Portal hypertension is characterized by a rise in portal venous pressure and the formation of portosystemic collaterals, which divert the blood to the portosystemic circulation. The measure of free and wedged hepatic venous pressures and the gradient between these two pressures—the hepatic venous pressure gradient (HVPG)—is a method that appears to reflect portal pressure accurately and reliably. In normal individuals, HVPG varies from 1 to 5 mmHg. If HVPG is above these levels, then portal hypertension is considered to exist. Clinically significant portal hypertension is defined by HVPG above 12 mmHg. In patients with chronic liver disease, HVPG above 12 mmHg is related to the development of oesophageal varices, risk of variceal bleeding and development of ascites.

Measurement of HVPG is a common and indirect way of assessing the portal pressure gradient in cirrhotic patients with a predominantly sinusoidal site of resistance. Baseline and repeated measurement of HVPG have been recommended for the management of patients with cirrhosis in the setting of pharmacological prophylaxis of variceal bleeding.

It has been shown that prophylaxis with beta-blockers decreases the risk of first variceal bleeding in cirrhotic patients with portal hypertension and oesophageal varices at risk of bleeding. The addition of long-acting nitrates has been shown to enhance the efficacy of beta-blockers. Pharmacotherapy decreases the risk of variceal bleeding by half or three-fourths, but does not abolish the risk of bleeding totally. Therefore, it is important to distinguish between patients who will benefit from treatment and those who will not, and who may be eligible for addition of other prophylactic treatments such as endoscopic band ligation. Such a subgroup of patients should be identified and can be offered alternative treatments. It is useful to know the factors predicting clinical response or non-response to treatment so that non-responders can be identified and managed with other modes of treatment.

In earlier studies, non-selective beta-blocker dose was empirical (i.e., to the maximum tolerated by the patient or to the reduction of the resting pulse rate to 55/minute). In patients on drugs for prevention of variceal bleeding, it has been shown that a decrease in portal pressure expressed as a decrease in HVPG is a good predictor of clinical efficacy. Decrease in HVPG to 12 mmHg or less or decrease by at least 20% of baseline values is associated with minimal risk of variceal bleeding. The risk of variceal bleeding remains high in patients not meeting these haemodynamic end points after drug therapy. In a study by Groszmann et al, it was found that a decrease in HVPG to 12 mmHg or less is a good predictor of effective prophylaxis, but percentage variations do not define any useful cut-off value. The clinical value of this predictor was limited because the haemodynamic end point was reached in less than one-fourth of patients, whereas the other two-thirds were not bleeding. This prediction rule was sensitive but not specific in predicting failure of treatment. The prognostic value of a 20% decrease in HVPG from baseline value was not assessed in this study.
Acute variceal bleeding

It has been shown that early measurement of portal pressure can provide useful prognostic information in cirrhotic patients admitted because of acute variceal bleeding. Increase in portal pressure is directly related to the tension exerted on the walls of varices, which is considered to be the main determinant of both variceal rupture and the magnitude of bleeding. Such patients with higher portal pressure are likely to have severe haemorrhage when they are bleeding; also, their bleeding will be difficult to control with a greater tendency for early rebleeding. The risk factor for failure of medical and endoscopic treatment of acute variceal bleeding is HVPG.

Moitinho et al found that HVPG was the only variable associated with the outcome of variceal bleeding, thereby supporting the concept that degree of portal pressure increase plays a key role in determining the magnitude of bleeding, its response to emergency treatment and the likelihood of early rebleeding. It was found that patients with HVPG >20 mmHg had a significantly increased risk of failing first line treatment of acute variceal bleeding, continued bleeding, early rebleeding and high mortality. Patients with variceal bleeding who were found to have HVPG >20 mmHg had a 5.21-fold likelihood of emergency treatment not controlling their bleeding or presenting with early rebleeding. These patients also required significantly more blood transfusions, more days of stay in the ICU and hospital and showed higher mortality on follow-up. HVPG monitoring in patients with acute variceal bleeding may allow one to select high-risk patients who require close surveillance and probably a more aggressive therapeutic approach. Monescillo et al reported the results confirming that a HVPG >20 mmHg is associated with poor outcome and thus this may be used as a criterion for patients requiring ICU admission in hospital. Monescillo et al assessed accuracy of HVPG as a predictor of treatment failure in acute variceal bleeding. HVPG was measured in all patients within 24 hours of admission. Using a cut-off value of 20 mmHg, 64 patients had HVPG below this value and were placed into the low-risk category. The 52 patients with HVPG >20 mmHg were deemed high risk. Treatment failure was defined as either failure to control acute bleeding or rebleeding within 5 days of initial therapy. The primary end point of the study was an assessment of HVPG cut-off value of 20 mmHg as a predictor of treatment failure. The sensitivity of HVPG of 20 mmHg as a predictor of treatment failure was 62%, specificity 81%, positive predictive value 50% and negative predictive value 87%. Multivariate analysis revealed HVPG >20 mmHg and Child-Turcotte Pugh (CTP) score as two independent predictors of treatment failure. HVPG was a significantly better predictor of 6-week mortality than the CTP score. Early measurement of HVPG reliably predicts treatment failure and survival.

It has been argued that it is difficult to carry out emergency HVPG measurement; however, now it has been shown that HVPG measurement is a simple, safe and highly reproducible procedure that does not take more than 20 minutes to execute. Also it may guide on the use of HVPG monitoring to assess the effects of therapy. In patients admitted with acute variceal bleeding who are found to have HVPG >20 mmHg, reduction of HVPG below this threshold by vasoactive drugs may improve the outcome.

Secondary prophylaxis

Recurrent variceal bleeding is very frequent after variceal haemorrhage unless pharmacological or endoscopic therapy is used for secondary prevention. Recently, baseline and repeated measurement of HVPG have been considered necessary to optimally manage patients receiving pharmacological therapy so as to reduce the frequency of rebleeding by defining two targets: ≥20% reduction from baseline HVPG and an absolute reduction to ≤12 mmHg. Bureau et al reported the results of adapting medical therapy to monitor HVPG response in the prevention of variceal rebleeding in patients with cirrhosis. HVPG was measured before and after drug therapy was initiated. Patients were considered to be responders if HVPG decreased below 12 mmHg or by at least 20% as compared to baseline value. Of 14 patients treated to prevent rebleeding, two of the six responders bled as compared with seven of the eight non-responders, even though all non-responders were treated by variceal ligation. Therefore, it is important to note that HVPG response can be used to identify the patients who are not efficiently protected.

Long-term drug therapy is emerging as an effective treatment for the prevention of variceal rebleeding. The role of HVPG monitoring as a guide to identify patients requiring further treatment needs to be evaluated further. Trials to determine the best treatment for patients who do not respond to drug therapy are also required.
Longitudinal haemodynamic studies have shown that if HVPG is decreased below the threshold value, then patients will have a lower risk of variceal rebleeding (Table).

A randomized trial of endoscopic band ligation and drug therapy versus endoscopic band ligation alone reported a 23% risk of rebleeding within 2 years in the combination group. This result is not better than the results in responders to drug therapy as defined by HVPG and has the disadvantage of increasing the cost and complications of endoscopic therapy.

Assessment of HVPG response will provide strong prognostic information, since responders on HVPG criteria do better than non-responders. HVPG assessment should be done early as Patch et al have shown that the risk of rebleeding is especially high during the first 6 weeks after the index haemorrhage. Others recommend adding isosorbide mononitrate (ISMN) in all patients, thus obviating the need to assess HVPG response. This idea seems reasonable in high-risk situations such as the prevention of recurrent bleeding. The best treatment for a patient who does not respond to combination drug therapy is unknown. If drug therapy is continued, the risk of rebleeding will be high. With only endoscopic band ligation, the risk of rebleeding is also high, 88% at 2 years in this group of patients. The low rate of rebleeding with a combination of endoscopic band ligation and beta-blockers suggests that endoscopic band ligation with continuation of beta-blockers may be an useful approach.

Targownik et al compared the cost effectiveness of HVPG monitoring in the prevention of recurrent variceal bleeding and found that compared to endoscopic band ligation for the secondary prophylaxis of variceal rebleeding, combination medical therapy guided by HVPG monitoring was more effective and only marginally more expensive.

### Primary prophylaxis

Merkel et al assessed the role of haemodynamic response to beta-blockers or beta-blockers plus nitrates in predicting the clinical efficacy of prophylaxis in 49 cirrhotic patients with varices at risk of bleeding but without prior variceal bleeding. Hepatic vein catheterization was performed before and after 1–3 months of treatment with nadolol or nadolol plus ISMN. A total of 30 patients (61%) were good haemodynamic responders and among them, 12 (44%) had HVPG ≤ 12 mmHg, nine had variceal bleeding, seven were poor responders and two were good responders during treatment. The probability of bleeding at 3 years of follow-up was significantly higher in poor responders (41%) than in good responders (7%). The probability of variceal bleeding was also higher in patients who had HVPG during treatment higher than 12 mmHg (9/37, 3-year risk of 28%) than in those who reached the threshold value of 12 mmHg (0/12). None of the patients reaching HVPG of 12 mmHg or less during treatment had variceal bleeding during follow-up. It was also found that, similar to the condition of prevention of rebleeding, a decrease in HVPG by 20% or more was also a strong predictor of success of prophylaxis. Sensitivity in predicting bleeding was 78% (7/9) and specificity was 70% (28/40). No difference in variceal bleeding was observed in relation to the initial value of HVPG. Poor haemodynamic response was found to be the main factor predicting bleeding. It was found that assessment of haemodynamic response to drugs in terms of HVPG is the best predictor of efficacy of prophylaxis of variceal bleeding in patients treated with beta-blockers or beta-blockers plus nitrates. The clinical value of HVPG changes remained stable also when other confounding factors such as size of varices, presence of red

#### Table. Risk of variceal rebleeding in responders versus non-responders on drug therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Drug</th>
<th>Non-responders (%)</th>
<th>Rebleeding rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Responders Non-responders</td>
<td></td>
</tr>
<tr>
<td>Feu et al⁸</td>
<td>69</td>
<td>Propranolol</td>
<td>64</td>
<td>8</td>
</tr>
<tr>
<td>Escorsell et al⁹</td>
<td>47</td>
<td>Propranolol</td>
<td>62</td>
<td>6</td>
</tr>
<tr>
<td>Villanueva et al¹⁰</td>
<td>31</td>
<td>Nadolol + ISMN</td>
<td>55</td>
<td>7</td>
</tr>
<tr>
<td>Bureau et al⁷</td>
<td>34</td>
<td>Nadolol + ISMN</td>
<td>49</td>
<td>16</td>
</tr>
<tr>
<td>Patch et al¹²</td>
<td>26</td>
<td>Propranolol + ISMN</td>
<td>45–63</td>
<td>7–13</td>
</tr>
</tbody>
</table>

ISMN = isosorbide mononitrate.
weal marks or North Italian Endoscopic Club (NIEC) index were taken into consideration. It was found that in the prediction of effectiveness of treatment, the haemodynamic response is much more useful than the initial size of varices and the presence of red weal marks. According to this study, it appears that good responders are at a negligible risk of bleeding (2/30, 6.6%), whereas poor responders have a rather high risk (7/29, 25%), which is similar to that expected in untreated patients. This difference appears more relevant if one considers that the two good responders who bled had precipitating factors that probably contributed to bleeding, such as the need to withdraw treatment due to side effects or the occurrence of portal vein thrombosis.

Bureau et al reported results of adapting medical therapy to the monitoring of haemodynamic response in the prevention of first variceal bleeding in patients with cirrhosis.7 HVPG was measured before and after 8.8 ± 12.1 days (median 4, range 1–60) of propranolol being initiated. Patients were considered to be responders if HVPG decreased below 12 mmHg or by at least 20% as compared to the baseline value. If patients were not responders, ISMN was added and a third haemodynamic study was performed after 17.1 ± 12.6 days (median 15.5, range 3–47) of initiation of ISMN. Thereafter, patients were followed up for a mean of 28.1 ± 18.8 months (median 24, range 1–96). Of 20 patients treated for the prevention of first variceal bleed, 14 (70%) were responders, 10 (50%) to propranolol alone and 4 (20%) to the combination of propranolol and ISMN. None of the responders had variceal bleeding during the follow-up period whereas 2/6 non-responders (10% of total and 33.3% of non-responders) experienced variceal bleeding. Post-treatment HVPG was significantly greater in patients who bled than in those who did not bleed (21 ± 0 mmHg vs. 13.5 ± 4.8 mmHg). Using multivariate analysis, only haemodynamic response was found to have an independent predictive value for the risk of variceal bleeding. Bureau et al concluded that haemodynamic response to drug therapy identifies patients who are efficiently protected from variceal bleeding as well as non-responders in whom an alternative treatment should be considered.7

In a study by Escorsell et al, it was shown that HVPG response closely correlated with the risk of variceal bleeding on follow-up.9 Reducing HVPG by 20% or more was associated with a very low risk of bleeding, only 7% at 3 years of follow-up and 0% when final HVPG was less than 12 mmHg. In contrast, the risk of variceal bleeding was 56% in HVPG non-responders. Achieving 20% reduction in HVPG was highly sensitive (85%) and specific (97%) in identifying patients who did not bleed during follow-up. These results have led to the recommendation of assessing portal pressure response whenever possible in high-risk patients.

The data on using HVPG measurements during primary prophylaxis are quite consistent. If patients achieve a haemodynamic response to pharmacological therapy, their risk of bleeding during the next 2–3 years falls to about 5%. If HVPG falls to ≤ 12 mmHg (about one-third of patients), then the risk of bleeding is close to zero. In contrast, in those who fail to respond, the risk of bleeding is 30–40% over the same period of time. About 40–55% of patients achieve a haemodynamic response with beta-blockers alone and another 20–30% with the addition of nitrates.

In the setting of primary prophylaxis of variceal bleeding, HVPG measurements in principle could change management in two ways: (i) addition of a second drug, and (ii) the use of endoscopic variceal band ligation.15 Merkel et al have shown that the cumulative risk of bleeding was decreased from 29% in those receiving nadolol alone to 12% in those who received the combination of nadolol and ISMN.16 This data suggest that HVPG can guide the decision to add nitrates to the pharmacological treatment of portal hypertension. Combination therapy with beta-blockers and nitrates should be restricted to patients selected on the basis of failure to respond to beta-blockers. HVPG measurement may be used to guide the selection. The second way in which management strategy could be influenced by HVPG measurement concerns the use of endoscopic variceal band ligation. Several studies have shown that band ligation is superior to no treatment for primary prophylaxis of variceal bleeding and one has found it superior to beta-blockers.9,15 HVPG measurement can identify the subgroup of patients who do not meet the haemodynamic criteria for success with beta-blockers or beta-blockers plus ISMN therapy and who might, therefore, benefit from band ligation.

**Non-bleeding complications**

The complications of cirrhosis, such as ascites, hepatorenal syndrome or hepatic encephalopathy, are also related to portal hypertension. There is very little data on the assessment of long-term maintenance of haemodynamic
response to the pharmacological treatment of portal hypertension and the influence of such a response on complications of cirrhosis other than variceal bleeding. An increase in the portal pressure gradient to a threshold of above 10–12 mmHg has also been established for the development of ascites. When reduction below this target is not achieved, a substantial decrease in portal pressure (<20% from the baseline value) also has a great impact on the development of ascites and other complications. Villanueva et al reported that haemodynamic responders have lower incidence of rebleeding from oesophageal varices and lower treatment failures.17 The probability of developing or worsening of ascites was significantly lower in responders than in poor responders. During follow-up, hepatorenal syndrome and spontaneous bacterial peritonitis developed more often in poor responders. The likelihood of developing at least one episode of hepatic encephalopathy during follow-up was lower in responders. Among patients without previous episodes, encephalopathy occurred more frequently in poor responders. On follow-up, the improvement in CTP score was greater in responders and the possibility of requiring orthotopic follow-up, the improvement in CTP score was greater in responders than in poor responders. During follow-up, hepatorenal syndrome and spontaneous bacterial peritonitis developed more often in poor responders. The likelihood of developing at least one episode of hepatic encephalopathy during follow-up was lower in responders. Among patients without previous episodes, encephalopathy occurred more frequently in poor responders. On follow-up, the improvement in CTP score was greater in responders and the possibility of requiring orthotopic liver transplantation was lower in responders. The likelihood of survival was also higher in responders. In another study, Abraldes et al evaluated whether achieving haemodynamic responders prevent complications of portal hypertension and improves long-term survival.18 Over an 8-year follow-up, it was found that non-responders had a significantly higher risk of developing variceal rebleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome and hepatic encephalopathy than responders. On multivariate analysis, being a non-responder was independently associated with the risk of developing rebleeding, ascites, spontaneous bacterial peritonitis and lower survival.

Haemodynamic studies are usually considered invasive. However, in a sample of 1,000 patients with liver disease undergoing transjugular liver biopsy, it was reported that complications were related to liver biopsy itself and not to the catheterization of hepatic veins.7

There is an issue of ideal timing of the control of haemodynamic response to treatment: too early and the number of responders will be underestimated; too late and patients who have experienced bleeding episodes will be excluded. The interval between two haemodynamic measurements should be shortened as much as possible to permit assessment of all patients and to avoid the problem of bleeding in patients before the second haemodynamic assessment. Merkel et al suggested 1 month to be the optimal time interval between two haemodynamic assessments.2

However, the key issue is whether target reduction of portal pressure, which involves a baseline and a repeated HVPG measurement, is necessary in routine clinical practice. It significantly adds to the cost of pharmacotherapy, is not universally available and several issues regarding its use are still not clear.19,20 Unrecognized notable heterogeneity has been demonstrated in intrahepatic vasculature and HVPG measurements in cirrhosis. The presumption of interposition of non-flowing blood between the catheter tip and the portal system for the measurement of HVPG may be violated in about one-third of cirrhotic cases because of abnormal outlet into hepatic venous shunts and in a minor fraction because of abnormal arterial inlet.21 Sixty percent of cirrhosis patients have shown larger intrahepatic variations among HVPG measurements performed in separate hepatic veins that could be attributed to technical and physiological variations.21 Also, there are some problems with the interpretation of data on HVPG monitoring, clinical validity and applicability, which make its use controversial. The cumulative data raise a question: should HVPG measurement be used routinely to follow patients receiving pharmacological treatment for primary prophylaxis? Invasive intervention should be performed only if the data obtained substantially affect management strategy. The cost-effectiveness of measuring HVPG response to medical treatment in patients undergoing primary prophylaxis has been questioned. The cost can easily be evaluated but the effectiveness is related to the efficacy of alternative treatment in patients classified as poor responders. HVPG measurement to guide primary prophylaxis has been found to be an expensive strategy for reducing variceal bleeding or death, especially in patients with limited life expectancy such as advanced decompensated cirrhosis.22

Identifying the effective dose of beta-blockers for each patient by assessing the haemodynamic response “step by step” would require too many measurements and is incompatible with clinical practice. Also, in primary prevention, the low bleeding rate (≤20%) and the protection offered by non-selective beta-blockers do not justify HVPG monitoring, particularly with invasive procedure. Moreover, the cost-effectiveness of this approach has been questioned.22

HVPG measurement is safe and relatively simple. The information obtained may be predictive for the occurrence
of first variceal bleeding and can potentially help in determining whether pharmacological therapy is effective or not.\textsuperscript{17} We need a safe and accurate noninvasive method for the measurement of portal pressure. Until that goal is achieved, HVPG measurement remains the only way to assess responses to pharmacological therapy and to develop a tailored approach to prevent variceal bleeding in patients with portal hypertension.

The question that arises is, to what extent is the better outcome of responders due to reduction in portal pressure, and does the lack of response reflect more advanced liver disease? It has been found that lack of response is indeed a major determinant of worse prognosis seen in non-responders as compared with responders. On multivariate analysis, lack of haemodynamic response has been found to be an independent predictor of worse outcome in terms of rebleeding, development of ascites, spontaneous bacterial peritonitis and survival. However, multivariate analysis has selected other additional variables influencing prognosis. These variables are albumin, bilirubin and prothrombin ratio, which are clearly related to the degree of liver failure. Therefore, both severity of liver disease and HVPG response are major independent determinants of prognosis in patients with advanced liver disease receiving pharmacological therapy for portal hypertension.

For primary prophylaxis of variceal bleeding, drug therapy is initiated with oral propranolol twice a day. Adjustment of the dose is done by stepwise increases, carefully looking at clinical tolerance, heart rate and arterial blood pressure. The dose is increased every 2 days until the heart rate decreases by 25% of the baseline value but not below 55 beats/minute. Other methods to assess the response to drugs have been investigated, namely Doppler ultrasonography, direct variceal pressure measurement, variceal pressure measurement using pressure gauge, plethysmography and serum catecholamine levels. Doppler ultrasonography has unequivocally been shown to be unreliable. Doppler ultrasound as a noninvasive standard has not been substantiated by prospective studies and has limitations due to its relatively large variability and observer dependency. The studies assessing accuracy of Doppler ultrasonography in predicting HVPG response to use of beta-blockers alone or associated with ISMN show discouraging results. Variceal pressure measurement by venous puncture through endoscopy is actually an invasive technique and it must be followed by variceal sclerotherapy or ligation; therefore, it is not a suitable technique for repeated measurements. A gauge to measure variceal pressure has been designed but is available in only very few centres and can only be used with large varices and should be considered as an experimental procedure.

Escorsell et al showed that the measurement of variceal pressure using pressure gauge during diagnostic endoscopy represents a noninvasive method to predict clinical response to drug therapy for patients with portal hypertension.\textsuperscript{9} A fall in variceal pressure of more than 20% from the baseline value was associated with very low risk of variceal bleeding on follow-up. After achieving such a response, the actual probability of variceal bleeding was only 7% at 3 years, whereas it was 46% in patients failing to achieve this target, despite receiving the same therapy. The predictive value of 20% or more decrease in variceal pressure is likely to be related to the fact that it determines a marked fall in variceal wall tension, which is a major determinant of bleeding. It was shown that variceal pressure and HVPG response to drug therapy were the only independent predictors of variceal bleeding on follow-up. Measurement of variceal pressure response and HVPG response is complementary because some variceal pressure responders are not HVPG responders and vice versa. This can be due to variability of variceal pressure measurement and reflection of slightly different haemodynamic events by these measurements. It has been shown that in some patients, propranolol causes a more pronounced decrease in gastroesophageal collateral blood flow and variceal pressure than in hepatic blood flow and HVPG.

**Recommendations**

1. In patients with cirrhotic liver without prior variceal bleeding with oesophageal varices at high risk of bleeding (large oesophageal varices [grade III or IV], presence of red colour signs on varices), if beta-blocker therapy is contemplated, HVPG measurement is recommended.
2. After HVPG measurement, beta-blocker (propranolol) is started as 20 mg twice a day and a stepwise increase in dose is made every 2 days until a maximum tolerated dose is reached or the reduction in heart rate to 55 beats/minute is achieved.
3. HVPG measurement is to be repeated 1 month after achieving adequate beta-blockage.
4. Assessment of response: HVPG decrease ≤ 12 mmHg or decrease by at least 20% of baseline value.
   (a) Responder (yes): continue same dose of beta-blockers.
   (b) Non-responder (no): add ISMN.
5. In patients non-responsive to beta-blockers and receiving a combination of beta-blockers and ISMN, repeat HVPG measurement is recommended 1 month after addition of ISMN.
6. Assessment of response: HVPG decrease ≤ 12 mmHg or decrease by at least 20% of baseline value.
   (a) Responder (yes): continue the combination of beta-blockers and ISMN in the same doses.
   (b) Non-responder (no): recommendations are:
      - In clinical practice: endoscopic band ligation of oesophageal varices for primary prophylaxis.
      - In research protocols: addition of other drugs such as carvedilol or prazosin and repeat HVPG measurement 1 month after addition of the new drugs.

References