JAMA Surgery | Original Investigation

Effectiveness of a Medical vs Revascularization Intervention for Intermittent Leg Claudication Based on Patient-Reported Outcomes

Emily B. Devine, PhD, PharmD, MBA; Rafael Alfonso-Cristancho, MD, MSc, PhD; N. David Yanez, PhD; Todd C. Edwards, PhD; Donald L Patrick, PhD, MSPH; Cheryl A. L. Armstrong, RN, MPH; Allison Devlin, MS; Rebecca G. Symons, MPH; Mark H. Meissner, MD; Ellen L. T. Derrick, MD, MPH; Danielle C. Lavallee, PhD, PharmD; Larry G. Kessler, ScD; David R. Flum, MD, MPH; for the Comparative Effectiveness Research Translation Network (CERTAIN) Collaborative

Invited Commentary

IMPORTANCE Intermittent claudication (IC) is the most common presentation of infrainguinal peripheral artery disease. Both medical and revascularization interventions for IC aim to increase walking comfort and distance, but there is inconclusive evidence of the comparative benefit of revascularization given the possible risk of limb loss.

OBJECTIVE To compare the effectiveness of a medical (walking program, smoking cessation counseling, and medications) vs revascularization (endovascular or surgical) intervention for IC in the community, focusing on outcomes of greatest importance to patients.

DESIGN, SETTING, AND PARTICIPANTS Longitudinal (12-month follow-up) prospective observational cohort study conducted between July 3, 2011, and November 5, 2014, at 15 clinics associated with 11 hospitals in Washington State. Participants were 21 years or older with newly diagnosed or established IC.

INTERVENTIONS Medical or revascularization interventions.

MAIN OUTCOMES AND MEASURES Primary end points were 12-month change scores on the distance, speed, and stair-climb domains of the Walking Impairment Questionnaire (score range, 0-100). Secondary outcomes were change scores on the Walking Impairment Questionnaire pain domain (score range, 0-100), Vascular Quality of Life Questionnaire (VascuQol) (score range, 1-7), European Quality of Life–5 Dimension Questionnaire (EQ-5D) (score range, 0-1), and Claudication Symptom Instrument (CSI) (score range, 0-4).

RESULTS A total of 323 adults were enrolled, with 282 (87.3%) in the medical cohort. At baseline, the mean duration of disease was longer for participants in the medical cohort, while those in the revascularization cohort reported more severe disease. Other characteristics were well balanced. At 12 months, change scores in the medical cohort reached significance for the following 3 outcomes: speed (5.9; 95% CI, 0.5-11.3; *P* = .03), VascuQol (0.28; 95% CI, 0.08-0.49; *P* = .008), and EQ-5D (0.038; 95% CI, 0.011-0.066; *P* = .006). In the revascularization cohort, there were significant improvements in the following 7 outcomes: distance (19.5; 95% CI, 7.9-31.0; *P* = .001), speed (12.1; 95% CI, 1.4-22.8; *P* = .03), stair climb (11.4; 95% CI, 1.3-21.5; *P* = .03), pain (20.7; 95% CI, 11.0-30.4; *P* < .001), VascuQol (1.10; 95% CI, 0.80-1.41; *P* < .001), EQ-5D (0.113; 95% CI, 0.067-0.159; *P* < .001), and CSI (−0.63; 95% CI, −0.96 to −0.31; *P* < .001). Relative improvements (percentage changes) at 12 months in the revascularization cohort over the medical cohort were observed as follows: distance (39.1%), speed (15.6%), stair climb (9.7%), pain (116.9%), VascuQol (41%), EQ-5D (18%), and CSI (13.5%).

CONCLUSIONS AND RELEVANCE Among patients with IC, those in the revascularization cohort had significantly improved function (Walking Impairment Questionnaire), better health-related quality of life (VascuQol and EQ-5D), and fewer symptoms (CSI) at 12 months compared with those in the medical cohort, providing important information to inform treatment strategies in the community.

JAMA Surg. 2016;151(10):e162024. doi:10.1001/jamasurg.2016.2024
Published online August 17, 2016. Corrected on October 19, 2016.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Comparative Effectiveness Research Translation Network (CERTAIN) Collaborative members are listed at the end of this article.

Corresponding Author: Emily B. Devine, PhD, PharmD, MBA, Pharmaceutical Outcomes Research and Policy Program, University of Washington, PO Box 357630, Seattle, WA 98195 (bdevine@uw.edu).

Atherosclerotic peripheral arterial disease (PAD) affects 8 million Americans.[1,2] Intermittent claudication (IC), the most common presentation of infrainguinal PAD, manifests as pain in the calf or foot with walking and is present in more than 8 million people worldwide.[3]

Medical management addresses modifiable risk factors, such as obesity,[4] diabetes,[5] hypertension,[5] and dyslipidemia.[2,5,6] Management includes a regular walking program,[7] smoking cessation,[8] and medications.[9,10] The American College of Cardiology and American Heart Association[11] recommend a supervised walking program and medications for all patients with PAD, but because claudication seldom progresses to limb loss, endovascular or surgical revascularization is indicated only for those with the most severe symptoms. Despite these recommendations, with the widespread availability of specialists trained in endovascular procedures, the use of revascularization for patients with moderate to severe claudication appears to be increasing.[11] Furthermore, decisions about medical management have not been standardized, resulting in wide practice variation.[12,13]

In this era of patient-centered care, it is important that clinicians identify what matters most to patients, incorporate such metrics into comparative evaluations of treatment effectiveness, and involve them in shared decision making.[14] Increasingly, patient-reported outcomes (PROs) that incorporate functional status, health-related quality of life (HRQoL), and symptom burden are used to incorporate the patient's voice.[15]

Although randomized clinical trials (RCTs) are the criterion standard for evaluating safety and efficacy, their conduct is not always feasible. In these instances, population-level comparative effectiveness research using observational data provides information about the way treatments work in the community. Comparative effectiveness research studies enable identification of important variations that may inform treatment strategies.[16] However, observational comparative effectiveness research studies must account for potential confounding bias that is inherently minimized in RCTs. This issue may be somewhat mitigated when important characteristics are incorporated into the study design. This study conducted by the Comparative Effectiveness Research Translation Network (CERTAIN) Collaborative[17,18] in Washington State compared the effectiveness of a medical vs revascularization intervention for IC in the community and focused on patient-centered outcomes.

Key Points

Question What is the comparative effectiveness of revascularization procedures vs medical management on function, health-related quality of life, and symptoms in patients with intermittent claudication?

Findings In this longitudinal prospective observational cohort study that included 323 adults, relative improvements (percentage changes) at 12 months in the following 5 outcomes in the revascularization cohort were significantly improved over the medical cohort: walking distance (39.1%), pain (116.9%), Vascular Quality of Life Questionnaire (41.0%), European Quality of Life–5 Dimension Questionnaire (18.0%), and Claudication Symptom Instrument (13.5%).

Meaning Adults with intermittent claudication in the revascularization cohort had significantly improved function, better health-related quality of life, and fewer symptoms at 12 months compared with those in the medical cohort, providing important information to inform treatment strategies in the community.

Methods

This multisite longitudinal (12-month follow-up) prospective observational cohort study was conducted at 15 clinics associated with 11 hospitals in Washington State. The University of Washington Human Subjects Committee served as the study's institutional review board of record and approved the study. Preliminary consent was obtained via a scripted telephone conversation. This was followed by completion of a written consent form and Health Insurance Portability and Accountability form, both of which were returned to the study coordinator via US mail. All study data were deidentified. The study examined the comparative effectiveness of the following 3 treatment strategies for infrainguinal IC: medical management (physician-recommended walking program, smoking cessation, and phosphodiesterase III inhibitors) vs endovascular or surgical revascularization. We compared the change from baseline to 6- and 12-month physical function, HRQoL, and symptom scores using PRO measures. The primary outcomes were scores on the following 3 domains of the modified Walking Impairment Questionnaire (WIQ): distance, speed, and stair climb.[19,20] Secondary outcomes were scores on the WIQ pain domain, Vascular Quality of Life Questionnaire (VascuQoL),[21] European Quality of Life–5 Dimension Questionnaire (EQ-5D),[22] and Claudication Symptom Instrument (CSI) (a claudication-specific measure developed and validated for use in this study).

This study population consisted of English-speaking patients 21 years or older with newly diagnosed or established IC. Those with acute ischemia, rest pain or ulceration, or isolated aortic or iliac claudication were excluded. Potential participants were identified from clinician appointment schedules, followed by review of electronic medical records. Once the diagnosis was confirmed, recruitment and enrollment adhered to standard protocols. After participants completed a baseline survey, they were categorized into 1 of the following 3 cohorts: medical management, endovascular revascularization, or surgical revascularization. Patient-reported outcomes were measured by self-report at baseline, 6 months, and 12 months. Data were collected using a secure web-based platform (DatStat; DatStat Inc). Patient characteristics (demographic information, insurance, risk factors, comorbidities, current medications, surgical history, claudication severity, duration of disease before enrollment, and ankle brachial index) were obtained at baseline through medical record abstraction or self-report. Study data were managed using research electronic data capture.[23]

The modified WIQ is a disease- and function-specific measure of a patient's walking ability and has been validated in patients with IC.[20] It contains 16 questions across the following

4 domains: pain in calves or buttocks (2 items), walking distance (7 items), walking speed (4 items), and stair climb (3 items). For distance, the participant is asked to rate the degree of difficulty in walking distances ranging from walking indoors to walking 1500 ft (457.2 m or 5 blocks). For speed, the participant is asked to rate the degree of difficulty in walking 1 block, with speeds ranging from slow to jogging. For stair climb, the participant is asked to rate the degree of difficulty in climbing 1 to 3 flights of stairs. A standardized percentage score ranging from 0 (inability) to 100 (no difficulty) is calculated for each domain. A total score is not calculated for the modified WIQ.[24] Improvements in WIQ scores have been shown to be correlated with supervised exercise programs[25] and lower extremity revascularization,[26] although there is no well-established minimally important difference (MID) for the modified WIQ.

The 25-item VascuQoL is a validated measure that reliably measures the effect of PAD across the following 5 domains: pain (4 items), symptoms (4 items), activities (8 items), social (2 items), and emotional (7 items).[21,27,28] Each domain is scored using an ordered 7-point response scale, and overall (total) scores range from 1 (worst HRQoL) to 7 (best HRQoL). The VascuQoL has been shown to correlate closely with outdoor walking capacity in IC.[29] Minimally important differences for use with the VascuQoL in IC have recently been estimated to be 0.87 for improvement and 0.23 for deterioration.[30]

The 3-level EQ-5D is a validated, generic, preference-based HRQoL assessment that quantifies overall health and is a reliable outcome measure for use in cardiovascular medicine.[31] It is composed of 1 question in each of the following 5 domains: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. The 3 levels of scoring are no problems, some problems, and extreme problems. An algorithm transforms these scores to between 0 (death) and 1 (full health).[32] The MID is 0.074 for the EQ-5D.[33] The EQ-5D is useful in both clinical and economic evaluations.

The CSI is a claudication-specific measure created for use in this study. It consists of the following 5 items that assess claudication symptoms in the leg or foot: pain, numbness, heaviness, cramping, and tingling. Each item is rated on an ordered 5-point intensity scale for the worst intensity experienced in the past 7 days (ranging from 0 [none] to 4 [extreme]). A total score is calculated as the mean intensity of the 5 symptoms.

The primary a priori alternative hypothesis stated that, after controlling for traditional risk factors for IC, the mean decline in function at 12 months on each of 3 domains of the WIQ (distance, speed, and stair climb) would be greater in the medical cohort than in the endovascular and surgical cohorts combined. With an anticipated enrollment of 450 participants using a 1:1:1 enrollment schema (ratio of medical cohort to endovascular cohort to surgical cohort), a within-participant correlation coefficient of 0.7, and a percentage decline in WIQ score from baseline of 15% (medical cohort), 7% (endovascular cohort), and 5% (surgical cohort), we estimated 89% power to detect a difference in WIQ distance, 80% power to detect a difference in WIQ speed, and 94% power to detect a difference in WIQ stair climb.

For the revascularization cohort, the index date was the date of revascularization. For the medical cohort, the index date was defined as 28 days after the date of study enrollment because this period was the average time from the last clinic visit to the surgery visit for patients in our vascular surgical registry. We used an intent-to-treat analysis throughout and did not reassign participants if they crossed over from the medical cohort to the revascularization cohort at any time during the study follow-up period. For all analyses, the endovascular and surgical cohorts were combined into 1 revascularization cohort.

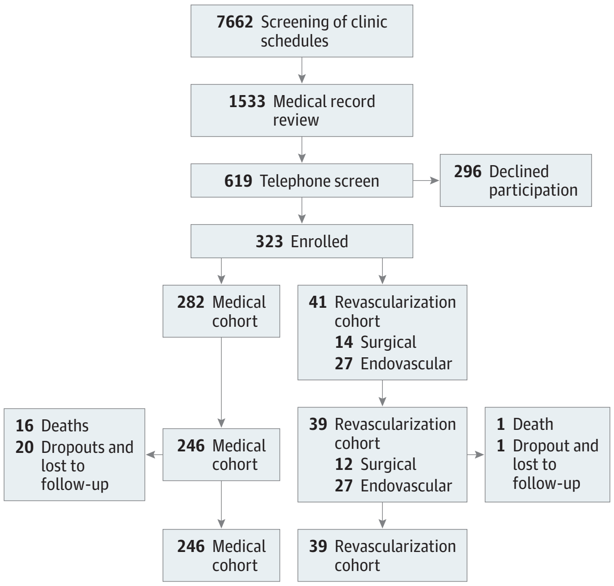
We used descriptive statistics to summarize baseline characteristics and t tests and χ^2 tests to compare these variables between cohorts. Adjusted analyses were conducted using generalized estimating equations with a robust variance estimator. To account for repeated measures, we clustered on patient identifier. Each dependent variable of interest was the domain or total score on each PRO measure. The independent variable of interest was the observed intervention, namely, medical management vs revascularization. We calculated the mean difference between cohorts at each time frame (baseline, 6 months, and 12 months) and the mean and percentage change scores within cohorts over time. Percentage change scores were calculated by subtracting the score at follow-up from the score at baseline and dividing that quantity by the baseline score. We then calculated the difference in differences between cohorts over time and the percentage change scores between cohorts over time. These percentage change scores were calculated by subtracting the percentage change score in the revascularization cohort from the percentage change score in the medically managed cohort.

All analyses were adjusted for age, sex, physician type, hypertension, diabetes, smoking status, number of comorbidities, body mass index, duration of disease before enrollment, and claudication severity. Separately, during the follow-up period, we counted the number of any-cause hospitalizations occurring after the index date and the number of deaths. We evaluated the sensitivity of the results using multiple imputation for missing data. Regression results were robust to these imputations, so we present the results of the complete case analysis. All analyses were performed using statistical software (Stata, version 13; StataCorp LP).

Results

Between July 3, 2011, and September 5, 2013, screening of clinic schedules identified 7662 patients, of whom 1533 were considered potential participants with claudication by medical record review. Detailed medical record review, followed by telephone screen, confirmed 619 patients with IC, 296 of whom declined to participate and 323 of whom enrolled at the 15 study sites. The last index date of enrollment was September 5, 2013. Patients were followed up for 12 months and given 2 additional months to return surveys, with a study end date of November 5, 2014. A total of 282 participants (87.3%) were cared for in the medical cohort, and 41 participants (12.7%) were cared for in the revascularization cohort (**Figure 1**). Of the 305 participants for whom physician type was reported, 265 (86.9%)

Figure 1. Participant Flow Diagram



Shown are the numbers of patients from baseline to 12 months.

were cared for by vascular surgeons, 33 (10.8%) were cared for by cardiologists, and 7 (2.3%) were cared for by interventional radiologists. At 12 months, survey response rates were 246 of 282 (87.2%) in the medical cohort and 39 of 41 (95.1%) in the revascularization cohort.

Baseline characteristics between the 2 cohorts differed by physician type, duration of disease before enrollment, and physician-reported claudication severity, with the latter determined either by clinician use of the Rutherford clinical staging system[34] or by a record of walking distance. Mild disease was defined as a walking distance of 900 ft (274.5 m or 2-3 blocks), moderate disease as a walking distance of 600 ft (183.1 m or 1-2 blocks), and severe disease as a walking distance of 300 ft or less (≤91.4 m or <1 block).[35] In the medical cohort, smoking cessation counseling was offered to 60.6% (40 of 66) of smokers, a walking program was discussed for 44.7% (126 of 282), and cilostazol or pentoxifylline was prescribed for 93.7% (89 of 95) and 6.3% (6 of 95), respectively (**Table 1**). Eighteen participants crossed over from the medical cohort to the revascularization cohort. Baseline characteristics of these participants were not appreciably different from those in the remainder of the medical cohort, so they were retained in the medical cohort for analysis.

The baseline scores for 6 of 7 domains or outcomes suggested no differences between the medical and revascularization cohorts, with the exception being the EQ-5D (0.056; 95% CI, 0.005-0.107). However, at 6 and 12 months, scores for 5 of 7 outcomes in the revascularization cohort were significantly greater than in the medical cohort (**Table 2**, **Figure 2**, and **Figure 3**).

In the medical cohort, the mean improvements in PRO measures at 12 months were statistically significant for the following 3 outcomes: speed (5.9; 95% CI, 0.5-11.3; *P* = .03), VascuQoL (0.28; 95% CI, 0.08-0.49; *P* = .008), and EQ-5D (0.038; 95% CI, 0.011-0.066; *P* = .006). These percentage improvements were 21.9%, 17%, and 11.7%, respectively (Table 2, Figure 2B, and Figure 3A and B). The remaining scores remained stable over time.

In the revascularization cohort, there were significant mean improvements in all outcomes between baseline and 12 months as follows: distance (19.5; 95% CI, 7.9-31.0; *P* = .001), speed (12.1; 95% CI, 1.4-22.8; *P* = .03), stair climb (11.4; 95% CI, 1.3-21.5; *P* = .03), pain (20.7; 95% CI, 11.0-30.4; *P* < .001), VascuQoL (1.10; 95% CI, 0.80-1.41; *P* < .001), EQ-5D (0.113; 95% CI, 0.067-0.159; *P* < .001), and CSI (−0.63; 95% CI, −0.96 to −0.31; *P* < .001). These percentage improvements were 56.9%, 37.6%, 26.6%, 141.8%, 57.9%, 29.7%, and 16.1%, respectively. Twelve-month scores were slightly lower than 6-month scores (Table 2, Figure 2, and Figure 3). At 12 months, the improvements in scores in the revascularization cohort compared with the medical cohort (difference in differences) were as follows: distance (13.6; 95% CI, 0.7-26.6), speed (6.2; 95% CI, −5.8 to 18.2), stair climb (6.2; 95% CI, −5.6 to 18.1), pain (16.8; 95% CI, 6.2-27.4), VascuQoL (0.82; 95% CI, 0.45-1.19), EQ-5D (0.075; 95% CI, 0.021-0.128), and CSI (−0.53; 95% CI, −0.90 to −0.15). These percentage changes were 39.1%, 15.6%, 9.7%, 116.9%, 41%, 18%, and 13.5%, respectively.

In the revascularization cohort, improvements in the VascuQoL at 6 months (mean change, 1.17) and 12 months (mean change, 1.10) exceeded the MID for improvement of 0.87, while in the medical cohort they did not (0.22 from baseline to 6 months and 0.28 from baseline to 12 months) (Table 2). The same held true for the EQ-5D. In the revascularization cohort, the improvements at 6 months (mean change, 0.112) and 12 months (mean change, 0.113) exceeded the MID of 0.074, while in the medical cohort they did not (0.034 at 6 months and 0.038 at 12 months). Although Conjin and colleagues[30] estimated an MID for the WIQ, we did not think it was appropriate to apply this value because their MID was based on the Dutch version of the original WIQ, for which they calculated a total WIQ score. We used the English version of the modified WIQ, for which no total score has been calculated, to our knowledge.

Separately, during the follow-up period, 128 participants reported any admission to the hospital, and 17 participants died. Cohort-specific proportions for these events were similar to the overall proportions enrolled in each cohort. Specifically, 116 of 128 admissions (90.6%) and 16 of 17 deaths (94.1%) occurred in the medical cohort, while 282 of 323 participants (87.3%) were medically managed overall.

Discussion

Revascularization procedures have traditionally been offered only to patients with the most incapacitating claudication, in part because of a low risk of progression of claudication to limb loss and the potential for procedure-related complications that might result in limb loss. The results of this multisite prospective cohort study of patients with IC with moderate to severe claudication suggest that function, HRQoL, and symptoms improved between baseline and 12 months in

Table 1. Patient Baseline Characteristics

Variable	Total No.	Total Value	Medical Cohort No.	Medical Cohort Value	Revascularization Cohort No.	Revascularization Cohort Value
Age, mean (SD), y[a]	323	71 (10)	282	71 (10)	41	71 (9)
BMI, mean (SD)[a]	223	28.3 (5.0)	189	28.2 (5.2)	34	28.8 (3.9)
Duration of disease before enrollment, mean (SD), y[a,b]	291	6.3 (6.9)	255	6.8 (7.1)	36	2.9 (3.1)
Ankle brachial index, mean (SD)[c]	258		227		31	
Right		0.75 (0.23)		0.75 (0.23)		0.80 (0.23)
Left		0.77 (0.22)		0.76 (0.21)		0.82 (0.32)
Male sex, No. (%)[a]	323	226 (70.0)	282	198 (70.2)	41	28 (68.3)
Race/ethnicity, No. (%)[a]	185		151		34	
Black		21 (11.4)		19 (12.6)		2 (5.9)
White		161 (87.0)		129 (85.4)		32 (94.1)
Asian		3 (1.6)		3 (2.0)		0
Insurance, No. (%)[a]	323		282		41	
Private		193 (59.8)		168 (59.6)		25 (61)
Medicare		222 (68.7)		191 (67.7)		31 (75.6)
Medicaid		23 (7.1)		23 (8.2)		0
Physician type, No. (%)[c,d]	305		265		40	
Surgeon		265 (86.9)		237 (89.4)		28 (70)
Cardiologist		33 (10.8)		27 (10.2)		6 (15)
Interventional radiologist		7 (2.3)		1 (0.4)		6 (15)
Smoking status, No. (%)[a]	323		282		41	
Never		41 (12.7)		36 (12.8)		5 (12.2)
Former		179 (55.4)		152 (53.9)		27 (65.9)
Current		73 (22.6)		66 (23.4)		7 (17.1)
Smoking cessation counseling offered to current smokers			66	40 (60.6)		
Unknown		30 (9.3)		28 (9.9)		2 (4.9)
Walking program discussed at visit, No. (%)[c]			282	126 (44.7)		
Medication currently prescribed, No. (%)[c]			282	95 (33.7)		
Cilostazol			95	89 (93.7)		
Pentoxifylline			95	6 (6.3)		
Comorbidities, No. (%)[a]						
Hypertension	320	268 (83.8)	279	234 (83.9)	41	34 (82.9)
Diabetes	319	109 (34.2)	278	93 (33.5)	41	16 (39)
Coronary artery disease	320	148 (46.3)	279	126 (45.2)	41	22 (53.7)
Stroke	319	30 (9.4)	278	27 (9.7)	41	3 (7.3)
Chronic obstructive pulmonary disease	319	43 (13.5)	278	39 (14.0)	41	4 (9.8)
Functional status, No. (%)[a]						
Totally independent	321	318 (99.1)	281	278 (98.9)	40	40 (100)
Ambulatory status, No. (%)[a]	231		201		30	
Independent		212 (91.8)		183 (91.0)		29 (96.7)
With assistance		19 (8.2)		18 (9.0)		1 (3.3)
Previous noncardiac vascular procedure, No. (%)[c]	323	162 (50.2)	282	143 (50.7)	41	19 (46.3)
Previous peripheral revascularization[c]		92 (28.5)		80 (28.4)		12 (29.3)
Claudication severity, No. (%)[c,d]	202		170		32	
Mild		66 (32.7)		66 (38.8)		0
Moderate		54 (26.7)		46 (27.1)		8 (25)
Severe		82 (40.6)		58 (34.1)		24 (75)
Patient report of general health, No. (%)[a]	312		272		40	
Poor		13 (4.2)		12 (4.4)		1 (2.5)
Fair		90 (28.8)		80 (29.4)		10 (25)
Good		139 (44.6)		121 (44.5)		18 (45)
Very good		67 (21.5)		57 (21.0)		10 (25)
Excellent		3 (1.0)		2 (0.7)		1 (2.5)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Obtained from patient self-report.

[b] $P < .01$.

[c] Obtained from medical record.

[d] $P < .001$.

Table 2. Adjusted Change Scores for Patient-Reported Outcomes

Cohort	Time, mo	Mean (95% CI) Change
WIQ Distance		
Between cohort		
Medical vs revascularization	6	29.0 (15.3 to 42.7)[a]
Medical vs revascularization	12	14.6 (−0.3 to 29.5)
Within cohort		
Medical	Baseline vs 6	4.1 (−1.4 to 9.7)
Medical	Baseline vs 12	5.8 (−0.2 to 11.8)
Medical	6 vs 12	1.7 (−3.2 to 6.6)
Revascularization	Baseline vs 6	32.2 (19.7 to 44.7)[a]
Revascularization	Baseline vs 12	19.5 (7.9 to 31.0)[a]
Revascularization	6 vs 12	−12.7 (−23.4 to −2.1)[b]
Difference in differences		
Medical vs revascularization	Baseline vs 6	28.0 (14.4 to 41.7)[a]
Medical vs revascularization	Baseline vs 12	13.6 (0.7 to 26.6)[b]
WIQ Speed		
Between cohort		
Medical vs revascularization	6	26.3 (11.9 to 40.8)[a]
Medical vs revascularization	12	11.6 (−1.7 to 24.8)
Within cohort		
Medical	Baseline vs 6	2.6 (−2.8 to 8.1)
Medical	Baseline vs 12	5.9 (0.5 to 11.3)[b]
Medical	6 vs 12	3.3 (−2.0 to 8.5)
Revascularization	Baseline vs 6	23.6 (10.0 to 37.2)[c]
Revascularization	Baseline vs 12	12.1 (1.4 to 22.8)[b]
Revascularization	6 vs 12	−11.6 (−22.1 to −1.0)[b]
Difference in differences		
Medical vs revascularization	Baseline vs 6	21.0 (6.4 to 35.6)[c]
Medical vs revascularization	Baseline vs 12	6.2 (−5.8 to 18.2)
WIQ Stair Climb		
Between cohort		
Medical vs revascularization	6	21.3 (6.3 to 36.2)[c]
Medical vs revascularization	12	18.4 (1.5 to 35.5)[b]
Within cohort		
Medical	Baseline vs 6	3.5 (−2.3 to 9.3)
Medical	Baseline vs 12	5.2 (−1.2 to 11.5)
Medical	6 vs 12	1.7 (−5.0 to 8.3)
Revascularization	Baseline vs 6	12.6 (2.3 to 23.0)[b]
Revascularization	Baseline vs 12	11.4 (1.3 to 21.5)[b]
Revascularization	6 vs 12	−1.2 (−11.6 to 9.1)
Difference in differences		
Medical vs revascularization	Baseline vs 6	9.1 (−2.8 to 21.1)
Medical vs revascularization	Baseline vs 12	6.2 (−5.6 to 18.1)
WIQ Pain		
Between cohort		
Medical vs revascularization	6	16.4 (5.7 to 27.1)[c]
Medical vs revascularization	12	15.7 (4.7 to 26.7)[c]
Within cohort		
Medical	Baseline vs 6	4.0 (−0.6 to 8.6)
Medical	Baseline vs 12	3.9 (−0.2 to 8.0)
Medical	6 vs 12	<0.1 (−3.8 to 3.7)
Revascularization	Baseline vs 6	21.4 (12.8 to 30.1)[a]
Revascularization	Baseline vs 12	20.7 (11.0 to 30.4)[a]
Revascularization	6 vs 12	−0.7 (−7.6 to 6.1)
Difference in differences		
Medical vs revascularization	Baseline vs 6	17.5 (7.6 to 27.3)[a]
Medical vs revascularization	Baseline vs 12	16.8 (6.2 to 27.4)[c]
VascuQoL Total		
Between cohort		
Medical vs revascularization	6	1.14 (0.66 to 1.61)[a]
Medical vs revascularization	12	1.00 (0.55 to 1.45)[a]
Within cohort		
Medical	Baseline vs 6	0.22 (0.03 to 0.40)[b]
Medical	Baseline vs 12	0.28 (0.08 to 0.49)[c]
Medical	6 vs 12	0.07 (−0.10 to 0.23)
Revascularization	Baseline vs 6	1.17 (0.83 to 1.52)[a]
Revascularization	Baseline vs 12	1.10 (0.80 to 1.41)[a]
Revascularization	6 vs 12	0.07 (−0.39 to 0.24)
Difference in differences		
Medical vs revascularization	Baseline vs 6	0.96 (0.57 to 1.35)[a]
Medical vs revascularization	Baseline vs 12	0.82 (0.45 to 1.19)[a]
EQ-5D		
Between cohort		
Medical vs revascularization	6	0.133 (0.075 to 0.192)[a]
Medical vs revascularization	12	0.131 (0.071 to 0.190)[a]
Within cohort		
Medical	Baseline vs 6	0.034 (0.006 to 0.063)[b]
Medical	Baseline vs 12	0.038 (0.011 to 0.066)[c]
Medical	6 vs 12	0.004 (−0.021 to 0.029)
Revascularization	Baseline vs 6	0.112 (0.066 to 0.157)[a]
Revascularization	Baseline vs 12	0.113 (0.067 to 0.159)[a]
Revascularization	6 vs 12	0.001 (−0.036 to 0.038)
Difference in differences		
Medical vs revascularization	Baseline vs 6	0.077 (0.024 to 0.131)[c]
Medical vs revascularization	Baseline vs 12	0.075 (0.021 to 0.128)[c]
CSI		
Between cohort		
Medical vs revascularization	6	−0.77 (−1.16 to −0.38)[a]
Medical vs revascularization	12	−0.79 (−1.23 to −0.35)[a]
Within cohort		
Medical	Baseline vs 6	−0.07 (−0.24 to 0.10)
Medical	Baseline vs 12	−0.11 (−0.29 to 0.08)
Medical	6 vs 12	−0.04 (−0.19 to 0.11)
Revascularization	Baseline vs 6	−0.57 (−0.86 to −0.29)[a]
Revascularization	Baseline vs 12	−0.63 (−0.96 to −0.31)[a]
Revascularization	6 vs 12	−0.06 (−0.43 to 0.31)
Difference in differences		
Medical vs revascularization	Baseline vs 6	−0.51 (−0.84 to −0.17)[c]
Medical vs revascularization	Baseline vs 12	−0.53 (−0.90 to −0.15)[c]

Abbreviations: CSI, Claudication Symptom Instrument; EQ-5D, European Quality of Life–5 Dimension Questionnaire; VascuQoL, Vascular Quality of Life Questionnaire; WIQ, Walking Impairment Questionnaire.

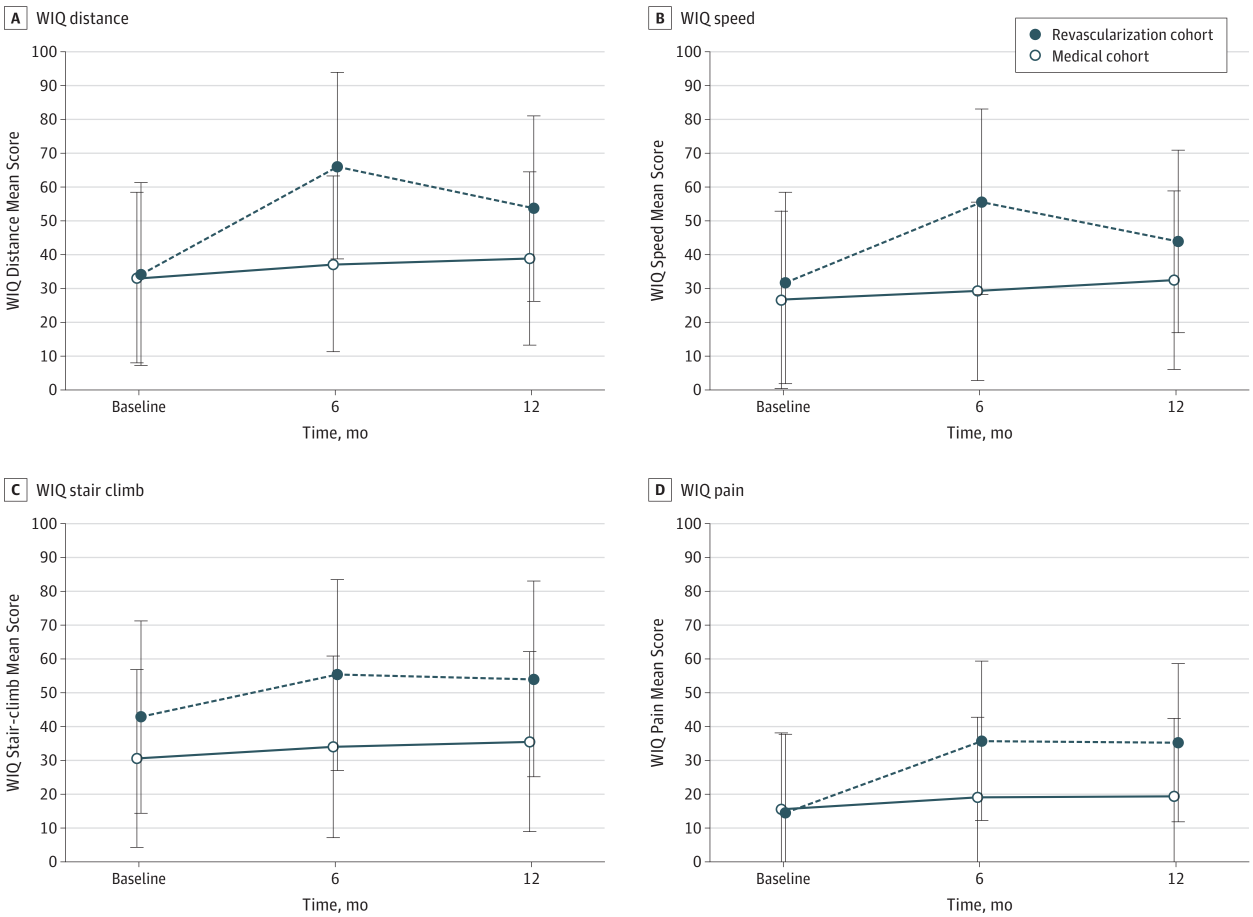
[a] $P < .001$.

[b] $P < .05$.

[c] $P < .01$.

both the medical and revascularization cohorts, but the findings indicate that gains were much greater in the revascularization cohort. The comparative effectiveness of revascular-

Figure 2. Walking Impairment Questionnaire (WIQ)



Shown are adjusted score estimates over time. Bars represent SEs.

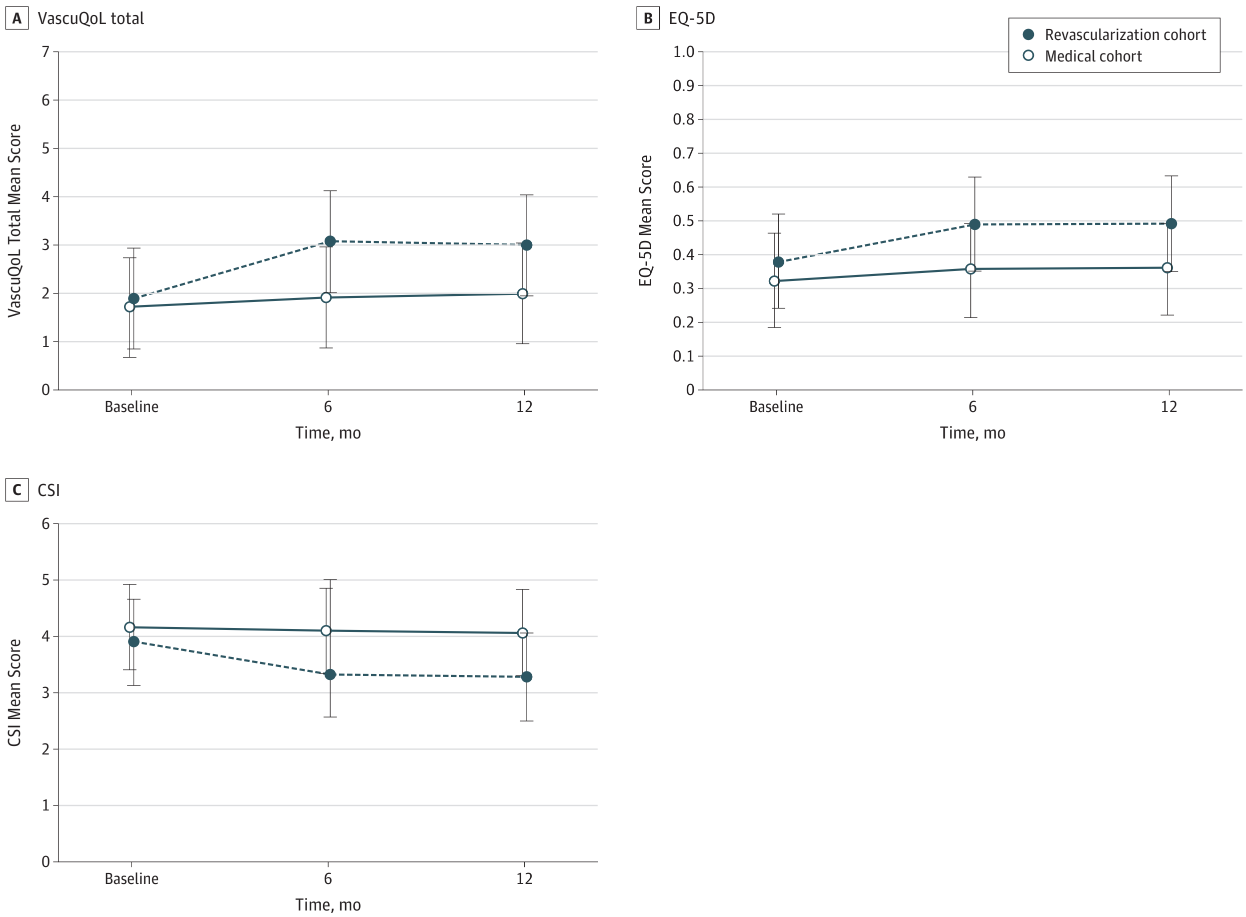
ization in participants with less than severe claudication suggests a broader role for these interventions, information that may be helpful in clinical decision making.

When comparing our work with that of others, we find that the benefits of supervised exercise therapy in patients with IC is well documented.[36] The added effect of medication therapy is mixed, with evidence from the recent Cochrane systematic review[36] suggesting beneficial effects and a network meta-analysis[37] suggesting none. Investigators in the Claudication: Exercise Vs Endoluminal Revascularization (CLEVER) study,[38] a multisite RCT of patients with aortoiliac PAD, randomized 111 patients to receive optimal medical care with or without supervised exercise or stent revascularization. Their results suggest that at 6 months the change in peak walking time was greatest for the supervised exercise group, intermediate for the endovascular revascularization group, and least for those who received only optimal medical care. In contrast, greater improvements in WIQ scores were observed in the endovascular revascularization group than in the supervised exercise group. These authors called for further study of the contrast between better walking performance for patients receiving exercise only and better overall function for patients receiving endovascular care. Our results are consistent with the CLEVER study in that walking speed improved slightly in the medical cohort, although the exercise component of our study was not supervised. Moreover, our combined revascularization cohort had better functional and HRQoL scores than patients in our medical cohort.

At 18 months of follow-up, the CLEVER study[39] investigators reported that the differences in peak walking time between the exercise and endovascular groups were no longer significant but that both were significant compared with medical care. The results in quality-of-life outcomes were durable for the endovascular group and the exercise group, although, similar to our study, these results declined slightly after 6 months. These findings and those by McDermott and colleagues[25,40] suggest that exercise training, whether supervised[25] or home based,[40] improves functional status.

Using network meta-analytic techniques to compare the results of various RCTs of different treatments, Vemulapalli and colleagues[37] found that, compared with usual care, exercise training improved walking distance, while revascularization did not. All treatment modalities were associated with improved quality of life as measured by the physical function domain on the 36-Item Short Form Health Survey, but there were no differences between treatments. We, too, found that both

Figure 3. Quality of Life and Symptom Assessment



Shown are adjusted score estimates over time. Bars represent SEs. CSI indicates Claudication Symptom Instrument; EQ-5D, European Quality of Life–5 Dimension Questionnaire; and VascuQoL, Vascular Quality of Life Questionnaire.

the medical and revascularization cohorts reported improved function and quality of life, although our study did not allow us to disaggregate exercise from other components of medical management.

The strengths of this study include that it was performed in the community, following up participants with high fidelity through 1 year (88.2% [285 of 323] follow-up), with 246 in the medical cohort and 39 in the revascularization cohort, to track outcomes that are most meaningful to patients. A patient-reported, validated, functional status measure (WIQ) was the primary outcome and was used to determine study power. Twelve-month study follow-up provides valuable information compared with studies of shorter duration. Using an intent-to-treat approach, we believe that the effects observed for our comparisons between the cohorts are conservative. We also investigated the effects of missing data using multiple imputation methods. The effects observed under multiple imputation scenarios were consonant with the complete case results presented herein.

Limitations include that, despite intense screening and recruitment efforts, only a modest number of participants enrolled in the revascularization cohort. That our seasoned investigator team experienced such difficulty in enrolling patients into a well-designed and properly executed cohort study provides further evidence of this already recognized phenomenon. Response rates in cohort studies have dropped over the years, from 69% in the 1950s[41,42] to 24% in 1989 in the Nurses' Health Study.[43] Recently, to maintain targeted enrollment rates, the US National Children's Study[44] has required the addition of study sites and modification of sampling plans. Investigators who conducted the United Kingdom Cohort Study of Mobile Phone Use in Health (COSMOS)[45] outline 21st-century technology-enabled solutions to address these challenges. Given this limitation, our results are less precise and the power lower than for the prespecified effect sizes. Even so, there were significant differences in HRQoL outcomes between cohorts. Separately, participants undergoing revascularization were those with moderate to severe disease but of shorter duration, while more than one-third (38.8%) of those in the medical cohort were patients with mild disease. We are unable to determine the extent to which coding bias contributes to this difference because lifestyle-limiting claudication is the only widely accepted indication for revascularization at present. While these differences were accounted for in the analyses, they limit the generalizability of the findings to those with similar disease duration and levels of severity. Most participants were managed by vascular surgeons using medical interventions, and it is possible that including nonprocedural care provided by clinicians who are not proceduralists might have resulted in different findings. That patients in the medical cohort remained stable or improved slightly or over time suggests that these interventions were administered properly, despite our inability to assess adherence. Finally, the focus of this study was PROs. Because our method of follow-up data collection was limited to self-report, we were able to capture only a few clinical outcomes, including walking distance (through WIQ distance), any-cause readmissions, and death. More objective surrogate metrics, such as ankle brachial index or Doppler arterial flow, were not assessed.

Although our findings suggest that revascularization interventions may be a superior alternative to more conservative approaches, caution is warranted. These procedures are expensive, frequently require reintervention, and in the long run carry a substantial risk of worse outcomes in the patient. Furthermore, the lack of greater improvement in function, HRQoL, and symptoms in our medical cohort could have been due to the fact that our definition of a walking program, although prescribed by a physician, did not require supervision. Supervised exercise programs are not reimbursed and are rarely available in the community. We believe that a sound argument can be made for the development and reimbursement of supervised exercise programs, which the literature supports. Although this study shows that standard revascularization care is better than standard medical care in the community, it does not demonstrate that revascularization care is better than optimal medical care, for which we should continue to strive.

Conclusions

This comparative effectiveness research study of interventions for IC demonstrated significantly higher function (WIQ), better HRQoL (VascuQoL and EQ-5D), and fewer symptoms (CSI) for those in the revascularization cohort compared with the medical cohort. These results suggest that revascularization interventions for patients with moderate to severe IC represent a reasonable alternative to medical management, providing important information to inform treatment strategies in the community.

ARTICLE INFORMATION

Correction: This article was corrected on October 19, 2016, to fix the Figure 1 caption.

Accepted for Publication: May 10, 2016.

Published Online: August 17, 2016. doi:10.1001/jamasurg.2016.2024

Author Affiliations: Pharmaceutical Outcomes Research and Policy Program, University of Washington, Seattle (Devine, Alfonso-Cristancho, Patrick, Lavallee, Kessler, Flum); Surgical Outcomes Research Center, University of Washington, Seattle (Devine, Alfonso-Cristancho, Armstrong, Devlin, Symons, Lavallee, Flum); Department of Health Services, University of Washington, Seattle (Devine, Edwards, Patrick, Kessler, Flum); Department of Biomedical Informatics, University of Washington, Seattle (Devine); Centers for Comparative and Health Systems Effectiveness (CHASE) (CHASE Alliance), University of Washington, Seattle (Devine, Alfonso-Cristancho, Edwards, Patrick, Devlin, Lavallee, Kessler, Flum); Department of Biostatistics, University of Washington, Seattle (Yanez); School of Public Health, Oregon Health & Science University, Portland (Yanez); Seattle Quality of Life Group, University of Washington, Seattle (Edwards, Patrick); Department of Surgery, University of Washington, Seattle (Meissner); Providence Everett Medical Center, Everett, Washington (Derrick).

Author Contributions: Dr Devine had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Devine, Armstrong.
Critical revision of the manuscript for important intellectual content: All authors.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was funded by grant R01HS020025 from the Agency for Healthcare Research and Quality (Dr Flum, principal investigator).

Role of the Funder/Sponsor: The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Group Information: Members of the Comparative Effectiveness Research Translation Network (CERTAIN) Collaborative are as follows: Emily B. Devine, PhD, PharmD, MBA; Rafael Alfonso-Cristancho, MD, MSc, PhD; N. David Yanez, PhD; Todd C. Edwards, PhD; Donald L Patrick, PhD, MSPH; Cheryl A. L. Armstrong, RN, MPH; Allison Devlin, MS; Rebecca G. Symons, MPH; Mark H. Meissner, MD; Ellen L. T. Derrick, MD, MPH; Danielle C. Lavallee, PhD, PharmD; Larry G. Kessler, ScD; and David R. Flum, MD, MPH.

Additional Contributions: We acknowledge the participation of additional clinical investigators led by the late Alexander Clowes, MD (Department of Surgery, University of Washington, Seattle), and by Ellen Thomason, MD, MPH (Providence Everett Medical Center, Everett, Washington). Dr Clowes received compensation for his contributions. We appreciate the helpful comments of the 2 anonymous reviewers. The following individuals provided leadership for the acquisition of data at their respective study sites and did not receive compensation for their contributions: Riyad Karmy-Jones, MD (PeaceHealth Southwest Medical Center, Vancouver, Washington), Todd Kihara, MD (CHI Franciscan Health, Tacoma, Washington), Stephen Murray, MD (Providence Sacred Heart Medical Center, Spokane, Washington), Leonard Su, MD (Lake Washington Vascular, Seattle, Washington), and Felix Vladimir, MD (MultiCare Health System, Tacoma, Washington).

REFERENCES

1. McDermott MM. Lower extremity manifestations of peripheral artery disease: the pathophysiologic and functional implications of leg ischemia. *Circ Res*. 2015;116(9):1540-1550.

2. Ostchega Y, Paulose-Ram R, Dillon CF, Gu Q, Hughes JP. Prevalence of peripheral arterial disease and risk factors in persons aged 60 and older: data from the National Health and Nutrition Examination Survey 1999-2004. *J Am Geriatr Soc*. 2007;55(4):583-589.

3. Ouriel K. Peripheral arterial disease. *Lancet*. 2001;358(9289):1257-1264.

4. Cronin O, Morris DR, Walker PJ, Golledge J. The association of obesity with cardiovascular events in patients with peripheral artery disease. *Atherosclerosis*. 2013;228(2):316-323.

5. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004;110(6):738-743.

6. Agrawal K, Eberhardt RT. Contemporary medical management of peripheral arterial disease: a focus on risk reduction and symptom relief for intermittent claudication. *Cardiol Clin*. 2015;33(1):111-137.

7. Chang P, Nead KT, Olin JW, Myers J, Cooke JP, Leeper NJ. Effect of physical activity assessment on prognostication for peripheral artery disease and mortality. *Mayo Clin Proc*. 2015;90(3):339-345.

8. Willigendael EM, Teijink JA, Bartelink ML, Peters RJ, Büller HR, Prins MH. Smoking and the patency of lower extremity bypass grafts: a meta-analysis. *J Vasc Surg*. 2005;42(1):67-74.

9. Regensteiner JG, Ware JE Jr, McCarthy WJ, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with

intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. *J Am Geriatr Soc*. 2002;50(12):1939-1946.

10. Coppola G, Novo S. Statins and peripheral arterial disease: effects on claudication, disease progression, and prevention of cardiovascular events. *Arch Med Res*. 2007;38(5):479-488.

11. Rooke TW, Hirsch AT, Misra S, et al; American College of Cardiology Foundation Task Force; American Heart Association Task Force. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61(14):1555-1570.

12. Vogel TR, Dombrovskiy VY, Carson JL, Haser PB, Graham AM. Lower extremity angioplasty: impact of practitioner specialty and volume on practice patterns and healthcare resource utilization. *J Vasc Surg*. 2009;50(6):1320-1324.

13. Simons JP, Schanzer A, Nolan BW, et al; Vascular Study Group of New England. Outcomes and practice patterns in patients undergoing lower extremity bypass. *J Vasc Surg*. 2012;55(6):1629-1636.

14. Addington-Hall J, Kalra L. Who should measure quality of life? *BMJ*. 2001;322(7299):1417-1420.

15. Rumsfeld JS, Alexander KP, Goff DC Jr, et al; American Heart Association Council on Quality of Care and Outcomes Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Stroke Council. Cardiovascular health: the importance of measuring patient-reported health status: a scientific statement from the American Heart Association. *Circulation*. 2013;127(22):2233-2249.

16. Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med*. 2009;151(3):203-205.

17. Flum DR, Alfonso-Cristancho R, Devine EB, et al; CERTAIN Collaborative. Implementation of a "real-world" learning health care system: Washington State's Comparative Effectiveness Research Translation Network (CERTAIN). *Surgery*. 2014;155(5):860-866.

18. Devine EB, Alfonso-Cristancho R, Devlin A, et al; CERTAIN Collaborative. A model for incorporating patient and stakeholder voices in a learning health care network: Washington State's Comparative Effectiveness Research Translation Network. *J Clin Epidemiol*. 2013;66(8)(suppl):S122-S129.

19. Regensteiner JG, Steiner JF, Panzer RJ, Hiatt WR. Evaluation of walking impairment by questionnaire in patients with peripheral arterial disease [abstract]. *Clin Res*. 1990;38(2):A515.

20. Coyne KS, Margolis MK, Gilchrist KA, et al. Evaluating effects of method of administration on Walking Impairment Questionnaire. *J Vasc Surg*. 2003;38(2):296-304.

21. Morgan MB, Crayford T, Murrin B, Fraser SC. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. *J Vasc Surg*. 2001;33(4):679-687.

22. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37(1):53-72.

23. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.

24. Jain A, Liu K, Ferrucci L, et al. The Walking Impairment Questionnaire stair-climbing score predicts mortality in men and women with peripheral arterial disease. *J Vasc Surg*. 2012;55(6):1662-1673.e2. doi:10.1016/j.jvs.2011.12.010.

25. McDermott MM, Ades P, Guralnik JM, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. *JAMA*. 2009;301(2):165-174.

26. Nicolaï SP, Kruidenier LM, Rouwet EV, Graffius K, Prins MH, Teijink JA. The Walking Impairment Questionnaire: an effective tool to assess the effect of treatment in patients with intermittent claudication. *J Vasc Surg*. 2009;50(1):89-94.

27. de Vries M, Ouwendijk R, Kessels AG, et al. Comparison of generic and disease-specific questionnaires for the assessment of quality of life in patients with peripheral arterial disease. *J Vasc Surg*. 2005;41(2):261-268.

28. Mehta T, Venkata Subramaniam A, Chetter I, McCollum P. Assessing the validity and responsiveness of disease-specific quality of life instruments in intermittent claudication. *Eur J Vasc Endovasc Surg*. 2006;31(1):46-52.

29. Nordanstig J, Wann-Hansson C, Karlsson J, Lundström M, Pettersson M, Morgan MB. Vascular Quality of Life Questionnaire–6 facilitates health-related quality of life assessment in peripheral arterial disease. *J Vasc Surg*. 2014;59(3):700-707.

30. Conijn AP, Jonkers W, Rouwet EV, Vahl AC, Reekers JA, Koelemay MJ. Introducing the concept of the minimally important difference to determine a clinical relevant change on patient-reported outcome measures in patients with intermittent claudication. *Cardiovasc Intervent Radiol*. 2015;38(5):1112-1118.

31. Dyer MT, Goldsmith KA, Sharples LS, Buxton MJ. A review of health utilities using the EQ-5D in studies of cardiovascular disease. *Health Qual Life Outcomes*. 2010;8:13.

32. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care*. 2005;43(3):203-220.

33. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res*. 2005;14(6):1523-1532.

34. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26(3):517-538.

35. Imparato AM, Kim GE, Davidson T, Crowley JG. Intermittent claudication: its natural course. *Surgery*. 1975;78(6):795-799.

36. Lane R, Ellis B, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2014;(7):CD000990.

37. Vemulapalli S, Dolor RJ, Hasselblad V, et al. Comparative effectiveness of medical therapy, supervised exercise, and revascularization for patients with intermittent claudication: a network meta-analysis. *Clin Cardiol*. 2015;38(6):378-386.

38. Murphy TP, Cutlip DE, Regensteiner JG, et al; CLEVER Study Investigators. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study. *Circulation*. 2012;125(1):130-139.

39. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. *J Am Coll Cardiol*. 2015;65(10):999-1009.

40. McDermott MM, Liu K, Guralnik JM, et al. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. *JAMA*. 2013;310(1):57-65.

41. Doll R, Hill AB. The mortality of doctors in relation to their smoking habits: a preliminary report: 1954. *BMJ*. 2004;328(7455):1529-1533.

42. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. *Ann N Y Acad Sci*. 1963;107:539-556.

43. Nurses' Health Study. History. http://www.nurseshealthstudy.org/about-nhs/history. Published 2014. Accessed May 3, 2016.

44. Duncan GJ, Kirkendall NJ, Citro CF, eds. *The National Children's Study 2014: An Assessment*. Washington, DC: National Academies Press; June 2014.

45. Toledano MB, Smith RB, Brook JP, Douglass M, Elliott P. How to establish and follow up a large prospective cohort study in the 21st century: lessons from UK COSMOS. *PLoS One*. 2015;10(7):e0131521. doi:10.1371/journal.pone.0131521.