Meta-analysis of polytetrafluoroethylene bypass grafts to infrapopliteal arteries

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Context: **Reports of polytetrafluoroethylene (PTFE) bypass grafting to the infrapopliteal arteries have often used survival analysis of acceptable quality to describe a wide range of long-term results. In theory, these results may be combined if variability between series and time intervals is considered.**

Objective: **Meta-analysis was performed to gain insight into long-term graft patency and foot preservation after PTFE bypass grafting to infrapopliteal arteries.**

Data source: **Studies published from 1982 through 2001 were identified from the PubMed database and pertinent original articles.**

Study selection: **Three investigators selected 43 studies that used survival analysis, reported 2-year patency rates, and included at least 15 bypass procedures.**

Data extraction and transformation: **Based on standard life-tables or survivor curves, an interval success rate was calculated for each month in each series. The monthly success rates were combined across series, enabling construction of pooled survivor curves.**

Data synthesis: **Random-effects meta-analysis yielded 5-year pooled estimates (SE) of 30.5% (7.6%) for primary graft patency, 39.7% (5.5%) for secondary graft patency, and 55.7% (5.0%) for foot preservation. During the entire follow-up, pooled estimates were slightly higher for series of PTFE grafts with adjunctive procedures compared with series of PTFE grafts only.**

Sensitivity analysis: **A simulation using only unfavorable assumptions showed a decrease of less than 5% at 5 years for all outcomes, and smaller differences at subgroup meta-analysis. Funnel plots suggested that publication bias was unlikely.**

Conclusion: **This meta-analysis indicated moderate success for PTFE bypass grafts to infrapopliteal arteries, but the role of adjunctive procedures at the distal anastomosis remains uncertain. (J Vasc Surg 2003;37:1263-9.)**

The great saphenous vein compares favorably with other materials in bypass grafting to infrapopliteal arteries, but this vein and other autologous veins also suitable for bypass grafting may be lacking even when pursuing a policy of maximal use of autologous tissue. The microporous expanded polytetrafluoroethylene (PTFE) graft has been used alternatively, but earlier reports on plain PTFE grafts showed poor results. Further attempts at improving patency have included use of adjunctive procedures at distal anastomosis and PTFE conduits that incorporated a thin wall, an external support, or a tapered end. These changes, along with other factors, are associated with better results, but there has been renewed interest in cryopreserved allografts. A systematic review to appraise usage and combine results of PFTE bypass grafting to infrapopliteal arteries seemed opportune.

Surgical series are potential targets for meta-analysis,[1] but variability among surgeons and patients at different centers challenges validity. This interpretation may be too restrictive when studies deal with a well-defined problem and the severity of disease or use of poorly effective techniques has an important role.[2] Distal PTFE bypass grafting is one such problem, because most studies of patients with rest pain or tissue loss include few pedal bypass procedures and describe less than optimal outcomes. Although surgeon skills may influence early results, the final outcome of an initially patent PTFE graft cannot be considered surgeon-dependent. To understand the role of distal PTFE grafts better, we conducted meta-analysis of published studies of PTFE bypass grafting to infrapopliteal arteries to assess midterm graft patency and foot salvage.

METHODS

Study identification. We read pertinent articles at random to refine research questions and develop the initial version of an instrument for data collection. To comply with broad inclusiveness of studies,[1] we made several modifications to the initial version before defining the final protocol. Using the PubMed database and "PTFE" and "bypass" as descriptors, we performed a search of articles published from January 1980 through December 2001. As a result, we examined the full text of more than 100 articles

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Competition of interest: none.

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for possible inclusion and used the cited references to identify additional studies. The senior author (M.A.), who had participated in a similar meta-analysis,[2] and two undergraduate medical students (V.M.B., A.A.E.R.) conducted the search. The authors were prepared to read articles written in Spanish, French, Italian, and Portuguese, but no useful article was found in a language other than English.

We prevented repeat inclusion of bypass procedures by averting overlap of periods of patient inclusion in studies from the same source, and used 43 studies to include 40 series in analysis of primary graft patency (PP),[3-35] 35 series in analysis of secondary graft patency (SP),[5-22,32-44] and 31 series in analysis of foot preservation (FP) (Appendix A, online only).[4,6,7,9-14,18-25,29,32-39,43,45] In an attempt to retrieve missing data, we sent a letter to the authors of 22 single studies, but the response was disappointing.

Criteria for inclusion. Included articles satisfied the following criteria: publication year from 1982 through 2001; series including at least 15 PTFE bypass grafts to an infrapopliteal artery; use of survival analysis of any type; units at risk for some intervals shown in survivor curves, when life-tables were unavailable; use of PP or SP clearly indicated; and follow-up of 2 or more years.

We violated the above criteria by accepting 7 series with 8% to 29% bypasses to the below-knee popliteal artery,[19-21,35,42,43] 8 series with 36% to 100% composite PTFE-vein grafts in which the PTFE component did not cross the knee joint,[9,15,28,31,40,41,43,44] 1 series with two above-knee PTFE grafts,[35] numbers at risk omitted in one Kaplan-Meier curve,[29] and uncertainty about type of patency or units at risk in 11 studies.[12,15,17,34-37,39-41,44]

Data extraction. The junior authors extracted the data independently from standard life-tables (PP, n = 18; SP, n = 12; FP, n = 8), actuarial survivor curves (PP, n = 18; SP, n = 19; FP, n = 19), or Kaplan-Meier survivor curves (PP, n = 4; SP, n = 4; FP, n = 4). The senior author checked all abstracted data to detect and resolve discordance. When only survivor curves were available, we measured distance between convenient points in these curves to both the time axis and the success axis to obtain survival times and cumulated success rates, respectively. In 44 series (PP, n = 11; SP, n = 15; FP, n = 18), numbers of grafts or feet at risk allowed for reliable reconstructed life tables. These indicators were not supplied for all intervals in 17 series (PP, n = 9; SP, n = 6; FP, n = 2) and were completely lacking in 7 series (PP, n = 2; SP, n = 2; FP, n = 3); consequently, the retrieved life table was less reliable.

For the sake of broad inclusiveness of studies, we often inferred SP from PP data by using information available in the text[11,13,18,21,22,34,35] or assumed SP to be equivalent to "cumulated patency rate."[36,40-42,44] In one study we replaced declared primary-assisted patency with SP.[15] Occasionally we inferred FP from survivor curves for PP or SP.[14,29,34,38] In two series we inferred PP from SP data.[17,38] When life tables or survivor curves omitted outcomes at 1 month, we looked for these data in the Results section. Inasmuch as these outcomes were still missing for 26 series (PP, n = 8; SP, n = 9; FP, n = 9), we restricted analysis of these series to the second follow-up interval and beyond.

Study quality. An ideal study should contain the reasons for using PTFE grafts as well as the proportion of patients requiring these grafts, life tables rather than graphs, 1-month follow-up intervals, losses to follow-up, and description of PP, SP, and FP. Also important are a demographic profile linked to survival analysis, rates of previous operation and tissue loss, regimen of postoperative anticoagulant therapy, incidence of perigraft infection, and data on further bypass grafting. We graded each of these items 1 or 0 so that a perfect study would have a score of 14, with a decrease of 1 point for each unmet requirement. The main features of survival analysis and the measures of study quality are presented in Appendix B (online only).

Selection of outcomes. Outcome measures of interest were PP, SP, and FP. Qualification for PP required uninterrupted patency with no further intervention in the graft or its anastomoses; SP after graft occlusion was achieved when patency was restored and most of the original graft and at least one anastomosis were retained in continuity.[46] Since few studies reported the final level of amputation and none reported survival times,[3,11,15,17,29,35,38,40] this outcome was reviewed only briefly.

Meta-analysis of subsets. We focused on the configuration of PTFE grafts and study quality in subgroup meta-analysis. Pure PTFE grafts were described for PP in 13 series, for SP in 12 series, and for FP in 10 series. PTFE grafts with distal adjuvant procedures were described for PP in 27 series, for SP in 23 series, and for FP in 21 series. Adjunctive procedures included composite PTFE-vein grafts (PP, n = 7; SP, n = 8), patches (PP, n = 6; SP, n = 4), cuffs (PP, n = 4; SP, n = 2), arteriovenous fistulas (AVF) (PP, n = 1, SP, n = 2), or two or more of these procedures combined (PP, n = 9; SP, n = 7). Of the combination procedures, most (PP, n = 7; SP, n = 6) combined AVF and another adjunctive procedure, and few (PP, n = 2; SP, n = 1) combined adjunctive procedures other than AVF. We analyzed all series describing PTFE grafts with adjunctive procedures together, but also considered the influence of adjunctive procedures containing AVF. For convenience, we used 7.5 as the cutoff to categorize scores for study quality. The demographic profile and usual set of risk factors was unavailable for 29 series (PP, n = 13; SP, n = 10; FP, n = 6), limiting subgroup meta-analysis and precluding meta-regression analysis. With two exceptions,[5,44] that information had been linked to a wider group of infrainguinal grafts in these studies.[3,8,18,22,25-28,34,37,41]

Statistical methods. Initially for each series we calculated the success rate for each month of follow-up, and used this rate as the treatment effect. In addition, for each series we obtained within-series variance for each monthly success rate, between-series variance for each month, and between-interval variance (Appendix C, online only).[47-49] These variances were summed to weigh success rates and obtain a

Table I. Pooled estimates of outcomes with random-effects meta-analysis

Follow-up (mo)	*Primary graft patency (n = 40)*	*Secondary graft patency (n = 35)*	*Foot preservation (n = 31)*
1	83.9 (80.4, 87.5)	88.3 (84.9, 91.7)	93.2 (92.8, 93.6)
3	78.0 (73.5, 82.6)	82.3 (77.9, 86.8)	88.4 (84.6, 92.1)
6	69.9 (64.6, 75.2)	75.1 (69.6, 80.7)	83.2 (77.7, 88.7)
12	59.0 (53.3, 64.7)	66.4 (60.1, 72.7)	77.7 (71.7, 83.7)
18	53.9 (48.1, 59.6)	61.4 (55.1, 67.8)	74.1 (67.9, 80.3)
24	48.2 (42.3, 54.0)	56.5 (49.4, 63.6)	70.9 (64.5, 77.3)
36	40.8 (34.3, 47.4)	51.0 (43.2, 58.8)	66.2 (59.6, 72.8)
48	35.1 (27.8, 42.3)	45.5 (35.9, 55.1)	63.1 (55.1, 71.1)
60	30.5 (22.9, 38.2)	39.7 (28.9, 50.5)	55.7 (45.9, 65.5)

Values in parentheses represent 95% confidence interval.
n, Number of series combined.

pooled measure of monthly success in a random-effects meta-analysis, which assumes that included studies are a random sample of the universe of studies. Finally, the product of successive monthly pooled measures of treatment effect allowed us to obtain pooled measures of cumulative success and to calculate approximate confidence intervals.

We investigated Weibull models that best fitted the pooled survival curves. The Weibull model is a statistical survivor function that uses two parameters to describe survival along time. Compared with the Kaplan-Meier product-limit method, the Weibull survival curve decreases continuously, without steps and long flat tails, and better captures continuity in nature.

Sensitivity analysis. Bias was introduced when the included series contained either bypass grafts to the popliteal artery or composite PTFE-vein grafts with above-knee PTFE segments only. To estimate such bias we calculated the median of the appropriate relative risk for graft failure at late follow-up from other studies.[3,4,6,7,18-20,23-29,36,37,41,50-52] For below-knee popliteal grafts, the median was 0.78 for PP and 0.85 for SP, whereas for above-knee popliteal grafts and composite grafts with an above-knee PTFE only, the median was 0.65 for PP and 0.60 for SP.

A second source of bias was loss to follow-up, because up to 60% of grafts lost within the first year may represent failed grafts.[53] We used data from six studies to calculate averages for the proportion of lost units relative to censored units.[9,16,22,30,31,32] These averages were 22% for the first month, 47% from 2 to 6 months, and 18% from 7 to 12 months. To mount a plausible scenario, we used 60% of the grafts possibly lost within the first year of follow-up as additional failures and a relative risk for failure of 0.75 for below-knee popliteal grafts. For above-knee PTFE grafts and composite grafts with the PTFE part above the knee joint, our data would not tolerate a relative risk for primary graft failure lower than 0.89; consequently, we used this risk for PP, and 0.60 for both SP and FP.

Publication bias in meta-analysis of comparative studies has been investigated with funnel-plot graphs. This technique plots study size against the treatment effect and enables the meta-analyst to see, among studies of small size, whether those describing higher results are in greater number than those describing lower results.[54] Symmetric plots around the pooled estimate indicates absence of publication bias. In this meta-analysis we plotted study size against 18-month outcomes in individual series.[54]

RESULTS

Pooled estimates for PP, SP, and FP and their corresponding confidence intervals at some selected points in follow-up are shown in Table I. Risk for secondary graft failure exceeded risk for foot loss by a multiplication factor of 1.36 to 1.72. In eight studies reviewed, thigh amputation accounted for 8% to 100% (median 49%) of foot losses.

Random-effects plots were nicely fitted by Weibull models, and sensitivity analysis with these models showed absolute decrease at 5-year follow-up of 2.9% for PP, 3.0% for SP, and 4.9% for FP (Fig 1). Assumptions on loss to follow-up were the main contributors to such decreases: 94% for PP, 97% for SP, and 96% for FP. When we considered fixed-effects modeling, absolute increase in the 5-year estimate was 2.2% for PP, 1.7% for SP, and 4.4% for FP.

Subgroup meta-analyses showed higher pooled estimates for PTFE grafts with adjunct procedures than for PTFE grafts alone, but confidence regions overlapped (Table II). Sensitivity analysis of this comparison decreased the difference in 5-year estimates, from 5.0% to 3.4% for PP (Fig 2), from 9.8% to 5.2% for SP, and from 2.6% to −1.9% for FP. Series of superior quality performed better for PP and FP but not SP (Table II). Funnel plots symmetric around averaged outcomes indicated that severe publication bias was unlikely (Appendix D, online only).

DISCUSSION

Uncontrolled series are naturally available from surgical practice and do not pose complex ethical issues, but they are a poor source of scientific evidence. Meta-analysis targets this weakness, and may expand the scientific importance of such series, although this possibility depends on general acceptance of some standards. Of prime interest for the particular case of distal PTFE grafts, all patients should be followed up for at least 1 year; reporting of both PP and SP should be mandatory; and an outcome measure com-

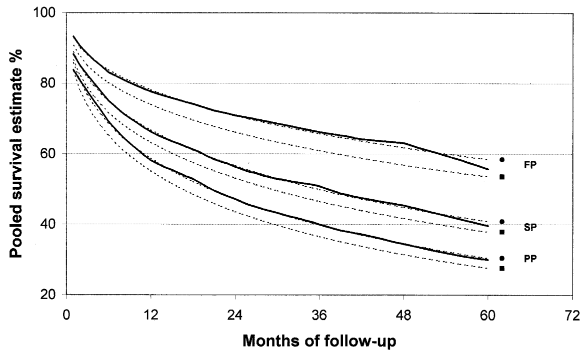

Fig 1. Pooled survivor curves for primary graft patency *(PP)*, secondary graft patency *(SP)*, and foot preservation *(FP) (continuous lines)* closely match Weibull survivor curves *(dotted lines with circles)*. Sensitivity analysis at a plausible scenario *(dotted lines with squares)* is also represented.

bining patient survival, FP, and SP should be used. These measures will reduce bias and better reflect patient experience. Second, standard life tables are preferred to survivor curves and separate loss to follow-up from other mechanisms of censoring. In addition to being imprecise and prone to error, life tables reconstructed from survivor curves cannot retrieve losses to follow-up. Third, first follow-up at 1 month is an obvious need, and subsequent follow-up intervals should be as short as possible and encompass all available data. This should prevail over the recommendation of omitting estimates with SE greater than 10%. Except for the latter, the preceding items have all been recommended.[46]

Pooled patencies for distal PTFE grafts compared favorably with published estimates for allograft vessels. For the 18-month follow-up, pooled PP of 53.9% was surpassed in one study with 26 venous allografts[55] and another study with 17 arterial allografts,[56] but a set of nine allograft series published in the last decade showed a dismal median PP rate of 36%.[55-63] Although illustrative, the foregoing must be interpreted carefully. Indeed, allografts have been used mainly as a last resort alternative, and secondary PTFE grafts sometimes account for fewer than half the cases.[4,9,13,23,25,35,36,40] Several allograft series have also included a greater proportion of either more favorable popliteal bypass grafts or less favorable pedal bypass grafts.

Despite the importance of achieving acceptable graft patency rates, FP is of utmost importance, mainly for patients, and a 1-year FP rate as low as 45% may justify infrainguinal bypass grafting in terms of walking ability and quality of life.[64] The present study was thus reassuring for the use of distal PTFE grafts, because the lower limits of the confidence intervals for pooled FP were greater than 45% in the main meta-analysis (Table I) and the subgroup meta-analyses (Table II). With properly selected patients with critical ischemia at baseline, ischemic symptoms are likely to reappear after graft failure, although this may be less valid if the graft has functioned for a year or longer.[14,31,34] This idea is compatible with the pooled curves for FP being nearer to the pooled curves for SP than to 100%. Clearly, FP does not mean absence of critical ischemia, and the differences between pooled estimates of FP and SP reflect the joint effect of multiple PTFE grafts per limb, repeat bypass procedures with other graft materials, and the inevitable inclusion of some patients at low risk for amputation. Since the gap between SP and FP rates seems exaggerated, SP rates may be more reliable, but this interpretation still supports the merits of PTFE grafts.

For all three outcome measures, pooled estimates were higher along follow-up for series of PTFE grafts with adjunct procedures compared with series of plain PTFE grafts; however, the overlap of confidence regions gave poor statistical support to the corresponding differences. Inconsistencies were found for the influence of study quality and use of AVF with regard to SP. In addition, the difference of 1.2% between SP and PP within series of PTFE grafts containing an adjuvant AVF can suggest that AVFs were used in more adverse situations. On the contrary, the difference of 1.3% for FP would indicate similar risks for AVFs and other adjuncts. Further studies are necessary to determine the role of adjuncts in general.

Weibull models gave the best fit for all three outcomes with surprisingly good precision. This capture of continuity in nature may strengthen this meta-analysis in particular and the meta-analysis of survival data in general. Weibull models were also useful for sensitivity analysis and to show this analysis graphically. Changes of less than 5% were observed in the main meta-analysis, and the differences in favor of PTFE grafts with adjuncts decreased in subgroup meta-analysis. As strongly recommended approaches,[1,54] sensitivity analysis and investigation of selective publication indicated the robustness of our results and resistance to bias from many sources.

This meta-analysis averted the inconvenience of estimating event rates at a specific time by constructing more informative pooled survivor curves. Which intervals to target in such meta-analysis depends on the research problem and on the intervals used in the articles reviewed. Longer intervals were used in meta-analysis of infrainguinal bypass surgery,[2] but early events after PTFE grafting are frequent enough to justify monthly intervals here. To better account for variability, we used random-effects modeling and consequently obtained estimates that were slightly less optimistic and approximately 50% less accurate. In contrast, other authors have simply used numbers at risk to weigh survival rates,[65] but this approach omits variability of any sources and does not represent a typical meta-analysis. More complex Bayesian methods have been reported.[66]

At least two limitations must be recognized. First, this was an observational study of other observational studies, so the possibility of bias increases. Second, the reconstructed life tables were but an approximation. However, this meta-analysis outlined a strategy for dealing with survival data and provided solutions for some problems commonly encountered in the reviewed studies. It also confirmed that variability among series is an important issue to

Table II. Subgroup meta-analysis based on 18-month follow-up

	Primary graft patency		*Secondary graft patency*		*Foot preservation*	
	Size	*Pooled estimate (%)*	*Size*	*Pooled estimate (%)*	*Size*	*Pooled estimate (%)*
All series	40	53.9 (48.1, 59.6)	35	61.4 (55.1, 67.8)	31	74.1 (67.9, 80.3)
Type of graft						
Without adjuncts	13	45.3 (35.8, 54.8)	12	55.3 (44.7, 65.9)	10	71.7 (61.0, 82.5)
With adjuncts	27	56.8 (49.9, 63.6)	23	64.2 (56.5, 71.8)	21	74.5 (66.9, 82.1)
Adjuncts with an arteriovenous fistula	8	57.2 (47.0, 67.4)	8	58.4 (49.2, 67.7)	8	75.4 (63.1, 87.7)
Other adjuncts	19	56.6 (48.1, 65.0)	15	66.0 (55.7, 76.4)	13	74.1 (64.4, 83.7)
Quality score						
3–7	21	50.3 (41.3, 59.3)	18	63.0 (51.6, 74.3)	14	67.5 (55.4, 79.5)
8–12	19	56.4 (49.1, 63.6)	17	60.4 (53.4, 67.5)	17	76.8 (71.5, 82.1)

Values in parentheses represent 95% confidence interval.

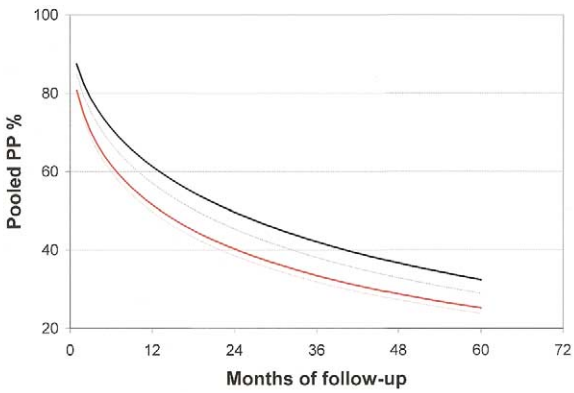

Fig 2. Weibull survivor curves describing primary patency for series of PTFE grafts with adjuncts *(black line)* and series of plain PTFE grafts *(red line)*. Sensitivity analysis demonstrated by *dotted line*).

consider, at least for earlier months of follow-up. In favor of validity, distinctive features of the studies reviewed included survival analysis of acceptable quality, high response rates that increased the precision of estimates, use of similar designs to answer some research questions, and existence of a reference population to which the conclusions drawn can be applied. Since graft material, degree of ischemia, and level of distal anastomosis were restricted by design, the effects of other possible confounders were judged tolerable. In conclusion, meta-analysis revealed moderate success for distal PTFE bypass grafts, but the usefulness of adjunctive procedures at the distal anastomosis remains uncertain.

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