Eur J Vasc Endovasc Surg **22**, 294–300 (2001)
doi:10.1053/ejvs.2001.1469, available online at http://www.idealibrary.com on IDEAL®

REVIEW ARTICLE

A Meta-analysis of Infrainguinal Arterial Reconstruction in Patients with End-stage Renal Disease

M. Albers*[1,2], M. Romiti[1], C. A. Bragança Pereira[3], R. L. A. Fonseca[1] and M. da Silva Júnior[1]

[1]*Vascular Surgery Section, Department of Surgery, Setor de Ciências Médicas e da Saúde, Centro Universitário Lusíada UNILUS, Fundação Lusíada, Santos-SP, Brazil,* [2]*Vascular Surgery Section, Department of Surgery, Faculdade de Medicina da Universidade de São Paulo, São Paulo-SP, Brazil,* [3]*Institute for Mathematics and Statistics, Universidade de São Paulo, São Paulo-SP, Brazil*

Objectives: *to determine graft patency, limb salvage, and patient survival following infrainguinal bypass grafting in patients with end-stage renal disease (ESRD).*
Methods: *studies published from 1987 through 2000 were identified from the PUBMED database and pertinent original articles. Sixteen studies were found that used survival analysis to report the outcomes of interest. Two investigators independently extracted the data from standard life-tables, survival curves and texts. A new method was developed for meta-analysis of uncontrolled studies that use survival analysis with different follow-up intervals.*
Results: *random-effects modelling yielded the following summary estimates at one- and two-year follow-up: 79% (95% CI, 70–87%) and 74% (63–85%) for graft patency; 77% (69–84%) and 73% (64–81%) for limb salvage; and 59% and 42% for patient survival.*
Conclusion: *despite a severely limited life span, infrainguinal bypass grafting for the treatment of critical ischaemia is worthwhile in selected patients with ESRD.*

Key Words: Meta-analysis; Bypass grafts; Renal failure.

Introduction

Since diabetes mellitus and high blood pressure are risk factors common to renal failure and peripheral arterial disease, it is not surprising that some patients with end-stage renal disease (ESRD) also develop critical limb ischaemia. The negative impact of the latter condition, which is similar to that of advanced cancer,[1] further aggravates the already poor functional status of patients on long-term dialysis. As a consequence, arterial reconstruction or primary amputation must be considered for these patients, most of whom typically present widespread arterial disease, extensive occlusion in the infragenicular arteries and a high degree of arterial calcification.[2–8] However, such accelerated arterial disease combined with impaired immunity, susceptibility to infection, and poor wound healing adversely affect surgical outcomes.[2,6,7,9–11] Although early graft patency rates are satisfactory, arterial reconstruction in the presence of ESRD is associated with higher rates of early amputation and poorer long-term survival.[2,5,7,8,10] In such an adverse scenario, it is useful, for patient information and surgical decision-making, to estimate the above outcomes as accurately as possible.

However, only a few studies of small to moderate size have dealt with infrainguinal bypass grafting in patients with ESRD. In these studies, cumulative success rates at two-year follow-up have ranged from 47–86% for graft patency, 35–91% for foot salvage, and 0–100% for patient survival.[3,5,6,12–15] Because of this wide variability and the opposing view that primary amputation

* Please address all correspondence to: M. Albers, Rua Ministro Godói, 1584, AP 74, ZIP 05015-001 São Paulo, Brazil.

1078–5884/01/100294 + 07 $35.00/0

should be done more frequently,[3,10,16] the present meta-analysis was done to obtain more precise estimates for the above outcomes in this high risk population.

Methods

Study search

An electronic search of the PUBMED database covering January 1, 1987 to September 15, 2000 was done using the descriptors "end-stage renal disease" and "bypass". Of a total of 195 references retrieved, 14 studies were initially selected.[2–6,8,10,12–14,17–20] Two additional studies were identified by other means. One of these had been cited frequently in the pertinent literature, while the other was identified by pure chance.[7,15] Therefore, a total of 16 studies were finally reviewed.

Criteria for inclusion

The results of arterial reconstructive surgery in patients with ESRD had to be presented separately. A survival analysis describing the success rates for at least one year was also required. The accepted sources of information included standard life-tables, related curves showing numbers of units at risk, at least for some intervals, individual patient information, and sparse estimates of graft patency and the corresponding standard-errors. In all cases, these sources should allow for the approximate reconstruction of the original life-tables.[21]

In the individual studies, the expression ESRD was mostly applied to patients who were dialysis-dependent or had a functioning kidney transplant. However, in three reports such expression also designated abnormally higher serum creatinine in patients not yet requiring renal replacement therapy. Two of these reports were excluded because most patients were in such a situation.[11,22] The third report, which described only a few such patients, all of whom had serum creatinine above 500 μmol/l, was included in the review.[14]

Data extraction

Life-tables describing graft patency were available in eight studies, of which only one failed to include information regarding foot salvage. In this particular study, a life-table showing secondary graft patency combined to text information supplied a highly plausible life-table for foot salvage.[7] Survival curves also showing the numbers of units at risk for most intervals were used in five studies thus allowing reliable reconstruction of the original life-tables. In another study using survival curves, the numbers at risk were not shown for all intervals and the information retrieved was thus only an approximation.[19] The distances between points on survival curves relative to the x-axis and the y-axis were measured independently by two authors (RLAF and MS) and any discrepancies were resolved in discussion with the senior author (MA). Finally, individual patients in one study and text information in the remaining study were used as the source of data.

Only one study reported patient survival in a standard life-table. Survival curves were used in six studies, of which three appropriately showed numbers at risk and three did not. Sparse information regarding some point estimates was used in six instances. One study described the outcome of individual patients and text information was available in the remaining study. The main features of the 16 studies are summarised in Table 1. Follow-up techniques included Duplex-scanning in 11 studies, were restricted to measurements of segmental blood pressures in four studies, and were not mentioned in the remaining study.

Table 1. Covariates at study level in 16 studies included in the meta-analysis.

	Median	Range	Missing information
Number of patients	23.5	10–52	
Number of procedures	32.5	11–69	
Publication year	1995	1988–2000	
Years of patient inclusion	6.5	4–15	
Mean age	58.5	45–67	2
Women %	42	18–56	3
Diabetes %	73	55–100	1
Heart disease %	55	18–82	4
Smokers %	41	15–74	4
Claudication %	0	0–7	1
Rest pain %	16	0–30	3
Tissue loss %	80	57–100	3
Infrainguinal bypass %	100	79–100	
Infrapopliteal bypass %	71	0–100	4
Bypasses/year	5	1–9.5	
Vein usage %	88	48–100	2
Follow-up intervals	7	1–24	

Statistical methods

Since no method was available for the meta-analysis of uncontrolled studies that use survival analysis with different follow-up intervals, a strategy was developed to combine results across studies. In the first step, units of analysis leaving the study at intervals of two or more months were redistributed to one-month intervals. Simple division redistributed censored units whereas uncensored units were reallocated under the assumption of a constant interval failure rate. Although a fractional number was frequently obtained for the number of failures and withdrawals in each month, a standard structure was provided for all the life-tables and thus allowed for the pooling of results at any desired point in time.

For each study *i* and each month *j* of follow-up, an interval success rate, λ_{ij}, was calculated. For the follow-up interval from zero to three months, Kaplan–Meier estimates of survival, $L_{i(1,3)}$, were the product $\lambda_{i1}.\lambda_{i2}.\lambda_{i3}$. The within-study variance, $v_{i(1,3)}$, as well as the between-study variance, $\tau_{(1,3)}^2$, was calculated for $L_{i(1,3)}$.[24]

Random-effects modelling yielded a summary measure of the treatment effect, $L_{(1,3)}$.[25] This was done by weighing $L_{i(1,3)}$ with $w_{i(1,3)}$, which is the inverse of the total variance, $v_{i(1,3)} + \tau_{(1,3)}^2$. Next, the entire procedure was repeated to obtain $L_{(4,12)}$, which was the product of successive terms λ_{i4}, $\lambda_{i5,...}$, λ_{i12}. Similarly, $L_{(13,20)}$ and $L_{(21,24)}$ were also obtained. For simplicity, $L_{(1,3)}$ as the common estimate for cumulative survival at three months may also be written as G_3.

The product $G_3.L_{(4,12)}$ was used to obtain the common estimate for cumulative survival at 12-month follow-up, G_{12}. Similarly, the product $G_{12}.L_{(13,20)}$ yielded G_{21}, and the product $G_{21}.L_{(21,24)}$ yielded G_{24}. Such estimators G_j will be consistent and approximately normal, and are derived based on the fact that the estimators for each study are approximately normal with an estimable variance.

Finally, 95% confidence intervals were constructed for G_3, G_{12} and G_{24} by using the w_{i3}, w_{i12} and w_{i24}, respectively. The Appendix shows the statistical formulae used.

In the meta-analysis of patient survival, average estimates were calculated, because most single studies failed to describe this outcome in sufficient detail.

Sensitivity analyses included cumulative meta-analysis and assessment of publication bias. Such analyses were restricted to foot salvage because this outcome is clinically more relevant than graft patency and does not depend on the type of patency reported. Cumulative meta-analysis included one study each time in the review, according to publication year, while a funnel graph plotted the one-year cumulated success rate in single studies against the corresponding sample size to assess publication bias.[26]

In the set of 16 single studies, the one-year foot salvage rate correlated poorly with publication year ($n=16$, $r=-0.39$), type of renal replacement therapy ($n=16$, $r=-0.02$), diabetes mellitus ($n=14$, $r=-0.30$), heart disease ($n=12$, $r=0.10$), hypertension ($n=12$, $r=0.35$), history of smoking ($n=12$, $r=0.13$), type of graft ($n=14$, $r=0.52$), and site of distal anastomosis ($n=12$, $r=0.49$). Because of extensive missing information and the lack of a strong correlation between any covariate and foot salvage at study-level, secondary analysis of single studies was kept simple and restricted to publication year.

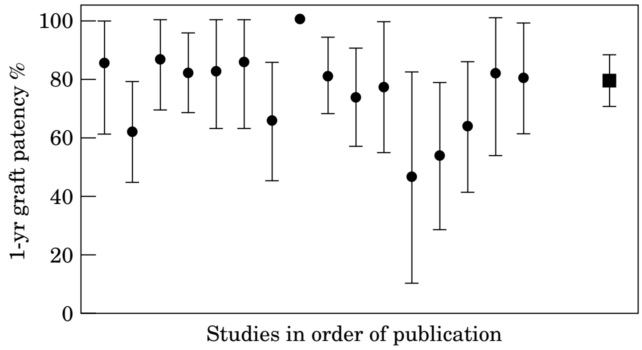

Fig. 1. One-year secondary graft patency for 16 studies (circles) and the corresponding summary measure using random-effects modelling (square). Bars indicate the 95% confidence intervals.

Results

Graft patency

The pooled estimate for graft patency was 89% (95% CI: 83–95%) at three months, 79% (70–87%) at 1 year, and 74% (63–85%) at 2 years of follow-up. Figure 1 shows the one-year graft patencies in single studies and the corresponding summary measure. The correction of secondary graft patencies in four studies that reported only primary patencies increased the summary one-year graft patency from 79 to 80%. Finally, the eight more recent studies showed a lower average estimate than the eight oldest studies (67 vs 81%).

Foot salvage

The pooled estimate for foot salvage at three months, one year, and two years of follow-up was 85% (95%

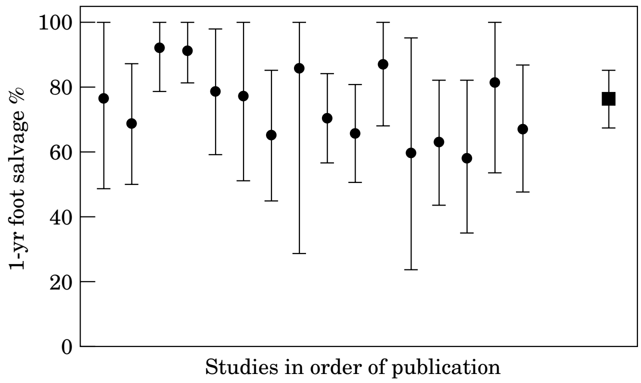

Fig. 2. One-year foot salvage for 16 studies (circles) and the corresponding summary measure using random-effects modelling (square). Bars indicate the 95% confidence intervals.

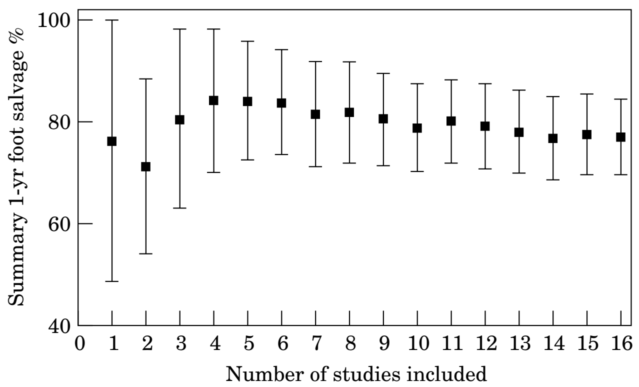

Fig. 3. Cumulative random-effects meta-analysis included studies stepwise according to their year of publication. Bars indicate the 95% confidence intervals.

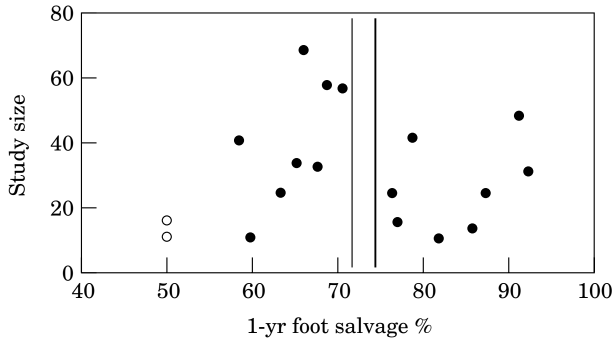

Fig. 4. A modified funnel graph revealed an asymmetry for study size less than 20 that suggested some publication bias. When two fictional studies of small size and poor results (open circles) were added to the 16 published studies (full circles), the average estimate decreased from 74% (solid vertical line) to 72% (dotted vertical line).

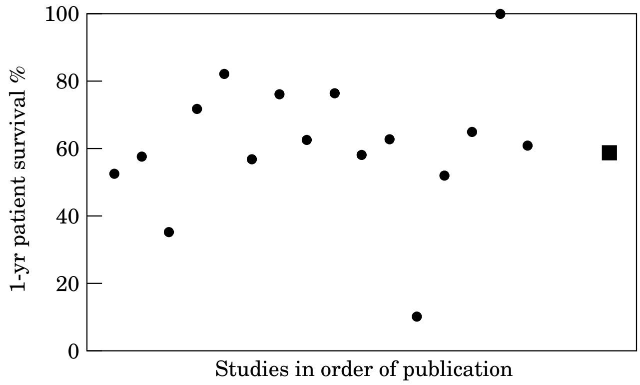

Fig. 5. One-year patient survival for 16 studies (circles) and the corresponding summary measure using random-effects modelling (square).

CI, 81–90%), 77% (69–84%), and 73% (64–81%), respectively. Figure 2 shows foot salvage estimates in single studies and the corresponding summary measure for the one-year follow-up.

The first published series of 25 bypasses described a one-year foot salvage rate of 76% (95% CI, 49–100%). When other seven studies were included in a cumulative meta-analysis, the number of bypasses increased to 288 and the one-year summary estimate of foot salvage was 82% (72–92%). Inclusion of all the studies yielded the final result of 77% (69–84%) (Fig. 3).

A small degree of publication bias was detected, but when this was arbitrarily adjusted by adding two small fictional studies with the poorest results, the average of the Kaplan–Meier estimates for the one-year foot salvage decreased from 74 to 72% (Fig. 4). This empirical procedure was similar to the "trim and fill" method of evaluating publication bias on meta-analyses of controlled trials.[27]

Summary point estimates were lower for foot salvage than graft patency during the entire follow-up period, and the corresponding difference was 4% at three months, 2% at one and two years. The eight more recent studies showed a lower average estimate for foot salvage than the eight oldest studies (69 vs 79%).

Patient survival

The pooled estimates for patient survival at three months, one year, and two years were 81, 59 and 42%, respectively. Since this analysis used only average estimates, confidence intervals could not be calculated. Figure 5 shows the one-year patient survival in single studies and the corresponding summary measure. The one-year average estimate of patient survival was similar when the eight more recent and the eight oldest studies were compared (61 vs 62%).

Discussion

The enormous potential for bias represents a major problem in the meta-analysis of uncontrolled studies in general and surgical series in particular. In such a situation, careful appraisal of the methods, clinical judgement, and common sense are required and feasibility is not always assured.[26,28–30] However, the present meta-analysis was judged to be meaningful because the reviewed studies clearly presented several favourable features such as a specific clinical problem, the existence of a population to which conclusions can be generalised, three well-defined research questions, and similar designs. On statistical grounds, these articles described high response rates in sufficient detail, at least for graft patency and foot salvage, and also allowed several sensitivity analyses and an assessment of publication bias to be made.

Although they had only a minor impact on the results, some methodological drawbacks included a follow-up shorter than two years in three studies, the lack of reporting secondary graft patencies in six studies, the approximate reconstruction of original life-tables from survival curves or texts in half the studies, the need to redistribute units of analysis to monthly intervals, and poor information on patient survival. Standard statistical methods were used and the resulting procedure was easy to apply and may be useful in other similar situations.

Most series of infrainguinal bypass grafting in patients without ESRD describe foot salvage rates far exceeding graft patency rates. In contrast, a typical finding in the reviewed studies was early major amputation of a limb in which a patent bypass was insufficient to heal complex ischaemic or infected skin lesions.[5,7,8,10,18] Such problem was reflected in this meta-analysis since the difference between the summary measures of graft patency and foot salvage reached 4% at three months of follow-up. Beyond this time, however, the difference in favour of graft patency decreased to 2% at 24 months. Such a trend was possibly the result of asymptomatic late graft failure or further arterial reconstruction to deal with recurrent symptoms.[6] The extremely poor patient survival reported elsewhere[3,8,17,18] was also confirmed.

Publication bias was of particular concern because authors and editors are unlikely to be enthusiastic about writing and publishing small uncontrolled studies with low success rates.[26] Such bias is a more serious problem for uncontrolled than controlled studies because the potential number of unpublished series is far greater. However, a small degree of publication bias was detected and the adjusted summary estimate for one-year foot salvage was only 3% lower than the unadjusted one (Fig. 4). Cumulative meta-analysis of foot salvage showed stable results in terms of precision when nine studies were included, but there was a trend for decreasing point estimates (Fig. 3). The other sensitivity analyses yielded unimpressive results.

Despite the clinical heterogeneity across the studies, there was no coherent and explicable correlation of any covariate at study-level with one-year graft patency and foot salvage. Possibly, ESRD exerts such a powerful influence on these outcomes that the effects of different modelling strategies, minor faults in design, and unbalanced covariates become unimportant. However, the comparison of the eight most recent studies with the older studies revealed, perhaps more realistically, worse results for graft patency and foot salvage.

Even when different sources of bias and the subgroup of more recent studies were considered, the one-year summary measure for foot salvage remained above 65%. This was an important result, since in patients without ESRD the foot salvage rate must exceed 44% to justify infrainguinal bypass, at least in terms of walking ability and quality of life.[1] Although graft patency and foot salvage may improve further with the use of pedal branch arteries and perigeniculate arteries as recipient vessels for bypass,[14,31,32] the clinical benefits are limited by poor patient survival. Although it would have been useful to assess actual palliation, which implies an alive patient and a salvaged foot, the pertinent data available in only three small studies were insufficient to allow this assessment. Unusually high rates of primary amputation ranging 20–44% clearly suggest how selected are patients with ESRD who undergo infrainguinal bypass grafting.[4,7,10,16]

This meta-analysis confirmed that poor survival is of most concern for patients with ESRD and severe limb ischaemia, but it also showed that infrainguinal arterial reconstruction is worthwhile for carefully selected such patients.

References

1 Albers M, Fratezi AC, De Luccia N. Walking ability and quality of life as outcome measures in a comparison of arterial reconstruction and leg amputation for the treatment of vascular disease. *Eur J Vasc Endovasc Surg* 1996; **11**: 308–314.
2 Leers SA, Reifsnyder T, Delmonte R, Caron M. Realistic expectations for pedal bypass grafts in patients with end-stage renal disease. *J Vasc Surg* 1998; **28**: 976–980.
3 Peltonen S, Biancari F, Lindgren L *et al.* Outcome of infrainguinal bypass surgery for critical leg ischaemia in patients with chronic renal failure. *Eur J Vasc Endovasc Surg* 1998; **15**: 122–127.
4 Whittemore AD, Donaldson MC, Mannick JA. Infrainguinal reconstruction for patients with chronic renal insufficiency. *J Vasc Surg* 1993; **17**: 32–39.
5 Wassermann RJ, Saroyan RM, Rice JC, Kerstein MD. Infrainguinal revascularization for limb salvage in patients with end-stage renal disease. *South Med J* 1991; **84**: 190–192.
6 Harrington EB, Harrington ME, Schanzer H, Haimov M.

End-stage renal disease – is infrainguinal limb revascularization justified? *J Vasc Surg* 1990; **12**: 691–695.
7 Sanchez LA, Goldsmith J, Rivers SP *et al.* Limb salvage surgery in end stage renal disease: Is it worthwhile? *J Cardiovasc Surg* 1992; **33**: 344–348.
8 Edwards JM, Taylor LM Jr, Porter JM. Limb salvage in end-stage renal disease (ESRD). Comparison of modern results in patients with and without ESRD. *Arch Surg* 1988; **123**: 1164–1168.
9 Dossa CD, Shepard AD, Amos AM *et al.* Results of lower extremity amputations in patients with end-stage renal disease. *J Vasc Surg* 1994; **20**: 14–19.
10 Johnson BL, Glickman MH, Bandyk DF, Esses GE. Failure of foot salvage in patients with end-stage renal disease after surgical revascularization. *J Vasc Surg* 1995; **22**: 280–285.
11 Blankensteijn JD, Gertler JP, Petersen MJ *et al.* Avoiding infrainguinal bypass wound complications in patients with chronic renal insufficiency: the role of the anatomic plane. *Eur J Vasc Endovasc Surg* 1996; **11**: 98–104.
12 Lumsden AB, Besman A, Jaffe M, MacDonald MJ, Allen RC. Infrainguinal revascularization in end-stage renal disease. *Ann Vasc Surg* 1994; **8**: 107–112.
13 Baele HR, Piotrowski JJ, Yuhas J, Anderson C, Alexander JJ. Infrainguinal bypass in patients with end-stage renal disease. *Surgery* 1995; **117**: 319–324.
14 Treiman GS, Lawrence PF, Rockwell WB. Autogenous arterial bypass grafts: durable patency and limb salvage in patients with inframalleolar occlusive disease and end-stage renal disease. *J Vasc Surg* 2000; **32**: 13–22.
15 Sakurai T, Kobayashi M, Harasawa H *et al.* Infrainguinal arterial reconstruction in end-stage renal disease. *Cardiovasc Surg* 1995; **3**: 46–49.
16 Simsir SA, Cabellon A, Kohlman-Trigoboff D, Smith BM. Factors influencing limb salvage and survival after amputation and revascularization in patients with end-stage renal disease. *Am J Surg* 1995; **170**: 113–117.
17 Chang BB, Paty PS, Shah DM, Kaufman JL, Leather RP. Results of infrainguinal bypass for limb salvage in patients with end-stage renal disease. *Surgery* 1990; **108**: 742–746.
18 Hakaim AG, Gordon JK, Scott TE. Early outcome of in situ femorotibial reconstruction among patients with diabetes alone versus diabetes and end-stage renal failure: analysis of 83 limbs. *J Vasc Surg* 1998; **27**: 1049–1054.
19 Korn P, Hoenig SJ, Skillman JJ, Kent KC. Is lower extremity revascularization worthwhile in patients with end-stage renal disease? *Surgery* 2000; **128**: 472–479.
20 Harpavat M, Gahtan V, Ierardi R, Kerstein MD, Roberts AB. Does renal failure influence infrainguinal bypass graft outcome? *Am Surg* 1998; **64**: 155–159.
21 Rutherford RB, Baker JD, Ernst C *et al.* Recommended standards for reports dealing with lower extremity ischemia. *J Vasc Surg* 1997; **26**: 517–538.
22 Mills JL, Gahtan V, Fujitani RM, Taylor SM, Bandyk DF. The utility and durability of vein bypass grafts originating from the popliteal artery for limb salvage. *Am J Surg* 1994; **168**: 646–651.
23 Fleiss JL. Statistical methods for rates and proportions, 2nd ed. New York: John Wiley & Sons, 1981: 13–18; 138–159.
24 Abrams K, Sansó B. Approximate Bayesian inference for random effects meta-analysis. *Stat Med* 1998; **17**: 201–218.
25 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials* 1986; **7**: 177–188.
26 Lau J, Ioannidis JPA, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997; **127**: 820–826.
27 Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. *BMJ* 2000; **320**: 1574–1577.
28 Fleiss JL, Gross AJ. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: A critique. *J Clin Epidemiol* 1991; **44**: 127–139.
29 Blettner M, Sauerbrei W, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol* 1999; **28**: 1–9.
30 Jones DR. Meta-analysis of observational epidemiological studies: A review. *J Royal Soc Med* 1992; **85**: 165–168.
31 Barral X, Salari GR, Toursarkissian B *et al.* Bypass to the perigeniculate collateral vessels. A useful technique for limb salvage: Preliminary report on 22 patients. *J Vasc Surg* 1998; **27**: 928–937.
32 Connors JP, Walsh DB, Nelson PR *et al.* Pedal branch artery bypass: A viable limb salvage option. *J Vasc Surg* 2000; **32**: 1071–1079.

Accepted 4 July 2001

Appendix

Interval survival

For each study *i* and each month *j* of follow-up, a monthly survival rate, λ_{ij}, was determined as follows:

$$\lambda_{ij} = 1 - f_{ij}/n_{ij},$$

where f_{ij} is the number of failures and n_{ij} is the number of units (grafts or feet) at risk.

Several intervals $t_{(x,y)}$ may be considered provided that $1 \leq x < y \leq j$. For convenience, this study used $t_{(1,3)}$, $t_{(4,12)}$, $t_{(13,20)}$ and $t_{(21,24)}$. Wherever possible, $t_{(x,y)}$ will be written simply as t.

Within any given interval t, the product of successive terms λ_{ij} yields the interval survival rate, L_{it}.

Variances

For each t, the within-study variance, v_{it}, was obtained as follows:[21]

$$v_{it} = L_{it}^2 (1 - L_{it})/n_{it},$$

whereas the between-study variance, τ_t^2, was calculated as follows:

$$\tau_t^2 = \Sigma (L_{it} - m_t)^2/(k_t - 1),$$

where k_t and m_t are, respectively, the number of individual studies and the average for L_{it}.

Weighting and combining the L_{it}

Let w_{it} be the weight attributed to each L_{it}. When using the random-effects model, it follows that:

$$w_{it} = 1/(v_{it} + \tau_t^2).$$

A summary survival estimate, L_t, was obtained for interval t as follows:

$$L_t = \Sigma L_{it} w_{it} / \Sigma w_{it}.$$

Since $t_{(1,3)}$ months is the first follow-up interval, $L_{(1,3)}$ is also the summary estimate for survival and may be written simply as G_3. As explained before, L_t was also obtained for $t_{(4,12)}$, $t_{(13,20)}$, and $t_{(21,24)}$. Therefore, the summary estimate of survival at 12-month follow-up, G_{12}, is simply the product $G_3.L_{(4,12)}$. Similarly, G_{21} can be obtained from G_{12} and $L_{(13,20)}$, and G_{24} from G_{21} and $L_{(21,24)}$.

Variance and confidence interval for G_t

To obtain a variance $V_{\{Gt\}}$ for G_t, the following formula was used:

$$V_{\{Gt\}} = \Sigma(1/w_{it}).$$

Confidence intervals for G_t were then easily obtained.