Research Article

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Journal of Vascular and Endovascular Therapy
ISSN 2634-7156

2022
Vol. 7 No. 1

Temsirolimus Adventitial Delivery to Improve ANGiographic Outcomes below the Knee (TANGO)

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Citation: Cawich I, Armstrong EJ, George JC, Golzar J, Shishehbor MH, et al. (2021) Temsirolimus Adventitial Delivery to Improve ANGiographic Outcomes Below the Knee (TANGO). Int J Vasc Endovasc Ther. Vol.7 No.1:4603.

Abstract

Background: Current endovascular treatments of Below-The-Knee (BTK) popliteal or tibial/peroneal arteries including investigational drug-coated balloons have limited long-term efficacy.

Objectives: This Phase 2 trial assessed the feasibility of adventitial deposition of temsirolimus to reduce neointimal hyperplasia and clinically relevant target lesion failure 6 months after BTK arterial revascularization.

Methods: This prospective, multicenter, double-blinded, comparative, dose-escalation trial enrolled 61 patients with Rutherford 3-5 symptoms undergoing endovascular revascularization of ≥ 1 angiographically significant BTK lesions. Perivascular infusion after completion of arterial revascularization was randomized into control (saline) vs. low-dose (0.1 mg/mL) temsirolimus groups for the first 30 patients. In the second part of the trial patients were randomized to control vs. high-dose (0.4 mg/mL) temsirolimus groups. Primary and secondary efficacy endpoints were target lesion Transverse-View Vessel Area Loss Percentage (TVAL%) and Clinically Relevant Target Lesion Failure (CR-TLF) at 6 months, respectively. CR-TLF was defined as a composite of ischemia-driven major amputation of the target limb, clinically driven target lesion revascularization, and clinically relevant target lesion occlusion. The primary safety endpoint was freedom from Major Adverse Limb Events or Perioperative Death (MALE+POD) at 30 days.

Results: There was no discernable difference in effect between temsirolimus doses, therefore the low- and high-dose cohorts were pooled for the analyses. The principal analysis on the per protocol group of 53 patients revealed superior primary efficacy of the treatment arm, with a reduction in TVAL% of 13.9% absolute (37.3% relative) and the rate of CR-TLF reduced by 27.1% absolute (51.3% relative), at 6 months. Subgroup analysis of all TASC B-D lesions (N=36) revealed TVAL% reduction of 22.3% absolute (48.3% relative) and the rate of CR-TLF reduced by 39.2% absolute (56.6% relative). Freedom from 30-day MALE+POD was 100% in all groups.

Conclusion: This hypothesis-generating trial suggests that adventitial infusion of temsirolimus in BTK arteries improves TVAL% and CR-TLF with no adverse safety signals through 6-months, supporting the move to a phase 3 trial.

Keywords: Endovascular; Neointimal hyperplasia; Ischemia; Revascularization

Received date: 31-Jan-2022, Manuscript No. IPJVES-22-12488;
Editor assigned date: 02-Feb-2022, PreQC No. IPJVES-22-12488(PQ);
Reviewed date: 16-Feb-2022, QC No. IPJVES-22-12488;
Revised date: 23-Feb-2022, Manuscript No. IPJVES-22-12488(R);
Published date: 02-Mar-2022, DOI: 10.21767/2634-7156.22.07.4603

Introduction

Critical Limb Threatening Ischemia (CLTI) is the end stage of lower extremity peripheral artery disease, characterized by incapacitating pain at rest, ulceration, and/or gangrene. If left untreated, up to 40% of patients with CLTI will require major amputation within 6 months [1]. CLTI is often associated with multivessel Below-The-Knee (BTK) arterial occlusion, necessitating open surgical bypass or endovascular interventions of smaller and often chronically occluded and heavily diseased infrapopliteal arteries [2]. The frequent coexistence of coronary atherosclerotic disease, diabetes, renal insufficiency, and smoking-related pulmonary disease renders CLTI patients at high risk for open surgical procedures and underlies the rising popularity of endovascular interventions such as balloon angioplasty and atherectomy [3].

The outcome of tibial interventions, however, has historically been suboptimal. A meta-analysis of tibial angioplasty published by Romiti and colleagues included 30 articles published prior to 2006, when uncoated Percutaneous Balloon Angioplasty (PTA) was the principal endovascular option [4]. At 12 months, patency after tibial PTA was 52%, with limb loss in 15% of patients. More recent trials comparing PTA with Drug Coated Balloon (DCB) angioplasty confirmed poor results with PTA and no clear improvement based on the use of DCB. In one clinical trial of paclitaxel DCB, at 12 months, target lesion occlusion occurred in 16% and 11% with major amputation in 4% and 9% in the PTA and DCB arms, respectively [5]. In another clinical trial, at 6 months, the rate of primary efficacy success (freedom from occlusion, CD-TLR, or above-ankle amputation) was 75.5% for the DCB group and 63.5% for the PTA group, which did not reach statistical significance based on the trial design.

While DCB has demonstrable benefits over PTA above the knee [6-8], there remain no approved DCB for infrapopliteal use in the United States. Furthermore, safety concerns for use of paclitaxel in the femoropopliteal and infrapopliteal segments have been raised in systematic reviews and meta-analyses by Katsanos et al. in 2018, 2020 and 2022 [9-11]. While these studies have been criticized based on the absence of patient level data, the analyses nonetheless have found mortality and amputation signals associated with paclitaxel DCB.

The use of sirolimus analogs to reduce restenosis offers an alternative to paclitaxel. The use of microinjection of antiproliferative agents directly into the periadventitial space is a novel approach that may potentially achieve more effective drug delivery. The TANGO Trial (Temsirolimus Adventitial Delivery to Improve Angiographic Outcomes Below the Knee) was a Phase 2, double-blinded randomized controlled trial. The trial aimed to assess the 6-month efficacy and safety of the Bullfrog micro-infusion device adventitial deposition of two escalating doses of temsirolimus or saline placebo, based on evaluation of angiographic evidence of neointimal hyperplasia and target lesion failure after revascularization of BTK popliteal or tibial/peroneal arteries. Results were informative in generating a clinical hypothesis for a future phase 3 trial.

Methods

Trial design

The TANGO trial was a prospective, multicenter, dose-escalation, comparative, double-blinded trial designed to investigate the feasibility of adventitial delivery of temsirolimus in reducing intimal hyperplasia and restenosis following revascularization of Below The Knee (BTK) lesions in patients with symptomatic peripheral arterial disease. This was a phase 2 trial conducted at seven clinical centers in the United States and was conducted in compliance with the ethical principles highlighted in the declaration of Helsinki. Institutional Review Board (IRB) approval was obtained for the clinical protocol at all participating sites, and patients provided written informed consent before undergoing any study procedures.

Investigators and subjects remained blinded through-out the duration of the trial and were only told of subject assignment upon completion of the trial. The investigators received a syringe containing saline or drug from the study pharmacy with only a numeric label, to keep them blinded to the therapy. To avoid bias, the core laboratories were also blinded to patient treatment assignment. Each subject was followed up through 12 months after their procedure.

Patient eligibility

The study population was intended to be representative of typical patients in the community being treated for symptomatic peripheral vascular disease affecting the BTK arteries. Eligible patients included those with Rutherford classification of 3 to 5, and who met all necessary screening and procedural eligibility criteria (i.e., angiographic criteria). Detailed inclusion and exclusion criteria are provided in Supplemental Table 1. Once deemed eligible, patients were randomized 2:1 to receive either temsirolimus or saline placebo injections at a volume of 0.25 mL per cm-0.50 mL per cm of lesion length. During the first half of the trial, temsirolimus was administered at a dose of 0.1 mg/mL, for 0.025 mg/cm-0.050 mg/cm of lesion length. After a pre-designated safety stop, the trial advanced to the second half, in which temsiorlimus was administered at a dose of 0.4 mg/mL, for 0.10 mg/cm-0.20 mg/cm of lesion length. While screening criteria were assessed pre-procedure, procedural eligibility was assessed intra-operatively. All included subjects were required to have ≥ 1 atherosclerotic target lesion with ≥ 70% stenosis in a BTK artery that had undergone successful endovascular revascularization (<30% residual stenosis and run-off to the foot) during the index procedure (Supplemental Table 1).

Table 1 Baseline demographic characteristics and medical history-All PP subjects. ATK: Above The Knee; BMI: Body Mass Index; BTK: Below The Knee; CLI: Critical Limb Ischemia; IQR: Inter-Quartile Range; PP: Per-Protocol; SD: Standard Deviation. Numbers are % (counts/sample size) unless otherwise stated.

*Minor amputation levels: Forefoot: Toe, ray (metatarsal & toe) or trans-metatarsal

Midfoot: Lisfranc (tarsometatarsal joint) or chopart (transverse tarsal joint)

Hindfoot: Syme, boyd, pirogoff or modified pirogoff Site reported data

Subject characteristics	Statistics	Temsirolimus N=35	Control N=18	Difference [95%CI]
Age (years)	N	35	18	
	Mean ± SD	72.2 ± 9.49	73.4 ± 8.18	1.2 [-4, 6.5]
	Median (IQR)	74 (67-80)	74.5 (68-80)	
	Min-Max	53-87	57-85	
BMI (kg/m2)	N	35	18	
	Mean ± SD	28.1 ± 6.12	28.8 ± 6.71	0.6 [-3, 4.3]
	Median (IQR)	27.6 (23.8 - 31.3)	28.1 (25.3 - 31)	
	Min-Max	19.3 - 45	20.2 - 45.7	
Obesity (BMI ≥ 30 kg/m2)	% (n/N)	37.1% (13/35)	27.8% (5/18)	9.4% [-16.8%, 35.5%]
Male	% (n/N)	65.7% (23/35)	66.7% (12/18)	-1% [-27.8%, 25.9%]
Race				
White	% (n/N)	68.6% (24/35)	55.6% (10/18)	13% [-14.6%, 40.6%]
Black or African descent	% (n/N)	31.4% (11/35)	33.3% (6/18)	-1.9% [-28.6%, 24.8%]
Asian	% (n/N)	0.0% (0/35)	5.6% (1/18)	-5.6% [-16.1%, 5%]
Native Hawaiian or other Pacific islander	% (n/N)	0% (0/35)	0% (0/18)	NA
American Indian or Alaska native	% (n/N)	0% (0/35)	0% (0/18)	NA
Unknown/decline to state	% (n/N)	0.0% (0/35)	5.6% (1/18)	-5.6% [-16.1%, 5%]
Ethnicity				
Hispanic or Latino	% (n/N)	17.1% (6/35)	16.7% (3/18)	0.5% [-20.8%, 21.7%]
Not Hispanic or Latino	% (n/N)	82.9% (29/35)	83.3% (15/18)	-0.5% [-21.7%, 20.8%]
Unknown/decline to state	% (n/N)	0% (0/35)	0% (0/18)	NA
Hypertension	% (n/N)	85.7% (30/35)	88.9% (16/18)	-3.2% [-21.8%, 15.4%]
Hyperlipidemia	% (n/N)	88.6% (31/35)	83.3% (15/18)	5.2% [-14.9%, 25.4%]
Diabetes mellitus	% (n/N)	57.1% (20/35)	72.2% (13/18)	-15.1% [-41.5%, 11.3%]
Insulin dependent diabetes mellitus	% (n/N)	34.3% (12/35)	33.3% (6/18)	1% [-25.9%, 27.8%]
Carotid artery disease	% (n/N)	20.0% (7/35)	16.7% (3/18)	3.3% [-18.4%, 25.1%]
Coronary artery disease	% (n/N)	57.1% (20/35)	66.7% (12/18)	-9.5% [-36.8%, 17.7%]
Renal artery disease	% (n/N)	17.1% (6/35)	11.1% (2/18)	6% [-13.1%, 25.2%]
Cerebrovascular event	% (n/N)	17.1% (6/35)	22.2% (4/18)	-5.1% [-28%, 17.8%]
Current smoker	% (n/N)	11.4% (4/35)	16.7% (3/18)	-5.2% [-25.4%, 14.9%]
Other lower limb history				
Chronic CLI BTK in target limb	% (n/N)	82.9% (29/35)	94.4% (17/18)	-11.6% [-28%, 4.8%]
Active foot infection in any limb	% (n/N)	0% (0/35)	0% (0/18)	NA
Active heel ulcers on any limb	% (n/N)	0.0% (0/35)	5.6% (1/18)	-5.6% [-16.1%, 5%]
Minor amputation-target limb*				
Forefoot	% (n/N)	8.6% (3/35)	11.1% (2/18)	-2.5% [-19.8%, 14.7%]
Midfoot	% (n/N)	0% (0/35)	0% (0/18)	NA
Hindfoot	% (n/N)	0% (0/35)	0% (0/18)	NA

Minor amputation-contralateral limb*				
Forefoot	% (n/N)	11.4% (4/35)	16.7% (3/18)	-5.2% [-25.4%, 14.9%]
Midfoot	% (n/N)	2.9% (1/35)	0.0% (0/18)	2.9% [-2.7%, 8.4%]
Hindfoot	% (n/N)	2.9% (1/35)	0.0% (0/18)	2.9% [-2.7%, 8.4%]
Major amputation-contralateral limb				
Trans-tibial (BTK)	% (n/N)	5.7% (2/35)	11.1% (2/18)	-5.4% [-21.8%, 11%]
Through the knee (Gritti-Stokes)	% (n/N)	0% (0/35)	0% (0/18)	NA
Trans-femoral (ATK)	% (n/N)	0% (0/35)	0% (0/18)	NA
Hip disarticulation	% (n/N)	0% (0/35)	0% (0/18)	NA
Prior vascular disease intervention in target limb				
Popliteal artery revascularization ATK	% (n/N)	14.3% (5/35)	16.7% (3/18)	-2.4% [-23.1%, 18.4%]
Popliteal artery revascularization BTK	% (n/N)	14.3% (5/35)	22.2% (4/18)	-7.9% [-30.4%, 14.5%]
Tibial/peroneal revascularization	% (n/N)	14.3% (5/35)	44.4% (8/18)	-30.2% [-55.9%, -4.4%]
Brachytherapy, infrapopliteal arteries	% (n/N)	0% (0/35)	0% (0/18)	NA
Drug eluting stent	% (n/N)	0.0% (0/35)	11.1% (2/18)	-11.1% [-25.6%, 3.4%]
Drug eluting balloon or drug coated balloon	% (n/N)	14.3% (5/35)	27.8% (5/18)	-13.5% [-37.2%, 10.2%]
Vascular graft implanted	% (n/N)	2.9% (1/35)	0.0% (0/18)	2.9% [-2.7%, 8.4%]

Delivery of the investigational drug

Study subjects received standard endovascular revascularization with or without bailout stenting (if needed) and either saline (control group), 0.1 mg/mL (low-dose treatment group) or 0.4 mg/mL (high-dose treatment group) temsirolimus. Standard endovascular revascularization options could be atherectomy, balloon angioplasty, provisional stenting, or combined revascularization methods. Every effort was made to achieve a final artery diameter with <30% residual narrowing; if not, stenting (but not a drug-eluting stent) was considered.

Treatment was performed immediately after the primary revascularization procedure and before any provisional stenting. The treatment or control agent was administered into the perivascular tissues surrounding the treated lesions using the Bullfrog micro-infusion device. This device is CE-marked and FDA-cleared for the delivery of medications into the perivascular space of coronary or peripheral vessels (Figure 1). Drug administration was made to the target lesion only, with a volume of 0.2 mL to 0.3 mL for each 1 cm of tibial artery lesion length and 0.4 mL to 0.6 mL for each 1 cm of popliteal artery lesion length. During treatment the operator could administer drug to multiple sites along the target lesion via repositioning of the micro-infusion device as needed to establish successful distribution of the drug. Co-infusion of contrast medium was also performed to allow fluoroscopic visualization to determine infusion success.

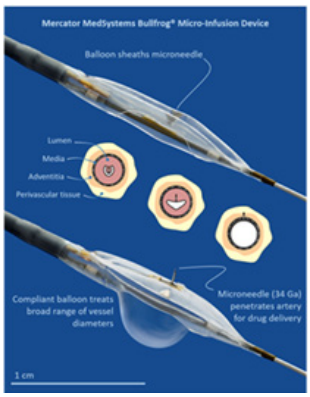

Figure 1 Bullfrog micro-infusion device and method of study drug administration.

Endpoints and definitions

The primary efficacy endpoint was an angiographic measurement of Transverse-View Vessel Area Loss Percentage (TVAL%) along the target lesion by Quantitative Vascular Angiography (QVA) through 6-months post-index procedure or before any re-intervention (if performed prior to 6 months). The Transverse-View Vessel Area (TVA) of the Target Lesion (TL) was calculated as the area filled by contrast visualized from a transverse view of the vessel, as constrained by the ends of the lesion length and the vessel side walls. TVAL% was calculated as: 100%-[TVA(follow-up)/TVA(baseline)] (Supplemental Figure 1). Because angiographic outcomes are not always informative of patient functional outcomes, a secondary, clinical efficacy endpoint of freedom from Clinically Relevant Target Lesion Failure (CR-TLF) was also

measured through 6-months post-index procedure. CR-TLF was defined as the composite of ischemia-driven major amputation of the target limb, Clinically Driven Target Lesion Revascularization (CD-TLR), and clinically relevant target lesion occlusion. Clinically relevant restenosis, a secondary endpoint of the trial, was defined as the presence of a 50% or greater narrowing accompanied by a judgement of clinical relevance. Clinical relevance was adjudicated by an independent medical monitor for the trial based on worsening of Rutherford score, non-healing of wounds, ABI drop of ≥ 0.15, TBI drop of ≥ 0.10, each as compared to post-procedural outcomes, or absolute toe pressure ≤ 30 mmHg. Scheduled subject follow-up for this trial occurred at 1 month, 6 months, and 12 months post-procedure.

The primary safety endpoint was freedom from any Major Adverse Limb Event and Perioperative Death (MALE + POD) at 30 days. MALE was defined as including any of the following: Surgical bypass of the target lesion, target limb amputation above the ankle, and/or embolization or vessel thrombosis requiring thrombolysis in the target limb.

Data Analysis

Once data was collected, descriptive data was provided by treatment groups and dose arms and the statistical analysis was performed using SAS (Version 9.4 or higher) or STATA Version 16 or higher. The full trial/intent-to-treat population (ITT group) consisted of all subjects that were enrolled, randomized, and had attempted injections with the Bullfrog device. While data was collected on the ITT group, the determination was made post hoc that the principal analysis would be performed on the Per Protocol (PP) group, as defined in the statistical analysis plan for the trial. The PP group excluded four subjects with unstented severe dissections (type C or greater) and four subjects with unstented proximal total occlusions that received angioplasty during the index procedure. The rationale for this determination was that both of these groups had confounding modes of early treatment failure unrelated to target lesion restenosis, and both are intended to be excluded from future clinical trial enrollment. As such, the focus of the data presented within this manuscript is on the PP group.

Subjects with worse TASC classification tend to have poorer outcomes in general after interventional therapy [12]. For this reason, an additional analysis was performed on subjects most likely to benefit from augmented drug therapy: Those with TASC B, C or D lesions. The primary and secondary efficacy endpoints (including clinical efficacy endpoints) through the 6-month visit window were therefore evaluated in this subgroup of patients from within the PP population.

Angiographic enrollment criteria were adjudicated by the angiographic core laboratory (cardiovascular research foundation, New York, NY). The 12-month patency was evaluated via duplex Doppler ultrasound examination of the target lesion and target limb. The results were analyzed by a duplex core laboratory (VasCore, Boston, MA).

For statistical analyses, the differences in proportions between the treatment and control arms were determined, and the confidence intervals of the differences using the normal approximation were reported. For binary or categorical variables, the number and percentage within each category of the parameter was calculated. For continuous variables, the N, median, Interquartile Range (IQR), mean, Standard Deviation (SD), minimum, and maximum values were presented. For time-to-event endpoints, the Kaplan-Meier (KM) curves were generated, the KM estimates and confidence interval were reported at monthly intervals.

Results

Enrollment and Follow-up

A total of 61 subjects were enrolled in the trial, with 41 subjects in the treatment group, and 20 in the control group (Figure 2). Within the treatment group, 21 subjects were randomized to high-dose temsirolimus, and 20 to low-dose. A total of 36 (88%) treatment subjects and 19 (95%) control subjects completed their 6-month follow-up visit. Five (12%) treatment subjects and one (5%) control subject withdrew participation prior to the 6-month follow-up. Of the 56 ITT patients with 6-month follow-up, 8 were disqualified from the PP group (4 due to severe dissection and 4 due to proximal total occlusions that were revascularized without stenting) and not included in the principal data analyses.

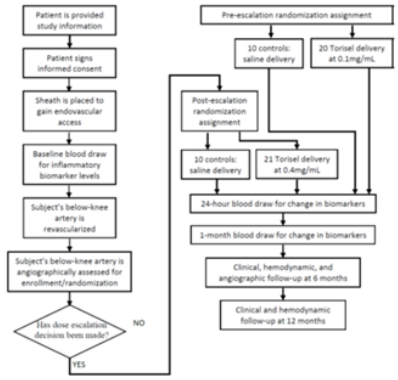

Figure 2 Schematic of subject flow.

Demographic and baseline characteristics

Demographics and baseline characteristics are summarized in Table 1 for the PP population. The median age was similar between groups (74 years for the treatment group and 74.5 years for the control group), as was the Body Mass Index (BMI; treatment group, 28.1 kg/m2; control, 28.8 kg/m2 group). The percentage of male patients was 65.7% in the treatment group and 66.7% in the control group. There were no significant differences in age, gender, comorbid conditions, or incidence of prior target limb vascular intervention between the treatment and control groups. Demographic data for the ITT group and for subset group (PP population with TASC B, C or D lesions) are presented in the supplemental data (Table 1) (Supplemental Tables 2 and 3).

Table 2 Clinical and lesion characteristics-All PP subjects. IQR: Inter-Quartile Range; MLD: Minimum Lumen Diameter; RVD: Reference Vessel Diameter; SD: Standard Deviation; TASC: Trans-Atlantic Inter-Society Consensus; TBI: Toe-Brachial Index. Numbers are % (counts/sample size) unless otherwise stated.

*More than one may be chosen.

Site and core lab reported data

N=35	Temsirolimus N=35	Control N=18	Difference [95%CI]
Target limb			
Left	45.7% (16/35)	44.4% (8/18)	1.3% [-27%, 29.5%]
Right	54.3% (19/35)	55.6% (10/18)	-1.3% [-29.5%, 27%]
Rutherford class			
3	45.7% (16/35)	38.9% (7/18)	6.8% [-21.1%, 34.7%]
4	17.1% (6/35)	11.1% (2/18)	6% [-13.1%, 25.2%]
5	37.1% (13/35)	50.0% (9/18)	-12.9% [-41%, 15.2%]
Walking capability			
N	35	18	
Median (IQR)	1 (1 - 2)	1.5 (1 - 2)	
Walking capability			
1: Ambulatory	71.4% (25/35)	50.0% (9/18)	21.4% [-6.1%, 49%]
2: Assisted ambulation	20.0% (7/35)	44.4% (8/18)	-24.4% [-51%, 2.1%]
3: Wheelchair	5.7% (2/35)	5.6% (1/18)	0.2% [-12.9%, 13.2%]
4: Bedridden	2.9% (1/35)	0% (0/18)	2.9% [-2.7%, 8.4%]
ABI (mmHg)			
N	31	17	
Mean ± SD	0.8 ± 0.42	0.9 ± 0.37	0 [-0.2, 0.3]
Median (IQR)	0.8 (0.6 - 1)	0.8 (0.6 - 1.1)	
Min-Max	0 - 2	0.4 - 1.6	
TBI (mmHg)			
N	24	15	
Mean ± SD	0.3 ± 0.2	0.4 ± 0.15	0.1 [-0.1, 0.2]
Median (IQR)	0.3 (0.2 - 0.5)	0.4 (0.3 - 0.5)	
Min-Max	0 - 0.8	0.1 - 0.6	
Inflow tract patency (<50% stenosis)	60.0% (15/25)	69.2% (9/13)	-9.2% [-40.8%, 22.4%]
Outflow (perfusion of foot)	88.2% (30/34)	100.0% (17/17)	-11.8% [-22.6%, -0.9%]
Target Vessel*			
Popliteal	17.6% (6/34)	22.2% (4/18)	-4.6% [-27.7%, 18.5%]
Anterior tibial	23.5% (8/34)	33.3% (6/18)	-9.8% [-35.8%, 16.2%]
Tibio-peroneal trunk	38.2% (13/34)	38.9% (7/18)	-0.7% [-28.5%, 27.2%]
Peroneal	17.6% (6/34)	38.9% (7/18)	-21.2% [-47.2%, 4.7%]
Posterior tibial	47.1% (16/34)	27.8% (5/18)	19.3% [-7.4%, 45.9%]
Target lesion length (cm)			
N	35	18	
Mean ± SD	10.1 ± 8.06	11.5 ± 7.3	1.4 [-3.1, 6]
Median (IQR)	7 (4 - 16)	10 (5 - 19.9)	
Min-Max	1.5 - 29.1	1.9 - 24.9	
RVD (mm)			
N	35	18	
Mean ± SD	2.8 ± 0.88	2.8 ± 0.78	0 [-0.5, 0.5]
Median (IQR)	2.4 (2.2 - 3.3)	2.8 (2.2 - 3.6)	
Min-Max	1.4 - 4.9	1.5 - 4.1	
MLD (mm)			
N	35	18	
Mean ± SD	0.8 ± 0.55	0.5 ± 0.56	-0.2 [-0.5, 0.1]
Median (IQR)	0.8 (0 - 1.1)	0.7 (0 - 0.9)	
Min-Max	0 - 1.9	0 - 1.8	

Grade of calcification			
None/Mild	82.4% (28/34)	72.2% (13/18)	10.1% [-14.2%, 34.5%]
Moderate	2.9% (1/34)	16.7% (3/18)	-13.7% [-31.9%, 4.4%]
Severe	14.7% (5/34)	11.1% (2/18)	3.6% [-15.2%, 22.4%]
TASC classification			
A	37.1% (13/35)	22.2% (4/18)	14.9% [-10.1%, 39.9%]
B	20.0% (7/35)	27.8% (5/18)	-7.8% [-32.3%, 16.8%]
C	20.0% (7/35)	5.6% (1/18)	14.4% [-2.5%, 31.4%]
D	22.9% (8/35)	44.4% (8/18)	-21.6% [-48.4%, 5.3%]

Table 3 Safety endpoints by treatment arm- PP subjects. CD TLR: Clinically-Driven Target Lesion Revascularization; MALE: Major Adverse Limb Event; POD: Post-Operative Death at 30 days. Numbers are % (counts/sample size) unless otherwise stated. Site reported, medical monitor adjudicated data

N=35	**Temsirolimus**	**Control**	**Difference [95%CI]**
	N=35	**N=18**	
Freedom from (through 30 Days)			
MALE+POD composite	100% (33/33)	100% (18/18)	NA
Ischemia-driven amputation above the ankle	100% (33/33)	100% (18/18)	NA
Post-operative death at 30 days	100% (33/33)	100% (18/18)	NA
Surgical bypass of target lesion	100% (33/33)	100% (18/18)	NA
Embolization requiring thrombolysis	100% (33/33)	100% (18/18)	NA
All-cause death	100% (33/33)	100% (18/18)	NA
MALE	100% (33/33)	100% (18/18)	NA
CD TLR	100% (33/33)	100% (18/18)	NA
Freedom from (through 204 Days)			
MALE+POD composite	93.5% (29/31)	100.0% (16/16)	-6.5% [-15.1%, 2.2%]
Ischemia-driven amputation above the ankle	93.5% (29/31)	100.0% (16/16)	-6.5% [-15.1%, 2.2%]
Post-operative death at 30 days	100% (31/31)	100% (16/16)	NA
Surgical bypass of target lesion	100% (31/31)	100% (16/16)	NA
Embolization requiring thrombolysis	100% (31/31)	100% (16/16)	NA
All-cause death	100.0% (30/30)	94.1% (16/17)	5.9% [-5.3%, 17.1%]
MALE	90.6% (29/32)	100.0% (16/16)	-9.4% [-19.5%, 0.7%]
CD TLR	86.7% (26/30)	70.6% (12/17)	16.1% [-8.8%, 40.9%]

Table 4 Angiographic efficacy endpoints by treatment arm-PP subjects. IQR: Inter-Quartile Range; SD: Standard Deviation; TVAL%: Transverse-View Vessel Area Loss Percentage. Core lab reported data.

Outcome	**Temsirolimus**	**Control**	**Difference [95%CI]**
	N=35	**N=18**	
TVAL%			
N	27	16	
Mean ± SD	23.4 ± 20.85	37.3 ± 32.24	13.9 [-2.4, 30.2]
Median (IQR)	21.7 (6.7-33.4)	37.6 (4-60)	
Min-Max	-84.8	-101.1	
Increase % diameter stenosis			
N	28	17	
Mean ± SD	32.7 ± 25.87	45 ± 28.26	12.3 [-4.3, 28.9]
Median (IQR)	26.1 (14.3 - 44.3)	52.8 (22.6-65.9)	
Min-Max	-96.2	-94.4	

Clinical and lesion characteristics

Clinical and lesion characteristics for the PP population are summarized in Table 2 (Table 2). Overall, less than a third of the patients were TASC A, and the most common Rutherford classes were 3 and 5. The mean lesion length in the treatment group was 10.1 cm and 11.5 cm in the control group. Both the treatment and control groups had lesions with primarily mild or no calcification, which was expected based on the exclusion criteria. There were no significant differences between the control and treatment groups in regard to Rutherford class, TASC classification, target vessel, target lesion length or calcification. Clinical and lesion characteristics for the ITT group and for subset group (PP population with TASC B, C or D lesions) are presented in the supplemental data (Supplemental Tables 4 and 5).

Dose effect

When analysis by treatment dose was performed, it was revealed that the low-dose temsirolimus cohort did not have inferior results to the high-dose temsirolimus cohort, and was superior to the control in regards to clinically relevant target lesion occlusion. There was a significant difference at 6 months in freedom from clinically relevant target lesion occlusion between the low-dose treatment group (17/19) vs. control (12/19), of 26.3%. Results at the 12-month follow-up period were similar, with a numerical difference in freedom from clinically relevant target lesion occlusion between the low-dose treatment group (14/17) vs. control (12/19), of 19.2%. No difference was seen between the high-dose treatment group compared to control, nor were there differences in overall target lesion failure or CR-TLF. Up to the 30-day follow-up there were no instances of ischemia driven major amputations, TLR, and there were no notable differences in the other endpoints between doses. At 6 months, 2 subjects in the high-dose group underwent ischemia driven major amputation and 1 subject in the control group developed new wounds on the target limb. Due to the lack of significant difference or observable dose effect between doses, both temsirolimus cohorts were pooled for all subsequent analyses described herein.

Table 5 Angiographic efficacy endpoints by treatment arm-PP TASC BCD Subjects. IQR: Interquartile Range; SD: Standard Deviation; TVAL%: Transverse-View Vessel Area Loss Percentage. Core lab reported data.

Outcome	Temsirolimus N=35	Control N=18	Difference [95%CI]
TVAL%			
N	17	12	
Mean ± SD	23.9 ± 21.74	46.2 ± 30.98	22.3 [2.2, 42.3]
Median (IQR)	24.4 (9-33.4)	50 (21.3-63.2)	
Min-Max	-84.8	0.8 - 100	
Increase % diameter stenosis			
N	18	13	
Mean ± SD	34.1 ± 25.66	51.7 ± 26.23	17.6 [-1.7, 36.9]
Median (IQR)	29.1 (14.6-44.8)	58.3 (38.4-68.8)	
Min-Max	-91.1	-86.5	

Primary safety endpoint

Both the treatment and control groups experienced favorable safety outcomes, which are summarized for the PP group in Table 3 (Table 3). Two treatment subjects withdrew from the trial prior to the 30-day follow-up. For the remaining patients, the primary safety endpoint of freedom from (MALE + POD) at 30 days was 100% in all study groups. When the primary safety endpoint was evaluated in the full study (ITT) population, freedom from (MALE + POD) at 30 days was also 100% in both groups (Supplemental Table 6).

Table 6 Clinical efficacy endpoints by treatment arm-PP subjects. Difference [95% CI].*Data from follow-up visit, up to end of the visit window (204 days for 6-month visit). Numbers are % (counts/sample size) unless otherwise stated. Site reported, medical monitor classified data.

Subject characteristics	Temsirolimus N=35	Control N=18	Difference [95%CI]
Freedom from (through 30 Days)			
Clinically Relevant Target Lesion Failure Composite (CR-TLF)	100.0% (33/33)	94.4% (17/18)	5.6% [-5%, 16.1%]
Ischemia-driven major amputation	100% (33/33)	100% (18/18)	NA
Clinically relevant target lesion occlusion	100.0% (33/33)	94.4% (17/18)	5.6% [-5%, 16.1%]
CD-TLR	100% (33/33)	100% (18/18)	NA
Unplanned target limb amputation	97.0% (32/33)	88.9% (16/18)	8.1% [-7.6%, 23.7%]
Freedom from (through 4-week visit)*			

Occurrence of new wounds	100.0% (33/33)	94.4% (17/18)	5.6% [-5%, 16.1%]
Clinically relevant restenosis	100.0% (33/33)	94.4% (17/18)	5.6% [-5%, 16.1%]
Freedom from (through 204 days)			
Clinically Relevant Target Lesion Failure Composite (CR-TLF)	74.2% (23/31)	47.1% (8/17)	27.1% [-1.2%, 55.4%]
Ischemia-driven major amputation	93.5% (29/31)	100.0% (16/16)	-6.5% [-15.1%, 2.2%]
Clinically relevant target lesion occlusion	86.7% (26/30)	58.8% (10/17)	27.8% [1.5%, 54.2%]
CD-TLR	86.7% (26/30)	70.6% (12/17)	16.1% [-8.8%, 40.9%]
Unplanned target limb amputation	81.3% (26/32)	81.3% (13/16)	0% [-23.4%, 23.4%]
Freedom from (through 6-month visit)*			
Occurrence of new wounds	96.7% (29/30)	82.4% (14/17)	14.3% [-4.9%, 33.5%]
Clinically relevant restenosis	60.0% (18/30)	35.3% (6/17)	24.7% [-4%, 53.4%]

Through the 6-month follow-up period, freedom from all-cause mortality was 100% in the treatment group and 94.1% in the control group, and limb salvage was 93.5% in the treatment group and 100% in the control group. The differences were not noted to be statistically significant.

Primary efficacy/Angiographic endpoint

Primary efficacy analysis with the ITT population demonstrated a modest trend in favor of treatment over control (Supplemental Table 7), with treatment effect noted to be more apparent in the PP and PP-TASC B-D sub-group analyses. Results are demonstrated in Table 4 and Table 5, respectively. TVAL% reduction through the 6-month visit window was 13.9% in the PP treatment group as compared to control. This TVAL% reduction increased to 22.3% once analysis was focused on the higher TASC classification sub-group (Table 4 and Table 5).

Clinical efficacy endpoints

When evaluating the secondary endpoint of freedom from Clinically Relevant Target Lesion Failure (CR-TLF), few differences were appreciated between the treatment and control groups of the ITT population (Supplemental Table 8). However, the treatment group had favorable results over the controls within the PP population after confounding factors were removed. Results are summarized in Table 6 (Table 6). There was a 27.1% difference in freedom from CR-TLF through the end of the 6-month visit window (204 days) (74.2% of treatment were free from CR-TLF vs. 47.1% of controls). Kaplan-Meier analysis showed a freedom from CR-TLF difference of 27.2% between treatment (74.4%) and control (47.2%) through the same follow-up period (Figure 3).

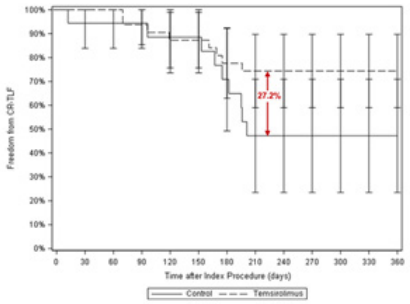

Figure 3 Kaplan-Meier-Freedom from CR-TLF -All PP subjects.

Difference in clinical efficacy between treatment and control was even more apparent when examining only the PP-TASC B-D patients, where there was a 39.2% difference in freedom from CR-TLF through the end of the 6-month visit window (70.0% of treatment vs. 30.8% of controls). This data is summarized in Table 7 (Table 7). Kaplan-Meier analysis further supported this trend, with a difference of 39.2% in rates of freedom from CR-TLF between treatment (70.2%) and control (31.0%) through the same follow-up period of 204 days (Figure 4). This difference was statistically significant in this subgroup. There were no instances of ischemia-driven target limb amputation within 30 days in any study group.

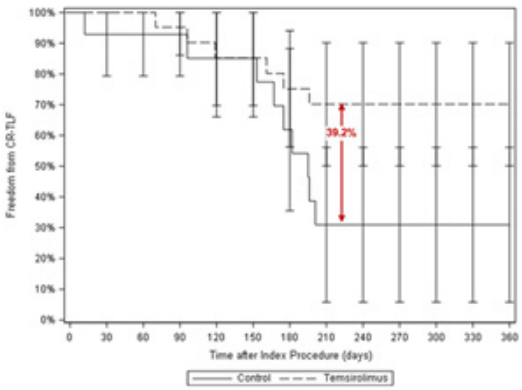

Figure 4 Kaplan-Meier –Freedom from CR-TLF -All PP TASC BCD subjects.

Discussion

TANGO was a hypothesis-generating trial with no formal statistical hypotheses, and outcomes were intended to guide design for upcoming phase 3 trials. However, there was a clear improvement in angiographic measurements and clinical measures when comparing the treatment group to the controls in the PP population.

Historically, most BTK drug therapies aimed at reducing rates of target lesion failure or patency loss have failed in randomized clinical trials. A possible cause for this poor performance may be the high volume of tissue and plaque burden that is generally seen inside the smaller lumen arteries. Luminal application of

Table 7 Clinical efficacy endpoints by treatment arm –All PP TASC BCD subjects. Difference [95% CI]. *Data from follow-up visit, up to end of the visit window (204 days for 6-month visit). Numbers are % (counts/sample size) unless otherwise stated. Site reported, medical monitor classified data.

Subject characteristics	Temsirolimus N=35	Control N=18	Difference [95%CI]
Freedom from (through 30 Days)			
Clinically Relevant Target Lesion Failure Composite (CR-TLF)	100.0% (21/21)	92.9% (13/14)	7.1% [-6.3%, 20.6%]
Ischemia-driven major amputation	100% (21/21)	100% (14/14)	NA
Clinically relevant target lesion occlusion	100.0% (21/21)	92.9% (13/14)	7.1% [-6.3%, 20.6%]
CD-TLR	100% (21/21)	100% (14/14)	NA
Unplanned target limb amputation	95.2% (20/21)	92.9% (13/14)	2.4% [-13.9%, 18.7%]
Freedom From (through 4-Week Visit)*			
Occurrence of new wounds	100.0% (21/21)	92.9% (13/14)	7.1% [-6.3%, 20.6%]
Clinically relevant restenosis	100.0% (21/21)	92.9% (13/14)	7.1% [-6.3%, 20.6%]
Freedom from (through 204 Days)			
Clinically Relevant Target Lesion Failure Composite (CR-TLF)	70.0% (14/20)	30.8% (4/13)	39.2% [7.1%, 71.4%]
Ischemia-driven major amputation	90.0% (18/20)	100.0% (12/12)	-10% [-23.1%, 3.1%]
Clinically relevant target lesion occlusion	84.2% (16/19)	46.2% (6/13)	38.1% [6.4%, 69.7%]
CD-TLR	89.5% (17/19)	61.5% (8/13)	27.9% [-1.9%, 57.8%]
Unplanned target limb amputation	81.0% (17/21)	83.3% (10/12)	-2.4% [-29.3%, 24.6%]
Freedom From (through 6-month visit)*			
Occurrence of new wounds	94.7% (18/19)	76.9% (10/13)	17.8% [-7.2%, 42.8%]
Clinically relevant restenosis	52.6% (10/19)	23.1% (3/13)	29.6% [-2.5%, 61.6%]

drugs-such as with coated balloons-cannot penetrate this burden to reach the cells of the arterial wall. It has been proposed that adventitial application of drug could avoid the problems caused by this intra-luminal tissue burden and more effectively deposit the active components where needed. The TANGO trial tested this idea via adventitial deposition of temsirolimus in BTK arteries of patients with significant peripheral arterial disease requiring endovascular therapy.

The primary outcome of the trial was an angiographic endpoint of TVAL% (Transverse-view Vessel Area Loss Percentage). Often, studies in BTK arteries use Late Lumen Loss (LLL) as an angiographic endpoint to determine therapeutic success, but LLL only provides a focused outcome at the cross-section with the minimal lumen diameter. In vessels with lesions often spanning more than 20 cm, this focused outcome does not provide sufficient information to determine clinical success with localized drug therapy along the complete lesion length. The TVAL% endpoint was derived in an effort to broadly capture the therapeutic outcome along the entire length of the lesion, and it can be generalized as the average percent lumen loss along the lesion length. However, TVAL% is not a standard measurement among lower extremity revascularization studies, thus there are no comparators for these results in the literature.

Secondary clinical efficacy endpoints included similar patency measures as have been used in other BTK trials. For purposes of comparison, the Lutonix BTK trial examining a paclitaxel-coated angioplasty balloon showed an absolute difference in the 6-month primary efficacy endpoint (freedom from vessel occlusion, clinically driven target-lesion revascularization, and above-ankle amputation measured at 6 months) between the treatment and control groups (i.e., an absolute treatment effect) of 11.0% for all subjects and 13.1% when only examining proximal segments. The difference between the patency endpoint used in the Lutonix BTK trial and the TANGO trial is that asymptomatic occlusion of the target lesion was considered a loss of the primary efficacy endpoint in Lutonix BTK, but is not considered as Clinically Relevant Target Lesion Failure (CR-TLF) in TANGO, since it lacks clinical relevance. With this caveat, the CR-TLF results from the TANGO trial appear promising in comparison to the Lutonix BTK trial, with absolute treatment effect of 27.1% when examining the PP group and 39.2% with the PP TASC B-D subgroup through the 6-month follow-up. The CD-TLR results of this trial (rates of 86.7% and 89.5% freedom from CD-TLR for the temsirolimus treated PP subjects and PP TASC B-D subgroup, respectively) also compare well to the interim results from the Lutonix 014 DCB global BTK registry trial, which showed freedom from CD-TLR of 87.9% at 6 months. Although statistical means of directly measuring the extent of difference in outcomes between the studies are lacking, the findings of the TANGO trial do suggest that sub adventitial deposition is a potentially more effective means of treating BTK arteries with anti-proliferative drug therapy.

There was no significant difference in safety outcomes when subjects were treated with temsirolimus compared with control.

Indeed, the early safety outcomes in this trial were notable for 100% freedom from both perioperative mortality and MALE+POD at 30 days post-procedure. Freedom from target lesion embolization and surgical bypass of the target lesion was also 100% through 12 months. However, the sample size is small and larger studies are required to fully determine the benefit-risk profile for use of the device in administration of temsirolimus in patients with BTK lesions.

A study by Tan et al. looked at outcomes following treatment of BTK arteries with plain balloon angioplasty vs. atherectomy, and demonstrated similar early safety outcomes. That study noted 100% freedom from 30-day mortality in both of their treatment groups. The overall limb salvage in both the balloon angioplasty vs. atherectomy cohorts was 81% and was similar between both groups (78% angioplasty versus 88% atherectomy) through the 6-month window [13]. In comparison, the limb salvage rate in the temsirolimus treatment group in this trial was 93.5% through the 6-month window.

Studies using the Bullfrog® micro-infusion device in a porcine model conducted by Mercator showed no local or systemic toxicity, or clinical pathology. The concentration of temsirolimus in the blood was almost non-detectable three days post-treatment and was fully undetectable in the blood at seven days post-treatment, although the drug was still detectable locally in the treated tissue at the time of necropsy (28 days post-treatment). These findings, in addition to the safety outcomes of the TANGO trial, suggest that adventitial and perivascular administration of temsirolimus via the Mercator Bullfrog® micro-infusion device is unlikely to contribute incremental safety risks above those already associated with the underlying revascularization procedure.

As discussed above, the PP population excluded patients with severe, un-treated dissections, and those with treated but unstented occlusions within ipsilateral proximal (femoropopliteal) segments. These two factors result in hemodynamic changes that are known to negatively impact patency, even though they have a distinct pathophysiology from neointimal hyperplasia-induced restenosis, which this trial was intended to treat. Inclusion of subjects with these confounding variables within the trial and within the analysis would impact the accuracy of measuring treatment effectiveness.

It is notable that differences in efficacy between treatment and control were most appreciable in the PP-TASC B-D subgroup analysis. This may be due to the evidence that TASC A lesions generally respond well to standard therapy alone [14]. Since TASC A patients would expect to have excellent clinical and patency outcomes regardless of whether they are administered treatment or placebo, it would be expected that the more complex, non-TASC A lesions would accrue greater angiographic improvement and clinical benefit from adjunctive revascularization therapies. The outcomes of this trial support the concept that removal of TASC A patients from the analysis resulted in a strengthened efficacy signal, without altering the integrity of the trial. This is consistent with prior studies that have shown that TASC class, Fontaine stage, and postoperative infection are all factors that increase risk for loss of primary patency and major amputation. The above information provides valuable guidance on eligibility criteria for a future phase 3 trial and targeting the appropriate patient population to demonstrate the clinical efficacy of the sub-adventitial temsirolimus treatment most accurately.

There are several limitations to this trial. No formal statistical hypothesis was tested for the primary efficacy or for the primary safety endpoints, thus no statistically driven conclusions can be made with this data. The primary efficacy endpoint is purely angiographic in nature, and there is no published information to date that can correlate the measure of TVAL% to clinical or functional performance in the patient. The sample size is relatively small, which may result in higher sampling variability and potential bias. Another limitation is that clinical relevance was determined by a medical monitor, rather than a clinical events committee.

Conclusion

Results of the TANGO trial suggest that sub-adventitial temsirolimus can safely be administered following standard endovascular revascularization of BTK arteries for the purpose of improving patency. Efficacy of this treatment in maintaining vessel lumen area patency (as measured by TVAL%) was most appreciable in the PP population, which excluded patients with two key confounding characteristics. Patients receiving the investigational therapy also demonstrated clinical improvement, as measured by incidence of CR-TLF when compared to controls. This was most appreciable in the PP subjects with higher baseline TASC lesions (B, C or D). The results of this trial provide guidance on appropriate eligibility criteria for a future phase 3 trial.

References

1 Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, LipsitZ SR, et al. (2009) Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg 50: 1462-73.e1-3.

2 Kang IS, Lee W, Choi BW, Choi D, Hong MK, et al. (2016) Semiquantitative assessment of tibial artery calcification by computed tomography angiography and its ability to predict infrapopliteal angioplasty outcomes. J Vasc Surg 64: 1335-1343.

3 Mustapha JA, Katzen BT, Neville RF, Lookstein RA, Zeller T, et al. (2018) Determinants of long-term outcomes and costs in the management of critical limb Ischemia: A Population-Based Cohort Study. J Am Heart Assoc 7: e009724.

4 Romiti M, Albers M, Brochado-Neto FC, Durazzo AE, Pereira CA, et al. (2008) Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. J Vasc Surg 2008;47: 975-981.

5 Zeller T, Baumgartner I, Scheinert D, Brodmann M, Bosiers M, et al. (2014) Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. J Am Coll Cardiol 64: 1568-76.

6 Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, et al. (2015) Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. N Engl J Med 373: 145-53.

7 Tepe G, Laird J, Schneider P, Brodmann M, Krishnan P, et al. (2015) Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery

disease: 12-month results from the IN.PACT SFA randomized trial. Circulation 131: 495-502.

8 Krishnan P, Faries P, Niazi K, Jain A, Sachar R, et al. (2017) Stellarex drug-coated balloon for treatment of femoropopliteal disease: Twelve-month outcomes from the randomized illumenate pivotal and pharmacokinetic studies. Circulation 136: 1102-1113.

9 Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D (2018) 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. J Am Heart Assoc 7: e011245.

10 Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Paraskevopoulos I, et al. (2020) Risk of death and amputation with use of paclitaxel-coated balloons in the infrapopliteal arteries for treatment of critical limb ischemia: A systematic review and meta-analysis of randomized controlled trials. J Vasc Interv Radiol 31: 202-212.

11 Katsanos K, Spiliopoulos S, Teichgräber U, Kitrou P, Del Giudice C, et al. (2022) Editor's choice-Risk of major amputation following application of paclitaxel coated balloons in the lower limb arteries: A systematic review and meta-analysis of randomised controlled trials. Eur J Vasc Endovasc Surg 63: 60-71.

12 Giles KA, Pomposelli FB, Spence TL, Hamdan AD, Blattmann SB, et al. (2008) Infrapopliteal angioplasty for critical limb ischemia: relation of TransAtlantic InterSociety consensus class to outcome in 176 limbs. J Vasc Surg 48: 128-36.

13 Tan TW, Semaan E, Nasr W, Eberhardt RT, Hamburg N, et al. (2011) Endovascular revascularization of symptomatic infrapopliteal arteriosclerotic occlusive disease: Comparison of atherectomy and angioplasty. Int J Angiol 20: 19-24.

14 Sigala F, Kontis E, Hepp W, Filis K, Melissas J, et al. (2012) Long-term outcomes following 282 consecutive cases of infrapopliteal PTA and association of risk factors with primary patency and limb salvage. Vasc Endovascular Surg 46: 123-30