Editorial

The conundrum of covered versus bare stents for transjugular intrahepatic portosystemic shunt: should we adopt the parachute approach?

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Transjugular intrahepatic portosystemic shunts (TIPS) are now routinely utilized for the treatment of the complications of cirrhosis-related portal hypertension: indeed TIPS has now a clear indication for active bleeding or to prevent rebleeding after failure of combined medical/endoscopic procedures; it is also indicated for refractory ascites and, at some extent in refractory hydrothorax in cirrhotic patients and type II hepatorenal syndrome.

The initial experience with TIPS was based on the use of bare stents (1,2). These stents were prone to allow intra-stent neointimal proliferation, with the direct consequence of a greater risk of stent dysfunction.

The major drawbacks of TIPS are shunt dysfunction and hepatic encephalopathy (HE), reported up to 77% and 50% within the first year (3,4), respectively. The availability of expanded polytetrafluoroethylene (ePTFE)-covered stents has dramatically improved the long-term patency of TIPS but the HE incidence has remained relatively high, ranging from 35–45% at 1 year, even since the advent of covered stents (5,6) and can probably be reduced with a more careful selection of patients. The cost-effectiveness issue of adopting covered (most expensive) and bare stent has been frequently raised but has never been properly addressed.

In their recent meta-analysis Qi X *et al.* (7) compare the outcome of covered versus bare stents for TIPS in cirrhotic patients with portal hypertension. The goals of the meta-analysis were to compare the outcome in term of shunt patency, overall survival and HE when using different stent.

The paper dealt with the following issues:

(I) *The patients having covered stents have significantly better shunt patency than those with bare stents.*

We must say that most of the available randomized controlled trials (RCTs) had already shown adequate proofs of the superiority of ePTFE-covered TIPS (8,9). Indeed, recent guidelines (10,11) and other RCTs (6,12,13) clearly promote the use of covered stent for all the known indications for TIPS and for the control arm of studies comparing TIPS with other strategies. Indeed the evidence of the superiority of covered stents in overcoming many technical issues, led to the unblinding of one of the RCT included in the meta-analysis (8) which allowed the use of the covered stent instead of a bare one in 6/129 pts.

In addition to the long term benefit, covered stents have proven to reduce the incidence of early dysfunction (during the first 2 weeks) likely as the result of their "easiness" of handling due to their extended length compared to bare ones, which facilitates correct placement (14).

However, we have to keep in mind that both short and long term patency of TIPS depend also on factors other than the type of device, like the experience of the radiologist and stent misplacement, anatomical variants in the vascular tree, an underlying myeloproliferative neoplasm with the associated prothrombotic state and increased technical issues and other less defined factors such as ongoing active

liver injury (alcohol abuse can cause steatotic hypertrophy of the liver, resulting in a misfit between the vena cava and the upper end of the stent).

(II) *The patients having covered stents have significantly better overall survival.*

As the authors clearly stated at the end of their article, available RCTs don't allow any conclusion regarding this topic mainly because of their paucity, the small number of patients enrolled and their heterogeneity in terms of TIPS indications, etiology of cirrhosis and stage of liver disease (Child and MELD scores are not routinely reported). Even in absence of a statistical demonstration, we can speculate that some survival benefits might well derive from the higher rate of patency and clinical efficacy of the TIPS. However, we should not draw any conclusion without stratifying patients for the known prognostic factors: age, stage of liver disease, associated renal dysfunction and etiology of liver disease as a minimum. Moreover, when evaluating survival as an outcome we should not forget that we are dealing with truly complex patients, in whom several confounding factors might be involved. With the onset of decompensation (ascites, hemorrhagic complications) cirrhotic patients foresee an abrupt reduction of life expectancy. Indeed, refractory ascites is associated with a 2-year survival rate of 30% in absence of liver transplantation (15) and TIPS, even reducing the need of paracentesis, confers a scanty advantage in terms of life expectancy only in selected patients (11). Moreover most, but not all the times, they might be able to treat the underlying disease leading to portal hypertension (i.e., alcohol abstinence, HBV or HCV treatment) thus contributing to a better chance of survival, despite the "emergent" use of a TIPS procedure. On the other hand patients with an extremely advanced liver dysfunction (Child-Pugh score C or high MELD score) may not be prone to benefit from a TIPS procedure due to the grim prognosis.

(III) *The covered stents might cause less development of hepatic encephalopathy (HE).*

Encephalopathy is the expected physiopathological result of the creation of a portosystemic shunt and its reported frequency remains around 40% also in more recent studies adopting covered stents (6,16). So, even though the current meta-analysis shows a protective effect of covered stent, several aspects must be analyzed before drawing any conclusion: (I) only 3 out of 4 RCTs included in the analysis properly recorded the rate of being free of HE; (II) stents with different diameter and brand have been employed in the RCTs and HE can indeed be influenced by both of these variables; (III) in none of the RCTs a clear distinction between shunt-related HE (treatable with shunt reduction) and HE related to complication (i.e., infections) or decline in liver function was made; (IV) the RCTs didn't systematically report data on the well-known risk factors for HE (age, Child/MELD score, history of encephalopathy, associated renal insufficiency and etiology of liver disease) and of course underestimate the impact of less quantifiable ones such as covert HE, sarcopenia, extensive portosystemic shunts, active prophylactic therapy for HE and etiology of liver cirrhosis as a determinant of brain reserve. Somehow, these factors are clinically more relevant than TIPS-related variables (diameter, drop in portosystemic pressure gradient, brand of the stent) in determining the risk of HE (6,16).

(IV) *The indications for TIPS should be revised in the era of covered stents.*

It is a fact that the introduction of covered stents, thanks to the higher rate of patency, has already allowed the expansion of the indications for TIPS to fields previously forbidden like portal vein thrombosis even in patients awaiting liver transplantation, thrombotic conditions (Budd Chiari syndrome), management of portal hypertension in transplanted patients and extra-hepatic surgery (17-20). However safety and efficacy of TIPS in these delicate clinical conditions should be further evaluated owing to the high rate of failure and complications reported.

In conclusion, we do agree that the availability of covered stents has dramatically improved the management and the outcome of TIPS procedures. However, the available literature on this topic lends itself more to a systematic review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012358/full), which can include less powerful studies, aiming at a better definition of the potentially unidentified drawbacks of the covered stents (21).

On one side we should avoid concluding that more patency rate means ever longer survival without relying on solid evidence especially in the context of cost-efficacy, which still lacks of properly designed studies.

On the other hand we should also avoid the rising of an unnecessary debate such as the one raised upon the fact that we do not have high grade evidence of the need of the use of a parachute when jumping from a plane. As literally stated by Smithras GC and Pell JP (22): "*Only two options exist. The first is that we accept that, under exceptional circumstances, common sense might be applied when considering the potential risks and benefits of interventions. The second is that we continue our quest for the holy grail of exclusively evidence*

based interventions and preclude parachute use outside the context of a properly conducted trial".

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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