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Covered Transjugular Intrahepatic Portosystemic Shunt Versus Endoscopic Therapy + β -blocker for Prevention of Variceal Rebleeding

I. Lisanne Holster,¹ Eric T.T.L. Tjwa,¹ Adriaan Moelker,² Alexandra Wils,² Bettina E. Hansen,¹ J. Reinoud Vermeijden,³ Pieter Scholten,⁴ Bart van Hoek,⁵ Jan J. Nicolai,⁶ Ernst J. Kuipers,^{1,7} Peter M.T. Pattynama,² and Henk R. van Buuren¹

Gastroesophageal variceal bleeding in patients with cirrhosis is associated with significant morbidity and mortality, as well as a high rebleeding risk. Limited data are available on the role of transjugular intrahepatic portosystemic shunt (TIPS) with covered stents in patients receiving standard endoscopic, vasoactive, and antibiotic treatment. In this multicenter randomized trial, long-term endoscopic variceal ligation (EVL) or glue injection + β -blocker treatment was compared with TIPS placement in 72 patients with a first or second episode of gastric and/or esophageal variceal bleeding, after hemodynamic stabilization upon endoscopic, vasoactive, and antibiotic treatment. Randomization was stratified according to Child-Pugh score. Kaplan-Meier (event-free) survival estimates were used for the endpoints rebleeding, death, treatment failure, and hepatic encephalopathy. During a median follow-up of 23 months, 10 (29%) of 35 patients in the endoscopy + β -blocker group, as compared to 0 of 37 (0%) patients in the TIPS group, developed variceal rebleeding ($P = 0.001$). Mortality (TIPS 32% vs. endoscopy 26%; $P = 0.418$) and treatment failure (TIPS 38% vs. endoscopy 34%; $P = 0.685$) did not differ between groups. Early hepatic encephalopathy (within 1 year) was significantly more frequent in the TIPS group (35% vs. 14%; $P = 0.035$), but during long-term follow-up this difference diminished (38% vs. 23%; $P = 0.121$). **Conclusions:** In unselected patients with cirrhosis, who underwent successful endoscopic hemostasis for variceal bleeding, covered TIPS was superior to EVL + β -blocker for reduction of variceal rebleeding, but did not improve survival. TIPS was associated with higher rates of early hepatic encephalopathy. (HEPATOLOGY 2016;63:581-589)

Gastroesophageal variceal bleeding (GEVB) is a severe complication of portal hypertension. Rebleeding is associated with significant morbidity and mortality. Hospitalization costs for rebleeding range between \$6,600 and \$23,000 in the United States.

For these reasons, management should be directed at its prevention.^{1,2} Secondary prevention is first achieved by endoscopic treatment (endoscopic variceal ligation [EVL] for esophageal varices and N-butyl cyanoacrylate injection for gastric varices) in combination with β -

Abbreviations: CI, confidence interval; EVL, endoscopic variceal ligation; GEVB, gastroesophageal variceal bleeding; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; PTFE, polytetrafluorethylene; TIPS, transjugular intrahepatic portosystemic shunt.

From the Departments of ¹Gastroenterology and Hepatology; ²Radiology, and ⁷Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands; Department of Gastroenterology and Hepatology, and ³Meander MC, Amersfoort, The Netherlands; ⁴Sint Lucas Andreas Hospital, Amsterdam, The Netherlands; ⁵LUMC, Leiden, the Netherlands; ⁶HagaHospital, Den Haag, The Netherlands.

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Current address for Dr. Tjwa: Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Dutch trial register: www.trialregister.nl; no.: NTR973.

blocker therapy. Transjugular intrahepatic portosystemic shunt (TIPS) placement forms an alternative.³ EVL requires multiple sessions to achieve successful eradication of varices and is associated with frequent rebleeding from varices or banding ulcers. TIPS, on the other hand, is an expensive procedure that carries a risk, albeit low, of severe complications including bleeding, liver injury, and heart failure. It is associated with a relatively high risk of hepatic encephalopathy.^{4,5} Currently, the combination of EVL and β -blockers is the standard of care. TIPS is recommended in patients who fail endoscopic and pharmacological therapy and is considered in those at high risk of treatment failure.³

In patients with cirrhosis with GEVB, TIPS with uncovered stents proved more effective than endoscopic therapy in reducing variceal rebleeding, but did not improve survival. This was paralleled by an increment of TIPS-related hepatic encephalopathy and a high number of reinterventions for TIPS dysfunction.⁶

Uncovered stents have been increasingly replaced by polytetrafluorethylene (PTFE)-covered stents.⁷⁻¹¹ These covered stents have the advantage of prolonged patency. We compared the efficacy and safety of TIPS using PTFE-covered stents with endoscopic therapy plus β -blocker for the secondary prevention of GEVB in patients with cirrhosis, irrespective of the severity of liver failure, after successful treatment of a first or second variceal bleeding.

Patients and Methods

Study Population. Patients were eligible for the study if they were between 18 and 75 years and presented with a first or second episode of endoscopically documented esophageal or gastric variceal bleeding.¹² After stabilization and successful endoscopic hemostasis, patients were randomly assigned to receive long-term endoscopic therapy (EVL or injection therapy) plus β -blocker or TIPS placement.

Exclusion criteria included: a history of serious or refractory hepatic encephalopathy unrelated to gastrointestinal bleeding; a history of significant heart failure (New York Heart Association class III and IV); portal hypertension resulting from other causes than liver disease (e.g., portal or splenic vein thrombosis); previous

TIPS placement; advanced hepatocellular carcinoma (HCC); a Child-Pugh score >13 ; sepsis and/or multiorgan failure; and inability or unwillingness to give informed consent.

The trial was performed in accord with the provisions of the Declaration of Helsinki and local regulations. The institutional review board at each center approved the protocol, and written informed consent was obtained from all patients before randomization. The trial protocol, including data analysis plan, is available online with the full text of this article. All authors contributed to the writing of the manuscript, had full access to all the data and analyses, vouch for the accuracy and completeness of the data reported, and reviewed and approved the final manuscript.

Study Design. Randomization was performed after hemodynamic stabilization and sustained endoscopic hemostasis, preferably within 1-2 days after admission. Patients were randomly assigned through a permanently available central telephone system to receive further endoscopic therapy in combination with β -blocker therapy (standard of care) or TIPS placement. The randomization sequence was computer generated with the use of a concealed block size of four, stratified by Child-Pugh class.

Treatment. Initial stabilization in all patients included broad-spectrum antibiotics, vasoactive drugs, fluid and packed cell administration, and endoscopic treatment according to international consensus guidelines.³ Vasoactive drugs (octreotide 50 μ g bolus followed by 50 μ g/h, terlipressin 6-12 mg intravenously per day, or somatostatin 250 μ g bolus followed by 250 μ g/h) were started at admission for 5 days. Endoscopic treatment of esophageal varices consisted of EVL (6-Shooter Saeed Multi-band Ligator; Cook Medical, Winston-Salem, NC; Speedband Superview Super 7 Multiple Band Ligator [Boston Scientific Corp, Natick, MA]). Gastric varices were injected with cyanoacrylate glue (HistoAcryl; B. Braun, Melsungen, Germany) with lipiodol (Lipiodol; Guerbet, Villepinte, France). Successful endoscopic therapy was ascertained by 5-minute visual confirmation of hemostasis.

In the endoscopic arm, a nonselective β -blocker (preferably slow-release propranolol, titrated to the maximum tolerated dose aiming to decrease the heart rate in

Address reprint requests to: I. Lianne Holster, M.D., Erasmus MC University Medical Center, Room Hs-306, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.
E-mail: i.holster@erasmusmc.nl; fax: +(31) 107034682.

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rest by 25%, with a lower limit of 50 beats per minute) was started at day 5 after the index bleeding, unless a contraindication was present (severe arrhythmia, severe obstructive chronic obstructive pulmonary disease, or known intolerance). Elective EVL sessions started 2 weeks after the index bleeding and were performed every 2–4 weeks thereafter until eradication of varices, followed by endoscopic surveillance and retreatment, if indicated, every 6–12 months.

In patients allocated by randomization to endoscopic treatment, further endoscopic management occurred on-site by gastroenterologists experienced in variceal ligation. Patients assigned to TIPS placement were transferred to one of the four main trial centers (i.e., university hospitals experienced in TIPS procedures).

The TIPS procedures were performed by experienced interventional radiologists. At the start of the procedure, all patients received one injection of cephalosporin. TIPS placement was performed under general anesthesia after transhepatic portography. PTFE-covered stents (Viatorr; W.L. Gore and Associates, Flagstaff, AZ) were used with initial balloon dilatation to 8 mm, aiming for a decrease in portal-venous pressure gradient to less than 12 mm Hg. If necessary, additional dilatation to 10 mm was performed. Embolization of the coronary vein or other collaterals was considered when there was evidence of active variceal bleeding during the procedure and when portography showed marked collateral filling despite an otherwise successful procedure in terms of the portal-venous pressure gradient. TIPS function was primarily monitored by clinical evaluation every 6 weeks to 3 months. When signs of possible dysfunction were present (in particular, new onset or progressive ascites, or variceal rebleeding), duplex ultrasound was performed. Furthermore, ultrasound examination of the liver was performed every 6 months according to the guidelines for HCC surveillance.

Outcomes and Follow-up. The primary outcome of the study was clinically significant variceal rebleeding. This was defined as recurrent melena or hematemesis resulting in either hospital admission, blood transfusion, drop in hemoglobin of at least 3 g/L, or death within 6 weeks after rebleeding. Variceal rebleeding was further divided into failure to control bleeding (within 120 hours after index endoscopic treatment) or failure of secondary prophylaxis (after 120 hours) according to the Baveno Guidelines.³

Secondary outcomes were occurrence of treatment failure (either switch to other therapy or death), bleeding-related mortality, liver transplantation, and hepatic encephalopathy based on clinical parameters.¹³ All outcomes were scored centrally by two physicians

(I.L.H., E.T.T.L.T.) independently and discussed with a third person (H.R.B.) in case no consensus could be reached. E.T.T.L.T. and H.R.B. were blind to the allocated treatment.

All patients were followed from inclusion until study termination at September 1, 2013. Outcomes were reported after 2 years and after total follow-up. The first year after inclusion, patients were followed with 3-monthly intervals and thereafter every 6 months.

Statistical Analysis. Initial sample size was determined at 124 patients, with an alpha level of 0.05 and a power of 80%. However, during the course of this study, the results of a trial suggested more benefit from early TIPS in terms of the primary endpoint (rebleeding) than expected.¹¹ It was decided to recalculate the sample size, resulting in a required population of 72 patients.

Intention-to-treat analyses were based on all randomized patients. Patients were censored at the time of liver transplantation, loss-to-follow-up, or last outpatient visit before study closure. In the “as-treated” analysis, patients were analyzed according to the treatment regimen that they received. In addition to the censoring time points in the intention-to-treat analysis, patients were censored at the moment they switched therapy.

Independent-sample *t* tests were used for continuous variables and chi-square tests for categorical variables. Kaplan-Meier (event-free) survival analyses with log-rank tests and Cox’s proportional hazard analyses were performed for the endpoints rebleeding, treatment failure, death, and hepatic encephalopathy. In case of zero events in one arm, likelihood ratio test with Firth’s correction and 95% hazard ratio profile with likelihood confidence limits were used.¹⁴ Data were analyzed using PASW statistics (version 21.0 for Windows; SPSS, IBM, Armonk, NY) and SAS software (version 9.3; SAS Institute Inc., Cary, NC). A two-sided *P* value <0.05 was considered statistically significant.

This trial was registered with trialregister.nl (no.: NTR973).

Results

Patients, Recruitment, and Follow-up. Between July 2007 and June 2013, 174 patients were screened in 12 centers in The Netherlands, and, of these, 72 patients were included and randomized after a median of 4 days from index bleeding (interquartile range [IQR]: 1–7; Fig. 1). Thirty-five were assigned to receive endoscopic therapy plus a β -blocker and 37 to receive TIPS (intention-to-treat population). Mean age was 55 years (range, 30–75) and 57% were male. Eighty-five percent were Caucasian. Alcohol was the most common cause of

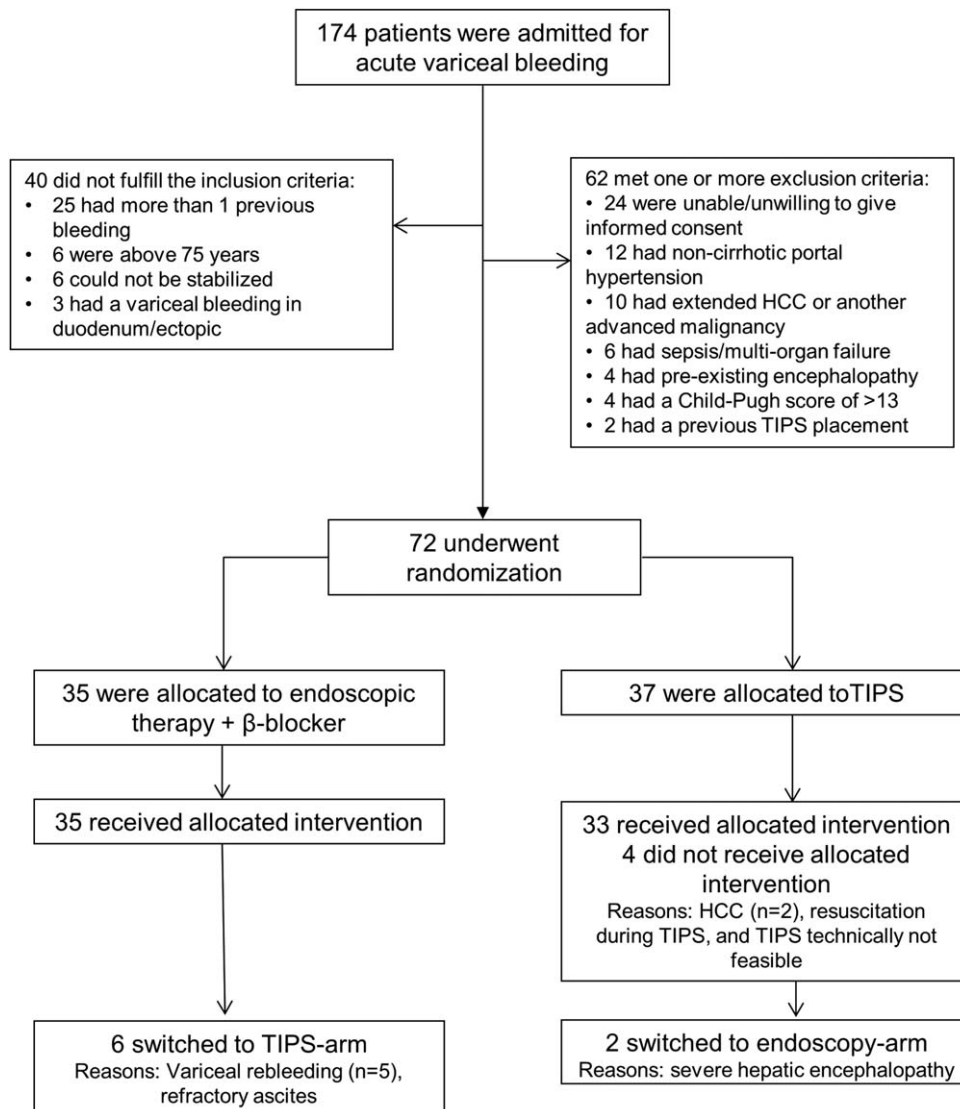


Fig. 1. Participant flow.

cirrhosis (Table 1). Median follow-up was 23.4 months (IQR, 5.9-30.7) and did not differ between groups. Six patients (8%; 4 in the endoscopy + β-blocker arm, 2 in the TIPS arm) were lost-to-follow-up after a median of 22.5 months (IQR, 4.2-34.3). Twelve (17%) patients underwent liver transplantation (7 endoscopic + β-blocker arm vs. 5 TIPS arm; $P=0.627$) after a median of 19.9 months (IQR, 6.9-38.5).

Six (16%) of the thirty-seven patients randomized to TIPS crossed over to the EVL + β-blocker group. Four of them were not treated with TIPS placement for reasons of advanced HCC diagnosed after randomization ($n=2$), technical infeasibility owing to extensive Budd-Chiari syndrome, and periprocedural resuscitation because of ventricular fibrillation. Two patients with TIPS developed severe untreatable hepatic encephalopathy, for which the only alternative finally proved to be

TIPS closure. Six (17%) of the thirty-five patients randomized to EVL + β-blocker switched to TIPS during the course of the study; 5 because of recurrent/uncontrollable variceal rebleeding and 1 because of refractory ascites.

Treatments. In the endoscopy + β-blocker arm, a total of 103 upper endoscopies (mean, 2.9 ± 2.4 per patient) were performed in the first year after randomization. The majority (56%) of procedures included EVL with placement of a mean 4.3 bands per procedure, 5% included injection therapy, and in 38% no treatment was considered necessary. All except 1 patient used propranolol slow release, titrated on heart rate and/or tolerance.

In the TIPS group, 31 patients received one stent and 2 patients two stents. Median time from bleeding to TIPS was 6 days (IQR, 3-9). Fourteen patients received

Table 1. Baseline Characteristics*

	Overall (N = 72)	Endoscopic + β -Blocker Group (N = 35)	TIPS Group (N = 37)
Age (years), mean (range)	55 (30-75)	54 (30-71)	56 (37-75)
Male sex	41 (57)	23 (49)	18 (66)
Cause of cirrhosis			
Alcohol	31 (43)	18 (51)	13 (35)
Hepatitis B/C	8 (11)	1 (3)	7 (19)
Alcohol and hepatitis B/C	6 (8)	3 (8)	3 (8)
Autoimmune liver/biliary disease [†]	18 (25)	9 (26)	9 (24)
Other	9 (13)	4 (11)	5 (14)
Child-Pugh classification			
A (5-6)	26 (36)	13 (37)	13 (35)
B (7-9)	37 (51)	18 (51)	19 (51)
C (10-13)	9 (13)	4 (11)	5 (14)
Child-Pugh score [‡]	7.4 $\pm$ 2.0	7.3 $\pm$ 1.9	7.5 $\pm$ 2.0
MELD score [§]	13.1 $\pm$ 5.2	12.7 $\pm$ 3.8	13.5 $\pm$ 6.3
MELD-Na score [§]	14.4 $\pm$ 5.6	13.8 $\pm$ 4.2	14.9 $\pm$ 6.6
Albumin (g/L)	30.6 $\pm$ 6.1	30.9 $\pm$ 6.9	30.4 $\pm$ 5.2
Bilirubin (mg/dL)	3.3 $\pm$ 4.0	2.7 $\pm$ 2.2	3.8 $\pm$ 5.2
Creatinine (mg/dL)	0.8 $\pm$ 0.2	0.8 $\pm$ 0.2	0.8 $\pm$ 0.2
INR	1.4 $\pm$ 0.5	1.4 $\pm$ 0.3	1.5 $\pm$ 0.6
Platelets ($\times 10^9$ /L)	112.7 $\pm$ 64.2	107.0 $\pm$ 49.6	118.1 $\pm$ 75.9
Ascites	28 (39)	13 (37)	15 (41)
Previous variceal bleeding	14 (19)	9 (26)	5 (14)
β -blocker prophylaxis before index bleed	11 (15)	5 (14)	6 (16)
Endoscopic prophylaxis $\pm$ β -blocker before index bleed	17 (24)	11 (31)	6 (16)
Active bleeding at index gastroscopy	32 (44)	16 (46)	16 (43)
Location of varices at index gastroscopy			
Esophageal varices only	59 (82)	30 (86)	29 (78)
Gastric varices only	4 (6)	2 (6)	2 (5)
Esophageal and gastric varices	9 (13)	3 (9)	6 (16)
Endoscopic therapy at index bleed			
Endoscopic band ligation	59 (82)	26 (74)	33 (89)
Injection sclerotherapy	5 (7)	5 (14)	0 (0)
Injection histoacryl-lipiodol	6 (8)	4 (11)	2 (5)
Hemoglobin at admission (mmol/L)	6.2 $\pm$ 0.9	6.3 $\pm$ 1.0	6.1 $\pm$ 0.9
Previous episode of HE	2 (3)	2 (6) [¶]	0 (0)

*Intention-to-treat population. Plus-minus values are means $\pm$ standard deviation, other values are no. (%). There were no significant differences between the two study groups. 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.

[†]Includes primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis.

[‡]The Child-Pugh score ranges from 5 to 15, class A (5-6 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 with a Child-Pugh score of >13 were not included in the study.

[§]MELD and MELD-Na scores range from 6 to 40, with higher scores indicating more severe disease.

^{||}According to the selection criteria, patients with more than one previous episode of variceal bleeding were not eligible.

[¶]One patient with grade 1 and 1 with grade 2 hepatic encephalopathy.

Abbreviations: HE, hepatic encephalopathy; INR, international normalized ratio; NASH, nonalcoholic steatohepatitis.

TIPS within the first 5 days of the index bleeding, and 19 underwent TIPS after 6 days or later (median, 9). The mean portal pressure gradient dropped from 13.4 ± 3.3 mm Hg before the procedure to 4.4 ± 2.1 mm Hg after the procedure. For this, the shunt was balloon-dilated to 8 mm in 21 patients and to 10 mm in 10 patients. Embolization of collaterals was performed in 8 (24%) patients. The 2-year patency rate was 94%; 2 patients underwent a successful revision of the TIPS for partial/complete occlusion.

Primary Endpoint: Rebleeding. During total follow-up, 10 (29%) patients in the endoscopy +

β -blocker arm experienced a total of 15 variceal rebleeds compared to none of the patients in the TIPS arm ($P = 0.001$; Fig. 2A). Endoscopic hemostasis was achieved in all cases; 5 patients switched to TIPS and remained free from rebleeding thereafter. Nine of ten patients experienced the first rebleed within 2 years of follow-up; 2 met the criteria of failure to control bleeding and 8 had failure of secondary prophylaxis. Additionally, 6 nonvariceal upper gastrointestinal bleeds, mostly post-EVL ulcer bleeds, occurred during 2-year follow-up (Table 2). In the as-treated analysis, 10 (26%) patients treated with endoscopy + β -blocker

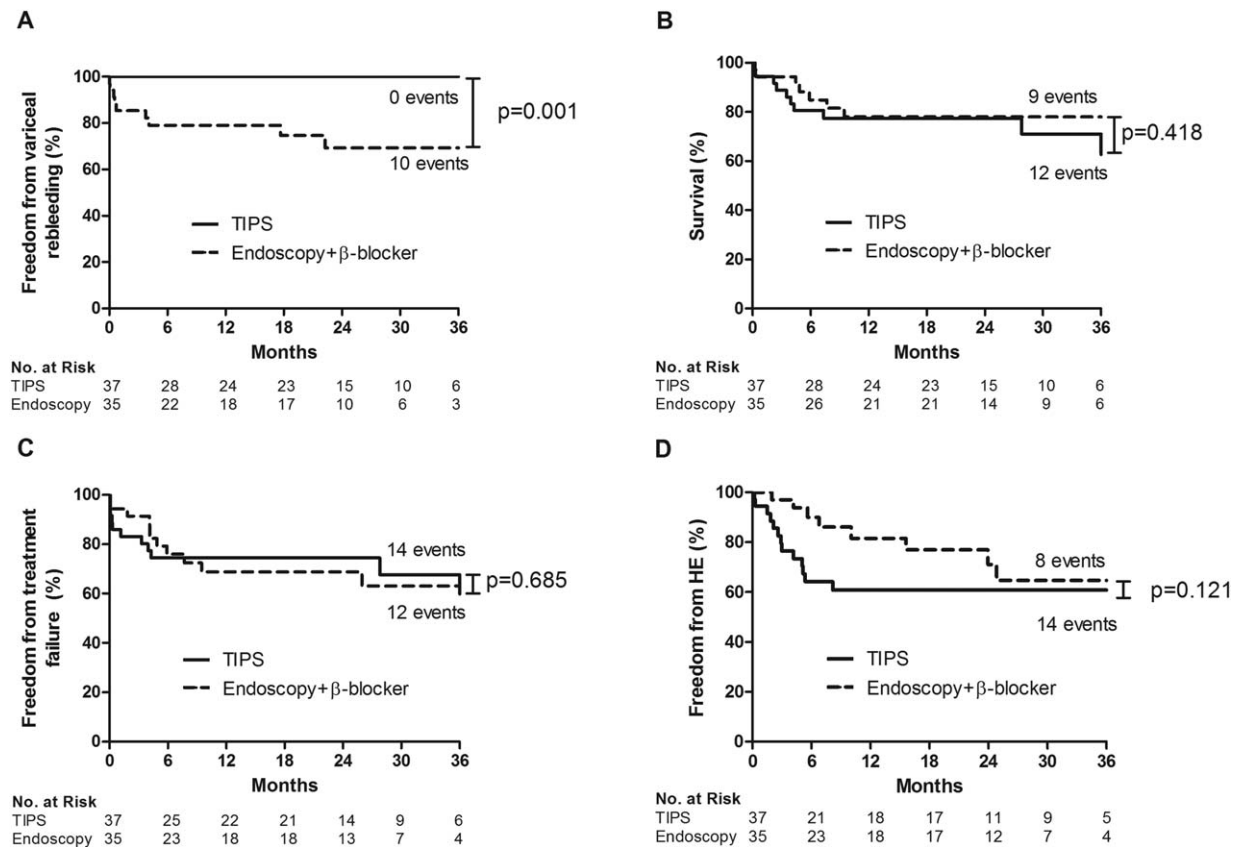


Fig. 2. Kaplan-Meier analysis of freedom of variceal rebleeding, survival, treatment failure, and hepatic encephalopathy. (A) Probability of remaining free from significant variceal rebleeding. (B) Probability of survival. (C) Probability of remaining free from treatment failure. (D) Probability of remaining free from hepatic encephalopathy.

experienced a variceal rebleed compared to none of the patients treated with TIPS ($P = 0.002$; Supporting Fig. 1A). In the univariate Cox regression analysis, active bleeding at index gastroscopy (hazard ratio [HR]: 2.99; 95% confidence interval [CI]: 0.77-11.59; $P = 0.11$), Child-Pugh C (HR, 4.08; 95% CI: 0.86-19.41; $P = 0.08$), previous variceal bleeding (HR, 2.68; 95% CI: 0.73-9.82; $P = 0.14$), randomization to endoscopy (HR, 24.13; 95% CI: 3.11-infinite; $P < 0.001$), and baseline platelets $<100 \times 10^9/L$ (HR, 2.59; 95% CI: 0.67-10.03; $P = 0.17$) showed a trend toward more variceal rebleeding. In the multivariate analysis, endoscopic treatment was the only parameter that was significantly associated with rebleeding (HR, 25; 95% CI: 3.13-infinite; $P < 0.001$).

Secondary Endpoints: Mortality and Treatment Failure. Nine (26%) patients in the endoscopy + β -blocker arm died, compared to 12 (32%) patients in the TIPS arm ($P = 0.41$; Fig. 2B). None of the patients in either group died from gastroesophageal variceal rebleeding, but in the endoscopy + β -blocker group 1 patient died from intraperitoneal variceal bleeding. Two-year survival was 92% in patients with Child-Pugh

A, 76% in Child-Pugh B, and 56% in Child-Pugh C ($P = 0.049$). Most common causes of death were: hepatocellular- or cholangiocarcinoma, liver failure, and systemic infection/sepsis (Table 2). In the univariate analysis, Model for End-Stage Liver Disease (MELD) score (HR, 1.14; 95% CI: 1.05-1.24; $P = 0.002$), Child-Pugh score (HR, 1.26; 95% CI: 1.03-1.53; $P = 0.022$), and platelets $<100 \times 10^9/L$ (HR, 1.90; 95% CI: 0.76-4.76; $P = 0.169$) were associated with mortality. In the multivariate analysis, only MELD score was a significant predictor for mortality (HR, 1.15; 95% CI: 1.06-1.25; $P = 0.001$).

The composite endpoint treatment failure did not differ between treatment groups (EVL + β -blocker 34% vs. TIPS 38%; $P = 0.685$; Fig. 2C). Mortality and treatment failure did also not significantly differ in the as-treated population (Supporting Fig. 1B,C).

For the endpoint 2-year mortality, we performed a post-hoc sensitivity analysis, excluding those 14 patients who received TIPS within 5 days ("early TIPS"). Seven (20%) patients in the endoscopy + β -blocker arm died, compared to 4 (21%) in the late-TIPS group ($P = 0.85$). Furthermore, 2-year mortality in the early ($n = 2$;

Table 2. Summary of Outcome Measurements After 2 Years of Follow-up*

	Endoscopic + β -Blocker Group (N = 35)	TIPS Group (N = 37)	P Value
Total upper GI bleeding	13 (37)	2 (5)	0.001
Significant variceal rebleeding (primary endpoint)	9 (26)	0 (0)	0.001
Failure to control bleeding (<120 hours)	2	0	
Failure of secondary prophylaxis (>120 hours)	7	0	
Other significant upper GI rebleeding	4 (11)	2 (5)	
Portal hypertensive gastropathy	1	1	
Post-EVL ulcer	2	1 [†]	
Peptic ulcer	1	0	
Treatment failure [‡]	10 (29)	10 (27)	0.976
Liver transplantation	3 (9)	4 (11)	0.760
Encephalopathy, grade	7 (20)	13 (35)	0.117
1-2	3	5	
3-4	4	8	
Death	7 (20)	8 (22)	0.818
Hepatocellular- or cholangiocarcinoma	2	2	
Liver failure [§]	0	3	
Sepsis/pneumonia	0	2	
Peptic ulcer bleeding	1	0	
Intra-abdominal bleeding	2 [¶]	0	
Other [#]	2	1	
Bleed to TIPS time (days), median (IQR)	NA	6 (3-9)	
Transfusion of RBC during index admission	2.8 $\pm$ 2.8	2.6 $\pm$ 3.5	0.73
Time in hospital during index admission (days)	8.8 $\pm$ 5.4	12.4 $\pm$ 11.2	0.095

*Outcomes were reported from trial inclusion to 2 years of follow-up or shorter in case an endpoint had been reached or until study termination. Intention-to-treat population. Plus-minus values are means $\pm$ standard deviation, other values are no. (%).

[†]In the interval between randomization and TIPS placement.

[‡]Combination of switch to other therapy or death.

[§]All deaths occurred within 4 months after TIPS placement.

^{||}Etiology of liver disease was primary sclerosing cholangitis and cryptogenic and alcohol + viral hepatitis in 1 case each.

[¶]One intra-abdominal bleeding from an intra-abdominal varix, one from a laceration of the hepatic artery during TIPS placement (after switch from endoscopic arm to TIPS for reasons of variceal rebleeding).

[#]Cerebrovascular accident, myocardial infarction, and respiratory insufficiency.

Abbreviations: GI, gastrointestinal; NA, not applicable.

14%) and late (n = 4; 21%) TIPS groups was comparable ($P = 0.58$).

Secondary Endpoint: Hepatic Encephalopathy. Hepatic encephalopathy occurred in 22 patients (31%) in total; 14 in the TIPS group compared to 8 in the endoscopy + β -blocker group (Fig. 2D). Early hepatic encephalopathy (within 1 year) was significantly more frequent in the TIPS group (35% vs. 14%; $P = 0.035$), but during long-term follow-up this difference disappeared (38% vs. 23%; $P = 0.121$). Among those cases with encephalopathy, 64% in the TIPS group and 50% in the endoscopy + β -blocker group developed severe encephalopathy (grade 3 or 4; $P = 0.131$). Treatment consisted of lactulose (n = 17) and/or rifaximin (n = 2). In 1 patient, no treatment was necessary, and in 2 TIPS-treated patients with refractory encephalopathy, the shunt was closed. In the as-treated analysis, we found a significantly higher proportion of encephalopathy in the TIPS group both after 1 year as well as during long-term follow-up ($p = 0.002$ and $p = 0.017$, respectively; Supporting Fig. 1D). Univariate proportional hazard analysis showed that the risk of newly developing encephal-

opathy was higher in males (HR, 4.23; 95% CI: 1.43-12.54; $P = 0.009$). In the multivariate analysis, male sex ($P = 0.004$) and treatment with TIPS ($P = 0.033$) were independent predictors of encephalopathy.

In a post-hoc analysis, we tested treatment effect on Child-Pugh A versus BC for the endpoints variceal rebleeding, mortality, and hepatic encephalopathy. There was no significant difference in treatment effect across Child-Pugh class.

Other Events. Overall, 24 (69%) patients in the endoscopy + β -blocker arm and 24 (65%) in the TIPS arm experienced at least one severe adverse event ($P = 0.74$). There were no significant differences in the number of patients who experienced a specific adverse event between both arms (Table 3).

Discussion

In this multicenter randomized, controlled trial, we showed that TIPS placement is superior to EVL + β -blocker treatment for secondary prevention of variceal

Table 3. Adverse Events

	No. of Events (No. of Patients)			
	Endoscopy Group Group <2 Years	TIPS Group <2 Years	Endoscopy Group TIPS Group >2 Years Until End Follow-up	TIPS Group >2 Years Until End Follow-up
Severe adverse events				
Bleeding complications				
Variceal rebleeding	14 (9)		1	
Bleeding from banding ulcer	2 (2)	1		
Bleeding from portal hypertensive gastropathy	1	1		1
Other upper GI bleeding	1			1
Intra-abdominal bleeding from collaterals	1			
Laceration hepatic artery (during TIPS placement)	1			
Other complications				
Hepatic encephalopathy	6 (6)	18 (12)	2 (2)	2 (2)
Ascites	11 (6)	4 (3)	2 (2)	1
Spontaneous bacterial peritonitis	3 (2)			2 (2)
Hepatorenal syndrome			1	
Hepatocellular- or cholangiocarcinoma	3 (3)	2 (2)	1	
Acute-on-chronic liver failure	2 (1)	3 (3)	1	1
Spontaneous TIPS occlusion		2 (2)		1
Cholangitis	2 (2)			6 (3)
Alcoholic hepatitis	2 (2)			1
Sepsis/systemic infection	1	3 (2)		1
Cardiac events (ventricular fibrillation, third-degree AV block after start β -blocker, myocardial infarction)	2 (2)	1	1	
Neurological disorders (delirium tremens, Korsakoff syndrome, cerebellar ataxia)	2 (2)		1	1
Other (allergic reaction, peripheral edema, diabetes mellitus, erysipelas, gastroenteritis, incarcerated hernia inguinalis)	2 (2)	2 (2)	1	1
Nonserious adverse events				
Severe itching	1	1		
Hepatic encephalopathy	1			
Gynecomastia		1		

Abbreviations: AV, atrioventricular; GI, gastrointestinal.

bleeding (i.e., the prevention of rebleeding), but this does not translate into improved survival. However, our study was not powered for the endpoint mortality.

The importance of secondary prophylaxis after variceal bleeding has been extensively acknowledged, yet the most successful method for this purpose has been of much debate.³ So far, most evidence supporting the use of TIPS for secondary prevention of variceal bleeding comes from studies on bare metal stents. One trial compared EVL with uncovered TIPS in 80 patients with cirrhosis with variceal bleeding. TIPS significantly reduced the incidence of variceal rebleeding, but did not increase 2-year survival.¹⁵ Another trial compared drug therapy (propranolol + isosorbide-5-mononitrate) with uncovered TIPS in Child-Pugh B or C patients after a first episode of variceal bleeding. They found similar survival, but more hepatic encephalopathy in the TIPS group, and a relatively high number of reinterventions in both groups (angioplasty $\pm$ restenting in the TIPS group (90 of 98) and endoscopic therapy for rebleeding in the medical group (45 of 62)).¹⁶ Because of the high

number of in-stent thrombosis, use of bare-metal stents is increasingly replaced by covered stents.

Data on treatment with early covered-TIPS versus endoscopic + β -blocker therapy for treatment of acute variceal bleeding are limited to two studies and show survival benefit in selected, high-risk populations with either Child-Pugh class C disease or Child B disease with active bleeding at diagnostic endoscopy.^{9,11} In this regard, the results of a recent uncontrolled study, using the proposed Child-Pugh and endoscopic criteria, are of importance. No survival benefit of early TIPS for secondary prophylaxis (i.e., after control of bleeding) was reported when the outcome was compared with that observed in a historical cohort of EVL-treated patients.¹⁰ These data suggest that additional studies, addressing optimal selection criteria for TIPS in patients presenting with variceal bleeding, remain highly relevant.

Because rebleeding is associated with increased risk of mortality,³ preventing variceal rebleeding may be a substitute outcome of survival.¹⁷ As prevention of

rebleeding in our study did not result in improved survival, other factors than rebleeding may have contributed to the observed mortality in both groups. Indeed, liver failure, hepatobiliary cancer, and sepsis were the predominant causes of death in our study.

In line with earlier studies on bare-metal TIPS,⁶ we found a higher proportion of early hepatic encephalopathy in the TIPS group. Remarkably, the difference in encephalopathy between treatment groups was the largest in the first year. The portal pressure gradient, both before and after TIPS placement, was lower than expected. However, we found no association between risk of encephalopathy and portal pressure gradient, nor postdilatation diameter of the stent.

A few issues need to be addressed. First, in this study, a relatively high proportion of patients with primary sclerosing cholangitis, primary biliary cirrhosis, and autoimmune hepatitis was included. The randomization was stratified by Child-Pugh score, but not by etiology. Although not significant, the etiology of liver disease was not completely balanced between treatment arms. Second, we included both patients with esophageal, gastric, and gastroesophageal varices to mimic daily practice. Six percent of patients had only gastric varices. Current guidelines recommend TIPS for the prevention of further rebleeding after one rebleeding in these cases instead of continued endoscopic glue treatment and β -blockade.

In conclusion, covered TIPS is clearly superior to endoscopic therapy in combination with pharmacotherapy for prevention of variceal rebleeding, but does not result in early or late survival benefit in unselected patients with cirrhosis after endoscopic controlled variceal bleeding. Rebleeding may not be a good predictor for mortality, given that prognosis is largely linked to factors other than rebleeding. Additional results of studies on cost-effectiveness, quality of life, and randomization between early and elective TIPS placement will contribute to further define the optimal treatment regimen for patients presenting with GEVB.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28318/supinfo.

SUPPLEMENTAL MATERIAL

Figure S1

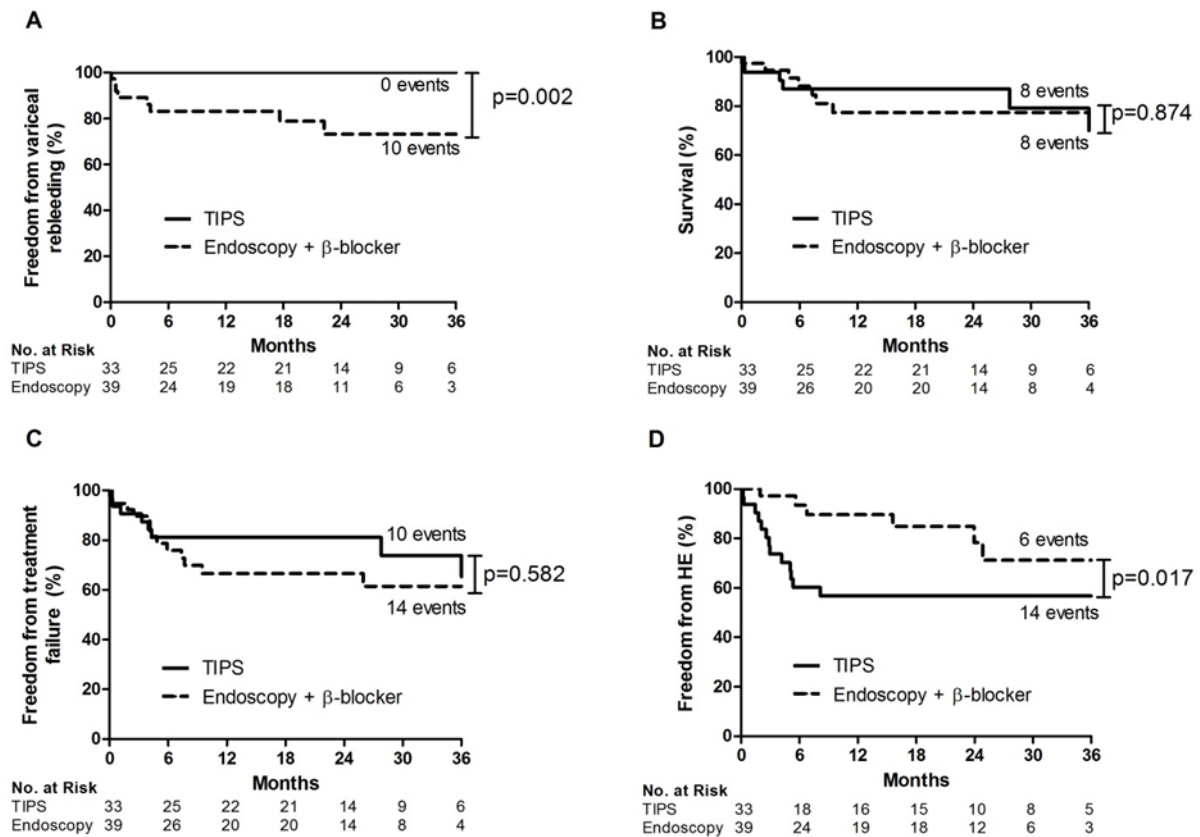


Figure S1: Kaplan-Meier analysis of freedom of variceal rebleeding, survival, treatment failure and hepatic encephalopathy for the “as treated” population

Panel A shows the probability of remaining free from significant variceal rebleeding.

Panel B shows the probability of survival. Panel C shows the probability of remaining

free from treatment failure. Panel D shows the probability of remaining free from hepatic encephalopathy.

TIPS denotes transjugular intrahepatic portosystemic shunt.