An updated meta-analysis of infrainguinal arterial reconstruction in patients with end-stage renal disease

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Background: **A previous meta-analysis reported on the mid-term outcomes of infrainguinal bypass grafts in patients with critical limb ischemia and end-stage renal disease. Given the competing interest in endovascular procedures, the results of bypass surgery must be assessed as precisely as possible for future comparison. In this study, the original meta-analysis was refined and updated by increasing the number of studies reviewed, estimating primary graft patency, extending follow-up time, and investigating the problem of early amputation despite a patent graft.**

Methods: **Studies published from 1987 through 2005 were identified from two electronic databases. Two investigators independently extracted the survival data from life tables, survival curves, and texts. Pooled survival curves were then constructed for graft patency, limb salvage, and patient survival according to a random-effects protocol for meta-analysis.**

Results: **Of 28 articles included, 18 reported amputation despite a patent graft in 84 (10%) out of 844 limbs, and 25 described a perioperative mortality of 88 (8.8%) out of 996 patients. The 5-year pooled estimate (SE) was 50.4% (15.4%) for primary patency, 50.8% (19.0%) for secondary patency, 66.6% (11.2%) for limb salvage, and 23.0% (11.7%) for patient survival. No publication bias was detected.**

Conclusions: **Limb salvage can be achieved in most end-stage renal disease patients who undergo bypass surgery for critical ischemia, but survival is poor. To avoid early amputation despite a patent graft, bypass grafting should not be offered to patients with a great amount of tissue loss or extensive infection. (J Vasc Surg 2007;45:536-42.)**

Widespread atherosclerosis is common in patients with end-stage renal disease (ESRD), defined as the requirement for renal replacement therapy. Because diabetes mellitus and high blood pressure are risk factors common to both diseases, it is not surprising that approximately 5% of ESRD patients develop critical limb ischemia.[1,2] Consequently, some form of revascularization or primary amputation must be considered for these patients, who also have impaired immunity, susceptibility to infection, and poor wound healing.[3,4] Given the competing interest in endovascular procedures,[1] the results of bypass surgery must be assessed as precisely as possible for future comparison. A previous meta-analysis of infrainguinal bypass grafts in ESRD patients that was published in 2001 estimated the graft patency, limb salvage, and patient survival,[2] but many other reports have been published in the intervening period. For this reason, this study aimed to refine and update that meta-analysis by assessing primary and secondary patency separately, obtaining more precise estimates for all of the targeted outcomes, and extending the follow-up period. Secondary objectives included an investigation of both duplex scanning for graft surveillance and early amputation despite a patent graft.

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Competition of interest: none.

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0741-5214/$32.00

doi:10.1016/j.jvs.2006.11.036

METHODS

Study search. An electronic search of the PUBMED and EMBASE databases covering January 1, 1987, to December 31, 2005, was performed by using the descriptors "end-stage renal disease" and "bypass." Abstracts of articles selected by title were read online to reduce the number of articles for full-text examination. Finally, additional titles were sought in the bibliographies of the retrieved articles.

Criteria for inclusion. The articles included satisfied the following requirements: (1) patients with ESRD were analyzed separately; (2) graft patency or limb salvage was the outcome of interest; (3) survival analysis was used to describe at least one outcome or sufficient data were presented that allowed the reconstruction of a life table; (4) a follow-up period of 1 year or more, at least for some patients; (5) publication in 1987 or later; and (6) no repeat inclusion of patients. Whereas the original meta-analysis included 16 articles,[3-18] this update added another 12 articles[19-30] (Table I). Two articles that included the same 10 patients were used to assess different outcomes.[11,27]

Data extraction. Two authors (M.A. and M.R.) extracted the data independently and resolved disagreements by discussion on several occasions. The outcome measures of interest were recommended standards that included primary and secondary graft patency, limb salvage, and patient survival.[31] The survival data were extracted from 15 life tables, 44 survival curves that showed the number of

Table I. Articles included in the updated meta-analysis

Author	*Year*	*n*	*m*	*Graft patency*		*Limb salvage*	*Patient survival*
				Primary	*Secondary*		
Edwards[15]	1988	19	25	+	+	+	+
Chang[18]	1990	24	32	+	−	+	−
Harrington[5]	1990	39	56	+	+	+	+
Wasserman[14]	1991	37	37	−	+	+	+
Sanchez[6]	1992	47	69	−	+	+	+
Whittemore[8]	1993	12	16	+	+	+	+
Lumsden[16]	1994	27	34	+	−	+	+
Sakurai[17]	1995	11	14	+	+	+	+
Baele[7]	1995	44	57	+	+	+	+
Johnson[4]	1995	53	69	+	−	+	+
Harpavat[12]	1998	20	25	+	+	+	+
Peltonen[11]	1998	10	11	+	−	−	−
Hakaim[10]	1998	23	25	+	−	+	+
Leers[3]	1998	34	41	−	+	+	+
Nicholas[29]	2000	57	66	−	−	+	+
Treiman[9]	2000	11	11	+	+	+	+
Korn[13]	2000	23	33	+	+	+	+
Cox[20]	2001	63	78	+	+	+	+
Lantis[25]	2001	60	78	+	+	+	+
Meyerson[24]	2001	64	84	+	+	+	+
Reddan[21]	2001	20	31	−	−	+	−
Biancari[27]	2002	21	25	−	+	+	+
Ramdev[22]	2002	146	177	+	+	+	+
Kimura[23]	2003	22	33	−	+	+	+
Wölfle[26]	2003	34	37	+	+	+	+
Schwarzbach[30]	2004	36	50	−	−	+	+
Georgopoulos[28]	2005	39	56	+	+	+	+
Chambon[19]	2005	41	50	+	+	+	−

n, Number of patients; *m,* number of bypasses; −, not included in the meta-analysis; +, included in the meta-analysis.

grafts at risk for at least some intervals, and 7 plain survival curves that omitted the number at risk. The survival data were also extracted from the text and another source: either a life table or a survival curve describing a different outcome in 10 instances, from the text alone in 14 instances, and from individual patient data in 4 instances. Authors of four articles kindly provided additional information on request.[19-22]

Study quality. An ideal study should contain life tables rather than graphs, the 1-month follow-up, a 5-year follow-up, no flat tails, and a report of primary and secondary patency, limb salvage, and patient survival. Also important are a demographic profile linked to survival data, the type of renal replacement therapy, the rate of previous operation and tissue loss, a measurement of runoff, regimens of postoperative anticoagulant therapy, the rate of vein use, the rate of amputation despite a patent graft, mention of the use of duplex scanning for graft surveillance, and data on further procedures. Each of the preceding items was graded as 1 or 0, so that a perfect study would score 18.

Statistical methods. Random-effects meta-analysis combined monthly rates of success from single series to yield a pooled estimate of success for each month of follow-up. The product of successive monthly pooled estimates of success then yielded a pooled measure of cumulative success. Within-study and between-study variances, calculated as previously reported,[2] reduced the influence of study size on the pooled estimates, and a standard error was calculated for these estimates at selected intervals (Appendix). The hazard rate or the instantaneous risk of an event (graft failure, amputation, or death) was calculated at monthly intervals to investigate the relationships between outcomes.

Sensitivity analysis. Sensitivity analysis was mostly restricted to limb salvage because this outcome was more relevant than graft patency, did not depend on the type of patency reported, and was described in more articles. Funnel plots were used to assess publication bias, and the effects of a fixed-effects model of meta-analysis, which assumes null between-study variances, were also investigated. To better investigate the relationship between any two outcomes, the articles that did not report both of the outcomes were excluded. Finally, studies that contained inflow procedures alone were excluded.

RESULTS

Characteristics of the original studies. This update of 28 articles included 1314 procedures performed in 1272 lower limbs of 1027 patients, of whom 964 were dialysis dependent, 58 had a renal transplant, and 5 had renal insufficiency not necessitating dialysis. There were 1285 infrainguinal surgical procedures (bypasses, 99%; other, 1%), 14 axillofemoral bypasses, 2 aortofemoral bypasses, 5 iliofemoral bypasses, and 8 percutaneous transluminal an-

Table II. Covariates at the study level in 28 studies included in the updated meta-analysis

Variable	*Median*	*Range*	*Missing data*
No. patients	34	10-146	
No. procedures	39	11-177	
Publication year	1999	1988-2005	
Score of quality	10	4-13	
Mean age (y)	63	45-67	3
Women (%)	41	12-56	5
Diabetes (%)	80	55-100	2
Smokers (%)	39	0-74	7
Claudication (%)	0	0-12	2
Rest pain (%)	20	0-67	5
Tissue loss (%)	79	33-100	4
Infrapopliteal bypass (%)	69	7-100	5
Vein use (%)	85	43-100	5

gioplasties. The study design was retrospective in all of the 28 studies, but only 14 of these reported all of the outcomes. Demographic and surgical variables of interest were reported in most articles (Table II), but only three articles reported a measure of runoff. The number of articles that contributed at least 1 series to follow-up was 22 (81%) at 2 years, 16 (59%) at 3 years, 10 (37%) at 4 years, and 7 (26%) at 5 years. The average follow-up time ranged 5.5 to 27 months (median, 12 months).

Limb salvage was reported in all but one article, whereas primary patency was omitted in 7 articles (274 patients), secondary patency was omitted in 8 articles (250 patients), and patient survival was omitted in 4 articles (95 patients). Only 5 studies with a total of 257 grafts (vein, n = 243; prosthetics, n = 14) used graft surveillance with duplex scanning routinely and also assessed primary and secondary patency. The rate of limb salvage at 1 year varied widely among the studies (Fig 1), and only two studies did not show a flat tail for at least one outcome. Eighteen articles reported amputation despite a patent graft for 84 (10%) of 844 limbs, whereas 25 articles described a perioperative mortality of 88 (8.8%) of 996 patients.

Main outcomes. The pooled estimates of the targeted outcomes are shown in Table III. The difference between primary and secondary patency was 6.0% or less at all yearly intervals but reached a maximal value of 7.8% at 30 months (Fig 2). There was an absolute decrease in the crude rate of graft failure of 5.1% for 18 studies that assessed both types of patency and 10.1% for five of these studies that used graft surveillance with duplex scanning routinely. When the latter studies were pooled, the maximal difference between primary and secondary patency became 12.6% at 36 months. In a graphical display of pooled survival curves (Fig 2), primary patency and patient survival were almost identical up to 7 months, but the curve for the latter decreased much faster thereafter.

During the first 2 years of follow-up, the difference in the hazard rates for amputation and loss of secondary patency was 2.9% (7.5% vs 4.6%) in the first month, less than 1.0% up to 9 months, and predominantly negative in the remaining 15 months (Fig 3). Consequently, the curve for limb salvage crossed the curve for secondary patency to occupy a higher position at 2 years and beyond.

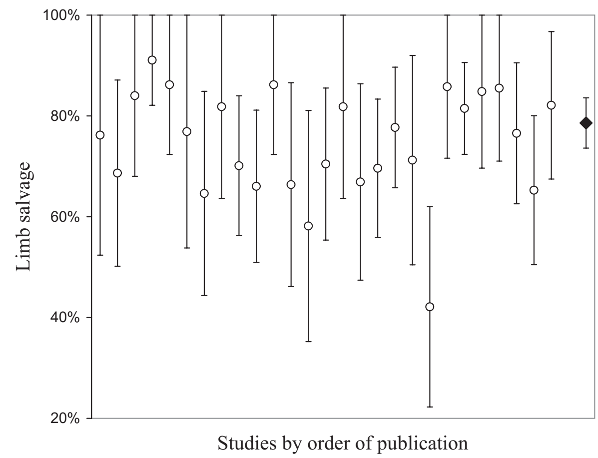

Fig 1. One-year limb salvage in 28 studies *(circles)* and in the updated meta-analysis *(diamond)*. *Bars* indicate the 95% confidence interval.

Table III. Meta-analysis estimates of graft patency, limb salvage, and patient survival

Month	*Primary patency*	*Secondary patency*	*Limb salvage*	*Patient survival*
1	94.2 (1.8)	95.4 (1.5)	92.5 (1.6)	95.2 (1.8)
3	88.2 (2.2)	91.0 (2.1)	88.7 (1.9)	89.6 (1.0)
6	81.4 (3.2)	87.8 (2.8)	84.2 (2.3)	82.7 (1.0)
12	74.9 (3.1)	80.9 (2.5)	78.6 (2.6)	71.6 (1.2)
24	69.8 (4.5)	74.6 (3.9)	74.7 (3.7)	53.3 (4.1)
36	60.8 (6.6)	66.6 (7.3)	69.3 (5.8)	41.0 (5.1)
48	55.6 (9.6)	57.6 (12.7)	66.6 (7.4)	32.5 (8.7)
60	50.4 (15.4)	50.8 (19.0)	66.6 (11.2)	27.5 (11.7)

Values are pooled estimates (SE).

In the studies reviewed, the 1-year limb salvage rates correlated weakly with the rates of black patients (r = 0.37), distal anastomosis at the popliteal artery (r = 0.33), and vein use (r = −0.38); the rates of amputation despite a patent graft correlated weakly with the rates of black patients (r = 0.49), diabetic patients (r = 0.45), and vein use (r = 0.48). In the updated meta-analysis, the 1-year pooled limb salvage for eight studies that used duplex scanning for graft surveillance routinely did not differ importantly from the remaining studies that used this tool less frequently or omitted the strategy adopted (68.8% vs 64.9%).

Sensitivity analysis. A modified funnel graph was symmetrical for a study size of less than 30, thus indicating that there was no publication bias, at least for limb salvage (Fig 4); in addition, the 5-year pooled limb salvage increased from 66.6% to 69.7% when a fixed-effects model of meta-analysis was used. With regard to the relationship between outcomes, the difference between primary and

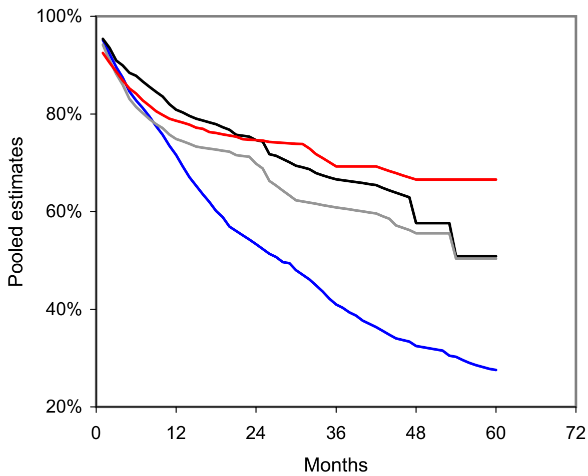

Fig 2. Pooled survival curves of primary *(gray)* and secondary *(black)* graft patency, limb salvage *(red)*, and patient survival *(blue)*.

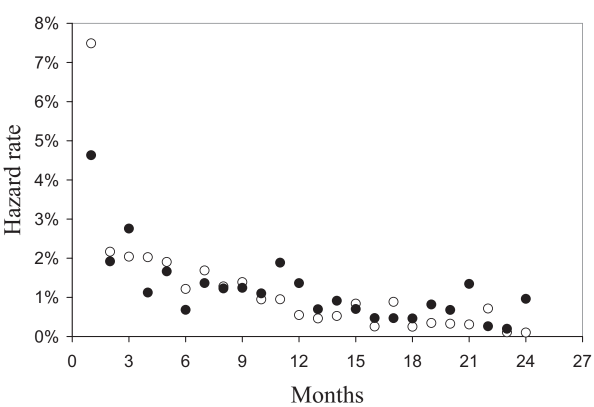

Fig 3. Hazard rates for amputation *(open circles)* and loss of secondary patency *(full circles)*.

secondary patencies increased from 7.8% to 8.1% at 30 months, whereas the crossing point of the survival curves for limb salvage and secondary patency moved from 24 to 18 months. When five studies that contained inflow procedures alone were excluded, the 5-year estimate of limb salvage increased by 0.8%.

DISCUSSION

This updated meta-analysis more than doubled the number of procedures and patients included in the original meta-analysis and extended the length of follow-up from 2 to 5 years. Moreover, the methods used were refined by summarizing primary and secondary patency separately and using pooled survival curves for the main outcomes. Because flat tails in the pooled survival curves overestimated graft patency and limb salvage in the long run, it would be better to examine the 4-year results.

The use of primary and secondary patency yielded more reliable estimates of graft function than in the original

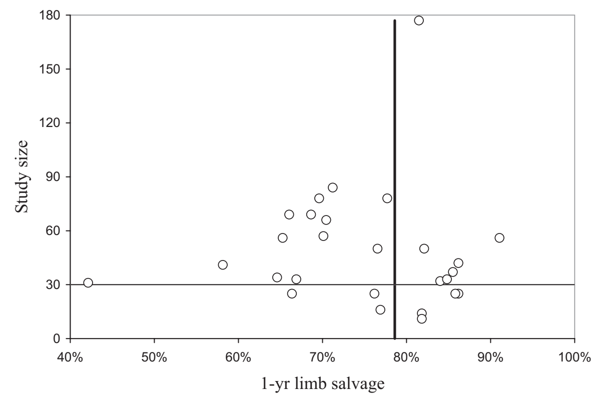

Fig 4. A funnel graph symmetric around the pooled estimate *(vertical line)* for study size less than 30 did not indicate the presence of publication bias.

meta-analysis, in which primary patency was not studied and secondary patency was clearly defined in only 10 of the 16 studies. The updated pooled estimates of early graft patency were similar to the rates obtained for non-ESRD patients,[5,23-25] possibly because skilled surgeons were involved and because an autogenous vein was used in 85% of the reconstructions.

The close proximity between the pooled curves of primary and secondary patency indicated that revision of failing or failed grafts was uncommon or often unsuccessful. Indeed, when the small subgroup of five studies that used duplex scanning for graft surveillance routinely was compared with Mills and Taylor's[32] report of non-ESRD patients, there was little difference between the crude rates of graft failure, 10.1% vs 9.1%, and in the pooled patency at 36 months, 12.6% vs 16%, respectively. Although a limited use of duplex scanning for graft surveillance plausibly explains the proximity between the pooled curves of graft patency, a poor health condition or limb status discouraging graft revision cannot be neglected.[1]

The pooled limb salvage at 2 years was 73.0% (4.3%) in the original meta-analysis vs 74.7% (3.7%) in the updated meta-analysis, with little change in the pooled estimate and a small gain in precision. As for secondary patency, it was reasonable to expect higher pooled estimates of limb salvage in the updated meta-analysis. Perhaps a more rigorous selection of patients obscured some improvement in surgical management. Indeed, this update compared with the original meta-analysis showed a slightly higher median value for mean age (63 vs 58.5 years) and for the prevalence rates of both diabetes mellitus (80% vs 73%) and prosthetic grafts (15% vs 12%). A comparison of the hazard rates for amputation and loss of secondary patency showed that major amputation despite a patent graft occurred predominantly in the short-term follow-up. This finding was in contrast to non-ESRD patients, for whom the limb salvage rate usually outweighs the secondary patency rate during the entire follow-up.[18,24] Hence, when treating ESRD patients, the potentials of bypass surgery in achieving hemodynamic improvement, thereby reverting critical ischemia, must be tempered by the high rates of perioperative death and early amputation despite a patent graft. According to Walsh,[33] bypass surgery in ESRD patients should be contemplated only when every condition is optimal, ie, the best vein, the best skin, and the best sort of everything. This means that revascularization should not be considered for patients with forefoot and deep heel defects or extensive infection.[6,13,22,26]

Although more clinically relevant than graft patency, limb salvage overestimates the potentials of surgical revascularization because a salvaged limb may still show signs and symptoms of critical ischemia, severe diabetic neuropathy, or extensive infection, thereby reducing patient benefit.[17] Notably, Nicholas et al[29] reported rates of independent ambulation of 56% and 10% at 1 year for patients without and with ESRD, respectively, whereas for patients with ESRD Harpavat et al[12] reported ambulation of some level for 61% and Korn et al[13] reported sustained benefit for 45% at 1 year. With regard to amputation-free survival, the difference between survival and amputation-free survival was 6% or less at 1 year.[26,27] Measures of the quality of life in non-ESRD patients have indicated that infrainguinal revascularization is superior to primary amputation,[34] but this is less certain for ESRD patients.[17,20,21] Because the benefit of surgical revascularization may be modest for ESRD patients, several authors have recognized a role for primary amputation when tissue loss is extensive.[3,6,13-15,25-27] Conversely, modern techniques of skin coverage have been used with moderate success in selected patients.[3,35]

The remarkable similarity between the pooled curves of primary patency and patient survival up to 7 months suggested that the loss of primary patency possibly contributed to death during this interval. However, this remains speculative because the studies considered here reported only the final causes of death, with the notable exception of Sanchez et al,[6] who reported graft complication leading to death in 3 (23%) of 13 early deaths. In any case, the perioperative mortality was not negligible (5.1% in the updated meta-analysis, but 8.8% in the summation analysis). A recent survey has shown a perioperative mortality of 12.6% for 508 bypasses and 7.7% for 292 angioplasties, but the ESRD patients in these 2 groups may not have been strictly comparable.[1] Because mortality is the major problem for ESRD patients with critical ischemia and because angioplasty likely reduces early mortality, this procedure may extend revascularization to less compromised patients, replace or complete surgical revascularization, and be used in a last attempt before amputation.[27,36] However, the final utility of angioplasty in improving limb salvage remains uncertain.[33]

In strong support of the inferences from this updated meta-analysis, the study design was compatible with real life and allowed an adequate sampling of a hypothetical population of studies. Moreover, the studies were reviewed in sufficient number, adopted similar outcomes, and reported high response rates. Finally, the comparisons of primary and secondary patency, as well as the comparisons between limb salvage and secondary patency, were robust in sensitivity analysis.

Most of the limitations in this study were attributable to the nonrestrictive inclusion criteria adopted. Often, the individual articles reported outcomes selectively, did not use standard patencies, described a short follow-up time, omitted losses to follow-up, or showed a flat tail in the survival curves. In addition, it was not possible to investigate amputation-free survival, functional status, or any aspect of quality of life. These problems were not completely overcome.

In conclusion, limb salvage can be achieved in most ESRD patients who undergo bypass surgery for chronic critical limb ischemia, but survival is poor. To avoid early amputation despite a patent graft, bypass grafting should not be offered to patients with a great amount of tissue loss or extensive infection.

AUTHOR CONTRIBUTIONS

Conception and design: MA, NDL, FCB-N, IN, CABP
Analysis and interpretation: MA, IN, CABP
Data collection: MA, MR
Writing the article: MA, MR, NDL
Critical revision of the article: FCB-N, IN, CABP
Final approval of the article: MA, MR, NDL, FCB-N, IN, CABP
Statistical analysis: MA, IN, CABP
Overall responsibility: MA

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Submitted Jul 28, 2006; accepted Nov 13, 2006.

APPENDIX: STATISTICAL NOTES

The strategy. We constructed a strategy to combine survival data because different grids of time intervals had been used in the series reviewed. In the first step, we redistributed in equal quantities at 1-month intervals the units of analysis censored at intervals greater than 1 month. A unit of analysis was a graft, a limb, or a patient. This approach assumed constant hazard rates within long time intervals and the midpoint of such intervals as the survival time for censored units, as is usual in actuarial survival analysis. Next, we obtained the numbers of failed units for intervals of 1 month by using the units at risk at the start of an interval, the redistributed censored units, and the interval hazard rate. We then calculated the Kaplan-Meier success rate for each series and each month of follow-up and used this rate as the treatment effect.

In the second step, we calculated a within-series variance (s^2) for each monthly success rate in each series; next we calculated a between-series variance (ι^2) for each month. To obtain pooled measures of treatment effect for each month of follow-up, we used in the third step random-effects modeling, which assumes that studies at hand are independent and equally distributed. Finally, the product of successive monthly pooled measures of treatment effect allowed us to estimate the survival function and to calculate approximate standard errors.

The statistical problem. Because this meta-analysis dealt with case series, our primary problem was one of estimation, not hypothesis testing. Consequently, we estimated survival functions and calculated standard errors for primary and secondary patency, limb salvage, and patient survival.

Survival probability in each month. For each series i and each month j of follow-up, the estimated survival probability, λ_{ij}, was determined as follows:

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

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

Within-series variance. The within-series variance, s_{ij}^2, was obtained as follows:

$$S_{ij}^2 = n_{ij}(n_{ij} + 2)^2/[(f_{ij} + 1)(n_{ij} - f_{ij} + 1)]$$

Between-series variance. For each month j, the between-series variance, τ_j^2, was calculated as follows:

$$\tau_j^2 = \sum [n_{i.}(\lambda_{i.} - m_j)^2]/[(k_j - 1)]/k_j \sum n_{i.}],$$

where, in the target month j, $\lambda_{i.}$ is the estimated survival probability in study i, m_j is the average for $\lambda_{i.}$, $n_{i.}$ is the number of units at risk, and k_j is the number of series available.

Weighting and combining the λ_{ij}. Let w_{ij} be the weight attributed to each λ_{ij}. When using random-effects modeling, it follows that

$$W_{ij} = 1/(S_{ij}^2 + \tau_j^2)$$

A value for the survival function in month j, L_j, was obtained as follows:

$$L_j = \sum (\lambda_{i.} w_{i.})/\sum w_{i.},$$

where $\lambda_{i.}$ is the estimated survival probability in the target month j, and $w_{i.}$ is the weight attributed to $\lambda_{i.}$.

Such estimators L_j will be consistent and approximately normal and are derived on the basis of 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 estimated survival probability at month j.

Variance for G_j. After they were properly corrected, Kaplan-Meier estimates and their respective variances in the individual series were used to obtain the variance of G_j. This was performed by using again random-effects modeling 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. Because K_j and G_j differed a little, the variance of G_j, $V_{\{Gj\}}$, was obtained as follows:

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

The standard error for G_j was the square root of $V_{\{Gj\}}$.