
Antiplatelet Treatment Prolongs Survival After Carotid Bifurcation Endarterectomy

Analysis of the Clinical Series Followed by a Controlled Trial

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To examine the role of antiplatelet drugs in the secondary prevention of arteriosclerotic arterial disease following carotid endarterectomy, a clinical series (n = 252) was analyzed. Based on these results a prospective randomized trial was initiated, comparing the effect of antiplatelet drugs (acetyl-salicylic acid [ASA] 1000 mg/day) versus untreated controls. In both investigations patient survival was the primary end point. A cardiac risk (n = 91) implied a significant reduction in patient survival (p < 0.019 Breslow, p < 0.052 Mantel). Antiaggregating drugs prolonged survival in the collective series (p < 0.0001 Breslow, p < 0.0002 Mantel) and in the subgroup of patients with cardiac risk (p < 0.014 Breslow, p < 0.020 Mantel) as well. In the prospective trial 66 patients were recruited, receiving ASA (n = 32) versus no therapy (n = 34). During follow-up 15 patients died, 4 in the treatment, and 11 in the control group. Between both groups there was a significant difference in the probability of survival (p < 0.021 Breslow, p < 0.048 Mantel).

THE EFFECTIVENESS OF antiplatelet drugs in preventing events of arteriosclerotic arterial disease has been studied recently.¹ The value of platelet function-stabilizing agents in the prevention of myocardial infarction has been investigated by two major randomized placebo-controlled trials involving physicians in the United States² and Great Britain.³ However the results are controversial. In the natural course of peripheral arterial occlusive disease (PAOD), more than 50% of patients succumb to cardiac complications,^{4,5} a risk that is particularly evident in patients with lesions of the carotid bifurcation that have progressed to a degree requiring surgical intervention.⁶ Carotid lesions of this kind virtually herald the presence of concomitant coronary disease.⁷ This observation stimulated the hypothesis that survival after carotid thrombendarterectomy (TEA) is possibly prolonged if cardiac events are prevented by means of platelet function inhibitors.

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Based on these reflections we have analyzed our clinical series and, in view of the results, we subsequently initiated a controlled clinical trial, investigating the effect of acetyl-salicylic acid (ASA) on patient survival.

Patients and Methods

Altogether 252 patients with lesions of carotid bifurcation, in whom elective surgery was considered to be indicated, were eligible for analysis. One hundred thirteen were asymptomatic, whereas 139 had experienced one or more transient ischemic attacks. Preoperative clinical status was assessed according to clinical neurologic investigation.

The operative procedure was a typical TEA of the carotid bifurcation under general anaesthesia without cerebral protection by an intraluminal shunt. The arteriotomy was closed with direct suture. Ultrasound examinations were used to monitor patency of the endarterectomized vessel.

Perioperative management foresaw a daily dosage of up to 1.5 g of ASA in 118 patients, or no antiaggregating medication at all (N = 134). Regular postoperative control examinations were carried out on an out-patient basis, with intervals of 3 months initially, and of 6 months in the long-term. Particular attention was directed to checking and warranting reliable consumption of aggregation inhibitors. In general, therapy was continued for more than 1 year, or until the patient's death. In 91 patients a particular cardiac risk could be identified conclusively as a history of pre-existent myocardial infarction or as signs of ischemic cardiomyopathy.

The prospective trial was initiated in 1982. Until November 1985 a total of 66 patients had undergone carotid

endarterectomy and were assigned either to the therapy group (n = 32) starting on 1000 mg ASA 2 days before surgery, or the control group (n = 34), which received no antiaggregating medication. The functional results were assessed with ultrasound investigations on days 3, 7, and 14 after surgery and in monthly and subsequent 3-month intervals. Beyond the first postoperative year the intervals were prolonged to 6-monthly follow-up appointments.

Disregarding local findings, the probability of patient survival was chosen as the primary end point for evaluation of this series. The final assessment of the participants' survival status was made by the end of 1988.

Standard laboratory tests were used to assess hypercholesterinemia and hyperlipidemia.

Statistical Methods

Information concerning courses of disease and details of therapeutic procedures were obtained using the documentation system of the Austrian Vascular Surgical Society (180 variables per surgical procedure, more than 8000 operations stored since 1965). For the purpose of the present investigation the system was modified to allow discrimination between patients of the analysis from those participating in the prospective trial. Statistical procedures were carried out with the IBM 4381 computer of the Medical Faculty of the University of Vienna.

For data storage and retrieval, SAS-software that also facilitated scheduling and organization of follow-up appointments and out-patient examinations was used.⁸ BMDP-1L software allowed us to assess probabilities of survival.⁹ Within the prospective clinical trial, patients were assigned to either group by means of adaptive randomization.¹⁰ Prognostic factors that were accounted for included patient sex, age, history of diabetes mellitus and/or hypertension, smoking habits, and preoperative clinical staging.

Survival curves were estimated according to the Kaplan-Meier method,¹¹ and possible statistical differences were calculated with the tests of Breslow¹² and Mantel¹³ in a bitailed mode (2p). The graphic design of Kaplan-Meier curves followed the recommendations established by the Ad Hoc Committee on reporting standards of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery.¹⁴

The most recent information regarding the state of survival was conveyed through the Austrian Central Statistical Office and transferred to the computer by electromagnetic tape. The national law of compulsory registration warrants that the present investigations are based on reliable data.

In three patients the therapy was discontinued due to

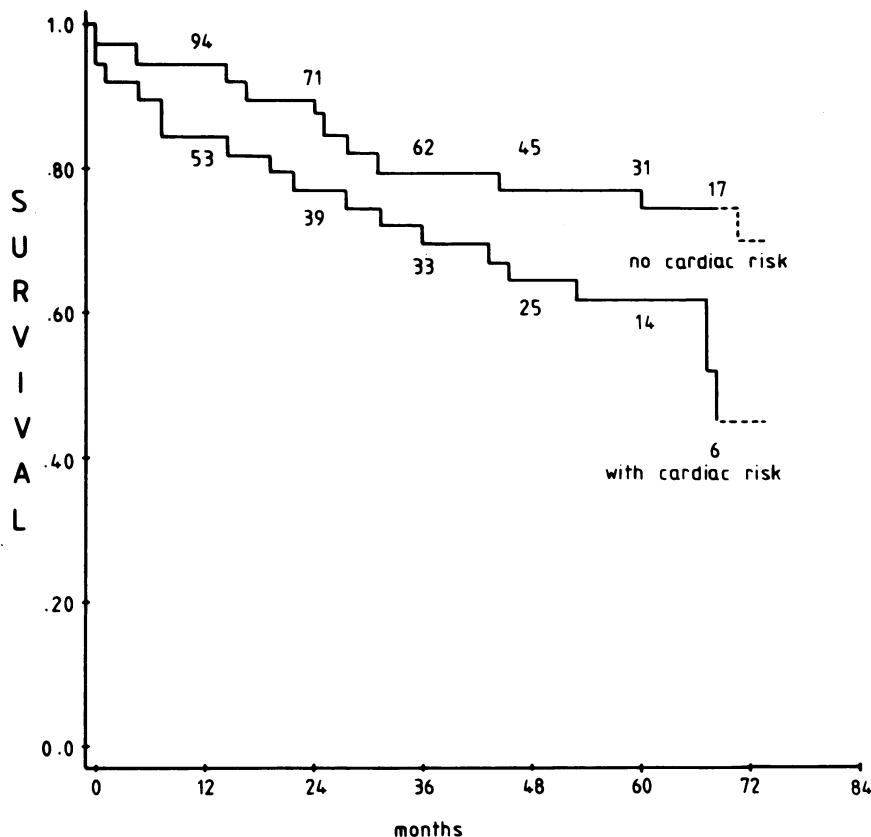


FIG. 1. Carotid endarterectomy; analysis of the clinical series; probability of patient survival; Kaplan-Meier estimates; patients with versus without cardiac risk; the numbers above or below the curves show the patients at risk; the interrupted line indicates the interval, when the standard error exceeds 10%.

FIG. 2. Carotid endarterectomy; analysis of the clinical series; probability of patient survival; Kaplan-Meier estimates; treatment group *versus* untreated group; the numbers above or below the curves show the patients at risk; the interrupted line indicates the interval, when the standard error exceeds 10%.

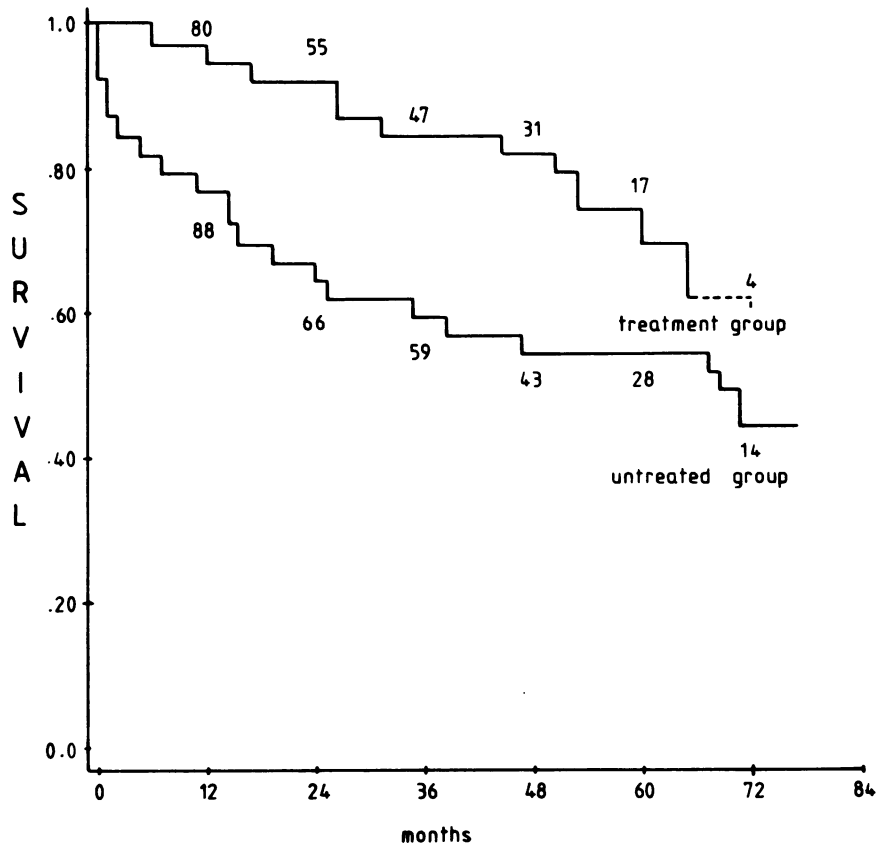


FIG. 3. Carotid endarterectomy; analysis of the clinical series; probability of patient survival; Kaplan-Meier estimates; patients with cardiac risk; treatment group *versus* untreated group; the numbers above or below the curves show the patients at risk; the interrupted line indicates the interval, when the standard error exceeds 10%.

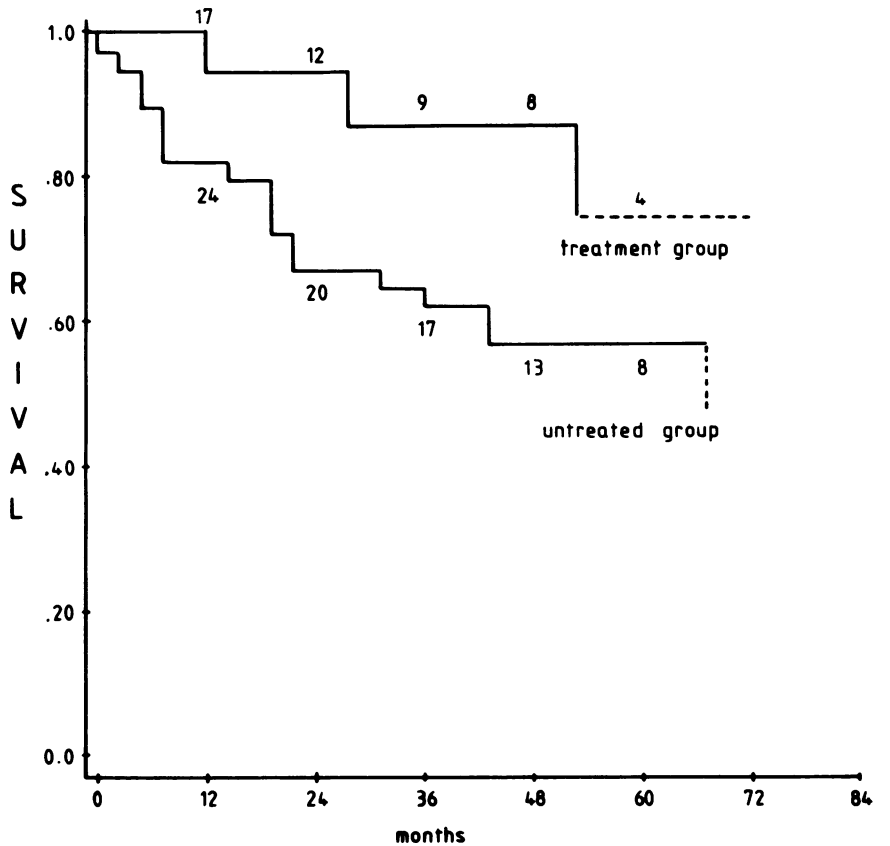


TABLE 1. Analysis of the Clinical Series; Causes of Death in the Subgroup of Patients with Cardiac Risk as Defined in the Text; Influence of Postoperative Treatment

Causes of Death	Treatment	No Treatment
Cardiac	0	9
Cerebral	1	1
Other (diabetes, cirrhosis, unknown)	2	6

gastrointestinal intolerance. For evaluation these patients remained in the group to which they had been originally assigned (*i.e.*, intention to treat principle).

Results

Clinical Series

The presence of a cardiac condition, as previously defined, produced a statistically significant reduction in the probability of survival ($p < 0.019$ Breslow, $p < 0.052$ Mantel; Fig. 1). But survival was prolonged by antiaggregating medication in the collective series ($p < 0.0001$ Breslow, $p < 0.0002$ Mantel; Fig. 2) as well as in the particular subgroup of patients with cardiac risks ($p < 0.014$ Breslow, $p < 0.020$ Mantel; Fig. 3). Throughout there were more fatal cardiac complications than cerebral causes of death. Aggregation-inhibiting therapy effectively reduced the incidence of cardiac deaths, thereby obviously prolonging patient survival time (Table 1).

Prospective Trial

The various risk factors were evenly distributed among the 66 patients recruited for the trial (Table 2). During follow-up 15 patients died, 4 in the treatment group and 11 in the untreated group. Both groups differed significantly in the probability of survival ($p < 0.021$ Breslow, $p < 0.048$ Mantel; Fig. 4).

Although surgery was performed under antiaggregating therapy in one group, there was no difference in the frequency of local hematomas (ASA: 3 of 32 patients, controls: 3 of 34 patients). Postoperative central neurologic deficits were also equally balanced between both groups (ASA: 1 of 32 patients; controls: 2 of 34 patients).

Discussion

The present investigation's object was to evaluate the effect of platelet inhibitors in the secondary prevention shown in patients with PAOD after surgery. The initial information derived from an analysis of our patients was reproduced in a randomized clinical trial. In both studies, retrospective and prospective, patient death was the primary endpoint, a criterion beyond any doubts.

With respect to various risk factors, both groups (therapy and controls) proved perfectly comparable when entering the clinical trial.

Because no arm of the study was intended for placebo control, side-effects of the medication cannot be assessed.

For 30 years TEA of the carotid bifurcation is being done with the conviction that the operation eventually reduces the risk of cerebral stroke.^{15,16} Indeed the promising results of carotid surgery, reported over the past years, appear to confirm the issue. To obtain and preserve an acceptable standard, neither the rate of perioperative neurologic deficits nor the mortality rate should rise above 5%,¹⁶ a limit that was not exceeded in our own clinical series.¹⁷

So far no study has proved that carotid endarterectomy combined with medication is superior to pharmacotherapy only.¹⁵ TEA of the carotid bifurcation alone cannot prolong patient survival. On the other hand it is unlikely that epidemiologic data, concerning the natural course of disease in patients with symptomatic carotid lesions, will become available. Altogether these facts suggest that presently there is no conclusive information to prove the value of operative therapy.¹⁵

TABLE 2. The Prospective Trial: Balancing of Risk Factors in the Treatment Group (TG) Versus the Control Group (0)

Variables	TG (n = 32)	0 (n = 34)
Sex		
Male	24	23
Female	8	11
Age		
<55 years	5	4
55-65 years	12	14
>65 years	15	16
Blood Pressure		
<160/90 mmHg	20	21
>160/90 mmHg	12	13
Diabetic State		
Nondiabetic	20	20
Diabetes	9	14
Insulin-dependent	3	0
Hyperlipidemia and/or Hypercholesterinemia		
Yes	17	18
No	15	16
Smoking Habits		
Nonsmokers	16	16
Less than 10 cigarettes/day	3	4
More than 10 cigarettes/day	13	14
Clinical Status Before Surgery		
Asymptomatic	12	13
Transient ischaemic attack	20	21
Cardiac Pathology		
Nil	13	15
Arrhythmia	3	3
Ischaemic myocardiopathy	2	2
Myocardial infarction	5	5
Other	3	3
Combination	6	6

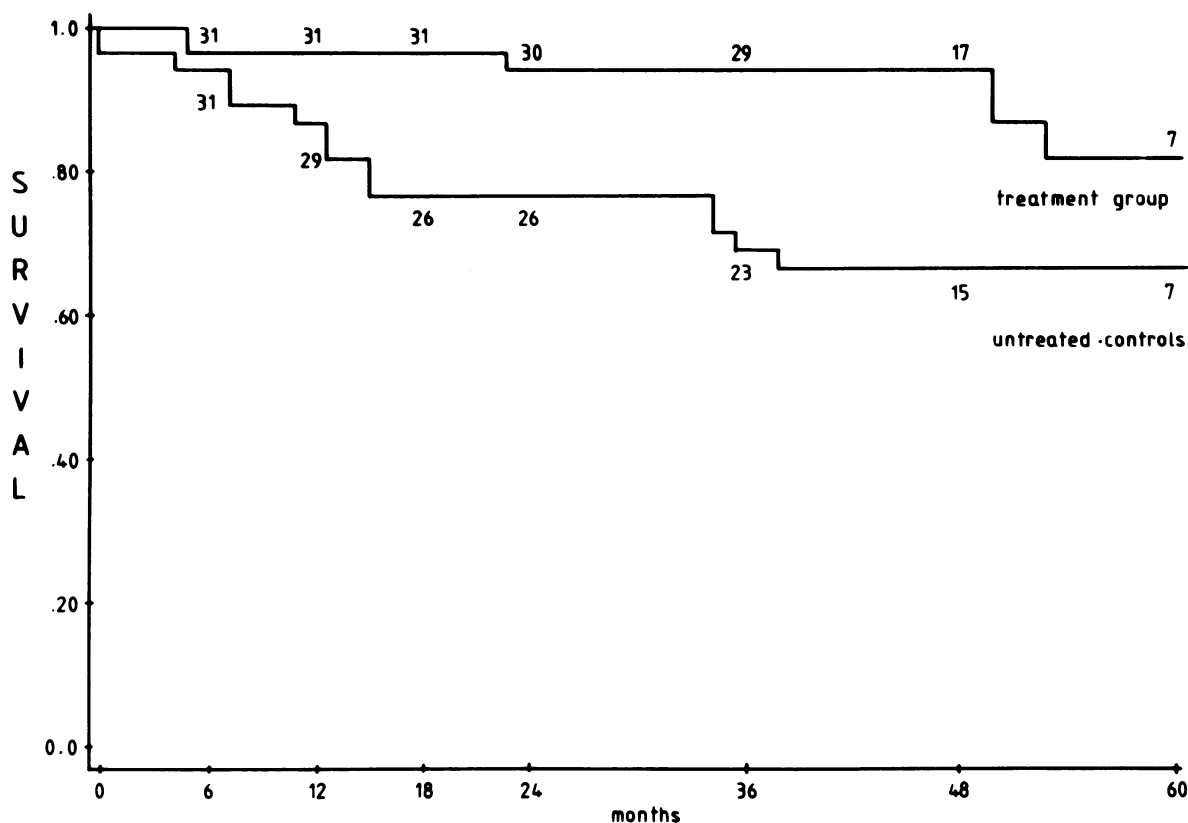


FIG. 4. Carotid endarterectomy; the prospective trial probability of patient survival; Kaplan-Meier estimates, therapy group *versus* untreated controls; the numbers above or below the curves show the patients at risk.

However the analysis of secondary studies¹ discloses the positive effect of aggregation inhibitors in the secondary prevention of AOD. If we set out to compare studies such as those from the ESPS,¹⁸ the UK-TIA,¹⁹ and the PARIS II-trial,²⁰ certain differences among the results become obvious, probably depending on the criteria for inclusion of patients and evaluation of results.

The present analyses were intended to examine whether, in patients with PAOD requiring surgery and restitution of the carotid lumen, the survival rate may be influenced by postoperative medication. It is tempting to assume that, in high-risk patients of this kind, the cerebral prognosis is improved by TEA of the carotid bifurcation,¹⁶ while cardiac complications are successfully prevented by stabilizing platelet function.

Cardiac events constitute the factor that actually determines the fate of patients after carotid TEA.^{6,7,21-23} In this context the investigation of a relatively small series from one center could demonstrate a positive effect of medication on one undisputable criterion of evaluation, the postoperative survival of patients. Generally this result is in accord with the findings of various studies (reviewed in reference 1) that have evaluated the role of platelet-function inhibitors.

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