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Economic evaluation of covered stents for transjugular intrahepatic portosystemic stent shunt in patients with variceal bleeding and refractory ascites secondary to cirrhosis

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ABSTRACT

Objectives Transjugular intrahepatic portosystemic stent shunt (TIPSS) is clinically effective in variceal bleeding and refractory ascites; however, the cost-effectiveness of TIPSS has yet to be evaluated in the UK. This study aimed to establish the cost-effectiveness of (i) pre-emptive TIPSS versus endoscopic band ligation (EBL) in populations with variceal bleeding and (ii) TIPSS versus large volume paracentesis (LVP) in refractory ascites.

Methods A cost-utility analysis was conducted with the perspective including healthcare costs and quality-adjusted life years (QALYs). A Markov model was constructed with a 2-year time horizon, health states for mortality and survival and probabilities for the development of variceal bleeding, ascites and hepatic encephalopathy. A survival analysis was conducted to extrapolate 12-month to 24-month mortality for the refractory ascites indication. Uncertainty was analysed in deterministic and probabilistic sensitivity analyses.

Results TIPSS was cost-effective (dominant) and cost saving for both indications. For variceal bleeding, pre-emptive TIPSS resulted in 0.209 additional QALYs, and saved £600 per patient compared with EBL. TIPSS had a very high probability of being cost-effective (95%) but was not cost saving in scenario analyses driven by rates of variceal rebleeding. For refractory ascites, TIPSS resulted in 0.526 additional QALYs and saved £17 983 per patient and had a 100% probability of being cost-effective and cost saving when compared with LVP.

Conclusions TIPSS is a cost-effective intervention for variceal bleeding and refractory ascites. TIPSS is highly cost-saving for refractory ascites. Robust randomised trial data are required to confirm whether pre-emptive TIPSS is cost saving for variceal bleeding.

Summary box

What is already known about this subject?

- Pre-emptive transjugular intrahepatic portosystemic stent shunt (TIPSS) is considered to be clinically effective versus endoscopic band ligation (EBL) plus drug therapy in patients with cirrhosis and variceal bleeding who are haemodynamically stable. TIPSS is also clinically effective versus large volume paracentesis (LVP) plus human albumin in the management of patients with cirrhosis and refractory ascites.
- Robust economic analysis with regard to use of TIPSS for these clinical indications is lacking.

What are the new findings?

- Economic modelling, using methodology endorsed by National Institute for Health and Care Excellence (NICE), found that pre-emptive TIPSS was likely to be cost-effective in patients with cirrhosis and variceal bleeding versus treatment with EBL and beta blockers. However, there are high levels of uncertainty as to whether TIPSS is cost-saving in the context of the National Health Service (NHS).
- TIPSS was cost-effective as well as cost saving when compared with LVP plus albumin in patients with cirrhosis and refractory ascites. Substantial cost savings to the NHS are forecast from a reduced need for continued LVP sessions to drain ascitic fluid.

How might it impact on clinical practice in the foreseeable future?

- The evidence from this study supports the continued use of TIPSS in patients with cirrhosis and refractory ascites. Further well-conducted multicentre trials are required to confirm the cost saving potential of TIPSS for the variceal bleeding indication.
- These results could be used to revise recommendations made by commissioners and inform regulators, such as NICE and NHS England.

BACKGROUND

Cirrhosis of the liver imposes a substantial and increasing health burden being responsible for 2.4% of all deaths in the UK.[1] The NHS cost of liver disease were forecast to exceed £1 billion in 2015–2016.[2] The majority of the clinical and economic burden in cirrhosis occurs in patients with decompensated cirrhotic disease, the most common clinical manifestations of which are recurrent

variceal bleeding and recurrent and refractory ascites (RA).[3] Both variceal bleeding and RA are associated with significant impairment in length and quality of life.[4–6]

Treatment options for variceal bleeding and ascites include endoscopic band ligation (EBL) and large-volume paracentesis (LVP), respectively. Both indications can also be managed by transjugular intrahepatic portosystemic stent shunt (TIPSS). TIPSS procedures were originally conducted using bare metal stents, but these had relatively poor patency, requiring re-interventions and are associated with an increase in the incidence of hepatic encephalopathy (HE).[7] Clinical outcomes have improved since the early 2000s following the introduction of expanded polytetrafluoroethylene (ePTFE) covered stents.[7–9]

When compared with EBL, randomised controlled trial (RCT) evidence indicates TIPSS with an ePTFE covered stent is likely to be clinically effective if delivered as a pre-emptive procedure in populations with haemodynamically stable variceal bleeding. Conclusive RCT evidence has identified increased survival and reduced cirrhosis related adverse event rates for TIPSS vs LVP in RA populations.[10 11] Such findings informed UK clinical guidelines which recommend TIPSS with covered stents for the management of variceal bleeding and RA in these patient populations.[12 13]

While TIPSS improves health morbidity and mortality, the procedure incurs substantial healthcare costs and is delivered to populations with relatively severe disease and poor long-term prognosis.[10 11] It is questionable whether TIPSS offers value for money when compared with other interventions that could be funded within the budget constrained UK health sector. There is a paucity of evidence establishing the cost-effectiveness of TIPSS with ePTFE covered stents for variceal bleeding and RA in the UK.[14] Uncertainty regarding the cost-effectiveness of TIPSS may be reflected in National Institute for Health and Care Excellence (NICE) guidelines which include 'consider' rather than 'offer' recommendation for TIPSS for RA.[14–16]

The aim of this study was to examine the cost-effectiveness of TIPSS using ePTFE covered stents in the UK, for the following indications:

- Indication 1: Patients with cirrhosis, haemodynamically stable variceal bleeding and moderate to severe hepatic dysfunction. Pre-emptive TIPSS is delivered within the first 72 hours of the index bleed following first-line EBL and drug therapy. The comparator is continued EBL and drug therapy.
- Indication 2: Patients with cirrhosis and RA. The comparator is LVP plus albumin.

METHODOLOGY

A cost-utility analysis was conducted for a UK population adopting methods specified by NICE[16] including costs incurred by the NHS and personal social services and health benefits measured as quality-adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER) of TIPSS versus standard care was estimated using a cost-effectiveness threshold of £20 000/QALY. A discount rate of 3.5% was applied to costs and QALYs.[16] The impact of TIPSS on healthcare resources, primarily hospital bed-days, was also reported.

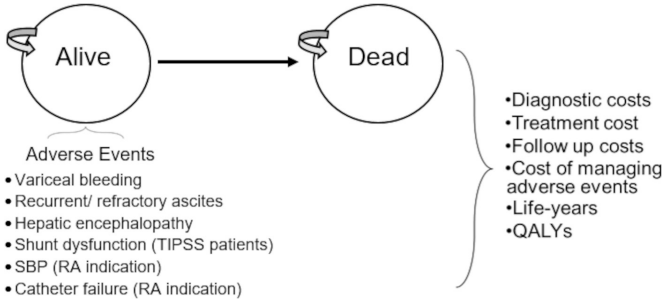

Figure 1 Structure of the Markov model. QALY, quality-adjusted life year; RA, refractory ascites; SBP, spontaneous bacterial peritonitis; TIPSS, transjugular intrahepatic stent shunt.

Authors DT, GA and DP provided expert clinical advice as key opinion leaders (KOLs) to:

- Validate the model structure, treatment pathways, clinical data and model parameters for TIPSS and standard care.
- Provide costs where no published data were available.

Economic model

A Markov model was developed with health states of 'alive' and 'dead', over a 2-year time horizon, with cycle lengths equal to 1 month with a half-cycle correction (figure 1). Monthly all-cause mortality rates were estimated based on survival curves sourced from RCT evidence. Key adverse events associated with liver cirrhosis were assigned per cycle to the 'alive' population based on monthly probabilities. Three adverse events were assigned to all populations: variceal bleeding, recurrent and RA and HE, classified as mild (grade I or II) or severe (grade III or IV).[17] Shunt dysfunction was included as a procedure-related adverse event for TIPSS. Spontaneous bacterial peritonitis (SBP) and catheter failure were included as adverse events for RA populations receiving standard care. To avoid double counting, we did not include specific mortality risk per adverse event as these were captured within the all-cause rates.

Prior to entering the model, TIPSS populations were assigned to a treatment pathway based on procedural technical success rates. Where TIPSS resulted in a technical failure, patients entered the standard care arm.

In both arms, the following are summed:

- Total costs of: relevant diagnostics, treatments, follow-up and management of complications/adverse events.
- Total QALYs.

Population and clinical pathways

The analysis was conducted for two indications recommended by UK clinical guidelines for TIPSS.[12–15]

Indication 1

Patients with cirrhosis and variceal bleeding who were haemodynamically stable. Populations received a pre-emptive TIPSS procedure within 72 hours of the index bleed, following first-line treatment with EBL and pharmaceuticals. The population were age 18 or over including both Child's C and B disease with a maximum score of 13. Patients in whom acute variceal bleeding was refractory to endoscopic and pharmacological measures who received salvage TIPSS were excluded. The comparator, standard care, comprised of:

- Four outpatient EBL sessions, during the first 2 months
- Three follow-up outpatient EBL sessions at 6, 12 and 24 months.
- A beta-blocker (either carvedilol, propranolol or nadolol).

Indication 2

Patients with cirrhosis and RA. Refractory status was defined as per UK guidelines, that is, ascites that cannot be mobilised or early recurrence of which (after therapeutic paracentesis) cannot be prevented by medical therapy.[13] TIPSS was performed as an elective inpatient procedure following initial treatment with LVP. The comparator, standard care, comprised of further LVP and albumin. KOLs advised that patients in standard care with RA would require LVP sessions every 14 days.

In both indications, common exclusion criteria for TIPSS included: significant pulmonary hypertension, heart failure, rapidly progressing liver failure, severe or uncontrolled HE, sepsis, unrelieved biliary obstruction, primary or metastatic hepatic malignancy and polycystic liver disease.[12]

Model parameters

Clinical parameters

Clinical parameters were identified through a systematic literature review (online supplemental appendix 1).[18] In summary, an electronic literature search was conducted for clinical, safety and economic studies of TIPSS in portal hypertension, oesophageal and gastric varices and ascites. After deduplication, 5502 remained for screening, 5209 were excluded at title and abstract review, with 293 included for full text review. In total, 10 RCTs and 10 economic studies were identified.

Indication 1—variceal bleeding

Base case parameter values were informed predominantly by the Garcia-Pagán *et al* RCT.[10] The study reported actuarial probabilities of survival at 12 months equal to 86% (TIPSS) and 61% (EBL), with no additional mortality reported between months 12 and 24. Probabilities for adverse events were obtained at 12-month and/or 24-month endpoints as reported by Garcia-Pagán *et al*.[10]

Indication 2—refractory ascites

Bureau *et al* was considered to be the most relevant RCT, reporting 12-month actuarial survival curves for TIPSS versus LVP in RA.[11] We calculated survival probabilities at 24 months by constructing parametric survival curves with a log normal survival function based on the 12-month patient data in Bureau *et al* (online supplemental appendix 2).[11]

Clinical parameter values are reported in table 1. All values were converted to rates per month to align with the model's cycle duration. Where published data were only available across a 12-month time horizon, monthly event rates for months 1–12 were applied across the full 24 months. All data were obtained from RCTs or meta-analyses excluding two observational studies which informed the technical success rate for TIPSS, equal to 98%,[19] and the rate of catheter failure for patients with LVP equal to 3.8%.[20] In addition, we followed methods by Shen *et al*[21] and applied a conservative assumption for the rate of recurrent bleeding for TIPSS patients in the RA indication, set equal to 4.4% as opposed to 0% in Bureau *et al*.[11]

Healthcare resource usage and unit costs

TIPSS and standard care

We conducted pragmatic literature searches of UK and European clinical guidelines and economic studies to identify resource use and unit costs. Resources required for the preoperative, intraoperative and postoperative phases of TIPSS were extracted from UK clinical guidelines.[12 13] The KOLs estimated an average length of stay equal to 2 days per elective and 5 days per non-elective TIPSS. Costs per excess bed day were calculated from NHS reference costs as weighted average across TIPSS tariffs YR16A and YR16B.[22] Resources for standard care were identified from published literature, with KOLs advising on consistency with UK clinical practice. Unit costs were from national databases,[22–24] with gaps informed by the KOLs. The model used 2017/2018 prices. Dossiers reporting the resources and unit cost were reviewed by KOLs, in an iterative process, until a consensus was reached.

Resource and unit cost for TIPSS and standard care are summarised in table 2 and fully detailed in online supplemental appendix 3. TIPSS for variceal bleeds were non-elective, costing £5398; TIPSS for RA were elective, costing £4646 per procedure. All cases of technical failure had an additional procedure time of 2 hours and required an additional VIATORR stent. In comparison, standard care costs for variceal bleeding (EBL plus beta-blockers) were £3862, per patient assuming 24-month survival. Standard care costs for RA were £800 per LVP session, occurring every 14 days, summing to £41 618 per patient assuming 24-month survival.

Complications and adverse events

Table 2 and online supplemental appendix 3 detail the treatment assumptions applied per adverse event. In brief, a TIPSS shunt dysfunction required reintervention with a balloon catheter costing £4095. Variceal bleeding episodes were treated with terlipressin and required an

Table 1 Clinical parameters

	Indication 1: variceal bleeding			Indication 2: refractory ascites		
	TIPSS	Standard care	Source	TIPSS	Standard care	Source
Survival at 12 months	0.860	0.610	10	0.928*	0.553*	11
Survival at 24 months	0.860	0.610	10	0.890*	0.241*	11
TIPSS technical success	0.980	N/A	19	0.980	N/A	19
Shunt dysfunction	0.070	N/A	40	0.030	N/A	11
Variceal bleeding at 12 months	0.030	0.500	10	0.044†	0.182	21; 11
Variceal bleeding at 24 months	0.030	0.500	10	Assume same rates as 12 months		
Ascites at 12 months	0.130	0.330	10	0.510	1.000	41
HE at 12 months	0.280	0.400	10	0.345	0.333	11
% HE severe‡	0.250	0.250	KOLs	0.400	0.636	11
SBP at 12 months	N/A	N/A	N/A	N/A	0.060	11
Catheter failure at 12 months	N/A	N/A	N/A	N/A	0.038§	20

*Survival rates for indication 2 were obtained by estimating parametric survival curves with a lognormal survival function, using 12-month patient data reported in Bureau *et al*. For further details, see online supplemental appendix 2).
†Conservative assumption applied as per economic evaluation of TIPSS for RA by Shen *et al*.[21] The rate of variceal bleeding from Bureau *et al* is equal to 0% for TIPSS and 18.2% for standard care.[11]
‡Absolute % of severe HE calculated as overall HE rate multiplied by % HE severe. The remaining HE episodes are classified as mild. % of severe HE obtained from: KOL assumption for variceal bleeding; Bureau *et al*[11] as number of OHE episodes grade >2/total number of OHE episodes.
§% with catheter failure at 12 months obtained by extrapolating value from source at 41 weeks (3%), assuming proportional rates between weeks 41 and 52.
HE, hepatic encephalopathy; KOL, key opinion leader; N/A, not applicable; RA, refractory ascites; SBP, spontaneous bacterial peritonitis; TIPSS, transjugular intrahepatic stent shunt.

inpatient/emergency hospital stay and cost £3081. Fifty per cent of variceal bleeding episodes for patients with RA were treated with TIPSS, 14% received a further EBL session and 36% were managed by watchful waiting, giving an average cost of £6454 per episode.

Uncomplicated moderate ascites[13] were treated with spironolactone (£5.90), while uncomplicated large ascites required 1.2 sessions with LVP and albumin (£960).

Lactulose (1 month) and rifaximin (6 months) to treat mild HE (grade I & II) cost £91 per month. Twenty-five per cent of severe HE (grade III and IV) cases received a TIPSS reduction procedure, with the remainder managed on rifaximin for 6 months, giving an average cost of £1377.

Antibiotics, albumin and hospital bed-days per SBP episode were estimated to cost £1308, while catheter failure was estimated to cost £552.

Utilities

Utility values were identified through a pragmatic literature search, including handsearching of the 10 retrieved economic studies. Baseline utilities for the bleeding indication were 0.67 for Child-Pugh B and 0.56 for Child-Pugh C.[25] We applied population weightings by Child-Pugh B/C in line with the Garcia-Pagan (2010) RCT population,[10] resulting in a baseline utility for variceal bleeding of 0.62.

A baseline utility of 0.65 for people with liver cirrhosis without ascites was obtained from Moscucci *et al*.[26]

Disutilities were applied to each adverse event. Disutilities of 0.15 for TIPSS procedures, including shunt dysfunction were applied during the hospital stay.[27] All other disutilities were applied to the full month cycle and are reported in table 2.

Sensitivity and scenario analyses

Extensive deterministic sensitivity analysis (DSA) was conducted across ranges equal to the 95% CI or ±15% of the mean if CIs were unavailable. Results were plotted on Tornado diagrams to identify key drivers of cost-effectiveness. Threshold analyses for several influential parameters determined the lower/upper bounds for TIPSS to be cost-effective and cost saving vs standard care.

Probabilistic sensitivity analysis (PSA) was conducted using 10 000 iterations to establish the uncertainty in the cost-effectiveness results given the combined uncertainty of the parameter values. All probabilistic parameter distributions followed recommendations by Briggs *et al* (online supplemental appendix 4).[28]

Scenario analyses were conducted for the variceal bleeding indication using clinical parameters from a random effects meta-analysis (online supplemental appendix 1), which pooled values from Garcia-Pagán *et al*[10] and a recent UK RCT by Dunne *et al*.[29] The meta-analysis was not used as the base case due to a high risk of bias in Dunne *et al* where only 13 of 29 participants received 'early' TIPSS within 72 hours. As outlined in the Cochrane risk-of-bias tool

Table 2 Resource usage, unit and total costs (2017/2018 prices) and utilities

	Units	Costs	Source
TIPSS procedure			
TIPSS procedure plus consumables	1.00	£2353	KOLs; Gore
Diagnostic tests (elective only)	3.13	£396	KOLs[22]
Pre-procedure HCP (hours)	0.33	£36	KOLs[24]
Procedure HCP (hours)	14.00	£796	KOLs[24]
Hospital stay (elective) days	2.00	£1064	KOLs[22]
Hospital stay (non-elective) days	5.00	£2212	KOLs[22]
Total (elective)		*£4646*	
Total (non-elective)		*£5398*	
Standard care: indication 1 (variceal bleeding)			
Outpatient EBL (months 1–2)	4.00	£2177	KOLs[22]
Outpatient EBL (months 3–24)	3.00	£1633	KOLs[22]
Pharmaceuticals (per month)	Various	£4.42	23
Total costs (24 month survival)		*£3862*	
Standard care: indication 2 (refractory ascites)			
LVP per procedure			
Consumables/sundries	1.00	£180	42
HCP time (nurse: hours)	0.50	£19	KOLs[22]
Human albumin (dose 52 mg)	1.00	£34	KOLs[23]
Hospital stay	1.90	£568	KOLs[22]
Cost per LVP +human albumin	1.00	£800	
Total cost (24-month survival)	*52.00*	*£41 618*	

	Total cost	Disutility	Source (utility)
Cost and disutility per adverse event			
TIPSS*	Reported above	0.010	27
Shunt dysfunction*	£4095	0.010	27
Variceal bleeding†			27
TIPSS (indications 1 and 2)	£,3081	0.154	
Standard care (indication 1)	£6454	0.154	
Standard care (indication 2)	£3081	0.154	
Ascites†			26
Uncomplicated, moderate	£6	0.125	
Uncomplicated, large	£960	0.125	
Hepatic Encephalopathy			32
Mild HE (grade I and II)†	£91	0.070	
Severe HE (grade III and IV)†	£1377	0.130	
SBP†	£1308	0.120	43
Catheter failure	£552	0.000‡	N/A

Cost components and sources are reported in full in online supplemental appendix 3.
*Utility decrement applied only to length of hospital stay.
†Utility decrement applied to full cycle (monthly per event rate).
‡Utility decrement equal to zero as no published evidence to the contrary.
EBL, endoscopic band ligation; HCP, healthcare provider; HE, hepatic encephalopathy; KOL, key opinion leader; LVP, large vol paracentesis; SBP, spontaneous bacterial peritonitis; TIPSS, transjugular intrahepatic stent shunt.

for RCTs, deviations from the intended interventions can lead to heterogeneity in meta-analyses of intention-to-treat studies.[30] Consequently, two scenario analyses were conducted where the meta-analyses included (i) intention-to-treat and (ii) per-protocol data from Dunne *et al*.[29] The clinical parameters for each scenario are presented in table 3; all other parameters retain the values reported in table 1.

In the RA indication, a scenario analysis was conducted reducing the frequency of LVP sessions from 2.17 per month to 0.71 per month, this value being informed by findings from a UK observational study by Parker *et al*.[31] In addition, two scenario analyses were conducted which applied the Weibull and exponential distributions as the parametric function used to estimate 24-month survival as opposed to the log normal distribution used in the base case analysis (online supplemental appendix 2).

RESULTS

Results from the base-case and scenario analyses are reported in table 4, with Tornado diagrams presented in online supplemental appendix 5.

TIPSS for variceal bleeding

In the base case analysis, TIPSS had 0.209 additional QALYs and NHS savings of £600 per person when compared with EBL and pharmaceuticals. Hence, TIPSS dominated standard care. Savings were predominantly related to treatment (£4059) and hospital stay (£1949) for recurrent bleeding episodes. NHS savings due to reductions in adverse events outweighed the average cost of £5613 per patient for a TIPSS procedure and subsequent hospital stay. The major resource saving (per 1000 population) was 400 fewer bed-days for TIPSS compared with standard care (23 vs 424). There were also fewer HE events (44 vs 52), ascites events (25 vs 55) and angiographies (4 vs 53).

TIPSS remained cost-effective for both scenario analyses, but was no longer cost saving. The incremental costs of TIPSS was equal to £445 (scenario 1) and £372 (scenario 2) while incremental QALYs were equal to 0.21 (scenario 1) and 0.22 (scenario 2). The resultant ICERs for scenarios 1 and 2 were well below the £20 000/QALY threshold and equal to £4128 and £3267, respectively.

The base case results were also sensitive to changes in EBL survival rates, TIPSS procedural costs and the cost and frequency of EBL procedures. TIPSS was cost incurring for these DSAs but cost saving for all others. In all DSAs, ICERs remained below £20 000/QALY. Threshold analyses established that TIPSS would remain cost-saving if the frequency of outpatient EBL procedures for the initial bleed reduced from 4.00 to 2.82, the technical success rate for TIPSS reduced from 98% to 88%, and if the cost per non-elective bed day for TIPSS patients increased from £442 to £995.

PSA results are displayed in figure 2. TIPSS was cost-effective in 95% and cost-saving in 75% of 10 000 iterations.

Table 3 Clinical outcomes used in scenario analyses for variceal bleeding

	Scenario 1		Scenario 2	
	TIPSS	Standard care	TIPSS	Standard care
Survival at 12 months	0.827	0.683	0.834	0.683
Survival at 24 months	0.827	0.683	0.834	0.683
Variceal bleeding at 12 months	0.070	0.367	0.029	0.367
Variceal bleeding at 24 months	0.070	0.367	0.029	0.367
Ascites at 12 months	0.230	0.380	0.160	0.290
HE at 12 months	0.340	0.280	0.360	0.280

HE, hepatic encephalopathy; TIPSS, transjugular intrahepatic stent shunt.

TIPSS for refractory ascites

In the base-case analysis, TIPSS resulted in 0.526 additional QALYs and NHS savings of £17 983 per patient versus LVP. Hence, TIPSS dominated standard care. TIPSS substantially increased survival resulting in 0.630 incremental life-years gained per patient. The major savings were from avoided LVP sessions. Each person treated with LVP incurred £22 322 additional costs to manage ascites over 24 months. These exceeded the average cost of £4877 per patient for a TIPSS procedure. TIPSS also saved £452 from fewer variceal bleeds, £116 from reduced cases of SBP and £116 from fewer catheter failures; however, there was an increase of £31 for HE (table 3). The major resource saving for TIPSS versus LVP (per 1000 population) was 4550 fewer bed-days (446 vs 4996). There were also fewer recurrent bleeds (9 vs 15) but more episodes of mild HE (49 vs 17). SBP and catheter failure had event rates of 7 and 5, respectively, in standard care.[1]

Results were robust across all DSA scenarios with TIPSS remaining cost saving. This included scenarios which reduced the frequency of LVP sessions from 2.17 per month to 0.71 per month, consistent with findings from an observational study by Parker *et al*[31] and applied different functions to estimate 24-month survival (online supplemental appendix 2).

PSA results are displayed in figure 2. TIPSS was cost-saving in all 10 000 iterations. There was, however, uncertainty in the value of cost savings associated with TIPSS which ranged substantially from a minimum of £29 to a maximum of £46 608.

DISCUSSION

Key findings

Our analysis suggests that TIPSS with an ePTFE covered stent is cost-saving and cost-effective in the UK, for patients with cirrhosis and variceal bleeding or RA. The results are driven by reductions in reinterventions for bleeding and RA. In particular, TIPSS was highly cost-saving for the RA indication, including across all sensitivity analyses.

While TIPSS was dominant (QALY gains and cost savings) in the base case for the bleeding indication, TIPSS was not cost saving in either of the scenario analyses. The uncertainty was due to large differences in recurrent bleeding rates (base case: 3% TIPSS, 50% standard care; scenario 1: 7% TIPSS, 36.7% standard care; scenario 2: 2.9% TIPSS, 36.7% standard care) which accounted for 86% of the total difference in NHS costs between scenarios. We suggest that further research is required to support robust economic modelling results for this indication.

Consistency with other studies

Our economic searches did not identify any UK-based cost-utility analyses indicating this is the first UK economic evaluation of ePTFE covered stents for either indication. Our results are in line with two cost-utility analyses conducted in the USA, by Shen *et al*[21] and Kwan *et al*,[32] where TIPSS was highly cost-effective, although neither found TIPSS to be cost-saving. Differences may have occurred due to the shorter time horizon (1 year) adopted by Shen *et al*,[21] and the use of bare metal stents studies to inform clinical parameters by Kwan *et al*.[32]

Our results in RA are consistent with a real-world retrospective cost analysis by Parker *et al* of 24 TIPSS patients with RA managed at an NHS hospital.[31] Mean savings using TIPSS as opposed to LVP with albumin were £2759 per person (2012/2013 prices) which increased to £4570 per person when removing an outlier.[31] Cost savings were higher for TIPSS in our analysis (£17 983) due to larger number of LVP sessions, equal to 2.17 per month. When reducing the number of LVP sessions to 0.71 per month, as observed by Parker *et al*,[31] we identified similar levels of cost savings for TIPSS, equal to £2053.

Limitations

There was considerable uncertainty in the cost-effectiveness of pre-emptive TIPSS compared with EBL for the bleeding indication due to limitations in the clinical evidence. It was not considered appropriate to use the meta-analysis for the base case analysis due to the high risk of bias associated with the Dunne *et al*[29] study; thus, the clinical parameters were informed predominantly from a single RCT.[10]

A major concern regarding the study by Garcia-Pagán *et al*[10] is the small sample (n=63) and imprecise parameter values. In particular, the rate of variceal bleeding for TIPSS versus EBL had a 95% CI ranging from 25%

Table 4 Deterministic results: TIPSS vs standard care, mean outcomes per person

	Cost-utility analysis				Resource impact: Total discounted costs (£) 2017/2018							
					TIPSS*		Variceal bleeding		Ascites			
	Costs	QALYs	Life years	ICER	Treatment†	Bed days	Treatment†	Bed days	Treatment†	Bed days	HE	SBP +CF
Indication 1: TIPSS for variceal bleeding												
Base case results												
TIPSS	£6174	1.028	1.720		£3383	£2230	£81	£114	£52	£82	£232	N/A
Standard care	£6773	0.819	1.354		£0	£0	£4141	£2063	£113	£178	£279	N/A
Incremental	–£600	0.209	0.366	Dominant	£3383	£2230	–£4059	–£1949	–£61	–£96	–£47	N/A
Scenario 1: clinical parameters from meta-analysis with Intention-to-treat data for Dunne et al[29]												
TIPSS	£6428	0.997	1.674		£3378	£2229	£96	£198	£95	£149	£284	NA
Standard care	£5983	0.889	1.465		£0	£0	£3960	£1446	£147	£231	£199	N/A
Incremental	£445	0.108	0.209	£4128	£3378	£2229	–£3864	–£1248	–£52	–£82	£85	N/A
Scenario 2: clinical parameters from meta-analysis with per-protocol data for Dunne et al[29]												
TIPSS	£6246	1.005	1.684		£3379	£2229	£81	£99	£61	£97	£300	N/A
Standard care	£5875	0.891	1.465		£0	£0	£3960	£1446	£105	£165	£199	N/A
Incremental	£372	0.114	0.219	£3267	£3379	£2229	–£3879	–£1347	–£43	–£68	£101	N/A
Indication 2: TIPSS for refractory ascites												
Base case												
TIPSS	£7302	1.136	1.788		£3797	£1080	£34	£225	£528	£1287	£349	£2
Standard care	£25 285	0.610	1.158		£0	£0	£93	£618	£7022	£17 117	£318	£118
Incremental	–£17 983	0.526	0.630	Dominant	£3797	£1080	–£59	–£393	–£6493	–£15 829	£31	–£116
Scenario 1: reduction LVP procedure frequency												
TIPSS	£6973	1.136	1.788		£3797	£1080	£34	£225	£432	£1054	£349	£2
Standard care	£9026	0.610	1.158		£0	£0	£93	£618	£2292	£5587	£318	£118
Incremental	–£2053	0.526	0.630	Dominant	£3797	£1080	–£59	–£393	–£1860	–£4533	£31	–£116

*Includes costs for all repeat procedures due to shunt dysfunction but excludes TIPSS to treat adverse events. These are included as treatment costs for bleeding and HE.
†Treatment costs include all consumables for TIPSS, EBL and LVP, healthcare professional time, diagnostic tests and pharmacotherapy.
CF, Catheter Failure; EBL, endoscopic band ligation; HE, hepatic encephalopathy; ICER, incremental cost-effectiveness ratio; LVP, large-volume paracentesis; QALY, quality-adjusted life year; SBP, spontaneous bacterial peritonitis; TIPSS, transjugular intrahepatic stent shunt.

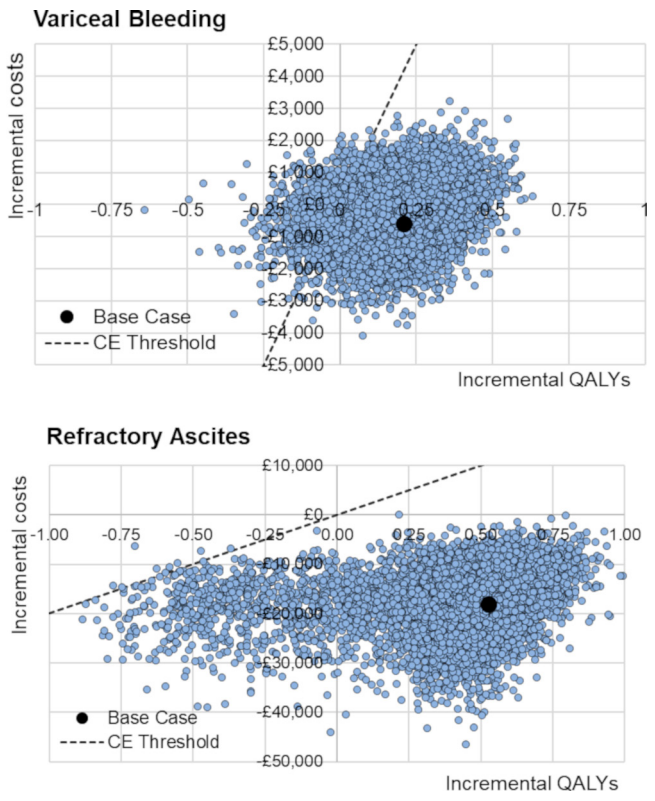

Figure 2 PSA results. PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; CE, cost-effectiveness.

to 69%. Imprecision in the clinical parameters did not translate to high levels of uncertainty in the PSA, where TIPSS had a 95% and 75% probability of being cost-effective and cost-saving, respectively. However, in our most pessimistic scenario, application of the lower 95% CI changed the result of the cost analysis where TIPSS became cost incurring to the NHS.

A second concern relates to improvements in standard care, including survival, since the Garcia-Pagán *et al*[10] RCT.[33] Propranolol was used in the standard care arm[10] while Dunne *et al*[29] adopted more recent practice with 62% of patients treated with carvedilol. The latter may have a greater effect on portal pressure although there are no data to confirm this in secondary prophylaxis. This and other improvements in cirrhosis care may account for some of the increased survival observed between the two studies, rising from 61%[10] to 76%.[29] Increased survival for standard care may not impact the cost-effectiveness results materially as survival for TIPSS patients is likely to substantially exceed current standard care.

A third concern relates to patient selection. Our results are not specific by Child-Pugh classification as in Garcia-Pagan (2010) about half of patients were class B and half class C.[10] A recent editorial noted several observational studies have shown survival benefit of TIPSS in Child-C but not in Child-B patients, regardless of active bleeding. It concluded that large multicentre RCTs are necessary to draw firm conclusions on survival benefit of TIPSS in all high-risk groups.[34]

The RA indication was also limited by the use of the single study by Bureau *et al*[11] to inform the majority of parameter values. Again, there were limitations with study size (n=62) and also generalisability of French data to the UK setting. Any biases in the RCT design will be applicable to the economic results, for example, alcohol cessation is identified as a potential confounder for improved liver function by Bureau *et al*.[11] In addition, Bureau *et al*[11] excluded patients requiring LVPs within the previous 3 months. Our base-case analysis modelled patients who require six LVPs every 3 months and thus at the extreme range of disease severity included in the RCT, but this was supported by KOL opinion. Uncertainties in the clinical parameters did not, however, translate to decision uncertainty for the RA indication: TIPSS remained dominant across all sensitivity analyses and was cost-effective and cost-saving in 100% of the PSA iterations.

There was additional uncertainty in other parameter values. For the bleeding indication, TIPSS was cost-effective but not cost-saving when follow-up EBL sessions during the first 2 months for standard care were reduced below 2.82. Dunne (2020)[29] report a median of 4 (range 0 to 8) elective EBL procedures over 12 months for 29 patients receiving standard care; however, this outcome was not well reported and may not be directly comparable to the number of EBL sessions in our model which are conditional on survival. Across both indications, no intervention specific utilities were applied and all included values came from low quality and somewhat dated studies that did not apply the EQ-5D measure preferred in the NICE reference case. However, the values are reasonably consistent with the recent NICE cirrhosis guideline which reported no difference in utilities between TIPSS and LVP.[14]

Finally, our analysis relied on tariff price for the estimation of in-hospital costs separately for elective (suitable for indication 1 including ICU bed occupancy) and non-elective TIPSS admissions. There may have been relevant costs that were not captured within the tariff such as patient transfer for TIPSS. The cost per bed day threshold analysis indicates tariff excluded costs need to be substantial to alter the findings as such costs are also applicable to recurrent bleeding episodes which have higher rates in standard care.

Future research

Management of the complications of decompensated cirrhosis remains an area of intense research and the treatment landscape is evolving for both indications. For variceal bleeding, the ongoing CALIBRE trial compares carvedilol with EBL in a multicentre UK setting,[35] while the benefits of long-term albumin in RA has been reported in the ANSWER trial.[36] The ePTFE covered stent has also evolved, with a controlled expansion feature. Early studies of the device suggest improved outcomes for survival and lower adverse events, particularly HE and cardiac complications,

which may be due to the improved haemodynamic control of the ePTFE covered stent.[37–39]

Future economic models will require robust clinical evidence. Future studies should prioritise the inclusion of patients who are treated with contemporaneous standard of care and be powered sufficiently to detect differences on key clinical outcomes. It is critical that clinical trials capture aspects of the service delivery of TIPSS at national level, including optimal volume of procedures, in a multicentre format. Further cost-effectiveness evidence by Child-Pugh subgroup should be obtained when robust clinical evidence becomes available. Analyses would be enhanced by the availability of validated utility or mapped quality of life values.

CONCLUSION

Using the best available evidence, our study indicates that TIPSS with an ePTFE covered stent improves survival and is cost-effective for the two indications. There is a very high likelihood of TIPSS being cost saving for populations with RA. There is considerably less certainty that pre-emptive TIPSS is cost saving for populations with haemodynamically stable variceal bleeding. An adequately powered RCT capturing the current treatment landscape and quality of life is required to inform robust modelling, particularly for the bleeding indication.

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Contributors RM: primary author of manuscript and involved in all stages of research including model design, build, review of clinical and economic evidence. FON: involved in design of the study, analysis and interpretation of data; reviewed and edited the manuscript and primary author of several paragraphs. JC: involved in design of the study, analysis and interpretation of data; reviewed and edited the manuscript and primary author of several paragraphs. JT: involved in review of the economic model design and clinical evidence; reviewed and edited the manuscript. DT, DP, GA: provided key clinical input for this research; acted as key opinion leaders (KOLs) and informed parameter values and provided validation for the model design; reviewed and edited the manuscript.

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Competing interests RM is an employee of York Health Economics Consortium who were commissioned by W.L. Gore & Associates to provide consultancy, develop the economic model and write the manuscript.

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SUPPLEMENTARY MATERIAL

Supplementary Appendix 1: Systematic Literature Review and Meta-Analysis

The clinical parameters for the economic model were identified through a systematic literature review. An electronic literature search was conducted for clinical, safety and economic studies of TIPSS in portal hypertension, oesophageal and gastric varices and ascites. The search strategy was informed by the PICO criteria (See Table S1.1). A single search was conducted which obtained relevant studies for both the variceal bleeding and refractory ascites indications. Studies were assigned as being relevant to the variceal bleeding or refractory ascites indication after screening.

Table S1.1: Pico Criteria for Systematic Literature Review

Population	People with portal hypertension and one of the following complications: • Acute variceal bleeding who have failed to respond to standard medical treatment • Refractory ascites
Intervention	TIPS procedure with VIATORR stents
Comparators	• Pharmaceuticals plus endoscopic procedures (variceal bleeding indication) • Large volume paracentesis (refractory ascites indication) • TIPS procedure with other stents (both indications)
Outcomes	• Survival rates • Bleeding/recurrent bleeding • Complications relating to refractory ascites • Recurrence of ascites • Hepatic encephalopathy episodes • Re-intervention • Any device related adverse event
Study designs	• RCTs • Prospective, comparative studies • Economic evaluations [1]

All studies were screened on title and abstract, and were excluded if they didn't meet the PICO criteria. All non-excluded studies entered a second screening phase, where manuscripts were read in full. The PRISMA chart in Figure S1.1 summarises the included studies. The review identified 10 relevant studies across 16 documents, these are summarised in Table S1.2

[1] The search strategy included economic evaluations as these study designs were used to inform the clinical assumptions and treatment pathways in the economic model. Economic evaluations were excluded from the literature review informing the clinical parameters.

Figure S1.1: PRISMA Flow Chart for the Systematic Literature Review

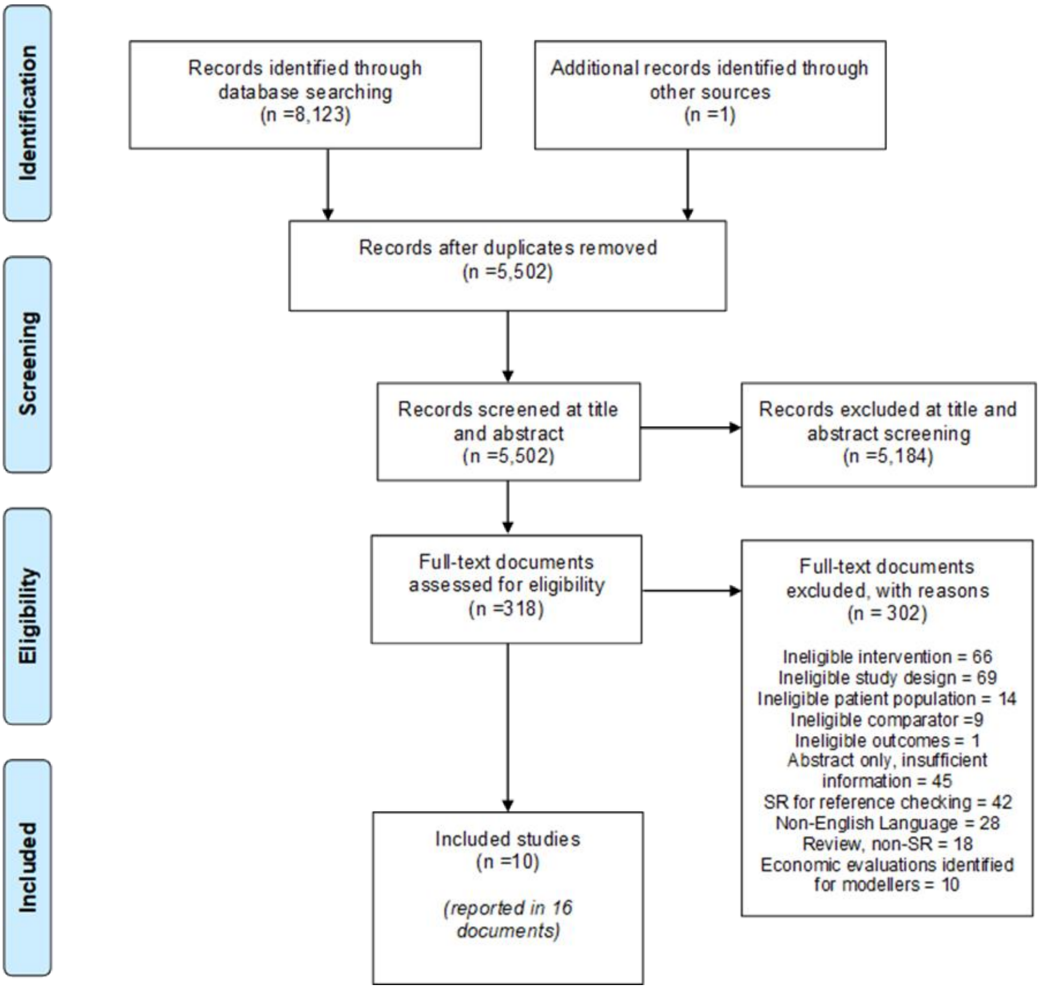


Table S1.2: List of Included Studies

Study	Reference
Bureau 2004	Bureau C, Garcia-Pagan JC, Otal P, Pomier-Layrargues G, Chabbert V, Cortez C, et al. Improved clinical outcome using polytetrafluoroethylene-coated stents for TIPS: results of a randomized study. Gastroenterology. 2004;126(2):469-75.
	Bureau C, Pagan JCG, Layrargues GP, Metivier S, Bellot P, Perreault P, et al. Patency of stents covered with polytetrafluoroethylene in patients treated by transjugular intrahepatic portosystemic shunts: Long-term results of a randomized multicentre study. Liver Int. 2007;27(6):742-47.
Clark 2011	Clark W, Golkar F, Luberice K, Toomey P, Paul H, Marcadis A, et al. Uncovering the truth about covered stents: is there a difference between covered versus uncovered stents with transjugular intrahepatic portosystemic shunts? Am J Surg. 2011;202(5):561-64.

Dunne 2019	Dunne S, Stanley L, Hayes P. Early Use of TIPSS in Patients with Cirrhosis and Oesophageal Variceal Bleeding: A Duel Centre UK Randomised Control Trial. Edinburgh: British Society of Gastroenterology; 2019.
Holster 2016 (NTR973	Holster IL, Tjwa ETTL, Moelker A, Wils A, Hansen BE, Vermeijden JR, et al. Covered transjugular intrahepatic portosystemic shunt versus endoscopic therapy + beta-blocker for prevention of variceal rebleeding. Hepatology. 2016;63(2):581-89.
ISRCTN58150114	Garcia-Pagan JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med. 2010;362(25):2370-79.
	Garcia-Pagan JC, Caca K, Laleman W, Sauerbruch T, Luca A. An early decision for ptfe-tips improves survival in high risk cirrhotic patients admitted with an acute variceal bleeding. A multicenter RCT. J Hepatol. 2008;48(suppl 2):S371**.**
	Garcia-Pagán JC, Caca K, Laleman W, Appenrodt B, Luca A, Nevens F, et al. An early decission for PTFE-TIPS improves survival in high risk cirrhotic patients admitted with an acute variceal bleeding. A multicenter RCT. Hepatology. 2008;48(suppl 1):373A-74A.
NASTRA	Campbell MS, Brensinger CM, Sanyal AJ, Gennings C, Wong F, Kowdley KV, et al. Quality of life in refractory ascites: transjugular intrahepatic portal-systemic shunting versus medical therapy. Hepatology. 2005;42(3):635-40.
	Sanyal AJ, Genning C, Reddy KR, Wong F, Kowdley KV, Benner K, et al. The North American Study for the Treatment of Refractory Ascites. Gastroenterology. 2003;124(3):634-41
NCT00222014	Bureau C, Thabut D, Oberti F, Dharancy S, Carbonell N, Bouvier A, et al. Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites. Gastroenterology. 2017;152(1):157-63.
	Bureau C, Thabut D, Oberti F, Dharancy S, Cabarrou P, Carbonell N, et al. TIPS with PTFE-covered stent improves liver transplant free survival in patients with cirrhosis and recurrent ascites : Results of a multicentre randomized trial. Hepatology. 2015;62(suppl 1):347A.
	Bureau C, Thabut D, Oberti F, Dharancy S, Bouvier A, Mathurin P, et al. Correction Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites. Gastroenterology. 2017;153(3):870.
Ockenga 2004	Ockenga J, Kroencke TJ, Schuetz T, Plauth M, Kasim E, Petersein J, et al. Covered transjugular intrahepatic portosystemic stents maintain lower portal pressure and require fewer reinterventions than uncovered stents. Scand J Gastroenterol. 2004;39(10):994-99.
Pomier-Layrargues 2001	Pomier-Layrargues G, Villeneuve JP, Deschênes M, Bui B, Perreault P, Fenyves D, et al. Transjugular intrahepatic portosystemic shunt (TIPS) versus endoscopic variceal ligation in the prevention of variceal rebleeding in patients with cirrhosis: a randomised trial. Gut. 2001;48(3):390-96.
Sauerbruch 2015	Sauerbruch T, Mengel M, Dollinger M, Zipprich A, Rossle M, Panther E, et al. Prevention of Rebleeding From Esophageal

	Varices in Patients With Cirrhosis Receiving Small-Diameter Stents Versus Hemodynamically Controlled Medical Therapy. Gastroenterology. 2015;149(3):660-68.e1.

Meta-analysis results for indication 1

Scenario 1: Meta-analysis uses intention to treat data from Garcia-Pagan (2010)(10) and Dunne (2020).(34)

Scenario 2: Meta-analysis uses intention to treat data from Garcia-Pagan (2010)(10) and per-protocol data from Dunne (2020).(34)

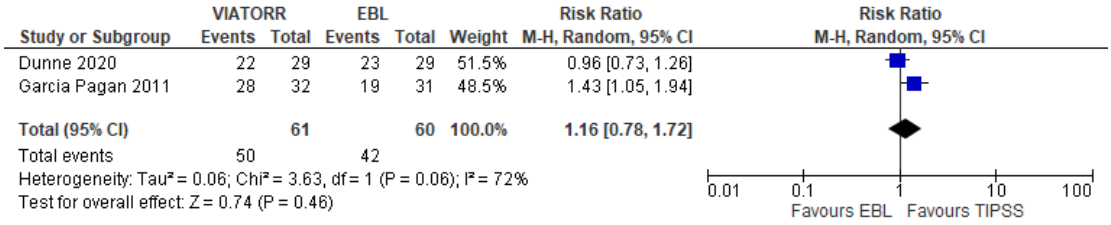
Table S1.3: Clinical Parameters for Scenario Analyses

	Scenario 1			**Scenario 2**		
	TIPS	**Standard Care**	**Source**	**TIPS**	**Standard Care**	**Source**
Survival at 12-months	0.827	0.683	MA (ITT)	0.834	0.683	MA (PP)
Survival at 24-months	Assume same rate as 12-months [a]			Assume same rate as 12-months [a]		
TIPSS technical success	0.980	N/A	(19)	0.980	N/A	(19)
Shunt dysfunction	0.070	N/A	(22)	0.070	N/A	(22)
Variceal bleeding at 12-months	0.070	0.367	MA (ITT)	0.029	0.367	MA (PP)
Variceal bleeding at 24 months	Assume same rate as 12-months [a]			Assume same rate as 12-months [a]		
Ascites at 12 months	0.230	0.380	MA (ITT)	0.160	0.290	MA (PP)
Mild HE[b] at 12-months (grade I & II)	0.257	0.213	MA (ITT)	0.268	0.213	MA (PP)
Severe HE[c] at 12 months (grade III & IV)	0.086	0.071	MA (ITT)	0.089	0.071	MA (PP)

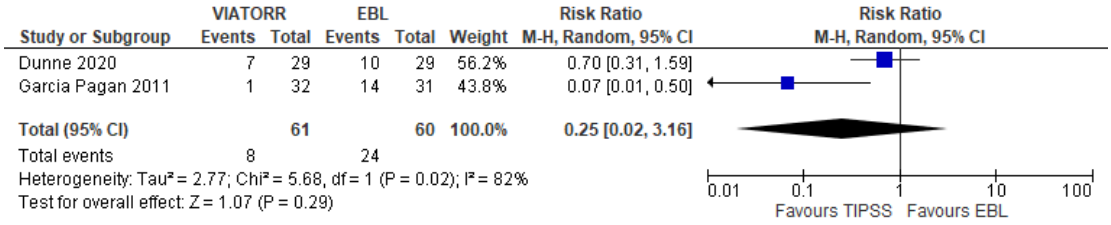
a: Assumption based on probabilities reported by Garcia-Pagan (2010) where survival and bleeding rate is unchanged from 12-months to 24-months.
b: calculated by multiplying the rate of any HE from MA by proportion of HE that is mild (75%)
c: calculated by multiplying the rate of any HE from MA by proportion of HE that is mild (25%)
MA (ITT) = Meta-analysis with intention to treat data for Dunne (2020)
MA (PP) = Meta-analysis with per protocol data for Dunne (2020)
HE = Hepatic encephalopathy
N/A= Not applicable

Figure S1.2 Meta-analysis forest plots for scenario 1

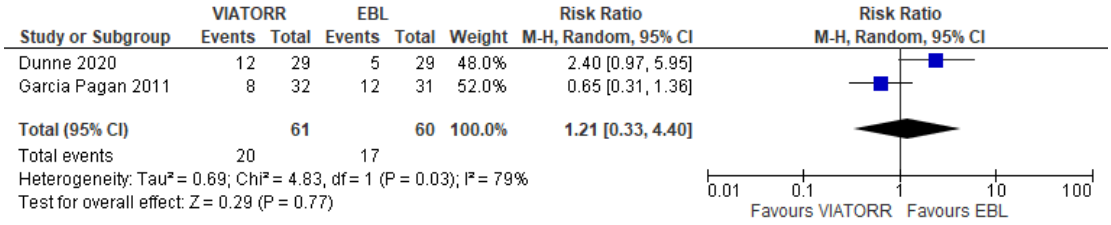
Survival at 12-months



Variceal bleeding at 12-months



Hepatic encephalopathy at 12-months (includes severe and mild)



Ascites at 12-months

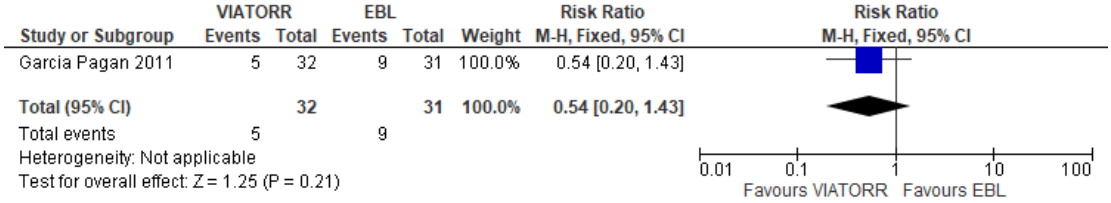
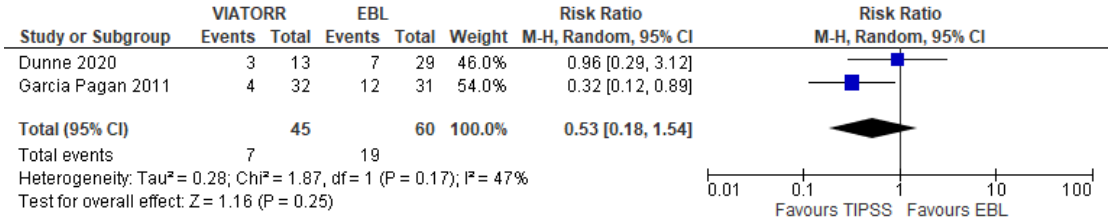
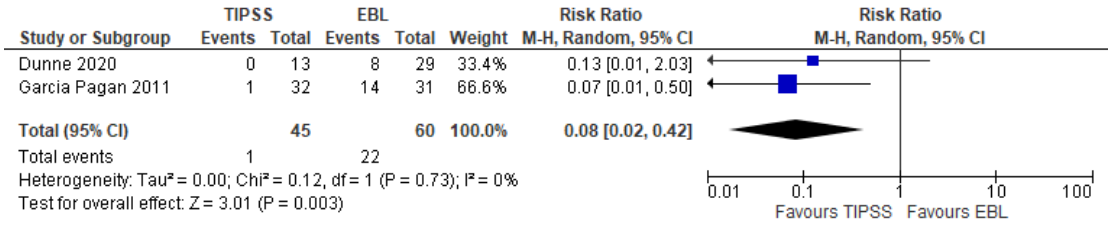


Figure S1.3 Meta-analysis forest plots for scenario 2

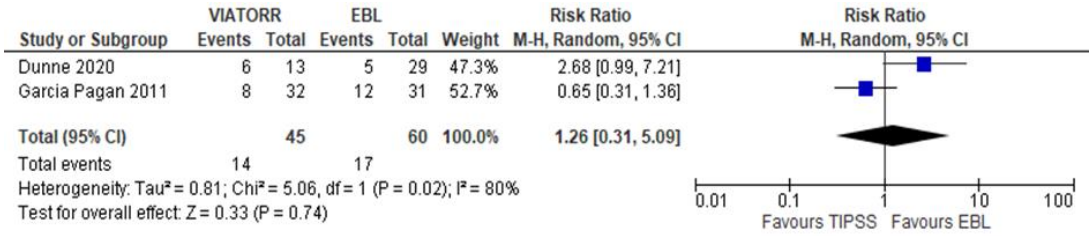
Survival at 12-months



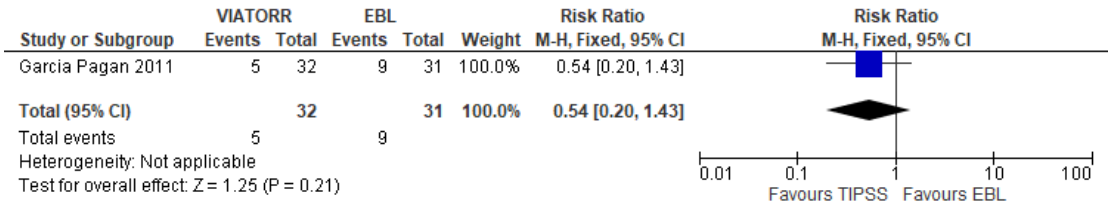
Variceal bleeding at 12-months



Hepatic encephalopathy at 12-months (includes severe and mild)



Ascites at 12-months



Supplementary Appendix 2: Calculation of 24-month survival for indication 2

In order to conduct the economic evaluation, mean survival estimates were required for TIPSS and standard care across the 24-month time horizon. For indication 1, 24-month survival was obtained directly from Garcia-Pagan (2010).(10) For indication 2, only 12-month survival was available from the RCT by Bureau (2017).(11) Therefore, a post-hoc analysis was conducted to establish mean survival at 24-months in patients receiving TIPs or LVP + human albumin, by extrapolating 12-month survival rates reported in Bureau (2017).(11)

We conducted the survival analysis using the software R studio, version 3.6.0. We used parametric time-to event analysis to extrapolate 12-month survival to 24-month survival. First, we generated Kaplan Meier curves using the individual patient data (IPD) reported in the study by Bureau (2017).(11) The survival probabilities and at-risk tables for TIPSS and LVP patients between 0 and 12 months were used directly as reported in Figure 1 in the study by Bureau (2017).(11)

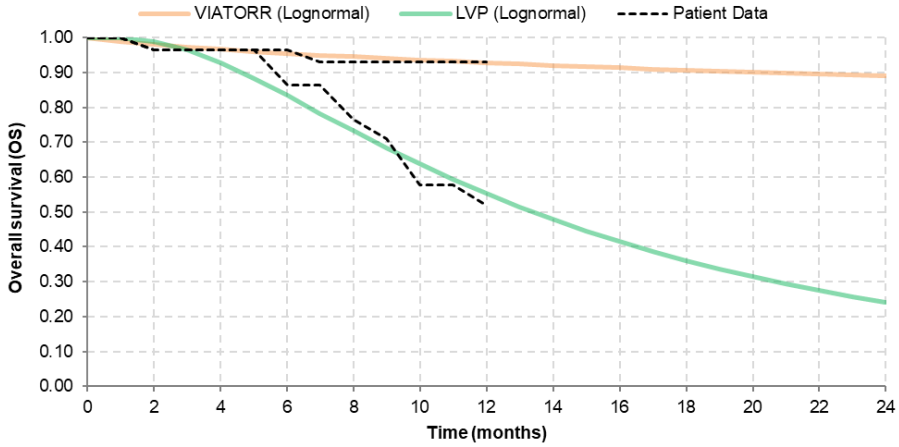
Next, we fitted six standard parametric functions (exponential, Gompertz, Weibull, log-normal, log-logistic and generalised gamma) to the IPD, and used these functions to extrapolate survival up to 24-months. The log-normal was selected as the most appropriate parametric survival function. The selection was made based on visual inspection of each survival curve, the clinical feasibility of the 24-month mortality outcome validated by the KOLs, and the associated Akaike information criterion (AIC) and Bayesian information criterion (BIC) which are shown in Table S2.1.

Table S2.1: AIC and BIC criterion for the parametric survival analysis

Distribution	TIPS			LVP		
	AIC	BIC	Rank	AIC	BIC	Rank
Exponential	39.95	41.32	1	154.17	155.67	5.5
Gompertz	41.36	44.10	1.5	150.40	153.39	1
Log-normal	41.53	44.27	2	151.51	154.50	1
Log-logistic	41.70	44.44	2.5	149.88	152.88	1
Weibull	41.72	44.46	3	149.85	152.84	1
Generalised Gamma	41.87	45.97	3.5	151.84	156.33	3.5

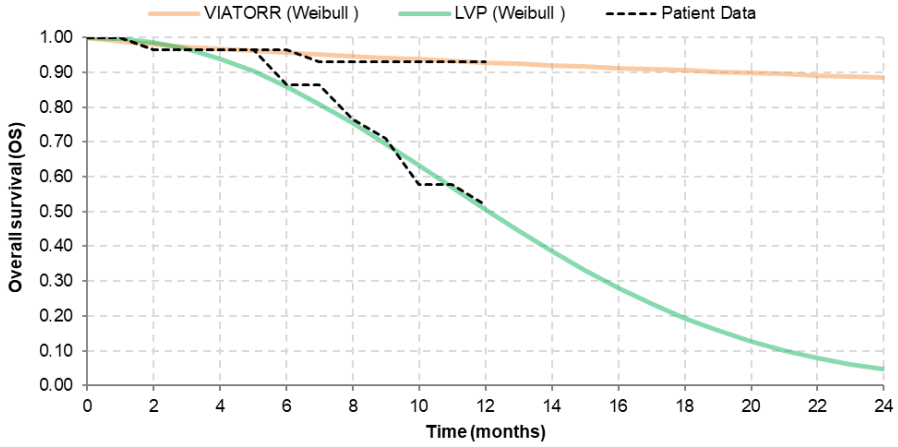
The log normal parametric survival function was used to directly inform each monthly transition probability of mortality in the economic model for indication 2, across the full 24-month time horizon. Figures S2.1, S2.2, and S2.3 depict survival curves and tabulated survival rates for the three best fitting functions (log-normal, Weibull and exponential), alongside survival rates for the 12-month patient data in Bureau (2017).(11) The cost-effectiveness results for each function are reported in Tables S2.2.

Figure S2.1: Survival rates for lognormal function



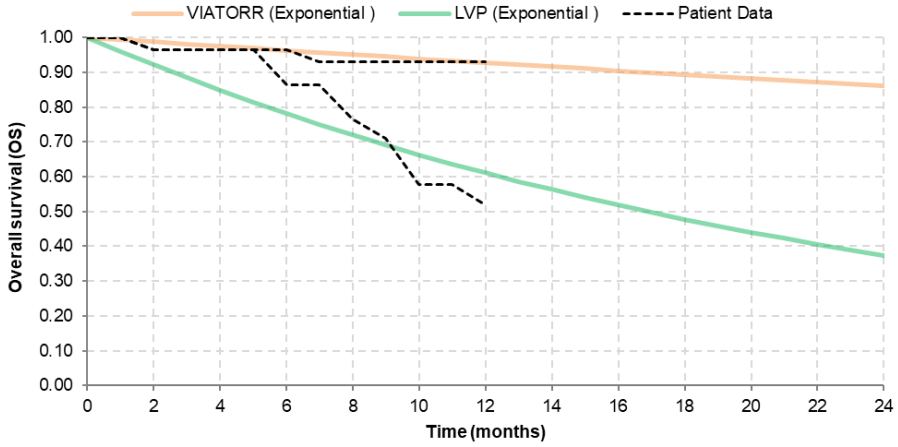
	TIPs survival rates		LVP survival rates	
Month	**Patient Data**	**S(t) [Lognormal]**	**Patient Data**	**S(t) [Lognormal]**
0	1.000	1.000	1.000	1.000
1	1.000	0.989	1.000	0.999
2	0.966	0.981	0.966	0.989
3	0.966	0.973	0.966	0.964
4	0.966	0.966	0.966	0.927
5	0.966	0.960	0.966	0.882
6	0.966	0.955	0.863	0.833
7	0.930	0.950	0.863	0.783
8	0.930	0.945	0.766	0.733
9	0.930	0.940	0.710	0.684
10	0.930	0.936	0.577	0.638
11	0.930	0.932	0.577	0.594
12	0.930	0.928	0.520	0.553
13		0.924		0.515
14		0.920		0.479
15		0.917		0.446
16		0.913		0.415
17		0.910		0.387
18		0.907		0.361
19		0.904		0.337
20		0.901		0.315
21		0.898		0.294
22		0.895		0.275
23		0.892		0.258
24		0.890		0.241

Figure S2.2: Survival rates for the Weibull function



	TIPs survival rates		LVP survival rates	
Month	**Patient Data**	**S(t) [Weibull]**	**Patient Data**	**S(t) [Weibull]**
0	1.000	1.000	1.000	1.000
1	1.000	0.988	1.000	0.997
2	0.966	0.980	0.966	0.986
3	0.966	0.973	0.966	0.967
4	0.966	0.967	0.966	0.939
5	0.966	0.962	0.966	0.903
6	0.966	0.956	0.863	0.860
7	0.930	0.951	0.863	0.809
8	0.930	0.946	0.766	0.754
9	0.930	0.942	0.710	0.694
10	0.930	0.937	0.577	0.632
11	0.930	0.933	0.577	0.569
12	0.930	0.929	0.520	0.506
13		0.924		0.445
14		0.920		0.387
15		0.916		0.332
16		0.913		0.281
17		0.909		0.235
18		0.905		0.194
19		0.902		0.158
20		0.898		0.127
21		0.895		0.101
22		0.891		0.079
23		0.888		0.061
24		0.884		0.047

Figure S2.3: Survival rates for exponential function



	TIPs survival rates		LVP survival rates	
Month	**Patient Data**	**S(t) [exponential]**	**Patient Data**	**S(t) [exponential]**
0	1.000	1.000	1.000	1.000
1	1.000	0.994	1.000	0.960
2	0.966	0.988	0.966	0.921
3	0.966	0.981	0.966	0.884
4	0.966	0.975	0.966	0.849
5	0.966	0.969	0.966	0.815
6	0.966	0.963	0.863	0.782
7	0.930	0.957	0.863	0.750
8	0.930	0.951	0.766	0.720
9	0.930	0.945	0.710	0.691
10	0.930	0.939	0.577	0.663
11	0.930	0.933	0.577	0.637
12	0.930	0.928	0.520	0.611
13		0.922		0.587
14		0.916		0.563
15		0.910		0.540
16		0.905		0.519
17		0.899		0.498
18		0.893		0.478
19		0.888		0.459
20		0.882		0.440
21		0.877		0.422
22		0.871		0.405
23		0.866		0.389
24		0.860		0.373

Table S2.2: Results for refractory ascites indication by parametric function

	Cost-utility analysis			
	Costs	QALYs	Life years	ICER
Log-normal distribution (i.e. base case results)				
TIPSS	£7,302	1.136	1.788	
Standard care	£25,285	0.610	1.158	
Incremental	-£17,983	0.526	0.630	Dominant
Weibull distribution				
TIPSS	£7,241	1.134	1.784	
Standard care	£22,295	0.537	1.021	
Incremental	-£15,054	0.596	0.763	Dominant
Exponential distribution				
TIPSS	£7,332	1.132	1.782	
Standard care	£26,956	0.650	1.235	
Incremental	-£19,624	0.481	0.548	Dominant

Supplementary Appendix 3: Healthcare costs per person (UK prices 2017/18)

Table S3.1: TIPs procedural costs per person

	Units	Total Cost [a]	Source
Consumables			
All procedure consumables [b]	1.00	£1,700	KOLs; GORE; (24)
Diagnostic Tests (elective procedures only)			
Abdomen CT scan	1.00	£94	KOLs; (26)
Doppler ultrasound	1.00	£52	
Echocardiogram	0.03	£3	
Electroencephalography	0.10	£20	
Electrocardiogram	1.00	£228	
Healthcare professionals time: pre-procedure (units in hours)			
Hepatologist consultant	0.17	£18	KOLs; (25)
Radiologist consultant	0.17	£18	
Healthcare professionals time: procedure (units in hours)			
Radiologist consultant	2.00	£216	KOLs; (25)
Radiologist trainee (band 4)	2.00	£68	
Radiographer (band 5)	2.00	£74	
Nurse (band 5)	4.00	£148	
Anaesthetist consultant	2.00	£216	
Anaesthetist nurse (band 5)	2.00	£74	
Hospital excess bed days			
Elective [c]	2.00	£1,064	KOLs; (26)
Non-elective [d]	5.00	£2,212	
Total costs			
Total (elective)	**£4,646**		
Total (non-elective)	**£5,398**		

a: Total costs are reported per person based on the required units. For example, the cost of an Echocardiogram is £100 per procedure but is only required in 3% of all procedures, thus total costs are equal to £3 per person.

b: Procedure consumables include VIATORR stent, TIPSS kit, ciprofloxacin, balloon catheter and X-ray dye.

c: Weighted average of elective excess bed days from 2017/18 NHS Reference Costs, tariffs YR16A (Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 6+) and YR16B (Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 0-5).

d: Weighted average of non-elective excess bed days from 2017/18 NHS Reference Costs, tariffs YR16A (Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 6+) and YR16B (Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 0-5).

Table S3.2: EBL + pharmaceuticals costs (standard care, indication 1) per person

	Dose/units	Total Cost	Source
Pharmaceuticals (total costs per month)			
Carvedilol	12.5mg daily	£2	(24)
Propranolol	160mg twice daily	£6	
Nadolol	240mg daily	£20	
Endoscopic band ligation			
Inpatient EBL (first bleed)	4.00	£2177	KOLs; (26)
Outpatient EBL (follow up)	3.00	£1,633	
Total costs (24-month survival) [1]	£3,862.43		

1: Proportion using carvedilol = 75%, propranolol =12.5%, nadolol = 12.5%.

Table S3.3: LVP + human albumin costs per procedure (standard care, indication 2) per person

	Units	Total Cost	Source [Units; costs]
Procedure costs:			
Sundries	1.00	£132	(27)
Consumables (total)	1.00	£49	
Catheter and pack		£35	
Connector		£8	(27)
Drain		£5	
2L drainage bag		£1	
Human albumin	55.2mg	£34	(27); (24)
Nurse, band 5 (units = hours)	0.5	£19	KOLs; (25)
Hospital stay (units = days)			
Day case	1.00	£350	
Elective	2.80	£974	
Non-elective	2.80	£1,009	KOLs; (26)
Weighted mean hospital stay per LVP [a] (day case= 66%, elective=22%, non-elective =12%)		£568	
Total costs: LVP + human albumin	1.00	£800	

a: Costs are applied for length of stay per LVP procedure. Overall cost of stay is weighted in the model to include day case, elective and non-elective procedures. Weighting is based on KOL assumption.

Complication costs

Table S3.4: Complication cost per person: Shunt dysfunction

	Unit Costs	% receiving procedure	Total costs	Source [Costs; %]
Angioplasty	£3,686	67.50%	£2,488	(26); KOLs
TIPs reintervention	£4,943	32.50%	£1,607	
Non-elective TIPS [1]	£4,063			Table S2.1; KOLs
Balloon expandable stent	£881			(43)[2]; KOLs
Total cost shunt dysfunction			£4,095	

1: Equal to the cost of the non-elective TIPS procedure in table S2.1 but with the number of bed days reduced from 5.0 to 2.0.

2: Cost uprated using Hospital and Community Services Pay and Prices index

Table S3.5: Adverse event cost per person: Variceal bleeding

	TIPS		Standard Care		Source [Units; costs]
	Units	Total Cost	Units	Total Cost	
Indication 1					
Angiography	1.00	£94	1.00	£94	KOLs, (26)
Terlipressin (1.5mg/5 hrs)	21.6mg	£308	21.6mg	£308	KOLS, (24)
Non-elective TIPs [1]	N/A	N/A	0.50	£1,593	KOLs, Table S2.1
Inpatient EBL [2]	N/A	N/A	0.14	£3,542	KOLs, (26)
Non-elective excess bed days	5.10	£2256	7.97	£494	(44); (45); (26)
ICU stay (per FCE [3])	0.25	£423	0.25	£423	KOLs; (26)
Total cost indication 1	£3081		£6,454		
Indication 2					
Angiography	1.00	£94	1.00	£94	KOLs, (26)
Terlipressin (1.5mg/5 hrs)	21.6mg	£308	21.6mg	£308	KOLs, (24)
Non-elective excess bed days	5.10	£2256	5.10	£2256.19	(44); (26)
ICU stay (per FCE [3])	0.25	£423	0.25	£423.00	KOLs; (26)
Total cost indication 2	£3081		£3081		

1: 50% of patients receiving EBL + medical therapy received non-elective TIPs for variceal rebleed. Costs as reported in Table S2.1 but exclude cost per excess bed days.
2: 14% of patients receiving EBL + medical therapy received an inpatient EBL session following variceal rebleed. Cost per inpatient EBL session equal to £3,185.70.
3: 25% of patients required an ICU, and a cost of £1,692 per finished consultant episode (FCE).

Table S3.6: Adverse event cost per person: Ascites

	Units/ Dose	Total costs	Source (units: costs)
Uncomplicated moderate ascites			
Spironolactone (1-month course)	250mg/day	£6	(46); (24)
Uncomplicated large ascites			
LVP + human albumin	1.20	£960	KOLs; Table S2.3
Spironolactone	250mg/day	£6	(46); (24)

Table S3.7: Adverse event cost per person: Hepatic Encephalopathy

	Dose	% requiring item	Total costs	Source (units: costs)
Mild HE (grade I & II)				
Lactulose (1-month)	120ml daily	100%	£20	(46); (24)
Rifaximin	1,100mg daily	50% [1]	£70	KOLs; (24)
Total costs mild HE			£91	
Severe HE (grade III & IV)				
Rifaximin	1,100mg daily	100% [1]	£141	KOLs; (24)
Non-elective TIPs [2]	N/A	25%	£1,236	(12), table S2.4
Total costs severe HE			£1,377	

1: Rifaximin prescribed for six months per year. Cost per person per month equals £140.90 (accounting for six months of non-treatment per year).

2: Non-elective TIPs procedure with balloon expandable stent and 2-day length of stay cost per procedure equal to £4,943.31 as described in Table S2.4.

Table S3.8: Adverse event cost per person: Spontaneous Bacterial Peritonitis

	Units	Total costs	Source (units: costs)
IV albumin (87.5mg)	2.00	£107	(46); (24)
Non-elective excess bed days	3.50	£1,181	KOLs; (26)
Antibiotics [1]		£20	KOLs; (24)
Cefotaxime 5-day course	0.50	£19	
Ciprofloxacin 7-day course (4g/day)	0.50	£1	
Total cost SBP		£1,308	

1: 50% take cefotaxime, with full course cost equal to £37.50; 50% take ciprofloxacin with full seven day cost equal to £2.01.

Table S3.9: Complication cost: Catheter Failure

	Units	Total costs	Source (units: costs)
Catheter replacement [1]	1.00	£181	KOLs; Table S2.3
Non-elective excess bed days 2	1.00	£338	KOLs; (26)
Total costs catheter failure		£552	

1: Catheter replacements incurs LVP procedure and sundries costs
2: 50% of people require further surveillance for a mean of 2.0 bed days. Mean bed days per person (surveillance and non-surveillance) = 1.0 day.

Supplementary Appendix 4: Probabilistic Distributions

Table S4.1: PSA Parameters for Indication 1

Parameter	Distribution	Mean	SE	Alpha	Beta	Source (SE or alpha & beta)
Survival rates						
TIPS (12-months)	Beta	0.86	0.13			(10)
TIPs (24 months)	Beta	0.86	0.13			
EBL (12-months)	Beta	0.61	0.09			
EBL (24-months)	Beta	0.61	0.09			
TIPs procedure						
Technical success	Beta	0.98	0.05			KOLs
Procedure time	Gamma	2.00	0.30			Assumption
EBL						
No. of EBL procedures	Gamma	4.00	0.60			Assumption
Clinical parameters						
Prob bleed variceal (TIPs)	Beta	0.03	0.01			(10)
Prob bleed variceal (EBL)	Beta	0.47	0.07			
Prob shunt dysfunction (TIPs)	Beta	0.07	0.03	6	76	(22)
Prob severe or mild HE (TIPs)	Beta	0.28	0.04			(10)
Prob severe or mild HE (EBL)	Beta	0.40	0.06			
% severe HE| any HE (TIPS)	Beta	0.25	0.08	5	24	(21)
% severe HE| any HE (EBL)	Beta	0.25	0.04	4	12	
Prob ascites (TIPS)	Beta	0.13	0.02			(10)
Prob ascites (EBL)	Beta	0.33	0.05			
Utilities						
Child Pugh-2 baseline utility	Beta	0.65	0.10			Assumption
Child Pugh-3 disutility	Beta	0.11	0.02			Assumption
TIPs procedure disutility	Beta	0.15	0.02			Assumption
Variceal bleeding disutility	Beta	0.15	0.02			Assumption
Mild HE disutility	Beta	0.07	0.01			Assumption
Severe HE disutility	Beta	0.13	0.02			Assumption
Ascites disutility	Beta	0.13	0.02			Assumption
Costs						
Unit Costs [1]	Gamma	SE for all unit costs assumed = 15% of mean				
Length of stay [2]	Gamma	SE for all length of stay assumed = 15% of mean				
% using healthcare resource [3]	Beta	SE for all parameters assumed = 15% of mean				

For all assumptions: SE = 15% of mean.
Alpha and beta were obtained through the method of moments using reported SE if unavailable from the published literature.
1: Distribution applied to all unit cost parameters
2: Distribution applied to all length of stay parameters
3: Distribution applied to all % healthcare resource usage parameters. Examples include: % of mild HE patients requiring rifaximin; % of EBL recurrent bleeding patients treated with TIPs/further EBL; % of shunt dysfunction requiring angioplasty.

Table S4.2: PSA Parameters for Indication 2

Parameter	Distribution	Mean	SE	Alpha	Beta	Source (SE or alpha & beta)
Survival rates *(log normal parametric function)*						
TIPs: mean log	Correlated normal variables obtained using Cholesky decomposition see table S4.3					
TIPs: SD log						
LVP: meanlog						
LVP: SDlog						
TIPs procedure						
Technical success	Beta	0.98	0.05			KOLs
Procedure time	Gamma	2.00	0.30			Assumption
LVP procedure						
LVP frequency	Gamma	2.17	0.33			Assumption
LVP required in TIPS arm	Gamma	1.10	0.03			(11)
LoS (non-day case)	Gamma	2.80	0.42			Assumption
Clinical parameters						
Prob recurrent ascites (TIPs)	Beta	0.51	0.04	98	94	(23)
Prob variceal bleed (TIPs)	Beta	0.04	0.02			(11)
Prob variceal bleed (LVP)	Beta	0.18	0.05			
Prob shunt dysfunction (TIPs)	Beta	0.03	0.03	1	28	
Prob severe or mild HE (TIPs)	Beta	0.35	0.09	10	19	
Prob severe or mild HE (TIPs)	Beta	0.33	0.08	11	22	
% severe HE| any HE (TIPS)	Beta	0.40	0.15	4	6	
% severe HE| any HE (LVP)	Beta	0.64	0.14	7	4	
Prob SBP (TIPs)	Beta	0.00	0.00	0	29	
Prob SBP (LVP)	Beta	0.06	0.04	2	31	
Prob Catheter Failure (LVP)	Beta	0.04	0.03			Assumption
Utilities						
Child Pugh-2 baseline utility	Beta	0.65	0.10			Assumption
Ascites disutility	Beta	0.13	0.02			Assumption
TIPs procedure disutility	Beta	0.15	0.02			Assumption
Variceal bleeding disutility	Beta	0.15	0.02			Assumption
Mild HE disutility	Beta	0.07	0.01			Assumption
Severe HE disutility	Beta	0.13	0.02			Assumption
SBP disutility	Beta	0.12	0.02			Assumption
Costs						
Unit Costs [1]	Gamma	SE for all unit costs assumed = 15% of mean				
Length of stay [2]	Gamma	SE for all length of stay assumed = 15% of mean				
% using healthcare resource [3]	Beta	SE for all parameters assumed = 15% of mean				

For all assumptions: SE = 15% of mean.
Alpha and beta were obtained through the method of moments using reported SE if unavailable from the published literature.
1: Distribution applied to all unit cost parameters
2: Distribution applied to all length of stay parameters
3: Distribution applied to all % healthcare resource usage parameters. Examples include: % of mild HE patients requiring rifaximin; % of LVP procedures that are day cases/hospital cases; % of shunt dysfunction requiring angioplasty.

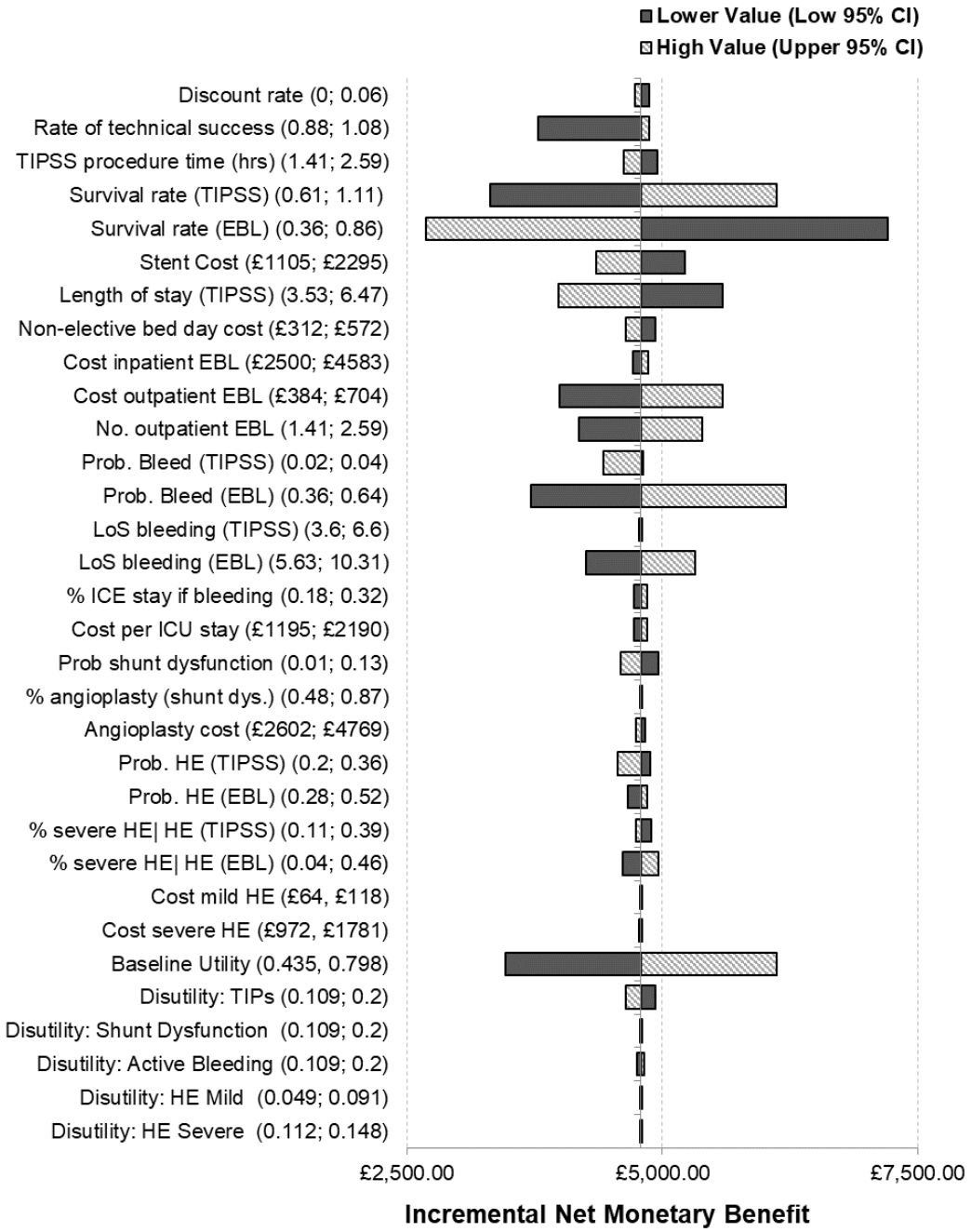
Table S4.3: Survival Rates PSA Parameters (Indication 2)

TIPS				**LVP**		
Covariance Matrices						
	Log (shape)	Log (scale)			Log (shape)	Log (scale)
Log (shape)	9.7386	1.8494		Log (shape)	0.0564	0.0337
Log (scale)	1.8494	0.3940		Log (scale)	0.0337	0.0540
Cholesky Matrices						
	Log (shape)	Log (scale)			Log (shape)	Log (scale)
Log (shape)	3.1207			Log (shape)	0.2375	
Log (scale)	0.5926	0.2069		Log (scale)	0.1420	0.1841

Survival rates estimated using the lognormal survival function which includes shape and scale parameters on the log scale. The Cholesky matrices were used to generate correlated shape and scale variables for the PSA.

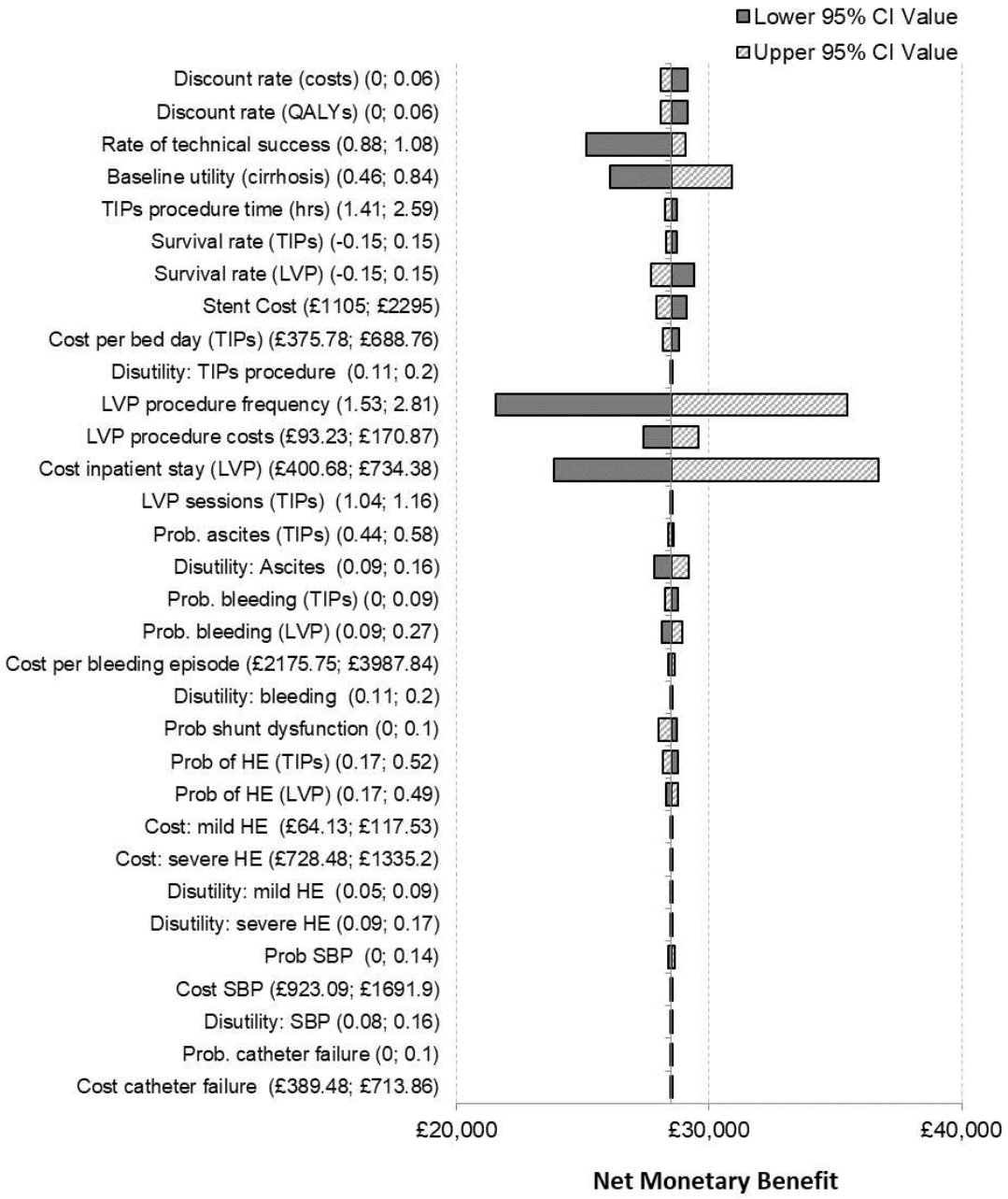
Supplementary Appendix 5: Tornado Diagrams

Figure S5.1: Tornado Diagram Cost-Utility Analysis (Indication 1: Variceal Bleeding)



Plots incremental net monetary benefit (NMB) for TIPs vs. EBL + pharmaceuticals, when varying individual parameter values in the DSA. Any NMB > £0 indicates TIPs is cost-effective vs. EBL + pharmaceuticals

Figure S5.2: Tornado Diagram Cost-Utility Analysis (Indication 2: Refractory Ascites)



Plots incremental net monetary benefit (NMB) for TIPs vs. LVP + albumin, when varying individual parameter values in the DSA. Any NMB > £0 indicates TIPs is cost-effective vs. LVP + albumin.