Klin Wochenschr (1986) 64:1267–1275

Klinische Wochenschrift

Clinical Progress

Prophylaxis of First Variceal Hemorrhage in Patients with Liver Cirrhosis

T. Sauerbruch, G. Kleber, A. Gerbes, and G. Paumgartner
Medizinische Klinik II, Klinikum Grosshadern, Universität München

Summary. Prophylaxis of bleeding from esophageal varices is a very tempting concept at first glance, especially under the assumption of a high mortality associated with first variceal hemorrhage. Up to now four different measures have been tried for prophylaxis: portacaval shunt operation, devascularization procedures, sclerotherapy, and drugs. With the exception of portacaval shunts, ongoing controlled trials show a weak trend toward reduction of variceal bleeding and prolongation of survival in selected patients with compensated cirrhosis and large varices. However, prophylaxis of first variceal bleeding must still be regarded as experimental and should be restricted to controlled clinical studies.

Key words: First variceal hemorrhage – Prophylaxis

Although variceal hemorrhage in patients with liver cirrhosis may be life threatening, prophylaxis of variceal bleeding is still a matter of controversy. The decision to initiate prophylactic regimens depends as much on the knowledge about epidemiology and pathogenesis of variceal bleeding as on the results of controlled trials with respect to both the beneficial and adverse effects.

Epidemiology of First Variceal Bleeding

Thirty to seventy percent of patients with liver cirrhosis develop esophageal varices [14], but only 20%–40% of these patients bleed from their varices during a follow-up period of about 2 to 14 years [1, 15, 16, 31, 67]. Overall mortality of first variceal hemorrhage was 50% in the Copenhagen study [89]. However, it largely depends on hepatic function. In the Royal Free Hospital of London [8], only 33% of 198 cirrhotics died within 6 weeks after first variceal bleeding (Child A and B 12%, Child C 61%). In our own setting, the 6 months' mortality in patients with active bleeding ($n=116$) was 12% in Child's group A and B and 64% in Child's group C [74]. The risk of death from variceal bleeding may be calculated as 3%–5% per year in patients with liver cirrhosis and proven esophageal varices [90].

Abbreviations: ICG = Indocyanine-green; WHVP/FHVP-gradient = Wedged hepatic venous pressure minus free hepatic venous pressure gradient

Pathogenesis of Variceal Bleeding

Hemodynamic Parameters

It is widely accepted that the rupture of any vessel is due to an increase in tension of the vessel's wall overriding its elastic and mechanical properties. According to La Place's law, tension of the wall equals the product of the radius of the tube and the transmural pressure, whereas it is inversely related to the thickness of the wall [45]. Therefore, parameters which are involved in the pathogenesis of variceal hemorrhage must influence the diameter, the transmural pressure gradient, properties of the wall of the varices, or a combination of those.

When thinking of pressure parameters which might increase the risk of variceal hemorrhage, it is more logical to look at pressure gradients than at the absolute blood pressure in the vessels. This has been understood only lately. Esophageal varices are fed by the venous portal system lying in the relatively high pressure zone of the abdomen and drain into the relatively low pressure zone of the thoracic venous system. During deep inspiration this abdomino-thoracic pressure gradient increases and approximates as much as 40 mmHg [14]. Thus, respiration may significantly influence variceal blood flow, transmural varix pressure, and the risk of variceal hemorrhage [14, 65].

Most of the esophageal varices rupture at or just above the gastroesophageal junction [54, 84]. Variceal pressure at this point is presumably identical or only slightly inferior to portal pressure, while the intraesophageal pressure probably comes close to the relatively low intrathoracic pressure. Therefore, the intravascular pressure of the collaterals in this region is no longer counteracted by the high intraabdominal pressure surrounding the vessel.

Hemodynamic studies undertaken to date have investigated the possible roles of portal pressure, variceal pressure, and of azygos blood flow in determining variceal hemorrhage.

Portal Vein Pressure

Besides the direct assessment of portal vein pressure by direct cannulation [14, 60] the pressure gradient of wedged hepatic venous pressure minus free hepatic pressure (WHVP/FHVP gradient) has been used in most studies since it approximates closely the portal venous pressure at least in alcoholic cirrhosis [7]. In nonalcoholic cirrhosis this pressure gradient may be slightly lower than the portal venous pressure [7].

In several retrospective studies there was no significant difference in the WHVP/FHVP gradient between patients with and without previous variceal hemorrhage [18, 40, 70, 93]. Analysis of the available data shows that the WHVP/FHVP gradient in patients with previous variceal hemorrhage was nearly always higher than 12 mmHg. However, according to recent observations [25, 92], this is the threshold for the appearance of esophageal varices rather than an indicator for their rupture.

It may be derived from these studies that after assessment of esophageal varices by more simple means (e.g., endoscopy), portal pressure measurements have a limited value for the prediction of variceal hemorrhage. For the individual patients, however, these data do not contradict the hypothesis that lowering portal pressure will reduce the risk of hemorrhage.

Esophageal Variceal Pressure

Portal pressure may not relate closely to intravariceal pressure owing to variable resistances interposed between the two veins [69]. Therefore, knowledge of esophageal variceal pressure is important [27]. In earlier studies by Palmer and Brick [56] intravariceal pressure was not significantly correlated to the risk of variceal hemorrhage. However, recently Staritz et al. have found [82, 83] a significantly higher variceal pressure in patients with previous variceal bleeding than in those without bleeding ($\bar{x}$27 vs 16 mmHg). The same group also showed a higher pressure in large rather than small varices. The esophageal lumen was taken as reference pressure by these authors.

Azygos Blood Flow

Measurement of azygos blood flow by thermodilution [5, 6] showed a significant correlation with variceal pressure and variceal size. However, no significant correlation with the bleeding risk could be demonstrated [10]. The azygos vein carries not only blood from the intraesophageal varices (the only vessels exposed to rupture), but also from the periesophageal varicosities and from other veins in the thorax. This may explain why a correlation with the bleeding risk was not found

Histological and Endoscopic Parameters

Esophagitis

Endoscopic studies on the prevalence of esophagitis in patients with and without variceal bleeding are controversial [3, 45, 46, 54, 61, 62, 79–81]. Most of these studies found no good correlation between the endoscopic finding of reflux esophagitis and history of bleeding [64]. Therefore, this is probably not an important risk factor. Using long-term pH monitoring, we found no significant difference of the percentage of acid gastroesophageal reflux between patients with and without prior bleeding as well as between cirrhotics with and without varices (unpublished observations). This fact underlines the minor role of acid reflux [19, 46] for pathogenesis of variceal bleeding provided there is no enhanced susceptibility of the mucosa in patients with varices. Furthermore, histological studies of esophageal rings obtained during transection and stapling of variceal bleeding showed no evidence of esophagitis [62, 79, 81].

Red Color Sign

Certain endoscopically visible mucosal changes on top of the varices [3, 30], called cherry red spots, hematocystic spots or varix on varix are summarized as the red color sign by the Japanese Society of Portal Hypertension. This red color sign is associated with a history of bleeding in up to 100% of the patients when evaluated retrospectively [3]. However, so far no prospective study has established the sensitivity and specificity of this sign for

the prediction of bleeding. In addition, there are no data on the association of this sign with other parameters such as size of varices or hepatic functional status. It is thought that the red color sign corresponds histologically to dilated intraepithelial or subepithelial blood filled vascular channels which are connected to submucosal varices. There were significantly more and larger channels visible in patients with portal hypertension than in a control population [53, 80, 81]

Variceal Size and Number

As derived from La Place's law, the diameter of varices directly determines the tension of the vessel and therefore the risk of its rupture. Initial distension of the venous vessel needs a relatively high increment of pressure. On the other hand, in large, thin-walled vessels a small pressure rise suffices for a further dilatation of the varix up to its rupture. According to Ohm's law, this pressure rise requires a higher blood flow in vessels with a large diameter than in vessels with a small diameter.

The theoretical considerations mentioned above are in line with retrospective studies [1, 17, 25, 34, 40, 56] which revealed that the bleeding risk of large varices is about three times higher than that of small varices. In fact, variceal size is the best documented risk factor for variceal bleeding.

Ascites and Liver Function

Ascites increases the abdominal and therefore the portal pressure with a subsequent increase in the thoracal abdominal pressure gradient. This may cause a higher bleeding risk. In the first study on prophylactic portacaval shunt operation [15] ascites was present at time of inclusion in all patients who experienced variceal hemorrhage later on. However, this strong correlation between ascites and the risk of first variceal hemorrhage has not been found by others. It should be noted that together with an intraabdominal pressure rise caused by ascites, resistance of the portal collateral system may also increase and may blunt the transduction of increased portal pressure to transmural variceal pressure.

A number of other parameters related to the hepatic functional status such as jaundice or a low prothrombin time may predict an increased bleeding risk. A disturbed liver function could also influence other ill-defined hemostatic factors which contribute to the pathogenesis of variceal bleeding. On the other hand, a significant proportion of patients with good liver function (Child A) bleed from their varices [8, 73, 74].

In summary, size and number of varices are probably the best-defined parameters for the prediction of first variceal hemorrhage. However, for the initiation of prophylactic measures it is very important to have more information on sensitivity, specificity, and predictive value of these parameters in relation to predicting variceal hemorrhage.

Prophylaxis of First Variceal Bleeding

Early reports [12, 68] showed an enormous 30%–80% mortality associated with variceal hemorrhage. Therefore, prophylaxis is a very tempting concept at first glance. Up to now four different therapeutic measures have been tried for prophylaxis of variceal bleeding: portacaval shunt operation, devascularization procedures, sclerotherapy, and drugs. Yet, at the moment, none of these regimens has become the therapy of choice for prevention of first variceal bleeding.

Prophylactic Shunt Operations

When it had been shown that portacaval shunts efficiently reduce the variceal bleeding risk, the question arose whether this procedure should be carried out as a prophylactic measure. Four randomized controlled trials [15, 16, 31, 67] have been carried out in the 1960s and early 1970s. All of these studies showed that despite preventing variceal hemorrhage, prophylactic shunts failed to prolong survival [11]. On the contrary, there was even a trend to diminution of survival after the operation despite the virtual elimination of hemorrhage from esophageal varices. The control groups comprised a total of 160 patients and the shunt groups 130 patients [11]. During a follow-up period of 5 to 14 years, 44% of the patients died in the non-operated and 58% in the shunted group. The percentage of first variceal bleeding in the control patients and in the patients who had refused treatment ranged between 20% and 40%. The lack of a positive effect of the portacaval shunt on survival was mainly attributed to operative mortality and increased long-term mortality due to hepatic failure in the shunted patients after loss of portal blood supply of the liver. Therefore, a logical approach to prophylactic operation would be a method that significantly reduces the risk of variceal bleeding with low operative mortality and maintenance of portal blood flow. Devascularization procedures and sclerotherapy fulfill these requirements.

Devascularization Procedures

In Japan, nonshunting operations and selective shunts are carried out as a standard operation with satisfactory clinical results. Inokuchi et al. [30] published an interim report on prophylactic portal nondecompressing surgery in patients with esophageal varices. All patients had no prior variceal bleeding, although patients with a history of bleeding of nonvariceal origin were included. Etiology of cirrhosis was nonalcoholic in most of the patients and the varices were of at least moderate size with local potential risk factors such as cherry red spots [3]. Child C patients were omitted. The nonoperative group comprised 52 patients and the operated group 60 patients. Fifty of these received operations causing direct interruption of the varices (e.g., transection) and 10 selective shunts. During a follow-up of 24 months, the cumulative death rate was 17% in the operated group and 30% in the controls. The survival curves were not significantly different. The cumulative bleeding rate in the nonoperated patients was 32%, while none of the operated patients bled. Mortality rate for the first bleeding event in the controls was 50%. About half of the deaths in the nonoperated group was due to bleeding. The authors speculate that nonportal decompression surgery may also achieve a significant improvement in survival when a longer follow-up has been studied.

Prophylactic Sclerotherapy

The need for prophylactic sclerotherapy has been debated since results of two controlled trials were published [57, 95]. In both trials, the control group received only conservative management, that is, balloon tamponade and/or vasopressin in case of bleeding. First variceal hemorrhage occurred in 66% and 57% of the controls vs 6% and 9% in the prophylactically treated patients during a follow-up period of up to 5 years. Also the survival rate was significantly reduced in the controls (42% vs 6% and 55% vs 21%) as compared with the prophylactically treated patients. However, both trials found a considerably higher incidence of first variceal hemorrhage in the control group than other studies [1, 15, 31, 67], a fact which is difficult to explain. Paquet [57] selected patients with large varices and/or clotting abnormalities while Witzel and coworkers [95] made no selection concerning hepatic function status or size of varices. As concerns etiology, no data are given in Paquet's paper. In Witzel's study about 80% of the patients had alcoholic disease. Were there other local factors such as presence of the red color sign that increased the risk of bleeding? In Paquet's study these factors were present in most of the patients. The other study does not consider this point. According to our own observations [34] these local factors are only of minor importance as compared with size and number of varices.

With regard to risk-benefit considerations the complications of prophylactic sclerotherapy have to be kept in mind. They can be divided into those occurring at the site of injection (mostly ulcerations and esophageal fibrosis [20]) and into those originating from injection and systemic dissemination of the sclerosant (mostly fever, bacteremia [72, 76], or pulmonary side effects [32, 52, 71]). In prospective therapeutic clinical trials [38, 47, 58, 73, 77, 78, 87–89, 94] fatal complications ranged between 0% and 13% (median 2.5%), mostly caused by perforation of the esophagus, aspiration pneumonia, and bleeding esophageal ulcers. Although the risk of fatal complications is supposed to be lower in patients undergoing elective sclerotherapy, it has to be kept in mind that 1% to 2% of the patients may die by endoscopic prophylaxis. Bleeding ulcerations are observed in up to 15% in the therapeutic studies (median 9%). In other words it is highly improbable that prophylactic sclerotherapy reduces the bleeding risk to zero because 5% to 10% of the patients who never bled may exhibit bleeding induced by sclerotherapy. In addition, some patients may bleed from gastric varices occurring in 10% to 20% of patients with esophageal varices. Hemorrhage from gastric varices cannot be prevented by prophylactic sclerotherapy.

If we assess sample size requirements for a prophylactic sclerotherapy trial by assuming from the literature that about 30% of the control population will bleed from varices and if we assess that the risk is to be reduced by sclerotherapy from 30% to 10%, about 70 patients are required in each group in order to obtain a statistically significant difference with a type I error of 5% and a type II error of 20%. If the bleeding risk is to be reduced from 30% to 15% by sclerotherapy, a number of 125 patients is needed in each group. These figures show that the proof of a beneficial effect of sclerotherapy, if present, requires a large number of patients. Selection of patients with a considerable bleeding risk may allow sclerotherapy to be used where its benefits are more certain and require smaller sample sizes in controlled trials. During a symposium on prophylaxis of variceal hemorrhage at our department in January 1986, apart from the studies already published [57, 95], preliminary results on prophylactic sclerotherapy

were presented [21, 24, 29, 36, 75, 96]. If we combine these results, a total of 339 patients without previous gastrointestinal bleeding were reported on. In this group 162 patients were randomized to sclerotherapy and 177 to no prophylactic treatment. Follow-up ranged from a few months to 7 years. Most centers selected patients with large varices and when bleeding occurred most of the patients received sclerotherapy. Bleeding occurred in 22% of the sclerotherapy group and in 35% of the controls. The mortality rate was 28% in the sclerotherapy patients and 35% in the controls. None of these preliminary individual studies found a statistically significant improvement of survival and only one study [96] showed a significantly reduced bleeding rate after sclerotherapy. None of the studies found a higher bleeding risk after initiation of sclerotherapy. All studies suffered from a relatively small number of patients. In the final discussion the panel agreed that prophylactic sclerotherapy should only be carried out within controlled trials [86].

Beta-Blockers for Prophylaxis of First Variceal Hemorrhage

Beta-adrenoceptor blocking agents cause a reduction in portal blood flow leading to a moderate decrease of portal hypertension [5, 39, 42]. This effect is probably achieved by a reduction of cardiac output together with splanchnic vasoconstriction [42]. Based on these hemodynamic studies, prolonged oral therapy with beta-blockers was used to lower portal pressure [41, 43] and to prevent recurrent variceal bleeding. Three different types of beta-adrenoceptor blocking agents were used: substances that preferably bind to beta 1 receptors and reduce cardiac output, such as atenolol [28], agents that selectively interact with beta 2 receptors (these receptors are found in the peripheral and splanchnic circulation), causing splanchnic vasoconstriction [4, 33, 39], and nonselective beta-blockers that influence both beta 1 and beta 2 receptors [42]. Most clinical experience in cirrhotic patients with portal hypertension has been obtained with the nonselective beta-blocker propranolol. Lebrec's [41, 43] report of a significant decrease of gastrointestinal rebleeding events after continuous oral administration of propranolol was not confirmed by Burroughs et al. [9]. Explanations for these discrepant results might be differences in etiology or severity of cirrhosis, selection or randomization bias or possibly a reduced hemodynamic response to propranolol due to down regulation of beta-adrenoceptors in decompensated cirrhotics who were included in the British, but not in the French study [11, 26, 50].

There are several well-known side effects of chronic beta-blocker therapy such as Raynaud's phenomenon, peripheral ischemia, dyspnea, impotence, lethargy or skin disorders, which range between 1% and 10% [48]. In addition to these side effects, impairment of renal or liver function due to a reduction of hepatic perfusion [5] with precipitation of hepatic encephalopathy [85, 91] and a decreased natriuretic effect of diuretics in patients with liver cirrhosis [63] have been suggested. The frequency of these side effects is still a matter of controversy [2, 5] and their relevance will depend on the benefits of prophylactic beta-blockade which may be shown in ongoing trials.

At present, there are only few data on beta-blockers for the prophylaxis of first variceal hemorrhage. Several prospective randomized trials have been started [44, 55, 59]. When combined, a total of 456 patients were included in these trials. Of these 225 were assigned to beta-blockers and 231 to placebo. It is rather difficult to draw any definite conclusions from these preliminary results. Only nonselective blockers, propranolol [55, 59] or nadolol [23, 44] have been administered. Patients with end-stage cirrhosis (Child-Pugh score above 13) were not included in any of these studies. In one study, a vast majority (90%) were alcoholic cirrhotics [59]. The other study [55] comprised 40% alcohol-induced cirrhosis and no data on the etiology of cirrhoses are available from the third trial [44]. A wide range of about 20% [59] to 80% [55] of the consecutively observed patients were included in the studies. Thus, differences in severity and etiology of cirrhosis as well as selection bias will have to be discussed once the final results of these prophylactic trials are presented. At the present stage, the following preliminary results can be derived from the ongoing trials: An overall reduction of first bleeding events was observed in selected groups of compliant patients with compensated cirrhosis in two studies [44, 55]. However, contrary to these trials and to the studies on prevention of rebleeding, Pascal et al. [59] presented a reduction of first variceal hemorrhage and prolonged survival especially in Child C patients.

Nonselective beta-blockers may reduce the bleeding risk in compliant patients. However, at the moment the selection of patients in whom survival and risk of bleeding may be improved (alcoholic or nonalcoholic cirrhotics, compensated or decompensated cirrhotics) is unclear. It is still questionable whether beta-blocker prophylaxis really offers an overall benefit.

When patients, in whom treatment was stopped because of side effects or noncompliance are included in the calculations, the beneficial effect of beta-blocker therapy probably cannot be proved. Patients who stopped treatment may have an increased risk of bleeding, possibly due to a rebound effect at upregulated receptors.

In conclusion, prophylactic treatment with beta-blockers might turn out to be beneficial for selected patients with large varices who do not exhibit contraindications to beta-blockers and who are compliant. At present, however, beta-blockade for prophylaxis of variceal hemorrhage of cirrhotics should be limited to controlled trials.

Other Drug Candidates for Prophylaxis of Variceal Bleeding

The pressure gradient in a vessel is proportional to flow and resistance [66]. Acute and chronic pharmacotherapy of portal hypertension in its present state is carried out with beta-blockers, vasopressins, or somatostatin which lower portal pressure by decreasing portal venous flow. This theoretically may worsen liver function. Therefore, according to Reichen [66], the ideal portal antihypertensive agent should have the following properties: high first-pass extraction to maximize hepatic and minimize systemic effects after oral administration, in order to act by decreasing portal resistance rather than flow and by this maintain or improve hepatic function. Candidates which might fulfill these criteria include nitrates [22] and calcium antagonists [37, 50, 51, 66]. While nitrates decrease hepatic blood flow, the calcium antagonists may increase hepatic blood flow at least in noncirrhotic humans [51]. It has been shown in rats with alcoholic liver damage that the calcium antagonist verapamil which has a much higher first-pass effect than nifedipin improves blood flow and hepatic function and decreases splenic pulp pressure. Also in man (nine cirrhotic patients) verapamil (50 mg per os) improved the ICG clearance without affecting pulse rate or systemic blood pressure [50, 51, 66]. According to Reichen [66] this effect of verapamil might be explained by an action on the hepatic microvascular bed by decreasing intrahepatic shunting and redistributing blood flow into sinusoids with better exchange characteristics. Therefore, clinical trials on the prophylactic effect of verapamil in patients with portal hypertension and esophageal varices seem to be reasonable. With regard to portal hypertension and liver function alpha-adrenocepter blocking agents may be further candidates [49].

Already more than 25 years ago [45] it had been shown that diuretics may reduce portal pressure, possibly due to a reduction of the plasma volume [97]. In this context recent findings on lowering portal pressure by chronic application of spironolactone are interesting [35] and warrant further confirmation.

Conclusions

Prophylaxis of first variceal hemorrhage has two major aims: first, improvement of survival and second, reduction of the bleeding risk with improvement of life quality. Prophylactic measures may theoretically improve life quality by reducing the risk of variceal bleeding in patients with good or moderate hepatic functional status (Child A and B), provided the regimen is not too aggressive. However, in these patients it is questionable whether it prolongs survival. Most of them will not die from the first bleeding event. On the other hand, hemorrhage in patients with bad functional status (Child C) may be life threatening and prevention of bleeding could lead to an improvement of survival in this group. Yet, especially these patients may be very susceptible to adverse effects of prophylactic regimens and their life quality might suffer badly. Furthermore, it is highly questionable whether Child C patients with end-stage liver disease, in whom bleeding is more a complication than cause of terminal illness, will profit from any prophylactic regimen.

From the controlled trials on prophylaxis of variceal bleeding we may draw the following conclusions:

Prophylactic portacaval shunt operations have been abandoned although they lower the bleeding risk by 90% because survival may be reduced by the operation.

Nonportal decompression surgery (mostly esophageal transection) is a relatively safe operation in Japan reducing the bleeding risk as effectively as portacaval shunt operations, but with a lower early and late mortality. This procedure might have a beneficial effect on survival in compensated nonalcoholic cirrhotics with large varices. However, the results have been obtained in a Japanese population and need to be reproduced in Western countries.

Prophylactic sclerotherapy reduces the bleeding risk to a lesser extent than portacaval shunts or the Japanese transection procedures. Most trials showed a trend toward prolongation of survival. However, in several recent studies this effect is not impressive.

Although most trials selected patients with high bleeding risk, mostly based on the finding of large

varices, the cumulative percentage of hemorrhage in the controls was only about 30%. This means that about 70% of the patients were treated unnecessarily. Therefore, further research should focus on epidemiology and pathogenesis of variceal bleeding for better identification of patients who might benefit from prophylaxis. At the moment, variceal size is still the best predictor of variceal bleeding. However, in the future, other parameters may be defined.

In the ongoing studies patients randomized to beta-blockers, sclerotherapy, or transection did not fare worse than the controls. Therefore, it appears justified to continue these trials until statistically valid results are obtained. Until this goal is reached, present methods for prophylaxis of first variceal bleeding must be regarded as experimental and their application should be restricted to controlled trials. Centers conducting such studies should have some basic knowledge on etiology and natural history of variceal hemorrhage in the population to be studied. During the trial, endoscopic appearance of varices, adverse effects of the prophylactic measures, frequency of follow-up visits, alcohol drinking habits, and compliance of these patients should be registered. Results of such future studies may provide a better basis for selection of patients in whom prophylactic treatment is mandatory.

Acknowledgement. This article is partly based on an international symposium on prophylaxis of variceal bleeding held at the Department of Medicine II, Klinikum Grosshadern, University of Munich, in January 1986. We thank the following speakers for their contributions: J. Bosch, A.K. Burroughs, M. Classen, H.O. Conn, W. Fleig, W.J. Jenkins, Ch.P. Klein, W. Köpcke, D. Lebrec, K.J. Paquet, J.P. Pascal, J. Reichen, T.B. Reynolds, N. Soehendra, R.A.J. Spence, M. Staritz, J. Terblanche, N. Tygstrup, D. Westaby, L. Witzel. We are indebted to A.K. Burroughs for review of the manuscript. We thank Ms. J. Steinberg for secretarial help. The authors acknowledge the support of the Wilhelm Sander-Stiftung (grant 84.023.2), Smith Kline Dauelsberg GmbH and Boehringer Mannheim GmbH.

References

1. Baker LA, Smith C, Lieberman G (1959) The natural history of oesophageal varices. Am J Med 26:228–237
2. Bataille C, Bercoff E, Pariente EA, Valla D, Lebrec D (1984) Effects of propranolol on renal blood flow and renal function in patients with cirrhosis. Gastroenterology 86:129–133
3. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, Kobayashi M (1981) Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc 27:213–218
4. Bihari D, Westaby D, Gimson A, Crossley J, Harry J, Williams R (1984) Reductions in portal pressure by selective beta-2-adrenoceptor blockade in patients with cirrhosis and portal hypertension. Br J Clin Pharmacol 17:753–757
5. Bosch J (1985) Effect of pharmacological agents on portal hypertension. A haemodynamic appraisal. Clin Gastroenterol 14:169–184
6. Bosch J, Groszmann RJ (1984) Measurement of azygos venous blood flow through gastroesophageal collaterals in cirrhosis. Hepatology 4:424–429
7. Boyer ThD, Triger DR, Horisawa M, Redeker AG, Reynolds TB (1977) Direct transhepatic measurement of portal vein pressure using a thin needle. Gastroenterology 72:584–589
8. Burroughs AK, D'Hygere F (1986) Pitfalls of prophylactic studies in portal hypertension. Abstract. International symposium on prophylaxis of variceal bleeding. Munich, January 24–25
9. Burroughs AK, Jenkins WJ, Sherlock S et al. (1983) Controlled trial of propranolol for the prevention of recurrent variceal hemorrhage in patients with cirrhosis. N Engl J Med 309:1539–1542
10. Cales P, Braillon A, Jiron MI et al. (1984) Superior portosystemic collateral circulation estimated by azygos blood flow in patients with cirrhosis. Lack of correlation with oesophageal varices and gastrointestinal bleeding. Effect of propranolol. J Hepatol 1:37–46
11. Conn HO (1974) The rational evaluation and management of portal hypertension. In: Schaffner F, Sherlock S, Leevy C (eds) The liver and its disease. Thieme, Stuttgart, pp 289–306
12. Conn HO (1982) Cirrhosis. In: Schiff L, Schiff E (eds) Diseases of the liver. Lippincott, Philadelphia Toronto, pp 847–977
13. Conn HO (1984) Propranolol in portal hypertension: problems in paradise? Hepatology 4:560–564
14. Conn HO, Groszmann RJ (1982) The pathophysiology of portal hypertension. In: Arias I, Popper H, Schachter D, Shafritz DA (eds) The liver: biology and pathobiology. Raven, New York, pp 821–848
15. Conn HO, Lindenmuth WW (1965) Prophylactic portacaval anastomosis in cirrhotic patients with esophageal varices. N Engl J Med 272:1255–1263
16. Conn HO, Lindenmuth WW (1969) Prophylactic portacaval anastomosis in patients with esophageal varices and ascites: experimental design and preliminary results. Am J Surg 117:656–661
17. Dagradi A (1972) The natural history of esophageal varices in patients with alcoholic liver cirrhosis. Am J Gastroenterol 57:520–540
18. Doffoel M, Brandt CM, Fincker JL et al. (1980) Relationship between portal hypertension, ascites, gastro-esophageal varices, and gastrointestinal bleeding in patients with alcoholic cirrhosis. Gastroenterol Clin Biol 4:376–382
19. Eckardt VF, Grace D, Kantrowitz DA (1976) Does lower esophageal sphincter incompetency contribute to esophageal variceal bleeding? Gastroenterology 71:185–189
20. Evans DM, Jones DB, Cleary BK, Smith PM (1982) Oesophageal varices treated by sclerotherapy: a histopathological study. Gut 23:615–620
21. Fleig W, Stange EF, Wördehoff D, Rainer K, Ditschuneit H (1986) Endoscopic sclerotherapy for the primary prophylaxis of variceal bleeding in cirrhotic patients. Preliminary results of a randomized, controlled trial (abstract). International symposium on prophylaxis of variceal bleeding, Munich, January 24–25
22. Freeman JG, Barton JR, Record CO (1985) Effect of isosorbide dinitrate, verapamil, and labetalol on portal pressure in cirrhosis. Br Med J 291:561–562
23. Frishman WH (1981) Nadolol: a new β-adrenergic antagonist. N Engl J Med 305:678–682
24. Gangl A (1986) Personal communication, International

symposium on prophylaxis of variceal bleeding, Munich, January 24–25
25. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickmann M (1985) Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology 5:419–424
26. Gerbes AL, Remien J, Jüngst D, Sauerbruch T, Paumgartner G (1986) Evidence for down-regulation of beta-2-adrenoceptors in cirrhotic patients with severe ascites. Lancet I:1409–1410
27. Gertsch PH, Loup P, Diserens H, Mosimann R (1982) Endoscopic non-invasive manometry of oesophageal varices: prognostic significance. Am J Surg 144:528–530
28. Hillon P, Lebrec D, Munoz C, Jungers M, Goldfarb G, Benhamou JP (1982) Comparison of the effects of a cardioselective and a non-selective beta-blocker on portal hypertension in patients with cirrhosis. Hepatology 2:528–531
29. Hosking DR (1986) Personal communication, International symposium on prophylaxis of variceal bleeding, Munich, January 24–25
30. Inokuchi K (1984) Prophylactic portal nondecompression surgery in patients with esophageal varices. Ann Surg 200:61–65
31. Jackson FC, Perrin EB, Smith AG, Dagradi AE, Nudal HM (1968) A clinical investigation of the portacaval shunt. II Survival analysis of the prophylactic operation. Am J Surg 115:22–42
32. Janson R, Thelen M, Paquet KJ (1976) Mediastinale und pulmonale Komplikationen der Sklerosierungsbehandlung von Ösophagusvarizen. Fortschr Röntgenstr 124:44–47
33. Jenkins SA, Baxter JN, Johnston JN, Devitt P, Shields R (1985) Effects of a selective beta 2 blocker (ICI 118.551) on hepatic hemodynamics in the cirrhotic and non-cirrhotic rat. Br J Surg 72:653–656
34. Kleber G, Sauerbruch T, Ansari H, Paumgartner G (1986) Bleeding risk factors in patients with portal hypertension and oesophageal varices (abstract). Z Gastroenterol [Suppl 1] 24:52
35. Klein Ch-P (1985) Spironolacton in der Behandlung der portalen Hypertonie bei Leberzirrhose. Dtsch Med Wochenschr 110:1774–1776
36. Koch H, Henning H, Grimm H, Soehendra N (1986) Prophylactic sclerosing of esophageal varices – results of a prospective controlled study. Endoscopy 18:40–43
37. Kong CW, Lay CS, Tsai YT, Yeh CL, Lai KH, Lee SD, Lo KJ, Chiang BN (1986) The hemodynamic effect of verapamil on portal hypertension in patients with postnecrotic cirrhosis. Hepatology 6:423–426
38. Korula J, Balart LA, Radvan G, Zweiban BE, Larson AW, Kao HW, Yamada S (1985) A prospective, randomized controlled trial of chronic esophageal variceal sclerotherapy. Hepatology 5:584–589
39. Kroeger RJ, Groszman RJ (1985) Effect of selective blockade of beta 2 adrenergic receptors on portal and systemic hemodynamics in a portal hypertensive rat model. Gastroenterology 88:896–900
40. Lebrec D, De Fleury P, Rueff B, Nahum H, Benhamou JP (1980) Portal hypertension, size of esophageal varices, and risk of gastrointestinal bleeding in alcoholic cirrhosis. Gastroenterology 79:1139–1144
41. Lebrec D, Poynard T, Hillon P, Benhamou JP (1981) Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study. N Engl J Med 305:1371–1374
42. Lebrec D, Hillon P, Munoz C, Goldfarb G, Nouel O, Benhamou JP (1982) The effect of propranolol on portal hypertension in patients with cirrhosis: a hemodynamic study. Hepatology 2:523–527
43. Lebrec D, Poynard T, Bernuau J, Bercoff E, Nouel O, Capron JP, Poupon R, Bouvry M, Rueff B, Benhamou JP (1984) A randomized controlled study of propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis. A final report. Hepatology 4:355–358
44. Lebrec D, Poynard T, Capron JP, Hillon P, Geoffroy P, Arsène P, Roulot D, Chaput JC, Benhamou JP (1986) A randomized trial of nadolol for prevention of gastrointestinal bleeding in patients with cirrhosis (abstract). Gastroenterology 90:1740
45. Liebowitz HR (1961) Pathogenesis of esophageal varix rupture. JAMA 175:874–879
46. MacDougall BRD, Williams R (1983) A controlled clinical trial of cimetidine in the recurrence of variceal hemorrhage: implications about the pathogenesis of hemorrhage. Hepatology 3:69–73
47. MacDougall BRD, Westaby D, Theodossi A et al. (1982) Increased long-term survival in variceal haemorrhage using injection sclerotherapy. Lancet I:124–127
48. Medical Research Council Working Party (1985) MRC trial of treatment of mild hypertension: principal results. Br Med J 291:97–104
49. Mills PR, Rae AP, Farah DA, Russell R, Lorimer AR, Carter DC (1984) Comparison of three adrenoreceptor blocking agents in patients with cirrhosis and portal hypertension. Gut 25:73–78
50. Miotti T, Reichen J (1985) Pharmakologische Therapie der portalen Hypertonie. Schw Med Wochenschr 115: 1468–1475
51. Miotti T, Reichen J (1985) Verapamil improves fractional clearance of indocyanine green in patients with liver cirrhosis. J Hepatol Suppl 2:291
52. Monroe P, Morrow CF, Millen JE, Fairman RP, Glanser FL (1983) Acute respiratory failure after sodium morrhuate esophageal sclerotherapy. Gastroenterology 85:693–699
53. Noda T (1984) Angioarchitectural study of esophageal varices. Virchows Arch 404:381–392
54. Orloff MJ, Thomas HS (1963) Pathogenesis of esophageal varix rupture. Arch Surg 87:301–306
55. Pagliaro L, Pastu L, D'Amico G et al. (1986) A randomized clinical trial of propranolol for the prevention of initial bleeding in cirrhosis with portal hypertension (letter). N Engl J Med 314:244–245
56. Palmer ED, Brick IB (1956) Correlation between the severity of esophageal varices in portal cirrhosis and their propensity towards hemorrhage. Gastroenterology 30:85–90
57. Paquet KJ (1982) Prophylactic endoscopic sclerosing treatment of the esophageal wall in varices – a prospective controlled trial. Endoscopy 14:4–5
58. Paquet KJ, Oberhammer E (1978) Sclerotherapy of bleeding oesophageal varices by means of endoscopy. Endoscopy 10:7–12
59. Pascal JP and a Multicenter Study Group (1986) Controlled trial of prophylactic β-blocker therapy. International symposium on prophylaxis of variceal bleeding, Munich, January 24–25
60. Paumgartner G (1984) Pathophysiologische Grundlagen und Abklärung von Patienten mit Ösophagusvarizen. Verh Dtsch Ges Inn Med 90:269–272
61. Polish E, Sullivan BH (1961) Esophagitis associated with hemorrhage from esophageal varices. Ann Intern Med 54:908–911
62. Ponce J, Froute A, de la Morena E, Mir J, Rayón M, Pina R, Berenguer J (1981) Morphometric study of the esophageal mucosa in cirrhotic patients with variceal bleeding. Hepatology 1:641–646
63. Rector WG, Reynolds TB (1984) Propranolol in the treatment of cirrhotic ascites. Arch Intern Med 144:1761–1763

64. Rector WG, Reynolds TB (1985) Risk factors for haemorrhage from oesophageal varices and acute gastric erosions. Clin Gastroenterol 14:139–153
65. Reding P, Urbain D, Griregnee A, Frere D (1986) Portal venous-esophageal luminal pressure gradient in cirrhosis. Hepatology 6:98–100
66. Reichen J (1986) Drug candidates for pharmacotherapy of portal hypertension. International symposium on prophylaxis of variceal bleeding, Munich, January 24–25
67. Resnick RH, Chalmers TC, Ishihara AM, Garceau AJ, Callow AD, Schimmel EM, O'Hara ET, Boston Inter-Hospital Liver Group (1969) A controlled study of the prophylactic portacaval shunt. A final report. Ann Intern Med 70:657–688
68. Reynolds TB (1982) Portal hypertension. In: Schiff L, Schiff ER (eds) Diseases of the liver. Lippincott, Philadelphia, Toronto, pp 393–431
69. Reynolds TB (1986) Role of portal pressure. International symposium on prophylaxis of variceal bleeding, Munich, January 24–25
70. Reynolds TB, Redeker AG, Geller HM (1957) Wedged hepatic venous pressure. Am J Med 22:341–350
71. Saks BJ, Kilby AE, Dietrich PA, Coffin LH, Krawitt EL (1983) Pleural and mediastinal changes following endoscopic injection slerotherapy of esophageal varices. Radiology 149:639–642
72. Sauerbruch T, Holl J, Ruckdeschel G, Förstl J, Weinzierl M (1985) Bacteriaemia associated with endoscopic sclerotherapy of oesophageal varices. Endoscopy 17:170–172
73. Sauerbruch T, Weinzierl M, Köpcke W, Paumgartner G (1985) Long-term sclerotherapy of bleeding esophageal varices in patients with liver cirrhosis. An evaluation of mortality and rebleeding risk factors. Scand J Gastroenterol 20:51–58
74. Sauerbruch T, Ansari H, Weinzierl M, Holl J (1986) Akute Blutung aus Ösophagusvarizen. Diagnose und Therapie. Therapiewoche 36:1000–1006
75. Sauerbruch T, Wotzka R, Köpcke W, Härlin M, Kühner W, Sander R, Heldwein M, Ultsch B, Ansari H, Paumgartner G (1986) Endoscopic sclerotherapy (ST) for prophylaxis of first variceal bleeding in liver cirrhosis. Early results of a prospective randomized trial (abstract). Gastroenterology 90:1765
76. Snady H, Korsten MA, Wayne JD (1985) The relationship of bacteremia to the length of injection needle in endoscopic variceal sclerotherapy. Gastrointest Endoscopy 31:243–246
77. Söderlund C, Ihre Th (1985) Endoscopic sclerotherapy vs conservative management of bleeding oesophageal varices. Acta Chir Scand 151:449–456
78. Soehendra N, de Heer K, Kempenears I, Runge M (1983) Sclerotherapy of oesophageal varices: acute arrest of gastrointestinal hemorrhage or long-term therapy? Endoscopy 15:136
79. Spence RAJ, Sloan JM, Johnston GW (1983) Oesophagitis in patients undergoing oesophageal transection for varices – a histological study. Br J Surg 70:332–334
80. Spence RAJ, Sloan JM, Johnston GW, Greenfield A (1983) Oesophageal mucosal changes in patients with varices. Gut 24:1024–1029
81. Spence RAJ, Sloan JM, Johnston GW (1984) Histologic factors of the esophageal transection ring as clues to the pathogenesis of bleeding varices. Surg Gynecol Obstet 159:253–259
82. Staritz M, Manns M, Poralla T, Meyer zum Büschenfelde KH (1985) A new method for measurement of the intravascular oesophageal variceal pressure (IOVP) and assessment of IOVP in cirrhotic patients with and without recent variceal hemorrhage (abstract). Gastroenterology 88:1697
83. Staritz M, Poralla T, Meyer zum Büschenfelde K-H (1985) Intravascular oesophageal variceal pressure (IOVP) assessed by endoscopic fine needle puncture under basal conditions. Valsalva's manoeuvre and after glyceryltrinitrate application. Gut 26:525–530
84. Stelzner F, Lierse W (1968) Der angiomuskuläre Dehnverschluß der terminalen Speiseröhre. Langenbecks Arch Klin Chir 321:35–64
85. Tarver D, Walt RP, Dunk AA et al. (1983) Precipitation of hepatic encephalopathy by propranolol in cirrhosis. Br Med J 287:585
86. Terblanche J (1986) Sclerotherapy for prophylaxis of variceal bleeding. Lancet I:961–963
87. Terblanche J, Northover JMA, Bornman P, Kahn D, Silber W, Barbezat GO, Sellars S, Campbell JA, Saunders SJ (1979) A prospective controlled trial of sclerotherapy in the long-term management of patients after esophageal variceal bleeding. Surg Gynecol Obstet 148:323–333
88. Terblanche J, Northover JMA, Bornman P, Kahn D, Barbezat GO, Sellars SL, Saunders SJ (1979) A prospective evaluation of injection sclerotherapy in the treatment of acute bleeding form esophageal varices. Surgery 85:239–244
89. The Copenhagen Esophageal Varices Sclerotherapy Project: Sclerotherapy after first variceal hemorrhage in cirrhosis. A randomized multicenter trial (1984) N Engl J Med 311:1594–1600
90. Tygstrup N (1986) Epidemiology and mortality of first variceal bleeding in cirrhotics (abstract). International symposium on prophylaxis of variceal bleeding, Munich, January 24–25
91. Van Buuren HR, Koorevaar G, van der Velden PC (1982) Propranolol increases arterial ammonia in cirrhosis. Lancet II:951–952
92. Viallet A, Marleau D, Huet M, Martin F, Farley A, Villeneuve J-P, Lavoie P (1975) Hemodynamic evaluation of patients with intrahepatic portal hypertension. Relationship between bleeding varices and the portohepatic gradient. Gastroenterology 69:1297–1300
93. Vinel JP, Gassigneul J, Louis A (1982) Clinical and prognostic significance of portohepatic gradients in patients with cirrhosis. Surg Gynecol Obstet 155:347–352
94. Westaby D, Melia WH, MacDougall BRD, Hegarty JE, Williams R (1984) Injection sclerotherapy for oesophageal varices: a prospective randomized trial of different treatment schedules. Gut 25:129–132
95. Witzel L, Wolbergs E, Merki H (1985) Prophylactic endoscopic sclerotherapy of oesophageal varices. Lancet I:773–775
96. Wördehoff D (1986) Personal communication, International symposium on prophylaxis of variceal bleeding, Munich, January 24–25
97. Zimmon DS, Kessler RE (1974) The portal pressure-blood volume relationship in cirrhosis. Gut 15:99–101

Received September 4, 1986
Accepted September 17, 1986

T. Sauerbruch, M.D.
Medizinische Klinik II
Klinikum Grosshadern
Marchioninistr. 15
D-8000 München 70