Portal Hypertension III
Proceedings of the
Third Baverno International Consensus Workshop
on Definitions, Methodology and
Therapeutic Strategies

EDITED BY
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Portal hypertension is the haemodynamic abnormality associated with the most severe complications of cirrhosis, including ascites, hepatic encephalopathy and bleeding from gastroesophageal varices. Since variceal bleeding is a medical emergency associated with significant morbidity and mortality, the evaluation of diagnostic tools and the design and conduct of good clinical trials for the treatment of this condition 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 conduct of trials in this field. Such meetings took place in Groningen, the Netherlands in 1986, in Baveno, Italy in 1990 (Baveno I) and in 1995 (Baveno II), in Milan, Italy in 1992, and in Reston, USA, in 1996. All these meetings were successful and produced consensus statements on some important points, although several issues remained unsettled.

In addition, since the Baveno II meeting, a great number of studies have expanded our knowledge on the pathophysiology of portal hypertension. Moreover, new diagnostic tools and new therapeutic approaches have been developed, which might lead to important changes in the management of this condition. Thus, my colleagues in the New Italian Endoscopic Club and I considered that the time had come to evaluate the impact of this new knowledge and of these new tools on the diagnostic and therapeutic strategies that we follow in managing patients with portal hypertension. Therefore, with the help and encouragement of a group of friends from 13 countries, many of whom had taken part in the previous two Baveno meetings, we organised a Baveno III workshop which took place on April 13–14, 2000. We decided to keep the name Baveno, although the workshop took place in Stresa, because we felt that Baveno had become a trademark for consensus in portal hypertension.

The aims of the Baveno III workshop were the same as in Baveno I and II, i.e. to refine and extend the definitions of key events concerning the bleeding episode, and to review and put into perspective the recent advances in our knowledge of the pathophysiology of portal hypertension, as well as the role
of the available diagnostic and therapeutic techniques that have been developed in studies carried out during the past five years. In addition, we continued the effort that was begun in Groningen and continued in the following workshops, of producing updated guidelines aimed at improving the quality of our future studies. We were very fortunate in being able to bring to this workshop many of the experts responsible for most of the major achievements of the last five years in this field.

The structure of the Baveno III workshop comprised nine sessions and four lectures. The first session was devoted to verifying the appropriateness and practicality of the definitions of key events that had been given in Baveno I and II, and an attempt was made to develop consensus definitions on points that were not addressed—or not agreed upon—in the previous workshops. In each of sessions 2 to 7 the Chairpersons and the Panellists reviewed an important topic related to the diagnosis or the treatment of portal hypertension. At the end of each session, the Chairpersons proposed a series of statements which were discussed within the panel and with the other experts on the floor, with the aim of reaching consensus on some important diagnostic or therapeutic issues. Session 8 was devoted to develop consensus definitions on the most important complications of therapies for portal hypertension. Such definitions should be adopted when reporting future trials, in order to make interpretation of the value of new treatments easier. Session 9 focused on three important methodological issues, i.e. prognostic stratification, quality of life evaluation and cost analysis, all three of which should be addressed in major future studies.

The four lectures were different in scope. The first one summarised the consensus reached in the Baveno I and II workshops and the impact of publications derived from those workshops in the medical literature. The second and third lectures addressed two exciting new areas of research, i.e. the possible role of stellate cells and of anti-fibrotic drugs in the pathophysiology and treatment of portal hypertension. The fourth lecture analysed the quality of trials in portal hypertension and other fields of hepatology.

These proceedings follow closely the structure of the workshop. The order of lectures and sessions is exactly the same, and the consensus statements that were agreed upon at the end of each session are reported at the end of the pertinent chapters.

Our deepest thanks go to all the friends who agreed to give lectures and to serve as Chairpersons and Panellists of the sessions, and who helped us by working hard in the preparation of the workshop and of the chapters. We also wish to thank Sandra Covre and her staff of Area Congressi, who managed brilliantly the organisation of the workshop, and Paolo Carnevale and Luca de Franchis who skillfully operated the computer-videoprojector systems throughout the workshop. In addition, we are grateful to the European As-
sociation for the Study of the Liver (EASL), the Associazione Italiana per lo Studio del Fegato (AISF) and the Società Italiana di Gastroenterologia, (SIGE) who endorsed the meeting, to the companies who sponsored the workshop and especially to UCB Pharma S.A., who made the publication of this book possible through a generous grant, to Catherine Pelissier and Nirjihar Chatterjee for their encouragement and co-operation in this project, and to Blackwell Science for the timely and excellent production of this volume.

ROBERTO DE FRANCHIS

On behalf of the New Italian Endoscopic Club
LEcTURE

What Have We Accomplished?

Roberto de Franchis

INTRODUCTION

The idea of holding consensus meetings on portal hypertension was born in 1986, when Andy Burroughs organized the first such meeting in Groningen, the Netherlands [1]. After Groningen, other meetings followed, in Baveno, Italy in 1990 (Baveno I) [2] and in 1995 (Baveno II) [3,4], in Milan, Italy in 1992 [5], and in Reston, USA [6]. This is the sixth meeting of this kind.

This review covers the following points:

1. A summary of the consensus reached at the Baveno I and II meetings.
2. The publications derived from the Baveno I and II workshops.
3. The quantitative impact of the Baveno I and II consensus on the medical literature.
4. The attendance at the Baveno workshops.

SUMMARY OF THE CONSENSUS REACHED AT THE BAVENO I AND II MEETINGS

- Definitions of key events.
- Diagnostic evaluation of patients with portal hypertension.
- Prognostic factors for first bleeding, rebleeding and survival.
- Therapeutic strategies in patients with portal hypertension.
- Methodological requirements of future trials.

Definitions of key events

**I Time zero**

The time of admission to the first hospital the patient is taken to is time zero.
II Bleeding

Haematemesis and/or melaena, or gastric aspirate containing blood.

III Clinically significant bleeding

A bleeding episode is clinically significant when there is:
1. transfusion requirement of ≥ 2 units of blood within 24 hours of time zero,
2. systolic blood pressure < 100 mmHg or a postural change of > 20 mmHg,
3. pulse rate > 100/min at time zero.

IV Death related to variceal bleeding

Any death within 6 weeks of time zero would be a death related to variceal bleeding, regardless of the mode of death. Thirty-day mortality (a surgical convention) and deaths during admission should also be reported. The starting point for all three intervals is time zero. The immediately precipitating causes of death should be described, and represent the mode of death.

V Time frame for acute bleeding

The acute bleeding episode is represented by an interval of 48 hours from time zero with no evidence of clinically significant bleeding between 24 and 48 hours. Evidence of any bleeding after 48 hours is the first rebleeding episode.

VI Failure to control bleeding

The definition of failure to control bleeding was divided into 2 time frames:

Within 6 hours: any of the following factors:
1. transfusion of 4 units of blood or more, and inability to achieve an increase in systolic blood pressure of 20 mmHg or to 70 mmHg or more, and/or
2. pulse reduction to less than 100 mmHg or a reduction of 20/min from baseline pulse rate.

After 6 hours: any of the following factors:
1. the occurrence of haematemesis,
2. reduction in blood pressure of more than 20 mmHg from the 6-hour point, and/or
3. increase of pulse rate of more than 20/min from the 6-hour point on 2 consecutive readings 1 hour apart,
WHAT HAVE WE ACCOMPLISHED?

4 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.

VII Rebleeding

The occurrence of new haematemesis or new melaena after a period of 24 hours or more from the 24-hour point of stable vital signs and hct/hb following an episode of acute bleeding.

VIII Rebleeding index

Episodes of rebleeding + 1/months of follow-up per patient
This index should be used to evaluate:
1 patients with > 1 rebleed;
2 patients who never rebleed;
3 the interval without rebleeding;
4 as a measure of distribution.

Diagnostic evaluation of patients with portal hypertension

I Diagnosis of portal hypertension

1 Endoscopy and ultrasonography (preferably with Doppler) should be used routinely for the assessment of portal hypertension in patients with cirrhosis without previous bleeding.
2 The main parameter to use for assessing the risk of bleeding is variceal size. Optional parameters are the Child–Pugh score, hepatic vein pressure gradient (HVPG), variceal pressure and Doppler ultrasound.
3 In nontreated patients at low or intermediate bleeding risk, follow-up endoscopy should be done at 12-month intervals
4 The efficacy of new pharmacological treatments must be evaluated by HVPG measurement

II Criteria for diagnosis of variceal bleeding:

1 Endoscopy should be done as soon as possible.
2 The timing of endoscopy with respect to bleeding must be reported.
3 Active bleeding: diagnosis certain.
4 Signs of recent bleeding:
   (a) 'white nipple'—certain;
   (b) if clot—wash!
Varices without other potential bleeding sources: diagnosis certain when blood is present in stomach and/or if endoscopy is made within 24 hours.

**III Criteria for diagnosis of bleeding due to portal hypertensive gastropathy (PHG)**

1. Acute bleeding: endoscopic evidence of an active bleeding lesion, assessed after washing or removing clots, with the stomach fully distended. If gastric or oesophageal varices are present, endoscopy should be repeated after 24 hours.

2. Chronic bleeding should be assessed by the following criteria:
   - (a) presence of endoscopic lesions;
   - (b) evidence of faecal blood loss;
   - (c) > 2 g drop in Hb level in 3 months;
   - (d) low serum transferrin saturation

   in the absence of:
   - (a) portal-hypertension related colonic or duodenal lesions;
   - (b) bone marrow suppression;
   - (c) associated renal disease and
   - (d) history of nonsteroidal anti-inflammatory drugs (NSAID) use.

**IV Criteria for diagnosis of bleeding from gastric varices**

The relationship between the existing classifications and bleeding events needs to be evaluated.

**Prognostic factors for first bleeding, rebleeding and survival**

**I Risk factors for first bleeding**

1. Assessment of the risk of first bleeding is important.

2. Simple endoscopic criteria such as variceal size and red colour signs must be used, possibly in conjunction with the Child–Pugh score as in the NIEC index.

3. The existing prospective information on the risk of first bleeding is insufficient and should be extended by further studies, including possibly additional parameters.

**II Risk factors for early and late rebleeding and death**

No consensus was reached on these points, mainly because of insufficient available information.
Therapeutic strategies in patients with portal hypertension

I Prevention of the first bleeding episode

1 Pharmacologic treatment with vasoactive drugs is the only recommended therapy.
2 Non-cardioselective β-adrenergic blockers are the drugs of choice.
3 Isosorbide-5-mononitrate is a possible alternative in case of intolerance or contraindications to β-blockers.
4 Sclerotherapy is definitely not indicated
5 Endoscopic rubber-band ligation needs further evaluation.

II Treatment of acute variceal bleeding

1 Both endoscopic treatments (sclerotherapy and band ligation) and pharmacologic treatments (terlipressin and somatostatin) are effective. More information is needed on octreotide.
2 Injection of tissue adhesives or thrombin for bleeding gastric varices appears to be effective but requires confirmation.
3 TIPS can be used as salvage treatment in variceal bleeding uncontrolled by endoscopic and pharmacologic therapy.

III Prevention of rebleeding

1 Band ligation has replaced injection sclerosis as the optimum endoscopic treatment to prevent recurrent bleeding from oesophageal varices.
2 Drug treatment with nonselective β-blockers is also a valuable option.
3 If there are no contraindications, the association of β-blockers and endoscopic therapy could be used.
4 Insufficient information is available on the use of combinations of drugs. This option needs to be tested.
5 Only patients with severe PHG and bleeding should be treated with vasoactive drugs to prevent rebleeding.
6 TIPS could be used to prevent rebleeding in patients with frequent repeated episodes of variceal haemorrhage, despite adequate elective treatment. However, this indication needs testing in appropriately designed randomized controlled trials.
7 Surgical shunts and, in selected cases, devascularization are appropriate treatments for patients with portal hypertension and preserved liver function who cannot be managed by endoscopic an/or pharmacologic therapy.
Liver transplant is the treatment of choice in patients with portal hypertension and end-stage liver disease. The decision to transplant is based on appropriate selection criteria which may vary according to the disease.

Methodological requirements of future trials

I General requirements

1 Randomized clinical trials (RCTs) should meet good clinical practice (GCP) requirements.
2 Larger trials should be performed to achieve sufficient statistical power.
3 If possible, RCTs should include complications, quality of life and health-economic assessments using appropriate methodology; they should include data on end-points on which there exists consensus, and should use structured reporting.
4 All therapies should be monitored by cumulative meta-analysis in order to avoid unnecessary duplication.
5 Meta-analysis on individual patient data could be performed in order to identify prognostic and therapeutic variables.

II Major outcome measures

1 Prevention of first bleeding:
   (a) first variceal bleeding;
   (b) death before variceal bleeding;
   (c) course, including death, after variceal bleeding.
2 Treatment of acute bleeding:
   (a) control of bleeding;
   (b) death within 42 days after bleeding.
3 Prevention of rebleeding:
   (a) variceal rebleeding;
   (b) death before variceal rebleeding;
   (c) course, including death, after variceal rebleeding.

III Subsidiary outcome measures

1 Clinical course:
   (a) causes of death, especially bleeding;
   (b) liver function (encephalopathy);
   (c) upper gastrointestinal bleeding from nonvariceal sources.
2 Cost of treatment:
   (a) side effects and complications;
(b) time in hospital and intensive care unit.

3 Additional treatments:
   (a) transfusion;
   (b) ancillary treatment.

4 Overall result
   (a) quality of life;
   (b) cost-benefit.

5 Paraclinical effects as surrogates of potential clinical effects:
   (a) variceal size;
   (b) haemodynamics.

IV Sample size calculation

1 Essential part of the planning of trials expected to produce conclusive results on major end-points.
2 It should be included in the final report of any trial.

V Double blindness

1 Useful to avoid biased assessment of outcomes in which there is a subjective component, either for the physician or the patient.
2 Useful to avoid biased approaches to patients, by physicians, staff, relatives, and patients themselves, with possible influence on the clinical course.
3 Necessary for the distinction between specific biological effects and general effects of administration of the treatment.
4 Should be used whenever possible.

VI Randomization

1 Use randomization for allocation of treatments to be compared.
2 Randomization must be closed, i.e. the treatment must not be known before the decision to include the patients is made.

VII Stratification in randomization

1 Always by centre in multicentre trials.
2 By one or two well-defined and easily accessible variables of great prognostic significance in trials including less than 100 patients.
VIII Exclusion before randomization

1 Patients evaluated and fulfilling the entry criteria, but not randomized must be reported.

IX Intention to treat analysis

1 Include all randomized patients with outcomes recorded at any time until closure of the trial in the analysis.
2 An analysis ‘as per treatment received’ should be performed that excludes only patients who did not actually start the treatment. This analysis should include entry characteristics to establish balance.

X Exclusion after randomization

1 Patients withdrawn from the trial or lost to follow-up need to be described and analysed.

XI Competing end-points

1 Should be taken into account in the analysis and interpretation of the results.

XII Stratification in analysis

1 Several variables may be taken into account in multivariate analysis, but it is advisable to decide which variables in the planning of the trial.
2 The variables used in stratification before randomization should be included.

XIII Management of patients in the control group

1 Prevention of first bleeding: no consensus was reached on whether no treatment is still justified.
2 Treatment of acute bleeding: some accepted form of treatment should be given.
3 Prevention of rebleeding: no treatment is not justified—sclerotherapy, band ligation, β-blockers or surgery must be used.