Cost-Effectiveness of Percutaneous Deep Vein Arterialization for Patients With No-Option Chronic Limb-Threatening Ischemia: An Exploratory Analysis Based on the PROMISE I Study

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Abstract

Background. As the most advanced stage of peripheral arterial disease (PAD), chronic limb-threatening ischemia (CLTI) is associated with a high risk of lower-limb loss and mortality. Percutaneous deep vein arterialization (pDVA) is a promising new treatment alternative for CLTI patients who cannot be treated with conventional revascularization techniques. Our study objective was to explore the potential cost-effectiveness of treatment with the LimFlow pDVA system (LimFlow SA) in the United States healthcare system. **Methods.** We developed a decision-analytic Markov model to project costs and outcomes over the patients' lifetimes, together with the corresponding incremental cost-effectiveness ratio (ICER) in dollars per quality-adjusted life year (QALY) gained. Amputation-free survival (AFS), reintervention, and wound healing data for pDVA and for the status quo treatment were obtained from 1-year data of the recent PROMISE I study, from a historical control identified through systematic search and meta-analysis, and from other published data. Treatment costs were obtained from Medicare claims and published sources. Extensive sensitivity and scenario analyses were conducted to explore the effects of uncertainty about long-term outcomes and of a potential add-on reimbursement for the pDVA system. **Results.** The 12-month AFS rates for the pDVA and status quo groups were 69.7% and 33.3%, respectively. In the base case analysis, pDVA added 1.45 QALYs (2.80 vs 1.35) and incurred $23,903 in additional costs ($122,341 vs $98,438), resulting in an ICER of $16,522 per QALY gained. Incorporating a new technology add-on payment of $15,000 for pDVA increased the ICER to $26,891 per QALY gained. The pDVA procedure remained cost-effective across all tested scenarios, including scenarios for which pDVA was assumed not to have a survival benefit beyond 12 months when compared with the status quo treatment (range of QALY gains in scenarios, 0.30-1.93). **Conclusion.** This study indicates that pDVA performed with the LimFlow system, based on preliminary data, may contribute substantial improvements in clinical outcomes at incremental costs that would render it a cost-effective, high-value intervention.

J CRIT LIMB ISCHEM 2021;1(4):E148-E157. Epub 2021 July 26.

Key words: angioplasty, cost-benefit analysis, economic/cost-effectiveness, peripheral arterial disease

Chronic limb-threatening ischemia (CLTI) is the most advanced stage of peripheral arterial disease (PAD) and is associated with a high risk of lower-limb loss.[1-3]

When treating CLTI, the major goals are to maximize amputation-free survival and to maintain or improve patient quality of life. Treatment of CLTI focuses on revascularization to relieve ischemic rest pain and heal ischemic ulceration or gangrene. Current approaches to treatment include both endovascular and open arterial reconstruction, with an "endovascular first" strategy frequently pursued.[4] However, up to 20% of the CLTI population is estimated to be unreconstructable by means of conventional revascularization techniques due to the absence of a viable target vessel or viable conduit, or the presence of other comorbidities. Without any possibility of revascularization, such "no-option" patients have a dire prognosis, and suffer a high burden of major amputation and mortality.[3,5]

Percutaneous deep vein arterialization (pDVA) has recently been shown to provide a promising treatment alternative for no-option patients. The pDVA procedure creates a connection between the arterial system at the level of the proximal tibial artery and a tibial vein in order to provide pressurized arterial flow to the venous system of the foot. A purpose-built system (LimFlow pDVA system; LimFlow SA) with dedicated arteriovenous crossing tools, stent grafts that vary in length and shape, and an antegrade wire-based valvulotome that allows for a fully percutaneous procedure is used to accomplish the desired venous arterialization. Clinical data about pDVA are available from earlier studies conducted in the European Union and Singapore (ALPS cohort; n = 32 patients, 2-year follow-up) and the recent PROMISE I early feasibility study conducted in the United States (ClinicalTrials.gov identifier NCT03124875; 1-year follow-up).[6] The potential health-economic value proposition of the pDVA procedure has not yet been studied.

Our objective was to perform an exploratory cost-effectiveness analysis of pDVA vs standard of care in the United States healthcare system based upon available clinical outcomes with the LimFlow system and historical control data derived from a systematic search of the published literature.

Methods

Overview. We developed a decision-analytic Markov model for assessing the clinical and economic consequences of pDVA compared to conventional "status quo" treatment. In the absence of a randomized study, the effectiveness of the status quo strategy was derived from a concurrently published meta-analysis of studies identified through a systematic literature search.[7] The base case analysis evaluated incremental cost-effectiveness in dollars per quality-adjusted life year (QALY) gained, considering a lifetime analysis horizon.

Clinical data. Clinical data for pDVA were obtained from the PROMISE I study, and — for scenario analyses — from the ALPS study.[6,8] Conducted under an FDA investigational device exemption, that study was a prospective, multicenter, single-arm, early feasibility study of the LimFlow pDVA approach to treating no-option CLTI. The study enrolled 32 patients (mean age, 67 ± 14 years; 62.5% male) at 7 trial centers in the United States. Enrolled patients were diagnosed by an independent review committee as having *no-option CLTI*, defined as being ineligible for conventional surgical or endovascular revascularization due to the absence of a pedal artery target or suitable vein conduit and a salvageable foot with either open wounds or gangrene (ie, Rutherford classes 5 or 6).[8] For our analysis, the modeled inputs representing the pDVA strategy included study-reported 12-month amputation-free survival (AFS), all-cause mortality, wound healing, and endovascular interventions beyond the index treatment.

Data for the status quo cohort were derived from several sources. The 12-month AFS rate was derived from a meta-analysis of 17 studies identified through a systematic search. This body of evidence included studies of the natural progression of CLTI, and data from the control arms of randomized studies totaling 862 subjects. As most studies reporting AFS among no-option CLTI patients include subjects in Rutherford classes 4, 5, and 6, the observed historical event rates needed to be adjusted to match the characteristics of the pDVA study population, which was limited to patients in Rutherford classes 5 and 6. Statistical details about calculation of the adjusted AFS rate are provided in a companion article.[7] A tabular overview of included studies is provided in the supplementary materials.

Data on wound healing and endovascular reintervention were obtained from subgroups of a retrospective study of 250 CLTI patients with non-healing ulcers or gangrene in Rutherford classes 5 or 6.[9] Specifically, data on wound healing were derived from the study's "Group C" subgroup — the highest severity group in the study — comprising patients with three or more endovascular reintervention events. The AFS rate for this subgroup closely matched the AFS rate derived from the meta-analysis used for our study, supporting the notion that this group was acceptably representative for the purposes of our analysis. For the base case scenario, some patients in the status quo cohort were assumed to still undergo an endovascular intervention, as it is likely a revascularization attempt is made in some patients before the decision to amputate is finalized. The endovascular reintervention rate for the status quo cohort was thus obtained from that study's subgroup of 70 patients classified in the highest stage of threatened-limb severity (CS4) according to the Society for Vascular Surgery's lower extremity threatened limb classification system.[10] A scenario with no reintervention events in the status quo cohort was explored in sensitivity analysis.

In the absence of study-collected quality of life data, we adopted a set of health-state specific utilities identified in a prior cost-utility study of CLTI patients.[11,12] Previously reported by the collaborating authors of the MOVIE study, these utilities were derived from a comprehensive review of published limb salvage literature, with emphasis on studies of high methodological quality.

Cost data. Costs for endovascular treatment and amputation events were derived from 2019 records in Medicare's MedPAR dataset, which captures claims data on all inpatient stays of the Medicare population. To represent the pDVA population, our analysis included patients with a primary diagnosis of PAD (ICD-10 CM I70.2) who underwent an endovascular intervention. The same inclusion criteria applied to patients who underwent an amputation event. More details, including pertinent ICD-10 procedural classification system codes, are provided in **Supplemental Table S1** and **Supplemental Table S2**.

In the absence of a defined cost for a pDVA system, we explored scenarios for add-on payments beyond the current Medicare

TABLE 1. Input parameters for the decision-analytic Markov model developed to assess the clinical and economic consequences of percutaneous deep vein arterialization compared with conventional status quo treatment.

Variable	Definition	Source
Clinical parameters		
Age (years)	67 ± 14	[7]
Gender (% male)	62.5	[7]
Effectiveness: amputation-free survival (AFS)		
AFS status quo	33.3%	Derived from meta-analysis of studies identified in systematic search [17-33] (see companion article [7])
AFS pDVA	69.7%	Derived from PROMISE I 12-month data [8]
Ratio of amputation vs mortality in AFS	1.75	Derived from PROMISE I 12-month data [8]
Effectiveness: relative risks (RRs) for mortality and amputation (pDVA vs status quo)		
RR mortality	0.39	Calibrated to match 12-month AFS observed in PROMISE I (see above; using amputation to mortality ratio of 1.75 and PROMISE I 12-month survival of 90.5%) [8]
RR amputation	0.49	
Effectiveness: 12-month target vessel revascularization (TVR)		
12-month TVR status quo	45.7%	CS4 subgroup[9]
12-month TVR deep vein arterialization	51.6%	PROMISE I 12-month data [8]
Effectiveness: wound healing		
Proportion of patients with wounds at index	100%	Inclusion criteria of PROMISE I study
Proportion of wounds healed within 12 months, status quo	27.3%	C3 subgroup [9]
Proportion of wounds healed within 12 months, pDVA	56.0%	PROMISE I 12-month data [8]
Cost parameters		
Index intervention (pDVA)	$23,580	FY2019 CMS MedPAR data,[a] inflated to 2020
pDVA add-on payment	$0-15,000	Potential CMS new technology add-on payment (NTAP). Explored in scenario analysis
TVR event (both strategies)	$23,580	FY2019 CMS MedPAR data[a], inflated to 2020
Amputation	$29,847	FY2019 CMS MedPAR data[a], inflated to 2020
Cost of rehabilitation (post amputation)	$16,418	Inflated to 2020 [12]
Cost of prosthesis (post amputation)	$13,627	Inflated to 2020 [12]
Annual maintenance cost prosthesis	$1,022	Inflated to 2020 [12]
Cost of chronic wound care, per week	$551	Inflated to 2020 [12]
Health-related quality of life		
Utility, post pDVA treatment	0.62	Post endovascular treatment [11, 12]
Utility, unhealed arterial ulcer	0.46	[11, 12, 41]
Utility, healed arterial ulcer	0.63	[11, 12, 41]
Utility, post amputation, long term	0.54	[11, 12]
QALY decrement for TVR	0.059	[42]
QALY decrement for amputation	0.118	Assumed twice as high as TVR-related decrement
Discounting		
Discount rate on costs and effects, per annum	3.0%	[15]

AFR = amputation-free survival; HR = hazard ratio; pDVA = percutaneous deep vein arterialization; QALY = quality-adjusted life year; RR = relative risk; TVR = target-vessel revascularization. Numbers within brackets indicate reference numbers. [a]See supplemental materials.

reimbursement for endovascular procedures. Physician reimbursement rates for endovascular procedures and amputations were determined based on applicable CPT procedure codes and added to claims-derived costs (see **Supplemental Table S1** and **Supplemental Table S2** for details). Costs for wound care, rehabilitation after amputation, and prostheses were obtained from the published literature (**Table 1**).

Model-based projections and scenarios. The decision-analytic Markov model encompassed three primary health states: alive without amputation, alive post amputation, and death. For the alive states, the model included nested sub-health states to account for the presence of wounds requiring treatment. All patients started in the alive with no amputation state, with pDVA patients undergoing the procedure at the initiation of the analysis. At baseline, all patients in the study population were assumed to have a wound that required treatment, in line with the inclusion criteria of the PROMISE I study, which was limited to patients with lesions of Rutherford class 5 (ulcer) or class 6 (gangrene). Patients who had undergone an amputation event were considered as no longer requiring wound care, although the authors acknowledge that up to 30% of patients undergoing major limb amputation for CLTI will have surgical wound-related complications that require continued wound care and possibly surgical revision.[13]

The cycle length of the analytical model was 3 months. Unless otherwise reported in the source data for the respective cycle, event rates for each cycle were converted from the reported 12-month event rate, assuming a constant hazard rate. Amputation and mortality rates were calculated from the strategy-specific AFS rate, assuming an amputation-to-mortality ratio of 1.75. This ratio was obtained from the 12-month PROMISE I data, in keeping with data from published evidence (see supplementary materials for details).

The effectiveness of pDVA vs status quo treatment for the amputation and mortality endpoints, expressed as relative risks, were calculated to match the PROMISE I-observed 12-month AFS rate. Survival beyond 1 year was projected using gender- and age-matched mortality data from United States (U.S.) life tables, adjusted by a hazard ratio informed by the mortality rate during the first year.

Wound healing rates beyond the reported 12-month rate were projected as follows. We calculated healing rates based on the 12-month proportion, assuming a constant hazard rate, and adjusted the derived healing rates by a hazard ratio to reflect less pronounced healing of wounds beyond the first year. This adjustment factor was calibrated to match the 24-month wound healing rate of 72.7% observed for pDVA in the ALPS study.[6] The same adjustment factor was applied to the status quo cohort — an assumption supported by longer-term healing rates observed in the infrapopliteal disease subgroup of the BASIL study.[14] For wound care resource utilization, the average between prior cycle and current cycle proportions was used to approximate actual utilization of care in the respective cycle.

The primary study outcome was the incremental cost-effectiveness ratio (ICER), defined as the ratio of incremental costs and incremental effectiveness between the pDVA and status quo strategies, expressed in QALYs. Total costs were further stratified by index procedure costs vs follow-up treatment costs. The base case considered a lifetime horizon. In line with applicable recommendations for U.S. cost-effectiveness analyses, costs and health outcomes were discounted by 3% per year.[15,16] We evaluated cost-effectiveness considering willingness-to-pay thresholds of $50,000 per QALY gained ("high-value" intervention per ACC/AHA statement on cost-effectiveness) and $150,000 per QALY gained ("intermediate value" per ACC/AHA statement on cost-effectiveness).[16]

To evaluate the effect of variations in clinical and cost parameters on outcomes of interest, we conducted single- and multi-parameter sensitivity analyses.

Statistical analyses were performed using Stata MP15 (Stata Corp), Microsoft Excel, and JMP 15 (SAS Institute).

Results

The systematic literature search conducted to establish AFS in the status quo cohort identified a total of 17 studies that reported 12-month outcomes[5,17-33] (see companion article[7]). The meta-analytic estimate for the adjusted AFS rate derived in that study was 33.3% (95% CI, 21.1-45.5). The unadjusted 12-month AFS rate (ie, encompassing patients in Rutherford class 4 who were included in the respective studies) was 50.3%. Based on the PROMISE I-observed 12-month AFS rate of 69.7% and 12-month mortality rate of 9.5%, we calculated the relative risks to be 0.39 for mortality and 0.49 for amputation meaning that pDVA reduced 1-year mortality by 61% and amputation by 51% compared to the historical control represented by the status quo cohort. The 12-month hazard ratios for mortality and amputation, compared to age- and gender-matched data for the U.S. general population, were 5.5 and 14.0, respectively.

For the status quo and pDVA cohorts, respectively, projected life years were 2.99 years and 5.98 years (+2.99 years), and discounted QALYs gained were 1.35 and 2.80 (+1.45). Lifetime discounted costs were $98,438 for the status quo cohort and $122,341 for the pDVA cohort (+$23,903), yielding a lifetime ICER of $16,522 per QALY gained.

The absolute cost difference between the two strategies was $23,580 at the time of the pDVA index procedure (reflecting the index procedure cost); it subsequently declined to a minimum of $11,385 at 27-month follow-up, and then increased gradually to $23,903 over the lifetime analysis horizon. Incremental QALYs for pDVA were 0.06 at 1 year, and then gradually increased to a total cumulative incremental QALY gain of 1.45 at the end of the analysis horizon (**Figure 1**). Taken together, these factors led to

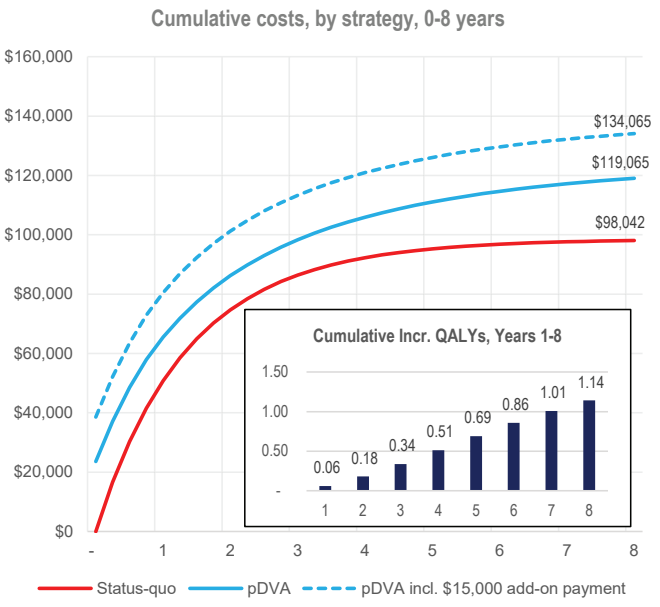

FIGURE 1. Projected cumulative costs for status quo and pDVA treatment strategies, and incremental quality-adjusted life year (QALY) gain of percutaneous deep vein arterialization (pDVA) vs status quo, over 8 years. The dashed line represents total cost including a potential new technology add-on payment of $15,000 for the pDVA system.

short-term ICER estimates of $35,134 at 3 years and $22,922 at 5 years, then gradually declining to the earlier reported lifetime ICER of $16,522.

Sensitivity analysis showed a robust cost-effectiveness finding, with ICERs ranging from $1,122 to $39,222 across a wide spectrum of inputs and explored scenarios. The cost differences between pDVA and status quo for these scenarios ranged between $442 (for a scenario in which mortality was the same for both strategies at a hazard ratio of 8.0 vs general population life tables) and $53,930 (for a scenario that assumes 0% endovascular interventions in the status quo cohort, with a concurrent 12-month wound healing rate of 50%). Across the investigated scenarios, incremental QALYs gained ranged from 0.30 (where the hazard ratio for long-term mortality is the same for both the pDVA and status quo cohorts) to 1.93 (where pDVA achieves AFS of 80.0%) (**Figure 2** and **Table 2**).

Given the Breakthrough Device designation granted by the FDA in 2018, the LimFlow pDVA system qualifies for a possible New Technology Add-on Payment (NTAP) from Medicare that can cover up to 65% of the additional cost of the technology and procedure in excess of the DRG payment. Incorporating such a potential new technology "add-on" payment of $15,000 for pDVA led to an increase in lifetime costs in this amount, for a lifetime cost difference of $38,903 and a lifetime ICER of $26,891 per QALY gained. Applying this hypothetical add-on payment across all tested scenarios resulted in ICER values ranging from $16,275 to $63,410 per QALY gained (**Table 2**).

Discussion

The vast majority of "no option" CLTI patients undergo major lower extremity amputation, and most of these occur within the first year of diagnosis. We developed an analytical framework to explore the potential cost-effectiveness of pDVA as a novel treatment to achieve limb salvage in no-option CLTI patients. Based on 12-month data from the PROMISE I study, we projected lifetime outcomes and costs relative to a historical control derived from a systematic literature search. We found pDVA to be associated with improved limb salvage and substantive gains in unadjusted and quality-adjusted survival, rendering the procedure a cost-effective, "high-value" intervention in spite of its higher cost. These findings were consistent across a wide range of tested assumptions and scenarios, including exploration of a potential new technology add-on payment of $15,000 for the pDVA system.

From a clinical perspective, the pronounced survival benefit projected for the pDVA cohort is particularly noteworthy, with a reduction in 1-year mortality from 24.3% to 9.5%. Presuming such a survival benefit would continue beyond 1 year, our study projected a lifetime gain in survival of almost 3 years for pDVA recipients.

Cost-effectiveness. A surprising insight of our analysis was the robustness of its cost-effectiveness findings. Even in a scenario where the pDVA procedure resulted in a lifetime QALY gain less than one-fourth that of the base case, the incremental cost-effectiveness of pDVA was almost the same, with an ICER of around $13,000 per QALY gained, compared with $16,500 per QALY gained in the base case. The reason for this dynamic is as follows: with the increasing clinical effectiveness of the pDVA strategy, improved survival leads to greater healthcare resource utilization among pDVA patients—resulting in costs that patients in the status quo cohort would not incur because of their earlier death. In the base case, the same dynamic can also be observed in the evolution of incremental costs over time, which reach their minimum at around 2 years, and subsequently increase continuously over the patient's lifetime.

For a contrary scenario in which pDVA is presumed to have lower clinical effectiveness, our model projects lower survival and reduced QALYs gained. This scenario projects lower incremental costs for pDVA compared to the cost of status quo treatment, thus maintaining the ratio of costs to outcomes, and supporting the cost-effectiveness findings of our study.

The robustness of such cost-effectiveness findings is especially significant in light of any uncertainty about the comparative clinical effectiveness of pDVA. In the absence of data from a randomized study, our model represented the clinical effectiveness of pDVA by reference to historical control data. However, even if the incremental performance of pDVA was less than projected from the base case, the health-economic value proposition of

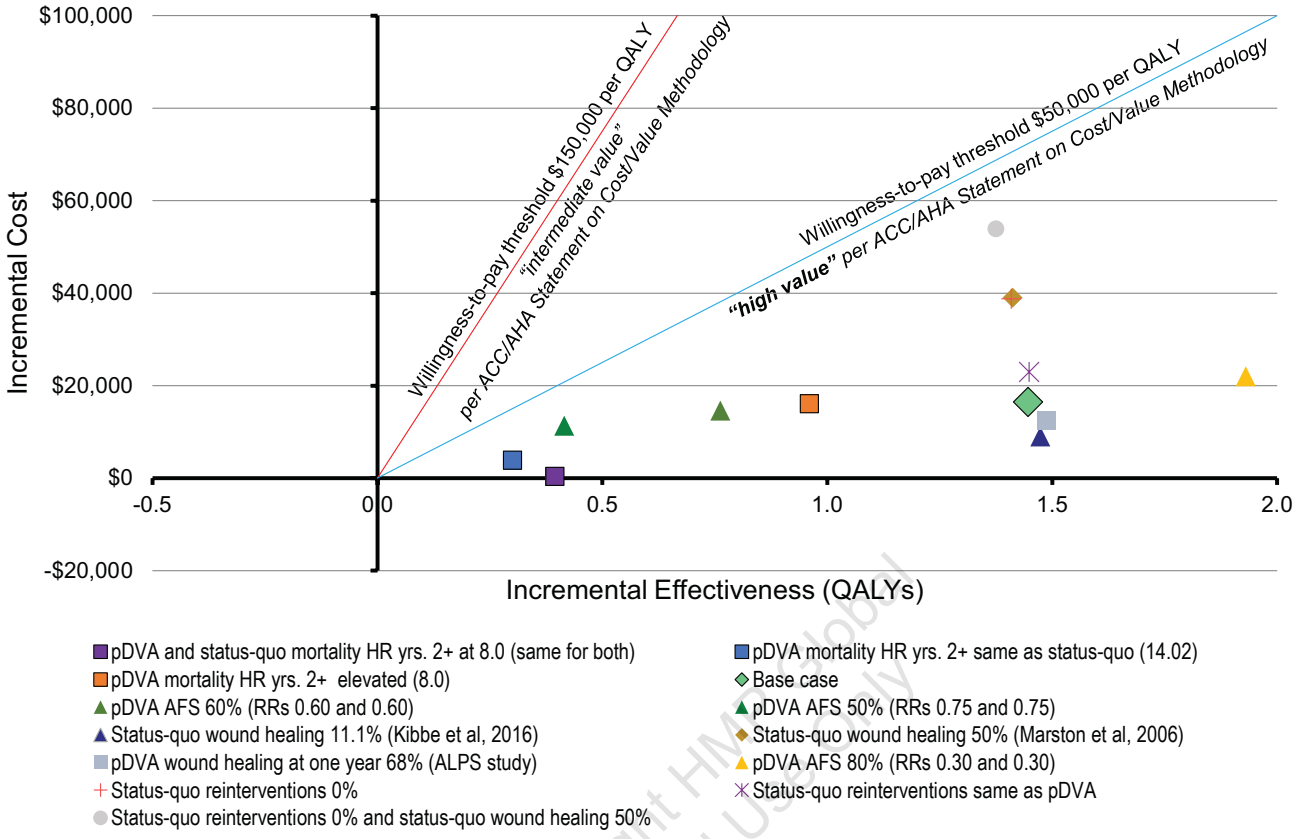

FIGURE 2. Cost-effectiveness plane showing the projected incremental QALY gains (x axis) and incremental costs (y axis) for pDVA versus status-quo therapy for different analysis scenarios. Also shown are the willingness-to-pay thresholds of $50,000 per QALY gained and $150,000 per QALY gained that are commonly used to define "highly cost-effective" and "cost-effective."[16] A scenario that falls below the WTP line meets the respective criterion. Consideration of a new-technology "add-on" payment for p-DVA would increase the y-axis value for each scenario by the considered "add-on" amount.

the procedure could reasonably be expected to be stable and consistently attractive.

Model-derived projections. As with any model-based analysis, the validity of our results hinge on the internal and external validity of the model. Relevant health states and disease progression need to be reflected with sufficient granularity, and all input parameters need to be well sourced. Model-derived event and cost projections should be validated against external evidence. In the context of our model, such caveats pertain especially to the frequency of amputation events, cohort mortality, and overall cost projections.

Our model projects six-month and 1-year amputation rates for the status quo cohort at 24% and 42%, respectively, in close keeping with data from prior studies. Benoit et al report a six-month amputation rate of 23% derived from a meta-analysis of 804 subjects from eight studies involving "no-option" CLTI patients.[24] Similarly, in a retrospective analysis of prospectively collected data of CLTI patients with unhealed ulcers not candidates for revascularization, Marston et al report a 12-month amputation rate of 38%.[17] In an analysis of CLI patients undergoing vascular intervention captured in the SPARCS database, O'Brien-Irr et al report 26.7% amputations at 1 year among Rutherford class 5 patients, and 55% among Rutherford class 6 patients.[34] And in an analysis of German health insurance data on hospitalized CLI patients, Reinecke et al found a 1-year amputation rate of 59.6% among a subset of Rutherford class 6 patients.[35]

Our model further projects a 1-year mortality rate of 24.3% for patients in the status quo cohort. By comparison, in a meta-analysis of eight randomized controlled trials and five case studies identified through a systematic search of the published literature, Abu Dabrh et al found 1-year mortality among CLTI patients not receiving revascularization in the range of 18%-22%.[36] In an analysis of data from the Swedish National Quality Register for Vascular Surgery, Baubeta Fridh et al found 1-year mortality of 20.5% among CLTI patients who had undergone a revascularization treatment.[37] In an analysis of prospectively collected data from the Vascular Study Group of New England, Vierthaler et al report 20% mortality at 1 year for a sample of 883 CLI patients with tissue loss who received endovascular treatment.[38]

Finally, in an analysis of Medicare fee-for-service parts A and B claims for the period 2011–2015, Mustapha et al found 1-year mortality of 23.9% among patients with ulcer and 33.2% among patients with gangrene.[39] At 4-year follow-up, our model

TABLE 2. Results of base case and sensitivity and scenario analyses showing total life years, quality-adjusted life years, and costs for each strategy and resulting differences for percutaneous deep vein arterialization (pDVA) vs status quo, and lifetime incremental cost-effectiveness ratio (ICER) for no pDVA add-on payment considered and add-on payments of $7500 and $15,000.

	Life Years (Undiscounted)			QALYs (Discounted)			Costs (Discounted $)			ICER (Per QALY Gained)		
	Status quo	pDVA	Diff.	Status quo	pDVA	Diff.	Status quo	pDVA Without Add-On Payment	Diff.	No Add-On Payment	With $7500 Add-On Payment	With $15,000 Add-On Payment
Base case	2.99	5.98	2.99	1.35	2.80	1.45	98,438	122,341	23,903	16,522	21,706	26,891
pDVA and status quo mortality HR years 2+ at 8.0 (same for both)	4.27	4.88	0.61	1.91	2.31	0.39	114,139	114,581	442	1,122	20,145	39,168
pDVA mortality HR years 2+ same as status quo (13.81)	2.99	3.45	0.46	1.35	1.65	0.30	98,438	102,376	3,937	13,115	38,095	63,076
pDVA mortality HR years 2+ elevated (8.0)	2.99	4.88	1.90	1.35	2.31	0.96	98,438	114,581	16,142	16,815	24,628	32,441
pDVA AFS 60% (RRs 0.61 and 0.61)	2.99	4.51	1.52	1.35	2.11	0.76	98,438	113,052	14,614	19,170	29,008	38,846
pDVA AFS 50% (RRs 0.76 and 0.76)	2.99	3.80	0.82	1.35	1.76	0.42	98,438	109,796	11,358	27,324	45,367	63,410
pDVA AFS 80% (RRs 0.30 and 0.30)	2.99	6.89	3.91	1.35	3.28	1.93	98,438	120,512	22,074	11,436	15,321	19,207
Status quo AFS 22.4% (lower bound of 95% CI)	2.56	5.98	3.42	1.15	2.79	1.64	92,994	122,361	29,367	17,854	22,414	26,974
Status quo AFS 46.2% (upper bound of 95% CI)	3.57	5.96	2.39	1.62	2.79	1.17	105,083	122,210	17,127	14,617	21,018	27,419
pDVA wound healing constant hazard 12M	2.99	5.98	2.99	1.35	2.80	1.45	98,438	121,450	23,012	15,853	21,020	26,187
Status quo wound healing 11.1% (Kibbe et al, 2016)	2.99	5.98	2.99	1.32	2.80	1.47	113,351	122,341	8,990	6,099	11,187	16,275
Status quo wound healing 50% (Marston et al, 2006)	2.99	5.98	2.99	1.38	2.80	1.41	83,313	122,341	39,028	27,634	32,945	38,255
pDVA wound healing at one year 68% (ALPS study)	2.99	5.98	2.99	1.35	2.84	1.49	98,438	110,997	12,559	8,447	13,491	18,536
Status quo reinterventions 0%	2.99	5.98	2.99	1.39	2.80	1.41	83,536	122,341	38,805	27,533	32,854	38,175
Status quo reinterventions 10%	2.99	5.98	2.99	1.37	2.80	1.42	88,799	122,341	33,542	23,578	28,850	34,122
Status quo reinterventions 20%	2.99	5.98	2.99	1.36	2.80	1.43	92,557	122,341	29,785	20,799	26,037	31,274
Status quo reinterventions 30%	2.99	5.98	2.99	1.36	2.80	1.44	95,330	122,341	27,012	18,772	23,984	29,196
Status quo reinterventions same as pDVA	2.99	5.98	2.99	1.35	2.80	1.45	99,346	122,341	22,995	15,870	21,046	26,222
Apply first-year amputations LimFlow in first 3 months	2.99	5.98	2.99	1.35	2.79	1.44	98,438	122,866	24,427	16,912	22,105	27,297

Continued

TABLE 2. Results of base case and sensitivity and scenario analyses showing total life years, quality-adjusted life years, and costs for each strategy and resulting differences for percutaneous deep vein arterialization (pDVA) vs status quo, and lifetime incremental cost-effectiveness ratio (ICER) for no pDVA add-on payment considered and add-on payments of $7500 and $15,000. *(continued)*

	Life Years (Undiscounted)			QALYs (Discounted)			Costs (Discounted $)			ICER (Per QALY Gained)		
	Status quo	pDVA	Diff.	Status quo	pDVA	Diff.	Status quo	pDVA Without Add-On Payment	Diff.	No Add-On Payment	With $7500 Add-On Payment	With $15,000 Add-On Payment
Assume status quo treatment is 100% amputation at outset (and consider added maintenance cost)	2.99	5.98	2.99	1.34	2.80	1.46	129,946	175,371	45,425	31,207	36,359	41,511
Status quo reinterventions 0% and status quo wound healing 50%	2.99	5.98	2.99	1.42	2.80	1.38	68,411	122,341	53,930	39,222	44,676	50,131
No more change in % of healed wounds beyond 12 months	2.99	5.98	2.99	1.34	2.63	1.29	109,477	151,240	41,763	32,343	38,152	43,960
Reintervention event cost low (25th percentile: $17,244)	2.99	5.98	2.99	1.35	2.80	1.45	94,434	117,091	22,657	15,661	20,845	26,029
Reintervention event cost high (75th percentile: $25,448)	2.99	5.98	2.99	1.35	2.80	1.45	99,619	123,889	24,270	16,776	21,960	27,144
Amputation event cost low (25th percentile: $16,458)	2.99	5.98	2.99	1.35	2.80	1.45	90,290	114,378	24,088	16,650	21,834	27,018
Amputation event cost high (75th percentile: $39,927)	2.99	5.98	2.99	1.35	2.80	1.45	104,573	128,337	23,764	16,426	21,610	26,794
Wound care cost low ($499 per week)	2.99	5.98	2.99	1.35	2.80	1.45	93,753	118,010	24,256	16,767	21,951	27,135
Wound care cost high ($674 per week)	2.99	5.98	2.99	1.35	2.80	1.45	108,187	131,354	23,167	16,014	21,198	26,382
Cost of rehab low ($8209)	2.99	5.98	2.99	1.35	2.80	1.45	93,443	117,459	24,016	16,601	21,785	26,969
Cost of rehab high ($32,836)	2.99	5.98	2.99	1.35	2.80	1.45	108,430	132,106	23,676	16,366	21,550	26,734
Cost of prosthesis low ($8254)	2.99	5.98	2.99	1.35	2.80	1.45	95,168	119,145	23,977	16,573	21,758	26,942
Cost of prosthesis high ($19,859)	2.99	5.98	2.99	1.35	2.80	1.45	102,231	126,048	23,817	16,463	21,647	26,831

CI = confidence interval; Diff. = difference; HR = hazard ratio

projects 28.2% survival among the status quo cohort, compared to Mustapha et al's finding of 31.5% survival among patients with gangrene and 22.6% in patients with major amputation.[39]

Cost projections for the model are informed in significant part by a detailed analysis of Medicare claims data on inpatient admissions for endovascular treatment and major amputation. These analyses were complemented by published data on wound care and rehabilitation.[12] The resulting total undiscounted 1-year costs for the status quo cohort were $51,684. This finding is in keeping with the costs found by Mustapha et al in their analysis of Medicare data. For the period 2011–2015, those researchers report 1-year costs of $49,700 for patients treated with endovascular revascularization, $49,200 for surgical revascularization, and $55,700 for CLTI patients undergoing major limb amputation.[39] Similarly, our undiscounted lifetime cost for the status quo strategy of $103,123 is in line with the lifetime costs observed in

that Medicare population study, which ranged from $91,200 for ulcer patients to $116,400 for gangrene patients.[39]

Relative to other pDVA data, our analysis compares as follows. Overall survival for the pDVA cohort reported in the ALPS registry was 80% at 24 months, which is in agreement with our model-projected 24-month survival rate of 81.3%. Limb salvage in the ALPS registry was 79.8% at 1 year, compared with our 12-month projection of 79.1%. Adopting a constant hazard assumption, our model projected 62.6% limb salvage for the pDVA cohort at 24 months. This contrasts with findings from the ALPS registry, in which no further amputation events were observed between 12 and 24 months, resulting in a maintained rate of 79.2% for limb salvage at 24 months. For wound healing, our model projected 56% complete wound healing at 12 months based on the core lab-adjudicated data reported from the PROMISE I study. This contrasts with a rate of 68.2% reported in the ALPS registry at 12 months and core lab-adjudicated wound healing status of "fully healed" or "healing" of 75% reported in PROMISE I at 12 months.[6,8]

Our lifetime QALY estimate of 2.80 for the pDVA cohort is slightly higher than the projection of 2.45 by Barshes et al for endovascular treatment of critical limb ischemia patients with tissue loss.[12] Similarly, in their analysis of CLTI patients, Holler et al projected 2.39 QALYs for patients who underwent endovascular treatment, with bypass in case of failure.[40] In our scenario analyses, lifetime QALYs for pDVA ranged from 1.65 to 3.28, with both of these scenarios associated with similarly favorable incremental cost-effectiveness ratios of $13,115 and $11,436 per QALY, respectively.

Study limitations. Our study is subject to a several limitations. First, as discussed previously, the PROMISE I clinical study informing the pDVA strategy is a single-arm early feasibility study only, reporting a total of 32 subjects. Second, our model's analysis horizon spans the patient's lifetime. However, data from the 24-month follow-up of the ALPS cohort informed longer-term healing rates, and different assumptions about healing were explored in sensitivity analysis. Third, to derive estimates for mortality and amputation events from the literature-derived AFS rate, we needed to define a ratio of amputation vs death events. Our ratio of 1.75 was informed by the ratio in PROMISE I and was reasonably consistent with ratios observed in other CLTI studies. However, we explored the effect of other ratios in sensitivity analysis. Finally, we assumed a mortality hazard ratio relative to life tables that was kept constant beyond 12 months. While this seems a reasonable assumption that is also supported by the shape of survival curves from prior observational CLTI studies with longer follow-up, future studies—such as the CLariTI study (NCT04304105) and longer-term follow-up from the PROMISE I study—will help to further inform this assumption.[39]

Conclusion

In the clinical community, there is emerging consensus that avoiding major amputation should always be a treatment goal in CLTI due to its associated high costs, loss of functional status and quality of life, and high mortality. Our exploratory cost-effectiveness analysis suggests percutaneous deep vein arterialization with the LimFlow system may provide significant clinical and health-economic value, with projected outcome improvements that would justify its incremental costs and — based on established willingness-to-pay thresholds — would render pDVA a high value intervention for "no-option" CLTI patients. This analysis should be updated and further refined as additional clinical data become available.

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Funding: This research was supported by LimFLow SA. The authors retained the right to publish without approval of the funding source.

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. JB Pietzsch is president, CEO, and shareholder of Wing Tech, Inc., an independent research firm conducting health economic analyses. Wing Tech received consulting fees from LimFlow SA to conduct the analyses underlying this study. Dr Pietzsch reports consulting income from LimFlow SA, Philips/Intact Vascular, and Medtronic. M Ederhof reports employment with Wing Tech; consulting fees from LimFlow SA, Philips/Intact Vascular, and Medtronic. BP Geisler reports employment with Wing Tech, Inc. during the study period; consultant to LimFlow, Surmodics, CSI, Silk Road, Philips, Boston Scientific, PQ Bypass, Medtronic, and Cagent; advisory board for Abbott. P Schneider reports consultant income from LimFlow, Surmodics, CSI, Silk Road, Philips, Boston Scientics, PQ Bypass, Medtronic, and Cagent; advisory board for Abbott.

Manuscript accepted May 28, 2021.

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Supplemental Materials

SUPPLEMENTAL TABLE S1. Additional detail on claims analysis and cost inputs.

Costs for endovascular treatment and amputation events were derived from 2019 records in Medicare's MedPAR dataset, which captures claims data on all inpatient stays of the Medicare population.
Cost of endovascular treatment: To represent the pDVA population, our analysis included patients with a primary diagnosis of PAD (ICD-10 CM I70.2) who underwent a below-the-knee endovascular intervention, specified by one of the following ICD-10 PCS procedure codes: 047P3, 047Q3, 047R3, 047S3, 047T3, 047U3. Further, we limited the analysis to Medicare claim type 60 (Medicare inpatient), DRGs 252, 253, 254 (the endovascular treatment DRGs that apply if the episode of care is primarily related to the endovascular treatment), and excluded claims with zero payment. This resulted in the following Medicare reimbursed cost:

Mean	Median	Standard Deviation	95% Confidence Interval (Lower Bound)	95% Confidence Interval (Upper Bound)
$20,904	$18,863	$10,182	$10,078	$45,855

In addition to this facility payment amount, we added physician fees from the 2020 CMS Physician Fee Schedule for the following CPT codes considered representative of procedural and imaging services: 37225, 37231, 37252, 75820, 75710, 76,937. This yielded a total of $1816, which was added to the mean cost after they had been inflated to 2020 cost, for total of $23,580.
Cost of amputation:
The same inclusion criteria applied to patients who underwent an amputation event. We included patients with a primary diagnosis of PAD (ICD-10 CM I70.2) who underwent a lower leg amputation, specified by one of the following ICD-10 PCS procedure codes: 0Y6F, 0Y6G, 0Y6H, 0Y6J. Further, we limited the analysis to Medicare claim type 60 (Medicare inpatient), and excluded claims with zero payment. This resulted in the following Medicare reimbursed cost:

Mean	Median	Standard Deviation	95% Confidence Interval (Lower Bound)	95% Confidence Interval (Upper Bound)
$27,669	$23,673	$24,489	$6996	$83,071

In addition to this facility payment amount, we added physician fees from the 2020 CMS Physician Fee Schedule for CPT 27880 (major amputation). The corresponding amount of $1039 was added to the mean costs after they had been inflated to 2020 cost, for total amount of $29,847.

SUPPLEMENTAL TABLE S2. Included studies from meta-analysis.

Amputation-free Survival (AFS) for the control group was derived from a systematic search and meta-analysis described in a companion paper (Ghare et al, 2021[7]). Below, is the list of included studies and the adjusted AFS rates to account for no-option Rutherford 5 and 6 patients. The meta-analytic estimate of the historical rate of AFS at 12 months is 33.3% (95% CI, 21.1-45.5). This figure has been used in our analysis.

Study	N	Event-free survivors (n)	Observed AFS Rate	Included Rutherford Categories	Observed Proportion R4	Observed Proportion R 5/6	Imputed Proportion R 5/6	Adjusted AFS Rate
Marston et al. 2006	142	105	73.9%	4, 5, 6	NR	NR	60.3%	50.3%
Nikol et al. 2008	56	27	48.2%	4, 5, 6	NR	NR	60.3%	32.8%
Belch et al. 2011	259	173	66.8%	4, 5, 6	NR	NR	60.3%	45.5%
Losordo et al. 2012	12	6	50.0%	4,5	41.7%	58.3%	NA	33.5%
Teraa et al. 2015	79	53	67.1%	3, 4, 5, 6	31.6%	63.3%	NA	46.8%
Raval et al. 2014	3	1	33.3%	4, 5, 6	NR	NR	60.3%	22.7%
Powell et al. 2012	24	16	66.7%	4, 5, 6	NR	NR	60.3%	45.4%
Benoit et al. 2011	14	9	64.3%	4,5	50.0%	50.0%	NA	40.4%
Kibbe et al. 2016	11	9	81.8%	4, 5	63.6%	36.4%	NA	46.7%
Idei et al. 2011	30	0	0.0%	4, 5, 6	27.0%	73.0%	NA	0.0%
Szabo et al 2013	10	4	40.0%	4, 5, 6	NR	NR	60.3%	27.2%
Pignon et al. 2017	19	14	73.7%	4, 5	35.0%	65.0%	NA	52.1%
Wang et al. 2018	36	25	69.4%	4,5	66.7%	33.3%	NA%	38.8%
Faglia et al. 2010	27	1	3.7%	4,5,6	37.0%	63.0%	NA	2.6%
Dalla Paola et al. 2019	84	29	34.5%	4,5,6	NR	NR	60.3%	23.5%
Dubsky et al. 2019	44	23	52.3%	4,5,6	NR	NR	60.3%	35.6%
Faglia et al. 2012	12	3	25.0%	5.6	0.0%	100.0%	NA	25.0%

Simple Average	50.0%	**Simple Average**	33.5%
Weighted Average	57.8%	**Weighted Average**	39.1%
Meta-Analytic Average	50.3%	Meta-Analytic Average	33.3%
Min	0.0%	**Min**	0.0%
Max	81.8%	**Max**	52.1%
SD	24.3%	**SD**	15.3%