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REVIEW

Meta-Analysis of Allograft Bypass Grafting to Infrapopliteal Arteries

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Objective. *To determine graft patency and limb preservation after allograft bypass grafting to infrapopliteal arteries for different allograft materials.*
Design. *Meta-analysis of case series that used survival analysis to describe outcomes.*
Methods. *Studies published from 1982 through 2003 were identified from electronic databases and pertinent original articles. Four series of cryopreserved arterial allografts, 10 series of cryopreserved vein allografts, three series of cold-storaged vein allografts, and 16 series of umbilical-cord vein allografts were included in separate random-effects meta-analyses.*
Results. *A graphical display of pooled survival curves of graft patency showed cold-storaged veins to have the best outcome in the first 4 years, followed by cryopreserved arteries, umbilical-cord veins, and cryopreserved veins. The respective 5-year pooled patency were 24, 21, 30, and 19%. For foot preservation, the best outcome was achieved with cryopreserved arteries followed by cryopreserved veins, umbilical-cord veins, and cold-storaged veins. A reference meta-analysis of polytetrafluoroethlylene grafts occupied the top position for graft patency and the second position for foot preservation.*
Conclusion. *In leg revascularisation for critical ischaemia, graft patency is poor for allografts generally, but using peripheral allografts in repeat attempts at revascularisation is a valid strategy to prevent major amputation. A role for umbilical-cord vein allografts remains uncertain.*

Keywords: Allograft; Bypass; Meta-analysis.

Introduction

There is no consensus about the alternative graft that should be used for infrapopliteal bypass grafting when the great saphenous vein is unavailable. A policy of using all-autologous tissue grafts may yield superior graft patency rates in the long term, but this is achieved at the cost of harvesting veins from distant sites and constructing composite grafts. In contrast, the use of nonautologous grafts reduces the need for multiple incisions at the cost of decreased durability and increased risk of graft-related complications.

Polytetrafluoroethylene (PTFE) grafts have been used regularly for more than two decades. When placed distally into an infrapopliteal artery, such grafts often include an adjunctive procedure and may require permanent anticoagulation. Despite the proven success of the umbilical-cord vein allograft (UVA) in above-knee femoropopliteal revascularisation,[1] the use of this allograft as a femorocrural bypass has declined markedly. Greater attention has been given to allografts sourced from peripheral vessels and submitted to cryopreservation. Easy handling, increased pliability and a higher resistance to infection have been cited as distinct advantages of peripheral allografts over UVAs and PTFE grafts, but immunological rejection is a major limitation.

Despite the conflicting results reported for the cryopreserved vein allograft (CVA),[2,3] there is reason for moderate optimism with the cryopreserved arterial allograft (CAA)[4–7] and the modern UVA.[8] Sparse studies with the cold-storaged vein allograft (CSVA)

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are also encouraging.[9–12] Because of uncertainty regarding allograft bypass grafting to the infrapopliteal arteries, meta-analysis was used to assess long-term graft patency and foot preservation for each allograft material separately.

Materials and Methods

Study identification

Two undergraduate medical students with no previous experience in meta-analysis and the senior author (M.A.) searched articles in PUBMED, LILACS and OVID databases. *Excerpta Medica Surgery*, vascular surgery section, was reviewed manually. The search covered January 1980 through December 2003 and combined the primary descriptors bypass, revascularisation and arterial reconstruction with the secondary descriptors allograft, homograft, umbilical cord vein and cryopreserved. After identifying suggestive titles, the corresponding abstracts were read online to select articles for printing. Printed full-text articles were reviewed and their reference lists were used to identify additional articles and new descriptors. A final search used Dardik and biograft delimited by Title. Two articles from periodicals not indexed in the databases used were also read,[9,13] and additional data were obtained from authors to construct life-tables for two studies[5,14] and to update the follow-up for another study.[6] An anonymous reviewer identified another article.[7]

Criteria for inclusion

The articles included satisfied the following criteria: (1) a minimum of 15 allograft bypasses distally inserted into an infrapopliteal artery; (2) a predominance (more than half) of these bypasses over bypasses to the popliteal artery, when both were analysed together, (3) time-to-event description of graft patency, (4) type of graft patency clearly indicated, and (5) a follow-up of a year, at least for some grafts. Meta-analysis was done separately for four series of CAAs, 10 series of CVAs, three series of CSVAs, and 16 series of UVAs.[2–35] Surgeons from two centers had published more than one study on allograft bypass grafting, but the repeated inclusion of bypasses was avoided (Table 1 and Appendix A). These criteria complied with the recommendation of broad inclusiveness for meta-analysis of epidemiological studies.[36] A total of 64 papers were identified in the literature and rejected according to the inclusion criteria.

Outcome parameters

The main parameters were secondary graft patency (SP) and foot preservation (FP) according to recommended standards.[37] Primary graft patency (PP) was described in only a few studies and therefore it was not considered further. A stability ratio defined ad hoc as the ratio between the pooled estimates of success at 5 years and at 1-month was calculated for both SP and FP.[38]

Graft patency was reported as SP in 3 CAA series, 4 CVA series, 1 CSVA series, and 6 UVA series; but it was reported simply as cumulative patency for 1 CVA series, 1 CSVA series, and 9 UVA series (Appendix B). Data from the text were used to infer SP from PP for 1 CVA series, 1 CSVA series, and 1 UVA series.[9,20,25] One CAA study and 3 CVA studies described PP, but it was interpreted as SP because reoperation for rupture or aneurysmal degeneration had not been computed as graft failure.[3,7,15,16] Finally, the reported assisted PP was used as SP for 1 CVA series and 1 UVA series.[2,34]

Study quality

An ideal study should contain the reasons for using allografts, the proportion of patients requiring these grafts, life-tables rather than graphs, the 1-month follow-up interval, an account for loss to follow-up, and descriptions of PP, SP, and FP. Of particular relevance is the link between predictive variables and each life-table. Other relevant items are the proportion of secondary procedures and tissue loss, the regimens of postoperative antithrombotic therapy, the proportion of grafts that suffered degeneration or became infected, and data on further bypasses. A perfect study would score 14, with a decrease of one point for each unmet requirement (Table 2, Appendix A).

Data extraction

Two junior authors extracted independently the data from standard life-tables and from survival curves that showed the number of units at risk for all intervals, while the senior author retrieved life-table data from survival curves that showed number of units at risk for some intervals and from plain survival curves that omitted any number. All the 17 series of peripheral allografts and 10 of the 16 series of UVAs were included in meta-analysis of both SP and FP, whereas 6 UVA series could not be included in the meta-analysis of FP.[13,23,24,30,32,33] The data were obtained from 12 (SP, $n=8$; FP, $n=4$) life-tables,[5–7,9,12–14,20,31] 8 (SP, $n=3$; FP, $n=5$) survival curves that showed number of units at

Table 1. Main features of published allograft series and meta-analysis results

Author	Year	*n*	1-year SP (se)	1-year FP (se)
CAA-cryopreserved arterial allografts				
Simeón et al.[7]	1998	35	52 (10)	70 (9)
Alonso et al.[6]	1999	17	93 (8)	94 (8)
Castier et al.[4]	1999	35	76 (9)	81 (87)
Albertini et al.[5]	2000	131	57 (5)	84 (3)
Meta-analysis		218	64 (10)	80 (5)
CVA-cryopreserved vein allografts				
Ochsner et al.[18]	1984	75	50 (7)	77 (9)
Harris et al.[14]	1993	25	37 (13)	76 (18)
Walker et al.[19]	1993	39	45 (9)	71 (9)
Martin et al.[21]	1994	115	39 (5)	84 (4)
Posner et al.[15]	1996	21	48 (13)	62 (12)
Carpenter and Tomaszewski[16]	1997	40	11 (6)	42 (11)
Leseche et al.[17]	1997	25	53 (13)	79 (11)
Buckley et al.[3]	2000	27	84 (7)	89 (7)
Harris et al.[20]	2001	80	47 (9)	69 (7)
Farber et al.[2]	2003	240	30 (3)	81 (3)
Meta-analysis		687	48 (6)	78 (5)
CSVA-cold-storaged vein allografts				
van Reed Dortland et al.[12]	1991	51	71 (6)	87 (5)
Rebane et al.[10]	1997	67	67 (6)	69 (5)
Sacilotto et al.[9]	1998	39	43 (9)	67 (10)
Meta-analysis		157	64 (10)	76 (8)
UVA-UVAs umbilical-cord vein allografts				
Cranley and Hafner[28]	1982	40	40 (10)	84 (7)
Klimach and Charlesworth[22]	1983	112	33 (6)	57 (7)
Robison et al.[29]	1983	32	46 (12)	54 (11)
Raithel et al.[30]	1984	60	62 (7)	
Sciacca et al.[32]	1984	15	31 (14)	
Harris et al.[35]	1984	60	35 (7)	54 (9)
Guasch et al.[13]	1985	26	61 (11)	
Barry et al.[33]	1985	18	41 (16)	
Largiader et al.[23]	1985	72	75 (5)	
Nevelsteen et al.[34]	1986	65	65 (7)	64 (7)
Harling et al.[24]	1987	23	51 (12)	
Dardik et al.[31]	1988	388	54 (3)	77 (3)
Batt et al.[25]	1990	52	19 (7)	32 (9)
Sommeling et al.[26]	1990	37	56 (9)	77 (8)
Moody et al.[27]	1991	80	44 (7)	43 (6)
Dardik et al.[8]	2002	174	79 (3)	86 (3)
Meta-analysis		1254	54 (5)	70 (6)

Table 2. Summary characteristics of the series included in the meta-analyses

	CAA $n=4$	CVA $n=10$	CSVA $n=3$	UVA $n=16$
Number of bypasses	218	687	157	1254
Year of publication	1999 (1998, 2000)	1996 (1984, 2003)	1997 (1991, 1998)	1985 (1982, 2002)
Year of beginning	1994 (1991–1995)	1991 (1966, 1995)	1984 (1978, 1991)	1978 (1975, 1990)
Score of quality	11.5 (9, 12)	9.5 (5, 10)	8 (6, 11)	5.5 (3, 10)
Secondary bypass %	75 (60, 100)	70 (27, 94)	50 (36, 67)*	44 (27, 77)*
Claudication %	0 (0, 0)	0 (0, 18)*	0*	0 (0, 8)*
Popliteal bypass %	9 (0, 14)*	9 (0, 36)	0 (0, 13)	0 (0, 45)
Pedal bypass %	0 (0, 12)*	6 (0, 29)	0 (0, 8)	0 (0, 0)
Censored 1-year %	29 (20, 53)	10 (19, 40)	16 (13, 23)	18 (8, 25)

Values are median (range).
* Indicates data not available in all of the series.

risk for all intervals,[3,4,16,27,35] 9 (SP, $n=5$; FP, $n=4$) survival curves that showed this number for some intervals,[12,17,19,21,25,34] and 12 (SP, $n=9$; FP, $n=3$) plain survival curves.[2,8,10,15,18,22,23,29,32,33] Data of FP were extracted from both the text and the retrieved life-table of SP in 4 UVA studies[22,26,28,29] and 7 peripheral allograft studies.[6,7,14,15,18,19,21] For the interval between 25- and 36-months, a plain survival curve from a UVA study admitted two solutions for SP; the solution that offered the smallest numbers at risk was used,[23] whereas sensitivity analysis investigated the other alternative. Inclusion in meta-analysis was restricted to the second interval and beyond when the 1-month pooled success of SP or FP was omitted.[3,18,23,32]

Confounding in the original studies

Most studies focused on chronic critical ischaemia, but 4 CVA series and 1 UVA series included a few bypasses done for claudication; pertinent information was lacking for 1 CVA series, 1 CSVA series, and 6 UVA series. Rates of secondary bypass ranged from 60 to 100% in the CAA series, from 27 to 94% in the CVA series, from 33 to 67% in two of the 3 CSVA series, and from 27 to 77% in seven of the 16 UVA series; pertinent information was lacking for 1 CAA series, 1 CSVA series and 9 UVA series. Femoropopliteal bypasses were included in 3 CAA series, 8 CVA series, 1 CSVA series, and 1 UVA series. Likewise, pedal bypasses were included in 2 CAA series, 9 CVA series, and 1 CSVA series; not a single UVA series contained pedal bypasses (Appendix A).

Statistical methods

Random-effects meta-analysis combined monthly success rates from original series to calculate a pooled estimate of success for each month of follow-up. In this calculation, within-study variability, between-study variability and between-interval variability were all considered in the weighting scheme.[39] The product of successive monthly pooled estimates of success then yielded a pooled measure of cumulative success for each targeted allograft (Appendix B). The quantity that a random-effects meta-analysis estimates is a mean across a universe of studies and hence across a universe of surgical centres. Since, the outcome at different surgical centres varies, a fixed-effects model would not be a plausible choice.

Sensitivity analysis for SP

Bias was possibly introduced because independence was assumed between graft failure and loss to follow-up and because 15 of the 17 series of peripheral allografts also contained popliteal or pedal bypasses. Based on published data,[39,40] the following assumptions were made to investigate bias from those sources: (1) the reduced risk of graft failure for popliteal bypasses and the increased risk of failure for pedal bypasses were concentrated within the first month of follow-up, (2) a relative-risk of graft failure of 0.60 for above-knee popliteal bypasses, 0.75 for below-knee popliteal bypasses, and 1.14 for pedal bypasses, (3) the percentage of censored units representing losses to follow-up was 22% in the first month, 47% from the second through the sixth month, and 18% from the seventh through the twelfth month, and (4) 60% of the grafts considered as lost within the first year of follow-up represented additional failures. Sensitivity analysis also investigated publication bias and measured the impact of a study for which SP was subjectively inferred from the reported PP. Fixed-effects meta-analysis was performed for illustration.

Reference meta-analysis of PTFE grafts

The electronic databank of a published meta-analysis from our group was investigated.[39] There were 1379 PTFE grafts with adjunctive procedures, which came from 23 series described in 19 studies. That meta-analysis was used in a graphical comparison of outcomes with the present meta-analyses.

Results

Differences between sets of series

UVA studies were older on average, contained a greater number of grafts, were scored the lowest for quality, and did not contain a single pedal bypass. Although information regarding risk variables was incomplete, the available data showed that the UVA series contained less women, less diabetic patients, and less secondary bypasses (Table 2).

Meta-analysis of UVAs

The meta-analysis of UVA series included a greater number of studies. The pooled estimates (standard-error) of SP and FP were 76% (3%) and 83% (4%) at

1-month, 54% (5%) and 70% (6%) at 1-year, and 30% (9%) and 55% (4%) at 5-years, respectively. The pooled survival curves of SP and FP were divergent, with a difference of 25% at 5-years (Figs. 1 and 2). The median difference between FP and SP at 1-year follow-up was 15% for four series that contained only one UVA bypass per limb and 16% for six series that contained two or more UVA bypasses per limb. Study quality, which correlated moderately with year of publication (Pearson $r=0.64$; $P<0.008$), did not correlate with 1-year SP (Pearson $r=-0.09$).

Meta-analysis of peripheral allografts

In the meta-analysis of CVA series, the pooled estimates (standard error) of SP and FP were 90% (3%) and 94% (2%) at 1-month, 48% (6%) and 78% (5%) at 1-year, and 19% (13%) and 60% (11%) at 5-years. Similarly, meta-analysis of CAA series showed pooled estimates of SP and FP of 89% (5%) and 93% (4%) at 1-month, 64% (10%) and 81% (5%) at 1-year, and 21% (10%) and 68% (9%) at 5-years (Figs. 1 and 2). In the meta-analysis of CSVA series, the corresponding pooled estimates were 92% (5%) and 89% (6%) at 1-month, 64% (10%) and 76% (8%) at 1-year, and 24% (19%) and 39% (29%) at 5-years, respectively; SP was lower than the pooled FP in the first 3-months only (Figs. 1 and 2). Overall, the median difference between FP and SP at 1-year follow-up was 15% for 10 series that contained only one peripheral allograft bypass per limb and 27% for seven series that contained two or more peripheral allograft bypasses per limb.

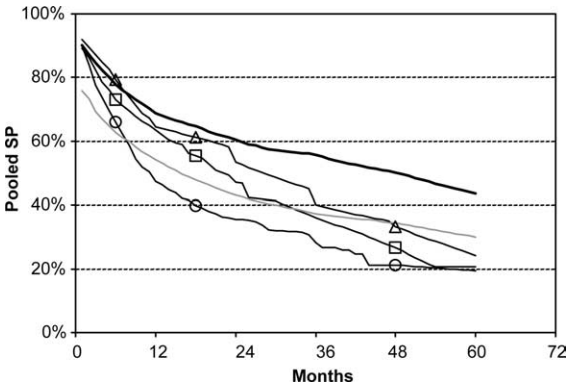

Fig. 1. Pooled survival curves of secondary graft patency (SP) for cryopreserved arterial allografts (CAA) (squares), cryopreserved vein allografts (CVA) (circles), CSVAs cold-storaged vein allografts (CSVA) (triangles), UVAs umbilical-cord vein allografts (UVA) (thick gray line), and PTFE grafts (thick black line).

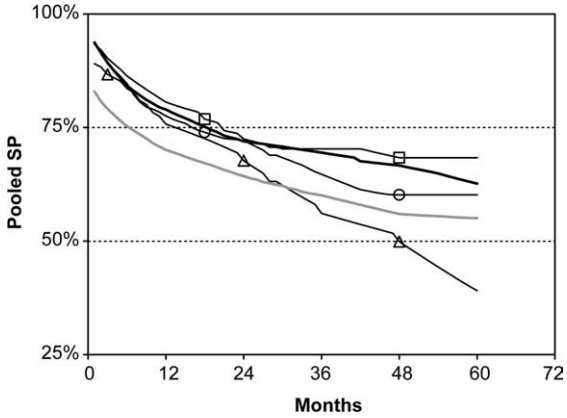

Fig. 2. Pooled survival curves of foot preservation (FP) for cryopreserved arterial allografts (CAA) (squares), cryopreserved vein allografts (CVA) (circles), CSVAs cold-storaged vein allografts (CSVA) (triangles), UVAs umbilical-cord vein allografts (UVA) (thick gray line), and PTFE grafts (thick black line).

In CVA series, the scores of study quality correlated strongly with year of publication (Pearson $r=0.74$; $P<0.02$) but, as for UVAs, they did not correlate with 1-year SP rates (Pearson $r=-0.12$). Because only a few studies were available, the assessment of correlations would be meaningless in both CSVA series and CAA series.

Comparison of meta-analyses

A graphical display of pooled survival curves of SP showed that the reference PTFE grafts occupied the uppermost position beyond the 7-month follow-up and that the curve for UVAs eventually crossed up across the curves for all peripheral allografts, ending up more favorable. The latter were initially divergent, but tended to convergence beyond 24-months (Fig. 1). The pooled survival curve of FP for PTFE grafts occupied the second position, below the curve for CAAs and above the curves for CVAs UVAs and CSVAs, in that order (Fig. 2). When only allografts were compared, CSVAs performed the best for SP and the worst for FP. The 5-year patency stability ratio was 23% for CAAs, 22% for CVAs, 26% for CSVAs, 40% for UVAs, and reached 48% for the reference PTFE grafts. Overlapping of 95% confidence intervals for the pooled SP was generally extensive and tended to increase with time, but it did not occur at 1-month in the comparison between CAAs and UVAs nor at 3-months in the comparison between CSVAs and UVAs.

Sensitivity analysis

Sensitivity analysis for distal anastomosis and loss to follow-up decreased the 5-year pooled SP by 3% in the meta-analysis for CAAs, and by less than 2% in the other meta-analyses.

The exclusion of 1 CAA series, 4 CVA series and 1 UVA series that described PP or assisted PP decreased the corresponding 5-year pooled SP by 0.8, 3 and 0.8%, respectively. However, the exclusion of the most successful UVA graft series decreased the 5-year pooled SP by 5% and the corresponding graft stability ratio by 6%. Alternatives in the reconstruction of a life-table for a UVA series decreased the 5-year pooled SP by 0.9%.

For series with less than 50 grafts, the 1-year SP was lower than the corresponding pooled estimate in six of the nine series of peripheral allografts and in six of the seven series of UVAs, which did not suggest the presence of publication bias in its usual form of small series with worse outcomes remaining unpublished. Admittedly, 41 UVAs performed from 1986 through 1989 were not included in a large study.[8]

Fixed-effects modeling

The fixed-effects model increased the 5-year pooled SP by 3% for CAAs, 6% for CVAs, and 3% for both CSVAs and UVAs. With this modelling strategy, 95% confidence intervals for the 1-month pooled SP did not overlap in the comparison between UVAs and each peripheral allograft.

The contribution of between-interval variances

When between-interval variances were not used, the 5-year pooled SP increased by 0.4% for CAAs whereas it decreased by 0.6% for UVAs, 0.5% for CVAs, and 0.3% for CSVAs. However, the difference in 1-year pooled SP between CAAs and UVAs increased by 3%.

Discussion

This study followed a plan of overviewing studies on bypass revascularisation of infrapopliteal arteries, which began with a meta-analysis of PTFE grafts that now served for informal comparison of outcome parameters.[39] Since, SP better reflects the fate of arterial reconstructions and is usually described precisely, this parameter is a natural target to meta-analysis aimed to assess outcomes for different graft materials. On the other hand, FP describes the fate of revascularised limbs, which does not depend solely on graft patency. Besides, being inflated by the inevitable inclusion of some patients at low risk of amputation, FP does not mean absence of critical ischaemia nor does it always reflect the effects of a single graft per limb. Not surprisingly, often the primary literature omitted FP, mentioned it briefly, or measured it inadequately.

Since, the confidence intervals for the pooled estimates overlapped so extensively, there are probably no statistically significant differences between the graft types. Although these differences are explainable by chance, surgeons must rely on available data and search for trends in these data.

A superior early SP for peripheral allografts compared to UVAs likely was the consequence of a thinner wall and better handling characteristics, but since peripheral allografts were on average 10 years more recent, improved surgical skills over time should also be considered as a factor. On the contrary, the fate of initially patent grafts was less favorable for peripheral allografts, probably because of immunological rejection, which seemingly does not interfere at the same extent with glutaraldehyde-tanned UVAs. Interestingly, CSVAs showed better SP and worse FP than cryopreserved allografts, possibly because of inclusion of patients with more advanced limb ischaemia in meta-analyses for CSVA series. That the pooled SP was lower than the pooled FP at 1-month indicated that many CSVA patients were beyond the scope of limb revascularisation. In addition, the small gap between the survival curves of SP and FP revealed a close dependence of FP on a functioning CSVA bypass, which is typical of end-stage vascular disease. However, even the provisional acceptance of any advantage for CSVAs must be tempered by a lack of biological plausibility, insufficient data and possible hidden bias. Preventing transmission of viral infection remains a major challenge, to the point that using CSVAs became arguably unethical.[5]

Longer storage of cryopreserved allografts allows a time interval for better screening of viral agents,[5] but even the avoidance of bacterial and fungal infection remains problematic.[2] Since, these allografts had superior early SP, they may be useful in overcoming critical ischaemia for a short time, especially when a pedal bypass is indicated or the risk of wound infection is increased. Presumably in such a situation UVAs, which include a surrounding synthetic mesh, and PTFE grafts are useless. Cryopreserved allografts may benefit from standard antirejection therapy,[3] but this is hardly acceptable for the aged patient with severe atherosclerosis, ischaemic, and often infected ulcers. Since, repeat

attempts at revascularisation were evident in two series that included 49% of the CVAs,[2,21] and in one series that contained 60% of the CAAs,[5] the wide gaps between the pooled survival curves of SP and FP for cryopreserved allografts were misleading. On the other hand, the acceptable FP rates indicated that a policy of using these allografts to avoid major amputation may be more effective than a strategy that resorts to UVAs.

When compared to meta-analyses of peripheral allografts, the meta-analysis of UVAs showed a lower early pooled SP, but the pooled survival curve of 16 UVA series crossed the pooled survival curve of 10 CVA series relatively early in follow-up. Although the time of crossing the curves of CAAs and CSVAs was delayed until 31- and 48-months, respectively, the meta-analyses for these peripheral allografts included only a few studies. These findings reflect a higher patency stability for UVAs which was resistant to exclusion of the most successful study and to sensitivity analysis done under extreme assumptions. This property of the UVA may reflect a lesser degree of immunological rejection and also an inherent resistance to thrombosis, as already found for this graft in above-knee femoropopliteal revascularisation.[1] Since, the pooled FP was uniformly lower for UVAs than for cryopreserved peripheral allografts, with no crossing points in their pooled survival curves, FP was also influenced by causes other than SP and patency stability. Less opportunity for, and less inclination towards repeat revascularisation in the past are plausible causes.

Of note, Dardik's et al.[8] achieved high success with UVAs, and the results were only inferior to two series of PTFE grafts.[41,42] The improvement achieved in that singular UVA series was a consequence of both increased SP and increased patency stability. Indeed, sensitivity analysis that excluded that study decreased the 1-month SP by 5.0% and the 5-year patency ratio by 6.0%. Although it remains unclear whether the most important factor were the use of a distal arteriovenous fistula, oral anticoagulation, or new graft technology that eliminated problems of graft degradation,[8] the results of that study represent a favorable prospect for UVAs.

The future seems less uncertain for peripheral allografts. In a comparison with the reference meta-analysis of PTFE grafts, the pooled SP was equivalent for CSVAs until 2-years of follow-up, although this measure was less successful for cryopreserved allografts. In contrast, the pooled FP for the latter was encouraging, probably as an effect of repeat revascularisation procedures. In addition to strategic use in preventing major amputation, peripheral allografts are especially useful for *in situ* replacement of infected prosthetic grafts.[43]

In the assessment of graft patency, it is widely recognised that graft material, degree of ischaemia, level of distal anastomosis and secondary bypass are strong predictive variables. All except the latter were naturally restricted by design thus providing an effective protection against bias. Since, UVA series did not contain pedal bypasses and apparently included fewer secondary bypasses, UVA patients possibly had a lower underlying risk, which only reinforces the evidence against UVAs.

Most of the potential sources of bias in the original studies proved to be unfounded and did not impair internal validity of the meta-analyses. First, UVA studies as older studies followed methodological standards of the past. Overestimation of the pooled SP was a possibility because of the use of 'cumulative patency,' but this expression likely described SP in those studies. Still because UVA studies were older, their lower scores of quality do not mean unreliable assessment of outcomes. Indeed, there was no correlation between quality score and 1-year SP neither in peripheral allograft series nor in UVA series. Second, the inclusion of a series[20] for which SP was subjectively inferred from PP decreased the pooled SP by only a little, 1.4% at 5-year follow-up. Third, inclusion of popliteal and pedal bypasses in most series of peripheral allografts, and loss to follow-up generally, were concerns that sensitivity analysis under extreme assumptions eliminated. However, at least three limitations should be recognised. First, these were meta-analyses of observational studies, so the possibility of bias increases. Second, the life-tables reconstructed were but an approximation in 15 of the 33 studies used in meta-analysis of SP. Third, often it was unclear whether events related to graft degradation counted as graft failures.

Bias from sources other than the original studies was also unlikely. Publication bias was not detected, though several grafts were omitted in the most successful series of UVAs. Random-effects modelling avoided overestimation of parameters and undue precision in all the meta-analyses. In conclusion, meta-analysis indicated that graft patency after distal bypass surgery is poor for allografts generally. While the use of peripheral allografts in repeat attempts at revascularisation is a valid strategy to prevent major amputation, a precise role for UVAs remains uncertain.

Appendix A. Assessment of survival analysis and quality scores in 33 series of allograft bypasses

Author	Claudication (%)	Secondary bypass (%)	Popliteal/ pedal bypass (%)	Life-table	1-mo interval	Losses described (%)	Censored 1-year (%)	Measures	Risk-set	Quality score
CAA-cryopreserved arterial allografts										
Simeón[7]	0	60	?	+	+	+	20	SP, FP		10
Alonso[6]	0	75	7/0		+		53	PP, SP	+	11
Castier[4]	0	74	14/0		+		34	PP, SP, FP	+	12
Albertini[5]	0	100	0/13	+	+	+	23	PP, SP		9
CVA-cryopreserved vein allografts										
Ochsner[18]	4	83	36/1				23	CPR	+	5
Harris[14]	0	76	8/4	+	+	+	28	SP	+	10
Walker[19]	13	87	7/3		+		10	PP, SP	+	9
Martin[21]	18	94	12/1		+		10	PP, SP, FP	+	11
Posner[15]	0	62	9/29		+		19	SP	+	8
Carpenter[16]	0	90	8/15		+		13	SP, FP	+	9
Lesèche[17]	0	64	0/8		+		36	SP, FP	+	10
Buckley[3]	0	27	0/0		+		15	SP, FP	+	10
Harris[20]	?	46	31/9	+	+		40	PP, FP	+	9
Farber[2]	2	59	0.5/9		+		20	PP, SP, FP	+	12
CSVA-cold-storaged vein allografts										
Van Reed Dortland[12]	?	?	0/0	+			16	CPR		6
Rebane[10]	0	33	37/0		+		4	SP		8
Sacilotto[9]	0	67	13/8	+	+		23	SP, FP	+	11
Cranley[28]	0	?	0/0		+		20	CPR		4
UVA-UVAs umbilical-cord vein allografts										
Klimach[22]	0	27	0/0		+	+	21	CPR	+	7
Robison[29]	0	44	0/0		+		25	CPR		5
Raithel[30]	?	?	0/0	+	+	+	12	CPR		5
Sciacca[32]	0	?	0/0				20	CPR		3
Harris[35]	8	77	45/0		+		15	CPR, FP	+	7
Guasch[13]	?	?	0/0	+	+		15	SP		7
Barry[33]	0	?	0/0		+		22	CPR		4
Largiader[23]	?	?	0/0				8	CPR		4
Nevelsteen[34]	0	29	0/0		+		20	PP, SP, FP		5
Harling[24]	0	?	0/0		+		22	CPR		5
Dardik[31]	4	?	0/0	+	+		14	PP, SP, FP		7
Batt[25]	0	42	0/0		+		15	PP, SP, FP	+	10
Sommeling[26]	?	?	0/0		+		14	SP		6
Moody[27]	0	54	0/0		+		25	SP, FP	+	8
Dardik[8]	?	47	0/0	+			16	PP, SP, FP	+	9

++: use in all or most patients; +: use in few patients; -: no use; ?: not informed; +: presence of required item; CPR refers to cumulative patency rate.

Appendix B. Statistical notes

The Strategy

A strategy was constructed to combine survival data because different grids of time intervals had been used in the series reviewed. In the first step, units of analysis (grafts or limbs) censored at intervals greater than 1-month were redistributed in equal quantities at 1-month intervals. Next, the numbers of failed grafts or lost feet were obtained for intervals of 1-month; this was done by using the units at risk at the start of an interval, the redistributed censored units, and the interval hazard rates. Kaplan–Meier success rates were then calculated for each series and each month of follow-up and used as treatment effects. This approach assumed constant hazard rates within long time intervals and the mid-point of such intervals as the survival time for censored units as is usual in actuarial life-tables.

In the second step, an *ad hoc* procedure was used to obtain a within-series variance (s^2) for each monthly

success rate in each series; next, a between-series variance (τ^2) was calculated for each month and a between-interval variance (δ^2) was calculated for each series.

In the third step, random-effects modelling was used to obtain pooled measures of treatment effect for each month of follow-up and it was assumed that the treatment effect in each study varies monotonically with time. Random-effects modelling assumes that included studies are a random sample of the universe of studies.

Finally, the product of successive monthly pooled measures of treatment effect yielded pooled measures of cumulative success, for which approximate confidence intervals were calculated.

The statistical problem

Since, this meta-analysis dealt with case series studies, the problem here was one of parameter estimation, not hypothesis testing. Consequently, pooled measures were estimated and standard-errors were calculated for them. It would not be possible to derive *P*-values because formal statistical comparisons were not pursued.

Interval success rate

For each series i and each month j of follow-up, an interval success rate, λ_{ij}, was determined as follows:

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

where f_{ij} is the number of failed grafts and n_{ij} is the number of grafts at risk.

Within-series variance

Since, λ_{ij} was frequently 1.00 or close to 1.00, an *ad hoc* procedure was applied to calculate the within-series variance, s^2_{ij}, as follows:

$$s^2_{ij} = \frac{(f_{ij} + 1)(n_{ij} - f_{ij} + 1)}{(n_{ij} + 2)^3}$$

Between-series variance

For each month j (j=1,2,…,60) the between-series variance, τ^2_j, was calculated as follows:

$$\tau^2_j = \frac{\{[\sum n_i(\lambda_i - \lambda_{i.})^2]/\sum n_i\}k_j}{(k_j - 1)}$$

where, in the target month j, λ_i is the success rate in study i(i=1,2,…,k_j), $\lambda_{i.}$ is the average for $\lambda_{i,}$ n_i is the number of units at risk in study i, and k_j is the number of series available.

Between-interval variance

For each series i the between-interval variance, δ^2_i, was calculated as follows:

$$\delta^2_j = \frac{[\sum(\lambda_j - 1 + W_j)^2]}{(t_i - 1)},$$

where, in the target series i, n_j is the number of grafts at risk at month j, λ_j is the success rate at month j, W_j is the Weibull hazard rate at month j, and t_i is the number of time intervals available.

The Weibull model uses the shape parameter (α) and the scale parameter (β) to describe the hazard function according to the equation below:

$$W_{(t)} = \alpha\beta(\alpha t)^{(\alpha-1)}.$$

The parameters α and β were calculated for each study separately and were obtained by a linear regression of $\ln[-\ln S_{(t)}]$ on $\ln t$, in which ln refers to natural logarithms and $S_{(t)}$ is the survival estimate at time t. The slope of the regression line is an estimate of α and the $\ln t$ intercept an estimate of $-\ln \alpha$.

Weighting and combining the λ_{ij}

Let ω_{ij} be the weight attributed to each λ_{ij}. When using random-effects modelling, it follows that:

$$\omega_{ij} = \frac{1}{(s^2_{ij} + \delta^2_i + \tau^2_j)}.$$

A summary effect estimate, L_j, was obtained for interval graft patency in month j (j=1,2,…,60) as follows:

$$L_j = \frac{\sum \lambda_i\omega_i}{\sum \omega_i},$$

where λ_i is the success rate in the target month j, and ω_i is the weight attributed to λ_i.

Such estimators L_j will be consistent and approximately normal, and are derived based on the fact that the estimators for each series are approximately normal with an estimable variance. Finally, the

product of successive L_j yielded G_j, the summary estimate for cumulated success at month j.

Variance and confidence interval for G_j

After properly corrected, Kaplan–Meier estimates and their respective variances in the original series were used to obtain the variance of G_j. This was done by using again random-effects modelling in a way similar to that of obtaining L_j. The difference was that Peto's within-series variances in study i at month j and τ_j^2 were summed up to weigh the Kaplan–Meier estimates at month j. A summary Kaplan–Meier estimate, K_j, and its variance, $V_{\{Kj\}}$, were thus obtained for month j. Since, K_j and G_j differed a little, the variance of G_j, $V_{\{Gj\}}$, was obtained as follows:

$$V_{\{Gj\}} = \frac{V_{\{Kj\}}[L_j^2(1-L_j)]}{[K_j^2(1-K_j)]}.$$

Confidence intervals for G_j were then obtained by using $V_{\{Gj\}}$.

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