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### **Under-dilated TIPS Associate With Efficacy and Reduced Encephalopathy in a Prospective, Non-randomized Study of Patients**

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# Accepted Manuscript

Under-dilated TIPS Associate With Efficacy and Reduced Encephalopathy in a Prospective, Non-randomized Study of Patients With Cirrhosis

Filippo Schepis, Francesco Vizzutti, Guadalupe Garcia-Tsao, Guido Marzocchi, Luigi Rega, Nicola De Maria, Tommaso Di Maira, Stefano Gitto, Cristian Caporali, Stefano Colopi, Mario De Santis, Umberto Arena, Antonio Rampoldi, Aldo Airoidi, Alessandro Cannavale, Fabrizio Fanelli, Cristina Mosconi, Matteo Renzulli, Roberto Agazzi, Roberto Nani, Pietro Quaretti, Ilaria Fiorina, Lorenzo Moramarco, Roberto Miraglia, Angelo Luca, Raffaele Bruno, Stefano Fagioli, Rita Golfieri, Pietro Torricelli, Fabrizio Di Benedetto, Luca Saverio Belli, Federico Banchelli, Giacomo Laffi, Fabio Marra, Erica Villa



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6

7 **SHORT TITLE**8 **SMALL TIPS REDUCES ENCEPHALOPATHY**

9

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1

**2 ABBREVIATIONS**

3 CI, confidence interval; CG, control group; CT, computed tomography; HCC,  
4 hepatocellular carcinoma; HVW, hepatic vein wall; IP, intra-parenchymal; IVC, inferior  
5 vena cava; LVP, large volume paracentesis; MELD, model for end-stage liver disease;  
6 OLT, orthotopic liver transplantation; MRI, magnetic resonance imaging; PCG, porto-caval  
7 pressure gradient; PRX, proximal end; PSE, portosystemic encephalopathy; PTFE-SG,  
8 polytetrafluoroethylene-covered stent graft; PVW, portal vein wall; RA, refractory ascites;  
9 ROC, receiver operating characteristic curve; TG, training group; TIPS, trans-jugular intra-  
10 hepatic porto-systemic shunt; US, ultrasound; VG, validation group; VH, variceal  
11 hemorrhage.

12

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18

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23

**1 AUTHOR CONTRIBUTIONS**

2 Filippo Schepis and Francesco Vizzutti: study concept and design; acquisition of data;  
3 study supervision; analysis and interpretation of data; critical revision of the manuscript for  
4 important intellectual content; obtained funding.

5 Guadalupe Garcia-Tsao: study supervision; interpretation of data; drafting of the  
6 manuscript; critical revision of the manuscript for important intellectual content.

7 Guido Marzocchi and Luigi Rega: Image analysis.

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15 critical revision of the manuscript for important intellectual content; obtained funding.

16 Federico Banchelli: statistical analysis.

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20

21

**Abstract:**

**Background & Aims:** Portosystemic encephalopathy (PSE) is a major complication of trans-jugular intrahepatic porto-systemic shunt (TIPS) placement. Most devices are self-expandable polytetrafluoroethylene-covered stent grafts (PTFE-SGs) that are dilated to their nominal diameter (8 or 10 mm). We investigated whether PTFE-SGs dilated to a smaller caliber (under-dilated TIPS) reduce PSE yet maintain clinical and hemodynamic efficacy. We also studied whether under-dilated TIPS self-expand to nominal diameter over time.

**Methods:** We performed a prospective, non-randomized study of 42 unselected patients with cirrhosis who received under-dilated TIPS (7 and 6 mm) and 53 patients who received PTFE-SGs of 8 mm or more (controls) at referral centers in Italy. After completion of this study, dilation to 6 mm became the standard and 47 patients were included in a validation study. All patients were followed for 6 months; Doppler ultrasonography was performed 2 weeks and 3 months after TIPS placement and every 6 months thereafter. Stability of PTFE-SG diameter was evaluated by computed tomography analysis of 226 patients with cirrhosis whose stent grafts increased to 6, 7, 8, 9, or 10 mm. The primary outcomes were incidence of at least 1 episode of PSE grade 2 or higher during follow up, incidence of recurrent variceal hemorrhage or ascites (based on need for at least 1 large-volume paracentesis by 4 weeks after TIPS placement), incidence of shunt dysfunction requiring TIPS recanalization, and reduction in porto-caval pressure gradient.

**Results:** PSE developed in a significantly lower proportion of patients with under-dilated TIPS (46%) than controls (73%) during the first year after the procedure ( $P=.015$ ), but the proportions of patients with recurrent variceal hemorrhage or ascites did not differ significantly between groups. No TIPS occlusions were observed. These results were confirmed in the validation cohort. In an analysis of self-expansion of stent grafts, during a mean follow-up period of 252 days after placement, none of the PTFE-SGs self-expanded to the nominal diameter in hemodynamically relevant sites (such as portal and hepatic vein vascular walls).

**Conclusion:** In prospective, non-randomized study of patients with cirrhosis, we found under-dilation of PTFE-SGs during TIPS placement to be feasible, associated with lower rates of PSE, and effective.

**KEY WORDS:** portal hypertensive bleeding, liver, vascular disease, treatment

**1 LAY SUMMARY**

2 Portosystemic encephalopathy (PSE) is the most feared complication after transjugular  
3 intrahepatic porto-systemic shunt (TIPS) in cirrhotic patients. This study showed that  
4 placement of TIPS under-dilated up to 6 mm halves the post-procedural risk of PSE while  
5 maintaining clinical and hemodynamic efficacy.

**6**  
**7 KEYWORDS**

8 Liver, portal hypertensive complications, treatment

9

1 The transjugular intrahepatic portosystemic shunt (TIPS) is an invasive treatment of portal  
2 hypertensive bleeding, refractory ascites and vascular diseases of the liver, which  
3 improves survival<sup>1-5</sup>. The availability of self-expandable polytetrafluoroethylene-covered  
4 stent grafts (PTFE-SGs) has dramatically improved the long-term patency of TIPS<sup>1,2</sup>.  
5 However, its major drawback is portosystemic encephalopathy (PSE), reported in 23-55%  
6 within the first year<sup>3-10,11</sup>. Current guidelines recommend that post-TIPS porto-caval  
7 pressure gradient (PCG) should be reduced below 12 mmHg, particularly for re-bleeding  
8 prevention<sup>1,2</sup>. A PCG reduction of more than 50% has been suggested as an alternative  
9 target<sup>1</sup>.

10 TIPS diameter influences PCG reduction and the eventual appearance of PSE due to a  
11 greater amount of portal blood diverted to the systemic circulation and a reduction in  
12 residual liver perfusion<sup>10-12</sup>. It is conceivable that balloon dilation of TIPS to diameters  
13 smaller than those currently indicated (i.e. below or equal to 7 mm) result in a lower risk of  
14 PSE<sup>12,13</sup>. However, this under-sizing is not considered permanent because PTFE-SGs are  
15 expected to expand to their nominal diameter (i.e. inner maximal diameter of a fully  
16 expanded stent graft)<sup>13,14</sup>.

17 We hypothesized that, within the cirrhotic parenchyma, under-dilated PTFE-SGs would not  
18 self-expand to nominal diameter and could reduce post-TIPS encephalopathy. Thus, the  
19 aims of this study were: a) to determine whether under-dilated TIPS reduce the incidence  
20 of PSE while maintaining clinical efficacy, and b) to determine whether under-dilated TIPS  
21 maintain their size with time.

22

## 23 **MATERIALS AND METHODS**

### 24 ***Study design and Patients***

#### 25 A) Clinical Study

1 This part of the study was a prospective, non-randomized<sup>15</sup> analysis of clinical  
2 outcomes in consecutive patients with cirrhosis scheduled for TIPS placement at the  
3 referral Centers of Modena and Florence, who agreed to participate in the study. In a first  
4 set of patients PTFE-SGs ballooned to 7 mm were studied to evaluate the feasibility and  
5 safety of under-dilation. Patients enrolled thereafter had PTFE-SGs under-dilated to 6 mm.  
6 The latter (Training group, TG) was compared to a control group (CG) including patients  
7 who had standard TIPS placed before the initiation of the study, patients who refused  
8 under-dilated TIPS, and those of the TG in whom TIPS was dilated to 8 mm for technical  
9 reasons (Figure 1A). After completion of this initial study, dilation to 6 mm became the  
10 standard and all patients were included in a validation group (VG) to confirm TG results  
11 (Figure 1A). Table 1 shows inclusion and exclusion criteria. All patients were followed in a  
12 dedicated outpatient clinic for six months, and then in a general Hepatology clinic unless  
13 TIPS dysfunction or other complications, including PSE, were observed. Doppler  
14 ultrasonography of TIPS was performed 2 weeks and 3 months after TIPS placement and  
15 every 6 months thereafter<sup>2</sup>. No patients received pharmacological prophylaxis for PSE  
16 after TIPS.

17 Outcomes evaluated were: 1) incidence of at least one episode of PSE grade 2 or higher  
18 as evaluated by two observers at follow-up<sup>8,9,16</sup>; 2) incidence of recurrent VH or ascites,  
19 defined as the need for at least one large-volume paracentesis (LVP) by 4 weeks after  
20 TIPS; 3) incidence of shunt dysfunction requiring TIPS recanalization; and 4) reduction in  
21 PCG. TIPS would be revised in case of recurrent VH, continued need for LVP, and/or if  
22 flow reversal in the intrahepatic portal branches was observed on Doppler  
23 ultrasonography<sup>2</sup>. PTFE-SGs (Viatorr<sup>®</sup>, Gore, Flagstaff, AZ) were placed as previously  
24 described<sup>4,5,7,8</sup>, using semi-compliant balloon catheters (FoxCross, Abbott Park, IL).

25 In the CG, the intra-parenchymal tract was initially dilated to 8 mm. Patients with post-TIPS  
26 PCG above or equal to 12 mmHg had further dilation to 9 or 10 mm, unless post-TIPS

1 PCG was at or near the hemodynamic target and/or the patient was considered with  
2 limited functional reserve of the liver<sup>2,17</sup>.

3 In the TG and VG, the intra-parenchymal tract was pre-dilated to 6 mm, and the PTCE-SG  
4 was dilated to 7 or 6 mm unless the final TIPS path was angled. During dilation of the  
5 intra-parenchymal tract, balloon pressure was kept at the nominal value for 15-30  
6 seconds, even in the lack of a complete flattening of notches at the level of portal (PVW)  
7 and hepatic vein (HVW) walls.

8 Immediately after TIPS placement, pressures in the portal vein, along the intra-  
9 parenchymal tract of TIPS, and in the inferior vena cava (IVC) were recorded until a stable  
10 tracing was obtained in each position (45-60 seconds). Permanent tracings were obtained  
11 with PowerLab (ADInstruments, Inc., CO). Post-TIPS PCG was calculated by subtracting  
12 the IVC pressure from the portal vein pressure. All procedures were performed by FS, FV,  
13 CC, SC, and MDS under monitored anesthesia, without intubation and using midazolam  
14 and fentanyl as sedative and analgesic, respectively<sup>2,17</sup>.

15 Comparisons were made between patients who had the TIPS dilated to below or equal to  
16 7 mm (under-dilated TIPS) vs. those with diameters above or equal to 8 mm (standard  
17 TIPS).

#### 18 B) Imaging Study

19 Patients with cirrhosis from eight Italian referral centers (including those participating in the  
20 Clinical Study), who had TIPS placed using PTFE-SGs in the study period and who had an  
21 abdominal CT scan performed after TIPS placement were included (details on image  
22 analysis are reported in Supplementary Materials and Supplementary Figure 1). Table 1  
23 shows inclusion and exclusion criteria. The PTFE-SG inner diameter was measured at four  
24 sites: 1) where the PTFE-SG traverses the PVW and 2) the HVW; 3) at an intra-  
25 parenchymal (IP) site equidistant from PVW and HVW; and 4) at a site close to the  
26 proximal end (PRX), just before the PTFE-SG exit into IVC. The average of the largest

1 diameters at each of the four sites was calculated in the entire population grouped on the  
2 basis of both the PTFE-SG nominal diameters and the dilation diameters (Supplementary  
3 Figure 2). To determine whether PTFE-SG self-expansion occurred, the average value of  
4 the maximal diameter at the two sites considered hemodynamically critical (i.e. PVW and  
5 HVW, Supplementary Figure 2 and data not shown) was plotted for each patient against  
6 time from TIPS placement. It was considered that a PTFE-SG had not self-expanded if the  
7 follow-up diameter was within  $\pm 0.5$  mm of dilation diameter.

8 The study protocols conformed to the ethical guidelines of the 1975 Declaration of  
9 Helsinki. The Institutional Review Board gave approval to collect both prospective and  
10 retrospective clinical, hemodynamic and CT data. The need for informed consent was  
11 waived for patients no longer being followed at the time of data collection.

12

### 13 **Statistical analysis**

14 Results are expressed as mean $\pm$ SD (or SE if specified) or percentage. Comparisons of  
15 continuous data and proportions were performed by the Student's t-test and the chi-square  
16 test, respectively. Either Spearman's rank-order or Person's correlation were run to  
17 determine relationship between continuous variables. The Kaplan-Meier method was used  
18 to estimate time related events. Patients were censored at first episode of post-TIPS PSE,  
19 first LVP after TIPS, OLT or death or last available follow-up. Differences in observed  
20 probability were assessed using the log-rank test. Post-hoc competing risks analyses were  
21 also performed using Gray's test, with death and OLT as competing events. A Fine & Gray  
22 competing risks proportional hazards model was used to identify risk factors for PSE in the  
23 pooled groups. Post-TIPS death/OLT were treated as the competing events. Age, sex  
24 (female vs. male), pre-TIPS MELD score, TIPS indications (ascites vs. re-bleeding  
25 prevention), pre-TIPS PSE, PTFE-SG dilation (6 mm vs. above 6 mm), and either post-  
26 TIPS PCG below 10 mmHg or post-TIPS decrease more than 50% were incorporated in

1 two alternative models. Proportional hazards assumption of the Fine & Gray models was  
2 checked by means of graphical assessment of weighted Schoenfeld-type residuals.  
3 Finally, a propensity score analysis was performed (further details in Supplementary Table  
4 4).

5 Due to its exploratory nature the study lacks a sample size calculation.

6 PASW Statistics 20 (IBM Corp., Armonk, NY, U.S.A.) and R 3.1.2 (The R Foundation for  
7 Statistical Computing, Wien) were employed to analyze data.

8

## 9 **RESULTS**

### 10 **A) Clinical Study**

11 Between November 2009 and December 2012, 117 patients had a TIPS placed, of whom  
12 95 were included in this part of the study (Figure 1A). Indications for TIPS were refractory  
13 ascites (RA) in 58 (61%) patients and prevention of recurrent variceal hemorrhage (VH) in  
14 37 (39%) patients. In the latter group, TIPS was performed within 6 weeks of the index  
15 hemorrhage in the majority of patients (Table 2). Mean follow-up for the whole cohort was  
16 326 days. No patient was lost to follow-up. Patient allocation to the different groups and  
17 clinical characteristics before and after TIPS are reported in Figure 1A and Table 2.

18

#### 19 **a) Clinical outcomes**

20 The initial comparison was made between 42 patients with a PTFE-SG dilated to 7 or 6  
21 mm (TG) and 53 patients with dilation above or equal to 8 mm (CG). Patients in both  
22 groups were comparable, except that in the under-dilated group RA tended to be a more  
23 frequent indication and pre-TIPS PCG was lower. No patients in either group had acute  
24 shunt occlusion. Among the 5 patients (2 in TG and 3 in CG) who underwent PCG  
25 reassessment because they still required LVP 12 weeks after TIPS placement, none

1 required TIPS dilation (i.e., PCG below 12 mmHg) and none needed further LVP 6 months  
2 after TIPS placement (Table 2). Two patients in the CG underwent TIPS reduction for  
3 persistent PSE and heart failure, respectively.

4 There were no cases of recurrent VH in the 37 patients in whom TIPS was placed to  
5 prevent bleeding, including those (8 out of 12) with under-dilated TIPS in whom PCG did  
6 not decrease below 12 mmHg. Among the 58 patients with RA, 13 (22.4%) required at  
7 least one LVP during a mean follow-up of 317 days. The probability of remaining free of  
8 LVP was 74.6% (95% CI=57.6–91.6) and 78.6% (95% CI=62.6–94.6) ( $P=.728$ ; Gray's  
9 test  $P=.923$ ) in the TG and CG, respectively (Figure 2A).

10 During follow-up at least one episode of PSE occurred in 39 out of 95 patients (41%). The  
11 1-year cumulative probability of remaining free of PSE was significantly greater in TG  
12 [73.1% (95% CI=59.2–87.1%)] than in CG [46.0% (95% CI=32.2–59.8%)] ( $P=.015$ , Gray's  
13 test  $P=.026$ ) (Figure 2B).

14 Post-TIPS MELD score at different time points was significantly lower in TG than in CG  
15 (Table 2).

16

### 17 **b) Hemodynamic effects**

18 In the 95 patients the mean post-TIPS decrease of PCG was  $-53\pm 15\%$  (range -22% to -  
19 93%). Post-TIPS PCG was significantly greater and the percent decrease in PCG lower in  
20 the under-dilated group (Table 2). Moreover, TIPS dilation (i.e., 6, 7, 8, 9 and 10 mm)  
21 inversely correlated with final PCG and directly with its percent change ( $r_s=-0.285$ ,  $P=.001$   
22 and  $r_s=0.380$ ,  $P=.0003$ , respectively). Post-TIPS PCG below 12 mmHg<sup>1,4,5,11,18</sup> tended to  
23 be reached less frequently in the under-dilated group, while PCG values below 10 mmHg,  
24 a threshold that has been associated with increased risk of PSE<sup>6,11</sup>, were significantly less  
25 frequent than in the standard TIPS group (Table 2).

26

**c) Validation group**

We separately analyzed 59 patients with TIPS placed in the same centers after completion of the initial study (Figure 1A). No significant differences in clinical, endoscopic and hemodynamic baseline features were found between this 6 mm dilated validation group (VG) and the TG (Table 2) or its 6 mm subgroup (Supplementary Table 1). After TIPS placement in the VG, the probabilities of remaining free of LVP (69.6%; 95% CI=49.7.2–93.6% vs. 78.6%; 95% CI=62.6–94.6%;  $P=.625$ ; Gray's test  $P=.789$ ) and PSE episodes (77.8%; 95% CI=65.3–90.3% vs. 79.5%; 95% CI=62.6–96.4%;  $P=.871$ ; Gray's test  $P=.872$ ) were comparable to those of the TG dilated to 6 mm (Figure 2A and 2B). Post-TIPS hemodynamic parameters and MELD score were also similar (Supplementary Table 1).

**d) Risk factors for post-TIPS PSE**

Table 3 shows the competing risk models to identify independent predictors of post-TIPS PSE. There were 49 events (PSE) and 9 competing events (death/liver transplant). Age, female sex, pre-TIPS PSE, PTFE-SG dilatation above 6 mm, and post-TIPS PCG below 10 mmHg were independently associated with one-year post-TIPS PSE. No evidence of lack of proportional hazards was found (data not shown). Supplementary Table 2 shows the multivariate models after removing patients with pre-TIPS PSE. Propensity score adjusted multivariate analyses showed PTFE-SG dilatation above 6 mm and either post-TIPS PCG below 10 mmHg or post-TIPS PCG decrease more than 50% independently associated with one-year post-TIPS PSE (Supplementary Table 3).

Supplementary Table 4 shows the comparison of main characteristics of pooled groups stratified according to PTFE-SG dilation. Supplementary Figure 3 shows the cumulative risk of PSE in patients grouped according to categorical variables and the best cutoff for age (i.e., 55 years) selected after ROC analysis (data not shown). Supplementary Figure 4

1 shows bilirubin time course in patients stratified according to PTFE-SG dilation.  
2 Supplementary Figure 5 shows cumulative probability of remaining free of PSE in the  
3 subgroup of patients (N=24) with characteristics similar to those of patients enrolled in the  
4 study by Bureau et al<sup>5</sup> (i.e., ascites as an indication, pre-TIPS MELD score below or equal  
5 to 12, no history of pre-TIPS PSE, and post-TIPS PCG below 12 mmHg).

6

## 7 **B) Imaging Study**

8 Two hundred twenty-six CT scans were evaluated in this part of the study (Figure 1B). The  
9 mean time between PTFE-SG placement and CT scan was 252 days (median 286 and  
10 range 1–1440 days). Supplementary Figure 2 shows average maximal diameter (i.e. the  
11 largest cross-sectional inner diameter) at each of the four sites. PVW and HVW had the  
12 smallest diameter in underdilated PTFE-SGs, indicating that these are the  
13 hemodynamically relevant sites along the TIPS (data not shown). Therefore, diameters at  
14 these two sites were used to analyze stability of TIPS diameter over time in individual  
15 patients (Figure 3) and to create the groups at risk of PSE (Figure 2C and 2D).

16 Of the 8 mm PTFE-SG placed, none of those dilated to 6 or 7 mm self-expanded and none  
17 of those dilated to nominal diameter (8-mm) maintained this diameter (they were all under  
18 7.5 mm at follow-up) (Figure 3A to 3C).

19 Of the 10 mm PTFE-SG placed, 74% of those balloon dilated to 6 mm underwent self-  
20 expansion to 7 (67%) or 8 mm (7%) but none to nominal diameter (Figure 3A). Of those  
21 dilated to 7 mm, self-expansion occurred in 32% (all to 8 mm, none to nominal diameter)  
22 (Figure 3B). Of those dilated to 8 mm, self-expansion occurred in 20% (all of them to 9  
23 mm, none to nominal diameter) (Figure 3C). Of those dilated to 9 mm, none self-expanded  
24 (Figure 3D) and of those dilated to 10 mm none maintained nominal diameter (Figure 3E).

25 A follow-up PTFE-SG diameter of 6 mm ( $\pm$  0.5 mm) at PVW and/or HVW on CTs  
26 performed within 1 year after TIPS placement on 79 patients included in the Clinical Study

1 (Supplementary Table 5) was associated with a significantly lower incidence of PSE  
2 (Figure 2D) without differences in the recurrence of ascites (Figure 2C).

3

#### 4 **DISCUSSION**

5 This is the first published study demonstrating the feasibility of under-dilating PTFE-SGs at  
6 diameters as low as 6 mm and indicating that this strategy is associated with a significant  
7 decrease in the incidence of post-TIPS PSE. Importantly, the lower burden of PSE was  
8 accompanied by unchanged clinical efficacy in patients with both VH and RA.

9 The incidence of post-TIPS PSE was inversely related to the diameter of PTFE-SG  
10 deployment, and to post-TIPS PCG. Accordingly, the percentage of patients with post-  
11 TIPS PCG below 10 mmHg, the threshold identified as predictive of post-TIPS PSE<sup>6,11</sup>,  
12 was significantly lower in the under-dilated group. Therefore, dilation to 6 mm may be  
13 proposed as the initial option for TIPS placement, in particular in patients with risk factors  
14 for post-TIPS PSE<sup>2,10</sup>. These results, if confirmed in randomized trials, have the potential  
15 to change clinical practice.

16 Several studies have compared clinical efficacy, incidence of PSE, and hemodynamics  
17 after TIPS with different diameters, with divergent results. In two studies (one early  
18 interrupted randomized<sup>8</sup> and one retrospective<sup>18</sup>) comparing 10 vs. 8 mm PTFE-SG dilated  
19 to nominal diameters, patients with 8-mm PTFE-SG had similar PSE rates but lower  
20 clinical efficacy (mostly recurrence of ascites). Notably, the post-TIPS PCG was below 10  
21 mmHg in both groups, making it hard to reconcile their results on clinical efficacy.  
22 Moreover, in the study by Miraglia et al<sup>18</sup>, 50% of patients undergoing TIPS revision during  
23 follow-up for failure to control ascites had a PCG already below the target of 12  
24 mmHg<sup>1,2,5,11,17</sup>. On the other hand, a recent large randomized study reported that 8 mm  
25 PTFE-SG had similar efficacy in preventing VH compared to 10 mm, while decreasing  
26 post-TIPS PSE independent of post-TIPS PCG<sup>9</sup>.

1 Our results are in agreement with previous studies showing a close correlation between  
2 post-TIPS PCG and the incidence of PSE<sup>6,11</sup>. However, finding that both post-TIPS PCG  
3 below 10 mmHg and PTFE-SG dilation to 6-mm are independent predictors of PSE  
4 indicates that under-dilated TIPS may protect from PSE by mechanisms other than PCG,  
5 probably by preserving liver function. The similar efficacy of under-dilated and standard  
6 TIPS on VH and RA recurrence is even more complex to explain. At least 50% of patients  
7 receiving under-dilated PTFE-SG had a PCG below 12 mmHg after placement. In the  
8 remaining patients it is conceivable that a partial but substantial hemodynamic response  
9 may have been sufficient to prevent rebleeding<sup>9,19</sup>, similar to patients on pharmacological  
10 prophylaxis of rebleeding<sup>20</sup>. However, our results on bleeding recurrence cannot be  
11 generalized to the setting of early-TIPS<sup>4</sup> and continuous bleeding or early rebleeding<sup>1,2</sup>.  
12 Some patients with RA may also benefit from a partial hemodynamic response and others  
13 may benefit from further decrease in PCG due to a further expansion, albeit limited, of  
14 PTFE-SG with time. However, the fact that some patients required LVP 12 weeks despite  
15 a reassessed PCG below 12 mmHg indicates the need to further investigate the  
16 multifactorial nature of post-TIPS RA<sup>1,2,18,22</sup>.

17 PTFE-SGs are believed to self-expand to nominal diameter even when not fully balloon-  
18 dilated at the time of TIPS placement, but the fate of PTFE-SG under-dilation to less than  
19 8-mm in the setting of a cirrhotic liver had not been previously explored<sup>13,14</sup>. Herein we  
20 showed that underdilated PTFE-SGs do not self-expand to nominal diameter, and rarely  
21 expand beyond 1 mm of the dilation diameter at the hemodynamically relevant sites HVW  
22 and PVW. Of note, deployment to 6 mm of an 8 mm PTFE-SG appears to be more stable  
23 over time compared to 10 mm stent grafts. If our results are confirmed, dilating to 6 mm (or  
24 using stent grafts with nominal diameter below or equal to 8 mm) may be the  
25 recommended strategy, especially in patients with RA and in those with more  
26 compromised liver function.

1 A clear limitation of our study is the lack of randomization. Nevertheless, groups were  
2 comparable at baseline for most clinical parameters, including factors predictive of post-  
3 TIPS encephalopathy. A higher number of patients with RA was included in the under-  
4 dilated TG, and pre-TIPS PCG was lower in the same group, likely reflecting decreased  
5 circulating blood volume secondary to diuretic use and heart dysfunction. However, the  
6 VG, that confirmed the results obtained in the TG, was very similar to the CG in terms of  
7 indications and pre-TIPS PCG.

8 In conclusion, the present study shows that TIPS placement using PTFE-SGs under-  
9 dilated to 6 mm is associated with a lower rate of encephalopathy and with the same  
10 clinical efficacy compared to PTFE-SG TIPS dilated to standard diameters. These results  
11 require confirmation in randomized trials.

12

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20

1 **FIGURE LEGENDS**

2

3 **Figure 1**

4 Study Cohorts of the Clinical (A) and Imaging (B) Studies.

5 CT, computed tomography; PH, portal hypertension; PTFE-SG, polytetrafluoroethylene-  
6 covered stent graft; TIPS, trans-jugular intra-hepatic porto-systemic shunt.

7

8 **Figure 2**

9 Cumulative probability of remaining free of LVP (A and C)\* and PSE (B and D)\* in the  
10 Clinical Study and Imaging Study groups, respectively.

11 \*A and C include patients with RA; B and D include all patients.

12 A: no significant differences between paired groups were observed.

13 B: 6 & 7 mm (TG) vs.  $\geq 8$  mm (CG),  $P=.015$ ; 6-mm (TG) vs.  $\geq 8$  mm (CG),  $P=.011$ ; 6 mm  
14 (VG) vs.  $\geq 8$  mm (CG),  $P=.002$ . The remaining comparisons were not significant.

15 No difference in the comparisons of CG vs. underdilated groups was observed after  
16 removing the 7 patients dilated to 8-mm for technical reasons or for refusal of underdilated  
17 TIPS.

18 C-D: patients in the 6 mm group had a PTFE-SG diameter of  $6\pm 0.5$  mm at PVW and/or  
19 HVW as measured on CT images obtained within 1 year after TIPS placement.

20 CG, control group; CT, computed tomography; HVW, hepatic vein wall; LVP, large volume  
21 paracentesis; PTFE-SG, polytetrafluoroethylene-covered stent graft; PSE, porto-systemic  
22 encephalopathy; PVW, portal vein wall; TG, training group; TIPS: trans-jugular intra-  
23 hepatic porto-systemic shunt; VG, validation group.

24

**Figure 3**

Relationship between average inner diameters of individual PTFE-SG dilated to different diameters and the time elapsed from TIPS placement and CT examination. The grey areas include cases whose average maximum diameter falls within the expected values for each dilatation subgroup  $\pm 0.5$  mm. Solid lines represent regression lines. Values of both regression coefficient  $r$  and  $p$  are as follow for each PTFE-SG nominal diameter group: (8 mm group) 6 mm,  $r=.27$ ,  $P=.52$ ; 7 mm,  $r=.05$ ,  $P=.91$ ; 8-mm,  $r=.42$ ,  $P=.18$ ; (10 mm group) 6 mm,  $r=.01$ ,  $P=.96$ ; 7 mm,  $r=.42$ ,  $P=.07$ ; 8 mm,  $r=.17$ ,  $P=.09$ ; 9 mm,  $r=.07$ ,  $P=.75$ ; 10 mm,  $r=.01$ ,  $P=.93$ .

CT, computed tomography; PTFE-SG, polytetrafluoroethylene-covered stent graft; TIPS, trans-jugular intra-hepatic porto-systemic shunt.

**Supplementary Figure 1**

Rendering of the phantom used to test accuracy of CT measurement protocol (A). Representative section of the phantom and maximum diameters measured at this level (B). Distribution of measured diameters at 10 sections of the phantom (C). Serial measurements of a phantom were made on both 8 mm and 10 mm nominal diameter PTFE-SGs (A). These were released in a 37°C water bath and dilated to their nominal diameter by means of semi-compliant balloon catheters (FoxCross PTA Catheter, Abbott Laboratories, Abbott Park, IL). After two hours at 37°C, the phantom was scanned by CT. Inner diameters of 8 and 10 mm PTFE-SG were measured (B). Means of ten random slices orthogonal to the main axes of the PTFE-SGs were  $8.08 \pm 0.11$  mm and  $10.1 \pm 0.16$  mm, respectively (C). Deviation from the theoretical nominal diameter ranged from -1.3% to 3.8% (mean  $0.88 \pm 1.45\%$ ) and from -1% to 4% (mean  $1.0 \pm 1.63\%$ ), respectively.

CT, computed tomography; PTFE-SG, polytetrafluoroethylene-covered stent graft.

**1 Supplementary Figure 2**

2 Average maximal inner diameter of PTFE-SGs at each standard site after CT images  
3 processing (A and B: 8 mm and 10 mm nominal diameter PTFE-SGs, respectively). Bars  
4 represent mean $\pm$ SE of different dilatation groups. In C an example case of implanted  
5 PTFE-SG showing a narrowing of its lumen at the level of PVW and HVW. The effects of  
6 these strictures on blood pressure curve along the PTFE-SG length are also shown  
7 (double-headed dashed-arrow indicates pressure values recorded along the intra-  
8 parenchymal tract). Inter-observer agreement regarding measurement of the inner  
9 diameter at each site of PTFE-SG was excellent, as indicated by a coefficient for  
10 agreement of .96 (95% CI=0.9-1.0).

11 CT, computed tomography; HVW, hepatic vein wall; IVC, inferior vena cava; IP, intra-  
12 parenchymal tract; PRX, proximal outflow; PTFE-SG, polytetrafluoroethylene-covered  
13 stent graft; PV, portal vein; PVW, portal vein wall.

**15 Supplementary Figure 3**

16 Cumulative probability of remaining free of PSE in the entire study cohort (142 patients)  
17 stratified according to the risk factors identified by multivariate analysis.

18 Abbreviations: PCG, porto-caval pressure gradient; PSE; porto-systemic encephalopathy;  
19 TIPS, trans-jugular intra-hepatic porto-systemic shunt.

**21 Supplementary Figure 4**

22 Time-course of total serum bilirubin after TIPS positioning in patients grouped according  
23 PTFE-SG dilation.

24 In parenthesis are reported the number of patients at each time point in the control group,  
25 training group, and validation group, respectively.

26 Bars represent mean $\pm$ SE.

1 PTFE-SG, polytetrafluoroethylene-covered stent graft; TIPS: trans-jugular intra-hepatic  
2 porto-systemic shunt.

3

#### 4 **Supplementary Figure 5**

5 Cumulative probability of remaining free of PSE in the subgroup of patients (N=24) with  
6 ascites as an indication, pre-TIPS MELD score  $\leq 12$ , no history of pre-TIPS PSE, and post-  
7 TIPS PCG  $< 12$  mmHg<sup>5</sup>. Patients are also stratified according to diameter of TIPS dilation.

8 Follow-up (mean $\pm$ SE): 309.6 $\pm$ 15.0.

9 MELD, model for end-stage liver disease; PCG, porto-caval pressure gradient; PSE; porto-  
10 systemic encephalopathy; RA, refractory ascites; TIPS, trans-jugular intra-hepatic porto-  
11 systemic shunt.

12

**Table 1:** Inclusion and exclusion criteria for Clinical and Imaging Studies.

	<b>Clinical Study</b>	<b>Imaging Study</b>
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>a) diagnosis of cirrhosis determined on the basis of clinical history, histological examination, morphological characteristics of the liver at US, CT and MRI;</li> <li>b) TIPS placed to prevent recurrent VH<sup>1,2</sup> or to control RA<sup>21</sup>;</li> <li>c) TIPS creation using PTFE-SG.</li> </ul>	<ul style="list-style-type: none"> <li>a) diagnosis of cirrhosis determined on the basis of clinical history, histological examination, morphological characteristics of the liver at US, CT and MRI;</li> <li>b) TIPS creation using PTFE-SG.</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>a) placement of two or more coaxial stentgrafts;</li> <li>b) refusal to consent to have PTFE-SG dilated to a small diameter and/or to attend follow-up visits;</li> <li>c) TIPS placed in the setting of acute variceal hemorrhage either as “early” TIPS or as salvage TIPS for continued bleeding or early rebleeding;</li> <li>d) recurrent or persistent PSE;</li> <li>e) common absolute contraindications to TIPS<sup>1,2</sup></li> </ul>	<ul style="list-style-type: none"> <li>a) placement of two or more coaxial stentgrafts;</li> <li>b) evidence of lumen occlusion on CT;</li> <li>c) presence of solid or cystic lesions adjacent to the PTFE-SG;</li> <li>d) CT images that did not comply with the standards of quality detailed in Supplementary Materials and Methods.</li> </ul>

US, ultrasound; CT, computed tomography; MRI magnetic resonance imaging, PSE, porto-systemic encephalopathy; TIPS, trans-jugular intra-hepatic porto-systemic shunt; PTFE-SG, polytetrafluoroethylene-covered stent graft.

**Table 2:** Comparison of clinical and hemodynamic characteristics of the patients included in the Clinical Study according to employed dilatation balloon catheters.

	Standard TIPS	Under-dilated TIPS	
	≥8 mm (N=53) (CG) <sup>o</sup>	7 & 6 mm (N=42) (TG)	6 mm (N=47) (VG)
<b>Pre-TIPS</b>			
Alcohol as an etiology, N (%)	15 (28.3)	12 (28.6)	14 (29.8)
RA as an indication, N (%)	28 (52.8)	30 (71.4)	28 (59.6)
Days from index bleeding * (median)	28.6±24.1 (18) <sup>oo</sup>	18.8±11.6 (18) <sup>o</sup>	27.1±18.1 (20) <sup>o</sup>
Male gender, N (%)	35 (66.0)	27 (64.3)	32 (68.1)
Age (years) *	55.7±9.5	57.8±9.8	59.6±10.9
MELD score *	13.3±4.9	13.0±3.9	12.3±3.1
PSE, N (%)	4 (7.5)	2 (4.5)	4 (8.5)
Esophageal varices, N (%)	36 (67.9)	27 (64.3)	31 (65.9)
PCG (mmHg) *	24.7±4.6	22.8±3.8 <sup>^</sup>	23.3±5.1
<b>Post-TIPS</b>			
10 mm PTFE-SG, N (%)	45 (84.9)	30 (71.4)	37 (78.7)
Dilatation groups			
6 mm, N (%)	0 (0)	25 (59.5)	47 (100.0)
7 mm, N (%)	0 (0)	17 (40.5)	0 (0)
8 mm, N (%)	38 (71.7)	0 (0)	0 (0)
9 mm, N (%)	9 (17.0)	0 (0)	0 (0)
10 mm, N (%)	6 (11.3)	0 (0)	0 (0)
PCG (mmHg) *	10.5±5.2	11.3±3.7	12.6±3.1 <sup>^^</sup>
PCG <12 mmHg, N (%)	36 (67.9) <sup>#</sup>	21 (50.0)	23 (48.9)
PCG <10 mmHg, N (%)	30 (56.6)	12 (28.6) <sup>^</sup>	11 (23.4) <sup>^^</sup>
PCG ≥10<12 mmHg, N (%)	6 (11.3)	9 (21.4)	12 (25.5)
Percent PCG decrease *	56.8±15.1	49.0±13.2 <sup>^</sup>	44.5±12.6 <sup>^^</sup>

PCG reduction >50%, N (%)	39 (73.6)	20 (47.6) <sup>^</sup>	17 (36.2) <sup>^^</sup>
PCG re-evaluation during follow-up, N (%) <sup>†</sup>	6 (11.3)	6 (14.3)	7 (14.9)
MELD score after 30 days * (N)	16.3±5.3 (53)	14.3±4.1 (42) <sup>^</sup>	13.9±5.1 (47) <sup>^^</sup>
MELD score after 90 days * (N)	16.5±4.3 (52)	14.6±3.8 (38) <sup>^</sup>	13.6±4.8 (45) <sup>^^</sup>
MELD score after 180 days * (N)	15.9±5.0 (48)	14.4±4.3 (38)	13.8±4.3 (43) <sup>^^</sup>
MELD score at 1 year * (N)	15.7±4.0 (43)	14.1±4.4 (31)	13.5±4.7 (18)
1-year probability of PSE, (95% CI)	53.8 (40.2–67.8)	26.9 (12.9-40.8)	22.2 (9.7-34.7)
PSE severity, N (%)			
Grade II	12 (42.9)	7 (63.6)	6 (60)
Grade III	13 (46.4)	4 (36.4)	4 (40)
Grade IV	3 (10.7)	0	0 (0)
PSE time course, N (%)			
Episodic	23 (82.1)	9 (81.8)	8 (80)
Recurrent	4 (14.3)	2 (18.2)	2 (20)
Persistent	1 (3.6)	0 (0)	0 (0)
Triggered PSE, N (%)	6 (21.4)	3 (27.3)	3 (30)
Constipation	2 (7.1)	1 (9.1)	0 (0)
Infections	2 (7.1)	1 (9.1)	2 (20)
Dehydration (diuretic related)	2 (7.1)	1 (9.1)	1 (10)
TIPS reduction, N (%)	2 (3.8)	0 (0)	0 (0)
Esophageal varices, N (%)	2/17 <sup>§</sup> (11.8)	2/14 <sup>§§</sup> (14.3)	3/24 <sup>§§§</sup> (12.5)
HCC, N (%)	7 (13.2)	5 (11.9)	7 (14.9)
Death, N (%)	5 (9.4)	5 (11.9)	6 (12.8)
Liver disease related, N (%)	4 (80)	4 (80)	5 (83)
Liver transplant, N (%)	1(1.9)	1 (2.4)	3 (6.3)
Follow-up (days) **	348.6±11.6	325.9±15.1	301.2±17.9

7 patients of the TG were added to the CG due to PTFE-SG dilatation to 8 mm (Supplementary Figure 1). No difference in the comparisons of CG vs. TG was observed after removing these patients from the analysis.

<sup>¶</sup>5, 1 and 3 patients in CG, TG, and VG, respectively have been referred for TIPS after 6 weeks from index bleeding.

\*mean±SD; \*\*mean±SE.

<sup>^</sup>TG vs. CG, p<0.05; <sup>^^</sup>VG vs. CG, p<0.05.

<sup>#</sup>Among the 17 patients with a PCG ≥12 mmHg 5 had an 8 mm PTFE-SG, 2 were dilated to 10 mm, 10 had a too advanced liver disease and/or a PCG very close to the target.

<sup>¶¶</sup>PCG re-evaluation performed in the 7 patients (3, 2, and 2 in CG, TG, and VG, respectively) needing paracentesis 12 weeks after TIPS showed a PCG <12 mmHg (none of them needed LVP 6 months after TIPS). In the remaining 12 patients, PCG re-evaluation was performed for suspicious of TIPS dysfunction at follow-up US, but none of them showed significant increase of PCG in comparison to immediate post-TIPS values.

<sup>§</sup>17/37, <sup>§§</sup>14/26 <sup>§§§</sup>3/24 patients who had varices pre-TIPS had a post-TIPS endoscopy, respectively.

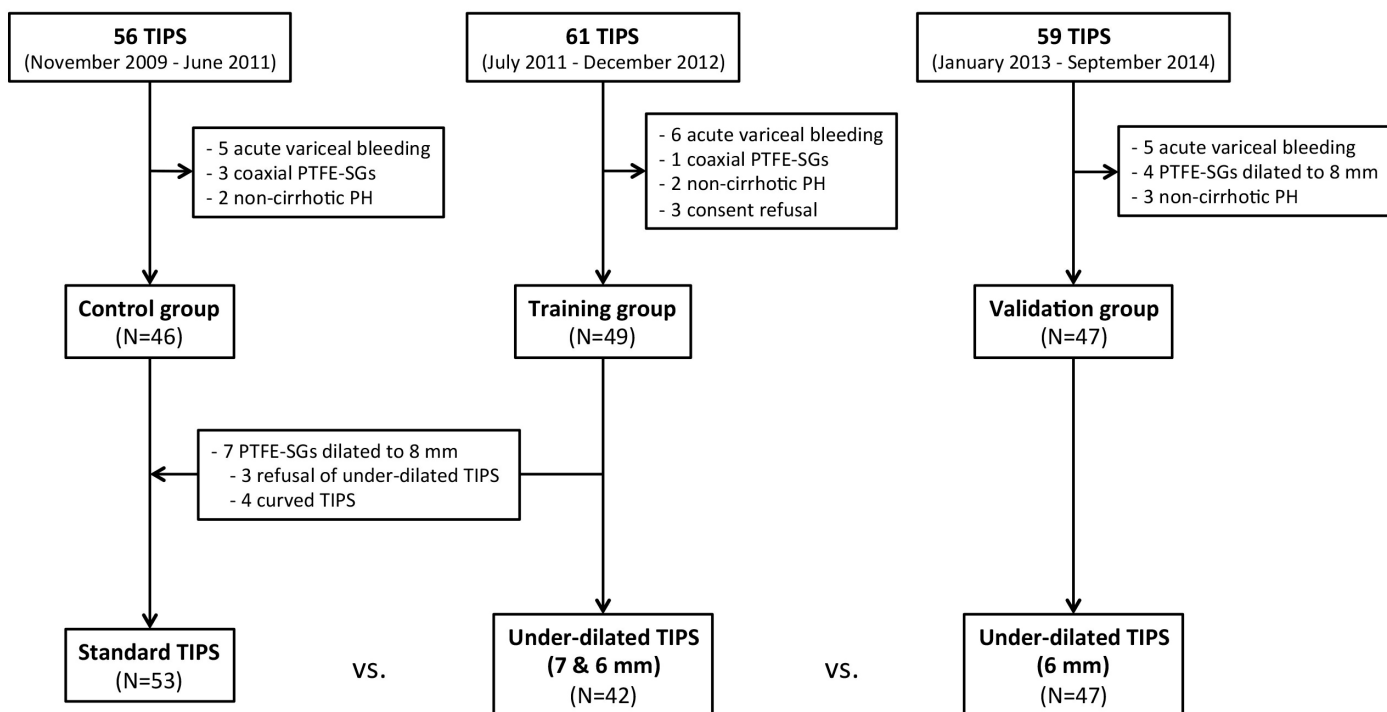
CG, control group; CI, confidence interval; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; PCG, porto-caval pressure gradient; PTFE-SG, polytetrafluoroethylene-covered stent graft; RA: refractory ascites; PSE, porto-systemic encephalopathy; TG, training group; TIPS, trans-jugular intra-hepatic porto-systemic shunt; US, ultrasound; VG, validation group.

**Table 3:** Competing risks regression models for 1-year post-TIPS PSE in the pooled groups of the Clinical Study (N=142).

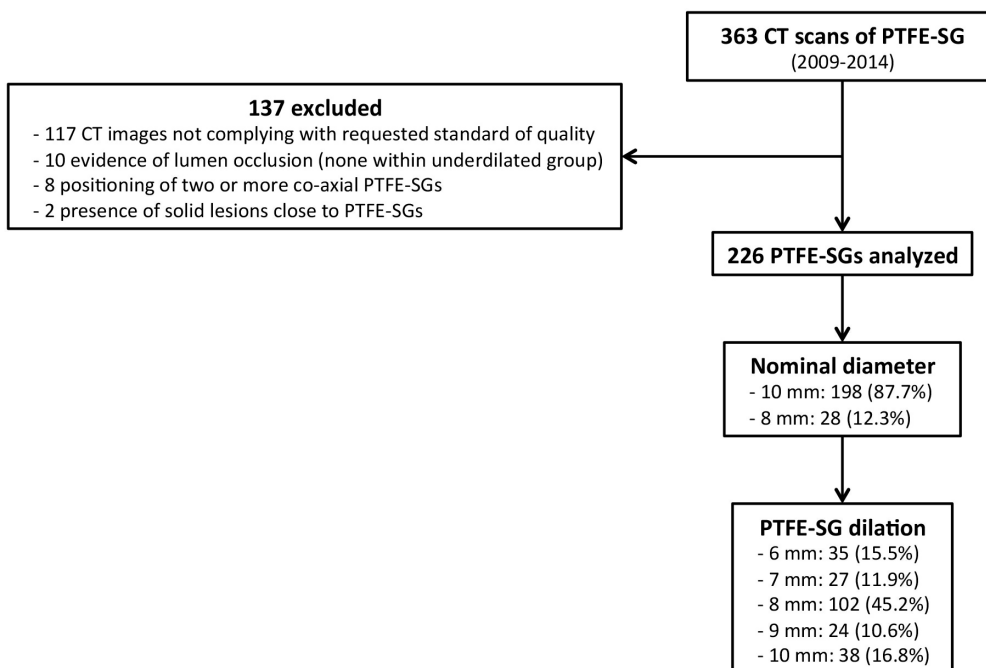
Model 1	Univariate analysis				Multivariate analysis		
	HR	95% CI	P value		HR	95% CI	P value
Indication (RA vs. VH)	0.85	0.49-1.18	.570		1.03	0.59-1.79	.920
Sex (Female vs. Male)	2.21	1.20-3.70	.009		1.91	1.07-3.40	.029
Age (years) (one unit increment)	1.04	1.01-1.06	.004		1.04	1.01-1.07	.003
MELD score (one unit increment)	1.04	0.98-1.11	.170		1.00	0.94-1.07	.880
Pre-TIPS PSE (Yes vs. No)	4.21	2.24-7.91	.00001		3.83	1.96-7.49	.0001
PTFE-SG dilatation (6 mm vs. >6 mm)	2.74	1.49-5.02	.001		2.17	1.16-4.05	.01
Post-TIPS PCG <10 mmHg (Yes vs. No)	2.98	1.71-5.20	.0001		1.89	1.04-3.44	.037
Model 2	HR	95% CI	P value		HR	95% CI	P value
Indication (RA vs. VH)	0.85	0.49-1.18	.570		0.99	0.56-1.75	.980
Sex (Female vs. Male)	2.21	1.20-3.70	.009		1.83	1.03-3.25	.039
Age (years) (one unit increment)	1.04	1.01-1.06	.004		1.04	1.01-1.07	.003
MELD score (one unit increment)	1.04	0.98-1.11	.170		1.01	0.95-1.07	.730
Pre-TIPS PSE (Yes vs. No)	4.21	2.24-7.91	.00001		4.18	2.28-7.68	.00001
PTFE-SG dilatation (6 mm vs. >6 mm)	2.74	1.49-5.02	.001		2.23	1.19-4.18	.01
Post-TIPS PCG reduction >50% (Yes vs. No)	2.70	1.47-4.96	.001		1.68	0.86-3.30	.130

CI, confidence interval; HR, hazard ratio; MELD, model for end-stage liver disease; PCG, porto-caval pressure gradient; PTFE-SG, polytetrafluoroethylene-covered stent graft; PSE, porto-systemic encephalopathy; RA, refractory ascites; TIPS, trans-jugular intra-hepatic porto-systemic shunt; VH, variceal hemorrhage.

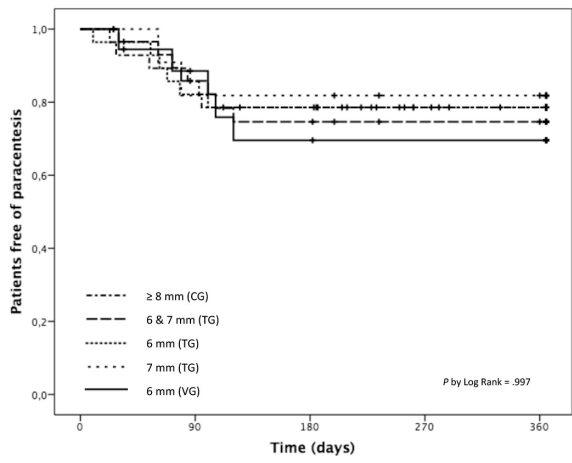
## (A) Clinical Study



## (B) Imaging Study



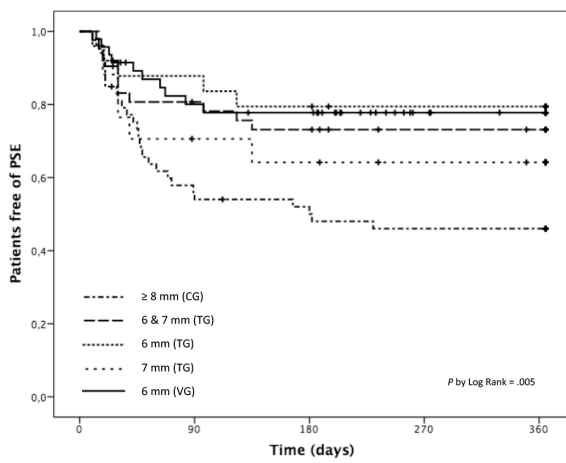
A



No. at Risk

- - - - -	28	24	20	18	17
- - - - -	30	23	20	17	16
·····	19	14	11	10	10
·····	11	9	9	7	6
———	28	23	22	12	9

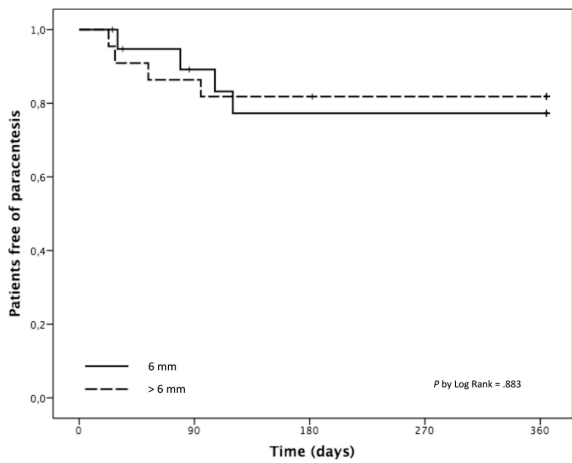
B



No. at Risk

- - - - -	53	28	25	23	23
- - - - -	42	32	29	25	24
·····	25	21	19	17	17
·····	17	11	10	8	7
———	47	35	33	17	14

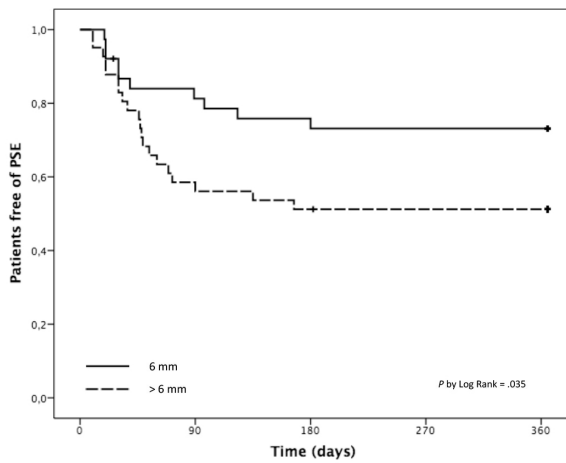
C



No. at Risk

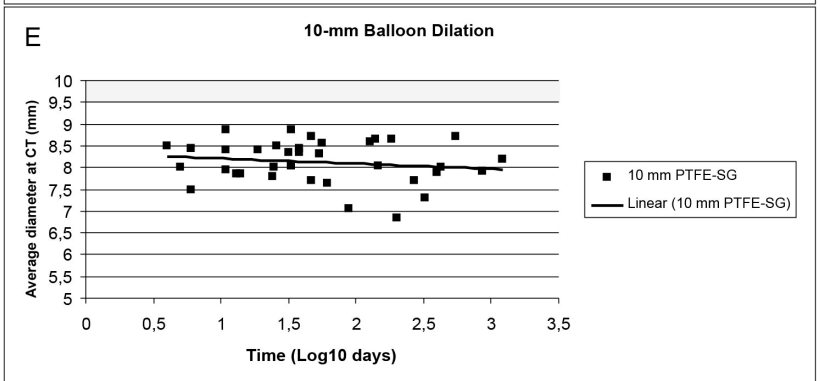
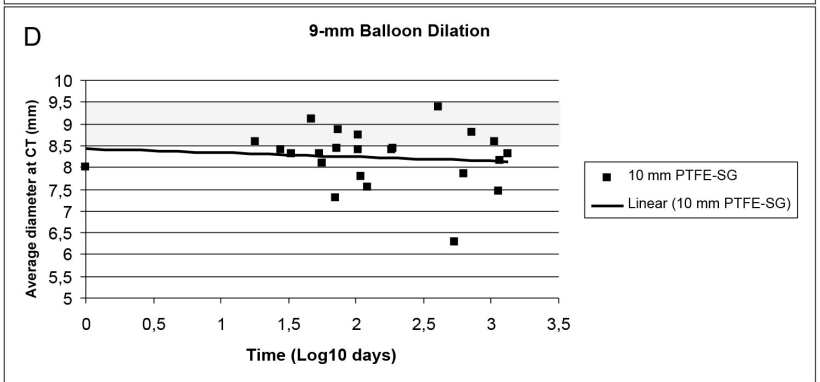
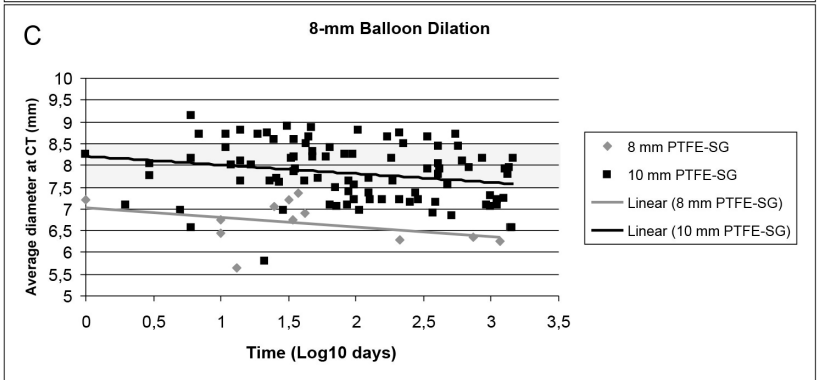
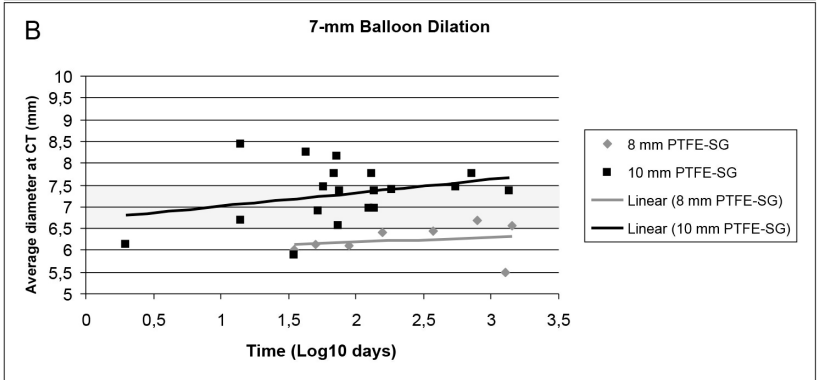
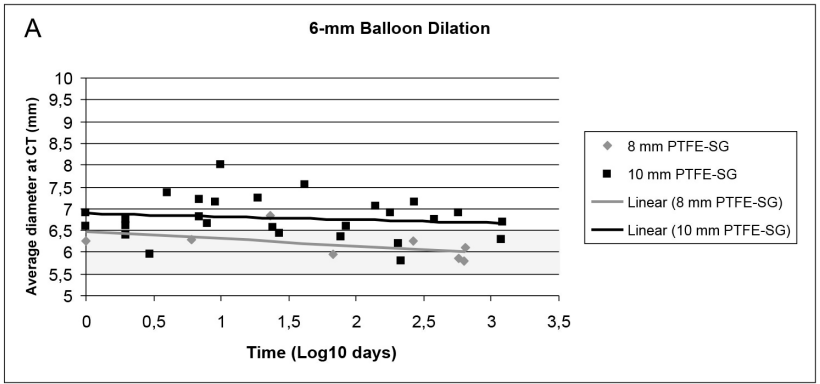
———	20	15	12	12	12
- - -	22	19	18	17	17

D



No. at Risk

———	38	30	27	27	27
- - -	41	23	21	20	20



## Supplementary Material and Methods

CT studies were sent in DICOM format to the coordinating Centers and analyzed by two independent radiologists (G.M. and L.R.) both unaware of the PTFE-SG nominal and dilatation diameters. The inter-observer agreement was evaluated in the whole cohort. Quantitative analysis was performed on CT scans meeting the following quality criteria: CT scanner with  $\geq 64$  detectors; acquisitions timed to study venous hepatic components; slice thickness of 2.5 mm or less with an interval of 1.25 mm or less; attenuation based automatic tube voltage limits between 120 and 500 mA; 120 kv tube current; absence of major respiratory-/motion-induced or beam hardening artifacts. To obtain homogeneous enhancement of the stent-graft lumen, wall scans were reconstructed using the venous phase of CT studies. Reformatted images of the planes perpendicular to the stent-graft at each of the four standard sites were obtained using Advantage Workstation 4.6 reconstruction console (GE Healthcare, Waukesha, Wisconsin) optioned with the double oblique multi-planar reconstruction application. By simultaneously working on two windows, it was possible to identify sections perpendicular to the stent-graft at each given point, regardless of its in vivo spatial orientation. Keeping the image centered on the lumen of the stent graft on a pure axial plane, a para-coronal plane was selected, which contained the luminal tract to be measured. On this second image a plane orthogonal to the stent-graft was obtained and used to measure the true largest inner diameter. To minimize blooming artifacts, the window settings were adjusted at 1500 Hounsfield Unit with a center of 300 HU.

**Supplementary Table 1:** Comparison of main clinical and hemodynamic characteristics of patients included in the Clinical Study with PTFE-SG under-dilated to 6 mm.

	6 mm (N=25) (TG)	6 mm (N=47) (VG)
<b>Pre-TIPS</b>		
Alcohol as an etiology, N (%)	7 (28)	14 (29.8)
RA as an indication, N (%)	19 (76)	28 (59.6)
Days from index bleeding * (median)	15.5±4.9 (15) <sup>o</sup>	27.1±18.1 (20) <sup>o</sup>
Male gender, N (%)	17 (68)	32 (68.1)
Age (years) *	55.6±9.7	59.6±10.9
MELD score *	12.6±3.8	12.3±3.1
PSE, N (%)	1 (4)	4 (8.5)
Esophageal varices, N (%)	16 (64)	31 (65.9)
PCG (mmHg) *	22.1±3.7	23.3±5.1
<b>Post-TIPS</b>		
10 mm PTFE-SG N,(%)	19 (76.0)	37 (78.7)
PCG (mmHg) *	11.6±2.0	12.6±3.1
PCG <12 mmHg, N (%)	13 (52)	23 (48.9)
PCG <10 mmHg, N (%)	6 (24)	11 (23.4)
PCG ≥10<12 mmHg, N (%)	7 (28)	12 (25.5)
Percent PCG decrease *	46.7±9.2	44.5±12.6
PCG reduction >50%, N (%)	9 (36)	17 (36.2)
PCG re-evaluation, N (%) <sup>¶</sup>	4(16)	7(14.9)
MELD score after 30 days * (N)	13.5±4.9 (25)	13.9±5.1 (47)
MELD score after 90 days * (N)	13.7±4.7 (22)	13.6±4.8 (45)
MELD score after 180 days * (N)	13.4±5.0 (21)	13.8±4.3 (43)
MELD score at 1 year * (N)	13.3±5.1 (18)	13.5±4.7 (18)
1-year probability of PSE, (95% CI)	20.5 (4.2-36.3)	22.2 (9.7-34.7)

PSE severity, N (%)		
Grade II	3 (60)	6 (60)
Grade III	2 (40)	4 (40)
Grade IV	0 (0)	0 (0)
PSE time course, N (%)		
Episodic	4 (80)	9 (80)
Recurrent	1 (20)	2 (20)
Persistent	0 (0)	0 (0)
Triggered PSE, N (%)	2 (40)	3 (30)
Constipation	0 (0)	0 (0)
Infections	1 (20)	2 (20)
Dehydration (diuretic related)	1 (20)	1 (10)
TIPS reduction, N (%)	0(0)	0(0)
Esophageal varices, N (%)	1/10 <sup>§</sup> (10)	3/24 <sup>§§</sup> (12.5)
HCC, N (%)	3 (12)	7 (14.9)
Death, N (%)	4 (16)	6 (12.8)
Liver disease related, N (%)	3 (75)	5 (83)
Liver transplant, N (%)	1 (40)	3 (6.3)
Follow-up (days) **	335±15.6	301±17.9

0 and 3 patients in 6 mm and >6 mm, respectively have been referred for TIPS after 6 weeks from the index bleeding.

\*mean±SD; \*\*mean±SE.

<sup>¶</sup>PCG re-evaluation performed in the 4 patients (2 in each group) needing paracentesis 12-weeks after TIPS showed a PCG <12 mmHg (none of them needed LVP 6 months after TIPS). In the remaining 7 patients, PCG re-evaluation was performed for suspicious of TIPS dysfunction at follow-up US, but none of them showed significant increase of PCG in comparison to immediate post-TIPS values.

<sup>§</sup>10/16 and <sup>§§</sup>3/24 patients who had varices pre-TIPS had a post-TIPS endoscopy, respectively.

CG, control group; CI, confidence interval; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; PCG, porto-caval pressure gradient; PTFE-SG, polytetrafluoroethylene-covered stent graft; RA: refractory ascites; PSE, porto-systemic encephalopathy; TG, training group; TIPS, trans-jugular intra-hepatic porto-systemic shunt; US, ultrasound; VG, validation group.

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**Supplementary Table 2:** Competing risks regression models for 1-year post-TIPS PSE in the pooled groups of the Clinical Study after removing patients with pre-TIPS PSE (N=132).

Model 1	Univariate analysis				Multivariate analysis		
	HR	95% CI	P value		HR	95% CI	P value
Indication (RA vs. VH)	0.89	0.48-1.64	.700		1.02	0.51-2.01	.960
Sex (Female vs. Male)	2.63	1.20-4.07	.011		1.54	0.79-2.97	.200
Age (years) (one unit increment)	1.04	1.01-1.07	.004		1.05	1.02-1.08	.002
MELD score (one unit increment)	1.04	0.97-1.11	.280		1.01	0.93-1.10	.770
PTFE-SG dilatation (6 mm vs. >6 mm)	2.94	1.50-5.73	.001		2.50	1.22-5.13	.012
Post-TIPS PCG <10 mmHg (Yes vs. No)	2.99	1.63-5.84	.00001		2.18	1.15-4.12	.017
Model 2	HR	95% CI	P value		HR	95% CI	P value
Indication (RA vs. VH)	0.89	0.48-1.64	.700		0.92	0.47-1.82	.820
Sex (Female vs. Male)	2.63	1.20-4.07	.011		1.56	0.81-3.01	.190
Age (years) (one unit increment)	1.04	1.01-1.07	.004		1.04	1.01-1.08	.004
MELD score (one unit increment)	1.04	0.97-1.11	.280		1.02	0.95-1.10	.540
PTFE-SG dilatation (6 mm vs. >6 mm)	2.94	1.50-5.73	.001		2.42	1.13-5.19	.023
Post-TIPS PCG reduction >50% (Yes vs. No)	2.90	1.48-5.67	.002		1.90	0.91-3.98	.088

CI, confidence interval; HR, hazard ratio; MELD, model for end-stage liver disease; PCG, porto-caval pressure gradient; PTFE-SG, polytetrafluoroethylene-covered stent graft; PSE, porto-systemic encephalopathy; RA, refractory ascites; TIPS, trans-jugular intra-hepatic porto-systemic shunt; VH, variceal hemorrhage.

**Supplementary Table 3:** Propensity score\* adjusted multivariate models for 1-year post-TIPS PSE in the pooled groups of the Clinical Study (N=142) (A) and in patients without pre-TIPS PSE (N=132) (B).

<b>A</b>			
<b>Model 1</b>	<b>HR</b>	<b>95% CI</b>	<b>P value</b>
PTFE-SG dilatation (6 mm vs. >6 mm)	2.06	1.07-3.95	.030
Post-TIPS PCG <10 mmHg (Yes vs. No)	2.54	1.40-4.59	.002
<b>Model 2</b>	<b>HR</b>	<b>95% CI</b>	<b>P value</b>
PTFE-SG dilatation (6 mm vs. >6 mm)	2.23	1.16-4.29	.016
Post-TIPS PCG reduction >50% (Yes vs. No)	2.25	1.17-4.33	.015
<b>B</b>			
<b>Model 1</b>	<b>HR</b>	<b>95% CI</b>	<b>P value</b>
PTFE-SG dilatation (6-mm vs. >6 mm)	2.22	1.07-4.61	.032
Post-TIPS PCG <10 mmHg (Yes vs. No)	2.60	1.34-5.02	.004
<b>Model 2</b>	<b>HR</b>	<b>95% CI</b>	<b>P value</b>
PTFE-SG dilatation (6 mm vs. >6 mm)	2.35	1.12-4.92	.023
Post-TIPS PCG reduction >50% (Yes vs. No)	2.36	1.13-4.94	.023

\*Propensity scores were the estimated probabilities of >6 mm PTFE-SG dilatation, calculated by means of a logistic regression model including all available pre-TIPS covariates (age, sex, pre-TIPS MELD score, TIPS indication, pre-TIPS PSE, pre-TIPS PCG). In this latter model only pre-TIPS PCG was associated to >6 mm PTFE-SG dilatation (OR=1.09; 95%CI: 1.00–1.17;  $P=.0392$ ). A Fine & Gray model was fit using cubic polynomial smoothing based on propensity score values, PTFE-SG dilatation (>6 mm vs. 6 mm) and either post-TIPS PCG <10 mmHg or post-TIPS PCG decrease >50% as independent variables.

CI: confidence interval; HR: hazard ratio; PCG, porto-caval pressure gradient; PTFE-SG, polytetrafluoroethylene-covered stent graft; PSE, porto-systemic encephalopathy; TIPS, trans-jugular intra-hepatic porto-systemic shunt.

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**Supplementary Table 4:** Comparison of main clinical and hemodynamic characteristics of patients included in the Clinical Study according to PTFE-SG dilatation equal or above 6 mm at TIPS positioning.

	<b>ALL (N=142)</b>	<b>6 mm (N=72)</b>	<b>&gt;6 mm (N=70)</b>	<b>P value</b>
RA as an indication, N (%)	86 (60.6)	47 (65.3)	39 (55.7)	.320
Male gender, N (%)	94 (66.2)	49 (68.1)	45 (64.3)	.227
Age (years) *	57.6±10.2	58.2±10.7	57.0±9.7	.471
MELD score *	12.8±4.1	12.4±3.4	13.1±4.3	.205
Pre-TIPS PSE, N (%)	10 (7.0)	5 (6.9)	5 (7.1)	.999
Pre-TIPS PCG (mmHg) *	23.7±4.6	22.9±4.6	24.5±4.4	.038
Post-TIPS PCG (mmHg) *	11.5±3.5	12.2±2.8	10.7±3.9	.006
Post-TIPS PCG <10 mmHg, N (%)	53 (37.3)	17 (23.6)	36 (51.4)	.0009
Post-TIPS percent PCG decrease *	50.4±14.6	45.3±11.5	55.7±15.7	.00002
Post-TIPS PCG reduction >50%, N (%)	76 (53.5)	26 (36.1)	50 (71.4)	.0001

\*mean±SD

MELD, model for end-stage liver disease; PCG, porto-caval pressure gradient; PTFE-SG, polytetrafluoroethylene-covered stent graft; PSE, porto-systemic encephalopathy; RA: refractory ascites; TIPS, trans-jugular intra-hepatic porto-systemic shunt.

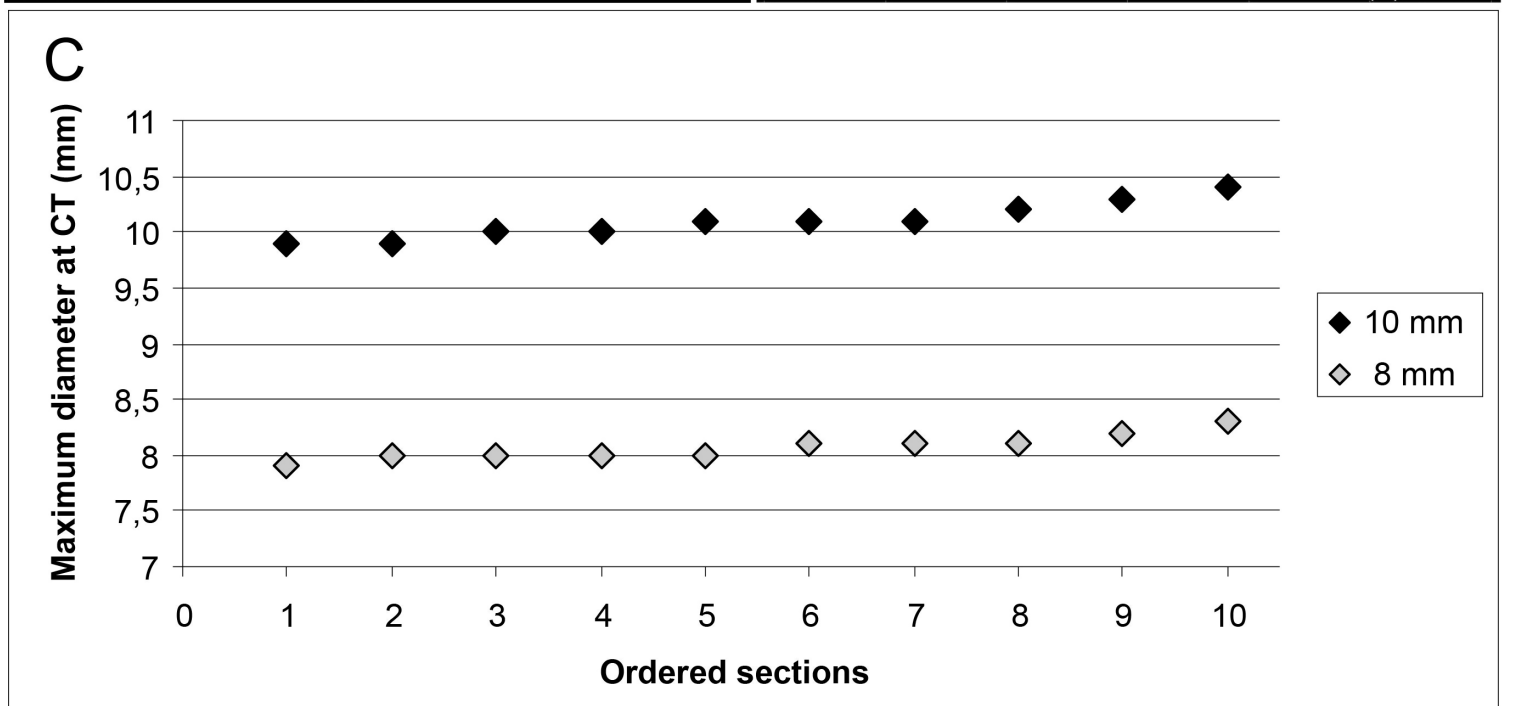
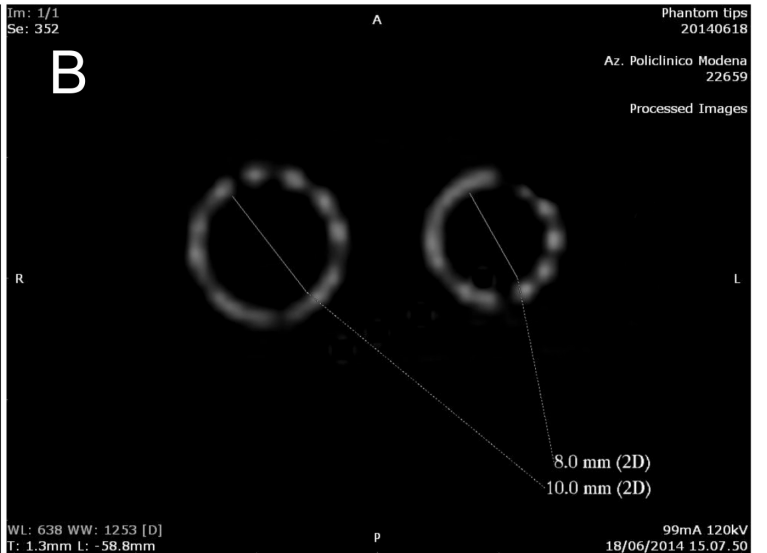
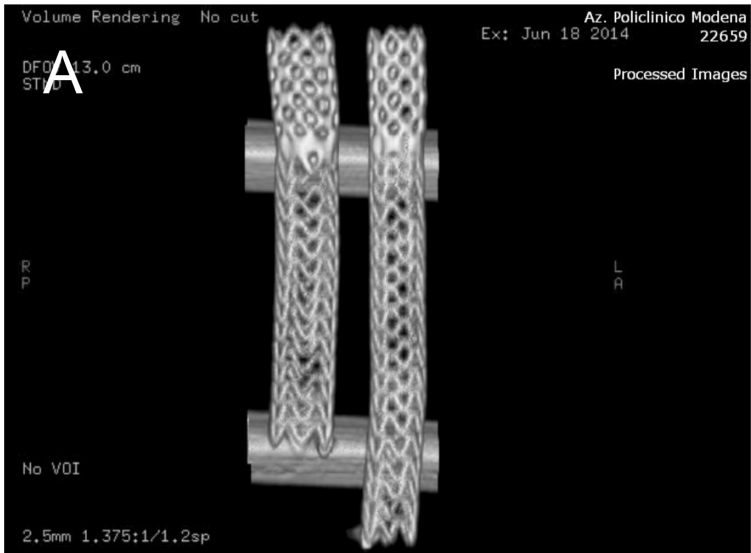
**Supplementary Table 5:** Main clinical and hemodynamic characteristics of the patients included in the Clinical Study and grouped according PTFE-SG diameter measured at CT (N=79).

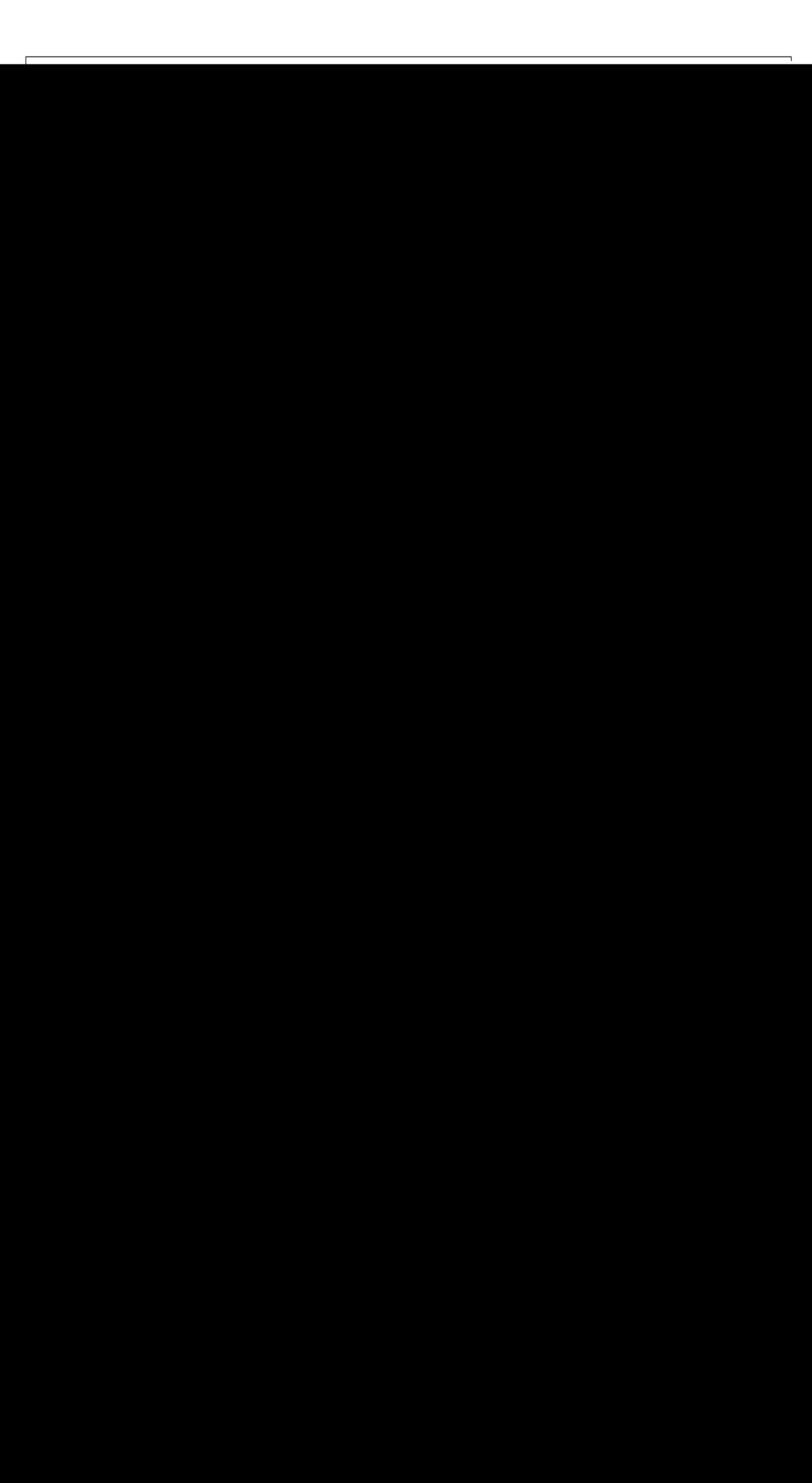
	6 mm (N=38) <sup>§</sup>	>6 mm (N=41)
Alcohol as an etiology, N (%)	11 (28.9)	13 (31.7)
RA as an indication, N (%)	20 (52.6)	22 (53.7)
Male gender, N (%)	24 (63.2)	30 (73.2)
Age (years) *	57.0±9.9	58.6±9.4
MELD score *	13.5±4.9	12.9±4.1
Pre-TIPS PSE, N (%)	2(5.3)	3(7.3)
Pre-TIPS PCG (mmHg) *	23.2±3.4	24.1±4.1
Post-TIPS PCG (mmHg) *	11.7±2.8	10.1±3.4 <sup>^</sup>
Post-TIPS percent PCG decrease, *	47.8±13.6	58.5±14.9 <sup>^</sup>
1-year probability of PSE, (95% CI)	26.7 (15.8-38.5)	48.2 (38.9-59.3)
Follow-up (days) **	315.6±18.7	339.6±12.8

<sup>§</sup>Patients in the 6-mm group had a PTFE-SG diameter of 6±0.5-mm at PVW and/or HWV;

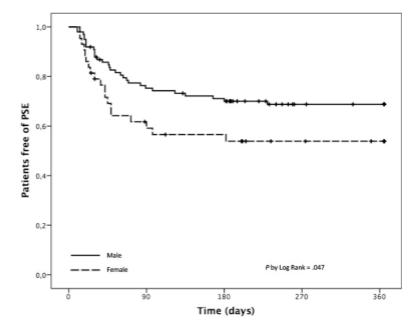
\*mean±SD; \*\*mean±SE; <sup>^</sup>p<0.05; <sup>^</sup>p<0.05

CI, confidence interval; MELD, model for end-stage liver disease; PCG, porto-caval pressure gradient; PTFE-SG, polytetrafluoroethylene-covered stent graft; RA: refractory ascites; PSE, porto-systemic encephalopathy; TIPS, trans-jugular intra-hepatic porto-systemic shunt.





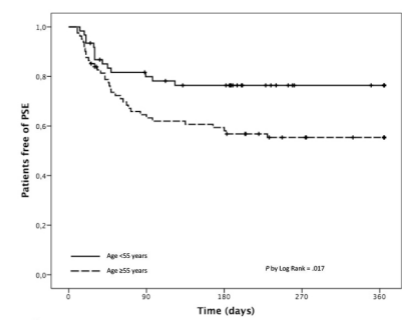
**A**



No. at Risk

—	99	72	66	49	47
- - -	43	24	21	16	14

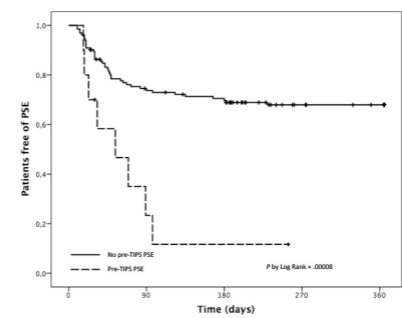
**B**



No. at Risk

—	61	46	42	28	27
- - -	81	49	45	37	34

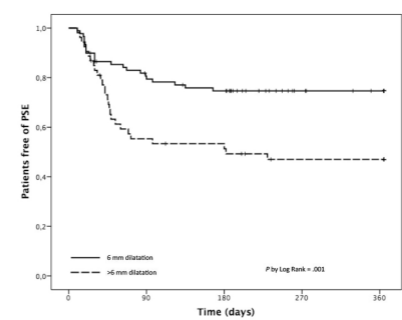
**C**



No. at Risk

—	132	93	86	65	61
- - -	10	2	1	0	0

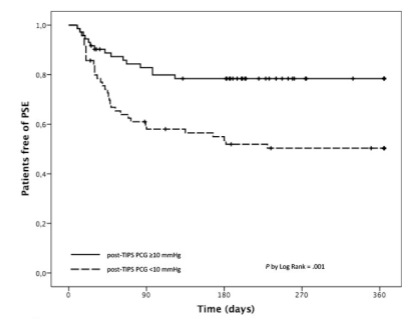
**D**



No. at Risk

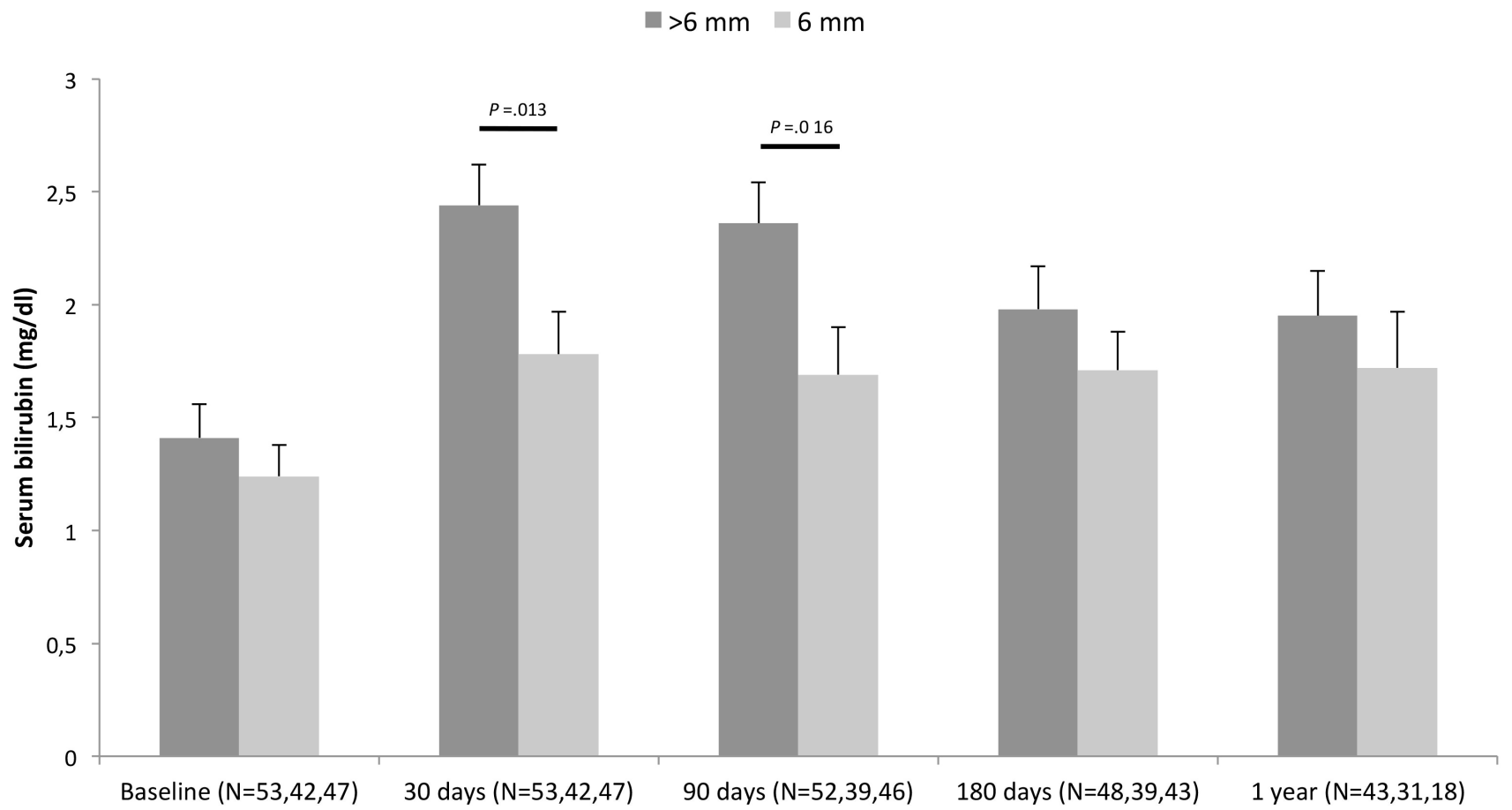
—	72	56	52	34	31
- - -	70	39	35	31	30

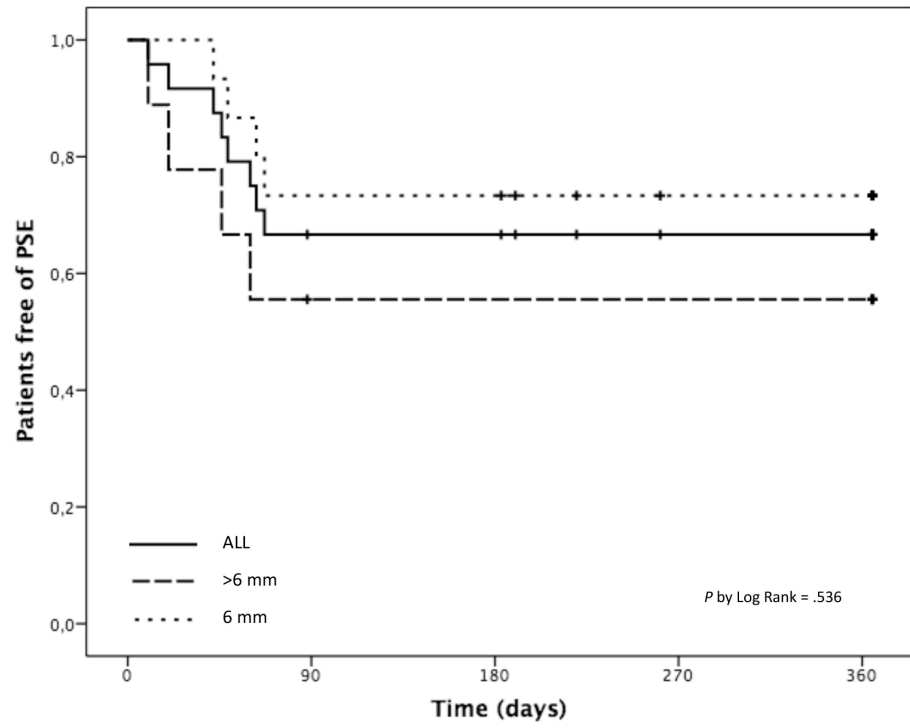
**E**



No. at Risk

—	89	67	62	45	41
- - -	53	28	25	20	20





**No. at Risk**

Time (days)	0	90	180	270	360
— ALL	24	15	15	11	11
- - - >6 mm	9	4	4	4	4
..... 6 mm	15	11	11	7	7