

Special report

Evolving Consensus in Portal Hypertension Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension

Roberto de Franchis^{*,†}

*Gastroenterology and Gastrointestinal Endoscopy Service, Department of Internal Medicine, University of Milan,
IRCCS Ospedale Maggiore Policlinico, Via Pace 9, 20122 Milan, Italy*

Portal hypertension is the haemodynamic abnormality associated with the most severe complications of cirrhosis, including ascites, hepatic encephalopathy and bleeding from gastroesophageal varices. Variceal bleeding is a medical emergency associated with a mortality that, in spite of recent progress, is still in the order of 20% at 6 weeks. The evaluation of diagnostic tools and the design and conduct of good clinical trials for the treatment of portal hypertension have always been difficult. Awareness of these difficulties has led to the organisation of a series of meetings aimed at reaching consensus on the definitions of some key events related to portal hypertension and variceal bleeding, and at producing guidelines for the management of patients and for the conduct of trials in this field. Such meetings took place in Groningen, the Netherlands in 1986 [1], in Baveno, Italy in 1990 (Baveno I) [2] and in 1995 (Baveno II) [3,4], in Milan, Italy in 1992 [5], in Reston, USA [6], in 1996 and in Stresa, Italy, in 2000 (Baveno III) [7,8]. All these meetings were successful and produced consensus statements on some important points, although several issues remained unsettled.

To continue the work of the previous meetings, a Baveno IV workshop was held on April 28–29, 2005. The workshop was attended by many of the experts responsible for most of the major achievements of the last years in this field. The majority of them had attended the Groningen, Baveno I, Baveno II, Reston and Baveno III meetings as well.

The main fields of discussion of the Baveno IV workshop were the same as in Baveno I–III, i.e. the definitions of key

events concerning the bleeding episode, the therapeutic options in patients with portal hypertension, and the methodological requirements for future studies in this field. For each of these topics, a series of consensus statements were discussed and agreed upon. Whenever applicable, the level of existing evidence was evaluated and the recommendations were ranked according to the Oxford System [9] (i.e. level of evidence from 1 = highest to 5 = lowest; grade of recommendation from A = strongest to D = weakest). The presentations given during the workshop are reported 'in extenso' in the Baveno IV proceedings [10]. A summary of the most important conclusions is reported here.

1. Definition of key events regarding the bleeding episode

Definitions and criteria to evaluate failure to control bleeding and failure to prevent rebleeding were introduced at Baveno II [3,4] and reviewed at Baveno III [7,8]. Since then, these definitions and criteria have been extensively applied in trials; it has been found that some of them are rather difficult to apply and do not reflect adequately the situation in clinical practice; therefore, new definitions and criteria were proposed at Baveno IV. Given the lack of validated parameters to define failure, these new criteria are necessarily arbitrary (level of evidence 5; grade of recommendation D) [9], and must be validated in future studies, in particular as surrogate markers of outcome. It is proposed that current and future studies should incorporate both Baveno II–III and Baveno IV criteria, and evaluate failure to control bleeding using both sets of criteria. A judgment of the validity of the new criteria will be possible only after their extensive application in such studies.

* Tel.: +39 02 5503 5331/2; fax: +39 02 5032 0747.

E-mail address: roberto.defranchis@unimi.it (R. de Franchis).

† On behalf of the Baveno IV Chairpersons and panellists.

The Baveno II–III and the Baveno IV definitions and criteria are reported below.

1.1. Baveno II–III definitions and criteria for failure to control bleeding

The definition of failure to control bleeding is divided into two time frames:

- (1) Within 6 h: any of the following factors: (a) transfusion of 4 units of blood or more, and (b) inability to achieve an increase in systolic blood pressure of 20 mmHg or to 70 mmHg or more, and/or (c) a pulse reduction to less than 100/min or a reduction of 20/min from baseline pulse rate.
- (2) After 6 h: any of the following factors: (a) the occurrence of hematemesis, (b) reduction in blood pressure of more than 20 mmHg from the 6-h point, and/or (c) increase of pulse rate of more than 20/min from the 6-h point on two consecutive readings 1 h apart, (d) transfusion of 2 units of blood or more (over and above the previous transfusions) required to increase the Hct to above 27% or Hb to above 9 g/dL.

1.2. Baveno IV definitions and criteria for failure to control bleeding

- (1) The time frame for the acute bleeding episode should be 120 h (5 days)
- (2) Failure signifies need to change therapy: one criterion defines failure, whichever occurs first:
 - (a) Fresh hematemesis ≥ 2 h after start of specific drug treatment or therapeutic endoscopy. In the minority of patients who have a naso-gastric tube in place, aspiration of greater than 100 mL of fresh blood represents failure
 - (b) 3 g drop in Hb ($\approx 9\%$ drop in Ht) if no transfusion is administered
 - (c) Death
 - (d) Adjusted blood transfusion requirement index (ABRI, see below) ≥ 0.75 at any time point. (The threshold of ABRI defining failure requires validation).

Adjusted blood requirement index (ABRI)

$$\text{ABRI} = \frac{\text{Blood units transfused}}{[(\text{final Ht} - \text{initial Ht}) + 0.01]}$$

- Ht (or Hb) is measured at least every:
 - 6 h for the first 2 days
 - 12 h for days 3–5
- The transfusion target should be an haematocrit of 24% or a haemoglobin of 8 g/dL

1.3. Notes for the Baveno IV definitions and criteria

For the purposes of analysis the following criteria should be adopted:

- Time to failure—first occurrence of any of the above criteria for failure (cumulative hazard plots and Cox regression analysis)
- Failure occurring at 120 h is considered as YES or NO
- The use of both time to failure and final evaluation at 120 h is encouraged
- All specific therapeutic procedures should be documented with time points
- Intention to use further specific therapy should be documented even if not used
- Transfusion requirements should be recorded as a function of time for the whole interval of acute bleeding if no failure has occurred, e.g. units transfused/120 h or units transfused up to time of failure.

1.4. Baveno II–III definitions and criteria for failure of secondary prophylaxis

Failure to prevent rebleeding is defined as a single episode of clinically significant rebleeding from portal hypertensive sources

Clinically significant rebleeding:

- (a) transfusion requirement of 2 units of blood or more within 24 h of time zero (the time of admission of a patient to the first hospital he is taken to [2])
- (b) together with a systolic blood pressure < 100 mmHg or
- (c) a postural change of > 20 mmHg and/or
- (d) pulse rate > 100 /min at time zero.

1.5. Baveno IV definitions and criteria for failure of secondary prophylaxis

Failure to prevent rebleeding is defined as a single episode of clinically significant rebleeding from portal hypertensive sources

Clinically significant rebleeding:

- (a) Hematemesis/melaena. In the minority of patients who have a naso-gastric tube in place, aspiration of greater than 100 mL of fresh blood represents failure plus
- (b) Adjusted Blood Requirement Index (ABRI) ≥ 0.5 (The threshold of ABRI defining failure requires validation) or
- (c) Decrease 3 g of Hb if no transfusion is given

2. Predictive models for portal hypertension

Because of the growing importance of prognostic models in hepatology, and particularly in portal hypertension, a session devoted to this topic was introduced in Baveno IV,

to replace the session that was dedicated to the diagnosis of portal hypertension in Baveno III.

Status classification of cirrhosis

- Varices, ascites and bleeding in patients with cirrhosis identify four clinical statuses of increasing severity: stage 1: no varices, no ascites; stage 2: varices, no ascites; stage 3: ascites \pm varices; stage 4: bleeding \pm ascites [11]
- The outcome of a clinical status is transition to another status, death or OLT. Prognostic models specific to each clinical status should be developed

Indicators of varices, and predictors of their development

- There are no satisfactory non-endoscopic indicators of the presence of varices
- While further studies are awaited, endoscopic screening is still the best practice to detect varices
- The hepatic vein pressure gradient (HVPG) is presently the most reliable predictor of variceal development

Outcome prediction in compensated patients

- In compensated patients the development of ascites and portal hypertensive bleeding are the most relevant outcomes
- HVPG is the only known predictor of the development of ascites; other potential predictors should be investigated
- The NIEC score is presently the most reliable predictor of variceal rupture; the contribution of HVPG and other predictors should be investigated

Outcome prediction in decompensated patients

- Child-Pugh and MELD predict overall mortality
- The additional role of HVPG and other potential predictors (sodium, spontaneous bacterial peritonitis, hepatorenal syndrome, others) should be assessed

3. Therapeutic options in patients with portal hypertension

3.1. Pre-primary prophylaxis (prevention of the formation/growth of varices)

Background

- Prevention of the development of complications of portal hypertension is clearly an important area for future research.
- Portal-systemic collaterals may develop before the appearance of varices, and can be diagnosed non-invasively. However, their clinical importance is uncertain (5;D).

- HVPG is predictive of varices formation (1b;A).

Recommendations for management

- All cirrhotic patients should be screened for varices at diagnosis (5;D).
- Despite some pharmaco-economical analysis, it is not indicated to treat cirrhotic patients with beta-blockers without prior assessment of the presence of esophageal varices (5;D).
- There is no indication, at this time, to treat patients to prevent the formation of varices (1b;A).

Areas requiring further study

- Basic mechanisms in the development and progression of portal hypertension
- Natural history of low-risk varices (epidemiology and predictive factors of progression)
- Routine use of HVPG in clinical trials involved in investigating the complications of portal hypertension
- Treatment to decrease or prevent the progression and/or prevent the development of varices
- Biliary atresia (a very interesting entity of pediatric portal hypertension with rapid rate of progression).

Non-invasive tests

- Non-invasive tests might be useful to identify patients at risk of having or prone to develop varices (HVPG > 12 mmHg), but prospective studies are required (4;C).

3.2. Prevention of the first bleeding episode

Patients with small varices

- Patients with small varices could be treated with non-selective beta-blockers to prevent progression of varices and bleeding, but further studies, especially as relates to prevention of bleeding, are required before a formal recommendation on their use can be made (5;D).
- Patients with small varices with red wale signs or of Child C class have an increased risk of bleeding and may benefit from treatment (5;D).

Pharmacological treatments

- Non-selective beta-blockers reduce the risk of first variceal bleeding in patients with medium and large oesophageal varices (1a;A).
- Isosorbide mononitrate administered alone must not be used (1a;A).
- There is not enough data to recommend the use of the combination of beta-blockers plus ISMN or

spironolactone plus beta-blockers for primary prophylaxis (1b;A) [9].

- Other pharmacological agents able to reduce portal pressure must be adequately tested before their clinical use (5;D).

Use of HVPG measurements

- HVPG monitoring identifies patients with cirrhosis who will benefit from non-selective beta-blocker therapy in primary prophylaxis (1b;A).
- ‘a la carte’ treatment using HVPG response in primary prophylaxis needs to be evaluated, especially in high-risk patients. Until then, routine use of HVPG cannot be recommended (5;D).

Endoscopic treatment

- Prophylactic endoscopic band ligation (EBL) is useful in preventing variceal bleeding in patients with medium and large esophageal varices (1a;A).
- EBL is more effective than non-selective beta blockers in preventing first variceal bleeding but does not improve survival. However, the long-term benefits of EBL are uncertain because of the short duration of follow-up (1a;A).
- EBL should be offered to patients with medium/large varices and contraindications or intolerance to beta-blockers (5;D).

Gastric varices

- In the absence of specific data on prophylactic studies, RCTs should be performed in patients with gastric varices.

Cost-effectiveness analysis

- Markov models are not a substitute for well designed clinical trials. However, well-designed Markov models are complementary to clinical studies and should be pursued for exploratory purposes and to establish the cost-effectiveness of various strategies. Markov models may fill in a void where clinical trials are simply not feasible.

Areas requiring further study (5;D)

- Comparison of EBL and beta-blockers with respect to cost-effectiveness and quality of life to determine the treatment of choice.
- Studies to clarify whether the use of EBL + beta-blockers is better than each treatment alone.

3.3. Treatment of acute bleeding from varices

Blood volume restitution

- Blood volume restitution should be done cautiously and conservatively, using plasma expanders to maintain

haemodynamic stability and PRBC to maintain the haemoglobin at approximately 8 g/dL, depending on other factors such as patients co-morbidities, age, haemodynamic status, and presence of ongoing bleeding clinically (1b;A).

- Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data (5;D).

Use of antibiotics for preventing bacterial infections/spontaneous bacterial peritonitis

- Antibiotic prophylaxis is an integral part of therapy for patients presenting with variceal bleeding and should be instituted from admission (1a;A).

Prevention of hepatic encephalopathy

- In patients who present or develop encephalopathy, this should be treated with lactulose/lactitol or other drugs (5;D).
- There are no studies evaluating the usefulness of lactulose/lactitol for the prevention of hepatic encephalopathy (5;D).

Assessment of prognosis

- No adequate prognostic model has been developed to predict outcomes (2b;B).
- No individual characteristic sufficiently predicts prognosis (2b;B).
- Child-Pugh class, active bleeding at endoscopy, HVPG, infection, renal failure, severity of initial bleeding, presence of portal vein thrombosis or of HCC, and ALT have been identified as indicators of poor prognosis (2b;B).

Timing of endoscopy

- Endoscopy should be performed as soon as possible after admission (within 12 h), especially in patients with clinically significant bleeding or in patients with features suggesting cirrhosis (5;D).

Use of balloon tamponade

- Balloon tamponade should only be used in massive bleeding as a temporary ‘bridge’ until definitive treatment can be instituted. (For a maximum of 24 h, preferably in an intensive care facility) (5;D).

Pharmacological treatment

- In suspected variceal bleeding, vasoactive drugs should be started as soon as possible—before diagnostic endoscopy (1b;A),

- Vasoactive drug therapy (terlipressin, somatostatin, vapreotide, octreotide) should be maintained in patients with oesophageal variceal bleeding for 2–5 days (1a;A).

Endoscopic treatment

- Endoscopic therapy is recommended in any patient who presents with documented upper GI bleeding and in whom esophageal varices are the cause of bleeding (1a;A).
- Ligation is the recommended form of endoscopic therapy for acute esophageal variceal bleeding although sclerotherapy may be used in the acute setting if ligation is technically difficult (1b;A).
- Endoscopic therapy with tissue adhesive (e.g. *N*-butyl-cyanoacrylate) is recommended for acute gastric variceal bleeding (1b;A).
- Endoscopic treatments are best used in association with pharmacological therapy, which preferably should be started before endoscopy (1a;A).

Management of treatment failures

- Failures of initial therapy with combined pharmacological and endoscopic therapy are best managed by a second attempt at endoscopic therapy or TIPS (preferably with PTFE covered stents) (2b;B).

Areas requiring further study (5;D)

- Optimal duration of vasoactive drug therapy,
- Effectiveness of early TIPS placement and of covered stents,
- Best treatment for gastric varices (especially glue vs. TIPS),
- The potential of rFVIIa,
- The best treatment of patients with no active bleeding at time of endoscopy on drug therapy,
- Prognostic factors/models for acute bleeding (MELD score, variceal size, age, etiology of portal hypertension and other comorbidities).

3.4. Prevention of rebleeding

Time to start secondary prophylaxis

- Secondary prophylaxis should start as soon as possible from day 6 of the index variceal bleeding episode (5;D).
- The start time of secondary prophylaxis should be documented.

Patients with cirrhosis who have not received primary prophylaxis

- Beta blockers (1a;A), band ligation (1a;A) or both (1b;A) should be used for prevention of recurrent bleeding.

- Combination of beta blockers and band ligation is probably the best treatment (1b;A) but more trials are needed.
- Assessment of haemodynamic response to drug therapy provides prognostic information about rebleeding risk (2b;B).

Patients with cirrhosis who are on beta blockers for primary prevention and bleed

- Band ligation should be added (5;D).

Patients who have contraindications or intolerance to beta blockers

- Band ligation is the preferred treatment for prevention of rebleeding (5;D).

Patients who fail endoscopic and pharmacological treatment for prevention of rebleeding

- TIPS or surgical shunts (distal splenorenal shunt or 8 mm H-graft) are effective for those with Child class A/B cirrhosis and should be used (2b;B).
- In non-surgical candidates, TIPS is the only option (5;D).
- Transplantation provides good long-term outcomes in Child class B/C cirrhosis and should be considered (2b;B). TIPS may be used as a bridge to transplantation (4;C).

Patients who have bled from isolated gastric varices, type 1 (IGV1) [12] or gastro-oesophageal varices, type 2 [12] (GOV 2)

- *N*-butyl-cyanoacrylate (1b;A), TIPS (2b;B) or beta blockers (2b;B) are recommended.

Patients who have bled from gastro-oesophageal varices, type 1 (GOV 1)

- May be treated with *N*-butyl-cyanoacrylate, band ligation of oesophageal varices or beta blockers (2b;B).

Patients who have bled from portal hypertensive gastropathy

- Beta blockers (1b;A) should be used for prevention of recurrent bleeding.

Patients in whom beta blockers are contraindicated or fail and who cannot be managed by non-shunt therapy

- TIPS (4;C) or surgical shunts (4;C) should be considered.

Areas requiring further study (5;D)

- Combination of beta blockers plus nitrates.
- Use of HVPG monitoring for decision making and its effect on patients' outcome.

4. Non-cirrhotic portal hypertension

A session devoted to non-cirrhotic portal hypertension was introduced at Baveno IV, in view of the increasing recognition and growing interest of this clinical entity. Due to time constraints, the discussion was limited to the Budd-Chiari syndrome [BCS—hepatic venous outflow tract obstruction (HVOTO)] and to extra-hepatic portal vein obstruction (EHPVO).

This session replaced the session that in Baveno III was devoted to portal hypertensive gastropathy and gastric varices.

4.1. Budd-Chiari syndrome [BCS—hepatic venous outflow tract obstruction (HVOTO)]

Definition

- Budd-Chiari syndrome (BCS) is an eponym for hepatic venous outflow tract obstruction (HVOTO) which can be located from the level of the small hepatic veins to the level of the termination of inferior vena cava into the right atrium.
- BCS is a heterogeneous condition with regard to causes and pathogenesis.
- BCS is considered secondary when the mechanism for HVOTO is compression/invasion by a benign or malignant tumor, abscess or cyst.
- BCS is considered primary otherwise.
- Hepatic congestion secondary to heart failure and pericardial disease are excluded from the definition of BCS.
- Obstruction confined to small hepatic veins or sinusoids in the context of liver irradiation, chemotherapy, stem cell transplantation or exposure to toxic agents is excluded from the definition of BCS.
- The terms veno-occlusive disease and sinusoidal obstruction syndrome require further definition.

Etiology

- Primary BCS is frequently associated with one or several risk factors for thrombosis. These underlying disorders are often occult at presentation with BCS.
- Myeloproliferative disorders should be investigated in any patient with BCS, irrespective of the peripheral blood picture.
- When liver synthetic function is impaired, low plasma levels of antithrombin, protein C, and protein S are not specific for an inherited defect.

Diagnosis

- BCS is diagnosed by the demonstration of an obstruction of the venous lumen, or by the presence of hepatic vein collaterals.

- Liver biopsy is not necessary to make a diagnosis of BCS when vascular imaging has demonstrated obstruction of the hepatic venous outflow tract.
- Liver biopsy is the only means to make a diagnosis of BCS of the small intrahepatic veins.
- Clinical trials for therapy of BCS have not been performed so that current therapy is based on less rigorous information.

Treatment

On the basis of current expert opinion (5;D)

- Anticoagulation should be recommended to all patients, in the absence of major contra-indications. However, there is no consensus on the optimal duration of anticoagulation.
- Previous bleeding related to portal hypertension is not considered a major contra-indication for anticoagulation, provided appropriate prophylaxis for recurrent bleeding is initiated.
- Complications of portal hypertension may be treated as recommended for the other types of liver diseases.
- Stenoses that are amenable to percutaneous angioplasty/stenting should be actively looked for, and treated accordingly.
- TIPS insertion should be attempted when angioplasty/stenting is not feasible, and when the patient does not improve on medical therapy.
- Liver transplantation should be considered in patients with manifestations refractory to the above procedures.

Areas requiring further studies (5;D)

- Accurate diagnostic tests for myeloproliferative disorder and antiphospholipid syndrome.
- Benefit and risk of prolonged anticoagulation therapy.
- Benefit and risk of pharmacological therapy for portal hypertension.
- Optimal timing of angioplasty and TIPS with respect to severity of symptoms.
- Indications for thrombolysis.

4.2. Extra-hepatic portal vein obstruction (EHPVO) [13]

Definition

- EHPVO is defined by obstruction of the extra-hepatic portal vein with or without involvement of the intra-hepatic portal veins.
- EHPVO often manifests as portal cavernoma, which is a network of porto–porto collaterals and develops as a sequel of portal vein obstruction.
- Isolated thrombosis of the splenic vein or superior mesenteric vein with patent portal vein is excluded.
- The definition should be augmented by a statement of presence or absence of cirrhosis and neoplasia.

Etiology

- EHPVO is a heterogeneous entity with regards to causes and pathogenesis, particularly between children and adults.
- EHPVO in adults is frequently associated with one or several risk factors for thrombosis which may be occult at presentation.
- Presence of cirrhosis, neoplasia and other intra-abdominal causes such as inflammation, trauma, etc. do not exclude the presence of systemic risk factors.

Clinical presentation

- EHPVO can be acute or chronic.
- EHPVO can be assumed to be recent when patients present with symptoms such as abdominal pain, ascites, fever or symptoms suggestive for intestinal ischaemia, in the absence of portal cavernoma and porto-systemic collaterals.
- Chronic EHPVO is associated with portal cavernoma and may present with variceal bleed, splenomegaly, abnormal blood cell counts and occasionally jaundice. A proportion of children have growth retardation.

Diagnosis

- EHPVO is diagnosed by imaging techniques like Doppler US, CT or MRI which demonstrate portal vein obstruction, presence of intraluminal material or portal vein cavernoma.

Natural history

- Most patients with EHPVO in the absence of cirrhosis and neoplasia have a relatively benign course.
- Morbidity is mainly related to variceal bleed, recurrent thrombosis, symptomatic portal biliopathy and hypersplenism.
- The natural course of EHPVO is mainly determined by the presence or absence of associated diseases such as cirrhosis or neoplasia.

Treatment (in the absence of cirrhosis and neoplasia)

- Chronic EHPVO
- For primary prophylaxis of variceal bleeding there is insufficient data on whether beta-blockers or endoscopic therapy should be preferred.
- For the control of acute variceal bleeding, endoscopic therapy is effective (1b;A). In the absence of specific data on patients with EHPVO, it is presumed that the same treatments used in bleeding cirrhotic patients could be applied (5;D).
- For secondary prophylaxis, endoscopic therapy is effective (1b;A). There is insufficient evidence to recommend beta-blockers.

- There is no consensus on the indication for anticoagulant therapy.
- However, in those patients with a persistent documented prothrombotic state, anticoagulant therapy can be considered.
- There is insufficient evidence in favor of interventional therapy such as TIPS and local thrombolysis.
- Decompressive surgery should only be considered for patients with failure of endoscopic therapy (5;D).
- For portal biliopathy with obstructive jaundice, endoscopic therapy is recommended (5;D). In case of failure, shunt surgery may be considered (5;D).
- Recent EHPVO
- Recent EHPVO rarely resolves spontaneously.
- The evidence on which to base recommendations for anti-coagulant therapy is weak.

On the basis of current expert opinion (5;D), in patients with *recent EHPVO*

- Anticoagulation should be given for at least 3 months in all patients.
- When an underlying persistent prothrombotic state has been documented, life-long anticoagulant therapy is recommended.
- In patients with EHPVO and *associated* cirrhosis, hepatocellular carcinoma should be excluded. There is insufficient data on which to base recommendations for giving anticoagulant therapy to these patients.

Areas requiring further studies (5;D)

- Natural history of EHPVO in children vs. adults: hepatic dysfunction, portal biliopathy, growth retardation
- Etiology—role of various prothrombotic states in EHPVO (in the East), identification of susceptible population.
- Assessment of thrombosis, progression and recurrence.
- Definitions of variceal bleeding and predictors of first bleed and rebleed.
- Role of beta-blockers and comparison with endoscopic therapy.
- Usefulness of long-term anticoagulants, TIPS, shunt surgery.
- Development of good experimental models.

5. Providing scientific evidence: RCTs and beyond

In previous Baveno workshops, a session was devoted to the methodological requirements for future trials in portal hypertension. At Baveno IV this session was replaced by one addressing some aspects of therapy in clinical practice that have not been or cannot be evaluated by RCTs, due to: (a) inadequate quality of trials, (b) uncommon diseases or (c) distinct features of the more common diseases.

Addressing these issues should contribute to EBM when adequate information from RCTs is not possible to obtain or not yet available.

Possible use of per protocol analysis

- In superiority trials, ITT strategies are preferred and PP analysis regarded only as supportive.
- In non-inferiority trials, ITT and PP approaches (if appropriately pre-defined) may both contribute.
- When PP results differ from ITT results, the population excluded from PP analysis should be scrutinized. The applicability of the intervention may be questioned.

Assessing changes in therapeutic effects with progression of the disease

- To assess how treatment effect may change with disease progression, use interaction tests between outcome predictors and the intervention(s).
- Both unadjusted results and results adjusted for strong outcome predictors should be provided, regardless of baseline comparisons.
- Any subgroup analyses should be pre-defined, have sufficient power and usually be limited to primary outcome. Otherwise, they are exploratory methods that can help design further studies but should not modify the conclusions of RCTs.

Handling the heterogeneity of RCTs in meta-analysis

- Heterogeneity can be used cautiously to suggest indications for a particular intervention.
- This requires that:
 - differences in trial methodology are not present
 - Clinical source of heterogeneity is identified
- Stratified analysis of pooled individual data can be done.
 - Primary/secondary aims should be defined.
 - Plan for statistical analysis should be pre-defined (including multiple testing).
 - Subsequent analysis can use the same pooled data as long as the above protocol is followed.

Identification of factors that modify therapeutic effects in a clinically significant way

- Physicians must learn how to identify the factors that most often modify the clinical outcome at variance with the results of RCTs.
- The quality of RCTs (internal and external validity) should be evaluated.
- The internal validity can be assessed according to the CONSORT statement.
- The external validity can be assessed according to a list of variables which define the peculiarity of the trial population: differences in demography, co-morbidities, limitations due to inclusion/exclusion criteria, variability

in the schedules and dosages of drugs, usage of interfering drugs, low compliance, duration of treatment.

Approach to the diagnosis and treatment of uncommon cases where evidence from RCT is not forthcoming

- Consensus-driven, clinical protocols are required to define the optimal methods for clinical management of uncommon conditions where RCTs cannot be performed
- Treatment of uncommon manifestations of portal hypertension with evidence-based medicine awaits the identification of biologically plausible surrogate markers
- Alternative study designs (clinical databases, *N* of 1 trials) should be adapted to identify effective treatments for uncommon manifestations of portal hypertension
- Observational studies of treatment effect require statistical techniques to minimize confounding by indication

Continuous monitoring of the clinical outcome of treatments in so-called clinical databases

- Development of a database to monitor outcomes is desirable.
- Goals should include monitoring outcome in:
 - Three major clinical areas in portal hypertension
 - Specific sub-groups
- Funding mechanisms should be identified.
 - Focus on complications of cirrhosis rather than portal hypertension.
 - Selected mix of institutions
 - Potential interest from both government and industry for funding such a database.

'Survival analysis' for competing end-points other than death

- The Kaplan–Meier plot is often used to estimate the probability of survival free of other end-points, e.g. variceal bleeding. This produces non-interpretable results that may also be biased. The cause is that analysis using censoring of patients assumes that those who die or reach other competing end-points are still at risk for the primary end-point, which is not true [14].
- For this type of analysis, cumulative hazard plots and Cox regression analysis are better.

Need for international collaboration on clinical trials

- Almost all, if not all, RCTs in portal hypertension are underpowered.
- This applies to uncommon but also common types of conditions associated with portal hypertension.
- In cardiology and oncology, very large international—multinational—trials are conducted, so it is feasible!
- We should do the same for solving our problems in management of portal hypertension.

6. Conclusions

The purpose of the consensus definitions about the variceal bleeding episode is to use them in trials and other studies on portal hypertension, as well as in clinical practice. This does not mean that authors cannot use their own definitions, but they are encouraged to use and evaluate in parallel these Baveno IV consensus definitions. This should result in some measure of standardisation and increased ease of interpretation among different studies. Equally important, if there are uniformly defined end-points, meta-analyses will be based on more homogeneous studies, which is an essential pre-requisite of this methodology. It is desirable that future studies be reported using these definitions as part of the evaluation. Change or refinement can then take place, as they have at Baveno IV with respect to Baveno II, Reston and Baveno III, to ensure that the consensus definitions do have clinical relevance and are easily applied in practice.

Several definitions agreed upon in Baveno I [2], II [3,4] and III [7,8] were taken for granted and not discussed in Baveno IV. Interested readers can refer to the Baveno I, II [2–4] and III [7,8] reports.

The suggestions about the topics of future studies reflect the opinions of the experts about the areas where new information is most needed.

As long as new diagnostic tools and new treatments appear, they will have to be assessed in comparison with present-day standards.

7. Participants

The following chaired sessions during the Workshop:

Jaime Bosch, M.D., Barcelona, Spain; Andrew K Burroughs, M.D., London, U.K.; Gennaro D'Amico, M.D., Palermo, Italy; Juan Carlos Garcia-Pagan, M.D., Barcelona, Spain; Guadalupe Garcia-Tsao, M.D., New Haven, CT, USA; Norman D Grace, M.D., Boston, MA, USA; Roberto Groszmann, M.D., New Haven, CT, USA; Patrick Kamath, M.D., Rochester, MN, USA; Loren Laine, M.D., Los Angeles, CA, USA; Didier Lebrec, M.D., Clichy, France; Carlo Merkel, M.D., Padua, Italy; Juan Rodès, M.D., Barcelona, Spain; Shiv K Sarin, New Delhi, India; Tilman Sauerbruch, M.D., Bonn, Germany; Thorkild I.A. Sørensen, M.D., Copenhagen, Denmark; Dominique Valla, M.D. Clichy, France.

The following participated in the presentations and the discussion as panellists:

Argentina: J. Vorobioff, M.D., Rosario; *Belgium:* F. Nevens, M.D., Leuven; *Canada:* J. Heathcote, M.D., Toronto; N. Marcon, M.D., Toronto; I. Wanless, M.D., Toronto; *Denmark:* F. Bendtsen, M.D., Copenhagen; E. Christensen, M.D., Copenhagen; *Egypt:* G. Shiha, M.D., al Mansoura; *France:* B. Bernard-Chabert, M.D., Reims; P. Calès, M.D., Angers, R. Moreau, M.D., Clichy, C. Silvain,

M.D., Poitiers; D. Thabut, M.D., Paris; J.P. Vinel, M.D., Toulouse; *Germany:* M. Schepke, M.D., Bonn; *India:* Y.C. Chawla, M.D., Chandigarh; *Italy:* M. Angelico, M.D., Rome; G. Barosi, M.D., Pavia, M. Merli, M.D., Rome, A. Morabito, M.D., Milano; M. Primignani, M.D., Milan; F. Salerno, M.D., Milan; F. Schepis, M.D., Modena; M. Zoli, M.D., Bologna; *Spain:* J.G. Abraldes, M.D., Barcelona; A. Albillos, M.D., Madrid, R. Bañares, M.D., Madrid; P Ginès, M.D., Barcelona; R. Planas, M.D., Badalona; C. Villanueva, M.D., Barcelona; *Switzerland:* A. Hadengue, M.D., Geneva; *Taiwan:* H.C. Lin, M.D., Taipei; G.H. Lo, M.D., Kaohsiung; *The Netherlands:* H. Janssen, M.D., Rotterdam; H. van Buuren, M.D., Rotterdam; *United Kingdom:* E. Elias, M.D., Birmingham; D. Patch, M.D., London; *USA:* A. Blei, M.D., Chicago, IL; T. Boyer, M.D., Atlanta, GA; N. Chalasani, M.D., Indianapolis, IN; J.M. Henderson, M.D., Cleveland, OH; Y. Iwakiri, M.D., New Haven, CT; W.R. Kim, Rochester, MN; D. Kravetz, San Diego, CA; A. Sanyal, M.D., Richmond, VA; V. Shah, M.D., Rochester, MN; B. Shneider, M.D., New York, NY; J. Talwalkar, Rochester, MN.

The following gave review lectures during the Workshop

Michael Fallon, M.D., Birmingham, AL, USA; Pere Ginès, M.D., Barcelona, Spain; Christian Gluud, M.D., Copenhagen, Denmark; Pier Mannuccio Mannucci, M.D., Milan, Italy; Miguel Navasa, M.D., Barcelona, Spain; Luigi Pagliaro, M.D., Palermo, Italy.

Acknowledgements

The Baveno IV workshop was endorsed and supported in part by a unrestricted educational grant of the European Association for the Study of the Liver (EASL).

The Baveno IV workshop was also endorsed by the Italian Association for the study of the liver (AISF), the Italian Association of hospital gastroenterologists and endoscopists (AIGO), the Italian association for digestive endoscopy (SIED) and the Italian Society of Gastroenterology (SIGE).

References

- [1] Burroughs AK, editor. Methodology and review of clinical trials in portal hypertension. Excerpta medical congress service no. 763. Amsterdam, New York, Oxford.
- [2] de Franchis R, Pascal JP, Ancona E, Burroughs AK, Henderson JM, Fleig W, et al. Definitions, methodology and therapeutic strategies in portal hypertension. A consensus development workshop. *J Hepatol* 1992;15:256–261.
- [3] de Franchis R. Developing consensus in portal hypertension. *J Hepatol* 1996;25:390–394.
- [4] de Franchis R, editor. Portal hypertension II. Proceedings of the second Baveno international consensus workshop on definitions, methodology and therapeutic strategies. Oxford: Blackwell Science; 1996.

- [5] Spina GP, Arcidiacono R, Bosch J, Pagliaro L, Burroughs AK, Santambrogio R, Rossi A. Gastric endoscopic features in portal hypertension: final report of a consensus conference. *J Hepatol* 1994; 21:461–467.
- [6] Grace ND, Groszmann RJ, Garcia-Tsao G, Burroughs AK, Pagliaro L, Makuch RW, et al. Portal hypertension and variceal bleeding: an AASLD single topic symposium. *Hepatology* 1998;28:868–880.
- [7] de Franchis R. Updating consensus in portal hypertension: report of the Baveno III consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension. *J Hepatol* 2000;33: 846–852.
- [8] de Franchis R, editor. Portal hypertension III. Proceedings of the IIIrd Baveno international consensus workshop on definitions, methodology and therapeutic strategies. Oxford: Blackwell Science; 2001.
- [9] http://www.cebm.net/downloads/Oxford_EBM_Levels_5.rtf.
- [10] de Franchis R, editor. Portal hypertension IV. Proceedings of the IVth Baveno international consensus workshop on methodology of diagnosis and treatment in portal hypertension. Oxford, UK: Blackwell Science; in press.
- [11] D'Amico G. Esophageal varices: from appearance to rupture; natural history and prognostic indicators. In: Groszmann RJ, Bosch J, editors. Portal hypertension in the 21st century. Dordrecht: Kluwer; 2004. p. 147–154.
- [12] Sarin SK, Lahoti D, Saxena SP, Murthi NS, Makwane UK. Prevalence, classification and natural history of gastric varices: long-term follow-up study in 568 patients with portal hypertension. *Hepatology* 1992;16:1343–1349.
- [13] Sarin SK, Agarwal SR. Extrahepatic portal vein obstruction. *Semin Liver Dis* 2002;22:43–58.
- [14] Thomsen BL, Møller S, Sørensen TIA. The Copenhagen Esophageal Varices Sclerotherapy Project. Optimised analysis of recurrent bleeding and death in patients with cirrhosis and oesophageal varices: application of a multi-stage competing risk model. *J Hepatol* 1994;21: 367–375.