REVIEW ARTICLE

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

M. Albers*, M. Romiti†, C. A. Bragança Pereira‡, R. L. A. Fonseca† and M. da Silva Júnior†

1Vascular Surgery Section, Department of Surgery, Setor de Ciências Médicas e da Saúde, Centro Universitário Lusíada UNILUS, Fundação Lusíada, Santos-SP, Brazil, 2Vascular Surgery Section, Department of Surgery, Faculdade de Medicina da Universidade de São Paulo, São Paulo-SP, Brazil, 3Institute 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, 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. However, such accelerated arterial disease combined with impaired immunity, susceptibility to infection, and poor wound healing adversely affect surgical outcomes. 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. 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. Because of this wide variability and the opposing view that primary amputation...
should be done more frequently, 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. 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. 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.

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. 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.

**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. 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. 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.

**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, $\lambda_{ij}$, was calculated. For the follow-up interval from zero to three months, Kaplan–Meier estimates of survival, $L_{ij}(1,3)$, were the product $\prod_{a<i} \lambda_{ia} \prod_{a>i} \lambda_{ai}$. The within-study variance, $v_{ij}(1,3)$, as well as the between-study variance, $\tau_{ij}(1,3)$, was calculated for $L_{ij}(1,3)$. Random-effects modelling yielded a summary measure of the treatment effect, $L_{ij}(1,3)$. This was done by weighing $L_{ij}(1,3)$ with $w_{i1,3}$, which is the inverse of the total variance, $v_{ij}(1,3) + \tau_{ij}(1,3)^2$. Next, the entire procedure was repeated to obtain $L_{ij}(1,3)$, which was the product of successive terms $\lambda_{i4}, \lambda_{i5}, \ldots, \lambda_{i12}$. Similarly, $L_{ij}(12,20)$ and $L_{ij}(21,24)$ were also obtained. For simplicity, $L_{ij}(1,3)$ as the common estimate for cumulative survival at three months may also be written as $G_i$. The product $G_i L_{ij}(1,3)$ was used to obtain the common estimate for cumulative survival at 12-month follow-up, $G_i$. Similarly, the product $G_i L_{ij}(12,20)$ yielded $G_i$, and the product $G_i L_{ij}(21,24)$ yielded $G_i$. Such estimators $G_i$ 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 $G_i$, $G_{i12}$, and $G_i$ 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.

In the set of 16 single studies, the one-year foot salvage rate correlated poorly with publication year ($r = -0.39$), type of renal replacement therapy ($r = -0.02$), diabetes mellitus ($r = -0.30$), heart disease ($r = 0.10$), hypertension ($r = 0.35$), history of smoking ($r = 0.13$), type of graft ($r = 0.52$), and site of distal anastomosis ($r = 0.49$). 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.

### 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%
Infrainguinal Bypass in End-stage Renal Disease

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.

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 elsewhere3,8,17,18 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

6. Harrington EB, Harrington ME, Schanzer H, Haimov M.

Accepted 4 July 2001

Appendix

Internal survival

For each study i and each month j of follow-up, a monthly survival rate, $\lambda_{ij}$, 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 $t_{ij}$ may be considered provided that $1 \leq x < y \leq j$. For convenience, this study used $t_{ij}$, $t_{12j}$, $t_{13,20}$ and $t_{21,12j}$. Wherever possible, $t_{ij}$ will be written simply as $t$.

Within any given interval $t$, the product of successive terms $\lambda_t$ yields the interval survival rate, $L_t$.

Variance

For each $t$, the within-study variance, $v_{it}$, was obtained as follows:25

$$v_{it} = L_t(1 - L_t)/n_{it}$$

whereas the between-study variance, $\tau_t^2$, was calculated as follows:

$$\tau_t^2 = \sum L_t(m_t - m)^2/(k_t - 1),$$

where $k_t$ and $m_t$ are, respectively, the number of individual studies and the average for $L_t$.

Eur J Vasc Endovasc Surg Vol 22, October 2001
**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:

\[
w_{it} = \frac{1}{(v_{it} + \tau^2)}.
\]

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

\[
L_t = \sum L_{it} w_{it} / \sum w_{it}.
\]

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 \( V_{(G_t)} \) for \( G_t \) the following formula was used:

\[
V_{(G_t)} = \sum (1/w_{it}).
\]

Confidence intervals for \( G_t \) were then easily obtained.