Alimentary Pharmacology & Therapeutics

# Early identification of haemodynamic response to pharmacotherapy is essential for primary prophylaxis of variceal bleeding in patients with 'high-risk' varices

P. SHARMA*,†, A. KUMAR*,†, B. C. SHARMA* & S. K. SARIN*,†

*Department of Gastroenterology, GB Pant Hospital, New Delhi, India;
†Department of Hepatology, Institute of Liver & Biliary Sciences (ILBS), New Delhi, India

Correspondence to:
Dr S. K. Sarin, Room 201, Academic Block, Department of Gastroenterology, G B Pant Hospital, Affiliated to University of Delhi, New Delhi – 110 002, India.
E-mail: sksarin@nda.vsnl.net.in

*Publication data*
Submitted 28 February 2009
First decision 10 March 2009
Resubmitted 16 March 2009
Resubmitted 23 March 2009
Accepted 2 April 2009
Epub Accepted Article 8 April 2009

## SUMMARY

### Background
A beta-blocker is recommended for primary prophylaxis of variceal bleeding; however, only one-third have hepatic venous pressure gradient (HVPG) response. The role of addition of isosorbide-5-mononitrate (ISMN) to beta-blocker and benefits of HVPG-guided '*a la carte*' approach remain unclear.

### Aim
To determine the benefits of HVPG-guided pharmacotherapy in primary prophylaxis of variceal bleeding using beta-blocker and ISMN.

### Patients and methods
Consecutive patients of cirrhosis, with high-risk varices, with no previous variceal bleeding were included. After baseline HVPG, patients received incremental propranolol to achieve HR of 55/min. After one-month, HVPG was repeated to determine response (<12 mmHg or ≥20% reduction). ISMN was added in nonresponders and HVPG repeated. Patients were followed up for 24 months.

### Results
Of 56 patients (age 47 ± 13, males 79%) from 89 eligible patients, 21 (38%) responded to beta-blocker alone. Six additional patients responded to combination. Thus, overall 48% (27/56) patients responded. Variceal bleeding occurred in seven of 56 (13%) patients [one of 27 (4%) responder, five of 23 (22%) nonresponders and one of six (17%) with unknown response; $P$ = N.S.]. The actuarial probability of variceal bleeding at median 24 months was 4% in responders and 22% in nonresponders ($P < 0.05$). Ten (18%) patients developed adverse effects to propranolol and six of 35 (17%) to nitrates requiring dose reduction. Risk factors of variceal bleed were grade IV varices and haemodynamic nonresponse.

### Conclusions
For primary prophylaxis, a beta-blocker is effective in 38% and addition of ISMN raises the response rate to about half of patients. The HVPG-guided '*a la carte*' approach may be considered for these patients.

*Aliment Pharmacol Ther* **30**, 48–60



© 2009 Blackwell Publishing Ltd
doi:10.1111/j.1365-2036.2009.04015.x

## INTRODUCTION

The lifetime prevalence of varices in cirrhotics has been reported to be as high as 80–90%. Variceal bleeding is a serious complication and it occurs in 30–40% of the patients with varices. The mortality of acute variceal haemorrhage has decreased significantly, but still ranges between 15 and 20% even with optimal management.[1–3] The incidence of the first variceal bleeding is up to 15% per year in patients with medium–large varices.[4] Because of the high rates of bleeding and mortality, primary prophylaxis of variceal bleeding is indicated for patients with 'high-risk' varices. Nonselective beta-blocker is the recommended therapy for primary prophylaxis of variceal bleeding in these patients.[5–7] Beta-blockers reduce the 2-year incidence of first bleeding in these patients by 40%.[8]

However, only one-third of patients on beta-blockers have a significant reduction in portal pressure in the form of hepatic venous pressure gradient (HVPG) response (defined as decrease in HVPG to <12 mmHg or ≥20% reduction in HVPG from baseline). The role of addition of isosorbide 5-mononitrate (ISMN) to beta-blocker for primary prophylaxis is not clear. Addition of ISMN significantly increases HVPG response to beta-blockers[9] and lowers the rate of first haemorrhage.[10, 11] However, a recent larger trial was unable to confirm these favourable clinical results and a greater number of side effects were noted in the combination therapy group.[12]

Another question is whether HVPG monitoring should be performed in patients on pharmacological therapy. Studies have demonstrated that an HVPG response is associated with an effective protection from first variceal bleeding.[13–15] However, there are conflicting results on cost-effectiveness of HVPG monitoring in primary prophylaxis,[16, 17] and the benefits of HVPG guided '*a la carte*' approach in primary prophylaxis of variceal bleeding are uncertain, because the previous trial based on this approach was small and used a fixed dose of beta-blocker.[18]

To answer these questions, we aimed in this study to determine the clinical and haemodynamic benefits of HVPG guided pharmacotherapy in primary prophylaxis of variceal bleeding using beta-blocker and ISMN. The haemodynamic responders were compared with haemodynamic nonresponders for development of first variceal bleeding.

## PATIENTS AND METHODS

### Patients

From January 2004 to February 2005, consecutive patients with cirrhosis, without history of upper gastrointestinal (UGI) bleeding were recruited from the in-patient and out-patient departments of GB Pant Hospital, New Delhi. Eligible patients who were included had a diagnosis of cirrhosis based on clinical criteria, laboratory tests, endoscopic evidence, imaging findings and liver histology (if available). Patients were aged 18–70 years and had grade III or IV oesophageal varices as per Conn's classification[19] with the presence of red colour signs (the 'high-risk' varices). None had history of previous variceal bleeding. The exclusion criteria were: (i) previous endoscopic treatment – endoscopic sclerotherapy (EST) or endoscopic variceal ligation (EVL); (ii) history of use of beta-blockers in previous 3 months; (iii) history of surgery for portal hypertension; (iv) additional noncirrhotic cause of portal hypertension (extra-hepatic portal vein obstruction or hepatic venous outflow tract obstruction); (v) Child–Pugh score ≥13; (vi) significant cardiopulmonary or renal disease; (vii) presence of any neoplasm; (viii) contraindications to use of beta-blockers (atrio-ventricular block, sinus bradycardia with heart rate <50 beats/min, arterial hypotension with systolic blood pressure <90 mmHg, heart failure, bronchial asthma, peripheral arterial disease or diabetes needing insulin treatment); (ix) angle-closure glaucoma, (x) concomitant treatment for hepatitis B or C; (xi) inability to attend follow-up and (xii) failure to give consent. The study protocol conformed to the Helsinki Declaration of 1975 and was approved by the institutional ethical committee. Informed consent was obtained from all the participating subjects. The study was an open-labelled, non-randomized, single-centre study. Patients were allotted an enrolment number as per their sequence.

### Study design

The study design is shown in Figure 1. Following inclusion of patients and baseline evaluation, baseline HVPG was measured. Patients then received beta-blocker treatment. After 1 month of treatment with beta-blocker (after achieving the target heart rate), the HVPG measurement was repeated to determine the HVPG response. Response was defined as a


© 2009 Blackwell Publishing Ltd

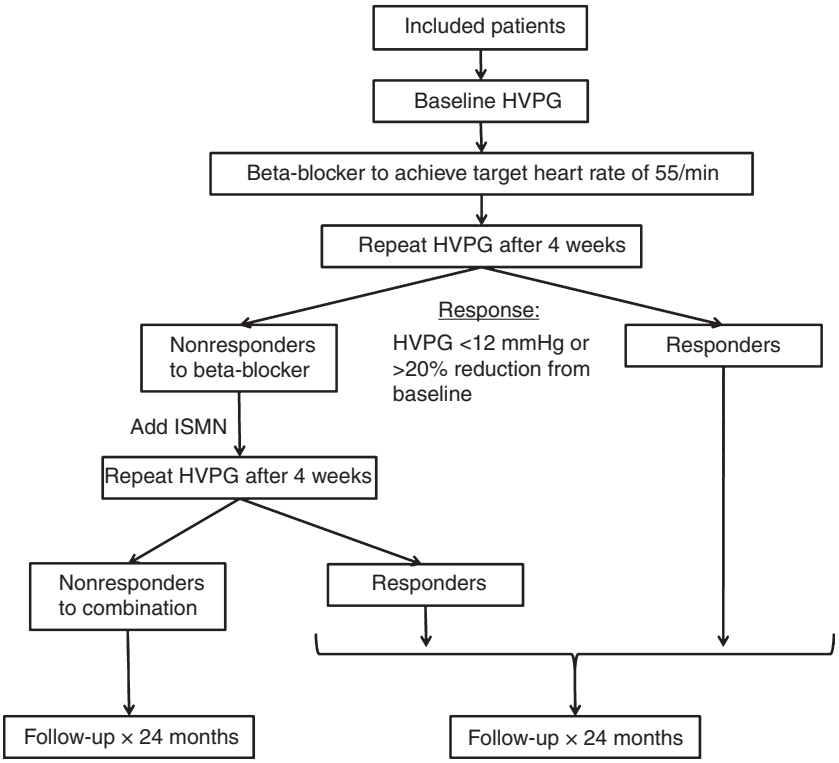


**Figure 1.** Study design.

decrease in HVPG to <12 mmHg or a ≥20% reduction in HVPG from baseline. If the patient was found not to have responded, ISMN was added. The measurement of HVPG was then repeated in these patients, for the third time, after 1 month of ISMN therapy. Patients who did not respond haemodynamically to propranolol and ISMN and who did not bleed were continued on the same drugs. This was done so with a presumption that such patients may ultimately derive some benefit from drug therapy even with suboptimal reduction in portal pressure. Both responders and nonresponders were followed up for a median of 24 months for development of first variceal bleeding. The nonresponders served as a comparative group.

## Treatment

The principle of incremental dosing was used to achieve the target heart rate for propranolol. Propranolol was started at a dose of 20 mg twice daily and increased on alternate day to achieve a target heart rate of 55 beats/min or to the maximal dose of 360 mg/day and continued if the medication was well tolerated and the systolic blood pressure remained >90 mmHg.

ISMN was started to the nonresponders to beta-blockers at 10 mg twice daily and increased to 20 mg twice daily after 3 days and was continued if it was well tolerated and the systolic blood pressure remained >90 mmHg.

On the occurrence of intolerable adverse effects, systolic blood pressure dropping to <90 mmHg or pulse rate decreasing to <55/min, the dose of the medication was decreased stepwise and, if these adverse events persisted, eventually stopped. Reintroduction of the medication was attempted if cessation of the medication did not result in improvement of the reported adverse effects.

Compliance was assessed by interview with the patients as well as corroboration of the patient's history by a member of the family, if present, during consultation. Blood levels of propranolol and ISMN were not measured. Noncompliance was defined as at least one episode of stopping the medication for more than 3 days. Patients with intolerable side effects related to ISMN were continued on propranolol alone.

## Follow-up

This included clinical assessment once a month for the first 3 months, then every 3 months till the end of follow-up or in between, if the patient had any complaints. Patients who did not attend the follow-up visits were called over the telephone or by letter.


© 2009 Blackwell Publishing Ltd

## Endpoints

The primary endpoint of the study was the development of first variceal bleeding. Secondary endpoints were haemodynamic response (to therapy with beta-blocker alone and to therapy with combination of drugs in beta-blocker nonresponders), UGI bleeding from any other source, development of adverse effects and the effect of treatment on systemic and pulmonary haemodynamics, renal function, ascites and survival.

All patients were instructed to go to the hospital whenever they experienced melena or hematemesis. In case of an episode of UGI bleeding, the patient was admitted to the hospital and evaluated for the cause of bleeding. An emergency endoscopy was performed. Variceal bleeding was diagnosed when varices were actively bleeding or had stigmata of recent bleeding and/or if fresh blood was observed in the stomach and varices were the only potential source of bleeding. Bleeding from portal hypertensive 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). If the UGI bleeding was arising from the varices, the patient was treated with EVL plus somatostatin or terlipressin for 5 days in the ICU. Blood transfusion was given to keep the haemoglobin level above 8 gm/dL.

## Measurement of HVPG

The haemodynamic studies were performed after an overnight fast, with full aseptic precautions and under antibiotic cover. Under local anaesthesia, a 7F central venous catheter (Arrow; Arrow Medical, Athens, TX, USA) was placed in the right femoral vein or right internal jugular vein under fluoroscopic guidance, using the Seldinger technique.

Hepatic venous pressure gradient was measured by the standard technique[20] in which a 7F balloon tipped Swan Ganz catheter (Boston Scientific, Natick, MA, USA) was introduced into the right hepatic vein under fluoroscopic guidance. The zero reference point was set at the mid-axillary point. The free hepatic venous pressure (FHVP) was obtained by keeping the catheter free into the lumen of the hepatic vein. The balloon of the catheter was then inflated to wedge the lumen of the hepatic vein. The pressure tracing at this juncture showed absence of wave forms and the pressure was labelled as wedged hepatic venous pressure (WHVP). Presence of wedging was confirmed by injection of 2 mL intravenous contrast which showed absence of reflux into inferior vena cava and appearance of a sinusoidogram. HVPG was obtained by subtracting free from WHVPs (HVPG = WHVP − FHVP). All measurements were performed in triplicate. If the difference between the two readings of HVPG was more than 1 mmHg, all the readings were discarded and fresh set of measurements were taken. The normal value of HVPG in our haemodynamic laboratory is between 1 and 4 mmHg.

## Measurement of cardiac output, systemic vascular resistance and pulmonary vascular resistance

After measuring HVPG, the balloon catheter was advanced into the right atrium, pulmonary artery and then pulmonary capillaries for measurement of the right atrial pressure (RAP), pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP) respectively. Mean arterial pressure (MAP) was measured simultaneously by introducing the catheter through femoral artery. Blood samples were obtained from the pulmonary artery and the femoral artery for estimating oxygen saturation. Heart rate was derived from continuous electrocardiogram monitoring. Cardiac output (CO) was calculated by Fick's oxygen method[21] as follows: [oxygen consumption (mL/min)]/[Arterio-venous oxygen difference (mL/L)]. The systemic vascular resistance (SVR, in dynes × s/cm$^5$) was calculated as: (MAP in mmHg − RAP in mmHg) × 80/[CO (in L/min)]. The pulmonary vascular resistance (PVR, in dynes × s/cm$^5$) was calculated as: (PAP in mmHg − PCWP in mmHg) × 80/[CO (in L/min)]. CO was indexed by body surface area and expressed as cardiac index (CI) (L/min/m$^2$).

## Statistical analysis

Results were expressed as mean (±SD), median (range) or frequency (%). Comparisons of quantitative variables were performed by the Student's *t*-test or Mann–Whitney *U*-test and for qualitative variables by Fisher exact test. Paired sample *t*-test or Wilcoxon test was used to compare paired data. A *P*-value of <0.05 was considered significant. Risks of bleeding were calculated with Kaplan–Meier plots and compared by log-rank test. For analysing the risk factors for first variceal bleeding, univariate and multivariate analyses were performed. Quantitative variables were categorized


© 2009 Blackwell Publishing Ltd

based on their mean or median values. An intent-to-treat strategy was used in the analysis of the results. Statistical analyses were performed with the SPSS 15.0 statistical package (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Patients

Eighty-nine cirrhotic patients with high-risk oesophageal varices were enrolled in the study. Fifty-six patients were included in the study and rest excluded as per the exclusion criteria (Child–Pugh score ≥13 in 14, hepatic venous outflow tract obstruction in six, type 1 diabetes mellitus in five, renal failure in four, hepatocellular carcinoma in two and bronchial asthma in two patients). The baseline characteristics of the included patients are shown in Table 1.

**Table 1.** Baseline characteristics of patients

| Parameters | Value ($n$ = 56) |
|---|---|
| Age (years), mean (±SD) | 47 (±13) |
| Gender, *n* (%) | |
| Male | 44 (79) |
| Female | 12 (21) |
| Aetiology, *n* (%) | |
| Hepatitis B | 22 (39) |
| Hepatitis C | 12 (22) |
| Alcohol | 13 (23) |
| Cryptogenic | 8 (14) |
| Autoimmune | 1 (2) |
| Ascites, *n* (%) | 27 (48) |
| CTP class, *n* (%) | |
| A | 16 (29) |
| B | 27 (48) |
| C | 13 (23) |
| CTP score (*n*/15), mean (±SD) | 7.8 (±1.9) |
| Serum bilirubin (mg/dL), median (range) | 1.5 (0.6–6.6) |
| Serum albumin (g/dL), mean (±SD) | 3.3 (±0.6) |
| PT prolongation (s), *n* (%) | |
| 0–3 | 17 (30) |
| 4–6 | 17 (30) |
| >6 | 22 (40) |
| Serum creatinine (mg/dL), mean (±SD) | 0.7 (±0.3) |
| Oesophageal varices, *n* (%) | |
| Grade III | 45 (80) |
| Grade IV | 11 (20) |
| Heart rate (beats/min), mean (±SD) | 89 (±9) |
| MAP (mmHg), mean (±SD) | 90 (±10) |
| HVPG (mmHg), mean (±SD) | 18.0 (±4.5) |
| CI (L/min/$m^2$), mean (±SD) | 5.0 (±1.3) |
| SVRI (dynes·s/$cm^5$), mean (±SD) | 1467 (±420) |
| PVRI (dynes·s/$cm^5$), mean (±SD) | 84 (±33) |

SD, standard deviation; CTP, Child–Turotte–Pugh; PT, prothrombin time; MAP, mean arterial pressure; HVPG, hepatic venous pressure gradient; CI, cardiac index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index.

### Study profile

Study profile in terms of HVPG response is shown in Figure 2. The median dose of propranolol used was 120 mg (range 60–300 mg). On HVPG measurement performed at 1-month, 21/56 (38%) responded to beta-blocker alone, while 35/56 (62%) remained non-responders. These nonresponders were treated with combination therapy with a median dose of ISMN of 40 mg (range 20–40 mg). Twenty-nine of 35 of these patients underwent HVPG measurement at 2 months, while six did not give consent. At 2-month HVPG, six additional patients became responders, while 29 still remained nonresponders to combination therapy (including six who had not given consent for HVPG).

Thus, overall 48% (27/56) patients responded, either to beta-blocker alone ($n$ = 21) or to combination ($n$ = 6). Rest 52% (29/56), were overall nonresponders. These nonresponders were, however, continued on the combination regimen at the same doses, without changing the treatment options.

### Haemodynamic response

*Response to beta-blocker alone.* The mean baseline HVPG was 18.0 ± 4.5 mmHg. Haemodynamic response to beta-blocker alone was achieved in 21 (38%) patients and rest 35 (62%) were nonresponder to beta-blocker alone (Table 2). The median HVPG reduction achieved was 26% in responders. Nonsignificant reduction in HVPG was noted in the nonresponders to beta-blocker alone. The mean reduction in the heart rate between responders and nonresponders did not show any difference ($P$ = N.S.). Responders to beta-blockers had a significant increase in the systemic vascular resistance index (SVRI: 1459 ± 393 vs. 1683 ± 457 dynes·s/$cm^5$, $P$ = 0.009) and decrease in CI (4.8 ± 1.3 vs. 4.2 ± 1.2 L/min/$m^2$, $P$ = 0.001), whereas pulmonary vascular resistance index (PVRI) did not show any change (80 ± 36 vs. 83 ± 43 dynes.s/$cm^5$, $P$ = 0.752). Nonresponders to beta-blocker did not have any significant change in SVRI and PVRI, whereas the CI decreased


© 2009 Blackwell Publishing Ltd

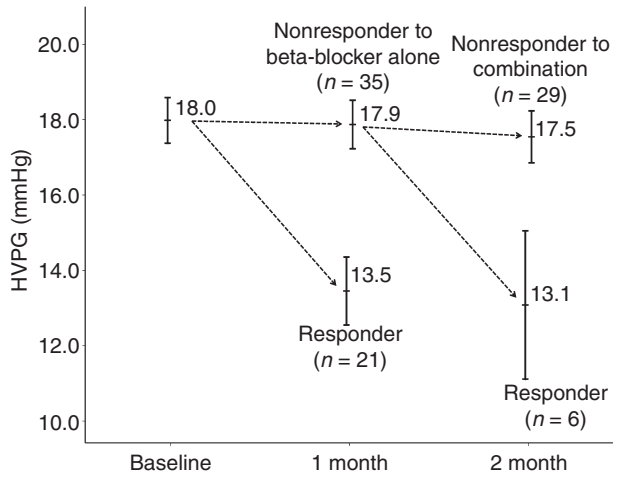


**Figure 2.** Hepatic venous pressure gradient (HVPG) response to therapy.

significantly (5.0 ± 1.3 vs. 4.5 ± 1.5 L/min/m$^2$, $P$ = 0.02) (Table 2).

*Response to combination.* Nonresponders ($n$ = 35) were started on ISMN along with their previous dosage of propranolol. Repeat HVPG on this combination could be performed in 29 patients while six patients did not consent for the repeat HVPG measurement.

Six of 29 (21%) patients responded to the combination treatment. They also had a significant increase in CI and SVRI, while no difference in PVRI. Nonresponders had significant reduction in CI, but not in SVRI and PVRI (Table 3).

*Overall response.* The overall haemodynamic effect of therapy in all patients is given in Table 4. There was a significant reduction in heart rate, HVPG and CI, while SVRI increased significantly. However, there was no change in MAP and PVRI.

For analysis, the six patients who did not undergo third HVPG were included in the nonresponder to combination treatment group. On comparing patients with HVPG response ($n$ = 27) with HVPG nonresponders ($n$ = 29), it was found that no baseline clinical or laboratory parameter could predict response (Table 5). Post-therapy heart rate, MAP, CI, SVRI and PVRI were also not different in these two groups.

## Primary endpoint

During a median follow-up of 24 months (range 12–36 months), first variceal bleeding occurred in seven of 56 (13%) patients. This bleeding occurred in one of 27 (4%) responders and six of 29 (21%) nonresponders (log-rank test $P$ = 0.097) (Figure 3). The actuarial probability of first variceal bleeding at median 24 months of follow-up was 4% in responders and 24% in nonresponders ($P$ < 0.05). The variceal bleeding in the single responder occurred at 28 months of follow-up, while the bleeding in six nonresponders occurred at 13, 14, 17, 19, 24 and 27 months respectively. No variceal bleeding occurred within the first year of follow-up.

On excluding the six patients who did not undergo the third HVPG measurement from the analysis, of 50 patients, 27 (54%) were responders and 23 (46%) were nonresponders. The first variceal bleeding occurred in six of 50 (12%) patients. This bleeding occurred in one

**Table 2.** Haemodynamic response to treatment with beta-blocker alone ($n$ = 56)

| | Responders ($n$ = 21) | | | Nonresponders to beta-blocker alone ($n$ = 35) | | |
|---|---|---|---|---|---|---|
| Parameter | Before | After | $P$-value | Before | After | $P$-value |
| Heart rate (beats/min) | 88 (±10) | 57 (±3) | <0.01 | 89 (±9) | 57 (±3) | <0.01 |
| MAP (mmHg) | 89 (±10) | 89 (±9) | 0.857 | 91 (±10) | 89 (±10) | 0.078 |
| HVPG (mmHg) | 18.4 (±5.3) | 13.4 (±4.1) | <0.01 | 17.7 (±4.1) | 17.9 (±3.8) | 0.656 |
| CI (L/min/m$^2$) | 4.8 (±1.3) | 4.2 (±1.2) | 0.001 | 5.0 (±1.3) | 4.5 (±1.5) | 0.028 |
| SVRI (dynes·s/cm$^5$) | 1459 (±393) | 1683 (±457) | 0.009 | 1483 (±452) | 1563 (±486) | 0.217 |
| PVRI (dynes·s/cm$^5$) | 80 (±36) | 83 (±43) | 0.752 | 86 (±32) | 87 (±34) | 0.817 |

Values are given as mean (±SD) except the $P$-values.
SD, standard deviation; MAP, mean arterial pressure; HVPG, hepatic venous pressure gradient; CI, cardiac index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index.


© 2009 Blackwell Publishing Ltd

**Table 3.** Haemodynamic response to treatment with combination of beta-blocker and ISMN in patients who did not respond to beta-blocker alone ($n$ = 35)

| | Responders ($n$ = 6) | | | Nonresponders to combination treatment ($n$ = 29) | | |
|---|---|---|---|---|---|---|
| Parameter | Before | After | $P$-value | Before | After | $P$-value |
| Heart rate (beats/min) | 85 (±3) | 58 (±4) | <0.01 | 90 (±10) | 58 (±3) | <0.01 |
| MAP (mmHg) | 95 (±16) | 98 (±18) | 0.125 | 90 (±8) | 88 (±6) | 0.585 |
| HVPG (mmHg) | 18.0 (±6.1) | 13.1 (±4.2) | <0.01 | 16.9 (±3.1) | 17.5 (±3.3) | 0.292 |
| CI (L/min/$m^2$) | 5.0 (±0.9) | 4.1 (±0.7) | 0.024 | 5.1 (±1.4) | 4.4 (±1.3) | 0.044 |
| SVRI (dynes·s/$cm^5$) | 1418 (±351) | 1954 (±479) | 0.005 | 1454 (±435) | 1645 (±506) | 0.226 |
| PVRI (dynes·s/$cm^5$) | 84 (±27) | 83 (±31) | 0.976 | 92 (±35) | 94 (±28) | 0.479 |

Values are given as mean (±SD) except the $P$-values.
SD, standard deviation; MAP, mean arterial pressure; HVPG, hepatic venous pressure gradient; CI, cardiac index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index.

**Table 4.** Overall haemodynamic effect of therapy in all patients

| Parameters | Baseline | Post-therapy | $P$-value |
|---|---|---|---|
| Heart rate (beats/min) | 89 (±9) | 58 (±3) | <0.01 |
| MAP (mmHg) | 90 (±10) | 90 (±9) | 0.795 |
| HVPG (mmHg) | 18.0 (±4.5) | 15.8 (±4.7) | <0.01 |
| CI (L/min/$m^2$) | 5.0 (±1.3) | 4.4 (±1.4) | <0.01 |
| SVRI (dynes·s/$cm^5$) | 1467 (±420) | 1662 (±491) | 0.001 |
| PVRI (dynes·s/$cm^5$) | 84 (±33) | 85 (±35) | 0.793 |

Values are given as mean (±SD) except the $P$-values.
SD, standard deviation; MAP, mean arterial pressure; HVPG, hepatic venous pressure gradient; CI, cardiac index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index.

of 27 (4%) responders and five of 23 (22%) nonresponders (log-rank test $P$ = 0.108). The actuarial probability of first variceal bleeding at median 24 months of follow-up was 4% in responders and 22% in nonresponders ($P$ < 0.05).

### Other secondary endpoints

Five nonresponder patients (17%) developed new ascites while none of responders developed new ascites ($P$ = 0.052).

Two patients died during the follow-up, one each in the responder and nonresponder groups ($P$ = 1.0). Cause of death in the responder was liver failure, while in the nonresponder, it was variceal bleeding.

No patient developed renal failure. None of the patients developed nonvariceal upper GI bleed.

### Adverse effects

Ten (18%) patients developed adverse effects to propranolol (Table 6) requiring dose reduction [seven (20%) nonresponders and three (14%) responders]. Median duration of development of adverse effects was 15 days. Six of 35 (17%) patients on ISMN developed adverse effects to ISMN (Table 6) requiring dose reduction. Median duration of development of adverse effects was 4 days.

### Risk factors for first variceal bleeding

Univariate analysis for risk factors for first variceal bleed revealed that grade IV oesophageal varices was the most important risk factor for variceal bleed ($P$ = 0.002) followed by haemodynamic nonresponse to therapy ($P$ = 0.097) (Table 7). Multivariate analysis also showed the same two factors as independent risk factors for first variceal bleeding (Table 8).

## DISCUSSION

The results of this study demonstrate that for primary prophylaxis of variceal bleeding, in patients of cirrhosis with 'high-risk' varices, when beta-blocker is


© 2009 Blackwell Publishing Ltd

**Table 5.** Comparison of overall responders and overall nonresponders

| Parameters | Overall responders ($n$ = 27) | Overall nonresponders ($n$ = 29) | $P$-value |
|---|---|---|---|
| Baseline | | | |
| Age (years) mean (±SD) | 44 (±14) | 49 (±11) | 0.155 |
| Gender, $n$ (%) | | | |
| Male | 20 (74) | 24 (83) | 0.523 |
| Female | 7 (26) | 5 (17) | |
| Aetiology, $n$ (%) | | | |
| Hepatitis B | 11 (41) | 11 (38) | 0.080 |
| Hepatitis C | 2 (7) | 10 (34) | |
| Alcohol | 7 (26) | 6 (21) | |
| Cryptogenic | 6 (22) | 2 (7) | |
| Autoimmune | 1 (4) | 0 (0) | |
| Ascites, $n$ (%) | 15 (56) | 12 (41) | 0.422 |
| CTP class, $n$ (%) | | | |
| A | 8 (30) | 8 (28) | 0.979 |
| B | 13 (48) | 14 (48) | |
| C | 6 (22) | 7 (24) | |
| CTP score ($n$/15), mean (±SD) | 7.7 (±1.9) | 7.9 (±2.0) | 0.818 |
| Serum bilirubin (mg/dL), median (range) | 1.6 (0.6–3.7) | 1.4 (0.7–6.6) | 0.417 |
| Serum albumin (g/dL), mean (±SD) | 3.3 (±0.7) | 3.2 (±0.6) | 0.729 |
| PT prolongation (s), $n$ (%) | | | |
| 0–3 | 8 (30) | 9 (31) | 0.977 |
| 4–6 | 8 (30) | 9 (31) | |
| >6 | 11 (40) | 11 (38) | |
| Serum creatinine (mg/dL), mean (±SD) | 0.7 (±0.3) | 0.6 (±0.2) | 0.402 |
| Oesophageal varices, $n$ (%) | | | |
| Grade III | 22 (82) | 23 (79) | 1.000 |
| Grade IV | 5 (18) | 6 (21) | |
| Heart rate (beats/min), mean (±SD) | 87 (±8) | 90 (±10) | 0.216 |
| MAP (mmHg), mean (±SD) | 91 (±11) | 90 (±8) | 0.667 |
| HVPG (mmHg), mean (±SD) | 18.3 (±5.3) | 17.6 (±3.7) | 0.586 |
| Follow-up, mean (±SD) | | | |
| Heart rate (beats/min) | 58 (±3) | 58 (±3) | 0.731 |
| MAP (mmHg) | 91 (±12) | 88 (±6) | 0.275 |
| HVPG (mmHg) | 13.4 (±4.2) | 18.2 (±4.0) | <0.01 |
| CI (L/min/m$^2$) | 4.2 (±1.1) | 4.6 (±1.5) | 0.285 |
| SVRI (dynes·s/cm$^5$) | 1744 (±467) | 1585 (±508) | 0.231 |
| PVRI (dynes·s/cm$^5$) | 83 (±40) | 87 (±31) | 0.707 |

SD, standard deviation; CTP, Child–Turotte–Pugh; PT, prothrombin time; MAP, mean arterial pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; HVPG, hepatic venous pressure gradient.

administered alone, at a dose to bring down the heart rate to 55 beats/min, the HVPG response rate is 38%. When ISMN is added to the beta-blocker nonresponders, the overall HVPG response rate increases to about half of all patients. This '*a la carte*' approach, with sequential addition of ISMN to nonresponders of beta-blockers and repeating HVPG for early identification of overall nonresponders, helps in categorizing patients to their bleeding risk profile. The 2-year actuarial probability of first variceal bleeding in


© 2009 Blackwell Publishing Ltd

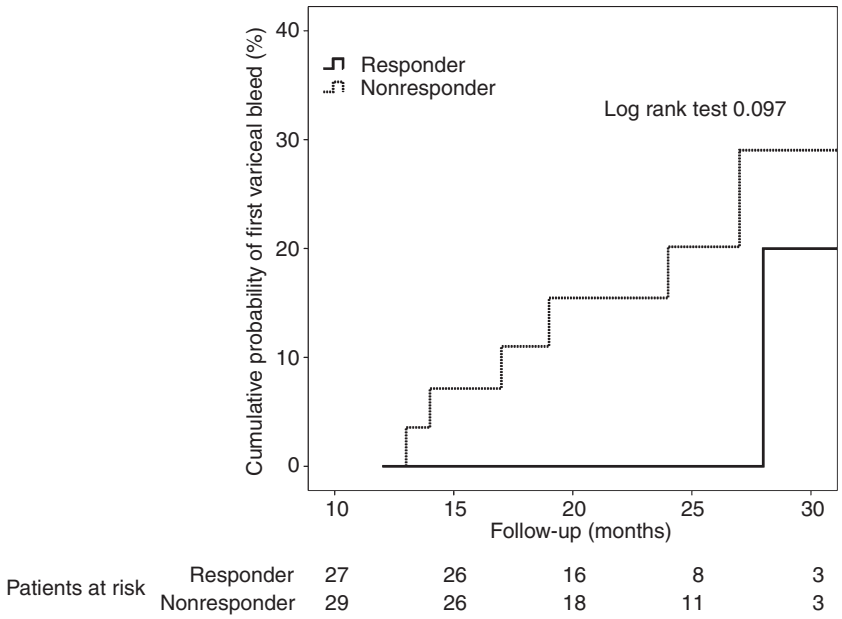


**Figure 3.** Kaplan–Meier graph showing cumulative probability of first variceal bleeding in responders and nonresponders.

**Table 6.** Adverse effects observed in patients treated with propranolol and ISMN

| | Propranolol ($n$ = 10) | | ISMN ($n$ = 6) |
|---|---|---|---|
| Tiredness | 10 (100) | Headache | 6 (100) |
| Dizziness | 7 (70) | Dizziness | 4 (67) |
| Breathlessness | 6 (60) | Breathlessness | 1 (17) |
| Poor memory | 2 (20) | Nausea | 1 (17) |

Values in parenthesis represent percentages.
ISMN, isosorbide mononitrate.

responders is 4% and that in nonresponders is 22–24%. The addition of ISMN causes adverse effects in 17% patients; however, these are usually mild and subside with dose reduction and the combination can be continued safely. The only independent risk factors for first variceal bleeding are grade IV oesophageal varices and haemodynamic nonresponse to therapy.

As up to two-thirds of patients on beta-blockers do not have a haemodynamic response, these patients are exposed to a significant risk of first variceal bleeding. The role of addition of ISMN to these patients was not clear. Although it was shown previously by García-Pagán[9] that combination of beta-blocker with ISMN leads to a higher HVPG response rate, there were controversial results as far as clinical efficacy of combination treatment in primary prophylaxis is concerned. In a multicentre randomized trial on 146 patients, nadolol plus ISMN was found to be significantly more effective than nadolol alone in the long-term (up to 7 years) use with few side effects,[10, 11] Contrary to these results, in another multicentre study of 349 patients,[12] the cumulative probability of first variceal bleeding in propranolol plus ISMN group was similar to propranolol plus placebo group. Moreover, adverse effects were significantly more frequent in the propranolol plus ISMN group due to a greater incidence of headache. However, this study was different from ours due to inclusion of patients with varices of any size, shorter follow-up of 16 months and a higher drop-out rate. Moreover, all the reported side effects due to ISMN disappeared promptly after discontinuation of the drug with no deterioration of renal function or worsening of control of ascites.[22] In our study, we found that addition of ISMN was safe, with minor adverse effects in one sixth of patients that disappeared with dose reduction. Thus our study suggests that the combination of beta-blocker and ISMN for primary prophylaxis appears to be more effective and safe.

Our study suggests that pharmacotherapy for primary prophylaxis should be HVPG guided. This allows early identification of beta-blocker nonresponders and only these patients should be offered ISMN. Subsequent HVPG allows early identification of nonresponders to combination therapy whose bleeding risk is much higher than the responders. These patients may be switched over to an alternative therapy. Short of


© 2009 Blackwell Publishing Ltd

**Table 7.** Univariate analysis of risk factors for first variceal bleed

| Variable* | *P*-value (Log-rank test) |
|---|---|
| Baseline | |
| Age (years) | |
| <47 vs. ≥47 | 0.561 |
| Gender | |
| Male vs. female | 0.428 |
| Aetiology | |
| Hepatitis B vs. rest | 0.412 |
| Hepatitis C vs. rest | 0.724 |
| Alcohol vs. rest | 0.252 |
| Cryptogenic vs. rest | 0.792 |
| Ascites | |
| Present vs. absent | 0.701 |
| CTP class | |
| A vs. B/C | 0.586 |
| Serum bilirubin (mg/dL) | |
| <1.5 vs. ≥1.5 | 0.154 |
| Serum albumin (g/dL) | |
| <3.3 vs. ≥3.3 | 0.831 |
| PT prolongation (s) | |
| ≤6 vs. >6 | 0.439 |
| Serum creatinine (mg/dL) | |
| <0.7 vs. ≥0.7 | 0.470 |
| Oesophageal varices | |
| Grade III vs. grade IV | 0.002 |
| Heart rate (beats/min) | |
| <89 vs. ≥89 | 0.713 |
| Mean arterial pressure (mmHg) | |
| <90 vs. ≥90 | 0.547 |
| HVPG (mmHg) | |
| <17.9 vs. ≥17.9 | 0.775 |
| Follow-up | |
| Heart rate (beats/min) | |
| <57 vs. ≥57 | 0.973 |
| Mean arterial pressure (mmHg) | |
| <89 vs. ≥89 | 0.936 |
| Haemodynamic response in HVPG | |
| Responder vs. nonresponder | 0.097 |

* For quantitative variables mean or median values were used for categorization.
SD, standard deviation; CTP, Child–Turotte–Pugh; PT, prothrombin time; MAP, mean arterial pressure; HVPG, hepatic venous pressure gradient.

HVPG, no parameter can differentiate between responder and nonresponder. Both responders and nonresponders had similar heart rate reduction (almost 55 beats/min). Similarly, no baseline clinical or laboratory parameter can predict response to pharmacotherapy (Table 4).

**Table 8.** Multivariate analysis of risk factors for first variceal bleed

| Variable | *P*-value | Odds ratio | 95% CI |
|---|---|---|---|
| Serum bilirubin ≥1.5 mg/dL | 0.098 | 7.7 | 0.7–85.4 |
| Grade IV oesophageal varices | 0.035 | 8.6 | 1.2–63.0 |
| Haemodynamic nonresponder | 0.045 | 12.4 | 1.1–145.7 |

Variables with *P*-value <0.2 using univariate analysis were entered into multivariate analysis.
CI, confidence interval.

The '*a la carte*' approach for pharmacotherapy in prevention of variceal bleeding was first adopted by Bureau *et al.* in 2002.[18] In their trial, 34 patients were treated to prevent a first bleeding episode ($n$ = 20) and a rebleeding ($n$ = 14). Thirteen patients (38%) were responders to propranolol. ISMN improved haemodynamic response in seven cases. Among these 20 (59%) haemodynamic responders, only two (10%) experienced variceal bleeding compared with nine of 14 (64%) nonresponders ($P < 0.05$). Using multivariate analysis, only haemodynamic response was found to have an independent predictive value for the risk of variceal bleeding.[18] However, there were many criticisms to that study, the first being relatively low number of patients analysed, thereby leading to a lack of statistical power, particularly in the subgroup analysis of patients receiving primary prophylaxis. A second criticism is that they used a fixed dose of propranolol in all patients. The individual sensitivity to beta-blockers differs markedly from patient to patient, so an incremental dose of propranolol gives a better response.[23] Our study overcame both these shortcomings. Our patient numbers is almost three times that of the study by Bureau *et al.* and we used the principle of incremental dosing for beta-blocker therapy. Hence, our results are more robust and the menu offered is actually '*a la carte*' rather than '*menu fixe*'.

The nonresponders to combination therapy have a higher risk of first variceal bleeding (up to 24% in median 2 years in our study). This bleeding risk is almost similar to those not on any therapy.[4] Thus, it is essential that we identify them early so that alternative form of therapy (like EVL) can be offered to them.


© 2009 Blackwell Publishing Ltd

Although EVL and beta-blocker therapy is considered to have same efficacy,[24] EVL therapy in pharmacotherapy nonresponders would be a logical and a definitely more effective choice. In our study, the stepwise haemodynamic approach allowed us to identify nonresponders by the end of 8 weeks itself.

Although HVPG measurement is a safe procedure, the acceptability of repeated HVPG measurements in '*a la carte*' approach needs to be assessed. In our study, all patients underwent a second HVPG, but six of 35 (17%) nonresponder patients to beta-blocker did not give consent for a third HVPG study. Their apprehension was partly because of the repeated invasive nature of the procedure and also because of the uncertainty regarding the benefit and success of the combination therapy. Nevertheless, till a reliable noninvasive portal pressure measuring method becomes available, we have to rely on HVPG measurements for guiding therapy in '*a la carte*' approach.

We found that the independent risk factors for first variceal bleeding are large variceal size and haemodynamic nonresponse. Even though all our patients had 'high-risk' varices, our finding that grade IV varices had a higher risk of bleeding than grade III suggests that it makes more sense to classify them into four grades as per Conn's classification[19] rather than just small and large as per recent guidelines.[5–7] However, bleeding risk profile of grade IV varices compared to grade III varices needs to be further studied in larger trials.

We also studied effects of treatment on systemic and pulmonary haemodynamics in these patients. We found that with beta-blocker or combination therapy, there was a significant reduction in CI and a significant increase in SVRI. PVRI remained unchanged with treatment (Table 4). These changes in systemic haemodynamics were more marked in HVPG responders than in nonresponders (Tables 2 and 3), thus indicating that these changes are mediated by both beta-1 and beta-2 blockade. Data are scarce in literature on the effect of beta-blocker or combination therapy on systemic and pulmonary haemodynamics. A study by Garcia-Pagán *et al.*[25] found that addition of oral ISMN caused a further and marked fall in portal pressure, without additional changes in azygos blood flow, but with significant additional reductions in hepatic blood flow (−15.5%), CO (−11.5%) and MAP (−22%). Our study provides further evidence that the hyperdynamic circulatory state of cirrhosis is significantly ameliorated by this therapy.

In our study, five nonresponder patients (17%) developed new ascites, whereas none of responders developed new ascites ($P = 0.052$). This is an interesting observation and needs further prospective trials addressing the issue whether haemodynamic response to portal pressure reducing drugs also helps in prevention of ascites.

Reduction in blood pressure has been an important concern while using beta-blockers with or without nitrates and in many series, a significant proportion of patients are unable to tolerate beta-blockers due to hypotension. However, in our study, it was interesting to note that in spite of median 120 mg of propranolol (all patients) plus 40 mg of ISMN ($n = 35$), there was no reduction in MAP (Table 4). In a few previous studies also, it was noted that beta-blockers with or without nitrates did not have a significant systemic hypotensive effect.[26–29] The reason for this variation in effect on MAP in various studies remains unknown.

There are several limitations in our study. First, in spite of this being the largest study on primary prophylaxis using the '*a la carte*' approach, the number of patients is less than what is needed to show significant difference in bleeding risk of responders and nonresponders. We found a nonsignificant *P*-value of 0.097 (log-rank test) on comparing cumulative risk of bleeding in responders and nonresponders. Second, we did not have a control arm (i.e. a standard propranolol treatment arm without haemodynamic measurement). A controlled study would have had much more impact on clinical decision making. Such a study would have given us the opportunity to demonstrate, whether the reduction in the bleeding risk is really worth the effort of 2 (or even 3) HVPG measurements in asymptomatic patients. This question cannot be answered conclusively due to the uncontrolled design of the current study. Third, we did not offer any rescue therapy for nonresponders. This, however, was intentional, as we wanted to see whether continuing pressure reducing drugs in nonresponders is of any benefit at all. It was disappointing to note that this was not demonstrable in nonresponders. Fourth, the main aetiology in our study was predominantly viral. Whether studies on patients with alcoholic liver disease will show similar results both with the haemodynamics and compliance is not known.

It has to be conceded that two or three haemodynamic assessments are undoubtedly invasive and represents a major disincentive to use this approach in


© 2009 Blackwell Publishing Ltd

primary prophylaxis. With the invasiveness of this approach and the cost involved, it could well be argued that, band ligation may be a preferable approach. Thus, '*a la carte*' approach, which identifies approximately half the patients as being nonresponders, despite the high intensity work involved, may represent a limitation of pharmacological approach to primary prophylaxis.

In conclusion, for primary prophylaxis of variceal bleeding from 'high-risk' varices, beta-blocker is effective in 38% which increases to 48% on addition of ISMN to beta-blocker nonresponders. The HVPG guided '*a la carte*' approach may help in early identification of pharmacotherapy nonresponders who have 24% 2-year actuarial probability of first variceal bleeding. We also showed that the addition of ISMN to beta-blockers is safe with minor adverse effects. The risk factors for first variceal bleeding are grade IV oesophageal varices and haemodynamic nonresponse to therapy.

## ACKNOWLEDGEMENTS

*Declaration of personal interests*: There is no conflict of interest to disclose by any of the authors. *Declaration of funding interests*: None.

## STUDY HIGHLIGHTS

### What is current knowledge?

- Nonselective beta-blocker is the recommended therapy for primary prophylaxis of variceal bleeding in patients with 'high-risk' varices.
- Only one-third of patients on beta-blockers have a significant portal pressure reduction.
- The role of addition of isosorbide 5-mononitrate (ISMN) to beta-blocker is controversial.
- Benefits of hepatic venous pressure gradient (HVPG) guided '*a la carte*' approach in primary prophylaxis of variceal bleeding are also unclear.

### What is new here?

- Addition of ISMN to beta-blocker nonresponders raises the response rate to 48% from 38%.
- Early identification of haemodynamic response to pharmacotherapy is essential for primary prophylaxis of variceal bleeding in patients with 'high-risk' varices.
- As haemodynamic nonresponse to therapy is the most important risk factor for bleeding, the HVPG guided '*a la carte*' approach is recommended for all patients on primary prophylaxis.

## REFERENCES

1 Jensen DM. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. *Gastroenterology* 2002; **122**: 1620–30.
2 D'Amico G, De Franchis R, Cooperative Study Group. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003; **38**: 599–612.
3 Carbonell N, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology* 2004; **40**: 652–9.
4 Tiani C, Abraldes JG, Bosch J. Portal hypertension: pre-primary and primary prophylaxis of variceal bleeding. *Dig Liver Dis* 2008; **40**: 318–27.
5 de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005; **43**: 167–76.
6 Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; **46**: 922–38.
7 Sarin SK, Kumar A, Angus PW, *et al.* Primary prophylaxis of gastroesophageal variceal bleeding: consensus recommendations of the Asian Pacific Association for the Study of the Liver. *Hepatol Int* 2008; **1**: 398–413.
8 D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis* 1999; **19**: 475–505.
9 García-Pagán JC, Feu F, Bosch J, Rodés J. Propranolol compared with propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis. A randomized controlled study. *Ann Intern Med* 1991; **114**: 869–73.
10 Merkel C, Marin R, Enzo E, *et al.* Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. Gruppo-Triveneto per L'ipertensione portale (GTIP). *Lancet* 1996; **348**: 1677–81.
11 Merkel C, Marin R, Sacerdoti D, *et al.* Long-term results of a clinical trial of nadolol with or without isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2000; **31**: 324–9.
12 García-Pagán JC, Morillas R, Bañares R, *et al.* Propranolol plus placebo versus propranolol plus isosorbide-5-mononitrate in the prevention of a first variceal bleed: a double-blind RCT. *Hepatology* 2003; **37**: 1260–6.


© 2009 Blackwell Publishing Ltd

13 Groszmann RJ, Bosch J, Grace ND, *et al.* Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990; **99**: 1401–7.
14 Merkel C, Bolognesi M, Sacerdoti D, *et al.* The hemodynamic response to medical treatment of portal hypertension as a predictor of clinical effectiveness in the primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2000; **32**: 930–4.
15 Turnes J, Garcia-Pagan JC, Abraldes JG, Hernandez-Guerra M, Dell'Era A, Bosch J. Pharmacological reduction of portal pressure and long-term risk of first variceal bleeding in patients with cirrhosis. *Am J Gastroenterol* 2006; **101**: 506–12.
16 Imperiale TF, Chalasani N, Klein RW. Measuring the hemodynamic response to primary pharmacoprophylaxis of variceal bleeding: a cost-effectiveness analysis. *Am J Gastroenterol* 2003; **98**: 2742–50.
17 Hicken BL, Sharara AI, Abrams GA, Eloubeidi M, Fallon MB, Arguedas MR. Hepatic venous pressure gradient measurements to assess response to primary prophylaxis in patients with cirrhosis: a decision analytical study. *Aliment Pharmacol Ther* 2003; **17**: 145–53.
18 Bureau C, Péron JM, Alric L, *et al.* ''A La Carte'' treatment of portal hypertension: adapting medical therapy to hemodynamic response for the prevention of bleeding. *Hepatology* 2002; **36**: 1361–6.
19 Conn HO. Ammonia tolerance in the diagnosis of esophageal varices. A comparison of endoscopic, radiologic, and biochemical techniques. *J Lab Clin Med* 1967; **70**: 442–51.
20 Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. *Hepatology* 2004; **39**: 280–2.
21 Hoeper MM, Maier R, Tongers J, *et al.* Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. *Am J Respir Crit Care Med* 1999; **160**: 535–41.
22 Merkel C. Nonselective beta-blockers plus nitrates in portal hypertension: an open question. *Hepatology* 2003; **37**: 1254–6.
23 Bosch J. A la carte or menu fixe: improving pharmacologic therapy of portal hypertension. *Hepatology* 2002; **36**: 1330–2.
24 Gluud LL, Klingenberg S, Nikolova D, Gluud C. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. *Am J Gastroenterol* 2007; **102**: 2842–8.
25 Garcia-Pagán JC, Navasa M, Bosch J, Bru C, Pizcueta P, Rodés J. Enhancement of portal pressure reduction by the association of isosorbide-5-mononitrate to propranolol administration in patients with cirrhosis. *Hepatology* 1990; **11**: 230–8.
26 Silva G, Segovia R, Ponce R, *et al.* Effects of 5-isosorbide mononitrate and propranolol on subclinical hepatic encephalopathy and renal function in patients with liver cirrhosis. *Hepatogastroenterology* 2002; **49**: 1357–62.
27 Gatta A, Sacerdoti D, Merkel C, Milani L, Battaglia G, Zuin R. Effects of nadolol treatment on renal and hepatic hemodynamics and function in cirrhotic patients with portal hypertension. *Am Heart J* 1984; **108**: 1167–72.
28 Bañares R, Moitinho E, Matilla A, *et al.* Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. *Hepatology* 2002; **36**: 1367–73.
29 González-Abraldes J, Albillos A, Bañares R, *et al.* Randomized comparison of long-term losartan versus propranolol in lowering portal pressure in cirrhosis. *Gastroenterology* 2001; **121**: 382–8.


© 2009 Blackwell Publishing Ltd