Tack-Optimized Balloon Angioplasty as a Novel Approach to Dissection Treatment in Below-the-Knee Peripheral Artery Disease: An Exploratory Cost-Effectiveness Analysis

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Abstract

Background. The Tack Endovascular System is an emerging therapy for dissections post-percutaneous transluminal angioplasty (PTA) in peripheral arterial disease. The potential cost-effectiveness in infra-popliteal intervention of Tack-optimized balloon angioplasty (TOBA) compared to PTA was evaluated using clinical data from the single-arm TOBA BTK II trial in this exploratory study.

Methods. A decision-analytic, health-economic model was constructed to project therapy-specific costs and effects over a time horizon of 24 months, with consideration for target lesion revascularization (TLR) and major amputation (MA) as clinical events. Event rates for the PTA cohort were estimated using a systematic literature search. Outcomes were expressed as an incremental cost-effectiveness ratio (ICER) and evaluated against the US willingness-to-pay thresholds of $50,000 and $150,000 per quality-adjusted life year (QALY) gained. Uncertainty analyses were conducted to evaluate the robustness of outcomes.

Results. The literature search identified 4 studies with PTA-treated subjects (n=578) as the control population. Calculated 24-month TLR and MA events for PTA were 32.6% and 13.1%, compared to TOBA II BTK study-observed event rates of 26.4% and 4.3%. Over 24 months, TOBA was projected to add 0.02 QALYs at concurrent cost savings of $3,546. In uncertainty and scenario analyses, TOBA remained cost-saving against PTA across a broad range of scenarios. Outcomes were more sensitive to changes in MA than TLR.

Conclusion. Focal treatment of post-angioplasty dissections in below-the-knee lesions with the novel Tack Endovascular System might provide an attractive treatment approach that contributes clinical benefit at concurrent cost savings at 2-year follow-up. Further studies are warranted to confirm these exploratory findings.

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Key words: focused stenting, percutaneous transluminal angioplasty, dissection, cost-effectiveness analysis

Peripheral artery disease (PAD), which involves the luminal narrowing of arteries of the lower extremities due to atherosclerosis, is a systemic condition that affects over 230 million individuals worldwide and is increasingly recognized as a significant cause of cardiovascular morbidity and mortality.[1] Chronic limb-threatening ischemia (CLTI) is a severe form of PAD with rest pain, gangrene, or a lower limb ulceration for a duration greater than 2 weeks with a significant survival reduction.[2] Over 45% of subjects with CLTI have infrapopliteal or below-the-knee (BTK) involvement[3] which can be challenging to manage due to chronic total occlusions, calcification, or poor outflow.[4]

Percutaneous transluminal angioplasty (PTA) is the principle method of revascularization therapy which mechanically

dilates the atherosclerotic artery and is currently the standard-of-care for CLTI.[5] PTA has been reported to lead to dissections in up to one-third of treated infrapopliteal lesions, which can negatively impact clinical outcomes and predict restenosis.[4] Recently, Tack-optimized balloon angioplasty (TOBA), using the Tack Endovascular System (Philips), has been evaluated as a novel treatment approach to repair dissections post balloon angioplasty. The system utilizes short, small, self-expanding focal stents which apply an outward radial force to appose dissected vascular tissue.[4] In the recent TOBA II BTK single-arm study in subjects with post-PTA infrapopliteal dissections (n=233), TOBA was reported to yield a 24-month freedom from clinically-driven target lesion revascularization (CD-TLR) of 73.6% and a freedom from major amputation (MA) of 95.7%, indicating therapeutic potential in this challenging clinical population.[4]

The cost-effectiveness of TOBA compared to PTA in the management of infrapopliteal lesions has not yet been explored in the published literature. This study therefore sought to evaluate the expected costs and outcomes of TOBA compared to PTA to determine the cost-effectiveness of Tack therapy. The analysis was conducted as an exploratory, rather than definitive analysis because of the single-arm nature of the clinical evidence to date.

Methods

The model-based analysis examined the cost-utility of TOBA compared to PTA at a time-horizon of 24 months considering TLR and MA as clinical events. The estimated performance of the comparator group was based on a systematic search of available PTA studies with similar cohort and lesion characteristics to those of the TOBA II BTK study.

Systematic search of PTA evidence. A systematic search was conducted and reported with adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al, 2021). Articles were screened and data collected using Covidence (Melbourne). The MEDLINE, Embase and Cochrane databases were searched for eligible articles published in a contemporary period between 1 January 2007 to 31 May 2022. Searches combined clinical condition, anatomical location, and therapy (complete search strategy in **Supplementary S1)** through the following keywords:

- Condition: peripheral artery disease, peripheral vascular disease, arteriosclerosis obliterans, chronic limb-threatening ischemia, arterial occlusive disease, arterial obstructive disease
- Anatomy: below the knee, infrapopliteal arteries, tibial artery, peroneal artery, crural arteries
- Treatment: angioplasty, balloons, stents, atherectomy, endoluminal repair

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
• Human subjects with peripheral artery disease in below-the-knee vessels.
• Randomized-controlled trial, prospective or retrospective study.
• Greater than 50 subjects in treatment groups of interest.
• Full text available and study is published in English.
• Study reports CD-TLR, primary patency or amputation rates.
Exclusion criteria
• Case reports/studies, reviews, commentaries, editorials, letters to the editor, conference proceedings, study designs, protocol papers, interim study reports without outcomes
• No novel techniques, combined procedures or retrograde procedures
• No urgent revascularization cases, bypass/graft restenosis or infected vascular lesions
• No studies which examine only survival/mortality
• No cryoplasty, brachytherapy or cell therapy

CD-TLR = clinically driven total-lesion revascularization

The inclusion and exclusion criteria are summarized in **Table 1**.

Data collection and extraction. After the removal of duplicates, one author (KC) screened the titles and abstracts for relevance. Full texts were then independently assessed by two authors (KC, JP) to identify studies for inclusion. The review process of papers was summarized in a PRISMA flow diagram **(Figure 1)**. The primary outcomes extracted from the included studies were TLR and MA at the study timeframe. Secondary outcomes included amputation-free survival, limb salvage rate and wound healing. Further data extracted included primary and secondary outcomes in addition to year of publication, device manufacturer, sample size, follow-up duration, study-specific populations, mean lesion length (MLL) and mean Rutherford category (RC).

Selection of studies for analysis model. To calculate event rates for the model-based analysis, the selected studies were further reduced to those reporting a mean lesion length within 30 mm of the TOBA II BTK cohort (116mm +/- 30mm, 86-146mm, site-reported).

As most studies used site-reported lesion length as opposed to core lab-adjudicated lesion length, this study relied on site-reported lesion length for selection purposes. If a study reported additional follow-up data beyond the identified publication, these data were included for purposes of event rate calculations.

Table 2. Model inputs.

Parameter	Value	Source
Age	74.4 years	(4)
Gender (% Female)	32.6%	(4)
Discount rate (costs)	3.0% p.a.	(8)
Discount rate (effects)	3.0% p.a.	(8)
Mortality hazard ratio for TOBA and PTA	2.45	(18)
24 mo TLR for PTA	32.6%	Weighted average from systematic review
24 mo TLR for TOBA	26.4%	(4)
24 mo MAR for PTA	13.1%	Weighted average from systematic review
24 mo MAR for TOBA	4.3%	(4)
Percent of procedures in outpatient	61%	(19)
Percent of outpatient procedures in office-based lab	45%	(19)
Costs		
Endovascular therapy (inpatient)	$19,465	(20)
Balloon therapy (outpatient)	$10,805	
Stent therapy (outpatient)	$11,480	(21)
Balloon therapy		
(office-based labs)	$4,506	(21)
Stent therapy		
(office-based labs)	$9,730	(21)
Amputation	$24,538	(21)
Post-amputation rehabilitation	$18,009	(22)
Post-amputation prosthesis	$14,948	(22)
Utilities		
Post-endovascular treatment	0.62	(22)
Post-amputation	0.54	(22)
QALY Decrement for TLR	0.059	(23)
QALY Decrement for Amputation	0.118	(23)

TOBA = Tack-optimized balloon angioplasty; PTA = percutaneous transluminal angioplasty; TLR = target lesion revascularization; MAR = major amputation rate; QALY = quality-adjusted life years; CMS = Center for Medicare and Medicaid Services; IPPS = inpatient prospective payment system; HOPPS = hospital outpatient prospective payment system.

Health economic model. For projection of costs and outcomes associated with the TOBA and PTA strategies, a health-economic, decision-analytic Markov model was developed. This model was constructed from a US Medicare payer perspective with a cycle length of 3 months and a time-horizon of 24 months. Clinical event rates for TLR and MA were obtained from the TOBA II BTK study and the literature search. For analysis purposes, publications which reported TLR and MA at 12 months were extrapolated to 24 months using a constant hazard assumption that was further calibrated to reflect observed lower event rates in year 2 as opposed to year 1 (see **Supplementary S2**). The PTA event rate was calculated as a sample-size weighted average across selected publications.

Treatment and event costs were derived from 2022 Medicare fee schedules and reflected a site-of-service mix (inpatient, hospital outpatient, office-based lab) reported for BTK endovascular procedures. Health-related quality of life (utilities) were obtained from published literature.[6,7] All costs were expressed in 2022 US dollars, and all costs and effects in the analysis discounted at 3.0% per annum as per US pharmacoeconomic guidelines.[8] Mortality between the TOBA and PTA cohorts was assumed to be the same and was modeled using most recent US lifetable data (CDC, 2022) that were calibrated to trial-observed survival at one

Table 3. Selected publications from systematic review.

	Adams et al 2022	Kokkinidis et al 2021	Lutonix LINC presentation (Geraghty)	Liistro et al 2013	Zeller et al 2020
Years	2017-2018	2006-2018	2013-2017	2010-2011	2009-2012
Study type	Prospective, single-arm study	Retrospective analysis	Prospective RCT	Prospective RCT	Prospective RCT
Intervention	TOBA	PTA	PTA	PTA	PTA
Timeframe (months)	24	12	12	12	12, 24, 36, 48, 60
Target vessels	Popliteal, Tibial, TPT, Peroneal	TPT, Tibial, Peroneal	Popliteal, TPT, Tibial, Peroneal	Tibial, TPT, Peroneal	Tibial
Sample size	233	237	155	67	119
Age (years)	74.4	70.1	72.9	75.0	71.7
Female (%)	32.6%	33.0%	32.9%	22.4%	29.4%
Diabetes (%)	65.7%	78.0%	68.4%	100.0%	68.9%
Renal insufficiency (%)	24.6%	25% (ESRD)	16.8%	-	12.5%
Dialysis (%)	0.4%	-	-	10.40%	-
Smoking (%)	62.2%	54.0%	57.4%	10.40%	49.6%
Hypertension (%)	93.6%	86.0%	95.5%	77.6%	89.1%
Occlusion (%)	47.6% (CTO)	43.0% (CTO)	33.3% occlusion, 2.2% re-occlusion	80% (CTO)	45.9% (CTO)
Mean lesion length (mm)	116.0	94.1	94.7	131	128.6
Rutherford criteria	3-5	4-6	3-5	4-6	3-6
Mean Rutherford category	4.34	Not reported	4.50	5.09	4.85
MRC breakdown	3 (16.3%), 4 (33.5%), 5 (50.2%)	Not reported	3 (10.3%), 4 (33.5%), 5 (56.1%)	4 (4.2%), 5 (81.9%), 6 (13.9%)	3 (0.8%), 4 (17.6%), 5 (77.3%), 6 (4.2%)
Freedom from TLR (%), at timeframe(s) specified above	73.6% (85.4% for RC3, 70.9% for RC4-5)	72.0%	79.4%	64.0%	80%, 80%, 80%, 80%, 78.4%
Major amputation rate (%), at timeframe(s) specified above	3.9%	18.0%	2.0%	1.5%	3.6%, 5%, 5%, 8%, 10.6%
Amputation-free survival (%), at timeframe(s) specified above	75.4% (86.2% for RC3, 73.0% for RC4-5)	-	-	-	-
Limb salvage (%), at timeframe(s) specified above	95.7% (100% for RC3, 94.7% for RC4-5)	-	-	-	-
Dissection (%)	100%	2%	-	-	-
Wound healing reported?	Yes	No	Yes	Yes	No

year (Geraghty et al, 2020). See **Table 2** for detailed overview of all model inputs, and **Table 3** for underlying clinical studies.

Analysis outcomes and interpretations. The primary analysis outcome was the incremental cost-effectiveness ratio (ICER), defined as the ratio of incremental costs and incremental QALYs at 24 months post-index procedure. ICERs were evaluated against the commonly cited willingness-to-pay threshold ranges of <$50,000 per QALY (high value), and $50,000-150,000 per QALY (intermediate value), with ICERs below $150,000 per QALY considered cost-effective.[9,10,11]

Several analyses were completed to examine model uncertainty. Structural uncertainty was examined by extending the analysis horizon from 24 to 60 months, considering TLR or MA benefit only, and exploring the effect of variation in the site-of-service mix. TLR, MA and both TLR and MA were modified to

Table 3. Selected publications from systematic review (cont).

	Adams et al 2022	Kokkinidis et al 2021	Lutonix LINC presentation (Geraghty)	Liistro et al 2013	Zeller et al 2020
TLR definition	Placement of a new bypass graft, jump/interposition graft revision or performance of thrombectomy/ thrombolysis	Lesions requiring retreatment from surgical or endovascular technique	Reintervention from delayed or worsening wound healing, new or recurrent wound or worsening Rutherford, as adjudicated by clinical events committee	Repeat percutaneous intervention or surgical bypass graft resulting from angiographic evidence of restenosis at the level of the treated lesion +/- 10mm in the presence of recurrent pain in foot at rest that increased in supine position, recurrence of foot lesion or evidence during follow-up of foot lesion size decrease-increase behavior or appearance of a new foot lesion, major amputation or target vessel occlusion by angiography or DUS	Any TLR associated with deterioration of Rutherford category, increasing size of pre-existing wounds, occurrence of new wounds as adjudicated by a wound core lab.
Follow-up	Clinical follow-up with observational endpoints as reported	Peak systolic velocity ratio <2.5 on duplex ultrasound	DUS, clinical evaluation	DUS, angiography	Phone follow-up covering occurrence of reintervention, wound status and health status
Notes		8% had bailout stenting and 0.8% had DCB, CLI population, not clinically driven	Unpublished LINC presentation for Lutonix BTK Study 12 Months, any wound present reduced from 56.1% at baseline to 25.9% at 12 months	ffTLR estimated from Kaplan-Meier	

RCT = randomized controlled trial; TOBA = Tack-optimized balloon angioplasty; PTA = percutaneous transluminal angioplasty; TPT = tibioperoneal trunk; ESRD = end-stage renal disease; TLR = total lesion revascularization; CTO = chronic total occlusion, RC = Rutherford category; DUS = duplex ultrasound; DCB = drug-coated balloon; CLI = chronic limb ischemia; BTK = below the knee; ffTLR = freedom from total lesion revascularization

span clinically plausible values from included studies from 25% to 150% of their base case values in increments of 25% for each therapy to understand parameter sensitivity. Finally, to explore the effect of variation in PTA study outcomes on cost-effectiveness, separate ICER calculations were performed for TOBA vs each of the identified individual studies.

Results

Systematic search and literature review. The PRISMA flow diagram is depicted in **Figure 1**. From 9,985 publications, 787 were assessed for eligibility, 229 for full text and 19 included in the review. Out of the 19 publications, 5 publications spanning 4 studies were included for analysis based on mean lesion length **(Table 3)**.

In summary, Kokkinidis et al reported a retrospective analysis in 2021 which examined PTA in 237 subjects over a period of 12 years.[12] The Lutonix study reported the results of a large prospective randomized-controlled trial, from which a control group treated with PTA was obtained (n=155).[13] Liistro et al 2013 (n=67) reported on the results of the DEBATE-BTK trial which examined the use of drug-coated balloons and PTA in diabetic

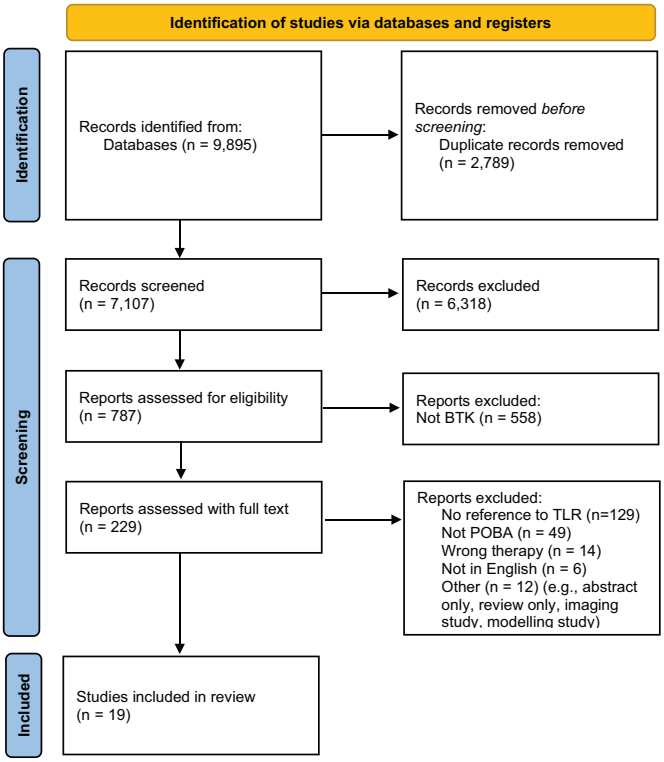

FIGURE 1. PRISMA flow diagram.
BTK = below the knee; TLR = total lesion revascularization; PTA = percutaneous transluminal angioplasty

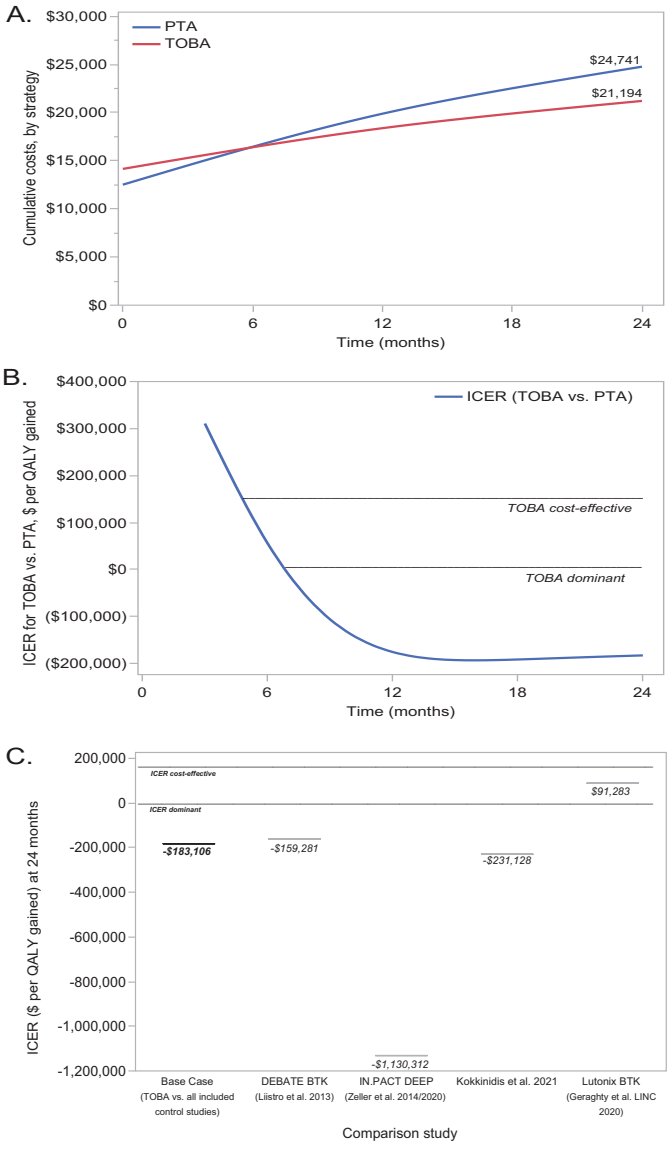

FIGURE 2. (A) Total costs by strategy. (B) Projected ICER over 24-month analysis horizon. (C) ICER for base case (TOBA vs. PTA from all selected control studies) and relative to each of the identified control studies. PTA = percutaneous transluminal angioplasty; TOBA = Tack-optimized balloon angioplasty; ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year

subjects.[14] Finally, Zeller et al 2014 and Zeller et al 2020 reported on the 5-year results of the IN.PACT DEEP trial in 358 subjects.[15,16] All publications reported TLR and MA at 12 months.

Economic evaluation

In the base case analysis, TOBA was associated with fewer TLR events [26.4% vs. 32.6% (-6.2%)] and lower MA [4.3% vs. 13.8% (-8.8%)] at the 24-month analysis horizon. These lower event rates led to an incremental cost reduction of $3,546 ($21,194 vs. $24,741) and concurrent QALY gain of 0.02 (1.10 vs. 1.08), rendering TOBA the 'dominant' strategy from a health-economic perspective. As shown in **Figures 2A and 2B**, higher upfront costs of the TOBA implant strategy were projected to be amortized within the first 6 months, with cost savings of TOBA vs. PTA accumulating over time, rendering TOBA cost-effective after approximately 5 months and cost-saving and thus 'dominant' in light of incremental QALYs at around 7 months. With an extended analysis horizon of 60 months, cost savings and QALY gain with TOBA increased further to $6,798 and 0.05. Under the hypothetical assumption of no difference in amputation events (ie, only TLR benefit considered), the ICER was $158,562 per QALY. Conversely, in the absence of an improvement in TLR from Tack but maintaining an improvement in MA, TOBA remained dominant over PTA. In-hospital inpatient and hospital outpatient settings, TOBA was dominant over PTA, while in office-based labs, the ICER was $4,675 per QALY, indicating high value for TOBA over PTA across different settings-of-care.

Modification of TLR and MA across clinically plausible values and resultant ICERs are shown in **Figure 3**, where negative ICERs represented dominance of TOBA over PTA. TOBA dominated PTA across a broad range of TLR, MA and TLR/MA assumptions, including in the scenarios that the PTA TLR was half of the reported rate (16.3%), that PTA MA was

A.

	TLR	PTA HR (Rate %) 0.25 (8.2%)	0.5 (16.3%)	0.75 (24.5%)	1 (32.6%)	1.25 (40.8%)	1.5 (48.9%)
TOBA HR (Rate %)	0.25 (6.6%)	$ (163,413)	$ (207,355)	$ (231,236)	$ (243,620)	$ (248,798)	$ (249,152)
	0.5 (13.2%)	$ (107,517)	$ (173,340)	$ (207,537)	$ (225,402)	$ (233,727)	$ (235,987)
	0.75 (19.8%)	$ (21,946)	$ (129,041)	$ (179,763)	$ (205,531)	$ (218,066)	$ (222,732)
	1 (26.4%)	$ 140,276	$ (64,527)	$ (145,076)	$ (183,106)	$ (201,548)	$ (209,347)
	1.25 (33.0%)	$ 636,129	$ 49,011	$ (97,211)	$ (156,425)	$ (183,720)	$ (195,772)
	1.5 (39.6%)	Dominated	$ 344,671	$ (19,063)	$ (121,852)	$ (163,741)	$ (181,902)

B.

	MA	PTA HR (Rate %) 0.25 (3.3%)	0.5 (6.6%)	0.75 (9.8%)	1 (13.1%)	1.25 (16.4%)	1.5 (19.7%)
TOBA HR (Rate %)	0.25 (1.1%)	$ (68,257)	$ (151,744)	$ (183,164)	$ (199,489)	$ (209,381)	$ (215,933)
	0.5 (2.2%)	$ (72)	$ (134,064)	$ (175,168)	$ (194,928)	$ (206,419)	$ (213,841)
	0.75 (3.2%)	$ 147,407	$ (109,003)	$ (165,154)	$ (189,550)	$ (203,049)	$ (211,517)
	1 (4.3%)	$ 706,296	$ (70,662)	$ (152,233)	$ (183,106)	$ (199,177)	$ (208,918)
	1.25 (5.4%)	Dominated	$ (4,571)	$ (134,897)	$ (175,233)	$ (194,676)	$ (205,989)
	1.5 (6.5%)	Dominated	$ 136,765	$ (110,382)	$ (165,386)	$ (189,372)	$ (202,660)

C.

	TLR/MA	PTA HR (Rate %) 0.25	0.5	0.75	1	1.25	1.5
TOBA HR (Rate %)	0.25	$ 60,261	$ (189,737)	$ (231,639)	$ (245,299)	$ (249,661)	$ (249,814)
	0.5	Dominated	$ (107,652)	$ (203,268)	$ (229,057)	$ (238,154)	$ (240,681)
	0.75	Dominated	$ 163,485	$ (159,845)	$ (209,311)	$ (225,630)	$ (231,326)
	1	Dominated	Dominated	$ (74,320)	$ (183,106)	$ (211,530)	$ (221,657)
	1.25	Dominated	Dominated	$ 242,144	$ (142,857)	$ (194,788)	$ (211,525)
	1.5	Dominated	Dominated	Dominated	$ (61,459)	$ (173,099)	$ (200,671)

FIGURE 3. Sensitivity analysis of ICERs with modification of TLR and MA using hazard ratios. *In these 'heat map' tables, a wide range of potential clinical performance is explored that might stretch well beyond the credible range of performance. The objective is to provide perspective on when the analysis findings would materially change, even if outside the credible range. The 'base case' analysis is always reflected by HR of 1.0, with corresponding clinical event rate shown in parenthesis. Negative values reflect scenarios where PTA is dominant, values between $0 and $150,000 per QALY where TOBA is considered cost-effective, values above $150,000 per QALY where TOBA is found not cost-effective. TLR/MA refers to a scenario where the HRs are applied to both event types concurrently.* TLR = total lesion revascularization, MA = major amputation, HR = hazard ratio, PTA = percutaneous transluminal angioplasty; TOBA = Tack-optimized balloon angioplasty.

half of the reported rate (6.6%) and that PTA TLR/MA was at 75% of the reported rate. The model was more sensitive to MA than TLR.

ICERs based on comparison to each individual control study are shown in **Figure 2C**. Assuming the TLR and MA from Kokkinidis et al 2013, Liistro et al 2013 and Zeller et al 2020, TOBA dominated in PTA across the majority of publications. With the Lutonix study values, TOBA was associated with higher cost, but remained cost-effective at an ICER of $91,283 per QALY gained.

Discussion

TOBA is a new therapy option for post-PTA dissections that has demonstrated promising clinical outcomes in above and below-the-knee dissections. Among the benefits of this novel intervention is its ability to 'spot-stent' for the focal repair of dissection lesions that would otherwise be left untreated. However, the question remains whether the costs of focused stenting are justified considering the potential clinical improvements compared to PTA alone. In this study, we constructed a health economic model to assess the therapy-specific costs and effects of both TOBA and PTA. Compared to PTA, TOBA was cost-effective in both the base case and a broad range of sensitivity and scenario analyses, including different settings-of-care, clinically plausible TLR and MA values from the systematic review, and across publication values for selected studies. Although exploratory, the analysis indicates that TOBA is likely to be a cost-effective and a potentially cost-saving medical therapy for dissections following PTA.

Due to the utilization of a time horizon of 2 years, which was in accordance with available clinical data and represented a more conservative analysis, the QALY gain was small and therefore the findings were relatively sensitive to variations in clinical event rates. In particular, the outcomes were sensitive to variations in major amputation rate, indicating that the amputation reduction benefit of TOBA is likely to provide a greater contribution to potential cost-savings and therapy cost-effectiveness than target lesion revascularization. The findings were also dependent on setting-of-care. Although all three settings-of-care indicated that TOBA was cost-saving or high value compared to PTA, TOBA was least cost-effective in the office-based lab setting due to differing reimbursement for PTA and stent procedures.

Selected studies from the systematic search and review were also heterogeneous regarding patient demographics, baseline clinical characteristics including Rutherford category, and TLR definition. The majority of PTA subjects from selected studies did not have dissections and so projections may be conservative, as the risk of TLR and MA has been demonstrated to be elevated in the presence of a dissection.[17] Although the populations were relatively small, several studies also recruited Rutherford Category 6 subjects, which may have led to overestimation of clinical event rates in the control group, although — at least partly — this may have been mitigated by the higher-risk dissection population of the Tack study. The definition of TLR also diverged between studies, indicating potential different clinical thresholds for re-intervention.

The study has several limitations which commonly occur in cost modeling based on observational data. First, only single-arm evidence has been available for TOBA to-date, and the analysis therefore had to rely on published data from the literature to characterize clinical event rates for the PTA control group, as opposed to a control group under the same experimental conditions. The analysis is therefore exploratory, and a more definitive analysis may be completed in the future once randomized-controlled trials have been conducted. Second, the analysis did not account for potential benefit of Tack with wound healing, which was not routinely reported by identified publications but has been increasingly recognized as an important endpoint following PAD treatment. Including wound healing is likely to have conferred additional health benefit and improve the cost-effectiveness of Tack. Third, reimbursement costs modeled in this analysis relied on classification of the therapy as either a ballooning or a stenting procedure. The PTA cohort was assumed to be 100% ballooning, which does not consider the possibility of bailout stenting. If we

had accounted for bail-out stenting, the TOBA strategy would have been even more favorable. Finally, TLR costs post-PTA and TOBA were assumed to be identical, which may not be with the case for an untreated dissection. TOBA may also provide future therapeutic flexibility for lesion revascularization, which has not been captured in the analysis.

Conclusion

Based on the findings of this exploratory analysis, Tack-optimized balloon angioplasty appears to provide good health-economic value, with potential cost savings at concurrent increase in health benefit. Further analyses are warranted to confirm these findings.

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Supplement S1. Search strategy.

The search strategy was as follows:

("Peripheral Arterial Disease*" OR "Peripheral Artery Disease*" OR "PAD" OR "Artery Disease, Peripheral" OR "Arterial Disease, Peripheral" OR "Disease, Peripheral Arterial" OR "Disease, Peripheral Artery" OR "Diseases, Peripheral Arterial" OR "Diseases, Peripheral Artery" OR "Peripheral Vascular Disease" OR "Arteriosclerosis Obliterans" OR "Chronic Limb-Threatening Isch*" OR "Critical Limb Isch*" OR "CLI" OR "CLTI" OR "Critical Lower-Extremity Ischemia" OR "Chronic Limb Ischemia" OR "Lower Limb Critical Ischemia" OR "Arterial Occlusive Disease*" OR "Arterial Obstructive Disease*") AND ("Below Knee" OR "Below the Knee" OR "Infrapopliteal" OR "Popliteal" OR "Tibial Arter*" OR "Peroneal") AND ("Angioplast*" OR "Drug Coated*" OR "Drug Eluting*" OR "Stent*" OR "Atherectom*" OR "Balloon*" OR "PTA" OR "Percutaneous Transluminal Angioplasty" OR "Endoluminal Repair")

Supplement S2. Clinical event extrapolation.

Selected publications which reported 12-month event rates were extrapolated to 24-months using a constant hazard assumption adjusted to reflect reduced event rates during the second year using publications which did report 24-month data. Adjustments were completed with a multiplicative "calibration factor" for the second year. The calibration factor for target lesion revascularization was 0.72 and for major amputation rate was 0.787. Once 24-month event rates were calculated for each selected publication, a weighted average was obtained using the sample size as weights.