Angioplasty and stenting for peripheral arterial disease of the lower limbs

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Angioplasty and stenting for peripheral arterial disease of the lower limbs: an overview of Cochrane Reviews (Protocol)

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[Overview of Reviews Protocol]

Angioplasty and stenting for peripheral arterial disease of the lower limbs: an overview of Cochrane Reviews

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ABSTRACT

This is a protocol for a Cochrane Review (Overview). The objectives are as follows:

To summarise the evidence from relevant Cochrane Reviews regarding effectiveness of angioplasty and stenting for peripheral arterial disease of the lower limbs.

BACKGROUND

Description of the condition

Peripheral arterial disease (PAD) is usually caused by atherosclerosis that leads to stenosis (narrowing) or blockage in the major vessels supplying the lower extremities. Approximately 10% of the worldwide population have PAD (Peach 2012). The prevalence of PAD increases with age. A study from the National Health and Nutrition Examination Survey showed that the prevalence of PAD is 7.0% (95% confidence interval (CI) 5.6% to 8.4%) for individuals aged 60 to 69, 12.5% (95% CI 10.4% to 14.6%) for people aged 70 to 79, and 23.2% (95% CI 19.8% to 26.7%) , for people aged 80 years or older (Ostchega 2007). The vast majority of people with PAD are either asymptomatic or do not have any functional limitation (McDermott 2001). Many people with PAD, however, have limited walking ability and therefore reduced quality of life. Most of the patients with walking limitations due to PAD do not have classic claudication symptoms but complain of atypical symptoms such as fatigue or weakness (McDermott 2001). Besides the limited walking ability, people with advanced PAD/critical limb ischaemia are at risk of limb loss. In addition to affecting the limbs, PAD is a "manifestation of systemic atherosclerosis that involves other major circulation, such as the cerebral and coronary arteries" (Hiatt 2006). Authors have estimated that people diagnosed with PAD are at a two- to three-fold increased risk of mortality, myocardial infarction (MI) and stroke compared to age- and sex-matched people without PAD (Norgren 2007).

PAD may be asymptomatic or present in the form of intermittent claudication (IC) or critical limb ischaemia (CLI) (Peach 2012). The Fontaine classification is commonly used to measure the severity of disease (Fontaine 1954).

- Stage I: asymptomatic, incomplete blood vessel obstruction.
- Stage II: mild claudication pain in limb.
- Stage IIA: claudication at a distance of greater than 200 metres.
- Stage IIB: claudication distance of less than 200 metres.
- Stage III: rest pain, mostly in the feet.
- Stage IV: necrosis and/or gangrene of the limb.

While the Fontaine classification is used clinically, the Rutherford-Baker classification is a better guide for scientific publications (Rutherford 1997).

- Category 0: asymptomatic – no haemodynamically significant occlusive disease.
- Category 1: mild claudication.
- Category 2: moderate claudication.
- Category 3: severe claudication.
- Category 4: ischaemic rest pain.
- Category 5: minor tissue loss – non-healing ulcer, focal gangrene with diffuse pedal ischaemia.
- Category 6: major tissue loss – extending above transmetatarsal level, functional foot no longer salvageable.

Although many asymptomatic people with PAD may never develop symptoms, approximately 7% to 15% develop IC (stage II Fontaine, Rutherford category 1) within five years (Fowkes 1991). IC is defined as pain in one or both legs when walking that is rapidly relieved by rest. People with IC have adequate blood flow at rest and therefore no symptoms. When walking, "occlusive lesions in the arterial supply of the leg muscles limit the increase in blood flow, resulting in a mismatch between oxygen supply and muscle metabolic demand that is associated with symptoms of claudication" (Hiatt 2006). The pain is usually in the calves with femoro-popliteal lesions (but also in the thigh, buttocks and lower back with iliac lesions), and it is worse when walking fast or uphill, when the volume of oxygen required by the muscle is greatest (Peach 2012).

CLI (Fontaine stages III and IV, Rutherford category 5 and 6) is the most severe chronic manifestation of PAD and is defined as chronic ischaemic rest pain, ulcers, or gangrene for more than two weeks. If left untreated, CLI can lead to loss of the limb and in severe cases, death. Each year, there are 500 to 1000 new cases of CLI per million population (Norgren 2007), with an estimated annual cost to the UK National Health Service (NHS) of more than GBP 200 million (Beard 2000). People with CLI have a poor prognosis: approximately 12% of people with CLI require amputation within three months of presentation, and 20% to 25% die within a year (Norgren 2007).

Risk factors for PAD are shared with the other atherosclerotic cardiovascular disorders and include increased age, smoking, diabetes mellitus, hypertension and hypercholesterolaemia (Selvin 2004a). Some authors have estimated that smoking accounts for 50% of all PAD cases (Willigendael 2004). Smokers develop symptoms of PAD approximately 10 years earlier than non-smokers (Lassila 1988), and they are more likely to require amputation of the lower limb (Dormandy 2000). The number of cigarettes smoked is directly associated with the severity of PAD (Price 1999). However, smoking cessation is associated with a decline in the incidence of IC. A recent meta-analysis suggested that, for an ex-smoker, the relative risk of IC lies between that of current and never smokers (Lu 2014). Diabetes is associated with a two-fold increased risk of PAD (Norgren 2007). Results from a meta-analysis determined that a 1% increase in glycaemic haemoglobin (HbA_{1c}) was associated with a 26% increase in the risk of developing PAD (Selvin 2004b). In people with diabetes, PAD is more aggressive, and the risk of amputation is 5 to 10 times higher than in non-diabetics (Diabetes Control and Complications Trial 1995). Lastly, hypertension and hypercholesterolaemia are risk factors for developing PAD. Results from the Framingham Study showed that in men and women with high blood pressure (greater than 160/95 mmHg), the risk of developing IC was 2.5-fold and four-fold higher, respectively, while people with elevated fasting cholesterol levels (greater than 7 mmol/L) were twice as likely to develop IC than those with normal cholesterol levels (Murabito 1997).

The initial evaluation of people with suspected PAD includes the measurement of the ankle-brachial index (ABI). Measuring the ratio of ankle to brachial systolic pressure helps to distinguish patients with true PAD from those with leg pain due to other causes. The conventional cut-off point for diagnosing PAD is 0.90 or higher at rest, which has been shown to be 95% and 99% sensitive in detecting symptomatic and asymptomatic disease respectively (Fowkes 1988b). A low ABI is not necessary for diagnosing PAD in patients with diabetes mellitus or those undergoing dialysis. Many diabetic and renal patients have non-compressible lower limb arteries due to arterial calcification and thus an artificially elevated ABI. In this context, in patients with diabetes, an ABI of more than 1.45 is associated with an almost seven-fold increased risk of PAD (odds ratio (OR) 6.97, 95% CI 4.06 to 11.98; Li 2015). People with clinical signs of PAD and a low ABI may be referred for imaging

(angiography or duplex ultrasound) to measure the anatomical location and extent of disease and determine the suitability of treatment according to the severity of their symptoms (SIGN 2006). Initially, physicians will perform a duplex ultrasound scan to assess the severity and degree of PAD. Angiography is reasonable when there is indication for revascularisation (e.g. CLI, rest pain).

Atherosclerotic disease patterns in the lower extremities are classified by the Inter-Society Consensus (TASC II) according to anatomic distribution and the number and nature of lesions (stenosis, occlusion) (Norgren 2007).

- *Type A lesions*.
  - Aortoiliac - unilateral or bilateral stenoses of common iliac artery (CIA); unilateral or bilateral single short (≤ 3 cm) stenosis of external iliac artery (EIA).
  - Femoral popliteal - single stenosis ≤ 10 cm in length; single occlusion ≤ 5 cm in length.
- *Type B lesions.*
  - Aortoiliac - short (≤ 3 cm) stenosis of infrarenal aorta; unilateral CIA occlusion; single or multiple stenoses totalling 3 cm to 10 cm, involving the EIA and not extending into the common femoral artery (CFA); unilateral EIA occlusion not involving the origins of the external iliac or CFA.
  - Femoral popliteal - multiple lesions (stenoses or occlusions), each ≤ 5 cm; single stenosis or occlusion ≤ 15 cm not involving the infrageniculate popliteal artery; single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass; heavy calcified occlusion ≤ 5 cm in length; single popliteal stenosis.
- *Type C lesions.*
  - Aortoiliac - bilateral CIA occlusions; bilateral EIA stenoses 3 cm to 10 cm long and not extending into the CFA; unilateral EIA stenosis extending into the CFA; unilateral EIA occlusion that involves the origins of internal iliac and/or CFA; heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA.
  - Femoral popliteal - multiple stenoses or occlusions totalling > 15 cm, with or without heavy calcification; recurrent stenoses or occlusions that need treatment after two endovascular interventions.
- *Type D lesions.*
  - Aortoiliac - infrarenal aortoiliac occlusion; diffuse disease involving the aorta and both iliac arteries requiring treatment; diffuse multiple stenoses involving the unilateral CIA, EIA and CFA; unilateral occlusions of both CIA and EIA; bilateral occlusions of EIA.
  - Femoral popliteal - chronic total occlusions of CFA or SFA (> 20 cm, involving the popliteal artery); chronic total occlusion of popliteal artery and proximal trifurcation vessels.

There has been a recent update of the TASC to include a classification for below-the-knee arteries (Jaff 2015).

- *TASC A lesions* - single focal stenosis, ≤ 5 cm in length, in the target tibial artery with occlusion or stenosis of similar or worse severity in the other tibial arteries.
- *TASC B lesions* - multiple stenoses, each ≤ 5 cm in length, or total length ≤ 10 cm or single occlusion ≤ 3 cm in length, in the target tibial artery with occlusion or stenosis of similar or worse severity in the other tibial arteries
- *TASC C lesions* - multiple stenoses in the target tibial artery and/or single occlusion with total lesion length > 10 cm with occlusion or stenosis of similar or worse severity in the other tibial arteries.
- *TASC D lesions* - multiple occlusions involving the target tibial artery with total lesion length > 10 cm, dense lesion calcification or non-visualisation of collaterals. The other tibial arteries are occluded or have dense calcification.

Treatment of PAD can be grouped into two categories: medical management and endovascular and surgical management (NICE 2012).

Medical management

People with PAD are advised to stop smoking, lose weight and increase physical activity in an effort to halt the process of atherosclerosis (Hirsch 1997; NICE 2012; Pfaffenbarger 1993; Smith 1996). Clinicians may also prescribe secondary measures to target hypertension and hypercholesterolaemia, such as cholesterol-lowering agents (statins), antihypertensives and antiplatelets (Kügler 2003). All patients with PAD should receive antiplatelet treatment (clopidogrel 75 mg/day or aspirin 75 mg/day to 150 mg/day in case of clopidogrel intolerance or side effects). A collaborative meta-analysis (287 studies; N = 135,000 participants) of antiplatelet therapy for preventing death, myocardial infarction and stroke in high-risk patients showed that antiplatelet therapy was associated with a 23% reduction in serious vascular events in the subset of more than 9000 patients with PAD (Antithrombotic Trialists' Collaboration 2002). A post hoc analysis of the **c**lopidogrel versus **a**spirin in **p**atients at **r**isk of **i**schaemic **e**vents (CAPRIE) study showed that clopidogrel is more effective than aspirin for reducing myocardial infarction, ischaemic stroke and vascular death in people with PAD (CAPRIE 1996). Exercise therapy can increase walking capacity and improve quality of life (Fokkenrood 2013; Lane 2014; NICE 2012). People for whom exercise therapy is not suitable may receive medical interventions such as vasoactive drugs (cilostazol, buflomedil, pentoxifylline, naftidrofuryl and prostaglandins) to improve walking distance. Comparing the efficacy of all the available vasoactive drugs is beyond the scope of the current review.

Endovascular and surgical management

In cases where medical management is not suitable or effective or in severe cases of PAD, endovascular and surgical interventions are available (NICE 2012).

Description of the interventions

Endovascular and surgical interventions include percutaneous transluminal angioplasty (PTA) or open surgical techniques. In PTA an artery, usually the femoral artery, is cannulated; a guidewire inserted under x-ray control; and a deflated balloon catheter inserted and pushed forward along the guidewire to the site(s) of obstruction. Inflation of the balloon then opens up the stenosis or occlusion. In addition, physicians may insert a cylindrical piece of metal mesh called a stent at the site where the artery has been dilated with the aim of holding the narrowing open for the future. PTA can be used to either dilate shorter stenosis or recanalise an entire artery (White 2007). If the blockage is not suitable for PTA and stenting, patients may undergo an open surgical intervention such as an open bypass operation. This involves redirecting blood

through a bypass (usually a healthy vein or a graft of synthetic material).

PTA offers several potential advantages over open surgical revascularisation. People undergoing PTA receive local anaesthesia, so even those at high risk of general anaesthesia can still receive treatment. There are few complications, and the recovery is quick, so people can usually return to normal activity within 24 to 48 hours (Isner 1993; O'Keeffe 1991). While results are not always as durable or as long-term as with open surgery, people can undergo repeated PTA procedures with similar effectiveness, without influencing the outcomes of subsequent surgery (White 2007). In contrast, open surgery can often last between two to five hours under general anaesthetic, and patients are typically required to stay in hospital for up to seven days after the procedure.

According to the TASC II recommendations (Norgren 2007), endovascular therapy is the treatment of choice for type A lesions, and surgery is the treatment of choice for type D lesions. Endovascular therapy is the preferred treatment for type B lesions, and surgery is the preferred treatment for low-risk patients with type C lesions. Treatment recommendations for type B and type C lesions should take into account patients' comorbidities, their preferences, and the local operator's long-term success rates (Norgren 2007).

The success of PTA depends on the severity of PAD (IC or CLI), the type of PAD (stenosis or occlusion), the length of the lesion, the quality of the vessels, concomitant disease (diabetes or coronary artery disease) and persistent risk factors (smoking, blood pressure) (White 2007). Lesions may be suprainguinal (above the inguinal ligament, i.e. involving the aorta and iliac arteries), femoropopliteal or infrapopliteal. The effectiveness of PTA is greatest for lesions in the iliac arteries and progressively decreases for more distal vessels (Norgren 2007). A meta-analysis of six studies reported that the immediate technical success of PTA and stenting for aortoiliac occlusive disease was 96%, a higher success rate than for PTA alone (Bosch 1997). Furthermore, primary and secondary patency rates at five years are 63% and 86%, respectively, close to the success rate achieved with a surgical graft (Cikrit 1995). In a quality of life study, patients who had undergone PTA with stenting for aortoiliac occlusive disease saw a 26% increase in walking distance within 24 months of the procedure, improved physical functioning and a decrease in leg pain (Bosch 1999). Meanwhile for the femoral system, stenting is used for treating patients in whom initial PTA was a failure or who had restenosis within 90 days of the procedure. Patency in the superficial femoral artery (SFA) is estimated at 75% to 81% within one year in lesions of less than 4 cm (Gray 1997). Finally, PTA with stenting in the infrapopliteal artery is reserved for patients with chronic CLI. Primary patency rates for all patients (stenosis and occlusion) is 36% within three years of the procedure (Lofberg 1996). Despite this, there is no real consensus on when patients should receive stents. A recent systematic review and meta-analysis of randomised controlled trials showed that drug-eluting stents in the infrapopliteal arteries were associated with significantly lower rates of restenosis, target lesion revascularisation and amputations, as well as improved wound healing compared with balloon angioplasty and bare metal stents (Katsanos 2016).

The current literature now contains a significant number of randomised controlled trials evaluating the efficacy of drug-eluting balloons (DEBs) (Katsanos 2016; Laird 2015; Rosenfield 2015; Scheinart 2014; Scheinart 2015; Tepe 2015a; Tepe 2015b; Werk 2008; Werk 2012; Zeller 2014). DEBs are now clinically relevant and displacing stents as common therapy. The present overview will also assess the available information from DEBs.

Why it is important to do this overview

A single Cochrane Review rarely addresses all of the potential interventions and outcomes for a given condition. Furthermore clinicians, policy makers and guideline writers may have difficulty finding and comparing all the different Cochrane Reviews. An overview of all Cochrane Reviews in a single area would consolidate evidence and information for decision makers and others.

Specifically, an overview of all Cochrane Reviews on angioplasty and stenting for PAD of the lower limbs will combine evidence of the effect of stenting over and above PTA and elucidate any differences between the various available stents and angioplasty over the whole spectrum of PAD.

To date, there have been three published Cochrane Reviews on this topic (Bekken 2015; Chowdhury 2014; Kayssi 2016), as well as three protocols (Chua 2007; Hsu 2011; Kayssi 2017). An overview would compile evidence from these reviews into one usable and accessible document, allowing the reader a summary based on multiple Cochrane Reviews.

OBJECTIVES

To summarise the evidence from relevant Cochrane Reviews regarding effectiveness of angioplasty and stenting for peripheral arterial disease of the lower limbs.

METHODS

Criteria for considering reviews for inclusion

In this overview we will include any published Cochrane Reviews of randomised controlled trials focusing on angioplasty and stenting for peripheral arterial disease of the lower limbs. We will not include non-Cochrane systematic reviews.

We will include randomised controlled trials (single or multicentre) that compare the use of different types of angioplasty and stents for occlusions or stenoses of the iliac, superficial femoral or popliteal (including distal) arteries.

We will use the definitions of intermittent claudication and CLI as used by the included Cochrane Reviews.

The participants included in this overview will be people undergoing angioplasty or stenting for peripheral arterial disease of the lower limbs.

We will compare stenting plus percutaneous transluminal angioplasty (PTA) versus PTA alone. We will also compare different types of stents (such as drug eluting or nitol stents) and compare different types of angioplasty (such as drug-eluting or uncoated balloon angioplasty).

We will include the following outcomes.

- Primary and secondary patency as defined by the individual reviews.
- Quality of life as defined by the individual reviews.

- Limb salvage/major amputation/amputation free survival.
- Maximum walking distance and pain free walking distance: change in walking distance and distance at end of the trial (in metres and assessed by treadmill).
- Immediate and procedural complications.

We will also report other outcomes described in the individual reviews.

Where possible, we plan to present the data by the following subgroups.

1. Stent locations (iliac, superficial femoral or infrapopliteal, including distal, arteries).
2. Severity of disease (IC or CLI).
3. Stent type.
4. Lesion length (TASC A and B).
5. Stenosis versus occlusion.
6. Diabetic status.
7. Primary lesions versus recurrent lesions.

Search methods for identification of reviews

We will liaise with the Cochrane Vascular Information Specialist to identify all relevant Cochrane Reviews on angioplasty and stenting for peripheral arterial disease of the lower limbs in the *Cochrane Database of Systematic Reviews*.

Data collection and analysis

The methodology for data collection and analysis is based on Chapter 22 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of reviews

Two review authors (LR, MS) will independently assess all identified Cochrane Reviews for inclusion. We will resolve any disagreements through discussion.

Data extraction and management

Two review authors (LR, MS) will independently extract data from the reviews using a predefined data extraction form. We will resolve any discrepancies through discussion. One review author (LR) will enter data into Review Manager (RevMan 2014), and a second (MS) will check them for accuracy. If any information from the reviews is unclear or missing, we will access the published reports of the trials. If we cannot obtain the information from the published reports, we will contact the trialists to provide clarification, further details or both.

Assessment of methodological quality of included reviews

We will address two different quality assessments in this overview: methodological quality of the systematic reviews and the quality of the evidence in the included reviews. Two review authors (LR, MS) will assess methodological quality independently. We will resolve any disagreements through discussion.

Methodological quality of the systematic reviews

Two review authors (LR, MS) will independently assess the methodological quality of the included reviews using the 'Assessment of multiple systematic reviews' (AMSTAR) measurement tool (Shea 2007). The AMSTAR tool consists of 11 items:

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?

Quality of the evidence in the included reviews

Two review authors (LR, MS) will independently assess the overall quality of the evidence presented in the included reviews by examining the methodology used for assessing risk of bias of the individual included studies. We will assess whether the Cochrane Reviews have used the 'Risk of bias' tool as described by Higgins 2011. We will critically appraise the judgements to assess their consistency across reviews.

Data synthesis

We will undertake a narrative summary of the results for the individual reviews for each of the primary outcomes and present these using tables and figures (e.g. 'Characteristics of included reviews', 'Summary of quality of evidence within individual reviews', AMSTAR ratings for each review). For future updates of this overview, if the data allow, we may perform indirect comparisons of the interventions across reviews for the primary outcomes.

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LR, MS and KIP drafted the protocol. LR and MS will perform review selection and data extraction and will write the review with input from KIP.

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