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STATE-OF-THE-ART REVIEW

Exercise Training and Revascularization in the Management of Symptomatic Peripheral Artery Disease

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HIGHLIGHTS

- **In the management of symptomatic peripheral artery disease, aerobic exercise therapy and lower extremity revascularization are the mainstays of therapy.**
- **In this structured review, the most effective therapies, with 6 to 18 months of follow-up, indicated that exercise therapy and lower extremity revascularization each independently improve peak walking performance.**
- **The combination of therapies was superior to either therapy alone and may decrease the need for subsequent revascularization.**
- **Further research is needed to evaluate the long-term durability of these interventions, their impacts on subsequent invasive procedures, and predictors of response.**

SUMMARY

Exercise therapy and lower extremity revascularization both improve walking performance in symptomatic patients with peripheral artery disease. The combination of therapies provides greater benefit than either alone and may reduce the need for subsequent revascularization procedures, but further trials with longer follow-up are needed for the outcome of subsequent revascularization. (J Am Coll Cardiol Basic Trans Science 2021;6:174–88) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Peripheral artery disease (PAD) is a manifestation of systemic atherosclerosis (1), affecting more than 200 million individuals worldwide (2). PAD is associated with functional limitations, significant morbidity, and increased risks of cardiac and limb ischemic events (3–6). The clinical presentation ranges from classically described intermittent claudication, which is pain in the calves on walking that is relieved within 10 min of rest (4), to atypical exertional leg symptoms that are also associated with an exercise limitation and reduced quality of life.

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Given the reduced functional capacity in patients with claudication, therapy is aimed at improving functional status and quality of life. Although PAD-specific pharmacologic therapies, such as pentoxifylline 400 mg oral twice daily and cilostazol 200 mg oral twice daily, have been developed, these drugs have minimal or variable efficacy in PAD (4,7). As a result, on a background of cardiovascular risk reduction and lifestyle counseling, aerobic exercise therapy (ET) and lower extremity revascularization (LER) are the preferred management strategies in clinical practice and are strongly recommended by current guidelines (8,9). Despite numerous studies examining these treatment modalities, it remains unclear which treatment, if any, should be favored in a typical patient with claudication. The goal of this structured review is to improve the clinician's understanding of the effectiveness of these preferred management interventions in this highly prevalent and limiting disorder and to highlight areas for future research endeavors.

CHALLENGES IN PUBLISHED REPORTS ON PAD SYMPTOMATIC THERAPY

Although published reports evaluating management strategies for PAD spans many decades, there are challenges when comparing treatment modalities because of significant heterogeneity in quality and conduct among studies (10–12), including a lack of uniformity in how ET and LER strategies are defined, how outcomes are measured, and the assessment of durability of the treatment in follow-up. The assessment of durability of benefit over time from these interventions is underreported in existing published reports despite the fact that ET requires regular training to remain effective and LER procedures can fail over time. Therefore, quantitative meta-analyses on this topic are limited and focus on a narrow range of quantitatively compatible studies and timepoints that emphasize efficacy but not effectiveness. For this structured review, we focused on qualitative trends of benefit over time for each of the general therapeutic strategies and took a more inclusive approach by including all eligible studies for each follow-up timepoint. This novel approach allowed for a more comprehensive view of the effects of these treatment modalities.

To overcome some of the heterogeneity in published reports, the search definitions adapted for this review included supervised ET, defined as a structured aerobic exercise program performed at a facility under direct supervision; home-based exercise [HBE] therapy, defined as a structured aerobic exercise program performed mostly at home; and walking advice, defined as advice to ambulate without significant supervision or oversight. LER was defined as restoration of blood flow to the lower extremities by either open surgical or endovascular techniques. Exercise performance measures (further defined in the Methods section) included peak walking distance (PWD) or time and claudication onset distance or time (as measured by treadmill tests, 6-min walk [6MW] tests, or shuttle walk tests). Although these measurement methods are not identical, they do evaluate similar aspects of physical exercise performance and can assess the relative improvements in performance with an intervention.

This review provides summary tables presented in the main article, supported by more detailed Supplemental Tables reviewing the published reports, which serve as a helpful resource for those interested in individual studies and the current state of the field (see Supplemental Appendix). Understanding these challenges, limitations, and assumptions should clarify gaps in published reports.

ABBREVIATIONS AND ACRONYMS

6MW = 6-minute walk

CMS = Centers for Medicare and Medicaid Services

ET = exercise therapy

HBE = home-based exercise

LER = lower extremity revascularization

MCID = minimum clinically important difference

PAD = peripheral artery disease

PRO = patient-reported outcome

PWD = peak walking distance

PWT = peak walking time

SET = supervised exercise training

SF-36 = Medical Outcomes Short Form-36

VascuQOL = Vascular Quality of Life

WIQ = Walking Impairment Questionnaire

METHODS

OUTCOME DEFINITIONS. Heterogeneity in outcomes measured across different studies evaluating ET and LER for symptomatic PAD makes comparisons of treatments among studies challenging. For example, although PWD and maximal peak walking time (PWT) on a treadmill both measure peak physiologic performance, they cannot be quantitatively combined without knowing the specific treadmill protocol used. The maximal walking distance on a 6MW test is another objective measure of walking performance used in this population. Both of these measures can detect improvements in exercise performance with ET or LER. One distinguishing feature is that the treadmill test, when repeated over time, will show an improvement in patients randomized to the control group (commonly called a placebo effect), whereas the 6MW test declines over time, representing the natural history of claudication, compared to a nonexercise control group (13). When both exercise testing methods were assessed in a study of supervised exercise compared to HBE, the ET outcome had a quantitatively greater increase than the 6MW test, but both tests demonstrated a treatment benefit for supervised exercise and HBE (13). Therefore, we focused on these exercise endpoints as different, independent measures of functional capacity rather than making direct

TABLE 1 Search Terms Used to Identify Relevant Articles for Inclusion

1	2	3	4
Peripheral artery disease	Intermittent claudication	Clinical trial	Supervised exercise
English	Claudication	Randomized controlled trial	Home-based exercise
Not coronary		Controlled clinical trial	Exercise
		Trial	Revascularization
		Randomized	Surgical
			Endovascular

Search terms were ordered as follows: items from column 1 were required plus at least 1 option from columns 2 and 3, and then "or" combinations from column 4.

comparisons of the net percent benefit between these tests. We instead chose to bundle exercise test outcomes of interest to assess the qualitative impact of therapy in this review and defined this as "peak walking performance," which is the maximum distance or time walked, measured by an exercise treadmill, 6MW, or shuttle walk within an individual study. This outcome of interest was chosen as primary because it is an objective measure of exercise performance common to all included studies (using the broad definition). Secondary outcomes included claudication onset (distance or time walked before the onset of claudication); patient-reported outcomes (PROs) assessed by questionnaires; and the need for subsequent LER, which is a key outcome of interest not covered in previous reviews, to our knowledge.

Complementary disease-specific and nonspecific questionnaires were combined in assessing clinical benefit with the advantage of being able to extrapolate changes in exercise performance to measures of health status, which is the ultimate goal of any therapy for claudication (14,15). The most frequently used health status questionnaires include the Medical Outcomes Short Form-36 (SF-36) and its variations, the Walking Impairment Questionnaire (WIQ), and the Vascular Quality of Life Assessment (VascuQOL) (14). The SF-36 and its variations assess functional status (14,16), and although they are non-disease-specific assessments, they provide reliable measures of quality of life measures in large populations, including those individuals with PAD (16–18). The WIQ assessment relies on self-reported measures of walking limitations and is a PAD-specific questionnaire that incorporates walking speed, walking distance, and stair climbing (14,19,20). The VascuQOL is another PAD-specific questionnaire and includes assessments of social and emotional well-being, pain, symptoms, and activities (14,21,22). This questionnaire captures the combination of the disease-specific physical, psychosocial, and emotional effects of PAD, quantifies the subjective patient experience, and helps address the impact of PAD on those living with the disease (23,24).

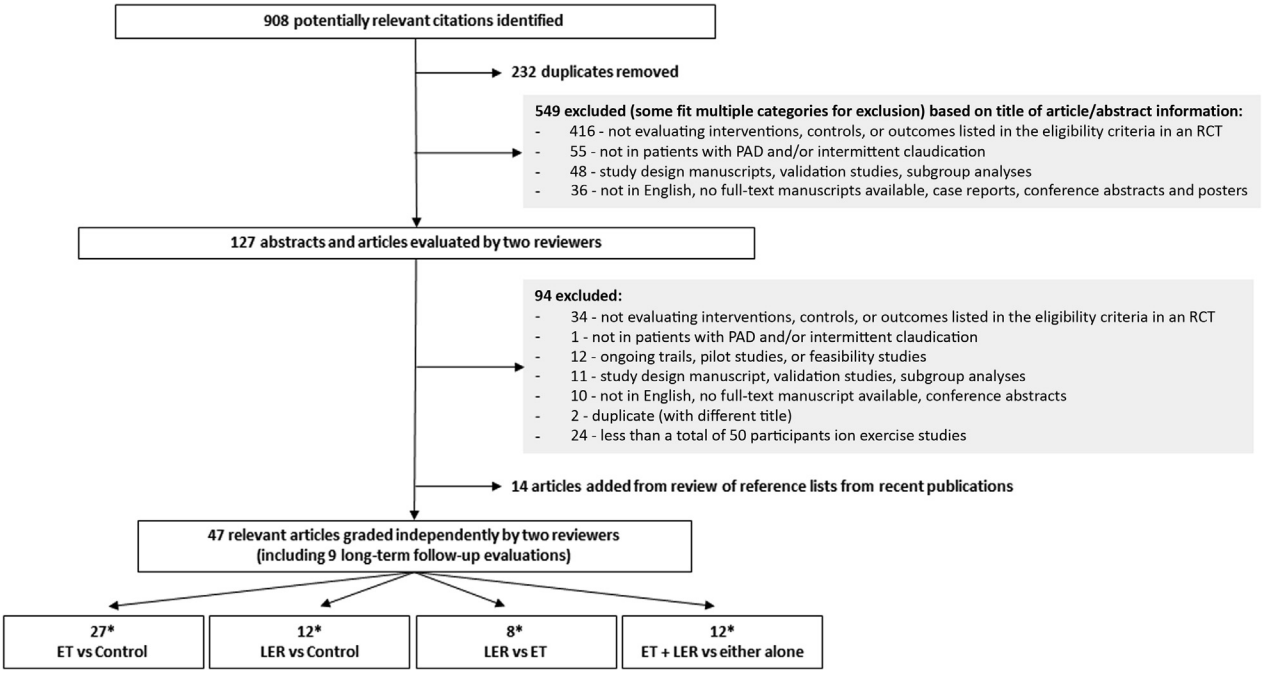
A different clinical outcome assessed in this review included the need for a subsequent revascularization following an initial intervention. This outcome (proportion of participants in each study arm needing a revascularization procedure after completing the initial treatment) highlights the potential impact of an intervention as part of the initial therapy on the subsequent need for LER.

DATA SOURCES. The first author (M.P.B.) conducted searches in Ovid MEDLINE from 1946 to 2020, CINAHL (EBSCO) from 1981 to 2020, Embase, PubMed, Cochrane Reviews, and Cochrane Clinical Trials databases using the search terms detailed in Table 1. Search terms were ordered as follows: items from column 1 were required plus at least 1 option from columns 2 and 3, and then "or" combinations from column 4. The resultant studies were reviewed by M.P.B. and W.H.C. with additional oversight for consensus by W.R.H.

ELIGIBILITY CRITERIA. Randomized controlled trials including participants with symptomatic PAD who were treated with aerobic ET versus nonintervention control, LER versus nonintervention control, LER versus ET, or any combination of LER with ET versus either intervention alone or nonintervention control were included. In addition, the studies had to report at least 1 of the following outcome assessments: PWT or PWD; claudication onset time or distance; or the SF-36 (or SF-12) physical function scale, WIQ distance, or VascuQOL PROs. The availability of these key measures was used for trial selection because they represent the most consistently used objective and subjective outcome measures in this field. Trials that were not available as full-text articles; were not in English; were drug- or device-based trials; or were in populations of solely asymptomatic PAD, acute limb ischemia, or chronic limb-threatening ischemia were excluded. In addition, studies without a nonintervention control group, those comparing revascularization strategies without an exercise comparison, or those comparing exercise strategies alone were excluded. Given the number of small studies of ET in published reports, the authors required that the total sample size for inclusion in this review be >50 participants in total to improve generalizability.

STUDY APPRAISAL AND SYNTHESIS METHODS. A total of 908 articles were identified (Figure 1). After removing duplicates and studies not meeting eligibility criteria, 127 articles remained. Two reviewers

FIGURE 1 Consolidated Standards of Reporting Trials (Consort) Flow of Studies in the Systematic Review



Some studies evaluated more than 1 intervention–control combination, resulting in a total of 59 comparisons. ET = exercise therapy; LER = lower extremity revascularization; PAD = peripheral artery disease.

(M.P.B. and W.H.C.) evaluated the remaining 127 articles with additional selection based on the described eligibility criteria. Fourteen studies were added back manually upon closer review. Ultimately, 38 primary studies were included, resulting in 47 publications (Supplemental Table 1).

Basic information about interventions, controls, and outcomes were recorded for each study. For each trial, potential pre-randomization selection bias was recorded and defined as the number of eligible individuals following screening who did not subsequently participate in the trial. Reasons for potential pre-randomization selection bias included patient refusal, failure to adhere to run-in requirements, or other reasons where the study did not provide a clear scientific basis for exclusion. This measure was intended to reflect the possibility of a selection bias of individuals who were likely to benefit from the intervention tested (Supplemental Table 2). The direction of benefit (intervention relative to control) was also determined for each outcome.

NET PERCENT BENEFIT. The net percent benefit of 1 intervention relative to another was calculated as the percent change in the intervention group minus the percent change in the control group. The calculated net percent benefit is displayed for each measured endpoint in each trial in the Supplemental Tables 3 to 83. The net percent benefit can help gauge a normalized relative response to an intervention. When reporting overall net percent benefit for an intervention compared with another, we relied on the highest-quality available data (only higher-quality studies, where available, in the 6- to 18-month follow-up range), and we calculated the averages of effect size weighted by trial sample size. We focused on exercise treadmill test outcomes, which was the predominant measure of functional capacity across most trials, with 6MW commonly used only in the evaluation of ET interventions. Unique trials were used to calculate net percent benefit; when a trial reported outcomes at more than 1 timepoint within this range, including in a separate follow-up publication of the same trial, the values were averaged to contribute to the weighted average.

The trials were evaluated by using a grading process that was adapted from the Cochrane risk of bias tool (25) using 7 domains, as detailed in Supplemental Table 2. Two reviewers (M.P.B. and W.H.C.) independently graded each article, after which the scores were compared. Any discrepancies were resolved by a third

reviewer (W.R.H.) with consensus or discussion. Based on these scores, a quality assessment was assigned for each study, with a lower risk of bias indicating a relatively higher-quality study, and a higher risk of bias equating to a relatively lower-quality study, as detailed in **Table 2**. The inherent lack of participant blinding is a fundamental limitation across this body of published reports for studies of ET and LER, but its impact can be attenuated by blinding outcome assessors. As a result, lack of participant blinding was considered a minor factor when grading the relative quality among studies, whereas the lack of blinding of outcome assessors was considered a major factor (25). In addition, because the eligibility criteria included randomized trials and all studies were deemed to be appropriately randomized, this source of bias was considered a minor factor when grading the relative quality. However, the methods of allocation were not always well defined or sufficient, and therefore, allocation bias was considered a major factor when grading the relative quality.

To assess relative quality of evidence, each measured outcome at a given follow-up timepoint for each reported intervention-control comparison was separately assessed (26). As shown in Supplemental Tables 3 to 83, each intervention, control, outcome, and follow-up time combination was evaluated for relative quality. Adapted from Bellet et al. (27) and as shown in **Table 3**, the strength of evidence was determined based on the relative quality of the studies contributing to the data and the consistency within the available data. Higher-quality studies were relied on for evidence in the face of conflicting lower-quality studies (28).

TABLE 2 Study Quality Assessment and Grading

Quality assessment	
• 1 (randomization methods)	Minor
• 2 (allocation bias)	Major
• 3 (participant/investigator blinding)	Minor
• 4 (outcome assessment bias)	Major
• 5 (attrition)	Major
• 6 (selective reporting)	Minor
• 7 (other potential bias)	Minor
Graded as lower quality if any of the following:	
• 2 major issues	
• 1 major + 2 minor issues	
• 4 minor issues	

By using the scoring tool described in Supplemental Table 1, studies were evaluated for quality based on these criteria. Because the quality assessment is relative to the population of studies assessed, participant/investigator blinding was de-emphasized for this assessment, given that all articles were unblinded to either participants or investigators. In contrast, outcome assessment blinding was emphasized as a major contributor to the relative quality of the studies. All studies were also randomized as part of the inclusion criteria, so randomization methods were also de-emphasized for this assessment.

RESULTS

CHARACTERISTICS OF THE INCLUDED RANDOMIZED CONTROLLED TRIALS. A total of 4,193 participants from 38 primary studies (with 47 publications) were included. The additional 9 references were separate publications based on longer-term follow-up from the original 38 primary studies. In addition, many of the 38 primary articles included important subgroups involving more than 1 intervention-control combination, leading to a total of 59 possible treatment comparisons.

The trials, shown in Supplemental Table 1, spanned from 1989 to 2020 and included a median of 100 participants per study. The duration of follow-up ranged from 6 weeks to 7 years, with a median follow-up of 13 months. Thirty trials evaluated timepoints between 6 months and 18 months. Of the 38 included studies, 27 evaluated ET versus control (including 3 extended-timepoint evaluations), 12 evaluated LER versus control (including 5 extended-timepoint evaluations), 8 compared ET versus LER (including 2 extended-timepoint evaluations), 6 compared the combination of LER and ET versus ET alone (including 4 extended-timepoint evaluations), and 6 compared the combination of therapies to LER alone (including 1 extended-timepoint evaluation). Participants' ages ranged from 38 to 86 years, and there a median of 36% (range 2% to 52%) were women. Approximately two-thirds of the trials were conducted in Europe; only one-third of the studies, primarily those conducted in the United States, reported participants' race. Of those studies reporting race, 43% (range 6% to 70%) of participants were non-White.

ASSESSMENT OF TRIAL QUALITY. An important factor with the potential to affect results across trials of therapy for claudication is participant attrition. These values are displayed in Supplemental Tables 3 to 83. Attrition, reported as a percentage of the total number of enrolled patients, included those who were lost to follow-up or did not complete final outcome measures. The attrition in the included trials ranged from 0% to 39% (with a median attrition rate of 13%), excluding the studies that were long-term follow-up evaluations of trials within the cohort of studies. Those that evaluated ET (without LER) had a median attrition rate of 13%, and those that included an evaluation of LER also had a median attrition rate of 13%. The attrition rate in the long-term follow-up studies was as high as 51%, which highlighted the fact that longer follow-up periods were associated with

much higher attrition rates, leading to risk of selective reporting of outcomes and competing risks, especially in those trials that were not originally designed to evaluate long-term outcomes.

AEROBIC EXERCISE VERSUS NONINTERVENTION CONTROL. There were 27 randomized trials that evaluated ET versus nonintervention control (including 3 extended-timepoint evaluations) (Table 4). In these studies, ET was consistently superior to nonintervention control through 18 months of follow-up in terms of peak walking performance. The higher-quality studies demonstrated a variable degree of improvement in peak walking performance; among unique trials, there was a weighted average net percent improvement of 54% (as measured by ETT; 6 higher-quality trials) and 8% (as measured by the 6-min walk distance [6MWD]; 4 higher-quality trials) in PWD/PWT between 6 and 18 months of follow-up (Supplemental Tables 3 to 6). A similar pattern of benefit was seen in measures of claudication onset. Concordant benefits for ET were evident by SF and WIQ measures, with no data evaluating PROs beyond 18 months.

LER VERSUS NONINTERVENTION CONTROL. Twelve randomized trials compared LER versus nonintervention control (including 5 extended-timepoint evaluations), with only 1 higher-quality study assessing peak walking performance beyond 6 months of follow-up. As shown in Table 5, LER was consistently superior to non-intervention control in peak walking performance, claudication onset, and subjective outcomes when measured between 6 and 18 months of follow-up, based largely on strong evidence (strength of evidence B). The average net percent benefit of peak walking performance for LER over this timeframe was 54% (as measured by ETT; 1 higher-quality trial) (Supplemental Tables 7 to 10). There was strong evidence of sustained benefit beyond 18 months of follow-up in the case of claudication onset but not for peak walking performance.

LER VERSUS AEROBIC EXERCISE. Eight randomized trials evaluated LER versus ET (including 2 extended-timepoint evaluations) (Table 6). All trials used treadmill walking performance as the objective assessment of walking ability. ET was favored for peak walking performance over LER after 6 to 18 months of follow-up (Supplemental Tables 11 to 14), with a weighted average net percent benefit of peak walking performance for ET of 94% (as measured by ETT; 2 higher-quality trials) compared to LER in this time-frame. There was a suggestion of benefit of LER therapy in the short-term (<6 months) and long-term (>18 months) evaluations, although overall evidence was limited or weak. Evidence evaluating subjective outcomes between LER and ET were weak or conflicting. The strongest evidence suggested no differences between treatments by VascuQOL; otherwise, there were some suggestions of benefit of LER on quality of life by SF and WIQ.

TABLE 3 Strength of Evidence

A	Very strong	Consistent findings from 2 or more higher-quality studies
B	Strong	Findings from at least 1 higher-quality study, supported by at least 1 lower-quality study
C	Limited	Findings from a single higher-quality study Consistent findings from 1 or more lower-quality studies
D	Weak	Findings from a single lower-quality study
E	Inconclusive	Conflicting or inconsistent findings irrespective of study quality Unable to draw conclusions based on the available data

Adapted from Bellet et al. (27), the strength of evidence is based on individual trial quality and consistency in trial results at each duration of follow-up. Strength of evidence A is very strong, strength of evidence B is strong, strength of evidence C is limited, strength of evidence D is weak, and strength of evidence E is inconclusive.

COMBINATION OF REVASCULARIZATION AND AEROBIC EXERCISE VERSUS AEROBIC EXERCISE ALONE. Six randomized trials (including 4 extended-timepoint evaluations) evaluated the combination of LER and ET versus ET alone. For all the assessed outcomes, with there was 1 relatively higher-quality study for the 6-month to 12-month and 12-month to 18-month follow-up timepoints, with generally concordant lower-quality studies supporting these trends (Table 7). At these timepoints, the combination of therapies was favored over ET alone, with an average net percent benefit of 156% (as measured by ETT; 1 higher-quality trial) (Supplemental Tables 15 to 17). Long-term outcomes were informed only by relatively lower-quality studies that still favored the combination of therapies over ET alone.

COMBINATION OF REVASCULARIZATION AND AEROBIC EXERCISE VERSUS REVASCULARIZATION ALONE. The combination of therapies versus LER alone was evaluated in 6 randomized trials (including 1 extended-timepoint evaluation) (Table 8). Similar to combination therapy versus ET alone, there was a benefit of combination therapy when compared to LER alone with regard to peak walking performance through 18 months of follow-up. Overall, very limited data existed evaluating peak walking performance, with a weighted average net percent improvement of 73% (as measured by ETT; 3 lower-quality studies) (Supplemental Tables 18 to 21). Evaluating the subjective outcomes, at the 6- to 12-month follow-up timepoints, there were no differences between the combination of therapies compared to LER alone. Other than these

TABLE 4 Comparison of Randomized Controlled Trials Evaluating Aerobic Exercise Therapy Versus Nonintervention Control

Intervention	Control	Outcome	<6 Months	6–12 Months	12–18 Months	>18 Months
Exercise	Nonintervention control	Peak walking performance				
Direction of benefit			↑	↑	↑	↑
Strength of evidence (number of higher- vs. lower-quality studies)			A (4 vs. 7)	A (8 vs. 5)	A (5 vs. 5)	D (0 vs. 1)
Exercise	Nonintervention control	Claudication onset				
Direction of benefit			↑	↑	↑	–
Strength of evidence (number of higher- vs. lower-quality studies)			B (1 vs. 7)	A (3 vs. 4)	B (1 vs. 2)	–
Exercise	Nonintervention control	Need for post-randomization revascularization				
Direction of benefit			–	–	–	–
Strength of evidence (number of higher- vs. lower-quality studies)			–	–	–	–
Exercise	Nonintervention control	SF-36, SF-12				
Direction of benefit			↑	↑	↑	–
Strength of evidence (number of higher- vs. lower-quality studies)			B (1 vs. 3)	A (4 vs. 3)	A (3 vs. 2)	–
Exercise	Nonintervention control	Walking Impairment Questionnaire				
Direction of benefit			↑	↑	↑	–
Strength of evidence (number of higher- vs. lower-quality studies)			C (0 vs. 2)	A (4 vs. 4)	A (3 vs. 3)	–

Follow-up time periods included <6 months, 6 to 12 months, 12 to 18 months, and long-term follow-up extending beyond 18 months. ↑ indicates that the results favored the intervention, ↓ indicates that the results favored the control, ↔ indicates that the results were neutral and favored neither the intervention nor the control, and ∅ indicates equivocal results and cannot be determined because of conflicting results among studies. Nineteen articles contributed to the data shown in this table.

SF-12 = Medical Outcomes Short Form-12; SF-36 = Medical Outcomes Short Form-36.

observations, there was a paucity of data to draw on, with no consistent trends among the few studies comparing these treatments.

EVALUATING THE NEED FOR REVASCULARIZATION AFTER RANDOMIZATION. Whether PAD therapies can delay or prevent the need for a future invasive revascularization procedure is of critical clinical importance. Tables 4 to 8 show reported results on this outcome for the different combinations of therapies. Unfortunately, subsequent revascularization was reported in relatively few studies (11 trials) and in none of the studies evaluating ET only, despite the outcome's importance. Based on limited evidence, the subsequent need for revascularization was increased in participants randomized to LER compared to nonintervention controls beyond 12 months of follow-up. When LER was compared to ET, the results for this endpoint were not different. However, when LER and ET were combined, as compared to ET alone, there was less need for subsequent LER with the combination, with strong evidence at 12 to 18 months and weaker evidence for follow-up longer than 18 months. It should be noted that these benefits at 12 to 18 months were reported in 2 higher-quality trials with a difference in events between groups of 15 patients in 1 study and 6 patients in a second study (Supplemental Table 44). When the same combination of LER plus ET was compared with LER alone, there was weak evidence from lower-quality trials that the combination also reduced the need for subsequent LER. However, given the relatively small number of events, no definitive conclusions can be made.

The Central Illustration provides comparative data for the relative improvements in peak walking performance for the primary and different combinations of therapies. The colors of the bars indicate strength of evidence for the follow-up timeframe of 6 to 18 months.

DISCUSSION

This structured review identified a large body of published reports examining treatment options to improve the exercise limitation and quality of life of patients with symptomatic PAD. Most data were based on follow-up timepoints between 6 and 18 months. Within this range, commonly used individual treatments, including aerobic ET and LER, provided significant improvement in peak walking performance and quality of life over nonintervention control groups. Over this same timeframe, ET improved peak walking performance more than LER when compared directly in randomized trials over a follow-up period of 6 to 18 months, with much less evidence for a sustained benefit at longer than 18 months. The combination of LER and ET was superior to ET alone. Although the same combination may also improve outcomes compared to LER alone, only 1 higher-quality study evaluated this comparison.

TABLE 5 Comparison of Randomized Controlled Trials Evaluating Lower Extremity Revascularization Versus Nonintervention Control

Intervention	Control	Outcome	<6 Months	6-12 Months	12-18 Months	>18 Months
LER	Nonintervention control	Peak walking performance				
Direction of benefit			↑	↑	↑	↔
Strength of evidence (number of higher- vs. lower-quality studies)			D (0 vs. 1)	B (1 vs. 2)	B (1 vs. 4)	B (1 vs. 5)
LER	Nonintervention control	Claudication onset				
Direction of benefit			↑	↑	↑	↑
Strength of evidence (number of higher- vs. lower-quality studies)			D (0 vs. 1)	B (1 vs. 1)	B (1 vs. 2)	B (1 vs. 3)
LER	Nonintervention control	Need for post-randomization revascularization				
Direction of benefit			–	–	↓	↓
Strength of evidence (number of higher- vs. lower-quality studies)			–	–	D (0 vs. 1)	C (1 vs. 2)
LER	Nonintervention control	SF-36, SF-12				
Direction of benefit			–	↑	↑	⊘
Strength of evidence (number of higher- vs. lower-quality studies)			–	C (1 vs. 0)	A (1 vs. 2)	E (1 vs. 3)
LER	Nonintervention control	Walking Impairment Questionnaire				
Direction of benefit			↔	↑	↑	–
Strength of evidence (number of higher- vs. lower-quality studies)			D (0 vs. 1)	C (1 vs. 0)	B (1 vs. 1)	–
LER	Nonintervention control	VascuQOL				
Direction of benefit			–	–	↑	⊘
Strength of evidence (number of higher- vs. lower-quality studies)			–	–	C (1 vs. 0)	E (1 vs. 1)

Follow-up time periods included <6 months, 6 to 12 months, 12 to 18 months, and long-term follow-up extending beyond 18 months. ↑ indicates that results favored the intervention, ↓ indicates that results favored the control, ↔ indicates that results were neutral and favored neither the intervention nor the control, and ⊘ indicates equivocal results and cannot be determined because of conflicting results among studies. Seven articles contributed to the data shown in this table.

LER = lower extremity revascularization, SF-12 = Medical Outcomes Short Form-12; SF-36 = Medical Outcomes Short Form-36; VascuQOL = vascular quality of life assessment.

A unique finding of this review was that LER as a single treatment strategy may increase the need for subsequent LER procedures. However, when LER and ET were combined, the opposite outcome occurred with the data, suggesting that when ET is part of the treatment strategy for LER, the risk for subsequent LER may be decreased. These conclusions should be taken with caution given the small number of trials reporting only a few events. Larger trials of longer duration will be needed to confirm these results.

LER primarily addresses the perfusion abnormalities due to the large and medium artery occlusive disease in PAD. A successful LER can relieve the exercise-induced mismatch of oxygen supply to the demand imposed by walking activities. Although the symptomatic benefits of LER are relatively immediate, recent publications suggest there may be a cost, in particular with an increased risk of acute limb ischemia and need for repeated hospitalizations and procedures (29,30). A prior history of LER has been associated with an increased risk of acute leg ischemia (31), and subsequent LER procedures are associated with increased risk for major adverse limb events, including acute limb ischemia and major amputation (32). These recent reports are based on large prospective datasets but are limited in that they are not randomized with respect to prior revascularization. The lack of randomization increases the possibility that patients who undergo revascularization have a higher baseline risk of future events. Our review examined trials in which revascularization therapy was randomized, adding an important perspective to this emerging question. Our data lend some additional support to the observation that LER therapy may increase the subsequent need for future LER by 12 months post-randomization when compared to control. More importantly, there may be an additive effect of combining ET and LER compared to either treatment alone, which may ultimately mitigate downstream risks necessitating additional revascularization procedures. As evidenced in our summary tables, data are somewhat limited to provide clear answers to this question. Given the clinical importance of a future invasive revascularization procedure, more studies randomizing ET and LER treatments, and all studies examining any form of treatment for symptomatic PAD, should include a rigorous accounting of the subsequent need for revascularization through follow-up.

In contrast to LER, the benefits of ET require long-term adherence to an exercise program, and such programs are not universally available. The most commonly used modalities for aerobic ET include treadmill-based supervised exercise training (SET),

TABLE 6 Comparison of Randomized Controlled Trials Evaluating Lower Extremity Revascularization Versus Aerobic Exercise Therapy

Intervention	Control	Outcome	<6 Months	6–12 Months	12–18 Months	>18 Months
LER	Exercise	Peak walking performance				
Direction of benefit			↑	↓	↓	↑
Strength of evidence (number of higher- vs. lower-quality studies)			D (0 vs. 1)	A (2 vs. 3)	A (2 vs. 4)	C (0 vs. 3)
LER	Exercise	Claudication onset				
Direction of benefit			↑	⊘	↓	↑
Strength of evidence (number of higher- vs. lower-quality studies)			D (0 vs. 1)	E (2 vs. 1)	A (2 vs. 1)	C (0 vs. 2)
LER	Exercise	Need for post-randomization revascularization				
Direction of benefit			–	↔	–	⊘
Strength of evidence (number of higher- vs. lower-quality studies)			–	B (1 vs. 1)	–	E (0 vs. 3)
LER	Exercise	SF-36, SF-12				
Direction of benefit			↑	⊘	⊘	↑
Strength of evidence (number of higher- vs. lower-quality studies)			D (0 vs. 1)	E (2 vs. 1)	E (2 vs. 1)	C (0 vs. 2)
LER	Exercise	Walking Impairment Questionnaire				
Direction of benefit			–	↑	↑	–
Strength of evidence (number of higher- vs. lower-quality studies)			–	C (1 vs. 0)	C (1 vs. 0)	–
LER	Exercise	VascuQOL				
Direction of benefit			–	↔	↔	⊘
Strength of evidence (number of higher- vs. lower-quality studies)			–	B (1 vs. 1)	B (1 vs. 1)	E (0 vs. 2)

Follow-up time periods included <6 months, 6 to 12 months, 12 to 18 months, and long-term follow-up extending beyond 18 months. ↑ indicates that results favored the intervention, ↓ indicates that results favored the control, ↔ indicates that results were neutral and favored neither the intervention nor the control, and ⊘ indicates equivocal results and cannot be determined because of conflicting results among studies. Seven articles contributed to the data shown in this table.

LER = lower extremity revascularization, SF-12 = Medical Outcomes Short Form-12; SF-36 = Medical Outcomes Short Form-36; VascuQOL = vascular quality of life assessment.

HBE, and upper extremity and lower extremity ET including arm ergometry and cycling. Differentiating SET from HBE was beyond the scope of the current review. However, in choosing among these different ET programs, SET improves treadmill walking distance more than HBE, likely because of a train-to-the-test phenomenon, but there is no difference between SET and HBE for PROs (33). The most effective HBE programs have included established behavioral change methods and more frequent visits to the medical center (34), as reflected in the guidelines (35). In this review, regardless of whether patients underwent a SET or HBE program, there was improvement in the ET arm of the studies compared to the control group.

ET and LER are well supported individually and in combination, as evidenced by our review and by guidelines across specialties (35-39). The current guidelines recommend an exercise-first approach, which the authors agree with. SET programs and HBE programs are recommended to improve functional status and health status and to reduce leg symptoms (Class I, Level of Evidence: A and Class IIa, Level of Evidence: A, Respectively) (35). In addition, alternative aerobic strategies of ET should be considered (Class IIa, Level of Evidence: A), including upper body ergometry and cycling (35,37). LER should be considered in the management of intermittent claudication in those who have had an inadequate response to guideline-directed medical therapy, including ET (Class IIa, Level of Evidence: A) (35), and as evidenced by the stronger evidence supporting an exercise-first strategy in this review. In addition, endovascular revascularization may be considered in aortoiliac occlusive disease (Class I, Level of Evidence: A) and in femoral-popliteal occlusive disease (Class IIa, Level of Evidence: B).

Our review of published reports also supports the combined approach of ET plus LER if an exercise-first approach has been tried as recommended by most guidelines. This conclusion is based on the notable net percent increases in peak walking performance in direct comparisons of ET to LER and of combination therapy to either treatment alone. Our conclusion is further bolstered by decreasing barriers to accessing ET programs and the greater cost effectiveness of ET. Previously, a significant practical barrier to the widespread use of SET programs was a lack of insurance coverage from the Centers for Medicare and Medicaid Services (CMS). In 2017, however, CMS approved coverage for SET programs for the management of symptomatic PAD patients, aligned with the Class I recommendations. Despite reimbursement, recent evidence shows that SET remains underused, with more than 50% of physicians surveyed

TABLE 7 Comparison of Randomized Controlled Trials Evaluating the Combination of Lower Extremity Revascularization With Aerobic Exercise Therapy Versus Aerobic Exercise Therapy Alone

Intervention	Control	Outcome	<6 Months	6–12 Months	12–18 Months	>18 Months
LER + exercise	Exercise alone	Peak walking performance				
Direction of benefit			–	↑	↑	↑
Strength of evidence (number of higher- vs. lower-quality studies)			–	B (1 vs. 2)	B (1 vs. 3)	C (0 vs. 2)
LER + exercise	Exercise alone	Claudication onset				
Direction of benefit			–	↑	↑	⊘
Strength of evidence (number of higher- vs. lower-quality studies)			–	C (1 vs. 1)	B (1 vs. 2)	E (0 vs. 2)
LER + exercise	Exercise alone	Need for post-randomization revascularization				
Direction of benefit			–	–	↑	↑
Strength of evidence (number of higher- vs. lower-quality studies)			–	–	B (1 vs. 1)	D (0 vs. 1)
LER + exercise	Exercise alone	SF-36, SF-12				
Direction of benefit			–	↑	↑	⊘
Strength of evidence (number of higher- vs. lower-quality studies)			–	B (1 vs. 1)	B (1 vs. 1)	E (0 vs. 2)
LER + exercise	Exercise alone	Walking Impairment Questionnaire				
Direction of benefit			–	–	–	–
Strength of evidence (number of higher- vs. lower-quality studies)			–	–	–	–
LER + exercise	Exercise alone	VascuQOL				
Direction of benefit			–	↑	↑	↑
Strength of evidence (number of higher- vs. lower-quality studies)			–	C (1 vs. 1)	B (1 vs. 1)	D (0 vs. 1)

Follow-up time periods included <6 months, 6 to 12 months, 12 to 18 months, and long-term follow-up extending beyond 18 months. ↑ indicated that results favored the intervention, ↓ indicated that results favored the control, ↔ indicated that results were neutral and favored neither the intervention nor the control, and ⊘ indicated equivocal results and cannot be determined because of conflicting results among studies. Three articles contributed to the data shown in this table.

LER = lower extremity revascularization, SF-12 = Medical Outcomes Short Form-12; SF-36 = Medical Outcomes Short Form-36; VascuQOL = vascular quality of life assessment.

in the United States indicating they had never referred a patient for SET even after CMS coverage began (40). Although a specific comparison of SET versus HBE was beyond the scope of this review, HBE should be considered as an alternative in those who are unable or unwilling to participate in a SET program (41), with the most effective HBE programs including behavioral change techniques and more frequent visits to the medical center (35).

Costs related to these interventions have also been previously evaluated (42–44). These studies conclude that SET is more cost effective compared to unsupervised exercise (42) and that ET at 6 months costs less that LER (in the form of percutaneous transluminal angioplasty) (44). Comparing ET to LER in 98 individuals within the CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) study, at 18 months of follow-up, the health care costs exceeded $5,000, $9,800, and $14,500 for optimal medical care, ET, and LER, respectively (43), suggesting that in addition to having stronger evidence to support an exercise-first approach, the expenses related to LER may also favor ET. To date, the cost related to the combination of therapies has not been evaluated or compared to that of either intervention alone.

Strengths of this structured review include an inclusive approach to selecting relevant articles for evaluation. This review also addresses the broad range of follow-up timepoints in this body of published reports. This is particularly important when adherence to exercise can decline over time, and for LER, some interventions may fail over time, leading to loss of benefit. Past quantitative meta-analyses have lumped together differing follow-up intervals. Our review, examining qualitative benefit as a function of time, provides additional longitudinal insights. The summary results can help guide the clinician to what we believe is the strongest available evidence to support the conclusions. Finally, the review emphasizes the gaps in published reports and areas for future study.

The review has limitations. First, conclusions about the benefits of ET and LER in symptomatic PAD are based on trials of unblinded participants (and often unblinded assessors). Despite the inclusion of more objective performance outcomes, participant knowledge of treatment could influence outcomes. Head-to-head comparisons of open-label therapies may produce more robust results but are still not immune to the biases of patient and provider pre-intervention beliefs. The higher-quality studies relied on to draw

TABLE 8 Comparison of Randomized Controlled Trials Evaluating the Combination of Lower Extremity Revascularization With Aerobic Exercise Therapy Versus Lower Extremity Revascularization Alone

Intervention	Control	Outcome	<6 Months	6-12 Months	12-18 Months	>18 Months
LER + exercise	LER alone	Peak walking performance				
Direction of benefit			↑	↑	↑	↓
Strength of evidence (number of higher- vs. lower-quality studies)			B (1 vs. 1)	C (0 vs. 2)	D (0 vs. 1)	D (0 vs. 1)
LER + exercise	LER alone	Claudication onset				
Direction of benefit			↑	↓	↔	↓
Strength of evidence (number of higher- vs. lower-quality studies)			C (1 vs. 0)	D (0 vs. 1)	D (0 vs. 1)	D (0 vs. 1)
LER + exercise	LER alone	Need for post-randomization revascularization				
Direction of benefit			–	↔	↑	↑
Strength of evidence (number of higher- vs. lower-quality studies)			–	D (0 vs. 1)	D (0 vs. 1)	D (0 vs. 1)
LER + exercise	LER alone	SF-36, SF-12				
Direction of benefit			–	↔	↔	↓
Strength of evidence (number of higher- vs. lower-quality studies)			–	B (1 vs. 1)	D (0 vs. 1)	D (0 vs. 1)
LER + exercise	LER alone	Walking Impairment Questionnaire				
Direction of benefit			–	↑	–	–
Strength of evidence (number of higher- vs. lower-quality studies)			–	D (0 vs. 1)	–	–
LER + exercise	LER alone	VascuQOL				
Direction of benefit			–	↔	↓	↓
Strength of evidence (number of higher- vs. lower-quality studies)			–	D (0 vs. 1)	D (0 vs. 1)	D (0 vs. 1)

Follow-up time periods included <6 months, 6 to 12 months, 12 to 18 months, and long-term follow-up extending beyond 18 months. ↑ indicates that results favored the intervention, ↓ indicates that results favored the control, ↔ indicates that results were neutral and favored neither the intervention nor the control, and ∅ indicates equivocal results and cannot be determined because of conflicting results among studies. Five articles contributed to the data shown in this table.

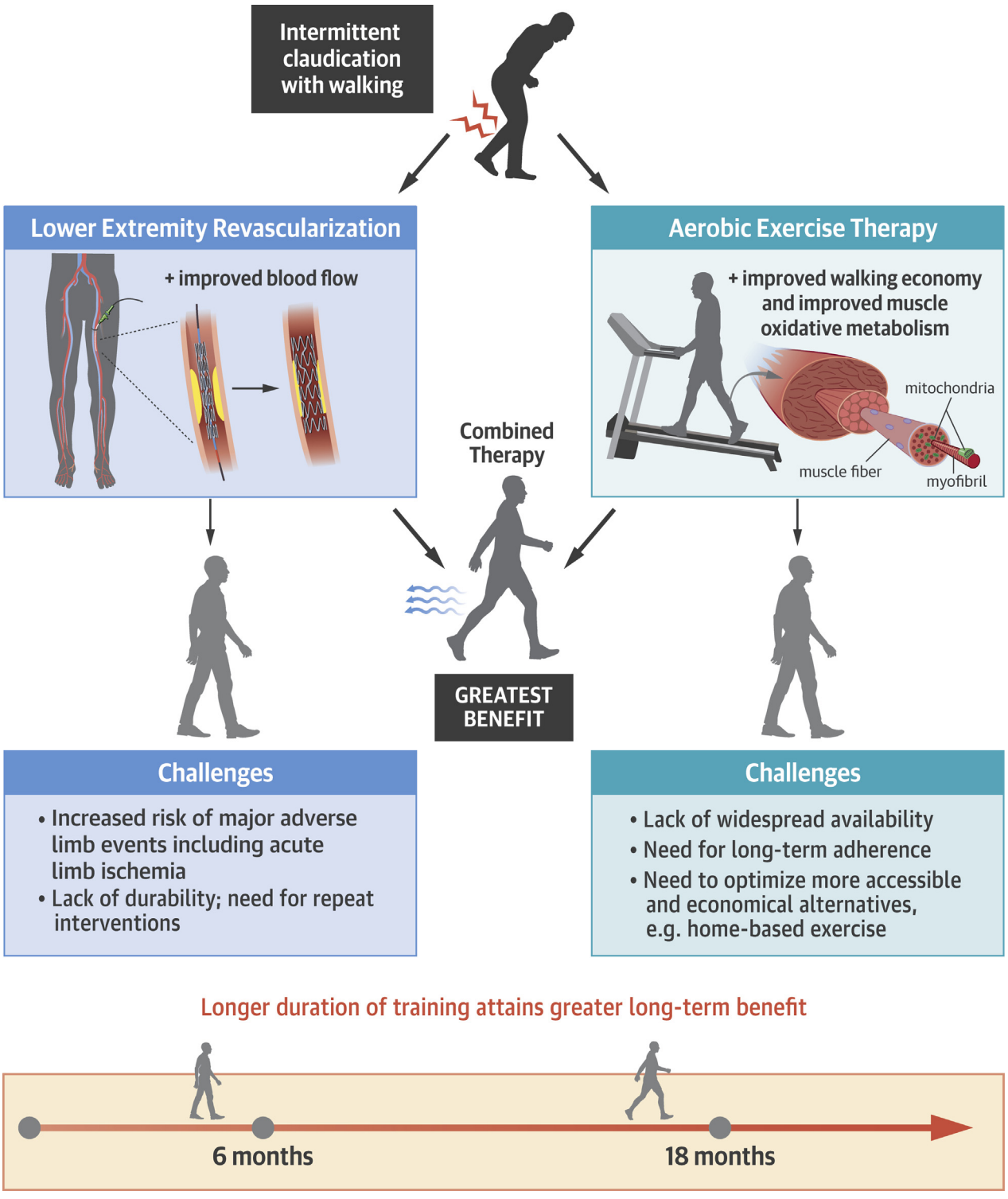
LER = lower extremity revascularization, SF-12 = Medical Outcomes Short Form-12; SF-36 = Medical Outcomes Short Form-36; VascuQOL = vascular quality of life assessment.

conclusions tended to blind the outcome assessors, which may help mitigate this source of bias. Second, potential pre-randomization selection bias (as defined in Methods section) may affect results as well. Twenty-three of the 38 trials provided sufficient methodologic information to determine whether patients were excluded for reasons outside of the study-specific exclusion criteria and could contribute to potential selection biases. Some possible reasons for exclusion included unwillingness to participate in a control group, failure to complete run-in, refusal due to time or transportation demands, being not interested, or being unable to attend 3 sessions per week. The potential pre-randomization selection bias was reported in 24 trials and ranged from 5% to 77% (with a median of 46.5%); the higher this value, the more likely a trial population was pre-selected to respond to the intervention or that results may not be generalizable. Those studies that evaluated ET (without LER) had a median potential pre-randomization selection bias of 46.5%, whereas those that included an evaluation of LER had a median of 47%. Combined with lack of participant blinding, the reported results should be viewed as a best-case scenario for these treatment modalities.

Another limitation is that the review is not a formal meta-analysis because of the heterogeneity of published reports. As noted in a recent meta-analysis of 7 trials, the I^2 statistics for maximum walking distance were 87.5% and 88.2% for the comparison of LER versus SET and of the combination of LER plus SET versus SET alone, respectively (45). We instead focused on a qualitative evaluation of the direction of benefit to compensate for the varied study designs and outcomes; this approach allowed for a more comprehensive summary of studies using a variety of peak performance measures. A weakness of this approach is that it gives all studies equal weight regardless of the peak exercise outcome used, some of which may be more rigorous or provide different absolute distances than others. This difference among endpoints is illustrated in the different net percent benefit seen between treadmill versus 6MW test as the primary outcome (see Supplemental Tables). The well-established learning effect of treadmill testing is associated with greater percent improvements (training to the test), particularly after a supervised treadmill exercise intervention (13).

A final limitation is the fact that most studies did not include measurement of peak oxygen consumption, which assesses an objective parameter of exercise training. For example, in a study of supervised treadmill versus strength training, both training modalities improved PWT on a treadmill, but only

CENTRAL ILLUSTRATION **The Differences in the Net Percent Change in Peak Walking Performance**



Biswas, M.P. et al. J Am Coll Cardiol Basic Trans Science. 2021;6(2):174–88.

Peak walking performance was defined as the maximum walking distance or time, as measured by treadmill, 6-min walk, or shuttle walk tests.

treadmill training improved peak oxygen uptake (46). This suggests that strength training may be less effective at eliciting a physiologic training response than treadmill training.

For the trialists, questions still remain, including the need to define the optimal treatment strategy, which would likely include starting with ET with the option to add LER, depending on the response of the patient, while continuing the ET post-intervention. A particularly intriguing finding was that LER alone may increase the need for subsequent LER procedures (consistent with other published reports) but that when combined with ET, the risk of subsequent LER may be decreased. This needs to be confirmed in larger, dedicated trials, but 1 possible mechanism would be that the additional functional improvement provided by ET after LER may lead to improved quality of life and less patient need for further invasive treatments. If confirmed, these results have implications for reducing the health costs and risks of recurrent procedures coupled with improved patient outcomes.

Further study is also needed to better understand the reasons for variability in response to ET in people with PAD, which has limited study but indicated obesity in men (47), including methods to improve adherence to ET programs. Additional studies of combination therapy compared to LER alone are needed, given that there is only 1 higher-quality study evaluating this comparison. The durability of these interventions alone and in combination still remains unanswered. Often, the trials evaluating long-term outcomes provided weak or inconclusive evidence, and the interventions were not always continued through the long-term follow-up, because the long-term follow-up was not pre-specified. Similarly, questions surrounding the future need for revascularization remain after either intervention alone or in combination and are of significant interest, although there appears to be a benefit of the combination of therapies over either therapy alone. In addition, the role of ET in preventing the need for future revascularization is not entirely clear. If either therapy increases the future risk of adverse limb events or the need for repeat procedures, this is an important consideration in the benefit-risk discussion with patients. Future trials of any therapy in symptomatic PAD should report this outcome. Questions also still remain regarding why PROs do not align well with objective measures of improvement. The evaluation of the minimum clinically important difference (MCID) in exercise or revascularization treatments for symptomatic PAD has not been well assessed. For example, the MCID for a treadmill-assessed PWD is not the same as the MCID for a 6MW-assessed PWD, and they are not interchangeable (13). However, more recently, studies have attempted to evaluate the potential MCID for various measures including ETT outcomes, 6MW test outcomes (48), and VascuQOL outcomes (49). Most importantly, trials should attempt to obtain complete follow-up, report on adverse events, and include more racially and gender-diverse populations.

For the clinician caring for those individuals with PAD, this review should provide information about the specific benefits of the primary treatment options for symptomatic PAD and provide new insight into the additive benefits of combined ET plus LER, particularly as it pertains to durability of the benefit and the potential to decrease the risk for future interventions.

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KEY WORDS evidence, exercise therapy (supervised exercise training, home-based exercise programs), lower extremity revascularization

APPENDIX For supplemental tables, please see the online version of this paper.