Predictors of post-operative outcomes in patients with peripheral arterial disease and critical limb ischaemia: a systematic review and meta-analysis

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SUMMARY

Background: A very small proportion (1%) of patients with peripheral artery disease (PAD) present with critical limb threatening ischaemia (CLTI) with poor prognosis. The present review showcased several pre-operative predictors and key post-operative outcomes. Identification of any modifiable predictors may impact positively on surgical outcomes.

Design: PubMed/Medline, Google scholar and Cochrane databases were searched using terms such as “peripheral arterial disease” AND “critical limb ischemia,” “post-operative outcome,” AND “predictors of post-operative outcomes”. Search was for relevant English-language articles published between January 1997 and December 2007. Selected articles were screened first by title and abstract, and selection of full articles was based on relevance using our inclusion and exclusion criteria and quality ratings performed with the MINORS score.

Results: The included studies were published between 1997 and 2007. Only six (6) articles out of a total of 2,114 were deemed suitable for analysis. Ambulatory recovery was >70% at six months, 86.7% and 70.0% at one year and five years respectively. Rate of local wound complications was between 12% and 24%. Reported limb salvage rates were >90% at six months, >70% at one year and 70.0-90.0% at five years. Primary graft patency rate at one year ranged from 63% and 76.6%. Gangrene, diabetes and impaired pre-operative ambulatory function are associated with more wound complications, low limb salvage, reduced graft patency and poor functional outcome.

Conclusion: Pre-operative ambulatory status was the most important predictor of post-operative ambulatory recovery. Diabetes mellitus was an important risk factor for prolonged wound healing, local wound complications and major amputation.

Keywords: Peripheral arterial disease, critical limb ischemia, post-operative outcomes

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INTRODUCTION

Assessment of post-operative outcomes of vascular intervention for CLTI is increasingly shifting from traditional technical outcomes such as graft patency and limb-salvage,¹ to functional outcomes such as ambulatory recovery and wound healing rates.²⁻⁶ Functional outcomes have been shown in recent reports to be better outcome measures to assess clinical success of operative interventions for CLTI. Simons et al. showed that despite adequate (>70%) graft patency and limb salvage, 10% of patients with patent grafts at 1 year still could not attain clinical success of ambulatory recovery and independent living.⁵ In a study by Taylor et al., clinical success was defined as achieving all the following criteria: graft patency to the point of wound healing; limb salvage at one year; maintenance of ambulatory status for one year; and survival at six months. Despite >70% limb salvage and graft patency at three years, only 44.4% of the patients achieved the composite endpoint of clinical success as stated above.⁶ Goshima et al showed that time to heal exceeded three months in >50% of patients and that diabetes mellitus was a risk factor for prolong wound healing.² Taylor et al. have suggested that a combination of traditional and functional outcomes is superior in the assessment of post-operative outcome post-intervention for CLTI.³

We undertook this meta-analysis in an effort to showcase—from the available literature—what specific pre-operative predictors most definitely affect both technical and functional post-operative outcomes.
METHODS

Literature search
PubMed/Medline, Google scholar and Cochrane databases were systematically searched for relevant English-language articles published between January 1997 and December 2007 using the terms “peripheral arterial disease”, “critical limb ischemia,” AND “predictors of post-operative outcome”. Selected articles were screened first by title and abstract, and selection of full-text articles was based on relevance. This study was approved by the Departmental (Surgical) Research Committee of Groote Schuur Hospital and the Human Research Ethics Committee of the University of Cape Town.

Inclusion criteria was published articles on CLTI involving patients’ risk factor profile and at least three post-operative outcome measures (technical, functional or both). Reviews, case reports, abstracts only, meta-analysis and non-English articles and duplicate articles were excluded. Primary endpoint was technical and/or functional post-operative outcomes. Secondary endpoint was predictors of post-operative outcomes.

Validity assessment
Article screening, selection and data extraction were done by two individuals independently to minimize bias. Identified relevant titles were selected as an initial step. All abstracts were read, and articles with clearly stated objectives of evaluation of predictors of post-operative outcomes of surgical treatment of CLTI were chosen. Full articles were read, and selection made based on the presence of at least three outcome measures as defined in the reporting standards of revascularization for CLTI (technical outcome measures) and/or functional outcomes or both. All related publications/electronic links of the selected articles were downloaded and the references carefully reviewed to generate any further relevant publications. The quality of the selected articles was assessed using the MINORS quality score, with a maximum score of 16 for non-comparative studies and 24 for comparative studies (Figure 1).

RESULTS

Description of studies
The literature search yielded 2,114 publications. A total of 1,147 articles were selected after excluding irrelevant articles based on the titles and abstracts.

Over a 10-year period, 821 articles were selected. Based on human subjects above the age of 19 years, 590 articles were identified. Only six publications were identified as suitable for our study with three or more post-operative outcome measures (Figure 2). The included studies were published between 1997 and 2007. MINORS scoring scale (Table 1).
The selected studies were of moderate quality using the MINORS scoring scale (Table 1).

Table 1 MINORS Score (6 Best performing Studies)

| MINORS Score                                | Study Number (see KEY) |
|---------------------------------------------|------------------------|
| A clearly stated aim                        | 1 2 3 4 5 6            |
| Inclusion of consecutive patients           | 2 2 2 2 2 2            |
| Prospective collection of data              | 2 2 2 2 2 2            |
| Endpoints appropriate to the aim of the study | 2 2 2 2 2 2        |
| Unbiased assessment of the study endpoints  | 2 2 2 2 2 2            |
| Follow-up period appropriate to the aim of the study | 1 2 2 0 2 2  |
| Loss to follow up less than 5%              | 2 0 2 0 0 0            |
| Prospective calculation of the study size   | 0 0 0 0 0 0            |
| Total                                       | 11 10 14 8 10 10       |

KEY: 1. Goshima et al, 2. Taylor et al, 3. Taylor et al 4. Abou-Zamzam et al, 5. Nicoloff et al, 6. Chung et al.

The total sample size of the six eligible studies was 2,446 (Sample size range: 112-841 patients) with a mean follow-up of 40.5 months for four studies. In the remaining two studies, the duration of follow up was not stated. All six studies reported a combination of technical and functional outcomes but at different timelines. Technical outcome measures were based on the standards for reporting by the Society for Vascular Surgery/International Society for Cardiovascular Surgery.1,7 Five of them were retrospective studies and one was a prospective study (Table 2a). The study population was grouped based on the investigated outcome measures and timelines at which the outcomes were assessed (Table 2b).

Outcome measures and predictive factors
Ambulatory recovery varied significantly, 72% to 92% at six months, 86.7% at one year, 73% at three years and
70.6% at five years. Rates of local wound complications reported were between 12% and 24%. In some studies, more than 50% of the ischemic wounds took longer than four months to heal. In one study, the wound healing rates at six months and one year were 42% and 75% respectively. Reported limb salvage rates were from 94.2% at six months to 76.5-85.0% at one year. The five years’ limb salvage rates were 72.1-91%. Primary graft patency rate at one year was between 63% and 76.6%. Major amputation rates varied widely from 3.5% at three months to 23.2% at three years. Survival at six months, one year and five years were >80%, 89% and 48% respectively.

Table 2c shows some of the reported pre-operative risk factors. Only three included studies expressed those factors as odds ratios or hazard ratios while others reported as percentage or just in narrative format. Multiple factors influenced post-operative outcomes. Tissue loss and diabetes mellitus were associated with multiple re-operations and prolong wound healing. Gangrene, Diabetes, ESRD and impaired pre-operative ambulatory function predicted low limb salvage, reduced graft patency and poor functional outcome. Pre-operative impaired ambulatory function was reported in most of the studies to be the most important predictor of sub-optimal post-operative functional outcome. A composite endpoint of limb salvage and ambulation at one year, survival at six months and graft patency up to the point of healing was achieved in only 44% of patients.

Some studies investigated predictors of post-operative outcome but the spectrum of outcome measures assessed were fewer than the minimum of 3 selected for our study and therefore were excluded. Other studies with sample population of patients who had re-intervention for failed previous vascular interventions were also excluded (Table 3).

Out of the total of six eligible studies, only five studies were used in conducting the meta-analysis. The study that was excluded from meta-analysis did not report the outcomes at the timelines of interest. There is a high level of heterogeneity in the timelines for the various outcome measures in the papers evaluated (Figure 3a, b, c, d). Multiple factors predict post-operative outcomes.

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**Table 2a** Included studies

| Study                  | n  | Type of Study | Follow up (months) | Type of operation                           |
|------------------------|----|---------------|--------------------|---------------------------------------------|
| Goshima et al 2004     | 315| Retrospective | Not reported       | Infra-inguinal bypass surgery               |
| Taylor et al 2007      | 331| Retrospective | 72                 | Infra-inguinal and supra-inguinal bypass surgery |
| Taylor et al 2006      | 841| Prospective   | 60                 | Open revascularization, Endovascular interventional and hybrid procedures |
| Abou-Zamzam et al 1997 | 513| Retrospective | Not reported       | Infra-inguinal bypass surgery               |
| Nicoloff et al 1998    | 112| Retrospective | 36                 | Infra-inguinal bypass surgery               |
| Chung et al 2006       | 334| Retrospective | 30                 | Infra-inguinal bypass surgery               |
| **Total**              | 2346|              |                    |                                             |

n = Number of Patients (Sample size)

**Table 2b** Included studies

| Study                     | Goshima et al 2004 | Taylor et al 2007 | Taylor et al 2006 | Abou-Zamzam et al 1997 | Nicoloff et al 1998 | Chung et al 2006 |
|---------------------------|--------------------|-------------------|-------------------|------------------------|---------------------|------------------|
| **Limb Salvage (%)**      |                    |                   |                   |                        |                     |                  |
| 6 months                  | 94.2               | 94.9              | 85                |
| 1 year                    | 80.6               | 76.5              |                   |
| 3 years                   | 93.5               | 79.0              |                   |
| 5 years                   | 91                 | 72.1              | 85.2              |
| Primary Graft Patency (%) |                    |                   |                   |                        |                     |                  |
| 6 months                  | 92.0               | 93.1              |                   |
| 1 year                    | 76.6               | 63.0              |                   |
| 3 years                   | 87.6               | 50.0              |                   |
| 5 years                   | 72.4               |                   |                   |
| Ambulatory recovery (%)   |                    |                   |                   |                        |                     |                  |
| 6 months                  | 80.0               | 92.0              | 72.0              |
| 1 year                    | 86.7               |                   |                   |
| 3 years                   | 73.0               |                   |                   |
| 5 years                   | 70.6               |                   |                   |
| Wound Healing (%)         |                    |                   |                   |                        |                     |                  |
| 6 months                  | 54.0               | 12.0              | 42.0              |
| 1 year                    | 86.7               |                   | 75.0              |
Table 2c: Included studies with reported pre-operative risk factors

| Included studies | Outcomes                        | Reported pre-operative risk factors                        |
|------------------|---------------------------------|-----------------------------------------------------------|
| Goshima [2]      | Delayed wound healing            | Diabetes mellitus (odds ratio [OR] = 3.4)                 |
|                  | Reoperation < 3 months           | Ischemic tissue loss (OR = 3.1)                           |
|                  | Readmission < 6 months           | Minority status (OR = 2.2)                                |
|                  |                                 | Ischemic tissue loss (OR = 2.8)                           |
|                  |                                 | Renal failure (OR = 2.3)                                  |
| Taylor [3]       | Impaired ambulatory ability at the time of presentation | 5-year mortality (hazard ratio [HR] = 3.34)               |
|                  |                                 | Failure to eventually ambulate (HR = 2.83)               |
|                  |                                 | Loss of independent living status (HR = 7.97)            |
|                  | The presence of dementia         | Late mortality (HR = 1.57)                               |
|                  |                                 | Failure to eventually ambulate (HR = 2.20)               |
|                  | Surgical revascularization failure | Loss of independent living status (HR = 5.44)            |
| Taylor [4]       |                                 | Impaired ambulatory status at presentation (OR = 6.44)   |
|                  |                                 | Presence of infranigual disease (OR = 3.93)              |
|                  |                                 | End-stage renal disease (OR = 2.40)                      |
|                  |                                 | Presence of gangrene (OR = 2.40)                         |
|                  |                                 | Hyperlipidemia (OR = 0.56)                               |

Table 3: Excluded studies  

| Source           | Type of study | n | Reasons for exclusion                                                                 | Conclusion                                                                 |
|------------------|---------------|---|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Kudo et al       | Retrospective | 192 | Different objective (procedure volume over different time-period and outcomes)       | open revascularization for the treatment of CLI have been largely replaced by angioplasty procedures without compromising outcomes |
| Vinit et al      | Review        | 331 | Review                                                                                | Patients with CLI should be offered revascularization if the procedure can be tolerated and the patient is ambulatory and living independently preoperatively. Amputation should be considered if the above criteria is not met. |
| Goodney et al    | Retrospective | 2,031 | <3 post-operative outcomes. Examined risk factors that predict amputation or graft occlusion within the first year following lower extremity bypass. | Risk factors can predict the risk of amputation and graft occlusion post-revascularization for CLI |
| Simons et al     | Retrospective | 513 | Less than 3 post-operative outcome measures investigated (assessed predictors of clinical failure defined as amputation and worsening ischaemia at 1 year) | 10% of patients with patent grafts at 1 year still could not attain clinical success. One of the predictors of failure to attain clinical success was ESRD. |
| Rutherford et al | Review        | 513 | Review                                                                                | The initial published standards for reporting post-operative outcome for CLI requires periodic revision |
| Gibbons et al    | Retrospective | 318 | Qualitative study                                                                    | Baseline health status is a predictor of post-operative functional recovery and well-being. |
| Kudo et al       | Retrospective | 111 | Evaluated post-operative outcome (effectiveness) of only percutaneous transluminal angioplasty (PTA) | PTA is feasible, safe and effective for the treatment of CLI |
| Ambler et al     | Retrospective | 111 | Evaluated only 1 outcome measure, ambulation                                         | Poor pre-operative ambulation predict poor post-operative ambulation and long LOS |
| Total            |               | 3,586 |                                                                                       |                                                                           |

Figure 3a: Forest plot of meta-analysis of the proportion estimates for post-operative outcome: limb salvage
| Study                          | Sample size | Proportion (%) | 95% CI         | Weight (%) | Test for heterogeneity |
|-------------------------------|-------------|----------------|----------------|------------|------------------------|
| Goshima et al 2004            | 318         | 90.811         | 87.166 to 93.807 | 32.82      | Random Q               |
| Taylor et al 2007             | 841         | 72.057         | 68.891 to 75.067 | 33.78      | DF                     |
| Abou-Zamzam et al 1997        | 513         | 85.185         | 81.811 to 88.147 | 33.40      | I² (inconsistency) 97.12% |
| Total (random effects)        | 1672        | 83.229         | 70.999 to 92.617 | 100.00     | 95% CI for I² 94.24 to 98.56 |

Figure 3b Forest plot of meta-analysis of the proportion estimates for post-operative outcome: primary graft patency

| Study                          | Sample size | Proportion (%) | 95% CI         | Weight (%) | Test for heterogeneity |
|-------------------------------|-------------|----------------|----------------|------------|------------------------|
| Nicoloff et al 1998           | 112         | 87.500         | 79.917 to 92.995 | 49.58      | Random Q               |
| Chung et al 2006               | 334         | 50.000         | 44.509 to 55.491 | 50.42      | DF                     |
| Total (fixed effects)          | 446         | 60.492         | 55.797 to 65.048 | 100.00     | I² (inconsistency) 98.32% |
| Total (random effects)         | 446         | 70.187         | 30.262 to 97.240 | 100.00     | 95% CI for I² 96.22 to 99.25 |

Figure 3c Forest plot of meta-analysis of the proportion estimates for post-operative outcome: ambulatory recovery

| Study                          | Sample size | Proportion (%) | 95% CI         | Weight (%) | Test for heterogeneity |
|-------------------------------|-------------|----------------|----------------|------------|------------------------|
| Abou-Zamzam et al 1997        | 513         | 79.922         | 76.190 to 83.305 | 35.31      | DF                     |
| Nicoloff et al 1998           | 112         | 91.964         | 85.293 to 96.260 | 30.25      | DF                     |
| Chung et al 2006               | 334         | 72.156         | 67.016 to 76.897 | 34.44      | I² (inconsistency) 91.63% |
| Total (random effects)         | 959         | 81.472         | 71.495 to 89.699 | 100.00     | 95% CI for I² 78.61 to 96.73 |
DISCUSSION
There is a high level of heterogeneity in the timelines for the various outcome measures in the papers evaluated. Multiple factors predict post-operative outcomes. Goshima et al. studied the outcomes after infrainguinal bypass surgery to determine risk factors for adverse outcomes. Time to heal exceeded three months in >50% of patients and diabetes mellitus among other factors was a major risk factor for prolong wound healing. In a study by Taylor et al., predictors of failure to achieve clinical success were the presence of gangrene, ESRD, hyperlipidaemia and impaired pre-operative ambulatory function. In that same study by Taylor et al., clinical success was defined as achieving all the following criteria: graft patency to the point of wound healing; limb salvage at one year; maintenance of ambulatory status for one year; and survival at six months. Despite >70% limb salvage and graft patency at three years, only 44.4% of the patients achieved the composite endpoint of clinical success as stated above. Taylor et al. again examined the determinants of functional outcome after revascularization for critical limb ischemia. Findings were that, at five years, graft patency and limb salvage were acceptable at 70%. However, functional outcomes at five years were low, survival was only 41% with 70% ambulatory recovery. Sub-optimal post-operative ambulation was predicted by poor pre-operative ambulatory function. The large number of retrospective studies did not allow for standardization of timelines for outcome measurement. In terms of the type of revascularization procedure, many studies reported on only infra-inguinal bypass surgeries, but some studies reported also on supra-inguinal bypass as well as endovascular interventions. This makes it difficult to conduct comparative analysis. The small number of studies eligible for the meta-analysis resulted in restricted analysis and non-comprehensive results. There may be recall and selection bias due to the large number of retrospective studies.

CONCLUSION
There is wide variation in the parameters and timelines for reporting post-operative outcomes. This limits the effectiveness and quality of systematic review and accounts for the heterogeneity of the selected studies for the meta-analysis. Many more patients who were ambulant pre-operative continued to ambulate post-operative than those who were non-ambulant pre-operative. Diabetes mellitus was an important risk factor for prolonged wound healing, local wound complications and major amputation. Effective pre-operative glycemic control may improve post-operative outcome.

| Study                  | Sample size | Proportion (%) | 95% CI     | Weight (%) | Test of heterogeneity |
|------------------------|-------------|----------------|------------|------------|-----------------------|
| Goshima et al 2004     | 318         | 54.088         | 48.437 to 59.662 | 33.28      | Q 200.9922            |
| Abou-Zamzam et al 1997 | 513         | 12.086         | 9.393 to 15.224  | 33.43      | Significance level P < 0.0001 |
| Chung et al 2006       | 334         | 41.916         | 36.567 to 47.410  | 33.30      | I² 99.00%             |
| Total (random effects) | 1165        | 34.571         | 10.951 to 63.280  | 100.00     | 95% CI for I² 98.37 to 99.39 |
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REFERENCES
1. Rutherford R, Flanigan D, Gupta S, Johnston K, Karmody A, Whittemore A. Suggested standards for reports dealing with lower extremity ischemia. *J Vasc Surg*. 1986;4(1):80-94.
2. Goshima K, Mills J, Hughes J. A new look at outcomes after infrainguinal bypass surgery: traditional reporting standards systematically underestimate the expenditure of effort required to attain limb salvage. *J Vasc Surg*. 2004;39(2):330-335.
3. Taylor S, Cull D, Kalbaugh C, Cass A, Harmon S, Langan E. Critical analysis of clinical success after surgical bypass for lower-extremity ischemic tissue loss using a standardized definition combining multiple parameters: a new paradigm of outcomes assessment. *J Am Coll Surg*. 2007;204(5):831-838.
4. Taylor S, Kalbaugh C, Blackhurst D, Cass A, Trent E, EM L. Determinants of functional outcome after revascularization for critical limb ischemia: an analysis of 1000 consecutive vascular interventions. *J Vasc Surg*. 2006;44(4):747-756.
5. Simons JP, Goodney PP, Nolan BW, et al. Failure to achieve clinical improvement despite graft patency in patients undergoing infrainguinal lower extremity bypass for critical limb ischemia Jessica. *J Vasc Surg*. 2010;51(6):1419-1424. doi:10.1016/j.jvs.2010.01.083.
6. Nicoloff AD, Taylor LM, McLaugherty RB, Moneta GL, Porter JM. Patient recovery after infrainguinal bypass grafting for limb salvage. *J Vasc Surg*. 1997;27(2):256-266.
7. Rutherford R, Baker J, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26(3):517-538.
8. Slim K, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. *ANZ J Surg*. 2003;73(9):712-716.
9. Abou-Zamzam A, Lee R, Moneta G, Taylor L, JM P. Functional outcome after infrainguinal bypass for limb salvage. *J Vasc Surg*. 1997;25(2):287-297.
10. Chung J, Bartelson B, Hiatt W, et al. Wound healing and functional outcomes after infrainguinal bypass with reversed saphenous vein for critical limb ischemia. *J Vasc Surg*. 2006;43(6):1183-1190.
11. Ambler G, Dapaah A, Zuhiir N, et al. Independence and mobility after infrainguinal lower limb bypass surgery for critical limb ischemia. *J Vasc Surg*. 2014;59(4):983-987.
12. Goodney P, Nolan B, Schanzer A, et al. Factors associated with amputation or graft occlusion one year after lower extremity bypass in northern New England. *Ann Vasc Surg*. 2010;24(1):57-68.
13. Kudo T, Chandra F, Ahn S. The effectiveness of percutaneous transluminal angioplasty for the treatment of critical limb ischemia: a 10-year experience. *J Vasc Surg*. 2005;41(3):423-435.
14. Gibbons G, Burgess A, Guadagnoli E, et al. Return to well-being and function after infrainguinal revascularization. *J Vasc Surg*. 1995;21(1):35-45.