

EARLY ADMINISTRATION OF VAPREOTIDE FOR VARICEAL BLEEDING  
IN PATIENTS WITH CIRRHOSIS

PAUL CALÈS, M.D., CLAUDE MASLIAH, M.D., BRIGITTE BERNARD, M.D., PIERRE-PHILIPPE GARNIER, M.D.,  
CHRISTINE SILVAIN, M.D., NATHALIE SZOSTAK-TALBODEC, M.D., JEAN-PIERRE BRONOWICKI, M.D., DIDIER RIBARD, M.D.,  
DANIÈLE BOTTA-FRIDLUND, M.D., PATRICK HILLON, M.D., KAMEL BESSEGHIR, M.D., AND DIDIER LEBREC, M.D.,  
FOR THE FRENCH CLUB FOR THE STUDY OF PORTAL HYPERTENSION\*

**ABSTRACT**

**Background** In patients with cirrhosis, pharmacologic or endoscopic treatment may control variceal bleeding. However, the effects of early administration of a somatostatin analogue followed by endoscopic treatment are unknown.

**Methods** We studied the effects of treatment with vapreotide, a somatostatin analogue, begun before endoscopic treatment in 227 patients with cirrhosis who were hospitalized for acute upper gastrointestinal bleeding. The patients were randomly assigned to receive vapreotide (a 50- $\mu$ g intravenous bolus followed by an infusion at a rate of 50  $\mu$ g per hour for five days) or placebo within a mean ( $\pm$ SD) of 2.3 $\pm$ 1.5 hours after admission. The patients received endoscopic treatment a mean of 2.6 $\pm$ 3.3 hours after the infusion was begun. After the exclusion of 31 patients whose bleeding was not caused by portal hypertension, there were 98 patients in each group.

**Results** At the time of endoscopy, active bleeding was evident in 28 of 91 patients in the vapreotide group (31 percent), as compared with 43 of 93 patients in the placebo group (46 percent,  $P=0.03$ ); in 12 patients endoscopy was either impossible or showed portal hypertensive gastropathy. During the five-day infusion, the primary objective — survival and control of bleeding — was achieved in 65 of 98 patients in the vapreotide group (66 percent) as compared with 49 of 98 patients in the placebo group (50 percent) ( $P=0.02$ ). The patients in the vapreotide group received significantly fewer blood transfusions (2.0 $\pm$ 2.2 vs. 2.8 $\pm$ 2.8 units,  $P=0.04$ ). Overall mortality rates at 42 days were not significantly different in the two groups.

**Conclusions** In patients with cirrhosis and variceal bleeding, the combination of vapreotide and endoscopic treatment is more effective than endoscopic treatment alone as a method of controlling acute bleeding. However, the use of combination therapy does not affect mortality rates at 42 days. (N Engl J Med 2001;344:23-8.)

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**B**LEEDING from esophageal varices is an important complication of portal hypertension in patients with cirrhosis and is associated with a high mortality rate.<sup>1,2</sup> Hemostasis must be achieved immediately to control acute bleeding and to prevent early recurrence of bleeding (recurrence on days 3 to 5 after the onset of bleeding). Since acute bleeding can be controlled and early recurrence of bleeding can sometimes be prevented with drugs

or endoscopic therapy,<sup>3,4</sup> the combination of these two approaches should be beneficial. However, the results of treatment with terlipressin or somatostatin (or one of its analogues) in combination with endoscopic sclerotherapy or band ligation have sometimes not been better than the results of either method alone.<sup>5-10</sup> The administration of a somatostatin analogue before endoscopic therapy has not been studied. We designed a trial to evaluate the administration of vapreotide, a somatostatin analogue, before endoscopic treatment and its effects on initial hemostasis (hemostasis during the first two days after the onset of bleeding), the rate of early recurrence, and short-term mortality in patients with cirrhosis and variceal bleeding.

**METHODS****Patients**

From July 1997 to December 1998, all patients with cirrhosis who were admitted to 1 of 22 centers with hematemesis, melena, or both were enrolled in the study. To be included, patients were required to meet the following criteria: the presence of cirrhosis, as documented by previous liver-biopsy findings or typical clinical signs; an age between 18 and 75 years; an interval of less than 24 hours between the initial episode of bleeding and enrollment; and an interval of less than 6 hours between hospital admission and enrollment. Patients were excluded if they were in a coma, had a Child–Pugh score<sup>11</sup> greater than 13, or had previously had variceal bleeding within the past six weeks; if they had known hepatocellular carcinoma, complete portal-vein thrombosis, noncirrhotic portal hypertension, or allergies to somatostatin or its analogues; if they were pregnant or breast-feeding; or if they had patent intrahepatic portosystemic shunts or surgical shunts. The Child–Pugh score is a measure of liver dysfunction and is based on the extent of ascites, extent of encephalopathy, plasma prothrombin time, and serum albumin and bilirubin concentrations; the score ranges from

From the Services d'Hépatogastroentérologie, Centres Hospitaliers of Angers (P.C.), Nantes (C.M.), Paris (La Pitié–Salpêtrière) (B.B.), La Réunion (P.-P.G.), Poitiers (C.S.), Lille (N.S.-T.), Nancy (J.-P.B.), Nîmes (D.R.), Marseille (D.B.-E.), and Dijon (P.H.) — all in France; the Laboratoire d'Hémodynamique Splanchnique, Université d'Angers, France (P.C.); Debiopharm, Lausanne, Switzerland (K.B.); and the Service d'Hépatologie and INSERM Unité 481, Hôpital Beaujon, Clichy, France (D.L.). Address reprint requests to Dr. Calès at the Service d'Hépatogastroentérologie, Centre Hospitalier Universitaire, 49033 Angers CEDEX 01, France, or at paul.cales@med.univ-angers.fr.

Other authors were T. Poynard, M.D., Paris; P. Verger, M.D., La Réunion; J.C. Paris, M.D., Lille; F. Durand, M.D., and D.-C. Valla, M.D., Clichy; A. Lemaire, M.D., and M. Rouch, M.D., Aurillac; A. Blanchi, M.D., Le Mans; O. Ink, M.D., Soissons; F. Saliba, M.D., Villejuif; G. Galula, M.D., Paris (St. Antoine); B. Pilleland, M.D., Limoges; T. Davion, M.D., Lens; T. Dao, M.D., Caen; C. Bonny, M.D., Clermont-Ferrand; J.-P. Zarski, M.D., Grenoble; and F. Mion, M.D., Lyons — all in France.

\*Other participants in the study are listed in the Appendix.

5 to 15, with a score of 5 or 6 representing class A, 7 to 9 class B, and 10 to 15 class C.<sup>11</sup> These classes correspond to mild, moderate, and severe cirrhosis, respectively.

### Pharmacologic Treatment

Once enrolled, the patients were randomly assigned to receive either vapreotide (Octastatin, Debiopharm, Lausanne, Switzerland), given as an intravenous bolus of 50  $\mu\text{g}$  followed by a continuous infusion of 50  $\mu\text{g}$  per hour for five days, or placebo, in a double-blind manner. Vapreotide, a synthetic analogue of somatostatin, is a cyclic octapeptide that has high affinity for somatostatin-receptor subtypes 2 and 5 and some affinity for subtype 4<sup>12</sup> and that has a longer half-life than the native hormone (30 minutes vs. 3 minutes). Each center received a series of consecutively numbered, sealed boxes, which contained equal numbers of vapreotide and placebo treatments. The infusion was stopped after endoscopy in patients in whom the bleeding was determined to be unrelated to portal hypertension.

### Endoscopic Treatment

Diagnostic and therapeutic endoscopy was scheduled to be conducted within 12 hours after the initiation of the infusion of vapreotide or placebo. Either sclerotherapy or band ligation, according to the preference of the physician, was performed in patients with esophageal varices. In patients with gastric varices, banding was recommended for varices in the cardia, and banding or application of cyanoacrylate was recommended for varices in the fundus. After the completion of the five-day infusion, patients in both groups underwent additional weekly sessions of sclerotherapy or band ligation, according to the physician's judgment and as required by their clinical condition, until all their varices had disappeared.

### Other Treatments

Norfloxacin at a dose of 400 to 800 mg per day (or another fluoroquinolone at an equivalent dose) was given orally for at least five days beginning on day 1 of the study.<sup>13</sup> Blood transfusions were given to produce hematocrit values of 27 percent or higher and hemoglobin concentrations of 9 g per deciliter (5.6 mmol per liter) or higher.<sup>14,15</sup> Fresh plasma or plasma substitutes were given to maintain hemodynamic stability. No other clotting factors or other vasoactive substances were allowed unless treatment failure (lack of control of bleeding) occurred.

### Clinical Evaluation

Patients were followed for 42 days (the 5 days of treatment and the following 37 days). The blood pressure, heart rate, body temperature, any clinical signs of hemorrhage, the hematocrit, and the number of units of blood, plasma, or plasma substitutes administered were recorded at admission, at the end of the initial endoscopic procedure, every 6 hours for the next 48 hours, and then every 12 hours until the end of the five-day treatment period. Hemoglobin was measured at admission and at the end of the five-day treatment period and whenever the hematocrit was below 26 percent. Serum glucose, sodium, creatinine, aspartate aminotransferase, and alanine aminotransferase were measured at admission and after two days and five days of treatment. The Child-Pugh score was determined and blood counts were performed at admission and after five days of treatment. Hepatic ultrasonography was performed on day 5. The patients underwent additional clinical examinations on days 7, 30, and 42. The patients were closely monitored for adverse events throughout the study period.

The centers were classified into three categories according to the number of patients enrolled ( $\leq 5$ , 6 to 9, and  $\geq 10$ ) to allow analysis of the effect of center on the main outcomes. The protocol was approved by the ethics committee of the Centre Hospitalier Universitaire of Angers, and written informed consent was obtained from each patient or from family members if the patient was mentally unable to provide consent. Data on concomitant disorders and adverse effects were recorded for the entire population

of 227 patients, since all these patients received at least one dose of study medication.

### Objectives of the Study

The primary objective was to compare the two groups of patients with respect to the combined end point of control of bleeding and survival for five days, as in previous studies<sup>5-10</sup>; treatment was declared successful in patients in whom initial bleeding was controlled and early recurrence of bleeding was prevented and who remained alive on day 5. The secondary objectives were to assess the control of bleeding (absence of active bleeding) at the time of the initial endoscopic procedure and thus whether treatment facilitated endoscopy; the control of bleeding six hours after randomization; the number of units of blood administered during the 5 days of treatment; the incidence of late recurrence (bleeding from days 6 to 42); and survival during the 42 days of follow-up. Active bleeding was defined as spurting or oozing of blood from a varix.

With respect to the primary objective, control of bleeding was defined as the control of bleeding at 6 hours and 48 hours after endoscopy, with no early recurrence of bleeding. These three events were assessed according to the guidelines of the second Baveno consensus conference as follows.<sup>14,15</sup> For the six-hour period after the initial endoscopic procedure, hemostasis was defined as a transfusion requirement of 4 units of blood or less, a systolic blood pressure above 80 mm Hg, and a heart rate below 100 beats per minute. From 7 to 48 hours after endoscopy, hemostasis was defined as a transfusion requirement of 2 units of blood or less, the absence of hematemesis, a heart rate below 100 beats per minute, and a hematocrit that did not decrease by 10 percentage points or more during this interval. An episode of clinically important bleeding on days 3 through 5 was defined as bleeding accompanied by at least one of the following of the Baveno criteria: a decrease in systolic blood pressure of at least 20 mm Hg, an increase in heart rate of at least 20 beats per minute as compared with the average of the two preceding values, and a decrease in the hematocrit of at least 5 percentage points as compared with the preceding value. Tachycardia and hypotension were not taken into account if they could be clinically explained by a cause other than bleeding. After day 5, recurrent bleeding was defined as any new episode of hematemesis or melena.

### Statistical Analysis

Analysis was performed according to the intention to treat. All P values are two-tailed. Qualitative variables in the two groups were compared with use of the chi-square test with Yates' correction or Fisher's exact test, when necessary. In the calculation of the rate of treatment success (the combination of the control of bleeding and survival for five days), patients who were lost to follow-up on or before day 5 were included among those with treatment failure. The resulting contingency table (success vs. failure) was analyzed with the chi-square test and with the Cochran-Mantel-Haenszel method and the Breslow-Day test<sup>16</sup> to evaluate possible confounding factors. The Mann-Whitney test was used to compare quantitative variables, which were expressed as means  $\pm$ SD. Life-table analysis as described by Kaplan and Meier<sup>16</sup> was used to evaluate the rates of treatment failure and death. The resulting curves were compared with use of the log-rank test or the Wilcoxon test to evaluate the early effects of vapreotide.<sup>16</sup>

A crude comparison of blood-transfusion requirements between the study groups would be biased, since such data tend to be censored earlier in placebo groups than in active-treatment groups because of the higher failure rates with placebo.<sup>10</sup> To compensate for this source of bias, life-table analysis was used to compare the proportion of patients in each study group who received a defined number of units of blood; in this analysis, the number of units of blood transfused replaced the usual time scale on the x axis of the curves.

A prognostic analysis was performed to identify the possible effects of other variables on the occurrence of bleeding. First, the predictive value of the variables was evaluated by univariate analysis. Then, variables with a P value of less than 0.05, nonsignificant

variables that had potential clinical interest, and variables that were not balanced in the randomization were included in a multivariate logistic-regression analysis.<sup>16</sup>

## RESULTS

A total of 227 of 892 patients (25 percent) who were admitted to 22 centers with gastrointestinal bleeding met the criteria for inclusion. Five of the centers had 5 or fewer enrolled patients, 10 had 6 to 9 enrolled patients, and 7 had more than 10 enrolled patients. The main reasons for exclusion were delays in the interval between the initial episode of bleeding or hospitalization and enrollment (35 percent of the 892 admitted patients) and previous administration of a vasoactive drug or previous inclusion in a study (16 percent). Of the 227 patients who were enrolled, 116 were randomly assigned to receive placebo and 111 to receive vaptotide. At the initial endoscopic procedure 31 of the 227 enrolled patients (14 percent) were found to have bleeding from lesions not related to portal hypertension, and therefore the infusion of study medication was discontinued. Ninety-eight patients for whom data were available remained in each group. Twelve of these patients did not receive endoscopic treatment (six were found to have portal hypertensive gastropathy, two could not undergo endoscopy because of massive bleeding or coma, one refused endoscopy, and one died). Seven patients in the vaptotide group and four in the placebo group were subsequently lost to follow-up.

At enrollment, there were no significant differences between the two groups in clinical characteristics or the results of biochemical tests, except that there were more men and a higher mean serum glucose concentration in the placebo group (Table 1). The mean times from the onset of hemorrhage to admission, to the start of the infusion of vaptotide or placebo, and to the initial endoscopic procedure were  $8.3 \pm 6.0$ ,  $10.6 \pm 6.1$ , and  $13.3 \pm 6.6$  hours, respectively, for the entire population of 196 patients and did not differ significantly between the two study groups. The mean time from admission to the start of the infusion was  $2.3 \pm 1.5$  hours. The mean time between the initiation of the infusion and the initial endoscopic procedure was  $2.6 \pm 3.3$  hours.

### Control of Bleeding

At the time of the initial endoscopic procedure, control of bleeding (a secondary objective) was observed in a significantly greater proportion of the patients in the vaptotide group than in the placebo group ( $P=0.03$ ) (Table 2). The proportion of patients in whom bleeding was controlled and who survived for five days (the primary, combined objective) was significantly greater in the vaptotide group than in the placebo group ( $P=0.02$ ). Kaplan-Meier analysis revealed that the difference between the two

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT ENROLLMENT.\*

VARIABLE	VAPREOTIDE (N=98)	PLACEBO (N=98)	P VALUE
Age — yr	55±11	55±11	0.98
Male sex — no. (%)	67 (68)	81 (83)	0.02
Weight — kg	72±15	73±15	0.90
Duration of cirrhosis — yr	2.7±4.4	2.7±4.5	0.73
Alcoholic cirrhosis — no. (%)	82 (84)	84 (86)	0.89
Previous episode of liver decompensation — no. (%)†	39 (40)	40 (41)	0.93
Previous known esophageal varices — no. (%)	62 (63)	57 (58)	0.41
Previous treatment for portal hypertension — no. (%)	49 (50)	42 (43)	0.28
Beta-blockers	43 (44)	45 (46)	0.89
Endoscopy	24 (24)	21 (21)	0.73
Previous episode of portal hypertensive bleeding — no. (%)	38 (39)	38 (39)	0.95
Mean arterial pressure — mm Hg	89±15	86±16	0.14
Heart rate — beats/min	98±22	104±22	0.06
Child-Pugh class — no. (%)‡			0.95
A	14 (15)	14 (15)	
B	42 (46)	41 (44)	
C	36 (39)	39 (41)	
Child-Pugh score‡	8.7±2.1	9.1±2.4	0.39
Serum glucose — mg/dl	166±92	180±81	0.04
Serum aspartate aminotransferase — U/liter§			
Median	52	64	0.32
Range	6–417	8–330	
Serum alanine aminotransferase — U/liter§			
Median	28	29	0.15
Range	4–139	2–210	
Serum creatinine — mg/dl			
Median	0.8	0.9	0.07
Range	0.4–12.1	0.5–5.4	
Serum sodium — mmol/liter	138±5	138±6	0.92
Hematocrit — %	29.0±9.9	26.5±7.9	0.05
Hemoglobin — g/dl	9.5±2.4	8.8±2.8	0.11

\*Plus-minus values are means ±SD. To convert the values for serum glucose to millimoles per liter, multiply by 0.056; to convert the values for serum creatinine to micromoles per liter, multiply by 88.4; and to convert the values for hemoglobin to millimoles per liter, multiply by 0.62.

†Liver decompensation was defined as ascites or encephalopathy.

‡The Child-Pugh score is a measure of liver dysfunction and ranges from 5 to 15, with a score of 5 or 6 representing class A (mild cirrhosis), 7 to 9 class B (moderate cirrhosis), and 10 to 15 class C (severe cirrhosis). The Child-Pugh score could be determined in only 92 patients in the vaptotide group and 94 patients in the placebo group.

§The normal value is <35 U per liter.

groups in this combined objective was already present at six hours ( $P=0.002$  by the Wilcoxon test) and that it persisted at 42 days ( $P=0.006$ ) (Fig. 1). The rates of early recurrence of bleeding and of late recurrence of bleeding (days 6 to 42) (secondary objectives) were low and were not significantly different in the two groups.

The rate of treatment success with vaptotide on day 5 (the primary objective) was independent of the presence or absence of active bleeding at the first

TABLE 2. OUTCOMES ACCORDING TO TREATMENT GROUP.\*

VARIABLE	VAPREOTIDE (N=98)	PLACEBO (N=98)	P VALUE
Cause of bleeding — no. (%)			0.31
Esophageal varices	91 (93)	95 (97)	
Gastric varices	2 (2)	2 (2)	
Portal hypertensive gastropathy	5 (5)	1 (1)	
Endoscopic treatment — no. (%)			0.48
Sclerotherapy	49 (50)	55 (56)	
Band ligation	30 (31)	30 (31)	
Other (e.g., cyanoacrylate) or none	19 (19)	13 (13)	
Control of bleeding and survival — no. (%)			
At endoscopy†	63 (69)	50 (54)	0.03
6 hr after endoscopy	86 (88)	59 (60)	0.001
48 hr after endoscopy	72 (73)	53 (54)	0.005
Day 5	65 (66)	49 (50)	0.02
Recurrent bleeding — no. (%)			
Days 3–5	3 (3)	4 (4)	0.71
Days 6–42	16 (16)	11 (11)	0.38
Transfusion — no. (%)‡			
6 hr after endoscopy	44 (45)	49 (50)	0.47
7–47 hr after endoscopy	25 (26)	40 (41)	0.006
48 hr after endoscopy	39 (40)	51 (52)	0.08
Days 3–5	11 (11)	12 (12)	0.70
Day 5	43 (44)	53 (54)	0.15
Death — no. (%)			
Day 5	5 (5)	7 (7)	0.55
Day 42	14 (14)	21 (21)	0.21
Beta-blocker administration after day 5 — no. (%)	50 (51)	45 (46)	0.57
Duration of hospitalization — days§	15±8	15±8	0.85
At least one concomitant disorder (including recurrent bleeding) — no. (%)¶			
Day 5	44 (40)	49 (42)	0.69
Days 6 to 42	41 (37)	47 (41)	0.58

\*Plus-minus values are means ±SD. All times are given relative to the time of the initial endoscopy.

†Percentages were calculated for 91 patients in the vaptotide group and 93 patients in the placebo group; for 12 patients endoscopy was either impossible (because of early death, refusal, massive bleeding, or coma) or showed portal hypertensive gastropathy.

‡Values are based on the numbers of patients who received at least 1 unit of blood or fresh plasma or plasma substitutes.

§Mean values were calculated for the 84 patients in the vaptotide group and the 77 patients in the placebo group who were alive at 42 days.

¶Percentages were calculated for the total population of patients before exclusions (111 patients in the vaptotide group and 116 patients in the placebo group), all of whom received at least one dose of study treatment.

endoscopic procedure ( $P=0.53$  by the Breslow–Day test), the severity of liver impairment according to the Child–Pugh class (class A or B vs. class C,  $P=0.41$ ), the type of endoscopic treatment ( $P=0.98$ ), and the use or nonuse of preventive beta-blocker treatment at admission ( $P=0.74$ ). The rate of success on day 5 in the subgroup of patients with active bleeding at the initial endoscopy was not significantly lower than that in the subgroup with bleeding other than active bleeding (51 percent vs. 65 percent,  $P=0.07$ ).

Multivariate analysis revealed that at the time of enrollment, a high mean arterial pressure ( $P=0.004$ ), a previous episode of bleeding related to portal hypertension ( $P=0.01$ ), assignment to treatment with vaptotide ( $P=0.02$ ), and small varices ( $P=0.02$ ) were

independent predictors of the control of bleeding and survival during the five-day treatment period. Significantly fewer units of blood were transfused in the vaptotide group than in the placebo group during the initial five-day period ( $2.0\pm 2.2$  vs.  $2.8\pm 2.8$  units,  $P=0.04$  by the log-rank test for the Kaplan–Meier estimates).<sup>10</sup> During the entire 42-day follow-up period, the total blood requirements were  $3.5\pm 3.7$  units in the placebo group and  $2.8\pm 3.6$  units in the vaptotide group ( $P=0.09$ ).

### Survival

Death rates are presented in Table 2. Kaplan–Meier estimates of survival at 42 days (a secondary objective) were not significantly different in the two groups ( $P=0.19$ ;  $P=0.25$  after adjustment for the administration of a beta-blocker after the initial episode of acute bleeding). According to multivariate analysis, independent predictors of survival were a low Child–Pugh score ( $P<0.001$ ), the source of bleeding (esophageal varices vs. other sources of portal hypertensive bleeding,  $P=0.001$ ), and younger age ( $P=0.002$ ), but not assignment to treatment with vaptotide ( $P=0.07$ ).

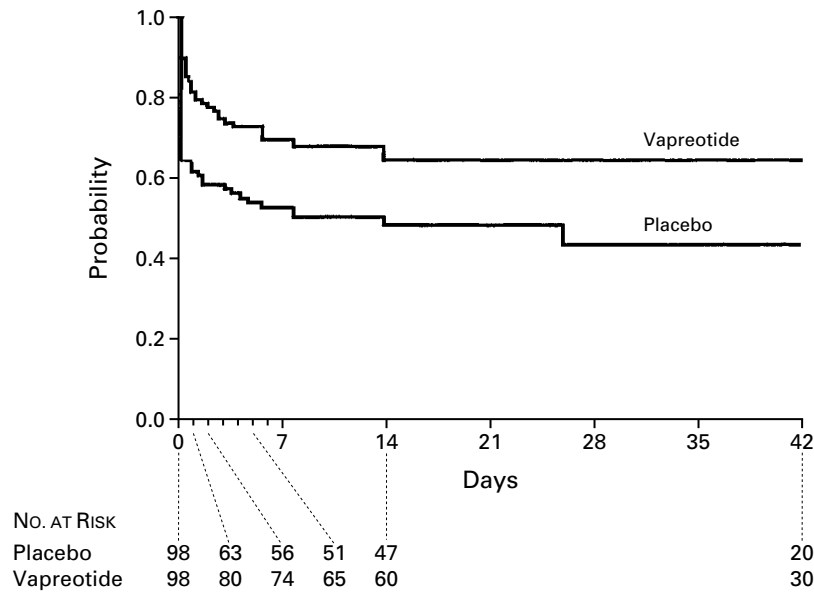
### Concomitant Disorders

The incidence of concomitant disorders during treatment or of adverse effects attributable to the study medication (vaptotide or placebo) was not significantly different in the two groups (Tables 2 and 3). Biochemical changes, including changes in the serum aspartate aminotransferase and alanine aminotransferase levels, were also not significantly different in the groups (data not shown). The number of patients enrolled at each center ( $\leq 5$ , 6 to 9, and  $\geq 10$ ) had no effect on outcomes.

### DISCUSSION

In patients with variceal bleeding, we found that vaptotide was effective in controlling bleeding, was well tolerated, and significantly decreased transfusion requirements during a five-day treatment period. The beneficial clinical effects of vaptotide as compared with placebo were evident soon after treatment with vaptotide was initiated. The improved control of bleeding observed soon after endoscopy in the vaptotide group may have been due to easier implementation of endoscopy in this group — an effect that has been reported previously.<sup>10</sup> The incidence of early recurrent bleeding was low and was not significantly different in the two groups.

The efficacy of native somatostatin alone, as compared with placebo, for hemostasis in patients with variceal bleeding is controversial.<sup>18,19</sup> In our study, vaptotide significantly improved hemostasis before endoscopic treatment. The discrepancy could not be due to the type of somatostatin used, because early infusion of native somatostatin decreases active bleed-



**Figure 1.** Probability of Survival with Control of Initial Bleeding (Days 1 to 5) and without Late Recurrence of Bleeding (Days 6 to 42), According to Treatment with Vapreotide or Placebo. P=0.02 at day 5 and P=0.006 at day 42 by the log-rank test.

ing at endoscopy.<sup>10</sup> This finding and our data suggest that somatostatin and its analogues are more effective than placebo in controlling acute bleeding. The efficacy of these compounds has been confirmed in a meta-analysis that revealed that somatostatin or octreotide alone is as effective as endoscopic sclerotherapy for controlling bleeding.<sup>20</sup>

Our results emphasize the importance of the timing of drug administration. The protocol included stringent guidelines for eligibility according to the length of time before treatment; one third of the screened patients did not meet these criteria and were excluded. Two studies have evaluated the early administration of vasoactive agents: one used somatostatin, started after hospitalization,<sup>10</sup> and one used terlipressin plus nitroglycerin, started before hospitalization.<sup>21</sup> In both studies there was significant improvement in the initial control of bleeding with active drug, as compared with placebo, similar to that in the present study. The death rate was significantly lower with active drug only in the study of terlipressin.<sup>21</sup>

The rate of control of bleeding with vapreotide in our study could be considered low, as compared with that in previous studies.<sup>6,8</sup> However, our results must be considered in relation to the criteria set by the second Baveno consensus conference.<sup>14,15</sup> The overall rates of hemostasis that we observed were similar in recent trials that also used these criteria: 65 percent with somatostatin plus sclerotherapy<sup>10</sup> and 67 percent with terlipressin.<sup>22</sup>

The optimal duration of the infusion of somato-

**TABLE 3.** CONCOMITANT DISORDERS AND ADVERSE EFFECTS DURING THE INFUSION PERIOD.\*

DISORDER OR ADVERSE EFFECT	VAPREOTIDE	PLACEBO	P VALUE
	(N=111)	(N=116)	
	no. of events		
<b>Concomitant disorders</b>			
Disorders of the central or peripheral nervous system (including convulsions and encephalopathies)	20	21	0.45
General disorders (including fever, multi-organ failure, and alcohol withdrawal syndrome)	10	5	0.06
Respiratory-system disorders	6	6	0.66
Psychiatric disorders (including delirium and agitation)	2	8	0.18
Cardiovascular disorders (including cardiac failure, hypertension, arrhythmias, and angina)	4	9	0.38
Liver and biliary disorders (including hepatic coma and failure)	1	5	0.23
Urinary-system disorders (including acute renal failure)	1	4	0.38
Other disorders (including clotting disorders, infections, pancytopenia, and cerebrovascular accidents)	4	5	0.51
<b>Adverse effects</b>			
Metabolic disorders (including hyperglycemia and diabetes mellitus)	2	3	1.00
Gastrointestinal-system disorders (including abdominal pain and bleeding from esophageal ulcerations)	4	5	1.00

\*This analysis included all 227 patients who received at least one injection of study medication. Adverse events were classified according to *WHO Adverse Reaction Terminology*.<sup>17</sup> Episodes of recurrent bleeding were not considered adverse effects in this analysis. Patients may have had more than one adverse effect.

statin or its analogues is not known. In several trials,<sup>6,8,10</sup> the duration of infusion was five days, since this corresponds to the period during which the risk of recurrence of bleeding is highest.<sup>20</sup> In this study, the beneficial effects of vapreotide, noted soon after treatment was begun, continued throughout the 42-day study period. Vapreotide administration might have been stopped sooner, but other studies have suggested that somatostatin or octreotide should be infused for five and not two days.<sup>23,24</sup> In another trial, a five-day infusion of somatostatin was as effective as sclerotherapy in preventing early recurrence of bleeding.<sup>25</sup> Taken together, these data suggest that somatostatin or its analogues should be administered for five days.

In our study, mortality during the first five days was slightly but not significantly lower in the vapreotide group than in the placebo group. The differences in death rates were similar to those found in previous studies of somatostatin or octreotide<sup>6,8,10</sup> in combination with endoscopic treatment.

In conclusion, we found that in patients with cirrhosis and variceal bleeding, the combination of vapreotide and endoscopic treatment is more effective than endoscopic treatment alone.

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## APPENDIX

In addition to the authors, the following persons participated in the study: *France* — B. Person, P. Burtin, F. Oberti, C. Pilette, E. Vuillemin, H. Audubertau, V. Croquet, and L. Braconnier (Angers); J. Gournay (Nantes); V. Ratzu (Paris, La Pitié-Salpêtrière); J. Blais (La Réunion); M. Beauchant, C. Borderie, and M.P. Ripault (Poitiers); D. Kozlowski and V. Asnar (Lille); L. Choné, J.L. Mouguel, P.C. Gaucher, M.A. Bigard, H. Hudziak, and C. Clavière (Nancy); J.L. Balmes (Nîmes); T. Constant and P. Castellani (Marseille); F. Boschi, A.C. Tanimura, and S. Manfredi (Dijon); C. Yaghi (Clichy); J. Florence (Aurillac); B. Bour, S. Dohin, and P. Bourrier (Le Mans); P.Y. Lallement, S. Berber, and V. Nicolas (Soissons); H. Bismuth, P. Ichai, and A. Ladouzi (Villejuif); F. Cessot, A. Le Sidaner, D. Sauterau, P. Adam, and J.L. Parneix (Limoges); J.P. Evrard (Lens); S. Dargère, T. Collet, D. Luet, and M. Boin (Caen); M. Dapoigny, S. Mathieu, J. Genes, A. Abergel, and G. Bommeleer (Clermont-Ferrand); A. Rolachon and M. Maynard (Grenoble); P. Jacob (Lyons); *Switzerland* — A. Hadenue (Geneva); and P.A. Uldry (Lausanne).

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