Aspects of the Natural History of Gastrointestinal Bleeding in Cirrhosis and the Effect of Prednisone

ERIK CHRISTENSEN, LIS FAUERHOLDT, POUL SCHLICHTING, ERIK JUHL, HEMMING POULSEN, NIELS TYGSTRUP and CSL

Medical Department A, Division of Hepatology, Rigshospitalet; Medical Department, Division of Hepatology, and Department of Pathology, Hvidovre Hospital, Copenhagen, Denmark

The natural history of gastrointestinal bleeding in cirrhosis has been studied using prospectively collected data of 532 patients included in a randomized clinical trial with a regular follow-up of up to 12 yr. Of the total 199 patients who experienced gastrointestinal bleeding, 95 (48%) bled from esophageal or gastric varices, 67 (34%) bled from peptic ulcer or gastritis, and 37 (18%) had either insufficient evidence of the source (33) or mixed sources (4). In the total group of patients the cumulative percentage of patients in whom varices had been demonstrated by radiography increased from 12 to 90 in 10 yr, while that of bleeding from varices increased from 7 to 40. In 104 patients who bled for the first time during the trial period (trial bleeding patients) the median number of bleeding episodes was one (range 1–8). In these patients the fatality from bleeding from varices was 82%. The risk of rebleeding from varices was 81%, and 4 yr after the first bleeding the cumulative survival had decreased to less than 10%. Rebleeding was significantly less frequent and survival significantly higher in patients bleeding from sources other than varices. Prednisone reduced the occurrence rate of varices, bleeding from varices, and death from bleeding varices in nonalcoholic females without ascites, 40% of whom fulfilled the histologic criteria of chronic active hepatitis. Prednisone significantly increased the occurrence rate of varices in patients with ascites and of bleeding from varices in alcoholic patients. Prednisone significantly increased the occurrence rate of peptic ulcer in males and in patients without chronic active hepatitis.

Gastrointestinal (GI) bleeding is a common and serious complication of liver cirrhosis. The most important source is esophageal varices, but bleeding from peptic ulcer or gastritis is also common (1–7). Although the problem of GI bleeding in cirrhosis has been dealt with in numerous reports, nearly all have been retrospective in nature (8–13), and most have been based on relatively small samples.

Treatment with prednisone improves survival in nonalcoholic females without ascites but seems to reduce survival in patients with ascites (14,15). The extent to which these effects may be explained by the influence of prednisone on the risk of GI bleeding has not previously been evaluated.

Based on prospectively collected data from a multicenter randomized clinical trial with a regular follow-up of up to 12 yr, this report analyzes some aspects of the natural history of GI bleeding in cirrhosis and the influence of prednisone.

Patients and Methods

Data from 532 patients in a randomized clinical trial, evaluating the effect of prednisone vs. placebo on survival of patients with cirrhosis were analyzed (14,15). At the time of entry into the trial, after 3, 6, 12 mo, and thereafter once a year, each patient underwent a detailed assessment including clinical and laboratory findings. Liver

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Address requests for reprints to: Niels Tygstrup, Medical Department A 2152, Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen, Denmark.

Members of the Copenhagen Study Group for Liver Diseases (CSL) are as follows: T. Balslev, M. Bjørneboe, P. Christoffersen, K. Eghøje, V. Faber, S. Gjørup, B. Harvald, K. Iversen, O. Jessen, E. Juhl, H.E. Jørgensen, A. R. Krogsgaard, S. A. Nørregaard, T. Steen Olsen, H. Poulsen, F. Quaade, L. Ranek, F. Raaschou, Å. C. Thomsen, N. Tygstrup, P. Winkel.

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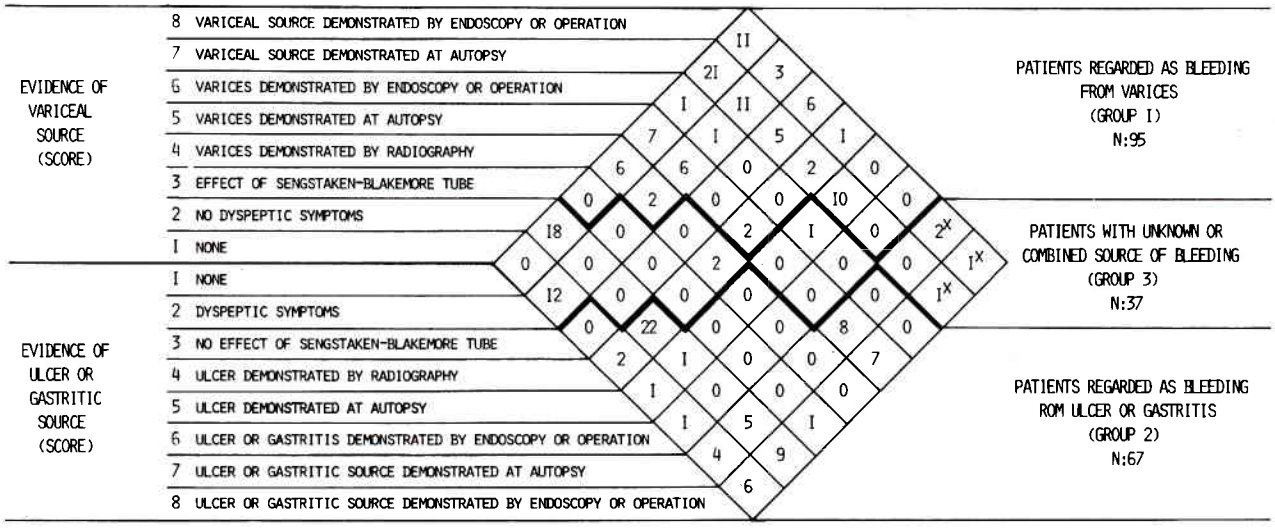

Figure 1. Classification of patients with GI bleeding according to source. For each combination of maximum scores the number of patients is given Thirty of the patients had endoscopy performed. This corresponds to 73% of those having scores of 6 or 8. X: Proved bleeding from varices at one time and from ulcer or gastritis at another time.

biopsies and radiologic examinations were planned to take place at yearly intervals but were performed less regularly in some patients. Patients were admitted to the trial between 1962 and 1969 and were followed regularly within the trial up to September 1974. Additional information on causes of death and autopsy findings have been obtained up to January 1978. The allocation was based on date of birth; 272 patients received prednisone and 260 received placebo. The initial 40 mg/day dosage of prednisone was reduced within 1 to 2 mo to a maintenance dose of 10–15 mg/day. In 488 patients reevaluation of the initial biopsy using restrictive histologic criteria was possible. Cirrhosis was confirmed in 287 patients (59%), probable in 101 (21%), compatible in 89 (18%), and not probable in 11 (2%) (16). The morphologic criteria of chronic active hepatitis were fulfilled in 98 of the 488 patients.

Patients who had hematemesis, melena, or both were divided according to the source of bleeding into three groups: patients bleeding from varices (group 1), patients bleeding from peptic ulcer or gastritis (group 2), and patients with undetermined or mixed source(s) (group 3). For each of the patients who bled, a score for evidence of bleeding from varices and one for evidence of bleeding from ulcer or gastritis was given using the criteria shown in Figure 1. In patients with more bleeding episodes the maximum score for each of the two types of evidence was used. Bleeding episodes separated by at least 2 wk without bleeding were regarded as individual episodes. The distribution of the scores is shown in Figure 1 for all 199 patients with GI bleeding. The patients were classified according to the lines of separation given in Figure 1. Ninety-five patients were classified as having bled from varices (92 from esophageal, 3 from gastric varices), 67 as having bled from ulcer or gastritis (29 from duodenal ulcer, 28 from gastric ulcer, 10 from hemorrhagic gastritis), and 37 had insufficient or conflicting evidence of the source of bleeding. Four patients in the latter group (Figure 1) had direct evidence (scores of 7 or 8) of bleeding from varices at one time and from ulcer or gastritis at another time. No other patients had direct evidence of more than one type of bleeding source. It appears that 70 patients bleeding from varices (74%) and 40 bleeding from ulcer or gastritis (60%) had direct evidence of the source of bleeding.

Table 1. Incidence of Bleeding Types

	Pretrial bleeding patients[a]	Trial bleeding patients[b]	Total
Bleeding from varices	38	57	95
Bleeding from ulcer or gastritis	37	30	67
Bleeding from undetermined source	20	17	37
Total	95	104	199

[a] First bleeding before entry into trial. [b] First bleeding after entry into trial.

Of the 199 patients with bleeding, 104 bled for the first time after entry into the trial (trial bleeding patients). The remaining 95 patients who had their first bleeding before entry into the trial (pretrial bleeding patients) form a selected group since they all survived their first (pretrial) bleeding occurring before or at the time of diagnosis (those who died at that early time were not included in the trial). The incidence of bleeding types in these two groups of patients is shown in Table 1.

Statistical analysis has been performed using χ^2 tests (discontinuous variables) or the Mann-Whitney or Kruskal-Wallis nonparametric tests (continuous variables). Using the time from entry into the trial to the first occurrence of an abnormal feature (e.g., the first bleeding episode), the cumulative percentage of patients in whom the feature had appeared at any time was estimated by the lifetable method, which allows for incomplete follow-up (17). The occurrence rates of abnormal features in patients without these features at entry were compared in subgroups using the logrank test (17). The relative occurrence

rate of an abnormal feature after entry in two subgroups was termed the occurrence rate ratio (relative risk), estimated as $(O_1/E_1)/(O_2/E_2)$, where O_1 and O_2 are the numbers of patients observed and E_1 and E_2 the numbers expected to develop the feature in each subgroup during the observation period. The estimation of E_1 and E_2 utilizes the temporal pattern of the occurrences and assumes that the risk of occurrence is the same in both groups. An occurrence rate ratio of 2:1 means that the feature is twice as likely to occur in one subgroup than in the other during the observation period.

Results

The cumulative percentage of patients in whom varices and ulcer were demonstrated by radiography is shown in Figure 2. While the occurrence rate of ulcer is rather constant in time, the occurrence rate of varices increases with time and after 10 yr this abnormality will have been demonstrated in about 90% of the patients.

The cumulative percentage of patients in whom bleeding occurred is shown in Figure 3. The occurrence rate of bleeding is highest in the first year after entry into the trial but after 8 yr an increase is also found, mainly in bleeding from varices. However, at that time the number of patients at risk is relatively small.

As expected, the number of bleeding episodes was higher in pretrial bleeding patients (median 2, range 1–11) than in trial bleeding patients (median 1, range 1–8), $p < 0.05$. Thus more than 50% of the trial bleeding patients had only one bleeding episode. This was the case for all three types of bleeding. Only 9 patients had more than five bleeding episodes. No significant difference in the distribution of the number of bleeding episodes was found in the three bleeding type groups.

The risk of rebleeding from varices was higher than that of rebleeding from ulcer or gastritis (Table 2). The risk of rebleeding did not differ significantly in pretrial and trial bleeding patients (Table 2).

The fatality from bleeding including causes of death directly related to the bleeding (coma and surgery) tended to be higher in patients bleeding from varices than in patients bleeding from ulcer, gastritis, or undetermined sources (Table 3). The fatality from bleeding tended to be less in pretrial than in trial bleeding patients (Table 3). Since very few patients had surgery performed (Table 3) the findings mainly reflect the course during conservative treatment.

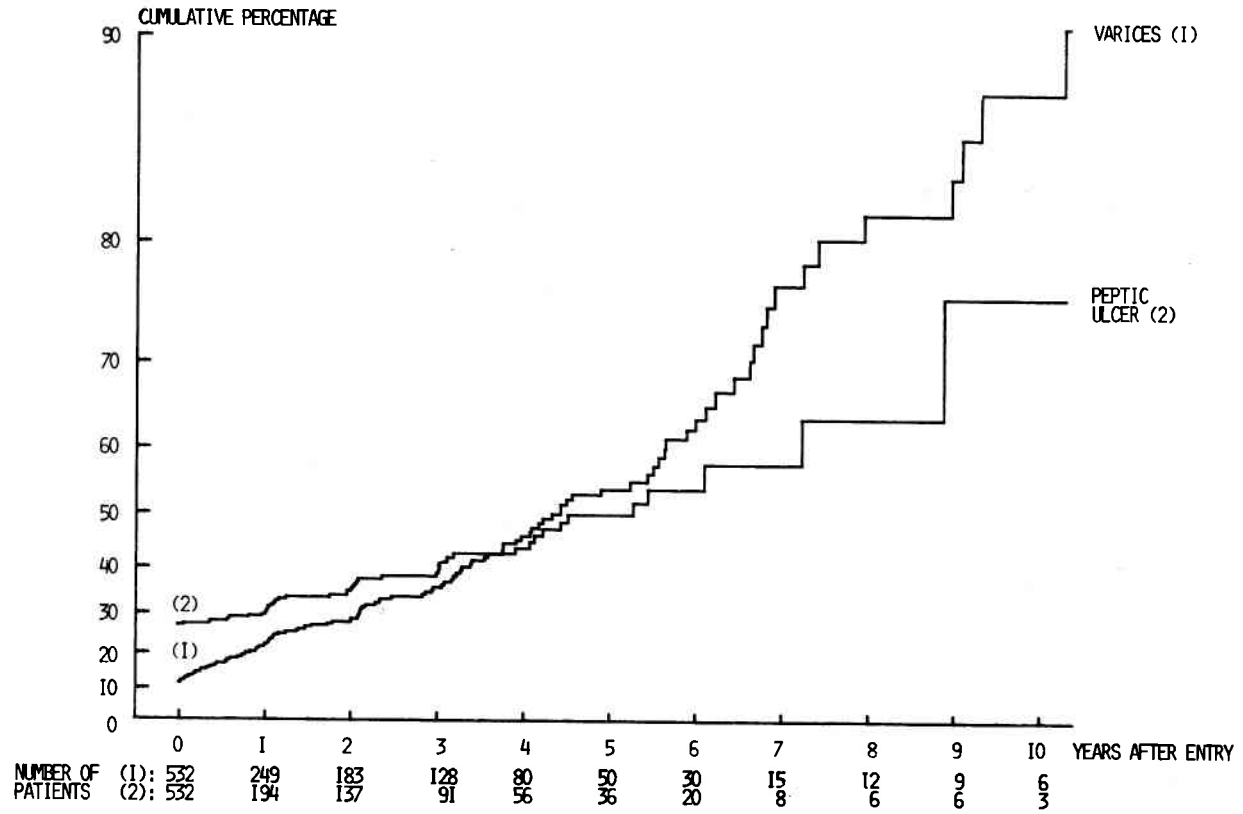

Figure 2. Cumulative percentage of patients in whom esophageal varices or peptic ulcer was demonstrated by radiography. Patients in whom the analyzed features had appeared at the time of entry are included. Analyses excluding pretrial bleeding patients gave similarly shaped curves with the following 10-yr increases: varices 8%–83%, peptic ulcer 23%–75%. Due to the inverse logarithmic (exponential) scale of the ordinate the slope is proportional to the occurrence rate (17).

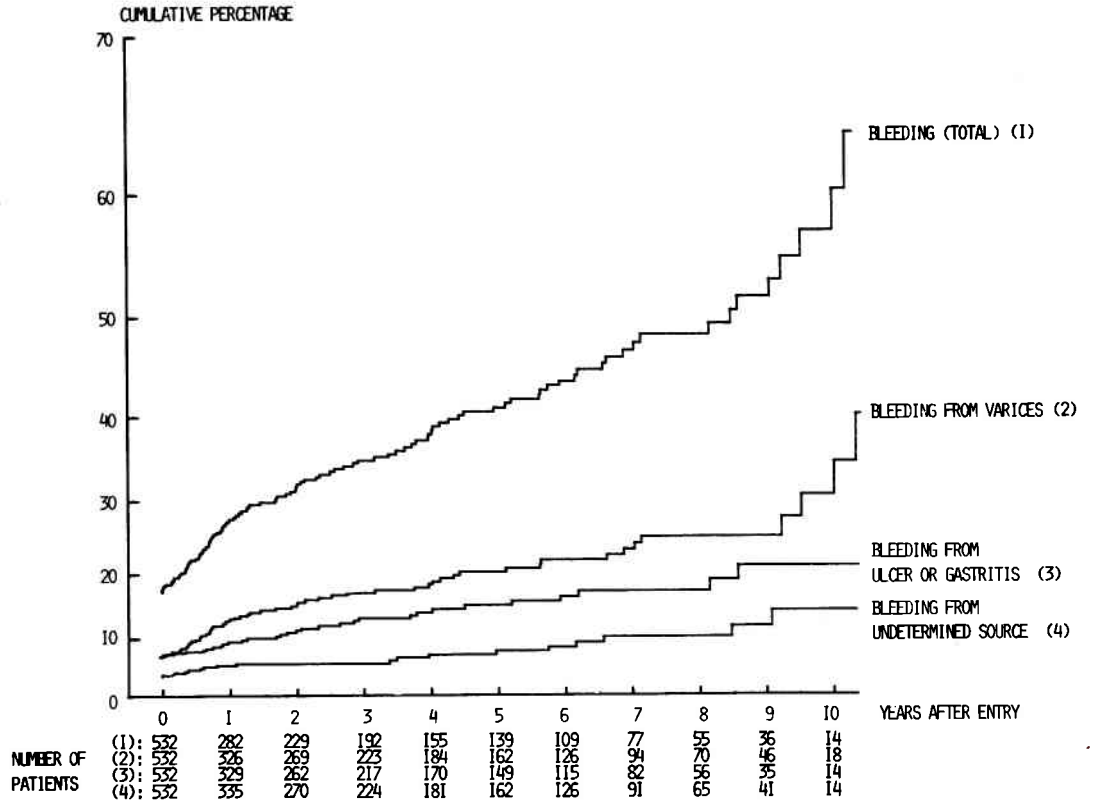

Figure 3. Cumulative percentage of patients in whom GI bleeding occurred. All patients are included. Analyses excluding pretrial bleeding patients gave similarly shaped curves with the following 10-yr increases: bleeding (total) 0%–52%, bleeding from varices 0%–26%, bleeding from ulcers or gastritis 0%–15%, bleeding from undetermined source 0%–11%. Due to the inverse logarithmic (exponential) scale of the ordinate the slope is proportional to the occurrence rate (17).

Lifetable analyses showed that survival after the first bleeding was significantly higher in pretrial than in trial bleeding patients, especially in bleeding from varices (Figure 4), reflecting the influence of selection caused by pretrial bleeding fatalities.

Considering only deaths from bleeding the survival after first bleeding for the three bleeding types in the trial bleeding patients is shown in Figure 5. Patients bleeding from varices have a 4-yr survival after the first bleeding of about 10% while survival was significantly higher in patients bleeding from ulcer, gastritis, or undetermined sources.

Of all trial bleeding patients who have died, death from GI bleeding, hepatic failure, or both was more frequent in patients bleeding from varices (54/56 = 96%) than in patients bleeding from ulcer or gastritis (21/28 = 75%), or from undetermined sources (8/13 = 61%), $p < 0.01$.

Effect of Prednisone

The analysis of the prednisone effect is based entirely on the data obtained during the trial period. At the time of randomization the prednisone and

Table 2. Risk of Rebleeding (No. of Rebleedings/Survived Bleedings)

Source of bleeding	Trial bleeding patients	Pretrial bleeding patients	p-Value	All bleeding patients
Varices (group 1)	42/52 (81%)	72/84 (86%)	0.60	114/136 (84%)
Ulcer or gastritis (group 2)	13/24 (54%)	62/85 (73%)	0.14	75/109 (69%)
Undetermined (group 3)	13/22 (59%)	30/44 (68%)	0.65	43/66 (65%)
p-Value				
Group 1 vs. 2	0.04	0.07		0.009
Group 1 vs. 3	0.09	0.04		0.005
Group 2 vs. 3	0.97	0.72		0.75

Table 3. Fatality from GI Bleeding (No. of Deaths from Bleeding/Patients Bleeding)

Source of bleeding	Trial bleeding patients	Pretrial bleeding patients	p-Value	All bleeding patients
Varices (group 1)	47/57 (82%)[a]	26/38 (68%)[b]	0.18	73/95 (77%)
Ulcer or gastritis (group 2)	19/30 (63%)[c]	14/37 (38%)[d]	0.04	33/67 (49%)
Undetermined (group 3)	8/17 (47%)	6/20 (30%)	0.47	14/37 (38%)
p-Value				
Group 1 vs. 2	0.09	0.02		0.0005
Group 1 vs. 3	0.009	0.01		0.00005
Group 2 vs. 3	0.44	0.76		0.36

[a] Acute shunt operation in 1 patient who survived; sclerotherapy in 6, 1 survived, 5 died. [b] Acute shunt operation in 5 patients, 3 survived, 2 died; sclerotherapy in 9, 6 survived, 3 died. [c] Acute gastric surgery in 6 patients, 2 survived, 4 died. [d] Acute gastric surgery in 9 patients, 6 survived, 3 died.

placebo groups were comparable. The distribution of the various types of bleeding before entry into the trial did not differ in the two groups.

Neither the number of patients with GI bleeding, nor the number of their bleeding episodes after entry into the trial was significantly different in any of the three defined subgroups during prednisone and placebo treatment. There was a trend towards a higher fatality of bleeding from varices and from ulcer or gastritis during prednisone treatment, but this was not statistically significant.

The occurrence rate of varices demonstrated by radiography (Table 4) was increased by prednisone in patients with ascites but decreased in nonalcoholic females without ascites and in patients with chronic active hepatitis. The occurrence rate of peptic ulcer demonstrated by radiography was increased by prednisone in males and in patients without chronic active hepatitis.

The occurrence rate of bleeding from varices (Table 5) was increased by prednisone in alcoholic patients but decreased in nonalcoholic females without ascites. Prednisone did not significantly influence the occurrence rate of bleeding from other sources.

The rate of death from bleeding varices (Table 6)

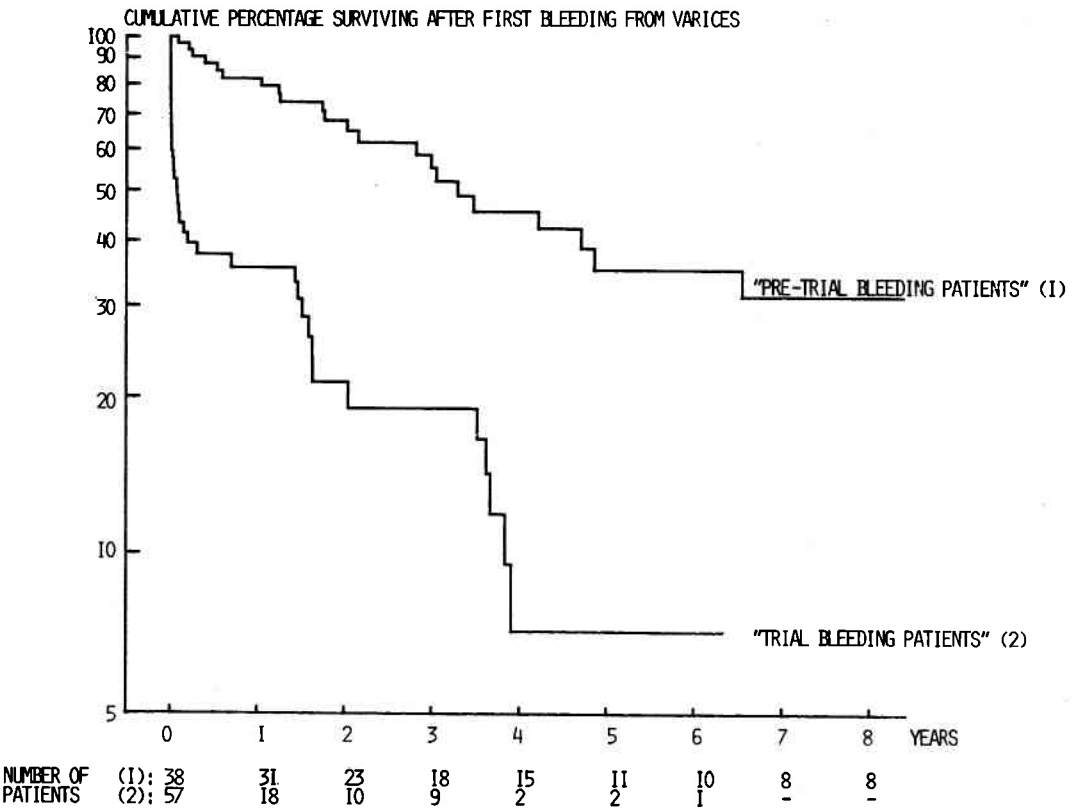

Figure 4. Cumulative survival after first bleeding from varices in pretrial and trial bleeding patients. Due to the logarithmic scale of the ordinate the slope is proportional to the death rate (17) ($p < 0.01$).

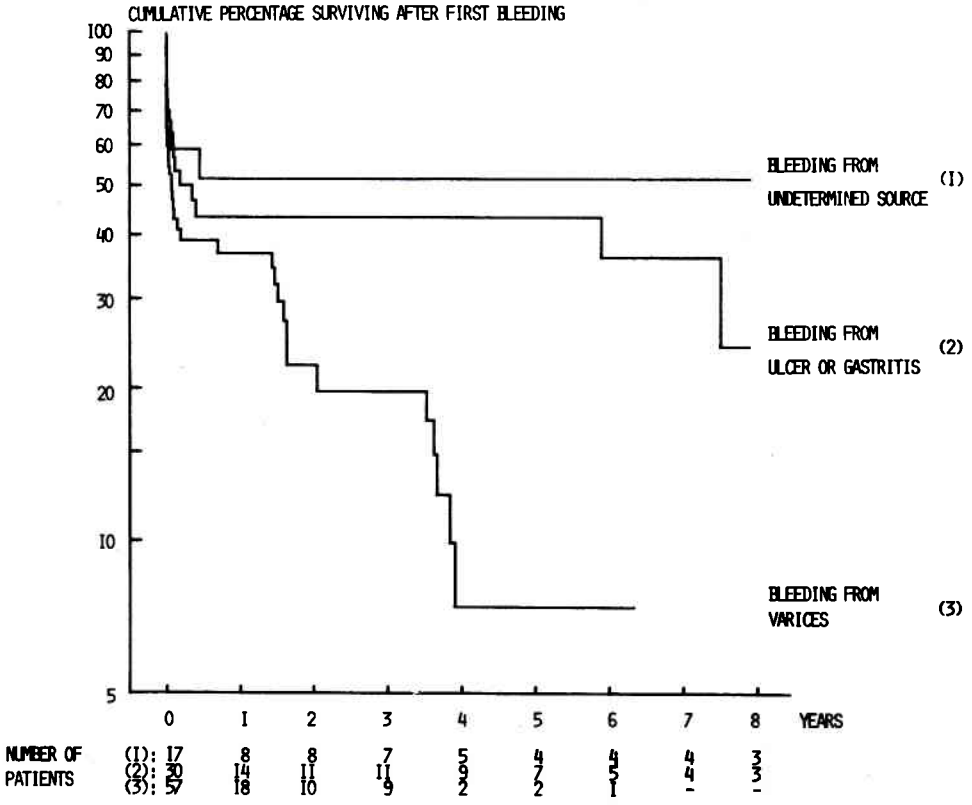

Figure 5. Cumulative survival after first bleeding from varices in the trial bleeding patients. Due to the logarithmic scale of the ordinate the slope is proportional to the death rate (17) ($p < 0.01$).

was reduced significantly in nonalcoholic females without ascites. The rate of death from bleeding from sources other than varices was not significantly influenced by prednisone in any group. The rate of death from causes other than bleeding was increased by prednisone in patients with ascites and decreased in patients with chronic active hepatitis.

Analyses that did not include pretrial bleeding patients gave similar results.

Discussion

This report is based on prospectively collected data from a large number of patients. A large number of clinicians has been involved in the trial but differences in patient selection and management between the participating centers have been minimized by the common protocol.

Since acute endoscopy was not routinely per-

Table 4. Effect of Prednisone on the Occurrence Rate of Varices and Peptic Ulcer

Variable	Group or subgroup[a] of patients	No. of patients at risk[b]		O/E-Ratio		Occurrence rate ratio	
		Prednisone	Placebo	Prednisone	Placebo	Predisone:Placebo	p-Value
Varices	Total	243	225	60/63.6	65/61.4	1:1.1	0.52
	Patients with ascites	22	21	9/4.7	8/12.3	2.9:1	0.02
	Nonalcoholic females without ascites	77	73	11/17.1	20/13.9	1:2.2	0.03
	Patients with chronic active hepatitis	47	44	11/14.8	9/5.2	1:2.3	0.05
Peptic ulcer	Total	201	185	28/23.6	18/22.4	1.5:1	0.19
	Males	116	98	20/14.8	9/14.2	2.1:1	0.05
	Patients without chronic active hepatitis	151	133	19/13.0	11/17.0	2.2:1	0.03

[a] Only results of subgroups in which the occurrence rate differed significantly ($p \leq 0.05$) have been included in the table. [b] Patients in whom the analyzed features had appeared at the time of entry into the trial are not included.

Table 5. Effect of Prednisone on the Occurrence rate of First GI-bleeding

Variable	Group or subgroup[a] of patients	No. of patients at risk[b]		O/E-Ratio		Occurrence rate ratio	p-Value
		Prednisone	Placebo	Prednisone	Placebo	Prednisone:Placebo	
Bleeding from varices	Total	258	237	31/30.1	27/27.9	1.1:1	0.82
	Alcoholic patients	99	83	13/8.9	3/7.1	3.5:1	0.04
	Nonalcoholic females without ascites	83	77	5/10.3	13/7.7	1:3.5	0.01
Bleeding from peptic ulcer or gastritis	Total	256	239	19/15.8	11/14.2	1.6:1	0.24
Bleeding from undetermined source	Total	264	248	7/8.7	10/8.3	1:1.5	0.40

[a] Only results of subgroups in which the occurrence rate differed significantly ($p \leq 0.05$) have been included in the table. [b] Patients in whom the analyzed features had appeared at the time of entry into the trial are not included.

formed during the period where patients entered the trial, the source of GI bleeding was not directly visualized in many cases and had to be determined by indirect methods (Figure 1). More than 80% of the patients could be classified as having bled from varices (group 1) or peptic ulcer or gastritis (group 2); in 74% of group 1 and in 60% of group 2 the bleeding source had been visualized directly at some time. Since patients with more bleedings tend to bleed from the same type of source each time (18), it is likely that the vast majority of the patients have been correctly classified. The frequency of patients with bleeding from varices or ulcer and gastritis agrees with that previously published (1–7) with the exception, perhaps, that cases with hemorrhagic gastritis tend to be more frequent in the literature. It is likely, however, that many patients with undetermined bleeding source (group 3) had hemorrhagic gastritis or acute erosions of the gastric mucosa, as such lesions are not reliably demonstrated by radiography. Thus there may be some overlap between group 2 and 3. This is supported by the small and in all cases insignificant difference between these groups in regard to number of bleedings, fatality of bleeding, survival from first bleeding, and cause of death.

The occurrence rate of varices demonstrated by radiography increases with time and is higher than

Table 6. Effect of Prednisone on Death-Rates

Variable	Group or subgroup of patients	No. of patients at risk		O/E-Ratio		Occurrence rate ratio	p-Value
		Prednisone	Placebo	Prednisone	Placebo	Prednisone:Placebo	
Death from bleeding varices	Total	272	260	30/30.1	29/28.9	1:1.0	0.99
	Patients with ascites	31	28	9/6.4	6/8.6	2.0:1	0.17
	Nonalcoholic females without ascites	85	86	4/8.5	12/7.5	1:3.4	0.03
	Patients with chronic active hepatitis	51	47	3/3.3	3/2.7	1:1.2	0.81
Death from bleeding ulcer or gastritis	Total	272	260	15/14.9	14/14.1	1.0:1	0.97
	Patients with ascites	31	28	2/2.1	2/2.9	2.1:1	0.41
	Nonalcoholic females without ascites	85	86	5/4.8	4/4.2	1:1.1	0.88
	Patients with chronic active hepatitis	51	47	3/2.1	2/2.9	2.1:1	0.41
Death from bleeding from undetermined source	Total	272	260	5/6.1	7/5.9	1:1.5	0.52
	Patients with ascites	31	28	1/1.1	3/2.9	1:1.2	0.89
	Nonalcoholic females without ascites	85	86	1/1.0	1/1.0	1.1:1	0.96
	Patients with chronic active hepatitis	51	47	0/0.5	1/0.5	—	—
Death from other causes	Total	272	260	112/119.6	121/113.4	1:1.1	0.32
	Patients with ascites	31	28	16/11.1	13/17.9	2.0:1	0.05
	Nonalcoholic females without ascites	85	86	28/34.6	36/29.4	1:1.5	0.10
	Patients with chronic active hepatitis	51	47	16/23.8	23/15.2	1:2.3	0.01

the occurrence rate of bleeding from varices, showing that varices do not necessarily cause bleeding. This probably reflects that it may take some time before the varices reach a size that makes them likely to bleed (13), and patients may die from other causes in the meantime. Furthermore, varices may regress in some patients (13). Therefore, the actual percentage of patients with varices may not be equal to the cumulative percentage of patients in whom varices have been demonstrated.

The occurrence rate of peptic ulcer and of bleeding from ulcer or gastritis is rather constant in time, indicating that peptic ulcer in cirrhosis may be less related to liver disease and more to factors (e.g., alcohol) that may cause cirrhosis. The lack of association between peptic ulcer and portal hypertension (19) may support this.

Regarding bleeding from varices, the higher survival rate after the first bleeding in pretrial compared with trial bleeding patients clearly shows the effect of selection caused by bleeding fatalities. The least biased picture of the natural history is thus provided by the trial bleeding patients. More than half of these died from their first bleeding. The results are interesting in relation to the findings that prophylactic portacaval shunt decreases survival, (20–23) while therapeutic portacaval shunt does not increase survival (24–26) except, perhaps, in patients with good liver function who have bled an average of 2.7 times before shunting (27). These divergent results may be explained by the effect of selection by previous bleeding. The high-risk patients who would die from the first bleeding could not be included in trials evaluating the therapeutic shunt, whereas such patients were included in trials evaluating the prophylactic shunt. In the high-risk patients death was probably speeded by the side effects of the shunt. Since the abandonment of the prophylactic shunt, only patients who survive one or more bleedings are now being considered for shunting. As these patients form a minority of the patients who bleed from varices, we need better means of identifying patients who are going to bleed (28) and improved criteria for selection of patients for shunting (or injection sclerotherapy).

An unfavorable effect of prednisone on the occurrence rate of peptic ulcer was statistically significant in males and in patients without chronic active hepatitis. These results are not readily explainable and the statistical significance may be accidental. Results from randomized clinical trials indicate that the ulcerogenic effect of steroids is important mainly in patients with hypoalbuminemia (29), but serum albumin was not lower in males than in females, nor was it lower in patients without than in those with chronic active hepatitis.

Why prednisone promoted the development of varices in patients with ascites and of bleeding from varices in alcoholic patients is not known, but it may be that in these relatively advanced cases the protein catabolic side effects, leading to weakening of the tissues including the esophageal veins, were of greater importance than the beneficial effect of the drug.

However, in less advanced cases, i.e., nonalcoholic females without ascites (40% of whom fulfilled the histologic criteria of chronic active hepatitis) prednisone significantly reduced the occurrence rate of varices, bleeding from varices, and death from bleeding varices. These results agree with results from the Mayo clinic (30). However, since the group of nonalcoholic females without ascites is more than twice as large as the group of females with histologic signs of chronic active hepatitis, and the effect of prednisone is not more favorable in the latter group, histologic features of activity are not mandatory for a beneficial effect of prednisone.

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