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Cost-effectiveness of pharmacomechanical catheter-directed thrombolysis versus standard anticoagulation in patients with proximal deep vein thrombosis: Results from the ATTRACT Trial

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Cost-Effectiveness of Pharmacomechanical Catheter-Directed Thrombolysis vs. Standard Anticoagulation in Patients with Proximal Deep-Vein Thrombosis: Results from the ATTRACT Trial

Running Title: Cost of PCDT vs. Standard Anticoagulation for DVT

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ABSTRACT

Background: In patients with acute deep vein thrombosis (DVT), pharmacomechanical catheter-directed thrombolysis (PCDT) in conjunction with anticoagulation therapy is increasingly used with the goal of preventing post-thrombotic syndrome. Long-term costs and cost-effectiveness of these two treatment strategies from the perspective of the US healthcare system have not been compared.

Methods: Between 2009 and 2014, the ATTRACT trial randomized 692 patients with acute proximal DVT to PCDT plus anticoagulation (n=337) or standard treatment with anticoagulation alone (n=355). Costs (2017 US dollars) were assessed over a 24-month follow-up period using a combination of resource-based costing, hospital bills, Medicare reimbursement rates, and the Drug Topics Red Book. Health state utilities were obtained from the SF-36. In-trial results and U.S. life tables were used to develop a Markov cohort model to evaluate lifetime cost-effectiveness.

Results: For the PCDT group, mean costs of the initial procedure were $13,600; per-patient costs associated with the index hospitalization were $21,509 for PCDT and $3877 for standard care (difference=$17,632; 95% confidence interval (CI): $16,117 to $19,243). The 24 month difference in costs was $20,045 (95% CI: $16,093 to $24,120). Utility scores increased significantly between baseline and 6 months for both groups, with no significant differences between groups at any follow-up time point. Projected differences in lifetime costs of $16,740 and quality-adjusted life years (QALYs) of 0.08, yield an incremental cost-effectiveness ratio (ICER) for PCDT of $222,041/QALY gained. In probabilistic sensitivity analysis the probability that PCDT would achieve a lifetime ICER <$50,000/QALY or <$150,000/QALY was 1% and 25%, respectively. For iliofemoral DVT, QALY gains with PCDT were greater, yielding an ICER of $137,526/QALY; for femoral-popliteal DVT, standard therapy was an economically dominant strategy.

Conclusions: With an ICER >$200,000/QALY gained, PCDT is not an economically attractive treatment for proximal DVT. PCDT may be of intermediate value in patients with iliofemoral DVT.

Clinical Trial Registration Information: URL: https://clinicaltrials.gov. Unique identifier: NCT00790335

Key words: cost-effectiveness; deep vein thrombosis; thrombolysis; anticoagulation

INTRODUCTION

Approximately 300,000 individuals in the United States are diagnosed with an initial episode of deep vein thrombosis (DVT) each year. Despite standard anticoagulant therapy, roughly 40% subsequently develop post thrombotic syndrome (PTS), with resulting physical limitations and impaired quality of life.[1] While systemic anticoagulation is the cornerstone of treatment for DVT, interventional approaches using catheter-directed thrombolysis (CDT) or CDT in combination with mechanical thrombus disruption (pharmacomechanical CDT [PCDT]) may rapidly restore venous patency and preserve venous valvular function, two key etiologic factors with respect to the development and/or progression of PTS.

Recently, 2 clinical trials have compared CDT or PCDT with the standard therapy of anticoagulation alone for patients with a proximal femoral or iliac vein thrombosis. In the Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis (CaVenT) trial, CDT was found to reduce PTS at both 2 and 5 years.[2,3] More recently, the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial compared PCDT with anticoagulant therapy alone in patients with proximal DVT.[4] Although PCDT did not reduce the proportion of patients who developed PTS between 6 and 24 months, there was a significant reduction in PTS severity scores at 6 months, and a reduction in the prevalence of moderate-to-severe PTS at 24 months, particularly among patients with thrombus that involved the common femoral or iliac veins (iliofemoral DVT).[5, 6,7] Given higher upfront costs with PCDT, it is important to know whether this more aggressive treatment is associated with meaningful health benefits or “downstream” cost savings and whether the higher initial costs are justified. Accordingly, a prospective health economic evaluation was

incorporated into the ATTRACT trial protocol and is the focus of the current report.

METHODS

The design and methods of the ATTRACT trial have been described previously.[4] Between December 2009 and April 2014, at 56 U.S. sites, a total of 692 patients with symptomatic proximal DVT involving the femoral, common femoral, or iliac veins were randomly assigned in a 1:1 ratio to PCDT in addition to anticoagulation or anticoagulation alone. Patients in each treatment arm received initial and long-term anticoagulation therapy consistent with published guidelines; this included the option of rivaroxaban once it became available for this indication. Patients in each treatment arm were provided knee-high elastic compression stockings at the 10-day and every 6-month follow-up. PCDT was performed in accordance with published guidelines, with thrombolytic therapy (recombinant tissue plasminogen activator [rt-PA], alteplase [Activase, Genentech, South San Francisco]) delivered by one of three methods. For patients with occlusion of the popliteal vein or inferior vena cava, an "infusion-first" strategy with rt-PA infusion through a multi-side hole catheter for 30 hours was recommended. For other patients, single-session thrombus removal with rapid delivery of rt-PA via the AngioJet Rheolytic Thrombectomy System (Boston Scientific, Marlborough, MA) or the Trellis Peripheral Infusion System (Covidien, Inc., Mansfield, MA) was recommended followed by infusion of rt-PA for up to 24 hours for patients with residual thrombus. After initial rt-PA delivery, for patients with residual thrombus or obstructive lesions, a variety of techniques could be used until ≥ 90% thrombus removal was achieved with restoration of flow or a serious complication occurred. The protocol allowed repeat PCDT procedures within the first 3 months in PCDT arm patients who presented with acute recurrent thrombosis, but strongly discouraged endovascular

procedures (crossovers) in the control arm throughout the 24 months of follow-up.

In-person assessments were performed by clinician examiners who were blinded to treatment arm allocation at 6, 12, 18, and 24 months post-randomization. The primary clinical endpoint of the trial was the development of PTS as indicated by a Villalta scale score of 5 or higher[8], or an ulcer in the leg with the index DVT. In addition, patients with an unplanned endovascular procedure to treat severe venous symptoms beyond 6 months were considered to have PTS, provided that there was no Villalta score lower than 5 in the previous 4 weeks. All sites obtained Institutional Review Board approval of the protocol, and all patients provided informed consent. The trial is registered at the U.S. National Library of Medicine website (http://www.clinicaltrials.gov as identifier NCT00790335). The data and study materials will be made available to other researchers in accordance with the NIH Public Access Policy, at www.clinicaltrials.gov or by contacting Dr. Suresh Vedantham (vedanthams@wustl.edu).

Estimation of direct medical care costs. Medical care costs for the index hospitalization and 24-month in-trial follow-up period were assessed using a combination of resource-based accounting, hospital billing data, and event-based methods as previously described.[9] All costs were assessed from the perspective of the U.S. healthcare system and are reported in 2017 U.S. dollars. Costs from years prior to 2017 were converted to 2017 dollars using the medical care component of the Consumer Price Index. Complete details relating to the costing methods, including resource use relating to the index PCDT procedure, are provided in the Supplemental Material.

Estimation of indirect costs. Data relating to time lost from work and informal caregivers' time were collected at each follow-up time point. Costs associated with time lost

from work were assigned based on age-, sex- and race-specific median earnings for 2017 according to the Bureau of Labor Statistics (https://www.bls.gov/news.release/pdf/wkyeng.pdf). Informal caregiver time was assigned a cost of $11/hour based on the median hourly wage of a home health aide in 2017 (https://www.bls.gov/oes/current/oes311011.htm).

Quality of life. The SF-36 generic quality of life instrument[10] was used to assess quality of life for each study patient at baseline and at 6, 12, 18, and 24 months. Health state utility weights were obtained from the SF-36 data using a publicly available algorithm.[11]

Statistical analysis. Categorical data are reported as frequencies, and continuous data are reported as mean ± standard deviation. Categorical variables were compared by Fisher's exact test. Normally distributed continuous variables were compared by Student's t-test, and non-normally distributed data were compared by the Wilcoxon rank-sum test. Hospitalization rates were compared by means of Poisson regression. Summaries of resource use and costs of the index PCDT procedure and associated hospital stay are presented for patients who were randomized to and underwent an index PCDT procedure. Treatment arm comparisons of hospitalization rates and healthcare costs are based on the overall trial population, according to intention-to-treat. Cost data are reported as mean values, and confidence intervals (CI) for the differences (Δ) in mean costs between treatment groups were obtained via bootstrapping.[12] Missing utility scores were estimated using multiple imputation, with baseline patient characteristics, previous utility values, previous bleeding, and PTS events informing the imputation. Utility scores were compared at each follow-up time point using analysis of covariance, adjusting for baseline score. Paired t-tests were used to evaluate the significance of changes within treatment groups between time points. All analyses of data from the trial period were performed using SAS 9.4 (SAS Institute, Cary, NC).

Adjustment for varying length of follow-up. To adjust for varying length of follow-up, methods for the analysis of censored data were used to obtain estimates of cumulative costs over time.[13] An inverse probability-weighted estimator was applied, whereby the time axis was divided into intervals (0-10 days, 11-30 days, 31 days to 6 months, and 6-month intervals thereafter through 24 months). Treatment group specific costs for each interval were estimated as the observed costs during the interval for patients with complete data divided by the probability of not being censored within the interval.

Cost-effectiveness analysis. Although the ATTRACT trial followed patients for 24 months, it is reasonable to expect that any benefits of PCDT observed during the trial (such as a reduction in the risk and/or severity of PTS), and any related effect on costs and quality of life would continue to evolve beyond the trial period. Therefore, in-trial results and U.S. life tables were used to develop a Markov (state-transition) model[14] to evaluate lifetime cost-effectiveness beginning at the time of the initial treatment. Our general approach was to base the model to the greatest extent possible on the observed results from ATTRACT. The model was programmed as a cohort model using TreeAge Pro 2018 (TreeAge, Inc, Williamstown, MA). A diagram of the model is provided in Supplemental Figure 1. Over cycles of 6-month duration, the model applied acute and long-term costs and utilities to PTS states to project lifetime healthcare costs and quality-adjusted life years (QALYs) for patients with acute proximal DVT treated with the 2 treatment strategies.

To inform the Markov model, regression models were developed to predict PTS and bleeding outcomes, health state utility, and costs as a function of treatment assignment, age, sex, BMI, and baseline thrombus extent (iliofemoral vs. femoral-popliteal). Of note, randomization in ATTRACT was stratified according to thrombus extent, specifically, whether the thrombus

involved the iliac and/or common femoral vein (iliofemoral), or not (femoral-popliteal). The clinical results from ATTRACT showed a greater risk and severity of PTS in patients with iliofemoral DVT as well as a suggestion of greater benefit with PCDT in the iliofemoral subgroup[5]. Accordingly, for the evaluation of cost-effectiveness in the iliofemoral and femoral-popliteal subgroups, separate models for the prediction of PTS were developed for each subgroup. For all other regression models, thrombus extent was examined as a covariate in the model optimization process.

Clinical results from ATTRACT showed that PCDT was associated with a significant reduction in the risk of PTS at 6 months, but that no significant reduction in PTS occurrence was observed at any of the later follow-up time points. Therefore, for the generation of transition probabilities corresponding to PTS states (none, mild, moderate and severe), separate ordinal logistic regression models were developed for the 6-month outcomes and the PTS outcomes at subsequent 6-month intervals. The model for post-6-month PTS outcomes was a generalized linear mixed model (SAS PROC GLIMMIX) to account for the repeated PTS observations within patients. Because PTS is a chronic condition that rarely involves spontaneous major recovery, we assumed that transitions to less severe PTS categories would not occur. In ATTRACT, bleeding events were rarely reported after 6 months; the Markov model therefore did not incorporate a risk of bleeding beyond 6 months. For the prediction of 6-month bleeding outcomes, ordinal logistic regression was used to predict the occurrence of major and minor bleeds at 6 months, using the same approach as for the 6-month PTS outcomes.

Linear regression was used to develop a prediction model for index hospitalization costs (separate models for PCDT and control) and follow-up utility as a function of interval PTS and bleeding outcomes, and other covariates. For the prediction of long-term costs, a repeated

measures linear regression model was developed on post-index procedure costs (repeated measure at 6-month intervals) as a function of the same covariates, as well as interval-specific PTS and bleeding events, and an indicator for 6-month vs. later time point to capture the possibility of differential follow-up costs based on time from randomization. Backward stepwise elimination was used in the optimization of all models, with covariates eliminated if $p>0.10$, unless otherwise stated.

The analysis assumed a healthcare system perspective and estimated direct healthcare costs and QALYs over a lifetime horizon; productivity costs were not included in the model. Within each 6-month cycle, a patient's risk of death was estimated based on age-, sex- and race-matched risks of death obtained from U.S. life tables (https://www.cdc.gov/nchs/data/nvsr66/nvsr66_04.pdf), calibrated to the observed 2-year mortality for the trial population (comparison of the observed 2-year mortality for the trial population with that of an age-, sex-, and race-matched U.S. population yielded a mortality multiplier of 1.015). Baseline characteristics for the model cohort were based on mean baseline values for patients enrolled in the ATTRACT trial. To ensure that the model was conservative with respect to the benefit of PCDT, we assumed no further benefit of PCDT on PTS beyond 5 years and no further effect of PCDT on costs beyond 24 months; however, any benefit from PCDT at 5 years was assumed to persist for the remainder of the patient's' life. All projected life-years, QALYs, and costs were discounted 3% annually. Sensitivity of model results to input parameters and other assumptions were examined using 1-way, 2-way, and probabilistic sensitivity analyses. Internal validation of the model was carried out by comparing model predicted costs and QALYs at 24 months to the in-trial results.

RESULTS

Index PCDT procedure and hospitalization costs. As previously described[5], in the PCDT arm, one patient was found not to have an anatomically qualifying DVT immediately after randomization and was not included in any analyses; 17 additional patients did not undergo PCDT. Index procedure resource use for the 319 patients who were assigned to and underwent an index PCDT procedure are presented in Supplemental Table 1, for both the overall population and according to procedural technique. A total of 16%, 23%, and 61% of patients were treated using Trellis PCDT, Angiojet PCDT, and infusion first PCDT, respectively. On average, the initial PCDT procedures required 1.8 basic angiographic catheters, 0.5 guiding catheters, 3.8 guidewires, 1.4 balloon catheters, and 0.6 stents. Mean procedural cost was $13,600 -- $11,691 for Trellis PCDT, $13,892 for Infusion-first PCDT, and $14,117 for Angiojet PCDT (Supplemental Table 2).

Mean length of stay (LOS) was 6.4 days, with 3.3 days accounted for by the post-procedure period. Among patients who underwent the PCDT procedure, mean cost for the index hospitalization was $22,316 and did not differ significantly between the 3 types of procedure (Supplemental Table 2). After including the 17 patients randomized to PCDT who did not undergo the procedure, mean costs were $21,509. 210/355 patients in the standard care arm had an index hospitalization for which the mean LOS (post randomization) was 3.7 days; mean index hospitalization cost per patient in the standard therapy arm was $3877, yielding a difference in index hospitalization costs between treatment groups of $17,632 (95% CI $16,117 to $19,243).

Follow-up resource utilization and costs: procedures and hospital care. Rates and associated costs of endovascular venous procedures and hospitalizations during the 24-month follow-up period are presented in Supplemental Tables 3 and 4, respectively. Compared with

standard care, patients randomized to PCDT had a higher rate of endovascular venous procedures during follow-up (8.4 vs. 4.8 per 100 patients, p=0.0016). The rate of hospitalization for a venous indication other than an endovascular venous procedure did not differ between the PCDT and standard care groups (17.5 vs. 19.0 per 100 patients, p=0.62; Supplemental Table 3), although there were differences in some indications for hospitalization with some favoring PCDT and some favoring standard care. Overall, there were trends toward higher procedure-related (Δ=$1010) and other hospitalization-related (Δ=$693) costs during follow-up among the PCDT group, but these differences were not statistically significant (Supplemental Table 4).

Other costs: Outpatient care, rehabilitation/chronic care, lost productivity. Outpatient care costs, including emergency room visits, physician/nurse visits, and home health services, were higher for patients in the PCDT arm at 24 months ($1490 vs. $904, Δ=$585; 95% CI: $149 to $1103), with much of this difference related to high costs associated with home health services for 2 patients in the PCDT arm who experienced moderate to severe PTS during the second year of follow-up (Table 1). Costs associated with inpatient stays in rehabilitation, skilled nursing, or other chronic care facilities did not differ between treatment groups, nor did costs associated with intermittent pneumatic compression devices or compression stockings. Finally, costs associated with lost productivity on the part of the patient or informal caregiving time on the part of family did not differ between treatment groups.

Cumulative in-trial costs. At 24 months, cumulative costs for the PCDT and standard therapy arm were $30,591 and $10,546, respectively (Δ=$20,045; 95% CI for difference: $16,093 to $24,120), driven mainly by the difference in initial procedural/hospitalization costs (Table1). Incremental follow-up costs within each treatment group at each follow-up time point, and cumulative costs over time, including the index procedure, are summarized in Figure 1.

Follow-up costs were higher for the PCDT group than for the standard therapy group during the first 6 months of follow-up ($5698 vs. $3280, Δ=$2418, 95% CI for difference $375 to $4634), with little difference between the 2 groups thereafter (Figure 1). After adjusting for greater loss to follow-up in the control arm, the 24-month difference was $18,922 (95% CI: $14,367 to $23,499).

Health utilities. Baseline utilities were 0.61 and 0.62 for the PCDT and standard care groups, respectively. There was a significant increase in utilities (~0.12 points, $p<0.001$) for both groups between baseline and 6 months, and a smaller increase between 6 and 24 months (0.016 points, $p=0.004$). There were no significant differences in utilities between treatment arms at any follow-up time point, either before or after adjusting for missing data via multiple imputation (Figure 2).

Regression results used to inform long-term cost-effectiveness model. Regression model results from analyses of the ATTRACT data, which provide inputs into the Markov model, are summarized in Supplemental Tables 6-16. At 6 months, PCDT was associated with a lower risk of PTS (odds ratio=0.54, $p<0.001$) and a higher risk of bleeding (odds ratio=1.88, $p=0.03$), compared with standard therapy. The impact of PCDT on PTS outcomes, however, was not sustained. Beyond 6 months, there was no significant difference in the risk of PTS, although the covariate for the treatment effect (odds ratio=0.98, $p=0.90$) was retained in the model to enable sensitivity analyses to be run on that parameter. Models predicting follow-up utility scores and post-index procedure costs demonstrated a relationship between PTS severity and both utilities and costs such that increased PTS severity was associated with higher cost (compared to no PTS, estimated increased cost per 6-month interval for mild PTS: $726, $p=0.008$; moderate PTS: $1606, $p=0.0002$; severe PTS: $3044, $p<0.0001$) and with lower utility

(compared to no PTS, estimated impact of mild, moderate and severe PTS on utility: -0.09, -0.12 and -0.17, respectively; all $p<0.001$). Major bleeding was associated with an incremental cost of $12,114 and a disutility of 0.09 during the 6-month cycle in which the bleeding occurred, while minor bleeding was associated with an incremental cost of $4798 and a disutility of 0.03.

Internal validation of the Markov model. Model outputs for costs and QALYs for each treatment group were generated at the 2-year time point (4 6-month cycles) and were close to those obtained from the trial data (Supplemental Table 17).

Cost-effectiveness. Under the base case assumptions, our model projected discounted lifetime costs for PCDT and standard care of $168,496 and $151,756 and lifetime QALYs of 17.15 and 17.07, respectively, yielding an incremental cost-effectiveness ratio (ICER) of $222,041 per QALY gained with PCDT (Table 2). Probabilistic sensitivity analysis demonstrated that the probability that PCDT would achieve a lifetime ICER <$50,000/QALY was 1% and the probability that PCDT would achieve a lifetime ICER <$150,000/QALY was 25% (Figure 3; Supplemental Table 18).

One-way sensitivity analyses revealed that the cost-effectiveness of PCDT was most sensitive to variation in the relative risk of PTS with PCDT vs. standard therapy at 6 months (Figure 4). Under the base case assumptions, PCDT would need to reduce the risk of PTS at 6 months by 62% (vs. 46% in our base case) to achieve an ICER of $150,000/QALY, whereas there was no level of benefit at 6 months sufficient to achieve an ICER <$50,000/QALY. Alternatively, PCDT would be cost-effective at a threshold of $150,000/QALY if the long-term relative risk of PTS with PCDT beyond 6 months was 0.90 or less (as compared with 0.98 in ATTRACT). The long-term relative risk of PTS with PCDT would need to be 0.65 or less to be economically attractive at a threshold of $50,000/QALY. The cost of the PCDT hospitalization

would need to be $13,551 for PCDT to be economically attractive at a threshold of $150,000. Figure 5 presents results from a 2-way sensitivity analysis examining the joint influence of the relative risk of PTS with PCDT vs. standard care after 6 months and the duration of the impact of PCDT on the risk of worsening PTS, and Figure 6 presents 2-way sensitivity analysis varying the two relative risks for worse PTS with PCDT vs. standard care - at 6 months, and beyond 6 months.

Impact of thrombus extent. For patients with iliofemoral DVT, mean index hospitalization and total follow-up costs were higher in both treatment groups than for patients with femoral-popliteal DVT (Supplemental Tables 10-21). For patients with iliofemoral DVT, projected incremental lifetime costs and QALYs with PCDT vs. standard therapy were $16,473 and 0.12 years, yielding an ICER of $137,526/QALY gained, with 4%, 29% and 55% of the joint distribution of cost and QALY differences falling below ICER thresholds of $50,000, $100,000, and $150,000/QALY gained (Table 2; Supplemental Figure 2). For patients with femoral-popliteal DVT, projected incremental lifetime costs with PCDT were $17,978 and projected quality adjusted life expectancy was slightly lower with PCDT than with standard treatment (Δ= -0.004 years). Thus, for patients with femoral-popliteal DVT, our model projected that PCDT would be dominated by standard therapy (higher costs and lower QALYs), with only a 13% probability of achieving an ICER <$150,000/QALY gained (Table 2; Supplemental Figure 3).

DISCUSSION

To our knowledge, this is the first direct comparison of economic outcomes of PCDT vs. standard anticoagulant therapy among patients with acute proximal DVT from the perspective of the U.S. healthcare system. This prospectively designed study demonstrated several key findings. First, initial treatment costs for PCDT exceed those for standard care by approximately $17,000, driven by both the procedural costs and greater length of initial hospitalization. Second, over the ensuing 24 months, PCDT did not lead to significant cost offsets. In fact, follow-up costs were roughly $2500/patient higher with PCDT, which appeared to be due to more frequent late endovascular procedures, more other hospitalizations, and greater home health care needs in the PCDT arm. Third, although the development of PTS--and especially severe PTS--was associated with a significant reduction in health utility (compared with no PTS), there were no significant differences between PCDT and standard therapy in utility at any follow-up time point from 6 to 24 months.

While the main clinical results from the ATTRACT trial demonstrated similar rates of PTS over 2 years with PCDT, the procedure did lead to several benefits which impacted its cost-effectiveness. Specifically, PCDT reduced PTS at 6 months, reduced the severity of PTS over 2 years and, perhaps most importantly, was of greater benefit to patients with iliofemoral DVT. Using the empirical data from ATTRACT to the greatest extent possible (and assuming that any impact of PCDT on post-6-month outcomes would not continue beyond 5 years), our model projected a lifetime ICER of $222,041/QALY gained with PCDT. According to current American College of Cardiology/American Heart Association (ACC/AHA) guidelines, an ICER <$50,000/QALY represents high value, an ICER between $50,000 and $150,000/QALY represents intermediate value, and an ICER >$150,000/QALY represents low value. Thus, our

study suggests that using PCDT for most patients with acute proximal DVT represents a low value treatment strategy.[15] While there is uncertainty around the ICER estimate, 75% of the distribution of estimates from probabilistic sensitivity analyses were >$150,000/QALY gained. One-way sensitivity analyses demonstrated that the factor with the greatest influence on this ICER was the impact of PCDT on PTS at 6 months. Holding all other assumptions constant, the relative risk for the impact of PCDT on 6-month PTS would need to be reduced from 0.54 (base case estimate) to 0.38 to yield an ICER of $150,000.

Cost-effectiveness results were more favorable among patients with iliofemoral DVT. For this subgroup, PCDT was projected to provide 0.12 QALY gained and an ICER of $137,526, suggesting that PCDT may be of intermediate value in this population. It is important, however, to recognize the uncertainty associated with this estimate, as 45% of estimates from probabilistic sensitivity analysis were >$150,000/QALY gained. In contrast, for patients with femoral-popliteal DVT, in addition to being more costly, PCDT did not reduce the incidence or severity of PTS at any time point. The more favorable ICER for patients with iliofemoral DVT was driven by a combination of higher background risk of moderate or severe PTS with standard therapy (24% vs. 18% at 2 years with iliofemoral and femoral-popliteal DVT, respectively) and the greater (and statistically significant) benefit of PCDT at 6 months in the iliofemoral subgroup. These findings are consistent with previous studies demonstrating that patients with more extensive and proximal DVT experience a higher rate of PTS and more severe PTS than patients with less extensive DVT.[1,16]

Comparison with Previous Studies. Prior to ATTRACT, the largest study to evaluate the cost-effectiveness of catheter-based thrombus removal vs. standard therapy in patients with proximal DVT was the CaVenT Trial.[17] In CaVenT, the ICER for CDT vs. standard treatment

was $20,439/QALY gained, considerably more favorable than in ATTRACT. Several factors likely account for this discrepancy. First, the incremental initial treatment costs of CDT were estimated to be only ~$13,000 in CaVenT, which is nearly $5000 lower than the incremental costs of PCDT in ATTRACT. This may reflect the costs of mechanical thrombectomy devices (used in PCDT but not CDT), stents (used more frequently in ATTRACT than CaVenT), and differences between the health systems of the U.S. and Norway. Moreover, in CaVenT, CDT resulted in a sustained reduction in PTS at both 2 and 5 years, leading to a gain of 0.63 QALYs over a lifetime horizon. In contrast, in ATTRACT, the benefit of PCDT on PTS was limited to the first 6-months of follow-up, yielding much lower QALY gains over a lifetime.

Clinical and Policy Implications. In treatment of cardiovascular disease, novel procedural approaches to patient management are invariably associated with substantial up-front costs compared with medical therapy. Consequently, achieving favorable cost-effectiveness results depends upon demonstrating substantial downstream cost offsets and/or QALY gains due to survival benefit, quality of life improvement, or both.[18-20] In the case of ATTRACT, for patients with femoral-popliteal DVT, the high up-front costs of PCDT coupled with the lack of measurable benefit across a range of domains provides further support to the recommendation that PCDT should not be standard of care for such patients. While the cost-effectiveness of PCDT for patients with iliofemoral DVT is more favorable, these results should be viewed with caution given both the exploratory nature of this secondary analysis and the degree of uncertainty around the ICER. Finally, our sensitivity analyses demonstrating the importance of the incidence of PTS in addition to the relative benefit of PCDT suggest that efforts to identify which patients with iliofemoral DVT are at highest risk for development of PTS could further enhance the cost-effectiveness of PCDT for this subgroup.

Limitations. The results of this economic study should be considered in light of several limitations. The ATTRACT trial protocol discouraged late procedures--especially in the control arm--and this recommendation was followed closely by the enrolling investigators. This change in clinical practice may have altered the incremental cost effectiveness of PCDT. While the cost of inpatient care during the trial was based on a combination of hospital billing data and extensive resource utilization data collected and validated according to protocol, unit costs applied to most resources are based on costs at Saint Luke's Mid America Heart Institute and are assumed to be representative of costs at all enrolling sites. Other costs including those for outpatient resource use and indirect costs were based on patient self-report; those components of cost are relatively small, however, and are unlikely to have meaningfully biased the comparisons between treatment groups. The long-term projections of costs and QALYs over a lifetime horizon required several assumptions regarding the magnitude and durability of the impact of PCDT on long-term costs, PTS outcomes, and quality of life that are not empirically verifiable. To address this concern, we varied those assumptions in sensitivity analyses to identify influential factors, and we used probabilistic sensitivity analysis to capture the uncertainty of our cost-effectiveness projections. Finally, the results have limited generalizability due to the restricted eligibility criteria of the ATTRACT trial, which included only U.S. sites, and the U.S. healthcare system perspective of the costing.

Conclusions. In patients with acute proximal DVT, PCDT as compared with standard anticoagulation alone led to substantial increases in 2-year medical care costs and a projected lifetime ICER that is not economically attractive from the perspective of the US healthcare system. Stratified analyses suggest that restricting PCDT to patients with iliofemoral DVT may

provide intermediate healthcare value by US standards, but given the secondary nature of this subgroup analysis, these findings should be confirmed in further prospective studies. Future studies to identify patients at highest risk of PTS and to enhance the effectiveness of PCDT are warranted to improve the cost-effectiveness of this approach over standard anticoagulation.

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FIGURE LEGENDS

FIGURE 1. Mean incremental follow-up costs (bars), and cumulative (index plus follow-up) costs (lines), for the PCDT and Standard Care groups. Error bars represent standard errors,

FIGURE 2. Mean SF-36 Utility scores over time for the PCDT and Standard Care groups, after adjusting for missing data via multiple imputation. Error bars represent standard errors.

FIGURE 3. Joint distribution of projected lifetime incremental costs and quality-adjusted life years for PCDT vs Standard Care based on probabilistic sensitivity analysis, plotted in the cost-effectiveness plane. (Red dot represents the estimated mean values (incremental cost=$16,740, incremental QALYs=0.08. Green dashed line indicates a cost-effectiveness threshold of $150,000/QALYs gained; orange dot-dashed line indicates a threshold of $50,000/QALYs gained.)

FIGURE 4. One-way sensitivity analysis (tornado diagram) on ICER (PCDT vs. Standard Care). (The dotted vertical line represents the base-case incremental cost-effectiveness ratio for PCDT compared with standard care. Horizontal bars indicate the range of incremental cost-effectiveness ratios obtained by setting each variable to the values shown at the ends of the bar while holding all other values constant.)

FIGURE 5. Results from two-way sensitivity analysis, varying the relative risk of worse PTS with PCDT after 6 months, and the duration of the impact of of PCDT on worsening PTS. (Chart shows the joint effect of two variables on the cost-effectiveness of PCDT at a willingness-to-pay threshold of $150,000 per QALY gained. The blue area represents values of the 2 parameters at which PCDT is favored, whereas the red area represents values of the 2 parameters at which standard care is favored. Black horizontal and vertical lines indicate basecase values of the two variables.)

FIGURE 6. Results from two-way sensitivity analysis, varying the relative risk of worse PTS with PCDT at 6 months, and after 6 months (PCDT vs. control). (Chart shows the joint effect of two variables on the cost-effectiveness of PCDT at a willingness-to-pay threshold of $150,000 per QALY gained. The blue area represents values of the 2 parameters at which PCDT is favored, whereas the red area represents values of the 2 parameters at which standard care is favored. Black horizontal and vertical lines indicate basecase values of the two variables.)

Table 1. Costs and Cost Differences between Treatment Arms through 24 Months: Overall Population*

Cost Item	PCDT N=336	Standard Care N=355	Cost Difference (PCDT - Standard)
Index hospitalization	$21,509 (20,327 to 22,843)	$3877 (3069 to 4803)	$17,632 (16,117 to 19,243)
Follow-up endovascular procedures	$2958 (1647 to 4545)	$1948 (593 to 4208)	$1010 (-1521 to 3276)
Hospitalizations not involving endovascular procedures	$3815 (2178 to 6024)	$3122 (1877 to 4616)	$693 (-1487 to 3296)
Outpatient care, non-acute inpatient stays, intermittent pneumatic compression devices, compression stockings:	$1490 (1102 to 2008)	$904 (714 to 1141)	$585 (149 to 1103)
• Outpatient care (emergency room visits, outpatient physician/nurse visits, home health visits):	$897 (642 to 1273)	$380 (323 to 442)	$517 (254 to 897)
o Emergency room visits (not requiring hospitalization)	$42 (31to 56)	$55 (43 to 69)	-$13 (-32 to 5)
o Outpatient physician/nurse visits	$239 (185 to 298)	$222 (185 to 264)	$17 (-50 to 85)
o Home health visits	$617 (378 to 999)	$103 (69 to 138)	$514 (276 to 890)
• Non-acute inpatient stays (rehab/ skilled nursing/other chronic care)	$378 (224 to 615)	$327 (168 to 541)	$51 (-204 to 323)
• Intermittent pneumatic compression devices	$174 (111 to 266)	$148 (102 to 208)	$26 (-66 to 131)
• Compression stockings	$41 (32 to 52)	$49 (38 to 62)	-$8 (-23 to 8)
Lost Productivity/Caregiver costs	$820 (389 to 1601)	$695 (463 to 1010)	$126 (-477 to 982)
TOTAL 24 MONTH COST	**$30,591** (27,714 to 34,043)	**$10,546** (8156 to 13,445)	**$20,045** (16,093 to 24,120)

Values are mean costs (95% confidence intervals in parentheses)

*missing data estimated using multiple imputation; no adjustment for censoring/losses to follow-up

Table 2. Projected* Lifetime Costs, QALYs and Cost-Effectiveness Ratios

Strategy	Undiscounted Cost	Discounted Cost	Incremental Cost (disc)	Undiscounted QALYs	Discounted QALYs	Incremental QALYs (disc)	ICER ($/QALY gained)
OVERALL POPULATION:							
PCDT	$182,513	$168,496		18.55	17.15		
Standard care	$165,843	$151,756	$16,740	18.48	17.07	0.08	$222,041
ILIOFEMORAL DVT:							
PCDT	$187,130	$173,026		18.52	17.12		
Standard care	$170,777	$156,552	$16,473	18.4	17	0.12	$137,526
FEMORAL-POPLITEAL DVT:							
PCDT	$174,854	$161,048		18.62	17.21		
Standard care	$156,832	$143,071	$17,978	18.63	17.22	-0.0042	*Dominated*

*Projections based on a Markov model based on the 2-year ATTRACT trial results (see Methods for details)

REFERENCES

1. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. Arch Intern Med 2004;164:17-26.
2. Enden T, Haig Y, Klow NE, Slagsvold CE, Sandvik L, Ghanima W, Hafsahl G, Holme PA, Holmen LO, jaastad AM, Sandbaek G, Sandset PM; CaVEnT Study Group. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 2012;379:31-8.
3. Haig Y, Enden T, Grotta O, Klow NE, Slagsvold CE, Ghanima W, Sandvik L, Hafsahl G, Holme PA, Holmen LO, Njaaastad AM, Sandbaek G, Sandset PM; CaVenT Study Group. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. Lancet Haematol 2016;3:e64-71.
4. Vedantham S, Goldhaber SZ, Kahn SR, Julian J, Magnuson E, Jaff MR, Murphy TP, Cohen DJ, Comerota AJ, Gornik HL, Razavi MK, Lewis L, Kearon C.. Rationale and design of the ATTRACT Study: a multicenter randomized trial to evaluate pharmacomechanical catheter-directed thrombolysis for the prevention of postthrombotic syndrome in patients with proximal deep vein thrombosis. Am Heart J 2013;165:523-30 e3.
5. Vedantham S, Goldhaber SZ, Julian JA, Kahn SR, Jaff MR, Cohen DJ, Magnuson E, Razavi MK, Comerota AJ, Gornik HL, Murphy TP, Lewis L, Duncan JR, Nieters P, Derfler MC, Filion M, Gu CS, Kee S, Schneider J, Saad N, Blinder M, Moll S, Sacks D, Lin J, Rundback J, Garcia M, Razdan R, VanderWoude E, Marques V, Kearon C; ATTRACT Trial Investigators. Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis. N Engl J Med 2017;377:2240-52.
6. Comerota AJ, Kearon C.; Gu, C-S, Julian JA, Goldhaber SZ, Kahn SR, Jaff MR, Razavi MK, Kindzelski AL, Bashir R, Patel P, Sharafuddin M, Sichlau MJ, Saad WE, Assi Z, Hoffman LC, Kennedy M, Vedantham S; ATTRACT Trial Investigators. Endovascular thrombus removal for acute iliofemoral deep vein thrombosis" analysis from a stratified multicenter randomized trial. Circulation 2019139:1162-1173.
7. Kearon C, Gu, C., Julian, J.A., Goldhaber S.z., Comerota, A.J., Gornik, H.L., Murphy, T.P., Lewis, L., Kahn, S.R., Kindzelski, A.L., Slater, D., Geary, R., Winokur, R., Natarajan, K., Dietzek, A., Leung, D.A., Kim, S., Vedantham, S., for the ATTRACT Trial Investigataors. Pharmacomechanical catheter-directed thrombolsis for acute femoral-popliteal deep-vein thrombosis: analysis from a stratified randomized trial. Thromb Haemost 2019;119:633-644.
8. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. J Thromb Haemost 2009;7:879-83.
9. Reynolds MR, Magnuson EA, Wang K, Lei Y, Vilain K, Walczak J, Kodali SK, Lasala JM, O'Neill WW, Davidson CJ, Smith CR, Leon MB, Cohen DJ; PARTNER Investigators. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B). Circulation 2012;125:1102-9.
10. Ware JE, Kosinski, M., Keller S. SF-36 physical and mental summary measures: a users manual. Boston, MA: The Health Institute, New England Medical Center; 1994.
11. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002;21:271-92.
12. Efron B. Better bootstrap confidence intervals. JASA 1987;82:171-200.
13. Bang H, Tsiatis, A.A. Estimating medical costs with censored data. Biometrika 2000;87:329-43.
14. Beck JR, Pauker SG. The Markov process in medical prognosis. Med Decis Making 1983;3:419-58.

15. Anderson JL, Heidenreich PA, Barnett PG, Creager MA, Fonarow GC, GIbbons RJ, Halperin JL, Hlatky MA, Jacobs AK, Mark DB, Masoudi FA, Peterson ED, Shaw LJ. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. Circulation 2014;129:2329-45.
16. Douketis JD, Crowther MA, Foster GA, Ginsberg JS. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? Am J Med 2001;110:515-9.
17. Enden T, Resch S, White C, Wik HS, Klow NE, Sandset PM. Cost-effectiveness of additional catheter-directed thrombolysis for deep vein thrombosis. J Thromb Haemost 2013;11:1032-42.
18. Cohen DJ, Bakhai A, Shi C, Glithiora L, Lavelle T, Berezin RH, Leon MB, Carrozza JP Jr, Zadar JP, Kuntz RE; SIRIUS Investigators. Cost-effectiveness of sirolimus-eluting stents for treatment of complex coronary stenoses: results from the Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SIRIUS) trial. Circulation 2004;110:508-14.
19. Mushlin AI, Hall WJ, Zwanziger J, Gajary E, Andrews M, Marron R, Zou KH, Moss AJ. The cost-effectiveness of automatic implantable cardiac defibrillators: results from MADIT. Multicenter Automatic Defibrillator Implantation Trial. Circulation 1998;97:2129-35.
20. Reynolds MR, Magnuson EA, Wang K, Lei Y, Vilain K, Walczak J, Kodali SK, Lasala JM, O'Neill WW, Davidson CJ, Smith CR, Leon MB, Cohen DJ; PARTNER Investigators. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B). Circulation 2012;125:1102-9.

FIGURE 1.

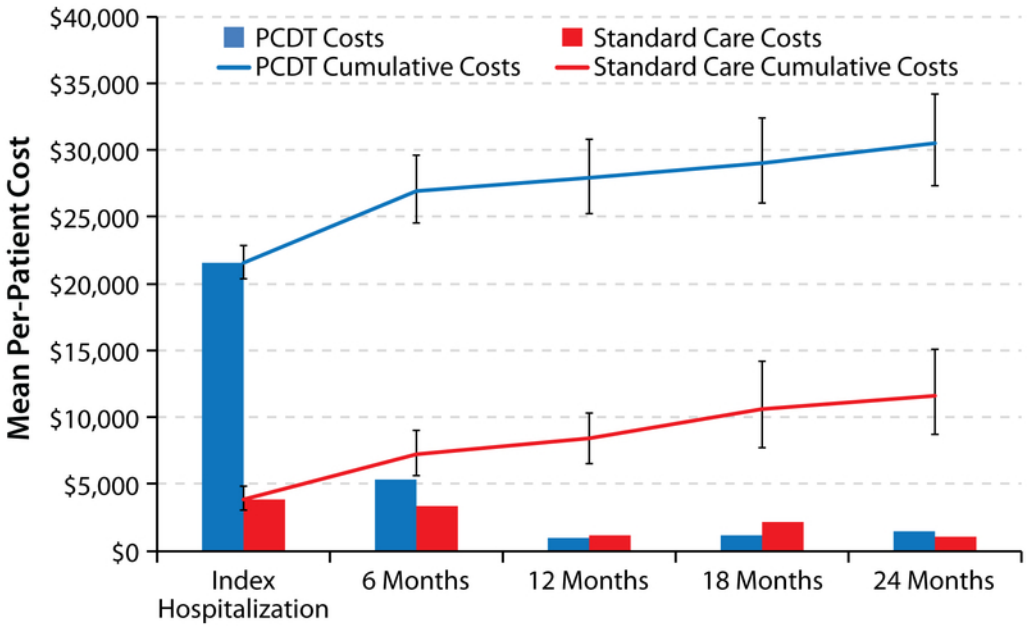
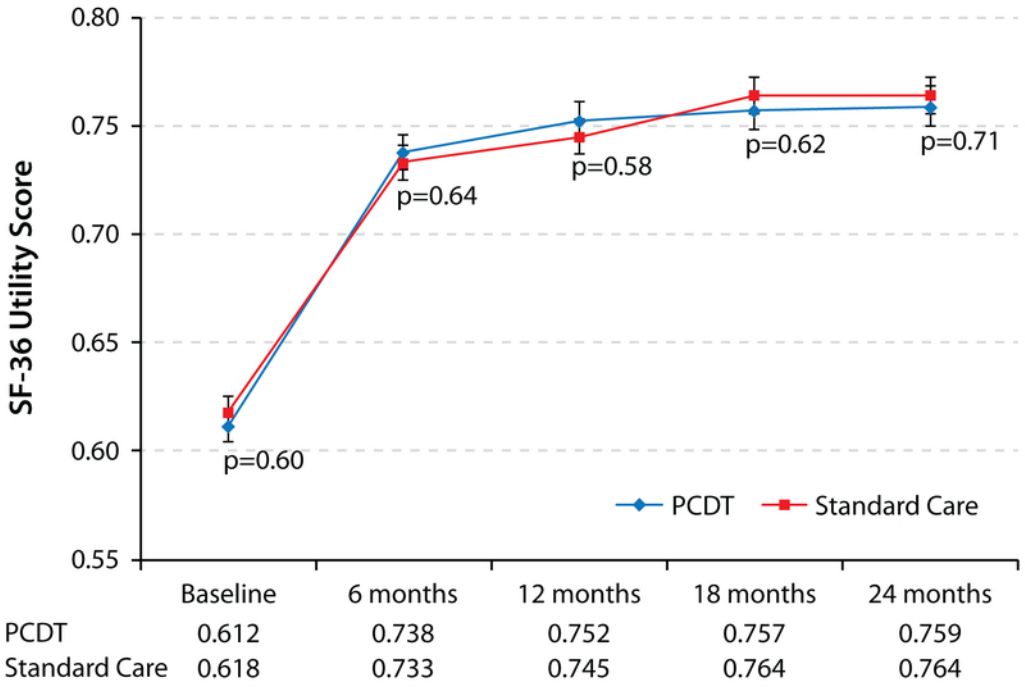

$40,000
$35,000
$30,000
$25,000
$20,000
$15,000
$10,000
$5,000
$0
Mean Per-Patient Cost
PCDT Costs
Standard Care Costs
PCDT Cumulative Costs
Standard Care Cumulative Costs
Index Hospitalization
6 Months
12 Months
18 Months
24 Months

FIGURE 2.



	Baseline	6 months	12 months	18 months	24 months
PCDT	0.612	0.738	0.752	0.757	0.759
Standard Care	0.618	0.733	0.745	0.764	0.764

FIGURE 3.

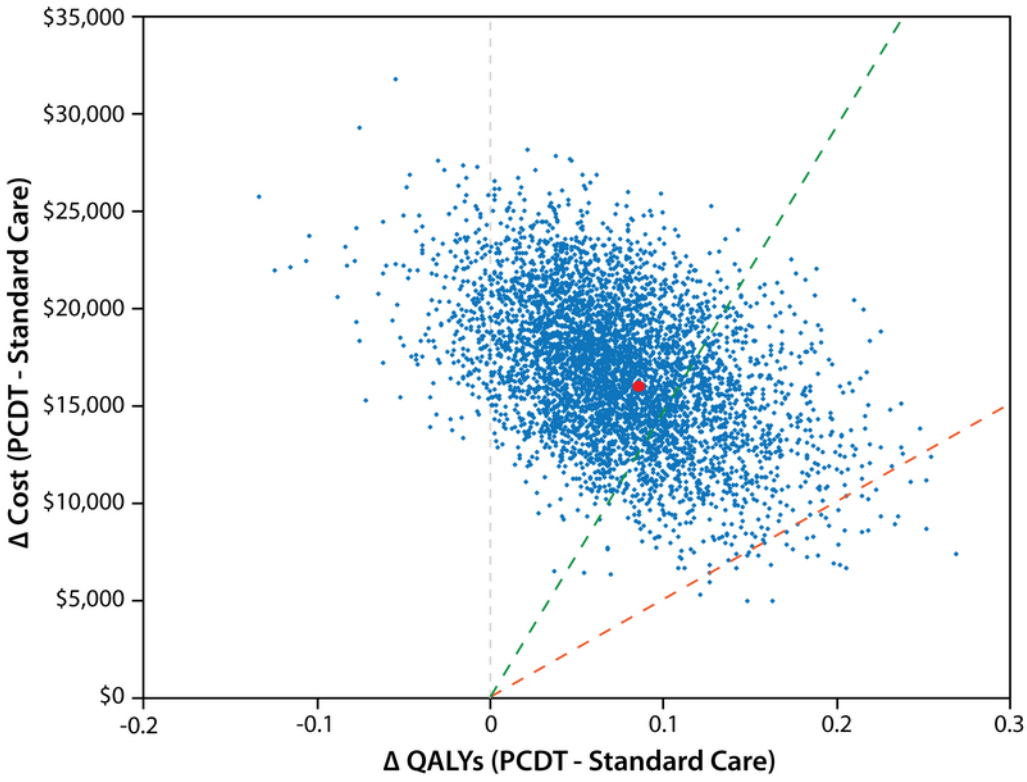

$35,000
$30,000
$25,000
$20,000
$15,000
$10,000
$5,000
$0
Δ Cost (PCDT - Standard Care)
-0.2
-0.1
0
0.1
0.2
0.3
Δ QALYs (PCDT - Standard Care)

FIGURE 4.

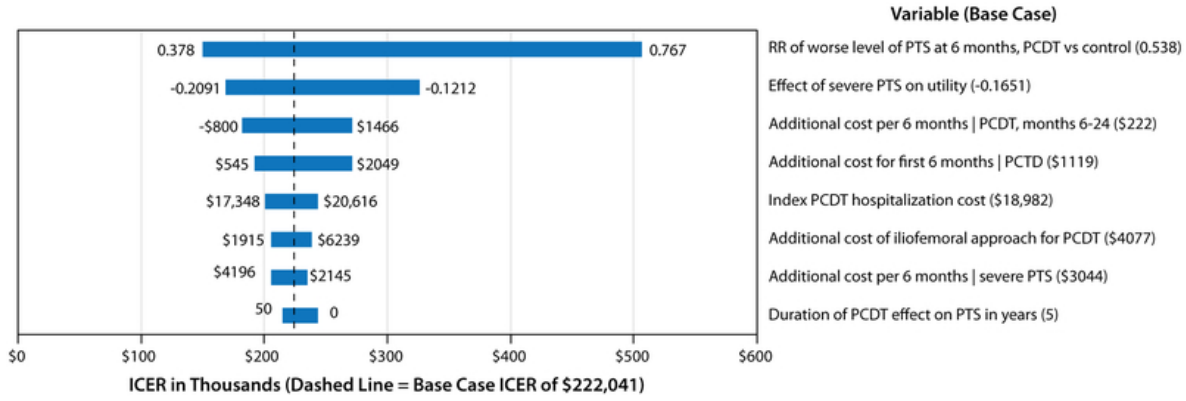

Variable (Base Case)
0.378
0.767
RR of worse level of PTS at 6 months, PCDT vs control (0.538)
-0.2091
-0.1212
Effect of severe PTS on utility (-0.1651)
-$800
$1466
Additional cost per 6 months | PCDT, months 6-24 ($222)
$545
$2049
Additional cost for first 6 months | PCTD ($1119)
$17,348
$20,616
Index PCDT hospitalization cost ($18,982)
$1915
$6239
Additional cost of iliofemoral approach for PCDT ($4077)
$4196
$2145
Additional cost per 6 months | severe PTS ($3044)
50
0
Duration of PCDT effect on PTS in years (5)
$0
$100
$200
$300
$400
$500
$600
ICER in Thousands (Dashed Line = Base Case ICER of $222,041)

FIGURE 5.

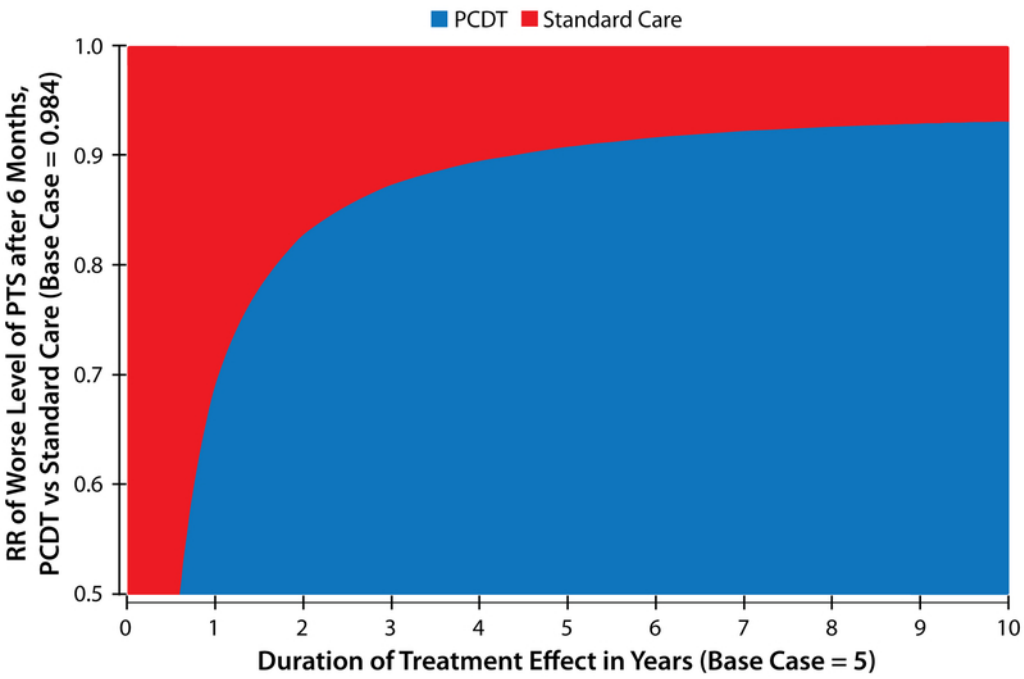
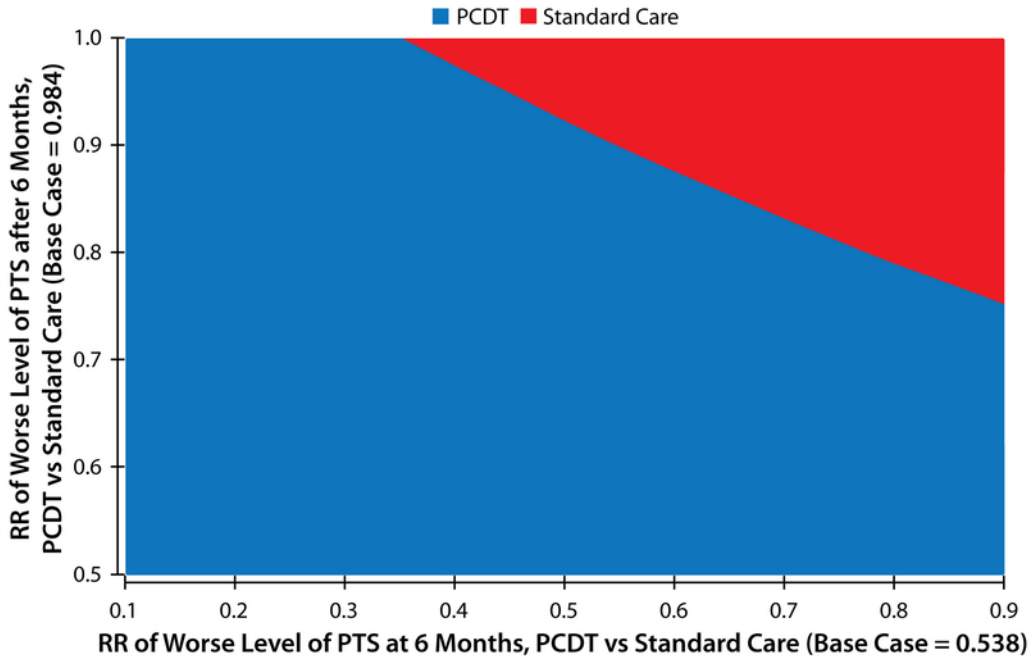

PCDT
Standard Care
RR of Worse Level of PTS after 6 Months, PCDT vs Standard Care (Base Case = 0.984)
1.0
0.9
0.8
0.7
0.6
0.5
0
1
2
3
4
5
6
7
8
9
10
Duration of Treatment Effect in Years (Base Case = 5)

FIGURE 6.


PCDT
Standard Care
1.0
0.9
0.8
0.7
0.6
0.5
RR of Worse Level of PTS after 6 Months, PCDT vs Standard Care (Base Case = 0.984)
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
RR of Worse Level of PTS at 6 Months, PCDT vs Standard Care (Base Case = 0.538)