The Prophylactic Value of Long-Term Anticoagulant Therapy

By A. Boyd Thomas, M.D., Raymond W. Scallen, M.D., and I. Richard Savage, Ph.D.

Since the discovery of Dicumarol by Link in 1939, many papers have appeared on the use of anticoagulants in various thromboembolic conditions. Marple and Wright\(^1\) have provided an extensive review of the literature up to 1950 covering theoretical aspects of the problem and results of treatment in many, chiefly acute, conditions.

Beginning in 1944 with the initial report of Nichol and Fawcett\(^2\), long-term, or prophylactic, anticoagulant therapy has received increasing attention in different thromboembolic conditions. In 1957, Bjerkelund\(^3\) reviewed the many published reports on long-term therapy in myocardial infarction. The few papers on treatment in cerebral vascular disease were reviewed in the report of the Second Conference on Cerebral Vascular Diseases, edited by Wright and Millikan\(^4\).

Despite the developing abundance of reports the prophylactic value of long-term anticoagulant therapy remains equivocal, largely because many of the studies lack suitable controls and do not lend themselves to statistical analysis. Although most of the reports have found the treatment beneficial, they do not make clear the degree to which this is the case; nor are indications for treatment or discontinuance entirely agreed upon. Furthermore, there are not yet adequate data with which to estimate the probability of recurrence and death during and after discontinuing treatment. The present report attempts to clarify these questions.

Rationale of Anticoagulant Therapy

Whether or not a hypercoagulable state exists in thromboembolic conditions, a local surface or disease process must be present, since clotting does not occur throughout the entire vascular system but only in local areas. The experimental and clinical evidence suggests that under normal circumstances the intima maintains a negative charge from a continuous layer of negatively charged heparin-like material. With intimal damage there presumably is a reversal or reduction of the negative charge; this alteration is associated with the disappearance of heparin-like properties and with the appearance of cephalin-like material at the surface, giving rise to platelet stickiness. As a result, thrombosis may occur when the blood components are in a condition to respond to these intimal changes. If such a hypothesis is correct, heparin would be valuable in affecting the intimal cells and in neutralizing any circulating, active plasma thromboplastin (factor V or ac-globulin). Heparin might also prevent platelet stickiness and, in large doses, might exert an anti thrombic effect. Antiprothrombin drugs also may decrease activity of plasma thromboplastin component; they are known to decrease the activity of plasma thromboplastin antecedent (factor VII), which is necessary for the normal action of tissue thromboplastin\(^5\).

In coronary and cerebral arterial diseases atherosclerosis is generally recognized as the primary process. Considerable disagreement, however, exists as to the pathogenesis of atherosclerosis. Until recently the general opinion has been that atherosclerosis begins as a degenerative change with a deposition of cholesterol in the deep layers of the intima followed by fibrous tissue proliferation. Recently Duguid and Robertson\(^6\) have revived interest in the old theory of Rokitansky\(^7\), who stated that atheroma was the result of excessive deposition of blood derivatives, particu-
larly fibrin, on the inner surface of the arteries. Some experimental evidence has subsequently supported this view, i.e., that fibrinous thickening of the intima with narrowing of the lumen can result from gradual organization of thrombi in the arteries. Thus thrombogenic intimal changes may ultimately form a site for secondary thrombotic deposition. Continuous and prolonged anticoagulant therapy may therefore be of significance in preventing further development of atherosclerosis as well as in preventing thrombosis at the site of an atherosclerotic plaque.

Experimental evidence also indicates that anticoagulant therapy increases the natural tendency to recanalization of occluding thrombi.

A wide variety of circumstances have been suggested as causes of the hypothetical state of hypercoagulability. These include a postprandial hypercoagulability that is apparently related to the intake of saturated fatty acids. It is believed that such a condition would be minimized by prolonged anticoagulant therapy.

Thrombolysis must also be considered in the pathogenesis of thrombosis. Greig and Rundle have demonstrated in vitro a marked reduction in fibrinolysis in the plasma of subjects after a high-fat meal; they have found, however, that the lipemia resulting from the ingestion of unsaturated fatty acids does not inhibit fibrinolysis. If postprandial inhibition of fibrinolysis does occur, then the other factors involved in thrombogenesis should be minimized by the use of anticoagulants.

Methods and Material

The present study is an evaluation of the results of long-term anticoagulant therapy in a group of 336 patients encountered in a stable urban midwestern practice with various thromboembolic conditions, classified as follows: 1. Coronary disease: myocardial infarction, mild, moderate, or severe; impending infarction; angina pectoris. 2. Cerebral vascular disease: involving carotid or vertebral-basilar arterial system, transient, progressive, or complete. 3. Phlebitis; classified as to site. 4. Pulmonary embolism: single or multiple. 5. Peripheral arterial thrombosis or embolism: classified as to site.

To achieve uniformity the diagnoses were all re-evaluated at the time of classification.

Anticoagulant therapy (90 per cent of patients received Dicumarol, Danilone, or Cumopyran) was usually started in the hospital, although in some instances it was initiated in ambulatory patients. Prothrombin times as a rule were measured daily during hospitalization and less frequently on long-term programs with outpatients. With most long-term patients, prothrombin time determinations were made every 3 weeks with the Quick 1-stage method. A "therapeutic prothrombin time" has been arbitrarily defined as falling between 18 and 35 seconds. The control was almost always 12 seconds or less.

The study is entirely a retrospective evaluation and is in no sense a planned experiment. Accordingly, various therapeutic measures in addition to anticoagulant treatment were used.

The present report compares the rates of first nonfatal recurrence in persons on continuous anticoagulant therapy with the rates after discontinuing therapy in the entire group. It further presents the mortality rates, and describes the pattern of recurrence after discontinuance of therapy in persons with brief, intermediate, and prolonged initial periods of continuous therapy.

To manage the large and varied assortment of data a code sheet of 80 items was filled out for each patient; the data on this sheet were then transferred to IBM punch cards for sorting analysis. The items recorded include the initial diagnosis; various biographical data (sex, age, occupation, ethnic group, height and weight, family history, past history of prior thromboembolic and other significant diseases); laboratory data; electrocardiographic measurements; appropriate time measurements; the nature and dates of first and subsequent recurrences during therapy and after therapy; the incidence and nature of hemorrhagic complications; the stability of office and hospital prothrombin times; subsequent clinical status of the patient; and the incidence, time, and nature of death.

All thromboembolic episodes occurring after the episode leading to inclusion in the study were considered to be recurrences. Episodes of prolonged angina were classed as recurrences, even though the diagnosis of infarction could not always be made. Likewise, transient attacks of cerebral arterial insufficiency were included, despite the fact that some of these may not have been thromboembolic in origin.

Three time-periods were used in the evaluation. The first, called the "total period of observation," was measured from the date on which the patient was first seen for the episode leading to inclusion in the study until the date on which the patient's
Analysis of 336 cases.

chart was drawn for coding or the date of death. This period was then subdivided into an initial period called the “duration of continuous therapy” and a subsequent period called the “period of observation after first discontinuation.”

The “first nonfatal recurrence on continuous therapy” was measured on the time-scale dating from the date of inclusion in the study and corresponding to the scale used for “duration of continuous therapy.” The “first nonfatal recurrence after discontinuing therapy” was measured from the date of the first discontinuance of therapy and corresponds to the time-scale covering the “period of observation after the first discontinuance.” The death time-scales are similar.

For easy interpretation, comparison, and determination of the statistical significance and reliability of the results, the method of constructing survivorship tables has been chosen. This method consists in determining rates of death or first recurrence at successive periods of time. Then the estimated number of persons per original 1,000 with nonrecurrence or survival at successive time periods can be determined. The standard errors of these estimates of the number of survivors were used to compute the significance of differences noted in various groups. (See Appendix.)

Comparison of the Groups

The general outline of anticoagulant therapy for the entire sample of 336 cases is shown in Figure 1. Patients who died in the first month (acute death) were excluded from the study, as were those who received only heparin (no continuous treatment). For simplicity’s sake, the term “treated group” is used to describe the 308 patients who had a period of continuous treatment; the term “discontinued group” to describe the 203 observed after discontinuing treatment (including 4 patients whose treatment was very brief); and the term “never-discontinued group” to describe the 109 patients who received treatment throughout their entire period of observation. Substantially, then, the “treated group” consists of the “discontinued group” plus the “never-discontinued group.”

Tables 1 to 4 compare the diagnostic composition, age and sex, prior thromboembolic history, and associated pathologic conditions in the discontinued and the never-discontinued groups. As compared with the discontinued group, the never-discontinued group is seen to contain a larger percentage of cases of coronary and cerebral arteriosclerosis, patients of somewhat greater average age, a higher incidence of prior thromboembolic
episodes and of angina pectoris, and a larger percentage of prior abnormal electrocardiograms. The incidence of hypertension, cardiac decompensation, and diabetes is similar in the 2 groups.

Thus, the 109 patients in the never-discontinued group are clearly shown to be poorer risks by virtue of age, sex, prior history, and associated pathologic conditions. Moreover, this greater severity of involvement in those who were continued on treatment was noted uniformly for each disease category. 16, 17

The patients in the discontinued group did in fact show a lesser tendency to have thromboembolic recurrences during their period of continuous therapy. Compared with the patients whose therapy was never discontinued, they had a lower incidence of recurrence during the first year on therapy and no recurrences during the subsequent course of treatment.

The Use of the Discontinued Group as a "Control"

Comparison of the rates of first nonfatal recurrence during therapy and after discontinuing therapy raises the question of the validity of using the discontinued group as a "control" to be compared with the treated group. In the present study the use of the discontinued group as a control can be justified in several ways:

1. The discontinued group originally comprised two thirds of the treated group, and it thus serves as a control for itself (tables 1 to 4).

2. The never-discontinued group (the remaining third of the treated group) has been shown to be actually a poorer risk group than the discontinued group.

3. The incidence of recurrence among the members of the discontinued group while on their initial continuous treatment was not higher than that for those who remained on treatment.

4. Unfavorable response to treatment and complications of treatment were not significant factors in determining discontinuance. The reasons for discontinuing treatment were

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td><strong>Comparison of Discontinued and Never-Discontinued Groups: Diagnostic Categories</strong></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Coronary</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
</tr>
<tr>
<td>Phlebitis</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Peripheral thrombosis</td>
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<tr>
<td>Total</td>
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</tbody>
</table>

indication over (121 instances), initiative of patient (35 instances), other diseases or operation (30 instances), and complication of treatment (13 instances). Of the 13 who discontinued because of complications, 4 died and 2 had nonfatal recurrences in the first year after discontinuance. These numbers are not large enough to affect the first-year recurrence and death rates substantially.

Results

Incidence of First Nonfatal Recurrence

None of the patients in the discontinued group received anticoagulant therapy after its discontinuation, in the absence of recurrence. Thus in the time periods being considered the entire treated group was on therapy, and the entire discontinued group was off therapy.

During the first year of continuous therapy, there were 23 nonfatal recurrences; of these 16 occurred with subtherapeutic prothrombin times and 7 with therapeutic prothrombin times. In the second year there were 2 recurrences with subtherapeutic prothrombin times, and, thereafter, none occurred with subtherapeutic prothrombin times.

The pattern of first nonfatal recurrence during therapy and after discontinuing therapy is shown in table 5. The first year on treatment is subdivided into 4 smaller units to record changes in rate during that period. The rates are based on the ratio of the num-

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Table 2
Comparison of Discontinued and Never-Discontinued Groups: Age and Sex

<table>
<thead>
<tr>
<th>Sex</th>
<th>Observed after discontinuing therapy</th>
<th>Never discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. patients</td>
<td>%</td>
</tr>
<tr>
<td>Male</td>
<td>114</td>
<td>56</td>
</tr>
<tr>
<td>Female</td>
<td>89</td>
<td>44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. pts.</td>
<td>%</td>
</tr>
<tr>
<td>20-29</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>30-39</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>40-49</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>50-59</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>60-69</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>70-79</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>80-89</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Average age</td>
<td>58</td>
<td>58</td>
</tr>
</tbody>
</table>

**Figure 2**

Time of first nonfatal recurrence (abscissa). Number of persons with no recurrence of original hypothetical groups of 1,000 (ordinate). Brackets enclose ±1 standard error of the estimate of the number of persons with no recurrence.

The table indicates the number of persons in every 1,000 who would have had no recurrence during successive time periods. The numbers in parentheses indicate the standard errors of these estimates.

This table allows quick comparison of the fate of persons who remained on continuous treatment with the fate of those who discontinued. The lower section of table 5 presents the rate of first nonfatal recurrence after discontinuing therapy. The first year after discontinuing therapy is not subdivided. Approximately 821 persons would have had no recurrence after 60 months on continuous therapy as compared with 396 with no recurrence 60 months after having discontinued therapy.

Figure 2 presents the data from table 5 in graphic form. The curves show the number of persons who could be expected to have no recurrence at the successive intervals indicated on the time scale. The brackets enclose ±1 standard error. The rate of recurrence in the group on treatment is initially high and rapidly diminishes during the first few months, the curve becoming nearly horizontal by the end of the first year. The rate remains low throughout the first 5 years. The drop at the end of the curve is associated with a very small number of cases, and the standard error of the estimate is therefore greater. The curve for the recurrence rate in persons who discontinued therapy is also high initially, but, by contrast, it remains high throughout the period of observation.

**Effects of Different Durations of Continuous Treatment on the Recurrence Rates after Discontinuing Therapy**

The patients in whom treatment was discontinued were separated into those whose...
LONG-TERM ANTICOAGULANT THERAPY

**Figure 3**

Number of persons with no recurrence of original hypothetical groups of 1,000 (ordinate) for number of years (abscissa) after discontinuing therapy in groups with different durations of initial treatment.

Initial treatment was brief (0 to 3 months), intermediate (3 to 12 months), and long (12 to 60 months).* The rate of first nonfatal recurrence after discontinuing therapy was determined for each of the 3 groups (fig. 3). The date of onset of the prior continuous therapy was used as the zero time point, and the rate curves begin at the average time of discontinuance for the 3 groups. The 3 curves merge at 40 per cent still free of recurrence in 5½ years. The recurrence rate for patients who were treated longer initially is somewhat greater after discontinuance.

**Death Rates during Treatment and after Discontinuation**

In comparison of the mortality in the treated and discontinued groups it must be noted that the discontinued group includes a substantial number of patients whose therapy had been resumed after a nonfatal recurrence. As far as mortality is concerned, then, the discontinued group is to be viewed as a group on intermittent therapy.

Eighteen deaths occurred in the group on continuous treatment. Of these, 1 occurred with a subtherapeutic prothrombin time, 2 occurred with a prothrombin time greater than 40 seconds (the prothrombin time determination nearest to the time of the fatal episode), and 15 occurred with a prothrombin time in the therapeutic range. There were 46 deaths in the discontinued group.

The mortality rates are shown in figure 4. Since the range of ±1 standard error overlaps at each anniversary (brackets), no significant difference exists between the 2 curves. The group on continuous treatment has a somewhat lower death rate for the first 5 years, after which the rates are about the same. At the end of 5 years, approximately 737 persons of an original 1,000 would have survived in the group on continuous therapy. In the group observed after discontinuing therapy, 702 of 1,000 would have survived. The larger percentage of more serious cases in the group treated for prolonged periods probably affects its later mortality adversely.

**Effects and Complications of Treatment**

When treatment was initiated during hospitalization, a prothrombin time of 20 seconds or more was achieved by the third morning of hospitalization in 92 per cent of the cases. During hospitalization the prothrombin time was in the therapeutic range 80 per cent or more of the time in 80 per cent of the cases. The percentage of prothrombin times in the therapeutic range was computed for each patient who had had office prothrombin determinations. The average of these per-
centages was 70.4 per cent. Little difference in the average stability of prothrombin control was observed with longer or briefer periods of treatment.

Hemorrhagic complications were observed in 19 per cent of the patients, with 12 per cent having only 1 episode, 5 per cent having 2 episodes, and 3 per cent having 3 or more episodes. Of a total of 95 bleeding episodes, 78 were considered minor, and 17 were considered severe. Two deaths occurred in patients whose prothrombin times were greater than 40 seconds.

Discussion

The pattern of first nonfatal recurrence in persons on continuous therapy was described in Table 5. This table can be thought of also as presenting the probability of remaining free from subsequent recurrence. Two important factors must be considered in viewing the first recurrence rates on continuous therapy: (1) the tendency to recurrence is very strong during the immediate post-thrombotic period; and (2) anticoagulant therapy requires some time to become established. During the first month the recurrence rate is 3.6 per cent. Thereafter, the rate decreases to an average of 1.25 per cent, 0.73 per cent, and 0.85 per cent per month for the remaining 3 time periods of the first year. The average monthly rate during the second year is only 0.26 per cent. Thus, once the initially high rates have passed, the likelihood of further nonfatal recurrence remains small.

During the first year on treatment a subtherapeutic prothrombin time was frequently associated with recurrence. Despite the relative frequency of subtherapeutic prothrombin times in later years, associated recurrence almost never took place.

Thus, the rate of recurrence in patients on continuous therapy appears to be initially high. The early high rate suggests the importance of maintaining therapeutic prothrombin time levels during the first several months. Coincident with the establishment of anticoagulant therapy, the recurrence rate becomes lower rapidly and approaches zero for several years. At the end of 5 years, 821 of the original hypothetical 1,000 receiving treatment continuously would have had no recurrence (Table 5).

The pattern of recurrence in patients who discontinued therapy is quite different. In this group the recurrence rate is high during the first year after discontinuing therapy, namely, 20.9 per cent or about 1.74 per cent per month. This average rate per month is not so high as the rate observed for the first month on con-
continuous therapy; but in the discontinued group the rate of recurrence remains high, with no sign of the tendency to level out observed in the group on continuous therapy. Thus, at the end of 5 years, only 396 persons of 1,000 who had discontinued treatment would still be free of recurrence. The difference in rate of first nonfatal recurrence has been shown to be statistically significant throughout the period of observation. (See Appendix.)

To date there has been no useful guide to the indications for discontinuing anticoagulant therapy. The decision to continue should be made when the patient is presumably as safe off therapy as he is on therapy. The curves in figure 2 show clearly that the tendency to recurrence after discontinuance is not favorably affected by a longer duration of initial continuous therapy. There appears to be no significant difference between the rates of recurrence after discontinuance following brief (0 to 3 months) and intermediate (3 to 12 months) durations of initial therapy. Following more prolonged initial therapy (average of 3 years) the rate of recurrence after discontinuance actually appears to be higher. It is true that the latter group contains a higher percentage of coronary cases and a smaller percentage of venous thromboembolic cases.

These data indicate that maintaining anticoagulant therapy does not arrest the underlying disease process and that upon discontinuance, the thrombotic tendency again becomes manifest and even shows a tendency to 'catch up.' Thus, the evidence suggests that there is no time when it is safe to discontinue anticoagulant therapy in the more serious thromboembolic diseases.

Appendix

The estimates of numbers of survivors or nonrecurrences per 1,000 (table 5), involve statistical variations. The standard errors of these estimates can be used in the following ways: 1. The interval equal to the 'number of survivors plus or minus twice the standard error' will cover the 'true' or 'long-run average' of the number of survivors 95 per cent of the time. 2. The standard errors can be used to determine

<table>
<thead>
<tr>
<th>Time Interval (months)</th>
<th>Observed Percentage with no Recurrence</th>
<th>Number with no recurrence / number exposed to risk</th>
<th>Estimated no. with no recurrence for 1,000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>96.4</td>
<td>266.0/276.0</td>
<td>1000</td>
</tr>
<tr>
<td>1 month</td>
<td>97.5</td>
<td>192.5/197.5</td>
<td>964 (11)</td>
</tr>
<tr>
<td>3 months</td>
<td>97.8</td>
<td>132.5/135.5</td>
<td>940 (15)</td>
</tr>
<tr>
<td>6 months</td>
<td>94.9</td>
<td>92.5/97.5</td>
<td>919 (19)</td>
</tr>
<tr>
<td>12 months</td>
<td>96.9</td>
<td>62.5/64.5</td>
<td>872 (27)</td>
</tr>
<tr>
<td>24 months</td>
<td>97.2</td>
<td>34.5/35.5</td>
<td>845 (33)</td>
</tr>
<tr>
<td>36 months</td>
<td>100</td>
<td>17.5/17.5</td>
<td>821 (39)</td>
</tr>
<tr>
<td>48 months</td>
<td>100</td>
<td>10.5/10.5</td>
<td>821 (39)</td>
</tr>
<tr>
<td>60 months</td>
<td>83.3</td>
<td>5.0/6.0</td>
<td>821 (39)</td>
</tr>
<tr>
<td>72 months</td>
<td>100</td>
<td>1.0/2.0</td>
<td>684 (129)</td>
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<table>
<thead>
<tr>
<th>Time Interval (months)</th>
<th>Observed Percentage with no Recurrence</th>
<th>Number with no recurrence / number exposed to risk</th>
<th>Estimated no. with no recurrence for 1,000 patients</th>
</tr>
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<tr>
<td>0</td>
<td>79.1</td>
<td>148.0/187.0</td>
<td>1000</td>
</tr>
<tr>
<td>12 months</td>
<td>82.4</td>
<td>98.5/119.5</td>
<td>791 (30)</td>
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<td>24 months</td>
<td>82.8</td>
<td>62.5/75.5</td>
<td>652 (37)</td>
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<td>36 months</td>
<td>88</td>
<td>36.5/41.5</td>
<td>540 (42)</td>
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<td>48 months</td>
<td>83.3</td>
<td>20.0/24.0</td>
<td>475 (46)</td>
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<td>60 months</td>
<td>87.5</td>
<td>14.0/16.0</td>
<td>396 (53)</td>
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<tr>
<td>72 months</td>
<td>78.9</td>
<td>7.5/9.5</td>
<td>346 (57)</td>
</tr>
<tr>
<td>84 months</td>
<td>66.7</td>
<td>2.0/3.0</td>
<td>273 (64)</td>
</tr>
</tbody>
</table>

*The numbers in parentheses indicate the standard error of the estimate of the number of persons with no recurrence.

1 Time measured from date of inclusion in study.

The significance of differences between 2 groups. To test the hypothesis that the treated group has a larger number of nonrecurrences than the discontinued group, the observed difference in the number with no recurrence is compared with the square root of the sum of the squared estimates of the standard errors. If the observed difference is greater than 1.65 times the latter figure, the difference can be considered significant at the 5 per cent level. Thus, to compare the treated group with the discontinued group at 1 year, for example, the difference in the observed number of cases with no recurrence is 81 (table 5), while 1.65 times the square root of the sum of the squares of the estimates of the standard errors is only 66; therefore the difference is significant. Since a band of 1 standard error has been marked off in the graphs around each estimate of the number of persons with no recurrence, and these standard errors for the 2 groups are similar at corresponding time intervals, the differences can be considered significant if the
bands are separated by 0.3 or more of 1 standard error.

Thus, the treated group has a significantly greater number with no recurrence at the end of the first year and throughout the period of observation (fig. 2).

In interpreting the statistical analysis 2 technical points should be made. Insofar as the discontinued group represents a (random) sample of the treated group, the estimates of rates and differences of rates in the various groups are unbiased; i.e., the averages of these rates for large samples would correspond to the population values. The standard deviations for a single group are valid whenever the estimate of the rate is unbiased. In comparing 2 groups with the use of the standard deviations, the results are correct with no further assumptions when the groups are disjoint, e.g., never-discontinued and discontinued. To use the standard deviations when the groups are not disjoint, e.g., continuous therapy and discontinued therapy, one would need to assume exponential survival distributions.16

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Summario in Interlingua

In recente tempores, therapia anticoagulante a longe vista pro le prevention de morbo thromboembolique ha esse e un tema de considerable interesse. In le presente studio un meticulose tentativa essese facete de evalutar su efficacia in un grande gruppo de patieentes ineontrate in practica private.

Le resultatos del studio indica que mantenier therapia anticoagulante non arresta le subjaecente processo pathologic e que, post le discontinuation del therapia, le tendentia thrombotic redeveni manifeste e mesmo revela un certe intensification. Isto significa que il non existe un momento al qual il es salve discontinuar le therapia anticoagulante in casos del plus serie morbos thromboembolique.

References


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