

# Covered versus bare stents for transjugular intrahepatic portosystemic shunt: an updated meta-analysis of randomized controlled trials

Xingshun Qi\*, Yulong Tian\*, Wei Zhang\*, Zhiping Yang\* and Xiaozhong Guo

## Abstract

**Background:** Transjugular intrahepatic portosystemic shunt (TIPS) is a standard treatment option for the management of portal hypertension in liver cirrhosis. Since the introduction of covered stents, shunt patency has been greatly improved. However, it remains uncertain about whether covered stents could improve survival. A meta-analysis of randomized controlled trials has been performed to compare the outcomes of covered versus bare stents for TIPS.

**Methods:** PubMed, EMBASE, and Cochrane Library databases were searched to identify the relevant randomized controlled trials. Overall survival, shunt patency, and hepatic encephalopathy were the major endpoints. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Heterogeneity was calculated. Cochrane risk of bias tool was employed.

**Results:** Overall, 119 papers were identified. Among them, four randomized controlled trials were eligible. Viatorr covered stents alone, Fluency covered stents alone, and Viatorr plus Fluency covered stents were employed in one, two, and one randomized controlled trials, respectively. Risk of bias was relatively low. Meta-analyses demonstrated that the covered-stents group had significantly higher probabilities of overall survival (HR=0.67, 95% CI=0.50–0.90,  $p=0.008$ ) and shunt patency (HR=0.42, 95% CI=0.29–0.62,  $p<0.0001$ ) than the bare-stents group. Additionally, the covered-stents group might have a lower risk of hepatic encephalopathy than the bare-stents group (HR=0.70, 95% CI=0.49–1.00,  $p=0.05$ ). The heterogeneity among studies was not statistically significant in the meta-analyses.

**Conclusions:** Compared with bare stents, covered stents for TIPS may improve the overall survival. In the era of covered stents, the indications for TIPS may be further expanded.

**Keywords:** liver cirrhosis, portal hypertension, transjugular intrahepatic portosystemic shunt

## Introduction

Nowadays, transjugular intrahepatic portosystemic shunt (TIPS) is a well established and widely used interventional procedure for the management of portal hypertension [Boyer and Haskal, 2005, 2010; Keller *et al.* 2016; Patidar *et al.* 2014; Rosch, 2015; Rossle, 2013]. The current status of TIPS is irreplaceable in the therapeutic algorithm of portal hypertension. For example, the updated UK guideline on the management of variceal hemorrhage in liver cirrhosis clearly recommended that ‘the units that do not offer a TIPS service should identify a specialist

center which offers a 24-hour emergency TIPS service and have appropriate arrangements for safe transfer of patients in place’ [Tripathi *et al.* 2015]. Also, the updated Baveno consensus clearly recommended that ‘early TIPS must be considered in cirrhotic patients with ‘high-risk’ acute variceal bleeding’ [De Franchis, 2015].

Since its first clinical application, the indications for TIPS have been largely and rapidly expanded [Smith and Durham, 2016]. Undoubtedly, the use of covered stents may be one of the major contributing factors for the

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evolution of the indications for TIPS [Ferral *et al.* 2016; Qi *et al.* 2014a]. This was primarily because covered stents significantly decreased the incidence of shunt dysfunction and recurrence of portal hypertension-related complications [Yang *et al.* 2010]. However, its survival benefit remained unclear [Qi *et al.* 2015a; Yang *et al.* 2010]. Herein, we conducted a meta-analysis of randomized controlled trials (RCTs) to compare the outcomes of covered *versus* bare stents for TIPS.

## Methods

This work was performed according to the PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions [Moher *et al.* 2009].

### Study registration

This meta-analysis was registered on PROSPERO [unique ID: CRD42016037893].

### Search strategy

We searched three major databases, including the PubMed, EMBASE, and Cochrane Library databases on 17 April 2016. The search items were: '(Covered stent) OR (Fluency) OR (Viatorr)' AND '(transjugular intrahepatic portosystemic shunt) OR (TIPS)' AND 'randomized'.

### Eligibility criteria

We identified all RCTs that compared the outcomes of covered *versus* bare stents for TIPS. In details, according to the PICOS rule, the participants should be patients who underwent TIPS, the interventional group should be patients who underwent TIPS with covered stents, the control group should be patients who underwent TIPS with bare stents, the outcomes should be overall survival, shunt patency, with or without hepatic encephalopathy, and the study design should be RCTs. Exclusion criteria were as follows: (1) duplicates; (2) narrative or systematic reviews; (3) protocols; (4) case reports; (5) nonrandomized studies; (6) TIPS with covered stents was not the interventional group; and (7) the type of stent for TIPS was not compared. Additionally, if the data were overlapping among two or more studies, only one study with a longer follow-up duration would be included.

### Data extraction

We extracted the following data: journal, publication year, region, enrollment period, indication for TIPS, number of patients randomized, type of stents, mortality, rate of shunt patency, and rate of being free of hepatic encephalopathy.

### Risk of bias

We employed the revised 'risk of bias' tool described in the Cochrane Handbook version 5.1.0 to evaluate the study quality. It included five major domains (i.e. selection bias, performance bias, detection bias, attrition bias, and reporting bias) using six questions (i.e. random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting). The judgment for every question should be expressed as 'low risk', 'high risk', or 'unclear risk' of bias.

### Data analysis

We performed all meta-analyses by using random-effect models in the Review Manager 5.3. Forest plots were drawn. Because the overall survival, shunt patency, and hepatic encephalopathy produced the time-to-event data, hazard ratios (HRs) with 95% confidence intervals (CIs) and *p* values were calculated as the effect size that was mentioned previously [Qi *et al.* 2014b, 2015b, 2015c]. Specifically, we firstly collected the rates of overall survival, shunt patency, and being free of hepatic encephalopathy at different times. If only the rate of shunt dysfunction was provided, the rate of shunt patency would be estimated as '100% – rate of shunt dysfunction'. Similarly, if only the rate of hepatic encephalopathy was provided, the rate of being free of hepatic encephalopathy would be estimated as '100% – rate of hepatic encephalopathy'. If the relevant data were not available in the text, we extracted the rates of overall survival, shunt patency, and being free of hepatic encephalopathy at three different times from Kaplan–Meier curves by using the Distance Tool in the Measurements menu of Foxit PDF Reader software (Foxit Cooperation, California, USA). Then, the data were entered into the calculation sheets developed by Tierney and colleagues [Tierney *et al.* 2007]. After that, the natural logarithm of the HR with standard error would be automatically calculated. Finally, we selected the Generic Inverse Variance as the data

type to calculate the HRs with 95% CIs in the Review Manager 5.3.  $p < 0.05$  was of statistically significant difference.

Here,  $I^2$  and  $p$  values calculated by Chi-square tests were expressed as the heterogeneity among studies. Specifically,  $I^2 > 50\%$  and  $p < 0.1$  were of statistically significant heterogeneity. Otherwise, the heterogeneity was not statistically significant. Funnel plots were not drawn due to a small number of included studies.

Subgroup analyses were performed according to the brands of covered stents (Viatorr alone, Fluency alone, and mixed) and regions (Western countries and China).  $I^2$  and  $p$  values were also calculated to evaluate the subgroup differences among studies. Of note,  $I^2 > 50\%$  and/or  $p < 0.1$  were of statistically significant subgroup difference. Otherwise, the subgroup difference was not statistically significant.

## Results

### Study selection and characteristics

A total of 111 papers were searched via the three databases, including 29 papers in PubMed database, 30 papers in EMBASE database, and 52 papers in Cochrane Library database. After excluding irrelevant papers, five papers reporting the results of four RCTs were eligible [Bureau *et al.* 2004, 2007; Huang *et al.* 2010; Perarnau *et al.* 2014; Wang *et al.* 2016]. Notably, the short-term and long-term follow-up results of one RCT were published in two papers [Bureau *et al.* 2004, 2007]. Thus, only one of them with long-term follow-up results was finally included in the meta-analysis [Bureau *et al.* 2007; Huang *et al.* 2010; Perarnau *et al.* 2014; Wang *et al.* 2016] (Figure 1).

Study characteristics were briefly summarized in Table 1. According to the enrollment period, all of the four included studies were performed between 2000 and 2010. According to the regions where the studies were conducted, one study was conducted in three countries [Bureau *et al.* 2007], one study in France [Perarnau *et al.* 2014], and two studies in China [Huang *et al.* 2010; Wang *et al.* 2016]. The sample size was 527 in all of the four included studies, ranging from 60 to 258 in each study. The main indications for TIPS were variceal bleeding and ascites or hydrothorax.

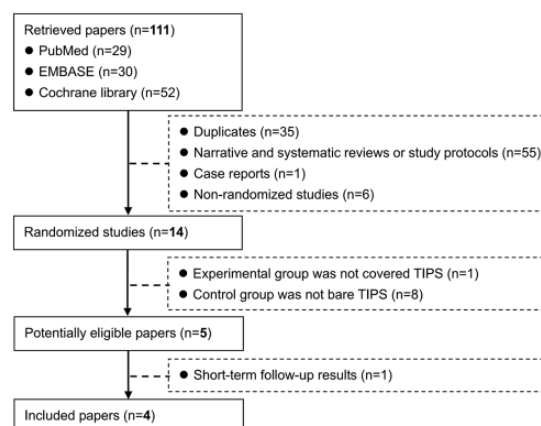


Figure 1. Flowchart of study inclusion.

Characteristics of two different groups are summarized in Table 2. According to the brands of covered stents for TIPS, one study employed only Viatorr stents [Bureau *et al.* 2007], one study employed both Viatorr and Fluency stents [Perarnau *et al.* 2014], and two studies employed only Fluency stents [Huang *et al.* 2010; Wang *et al.* 2016]. The brands of bare stents were largely heterogeneous. Severity of liver dysfunction, etiology of liver cirrhosis, and indications for TIPS were similar between the two groups.

### Risk of bias

Risk of bias for each study is summarized in Supplementary Tables S1–S4. Notably, an unclear risk of bias in the question ‘random sequence generation’ was observed in two studies [Bureau *et al.* 2007; Huang *et al.* 2010]; a high risk of bias in the question ‘blinding of participants and personnel’ was observed in three studies [Bureau *et al.* 2007; Huang *et al.* 2010; Perarnau *et al.* 2014]; and an unclear risk of bias in the question ‘blinding of outcome assessment’ was observed in two studies [Bureau *et al.* 2007; Huang *et al.* 2010].

### Overall survival

All of the four included studies provided the cumulative data regarding overall survival [Bureau *et al.* 2007; Huang *et al.* 2010; Perarnau *et al.* 2014; Wang *et al.* 2016]. The meta-analysis demonstrated that the covered-stents group had a significantly better overall survival than the bare-stents group (HR = 0.67, 95% CI = 0.50–0.90,  $p = 0.008$ ) (Figure 2). The heterogeneity

**Table 1.** Characteristics of RCTs.

Study	Center (regions)	Enrollment period	Patients analyzed ( <i>n</i> )	Indication for TIPS
Bureau <i>et al.</i> [2004, 2007]	Multicenter (i.e. 39 in Toulouse, France; 20 in Barcelona, Spain; 15 in Montreal, Canada; and 6 in Pamplona, Spain)	Feb 2000–Apr 2002	80	Uncontrolled variceal bleeding ( <i>n</i> =23), recurrent variceal bleeding after failure of the usual pharmacological and endoscopic methods ( <i>n</i> =25), refractory ascites ( <i>n</i> =32)
Huang <i>et al.</i> [2010]	Single-center (Nanjing, China)	Apr 2007–Apr 2009	60	Gastrointestinal bleeding ( <i>n</i> =51), ascites or hydrothorax ( <i>n</i> =9)
Perarnau <i>et al.</i> [2014]	Multicenter (i.e. 10 French TIPS centers)	Mar 2008–Jul 2009	129	Prevention of rebleeding ( <i>n</i> =42), refractory ascites ( <i>n</i> =100), hydrothorax ( <i>n</i> =9)
Wang <i>et al.</i> [2016]	Single-center (Beijing, China)	Jan 2006–Dec 2010	258	Gastrointestinal bleeding ( <i>n</i> =245), refractory hydrothorax and ascites ( <i>n</i> =42)

among studies was not statistically significant ( $I^2=0\%$ ,  $p=0.78$ ).

In the subgroup analyses according to the brands of covered stents, the benefit in the improvement of overall survival remained statistically significant in studies with Fluency alone covered stents, rather than those with Viatorr alone or mixed covered stents. Subgroup difference was not statistically significant ( $I^2=0\%$ ,  $p=0.58$ ). In the subgroup analyses according to the regions, the benefit in the improvement of overall survival remained statistically significant in Chinese studies, rather than Western studies. Subgroup difference was not statistically significant ( $I^2=0\%$ ,  $p=0.38$ ).

#### Shunt patency

All of the four included studies provided the cumulative data regarding the rate of shunt patency or dysfunction [Bureau *et al.* 2007; Huang *et al.* 2010; Perarnau *et al.* 2014; Wang *et al.* 2016]. The meta-analysis demonstrated that the covered-stents group had a significantly higher probability of shunt patency than the bare-stents group (HR=0.42, 95% CI=0.29–0.62,  $p<0.0001$ ) (Figure 3). The heterogeneity among studies was not statistically significant ( $I^2=50\%$ ,  $p=0.11$ ).

Regardless of the brands of covered stents, the benefit in the improvement of shunt patency remained statistically significant. Subgroup

difference was statistically significant ( $I^2=65.5\%$ ,  $p=0.06$ ). Regardless of the regions, the benefit in the improvement of shunt patency remained statistically significant. Subgroup difference was not statistically significant ( $I^2=0\%$ ,  $p=0.60$ ).

#### Free of hepatic encephalopathy

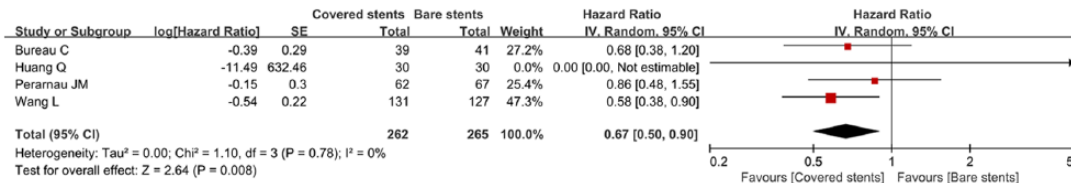
Three of the four included studies provided the cumulative data regarding the rate of being free of hepatic encephalopathy [Bureau *et al.* 2007; Huang *et al.* 2010; Perarnau *et al.* 2014]. The remaining study provided only the data regarding the overall incidence of hepatic encephalopathy [Wang *et al.* 2016]. The meta-analysis of three studies demonstrated that the covered-stents group might have a higher probability of free-of-hepatic encephalopathy than the bare-stents group (HR=0.70, 95% CI=0.49–1.00,  $p=0.05$ ) (Figure 4). The heterogeneity among studies was not statistically significant ( $I^2=0\%$ ,  $p=0.45$ ).

In the subgroup analyses according to the brands of covered stents, the benefit in the improvement of hepatic encephalopathy was statistically significant in studies with Viatorr alone covered stents, rather than those with Fluency alone or mixed covered stents. Subgroup difference was not statistically significant ( $I^2=0\%$ ,  $p=0.45$ ). Regardless of the regions, the benefit in the improvement of hepatic encephalopathy was not statistically significant. Subgroup difference was not statistically significant ( $I^2=0\%$ ,  $p=0.71$ ).

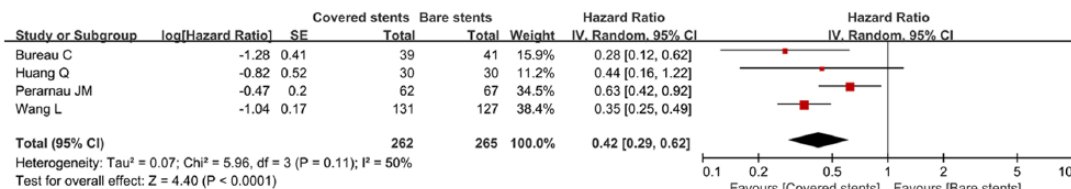
**Table 2.** Characteristics of the two different stent groups.

Study	Groups	Stents	Pts (n)	Severity of liver function	MELD score	Etiology of liver cirrhosis	Indications for TIPS	Follow-up duration
Bureau <i>et al.</i> [2004, 2007]	Covered stents	Covered (GORE®, Viatorr®, Flagstaff, AZ, USA)	39	Child-Pugh score: 9 ± 2	MELD score: NA	Alcoholic cirrhosis: 22	Ascites: 20 Active digestive bleeding: 9 Prevention of rebleeding: 10	585 ± 438 days; median 678 days
	Bare stents	Memotherm® Flexx (BARD, Voisins le Bretonneux, France) in 22 patients, Wallstent® (Boston Scientific, Barcelona, Spain) in 15 patients, Luminexx® (BARD, Ontario, Canada) in 2 patients, and Sinus Stent (MEDCARE, Franconville, France) in 2 patients	41	Child-Pugh score: 9 ± 2	MELD score: NA	Alcoholic cirrhosis: 22	Ascites: 12 Active digestive bleeding: 14 Prevention of rebleeding: 15	430 ± 368 days; median 322 days
Huang <i>et al.</i> [2010]	Covered stents	ePTFE-coated stent-grafts (Fluency®, Angiomed GmbH Co., subsidiary of C.R. Bard, Inc) 6 cm long and 8 mm in diameter	30	Child-Pugh score: 8.6 ± 2.1	MELD score: NA	Alcoholic: 2 Viral: 28	Gastrointestinal bleeding: 25 Ascites or hydrothorax: 5	6.2 ± 3.9 months
	Bare stents	Bare stents (Wallstent®, Angiomed GmbH Co., subsidiary of C.R. Bard, Inc, New York, America) of 10 mm diameter and variable length	30	Child-Pugh score: 8.4 ± 2.0	MELD score: NA	Alcoholic: 1 Viral: 29	Gastrointestinal bleeding: 26 Ascites or hydrothorax: 4	8.3 ± 4.4 months
Perarnau <i>et al.</i> [2014]	Covered stents	Fluency® alone (Bard, Tempe, AZ, USA) Fluency® + Bare Stent Viatorr® (Gore, Flagstaff, AZ, USA)	66	Child-Pugh score: Median (IQR): 8 (7–9)	MELD score: Median (IQR): 11.2 (9.0–13.4)	Alcoholic: 52 Viral: 10 NASH: 6 Others: 1	Prevention of rebleeding: 22 Refractory ascites: 46 Hydrothorax: 6	Median (IQR): 23.6 months (14.0–24.1)
	Bare stents	Luminexx® (Bard, Tempe, AZ, USA) Palimaz Genesis® (Cordis Bridgewater, NJ, USA) Smart® (Cordis Bridgewater, NJ, USA) Wallstent® (Boston Scientific, Natick, MA, USA) Zilver® (Cook Bloomington, IN, USA)	71	Child-Pugh score: Median (IQR): 8 (7–9)	MELD score: Median (IQR): 11.6 (9.6–14.7)	Alcoholic: 61 Viral: 8 NASH: 1 Others: 2	Prevention of rebleeding: 20 Refractory ascites: 54 Hydrothorax: 3	Median (IQR): 21.8 months (5.7–24.1)
Wang <i>et al.</i> [2016]	Covered stents	Covered stents (Bard, Fluency®)	131	Child-Pugh score: 6.98 ± 1.4	MELD score: NA	Hepatitis: 104 Others: 27	Gastrointestinal bleeding: 123 Refractory ascites: 20	NA
	Bare stents	Bare stents (EV3, protégé; Cordis, Smart®)	127	Child-Pugh score: 7.10 ± 1.8	MELD score: NA	Hepatitis: 102 Others: 25	Gastrointestinal bleeding: 122 Refractory ascites: 22	NA

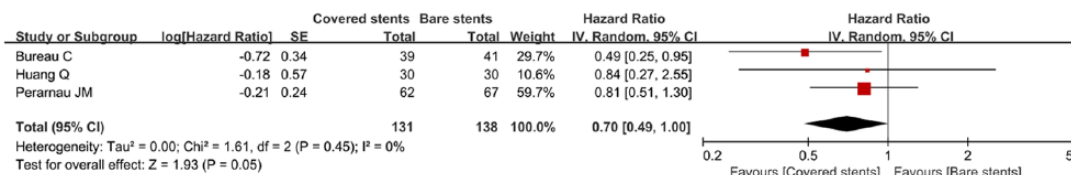
MELD, model for end-stage liver disease score; ePTFE, a specific type of polytetrafluoroethylene; IQR, interquartile range; NA, not applicable.



**Figure 2.** Forest plot comparing overall survival between covered and bare-stent groups. SE, standard error; CI, confidence interval; DF, degrees of freedom; IV, inverse variation.



**Figure 3.** Forest plot comparing shunt patency between covered- and bare-stent groups. SE, standard error; CI, confidence interval; DF, degrees of freedom; IV, inverse variation.



**Figure 4.** Forest plot comparing the rate of being free of hepatic encephalopathy between covered and bare-stent groups. SE, standard error; CI, confidence interval; DF, degrees of freedom; IV, inverse variation.

## Discussion

In 2010, we published for the first time a meta-analysis of one RCT and five observational studies to compare the patency and clinical outcomes of TIPS with covered *versus* bare stents [Yang *et al.* 2010]. The statistical analyses demonstrated that shunt patency, hepatic encephalopathy, and survival were significantly improved by the use of covered stents. However, given the quality of included studies, the conclusions might be unreliable. Therefore, the conclusions were that covered stents improved shunt patency without any increased risk of hepatic encephalopathy and with a trend towards better survival.

In 2015, we published another meta-analysis of two RCTs from Western countries to further explore the survival benefit of covered stents for TIPS [Qi *et al.* 2015a]. The statistical analysis showed only a borderline survival benefit.

The present meta-analysis had three major strengths. First, four RCTs were included. No

observational studies were considered. Second, the relevant studies were systematically searched. Third, only a random-effect model was employed. The statistical results were more conservative. By comparison, our previous meta-analysis employed a fixed-effect model, in which the results were more aggressive [Qi *et al.* 2015a]. Fourth, the risk of bias was relatively low. According to the common practice for Cochrane reviews of endoscopic or surgical RCTs while physicians could not be blinded, the question ‘blinding of participants and personnel’ was judged as ‘high risk of bias’ in three studies. However, considering that the outcomes (i.e. overall survival, shunt patency, and hepatic encephalopathy) are objective, we believed that the outcome measurement might not be largely influenced by the absence of blinding of types of stents.

In the present meta-analysis, we found that covered stents not only significantly improved the shunt patency, but also significantly decreased the risk of death. Additionally, the risk of hepatic

encephalopathy was not increased by the use of covered stents. Notably, the heterogeneity among studies was not statistically significant, suggesting that the statistical results should be stable. Although the findings were heterogeneous in some subgroup analyses, we should fully acknowledge that the results of subgroup meta-analyses were unpowered due to a small number of relevant studies.

Our findings were of importance in clinical practice and future trial design, because most indications for TIPS were established in the era of bare stents. For example, early evidence suggested that TIPS with bare stents should be superior to endoscopic and pharmacological treatment for decreasing the risk of variceal rebleeding, but inferior in relation to hepatic encephalopathy and not advantageous in terms of overall survival [Zheng *et al.* 2008]. Considering the benefits of covered stents, we had some confidence about the theoretical possibility that TIPS with covered stents would result in better survival. However, the evidence from at least three recent clinical trials with covered stents did not remarkably upgrade the role of TIPS for the prevention of variceal rebleeding. Sauerbruch and colleagues reported the results of a German multicenter prospective randomized trial regarding the prevention of variceal rebleeding in liver cirrhosis [Sauerbruch *et al.* 2015]. The experimental group was TIPS with covered stents. The control group was hepatic-venous-pressure-gradient-guided medical-therapy prophylaxis (propranolol and isosorbide-5-mononitrate followed by variceal-band ligation and TIPS). They suggested that TIPS was more straightforward and prevented variceal rebleeding more effectively, but did not improve the survival. Luo and colleagues reported the results of a Chinese single-center randomized trial regarding the prevention of recurrent variceal bleeding in liver cirrhosis with portal vein thrombosis [Luo *et al.* 2015]. The experimental group was TIPS with covered stents. The control group was endoscopic-band ligation plus propranolol. They suggested that TIPS had a significantly lower risk of variceal bleeding, but a similar risk of hepatic encephalopathy and death. Holster and colleagues also reported the results of a Dutch multicenter prospective randomized trial regarding the prevention of variceal rebleeding in liver cirrhosis [Holster *et al.* 2016]. The experimental group was TIPS with covered stents. The control group was endoscopic variceal ligation, or glue injection plus beta-blocker treatment. Similarly,

they also suggested that TIPS had a significantly lower risk of variceal bleeding, but the risk of hepatic encephalopathy and death was not significantly different. Taken together, the results of each clinical trial did not favor the covered TIPS over the traditional first-line treatment option. Certainly, more accumulative data and subsequent meta-analyses should reiterate this.

On the other hand, the practice guideline suggested that TIPS with bare stents should be superior to large-volume paracentesis for controlling ascites, but inferior in treatment of hepatic encephalopathy and not advantageous in terms of overall survival [Albillos *et al.* 2005; Deltenre *et al.* 2005; Saab *et al.* 2006]. More recently, Bureau and colleagues have shown the preliminary results of an RCT examining TIPS with covered stents *versus* large-volume paracentesis plus albumin infusion in cirrhotic patients with recurrent ascites [Bureau *et al.* 2015]. They found a statistically significant difference in the transplant-free survival and a similar rate of hepatic encephalopathy between them. Specifically, TIPS with covered stents had a nearly twofold survival rate compared with large-volume paracentesis plus albumin infusion (93% *versus* 52%). Collectively, the use of covered stents might upgrade the role of TIPS in patients with refractory ascites.

Our meta-analysis suggested that the covered-stents group might have a lower risk of hepatic encephalopathy than the bare-stents group. This phenomenon might be explained by the consideration that the covered-stents group had a significantly lower risk of shunt dysfunction and recurrence of portal hypertension-related complications that were often the main precipitating factors for hepatic encephalopathy. However, we should be very cautious about whether the diameters of stents were comparable between the two groups. First, as thoroughly analyzed by Rossle and Mullen [Rossle and Mullen 2004], a significant difference in the diameters of shunt observed in the RCT by Bureau and colleagues ( $10.5 \pm 0.9$  in the covered-stents group *versus*  $11.7 \pm 0.8$  mm in the bare-stents group) [Bureau *et al.* 2004] might result in the difference in the incidence of hepatic encephalopathy. Second, in the RCT by Huang and colleagues, the diameter of stents was heterogeneous (10 mm in the bare-stents group and 8 mm in the covered-stents group) [Huang *et al.* 2010]. Third, in the RCTs by Perarnau and colleagues and Wang and colleagues, the

information regarding the diameter of stents was not available [Perarnau *et al.* 2014; Wang *et al.* 2016]. Collectively, if the diameters of stents were similar between the two groups, we would be still unsure about the benefits of covered stents in the development of hepatic encephalopathy.

In addition, our previous systematic review showed that age, a previous history of hepatic encephalopathy prior to TIPS insertion, and severity of liver dysfunction might influence the development of hepatic encephalopathy after TIPS [Bai *et al.* 2011]. Therefore, we should also pay attention to the comparability of the three major predictors between the two groups. First, all included studies demonstrated a statistically similar age between the two groups. However, three of them demonstrated that the covered-stents group had an older age than the bare-stents group (Huang's study:  $47 \pm 11$  in the covered-stents group *versus*  $50 \pm 10$  in the bare-stents group; Perarnau's study: 57 (53-64) in the covered-stents group *versus* 59 (52-65) in the bare-stents group; Wang's study:  $45.4 \pm 7.0$  in the covered-stents group *versus*  $46.7 \pm 5.0$  in the bare-stents group,  $p=0.088$ ). Second, all included studies demonstrated a similar Child-Pugh score or class between the two groups. Third, all included studies did not report any information regarding prior hepatic encephalopathy.

Our study had several limitations. First, the number of relevant RCTs was small. Second, no direct comparison between Fluency *versus* Viatorr covered stents was available. Thus, it remained unclear about which one covered stent was more beneficial. Third, the brands and types of bare stents in the control group were heterogeneous among studies. Fourth, the indications for TIPS were heterogeneous among these included studies. Additionally, no individual data regarding survival, patency, and hepatic encephalopathy were available according to the different indications for TIPS. Thus, we could not conclude the superiority of covered over bare stents in some specific target populations (i.e. acute variceal bleeding, variceal rebleeding or refractory ascites). Fifth, in the included study by Wang and colleagues, the legend of Figure 1 was 'Inclusion and exclusion criteria for patient recruitment in this retrospective study' [Wang *et al.* 2016], so the nature of this study should be suspected. Sixth, the included study by Wang and colleagues started patient enrollment in 2006, but was

registered in 2015 [Wang *et al.* 2016]. Seventh, no trial registration information was provided in the included studies by Bureau and colleagues and Huang and colleagues [Bureau *et al.* 2007; Huang *et al.* 2010].

In conclusion, the updated meta-analysis of RCTs suggested the survival benefit of covered stents for TIPS. It is very likely that the indications for TIPS are revised in future.

### Key points

1. The patients having covered stents for TIPS had significantly better overall survival than those with bare stents.
2. The patients having covered stents for TIPS had significantly better shunt patency than those with bare stents.
3. The covered stents for TIPS might cause less development of hepatic encephalopathy than the bare stents.
4. The indications for TIPS should be revised in the era of covered stents.

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### References


- Albillos, A., Banares, R., Gonzalez, M., Catalina, M. and Molinero, L. (2005) A meta-analysis of transjugular intrahepatic portosystemic shunt versus paracentesis for refractory ascites. *J Hepatol* 43: 990–996.
- Bai, M., Qi, X., Yang, Z., Yin, Z., Nie, Y., Yuan, S. *et al.* (2011) Predictors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in cirrhotic patients: a systematic review. *J Gastroenterol Hepatol* 26: 943–951.
- Boyer, T. and Haskal, Z. (2005) The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. *Hepatology* 41: 386–400.
- Boyer, T. and Haskal, Z. (2010) The role of transjugular intrahepatic portosystemic shunt (TIPS)



- in the management of portal hypertension: update 2009. *Hepatology* 51: 306.
- Bureau, C., Garcia-Pagan, J., Otal, P., Pomier-Layrargues, G., Chabbert, V., Cortez, C. *et al.* (2004) Improved clinical outcome using polytetrafluoroethylene-coated stents for TIPS: results of a randomized study. *Gastroenterology* 126: 469–475.
- Bureau, C., Pagan, J., Layrargues, G., Metivier, S., Bellot, P., Perreault, P. *et al.* (2007) Patency of stents covered with polytetrafluoroethylene in patients treated by transjugular intrahepatic portosystemic shunts: long-term results of a randomized multicentre study. *Liver Int* 27: 742–747.
- Bureau, C., Thabut, D., Oberti, F., Dharancy, S., Cabarron, P., Carbonell, N. *et al.* (2015) TIPS with PTFE-covered stent improves liver transplant free survival in patients with cirrhosis and recurrent ascites: results of a multicentre randomized trial. *Hepatology* 62: 347A.
- De Franchis, R. (2015) Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol* 63: 743–752.
- Deltenre, P., Mathurin, P., Dharancy, S., Moreau, R., Bulois, P., Henrion, J. *et al.* (2005) Transjugular intrahepatic portosystemic shunt in refractory ascites: a meta-analysis. *Liver Int* 25: 349–356.
- Ferral, H., Gomez-Reyes, E. and Fimmel, C. (2016) Post-transjugular intrahepatic portosystemic shunt follow-up and management in the VIATORR era. *Tech Vasc Interv Radiol* 19: 82–88.
- Holster, I., Tjwa, E., Moelker, A., Wils, A., Hansen, B., Vermeijden, J. *et al.* (2016) Covered transjugular intrahepatic portosystemic shunt versus endoscopic therapy +  $\beta$ -blocker for prevention of variceal rebleeding. *Hepatology* 63: 581–589.
- Huang, Q., Wu, X., Fan, X., Cao, J., Han, J., Xu, L. *et al.* (2010) Comparison study of Doppler ultrasound surveillance of expanded polytetrafluoroethylene-covered stent versus bare stent in transjugular intrahepatic portosystemic shunt. *J Clin Ultrasound* 38: 353–360.
- Keller, F., Farsad, K. and Rosch, J. (2016) The transjugular intrahepatic portosystemic shunt: technique and instruments. *Tech Vasc Interv Radiol* 19: 2–9.
- Luo, X., Wang, Z., Tsao, J., Zhou, B., Zhang, H. and Li, X. (2015) Advanced cirrhosis combined with portal vein thrombosis: a randomized trial of tips versus endoscopic band ligation plus propranolol for the prevention of recurrent esophageal variceal bleeding. *Radiology* 276: 286–293.
- Moher, D., Liberati, A., Tetzlaff, J. and Altman, D. (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 151: 264–269, W64.
- Patidar, K., Sydnor, M. and Sanyal, A. (2014) Transjugular intrahepatic portosystemic shunt. *Clin Liver Dis* 18: 853–876.
- Perarnau, J., Le Gouge, A., Nicolas, C., D’Alteroche, L., Borentain, P., Saliba, F. *et al.* (2014) Covered vs. uncovered stents for transjugular intrahepatic portosystemic shunt: a randomized controlled trial. *J Hepatol* 60: 962–968.
- Qi, X., Bai, M., Yang, Z. and Fan, D. (2014a) Selection of a TIPS stent for management of portal hypertension in liver cirrhosis: an evidence-based review. *World J Gastroenterol* 20: 6470–6480.
- Qi, X., Guo, X. and Fan, D. (2015a) A trend toward the improvement of survival after TIPS by the use of covered stents: a meta-analysis of two randomized controlled trials. *Cardiovasc Intervent Radiol* 38: 1363–1364.
- Qi, X., Liu, L., Wang, D., Li, H., Su, C. and Guo, X. (2015b) Hepatic resection alone versus in combination with pre- and post-operative transarterial chemoembolization for the treatment of hepatocellular carcinoma: a systematic review and meta-analysis. *Oncotarget* 6: 36838–36859.
- Qi, X., Tang, Y., An, D., Bai, M., Shi, X., Wang, J. *et al.* (2014) Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: a meta-analysis of randomized controlled trials. *J Clin Gastroenterol* 48: 450–457.
- Qi, X., Wang, D., Su, C., Li, H. and Guo, X. (2015c) Hepatic resection versus transarterial chemoembolization for the initial treatment of hepatocellular carcinoma: a systematic review and meta-analysis. *Oncotarget* 6: 18715–18733.
- Rosch, J. (2015) Development of transjugular intrahepatic portosystemic shunt. *J Vasc Interv Radiol* 26: 220–222.
- Rossle, M. (2013) TIPS: 25 years later. *J Hepatol* 59: 1081–1093.
- Rossle, M. and Mullen, K. (2004) Long-term patency is expected with covered TIPS stents: this effect may not always be desirable! *Hepatology* 40: 495–497.
- Saab, S., Nieto, J., Lewis, S. and Runyon, B. (2006) TIPS versus paracentesis for cirrhotic patients with refractory ascites. *Cochrane Database Syst Rev* 4: CD004889.
- Sauerbruch, T., Mengel, M., Dollinger, M., Zipprich, A., Rossle, M., Panther, E. *et al.* (2015) Prevention

- of rebleeding from esophageal varices in patients with cirrhosis receiving small-diameter stents versus hemodynamically controlled medical therapy. *Gastroenterology* 149: 660.e1–668.e1.
- Smith, M. and Durham, J. (2016) Evolving indications for TIPS. *Tech Vasc Interv Radiol* 19: 36–41.
- Tierney, J., Stewart, L., Ghersi, D., Burdett, S. and Sydes, M. (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 8: 16.
- Tripathi, D., Stanley, A., Hayes, P., Patch, D., Millson, C., Mehrzad, H. *et al.* (2015) UK guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut* 64: 1680–1704.
- Wang, L., Xiao, Z., Yue, Z., Zhao, H., Fan, Z., Zhao, M. *et al.* (2016) Efficacy of covered and bare stent in TIPS for cirrhotic portal hypertension: a single-center randomized trial. *Sci Rep* 6: 21011.
- Yang, Z., Han, G., Wu, Q., Ye, X., Jin, Z., Yin, Z. *et al.* (2010) Patency and clinical outcomes of transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene-covered stents versus bare stents: a meta-analysis. *J Gastroenterol Hepatol* 25: 1718–1725.
- Zheng, M., Chen, Y., Bai, J., Zeng, Q., You, J., Jin, R. *et al.* (2008) Transjugular intrahepatic portosystemic shunt versus endoscopic therapy in the secondary prophylaxis of variceal rebleeding in cirrhotic patients: meta-analysis update. *J Clin Gastroenterol* 42: 507–516.

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