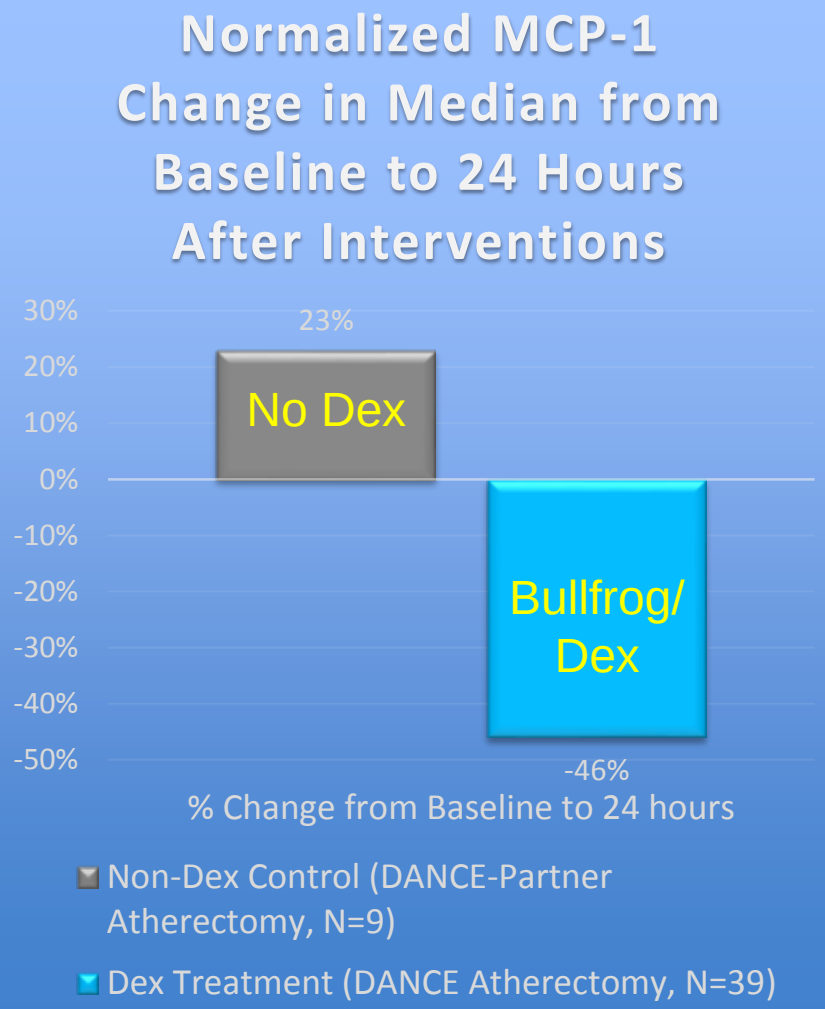


Biomarkers: MCP-1

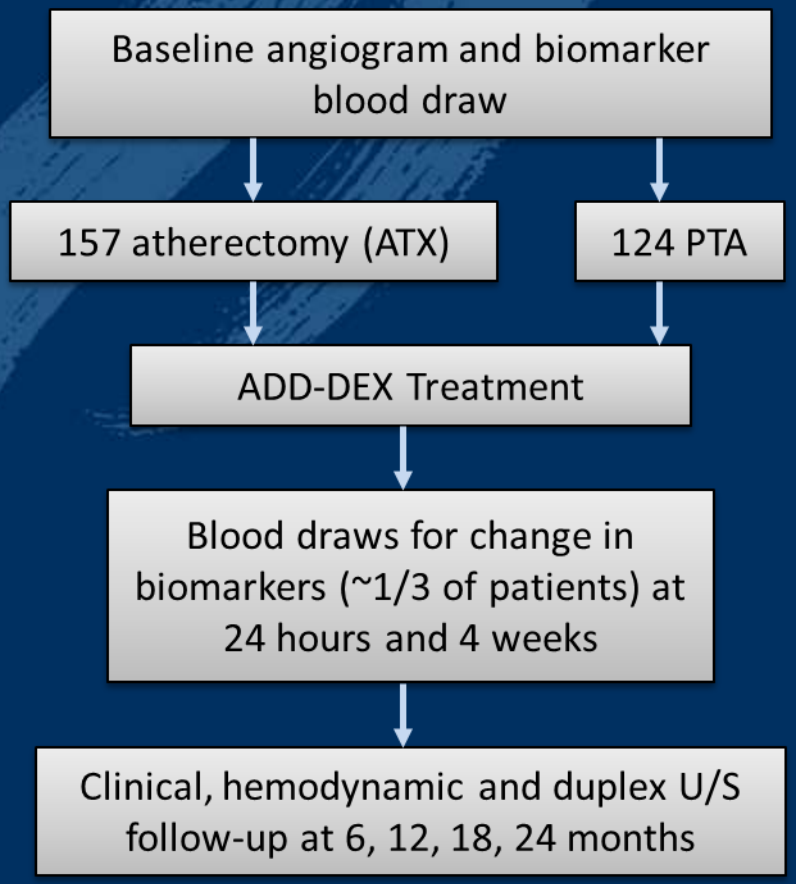
Monocyte Chemoattractive Protein-1 (MCP-1)



- Recruits monocytes, memory T cells, and dendritic cells to the sites of inflammation produced by either tissue injury or infection
- Dexamethasone destabilizes the mRNA that codes for MCP-1, shutting off its production
- Elevations tied to restenosis [Cipollone F, et al. Arterioscler Thromb Vasc Biol 2001;21:327-334.]



Data from the DANCE Trial (Trial Overview)



- Multicenter, open-label trial in two populations: primary atherectomy (ATX) and primary angioplasty (PTA)
- Primary Endpoints

  Safety

  – Composite of freedom from all cause peri-operative (30 day) death and freedom at 1 year in the index limb from major amputation (ATK or BTK), bypass surgery or thrombolysis

  Efficacy

  – Primary patency of the target lesion at 1 year: Core lab adjudicated absence of binary restenosis (DUS PSVR > 2.4 or angiographic narrowing >50%) & freedom from clinically-driven target lesion revascularization (CD-TLR)

DANCE Patient and Lesion Characteristics

	PTA	ATX
N (legs)	124	157
Age (years)	68.9±9.1	68.4±9.6
Male	65%	57%
Caucasian	77%	80%
African American	20%	17%
Diabetes	52%	50%
CAD	55%	67%
Hypertension	90%	92%
Hyperlipidemia	83%	80%
Obesity (BMI≥30 kg/m^2)	34%	34%
Creatinine (mg/dL)	1.02±0.28	1.10±0.51
CRP, pre (mg/dL)	5.01±9.37	5.78±7.25

	PTA	ATX
Rutherford Category	2: 36.3% 3: 60.5% 4: 3.2%	2: 22.9% 3: 59.9% 4: 17.2%
TASC II Classification	A: 53% B: 40% C: 6% D: 1%	A: 30% B: 62% C: 6% D: 1%
Severe Calcification	21.3%	29.4%
Popliteal Involvement	15.3%	17.2%
Mean Lesion Length (cm)	7.4 ± 4.0	8.8 ± 5.2
Mean % Diameter Stenosis (Pre)	73% ± 16%	70% ± 17%
Total Occlusions	17%	15%
Grade B-D Dissection	44%	26%
Stent Utilization	52%	35%
Mean % Diameter Stenosis (Post)	24%±12%	23%±9%

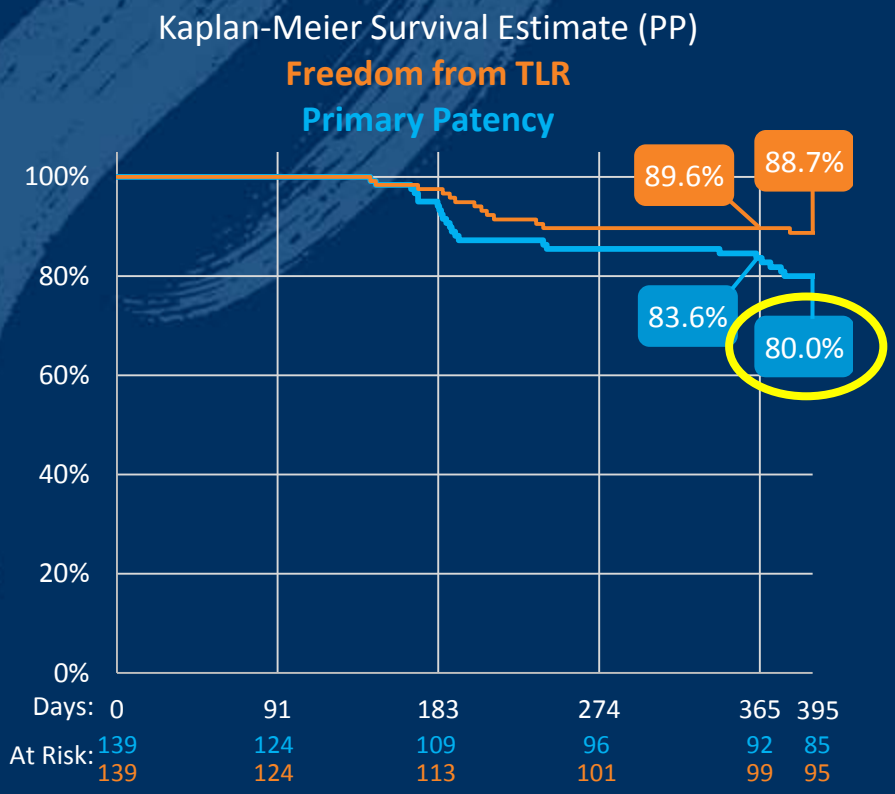
DANCE 12-Month Safety

Safety Outcomes (ITT population)	DANCE-PTA	DANCE-ATX
Device-related SAE 0-365 Days	0/124 (0.0%)	0/157 (0.0%)
Drug-related SAE 0-365 Days	0/124 (0.0%)	0/157 (0.0%)
Major Adverse Limb Events 0-365 Days		
Amputation	0/114 (0.0%)	1/126 (0.8%)**
Bypass	2/114 (1.8%)*	2/126 (1.6%)***
Thrombolysis	0/114 (0.0%)	0/126 (0.0%)
Death 0-30 Days	0/244 (0.0%)	
Death 0-365 Days		
Non-Cardiovascular	2/231 (0.9%)	
Cardiovascular or Unknown	7/231 (3.0%)	

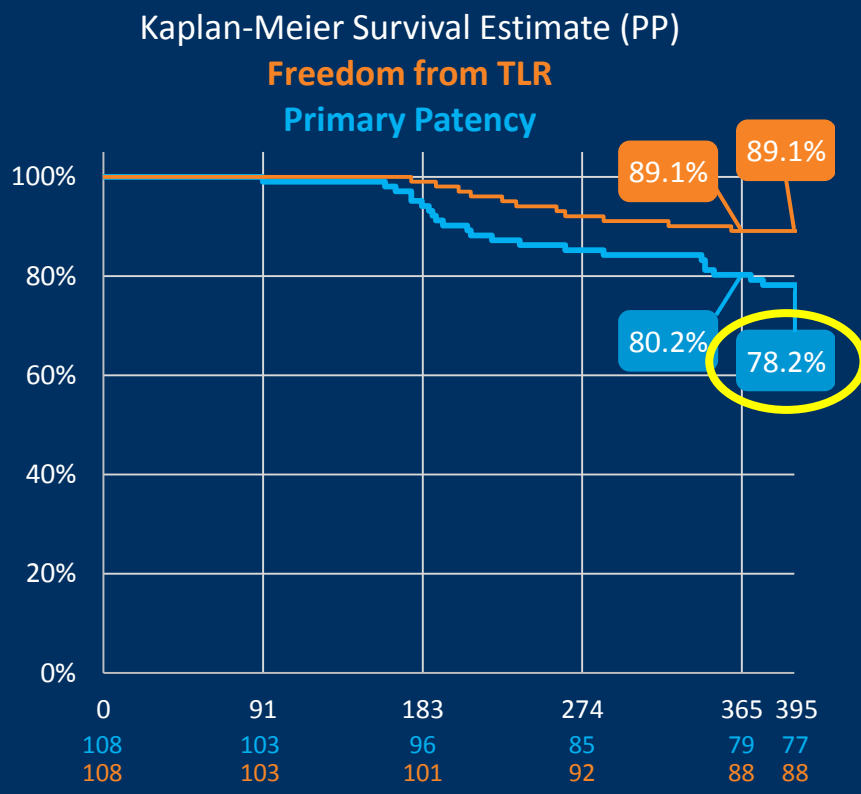
*1 of 2 bypasses were performed after TLR endpoint was reached
**The amputation was performed after TLR endpoint was reached
***1 of 2 bypasses were performed after TLR endpoint was reached

DANCE 13-Month Efficacy

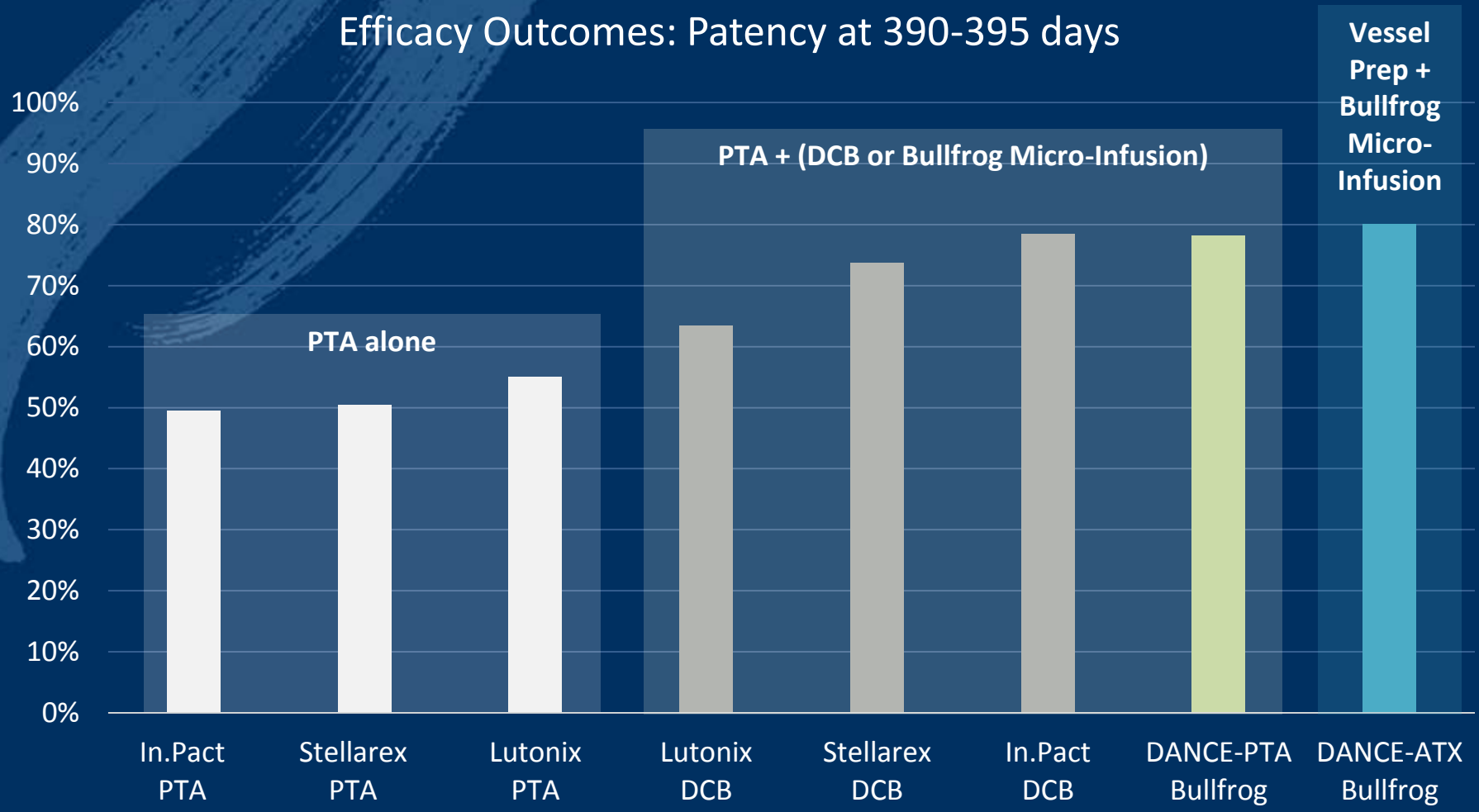
DANCE-ATX



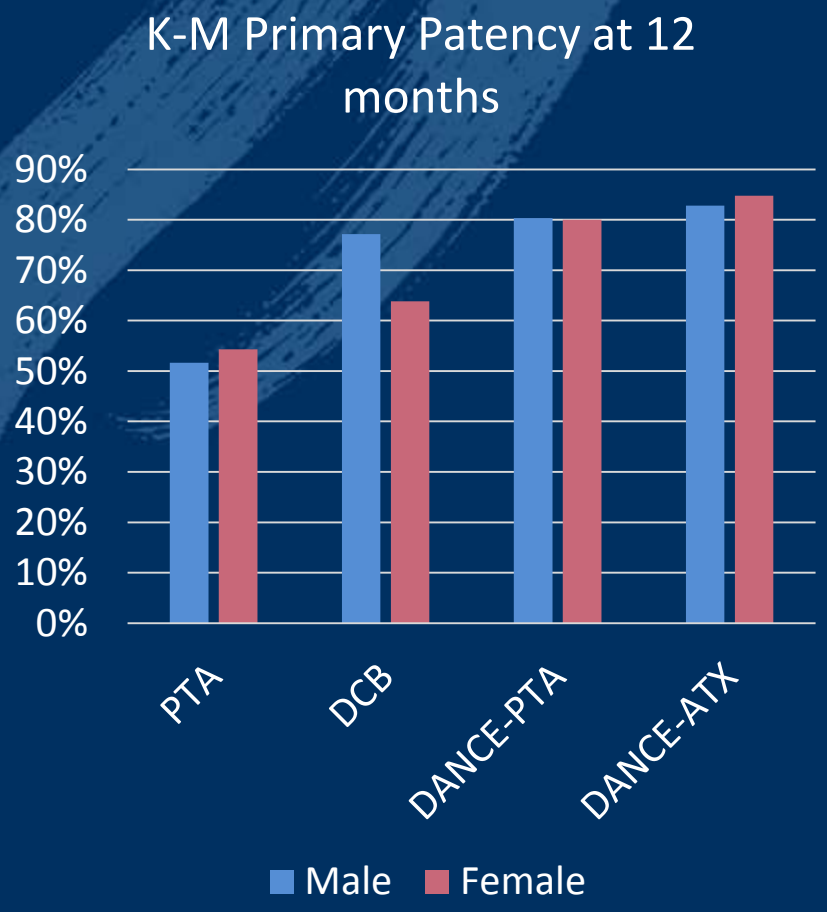
DANCE-PTA



Gaining Perspective: DANCE compared to DCB Trials

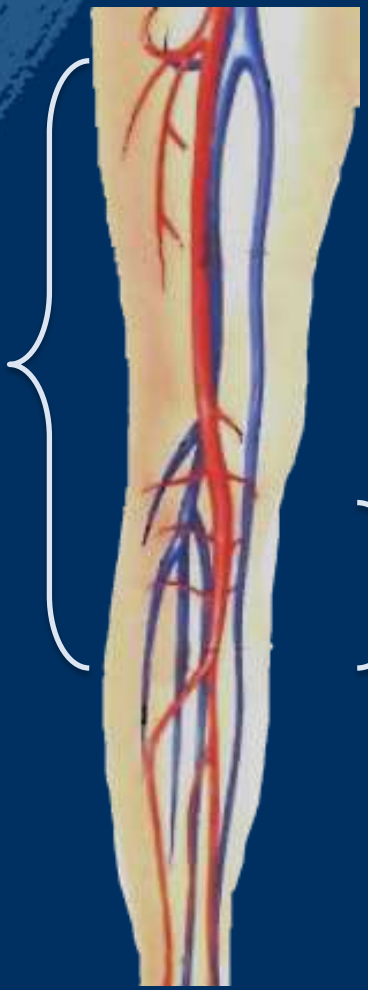


Gaining Perspective: DANCE and DCB Subgroups



- PTA and DCB results are a weighted average of Levant-2 and In.Pact-SFA results (assumes class effect)
- Is there a gender gap with DCB?
- Anti-inflammatory nature of DANCE
  - Women lack estrogen production post-menopause
  - Women have smaller vessels (less dose with DCB?) (more friable vessels?)

DANCE Subgroup Analysis
(13-Month Primary Patency)
Distal anatomy results justify examination in BTK



SFA and Popliteal
ATX: 80% patency
(N=139, LL_{avg}=8.8cm)
PTA: 78% patency
(N=108, LL_{avg}=7.4cm)

Popliteal Involvement
ATX: 95% patency
(N=23, LL_{avg}=6.3)
PTA: 77% patency
(N=15, LL_{avg}=5.8)

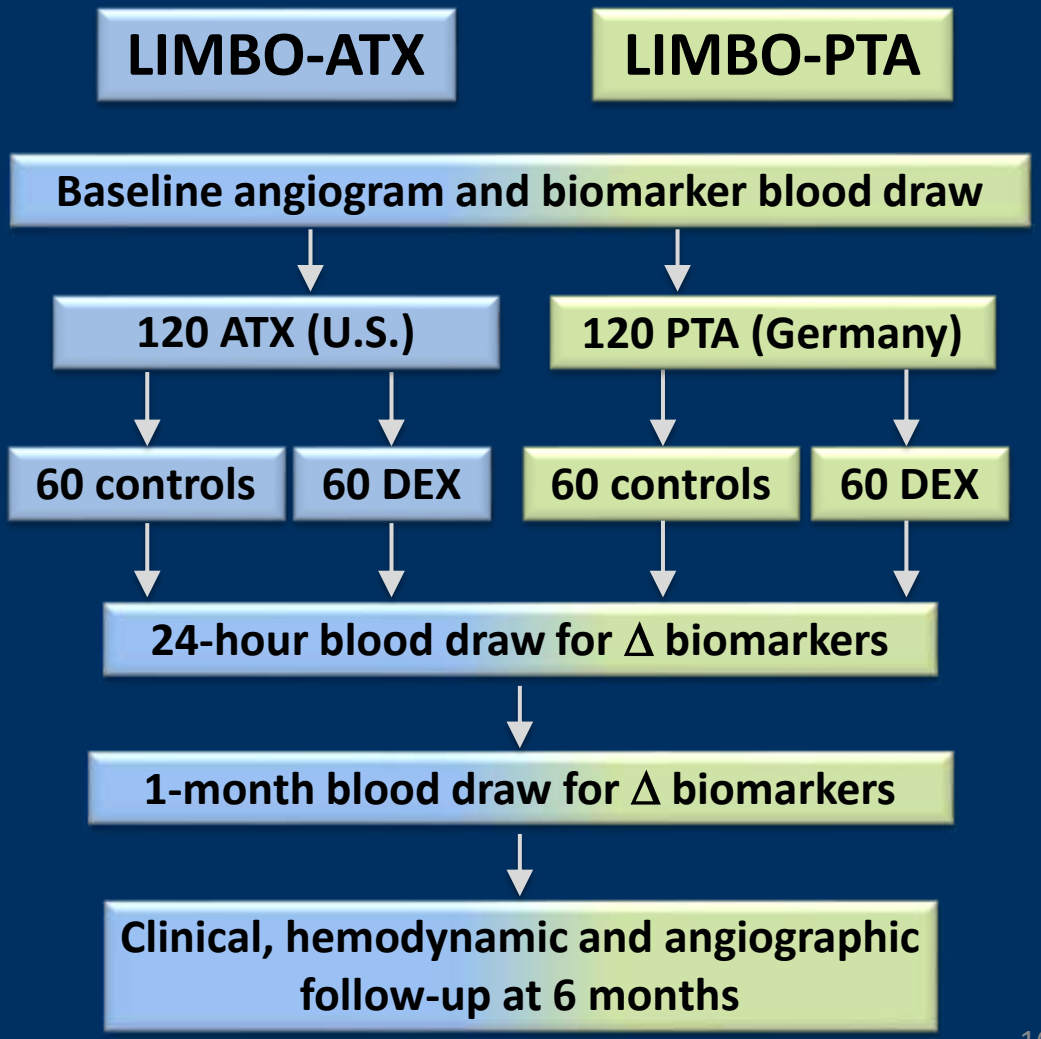
P2-P3 Involvement
ATX: 100% patency
(N=10, LL_{avg}=4.7)
PTA: 75% patency
(N=4, LL_{avg}=8.8)

BTK: LIMBO Trials Underway

- Below-Knee Study in CLI
- 2 trials: Adventitial Dexamethasone added to PTA (Germany) or atherectomy (U.S.)

- LIMBO-PTA PI: Dierk Scheinert, MD, University Hospital Leipzig, Germany (Began January 2016)

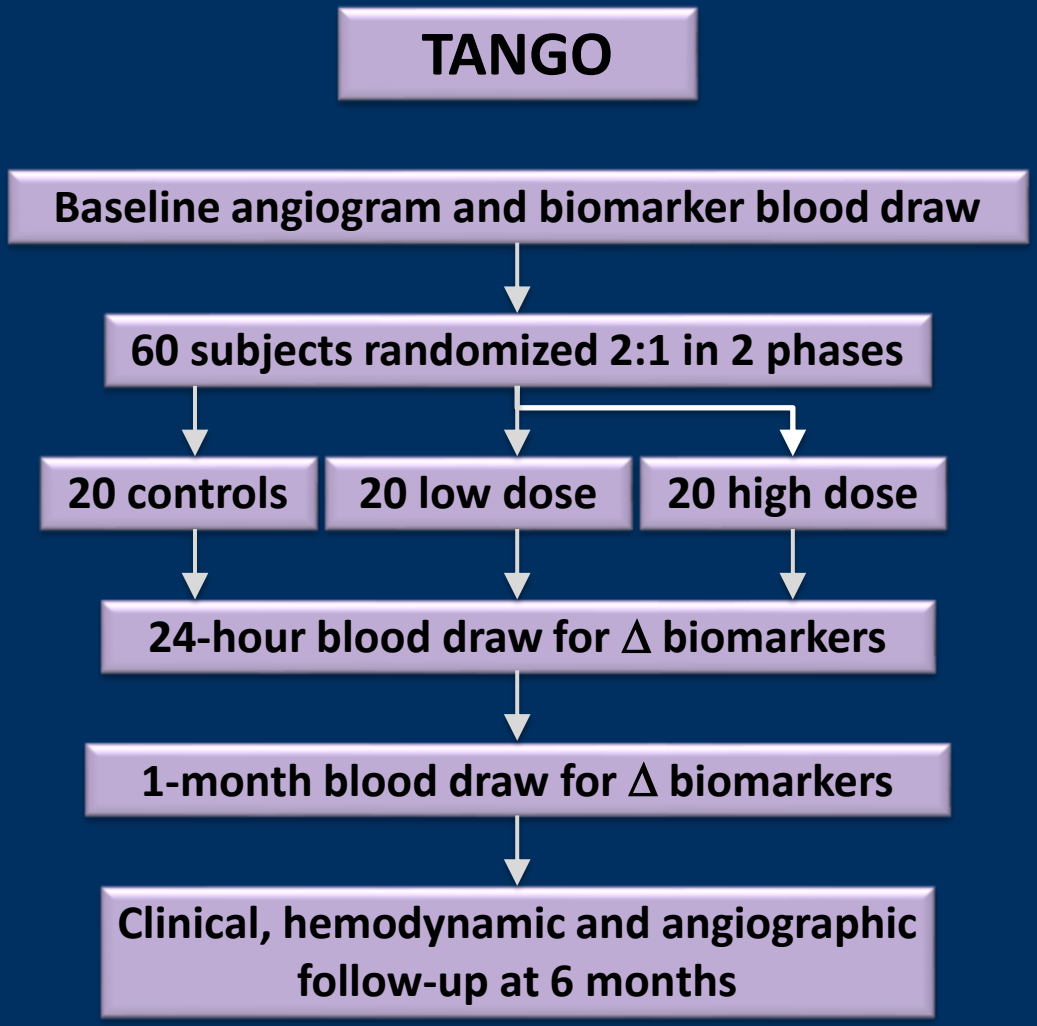
- LIMBO-ATX co-PIs: George Adams, MD, UNC-Rex, Raleigh, NC
  Don Jacobs, MD, St. Louis University, MO



BTK: TANGO Trial in Preparation

- Phase 2, Below-Knee Study in CLI
- Adventitial Temsirolimus added to PTA or atherectomy revascularization
- Anticipated FIM 1Q2017 and expansion into European sites 3Q2017

- PI: Ian Cawich, MD, Arkansas Heart Hospital, Little Rock, AR, USA



Looking Forward

- Bullfrog delivery of dexamethasone after atherectomy in SFA and popliteal arteries has produced exceptional results compared to other drug delivery platforms in a challenging patient population
- This represents a paradigm shift in drug delivery to treat lower extremity atherosclerotic disease (an inflammatory process requires an anti-inflammatory remedy)
- DANCE may represent the first outcomes of the ability to target the therapy to the patient (personalized/precision medicine)
- Bullfrog delivery into the BTK area has begun with the LIMBO and TANGO trials, and with an elastase therapy from Proteon Therapeutics

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