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Complications of portal hypertension - clinical studies

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Doctor of Medicine

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Declaration

I declare that this thesis is of my own composition, that the work contained herein is my own except where explicitly stated otherwise by way of acknowledgement within the text, and that this work has not been submitted for any other degree or personal qualification.

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28th March 2023

Abstract

Introduction

With over 1.32 million global liver cirrhosis related deaths annually, the burden of liver disease is still rising, predominantly due to alcohol and the metabolic syndrome. The development of portal hypertension occurs in almost 90% of patients with cirrhosis. It marks the transition from compensated to decompensated disease, it is the pathophysiological hallmark of cirrhosis related complications, and is the prequel to mortality. Oesophageal varices are the most clinically significant of these complications due to their tendency to rupture and haemorrhage, contributing to 25-50% of overall deaths. Varices often develop before other portal hypertension related complications such as ascites, hepatorenal syndrome and hepatic encephalopathy. Despite significant developments in understanding the pathophysiological mechanisms of portal hypertension over the last few decades, treatment options for this condition are disproportionately limited. Non-selective beta blockers (NSBBs) have been the cornerstone of therapy for 40-years; they reduce portal pressure by reducing cardiac output and increasing splanchnic vascular resistance. NSBBs are most often initiated upon the finding of oesophageal varices on screening endoscopy to prevent a first bleeding episode, or after stabilisation of a patient admitted to hospital with oesophageal variceal bleeding (OVB) to prevent rebleeding. Despite clinicians' familiarity with oesophageal varices and OVB, no clear strategy for primary or secondary prophylaxis of OVB exists, with endoscopic band ligation (EBL) of varices often used in place of, or as an adjunct to NSBBs. Furthermore, reduction in portal pressure with more invasive procedures such as transjugular intra-hepatic porto-systemic shunt (TIPSS) has been used as rescue therapy in emergency OVB situations as well as for pharmacotherapy refractory ascites. However, TIPSS placement within 72 hours of successfully treated OVB has also been adopted for use "pre-emptively" to prevent rebleeding in high-risk patients. Carvedilol, a NSBB that also exhibits intrinsic anti- α 1 adrenergic effects, offers interest to clinicians due to its superior effect on portal pressure reduction compared to other NSBBs, improvement in intrahepatic vascular resistance, and potential influence on pleiotropic mechanisms

that contribute towards liver decompensation out with portal hypertension. Regardless, data supporting novel approaches in the management of portal hypertension are lacking, with studies often limited by low patient numbers, observational design or absence of long-term outcomes.

Aims

The aims of the studies presented in this thesis were: (i) to determine if early / pre-emptive TIPSS (pTIPSS) offers survival benefit over modern standard of care (SOC) following OVB; (ii) to determine if the timing of pTIPSS insertion following OVB alters patient outcome; (iii) to determine the long-term outcomes for patients receiving either carvedilol or EBL following OVB; and (iv) to determine the long-term outcomes for patients receiving pTIPSS.

Methods

1. In a two-centre open-label parallel-group randomised controlled trial (RCT), patients with cirrhosis and OVB were recruited following haemostasis with vasoactive drugs and EBL. Participants were randomised to SOC (EBL + carvedilol) or pTIPSS (formerly known as “early-TIPSS”). The primary outcome was 1-year survival, secondary outcomes included early and late re-bleeding, and other complications of portal hypertension.
2. A multicentre cohort study of continuous, unselected patients referred to four UK tertiary centres for pTIPSS between 01/01/2010 – 31/12/2018. Time from OVB to pTIPSS was recorded and pre-defined clinically relevant outcomes were observed relative to two groups: early pTIPSS (<72hrs of achieving endoscopic haemostasis) and late pTIPSS (72 hours – 28 days). Primary outcome was 1-year transplant free survival. Patients’ clinical progress was observed from pTIPSS insertion to the close of the study, 31/12/2020.
3. Long-term follow up of a multi-centre, randomised controlled trial in which cirrhotic patients with OVB presenting between 2006-2011 were randomised to receive either carvedilol or EBL as secondary prophylaxis of OVB. Follow-up was

undertaken to April 2020 by review of electronic patient records. The primary outcome was long-term survival. Other outcomes including variceal rebleeding and liver decompensation events were compared.

4. Long-term follow-up of a RCT (above) in which cirrhotic patients presenting with OVB were randomised to receive either SOC or pTIPSS. Follow up was extended to three years from recruitment, with the study closing on 04/01/2021. Primary outcome was 3-year transplant free survival on intention to treat and per-protocol analysis. Secondary outcomes included cause of death, rates of variceal rebleeding, rates of ascites and rates of encephalopathy.

Results

1. pTIPSS RCT: 58 patients (58 ± 11.12 years; 32.7% female) were randomised. After one year, seven patients died in the standard of care group and six in the early-TIPSS group, a 1-year survival of 75.9% versus 79.3% respectively ($p=0.79$). Variceal rebleeding occurred in eight patients in the standard of care group compared with three patients in the early-TIPSS group ($p=0.09$). Not all participants randomised to early-TIPSS received the intervention within the required 72 hours (13 within 72hrs, ten between 3-5 days, and no TIPSS placed in six. For those receiving TIPSS per-protocol, variceal rebleeding rates were reduced (0.0% versus 27.6%, $p=0.04$) but this had no effect on survival (76.9% versus 75.9%, $p=0.91$). Serious adverse events were similar in both treatment groups, except rates of hepatic encephalopathy which were higher in patients receiving TIPSS (46.1% vs. 20.7%, $p<0.05$).

2. UK pTIPSS cohort study: 171 patients were observed, 83 received early pTIPSS and 88 received late pTIPSS. Baseline characteristics were similar with no requirement for propensity score matched analysis. There was no difference between early and late pTIPSS groups for the predefined outcomes; 1-year transplant free survival rate (69.9% vs. 71.6%, $p=0.73$, HR 0.91, 95% CI 0.52-1.58), long-term survival ($p=0.52$, HR 1.132, 95% CI 0.77 – 1.65), variceal rebleeding (4.8% vs. 11.4%, $p=0.09$, HR 0.411, 95% CI 0.14-1.17), hepatic encephalopathy (43.9% vs. 34.6%, $p=0.26$), and new or worsening ascites (16.6% vs. 13.5%, $p=0.79$). Death due to liver failure was

significantly more prevalent in those undergoing early pTIPSS compared to late pTIPSS (44.0% vs. 16.0%, $p=0.046$, HR 2.79, 95%CI 1.02-8.32).

3. Carvedilol vs. EBL secondary prophylaxis RCT – long-term follow-up: Of the 64 patients recruited and randomised, 26 out of 33 received carvedilol in the follow-up period and 28 out of 31 attended for regular EBL sessions. The median number of follow-up days for all patients recruited was 1459 (SE = 281.74). On intention to treat analysis, there was a trend towards improved survival in the carvedilol group ($p=0.09$). On per-protocol analysis, carvedilol use was associated with improved long-term survival ($p=0.005$, HR 3.083, 95%CI 1.397-6.809), fewer liver related deaths (0% vs. 22.8%, $p=0.013$, OR ∞ , 95%CI 1.565 - ∞), and fewer unscheduled hospital admissions with decompensated liver disease (12.0% vs. 64.3% ($p=0.0002$, OR 13.2, 95%CI 3.026 – 47.23) compared to the EBL group. There was no statistically significant difference in variceal rebleeding rates.

4. pTIPSS RCT – long-term follow-up: On intention to treat analysis, 3-year transplant free survival rate in the SOC group was significantly higher than that of the pTIPSS group (55.2% vs. 20.1%, $p=0.006$, HR 2.5, 95%CI 1.3-4.87). On per-protocol analysis, 3-year transplant free survival rate in the SOC group was, again, significantly higher than that of the pTIPSS group (55.2% vs. 15.4%, $p=0.03$, HR 2.93, 95%CI 1.27-7.94). There were significantly higher rates of sepsis related death or sepsis induced liver decompensation related death in the pTIPSS group compared to the SOC group (48.2% vs. 3.6%, $p<0.001$, reciprocal of RR 13.0, 95% CI 2.46 – 75.45). There were no differences in other outcomes associated with portal hypertension on intention to treat analysis.

Conclusion

In a randomised trial, early / pTIPSS had no effect on 1-year transplant free survival in high-risk patients presenting with OVB when compared to SOC using EBL and carvedilol. An important finding was that pTIPSS within the recommend 72 hours timeframe may not be feasible in many centres due to its semi-elective nature set amongst real world clinical practice and emergency care. The 72-hour timeframe is

somewhat arbitrary and based on historical variceal rebleeding data. In a novel, dedicated cohort study to investigate this, placement of pTIPSS within 72 hours offered similar short and long-term survival benefit compared to pTIPSS placed between 72 hours – 28 days. This observation may help improve access to pTIPSS in centres wishing to pursue this service for their patients. However, early pTIPSS may be associated with increased risk of liver failure related mortality which raises concerns over the current patient selection recommendations. Given the reasonable 1-year survival rates reported for cirrhotic patients following OVB, it is sensible to explore the impact of the interventions used over a long-term period, particularly as corresponding data are lacking. Carvedilol use was associated with long-term survival benefit, fewer liver failure related deaths and fewer hospital admissions with decompensated disease when compared to EBL, in the setting of a RCT. Furthermore, in a separate long-term follow-up study, pTIPSS was associated with significantly reduced rates of transplant free survival at 3-years compared to SOC using EBL and carvedilol together. This may be due to higher rates of sepsis related mortality observed for those receiving pTIPSS. However, it is unclear whether pTIPSS is an independent risk factor for sepsis, or whether carvedilol protects against sepsis and subsequent acute decompensation in an otherwise at-risk population. Further large, randomised studies are required to validate these findings.

Lay Summary

Ordinarily, blood travels from the spleen to the liver in a blood vessel called the portal vein (PV). The purpose of this blood is to provide nutrients previously absorbed from the bowel, to the liver, as well as allowing the liver to clean the blood of any potential toxins before they are passed to the rest of the body. However, when liver scarring develops (cirrhosis) the liver becomes stiff which makes it difficult for the blood in the portal vein to enter the liver – similar to a blocked drain, or a bottle neck traffic jam. Subsequently, the pressure in the in the PV rises – a condition known as portal hypertension (PH). When PH occurs, the blood in the PV tries to find an alternate route back to the heart so it bypasses the liver by filtering into small blood vessels that line the gut. These small blood vessels, not being accustomed to the additional blood flow, swell due to the extra pressure. They are most commonly found protruding into the lower gullet (in 90% of patients) and are known as oesophageal varices (OV) – i.e., varicose veins of the gullet. When the pressure becomes too high, OV can rupture and cause internal bleeding (OVB) which is a life threatening medical emergency and is associated with early death in around 20% of cases.

The presence of PH can cause further complications in the longer term, however these may take years to develop. Issues with brain function e.g., confusion and coma can develop due the build-up of toxins, such as ammonia, not being cleansed from the blood by the liver. Additionally, PH can cause discoordination within the complex systems in the body that interact to monitor and control the liver, kidneys and blood circulation. This results in kidney failure, abnormal blood salt levels, as well as fluid build-up in the abdomen and under the skin. When these complications occur, they are defined under the umbrella term – decompensated liver disease.

The treatment of PH is limited, with few advancements made in recent decades. The cornerstone of therapy to reduce PH is with medications classed as “beta blockers”. The aim of the studies presented in this thesis were: (i) to determine if patients with OVB survive longer if reduction of PH is achieved by (a) placing an artificial tube into

the PV to divert the trapped blood away (known as TIPSS procedure) or, (b) with the recommended, modern standard practice using a beta-blocker called carvedilol, coupled with ablation of OV via a telescopic camera into the gullet; (ii) to determine if undertaking the TIPSS procedure early in a patient's admission for OVB results in better outcomes compared to waiting >3 days for the TIPSS procedure, and vice-versa; (iii) to determine if there is any long-term benefit of carvedilol after OVB; and (iv) to determine if there is any long-term benefit of the TIPSS procedure following OVB, compared to carvedilol coupled with telescopic camera intervention.

The main results found that: (i) the TIPSS procedure was of no added to benefit to patients' 1-year survival over modern standard practice and may increase the risk of reduced brain function after OVB. These findings contrasted with less modern studies; (ii) the timing of the TIPSS procedure does not alter 1-year survival rates, but if the TIPSS procedure is undertaken within the first three days of a patient's hospital admission for OVB, it may increase the risk of death from liver failure; (iii) drug therapy after OVB using carvedilol may improve long-term survival in patients with PH and is associated with reduced liver decompensation events; and (iv) patients who received the TIPSS procedure for OVB had lower rates of survival at 3-years, and higher rates of infection related liver decompensation and infection related death compared to those who had modern standard practice.

Each of these studies produced results never before seen. In conclusion, carvedilol use following OVB appears to be the optimal way to improve long-term survival rates and reduce rates of liver decompensation in patients with cirrhosis and PH, compared to other treatment methods currently in use. Although carvedilol reduces PH it may have other medical properties, which improve outcomes for patients with cirrhosis, that are not yet fully understood.

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Each of the studies presented in this thesis include patients, some of whom I have never met, but without whom this work would not be possible. Of course, beyond these pages they are not just patients, nor participants, nor any other form of medical terminology, they are real people living with real disease and some, sadly, are no longer alive. I have endeavoured to be conscious of this and reflect as I write.

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Relevant publications

Publications (full)

Dunne PDJ, Stanley AJ. Textbook Chapter: Management of acute variceal bleeding and prevention of rebleeding. SMGebooks – Liver Disease (2016)

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Manship T, Dunne P, Smith R, *et al* P27 Survival after early TIPSS – a follow up study *Gut* 2022;71:A52.

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Prizes

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British Society of Gastroenterology, Annual Conference 2019: Abstract of Distinction - Does the timing of TIPSS effect outcome following Oesophageal Variceal Bleeding, a cohort study.

Glasgow Gastro Conference, Royal College of Physicians and Surgeons, Glasgow, 2020: Best Presentation - Carvedilol versus endoscopic band ligation for secondary prophylaxis of variceal bleeding - long term follow-up of a multicentre randomised controlled study

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Abbreviations

AKI	Acute kidney injury
ArLD	Alcohol related liver disease
AUROC	Area under receiver operating characteristic
CLD	Chronic liver disease
CSPH	Clinically significant portal hypertension
CP	Child-Pugh
EBL	Endoscopic band ligation
e-PFTE	e-polytetrafluoroethylene
FHVP	Free hepatic-venous pressure
GGH	Gartnaval General Hospital
GI	Gastrointestinal
GRI	Glasgow Royal Infirmary
HCC	Hepatocellular Carcinoma
HE	Hepatic Encephalopathy
HRS	Hepatorenal syndrome
HVPG	Hepatic-venous pressure gradient
ICU	Intensive care unit
INR	International normalised ratio
IQR	Inter-quartile range
IR	Interventional Radiology
ISMN	Isosorbide mononitrate
IVC	Inferior vena cava
LSM	Liver stiffness measurement
LVP	Large volume paracentesis
MELD	Model for end-stage liver disease
NAFLD	Non-alcoholic fatty liver disease
NO	Nitric oxide
NSBB	Non-selective beta-blocker
OLT	Orthotopic liver transplant
OV	Oesophageal varices
OVB	Oesophageal Variceal Bleeding

PH	Portal hypertension
PPG	Portal pressure gradient
PV	Portal vein
PVS	Portal venous system
PPG	Portal pressure gradient
RAAS	Renin-angiotensin-aldosterone system
REC	Regional Ethics Committee
RFH	Royal Free Hospital
RIE	Royal Infirmary Edinburgh
RCT	Randomised controlled trial
SBP	Spontaneous bacterial peritonitis
SD	Standard deviation
SE	Standard error
SGH	Southern General Hospital
SOC	Standard of care
SOC+	Standard of care plus
SS	Splenic stiffness
TE	Transient elastography
TIPSS	Transjugular intrahepatic porto-systemic shunt
UHB	University Hospitals Birmingham
VEGF	Vascular endothelial growth factor
VRB	Variceal rebleeding
WHVP	Wedged hepatic-venous pressure

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Chapter 1 Introduction

1.1 Epidemiology of chronic liver disease

Globally, chronic liver disease (CLD) is a dominant cause of mortality and morbidity – in 2016, it was the 11th leading cause of death and 15th most common cause of morbidity (1). In 2017, 1.32 million deaths worldwide were attributed to CLD (2). Although there has been notable improvement in the mortality and morbidity of other common chronic diseases over the preceding 30 years including cardiovascular, cerebrovascular, and cancer disease, there has been limited progress made in reducing the morbidity and mortality of liver disease (3). The absolute number of international CLD cases is estimated at 1.5 billion with viral hepatitis historically been the leading aetiology for CLD (4). However, cases of CLD are still rising despite the reduction in prevalence of hepatitis B (due to vaccination) and hepatitis C (due to treatment). The driving factor here is an increasing prevalence of the metabolic syndrome and alcohol consumption, particularly in developed countries (4). In the UK, this has resulted in a four-fold increase in the standardised mortality rates for CLD since 1970 (3). With 39% of the world's population now overweight and 13% clinically obese, the prevalence of non-alcoholic fatty liver disease (NAFLD) has escalated dramatically (5, 6). Alcohol accounts for 30-50% of global cirrhosis related deaths, a burden which is expected increase in coming years (7). Unfortunately, CLD has an indolent progression which means patients often present late, at which point liver cirrhosis is already established, resulting in end-stage, irreversible liver disease and ultimately death (8).

1.2 Pathophysiology of portal hypertension

In patients with liver cirrhosis, the evolution of portal hypertension (PH) accounts for the majority of complications, marks the transition from compensated to decompensated disease, and is the primary cause of death and liver transplant (9). The development of increased intrahepatic vascular resistance is the key factor in the pathogenesis of PH.

1.2.1 Anatomy and function of the portal venous system

The portal venous system (PVS) drains blood from the upper gastrointestinal tract, pancreas, gallbladder and spleen into the liver. The portal vein (PV) is the main vessel of the PVS, is 6-8cm long, 1.2cm in diameter, originates from the confluence of superior mesenteric veins / splenic vein and terminates within the liver after dividing into its subsidiary branches. The PV is, ordinarily, a low-pressure resistance circuit (6-10 mmHg) that carries nutrients and toxins extracted from digested contents, which accounts for 75% of blood flow to the liver (10). The remaining 25% comes from the hepatic artery which provides oxygenated blood to the liver in a high-pressure system.

1.2.2 Increased intrahepatic vascular resistance

In a non-diseased state, the liver is extremely compliant and can maintain equilibrium of pressure by distention of the vascular bed in response to increased portal inflow (10). However, in the setting of liver cirrhosis, this physiological response is impaired as, simply put, the liver has become stiff. This fixed obstruction, which drives increased intrahepatic vascular resistance, is provoked by changes in hepatic structure and alteration of hepatic vascular tone.

Vascular obliteration by the formation of scar tissue and regenerative nodules in the cirrhotic liver during remodelling contributes to around 70% of increased intrahepatic vascular resistance (11). Activated hepatic stellate cells, responsible for excessive production of extracellular matrix, promote scar tissue formation thereby replacing functional liver tissue with a fibrous matrix – resulting in fibrotic change of the sinusoidal hepatic architecture (12). Furthermore, hepatocyte swelling, capillarisation of hepatic sinusoids and collagen deposition cause further mechanical obstruction to blood flow (13).

The remaining 30% increase in intrahepatic vascular resistance is governed by the contraction of activated hepatic stellate cells and vascular smooth muscle cells which are modulated by peptides such as angiotensin-2 and endothelin-1, both potent

vasoconstrictors of the renin-angiotensin-aldosterone system (RAAS). These vasoconstrictor peptides are elevated in the cirrhotic liver (14, 15). Moreover, cyclooxygenase-derived prostaglandins, and lipoxygenase-derived leukotrienes are also over-produced in the cirrhotic liver and have been suggested as additional modulators of hepatic vascular tone (16, 17).

1.2.3 Increased splanchnic blood flow

In contrast to the maladaptive endothelial response and resulting vasoconstriction within the intrahepatic vasculature outlined above, the opposite occurs in cirrhotic splanchnic vessels. Over production of vasodilators such as Nitric Oxide (NO) in response to inflammatory cytokines and vascular endothelial growth factors (VEGF) promotes increased blood flow through the splenic vein into the PVS, contributing further to the pathogenesis of PH (18).

1.2.4 Circulatory changes

The dual effect of hepatic vasoconstriction acting as a roadblock to the inflow of blood to the liver from the portal vein, combined with excess blood entering the portal vein from the spleen due to splanchnic vasodilation is a double-edged sword in the development of PH. Furthermore, splanchnic vasodilation leads to blood pooling and a subsequent fall in systemic blood pressure. This is overcome by increased cardiac output and the development of hyperdynamic circulation by upregulation of neuro-hormonal mechanisms such as the RAAS and sympathetic nervous system (16). A vicious cycle, to say the least.

To decompress the PVS, formation of collateral blood vessels occurs by activation of angiogenesis modulating growth factors such as VEGF, placental growth factor and platelet derived growth factor, likely in response to systemic hypoxia and circumferential wall stress (11, 19 - 20). The formation of collaterals and diversion of blood around the liver has clinical implications which will be discussed in due course.

1.3. Diagnosis of portal hypertension

Patients with CLD may stay in a compensated state for decades (median survival >12 years). The progression to decompensated cirrhosis and the occurrence of clinical complications are directly related to the onset of clinically significant portal hypertension (CSPH) and is associated with a much shorter median survival of around 2 years (21, 22). Therefore, identification and recognition of CSPH is crucial.

1.3.1 Hepatic venous pressure gradient

PH may be defined as a sustained increase in the pressure gradient between the portal and systemic circulation (23). The hepatic venous pressure gradient (HVPG) is the measured difference in pressure between the PV and inferior vena cava (IVC), and is considered the “gold standard” technique for quantitative assessment of PH. In healthy individuals, HVPG is normally 1-5 mmHg. In compensated cirrhosis HVPG is 6-10 mmHg whereas CSPH and complications develop when it exceeds 10 mmHg (24, 25). HVPG >12 mmHg is classed as severe PH. (22)

1.3.1.1 HVPG clinical applications

HVPG has been utilised to predict advanced liver fibrosis, with a positive correlation noted and an area under receiver operating characteristic (AUROC) of 0.906 (26). HVPG of <10 mmHg is associated with a 90% likelihood of not developing decompensated liver cirrhosis (25). Oesophageal varices (OV) appear to develop when the HVPG is 10 mmHg, bleed when the HVPG exceeds 12 mmHg, and when HVPG rises >20 mmHg in the context of variceal bleeding it is associated with worse clinical outcomes and reduced 1-year survival rates (27, 28). HVPG has also been shown to predict risk of decompensation, hepatocellular carcinoma (HCC) as well as hepatic decompensation in patient with cirrhosis after HCC resection (29, 30). A reduction in HVPG to <12 mmHg, or by >20% from baseline is often used the target for haemodynamic response in interventional studies (31).

1.3.1.2 HVPG measurement technique

A central venous catheter is placed in either the right internal jugular vein or the femoral veins. A wire is then passed through the catheter and guided to the right hepatic vein, with the assistance of fluoroscopy. Once in place, a 6 French balloon tipped catheter is placed over the wire and guided to the right hepatic vein. The balloon is inflated wedged in place and the pressure reading is taken – the wedged hepatic-venous pressure (WHVP). The balloon is deflated, and the pressure is recorded again – the free hepatic-venous pressure (FHVP). Generally, these readings are repeated several times and an average is taken. $HVPG = WHVP - FHVP$.

1.3.2 Non-invasive markers of clinically significant portal hypertension

Although HVPG assessment provides accurate assessment of PH by directly recording intra-vascular pressure, it is a highly invasive procedure, has low acceptance rates from patients and requires high levels of expertise (32). Therefore, it is primarily reserved for research purposes. Efforts have been made to develop less invasive methods of PH quantification.

1.3.2.1 Liver stiffness

Liver stiffness measurement (LSM) using transient elastography (TE) is recommended for use as a safer and more readily available alternative to liver biopsy, and for the diagnosis of liver fibrosis and cirrhosis (33). LSM using TE for the diagnosis of cirrhosis is associated with AUROC of 0.9-0.99 for cut-off values ranging from 9 – 26.6 KPa, however 13.01 KPa appears to be optimal (34). LSM has also effectively been used as a prognostic tool to predict complications of cirrhosis including clinical decompensation, HCC and mortality, with a risk ratio of 1.07, 1.11 and 1.22, respectively (35). Its role in the diagnosis of CSPH is less convincing. The correlation between LSM and HVPG shows the loss of linearity for HVPG values > 12 mmHg. Whilst the correlation coefficient for HVPG < 12 is good, ($r = 0.67 - 0.95$), when analysed for HVPG values > 12, it decreases by 0.17-0.538 and the near perfect linear correlation is completely lost (36, 37). This may be explained by the

severity of PH becoming predominantly independent from increased hepatic resistance (which is assessed by LSM) in advanced cirrhosis, whilst extrahepatic components such as the hyper-dynamic circulation as well as peripheral and splanchnic vasodilatation predominate (37).

1.3.2.3 Splenic stiffness

TE has also been used to measure splenic stiffness (SS). SS not only reflects increased hepatic resistance but may also capture dynamic pre-sinusoidal vasoconstriction and congestion of the portal blood inflow, PH induced splenic fibrosis, and be less influenced by liver necroinflammation than LSM (38, 39). SS measured by TE shows good correlation with HVPG, detecting CSPH with a sensitivity and specificity of 0.88 and 0.92, respectively, and severe PH with a sensitivity and specificity of 0.92 and 0.79, respectively (40). SS may be superior to LSM in predicting oesophageal varices and be better than LSM (but similar to HVPG) in predicting the first decompensation event (41, 42). SS is limited by the detectable upper limit of splenic tissue stiffness and the difficulty of obtaining the measurement in patients with large body habitus. As LSM is the most validated non-invasive test for PH, clinical practice guidelines only currently recommend SS as an adjunct to LSM in order to improve risk stratification for high-risk oesophageal varices and CSPH (43).

1.4 Complications of portal hypertension

Portal hypertension is the main driver of cirrhosis related decompensation. As mentioned, the transition from compensated to decompensated disease correlates with the onset of complications and a marked reduction in life expectancy. One-year mortality in compensated cirrhosis is 7% compared with 20% following liver decompensation (44). The transition to decompensation cirrhosis may be due to progression of the underlying liver disease, or, following a super-imposed acute insult with notable precipitants including infection, gastrointestinal (GI) bleeding, alcohol intake / alcoholic hepatitis, and drug-induced liver injury. Although, no specific cause is found in approximately 50% of cases (45).

1.5 Decompensated cirrhosis

Decompensated cirrhosis is defined as an acute deterioration in baseline liver function in a patient with cirrhosis and is characterised by either an individual or combination of clinical events including jaundice, ascites, hepatorenal syndrome, hepatic encephalopathy, infection, or variceal haemorrhage.

1.5.1. Jaundice

Jaundice occurs due to hepatocyte failure to conjugate bilirubin via the enzyme glucuronyl transferase, for absorption in the bile. Additionally, intrahepatic inflammation may cause cholestasis and disrupt the transport of conjugated bilirubin. Bilirubin alone has been shown to be an effective biomarker in predicting short-term mortality in acute on chronic liver failure (46).

1.5.2 Ascites

Ascites (from the Greek *Askos* – wine bag or sac) is the pathological accumulation of fluid within the peritoneal cavity and is the most commonly found complication of cirrhosis, with up to 60% of patients developing ascites within 10 years of diagnosis (47). The pathogenesis of ascites is incompletely understood but follows on from the pathophysiology of portal hypertension which, as previously noted, causes activation of the RAAS resulting in sodium and water retention (48). Splanchnic arterial vasodilatation also alters intestinal capillary pressure and permeability, facilitating the accumulation of retained fluid within the abdomen. Treatment is typically with dietary salt restriction coupled with diuretics - primarily spironolactone given its aldosterone opposing mechanism of action. Ascites which cannot be mobilised by medical therapy is termed “refractory”. Two forms of refractory ascites are recognised: “diuretic-resistant”, which is unresponsive to optimal doses of diuretics, and “diuretic-intractable”, which occurs when diuretic use is precluded due side effects such as hyponatraemia, hyperkalaemia, hepatic encephalopathy, and renal dysfunction (49).

Patients with refractory ascites have a poor prognosis - median survival of 6 months (50). Repeated large volume paracentesis (LVP) is the mainstay of treatment however, this may precipitate a circulatory disturbance resulting in dilutional hyponatraemia and renal dysfunction, therefore intravenous human albumin is administered concurrently to minimise risk (51). Placement of a transjugular intrahepatic portosystemic shunt (TIPSS) is used in refractory ascites but increases the risk of hepatic encephalopathy. TIPSS may improve survival in carefully selected patients with refractory ascites requiring frequent LVP (52). Refractory ascites is an indication for orthotopic liver transplant (OLT) in suitable patients.

Patients with ascites are at increased risk of spontaneous bacterial peritonitis (SBP) given the dynamic interface between the ascitic fluid and intestinal microbiota. For hospitalised patients the prevalence of SBP is around 15% and, despite optimal management with antibiotics, carries an in-hospital mortality rate of 20.2% (53, 54).

1.5.3 Hepatorenal syndrome

Acute Kidney Injury (AKI) is common in decompensated cirrhosis and can occur secondary to pre-renal AKI, or primary renal disease e.g., acute tubular necrosis. In the absence of these causes of renal impairment, a diagnosis of hepatorenal syndrome (HRS) should be considered, which is a marker of end-stage disease. HRS is the most severe form of renal impairment in cirrhosis and develops in more than 50% of patients with cirrhosis who die (55). The median survival time for patients with the acute form of HRS (type 1) is only four weeks (56).

The pathophysiology of HRS involves activation of the sympathetic nervous system and RAAS causing renal vasoconstriction and a shift in the renal autoregulatory curve, making renal blood flow much more sensitive to changes in systemic blood pressure (57). Concurrent impairment of cardiac function due to the development of cirrhotic cardiomyopathy leads to ineffective compensatory increases in cardiac volume. In addition, there may be also increased synthesis of several vasoactive mediators which

affect renal blood flow and the haemodynamics of renal microcirculation (58). Together, these processes contribute to reduced renal blood flow.

Terlipressin is the main therapeutic option for HRS and acts by causing vasoconstriction of the extremely dilated splanchnic vascular bed and increasing arterial pressure thus improving renal perfusion. However, HRS reversal may only occur in 19.6% of patients receiving terlipressin, and the drug is discontinued in 20.4% due to adverse (mainly ischaemic) events (59).

1.5.4 Hepatic encephalopathy

Hepatic encephalopathy (HE) refers to the neurological or psychiatric abnormalities in patients with cirrhosis and is comprised of cognitive and fine motor disturbances of varying severity. HE eventually occurs in 50% of cirrhotics and symptoms are characterised by asterix with additional clinical features ranging from a trivial lack of awareness to coma (60).

Ammonia is predominantly produced in the GI tract through the action of colonic bacteria as well as small bowel enterocytic glutaminase. Ordinarily, periportal hepatocytes eliminate ammonia by urea synthesis however in PH, hyperammonaemia develops due to portal blood escaping to the systemic circulation through porto-systemic shunts before liver metabolism. Ammonia crosses the blood-brain barrier, and HE ensues due to low grade cerebral oedema, astrocyte swelling, oxidative stress and inflammatory cytokines. This results in slowing of cerebral oscillatory networks (61).

A precipitating event can usually be identified in an acute bout of HE, commonly a gastrointestinal bleed, infection, electrolyte disturbance or the use of sedatives, especially opiates and benzodiazepines. Furthermore, therapeutic shunts used in the treatment of other portal hypertensive complications (i.e., TIPSS) are associated with increased risk of HE. (62)

Treatment and prevention is with Lactulose, a non-absorbable disaccharide which acidifies the colon resulting in conversion of ammonia to ammonium, and shift of the colonic flora from urease to non-urease producing bacterial species. In cases where HE is refractory to initial therapy, and underlying precipitating factors have been addressed, rifaximin may be used. The mechanism of action of rifaximin as an ammonia lowering agent is unclear, it may be due to reduction of urease producing bacteria in the gut (61).

1.5.6 Infection and gut bacterial translocation

Bacterial infections are common in cirrhotic patients and frequently results in hospitalisation, with the incidence and severity being two to three-fold higher than that of the general population (63 – 65). Up to 40% of hospitalised cirrhotic patients will develop bacterial infection (66). The most common causes of bacterial infection are SBP, pneumonia, urinary tract infection, and spontaneous bacteraemia (67). Most bacterial infections are gram negative in taxonomy and are therefore presumed to have a predominantly enteric origination. Bacterial translocation is the migration of bacterial endotoxin, bacterial DNA, or live micro-organisms from the intestinal lumen to mesenteric lymph nodes and other extra-intestinal sites (68, 69). In cirrhosis, bacterial translocation is thought to occur at higher rates due to PH related consequences. Increased intestinal permeability occurs in PH due to impaired microcirculation within the intestinal mucosa, resulting in reduced blood flow to the luminal mucosa, mucosal oedema, and potentially erosions which, in turn, disorder the gut's natural defence mechanisms against microorganisms (70, 71). PH also facilitates bacterial overgrowth of the small bowel, resulting from slow intestinal transit and reduced secretion of gastric and bile acids (70). NO induced vasodilatation and hyperaemia of submucosal capillaries may facilitate bacterial overgrowth further (71 – 73). Lastly, the phagocytic role of the reticuloendothelial system (represented by the Kupffer cells of the liver) may be altered, particularly in the presence of PH

related portosystemic shunts given that blood absorbed from the GI tract is redistributed, bypassing the liver (74).

Prompt identification and treatment of infection is important as, otherwise, there is a significant risk acute on chronic liver failure, further decompensation events including HRS, HE, and death (64, 75). Treatment is with early empirical antibiotic therapy, whilst local policies accounting for multiple drug resistant pathogens should be followed.

1.5.7 Varices

Varices are dilated collateral venous communications formed between the portal and systemic circulation, directing almost 90% of portal flow back to the heart (23). Although varices can appear anywhere in the GI tract (e.g., duodenum and rectum), they are most commonly found in the upper gastrointestinal region, in particular the oesophagus and stomach. Upon diagnosis of cirrhosis, oesophageal varices are found in 50%-60% of patients with decompensated disease (76, 77). Oesophageal varices are often the first clinical development in PH and are the most relevant not only because of their prevalence, but due to their tendency to rupture and bleed. Bleeding varices are the most severe consequence of PH and leading cause of death in cirrhotic patients, with a 6-week mortality rate of approximately 20% (78).

Gastro-oesophageal varices and variceal bleeding will be discussed in more depth later in the introduction, and strategies to optimise outcomes of oesophageal variceal bleeding will be the focus of this thesis.

1.6. Treatment of portal hypertension

Medical therapies for the treatment of PH can be classed as those targeting splanchnic vasodilation such as non-selective beta-blockers (NSBBs), or those which target increased intra-hepatic resistance. Other more invasive therapies such as TIPSS offer a more direct, mechanical option.

1.6.1 Traditional non-selective beta-blockers

NSBBs were first introduced in 1981 as a preventive therapy for cirrhotic patients with reoccurring variceal bleeding (79). NSBBs lower HVPG by two principal mechanisms; firstly, by reducing cardiac output through myocardial β -1 adrenergic blockade that leads to a subsequent reduction in splanchnic blood flow, and secondly, by decreasing splanchnic vasodilatation and allowing unopposed vasoconstrictive α -adrenergic activity (splanchnic β -2 adrenergic blockade) thereby reducing portal blood flow further (80, 81). The traditional and most widely used NSBBs are propranolol and nadolol. Propranolol was the first to demonstrate beneficial effect on HVPG (79). Nadolol has been shown to have similar clinical effectiveness to propranolol, however its low-lipid solubility and hepatic metabolism results in a longer half-life, thus, patients can be dosed less frequently and may have fewer side-effects (82).

In recent years, studies have shown that NSBBs are not only useful in their role to prevent variceal bleeding but may also lower the incidence of any decompensating event (83). Despite their proven clinical effectiveness, traditional NSBBs are contraindicated or poorly tolerated in up to 15%-20% of patients, and up to 60% of patients do not achieve any therapeutic fall in HVPG (84, 85).

1.6.2 Carvedilol

Carvedilol is a novel 3rd generation NSBB that also has weak alpha blocking ability in the intrahepatic and systemic circulation. It is comprised of two isomeric forms, R-carvedilol which antagonises alpha-1 and beta receptors equally, and S-carvedilol which antagonises beta receptors only. It undergoes extensive first-pass hepatic metabolism and has a rapid onset of action – within 2 hours.

Carvedilol was first introduced for the treatment of arterial hypertension, heart failure and ischaemic heart disease and later was found to have a beneficial effect on portal haemodynamics in both the short and long term (86, 87). Whilst carvedilol,

like traditional NSBBs, reduces cardiac output and increases splanchnic vascular resistance, its alpha blocking ability also helps decrease intra-hepatic resistance and tone. Optimal daily dosing of carvedilol for the treatment of PH is 6.25-12.5mg, which results in optimal effect on HVPG without inducing systemic hypotension or worsening of ascites and renal function (88).

1.6.2.1 Carvedilol in comparison to other non-selective beta-blockers

Haemodynamic studies of HVPG show that carvedilol is more effective than propranolol in reducing portal pressure (89, 90). Furthermore, low dose carvedilol (<12.5mg daily) may even be as effective as optimal dose propranolol (91). Carvedilol has also been shown to have an effect on HVPG in patients who had no HVPG response to propranolol (92). There is also interest in the potential extra-hepatic effects of carvedilol that may benefit pleiotropic mechanisms contributing to liver decompensation that are not yet fully understood (93).

1.6.2.2 Extra-hepatic effects of carvedilol

Animal studies demonstrate that carvedilol has antioxidant, anti-fibrotic and anti-inflammatory properties (94, 95). In clinical studies, carvedilol has been shown to increase insulin sensitivity, reduce glycosylated haemoglobin levels, slow the progression to microalbuminaemia, and have a survival benefit compared to other NSBB in patients with heart disease (96 – 98).

1.6.3 Other therapies targeting splanchnic vasodilatation

1.6.3.1 Vasopressin / Terlipressin

Vasopressin reduces portal pressure by provoking vasoconstriction, thereby reducing portal venous blood flow. The vasoconstricting action is potent and commonly produces multiple cardiac side effects including ventricular tachy-arrhythmias, as well as cardiac, bowel and peripheral ischaemia (82). Terlipressin is a synthetic vasopressin analogue, sensitive for the V1 vasopressin receptor, however V2 blockade may still occur and result in free water absorption in the collecting ducts evident clinically as a

resulting dilutional hyponatraemia (99). Terlipressin has significantly fewer side effects than vasopressin, albeit adverse events are still common (100).

1.6.3.2 Octreotide / somatostatin

Somatostatin and its analogue octreotide induce splanchnic vasoconstriction via inhibition of vasodilatory peptide glucagon, as well as having local adrenergic-1 receptor mediated effects which counteract splanchnic vasodilatation (23).

1.6.4 Therapies targeting increased intrahepatic resistance

Isosorbide 5-mononitrate (ISMN) is an organic nitrate that may increase hepatic production of NO, having a subsequent vasodilatory effect within the liver, albeit the exact mechanism is unknown (101). In clinical studies, ISMN is ineffective as monotherapy, but has previously been used alongside NSBBs to optimise HVPg reduction, particularly if no HVPg response is exhibited (102).

Statins have been described as “true liver-selective dilators” owing to their effect on enhancing NO production in hepatic sinusoidal endothelial cells (23, 103). They have been shown to have some effect on HVPg and may reduce the progression of CLD to decompensated cirrhosis (103, 104). Use of statins in CLD, however, is an evolving field of research and they are currently not routinely prescribed for their potential effects on portal pressure.

1.6.5 Transjugular intrahepatic portosystemic shunt

TIPSS is a radiologically guided PH decompression procedure. Via initial access to the jugular or femoral vein, a balloon catheter is passed to the hepatic vein following which a connection is made to the PV. A stent is placed which joins the two vessels resulting in an artificial shunt between the portal and systemic circulation. The current use of expandable polytetrafluoroethylene (e-PTFE) covered stents has overcome much of the initial difficulty in maintaining stent patency attributed to bare-

metal stents, with 1-year stent patency rates of 80-90% compared to 30-70%, respectively (105).

A decrease in portocaval pressure gradient to <12 mm Hg should be achieved by TIPSS placement resulting in a significant reduction in sinusoidal and extrahepatic PVS pressure secondary to the dramatic drop in intrahepatic vascular resistance to portal flow (106). Furthermore, as the blood flow through the stent dissipates the blood pooled in the splanchnic circulation, increased venous return to the heart replenishes the central blood volume - normalising the effective arterial blood volume and decreasing RAAS upregulation (107).

1.6.5.1 Complications of TIPSS

TIPSS is known to increase the risk of HE due to altered hepatic function and porto-systemic shunting (108). Post-TIPSS HE is the most relevant outcome predicting mortality; three risk factors have been identified: age over 65, prior HE and Child-Pugh (CP) score >9 (109). Treatment is as per standard for PH related HE, however reduction of the shunt may be required in refractory cases. The increased venous return to the right heart acts as a potentially harmful volume challenge in some cirrhotic patients and may worsen undiagnosed porto-pulmonary hypertension or unmask subclinical cardiomyopathy, leading to heart failure (106). After TIPSS insertion, some individuals evidence the inability of their hepatic artery to provide adequate hepatic sinusoidal perfusion in the absence of portal flow. This critical aspect has been associated with progressive liver failure (110). Infection of the TIPSS stent itself (endotipsitis) is rare but difficult to diagnose (111).

1.7 Oesophageal varices

1.7.1 Development and natural history

There are two concepts for the development and evolution of oesophageal varices (OV). The traditional view is that closed off, pre-existing sites of embryonic connections between portal and systemic circulations are re-opened under enhanced

portal pressure. These sites become collateral vessels and overtime evolve to become varicose. The submucosal oesophageal venous plexus drains into these collateral veins. The oesophagus is likely the most common site due to lack of external tissue support as well as negative oesophageal pressure during inspiration, contributing to further dilatation and increase in size (112). A more recent theory is that varices and other porto-systemic collaterals evolve under modulation by active angiogenesis, specifically under the control of VEGF (113). In laboratory studies, inhibition of VEGF using sorafenib as well as inhibition of platelet derived growth factor using was linked to a >50% inhibition in collateral formation and regression of collaterals which were already formed (114, 115).

Varices develop and increase in size over time, and the annual progression of varices is thought to be around 10% (116 – 118). In most cases, portal pressure reflects intra-variceal pressure and a HVPg >10 mmHg is necessary for the development of OV (81).

1.7.2 Oesophageal variceal bleeding

1.7.2.1 Prevalence and risk factors

Oesophageal variceal bleeding (OVB) carries a significant risk of mortality. OVB is reported in 20-50% of patients with cirrhosis and about 70% of these bleeding episodes occur within the first two years from diagnosis (116). There appears to be no linear correlation between severity of PH and the risk of OVB, however HVPg >12 mmHg is the accepted threshold for bleeding first reported in historic studies and used a reference point to inform future work (27, 119).

Varices bleed due to rupture of the thin walls, caused by an exertion of tension beyond the blood vessel's elastic limit. According to Laplace's law, variceal wall tension (Wt) is defined by the equation: $Wt = (Pv - Po) \times r / t$, where Pv is the intra-variceal pressure, Po is the opposing pressure of the oesophageal lumen, r is the radius of the varix, and t the thickness of the vessel wall. Therefore, wall tension

increases with increased portal pressure, an effect that is multiplied by increased variceal size and decreased variceal wall thickness (120).

Risk of OVB increases with increasing size of varix (greater diameter), red spots (which likely indicate areas of decreased wall thickness, and severity of liver disease (which correlates with higher portal pressure) (119 – 121).

1.7.2.2. Endoscopic therapy for oesophageal varices

Endoscopic band ligation (EBL) is the preferred endoscopic modality for eradication of OV and has current roles in the prevention of first OVB (primary prophylaxis), the management of acute OVB, and in the prevention of further OVB after first bleeding event (secondary prophylaxis). EBL works to obliterate varices through mechanical strangulation using elasticated bands placed on the variceal columns. This has a local effect to reduce risk of OVB but has no effect on portal pressure. Eradication of OV is usually achieved in 90% of patients and routinely takes 2-4 EBL sessions (122, 123).

Endoscopic sclerotherapy was used in the management of variceal bleeding for around 50 years and involved injecting a sclerosing agent such as absolute alcohol into or adjacent to the OV. However, it is no longer used due to inferiority in achieving variceal eradication as well as higher complication rate compared to EBL (124). Major complications such as recurrent bleeding, sepsis and death have been noted in 2% of patients receiving endoscopic sclerotherapy (125).

1.7.3 Primary prophylaxis of oesophageal variceal bleeding

1.4.3.1 Identification of at-risk patients

As up to half of cirrhotic patients will experience OVB and 20% will have early mortality, it is essential to have prophylactic regimens to prevent such an occurrence (126). Although HVPG is the “gold standard” tool for determining portal pressure which may determine bleeding risk, it is widely unavailable and invasive. Endoscopy is the preferred test for identifying OV. To avoid mass endoscopic screening of all patients with suspect CLD, efforts have been made to refine its use. LSM with TE has

been adapted for use to identify patients in whom OV are likely. Patients with a LSM < 20 KPa with a concurrent platelet count >150 x10⁹/L are highly unlikely to have OV and can thus avoid endoscopy safely (127). These recommendations have been extensively used and validated in many subsequent studies, with around 2% of patients who don't have a screening endoscopy per the criteria later found to have OV (128 – 130).

If OV are detected they can be graded by the following criteria: grade 0 refers to lack of presence of OV; grade 1 varices are small, narrow and flatten easily with air; grade 2 varices are usually broader and flatten with difficulty; and grade 3 varices are large enough to occlude the oesophageal lumen (126). Whereas grade 0-1 OV require follow-up surveillance endoscopies, patients who have grade 2-3 OV require OVB prophylactic treatment, however no well powered studies have assessed the optimum approach in this setting,

1.4.3.2 Non-selective beta-blockers or endoscopic band ligation

NSBBs are the mainstay of pharmacotherapy in the primary prophylaxis of OVB. A meta-analysis of nine placebo-controlled primary prophylaxis randomised controlled trials (RCT) found the pooled risk difference for bleeding was -11% in favour of propranolol (131). Two placebo-controlled trials showed that Nadolol is effective in reducing bleeding (132, 133). Carvedilol was found to be associated with significantly reduced bleeding compared to EBL in a RCT but had no effect on 1-year survival (134). When the follow-up of patients recruited to this study was extended to 20-years, a significant reduction in all-cause mortality was seen for patients taking carvedilol (135). In an observational study, patients who were haemodynamic non-responders or intolerant to carvedilol and treated with EBL as an alternative, were found to have significantly higher rates of first OVB and death (92). Alternatively, EBL has been compared with NSBB in 19 trials in a recent Cochrane meta-analysis of 1504 patients. Variceal bleeding rates were reduced for those receiving EBL, but there was no

difference in overall mortality and bleeding-related mortality. This finding was not replicated when trials with high selection or attrition bias were excluded (136).

Currently, NSBBs are preferentially used for primary prophylaxis of OVB treatment, however in patients who do not tolerate NSBB due to side effects, or whom NSBBs may be contraindicated, EBL is recommended (126).

To address the lack of well powered studies, two major UK RCTs are currently in progress – one to determine the outcomes of carvedilol vs. placebo for the primary prophylaxis of OVB (BOPP) (137) and the other, a RCT of carvedilol vs. EBL (CALIBRE) (138).

1.7.4 Management of acute oesophageal variceal bleeding

Acute OVB is a medical emergency and is defined as rupture of the variceal wall with active bleeding seen during endoscopy, or stigmata of recent bleeding such as red spots in a patient with other clinical factors suspicious of a GI bleed. Endoscopic management is with EBL however, initiation of both pre-endoscopic and post endoscopic management strategies are imperative to improve patient outcomes, particularly to prevent rebleeding and mortality.

1.7.4.1 Volume resuscitation and blood transfusion

Intravenous fluid plasma expanders should be initiated with the aim of maintaining systolic blood pressure around 100 mmHg. A restrictive transfusion policy is recommended with the target haemoglobin level between 70 and 80 g/L (139). Over transfusion has been shown to have a damaging effect on outcome, as increases in HVPG may provoke further uncontrolled bleeding (140).

1.7.4.2 Antibiotics

Prophylactic antibiotics improve outcome in variceal haemorrhage, having been shown to reduce mortality and early rebleeding in addition to reducing bacterial

infections (141). Therefore, standard practice includes the administration of antibiotics to all cirrhotic patients who present with upper GI bleeding. The antibiotic of choice should be guided by local resistance patterns with gram-negative cover being essential (126).

1.7.4.3 Vasoconstrictors

Terlipressin is the only vasoconstrictor that has been shown to improve control of bleeding and survival in placebo controlled RCTs (142, 143). Terlipressin can be continued for up to five days after OVB, although should be discontinued when satisfactory haemostasis has been achieved. In patients who are intolerant of terlipressin or in centres where it is not available, alternative vasoconstrictor therapy should be considered. Somatostatin and Octreotide can be used in this setting (144, 145).

1.7.4.3 Timing of endoscopy

All patients with suspected variceal bleeding should have endoscopy performed within 24 hours of presentation. There is no clear evidence that performing endoscopy within 12 hours improves outcome (146). However, patients with haemodynamic instability, particularly those with advanced liver disease, other comorbidities and older age, should have endoscopy performed immediately after resuscitation.

1.7.4.4 Failure of endoscopic therapy

Balloon tamponade using a Sengstaken-Blackmore or Linton tube should only be used to control refractory OVB as a bridge to other treatment modalities. Although a potential life-saving measure, balloon tamponade can be associated with severe adverse events including aspiration pneumonia, oesophageal ulceration and rebleeding on balloon deflation (147). The balloon should be in situ no longer than 24-48 hours (148).

Persistent bleeding despite combined endoscopic and pharmacological treatment is best managed with ePTFE covered TIPSS. Studies assessing TIPSS insertion as a rescue / salvage procedure for variceal bleeding refractory to endoscopic therapy show that control of bleeding is observed in 90-100% of cases, with rebleeding rates of 6-16% (149).

1.7.5 Secondary prophylaxis of oesophageal variceal bleeding

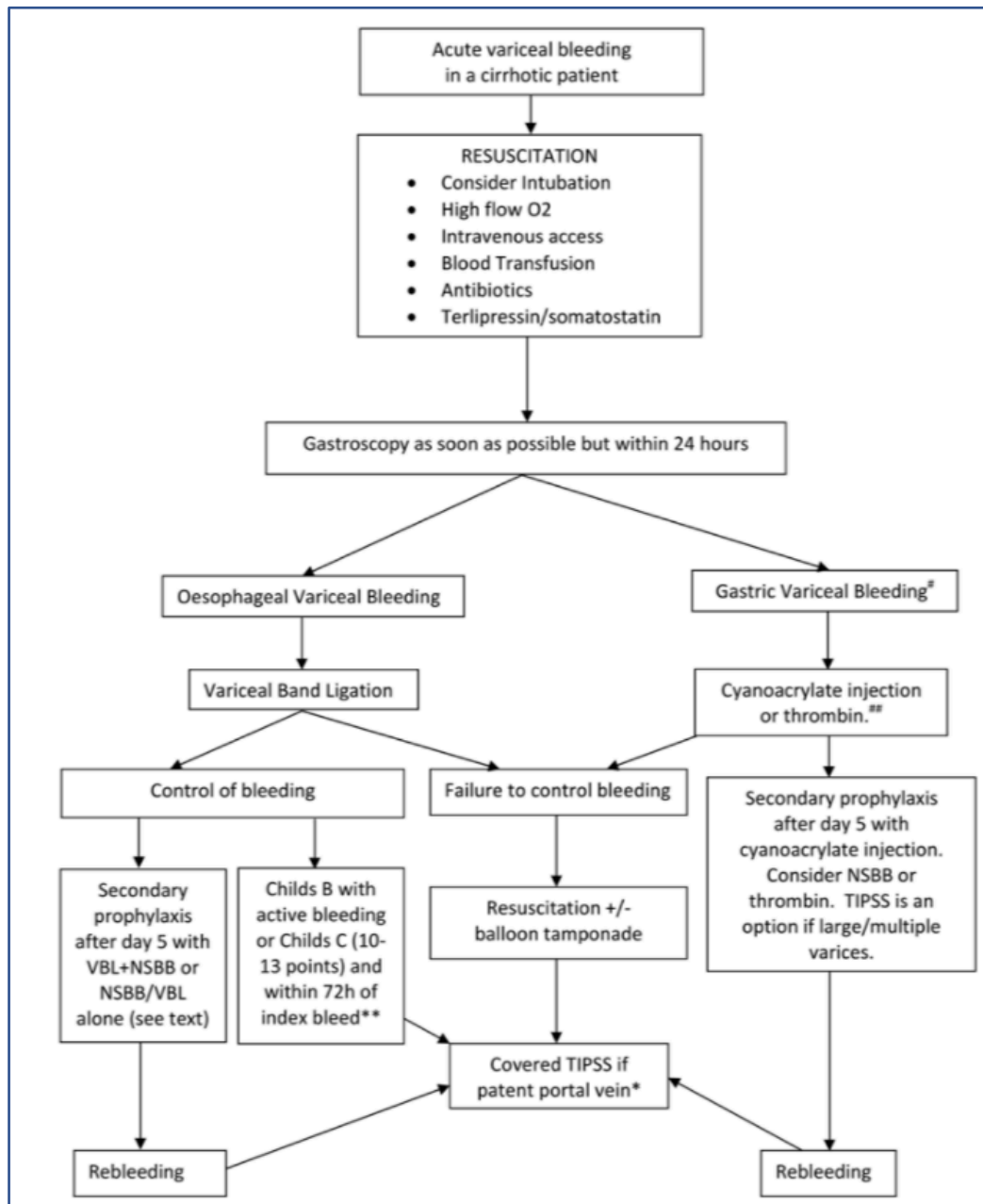
1.7.5.1 Standard of care

Combination therapy of repeated EBL and NSBBs is the treatment of choice for secondary prophylaxis of oesophageal variceal rebleeding (VRB). Studies suggest reduced rebleeding and improved survival with this combination of therapy compared with monotherapy of either EBL or NSBBs (150 – 153). In patients with contraindication to or intolerance of NSBB, VBL monotherapy should be used. EBL of varices should be undertaken every 2-4 weeks until eradication is achieved. Thereafter, patients undergo endoscopy at 3 months and then 6 monthly. Identification of recurrent varices should be treated with repeat EBL as per the above intervals until eradication is achieved (126).

1.7.5.2 Pre-emptive TIPSS

Placement of pre-emptive TIPSS (pTIPSS), previously referred to as “early-TIPSS”, within 72 hours of endoscopically achieved haemostasis is recommended in high-risk patients, these being CP grade B with active bleeding seen on index endoscopy, and any CP C patient with suspected OVB (126, 127) (Figure 1.1 (126)). This recommendation was proposed following a single RCT in which patients who received pTIPSS placement had significantly higher survival rates compared to the group receiving standard of care (SOC), however the practices used in the SOC group included some endoscopic and pharmacological treatments that are no longer up to date (154). Subsequent observational studies have failed to confirm any true survival benefit with pTIPSS, and demonstrate that only a small minority of patients who are suitable for pTIPSS are being referred for stent placement (155 – 157).

Figure 1.1 British Society of Gastroenterology guidelines on the management of acute variceal haemorrhage



1.8 Aims

The primary aims of the studies presented in this thesis are:

- To determine if pre-emptive TIPSS (pTIPSS) offers survival benefit over modern standard of care (SOC) following OVB
- to determine if the timing of pre-emptive TIPSS insertion following OVB alters patient outcome
- to determine the long-term outcomes for patients receiving either carvedilol or EBL following OVB
- to determine the long-term outcomes for patients receiving pre-emptive TIPSS.

Chapter 2 Randomised control trial of early-transjugular intrahepatic portosystemic shunt (TIPSS) versus standard of care

The original study protocol was written by Dr A. Shams, for whom I extend my gratitude. I am also thankful for the numerous other colleagues who helped with the identification and recruitment of patients throughout the study period.

2.1 Introduction

Variceal haemorrhage is a major complication of portal hypertension and a common cause of death in patients with liver cirrhosis. For patients with uncontrolled oesophageal variceal bleeding (OVB) despite endoscopic band ligation (EBL) therapy, placement of a transjugular intrahepatic portosystemic shunt (TIPSS) decreases portal pressure in an attempt to reduce haemorrhage and blood loss: so-called “rescue TIPSS”. This concept of TIPSS implantation to reduce portal pressure has led some to promote this approach in order to avoid and prevent early rebleeding in high-risk patients in which haemostasis was initially achieved. In a previous landmark multicentre randomised controlled, early-TIPSS placement (within 72 hours from index endoscopy for oesophageal variceal bleeding) in 63 patients with Child-Pugh (CP) B disease with active bleeding or CP C disease reduced rates of rebleeding and was also associated with improved 1-year survival (86% compared to 61% in the standard of care group) (154). Although patients with CP B disease and active bleeding during endoscopy are deemed high risk, the premise of active bleeding is unclear from the previous study thus open to interpretation by the endoscopist. Nonetheless, based on these data, international guidelines currently recommend consideration of early-TIPSS for all high-risk patients presenting with OVB following initial haemostasis using pharmacological management and endoscopic band ligation (126, 127).

Despite the reported survival benefit of early-TIPSS and the current clinical recommendations, the use of early-TIPSS is rarely adopted. In a recent observational study of 58 centres in France, only 6.7% of the suitable patients were treated with early-TIPSS (157). This was a negative study, with the only independent predictor of survival being severity of liver disease itself. In a similar observational study, early-TIPSS placement was used in only 9.8% of suitable high-risk patients across 34 centres (158). A survival benefit of early-TIPSS was only seen in those with CP C disease. These large observational multicentre studies underscore continued equipoise regarding the value of early-TIPSS and perhaps highlights the difficulty in accessing suitable interventional radiology (IR) to provide a non-emergency early-TIPSS service in real-world clinical practice. In addition, they also highlight that the process of patient selection for early-TIPSS needs to be refined.

2.2 Aims

To replicate the landmark study (154) in a UK population given the uncertainty and inconsistent evidence base supporting the use of early-TIPSS in the relevant patient groups.

2.3 Methods

2.3.1 Participants and Settings

This was an open-label, parallel-group, RCT carried out at two UK centres, Royal Infirmary of Edinburgh (RIE) and Glasgow Royal Infirmary (GRI), between April 2012 and January 2018. Both centres have an experienced 24-hour emergency TIPSS service. The trial complied with Good Clinical Practice Guidelines and was approved by the East of Scotland Regional Ethics Committee (REC: reference number 12/SS/0008). The trial protocol is available at:

<https://clinicaltrials.gov/ct2/show/NCT02377141>

Patients with liver cirrhosis presenting with acute OVB and subsequent haemostasis following treatment with vaso-active drugs and EBL were considered for inclusion in the trial. Exclusion criteria included age less than 18 or more than 75 years, pregnancy, CP score <8 and >13, inability to control bleeding at index endoscopy, previous portosystemic shunt or TIPSS, previous pharmacotherapy and EBL, bleeding from isolated gastric or ectopic varices, known portal vein thrombosis, active cancer including hepatocellular carcinoma (HCC), and recurrent hospital admissions with hepatic encephalopathy. (HE). Patients, or their next of kin, for those with fluctuating conscious level due to hepatic encephalopathy, provided written informed consent.

2.3.2 Study design

After achieving endoscopic haemostasis, consenting participants were randomised 1:1 to either standard of care (continued EBL sessions ± pharmacotherapy) or early-TIPSS, using a 24-hour web-based randomisation service [<https://www.aleaclinical.eu> (ALEA Clinical, Abcoude, The Netherlands)].

2.3.3 Study Procedures

Patients with suspected acute OVB and cirrhosis who presented to the Emergency Department at either centre were resuscitated as appropriate. Pre-endoscopic management included the use of antibiotics and vaso-active drugs (terlipressin) unless contraindicated. Policy was to perform endoscopy within 12 hours of presentation. During endoscopy, EBL was performed to either gain haemostasis for actively bleeding varices or to treat pre-existing varices with high-risk stigmata of recent bleeding e.g., red spots or fibrin plugs. EBL performed at RIE was carried out using the Boston Scientific Speedband SuperView Super 7™, and at GRI using the Cook 6-Shooter Saeed Multi-Band Ligator™.

Following endoscopy, participants randomised to standard of care (SOC) had terlipressin continued for up to five days, antibiotics for five to seven days and were entered into an outpatient endoscopic variceal EBL programme. The standard practice in both centres was to undertake endoscopy at two to four-weekly intervals

until variceal eradication, and then repeat endoscopy in three, then six monthly intervals (126). Carvedilol, a non-selective beta blocker, was commenced prior to discharge from hospital at a dose of 6.25 mg and titrated thereafter, depending on participant tolerability.

For those randomised to early-TIPSS, the aim was to perform TIPSS within 72 hours after initial endoscopy. Terlipressin was continued until TIPSS was performed and antibiotics were continued for five to seven days. TIPSS procedures were carried out by interventional radiologists experienced in this technique. The e-polytetrafluoroethylene (e-PTFE) covered stents (Viatorr TIPSS endoprosthesis, W. L. Gore & Associates, Inc, Newark, USA) were initially dilated to eight or nine mm. If the portal-pressure gradient (the difference between portal-vein pressure and inferior vena caval pressure) did not decrease to below 12 mm Hg, the stent was dilated further to nine or ten mm. TIPSS patency was checked at six months and one year using Doppler ultrasonography or TIPSS venography. If TIPSS dysfunction was confirmed, balloon angioplasty was performed, or a further e-PTFE-covered stent was placed.

A dedicated member of the study team performed the randomisation and was responsible for data collection of that participant. The principal investigator oversaw the running of the study at each site (Dr Philip Dunne – RIE, Prof Adrian Stanley – GRI).

2.3.3.1 Follow-up

Follow-up visits were scheduled at six weeks, six months, and one year at which participants underwent clinical examination, blood testing and any interim hospital attendances were reviewed.

2.3.4 Study Outcomes

The primary outcome was survival at one year. Secondary outcomes included survival at six weeks; rates of early rebleeding (within six weeks) and late rebleeding (between six weeks and one year); and the development of hepatic encephalopathy. Subsidiary

outcomes were the development of new ascites, the number of days in the intensive care unit, hospital attendances (including to the endoscopy unit), the use of alternative treatments including non-selective beta-blockers (NSBBs), and safety profile.

2.3.5 Analysis

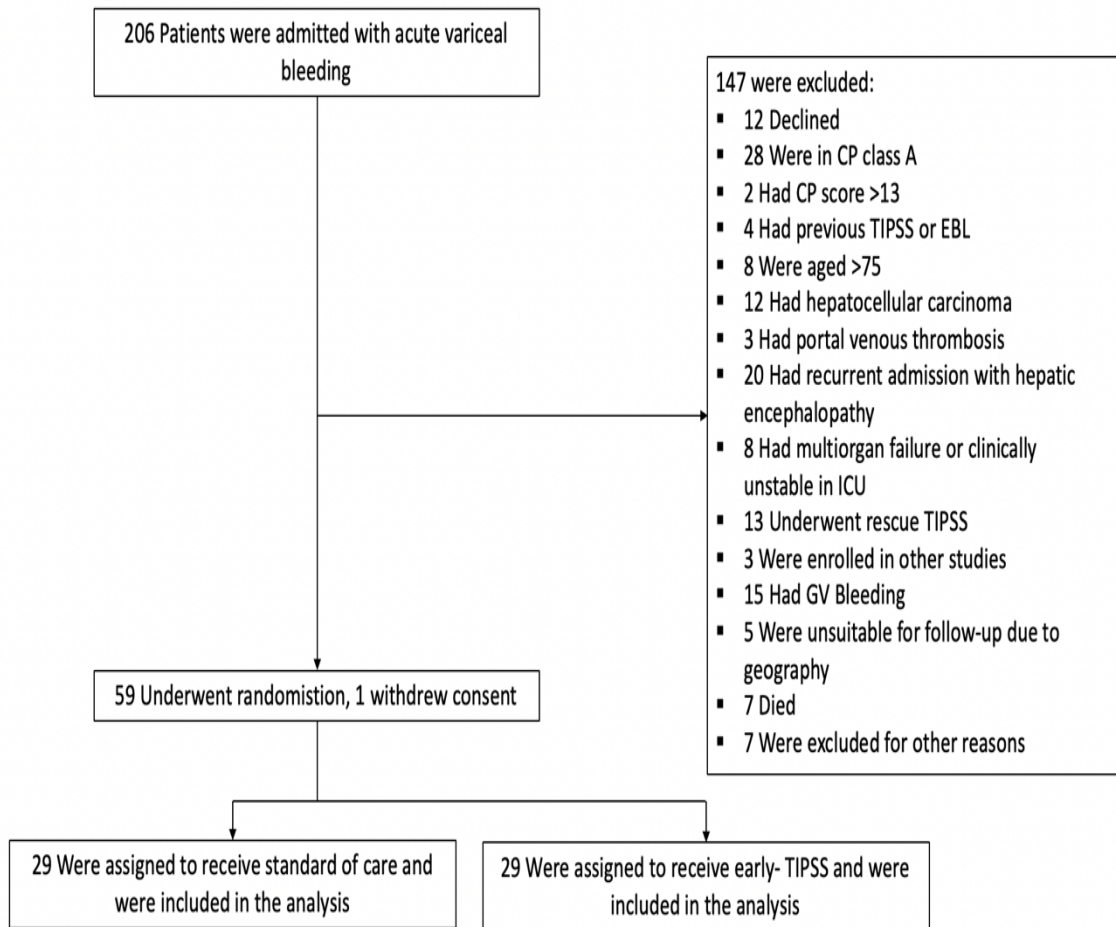
This study aimed to confirm the results of the first early-TIPSS RCT (154). The authors observed 14% and 39% deaths in the two trial arms. Therefore, we calculated a need for 48 patients per group to find a difference in survival between the two trial arms using two-sided log-rank test ($\alpha=0.05$, power of 80%) with four extra patients per group to allow for drop out and non-compliance. Initial data analyses were performed on an intention to treat basis, with further per-protocol analysis provided thereafter. A two-sided p-value of less than 0.05 was considered as statistically significant. Dichotomous variables were compared by means of Fisher's exact test, and continuous variables were compared by means of the nonparametric Mann–Whitney rank-sum test. The probabilities of reaching the primary end point of survival were estimated by the Kaplan–Meier method and were compared by means of the log-rank test. Hazard ratios are not provided in the setting of crossing lines. Safety assessments were made on analysis of all patients who received the intended treatment, rather than on intention to treat. The statistical software packages used for the analysis were SPSS (v17, IBM, Armonk, USA) and Prism (v8, GraphPad software, CA, USA).

2.3 Results

2.3.1 Screening and randomisation

Two-hundred and six patients with acute OVB were admitted to the participating centres and screened for eligibility (Figure 2.1); 147 patients were excluded and of the remaining 59 patients, one later withdrew consent. Fifty-eight patients were randomised to either the SOC group or the early-TIPSS group (29 patients per group). There were no differences in baseline characteristics between the two treatment groups at study entry (Table 2.1). No participants were lost to follow-up.

Figure 2.1 Screening and Randomisation of patients



Of the 29 randomised to receive early-TIPSS, 13 received TIPSS within 72 hours, 10 received TIPSS beyond 72 hours and 6 did not undergo TIPSS placement - these participants crossed over to the standard of care arm.

CP= Childs-Pugh, EBL= Endoscopic Band Ligation, ICU= Intensive Care Unit, GV= Gastric Varices, TIPSS= Transjugular Intrahepatic Porto-Systemic Shunt

Table 2.1 Summary of Patient Characteristics

Clinical characteristic	Standard of Care (n=29)	Early-TIPSS (n=29)
Age (SD)	48 (±12)	53 (±10)
Female (%)	10 (34)	9 (31)
Cause of cirrhosis (%)		
ArLD	26 (90)	28 (97)
NAFLD	2 (7)	1 (3)
Viral	1 (3)	0 (0)
Active alcoholism (%)	24 (83)	25 (86)
Child-Pugh score (SD)	9.8 (±1.5)	9.8 (±1.2)
Child-Pugh class		
Class B (%)	12 (41)	13 (45)
Class C (%)	17 (59)	16 (55)
MELD score (SD)	17 (±3.8)	17 (±3.4)
Ascites		
None (%)	12 (41)	9 (31)
Mild (%)	10 (34)	14 (48)
Severe (%)	7 (24)	6 (20)
Bilirubin (IQR)	62 (39)	58 (50)
Albumin (SD)	24 (± 5.7)	25 (± 4.9)
Prothrombin time (SD)	19 (± 3.8)	20 (± 4.7)
Creatinine (IQR)	62 (33)	60 (26)
Serum sodium (SD)	135 (± 4.3)	135 (± 6.3)
Previous Hepatic Encephalopathy		
None (%)	28 (97)	26 (90)
Grade I-II (%)	1 (3)	3 (10)
Systolic blood pressure (SD)	125 (± 16)	118 (15)
Heart rate (SD)	98 (± 24)	98 (± 21)
Antibiotic use (%)	29 (100)	29 (100)
Vasoactive drug therapy (Terlipressin) at the time of bleeding (%)	13 (44)	14 (48)
Active bleeding at endoscopy (%)	10 (34)	8 (28)
Bands applied at index endoscopy (SD)	5 (±1.3)	4.8 (±1.0)

IQR = Inter-quartile range; MELD = Model for end-stage liver disease; SD = Standard deviation

2.3.2 Compliance with protocol

In the SOC group, 21 participants were maintained on NSBB therapy with 18 receiving carvedilol (median dose, 6.25 mg [range, 3.125 to 12 mg]) and three on pre-existing cardio-selective preparations prescribed for other clinical reasons. In the remaining eight patients, carvedilol was not initiated because of contraindications in six and early rebleeding or death in two. Median number of planned (non-emergency) EBL endoscopies performed in the follow-up period was four (range, 0-8). Eradication of varices was achieved in 14 participants after a median of three endoscopic band ligation sessions (range, 1-6). In the remaining 15 patients, eradication was not achieved in seven despite a median of six endoscopic band ligation sessions (range, 4-8), or because of rebleeding resulting in rescue TIPSS in two, death in three, and refusal of further endoscopies in three. One patient underwent liver transplantation during follow-up.

Of the 29 participants randomised to the early-TIPSS group, 23 received shunt placement and six participants did not undergo TIPSS placement due to logistical and practical issues. The mean time from endoscopy to TIPSS placement for all participants was 65 ± 37 h. Ten participants received TIPSS placement outside the 72-hour window due to a delay in randomisation, with a mean time from endoscopy to randomisation of 37 ± 22 hours. In comparison, the remaining 13 participants who received TIPSS placement within the 72-hour window had a mean time from endoscopy to randomisation of 18 ± 12 hours. Of the 23 participants who received TIPSS placement, 22 received it within 72 hours of randomisation, rather than from endoscopy. There were no technical failures or major complications of the TIPSS procedures. A total of 21 participants required one stent, and two participants required two stents. The mean portal-pressure gradient dropped from 17 ± 5 mmHg to 7 ± 3 mmHg. Despite dilation to 10 mm, the portal-pressure gradient after TIPSS remained above 12 mmHg in three patients, although all participants achieved a portal pressure gradient fall $>20\%$ (mean $58\pm 18\%$). Additional variceal embolisation was performed in one patient.

2.3.3 Survival

The six-week survival rate in SOC group was 96.5% versus 89.6% in the early-TIPSS group. There were no differences in 1-year survival rates between the SOC and early-TIPSS group (75.9% vs. 79.3% $p=0.79$) (Figure 2.2). Causes of death in both groups are summarised (Table 2.2). Thirty-three trial participants had CP-C cirrhosis of whom 17 were in the standard of care group and 16 in the early-TIPSS group, with 1-year survival rates being 70.6% and 68.7%, respectively, $p=0.80$ (Figure 2.3). Considering all participants who were randomised to early-TIPSS and received TIPSS placement, there was no difference in survival compared to the SOC group respectively (78.3% vs. 75.9%, $p=0.85$) (Figure 2.4).

Figure 2.2 Survival: Early-TIPSS vs. Standard of Care (Intention to treat)

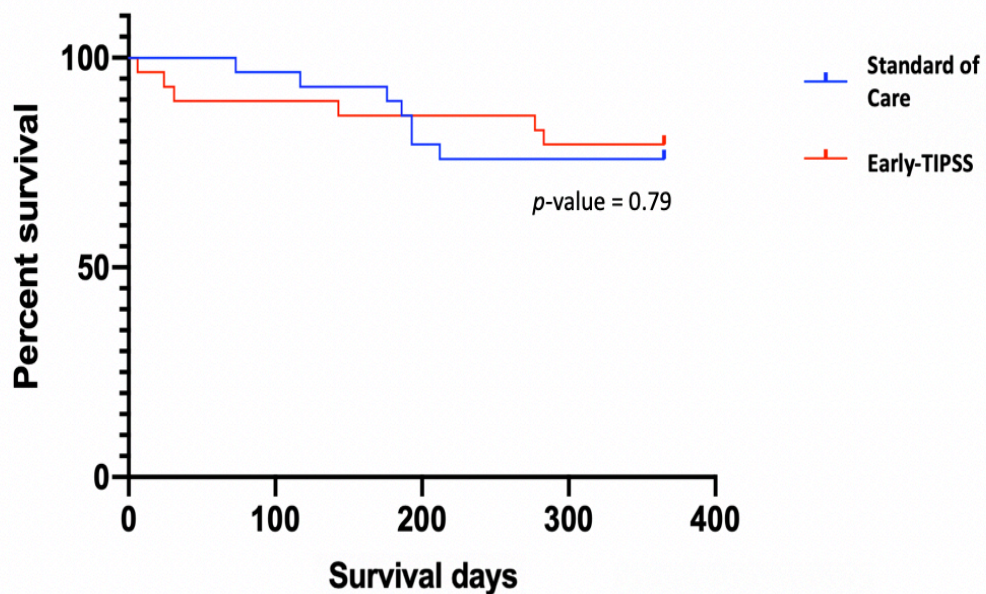


Table 2.2 Secondary and subsidiary outcomes (Intention to treat)

Variable	Standard of Care (n=29)	Early-TIPSS (n=29)	p value
Cause of death:			
GI bleed	1	1	
Liver failure	4	2	
Sepsis	1	2	
Cardiovascular	1	1	
All Cause Rebleeding (number of patients):			
<6 weeks	5	1	0.08
6 weeks – 1 year	5	6	0.79
Total	10	7	0.86
All Cause Re-bleeding (all episodes):			
<6 weeks	5	2	
6weeks – 6months	4	3	
6months -12months	3	6	
Total at 1 year	12	11	
Variceal Rebleeding (number of patients):	8	3	0.09
Causes of Rebleeding (all episodes):			
Variceal	9	4	
Banding ulcer	2	3	
Mallory Weiss	1	2	
Hepatic Encephalopathy	5	12	0.05
New or Worsening Ascites	3	4	0.71
Median days in Intensive care	1	1	0.32
Orthotropic liver transplantation	1	0	

Figure 2.3 Survival: Early-TIPSS vs. standard of care, Child-Pugh C (Intention to treat)

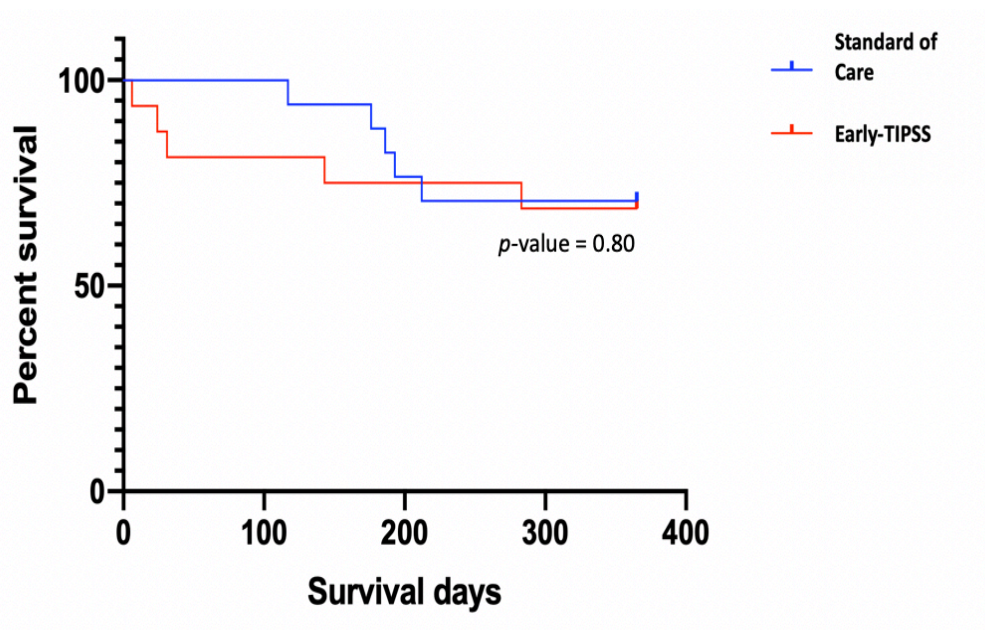
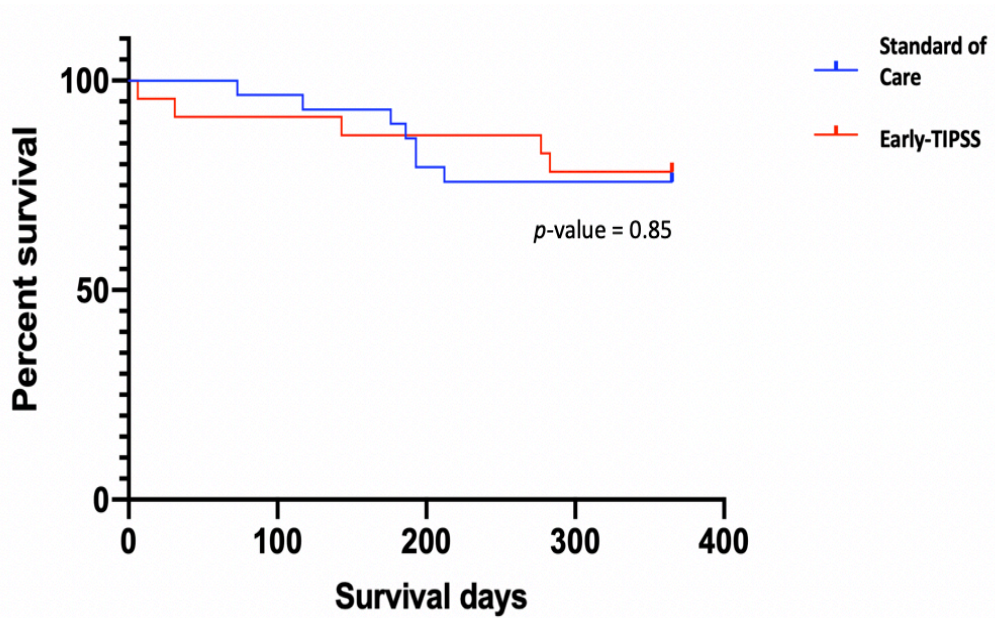


Figure 2.4 Survival: All Early-TIPSS vs. Standard of Care



2.3.4 Rebleeding

In the SOC group, ten participants experienced a rebleeding episode with eight having variceal rebleeding. Six of these participants later died during the follow-up period. In three participants, TIPSS was used as rescue therapy. Although bleeding was controlled in all and portal pressure gradient brought below 12 mmHg, all three patients died at a median of 143 days (range, 15 to 185). The remaining two patients who experienced variceal rebleeding and did not die in the follow-up period underwent additional EBL sessions. In total, there were twelve rebleeding episodes in this group, nine of which were variceal.

In the early-TIPSS group, seven participants experienced a rebleeding episode, three of which had variceal rebleeding. Of the three, two participants did not receive early-TIPSS after randomisation and one had TIPSS placed >72 hours after endoscopy but required two stent insertions as well as a TIPSS redilatation. There were eleven bleeding episodes in this group, four of which were variceal.

There was no difference in the number of participants experiencing all cause rebleeding at 1-year between the SOC and early-TIPSS groups (24.1% vs. 34.6% respectively, $p=0.86$). At the specified time points, there were no differences in rates of all cause rebleeding between SOC and early-TIPSS groups respectively; 0-6 weeks (17.2% vs. 3.4%, $p=0.08$); 6-weeks to 1-year (17.2% vs. 20.7%, $p=0.79$). In relation to rates of variceal rebleeding (Table 2.2), there was an apparent trend for lower rates in the early-TIPSS group after 1-year of follow up (10.3% vs. 27.6% in standard of care group, $p=0.09$) (Figure 2.5). Of the 23 participants who received TIPSS, only one (4.3%) experienced variceal rebleeding compared with eight (27.6%) in the standard of care group ($p=0.04$).

Figure 2.5 Free from variceal rebleeding: All TIPSS vs. Standard of Care (intention to treat)

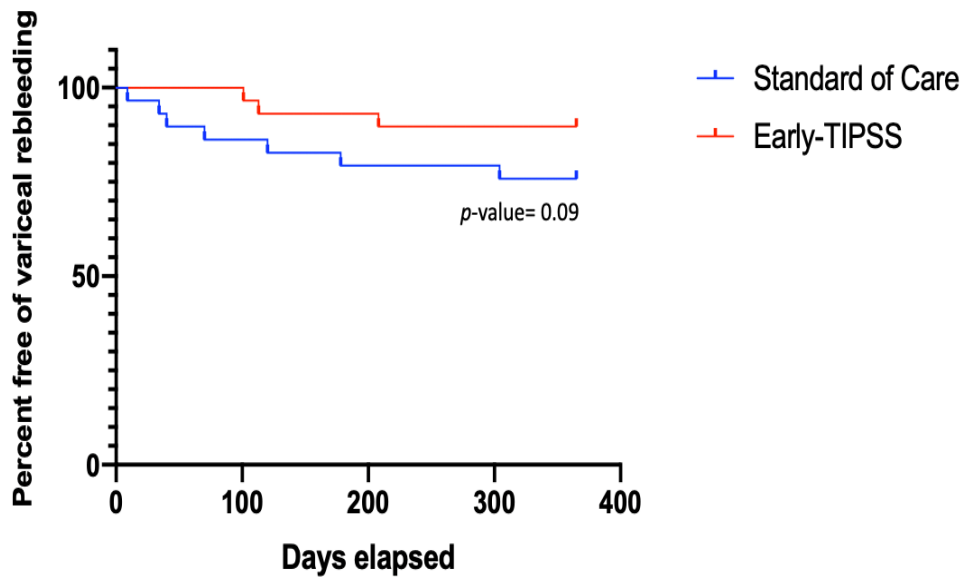
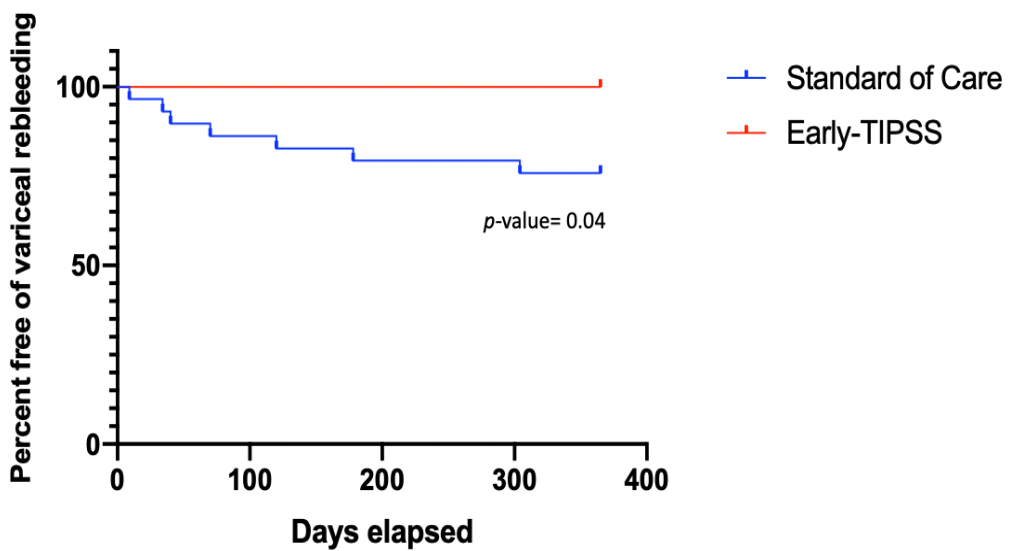


Figure 2.6 Free from variceal rebleeding: Early-TIPSS vs. Standard of Care (per-protocol)



2.3.5 Other complications of portal hypertension

2.3.5.1 Hepatic encephalopathy

In the early-TIPSS group, twelve patients had at least one episode of HE in the follow-up period, compared to five in the standard of care group ($p=0.05$) (Table 2.2). Similarly, in those who received a TIPSS, HE was experienced by ten (43.5%) patients compared with five (17.2%) patients in the standard of care group ($p=0.04$).

2.3.5.2 Ascites

Fourteen of the 29 (48.3%) participants in the standard of care group had ascites during their follow-up period compared to 9 of the 29 (31.0%) participants in the early-TIPSS group. The rates of developing new or worsening ascites were 10.3% in the standard of care group and 13.8% in the early-TIPSS group ($p=0.71$)

There were no significant differences between groups in other adverse events (Table 2.3).

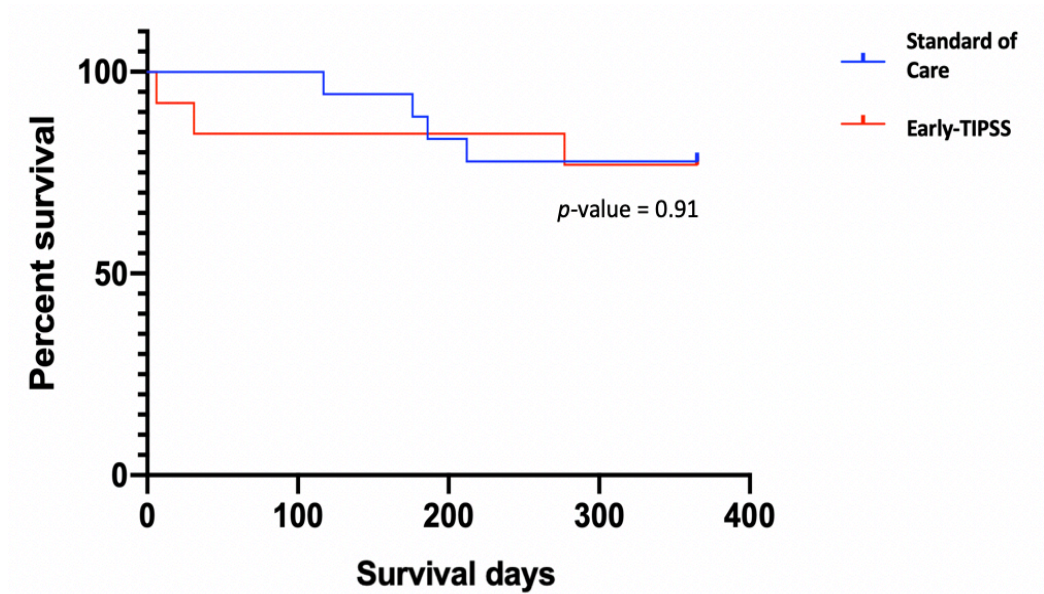
2.3.6 Per-Protocol Analysis

Given that some patients randomised to early-TIPSS either did not receive TIPSS or received TIPSS out with the 72-hour window, a per-protocol analysis was also performed. One-year survival rate in the 13 participants who received TIPSS within 72 hours of index endoscopy was 76.9% (10/13) compared with 75.9% (22/29) in the standard of care group ($p=0.91$) (Figure 2.7). The 1-year survival rate for those who received TIPSS placement beyond 72 hours from index endoscopy was 80.0% (8/10). For the 13 who received TIPSS placement within the pre-defined time period of 72 hours from endoscopy, none suffered variceal rebleeding which was significantly less than the 27.6% (8/29) in the SOC ($p=0.04$). One-year variceal rebleeding rate in those who received TIPSS out with 72 hours was 10.0% (1/10). HE was experienced in 46.1% (6/13) of those who received early-TIPSS which was significantly higher than 20.7% (5/29) in the standard of care group ($p<0.05$).

Table 2.3 Summary of other adverse events

Adverse Event	Standard of Care (n=29)	Early-TIPSS (n=23)
Seizure	0	2
Fractured bone	2	3
Cellulitis	0	1
Arrhythmia	1	1
Abscess	1	0
Compartment Syndrome	1	0
Urinary Tract Infection	1	1
Alcoholic Hepatitis	2	1
Left Ventricular Thrombus	0	1
Pneumonia	0	2
Spontaneous Bacterial Peritonitis	2	1
Spontaneous Retroperitoneal Bleed	0	1
Hyponatraemia	0	1

Figure 2.7 Survival: Early-TIPSS vs. Standard of Care (per protocol)



2.4 Key findings

Placement of early-TIPSS appears to reduce rates of variceal rebleeding but increases rates of hepatic encephalopathy with no effect on survival in patients who have Child Pugh B and C cirrhosis. It was not possible to arrange early-TIPSS for all participants therefore, a consistent early-TIPSS service may not be feasible in some centres.

Chapter 3 Effect of timing on pre-emptive transjugular intrahepatic portosystemic shunt timing on patient outcome, a UK multicentre cohort study

I would like to express my thanks to Dr J. Finkel and Dr F. Khan who kindly collected the data for the centres outside Scotland.

N.B. A change to reflect updated nomenclature in the medical literature over time is presented in the text. The previously referred to “early-TIPSS” procedure is now known as “pre-emptive TIPSS”.

3.1 Introduction

International guidelines recommend consideration of pre-emptive transjugular intrahepatic portosystemic shunt (pTIPSS) following endoscopically controlled oesophageal variceal bleeding (OVB) in carefully selected “high-risk” patients (21, 126, 127, 159, 160). Although these guidelines differ in their definition of “high-risk” (Child-Pugh (CP) C <14, or CP-B with active bleeding, or Model for End-Stage Liver Disease (MELD) >19), they are consistent in their recommendation to perform pTIPSS placement within 72 hours of index endoscopy. pTIPSS has been shown to improve variceal rebleeding rates but the effect on survival remains undetermined.

Historic data suggests the greatest occurrence of variceal rebleeding is between 48-72 hours after the initial bleeding episode (161). Therefore, a 72-hour timeframe from index endoscopy to TIPSS insertion was first chosen in a randomised control trial (RCT) investigating the effects of pTIPSS placement compared to standard of care following OVB (154). However, the most recent pTIPSS RCT (*Chapter 2*) revealed that 35% of participants randomised to receive pTIPSS waited beyond 72 hours to receive TIPSS placement, albeit their survival rates were unaffected. (162) Difficulties in sourcing anesthetic and interventional radiology (IR) support were cited as hurdles.

In a large observational study, only 6.7% of high-risk patients received pTIPSS within 72hrs, with a further 6.4% undergoing pTIPSS placement between 72 hours and 42 days (157). Notably, early shunt placement was not an independent predictor of survival. In another similarly large observational study, pTIPSS placement was used in only 9.8% of high-risk patients and inconsistent availability of the TIPSS service in nine of the “TIPSS centres” was reported (158). These studies highlight the important difference between feasibility and practicality of providing a non-emergency TIPSS service within a relatively short 72-hour window in real-world clinical practice.

3.2 Aims

Despite growing evidence on the optimal timing of endoscopy for upper GI bleeding, there is a significant lack of evidence regarding timing of pTIPSS. The aim was to determine if the time taken to perform pTIPSS following index endoscopy for OVB alters patient outcome.

3.2 Methods

3.2.1 Patients and settings

This was a multicentre cohort study with non-selective, continuous data collected on patients referred for pTIPSS between January 2010 and December 2018 following endoscopically stabilised acute OVB at four UK tertiary centres; Royal Infirmary of Edinburgh (RIE), University Hospitals Birmingham (UHB), Royal Free Hospital London (RFH), and Glasgow Royal Infirmary (GRI).

Patients with liver cirrhosis and OVB achieving endoscopic haemostasis following endoscopic band ligation (EBL), vasoactive drugs and antibiotics who then received pTIPSS were included. Those who underwent TIPSS following failure of endoscopic haemostasis, as well as those with early rebleeding, were deemed as having had “rescue-TIPSS” and therefore not suitable for consideration in this study. For patients

whom TIPSS placement was precluded by other clinical factors such recurrent hepatic encephalopathy (HE), unsuitable anatomy or portal vein thrombosis were not considered. Study specific exclusion criteria included age less than 18 or more than 75 years, pregnancy, CP score <8 and >13 with or without active bleeding, previous TIPSS, and active cancer including hepatocellular carcinoma (HCC).

3.2.2 Study procedures

Vasoactive drugs were continued until TIPSS placement, or for a maximum of five days. TIPSS placement was carried out by interventional radiologists experienced in the technique. The e-polytetrafluoroethylene (e-PTFE) covered stents (Viatorr TIPSS endoprosthesis, W. L. Gore & Associates, Inc, Newark, USA) were initially dilated to eight or nine mm. Pre and post-TIPSS portal pressure gradients (PPG) were recorded, and the PPG change calculated. If the PPG (the difference between portal-vein pressure and inferior vena caval pressure) did not decrease to below 12 mm Hg, the stent was dilated further to nine or ten mm.

The time of index endoscopy achieving haemostasis (time point zero) was recorded and the time to pTIPSS insertion (hours) was calculated. Patients were classified as having had “early pTIPSS” (≤ 72 hrs from index endoscopy) or “late pTIPSS” (between 72 hours – 28 days from index endoscopy), these being the two groups compared in the analysis. No specific patient factors determined the timing of pTIPSS placement. The decision to pursue pTIPSS was made by the treating clinician, and the timing of the procedure was dependent upon patient consent and IR availability. All cases were followed up from the date of TIPSS insertion until the date of death, orthotopic liver transplant (OLT), or study closure date – 31st December 2020, whichever was earlier. TIPSS patency was checked at six months and one year (or earlier if clinically indicated) using Doppler ultrasonography or TIPSS venography. If TIPSS dysfunction was confirmed, balloon angioplasty was performed, or a further e-PTFE-covered stent was placed.

All patients were consented to receive pTIPSS and informed that their anonymised clinical details would be added to a database for study purposes. Local clinical governance teams did not request formal ethics approval for the study as the data was categorised for use as audit and quality improvement.

3.2.3 Data collection

Once the pTIPSS was performed and the patient eligible for inclusion, relevant patient data were added to an electronic database that was later cross checked with electronic patient admissions records to ensure no patients were missed or falsely included. Data were collected by a dedicated member of the study team and obtained from electronic integrated clinical records systems. Baseline data included age, sex, primary aetiology of liver disease as well as clinical and laboratory parameters to calculate the severity of liver disease using the CP and MELD classification.

3.2.4 Study outcomes

The primary outcome for this study was 1-year liver transplant free survival. Secondary outcomes include long term transplant free survival, 1-year and long-term liver failure related mortality, 1-year variceal rebleeding rates, 1-year post-TIPSS HE rates, and 1-year rates of new or worsening ascites.

3.2.5 Analysis

Data were presented as mean (SD), median (IQR) for continuous variables and frequencies or percentages for categorical variables. Student-t and Mann–Whitney U tests were used to compare normally distributed continuous variable and non-parametric continuous variables respectively. χ^2 analysis or Fisher's exact test was used to compare categorical variables. p -value <0.05 was considered statistically significant. In the setting of unmatched groups, propensity score matching was to be used. The probability of reaching the primary end point of survival was estimated by the Kaplan–Meier method and compared by means of the log-rank test. Patients who were lost to follow-up were censored at their last know alive date, e.g., attendance at

a hospital appointment. Logistic regression analyses were used to estimate the association between time to pTIPSS placement and transplant free survival. The statistical software package used was Prism (v8, GraphPad software, CA, USA).

3.3 Results

3.3.1 Study groups

192 patients underwent pTIPSS in the four centres, 21 were excluded due to CPS <8 in nine patients, CPS >13 in three, age >75yrs in four, and concurrent HCC in five. Of the 171 included in the analysis, 83 received early pTIPSS and 88 received late pTIPSS. 71 patients had CP-C disease. 58 patients had pTIPSS placement at RIE, 46 at RFH, 37 at GRI and 30 at UHB. There were no differences in individual patient characteristics per group, Table 3.1.

3.3.2 Survival

There was no difference in 1-year transplant free survival rates between early and late pTIPSS groups respectively (69.9% vs. 71.6%, $p=0.73$, HR 0.91, 95% CI 0.52-1.58), (Figure 3.1). For those with CP-C cirrhosis undergoing pTIPSS (36 early, 35 late), again no difference in 1-year transplant free survival rate was seen between early and late groups respectively (58.3% vs. 59.5%, $p=0.9$, HR 0.95, 95%CI 0.47-1.93), (Figure 3.2). There was no difference in long term transplant free survival rates between early and late pTIPSS groups respectively, ($p=0.52$, HR 1.132, 95% CI 0.77 – 1.65), (Figure 3.3).

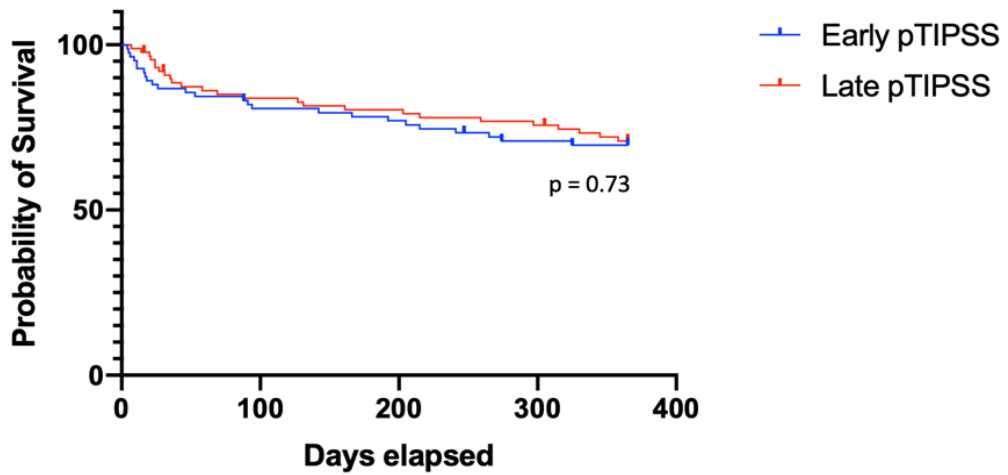
Liver failure was the commonest cause of death throughout. Of those who died within 1-year following TIPSS placement, liver failure was more common in the early pTIPSS group compared to the late pTIPSS group (44.0% vs. 16.0%, $p=0.046$, HR 2.79, 95%CI 1.02-8.32). For deaths beyond one year from the TIPSS procedure, liver failure was the cause in 23/51 (45.1%) of early pTIPSS and 22/56 (39.29%) in the late pTIPSS group ($p=0.56$, HR 1.129, 95% CI 0.77-1.65). There were no other significant differences in cause of death between groups. All causes of death are summarised (Table 3.2).

Table 3.1 Patient Characteristics

Characteristic	Early pTIPSS N= 83	Late pTIPSS N= 88	Significance
Age (SD)	53.38 (12.18)	52.04 (11.69)	0.69
Male sex	71.1	61.4	0.58
Aetiology			0.78
ArLD	53	66	
NAFLD	6	4	
Viral	6	3	
INR	1.57 (0.48)	1.46 (0.33)	0.33
Bilirubin (µmol/L)	63.44 (68.2)	67.76 (89.4)	0.37
Sodium (µmol/L)	137.2 (6.3)	136.9 (6.35)	0.72
Albumin (g/L)	27.81 (5.723)	28.65 (5.98)	0.93
Creatinine (µmol/L)	91.15 (81.95)	78.74 (44.78)	0.34
Ascites			0.28
None	28	18	
Mild	36	37	
Mod/severe	19	33	
Hepatic encephalopathy	23	23	0.89
MELD Score	16.42 (6.11)	15.52 (6.21)	0.67
Child Pugh Score	9.05 (1.774)	8.9 (1.83)	0.533
Child Pugh Class			0.48
Class B (%)	47 (56.6))	53 (60.2)	
Class C (%)	36 (43.4)	35 (39.8)	
PPG pre (mmHg)	20.6 (7.49)	21.58 (9.28)	0.71
PPG post (mmHg)	6.93 (3.13)	8.18 (3.14)	0.79
PPG fall (mmHg)	14.67 (6.36)	12.41 (5.45)	

Data expressed in brackets = Median (IQR), ArLD = Alcohol related liver disease, INR = International normalized ratio, MELD = Model for end-stage liver disease, NAFLD = Non-alcoholic fatty liver disease, PPG = Portal pressure gradient

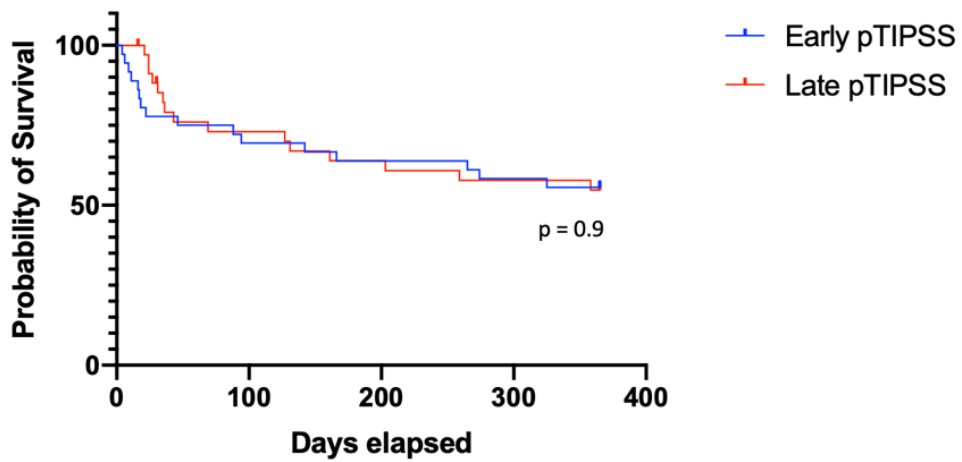
Figure 3.1 Survival at 1-year: Early vs. Late pTIPSS



Numbers at risk:

Days	0	7	28	90	180	270	365
Early pTIPSS	83	81	73	68	65	59	54
Late pTIPSS	88	88	81	73	70	97	60

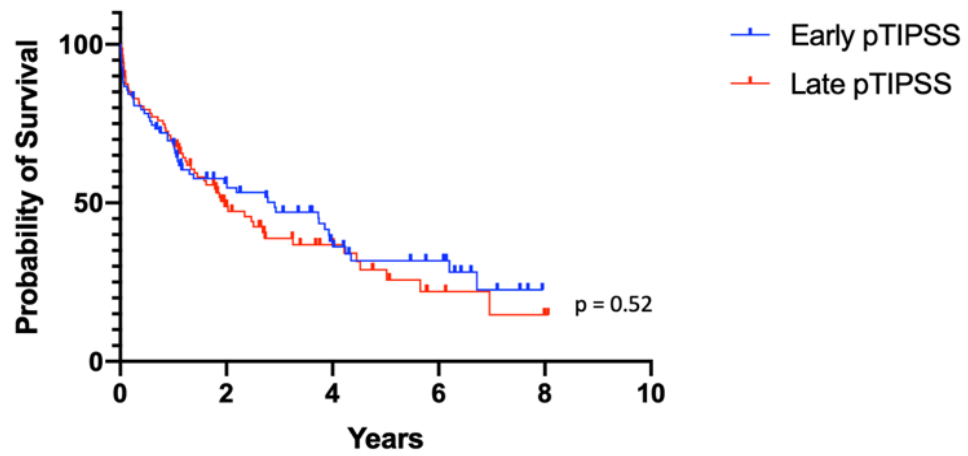
Figure 3.2 Survival at 1-year: Early vs. Late pTIPSS, Child-Pugh C



Numbers at risk:

Days	0	7	28	90	180	270	365
Early pTIPSS	36	35	29	27	24	23	20
Late pTIPSS	35	35	31	25	22	20	18

Figure 3.3 Long term survival: Early vs. late pTIPSS



Numbers at risk:								
Years	1	2	3	4	5	6	7	8
Early pTIPSS	57	39	31	21	15	13	5	1
Late pTIPSS	60	32	21	16	10	5	3	2

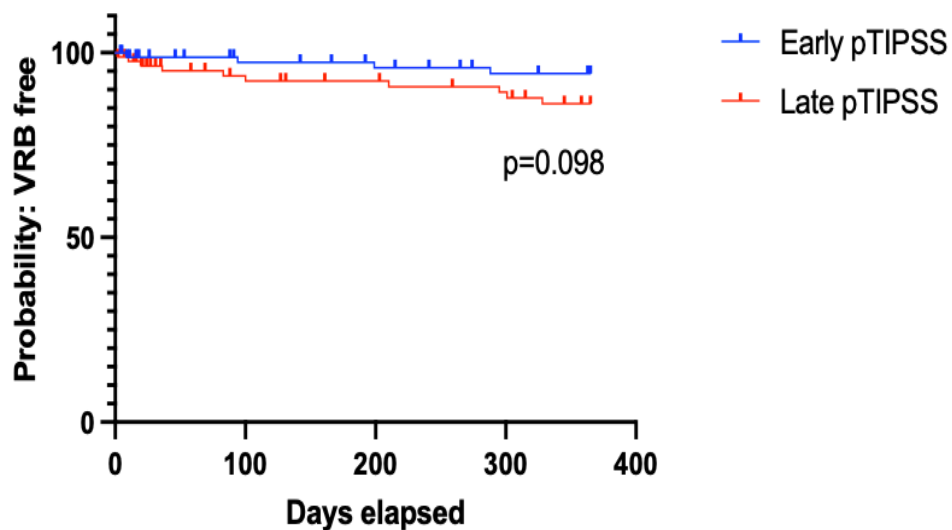
Table 3.2 Causes of death

Cause of death	1 year			Long term		
	Early pTIPSS n=83	Late pTIPSS n=88	P-value	Early pTIPSS n=83	Late pTIPSS n=88	P-value
Liver failure	11	4	0.046	23	22	0.56
GI Bleeding	2	6	0.279	5	9	0.41
Cardiovascular	2	1	0.612	3	3	0.99
Sepsis	6	9	0.595	10	14	0.51
Other	4	5	0.989	10	8	0.621
Total	25	25	--	51	56	--

3.3.3 Variceal rebleeding

1-year variceal rebleeding rates between early and late pTIPSS groups were 4.8% and 11.4%, respectively ($p=0.09$, HR 0.411, 95% CI 0.14-1.17). The probability of remaining free of variceal rebleeding at 1-year is shown (Figure 3.4).

Figure 3.4 Probability of remaining free of variceal rebleeding (VRB) at 1-year: Early vs. late TIPSS



3.3.4 Other complications of portal hypertension

1-year follow-up data on post-TIPSS HE, and new or worsening ascites was available for 118 patients in the study (66 early pTIPS, 52 late). 29 (43.9%) patients receiving early pTIPSS experienced at least one episode of HE compared to 18 (34.6%) in the late pTIPSS group ($p=0.26$, HR1.61, 95%CI 0.74-3.41). Eleven (16.6%) patients in the early pTIPSS group developed new or worsening ascites compared to 7 (13.5%) in the late pTIPSS group ($p=0.79$, HR 1.286, 95% CI 0.441-3.33).

3.3.5 Independent predictors of survival

Independent predictors of 1-year and long-term survival are shown (Table 3.3). Individual time (days) to pTIPSS did not influence probability of 1-year survival ($p=0.72$, SE 1.42, 95%CI -3.32 to 2.3) however, age ($p=0.002$, SE 0.77, 95% CI -3.94 to -0.91) and MELD ($p<0.001$, SE 2.008, 95% CI -11.67 to -3.74) did. In relation to long-term survival, age, MELD and previous HE were the only individual predictors.

Table 3.3 Competing risk model: multivariate regression analysis, 1-year and long-term survival

Variable	1-year survival			Long term survival		
	Standard error	95% CI	p-value	Standard error	95% CI	p-value
Child Pugh Score	8.674	-24.18 to 10.07	0.42	56.66	-99.38 to 124.4	0.82
MELD	2.008	-11.67 to -3.738	0.0002	13.12	-53.67 to -1.867	0.03
Age	0.7683	-3.945 to -0.9105	0.002	5.018	-23.26 to -3.442	0.008
Sex	18.92	-14.31 to 60.43	0.22	123.6	-196.3 to 291.9	0.7
Ascites	22.17	-25.10 to 62.45	0.41	147.6	-517.4 to 65.36	0.13
Encephalopathy	13.01	-48.17 to 3.207	0.08	84.98	-325.9 to 9.746	0.046
Days to pTIPSS	1.426	-3.325 to 2.305	0.72	9.312	-31.68 to 5.092	0.15

3.4 Key findings

Undertaking pTIPSS within 72 hours offers no benefit over pTIPSS placement between 72 hours and 28 days. However, early pTIPSS was associated with an increase rate of liver failure related mortality at 1-year. The use of MELD score rather than CP score may help improve patient selection.

Chapter 4 Long term follow-up of a randomised control trial: Carvedilol versus endoscopic band ligation for secondary prophylaxis of variceal bleeding

I would like to recognise the work undertaken by authors Prof A. J. Stanley et al. who wrote the protocol for the index trial, recruited the patients, and published the initial study results. Additionally, Dr D Young provided statistical guidance.

4.1 Introduction

Several randomised controlled trials (RCT) have demonstrated the efficacy of non-selective beta blockers (NSBBs) for both primary and secondary prevention of oesophageal variceal bleeding (OVV) (134, 163, 164). Current clinical guidelines recommend the combination of endoscopic band ligation (EBL) and NSBB following OVB, with combination therapy thought to be advantageous over monotherapy in the prevention of variceal rebleeding (VRB) (126, 159). However, there has been much interest of late in the potential additional benefits of NSBBs compared with other standards of care such as improved survival following OVB compared to EBL (165), improved survival for cirrhotic patients on a liver transplant waiting list (166), reduction in decompensation due to ascites and spontaneous bacterial peritonitis (SBP) (83, 167), and reduction in rates of hepatocellular carcinoma (HCC) (168).

Carvedilol is a NSBB that has an additional intrinsic anti- α 1 adrenergic effect. It has been shown to have a greater reduction in hepato-venous pressure gradient (HVPG) compared to other NSBB including propranolol and nadolol. HVPG is used as a surrogate marker for portal pressure and higher levels are associated with variceal bleeding and other complications associated with portal hypertension. On comparison to other NSBBs, carvedilol has also been shown to have clinical effectiveness in propranolol “non-responders” (92), better clinical tolerance (83), reduced long-term progression to ascites (169), and improved renal perfusion and

clinical outcomes in cirrhotics with ascites (89, 90). Additionally, carvedilol is associated with improved long-term survival when given as primary prophylaxis for OVB (135).

The index study reported that carvedilol and EBL were equally effective for secondary prophylaxis of variceal bleeding (170). Additionally, there was a trend towards improved survival in carvedilol treated patients, after a median follow-up of 26.3 months, albeit short of statistical significance.

4.2 Aims

To date, most studies assessing carvedilol in the prophylaxis of OVB had short-term follow-up. The aim was to investigate the long-term outcomes for patients taking carvedilol following OVB, with survival (intention to treat and per-protocol) as the primary endpoints.

4.3 Methods

4.3.1 Study design

This is a retrospective cohort analysis of 64 patients recruited to a multicentred randomised control study between June 2006 and December 2011. All patients had extended follow-up until April 2020. The index study was registered under trial number ISRCTN 69643049 and ethical approval was granted for each centre.

4.3.2 Index study protocol, procedures and participants

Patients with cirrhosis and endoscopically proven OVB who were stabilised following relevant initial endoscopic and pharmacological therapy (i.e., EBL, terlipressin and antibiotics) were recruited from four centres: Glasgow Royal Infirmary (GRI), Royal Infirmary Edinburgh (RIE), Gartnavel General Hospital Glasgow (GGH), and Southern General Hospital (SGH) Glasgow. Following the index endoscopy and after informed consent, clinically stable participants were randomised, at day five, on a 1:1 ratio to

receive either carvedilol 6.25mg (titrated to 12.5mg if tolerated after one week), or to undergo further EBL at two weekly intervals until variceal eradication, with six monthly surveillance endoscopies thereafter.

Exclusion criteria were: age <18 or >75 years; advanced malignancy or comorbidity resulting in life expectancy <6 months; obstructive airways disease; baseline pulse rate <50 bpm or systolic blood pressure <90 mmHg; severe peripheral vascular disease; heart block or severe heart failure; pregnancy; type-I diabetes; portal vein thrombosis; previous transjugular intra-hepatic portosystemic shut (TIPSS) or porto-caval shunt surgery; a gastric variceal bleed; or treatment with NSBBs within four weeks of the index bleed.

4.3.3 Long term follow-up data collection

A standardised electronic data collection proforma was used across all centres and populated by a local, lead clinician following interrogation of electronic patient records. All data were cross-checked against the original data set. Long-term follow-up data regarding the progress of patients' chronic liver disease were collected. These included hospital admissions related to decompensated liver disease (variceal rebleeding, development or worsening of ascites, SBP, HE, acute alcoholic hepatitis, sepsis); orthotopic liver transplantation (OLT); and TIPSS insertion. Mortality data were also collected including date and cause of death. Death certification was cross-referenced with records held by the National Records of Scotland. Carvedilol compliance and side effect profile were assessed by patient history, review of liver clinic appointment letters and review of primary care repeat prescriptions. EBL compliance and outcome were assessed by review of electronic patient records including attendance at hospital for planned EBL sessions and procedure reports. Any cross-over between treatment groups during follow-up was documented.

4.3.4 Primary and secondary outcomes

Primary outcomes were transplant free survival on intention to treat and per-protocol analysis. Secondary outcomes were variceal rebleeding and liver decompensation events on both intention to treat and per-protocol analysis; compliance with treatment; and cross-over between groups.

4.3.5 Analysis

Initial data analyses were performed on an intention-to-treat basis, with per-protocol analysis undertaken thereafter. Per protocol analysis was performed on participants randomised to carvedilol who had taken the medication for any duration, and for those randomised to EBL who attended more than the first two planned EBL sessions. Participants were censored in the event of failure of compliance, crossover of treatment arms, TIPSS placement, or at the end of the study period.

All statistical tests were two-sided using a 5% significance level. The probabilities of reaching the primary end point of survival were estimated by the Kaplan–Meier method and were compared using the log-rank test. Cox regression analysis was undertaken to determine if the following variables individually contributed towards survival: age, CP Score, MELD, ascites, variceal rebleeding, and liver related hospital admissions. The statistical software packages used for the analysis were SPSS (v17, IBM, Armonk, USA) and Prism (v8, GraphPad software, CA, USA).

4.4 Results

4.4.1 Randomisation

All 64 patients included in the index study were followed up, 33 of whom were initially randomised to receive carvedilol, and 31 to receive EBL. Baseline patient characteristics are shown (Table 4.1). The median number of follow-up days for all patients recruited was 1459 (SE = 281.74).

Table 4.1 Patient characteristics at recruitment

Characteristic	Carvedilol (n=33)	EBL (n=31)
Age, years; mean \pm SD	51.4 \pm 10.8	49.6 \pm 12.87
Alcohol Aetiology (%)	27 (87.1)	31 (93.9)
Male : Female	22:11	21:10
Child-Pugh Score	9 (7.0 – 10.5)	9 (8.0 – 11.0)
MELD	13 (8.25 – 18.5)	14 (11.0 – 16.0)
Bilirubin, μ mol/L	39 (19.5 – 63.0)	35 (23.0 – 82.0)
Albumin, g/L	27 (22.5 – 31.5)	27 (24.0 – 33.0)
Prothrombin, time (s)	15 (13.0 – 19.0)	16 (14.0 – 17.0)
Ascites, n (%)	12 (36.3%)	12 (38.7%)

All values expressed as Median (IQR) unless otherwise stated

4.4.2 Compliance and censoring

Of the 33 patients randomised to carvedilol, five did not commence the medication due to early rebleeding in four (two of whom died) and one due to poor cognition. Three patients discontinued the medication within 30 days due to side effects. Eleven took the medication through to death or closure of the study period and further one patient until OLT. A second patient underwent OLT in the carvedilol group but had crossed over to EBL prior. One patient received TIPSS due to rebleeding. Six patients crossed over to receive EBL, five due to rebleeding and one due to patient preference. Four patients stopped carvedilol due to late side effects and a further one patient due to reasons unknown. Only one patient died within 100 days of discontinuing the medication. The overall median days of per protocol carvedilol administration was 1956 (SE = 548.01).

Of the 31 randomised to EBL, three did not attend their planned follow-up EBL sessions. Of these three, one had a variceal rebleed and underwent urgent EBL (605 days). Of the 28 patients who complied with the planned EBL sessions, two experienced variceal rebleeding prior to their first planned follow-up EBL session and underwent further unscheduled EBL (8 and 14 days) and both attended planned EBL thereafter. Five underwent TIPSS placement for variceal rebleeding, one had TIPSS for hydrothorax, and one had TIPSS for ascites. One crossed over to receive carvedilol for rebleeding, and one attended regular EBL until OLT.

4.4.3 Survival

On intention to treat analysis, there was no difference in median survival days between the Carvedilol and EBL groups, respectively (1956 vs. 1125, $p=0.16$, HR 1.521, 95%CI 0.851-2.679) (Figure 4.1). However, on per-protocol analysis (EBL $n=28$, Carvedilol $n=28$), patients taking carvedilol were more likely to survive than those attending EBL sessions ($p=0.005$, HR 3.083, 95%CI 1.397-6.809) (Figure 4.2).

Figure 4.1. Survival: Endoscopic band ligation vs. carvedilol (intention to treat)

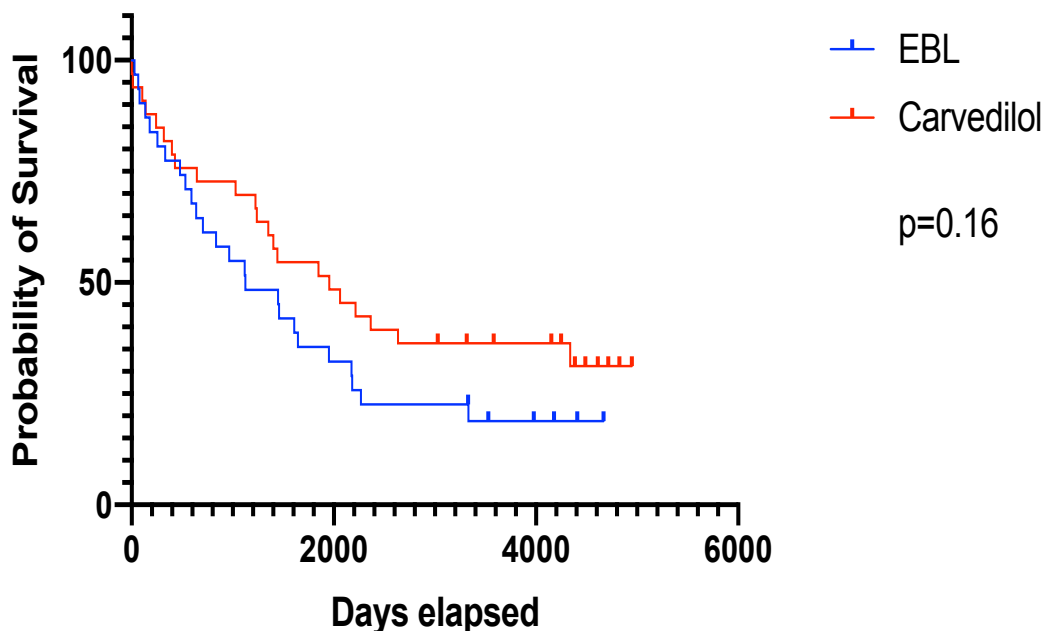
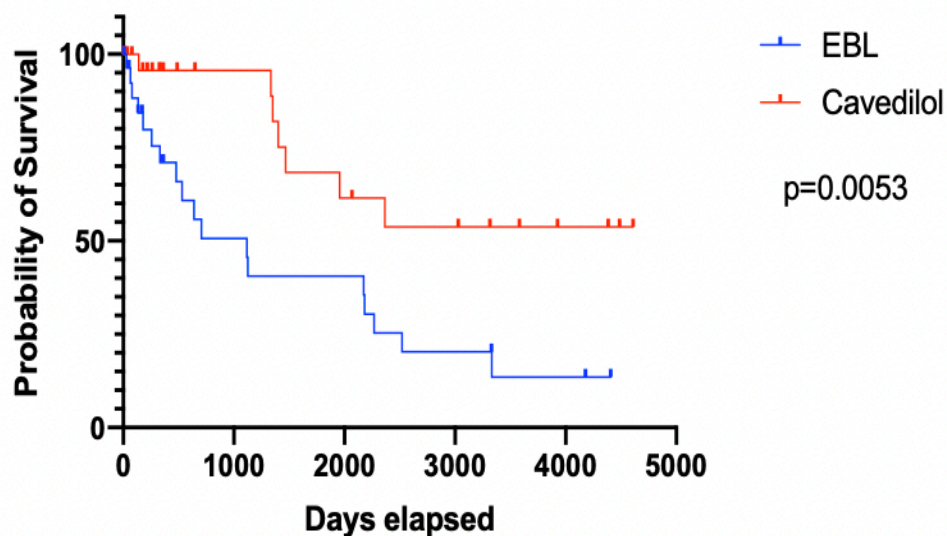


Figure 4.2 Survival: Endoscopic band ligation vs. carvedilol (per protocol)



4.4.4 Cause of death

Overall causes of death are summarised (Table 4.2). On intention to treat analysis, there were no significant differences in causes of death between EBL and Carvedilol groups, in particular death due to liver failure = 25.8% vs. 9.1% ($p=0.102$), respectively. However, on per protocol analysis, those taking carvedilol were significantly less likely to experience death due to liver failure compared to those in the banding group 0.0% vs. 22.6% ($p=0.013$, OR ∞ , 95%CI 1.565 - ∞), respectively.

4.4.5 Variceal rebleeding

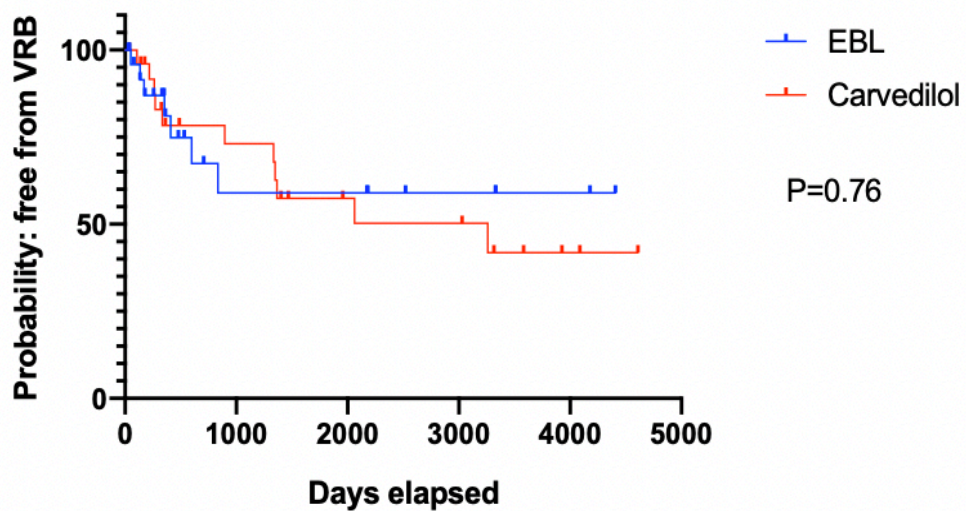
Similar to the index study, there was no difference between EBL and carvedilol groups in days free of VRB in both intention to treat ($p=0.66$, HR 1.191, HR 0.548-2.592), and per-protocol analysis ($p=0.76$, HR 1.156, 95%CI 0.451-2.962) (Figure 4.3).

Table 4.2 Causes of death

Cause of Death	Carvedilol (n=33)	EBL (n=31)	P-value
Liver failure:			
- Intention to treat (%)	3 (9.08)	8 (25.81)	0.102
- Per-protocol (%)	0 (0.0)	7 (22.57)	0.004
GI Bleeding	3	6	0.296
Cardiovascular	4	1	0.356
Sepsis	2	4	0.419
HCC	0	1	0.484

GI = Gastrointestinal, HCC = Hepatocellular Carcinoma

Figure 4.3 Variceal rebleeding (VRB): Endoscopic band ligation vs. carvedilol (per-protocol)



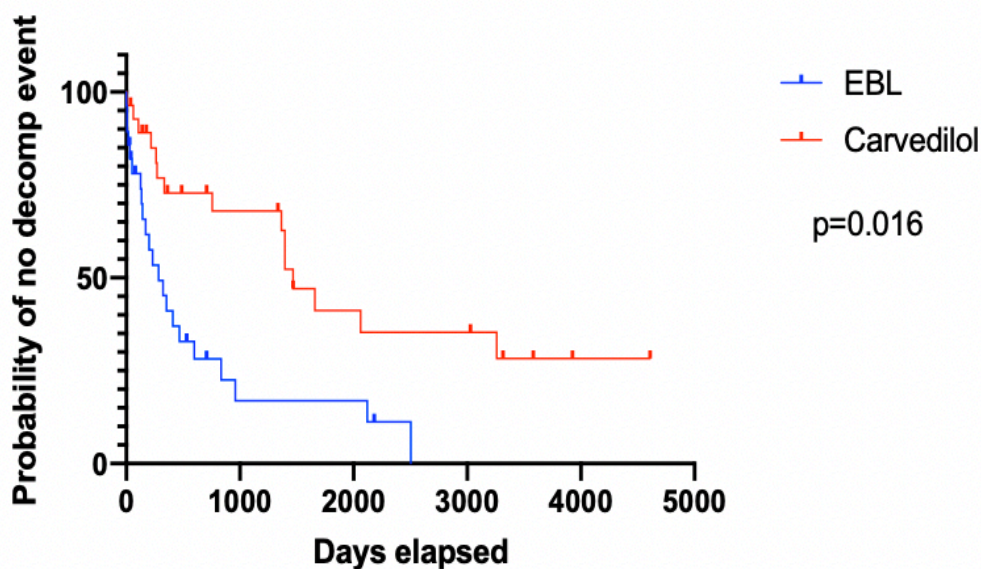
4.4.6 Decompensated liver disease related hospital admissions

Total, cumulative admissions to hospital with decompensated liver disease (excluding admissions due to variceal rebleeding) are summarised (Table 4.3). On both intention to treat and per-protocol analysis, participants in the EBL group were more likely to experience a decompensated liver disease related hospital admission than the carvedilol group, respectively; intention to treat = 64.5% vs. 30.3% (p=0.012, OR 4.182, 95%CI 1.442 – 12.42), per-protocol = 64.3% vs. 12.0% (p=0.0002, OR 13.2, 95%CI 3.026 – 47.23). On per-protocol analysis, those in the carvedilol group had a higher probability than those in the EBL group of remaining free of decompensated liver disease throughout the follow-up period, median days 1467 vs. 286 (p=0.016, HR 3.069, 95% CI 1.532-6.148), (Figure 4.4). Rates of active alcohol consumption were comparable between EBL and carvedilol groups respectively, 48.4% vs. 48.4%

Table 4.3 Overall hospital admission with decompensated liver disease

Decompensation	Carvedilol (n=33)	EBL (n=31)
Ascites	5	14
Hepatic Encephalopathy	7	8
Hepatorenal Syndrome	2	2
Acute Alcoholic Hepatitis	4	7
Spontaneous Bacterial Peritonitis	1	4
TOTAL	19	35

**Figure 4.4 Days to first decompensated liver disease hospital admission:
Endoscopic band ligation versus carvedilol (per-protocol)**



4.4.7 Multivariate regression analysis for survival

Age, MELD, child-pugh score, ascites, carvedilol use and attendance at banding sessions were variables used to determine their individual impact on survival. Carvedilol was the only independent predictor, (Table 4.4).

Table 4.4 Multivariate Cox regression analysis for survival

Variable	Standard error	95% CI	P value
Age	16.51	-44.14 to 22.02	0.5057
MELD	38.82	-135.0 to 20.56	0.1462
Child Pugh Score	83.27	-150.2 to 183.4	0.8426
Ascites [yes]	422.4	-719.2 to 973.2	0.7648
Carvedilol use	0.1578	0.3008 to 0.9329	0.0003
Attended banding [yes]	405.0	-867.0 to 755.7	0.8912

4.5 Key findings

Following OVB, carvedilol use is associated with improved survival, reduced liver related mortality and fewer hospital admissions with decompensated liver disease during long-term follow-up. Monotherapy with carvedilol or EBL has similar variceal rebleeding rates. These results suggest that carvedilol use provides additional benefits in cirrhotic patients, beyond the reduction of rebleeding.

Chapter 5 Long term follow-up of a randomised clinical trial: standard of care versus pre-emptive transjugular intrahepatic porto-systemic shunt (TIPSS)

The study presented in this chapter is an independent long-term follow-up study of the randomised trial presented in Chapter 2.

5.1 Introduction

International guidelines continue to recommend placement of pre-emptive transjugular intrahepatic portosystemic shunt (pTIPSS) within 72 hours following endoscopically controlled oesophageal variceal bleeding (OVV) in carefully selected “high-risk” patients (21, 160, 171). Although pTIPSS has been proven to reduce rates of variceal bleeding, opinion is divided on whether pTIPSS improves overall survival, and if so, whether it can be effectively utilized (172). A recent meta-analysis inclusive of all pTIPSS randomised controlled trials (RCT) found no survival benefit of pTIPSS but stated that the current data was insufficient to confer any true advantage (173). Difficulties in interpreting these data are due to the low numbers of patients typically receiving pTIPSS, and the heterogeneity of medical therapy used across these studies for patients not receiving pTIPSS.

The prior RCT of pTIPSS versus standard of care (SOC) (*Chapter 2*) was the first to show that, when using modern medical therapies, there is no survival advantage of pTIPSS at 1-year (162). Carvedilol was used as SOC, which has subsequently become the non-selective beta-blocker (NSBB) of choice for cirrhotic patients (171). **Error! Bookmark not defined.** Nevertheless, in pTIPSS RCTs, survival at 1-year is routinely assessed as a primary or secondary endpoint, with such survival

rates following pTIPSS insertion being reported at 79% - 86% (154, 174). Despite this, no study has assessed clinically relevant outcomes for these patients beyond the 1-year point. Furthermore, recent data from RCTs (*Chapter 4*) has shown long-term benefits of carvedilol for both primary and secondary prophylaxis of OVB, including the reduction of liver decompensation and mortality rates (135, 175).

5.2 Aims

By undertaking extended follow-up of patients recruited to the index study (162), we aimed to assess long-term outcomes for patients receiving pTIPSS following OVB, and whether pTIPSS confers any advantage over the SOC used.

5.3 Methods

5.3.1 Study design, participants and procedures

For detailed information regarding the design of the index study, as well as the study procedures and inclusion / exclusion criteria, refer to: *Chapter 2, Methods, section; 2.3.1 – 2.3.3*

5.3.2 Long term follow-up data collection

A standardised electronic data collection proforma was used and populated following interrogation of electronic patient records. All data were cross-checked against the original data set. Long-term follow-up data pertaining to the study outcomes (below) as well as the progress of patients' chronic liver disease were obtained by review of planned and unscheduled hospital admissions, liver clinic reviews and relevant primary care correspondence. Mortality data were also collected including date and cause of death.

5.3.3 Primary and secondary outcomes

Primary outcomes were 3-year transplant free survival on intention to treat and per-protocol analysis. Secondary outcomes were variceal rebleeding and liver decompensation events including new or worsening ascites and hepatic encephalopathy; compliance with treatment; and causes of death.

5.3.4 Analysis

Initial data analyses were performed on an intention-to-treat basis, with per-protocol analysis undertaken thereafter. Per protocol analysis was performed on participants randomised TIPSS who received stent placement with 72 hours. Participants in the standard of care group who received TIPSS placement in the follow-up period for other reasons (e.g., ascites) were not censored as this was deemed to be part in parcel of the natural progression and standard management of chronic liver disease for some patients. All patients who received pTIPSS regardless of time taken were assessed separately as a post-hoc group. Additionally, a “standard of care plus” group (SOC+) was created, post-hoc, by including patients who were randomised to pTIPSS but didn’t receive shunt placement, to the primary SOC group.

All statistical tests were two-sided using a 5% significance level. The probabilities of reaching the primary end point of survival were estimated by the Kaplan–Meier method and were compared using the log-rank test. Cox regression analysis was undertaken to determine if the following variables individually contributed towards survival: age, MELD, Child Pugh Score, ascites, hepatic encephalopathy (HE) variceal rebleeding (VRB), NSBBs and pTIPSS insertion. The statistical software packages used for was Prism (v8, GraphPad software, CA, USA).

5.4 Results

5.4.1 Patient groups

Fifty-eight patients were recruited to the index study and randomised to either the SOC or the pTIPSS group (29 patients per group). There were no differences in baseline characteristics between the two treatment groups at randomisation (Table 2.1). All participants were followed-up until death, or for three years following recruitment to the study, whichever was earlier.

5.4.2 Compliance and censoring

Twenty-three of 29 patients in the pTIPSS group received TIPSS placement, all within five days of index endoscopy (13 within 72 hours). Six patients did not receive TIPSS placement due to either lack of anaesthetic support or IR availability because of higher priority cases. These six patients received standard of care. Three participants had their TIPSS reduced in the follow-up period.

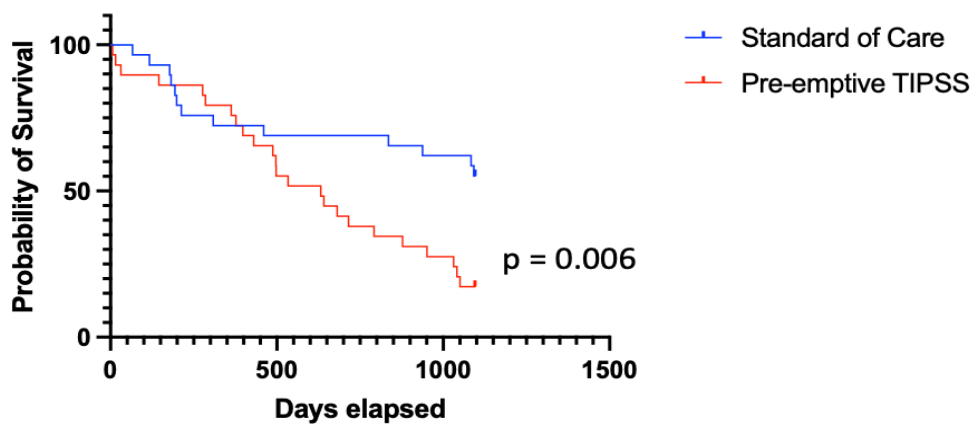
In the SOC group, 18 of 29 patients took carvedilol initially, plus an additional two who were on cardio-selective preparations prior to recruitment and were converted to carvedilol at a later date. Of these 20 patients, the median dose was 6.25mg. Ten patients were still taking the medication at three years, seven had taken it up to death / orthotopic liver transplantation (OLT), two discontinued due to placement of TIPSS (rebleeding in one, hepatic hydrothorax in one), and two patients discontinued due to side effects. Of the six patients in the TIPSS group who didn't receive TIPSS, all received EBL and four were given carvedilol – one was still taking at three years, one took until death and two stopped due to side effects. All SOC group patients partook in an EBL program. A total of 145 planned EBL endoscopies were carried out in the study. The median number of EBL endoscopies

per patient was 4.5 (IQR 2.25-7). Eleven patients were noted to have eradication of varices prior to death, or at the 3-year time point.

5.4.3 Survival

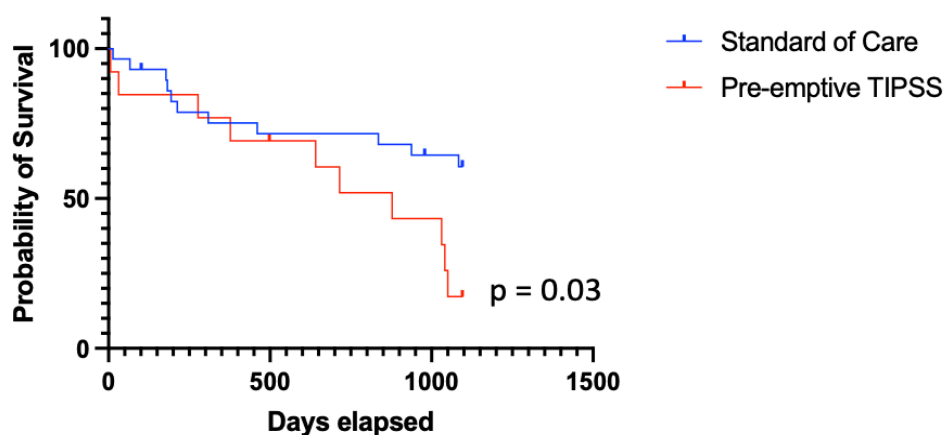
As reported in *Chapter 2, section; 2.3.3*, there were no difference in 1-year transplant free survival rates between the SOC and pTIPSS group (75.9% vs. 79.3% $p=0.79$), respectively. One patient in each group received OLT. On intention to treat analysis, 3-year transplant free survival rate in the SOC group were significantly higher than that of the pTIPSS group (55.2% vs. 20.1%, $p=0.006$, HR 2.5, 95%CI 1.3-4.87), (Figure 5.1). On per-protocol analysis, 3-year transplant free survival rate in the SOC group was again significantly higher than that of the pTIPSS group (55.2% vs. 15.4%, $p=0.03$, HR 2.93, 95%CI 1.27-7.94), (Figure 5.2).

Figure 5. 1 Transplant free survival at 3 years: Standard of care vs. pre-emptive TIPSS (intention to treat)



Numbers at risk							
Days	0	182	365	547	729	911	1095
Standard of Care	29	26	22	21	21	20	16
Pre-emptive TIPSS	29	26	23	16	12	10	5

Figure 5.2. Transplant free survival at 3 years: Standard of care vs. pre-emptive TIPSS (per-protocol)

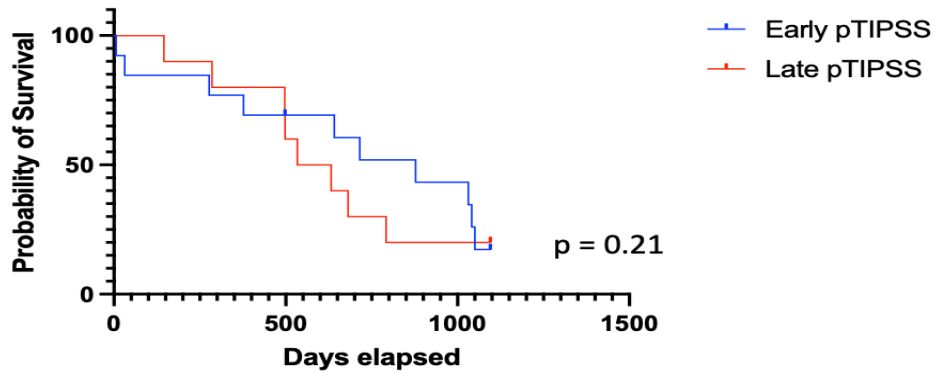


Numbers at risk							
Days	0	182	365	547	729	911	1095
Standard of Care	29	25	22	21	21	20	16
Pre-emptive TIPSS	13	12	11	9	7	6	2

On a subgroup analysis of patients who received TIPSS placement within 72 hours vs. those who had TIPSS placement beyond 72 hours (up to five days), there was no significant difference in 3-year transplant free survival (15.4% vs. 20%, $p=0.64$, HR 1.2, 95%CI 0.48- 3.26), respectively, (Figure 5.3).

On a post-hoc analysis of the SOC group versus all 23 patients who received pTIPSS, 3-year transplant free survival was significantly higher in the SOC group (55.2% vs. 17.4%, $p=0.008$, HR 2.77, 95%CI 1.3-5.92), (Figure 5.4a). On a post-hoc analysis of the SOC group including the six patients randomised to receive TIPSS that were treated with SOC (SOC+ group), versus all patients who received pTIPSS, 3-year transplant free survival rates were significantly higher in the SOC+ group (54.2% vs. 17.4%, $p=0.01$, HR.2.54, 95%CI 1.22-5.31), Figure 5.4b).

Figure 5.3. Transplant free survival at 3 years: Early pre-emptive TIPSS vs. late pre-emptive TIPSS

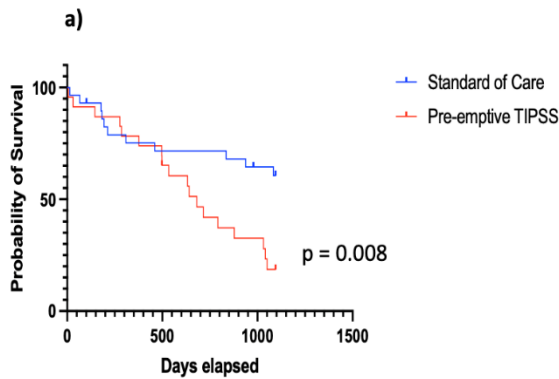


Numbers at risk							
Days	0	182	365	547	729	911	1095
Early pTIPSS	13	12	10	9	7	6	3
Late pTIPSS	10	10	8	6	4	3	2

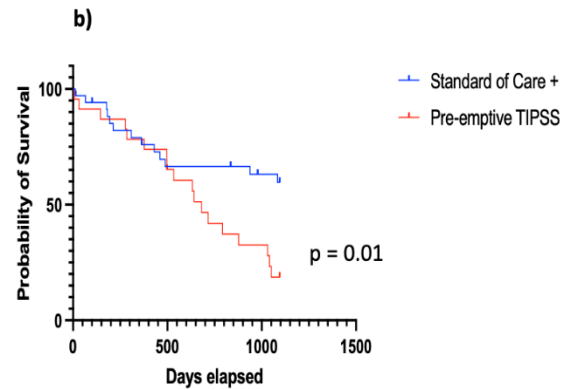
Figure 5.4

a) Transplant free survival at 3-years: Standard of care vs. All pre-emptive TIPSS

b) Transplant free survival at 3-years: Standard of care + vs. All pre-emptive TIPSS



Numbers at risk							
Days	0	182	365	547	729	911	1095
Standard of Care	29	25	22	21	21	20	16
Pre-emptive TIPSS	23	21	19	14	10	8	4



Numbers at risk							
Days	0	182	365	547	729	911	1095
Standard of Care +	35	30	25	22	22	21	17
Pre-emptive TIPSS	23	21	19	14	10	8	4

On a post-hoc analysis of all Child-Pugh C (CP) C patients in the SOC+ group (n=20) versus all CP-C patients in the TIPSS group who received pTIPSS (n=13), the 3-year transplant free survival rate was higher in the SOC+ group (50.0% vs. 15.4%, p=0.03, HR 2.81, 95%CI 1.13-6.99), Figure 5.5.

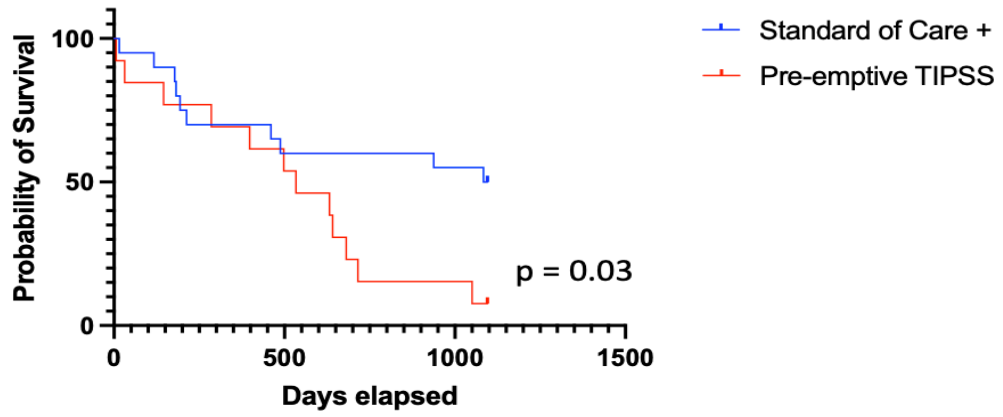
5.4.4 Cause of death

Twelve patients died in the SOC group and 23 died in the pTIPSS group. Causes of death are summarised. (Table 5.1). Although death due to liver decompensation, overall, was the most common in both groups, there were significantly higher rates of sepsis related death or sepsis induced liver decompensation related death in the pTIPSS group compared to the SOC group (48.2% vs. 3.6%, p<0.001, reciprocal of RR 13.0, 95% CI 2.46 – 75.45).

5.4.4 Variceal rebleeding

There were higher rates of variceal rebleeding (VRB) in the SOC group compared to the TIPSS group (intention to treat) however this was just short of statistical significance (p=0.051), (Table 5.2). However, considering all patients who received standard of care (SOC+) versus all patients who received pTIPSS, there were significantly higher rates of VRB in the SOC+ group (45.7% vs. 17.4%, p=0.047, RR 2.63, 95%CI 1.12 – 6.92).

Figure 5.5 Childs-Pugh C transplant free survival at 3-years: Standard of care + vs all pre-emptive TIPSS



Numbers at risk

Days	0	182	365	547	729	911	1095
Standard of Care +	20	17	15	13	13	13	10
Pre-emptive TIPSS	13	11	10	7	3	3	1

Table 5.1 Secondary outcomes: Causes of death, variceal rebleeding and other features of portal hypertension (intention to treat)

Variable	Standard of Care (n=29)	Early-TIPSS (n=29)	p value
<u>Cause of death:</u>			
○ GI bleed	2	2	>0.999
○ Liver decompensation due to progression of disease	6	4	0.73
○ Sepsis and/or sepsis induced liver decompensation	1	13	<0.001
○ Cardiovascular	1	4	0.35
○ Other:	2	0	0.49
- Subarachnoid haemorrhage	1	--	--
- Status epilepticus	1	--	--
Variceal Rebleeding (number of patients):	14	6	0.051
Hepatic Encephalopathy	10	18	0.06
New or Worsening Ascites	10	7	0.56
Spontaneous Bacterial Peritonitis	5	1	0.18
Orthotopic liver transplantation	1	1	>0.99
Non-liver related unscheduled hospital admission	13	9	0.29

5.4.5 Other features of portal hypertension

A summary of rates of patients experiencing other features of portal hypertension in the follow-up period are summarised, (Table 5.1)

There were lower rates of hepatic encephalopathy in the SOC group compared to the TIPSS group (intention to treat) however this was just short of statistical significance ($p=0.06$). However, considering all patients who received standard of care (SOC+) versus all patients who received pTIPSS, there were significantly lower rates of HE in the SOC+ group (31.4% vs 69.6%, $p=0.007$, Reciprocal of RR 2.21, 95%CI 1.28 – 3.94).

There was no difference in rates of new or worsening ascites in the SOC group compared to the TIPSS group (intention to treat) ($p=0.56$). When considering all patients who received standard of care (SOC+) versus all patients who received pTIPSS, there were higher rates of new or worsening ascites in the SOC+ group compared to the pTIPSS group, but this was not significant (37.1% vs 17.4%, $p=0.14$, RR 2.136, 95%CI 0.87 – 5.74).

5.4.6 Multivariate regression analysis for 3-year mortality

Age, admission MELD and CPS, development of ascites, HE and VRB, NSBB use, and pTIPSS insertion were variables used to determine individual impact on mortality. pTIPSS insertion was the only independent predictor, (Table 5.2).

Table 5.2 Multivariate regression analysis for 3-year mortality

Variable	Standard error	95% CI	P value
Age	0.01	-0.01 to 0.01	0.88
MELD	0.02	-0.02 to 0.07	0.25
Child Pugh Score	0.06	-0.13 to 0.11	0.83
New or worsening ascites	0.13	-0.42 to 0.12	0.26
Hepatic encephalopathy	0.13	-0.11 to 0.41	0.25
Variceal rebleed	0.12	-0.01 to 0.49	0.05
NSBB use	0.18	-0.24 to 0.48	0.49
pTIPSS insertion	0.19	0.04 to 0.81	0.03

5.5 Key findings

Standard of care with EBL +/- carvedilol following OVB is associated with higher rates of long-term survival compared to pTIPSS. pTIPSS is associated with reduced long-term risk of variceal rebleeding but increased long-term risk of HE. Interestingly, the difference in long-term survival appears to be due to higher rates of sepsis in the pTIPSS groups. This is a novel finding and requires further investigation.

Chapter 6 Discussion

6.1 Opening statement

The development of liver cirrhosis and subsequent clinically significant portal hypertension has a profound effect on patient's lives. Not only is life-expectancy reduced but lifestyle changes and treatment intervention have significant impact. The purpose of this research was to determine optimal treatment strategies for what is the commonest cause of death in patients living with cirrhosis – oesophageal variceal bleeding (OVV). The aims were to provide fresh, up-to-date studies that address some of the more controversial aspects to post-OVV management and explore further some of the evolving themes.

6.2 Randomised control trial of early-transjugular intrahepatic portosystemic shunt (TIPSS) versus standard of care (Chapter 2)

6.2.1 Recapitulation

The first relevant study in cirrhotic patients who were admitted with acute oesophageal variceal bleeding (OVV) favoured the early use of early-TIPSS with an e-PTFE covered stent, demonstrating significant reductions in variceal rebleeding (VRB) and mortality in patients with Child-Pugh (CP) C disease or CP B disease with active bleeding during endoscopy (154). Although that study was not designed to assess survival and no other comparable randomised control trial (RCT) has been performed since, international clinical guidelines suggested placement of an e-PTFE covered TIPSS within 72 hours following acute OVV (126, 127). Despite this,

physician adherence to these guidelines has been poor, with a lack of technical availability and the ambiguity of current data suggested as possible explanations (176, 177). In contrast to previous work, the findings presented here do not support use of early-TIPSS placement for the improvement of survival in cirrhotic patients following OVB.

6.2.2 Survival difference compared to previous the literature

The 1-year survival rate in the early-TIPSS group of the *Chapter 2* study was 79.3%. This is less than the 1-year survival rates of 86% as previously reported (154). However, the 1-year survival rate of 75.9% in the standard of care (SOC) group is much superior to the 61% reported in the previous study, which likely explains the difference in statistically significant survival outcomes between the two studies.

Here, endoscopic band ligation (EBL) was used at index endoscopy to gain haemostasis in all participants. This is in line with current standards of care whereas in the previous study, 25% of patients received sclerotherapy which is no longer indicated for use in acute OVB (126). Additionally, there were pharmacological differences in vaso-active agents administered with somatostatin, terlipressin and octreotide all being given previously (154). Although head-to-head trials have failed to prove any efficacy difference between these agents in relation to short-term rebleeding and mortality, the long-term outcomes remain unstudied (144). Only terlipressin was used in the *Chapter 2* study, which is currently the only agent shown to reduce mortality in placebo-controlled trials (142). It is therefore an advantage that all participants received the same vaso-active agent throughout as this removes potential for confounding. Similarly, in addition to EBL, carvedilol was used for secondary prophylaxis of oesophageal variceal bleeding whereas either propranolol or nadalol, in combination with isosorbide mono-nitrate (ISMN),

was used previously (154). Haemodynamic studies show that carvedilol is more effective than propranolol in reducing portal pressure, which correlates with reduction in rebleeding and therefore survival (178, 179). The combination of NSBB and ISMN used previously has been proven to be no more effective in reducing mortality than NSBB alone, is associated with more side effects, and is more likely to lead to poor medication compliance (180, 181).

Failure to control bleeding is an important predictor of survival (182). It could be argued that the now dated and inconsistent practice to achieve and maintain haemostasis in the previous randomised control trial, as outlined above, led to suboptimal bleeding control. The early placement of a TIPSS would counteract this deleterious effect, thereby improving survival compared to the standard of care group.

6.2.3 Risk of hepatic encephalopathy

Previous studies evaluating the role of TIPSS in the prevention of recurrent variceal bleeding have clearly shown that TIPSS reduces VRB rates but increases rates of hepatic encephalopathy (HE). However, these studies used bare metal stents (183, 184). The benefits of e-PTFE covered stents are improved stent patency and functionality which, rationally, would most likely increase rates of HE further. The previous authors contradict this by reporting the early placement of TIPSS with an e-PTFE covered stent following OVB does not increase rates of HE (154). Indeed, there were fewer episodes of encephalopathy in their early-TIPSS group, although this was just short of being statistically significant. In the *Chapter 2* study, more participants experienced HE in the early-TIPSS group on intention to treat analysis however, this was not statistically significant. On a per-protocol analysis, as well as in a subgroup analysis for all non-emergency TIPSS placements regardless of

timing, TIPSS was associated with an increased risk of HE. More data are required on rates of HE with covered stents in this setting, as current evidence is significantly heterogenous, with conflicting outcomes reported (109, 185).

6.2.4 Similarities with previous literature

The 1-year survival rate of 75.9 % in the present SOC group is in keeping with modern studies. A similar Chinese RCT reported a SOC 1-year survival rate of 73% (174). Furthermore, observational data from a large European study revealed a 1-year survival rate of 74% in high-risk patients who were suitable for pTIPSS but did not receive shunt placement (186). Comparing baseline characteristics of the SOC group to the previous RCT (154), there were similar median MELD scores (17 vs 17), rates of ascites (59% vs 58%) and higher rates of CP C disease (59% vs 48%), respectively. The alternative SOC strategy used prior resulted in a 1-year survival rate of 61% (154). In light of the above, this is perhaps lower than expected and discounts the survival rates for the SOC group presented here from being inappropriately high.

Although there were no differences in rates of VRB observed on the intention to treat analysis, significantly reduced rates of VRB for those receiving early-TIPSS on a per-protocol analysis were noted, as well as in an analysis of all participants who received TIPSS placement regardless of timing. High rates of mortality in those participants who required rescue-TIPSS were also observed, a finding consistent with other studies (187, 188).

6.2.5 Additional available literature since study concept

Additional literature investigating the impact of early-TIPSS following OVB is available. A meta-analysis concluded that early-TIPSS increased survival however, the trials included were not designed to assess survival as a primary endpoint (189). Furthermore, the observational studies included did not find a statistically significant increase in survival (155, 156). A retrospective study from the US reported early-TIPSS reduced mortality and rebleeding (190). In a Chinese randomised control trial, early-TIPSS placement did correlate with improved liver transplant free survival, however it has been suggested that transplanted organs in China may not be complicit with international professional and ethical standards (174, 191). In addition, sclerotherapy was used in some patients, the study population was predominantly of CP B severity, viral in aetiology, and had higher portal pressures compared to other studies despite less severe disease, which was a novel observation (174).

6.2.6 Feasibility of early-TIPSS

One of the reasons for poor physician adherence to guidelines recommending the use of early-TIPSS following OVB is the inability to provide such a service. Remarkably, even the authors of the landmark early-TIPSS study report observational data from their own centres in which only 9.8% of their suitable patients received early-TIPSS placement (158). The fact that not all participants randomised to early-TIPSS in the *Chapter 2* study received shunt placement is an important finding. Despite the setting of a clinical trial, in two large tertiary centres with an experienced 24/7 emergency TIPSS service, TIPSS could not be performed within 72 hours of endoscopy in 16 participants. Therefore, it would seem unrealistic that an early-TIPSS service could be provided in smaller, non-academic and remote centres. This is echoed in the recent UK TIPSS guidelines for the

management of portal hypertension, in addition to highlighting the uncertainties in patient selection for the procedure (160).

6.2.7 Timing of early-TIPSS

Preliminary results from a large observational study of 281 patients in one of the recruiting centres in the study (Royal Infirmary Edinburgh), showed that timing of TIPSS does not alter outcome following acute oesophageal variceal bleeding therefore the 72-hour post endoscopy window chosen by previous authors may be arbitrary (192). Analysis of all participants randomised to early-TIPSS who received TIPSS placement regardless of timing has been included, and no survival benefit was seen when compared to the SOC group. The survival rate for participants who received late-TIPSS in this study was slightly higher than those who received early-TIPSS (80.0% vs. 76.9%) therefore the delay in TIPSS placement for some participants should not greatly detract from the overall findings. It should be noted that in studies which support the use of TIPSS for secondary prophylaxis following OVB, benefits have been observed for up to five days post endoscopy (193). Studies that assess the timing of early-TIPSS are needed.

6.2.8 Strengths and limitations

The multicentred, randomised nature may be considered as strengths of the study. Due to slow recruitment the study was closed early and therefore unpowered to detect difference in 1-year survival. The sample size was, however, sufficient to detect a survival difference at six weeks based on the results of the previous study (154). However, as the survival rates presented here were near identical between groups, a fully powered study would have been unlikely to yield a different result - a power calculation based on the survival rates would have required recruitment of over 4000 patients. Although both centres participating in the study operate a

24/7 emergency TIPSS service, not all participants randomised to early-TIPSS received shunt placement within the required 72 hour window (from endoscopy) therefore not deemed “early-TIPSS” by definition. This was primarily due to eligible patients presenting out-of-hours resulting in delayed contact with the study team and thus, the randomisation process. Additionally, unavailability of anaesthetic support for the procedure due to more pressing urgent clinical issues at the time meant elective early-TIPSS placement for the study could not be prioritised. This reflects real world clinical practice. Six participants who were randomised to receive early-TIPSS placement did not receive the shunt. This was due to a combination of the above factors resulting in a delay beyond the five-day acute bleeding window, thus, these participants underwent a second endoscopy for variceal banding and continued with standard of care treatment thereafter. Lastly, the population studied was predominantly alcohol related liver disease (ArLD) with ongoing alcohol consumption. This has obvious implications on long term survival. Although this reflects the primary aetiology behind chronic liver disease related presentations to UK hospitals, our findings may not be applicable to other countries in which alternate aetiologies are more prevalent.

6.2.9 Chapter 2 conclusion

As with all prior early-TIPSS studies, the study was underpowered for survival (194). The findings support the view that placement of early-TIPSS appears to reduce rates of VRB but without improving 1-year survival rates. Increased rates of hepatic encephalopathy were associated with early-TIPSS which contrasts with the previous study but in-line with general opinion. The study was undertaken in a UK population with predominantly ArLD therefore the findings may not be applicable to populations in which viral hepatitis remains the predominate aetiology. It was not possible to arrange early-TIPSS for all participants therefore,

a consistent early-TIPSS service may not be feasible in some centres. Previous studies which supported the use of early-TIPSS used clinical practices that are now somewhat dated, therefore larger multicentre randomised controlled trials are required to clarify the optimal management strategy for these patients.

6.3 Effect of timing of pre-emptive transjugular intrahepatic portosystemic shunt on patient outcome, a UK multicentre cohort study (Chapter 3)

6.3.1 Recapitulation

As noted throughout, guidelines state pTIPSS placement within 72 hours of endoscopically controlled OVB should be “considered” in high-risk patients. Despite consistent evidence suggesting pre-emptive TIPSS (pTIPSS, formally known as “early-TIPSS”) is impractical in real-world clinical practice, the timing of pTIPSS and the validity of this narrow therapeutic window remains vastly unchallenged in current literature. The multi-centre, observational study of the largest number of pTIPSS procedures ever reported, presented in this thesis (*Chapter 3*), found no difference in patient outcomes when undertaking pTIPSS within 72 hours compared to pTIPSS placement between 72 hours and 28 days.

6.3.2 pTIPSS and survival – founding concepts

The concept of pTIPSS originally came from a RCT in which patients with endoscopically treated OVB (sclerotherapy) and a hepatic-venous pressure gradient (HVPG) >20 mmHg were randomised to TIPSS placement within 24 hours, or further sclerotherapy and non-selective beta-blockers (NSBBs) (195). Patients receiving pTIPSS had improved survival but this was a secondary finding of the study. Notably, a patient in the TIPSS arm waited five days to receive TIPSS due to

failure of radiology equipment. Thereafter, a RCT with updated patient selection and clinical practices found improved survival rates in patients randomised to receive pTIPSS placement (i.e. within 72 hours) over standard of care (154). Although there were no prior survival data supporting the selection of the 72-hour window used, the use of this timeframe has become the *modus operandi* for subsequent pTIPSS studies. The 72-hour window is likely arbitrary, however historic data suggest the risk of VRB is highest in the first 72 hours after primary treatment for OVB (161). However, those data are now 40 years out of date, as are the standards of care that were used.

6.3.3 pTIPSS and survival – up to date literature

The most recent pTIPSS RCT (*Chapter 2*), and the first to show no survival advantage of pTIPSS (early-TIPSS) placement over the most up-to-date standards of care, highlights the difficulty in obtaining IR and anaesthetic support for pTIPSS placement within 72 hours (162). Of the participants randomised to receive pTIPSS, 35% were delayed beyond 72 hours. Interestingly, 1-year survival rates were slightly higher for these patients, but the numbers were too small to draw any firm conclusions. Moreover, the 2 largest observational studies investigating outcomes of pTIPSS placement, together show that <10% of over 1500 suitable patients received pTIPSS (157,158). These data emphasized the impracticality of providing a non-emergency <72hours TIPSS service in dynamic, real-world clinical practice.

In the *Chapter 3* study, there were no differences in 1-year transplant free survival rates between early and late pTIPSS groups. Recent data, as well as UK guidelines, suggest pTIPSS is only of benefit for those with CP C disease (158 – 160). In a subgroup analysis of CP C patients, timing of pTIPSS placement did not alter survival. Additionally, long-term survival rates were unaffected by the timing of

pTIPSS placement - the study is the first to report long-term survival data following pTIPSS.

6.3.4 Patient selection

Patient selection for pTIPSS is a common topic of debate. Multivariate regression analysis revealed that age, MELD, and prior HE were independent predictors of survival at 1-year, however CP score, previous ascites and individual days to pTIPSS were not. MELD of 19 or more has been previously shown to be associated with poor survival following pTIPSS.

6.3.5 Variceal rebleeding

There was a trend towards reduced 1-year rates of VRB in the early pTIPSS group however this was just short of statistical significance. The reduction of VRB rates with early pTIPSS placement is well documented. When considering other complications of portal hypertension, there were no difference in rates of HE and new or worsening ascites at 1-year between groups.

6.3.6 Previous data

A prior study published in abstract format only, assessed the effectiveness of early pTIPSS (<72hrs) vs. late pTIPSS (3-28 days) vs. EBL following endoscopically controlled OVB (196). Interestingly, bleeding related mortality at six weeks (early pTIPSS: 16.7%; late pTIPSS: 8.8%; EBL 35.7%. $p= 0.081$) and all-cause mortality at 1-year (early pTIPSS: 30.6%, late pTIPSS: 13.2%; EBL 53.6%; $p<0.001$) were lowest in the late pTIPSS group. Another study directly examined patient outcomes in relation to early (<72hrs) vs late (3-28 days) TIPSS placement following OVB (197). However, many patients underwent rescue-TIPSS and “extended criteria” for patient selection were adopted. Although that study does not directly inform

current pTIPSS practice, it may be relevant that 1-year mortality rates were significantly lower in the late pTIPSS group compared to the early pTIPSS group (13.2% vs. 40.8%, $p=0.001$). Given the sparsity of prior data, the pragmatic decision to use 28 days as the cut-off for the late-pTIPSS group in the *Chapter 3* study was on the basis of these prior data.

6.3.7 pTIPSS survival hypothesis

Hypothesis as to why pTIPSS undertaken within 72 hours may offer survival benefit over other standards of care in selected studies, includes the immediate reduction in portal hypertension, gut bacterial translocation and systemic inflammatory response (192). This has been demonstrated by data showing a reduction in endotoxin and tumor necrosis factor receptor levels post TIPSS, as well as reduced levels of chemokines such as CXCL9 (193, 198). Notably, these studies assessed patients undergoing all elective TIPSS procedures for varying indications rather than pTIPSS. It is intriguing that the *Chapter 3* data shows a significant increase in deaths due to liver failure in the early pTIPSS group. In light of the above, TIPSS placement and subsequent diversion of nutrient rich blood away from the liver in the immediate aftermath of the haemodynamic consequences of OVB, may lead to adverse consequences for some patients. Considering the data presented, as well the others mentioned, pTIPSS placement may be most beneficial with a period of recovery time prior to shunt insertion in order to see those potentially positive physiological effects in selected cases. However, as there was no difference in overall mortality rates between the groups, patient specific timing of pTIPSS in order to avoid liver related mortality is a topic for future study.

6.3.8 Strengths and limitations

One of the challenges in interpreting data from pTIPSS studies is the low number of patients who receive pTIPSS. A recent meta-analysis found no survival benefit of pTIPSS placement and stated that current data was insufficient to confer any true advantage (173). The large number of patients included in the *Chapter 3* study should be considered one of the strengths. Furthermore, its multicentered nature is an additional strength. As with all cohort studies, the data collection process is subject to selection bias. However, the two groups' characteristics were well matched, with near identical Child-Pugh and MELD scores, which provides some reassurance that the study centres were not selective over who received pTIPSS and when. Furthermore, this should dispel any argument that the late-pTIPSS patients were less unwell (199). Due to the tertiary nature of the centres included, it was not possible to gain follow-up data on ascites and HE rates for all patients, particularly those referred from smaller hospitals. Some may question the safety of waiting up to 28 days for an OVB secondary prophylaxis procedure, however it is worthwhile noting that for those undergoing EBL, guidelines recommend the second EBL session at up to four weeks after the index bleed (126). Although concurrent use of NSBBs are also suggested for those patients, the effect on HVPG may not yet be seen at four weeks, and some patients may not tolerate the medication (83, 200).

6.3.8 Chapter 3 conclusion

It is important to challenge dogma, particularly where evidence is lacking. Although the study may raise questions regarding the validity of the original pTIPSS concept, it may also prove a welcome relief to those centres wishing to pursue a pTIPSS service that has otherwise been restricted by the 72-hour time frame. These findings should be investigated further in large multi-centre RCTs. Given the 1-year

survival rates following OVB reported in modern studies, coupled with lack of difference in long-term survival reported in the *Chapter 3* study, outcomes for patients experiencing OVB beyond 1-year are of firm interest. This does not only apply to those receiving pTIPSS, but for those who are treated with EBL and NSBB, the more common approach.

6.4 Carvedilol versus endoscopic band ligation for secondary prophylaxis of variceal bleeding – long term follow-up of a randomised control trial (Chapter 4)

6.4.1 Recapitulation

The multicentre study presented in *Chapter 4* assessed the long-term outcomes of a randomised control trial, in which patients predominately with ArLD initially presenting with, and treated for, OVB received either carvedilol or EBL to prevent rebleeding. Long-term survival and variceal rebleeding were similar for carvedilol and EBL on intention to treat analysis. However, on per-protocol analysis, carvedilol use led to improved all-cause survival, in addition to a reduction in both liver related mortality and admissions to hospital with decompensated liver disease.

6.4.2 Survival and liver disease related mortality

Despite ongoing success in the treatment and eradication of the hepatitis C virus, the global burden of chronic liver disease is still rising, predominantly due to alcohol and the metabolic syndrome. As a result, liver related mortality has increased in recent years (4). The onset of portal hypertension is the main driving force that precedes the deterioration of liver disease, with complications such as

ascites, variceal bleeding or HE marking the transition from compensated to decompensated cirrhosis and is associated with a dramatic decrease in survival (25).

In the *Chapter 4* study, carvedilol use was associated with improved long-term survival compared to those who attended for at least two consecutive follow-up EBL sessions or achieved variceal eradication. The survival benefit found appears to be due to a reduction in liver related mortality. In a previous study assessing the long term outcomes of carvedilol versus EBL for primary prophylaxis of OVB, carvedilol was associated with survival benefit but not reduced liver related mortality or liver decompensation events (135). This led to speculation as to the potential extra-hepatic benefits of carvedilol. It is, however, likely that the patients in the *Chapter 4* study were at a more advanced stage of liver disease, given the nature of recruitment being for secondary prophylaxis of OVB. Fewer patients in the carvedilol group were admitted to hospital with decompensated liver disease, this was the first report of such a finding in the context of a randomised trial. Interestingly, more patients in the EBL group underwent TIPSS for various reasons however, despite this, the rates of admission with ascites were lower in the carvedilol group, perhaps emphasising the protective benefit of carvedilol even further.

6.4.3 Carvedilol benefits

Similar to other NSBBs, carvedilol reduces heart rate and cardiac output by antagonism of β 1-adrenergic receptors. Through β 2-adrenergic blockade, it causes splanchnic vasoconstriction due to unopposed adrenergic tone, leading to an additional decrease in portal-collateral blood flow. However, in contrast to other NSBBs, carvedilol also exhibits an intrinsic anti- α 1 adrenergic effect, causing

intrahepatic vasodilatation that decreases portal pressure further. Interestingly, carvedilol appeared to reduce liver decompensation events but did not prevent variceal bleeding, compared to EBL. This supports the suggestion that carvedilol influences pleiotropic mechanisms that contribute towards liver decompensation out with HVPg reduction. Animal studies have observed that carvedilol has antioxidant, anti-fibrotic and anti-inflammatory properties (94, 95). Furthermore, carvedilol has been shown to increase insulin sensitivity, reduce glycosylated haemoglobin levels, slow the progression to microalbuminaemia (96), and have a survival benefit compared to other NSBB in patients with heart disease (97, 98).

6.4.4 Carvedilol compliance

Compliance with carvedilol was less than compliance with regular EBL, perhaps due to adverse effects associated with carvedilol. Three patients did not take the drug beyond 30 days (the likely time required to have adequate effect on HVPg) (87, 88, 91, 202) due to side effects, and four more discontinued the medication beyond 30 days. However, the minimum time to discontinuation in those established on carvedilol for >30 days was longer than 12 months. At the doses taken in our study (6.25–12.5 mg/day) carvedilol does not appear to cause systemic hypotension but decreases portal pressure significantly more than propranolol, which may explain its better tolerability (83).

6.4.5 Strengths and limitations

The multicentre nature, pre-defined clinically relevant outcomes, and 100% patient follow-up should be considered strengths of the *Chapter 4* study. Additionally, this study is the first to assess long-term outcomes of carvedilol compared with EBL following OVB. One other study reported long-term of outcomes of carvedilol following OVB, however this was compared with propranolol (15). Limitations of

the study include the fact that long-term data collection was retrospective, therefore at risk of the biases associated with retrospective studies. However, this bias can be lessened given the patients observed were initially recruited through a randomised trial. The results should also be interpreted in the setting of an ArLD predominate population. Active alcohol intake may alter survival however, rates of active alcohol consumption was comparable between groups. Although a thorough process was undertaken to assess treatment compliance, it cannot be guaranteed that all participants continued their allocated treatment for the duration of the study. There are limitations to per-protocol analyses. Cross-over between treatments was low, however some participants required censoring, thus reducing the analysed numbers and subsequent power of this study. Furthermore, patients who discontinued carvedilol were censored and if death occurred thereafter, they would not be counted as carvedilol related deaths. However, only one patient died within 100 days of discontinuing carvedilol. In contrast, however, more patients in the EBL group received TIPSS for indications associated with severe disease (rebleeding, hydrothorax and ascites) and were also censored, therefore the survival benefit from carvedilol found here remains of significant interest.

6.4.6 Chapter 4 conclusion

Carvedilol has become increasingly synonymous with the term “pleiotropic effects”. Simply put, there is a disparity between the growing numbers of clinical studies reporting the array of benefits of carvedilol, and a sparsity of scientific studies to explain why (201). The long-term benefit of carvedilol following OVB for both survival and reduction liver decompensation events is consistent with modern opinion that carvedilol has additional properties that influence development of decompensated liver disease. Further large randomised

controlled trials are required to validate this finding and explore the potential benefits of carvedilol in other patients with chronic liver disease. Of note, in *Chapter 2*, patients treated with early-TIPSS (or pTIPSS) had similar 1-year survival rates to those who were given carvedilol. Therefore, given the findings presented to date, it seems logical to revisit the data presented in *Chapter 2* to determine long-term outcomes for both groups.

6.5 Long term follow-up of a randomised clinical trial: standard of care versus pTIPSS in patients with cirrhosis and oesophageal variceal bleeding (Chapter 5)

6.5.2 Recapitulation

This multicentre study presented in *Chapter 5* assessed the long-term outcomes of the *Chapter 2* RCT, in which patients with predominately ArLD received standard of care (SOC) with EBL +/- carvedilol, or placement of pTIPSS following presentation and initial management of OVB. Long-term transplant-free survival rates at 3-years were significantly superior for those who received SOC on both intention-to-treat and per protocol analysis, as well as in a post-hoc analysis of all patients who received pTIPSS regardless of timing, compared to all patients who received SOC regardless of randomisation. pTIPSS was an independent predictor of overall mortality and, more specifically, was associated with significantly higher rates of mortality due to sepsis and sepsis induced liver decompensation, compared to SOC. On the post-hoc analysis, pTIPSS was associated with significantly reduced rates of variceal rebleeding, however higher rates of HE.

6.5.3 pTIPSS and survival - updated

The survival benefit of pTIPSS continues to be debated. However, despite the current literature and recent conflicting studies, pTIPSS remains to be recommended following OVB in the most up-to-date guidelines (171). Prior studies have focused on 1-year survival, with 79% - 86% of patients receiving pTIPSS following OVB being alive at 1-year (154, 162, 174). 1-year survival rates of patients receiving pTIPSS in large observational studies have been reported at 78% - 85%, however patients receiving pTIPSS in these studies were highly selected (157, 158). Despite the good survival rates reported in these studies, the outcomes for survival, rebleeding and other features of portal hypertension beyond 1-year are unknown.

6.5.4 Long term survival

To determine clinical outcomes for patients receiving pTIPSS beyond 1-year, follow-up of the patients recruited to the *Chapter 2* RCT was extended to three years. Survival rates were superior for patients receiving SOC on intention to treat analysis, per-protocol analysis as well as a post-hoc analysis of all patients in the study who received SOC vs all patients who received pTIPSS, regardless of timing. Furthermore, pTIPSS placement was the only independent predictor of long-term mortality on multivariate analysis.

Recent data, as well as UK guidelines, suggest pTIPSS may only be of benefit those with CP C disease, removing CP B patients with active bleeding from the “high-risk” criteria (159, 160, 171). Although the study recruited both groups of patients, a subgroup analysis of CP C patients also found that SOC offered significantly better long-term survival rates compared to pTIPSS.

6.5.4 Sepsis related mortality

When examining causes of death, it appears that the poorer survival in the pTIPSS group was as a result of statistically higher rates of death from sepsis and/or sepsis induced liver decompensation. The overall numbers in the study are low therefore this may still be an aberrant result. Nonetheless, this is a novel and interesting finding which requires further research and thought.

It is not clear whether patients receiving pTIPSS are subsequently at higher long-term risk of sepsis, or whether SOC with NSBBs offer protection against sepsis in an otherwise at-risk population. The impact of NSBBs on specific causes of death is yet to be defined. Propranolol has been shown to reduce rates of liver decompensation events including Spontaneous Bacterial Peritonitis (SBP) (167). Carvedilol use, in particular, is associated with improved long-term survival when compared to EBL for both primary and secondary prophylaxis of OVB (*Chapter 4*) (135, 175). In both these long-term studies, cases of liver failure and sepsis related mortality were numerically lower for patients receiving carvedilol, although statistical significance was not examined. There is strong evidence in the cardiovascular literature that activation and recruitment of inflammatory cells is mediated by the adrenergic system, especially via β_2 -receptors and that anti-hypertensive drugs have a beneficial immunomodulatory effect (202, 203). In the setting of liver cirrhosis, NSBBs may further improve intestinal gut motility by reducing adrenergic stimulation and ultimately bacterial translocation - a process often considered to contribute to infection and decompensation (204).

Data reporting the long-term outcomes following pTIPSS or TIPSS for other indications, particularly with infection or sepsis considered, are limited. Infection in the six months preceding TIPSS for any indication was associated with post-TIPSS

infection rates of 26.4% over eight years, however mortality data was not reported (205). In a study examining 10-year outcomes of 472 patients receiving TIPSS for all indications, mortality was high with most deaths being due to liver failure and/or sepsis (65.5%) (206). In a modern study investigating the timing of pTIPSS in 171 patients, long term survival was assessed over eight years (*Chapter 3*) (207). The two most common causes of death were liver failure (55%) and sepsis independent of liver failure (24%). Blood in the portal vein partly originates from the gut, which may contain bacterial DNA. The purpose of TIPSS is to direct portal blood flow beyond the liver thus bypassing the reticuloendothelial system which plays a vital role in immune function. Theoretically, this may contribute to increased infection risk.

6.5.5 Timing of pTIPSS on long-term survival

A study of the largest number of pTIPSS to date found no difference in survival rates at 1-year for those who received pTIPSS within 72 hours vs those who received pTIPSS between 3-28 days (*Chapter 3*) (207). In a subgroup analysis of the *Chapter 5* study, no difference in long term survival rates were detected between those receiving pTIPSS within 72 hours of endoscopy and those receiving pTIPSS beyond this time point. The above data supports the rationale for examining all patients receiving pTIPSS against all those who received SOC.

6.5.6 Other clinical features of portal hypertension

When considering other features of portal hypertension, no significant difference was seen on intention to treat analysis between groups. However, analysis of all patients receiving SOC (i.e. the SOC+ group) and all patients who received pTIPSS, there was a significant reduction in the rates of VRB in the pTIPSS group. This is a commonly reported finding but was just short of significance when correlating

with mortality on multivariate analysis. Furthermore, pTIPSS was associated with increased rates of HE. TIPSS is a well-known risk factor for HE however, prior pTIPSS studies did not find a correlation of pTIPSS with HE, leading some to question the validity of the results (208). It is possible that the higher rate of HE in this study can be explained by the higher rates of sepsis.

6.5.7 Strengths and limitations

The multicentred randomised nature, pre-defined clinically relevant outcomes, and 100% patient follow-up should be considered strengths of this study. Additionally, the study is the first to report long-term outcomes of pTIPSS vs SOC, particularly in the setting of a RCT. The results should be interpreted in the setting of an ArLD predominate population. There are limitations of per-protocol analyses however, cross-over between treatments was low and patients who received TIPSS for other reasons, or who discontinued carvedilol were not censored, thus ensuring the potentially sicker patients and those with more advanced disease were not excluded from the SOC survival analysis.

6.5.8 Chapter 5 conclusion

Following OVB, most patients survive beyond one year thanks to modern approaches to therapy. It is interesting, however, that beyond this time point the patients who are treated with pTIPSS do not survive as long as those who receive SOC with EBL and carvedilol. The higher sepsis mortality related to sepsis with and without decompensated disease raises concerns that pTIPSS may increase the risk sepsis. Alternatively, it could be that carvedilol prevents sepsis. This novel finding requires further investigation.

6.6 Closing statement

The published studies in this thesis have had featured editorials, have prompted debate when presented at national and international conferences, and are referenced in review articles and guideline updates.

pTIPSS is an effective strategy to reduce portal pressure, prevent rebleeding and may improve 1-year survival however the approach to pTIPSS must be modernised. The rigid 72-hour timeframe to insert pTIPSS following endoscopy for OVB should be reviewed in future studies, not only to improve access to pTIPSS but to allow for a period of recovery time for select patients. Early implantation of pTIPSS may increase risk of liver failure, therefore improved methods of patient selection are required. Future work could consider focusing on the degree of haemodynamic instability at presentation with OVB and other concurrent features of liver failure such as jaundice as provoking factors for sub-optimal outcome. Until more robust evidence is available, pTIPSS should not be considered a mainstay in the management of acute OVB. In the meantime, we can be reassured that assiduously applied standard of care treatment has significantly improved outcome in recent years.

It has perhaps taken >40 years to realise that NSBB do more for patients with liver cirrhosis than prevent rebleeding. Of the NSBBs on offer, carvedilol appears to have clear benefits not only on portal pressure reduction but seemingly on other less well understood mechanisms contributing to liver decompensation and death. Literature reporting improved clinical outcomes of those who take carvedilol continues to evolve and strengthen. Regardless of the comparator group, carvedilol stands out as the treatment of choice, particularly when administered in the long term.

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Appendix

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1. CONSORT checklist: Chapter 2, Chapter 4, Chapter 5
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3. Early-TIPSS RCT - published article in print
4. Early-TIPSS RCT: Authors reply letter - published in print
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7. UK pTIPSS cohort study: Authors reply letter - published in print
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9. Carvedilol vs EBL long-term follow-up: Author's reply letter - published in print



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item
Title and abstract		
	1a	Identification as a randomised trial in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)
Introduction		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence	8a	Method used to generate the random allocation sequence
generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)

Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

**Please note that some items have been marked as N/A (not relevant) because the information has been reported elsewhere. The current manuscript is not the main results of the PAL trial (which has been published elsewhere and referred to throughout the manuscript).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results	18	Summarise key results with reference to study objectives
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Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Randomised clinical trial: Standard of care versus early-transjugular intrahepatic porto-systemic shunt (TIPSS) in patients with cirrhosis and oesophageal variceal bleeding

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Summary

Background: Early-transjugular intrahepatic porto-systemic shunt (TIPSS) has been recommended in international guidelines for high-risk patients with oesophageal variceal bleeding.

Aims: To validate the results of a previous randomised control trial which supports use of early-TIPSS.

Methods: In a two-centre open-label parallel-group randomised control trial, patients with cirrhosis and acute variceal bleeding were recruited following haemostasis with vaso-active drugs and endoscopic band ligation. Participants were randomised to standard of care or early-TIPSS. The primary outcome was 1-year survival, secondary outcomes included early and late rebleeding, and complications of portal hypertension.

Results: Fifty-eight patients (58 ± 11.12 years; 32.7% female) were randomised. After one year, seven patients died in the standard of care group and six in the early-TIPSS group, a 1-year survival of 75.9% vs 79.3% respectively ($P=0.79$). Variceal rebleeding occurred in eight patients in the standard of care group compared with three patients in the early-TIPSS group ($P=0.09$). Not all participants randomised to early-TIPSS received the intervention in time. For those receiving TIPSS per-protocol, variceal rebleeding rates were reduced (0% vs 27.6%, $P=0.04$) but this had no effect on survival (76.9% vs 75.9%, $P=0.91$). Serious adverse events were similar in both treatment groups, except that rates of hepatic encephalopathy were higher in patients receiving TIPSS (46.1% vs 20.7%, $P<0.05$).

Conclusion: Early-TIPSS reduced variceal rebleeding, increased encephalopathy but had no effect on survival in high-risk patients with oesophageal variceal bleeding. Early-TIPSS may not be feasible in many centres however, larger studies are needed.

The Handling Editor for this article was Professor Gideon Hirschfield, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Variceal haemorrhage is a major complication of portal hypertension and a common cause of death in patients with liver cirrhosis. For patients with uncontrolled variceal haemorrhage despite endoscopic band ligation therapy, placement of a transjugular intrahepatic portosystemic shunt (TIPSS) decreases portal pressure in an attempt to reduce haemorrhage and blood loss: so-called “rescue TIPSS”. This concept of TIPSS implantation to reduce portal pressure has led some to promote this approach in order to avoid and prevent early rebleeding in high-risk patients in which haemostasis was initially achieved. In a previous multicentre randomised controlled trial by Garcia-Pagan *et al*, pre-emptive early-TIPSS placement (<72 hours from index endoscopy for oesophageal variceal bleeding) in 63 patients with Child-Pugh B disease with active bleeding or Child-Pugh C disease reduced rates of rebleeding but was also associated with improved 1-year survival (86% compared to 61% in the standard of care group).¹ Although patients with Childs-Pugh B disease and active bleeding during endoscopy are deemed high risk, the premise of active bleeding is unclear from the previous study thus open to interpretation by the endoscopist. Nonetheless, based on these data, international guidelines currently recommend consideration of early-TIPSS for all high-risk patients presenting with oesophageal variceal bleeding following initial haemostasis using pharmacological management and endoscopic band ligation.^{2,3}

Despite the reported survival benefit of early-TIPSS and the current clinical recommendations, the use of early-TIPSS is rarely adopted. In a recent observational study of 58 centres in France, only 6.7% of the suitable patients were treated with early-TIPSS.⁴ This was a negative study, with the only independent predictor of survival being severity of liver disease itself. In a similar observational study, pre-emptive TIPSS placement was used in only 9.8% of suitable high-risk patients across 34 centres.⁵ A survival benefit of pre-emptive TIPSS was only seen in those with Childs-Pugh C disease.⁵ These large observational multicentre studies underscore continued equipoise regarding the value of early-TIPSS and perhaps highlight the difficulty in accessing suitable interventional radiology to provide a non-emergency early-TIPSS service in real-world clinical practice. In addition, they also highlight that the process of patient selection for early-TIPSS needs to be refined. In view of this ongoing uncertainty and modest evidence base,⁵ we performed an open label two-centre randomised controlled trial of early-TIPSS in high-risk patients with cirrhosis and oesophageal variceal bleeding.

2 | METHODS

2.1 | Participants and Settings

This was an open-label, parallel-group, randomised control trial carried out at two UK centres, Royal Infirmary of Edinburgh and Glasgow Royal Infirmary, between April 2012 and January 2018. Both centres have an experienced 24-hour emergency TIPSS service. The trial

complied with Good Clinical Practice Guidelines and was approved by the East of Scotland Regional Ethics Committee (REC reference number 12/SS/0008). The trial protocol is available at: <https://clinicaltrials.gov/ct2/show/NCT02377141>

Patients with liver cirrhosis presenting with acute oesophageal variceal bleeding and subsequent haemostasis following treatment with vaso-active drugs and endoscopic band ligation were considered for inclusion in the trial. Exclusion criteria included age less than 18 or more than 75 years, pregnancy, Child-Pugh score < 8 and > 13, inability to control bleeding at index endoscopy, previous porto-systemic shunt or TIPSS, previous pharmacotherapy and endoscopic band ligation, bleeding from isolated gastric or ectopic varices, known portal vein thrombosis, active cancer including hepatocellular carcinoma and recurrent hospital admissions with encephalopathy. Patients, or their next of kin, for those with fluctuating conscious level due to hepatic encephalopathy, provided written informed consent.

2.2 | Study design

After achieving endoscopic haemostasis, consenting participants were randomised 1:1 to either standard of care (continued endoscopic band ligation sessions ± pharmacotherapy) or early-TIPSS, using a 24-hour web-based randomisation service [<https://www.aleaclinical.eu> (ALEA Clinical, Abcoude, The Netherlands)].

2.3 | Study procedures

Patients with suspected acute oesophageal variceal bleeding and chronic liver disease who presented to the Emergency Department at either centre were resuscitated where appropriate. Pre-endoscopic management included the use of antibiotics and vaso-active drugs (terlipressin 2 mg QDS) unless contraindicated. Policy was to perform endoscopy within 12 hours of presentation. During endoscopy, band ligation was performed to either gain haemostasis for actively bleeding varices or to treat pre-existing varices with high-risk stigmata of recent bleeding such as red spots or fibrin plugs. Endoscopic band ligation performed at Royal Infirmary Edinburgh was carried out using the Boston Scientific Speedband SuperView Super 7™, and at Glasgow Royal Infirmary using the Cook 6-Shooter Saeed Multi-Band Ligator™.

Following endoscopy, participants randomised to standard of care had terlipressin continued for up to 5 days, antibiotics for 5-7 days and were entered into an outpatient endoscopic variceal band ligation programme. The standard practice in both centres was to undertake endoscopy at 2-4 weekly intervals until variceal eradication, and then repeat endoscopy in three, then six monthly intervals.² Carvedilol, a nonselective beta-blocker, was commenced prior to discharge from hospital at a dose of 6.25 mg and titrated thereafter, depending on participant tolerability.

For those randomised to early-TIPSS, the aim was to perform TIPSS within 72 hours after initial endoscopy. Terlipressin

was continued until TIPSS was performed and antibiotics were continued for 5-7 days. TIPSS procedures were carried out by interventional radiologists experienced in this technique. The e-polytetrafluoroethylene (e-PTFE) covered stents (Viatorr TIPSS endoprosthesis, W. L. Gore & Associates, Inc, Newark, USA) were initially dilated to 8 or 9 mm. If the portal pressure gradient (the difference between portal vein pressure and inferior vena caval pressure) did not decrease to below 12 mm Hg, the stent was dilated further to 9 or 10 mm. TIPSS patency was checked at six months and one year using Doppler ultrasonography or TIPSS venography. If TIPSS dysfunction was confirmed, balloon angioplasty was performed or a further e-PTFE-covered stent was placed.

A dedicated member of the study team performed the randomisation and was responsible for data collection of that participant. The principal investigator oversaw the running of the study.

2.4 | Follow-up

Follow-up visits were scheduled at six weeks, six months and one year at which participants underwent clinical examination, blood testing and any interim hospital attendances were reviewed.

2.5 | Study outcomes

The primary outcome was survival at one year. Secondary outcomes included survival at six weeks; rates of early rebleeding (within six weeks) and late rebleeding (between six weeks and one year); and the development of hepatic encephalopathy. Subsidiary outcomes were the development of new ascites, the number of days in the intensive care unit, hospital attendances (including to the endoscopy unit), the use of alternative treatments including beta-blockers and safety profile.

2.6 | Statistical analysis

This study aimed to confirm the results of the first early-TIPSS randomised controlled trial.¹ The authors observed 14% and 39% deaths in the two trial arms. Therefore, we calculated a need for 48 patients per group to find a difference in survival between the two trial arms using two-sided log-rank test ($\alpha = 0.05$, power of 80%) with four extra patients per group to allow for drop out and noncompliance. Initial data analyses were performed on an intention-to-treat basis, with further per-protocol analysis provided thereafter. A two-sided *P*-value of less than 0.05 was considered as statistically significant. Dichotomous variables were compared by means of Fisher's exact test, and continuous variables were compared by means of the nonparametric Mann-Whitney rank-sum test. The probabilities of reaching the primary end point of survival were estimated using the Kaplan-Meier method and were

compared by means of the log-rank test. Hazard ratios are not provided in the setting of crossing lines. Safety assessments were made on analysis of all patients who received the intended treatment, rather than on intention-to-treat. The statistical software packages used for the analysis were SPSS (v17, IBM, Armonk, USA) and Prism (v8, GraphPad software).

3 | RESULTS

Two-hundred and six patients with acute variceal bleeding were admitted to the participating centres and screened for eligibility (Figure 1); 147 patients were excluded and of the remaining 59 patients, one later withdrew consent. Fifty-eight patients were randomised to either the standard of care group or the early-TIPSS group (29 patients per group). There were no differences in baseline characteristics between the two treatment groups at study entry (Table 1). No participants were lost to follow-up.

In the standard of care group, 21 participants were maintained on beta-blocker therapy with 18 receiving carvedilol (median dose, 6.25 mg [range, 3.125 to 12 mg]) and three on pre-existing cardio-selective preparations prescribed for other clinical reasons. In the remaining eight patients, carvedilol was not initiated because of contraindications in six and early rebleeding or death in two. Median number of planned (non-emergency) band ligation endoscopies performed in the follow-up period was 4 (range, 0-8). Eradication of varices was achieved in 14 participants after a median of 3 endoscopic band ligation sessions (range, 1-6). In the remaining 15 patients, eradication was not achieved in seven despite a median of six endoscopic band ligation sessions (range, 4-8), or because of rebleeding resulting in rescue TIPSS in two, death in three and refusal of further endoscopies in three. One patient underwent liver transplantation during follow-up.

Of the 29 participants randomised to the early-TIPSS group, 23 received shunt placement and six participants did not undergo TIPSS placement due to logistical and practical issues. The mean time from endoscopy to TIPSS placement for all participants was 65 ± 37 hours. Ten participants received TIPSS placement outside the 72-hour window due to a delay in randomisation, with a mean time from endoscopy to randomisation of 37 ± 22 hours. In comparison, the remaining 13 participants who received TIPSS placement within the 72-hour window had a mean time from endoscopy to randomisation of 18 ± 12 hours. Of the 23 participants who received TIPSS placement, 22 received it within 72 hours of randomisation, rather than from endoscopy. There were no technical failures or major complications of the TIPSS procedures. A total of 21 participants required one stent, and two participants required two stents. The mean portal pressure gradient dropped from 17 ± 5 mm Hg to 7 ± 3 mm Hg. Despite dilation to 10 mm, the portal pressure gradient after TIPSS remained above 12 mm Hg in three patients, although all participants achieved a portal pressure gradient fall $>20\%$ (mean $58 \pm 18\%$). Additional variceal embolisation was performed in one patient.

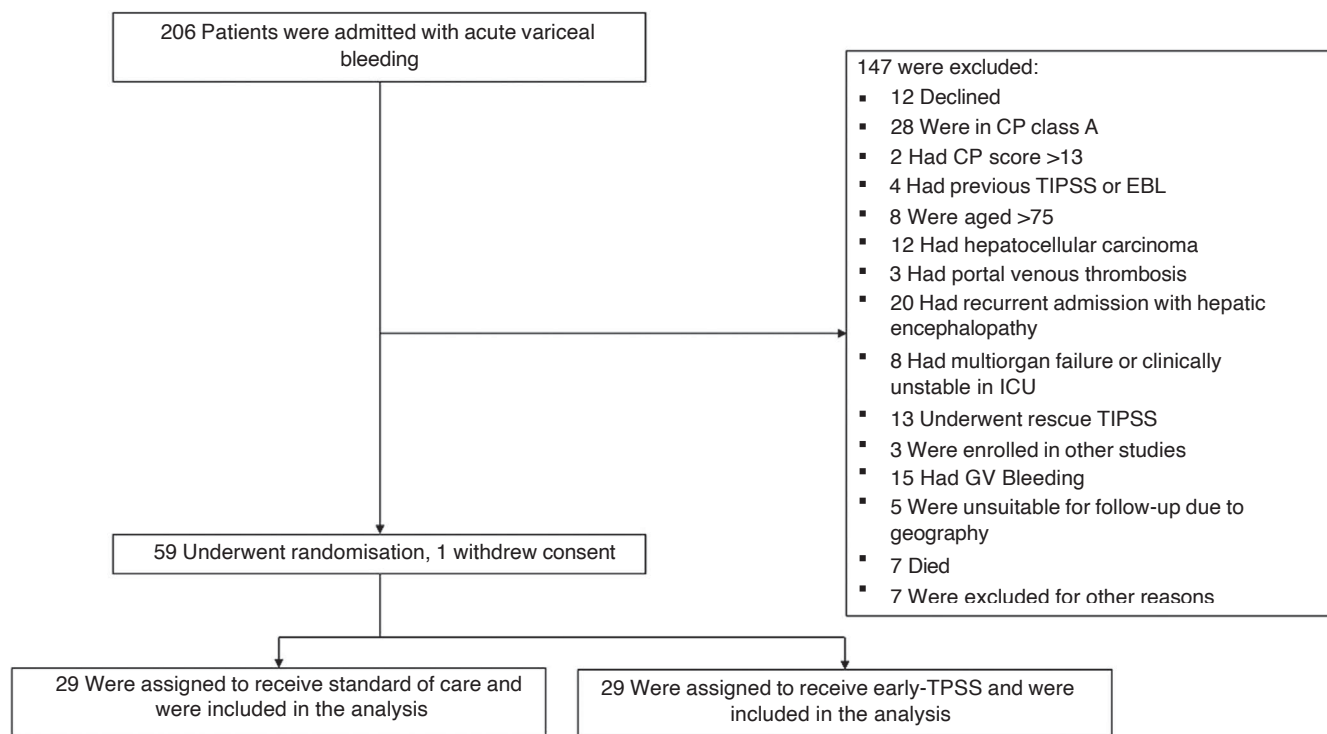


FIGURE 1 Screening and Randomisation of patients. Of the 29 randomised to receive early-TIPSS, 13 received TIPSS within 72 hours, 10 received TIPSS beyond 72 hours and 6 did not undergo TIPSS placement - these participants crossed over to the standard of care arm. CP, Childs-Pugh, EBL, Endoscopic Band Ligation, ICU, Intensive Care Unit, GV, Gastric Varices, TIPSS, Transjugular Intrahepatic Porto-Systemic Shunt

3.1 | Survival

A total of seven patients in the standard of care group died, compared with six in the early-TIPSS group (Table 2). The six-week survival rate in standard of care group was 96.5% vs 89.6% in the early-TIPSS group. There were no differences in 1-year survival rates between the standard of care and early-TIPSS group (75.9% vs 79.3% $P=0.79$; Figure 2). Causes of death in both groups are summarised in Table 2. Thirty-three trial participants had Childs-Pugh C cirrhosis of whom 17 were in the standard of care group and 16 in the early-TIPSS group with 1-year survival rates being 70.6% and 68.7% respectively, $P=0.80$ (Figure 3). Considering all participants who were randomised to early-TIPSS and received TIPSS placement, there was no difference in survival compared to the standard of care group respectively (78.3% vs 75.9%, $P=0.85$; Figure 4).

3.2 | Rebleeding

In the standard of care group, ten participants experienced a rebleeding episode with eight having variceal rebleeding. Six of these participants later died during the follow-up period. In three participants, TIPSS was used as rescue therapy, although bleeding was controlled in all and portal pressure gradient brought below 12 mm Hg, all three patients died at a median of 143 days (range, 15 to 185). The remaining two patients who experienced variceal rebleeding and did not die in the follow-up period underwent additional

endoscopic band ligation sessions. In total, there were twelve rebleeding episodes in this group, nine of which were variceal.

In the early-TIPSS group, seven participants experienced a rebleeding episode, three of which had variceal rebleeding. Of the three, two participants did not receive early-TIPSS after randomisation and one had TIPSS placed >72 hours after endoscopy but required two stent insertions as well as a TIPSS redilatation. There were eleven bleeding episodes in this group, four of which were variceal.

There was no difference in the number of participants experiencing all cause rebleeding at 1-year between the standard of care and early-TIPSS groups (24.1% vs 34.6% respectively, $P=0.86$). At the specified time points, there were no differences in rates of all cause rebleeding between standard of care and early-TIPSS groups respectively; 0-6 weeks (17.2% vs 3.4%, $P=0.08$); 6-weeks to 1-year (17.2% vs 20.7%, $P=0.79$). In relation to rates of variceal rebleeding (Table 2), there was an apparent trend for lower rates in the early-TIPSS group after 1-year of follow-up (10.3% vs 27.6% in standard of care group, $P=0.09$). Of the 23 participants who actually received TIPSS, only one (4.3%) experienced variceal rebleeding compared with eight (27.6%) in the standard of care group ($P=0.01$).

3.3 | Other complications of portal hypertension

In the early-TIPSS group, twelve patients had at least one episode of hepatic encephalopathy in the follow-up period, compared to five in the standard of care group ($P=0.05$; Table 2). Similarly, in those who

TABLE 1 Summary of patient characteristics

Clinical characteristic	Standard of Care (n = 29)	Early-TIPSS (n = 29)
Age (SD)	48 (±12)	53 (±10)
Female (%)	10 (34)	9 (31)
Cause of cirrhosis (%)		
ALD	26 (90)	28 (97)
NAFLD	2 (7)	1 (3)
Viral	1 (3)	0 (0)
Active alcoholism (%)	24 (83)	25 (86)
Child-Pugh score (SD)	9.8 (±1.5)	9.8 (±1.2)
Child-Pugh class		
Class B (%)	12 (41)	13 (45)
Class C (%)	17 (59)	16 (55)
MELD score (SD)	17 (±3.8)	17 (±3.4)
Ascites		
None (%)	12 (41)	9 (31)
Mild (%)	10 (34)	14 (48)
Severe (%)	7 (24)	6 (20)
Bilirubin (IQR)	62 (39)	58 (50)
Albumin (SD)	24 (± 5.7)	25 (± 4.9)
Prothrombin time (SD)	19 (± 3.8)	20 (± 4.7)
Creatinine (IQR)	62 (33)	60 (26)
Serum sodium (SD)	135 (± 4.3)	135 (± 6.3)
Previous Hepatic Encephalopathy		
None (%)	28 (97)	26 (90)
Grade I-II (%)	1 (3)	3 (10)
Systolic blood pressure (SD)	125 (± 16)	118 (15)
Heart rate (SD)	98 (± 24)	98 (± 21)
Antibiotic use (%)	29 (100)	29 (100)
Vaso-active drug therapy at the time of bleeding (%)	13 (44)	14 (48)
Active bleeding at endoscopy (%)	10 (34)	8 (28)
Bands applied at index endoscopy (SD)	5 (±1.3)	4.8 (±1.0)

actually received a TIPSS, hepatic encephalopathy was experienced by 10 (43.5%) patients compared with five (17.2%) patients in the standard of care group ($P=0.04$).

TABLE 2 Secondary and Subsidiary Outcomes (Intention-to-treat)

Variable	Standard of Care (n = 29)	Early-TIPSS (n = 29)	P-value
Cause of death:			
GI bleed	1	1	
Liver failure	4	2	
Sepsis	1	2	
Cardiovascular	1	1	
All Cause Rebleeding (number of patients):			
<6 weeks	5	1	0.08
6 weeks – 1 year	5	6	0.79
Total	10	7	0.86
All Cause Rebleeding (all episodes):			
<6 weeks	5	2	
6weeks – 6months	4	3	
6months –12months	3	6	
Total at 1 year	12	11	
Variceal Rebleeding (number of patients):	8	3	0.09
Causes of Rebleeding (all episodes):			
Variceal	9	4	
Banding ulcer	2	3	
Mallory Weiss	1	2	
Portal hypertensive gastropathy	0	1	
Oesophagitis	0	1	
Hepatic Encephalopathy	5	12	0.05
New or Worsening Ascites	3	4	0.71
Median days in Intensive care	1	1	0.32
Orthotopic liver transplantation	1	0	

Fourteen of the 29 (48.3%) participants in the standard of care group had ascites during their follow-up period compared to nine of the 29 (31.0%) participants in the early-TIPSS group. The rates of developing new or worsening ascites were 10.3% in the standard of care group and 13.8% in the early-TIPSS group ($P=0.71$).

There were no significant differences between groups in other adverse events (Table 3).

3.4 | Per-Protocol Analysis

Given that some patients randomised to early-TIPSS either did not receive TIPSS or received TIPSS outwith the 72-hour window, a

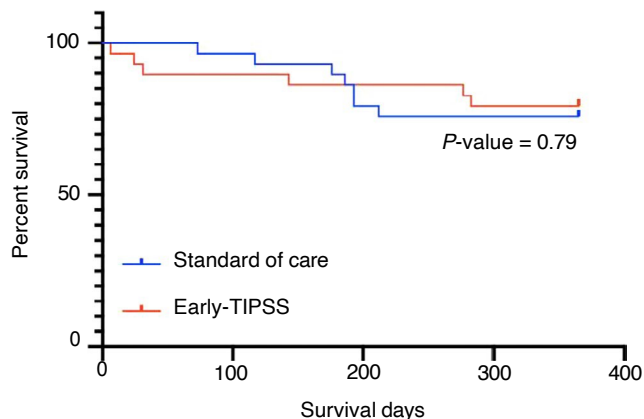


FIGURE 2 Kaplan-Meier Curve, Early-TIPSS vs Standard of Care (Intention-to-treat)

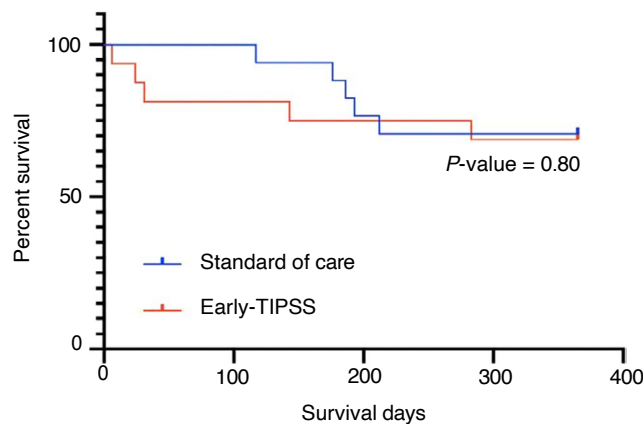


FIGURE 3 Kaplan-Meier Curve, Early-TIPSS vs Standard of Care in Childs-Pugh C Participants (Intention-to-treat)

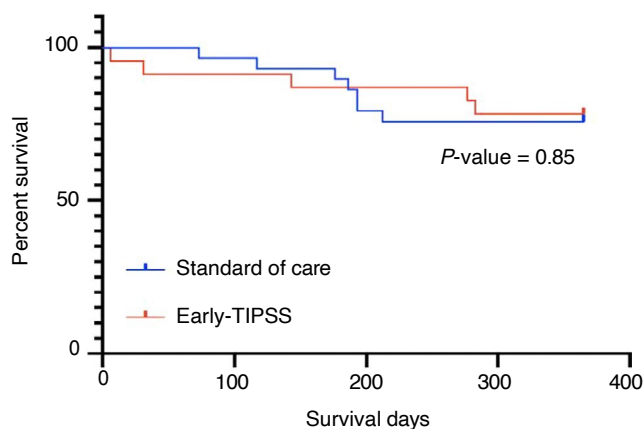


FIGURE 4 Kaplan-Meier Curve, All TIPSS vs Standard of Care

per-protocol analysis was performed. One-year survival rate in the 13 participants who received TIPSS within 72 hours of index endoscopy was 76.9% (10/13) compared with 75.9% (22/29) in the standard of care group ($P=0.91$), (Figure 5). The 1-year survival rate for those who received TIPSS placement beyond 72 hours from index endoscopy was 80.0% (8/10). For the 13 who received TIPSS placement within the pre-defined time period of 72 hours from endoscopy, none suffered variceal rebleeding which was significantly less than the 27.6% (8/29) in the standard of care group ($P=0.04$). One-year variceal rebleeding rate in those who received TIPSS out with 72 hours was 10.0% (1/10). Hepatic encephalopathy was experienced in 46.1% (6/13) of those who received early-TIPSS which was significantly higher than 20.7% (5/29) in the standard of care group ($P<0.05$).

4 | DISCUSSION

The index study in cirrhotic patients admitted with acute oesophageal variceal bleeding favoured the early use of TIPSS with an e-PTFE covered stent, demonstrating significant reductions in rebleeding and mortality in patients with Childs-Pugh C disease or Child-Pugh B disease with active bleeding during endoscopy.¹

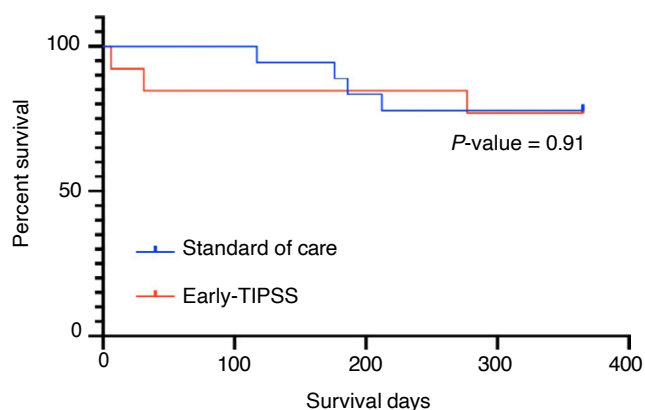
Although the study was not designed to assess survival and no other comparable randomised control trial has been performed since, international clinical guidelines now suggest placement of an e-PTFE covered TIPSS within 72 hours following acute oesophageal variceal bleeding.^{2,3} Despite this, physician adherence to these guidelines has been poor, with a lack of technical availability and the ambiguity of current data suggested as possible explanations.^{6,7} In contrast to previous work, our findings do not support use of early-TIPSS placement for the improvement of survival in cirrhotic patients following oesophageal variceal bleeding.

We report a 1-year survival rate of 79.3% in our early-TIPSS group. This is less than the 1-year survival rates of 86% as previously reported.¹ However, our 1-year survival rate of 75.9% in the standard of care group is much superior to the 61% reported in the previous study, which likely explains the difference in statistically significant survival outcomes between the two studies.

We used endoscopic band ligation at index endoscopy to gain haemostasis in all participants. This is in line with current standards of care² whereas in the previous study,¹ 25% of patients received sclerotherapy which is no longer indicated for use in acute variceal bleeding.² Additionally, there were pharmacological differences in vaso-active agents administered by Garcia-Pagan *et al* with somatostatin, terlipressin and octreotide all being given. Although head-to-head trials have failed to prove any efficacy difference between these agents in relation to short-term rebleeding and mortality, the long-term outcomes remain unstudied.⁸ We only used terlipressin, which is currently the only agent shown to reduce mortality in placebo-controlled trials.⁹ It is therefore an advantage that all participants in our study received the same vaso-active agent throughout as this removes potential for confounding. Similarly, in addition to endoscopic band ligation, we used carvedilol for secondary prophylaxis of oesophageal variceal bleeding whereas either propranolol or nadolol, in combination with isosorbide mono-nitrate (ISMN), was used previously.¹ Haemodynamic studies show that carvedilol is more effective than propranolol in reducing portal pressure, which correlates with reduction in rebleeding and therefore survival.^{10,11} The combination of non-selective beta-blockers (NSBB) and ISMN

TABLE 3 Summary of other adverse events

Adverse event	Standard of care (n = 29)	Early-TIPSS (n = 23)
Seizure	0	2
Fractured bone	2	3
Cellulitis	0	1
Arrhythmia	1	1
Abscess	1	0
Compartment Syndrome	1	0
Urinary Tract Infection	1	1
Alcoholic Hepatitis	2	1
Left Ventricular Thrombus	0	1
Pneumonia	0	2
Spontaneous Bacterial Peritonitis	2	1
Spontaneous Retroperitoneal Bleed	0	1
Hyponatraemia	0	1

**FIGURE 5** Kaplan-Meier Curve, Early-TIPSS vs Standard of Care (per protocol)

used previously has been proven to be no more effective in reducing mortality that NSBB alone, is associated with more side effects, and is more likely to lead to poor medication compliance.^{12,13}

Failure to control bleeding is an important predictor of survival.¹⁴ It could be argued that the now dated and inconsistent practice to achieve and maintain haemostasis in the previous randomised control trial,¹ as outlined above, led to suboptimal bleeding control. The early placement of a TIPSS would counteract this deleterious effect, thereby improving survival compared to the standard of care group.

Previous studies evaluating the role of TIPSS in the prevention of recurrent variceal bleeding have clearly shown that TIPSS reduces rebleeding rates but increases rates of hepatic encephalopathy. However, these studies used bare metal stents.^{15,16} The benefits of e-PTFE covered stents are improved stent patency and functionality which, rationally, would most likely increase rates of hepatic encephalopathy further. The previous authors contradict this by reporting

the early placement of TIPSS with an e-PTFE covered stent following oesophageal variceal bleeding does not increase rates of encephalopathy.¹ Indeed, there were fewer episodes of encephalopathy in their early-TIPSS group, although this was just short of being statistically significant. In our study, more participants experienced encephalopathy in the early-TIPSS group on intention-to-treat analysis however, this was not statistically significant. On a per-protocol analysis, as well as in a subgroup analysis for all non-emergency TIPSS placements regardless of time taken, TIPSS was associated with an increased risk of encephalopathy. More data are required on rates of hepatic encephalopathy with covered stents in this setting, as current evidence is significantly heterogenous, with conflicting outcomes reported.¹⁷⁻¹⁹

Our randomised controlled trial does have some similar findings to the previous work; although there were no differences in rates of rebleeding observed on an intention-to-treat analysis, we do report significantly reduced rates of variceal rebleeding for those receiving early-TIPSS on a per-protocol analysis as well as in an analysis of all participants who received TIPSS placement. We also observe high rates of mortality in those participants who required rescue TIPSS, a finding consistent with other studies.^{20,21}

Additional literature investigating the impact of early-TIPSS following oesophageal variceal bleeding is available. A meta-analysis concluded that early-TIPSS increased survival²² however, the trials included were not designed to assess survival as a primary endpoint.^{1,23} Furthermore, the observational studies included did not find a statistically significant increase in survival.^{24,25} A retrospective study from the US reported early-TIPSS reduced mortality and rebleeding.²⁶ In a Chinese randomised control trial,²⁷ early-TIPSS placement did correlate with improved liver transplant free survival, however it has been suggested that transplanted organs in China may not be complicit with international professional and ethical standards.²⁸ In addition, sclerotherapy was used in some patients, the study population was predominantly of Childs-Pugh B severity, viral in aetiology and had higher portal pressures compared to other studies despite less severe disease.

Our study has some limitations. Due to slow recruitment the study was closed early and therefore unpowered to detect difference in 1-year survival. The sample size was, however, sufficient to detect a survival difference at 6 weeks based on the results of the Garcia-Pagan et al study.¹ As our survival rates were near identical between groups, a fully powered study would have been unlikely to yield a different result. Although both centres operate a 24/7 emergency TIPSS service, not all participants randomised to early-TIPSS received shunt placement within the required 72-hour window (from endoscopy) therefore not deemed "early-TIPSS" by definition. This was primarily due to eligible patients presenting out-of-hours resulting in delayed contact with the study team and thus, the randomisation process. Additionally, unavailability of anaesthetic support for the procedure due to more pressing urgent clinical issues at the time, meant elective early-TIPSS placement for our study could not be prioritised. This reflects real-world clinical practice.

Six participants who were randomised to receive early-TIPSS placement did not receive the shunt. This was due to a combination of the above factors resulting in a delay beyond the five-day acute bleeding window, thus, these participants underwent a second endoscopy for variceal banding and continued with standard of care treatment thereafter. Lastly, the population studied was predominantly alcohol-related liver disease with ongoing alcohol consumption. This has obvious implications on long-term survival. Although this reflects the primary aetiology behind chronic liver disease related presentations to UK hospitals, our findings may not be applicable to other countries in which alternate aetiologies are more prevalent.

One of the reasons for poor physician adherence to guidelines recommending the use of early-TIPSS following oesophageal variceal bleeding is the inability to provide such a service. Remarkably, even the Spanish authors of the Garcia-Pagan *et al* study report observational data in which only 9.8% of their suitable patients received early-TIPSS placement.⁵ The fact that not all participants randomised to early-TIPSS in our study received shunt placement is an important finding. Despite the setting of a clinical trial, in two large tertiary centres with an experienced 24/7 emergency TIPSS service, TIPSS could not be performed within 72 hours of endoscopy in 16 participants. Therefore, it would seem unrealistic that an early-TIPSS service could be provided in smaller, non-academic and remote centres. This is echoed in the recent UK TIPSS guidelines for the management of portal hypertension, in addition to highlighting the uncertainties in patient selection for the procedure.²⁹

A potential explanation for reduced mortality after early-TIPSS placement is the immediate reduction in portal hypertension and associated pathophysiological changes facilitating a reduction in gut bacterial translocation that would have otherwise amounted to a systemic inflammatory response.^{30,31} Preliminary results from a large observational study of 281 patients in our centre, however, showed that time to TIPSS does not alter outcome following acute oesophageal variceal bleeding³² therefore the 72-hour post endoscopy window chosen by previous authors may be arbitrary.¹ We have provided analysis on all participants randomised to early-TIPSS who received TIPSS placement regardless of time taken, and no survival benefit was seen when compared to our standard of care group. The survival rate for participants who received late-TIPSS in this study was slightly higher than those who received early-TIPSS (80% vs 76.92%) therefore we do not believe the delay in TIPSS placement for some participants should greatly detract from our findings. It should be noted that in studies which support the use of TIPSS for secondary prophylaxis following oesophageal variceal bleeding, benefits have been observed for up to 5 days post endoscopy.³³

In conclusion, our underpowered study shows that placement of early-TIPSS appears to reduce rates of variceal rebleeding but increases rates of hepatic encephalopathy with no effect on survival in patients who have Child-Pugh B and C cirrhosis. The study was undertaken in a UK population with predominantly alcohol-related liver disease. It was not possible to arrange early-TIPSS for all participants therefore, a consistent early-TIPSS service may not

be feasible in some centres. Previous studies which supported the use of early-TIPSS used clinical practices that are now somewhat outdated, therefore larger, multicentred, randomised controlled trials are required to clarify the optimal management strategy.

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AUTHORSHIP

Guarantor of the article: Professor Peter Hayes.

Authors' contributions: Dr PDJ Dunne: Principal Investigator (RIE), recruitment of patients, collation of data, statistical analysis of data, composition of manuscript. Dr R Sihna: Recruitment of patients, statistical analysis, review and editing of manuscript. Prof. AJ Stanley: Principal Investigator (GRI), recruitment of patients, review and editing of manuscript. Dr N Lachlan: Recruitment of patients, review and editing of manuscript. Dr H Ireland: Review and editing of manuscript. Dr A Shams: Design of study, protocol author recruitment of patients, review and editing of manuscript. Dr R Kasthuri: Review and editing of manuscript. Dr EH Forrest: Recruitment of patients, review and editing of manuscript. Prof. PC Hayes: Senior Investigator, review and editing of manuscript. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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Letter: improve survival! Place early pre-emptive TIPSS in high-risk variceal bleeders—Authors' reply

EDITORS,

We thank Garcia-Pagan et al for their observations on our recent randomised control trial (RCT),^{1,2} confirming that our 1-year survival rate of 79% for patients receiving pre-emptive TIPSS (pTIPSS) is comparable to previous studies examining the use of pTIPSS in high-risk patients. Despite this, they also suggest our “excellent” 1-year survival rate of 76% in the standard of care (SOC) group could be due to exclusion of the very same high-risk patients. In the setting of a RCT, however, such differential recruitment would be unusual.

The 1-year survival rate of 76% in our SOC group is in keeping with modern studies. A similar Chinese RCT reported a SOC 1-year survival rate of 73%.³ Furthermore, observational data from a large European study revealed a 1-year survival rate of 74% in high-risk patients who were suitable for pTIPSS but did not receive shunt placement.⁴ Comparing baseline characteristics of our SOC group to the Garcia-Pagan RCT,⁵ we had similar median MELD scores (17 vs 17), and rates of ascites (59% vs 58%) and higher rates of Child Pugh-C disease (59% vs 48%). The alternative SOC strategy used by Garcia-Pagan resulted in a 1-year survival rate of 61%. In light of the above, this is perhaps lower than expected and discounts our SOC survival from being inappropriately high.

Regarding the comment pertaining to patients excluded from our study, further information is available. Seven patients died before recruitment: four were encephalopathic prior to death, two died during endoscopy and one had concurrent cerebral haemorrhage. Seven patients were excluded due to “other reasons”: four self-discharged from medical care, two had bleeding portal hypertensive gastropathy and one had concurrent small bowel obstruction. Rescue-TIPSS was only used for patients in whom haemostasis at index endoscopy was not possible. Evidently, the above patients would have also been excluded from previous pTIPSS studies.

44% of patients in our study received terlipressin “at time of endoscopy”, whereas all patients received terlipressin within the acute bleeding phase. A total of 18/29 received carvedilol per protocol at a median dose of 6.25 mg. Although 12.5 mg is recommended for optimal reduction in variceal bleeding risk,⁶ this does not consider

the pleotropic effects of carvedilol and the added survival benefit in cirrhotic patients.⁷ Our study was underpowered; however, a power calculation based on our survival rates would have required recruitment of over 4000 patients.

Studies that support the use of pTIPSS are heterogeneous, with no comparable benefit seen in consistent patient groups. Additionally, observational data support the difficulty in arranging pTIPSS within the 72-hour timeframe, with only 6%-11% of suitable patients receiving pTIPSS placement.^{4,8,9} The 1-year survival rate in our study was better for those who had TIPSS placed between 3-5 days from endoscopy (80%), which may question the role of precipitous shunt placement.

Until more robust evidence is available, with focus on patient selection and optimal timing, pTIPSS should not be considered a mainstay in the management of acute variceal haemorrhage. In the meantime, we can be reassured that assiduously applied SOC treatment has significantly improved outcome in recent years.

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The authors' declarations of personal and financial interests are unchanged from those in the original article².

LINKED CONTENT

This article is linked to Dunne et al and García-Pagán et al papers. To view these articles, visit <https://doi.org/10.1111/apt.15797> and <https://doi.org/10.1111/apt.15926>

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sustained virological response (cure) 12 weeks post treatment. 2 patients failed to achieve a cure. 17 patients are still on treatment or have not yet reached 12 weeks post treatment to assess for cure.

From July to September 2017 49 patients were tested for blood borne viruses in the needle exchange. 21 were HCV antibody negative and 28 antibody positive. Of the 28 HCV antibody positive patients 15 were HCV antigen positive thus having active HCV infection and were referred for treatment. For the 3 month period at the end of the retrospective look back exercise 33 patients were tested; 25 were negative and 8 HCV antibody positive but no patients had HCV antigen positivity. 5 patients were referred to the clinic following disclosure to needle exchange staff that they had previously tested HCV positive in another service or area.

Conclusions Chaotic HCV patients can be successfully treated in the community where outreach services can be offered alongside harm minimisation services. Treating active IVDUs is achievable and can have an impact on the local prevalence of HCV amongst small chaotic communities.

Abstracts of Distinction

ATU-06 DOES THE TIMING OF TIPSS IN PATIENTS WITH ACUTE OESOPHAGEAL VARICEAL BLEEDING ALTER PATIENT OUTCOME?

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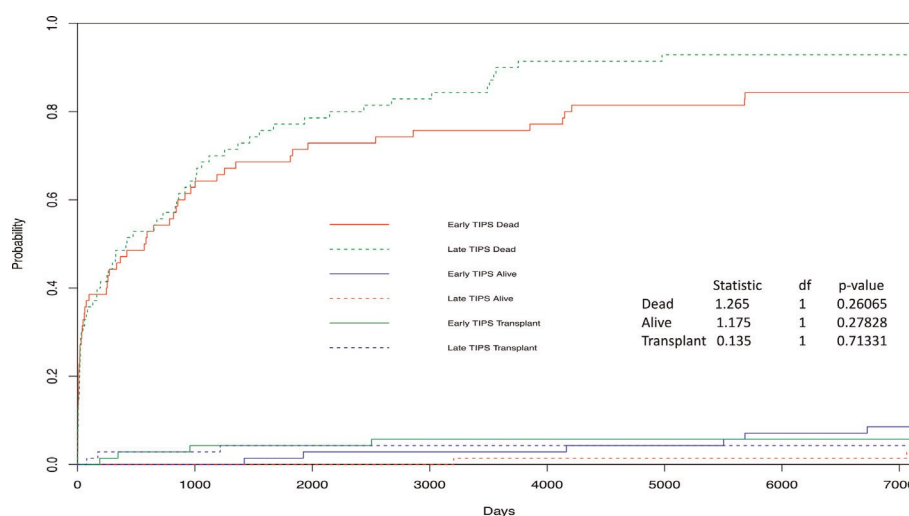
Introduction International guidelines recommend consideration of early-TIPSS (<72hrs) for high-risk patients presenting with oesophageal variceal bleeding (OVV). This advice follows a single randomised control trial reporting significant survival benefits of early-TIPSS in such patients. However, with the challenges of resourcing the widespread provision of early-TIPSS, we aim to determine if the time taken to carry out TIPSS alters patient outcome.

Methods This is a single centre cohort study of prospectively collected data in patients undergoing covered TIPSS following urgent (<12 hrs) endoscopic band ligation (EBL) for acute OVB between October 1998 - October 2014. Indications for progression to TIPSS include: failed haemostasis at index endoscopy; clinical evidence of further bleeding after haemostasis at index endoscopy; high risk of rebleeding after haemostasis at index endoscopy. Patients were defined by 2 groups; 'early-TIPSS' being those undergoing TIPSS <72 hours of index endoscopy, and 'late-TIPSS' being >72hrs. Primary outcome is all cause mortality. All cases were followed up from the date of OVB necessitating TIPSS insertion for a minimum of 4 years or until death/liver transplant.

Results 281 patients were included in the study with 199 undergoing early-TIPSS and 82 having late-TIPSS. Analysis was carried out on 70 patients in each group following propensity score matching. For early and late TIPSS respectively, there were no statistical differences between age (51.2 vs 54.0), female sex (31.4% vs 35.7%), Childs Pugh (CP) score (10.3 vs 10.0), MELD (16.8 vs 18.1), rates of ascites (71.4% vs 65.7%) or encephalopathy (31.4% vs 28.6%) on admission, portal pressure gradient fall (15.1 vs 14.9), rates of post-TIPSS encephalopathy (28.6% vs 24.3%) and rebleeding (24.3% vs 20%). Using competing risk analysis, median follow-up days were as follows: Early TIPSS dead: 259, alive: 5503, liver transplant: 651; Late-TIPSS dead: 322, alive: 5134, liver transplant: 172. Equality of cumulative incidence function across groups was non-significant and there was no statistical significance in the incidence of death between the two cohorts (figure 1). On multivariate competing risk regression analysis for the outcome of death, MELD, CP score, ascites and post-TIPSS rebleeding were all statistically significant predictors.

Conclusions To our knowledge this is the largest real-world study, with the longest follow-up times, carried out on patients undergoing TIPSS following urgent endoscopic treatment for acute OVB. With advanced statistical analysis, our

data suggest that timing of TIPSS does not alter survival in this group of patients.



Abstract ATU-06 Figure 1

Effect of time to pre-emptive transjugular intrahepatic portosystemic shunt on patient outcome, a UK multicentre cohort study

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Summary

Background: Pre-emptive transjugular intrahepatic portosystemic shunt (pTIPSS) should be considered within 72 hours following acute oesophageal variceal bleeding. However, recent studies highlight the difficulty in providing pTIPSS within this narrow timeframe. Delaying pTIPSS beyond 72 hours has not been studied.

Aim: To determine if the time taken to perform pTIPSS alters patient outcome.

Method: Patients referred to 4 UK tertiary centres for pTIPSS between 01 January 2010 and 31 December 2018 were included. Time from endoscopy to pTIPSS was recorded and pre-defined clinically relevant outcomes were observed relative to two groups: early pTIPSS (<72 h) and late pTIPSS (72 h–28 days). The primary outcome was transplant-free survival at 1-year. Follow-up was until 31 December 2020.

Results: A total of 83 patients received early pTIPSS and 88 received late pTIPSS. Baseline characteristics were similar with no requirement for propensity score-matched analysis. There was no difference between early and late pTIPSS groups for patient outcomes; 1-year transplant-free survival rate (69.9% vs 71.6%, $p = 0.73$, HR 0.91, 95% CI 0.52–1.58), long-term survival ($p = 0.52$, HR 1.132, 95% CI 0.77–1.65), variceal rebleeding (4.82% vs 11.36%, $p = 0.09$, HR 0.411, 95% CI 0.14–1.17), hepatic encephalopathy (43.93% vs 34.61%, $p = 0.26$) and new or worsening ascites (16.6% vs 13.46%, $p = 0.79$). Death due to liver failure was significantly more prevalent in those undergoing early pTIPSS compared to late pTIPSS (44% vs 16%, $p = 0.046$, HR 2.79, 95% CI 1.02–8.32).

Conclusion: Placement of pTIPSS within 72 hours offered similar short- and long-term survival benefits compared to pTIPSS placed between 72 hours and 28 days. Early pTIPSS may be associated with an increased risk of liver failure-related mortal-

1 | INTRODUCTION

International guidelines currently recommend consideration of pre-emptive transjugular intrahepatic portosystemic shunt (pTIPSS) following endoscopically controlled oesophageal variceal bleeding (OVB) in carefully selected 'high-risk' patients.^{1–5} Although these guidelines differ in their definition of 'high-risk' (Childs Pugh (CP) C < 14,^{1–5} or, CP-B with active bleeding,^{1–3} or Model for End-Stage Liver Disease (MELD) >19⁵), they are consistent in their recommendation to perform pTIPSS placement within 72 h of the index endoscopy. pTIPSS has been shown to improve variceal rebleeding rates but the effect on survival remains undetermined.

Historic data suggests the greatest occurrence of variceal rebleeding is between 48 and 72 h after the initial bleeding episode.⁶ Therefore, a 72 h timeframe from index endoscopy to TIPSS insertion was first chosen in a randomised control trial investigating the effects of pTIPSS placement compared to the standard of care following OVB.⁷ However, the most recent pTIPSS randomised control trial (RCT) revealed that 35% of participants randomised to receive pTIPSS waited beyond 72 h to receive TIPSS placement, albeit their survival rates were unaffected.⁸ Difficulties in sourcing anaesthetic and interventional radiology (IR) support were cited as significant hurdles.

In a recent large observational study,⁹ only 6.7% of high-risk patients received pTIPSS within 72 h, with a further 6.4% undergoing pTIPSS placement between 72 h and 42 days. Notably, early shunt placement was not an independent predictor of survival. In another similarly large observational study,¹⁰ pTIPSS placement was used in only 9.8% of high-risk patients. Inconsistent availability of the TIPSS service in 9 of the 'TIPSS centres' was reported. These studies highlight the important difference between the feasibility and practicality of providing a non-emergency TIPSS service within a relatively short 72 h window in real-world clinical practice.

Despite growing evidence on the optimal timing of endoscopy for upper GI bleeding, there is a significant lack of evidence regarding the timing of pTIPSS. We aimed to determine if the time taken to perform pTIPSS alters patient outcome.

2 | METHODS

2.1 | Patients and settings

This was a multicentre cohort study with non-selective, continuous data collected on patients referred for pTIPSS between January 2010 and December 2018 following endoscopically stabilised acute OVB at 4 UK tertiary centres; Royal Infirmary of Edinburgh (RIE), University Hospitals Birmingham (UHB), Royal Free Hospital London (RFH), and Glasgow Royal Infirmary (GRI).

Patients with liver cirrhosis and OVB achieving endoscopic haemostasis following endoscopic band ligation (EBL), vasoactive drugs and antibiotics who then received pTIPSS were included. Those who underwent TIPSS following the failure of endoscopic haemostasis,

as well as those with early rebleeding, were deemed as having had 'rescue-TIPSS' and, therefore, not suitable for consideration in this study. Patients for whom TIPSS placement was precluded by other clinical factors such as recurrent hepatic encephalopathy (HE), unsuitable anatomy or portal vein thrombosis were not considered for TIPSS placement. Study-specific exclusion criteria included age less than 18 or more than 75 years, pregnancy, Child-Pugh score (CPS) <8 and >13 with or without active bleeding, previous TIPSS, and active cancer including hepatocellular carcinoma.

Vasoactive drugs were continued until TIPSS placement, or for a maximum of 5 days. TIPSS placement was carried out by interventional radiologists experienced in the technique. The e-polytetrafluoroethylene (e-PTFE) covered stents (Viatorr TIPSS endoprosthesis, W. L. Gore & Associates, Inc) were initially dilated to 8 or 9 mm. Pre- and post-TIPSS portal pressure gradients (PPG) were recorded, and the PPG change was calculated. If the PPG (the difference between portal-vein pressure and inferior vena caval pressure) did not decrease to below 12 mm Hg, the stent was dilated further to 9 or 10 mm.

The time of index endoscopy achieving haemostasis (time point zero) was recorded and the time to pTIPSS insertion (hours) was calculated. Patients were classified as having had 'early pTIPSS' (≤ 72 h from index endoscopy) or 'late pTIPSS' (between 72 h and 28 days from index endoscopy), these being the two groups compared in the analysis. No specific patient factors determined the timing of pTIPSS placement. The decision to pursue pTIPSS was made by the treating clinician, and the timing of the procedure was dependent upon patient consent and IR availability. All cases were followed up from the date of TIPSS insertion until the date of death, orthotopic liver transplant (OLT), or study closure date—31 December 2020, whichever was earlier.

TIPSS patency was checked at 6 months and 1 year (or earlier if clinically indicated) using Doppler ultrasonography or TIPSS venography. If TIPSS dysfunction was confirmed, balloon angioplasty was performed, or a further e-PTFE-covered stent was placed.

All patients consented to receive pTIPSS and were informed that their anonymised clinical details would be added to a database for study purposes. Local clinical governance teams did not request formal ethics approval for the study as the data were categorised for use as audit and quality improvement.

2.2 | Data collection

Once the pTIPSS was performed and the patient was eligible for inclusion, relevant patient data were added to an electronic database that was later cross-checked with electronic patient admissions records to ensure no patients were missed or falsely included. Data were collected by a dedicated member of the study team and obtained from electronic integrated clinical records systems. Baseline data included age, sex, primary aetiology of liver disease as well as clinical and laboratory parameters to calculate the severity of liver disease using the MELD and CP classification.

2.3 | Predefined outcomes

The primary outcome of this study was 1-year liver transplant-free survival. Secondary outcomes include long-term transplant-free survival, 1-year and long-term liver failure-related mortality, 1-year variceal rebleeding rates, 1-year post-TIPSS HE rates and 1-year rates of new or worsening ascites.

2.4 | Statistical analysis

Data were presented as mean (SD), median (IQR) for continuous variables and frequencies or percentages for categorical variables. Student-*t* and Mann–Whitney U tests were used to compare normally distributed continuous variables and non-parametric continuous variables respectively. Chi-squared analysis or Fisher's exact test was used to compare categorical variables. $p < 0.05$ was considered statistically significant. In the setting of unmatched groups, propensity score matching was to be used. The probability of reaching the

primary end point of survival was estimated by the Kaplan–Meier method and compared by means of the log-rank test. Patients who were lost to follow-up were censored at their last known alive date, e.g., attendance at a hospital appointment. Logistic regression analyses were used to estimate the association between time to pTIPSS placement and transplant-free survival. The statistical software package used was Prism (v8, GraphPad Software).

3 | RESULTS

A total of 192 patients underwent pTIPSS in the 4 centres, 21 were excluded due to CPS <8 in 9 patients, CPS >13 in 3, age > 75 years in 4, and concurrent Hepatocellular carcinoma (HCC) in 5. Of the 171 included in the analysis, 83 received early pTIPSS and 88 received late pTIPSS. A total of 71 patients had CP-C disease. A total 58 patients had pTIPSS placement at RIE, 46 at RFH, 37 at GRI and 30 at UHB. There were no differences in individual patient characteristics per group, [Table 1](#).

TABLE 1 Patient characteristics

Characteristic	Early pTIPSS (N = 83)	Late pTIPSS (N = 88)	Significance
Age (SD)	53.38 (12.18)	52.04 (11.69)	0.69
Male sex	71.1	61.4	0.58
Aetiology			
ALD	53	66	0.78
NAFLD	6	4	
Viral	6	3	
INR	1.57 (0.48)	1.46 (0.33)	0.33
Bilirubin (μmol/L)	63.44 (68.2)	67.76 (89.4)	0.37
Sodium (μmol/L)	137.2 (6.3)	136.9 (6.35)	0.72
Albumin (g/L)	27.81 (5.723)	28.65 (5.98)	0.93
Creatinine (μmol/L)	91.15 (81.95)	78.74 (44.78)	0.34
Ascites			
None	28	18	0.28
Mild	36	37	
Mod/severe	19	33	
Hepatic encephalopathy	23	23	0.89
MELD Score	16.42 (6.11)	15.52 (6.21)	0.67
Child-Pugh Score	9.05 (1.774)	8.9 (1.83)	0.533
Child-Pugh Class			
Class B (%)	47 (56.6)	53 (60.2)	0.48
Class C (%)	36 (43.4)	35 (39.8)	
PPG mmHg PRE (%)	20.6 (7.49)	21.58 (9.28)	0.71
PPG mmHg POST (%)	6.93 (3.13)	8.18 (3.14)	0.79
PPG mmHg FALL (%)	14.67 (6.36)	12.41 (5.45)	

Note: Data expressed in brackets = Median (IQR).

Abbreviations: ALD, Alcoholic liver disease; INR, International normalised ratio; MELD, Model for end-stage liver disease; NAFLD, Non-alcoholic fatty liver disease; PPG, Portal pressure gradient.

3.1 | Survival

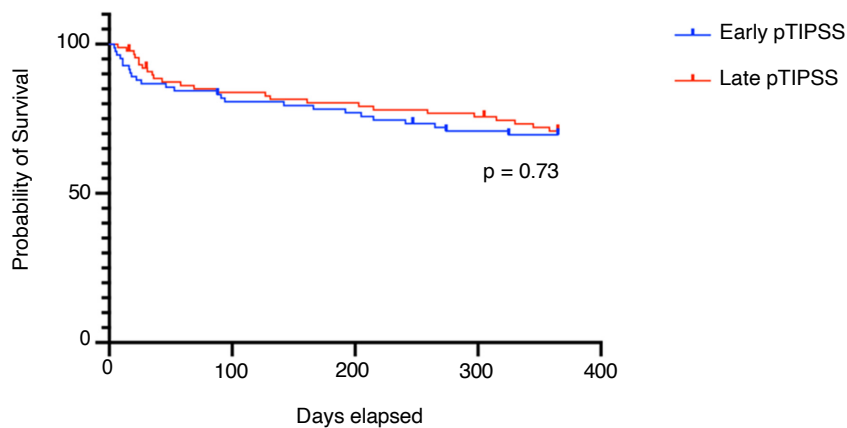
There was no difference in 1-year transplant-free survival rates between early and late pTIPSS groups, respectively (69.9% vs. 71.6%, $p = 0.73$, HR 0.91, 95% CI 0.52–1.58), **Figure 1**. For those with CP-C cirrhosis undergoing pTIPSS (36 early, 35 late), again no difference in 1-year transplant-free survival rate was seen between early and late groups, respectively (58.3% vs 59.5%, $p = 0.9$, HR 0.95, 95% CI 0.47–1.93), **Figure 2**. There was no difference in long-term transplant-free survival rates between early and late pTIPSS groups, respectively, ($p = 0.52$, HR 1.132, 95% CI 0.77–1.65), **Figure 3**.

Liver failure was the commonest cause of death throughout. Of those who died within 1 year following TIPSS placement, liver failure was more common in the early pTIPSS group compared to

the late pTIPSS group (44% vs 16%, $p = 0.046$, HR 2.79, 95% CI 1.02–8.32). For deaths beyond 1 year from the TIPSS procedure, liver failure was the cause in 23/51 (45.1%) of early pTIPSS and 22/56 (39.29%) in the late pTIPSS group ($p = 0.56$, HR 1.129, 95% CI 0.77–1.65). There were no other significant differences in the cause of death between groups. All causes of death are summarised in **Table 2**.

3.2 | Variceal rebleeding

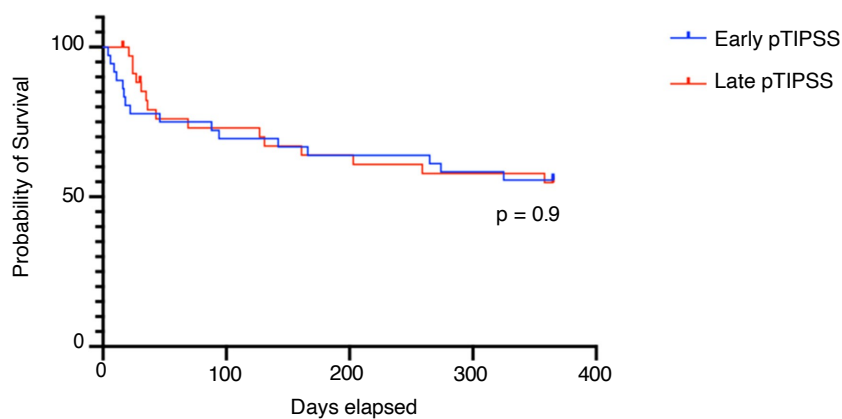
One-year variceal rebleeding rates between early and late pTIPSS groups were 4.82% and 11.36%, respectively ($p = 0.09$, HR 0.411, 95% CI 0.14–1.17). The probability of remaining free of variceal rebleeding at 1-year is shown in **Figure 4**.



Numbers at risk:

Days	0	7	28	90	180	270	365
Early pTIPSS	83	81	73	68	65	59	54
Late pTIPSS	88	88	81	73	70	97	60

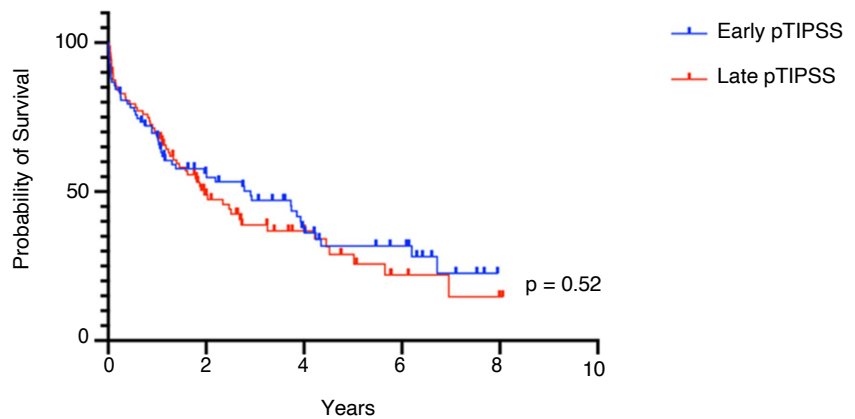
FIGURE 1 One-year transplant-free survival, early versus late pTIPSS



Numbers at risk:

Days	0	7	28	90	180	270	365
Early pTIPSS	36	35	29	27	24	23	20
Late pTIPSS	35	35	31	25	22	20	18

FIGURE 2 One-year transplant-free survival, early versus late pTIPSS in Child-Pugh C patients

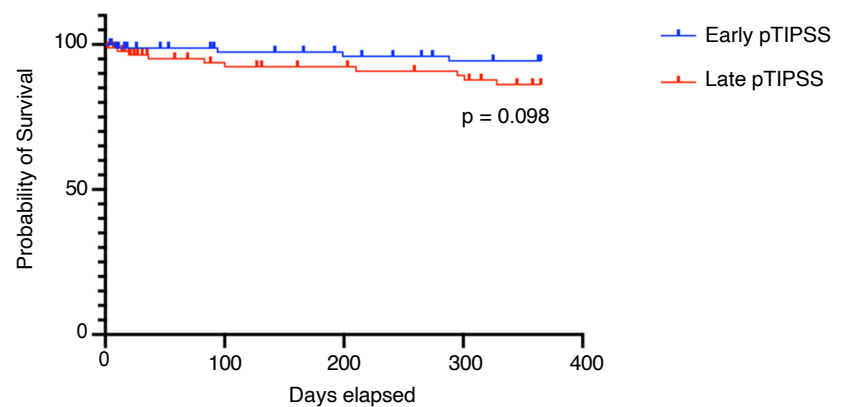
FIGURE 3 Long-term transplant-free survival, early versus late pTIPSS

Numbers at risk:

Days	1	2	3	4	5	6	7	8
Early pTIPSS	57	39	31	21	15	13	5	1
Late pTIPSS	60	32	21	16	10	5	3	2

TABLE 2 Causes of death

Cause of death	1 year		p-value	Long term		p-value
	Early pTIPSS (n = 83)	Late pTIPSS (n = 88)		Early pTIPSS (n = 83)	Late pTIPSS (n = 88)	
Liver failure	11	4	0.046	23	22	0.56
GI bleeding	2	6	0.279	5	9	0.41
Cardiovascular	2	1	0.612	3	3	0.99
Sepsis	6	9	0.595	10	14	0.51
Other	4	5	0.989	10	8	0.621
Total	25	25	—	51	56	—

FIGURE 4 Probability of remaining free of variceal rebleeding

Numbers at risk:

Days	0	7	28	90	180	270	365
Early pTIPSS	83	82	77	74	69	64	59
Late pTIPSS	88	84	75	68	64	61	53

3.3 | Other complications of portal hypertension

One-year follow-up data on post-TIPSS HE and new or worsening ascites were available for 118 patients in the study (66 early pTIPSS,

52 late). 29 (43.93%) patients receiving early pTIPSS experienced at least one episode of HE compared to 18 (34.61%) in the late pTIPSS group ($p = 0.26$, HR 1.61, 95% CI 0.74–3.41). Eleven (16.6%) patients in the early pTIPSS group developed new or worsening ascites

TABLE 3 Competing risk model: Multivariate regression analysis, 1-year and long-term survival

Variable	1-year survival			Long-term survival		
	Standard error	95% CI	p-value	Standard error	95% CI	p-value
Child-Pugh Score	8.674	-24.18 to 10.07	0.42	56.66	-99.38 to 124.4	0.82
MELD	2.008	-11.67 to -3.738	0.0002	13.12	-53.67 to -1.867	0.03
Age	0.7683	-3.945 to -0.9105	0.002	5.018	-23.26 to -3.442	0.008
Sex	18.92	-14.31 to 60.43	0.22	123.6	-196.3 to 291.9	0.7
Ascites	22.17	-25.10 to 62.45	0.41	147.6	-517.4 to 65.36	0.13
Encephalopathy	13.01	-48.17 to 3.207	0.08	84.98	-325.9 to 9.746	0.046
Days to pTIPSS	1.426	-3.325 to 2.305	0.72	9.312	-31.68 to 5.092	0.15

compared to 7 (13.46%) in the late pTIPSS group ($p = 0.79$, HR 1.286, 95% CI 0.441–3.33).

3.4 | Independent predictors of survival

Independent predictors of 1-year and long-term survival are shown in Table 3. Individual time (days) to pTIPSS did not influence probability of 1-year survival ($p = 0.72$, SE 1.42, 95%CI -3.32 to 2.3), however, age ($p = 0.002$, SE 0.77, 95% CI -3.94 to -0.91) and MELD ($p < 0.001$, SE 2.008, 95% CI -11.67 to -3.74) did. In relation to long-term survival, age, MELD and previous HE were the only individual predictors.

4 | DISCUSSION

Guidelines state pTIPSS placement within 72 h of endoscopically controlled OVB should be 'considered' in high-risk patients. Despite consistent evidence suggesting pTIPSS is impractical in real-world clinical practice, the timing of pTIPSS and the validity of this narrow therapeutic window remains vastly unchallenged in current literature. Our multi-centre, observational study of the largest number of pTIPSS procedures ever reported, found no difference in patient outcomes when undertaking pTIPSS within 72 h compared to pTIPSS placement between 72 h and 28 days.

The first RCT to show a survival advantage of pTIPSS over standard of care, randomised patients with endoscopically treated OVB (sclerotherapy) and a hepatic-venous pressure gradient (HVPG) >20 mmHg to TIPSS placement within 24 h, or further sclerotherapy and non-selective beta-blockers (NSBBs).¹¹ Notably, a patient in the TIPSS arm waited 5 days to receive TIPSS due to the failure of radiology equipment. Thereafter, a RCT with improved patient selection and clinical practices found superior survival rates in patients randomised to receive pTIPSS placement (i.e. within 72 h) over the standard of care.⁷ Although there were no prior survival data supporting the selection of the 72 h window used, the use of this timeframe has become the *modus operandi* for subsequent pTIPSS studies.

The most recent pTIPSS RCT,⁸ and the first to show no survival advantage of pTIPSS placement over the most up-to-date standards

of care, highlighted the difficulty in obtaining IR and anaesthetic support for pTIPSS placement within 72 h. Of the participants randomised to receive pTIPSS, 35% were delayed beyond 72 h. Interestingly, 1-year survival rates were slightly higher for these patients, but the numbers were too small to draw any firm conclusions. Moreover, the 2 largest observational studies investigating outcomes of pTIPSS placement, together show that $<10\%$ of over 1500 suitable patients received pTIPSS.^{9,10} These data emphasised the impracticality of providing a non-emergency <72 hrs service in dynamic, real-world clinical practice.

In our study, there were no differences in 1-year transplant-free survival rates between early and late pTIPSS groups. Recent data, as well as UK guidelines, suggest pTIPSS is only of benefit for those with CP-C disease.^{4,5,10} In our subgroup analysis of CP-C patients, the timing of pTIPSS placement did not alter survival. Additionally, long-term survival rates were unaffected by the timing of pTIPSS placement, and to our knowledge, our study is the first to report long-term survival data following pTIPSS.

Patient selection for pTIPSS is a common topic of debate. Multivariate regression analysis revealed that age, MELD, and prior hepatic encephalopathy were independent predictors of survival at 1-year, however, CP score, previous ascites and individual days to pTIPSS were not. MELD of 19 or more has been previously shown to be associated with poor survival following pTIPSS.¹²

There was a trend towards reduced 1-year rates of variceal rebleeding in the early pTIPSS group, however, this was just short of statistical significance. The reduction of variceal rebleeding rates with early pTIPSS placement is well documented. When considering other complications of portal hypertension, there was no difference in rates of HE and new or worsening ascites at 1-year between groups.

A prior study, published in abstract format only,¹³ assessed the effectiveness of early pTIPSS (<72 h) vs late pTIPSS (3–28 days) vs EBL following endoscopically controlled OVB. Interestingly, bleeding-related mortality at 6-weeks (early pTIPSS: 16.7%; late pTIPSS: 8.8%; EBL 35.7%, $p = 0.081$) and all-cause mortality at 1-year (early pTIPSS: 30.6%, late pTIPSS: 13.2%; EBL 53.6%; $p < 0.001$) were lowest in the late pTIPSS group. Another study directly examined patient outcomes in relation to early (<72 h) vs late (3–28 days) TIPSS placement following OVB.¹⁴ However,

many patients underwent rescue-TIPSS and 'extended criteria' for patient selection were adopted. Although that study does not directly inform current pTIPSS practice, it may be relevant that 1-year mortality rates were significantly lower in the late pTIPSS group compared to the early pTIPSS group (13.2% vs 40.8%, $p = 0.001$). Given the sparsity of prior data, our pragmatic decision to use 28 days as the cut-off for the late-pTIPSS group was on the basis of these two studies.

The previous hypothesis as to why pTIPSS undertaken within 72 h may have offered survival benefits over other standards of care in selected studies, includes the immediate reduction in portal hypertension, gut bacterial translocation and systemic inflammatory response.¹⁵ This has been demonstrated by data showing a reduction in endotoxin and tumour necrosis factor receptor levels post TIPSS, as well as reduced levels of chemokines such as CXCL9.^{16,17} Notably, these studies assessed patients undergoing all elective TIPSS procedures for varying indications rather than pTIPSS. It is intriguing that our data shows a significant increase in deaths due to liver failure in the early pTIPSS group. In light of the above, TIPSS placement and subsequent diversion of nutrient-rich blood away from the liver in the immediate aftermath of the haemodynamic consequences of OVB may lead to adverse consequences for some patients. Considering our data as well as the others mentioned, pTIPSS placement may be most beneficial with a period of recovery time prior to shunt insertion in order to see those potentially positive physiological effects in selected cases. However, as there was no difference in overall mortality rates between our groups, patient-specific timing of pTIPSS in order to avoid liver-related mortality is a topic for future study.

One of the challenges in interpreting data from pTIPSS studies is the low number of patients who receive pTIPSS. A recent meta-analysis found no survival benefit of pTIPSS placement and stated that current data was insufficient to confer any true advantage.¹⁸ The large number of patients in our study should be considered one of the strengths of this paper. Furthermore, its multicentered nature is an additional strength. As with all cohort studies, the data collection process is subject to selection bias. However, our two groups' characteristics were well matched, which provides some reassurance that our centres were not selective over who received pTIPSS and when. Due to the tertiary nature of the centres included, it was not possible to gain follow-up data on ascites and HE rates for all patients, particularly those referred from smaller hospitals. Some may question the safety of waiting up to 28 days for an OVB secondary prophylaxis procedure, however, it is worthwhile noting that for those undergoing EBL follow-up after OVB, guidelines recommend the second EBL session at up to 4 weeks after the index bleed.¹ Although concurrent use of NSBBs is also suggested for those patients, the effect on HVPG may not yet be seen at 4 weeks,¹⁹ and some patients may not tolerate the medication.²⁰

In conclusion, our study shows that undertaking pTIPSS within 72 h offers no benefit over pTIPSS placement between 72 h and 28 days. However, early pTIPSS was associated with an increased

rate of liver-related mortality at 1-year. The use of the MELD score rather than the CP score may help improve patient selection. Our results suggest the timeframe for pTIPSS placement may be extended to improve accessibility, which may be helpful to centres wishing to develop a pTIPSS service. These findings should be investigated further in large multi-centre RCTs.

AUTHOR CONTRIBUTIONS

Philip Dunne: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); project administration (lead); writing – original draft (lead); writing – review and editing (equal). **Faisal Khan:** Data curation (equal); writing – review and editing (equal). **Jemima Beatrice Finkel:** Data curation (equal); writing – review and editing (equal). **Neil Lachlan:** Data curation (equal); writing – review and editing (equal). **Adrian Stanley:** Supervision (equal); writing – review and editing (equal). **Dhiraj Tripathi:** Data curation (equal); supervision (equal); writing – review and editing (equal). **David Patch:** Data curation (equal); supervision (equal); writing – review and editing (equal). **Peter C Hayes:** Supervision (lead); writing – review and editing (lead). All authors approved the final version of the manuscript.

Guarantor of article: Peter C Hayes.

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Letter: improve survival in variceal bleeding in cirrhosis—place pTIPS as early as possible after index bleed. Authors' reply

Editors,

We thank authors Rudler et al for their comments on our recent publication^{1,2}—which, in the largest study of pTIPSS cases to date, revealed that pTIPSS undertaken within 72 h offered no improvement in patient outcome compared to pTIPSS undertaken between 72 h and 28 days.

Rarely, in medicine, do we get things right at the first time of asking and the concept of pTIPSS should be no different. Rudler et al's belief that pTIPSS should only be undertaken within, at most, 72 h of index bleeding (the timeframe used in the first RCT) must be modernised in light of our data.³ As we highlight in the rationale for our study, the 72 h timeframe was chosen following data which is now >40 years out of date.⁴ Rudler et al still highlight that same study in their letter. The authors fail to understand the concept of our study—pTIPSS beyond 72 h has never been studied and could still offer a prophylactic option, nor do they acknowledge the difficulty in providing a non-emergency pTIPSS service within a 72 h time frame in 'real world' clinical practice, despite the international recognition of this important issue.

Some unusual statements are made in the letter. The authors claim that by not recording a median time to pTIPSS we have excluded patients, prompting a huge selection bias. It is not clear how their conclusion was reached. Our exclusion criteria are clearly listed. In this regard, they also point to the exclusion of salvage TIPSS procedures in our study. Of course, readers will accept that patients requiring salvage TIPSS are a different patient group and are routinely excluded from all pTIPSS studies. Considering the heterogeneity of data and guidelines for the use of pTIPSS in CP-B patients with active bleeding,⁵⁻⁷ we also included a subgroup analysis of CP-C patients and still no difference in survival was identified between early and late pTIPSS groups. Rudler et al omit this important data from their letter. Furthermore, CP and MELD scores were near identical between our groups, which dispels the argument that our late pTIPSS patients were less unwell. The authors strangely claim an 'absence of time zero' in our study. Our methodology clearly states 'time zero'—defined as the time of index endoscopy for the initial bleeding episode. The highly selective study Rudler et al reference

for comprehensiveness is, in itself, uncomprehensive⁸—as it excluded the most up-to-date pTIPSS RCT⁹ and the largest pTIPSS cohort study,¹⁰ both of which were negative studies.

It is important to challenge dogma, particularly where evidence is lacking. Although our study may raise questions regarding the validity of the original pTIPSS concept, it may also prove a welcome relief to those centres wishing to pursue a pTIPSS service that has otherwise been restricted by the 72 h time frame. An important new multicentre U.K. RCT (REACT-AVB¹¹) aims to address some of the uncertainties regarding pTIPSS, with a focus on patient selection and timing of the procedure.

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AUTHOR CONTRIBUTIONS

Philip Dunne: Conceptualization (equal); writing – original draft (equal); writing – review and editing (equal). **Jemima Beatrice Finkel:** Writing – review and editing (equal). **Faisal Khan:** Writing – review and editing (equal). **Neil Lachlan:** Writing – review and editing (equal). **Adrian J Stanley:** Writing – review and editing (equal). **David Patch:** Writing – review and editing (equal). **Dhiraj Tripathi:** Writing – review and editing (equal). **Peter C Hayes:** Supervision (equal); writing – review and editing (equal).

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None.

DECLARATION

These are unchanged from the original manuscript.

LINKED CONTENT

This article is linked to Dunne et al papers. To view these articles, visit <https://doi.org/10.1111/apt.17252> and <https://doi.org/10.1111/apt.17322>

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Carvedilol versus endoscopic band ligation for secondary prophylaxis of variceal bleeding—long-term follow-up of a randomised control trial

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Summary

Background and Aims: Carvedilol reduces rates of variceal bleeding and rebleeding by lowering portal pressure. However, an associated pleiotropic survival benefit has been proposed. We aimed to assess long-term survival in a cohort of patients previously randomised to receive either carvedilol or endoscopic band ligation (EBL) following oesophageal variceal bleeding (OVB).

Methods: The index study randomised 64 cirrhotic patients with OVB between 2006 and 2011 to receive either carvedilol or EBL. Follow-up was undertaken to April 2020 by review of electronic patient records. The primary outcome was survival. Other outcomes including variceal rebleeding and liver decompensation events were compared.

Results: 26 out of 33 participants received carvedilol in the follow-up period and 28 out of 31 attended regular EBL sessions. The median number of follow-up days for all patients recruited was 1459 (SE = 281.74). On the intention to treat analysis, there was a trend towards improved survival in the carvedilol group ($p = 0.09$). On per-protocol analysis, carvedilol use was associated with improved long-term survival ($p = 0.005$, HR 3.083, 95% CI 1.397–6.809), fewer liver-related deaths (0% vs 22.57%, $p = 0.013$, OR ∞ , 95%CI 1.565– ∞) and fewer admissions with decompensated liver disease (12% vs 64.29%, $p = 0.0002$, OR 13.2, 95% CI 3.026–47.23) compared to the EBL group. There was no statistically significant difference in variceal rebleeding rates.

Conclusion: Following OVB in cirrhotic patients, carvedilol use is associated with survival benefit, fewer liver-related deaths and fewer hospital admissions with decompensation.

1 | INTRODUCTION

Several randomised control trials have demonstrated the efficacy of non-selective beta-blockers (NSBBs) for both primary and secondary prevention of oesophageal variceal bleeding (OVB)^{1–3} Current clinical guidelines recommend endoscopic band ligation (EBL) and NSBB following OVB, with combination therapy thought to be advantageous over monotherapy in the prevention of variceal rebleeding.^{4,5} However, there has been much interest of late in the potential additional benefits of NSBBs compared with other standards of care such as; improved survival following OVB compared to EBL,⁶ improved survival for cirrhotic patients on a liver transplant waiting list,⁷ reduction in decompensation due to ascites⁸ and spontaneous bacterial peritonitis (SBP),⁹ and reduction in rates of hepatocellular carcinoma (HCC).¹⁰

Carvedilol is an NSBB that has an additional intrinsic anti- α 1 adrenergic effect. It has been shown to have a greater reduction in hepatovenous pressure gradient (HVPG) compared to other NSBB including propranolol or nadolol.^{11–13} HVPG is used as a surrogate marker for portal pressure and higher levels are associated with variceal bleeding and other complications associated with portal hypertension. In comparison to other NSBBs, carvedilol has also been shown to have clinical effectiveness in propranolol “non-responders,”¹⁴ better clinical tolerance,⁸ reduced long-term progression to ascites,¹⁵ and improved renal perfusion and clinical outcomes in cirrhotics with ascites.¹⁶ Additionally, carvedilol is associated with improved long-term survival when given as primary prophylaxis for OVB.¹⁷

Our index study¹⁸ reported that carvedilol and EBL were equally effective for secondary prophylaxis of variceal bleeding. Additionally, there was a trend towards improved survival in carvedilol treated patients, after a median follow-up of 26.3 months, albeit short of statistical significance. To date, most studies assessing carvedilol in the prophylaxis of OVB have short-term follow-up. We aimed to investigate the long-term outcomes for patients taking carvedilol following OVB, with survival (intention to treat and per-protocol) as our primary endpoints.

2 | METHODS

2.1 | Study design

This is a retrospective cohort analysis of 64 patients recruited to a multicentred randomised control study between June 2006 and December 2011. All patients had extended follow-up until April 2020. The index study was registered under trial number ISRCTN 69643049 and ethical approval was granted for each centre.

2.2 | Index study protocol and participants

Patients with cirrhosis and endoscopically proven OVB who were stabilised following relevant initial endoscopic and pharmacological

therapy (i.e. EBL, terlipressin and antibiotics) were recruited from four centres: Glasgow Royal Infirmary, Royal Infirmary Edinburgh, Gartnavel General Hospital Glasgow and Southern General Hospital Glasgow. Following the index endoscopy and after informed consent, clinically stable participants were randomised, at day 5, on a 1:1 ratio to receive either carvedilol 6.25 mg (titrated to 12.5 mg if tolerated after 1 week), or to undergo further EBL at 2 weekly intervals until variceal eradication, with 6 monthly surveillance endoscopies thereafter.

Exclusion criteria were: age < 18 or >75 years; advanced malignancy or comorbidity resulting in life expectancy <6 months; obstructive airways disease; baseline pulse rate <50 bpm or systolic blood pressure <90 mmHg; severe peripheral vascular disease; heart block or severe heart failure; pregnancy; type-I diabetes; portal vein thrombosis; previous transjugular intra-hepatic portosystemic shut (TIPSS) or porto-caval shunt surgery; a gastric variceal bleed; or treatment with NSBBs within 4 weeks of the index bleed.

2.3 | Long term follow-up data collection

A standardised electronic data collection proforma was used across all centres and populated by a local, lead clinician following interrogation of electronic patient records. All data were cross-checked against the original data set. Long-term follow-up data regarding the progress of patients' chronic liver disease were collected. These included hospital admissions related to decompensated liver disease (variceal rebleeding, development or worsening of ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, acute alcoholic hepatitis, sepsis); orthotopic liver transplantation (OLT); and TIPSS insertion. Mortality data were also collected including date and cause of death. Death certification was cross-referenced with records held by the National Records of Scotland. Carvedilol compliance and side effect profile were assessed by patient history, review of liver clinic appointment letters and review of primary care repeat prescriptions. EBL compliance and outcome were assessed by review of electronic patient records including attendance at hospital for planned EBL sessions and the procedure reports. Any cross-over between treatment groups during follow-up was documented.

2.4 | Primary and secondary outcomes

Primary outcomes were transplant-free survival on intention to treat and per-protocol analysis. Secondary outcomes were variceal rebleeding and liver decompensation events on both intention to treat and per-protocol analysis; compliance with treatment; and cross-over between groups.

2.5 | Analysis

Initial data analyses were performed on an intention-to-treat basis, with per-protocol analysis undertaken thereafter. Per-protocol

analysis was performed on participants randomised to carvedilol who had taken the medication for any duration, and for those randomised to EBL who attended more than the first two planned EBL sessions. Participants were censored in the event of failure of compliance, crossover of treatment arms, TIPSS placement, or at the end of the study period.

All statistical tests were two-sided using a 5% significance level. The probabilities of reaching the primary end point of survival were estimated by the Kaplan–Meier method and were compared using the log-rank test. Cox regression analysis was undertaken to determine if the following variables individually contributed towards survival: age, MELD, Child-Pugh score, ascites, variceal rebleeding and liver-related hospital admissions. The statistical software packages used for the analysis were SPSS (v17, IBM) and Prism (v8, GraphPad Software).

3 | RESULTS

All 64 patients included in the index study were followed up, 33 of whom were initially randomised to receive carvedilol, and 31 to receive EBL. Baseline patient characteristics are shown in Table 1. The median number of follow-up days for all patients recruited was 1459 (SE = 281.74).

3.1 | Compliance and censoring

Of the 33 patients randomised to carvedilol, 5 did not commence the medication due to early rebleeding in 4 (2 of whom died) and 1 due to poor cognition. Three patients discontinued the medication within 30 days due to side effects. Eleven took the medication through to death or closure of the study period and further one patient until OLT. A second patient underwent OLT in the carvedilol group but had crossed over to EBL prior. One patient received TIPSS due to rebleeding. Six patients crossed over to receive EBL, five due to rebleeding and one due to patient preference. Four patients stopped

carvedilol due to late side effects and a further one patient due to reasons unknown. Only one patient died within 100 days of discontinuing the medication. The overall median days of per-protocol carvedilol administration was 1956 (SE = 548.01).

Of the 31 randomised to EBL, three did not attend their planned follow-up EBL sessions. Of these three, one had a variceal rebleed and underwent urgent EBL (605 days). Of the 28 patients who complied with the planned EBL sessions, two experienced variceal rebleeding prior to their first planned follow-up EBL session and underwent further unscheduled EBL (8 and 14 days) and both attended planned EBL thereafter. Five underwent TIPSS placement for variceal rebleeding, one had TIPSS for hydrothorax, and one had TIPSS for ascites. One crossed over to receive carvedilol for rebleeding, and one attended regular EBL until OLT.

3.2 | Survival

On the intention to treat analysis, there was no difference in median survival days between the Carvedilol and EBL groups, respectively (1956 vs 1125, $p = 0.16$, HR 1.521, 95%CI 0.851–2.679) (Figure 1). However, on per-protocol analysis (EBL $n = 28$, Carvedilol $n = 28$), patients taking carvedilol were more likely to survive than those attending EBL sessions ($p = 0.005$, HR 3.083, 95% CI 1.397–6.809) (Figure 2).

3.3 | Cause of death

Overall causes of death are summarised in Table 2. On the intention to treat analysis, there were no significant differences in causes of death between EBL and Carvedilol groups, in particular, death due to liver failure = 25.81% vs 9.08% ($p = 0.102$), respectively. However, on per-protocol analysis, those taking carvedilol were significantly less likely to experience death due to liver failure compared to those in the banding group 0% vs 22.57% ($p = 0.013$, OR ∞ , 95% CI 1.565– ∞), respectively.

TABLE 1 Patient characteristics at recruitment

Characteristic	Carvedilol ($n = 33$)	EBL ($n = 31$)
Age, years; mean \pm SD	51.4 \pm 10.8	49.6 \pm 12.87
Alcohol aetiology (%)	27 (87.1)	31 (93.9)
Male: female	22:11	21:10
Child-Pugh score	9 (7.0–10.5)	9 (8.0–11.0)
MELD	13 (8.25–18.5)	14 (11.0–16.0)
Bilirubin (μ mol/L)	39 (19.5–63.0)	35 (23.0–82.0)
Albumin (g/L)	27 (22.5–31.5)	27 (24.0–33.0)
Prothrombin, time (s)	15 (13.0–19.0)	16 (14.0–17.0)
Ascites, n (%)	12 (36.3%)	12 (38.7%)

Note: All values are expressed as median (IQR) unless otherwise stated.

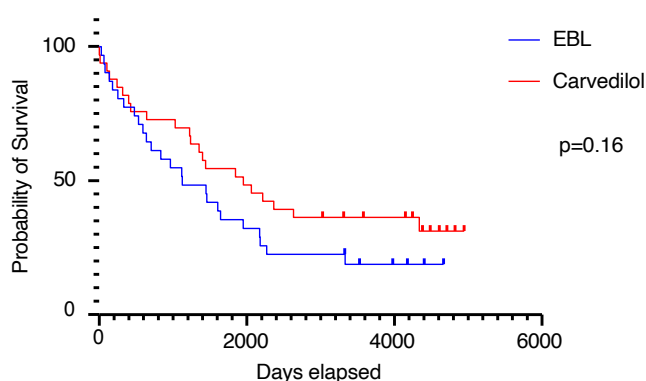


FIGURE 1 Survival: Endoscopic band ligation versus carvedilol, intention to treat

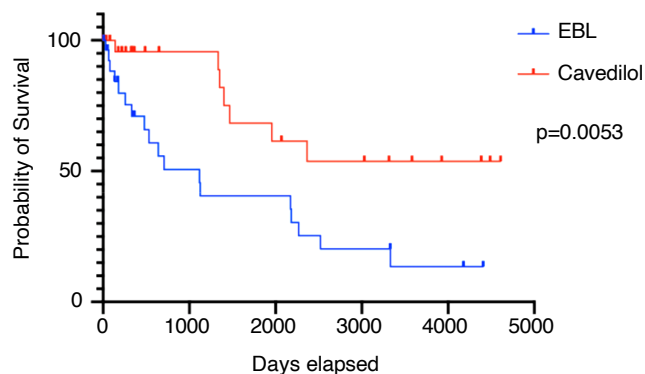


FIGURE 2 Survival: Endoscopic band ligation versus carvedilol, per-protocol

TABLE 2 Causes of death

Cause of death	Carvedilol (n = 33)	EBL (n = 31)	p-value
Liver failure (%)			
Intention to treat	3 (9.08)	8 (25.81)	0.102
Per-protocol	0 (0.0)	7 (22.57)	0.004
GI bleeding	3	6	0.296
Cardiovascular	4	1	0.356
Sepsis	2	4	0.419
HCC	0	1	0.484

$p > 0.05$ = non-significant (in bold).

3.4 | Variceal rebleeding

Similar to the index study, there was no difference between EBL and carvedilol groups in days free of variceal rebleeding in both intention to treat ($p = 0.66$, HR 1.191, HR 0.548–2.592), and per-protocol analysis ($p = 0.76$, HR 1.156, 95% CI 0.451–2.962) (Figure 3).

3.5 | Decompensated liver disease-related hospital admissions

Total, cumulative admissions to hospital with decompensated liver disease (excluding admissions due to variceal rebleeding) are summarised in Table 3. On both intention to treat and per-protocol analysis, participants in the EBL group were more likely to experience a decompensated liver disease-related hospital admission than the carvedilol group, respectively; intention to treat = 64.52% vs 30.3% ($p = 0.012$, OR 4.182, 95% CI 1.442–12.42), per-protocol = 64.29% vs 12% ($p = 0.0002$, OR 13.2, 95% CI 3.026–47.23). On per-protocol analysis, those in the carvedilol group had a higher probability than those in the EBL group of remaining free of decompensated liver disease throughout the follow-up period, median days 1467 vs 286 ($p = 0.016$, HR 3.069, 95% CI 1.532–6.148), Figure 4. Rates of active alcohol consumption were comparable between EBL and carvedilol groups respectively, 48.4% vs 48.4%.

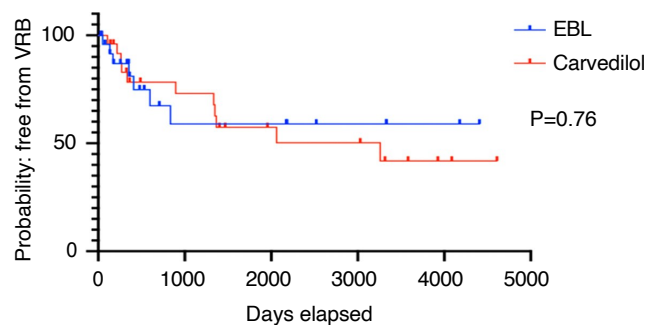


FIGURE 3 Variceal rebleeding: Endoscopic band ligation versus carvedilol, per-protocol

TABLE 3 Overall hospital admission with decompensated liver disease

Decompensation	Carvedilol (n = 33)	VBL (n = 31)
Ascites	5	14
Hepatic encephalopathy	7	8
Hepatorenal syndrome	2	2
Acute alcoholic hepatitis	4	7
Spontaneous bacterial peritonitis	1	4
Total	19	35

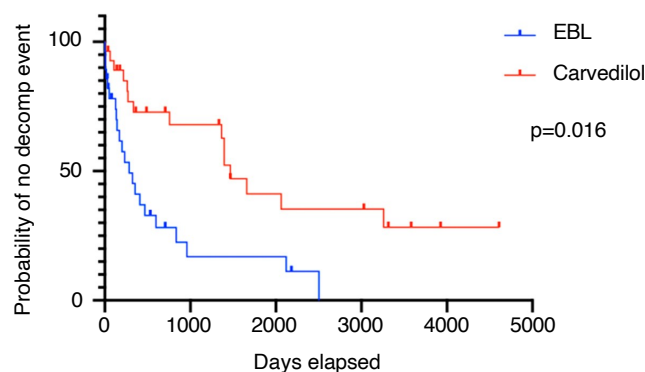


FIGURE 4 Days to first decompensated liver disease hospital admission: Endoscopic band ligation versus carvedilol, per-protocol

3.6 | Multivariate regression analysis for survival

Age, MELD, Child-Pugh score, ascites, carvedilol use and attendance at banding sessions were variables used to determine their individual impact on survival. Carvedilol was the only independent predictor, Table 4.

4 | DISCUSSION

This multicentre study assessed the long-term outcomes of a randomised control trial, in which patients with predominately

TABLE 4 Multivariate cox regression analysis for survival

Variable	Standard error	95% CI	p value
Age	16.51	-44.14 to 22.02	0.5057
MELD	38.82	-135.0 to 20.56	0.1462
Child-Pugh score	83.27	-150.2 to 183.4	0.8426
Ascites (yes)	422.4	-719.2 to 973.2	0.7648
Carvedilol use	0.1578	0.3008 to 0.9329	0.0003
Attended banding (yes)	405.0	-867.0 to 755.7	0.8912

$p > 0.05$ = non-significant (in bold).

alcohol-related liver disease initially presented with, and were treated for, OVB received either carvedilol or EBL to prevent rebleeding. We found that long-term survival and variceal rebleeding were similar for carvedilol and EBL on the intention to treat analysis. However, on per-protocol analysis, carvedilol use led to improved all-cause survival, in addition to a reduction in both liver-related mortality and admissions to hospital with decompensated liver disease.

Despite ongoing success in the treatment and eradication of the hepatitis C virus, the global burden of chronic liver disease is still rising, predominantly due to alcohol and metabolic syndrome. As a result, liver-related mortality has increased in recent years.¹⁹ The onset of portal hypertension is the main driving force that precedes the deterioration of liver disease, with complications such as ascites, variceal bleeding or hepatic encephalopathy marking the transition from compensated to decompensated cirrhosis and are associated with a dramatic decrease in survival.²⁰

In our study, carvedilol use was associated with improved long-term survival compared to those who attended at least two consecutive follow-up EBL sessions or achieved variceal eradication. The survival benefit found appears to be due to a reduction in liver-related mortality. In a previous study assessing the long-term outcomes of carvedilol versus EBL for primary prophylaxis of OVB, carvedilol was associated with survival benefit but not reduced liver-related mortality or liver decompensation events.¹⁷ This led to speculation as to the potential extra-hepatic benefits of carvedilol. It is, however, likely that the patients in our study were at a more advanced stage of liver disease, given the nature of recruitment being for secondary prophylaxis of OVB. We found that fewer patients in the carvedilol group were admitted to hospital with decompensated liver disease, and to our knowledge we are the first to report this finding in the context of a randomised trial. Interestingly, more patients in the EBL group underwent TIPSS for various reasons, however, despite this the rates of admission with ascites were lower in the carvedilol group, perhaps emphasising the protective benefit of carvedilol even further.

Similar to other NSBBs, carvedilol reduces heart rate and cardiac output by antagonism of β_1 -adrenergic receptors. Through β_2 -adrenergic blockade, it causes splanchnic vasoconstriction due to unopposed adrenergic tone, leading to an additional decrease in portal-collateral blood flow. However, in contrast to other NSBBs, carvedilol also exhibits an intrinsic anti- α_1 adrenergic effect, causing

intrahepatic vasodilatation that decreases portal pressure further. Interestingly, we found that carvedilol reduced liver decompensation events but did not prevent variceal bleeding, compared to EBL. This supports the suggestion that carvedilol influences pleiotropic mechanisms that contribute towards liver decompensation out with the HVPG. Animal studies have observed that carvedilol has antioxidant, anti-fibrotic and anti-inflammatory properties.^{21,22} Furthermore, carvedilol has been shown to increase insulin sensitivity, reduce glycosylated haemoglobin levels, slow the progression to microalbuminaemia,²³ and have a survival benefit compared to other NSBB in patients with heart disease.^{24,25}

Compliance with carvedilol was less than compliance with regular EBL, perhaps due to adverse effects associated with carvedilol. Three patients did not take the drug beyond 30 days (the likely time required to have an adequate effect on HVPG²⁶⁻²⁹) due to side effects, and four more discontinued the medication beyond 30 days. However, the minimum time for discontinuation in those established on carvedilol for >30 days was longer than 12 months. At the doses taken in our study (6.25–12.5 mg/day) carvedilol does not appear to cause systemic hypotension but decreases portal pressure significantly more than propranolol, which may explain its better tolerability.⁸

The multicentre nature, pre-defined clinically relevant outcomes and 100% patient follow-up should be considered strengths of this study. Additionally, we are the first to report long-term outcomes of carvedilol compared with EBL following OVB. One other study reported long-term outcomes of carvedilol following OVB, however, this was compared with propranolol.¹⁵ Limitations of our study include the fact that long-term data collection was retrospective, therefore at risk of the biases associated with retrospective studies. However, this bias can be lessened given the patients observed were initially recruited through a randomised trial. Our results should also be interpreted in the setting of an ALD predominant population. Active alcohol intake may alter survival, however, rates of active alcohol consumption was comparable between groups. Although a thorough process was undertaken to assess treatment compliance, we cannot guarantee that all participants continued their allocated treatment for the duration of the study. We also acknowledge the limitations of per-protocol analyses. Cross-over between treatments was low, however, some participants required censoring, thus reducing the analysed numbers and subsequent power of this study. Furthermore, patients who discontinued carvedilol were censored and if death occurred thereafter, they would not be counted as carvedilol-related deaths. However, only one patient died within 100 days of discontinuing carvedilol. Given that more patients in the EBL group received TIPSS for indications associated with severe disease (rebleeding, hydrothorax and ascites) and were also censored, we believe the survival benefit from carvedilol found in this study is of significant interest.

In conclusion, following OVB, carvedilol use is associated with improved survival, reduced liver-related mortality and fewer hospital admissions with the decompensated liver disease during long-term

follow-up. Monotherapy with carvedilol or EBL has similar variceal rebleeding rates. These results suggest that carvedilol use provides additional benefits in cirrhotic patients, beyond the reduction of rebleeding. Further, large randomised controlled trials are required to validate this finding and explore the potential benefits of carvedilol in other patients with chronic liver disease.

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AUTHOR CONTRIBUTIONS

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Letter: non-selective beta-blockers in cirrhosis—effect beyond portal hypertension. Authors' reply

Editors,

We would like to thank authors Chauhan and Bhatia for their letter¹ relating to our recent study—highlighting the potential long-term benefits of carvedilol following oesophageal variceal bleeding, in patients recruited to a randomised control trial (RCT).²

Carvedilol is becoming increasingly synonymous with the term 'pleiotropic effects'. Simply put, there is a disparity between the growing numbers of clinical studies reporting the array of benefits of carvedilol, and the sparsity of scientific studies to explain why. Although our understanding of these mechanisms is improving, the evident clinical outcomes are such that carvedilol is now suggested as the treatment of choice to prevent both variceal bleeding and decompensation in patients with clinically significant portal hypertension (CSPH), per the recent Baveno VII guidelines.³

Chauhan and Bhatia suggest that the availability of hepatic-venous pressure gradient (HVPG) and other non-invasive markers of fibrosis may have been useful in our study. They highlight previous data suggesting that HVPG >20 mmHg and raised markers of liver stiffness are associated with increased risk of decompensation and mortality in patients with compensated cirrhosis.⁴ However, by the very nature of our study being of secondary prophylaxis for variceal bleeding, our patients have already crossed the bridge from compensated to decompensated disease and are therefore a different and more challenging clinical group.

Although relative HVPG reduction post-OVB correlates with reduced rates of variceal rebleeding, we did not observe a difference in variceal rebleeding rates between carvedilol and endoscopic band ligation groups. In a separate secondary prophylaxis RCT,⁵ carvedilol was shown to be as good as pre-emptive TIPSS in improving survival, but not rebleeding. Therefore, the associated benefits of carvedilol appear to, again, be related to additional mechanisms and not purely HVPG response.

Data informing the value of HVPG in predicting other outcomes of portal hypertension in those with liver decompensation are limited and may be considered as a future area of study. However, HVPG is invasive and is not routinely adopted in clinical practice. Ongoing research assessing the effect of carvedilol on other scientific pathways

involved in the development of liver cirrhosis and CSPH may prove more valuable in answering the questions posed in the article's editorial.⁶

AUTHOR CONTRIBUTIONS

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LINKED CONTENT

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