Hemorrhage During Long-Term Anticoagulant Drug Therapy

Part 1. Intracranial Hemorrhage

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■ *Intracranial hemorrhage was the most serious hemorrhage as measured by death and disability, occurring during long-term anticoagulant drug therapy of 1,626 patients. Among 95 hemorrhagic episodes considered life-threatening or potentially crippling, 30 were intracranial and 56 were gastrointestinal. Over two-thirds of the patients with intracranial hemorrhage died, as against one-tenth of those with gastrointestinal hemorrhage.*

The incidence of intracranial hemorrhage is increased among hypertensive patients, but the results of a controlled study indicate that the incidence of intracranial hemorrhage is not affected by whether or not the hypertensive patient is receiving anticoagulant therapy. Hypertension is the important precipitating factor, not the prothrombin level. Even at excessively low prothrombin levels only one intracranial hemorrhage occurred in 337 instances.

In this series, reducing coagulability to a desirable range did not increase the probability of intracranial hemorrhage. Once bleeding occurred, however, it increased the risk of death and disability.

VIGOROUS APPRAISAL of the benefits of long-term coumarin therapy has limited the indications for such treatment to only a few conditions. The same intense appraisal has not been applied to the dangers based on the risk of hemorrhage, the chief hazard of coumarin therapy. The frequency of bleeding is often emphasized, but without precise data as to the actual incidence, without distinction between serious and minor hemorrhage and without emphasis on the need for a vascular break before bleeding may occur. It is far more important to identify or to suspect potential or actual bleeding lesions before anticoagulant drug therapy is started than to investigate thoroughly after bleeding has occurred.

This study will consider only the risks of hemorrhage after long-term therapy. Gangrenous necrosis of the skin, a rare hemorrhagic complication, has occurred only in the first few days after starting treatment, not as a delayed complication of prolonged therapy. Similarly hemopericardium is

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TABLE 1.—*Distribution and Mortality Rate of Serious Hemorrhages (Life-Threatening or Potentially Crippling) During Long-Term Anticoagulant Drug Therapy*

	Patients	Intracranial Hemorrhages		Died	Gastro-intestinal Hemorrhages		Died	Other Hemorrhagic Deaths	Other Serious Non-fatal Hemorrhages	Serious Hemorrhages (Total)	
		No.	Per Cent		No.	Per Cent				No.	Per Cent
Various diseases	366	7	1.9	4	11	3.0	0	1 Intra-abdominal	1 Retro-peritoneal	20	5.4
Coronary arterial disease	973	15	1.5	12	29	2.9	2	1 "Leaking aneurysm"	1 Hemothorax 1 "Subendo-cardial" 1 Pancreas 1 Kidney	49	5.0
Cerebral vascular disease	287	8	2.8	5	16	5.6	3	1 Adrenal 1 Retro-peritoneal		26	9.0
Total	1626	30		21	56		5	4	5	95	5.8

usually confined to the treatment of acute myocardial infarction, and is rarely seen during long-term therapy. Minor hemorrhage—such as surface bleeding, capillary oozing or slight hematuria—has not proved to be a precursor of dangerous "spontaneous" hemorrhage. This will be discussed in a subsequent study in this series. The risk of the primary disease, if untreated or if treatment is discontinued, is usually serious disability or death. The comparable risk from anti-coagulant therapy is life-threatening or potentially crippling bleeding —true "serious" hemorrhage. It is important to develop a realistic estimate of the incidence of serious hemorrhage after anticoagulant therapy, and to determine how successfully this risk can be avoided. Serious *but avoidable* hemorrhage cannot be cited as valid contraindication to anticoagulant drug therapy.

Incidence of Serious Hemorrhage

Ninety per cent of serious hemorrhages (those that are potentially crippling or fatal) are either intracranial or gastrointestinal (Table 1).* Intracranial hemorrhage, although less frequent, is more often fatal and is therefore the subject of the first study in this series.

The incidence of such hemorrhage and any correlation with hypertension or with the level of hypocoagulability will be considered. Subsequent studies will be concerned with gastrointestinal hemorrhage, with the significance of minor bleeding, with the selection and management of patients and with unusual clinical experiences with this therapy.

*Reference Nos. 2, 4, 6, 7, 9, 12, 16, 17, 21-23.

Material

In a series of 1,626 patients collected from other studies who received long-term anticoagulant drug therapy, there were 95 serious hemorrhages, of which 30 were intracranial (Table 2). Although it is widely believed that nearly all intracranial hemorrhages occurring during anticoagulant therapy result in death, nine of the 30 survived. Oddly, this is a better survival rate than found among patients with spontaneous intracranial hemorrhage in a recent study in Connecticut. Of 68 patients with intracranial hemorrhage in that report, only 12 (18 per cent) survived one month.[5] These groups obviously are not comparable as treated and control groups, but the results are still seemingly paradoxical, since the effect of anticoagulants on intracranial hemorrhage should be to increase mortality.

What Are the Clinical Correlates of Intracranial Hemorrhage?—Intracranial hemorrhage is a natural complication of hypertension and would be expected to occur more frequently among hypertensive patients on long-term anticoagulant drug

TABLE 2.—*Site and Mortality Rate in 30 Cases of Intracranial Hemorrhages Occurring During Long-Term Anticoagulant Drug Therapy*

	No.	Died	Lived
Cerebral or intracerebral hemorrhage	22	19	3
Possible intracranial bleeding	1	....	1
Intracranial bleeding	1	1	....
Possible intracerebral hemorrhage	1	....	1
Subarachnoid hemorrhage	4	1	3
Subdural hemorrhage	1	....	1*
	30	21	9

*Operation done.

TABLE 3.—*Data from Four Reported Series of Intracranial Hemorrhage in Hypertensives in Treated and Control Groups on Long-Term Anticoagulant Drug Therapy*

Author	Number of Treated	Number of Controls	Number of Hypertensives		Number of Intracranial Hemorrhages			
					Treated		Controls	
			Treated	Controls	No.	Died	No.	Died
Bjerkelund[2]	119	118	32	28	3	3	3	1
Millikan[10]	115	115	". . . essentially identical for . . . degrees and extent of hypertension . . ."		....	6	....	7
Suzman,[21] Ruskin and Goldberg	779	1111	Not definitely stated		5	Not stated*	10	Not stated*
Hill, Marshall, and Shaw[8]	71	71	24	24	5	5†	0	....
Fisher[6]	196	184	114	115	5	....	3	....
Total	1280	1599			24		23	

* Millikan reported only the fatal hemorrhages.
† Two were originally unrecognized cerebral hemorrhages.

therapy. Available controlled studies comparing the incidence of intracranial hemorrhage among hypertensive patients receiving long-term anticoagulant drug therapy and among untreated hypertensive patients (Table 3) show no significant difference in incidence of intracranial hemorrhage for the two groups. These findings indicate the importance of controlled clinical studies, for without such studies the 24 intracranial hemorrhages occurring in the treated group could have been attributed to the anticoagulant drug therapy.

Since even control studies may be open to the criticism of bias, statistically these reports can only be suggestive. The levels of prothrombin activity were not correlated with the hemorrhages. Although Millikan[10] did not give the levels of prothrombin activity, he said that "perhaps what these figures actually say, or reflect, is the fact that these patients [with cerebral hemorrhages] were hypertensive and did have diseased intracranial vessels." This idea is also expressed by other investigators.[12,21,22]

Fisher[6] in an analysis of all types of hemorrhage, mild and serious, concluded that "provided that the prothrombin level is maintained above 15 per cent (Quick one-stage test) anticoagulation is no more dangerous in hypertensive patients than in normotensives." He did not specifically relate prothrombin activity to intracranial hemorrhage.

The critical level of hypocoagulability below which serious hemorrhage is likely to occur has not been precisely determined. Owren[13,14,15,16] expressed belief it is 10 per cent by the prothrombin-proconvertin method. (This is equivalent to 20 per cent by the Quick one-stage method or a prothrombin time in seconds of twice the control figure minus 2.[18] Owren[13,14,15,16] found in an analysis of more than 1,000 cases with prothrombin-preconvertin (P-P) levels below 10 per cent that all four coagulation factors reduced by the coumarin drug (Factors II, prothrombin; VII, proconvertin; IX, plasma thromboplastin component; X. Stuart-Prower Factor) were below their individual "safe levels."

If hemorrhages can be initiated by deficiency of any of these four factors below their supposed "safe" levels, serious hemorrhage would be expected to be frequent in patients with hypocoagulability below 10 per cent by the P-P test or 20 per cent by the Quick one-stage test.

What Is the Relation of an "Unsafe" Level of Prothrombin Activity to the Onset of Intracranial Hemorrhage?—Unfortunately, the correlation of hemorrhage with the prothrombin level is usually based on tests made after the hemorrhage, a finding invalid for several reasons: First, the prothrombin level may have been in the safe range before hemorrhage; afterward it may be low because of loss of thrombotic elements.[3,19,20] Second, a single low reading obtained after hemorrhage does not indicate how often the same reduction may have occurred previously without the patient having serious bleeding. Third, and most important, a cerebral vascular lesion may be present which could bleed even at normal levels of coagulability.

Bjerkelund[3] expressed belief that the risk of thrombosis is better indicated by the number of tests at which the prothrombin activity exceeds the clinical level than by a single test following throm-

TABLE 4.—*Data from Four Reported Series on Frequency of Spontaneous Intracranial Hemorrhage in Long-Term Anticoagulant Drug Treatment in Relation to Times the Prothrombin Activity was Below the "Safe" Level (20 Per Cent Quick One-Stage or 10 Per Cent P & P Test)*

Authors	Diagnosis	Patients	Results of Prothrombin Tests*				Intracranial Hemorrhage (All Patients Died)	
			Total Number of Tests	At "Safe" Levels	Below "Safe" Levels		At "Safe" Levels	Below "Safe" Levels
					No.	Per Cent		
Bjerkelund[2]	Myocardial Infarction	119	11649	10654	995	8.5	3	2
Borchgrevink[4]	Angina Pectoris	103	2428	2115	313	12.9	0	0
Moseley, et al.[11]	Various	300	2668	2454	214	8.0	1	0
Askey[1]	Various	100	4326	3863	463	10.6	0	0
Total		622	21071	19086	1985	9.4	4	2

* Average interval between tests: Bjerkelund, 1 to 3 weeks; others, 4 weeks.

botic complication. Similarly, the risk of hemorrhage is better gauged by the frequency of its occurrence at periods of excessive prothrombin reduction rather than from single readings obtained after hemorrhage.

Accordingly, the frequency of spontaneous intracranial hemorrhage has been estimated in 622 patients in whom a total of 21,071 prothrombin tests were made (Table 4) at intervals of three weeks to a month.[1,2,4,11] The percentages of low readings in the four series here combined were 8.5, 12.9, 8 and 10.6 and the average was 9.4 per cent. These patients, therefore, were exposed to excessively low levels of prothrombin activity during nearly one-tenth of these tests. In the 1,985 periods of excessive reduction of prothrombin, there were only two episodes of intracranial hemorrhage.

What Is the Relation of an "Unsafe" Level of Prothrombin Activity to the Onset of Intracranial Hemorrhage in Hypertensive Patients?—In one of these series (119 cases) Bjerkelund[2] separated his findings on hypertensive and normotensive patients; I did the same on the last 100 patients so treated in private practice (Table 5). Among the 45 patients in these two groups with diastolic blood pressure over 100 mm of mercury, there were 337 instances of prothrombin reduction below 10 per cent (prothrombin-proconvertin test) or below 20 per cent (Quick one-stage method) with only one intracranial hemorrhage at this low level. (Two others occurred at a "safe" level.) Among the 174 normotensive patients in the two groups, there were 1,121 instances of excessive reduction with one such hemorrhage. In the 10,981 instances of a "safe" level of prothrombin activity, there was one intracranial hemorrhage.

In the absence of controlled series, these figures merely reflect what one would expect—that the lower the hypocoagulability, the greater the number of overt intracranial hemorrhages. This is true whether the patients be normotensive or hyper-

TABLE 5.—*Frequency of Spontaneous Intracranial Hemorrhage in Hypertensives and Normotensives in Relation to Prothrombin Test Results*

	Patients	Prothrombin Tests			Intracranial Hemorrhage (All Patients Died)	
		Total Number	Number At "Safe" Level	Number Below "Safe" Level	At "Safe" Level	Below "Safe" Level
HYPERTENSIVES*						
Bjerkelund[2]	32	3204	2929	274	2	1
Askey[1]	13	669	606	63	0	0
Totals	45	3873	3535	337	2	1
NORMOTENSIVES						
Bjerkelund[2]	87	8445	7724	721	1†	1‡
Askey[1]	87	3657	3257	400	0	0
Totals	174	12102	10981	1121	1	1

* Diastolic blood pressure over 100 mm of mercury.
† Bleeding caused by glioblastoma shown at autopsy.
‡ Diabetes and generalized arteriosclerosis (PP test—3 to 4 per cent)

tensive. Controlled clinical studies of hypertensive patients at "safe" and "low" levels of hypocoagulability obviously are not feasible.

Discussion

Intracranial hemorrhage, although infrequent, is the most dangerous of the life-threatening or potentially crippling complications of long-term anticoagulant drug therapy. Yet, the risk of intracranial hemorrhage among patients receiving anticoagulant drug therapy is comparable to the risk in untreated patients; the risk is increased predominantly among the hypertensives in each group.

Among 219 patients separated according to blood pressure, three intracranial hemorrhages occurred among the 45 hypertensives and two among the 174 normotensives (Table 5).

The risk in normotensive patients is apparently negligible unless there is an unrecognized underlying cerebral lesion. In over 10,000 instances when the prothrombin activity was at a desirable level in normotensives, only one intracranial hemorrhage occurred. (The bleeding was into a glioblastoma.) In over 1,000 instances when the prothrombin level was excessively low, only one intracranial hemorrhage occurred (Table 5).

Although the risk in hypertensive patients is higher, controlled clinical studies show no significant increase of such cerebrovascular accidents in treated patients compared with untreated patients (Table 3). The risk was low in this hypertensive group regardless of the level of prothrombin activity. There were only two intracranial hemorrhages during 3,535 "safe" test periods. There was only one instance of intracranial hemorrhage during 337 periods when the prothrombin level was excessively reduced (Table 5).

This evidence indicates that anticoagulant therapy does not increase the frequency of intracranial hemorrhage in hypertensives but does increase the seriousness. The risk of an intracranial hemorrhage occurring is apparently the risk associated with hypertension; if hemorrhage occurs, the intensity of the bleeding increases and nearly all patients die.

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