Conn HO, Grace ND, Bosch J, et al. Propranolol in the prevention of the first hemorrhage from esophagogastric varices: A multicenter, randomized clinical trial. The Boston-New Haven-Barcelona Portal Hypertension Study Group. Hepatology 1991;13:902-912. This double-blind, randomized trial compared the use of propranolol vs. placebo in the prevention of the first episode of variceal bleed in patients with documented portal hypertension and documented esophageal varices. Patients randomized to propranolol had a reduction in first variceal bleed compared to patients randomized to placebo (4% vs. 22%) after a mean follow-up of 16.3 months, but there was no significant decrease in mortality. The study used the hepatic vein pressure gradient (HVPG < 12 mm Hg) as a guide to dosing propranolol in the study. Since an HVPG < 12 mm Hg has been shown to virtually eliminate the risk of variceal bleeding, it is an ideal guide for beta-blocker dosing. However, HVPG measurement is both an invasive and expensive means to titrate beta-blocker dosing and is impractical in the clinical setting. Thus, titration of doses to HR 50-60 is generally used. This may, however, blunt the benefit that was seen in the study.
Propranolol in the Prevention of the First Hemorrhage from Esophagogastric Varices: A Multicenter, Randomized Clinical Trial

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To assess the effectiveness of propranolol in the prevention of initial variceal hemorrhage, a double-blind, randomized trial was carried out in three centers. Patients with cirrhosis (78% alcoholic), hepatic venous pressure gradients greater than 12 mm Hg and endoscopically proven esophageal varices were randomly assigned to propranolol (51 patients) or placebo (51 patients). Of the 102 patients, 58% were Child’s class A, 34% were Child’s class B and 8% were Child’s class C. Daily dosage was determined by the administration of progressively increasing doses of propranolol with the hepatic vein catheter in place to achieve a 25% decrease in hepatic venous pressure gradient, a decrease in hepatic venous pressure gradient to less than 12 mm Hg or a decrease in resting heart rate to less than 55 beats/min. During a mean follow-up period of 16.3 mo, 11 patients in the placebo group (22%) bled from esophageal varices compared with 2 in the propranolol group (4%) during a mean period of 17.1 mo (p < 0.01). Three additional patients (6%) in the placebo group bled from portal hypertensive gastropathy compared with none in the propranolol group. Propranolol appeared effective in preventing bleeding from large varices. Eleven deaths (22%) occurred in the placebo group compared with eight deaths (16%) in the propranolol group (NS). The mean dose of propranolol was 132 mg/day, and the median dose was 80 mg/day. Using a compliance index (pill count, clinic attendance, alcohol and propranolol levels and alcohol history), 81% of the propranolol patients and 77% of the placebo patients were considered compliant. Complications severe enough to require cessation of therapy occurred in eight patients (16%) in the propranolol group and four in the placebo group (8%) (NS). We conclude that propranolol effectively prevents the first variceal hemorrhage in patients with alcoholic cirrhosis and large esophageal varices but does not improve survival. (HEPATOL 1991;13:902-912.)

One third to one half of cirrhotic patients who bleed from esophagogastric varices (EGV) die during the initial bleeding episode or as a result of subsequent treatment to prevent recurrences of hemorrhage (1-4). Therefore prevention of the initial hemorrhage from varices appears to be a rational way of improving the survival of cirrhotic patients with EGV.

Several randomized clinical trials (RCTs) have shown that although prophylactic portacaval anastomosis virtually eliminates hemorrhage from EGV, it does not improve survival (5-8). In fact, cumulative survival in the unshunted control groups appears to be slightly better than in the shunt groups in these four investigations.

Prophylactic endoscopic sclerotherapy (EST) has been reported in peer-reviewed RCTs to reduce hemorrhage and mortality in some RCTs (9-11), to show no significant improvement in others (12-15) and to increase the risk of bleeding in another (16). Preliminary communications by other investigators have also noted improved, unchanged or detrimental effects after EST in individual investigations (17-21).

Based on the impressive results of Lebrec and colleagues (22) who have shown that propranolol decreases the frequency of recurrences of EGV hemorrhage in cirrhotic patients, we initiated an investigation in 1982

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to determine whether prophylactic propranolol could prevent hemorrhage and reduce mortality. Although several randomized trials have confirmed Lebrec's observation that β-blockade reduces the risks of recurrent bleeding (23-28), several others have failed to do so (29-31). At the time we began our investigation no prophylactic trial of β-adrenergic blockade had yet been reported.

This investigation was undertaken to determine whether propranolol can reduce the prevalence of the initial hemorrhage from varices and, thereby, improve survival. The protocol was designed as a double-blind, randomized clinical trial in which the dosage of propranolol or placebo was determined by the response of the hepatic vein pressure gradient (HVPG) to increasing doses of propranolol during hepatic vein catheterization. The hemodynamic responses of prospective patients were studied before randomization, and the dosage of either propranolol or placebo was then determined (32). This procedure permitted us to perform this investigation blindly because it avoided the necessity of adjusting the dose of propranolol by the resting heart rate, the endpoint used in the prior RCTs of β-adrenergic blockade and a procedure that often identifies which patients are receiving placebo. By using this design we attempted to determine whether the hemodynamic response to test doses of propranolol would predict those patients who would respond to long-term therapy and, indeed, whether reduction in portal venous pressure was the mechanism by which propranolol induces its beneficial effects. The hemodynamic results are presented separately (33).

METHODS AND MATERIALS

Patients with a well-established clinical diagnosis of cirrhosis, endoscopically documented esophageal varices and portal hypertension who had not previously bled from esophageal varices or from an unknown upper gastrointestinal site and who had been admitted to one of the participating hospitals between October 1982 and August 1986 were eligible for the investigation. Approximately 50% of the patients had had histological confirmation; no patient whose liver tissue was examined failed to show cirrhosis. Virtually all of the patients had been newly admitted to the hospitals. A few patients in whom a previous diagnosis of cirrhosis had been made were included after varices were discovered. The investigation was explained to each patient who satisfied these criteria, and each was invited to participate. Patients with known neoplasms or with severe hepatic disease (e.g., the hepatorenal syndrome) or nonhepatic disorders (e.g., cardiovascular, respiratory or renal failure) severe enough to interfere with participation in the investigation were excluded. All cirrhotic patients who agreed to undergo catheterization and whose HVPG (i.e., excluded hepatic venous pressure minus free hepatic venous pressure) was greater than or equal to 12 mm Hg had their pressure response to propranolol titrated using a technique previously described (32). This titration, which was used to determine the dosage of propranolol or placebo to be administered during the study, was performed with the catheter in situ over a period of hours using increasing amounts of oral propranolol and assessing hemodynamic responses to achieve predetermined endpoints (32, 33).

At the end of the titration procedure and after the dosage had been determined, the patients were randomly selected using a sealed envelope technique and computer-generated randomization to receive either placebo or propranolol therapy. The placebo and the propranolol to be randomized, identified by the patient's code, were dispensed according to the randomization schedule. The code was not broken in any of the patients withdrawn from the study because of side effects until the analysis of the data had been performed.

Laboratory tests were performed using the Sequential Multiple Analyzer system. Child's class was calculated using the Child-Turcotte criteria (34). Class A was defined as a score of 5 through 8, class B as 9 through 11 and class C as 12 through 15 (35). Medications were supplied by Ayerst Laboratories (New York, NY) as 40 mg tablets and by Imperial Chemicals Industries (Barcelona, Spain) as 40 mg, 80 mg, or 160 mg tablets of propranolol or placebo. Every 3 mo each patient received bottles containing 10% more tablets than were needed for that period. Patients were instructed to bring their medication bottles to each clinic visit. Patients were seen as outpatients monthly for 3 mo and every 3 mo thereafter. Resting heart rates were recorded by personnel who were not involved in the assessment of the results, and the results were not available to senior investigators.

Measurement of HVPG and endoscopy for semiquantitative assessment of esophagogastric varices were repeated 3 mo and 12 mo after randomization and annually thereafter. The method of grading the size of varices was: grade 1, 1 to 3 mm with Valasalva; grade 2, 1 to 3 mm without Valasalva; grade 3, 3 to 6 mm; and grade 4, greater than 6 mm (36).

The endpoints were defined as follows:

(a) Upper gastrointestinal hemorrhage was defined as hematemesis or melena that reduced the hematocrit by at least 6% or required blood transfusions. The diagnosis of hemorrhage from varices was based on the endoscopic visualization of an actively bleeding varix, a fresh clot or eschar on the surface of a varix or the presence of esophageal varices in the absence of any other possible bleeding site in the upper gastrointestinal tract. These examinations were performed during active hemorrhage or within 24 hr after cessation of bleeding. The endoscopists were unaware of the therapy the patients were receiving.

(b) Survival was expressed in months after randomization.

The cause of death was determined in conference by the principal investigators without knowledge of whether the patients had been receiving placebo or propranolol.

(c) Complications were defined as those adverse events that may have been caused by propranolol and that required cessation of therapy. Complications were recorded and therapy
was stopped if necessary without knowledge of the therapy being administered. Patients withdrawn from the study for complications or other reasons were censored at the time of withdrawal. Endpoints were calculated on an "intent to treat" basis.

Compliance was determined by (a) the percentage of outpatient appointments kept, (b) the percentage of prescribed but unconsumed tablets returned at each visit, (c) plasma propranolol levels taken every 3 mo and expressed as the percentage of measurements that showed therapeutic plasma levels, (d) the percentage of months of total abstinence based on a daily diary in which all alcoholic beverages consumed were to have been recorded and (e) by the percentage of alcohol-free blood samples. Alcohol and propranolol levels were not determined in Barcelona. A compliance index that represented the sum of the percentages of (a), (b), (c) and (d) was devised to assess compliance semiquantitatively. The alcohol diary assessment was corrected by subtracting twice the number of falsely negative consumption reports that were contradicted by the presence of alcohol in the blood. The sum of the mean percentage of the compliance components was divided by the number of compliance components available.

A sample calculation is as follows:

- Appointments: 32 of 40 appointments kept = 0.80
- Tablets: 720 of 1,000 tablets consumed = 0.72
- Propranolol plasma levels (propranolol group only): 15 of 15 samples positive = 1.00
- Alcohol diary: 36 of 40 records were alcohol free, but 5 were falsely negative: 
  - 5 × 2 = -10
- Corrected alcohol diary: 
  - 35 - 10 = 25
  - 25 / 40 = 0.62
- Sum of components = 3.14
- Compliance index = Sum of mean percentages of the components / Number of components = 3.14 / 4 = 0.78

If, for example, propranolol levels had not been measured, the score is calculated as follows:

- Appointments: 32 of 40 = 0.80
- Tablets: 720 of 1,000 = 0.72
- Corrected alcohol diary: 25 of 40 = 0.62
- Sum of components = 2.14
- Compliance index = 2.14 / 3 = 0.71

Heart rate was not used as a measure of compliance.

Side effects reported by the patients were recorded at the time of occurrence and were sought every 3 mo at the time of the outpatient visits.

The protocol was approved by the human investigation committees at each of the participating hospitals. All patients gave their informed, written consent to participate in the investigation.

Sample size calculations had been performed assuming that 30% of the untreated patients would bleed from varices and that half of the hemorrhages would be prevented by propranolol treatment (37). It was estimated that 112 patients would be needed to achieve statistical significance (p < 0.05) and to avoid type II error (β = 0.10).

Statistical analyses included unpaired Student's t tests, which were used to compare the placebo and treatment groups.

χ², Fisher’s exact and Maentel-Haenzel tests were used to compare the frequency of endpoints in this group. Kaplan-Meier survival and log rank analyses were performed using standard statistical software (38, 39). Relative risk ratios and confidence limits were calculated using the Maentel-Haenzel-Peto tests.

RESULTS

From October 1982 to September 1986, 39 patients from Barcelona, Spain, 33 from Boston, Massachusetts, and 30 from West Haven, Connecticut, met the criteria for inclusion. They represented about 40% of the cirrhotic patients admitted to these hospitals during this period. Approximately 10% bled before they could be assessed and randomized. Almost 20% had contraindications to β-blockade or were already receiving it. In about 5% of the patients HVPC levels were less than 12 mm Hg. Approximately 15% refused to have the endoscopy or hepatic vein catheterization procedure or declined to participate in the study. About 10% were considered to be noncompliant patients by the investigators and were not randomized. These screening data are based on the findings in Boston where a complete screening log was available because the screening logs were incomplete at the other hospitals.

Fifty-one patients were randomized to receive placebo, and 51 were randomized to receive propranolol. The subgroups from each of the three participating hospitals were similar except for the more frequent occurrence of nonalcoholic cirrhosis in the Spanish patients.

The placebo and propranolol groups were similar in demographic characteristics in the type of cirrhosis, clinical manifestations, laboratory tests, Child’s classification, size of varices and portal venous pressure (Table 1). Of the 102 patients, 80 (78%) had alcoholic cirrhosis. Only 2 of the 63 patients at the two American centers had nonalcoholic cirrhosis (3%), whereas half of the patients from Barcelona had alcoholic cirrhosis. These patients were evenly divided between the placebo and propranolol groups.

The mean dosage of both placebo and propranolol was 132 mg/day. The median dosage for both was 80 mg/day.

All patients were observed until the last patient randomized had been on therapy for at least 6 mo. The mean period of follow-up was 16.3 ± 12 mo for the placebo group and 17.1 ± 10.9 mo for the propranolol group.

Hemorrhage. Eleven (22%) of the patients in the placebo group bled from EVG compared with two (4%) in the propranolol group (Table 2). This difference is highly significant statistically (χ² = 7.07, p < 0.01; relative risk 6.7, 95% confidence limits 1.4 to 32.2). The effect of propranolol in preventing variceal bleeding was even more impressive in those patients with large varices (grades 3 and 4) than in those with small varices (grades 1 and 2) (Table 2). Nine of the 22 patients with large varices (41%) in the placebo group bled; none of the 27 patients with large varices in the propranolol group bled (p < 0.001). No such effect of propranolol was apparent in patients with small varices; 8% of the patients in both groups bled.
Table 1: Comparison of placebo and propranolol groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Propranolol</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>51</td>
<td>51</td>
<td>NS</td>
</tr>
<tr>
<td>Age (mean ± S.D.)</td>
<td>54 ± 11</td>
<td>54 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>35 (69)</td>
<td>35 (75)</td>
<td>NS</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>41 (80)</td>
<td>39 (76)</td>
<td>NS</td>
</tr>
<tr>
<td>Child's class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>24 (47)</td>
<td>35 (68)</td>
<td>NS</td>
</tr>
<tr>
<td>B</td>
<td>24 (47)</td>
<td>11 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>C</td>
<td>3 (6)</td>
<td>5 (10)</td>
<td>NS</td>
</tr>
<tr>
<td>Child's score (mean)</td>
<td>8.3</td>
<td>8.0</td>
<td>NS</td>
</tr>
<tr>
<td>Ascites</td>
<td>31 (61)</td>
<td>22 (43)</td>
<td>NS</td>
</tr>
<tr>
<td>PSE</td>
<td>5 (10)</td>
<td>6 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Total bilirubin (mean ± SD; mg/dl)</td>
<td>2.5 ± 1.8</td>
<td>2.7 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum albumin (mean ± SD; g/dl)</td>
<td>3.4 ± 0.6</td>
<td>3.3 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>14.3 ± 2.7</td>
<td>13.8 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Small varices</td>
<td>29 (57)</td>
<td>29 (51)</td>
<td>NS</td>
</tr>
<tr>
<td>Large varices</td>
<td>22 (43)</td>
<td>25 (49)</td>
<td>NS</td>
</tr>
<tr>
<td>HVPG (mean ± SD; mm Hg)</td>
<td>18.6 ± 6.8</td>
<td>18.1 ± 4.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

PSE = portosystemic encephalopathy.

Numbers in parentheses are percentages.

Furthermore, three patients were determined endoscopically to have bled from gastric mucosal lesions (i.e., portal hypertensive gastropathy). All three had been treated with placebo. No patients treated with propranolol bled from this lesion.

Freedom from variceal hemorrhage was significantly better in the propranolol-treated patients than in the placebo group (p < 0.01) (Fig. 1). Death was considered another endpoint, so this analysis addressed the probability of staying alive without bleeding.

In the placebo group the variceal hemorrhages occurred from 10 days to 1,047 days after randomization with a mean of 234 ± 276 days. The median was 183 days (Fig. 2). In the propranolol group the two patients bled 294 days and 468 days after randomization, respectively. Although not statistically significant, the trend suggests that propranolol may delay the development of hemorrhage from varices.

The prevention of bleeding by propranolol was observed almost exclusively in the patients with alcoholic cirrhosis, who made up 78% of the patients (Table 2). Ten of 41 patients with alcoholic cirrhosis (24%) in the placebo group bled from varices compared with 2 of 39 (5%) in the propranolol group (p < 0.01). Only 1 of the 22 patients with nonalcoholic cirrhosis bled from varices, and this patient had been receiving placebo.

Table 2: Gastrointestinal hemorrhage

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Propranolol</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>51</td>
<td>51</td>
<td>NS</td>
</tr>
<tr>
<td>Source of hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>11 (22)</td>
<td>2 (4)</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Portal hypertensive gastropathy</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Unknown site</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Size varices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>2/29 (7)</td>
<td>2/26 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Large</td>
<td>9/22 (41)</td>
<td>0/25 (0)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Type cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic</td>
<td>10/41 (24)</td>
<td>2/39 (5)</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Nonalcoholic</td>
<td>1/10 (10)</td>
<td>0/12 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Compliance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliant</td>
<td>8/35 (23)</td>
<td>2/41 (5)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Noncompliant</td>
<td>3/16 (19)</td>
<td>0/10 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Child's class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (score 5)</td>
<td>1/24 (4)</td>
<td>0/35 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>through 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B (score 9)</td>
<td>9/24 (38)</td>
<td>1/11 (9)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>through 12</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>C (score 13)</td>
<td>1/3 (33)</td>
<td>1/5 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>through 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1/20 (5)</td>
<td>0/29 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Present</td>
<td>10/31 (3)</td>
<td>2/22 (9)</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

Numbers in parentheses are percentages.

higher Child's class scores. Nine of 24 class B patients (38%) and 10 of 13 class B plus class C (37%) who received placebo bled from esophageal varices, whereas only 1 of 11 class B (9%) and only 2 of 16 (12%) class B plus class C who received propranolol bled. These differences are statistically significant (p < 0.05) (Fig. 3). The mean Child's score among the 13 patients who bled from varices was 9.9 compared with 7.8 among the 86 patients who did not have gastrointestinal bleeding, a highly statistically significant difference (p < 0.001). The three patients who bled from acute gastric erosions had a mean Child's score of 9.3.

Although more of the patients in the placebo group had ascites than in the propranolol group (NS) (Table 1), the effect of propranolol was significantly greater than placebo in preventing hemorrhage among the subgroup with ascites (p < 0.01) (Table 2).

Although the mean HVPG was slightly, but insignificantly, higher in the placebo patients than in the propranolol-treated subgroup (NS) (Table 1), the effects of propranolol in preventing variceal bleeding were greater in the propranolol than in the placebo subgroup. Indeed, none of the patients whose HVPG was less than 12 mm Hg bled from varices (33). Thus neither the slightly more abnormal Child's classification, the slightly greater incidence of ascites or the slightly higher mean HVPG among the placebo patients accounted for the higher prevalence of bleeding among the placebo-treated patients.
Propranolol also appeared more effective in preventing hemorrhage among the compliant patients (i.e., those who ingested more than 75% of the prescribed tablets) than among the noncompliant patients (Table 2). Almost 25% of the compliant patients in the placebo group bled from varices compared with 5% in the propranolol group (p < 0.05).

Survival. Survival analyses included all randomized patients whether they had bled from varices, dropped out because of side effects or failed to comply. Eleven patients (22%) in the placebo group died compared with eight (16%) in the propranolol group (Table 3). This difference is not significant statistically ($\chi^2 = 0.58$). Similarly, cumulative survival (Kaplan-Meier) was slightly better in the propranolol group, but the difference is not statistically significant (Fig. 4).

The causes of death were varied in both groups (Table 4). Death from variceal hemorrhage occurred in three patients in the placebo group and two in the propranolol group. Variceal hemorrhage may have contributed to the deaths of some other patients, but it was not the primary or precipitating cause of death. Those patients who bled from varices did not receive standardized treatment for the bleeding, but the therapy, which consisted of vasopressin-nitroglycerin infusions, endoscopic sclerotherapy or both, was performed in both groups as needed. Propranolol was stopped in patients who bled from varices. The frequency of death from hepatic failure was similar in both groups.
The mean Child's score among the patients who died was 9.5 compared with 7.8 for the survivors (p < 0.01). The mean Child's scores were similar in the placebo-treated and propranolol-treated patients who died (9.6 and 9.4, respectively) and among those who survived (8.0 and 7.7, respectively). These latter differences are not significant statistically.

**Complications.** Adverse events severe enough to require cessation of treatment occurred in three patients in the placebo group (6%) and in seven patients in the propranolol group (14%) (Table 5). This difference is not statistically significant. Only congestive heart failure, bronchospasm and, perhaps, diarrhea were expected side effects of propranolol. The other complications appear to have been coincidental adverse effects unrelated to the propranolol per se, as were the events noted among the placebo group. One patient in the placebo group was withdrawn when a rectal carcinoma developed, and one patient was withdrawn from the propranolol group after overt diabetes mellitus appeared.

All patients who dropped out for any reason were included in the analyses of hemorrhage, survival or complications until the day they ended their participation in the study.

**Compliance.** Patient compliance was similar in the two groups (Table 6). The patients attended the follow-up clinic in 88% of their scheduled visits. They consumed a mean of 83% of the tablets prescribed. Of the patients with alcoholic cirrhosis, 57% reported that they had abstained from alcohol completely throughout the study and that they had not drunk alcohol during 73% of the preceding 3-mo periods as determined by the daily diary of alcohol consumption. Either a history or biochemical evidence of alcohol consumption was found at one time or another in 25% of the placebo-treated patients and in 48% of the propranolol-treated patients. These differences between the placebo and propranolol groups are not statistically significant. Plasma propranolol levels were determined in 25 of the 32 patients in the placebo group and in 30 of the 31 patients in the propranolol group, an average of six times per patient. Plasma propranolol levels were positive in 91% of the specimens assayed in the propranolol group. Except for several trivial levels (less than 10 ng/mL) that were considered to be laboratory errors, all assays for propranolol in the placebo group were negative. The mean compliance index among the 63 patients studied in Boston and New Haven was 0.77 in the placebo group and 0.81 in the propranolol group (Table 6). This difference is not statistically significant.


<table>
<thead>
<tr>
<th>Group</th>
<th>Clinic attendance</th>
<th>Tablet consumption</th>
<th>Abstinence from alcohol</th>
<th>Propranolol plasma levels</th>
<th>Compliance index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>88</td>
<td>80</td>
<td>72</td>
<td>–</td>
<td>77</td>
</tr>
<tr>
<td>Propranolol</td>
<td>88</td>
<td>86</td>
<td>66</td>
<td>91</td>
<td>81</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>83</td>
<td>69</td>
<td>91</td>
<td>78</td>
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</tbody>
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All numbers are percentages. *Based on Boston and New Haven patients.

Compliance was assessed in relation to whether bleeding from varices occurred during the period of observation in those patients for whom all of the compliance components were known. In the placebo group compliance was better among the 22 patients who did not bleed from varices than among the 9 patients who had bled from varices for attendance at clinic visits, propranolol consumption, abstinence from alcohol and in the compliance index (Table 7). These differences were statistically significant, however, only for abstinence from alcohol. Thus in the placebo group the patients who subsequently bled tended to be generally less compliant than those who did not bleed. This was especially true for those who continued to consume alcohol. In the propranolol group compliance was not significantly different among the two patients who bled from varices and among the 26 who did not. Among the propranolol group compliance did not appear to be in any way related to or responsible for the occurrence of varical bleeding in two patients.

**DISCUSSION**

Our investigation shows convincingly that prophylactic propranolol can reduce the prevalence of the initial hemorrhage from esophageal varices. If the patients who bled from EGV and from portal hypertensive gastropathy are combined, the difference in the prevention of gastrointestinal bleeding between the placebo and propranolol groups becomes even more highly significant statistically (p < 0.0001). The observation that hemorrhage from portal hypertensive gastropathy as well as from varices may be preventable by β-blockade (40) supports the earlier observations of Lebrec et al. (22) and supports the concept that this lesion is a consequence of portal hypertension (41).

Despite its efficacy in preventing bleeding, propranolol did not significantly reduce mortality. The failure to improve survival may be a falsely negative (type 2) error, as the trend toward better survival in the propranolol-treated patients suggests. The causes of death in both groups are common in cirrhosis. The pattern does not show a reduction in mortality from bleeding varices or from related causes in the propranolol-treated patients. Even assuming that the death in the patient in the propranolol group who bled from an unknown gastrointestinal site was from varices, this trend persists (Table 5).

The results were comparable in the three hospitals that participated in the investigation (Table 3). Although the incidence of bleeding was higher in Boston than in New Haven or Barcelona, this difference is not statistically significant. Our data are in accord with four other published RCTs of prophylactic propranolol that had been performed concurrently between 1982 and 1987 and have been published since our study began (42–45). These five investigations, which are similar in concept and results, differ in details of design and execution. All compare the effects of nonselective β-blocker therapy with those of placebo or vitamin K, which had been used in one study (43). All four previous studies were single-blind, but physical differences in the appearance of the active and control medications may have compromised the blindness. Furthermore, attempts to reduce the heart rate by 25% may have identified the two groups to the investigators or to the patients themselves. All five investigations studied adult, cirrhotic patients with varices who had not previously bled from the upper gastrointestinal tract during the period from 1982 to 1986. The criteria for defining variceal size varied in these investigations. Two of these studies used propranolol (42, 43) and two used nadolol (44, 45). Exclusion criteria differed slightly in these studies. All five studies excluded patients with HCC or other neoplasms, lethal diseases of other types and disorders that required the use of β-blockers or medications that could interfere with β-blockers. Several excluded patients with the following disorders: peptic ulcer (42, 44, 45), intractable ascites (43, 45), cardiopulmonary disease (45), hepatic encephalopathy (43) or severe hepatic disease as shown by serum bilirubin levels (e.g., greater than 3 mg/dl (43), greater than 5 mg/dl (45) or Child’s class C status (44). In all five studies the patients were appropriately randomized to receive the active or the inert agent and were treated for at least 1 yr. The treated groups and control groups in each study were similar in age, sex, type of cirrhosis and in the severity and signs of the cirrhosis. The major difference between the various studies was the percentage of patients who had alcoholic cirrhosis, which ranged from 40% (43) to 90% (42).

Propranolol was used in two studies in mean doses of 160 mg/day to 179 mg/day with a range of 20 mg/day to 960 mg/day (43). In the other two studies nadolol was used once daily in mean doses of 79 mg/day (44) and 96
mg/day (45), respectively. These propranolol and nadolol doses are pharmacologically approximately equivalent. All four studies used similar reductions in the resting heart rate as the method of determining dosage.

Compliance was assessed by quantifying the amount of medication consumed, the heart rate and attendance at follow-up visits, although the exact methodology varied considerably from study to study. All these studies recorded side effects and complications in the β-blockade groups (but not in the placebo groups) and indicated how often medication had to be discontinued.

All five studies presented sample size calculations based on presumed basal bleeding rates of 25% to 50% per year and reductions with therapy from 5% to 20% per year. All studies achieved the estimated sample size.

Our study differs from the other studies in that portal pressure was measured as a criterion of inclusion, and those patients whose HVPG was 12 mm Hg or less were excluded. It also differs in that multiple measurements of compliance including plasma propranolol and alcohol levels were prospectively recorded and a composite compliance index calculated. The most important difference is that our study was performed as a double-blind investigation, which minimizes bias (46). The importance of performing such investigations as double-blind trials cannot be overestimated (46, 47). The true prevalence of the complications of therapy cannot be reliably determined without double-blind control groups (47). Indeed, complications were not reported in the control groups of the previous four studies (42-45). In addition, compliance cannot be objectively assessed in non-double-blinded trials. Finally, the use of double-blind methodological procedures provided us with the opportunity to determine whether the benefits observed were related to the reduction in portal pressure or to some other mechanism because we had randomized the patients whether or not they showed a decrease in the HVPG during propranolol testing. It is known, for example, that propranolol is an effective tranquilizer that suppresses anxiety and tremor (48, 49). Indeed, its beneficial results in alcoholic cirrhosis have been postulated to be caused by such tranquilizing effects (50).

Our trial also differs from the previously published studies in several other ways. The mean daily dosage of propranolol in our patients was 132 mg, which was lower than in the trials of both the French and Italian groups. Those dosages were 162 mg and 168 mg, respectively. The degree of blockade was probably lower than in the studies of Iede et al. (44) and Lebrec et al. (45) who administered mean doses of 78 mg and 96 mg of nadolol per day, respectively, although precisely equivalent doses of the two agents are uncertain. It has been shown that noncardioselective β-blockers induce a greater decrease on the HVPG than cardioselective agents (51).

In our trial side effects that required discontinuation of medication occurred with approximately the same frequency (14%) as in the French and Italian investigations in which propranolol was used (11% and 27%, respectively) (42, 43). However, the “complications” recorded in Table 5 are actually adverse events that cannot be unequivocally attributed to propranolol. Indeed, among the placebo group four patients were removed from the study because they had developed disorders that could have been caused by the propranolol had the patients been receiving propranolol. Clearly, several of the disorders were unlikely consequences of propranolol administration, but hepatic encephalopathy and psychosis are known complications. Episodes of encephalopathy and psychosis occurred after the placebo had been stopped in these patients. Among the propranolol group congestive heart failure in two patients and bronchospasm and diarrhea in one each are considered to be true complications. The others are probably coincidental adverse effects that occurred during propranolol administration rather than drug-induced side effects of propranolol. Thus only about 5% of the patients treated in this investigation exhibited side effects of clinical significance related to propranolol.

The prevalence of side effects that required discontinuation of β-blockade in the two studies in which nadolol was used was much lower, amounting to only 3% and 4%, respectively, in the Italian (44) and French investigations (45). This difference probably reflects the fact that nadolol is not metabolized by the liver and is not lipophilic, presumably rendering it less toxic. We observed, however, no overt central side effects among our patients who received propranolol.

All five RCTs of prophylactic β-blockade have shown
similar results. Prophylactic propranolol or nadolol reduced the risks of bleeding from varices but not of dying. These results have been confirmed by combined analysis of the data for bleeding (p < 0.001) but not for survival, using Mantel-Haenszel methodology and other metaanalytic techniques (52).

Pascal, Cales and the Multicenter Study Group (42) made no recommendations about the prophylactic use of propranolol and suggested that we await the results of further RCTs (42). The Italian group did not recommend prophylactic propranolol therapy even though it appeared to reduce bleeding in Child's class A patients (43). Ido et al. (44) and Lebrec et al. (45) found the risks of variceal hemorrhage to be reduced by nadolol, especially in compliant patients, but did not recommend its clinical use. None of these four studies, or ours, showed a significant reduction in mortality with β-blockade.

Despite virtual unanimity on the reduction of the prevalence of the initial hemorrhage by β-blockade in the five studies, which are findings supported by metaanalysis of the data (52), we, too, do not recommend β-blockade for all patients with portal hypertension and EGV. We have several reasons for the reluctance. First, none of these investigations has shown a statistically significant improvement in survival. Although it is axiomatic that if variceal bleeding is the most common cause of death among cirrhotic patients, decreasing the prevalence of variceal bleeding should improve survival. The failure of any one of these investigations to document such an effect is, therefore, surprising. Because the primary purpose of preventing the initial hemorrhage from varices is to improve survival, the decrease in bleeding represents an important step toward that goal. Furthermore, the treatment of bleeding varices is replete with therapies such as vasopressin, esophageal tamponade and portal decompressive surgery that prevent bleeding but do not improve survival (53, 54). Although therapeutic portal systemic shunts, endoscopic sclerotherapy and β-blockade all reduce the prevalence of recurrent bleeding from varices, only endoscopic sclerotherapy appears to have decreased the mortality of patients who have survived the initial hemorrhage from varices (52).

Second, some investigators suggest that statistically significant reductions in the prevention of bleeding from varices are only seen in compliant patients (43-45). In these studies, “compliant” is defined as being willing to take the drug and being able to tolerate it. From 8% to 20% of patients in RCTs who tolerate the drug without side effects have failed to take the medication consistently. Our data suggest that patients on placebo who did not bleed from EGV had better compliance than those who did bleed, but these differences are not statistically significant.

Third, variceal bleeding has been reported promptly after the cessation of β-blockade (42; 43; 45; Lebrec D, et al. N Engl J Med 1982;307:560, Correspondence; Maringhini A, et al. N Engl J Med 1982;307:1710, Correspondence; 55). It is postulated that a rebound increase in portal venous pressure after abrupt inter-

ruption in β-blockade may account for the bleeding. We did not observe this phenomenon.

Finally, our data indicate that bleeding from varices is almost invariably associated with HVP greater than 12 mm Hg (33). Propranolol, and probably nadolol, do not reduce the HVP in cirrhotic patients with portal hypertension and varices (32). Actually, only one third of patients showed a decrease of 20% or more, and one third showed a smaller decrease with propranolol administration.

On the basis of our investigations and those reported in the literature, we recommend that selected patients with alcoholic cirrhosis, portal hypertension and large esophageal varices who have no contraindications to therapy and who are compliant as demonstrated by abstinence from alcohol and regular attendance at follow-up visits be treated with β-blockade. Potential recipients should understand that the treatment is designed to prevent bleeding from varices, a complication that occurs in less than 25% of such patients. Furthermore this treatment has not yet been proved to enhance survival. They should also be aware of the danger of sudden cessation of therapy. For patients who resume drinking alcohol or who take the β-blocker irregularly, the drug should be slowly tapered off and then stopped.

Physicians who decide to try β-blockade may decide to substitute nadolol for propranolol because it may have theoretic advantages over propranolol (56). These benefits have not yet been established in clinical trials comparing these two agents.

Although this investigation shows that variceal bleeding tended to occur within 6 mo of entry into the study and that β-blockade therapy can prevent these hemorrhages, it does not indicate whether such successful prophylaxis eradicates or merely postpones the period of risk. Prolonged follow-up of the patients in this study suggests that propranolol postpones, rather than eradicates, the risks of hemorrhage (55).

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