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Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites

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BACKGROUND & AIMS: There is controversy over the ability of transjugular intrahepatic portosystemic shunts (TIPS) to increase survival times of patients with cirrhosis and refractory ascites. The high rate of shunt dysfunction with the use of uncovered stents counteracts the benefits of TIPS. We performed a randomized controlled trial to determine the effects of TIPS with stents covered with polytetrafluoroethylene in these patients. **METHODS:** We performed a prospective study of 62 patients with cirrhosis and at least 2 large-volume paracenteses within a period of at least 3 weeks; the study was performed at 4 tertiary care centers in France from August 2005 through December 2012. Patients were randomly assigned to groups that received covered TIPS (n = 29) or large-volume paracenteses and albumin as necessary (LVP+A, n = 33). All patients maintained a low-salt diet and were examined at 1 month after the procedure then every 3 months until 1 year. At each visit, liver disease–related complications, treatment modifications, and clinical and biochemical variables needed to calculate Child-Pugh and Model for End-Stage Liver Disease scores were recorded. Doppler ultrasonography was performed at the start of the study and then at 6 and 12 months after the procedure. The primary study end point was survival without a liver transplant for 1 year after the procedure. **RESULTS:** A higher proportion of patients in the TIPS group (93%) met the primary end point than in the LVP+A group (52%) ($P = .003$). The total number of paracenteses was 32 in the TIPS group vs 320 in the LVP+A group. Higher proportions of patients in the LVP+A group had portal hypertension-related bleeding (18% vs 0%; $P = .01$) or hernia-related complications (18% vs 0%; $P = .01$) than in the TIPS group. Patients in LVP+A group had twice as many days of hospitalization (35 days) as the TIPS group (17 days) ($P = .04$). The 1-year probability of remaining free of encephalopathy was 65% for each group. **CONCLUSIONS:** In a randomized trial, we found covered stents for TIPS to increase the proportion of patients with cirrhosis and recurrent ascites who survive transplantation-free for 1 year, compared with patients given repeated LVP+A. These findings support TIPS as the first-line intervention in such patients. ClinicalTrials.gov ID: NCT00222014.

Keywords: Liver Fibrosis; TIPS; Refractory Ascites; PHT.

Refractory or recurrent ascites is a severe complication of cirrhosis, with a mean 1-year survival rate of 50%.[1,2] Patients could benefit from liver transplantation, but <20% of them will receive transplants because of contraindication or advanced age. Another therapeutic option is repeated large-volume paracentesis with albumin (LVP+A) infusion. However, the underlying liver disease is not improved and clinical outcomes remain dismal.[3,4] Portal hypertension (PHT) is the main determinant of ascites, and decreasing portal pressure by portosystemic shunt has been shown to relieve ascites.[5]

Randomized controlled trials (RCT) on transjugular intrahepatic portosystemic shunt (TIPS) vs LVP in patients with refractory ascites showed an important reduction of recurrence of tense ascites in patients allocated to TIPS.[6–10] However, all of those studies were performed with uncovered stents, leading to a high rate of shunt dysfunction, which was the main drawback of this treatment.[6–11]

The development of polytetrafluoroethylene (PTFE)-covered stents was considered major progress in this field, owing to a substantial decrease in the rate of shunt dysfunction and to an improvement in clinical outcomes.[12–15] Furthermore, the selection of patients for TIPS has been shown to be crucial in order to observe a potential gain in term of survival.[10] Actually, an improved 1-year survival rate was demonstrated using covered stents in highly selected patients with cirrhosis and variceal bleeding.[16] We therefore hypothesized that both accurate selection[17] and the use of covered stents should improve the prognosis for patients with cirrhosis and recurrent ascites treated by TIPS.

Abbreviations used in this paper: **LVP+A, large-volume paracentesis with albumin; OHE, overt hepatic encephalopathy; PHT, portal hypertension; PPG, portal pressure gradient; PTFE, polytetrafluoroethylene; RCT, randomized controlled trials; TFS, transplantation-free survival; TIPS, transjugular intrahepatic portosystemic shunt.**

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The present RCT in patients with cirrhosis and recurrent ascites aimed to compare the efficacy of covered TIPS to LVP+A in terms of liver transplantation-free survival (TFS).

Methods

Study Design

Between August 2005 and December 2012, patients with cirrhosis and at least 2 LVPs within a minimum interval of 3 weeks were considered for inclusion.

Inclusion criteria were patients with cirrhosis, as documented by previous liver biopsy or a combination of usual clinical and biochemical signs; age older than 18 years and younger than 70 years; recurrent tense ascites; and signed informed consent form.

Exclusion criteria were patients who had required >6 LVPs within the previous 3 months; patients expected to receive transplants within the next 6 months or on waiting list; usual contraindications for TIPS, congestive heart failure, history or presence of pulmonary hypertension, complete portal vein thrombosis, recurrent overt hepatic encephalopathy (OHE), hepatocarcinoma, severe liver failure (defined by prothrombin index <35% or total bilirubin >100 μmol/L or Child-Pugh Score >12), serum creatinine >250 μmol/L, uncontrolled sepsis, known allergy to albumin, pregnant or breastfeeding women, refusal to participate, or patient unable to receive information or to sign written informed consent.

All patients provided written informed consent. The study protocol was approved by the local ethics committee (CCPPRB Toulouse II). Three centers were closed and replaced by 3 others because of noncompliance with good research practice and guidelines (the patients included in those centers were not analyzed) or no effective inclusion. Accordingly, the patients considered for analysis were included in Toulouse, Paris, Lille, and Angers.

The main end point was 1-year liver TFS. Secondary end points were ascites recurrence and treatment failure as defined here, the rate of OHE, PHT-related complications, other complications of cirrhosis, and the number of days in hospital during a 1-year period after inclusion.

Treatment Procedures

Diagnostic evaluation before randomization included clinical assessment of cirrhosis complications, usual blood tests, Doppler ultrasonography of the abdomen, and echocardiography to rule out exclusion criteria. After the investigator received written informed consent, randomization was generated online by computer, equilibrated for each center, stratified according to whether cirrhosis was alcoholic or not and adjusted every 10 patients. TIPS was performed under sedation as described previously.[13] For homogeneity reasons, technical recommendations for TIPS placement were as follows: a 10-mm covered stent was used (Viatorr; TIPS endoprosthesis, W.L. Gore & Associates, Inc, Flagstaff, AZ), dilated to 8 or 10 mm Hg according to the hemodynamic response. The aim was to reduce portal pressure gradient (PPG) <12 mm Hg.

Follow-Up

All patients were maintained on a low-salt diet. Patients had a clinical examination at 1 month and then every 3 months up to 1 year. At each visit, liver disease-related complications, treatment modifications, and clinical and biochemical variables needed to calculate Child-Pugh and Model for End-Stage Liver Disease scores were recorded. Doppler ultrasonography was performed at the beginning, and 6 and 12 months after. Patients were followed for 1 year or until liver transplantation or death.

Patients included in the LVP+A group were treated by LVP+A whenever required. Eight grams albumin per liter ascites extracted were infused when >3 L ascitic fluid had been removed. The use of diuretics was allowed at the maximal tolerated dose and compliance with low-sodium diet was assessed by direct questioning and natriuresis. In the group treated by LVP+A, failure was defined as the need for >6 LVPs within 3 months and alternative treatment, mainly TIPS or liver transplantation could be proposed. All of these patients with treatment failure were to be followed up to 1 year after inclusion. In the TIPS group, the relapse of ascites requiring at least 2 LVPs or its persistence after 2 months were considered as failure. When shunt dysfunction was suspected because of relapse of ascites or incomplete response 2 months after the procedure, an angiography with a PPG measurement was performed. If shunt dysfunction was confirmed, angioplasty or PTFE re-stenting aiming to reduce PPG <12 mm Hg were performed.

Statistical Analyses

The initial sample calculation, based on available published data in 2004, was 60 patients per group. During the course of the study, a 52% 1-year TFS among patients treated by LVP+A infusion was reported by a meta-analysis[18] and 2 studies[9,10] found an 80% 1-year TFS survival rate in patients treated by TIPS with uncovered stents. Accordingly, the number of patients needed for our study was recalculated based on the following updated hypotheses: 1-year TFS rate of 85% among patients treated with PTFE-covered stent and 52% among those treated by LVP+A. To detect such a difference, a minimum of 30 patients per group was needed (2-sided test, $\alpha = .05$ and $\beta = .2$), adjusted for a 5% loss of follow-up.

The SPSS statistical package (SPSS Inc, Chicago, IL) was used for the analysis according to an intention to treat strategy. Comparisons between the 2 groups were performed using Student t test or χ^2 test, as required. Actuarial probability curves were constructed using the Kaplan–Meier method and compared with the log-rank test. Patients in the LVP+A group who were switched to TIPS treatment were censored alive at the time of the shunt procedure for the TFS analysis. Cox regression analysis was used to identify independent predictors for the primary end point. Statistical significance was established at $P < .05$.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patients' Characteristics

Among the 137 patients admitted for recurrent ascites during the study period, 62 patients were included. Reasons for excluding the other 75 patients are listed in Supplementary Figure 1. Of the 62 included patients, 29 were enrolled in the TIPS group and 33 in the LVP+A group. The baseline characteristics of the patients were similar in

both groups (Table 1). TIPS insertion was successful in all 29 patients, with a decrease of mean PPG from 15.4 ± 4.6 mm Hg to 6.4 ± 4.2 mm Hg ($P < .001$). A value of PPG <12 mm Hg was achieved in all patients. No severe related procedure complications were reported in the 2 groups. Median follow-up of the whole cohort was 365 days (range, 31–483 days).

Transplantation-Free Survival

One patient in each group was lost to follow-up 274 and 284 days after inclusion. Two patients died in the TIPS group 35 and 205 days after the procedure and none received transplants. In the LVP+A group, 4 patients received transplants at a mean delay of 257 ± 60 days, and 5 died at a mean delay of 188 ± 107 days after inclusion. Reasons for liver transplantation and causes of death are listed in Supplementary Table 1. One-year actuarial rate of TFS was greater in the TIPS group than in the LVP+A group: 93% (95% confidence interval, 82%–100%) and 52% (95% confidence interval, 34%–60%), respectively ($P = .003$) (Figure 1).

Univariate analysis showed that a low international normalized ratio, low serum bilirubin, high serum sodium at baseline and assignment to TIPS group were associated with a higher 1-year TFS. The multivariate analysis using Cox model, including age and the 4 variables mentioned, showed that only the allocation to the TIPS group was associated with 1-year TFS (hazard ratio, 2.1; 95% CI, 1.1–4.0) (Table 2).

Table 1. Baseline Characteristics of the 62 Patients According to Assigned Treatment

Characteristic	TIPS (n = 29)	LVP+A (n = 33)	*P* value
Sex, *male/female*, n	17/12	27/6	.06
Age, *y*	56.7 ± 5.7	56.4 ± 7.9	.868
Weight, kg	67 ± 13	72 ± 13	.132
BMI, *kg/m*	23.6 ± 4.3	24.3 ± 3.3	.465
Etiology, %			
Alcohol	90	85	1.00
Stopped alcohol use	70	80	1.00
Chronic hepatitis C	3	9	.616
Other	7	6	1.00
History of SBP, %	7	15	.432
History of OHE, %	0	3	1.00
History of variceal bleeding, %	28	30	1.00
History of renal failure, %	21	18	1.00
No. of paracentesis, last 3 mo	4.5 ± 1.4	4.2 ± 1.3	.377
Duration of cirrhosis, *y*	3.7 ± 4.1	2.9 ± 3.4	.364
Trail making test A, *s*	71 ± 33	66 ± 44	.614
Bilirubin, *μmol/L*	17.8 ± 12.7	17.5 ± 16.4	.938
INR	1.39 ± 0.27	1.46 ± 0.30	.382
Albumin, *g/L*	30.7 ± 5.5	33.4 ± 5.4	.06
Serum creatinine, *μmol/L*	84.6 ± 30.1	85.6 ± 21.4	.888
Serum sodium, *mmol/L*	134 ± 4	132 ± 4	.06
Hemoglobin, *g/dL*	11.5 ± 1.7	11.8 ± 1.7	.543
Platelets, $10^3/mm^3$	179 ± 94	169 ± 90	.687
ASAT, *UL/N*	1.69 ± 0.79	1.63 ± 0.85	.771
ALAT, *UL/N*	1.09 ± 0.28	1.12 ± 0.38	.711
Child-Pugh score	9.1 ± 1.4	9.0 ± 1.6	.922
Child-Pugh class: B/C, n	19/10	22/11	1.00
MELD score	12.1 ± 3.5	13.1 ± 3.9	.289
Diuretics used			
Furosemide, *mg/d*	68 ± 67	58 ± 24	.474
Aldosterone antagonist, *mg/d*	109 ± 58	120 ± 56	.580
β-blockers, %	45	48	.804
Antibiotic prophylaxis, %	10	15	.713
Follow-up, *d*	350 ± 99	314 ± 93	.144

NOTE. Values are mean ± SD unless otherwise noted.
ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BMI, body mass index; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; SBP, spontaneous bacterial peritonitis.

Recurrence of Ascites and Failure of Treatment

During the 1-year follow-up, the total number of paracenteses was 32 (1.0 ± 1.6 per patient) in the TIPS group and 320 in the LVP+A group (10.1 ± 7.0 per patient) ($P < .001$). Fifteen patients from the TIPS group did not require further paracentesis during follow-up compared with none in the LVP+A group ($P < .05$). Total volume extracted and total albumin infusion were 169 L and 1170 g, respectively, in the TIPS group compared with 2061 L and 17,727 g in the LVP+A group ($P < .001$) (Table 3). Pressure gradient was not different before or after TIPS between patients who experienced failure and those who did not (respectively 15.6 ± 4.1 mm Hg vs 18.7 ± 3.8 mm Hg before and 5.5 ± 2.4 mm Hg vs 6.7 ± 0.6 mm Hg after).

In the LVP+A group, 15 patients were treated by TIPS during follow-up, 14 because they needed >6 LVPs within 3 months (according to the planned protocol) and 1 because of associated recurrent variceal bleeding. In the TIPS group, 1 patient developed an early thrombosis of the shunt, resulting in persistence of ascites after the procedure and was treated successfully by insertion of a second stent. As a whole, the probability of being free of treatment failure, as defined in Methods, was significantly greater in the TIPS group (89% vs 29% in the LVP+A group; $P < .001$; Supplementary Figure 2).

Hepatic Encephalopathy and Other Liver-Related Complications

The 1-year probability of remaining free of OHE was 65% in both groups (Supplementary Figure 3). No difference was observed when considering only patients with episodes of OHE grade >2 or the number of episodes per patient (Table 3). One patient in TIPS group required stent reduction because of severe recurrent OHE.

The rates of PHT-related bleeding and hernia-related complications were significantly greater in the LVP+A group, while spontaneous bacterial peritonitis, hepatorenal syndrome, infection, and hepatocellular carcinoma were found to be as frequent in both groups (Table 3). The number of days in hospital was doubled in the LVP+A group compared with the TIPS group (35 ± 40 vs 17 ± 28, $P = .04$).

The comparison between liver and renal function tests throughout a 6-month follow-up period showed that albumin, Child-Pugh score, creatinine, and serum sodium

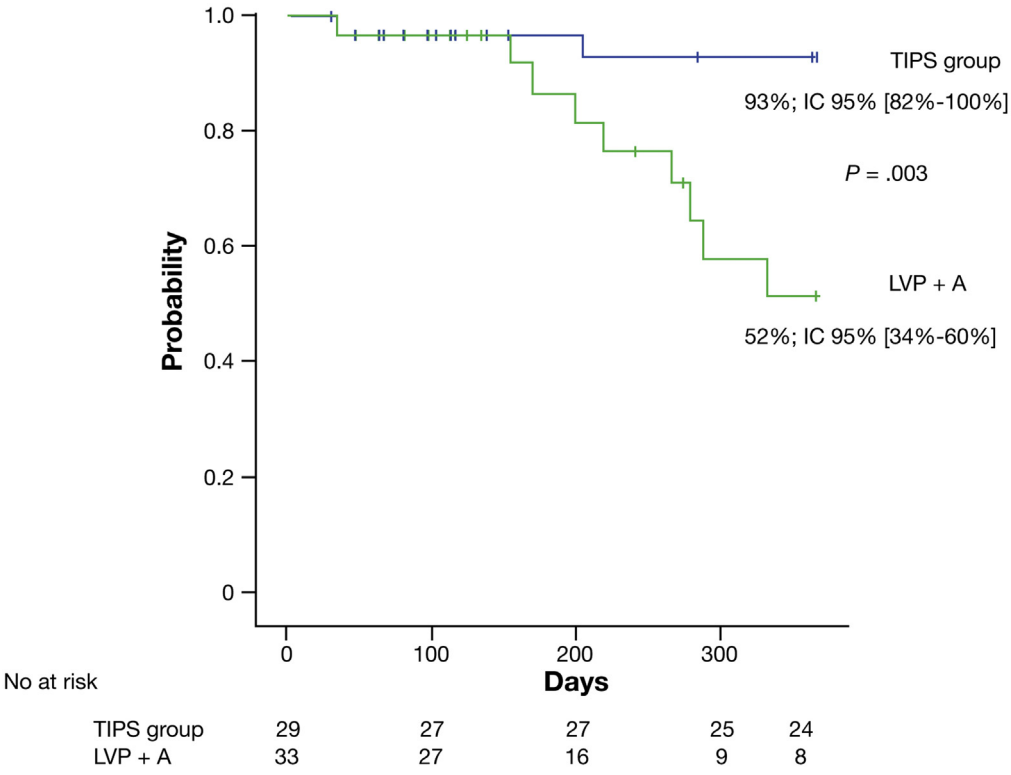

Figure 1. Probability of survival without liver transplantation in patients allocated to covered TIPS group and in those allocated to LVP+A group.

improved in the TIPS group only, while international normalized ratio and bilirubin did not change significantly in the 2 study arms (Table 4). Furthermore, both plasma renin activity and aldosterone concentration decreased in the TIPS group only during the same period (Table 4). Plasma renin activity was negatively correlated with systolic blood pressure ($r = -0.384$; $P < .05$) and blood pressure at 3 and 6 months was found to be greater in TIPS group compared with LVP+A group: 136 ± 19 mm Hg vs 116 ± 12 mm Hg, respectively; $P < .002$ (see Supplementary Table 2). At 3 months, heart rate was also found to be higher in TIPS group as compared with LVP group (85 ± 12 beats/min vs 73 ± 15 beats/min; $P = .03$).

Discussion

The present study showed that 1-year TFS of selected patients with cirrhosis and recurrent ascites was improved by using TIPS with covered stents as compared with paracentesis and albumin infusion. Treatment with TIPS was also associated with a decreased risk of other PHT-related complications and less hospitalizations. The risk of hepatic encephalopathy was similar in both groups.

In patients with tense ascites, although the benefit of TIPS in terms of recurrence has been established, the impact on survival remains controversial. RCTs and review meta-analyses did not observe any significant difference in survival between patients allocated to TIPS and those allocated to LVP. For that reason, the experts of the International ascites club stated that repeated paracenteses is the first-line treatment and TIPS should be considered in patients with very frequent requirement of LVP.[3] However, those studies, all performed with bare stents, did not take into account the confounding effect of liver transplantation on survival, which could constitute an important bias. A meta-analysis of individual data taking into account the competitive risk of being transplanted during the follow-up

Table 2. Prognostic Parameters Associated With Survival Without Liver Transplantation in Univariate and Multivariate Analyses

Parameter	Patients alive without LT (n = 11)	Patients dead or received transplant (n = 51)	Univariate *P* value	Multivariate HR (95% CI); *P* value
INR, mean ± SD	1.4 ± 0.3	1.5 ± 0.2	.09	0.8 (0.3–2.3); NS
Serum sodium, *mmol/L* mean ± SD	129 ± 3	134 ± 4	.001	0.9 (0.9–1.0); NS
Bilirubin, *μmol/L* mean ± SD	27 ± 21	15 ± 12	.05	1.0 (1.0–1.0); NS
TIPS/paracentesis, %	93/73	7/27	.048	2.0 (1.1–4.0); .03

HR, hazard ratio; INR, international normalized ratio; LT, liver transplantation.

Table 3. Clinical Outcomes in Patients According to Treatment Group

Outcome	TIPS (n = 29)	LVP+A (n = 33)
No. of paracenteses per patient, mean ± SD	1 ± 1	10 ± 7***
Volume extracted, *L/patient*, mean ± SD	6 ± 10	64 ± 47***
Albumin infusion, *g/patient*, mean ± SD	39 ± 70	550 ± 458***
Days in hospital, mean ± SD	17 ± 28	35 ± 40*
Patients with OHE, n	10	11
Episodes of OHE per patient, n, mean ± SD	1.6 ± 0.7	1.7 ± 0.8
Patients with OHE grade >2, n	4	7
Patients with PHT-related bleeding, n	0	6**
Patients with hernia-related complication, n	0	6**
Patients with HRS, n	0	1
Patients with SBP, n	0	2
Patients with sepsis, n	5	9
HCC, n	0	1

HCC, hepatocellular carcinoma; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.
*$P < .05$; **$P < .01$; ***$P < .001$.

reported a higher TFS in patients allocated to TIPS.[18] However, such a demonstration needs to be confirmed in the context of an RCT with a relevant study design taking into account the survival impact of liver transplantation. The accuracy of the selection process to consider a patient with recurrent ascites as a candidate for TIPS is also crucial to reduce potential biases related to the presence of confounding factors that could interfere in the evaluation of the impact of TIPS on survival. These considerations are the strength of the present work with the use of covered stents. Actually, we and others already reported that the use of covered stents improves clinical outcomes.[13,14] In addition, we found that an accurate selection of patients improves survival.[17] As a result, the prognosis of patients with a high-risk variceal bleeding has been improved.[16] Consequently, the same concept was applied, in the present study, to patients with recurrent ascites. The rate of 1-year TFS was 93% in the TIPS group, which is markedly better than rates reported previously (80% in the 2 more recent studies[9,10]). This could be related to greater experience with the TIPS procedure: no technical failure occurred in the present study, while the rate of failures reached 6% to 23% in the previous 5 studies. An optimized selection (most patients were Child B without prior encephalopathy and younger that 65 years) might have also contributed to these results, however, TFS in the paracentesis group was similar to that observed in most studies (52% in a previous meta-analysis[18]). Therefore, we believe that the use of covered stents was the main determinant of the observed improvement in outcomes. The rate of shunt dysfunction was close to 80% at 1 year in most previous studies, owing to a recurrence of PHT-related complications in >50% of patients randomized in the TIPS group.[6–11] Therefore, TIPS with uncovered stent should not be considered effective or recommended any longer for the long-term treatment of PHT. An improvement of general health and nutritional status could also have played a role, but this issue remains to be investigated.[19–21] Finally, plasma renin activity, a well-known prognostic parameter in patients with cirrhosis,[22] dramatically decreased after TIPS. This is a hallmark of hemodynamic changes after TIPS. This last consequence was probably the main beneficial effect of permanent shunting, owing to an enduring improvement of hemodynamic conditions that could have contributed to a better clinical outcome. Because it has been reported that β-blockers could worsen prognosis in patients with chronic ascites,[23,24] assessing the effects of β-blocker discontinuation in patients treated by TIPS deserves additional investigation. Stopping alcohol use could also have contributed to an improvement in liver functions, but it is noteworthy that abstinence was reported to be as frequent in both groups and the need for repeated paracenteses increased in most patients of the LVP+A group.

As already reported for variceal bleeding, a careful selection of patients restricts the number of potential candidates for TIPS. In previous RCTs, patients included represented 20% to 50% of screened patients compared with 45% in the present study. Accordingly, other strategies in non-candidates require additional studies: liver transplantation in patients with refractory ascites and high Model for End-Stage Liver Disease score, or new procedures still under investigation.[23,25]

Table 4. Evolution of Hepatic and Renal Functions Between Baseline and Month 6 According to the Group

Variable	Baseline	Month 6
Bilirubin, *μmol/L*		
TIPS	20.8 ± 14.4	21.5 ± 19.5
LVP+A	15.8 ± 12.1	17.4 ± 14.8
Albumin, *g/L*		
TIPS	31.2 ± 4.7	34.0 ± 5.6**
LVP+A	33.3 ± 4.8	32.2 ± 6.2
INR		
TIPS	1.38 ± 0.27	1.35 ± 0.22
LVP+A	1.52 ± 0.31	1.48 ± 0.29
Creatinine, *μmol/L*		
TIPS	86.1 ± 31.2	70.3 ± 27.3**
LVP+A	84.6 ± 23.7	81.6 ± 20.1
Serum sodium, *mmol/L*		
TIPS	135 ± 5	139 ± 2**
LVP+A	132 ± 5	133 ± 5
Child-Pugh score		
TIPS	9.0 ± 1.4	7.0 ± 1.7**
LVP+A	9.2 ± 1.8	8.6 ± 2.1
MELD score		
TIPS	12.3 ± 3.4	13.1 ± 5.9
LVP+A	14.2 ± 3.6	13.6 ± 4.3
Plasma renin activity, *μU/mL*		
TIPS	860 ± 1329	59 ± 46*
LVP+A	856 ± 1338	1046 ± 1993
Plasma aldosterone, *ηg/L*		
TIPS	325 ± 554	32 ± 54*
LVP+A	214 ± 201	294 ± 323

NOTE. In the LVP+A group, the values for patients treated by TIPS before month 6 were those measured just before the crossover for the TIPS procedure.
*$P < .05$ vs baseline; **$P < .01$ vs baseline; ***$P < .001$ vs baseline.

No difference regarding the risk of encephalopathy was observed. In the absence of a double-blind assessment, this must be considered with caution. However, this is in agreement with our previous observation showing that the use of covered stents did not increase this risk of OHE compared with bare stents,[13,14] probably by preventing events at risk of precipitating encephalopathy, such as variceal bleeding, ascites, use of diuretics, hospitalizations, and shunt revisions.

No difference was observed among centers or according to etiology of the liver disease, however, these results must be also interpreted with caution, as all other prognostic parameters, because of the small sample size. In addition, as most patients had alcoholic liver disease, no definitive conclusion can be drawn for patients with other chronic liver diseases. Finally, the results on survival could be rather different in patients with other characteristics than those of patients finally enrolled in the present study because assessment of cirrhosis severity is sometimes difficult in the context of refractory ascites.

In conclusion, TIPS with covered stents improved 1-year TFS in selected patients with recurrent ascites and should therefore be preferred to LVP with volume expansion.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.09.016.

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Conflicts of interest
These authors disclose the following: Christophe Bureau and Dominique Thabut have conflict of interest with Gore Inc as consultants and participants in expert panels. The remaining authors disclose no conflicts.

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