

# Use of early-TIPS for high-risk variceal bleeding: results of a post-RCT surveillance study

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**Title:** Use of early-TIPS for high-risk variceal bleeding: results of a post-RCT surveillance study

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## Summary

Acute variceal bleeding (AVB) is a severe and potentially life-threatening complication of portal hypertension in cirrhotic patients [1-4]. Over the past few decades there have been significant advances in the management of variceal bleeding resulting in decrease in mortality (from 42.6% in 1980 to 10-15% in 2010). Combined treatment with vasoactive drugs, prophylactic antibiotics, and endoscopic techniques is the recommended standard of care for patients with AVB [5]. However, treatment failure occurs in about 10-15% of patients, who require repeat endoscopic treatments and multiple transfusions. Transjugular intrahepatic portosystemic shunt (TIPS) creation has been used as a salvage method whenever the combined treatment fails [6-10]. Although TIPS is effective in controlling variceal bleeding, previous studies have shown that it increases hepatic encephalopathy without increasing survival [11,12]. Thus, it has been recommended only as a salvage therapy [13]. Unfortunately, mortality is very high among patients who receive TIPS after combined treatment failure, mainly because the patients are very sick at that point [14].

A recent multicenter randomized controlled trial (RCT) [1] studied the hypothesis that early decision to use TIPS made on the basis of clinical criteria can improve the prognosis of high-risk patients with variceal bleeding. Sixty three patients were randomized to receive either a combined treatment with vasoactive drugs and endoscopic treatment (endoscopic band ligation, EBL) or TIPS with the use of expanded polytetrafluoroethylene (e-PTFE)-covered stents. Only patients with an advanced risk of bleeding-related mortality (Child-Pugh class C<14 and B patients with active bleeding on endoscopy) were included. The study showed that the early use

of TIPS (within 3 days of admission) reduced the 6-week mortality rate to 3% (33% with medical treatment) and the 1-year mortality rate to 14% (39% with medical treatment). When TIPS was used as a rescue treatment after the failure of medical treatment, the mortality rate was high, and this was comparable to previous results. Other beneficial effects of early TIPS placement included reduced rates of ascites, hepatorenal syndrome and spontaneous bacterial peritonitis and significantly fewer days in the intensive care unit and in the hospital ( $P<0.014$ ).

The authors concluded that in high-risk patients Child-Pugh C<14 disease or class B disease with active bleeding who were admitted for AVB, the early use of TIPS with e-PTFE-covered stents resulted in significant improvement in bleeding control and in mortality, with no increase in the risk of hepatic encephalopathy.

These results are different from those of two recent meta-analyses regarding survival and post-TIPS encephalopathy. According to these meta-analyses survival of patients with AVB did not differ among patients treated endoscopically versus TIPS, while encephalopathy was more frequently encountered in the follow up after TIPS [15,16].

The results of this study suggest that the treatment strategy of patients with AVB should change: in Child-Pugh class C (score 9-13) and B patients with active bleeding on endoscopy, early TIPS may be used as a first-line treatment. In patients without these characteristics, the current step-up strategy may be continued.

However, the question remains whether this new strategy could be applied in an everyday clinical setting outside RCTs with the same excellent results.

The same authors conducted a retrospective review [3] of all patients admitted for AVB and at high risk of treatment failure (defined by Child C<14 or Child B plus active bleeding at endoscopy despite intravenous vasoactive drug treatment, as in the RCT) at the centers participating in the original RCT on the use of early TIPS. They found that patients treated with early-TIPS had a much lower incidence of failure to control bleeding or rebleeding than patients receiving drugs + endoscopic treatment (3 vs. 15;  $P<0.001$ ). The 1-year actuarial probability of remaining free of this composite endpoint was

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93% vs. 53% ( $P < 0.001$ ). The same was observed in mortality (1-year actuarial survival was 86% vs. 70% respectively;  $P = 0.056$ ). Actuarial curves of failure to control bleeding and rebleeding and of survival were well within the confidence intervals of those observed in the RCT.

## Opinion

This research article [3] confirms the results of the RCT [1]. This group of patients includes those with Child C <14 (9-13) or Child B (7-9) plus persistent bleeding at endoscopy.

According to this suggestion TIPS should be offered to this group of patients within 72 h instead of adopting a conservative treatment strategy with TIPS as a last resort.

A point that merits clarification is definition of "early TIPS". Early TIPS refers to treatment with e-PTFE covered stents within 72 h after admission to hospital. The initial management lies in administration of vasoactive drugs. Diagnostic endoscopy is performed within 12 h after admission and EBL or endoscopic injection of sclerotherapy are applied. TIPS is the next step for this group of high-risk patients.

The practicality of this article increases as it suggests a clinical, simple way to select the high-risk patients based on the Child-Pugh score and the findings at endoscopy. This is in pleasant contrast to previous studies that suggested more invasive criteria such as the hepatic venous gradient of 20 mmHg or higher [17].

An apparent problem to this suggested change in the treatment strategy of AVB with TIPS could be the increase in the demand of available interventional radiology departments.

However, in the current study only 75 of 659 patients admitted for AVB met the inclusion criteria, similar to the 63 of 359 observed in the RCT, suggesting that in real life conditions, about one-fifth to one-sixth of the patients bleeding from varices do benefit from an early-TIPS strategy. This shows that not all centers should be ready to offer early-TIPS. On the contrary, the patients should be selected according to the suggested criteria and referred to the interventional radiology departments with TIPS experience, because in this patient group early e-PTFE-covered TIPS can be considered a life-saving therapy.

In our institution, we have reserved TIPS for cirrhotic patients with uncontrolled variceal bleeding as recommended by the current guidelines. Our experience indicates that TIPS is very successful in controlling AVB. The use of early TIPS, as supported by the article and the RCT, seems a very promising treatment for the patients with variceal bleeding who are classified as high-risk patients. There are multiple benefits including reduction in treatment failure, mortality and rebleeding as well as in the rates of ascites, hepatorenal syndrome and spontaneous bacterial peritonitis and the days of hospitalization. We believe that this new approach should be adopted in every day clinical practice but with the same inclusion and exclusion criteria as in the RCT and the post-RCT surveillance study [1,3].

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