



# Prevention of Rebleeding From Esophageal Varices in Patients With Cirrhosis Receiving Small-Diameter Stents Versus Hemodynamically Controlled Medical Therapy

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**BACKGROUND & AIMS:** Patients with cirrhosis and variceal hemorrhage have a high risk of rebleeding. We performed a prospective randomized trial to compare the prevention of rebleeding in patients given a small-diameter covered stent vs those given hepatic venous pressure gradient (HVPG)-based medical therapy prophylaxis. **METHODS:** We performed an open-label study of patients with cirrhosis (92% Child class A or B, 70% alcoholic) treated at 10 medical centers in Germany. Patients were assigned randomly more than 5 days after variceal hemorrhage to groups given a small covered transjugular intrahepatic portosystemic stent-shunt (TIPS) (8 mm; n = 90), or medical reduction of portal pressure (propranolol and isosorbide-5-mononitrate; n = 95). HVPG was determined at the time patients were assigned to groups (baseline) and 2 weeks later. In the medical group, patients with an adequate reduction in HVPG (responders) remained on the drugs whereas nonresponders underwent only variceal band ligation. The study was closed 10 months after the last patient was assigned to a group. The primary end point was variceal rebleeding. Survival, safety (adverse events), and quality of life (based on the Short Form-36 health survey) were secondary outcome measures. **RESULTS:** A significantly smaller proportion of patients in the TIPS group had rebleeding within 2 years (7%) than in the medical group (26%) ( $P = .002$ ). A slightly higher proportion of patients in the TIPS group experienced adverse events, including encephalopathy (18% vs 8% for medical treatment;  $P = .05$ ). Rebleeding occurred in 6 of 23 patients (26%) receiving medical treatment before hemodynamic control was possible. Per-protocol analysis showed that rebleeding occurred in a smaller proportion of the 32 responders (18%) than in nonresponders who received variceal band ligation (31%) ( $P = .06$ ). Fifteen patients from the medical group (16%) underwent TIPS placement during follow-up evaluation, mainly

for refractory ascites. Survival time and quality of life did not differ between both randomized groups. **CONCLUSIONS:** Placement of a small-diameter, covered TIPS was straightforward and prevented variceal rebleeding in patients with Child A or B cirrhosis more effectively than drugs, which often required step-by-step therapy. However, TIPS did not increase survival time or quality of life and produced slightly more adverse events. Clinical Trial no: ISRCTN 16334693.

**Keywords:** Nonselective  $\beta$ -Blocker; HVPG; TIPS; Advanced Liver Disease.

Variceal bleeding is a major complication of cirrhosis, associated with a hospital mortality rate of 10%–20%.<sup>1–3</sup> Overall mortality may be higher owing to deaths before admission.<sup>4</sup> Surviving patients are at high risk for recurrent hemorrhage, which is decreased by nonselective  $\beta$ -blockers (NSBBs) with or without nitrates,<sup>5–7</sup> ligation of varices, mostly combined with NSBBs,<sup>8,9</sup> or placement of a transjugular intrahepatic portosystemic stent-shunt (TIPS). TIPS is the most effective method to prevent rebleeding,<sup>10</sup> however, it is burdened with increased hepatic encephalopathy and deterioration of liver function in patients with advanced cirrhosis.<sup>11</sup>

**Abbreviations used in this paper:** cTIPS, covered transjugular intrahepatic portosystemic stent-shunt; HVPG, hepatic venous pressure gradient (wedged hepatic venous pressure minus free hepatic venous pressure); ITT, intention-to-treat; NSBB, nonselective  $\beta$ -blocker; PPG, pressure gradient between portal vein and cava inferior vein; SF-36, Short Form-36; TIPS, transjugular intrahepatic portosystemic stent-shunt.

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Although most trials found no survival benefit, it recently was shown that TIPS placement within 72 hours after acute bleeding not only prevented recurrent bleeding but also improved survival.<sup>12</sup> This raises the question of whether ligation together with NSBB should remain the first choice for elective secondary prophylaxis.<sup>13-15</sup> NSBBs require lifelong treatment<sup>16</sup> and almost one third of patients have contraindications, side effects, or are non-compliant.<sup>4</sup> Patients with insufficient portal pressure reduction (<20%) assessed by measuring hepatic venous pressure gradient (HVPG) have a high rebleeding risk without further prophylaxis.<sup>17-20</sup> This challenges the rationale of drug treatment in these patients.

One trial compared the most potent combination of drug therapy (propranolol plus isosorbide-5-mononitrate) with an uncovered 10-mm TIPS after the first episode of variceal bleeding. TIPS was significantly more potent in the prevention of rebleeding but had an encephalopathy rate of nearly 40%.<sup>21</sup> Therefore, we examined whether 8-mm covered TIPS (cTIPS) is superior to a hemodynamically tailored rebleeding prophylaxis in patients with moderately decompensated cirrhosis. Patients with an insufficient decrease of HVPG underwent ligation of esophageal varices and drugs were stopped.

## Patients and Methods

### Study Design

This was an open-label, randomized, multicenter trial comparing TIPS (group A) with HVPG-guided drug application (group B) for prophylaxis of rebleeding from varices in patients with cirrhosis 5-21 days (stratum I) or more than 3 weeks (stratum II) after standard treatment of a variceal hemorrhage, using ligation, vasoactive therapy, and antibiotics. Treatment was initiated as soon as possible after randomization. Patients in group B were scheduled to receive 2 HVPG measurements. If they were found to be nonresponders they were switched to ligation only. The responders (decrease of portal pressure of 20% or greater or to less than 12 mm Hg at 2 weeks after a full dose of propranolol/nitrate) remained on the titrated medication without ligation.

### Randomization

After verification of inclusion and exclusion criteria the patients were assigned (1:1) into group A or group B by fax randomization following a block randomization scheme stratifying for centers and time after index bleed (strata). The scheme was generated at the Institut für Medizinische Biometrie, Informatik und Epidemiologie, University of Bonn. For allocation concealment, assignment to the respective group was performed by independent uninvolved individuals.

### Participating Centers

Ten centers participated. Eligibility criteria were as follows: a high level of experience with cirrhosis, TIPS placement, endoscopic ligation, medical decompressive therapy, and adequate facilities for clinical trials. All co-authors had access to the study data and reviewed and approved the final manuscript.

### Inclusion and Exclusion Criteria

Patients had to fulfill the following inclusion criteria: cirrhosis (histologic or clinical), Child-Pugh score<sup>22</sup> less than 12, bilirubin level of 3 mg/dL or less (51.3 umol/L), significant variceal bleeding more than 5 days before randomization, 2 or more esophageal varices, age 18-75 years, and written informed consent signed and dated by the investigator.

Exclusion criteria were as follows: overt hepatic encephalopathy, prehepatic portal hypertension, type II gastric varices as exclusive bleeding site, chronic drug treatment of portal hypertension with  $\beta$ -blockers and/or nitrates, listing for liver transplantation on T2 status or a high model for end-stage liver disease score (>30) at randomization, existing portosystemic shunt, heart failure greater than New York Heart Association 2, ejection fraction less than 40%, contraindication against propranolol or nitrates, platelet count less than 30 G/L, prothrombin index less than 30%, disseminated intravascular coagulation, advanced malignancy, severe infection, female patients of child-bearing potential not using contraceptive measures during the study, or female patients with a positive pregnancy test or nursing women.

### Interventions

In general, group A received an 8-mm polytetrafluoroethylene graft-lined TIPS (Gore Viatorr) insertion. In 5 (6%) of the 88 per-protocol group A patients, 8mm cTIPS was not feasible. Instead, they received a 10-mm stent but were not excluded. During this procedure, HVPG and the gradient between the portal pressure and inferior vena cava were assessed before and immediately after TIPS.

After assessment of baseline HVPG as described thoroughly,<sup>23</sup> group B received propranolol starting at 40 mg twice daily. Dosage was increased by 10 mg twice daily until a 25% reduction of basal heart rate occurred or the maximum tolerated dose was reached. After successful titration, isosorbide-5-mononitrate (20 mg twice daily) was added. After a 2-week intake of the established medication, response was assessed by a second HVPG measurement in the morning before drug intake. Responders remained on drugs only and nonresponders were switched to ligation only.

In case of bleeding, the patients received standard treatment (endoscopic hemostasis, vasoactive drugs, antibiotics), with further therapy according to their physician's discretion.

TIPS revision was performed according to the physician's judgment at the individual center, mainly on the basis of follow-up ultrasound (significant decrease of portal venous blood flow) and/or endoscopic examinations (recurrence of large varices).

Endoscopic band ligation was performed with a 6-shooter multiband device and repeated in case of recurrence of large varices.

### Follow-up Evaluation, Documentation, and Monitoring

Regular follow-up visits were scheduled on days 14, 90, 180, and thereafter every 6 months with the following assessments to be performed: physical examination, medication check, electrocardiography, encephalopathy score (West Haven criteria), Child-Pugh and model for end-stage liver disease scores, quality of life (Short Form-36 [SF-36]), laboratory values, Doppler sonography to monitor TIPS function, or endoscopy for the ligation patients.

Monitoring was performed by the Study Center Bonn with regular on-site visits.

### Outcome Measures

The primary objective was time to significant rebleeding as defined by Baveno III<sup>24</sup> (ie, hematemesis or melena together with >2 U of blood within 48 hours of time 0 plus a systolic pressure <100 mm Hg or a postural change >20 mm Hg or a pulse rate >100/min at time 0). The bleeding site had to be confirmed by endoscopy whenever possible. Secondary objectives were as follows: overall survival, safety (serious adverse events categorized according to system organ classes by MedDRA V17.0, follow-up evaluation of liver values), and quality of life assessed by the SF-36 health survey.<sup>25</sup> The pre-defined outcomes were assessed at the trial sites and were controlled by monitors. In case of liver transplantation patients were censored on the day of the procedure with the exception of 1 patient who died during surgery.

### Sample Size Calculation

Assuming that 10% of the medical responders<sup>19,26</sup> and 40% of the nonresponders allocated to ligation would have a rebleeding event and that half of the patients would be responders,<sup>27</sup> we expected rebleeding rates of 25% in group B and of 10% in group A<sup>10,11</sup> within an 18-month follow-up period. Anticipating a recruitment time of 3 years a sample size of 79 patients per group was calculated<sup>28</sup> to show a power of 90% (type I error rate 5%, 2-sided). Additional simulations taking into account the heterogeneity of the rebleeding risk in group B and a drop-out rate of 10% suggested a sample size of 93 patients per group.

### Statistical Analysis

For quantitative variables, the mean, SD, median, minimum, and maximum values were reported. For qualitative variables frequencies are shown. Analyses of clinical characteristics, rebleeding, hemorrhage-free episodes, and mortality were performed using the intention-to-treat (ITT) principle.

Comparisons between the treatment groups were performed with the Mann-Whitney-Wilcoxon rank-sum test for quantitative data. For qualitative data, the Fisher exact test was used. Time-to-event data are reported as Kaplan-Meier estimates, the log-rank test provided inference. Multivariate analysis of time to rebleeding and overall survival was performed with stepwise Cox regression. In a first step, univariate Cox regression was performed for each potentially explanatory variable, preselecting those with test score *P* values less than .1. Therapy always was selected. Selected variables then were tested in a stepwise regression procedure with *P* value criteria of .1 for inclusion and exclusion of explanatory variables into the model. SAS software version 9.2 was used.

### Ethics

The study protocol, informed consent form, and any additional related documents were approved by the ethics committee of the Medical Faculty of the University of Bonn in cooperation with the local ethics committees of the other centers. The study was in accordance with the revised Declaration of Helsinki (October 2000), the German drug law as amended,

and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (1996).

## Results

### Recruitment and Randomization

Of a total of 836 patients assessed for eligibility, 187 (22%) patients were randomized (Supplementary Appendix and Supplementary Figure 1). Important reasons for exclusion were refusal, ambiguous bleeding history, assumed bleeding from gastric and other nonesophageal varices, concomitant malignancy, or laboratory values that did not match the inclusion criteria. The required number of patients was recruited by 10 centers distributed throughout Germany. Ninety-two patients were allocated to the TIPS group A and 95 patients were allocated to the pharmacologic/ligation group B. The first patient was randomized in June 2006 and the last patient was randomized in September 2012. The study was closed in June 2013.

### Baseline Characteristics and Progress of the Randomized Groups

The flow of patients is shown in Supplementary Appendix. In the end, 185 patients were available for the intention-to-treat analysis (104 patients in stratum I and 81 patients in stratum II) and 169 patients were available for the per-protocol analysis.

The baseline characteristics, whether compared on an intention-to-treat or per-protocol basis, were balanced (Table 1).

**Table 1.** Baseline Characteristics of the Patients: Group A: TIPS, Group B: Drugs/Ligation

	Group A (n = 90)	Group B (n = 95)
Male	69%	66%
Alcoholic cirrhosis	67%	74%
Age, mean ± SD, y	55.4 ± 9.8	54.5 ± 9.7
Varices with red color sign	51%	49%
Hemoglobin level, g/dL	11 ± 2.0	10 ± 1.7
Hemoglobin level, mmol/L	6.8 ± 1.2	6.4 ± 1.0
Platelets, G/L	130 ± 74	134 ± 86
Ascites	48%	55%
Bilirubin level, mg/dL	1.4 ± 0.7	1.5 ± 0.8
Bilirubin level, μmol/L	23 ± 12	26 ± 13
Sodium level, mmol/L	138 ± 3.3	138 ± 3.6
INR	1.3 ± 0.2	1.2 ± 0.2
Creatinine level, mg/dL	0.9 ± 0.6	0.9 ± 0.6
Creatinine level, μmol/L	82 ± 51	83 ± 50
Child-Pugh score	6.9 ± 1.5	7.0 ± 1.7
Child A	45%	49%
MELD score	10 ± 2.8	10 ± 3.4
Portal pressure (HVP), mm Hg	20.4 ± 5.6	20.5 ± 6.1
Stratum I/II	57%/43%	56%/44%

INR, international normalized ratio; MELD, model for end-stage liver disease.

### Hemodynamic Response to Interventions

TIPS placement at a median of 4 days after randomization achieved an average decrease of portal pressure gradient (PPG) of 50% ( $22 \pm 6$  mm Hg to  $11 \pm 5$  mm Hg). In 43% of the patients, PPG was reduced to less than 10 mm Hg. In the remaining patients, the PPG averaged  $14.0 \pm 4$  mm Hg after TIPS. The PPG reduction to less than 12 mm Hg was achieved in 61% of patients. In group B, 19 patients received no second HVPG measurement owing to withdrawal (Supplementary Appendix) or rebleeding before the second HVPG measurement ( $n = 5$ ). Thus, 76 patients (80%) from group B received 2 HVPG measurements with 32 (42%) responders and 44 (58%) nonresponders, who were switched to ligation. In the responders, HVPG decreased on average by 29%, whereas the nonresponders showed only a slight decrease of 5% (Table 2). Changes in pulse rate, systemic blood pressure, and HVPG before and after medical treatment are shown in Table 2.

### Follow-Up Evaluation: Primary and Secondary Outcomes

Regarding the primary end point of rebleeding, the median follow-up period was 2.48 years (range, 0–6.97 y) in group A and 1.32 years (range, 0–6.44 y) in group B. During that time, 7 patients in group A and 23 patients in group B showed significant variceal bleeding (primary end point). The difference, predominantly caused by an effect in stratum I, was significant (ITT and per-protocol-treatment,  $P = .002$ ) (Figure 1 and Supplementary Figure 2). In 6 patients from group B (26% of the events in this group), variceal rebleeding occurred before the hemodynamic response could be assessed. The 2-year rebleeding rate was 7% (cTIPS) vs 26% (medical prophylaxis) (hazard ratio, 0.28; 95% confidence interval, 0.12–0.66;  $P = .002$ ). Time to

death and time to rebleeding did not differ in group A patients between those with PPG less than or greater than 12 mm Hg after TIPS placement ( $P = .836$  and  $.479$ , respectively). Per-protocol analysis of group B only showed that rebleeding events were lower ( $P = .06$ ) in the responder group (2-year rate, 18%) than in the nonresponder group ( $n = 44$ ) and early rebleeders ( $n = 5$ ) combined together (2-year rate, 31%) (Supplementary Figure 3A).

Fifteen patients in group B received TIPS as a result of refractory ascites ( $n = 9$ ), bleeding ( $n = 4$ ), portal vein thrombosis ( $n = 1$ ), or lack of compliance ( $n = 1$ ) at a median of 2 months (range, 0.3–36 mo) after randomization. The average baseline Child–Pugh score of these patients was higher ( $7.9 \pm 1.9$ ;  $P = .02$ ) than in the remaining group B patients ( $6.8 \pm 1.6$ ). HVPG ( $19.5 \pm 7.3$  vs  $20.6 \pm 5.9$  mm Hg) did not differ significantly. Of these TIPS patients, 73% (11 of 15) were hemodynamic nonresponders. They were kept in group B (ITT analysis). Censoring of these patients at the time of TIPS placement did not change our findings (log-rank  $P = .001$  for rebleeding and  $P = .965$  for death).

Twenty-seven patients in group A and 25 patients in group B died (Table 3). The majority of deaths were caused by liver failure or infection. One patient died after the TIPS procedure, and in 3 group B patients variceal hemorrhage was the cause of death. There were no significant differences in the survival curves within a median follow-up period of 3.20 years (range, 0–6.97 y) (group A) and 1.96 years (range, 0–6.97 y) (group B), regardless of whether analyzed by intention-to-treat, per-protocol, or per-stratum (Figure 2 and Supplementary Figure 4).

Five patients in group A received a liver transplantation after a median of 7 months (range, 6–66 mo) and 4 patients in group B after 11 months (range, 3–48 mo) with 1 perioperative death.

When analyzing the results with respect to combined end points (death or rebleeding), the advantage in favor of group A persisted (Supplementary Figure 5).

Multivariate analysis including the parameters treatment group, international normalized ratio, aminotransferases, bilirubin, albumin, creatinine, sodium, portal pressure, ascites, and stratum showed that allocation to group B, bilirubin, albumin, and creatinine were associated independently with rebleeding. Independent risk factors for death were albumin, portal pressure, and stratum I (Supplementary Tables 1 and 2).

In group B, the survival curve of medical responders ( $n = 32$ ) was similar to those of nonresponders (Supplementary Figure 3B).

### Safety: Follow-Up Evaluation of Laboratory Values and Adverse Events

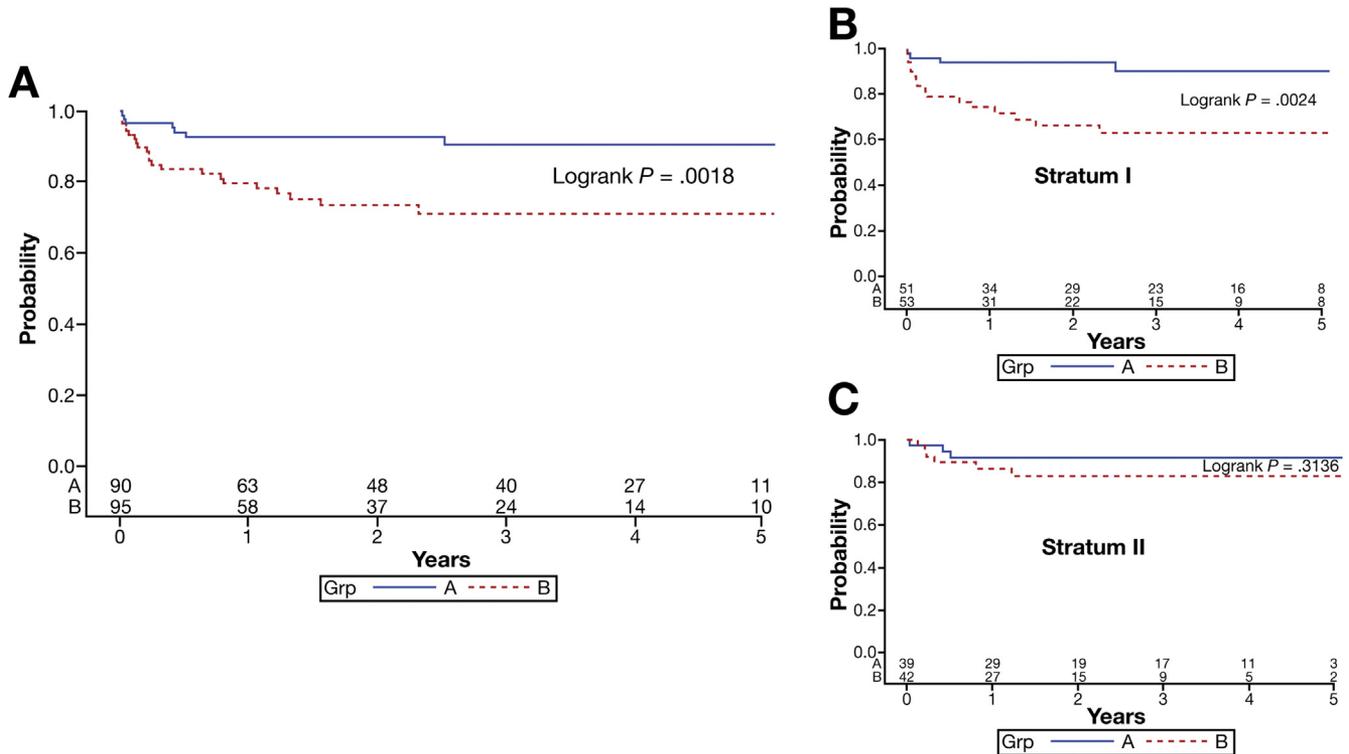
A slight increase of bilirubin level and the international normalized ratio was observed after TIPS in patients in group A. By contrast, creatinine values trended downward (Supplementary Figures 6–8).

Overall, there were 773 adverse events, classified as serious according to the International Conference on

**Table 2.** Hemodynamic Parameters at Baseline and After Application of Propranolol and Isosorbide-5-Mononitrate for Two Weeks in Group B Patients, Who Received Two HVPG Measurements

	Responder (n = 32)	Nonresponder (n = 44)
Propranolol dosage, mg/day	149 ± 73	125 ± 53
Pulse/min baseline	79 ± 14	79 ± 12
Pulse/min day 14	66 ± 12	62 ± 8
Baseline BP (systolic/diastolic), mm Hg	123 ± 21/71 ± 10	121 ± 19/70 ± 9
Day 14 BP (systolic/diastolic), mm Hg	118 ± 19/69 ± 10	118 ± 15/71 ± 10
Baseline HVPG, mm Hg	21 ± 6	20 ± 6
Day 14 HVPG, mm Hg	15 ± 5	19 ± 5

NOTE. Propranolol dosage ( $P = .12$ ) as well as baseline hemodynamic parameters were not significantly different between groups. HVPG decreased significantly in responders ( $P < .0001$ ) and nonresponders ( $P < .013$ ), whereas the change of systemic blood pressure (baseline vs day 14) was not significant. BP, systemic arterial blood pressure.



**Figure 1.** Kaplan–Meier plot (intention-to-treat) comparing time to rebleeding from varices in (A) all patients, and in (B) patients who were randomized 6–21 days after bleeding (104 patients stratum I), or (C) more than 3 weeks after bleeding (81 patients stratum II). Group A: TIPS, continuous blue line; group B: medical prophylaxis with change to ligation in hemodynamic nonresponders, dashed red line. The hazard ratio for bleeding in group A was 0.28 (95% confidence interval, 0.12–0.66) for all patients, 0.22 (95% confidence interval, 0.072–0.64) in stratum I, and 0.50 (95% confidence interval, 0.12–1.99) in stratum II.

Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice, 287 times (71 patients) in group A and 196 times (64 patients) in group B (Supplementary Table 3). Patients in group A had to be treated more often for nervous system disorders (mainly overt encephalopathy, 2-year rate, 18% vs 8%; hazard ratio, 2.4; 95% confidence interval, 0.99–5.9,  $P = .05$ ) (Figure 3), cardiac disorders, investigations, and medical procedures (mainly TIPS revisions) (Supplementary Figure 9) than patients in group B, who had more gastrointestinal disorders (mainly owing to bleeding and ligation) and hepatobiliary disorders (mainly associated with ascites). With respect to encephalopathy, there was no difference between patients with portal pressure gradients less than or greater than 12 mm Hg after TIPS placement ( $P = .939$ ). Later TIPS interventions were necessary in 8% of the patients with PPG less than 10 mm Hg and in 29% of patients with PPG of 10 mm Hg or greater as assessed immediately after insertion.

Analysis of safety with respect to groups and the 2 strata showed no major imbalance. In particular, TIPS induced no harm in stratum II (Supplementary Table 3). Serious adverse events occurred slightly more often in stratum I.

### Quality of Life

The SF-36 summary scores<sup>29</sup> concerning physical or mental components showed no difference between groups

at baseline and during follow-up evaluation (Supplementary Figures 10 and 11).

## Discussion

This was a large randomized study comparing TIPS with a primary pharmacologic approach for the prevention of rebleeding from esophageal varices in patients with moderately decompensated cirrhosis. It shows the superiority of an elective 8-mm cTIPS for the prevention of rebleeding. However, this had no effect on survival or quality of life.

There were more adverse events in the TIPS group, but the percentage of patients with serious adverse events was only slightly higher in this group. The overt encephalopathy rate was comparatively low, probably because of the small TIPS diameter.

The primary aim of the trial was the comparison between TIPS and hemodynamically controlled pharmacologic treatment. Although TIPS reduced portal pressure on average by 50%, propranolol and nitrates achieved a mean reduction of 15% after 2 weeks, similar to the value of 16% calculated in a recent meta-analysis.<sup>30</sup> Although NSBBs plus nitrates decrease portal pressure only moderately, it is an effective regimen for rebleeding prophylaxis with a possible beneficial effect on survival.<sup>6,9</sup> Sufficient portal pressure reduction prevents rebleeding, but nonresponders hardly are protected.<sup>17–19,26</sup> Forty-two percent of our patients in whom 2 measurements were possible responded adequately. This is well within the range assessed by a

**Table 3.** Causes of Death: Group A: TIPS, Group B: Drugs/Ligation

	Group A 27/90 (30%)	Group B 25/95 (26%)
Liver failure	11	9
Infection	6	8
Hepatocellular carcinoma	1	2
Bleeding	1	3
TIPS complication	1	-
Liver transplantation	-	1
Others	7 <sup>a</sup>	-
Unknown	-	2 <sup>b</sup>

<sup>a</sup>Kidney failure, gallbladder cancer, leukemia, stroke, bleeding peptic ulcer, and cardiac arrhythmia.

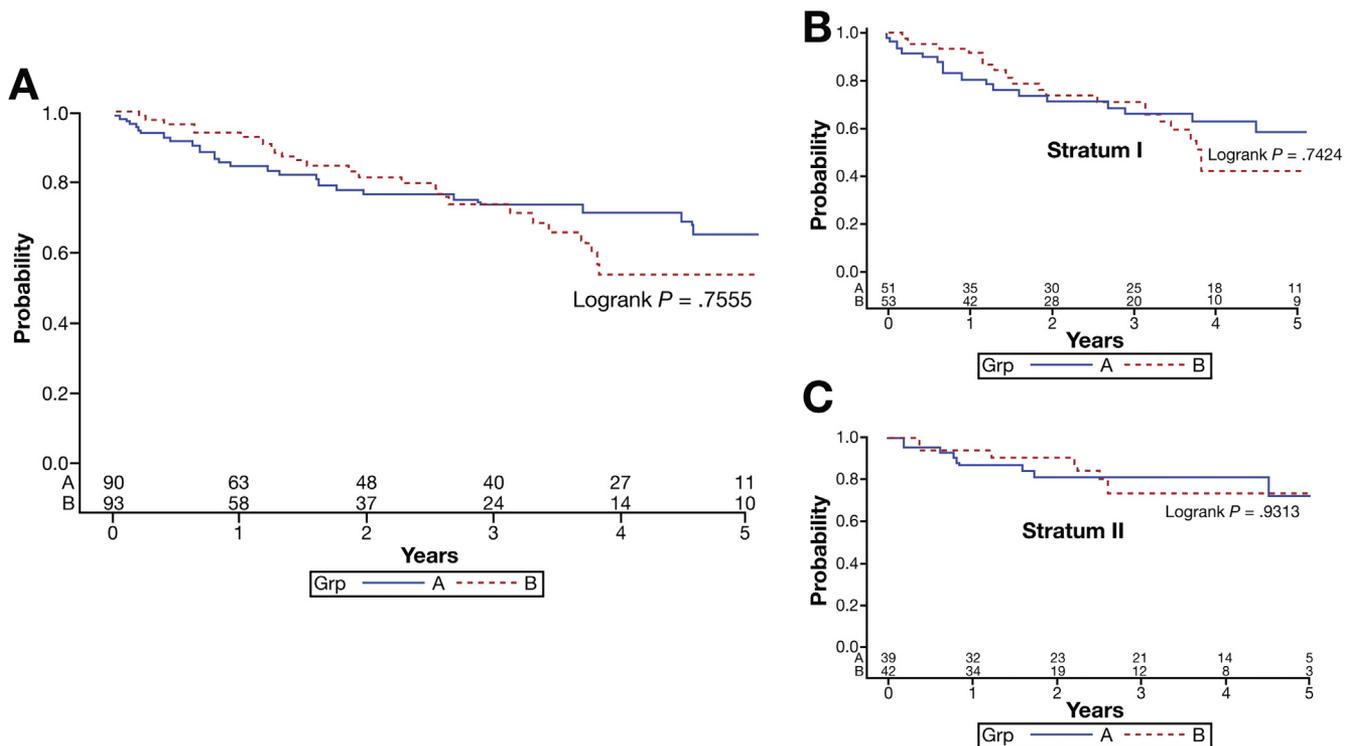
<sup>b</sup>Both patients died at home, 1 in Turkey, the other was found by police together with bottles of alcoholic beverages.

systematic review of several other studies.<sup>19</sup> The rebleeding rate in these patients did not differ significantly from the TIPS group at 2 years of follow-up evaluation (18% vs 7%;  $P = .15$ ). Carvedilol, a NSBB with additional  $\alpha$ 1-adrenoceptor-blocking properties, showed a better hemodynamic response rate,<sup>30,31</sup> but there are no randomized end point trials comparing this drug with propranolol. Thus, it probably is too early to favor this specific  $\beta$ -blocker for medical rebleeding prophylaxis.

Our study design showed a previously addressed problem.<sup>19,27</sup> Patients with sole pharmacologic treatment presented early rebleeding before hemodynamic analysis. The optimal time frame to assess the response is ill defined. We chose 14 days because we assumed patients to be in a good steady state after this period. Whether intravenous infusion of a test dose of propranolol is a valid prognostic substitute<sup>32,33</sup> remains to be investigated in randomized trials with clinical end points.

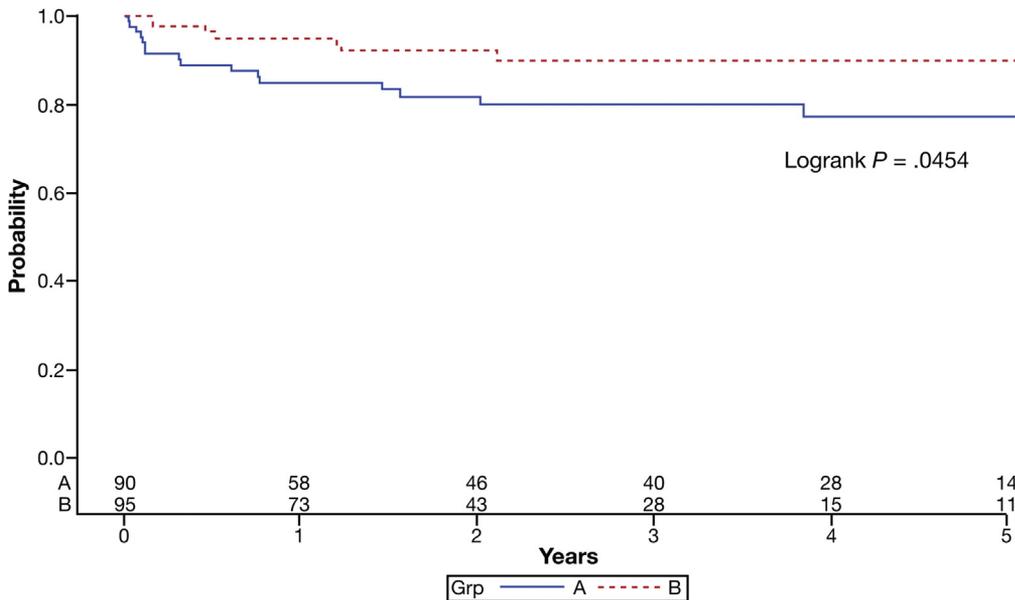
Patients who showed no response were switched to ligation only. This has the advantage that patients are no longer at risk for side effects of medical therapy.<sup>34-36</sup> It has repeatedly been argued that there are further beneficial effects of NSBBs beyond decreasing portal pressure.<sup>37</sup> We cannot refute this argument. We found that our patients who received only ligation showed a slightly higher rebleeding rate than the medical responders despite later TIPS placement in one fourth of the ligated patients. However, survival was not different between these groups (Supplementary Figure 3). Thus, once response to therapy has been assessed either ligation alone or drugs alone are possible options as a first step for elective rebleeding prophylaxis.

Independent factors associated with rebleeding were allocation to group B, bilirubin, and albumin. This confirms that rebleeding is associated with parameters of the Child classification. Interestingly, low baseline creatinine level also correlated with more rebleeding events. This was



**Figure 2.** Kaplan-Meier plot (intention-to-treat) comparing time to death in group A (TIPS, continuous blue line) with group B (medical prophylaxis and change to ligation in hemodynamic nonresponders, dashed red line). (A) All patients, (B) stratum I (randomization 6–21 days after bleeding, 104 patients), and (C) stratum II (randomization >3 weeks after bleeding, 81 patients). The hazard ratio for death in group A was 0.92 (95% confidence interval, 0.53–1.59) for all patients, 0.90 (95% confidence interval, 0.47–1.70) in stratum I, and 1.05 (95% confidence interval, 0.35–3.13) in stratum II.

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**Figure 3.** Kaplan–Meier plot comparing overt encephalopathy in patients receiving TIPS (group A, continuous blue line) or medical treatment with change to ligation in hemodynamic nonresponders (group B, dashed red line). The hazard ratio for encephalopathy in group A was 2.4 (95% confidence interval, 0.99–5.99), 18% at 2 years in group A and 8% in group B.

unexpected. One could speculate that patients with low creatinine level have more cachexia and are more prone to rebleed. Low albumin level, a short time after the index bleeding, and high portal pressure were independent parameters associated with death. This underlines earlier findings that assessment of portal pressure adds independent information for prediction of survival time in patients with cirrhosis.<sup>15,38</sup> However, interventions reducing portal pressure failed to improve survival in most controlled trials, probably because the intrahepatic inflammatory cascades of chronic liver disease are not targeted by this approach. Rebleeding did not correlate with the baseline portal pressure. This can be explained by the fact that all patients received interventions to decrease portal blood pressure, which might obscure its role in the natural history of variceal bleeding. Low albumin level was the only independent Child parameter associated with death.

We selected patients with compensated liver function, explaining a 2-year survival rate of 76% (group A) and 81% (group B). The 5-year survival rate was 65% (group A) vs 54% (group B). Thus, both approaches were equal. Causes of deaths and the rate of patients receiving liver transplantation also were very similar. Under these conditions, adverse events and quality of life should be compared. By using the SF-36 health survey we found no difference between groups or a major change over time. The TIPS group had more adverse events mainly owing to problems of the central nervous system (often hepatic encephalopathy) or TIPS revisions, whereas the conservative group experienced more adverse events caused by ascites, variceal banding, or bleeding.

We opted for placement of an 8-mm cTIPS. It showed adequate bleeding prophylaxis and a low overt encephalopathy rate. In this respect and in respect to hemodynamic control as well as the severity of liver disease our trial differed from another study that found a rather high

cumulative complication rate in the 8-mm stent group as compared with 10-mm cTIPS.<sup>39</sup> Overall, the PPG was halved by TIPS insertion despite the fact that in only 40% of the patients the PPG was reduced to less than 10 mm Hg. This might explain invasive TIPS revision over time in nearly one third of these individuals as compared with 8% in patients with a PPG less than 10 mm Hg after TIPS. Our approach probably is the best choice to lessen encephalopathy episodes. A PPG gradient less than 12 mm Hg is believed to be associated with complete protection from bleeding. This was achieved in 61% of TIPS patients.

It has been shown that the risk of rebleeding and death decreases with an increasing time interval between index bleeding and intervention.<sup>40</sup> We met this selection phenomenon by stratifying patients (see the Materials and Methods section). The most relevant effect was confined to stratum I (patients randomized within 6–21 days after the index bleeding who had received TIPS at a median of 15 days after the bleeding event), suggesting and confirming that the effect of TIPS probably is most pronounced when placed in close temporal relation to bleeding.<sup>12</sup> If the bleeding-free interval surpasses 6 weeks then the rebleeding risk may be close to the situation in primary prevention. In stratum II, 75% of our patients (77% in group A and 74% in group B) bled more than 42 days before randomization and the median time between the index bleeding and TIPS insertion in stratum II was 3.6 months. Although it can be argued that TIPS is harmful in this situation we found neither an excess mortality induced by TIPS nor a higher ratio of adverse events (group A to B) in stratum II. A slight trend toward less rebleedings remained in the TIPS group of stratum II.

Some patients in group B eventually received TIPS (16% in our trial) with refractory ascites as the main indication. Most of these patients belonged to the hemodynamic nonresponders. Censoring of these group B patients at the time

of TIPS insertion induced no relevant change in the Kaplan–Meier plots.

What new information does our trial contribute to the numerous other studies on TIPS insertion for prophylaxis of rebleeding? First, small-diameter cTIPS is effective in patients with moderately decompensated cirrhosis. Second, although hemodynamic responders are well treated with drugs only, we need the information on drug response early on. This problem has not been solved to date. Third, TIPS loses its superiority in the prevention of rebleeding if placed more than 3 weeks after the index bleeding, a possible selection phenomenon.

Our trial had some limitations. Only 22% of the screened patients were randomized; not all group B patients received 2 HVPG measurements; the time interval between the index bleeding and randomization had a large scatter; and the treatment approach in group B was more heterogeneous.

## Conclusions

Although according to our study small-diameter cTIPS is not mandatory as first-line elective rebleeding prevention, it is more simple and effective than primary medical portal pressure reduction with hemodynamic control. The latter approach requires further step-by-step therapy in the majority of patients. The percentage of patients with adverse events, as well as survival and quality of life, appear to be quite balanced between both approaches.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <http://dx.doi.org/10.1053/j.gastro.2015.05.011>.

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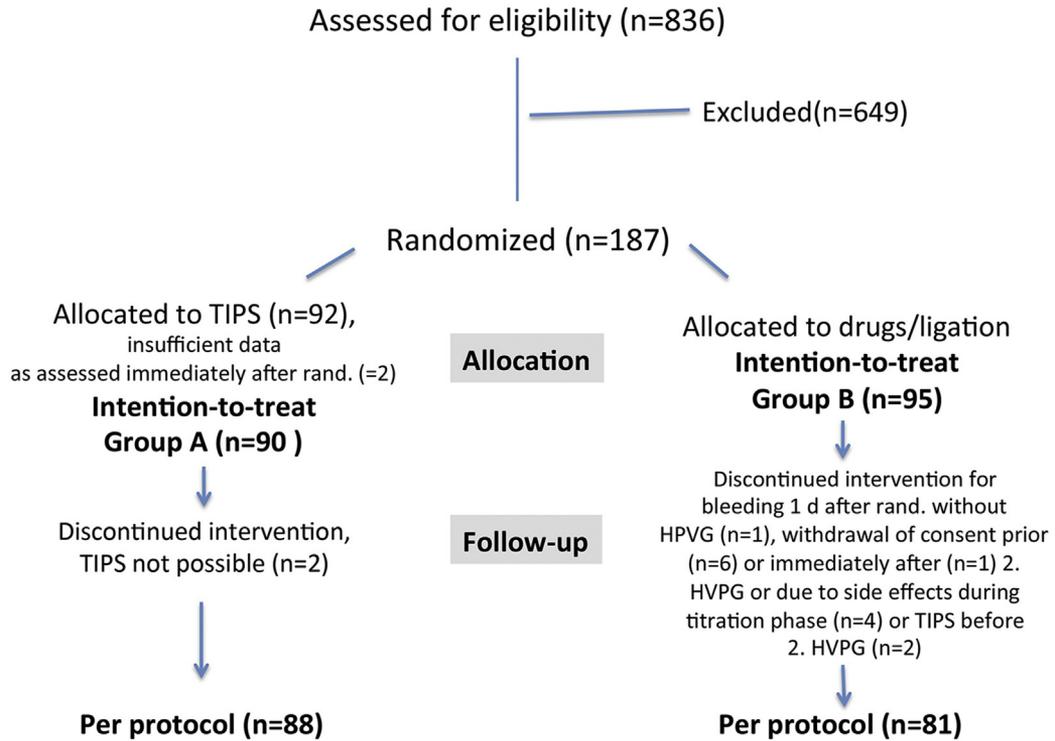
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#### Conflicts of interest

The authors disclose no conflicts.

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**Supplementary Appendix.** Chart showing the design of the study and the flow of patients. Please note that 5 of the 81 per-protocol group B patients had a bleeding end point before the second HVPG measurement. Within the first 24 months after randomization out of the per-protocol patients in group A, 6 patients were lost to follow-up evaluation before study end and censored, 2 patients because of transfer to another hospital for malignant disease (at months 5 and 12) and 4 patients because of withdrawal of consent for further follow-up evaluation (at months 1, 6, 7, and 12). Of the per-protocol patients in group B, 4 patients were lost before the end of study and censored, 1 patient was lost because of transfer to another hospital (at month 12), and 3 patients because of withdrawal of consent for further follow-up evaluation (at months 3, 3, and 6). The specific reasons why patients were not eligible for randomization are shown in [Supplementary Figure 1](#).