

## A Placebo-Controlled Clinical Trial of Nadolol in the Prophylaxis of Growth of Small Esophageal Varices in Cirrhosis

CARLO MERKEL,\* RENATO MARIN,† PAOLO ANGELI,\* PIERLUIGI ZANELLA,§ MARTINA FELDER,|| ELISABETTA BERNARDINELLO,\* GIORGIO CAVALLARIN,¶ MASSIMO BOLOGNESI,\* CARLO DONADA,# BARBARA BELLINI,\* PIERLUIGI TORBOLI,\*\* ANGELO GATTA,\* and the GRUPPO TRIVENETO PER L'IPERTENSIONE PORTALE

\*Department of Clinical and Experimental Medicine, University of Padua, Padua; †General Hospital of Dolo, Dolo; §General Hospital of Thiene, Thiene; ||General Hospital of Bolzano, Bolzano; ¶General Hospital of Chioggia, Chioggia; #General Hospital of Pordenone, Pordenone; and \*\*General Hospital of Trento, Trento, Italy

**Background & Aims:** Beta-blockers are extensively used to prevent variceal bleeding in patients with large esophageal varices. It is not established if beta-blockers delay the growth of small varices. **Methods:** A total of 161 patients with cirrhosis and small esophageal varices (F1 according to the classification of Beppu et al.) without previous bleeding were enrolled. A total of 83 patients were randomized to nadolol (dose adjusted to decrease resting heart rate by 25%; mean dose given,  $62 \pm 25$  mg/day) and 78 to placebo. The principal end point was occurrence of large esophageal varices (F2 or F3 according to the classification of Beppu et al.). Endoscopic examination was performed after 12, 24, 36, 48, and 60 months of follow-up. Mean follow-up was 36 months. **Results:** The 2 groups were well matched for demographic and clinical characteristics. During the study period, 9 patients randomized to nadolol and 29 randomized to placebo had growth of esophageal varices. At the end of follow-up, the cumulative risk was 20% versus 51% ( $P < 0.001$ ) (absolute risk difference, 31%; 95% confidence interval, 17%–45%). When possible confounding factors were taken into account, treatment was a significant factor predicting growth of varices (odds ratio, 4.0; 95% confidence interval, 1.95–8.4). The cumulative probability of variceal bleeding was also lower in patients randomized to nadolol ( $P = 0.02$ ). Survival was not different ( $P = 0.33$ ). Adverse effects resulting in withdrawal of drug occurred in 9 in the nadolol group and one in the placebo group ( $P = 0.01$ ). **Conclusions:** This study suggests that beta-blocker prophylaxis of variceal bleeding in patients with compensated cirrhosis should be started when small esophageal varices are present.

small to large, and variceal rupture with upper gastrointestinal bleeding, which carries an elevated risk of death.<sup>2</sup> Small esophageal varices show a tendency to grow to large esophageal varices; the rate of growth is variable according to the few published series.<sup>3–6</sup> As a rule, varices grow to large varices before bleeding, and most bleedings occur when varices have already reached the stage of large varices. Although no definite evidence is available, there is general agreement that the occurrence of variceal bleeding while varices are still small is very low.<sup>7</sup>

It is clearly established that beta-blocker prophylaxis decreases the risk of developing a first variceal bleeding in patients with large esophageal varices.<sup>8,9</sup> A series of studies have suggested that early treatment with beta-blockers inhibits the development of collateral circulation in experimental portal hypertension.<sup>10–12</sup> The clinical usefulness of beta-blockers in preventing the growth of small varices to large ones is still uncertain. A single study performed in a mixed group of patients without varices or with small esophageal varices did not show any benefit.<sup>13</sup> Therefore, there is general agreement that more clinical data are needed to define this point.<sup>7</sup>

In 1995, we started a multicenter randomized clinical trial aimed at evaluating beta-blockers as a treatment preventing the progression of small to large esophageal varices. A preliminary interim analysis, which showed that the study plan should be completed, was presented in 1998.<sup>14</sup> The present report contains the final results of this trial.

Portal hypertension is an important complication in the course of liver cirrhosis, leading to formation of esophageal varices and eventually to variceal bleeding.<sup>1</sup> The natural history of portal hypertension is characterized by formation of varices, progression of varices from

---

Abbreviation used in this paper: HVPG, hepatic venous pressure gradient.

© 2004 by the American Gastroenterological Association  
0016-5085/04/\$30.00

doi:10.1053/j.gastro.2004.05.004

**Table 1.** Main Clinical and Biochemical Data in the 2 Groups of Patients

| Variable                               | Nadolol (n = 83) | Placebo (n = 78) | P  |
|--|------------------|------------------|----|
| Age (yr)                               | 56 ± 9           | 57 ± 9           | NS |
| Sex (M/F)                              | 45/38            | 38/40            | NS |
| Etiology (alcoholic/viral/other)       | 47/34/2          | 45/28/5          | NS |
| Hepatitis B surface antigen positive   | 4                | 3                | NS |
| Time since diagnosis of cirrhosis (yr) | 3.1 ± 2.7        | 2.9 ± 2.8        | NS |
| Time since diagnosis of varices (mo)   | 2.9 ± 2.4        | 2.8 ± 2.5        | NS |
| Child–Pugh score                       | 6.8 ± 1.6        | 7.1 ± 1.9        | NS |
| Ascites                                | 18               | 23               | NS |
| Systolic blood pressure (mm Hg)        | 127 ± 11         | 125 ± 13         | NS |
| Diastolic blood pressure (mm Hg)       | 75 ± 7           | 76 ± 8           | NS |
| Heart rate (bpm)                       | 80 ± 7           | 78 ± 6           | NS |
| Time of follow-up (mo)                 | 36 ± 18          | 35 ± 15          | NS |
| HVPG (mm Hg) <sup>a</sup>              | 12.2 ± 1.1       | 12.3 ± 1.3       | NS |

NOTE. Continuous variables expressed as mean ± SD. P values according to Student *t* test or  $\chi^2$  test when applicable.

<sup>a</sup>Assessed in 10 patients randomized to nadolol and 9 randomized to placebo.

## Patients and Methods

The study was a multicenter randomized clinical trial coordinated by the Department of Clinical and Experimental Medicine of the University of Padua (Padua, Italy). Seven further departments of medicine of general hospitals in the northeastern part of Italy participated in the study.

### Patients

From December 1996 to April 2000, 161 patients with cirrhosis observed in the participating centers were included in the study if they fulfilled the following inclusion criteria: (1) a clinical or histologic diagnosis of cirrhosis, (2) age between 18 and 70 years, (3) presence of esophageal varices endoscopically classified as F1 without red signs according to Beppu et al.<sup>15</sup> (i.e., small straight varices, minimally elevated on the esophageal mucosal surface), (4) informed consent to participate in the study, and (5) absence of the following exclusion criteria: previous variceal bleeding; previous medical, surgical or endoscopic treatment for portal hypertension; Child–Pugh score<sup>16</sup> >11; neoplastic disease in any site; inability to perform follow-up; and a contraindication to beta-blockers. According to the exclusion criteria, 142 patients with F1 varices had to be excluded.

The study was a single-blind, 2-arm, randomized clinical trial comparing nadolol with placebo in the prevention of growth of small esophageal varices. The single-blind study design was chosen because it was considered unrealistic that blindness could be kept using a drug with evident clinical effects and because dose adjustments during follow-up were expected to be necessary to maintain the requested effect on heart rate. Randomization was generated by tables of random numbers, stratified by participating centers, prepared at the University of Padua, and administered by opaque sealed and consecutively numbered envelopes containing randomization. Immediately after randomization, patients started treatment. The protocol conformed to the Helsinki Declaration of 1975, as revised in 1983, and was approved by the ethics committee of the medical faculty of the University of Padua. Written

informed consent was obtained from every patient according to a predefined pro-forma. According to the randomization, 83 patients were assigned to nadolol and 78 to placebo (Table 1).

Patients randomized to nadolol were treated with increasing doses of drug starting from 40 mg/day in a single daily administration, according to the resting heart rate, with a target of a 25% decrease or a heart rate of 50 bpm. Patients randomized to placebo received consecutively a single tablet of placebo.

Patients were seen as outpatients every month for 3 months and then every 6 months and were admitted to the hospital when clinically indicated. All gastrointestinal bleedings were investigated by endoscopy (performed within 24 hours of occurrence). Biochemical and endoscopic controls were planned after 12, 24, 36, 48, and 60 months of follow-up. All endoscopic examinations were reported according to the classification of Beppu et al.<sup>15</sup> No patient received antiviral therapy during the study period. The study was ended in April 2002, when the first included patients had reached 64 months of follow-up. Mean follow-up was 36 months.

In 10 patients randomized to nadolol and in 9 randomized to placebo enrolled at the coordinating center of the study, hepatic venous pressure gradient (HVPG), an index of the severity of portal hypertension,<sup>17</sup> was measured by hepatic vein catheterization before and after 2 years of treatment according to a procedure described elsewhere.<sup>18</sup>

### End Points

The principal end point of the study was the occurrence of large esophageal varices (F2 or F3 with or without red signs according to the classification of Beppu et al.). Further end points were gastrointestinal bleeding from ruptured esophageal varices, death, adverse effects resulting in withdrawal from treatment, and regression of varices.

Because the occurrence of the main end point may be subject to interobserver and intraobserver variability<sup>19,20</sup> and may lead to some bias, the following procedures were performed. (1) All involved endoscopists participated in a series of

endoscopic training sessions, including discussions of video recordings, to decrease interobserver variability; after this training, the  $\kappa$  index for the diagnosis of size of varices was 0.71. (2) Patients were followed up in the outpatient clinic by physicians other than the endoscopists performing endoscopic examinations. (3) Endoscopists were kept unaware of the treatment arm to which the patients were randomized. (4) In every patient, endoscopy was always performed by the same endoscopist. (5) If F2 or F3 varices were seen during follow-up, a second endoscopy was always performed after 1 month to confirm the occurrence of the end point.

Adverse effects resulting in withdrawal were hypotension with systolic blood pressure <85 mm Hg, heart failure, asthma, atrioventricular block greater than 1 degree, diabetes with a need for insulin exceeding 20 U/day, hepatic encephalopathy unresponsive to lactulose, and hypersensitivity reactions.

Compliance with treatment was assessed at every follow-up visit by measuring resting heart rate in patients treated with nadolol and in all subjects by asking the patient how many times he or she did not follow the prescribed therapy.

### Treatment After Failure

Patients developing large varices were treated after failure with nadolol or associated nadolol plus isosorbide-5-mononitrate according to the clinical decisions of the attending physician. Bleeding from ruptured esophageal varices was treated by combined medical and endoscopic treatment and then with endoscopic treatment until eradication.

### Statistics

Data are reported as mean  $\pm$  SD. Sample size was calculated considering a 45% probability of developing large varices within 3 years in the placebo group and a decrease in this risk to 20% as the minimum clinically significant effect. Considering an  $\alpha$  error of 5%, a  $1 - \beta$  error of 20%, and a dropout rate of 10%, the number of patients to be included was calculated to be 160.<sup>21</sup> Adequacy of randomization was assessed comparing initial characteristics by Student *t* test or  $\chi^2$  test when applicable.

Results were analyzed according to the intention-to-treat principle. The rates of occurrence of each end point were compared in the placebo and nadolol groups using Kaplan-Meier plots and compared by Mantel-Cox test.<sup>22</sup> To assess the role of possible confounding factors in the occurrence of end points, Cox's multiple regression analysis was performed.<sup>23</sup>

### Results

Randomization resulted in 83 patients in the nadolol group and 78 patients in the placebo group; these 2 groups were well matched for demographic and clinical characteristics (Table 1 and Figure 1).

During follow-up, 11 patients randomized to nadolol and 10 patients randomized to placebo were lost to follow-up ( $P = 0.91$ ) after a mean of  $8 \pm 6$  and  $11 \pm 8$

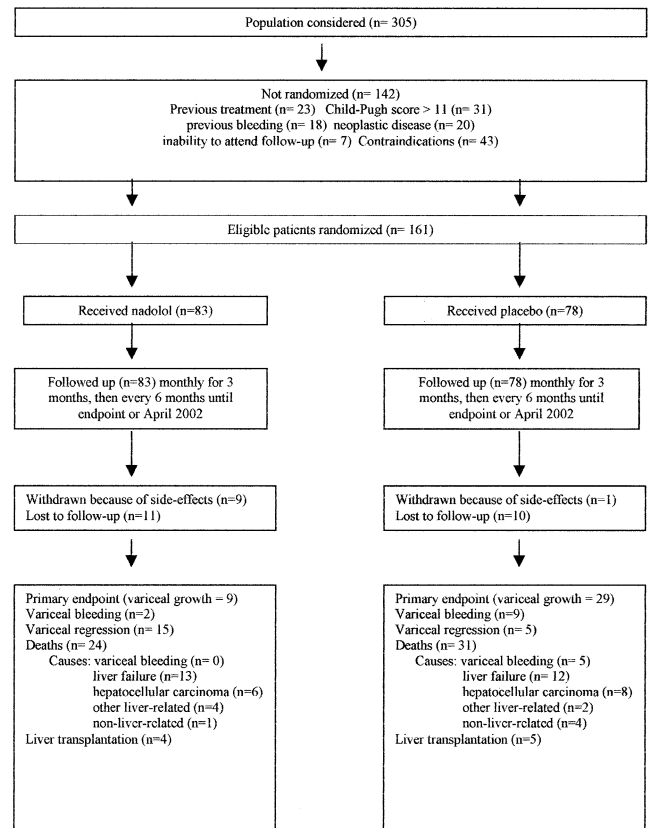
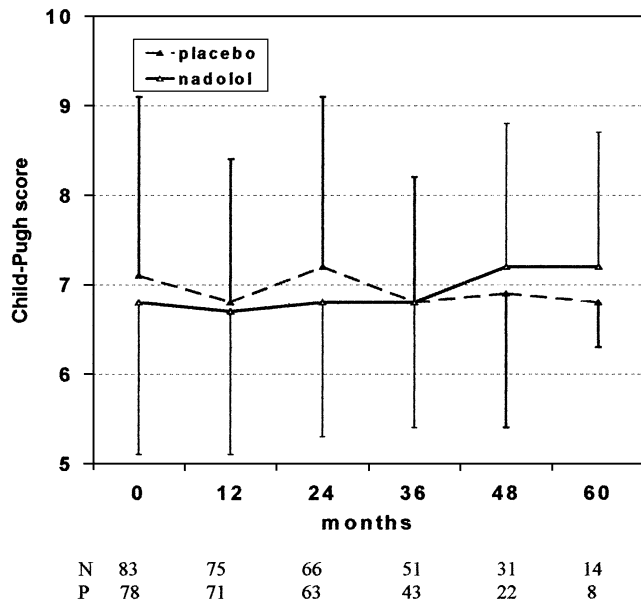


Figure 1. Trial profile.

months of follow-up, respectively (range, 3–24 and 3–30 months;  $P = 0.30$ ).

Nine patients in the nadolol group had to be withdrawn from treatment because of adverse effects (hypotension in 7 patients, asthma in one patient, and heart failure in one patient) compared with one patient in the placebo group (asthma) ( $P = 0.01$ ). Adverse effects occurred after a mean follow-up of  $14 \pm 9$  months (range, 3–28 months) and disappeared promptly after discontinuation of the drug.

The mean dose of nadolol given was  $62 \pm 25$  mg/day at 1 year (range, 40–160 mg/day). At 2, 3, 4, and 5 years of follow-up, the mean doses administered were  $64 \pm 24$ ,  $60 \pm 25$ ,  $61 \pm 25$ , and  $64 \pm 25$  mg/day, respectively. In the nadolol group, heart rate decreased from baseline values of  $80 \pm 7$  to  $58 \pm 5$  at 6 months ( $P < 0.001$ ) and remained nearly unchanged after 1, 2, and 3 years of follow-up; in patients randomized to placebo, heart rate showed only a slight decrease at 6 months ( $79 \pm 7$  vs.  $77 \pm 7$ ;  $P = 0.02$ ) and no change in the further follow-up. Mean arterial pressure slightly decreased in patients randomized to nadolol after 6 months (from  $93 \pm 8$  to  $91 \pm 9$  mm Hg;  $P < 0.01$ ) and did not change in the further follow-up; in patients randomized to placebo, no significant change was observed at any



**Figure 2.** Child-Pugh score during follow-up in patients randomized to nadolol or placebo. No significant difference at any time point.

time point. The course of Child-Pugh score during follow-up was very similar in the 2 treatment groups (Figure 2).

In patients with alcoholic cirrhosis, complete abstinence was reported in 30 of 47 patients randomized to nadolol and in 31 of 45 patients randomized to placebo ( $P = 0.61$ ). Of the 17 patients randomized to nadolol reporting incomplete abstinence or continued alcohol abuse, 11 (65%) showed progression of liver function impairment during follow-up (increase in Child-Pugh score by 2 points or more). Conversely, of the 14 patients randomized to placebo, 8 showed progression of liver function impairment (57%). The difference was not significant ( $\chi^2 = 0.18$ ;  $P = 0.67$ ). Compliance to treatment was considered inadequate in some part of the follow-up in 14 patients randomized to nadolol and in 10 patients randomized to placebo ( $P = 0.47$ ).

In the 10 patients randomized to nadolol in whom HVPG was measured before and after 2 years of follow-up, HVPG decreased in 6 and remained unchanged in 4; as an average, HVPG decreased from  $12.2 \pm 1.1$  to  $11.0 \pm 1.5$  mm Hg ( $P = 0.009$ ). In the 9 patients randomized to placebo in whom HVPG was measured, a decrease was observed in 2, no change in 4, and an increase in 3; as an average, no significant change was observed (from  $12.3 \pm 1.3$  to  $12.5 \pm 1.1$  mm Hg). HVPG after 2 years was significantly lower in patients randomized to nadolol than to placebo ( $P = 0.03$ ) (Figure 3).

### Growth of Esophageal Varices

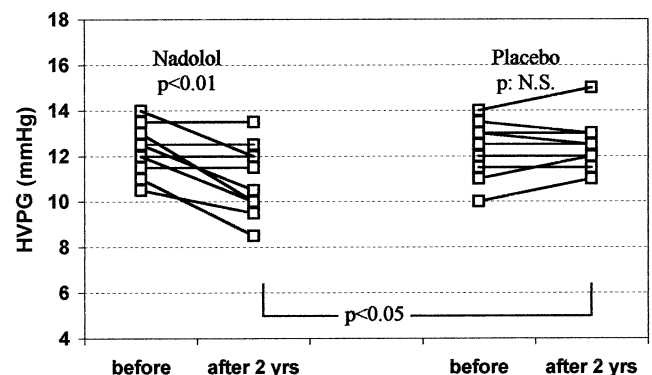
During the study period, 9 patients in the nadolol group and 29 in the placebo group had growth of esophageal varices to F2 or F3. The cumulative risk of growth of varices at 2, 3, 4, and 5 years of follow-up was 7%, 13%, 20%, and 20% in the nadolol group, respectively, compared with 31%, 41%, 51%, and 51% in the placebo group ( $P < 0.001$ ; Figure 4). At the end of follow-up, the absolute difference in risk was 31% (95% confidence interval, 17%–45%). Therefore, the number of patients to be treated for 5 years to prevent an aggravation of varices was 3.2 (95% confidence interval, 2.2–5.9).

When possible confounding variables (Child-Pugh score, aggravation of Child-Pugh score, alcoholic etiology, abstinence, compliance, age, time since diagnosis of varices, ascites, center) were assessed for possible influence on outcome according to Cox's regression analysis, treatment, Child-Pugh score, and aggravation of Child-Pugh score turned out to be the only predictors of aggravation of varices (Table 2). The value of the  $\beta$  coefficient for treatment implies an odds ratio in patients treated with nadolol compared with placebo of 4 (95% confidence interval, 1.95–8.4), with other prognostic factors being equal.

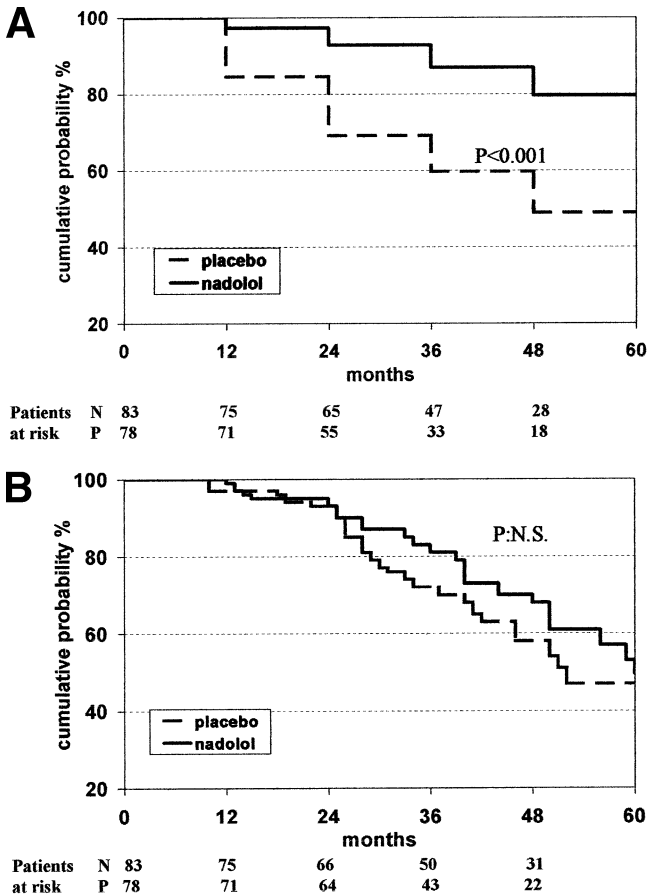
When patients were divided according to etiology of disease (alcoholic or nonalcoholic), the risk of growth of esophageal varices was significantly lower in patients randomized to nadolol in both groups (Figure 5).

### Further End Points

During follow-up, 2 patients in the placebo group experienced a variceal bleeding before a diagnosis of aggravation of varices was formulated and patients could enter a prophylaxis regimen. After the diagnosis of aggravation of esophageal varices, all patients in the 2 arms



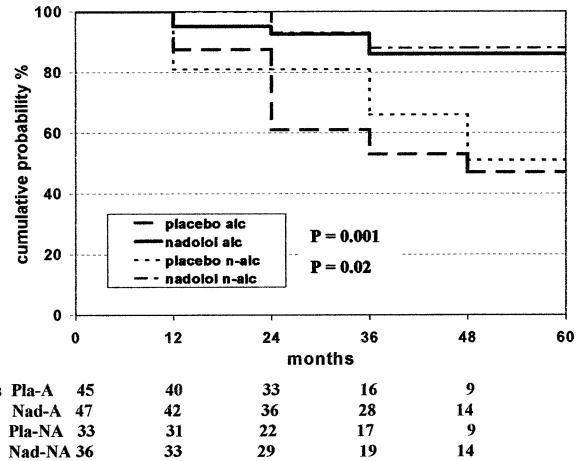
**Figure 3.** HVPG before and after 2 years of treatment in the subgroup of patients randomized to nadolol or placebo who were investigated by hepatic vein catheterization.



**Figure 4.** Cumulative probability of (A) remaining free of growth of esophageal varices and (B) survival.

were given pharmacologic prophylaxis; during further follow-up, 2 of the 9 patients who were failures in the nadolol group and 7 of the 29 patients who were failures in the placebo group experienced a variceal bleeding.

The cumulative probability of being free of variceal bleeding from randomization was significantly higher in patients randomized to nadolol (88% at the end of follow-up) than in patients randomized to placebo (78%;  $P = 0.02$ ; Figure 6). The absolute difference in risk was 10% (95% confidence interval, 4.3%–15.7%). At variance, the cumulative probability of remaining free of



**Figure 5.** Cumulative probability of remaining free of growth of esophageal varices in patients divided according to alcoholic or nonalcoholic etiology of cirrhosis.

variceal bleeding after a diagnosis of aggravation of esophageal varices was not significantly different ( $P = 0.74$ ; Figure 6). The severity of bleeding, as evaluated by the number of units of transfused blood, was similar (nadolol: median, 4 units; range, 2–9 units; placebo: median, 3 units; range, 2–11 units).

Regression of varices during follow-up occurred in 15 patients randomized to nadolol and 5 patients randomized to placebo. The cumulative probability of regression of varices at the end of follow-up was 24% in the nadolol group and 11% in the placebo group ( $P = 0.03$ ). In 3 patients, recurrence of small varices was observed after further follow-up. None progressed to F2 or F3 varices. Regression of varices was less frequent in nonabstainers with alcoholic cirrhosis (1 of 31) than in abstainers with alcoholic cirrhosis (10 of 61) or in patients with nonalcoholic cirrhosis (9 of 60), but this difference did not reach statistical significance ( $\chi^2, 4.51$ ;  $df = 2$ ;  $P = 0.10$ ).

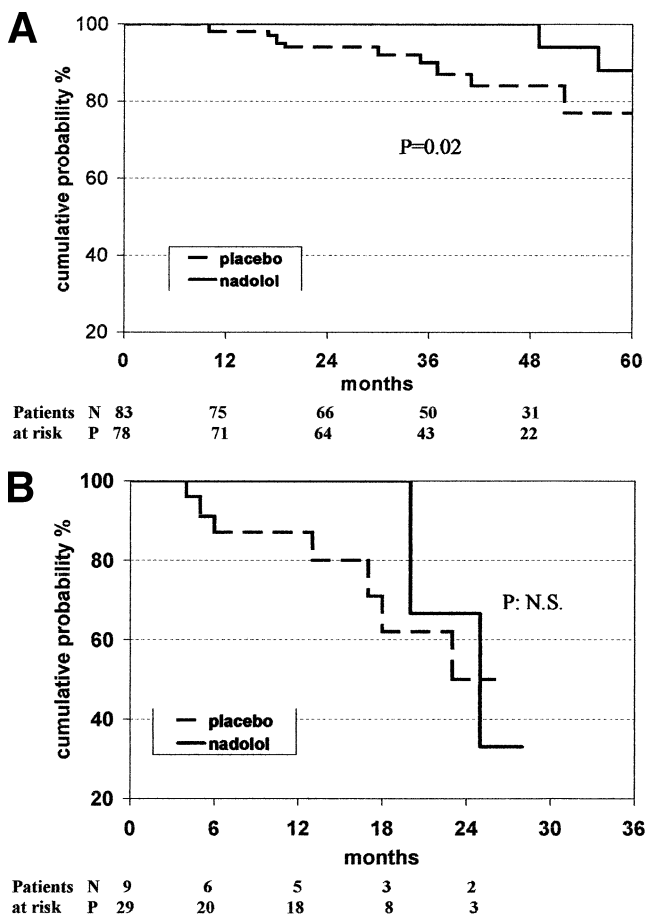
### Survival

Fifty-five patients died during the study period: 24 in the nadolol group and 31 in the placebo group.

**Table 2.** Cox's Regression Analysis of Factors Associated With Growth of Esophageal Varices or Survival

| Variable                                  | $\beta$ coefficient | SE ( $\beta$ ) | Improvement in $\chi^2$ | $P$    | Global $\chi^2$ | $P$    |
|---|---------------------|----------------|-------------------------|--------|-----------------|--------|
| Growth of esophageal varices              |                     |                |                         |        |                 |        |
| Treatment                                 | 1.40                | 0.39           | 15.49                   | <0.001 | 15.07           | <0.001 |
| Child-Pugh score                          | 0.25                | 0.09           | 5.27                    | 0.02   | 21.01           | <0.001 |
| Increase in Child-Pugh score <sup>a</sup> | 0.88                | 0.41           | 4.04                    | 0.04   | 24.30           | <0.001 |
| Survival                                  |                     |                |                         |        |                 |        |
| Child-Pugh score                          | 0.37                | 0.08           | 18.92                   | <0.001 | 20.86           | <0.001 |
| Duration of cirrhosis                     | 0.10                | 0.05           | 3.85                    | 0.05   | 24.81           | <0.001 |

<sup>a</sup>Increase by 2 points or more compared with baseline.



**Figure 6.** Cumulative probability of remaining free of variceal bleeding from (A) the time of inclusion and (B) the time of diagnosis of F2 or F3 esophageal varices.

One and 4 patients, respectively, died from non-liver-related causes (lymphoma, myocardial infarction, lung abscess, pancreatic tumor, accidental). The cumulative probability of not dying from hepatic causes at the end of follow-up was 50% in the nadolol group and 47% in the placebo group ( $P = 0.33$ ; Figure 4). Among possible confounding factors (Child-Pugh score, age, etiology, abstinence, compliance, duration of cirrhosis, time since diagnosis of varices), treatment did not turn out to be significantly linked to survival when Child-Pugh score and duration of cirrhosis were taken into account ( $P = 0.61$ ) (Table 2).

### Discussion

In the present trial, we observed that the administration of nonselective beta-blockers in patients with cirrhosis and small esophageal varices at low risk of bleeding markedly decreased the risk of growth of esophageal varices to large varices at relevant risk of bleeding. When designing the study protocol, we had to face the problem of whether it would be better to use a double-

blind trial design, which minimizes bias in assessment of outcome but implies evident difficulties in the management of dose adjustments that are to be done in relation to heart rate during follow-up, or to use a single-blind design and limit the blindness to the endoscopist. We decided, in agreement with the ethics committee, to use a single-blind design, also because it was considered unrealistic that blindness could be kept with a drug with an evident effect on heart rate. The value of our concerns about the needs for dose adjustments during follow-up was confirmed on a post-hoc basis by the observation that, despite the fact that the mean administered doses were very similar throughout the study period, at least one adjustment in dose regimen was required by 41% of our treated patients.

As a rule, portal hypertension is a progressive condition, and its course is characterized by a progressive development of collateral circulation, including esophageal varices. Initially varices appear as small linear veins faintly protruding on the esophageal surface and then grow to tortuous varices protruding into the lumen and occupying a progressively larger amount of the esophageal lumen. Bleeding usually occurs after development of large varices. The natural history of esophageal varices has been the subject of few studies.<sup>3-6</sup> The rate of growth of small esophageal varices ranged from 5% to 70% at 2 years of follow-up, with a median value of 30%. The reasons for this discrepancy are unclear but may include different selection of patients and different severity of the underlying liver disease. In the placebo arm of the present trial, the rate of growth of esophageal varices was very close to the median value reported in the literature.

Animal studies have already suggested that beta-blockers decrease the development of collateral circulation in portal vein-ligated rats,<sup>11</sup> in rats with secondary biliary cirrhosis,<sup>12</sup> and in a murine model of presinusoidal portal hypertension.<sup>10</sup> This effect is probably related to the decrease in blood inflow into the splanchnic system, which decreases the stimulus to a further collateralization of splanchnic blood flow. In human pathophysiologic studies, it was also shown that the effect of beta-blockers in decreasing portal pressure is more evident in patients with initial disease and with less developed collateral circulation.<sup>24</sup> In the present study, nadolol was also shown to be effective in decreasing HVPG in the subgroup of patients in which it was measured after 2 years of treatment, and the values of HVPG during treatment were significantly lower in patients who were treated with nadolol than in those receiving placebo (Figure 3).

Despite these promising animal and human studies, clinical evidence on this topic is limited to a single multicenter study<sup>13</sup> in which a mixed series of patients with small varices and without varices was investigated for a mean of 2 years. In that study, propranolol was unable to decrease the risk of growth of esophageal varices but showed a negative effect. When only patients with small varices were analyzed separately, no benefit from treatment was seen. Many drawbacks, however, limit the value of that report. First, a fixed dose of propranolol was used, and this might have been responsible for beta-blocker overdose in some patients or for an underdose in some other patients. In addition, the number of included patients with small esophageal varices was rather small, and 40% of patients treated with beta-blockers and 30% of patients receiving placebo were lost to follow-up. The elevated dropout rate is likely to have disrupted comparability of these small groups.

Our study differed from that by Calès et al.<sup>13</sup> in many aspects, including the drug used (nadolol), the dose regimen (regulated according to heart rate), the duration of follow-up (up to 5 years), the exclusion of patients without varices, and the lower percentage of patients with alcoholic cirrhosis. In addition, the number of dropouts was kept to a reasonable level despite a longer follow-up.

In our study, the cumulative risk of variceal bleeding from the start of treatment was rather low in both groups but was significantly lower in patients who started treatment with beta-blockers when varices were small (12% at 5 years) compared with patients who started prophylaxis once a diagnosis of large esophageal varices was obtained (22% at 5 years). These data are different from the few studies already reported. Indeed, a limited amount of information may be derived from 3 studies reporting the effect of propranolol compared with placebo in a mixed group of patients with small and large varices. In a Danish study,<sup>25</sup> which was prematurely interrupted after a mean follow-up of 1.5 years, the bleeding rate with propranolol was not significantly different from that with placebo in patients with either large or small esophageal varices, but exact numbers are not reported. Andreani et al.<sup>26</sup> and Conn et al.<sup>27</sup> reported subgroup analysis of small groups of patients with small varices; the former observed a smaller rate of bleeding in patients receiving beta-blockers (0% vs. 12% after a follow-up until 2 years), but this difference was not significant, and the latter did not observe any difference after a mean follow-up of 17 months. The difference between our results and the previous observations is likely to be due to the larger sample size and the longer

follow-up in our series, which allowed the observation of a larger number of events.

Because more than one half of the patients in the present study had alcoholic etiology of disease, possible relationships between alcohol and treatment effect could be analyzed. It was shown that treatment with nadolol was equally effective in patients with alcoholic or non-alcoholic etiology of disease (Figure 4), and Cox's regression analysis did not show any significant role in the occurrence of end points for alcoholic etiology or lack of abstinence from alcohol when other significant prognostic factors were taken into account. In addition, the number of patients who were abstinent during follow-up was very similar in patients randomized to nadolol or placebo; therefore, a possible effect of beta-blockers on alcohol abstinence seems unlikely.

The risk of bleeding, once patients reached the principal end point and were all treated pharmacologically, was nearly identical in patients initially treated with beta-blockers or with placebo. This indicates that, in our series, the benefit of early treatment with beta-blockers was related to the longer time patients remained in a condition of low-risk varices and to the smaller number of patients reaching a condition of high risk; once large varices developed and all patients were treated, the risk of bleeding became very similar. A further beneficial effect of early treatment may be due to the decrease in the risk of bleeding before a diagnosis of aggravation is made; indeed, in the placebo group of the present trial, 2 patients bled from varices and died of variceal bleeding before a diagnosis of aggravation was made.

The values of the risk of variceal bleeding observed in the present study imply that 10 patients need to be treated for 5 years to prevent a single bleed. These values are larger than those typically observed in prophylaxis of bleeding from large varices but are compatible with clinical use. It should be noted, however, that this study was primarily designed to assess possible effects on growth of esophageal varices and that the effect on risk of bleeding was only a secondary end point. Therefore, conclusions related to the effect on risk of bleeding should be considered preliminary. Further studies with a larger number of events are needed to give a definite answer to this question.

Mortality was not affected by treatment, but the sample size was insufficient to analyze this problem. Considering expected mortality in this kind of subject and possible improvement arising from a strategy of early treatment with beta-blockers, the sample size should have been much larger.

From the present study, it seems that treatment with beta-blockers in patients with small esophageal varices delayed the growth to large varices with a reasonable rate of adverse effects. From a clinical point of view, beta-blockers are already the first-choice treatment for patients with large esophageal varices. According to our data, anticipating the start of treatment to the stage of small esophageal varices delays the growth of varices and consequently decreases the overall risk of bleeding in the total population. In addition, this strategy decreases the risk of bleeding in the period in which varices may be increased but this is not already known (i.e., the period between 2 consecutive endoscopic examinations, which are usually planned at 1- to 2-year intervals). Considering the good safety profile, it may be considered reasonable to start beta-blockers earlier, at the stage of small esophageal varices.

In conclusion, the data reported in the present trial suggest that beta-blocker prophylaxis of variceal bleeding in patients with compensated cirrhosis should be started at the stage of small esophageal varices.

## References

- Bosch J, Abraldes JG, Groszmann RJ. Current management of portal hypertension. *J Hepatol* 2003;38(suppl 1):54–68.
- Pagliari L, D'Amico G, Pasta L, Tiné F, Aragona E, Politi F, Malizia G, Puleo A, Peri V, D'Antoni A, Simonetti R, Vizzini G, Spatolatore G. Efficacy and efficiency of treatments in portal hypertension. In: De Franchis R, ed. *Portal hypertension II*. London, England: Blackwell, 1996:159–179.
- Calès P, Desmorat H, Vinel JP, Caucanas JP, Ravaut A, Gerin P, Brouet P, Pascal JP. Incidence of large oesophageal varices in patients with cirrhosis: application to prophylaxis of first bleeding. *Gut* 1990;31:1298–1302.
- Pagliari L, D'Amico G, Pasta L, Tiné F, Aragona E, Politi F, Vizzini G, Traina M, Madonna S, Luca A, Guerrero D, Puleo A, D'Antoni A. Portal hypertension in cirrhosis: natural history. In: Bosch J, Groszmann RJ, eds. *Portal hypertension: pathophysiology and treatment*. London, England: Blackwell, 1994:72–92.
- Zoli M, Merkel C, Magalotti D, Gueli C, Grimaldi M, Gatta A, Bernardi M. Natural history of cirrhotic patients with small esophageal varices: a prospective study. *Am J Gastroenterol* 2000;95:503–508.
- Merli M, Nicolini G, Angeloni G, Rinaldi V, De Santis A, Merkel C, Attili AF, Riggio O. Incidence and natural history of small esophageal varices in cirrhotic patients. *J Hepatol* 2003;38:266–272.
- Merkel C, Escorsell A, Sieber CC, Lee FY, Groszmann RJ. Preprimary prophylaxis: can (and should) we prevent the formation and growth of varices? In: De Franchis R, ed. *Portal hypertension III*. London, England: Blackwell, 2001:97–111.
- D'Amico G, Pagliari L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis* 1999;19:475–505.
- Poynard T, Calès P, Pasta L, Ideo G, Pascal JP, Pagliari L, Lebrec D. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. Franco-Italian Multi-center Study Group. *N Engl J Med* 1991;324:1532–1538.
- Sarin SK, Groszmann RJ, Mosca PG, Mosca PG, Rojkind M, Stadecker MJ, Bhatnagar R, Reuben A, Dayal Y. Propranolol ameliorates the development of portal-systemic shunting in a chronic murine schistosomiasis model of portal hypertension. *J Clin Invest* 1991;87:1032–1036.
- Lin HC, Soubrane O, Cailmail S, Lebrec D. Early chronic administration of propranolol reduces the severity of portal hypertension and portal-systemic shunts in conscious portal vein stenosed rats. *J Hepatol* 1991;13:213–219.
- Garcia-Pagan JC, Fernandez M, Pizzueta MP, Bosch J, Rodes J. Continued propranolol administration attenuates the hemodynamic disturbances associated with the development of portal hypertension in rats with secondary biliary cirrhosis (abstr). *Biennial Scientific Meeting of IASL, Brighton 1992, Abstract OP 72*.
- Calès P, Oberti F, Payen JL, Naveau S, Guyader D, Blanc P, Abergele A, Bichard P, Raymond JM, Canva-Delcambre V, Vetter D, Valla D, Beauchant M, Hadengue A, Champigneulle B, Pascal JP, Poynard T, Lebrec D. Lack of effect of propranolol in the prevention of large esophageal varices in patients with cirrhosis: a randomized trial. French-Speaking Club for the Study of Portal Hypertension. *Eur J Gastroenterol Hepatol* 1999;11:741–745.
- Merkel C, Angeli P, Marin R, Zanella P, Felder M, Bernardinello E, Mazzaro C, Donada C, Cavallarin G, Bellini B, Sebastianelli G, Torboli P, Cardaioli C, Gatta A. Beta-blockers in the prevention of aggravation of esophageal varices in patients with cirrhosis and small esophageal varices. Interim analysis of a controlled clinical trial (abstr). *Hepatology* 1998;28(suppl 1):453A.
- Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, Kobayashi M. Prediction of variceal hemorrhage by esophageal endoscopy. *Gastrointest Endosc* 1981;27:213–218.
- Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the esophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646–664.
- Armonis A, Patch D, Burroughs AK. Hepatic venous pressure gradient: an old test as a new prognostic marker in cirrhosis? *Hepatology* 1997;25:245–248.
- Merkel C, Bolognesi M, Bellon S, Zuin R, Noventa F, Finucci G, Sacerdoti D, Angeli P, Gatta A. Prognostic usefulness of hepatic vein catheterization in patients with cirrhosis and esophageal varices. *Gastroenterology* 1992;102:973–979.
- The Italian Liver Cirrhosis Project. Reliability of endoscopy in the assessment of variceal features. *J Hepatol* 1987;4:93–98.
- Calès P, Zabotto B, Meskens C, Caucanas JP, Vinel JP, Desmorat H, Fermanian J, Pascal JP. Gastroesophageal endoscopic features in cirrhosis. Observer variability, interassociation, and relationship to hepatic dysfunction. *Gastroenterology* 1990;98:156–162.
- Freedman LS. Tables of the numbers of patients required in clinical trials using the logrank test. *Stat Med* 1982;1:121–129.
- Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:458–481.
- Cox DR. Regression model and life tables. *J Roy Stat Soc* 1972;34:187–220.
- Escorsell A, Ferayorni L, Bosch J, Garcia-Pagan JC, Garcia-Tsao G, Grace ND, Rodes J, Groszmann RJ. The portal pressure response to beta-blockade is greater in cirrhotic patients without varices than in those without varices. *Gastroenterology* 1997;112:2012–2016.
- PROVA Study Group. Prophylaxis of first hemorrhage from esophageal varices by sclerotherapy, propranolol or both in cirrhotic patients: a randomized multicenter trial. *Hepatology* 1991;14:1016–1024.
- Andreani T, Poupon RE, Balkau BJ, Trichet JC, Grange JD, Peigney N, Beaugrand M, Poupon R. Preventive therapy of first gastrointestinal bleeding in patients with cirrhosis: results of a controlled trial comparing propranolol, endoscopic sclerotherapy and placebo. *Hepatology* 1990;12:1413–1419.



27. Conn HO, Grace ND, Bosch J, Groszmann RJ, Rodés J, Wright SC, Matloff DS, Garcia-Tsao G, Fisher RL, Navasa M, 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.

---

Received January 19, 2004. Accepted April 29, 2004.

Address requests for reprints to: Carlo Merkel, M.D., Department of Clinical and Experimental Medicine, University of Padua, Policlinico, via Giustiniani, 2, 35128 Padova, Italy. e-mail: carlo.merkel@unipd.it; fax: (39) 049-8754179.

Supported by grants from the Italian Ministry of Education, University and Research (Rome, Italy) (National Project "Portal hypertension in cirrhosis") and from the Veneto Region (Venezia, Italy) (Regional Center for Epidemiology and Treatment of Liver Diseases).

Members of the Gruppo Triveneto per l'ipertensione Portale are as follows. Steering committee: A. Gatta and C. Merkel (University of

Padua, Padua, Italy); V. Donadon (General Hospital of Pordenone, Pordenone, Italy); P. Spandri (General Hospital of Thiene, Thiene, Italy); F. Tremolada (General Hospital of Belluno, Belluno, Italy); and G. Marin (General Hospital of Dolo, Dolo, Italy). Clinical investigators: E. Bernardinello, L. Chemello, and F. Vescovi (University of Padua, Padua, Italy); G. Marin (General Hospital of Dolo, Dolo, Italy); P. Spandri (General Hospital of Thiene, Thiene, Italy); L. Zancanella (General Hospital of Bolzano, Bolzano, Italy); C. Costan (General Hospital of Chioggia, Chioggia, Italy); C. Mazzaro (General Hospital of Pordenone, Pordenone, Italy); P. Torboli (General Hospital of Trento, Trento, Italy); and F. Tremolada (General Hospital of Belluno, Belluno, Italy). Endoscopists: P. Angeli (University of Padua, Padua, Italy); R. Marin (General Hospital of Dolo, Dolo, Italy); P. Zanella (General Hospital of Thiene, Thiene, Italy); M. Felder (General Hospital of Bolzano, Bolzano, Italy); G. Cavallarin (General Hospital of Chioggia, Chioggia, Italy); C. Donada (General Hospital of Pordenone, Pordenone, Italy); I. Avancini (General Hospital of Trento, Trento, Italy); and G. Sebastianelli (General Hospital of Belluno, Belluno, Italy). Statistical analysts: M. Bolognesi, B. Bellini, and C. Merkel (University of Padua, Padua, Italy).