Comparing Supervised Exercise Therapy to Invasive Measures in the Management of Symptomatic Peripheral Arterial Disease

Thomas Aherne, Seamus McHugh, Elrasheid A. Kheirelseid, Michael J. Lee, Noel McCaffrey, Daragh Moneley, Austin L. Leahy, and Peter Naughton

1 Department of Vascular Surgery, Beaumont Hospital, Dublin 9, Ireland
2 Department of Interventional Radiology, Beaumont Hospital, Dublin 9, Ireland
3 Department of Human and Health Performance, Dublin City University, Dublin 9, Ireland

Correspondence should be addressed to Thomas Aherne; thomasaherne@rcsi.ie

Received 1 June 2015; Revised 5 October 2015; Accepted 11 October 2015

1. Introduction

Peripheral arterial disease (PAD) affects 12–16% of the population over the age of 60 years with intermittent claudication (IC), its primary symptom, proving detrimental to patient quality of life [1–4]. Typically PAD follows a stable course with management confined to conservative measures; however one in ten PAD patients will develop critical limb ischaemia (CLI) with all-cause mortality in the CLI cohort rising to 50% at 5 years [5–7]. This reduction in life expectancy is due largely to concomitant cardiovascular disease [8, 9].

Therefore, treatment goals should focus not only on the alteration of disease progression and symptomatic relief but also on the improvement of patient long-term survival [10]. Approaches include the modification of risk factors through optimum medical therapy (OMT) and supervised exercise therapy (SET) with endovascular (EVR) and open surgical revascularization reserved for those failing conservative measures. Further novel therapies including kinesitherapy and electrotherapeutic procedures have also been proposed [11]. While endovascular treatment offers a minimally invasive revascularization option for many patients data supporting its ability to improve long-term survival is lacking. Regular exercise, on the other hand, is associated with a 50% reduction in cardiovascular mortality [12]. Supervised exercise training consists of a prescribed, evidence based exercise program which is performed under the direct observation of a trained practitioner. It is now well established as an initial noninvasive option in all PAD patients with robust supporting data [13–15].

Rationale for Review. Despite its intuitive benefits a wide variation in the use and availability of SET exists and it remains a greatly underutilized resource due to limited patient access [16]. The BASIL study highlights the deficiencies in the current medical optimization with few participants utilizing
clinically proven best medical therapy [7, 17]. The issue is further clouded by conflicting literature as to the optimal nonsurgical management of these patients [18–32]. Thus while its use is strongly supported by current literature it appears that SET is underutilized in mild-to-moderate PAD while its use in more advanced disease requires further clarification. With this likely in mind the Institute of Medicine has prioritized research into the comparative efficacy of the different treatment modalities for PAD [33]. Furthermore, the role of SET as an adjunct to or substitute for intervention remains unclear.

The aim of this review was to compare the use of supervised exercise therapy to invasive measures in the management of symptomatic peripheral arterial disease thus clarifying an exact role for SET in the management of this patient cohort.

2. Methods

2.1. Study Eligibility. All randomised controlled trials (RT) assessing exercise in conjunction with or in comparison to an endovascular or open intervention in the management of peripheral arterial disease were included for review (Table 1). All observational and review data were excluded from the results. Relevant papers were searched and evaluated independently by two assessors. Outcomes were tabulated where figures were included.

2.2. Literature Search. The online medical literature database PUBMED was systematically searched. All studies and relevant reviews were manually cross-referenced to identify any outstanding articles.

PubMed was last searched on September 18, 2015 (Figure 1). The database was comprehensively searched without date or language restriction using the following search strategy.

```
[[[[([(peripheral arterial disease] OR peripheral vascular
disease] OR claudication] AND angioplasty] OR revascularization] OR endovascular] OR open surgery] OR bypass]
AND exercise. A total of 8344 studies were identified. After
```

the filter for randomised controlled trials was applied 820 studies were identified. Relevant full articles were reviewed by two reviewers [TA, PN].

3. Results

A total of 15 papers (Table 1) report outcomes of 11 RT. These trials include a total of 969 patients and all directly compare supervised exercise with various invasive interventions. Maximum walking distance (MWD), intermittent claudication distance (ICD), and ankle brachial pressure index (ABPI) measurement form the cornerstones of vascular assessment in each study.

3.1. Quality Assessment of Assessed Data. The risk of bias in each included study is summarised in Table 2. Few papers reported any participant heterogeneity with regard to baseline function, comorbidities, and smoking status. Risk assessment was performed with guidance from the Cochrane Handbook for Systematic Reviews of Interventions [34].

3.2. Supervised Exercise versus Endovascular Intervention. Five trials including 519 patients directly compare the outcomes of EVR and SET in the management of peripheral arterial disease (Table 3).

At six months Murphy et al. reported significant improvements in maximum walk times in those undergoing SET compared to those in the EVR group [18]. However, at 18-month follow-up this benefit was lost with no significant difference in walk times identified [32]. ABPI were consistently higher in the EVR group. Creasy and Perkins noted significant improvements in the functionality of both groups [19, 20]. Again, no significant change in ABPI was noted in any SET cohort. Improvement in mobility was most significant when the disease affected the superficial femoral artery. Hobbs et al. only noted significant improvements in walk distances in those receiving EVR [21]. No improvement was seen with SET alone. Spronk et al. reported a 1-week clinical success rate of 88% following EVR decreasing to 68% at 12 months while the SET group had an early success rate of

---

**Table 1: Treatment groups and disease level.**

| Study                  | Patient number | EVR | SET | Intervention | Study Patient number | Intervention | Study Patient number | Intervention |
|------------------------|----------------|-----|-----|--------------|-----------------------|--------------|-----------------------|--------------|
| Lundgren et al. [30]   | 75             | 25  |     | EVR + SET    | 75                    | 25           | 25                    |
| Creasy et al./Perkins et al. [19, 20] | 56 | 30  | 26  | INV         | 75                    | 28           | 25                    |
| Gelin et al. [29]      | 164            | 88  |     | EVR + SET    | 88                    | 66           | Not recorded           |
| Hobb et al. [21]       | 23             | 9   | 7   | SET         | 23                    | 14           | 0                     |
| Badger et al. [31]     | 14             |     | 6   | SET         | 14                    | 8            | 0                     |
| Greenhalgh et al. [26] | 127            | 60  | 67  | SET         | 93                    | 94           |                       |
| Kruidenier et al. [27] | 70             | 35  |     | SET         | 70                    | 35           | 5                     |
| Mazari et al. [25]     | 178            | 60  | 60  | SET         | 58                    | Not recorded |
| Spronk et al./Fakhry et al. [22–24] | 151 | 76  | 75  | SET         | 44                    | 106          | —                     |
| Murphy et al. [18, 32] | 111            | 46  | 43  | SET         | 0                     | 111          | 0                     |
| Bø et al. [28]         | 50             | 21  | 29  | SET         | 25                    | 25           | 0                     |

EVR: endovascular revascularization; SET: supervised exercise therapy; INV: invasive management; Fem-pop: femoropopliteal.
| Study                        | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Incomplete outcome data | Selective reporting | Other sources of bias |
|-----------------------------|-----------------------------|------------------------|----------------------------------------|-------------------------|---------------------|----------------------|
| Lundgren et al. [30]        | Randomised but not described | Randomised but not described | Blinding not possible | Follow-up data in each group incomplete | Clear outcomes | Unclear risk of bias |
| Creasy et al./Perkins et al. [19, 20] | Randomised but not described | Randomised but not described | Blinding not possible | No loss to follow-up reported | Clear outcomes | Unclear risk of bias |
| Gelin et al. [29]           | Randomised via computer based algorithm | Randomised via computer based system | Blinding not possible | Some loss to follow-up | Clear outcomes | Low risk of bias    |
| Hobbs et al. [21]           | Randomised with 2 × 2 factorial design | Computer generated randomisation | Blinding not possible | Four withdrawals | Clear outcomes | Low risk of bias    |
| Badger et al. [31]          | Randomised but not described | Randomised but not described | Blinding not possible | All patients lost to 6-month follow-up | Clear outcomes | Unclear risk of bias |
| Greenhalgh et al. [26]      | Detailed description of Stata generated randomisation | Computer generated randomisation | Blinding not possible | Moderate loss to follow-up | Clear outcomes | Low risk of bias    |
| Kruidenier et al. [27]      | Computer generated block randomisation | Computer generated block randomisation | No blinding | Moderate losses to follow-up | Clear outcomes | Low risk of bias    |
| Mazari et al. [25]          | Sealed envelope used to randomise | Sealed envelope used to randomise | Blinding not described | Moderate loss to follow-up | Clear outcomes | Unclear risk of bias |
Table 2: Continued.

| Study            | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Incomplete outcome data | Selective reporting | Other sources of bias | Risk of bias |
|------------------|-----------------------------|------------------------|----------------------------------------|-------------------------|---------------------|----------------------|--------------|
| Spronk et al./Fakhry et al. [22–24] | Computer generated block randomisation | Computer generated block randomisation | Blinding not possible | Prolonged study with some loss to follow-up | Clear outcomes | None | Low risk of bias |
| Murphy et al. [18,32] | Web based randomisation | Web based randomisation | Observers blinded | Prolonged study with some loss to follow-up | Clear outcomes | None | Low risk of bias |
| Bø et al. [28] | Computer based randomisation | Computer based randomisation | Observers blinded | No loss to follow-up | Clear outcomes | None | Low risk of bias |

Figure 1: Flow diagram depicting study identification.

16% increasing to 65% by 12 months [22, 23]. Clinical success was defined as an improvement in at least one category in the Rutherford scale posttreatment. Long-term outcomes (7 years) from this RT show maintenance of the functional gains achieved at 1 year with no variance in amputation rate 10 between groups [24]. Finally, Mazari et al. identified significant functional improvements in both groups at one year; however no statistically significant difference was identified between cohorts [25]. Again, only EVR was associated with improved ABPI measurements.

3.3. Supervised Exercise Plus Invasive Measures (Open Surgery or EVR) versus Monotherapy. In total six studies inclusive of 514 patients compare the merits of combination therapy consisting of invasive intervention and SET and single intervention alone (Table 4). Two included studies examine the benefits of a combination of open arterial surgical reconstruction and SET [30, 31] while four articles assess dual therapy including both EVR and SET [25–28].

The earliest work in this area by Lundgren et al. compares open arterial reconstruction and SET with open surgery.
### Table 3: Supervised exercise versus endovascular revascularization.

| Study                     | Follow-up | ABPI Baseline | ABPI Endpoint | MWD Baseline | MWD Endpoint | ICD Baseline | ICD Endpoint | P  |
|---------------------------|-----------|---------------|---------------|--------------|--------------|--------------|--------------|-----|
| Hobbs et al. [21]         | 6 months  | 0.69          | 0.93          | 0.013        | 185          | 698          | 0.008        | 84  |
|                           |           | 0.66          | 0.70          | 0.46         | 111          | 124          | 0.35         | 59  |
| Mazari et al. [25]        | 12 months | 0.71          | 0.90          | 0.093        | 83           | 215          | 0.2          | 42  |
|                           |           | 0.72          | 0.84          | 0.115        | 59           | 92           | 0.074        |     |
| Spronk et al/Fakhry et al. [22–24] | 7 years  | 0.63          | 0.84          | 0.35         | 174          | 1248         | 0.48         | 82  |
|                           |           | 0.62          | 0.82          | 0.16         | 186          | 1168         | 0.48         | 104 |
| Murphy et al. [18, 32]    | 18 months | 0.7           | 5.2 min       | 8.4 min      | 1.8 min      | 4.8 min      |              |     |
|                           |           | 0.6           | <0.001        | 5.6 min      | 10.6 min     |              |              |     |

ABPI: ankle brachial pressure index; MWD: maximal walk distance; ICD: intermittent claudication distance; EVR: endovascular revascularization; SET: supervised exercise therapy. Distances in metres unless otherwise stated. * represents significant improvement favouring combined treatment. P value represents statistical comparison of interventions except in Hobbs et al. [21] where † represents change in measurement over study period.

### Table 4: Supervised exercise plus invasive measures (open surgery or EVR) versus monotherapy.

| Study                     | Follow-up | ABPI Baseline | ABPI Endpoint | MWD Baseline | MWD Endpoint | ICD Baseline | ICD Endpoint | P  |
|---------------------------|-----------|---------------|---------------|--------------|--------------|--------------|--------------|-----|
| Lundgren et al. [30]      | 13 months | 0.55          | —             | 209          | 570          | 85           | 405          |     |
| Surgery                   |           | 0.59          | —             | 180          | 654          | 70           | 559          |     |
| SET                       |           | 0.59          | —             | <0.001       | 183          | 459          | 0.05         | 67  |
| Surgery + SET             |           | —             | —             | —            | —            | —            | —            |     |
| Badger et al. [31]        | 6 months  | —             | —             | —            | —            | —            | —            |     |
| Surgery                   |           | —             | 0.02*         | —            | —            | —            | —            |     |
| Surgery + SET             |           | 0.59          | —             | <0.001       | 180          | 545          | 0.05         | 67  |
| Greenhalgh et al. [26]    | 24 months | 0.66          | 0.74          | 126          | 168          | —            | —            |     |
| (Aortoiliac) SET          |           | 0.68          | 0.90          | 114          | 354          | 0.05         | —            |     |
| EVR + SET                 |           | 0.66          | 0.83          | 133          | 245          | 0.4          | —            |     |
| Greenhalgh et al. [26]    | 24 months | 0.69          | 0.72          | 126          | 155          | —            | —            |     |
| (Femoropopliteal) SET     |           | 0.66          | 0.83          | 133          | 245          | 0.4          | —            |     |
| EVR + SET                 |           | 0.66          | 0.83          | 133          | 245          | 0.4          | —            |     |
| Kruidenier et al. [27]    | 6 months  | 0.71          | 0.93          | 282          | 685          | 343          | 547          |     |
| EVR                       |           | 0.69          | 0.88          | 0.755        | 186          | 956          | 0.001        | 293 |
| EVR + SET                 |           | 0.69          | 0.88          | 0.755        | 186          | 956          | 0.001        | 293 |
| Mazari et al. [25]        | 12 months | 0.71          | 0.9           | 77           | 146          | 31           | 75           |     |
| EVR                       |           | 0.72          | 0.84          | 83           | 215          | 42           | 97           |     |
| EVR + SET                 |           | 0.64          | 0.92          | 85           | 187          | 0.259        | 43           | 99  |
| Bo et al. [28]            | 3 months  | —             | —             | 213          | 427          | 94           | 267          |     |
| EVR                       |           | —             | —             | <0.001       | 385          | 584          | NS           | 101 |
| EVR + SET                 |           | —             | —             | 213          | 427          | 94           | 267          |     |

ABPI: ankle brachial pressure index; MWD: maximal walk distance; ICD: intermittent claudication distance; EVR: endovascular revascularization; SET: supervised exercise therapy. Distances in metres unless otherwise stated. * represents significant improvement favouring combined treatment. P value represents statistical comparison of interventions. — represents nonreported figures.
alone [30]. This study identified improvements in walk distances in both groups; however, those undergoing combination therapy experienced significantly improved walking performance at 13 months. Similarly, Badger et al. identified significant improvements in MWD and ICD with a lower incidence of reintervention compared to the monotherapy groups [25]. This benefit was further supported by randomised data from Greenhalgh et al. [26–28]. At six months Kruidenier et al. identified significantly lengthened walk distances when SET was used as an adjunct to EVR. Furthermore, both Greenhalgh and Bo et al. examined patients with both aortoiliac and infrainguinal disease in separate trial limbs. While Greenhalgh compared combination therapy with SET alone Bo et al. contrasted dual therapy with EVR alone. Both studies identified improvements in walk distances in both trial limbs for patients undergoing combination therapy versus monotherapy; however only Greenhalgh identified significantly better ABPI in the dual intervention group.

3.4. Invasive (EVR or Surgery) Management versus Supervised Exercise. Gelin alone compared invasive intervention (either EVR or open surgery based on preoperative angiography) and supervised exercise [29] (Table 5). At one year only those randomised to invasive measures experienced any improvement in walk distance or lower limb arterial pressures.

3.5. Open Surgery versus Supervised Exercise. Lundgren et al. included a comparison of open revascularisation and SET in the previously discussed RT [30]. At 13 months those undergoing open surgery had better functional performance than those undergoing SET alone. In addition, those undergoing surgery experienced a significantly higher ABPI to those in the exercise group.

| Study          | Follow-up | ABPI Baseline | ABPI Endpoint | MWD Baseline | MWD Endpoint | ICD Baseline | ICD Endpoint | P ABPI | P MWD | P ICD |
|----------------|-----------|---------------|---------------|--------------|--------------|--------------|--------------|--------|-------|-------|
| Gelin et al. [29] | 12 months | 0.55          | 0.71          | <0.01†       | 274          | 344          | <0.01†       | —      | —     | —     |
| SET            |           | 0.56          | 0.54          | —            | 258          | 247          | —            | —      | —     | —     |

TABLE 5: Invasive (EVR or surgery) management versus supervised exercise.

ABPI: ankle brachial pressure index; MWD: maximal walk distance; ICD: intermittent claudication distance; EVR: endovascular revascularization; SET: supervised exercise therapy. Distances in metres unless otherwise stated. P value represents statistical comparison of interventions. † represents change in measurement over study period.

has shown a 122% increase in walking distances in patients undergoing exercise therapy [15]. This has been reinforced by the more recent Cochrane review examining exercise for IC [36]. However, despite its success intensive programs continue to be associated with high dropout rates [37].

The exact physiological mechanism by which exercise improves performance is incompletely understood. Multiple physiological adaptations have been proposed as contributing factors. Arterial collateralization has the potential to improve peripheral blood flow in the ischaemic limb with the exercised muscle displaying increased levels of the proangiogenic vascular endothelial growth factor [38]. However, improved functional performance in the trained limb is not reflective of improved ABPI measurements as seen in endovascular revascularization [18, 39]. Increased arterial shear stress in exercise is associated with nitric oxide (NO) release, a powerful vasoactive agent [40]. This endothelial-mediated response is impaired in patients with PAD [41]. The concept of “hemorheologic fitness” suggests that a proven reduction in blood viscosity in the trained individual may result in improved peripheral metabolic efficiency [42]. In addition, gait proficiency, reversal of acquired metabolic myopathies, and modified inflammatory responses all have the potential to improve exercise related function [43–46].

This review suggests a number of roles for supervised exercise therapy in the symptomatic PAD patient (Figure 2). Significantly, no study reported exercise related complications.

(i) Direct comparison of SET and endovascular measures revealed similar functional outcomes for both interventions in the medium term across a number of studies with long-term data from one study identifying comparable limb salvage between groups. However, only EVR alone resulted in significant improvements in lower limb perfusion as measured by ABPI. These data have significant applicability to symptomatic patients whose comorbidities allow them to exercise to an adequate level for SET. Supervised exercise offers this group an acceptable, effective initial step in those capable and motivated to take part.

(ii) In those requiring intervention a combination of surgical intervention and SET offered superior outcomes to monotherapy across multiple studies. Two trials assessed open surgery with adjunctive SET with both suggesting significant benefits in walk distances.
Intermittent claudication

Underlying diagnosis confirmed with ABPI/duplex/walk testing

Optimal medical therapy + supervised exercise

Indication for endovascular therapy (10/13)
(i) Unfavourable response predicted or achieved using conservative measures
(ii) Markedly impaired activities of daily living
(iii) Suitable lesion morphology (TASC grade A ± B/C)
(iv) Positive overall patient prognosis
(v) Absence of other comorbidities that would limit function

Indication for open surgery (10/13)
(i) Unfavourable response to non operative methods
(ii) Favourable anatomy
(iii) Appropriate risk : benefit ratio

Adjuvant supervised exercise therapy

**Figure 2:** Management of intermittent claudication incorporating supervised exercise therapy.

in the dual therapy group. Similarly, all four trials assessing endovascular intervention in conjunction with SET compared to monotherapy found greater improvements in the walking distances of those undergoing dual therapy. These data would strongly support the use of SET as an adjunct to any operative intervention in the management of symptomatic PAD.

(iii) Only one study directly compared open surgery and SET. This strongly supported the surgical approach in terms of both function and perfusion outcomes.

Multiple exercise modalities including treadmill walking, resistance training, and upper limb ergometry have proven benefit in PAD [12, 36, 47, 48]. Unfortunately, the success of SET is reliant on excellent compliance and availability. Supervised exercise training has been shown to consistently result in improved functionality with superior outcomes to a "go home and walk" approach [49–51]. Compliance can further be augmented by regular exercise reminders, patient specific exercise prescriptions, target setting, and the incorporation of exercise into daily activities [52]. Gains in walk time and claudication onset occur rapidly over the initial 2 months and can be maintained with good compliance [53]. An exercise prescription of at least two 30-minute sessions per week offers optimal walking outcomes [54].

In those failing or unable to partake in an initial exercise program endovascular revascularization offers low rates of periprocedural morbidity and mortality with excellent initial success rates [55–57]. However the two main shortcomings of endovascular intervention include long-term durability and overall poor survival rates associated with concomitant cardiovascular disease. Supervised exercise addresses some of these concerns. By stimulating collateralization and the release of vasodilators such as nitric oxide exercise therapy should confer superior functional results in the longer-term. This is supported by a number of studies [58, 59]. Thus, for this patient group SET offers not only functional improvement but also significant benefits to the cardiovascular health of these patients [12].

4.1. Strengths and Limitations. This review is strengthened by the fact that all incorporated data are from well-designed randomised controlled studies. Follow-up ranged from 6 months to 12 years. Cumulatively these trials incorporate a significant number of claudicants. Individually papers provide strong data that exercise results in significant gains in walk distance. In addition, a number of studies have found that a combination of SET and intervention provides a superior outcome to monotherapy.

This review is however subject to a number of limitations. Firstly, while all patients had significant arterial symptoms a degree of heterogeneity exists in this cohort. Each included study describes slight variations in the level of disease, the symptomatic presentation, and the intervention received rendering definitive conclusion difficult. Secondly, many studies included small numbers of participants with a number reporting moderate losses to follow-up. Finally, due to the heterogeneity of outcome data meta-analysis was not performed as part of this review.
5. Conclusion

Exercise is an effective, safe, and economical method of treating symptomatic PAD [23]. Some randomised data now suggests that it may be comparable to EVR in the management of symptomatic noncritical ischaemia. Furthermore, there is emerging evidence that combining endovascular intervention following by supervised exercise achieves better long-term results than endovascular intervention alone; however, greater surgeon access to and awareness of this important adjuvant therapy is essential to maximize therapeutic outcomes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] M. H. Criqui, A. Fronek, E. Barrett-Connor, M. R. Klauber, S. Gabriel, and D. Goodman, “The prevalence of peripheral arterial disease in a defined population,” Circulation, vol. 71, no. 3, pp. 510–515, 1985.

[2] M. Schroll and O. Munck, “Estimation of peripheral atherosclerotic disease by ankle pressure measurements in a population study of 60-year-old men and women,” Journal of Chronic Diseases, vol. 34, no. 6, pp. 261–269, 1981.

[3] E. Selvin and T. P. Erlinger, “Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000,” Circulation, vol. 110, no. 6, pp. 738–743, 2004.

[4] I. C. Chetter, P. Dolan, J. I. Spark, D. J. A. Scott, and R. C. Kester, “Correlating clinical indicators of lower-limb ischaemia with quality of life,” Cardiovascular Surgery, vol. 5, no. 4, pp. 361–366, 1997.

[5] K. Bloor, “Natural history of atherosclerosis of the lower extremities—hunterian lecture delivered at the Royal College of Surgeons of England on 22nd April 1960,” Annals of the Royal College of Surgeons of England, vol. 28, no. 1, pp. 36–52, 1961.

[6] J. A. Dormandy, L. Heeck, and S. Vig, “The fate of patients with critical leg ischemia,” Seminars in Vascular Surgery, vol. 12, no. 2, pp. 142–147, 1999.

[7] A. W. Bradbury, D. J. Adam, J. D. Beard et al., “Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial,” The Lancet, vol. 366, no. 9501, pp. 1925–1934, 2005.

[8] M. H. Criqui, R. D. Langer, A. Fronek et al., “Mortality over a period of 10 years in patients with peripheral arterial disease,” The New England Journal of Medicine, vol. 326, no. 6, pp. 381–386, 1992.

[9] F. G. R. Fowkes, “Epidemiology of atherosclerotic arterial disease in the lower limbs,” European Journal of Vascular Surgery, vol. 2, no. 5, pp. 283–291, 1988.

[10] J. A. Dormandy and R. B. Rutherford, “Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC),” Journal of Vascular Surgery, vol. 31, no. 1, part 2, pp. S1–S296, 2000.

[11] M. D. Markovic, D. M. Markovic, M. V. Dragas et al., “The role of kinesitherapy and electrotherapeutic procedures in non-operative management of patients with intermittent claudications,” Vascular, 2015.

[12] K. E. Powell and M. Pratt, “Physical activity and health,” British Medical Journal, vol. 313, no. 7050, pp. 126–127, 1996.

[13] A. T. Hirsch, Z. J. Haskal, N. R. Hertzer et al., “ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary 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,” Journal of the American College of Cardiology, vol. 47, no. 6, pp. 1239–1312, 2006.

[14] L. Norgren, W. R. Hiatt, and J. A. Dormandy, “Inter-society consensus for the management of peripheral arterial disease (TASC II),” European Journal of Vascular and Endovascular Surgery, vol. 33, supplement 1, pp. S1–S75, 2007.

[15] A. W. Gardner and E. T. Poehlman, “Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis,” The Journal of the American Medical Association, vol. 274, no. 12, pp. 975–980, 1995.

[16] A. H. Stewart and P. M. Lamont, “Exercise for intermittent claudication. Supervised programmes should be universally available,” The British Medical Journal, vol. 323, no. 7315, pp. 703–704, 2001.

[17] P. Burns, S. Gough, and A. W. Bradbury, “Management of peripheral arterial disease in primary care,” British Medical Journal, vol. 326, no. 7389, pp. 584–588, 2003.

[18] T. P. Murphy, D. E. Cutlip, J. G. Regensteiner et al., “Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal recanalization (CLEVER) study,” Circulation, vol. 125, no. 1, pp. 130–139, 2012.

[19] T. S. Creasy, P. J. McMillan, E. W. L. Fletcher, J. Collin, and P. J. Morris, “Is percutaneous transluminal angioplasty better than exercise for claudication? Preliminary results from a prospective randomised trial,” European Journal of Vascular Surgery, vol. 4, no. 2, pp. 135–140, 1990.

[20] J. M. T. Perkins, J. Collin, T. S. Creasy, E. W. L. Fletcher, and P. J. Morris, “Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial,” European Journal of Vascular and Endovascular Surgery, vol. 11, no. 4, pp. 409–413, 1996.

[21] S. D. Hobbs, T. Marshall, C. Fegan, D. J. Adam, and A. W. Bradbury, “The constitutive procoagulant and hypofibrinolytic state in patients with intermittent claudication due to infrainguinal disease significantly improves with percutaneous transluminal balloon angioplasty,” Journal of Vascular Surgery, vol. 43, no. 1, pp. 40–46, 2006.

[22] S. Spronk, J. L. Bosch, P. T. den Hoed, H. F. Veen, P. M. T. Pattynama, and M. G. M. Hunink, “Intermittent claudication: clinical effectiveness of endovascular recanalization versus supervised hospital-based exercise training—randomized controlled trial,” Radiology, vol. 250, no. 2, pp. 586–595, 2009.
[23] S. Spronk, J. L. Bosch, P. T. den Hoed, H. F. Veen, P. M. T. Patynama, and M. G. M. Hunink, “Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial,” Journal of Vascular Surgery, vol. 48, no. 6, pp. 1472–1480, 2008.

[24] F. Fakhrly, E. V. Rouwet, P. T. Den Hoed, M. G. M. Hunink, and S. Spronk, “Long-term clinical effectiveness of supervised exercise therapy versus endovascular revascularization for intermittent claudication from a randomized clinical trial,” British Journal of Surgery, vol. 100, no. 9, pp. 1164–1171, 2013.

[25] F. A. K. Mazari, J. A. Khan, D. Carradice et al., “Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease,” British Journal of Surgery, vol. 99, no. 1, pp. 39–48, 2012.

[26] R. M. Greenhalgh, J. J. Belch, L. C. Brown, P. A. Gaines, L. Gao, and J. A. Reise, “The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotificemoropopliteal and aortoiliac arterial disease,” European Journal of Vascular and Endovascular Surgery, vol. 36, no. 6, pp. 680–688, 2008.

[27] L. M. Kruidenier, S. P. Nicola¨ı, E. V. Rouwet, R. J. Peters, M. H. Prins, and J. A. W. Teijink, “Additional supervised exercise therapy after a percutaneous vascular intervention for peripheral arterial disease: a randomized clinical trial,” Journal of Vascular and Interventional Radiology, vol. 22, no. 7, pp. 961–968, 2011.

[28] E. Bo, J. Hisdal, M. Cvanascarova et al., “Twelve-months follow-up of supervised exercise after percutaneous transluminal angioplasty for intermittent claudication: a randomised clinical trial,” International Journal of Environmental Research and Public Health, vol. 10, no. 11, pp. 5998–6014, 2013.

[29] J. Gelin, L. Jivegård, C. Taft et al., “Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training compared to no treatment in unselected randomised patients I: one year results of functional and physiological improvements,” European Journal of Vascular and Endovascular Surgery, vol. 22, no. 2, pp. 107–113, 2001.

[30] F. Lundgren, A.-G. Dahllöf, K. Lundholm, T. Schersten, and R. Volkmann, “Intermittent claudication—surgical reconstruction or physical training? A prospective randomized trial of treatment efficiency,” Annals of Surgery, vol. 209, no. 3, pp. 346–355, 1989.

[31] S. A. Badger, C. V. Soong, M. E. O’Donnell, C. A. G. Boreham, and K. E. McGuigan, “Benefits of a supervised exercise program after lower limb bypass surgery,” Vascular and Endovascular Surgery, vol. 41, no. 1, pp. 27–32, 2007.

[32] T. P. Murphy, D. E. Cutlip, J. G. Regensteiner et al., “Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study,” Journal of the American College of Cardiology, vol. 65, no. 10, pp. 999–1009, 2015.

[33] 100 initial topics for comparative effectiveness research, 2009, http://www.iom.edu/Reports/2009/ComparativeEffectiveness-ResearchPriorities.aspx.

[34] J. A. C. Sterne, M. Egger, and D. Moher, “Addressing reporting biases,” in Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, J. P. T. Higgins and S. Green, Eds., The Cochrane Collaboration, 2011.

[35] G. C. Leng, O. Papacosta, P. Whincup et al., “Femoral atherosclerosis in an older British population: prevalence and risk factors,” Atherosclerosis, vol. 152, no. 1, pp. 167–174, 2000.

[36] L. Watson, B. Ellis, and G. C. Leng, “Exercise for intermittent claudication,” The Cochrane Database of Systematic Reviews, no. 4, Article ID CD000990, 2008.

[37] B. L. Bendenmacher, E. M. Willigendael, S. P. Nicolai et al., “Supervised exercise therapy for intermittent claudication in a community-based setting is as effective as clinic-based,” Journal of Vascular Surgery, vol. 45, no. 6, pp. 1192–1196, 2007.

[38] T. Gustafsson, A. Puntschart, L. Kajser, E. Jansson, and C. J. Sundberg, “Exercise-induced expression of angiogenesis-related transcription and growth factors in human skeletal muscle,” American Journal of Physiology: Heart and Circulatory Physiology, vol. 276, no. 2, pp. H679–H685, 1999.

[39] R. Ekroth, A.-G. Dahllöf, B. Gunde vall, J. Holm, and T. Schersten, “Physical training of patients with intermittent claudication: indications, methods, and results,” Surgery, vol. 84, no. 5, pp. 640–643, 1978.

[40] M. Noris, M. Morigli, R. Donadelli et al., “Nitric oxide synthesis by cultured endothelial cells is modulated by flow conditions,” Circulation Research, vol. 76, no. 4, pp. 536–543, 1995.

[41] A. R. Yataco, M. C. Corretti, A. W. Gardner, C. J. Womack, and L. I. Katzel, “Endothelial reactivity and cardiac risk factors in older patients with peripheral arterial disease,” American Journal of Cardiology, vol. 83, no. 5, pp. 754–758, 1999.

[42] E. Ernst, “Influence of regular physical activity on blood rheology,” European Heart Journal, vol. 8, pp. 59–62, 1987.

[43] C. J. Womack, D. J. Sieminski, L. I. Katzel, A. Yataco, and A. W. Gardner, “Improved walking economy in patients with peripheral arterial occlusive disease,” Medicine & Science in Sports & Exercise, vol. 29, no. 10, pp. 1286–1290, 1997.

[44] T. A. Beckitt, J. Day, M. Morgan, and P. M. Lamont, “Calf muscle oxygen saturation and the effects of supervised exercise training for intermittent claudication,” Journal of Vascular Surgery, vol. 56, no. 2, pp. 470–475, 2012.

[45] P. V. Tisi, M. Hulse, A. Chulakadabba, P. Gosling, and C. P. Shearman, “Exercise training for intermittent claudication: does it adversely affect biochemical markers of the exercise-induced inflammatory response?” European Journal of Vascular and Endovascular Surgery, vol. 14, no. 5, pp. 344–350, 1997.

[46] K. J. Stewart, W. R. Hiatt, J. G. Regensteiner, and A. T. Hirsch, “Exercise training for claudication,” The New England Journal of Medicine, vol. 347, no. 24, pp. 1941–1951, 2002.

[47] M. M. McDermott, P. Ades, J. M. Guralnik et al., “Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial,” The Journal of the American Medical Association, vol. 301, no. 2, pp. 165–174, 2009.

[48] I. Zwierska, R. D. Walker, S. A. Cholksy, J. S. Male, A. G. Pockley, and J. M. Saxton, “Upper—vs lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: a randomized controlled trial,” Journal of Vascular Surgery, vol. 42, no. 6, pp. 1122–1130, 2005.

[49] F. A. Frans, S. Bipat, J. A. Reekers, D. A. Legemate, and M. J. W. Koellemay, “Systematic review of exercise training or percutaneous transluminal angioplasty for intermittent claudication,” British Journal of Surgery, vol. 99, no. 1, pp. 16–28, 2012.

[50] A. A. Ahimastos, E. P. Pappas, P. G. Buttner, P. J. Walker, B. A. Kingwell, and J. Gollledge, “A meta-analysis of the outcome of endovascular and noninvasive therapies in the treatment of
intermittent claudication,” *Journal of Vascular Surgery*, vol. 54, no. 5, pp. 1511–1521, 2011.

[51] B. L. Bendermacher, E. M. Willigendael, J. A. Teijink, and M. H. Prins, “Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication,” *Cochrane Database of Systematic Reviews*, no. 2, Article ID CD005263, 2006.

[52] L. Bourke, K. E. Homer, M. A. Thaha et al., “Interventions for promoting habitual exercise in people living with and beyond cancer,” *The Cochrane Database of Systematic Reviews*, vol. 9, Article ID CD010192, 2013.

[53] A. W. Gardner, P. S. Montgomery, and D. E. Parker, “Optimal exercise program length for patients with claudication,” *Journal of Vascular Surgery*, vol. 55, no. 5, pp. 1346–1354, 2012.

[54] S. P. A. Nicolai, E. J. M. Hendriks, M. H. Prins, and J. A. W. Teijink, “Optimizing supervised exercise therapy for patients with intermittent claudication,” *Journal of Vascular Surgery*, vol. 52, no. 5, pp. 1226–1233, 2010.

[55] V. G. Papavassiliou, S. R. Walker, A. Bolia, G. Fishwick, and N. J. M. London, “Techniques for the endovascular management of complications following lower limb percutaneous transluminal angioplasty,” *European Journal of Vascular and Endovascular Surgery*, vol. 25, no. 2, pp. 125–130, 2003.

[56] V. S. Kashyap, M. L. Pavkov, J. F. Bena et al., “The management of severe aortoiliac occlusive disease: endovascular therapy rivals open reconstruction,” *Journal of Vascular Surgery*, vol. 48, no. 6, pp. 1451.e3–1457.e3, 2008.

[57] G. S. R. Muradin, J. L. Bosch, T. Stijnen, and M. G. M. Hunink, “Balloondilation and stent implantation for treatment of femoropopliteal arterial disease: meta-analysis,” *Radiology*, vol. 221, no. 1, pp. 137–145, 2001.

[58] M. M. McDermott, T. J. Carroll, M. Kibbe et al., “Proximal superficial femoral artery occlusion, collateral vessels, and walking performance in peripheral artery disease,” *JACC: Cardiovascular Imaging*, vol. 6, no. 6, pp. 687–694, 2013.

[59] J. D. Allen, T. Stabler, A. Kenjale et al., “Plasma nitrite flux predicts exercise performance in peripheral arterial disease after 3 months of exercise training,” *Free Radical Biology and Medicine*, vol. 49, no. 6, pp. 1138–1144, 2010.