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IMPS (Intact Months of Patient Survival): An Analysis of the Results of Carotid Endarterectomy

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SUMMARY The literature on carotid surgery for lesions appropriate to prior episodes of ischemia has been reviewed. Only one randomized study and six non-controlled reports give useful data (this despite more than thirty years of surgical activity in this field). When analyzed by the IMPS (intact months of patient survival) criterion, the randomized study failed to show benefit from surgery. This failure can be attributed to a high (35%) operative stroke and death rate. That sufficiently low operative stroke and death rates are readily achievable is not clear, however, only two of six relevant non-controlled series reported in the literature had operative stroke and death rates below the 10.4% level calculated as necessary for a "break-even" situation. Three of the six non-controlled series contain sufficient follow-up data to permit IMPS comparison against the "standard" of the control group of the randomized study. Against this "standard" only one of the three non-controlled studies would have "shown benefit" from surgery. Barnett, Plum, and Walton have called for audits of endarterectomy results in institutions in which such surgery is performed. It is suggested that such audits be done by the IMPS method, which gives appropriate weight to the effects of operative, as well as of long-term follow-up, strokes and deaths.

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THIS COMMUNICATION has three purposes:

1. To review the published results of carotid endarterectomy on vessels in whose territory TIA (transient ischemic attack), RIND (reversible ischemic neurologic deficit), or minor stroke had occurred.
2. To analyze these results by the IMPS (intact months of patient survival) method.
3. To suggest the applicability of the IMPS analysis for the performance of institutional audits of the safety and efficacy of endarterectomy, as proposed by Barnett, Plum, and Walton.[1]

Reports on Carotid Endarterectomy

Warlow recently published a detailed review on endarterectomy.[2] It was his aim to focus on the results of surgery on carotid arteries in whose territory TIA had occurred. As he indicated, however, only one randomized study[3] devoted to surgery for TIA had been reported at the time he undertook his analysis. In the report of that study, the outcome of the patients who had had carotid TIA cannot be separated from the outcome of the approximately 46% who had had vertebrobasilar TIA only.

Since Warlow submitted his paper, Shaw et al[4] have published a controlled study (to which Warlow alluded in a footnote) of carotid surgery for TIA and minor stroke. Although this study is small (total of 41 patients), it has several virtues: all patients were randomized for surgically treatable stenoses in carotid arteries relevant to their symptoms; much detail was provided; and mean follow-up was long (greater than six years).

I herein review the results of Shaw et al and of six noncontrolled studies.[5–10] Relevant data from these seven reports are summarized in table 1. These seven reports are the only ones in the literature which meet the following rigorous criterion: they specify that they present results of surgery on carotid arteries *in whose territory* TIA, RIND, or minor stroke had occurred. (There are, of course, many other reports on surgery, but in those other reports data of the sort described above are either inextricably mixed with, or not specified as isolated from, results of surgery on patients with no symptoms, with symptoms in one vascular territory but surgery in another territory, with surgery on vertebral or subclavian arteries, with surgery after major stroke, etc.)

IMPS Analysis

Background

Warlow stated that the proper criterion for evaluating endarterectomy results is the subsequent *duration*

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TABLE 1 *TIA, RIND, or Minor Stroke in the Territory of an Operable Cervical Carotid Artery Lesion: The Randomized Study of Shaw et al and Six Non-controlled Studies*

Study	Years of study	Number of patients	Mean patient age (years)	Proportion male	Duration of operative or early period	Mean duration of total study (months)	End-point non-fatal + fatal strokes + deaths: During operative or early period	End-point non-fatal + fatal strokes + deaths: During long-term follow-up
Shaw et al[4]	1965–78							
85% TIA								
15% minor stroke								
surgical		20	57	0.90	1 month	78.0	4+1+2	1+1+4
control		21	57	0.87	1 month	73.2	0+0+0	5+1+9
Siekert et al[5]	1954–(62)	32					4+2+1	
100% TIA								
Whisnant et al[6]	1970–79	151	62	0.75	1 month	72*	5+0+1	(17+1+26)
72% TIA								
28% RIND								
Takolander et al[7]	1971–80	60	64	0.65	1 month	31	3+3+2	7+0+3
100% minor stroke								
Eriksson et al[8]	(1976–80)		(61)	(0.78)	2 weeks	21.5		
TIA		(31)					4+0+0	3+(0)+(0)
minor stroke		(54)					1+2+0	3+(0)+(0)
UK-TIA Study Group[9]	(1979–82)	41	(58.5)		1 week		6+4+(0)	
TIA or minor stroke								
Muuronen[10]	1980–83		58		4 days	(20)		
TIA		(69)					7+4+(0)	
minor stroke		(26)					0+0+0	

Blanks = data are unclear or not given.
Parentheses = interpretations or approximations.
TIA = transient ischemic attack.
RIND = reversible ischemic neurologic deficit.
*All were followed for at least five years. The authors have provided actuarial projections for six years.

of survival free of stroke. He did not actually analyze the available results in such a manner; the life-table data necessary for accurate analysis[11] were, as he indicated, not routinely published in the literature.

I herein employ a simple method, which can be applied to data of reports lacking life-table analyses, for estimating the effect of endarterectomy on the duration of survival free of stroke. This is the IMPS (intact months of patient survival) method.[12]

The key to the IMPS method is the IMPS *ratio*. For a population followed for a given period, the IMPS ratio is the ratio between the total patient-months of intact survival time actually enjoyed by the cohort and the maximum amount which the cohort would have enjoyed had no one died or suffered stroke during the observation period. For instance: suppose that 100 patients are followed for a year. If there are no strokes or deaths, then the cohort enjoys 100 × 12 = 1200 patient-months of intact survival for the year. Suppose, however, that ten deaths occur at the end of four months and ten strokes occur at the end of eight months, while the other 80 patients are intact at one year. For this situation there are (10 × 4) + (10 × 8) + (80 × 12) = 1080 intact months of patient survival for the year. The IMPS ratio is then 1080/1200 = 0.9.

It will be recognized that the above can be given graphic representation, as in figure 1a. Here the proportion, rather than the absolute number, of patients surviving intact is given on the ordinate. The IMPS ratio can then be conveniently considered as the ratio between the area under the step-curve and the area of the entire graph. The area under the step-curve (the sum of the areas of the three broad columns defined by the three steps) is (1.0) (4) + (0.9) (4) + (0.8) (4) = 10.8. The area of the entire graph is (1.0) (12) = 12. The IMPS ratio is 10.8/12 = 0.9.

With respect to the form of the curve, it should be noted that a slope (see fig. 1b) can substitute for a step-curve in IMPS ratio calculations, if the end-point events are distributed uniformly with respect to time. For figure 1b, the area under the curve is (1.0 + 0.8) × (12) (0.5) = 10.8 (12) (0.5) = 10.8, and the area of the entire graph is (1.0) (12) = 12.0; the IMPS ratio is 10.8/12 = 0.9, as before.

It will be noted that for figure 1B the calculations could have been simplified; one need merely take one-half of the sum of the initial ordinate value (1.0) and the final ordinate value (0.8): (1.0 + 0.8) (0.5) = 0.9.

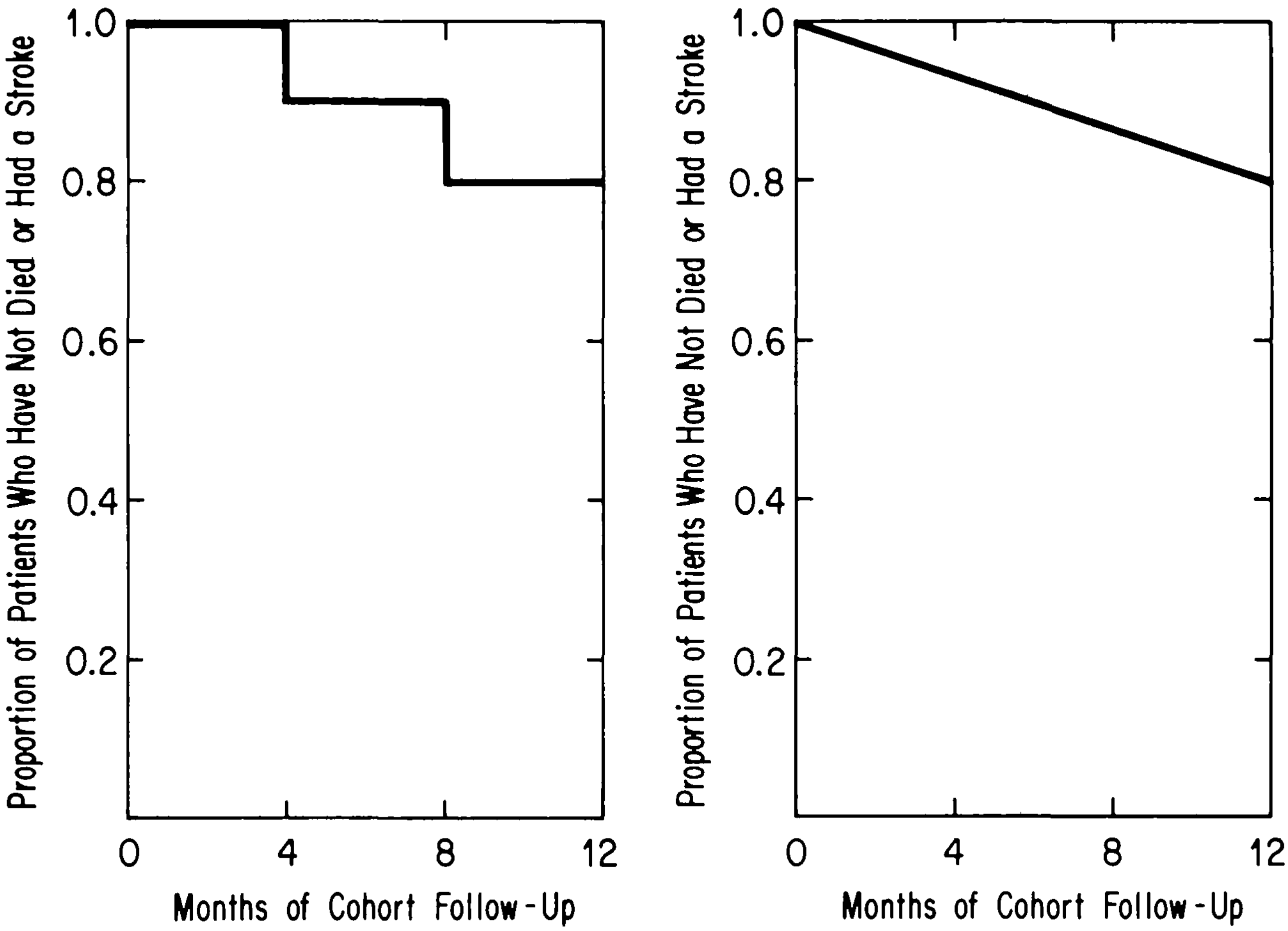

FIGURE 1. *1a shows a hypothetical step-curve for stroke or death (see quotes in text — IMPS Analysis). 1b is the step-curve of 1a, transformed into a slope (see quotes in text — IMPS Analysis).*

The simplification derives from the disappearance of the time unit, and all other units, from the results of a ratio calculation. It will also be noted that visually the IMPS ratio is "the area under the curve of intact survival".

The Results of the IMPS Analysis of Shaw et al

It will be seen from Table 1 that the 20 surgical patients of Shaw et al suffered 7 strokes and deaths in the operative period (during, and within one month after, surgery). There were 6 strokes and deaths among the intact survivors of surgery during a mean follow-up period of 77 months after the first month. For the 21 control patients the analogous figures were zero events in the first month, and 15 strokes and deaths in the 72.2 month mean follow-up period after the first month. With adjustment of the surgical late follow-up period from 77 months to 72.2 months, the total of all strokes + deaths becomes 7 + (6) (72.2)/(77) = 12.63 for the surgical cohort, a stroke + death rate of 12.63/20 = 0.631 for 73.2 months. For the control cohort the stroke + death rate is 15/21 = 0.714 for 73.2 months.

The results (0.631 versus 0.714) make surgery look better than non-surgical care (questions of statistical significance for sample size aside) as of 73.2 months. However, when the results are presented graphically, as in figure 2a (assumptions: the events of the first month are all assigned to zero time; all other events are distributed uniformly over the next 73.2 months), it will be seen that the area under the surgical curve is less than that under the nonsurgical curve. The relative numerical values for these areas (the IMPS ratios, calculated as described above in the discussion of fig. 1b) are 0.510 for surgery and 0.643 for non-surgical care. The surgical cohort thus had a *less* favorable outcome than the control cohort by the criterion of intact months of patient survival.

Questions Arising from Shaw et al IMPS Analysis

It will be noted from table 2 that the annual stroke and death rate among the patients of Shaw et al during long-term follow-up after the first month was lower after surgery (mean rate of 7.2% per year) than for non-surgical care (mean rate of 11.9% per year). It also has been noted that a smaller proportion of surgical patients (0.631) suffered stroke or death than did non-surgical patients (0.714) during the (adjusted) total observation period of 73.2 months.

Nevertheless, surgery failed to benefit the operated cohort in terms of duration of intact survival (as quantitatively estimated by IMPS ratio analysis). The reason, as figure 2a makes clear, is the burden of the 35%

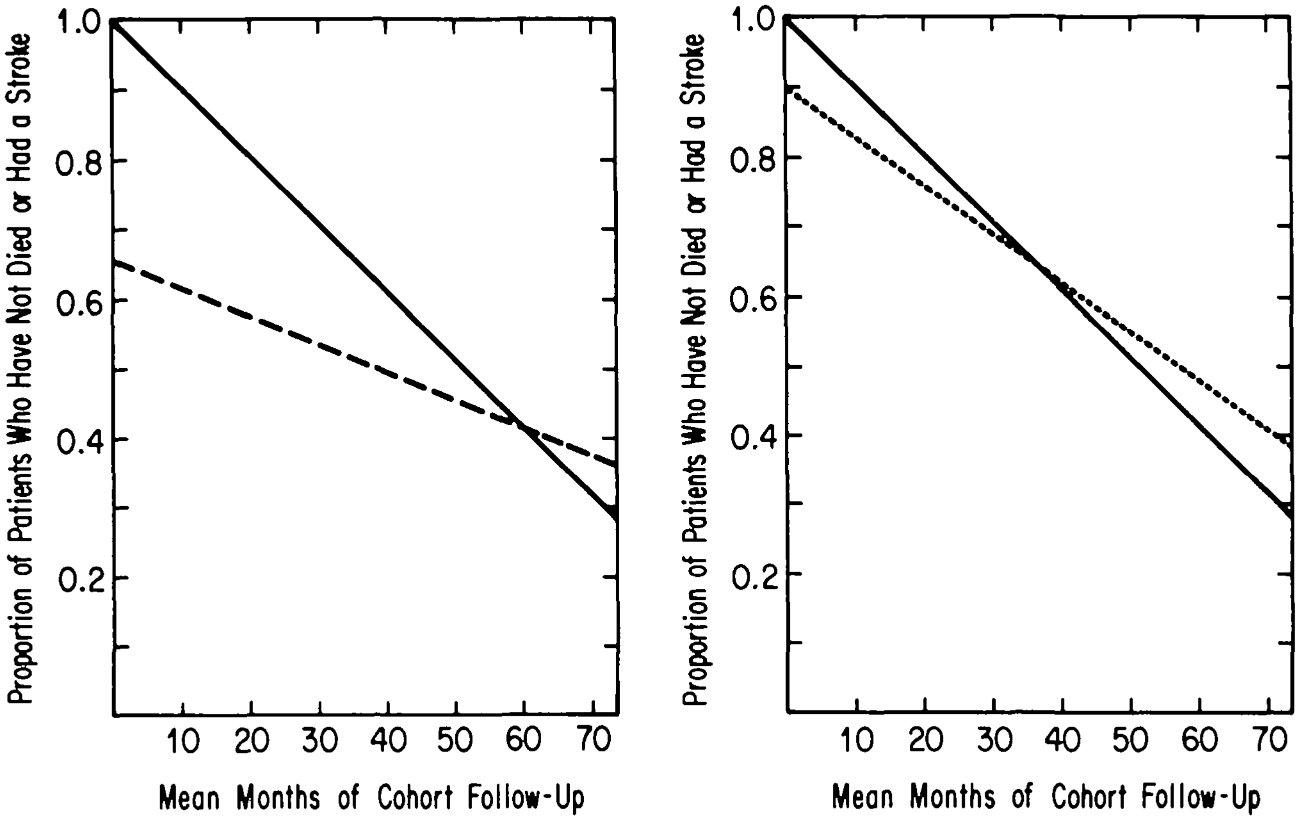

FIGURE 2. *2a shows the surgical (broken line) and the control (solid line) cohort results of Shaw et al,[4] projected as if all operative strokes and deaths had occurred on the day of surgery, and as if follow-up strokes and deaths had occurred at a uniform rate. The duration of surgical follow-up has been adjusted from 78 months to that of the control group: 73.2 months. 2b shows the same control curve as in 2a (solid line), plus a hypothetical surgical curve (dotted line) which is based on a 10.4% operative stroke and death rate and a 7.2% annual stroke and death rate among intact survivors of surgery during long-term follow-up.*

operative stroke death rate; the protection conferred upon the intact survivors of surgery was still not great enough to have permitted the surgical cohort to "catch up" with the control cohort as of 73.2 months: the area under the surgical curve (reflecting the IMPS ratio) is still less than the area under the control curve, even though the curves have crossed.

What if the operative stroke and death rate had been lower than 35%? Could the surgical cohort have "broken even"? IMPS analysis gives an answer. At an operative stroke + death rate of 10.4%, and with no change in the stroke + death rate during follow-up, the surgical cohort would have "broken even" with the control cohort at 73.2 months by the IMPS ratio criterion. Figure 2b, in which the area under the surgical curve has been made to equal the area under the control curve, gives graphic representation to this "what if . . ." analysis. One could speculate that it is unreasonable to expect no change in the stroke and death rate in follow-up in such circumstances. For instance, it might be that patients at more than "average" risk during surgery would have more than an average chance of stroke or death in follow-up after surviving surgery intact. There are no data with which to discuss this issue meaningfully.

Questions Arising from IMPS Analysis of Non-Controlled Results

In the absence of controls one has no direct way of defining how surgery influenced the over-all outcomes among the patients of the six non-randomized cohorts. By reasoning similar to that used in the "what if . . ." analysis above, however, one can define the "natural history" outcomes against which surgery would have "broken even" in the three studies[6–8] which provided follow-up as well as operative data. Thus (see table 3), one cohort[6] would have broken even against a control cohort having an annual stroke + death rate of 6.2%. The other two[7,8] would have broken even had the control rates been 16.7% and 12.4% per annum, respectively.

Interpretations

A rigorous interpretation of the above results is simple: in the one controlled study, surgery failed; therefore there is no reason to recommend carotid endarterectomy on a vessel in whose territory ischemia has occurred.

As has been pointed out, however, theoretically the Shaw surgical cohort could have "broken even" had the operative stroke death rate been 10.4%, and could

TABLE 2 *Stroke and Death Rates, and IMPS (Intact Months of Patient Survival) Ratio Calculations*

Study	Operative or early period: stroke and death rate	Mean annual stroke and death rate after operative period	As of end of study: Total rate for all strokes and deaths	As of end of study: IMPS ratio*
Shaw				
Surgical: follow-up adjusted to 73.2 months	0.350	0.072†	0.631	0.510
Control: 73.2 months	0.000	0.119	0.714	0.643
Siekert[5]	0.219			
Whisnant[6]	0.040	0.052	0.331	0.814
Takolander[7]	0.133	0.077	0.300	0.784
Eriksson[8]	0.082	0.037	0.141	0.889
UK-TIA Study[9]	0.244			
Muuronen[10]	0.116			

*For the calculation of the IMPS ratio it has been assumed that the data can be graphed as in figure 1b. The IMPS ratio is then one-half the sum of the initial ordinate value and the final ordinate value. The initial ordinate value is the proportion of patients intact after the operative or early period. The final ordinate value is the proportion intact at the end of the study. Graphing data as described above is, of course, an approximation. A more accurate way to derive the IMPS ratio would be to calculate the areas under a step-curve: either one reflecting the specific outcome of each patient if all patients had been followed for a uniform period, or one constructed from life-table data if there had been withdrawals or non-uniform durations of follow-up (see fig. 1a for a hypothetical step-curve). Such data are not available in the reports herein reviewed. For statistical analysis when such data *are* available, see Peto et al.[11]

†Yates-corrected chi-square analysis of the difference between surgical and control strokes and deaths during an adjusted 72.2 months of follow-up after the operative or early periods gives a value of 1.23: p is greater than 0.20 for 1 degree of freedom and the difference is therefore not statistically significant by the usual minimal (0.05) standard.

have "done better" (ignoring the question of statistical significance and sample size) than the non-surgical controls, had the operative stroke and death rate been lower than 10.4%. Is it reasonable, however, to think that a rate of 10.4% or less *could* have been achieved? The answer, based on the only applicable non-randomized data, those from the six studies cited, is not reassuring for the surgical proponent: only two of the six cohorts had operative stroke + death rates of 10.4% or less (see table 2).

By similar reasoning, as pointed out in the previous section, the three non-controlled surgical cohorts suitable for analysis could have "broken even" against "control cohort" long-term follow-up annual stroke and death rates of 6.4%, 12.4%, and 16.7%. Again, these results are not strongly reassuring for the proponent of surgery. For only one of these three cohorts would the Shaw control outcome of an 11.9% stroke and death rate per year of long-term follow-up have been "bad enough" to make surgery "successful" — ignoring, again, questions of statistical significance for sample size.

What if follow-up in these studies had been longer? Is it possible that a surgical cohort would, given more time, have been able to "catch up with" and then "do better than" a control cohort? Two studies on related (although not identical) matters are of interest. Whisnant et al[13] did a population study on carotid TIA, the patients having been identified without regard to surgical suitability. According to their figure 1, the cumulative stroke rate at 5 years (initial cohort size of 75) was approximately 42%; at 10 years it was approximately 44%. The randomized extracranial-intracranial (EC-IC) arterial bypass study[14] focused on patients who had had TIA or minor stroke in the territory of a stenotic or occluded internal carotid or middle cerebral artery. Six hundred sixty-three patients had arterial bypass surgery, and 714 were treated medically. Their figure 2 shows that the stroke and death rate was initially higher in the surgical group. After three years the curves ran parallel (surgery still worse). At 5 years the curves were showing no tendency toward crossing.

If the endarterectomy candidates behave similarly to the patients of either of these two studies, then longer follow-up would not "make surgery better".

What if one looked at relatively, rather than absolutely, intact survival? Suppose one considered the quality of life as a function of the severity and duration of disability after a non-fatal stroke. Conceivably post-surgical strokes might be less severe than control strokes. This must remain as speculation, however; no useful data are available.

In reviewing the above, it is important to recognize

TABLE 3 *Observed and "Break-Even" Stroke and Death Rates for Carotid Surgery Cohorts*

Study	Total months of observation; () = projected	Observed operative or early stroke + death rate	Mean annual stroke + death rate after operative or early period	For surgery to "break even" with non-surgical care by IMPS ratio criterion: Needed operative stroke + death rate	For surgery to "break even" with non-surgical care by IMPS ratio criterion: Needed annual control stroke + death rate
Shaw[4]					
surgical	(73.2)	0.350	0.072	0.104	
control	73.2	0.000	0.119		
Whisnant[6]	72	0.040	0.052		0.062
Takolander[7]	31	0.133	0.077		0.167
Eriksson[8]	21.5	0.082	0.037		0.124

that the "rigorous" rejection of surgery depends on only one controlled study covering 41 patients. However, it must also be recognized that any claim *for* surgery must be based on the immediate operative results of only six, and the follow-up results of only three, non-controlled series, as interpreted by the weak "historical control" method. It should be recognized that the basis for the "historical control" analysis is *only* the 21 control patients of the randomized study, there being no other report of patients accepted for surgery but treated non-surgically. It should be emphasized that these seven studies are the only studies germane to the question of relevant vessel surgery which are available in the literature after thirty years of the performance of carotid endarterectomy.

The Use of IMPS Analysis for Institutional Audits

Barnett, Plum and Walton[1] have expressed uncertainty that carotid endarterectomy can be accepted as a method for preventing stroke. They look forward to a large controlled trial to resolve the issue. Until such a trial is reported, they recommend that institutions audit non-controlled endarterectomy results, and that institutions with unsatisfactory results discontinue surgery.

Clearly such an audit must include the stroke + death rate from the surgical procedures (Barnett, Plum and Walton also recommend the inclusion of arteriographic morbidity and mortality). The audit must include as well the follow-up stroke and death rates among the intact survivors of surgery. These combined data would then be judged against a "model" of the expected "natural history" of such patients in the absence of surgery.

It is obvious from the present figure 2a that the judging of observed results against the "model" should not consist merely of the comparing of total strokes and deaths as of the end of the period of observation. Such an analysis would fail to give appropriate weight to the effect of the operative strokes + death: a late stroke, such as one occurring six years after entry, and an early stroke (e.g., during surgery) are clearly not "equal" events, either for the individual or for the cohort.

The appropriate way to conduct such an audit would be by IMPS analysis. An IMPS ratio for the institution's results would be determined (preferably from life-table data: the area under an actuarially constructed curve of results). This would then be compared to a "control IMPS ratio" estimated by the auditors to be "reasonable" for the surgical cohort being audited.

Acknowledgments

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