Endovascular revascularisation versus conservative management for intermittent claudication

[Intervention Review]

Endovascular revascularisation versus conservative management for intermittent claudication

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ABSTRACT

Background

Intermittent claudication (IC) is the classic symptomatic form of peripheral arterial disease affecting an estimated 4.5% of the general population aged 40 years and older. Patients with IC experience limitations in their ambulatory function resulting in functional disability and impaired quality of life (QoL). Endovascular revascularisation has been proposed as an effective treatment for patients with IC and is increasingly performed.

Objectives

The main objective of this systematic review is to summarise the (added) effects of endovascular revascularisation on functional performance and QoL in the management of IC.

Search methods

For this review the Cochrane Vascular Information Specialist (CIS) searched the Specialised Register (February 2017) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1). The CIS also searched trials registries for details of ongoing and unpublished studies.

Selection criteria

Randomised controlled trials (RCTs) comparing endovascular revascularisation (± conservative therapy consisting of supervised exercise or pharmacotherapy) versus no therapy (except advice to exercise) or versus conservative therapy (i.e. supervised exercise or pharmacotherapy) for IC.

Data collection and analysis

Two review authors independently selected studies, extracted data, and assessed the methodological quality of studies. Given large variation in the intensity of treadmill protocols to assess walking distances and use of different instruments to assess QoL, we used standardised mean difference (SMD) as treatment effect for continuous outcome measures to allow standardisation of results and calculated the pooled SMD as treatment effect size in meta-analyses. We interpreted pooled SMDs using rules of thumb (< 0.40 = small, 0.40 to 0.70 = moderate, > 0.70 = large effect) according to the *Cochrane Handbook for Systematic Reviews of Interventions*. We calculated the pooled treatment effect size for dichotomous outcome measures as odds ratio (OR).

Main results

We identified ten RCTs (1087 participants) assessing the value of endovascular revascularisation in the management of IC. These RCTs compared endovascular revascularisation versus no specific treatment for IC or conservative therapy or a combination therapy of endovascular revascularisation *plus* conservative therapy versus conservative therapy alone. In the included studies, conservative treatment consisted of supervised exercise or pharmacotherapy with cilostazol 100 mg twice daily. The quality of the evidence ranged from low to high and was downgraded mainly owing to substantial heterogeneity and small sample size.

Comparing endovascular revascularisation versus no specific treatment for IC (except advice to exercise) showed a moderate effect on maximum walking distance (MWD) (SMD 0.70, 95% confidence interval (CI) 0.31 to 1.08; 3 studies; 125 participants; moderate-quality evidence) and a large effect on pain-free walking distance (PFWD) (SMD 1.29, 95% CI 0.90 to 1.68; 3 studies; 125 participants; moderate-quality evidence) in favour of endovascular revascularisation. Long-term follow-up in two studies (103 participants) showed no clear differences between groups for MWD (SMD 0.67, 95% CI -0.30 to 1.63; low-quality evidence) and PFWD (SMD 0.69, 95% CI -0.45 to 1.82; low-quality evidence). The number of secondary invasive interventions (OR 0.81, 95% CI 0.12 to 5.28; 2 studies; 118 participants; moderate-quality evidence) was also not different between groups. One study reported no differences in disease-specific QoL after two years.

Data from five studies (n = 345) comparing endovascular revascularisation versus supervised exercise showed no clear differences between groups for MWD (SMD -0.42, 95% CI -0.87 to 0.04; moderate-quality evidence) and PFWD (SMD -0.05, 95% CI -0.38 to 0.29; moderate-quality evidence). Similarliy, long-term follow-up in three studies (184 participants) revealed no differences between groups for MWD (SMD -0.02, 95% CI -0.36 to 0.32; moderate-quality evidence) and PFWD (SMD 0.11, 95% CI -0.26 to 0.48; moderate-quality evidence). In addition, high-quality evidence showed no difference between groups in the number of secondary invasive interventions (OR 1.40, 95% CI 0.70 to 2.80; 4 studies; 395 participants) and in disease-specific QoL (SMD 0.18, 95% CI -0.04 to 0.41; 3 studies; 301 participants).

Comparing endovascular revascularisation *plus* supervised exercise versus supervised exercise alone showed no clear differences between groups for MWD (SMD 0.26, 95% CI -0.13 to 0.64; 3 studies; 432 participants; moderate-quality evidence) and PFWD (SMD 0.33, 95% CI -0.26 to 0.93; 2 studies; 305 participants; moderate-quality evidence). Long-term follow-up in one study (106 participants) revealed a large effect on MWD (SMD 1.18, 95% CI 0.65 to 1.70; low-quality evidence) in favour of the combination therapy. Reports indicate that disease-specific QoL was comparable between groups (SMD 0.25, 95% CI -0.05 to 0.56; 2 studies; 330 participants; moderate-quality evidence) and that the number of secondary invasive interventions (OR 0.27, 95% CI 0.13 to 0.55; 3 studies; 457 participants; high-quality evidence) was lower following combination therapy.

Two studies comparing endovascular revascularisation *plus* pharmacotherapy (cilostazol) versus pharmacotherapy alone provided data showing a small effect on MWD (SMD 0.38, 95% CI 0.08 to 0.68; 186 participants; high-quality evidence), a moderate effect on PFWD (SMD 0.63, 95% CI 0.33 to 0.94; 186 participants; high-quality evidence), and a moderate effect on disease-specific QoL (SMD 0.59, 95% CI 0.27 to 0.91; 170 participants; high-quality evidence) in favour of combination therapy. Long-term follow-up in one study (47 participants) revealed a moderate effect on MWD (SMD 0.72, 95% CI 0.09 to 1.36; P = 0.02) in favour of combination therapy and no clear differences in PFWD between groups (SMD 0.54, 95% CI -0.08 to 1.17; P = 0.09). The number of secondary invasive interventions was comparable between groups (OR 1.83, 95% CI 0.49 to 6.83; 199 participants; high-quality evidence).

Authors' conclusions

In the management of patients with IC, endovascular revascularisation does not provide significant benefits compared with supervised exercise alone in terms of improvement in functional performance or QoL. Although the number of studies is small and clinical heterogeneity underlines the need for more homogenous and larger studies, evidence suggests that a synergetic effect may occur when endovascular revascularisation is combined with a conservative therapy of supervised exercise or pharmacotherapy with cilostazol: the combination therapy seems to result in greater improvements in functional performance and in QoL scores than are seen with conservative therapy alone.

PLAIN LANGUAGE SUMMARY

Endovascular revascularisation for intermittent claudication (pain in the legs)

Background

Intermittent claudication, affecting approximately 4.5% of the general population aged 40 years and older, is a common symptomatic form of peripheral arterial disease and is characterised by pain in the calf or buttock in the legs that starts with walking and eases with rest. This leg pain is caused by reduced blood flow to leg muscles due to a blockage in the leg arteries as a consequence of atherosclerosis (hardening and plaque buildup in the arteries). People with intermittent claudication experience severely limited walking distances, resulting in a sedentary lifestyle and decreased quality of life.

Peripheral endovascular revascularisation (angioplasty) is a minimally invasive procedure performed to clear blockages in the leg arteries that cause decreased blood flow. This procedure is widely used for people with intermittent claudication. In this review we searched the available literature (current until February 2017) to assess the effectiveness of endovascular revascularisation compared with no specific therapy for intermittent claudication, or compared with a conservative therapy option such as supervised exercise or drug therapy.

Study characteristics and key results

Our search identified ten trials with a total of 1087 participants. Reviewers judged the overall methodological quality of these studies as moderate.

Data from three studies comparing endovascular revascularisation with no specific treatment for intermittent claudication except advice to exercise showed a moderate to large effect on walking distances in favour of endovascular revascularisation in the short term. However after long-term follow up in two studies, this short-term advantage of endovascular revascularisation had disappeared. The number of additional surgical procedures was not different between groups. One study reported no differences in disease-specific quality of life after two years.

Data from five studies comparing endovascular revascularisation with supervised exercise for intermittent claudication showed both therapies to be more or less comparable in terms of improving walking distances, number of additional surgical procedures, and quality of life.

Data from three studies comparing a combination therapy of endovascular revascularisation plus supervised exercise versus supervised exercise alone showed no clear differences between groups for walking distances in the short term, and data from one study showed a large effect on walking distances in favour of combination therapy over the long term. Disease-specific quality of life was comparable between study groups. The number of additional surgical procedures was lower following combination therapy.

Finally, when comparing a combination therapy of endovascular revascularisation plus drug therapy with cilostazol versus drug therapy alone, two studies provided data showing small to moderate effects on walking distance and on quality of life in favour of the combination therapy. The number of additional surgical procedures was comparable between study groups.

Quality of the evidence

Overall, reviewers rated the quality of evidence for outcomes in the comparison of endovascular revascularisation versus no specific therapy for intermittent claudication as low to moderate mainly owing to small study sample sizes and the possibility of serious risk of bias in these studies. For comparisons of endovascular revascularisation versus conservative therapy, and the combination therapy of endovascular revascularisation and conservative therapy versus conservative therapy alone, reviewers generally rated the quality of evidence for outcomes as moderate to high mainly owing to substantial differences between studies.

Conclusion

This review assessed results reported by a limited number of studies showing that endovascular revascularisation and supervised exercise are more or less comparable treatment options in improving walking distances and quality of life among individuals with intermittent claudication. Combination therapy (endovascular revascularisation with either supervised exercise or drug therapy (cilostazol)) seems to result in greater improvements in walking distance and in quality of life than are seen with supervised exercise or drug therapy alone.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Endovascular revascularisation compared with no specific therapy for intermittent claudication except verbal advice to exercise

Endovascular revascularisation compared with no specific therapy for intermittent claudication except verbal advice to exercise

Patient or population: intermittent claudication
Setting: hospital
Intervention: endovascular revascularisation
Comparison: no specific therapy[1]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no specific therapy	Risk with endovascular revascularisation				
Maximum walking distance	-	Mean maximum walking distance in the intervention group was 0.70 standard deviations higher (0.31 higher to 1.08 higher).	-	125 (3 RCTs)	⊕⊕⊕⊖ MODERATE [2,3]	
Maximum walking distance (long-term)	-	Mean maximum walking distance at long term in the intervention group was 0.67 standard deviations higher (0.30 lower to 1.63 higher).	-	103 (2 RCTs)	⊕⊕⊖⊖ LOW [3,4,5]	
Pain-free walking distance	-	Mean pain-free walking distance in the intervention group was 1.29 standard deviations higher (0.90 higher to 1.68 higher).	-	125 (3 RCTs)	⊕⊕⊕⊖ MODERATE [2,3]	
Pain-free walking distance (long-term)	-	Mean pain-free walking distance at long term in the intervention group was 0.69 standard deviations higher (0.45 lower to 1.82 higher).	-	103 (2 RCTs)	⊕⊕⊖⊖ LOW [3,4,5]	
Secondary invasive interventions	Study population		OR 0.81 (0.12 to 5.28)	118 (2 RCTs)	⊕⊕⊕⊖ MODERATE [3,4]	
	83 per 1000	69 per 1000 (11 to 324)				
Quality of life (disease-specific)	See comments.	See comments.	-	-	-	One study reported no significant differences in disease-specific

						QoL between study groups after 2 years without providing data

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). Pooled standardised mean differences were interpreted using rules of thumb (< 0.40 = small, 0.40 to 0.70 = moderate, > 0.70 = large effect) as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
CI: confidence interval; OR: odds ratio; QoL: quality of life; RCT: randomised controlled trial.

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] Treatment consisted of cardiovascular risk factor management and only verbal exercise advice without any form of supervision.
[2] In two studies, risk of bias on three or more domains judged as "unclear"; therefore quality of the evidence downgraded one level.
[3] The possibility of publication bias could not be ruled out, yet we did not consider it sufficient to downgrade the quality of the evidence.
[4] Small sample size with wide confidence interval for treatment effect; therefore quality of the evidence downgraded one level.
[5] Evidence of inconsistency due to substantial heterogeneity between studies; therefore quality of the evidence downgraded one level.

Summary of findings 2. Endovascular revascularisation compared with conservative therapy for intermittent claudication

Endovascular revascularisation compared with conservative therapy for intermittent claudication

Patient or population: intermittent claudication
Setting: hospital
Intervention: endovascular revascularisation
Comparison: conservative therapy (i.e. supervised exercise)[1]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with conservative therapy	Risk with endovascular revascularisation				
Maximum walking distance	-	Mean maximum walking distance in the intervention group was 0.42 standard deviations lower (0.87 lower to 0.04 higher).	-	345 (5 RCTs)	⊕⊕⊕⊖ MODERATE [2,3]	

Maximum walking distance (long-term)	-	Mean maximum walking distance at long term in the intervention group was 0.02 standard deviations lower (0.36 lower to 0.32 higher).	-	184 (3 RCTs)	⊕⊕⊕⊖ MODERATE [3,4]
Pain-free walking distance	-	Mean pain-free walking distance in the intervention group was 0.05 standard deviations lower (0.38 lower to 0.29 higher).	-	345 (5 RCTs)	⊕⊕⊕⊖ MODERATE [2,3]
Pain-free walking distance (long-term)	-	Mean pain-free walking distance at long term in the intervention group was 0.11 standard deviations higher (0.26 lower to 0.48 higher).	-	147 (2 RCTs)	⊕⊕⊕⊖ MODERATE [3,5]
Secondary invasive interventions	Study population		OR 1.40 (0.7 to 2.8)	395 (4 RCTs)	⊕⊕⊕⊕ HIGH [3]
	82 per 1000	112 per 1000 (59 to 201)			
Quality of life (disease-specific)	-	Mean quality of life (disease-specific) in the intervention group was 0.18 standard deviations higher (0.04 lower to 0.41 higher).	-	301 (3 RCTs)	⊕⊕⊕⊕ HIGH [3]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). Pooled standardised mean differences were interpreted using rules of thumb (< 0.40 = small, 0.40 to 0.70 = moderate, > 0.70 = large effect), as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
CI: confidence interval; OR: odds ratio; RCT: randomised controlled trial.

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] Supervised exercise consisted of only supervised exercise in four studies and a combination of supervised exercise and pharmacotherapy with cilostazol in one study.
[2] Evidence of inconsistency due to substantial heterogeneity between studies; therefore quality of the evidence downgraded one level.
[3] The possibility of publication bias could not be ruled out, yet we did not consider it sufficient to downgrade the quality of the evidence.
[4] In one of three studies, risk of attrition bias judged as "high"; therefore quality of the evidence downgraded one level.
[5] Small sample size with wide confidence interval for treatment effect; therefore quality of the evidence downgraded one level.

Summary of findings 3. Endovascular revascularisation plus conservative therapy compared with conservative therapy alone for intermittent claudication

Endovascular revascularisation plus conservative therapy compared with conservative therapy alone for intermittent claudication

Patient or population: intermittent claudication
Setting: hospital
Intervention: endovascular revascularisation plus conservative therapy (supervised exercise or pharmacotherapy with cilostazol)
Comparison: conservative therapy (supervised exercise or pharmacotherapy with cilostazol)[1]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with conservative therapy	Risk with endovascular revascularisation plus conservative therapy				
Conservative therapy consists of supervised exercise						
Maximum walking distance	-	Mean maximum walking distance in the intervention group was 0.26 standard deviations higher (0.13 lower to 0.64 higher).	-	432 (3 RCTs)	⊕⊕⊕⊖ MODERATE [2,3]	
Maximum walking distance (long-term)	-	Mean maximum walking distance at long term in the intervention group was 1.18 standard deviations higher (0.65 higher to 1.70 higher).	-	106 (1 RCT)	⊕⊕⊖⊖ LOW [2,4,5]	
Pain-free walking distance	-	Mean pain-free walking distance in the intervention group was 0.33 standard deviations higher (0.26 lower to 0.93 higher).	-	305 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2,3]	
Pain-free walking distance (long-term)	See comments.	See comments.	-	-	-	None of the studies reported any quantitative data on pain-free walking distance at long term
Secondary invasive interventions	Study population		OR 0.27 (0.13 to 0.55)	457 (3 RCTs)	⊕⊕⊕⊕ HIGH[2]	
	164 per 1000	50 per 1000 (25 to 97)				

Quality of life (disease-specific)	-	Mean quality of life (disease-specific) in the intervention group was 0.25 standard deviations higher (0.05 lower to 0.56 higher).	-	330 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2,3]	
Conservative therapy consists of pharmacotherapy (cilostazol)						
Maximum walking distance	-	Mean maximum walking distance in the intervention group was 0.38 standard deviations higher (0.08 higher to 0.68 higher).	-	186 (2 RCTs)	⊕⊕⊕⊕ HIGH [2]	
Maximum walking distance (long-term)	-	Mean maximum walking distance at long term in the intervention group was 0.72 standard deviations higher (0.09 higher to 1.36 higher).	-	47 (1 RCT)	See comments.	Only 1 small RCT included in this analysis, no meaningful grading of quality of evidence possible
Pain-free walking distance	-	Mean pain-free walking distance in the intervention group was 0.63 standard deviations higher (0.33 higher to 0.94 higher).	-	186 (2 RCTs)	⊕⊕⊕⊕ HIGH [2]	
Pain-free walking distance (long-term)	-	Mean pain-free walking distance at long-term in the intervention group was 0.54 standard deviations higher (0.08 lower to 1.17 higher).	-	47 (1 RCT)	See comments.	Only one small RCT included in this analysis, no meaningful grading of quality of evidence possible
Secondary invasive interventions	Study population		OR 1.83 (0.49 to 6.83)	199 (2 RCTs)	⊕⊕⊕⊕ HIGH [2]	
	69 per 1000	120 per 1000 (35 to 337)				
Quality of life (disease-specific)	-	Mean quality of life (disease-specific) in the intervention group was 0.59 standard deviations higher (0.27 higher to 0.91 higher).	-	170 (2 RCTs)	⊕⊕⊕⊕ HIGH [2]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). Pooled standardised mean differences were interpreted using rules of thumb (< 0.40 = small, 0.40 to 0.70 = moderate, > 0.70 = large effect), as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
CI: confidence interval; OR: odds ratio; RCT: randomised controlled trial.

GRADE Working Group grades of evidence.

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

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[1] Conservative therapy consisted of supervised exercise in three studies and of pharmacotherapy with cilostazol and only advice to exercise in two studies.
[2] The possibility of publication bias could not be ruled out, yet we did not consider it sufficient to downgrade the quality of the evidence.
[3] Evidence of inconsistency due to substantial heterogeneity between studies; therefore quality of the evidence downgraded one level.
[4] Small sample size with wide confidence interval for treatment effect; therefore quality of the evidence downgraded one level.
[5] In this study risk of bias on three domains judged as "unclear"; therefore quality of the evidence downgraded one level.

BACKGROUND

Description of the condition

Lower extremity peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and is considered a major cause of morbidity in the elderly population (Vogt 1992). Intermittent claudication, the most frequent symptomatic presentation of PAD, is defined as discomfort in the legs with exertion that resolves after a short period of rest. Intermittent claudication is highly prevalent in Western countries, affecting an estimated 4.5% of the general population aged 40 years and older (Norgren 2007), and is likely to become more prevalent given the ageing population. Although individuals with claudication have a relatively benign prognosis for their affected limb, with a major amputation risk of only 1% to 3% over a five-year period (Norgren 2007), their functional performance deteriorates significantly, and this results in a sedentary lifestyle (Sieminski 1997), along with severely limited quality of life (QoL) (Khaira 1996; Spronk 2007). Additionally, claudication is associated with significantly increased risk of all-cause and cardiovascular mortality independent of other atherosclerotic risk factors (Golomb 2006; Smith 1990).

Description of the intervention

Treatment of intermittent claudication consists of multiple components that focus on preventing future cardiovascular events and related mortality, as well as on ameliorating claudication symptoms. Pharmacotherapy and exercise therapy are established as effective first-line conservative treatment options, improving walking distance and QoL in patients with claudication (Fakhry 2012; Hiatt 2001; Watson 2008). However, in clinical practice, endovascular revascularisation is considered an attractive first-line alternative owing to its immediate effect and relatively low complication rates. Although both exercise therapy and endovascular revascularisation are effective in improving symptoms, it should be noted that neither therapy completely removes the disability in most patients (Sobieszczyk 2015). In 1964 Dotter and Judkins first performed and reported on endovascular revascularisation of the lower extremities (Dotter 1964). Since that time, important technological developments including the introduction of balloon angioplasty and drug-eluting balloons and stents has advanced endovascular revascularisation as a safe and durable treatment option for management of symptomatic PAD. Endovascular revascularisation is performed with the patient under local anaesthesia, and access to the stenosed or occluded peripheral artery is usually gained via the common femoral artery. Subsequently, an angioplasty procedure that involves (balloon) dilatation of a stenosed peripheral artery or recanalisation of an occluded peripheral artery is performed. This is followed by stent placement if suboptimal results are achieved with angioplasty only (Tetteroo 1998). After a successful endovascular revascularisation procedure, patients are usually ambulatory on the same day and are able to resume all normal activities within a few days. Furthermore, Stewart 2002 reported procedure-related morbidity and mortality lower than 0.5%, and Matsi 1998 described haematoma at the puncture site and embolisation as the most common procedure-related complications.

How the intervention might work

After successful revascularisation, whereby the obstruction or occlusion in the peripheral artery is resolved and improved blood flow is restored, arterial perfusion in the lower extremity improves significantly. This is confirmed by significant improvement in the ankle brachial index (ABI) immediately after the procedure. Randomised controlled trials (RCTs) have demonstrated the effectiveness of endovascular revascularisation in improving functional performance (i.e. walking distance and ABI) and QoL in individuals with intermittent claudication (Bosch 1999; Mazari 2012; Spronk 2009a).

Why it is important to do this review

Intermittent claudication is a serious lifestyle-limiting symptom of PAD that has a large impact on patients' functional performance and QoL. Conservative treatment strategies, including pharmacotherapy and supervised exercise therapy, are recommended as first-line therapy for claudication (Norgren 2007; Rooke 2011). Yet their value in clinical practice remains uncertain, as medical drugs for claudication (e.g. cilostazol, pentoxifylline, naftidrofuryl) have limited effects (Berger 2012), and supervised exercise programmes are under-utilised in clinical practice owing to limited access (Makris 2012), reimbursement issues, and poor patient compliance (Fakhry 2012). Consequently, researchers are noting an enormous increase in the use of endovascular revascularisation as first-line therapy for claudication (Anderson 2004; Beckman 2007). Nonetheless, the (long-term) effectiveness of endovascular revascularisation as first-line therapy for intermittent claudication remains debatable. The only Cochrane review on this topic, which included two studies with a total of 98 participants comparing angioplasty versus non-surgical therapy, concluded that limited data suggest short-term benefit in favour of angioplasty (Fowkes 2000). Since the last update of this review, new randomised trials assessing the efficacy of endovascular revascularisation compared with conservative treatment have published their findings. Furthermore, new clinical studies have investigated the combination of exercise therapy and endovascular revascularisation, which takes advantage of immediate short-term effects of revascularisation and long-term benefits of exercise therapy (Fakhry 2015; Greenhalgh 2008; Mazari 2012). However, clinical studies rarely have sufficient power to detect intervention effectiveness in terms of clinical outcomes such as functional performance, QoL, or cardiovascular events. Therefore, a Cochrane review identifying these studies systematically, evaluating their results independently, and updating results when new studies are published is important for reducing uncertainty about the (added) value of endovascular revascularisation in the management of patients with intermittent claudication.

OBJECTIVES

The main objective of this systematic review is to summarise the (added) effects of endovascular revascularisation on functional performance and QoL in the management of intermittent claudication.

METHODS

Criteria for considering studies for this review

Types of studies

We systematically searched for and included only RCTs with parallel-group design comparing outcomes of endovascular revascularisation (with and without conservative therapy) versus no specific therapy or versus conservative therapy (i.e. supervised

exercise or pharmacotherapy) in patients with intermittent claudication.

We included only studies comparing endovascular revascularisation (± conservative therapy) versus conservative therapies or no specific therapy for intermittent claudication. We excluded studies providing any kind of surgical revascularisation in the comparison group. We also excluded studies comparing different types of endovascular revascularisation procedures (e.g. angioplasty vs angioplasty plus stenting).

Types of participants

Patients with stable intermittent claudication, according to Rutherford category 1 to 3 or Fontaine stage II (Norgren 2007), who are eligible for both endovascular revascularisation and conservative management.

Types of interventions

In the intervention group, participants underwent endovascular revascularisation (± conservative therapy). We considered all percutaneous endovascular revascularisation procedures including angioplasty (any type, e.g. balloon, laser) or angioplasty plus (selective) stent placement (any type of stent including drug-eluting) for atherosclerotic lesion(s) in arteries of the lower extremity. In the comparison group, participants received only conservative therapy or no specific therapy for intermittent claudication. Conservative therapy included specific pharmacotherapy for intermittent claudication (e.g. cilostazol, pentoxifylline, naftidrofuryl) or supervised exercise therapy.

We considered the following comparisons.

- Endovascular revascularisation versus no specific therapy for intermittent claudication except verbal advice to exercise.
- Endovascular revascularisation versus conservative therapy (pharmacotherapy or supervised exercise).
- Endovascular revascularisation plus conservative therapy versus conservative therapy.

When investigators provided cardiovascular risk factor modification (e.g. lipid control, hypertension control, anti-smoking advice) in the intervention group, it was also provided equally in the comparison group.

Types of outcome measures

Primary outcomes

- Functional performance outcomes
  - Maximum walking distance (MWD), as assessed on a treadmill
  - Pain-free walking distance (PFWD), as assessed on a treadmill
- Secondary invasive interventions during follow-up
  - Endovascular or surgical revascularisation
  - Amputation

Secondary outcomes

- Quality of life, including health-related (general and disease-specific) QoL measures
- Procedure-related complications (e.g. local haematoma, artery dissection, embolisation)
- Cardiovascular events (e.g. myocardial infarction, stroke)
- Functional performance measures not assessed on a treadmill (e.g. six-minute walk test, self-reported walking distance)
- Mortality

Search methods for identification of studies

We applied no language restrictions.

Electronic searches

The Cochrane Vascular Information Specialist (CIS) searched the following databases for relevant trials.

- Cochrane Vascular Specialised Register (21 February 2017).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1) via the Cochrane Register of Studies Online.

See Appendix 1 for details of the search strategy used to search CENTRAL.

The Cochrane Vascular Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE Ovid, Embase Ovid, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Allied and Complementary Medicine Database (AMED), and through handsearching of relevant journals. We have provided the full list of databases, journals, and conference proceedings searched, as well as the search strategies used, in the Specialised Register section of the Cochrane Vascular Module in the Cochrane Library (www.cochranelibrary.com).

The CIS also searched the following trials registries for details of ongoing and unpublished studies (21 February 2017).

- ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch).
- International Standard Randomised Controlled Trial Number (ISRCTN) Register (www.isrctn.com/).

See Appendix 2.

Searching other resources

We handsearched the reference lists of all eligible studies for additional relevant studies.

Data collection and analysis

Selection of studies

Two review authors (FF and HF) initially selected identified studies independently upon reviewing titles and abstracts. Final selection was based on full-text evaluation of selected studies by the two review authors (FF and HF) working independently. Review authors discussed and resolved disagreements by consensus. If no consensus was reached, a third review author (MH) acted as arbiter.

Data extraction and management

Two review authors (FF and HF) extracted all required data from each included study using a standardised form, which consisted of (1) study characteristics including study design, year of publication, study location, source of funding, sample size estimation, follow-up, and applied inclusion and exclusion criteria; (2) participant baseline characteristics including number of participants in each group, mean age, and gender distribution; (3)

intervention characteristics, compliance, and losses to follow-up; and (4) primary and secondary outcomes, as specified under Types of outcome measures.

Assessment of risk of bias in included studies

Two review authors (FF and HF) independently assessed the methodological quality of included studies, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), for the following domains.

- Randomisation and sequence generation.
- Allocation concealment.
- Blinding (of participants, personnel, and outcome assessors).
- Incomplete outcome data.
- Selective outcome reporting.
- Publication and other sources of bias.

For each of the six domains, we assessed risk of bias as 'low' or 'high', or as 'unclear' when available information was insufficient to permit judgement on risk of bias.

Measures of treatment effect

To analyse the treatment effect of endovascular revascularisation in each study for continuous outcome measures, including the primary outcomes MWD and PFWD and the secondary outcome QoL, we extracted the value of each outcome measure at different time points (6 to 12 months and over the long term) for both intervention and comparison groups. For studies reporting treadmill walking time instead of treadmill walking distance, we calculated MWD and PFWD by converting walking time to distance using the reported treadmill speed.

Given large variation in the intensity of treadmill protocols to assess MWD and PFWD and use of different instruments to assess QoL in each study, we used standardised mean differences (SMDs) and 95% confidence intervals (CIs) as treatment effects for these outcome measures to allow standardisation of results to a uniform scale. We calculated the pooled SMD, which is the pooled treatment difference between groups normalised to the pooled standard deviation of the difference, as treatment effect size in meta-analysis. We interpreted pooled SMDs using rules of thumb (< 0 .40 = small effect, 0.40 to 0.70 = moderate effect, > 0.70 = large effect), as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

For dichotomous outcome measures, including secondary invasive intervention, procedure-related complications, cardiovascular events, or death during follow-up in each treatment group, we calculated odds ratios (ORs) and corresponding 95% CIs as measures of treatment effect, if appropriate.

Unit of analysis issues

In this systematic review, we included only RCTs with parallel-group design. The unit of randomisation was the individual participant.

Dealing with missing data

In the case of missing data on dropouts, withdrawals, and outcome measures, we contacted the original investigators and requested data when appropriate. If studies reported medians and interquartile ranges (IQRs) as measures of variance for walking distance, we converted these values to means and standard deviations (SDs), assuming a normal distribution for walking distance so we could include these studies in the meta-analysis. We tested this assumption by performing sensitivity analysis. Missing data indicating the variance of outcome measures (e.g. SD, CI) were to be expected, in which case we used the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to calculate or impute these data.

Assessment of heterogeneity

We assessed the statistical heterogeneity of outcome measures by calculating the Q statistics and the I^2 statistic, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of reporting biases

We created a funnel plot providing enough studies were included for each outcome measure, with effect size on the x-axis and precision on the y-axis to investigate possible publication bias.

Data synthesis

We calculated treatment effects using corresponding 95% CIs for both continuous and dichotomous outcome measures by applying random-effects models. Subsequently, when appropriate, we calculated the pooled treatment effect size from the random-effects model meta-analysis and presented this as a forest plot for each outcome measure separately. We considered two-sided P ≤ 0.05 as statistically significant and performed all data analyses using RevMan 5.3 (RevMan 2014), when appropriate.

Subgroup analysis and investigation of heterogeneity

We considered the following subgroup analyses for primary outcomes, provided we identified enough studies for each subgroup.

- Types of endovascular revascularisation procedures (e.g. angioplasty, angioplasty plus stenting).
- Types of pharmacotherapy (e.g. cilostazol, pentoxifylline, naftidrofuryl).
- Types of exercise therapy (i.e. supervised or non-supervised programme).
- Separate segments (i.e. aortoiliac, femoropopliteal, or combined).

Sensitivity analysis

We planned to perform several sensitivity analyses provided we could include enough studies in the meta-analysis. We assessed individual study effects by excluding each study separately from the analysis to examine whether exclusion of an individual study would significantly change the results. Likewise we planned to perform sensitivity analysis on the methodological quality of studies by removing studies with high risk of (methodological) bias to observe whether excluding these studies would significantly change the results. In addition, in performing sensitivity analyses, we removed from meta-analysis studies reporting only median and IQR walking distances, to observe whether excluding these studies would significantly change the results.

'Summary of findings'

We presented in 'Summary of findings' tables the main findings of this review concerning quality of evidence, magnitude of effect of interventions examined, and sum of available data for the outcomes MWD, PFWD, secondary invasive interventions, and disease-specific QoL, according to GRADE methods as described by Schünemann 2011 and Atkins 2004. We used GRADEprofiler (GRADEpro) software to assist in preparation of a 'Summary of findings' table for each comparison assessed in this review (GRADEPro 2015).

RESULTS

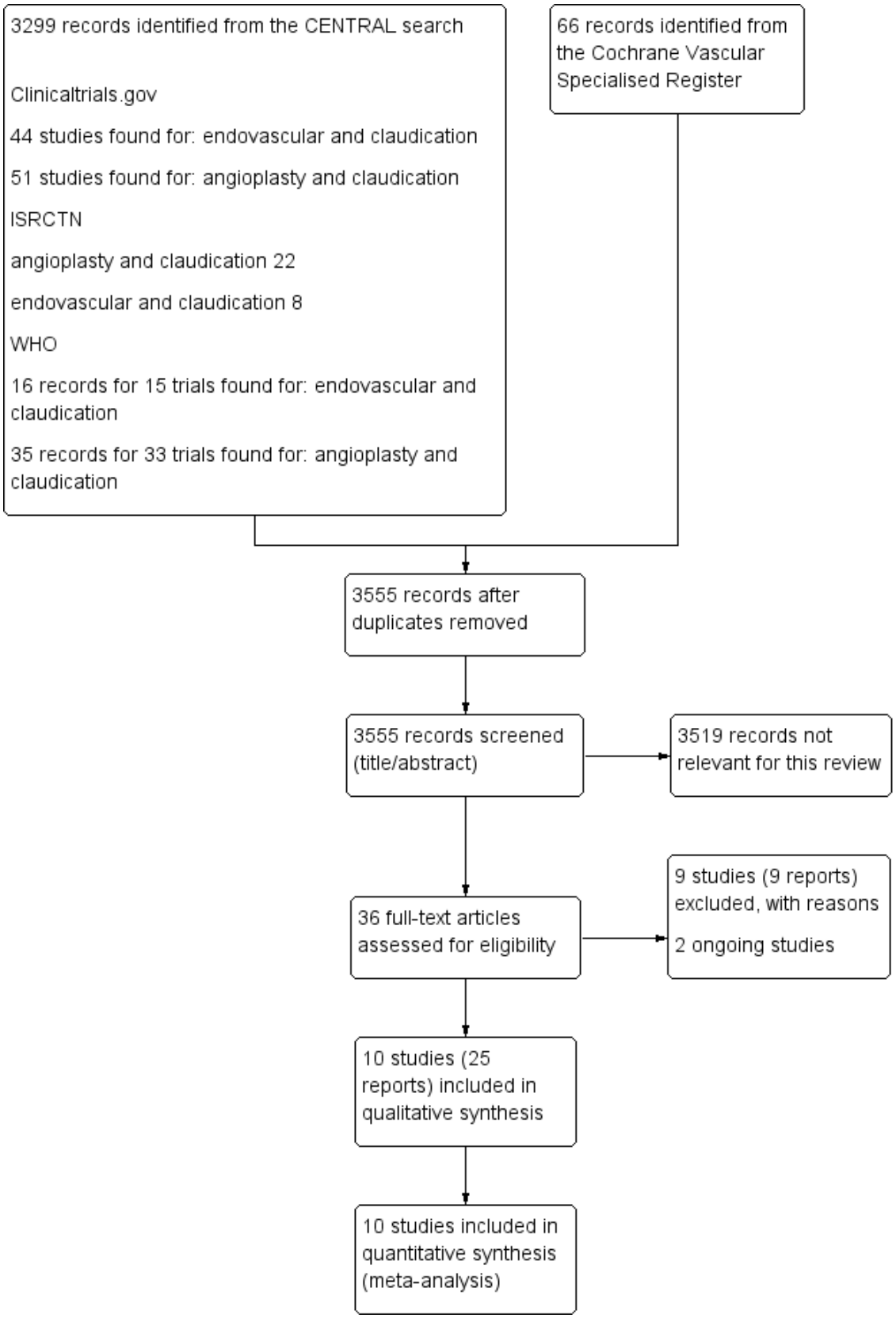
Description of studies

See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies.

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies.

After full-text assessment, we included in this systematic review ten studies described in 25 publications assessing the value of endovascular revascularisation in the management of patients with intermittent claudication (Creasy 1990; Fakhry 2015; Greenhalgh 2008; Hobbs 2006; Mazari 2011; Murphy 2015; Nordanstig 2014; Nylaende 2007; Spronk 2009; Whyman 1996). Results from all included studies had been published in peer-reviewed journals. Greenhalgh 2008 reported two separate trials that included participants in one of the two trials on the basis of lesion site (femoropopliteal or aortoiliac) and consequently randomised them to one of two treatment arms. Nordanstig 2014 randomised participants to a non-invasive treatment group or an invasive treatment group that included both open surgical or endovascular revascularisation procedures at baseline. To include this study in this systematic review, we sought and received from study authors outcome data from the subgroup of participants undergoing endovascular revascularisation.

All included studies used a parallel-group design, with seven studies randomising between two arms comparing endovascular revascularisation versus cardiovascular risk factor management alone (i.e. no specific therapy for intermittent claudication except verbal advice to exercise) (Nylaende 2007; Whyman 1996), endovascular revascularisation versus supervised exercise (Creasy 1990; Spronk 2009), endovascular revascularisation plus supervised exercise versus supervised exercise alone (Fakhry 2015; Greenhalgh 2008), or endovascular revascularisation plus cilostazol 100 mg twice daily versus cilostazol 100 mg twice daily (Nordanstig 2014). Three studies had three arms comparing endovascular revascularisation versus cardiovascular risk factor management alone (i.e. no specific therapy for claudication) versus supervised exercise (Hobbs 2006), endovascular revascularisation versus supervised exercise versus endovascular revascularisation plus supervised exercise (Mazari 2011), or endovascular revascularisation plus cilostazol 100 mg twice daily versus cilostazol 100 mg twice daily alone versus supervised exercise plus cilostazol 100 mg twice daily (Murphy 2015).

All studies were conducted in Europe (n = 9) and North America (n = 1) and recruited a total number of 1087 participants, ranging from 23 to 212 participants in each individual study. All participants had stable intermittent claudication, and most were recruited from outpatient clinics in university and non-university hospitals. Seven out of ten studies included participants with claudication due to both aortoiliac and femoropopliteal disease (Creasy 1990; Fakhry 2015; Greenhalgh 2008; Nordanstig 2014; Nylaende 2007; Spronk 2009; Whyman 1996), two studies included only participants with femoropopliteal disease (Hobbs 2006; Mazari 2011), and one study included only participants with aortoiliac disease (Murphy 2015). Most included participants were male (61%) with an average age ranging from 61 to 70 years.

All studies except Creasy 1990 reported to a greater or lesser extent some sort of cardiovascular risk factor management (e.g. providing smoking cessation advice, promoting physical activity, providing dietary advice or medical therapy for cardiovascular risk factors) offered to participants in each treatment arm at the start of the study, in addition to their specific treatment for intermittent claudication, if applicable. In all studies, endovascular revascularisation consisted of balloon angioplasty; in four studies, investigators placed a stent if initial balloon angioplasty results were unsatisfactory (selective stenting) (Fakhry 2015; Greenhalgh 2008; Nylaende 2007; Spronk 2009); Murphy 2015 always placed a stent after initial balloon angioplasty (primary stenting); Nordanstig 2014 always placed a stent in the aortoiliac segment (primary stenting) but placed a stent in the femoropopliteal segment only if angioplasty results were unsatisfactory (selective stenting); and four studies placed no stent and performed only balloon angioplasty (no stenting) (Creasy 1990; Hobbs 2006; Mazari 2011; Whyman 1996). In studies comparing endovascular revascularisation (± conservative therapy) versus conservative therapy for intermittent claudication, conservative treatment consisted of pharmacotherapy with cilostazol 100 mg twice daily in Murphy 2015 and Nordanstig 2014, comprised a supervised exercise programme in six studies (Creasy 1990; Fakhry 2015; Greenhalgh 2008; Hobbs 2006; Mazari 2011; Spronk 2009), and included a combination of cilostazol 100 mg twice daily and supervised exercise in Murphy 2015. The duration of supervised exercise programmes varied between studies, with most studies offering a programme of 12 weeks with a frequency of two to three sessions per week. Murphy 2015 and Spronk 2009 continued the supervised exercise programme until six months, and Fakhry 2015 continued the programme up to 12 months, with a declining number of sessions per week after the initial three months of training depending on participants' progress.

Duration of follow-up was homogeneous between studies, with all studies reporting a follow-up duration of at least six months. Eight out of ten studies recorded outcome measures at 12 months' follow-up (Creasy 1990; Fakhry 2015; Greenhalgh 2008; Mazari 2011; Murphy 2015; Nordanstig 2014; Nylaende 2007; Spronk 2009); six studies reported long-term follow-up (longer than 12 months), with follow-up duration of 18 months in one study (Murphy 2015), two years in three studies (Mazari 2011; Nylaende 2007; Whyman 1996), six years in one study (Creasy 1990), and seven years in another study (Spronk 2009).

In assessing functional performance measures (i.e. MWD and PFWD), studies used different treadmill protocols with varying treadmill speed and incline and total duration of assessment. Six studies used a 10% incline with treadmill speed between 2.5 km/h and 4 km/h and duration from 5 to 20 minutes (Creasy 1990; Greenhalgh 2008; Hobbs 2006; Mazari 2011; Nylaende 2007; Whyman 1996). Two studies used a treadmill protocol with constant speed of 3.2 km/h and graded incline starting at 0%, increasing each two minutes up to a maximum of 10% (Fakhry 2015; Murphy 2015). Fakhry 2015 recorded walking distances up to 30 minutes walking on the treadmill, and Murphy 2015 limited this time to 12 minutes. Nordanstig 2014 used a treadmill protocol with progressively increasing incline (0 to 12%) and speed (1.5 to 4.5 km/h). In the final study (Spronk 2009), the treadmill protocol allowed no graded incline and used a constant speed of 3.5 km/h, permitting participants to walk up to 30 minutes on the treadmill.

Nine out of ten studies reported secondary invasive (endovascular or surgical) interventions during follow-up (Creasy 1990; Fakhry 2015; Greenhalgh 2008; Mazari 2011; Murphy 2015; Nordanstig 2014; Nylaende 2007; Spronk 2009; Whyman 1996), but only four studies explicitly reported data on numbers of amputations (Fakhry 2015; Murphy 2015; Nordanstig 2014; Spronk 2009). Seven studies reported data on general QoL (Fakhry 2015; Greenhalgh

2008; Mazari 2011; Murphy 2015; Nordanstig 2014; Nylaende 2007; Spronk 2009), and six studies presented data on disease-specific QoL (Fakhry 2015; Mazari 2011; Murphy 2015; Nordanstig 2014; Nylaende 2007; Spronk 2009), yet the validated questionnaires used to assess QoL were quite heterogeneous between studies (see Characteristics of included studies for details).

Excluded studies

See Characteristics of excluded studies.

After full-text assessment, we excluded nine studies (Bo 2013; Brodmann 2013; Gabrielli 2012; Gelin 2001; Giugliano 2013; Heider 2009; Husmann 2008; Kruidenier 2011; Thomson 1999). Gelin 2001 reported outcome measures for participants randomised to open or endovascular revascularisation as one invasive treatment group, and corresponding authors could provide no data for the subgroup of participants receiving endovascular revascularisation. For this reason, we decided to exclude this study from further evaluation. We excluded another eight studies for not including a non-interventional control group (Bo 2013; Brodmann 2013; Gabrielli 2012; Kruidenier 2011), not providing relevant outcome measures for this systematic review (Heider 2009; Husmann 2008), not using a formal randomisation process (Giugliano 2013), or publishing only abstract data, with study authors not able to provide additional data (Thomson 1999).

Ongoing studies

We classified two studies as ongoing studies (Frans 2012a; NCT01230229) (see Characteristics of ongoing studies).

Risk of bias in included studies

See Figure 2 and Figure 3 for a graphical summary of risk of bias for the ten included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

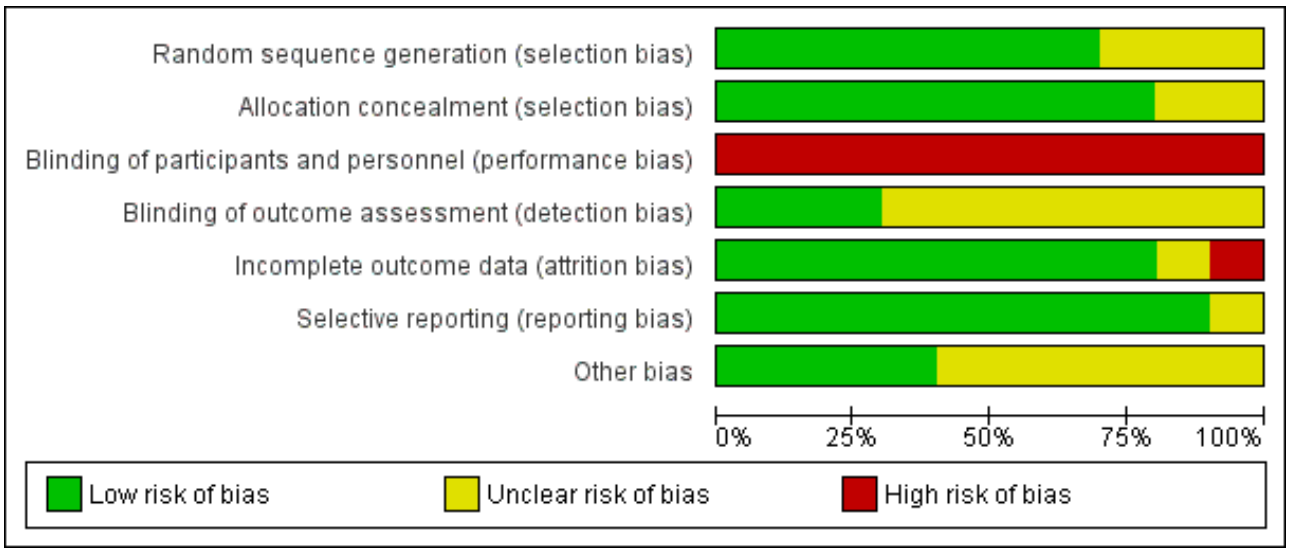
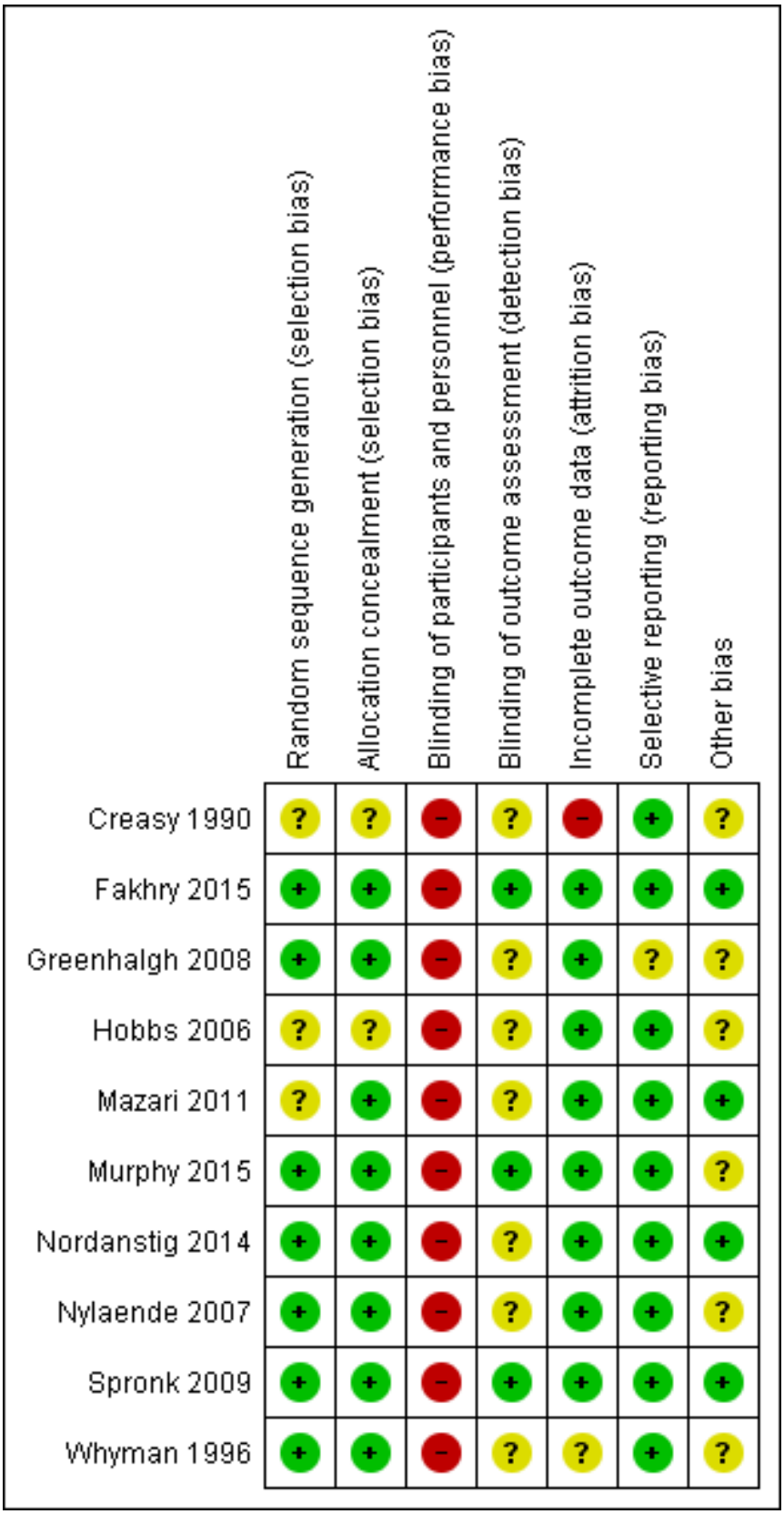


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Although all ten included studies were RCTs, seven studies described an adequate sequence generation method performed by means of computerised randomisation (Fakhry 2015; Greenhalgh 2008; Murphy 2015; Nordanstig 2014; Nylaende 2007; Spronk 2009; Whyman 1996). In the remaining three studies, researchers randomised participants to one of the treatment arms, yet did not report the exact sequence generation methods used, making adequate judgement of risk of bias impossible (Creasy 1990; Hobbs 2006; Mazari 2011). Similarly, most studies reported an adequate allocation concealment method (Fakhry 2015; Greenhalgh 2008; Mazari 2011; Murphy 2015; Nordanstig 2014; Nylaende 2007; Spronk 2009; Whyman 1996). Two studies provided insufficient information to allow a definitive judgement on concealment (Creasy 1990; Hobbs 2006).

Blinding

None of the included studies performed blinding of participants and personnel to the allocated treatment, given the nature of endovascular revascularisation as the intervention in each study. This might have introduced performance bias. Detection bias could be avoided by blinding outcome assessors, which three studies adequately performed and described (Fakhry 2015; Murphy 2015; Spronk 2009). The remaining seven studies provided no information on assessor blinding; thus we determined risk of detection bias to be unclear in these studies.

Incomplete outcome data

We determined risk of attrition bias to be low in eight studies, as censoring at 6 to 18 months' follow-up (if applicable) was minimal to moderate, and numbers and reasons for censoring across allocated groups were well balanced (Fakhry 2015; Greenhalgh 2008; Hobbs 2006; Mazari 2011; Murphy 2015; Nordanstig 2014; Nylaende 2007; Spronk 2009). For one study, we assessed risk of attrition bias to be high, as at 12 months' follow-up, a significant number of participants were not available for primary outcome assessment and information provided on distribution and reasons for dropouts was insufficient (Creasy 1990). Whyman 1996 excluded from analysis participants in the control group who underwent endovascular or open revascularisation, which might have introduced attrition bias, yet information on characteristics of these participants was insufficient to allow judgement for risk of bias.

Selective reporting

In nine studies (Creasy 1990; Fakhry 2015; Hobbs 2006; Mazari 2011; Murphy 2015; Nordanstig 2014; Nylaende 2007; Spronk 2009; Whyman 1996), investigators reported all relevant and expected outcome measures in the results section. In contrast to maximum walking distance, Greenhalgh 2008 reported no absolute values for pain-free walking distance but rather percentage of participants attaining 200 metres without claudication pain; this was not prespecified in the methods section of this study.

Other potential sources of bias

Nylaende 2007 received unrestricted grants from the industry, and Murphy 2015 and Whyman 1996 received partial support from the industry. Owing to slow recruitment in five studies (Creasy 1990; Greenhalgh 2008; Hobbs 2006; Murphy 2015; Nylaende 2007), investigators were unable to include their prespecified intended sample size based on power calculations for the primary outcome measure of walking distance, and this may have biased results.

Effects of interventions

See: **Summary of findings for the main comparison** Endovascular revascularisation compared with no specific therapy for intermittent claudication except verbal advice to exercise; **Summary of findings 2** Endovascular revascularisation compared with conservative therapy for intermittent claudication; **Summary of findings 3** Endovascular revascularisation plus conservative therapy compared with conservative therapy alone for intermittent claudication

Comparison 1. Endovascular revascularisation versus no specific therapy for intermittent claudication except verbal advice to exercise

Data from three studies comparing endovascular revascularisation versus no specific therapy for intermittent claudication (i.e. only cardiovascular risk factor management and verbal advice on exercise) were eligible for inclusion with a total sample size of 134 participants (Hobbs 2006; Nylaende 2007; Whyman 1996).

Maximum walking distance

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from three studies (n = 125) showed that participants had higher MWD following endovascular revascularisation than after no specific therapy (Analysis 1.1), with a pooled SMD of 0.70 (95% CI 0.31 to 1.08; P = 0.0004), which is equivalent to a moderate effect in favour of endovascular revascularisation. There was little heterogeneity (I^2 = 8%).

After long-term follow-up, use of a random-effects model and pooled data from two studies (n = 103) showed no clear differences in MWD between participants following endovascular revascularisation compared with those given no specific therapy (pooled SMD 0.67, 95% CI -0.30 to 1.63; P = 0.18) (Analysis 1.2). Heterogeneity was substantial (I^2 = 83%).

Pain-free walking distance

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from three studies (n = 125) showed that participants following endovascular revascularisation had higher PFWD compared with those given no specific therapy (Analysis 1.3), with a pooled SMD of 1.29 (95% CI 0.90 to 1.68; P < 0.00001); this is equivalent to a large effect in favour of endovascular revascularisation. There was little heterogeneity (I^2 = 0%).

After long-term follow-up, use of a random-effects model and pooled data from two studies (n = 103) showed no clear differences in PFWD between participants following endovascular revascularisation and those given no specific therapy (pooled SMD 0.69, 95% CI -0.45 to 1.82; P = 0.24) (Analysis 1.4). Heterogeneity was considerable (I^2 = 87%).

Secondary invasive interventions

Two studies reported data on the number of secondary invasive interventions during follow-up (Nylaende 2007; Whyman 1996). During two-year follow-up, investigators performed a secondary invasive intervention in 4 of 58 participants in the endovascular revascularisation group and in 5 of 60 participants in the no specific

therapy group (OR 0.8, 95% CI 0.12 to 5.28; P = 0.82). There was little heterogeneity (I^2 = 29%) (Analysis 1.5).

Quality of life

Nylaende 2007 assessed disease-specific QoL using Claudication Scale (CLAU-S) forms and reported no significant differences in all seven domains of the questionnaire between the two study groups after two years of follow-up.

Two studies assessed and reported on general health-related QoL (Nylaende 2007; Whyman 1996). Whyman 1996 used Nottingham Health Profile scores (six domains) to show no significant differences between groups in any domains during follow-up (P > 0.05). Nylaende 2007 used the Short Form-36 (SF-36) questionnaire to show statistically significant differences between groups in the domains of physical functioning in favour of the no specific therapy group and emotional role functioning in favour of the endovascular revascularisation group.

Procedure-related complications

None of the three studies provided data on the number of complications following endovascular revascularisation. However, two studies reported that no major procedure-related complications had occurred (Nylaende 2007; Whyman 1996).

Cardiovascular events

None of the included studies reported data on cardiovascular events during follow-up.

Non-treadmill functional performance measures

Two studies reported non-treadmill functional performance measures (Nylaende 2007; Whyman 1996). Whyman 1996 reported on self-reported walking distance and number of participants with at least 1 kilometre reported walking distance. At two years' follow-up for both outcome measures, study authors reported no statistically significant differences between groups (P ≥ 0.70). After two years' follow-up, Nylaende 2007 reported a higher visual analogue scale (VAS) score (functional status) following endovascular compared with no therapy.

Mortality

Three studies reported data on all-cause mortality (Hobbs 2006; Nylaende 2007; Whyman 1996). During follow-up, 2 of 68 participants in the endovascular revascularisation group and 3 of 68 participants in the no therapy group had died (OR 0.75, 95% CI 0.13 to 4.44; P = 0.75) (Analysis 1.6). There was little heterogeneity (I^2 = 0%).

Subgroup analysis

Given the limited number of studies, we performed no subgroup analysis.

Sensitivity analysis

Given the limited number of studies, we performed no sensitivity analysis.

Comparison 2. Endovascular revascularisation versus conservative therapy

Data from five studies comparing endovascular revascularisation versus conservative therapy for intermittent claudication were eligible for inclusion, with a total sample size of 412 participants (Creasy 1990; Hobbs 2006; Mazari 2011; Murphy 2015; Spronk 2009). The conservative therapy provided in these five studies was supervised exercise therapy.

Maximum walking distance

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from five studies (n = 345) showed no clear differences in MWD between participants following endovascular revascularisation and those given supervised exercise therapy (SMD -0.42, 95% CI -0.87 to 0.04; P = 0.07; Analysis 2.1). Heterogeneity was substantial (I^2 = 69%).

After long-term follow-up, use of a random-effects model and pooled data from three studies (n = 184) showed no clear differences in MWD between participants following endovascular revascularisation and those given supervised exercise therapy (pooled SMD -0.02, 95% CI -0.36 to 0.32; P = 0.90; Analysis 2.2). There was little heterogeneity (I^2 = 24%).

Pain-free walking distance

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from five studies (n = 345) showed no clear differences in PFWD between participants following endovascular revascularisation and those given supervised exercise therapy (SMD -0.05, 95% CI -0.38 to 0.29; P = 0.79; Analysis 2.3). Heterogeneity was substantial (I^2 = 53%).

After long-term follow-up, use of a random-effects model and pooled data from two studies (n = 147) showed no clear differences in PFWD between participants following endovascular revascularisation and those given supervised exercise therapy (pooled SMD 0.11, 95% CI -0.26 to 0.48; P = 0.54; Analysis 2.4). There was little heterogeneity (I^2 = 22%).

Creasy 1990 also assessed long-term PFWD (after 6 years' follow-up) but provided no data on PFWD except for the statement that data showed no significant differences between groups over the long term.

Secondary invasive interventions

Four studies reported data on the number of secondary invasive interventions during follow-up (Creasy 1990; Mazari 2011; Murphy 2015; Spronk 2009). During 6 to 18 months' follow-up, a secondary invasive intervention was performed in 22 of 201 participants in the endovascular revascularisation group, and in 16 of 194 participants in the supervised exercise therapy group (OR 1.40, 95% CI 0.70 to 2.80; P = 0.33). There was little heterogeneity (I^2 = 0%) (Analysis 2.5).

Two studies reported data on the number of secondary invasive interventions during long-term follow-up (Creasy 1990; Spronk 2009). In Creasy 1990, after six years' follow-up, 8 of 30 participants in the endovascular revascularisation group and 9 of 30 participants in the control group needed a secondary invasive revascularisation procedure. In Spronk 2009, after seven years' follow-up, 17 of 75 participants in the endovascular

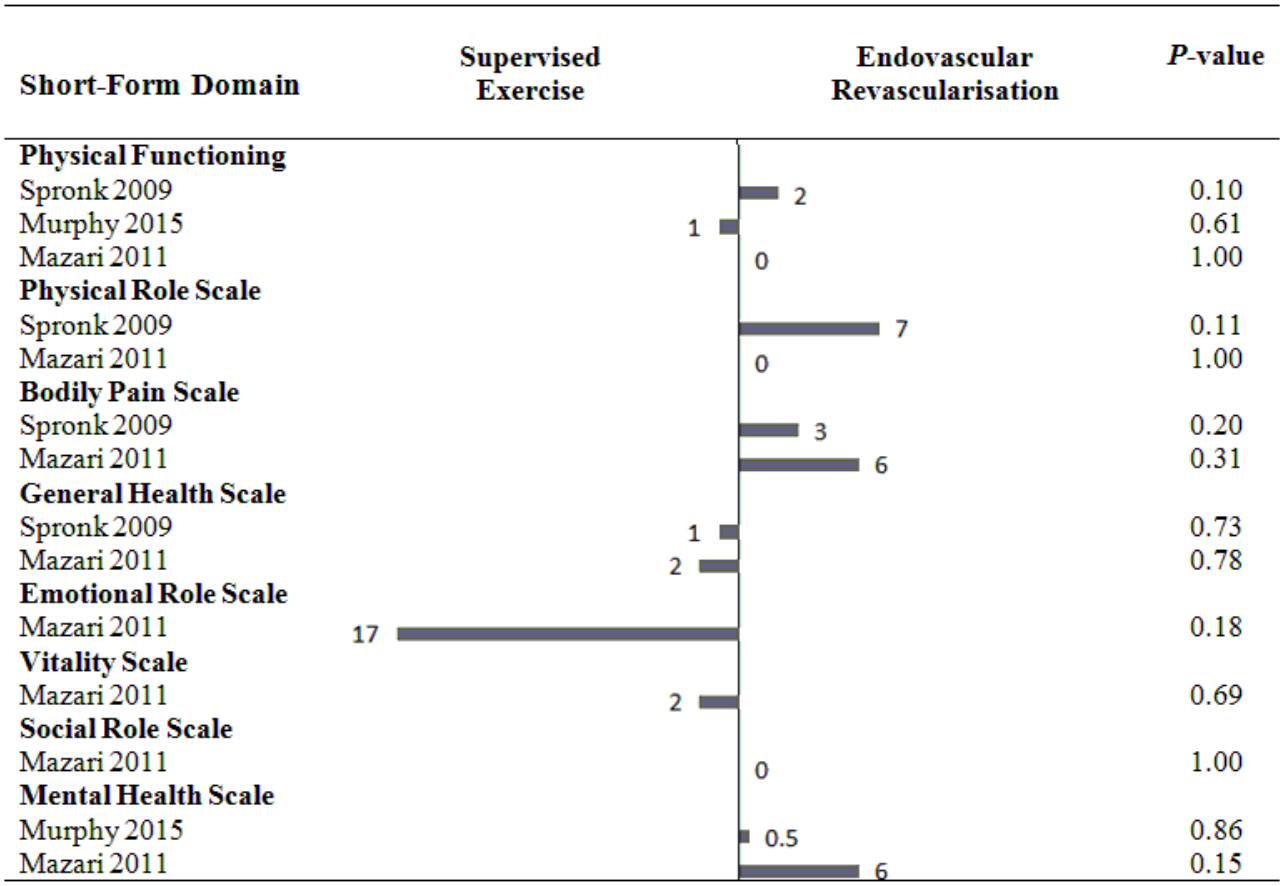
revascularisation group and 32 of 75 participants in the control group needed a secondary revascularisation procedure.

Quality of life

Three studies assessed and reported disease-specific QoL. Mazari 2011 and Spronk 2009 used the VascuQol questionnaire, and Murphy 2015 used the Peripheral Artery Questionnaire (PAQ). Pooled data from these studies (n = 301) produced a pooled SMD of 0.18 (95% CI -0.04 to 0.41; P = 0.11) showing no clear differences between study groups. There was little heterogeneity (I^2 = 0%) (Analysis 2.6).

Three studies assessed and reported general health-related QoL. Mazari 2011 and Spronk 2009 used one or more domains of Short Form-36, and Murphy 2015 used Short Form-12. We have provided a summary of their findings in Figure 4. None of the domains showed a clear difference between study groups.

Figure 4. Health-related quality of life (mean differences between groups).



Procedure related complications

Three studies provided data on the number of minor complications following endovascular revascularisation (Table 1) (Creasy 1990; Murphy 2015; Spronk 2009). Creasy 1990 and Murphy 2015 reported one arterial perforation during the procedure, which needed surgical revision. Mazari 2011 stated that no major procedure-related complications had occurred.

Cardiovascular events

No study reported data on cardiovascular events during follow-up.

Non-treadmill functional performance measures

Two studies reported non-treadmill functional performance measures including self-reported walking distance, hourly free-living steps measured with a pedometer, and functional status assessed with the walking impairment questionnaire (WIQ) and with PAQ (Mazari 2011; Murphy 2015). Mazari 2011 reported no clear differences in self-reported walking distance between the two study groups at one year of follow-up. After six months' follow-up, Murphy 2015 found no clear differences between study arms for change in hourly free-living steps. Similarly in this study, at 18 months' follow-up, PAQ and WIQ scores for all domains were comparable between groups, except for the PAQ physical limitation score and the PAQ summary score, both of which favoured the endovascular revascularisation group (P < 0.05).

Mortality

Five studies reported data on all-cause mortality (Creasy 1990; Hobbs 2006; Mazari 2011; Murphy 2015; Spronk 2009). During follow-up, 11 of 222 participants in the endovascular revascularisation group and 12 of 213 participants in the supervised exercise therapy group had died (OR 0.84, 95% CI 0.35 to 2.00; P = 0.69). There was little heterogeneity (I^2 = 0%) (Analysis 2.7).

Subgroup analysis

Given the limited number of studies and fact that conservative therapy in all studies consisted of supervised exercise therapy, we performed no subgroup analysis.

Sensitivity analysis

In sensitivity analysis excluding Hobbs 2006 and Mazari 2011, which reported only median (IQR) MWD or PFWD; or Mazari 2011, which measured walking distances on a treadmill during only five minutes, which probably underestimated the treatment effect, results compared with the main analysis showed changes for the following outcome: At 6 to 12 months' follow-up, pooled results for MWD from the three remaining studies (n = 232) -Creasy 1990, Murphy 2015, and Spronk 2009 - showed higher MWD in the supervised exercise therapy group than in the endovascular revascularisation group, with SMD of -0.52 (95% CI -0.98 to -0.07; P = 0.024) (Analysis 2.8). For all other outcomes, results from sensitivity analysis did not differ substantially from results obtained by the main analysis (Analysis 2.9).

We did not perform sensitivity analysis on the methodological quality of studies or on individual study effects owing to the limited number of included studies.

Comparison 3. Endovascular revascularisation plus conservative therapy versus conservative therapy

Data from three studies (n = 457) - Fakhry 2015, Greenhalgh 2008, and Mazari 2011 - comparing endovascular revascularisation plus supervised exercise versus supervised exercise alone and data from two studies (n = 199) - Murphy 2015 and Nordanstig 2014 - comparing endovascular revascularisation plus pharmacotherapy (i.e. cilostazol) versus pharmacotherapy for intermittent claudication were eligible for inclusion.

Maximum walking distance

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from three studies (n = 432) showed no clear differences in MWD between participants following combination therapy versus supervised exercise therapy alone (SMD 0.26, 95% CI -0.13 to 0.64; P = 0.19; Analysis 3.1). Heterogeneity was substantial (I^2 = 70%).

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from two studies (n = 186) showed that participants following combination therapy had a higher MWD than those given pharmacotherapy alone (Analysis 3.1), with an SMD of 0.38 (95% CI 0.08 to 0.68; P = 0.014), which is equivalent to a small effect in favour of combination therapy. There was little heterogeneity (I^2 = 0%).

Greenhalgh 2008 provided long-term data for MWD at two years' follow-up for comparison of combination therapy versus supervised exercise therapy alone, which showed a higher MWD in the combination therapy group than in the supervised exercise therapy alone group (SMD 1.18, 95% CI 0.65 to 1.70; P < 0.0001; 106 participants; Analysis 3.2).

Murphy 2015 provided long-term data for MWD at 18 months' follow-up for comparison of combination therapy versus pharmacotherapy alone, which showed a higher MWD in the combination therapy group than in the pharmacotherapy alone group (SMD 0.72, 95% CI 0.09 to 1.36; P = 0.02; 47 participants; Analysis 3.2).

Pain-free walking distance

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from two studies (n = 305) showed no clear differences in PFWD between participants following combination therapy and those given supervised exercise therapy alone (pooled SMD 0.33, 95% CI -0.26 to 0.93; P = 0.27; Analysis 3.3). Heterogeneity was substantial (I^2 = 83%).

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from two studies (n = 186) showed that participants following the combination therapy had a higher PFWD than those given pharmacotherapy alone (Analysis 3.3), with SMD of 0.63 (95% CI 0.33 to 0.94; P < 0.0001), which is equivalent to a moderate effect in favour of combination therapy. There was little heterogeneity (I^2 = 0%).

Greenhalgh 2008 compared combination therapy versus supervised exercise therapy alone in two separate trials - the aortoiliac trial and the femoropopliteal trial - and reported data on long-term PFWD after two years' follow-up. In the femoropopliteal trial, 63% of participants in the combination therapy group and 22% of those in the supervised exercise therapy group attained 200 metres without claudication pain, corresponding to an adjusted hazard ratio of 3.11 (95% CI 1.42 to 6.81; P < 0.01) in favour of combination therapy. Similarly, in the aortoiliac trial, 61% of participants in the combination therapy group and 25% of those in the supervised exercise therapy group attained 200 metres without claudication pain, corresponding to an adjusted hazard ratio of 3.6 (95% CI 1.0 to 12.8; P = 0.05) in favour of combination therapy.

Murphy 2015 provided long-term data for PFWD at 18 months' follow-up comparing combination therapy versus pharmacotherapy alone showing no clear differences between study groups (SMD 0.54, 95% CI -0.08 to 1.17; P = 0.09; 47 participants; Analysis 3.4).

Secondary invasive interventions

Three studies comparing combination therapy versus supervised exercise therapy alone reported data on the number of secondary invasive interventions during follow-up (Fakhry 2015; Greenhalgh 2008; Mazari 2011). During 12 to 24 months' follow-up, investigators performed a secondary invasive intervention in 10 of 231 participants in the combination therapy group and in 37 of 226 participants in the supervised exercise therapy group (OR 0.27, 95% CI 0.13 to 0.55; P = 0.0003) (Analysis 3.5). There was little heterogeneity (I^2 = 0%).

Two studies comparing combination therapy versus pharmacotherapy alone reported data on the number of secondary invasive interventions during follow-up (Murphy 2015; Nordanstig 2014). During 12 to 18 months' follow-up, researchers performed a secondary invasive intervention in 10 of 98 participants in the combination therapy group and in 7 of 101 participants in the pharmacotherapy group (OR 1.83, 95% CI 0.49 to 6.83; P = 0.37) (Analysis 3.5). There was little heterogeneity (I^2 = 17%).

Quality of life

Four studies assessed and reported disease-specific QoL. Fakhry 2015, Mazari 2011, and Nordanstig 2014 used the VascuQol

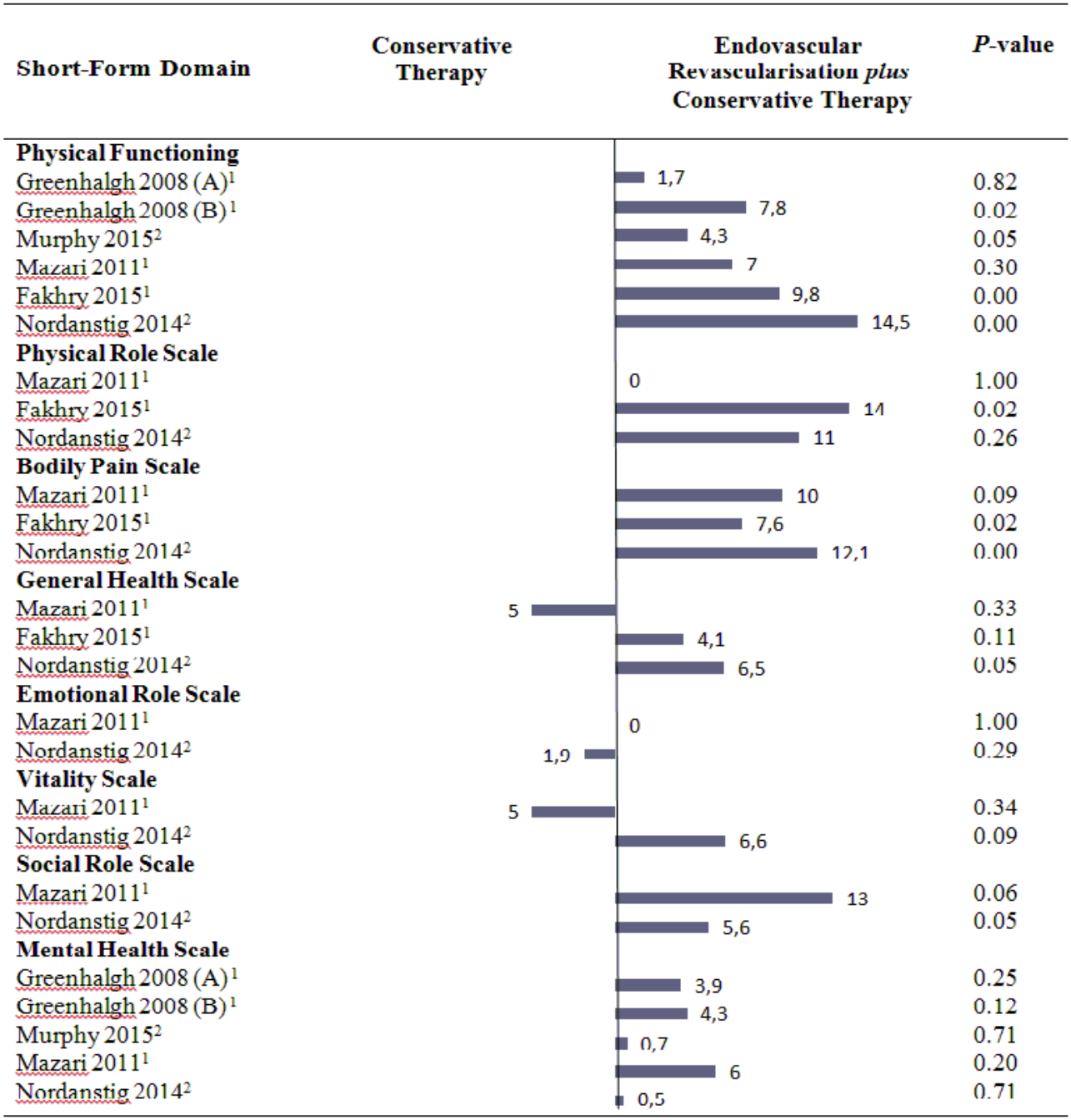
questionnaire, and Murphy 2015 used the Peripheral Artery questionnaire.

Pooled data from two studies (n = 330) comparing combination therapy versus supervised exercise therapy alone produced a pooled SMD of 0.25 (95% CI -0.05 to 0.56; P = 0.10) (Analysis 3.6) (Fakhry 2015; Mazari 2011). Heterogeneity was moderate (I^2 = 45%).

Pooled data from two studies (n = 170) comparing combination therapy versus pharmacotherapy alone produced a pooled SMD of 0.59 (95% CI 0.27 to 0.91; P = 0.0003) (Analysis 3.6), which is equivalent to a small effect in favour of combination therapy (Murphy 2015; Nordanstig 2014). There was little heterogeneity (I^2 = 0%).

Five studies assessed and reported general health-related QoL using one or more domains of Short Form-36 or Short Form-12 (Fakhry 2015; Greenhalgh 2008; Mazari 2011; Murphy 2015; Nordanstig 2014). We have provided a summary of findings from these five studies in Figure 5. For domains assessed on the physical functioning scale, the physical role scale, and the bodily pain scale, data show statistically significant differences in favour of combination therapy.

Figure 5. Health-related quality of life (mean differences between groups). A: Femoropoliteal trial. B: Aortoiliac trial. [1] In this study, the comparison was endovascular revascularisation *plus* supervised exercise *versus* supervised exercise.
[2] In this study, the comparison was endovascular revascularisation *plus* pharmacotherapy with cilostazol *versus* cilostazol.



Procedure related complications

Four studies provided data on the number of minor complications (Table 1) following endovascular revascularisation (Fakhry 2015; Greenhalgh 2008; Murphy 2015; Nordanstig 2014). Murphy 2015 reported one arterial perforation during the procedure, which needed a surgical revision. Nordanstig 2014 reported an emergency surgical exploration due to access site bleeding. Mazari 2011 stated that no major procedure-related complications had occurred.

Cardiovascular events

No study reported data on cardiovascular events during follow-up.

Non-treadmill functional performance measures

Three studies reported non-treadmill functional performance measures including self-reported walking distance, hourly free-living steps measured with a pedometer, and functional status assessed with WIQ and PAQ (Mazari 2011; Murphy 2015; Nordanstig 2014). At one year of follow-up, Mazari 2011 reported no statistically significant difference in self-reported walking distance between study groups, and Nordanstig 2014 reported a significant difference in self-reported MWD in favour of combination therapy over pharmacotherapy alone ($P < 0.01$). After six months' follow-up, Murphy 2015 reported no statistically significant differences between groups for change in hourly free-living steps. At 18 months' follow-up, Mazari 2011 reported that for all domains of WIQ and PAQ summary score, a statistically significant greater improvement favoured combination therapy ($P < 0.05$) over pharmacotherapy alone.

Mortality

Three studies comparing combination therapy versus supervised exercise therapy reported data on all-cause mortality showing that 5 of 231 participants in the combination therapy group and 7 of 226 participants in the supervised exercise therapy alone group had died (OR 0.67, 95% CI 0.20 to 2.21; P = 0.51) (Analysis 3.7) (Fakhry 2015; Greenhalgh 2008; Mazari 2011). There was little heterogeneity ($I^2 = 0\%$).

Two studies comparing combination therapy versus pharmacotherapy reported data on all-cause mortality showing that 5 of 99 participants in the combination therapy group and 1 of 102 participants in the pharmacotherapy alone group had died (OR 1.30, 95% CI 0.14 to 11.92; P = 0.82) (Analysis 3.7) (Murphy 2015; Nordanstig 2014). There was little heterogeneity ($I^2 = 8\%$).

Subgroup analysis

Given the limited number of studies, we performed no subgroup analysis.

Sensitivity analysis

In sensitivity analysis excluding Mazari 2011, which reported only median (IQR) MWD or PFWD and measured walking distances on a treadmill during only five minutes (probably underestimating the treatment effect), results compared with those of the main analysis showed changes in the following outcome: For the comparison of endovascular revascularisation plus supervised exercise versus supervised exercise alone, pooled results for MWD from the two remaining studies (n = 339) showed higher MWD in the combination therapy group than in the supervised exercise alone group, with SMD of 0.43 (95% CI 0.21 to 0.65; P < 0.0001) (Analysis 3.8), which is equivalent to a moderate effect in favour of combination therapy (Fakhry 2015; Murphy 2015). For PFWD, results from Fakhry 2015 showed higher PFWD in the combination therapy group than in the supervised exercise alone group (SMD 0.62, 95% CI 0.34 to 0.89; P = 0.0001; 212 participants) (Analysis 3.9).

DISCUSSION

In this review, we included ten RCTs with a total of 1087 participants assessing the (added) effect of endovascular revascularisation in the management of patients with stable intermittent claudication. It should be stated that overall the studies included are relatively small and show considerable heterogeneity in outcome assessment and outcome reporting; therefore trial results must be interpreted with caution.

Summary of main results

After comparing endovascular revascularisation versus no therapy (except exercise advice) for intermittent claudication, three studies (n = 134) provided data showing a moderate to large effect on walking distances in favour of endovascular revascularisation in the short term up to 12 months. However, after long-term follow-up, this short-term advantage of endovascular revascularisation was uncertain upon pooling of results from two studies. In addition, as reported in these two studies, quality of life (QoL) and the number of secondary invasive interventions during follow-up were not substantially different between study groups.

After comparing endovascular revascularisation versus supervised exercise for intermittent claudication, five studies (n = 412) provided data showing no specific preference for one of the two treatment options. Overall, participants in the supervised exercise therapy group tended to have higher walking distances, and participants in the endovascular revascularisation group tended to have better general and disease-specific QoL, yet these differences were not statistically significant. Similarly, the number of secondary invasive interventions during follow-up was comparable between the two study groups. Sensitivity analysis excluding studies reporting only median walking distances and one study that measured walking distances on a treadmill during only five minutes, which probably underestimated the treatment effect, showed that participants following supervised exercise had a higher maximum walking distance (MWD) after 6 to 12 months when compared with participants following endovascular revascularisation.

After comparing endovascular revascularisation plus conservative therapy versus conservative therapy alone for intermittent claudication, three studies (n = 457) comparing endovascular revascularisation plus supervised exercise versus supervised exercise alone provided data showing no clear difference in walking distances and in disease-specific QoL between groups up to 12 months' follow-up, and one study reported better walking distances in favour of combination therapy at 24 months' follow-up. In addition, participants following endovascular revascularisation plus supervised exercise tended to have higher general health-related QoL in favour of combination therapy for some of the Short Form (SF)-36 domains. Finally, the number of secondary invasive interventions during follow-up was significantly lower following combination therapy compared with supervised exercise alone. Sensitivity analysis excluding one study reporting only median walking distances and measuring walking distances on a treadmill during only five minutes, which probably underestimated the treatment effect, showed that participants following endovascular revascularisation plus supervised exercise had higher maximum walking distance (MWD) and pain-free walking distance (PFWD) after 6 to 12 months compared with participants following supervised exercise only.

When comparing endovascular revascularisation plus cilostazol versus cilostazol alone, two studies (n = 199) provided data showing a small to moderate effect on short- and long-term walking distances in favour of combination therapy. In addition, participants following combination therapy had higher disease-specific and general health-related QoL with differences favouring

endovascular revascularisation plus cilostazol for some of the SF-36 domains. The number of secondary invasive interventions during follow-up was not different between participants in the combination therapy group and those in the cilostazol only group.

Six studies with a total of 366 participants randomised to an endovascular revascularisation procedure provided data on the number of procedure-related complications. Overall endovascular revascularisation for claudication seems to be a relatively 'safe' procedure with an incidence of 8% (30/366) for minor procedure-related complications (groin haematoma and artery dissection) requiring conservative management only. Three studies reported one arterial perforation each during the procedure that required a surgical revision. None of the studies reported any major procedure-related complications leading to permanent disability or death. Yet, it should be noted that these data are based on complications within clinical studies, and complication rates in clinical practice might be much higher.

Overall completeness and applicability of evidence

In general, the ten included studies provided sufficient information on the predefined primary and secondary outcomes of this review, except for the number of cardiovascular events during follow-up, which was not reported by any of the studies.

Considerable heterogeneity in outcome assessment was evident between studies. The treadmill protocol (speed, grade, and time) used to assess primary outcome functional performance measures (i.e. MWD and PFWD) differed significantly between studies; therefore we used SMD as treatment effect for these outcomes to allow standardisation of study results to a uniform scale. In addition, some heterogeneity in outcome reporting was evident between studies, including three studies (Hobbs 2006; Mazari 2011; Whyman 1996) reporting only median (interquartile range (IQR)) MWD and PFWD. In sensitivity analysis excluding these studies and one study (Mazari 2011) limiting treadmill time to assess MWD and PFWD to only five minutes, the main results changed significantly for three analyses as summarised above.

Given the limited number of studies included in this review, we were unable to perform all of the predefined subgroup analyses to investigate existing clinical heterogeneity between studies based on the selected population (femoropopliteal vs aortoiliac vs combined disease) or heterogeneity due to the endovascular revascularisation procedure performed (angioplasty vs stenting).

Given these restrictions, applicability of this review is limited to the general population of patients with intermittent claudication, and review findings do not allow robust conclusions for specific groups of participants or specific types of interventions given.

Quality of the evidence

We used GRADE criteria according to Schünemann 2011 and Atkins 2004 to assess the quality of evidence for the outcomes MWD, PFWD, secondary invasive interventions, and disease-specific QoL. For each comparison, we created a summary of findings table by using GRADEpro software to summarise treatment effects and quality of evidence for each outcome.

For the comparison endovascular revascularisation versus no specific therapy for intermittent claudication, we rated the quality of evidence as low (MWD and PFWD at long term) or moderate (MWD and PFWD at 6 to 12 months and secondary invasive interventions). We downgraded the quality of evidence for this comparison mainly because of small study sample sizes and the possibility of serious risk of bias in two studies with three or more risk of bias domains labelled as having 'unclear' risk (Summary of findings for the main comparison).

For the comparison endovascular revascularisation versus conservative therapy (i.e. supervised exercise), quality assessment ranged from moderate (MWD and PFWD at 6 to 12 months and at long term) to high (secondary invasive interventions and disease-specific QoL). We downgraded the quality of evidence for this comparison mainly owing to substantial heterogeneity between studies and high risk of attrition bias in one of the five studies included in the analysis (Summary of findings 2) (Creasy 1990).

For the final comparison of combination therapy of endovascular revascularisation followed by conservative therapy versus conservative therapy alone, the quality assessment for the comparison combination therapy versus supervised exercise alone ranged from low (MWD at long term) to moderate (MWD and PFWD at 6 to 12 months and disease-specific QoL) to high (number of secondary invasive interventions). We downgraded the quality of evidence for this comparison mainly owing to substantial heterogeneity between studies. We assessed quality for the comparison combination therapy versus pharmacotherapy alone as high (MWD and PFWD at 6 to 12 months, disease-specific QoL, and number of secondary invasive interventions).

Potential biases in the review process

The Cochrane Vascular Information Specialist conducted a comprehensive search to identify all relevant studies for inclusion in this review. In addition, review authors handsearched the reference lists of all eligible studies and reviews for additional relevant studies. Nevertheless, unpublished studies or data may have been missed. We had to exclude two eligible studies because Gelin 2001 reported no outcome measures for the subgroup of participants receiving endovascular revascularisation, and Thomson 1999 published only abstract data with incomplete results. We attempted to contact study authors to ask for relevant data but received no response. Study authors from Nordanstig 2014 provided data on the subgroup of participants receiving endovascular revascularisation, which allowed us to include this study in the quantitative analysis. However, it should be noted that this study was not powered to detect a difference in outcomes between the subgroup of participants receiving endovascular revascularisation and control group participants.

A potential bias that deserves attention is the limitation of maximum walking time on a treadmill test for assessment of the primary outcomes MWD and PFWD during follow-up, which varied between studies and ranged from 5 minutes to 30 minutes. Particularly in studies such as Mazari 2011, which limited maximum walking time to only 5 minutes, and Whyman 1996, which limited walking time to 10 minutes, this may have caused serious underestimation of treatment effect, as participants might have been able to walk farther. This might explain the non-significant differences between treatment groups as reported by these studies. In addition, to pool trial data, we assumed normal distribution for walking distances in three studies (Hobbs 2006; Mazari 2011; Whyman 1996) and used reported median values in the meta-analysis; this may have biased pooled results. In sensitivity analysis

excluding these studies, the main results changed significantly for three analyses, as summarised above.

Agreements and disagreements with other studies or reviews

Results of this review are in line with those of two previously published systematic reviews comparing treatment strategies for patients with intermittent claudication (Ahimastos 2011; Frans 2012). Both reviews concluded that endovascular revascularisation alone provides no significant benefit over supervised exercise therapy alone, and combination therapy of endovascular revascularisation plus supervised exercise therapy may be superior to supervised exercise therapy alone. Since then, results from three sizeable RCTs have been published and are included in this review (Fakhry 2015; Murphy 2015; Nordanstig 2014), overall confirming the conclusions provided by those two earlier systematic reviews.

AUTHORS' CONCLUSIONS

Implications for practice

In the management of patients with intermittent claudication, endovascular revascularisation does not provide significant benefits compared with supervised exercise therapy alone in terms of improvement in functional performance or quality of life. Although the number of studies is small with presence of some clinical heterogeneity, evidence suggests a possible synergetic effect when endovascular revascularisation is combined with a conservative therapy of supervised exercise or pharmacotherapy with cilostazol: the combination therapy seems to result in greater improvements in functional performance and quality of life scores when compared with conservative therapy alone.

Implications for research

More large (and long-term) studies assessing the added effect of endovascular revascularisation over and above supervised exercise therapy, or assessing the effectiveness of a stepped care approach with supervised exercise followed by endovascular revascularisation if needed, are required to define the optimal treatment strategy for the growing population of patients with intermittent claudication. In addition, health economic analyses of these combined treatment strategies are scarce and are urgently needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Creasy 1990

Methods	**Study design:** parallel 2-arm RCT
	Number of sites: 1
	Sample size estimation: not reported
	Follow-up: 3, 6, 9, 12, 15 months and 6 years

Creasy 1990 *(Continued)*

Participants	**Country and setting:** United Kingdom, Oxford Regional Vascular Service **Inclusion criteria** - Stable unilateral claudication, with failure of conservative treatment for ≥ 3 months - Treadmill claudicating distance < 375 meters - Angiographically significant lesion(s) suitable for treatment by angioplasty, as agreed upon by both surgeon and radiologist **Exclusion criteria:** none **Number of participants assessed and randomised:** 36 participants fulfilled the entry criteria and were randomised **Demographics** - Age (years): Group 1: mean 63.6 (SD 8.9); Group 2: mean 62.2 (SD 8.6) - Gender (male): Group 1: 15 (75%); Group 2: 12 (75%)
Interventions	**Group 1:** endovascular revascularisation without stenting, n = 20 (n = 30 at 6 years' follow-up) **Group 2:** supervised exercise therapy for 6 months (2 sessions/week, 30 minutes/session), n = 16 (n = 26 at 6 years' follow-up) **Compliance with interventions** - Group 1: Two angioplasties were not successful - Group 2: Mean attendance over 6 months of exercise therapy was 0.89 sessions/week **Mortality** - Group 1: 4 participants after 6 years' follow-up - Group 2: 6 participants after 6 years' follow-up **Loss to follow-up** - Group 1: 4 participants after 6 years' follow-up - Group 2: 5 participants after 6 years' follow-up
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, procedure-related complications
Notes	**Source of funding:** Oxford District Research Committee **Notes:** New participants were added to the study after initial publication in 1990. Meta-analysis for long-term walking distances used numbers of participants at 6 years' follow-up. **Authors' conclusion:** "In patients with mild or moderate claudication, who do not require an immediate therapeutic response, supervised exercise therapy may ultimately produce greater symptomatic improvement than PTA."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Simple randomisation" was performed according to trial authors; exact randomisation technique was not reported

Creasy 1990 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment process
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	High risk	Not analysed according to intention-to-treat principle; participants who had technically unsuccessful angioplasties were excluded from analysis; at 1-year follow-up, walking distance in only 5 participants (25%) in the revascularisation group and in 7 participants (44%) in the exercise group assessed; characteristics of withdrawals not adequately discussed; new participants added to study after 1 year of follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Unclear risk	Sample size estimation not adequately discussed; low number of participants in whom primary endpoint was assessed (study underpowered)

Fakhry 2015

Methods	**Study design:** parallel 2-arm RCT **Number of sites:** 10 **Sample size estimation:** 210 participants to detect 30% difference in maximum walking distance between the 2 treatment groups based on 90% power, type I error rate of 0.01, and anticipating 10% censoring **Follow-up:** 1, 6, and 12 months
Participants	**Country and setting:** Netherlands, university and non-university hospitals **Inclusion criteria** - Patients with stable intermittent claudication - One or more vascular stenoses > 50% diameter reduction at the aortoiliac and/or femoropopliteal level established by non-invasive vascular imaging - Maximum walking distance between 100 and 500 meters as assessed on a graded treadmill **Exclusion criteria** - Targeted lesion deemed unsuitable for revascularisation - Prior treatment for the targeted lesion (including exercise therapy) - Limited life expectancy - Limited ambulation due to any other condition than intermittent claudication not allowing participant to follow treadmill training

Fakhry 2015 *(Continued)*

	Number of participants assessed and randomised: 666 participants assessed, 212 participants randomised to 1 of the treatment groups **Demographics** - Age (years): Group 1: mean 64 (SD 9); Group 2: mean 66 (SD 10) - Gender (male): Group 1: 60 (57%); Group 2: 72 (68%)
Interventions	**Group 1:** endovascular revascularisation with selective stenting plus supervised exercise therapy, n = 106 **Group 2:** supervised exercise therapy for 12 months (2 to 3 sessions/week 0 to 3 months, 1 session/week 3 to 6 months, 1 session/mo 6 to 12 months, 60 minutes/session), n = 106 **Compliance with interventions** - Group 1: endovascular revascularisation technically successful in 102 (96%) participants, on average per participant 30 sessions exercise followed - Group 2: on average per participant 43 sessions exercise followed **Mortality** - Group 1: 1 participant - Group 2: 3 participants **Loss to follow-up** - Group 1: 5 participants - Group 2: 8 participants
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, procedure-related complications, SF-36 Physical Functioning, SF-36 Physical Role, SF-36 Bodily Pain, SF-36 General Health, VascuQol
Notes	**Source of funding:** grant from Netherlands organization for health research and development **Authors conclusion:** "Among patients with intermittent claudication after 1 year of follow-up, a combination therapy of endovascular revascularization followed by supervised exercise resulted in significantly greater improvement in walking distances and health-related quality-of-life scores compared with supervised exercise only."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using Web-based randomisation software based on minimisation method
Allocation concealment (selection bias)	Low risk	Central Web-based allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias)	Low risk	Independent outcome assessors

Fakhry 2015 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis based on an intention-to-treat principle, censoring at 12 months low (6%) and comparable between groups
Selective reporting (reporting bias)	Low risk	All requested relevant outcome measures provided by study authors
Other bias	Low risk	No other forms of bias identified

Greenhalgh 2008

Methods	**Study design:** parallel 2-arm RCTs: (1) femoropopliteal disease trial; (2) aortoiliac disease trial **Number of sites:** 9 **Sample size estimation:** 170 participants in each trial based on 90% power and significance level of 0.05 to detect a difference of 60 metre improvement in absolute walking distance between groups **Follow-up:** 6, 12, and 24 months
Participants	**Country and setting:** United Kingdom, university and non-university hospitals **Inclusion criteria** - Positive outcome on the Edinburgh Claudication Questionnaire - ABPI < 0.9 or > 0.9 with a positive stress test (fall of > 30 mmHg in Doppler blood pressure following a treadmill test at 4 km/h, 10 slope for 1 minute) - Aortoiliac or femoropopliteal target lesion amenable to endovascular revascularisation as demonstrated by duplex mapping or diagnostic arteriography **Exclusion criteria** - Symptoms too mild to consider angioplasty or so severe that intervention was mandatory - Critical limb ischaemia (absolute Doppler blood pressure < 50 mmHg or presence of ulcers or gangrene with Doppler pressure > 50 mmHg) - Concomitant disease such as musculoskeletal or cardiac that was prohibitive to exercise Number of participants assessed and randomised: 144 participants assessed, 127 participants randomised (93 participants in the femoropopliteal trial and 34 participants in the aortoiliac trial) **Demographics** **Femoropopliteal disease trial** - Age (years): Group 1: 63.9 (SD: 9.0); Group 2: 68.5 (SD: 9.4) - Gender (male): Group 1: 33 (69%); Group 2: 26 (58%) **Aortoiliac disease trial** - Age (years): Group 1: mean 63.9 (SD 8.6); Group 2: mean 62.5 (SD 9.8) - Gender (male): Group 1: 12 (62%); Group 2: 10 (67%)
Interventions	**Group 1:** endovascular revascularisation with selective stenting *plus* supervised exercise therapy, n = 48 (femoropopliteal disease trial), and n = 19 (aortoiliac disease trial)

Greenhalgh 2008 *(Continued)*

Group 2: supervised exercise therapy for 6 months (≥ 1 session/week, 30 minutes/session), n = 45 (femoropopliteal disease trial), and n = 15 (aortoiliac disease trial)

Compliance with interventions

Femoropopliteal trial

- Group 1: in 11/44 participants, endovascular revascularisation recorded as failed, 62% attended available weekly exercise classes

- Group 2: 61% attended available weekly exercise classes

Aortoiliac trial

- Group 1: in 2/19 participants, endovascular revascularisation recorded as failed, 53% attended available weekly exercise classes

- Group 2: 48% attended available weekly exercise classes

Mortality

Femoropopliteal trial

- Group 1: 2 participants

- Group 2: 2 participants

Aortoiliac trial

- Group 1: 1 participants

- Group 2: 2 participants

Loss to follow-up

Femoropopliteal trial

- Group 1: 3 participants

- Group 2: 6 participants

Aortoiliac trial

- Group 1: 4 participants

- Group 2: 1 participants

Outcomes	Absolute walking distance, initial claudication distance, number of secondary interventions, SF-36 physical health score , SF-36 physical mental score, procedure-related complications
Notes	**Source of funding:** Camelia Botnar Arterial Research Foundation with independent educational grants from Bard Ltd., Boston Scientific Ltd., and Cook **Authors' conclusion:** "PTA confers adjuvant benefit over supervised exercise and best medical therapy in terms of walking distances and ABPI 24 months after PTA in patients with stable mild to moderate intermittent claudication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomisation technique using "randomly permuted blocks of unequal size generated by Stata"

Greenhalgh 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central allocation, "performed by the trial manager via a laptop computer whilst on site at each centre"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis based on an intention-to-treat principle, censoring at 24 months moderate (17%) and comparable between groups
Selective reporting (reporting bias)	Unclear risk	Prespecified maximum walking distance reported; for pain-free walking distance, no absolute distances reported during follow-up
Other bias	Unclear risk	Intended recruitment based on power calculations 170 participants in each trial, eventually including 93 participants in the femoropopliteal trial and 34 participants in the aortoiliac trial

Hobbs 2006

Methods	**Study design:** parallel 3-arm RCT **Number of sites:** 4 **Sample size estimation:** 21 participants (7 per group) required to detect a 75% reduction in the thrombin antithrombin complex in treatment groups with 80% power and a P value of 0.05 **Follow-up:** 3 and 6 months
Participants	**Country and setting:** United Kingdom, Department of Vascular Surgery at University of Birmingham **Inclusion criteria** - Confirmed mild to moderate intermittent claudication (defined as absolute claudication distance (of 50 to 500 m on a treadmill) due to infrainguinal disease - Suitable for unilateral infrainguinal endovascular revascularisation and participation in a supervised exercise programme - 3 to 6 months stabilised on best medical therapy before consideration for study entry **Exclusion criteria** - Significant aortoiliac disease - Equally severe bilateral symptoms (making them unsuitable for unilateral angioplasty) - Previous ipsilateral infrainguinal intervention - Unable to exercise to absolute claudication distance on treadmill **Number of participants assessed and randomised:** 372 participants screened for entry; from them 23 participants randomised to 1 of 3 treatment arms **Demographics**

Hobbs 2006 *(Continued)*

	- Age (years): Group 1: median 67 (IQR 57 to 77); Group 2: median 67 (IQR 58 to 71); Group 3: median 67 (IQR 57 to 77) - Gender (male): Group 1: 6 (67%); Group 2: 6 (86%); Group 3: 4 (57%)
Interventions	**Group 1:** endovascular revascularisation without stenting plus best medical therapy, n = 9 **Group 2:** supervised exercise therapy plus best medical therapy for 12 weeks (2 sessions/week, 60 minutes/session), n = 7 **Group 3:** best medical therapy based on cardiovascular risk factor management, n = 7 (for analysis, this group was labelled as 'no therapy') **Compliance with interventions:** not reported **Mortality** - Group 1: 0 participants - Group 2: 0 participants - Group 3: 0 participants **Loss to follow-up** - Group 1: 0 participants - Group 2: 1 participant - Group 3: 0 participants
Outcomes	Maximum walking distance, pain-free walking distance
Notes	**Source of funding:** Health Technology Assessment Grant **Authors' conclusion:** "The addition of lower limb revascularization by PTA to best medical therapy in patients with intermittent claudication due to infra-inguinal disease results in a medium-term improvement in the resting procoagulant and hypo fibrinolytic state."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants underwent "central randomisation", yet exact randomisation technique not specified
Allocation concealment (selection bias)	Unclear risk	Study did not address allocation concealment process
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	During 6-month follow-up, only 1 participant withdrew (4%) from the study

Hobbs 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Unclear risk	Study was not powered to consider walking distances as primary endpoint; study was closed early including only 10% of required participants

Mazari 2011

Methods	**Study design:** parallel 3-arm RCT **Number of sites:** 1 **Sample size estimation:** 60 participants in each treatment arm based on 80% power, α = 0.05, and anticipating a 20% dropout rate to detect a 20% difference between treatment arms in physical function domain of SF-36 **Follow-up:** 1,3, 6, and 12 months
Participants	**Country and setting:** United Kingdom, Vascular Surgical Unit of a university hospital **Inclusion criteria** - Symptomatic unilateral intermittent claudication - Femoropopliteal lesion amenable to angioplasty (as discussed in a multi-disciplinary meeting) - Symptoms stable after 3 months on best medical therapy **Exclusion criteria** - Critical limb ischaemia - Incapacitating systemic disease - Inability to tolerate treadmill testing (unrelated to limb ischaemia) - Significant Ischaemic changes on ECG during treadmill testing - Ipsilateral vascular surgery or peripheral angioplasty within previous 6 months **Number of participants assessed and randomised:** 1157 participants were assessed for inclusion; from them 178 participants were randomised to 1 of 3 treatment arms **Demographics** - Age (years): Group 1: median 69.5 (95% CI 64 to 79); Group 2: median 70 (95% CI 63 to 75); Group 3: median 69 (95% CI 63 to 76) - Gender (male): Group 1: 33 (57%); Group 2: 37 (62%); Group 3: 37 (62%)
Interventions	**Group 1:** endovascular revascularisation without stenting *plus* supervised exercise therapy, n = 58 **Group 2:** endovascular revascularisation without stenting, n = 60 **Group 3:** supervised exercise therapy for 12 weeks (3 sessions/week), n = 60 **Compliance with interventions:** not reported **Mortality** - Group 1: 1 participant

Mazari 2011 *(Continued)*

	- Group 2: 0 participants - Group 3: 0 participants **Loss to follow-up** - Group 1: 10 participants - Group 2: 8 participants - Group 3: 14 participants
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, SF-36 Physical Function, SF-36 Role Physical, SF-36 Bodily Pain, SF-36 General Health, SF-36 Vitality, SF-36 Social, SF-36 Emotional, SF-36 Mental, VascuQol, self-reported maximum walking distance
Notes	**Source of funding:** BJS research bursary, European Society of Vascular Surgery research grant, and support from the Academic Vascular Surgical Unit, University of Hull **Authors' conclusion:** "For patients with intermittent claudication due to femoropopliteal disease, PTA, supervised exercise and PTA plus supervised exercise were all equally effective in improving walking distance and quality of life after 12 months."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were "randomised into one of the three treatment arms"; exact sequence generation method not reported
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Sufficient number of participants (82%) analysed after 1 year of follow-up; censoring comparable between groups
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Low risk	No other forms of bias identified

Murphy 2015

Methods	**Study design:** parallel 4-arm RCT **Number of sites:** 22

Murphy 2015 *(Continued)*

	Sample size estimation: Allowing 30% premature withdrawal, 252 participants would be needed to have 80% power to detect relevant difference between supervised exercise and stenting groups. Sample size was adjusted to 217 after removal of stenting plus supervised exercise arm owing to slow enrolment. **Follow-up:** 6 and 18 months
Participants	**Country and setting:** United States, university and non-university hospitals **Inclusion criteria** - Symptoms of moderate to severe intermittent claudication (ability to walk 2 to 11 minutes on a graded treadmill test) - Objective evidence of a haemodynamically significant aortoiliac arterial stenosis established by non-invasive vascular testing **Exclusion criteria** - Critical limb ischaemia - Comorbid conditions limiting participants' walking ability - More than 25% deviation between 2 treadmill tests at baseline - Total aortoiliac occlusion from the level of the renal arteries to the inguinal ligaments **Number of participants assessed and randomised:** 999 participants screened, 119 participants randomised to 1 of 4 treatment arms **Demographics** - Age (years): Group 1: mean 65 (SD 10); Group 2: mean 64 (SD 10); Group 3: mean 62 (SD 8) - Gender (male): Group 1: 32 (70%); Group 2: 21 (49%); Group 3: 16 (73%)
Interventions	**Group 1:** endovascular revascularisation with primary stenting *plus* claudication pharmacotherapy (cilostazol), n = 46 **Group 2:** supervised exercise therapy for 26 weeks (3 sessions/week, 1 hour/session) supplemented by 12-month telephone-based (1 to 2 calls/mo) programme to adhere and maintain adherence *plus* claudication pharmacotherapy (cilostazol), n = 43 **Group 3:** claudication pharmacotherapy, including cilostazol 100 mg twice daily and advice on home exercise and diet, n = 22 **Group 4:** endovascular revascularisation *plus* supervised exercise therapy and claudication pharmacotherapy (cilostazol), n = 8 (inclusion in this study arm stopped prematurely and study arm excluded from further analysis) **Compliance with interventions** - Group 1: 43 participants received assigned intervention, all procedures technically successful, > 90% adherence to cilostazol treatment - Group 2: 29 (71%) participants attended at least 70% of 78 scheduled exercise sessions, > 90% adherence to cilostazol treatment - Group 3: > 90% adherence to cilostazol treatment **Mortality** - Group 1: 0 participants - Group 2: 1 participant

Murphy 2015 *(Continued)*

	- Group 3: 0 participants **Loss to follow-up** - Group 1: 5 participants - Group 2: 8 participants - Group 3: 4 participants
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, procedure-related complications, SF-12 Physical, SF-12 Mental, Walking Impairment Questionnaire Score, Peripheral Artery Questionnaire Score, hourly free-living steps on pedometer
Notes	**Source of funding:** grants from National Heart, Lung, and Blood Institute. Financial support from Cordis/Johnson & Johnson (Warren, NJ), eV3 (Plymouth,MN), and Boston Scientific (Natick, MA). Cilostazol was donated to all study participants by Otsuka America, Inc (San Francisco, CA). Pedometers were donated by Omron Healthcare, Inc (Lake Forest, IL). Krames Staywell (San Bruno, CA) donated print materials on exercise and diet. **Notes:** The endovascular revascularisation *plus* supervised exercise therapy treatment arm was stopped after including 8 participants owing to slow enrolment. **Authors' conclusion:** "Both supervised exercise and endovascular revascularization had better 18-month outcomes than medical treatment. Both treatments provided comparable durable improvement in functional status and in quality of life up to 18 months. The durability of claudication exercise interventions merits its consideration as a primary claudication treatment."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A real-time Web-based randomisation programme was used to randomise participants
Allocation concealment (selection bias)	Low risk	Central Web-based allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study reported to be an "observer-blinded" randomised trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses according to intention-to-treat principle; censoring was moderate (10%) after 6 months' follow-up and was well balanced between treatment groups
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Unclear risk	Intended recruitment based on power calculations was 252 participants; eventually 119 participants were included in the study

Nordanstig 2014

Methods	**Study design:** parallel 2-arm RCT **Number of sites:** 1 **Sample size estimation:** From power calculations, a total sample size of 158 participants was needed with the assumption of a maximum dropout rate of 25% and 80% power to detect relevant differences between the 2 groups. **Follow-up:** 6 and 12 months
Participants	**Country and setting:** Sweden, Department of Vascular Surgery at university hospital **Inclusion criteria** - Stable (≥ 6 months) intermittent claudication, without any other important activity-limiting medical condition - Aged ≤ 80 years **Exclusion criteria** - Very mild claudication symptoms - Severe claudication symptoms making invasive treatment mandatory - Weight > 120 kg - ≥ 2 previously failed ipsilateral vascular interventions - Inability to understand the Swedish language **Number of participants assessed and randomised:** 464 participants screened for inclusion; of these, 205 participants were eligible, and eventually 158 participants were randomised in the trial **Demographics** - Age (years): Group 1: mean 68 (SD 7); Group 2: mean 68 (SD 6) - Gender (male): Group 1: 41 (52%); Group 2: 38 (48%)
Interventions	**Group 1:** invasive vascular procedure including open surgery or endovascular revascularisation with primary stenting in the aortoiliac segment and selective stenting in the femoropopliteal segment *plus* claudication pharmacotherapy (cilostazol 100 mg twice daily), home-based exercise training advice, and cardiovascular risk factor management, n = 79 (of these, 52 participants received an endovascular revascularisation procedure) **Group 2:** non-invasive management including claudication pharmacotherapy (cilostazol 100 mg twice daily), home-based exercise training advice, and cardiovascular risk factor management, n = 79 **Compliance with interventions** - Group 1: 70 participants received invasive treatment; from them, 52 participants received an endovascular intervention, 60% adherence to cilostazol treatment at 12 months, no data on exercise adherence - Group 2: 60% adherence to cilostazol treatment at 12 months; no data on exercise adherence **Mortality** - Group 1: 1 participant of the 52 participants receiving endovascular revascularisation - Group 2: 0 participants **Lost to follow up:** - Group 1: 2 participants of 52 participants receiving endovascular revascularisation

Nordanstig 2014 *(Continued)*

	- Group 2: 3 participants
Outcomes	Maximum walking distance, intermittent claudication distance, number of secondary interventions, procedure-related complications, SF-36 Physical Function, SF-36 Role Physical, SF-36 Bodily Pain, SF-36 General Health, SF-36 Vitality, SF-36 Social, SF-36 Emotional, SF-36 Mental Health, and VascuQol
Notes	**Source of funding:** Study was funded by the Fred G. and Emma E. Kanolds Foundation/Gothenburg Medical Society; Helena Ahlin Foundation; Odd Fellow, Karlstad, Sweden; Swedish Heart and Lung Foundation; and Hjalmar Svensson Foundation. **Notes:** Outcome data from the subgroup of 52 participants who received an endovascular revascularisation at baseline in the invasive treatment group were provided by study authors and were included in the analyses in this systematic review. **Authors' conclusion:** "An invasive treatment strategy improves health-related quality of life and intermittent claudication distance after 1 year in patients with stable lifestyle-limiting claudication receiving current medical management. Long-term follow-up data and health-economic assessments are warranted to further establish the role for revascularization in intermittent claudication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed via computerised randomisation software based on minimisation method
Allocation concealment (selection bias)	Low risk	Allocation sequence was concealed using computerised randomisation software
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analysis performed by intention-to-treat principle; censoring during 12-month follow-up low and well balanced between treatment groups
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported in the results section
Other bias	Low risk	No other forms of bias identified

Nylaende 2007

Methods	**Study design:** parallel 2-arm RCT **Number of sites:** 1 **Sample size estimation:** approximately 100 participants in each group; thus a total of 200 participants to detect a difference of 20% in QoL between groups assuming type I error of 5% and power of 80% **Follow-up:** 3, 12, and 24 months

Nylaende 2007 *(Continued)*

Participants	**Country and setting:** Norway, Centre of Vascular Surgery at university hospital **Inclusion criteria** - < 80 years of age - Symptomatic IC > 3 months - Ankle brachial index < 0.9 without pain at rest and/or ischaemic skin changes - Lesion feasible for angioplasty evaluated by angiography - Subjective pain-free walking distance < 400 metres - Ability to exercise on a treadmill **Exclusion criteria** - Previous vascular or endovascular surgery - Diabetic skin ulceration - Renal insufficiency (defined as serum creatinine > 150 mmol/L) - Oral anticoagulant medication - Suffering from a physical or mental disorder expected to impede compliance **Number of participants assessed and randomised:** 826 participants were assessed for inclusion; finally 56 participants could be included and randomised to 1 of 2 treatment groups. **Demographics** - Age (years): Group 1: median 68 (25 to 75 percentiles: 56 to 72); Group 2: median 69 (25 to 75 percentiles: 61 to 75) - Gender (male): Group 1: 16 (57%); Group 2: 15 (54%)
Interventions	**Group 1:** endovascular revascularisation with primary stenting for iliac occlusions and selective stenting for iliac stenoses *plus* optimal medical treatment, n = 28 **Group 2:** optimal medical treatment including active smoking cessation, advice on home-based exercise therapy, individual nutritional advice, and acetylsalicylic acid 160 mg daily to all participants and cardiovascular risk factor management, n = 28 (for analysis, this group was labelled as 'no therapy') **Compliance with interventions** - Group 1: All procedures were technically successful. - Group 2: No data were provided on home-based exercise therapy compliance. **Mortality** - Group 1: 1 participant - Group 2: 0 participants **Loss to follow-up** - Group 1: 1 participant - Group 2: 4 participants
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, SF-36 Physical Function, SF-36 Role Physical, SF-36 Bodily Pain, SF-36 General Health, SF-36 Vitality, SF-36

Nylaende 2007 *(Continued)*

	Social, SF-36 Emotional, SF-36 Mental, SF-36 Health Transition, Claudication Score (5 domains), visual analogue scale
Notes	**Source of funding:** unrestricted grants from Pfizer AS, Norway **Authors conclusion:** "Early intervention with PTA in addition to optimal medical treatment seems to have a generally more positive effect compared to optimal medical treatment only, on haemodynamic, functional as well as quality of life aspects during the first 2 years in patients with intermittent claudication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A "computerized randomisation list" was used
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All relevant outcome measures as specified in the methods section were reported
Selective reporting (reporting bias)	Low risk	Censoring during 12-month follow-up minimal (9%) and well balanced between groups
Other bias	Unclear risk	Intended recruitment based on power calculations was 200 participants; eventually 56 participants were included in the study, Source of funding: unrestricted grants from Pfizer AS, Norway

Spronk 2009

Methods	**Study design:** parallel 2-arm RCT **Number of sites:** 1 **Sample size estimation:** 68 participants in each arm based on 80% power and significance level of 0.05 to detect 25% difference in improvement in physical functioning dimension of SF-36 between the 2 groups **Follow up:** 1, 6, 12 months and 7 years
Participants	**Country and setting:** Netherlands, outpatient clinic at a non-university hospital **Inclusion criteria** - Rutherford category 1, 2, or 3 claudication with duration ≥ 3 months

Spronk 2009 *(Continued)*

	- Maximum pain-free walking distance < 350 metres - Ankle-brachial index < 0.9 at rest or decreasing by more than 0.15 after the treadmill test - ≥ 1 vascular stenoses of > 50% diameter reduction at the iliac or femoropopliteal level on magnetic resonance angiography **Exclusion criteria** - Abdominal aortic aneurysm, life-incapacitating cardiac disease (New York Heart Association Class III and higher) - Multi-level disease (i.e. same-side stenoses at both iliac and femoral levels, requiring multiple revascularisation procedures) - Isolated tibial artery disease - Lesions deemed unsuitable for revascularisation - Prior treatment for the lesion (including exercise therapy) **Number of participants assessed and randomised:** 293 participants assessed, 151 participants randomised to 1 of 2 treatment groups **Demographics** - Age (years): Group 1: mean 65 (SD 11); Group 2: mean 66 (SD 9) - Gender (male): Group 1: 44 (59%); Group 2: 39 (52%)
Interventions	**Group 1:** endovascular revascularisation with selective stenting, n = 76 **Group 2:** supervised exercise therapy for 24 weeks (2 sessions/week, 30 minutes/session), n = 75 **Compliance with interventions** - Group 1: In 4 participants, revascularisation failed technically - Group 2: Per participant, on average 33 (SD 10) sessions of exercise followed **Mortality** - Group 1: 5 participants (after 7 years: 15) - Group 2: 3 participants (after 7 years: 17) **Loss to follow-up** - Group 1: 2 participants (after 7 years: 14) - Group 2: 0 participants (after 7 years: 22)
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, procedure-related complications, SF-36 Physical Functioning, SF-36 Physical Role, SF-36 Bodily Pain, SF-36 General Health, VascuQol
Notes	**Source of funding:** not applicable **Authors conclusion:** "After 6 and 12 months, patients with intermittent claudication benefited equally from either endovascular revascularization or supervised exercise."

Risk of bias

Bias	Authors' judgement	Support for judgement

Spronk 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	A "computer generated block-randomized list" was used, prepared in advance by an independent statistician
Allocation concealment (selection bias)	Low risk	Allocation was "sealed for every particular participant."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Walking distance evaluated by an independent assessor blinded to assigned treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analysis according to intention-to-treat principle; after 12 months' follow-up, censoring minimal (7%) and well balanced between the 2 groups
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Low risk	No other forms of bias identified

Whyman 1996

Methods	**Study design:** parallel 2-arm RCT **Number of sites:** 1 **Sample size estimation:** 54 participants based on 90% power and significance level of 0.05 to detect 40% difference in number of participants with symptomatic improvement between intervention and control groups **Follow-up:** 3, 6, and 24 months
Participants	**Country and setting:** United Kingdom, outpatient department of a university hospital **Inclusion criteria** - Predominantly unilateral intermittent claudication - Lesion suitable for endovascular revascularisation **Exclusion criteria** - Previous angioplasty or arterial surgery to the symptomatic leg - Iliac occlusion or > 10 cm length femoropopliteal occlusion, multiple stenoses or diffuse disease with long stenoses - Participants taking oral anticoagulants - Duration of symptoms < 1 month - Inability to manage the treadmill examination - Any psychiatric illness or other reason making follow-up difficult.

Whyman 1996 *(Continued)*

	Number of participants assessed and randomised: 425 participants assessed, 62 participants randomised **Demographics** - Age (years): Group 1: mean 60.6 (range 44 to 73); Group 2: mean 62.6 (range 45 to 78) - Gender (male): Group 1: 23 (77%); Group 2: 28 (88%)
Interventions	**Group 1:** endovascular revascularisation without stenting, n = 30 **Group 2:** conventional medical treatment including low-dose aspirin plus advice on smoking and exercise, n = 32 (for analysis, this group was labelled as 'no therapy') **Compliance with interventions:** not reported **Mortality** - Group 1: 0 participants - Group 2: 2 participants **Loss to follow-up** - Group 1: 1 participant - Group 2: 2 participants
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, Nottingham health profile scores, self-reported maximum walking distance
Notes	**Source of funding:** grant from the Scottish Home and Health Department, cost of balloon catheters from Meadox, UK **Authors' conclusion:** "Two years after PTA, patients had less extensive disease than medically treated patients, but this did not translate into a significant advantage in terms of improved walking or quality of life."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out via a computerised random allocation system
Allocation concealment (selection bias)	Low risk	Allocation was carried out via a computerised random allocation system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Censoring minimal (5%) and comparable between groups, yet participants in the control group who underwent angioplasty or surgery excluded from analysis

Whyman 1996 *(Continued)*

Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Unclear risk	Source of funding: cost of balloon catheters from Meadox, UK

ABI: ankle brachial pressure index.
IC: intermittent claudication.
IQR: interquartile range.
PTA: percutaneous transluminal angioplasty.
QoL: quality of life.
RCT: randomised controlled trial.
SD: standard deviation.
SF-36: Short Form-36.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bo 2013	All participants received endovascular revascularisation
Brodmann 2013	Two endovascular revascularisation techniques were compared; no non-interventional treatment group was included
Gabrielli 2012	Two endovascular revascularisation techniques were compared; no non-interventional treatment group was included
Gelin 2001	Intervention group included participants with open and endovascular revascularisation; no data could be provided for the subgroup of participants receiving endovascular revascularisation
Giugliano 2013	Participant assignment to a specific group of treatment was not randomised
Heider 2009	Participants were followed up to 4 weeks. No relevant outcome measures for this systematic review were reported
Husmann 2008	Walking distances were recorded only up to 1 month follow-up; no long-term data were provided. In addition, no other relevant outcome measures for this systematic review were reported
Kruidenier 2011	All participants received endovascular revascularisation
Thomson 1999	Abstract data only with incomplete results; no additional data could be provided

Characteristics of ongoing studies *[ordered by study ID]*

Frans 2012a

Trial name or title	SUPERvised Exercise Therapy or Immediate PTA for Intermittent Claudication in Participants With an Iliac Artery Obstruction
Methods	**Study design:** multi-centre randomised controlled trial **Sites:** 15 Dutch hospitals **Sample size estimation:** 400 participants to detect a clinically relevant difference in quality-adjusted life-years between the 2 groups based on 90% power and 2-sided significance level of 0.05

Frans 2012a *(Continued)*

	Follow up: 1 week, 1, 6, and 12 months
Participants	Consecutive outpatients with intermittent claudication due to aortoiliac disease with a walking distance between 100 and 300 metres on a treadmill at 3.2 km/h and 10% incline. All participants must have an iliac artery obstruction with a diameter reduction ≥ 50%
Interventions	**Group 1:** endovascular revascularisation with selective stenting **Group 2:** supervised exercise therapy for 6 months
Outcomes	Maximum walking distance, pain-free walking distance, complications, treatment failures, additional interventions, costs, AMC linear disability score, VascuQol, Short-Form 36, EuroQol
Starting date	Inclusion started in September 2011
Contact information	m.j.koelemaij@amc.uva.nl
Notes	Owing to slow enrolment, inclusion stopped prematurely (241 participants included per May 2015; www.superstudie.nl).

NCT01230229

Trial name or title	Primary Stenting vs Conservative Treatment in Claudicants - A Study on Quality of Life (NCT01230229)
Methods	**Study design:** randomised controlled trial **Estimated enrolment:** 100 participants **Follow-up:** 12 and 24 months
Participants	Patients with stable intermittent claudication (Fontaine IIa and IIb) due to superficial femoral artery disease
Interventions	**Group 1:** endovascular revascularisation with primary stenting (self-expanding stent) **Group 2:** best medical treatment including an exercise programme
Outcomes	**Primary:** improvement in quality of life scores (Short Form-36 and EuroQol-5D surveys) **Secondary:** ABI, walking distances, cost parameters
Starting date	January 2010
Contact information	Hans Lindgren, MD; e-mail: hanslindgren@gmail.com
Notes	Planned recruitment and randomisation of 100 participants; estimated study completion date June 2017 (https://clinicaltrials.gov/ct2/show/study/NCT01230229?term=endovascular+and+claudication#desc)

ABI: ankle brachial pressure index.
AMC: academic medical centre.
PTA: percutaneous transluminal angioplasty.
QoL: quality of life.

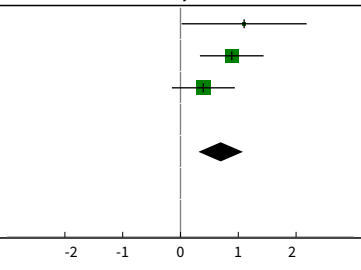
DATA AND ANALYSES

Comparison 1. Endovascular revascularisation versus no specific therapy except verbal advice to exercise

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum walking distance	3	125	Std. Mean Difference (IV, Random, 95% CI)	0.70 [0.31, 1.08]
2 Maximum walking distance (long-term)	2	103	Std. Mean Difference (IV, Random, 95% CI)	0.67 [-0.30, 1.63]
3 Pain-free walking distance	3	125	Std. Mean Difference (IV, Random, 95% CI)	1.29 [0.90, 1.68]
4 Pain-free walking distance (long-term)	2	103	Std. Mean Difference (IV, Random, 95% CI)	0.69 [-0.45, 1.82]
5 Secondary invasive interventions	2	118	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.12, 5.28]
6 Mortality	3	136	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.13, 4.44]

Analysis 1.1. Comparison 1 Endovascular revascularisation versus no specific therapy except verbal advice to exercise, Outcome 1 Maximum walking distance.

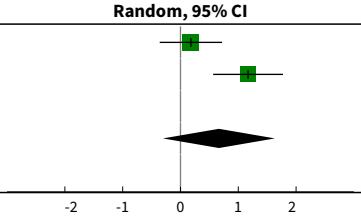
Study or subgroup	Endovascular therapy N	Endovascular therapy Mean(SD)	No therapy N	No therapy Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Hobbs 2006	9	698 (584)	7	145 (267)		12.28%	1.1[0.02,2.18]
Nylaende 2007	28	495 (204)	28	298 (233)		43.39%	0.89[0.34,1.44]
Whyman 1996	26	667 (332)	27	520 (396)		44.33%	0.4[-0.15,0.94]
Total ***	**63**		**62**			**100%**	**0.7[0.31,1.08]**
Heterogeneity: Tau^2=0.01; Chi^2=2.17, df=2(P=0.34); I^2=7.88%							
Test for overall effect: Z=3.54(P=0)							



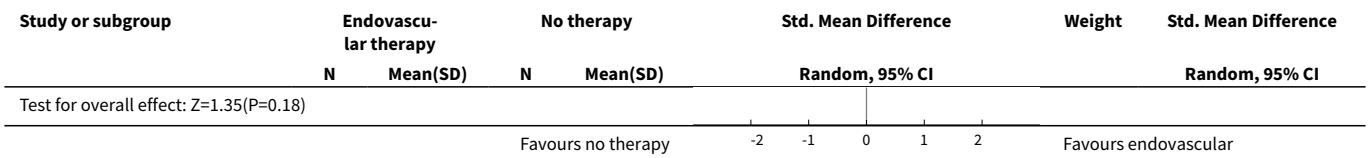
Favours no therapy — Favours endovascular

Analysis 1.2. Comparison 1 Endovascular revascularisation versus no specific therapy except verbal advice to exercise, Outcome 2 Maximum walking distance (long-term).

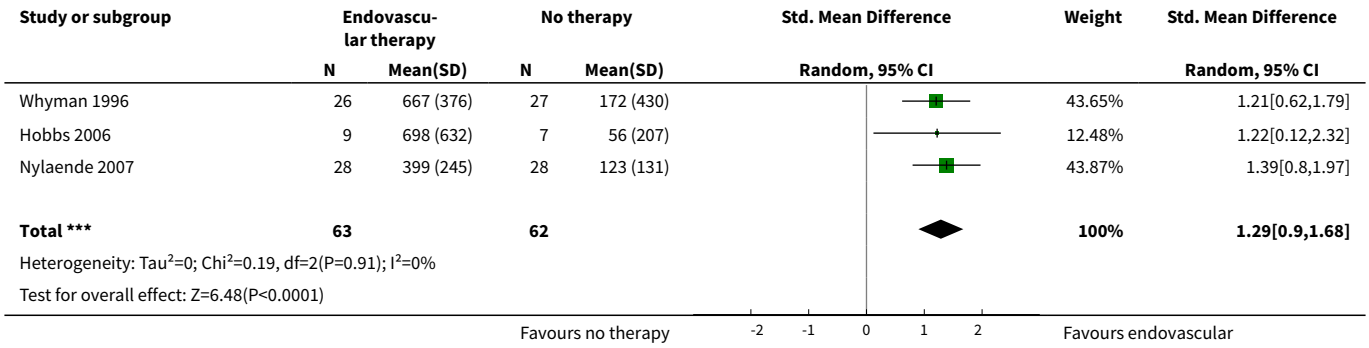
Study or subgroup	Endovascular therapy N	Endovascular therapy Mean(SD)	No therapy N	No therapy Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Whyman 1996	26	667 (393)	27	600 (338)		50.98%	0.18[-0.36,0.72]
Nylaende 2007	26	539 (144)	24	320 (220)		49.02%	1.17[0.57,1.77]
Total ***	**52**		**51**			**100%**	**0.67[-0.3,1.63]**
Heterogeneity: Tau^2=0.4; Chi^2=5.72, df=1(P=0.02); I^2=82.53%							



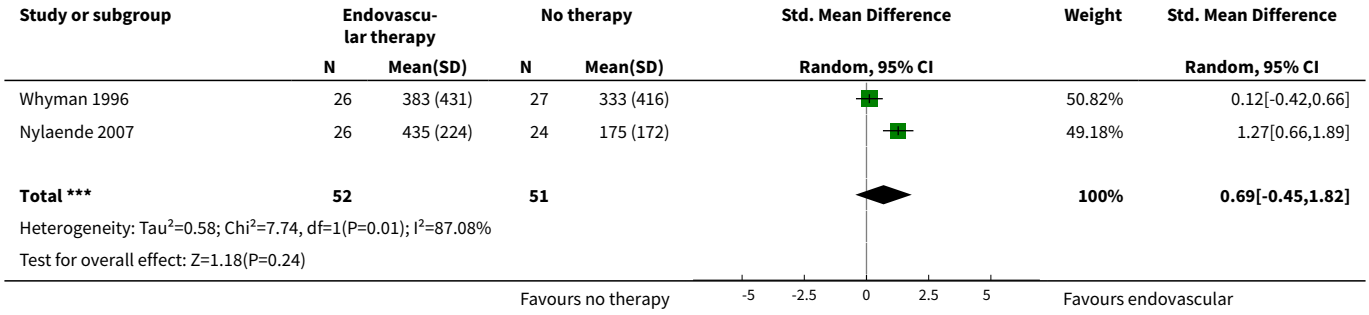
Favours no therapy — Favours endovascular



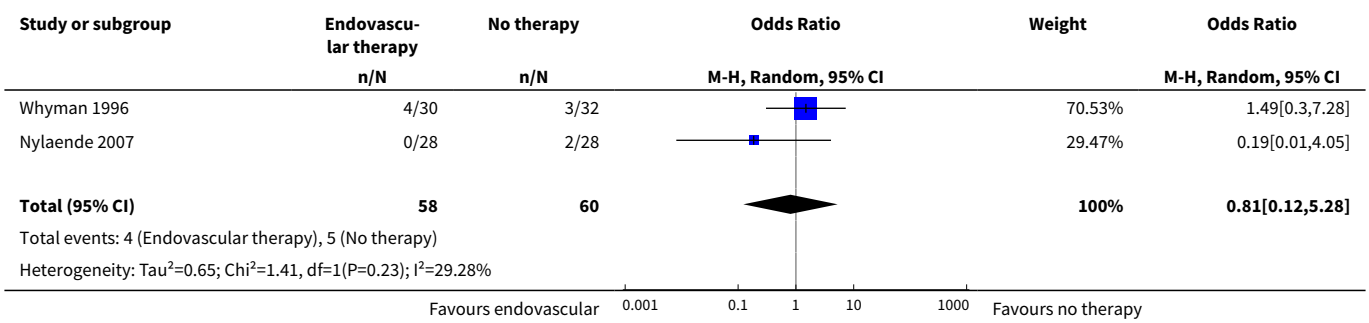
Analysis 1.3. Comparison 1 Endovascular revascularisation versus no specific therapy except verbal advice to exercise, Outcome 3 Pain-free walking distance.

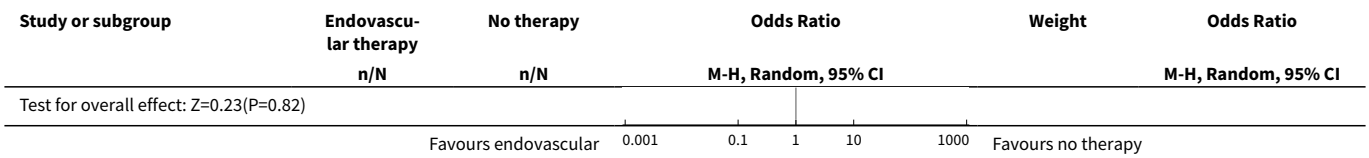


Analysis 1.4. Comparison 1 Endovascular revascularisation versus no specific therapy except verbal advice to exercise, Outcome 4 Pain-free walking distance (long-term).

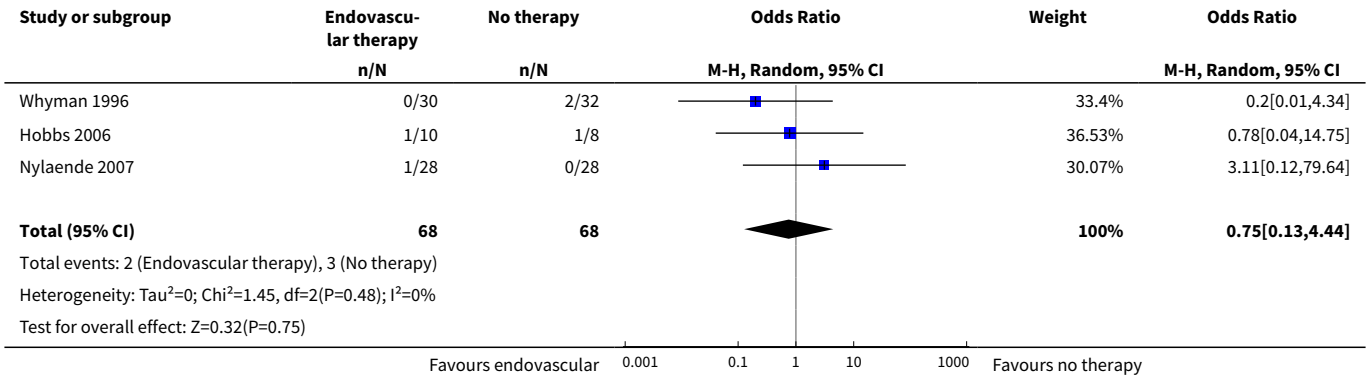


Analysis 1.5. Comparison 1 Endovascular revascularisation versus no specific therapy except verbal advice to exercise, Outcome 5 Secondary invasive interventions.





Analysis 1.6. Comparison 1 Endovascular revascularisation versus no specific therapy except verbal advice to exercise, Outcome 6 Mortality.



Comparison 2. Endovasular revascularisation versus conservative therapy in form of supervised exercise

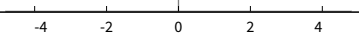
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum walking distance	5	345	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.87, 0.04]
2 Maximum walking distance (long-term)	3	184	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.36, 0.32]
3 Pain-free walking distance	5	345	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.38, 0.29]
4 Pain-free walking distance (long-term)	2	147	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.26, 0.48]
5 Secondary invasive interventions	4	395	Odds Ratio (M-H, Random, 95% CI)	1.40 [0.70, 2.80]
6 Quality of life (disease-specific)	3	301	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.04, 0.41]
7 Mortality	5	435	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.35, 2.00]
8 Sensitivity analysis: maximum walking distance	3	232	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.98, -0.07]
9 Sensitivity analysis: pain-free walking distance	3	232	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.46, 0.23]

Analysis 2.1. Comparison 2 Endovasular revascularisation versus conservative therapy in form of supervised exercise, Outcome 1 Maximum walking distance.

Study or subgroup	Endovascular therapy N	Endovascular therapy Mean(SD)	Conservative therapy N	Conservative therapy Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Creasy 1990	5	220 (179)	7	640 (212)		7.36%	-1.94[-3.43,-0.45]
Hobbs 2006	9	698 (584)	6	124 (206)		10.95%	1.14[-0,2.27]
Spronk 2009	69	1000 (613)	72	1220 (595)		29%	-0.36[-0.7,-0.03]
Mazari 2011	52	146 (109)	46	215 (92)		26.9%	-0.68[-1.08,-0.27]
Murphy 2015	41	197 (261)	38	309 (245)		25.8%	-0.44[-0.88,0.01]
Total ***	**176**		**169**			**100%**	**-0.42[-0.87,0.04]**

Heterogeneity: Tau^2=0.16; Chi^2=12.79, df=4(P=0.01); I^2=68.72%

Test for overall effect: Z=1.8(P=0.07)



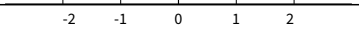
Favours conservative — Favours endovascular

Analysis 2.2. Comparison 2 Endovasular revascularisation versus conservative therapy in form of supervised exercise, Outcome 2 Maximum walking distance (long-term).

Study or subgroup	Endovascular therapy N	Endovascular therapy Mean(SD)	Conservative therapy N	Conservative therapy Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Creasy 1990	22	180 (281)	15	130 (194)		22.38%	0.2[-0.46,0.85]
Murphy 2015	32	171 (251)	32	267 (288)		35.25%	-0.35[-0.85,0.14]
Spronk 2009	47	1248 (661)	36	1161 (608)		42.37%	0.13[-0.3,0.57]
Total ***	**101**		**83**			**100%**	**-0.02[-0.36,0.32]**

Heterogeneity: Tau^2=0.02; Chi^2=2.63, df=2(P=0.27); I^2=23.85%

Test for overall effect: Z=0.13(P=0.9)



Favours conservative — Favours endovascular

Analysis 2.3. Comparison 2 Endovasular revascularisation versus conservative therapy in form of supervised exercise, Outcome 3 Pain-free walking distance.

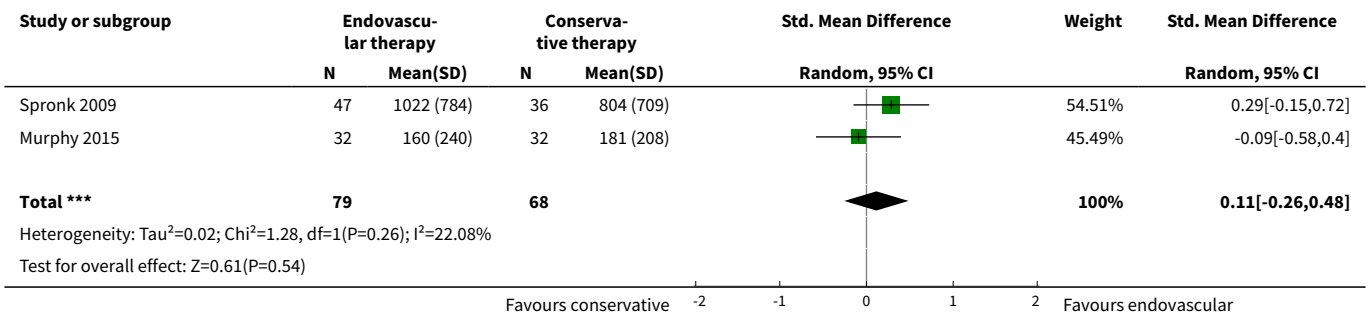
Study or subgroup	Endovascular therapy N	Endovascular therapy Mean(SD)	Conservative therapy N	Conservative therapy Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Creasy 1990	5	150 (179)	7	320 (265)		6.71%	-0.67[-1.86,0.52]
Hobbs 2006	9	698 (632)	6	92 (90)		7.28%	1.14[0.01,2.28]
Spronk 2009	69	888 (668)	72	1047 (685)		32.09%	-0.23[-0.57,0.1]
Mazari 2011	52	76 (121)	46	98 (117)		28.18%	-0.18[-0.58,0.21]
Murphy 2015	41	192 (224)	38	160 (155)		25.74%	0.16[-0.28,0.61]
Total ***	**176**		**169**			**100%**	**-0.05[-0.38,0.29]**

Heterogeneity: Tau^2=0.06; Chi^2=7.62, df=4(P=0.11); I^2=47.47%

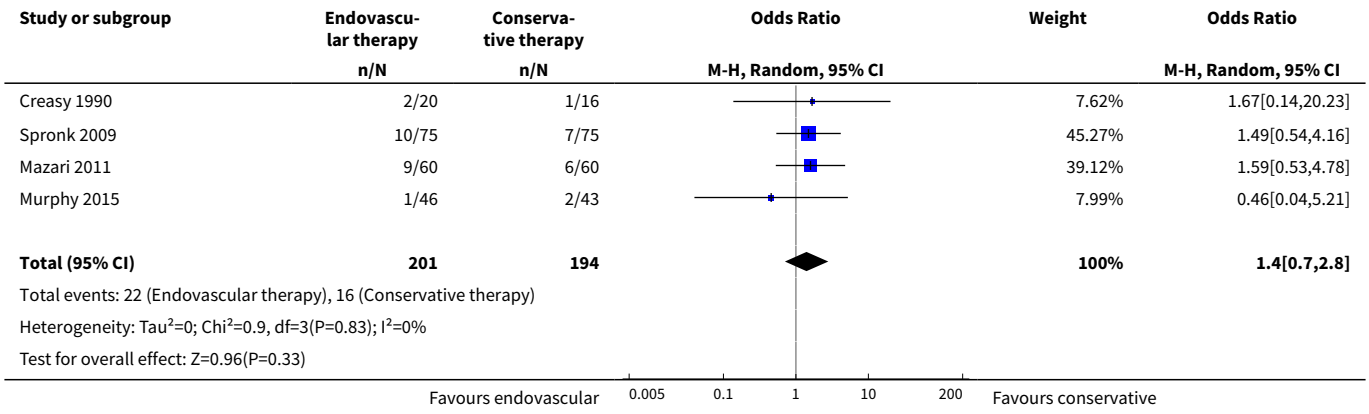
Test for overall effect: Z=0.27(P=0.79)

Favours conservative — Favours endovascular

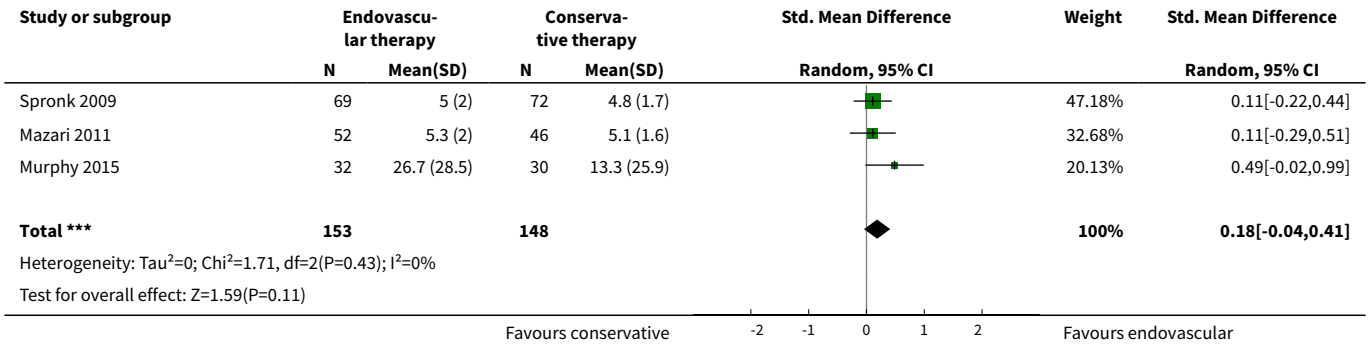
Analysis 2.4. Comparison 2 Endovasular revascularisation versus conservative therapy in form of supervised exercise, Outcome 4 Pain-free walking distance (long-term).



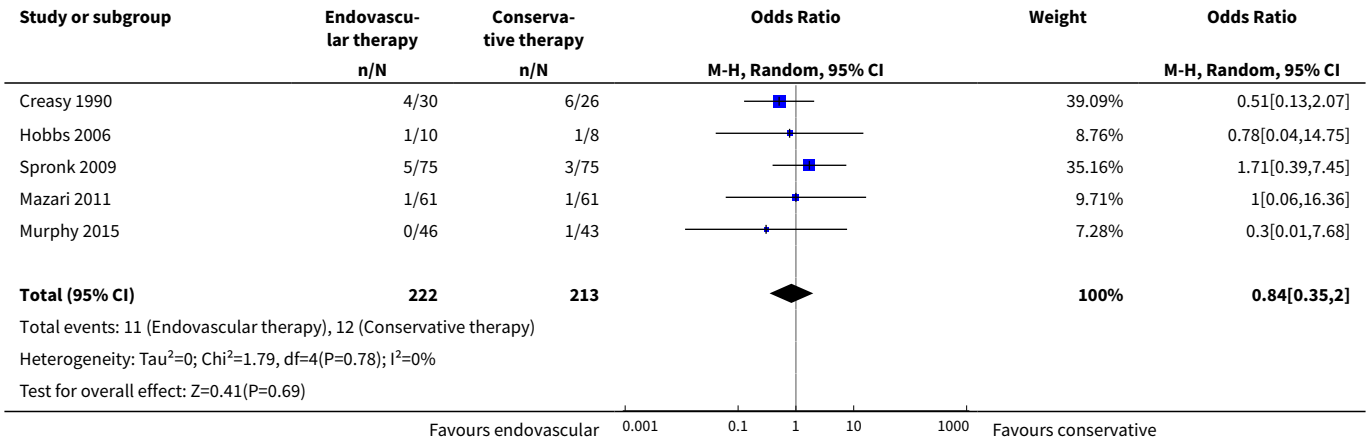
Analysis 2.5. Comparison 2 Endovasular revascularisation versus conservative therapy in form of supervised exercise, Outcome 5 Secondary invasive interventions.



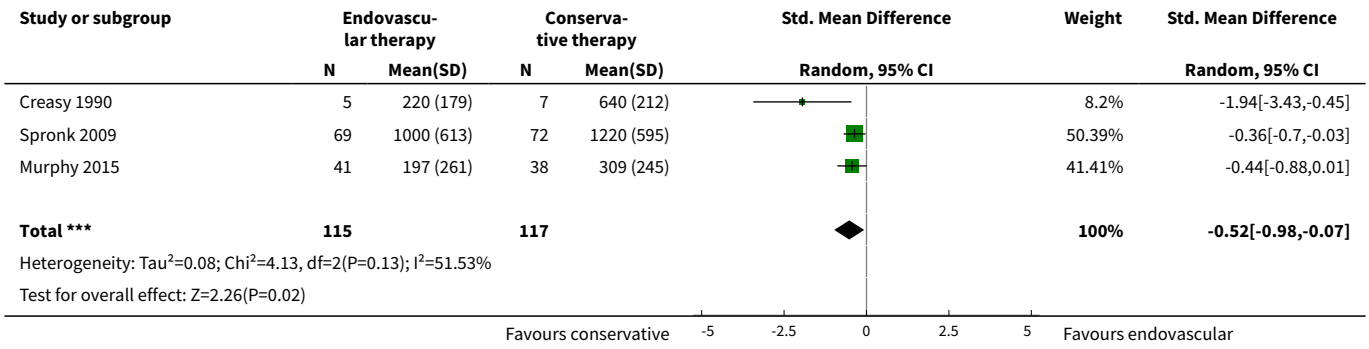
Analysis 2.6. Comparison 2 Endovasular revascularisation versus conservative therapy in form of supervised exercise, Outcome 6 Quality of life (disease-specific).



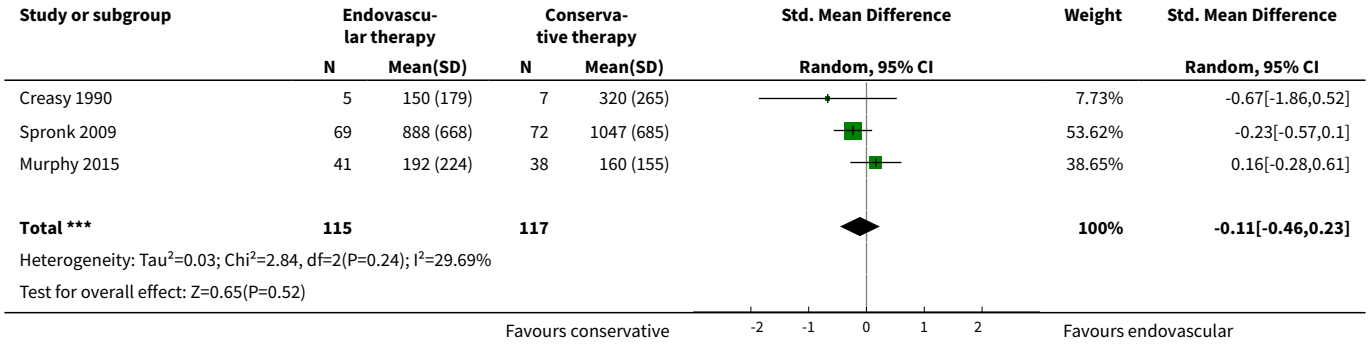
Analysis 2.7. Comparison 2 Endovasular revascularisation versus conservative therapy in form of supervised exercise, Outcome 7 Mortality.



Analysis 2.8. Comparison 2 Endovasular revascularisation versus conservative therapy in form of supervised exercise, Outcome 8 Sensitivity analysis: maximum walking distance.



Analysis 2.9. Comparison 2 Endovasular revascularisation versus conservative therapy in form of supervised exercise, Outcome 9 Sensitivity analysis: pain-free walking distance.



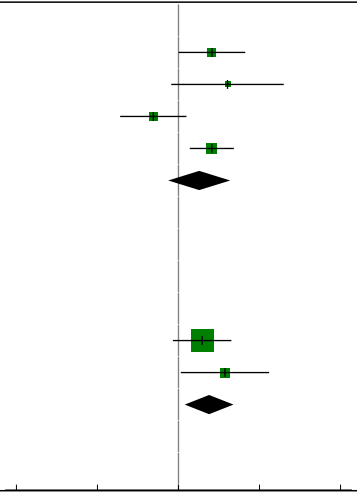
Comparison 3. Endovascular revascularisation plus conservative therapy versus conservative therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum walking distance	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Supervised exercise therapy	3	432	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.13, 0.64]
1.2 Pharmacotherapy	2	186	Std. Mean Difference (IV, Random, 95% CI)	0.38 [0.08, 0.68]
2 Maximum walking distance (long-term)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Supervised exercise therapy	1	106	Std. Mean Difference (IV, Random, 95% CI)	1.18 [0.65, 1.70]
2.2 Pharmacotherapy	1	47	Std. Mean Difference (IV, Random, 95% CI)	0.72 [0.09, 1.36]
3 Pain-free walking distance	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Supervised exercise therapy	2	305	Std. Mean Difference (IV, Random, 95% CI)	0.33 [-0.26, 0.93]
3.2 Pharmacotherapy	2	186	Std. Mean Difference (IV, Random, 95% CI)	0.63 [0.33, 0.94]
4 Pain-free walking distance (long-term)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Pharmacotherapy	1	47	Std. Mean Difference (IV, Random, 95% CI)	0.54 [-0.08, 1.17]
5 Secondary invasive interventions	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Supervised exercise therapy	3	457	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.13, 0.55]
5.2 Pharmacotherapy	2	199	Odds Ratio (M-H, Random, 95% CI)	1.83 [0.49, 6.83]
6 Quality of life (disease-specific)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Supervised exercise therapy	2	330	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.05, 0.56]
6.2 Pharmacotherapy	2	170	Std. Mean Difference (IV, Random, 95% CI)	0.59 [0.27, 0.91]
7 Mortality	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Supervised exercise therapy	3	457	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.20, 2.21]
7.2 Pharmacotherapy	2	201	Odds Ratio (M-H, Random, 95% CI)	1.30 [0.14, 11.92]
8 Sensitivity analysis: maximum walking distance	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Supervised exercise therapy	2	339	Std. Mean Difference (IV, Random, 95% CI)	0.43 [0.21, 0.65]
8.2 Pharmacotherapy	2	186	Std. Mean Difference (IV, Random, 95% CI)	0.38 [0.08, 0.68]
9 Sensitivity analysis: pain-free walking distance	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Supervised exercise therapy	1	212	Std. Mean Difference (IV, Random, 95% CI)	0.62 [0.34, 0.89]
9.2 Pharmacotherapy	2	186	Std. Mean Difference (IV, Random, 95% CI)	0.63 [0.33, 0.94]

Analysis 3.1. Comparison 3 Endovascular revascularisation plus conservative therapy versus conservative therapy, Outcome 1 Maximum walking distance.

Study or subgroup	Combined therapy N	Combined therapy Mean(SD)	Conservative therapy N	Conservative therapy Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.1.1 Supervised exercise therapy							
Greenhalgh 2008	48	224 (210)	45	150 (135)		25.98%	0.41[0,0.82]
Greenhalgh 2008	19	319 (299)	15	167 (150)		16.71%	0.61[-0.09,1.3]
Mazari 2011	47	188 (80)	46	215 (92)		26.06%	-0.31[-0.72,0.1]
Fakhry 2015	106	1237 (702)	106	955 (663)		31.25%	0.41[0.14,0.68]
Subtotal ***	**220**		**212**			**100%**	**0.26[-0.13,0.64]**
Heterogeneity: Tau^2=0.1; Chi^2=10.14, df=3(P=0.02); I^2=70.43%							
Test for overall effect: Z=1.31(P=0.19)							
3.1.2 Pharmacotherapy							
Nordanstig 2014	49	70 (185)	76	30 (92)		69.5%	0.29[-0.07,0.65]
Murphy 2015	41	197 (261)	20	64 (139)		30.5%	0.57[0.03,1.12]
Subtotal ***	**90**		**96**			**100%**	**0.38[0.08,0.68]**
Heterogeneity: Tau^2=0; Chi^2=0.71, df=1(P=0.4); I^2=0%							
Test for overall effect: Z=2.46(P=0.01)							



Analysis 3.2. Comparison 3 Endovascular revascularisation plus conservative therapy versus conservative therapy, Outcome 2 Maximum walking distance (long-term).

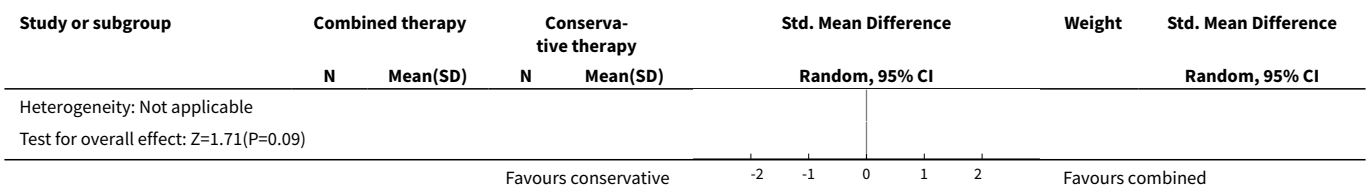
Study or subgroup	Combined therapy N	Combined therapy Mean(SD)	Conservative therapy N	Conservative therapy Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.2.1 Supervised exercise therapy							
Greenhalgh 2008	14	354 (120)	12	168 (102)		28.05%	1.61[0.7,2.51]
Greenhalgh 2008	43	245 (83)	37	155 (94)		71.95%	1.01[0.54,1.48]
Subtotal ***	**57**		**49**			**100%**	**1.18[0.65,1.7]**
Heterogeneity: Tau^2=0.04; Chi^2=1.32, df=1(P=0.25); I^2=24.09%							
Test for overall effect: Z=4.39(P<0.0001)							
3.2.2 Pharmacotherapy							
Murphy 2015	32	171 (251)	15	11 (112)		100%	0.72[0.09,1.36]
Subtotal ***	**32**		**15**			**100%**	**0.72[0.09,1.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.24(P=0.02)							

Analysis 3.3. Comparison 3 Endovascular revascularisation plus conservative therapy versus conservative therapy, Outcome 3 Pain-free walking distance.

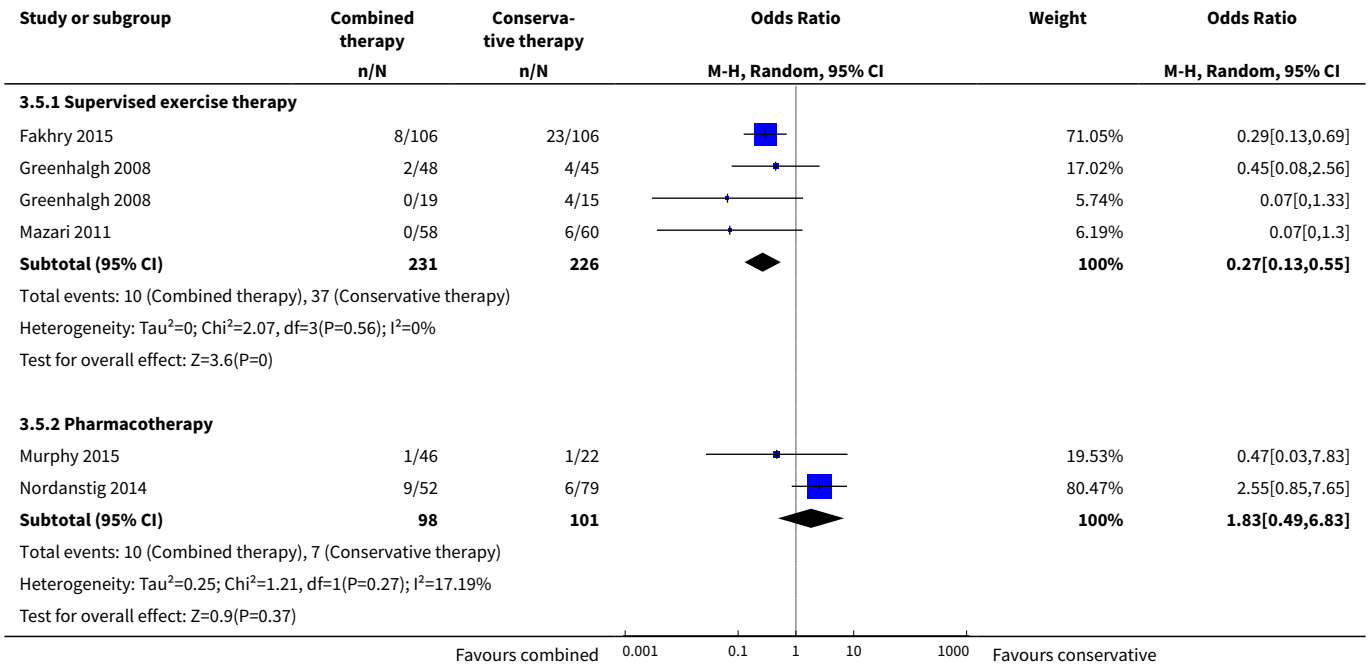
Study or subgroup	Combined therapy N	Combined therapy Mean(SD)	Conservative therapy N	Conservative therapy Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.3.1 Supervised exercise therapy							
Mazari 2011	47	99 (119)	46	98 (117)		46.88%	0.01[-0.4,0.41]
Fakhry 2015	106	1120 (675)	106	712 (640)		53.12%	0.62[0.34,0.89]
Subtotal ***	**153**		**152**			**100%**	**0.33[-0.26,0.93]**
Heterogeneity: Tau^2=0.15; Chi^2=5.92, df=1(P=0.01); I^2=83.11%							
Test for overall effect: Z=1.09(P=0.27)							
3.3.2 Pharmacotherapy							
Nordanstig 2014	49	141 (229)	76	50 (99)		69.72%	0.56[0.19,0.92]
Murphy 2015	41	192 (224)	20	37 (59)		30.28%	0.82[0.26,1.37]
Subtotal ***	**90**		**96**			**100%**	**0.63[0.33,0.94]**
Heterogeneity: Tau^2=0; Chi^2=0.59, df=1(P=0.44); I^2=0%							
Test for overall effect: Z=4.07(P<0.0001)							

Analysis 3.4. Comparison 3 Endovascular revascularisation plus conservative therapy versus conservative therapy, Outcome 4 Pain-free walking distance (long-term).

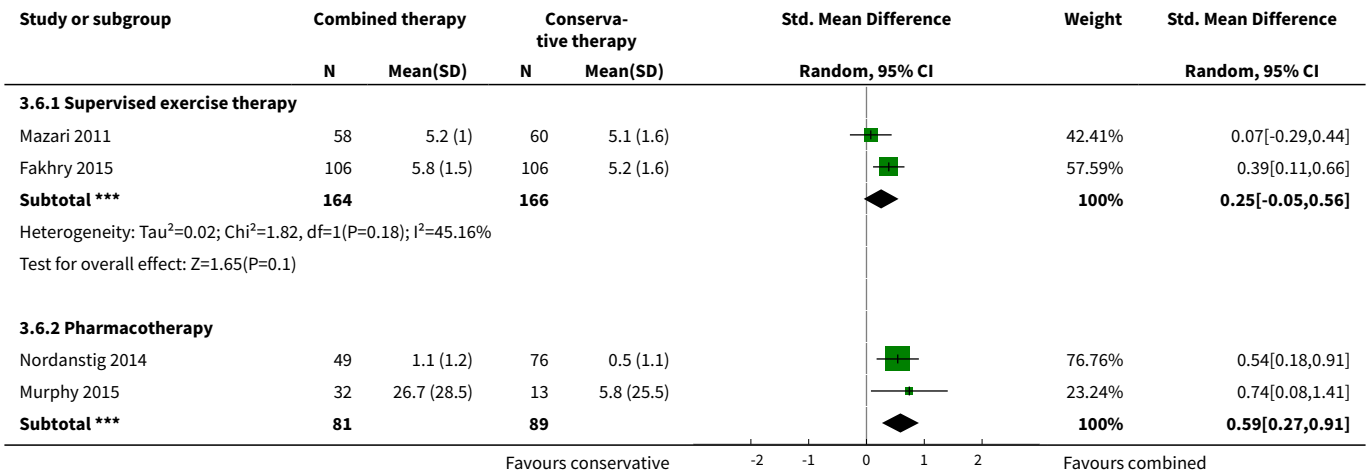
Study or subgroup	Combined therapy N	Combined therapy Mean(SD)	Conservative therapy N	Conservative therapy Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.4.1 Pharmacotherapy							
Murphy 2015	32	160 (240)	15	48 (69)		100%	0.54[-0.08,1.17]
Subtotal ***	**32**		**15**			**100%**	**0.54[-0.08,1.17]**

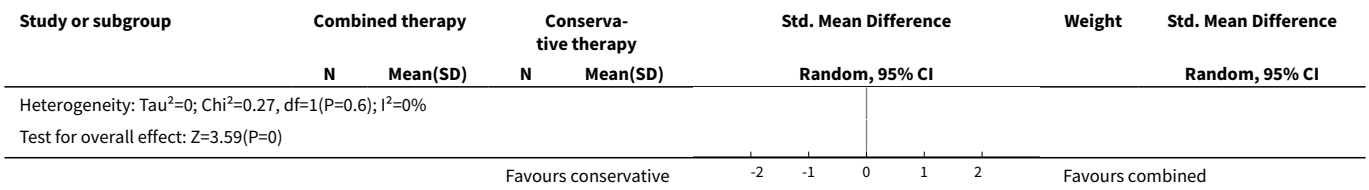


Analysis 3.5. Comparison 3 Endovascular revascularisation plus conservative therapy versus conservative therapy, Outcome 5 Secondary invasive interventions.

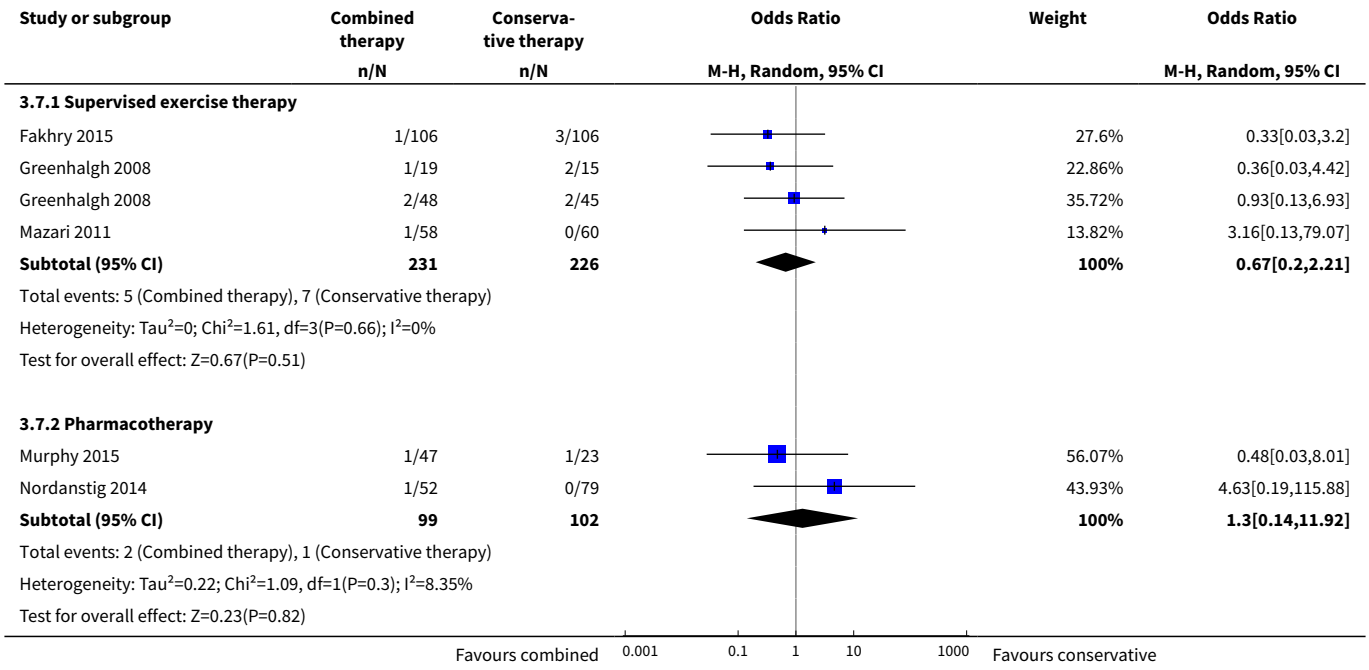


Analysis 3.6. Comparison 3 Endovascular revascularisation plus conservative therapy versus conservative therapy, Outcome 6 Quality of life (disease-specific).

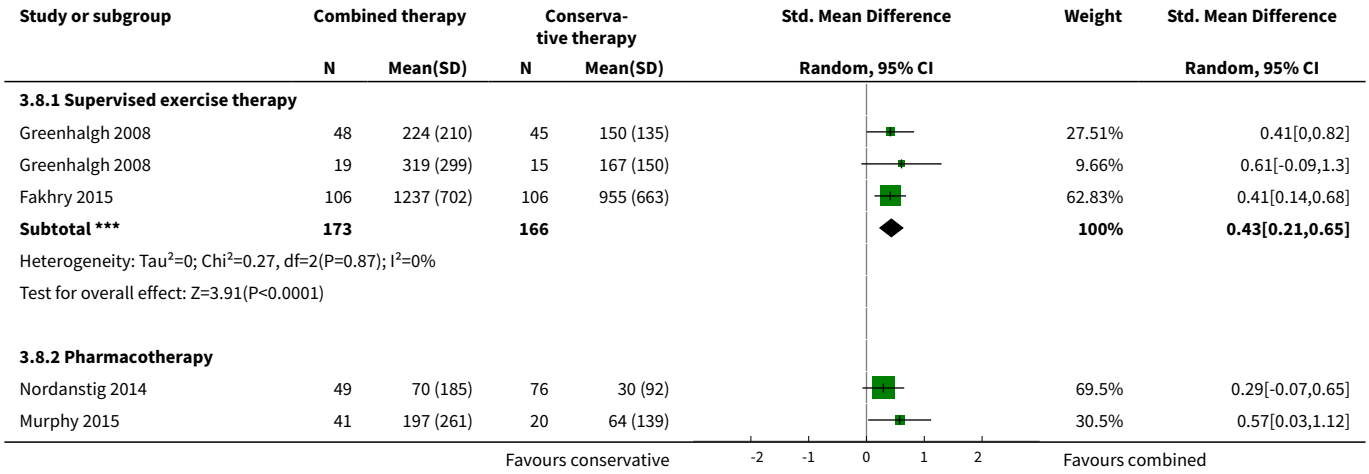


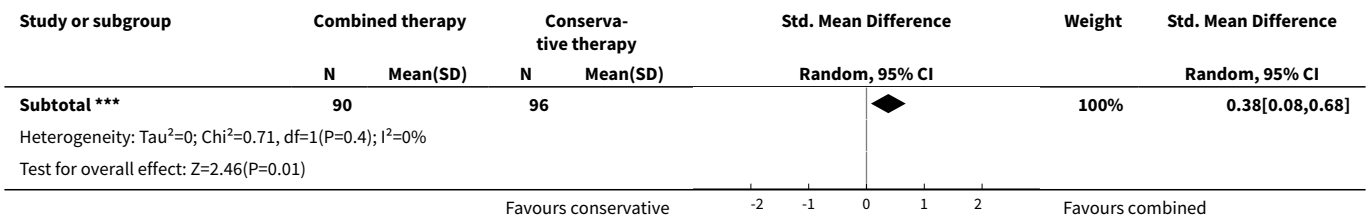


Analysis 3.7. Comparison 3 Endovascular revascularisation plus conservative therapy versus conservative therapy, Outcome 7 Mortality.

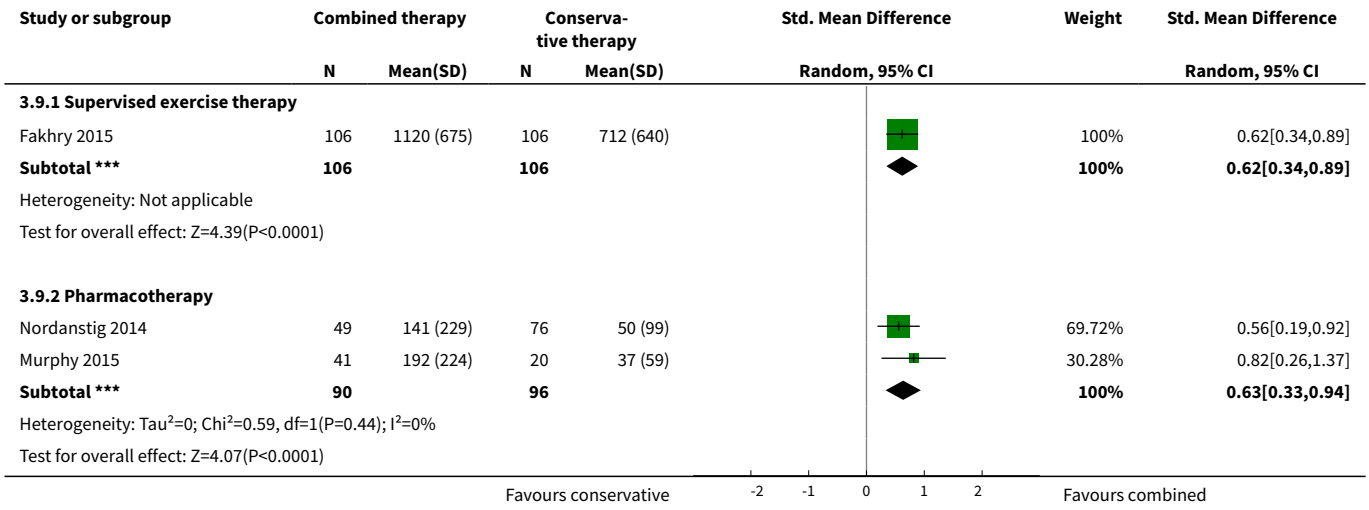


Analysis 3.8. Comparison 3 Endovascular revascularisation plus conservative therapy versus conservative therapy, Outcome 8 Sensitivity analysis: maximum walking distance.





Analysis 3.9. Comparison 3 Endovascular revascularisation plus conservative therapy versus conservative therapy, Outcome 9 Sensitivity analysis: pain-free walking distance.



ADDITIONAL TABLES

Table 1. Minor complications following endovascular revascularisation

Study	Groin haematoma	Artery dissection
Creasy 1990	3/20	1/20
Fakhry 2015	5/106	2/106
Greenhalgh 2008	8/67	1/67
Murphy 2015	nr	2/46
Nordanstig 2014	1/52	nr
Spronk 2009	6/75	1/75

nr: not reported.

APPENDICES

Appendix 1. CENTRAL search strategy

Search run on Tue Feb 21 2017		
#1	MESH DESCRIPTOR Arteriosclerosis	869
#2	MESH DESCRIPTOR Arteriolosclerosis EXPLODE ALL TREES	0
#3	MESH DESCRIPTOR Arteriosclerosis Obliterans	72
#4	MESH DESCRIPTOR Atherosclerosis	641
#5	MESH DESCRIPTOR Arterial Occlusive Diseases	734
#6	MESH DESCRIPTOR Intermittent Claudication	723
#7	MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES	2229
#8	(atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY	9486
#9	((arter* or vascular or vein* or veno* or peripher*) near3 (occlus* or steno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	8223
#10	(peripheral near3 dis*):TI,AB,KY	3524
#11	(claudic* or IC):TI,AB,KY	3216
#12	arteriopathic:TI,AB,KY	7
#13	dysvascular*:TI,AB,KY	11
#14	(leg near3 (occlus* or steno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	99
#15	(limb near3 (occlus* or steno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	155
#16	((lower near3 extrem*) near3 (occlus* or steno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	81
#17	((iliac or femoral or popliteal or femoro* or fempop* or crural) near3(occlus* or steno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	1046
#18	MESH DESCRIPTOR Leg EXPLODE ALL TREES WITH QUALIFIERS BS	1113
#19	MESH DESCRIPTOR Iliac Artery	146
#20	MESH DESCRIPTOR Popliteal Artery	280
#21	MESH DESCRIPTOR Femoral Artery	826

(Continued)

#22	MESH DESCRIPTOR Tibial Arteries	33
#23	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	24081
#24	MESH DESCRIPTOR Endovascular Procedures EXPLODE ALL TREES	6683
#25	MESH DESCRIPTOR Stents EXPLODE ALL TREES	3299
#26	MESH DESCRIPTOR Vascular Surgical Procedures	546
#27	MESH DESCRIPTOR Blood Vessel Prosthesis EXPLODE ALL TREES	411
#28	MESH DESCRIPTOR Blood Vessel Prosthesis Implantation EXPLODE ALL TREES	405
#29	endovasc*:TI,AB,KY	1649
#30	endostent*:TI,AB,KY	1
#31	endoluminal:TI,AB,KY	134
#32	endoprosthe*:TI,AB,KY	254
#33	endograft*:TI,AB,KY	80
#34	percutaneous*:TI,AB,KY	11010
#35	stent*:TI,AB,KY	8367
#36	(Palmaz or Zenith or Dynalink or Hemobahn or Luminex* or Memotherm or Wallstent):TI,AB,KY	395
#37	(Viabahn or Nitinol or Intracoil or Tantalum):TI,AB,KY	298
#38	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	20861
#39	#23 AND #38	3299

Appendix 2. Trials registries searches

Clinicaltrials.gov

44 studies found for: endovascular and claudication

51 studies found for: angioplasty and claudication

ISRCTN

angioplasty and claudication 22

endovascular and claudication 8

WHO

16 records for 15 trials found for: endovascular and claudication (7 NCT, 1 ISRCTN)

35 records for 33 trials found for: angioplasty and claudication (18 NCT, 5 ISRCTN)

CONTRIBUTIONS OF AUTHORS

FF: wrote the protocol; selected relevant studies, assessed methodological quality of included studies, extracted and analysed data, and wrote the review.
HF: contributed to the protocol; selected relevant studies, assessed methodological quality of included studies, extracted data, and contributed to the text of the review.
ER: contributed to the text of the review.
JT: contributed to the text of the review.
SS: contributed to the text of the review.
MH: resolved disagreements regarding inclusion of studies and contributed to the text of the review.

DECLARATIONS OF INTEREST

FF: none known.
HF: none known.
ER: none known.
JT: none known: Chairman ClaudicatioNet: ClaudicatioNet (a not-for-profit organisation) is an integrated care network that brings together patients, physiotherapists, family physicians, and vascular surgeons. ClaudicatioNet aims for transparent and high-quality care for all patients with peripheral vascular disease in the Netherlands.
SS: none known.
MH: MH's institution has received funding from ZonMW, Netherlands Organization for Scientific Research, National Institutes of Health, and Stichting Technische Wetenschappen for MH's research projects not related to this review. MH also reports receiving royalties from Cambridge University Press for the textbook, "Decision Making in Health and Medicine," and travel/meeting expenses from the 2010 and 2011 Clinical Update on Cardiac CT and MRI 2010 meetings, the 2011 International Society for Strategic Studies in Radiology (ISSSR) meeting, the 2012 ESR Referral Guidelines for Imaging Workshop, and the European Institute for Biomedical Imaging Research Scientific Advisory Board meetings.

To avoid potential bias regarding inclusion, one review author (HF) from this systematic review who was not involved in these studies independently performed study selection, data extraction and methodological quality assessment for two studies (Fakhry 2015; Spronk 2009).

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Internal sources

- No sources of support supplied

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since the time our protocol was published, we decided to use standardised mean difference (SMD) as treatment effect to account for the large variation in intensity of the treadmill protocols used to assess walking distances, instead of simulated metabolic equivalents (METS), as proposed in the protocol. We made this change because SMD could also be used to pool disease-specific quality of life data (measured by different instruments) and because with SMD, no potential bias could be introduced through simulation of data, which would have been inevitable if we had used METS to assess treatment effect.

INDEX TERMS

Medical Subject Headings (MeSH)

*Vascular Surgical Procedures; Cilostazol; Combined Modality Therapy [methods]; Conservative Treatment [*methods]; Exercise Therapy; Intermittent Claudication [*therapy]; Randomized Controlled Trials as Topic; Tetrazoles [therapeutic use]; Vasodilator Agents [therapeutic use]

MeSH check words

Humans