

# Subintimal angioplasty in critical limb ischaemia: a literature review

## Abstract

The aim of this review was to determine accurate estimates of the success rate of subintimal angioplasty and to compare those estimates with surgery in terms of ability to recanalise occluded vessels, patency over time and limb salvage rates.

Each study included was analysed for the three primary outcome measures of technical success, 12-month primary patency, and 12-month limb salvage rates. The results of each outcome are presented as a percentage.

Pooled estimates for technical success, primary patency at 12 months and limb salvage at 12 months were 87.7% (95% confidence interval: 86.8%-88.6%, 1,484 limbs), 55.8% (95% confidence interval: 51.9%-60%, 584 limbs), and 91.1% (95% confidence interval: 89.1%-93.1%, 762 limbs), respectively.

This study demonstrates that the outcomes for subintimal angioplasty are good and that it should be considered as an alternative to surgical bypass in the treatment of critical limb ischaemia.

**Keywords:** Subintimal, angioplasty, percutaneous intentional extraluminal revascularisation, critical limb ischaemia, peripheral arterial disease.

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## Introduction

Critical limb ischaemia (CLI) is defined as 'ischaemic rest pain' or Grade II Category IV on the Rutherford-Baker classification of peripheral arterial disease.<sup>1</sup> Rest pain is defined as a severe unremitting pain in the foot, which is aggravated by lying supine. It is partially relieved by dangling the foot over the edge of the bed or standing on a cold floor. Patients may also have gangrene or ulceration of the tissue.<sup>2</sup> The definition of CLI is summarised in **Table 1**.

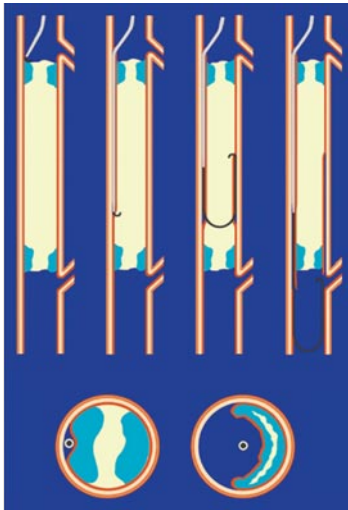
Studies have shown that CLI is associated with significant coronary artery disease in 75% of cases and 20% mortality in the first year post diagnosis. If their affected limb cannot be revascularised, 25% of these patients require a major amputation within one year.<sup>3</sup> In addition to aggressive risk factor modification, most require surgical bypass to ensure

limb vascular patency. Infra-inguinal bypass surgery for occlusive peripheral vascular disease is associated with high hospital costs, significant morbidity and mortality rates, and poor long-term outcomes in terms of both limb salvage and mortality.<sup>4</sup>

**Table 1: Definition of CLI.**

	Rest pain	Ankle blood pressure	Limb salvage without revascularisation
Subcritical limb ischaemia	Yes	>40mmHg	27%
Critical limb ischaemia	Yes	<40mmHg	5%

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### Technique of subintimal angioplasty

Following arterial puncture, an angled-tip catheter (e.g., Kumpe) is introduced proximally to the occlusion. 5,000IU of heparin is then administered. An angled guide wire (e.g., Terumo-0.035in) is then introduced, and it is encouraged to form a loop when the tip abuts the occlusion. During dissection, the loop will also appear to be slightly wider than the native vessel lumen diameter. If the wire is endoluminal the loop will appear narrow. Without the loop, the guide wire would not create a sufficiently wide subintimal channel and would also tend to go down collateral vessels or cause perforation. The loop also allows the stiffer part of the guide wire to be used to continue the dissection. While maintaining the loop in the guide wire, the catheter is then advanced behind it. The guide wire will naturally tend to re-enter the true lumen when it again encounters normal patent vessel. Successful re-entry into the lumen is usually heralded by a loss of resistance to the wire. This can be confirmed with injection of a small volume of contrast. There are now devices available to aid re-entry in difficult cases such as the Outback catheter and intravascular ultrasound (IVUS) guided Pioneer catheter. The whole length of the subintimal channel then undergoes angioplasty with rapid inflations of a long balloon (approximately 12-15cm) (Figure 2).

FIGURE 1 (from left): The wire beginning the dissection with the catheter; the dissection being continued with the looped wire; and, the wire breaking back into the lumen prior to angioplasty. (Courtesy: GE Healthcare.)

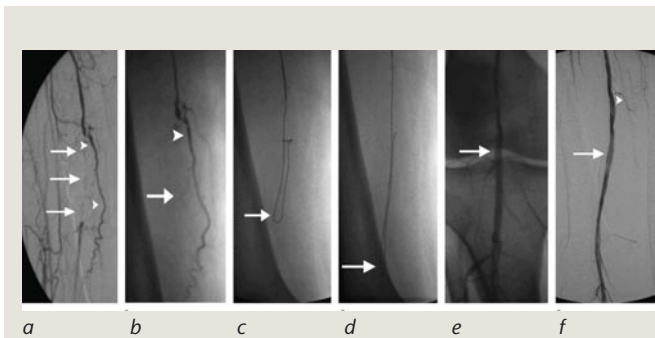


FIGURE 2: (a,b) Images from a 79-year-old man who presented with ulceration and rest pain of his right foot demonstrate a long right superficial femoral arterial occlusion (arrow) with a prominent collateral vessel (arrowhead) at the origin of the occlusion. (c) The lesion was crossed subintimally; note the wide diameter of the guide wire loop (arrow) as it travels within the subintimal space. (d) The diameter of the guide wire loop (arrow) reduces as it re-enters the patent lumen below the level of the occlusion. (e) Luminal re-entry is confirmed with contrast agent injection (arrow). (f) After successful balloon dilation, patency is restored (arrow), with preservation of the collateral vessel (arrowhead).<sup>11</sup>

Unfortunately, there are few alternatives other than major lower limb amputation in those patients with long arterial occlusions who are unsuitable for transluminal angioplasty.

Subintimal angioplasty (SIA) or percutaneous intentional extraluminal revascularisation involves intentional subintimal dissection with neolumen generation in occluded lower-limb arteries.<sup>11</sup> Initially applied to the femoro-popliteal segments, this technique has been extended to the crural and iliac vessels.<sup>5,6</sup> It was first reported by Bolia *et al.* in 1989, who inadvertently created a subintimal channel during the endovascular treatment of a long popliteal occlusion.<sup>7</sup> This was recognised and a balloon angioplasty was performed, with a subsequent patency duration greater than nine years<sup>8</sup> (Figure 1). According to the authors of this first report, vascular interventional radiology has been polarised into those who can reproduce these results and are proponents of SIA, and those who cannot.<sup>9</sup> The published literature reflects these polarised viewpoints, with some authors supporting the technique and others dismissing it. The majority of these reports feature small series of patients and, to date, there remains little long-term follow-up data. For SIA to be a viable alternative to surgical bypass, long-term patency and limb salvage rates need to be evaluated and compared with those associated with surgery. Such is the aim of this literature review.

## Methods

### Literature search

A systematic search of the literature was performed with the assistance of a clinical librarian in the medical databases Embase and Pubmed. The timeframe for the searches was January 1980 to March 2010; the period prior to the first description of SIA was included to ensure that no earlier references existed. The keywords “subintimal angioplasty”, “percutaneous intentional extraluminal revascularisation”, and “peripheral arterial disease” were used, along with synonyms of them.

### Study selection

Studies were included in the analysis if they provided details of patients with CLI undergoing treatment for a femoral, popliteal or crural occlusion by SIA and their outcomes (immediate technical success, primary patency and limb salvage). Technical success was defined as good antegrade flow at completion of the procedure. Articles were rejected if they contained no primary data, contained data previously or subsequently reported in other articles, and were reports of small case series (fewer than 10 patients) or highly selected subgroups of patients.

Table 2: Summary data for all 11 studies.

First author	Mid-date of study	R/P	Study type	Selection criteria	Disease severity	Lesion location	No. SIA	Technical success		12-month follow-up data provided or extractable		Maximum length of follow-up data provided (months)		Stents used?
								n	%	Primary patency	Limb salvage	Primary patency	Limb salvage	
Akesson <sup>12</sup>	01/07/2000	R	Case note review	Unless very fit for surgery	CLI	Infrainguinal	193	148	77	No	No	36	36	Yes
Desgrange <sup>13</sup>	19/01/2001	R	Case note review	Not stated	Claudication and CLI	Infrainguinal	100	88	88	No	No	24	24	No
Hynes <sup>14</sup>	01/08/2002	R	Case note/ database review	Not stated	CLI	Infrainguinal	158	158	100	No	Yes		12	No
Laxdal, 2003 <sup>15</sup>	01/04/2001	P	Registry review	Not stated	Claudication and CLI	Femoro-popliteal	104	88	85	No	No		12	No
Laxdal, 2004 <sup>16</sup>	03/07/1999	R	Case note review	Not stated	Claudication and CLI	Femoro-popliteal	124	112	90	No	Yes	18	12	No
Lazaris <sup>17</sup>	31/08/2001	R	Case note review	Diabetics with CLI	CLI	Infrainguinal	112	100	89	No	Yes		36	No
London <sup>18</sup>	16/08/1989	R	Case note review	All patients	Claudication and CLI	Infrainguinal	200	159	80	Yes	No			No
Scott <sup>19</sup>	01/06/2003	R	Case note review	Not stated	Claudication and CLI	Femoro-popliteal	105	91	87	Yes	No	36	6	Yes
Tartari <sup>20</sup>	15/04/2004	R	Case note review	All patients	CLI	Infrainguinal	109	92	84	No	Yes		9	Yes
Tisi <sup>21</sup>	02/07/1999	R	Case note review	All patients	Claudication and CLI	Popliteo-tibial	158	135	85	Yes	Yes		24	No
Trocciola <sup>22</sup>	02/03/2003	P	Registry review	All patients	Claudication and CLI	Femoro-popliteal	121	121	100	Yes	Yes	12	12	Yes

R = Retrospective; P = Prospective

All blank fields indicate that the required information was unavailable.

## Data extraction

The three principle outcome measures assessed in this study were immediate technical success rate of SIA, 12-month primary patency rate, and 12-month limb salvage rate. For each study, the total number of limbs treated and outcomes were recorded on a per-limb basis.

The location of the lesions treated in each study was also recorded. For both primary patency and limb salvage rates, data were recorded on an intention-to-treat basis with the numerator being the number of limbs saved or patent at each time point and the denominator being the number of limbs that underwent attempted SIA at the outset of the study. As a temporal reference point for each study the mid-date of the study was calculated (the date mid-way from the reported start of the study to the end of the study). Three variables that were of interest were extracted from each study, for the purposes of determining whether these had any effect on patient outcome: the degree of limb ischaemia in patients undergoing SIA; the use of adjunctive stents; and, lesion location/patient selection criteria for SIA. Data pertaining to study design (retrospective or prospective, randomisation, size) were also determined.

## Statistical methods

Each study included was analysed for the three primary outcome measures of technical success, 12-month primary patency and 12-month limb salvage rates. Results of each outcome are presented as a percentage. Tables were constructed to demonstrate these results. The confidence intervals around a mean result were calculated using online statistical testing.<sup>10</sup>

## Results

### Literature search

A total of 190 articles were identified by the literature search, of which 155 were excluded after screening of title and abstract. The most frequent reasons for exclusion were study design, technique (other than SIA), and location of lesion (iliac artery or

**Table 3: Percentage technical success accompanied by 95% confidence interval of all studies reporting patients with CLI. The location of lesions in all these studies is infrainguinal.**



extending from the femoral into the iliac artery). In view of the general aim of this literature review, the 11 largest studies were included.<sup>12-22</sup>

A larger sample size ensures a more accurate estimated confidence interval.

No randomised controlled trials were found. All of the studies were retrospective (n=9) or prospective (n=2) patient series.

## Study characteristics

The 11 studies included in the analysis gave details of 1,484 limbs treated by SIA over a period of 14.67 years (study mid-dates August 1989 to May 2004) and the characteristics of these studies are shown in **Table 2**.

## Analysis

Technical success rates are shown in **Tables 3** and **4**. In patients with critical limb ischaemia, technical success rates show a large variation. The mean estimate for technical success rates in these studies was 87.7% (95% confidence interval: 86.8%-88.6%). The definition of patency varied considerably between studies. Primary patency was defined differently among studies as either patency of segment without intervention or absence of occlusion and absence of >50% or <30% stenosis in the treated segment. The mean estimate for the 12-month primary patency rate (four studies, 584 limbs) was 55.8% (95% confidence interval: 51.9%-60%).<sup>18,19,21,22</sup> The mean 12-month limb salvage for the

**Table 4: Percentage technical success accompanied by 95% confidence interval of all studies reporting patients with mixed claudication and CLI, subdivided according to location of lesion; (a) femoropopliteal, (b) popliteotibial and (c) infrainguinal vessels.**

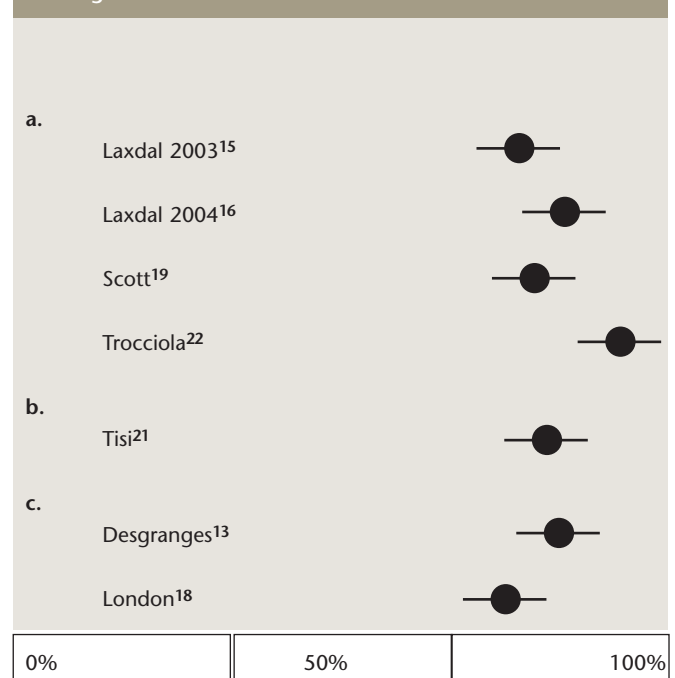


Table 5: Outcomes of studies reporting about patients with CLI (+/- claudication), subdivided according to location of lesion (femoropopliteal, popliteotibial or infrainguinal).

Study	Technical success (95% CI)	12-month primary patency (95% CI)	12-month limb salvage (95% CI)
<b>Lesion (mostly) in femoropopliteal artery</b>			
Laxdal 2003 <sup>15</sup>	84.6% (76.4%-90.4%)		90% (83.4%-94.2%)
Laxdal 2004 <sup>16</sup>	90.3% (83.7%-94.4%)		
Scott <sup>19</sup>	86.7% (78.7%-91.9%)	62% (52.4%-70.8%)	
Trocciola <sup>22</sup>	99.2% (94.4%-99.9%)	79.0% (70.8%-85.4%)	95% (89.4%-97.7%)
<b>Lesion (mostly) in popliteotibial artery</b>			
Tisi <sup>21</sup>	85.4% (79%-90.1%)	27% (20.6%-34.6%)	89% (83.1%-93%)
<b>Infrainguinal lesions</b>			
Akesson <sup>12</sup>	76.7% (70.2%-82.1%)		
Desgranges <sup>13</sup>	88% (80.0%-91.3%)		
Hynes <sup>14</sup>	99.5% (95.0%-99.9%)		97.8% (93.9%-99.2%)
Lazaris <sup>17</sup>	89.3% (82.1%-93.8%)		88% (80.6%-92.8%)
London <sup>18</sup>	79.5% (73.3%-84.5%)	55.9% (49.0%-62.7%)	
Tartari <sup>20</sup>	84.4% (76.4%-90.1%)		87% (79.3%-92.1%)

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six studies that reported this outcome (762 limbs) was 91.1% (95% confidence interval: 89.1%-93.1%).<sup>14,15,17,20-22</sup> The results of all outcomes are highlighted in **Table 5**.

### Discussion

This review demonstrates that the overall technical success rate for SIA in the published literature is acceptable (approximately 88%). While actual primary patency over time is approximately 56% and does not match this high initial success rate, long-term limb salvage is excellent at approximately 91%. This figure remains constant irrespective of the degree of ischaemia in patient groups undergoing SIA, the use of adjunctive stenting or the selection criteria used to identify patients for SIA.

There appears to have been no change in technical success, limb salvage or primary patency rates in the time period described, suggesting that the perceived learning curve for the technique is relatively steep in those centres that choose to pursue this method of angioplasty and have published their results.

The limitations of this review principally lie in the quality of the studies included in the analysis.

In the vast majority, the criteria used to select patients for SIA were not given. In addition, there was a lack of conformity to reporting data according to set standards, such as the Rutherford-Baker classification. This is probably because many of these criteria, such as degree of ischaemia, are difficult to define accurately.

As already indicated, information on additional variables was sought, namely the degree of limb ischaemia, the use of adjunctive stents and lesion location/patient selection criteria. No major influence on outcomes was seen. However, few of the studies used rigid definitions for any of these sub-classifications, except for lesion location, and in this case many authors reported on "infringuinal" groups of lesions. This lack of structured classification may have led to the fact that little difference is seen in the outcomes for each subgroup.

In this study, only primary patency data was extracted from the studies in the analysis.

While data on primary-assisted and, indeed, secondary patency would also have been useful to study, unfortunately few studies reported these outcomes. Specifically, two studies quoted primary-assisted patency and no studies quoted secondary patency.<sup>13,15</sup> Four studies quoted primary patency of the vessel, and all four studies did so at 12 months post procedure. Therefore, primary patency was deemed the most useful data to extract.

The BASIL trial is the only multicentre randomised controlled trial to have compared the clinical and cost-effectiveness of bypass surgery-first and conventional balloon angioplasty-first revascularisation strategies for infringuinal severe limb ischaemia.<sup>23</sup> Despite being associated with costs equivalent to about one-third higher than those with an angioplasty-first strategy, surgical bypass has been promoted as superior in some interpretations of the BASIL trial. A review by Beard *et al.*

concluded that the long-term results of the trial favoured surgery over angioplasty if there was a good vein and the patient was fit.<sup>28</sup>

However, the results for SIA demonstrated in this study are encouraging. In published series detailing outcomes following lower limb bypass surgery, primary patency rates are greater than those observed in this analysis. Particularly, the primary patency rates were 83% for an above-knee femoropopliteal bypass with a saphenous vein graft, 78% for a polytetrafluoroethylene (PTFE) graft and 82% even for a popliteal-to-distal vein bypass after one year.<sup>24,25</sup> The comparatively lower patency rates for SIA must be balanced against the fact that this technique is minimally invasive and requires only local anaesthesia, which are advantages with respect to surgical revascularisation procedures. In addition, failed SIA does not preclude the opportunity for such procedures.<sup>26</sup>

The source publications used in this study were, in the majority, retrospective case reviews. Only two were prospective studies, no randomised controlled studies have been published, and it is unlikely that any large datasets will be available in the near future.

The clearest inference that can be made from this work is that further research is required in this area if the place of SIA in modern interventional radiology is to be better defined.

As mentioned above, there are no randomised controlled trials of SIA. The reasons for this, although complex, principally lie in what technique to randomise patients against and which patients to randomise among these procedures. It is important to use standardised methods, such as the Rutherford-Baker classification, for reporting results of treatment for peripheral arterial disease and, especially, for lower-limb arterial endovascular procedures, in order to facilitate future meta-analyses.<sup>1,27</sup>

In conclusion, this literature review shows that, despite the moderate long-term patency rates of the revascularised segments, SIA can play an important role in the treatment of critical limb ischaemia. Further studies of higher methodological quality are required and should include entire cohorts of patients admitted for CLI, instead of selected series, to better appreciate this technique in relation to bypass surgery.

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