Indications for Bishydroxycoumarin (Dicumarol) in Acute Myocardial Infarction

By Henry I. Russek, M.D., Burton L. Zohman, M.D., Alexander A. Doernner, M.D., Allen S. Russek, M.D., and LaVerle G. White, M.D.

Many physicians find it difficult to decide whether or not a patient sustaining a mild episode of acute myocardial infarction should be treated with anticoagulant drugs. The Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Occlusion with Myocardial Infarction (American Heart Association) has recommended the employment of such therapy in patients with this disease, unless contraindications to anticoagulant therapy exist. Data are presented to show that in "good risk" patients treated conservatively without anticoagulants, the mortality rate and incidence of thromboembolism are strikingly low. Consequently, even the maximum benefit theoretically obtainable from the employment of dicumarol in these cases is not sufficient to justify the hazard entailed in its use. It is therefore recommended that anticoagulants be employed only in the more serious attacks of the disease.

Anticoagulant therapy is now widely employed in the management of acute myocardial infarction, and, since it is a costly and burdensome form of treatment, the indications for its use should be clearly defined. Comparisons of unselected control and treated groups do appear to indicate that anticoagulants significantly reduce the over-all mortality rate and incidence of thromboembolism in this disease. From such crude statistics, however, it is by no means certain that these agents should be routinely prescribed in the treatment of all cases of acute myocardial infarction. The possibility must be recognized that the anticoagulant, like any other drug, may be indicated only under certain well-defined circumstances.

In a previous publication, the writers pointed out that the results of conservative therapy in "uncomplicated" cases of acute myocardial infarction are unlikely to be improved (and may actually be made worse) by employment of bishydroxycoumarin (dicumarol). This conclusion was based upon an analysis of 424 cases of acute myocardial infarction which were treated by conservative methods at the U.S. Public Health Service Hospital in Staten Island and the Maimonides Hospital in Brooklyn, New York. By employing certain known prognostic criteria, it was found that 204 of these patients presented no unfavorable signs for recovery during the first 24 hours of hospitalization. The mortality rate for this "good risk" group was only 2.45 per cent. Moreover, when the fatalities which obviously could not have been avoided with bishydroxycoumarin were eliminated, the theoretically preventable mortality rate for this group was only 0.98 per cent. The incidence of thromboembolism was also less than 1 per cent. Inasmuch as the administration of bishydroxycoumarin, in itself, presents a small but definite risk to life, our findings appeared to challenge the current practice of prescribing this drug in all cases. The limited theoretic benefit from bishydroxycoumarin in the milder episodes of infarction did not seem to compensate adequately for the potential hazards of the induced hemorrhagic state.

In order to determine whether the low mortality rate which was observed among the "good risk" patients in our series might have
been purely the result of chance sampling, it was decided to investigate a new series of cases from an entirely different source. As in our previous study we established the following criteria as indicative of a guarded prognosis: (1) previous myocardial infarction, (2) intractable pain, (3) extreme degree or persistence of shock, (4) significant enlargement of the heart, (5) gallop rhythm, (6) congestive heart failure, (7) auricular fibrillation or flutter, ventricular tachycardia or intraventricular block, (8) diabetic acidosis, marked obesity, previous pulmonary embolism, varicosities in the lower extremities, thromboembolitis (past or present) or other states predisposing to thrombosis. Patients who showed none of these symptoms during the first day of hospitalization were classified as "good risks" to distinguish them from the "poor risk" group comprising those who manifested one or more of these unfavorable prognostic signs.

Composition of Sample

All of the patients in the present series were treated at the Kings County Hospital (State University, College Division). Selection was made of consecutive admissions for acute myocardial infarction from hospital records covering a five year period. Of the 623 patients studied, 473 were male and 150 were female. A history of previous hypertension was obtained in 28 per cent of the men and in 47 per cent of the women. The ages ranged from 30 to 88 years with a mean age of 58.1. Forty-seven per cent of the patients were 60 years of age or older, compared with only 32 per cent of the patients in the former series. A considerably higher proportion of the subjects in the present group were admitted to the hospital within 24 hours of the onset of their attack than in the former analysis. In the classification of patients into "good risk" and "poor risk" groups only the facts in the history and physical examination which were available on the first day of admission to the hospital were considered. After such classification was complete, a study was made of the clinical course and subsequent outcome in each case. Inasmuch as the selection of "good risk" cases was independent of the data recorded in the histories after the first day of admission to the hospital and was made without knowledge of the final result in each instance, the element of bias is believed to have been excluded. Moreover, the fact that the clinical data were obtained and recorded years before by physicians not taking part in the present study seemed to obviate the possibility of prejudice and to add to the validity of this method of analysis. In every instance the clinical diagnosis of acute myocardial infarction was confirmed by one or more electrocardiograms. All of the patients were treated by conservative methods without the use of anticoagulants.

Results

Of the 623 patients, 247 died during the period of hospitalization, giving an over-all mortality rate of 39.6 per cent (table 1). This crude death rate, therefore, is considerably greater than that in the former study in which it was computed at 24.3 per cent. Clinical thromboembolic phenomena occurred in 44 patients or 7.1 per cent of the present series as compared with 4.5 per cent of the group previously analyzed. Of the 623 patients in the present series there were 285 who qualified as "good risk" according to our criteria. The mortality rate for this selected group was 3.5 per cent (table 1), an incidence approximating that observed for the comparable group in our earlier study (2.45 per cent).

When the causes of death were analyzed among the "good risk" cases in order to determine the number of fatalities which theoretically might have been prevented bybishydroxycoumarin, the following data were obtained: five of the total of 10 deaths took place within the first 48 hours of admission to the hospital before dicumarol could have exerted significant effect; of the remaining five deaths, two resulted from causes independent of the cardiovascular system (one from perforation of a peptic ulcer, the other from septicemia and bronchopneumonia), one was caused by recurrent myocardial infarction and two by undetermined causes. If it is assumed that the latter three patients might have survived as a result of bishydroxycou-
marin therapy (an assumption lacking confirmatory evidence), the theoretically preventable mortality for the 285 “good risk” patients in this series would be 1.1 per cent. A strikingly similar figure for theoretically avoidable deaths was noted in our previous study (0.98 per cent). Thromboembolism occurred in only 2 of the 285 “good risk” cases for an incidence of 0.7 per cent. The latter, therefore, confirms the infrequency of the complication in this class of patient as previously reported by the writers.

Eighty per cent of the “good risk” cases in the present analysis were admitted to the hospital on the day of their attack. This unusually high incidence of immediate admissions indicates that the low mortality rate reported for “good risk” patients did not result from distortion produced by their delayed entrance to the hospital. This is confirmed by the finding that the death rate for the 228 “good risk” patients admitted on the day of their attack was identical with that for the total group of “good risk” patients (3.5 per cent).

In striking contrast with these survival statistics were those obtained for the 338 “poor risk” cases which manifested unfavorable prognostic signs (table 1). Thus the mortality rate for the latter group was 70.1 per cent and the incidence of thromboembolic complications was 12.4 per cent. Death was, therefore, 20 times more frequent and thromboembolism 18 times more frequent in the “poor risk” than in the “good risk” group.

Inasmuch as the findings of the present study closely approximate those obtained in our previous analysis with respect to survival statistics for “good risk” patients it appears reasonable to assume that our data offer a true representation of mortality rate in such selected cases. The death rate and incidence of thromboembolic complications in the combined series, totaling 1047 cases, is shown in table 2. It can be seen that the mortality rate for 489 “good risk” cases, classified according to our criteria, was 3.1 per cent while the incidence of thromboembolic complications for the same group was 0.8 per cent. Of great significance is the fact that the preventable mortality for these selected cases, under bishydroxycoumarin therapy, could not have exceeded 1.0 per cent.

### Table 1—Mortality Rate and Incidence of Thromboembolic Complications (Kings County Hospital Series)

<table>
<thead>
<tr>
<th>No. Cases</th>
<th>Mortality</th>
<th>Embolization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percentage</td>
</tr>
<tr>
<td>Total</td>
<td>623</td>
<td>247</td>
</tr>
<tr>
<td>“Good Risk”</td>
<td>285</td>
<td>10</td>
</tr>
<tr>
<td>“Poor Risk”</td>
<td>338</td>
<td>237</td>
</tr>
</tbody>
</table>

### Table 2—Mortality Rate and Incidence of Thromboembolic Complications (Combined Series from Three Hospitals)

<table>
<thead>
<tr>
<th>No. Cases</th>
<th>Mortality</th>
<th>Embolization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percentage</td>
</tr>
<tr>
<td>Total</td>
<td>1047</td>
<td>350</td>
</tr>
<tr>
<td>“Good Risk”</td>
<td>489</td>
<td>15</td>
</tr>
<tr>
<td>“Poor Risk”</td>
<td>558</td>
<td>335</td>
</tr>
</tbody>
</table>

### Discussion

In spite of the volume of literature concerned with survival statistics in acute myocardial infarction, little or no information is available regarding the outlook for the patient sustaining an “uncomplicated” first attack. It has been claimed that a fatal outcome occurs in no more than 10 per cent of patients suffering their initial episode. Master, Jaffe and Dack reported a mortality rate of only 8 per cent in their series of cases with first infarctions. These figures, however, represent crude mortality statistics in unselected patients with attacks of varying severity. In our series of 489 “good risk” cases, all of whom sustained a first attack without serious initial symptoms, the mortality rate was only 3.1 per cent and the incidence of thromboembolism was only 0.8 per cent.

In order to determine whether bishydroxycoumarin should be administered to all patients with acute myocardial infarction, it must be proved that even in the milder cases,
the preventable mortality and morbidity significantly exceeds the incidence of complications and death attributable to the drug itself. We have shown that the employment ofbishydroxycoumarin could not have prevented more than one death among every 100 patients in our series who sustained a “mild” attack. Moreover, if the drug worked to perfection (and this is certainly not the case) it could avert only eight clinical thromboembolic episodes in every 1000 patients, since this was the total incidence of the complication in our “good risk” group. Against such relatively small benefit involving a considerable expenditure of “time, trouble and money,” one must weigh the hazards inherent in any interference with blood clotting. Increasing numbers of case reports are appearing in the literature in which hemorrhagic complications and death have resulted from the use of anticoagulants. Sporadic reports of single cases or groups of cases give no assistance in determining the relative frequency of deaths due to bishydroxycoumarin but they do indicate that such results can be encountered by physicians experienced in anticoagulant therapy. The data collected by Nichol summarizing the experience of 136 physicians showed that major bleeding occurred in 2 per cent of approximately 15,500 anticoagulant-treated patients. The mortality rate in this group, from hemorrhage induced by dicumarol or heparin, was 0.18 per cent. Nichol himself encountered major hemorrhage in 10 per cent of 160 patients with acute myocardial infarction to whom he administered bishydroxycoumarin. In our opinion the true death rate and incidence of hemorrhagic complications from anticoagulants will be found to be considerably higher than has been realized, when careful necropsy studies replace “snap” judgment in establishing the cause of death in patients receiving these drugs.

Most of the available statistics concerned with the dangers of anticoagulant therapy reflect the experience of skilled investigators in large medical centers where excellent facilities for prothrombin determination exist. Consideration should be given to the probable results of therapy administered in smaller hospitals or in the patient’s home under the guidance of less skilled hands. It must not be overlooked that general practitioners and not “scientific investigators picked for their outstanding reputation in heart disease” treat the vast majority of patients with acute myocardial infarction. Moreover, it is in the milder cases that the general practitioner is likely to have exclusive control without benefit of consultation.

Regardless of the attending physician’s skill, however, or the reliability of laboratory facilities, we believe that it is neither necessary nor desirable to administer bishydroxycoumarin to cases of acute myocardial infarction which qualify as “good risks” according to our criteria. The evidence indicates that in such instances, this form of therapy may actually do more harm than good. Bishydroxycoumarin should be employed only in those patients in whom unfavorable prognostic signs are observed. Our statistics indicate that only in such cases is the incidence of clinical thromboembolism and thromboembolic deaths sufficiently high to justify the calculated risk from hemorrhage.

In a recent study it was shown that in the individual case, age has no influence upon immediate survival following acute myocardial infarction. The analysis demonstrates that the clinical picture alone provides the basis for formulating prognosis in any given case. Consequently, age should not be considered an important factor indicating or contraindicating the use of anticoagulants in this disease.

**SUMMARY AND CONCLUSIONS**

An analysis of the mortality and incidence of thromboembolism in 1047 cases of acute myocardial infarction treated conservatively shows no justification for the routine employment of bishydroxycoumarin (dicumarol) in this disease. The death rate in 489 “good risk” cases treated without anticoagulants was only 3.1 per cent and the incidence of thromboembolism in the same group was only 0.8 per cent. The preventable mortality under bishydroxycoumarin would have been, at most, only 1.0 per cent in these selected cases. Since such small benefit is more than likely to be
nullified or even overbalanced by complications induced by bishydroxycoumarin, its employment should be reserved for the more serious cases of acute myocardial infarction in which the frequency of thromboembolism justifies the risk entailed in its use.

REFERENCES
Indications for Bishydroxycoumarin (Dicumarol) in Acute Myocardial Infarction
HENRY I. RUSSEK, BURTÓN L. ZOHMAN, ALEXANDER A. DOERNER, ALLEN S. RUSSEK and LAVERE G. WHITE

Circulation. 1952;5:707-711
doi: 10.1161/01.CIR.5.5.707
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1952 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/5/5/707

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/