

## EDITORIAL



## Early TIPS to Improve Survival in Acute Variceal Bleeding

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Gastroesophageal varices are present in 50% of patients with cirrhosis, and variceal hemorrhage develops in up to one third of these patients. The risk of variceal hemorrhage is increased in patients who have large varices and advanced stages of liver disease, as assessed on the basis of the Child–Pugh class.<sup>1</sup> Several studies published between 1942 and 1981 showed poor outcomes after variceal hemorrhage, with mortality rates of 40% at 6 weeks and 70% at 1 year.<sup>2–5</sup> Over the past five decades, a number of randomized trials have shown an improvement in the efficacy of endoscopic, pharmacologic, surgical, and radiologic techniques for arresting hemorrhage, but most of these studies were not powered to determine whether these therapies resulted in a survival benefit. Subsequently, retrospective single-center and multicenter studies have shown a decrease in in-hospital mortality associated with variceal hemorrhage over the past two decades.<sup>6,7</sup> The decrease in mortality was largely due to the prevention of rebleeding with the use of earlier, more effective endoscopic therapy in combination with vasoactive medications and to the prevention of sepsis through the use of antibiotic prophylaxis. Despite this improvement, however, the mortality at 30 days among patients in Child–Pugh class C is still 32%, and 75% of the patients who require transjugular intrahepatic portosystemic shunt (TIPS) as rescue therapy to control index bleeding are in Child–Pugh class C.<sup>6,8</sup> In addition, a Child–Pugh score above 9 has been identified as an independent risk factor for death, with a hazard ratio of 1.45 for each 1-point increase in the score.<sup>9</sup>

Current practice guidelines for treating patients with acute variceal bleeding recommend fluid resuscitation, antibiotic prophylaxis, and vasoactive drugs such as glypressin or somatostatin analogues, followed by early endoscopy and either li-

gation or sclerosis of the varices.<sup>1</sup> Despite these measures, failure to control index bleeding occurs in 10 to 20% of patients. An elevated hepatic venous pressure gradient (>20 mm Hg) measured within 24 hours after the start of bleeding is the best predictor of treatment failure.<sup>10</sup> The use of TIPS to control variceal bleeding has largely been reserved for patients who require rescue therapy because hemostasis has not been achieved, either during the index bleeding or during the secondary-prophylaxis period. TIPS is extremely effective in controlling bleeding, with a reported rate of immediate hemostasis of 93% and with rebleeding in only 12% of patients. Nevertheless, mortality at 6 weeks among patients treated with rescue TIPS for uncontrolled index bleeding and rebleeding is very high (35%), reflecting the severity of their underlying liver disease as well as additional organ dysfunction that may have occurred owing to hypotension, infection, and aspiration.<sup>11</sup>

In this issue of the *Journal*, García-Pagán and colleagues<sup>12</sup> report the results of a randomized, multicenter study that compared early TIPS with optimal medical therapy (endoscopic therapy plus vasoactive drugs) in patients at high risk for rebleeding who were either in Child–Pugh class B with active bleeding at endoscopy or in Child–Pugh class C. After the acute bleeding, the medical-therapy group received endoscopic therapy until obliteration of the varices, followed by surveillance, beta-blockade (in 80% of patients), and nitrates (in 39% of patients). Thirty-one of the 32 patients randomly assigned to the early-TIPS group underwent shunting within 72 hours after endoscopy, and the portal-pressure gradient was reduced to less than 12 mm Hg in all but 2 of these 31 patients.

This study shows the benefit of early TIPS in patients with Child–Pugh class B or C disease who

are at high risk for uncontrolled bleeding with standard therapy. Patients who were randomly assigned to receive TIPS had a significantly better chance of remaining free of bleeding than did those who received the standard care (97% vs. 50%), possibly owing to a greater reduction in portal pressure with TIPS than could be achieved with pharmacologic therapy.

The rate of survival at 6 weeks was 97% in the TIPS group as compared with 67% in the medical-therapy group, as a result of reductions in rebleeding, sepsis, and liver failure. However, the 86% 1-year survival rate in the TIPS group is somewhat surprising for patients with Child–Pugh class B or C disease who have variceal bleeding.

Does early TIPS alter the natural history of cirrhosis, or were these findings attributable to abstinence from alcohol in the large proportion of study patients with a diagnosis of alcohol-related cirrhosis (66%), half of whom were actively drinking at the time of presentation? Given that abstinence has been associated with improvement in liver function, it would be interesting to know whether any of these patients had improvement in the Model for End-Stage Liver Disease (MELD) score or the Child–Pugh class. An alternative theory is that the placement of TIPS early in the illness results in a large reduction in portal pressure and preservation of liver function, with a reduction in the risk of liver decompensation that has not typically been associated with the use of rescue TIPS.

Use of the newer stents, which are covered with extended polytetrafluoroethylene (e-PTFE), probably has an important bearing on the outcome of this study. For reasons that are unclear, e-PTFE-covered stents, as compared with bare-metal stents, are associated with better long-term survival among patients undergoing TIPS.<sup>13</sup> This finding may be related to a reduced rate of TIPS dysfunction and thus fewer complications of portal hypertension with the newer stents, but there are no clearly established reasons for this phenomenon.<sup>14</sup>

In conclusion, the study by García-Pagán and colleagues should stimulate a reevaluation of how we approach variceal bleeding in patients with Child–Pugh class B or C disease. Instead of tak-

ing a wait-and-see approach, physicians should consider the early use of TIPS with an e-PTFE-covered stent as first-line therapy rather than as rescue treatment if rebleeding occurs in high-risk patients with Child–Pugh B or C disease. Additional clinical trials of adequate size should be performed to confirm these findings and to examine the effect of a rapid reduction in portal pressure on disease progression in patients with cirrhosis of other causes.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## ORIGINAL ARTICLE

# Early Use of TIPS in Patients with Cirrhosis and Variceal Bleeding

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## ABSTRACT

**BACKGROUND**

Patients with cirrhosis in Child–Pugh class C or those in class B who have persistent bleeding at endoscopy are at high risk for treatment failure and a poor prognosis, even if they have undergone rescue treatment with a transjugular intrahepatic portosystemic shunt (TIPS). This study evaluated the earlier use of TIPS in such patients.

**METHODS**

We randomly assigned, within 24 hours after admission, a total of 63 patients with cirrhosis and acute variceal bleeding who had been treated with vasoactive drugs plus endoscopic therapy to treatment with a polytetrafluoroethylene-covered stent within 72 hours after randomization (early-TIPS group, 32 patients) or continuation of vasoactive-drug therapy, followed after 3 to 5 days by treatment with propranolol or nadolol and long-term endoscopic band ligation (EBL), with insertion of a TIPS if needed as rescue therapy (pharmacotherapy–EBL group, 31 patients).

**RESULTS**

During a median follow-up of 16 months, rebleeding or failure to control bleeding occurred in 14 patients in the pharmacotherapy–EBL group as compared with 1 patient in the early-TIPS group ( $P=0.001$ ). The 1-year actuarial probability of remaining free of this composite end point was 50% in the pharmacotherapy–EBL group versus 97% in the early-TIPS group ( $P<0.001$ ). Sixteen patients died (12 in the pharmacotherapy–EBL group and 4 in the early-TIPS group,  $P=0.01$ ). The 1-year actuarial survival was 61% in the pharmacotherapy–EBL group versus 86% in the early-TIPS group ( $P<0.001$ ). Seven patients in the pharmacotherapy–EBL group received TIPS as rescue therapy, but four died. The number of days in the intensive care unit and the percentage of time in the hospital during follow-up were significantly higher in the pharmacotherapy–EBL group than in the early-TIPS group. No significant differences were observed between the two treatment groups with respect to serious adverse events.

**CONCLUSIONS**

In these patients with cirrhosis who were hospitalized for acute variceal bleeding and at high risk for treatment failure, the early use of TIPS was associated with significant reductions in treatment failure and in mortality. (Current Controlled Trials number, ISRCTN58150114.)

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**V**ARICEAL BLEEDING IS A SEVERE COMPLICATION of portal hypertension and a major cause of death in patients with cirrhosis. Advanced liver failure, failure to control variceal bleeding, early rebleeding, and marked elevations in portal pressure are associated with increased mortality.<sup>1-3</sup> Combined treatment with vasoactive drugs, prophylactic antibiotics, and endoscopic techniques is the recommended standard of care for patients with acute variceal bleeding.<sup>4,5</sup> However, treatment failure occurs in about 10 to 15% of patients,<sup>6,7</sup> who require repeat endoscopic treatments and multiple transfusions.<sup>8-10</sup> Treatment with a transjugular intrahepatic portosystemic shunt (TIPS) is highly effective in the control of bleeding in such patients, but mortality is still very high,<sup>9</sup> probably because of further deterioration due to liver failure.

In a study involving patients at high risk for treatment failure, as indicated by a hepatic venous pressure gradient of 20 mm Hg or more,<sup>11</sup> early treatment with TIPS improved the prognosis in comparison with medical treatment in a study by Monescillo et al.<sup>12</sup> However, the treatment administered in the medical-treatment group was not the current standard of care,<sup>12</sup> which may have resulted in a worse outcome than expected in this group.

We conducted a study to determine whether early treatment with TIPS, with the use of a stent covered with extended polytetrafluoroethylene (e-PTFE), can improve outcomes in patients with cirrhosis and variceal bleeding who are at high risk for treatment failure and death.

## METHODS

### SELECTION OF PATIENTS

We enrolled patients at nine European centers (see the Supplementary Appendix, available with the full text of this article at NEJM.org) between May 2004 and March 2007. Eligible patients had cirrhosis with acute esophageal variceal bleeding that was being treated with a combination of vasoactive drugs, endoscopic treatment, and prophylactic antibiotics. Patients had Child-Pugh class C disease (a score of 10 to 13) or they had class B disease (a score of 7 to 9) but with active bleeding at diagnostic endoscopy. Patients with scores higher than 13 were excluded from the study. (In the Child-Pugh classification of liver disease, class A [a score of 5 or 6] indicates the least severe disease, class B [7 to 9] moderately

severe disease, and class C [10 to 15] the most severe disease.) Endoscopic band ligation (EBL) or endoscopic injection sclerotherapy (EIS) was applied at the time of diagnostic endoscopy, performed within 12 hours after admission, while the patients were already receiving vasoactive drugs (terlipressin [2 mg every 4 hours], somatostatin [250 to 500  $\mu$ g per hour], or octreotide [50 to 100  $\mu$ g per hour]). Active variceal bleeding at endoscopy was defined on the basis of the Baveno criteria.<sup>13</sup>

Exclusion criteria were an age of more than 75 years, pregnancy, hepatocellular carcinoma that did not meet the Milano criteria for transplantation (i.e., a single lesion <5 cm or multiple lesions [maximum of three], the largest of which measures  $\leq$ 3 cm), a creatinine level greater than 3 mg per deciliter (265  $\mu$ mol per liter), a Child-Pugh score above 13 points, previous pharmacologic therapy combined with endoscopic treatment to prevent rebleeding, previous use of a portosystemic shunt or TIPS, bleeding from isolated gastric or ectopic varices, total portal-vein thrombosis, and heart failure.

All patients provided written informed consent. The study protocol was approved by the ethics committees of all participating hospitals and followed the Guidelines for Good Clinical Practice in clinical trials.

### STUDY DESIGN

Randomization was performed within 24 hours after admission. The randomization sequence was generated by computer with the use of a concealed block size of four. The coded treatment assignments were kept at the coordinating center in sealed, consecutively numbered, opaque envelopes. Randomized assignments to the study groups were made by contacting the coordinating center (available 24 hours a day) by telephone or fax.

### DRUG THERAPY PLUS EBL

Treatment with vasoactive drugs was continued until patients were free of bleeding for at least 24 hours and preferably up to 5 days, at which point treatment with a nonselective beta-blocker (either propranolol or nadolol) was started. The dose was increased in a stepwise fashion every 2 to 3 days to the maximum tolerated dose or to a maximum of 160 mg twice daily for propranolol and 240 mg per day for nadolol. After these doses were achieved, 10 mg of isosorbide-5-mononitrate was initiated at bedtime, with a stepwise increase in the dose to a maximum of 20 mg twice a day or

the maximum tolerated dose. In addition, within 7 to 14 days after the initial endoscopic treatment, the second, elective session of EBL was performed. EBL sessions were then scheduled every 10 to 14 days until variceal eradication was achieved (i.e., varices disappeared or could not be suctioned into the banding device).

EBL sessions were performed with the use of multiband devices (6-Shooter Saeed Multi-Band Ligator, Cook, or Speedband SuperView Super 7, Boston Scientific), and bands were applied starting at the gastroesophageal junction. Patients received proton-pump inhibitors until variceal eradication was accomplished. After eradication, endoscopic monitoring was performed at 1-month, 6-month, and 12-month intervals and then annually. If varices reappeared, further EBL sessions were initiated.

Treatment failure was defined as one severe rebleeding episode (i.e., requiring a transfusion of more than 2 units of blood) or two, less severe rebleeding episodes,<sup>13</sup> with TIPS and placement of an e-PTFE-covered stent used as rescue therapy when necessary.

#### EARLY TIPS

TIPS was performed within 72 hours after diagnostic endoscopy (or, when possible, within the first 24 hours), and vasoactive drugs were administered until then. The e-PTFE-covered stents (we purchased Viatorr TIPS endoprosthesis, Gore) were initially dilated to 8 mm. If the portal-pressure gradient (the difference between portal-vein pressure and inferior vena caval pressure) did not decrease to below 12 mm Hg, the stent was dilated to 10 mm.

TIPS revision was performed if there was clinical recurrence of portal hypertension or evidence of TIPS dysfunction on Doppler ultrasonography (i.e., portal blood-flow velocity of <28 cm per second, a change in the direction of flow in intrahepatic portal branches, or a drop in portal blood-flow velocity of >50%).<sup>14</sup> If TIPS dysfunction was confirmed, angioplasty was performed or another e-PTFE-covered stent was placed.

#### FOLLOW-UP

Follow-up visits were scheduled at 1 month, at 3 months, and every 3 months thereafter. Doppler ultrasonography was performed at the first visit, at 6 months, and every 6 months thereafter. Patients were followed until death or liver trans-

plantation up to a maximum of 2 years of follow-up or until the end of the study (September 2007).

#### STUDY END POINTS

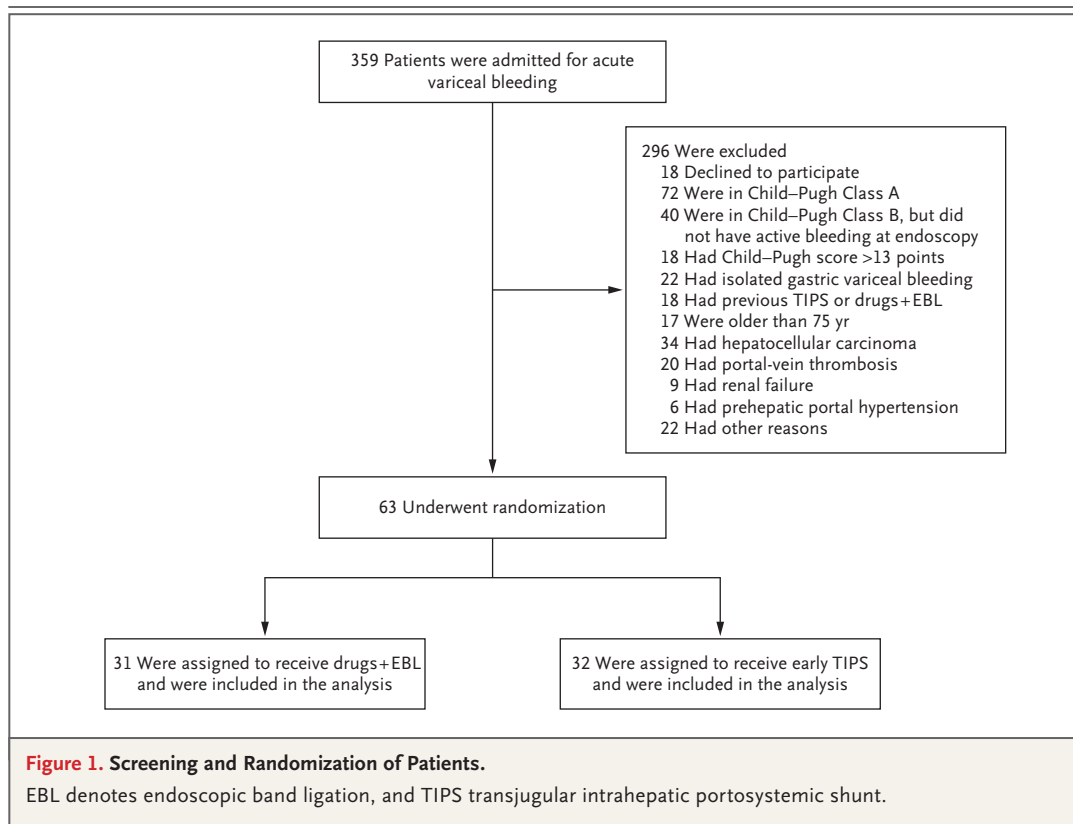
The primary end point of the study was a composite outcome of failure to control acute bleeding or failure to prevent clinically significant variceal rebleeding within 1 year after enrollment. Secondary end points were mortality at 6 weeks and at 1 year, failure to control acute bleeding, early rebleeding (rate of rebleeding at 5 days and at 6 weeks), rate of rebleeding between 6 weeks and 1 year, the development of other complications related to portal hypertension on follow-up, the number of days in the intensive care unit, the percentage of follow-up days spent in the hospital, and the use of alternative treatments.

#### STATISTICAL ANALYSIS

In a study by Villanueva et al. involving patients with active variceal bleeding at endoscopy, the rate of failure to control bleeding within 5 days, despite the combined use of drugs plus endoscopic treatment, was 27%.<sup>15</sup> Similarly, the rate of failure was 23% in a study involving patients with Child–Pugh class B or C disease who received combined pharmacologic and endoscopic treatment.<sup>16</sup> We assumed in our population a 25% rate of failure to control bleeding at 5 days. Considering that rebleeding occurred between day 5 and 1 year in an additional 20%,<sup>6,17</sup> the cumulative rate of failure to control bleeding or rebleeding at 1 year was estimated to be 45%. We hypothesized that this risk would be reduced to 10% by an early decision to use e-PTFE-covered TIPS. Because the only rationale for early use of TIPS would be evidence that this approach is better than the current standard treatment, the sample size was calculated with the use of a one-sided test.<sup>18,19</sup> We calculated that 31 patients per group would be needed to detect these differences, with an alpha level of 0.05 and a beta level of 0.20.

All data analyses were performed on an intention-to-treat basis according to a preestablished analysis plan. Dichotomous variables were compared by means of Fisher's exact test, and continuous variables were compared by means of the nonparametric Mann–Whitney rank-sum test. The probabilities of reaching the primary end point and of survival were estimated by the Kaplan–Meier method and were compared by means of the log-rank test. Absolute risk reductions and





number needed to treat, with 95% confidence intervals, were calculated as an estimate of the effect size and its precision. A P value of less than 0.05 was considered to indicate statistical significance, and all tests were two-sided. The statistical software packages used for the analysis were SPSS (version 16.0) and confidence interval analysis (CIA, version 2.1.2, University of Southampton, United Kingdom).

## RESULTS

### STUDY PATIENTS

We screened 359 patients with acute variceal bleeding who were admitted to the participating hospitals for study eligibility. A total of 296 patients were excluded (Fig. 1), and the remaining 63 patients were randomly assigned to either the pharmacotherapy-EBL group (31 patients) or the early-TIPS group (32 patients). There were no significant differences in baseline characteristics between the two groups at the time of entry into the study (Table 1). A total of 7 patients (3 in the pharmacotherapy-EBL group and 4 in the early-TIPS group) were lost to follow-up after a median

of 8 months (range, 0.5 to 12) without reaching the composite end point. The mean ( $\pm$ SD) follow-up period was  $10.6 \pm 9.9$  months in the pharmacotherapy-EBL group and  $14.6 \pm 8.4$  months in the early-TIPS group. A total of 6 patients (2 in the pharmacotherapy-EBL group and 4 in the early-TIPS group) underwent liver transplantation during follow-up.

In the pharmacotherapy-EBL group, 22 patients received propranolol (median dose, 55 mg [range, 10 to 160]), and only 3 received nadolol. In the remaining 6 patients, nonselective beta-blocker therapy was not initiated because of failure to control bleeding, early rebleeding, or death. In 12 patients, isosorbide-5-mononitrate was added to the nonselective beta-blocker (median dose, 25 mg [range, 10 to 40]), but it was not added in 13 patients because of arterial hypotension, the treating physician's preference, or early death. Variceal eradication was achieved in 12 patients after a median of 2 EBL sessions (range, 1 to 7) without rebleeding; in 4 patients, eradication was achieved after treatment of a rebleeding episode with additional EBL sessions. In the remaining 15 patients, eradication was not achieved (in 12 because

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Pharmacotherapy–EBL Group (N = 31)	Early-TIPS Group (N = 32)	P Value
Age (yr)	49±6	52±10	0.22
Sex (no. of patients)			0.78
Male	23	21	
Female	8	11	
Cause of cirrhosis (no. of patients)			0.91
Alcohol	20	22	
HCV	5	4	
Other	6	6	
Active alcoholism (no. of patients)	17	15	0.61
Child–Pugh classification (no. of patients)†			0.99
Class B	16	16	
Class C	15	16	
Child–Pugh score	9.5±1.8	9.3±1.8	0.66
MELD score‡	16.9±6.3	15.5±5	0.28
MELD–Na score§	19±7	17±6	0.25
Ascites (no. of patients)	18	19	0.99
Bilirubin (mg/dl)	4.4±4.9	3.7±4.8	0.34
Albumin (g/liter)	26±7	26±7	0.89
Prothrombin time (%)¶	50±15	53±15	0.33
Creatinine (mg/dl)	1±0.4	1±0.5	0.59
Previous hepatic encephalopathy (no. of patients)	0	6	0.03
Previous variceal bleeding in the absence of combined treatment (no. of patients)	5	11	0.15
Active bleeding at endoscopy (no. of patients)	22	23	0.99
Shock at time of admission (no. of patients)	7	7	0.99
Systolic blood pressure (mm Hg)	111±23	104±18	0.22
Hematocrit on admission (%)	27±8	26±6	0.49
Units of blood transfused before randomization (no.)	2.9±3	2.7±2	0.73
Endoscopic treatment at time of index bleeding (no. of patients)			0.17
Band ligation	26	21	
Injection sclerotherapy	5	11	
Vasoactive-drug therapy at time of index bleeding (no. of patients)			0.74
Terlipressin	14	12	
Somatostatin	16	18	
Octreotide	1	2	

\* Plus–minus values are means ±SD. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for creatinine to micromoles per liter, multiply by 88.4. HCV denotes hepatitis C virus, and TIPS transjugular intrahepatic portosystemic shunt.

† According to the Child–Pugh classification of liver disease, class A (5 to 6 points) indicates the least severe disease, class B (7 to 9 points) moderately severe disease, and class C (10 to 15 points) the most severe disease. Patients whose Child–Pugh score exceeded 13 points were not included in the study.

‡ The Model for End-Stage Liver Disease (MELD) score ranges from 6 to 40, with higher scores indicating more severe disease.

§ The MELD–Na score ranges from 6 to 40, with higher scores indicating more severe liver disease.

¶ The values shown represent a proportion of the mean prothrombin time in a group of control subjects.

**Table 2. Summary of Efficacy Measurements.\***

Variable	Pharmacotherapy+EBL Group (N=31)	Early-TIPS Group (N=32)	P Value
Composite end point reached (no. of patients)	14	1	0.001
Child–Pugh classification†			
Class B	5	0	
Class C	9	1	
Treatment failure at 5 days‡	4	1	
Rebleeding			
>5 days–6 wk	7	0	
>6 wk–1 yr	3	0	
Minor rebleeding (no. of patients)	3	1	0.35
Gastric ulcer	1		
Portal hypertensive gastropathy	1		
Varices	1		
Post-EBL ulcer		1	
Days in intensive care unit (no.)	8.6±9	3.6±4	0.01
Orthotopic liver transplantation (no. of patients)	2	4	0.67
Death (no. of patients)	12	4	0.01
Child–Pugh classification			
Class B	2	1	
Class C	10	3	
Cause of death			
Recurrent bleeding	5	0	
Sepsis	4	3	
Liver failure	2	0	
Hepatorenal syndrome	1	0	
Arrhythmia	0	1	
Time in hospital (% of follow-up)			0.014
Median	15	4	
Interquartile range	5–100	2–13	

\* Plus–minus values are means ±SD. EBL denotes endoscopic band ligation, and TIPS transjugular intrahepatic portosystemic shunt.

† According to the Child–Pugh classification of liver disease, class A (5 to 6 points) indicates the least severe disease, class B (7 to 9 points) moderately severe disease, and class C (10 to 15 points) the most severe disease. Patients whose Child–Pugh score exceeded 13 points were not included in the study.

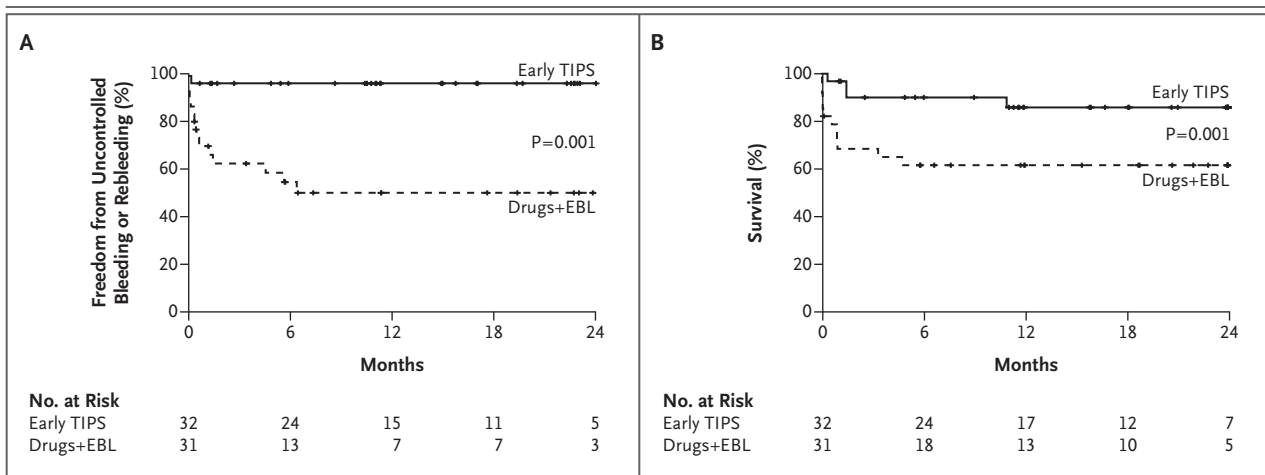
‡ Treatment failure was defined as one severe rebleeding episode (with transfusion requiring more than 2 units of blood) or two less severe rebleeding episodes.

the primary end point was reached [resulting in rescue TIPS in 7 and death in 5], in 2 who were lost to follow-up, and in 1 despite eight EBL sessions).

In the early-TIPS group, all but 1 patient, who withdrew consent, underwent early shunt placement. There were no technical failures or major complications of the TIPS procedure. Paroxysmal supraventricular tachycardia occurred in 1 patient

and was controlled medically. A total of 27 patients required one stent, and 4 required two stents. The mean portal-pressure gradient dropped from  $20.2 \pm 7$  mm Hg to  $6.2 \pm 3$  mm Hg ( $P < 0.001$ ). Despite dilation to 10 mm, the portal-pressure gradient after TIPS remained above 12 mm Hg in 2 patients. Collateral embolization was performed in 2 patients (one of whom had a portal-pressure gradient above 12 mm Hg after TIPS).





**Figure 2. Actuarial Probability of the Primary Composite End Point and of Survival, According to Treatment Group.**

The probability of remaining free from uncontrolled variceal bleeding or variceal rebleeding is shown in Panel A, and the probability of survival is shown in Panel B. EBL denotes endoscopic band ligation, and TIPS transjugular intrahepatic portosystemic shunt.

### REBLEEDING

In the pharmacotherapy–EBL group, 14 patients reached the primary composite end point (Table 2 and Fig. 2). In these patients, the Model for End-Stage Liver Disease (MELD) score (which ranges from 6 to 40, with higher scores indicating more severe disease) increased from a mean of  $18.8 \pm 6.4$  at randomization to  $22.6 \pm 11$  at the time the end point was reached. In 7 of these patients, TIPS with an e-PTFE–covered stent was used as rescue therapy; although bleeding was controlled, 4 of these patients died within 36 days (range, 1 to 36). In 5 patients, no further treatment was considered because of severe liver failure, and all died. In the 9 patients who died, the mean MELD score was  $28.2 \pm 9$  when they reached the primary end point of the study. The remaining 2 patients who reached the primary end point underwent additional EBL sessions and were alive at the end of the follow-up period.

Only 1 patient in the early-TIPS group, in whom the portal-pressure gradient remained above 12 mm Hg, reached the primary end point ( $P < 0.001$  for the comparison with the pharmacotherapy–EBL group) (Table 2). The 1-year actuarial probability of remaining free of failure to control bleeding and of variceal rebleeding was significantly higher in the early-TIPS group than in the pharmacotherapy–EBL group (97% vs. 50%; absolute risk reduction, 47 percentage points; 95% confidence interval [CI], 25 to 69; number needed to treat, 2.1 patients; 95% CI, 1.4 to 4.0) (Fig. 2). An

additional 4 patients (3 in the pharmacotherapy–EBL group and 1 in the early-TIPS group) had a rebleeding episode that was not clinically significant (i.e., it did not require hospital admission or blood transfusion) (Table 2).

### SURVIVAL

A total of 12 patients in the pharmacotherapy–EBL group died, as compared with 4 in the early-TIPS group ( $P = 0.001$ ). The 6-week survival rate was higher in the early-TIPS group than in the pharmacotherapy–EBL group (97% vs. 67%; absolute risk reduction, 30 percentage points; 95% CI, 12 to 48; number needed to treat, 3.3 patients; 95% CI, 2.1 to 8.3), as was the 1-year survival rate (86% vs. 61%; absolute risk reduction, 25 percentage points; 95% CI, 2 to 48; number needed to treat, 4.0 patients; 95% CI, 2.1 to 50.0) (Fig. 2). Causes of death are summarized in Table 2.

### OTHER COMPLICATIONS OF PORTAL HYPERTENSION

The 1-year actuarial probability of hepatic encephalopathy was 28% in the early-TIPS group as compared with 40% in the pharmacotherapy–EBL group (an absolute difference of 12 percentage points; 95% CI, –18 to 40;  $P = 0.13$ ). In the pharmacotherapy–EBL group, 12 patients had a total of 17 episodes of hepatic encephalopathy, whereas in the early-TIPS group, 8 patients had a total of 10 episodes (Table 3). Most of these episodes occurred during the index bleeding. After discharge, the 1-year probability of additional epi-

sodes of hepatic encephalopathy was similar in the two groups (10% in the pharmacotherapy–EBL group and 19% in the early-TIPS group,  $P=0.80$ ). A total of 3 patients in the pharmacotherapy–EBL group and 2 in the early-TIPS group had stage III hepatic encephalopathy, and 1 patient in each group had mild, recurrent hepatic encephalopathy.

The 1-year actuarial probability of new or worsening ascites was 33% in the pharmacotherapy–EBL group and 13% in the early-TIPS group — an absolute difference of 20 percentage points (95% CI, –8 to 47;  $P=0.11$ ). Spontaneous bacterial peritonitis developed during the index bleeding in 2 patients in the pharmacotherapy–EBL group, both of whom died. In addition, the hepatorenal syndrome developed during the index bleeding in 7 patients: 5 in the pharmacotherapy–EBL group, 4 of whom died, and 2 in the early-TIPS group, both of whom survived. The proportion of follow-up time that patients spent in the hospital was 15% (interquartile range, 5 to 100) in the pharmacotherapy–EBL group as compared with 4% (interquartile range, 2 to 13) in the early-TIPS group ( $P=0.01$ ).

#### OTHER ADVERSE EVENTS

As shown in Table 3, there were no significant between-group differences in the numbers of patients who had adverse effects.

#### DISCUSSION

In the study by Monescillo et al.,<sup>12</sup> early treatment with TIPS, as compared with medical treatment, was associated with an improved prognosis among patients at high risk for uncontrolled bleeding or rebleeding on the basis of a hepatic venous pressure gradient of 20 mm Hg or higher.<sup>11</sup> This study did not include continued pharmacologic therapy and EBL in the medical-treatment group, and bare stents were used in the early-TIPS group.<sup>12</sup> The use of e-PTFE–covered stents is associated with reductions in the incidence of TIPS dysfunction and recurrence of complications related to portal hypertension.<sup>20,21</sup> More important, the decision to perform TIPS was based on the measurement of hepatic venous pressure gradients, a test that is not widely available, especially under emergency conditions. Therefore, it is difficult to extrapolate the results of this study for application to clinical practice.

Our study was specifically designed to show

**Table 3. Adverse Events.\***

Adverse Event	Pharmacotherapy–EBL Group (N=31)	Early-TIPS Group (N=32)
<i>no. of patients</i>		
<b>Complications of portal hypertension</b>		
Hepatic encephalopathy	12	8
Ascites	9	5
Spontaneous bacterial peritonitis	2	0
Hepatorenal syndrome	5	2
<b>Other serious adverse events</b>		
Infections (other than pneumonia or spontaneous bacterial peritonitis)	4	4
Pneumonia	3	3
Acute episode in chronic liver failure	1	3
Delirium tremens	2	1
Korsakoff syndrome	0	1
Esophageal perforation	1	0
Dysphagia	1	0
Bleeding from banding-related ulcers	1	0
Cholelithiasis	0	1
Alcoholic hepatitis	0	1
Bleeding duodenal ulcer	0	1
<b>Nonserious adverse events</b>		
Gynecomastia	0	1
Edema	1	0
Sleep disorder	1	0
Chest pain (after EBL)	1	0
Epistaxis (after EBL)	1	0
Vomiting	1	0

\* EBL denotes endoscopic band ligation.

whether an early decision to use TIPS, with e-PTFE–covered stents and based on clinical criteria, can improve the prognosis for patients with variceal bleeding who are at high risk. We found that in patients treated early with TIPS, the risks of failure to control bleeding and of variceal rebleeding were reduced.

In addition, and even more important, the early use of TIPS was associated with a reduction in mortality. This beneficial effect on survival was observed even though rescue TIPS was used in patients in whom medical treatment failed. Mortality was very high among the patients who underwent rescue TIPS after treatment failure, a result that is consistent with the findings in previous

studies.<sup>9,22</sup> Remarkably, in five patients, TIPS was not even considered because of the severe deterioration in liver function, as evidenced by the increased MELD scores, which were higher than those associated with excessive mortality after TIPS.<sup>23</sup> These data make it clear that for patients in Child–Pugh class C or in class B with active variceal bleeding, failure to initially control the bleeding or early rebleeding contributes to further deterioration in liver function, which in turn worsens the prognosis and may preclude the use of rescue TIPS.

Previous studies evaluating the role of TIPS in the prevention of recurrent variceal bleeding clearly showed that TIPS reduces the rebleeding rate but increases hepatic encephalopathy without improving survival.<sup>24–26</sup> Because of these findings, TIPS is currently recommended only as a rescue therapy.<sup>4,5</sup> The results of the present study challenge this recommendation. It should be noted that previous studies of TIPS differed from our study in that they used bare stents or did not limit enrollment to patients at high risk for treatment failure. In the study by Escorsell et al.,<sup>26</sup> more than 15% of patients with variceal bleeding were excluded because of a need for emergency TIPS or death from uncontrolled bleeding before day 5. Therefore, the study design precluded the possibility of demonstrating a benefit of TIPS in these high-risk patients. Furthermore, in another study,<sup>7</sup> mortality was 66% among patients whose bleeding was not controlled by the initial treatment. In high-risk patients, the potentially deleterious effects of e-PTFE-covered TIPS appear to be counterbalanced by its high efficacy in controlling bleeding and thus preventing further clinical deterioration. In contrast, TIPS should not be used as the initial treatment in patients with Child–

Pugh class A disease, since the rates of medical-treatment failure and mortality are low among such patients.

Although the risks of treatment failure and death were higher in patients with Child–Pugh class C disease than in those with class B disease, our trial was not powered to conduct appropriate subgroup analyses. Therefore, further evaluation will be needed to determine whether the early use of TIPS equally benefits these two subgroups of patients.

The early use of TIPS was not associated with an increase in the number or severity of episodes of hepatic encephalopathy.

In conclusion, in patients with Child–Pugh class C disease or class B disease with active bleeding who were admitted for acute variceal bleeding, the early use of TIPS with an e-PTFE-covered stent was associated with significant reductions in the failure to control bleeding, in rebleeding, and in mortality, with no increase in the risk of hepatic encephalopathy.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## JOURNAL CLUB CRITIQUE

# 'The TIPSing point'

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### Expanded abstract

#### Citation

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#### Background

Patients with Child-Pugh class C or class B cirrhosis and **persistent** bleeding at endoscopy are at high risk for treatment **failure** and a **poor prognosis**. This study evaluated the early use of a transjugular intrahepatic portosystemic shunt (TIPS) in such patients.

#### Methods

**Objective:** The study was conducted to determine whether early treatment with extended polytetrafluoroethylene (e-PTFE) can improve outcomes in patients who have cirrhosis and acute variceal bleeding and who are at high risk for treatment failure and death.

**Design:** The study was a **randomized** clinical trial.

**Setting:** The study was conducted at nine **European** centers.

**Subjects:** Eligible patients had cirrhosis with acute esophageal variceal bleeding. Patients had Child-Pugh class **C** disease (a score of 10 to 13) or class **B** disease (a score of 7 to 9) but **with active** bleeding at diagnostic endoscopy.

**Interventions:** Endoscopic **band** ligation (EBL) or endoscopic **injection** sclerotherapy was applied at the time of diagnostic endoscopy in all patients and was performed **within 12 hours** after admission while the patients were already receiving vasoactive drugs.

**Pharmacotherapy-EBL group:** Treatment with vasoactive drugs was continued until patients were free of bleeding for at least 24 hours and preferably up to 5 days, at which

point treatment with a **non-selective beta-blocker** and, subsequently, **oral nitrate** therapy was started.

**Early-TIPS group:** **TIPS** was performed within **72 hours** after diagnostic endoscopy (or, if possible, within the first 24 hours), and **vasoactive** drugs were administered **until** then.

**Outcomes:** The primary end-point of the study was a composite outcome of failure to control acute bleeding or failure to prevent clinically significant variceal re-bleeding within 1 year after enrollment. Secondary end-points included mortality at 6 weeks and at 1 year.

#### Results

During a median follow-up of 16 months, re-bleeding or failure to control bleeding occurred in 14 patients in the pharmacotherapy-EBL group and in one patient in the early-TIPS group ( $P = 0.001$ ). The 1-year actuarial probabilities of remaining free of this composite end-point were 50% in the pharmacotherapy-EBL group and 97% in the early-TIPS group ( $P < 0.001$ ). Sixteen patients died (12 in the pharmacotherapy-EBL group and four in the early-TIPS group;  $P = 0.01$ ). The 1-year actuarial survival rates were 61% in the pharmacotherapy-EBL group and 86% in the early-TIPS group ( $P < 0.001$ ). Seven patients in the pharmacotherapy-EBL group received TIPS as rescue therapy, but four died. The number of days in the intensive care unit and the percentage of time in the hospital during follow-up were significantly higher in the pharmacotherapy-EBL group than in the early-TIPS group. No significant differences with respect to serious adverse events were observed between the two treatment groups.

#### Conclusions

In the cirrhosis patients who were hospitalized for acute variceal bleeding and were at **high risk** for treatment **failure**, the **early** use of **TIPS** was associated with **significant reductions** in treatment **failure** and in **mortality**.

#### Commentary

**Mortality** from acute variceal bleeding (AVB) remains **high despite** optimum medical and endoscopic therapy [1,2]. Treatment with transjugular intrahepatic portosystemic shunt (**TIPS**) is effective to control bleeding in

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this population, but has not increased survival rates, likely, as a result of subsequent liver decompensation [3,4]. The strongest evidence in favor of performing TIPS is for secondary prevention of AVB. Previous studies have shown that TIPS decreased the risk of recurrent variceal bleeding when compared with 'failed' endoscopic therapy [5,6]. The lack of mortality benefit and the increased rate of hepatic encephalopathy following TIPS have limited its use mainly to a salvage therapy [7]. Monescillo and colleagues [8] demonstrated improved survival when compared with medical treatment in patients who had a hepatic venous pressure gradient of at least 20 mm Hg, who were admitted for variceal bleeding, and who subsequently had TIPS within 24 hours. The study by García-Pagán and colleagues [9] attempts to address the role of early TIPS in patients with AVB.

The early use of TIPS improved outcomes in a highly select group of patients with Child-Pugh class C (a score of 10 to 13) or class B (a score of 7 to 9) cirrhosis with active variceal bleeding. The authors screened a total of 359 patients, of whom 31 were randomly assigned to the pharmacotherapy-EBL (endoscopic band ligation) and 32 to the early-TIPS group. The 1-year actuarial probability of remaining free of variceal re-bleeding was significantly higher in the early-TIPS group than in the pharmacotherapy-EBL group (97% versus 50%; absolute risk reduction was 47%, and number needed to treat was 2.1 patients). Mortality rates were lower in the early-TIPS group, and the risk of episodes of hepatic encephalopathy was similar in the two groups. Considering these findings, the authors recommended early TIPS in AVB patients deemed 'high risk for treatment failure' [9].

This was a well-designed, multi-center, randomized, controlled study with an intention-to-treat analysis. The objectives and inclusion and exclusion criteria were well defined, and the follow-up period was adequate. The study used clinical criteria for consideration of TIPS, whereas previous work used the invasively measured parameter of hepatic venous pressure gradient. The use of expanded polytetrafluoroethylene (e-PTFE)-covered stents, which are associated with reductions in the incidence of TIPS dysfunction, is another important difference between this study and that by Monescillo and colleagues [8].

We would like to point out that only small subsets of patients with AVB were recruited (18%), and it took over 34 months to recruit the 63 patients from nine centers. One quarter of patients received sclerotherapy, which is generally considered inferior to band ligation in the management of AVB [10]. The etiology of liver disease in over one half of patients in both groups was secondary to alcohol, with an overwhelming majority of these patients actively drinking. Unless one knows ongoing alcohol use after AVB in both groups, one cannot know whether abstinence may have played a role in survival rates.

Since the publication of the study, the original authors assessed the benefits of early TIPS in a follow-up retrospective cohort who were managed on the basis of the study findings [11]. Thirty patients who received medical-EBL therapy were compared with 45 patients who received early TIPS. The 1- and 2-year actuarial probabilities of recurrent variceal bleeding were 7% (95% confidence interval (CI) 2% to 17%) and 7% (95% CI 2% to 17%) in the early-TIPS group and 47% (95% CI 28% to 63%) and 51% (95% CI 31% to 67%) in the medical group, respectively. The 1-year mortality rate was higher in the medical-EBL therapy group than in the early-TIPS group (30%, 95% CI 15% to 47% versus 14%, 95% CI 6% to 27%;  $P = 0.056$ ). No significant difference in the 1-year actuarial probability of hepatic encephalopathy was noted.

The Baveno V consensus group recommended, on the basis of encouraging results, (class 1b; A) TIPS as an early treatment for high-risk patients [12]. Despite the promising results, we believe that, more than 2 years after the publication of the study, a state of equipoise continues to exist about the value and role of early TIPS versus medical/endoscopic management in the patient who presents with AVB. Although the results of the study by García-Pagán and colleagues [9] are provocative, several key questions remain unanswered. The mean Model for End-Stage Liver Disease (MELD) scores were  $15.5 \pm 5$  in the early-TIPS group and  $16.9 \pm 6.3$  in the pharmacotherapy-EBL arm, raising a number of questions. Should patients with similar Child-Pugh scores but higher MELD scores receive early TIPS? Should hepatic venous pressure gradient be completely ignored, or is there a role for pressure measurements in association with clinical criteria for delineating high-risk patients? Would the strategy be effective in patients with cirrhosis from hepatitis C virus or non-alcoholic steatohepatitis (NASH), in which the insult for liver injury is not so readily removable compared with alcohol, in which abstinence may slow progression of liver disease? Should we set aside the mountain of evidence that showed a high incidence of refractory and debilitating encephalopathy in older patients with advanced cirrhosis after TIPS?

To put these questions into a real-life clinical scenario, consider the following: A 64-year-old with NASH cirrhosis, Child-Pugh class C (score of 12), MELD score of 25, and two prior episodes of encephalopathy in the last two months (one of these episodes requiring intubation) is admitted with his first variceal bleed. An endoscopy reveals medium-sized esophageal varices, and a clear nipple sign is seen in the distal esophagus on the largest varix. Band ligation is performed with good decompression. Should this patient be sent for 'early' TIPS?

A larger study will be helpful to address these issues. Finally, TIPS is a procedure performed by highly trained



specialists, and local technical expertise should be a crucial factor to use early TIPS in a 'non-rescue' situation.

### Recommendation

Early TIPS should be **considered** in AVB after endoscopic intervention in patients with Child-Pugh class **C** (scores of 10 to 13) disease or patients with class **B** (scores of 7 to 9) disease with **active** bleeding at initial endoscopy when **MELD** scores are **not higher** than **22**. It must be emphasized that the study results do not apply to all cirrhosis patients presenting with variceal bleeding.

### Abbreviations

AVB, acute variceal bleeding; CI, confidence interval; EBL, endoscopic band ligation; MELD, Model for End-Stage Liver Disease; NASH, non-alcoholic steatohepatitis; TIPS, transjugular intrahepatic portosystemic shunt.

### Competing interests

The authors declare that they have no competing interests.

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