

## JOURNAL CLUB CRITIQUE

# 'The TIPSing point'

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### Expanded abstract

#### Citation

García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, Abraldes JG, Nevens F, Vinel JP, Mössner J, Bosch J; Early TIPS (Transjugular Intrahepatic Portosystemic Shunt) Cooperative Study Group: **Early use of TIPS in patients with cirrhosis and variceal bleeding.** *N Engl J Med* 2010, **362**:2370-2379.

#### Background

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

#### Methods

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

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

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

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

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

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

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

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

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

#### Results

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

#### Conclusions

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

#### Commentary

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

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

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

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

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

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

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

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

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

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

### Recommendation

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

### Abbreviations

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

### Competing interests

The authors declare that they have no competing interests.

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