Should Stent-Grafts Replace Bare Stents for Primary Transjugular Intrahepatic Portosystemic Shunts?

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ABSTRACT

Transjugular intrahepatic portosystemic shunt (TIPS) creation using bare stents is a second-line treatment for complications of portal hypertension due in part to the relatively high number of reinterventions and the occurrence of new or worsened encephalopathy. Initially, custom-made stent-grafts were used for TIPS revision in cases of biliary fistulae. Subsequently, custom stent-grafts were used for de novo TIPS creation. With the introduction of the VIATORR[®] TIPS endoprosthesis a dedicated stent-graft became available for TIPS creation and revision. The VIATORR[®] demonstrated its efficacy and superiority to uncovered stents in retrospective analyses, case-matched analyses, and randomized studies. The improved patency of stent-grafts has led many to question the role of TIPS as a second-line therapy. Currently, randomized trials are warranted to redefine the role of TIPS in the treatment of complications of portal hypertension.

KEYWORDS: Transjugular portosystemic shunt, stents, stent-grafts, complication, prognosis

Objectives: Upon completion of this article, the reader should understand the indications and expected results for placing stent-grafts for the de novo creation and revision of TIPS.

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The creation of a portosystemic shunt is an effective treatment for complications of portal hypertension such as prevention of variceal bleeding or refractory ascites. The major problem with transjugular intrahepatic portosystemic shunts (TIPS) is their limited and unpredictable patency. In a small proportion of patients, the tract remains stenosis free, but the majority of TIPS develop sporadic or frequent shunt tract stenoses, thromboses, and/or outflow hepatic venous stenoses, causing clinical dysfunction with

recurrence of portal hypertension. Depending on the definition of shunt patency used and the methods of follow-up and timing of surveillance, stenosis greater than 50% and recurrent portal hypertension develop in 25 to 50% of cases within 6 to 12 months after shunt creation.¹⁻⁵

TIPS hepatic tract stenoses or occlusions are caused by thrombus formation with or without bile leaks^{2,6-8} and fibrotic or inflammatory healing response to the stent. Although bile itself has no direct

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stimulatory effect on smooth muscle cell proliferation^{7,8} and hence neointima, it delays healing of the tract.⁶ Early shunt thrombosis may be related to biliary fistulas. If biliary fistulas are detected, they are associated with tract abnormalities in almost all cases.^{2,9-11} Detectable biliary fistulas occur in up to 12% of shunt dysfunctions, but the estimated number of unknown cases may be much higher. Jalan et al⁶ performed biopsy in stenotic TIPS and found bile incorporated within the thrombus in several cases, with major bile duct transection always closely related to shunt stenosis. An intriguing idea was to use stent-grafts for treatment or prevention of these problems—the exclusion of potential biliary fistulae. The expanded polytetrafluoroethylene (ePTFE)-covered stent-graft minimizes transmural permeation of bile and mucin (which are common causes of patency loss) and reduces tissue ingrowth into the graft, resulting in a much improved patency rate. Additionally an effective TIPS graft would address the three modes of shunt stenosis: bile-related and bile-unrelated hepatic tract stenoses and hepatic venous stenosis. TIPS creation with stent-grafts were reported in animal experiments; the first clinical reports were using the then available dacron-covered stent-grafts with equivocal results. The “modern era” of stent-graft for TIPS started with the development of the first dedicated TIPS stent-graft—the ePTFE-covered VIATORR[®] endoprosthesis. In the pig model experimental results (not published) had indicated a significantly higher patency rate than those obtained with a standard bare stent (the Wallstent, Boston Scientific, Natick, MA). The first clinical trial, the European Multicenter Feasibility trial, started in late 1999, also demonstrated improved shunt patency with the VIATORR[®] (W.L. Gore, Flagstaff, AZ) endoprosthesis compared with the bare stents.^{12,13,22}

“NON”-PTFE STENT-GRAFTS

After the introduction of stent-grafts for treatment of peripheral arterial stenosis and obstructions, these stent-grafts (mostly dacron covered) were used in experimental and animal studies.¹⁴⁻²¹ Silicone-covered Wallstents²¹ failed to demonstrate effectiveness in an experimental study in the pig, where 12 of 14 shunts were occluded after 3 weeks and all shunts were occluded after 6 weeks. This observation was attributed was increased thrombogenicity and relevant foreign body reaction. Polyurethane (corethane)-covered Wallstents¹⁹ with different porosities had better results—lower stenosis rates (26% for nonporous grafts, 46% with grafts with higher porosity) compared with 75% for control Wallstents after 8 weeks.

Polyurethane-coated polyethylene terephthalate (dacron)-covered stents performed far worse: five of six stents were occluded after 3 weeks and all were occluded after 6 weeks.²⁰

More experimental and clinical studies are available for standard polyethylene terephthalate (dacron)-covered stents, but all failed to demonstrate superior results compared with bare stents.

In an experimental study¹⁶ TIPS procedure was performed in nine pigs by using a dacron-covered nitinol stent. Shunt creation was possible in all pigs; two died of complications of the procedure. After 3 weeks only two shunts were patent; the remaining shunts were occluded. Histological examination showed pseudointimal hyperplasia associated, in the cases of occlusion, with a luminal thrombosis. This dacron-covered stent did not prevent pseudointima formation over the stent and resulted in a high early occlusion rate, probably related to a pronounced tissue fibrotic response likely due to dacron-induced inflammation. The explanation for their high reobstruction rate could be the high porosity of polyester-covered stent-grafts. This porosity allows transgraft tissue growth, a phenomenon that may limit the success of such covered stent-grafts in humans.

In two clinical studies^{14,15} the results obtained are difficult to evaluate. The patient number was relatively small: 8 and 13 patients, respectively. In the larger trial—that had used Cragg-EndoPro I (Min-Tec, Grand Bahamas) stent-grafts¹⁴—mortality rate was 23% and the 6-month primary patency rate was 76.9%. Cejna et al¹⁵ had used Cragg-EndoPro I and Passager (Boston Scientific, Natick, MA) stent-grafts; the 12-month patency rate was 50% and survival was 87.5%. The dacron cover is not impermeable to bile; evidence of the obvious bile permeability of polyester is the fact that bile has been detected in human tissue samples from TIPS neointima in these polyester stent-grafts.¹⁵ Haskal et al¹⁸ described three patients who underwent de novo creation of TIPS with PET-covered stent-grafts, which resulted in immediate and recurring TIPS thromboses despite repeated thrombectomies. After the failed TIPS were revised with PTFE stent-grafts, the presenting symptoms resolved and uninterrupted patency was achieved. Based on these three clinical reports one might suggest that dacron-covered stentgrafts would be comparable to bare stents in those patients who are not really at the risk of TIPS dysfunction because of biliary fistulae; but in those patients where biliary fistulae are detected, the porous dacron does not protect against thromboses. The primary use of polyester-covered stent-grafts for TIPS did not significantly increase primary patency rates in these series (when compared with historic controls).

CUSTOM-MADE AND COMMERCIALY AVAILABLE NONDEDICATED PTFE STENT-GRAFTS

Unlike non-PTFE grafts the use of custom-made or commercially available PTFE stent-grafts were

encouraging in experimental studies and were especially effective in the revision of stenosed TIPS.^{11,22-24} Nishimine et al²⁵ and Haskal et al¹⁰ reported the benefits of lining porcine TIPS with ePTFE graft material. Shunts created in pigs typically become highly stenotic or occluded within 2 to 4 weeks after TIPS creation. The 1-month patency rate was increased from 8 to 50% using ePTFE covering, but the devices used in these studies were custom-made, therefore preventing widespread routine use. Haskal and colleagues did not detect bile staining in 50 subsequent porcine ePTFE TIPS stent-grafts. In the Haskal et al study, the luminal surfaces of the porcine grafts were encompassed by a thick layer of myofibroblasts and extracellular collagen matrix identical to that seen narrowing the lumina of TIPS structures in humans.

Small clinical trials with custom-made ePTFE stent-grafts^{9-11,26} reported series of patients in whom a marked improvement in patency and clinical outcome was demonstrated. These studies led the way to the introduction of a dedicated TIPS stent-graft: the VIATORR[®] endoprosthesis.

DEDICATED ePTFE STENT-GRAFT: VIATORR[®] TIPS ENDOPROSTHESIS

The VIATORR[®] endoprosthesis (Fig. 1) was introduced in 1999. The European multicenter feasibility Trial was started in 1999, and the first results were available in 2001,^{12,13,27} which demonstrated the potential for high primary patency rates (Fig. 2). The VIATORR[®] endoprosthesis received Food and Drug Administration (FDA) approval for TIPS in December 2004.

Unlike with endografts for aneurysms and stents of all types for other applications, it has taken a long time

for a commercial stent-graft to be developed and tested for the TIPS application. An effective TIPS graft, or other shunt-directed therapy, ideally would address all three modes of shunt stenosis: bile-related and bile-unrelated tract stenoses and hepatic venous stenosis. With the advent of the VIATORR[®] device, that problem may now be addressed. The device has greater hoop strength than most self-expanding commercial bare stents, and consequently there is little recoil after placement. The evaluated endovascular TIPS prosthesis (Fig. 1) consists of an ultrathin inner ePTFE tube, externally radially reinforced by a wrapping of ePTFE film that is resistant to bile permeation. The latter argument is questioned by a recent publication by Wittkugel et al,²⁸ where the VIATORR[®] stent-graft, the Wallgraft (Boston Scientific, Natick, MA), and the JoStent stent-graft (Abbott Laboratories, Abbott Park, IL) were compared in regards to bile resistance; the Wallgraft was bile-resistant, but the VIATORR[®] was not.

The blood-contacting inner layer is made of ePTFE and has a microstructure and mechanical properties that are similar to those of the conventional vascular graft from the same manufacturer (GORE-TEX Vascular Graft; W.L. Gore, Flagstaff, AZ). Structural support is provided by an external self-expanding nitinol stent with high radial strength. The TIPS endoprosthesis has a bare nitinol stent portal region for preservation of the nutrient portal perfusion and the ePTFE-lined intrahepatic region. The interface between the lined and bare regions is demarcated by a radiopaque gold marker band. In addition, a radiopaque gold marker is incorporated into the proximal end of the endoprosthesis to facilitate fluoroscopic imaging during deployment. The ePTFE-lined portion of the device is secured on the delivery catheter with a

Figure 1 The VIATORR[®] endoprosthesis. The VIATORR[®] consists of an uncovered 2-cm-long self-expanding chain-linked portion and the ePTFE-covered nitinol portion, constrained by a suture.

Figure 2 Uninterrupted patency 5 years after de novo TIPS creation in a 52-year-old patient treated with two 12-mm VIATORR[®] endoprotheses. The PSG was initially 12 mm Hg and was 12 mm Hg at each follow-up. There was no episode of rebleeding during follow-up.

constraining sleeve made of ePTFE, and the entire endoprosthesis is secured beneath an introducer sleeve. The introducer sleeve is used to insert the endoprosthesis into the hemostatic valve. A radiopaque gold marker is located beneath the leading tip of the delivery catheter. The TIPS endoprosthesis is available in a range of sizes, with diameters of 8, 10, and 12 mm and lengths ranging from 4 to 8 cm. All sizes can be inserted through a 10-F sheath. The stent-graft delivery system accepts a 0.035-inch guide wire.

The technique required to create a TIPS with a VIATORR[®] stent-graft is more demanding than with an uncovered stent. Several publications have emphasized that great care is required to measure the distance from the portal vein wall to the junction of the hepatic vein with the inferior vena cava (IVC) and to choose an appropriate device size to cover this entire length. This is in some instances difficult because the marker catheter adapts better to a curved tract; this has to be taken into account, and for curved tracts 1 cm should be added to the obtained length measurement with the marker catheter, analogous to choosing an endograft for aneurysm repair in a patient with tortuous anatomy. If the hepatic venous confluence is not easily identified, a contrast series with simultaneous injection into the marker catheter and into the sheath, retracted into the vena cava in an oblique projection, helps to identify the confluence.

Placement of the graft too far into the portal vein or IVC can lead to venous obstruction. There has been at

least one case in which the IVC was occluded by placing the graft all the way across the IVC.

COMPARISON OF ePTFE STENT-GRAFT TO BARE STENT

Studies with Direct Comparison of the VIATORR[®] to Bare Stents

Currently three studies are available for direct comparison of the VIATORR[®] stent-graft and standard bare stent for the creation of TIPS. Two studies were randomized: a transatlantic multicenter randomized trial published in 2004 by Bureau et al,²⁹ then the U.S. multicenter randomized trial for the comparison of the VIATORR[®] endoprosthesis and the Wallstent. Data from the U.S. trial is available at the W.L. Gore homepage (www.goremedical.com; <http://164.109.63.17/library/Documents/AH1436EN1.pdf>) but, unfortunately, the results of this study have not been published in a peer-reviewed fashion. The following paragraphs discuss these data.

The study by Bureau et al is a direct randomized multicenter comparison of VIATORR[®] and Wallstent in patients suffering from complications of portal hypertension (recurrent variceal bleeding or intractable ascites). Eighty patients with cirrhosis and uncontrolled bleeding ($n = 23$), recurrent bleeding ($n = 25$), or refractory ascites ($n = 32$) were randomized to be treated by transjugular intrahepatic portosystemic shunts with either a polytetrafluoroethylene-covered stent (group 1, 39 patients) or a usual uncovered prosthesis (group 2, 41 patients: Memotherm (Bard, Murray Hill, NJ) $n = 22$, Wallstent $n = 15$, the rest being Luminexx (Bard, Murray Hill, NJ) and Sinus stents). Follow-up Doppler ultrasound was scheduled at day 7, at 1 month, and then every 3 months for 2 years. Angiography and portosystemic pressure gradient (PSG) measurements were performed 6, 12, and 24 months after the TIPS procedure and whenever dysfunction was suspected. Dysfunction was defined as a $> 50\%$ reduction of the lumen of the shunt at angiography or a $\text{PSG} > 12 \text{ mm Hg}$. After a median follow-up of 300 days, five patients (13%) in group 1 and 18 (44%) in group 2 experienced shunt dysfunction ($P < 0.01$). Clinical relapse occurred in three patients (8%) in group 1 and 12 (29%) in group 2 ($P < 0.05$). No early thrombosis was observed in the ePTFE group as compared with three cases in the uncoated group. The actuarial rates of primary patency in the covered and bare stent groups were 86 and 47%, respectively, at year 1 and 80 and 19%, respectively, at year 2. Encephalopathy was not more frequent in the ePTFE group, as had been feared; actuarial rates of encephalopathy were 21% in group 1 and 41% in group 2 at 1 year (not significant), and one shunt reduction was necessary for the ePTFE stent-graft, two for the bare

Table 1 Revisions Required to Obtain or Reestablish Patency in the de novo U.S. Multicenter Trial

	VIATORR [®] Device Group	Wallstent [®] Device Group	Reintervention Rate (VIATORR [®] Device: WALLSTENT [®] Device Group)
PSG > 12 only	11	12	
% DS > 50 only	1	3	
PSG > 12 and % DS > 50	1	19	
PSG > 12 and % DS unknown	1	2	
Neither (primary assisted patency)	2	3	
Total reinterventions	16 (15 subjects)	39 (37 subjects)	Number of reinterventions: 1:2.4 Number of subjects requiring a reintervention: 1:2.5 ($P < .001$)*

* P -value associated with the chi-square test of the difference between treatment groups in the proportions of subjects with reinterventions or revisions. VIATORR[®] device subjects required significantly fewer reinterventions.

Data from W.L. Gore and Associates, Inc. Available at: <http://164.109.63.17/library/Documents/AH1436EN1.pdf>.

stents. Estimated probabilities of survival were 71 and 60% at 1 year and 65 and 41% at 2 years in groups 1 and 2, respectively (not significant). Overall, not only did the ePTFE stent reduce the overall numbers of shunt dysfunction ($n = 5$ versus $n = 18$) and recurrence of clinical symptoms ($n = 3$ versus $n = 12$) but also increased patient survival ($n = 27$ versus $n = 22$, NS, death occurred from liver failure, sepsis, or gastrointestinal hemorrhage, each number being lower for the VIATORR[®]). The number of reinterventions was significantly reduced in the stent-graft group ($n = 6$ versus $n = 22$, $P < 0.05$). This study has another potential: to present the potential of nitinol stents for the creation of TIPS. The control group consisted mostly of nitinol stents (> 60%). Nitinol stents have been used with less³⁰ or more success for TIPS creation^{31–33}; in some studies patency rates came near those for ePTFE stent-grafts. In the study by Bureau et al the results for the bare stent control group were not better than historic controls.

The U.S. randomized trial (de novo creation of TIPS—VIATORR[®] versus Wallstent—sponsored by W.L. Gore) led to FDA approval of the VIATORR[®] endoprosthesis in 2004. To this date, the data have not been published. Preliminary results for a subset of the VIATORR[®] cohort were presented by Haskal at the annual SIR meeting in March 2004. A total of 253 patients were randomized in 14 centers ($n = 125$ VIATORR[®] versus $n = 128$ bare stent). The technical success rates were 100% for both groups, with hemodynamic success 94.5% for ePTFE and 92.4% for Wallstents, and venographic success in 96% for ePTFE versus 91.2% for the Wallstent. In the intention-to-treat analysis (patients who died or underwent orthotopic liver transplantation [OLT] were not excluded), treatment success (PSG < 12 mm Hg and shunt stenosis < 50%) was reported for 45.2% for the VIATORR[®] versus 22% for the Wallstent. Six-month primary patency (hemodynamic success) was 76% for the VIATORR[®] versus 48.5% for the Wallstent. Reinterventions were necessary in 15 patients in the

VIATORR[®] group versus 37 patients for the Wallstent group ($P < 0.001$; Table 1).

Surprisingly, encephalopathy rates ($P = \text{NS}$), rates of liver failure and death ($n = 18$ VIATORR[®], $n = 22$ Wallstent, $P = \text{NS}$) were lower for the VIATORR[®] group and cardiac adverse effects slightly higher for the VIATORR[®] (Table 2).

Recent data suggest that ePTFE-covered stent-grafts provide much improved patency rates, but their impact on survival is unclear. Direct comparisons can be performed in a prospective trial but also in retrospective but case-matched using regression analysis. Angermayr et al³⁴ have retrospectively demonstrated an improved survival rate of 88% at 1 year for patients treated with the VIATORR[®] endoprosthesis for TIPS, compared with 73% for a matched group receiving bare stents. This study is a retrospective comparison of patient survival when TIPS created with the VIATORR[®] are compared with standard bare stents (mostly Wallstent or nitinol stents). This is a matched (1:1 and 2:1) and unmatched comparison of 419 patients after creation of TIPS with bare stents to: 89 patients with VIATORR[®] placement using Cox regression models.

All suitable patients receiving either bare TIPS (419/466) or undergoing implantation of ePTFE endoprosthesis (89/100) in several centers in Austria up to 2002 were included in this retrospective analysis. Both patient groups were compared regarding survival with Kaplan-Meier and Cox regression analysis. Unmatched and 1:1-matched survival analyses were performed. Patients undergoing ePTFE stent-graft implantation had significantly higher survival rates in all analyses. The 3-month, 1-year, and 2-year survival rates were 93, 88, and 76% for the ePTFE group and 83, 73, and 62% for conventional TIPS patients, respectively. The matched survival analyses validated these findings. The model of the stent, patient age, and Child-Pugh class were independent predictors of survival. However, we note that Angermayr et al excluded patients who presented with significant cardiopulmonary and renal comorbidity,

Table 2 Adverse Events for the de novo U.S. Multicenter Trial

Adverse Event	VIATORR [®] Device Group (<i>n</i> = 125)	Wallstent [®] Device Group (<i>n</i> = 128)
Encephalopathy	47 (37.6%)	54 (42.2%)
Ascites	26 (20.8%)	25 (19.5%)
Hydrothorax	11 (8.8%)	6 (4.7%)
Anernia	11 (8.8%)	10 (7.8%)
GI other/bile duct	11 (8.8%)	3 (2.3%)
PSG > 12 mm Hg	10 (8.0%)	26 (20.3%)
Fever	10 (8.0%)	5 (3.9%)
Lower extremity edema	8 (6.4%)	8 (6.3%)
Pulmonary failure	7 (5.6%)	4 (3.1%)
Hypotension	7 (5.6%)	1 (0.8%)
Renal dysfunction	6 (4.8%)	8 (6.3%)
Pneumonia	6 (4.8%)	4 (3.1%)
Urinary tract infection	6 (4.8%)	2 (1.6%)
Myocardial infarction	6 (4.8%)	2 (1.6%)
Cardiac other	6 (4.8%)	6 (4.7%)
Sepsis	5 (4.0%)	4 (3.1%)
Liver failure	5 (4.0%)	10 (7.8%)
Coagulopathy	5 (4.0%)	2 (1.6%)
Other infection	5 (4.0%)	9 (7.0%)
Bowel other	5 (4.0%)	8 (6.3%)
Upper GI bleed	4 (3.2%)	0 (0.0%)
Liver other	4 (3.2%)	2 (1.6%)
Congestive heart failure	4 (3.2%)	4 (3.1%)
Electrolyte imbalance	4 (3.2%)	3 (2.3%)
Spontaneous bacterial peritonitis	3 (2.4%)	2 (1.6%)
Stenosis	3 (2.4%)	33 (25.8%)
Hepatic vein stenosis	3 (2.4%)	3 (2.3%)
Pulmonary edema	3 (2.4%)	1 (0.8%)

Data from W.L. Gore and Associates, Inc. Available at: <http://164.109.63.17/library/Documents/AH1436EN1.pdf>.

sepsis, and malignancy from their analysis. Overall this study suggests that the survival rate after TIPS creation with the VIATORR[®] device is higher than that after TIPS creation with an uncovered stent (2-year survival rate, 76 versus 62%).

These three studies have so far demonstrated clear superiority of the VIATORR[®] both in regard to patency as well as survival when compared with standard bare stents. Given these compelling data, it is my conclusion that the vast majority of TIPS creations and revisions should now be performed using the VIATORR[®] endoprosthesis,

Nonrandomized Studies

A summary of most studies for the VIATORR[®] stent-graft can be found in Table 3. Four larger series are identified including more than 50 patients each^{35–38}; two

studies were multicenter retrospective analysis,^{35,37} the other two were single-center retrospective series.^{36,38}

The largest series to date by Charon et al³⁵ is a retrospective analysis of 100 TIPS procedures. One hundred consecutive patients with portal hypertension, with a mean age of 52 years (range, 22 to 86 years), underwent implantation of the VIATORR[®] TIPS stent-graft at one of three hospital centers. The indications for TIPS creation were mostly variceal bleeding (*n* = 81) and refractory ascites (*n* = 19). Eighty-seven patients underwent de novo TIPS placements, with 13 treated for recurrent TIPS stenosis. Sixty-two patients were available for follow-up portal venography and PSG measurement commencing 6 months after VIATORR[®] stent-graft placement.

The technical success rate was 100%. TIPS creation resulted in an immediate decrease in mean PSG ($\pm$ SD) from 21 ± 6 mm Hg to 7 ± 3 mm Hg. Acute repeat intervention (within 30 days) was required for portal vein thrombosis (*n* = 1), continued bleeding (*n* = 3), and encephalopathy (*n* = 1). The all-cause 30-day mortality rate was 12%. Two patients developed acute severe refractory encephalopathy, which led to death in one case. New or worsening encephalopathy was identified in 14% of patients. Theoretical increase in TIPS-related encephalopathy was not demonstrated. The incidence of recurrent bleeding was 8%. The cumulative survival rate at 1 year was 65%. Sixty-two patients available for venographic follow-up had a mean PSG of 9 ± 5 mm Hg at a mean interval of 343 days (range, 56 to 967 days). There were four stent-graft occlusions (6%) and seven hemodynamically significant stenoses (11%), four within the stent-graft and three in the non-stent-implanted hepatic vein. The primary patency rate at 1 year by Kaplan-Meier analysis was 84%.

Data reported by Hausegger et al³⁷ present a series of 71 patients, all of whom received the covered stents. Clinical results of ePTFE-covered stent-grafts for TIPS were equally impressive in the study, with a 30-day mortality rate of 10% and an overall mortality rate of 28% (average follow-up, 16 months). The 1-year survival rate was 72%. All the patients who died in the first 30 days had advanced liver disease (six of seven patients had Child class C disease) and all died of liver failure. Only one patient (2.7%) developed recurrent upper gastrointestinal bleeding. Primary and secondary patency rates were 81 and 100%, respectively, at 1 year. Only 8% of patients (one of 13) who received 8-mm-diameter shunts developed new or worsened encephalopathy, versus 36% of patients (21 of 58) who received 10-mm-diameter shunts. The relative mortality in patients who received shunts of the two different diameters cannot be assessed from their data, but rates are likely to be lower with the 8-mm-diameter shunts because the vast majority of mortality occurred as a result

Table 3 Summary of Larger Nonrandomized Studies with the VIATORR[®] ePTFE TIPS Endoprosthesis

Author	Ref	n	Child-Pugh A/B/C	Variceal Bleeding (n)	Intractable Ascites (n)	De novo TIPS (n)	Revision	Technical Success (%)	30-Day Mortality	Shunt Patency at 1 year	Clinical Patency at 1 year	Survival	Encephalopathy (%)
Hausegger et al	37	71	10/43/18	44	27	71	0	100	9.9%	81	10/71	72%	31
Charon et al	35	100	20/46/34	81	19	87	13	100	12%	84%		65%	14
Maleux et al	36	56	8/13/35	28	28	44	12	100	7	53/56	52/56	71.50%	18
Rossi et al	38	53	16/24/9	28	21	53	0	100	4%	84/98	44/53	78% (OLT 7)	47
Otal et al	13	20	8/7/5	11 (4)	5 (4)	15	5	100	0%	80	19/20	16/18 (OLT 2)	5
Cejna et al	22	16	1/12/3	13	3	16	0	100	6%	100	9/11	10/13 (OLT 1)	9

of liver failure. There was only one recurrent bleeding episode in the entire cohort; it was not reported whether this happened in the 8-mm or 10-mm cohort.

The most important predictors of early mortality after TIPS creation are poor liver function, an emergent procedure, and comorbidity. Stent-grafts may prevent bile leaks as a cause of early mortality, but would not be expected to confer a major survival advantage over bare stents within the first 30 days because comorbidity and liver function have a greater impact on survival than on primary patency.

Another large series by Rossi et al³⁸ reported midterm follow-up data on the VIATORR[®]. Fifty-three consecutive patients underwent de novo TIPS with the VIATORR[®]. Minimum patient follow-up was 9 months (mean, 16.3 months). Fifty-six stent-grafts were implanted in 53 patients; eight of the devices were 8 mm in diameter and 48 were 10 mm in diameter. The stent length varied from 4 to 7 cm. Indications were recurrent variceal bleeding in 28 patients and refractory ascites or hydrothorax in 21 patients. A technical success rate of 100% was obtained, with an early clinical success rate of 96.2%. During the follow-up period, the recurrence rate was 3.4% (1 of 29 patients) for bleeding and 9.0% (2 of 22 patients) for ascites. Shunt malfunction occurred in nine of 53 patients (16.9%); in one of these nine patients, shunt occlusion was evident after revision, and a parallel shunt was created. The 1-year primary and secondary patency rates were 83.8 and 98.1%, respectively. In this series, the incidence of encephalopathy (included even as a single short-lived episode) was 47.1% (25 of 53 patients). The 30-day mortality rate was 3.8% (2 of 53), and the late mortality rate was 17.3% (8 of 46), excluding seven patients who underwent transplantation.

The last of these larger reported series by Maleux et al³⁶ reported the therapeutic efficacy and immediate and long-term safety of the VIATORR[®] in a cohort of 56 patients suffering from severe portal hypertension. In 44 patients, the stent-graft was placed during the initial TIPS procedure (de novo TIPS); in the other 12 patients, the stent-graft was placed for TIPS revision. Follow-up was performed with clinical assessment, duplex ultrasound and, if abnormal or inconclusive, with invasive venography and pressure measurements. The mean follow-up was 337 days (range 4 to 962 days). Immediate postprocedural complications occurred in four patients (4/56, 7%). None of them was lethal. During follow-up, stent occlusion appeared in one patient and stenosis in two; no recurrence of bleeding was noted in all patients treated for variceal bleeding ($n=28$), and 24 of the 28 patients (86%) suffering from refractory ascites and/or hepatic hydrothorax were free of regular paracenteses and/or drainage of pleural effusion after shunt creation. The 30-day and global mortality for the total study population ($n=56$)

was, respectively, 7% ($n=4$) and 28.5% ($n=16$). In the patient subgroup with variceal bleeding ($n=28$), 30-day mortality was 3.5% ($n=1$) and global mortality 14.2% ($n=4$). Primary patency rate by Kaplan-Meier analysis was 89.3%, secondary patency rates were 96.7%. In 10 patients of the 56 studied patients (18%), isolated hepatic encephalopathy occurred, which was lethal in four (Child C) patients (7%). Three of these four patients died within the first month after TIPS placement. The incidence of TIPS-induced hepatic encephalopathy was acceptable. The authors reported one patient with a thrombosis of the right hepatic vein and with a temporary disturbance of the liver function tests as seen as a partial Budd-Chiari syndrome after VIATORR[®] placement, but all these findings were completely asymptomatic.

Comparison of the VIATORR[®] to First-Line Treatment for the Complications of Portal Hypertension

There is no randomized study available for the comparison of the VIATORR[®] to first-line treatment:

1. sclerotherapy/banding for recurrent variceal bleeding or
2. paracentesis for intractable ascites

Because the VIATORR[®] has documented its superiority to bare stent TIPS these randomized trials are warranted for direct comparison to the standard first-line treatments.

CONCERNS AND COMPLICATIONS

Procedure- versus Stent-Graft-Related Complications

Complications could be divided into procedure- or stent-graft-related complications. Procedure-related complications associated with TIPS creation (liver capsule puncture, puncture/transection of the hepatic artery, etc.) can be considered equivalent for bare stent or stent-graft placement.

Other complications can be potentially influenced by the choice of stent type used. The biggest drawback from stent-graft use might arise from incorrect placement (too distal placement in the portal vein with occlusion of the main portal vein or portal vein branches) but this has not been an issue in larger studies. Occlusion of the vena cava was reported only as one case report.³⁹ For bare stents in retrospective studies stent migration to the portal vein (4%) and to the right atrium (4%) was reported⁴⁰ but not so for stent-grafts.

On the other hand, procedure-related complications might be reduced by the use of stent-grafts (e.g., use of stent-grafts might prevent complications arising

from extrahepatic puncture of the portal vein eventually resulting in fatal hem peritoneum).⁴¹ Stent-graft implantation has the potential to seal the puncture site and prevent further bleeding.^{32,42}

Encephalopathy: 8-mm versus Larger Shunts

Hepatic encephalopathy, along with TIPS dysfunction, is one of the major complications that has limited the effectiveness of TIPS. The incidence of new or worsening encephalopathy following TIPS is 20 to 31%.^{40,43-45} In controlled trials comparing TIPS with alternative forms of therapy, the incidence of encephalopathy is always greater in those who received a TIPS. It is important to note that if encephalopathy is precipitated by variceal bleeding, prevention of rebleeding should make it less likely that the patient will have recurrent encephalopathy. Only if the hepatic encephalopathy is uncontrollable is a TIPS contraindicated.⁴⁶ In most patients, the encephalopathy responds to standard therapy, and only rarely (~5%) must the TIPS be occluded to control the encephalopathy.^{44,47}

The VIATORR[®] has the potential to prolong patency; increased patency requires fewer hospitalizations, fewer invasive procedures, and fewer reinterventions but may increase the risk for encephalopathy. One of the big advantages of the VIATORR[®] stent-graft is that it achieves a stable shunt with a relative stable diameter and with good correlation to the chosen stent-graft diameter (due to its hoop strength). Fortunately, higher unobstructed patency rates do not correlate with a higher incidence of encephalopathy in randomized studies (Bureau et al⁴⁸ and the U.S. randomized trial). Bureau et al reported that the actuarial rates of encephalopathy were lower for the VIATORR[®] than for bare stents, and the difference was borderline significant ($P=0.0586$; log-rank test).⁴⁸ Rates were 22% (95% confidence interval [CI], 8.7 to 35.3%) versus 41% (95% CI, 25.6 to 56.4%) at 1 year for the VIATORR[®] and the bare stents, respectively. Overall, the number of episodes of encephalopathy per patient was 0.46 (VIATORR[®]) and 0.78 (Bare stent; not significant). Twelve patients were admitted with severe encephalopathy (VIATORR[®] $n=5$ and bare stents $n=7$), whereas encephalopathy was considered mild in 13 patients (VIATORR[®] $n=4$ and bare stents $n=9$). The risk of encephalopathy was the same (31% in both groups) regardless of the indication (bleeding versus ascites) for TIPS.

Wallstents, maybe the most widely used stent for TIPS creation in the early and mid 90s, has the tendency not to open to its nominal diameter. When 10- to 12-mm stents are used the resulting shunts generally range somewhat unpredictably from 8 mm to 11 mm in diameter. For bare stents pseudointimal proliferation

over time somehow reduces the risk of encephalopathy; in the uncoated stent group, the risk of hepatic encephalopathy reappeared whenever dysfunction was corrected. From the classic TIPS papers there is no answer to the question of whether smaller shunts would lead to adequate portal decompression and prevent recurrent symptoms while limiting the incidence of hepatic encephalopathy. Hausegger et al³⁷ suggested a relatively high potential for de novo hepatic encephalopathy (18 of 71 patients after 1 to 18 months [mean, 4.9 months]). Deterioration of an existing encephalopathy was observed in another four patients. The overall rate of increased symptomatic encephalopathy was 31% (22 of 71). Of these 22 patients, one had an 8-mm shunt and all others had 10-mm shunts. In nine patients, encephalopathy was effectively treated with strict diet. Seven patients with disabling hepatic encephalopathy died, five of liver failure, one of a myocardial infarction, and one of a cerebral stroke. One patient had persistent grade 3 encephalopathy and needed shunt reduction. This study emphasizes the potential for 8-mm stent-grafts to achieve lower encephalopathy rates when compared with 10-mm stent-grafts.

It is necessary to look in the surgical literature to compare the potential of different shunt diameters to cause de novo or worsened hepatic encephalopathy. H-shunts are created with graft diameters between 8 and 12 mm; all of these grafts enable relatively low encephalopathy rates. In larger series the incidence of de novo hepatic encephalopathy with mesocaval or portocaval interposition shunts (where grafts with defined diameters are used) varies between 5 and 9% during follow-up. Eight-millimeter shunts resulted in a de novo hepatic encephalopathy rate of 5% (initial 30-day mortality rate of 15%),⁴⁹ whereas 10-mm shunts resulted in an incapacitating de novo encephalopathy rate of 10% (30-day mortality rate of 0%).⁵⁰

In one of the best followed-up studies, the prospective randomized study by Rosemurgy et al,^{49,51,52} the incidence of hepatic encephalopathy at 10-year follow-up was 2 of 66 patients. In contrast TIPS (10-mm Wallstents) creation resulted in an encephalopathy rate of 3 of 66 patients randomized. It is noteworthy that 50% of the study population consisted of Child-Pugh C patients and 50% of patients with pretreatment encephalopathy died after the procedure. Consequently we can only speculate that the low encephalopathy rate in this surgical-interventional study for the control of recurrent variceal hemorrhage may be directly related to the type of reporting physician (or joint publications with gastroenterologists having the tendency to report higher encephalopathy rates).

Overall, based on surgical data, randomized comparison of 8-mm versus 10-mm VIATORR[®] stent-graft seems warranted, especially for the de novo occurrence of hepatic encephalopathy. In our series 8-mm

stent-grafts were not associated with the occurrence of de novo or worsened encephalopathy, but there was a tendency for TIPS dysfunction despite patent TIPS (data not published).

Liver Failure

Moreover, we do not have the ability from the data presented to analyze the relative mortality in patients who received shunts of the two different diameters, but rates are likely to be lower with the 8-mm-diameter shunts because the vast majority of mortality occurred as a result of liver failure. In randomized studies (Bureau et al²⁹) rates of liver failure were lower for the VIATORR[®] endoprosthesis versus bare stents.

"Endotipsitis"

Infection of TIPS stents is uncommon, with fever and/or bacteremia estimated in 1% to 10% of patients from large series. The term "definite endotipsitis" was coined for continuous bacteremia with an observed vegetation or thrombus in the TIPS stent, while "probable endotipsitis" refers to persistent bacteremia and fever with an apparently normal stent and no other obvious source of infection.^{53,54} A variety of organisms have been isolated from such cases, including gram-negative enteric pathogens, *Staphylococcus aureus*, and enterococci and also fungal TIPS stent infections,⁵⁵⁻⁵⁷ the latter as all other infections potentially lethal with sepsis and multiorgan failure. There were no special reports on increased incidence of endotipsitis after VIATORR[®] endoprosthesis placement.

Liver Infarction

One of the earliest concerns for stent-graft placement was occlusion of (then patent) hepatic veins with their potential occlusion and worsening of liver function. Initially, we aimed only for tract coverage up to the hepatic vein but tract stenosis at the hepatic vein caused shunt dysfunction. At that time there was 100% in-graft patency.¹² Thus, complete coverage from the portal vein to the IVC was seen as the only possibility to achieve uninterrupted patency. In animal studies the distribution of the hepatic arterial blood flow is affected by creation of a TIPS with a stent-graft but no relevant concerns were drawn from this experimental study.⁵⁸ In the feasibility trials there was one report describing hepatic necrosis.¹³ Overall only few cases have been described over the last years; unfortunately it seems that with stent-graft there seems to be a tendency to report more occurrences of liver ischemia or necrosis after TIPS.^{13,59-63} Episodes of infarcts or necrosis have been reported after initial wedged portograms as well as TIPS creation with bare stents.⁶²⁻⁶⁶ In the TIPS quality

improvement trial,⁶⁷ the incidence of hepatic infarction was considered to be less than 0.5%.

Stent-Graft Concerns: TIPS and OLT

TIPS is generally considered as a bridge to transplantation; therefore, TIPS creation should not interfere with OLT. For technical reasons stenting deep into the portal vein as well as stenting proximal to the hepatic vein-IVC confluence is surgically more demanding. This is because a cuff of hepatic vein or portal vein is required to complete the transplant in these patients. This is also true after stenting with bare stents. Bare stents grow (or are incorporated) into the vessel wall; their removal or resection is extremely difficult. When the stent extends into the IVC or atrium or deep into the main portal vein, transplantation difficulties can arise. In one series of 12 patients who had a TIPS preceding liver transplantation, four patients had portal vein stents near the coronary vein or extending into the superior mesenteric vein, and venous reconstruction was required in one patient.⁶⁸ In a second series of 24 patients who had a TIPS created before transplantation, eight patients had more complicated surgeries, which were attributed to the presence of a TIPS. Four of the stents were in the IVC; one was in the superior mesenteric vein and in three the portal vein was thrombosed. Despite being able to complete the transplant in all eight patients, patient and graft survival were somewhat worse in those with complications related to the presence of the TIPS.⁶⁹

However, in other series, despite the technical issues that arose during the transplant because of the presence of the shunt, operative time and patient and graft survival were the same in patients who were transplanted in the presence and absence of a TIPS.^{70,71} All patients who have a TIPS created should be considered possible liver transplant candidates; thus care should be taken to not extend the stents beyond the minimum necessary portions of the portal and hepatic vein-IVC junction required to insure a functioning shunt. If the patient is being considered for living related transplantation, then lining the entire hepatic vein to the IVC cava may complicate transplantation.

This is somehow different for the VIATORR[®] endoprosthesis. Upon optimal placement, the bare area protrudes just 2 cm into the portal vein. At this point, the diameter of the portal vein is almost always wider than the stent diameter; thus overlap does not increase technical difficulty during OLT. One major advantage of stent-grafts is the absence of complete vessel wall ingrowth, so removal of the TIPS prosthesis is relatively easy.⁷² The ePTFE stent-grafts have demonstrated that they—upon correct placement—pose no problem for OLT. In 48 patients ePTFE-covered endoprostheses were implanted (36 de novo, 12 for TIPS revision).

Eight of them (five de novo and three revision cases) later underwent an OLT. All OLTs were performed under venovenous bypass surgery. Visual surgical inspection confirmed correct positioning of the fully patent stent-graft, starting in the portal vein and ending at the junction of the hepatic vein to the IVC. No surgical difficulty was observed during proximal or distal clamping or during resection of the diseased liver.⁷²

CAN STENT-GRAFTS BE COST-EFFECTIVE?

The use of the PTFE-coated stent-grafts should decrease significantly the incidence of shunt dysfunction and recurrence of the complications of portal hypertension. Based on the current data regular follow-up regimen cannot be changed, including clinical follow-up, and ultrasound as well as venography is mandatory during the first year. But these are also major contributors to overall TIPS costs. Cost-effectiveness of stent-grafts can be due to a significantly reduced number of reinterventions during follow-up.

In a study by Meddi et al⁷³ 38 patients were treated with TIPS or sclerotherapy for recurrent variceal bleeding with bare stents. The authors compared the costs of the first 18 months of treatment. The number of days spent in the hospital for initial treatment and during follow-up was defined as cost of hospitalization. Additional sclerotherapy sessions, TIPS procedures, angioplasty, or addition of a second stent to maintain the shunt patency were defined as the costs of therapeutic procedures. The two groups were comparable for age, sex, and Child-Pugh score. Four patients died in the TIPS group, and two died and one was transplanted in the sclerotherapy group. The rebleeding rate was significantly higher in the sclerotherapy group. Despite this, the number of days spent in the hospital was similar in the two groups. This was because of a higher number of hospital admissions for the treatment of hepatic encephalopathy and shunt insufficiency in the TIPS group. The therapeutic procedures were more expensive for TIPS. Consequently, the cumulative cost was higher for patients treated with TIPS than for those treated with sclerotherapy (the cost for OLT not taken into account). The extra cost was because of the initial higher cost of the procedure and the difference was still maintained at the end of the 18-month follow-up. When the cumulative costs were expressed per month free of rebleeding, the disadvantage of TIPS disappeared.

In conclusion, a program of prevention of variceal rebleeding with TIPS, despite the longer interval free of rebleeding, is not a cost-saving strategy in comparison with sclerotherapy. In the light of this publication it would be interesting to see a comparison of the actuarial costs for stent-graft TIPS, with significantly higher cost

for the therapeutic procedure (the VIATORR[®] costs at least two times more than a standard Wallstent) with reduced number, thus reduced costs for treatment of dysfunction. This information may be available once the U.S. multicenter trial data are evaluated.

STENT-GRAFTS FOR TIPS: TOO EARLY? TOO LATE?

Despite a multitude of randomized trials and large retrospective studies, some important questions—relevant for use of stent-grafts—have not yet been answered:

1. What is the desired diameter of the TIPS?
 - a. Does the diameter correlate diameter with occurrence of HE and/ or liver failure?
 - b. Is the choice between 8-mm and 10-mm endoprosthesis enough (perhaps 9-mm stent-grafts could additionally be warranted)?
2. What is the role of nitinol stents? This has still to be evaluated; in peripheral arteries results of nitinol stents were superior to balloon-expandable stents or the Wallstent, with one potential being cost-effectiveness.

CONCLUSION

At that time the VIATORR[®] stent-graft was introduced, TIPS had no clear clinical benefit over other therapies of portal hypertension, including sclerotherapy or banding for the treatment of recurrent variceal bleeding, or paracentesis for the treatment of intractable ascites. Conclusions were drawn from insignificant differences in survival rates associated with higher encephalopathy rates. Consequently TIPS was considered as second-line treatment. Based on the published data the VIATORR[®] has the potential to increase survival rates, which has the potential to significantly change the results from these randomized trials

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