Eur J Vasc Endovasc Surg (2015) 50, 213–222

One Year Health Status Benefits Following Treatment for New Onset or Exacerbation of Peripheral Arterial Disease Symptoms: The Importance of Patients' Baseline Health Status☆

M. van Zitteren [a,b], J. Denollet [a], J.M. Heyligers [b], J.W.M. Elshof [b], M.J. Nooren [b], D.H. Burger [b], W.M. de Fijter [c], P.W. Vriens [b], K.G. Smolderen [a,d,*]

[a] Center of Research on Psychology in Somatic Diseases, Tilburg University, PO Box 90153, 5000 LE, Tilburg, The Netherlands
[b] St. Elisabeth Hospital, Department of Vascular Surgery, PO Box 90151, 5000 LC, Tilburg, The Netherlands
[c] TweeSteden Hospital, Department of Vascular Surgery, Tilburg, The Netherlands
[d] UMKC School of Medicine; Biomedical & Health Informatics, 1000 E24th Street, 5th Floor, Kansas City, MO, 64108, USA

WHAT THIS PAPER ADDS

This study evaluated 1 year changes in health status in patients with new onset or an exacerbation of peripheral arterial disease (PAD) symptoms. Thirty-nine per cent were referred for invasive treatment. Invasive treatment was offered across the whole spectrum of pre-procedural health status scores. Patients within the lowest quartile of pre-procedural health status scores had the greatest improvements, whereas those in highest quartiles did not improve substantially. One year invasive treatment and lower pre-procedural health status scores were independent associates for greater 1 year health status gains. This information may help to facilitate the discussion between patients and PAD specialists about which treatments should be considered for the patients' PAD.

Objective/Background: Limited information is available on expected health status gains following invasive treatment in peripheral arterial disease (PAD). One year health status outcomes following invasive treatment for PAD were compared, and whether pre-procedural health status was indicative of 1 year health status gains was evaluated.

Methods: Pre-procedural and 1 year health status (Short Form-12, Physical Component Score [PCS]) was prospectively assessed in a cohort of 474 patients, enrolled from 2 Dutch vascular clinics (March 2006–August 2011), with new or exacerbation of PAD symptoms. One year treatment strategy (invasive vs. non-invasive) and clinical information was abstracted. Quartiles of baseline health status scores and mean 1 year health status change scores were compared by invasive treatment for PAD. The numbers needed to treat (NNT) to obtain clinically relevant changes in 1 year health status were calculated. A propensity weight adjusted linear regression analysis was constructed to predict 1 year PCS scores.

Results: Invasive treatment was performed in 39% of patients. Patients with baseline health status scores in the lowest quartile undergoing invasive treatment had the greatest improvement (mean invasive 11.3 ± 10.3 vs. mean non-invasive 5.3 ± 8.5 [$p = .001$, NNT = 3]), whereas those in the highest quartile improved less (.8 ± 6.3 vs. −3.0 ± 8.2 [$p = .025$, NNT = 90]). Undergoing invasive treatment ($p < .0001$) and lower baseline health status scores ($p < .0001$) were independently associated with greater 1 year health status gains.

Conclusion: Substantial improvements were found in patients presenting with lower pre-procedural health status scores, whereas patients with higher starting health status levels had less to gain by an invasive strategy.

Article history: Received 26 September 2014, Accepted 6 April 2015, Available online 30 May 2015

Keywords: Atherosclerosis, Peripheral vascular disease, Revascularization

INTRODUCTION

The goals of treatment in symptomatic lower extremity peripheral arterial disease (PAD; Fontaine 2, mild to moderate symptoms of claudication) are to alleviate patients' symptoms and to improve their health status.[1–5] Despite these objectives, patients' health status may not always be

☆ The abstract was presented at the Quality of Care and Outcome Research (QCOR) in Cardiovascular Disease and Stroke Scientific Sessions of the American Heart Association (AHA), Atlanta, GA, USA, 9–11 May 2012, and at Best of AHA Specialty Conferences at Scientific Sessions 2012, Los Angeles, CA, USA, 3–7 November 2012.

* Corresponding author.
E-mail address: smolderenk@umkc.edu (K.G. Smolderen).

http://dx.doi.org/10.1016/j.ejvs.2015.04.003

a decisive factor in referring patients for invasive treatment.[6] In addition, in large clinical trials, outcomes of interest were often focused on hemodynamic success rates,[7–9] as opposed to clinically meaningful improvements in patients' health status.

It is also unclear whether invasive treatment is being applied in patients for whom the greatest health status benefit can be expected. One of the factors that may predict health status outcomes following invasive treatment is pre-procedural health status. In coronary disease, patients with lower health status scores undergoing percutaneous coronary intervention had the most to gain from this treatment when comparing their health status improvements with those having high pre-procedural health status scores.[10] This has never been evaluated for invasive treatments. It is also unknown whether invasive treatments are offered to patients with PAD across the whole spectrum of pre-procedural health status scores in daily practice.

Given these gaps in knowledge and the rapid increase in use of endovascular procedures and its associated costs,[11–13] it seems desirable to quantify and predict expected health status benefits by treatment strategy based on pre-procedural, measurable characteristics such as patients' health status. This study documented invasive treatment rates as a function of patients' pre-procedural health status, and quantifies the magnitude of 1 year benefits in patients' self reported health status across the range of pre-procedural health status scores.

METHODS

Study population and design

In this prospective observational study, 474 consecutive patients with new onset symptomatic lower extremity PAD or worsening of existing exertional PAD symptoms requiring new clinical work (Fontaine 2, mild to moderate symptoms of claudication) were enrolled in the period March 2006—August 2011 from two vascular surgery outpatient clinics (St. Elisabeth Hospital and TweeSteden Hospital, Tilburg, the Netherlands) (Appendix I). Patients were eligible for inclusion if they presented with exertional leg symptoms and if their resting ankle brachial index (ABI) was abnormal ($\leq$0.90) or decreased $\geq$15% from the resting ABI following a distance limited treadmill test. Exclusion criteria were a non-compressible ABI ($\geq$1.30), critical limb ischemia, severe cognitive impairment or severe somatic or psychiatric comorbidities, insufficient knowledge of the Dutch language, or other reasons (e.g., participation in another study, treatment started before study inclusion). Patients were additionally excluded if: (i) patients had >25% missing values on their health status assessments; (ii) patients died during the first year of follow up; or if (iii) no pre-procedural duplex ultrasound examination was available in the patients' medical charts 3 months prior to or after inclusion.

All patients underwent a vascular diagnostic work up on enrollment, including a clinical evaluation by their treating vascular surgeon (Appendix II).

The local ethics committee of each participating institution approved the study, which was designed in line with the Declaration of Helsinki. All participants provided written informed consent. Study participation did not influence the type of treatment patients received because the study was observational in nature.

Measures

Assessment of health status. The Dutch version of the Short Form 12 (SF-12), a generic health status instrument,[2,14] was used to assess patients' self reported pre-procedural (i.e., prior to treatment), and 1 year physical and mental health status (Physical Component Summary [PCS] score and Mental Component Summary (MCS) score). PCS and MCS scores (range 0—100, mean $\pm$ SD score 50 $\pm$ 10) were standardized against the Dutch general population norms.[15] Higher scores were indicative of better physical and mental functioning.[15] Based on ranges of scores to expect following invasive treatment in PAD in similar populations,[4,16–18] clinically relevant changes based on a 1 year change score (1 year health status score minus pre-procedural health status score) falling within the range of 0.5 SD ($\geq$5 points) and 1.0 SD ($\geq$10 points) were calculated. All treating vascular specialists were blinded to the initial SF-12 score, as this could have had the potential to influence the decision making process.

One year treatment strategies. A variety of treatment strategies were available at both enrolling centers, including non-invasive strategies: a formal supervised exercise therapy program supported by a regional network of certified physiotherapists; smoking cessation counseling; and optimal medical care (e.g., aspirin, anticoagulants, and statins).[6] Treatments were categorized for analytical purposes: if no hospital admissions for vascular reasons were documented within the first year following diagnosis, patients were considered to have had *non-invasive treatment* options only. Patients were assigned to the *invasive treatment* category if any invasive lower extremity procedure was documented in their medical records.[6] Patients received care for their PAD at the vascular surgery department. In any case, medical management of cardiovascular risk factors was initiated or sustained for all patients, and exercise therapy was also made available, regardless of whether patients were referred for invasive therapy for their PAD symptoms.

Disease severity. A handheld Doppler instrument (Imexlab 9000; Imex Medical Systems Inc., Golden, CO, USA) was used by trained vascular technicians to confirm the PAD diagnosis by measuring patients' resting and post-exercise ABI following a distance limited treadmill test.

Duplex ultrasound examination protocol. Based on his/her clinical evaluation during the diagnostic work up, a duplex ultrasound examination of the lower extremities was ordered by the treating vascular surgeon. Trained vascular technicians performed the ultrasounds with the Toshiba

Xario ultrasound system (Xario XG; Toshiba Medical Systems Europe, Zoetermeer, the Netherlands) from which lesion information was derived (i.e., anatomical location, and the number and severity of lesions). Lesion severity was measured by the peak systolic velocity (PSV [cm/s]) ratio, where a PSV ratio $\geq$2.5, or total occlusions, were considered significant. Lesions were scored as proximal or distal lesions only, having both proximal and distal lesions, or having non-significant lesions. A detailed description of the duplex ultrasound protocol has been published elsewhere.[19]

Clinical risk factors. Information on clinical risk factors was abstracted from patients' medical records and included cardiac history, cerebrovascular history, current smoking, diabetes mellitus, dyslipidemia, hypertension, body mass index (BMI; kg/m^2), chronic obstructive pulmonary disease (COPD), renal dysfunction, back pain, and knee/hip osteoarthritis. In addition, patients' medication use following their vascular diagnostic evaluation was also abstracted.

Socio-demographic and psychological factors. Patients' age and sex was documented through medical chart abstraction. Information on socio-demographic factors was derived from self report questionnaires that patients completed on enrollment, and included marital status (no partner vs. partner), educational background ($<$high school vs. $\geq$high school education), and work status (non-active vs. active work status). The presence of clinically relevant depression and anxiety was assessed by the Hospital Anxiety and Depression Scale using cut off scores $\geq$8 on both the anxiety and depression subscale.[20]

Statistical analysis

Patient baseline characteristics, as well as 1 year PCS change scores, were described for the total population and compared by quartiles of pre-procedural PCS scores. Invasive treatment rates were compared by quartiles of pre-procedural PCS and MCS scores to gain additional insights into differences in mental and physical health status. The chi-square test, ANOVA, and the Kruskal–Wallis test were used for descriptive purposes, as appropriate.

To quantify the magnitude of the health status change effects at 1 year following treatment referral, effect sizes (Cohen's D) were calculated for patients who underwent invasive vs. non-invasive treatment by quartiles of their pre-procedural PCS scores. Similarly, the number needed to treat (NNT) to obtain a clinically relevant improvement in physical health status falling within the range of 0.5 SD ($\geq$5 points) and 1.0 SD ($\geq$10 points) was calculated for quartiles of pre-procedural PCS scores. The NNT is defined as the number of persons needed to treat to prevent one outcome, and is calculated by the inverse of the absolute risk reduction.[21,22]

Since the study was observational in nature, propensity weights were calculated for all patients using all baseline characteristics for the propensity to undergo invasive versus non-invasive treatment. A propensity adjusted linear regression model was constructed to examine the association between treatment strategy (invasive vs. non-invasive), pre-procedural health status, and 1 year PCS change scores. The model was sequentially built by the following steps: (i) treatment strategy (invasive vs. non-invasive), pre-procedural PCS scores (to control for regression towards the mean), and the interaction between treatment strategy and pre-procedural PCS scores; (ii) demographics (age, sex), hospital site, marital status, educational background; (iii) anatomical lesion location, resting ABI; (iv) cardiac history, cerebrovascular history, current smoking, diabetes mellitus, BMI, renal dysfunction, COPD, back pain, and hip/knee osteoarthritis; and (v) depression. Finally, the explained variance (R^2) was calculated for all individual variables included in the model.

Missing SF-12 items were handled by multiple imputation (mean of five iterations) if $\geq$75% of all items were completed. Missing items were assumed to be missing at random. A total of 16 patients had $<$25% missing values at both baseline and 1 year follow up. Compared with the other 458 patients, these 16 were slightly older ($p = .005$, Cohen's D = .8) and more likely to use anticoagulants ($p = .040$, Cramér's V = .099). They were similar in terms of all other characteristics. A sensitivity analysis was performed based on complete case analyses.

PASW Statistics 19.0 for Windows (SPSS, IBM, Armonk, NY, USA) was used to perform all analyses. All tests were two-tailed and statistical significance was considered as a p value $<$.05.

RESULTS

Baseline characteristics

Table 1 presents patient characteristics for the total sample ($n = 474$), stratified by quartiles of pre-procedural health status scores. The mean age of the cohort was 65 years and 67% were male.

Patients with lower health status scores were more likely to have a lower educational status, a history of cardiovascular disease, other comorbidities or risk factors, and to receive cardioprotective medications and psychopharmaca than patients having higher health status scores. While the ABI did not differ across health status categories, patients with lower health status scores were more likely to have a shorter pain free walking distance, to have undergone a prior lower extremity surgical intervention, and to present with a proximal or non-significant lesion than those with higher health status scores. Also, the presence of psychological comorbidities increased along with decreasing health status scores.

Physical health status scores by the receipt of 1 year invasive treatment

A total of 183 (39%) patients underwent invasive treatment $\leq$1 year following diagnosis, ranging from 41% to 46% in the lowest three physical health status quartiles to 24% in the highest ($p = .001$). In line with the comparisons for the

Table 1. Baseline characteristics of the total sample and stratified by quartiles of baseline health status scores (physical component scores).[a]

	Total sample ($n = 474$)	Quartile 1 ($n = 119$)[b]	Quartile 2 ($n = 118$)[c]	Quartile 3 ($n = 119$)[d]	Quartile 4 (n = 118)[e]	*p*
Demographics						
Age, y (mean ± SD)	65.0 ± 9.4	63.8 ± 11.1	65.3 ± 9.3	65.1 ± 8.5	65.8 ± 8.6	.40
Male sex	315 (66.5)	69 (58.0)	76 (64.4)	82 (68.9)	88 (74.6)	.06
Socioeconomic factors						
No partner	112 (23.9)	33 (27.7)	29 (24.8)	26 (22.4)	24 (20.5)	.61
Less than high school education	**116 (24.9)**	**39 (33.1)**	**33 (28.9)**	**23 (20.0)**	**21 (17.8)**	**.023**
Non-active work status	335 (73.6)	88 (77.2)	84 (73.7)	87 (77.6)	76 (64.5)	.07
Cardiovascular history						
Angina pectoris	65 (13.7)	16 (13.5)	19 (16.1)	17 (14.3)	13 (11.0)	.74
Myocardial infarction	**87 (18.4)**	**22 (18.5)**	**28 (23.7)**	**25 (21.0)**	**12 (10.2)**	**.043**
CABG	58 (12.2)	13 (10.9)	21 (17.8)	16 (13.5)	8 (6.8)	.07
PCI	46 (9.7)	14 (11.8)	15 (12.7)	8 (6.7)	9 (7.6)	.25
Congestive heart failure	21 (4.4)	8 (6.7)	8 (6.8)	3 (2.5)	2 (1.7)	.08
Stroke	**39 (8.2)**	**10 (8.4)**	**15 (12.7)**	**11 (9.2)**	**3 (2.5)**	**.043**
TIA	41 (8.7)	9 (7.6)	14 (11.9)	10 (8.4)	8 (6.8)	.55
Clinical factors						
Smoking	220 (46.4)	59 (49.6)	48 (40.7)	50 (42.0)	63 (53.4)	.13
Diabetes mellitus	**108 (22.8)**	**33 (27.7)**	**35 (29.7)**	**27 (22.7)**	**13 (11.0)**	**.003**
Hypercholesterolemia	327 (69.0)	84 (70.6)	87 (73.7)	80 (67.2)	76 (64.4)	.48
Hypertension	**285 (60.1)**	**67 (56.3)**	**77 (65.3)**	**82 (68.9)**	**59 (50.0)**	**.016**
BMI (mean ± SD)	**26.8 (4.7)**	**27.9 (6.6)**	**26.5 (4.1)**	**27.1 (4.0)**	**25.9 (3.3)**	**.011**
COPD	**78 (16.5)**	**29 (24.4)**	**26 (22.0)**	**14 (11.8)**	**9 (7.6)**	**< .001**
Renal dysfunction	44 (9.3)	12 (10.1)	14 (11.9)	12 (10.1)	6 (5.1)	.35
Back pain	**69 (14.6)**	**35 (29.4)**	**15 (12.7)**	**11 (9.2)**	**8 (6.8)**	**<.0001**
Hip or knee osteoarthritis	98 (20.7)	33 (27.7)	26 (22.0)	19 (16.0)	20 (17.0)	.10
Vascular laboratory assessment						
PFWD, m (median ± SD)	**80.0 ± 123.9**	**70.0 ± 67.1**	**80.0 ± 120.0**	**80.0 ± 136.9**	**100.0 ± 147.6**	**< .0001**
Resting ABI (mean ± SD)[f]	65.9 ± 16.6	63.2 ± 18.2	66.7 ± 17.7	68.1 ± 14.6	65.8 ± 15.2	.13
Fontaine II class						
Fontaine IIB ≤200 m	411 (86.8)	114 (96.6)	102 (87.2)	102 (87.9)	93 (79.6)	.06
Fontaine IIA >200 m	57 (12.2)	4 (3.4)	15 (12.8)	14 (12.1)	24 (20.4)	
Prior lower extremity revascularization						
Endovascular	60 (12.7)	23 (19.3)	13 (11.0)	14 (11.8)	10 (8.5)	.07
Surgery	**33 (7.0)**	**17 (14.3)**	**8 (6.8)**	**5 (4.2)**	**3 (2.5)**	**.002**
Anatomical lesion location						**.021**
Proximal	**129 (28.5)**	**34 (31.8)**	**36 (31.9)**	**34 (29.1)**	**25 (21.7)**	
Distal	**234 (51.8)**	**46 (43.0)**	**53 (46.9)**	**60 (51.3)**	**75 (65.2)**	
Proximal and distal,	**44 (9.7)**	**9 (8.4)**	**11 (9.7)**	**13 (11.1)**	**11 (9.6)**	
Non-significant	**45 (10.0)**	**18 (16.8)**	**13 (11.5)**	**10 (8.6)**	**4 (3.4)**	
Medication use						
Aspirin	368 (77.6)	90 (75.6)	93 (78.8)	93 (78.2)	92 (78.0)	.96
Anticoagulants	**78 (16.5)**	**25 (21.0)**	**27 (22.9)**	**14 (11.8)**	**12 (10.2)**	**.013**
Statins	391 (82.5)	98 (82.4)	102 (86.4)	101 (84.9)	90 (76.3)	.20
Beta blocker	205 (43.2)	49 (41.2)	62 (52.5)	53 (44.5)	41 (34.7)	.050
Diuretics	**113 (23.8)**	**35 (29.4)**	**32 (27.1)**	**30 (25.2)**	**16 (13.6)**	**.025**
ACE inhibitor	157 (33.1)	45 (37.8)	44 (37.3)	39 (32.8)	29 (24.6)	.11
Calcium antagonist	**102 (21.5)**	**25 (21.0)**	**26 (22.0)**	**35 (29.4)**	**16 (13.6)**	**.024**
Nitroglycerine	**42 (8.9)**	**16 (13.5)**	**12 (10.2)**	**10 (8.4)**	**4 (3.4)**	**.050**
Digoxin	9 (1.9)	3 (2.5)	3 (2.5)	3 (2.5)	0 (0.0)	.34
Antiarrhythmics	12 (2.5)	5 (4.2)	3 (2.5)	3 (2.5)	1 (0.9)	.44
Antidepressants	**26 (5.5)**	**15 (12.6)**	**4 (3.4)**	**4 (3.4)**	**3 (2.5)**	**.001**
Anxiolytics	19 (4.0)	8 (6.7)	7 (5.9)	2 (1.7)	2 (1.7)	.10
Hypnotics	**22 (4.6)**	**10 (8.4)**	**7 (5.9)**	**4 (3.4)**	**1 (0.9)**	**.035**

Table 1-*continued*

	Total sample (n = 474)	Quartile 1 (n = 119)[b]	Quartile 2 (n = 118)[c]	Quartile 3 (n = 119)[d]	Quartile 4 (n = 118)[e]	p
Psychological factors						
Depression	**131 (27.9)**	**62 (52.1)**	**36 (30.8)**	**25 (21.6)**	**8 (6.8)**	**< .0001**
Anxiety	**109 (23.2)**	**45 (37.8)**	**29 (24.8)**	**30 (25.9)**	**5 (4.2)**	**< .0001**

Note. Data are given as *n* (%) unless otherwise indicated. Values in bold indicate statistical significance. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; PFWD = pain free walking distance; ABI = ankle brachial index; ACE = angiotensin converting enzyme inhibitor.

[a] Calculated column percentages for patient characteristics may deviate in case different denominators (owing to missingness) were used.

[b] Quartile 1 = Physical Component Summary (PCS) 12 of ≤31.5.

[c] Quartile 2 = PCS 12 of 31.6–38.5.

[d] Quartile 3 = PCS 12 of 38.6–46.8.

[e] Quartile 4 = PCS 12 of ≥46.9.

[f] Lowest ABI measured.

physical health status scores, a similar trend for quartiles of mental health status was observed as invasive treatment rates ranged from 37% to 44% in the lowest three mental health status quartiles to 34% in the highest, but failed to reach statistical significance ($p = .43$). When considering all patients' 1 year health status change scores by pre-procedural health status scores, a negative correlation between pre-procedural health status scores and change scores was observed for patients receiving both invasive ($r = -.38$, $p < .0001$) and non-invasive treatment ($r = -.39$; $p < .0001$) (Figs. 1 and 2), suggesting that lower pre-procedural health status scores were associated with improvements in patients' health status at 1 year follow up.

When categorizing patients by quartiles of their pre-procedural health status scores, patients in the lowest quartile undergoing invasive treatment had the greatest health status improvement (change scores ranging from 5.3 for non-invasive treatment to 11.3 for invasive treatment), whereas those in the highest quartile only improved minimally (change scores ranging from −3.0 for non-invasive treatment to 0.8 for invasive treatment) (Fig. 2).

Patients with pre-procedural health status scores in the lowest quartile who were treated invasively obtained larger health status benefits than patients who did not receive invasive treatment (mean ± SD PCS score for invasive treatment 11.3 ± 10.3 vs. non-invasive treatment 5.3 ± 8.5 [$p = .001$, Cohen's D = .5]; NNT = 3 to obtain 0.5 SD improvement, NNT = 3 to obtain 1 SD improvement). Patients with pre-procedural health status scores in the highest quartile had the least benefit when treated invasively (mean ± SD PCS score for invasive treatment 0.8 ± 6.3 vs. non-invasive treatment −3.0 ± 8.2 [$p = .025$, Cohen's D = .4]; NNT = 5 to obtain 0.5 SD improvement,

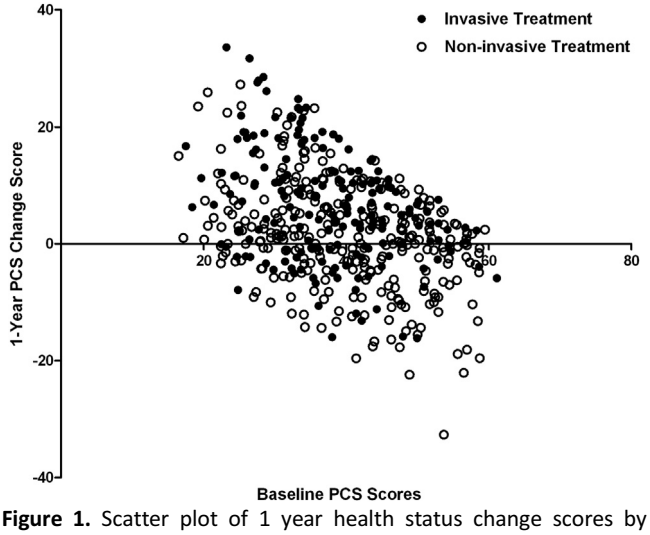


Figure 1. Scatter plot of 1 year health status change scores by baseline health status scores. All change scores of individual patients included in the analyses are presented as a function of the receipt of invasive (black) versus non-invasive (white) treatment. *Note.* PCS = Physical Component Summary score.

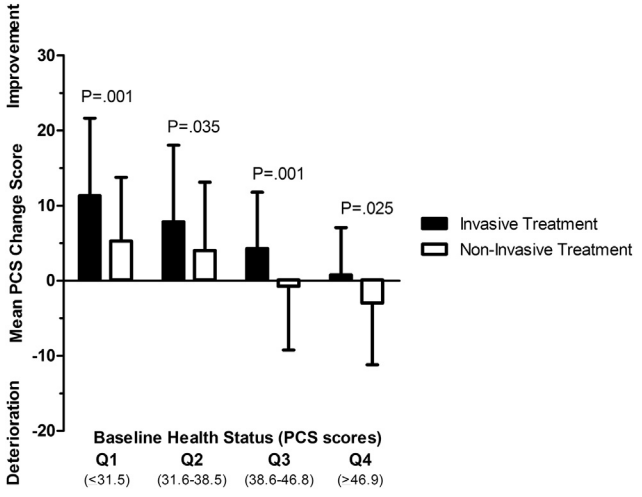


Figure 2. Mean ± SD changes in 1 year health status scores for patients that received invasive vs. non-invasive treatment, stratified by quartile categories of baseline health status scores. *Note.* Bars represent mean Physical Component Summary (PCS) change scores and SD for patients undergoing invasive versus non-invasive treatment. Categories represent baseline quartiles of physical health status scores for invasive versus non-invasive treatment. Q1 = lowest quartile; Q4 = highest quartile.

Table 2. Number needed to treat for 1 year clinically relevant health status improvement (≥5 or ≥ 10 points) for quartiles of patients' baseline health status scores, stratified by invasive versus non-invasive treatment.

	Improvement			
	≥5 points	NNT	≥10 points	NNT
Quartile 1		3		3
Invasive treatment	34/48 (71)		27/48 (56)	
Non-invasive treatment	28/71 (39)		17/71 (24)	
Quartile 2		11		9
Invasive treatment	29/52 (56)		21/52 (40)	
Non-invasive treatment	31/66 (47)		20/66 (30)	
Quartile 3		4		7
Invasive treatment	28/55 (51)		15/55 (27)	
Non-invasive treatment	17/64 (27)		9/64 (14)	
Quartile 4		5		90
Invasive treatment	8/28 (29)		0/28 (0)	
Non-invasive treatment	10/90 (11)		1/90 (1)	

Note. Data are given as *n*/total *n* (%). NNT = number needed to treat to obtain ≥5 points (0.5 SD) or ≥10 points (1.0 SD) change in 1 year Physical Component Summary score.

NNT = 90 to obtain 1 SD improvement). Similarly, for the intermediate quartiles, higher proportions of patients obtaining clinical benefit from invasive treatment were observed among those who had lower pre-procedural health status scores (Fig. 2; Table 2).

Determinants of 1 year change in self reported physical health status

Invasive treatment within 1 year of new onset or an exacerbation of PAD symptoms was independently associated with greater improvements in 1 year physical health status (unadjusted B = 5.49 [$p < .0001$]; fully adjusted B = 4.44 [$p < .0001$]) (see Table 3 for stepwise results). Other correlates of greater 1 year health status improvements were lower pre-procedural health status scores, a younger age, having a lower ABI, and the absence of depression. The variables in the fully adjusted model explained 32% of the total variance, with pre-procedural health status explaining the most ($R^2 = 0.22$). The interaction between 1 year treatment strategy and pre-procedural PCS scores was not included in the model because it failed to reach significance ($p = .44$). See Appendix III for full model results. Results were essentially replicated when repeating analyses based on complete cases (results available from the authors).

DISCUSSION

This study is the first to prospectively describe 1 year health status changes following a PAD diagnosis in a cohort of newly diagnosed patients (Fontaine 2, mild to moderate symptoms of claudication) in two PAD specialty clinics that had the infrastructure in place to offer all standard treatment modalities for PAD. While patients with lower pre-procedural health status scores presented with more comorbidities, the 1 year health status improvements following invasive treatment were among the highest

Table 3. The unadjusted and adjusted linear regression model results for 1 year change in physical health status (B) and 95% confidence intervals (CIs) are presented.

	B	95% CI	*p*
Unadjusted			
Invasive treatment	5.49	3.74−7.25	<.0001
Adjusted 1[a]			
Invasive treatment	4.59	2.66−6.51	<.0001
Baseline PCS 12 score	−0.36	−0.45 to 0.27	<.0001
Adjusted 2[b]			
Invasive treatment	4.57	2.67−6.47	<.0001
Baseline PCS 12 score	−0.36	−0.45 to 0.27	<.0001
Adjusted 3[c]			
Invasive treatment	4.59	2.71−6.48	<.0001
Baseline PCS 12 score	−0.35	−0.44 to −0.36	<.0001
Adjusted 4[d]			
Invasive treatment	4.59	2.71−6.48	<.0001
Baseline PCS 12 score	−0.40	−0.50 to −0.30	<.0001
Adjusted 5[e]			
Invasive treatment	4.44	2.59−6.29	<.0001
Baseline PCS 12 score	−0.47	−0.55 to −0.34	<.0001

Note. The following variables were sequentially included in the adjusted models.

[a] Adjusted model 1 = 1 year treatment strategy (invasive vs. non-invasive) and baseline Physical Component Summary (PCS) scores.

[b] adjusted model 2 = model 1 and demographics (age, sex), hospital site, marital status (partner vs. no partner), educational background (≥high school education vs. < high school education).

[c] adjusted model 3 = model 2 and anatomical lesion location (proximal lesions only, distal lesions only, both proximal and distal lesion, or non-significant lesions), 1 year change in resting ankle brachial index (ABI; 1 year ABI at rest minus baseline ABI at rest).

[d] adjusted model 4 = model 3 and cardiac history, cerebrovascular history, current smoking, diabetes mellitus, body mass index, renal failure, chronic obstructive pulmonary disease, back pain, and hip or knee osteoarthritis.

[e] adjusted model 5 = model 4 and depression. Full model results are presented in Appendix III.

compared with patients having higher pre-procedural health status scores. In line with the comparisons for the physical health status scores, a similar trend in mental health status score comparisons by invasive treatment rates was observed; however, these observations were not significantly different. Putting these numbers into perspective, it was calculated that only three patients needed to be treated invasively in the group with low pre-procedural health status scores in order for one patient to obtain a significant health status benefit compared with five patients among those with high pre-procedural scores. This number increased to 90 patients when varying the threshold for a minimal clinically important difference from 0.5 SD to 1 SD, a threshold that approximates the benefit magnitude observed in the latest CLEVER (claudication: exercise versus endoluminal revascularization results) study.[2] Undergoing invasive treatment and pre-procedural health status scores were important independent correlates of 1 year health status changes, even while adjusting for important confounders. The results were based on observational data,

and, as such, further replication of the expected health status change effects as a function of pre-procedural health status should occur in the context of controlled clinical trials evaluating health status benefits following different PAD treatments.[2]

Although smaller observational studies confirmed that invasive treatment in PAD is associated with improvements in health status changes,[4,23,24] none have described health status changes as a function of pre-procedural health status. Having a cohort with newly diagnosed PAD that had access to non-invasive and invasive options is unique, as the few studies quantifying health status after revascularization have been done in procedural cohorts, where patients were already triaged for invasive treatment,[25–28] and no information on pre-procedural health status had been analyzed.[27] In addition, as prior studies quantifying invasive treatment benefits mainly focused on hemodynamic success rates,[7–9] there is a need to evaluate outcomes that are more meaningful to the individual patient. This is underscored by current guidelines stating that the main PAD treatment goals are to relieve symptoms and to improve health status.[1,3,29] The present study specifically focuses on this goal and provides useful information on expected health status gains, which will help both patients and clinicians make informed treatment decisions. A longer term goal for the treatment decision making process in PAD would be to have information about patients' pre-procedural and expected health status outcomes following different treatment options as assessed by a validated (disease specific) health status instrument, while also discussing potential treatment risks, which could help inform both the patient and the provider in making a shared, informed, and evidence based treatment decision.

Prior single center observational studies found an association between undergoing invasive PAD treatment and improvements in self reported health status.[4,23,25–28] However, they did not use pre-procedural patient information. Providing such information to patients and clinicians would be tremendously helpful; currently, they can rely only on little pre-procedural information in deciding which treatment would most valuable to the individual, such as lesion characteristics that may be more amenable to invasive treatment.[1,3]

After all, all patients undergoing lower extremity endovascular interventions are exposed to procedure related risks and complications (4–8%),[30–32] while serious events for non-invasive options have rarely been documented. Benefits can equally be present (improvements in walking abilities, muscle strength/endurance, and cardiac function).[1,33–35] A free flow of information on risks and benefits, as well as patients' preferences, is essential in discussing treatment options. These efforts will help to improve decision quality in PAD and hopefully design appropriate criteria for invasive treatment.

Future research is needed to document individual components of decision quality in PAD, including a better evidence base on expected risks and benefits for different therapies and patient preferences. "Parallel", an agreed upon classification system for diagnostic information, is a prerequisite to standardize the clinical decision process. This has already been done and is ongoing in coronary artery disease,[36] but is lacking in PAD. Such efforts will help reduce unwanted treatment variations.

The following limitations should be noted when interpreting the results. The generic SF-12 and not a PAD specific health status assessment tool was used to assess patients' self reported health status. Next, patients were recruited from two vascular specialty clinics in the Netherlands; therefore, the results may have limited generalizability. Furthermore, whether or not patients adhered to the exercise therapy referral and protocol was not systematically captured in patients' medical records and, as such, analyses could not be adjusted for potential non-adherence. Finally, despite the methodological efforts to adjust for differences between patients who underwent invasive versus non-invasive treatment, observational data were relied upon, and the risk of confounding remains owing to known and unknown factors. Factors that were not examined in this study but that may explain allocation to either invasive or non-invasive therapy are provider, institutional and patient preferences, financial incentives related to reimbursement, experience of the vascular specialist, and other unknown comorbidities.

CONCLUSIONS

This study was able to predict which patients will benefit most from invasive treatment in PAD, based on pre-procedural information that is both meaningful to patients and clinicians. Similar to the CLEVER trial results,[2] most patients' health scores improved following invasive treatment. This was for patients with pre-procedural health status scores spanning the whole spectrum, although the benefit magnitude was lower among patients having high pre-procedural health status scores. Interestingly, these patients were also the least likely to receive invasive treatment. The findings are important to develop further research that documents expected health status outcomes as a function of available treatments and by individual patient characteristics. This information is needed for patients and clinicians to discuss which treatment would be most appropriate and preferable to the individual patient.

CONFLICT OF INTEREST

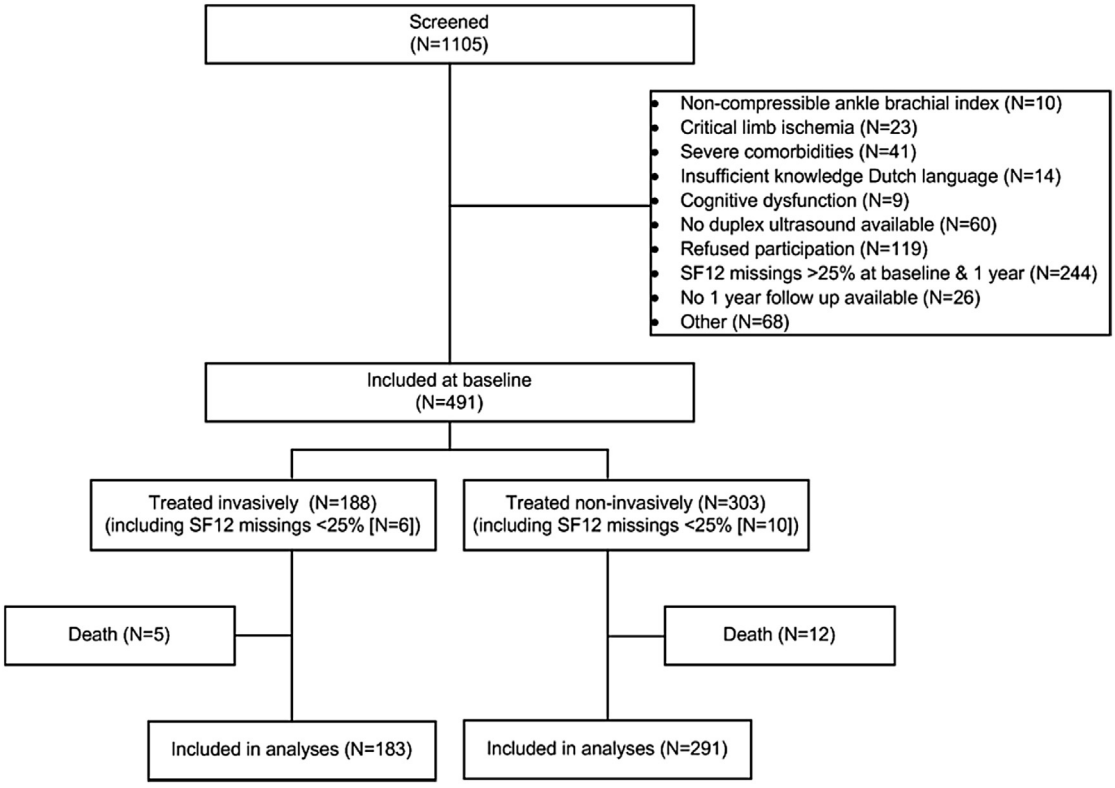
None.

FUNDING

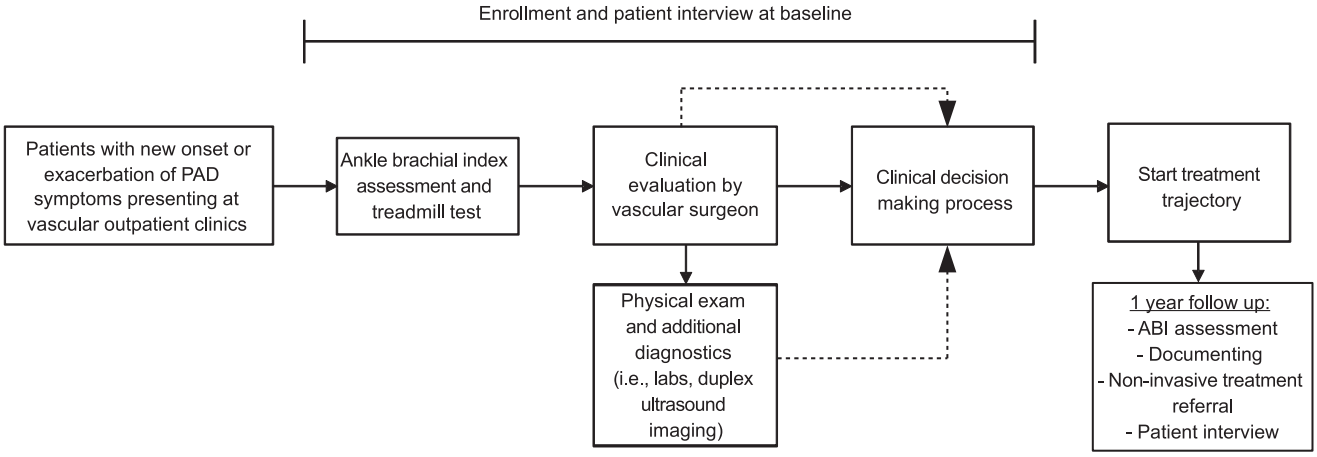
K.G.S. was supported by the Netherlands Organization for Scientific Research (VENI grant no.: 916.11.179), by an unrestricted grant from W.L. Gore & Associates, Inc. (Flagstaff, AZ, USA), and by the Patient-Centered Outcomes Research Institute (1 IP2 PI00753-01). The funding organizations and sponsors of this study had no impact on the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

APPENDIX I. OVERVIEW OF THE STUDY POPULATION.

Note. SF12 = Short Form-12.



APPENDIX II. PATIENTS' CLINICAL EVALUATION ON ENROLLMENT AND 1 YEAR FOLLOW UP SCHEME.



Note. PAD = peripheral arterial disease; ABI = ankle brachial index.

APPENDIX III. FULL MODEL RESULTS FOR 1 YEAR CHANGES IN PHYSICAL HEALTH STATUS (B).

	B	95% CI	*p*
Invasive treatment	**4.44**	**2.59−6.29**	**< .0001**
Baseline PCS12	**−0.45**	**−0.55 to 0.34**	**< .0001**
Age	−0.22	−0.34 to −0.10	< .0001
Male sex	−0.75	−2.72 to 1.23	.46
Hospital site	0.22	−3.71 to 4.15	.91
No partner	−0.15	−2.40 to 2.10	.90
<High school education	−0.32	−2.43 to 1.79	.77
Anatomical lesion location	−1.08	−2.27 to 0.12	.07
1 year ankle brachial index change	**−0.08**	**−0.14 to −0.02**	**.009**
Cardiovascular history	1.09	−0.86 to 3.05	.27
Cerebrovascular history	−1.45	−3.97 to 1.07	.26
Smoking	−0.37	−2.26 to 1.51	.70
Diabetes mellitus	**−1.56**	**−3.75 to 0.63**	**.16**
Obesity (body mass index >30)	−1.78	−4.10 to 0.54	.13
Renal dysfunction	−2.37	−5.51 to 0.76	.14
Chronic obstructive pulmonary disease	−1.85	−4.24 to 0.54	.13
Back pain	−0.09	−2.76 to 2.58	.95
Hip or knee osteoarthritis	−0.95	−3.17 to 1.27	.40
Depression	**−3.17**	**−5.31 to −1.02**	**.004**

Note. Values in bold indicate statistical significance. CI = confidence interval; PCS12 = Physical Component Summary score.

REFERENCES

1 Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with peripheral arterial disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006;**113**(11):e463−654.

2 Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al. 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):130−9.

3 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society Consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg* 2007;**33**(Suppl. 1):S1−75.

4 Safley DM, House JA, Laster SB, Daniel WC, Spertus JA, Marso SP. Quantifying improvement in symptoms, functioning, and quality of life after peripheral endovascular revascularization. *Circulation* 2007;**115**(5):569−75.

5 White CJ, Gray WA. Endovascular therapies for peripheral arterial disease: an evidence based review. *Circulation* 2007;**116**(19):2203−15.

6 van Zitteren M, Vriens PW, Burger DH, de Fijter WM, Gerristen GP, Heyligers JM, et al. Determinants of invasive treatment in lower-extremity peripheral arterial disease in a real-world clinical setting. *J Vasc Surg* 2014;**59**(2):400−8.

7 Banerjee S, Das TS, Abu-Fadel MS, Dippel EJ, Shammas NW, Tran DL, et al. Pilot trial of cryoplasty or conventional balloon post-dilation of nitinol stents for revascularization of peripheral arterial segments: the COBRA trial. *J Am Coll Cardiol* 2012;**60**(15):1352−9.

8 Laird JR, Katzen BT, Scheinert D, Lammer J, Carpenter J, Buchbinder M, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. *Circ Cardiovasc Interv* 2010;**3**(3):267−76.

9 Rastan A, Brechtel K, Krankenberg H, Zahorsky R, Tepe G, Noory E, et al. Sirolimus-eluting stents for treatment of infrapopliteal arteries reduce clinical event rate compared to bare-metal stents: long-term results from a randomized trial. *J Am Coll Cardiol* 2012;**60**(7):587−91.

10 Spertus JA, Salisbury AC, Jones PG, Conaway DG, Thompson RC. Predictors of quality-of-life benefit after percutaneous coronary intervention. *Circulation* 2004;**110**(25):3789−94.

11 Mahoney EM, Wang K, Keo HH, Duval S, Smolderen KG, Cohen DJ, et al. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. *Circ Cardiovasc Qual Outcomes* 2010;**3**(6):642−51.

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):1320−4.

13 Vogel TR, Su LT, Symons RG, Flum DR. Lower extremity angioplasty for claudication: a population-level analysis of 30-day outcomes. *J Vasc Surg* 2007;**45**(4):762−7.

14 Ware Jr J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;**34**(3):220—33.
15 Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. *Qual Life Res* 2009;**18**(4):403—14.
16 Sloan JA, Frost MH, Berzon R, Dueck A, Guyatt G, Moinpour C, et al. The clinical significance of quality of life assessments in oncology: a summary for clinicians. *Support Care Cancer* 2006;**14**(10):988—98.
17 Wyrwich KW, Bullinger M, Aaronson N, Hays RD, Patrick DL, Symonds T. Estimating clinically significant differences in quality of life outcomes. *Qual Life Res* 2005;**14**(2):285—95.
18 Sloan JA. Practical guidelines for assessing the clinical significance of health related quality of life changes within clinical trials. *Drug Inf J* 2003;**37**:23—31.
19 van Zitteren M, Vriens PW, Heyligers JM, Burger DH, Nooren MJ, de Fijter WM, et al. Self reported symptoms on questionnaires and anatomic lesions on duplex ultrasound examinations in patients with peripheral arterial disease. *J Vasc Surg* 2012;**55**(4):1025—1034 e2.
20 Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;**52**(2):69—77.
21 Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;**310**(6977):452—4.
22 Halvorsen PA, Selmer R, Kristiansen IS. Different ways to describe the benefits of risk-reducing treatments: a randomized trial. *Ann Intern Med* 2007;**146**(12):848—56.
23 Aquarius AE, Denollet J, Hamming JF, Breek JC, De Vries J. Impaired health status and invasive treatment in peripheral arterial disease: a prospective 1 year follow up study. *J Vasc Surg* 2005;**41**(3):436—42.
24 Safley DM, Kennedy KF, Stansby G, Flather M, Cohen DJ, Spertus JA. Prevalence and predictors of persistent health status impairment in patients referred to a vascular clinic with intermittent claudication. *Eur J Vasc Endovasc Surg* 2011;**42**(3):355—62.
25 Egberg L, Mattiasson AC, Ljungstrom KG, Styrud J. Health related quality of life in patients with peripheral arterial disease undergoing percutaneous transluminal angioplasty: a prospective one-year follow up. *J Vasc Nurs* 2010;**28**(2):72—7.
26 Keeling AN, Naughton PA, O'Connell A, Lee MJ. Does percutaneous transluminal angioplasty improve quality of life? *J Vasc Interv Radiol* 2008;**19**(2 Pt 1):169—76.
27 Mastenbroek MH, Hoeks SE, Pedersen SS, Scholte Op Reimer WJ, Voute MT, Verhagen HJ. Gender disparities in disease specific health status in post-operative patients with peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2012;**43**(4):433—40.
28 Smolderen KG, Safley DM, House JA, Spertus JA, Marso SP. Percutaneous transluminal angioplasty: association between depressive symptoms and diminished health status benefits. *Vasc Med* 2011;**16**(4):260—6.
29 Rooke TW, Hirsch AT, Misra S, Sidaway AN, Beckman JA, Findeiss LK, et al. 2011 ACCF/AHA focused Update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2011;**58**(19):2020—45.
30 Twine CP, Coulston J, Shandall A, McLain AD. Angioplasty versus stenting for superficial femoral artery lesions. *Cochrane Database Syst Rev* 2009;(2):CD006767.
31 Ratnam L, Raza SA, Horton A, Taylor J, Markose G, Munneke G, et al. Outcome of aortoiliac, femoropopliteal and infrapopliteal endovascular interventions in lesions categorised by TASC classification. *Clin Radiol* 2012;**67**(10):949—54.
32 Ye W, Liu CW, Ricco JB, Mani K, Zeng R, Jiang J. Early and late outcomes of percutaneous treatment of TransAtlantic Inter-Society Consensus class C and D aorto-iliac lesions. *J Vasc Surg* 2011;**53**(6):1728—37.
33 Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. *JAMA* 1995;**274**(12):975—80.
34 Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease. Implications for the mechanism of the training response. *Circulation* 1994;**90**(4):1866—74.
35 Pollock ML, Franklin BA, Balady GJ, Chaitman BL, Fleg JL, Fletcher B, et al. AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. *Circulation* 2000;**101**(7):828—33.
36 Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness criteria for coronary revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2009;**53**(6):530—53.