Long-Term Results of a Clinical Trial of Nadolol With or Without Isosorbide Mononitrate for Primary Prophylaxis of Variceal Bleeding in Cirrhosis

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It is clearly established that β-blockers decrease the risk of a first variceal bleeding in cirrhosis. We have recently shown that the addition of isosorbide mononitrate to nadolol decreases the rate of variceal bleeding in patients with cirrhosis and varices, compared with nadolol alone, after a median follow-up of 30 months. It is not established if the long-term treatment with the combination continues to be beneficial. Therefore, we assessed the long-term effect of this combination on first variceal bleeding, complications, and death. One hundred forty-six cirrhotic patients with esophageal varices included in a previously published multicenter, randomized study comparing nadolol (40-160 mg/d) with the combination nadolol plus isosorbide mononitrate (10-20 mg 3 times per day) were followed up for up to 7 years (median follow-up, 55 months). The primary end-point was variceal bleeding of any severity. Twenty-four patients (16 in the nadolol group, and 8 in the combination group) experienced variceal bleeding (log rank test, $P = .02$). Cumulative risk of bleeding was 29% and 12%, respectively (95% CI for the difference, 1%-23%). Two and 4 patients, respectively, had bleeding from portal hypertensive gastropathy (log rank test, $P = .20$). Thirty and 25 patients, respectively, died during follow-up (log rank test, $P = .13$). Twelve and 10 patients, respectively, had *de novo* occurrence of ascites during follow-up (log rank test, $P = .29$). In conclusion, nadolol plus isosorbide mononitrate is significantly more effective than nadolol alone in the long-term use. Side effects are few, and no deleterious effects on ascites occurrence or on survival occur after long-term use of this combination. (HEPATOLOGY 2000;31: 324-329.)

It has been known for a decade that the nonselective β-blockers, propranolol and nadolol, decrease the risk of a first variceal bleeding in cirrhosis.[1] This effect is the result of a decrease in portal pressure and in flow in the collateral circulation.[2] Because the bleeding risk is nearly halved by the treatment but not abolished, numerous attempts were performed to improve the efficacy of β-blockers. Pathophysiological studies have shown that the addition of long-acting nitrates enhances the portal hypotensive effects of β-blockers and decreases the number of patients classified as poor responders according to hemodynamic criteria.[3,4] For these reasons, in the past few years, we performed a randomized, multicenter study to assess the clinical usefulness of the addition of isosorbide mononitrate to nadolol in the primary prophylaxis of variceal bleeding in patients with cirrhosis and esophageal varices at risk for bleeding.[5] In that study, after a median follow-up of 30 months, we observed a significant decrease in the risk of a first variceal bleeding, a slight, nonsignificant decrease in death risk, and few side effects. Recently, some doubts arose about the use of nitrates in portal hypertension. Indeed, in a clinical trial comparing isosorbide mononitrate alone versus propranolol alone, Angelico et al.[6] reported a shorter survival in patients treated with isosorbide mononitrate, when patients older than 50 years were considered, and conflicting reports are available on the long-term effects of the combination of β-blockers plus nitrates on the risk of ascites occurrence.[7-9] In two recent trials, currently published only as abstracts, a marginally significant decrease in the rate of bleeding was observed in one,[10] and no difference was seen in the other,[11] and a tendency to increase in ascites occurrence was observed in the former[10] but not in the latter.[11]

Here, we report the long-term results of our trial after extending the observation period until 7 years. Besides

analyzing the rates of gastrointestinal bleeding and of side effects, for the reasons outlined above, the occurrence of *de novo* ascites and the survival in different age groups were also investigated.

PATIENTS AND METHODS

From December 1991 to February 1994, cirrhotic patients were recruited among in- and outpatients seen in 9 centers in Italy. Eligible patients had a diagnosis of cirrhosis; were aged 18 to 70 years; had esophageal varices classified as F2 or F3,[12] irrespective of the presence of red weal marks, or varices classified as F1 that had red weal marks; and had no previous variceal bleeding. The exclusion criteria were previous treatment for portal hypertension (medical or endoscopic); Child-Pugh score[13] of liver disease severity higher than 11 points; presence of any neoplastic disease; inability to attend follow-up (*e.g.*, patients living outside the catchment area of each center, or who showed poor compliance to treatment for other conditions); contraindications to β-blockers (atrioventricular block more severe than first degree, sinus bradycardia with heart rate < 50 beats per minute, arterial hypotension with systolic blood pressure < 85 mm Hg, heart failure, asthma, peripheral arterial disease, or diabetes needing insulin treatment); or long-acting nitrates (glaucoma), concomitant or recent treatment with interferon for hepatitis B or C.

The study protocol conformed with the Helsinki Declaration, and was approved by the local ethics authorities. Informed consent was obtained from all participating subjects. According to these criteria, 146 eligible patients were recruited from a group of 313 patients considered for the study. Reasons for exclusion are reported in the trial profile (Fig. 1). Further details were given in the previous report.[5]

The study was a single-blind, randomized, multicenter study, stratified according to participating centers. Randomization was generated by tables of random numbers, stratified by participating hospitals, prepared at the University of Padua, and administered by sealed, opaque, and consecutively numbered envelopes. Immediately after randomization, the patients started treatment.

Patients allocated to nadolol alone received the drug orally starting from a dose of 40 mg/d in a single daily administration. Every second day, the dose was titrated to achieve a 20% to 25% decrease in resting heart rate. The maximal administered dose was 160 mg/d. Once the desired dose was achieved, a placebo tablet was added.

Patients allocated to nadolol plus isosorbide mononitrate received nadolol by the same protocol as the nadolol alone group, then isosorbide mononitrate was added starting with 10 mg twice daily, which was increased to 20 mg twice daily, unless hypotension (systolic blood pressure < 85 mm Hg) or severe headache occurred. Patients were followed at monthly intervals for the first 3 months, then every 3 months for 3 years, and then every 6 months. Compliance was assessed by measuring heart rate, and asking the patients how often they did not take the medication. Patients reporting a lack of assumption of treatment for more than 5% of prescribed pills, or showing lack of decrease in heart rate in more than one control, were considered noncompliant. The study was ended in December 1998, when the first included patient had reached 84 months of follow-up. Median follow-up in censored patients was 55 months.

The main end-point of the study was the occurrence of variceal bleeding of any severity. Other end-points were side effects requiring withdrawal of treatment, death, occurrence of nonvariceal bleeding, and of ascites in patients who had no ascites at inclusion. A stratified survival analysis was also performed in patients older or younger than 50 years at the time of inclusion. All patients with upper gastrointestinal bleeding were investigated by emergency endoscopy. A diagnosis of variceal bleeding was made if there were actively bleeding varices, if there was a clot on a varix, or if no other possible origin of the bleed could be found. Bleeding from portal hyperten-
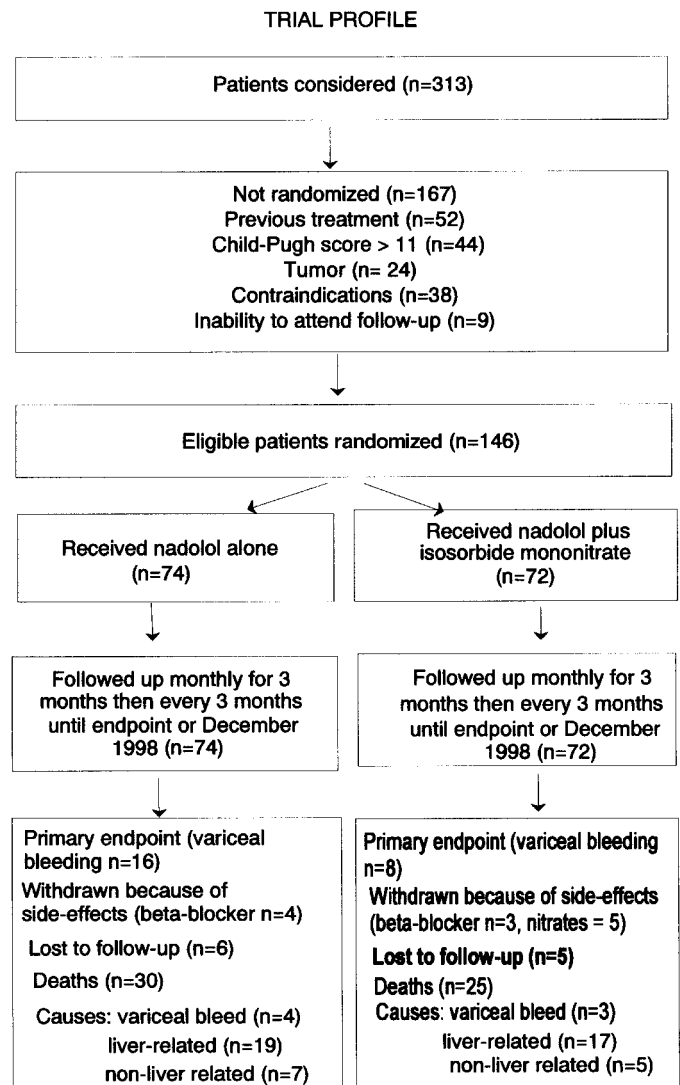
sive gastropathy (*i.e.*, nonvariceal bleeding related to portal hypertension) was diagnosed when such lesions were seen actively bleeding or had signs of recent bleeding (fibrin clots or black-brown spots). Variceal bleeding was treated with sclerotherapy, and medical treatment was discontinued when varices appeared to have been eradicated. Side effects necessitating withdrawal were: symptomatic hypotension with systolic blood pressure < 85 mm Hg, heart failure, atrioventricular block greater than first degree, asthma, hepatic encephalopathy untreatable with disaccharides, and diabetes needing more than 20 U insulin. In patients receiving isosorbide mononitrate, intolerable headache was also judged to be a side effect necessitating cessation of that drug. Patients with side effects related to β-blockers continued with placebo or isosorbide mononitrate, according to randomization; patients with side effects related to isosorbide mononitrate continued on nadolol alone. All patients were included in the analysis according to the intention-to-treat principle.

Statistical Analysis. We estimated that patients with esophageal varices that were at risk for bleeding treated with nadolol would have a 31% chance of variceal bleeding during follow-up, and that the minimal clinically relevant effect was the decrease of this risk to 12%. According to these estimates, using $\alpha = .05$, $\beta = .20$, and a two-sided test, we calculated required sample size to be approximately 145 patients for the primary end-point.[14] For secondary

TRIAL PROFILE

FIG. 1.   Trial profile.

end-points, as mortality or risk of ascites formation, it was accepted that sample size might not be adequate to demonstrate differences.

To assess adequacy of randomization, groups were compared by the χ^2 test or Student t test, when applicable. Risks of bleeding from esophageal varices or portal hypertensive gastropathy, of death from any cause, of death from liver-related causes, and of *de novo* occurrence of ascites were described using Kaplan-Meier plots,[15] and compared by log rank test.[16] The number of patients needed to prevent one bleeding was calculated according to Jaeschke et al.[17] To assess the possible influence of other prognostic variables as confounding factors in determining risk of bleeding or of death, Cox's regression analysis was used.[18] Confounding factors assessed were size of varices, red weal marks, Child-Pugh class in the model assessing risk of bleeding, and Child-Pugh class and age in the model assessing survival. Both forward and backward selection procedures were performed, using the maximal partial likelihood ratio test to assess the significance probability of each variable to be entered or removed. The assumption of proportionality of risk with time was checked by inspecting log minus log survivor function plots.

RESULTS

Randomization (Fig. 1, Table 1) gave two groups: 74 patients for nadolol alone and 72 patients for nadolol plus

TABLE 1. General Characteristics of Included Patients

	NAD (n = 74)	NAD + I5M (n = 72)
Gender (M/F)	45/29	46/26
Age (yr)	57 ± 9	58 ± 9
Etiology		
Alcoholic	39	40
Virus-related	27	26
Mixed	6	4
Other	2	2
Active alcoholism at the time of inclusion	22	19
Abstinent during whole follow-up	12	13
HBsAg$^+$	7	3
Anti-HCV$^+$	33	27
Months from diagnosis of esophageal varices	3 ± 4	2 ± 4
Mean arterial pressure (mm Hg)	98 ± 10	101 ± 10
Ascites		
Absent	40	45
Moderate	25	23
Severe	9	4
Encephalopathy	9	7
Esophageal varices		
F1	2	4
F2	51	44
F3	21	24
Red weal marks		
Absent	26	23
+	32	26
++/+++	16	23
Child-Pugh score	7.9 ± 1.8	7.5 ± 1.5
S-creatinine (mmol/L)	78 ± 18	80 ± 20
S-albumin (g/L)	33 ± 0.5	34 ± 0.6
S-bilirubin (mmol/L)	35.9 ± 18.4	31.3 ± 17.6
Prothrombin index (%)	59 ± 13	60 ± 13
Dose of nadolol	68 ± 25	67 ± 25
Dose of isosorbide mononitrate	—	34 ±
Time of follow-up (mo)	43 ± 25	48 ± 23
Time of follow-up in censored patients (mo)	54 ± 23	55 ± 23

Abbreviations: HBsAg, hepatitis B surface antigen; anti-HCV, hepatitis C virus antibody; NAD, nadolol; I5M, isosorbide mononitrate.

*No significant difference in any variable according to χ^2 test or Student t test, when applicable.

TABLE 2. End-points Observed During the Study

End-Points	Nadolol	Nadolol Plus Isosorbide Mononitrate
Variceal bleeding	16	8
Nonvariceal bleeding	2	5
Portal hypertensive gastropathy	2	4
Aspirin-induced gastric lesions	0	1
Death	30	25
Caused by variceal bleeding	4	3
Other liver-related causes	19	17
Non–liver-related causes	7	5
Side effects necessitating withdrawal	4	8
Caused by β-blockers	4	3
Caused by nitrates	—	5
Lost to follow-up	6	5

isosorbide mononitrate. The two groups were well matched for demographic, clinical, biochemical, and endoscopic characteristics, as described in details in the previous report.[5]

Observed end-points are analytically reported in Table 2. Eleven patients (6 in the nadolol-alone group and 5 in the group receiving nadolol plus isosorbide mononitrate group) were lost to follow-up, 6 in the first 6 months of treatment, 2 in the second year, and 3 in the third year of treatment. Four patients in the nadolol group and 3 patients from the group receiving nadolol plus isosorbide mononitrate had to be withdrawn from treatment because of β-blocker–related side-effects. Five patients had to be withdrawn from isosorbide mononitrate treatment because of severe headache. All these patients continued treatment with the other drug without further side effects. Side effects resulting from β-blockers mainly occurred in the first months of treatment (range, 1-10 months). Side effects resulting from nitrates occurred after the first few doses of the drugs. All side effects disappeared promptly after discontinuation of the relevant drug. Compliance was judged inadequate in 5 of the nadolol-alone patients and in 4 of the combined-treatment patients.

During the study period, 16 patients on nadolol alone and 8 on combination therapy had a variceal bleeding. The cumulative risk of variceal bleeding at the end of follow-up was 29% in the nadolol-alone group and 17% in the combination group ($P = .02$, log rank test) (Fig. 2). The absolute difference in risk was 12%, with a 95% CI of 1% to 23%. As a consequence, the number of patients to be treated to prevent a single bleed was 8. The number of transfusions required during bleeds was the same in the two groups (mean, 4 [SD, 3]), and 40-day mortality after bleeding was 4 of 16 (25%) and 3 of 8 (37%), respectively ($P = .87$; corrected χ^2).

When the role of size of varices and of presence and severity of red weal marks as possible confounding factors of the therapeutic effect were analyzed according to Cox's regression model, treatment resulted the only determinant of outcome, and size of varices was not statistically significant (Table 3). The value of the β coefficient for treatment implies an odds ratio in patients treated with nadolol versus nadolol plus isosorbide mononitrate of 2.36 (95% CI: 1.04-5.37), *i.e.*, a decrease in risk exceeding half, size of varices being equal.

During follow-up, 7 patients had a nonvariceal bleed; of those 7, 2 in the nadolol group and 4 in the group receiving nadolol plus isosorbide mononitrate had a bleeding from portal hypertensive gastropathy. One patient in the combina-
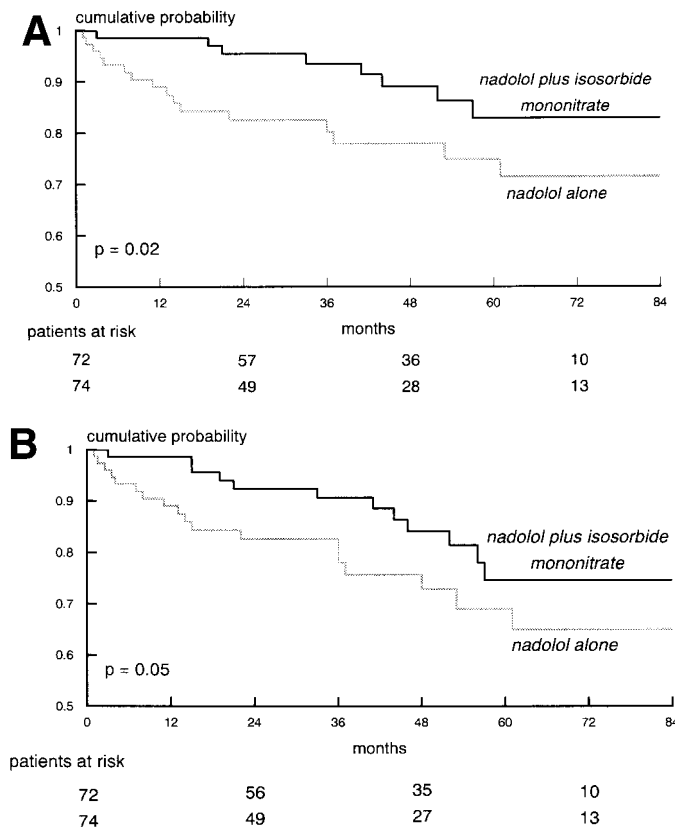
A

B

FIG. 2. Cumulative probability of remaining free of bleeding from varices (A) and of bleeding from varices or portal hypertensive gastropathy (B).

FIG. 3. Cumulative probability of survival.

tion group bled from an aspirin-induced gastric bleeding. Cumulative risk of nonvariceal bleeding at the end of the study was 6% and 9% (log rank test: $P = .20$). The cumulative risk of bleeding related to portal hypertension (varices and portal hypertensive gastropathy) at the end of the study was 34% in the nadolol group and 25% in the group receiving nadolol plus isosorbide mononitrate (log rank test: $P = .05$) (Fig. 2).

Fifty-five patients died during follow-up: 30 in the nadolol group and 25 in the group receiving nadolol plus isosorbide mononitrate. Cumulative probability of survival at the end of follow-up was 45% and 50%, respectively (log rank test: $P = .13$) (Fig. 3). Four and 3 patients, respectively, died of
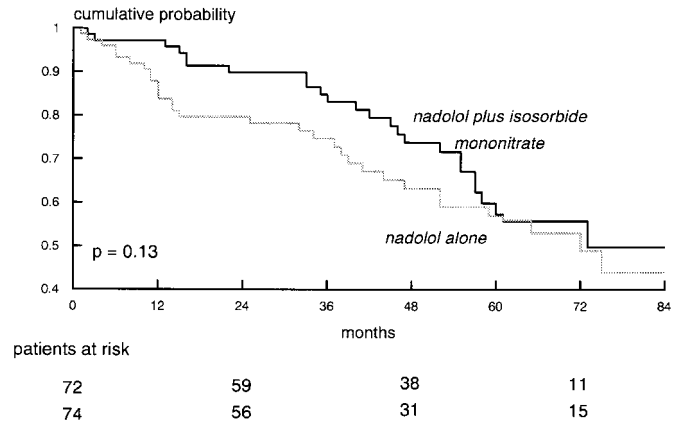
TABLE 3. Statistical Parameters of Cox's Regression Models

Variable	β Coefficient	SE (β)	β/SE	P
Bleeding				
Treatment	−0.86	0.43	−1.98	.04
Size of varices	0.62	0.37	1.67	.09
Child-Pugh class	0.16	0.31	0.51	.60
Red weal marks	0.14	0.30	0.47	.65
Death from any cause				
Child-Pugh class	0.77	0.21	3.62	.0003
Age	0.063	0.018	3.59	.0001
Treatment	−0.43	0.27	−1.59	.11
Death from liver-related causes				
Age	0.068	0.02	3.22	.0003
Child-Pugh class	0.655	0.23	2.75	.005
Treatment	−0.49	0.30	−1.63	.10

variceal bleeding. Nineteen and 17 patients, respectively, died of other liver-related causes. Seven and 5 patients, respectively, died of nonhepatic causes. Cumulative probability of not dying from liver-related causes at the end of follow-up was 49% and 55%, respectively (log rank test: $P = .13$).

When Child-Pugh class and age were assessed as possible confounding factors in predicting mortality according to Cox's regression analysis, treatment was not a significant predictor of death ($P = .11$), or of death from liver-related causes ($P = .10$) (Table 3).

When patients were stratified according to age at inclusion, in patients younger or older than 50 years, we observed a nonsignificantly different survival in the group receiving nadolol plus isosorbide compared with the group receiving nadolol alone in the stratum of patients older than 50 years (log rank test: $P = .07$) (Fig. 4). No difference at all was observed in patients younger than 50 years. Forty patients in the nadolol-alone group and 45 in the combination group had no ascites at the time of inclusion. Twelve and 10 patients, respectively, developed *de novo* ascites during follow-up. Cumulative probability of developing *de novo* ascites at the end of follow-up was 48% in both groups (log rank test: $P = .29$).

DISCUSSION

Long-term analysis of the present clinical trial confirms the results obtained after the first 3 years of follow-up,[5] which can be summarized in the following statements: 1) combined treatment decreases the risk of a first variceal bleeding by more than half in comparison with treatment with nadolol alone; 2) overall mortality and liver-related mortality is unchanged; and 3) side effects caused by nitrates are scanty (headache), rather infrequent, and always reversible. The present report adds the observation that combined treatment is devoid of detrimental effects on survival of older patients or on ascites formation.

Following the publication of the first report, we decided to prolong the observation period to obtain data on the long-term use of the combination. This decision was supported by the observation that prophylaxis of variceal bleeding is usually considered a life-long procedure, and that no further trial had already confirmed our results, making it unethical to continue the comparison. In addition, some doubts were cast about possible deleterious effects of long-term nitrates in the long-term use. Indeed, in a trial comparing propranolol alone
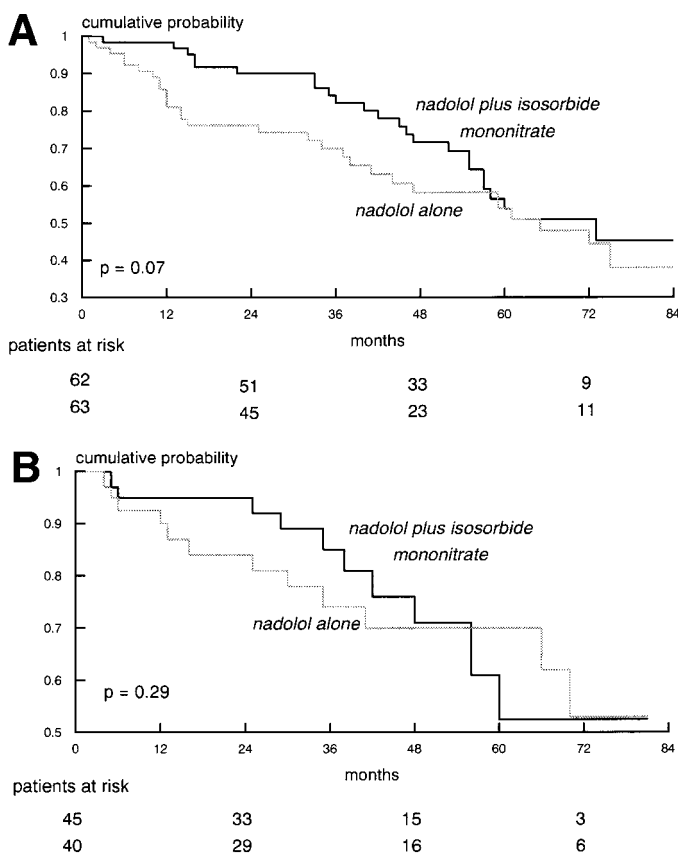
FIG. 4.   Cumulative probability of survival in the subgroup of patients older than 50 years at the time of randomization (A), and of remaining free of ascites in the subgroup of patients without ascites at the time of inclusion (B).

with isosorbide mononitrate alone for primary prophylaxis, Angelico et al.[6] reported that isosorbide mononitrate–treated patients had a significantly shorter survival in patients older than 50 years, and that this effect was not evident in the first years of follow-up, but could only be observed after prolonged observation. Finally, a tendency to imbalancing fluid homeostasis and promoting ascites formation, suggested in 1993 by Vorobioff et al.,[7] after propranolol and isosorbide dinitrate was also observed in an ongoing trial currently published only as an abstract,[10] but not in another one.[11]

Extending the observation period until 7 years, with a nearly doubled (55-month) median follow-up in censored patients, we observed (Fig. 2) that combination treatment is significantly more effective in preventing variceal bleeding, and that in absolute terms, the number of bleedings is decreased by half (8 vs. 16), and is more than halved according to a Cox's analysis, once the confounding effect of size of varices is taken into account. Risk reduction is of such an extent as to request the treatment of only 8 patients to prevent a single bleed. The significance of risk reduction is also maintained if bleeds from portal hypertensive gastropathy are considered together with those from varices (Fig. 2).

In the long-term study, no further side effect necessitating withdrawal from treatment occurred, confirming our previous observation that, usually, side effects resulting from β-blockers occur in the first few months of treatment, and those resulting from long-acting nitrates occur after the first doses. Overall mortality was not different between the two

treatment arms. The same pattern was observed as far as liver-related mortality is concerned. The stratified analysis of survival in patients older than 50 years at the time of randomization showed a nonsignificantly longer survival in patients treated with the combination, with a P value not far from statistical significance ($P = .07$). This observation diverges from that of Angelico et al.,[6] who observed a significantly shorter survival in older patients treated with nitrates. It should be kept in mind, however, that both analyses are *post hoc* stratified analyses, which are exposed to an important bias as a result of the number of possible comparisons,[19-21] and should only be considered exploratory. A further difference may be related to the difference in treatments, because in that study, patients received nitrates alone, and not combined with β-blockers. A clear-cut definition of a possible difference in the therapeutic effect of nitrates in different age groups will be available only from specially designed clinical trials, or meta-analyses of clinical trials cumulating a very large number of patients.

In the present series, the occurrence of *de novo* ascites was not different in the two groups, confirming the lack of deleterious effects of the combination on fluid homeostasis we previously reported after 6 months of treatment. The difference between our observation and other reports may be the result, at least in part, of the difference in the drug characteristics and in the dose schedule we selected.

The occurrence of a marked and significant reduction in bleeding risk without concomitant decrease in mortality is not surprising. Indeed, in the present study, only a few deaths were caused by bleeding (4 in the nadolol group and 3 in the group receiving nadolol plus isosorbide mononitrate), and it is rational that therapy may only increase survival by decreasing mortality directly or indirectly as a result of bleeding. A study having survival as the principal end-point should have been planned with a sample size far larger than the enrolling capabilities of our group. In the present study, hepatic venous pressure gradient was not systematically monitored during treatment. It would have been very interesting to confirm that failure of prophylaxis is associated with insufficient hemodynamic response in primary prophylaxis,[22] because it is also observed in patients treated for secondary prevention.[23-25]

In conclusion, treatment with the combination of nadolol plus isosorbide mononitrate is more effective than nadolol alone in the long-term prophylaxis of the first variceal bleeding in cirrhotic patients in relatively good conditions, with varices at risk of bleeding. Further side effects were not observed after those that occurred in the first months of treatment. No harmful influence on occurrence of ascites or mortality was observed during long-term treatment.

REFERENCES

1. Poynard T, Calés P, Pasta L, Ideo G, Pascal JP, Pagliaro L, Lebrec D, Franc-Italian Multicentric study group. Beta-adrenergic antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors form 589 patients from four randomized clinical trials. N Engl J Med 1991;324:1532-1538.
2. Conn HO. Prophylactic propranolol: the first big step. HEPATOLOGY 1988;8:167-170.
3. Garcia-Pagan JC, Feu F, Bosch J, Rodes J. Propranolol compared with propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis: a randomized controlled study. Ann Intern Med 1991;114:869-873.
4. Merkel C, Sacerdoti D, Bolognesi M, Enzo E, Marin R, Bombonato G, Angeli P, et al. Hemodynamic evaluation of the addition of isosorbide-5-

moninitrate to nadolol in cirrhotic patients with insufficient response to the beta-blocker alone. HEPATOLOGY 1997;26:34-39.

5. Merkel C, Marin R, Enzo E, Donada C, Cavallarin G, Torboli P, Sebastianelli G, et al. Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. Lancet 1996;348:1677-1681.

6. Angelico M, Carli L, Piat C, Gentile S, Capocaccia L. Effects of isosorbide-5-mononitrate compared with propranolol on first bleeding and long-term survival in cirrhosis. Gastroenterology 1997;113:1632-1639.

7. Vorobioff J, Picabea E, Gamen G, Villavicencio R, Bordato J, Bessone F, Tanno H, et al. Propranolol compared with propranolol plus isosorbide dinitrate in portal hypertensive patients; long term hemodynamic and renal effects. HEPATOLOGY 1993;18:477-484.

8. Morillas RM, Planas R, Cabre E, Galan A, Quer JC, Feu F, Garcia-Pagan JC, et al. Propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis: long-tern hemodynamic and renal effects. HEPATOLOGY 1994;20:1502-1508.

9. Merkel C, Gatta A, Donada C, Enzo E, Marin R, Amodio P, Torboli P, et al. Long-term effect of nadolol plus isosorbide-5-mononitrate on renal function and ascites formation in patients with cirrhosis. HEPATOLOGY 1995;22:808-813.

10. Pietrosi G, D'Amico G, Pasta L, Patti R, Vizzini G, Traina M, Madonia S, et al. Isosorbide mononitrate with nadolol compared to nadolol alone for prevention of first bleeding in cirrhosis. A double-blind placebo-controlled randomized trial [Abstract]. J Hepatol 1999;30(Suppl 1):66.

11. Spanish Variceal Bleeding Study Group. Propranolol + placebo vs. propranolol + isosorbide-5-mononitrate in the prevention of the first variceal bleeding. A multicenter double-blind randomized controlled trial [Abstract]. J Hepatol 1999;30(Suppl 1):55.

12. Beppu K, Inokuchi K, Koyanagy N, Nakayama S, Sakuta H, Kitano S, Kobayashi M. Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc 1981;27:213-218.

13. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the esophagus for bleeding esophageal varices. Br J Surg 1973;60:646-664.

14. Freedman LS. Tables of number of patients required in clinical trials using the logrank test. Stat Med 1982;1:121-129.

15. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:458-481.

16. Breslow N. A generalized Kruskal-Wallis test for comparing k samples subject to unequal pattern of censorship. Biometrika 1970;57:579-594.

17. Jaeschke R, Oxmann A, Guyatt G. To what extent do congestive heart failure patients in sinus rhythm benefit from dogoxin therapy? A systematic overview and meta-analysis. Am J Med 1990;88:279-286.

18. Cox DR. Regression model and life tables. J Roy Stat Soc 1972;34:187-220.

19. Lachin JM. Statistical analysis of the randomized clinical trial: subgroup analysis. In: Tygstrup N, Lachin JM, Juhl E, eds. The Randomized Clinical Trial and Therapeutic Decisions. New York: Dekker, 1982:181-184.

20. Pocock SJ, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. N Engl J Med 1987;317:426-432.

21. Bulpitt CJ. Medical statistics. Subgroup analysis. Lancet 1988;ii:31-34.

22. Groszmann RJ, Bosch J, Grace ND, Conn HO, Garcia-Tsao G, Navasa M, Alberts J, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. Gastroenterology 1990;99:1401-1407.

23. Sacerdoti D, Merkel C, Gatta A. Importance of the 1-month effect of nadolol on portal pressure in predicting failure of prevention of rebleeding in cirrhosis. J Hepatol 1991;12:124-125.

24. Feu F, Garcìa-Pagàn JC, Bosch J, Luca A, Terés J, Escorsell A, Rodés J. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal hemorrhage in patients with cirrhosis. Lancet 1995;346:1056-1059.

25. Villanueva C, Balanzò J, Novella MT, Soriano G, Sainz S, Torras X, Cussò X, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. N Engl J Med 1996;334:1624-1629.