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[Intervention Review]

Intravascular brachytherapy for peripheral vascular disease

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ABSTRACT

Background

Interventional treatment of arteries that are narrowed and obstructed by atherosclerosis involves either bypassing the blockage using a graft; widening the artery from the inside with a balloon, a procedure known as percutaneous transluminal angioplasty (PTA); or providing a strut to hold the vessel open, known as a stent. All of these treatments are, however, limited by the high numbers that fail within a year. Intravascular brachytherapy is the application of radiation directly to the site of vessel narrowing. It is known to inhibit the processes that lead to restenosis (narrowing) of vessels and grafts after treatment. This is an update of a review first published in 2002.

Objectives

To assess the efficacy of, and complications associated with, intravascular brachytherapy (IVBT) for maintaining patency after angioplasty or stent insertion in native vessels or bypass grafts of the iliac or infrainguinal arteries.

Search methods

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched their Specialised Register (last searched August 2013) and CENTRAL (2013, Issue 7).

Selection criteria

Randomised controlled trials of the use of brachytherapy as an adjunct to the endovascular treatment of people with peripheral arterial disease (PAD) or stenosed bypass grafts of the iliac or infrainguinal arteries versus the procedure without brachytherapy.

Data collection and analysis

Two review authors independently assessed trial quality and two other review authors independently extracted the data. Adverse event information was collected from the trials.

Main results

Eight trials with a combined total of 1090 participants were included in this review. All included studies used the femoropopliteal artery. We did not identify any studies that used the iliac arteries. All studies compared PTA with or without stenting plus IVBT versus PTA with or without stenting alone. No trials were found comparing IVBT to technologies such as drug eluting stents or balloons, or cryoplasty. Follow-up ranged from six months to five years. The quality of the included trials was moderate with our concerns relating to the difficulty of blinding due to the nature of the procedures and the small sample sizes for some studies. Primary outcomes (patency or restenosis and need for re-intervention) were reported in the majority of the trials, but reporting at various time points and the use of multiple definitions of the outcomes by the included studies meant that not all data were available for pooling. The secondary outcomes were not reported in many of the included studies.

For brachytherapy, cumulative patency was higher at 24 months (odds ratio (OR) 2.36, 95% confidence interval (CI) 1.36 to 4.10, $n = 222$, $P = 0.002$). A statistically significant difference was found for restenosis at six months (OR 0.27, 95% CI 0.11 to 0.66, $n = 562$, $P = 0.004$), 12 months (OR 0.44, 95% CI 0.28 to 0.68, $n = 375$, $P = 0.0002$) and 24 months (OR 0.41, 95% CI 0.21 to 0.78, $n = 164$, $P = 0.007$) in favour of IVBT. No difference was found after five years as measured in one study. The need for re-interventions was reported in six studies. Target lesion revascularisation was significantly reduced in trial participants treated with IVBT compared with angioplasty alone (OR 0.51, 95% CI 0.27 to 0.97, $P = 0.04$) at six months after the interventions. No statistically significant difference was found between the procedures on the need for re-intervention at 12 and 24 months after the procedures.

A statistically significant lower number of occlusions was found in the control group at more than three months (OR 11.46, 95% CI 1.44 to 90.96, $n = 363$, $P = 0.02$) but no differences were found at less than one month nor at 12 months after the procedures making the clinical significance uncertain. Ankle brachial index was statistically significantly better for IVBT at the 12 month follow-up (mean difference 0.08, 95% CI 0.02 to 0.14, $n = 100$, $P = 0.02$) but no statistically significant differences were found at 24 hours and at six months.

Quality of life, complications, limb loss, cardiovascular deaths, death from all causes, pain free walking distance and maximum walking distance on a treadmill were similar for the two arms of the trials with no statistically significant difference found between the treatment groups.

Authors' conclusions

The evidence for using peripheral artery brachytherapy as an adjunct to percutaneous transluminal angioplasty to maintain patency and for the prevention of restenosis in people with peripheral vascular disease is limited, mainly due to the inconsistency of assessment and reporting of clinically relevant outcomes. More data are needed on clinically relevant outcomes such as health related quality of life (HRQOL) or limb salvage and longer-term outcomes, together with comparisons with other techniques such as drug eluting balloons and stents. Adequately powered randomised controlled trials, health economics and cost-effectiveness data are required before the procedure could be recommended for widespread use.

PLAIN LANGUAGE SUMMARY

Intravascular brachytherapy (radiation treatment), inside arteries or bypass grafts, after angioplasty or stent surgery

Intravascular brachytherapy (radiation treatment) inside arteries after angioplasty, stent insertion, or bypass grafts may prevent narrowing of the arteries or grafts. Narrowed and blocked arteries can be treated by bypassing the blockage using a graft, angioplasty (widening the artery by inserting a balloon), or inserting a stent (thin metal sleeve) to hold the artery open. However, restenosis (return of the narrowing or obstruction) often occurs within a year. Intravascular brachytherapy (IVBT) aims to prevent restenosis by the application of radiation to the affected part of the artery after the angioplasty or stent insertion.

This review included eight studies with a total of 1090 participants. All eight included studies used the femoropopliteal artery. We did not identify any studies that used the iliac arteries. All trials compared angioplasty with or without stenting plus IVBT with angioplasty with or without stenting alone. No trials were found comparing IVBT to newer technologies such as drug eluting stents, balloons, or cryoplasty. Intravascular brachytherapy resulted in increased cumulative patency, reduced restenosis, and fewer occlusions on short-term follow-ups. However, results from the eight included trials were not consistent and long-term outcomes need to be fully assessed. Therefore, more research is needed especially regarding the long-term outcomes and complications of this treatment, and the health economics and cost-effectiveness data.

BACKGROUND

Description of the condition

In the UK and US, symptomatic peripheral arterial disease (PAD) occurs in 4.5% to 7% of people over the age of 55 years ([Dewhurst 1991](#); [Fowkes 1991](#); [Selvin 2004](#)). In 25% of these patients, the condition will deteriorate and require treatment but fewer than 5% will go on to develop limb threatening critical limb ischaemia (CLI) ([Dormandy 1991](#)). CLI is diagnosed only in 1% to 2% of all patients with PAD at the initial presentation ([Hirsch 2006](#)). More than 50% of those who require treatment will be suitable candidates for endovascular methods of intervention ([London 1995](#)) and patients with CLI have a 50% risk of major amputation if they do not undergo revascularisation ([Hirsch 2006](#)). Patients with PAD have a shorter life expectancy due to the coexistence of other cardiovascular disorders ([Stansby 2011](#)).

A Cochrane review of trials (which included only 98 participants in total) suggested that although angioplasty may be of short-term benefit, this may not be sustained in the long-term ([Fowkes 2006](#)). Narrowing of the artery following angioplasty (restenosis) is the major cause of long-term failure. Restenosis is caused by three processes, immediate elastic recoil of the vessel, myointimal hyperplasia (enlargement of the inner muscular layer of vessels), and late vascular remodelling (changes in the vessel, produced in response to physical stresses on the vessel wall, which affect the shape and volume of the vessel). The addition of acute thrombosis can lead to complete occlusion (obstruction or complete blockage) of a restenosed vessel.

Description of the intervention

Percutaneous balloon angioplasty is a technique for restoring blood flow through an artery that has become narrowed or blocked by atherosclerosis. A small balloon is inserted into the artery and inflated, thus rupturing the atheromatous plaque, stretching the smooth muscle cells within the middle of the vessel and widening the arterial lumen. Angioplasty is particularly effective in the iliac vessels, but the technique is also successful for treating femoropopliteal arteries. Two year patency rates for femoropopliteal disease is around 80% ([AHRQ 2013](#)). Five year patency rates for iliac and femoropopliteal angioplasty are 50% to 60% and 52% respectively ([Adar 1989](#); [Kudo 2005](#); [Kudo 2006](#); [Leu 1999](#); [Long 1991](#); [Martin 1995](#); [Murphy 1995](#); [Rutherford 1991](#); [Rutherford 1995](#)). More recent studies suggest a five year patency rate in the iliac artery of around 80% ([Leville 2006](#); [Park 2005](#); [Park 2007](#)).

An important cause of failure after angioplasty is myointimal hyperplasia, which is the unrestricted migration and proliferation of vascular smooth muscle cells into the vessel lumen leading to narrowing of the vessel and restriction of blood flow. The stimulus for this cellular migration is unclear and therapeutic approaches are being sought to regulate this process ([Clowes 1983](#); [Dilley 1988](#); [Mintz 1996](#); [Sottiurai 1983](#)). Myofibroblasts of the adventitia also contribute to the process of vascular lesion formation ([Scott 1996](#); [Scott 1998](#)).

Intravascular brachytherapy (IVBT) is a technique that is intended to suppress cellular proliferation and migration by directing radiation at the site of the vascular intervention. IVBT is based on the concept that proliferating smooth muscle cells and

myofibroblasts are more sensitive to the effects of low doses of radiation than non-proliferating cells ([Hall 1994](#); [Wilcox 1996](#)). It allows a localised delivery of radiation to inhibit the proliferative response seen after angioplasty ([Davies 2013](#); [Waksman 1997](#)).

How the intervention might work

Although two forms of radiation are commonly used for IVBT (gamma and beta), both have limitations when used in peripheral vessels ([Bertrand 1997](#)). Beta sources produce high-energy particle radiation which rapidly loses activity over short distances of the vessel wall. This limited penetration means that in order to guarantee that the entire arterial wall receives an equal dose, particularly with larger peripheral vessels, it is essential that the radiation source be centred in the lumen of the vessel. By comparison, electromagnetic gamma-radiation penetrates well beyond the vessel wall, thus removing the degree of precision that is required with beta-radiation. However, this increased penetration increases the risk of potential damage to surrounding tissues and, therefore, increases the oncogenic (cancer causing) potential of the intervention. Gamma-radiation also requires more elaborate and costly radiation protection measures for the operators. Both types of radiation can be delivered by either intravascular insertion of a catheter containing the radiation source in a balloon (beads, gel, liquid) or a wire source where the tip of the wire is radioactive. These sources are placed in the target vessel for a calculated period of time to deliver the required dose ([Nath 1999](#)). Alternative methods for delivering the radiation involve the insertion of a permanent low-activity radioactive stent with a radioactive half-life tailored to the purpose, for example phosphorus-32, with vanadium-48 and yttrium-90 considered as alternatives ([Feres 2005](#); [Hanefeld 2002](#); [Rorat 2005](#)).

Extensive work on animals has confirmed the inhibition of acute and late restenosis by IVBT and, more importantly, reported a low incidence of adverse effects ([Hehrlein 1996](#); [Verin 1995](#); [Waksman 1995a](#); [Waksman 1995b](#); [Weinberger 1996](#); [Wiedermann 1994](#)) thereby providing the impetus for human trials. Much of our understanding of IVBT has been gathered from studies of radiotherapy in coronary arteries. Published trials in coronary arteries have been uniformly optimistic. The first published trial of coronary artery IVBT was by Condado et al ([Condado 1995](#)) in Venezuela who treated 21 participants with gamma-irradiation after balloon angioplasty. Although two participants had immediate failures, none of the 19 remaining participants showed evidence of late occlusion at the two year angiographic follow-up ([Condado 1999](#)). The Coronary Radiation to Inhibit Proliferation Post Stenting (SCRIPPS) study showed similarly impressive results ([Teirstein 1997](#)). At three years, restenosis was nearly twice as common in the control group as in the brachytherapy group (64% versus 33%) ([Teirstein 2000](#)), a trend reproduced by several subsequent trials ([King 1998](#); [Leon 2001](#); [Mintz 2000](#); [Verin 2001](#); [Waksman 1999a](#); [Waksman 2000a](#)). IVBT has also been shown to have a profound effect on vascular remodelling in coronary arteries. Studies have demonstrated increases in initial luminal volume of almost 50% in arteries treated with gamma or beta-radiation ([Condado 1997](#); [Sabate 1999](#)).

Although the initial benefits of IVBT appear to be very promising, the long-term consequences remain unknown. For example, the longest running trial has published results that follow-up participants for only eight years ([Liermann 1998](#)). No evidence of clinical nerve damage or local malignancy has been observed.

However, early trials in coronary IVBT exposed a high incidence of late thrombosis, approaching 6.2% to 6.6%, in participants treated with IVBT (control participants showed an incidence of 0.7% to 0.8%) and this was significantly higher in participants who underwent simultaneous stent insertion (Costa 1999; Leon 2001; Teirsten 2000; Waksman 2000b). Treatment with radioactivity delays re-endothelialisation of inserted stents and may induce endothelial dysfunction causing arterial spasm (Bertrand 1997; Virmani 1999). High dose radiation is also known to induce thrombosis, perhaps by increasing platelet activation whilst inhibiting mechanisms involved in resolution (the physiological process by which the body repairs itself to become as close to the normal state as possible) (Salame 1999; Vodovotz 2001; Waksman 1999b). The US Federal Drug Agency (FDA) reviewed data from several trials in relation to this complication (Sapirstein 2001) and concluded that the high incidence in early studies was caused by premature cessation of antiplatelet therapy. Sapirstein et al recommended the avoidance of IVBT with simultaneous stent insertion and suggested the maintenance of antiplatelet therapy for a minimum of six months after IVBT and for one year if a new stent was implanted simultaneously (Sapirstein 2001). In general, all patients with PAD should be permanently on antiplatelet therapy unless contraindicated (Mannava 2007).

Fibrosis of irradiated vessels may weaken vessel walls, while initially favourable adaptive remodelling could lead to late aneurysm formation (Condado 1997; Sabate 1999). The combined effect of these processes could be exacerbated by asymmetric centring of the radiation source during IVBT, which could lead to some areas of the wall receiving a much higher dose of radiation than others.

There is also evidence that low dose radiation could stimulate myointimal hyperplasia (proliferation of cells into the innermost layer of vessels, particularly at the edges of stents. This leads to a characteristic luminal narrowing phenomenon known as the 'candy-wrapper' or edge effect (Albiero 2000; Eising 2001). The luminal narrowing phenomenon can be reduced in coronary arteries by using a longer brachytherapy source (Bagga 2005). In vitro experiments showed that beta-radiation treatment can alter the reactivity of certain proteins of the vessel wall extracellular matrix and the vessel wall becomes less prone to platelet adhesion resulting in a decrease of thrombus formation (Wu 2012).

Why it is important to do this review

Many questions about this technique remain unanswered at this stage, including the safety, efficacy and the cost-effectiveness of the brachytherapy. This meta-analysis of available trial data aims to evaluate the technique and would help direct further research into IVBT. This is an update of a review first published in 2002 (Hansrani 2002).

OBJECTIVES

To assess the efficacy of, and complications associated with, intravascular brachytherapy (IVBT) for maintaining patency after angioplasty or stent insertion in native vessels or bypass grafts of the iliac or infrainguinal arteries.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) in which people with peripheral arterial disease (PAD), or stenosed bypass grafts, of the iliac or infrainguinal arteries were randomised to brachytherapy with or without another procedure versus a procedure without brachytherapy.

Types of participants

Males and females of any age diagnosed with PAD by an expert clinician through clinical and investigative assessment (ankle brachial pressure index, duplex, exercise testing or angiography) and who required vascular intervention that could be appropriately managed with IVBT and were deemed fit to undergo such an intervention.

Types of interventions

Trials including any form of therapy that involved the use of brachytherapy applied intravascularly for the treatment of PAD were considered for inclusion. Trials were divided into subgroups according to the radioactive source (beta or gamma, and radioactive isotope) used; accompanying procedure (angioplasty, stent insertion, thrombectomy, etc.); short-term (catheter based) or long-term (radioactive stents) brachytherapy; total dosage and dosage profile; indication for intervention (CLI, intermittent claudication); and de novo or repeat procedure. Additional therapies, in particular the adjuvant use of antiplatelet or anticoagulant agents, were also assessed.

Types of outcome measures

Primary outcomes

The following primary outcome measures were considered:

- primary patency or restenosis;
- need for re-intervention (including target lesion revascularisation and target vessel revascularisation).

Clinical patency is defined as sustained clinical success without further intervention, whilst cumulative patency is defined as the percentage of lesions which have < 50% restenosis with or without further intervention during the follow-up period. Restenosis is the narrowing of a blood vessel after it has been opened, usually by balloon angioplasty. It is defined as $\geq 50\%$ luminal diameter stenosis.

Re-intervention is indicated in symptomatic restenosis or reocclusions post-intervention either in the treated segment (target lesion revascularisation (TLR)) or secondary to progression of the disease in non-treated segments of the vessel (target vessel revascularisation (TVR)).

Secondary outcomes

The following secondary outcome measures were considered:

- occlusion;
- immediate success of procedure (within 30 days);
- limb loss or amputation free survival;

- cardiovascular death (i.e. death from any atherogenic cause, cerebrovascular accident, myocardial infarction, aneurysm, etc., including death during surgery for these conditions);
- death from all causes;
- complications (e.g. early thrombosis, aneurysm formation, nerve damage, malignancy, lesions secondary to use of radiation);
- bleeding;
- ankle brachial index (the highest systolic pressure at the ankle compared to the highest of the right or left brachial systolic pressures) (ABI);
- pain free walking distance;
- maximum walking distance on treadmill;
- quality of life.

Cost-effectiveness in terms of morbidity and mortality and use of resources (for example bed days) was also considered if the information was provided.

Search methods for identification of studies

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched their Specialised Register (last searched August 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 7), part of *The Cochrane Library* (www.thecochranelibrary.com). See [Appendix 1](#) for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used, are described in the [Specialised Register](#) section of the Cochrane Peripheral Vascular Diseases (PVD) Group module in *The Cochrane Library* (www.thecochranelibrary.com).

Searching other resources

The reference lists of relevant articles retrieved as a result of the electronic searches were searched for additional citations.

Data collection and analysis

Selection of studies

The selection of trials for inclusion in the review was carried out by two review authors (MH, GS). All disagreements were successfully resolved by consensus.

Data extraction and management

Data collection was carried out in duplicate by two review authors (AA, MS) to ensure quality control and included information on participants (age and sex distribution, measures of severity of disease such as ABI), interventions and doses (element used, method of treatment) and outcomes (as above). All disagreements were successfully resolved by consensus.

Assessment of risk of bias in included studies

The methodological quality of each trial was assessed independently by two review authors (MH, GS). The risk of bias in the included studies was assessed using the Cochrane

Collaboration's tool for assessing risk of bias ([Higgins 2011](#)). This includes the domains of sequence generation; allocation concealment; blinding of participants, personnel and assessors; inappropriate outcome data; selective outcome reporting; and other sources of bias. The domains were judged to be either at 'low risk', 'high risk' or 'unclear risk' of bias according to [Higgins 2011](#).

Measures of treatment effect

We used Review Manager 5.2, provided by The Cochrane Collaboration, to analyse the data. For dichotomous outcomes, the statistical analysis was presented as odds ratio (OR) with 95% confidence interval (CI). We used mean differences (MD) with 95% CI for continuous outcomes.

Unit of analysis issues

Participating individuals in each RCT were the unit of analysis.

Dealing with missing data

Multiple attempts were made to contact study authors to clarify data. One of the three study authors who were contacted responded to our request for data. Data that remained missing or unclear were not included in the analyses.

Assessment of heterogeneity

We based all analyses on the intention-to-treat data from individual trials. We assessed trial heterogeneity using the I^2 statistic. Where heterogeneity was identified ($I^2 > 50\%$), we investigated the reason for heterogeneity. If no apparent reason was found, we conducted a random-effects model meta-analysis. In the absence of heterogeneity we used a fixed-effect model meta-analysis.

Assessment of reporting biases

We planned to use asymmetry in funnel plots to assess reporting bias. However, due to the small number of included trials, this was not performed as the power of analysis would have been too low to distinguish chance from real asymmetry ([Higgins 2011](#)).

Data synthesis

We used a random-effects model meta-analysis where clinical and statistical heterogeneity existed ($I^2 > 50\%$). We used a fixed-effect model meta-analysis in the absence of heterogeneity.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses where possible, including subgroup analyses for participants with grafts as opposed to participants being treated for native vessel disease, type and length of lesion, de novo or repeat procedures, the accompanying procedure (angioplasty, stent insertion, thrombectomy, etc.) and indication for intervention (CLI, intermittent claudication). We also planned to perform subgroup analysis for participants with vessels or grafts requiring re-intervention (with stratification for time from implantation to re-intervention), the radioactive source (beta or gamma-radiation, and radioactive isotope), total dosage and dosage profile, and short-term (catheter based) or long-term (radioactive stents) brachytherapy if sufficient data were available.

Sensitivity analysis

We planned to perform sensitivity analyses based on the risk of bias if there were studies with high risk of bias (that is, with high

risk methods of allocation concealment and random sequence generation) included in the analyses.

Results of the search

See [Figure 1](#).

RESULTS

Description of studies

For a detailed description of studies see [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

Figure 1. Study flow diagram.

For this update we identified seven additional included studies following screening of the CENTRAL and PVD Specialised Register search results. A further 10 additional studies were excluded.

Included studies

One study ([Vienna 2](#)) had been included in the original version of the review and an additional seven studies were included in this update ([Krueger 2004](#); [PAB](#); [PARIS II](#); [Swiss](#); [VARA](#); [Vienna 3](#); [Vienna 5](#)). The

eight included studies involved a total of 1090 participants ([Table 1](#)). All included studies used the femoropopliteal artery. All included studies compared PTA with or without stenting plus IVBT with PTA with or without stenting alone. No trials were found comparing IVBT to other technologies such as drug eluting stents, balloons, or cryoplasty.

In terms of primary outcome events, seven trials ([Krueger 2004](#); [PAB](#); [Swiss](#); [VARA](#); [Vienna 2](#); [Vienna 3](#); [Vienna 5](#)) reported patency or restenosis and six trials ([Krueger 2004](#); [PAB](#); [VARA](#); [Vienna 2](#); [Vienna 3](#); [Vienna 5](#)) reported technical success or need for re-intervention at various time points.

In terms of secondary outcome events, the following information was reported:

- occlusion was reported in five studies ([Krueger 2004](#); [Swiss](#); [VARA](#); [Vienna 3](#); [Vienna 5](#));
- immediate success of the procedure was reported by all eight studies ([Krueger 2004](#); [PAB](#); [PARIS II](#); [Swiss](#); [VARA](#); [Vienna 2](#); [Vienna 3](#); [Vienna 5](#));
- limb loss was reported by one trial ([Vienna 3](#));
- cardiovascular death was reported at different time points by three trials ([Krueger 2004](#); [PAB](#); [VARA](#));
- death from all causes was reported at different time points by seven trials ([Krueger 2004](#); [PAB](#); [Swiss](#); [VARA](#); [Vienna 2](#); [Vienna 3](#); [Vienna 5](#));
- complications were reported by six trials ([Krueger 2004](#); [Swiss](#); [VARA](#); [Vienna 2](#); [Vienna 3](#); [Vienna 5](#));
- bleeding was reported by one study ([Swiss](#));
- ABI was reported at different time points by four trials ([Krueger 2004](#); [Swiss](#); [Vienna 2](#); [Vienna 5](#));
- pain free walking distance was reported at one time point by one trial ([Krueger 2004](#));
- maximum walking distance on a treadmill was reported at different time points by two trials ([Krueger 2004](#); [Vienna 5](#));
- quality of life was reported by one trial ([Krueger 2004](#)).

[Krueger 2004](#) randomised 30 participants with de novo stenoses or occlusions resulting in claudication to PTA alone or PTA + 14 gray (Gy) from a centred iridium-192 (Ir-192) source. No participants were stented. All participants were treated with aspirin 100 mg daily and heparin peri-procedure. The primary endpoint was restenosis at 12 months. Follow-up to 24 months has also been reported.

The [PAB](#) (Probulcol And Brachytherapy) trial in Switzerland recruited 335 participants in a 2 x 2 factorial design into four groups: PTA alone, PTA + 14 Gy non-centred Ir-192, PTA + probucol, and PTA + probucol + 14 Gy non-centred Ir-192. Stenting was allowed and only claudicants with de novo femoropopliteal stenoses and occlusions were recruited. All participants received aspirin 100 mg daily and those in whom stents were placed received clopidogrel 75 mg daily. The primary endpoint was restenosis at six month follow-up. Twenty participants from the trial were used in an analysis of the effect of IVBT on vascular lumen dimensions as measured by magnetic resonance imaging (MRI) at three and 24 months ([Wytenbach 2004](#); [Wytenbach 2007](#)). A subgroup analysis of those participants in whom stents were placed was carried out to assess the effect of IVBT in addition to stenting on late thrombotic occlusions ([Bonvini 2003](#)). [Diehm 2005](#) pooled participants from

the [PAB](#) and [Swiss](#) trials to perform a subgroup analysis looking at recurrent versus de novo lesions and stenoses versus occlusions.

The only US based RCT was the Peripheral Artery Radiation Investigational Study ([PARIS II](#)), which was completed in 2002. Two hundred and three participants were enrolled to undergo PTA alone or PTA with 14 Gy from a centred Ir-192 source. Although the trial group published their initial feasibility study results ([PARIS I](#)), disappointingly they have not published the results from the completed RCT. Preliminary results from follow-up of 75 of the participants were presented at the 2003 Annual Transcatheter Cardiovascular Therapeutics meeting.

The [Swiss](#) trial recruited 100 participants with recurrent stenoses or occlusions of the femoropopliteal vessels resulting in claudication or CLI. The participants were randomised to PTA with or without stenting and with or without 12 Gy from a non-centred Ir-192 source. Information on antithrombotic or anticoagulant therapy was not provided. The primary endpoint was restenosis at 12 months follow-up.

The [VARA](#) (VAscular RAdiation) trial from the Netherlands was a multicentre (eight centres) RCT initiated in 1998 where participants with de novo stenoses or occlusions were randomised prior to undergoing initial PTA to receiving IVBT or not. Because of the protocol, 17 participants were excluded immediately leaving 60 participants, 33 controls treated with PTA with and without stenting and 27 treated with additional 14 Gy centred Ir-192. Participants with both claudication and CLI were included. All participants were treated with aspirin 100 mg daily long-term. The primary endpoint was restenosis rate at 12 months follow-up. [Hagenaars 2002](#) analysed a subgroup of 24 trial participants to assess vascular lumen dimensions as measured by duplex ultrasound.

After successfully conducting an initial feasibility study to assess the safety and efficacy of IVBT, in 10 participants with long segment stenosis who underwent non-centred 12 Gy IVBT without complications ([Vienna 1](#)), the Vienna group started recruiting in 1996 for the [Vienna 2](#) trial in which 113 participants were randomised after PTA to receiving IVBT 12 Gy by a non-centred Ir source or not. Included were de novo and recurrent lesions, both stenoses > 5 cm and occlusions. Participants with claudication and CLI were allowed. All participants received aspirin 100 mg/day (from at least two weeks prior to the procedure and continued indefinitely post-procedure) and heparin therapy for 24 hours peri-procedure. The primary endpoint was angiographic patency at six months. Secondary outcomes included restenosis rates, revascularisation rates, ABI and peak velocity ratios (ratio of peak systolic velocity within the stenosis to peak systolic velocity just prior to the stenosis) as determined by duplex measurements ([Vienna 2](#)). The group have published an update of the trial with 102 participants completing five year follow-up ([Wolfram 2006a](#)). Using a subgroup of 34 participants from this study, [Pokrajac 2002a](#) looked at the potential effect of using a non-centred source on restenosis. Trials run by this group following [Vienna 2](#) used a centred source. A very small randomised single centre study performed in 2000 in Salzburg ([Hofmann 2002](#)) (part of [Vienna 2](#)) randomised nine participants with de novo or recurrent lesions of the femoropopliteal vessels to 18 Gy centred Ir-192, or not, post-PTA ([Hofmann 2002](#)). All participants were treated with aspirin 100 mg daily and heparin peri-procedure. The focus of the publication was on thrombotic sequelae of the procedure. This was an analysis

of a subset of participants from a single centre participating in a multicentre trial ([Vienna 2](#)).

In the [Vienna 3](#) multicentre trial in 1998, 134 participants with de novo or recurrent stenoses or occlusions of the femoropopliteal vessels were randomised to receiving PTA with or without 18 Gy via a centred Ir-192 source. Participants requiring stenting were excluded but both claudicants and participants with CLI were included. All participants were treated with aspirin 100 mg daily and heparin. The primary endpoint of the study was arterial patency at 12 months follow-up. A subgroup analysis was performed to assess de novo versus recurrent lesions from participants enrolled in the Vienna 2 and 3 trials ([Wolfram 2005](#)).

The Vienna 4 trial was a non-randomised feasibility study of 33 participants ([Vienna 4](#)), which was performed prior to enrolment started for the double-blind multicentre [Vienna 5](#) trial. Ninety-four participants were enrolled with de novo or recurrent stenoses or occlusions of the femoropopliteal vessels. All participants underwent PTA and stenting with Wallstent or nitinol stents prior to randomisation to receiving additional 14 Gy from a centred Ir-192 source or not (control). The primary endpoint was restenosis at six months follow-up. All participants were treated with dual aspirin 100 mg and clopidogrel 75 mg daily therapy and peri-procedural heparin treatment. [Schillinger 2004](#) assessed the effect of IVBT and stenting on acute phase proteins in a small subset of participants from the [Vienna 3](#) and [Vienna 5](#) trials.

Excluded studies

See the table [Characteristics of excluded studies](#).

In total, 15 studies ([Boselli 2002](#); [Bottcher 1994](#); [Kruger 2002](#); [Liermann 1998](#); [LIMBER](#); [MOBILE](#); [PARIS I](#); [Pichler 1999](#); [Pokrajac 2009](#); [Schopohl 1996](#); [Vienna 1](#); [Vienna 4](#); [Walichiewicz 2002](#); [Walichiewicz 2003](#); [Werner 2012](#)) were excluded. Thirteen studies were excluded because they were non-randomised studies ([Boselli 2002](#); [Bottcher 1994](#); [Kruger 2002](#); [Liermann 1998](#); [PARIS I](#); [Pichler 1999](#); [Pokrajac 2009](#); [Schopohl 1996](#); [Vienna 1](#); [Vienna 4](#); [Walichiewicz 2002](#); [Walichiewicz 2003](#); [Werner 2012](#)), including the very first publication of the therapeutic use of brachytherapy in PAD ([Bottcher 1994](#)). None of these pilot or feasibility studies used a control group and they had very small numbers of participants (10 to 45 participants).

[Bottcher 1994](#) published his findings on the use of a non-centred Ir-192 gamma source to deliver 12 Gy IVBT to restenoses or reocclusions in the superficial femoral artery (SFA) of 13 participants. All participants were stented and the IVBT was performed without incident. They reported that all treated vessels remained patent at three to 27 months follow-up.

[Liermann 1998](#) reported the outcomes of 40 participants (a previous publication reported on 28 of these participants ([Schopohl 1996](#))) treated with 12 Gy from a non-centred Ir-192 source for recurrent stenoses or occlusions of the previously treated SFA segments, with a follow-up period of four months to 7.5 years. They reported freedom from restenosis in 33 of the 40 participants; one participant developed acute thrombosis at three months and another developed restenosis at 12 months. Pichler's group ([Pichler 1999](#)) successfully treated 24 de novo and recurrent lesions in the SFA segment with 14 Gy non-centred Ir-192. At 15 months they reported cumulative patency rates of 60%, with no

major adverse events. Similarly [Boselli 2002](#) treated the stented SFA segments of 45 participants with non-centred Ir-192. They reported immediate patency rates of 95%, with a 12 month patency of 80%.

[Kruger 2002](#) performed non-centred IVBT using a Ir-192 source to deliver 12 Gy in six participants with de novo SFA stenoses and gave one participant centred IVBT. They reported restenosis in only one of the seven participants, with follow-up out to four years. [Walichiewicz](#) also reported the results of their pilot study, in 2002 ([Walichiewicz 2002](#)). They treated 20 limbs of 19 participants with 15 Gy Ir-192 applied to de novo stenoses or occlusions of the SFA, with follow-up of one to 14 months. All participants underwent angiographic assessment at follow-up. At six months the trialists observed four (20%) acute thrombotic occlusions and no restenoses, and recommended six months of aggressive antiplatelet therapy with ticlopidine in participants who had stents in situ.

[Waksman \(PARIS I\)](#) reported the results of their feasibility pilot study, called PARIS 1, in 2001. They recruited 40 participants with claudication to undergo PTA to their SFA followed by 14 Gy delivered by a centred, specially designed afterloader, with follow-up at six months. The procedure was unsuccessful in five (12.5%) of their cases; two participants dropped out due to complications of PTA and in three the catheter kinked and would not allow passage of the radiation source. Two participants died and four refused angiographic follow-up before the initial assessment at six months. At six month angiographic follow-up the restenosis rate was 17.2% (6/35 participants) and three required revascularisation. At 12 months follow-up the clinical restenosis rate was 13.3% (in 30 participants).

The Vienna group published their initial feasibility study, Vienna 1, looking at 10 participants treated with PTA followed by 12 Gy IVBT from a non-centred Ir-192 source to de novo long SFA restenoses ([Vienna 1](#)). The procedure was performed with complications in all participants. At 12 months follow-up they reported a restenosis rate of 40%, with no reocclusions. [Vienna 4](#) reported the results of their second pilot study, Vienna 4, which was designed specifically to include PTA + stenting of the femoropopliteal segment with IVBT using a centred catheter to deliver 14 Gy. Thirty-three participants were successfully treated with no initial adverse events. Restenosis at six months occurred in 30%, with seven participants developing late thrombotic occlusions.

[Pokrajac 2009](#) published a case series using a beta source, strontium-90, for performing IVBT with a CO₂-filling centring balloon to treat 28 participants with either recurrent SFA stenoses or in-stent restenoses, providing 14 to 18 Gy. There were no adverse events and all procedures were successful, with two participants requiring stenting. Reported restenosis rates were 9% at one year, 28% at two years and 40% at three years, with target vessel revascularisation performed in 25%.

In the only reported study of IVBT to the iliac arteries, [Walichiewicz 2003](#) reported on 14 participants (15 arteries) treated with PTA with or without stenting and 15 Gy from a centred Ir-192 source. All participants received six months of antiplatelet therapy (ticlopidine) post-procedure. All procedures were successful and at six months the study authors reported one (6.7%) angiographically proven restenosis and one participant with transient limb ischaemia.

Werner 2012 reported on a non-randomised study evaluating 90 consecutive participants undergoing angioplasty and subsequent endovascular brachytherapy using a dose of 13 Gy at a depth of 2 mm into the vessel wall. Follow-up data continued for up to two years. All procedures were successful in all participants, with one early stent thrombosis but no other complications related to the irradiation. Primary patency was 95.2% and 79.8% at six and 12 months, respectively. The clinical status improved in 67.0% and 62.2% of the participants after six and 12 months, respectively.

LIMBER and MOBILE were excluded because they were halted and the results never published. LIMBER aimed to recruit 25

participants who would undergo PTA + IVBT with a 32P beta source applied to femoropopliteal segment lesions, whilst MOBILE aimed to perform a RCT of 400 participants from the US and Europe with in-stent restenosis of the femoropopliteal segment, with a lesion length of 4 to 30 cm, comparing PTA + stent versus PTA + stent + IVBT using a 32P beta source.

Risk of bias in included studies

See Figure 2; Figure 3 for graphical representations of the risks of bias.

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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Krueger 2004	+	+	+	+	+	+	+
PAB	+	?	-	+	+	-	-
PARIS II	?	?	?	?	?	?	?
Swiss	?	?	-	?	?	+	-
VARA	+	+	-	?	+	+	-
Vienna 2	+	+	-	+	+	+	+
Vienna 3	+	+	+	+	+	+	+
Vienna 5	+	+	+	+	?	+	+

Allocation

Six studies were at low risk of bias for random sequence generation (Krueger 2004; PAB; VARA; Vienna 2; Vienna 3; Vienna 5). Two studies

(PARIS II; Swiss) were deemed to have an unclear risk of bias because of inadequate reporting.

Five studies clearly demonstrated good allocation concealment (Krueger 2004; VARA; Vienna 2; Vienna 3; Vienna 5), whilst in

the remaining three studies (PAB; PARIS II; Swiss) the allocation concealment was not clearly described.

Blinding

Intravascular brachytherapy presents significant logistical hurdles, making bias difficult to prevent. In order to attempt at least one level of blinding, interpretation of results data ideally should be carried out by members of the team not involved in performing the interventional procedures. However, even this is open to bias as the participants would be aware of which treatment arm they were in.

A sham brachytherapy procedure was performed in several trials in order to blind the participants to the therapy they were undergoing. The sham procedure was performed by placing a dummy wire intravascularly in place of the radioactive source. The following studies used a sham procedure: Krueger 2004, Vienna 3 and Vienna 5. The other four studies (PAB; Swiss; VARA; Vienna 2) did not include a sham procedure, which therefore introduced a high risk of bias. In PARIS II blinding was unclear as the study was not published and was only reported in a meeting.

Three studies (PARIS II; Swiss; VARA) were at unclear risk of detection bias because details of outcome assessment were not reported. In the remaining five studies (Krueger 2004; PAB; Vienna 2; Vienna 3; Vienna 5) detection bias was judged to be at low risk because the clinical follow-up or outcome assessments were performed blinded to the treatment groups.

Incomplete outcome data

In five studies (Krueger 2004; PAB; VARA; Vienna 2; Vienna 3) all participants were accounted for and there were no missing data. In the remaining three studies (PARIS II; Swiss; Vienna 5) some participants were lost to follow-up with no information given on their status.

Selective reporting

In the PAB study there was high risk of bias due to selective reporting as the study authors did not report their secondary outcome of class change according to the Rutherford scale, but instead reported on absence of claudication. Due to the lack of publication of the results of the PARIS II study it was unclear if there was any reporting bias. The remaining six studies (Krueger 2004; Swiss; VARA; Vienna 2; Vienna 3; Vienna 5) showed low risk of bias.

Other potential sources of bias

In three studies (PAB; Swiss; VARA) there was a high risk of other potential sources of bias.

The PAB trial used a 2 x 2 factorial design looking at IVBT and probucol. This introduced a potentially high risk of bias as it was not possible to independently compare the main effects of each of the four treatment arms. The study stopped early due to the significant effect on the primary endpoint and the treatment group received clopidogrel in addition to the treatment.

The Swiss study reported the per protocol analysis rather than an intention-to-treat (ITT) analysis with seven participants crossing from brachytherapy to the control group, which introduced a high risk of bias.

The VARA trial introduced a high risk of bias with an inadequate number to give the study sufficient power, according to the trial report.

In the PARIS II study other potential sources of bias were unclear as the study was not published and was only reported in a meeting.

The remaining four studies (Krueger 2004; Vienna 2; Vienna 3; Vienna 5) had a low risk of bias as there was no indication of other sources of bias.

Effects of interventions

Primary outcomes

Primary patency or restenosis

Patency

Clinical patency is defined as sustained clinical success without further intervention, whilst cumulative patency is defined as the percentage of lesions which have < 50% restenosis with or without further intervention during the follow-up period.

Clinical patency at six and 12 months was measured by only one trial (Vienna 5) with no statistically significant differences between procedures (at six months: OR 0.79, 95% CI 0.31 to 1.99, n = 88; at 12 months: OR 1.36, 95% CI 0.58 to 3.20, n = 88) (Analysis 1.1).

Cumulative patency was reported by two trials (Vienna 3; Vienna 5) and at 24 months showed an improved patency in participants receiving IVBT compared with no IVBT (OR 2.36, 95% CI 1.36 to 4.10, n = 222, I² = 35%) (Analysis 1.2).

See Table 2.

Restenosis

Restenosis is the narrowing of a blood vessel after it has been opened, usually by balloon angioplasty. It is defined as ≥ 50% luminal diameter stenosis.

Restenosis at six months was measured in five studies (Krueger 2004; PAB; VARA; Vienna 2; Vienna 5). The OR was 0.27 (95% CI 0.11 to 0.66, n = 562, I² = 75%) showing low restenosis for participants receiving IVBT compared with no IVBT. Similar results were found at 12 months (Krueger 2004; Swiss; VARA; Vienna 2; Vienna 5) after the procedure (OR 0.44, 95% CI 0.28 to 0.68, n = 375, I² = 0%) and at 24 months (Krueger 2004; Vienna 3) (OR 0.41, 95% CI 0.21 to 0.78, n = 164, I² = 0%). There was no statistically significant difference at 60 months (Vienna 2) (OR 1.00, 95% CI 0.42 to 2.39, n = 102) (Analysis 1.3).

See Table 3.

Need for re-intervention

The need for re-intervention and revascularisation was well reported in the trials. Re-intervention was indicated by symptomatic restenosis or reocclusions post-intervention either in the treated segment (target lesion revascularisation) or secondary to progression of the disease in non-treated segments of the vessel (target vessel revascularisation). This set of participants included those in whom the need for revascularisation may have been due to luminal stenosis secondary to the edge effect, that is at the edges of the irradiated area.

Target lesion revascularisation (TLR)

TLR at six months was reported in three trials (Krueger 2004; Vienna 2; Vienna 5) and showed a statistical difference favouring IVBT (OR 0.51, 95% CI 0.27 to 0.97, $n = 220$, $I^2 = 0\%$) (Analysis 1.4).

TLR at 12 months was reported in three trials (Krueger 2004; VARA; Vienna 3) and showed no statistical difference between groups (OR 0.44, 95% CI 0.19 to 1.02, $n = 215$, $I^2 = 22\%$) (Analysis 1.5).

TLR at 24 months was reported in one trial (Krueger 2004) and showed no statistical difference between groups (OR 0.46, 95% CI 0.04 to 5.75, $n = 30$) (Analysis 1.6).

TLR at 60 months was reported in one trial (Vienna 2) and showed no statistical difference between groups (OR 0.92, 95% CI 0.41 to 2.06, $n = 102$) (Analysis 1.7).

See Table 4.

Target vessel revascularisation (TVR)

TVR at six months was reported in three trials (Krueger 2004; PAB; Vienna 5) and showed no statistical difference between groups (OR 0.55, 95% CI 0.30 to 1.01, $n = 393$, $I^2 = 0\%$) (Analysis 1.4).

TVR at 12 months was reported in two trials (Krueger 2004; Vienna 3) and showed no statistical difference between groups (OR 5.43, 95% CI 0.61 to 48.25, $n = 164$, $I^2 = 0\%$) (Analysis 1.5).

TVR at 24 months was reported in one trial (Krueger 2004) and showed no statistical difference between groups (OR 2.36, 95% CI 0.36 to 15.45, $n = 30$) (Analysis 1.6).

TVR at 60 months was reported in one trial (Vienna 2) and showed no statistical difference between groups (OR 0.91, 95% CI 0.38 to 2.15, $n = 102$) (Analysis 1.7).

See Table 5.

Need for re-intervention

The need for re-intervention not specifically identified as TLR or TVR was reported at 12 months in two trials (Swiss; Vienna 3) and showed no statistical difference between groups (OR 0.36, 95% CI 0.12 to 1.12, $n = 234$) (Analysis 1.5).

Secondary outcomes

Occlusions

Five studies (Krueger 2004; Swiss; VARA; Vienna 3; Vienna 5) looked at occlusion rates and showed no statistical difference at several time points (no time given: OR 3.21, 95% CI 0.12 to 85.20, $n = 30$ (Krueger 2004); at less than one month: OR 2.18, 95% CI 0.76 to 6.32, $n = 275$, $I^2 = 0\%$ (VARA; Vienna 3; Vienna 5); and at 12 months: OR 0.84, 95% CI 0.13 to 5.27, $n = 100$ (Swiss)). Occlusions were statistically significantly fewer in the control group at more than three months (OR 11.46, 95% CI 1.44 to 90.96, $n = 363$, $I^2 = 0\%$) (PAB; Vienna 5) (Analysis 1.8).

Immediate success of procedure (within 30 days)

Several of the studies excluded participants in whom initial PTA failed or in whom the lesion length was outside of the trial parameters. These participants were not included in this analysis. Three trials reported 100% success of the procedure (Vienna 2;

Vienna 3; Vienna 5). Five trials reported failures in the initial brachytherapy procedures (Krueger 2004; PAB; PARIS II; Swiss; VARA).

Krueger 2004 reported that one participant undergoing IVBT developed a thromboembolic occlusion of a lower limb vessel during the procedure, which was immediately treated successfully with thrombolysis. In the PAB trial, the standard balloon angioplasty was successful in 89% to 91% of participants in each of the four participant groups, with 24 angioplasty failures (nine occlusions were not crossed; 15 participants failed the angiographic criteria for successful angioplasty) and two cases of an incorrectly placed applicator catheter. The initial phase of the PARIS II trial had a procedural success of 35 out of 40 interventions, but no further information was provided for the main trial. In the Swiss trial all initial PTA interventions were successful, but in the IVBT group they had seven technical failures: five due to a missed segment and two due to failure to advance the catheter. The VARA reported that two participants in the IVBT group had unsuccessful treatment due to kinking of the catheter preventing correct placement.

Limb loss or amputation free survival

One study (Vienna 3) presented data for limb loss and showed no statistical difference between groups (OR 0.33, 95% CI 0.01 to 8.21, $n = 134$) (Analysis 1.9).

Cardiovascular death

The mortality data from three studies (Krueger 2004; PAB; VARA) were pooled and showed no statistical difference between the experimental and control groups (OR 2.69, 95% CI 0.39 to 18.40, $n = 365$, $I^2 = 0\%$) (Analysis 1.10).

The Swiss trial reported two cardiac deaths at nine months post-intervention, but did not specify the treatment groups. Five participants died from coronary heart disease during the Vienna 2 trial, but the treatment groups were not specified.

Death from all causes

The mortality data from seven studies (Krueger 2004; PAB; Swiss; VARA; Vienna 2; Vienna 3; Vienna 5) were pooled and showed no statistical difference between the experimental and control groups (OR 0.89, 95% CI 0.42 to 1.87, $n = 789$, $I^2 = 0\%$). No statistical significant difference was determined at any of the time points (Analysis 1.11).

Krueger 2004 reported one death at 15 months from gastric bleeding in the brachytherapy (BT) group.

There were three reported deaths in the PAB trial: two participants in the BT group died of myocardial infarction and one in the control group died of a ruptured abdominal aortic aneurysm.

There were three deaths reported at 12 months in the Swiss trial: two from cardiac causes and one from an accident.

The VARA trial reported two deaths: one from a myocardial infarction in the BT group and one due to cancer in the control group.

Causes of death were not given in Vienna 2 (17 deaths) or Vienna 3 (one death). For the 12 month follow-up in Vienna 5 there was one

death in the control group after a recurrence in the segment treated with a stent.

No details on deaths were available for the [PARIS II](#) trial.

Complications

The risk of complications was reported in six trials ([Krueger 2004](#); [Swiss](#); [VARA](#); [Vienna 2](#); [Vienna 3](#); [Vienna 5](#)) and appeared to favour the control group (OR 2.02, 95% CI 0.90 to 4.52, $n = 518$, $I^2 = 0\%$) ([Analysis 1.12](#)).

One procedural occlusion was reported by [Krueger 2004](#). The [Swiss](#) trial reported that there were no complications.

There were several complications reported in the [VARA](#) trial: two participants in the IVBT group required stenting due to severe dissections with partial luminal obstruction and one participant in the control group had acute thrombotic occlusion at 24 hours. Four participants had minor haematomas post-procedure and one participant complained of neuropathic pain in the groin, which resolved in six weeks, but it was not reported which groups these five participants were in.

[Vienna 2](#) reported one pseudoaneurysm, one haematoma and five moderate treatment site arterial ectasia in the BT group, and one pseudoaneurysm, one haematoma and one moderate treatment site arterial ectasia in the control group.

[Vienna 3](#) reported 12 pseudoaneurysms, which were detected with routine post-procedure ultrasound and successfully treated with ultrasound-guided compression or thrombin injection, though they did not comment on which groups these participants were in. They did, however, report three acute thrombotic occlusions and two acute embolisations in the BT group, and two acute thrombotic occlusions in the control group.

Minor procedural complications were reported in the [Vienna 5](#) trial: four in the IVBT group (three pseudoaneurysms and one distal embolisation that required embolectomy) and five in the control group (three pseudoaneurysms, one minor bleeding, and one distal embolisation that required embolectomy). All pseudoaneurysms were successfully treated with ultrasound-guided compression. The trialists also reported seven early thrombotic occlusions in the BT group and two in the control group.

There was no reporting of complications in two trials ([PAB](#); [PARIS II](#)).

Bleeding

One trial ([Swiss](#)) specified that there were no peri-procedural bleeding complications in either group. The remaining studies did not assess or report bleeding outcomes.

Ankle brachial index (ABI)

ABI is the highest systolic pressure at the ankle compared to the highest of the right or left brachial systolic pressures and was reported by four studies.

One study reported the ABI at 24 hours post-intervention ([Krueger 2004](#)) and one study reported the ABI at six months ([Swiss](#)), but these results were not significantly different between the treatment groups. However, at 12 months follow-up one study ([Swiss](#)) showed

a statistically significant difference favouring the IVBT group (MD 0.08, 95% CI 0.02 to 0.14, $n = 100$, $P = 0.02$) ([Analysis 1.13](#)).

Two more studies ([Vienna 2](#); [Vienna 5](#)) reported ABI results. In the [Vienna 2](#) study, the mean ABI was reported at 24 hours (control group: 0.79, range 0.40 to 1.13; IVBT: 0.85, range 0.48 to 1.09), at three months (control group: 0.77, range 0.15 to 1.14; IVBT: 0.88, range 0.47 to 1.20) and six months (control group: 0.74, range 0.21 to 1.25; IVBT: 0.84, range 0.27 to 1.25). [Vienna 5](#) reported the ABI measurements as mean $\pm$ standard deviation per extremities at 24 hours (control group: 0.84 ± 0.22 ; IVBT: 0.87 ± 0.20 ; $P = 0.55$), at six months (control group: 0.74 ± 0.25 ; IVBT: 0.89 ± 0.23 ; $P = 0.020$) and at 12 months (control group: 0.71 ± 0.25 ; IVBT: 0.91 ± 0.20 ; $P = 0.12$).

Pain free walking distance

Only [Krueger 2004](#) reported results for walking distance at one month post-intervention. No statistical difference between groups was shown (MD 20.40, 95% CI -117.41 to 158.21, $n = 30$) ([Analysis 1.14](#)).

Maximum walking distance on a treadmill

Two trials provided results for maximum walking distance on a treadmill with no statistically significant benefit for either group at one month (MD 23.40, 95% CI -101.03 to 147.83, $n = 30$) ([Krueger 2004](#)), at six months (MD 92.00, 95% CI -62.71 to 246.71, $n = 43$) ([Vienna 5](#)) or at 12 months (MD 55.00, 95% CI -130.65 to 240.65, $n = 29$) ([Vienna 5](#)) ([Analysis 1.15](#)).

[Vienna 2](#) stated that treadmill tests formed part of their clinical assessment of participants, but did not report these results in any of their publications.

Quality of life

One trial ([Krueger 2004](#)) reported scores for quality of life self-assessments, but the difference was not statistically significant for the two groups (MD 2.70, 95% CI -1.06 to 6.46, $n = 30$) ([Analysis 1.16](#)).

Other outcome measures

Cost-effectiveness

A cost-effectiveness analysis was considered, but no data were available in the included studies to perform such an analysis.

De novo restenosis

De novo restenosis was reported by trials at six months follow-up ([VARA](#); [Vienna 2](#)) and appeared to favour the IVBT group (OR 0.39, 95% CI 0.20 to 0.78, $n = 158$) ([Analysis 1.17](#)).

Binary restenosis

Two studies ([PARIS II](#); [Vienna 3](#)) reported binary restenosis and showed a statistically significant difference in favour of the IVBT group (OR 0.57, 95% CI 0.20 to 1.67, $n = 209$, $I^2 = 67\%$) ([Analysis 1.18](#)).

Peak velocity ratio

The peak velocity ratio of the stenosis is the ratio of peak systolic velocity within the stenosis to peak systolic velocity just prior to the stenosis.

Three studies ([Krueger 2004](#); [PAB](#); [Swiss](#)) reported the peak velocity ratios at different time points. No statistically significant difference was found between the experimental and control groups by two of

the studies (Krueger 2004; Swiss) immediately after the procedure (MD 0.12, 95% CI -0.06 to 0.29, $n = 130$, $I^2 = 0\%$), by one study (PAB) at 24 hours (MD -0.05, 95% CI -0.21 to 0.11, $n = 275$) or by one study (Swiss) at 12 months (MD -1.16, 95% CI -0.40 to 0.08, $n = 100$). However, at six months data from two studies (PAB; Swiss) showed a statistically significant difference in favour of the experimental group (MD -0.50, 95% CI -0.93 to -0.07, $n = 375$, $I^2 = 58\%$) (Analysis 1.19).

The peak velocity ratio was reported by three other studies (Vienna 2; Vienna 3; Vienna 5). Vienna 2 and Vienna 3 reported peak velocity ratio as the mean and range value, and did not include any statistical calculations. The values that were reported suggested that at six and 12 months the IVBT group was favoured as the values were lower than in the control group. The mean peak velocity ratio in the extremities was measured at 24 hours post-intervention and at six and 12 months in one study (Vienna 5), which showed a statistically significant difference between groups, favouring the IVBT group (control group: 2.20 ± 1.20 ; IVBT: 1.56 ± 0.62 ; $P = 0.03$), only at the six months follow-up.

Lumen area

Two studies (PAB; VARA) reported the lumen area at 24 hours and showed no statistically significant difference between the experimental and control groups (MD -1.10, 95% CI -3.52 to 1.32, $n = 44$). One study (VARA) reported the lumen area at six months and showed a statistically significant difference in favour of the IVBT group for an increase in the lumen area (MD 6.50, 95% CI 0.05 to 12.95, $n = 24$). One study (PAB) reported the lumen area at 24 months and showed a statistically significant difference in favour of the IVBT for an increase in the lumen area (MD 7.30, 95% CI 4.67 to 9.93, $n = 20$, $I^2 = 0\%$) (Analysis 1.20).

Vessel wall area

Two studies (PAB; VARA) provided data on vessel wall area at 24 hours, while one study (VARA) included data at six and 24 months (Analysis 1.21). They showed no significant difference between the two groups (at 24 hours: MD -4.10, 95% CI -12.09 to 3.90, $n = 44$, $I^2 = 51\%$; at six months: MD 6.40, 95% CI -4.16 to 16.96, $n = 24$; at 24 months: MD 2.70, 95% CI -3.89 to 9.29, $n = 20$).

Plaque area

Only the VARA study provided data on plaque area as determined by intravascular ultrasound at 24 hours and six months (Analysis 1.22). They showed no significant difference between the two groups (at 24 hours: MD -2.70, 95% CI -8.82 to 3.42, $n = 24$; at six months: MD 2.40, 95% CI -4.25 to 9.05, $n = 24$).

Other

Schillinger 2004 took a subset of 47 participants sequentially recruited to the Vienna 3 (no stenting) and Vienna 5 (stenting) trials to assess the effect of PTA with and without stenting and with or without BT on the acute phase inflammatory response using C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen levels as markers. Although they found a trend towards an enhanced response in those participants additionally treated with BT, this only achieved significance in participants undergoing BT and stenting at the 24 hour assessment (CRP: $P = 0.02$, SAA: $P = 0.04$, fibrinogen: $P = 0.88$), and was not sustained at 48 hours. However, the numbers of participants were very small (PTA + BT: $n = 8$, PTA alone: $n = 7$, PTA + stent + BT: $n = 15$, PTA + stent only: $n = 17$).

DISCUSSION

Summary of main results

A total of 1090 participants were included in the eight trials.

In this review, patency or restenosis were reported in seven studies. Overall, a statistically significant benefit for IVBT was found for cumulative patency at 24 months (OR 2.36, 95% CI 1.36 to 4.10, $n = 222$). Clinical patency after six and 12 months was not statistically significantly different between the procedures as reported in one study. A statistically significant difference for IVBT was found for restenosis at six months (OR 0.35, 95% CI 0.24 to 0.50, $n = 562$), 12 months (OR 0.42, 95% CI 0.42 to 0.65; $n = 375$) and 24 months (OR 0.41, 95% CI 0.21 to 0.78; $n = 164$). No difference was found after 60 months as measured in one study.

The need for re-interventions was reported in six studies. Target lesion revascularisation was significantly reduced in trial participants treated with IVBT compared with angioplasty alone (OR 0.51, 95% CI 0.27 to 0.97, $P = 0.04$) at six months after the interventions. No statistically significant difference between the procedures was found for need for re-intervention at 12 and 24 months after the procedures.

Occlusions were statistically significantly fewer in the control group at more than three months (OR 11.46, 95% CI 1.44 to 90.96, $n = 363$), but no differences were found after less than one month or 12 months after the procedures.

Limb loss was reported in one trial and showed no statistically significant difference between procedures.

The number of cardiovascular deaths was reported in three studies and showed no statistically significant difference between procedures.

Death from all causes was reported by seven trials at six different time intervals, ranging from six to 60 months, with no statistically significant difference found between interventions.

Complications were reported by seven trials with no statistically significant difference between the interventions.

ABI was reported in two studies and was statistically significant for IVBT only at the 12 month follow-up (MD 0.08, 95% CI 0.02 to 0.14, $n = 100$). No differences were found between the treatments at the 24 hour and six month intervals.

Pain free walking distance, maximum walking distance on a treadmill and quality of life were similar for the two arms of the trials with no statistically significant difference found between the procedures.

Cost-effectiveness was not assessed in any of the included studies.

Overall completeness and applicability of evidence

Overall, the benefits of brachytherapy following angioplasty over conventional angioplasty are limited. Use of brachytherapy may be recommended for a medium-term one year reduction in restenosis rate. As the included studies have a variety of outcomes, and time intervals for the outcomes, potentially the data do not represent the whole picture for using brachytherapy for PAD.

The literature search identified only RCTs using the femoropopliteal artery. We did not identify RCTs using the iliac arteries, therefore the available evidence cannot be interpreted for arteries other than the femoropopliteal artery.

All included studies compared PTA with and without stenting plus IVBT with PTA with and without stenting alone. No trials were found comparing IVBT to newer technologies such as drug eluting stents, balloons, or cryoplasty.

The very long-term outcomes (more than 10 years) remain unknown as no data beyond 60 months was identified. However, this may in some respects not be so relevant because of the low survival rate after five years as shown in [Vienna 2](#).

As well as clinical effectiveness, cost-effectiveness and quality of life will need to be evaluated before brachytherapy can be recommended for widespread use. Limited or no information is available for these outcomes.

Since the publication of the first version of this review, and indeed the publication of many of the included studies, the outcome measures deemed relevant to the success of peripheral vascular interventions have evolved from patency and stenosis to number of re-interventions and quality of life. We have reordered the outcomes of this review update to reflect the importance of the outcomes and current practice. However, we are unable to change the outcomes as reported by the published studies. It is possible that this change in importance of outcome measures over time has affected the findings of this review.

Quality of the evidence

The quality of the included trials was moderate, with our concerns relating to the difficulty of blinding due to the nature of the procedures and the small sample sizes for some studies. Primary outcomes (patency or restenosis and need for re-intervention) were reported in the majority of the trials, but reporting at various time points and the use of multiple definitions of the outcomes by the included studies meant that not all data were available for pooling. The secondary outcomes were not reported in many of the included studies.

The review included trials where brachytherapy was an adjunct to the treatment of participants with PAD or stenosed bypass grafts versus procedures without brachytherapy. The eight included studies involved a total of 1090 participants with PAD who required vascular intervention that could be appropriately managed by IVBT and who were deemed fit to undergo such an intervention. Some of the included studies incorporated small samples and this should be considered when interpreting the findings. The effect estimates for the primary outcomes (primary patency or restenosis, or need for re-intervention at various time points) produced narrow 95% confidence intervals. Together with the absence of heterogeneity between trials these suggest that the findings are robust. However, for the outcomes restenosis at six months, binary restenosis, peak velocity at six months and vessel wall area at 24 hours, where the heterogeneity was more than 50%, the findings should be interpreted with caution.

Potential biases in the review process

The methods used to conduct the review are described in detail in the *Cochrane Handbook for Systematic Reviews of Interventions*

([Higgins 2011](#)). Particular strengths are the independent application of the review eligibility criteria, independent data extraction, and assessment of the risk of bias. Two authors (AA, MS) independently extracted the data. We attempted to identify all relevant studies. Further data and information were obtained for specific outcomes of this review. The studies used individual participants as the unit of analysis.

Agreements and disagreements with other studies or reviews

There are several reviews that evaluated the use of brachytherapy as an adjuvant in people with PAD undergoing angioplasty procedures.

A review of the Vienna ([Vienna 1](#); [Vienna 2](#); [Vienna 3](#); [Vienna 4](#); [Vienna 5](#)), Frankfurt ([Liermann 1998](#)), PARIS ([PARIS I](#); [PARIS II](#)) and Bern ([Swiss](#)) studies concluded that brachytherapy is feasible and effective but could not give brachytherapy a definite role in the prophylaxis of restenosis ([Pokrajac 2002b](#)), a result that was similar to our review for long-term restenosis rates.

The use of peripheral artery brachytherapy as an adjunct to PTA for the prevention of restenosis in the femoropopliteal system did provide improved health outcomes in a review of two trials ([Krueger 2004](#); [Vienna 2](#)) but the study authors did not have enough evidence for the role of brachytherapy for the prevention of restenosis ([Technology 2003](#)).

[Gorenai 2009](#) reviewed intravascular brachytherapy (IVBT) in people with peripheral arterial occlusive disease and found that the use of brachytherapy after successful balloon dilatation showed a significant reduction in the rate of restenosis at six and 12 months (OR 0.62, 95% CI 0.46 to 0.84) and a significant delay in the time to recurrence of restenosis (17.5 versus 7.4 months, $P < 0.01$). The low restenosis result is similar to the low restenosis at six and 12 months in this systematic review. [Gorenai 2009](#) also showed an estimated additional cost of approximately EUR 1700 for brachytherapy to be used as an adjuvant to other treatments such as balloon dilatation, PTA with an optional stent, or after stenting.

A systematic review and meta-analysis of endovascular brachytherapy looked at restenosis following lower limb angioplasty ([Mitchell 2012](#)). The review included six trials, three of which ([VARA](#); [Vienna 2](#); [Vienna 3](#)) were included in our current systematic review with the same name while two other trials were included under different names (Cologne: [Krueger 2004](#); Bern: [Swiss](#)) and one was an update on a trial (Paris: [PARIS I](#); [PARIS II](#)). The authors concluded that endovascular brachytherapy cannot be recommended for routine clinical use because it has an increased risk of new lesions and it lacks a reduction in medium to long-term risk of restenosis. Our review determined that at 60 months there was no benefit when using brachytherapy in term of restenosis rate.

Interestingly, the use brachytherapy may increase in the future if beta-emitting sources become more widely available ([Minar 2012](#)). Using beta-emitting sources would improve logistics and have technical advantages. An open, non-randomised Limb Ischaemia Treatment and Monitoring post Vascular Brachytherapy to Prevent Restenosis ([LIMBER](#)) trial was halted after recruiting 25 participants, with no results published. The [MOBILE](#) (More Patency with Beta for In-stent Restenosis in the Lower Extremity) trial, the only RCT for femoropopliteal brachytherapy using a beta source, was also

halted by the company running it (Novoste) for financial reasons. The low penetration of beta-radiation would require exact centring of the source within the lumen, however the radiation dose to the vessel wall could be more accurately determined. The Vienna group have published an initial feasibility study using the beta source strontium-90 in a CO₂-filled centring catheter to deliver 14 to 18 Gy to recurrent stenoses or in-stent stenoses of the SFA with some success (Pokrajac 2009a). They reported 100% success for the procedure with no major adverse events and restenosis rates at one, two and three years of 9%, 28% and 40%. A RCT is urgently needed to explore this initial success further.

A systematic review and meta-analysis of additional technologies to enhance angioplasty for infrainguinal PAD looked at restenosis and the need for intervention as outcomes (Simpson 2013). This review included four studies which looked at brachytherapy (Diehm 2005; VARA; Vienna 2; Vienna 3) as an additional technology to angioplasty. Of these four studies, Diehm 2005 was a pooled subanalysis from the PAB and Swiss trials. When compared with PTA alone, IVBT had a significant effect with low restenosis rates at 12 months as shown by three studies (Diehm 2005; VARA; Vienna 3), but no significant effect at six months when two studies were considered (VARA; Vienna 2).

AUTHORS' CONCLUSIONS

Implications for practice

The evidence for using peripheral artery brachytherapy as an adjunct to percutaneous transluminal angioplasty in maintaining

patency and for the prevention of restenosis and other clinically relevant outcomes such as health related quality of life (HRQOL) and limb salvage in people with peripheral vascular disease is limited, mainly due to the inconsistencies of assessment and reporting of clinically relevant outcomes. In particular, more data on long-term outcomes and comparisons with other techniques such as drug eluting balloons and stents, together with health economics and cost-effectiveness data, are required before the procedure could be recommended for widespread use.

Implications for research

Longer-term follow-up in currently running and future trials is essential if the potential short and long-term complications and durability of this adjuvant therapy are to be properly evaluated. Future studies should aim to apply standardised outcomes and have complete reporting of findings. Angioplasty with adjuvant brachytherapy can be extended to other sites such as renal or carotid arteries. Brachytherapy should be studied with other technologies such as drug eluting balloons and drug eluting stents. HRQOL should be included and it will allow more detailed cost-effectiveness analyses to be done.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Krueger 2004

Methods	Allocation: restricted randomisation schedule with fixed block length between balance points. Sealed envelopes Blinded: double Exclusions: none Losses to follow-up: 1 refused to undergo 12 month and 24 month angiographic follow-up assessments Deaths: 1
Participants	Country: Germany No of participants: 30; 15 control, 15 treatment Inclusion criteria: > 50 y, Fontaine > 3, de novo femoropopliteal stenosis < 8 cm Exclusion criteria: residual stenosis > 30% post-PTA, less than one runoff vessel, malignant disease
Interventions	Treatment: post-PTA 14 Gy Ir-192 centred 2 mm Control: PTA alone
Outcomes	Restenosis, re-intervention, ABI, treadmill test, duplex assessment at 6 months, 12 months and 24 months

Intravascular brachytherapy for peripheral vascular disease (Review)

Krueger 2004 (Continued)

Notes Sham brachytherapy procedure used to blind participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	sequential participants who met inclusion criteria added to trial, computer generated allocation
Allocation concealment (selection bias)	Low risk	sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	sham procedure to blind participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	follow-up performed by doctors blinded to treatment arm and not involved in performing treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	all participants accounted for and outcome data presented
Selective reporting (reporting bias)	Low risk	all pre-reported outcomes reported
Other bias	Low risk	no evidence of other bias

PAB

Methods	Allocation: 2x2 factorial design Blinded: single Exclusions: 24 failures of angioplasty, 7 did not undergo angioplasty, 29 insufficient compliance with run-in period, 2 applicator catheters could not be placed, Losses to follow-up: 6 lost to follow-up, 4 withdrew Deaths: 3
Participants	Country: Switzerland No of participants: 335 (275 after exclusions) in 4 groups, 81 IVBT, 83 IVBT + probucol, 87 probucol, 84 control Inclusion criteria: > 50 y, Rutherford > 2, > 50% stenosis femoropopliteal segment or occlusion Exclusion criteria: rest pain or CLI, non-atherosclerotic disease, vascular surgery within 6/12 months, uncontrolled hypertension, liver disease, bleeding disorders, impaired renal function, prolonged QT, life expectancy < 6 months/12, inadequate visualisation of lesion, non-compliance, residual stenosis > 50% post-PTA
Interventions	Treatment: 1) post-PTA +/- stenting, Ir-192, 14 Gy non-centred 2 mm, 1.5 cm overlap + placebo

PAB (Continued)

2) post-PTA +/- stenting, Ir-192, 14 Gy non-centred 2 mm, 1.5 cm overlap + probucol 1 g/d from 1/12 month prior to treatment

3) post-PTA + probucol, no IVBT

Control: PTA alone

All participants underwent treatment with aspirin 100 mg daily and statins (atorvastatin 40 to 80 mg/day)

Outcomes	Restenosis > 50% at 6/12 months, revascularisation
Notes	No sham treatment Treatment group received clopidogrel in addition to treatment Study stopped early due to significant effect on primary endpoint For the analysis of this review we combined the IVBT treatment groups (groups 1 and 2) and the no IVBT groups (groups 3 and 4)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	2x2 factorial design
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	participants not blinded to treatment, participants transferred to separate suite for brachytherapy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical follow-up was blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	no incomplete outcomes, all participants accounted for
Selective reporting (reporting bias)	High risk	planned secondary outcome 'change in Rutherford class' not reported
Other bias	High risk	study stopped early due to significant effect on primary endpoint treatment group received clopidogrel in addition to treatment

PARIS II

Methods	Allocation: unpublished Blinded: unpublished Exclusions: unknown (unpublished)
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PARIS II (Continued)

Losses to follow-up: unknown (unpublished)

Participants	Country: USA No of participants: 203 enrolled, data available for 40 control and 35 treatment Inclusion criteria: unpublished Exclusions criteria: unpublished
Interventions	treatment: post-PTA 14 Gy centred Ir-192, 1 cm overlap, 2 mm control: no IVBT
Outcomes	6 months and 12 months patency, ABI, re-intervention rates
Notes	It is stated that this is a randomised controlled trial. However, full data/results are not published and results were partially presented at the 2003 Annual Transcatheter Cardiovascular Therapeutics meeting. The author (R Waksman) did not respond to email requests for further information. Methodology described in PARIS I

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	unpublished
Allocation concealment (selection bias)	Unclear risk	unpublished
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	unpublished
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	unpublished
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	unpublished
Selective reporting (reporting bias)	Unclear risk	unpublished
Other bias	Unclear risk	preliminary results of 75 participants out of total of 203 participants reported in 2003 meeting of the Annual Transcatheter Cardiovascular Therapeutics meeting. No other publication of this study available. Trialists were contacted but did not respond

Swiss

Methods	Allocation: not stated Blinded: no
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Intravascular brachytherapy for peripheral vascular disease (Review)

Swiss (Continued)

Exclusions: not stated (7 crossed over to control group following inadequate EVBT)

Losses to follow-up: none

Deaths: 3 (2 cardiac, 1 accident)

Participants	Country: Switzerland No of participants: 100, 51 treatment, 49 control Inclusion criteria: > 50% de novo or restenosis post-PTA in SFA, IC or CLI, > 50 y, informed consent Exclusion criteria: acute/subacute occlusion, non-atherosclerotic disease, vascular surgery within 3 months life expectancy < 6 months, inadequate visualisation of lesion on duplex
Interventions	treatment: post-PTA either Ir-192 12 Gy or 14 Gy non-centred Control: PTA alone
Outcomes	ABI at 60 months, clinical success and restenosis > 50% at 12 months, 24 months and 36 months
Notes	No sham treatment ITT analysis when treatment failed Participants were not included in the ABI and PVR analysis if they received additional interventions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	no sham treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	seven out of 51 failed brachytherapy procedures were included with the controls in the per protocol analysis. The number of controls increased from 49 to 56
Selective reporting (reporting bias)	Low risk	all outcomes reported
Other bias	High risk	per protocol analysis reported rather than ITT analysis resulting in 7 participants crossing from brachytherapy to control group

VARA

Methods	Allocation: computer generated from trial office with stratification for: 1) stenosis or occlusion 2) length of lesion 3) hospital randomised prior to PTA not after it Blinded: none Exclusions: 17 excluded after PTA, 2 withdrew consent, 2 treatment failure Losses to follow-up: 2 lost to follow-up (including one with treatment failure), 3 cases had clinical data only, no duplex survey (including 1 withdrew consent) Deaths: 2
Participants	Country: Netherlands No of participants: 77 randomised, 60 (33 C, 27 T) met the inclusion criteria after PTA Inclusion criteria: IC or non-acute CLI , femoropopliteal lesion < 10 cm, age 40 - 85 years, ref diameter of segment 4 to 8 mm, no significant haemodynamic iliac stenosis, written informed consent Exclusion criteria: unsuccessful revascularisation
Interventions	Treatment: PTA + Ir-192 14 Gy non-centred, 2 mm, 1 cm overlap Control: PTA alone
Outcomes	50% or more restenosis on duplex after 12 months Clinical patency by Rutherford class Mandatory revascularisation or amputation
Notes	No sham treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer generated from trial office with stratification
Allocation concealment (selection bias)	Low risk	computer generated from trial office with stratification
Blinding of participants and personnel (performance bias) All outcomes	High risk	no sham treatment in control group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not reported
Incomplete outcome data (attrition bias)	Low risk	consort diagram presented, all participants accounted for

VARA (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	all planned outcomes reported
Other bias	High risk	inadequate number to power study according to trial report

Vienna 2

Methods	<p>Adaptive randomisation, stratified for:</p> <ol style="list-style-type: none"> (1) de novo > 5 cm versus recurrent (any length) (2) stenosis versus occlusion (3) claudication versus critical limb ischaemia <p>Blinding: none</p> <p>Exclusions post-randomisation: 1 refused IVBT post-randomisation, 3 recurrences within 24 hours</p> <p>Losses to follow-up: 5 participants, reasons not described (1 control, 4 treatment, included 1 death)</p> <p>Deaths: 17</p>
Participants	<p>Country: Austria.</p> <p>117 consecutive participants (4 excluded post-randomisation)</p> <p>Mean age: 71 (43 - 89); 63 male, 50 female</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> (1) age > 40 yrs (2) claudication > 3 months or critical limb ischaemia (3) de novo stenosis > 5 cm (4) restenosis after former PTA, any length <p>Exclusion criteria: not reported</p>
Interventions	<p>Treatment: PTA + IVBT, aspirin 100 mg/day from 2 weeks prior to procedure, 5000 IU heparin peri- and 1000IU/hour heparin for 24 hours post-procedure</p> <p>Control: no IVBT</p> <p>Duration: 24 months</p>
Outcomes	Restenosis/occlusion rates at 6 months; re-intervention

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	adaptive randomisation
Allocation concealment (selection bias)	Low risk	adaptive randomisation
Blinding of participants and personnel (performance bias)	High risk	no sham treatment for control group

Vienna 2 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	team analysing follow-up imaging and haemodynamic outcomes were blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	all participants accounted for
Selective reporting (reporting bias)	Low risk	all outcomes have been reported
Other bias	Low risk	no indication of other bias

Vienna 3

Methods	Allocation: computer generated adaptive randomisation with stratification: 1) de novo versus recurrent 2) stenosis versus occlusion 3) claudication versus critical ischaemia 4) hospital of recruitment Blinding: double Exclusions: 10 residual stenosis post-PTA, 9 recurrences within one month Losses to follow-up: 19 Deaths: 1
Participants	Country: Austria No of participants: 134 (96 after exclusions), 67 (46) control, 67 (50) treatment Inclusion criteria: > 45 years, Rutherford >= 2 or CLI > 3 months, de novo or recurrent lesion in femoropopliteal Exclusion criteria: former irradiation to same site, thrombolysis, life expectancy < 12 months, stent insertion or crossover approach
Interventions	Treatment: post-PTA Ir-192 18 Gy centred 2 mm, 1 cm overlap Control: PTA alone
Outcomes	patency/restenosis at 12 months, revascularisation, ABI
Notes	Used sham treatment Further info on inflammatory response reported in Schillinger 2004
Risk of bias	
Bias	Authors' judgement Support for judgement

Vienna 3 (Continued)

Random sequence generation (selection bias)	Low risk	computer generated adaptive randomisation with stratification
Allocation concealment (selection bias)	Low risk	computer generated adaptive randomisation with stratification
Blinding of participants and personnel (performance bias) All outcomes	Low risk	sham treatment for participants in control group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	follow-up was performed by clinicians blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	all participants accounted for
Selective reporting (reporting bias)	Low risk	all pre-planned outcomes reported
Other bias	Low risk	no indication of other bias

Vienna 5

Methods	Allocation: computer aided adaptive randomisation Blinded: double Exclusions: 6: 2 refused post-consent, 4 due to residual stenosis > 30% post-stenting Losses to follow up: 1 unavailable for 12 month follow-up assessment Deaths: 1 by 12 month follow-up
Participants	Country: Austria No of participants: 94 (88 post-exclusion), 46 control, 42 treatment Inclusion criteria: > 50 years, Rutherford > 2 or CLI for > 3 months, adequate aortoiliac inflow, distal SFA lesion > 10 cm from origin, inadequate angiographic result with PTA alone (residual stenosis > 30% post-PTA) Exclusion criteria: withdrawn from study, insufficient result (> 30% residual stenosis) after stent implantation
Interventions	Treatment: PTA + insertion Wallstent or nitinol stent(s) + Ir-192 14 Gy centred 2 mm, 1 cm overlap Control: PTA + insertion Wallstent or nitinol stent(s)
Outcomes	ABI, treadmill and PSV at 6 months and 12 months, restenosis/patency and re-intervention rates at 6 months and 12 months
Notes	Sham IVBT done Further info on inflammatory response reported in Schillinger 2004

Vienna 5 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer aided adaptive randomisation
Allocation concealment (selection bias)	Low risk	computer aided adaptive randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	sham treatment in control group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	follow-up performed by team blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	all participants accounted for but not clearly described time points of missing angiogram data
Selective reporting (reporting bias)	Low risk	all outcomes reported
Other bias	Low risk	no indication of other bias

ABI: ankle brachial index

CLI: critical limb ischaemia

IC: intermittent claudication

ITT: intention to treat

IVBT: intravascular brachytherapy

PSV: peak systolic velocity

PTA: percutaneous transluminal angioplasty

PVR: pulse velocity rate

SFA: superficial femoral artery

vs: versus

y: year

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Boselli 2002	Non-randomised feasibility study, 45 participants, femoropopliteal stenoses, occlusions or recurrent stenoses, treated with PTA +/- stenting and 14 Gy Ir-192
Bottcher 1994	Non-randomised study, 13 participants SFA restenosis, PTA then stented then IVBT
Kruger 2002	Non-randomised feasibility study (German)
Liermann 1998	Non-randomised study, 40 participants, restenosed stents treated with IVBT
LIMBER	Trial stopped and results not published
MOBILE	Trial stopped and results not published

Intravascular brachytherapy for peripheral vascular disease (Review)

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Study	Reason for exclusion
PARIS I	Non-randomised feasibility study, 40 participants, 5 - 15cm SFA lesions, PTA then IVBT
Pichler 1999	Non-randomised feasibility study, 24 participants, > 5 cm femoropopliteal stenosis or occlusion or recurrent lesion, PTA +/- stenting and 14 Gy Ir-192
Pokrajac 2009	A non-randomised study of 28 participants, restenosis of SFA using strontium-90 beta source (14 Gy), two participants stented
Schopohl 1996	Non-randomised feasibility study, 28 participants, restenosis or reocclusions of femoropopliteal treated with PTA + stenting + 12 Gy Ir-192
Vienna 1	Non-randomised study, 10 participants, > 5 cm femoropopliteal lesion, PTA then IVBT
Vienna 4	Non-randomised study, 33 participants, 4 - 30 cm femoropopliteal lesions, PTA then stent then IVBT
Walichiewicz 2002	Non-randomised feasibility study, 20 participants, SFA stenoses or occlusions treated with PTA +/- stenting and 15 Gy Ir-192
Walichiewicz 2003	Non-randomised trial, 14 participants, iridium-192 source (15 Gy) with PARIS centring catheter; 7 participants received stents with 16% restenosis at six months
Werner 2012	Non-randomised trial, all participants received angioplasty followed by endovascular brachytherapy

IVBT: intravascular brachytherapy

PTA: percutaneous transluminal angioplasty

SFA: superficial femoral artery

DATA AND ANALYSES

Comparison 1. Brachytherapy versus no brachytherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical patency	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 6 months	1	88	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.31, 1.99]
1.2 12 months	1	88	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [0.58, 3.20]
2 Cumulative patency	2	222	Odds Ratio (M-H, Fixed, 95% CI)	2.36 [1.36, 4.10]
2.1 24 months	2	222	Odds Ratio (M-H, Fixed, 95% CI)	2.36 [1.36, 4.10]
3 Restenosis	7		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 6 months	5	562	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.11, 0.66]
3.2 12 months	5	375	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.28, 0.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 24 months	2	164	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.21, 0.78]
3.4 60 months	1	102	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.42, 2.39]
4 Need for re-intervention at 6 months	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Target lesion revascularisation	3	220	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.27, 0.97]
4.2 Target vessel revascularisation	3	393	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.30, 1.01]
5 Need for re-intervention at 12 months	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Target lesion revascularisation	3	215	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.19, 1.02]
5.2 Target vessel revascularisation	2	164	Odds Ratio (M-H, Fixed, 95% CI)	5.43 [0.61, 48.25]
5.3 Need for re-intervention	2	234	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.12, 1.12]
6 Need for re-intervention at 24 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Target lesion revascularisation	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Target vessel revascularisation	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Need for re-intervention at 60 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Target lesion revascularisation	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Target vessel revascularisation	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Occlusion	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 No time	1	30	Odds Ratio (M-H, Fixed, 95% CI)	3.21 [0.12, 85.20]
8.2 Less than 1 month	3	275	Odds Ratio (M-H, Fixed, 95% CI)	2.18 [0.76, 6.32]
8.3 More than 3 months	2	363	Odds Ratio (M-H, Fixed, 95% CI)	11.46 [1.44, 90.96]
8.4 12 months	1	100	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.13, 5.27]
9 Limb loss	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Cardiovascular death	3	365	Odds Ratio (M-H, Fixed, 95% CI)	2.69 [0.39, 18.40]
11 Death from all causes	7	789	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.42, 1.87]
11.1 no time	1	275	Odds Ratio (M-H, Fixed, 95% CI)	2.18 [0.20, 24.38]
11.2 6 months	1	134	Odds Ratio (M-H, Fixed, 95% CI)	3.05 [0.12, 76.10]
11.3 9 months	1	100	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.04, 5.36]
11.4 12 months	2	148	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.09, 5.31]
11.5 15 months	1	30	Odds Ratio (M-H, Fixed, 95% CI)	3.21 [0.12, 85.20]
11.6 60 months	1	102	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.23, 1.87]
12 Complications	6	518	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [0.90, 4.52]
13 ABI	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Pain free walking distance	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 1 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Maximum walking distance	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 1 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Quality of life (scores)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 1 month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 De novo restenosis	2	158	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.20, 0.78]
17.1 6 months	2	158	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.20, 0.78]
18 Binary restenosis	2	209	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.20, 1.67]
19 Peak velocity ratio	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 Immediately after procedure	2	130	Mean Difference (IV, Random, 95% CI)	0.12 [-0.06, 0.29]
19.2 24 hours	1	275	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.21, 0.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.3 6 months	2	375	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.93, -0.07]
19.4 12 months	1	100	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.40, 0.08]
20 Lumen	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 24 hours	2	44	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-3.52, 1.32]
20.2 6 months	1	24	Mean Difference (IV, Fixed, 95% CI)	6.50 [0.05, 12.95]
20.3 24 months	1	20	Mean Difference (IV, Fixed, 95% CI)	7.30 [4.67, 9.93]
21 Vessel wall area	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 24 hours	2	44	Mean Difference (IV, Random, 95% CI)	-4.10 [-12.09, 3.90]
21.2 6 months	1	24	Mean Difference (IV, Random, 95% CI)	6.40 [-4.16, 16.96]
21.3 24 months	1	20	Mean Difference (IV, Random, 95% CI)	2.70 [-3.89, 9.29]
22 Plaque area	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
22.1 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.2 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 1 Clinical patency.

Analysis 1.2. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 2 Cumulative patency.

Analysis 1.3. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 3 Restenosis.

Analysis 1.4. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 4 Need for re-intervention at 6 months.

Analysis 1.5. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 5 Need for re-intervention at 12 months.

Analysis 1.6. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 6 Need for re-intervention at 24 months.

Analysis 1.7. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 7 Need for re-intervention at 60 months.

Analysis 1.8. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 8 Occlusion.

Analysis 1.9. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 9 Limb loss.

Analysis 1.10. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 10 Cardiovascular death.

Analysis 1.11. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 11 Death from all causes.

Analysis 1.12. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 12 Complications.

Analysis 1.13. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 13 ABI.

Analysis 1.14. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 14 Pain free walking distance.

Analysis 1.15. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 15 Maximum walking distance.

Analysis 1.16. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 16 Quality of life (scores).

Analysis 1.17. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 17 De novo restenosis.

Analysis 1.18. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 18 Binary restenosis.

Analysis 1.19. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 19 Peak velocity ratio.

Analysis 1.20. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 20 Lumen.

Analysis 1.21. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 21 Vessel wall area.

Analysis 1.22. Comparison 1 Brachytherapy versus no brachytherapy, Outcome 22 Plaque area.

ADDITIONAL TABLES

Table 1. Included studies

Study	Number of participants	Exclusions/ Lost to follow-up	Complica- tions (documented)	Deaths	Age (y)	Male (n)	Mean lesion length - control	Mean lesion length - treated
Krueger 2004	30	1	1	1	61 (51 - 73)	23	2.8	3.2
PAB	335	72	-	3	72 ± 9	206	4.8	5.6
PARIS II	203	unpublished	unpublished	unpub- lished	unpublished	unpub- lished	unpublished	unpublished
Swiss	100	0	0	3	71 (45 - 84)	58	4.5	4.8
VARA	77	17 + 7	8	2	64 (43 - 85)	40	3.2	3.9
Vienna 2	117	8	10	17	71 (43 - 89)	63	8	8.5
Vienna 3	134	38	19	1	-	84	10.3	9.1
Vienna 5	94	7	9	1	70 (50 - 89)	58	10.5	12.1

y: years
n: number

Table 2. Summary of patency

Clinical patency	N	OR (95% CI)
6 months	88	0.79 (0.31 to 1.99)
12 months	88	1.36 (0.58 to 3.20)
Cumulative patency		
24 months	222	2.36 (1.36 to 4.10)

CI: confidence interval

N: number

OR: odds ratio

Table 3. Restenosis

Restenosis or reocclusions	N	OR (95% CI)
6 months	562	0.27 (0.11 to 0.66)
12 months	375	0.44 (0.28 to 0.68)
24 months	164	0.41 (0.21 to 0.78)
60 months	102	1.00 (0.42 to 2.39)

CI: confidence interval

N: number

OR: odds ratio

Table 4. Target lesion revascularisation

Target lesion revascularisation	N	OR (95% CI)
6 months	220	0.51 (0.27 to 0.97)
12 months	215	0.44 (0.19 to 1.02)
24 months	30	0.46 (0.04 to 5.75)
60 months	102	0.92 (0.41 to 2.06)

CI: confidence interval

N: number

OR: odds ratio

Table 5. Target vessel revascularisation

Target vessel revascularisation	N	OR (95% CI)
6 months	393	0.55 (0.30 to 1.01)

Table 5. Target vessel revascularisation *(Continued)*

12 months	164	5.43 (0.61 to 48.25)
24 months	30	2.36 (0.36 to 15.45)
60 months	102	0.91 (0.38 to 2.15)

CI: confidence interval

N: number

OR: odds ratio

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Arteriosclerosis] this term only	894
#2	MeSH descriptor: [Arteriolosclerosis] this term only	0
#3	MeSH descriptor: [Arteriosclerosis Obliterans] this term only	72
#4	MeSH descriptor: [Atherosclerosis] this term only	417
#5	MeSH descriptor: [Arterial Occlusive Diseases] this term only	771
#6	MeSH descriptor: [Intermittent Claudication] this term only	724
#7	MeSH descriptor: [Ischemia] this term only	767
#8	MeSH descriptor: [Peripheral Vascular Diseases] this term only	557
#9	atherosclero* or arteriosclero* or PVD or PAOD or PAD	17617
#10	(arter* or vascular or vein* or veno* or peripher*) near (*occlus* or steno* or obstruct* or lesio* or block*)	7499
#11	peripheral near/3 dis*	3355
#12	(claudic* or hinken*)	1471
#13	isch* or CLI	17274
#14	dysvascular*	27
#15	(leg or limb) near/4 (obstruct* or occlus* or steno*)	198
#16	#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	39121
#17	MeSH descriptor: [Radiotherapy] this term only	1099
#18	MeSH descriptor: [Brachytherapy] this term only	599
#19	(brachitherap* or brachytherap*)	957

(Continued)

#20	((radia* or gamma or beta) near 4 (treat* or therap*))	1864
#21	(irradiation)	4637
#22	(IVBT)	5
#23	#17 or #18 or #19 or #20 or #21 or #22	7793
#24	#16 and #23 in Trials	259

WHAT'S NEW

Date	Event	Description
6 December 2019	Review declared as stable	This Cochrane review has been made stable and will only be updated if new studies are identified

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 4, 2002

Date	Event	Description
15 November 2019	Amended	One conference abstract reassigned from Vienna 3 to Vienna 2. Flow diagram updated accordingly. No other changes required as information from abstract not used in review.
27 August 2013	New citation required but conclusions have not changed	Review updated, searches re-run, seven additional included studies and 10 additional excluded studies added. Risk of bias tables completed for all included studies. Two new authors have joined the review team.
27 August 2013	New search has been performed	Review updated, searches re-run, seven additional included studies and 10 additional excluded studies added.
21 July 2010	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Conceiving the review: GS
- Designing the review: GS, MH
- Co-ordinating the review: AA
- Designing electronic search strategy: Cochrane PVD Group editorial base
- Screening search results: GS, MH
- Obtaining copies of trials: GS, MH
- Appraising quality of papers: MH
- Abstracting data from papers: AA, MS
- Data management for the review: AA, MS

- Entering data into RevMan: AA
- Analysis of data: AA
- Interpretation of data: AA, MS, GS
- Writing the review: AA, MS, GS, MH
- Draft the final review: AA, MS, GS
- Guarantor for the review: GS

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The primary and secondary outcomes have been reordered to reflect the clinical importance of the outcomes and current practice in PAD. Two outcomes listed in previous versions of this review have been removed (grading of patency and time to restenosis) because they were deemed no longer relevant, the outcome bleeding has been added.

The assessment of the methodological quality of the included studies was changed to the updated Cochrane Collaboration's recommended 'Risk of bias' tool ([Higgins 2011](#)).

NOTES

This review has been marked stable and will only be updated if new studies are identified.

INDEX TERMS

Medical Subject Headings (MeSH)

Angioplasty; Brachytherapy [*methods]; Endovascular Procedures [*methods]; Femoral Artery; Peripheral Vascular Diseases [*radiotherapy] [therapy]; Popliteal Artery; Quality of Life; Radiotherapy, Adjuvant; Randomized Controlled Trials as Topic; Stents; Vascular Patency

MeSH check words

Humans