

**CLINICAL AND HAEMODYNAMIC
STUDIES IN PORTAL
HYPERTENSION**

by

Dhiraj Tripathi

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Declaration

I declare that the work contained in this thesis is composed by me. All studies were performed during my time as a research fellow in the Department of Medicine, Royal Infirmary of Edinburgh. I have not submitted the thesis for any other degree, postgraduate diploma or professional qualification.

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Abstract of thesis

Over the last 20 years, there have been significant advances in the management of portal hypertension, with the introduction of drug therapy and the transjugular intrahepatic portosystemic stent-shunt (TIPSS). This development continues at a strong pace as our understanding of the pathogenesis of portal hypertension deepens. There are 2 aims of this thesis:

1. To study the haemodynamic effects of two novel vasoactive agents on the portal and systemic circulations.

- a. Carvedilol, a vasodilating non-cardioselective beta-blocker with α_1 antagonism. The acute and chronic haemodynamic effects of this agent will be studied, with particular attention paid to patient tolerability.
- b. Losartan, an angiotensin II receptor antagonist. The chronic effects of this agent will be studied in patients with well compensated cirrhosis.

These laboratory based studies will assist in determining the suitability of these agents for use in controlled clinical trials on patients at risk of variceal bleeding.

2. TIPSS has been used extensively in the management of portal hypertension, particularly variceal bleeding. Two studies will be presented in this thesis aimed at answering the following questions.

- a. Is TIPSS effective for the management of gastric variceal bleeding?
Gastric variceal bleeding is less common than oesophageal variceal

bleeding, hence there are relatively few studies investigating the effect of TIPSS on bleeding gastric varices. This study will also compare gastric variceal bleeding with oesophageal variceal bleeding, and aim to correlate clinical outcomes with haemodynamic data.

b. Is it necessary to continue portographic TIPSS surveillance indefinitely if variceal band ligation is combined with TIPSS for the prevention of oesophageal variceal rebleeding? This is the hypothesis for a randomised controlled trial comparing TIPSS alone with TIPSS plus variceal band ligation. This study will address 2 drawbacks of TIPSS, namely the need for long-term portographic to ensure TIPSS patency and hepatic encephalopathy.

Abbreviations

ANG II	Angiotensin II
CO	Cardiac output
ET-1	Endothelin 1
FHVP	Free hepatic venous pressure
GOV	Gastro-oesophageal varices
GVB	Gastric variceal bleeding
HBF	Hepatic blood flow
HR	Heart rate
HSC	Hepatic stellate cell
HVPG	Hepatic venous pressure gradient
ICG	Indocyanine green
IGV	Isolated gastric varices
ISMN	Isosorbide-5-mononitrate
IVC	Inferior vena cava
MAP	Mean arterial pressure
OLT	Orthotopic liver transplantation
OVB	Oesophageal variceal bleeding
PPG	Portal pressure gradient
PRA	Plasma renin activity
PTFE	Polytetrafluoroethylene
RAP	Right atrial pressure
SVR (I)	Systemic vascular resistance (index)
TIPSS	Transjugular intrahepatic portosystemic stent-shunt
VBL	Variceal band ligation
WHVP	Wedged hepatic venous pressure

Chapter 1

Introduction

1.1 Pathophysiology of portal hypertension.

Portal hypertension results in elevated portal pressure accompanied by significant changes in the systemic circulation. Normal portal pressure is between 1 – 4 mm Hg, with progressive increases in the portal pressure with time until complications develop such as gastro-oesophageal varices. Despite reports of a “threshold” value of portal pressure above which varices develop, varices particularly of gastric origin can develop and bleed at relative low portal pressures (Stanley and others 1997a). The exact pathogenesis of portal hypertension is the topic of much debate and research.

1.1.1 Historical aspects.

The phenomenon of portal hypertension has been known for hundreds of years, and was identified as a potential cause of gastrointestinal bleeding by Vesalius and Morgagni (Sandblom 1993). The term ‘portal hypertension’ was first used in 1906 (Gilbert and Villaret 1906), and until 1937, the increase in portal pressure could only be measured directly at laparotomy (Sandblom 1993).

1.1.2 Basic principles.

Portal hypertension is a clinical syndrome that results from an increase in intrahepatic resistance and increased portal blood flow. Ohms law dictates that the change in portal pressure (ΔP) is the product of portal blood flow (Q) and the resistance to flow (R):

Equation 1: $\Delta P = Q \times R$.

Resistance cannot be quantitatively measured unlike blood flow and pressure. Poiseuille's Law for deriving resistance brings together coefficient of viscosity (η), length of vessel (L), and radius of vessel (r).

Equation 2: $R = \frac{8 \eta L}{\pi r^4}$

Incorporating equation 2 into equation 1 results in:

Equation 3: $\frac{Q \times 8 \eta L}{\Delta P} = \pi r^4$

Under normal physiological conditions, the length of the vessel is constant, while the viscosity is also unchanged if there are no large changes in the haematocrit. Therefore, the portal pressure under normal conditions is principally affected by the portal blood flow and the radius of the blood vessel.

Increased intrahepatic resistance

The initial event in the pathogenesis of portal hypertension is increased intrahepatic resistance (the "backward theory") (Vorobioff and others 1983; Grose and Hayes 1992). The non-diseased liver is very compliant and can respond to increased portal inflow by distension of the vascular tree, thus maintaining the normal equilibrium and maintaining normal portal pressure (Greenwark and Stark, 1971). However, in portal hypertension there is increased resistance to portal inflow, principally due to fibrosis and regenerative nodules compressing the vasculature. In addition, it has been

shown that swelling of hepatocytes and capillarisation of hepatic sinusoids (loss of endothelial fenestrations and collagen deposition in the space of Disse) are part of the increased vascular resistance.

There are fixed anatomical factors responsible for this increased resistance, and reversible factors. The latter is more complex and had been the focus of much research, and it has been demonstrated that intrahepatic resistance can be reduced by as much as 20-30% by pharmacological therapy (Bhathal and Grossman 1985).

The activated hepatic stellate cell (HSC), similar to pericytes in other organs, has been shown to contract or relax in response to vascular mediators such as endothelin-1 (ET-1) (Kojima and others 2001), and angiotensin II (ANG II) (Bataller and others 2000). Furthermore, the activated HSC also plays an important role in hepatic fibrosis (Poo and others 1999). The role of vascular mediators will be explored later.

Circulatory changes

Increased intrahepatic resistance leads to the formation of the collateral circulation to decompress the portal circulation. The increased collateral blood flow through the formation of porto-caval shunts may contribute to a reduction in the portal blood flow and hepatic perfusion (Lebrec and Moreau 2001). However, portal hypertension is sustained as a result of increased splanchnic blood flow in an attempt to rectify the reduced hepatic perfusion, or the “forward theory” (Vorobioff and others 1983; Grose and Hayes 1992). The presence of marked splanchnic vasodilatation in patients

with cirrhosis was reported by Kotelanski (Kotelanski and others 1972), although the exact pathogenesis remains uncertain.

Cirrhosis and portal hypertension results in the hyperdynamic circulation first described by Kowalski & Abelmann (Kowalaski and Abelmann 1953), and later validated by others (Murray and others 1958). The characteristic features are increased cardiac output and decreased systemic vascular resistance, the latter mainly due to splanchnic vasodilatation. It has been proposed that peripheral vasodilatation may also contribute to reduced systemic vascular resistance (Schrier and others 1988), although some investigators suggest the peripheral circulation is vasoconstricted due to increased vasoconstrictor mediators such as angiotensin II and endothelin (Newby and Hayes 2002). Heart rate and stroke volume are also increased and directly proportional to cardiac output. These findings occur in patients with both intrahepatic (Bayley and others 1964) and extrahepatic portal hypertension (Lebrec and others 1983). The arterial pressure in patients with portal hypertension is normal or lower than in controls (Lowke 1962; Mashford and others 1962). In addition, the severity of liver disease is inversely proportional to the arterial pressure (Plevris and others 1990). Furthermore, cardiac output is higher in patients with cirrhosis and liver failure with ascites than in patients with good liver function (Fernandez-Seara and others 1989) without ascites (Brailion and others 1986). Systemic haemodynamic alterations are associated with a significantly increased total plasma volume (Perera 1946), which is correlated with the severity of the liver disease and the presence of ascites. Effective blood volume or central blood volume, i.e. the volume in the heart cavities, lungs and central arterial

tree, appears to be reduced in patients with cirrhosis (Hendrickson and others 1989).

1.2 Development of varices and variceal haemorrhage.

1.2.1 Background.

The development of gastro-oesophageal varices and subsequent variceal haemorrhage is the most serious complication of portal hypertension. At the time of diagnosis, 30% of compensated cirrhotic patients and 60% of decompensated patients have varices (D'Amico, Balliers, 1997), and at least two thirds of cirrhotics will develop varices during long term follow up (Anonymous 1988). The in-hospital mortality following the first variceal bleed varies from 30% to 50% (D'Amico and others 1995; Stanley and Hayes 1997). Although this exceeds that of myocardial infarction, not every hospital in the UK has specialised units to manage variceal haemorrhage. These dismal statistics have been the stimulus for much research in the prevention of the first variceal bleed and the prevention of variceal rebleeding.

1.2.2 Anatomical considerations.

An understanding of the fundamentals of the anatomy of the portal system, and the formation of varices is essential to appreciate the phenomenon of variceal bleeding, and the therapies available to manage portal hypertension.

The portal vein is 6-8 cm long, 1.2 cm in diameter and is formed by the union of the superior mesenteric and splenic vein posterior to the neck of the pancreas. It then runs posterior to the duodenum to divide into the right and left branch. The system then drains into the liver.

Of interest to investigators in portal hypertension is the detailed venous drainage of the oesophagus. This comprises of the following components (Butler 1951):

- a. Intrinsic veins that are within the wall of the oesophagus comprising subepithelial and submucous veins, the latter of which have perforating veins that penetrate the muscle layers of the oesophagus.
- b. Extrinsic veins which form from the perforating veins. They drain to larger venous trunks in the neck (inferior thyroid veins), the thorax (azygous veins), and abdomen (left gastric vein).

The intrinsic circulation of the lower oesophagus and upper stomach is of particular relevance to clinicians, since it is at these sites that bleeding secondary to portal hypertension occurs most frequently. There are 4 clearly defined areas, which have been studied extensively (Vianna and others 1987) :

Gastric zone

This is 2-3 cm in length, extending downwards from the gastro-oesophageal junction. The veins are within the lamina propria and submucosa, which drain into the left gastric vein and splenic vein via the short gastric veins and polar gastric vein.

Palisade zone

This is 2-3 cm starting from the gastro-oesophageal junction, in continuity with the gastric zone. The veins are located predominantly in the lamina propria, with there being no anastomosis between the extrinsic and intrinsic circulations. The gastro-oesophageal junction is the only part of the alimentary canal that separates two luminal structures with opposite cavity pressures (Cohen and Harris 1972).

Perforating zone

This commences 2-3 cm above the gastro-oesophageal junction, extending for 2 cm proximally. The veins continue from the lamina propria of the palisade zone. The characteristic features of this zone are the perforating veins. These veins occur at the confluence of the veins from the palisade zone, form loops draining caudally, and then pass at right angles through the layers of the oesophagus to its outer surface. The similarity with the musical sign has led to them being referred to as “treble clef” veins. Thus, the perforating zone acts as the principal means of communication between the intrinsic and extrinsic systems.

Truncal zone

This zone extends for 8-10 cm above the perforating zone. The veins run in the submucosa, and drain distally into the perforating zone. There are also perforating veins scattered throughout this zone.

Anatomical changes during portal hypertension

In the presence of portal hypertension the collateral circulation develops in an attempt to decompress veins at the cardia, anal canal, falciform ligament, the abdominal wall and retroperitoneal tissues, the diaphragm, stomach, pancreas, spleen, adrenal, and testis via the left renal vein. Gastro-oesophageal varices occur within the framework of the intrinsic veins.

However, in portal hypertension the vessels are more dilated and tortuous, in addition to being more irregularly distributed. The main sites of variceal formation are thus:

Fundal gastric varices

Fundal varices were noted to be present in 40% of patients in one series (Vianna 1988), with the main source of supply being the short gastric veins (Smookler 1956).

Varices in the gastric and palisade zones

These varices are located predominantly within the submucosa, just below the gastro-oesophageal junction, being principally supplied by the left gastric vein. Also seen in the palisade zone are varices in the cardia that are in continuity with those at the lower oesophagus arranged in a longitudinal pattern.

Varices in the perforating and truncal zones

The perforating zone is the main site of oesophageal varices of clinical relevance. In the presence of portal hypertension the perforating veins become incompetent allowing the retrograde flow of blood from the extrinsic circulation to the intrinsic circulation (McCormack and others 1983). This turbulent blood flow can be exacerbated by pressure changes resulting from respiratory movements, coughing and stretching. The presence of much perforating veins at regular intervals in this zone explains why varices form in large nodular patterns here, and also tend to bleed in the distal rather than proximal oesophagus.

Para-oesophageal varices

The extrinsic circulation is dilated in two-thirds of patients with cirrhosis (Vianna 1988). The para-oesophageal varices are grossly dilated, with tortuous extrinsic vessels extending from the lower third of the oesophagus and proximal stomach, draining into the azygous system in the thorax, and left gastric vein in the abdomen. Interestingly, para-oesophageal varices may

occur without there being gastro-oesophageal varices in 13% of patients with portal hypertension in one series (Vianna 1988). These patients may have effective shunts diverting venous blood to the extrinsic circulation. The observation that the azygous blood flow is not related to the presence of oesophageal varices supports this (Cales and others 1985). There is also recent evidence to suggest that patients with large para-oesophageal varices have a greater risk of developing recurrent varices and rebleeding following endoscopic variceal eradication (Leung and others 1997).

1.3 The natural history of gastro-oesophageal varices.

1.3.1 Variceal formation.

Recent studies based on endoscopic appearances studies suggest that at least two thirds of cirrhotic patients will develop oesophageal varices during their lifetime (Lay and others 1997) (Anonymous 1988). Larger or high risk oesophageal varices as defined endoscopically are seen in 15–25 % of patients in these studies. Work by Schepis and colleagues demonstrated that the risk of developing varices is greater in those with prothrombin activity less than 70%, platelet count less than 100 000/mL, and ultrasonographic portal vein diameter greater than 13 mm (Schepis and others 2001).

There are relatively few studies reporting on the incidence of gastric varices. Sarin reported an incidence of just 4% in cirrhotic patients who had not bled (Sarin and others 1992), although this increased to 27% in patients who had a history of gastrointestinal bleeding. He defined four subtype of varices (Figures 1a-1d): 1) GOV 1 (gastro-oesophageal varices type 1), which are

oesophageal varices extending distally for 2-5 cm below the gastro-oesophageal junction; 2) GOV 2 (gastro-oesophageal varices type 2), which are oesophageal varices extending into the gastric fundus; 3) IGV 1 (isolated gastric varices type 1), which are gastric varices in the fundus not in communication with oesophageal varices; and 4) IGV 2 (isolated gastric varices type 2), which are gastric varices in other parts of the stomach. GOV1, the commonest at 70% of gastric varices, are also known descriptively as cardinal varices. GOV2 and IGV1, at 21% and 6.7% of gastric varices respectively, together are referred to as fundal varices. Others have shown that 25.1% of cirrhotics had gastric varices at screening endoscopy, with 18.2 % of patients having both oesophageal and gastric varices (Kim and others 1997).

Figures 1a-1d: Sarin's classification of gastric varices (Sarin and others 1992).

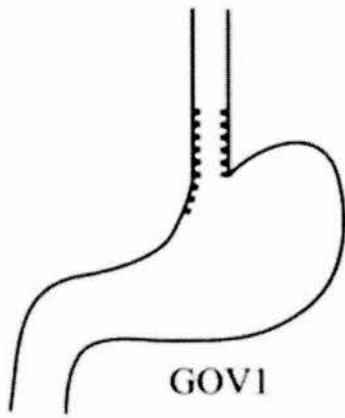


Figure 1a:
Gastro-oesophageal varices type 1

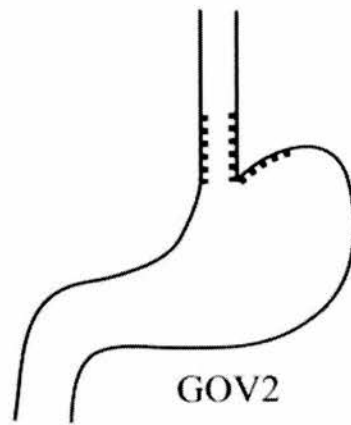


Figure 1b:
Gastro-oesophageal varices type 2

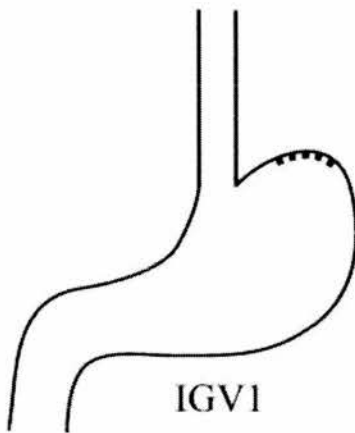


Figure 1c:
Isolated gastric varices type 1

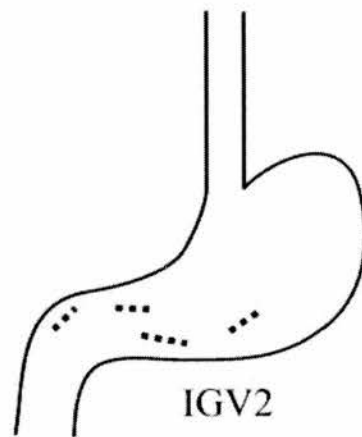


Figure 1d:
Isolated gastric varices type 2

1.3.2 Progression of varices.

Once oesophageal varices have developed, their rate of progression is very variable. They may even regress as has been demonstrated in one study of patients with alcoholic liver disease during periods of abstinence (Dagradi 1972). Others have reported an annual incidence of oesophageal varices of up to 12% per year in patients with severe primary biliary cirrhosis over a 5.6 year follow up period (Gores GJ, Gastroenterology 1989). A recent study published in abstract form reported on 484 cirrhotic patients who did not have oesophageal varices, followed up over 131 months (D'Amico and others 2001). 41% of patients developed oesophageal varices at 10 years, and the progression from small to large varices was 5% per year.

1.3.3 Risk factors for the first variceal haemorrhage.

The factors related to the development of the first variceal haemorrhage and variceal rebleeding has been extensively studied over the last two decades. The risk of the first variceal haemorrhage varies from 5% per year in an unselected population, up to 30% in patients with large oesophageal varices (D'Amico and others 1995; D'Amico and others 1999). The risk of bleeding in patients with small varices is 7%.

Clearly the size of varices is important in order to identify those most at risk. Where good views can be obtained, most endoscopists are in agreement about the size and colour of oesophageal varices (Anonymous 1987). A recent study of 251 patients screened for entry into a randomised

controlled trial revealed that 35% of patients had large or very large varices, 20.8% had medium sized varices, and 25.3% had small varices (Jensen 2002). A simplified way of grading oesophageal varices had been adopted by our unit (Jalan and Hayes 2000) as follows: 1) Grade 1 – varices that collapse after air insufflation; 2) Grade 2 – varices between grade 1 and 2; 3) Grade 3 – varices large enough to occlude the lumen.

It has also been reported that the presence of endoscopic appearances consistent with reduced variceal wall thickness, such as red signs and red whale markings signify a high risk of variceal bleeding (Dagradi 1972; Beppu and others 1981). Beppu and colleagues reported that 80% of patients with blue varices and cherry red spots bled, although subsequent studies suggest that this is probably an overestimate (Anonymous 1988).

The influence of portal pressure on the risk of variceal bleeding has been extensively studied. Variceal bleeding is uncommon below a threshold hepatic venous pressure gradient (HVPG) of 12 mm Hg (D'Amico and others 1995). Groszmann and associates looked at a larger number of patients in a randomised double-blind placebo controlled trial to investigate whether lowering the HVPG with propranolol protects against a variceal bleed over a 2-year follow-up period (Groszmann and others 1990). They found that a HVPG of < 12 mmHg protected patients from variceal haemorrhage and improved survival. However, it is not clear whether a higher value of HVPG increases the risk of varices.

Variceal wall tension also plays an important role in determining the risk of variceal bleeding (Polio and Groszmann 1986). Once variceal wall tension exceeds the elastic limit of the vessel the first variceal bleed will occur. The following equation defines the various factors responsible for variceal wall tension (WT):

$$WT = (P_i - P_e) \times r/w$$

P_i is intravariceal pressure, P_e the oesophageal luminal pressure, r the radius of the varix, and w the thickness of the variceal wall. It can be seen that the WT varies directly with the radius of the varix, and the difference between the intravariceal pressure and the intraluminal pressure. Another important concept is that varices can bleed even at low pressures if they are large as in the case of significant fundal gastric varices, a phenomenon previously reported in our unit (Stanley and others 1997a). The presence of a negative intrathoracic pressure also explains why oesophageal varices are more likely to bleed than varices at other sites.

The severity of liver disease on the risk of the first variceal bleed was originally confirmed by the North Italian Endoscopy Club (NIEC) in a prospective study of 321 patients over a median follow up of 23 months (Anonymous 1988). Multiple regression analysis revealed that the Child class, presence of red whale signs, and size of oesophageal varices were independent predictors of the first variceal haemorrhage. These variables were used to derive a prognostic NIEC index on the risk of variceal bleeding. There was a striking 40 times increased 1 year cumulative risk of bleeding between the lowest and highest risk patients.

1.3.4 Risk factors for variceal rebleeding.

The risk of variceal rebleeding is highest in the first 5 days, being as high as 40.5% (de Franchis and Primignani 2001), and is much reduced after 6 weeks (Graham and Smith 1981). A third of patients experience rebleeding within the first 6 weeks, and only a third of survivors rebleed thereafter. A significant number of early rebleeding episodes are associated with death, emphasising the need to develop therapies that prevent early rebleeding. The studies also highlight the need to scrutinise the timing of randomisation when comparing clinical trials of therapies to prevent early rebleeding.

The reported risk factors for early rebleeding include low albumin, the presence of gastric varices, high blood urea and infection. HVPG has also been studied and values of $>16-20$ mmHg have been associated with rebleeding (Ready and others 1991; Moitinho and others 1999b). A recent study with a 8 year follow up of patients on pharmacological therapy identified an increase in HVPG $> 20\%$ of baseline or a HVPG ≥ 12 mmHg as independent risk factors associated with rebleeding and increased mortality (Abralde and others 2003).

1.3.5 The outcome of patients with varices and variceal haemorrhage.

Despite all the advances in therapy, the mortality after variceal haemorrhage remains high. The development of varices in cirrhotic patients puts them in a worse prognostic group, even before they have bled. Studies indicate that once varices have developed the progression from compensated to decompensated cirrhosis doubles compared with patients who have not developed varices (D'Amico and others 1986; Pagliaro and others 1994).

The mortality of compensated cirrhotic patients is 1% per year, but in the presence of varices increases to 3.4% per year. After variceal bleeding and in the presence of ascites the mortality increases several fold to 57%, with most deaths occurring within the first 6 weeks after the index bleed. The long-term mortality after variceal rebleeding varies between 4 and 78%, with a mean of 46% (de Franchis and Primignani 2001).

The most important variable influencing the mortality after variceal bleeding the severity of liver as defined by the Child Pugh score (Jalan and Hayes 2000). The 1-year mortality for patients in Pugh Class A, B, and C are 5%, 25%, and 50% respectively. Markers of the severity of portal hypertension such as the HVPG are also important indicators of the mortality (Vinel and others 1986). A recent study by Moitinho and colleagues demonstrated that a HVPG of ≥ 20 mm Hg measured shortly following a variceal bleed was associated with a 64% 1 year mortality compared with 20% where the HVPG was < 20 mm Hg (Moitinho and others 1999b). A recent study over a 8 year follow up period of patients on pharmacological therapy identified HVPG $> 20\%$ of baseline or a HVPG ≥ 12 mmHg as independently associated with mortality (Abralde and others 2003).

1.3.6 Gastric varices.

Gastric variceal bleeding has not been so extensively studied. It is known that the natural history of bleeding gastric varices differs from that of oesophageal varices. Although the risk of bleeding from gastric varices is less than that of oesophageal varices, the outcome once bleeding has

occurred is worse, particularly for isolated gastric varices (IGV) (Sarin and others 1992). It has been reported that patients with large gastric varices have a lower portal pressure than those with oesophageal varices (Chao and others 1993; Stanley and others 1997a) which may be as a result of the development of gastro-renal porto-systemic shunts (Watanabe and others 1988) or large size of the varices resulting in increased variceal wall tension as noted above. Watanabe and colleagues also demonstrated increased collateral flow at the expense of reduced portal venous flow in patients with gastric varices. The authors proposed that reduced portocollateral resistance might account for the latter finding. However, it is unclear as to why patients bleed at portal pressures of < 12 mmHg. Other factors such as the presence of red spots, variceal size and that of gastritis may be important. Therefore, particularly in patients with gastric varices it would not be safe to regard reducing the portal pressure gradient of < 12 mmHg as a therapeutic goal.

1.4 Drug therapy for portal hypertension

There have been major advances in the primary and secondary prevention of variceal haemorrhage over the last 20 years involving endoscopic, radiological and pharmacological approaches. Many of these drugs have not been studied in clinical trials, but provide data about the underlying pathogenesis of portal hypertension (Table 1). Despite the recent increase in the use of alternative endoscopic therapies, an effective and well-tolerated drug remains a clinically important goal.

1.4.1 Haemodynamic studies of agents used in portal hypertension

Propranolol was the first drug used to reduce portal pressure in 1982 by Didier Lebrec (Lebrec and others 1982). Since then an improved understanding of the mechanisms behind portal hypertension has led to the use of a variety of pharmacological agents that act by altering portal haemodynamics favourably.

Many studies have looked at the HVPG as a prognostic marker and as a guide to the efficacy of pharmacological agents. The HVPG is the difference between the wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP). The HVPG correlates with the true portal pressure in patients with alcoholic cirrhosis (Boyer and others 1977), hepatitis B (Lin and others 1989) and hepatitis C (Perello and others 1999), but underestimates the true portal pressure in conditions such as primary biliary cirrhosis and chronic active hepatitis (Boyer and others 1977).

The aim of pharmacological therapy is to prevent or reduce the risk of variceal bleeding, and because this is unusual if the HVPG is less than 12 mmHg, this has been adopted as a haemodynamic target (Groszmann and others 1990). A reduction in the portal pressure of greater than 20% has also been proposed as a therapeutic goal (Feu and others 1995). In clinical practice it is also important to combine drug efficacy with tolerability.

Table 1: Drugs used in portal hypertension

B-blockers

Propranolol
Nadolol
Timolol
Atenolol
Metoprolol
ICI 11855
Mepindolol
Carvedilol

Nitrates

Isosorbide dinitrate
Isosorbide-5-mononitrate

Drugs acting on α adrenergic receptors

Prazosin
Clonidine

Drugs acting on the renin-angiotensin system

Losartan
Irbesartan

Drugs acting on serotonin S₂ receptors

Ketanserin
Ritanserin

Drugs affecting plasma volume

Spirolactone

Combination therapy

Isosorbide-5-mononitrate and β -blockers
Prazosin and β -blockers or isosorbide-5-mononitrate.

Beta-blockers

Propranolol

In 1982 Lebrech and colleagues investigated the portal hypotensive effect of propranolol in a placebo-controlled haemodynamic study in alcoholic cirrhotic patients (Lebrech and others 1982). Other studies have corroborated these findings reporting reductions in the HVPG of between 10 and 31% (Table 2). The fall in portal pressure is produced by a combination of reduced cardiac output (beta₁ antagonism) and reduced splanchnic blood flow (beta₂ antagonism). Changes in portal blood flow are probably mainly a result of beta₁ blockade (Bosch and others 1984). It was also observed by others that propranolol consistently reduced collateral blood flow as derived from the azygous blood flow, which is elevated in patients with portal hypertension (Mastai and others 1987).

Vorobioff and colleagues (Vorobioff and others 1987) studied the acute and chronic effects of propranolol on alcoholic cirrhotics with oesophageal varices over an average of 106 days. A portal hypotensive effect of 25% was maintained chronically. However, 30% of patients failed to respond after chronic dosing. This paper highlighted the considerable non-response rate to propranolol confirmed by later studies of up to 38% following long term follow up (Abraldes and others 2003). This may be explained by a portal hypertensive model demonstrating that a rise in the portocollateral resistance accompanies the reduction in portal blood flow thus reducing the overall portal hypotensive response to propranolol (Kroeger and Groszmann 1985).

Table 2: The effect of propranolol on portal and systemic haemodynamics.

Study	Dose	Child's Class	Acute / Chronic Study	Mean Arterial Pressure	Cardiac Output /Cardiac Index	Hepatic Venous Pressure Gradient	Estimated Hepatic Blood flow	Azygous blood flow
Lebrec, 1982	40mg	All A	Acute	Not stated	31	23	12	Not stated
Bosch, 1984	83mg	Not Stated	Acute	2	22.6	11.5	13.4	34.2
Mastai et, 1987	10mg IV	A/B/C: 9/3/0	Acute	NS	17	10	NS	31
Vorobioff, 1987	40mg – acute 158 mg-chronic	Not stated	Acute & Chronic	NS	21,27	17.6,22.5	Not stated	Not stated
Westaby, 1984	> or = 2mg IV	A/B: 2/7	Acute		13	31	21	Not stated
Braillon, 1987	10mg IV	Mean score: 5.3	Acute	NS	26	15	NS	36
Garcia-Pagan, 1990	IV 0.1mg/kg bolus 2mg/h 30min infusion	A/B/C: 9/10/1	Acute	NS	24	13	12.8	38
Groszmann, 1990	132mg*	Mean score: 8	Chronic	NS	22	29	Not stated	NS
Garcia-Pagan, 1991	*(actual doses not stated)	Mean score: 6.9	Chronic	NS	10	10	25	29
Bendtsen, 1991	160mg*	A/B/C: 7/5/2	Chronic	NS	20	24	39	47
Aramaki, 1992	90mg	A/B/C: 7/4/0	Chronic	NS	14	12	NS	Not stated
Vorobioff, 1993	140mg*	Mean score: 7	Chronic	NS	38	12.5	Not stated	Not stated

* - Dose required to reduce the mean pulse to 25% of baseline
NS – Not significant

Another chronic study with a longer follow-up period of 1 year failed to demonstrate a sustained fall in portal pressure gradient when propranolol was compared with placebo, despite significant reductions in hepatic blood flow, azygous blood flow and cardiac index (Aramaki and others 1992). The investigators suggested that the splanchnic hyperdynamic circulation observed in cirrhotics might be partly reversible in some patients without drug therapy. This may be explained by the fact that patients in the second study were clinically better and had reduced sympathetic tone, but probably more importantly all had stopped drinking alcohol. Patients who were not studied after 1 year due to bleeding episodes or death could introduce selection bias despite the initial haemodynamic parameters being comparable to that of the group who were studied. The findings add weight to the hypothesis that reduction in collateral blood flow and therefore variceal blood flow is the mechanism behind the beneficial effect of propranolol in preventing bleeding. Feu and colleagues investigated the concept of reduced variceal flow using a non-invasive pressure sensitive endoscopic technique (Feu and others 1993). Their findings suggested that even in patients in whom the HVPG did not fall significantly there appeared to be a fall in variceal pressure, of similar magnitude to those patients that responded to propranolol.

Groszmann and associates looked at a larger number of patients in a randomised double-blind placebo-controlled trial to investigate whether lowering the HVPG with propranolol protects against a variceal bleed over a 2-year follow-up period (Groszmann and others 1990). They found that a HVPG of less than 12 mmHg protected patients from variceal haemorrhage

and improved survival. It is of note that in this study almost all patients bled within the first year and that treatment with propranolol did not result in a greater portal pressure reduction than placebo after 3 months of treatment, suggesting propranolol had a protective effect earlier on. The authors did point out that this might have been due to a greater dropout rate of patients with the highest pressures in the placebo group from terminating events such as variceal bleed and death. Fifty-one patients were studied in both groups and after 24 months the final number was 9 and 12 in the placebo and propranolol groups respectively. It is questionable whether these small numbers allow meaningful analysis. Values for HVPG were higher in the patients who dropped out of the placebo group at 3–12 months. However, other papers (McCormack and others 1983; Stanley and Hayes 1997; Abraldes and others 2003) have supported this observation. The latter study concluded that an increase in HVPG ≥ 12 mmHg or a 20% increase in HVPG independently predicted death or bleeding (Abraldes and others 2003). Interestingly it has been demonstrated that bleeding may occur at pressures below the threshold level of 12 mmHg (Jalan and others 1995c), although the numbers quoted in this study are quite small.

Nadolol.

Nadolol is also a non-selective beta-blocker, which was first studied by Gatta and colleagues (Gatta and others 1984; Gatta and others 1985; Merkel and others 1986; Gatta and others 1987a). These studies suggested a similar mechanism of action and efficacy to propranolol. Nadolol, unlike propranolol, has low hepatic metabolism and lipid solubility resulting in a longer half life. The main chronic effects at a dose that reduced the heart

rate by 25% were of significant reductions in HVPG (19–22%), cardiac output and effective hepatic blood flow. Mean arterial pressure, liver and renal functions were all unaffected. Recent studies also suggest that nadolol therapy results in a significant reduction in portal blood flow and renal blood flow (Bolognesi and others 1994).

Timolol.

This is a non-selective beta-blocker that has only been studied in one haemodynamic study (Escorsell and others 1997). The mean reduction in the portal pressure gradient was 20%, which is comparable to that of propranolol and nadolol. The drug has not been studied in any clinical trials.

Atenolol.

Hillon and colleagues, in a comparative haemodynamic study with propranolol, first investigated atenolol, a selective beta₁ receptor antagonist in portal hypertensive patients with cirrhosis (Hillon and others 1982). They found a 16% reduction in HVPG, which significantly correlated with cardiac output. Propranolol produced a greater reduction of portal pressure, although the reduction in cardiac output was similar to that of atenolol. It was postulated that the extra-cardiac effects of propranolol were responsible for the difference.

Another comparative study looked at the effect of atenolol, propranolol and prazosin (an alpha blocker) on portal haemodynamics in a chronic study with an 8-week follow-up period (Mills and others 1984). Atenolol resulted in a non-significant 15% reduction in HVPG compared with a significant 25% reduction in HVPG with propranolol therapy. The findings again

suggested a significant correlation between cardiac output and portal pressure with atenolol but not with propranolol. Both beta-blockers were well tolerated.

Atenolol therefore appears less effective at reducing portal pressure than propranolol, which suggests that the beta₂ receptor blockade has a major role to play in the mechanism of action propranolol.

Metoprolol.

Metoprolol is another beta₁ selective beta-blocker. Initial haemodynamic studies suggested that it was of equal efficacy to propranolol in reducing portal pressure (Westaby and others 1984). The study also demonstrated significant falls in cardiac output in both groups, but a reduced hepatic blood flow only in the propranolol group. The latter finding led the authors to conclude that metoprolol may even be preferable to propranolol in patients with advanced liver disease. It has, however, been little studied.

Beta₂ receptor antagonists

ICI 11855 is a selective beta₂ antagonist, which was studied by Bihari et al. in 17 patients (Bihari and others 1984). There was a significant reduction in the portal pressure 60 min following administration of the drug, which was accompanied by significant reductions in the heart rate and cardiac index, both of which were not related to the fall in the portal pressure.

Another selective beta₂ antagonist mepindolol was compared with intravenous propranolol in patients with cirrhosis and portal hypertension by Brallion and colleagues (Brallion and others 1985). The effect on the HVPG

and systemic circulation was similar to that of propranolol, but at the expense of significantly reduced hepatic blood flow, which was not the case with propranolol. Clearly both these drugs have a significant effect on the systemic circulation, and mepindolol offers no benefit over propranolol in reducing portal pressure. This may explain why they have not been studied further.

Carvedilol

Carvedilol is a novel vasodilating non-selective beta-blocker with weak α_1 receptor antagonism and calcium channel antagonism. It has a rapid onset of action with 2–4 times greater beta-blocking action than propranolol.

Forrest and colleagues performed the first acute haemodynamic study on cirrhotic patients using 25 mg oral carvedilol (Forrest and others 1996a). A 20% fall in HVPG from 17 to 14 mmHg was achieved mainly due to a fall in wedge hepatic venous pressure. A significant fall in MAP of 10% was noted particularly in ascitic patients. Hepatic blood flow, azygous blood flow and renal blood flow were unaffected. This effect of carvedilol on HVPG was similar to that of propranolol as demonstrated in previous studies (Table 2). The chronic effect of carvedilol was investigated by Stanley et al (Stanley and others 1999). A 21% drop in HVPG was maintained chronically. The fall in HVPG was mainly as a result of a significant drop in the wedge hepatic venous pressure. There was no change in renal function or hepatic blood flow. Poor tolerability was noted in three out of the 17 patients who experienced dizziness, breathlessness or hypotension.

Further studies have demonstrated a reduction in HVPG of between 13% and 27% following acute administration of carvedilol, and greater efficacy than propranolol (Banares and others 1999) (Banares and others 2002) (De and others 2002). All studies demonstrated a significant reduction in the mean arterial pressure, an effect which may limit clinical efficacy. Lower dose regimes may address this issue, but such studies are relatively few (De and others 2002). To date there are no clinical studies looking at the effect of carvedilol in preventing variceal bleeding.

Nitrates

Isosorbide-5-mononitrate (ISMN) is a long acting organic nitrate, and is the only nitrate to be used in large randomised controlled trials for preventing variceal bleeding. The molecular mechanism of action of nitrates is uncertain. It is thought the vasodilatory actions may be a result of enhanced production of intrahepatic nitric oxide or cyclic-GMP (Abshagen 1992).

There have been a number of haemodynamic studies using ISMN in patients with portal hypertension (Table 3). All the studies with the exception of one (Tsai and others 1989), which included predominantly Childs A patients, demonstrated significant reductions in the HVPG. This appears to have been achieved by a fall in the WHVP. Three studies looking at the chronic effects show that the effect of reduced portal pressure is sustained (Garcia-Pagan and others 1990; Grose and others 1994; Jones and others 1995). Indeed the portal hypotensive effect seemed to be amplified after rechallenge following chronic dosing, confirming lack of tolerance.

Pronounced effects on other parameters may help to explain the mechanism underlying the fall in HVP, which is comparable to that of propranolol. Early studies (Hayes and others 1988) noted that the hepatic blood flow fell acutely, and this along with an increase in systemic vascular resistance index (SVRI) suggested that a baroreceptor-mediated splanchnic vasoconstriction may be responsible for the fall in portal pressure rather than portal venous dilation. However, recent work demonstrated a significant fall in the portal pressure gradient without affecting the portal blood flow in patients with a transjugular intrahepatic portosystemic shunt (TIPSS) (Forrest and others 1996b). It was clear, therefore, that in the study group of patients reflex baroreceptor-mediated vasoconstriction of the splanchnic bed could not be the case and that any vasoconstrictive effect to account for the rise in SVRI was limited to the periphery. The observed findings were attributed to reduced intrahepatic vascular resistance rather than a reduction in the liver blood flow (which would be undesirable). Chronic administration resulted in no change or even an increase in the hepatic blood flow (Navasa and others 1989; Garcia-Pagan and others 1990) and may reflect the buffer response of hepatic artery blood flow to a decrease in portal flow (Lautt 1985).

Isosorbide-5-mononitrate also reduces the cardiac preload and hence the cardiac output, at least acutely. Significant correlation between the reduction in portal pressure gradient and cardiac output suggests that this may partly be responsible for the reduced portal blood flow observed in this study (Hayes and others 1988). In all cases the mean arterial pressure fell acutely.

It is interesting to note that chronic administration does not appear to have a significant effect on cardiac output or mean arterial pressure.

Azygous blood flow has already been demonstrated as a useful indicator of variceal blood flow in patients with cirrhosis (Bosch and Groszmann 1984). Azygous blood flow responds in a variable fashion to ISMN. Jones and colleagues demonstrated no significant change in the azygous blood flow in response to varying doses of nitrates, both acutely and following chronic dosing (Jones and others 1995). However, a relationship was noted between baseline azygous blood flow and the response to nitrates, with those patients with a high azygous blood flow responding by reducing their flow and vice versa. The dose did not seem to influence the azygous blood flow.

Nitrate tolerance is clearly documented in cardiovascular medicine (Elkayam and others 1987; Jugdutt and Warnica 1989) However, of the studies looking at the chronic effects of ISMN therapy only one has reported partial tolerance in five out of 11 patients (Garcia-Pagan and others 1990), with others reporting no tolerance (Grose and others 1994; Jones and others 1995). The exact mechanism behind why patients with cirrhosis do not develop nitrate tolerance is unknown. It has been suggested that patients with cirrhosis may not be able to develop compensatory mechanisms that are necessary to bring about nitrate tolerance (Jones and others 1995).

An important observation with nitrate monotherapy has been the deleterious effect on renal function (Salmeron and others 1993). Activation of the renin-angiotensin system was felt to be a major factor. In particular, patients with ascites suffered from a reduced glomerular filtration rate, sodium excretion

and renal plasma flow. It is interesting that combination therapy with other portal hypotensive agents abolished these undesirable renal effects. The combination therapies will be covered later.

Table 3: The effect of isosorbide-5-mononitrate on portal and systemic haemodynamics.

Study	Number of patients	Dose	Child's Class	Acute/Chronic Study	Mean Arterial Pressure	Cardiac Output	Hepatic Venous Pressure Gradient	Estimated Hepatic Blood flow	Azygous blood flow	Systemic blood flow	Systemic vascular resistance index
Hayes, 1988	11	20mg - 60mins	A/B/C: 0/6/5	Acute	NS	-12.0	-8.8	-15.5	Not stated	Not stated	+10.9
Tsai, 1989	10	20mg - 60mins	A/B: 9/1	Acute	-10.9	NS	NS	Not stated	Not stated	NS	NS
Navasa, 1989	6	40mg - 1 week		Chronic	NS	NS	NS	Not stated	Not stated	NS	NS
	10	20mg - 60mins	A/B/C: 6/16/1	Acute	-8.0	-15.0	-9.8	+12.7	NS	+10.6	NS
	9	40mg - 60mins		Acute	-20.5	-13.5	-19.1	NS	-16.2	NS	NS
García-Pagan, 1990	11	80mg - 3 months		Chronic	-7.6	NS	-7.5	+14.4	NS	NS	NS
Grose, 1994	21	20mg - 60mins	A/B/C: 6/4/11	Acute	-10.1	Not stated	-10.3	Not stated	NS	Not stated	Not stated
	8	40mg - 1 month		Chronic	NS	Not stated	-15.8	Not stated	-38.9	Not stated	Not stated
Jones, 1995	12	10mg - 60mins	Mean: 8±0.6	Acute	-5.4	Not stated	-21.9	NS	NS	Not stated	Not stated
	13	20mg - 1 month		Chronic	NS	Not stated	-31.3	NS	NS	Not stated	Not stated
	13	40mg - 60mins	Mean: 8.1±0.6	Acute	-8.7	Not stated	-23.8	-22.3	NS	Not stated	Not stated
	12	80mg - 1 month		Chronic	NS	Not stated	-29.9	NS	NS	Not stated	Not stated
Escorsell, 1996	12	40mg - 40min	Mean: 5.8±1	Acute	-14.3	-15	-10	NS	-10.6	Not stated	Not stated
Forrest, 1996	8	20mg - 60mins	A/B: 1/7	Acute	-5.8	Not stated	-15.7	Not Stated	NS	Not stated	Not stated

NS – Not significant

Drugs acting on alpha-adrenergic receptors

Prazosin.

Prazosin is an alpha₁ receptor blocker, which was initially studied by Mills and colleagues in a comparative haemodynamic study with propranolol and atenolol over an 8-week follow-up period (Mills and others 1984). An 18% reduction of the HVPG was obtained with prazosin compared with 25% with propranolol. Prazosin did not affect the cardiac index or hepatic blood flow, and had no effects on renal function or sodium handling. It acts by reducing intra-hepatic resistance. In a recent study impressive results were obtained with acute and chronic reductions in the HVPG of 25.7% and 19.1% respectively, which are comparable to propranolol (Albillos and others 1994). However, this was accompanied by a significant fall in the MAP and systemic vascular resistance. An important finding in this study was the tendency to increased ascites and oedema as a result of a reduction in sodium excretion and expansion of the plasma volume. Tolerance was also felt likely to have occurred following chronic administration. Hepatic blood flow and liver function, as quantified by indocyanine green clearance and galactose elimination, were noted to have improved. These findings were mirrored in a subsequent study and thus the use of prazosin in clinical practice was not an attractive proposition (Albillos and others 1995). There are at present no clinical trials using prazosin in primary or secondary prophylaxis of variceal haemorrhage.

Clonidine.

Clonidine is a centrally acting alpha₂ agonist that acts by reducing peripheral noradrenaline outflow and thus the sympathetic tone in patients with cirrhosis (Willett and others 1986; Moreau and others 1987; Esler and others 1992). A fall in the HVPG was believed to occur secondary to reduced post sinusoidal hepatic vascular resistance. Azygous blood flow was reduced, but hepatic blood flow remained unaffected. The change in hepatic haemodynamic parameters was unrelated to changes in the systemic haemodynamics, where there was a reduction in the cardiac output and mean arterial pressure. The hepatomesenteric circulation was more sensitive to the actions of clonidine in cirrhotic patients compared with healthy controls. Clonidine resulted in a greater fall in the portal pressure compared with propranolol (Albillos and others 1992), and a recent study looking at the effects of clonidine and propranolol in cirrhotic patients found that only propranolol or a combination of propranolol and clonidine resulted in a fall in the portal blood flow (Tincani and others 1995). Despite these results, there are no randomised clinical trials using clonidine for primary or secondary prophylaxis in patients with varices. The effect on systemic haemodynamics may limit its use.

Drugs acting on the renin-angiotensin system

The interest in ANG II receptor antagonism stems from the observation that there is activation of the renin-angiotensin system in cirrhosis, the degree of which is proportional to the severity of cirrhosis, and portal hypertension (Bosch and others 1980). Studies have shown that ANG II has a direct effect on portal pressure, via AT1 type receptors (Campbell and others 1991).

Animal models demonstrate that ANGII mediates vasoconstriction of the portosystemic collaterals leading to increased portocollateral resistance (Campbell and others 1991), and to have diminished vasoconstrictive effects on the splanchnic circulation leading to increased portal blood flow (Sitzmann and others 1990). Recent interest has concentrated on the role of the activated hepatocyte stellate cells (HSC), particularly in light of the finding that AT1 type receptors on human activated HSC mediate the vasoconstrictive and mitogenic actions of ANG II (Bataller and others 2000; Rockey 2000). Blockade of the AT1 receptor may therefore result in relaxation of the activated HSC and reduced intra-hepatic resistance and portal pressure. This selective blockade may also result in the unopposed action of ANG II on AT2 type receptors, leading to endothelium mediated vasodilatation, further enhancing the pharmacological effects of such agents (Burnier 2001).

Saralasin

Initial attempts at ANG II receptor blockade were hindered by pronounced systemic hypotension (Arroyo and others 1981), although the latter was not seen at higher doses possibly due to the partial agonist effect of saralasin at such doses, leading to vasoconstriction and potentially hypertension (Burnier 2001). Newer agents such as losartan and irbesartan, which have no intrinsic agonist activity, have resulted in greater success (Debernardi-Vernon and others 1999; Schneider and others 1999).

Losartan

Losartan is a pro drug that is converted to the active metabolite E-3174, whose maximum plasma levels are obtained after 3-4 hours. It was used at a dose of 25 mg/day in 45 patients with cirrhosis and either moderate or severe portal hypertension, in a study by Schneider and colleagues (Schneider and others 1999). Both acutely after 4 hours and following chronic administration there was a significant reduction in the portal pressure approaching 45%, the largest reported to date for any pharmacological agent. This is particularly impressive considering the minimal effect on blood pressure, with only one patient experiencing symptomatic hypotension.

Two publications have compared losartan with propranolol, with different results (Gonzalez-Abraldes and others 2001; De and others 2003). The first paper does not support the observation by Schneider (Gonzalez-Abraldes and others 2001). This study randomised 25 patients to losartan at a mean dose of 47 ± 9 mg/day following a variceal haemorrhage, and compared the portal hypotensive effect of six weeks therapy with that of propranolol (n = 15). Propranolol produced a significantly greater reduction in the HVPG (10% versus 2%), despite the fact that losartan had a significant effect on MAP (-8%), which was not seen with propranolol. There was a significant reduction in the glomerular filtration rate in Childs B patients taking losartan, with propranolol having no detrimental effect on renal function. Adverse effects related to therapy were reported in 28% of patients. The second randomised study using 25 mg losartan (n = 19) reported a portal

hypotensive effect ($\geq 20\%$ reduction in HVPG from baseline) in 80% of patients compared with a 45% response rate for propranolol ($n = 20$), particularly in non-ascitic patients and in alcoholic liver disease (De and others 2003). There was no significant difference in the HVPG reduction between losartan and propranolol of 27% and 14% respectively. The findings are particularly striking considering the lack of adverse effects such as systemic hypotension or impairment of renal function.

Irbesartan.

Irbesartan, which has a longer half-life than losartan may have a more sustained effect on portal pressure. It also has the pharmacological benefit of not requiring hepatic conversion to the active metabolite, with no dosage adjustment necessary in hepatic impairment (Marino and others 1998). Two studies in cirrhotic patients have been published (Schepke and others 2001; Venon and others 2003). In the first study (Schepke and others 2001), cirrhotic patients randomised to irbesartan 150 mg/day experienced a mean HVPG reduction of 12 % ($p < 0.05$ compared with placebo). However, there was a significant reduction in creatinine clearance and a 22 % drop out rate due to systemic hypotension. Natriuresis remained unchanged. In the second study (Venon and others 2003), 300mg irbesartan for 2 months resulted in a 5% reduction in the HVPG compared with 20% for propranolol ($p < 0.001$). In addition, irbesartan was poorly tolerated compared with propranolol on account of systemic hypotension and a reduction in creatinine clearance. Irbesartan appears to have no additional benefit over propranolol in efficacy and tolerability.

Angiotensin receptor antagonists appear on the basis of the above studies not to have significant benefits over propranolol, with the exception of the study by Schneider and colleagues. Most of the studies have looked at patients with more advanced liver disease with ascites, resulting in the unfavourable side effect profile. Caution is also necessary because of the deleterious effect on renal function demonstrated in the past with captopril (Gentilini and others 1993).

Drugs acting on the serotonin 5HT₂ receptors

It has been shown in an experimental model that portal hypertensive animals are more sensitive to the vasoconstrictor effects of serotonin on mesenteric veins, and that administration of ketanserin, a 5HT₂ receptor blocker with alpha adrenergic antagonist activity, resulted in significant reductions in the portal venous inflow and portal pressure (Cummings and others 1986). The reduction in portal pressure caused by ketanserin was due mainly to a decrease in portal venous inflow secondary to a decreased cardiac output, an effect only seen in portal hypertensive rats. This would be consistent with venous dilatation and pooling of blood in the portal venous system secondary to 5HT₂ receptor blockade. These findings led to human studies investigating the effect of 5HT₂ receptor blockade on portal pressure.

Early trials in cirrhotic patients demonstrated a significant reduction of 23% in the HVPG following ketanserin administration, which was accompanied by reductions in the azygous blood flow and mean arterial pressure with the hepatic blood flow remaining unaffected (Hadengue and others 1987). Subsequent studies corroborated these findings (Deflandre and others 1988;

Vorobioff and others 1989). The chronic administration of ketanserin was associated with a sustained drop in the portal pressure of 14.6%, a reduction in the cardiac index, and a drop in the mean arterial pressure (Vorobioff and others 1989). This study also demonstrated that 50% of patients developed reversible portosystemic encephalopathy. Hypotension probably results from alpha receptor blockade.

Combination treatments have also been studied. Ketanserin in combination with propranolol, both administered intravenously, has been shown to reduce the HVPG in patients who did not initially respond to propranolol (Hadengue and others 1987). Ritanserin, a more selective serotonin S₂ blocker, was combined with propranolol in a study investigating the haemodynamic effects of the chronic dosing of these agents (Ladero Quesada and others 1994). An initial reduction in the portal pressure was noted, but this effect was not sustained during follow up.

These agents have not been studied in randomised controlled trials for the prevention of variceal bleeding or for the treatment of variceal bleeding. The high incidence of encephalopathy observed with monotherapy, and the potential for systemic hypotension may limit their clinical use. Combination therapy with non-selective beta-blockers seems more promising.

Drugs affecting plasma volume

The expansion of plasma volume leading to increased cardiac index is believed to play a major role in sustaining portal hypertension (Zimmon and Kessler 1974). Thus diuretics or a low sodium diet may in theory help to

reduce portal pressure. Early studies suggested that spironolactone had the potential to be as potent a portal hypotensive agent as propranolol (Klein 1985). A significant reduction in the portal pressure of between 10 and 15% was shown to be accompanied by reductions in plasma volume, cardiac output, mean arterial pressure and azygous blood flow (Katsuta and others 1993; Garciapagan and others 1994; Sugano and others 1998). Hepatic blood flow was unaffected. Although there was no significant correlation between the plasma volume and HVPG, a significant inverse relationship between post treatment serum aldosterone levels and the HVPG was noted, thus confirming the mode of action of aldosterone (Katsuta and others 1993). The reductions in the HVPG following spironolactone administration were not affected by dietary sodium content suggesting that a low sodium diet alone is not sufficient to reduce the portal pressure (Garciapagan and others 1994; Sugano and others 1998). A recent small study reported a good portal hypotensive response in patients who failed to respond to propranolol, particularly when the two drugs were combined (Sen and others 2002). In clinical practice the use of spironolactone, like propranolol, may be limited by its side effects, particularly painful gynaecomastia, present in 55% of male patients in one series (Nevens and others 1996).

Combination therapy

Combination therapy was first used for the treatment of portal hypertension using nitrates and vasopression (Groszmann and others 1982; Hallenmans and others 1983). Enhancement of the portal hypotensive effect was observed. Studies using propranolol, as already discussed, have revealed

that 30% of patients failed to reduce portal pressure (Vorobioff and others 1987). This observation and the fact that nitrate monotherapy consistently reduced portal pressure led to studies to investigate the effect of combined nitrate and beta-blocker therapy (Table 4), a combination that was first investigated in vitro by Kroeger and Groszmann (Kroeger and Groszmann 1985). In general there is an enhanced portal hypotensive effect of the combination therapy using ISMN leading to a further 13–16% fall in the HVPG. This effect is particularly striking in those patients who did not respond to a beta-blocker alone (GarciaPagan and others 1990). The mechanism proposed has been that of a decrease in the outflow resistance (Merkel and others 1997). It is of note that 1 year after combination therapy with nadolol there did not seem to be any additional effect of the nitrate either in the hepatic or systemic haemodynamics, despite there being a sustained effect after 3 months of therapy (Merkel and others 1999). This may be partly explained by a study by Bendsten and associates who demonstrated that placebo treatment had an equal effect to propranolol after 1 year suggesting that portal hypertension improves spontaneously in some patients (Bendtsen and others 1991). Although studies looking at the short term effect of nitrates failed to demonstrate tolerance (Grose and others 1994; Jones and others 1995), nitrate tolerance could still be an explanation for the lack of effect due to a longer follow-up period in this study (Grose and others 1994; Merkel and others 1999).

The hepatic blood flow and liver metabolic activity are unaffected, but the azygous blood flow decreased in most cases with the effect being less pronounced with longer duration of treatment. Mean arterial blood pressure

and cardiac output both fell, again with the effect most pronounced following acute administration.

Renal function and ascites formation have been the focus of some of the studies (Morillas and others 1994; Merkel and others 1995; Albillos and others 1998), particularly as ISMN has been associated with a deterioration in renal function (Albillos and others 1994). The findings suggest that the combination of ISMN with either propranolol or nadolol had no detrimental effect on renal function in patients with or without ascites, despite significant effects on hepatic haemodynamics. These encouraging findings have led to a number of clinical trials using such combinations.

Other combination therapies have also been studied. A small randomised study showed a greater portal hypotensive effect of prazosin and propranolol than ISMN and prazosin, with no effect on hepatic or renal function (Albillos and others 1998). Undesirable systemic effects unfortunately offset the impressive hepatic haemodynamic results with more patients experiencing symptomatic hypotension in the prazosin arm of the study, thus limiting its use in clinical practice.

Table 4: The effect of combination therapy on portal and systemic haemodynamics.

Study	Number of patients	Drug(s) / Dose	Child's Class / Score	Acute/ Chronic Study [#]	Mean Arterial Pressure [#]	Cardiac Output [#]	Hepatic Venous Pressure Gradient [#]	Estimated hepatic blood flow [#]	Azygous blood flow [#]	Systemic vascular resistance index [#]
Garcia Pagan, 1990	20	Propranolol IV (0.1mg/kg bolus 2mg/h 30min infusion) + ISMN 20/40mg	A/B/C: 9/10/1	Acute	-22 (-22)	-36 (-11.5)	-27 (-13.3)	-28.3 (-15.5)	-38 (0)	+15 (-7)
	8	Propranolol + ISMN 20mg	A/B: 7/1	Acute*	-12	-22	-10	-23	-10.8	NS
GarciaPagan, 1991	21	Propranolol + ISMN 80mg - 3 months	Mean - 6.6	Chronic	NS		-19 (-9)	NS		
Morillas, 1994	15	Propranolol 114mg* + ISMN 68mg* - 3 months	Mean - 7.6	Chronic	-10, n=20	-24	-19	Not Stated	-31	+25
Merkel, 1995	46	Nadolol 69mg* + ISMN 34mg* - 6 months	Mean - 7.9	Chronic	-5.2 (-0.6)	Not Stated	-30 (-15)	Not Stated	Not Stated	Not Stated
							n=6			
Merkel, 1997	9	Nadolol 80mg* + ISMN 40mg - 3 months ^o	Mean - 6	Chronic	NS	Not Stated	-26 (-16.8)	Not Stated	Not Stated	Not Stated
Albillos, 1998	28	Propranolol + ISMN - 3 months	Mean - 6	Chronic			-16	NS		
Merkel, 1999	11	Nadolol 80mg* + ISMN 60mg - 3 months ^o	Mean - 6.9	Chronic	NS (NS)	Not Stated	-27 (-16)	NS (NS)	Not stated	Not Stated
	7	Nadolol 80mg* + ISMN 60mg - 1 year	Mean - 6.9	Chronic	NS (NS)	Not Stated	-18 (NS)	NS (NS)	Not Stated	Not Stated

* - ISMN administered following 3 -12 months of propranolol therapy, average maintenance dose of 85mg. • - Mean maintenance dose

[#] - Results in brackets represent the additional effect of adding nitrate therapy. ^o - Following one month treatment with Nadolol

NS - Not significant

1.4.2 Clinical application of drugs in portal hypertension.

Primary prophylaxis

Beta-blockers versus placebo.

Propranolol and nadolol have been compared with placebo in 11 randomised controlled trials in patients with varices (Table 5), although 4 of these were published in abstract form (Cerbelaud and others 1986; Pascal and Cales 1987; Strauss and others 1988; Colman and others 1990). Another large trial involving 319 patients treated with either placebo or propranolol is not comparable with the other trials (Plevris and others 1994). Here patients were unselected with regard to the presence of cirrhosis and varices. This accounts for the low event rate with just 11 patients bleeding and probably explains why no difference was found in the two groups.

The results of meta-analyses of these trials are very favourable for the treatment group, with reductions in the number of bleeding episodes approaching 50% (Hayes and others 1990; Poynard and others 1991; D'Amico and others 1995; Cheng and others 2003). Overall deaths due to bleeding were significantly reduced by 45% in one of these studies and overall deaths by 22% ($p = 0.052$) (Hayes and others 1990). These results were mirrored in a recent meta-analysis (Cheng and others 2003). The other two analyses did not show any benefit on overall survival, although in one study mortality from bleeding episodes was reduced by 50% (Poynard and others 1991). This analysis also demonstrated that the presence of ascites was associated with greater mortality and bleeding risk. One of the main problems with many of the trials is the low number of patients, resulting in

insufficient power to detect a reduction in bleeding risk and especially mortality. The study by Colman et al (Colman and others 1990) is unique in showing an increase in bleeding rate in the treatment group. However, the sample size of this study is low and the very low event rate in the control group suggests that patient selection may have been responsible.

A recent randomised placebo controlled trial by Calès and colleagues involving 206 patients with no or only small (< 5 mm) varices was performed to investigate whether propranolol prevents the development of varices (Cales and others 1999). After a 2-year follow-up period 31% of patients in the propranolol arm and 14% of patients taking placebo developed large varices ($p < 0.05$). There was no difference in the rate of bleeding or mortality in the two groups. The low bleeding rate in the placebo group may reflect the small numbers of patients in Child's C class (13%). However, the high incidence of the development of varices in the propranolol group is striking. The authors postulated that above a certain portal pressure the development of varices is not directly related to portal pressure and other 'non-haemodynamics' play a part. Another mechanism proposed was that of increased vascular resistance in the collateral circulation following propranolol administration, although it is not clear what the relationship between collateral resistance and the development of varices is. Until further studies are performed it is not recommended that propranolol be prescribed for the prevention or the development of varices and bleeding in cirrhotic patients with small or no varices.

Studies have shown propranolol to be safe in long-term use in patients with cirrhosis, but up to a third of patients are intolerant of the side effects

resulting in discontinuation of the drug (Walle and others 1988). The dosage in most of the studies is that required to reduce the resting heart rate by 25%. This usually means starting therapy with a dose 40 mg twice daily and working up to an average maintenance dose of 160 mg/day. Nadolol is typically administered at a dose of 80 mg/day. Fatigue is the most important side effect. Compliance can be a major problem, especially in patients with alcoholic liver disease.

Table 5: Beta-blocker therapy in the primary prophylaxis of variceal haemorrhage.

Trial	Drug	Number of patients		Bleeding rate (%)		Death rate (%)	
		Control	Treatment	Control	Treatment	Control	Treatment
Pascal 1984	Propranolol	35	34	26	3	37	3
Mills, 1987	Propranolol	43	38	77	50	44	39*
Pascal, 1987	Propranolol	112	118	61	26	49	28
Anonymous 1989	Propranolol	89	85	41	26*	49	41*
Strauss, 1988	Propranolol	16	20	25	20*	44	35*
Colman, 1990	Propranolol	25	23	8	35	28	26*
Anreani, 1990	Propranolol	41	42	39	6*	46	34*
Conn, 1991	Propranolol	51	51	22	4	22	16*
PROVA, 1991	Propranolol	72	68	18	18*	19	10*
Ideo, 1988	Nadolol	49	30	30	6	18	10*
Lebrec, 1988	Nadolol	53	53	20	17*	19	19*

* - Not significant compared with control.

Isosorbide-5-mononitrate

There are 2 published randomised controlled trials comparing ISMN with placebo. In the first, there was a tendency towards reduced bleeding and death in the ISMN group, although the results did not reach statistical significance (Fassio and others 1993). It is also of note ISMN was well tolerated. The second study comparing ISMN (in patients intolerant of beta-blockers) with placebo in 133 consecutive cirrhotic patients with gastro-oesophageal varices, reported no difference in the rate of variceal bleeding following a 2-year follow-up period (Garcia-Pagan and others 2001). There was no significant difference in survival. There was no difference in the incidence of ascites or deterioration in renal function. The authors concluded that ISMN has no place in the primary prophylaxis against the first variceal haemorrhage.

Others have compared ISMN with propranolol (Angelico and others 1997). This was a large randomised trial over a 7-year follow-up period involving 118 patients. The probability of bleeding was identical in both the groups. Mortality was significantly greater in the nitrate group, but this was only in patients above 50 years of age.

A smaller study demonstrated that ISMN was less effective than nadolol in preventing bleeding in 27 patients with ascites (Borroni and others 2002). Mortality was unaffected, but sodium excretion was reduced by almost 50% in the nitrate group.

The use of nitrates in the primary prophylaxis is controversial, and the most up to date evidence is against its use. Also, the reduced mortality seen with

propranolol is not present in patients treated with nitrates. Caution is needed in prescribing nitrate monotherapy on account of the potential for deterioration in renal function and the increased mortality seen in the older age group (Angelico and others 1997). This may explain why there are not so many trials using nitrate monotherapy and many more looking at combination therapy.

Combination therapy.

As discussed earlier, combination therapy has been shown to be effective in producing a sustained portal hypotensive response. Nadolol monotherapy has been compared with nadolol and ISMN dual therapy by Merkel and colleagues with the results of long-term follow-up published recently (Merkel and others 1996; Merkel and others 2000). Initial results following a 30-month follow-up period in 146 patients demonstrated a significant reduction of greater than 50% in the cumulative risk of variceal bleeding in the combination treatment group compared with nadolol alone, with no effect on mortality. However, there was a high incidence of side effects in the combination group (51%), which were severe enough to cause withdrawal from the study in 11% of patients. This compares with 4% in the nadolol only group.

Long-term follow-up of these patients over 7 years has revealed a sustained effect of combination therapy in preventing variceal haemorrhage (Merkel and others 2000). Survival was unaffected. A larger sample size would be required to show up any survival differences. Two significant findings are of note. First, long-term administration did not result in further side effects

leading to withdrawal from the study. Thus, side effects usually occur early after the initial doses for nitrates, and in the first few months as in the case of beta-blockers. Secondly, there was no significant effect on the occurrence of de novo ascites in the two groups. Previous studies have shown a deleterious effect on renal function and sodium handling when using nitrate monotherapy (Salmeron and others 1993).

Three double-blind placebo-controlled randomised studies have been published (Pietrosi and others 1999; Abecasis and others 2003; Garcia-Pagan and others 2003) The first of these compared propranolol and placebo with propranolol and ISMN in 349 patients of whom 57% had > 5 mm size varices (Garcia-Pagan and others 2003). Bleeding rates at 2 years in both the groups were 10.6% and 12.5% respectively ($p = \text{NS}$). Mortality was also similar in both groups, but there were significantly more side effects in the combination group. Development of ascites and renal function were unaffected.

The second study published in abstract form involved fewer patients (Pietrosi and others 1999). Patients with large oesophageal varices and red colour signs were randomised to either nadolol plus placebo ($n = 27$), or nadolol plus ISMN ($n = 30$). There was no significant difference in the bleeding rate or mortality following a 2-year follow-up. Side effects were significantly more common in the combination group (53% vs. 26%, $p = 0.03$). However, the study was terminated early on account of excess mortality in patients treated with nadolol and ISMN in a parallel trial for the prevention of rebleeding (Patti and others 2001). Thus, it is not appropriate to make valid conclusions based on this trial.

The large randomised study compared nadolol plus spironolactone versus nadolol plus placebo, and found no differences in the incidence of the first variceal bleed but the combination therapy had a beneficial effect on the combined end-point of bleeding and ascites (Abecasis and others 2003).

Beta-blocker and ISMN combination therapy, in particular nadolol and ISMN, appears to be more effective than nadolol monotherapy in preventing the first variceal bleed. Until further studies are performed there does not appear to be any advantage in adding ISMN to propranolol. The side-effect profile of combination therapy is considerably worse, and this is likely to limit its clinical application. Outside of clinical trials patients and clinicians may not be so vigilant in continuing therapy that leads to so many side effects when alternatives such as endoscopic treatments are available.

Pharmacological agents compared with endoscopic treatments.

Sclerotherapy has been compared with placebo and propranolol in two studies (Andreani and others 1990; Anonymous 1991), and the efficacy of sclerotherapy and propranolol combination therapy assessed in one of these and a further study (Anonymous 1991; Avgerinos and others 2000). One study revealed that bleeding from a portal hypertensive source was significantly less in the propranolol group than the sclerotherapy group (4.7% vs. 21.4%, $p < 0.003$) (Andreani and others 1990). None of the studies showed differences in variceal bleeding, or mortality when propranolol was compared with sclerotherapy.

A recent trial, which selected patients with high intra-oesophageal variceal pressures, randomised patients to propranolol (42 patients) or to propranolol

plus sclerotherapy (44 patients) (Avgerinos and others 2000). After a 2-year follow-up period, 23% of the patients in the combination group bled due to varices or congestive gastropathy as compared with 14% in the propranolol group (not significant). Fifty-two per cent in the combination group developed complications as compared with 19% in the propranolol group ($p = 0.002$). The mortality rate was similar in both groups. The findings are similar to those in an earlier study where patients were unselected with regard to the characteristics of varices (Anonymous 1991).

Endoscopic band ligation is a recent technique that has been compared with sclerotherapy in a meta-analysis (Laine and Cook 1995), and was found to be superior to sclerotherapy in the secondary prophylaxis against variceal rebleeding with fewer complications and quicker eradication of varices. Band ligation has been compared with propranolol for the primary prophylaxis of variceal bleeding in three published trials (De and others 1999) (Lui and others 2002) (Sarin and others 1999) (Table 6). In the first study (De and others 1999), 30 patients with grade III or higher varices were studied over a 17-month follow-up period. There was no difference in the bleeding rate in the two groups. Sarin and colleagues (Sarin and others 1999) studied 89 patients with greater than 5 mm varices and observed that over a 17-month period the probability of bleeding was 43% in the propranolol group and 15% in the ligation group ($p = 0.04$). There was no difference in mortality. The very high bleeding rate in the propranolol group contrasts with that observed in other trials. The dose of propranolol was also lower than in other trials. A recent multicentre trial involving 172 patients compared propranolol, ISMN and band ligation over a mean follow up of 20

months (Lui and others 2002). Banding was superior to ISMN but similar to propranolol in preventing the first bleed. There was no difference in the overall mortality in the three groups. A very significant proportion of patients had to withdraw from drug therapy as result of side effects. A meta-analysis of these studies and additional studies published in abstract form (Gameel and others 1996; Chen and others 1997; Chen and others 1998) was recently published (Imperiale and Chalasani 2001). This revealed that banding reduced the risk of the first variceal bleed by 64% and mortality by 45% compared with controls. This compares with 52% risk reduction of the first bleed when banding was compared with propranolol, with no effect on mortality.

Clearly, of the two modes of endoscopic treatments, banding is preferable to sclerotherapy because there are fewer iatrogenic complications and it has been shown to be at least as good as if not better than propranolol. Banding is particularly useful where patients are intolerant of drug therapy.

Sclerotherapy combined with propranolol does not offer any further benefit over propranolol monotherapy. It remains to be seen whether this is also the case with banding. It appears that banding is at least as good as propranolol in the primary prevention of variceal bleeding and will probably be widely employed, because of its lack of dependence on compliance and the attraction of eradicating oesophageal varices.

Table 6: Studies^a of primary prophylaxis of variceal haemorrhage involving variceal band ligation

Study	Treatment arms	Number of patients	Bleeding Rate (%)	
			VBL	Control / Alternative therapy
Sarin, 1996	VBL/Control	35/33	9	39 ^b
Lay, 1997	VBL/Control	62/64	19	60 ^b
Lo, 1999	VBL/Control	64/63	22	35
Sarin, 1999	VBL/PPL	45/44	15	43 ^b
De BK, 1999	VBL/PPL	15/15	13	7
Gotoh, 1999	VBL/EVS	25/25	20	0 ^b
Svoboda, 1999	EVS/VBL/Control	52/55/50	29	54 ^c
Lui, 2002	VBL/PPL/ISMN	44/66/62	7	14/23

VBL: variceal band ligation

EVS: Endoscopic variceal sclerotherapy

ISMN: Isosorbide-5-mononitrate

PPL: Propranolol

^a: excludes abstracts

^b: $p < 0.05$

^c: $p < 0.05$ (VBL vs Control)

Secondary prophylaxis

It is clear that secondary prevention following a variceal bleed is essential in view of the high rate of rebleeding without intervention (Williams and Westaby 1994). There is a greater choice of endoscopic, pharmacological, radiological and surgical therapies for secondary prophylaxis than for primary prophylaxis.

Beta-blockers versus placebo.

There were several trials in the 1980s, and a meta-analysis of these performed in our centre revealed significant benefits of propranolol therapy (Hayes and others 1990). In a population of 1080 patients there was a 39% reduction in rebleeding episodes, a 40% reduction in deaths from bleeding and a 25% reduction in total mortality in the propranolol groups.

Heterogeneity was significant for rebleeding episodes, but not when deaths from bleeding or overall mortality were assessed. Although not all of these trials were randomised or placebo controlled, further analysis of selected trials that met more strict criteria and those where there was no significant heterogeneity, demonstrated significant benefits from propranolol therapy in the reduction of rebleeding and improved mortality rates.

There are 12 published randomised controlled trials comparing beta-blockers with placebo against variceal rebleeding (Burroughs and others 1983; Lebec and others 1984; Villeneuve and others 1986; Cerbelaud and others 1986; Queuniet and others 1987; Kobe and Schentke 1987; Gatta and others 1987b; Colombo and others 1989; Sheen and others 1989; Garden

and others 1990; Colman and others 1990; Rossi and others 1991) (Table 7). Propranolol was assessed in 11, nadolol in one and atenolol in another study which also included propranolol (Colombo and others 1989). The latter study found atenolol to be less effective than propranolol at reducing rebleeding and improving patient survival. A meta-analysis of these trials (D'Amico and others 1995) demonstrated a significant reduction in the rebleeding rate from 66% in the placebo group to 44% in the treatment group (pooled odds ratio of 0.4). There was no significant effect of drug therapy on survival, which may reflect the heterogeneity of the study populations, particularly with respect to aetiology, severity of the liver disease and the time to treatment from the index bleed. Only two of these studies included a significant proportion of Child's C patients (Villeneuve and others 1986; Garden and others 1990), and benefit for the Child's C patients was seen in one (Garden and others 1990).

A recent meta-analysis also revealed that there was a significantly greater reduction in the variceal rebleeding rate in the beta-blocker treated patients than in the placebo group (20% mean improvement rate, $p < 0.001$) (Bernard and others 1997a). In addition, this study also demonstrated that there was a significant improvement in the survival rate in the treatment group with a mean improvement of 5.5% ($p = 0.05$), with this being more marked in patients with more advanced liver disease. These findings were reinforced by a further meta-analysis (Cheng and others 2003). The methods of analysis did not reveal any significant heterogeneity amongst the trials. It would therefore seem appropriate that beta-blocker therapy for secondary prophylaxis can be recommended for patients regardless of the

degree of liver disease. Although the prevalence of adverse events was significantly higher in the treatment group, because adverse events were only mentioned in some of the studies it remains somewhat unclear of the impact of this on practice.

Table 7: Beta-blocker therapy in the secondary prophylaxis against variceal rebleeding.

Trial	Drug	Number of patients		Rebleeding rate (%)		Death rate (%)	
		Control	Treatment	Control	Treatment	Control	Treatment
Burroughs, 1983	Propranolol	22	26	59	54	23	15
Lebrec, 1984	Propranolol	36	38	64	21	22	8
Villeneuve, 1986	Propranolol	37	42	81	76	38	45
Carbelaud, 1986	Propranolol	50	50	78	40	33	26
Queuniet, 1987	Propranolol	48	51	64	57	21	23
Gatta, 1987	Nadalol	12	12	67	25	25	8
Kobe, 1987	Propranolol	28	26	46	38	32	23
Colombo, 1989	Propranolol	30	32	47	25	23	12
Colombo, 1989	Atenolol	30	32	47	31	23	9
Sheen, 1989	Propranolol	18	18	55	28	11	0
Garden, 1989	Propranolol	43	38	77	47	44	37
Colman, 1990	Propranolol	26	26	50	35	4	4
Rossi, 1991	Propranolol	27	27	63	48	33	26

Combination therapy.

There is only one published trial assessing the effect of combination drug therapy in preventing variceal rebleeding (Gournay and others 2000). In this randomised study involving 95 patients, after a 2-year follow-up period, overall rebleeding and survival was not improved by the addition of ISMN to propranolol compared with propranolol alone. However, there was a significant reduction in the risk of rebleeding when patients were stratified according to age, i.e. less than 50 years old versus over 50 year olds or by adding an extra year of follow up. It is also of note that more patients experienced side effects leading to discontinuation of medication with the combination therapy. However, no adverse events concerning renal function or effect on ascites was observed with the combination therapy.

Another two studies published in abstract form reinforce the findings of the above study that combining beta-blockers with ISMN offers no additional benefit in reducing the overall rebleeding rate and mortality (Pasta and others 1999) (Masliah and others 1997). In fact, one of these studies reported greater mortality in patients treated with nadolol and ISMN than nadolol alone (32% vs. 14%, $p = 0.02$) (Pasta and others 1999). Clearly the full paper would need to be published and analysed before firm conclusions can be made.

It appears that combination therapy may have a role in secondary prophylaxis, but adverse side effects may limit its clinical use. Further studies are necessary before confident recommendations can be made.

Pharmacological agents compared with endoscopic treatments.

There have been several trials comparing sclerotherapy with beta-blockers alone or beta-blockers combined with sclerotherapy. Meta-analysis of these studies demonstrated a small benefit of sclerotherapy over propranolol on the rebleeding rate but no effect on survival (Hayes and others 1990).

Sclerotherapy was associated with a greater number and severity of complications. Propranolol combined with sclerotherapy was found to be better than sclerotherapy in reducing the rebleeding rate, but there was no difference in survival. The rationale being that the addition of propranolol reduces the risk of rebleeding in the first few months before the varices are completely eradicated. However, the meta-analysis revealed significant heterogeneity in all these trials. A recent abstract found that propranolol and sclerotherapy were significantly more effective at reducing the rebleeding rate than sclerotherapy alone (11/35 vs. 16/30 patients, $p < 0.001$) (Benedeto-Stojanov and others 2000). It is interesting that most of the difference was accounted for by a greater incidence of bleeding from gastric varices and congestive gastropathy in the sclerotherapy only group.

Propranolol in combination with sclerotherapy was found to be superior, in terms of rebleeding rate and survival, to propranolol alone based on the results of two studies. In the meta-analysis the odds ratios for rebleeding in the above trial comparisons were not as low as that when comparing propranolol with placebo. The trials comparing the latter were also of a higher quality with a longer follow-up period. Another meta-analysis comparing propranolol with sclerotherapy mirrors these findings in that sclerotherapy was more effective at reducing variceal rebleeding, but was

associated with more iatrogenic adverse events (Bernard and others 1997b).

Survival was similar in the two groups.

The combination of nadolol and ISMN was found to be superior to sclerotherapy in a recent trial (Villeneuve and others 1986). Rebleeding rate and treatment related complications were significantly lower than in sclerotherapy. Overall survival was, however, identical in the two groups. It is interesting that patients in whom the hepatic venous wedge pressure fell by 20% or more had far fewer episodes of rebleeding.

Banding has been compared with beta-blocker and ISMN combination therapy in preventing recurrent variceal bleeding in 5 studies (Goulis and others 1998; Minyana and others 1999; Villanueva and others 2001; Patch and others 2002; Lo and others 2002), with 2 published in abstract form only (Goulis and others 1998; Minyana and others 1999). Of the studies published as full papers one concluded that nadolol and nitrate combination was superior to VBL, and those patients with a haemodynamic response defined as a reduction in the HVPG of > 20% or to <12 mm Hg, had a lower rebleeding rate and mortality than those who did not respond (Villanueva and others 2001). Lo and colleagues demonstrated greater efficacy of VBL over nadolol and ISMN therapy (Lo and others 2002), although the doses of the drugs was half that used by Villanueva and colleagues. The study by Patch and colleagues demonstrated similar efficacy of VBL versus propranolol plus ISMN in the prevention of variceal rebleeding, with no difference in the haemodynamic parameters during follow up (Patch and others 2002). The latter finding may have been due to the HVPG measurements being performed at a later stage than Villanueva et al, thus

missing those patients at most risk since the risk of rebleeding is highest in the first month. It should be noted that Patch and colleagues failed to recruit the target number of patients due to a large number requiring salvage TIPSS, thus the results are subject to a type II error. Furthermore, only 41% of patients actually received combination drug therapy and there were more patients with Child C disease than in the other two papers.

The combination of beta-blockers and ISMN appears to be promising, particularly if patients exhibit a haemodynamic response (Villanueva and others 2001). Future large multicentre studies would assist in fully evaluating combination therapy for the prevention of variceal rebleeding, and should incorporate HVPG measurements in response to therapy shortly after randomisation.

1.5 The transjugular intrahepatic portosystemic stent-shunt (TIPSS) in the management of variceal bleeding.

TIPSS has made a significant impact on the management of portal hypertension since its introduction in the 1980's. Randomised controlled trials and meta-analyses demonstrate its superiority over endoscopic methods in the prevention of variceal rebleeding, although most studies do not demonstrate any survival benefit (Papatheodoridis and others 1999). The severity of the underlying liver disease as defined by the Pugh score at the time of TIPSS has the greatest impact on survival. Most centres advocate the use of TIPSS as a salvage procedure where endoscopic methods fail to control variceal bleeding. There is also evidence to support the use of TIPSS for the prevention of variceal rebleeding in refractory ascites, hepatorenal syndrome, hepatic hydrothorax, and Budd Chiari Syndrome. Hepatic encephalopathy and shunt dysfunction are the principal disadvantages of TIPSS, although careful patient selection, TIPSS surveillance and probably the use of the newer covered stents can minimise these.

1.5.1 Historical aspects and basic principles.

The concept of TIPSS has been around since the late 1960's and 70's (Rosch and others 1969; Rosch and others 1971). The original investigators looked at imaging the portal circulation via the transjugular route. They succeeded in entering the portal vein through the hepatic parenchyma, and this led to the idea of creating a fistula between the hepatic vein and portal veins giving rise to a portosystemic shunt. Initial attempts at creating a TIPSS in animal models using non-expandable tubing (Rosch and others 1971), drilling (Koch and others 1973), and cryoprobe freezing (Reich and

others 1977) were hampered by shunt dysfunction, with primary patency limited to a maximum of 2 weeks.

The introduction of balloon angioplasty catheters in the latter half of the 1970's was key to the successful creation of TIPSS. Animal models demonstrated the potential for TIPSS to be kept patent for up to a year by regular dilatations, despite the high early occlusion rate (Burgener and Gutierrez 1988). The first clinical application of TIPSS was by Colapinto and colleagues in 1982, who used a 9mm catheter to significantly reduce portal pressure (Colapinto and others 1982). Further studies were performed in patients with cirrhosis and variceal bleeding, where despite a significant reduction in the portal pressure, most patients rebled and died or required surgery. The fact that most of the fistulae were patent at autopsy suggested that further measures were necessary to maintain portal decompression.

The use of expandable metal stents in the mid 1980s led to the development of 10mm Palmaz stents which were initially used in animal models (Palmaz and others 1985; Palmaz and others 1986). The patency of these shunts was much better in patients with chronic rather than acute portal hypertension, lasting for up to 48 weeks. These experiments led to the first clinical application of expandable metal stents involving the use of 2 Palmaz stents, resulting in both hemodynamic and clinical improvement in portal hypertension (Rockey 2000). The patient unfortunately died at day 12 from adult respiratory distress syndrome, although the shunt was noted to be patent at autopsy. These early experiences stimulated enormous interest among interventional radiologists and gastroenterologists, resulting in many

centres using TIPSS and further refining the technique and expanding its use for other indications.

1.5.2 Haemodynamic effects of TIPSS.

The effects of TIPSS on the hyperdynamic circulation in cirrhosis have been well studied.

Portal circulation

Successful TIPSS results in immediate reduction of portal pressure.

Traditionally the portal pressure gradient (PPG) is utilised and is:

Portal pressure – Inferior vena cava pressure

It was widely believed that variceal bleeding was very unlikely below a threshold HVP of 12 mm Hg (D'Amico and others 1995), leading to this being adopted as therapeutic goal following TIPSS insertion, and is achieved for most patients in our and others' series (Tripathi and others 2004). The azygous blood flow, which is a measure of the collateral blood flow, decreases acutely following TIPSS insertion, both acutely with a maximum decrease of 30% of baseline values 1 year following TIPSS insertion (Lotterer and others 1999). This study also identified a correlation between the change in PPG following TIPSS insertion and the azygous blood flow.

Systemic circulation

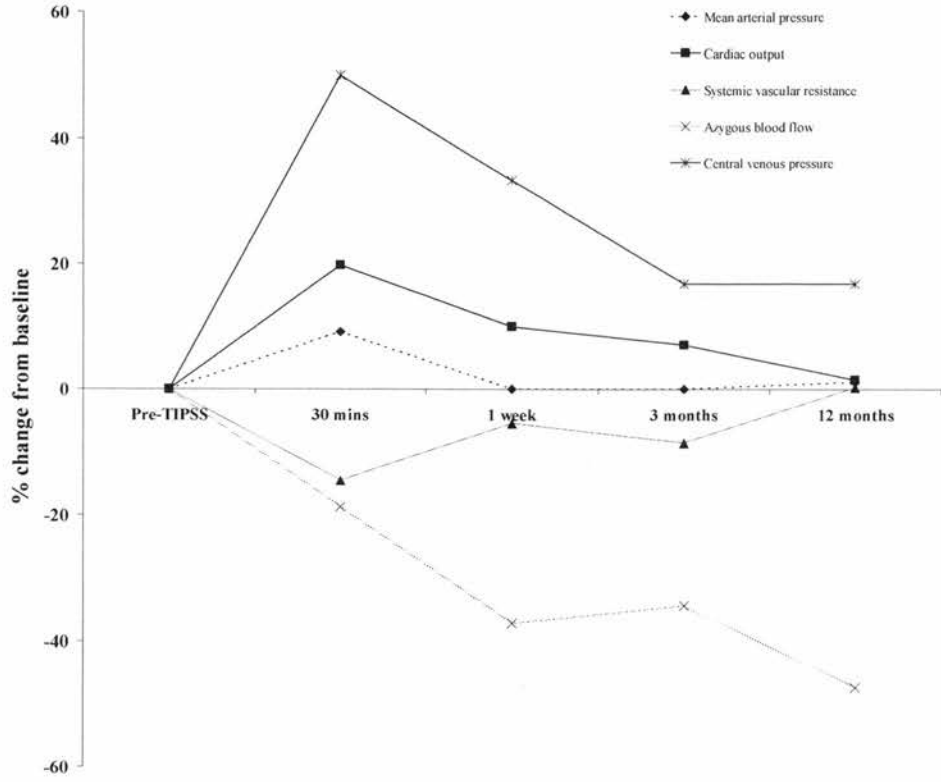
The potential for a TIPSS to aggravate an already hyperdynamic circulation was demonstrated in earlier studies in our unit (Stanley and others 1998a).

The acute effect at 30 minutes post TIPSS insertion is an increase in cardiac

output (CO), right atrial pressure (RAP), pulmonary artery, and pulmonary wedge pressure, with a fall in systemic vascular resistance (SVR). No change was observed in heart rate (HR) or mean arterial pressure (MAP). The fall in the portoatrial pressure gradient correlated with the rise in CO and drop in SVR. These changes were confirmed in a recent large cohort study over a 1 year period following TIPSS insertion (Lotterer and others 1999). In addition to the acute effects reported by Stanley and colleagues, there was an increase in MAP and HR. The acute increase in CO persisted for up to 3 months, although the SVR started to increase after a week (Figure 2). Other parameters of the systemic circulation returned to normal after a year.

Therefore, the acute detrimental effect on the hyperdynamic circulation following TIPSS insertion is not maintained in the long term. The acute increase in the cardiac output and increase in venous return may result in acute pulmonary edema or unmask pre-existing cardiomyopathy (Braverman and others 1995; Huonker and others 1999). Caution is needed in patients with pulmonary hypertension or known cardiac dysfunction.

Figure 2: Change in systemic and portal haemodynamics pre and post TIPSS (Lotterer and others 1999)



1.5.3 Complications of TIPSS.

The complications relate to the procedure itself, the underlying liver disease and the function of the shunt.

Procedural

The overall rate of procedure related mortality in our unit of almost 500 consecutive TIPSS over a 10-year period is 1.2% (Tripathi and others 2004). Direct complications of the TIPSS included gallbladder perforation and intraperitoneal haemorrhage. There are also other rare non-fatal procedure related complications such as portal vein to bile duct fistula, localized collection between gallbladder and liver, shunt migration, pneumothorax, and neck haematoma. An unusual complication was the presence of a right atrial clot noted at routine portography resulting in shunt insufficiency. This was successfully removed under ultrasound guidance.

Patients with liver disease are immunocompromised, and the insertion of a TIPSS does not appear to increase the risk of infection, although an unusual type of infection can occur in the presence of a thrombus or vegetation in the TIPSS known as “endotipitis” (Sanyal and Reddy 1998). The patient presents with fever, hepatomegaly and positive blood cultures. Prolonged antibiotic therapy is required. As in the case of infective endocarditis there is usually one organism isolated. We have a policy of administering intravenous 3rd generation cephalosporins pre and for 48 hours post TIPSS insertion. Nevertheless, TIPSS infection has to be considered when no other source of sepsis can be identified.

In around 13% of patients there may be clinically significant haemolysis, which may manifest as jaundice or anaemia (Jalan and others 1996b). This usually resolves within 3-4 weeks as the TIPSS becomes covered with a neointimal layer.

Hepatic encephalopathy

One of the principal concerns of TIPSS has been the increased risk of hepatic encephalopathy, and this is confirmed with the current studies. The overall risk of hepatic encephalopathy following TIPSS of 34% compares with 19% following endoscopic therapy, resulting in 1 episode of de novo or worsening hepatic encephalopathy for 1 in 8 patients treated with a TIPSS (Burroughs and Vangeli 2002). This obviously has major implications on the quality of life of patients, and the resources needed to manage encephalopathy including shunt occlusion in up to 5% (Tripathi and others 2004). Selecting patients free from hepatic encephalopathy prior to TIPSS insertion may reduce the incidence of post TIPSS encephalopathy (Jalan and others 1995a). However, in clinical practice this is difficult to accomplish particularly where TIPSS is used to rescue those who have failed endoscopic therapy, since these individuals are likely to be encephalopathic from recurrent bleeding and/or have limited alternative treatment options.

Shunt insufficiency

Shunt insufficiency is a significant limitation of TIPSS. Fifty percent of shunts will become insufficient i.e significantly stenosed or blocked within a year of TIPSS insertion (Table 8, Figure 3), (Jalan and others 1997b; Jalan and others 1998) with most episodes resulting from acute thrombosis and leading to variceal rebleeding, probably as a result of thrombogenic biliary

material entering the shunt (Jalan and others 1996a; Sze and others 1999). Early controlled studies revealed a lower incidence of complete occlusion after heparin with no reduction in the re-intervention rate (Sauer and others 1996). A recent study suggested that heparin combined with antiplatelet drugs reduces the risk of stenosis of the hepatic vein and variceal rebleeding, although no effect was seen for stenosis within the stent (Siegerstetter and others 1999).

Later episodes of shunt dysfunction result from pseudointimal hyperplasia. Regular invasive portographic surveillance, which is essential for maintaining shunt patency is not available in all centres, and places an additional burden on resources. Non-invasive methods of assessing TIPSS patency such as Doppler ultrasound are not as sensitive as regular portography (Ferguson and others 1995), and studies which used this method had a higher rebleeding rate (Papatheodoridis and others 1999). In any case, Doppler ultrasound does not allow for interventions, such as balloon angioplasty and re-stenting nor the measurement of portal pressure.

Variables identified as predicting shunt insufficiency include PPG pre-TIPSS of > 18 mmHg (Jalan and others 1995a), and the presence of diabetes has been shown to be associated with delayed shunt occlusion (Shah and others 2001). A recent study published in abstract form identified stent diameter, distance of shunt through IVC, duration of the procedure, and PPG post-TIPSS as independent predictors of early shunt insufficiency (Balata and others 2002).

The observations that variceal bleeding occurs rarely at PPG < 12 mmHg (Groszmann and others 1990) or if there is a > 25% reduction in the PPG , has led to shunt insufficiency being defined as an increase in the PPG to > 12 mm Hg or an increase in the PPG of more than 20% of the immediate post-TIPSS value if the pre-TIPSS PPG was \leq 12 mmHg (Jalan and others 1998). Primary patency is defined as patency without intervention.

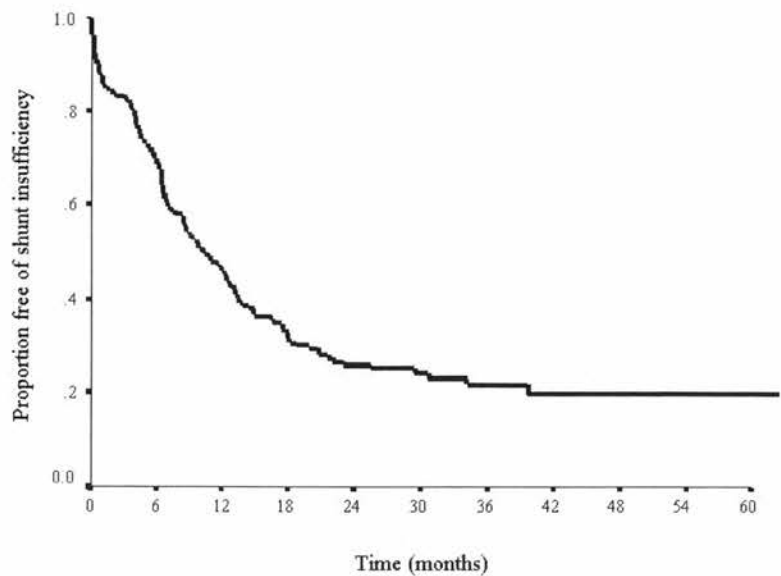
Secondary or assisted patency, defined as patency with intervention, is over 70% during a follow up period of 20 months in our series (Tripathi and others 2004).

An interesting observation in our experience is that the risk of variceal rebleeding 2 years post TIPSS is very low, even in the presence of shunt insufficiency (Tripathi and others 2004). This may reflect the fact that patients who survive this long post-TIPSS are usually in the better prognostic group, and therefore have a lower risk of variceal bleeding. This finding brings into question the need for continued portographic surveillance 2 years post TIPSS insertion, and merits further study.

Table 8: Shunt insufficiency: Portographic appearances. (Tripathi and others 2004)

Abnormality on portography	Frequency (%)
Intimal hyperplasia	60
Hepatic vein stenosis	21
Thrombosis within shunt	6
Occluded shunt	12
Portal vein thrombosis	<1%

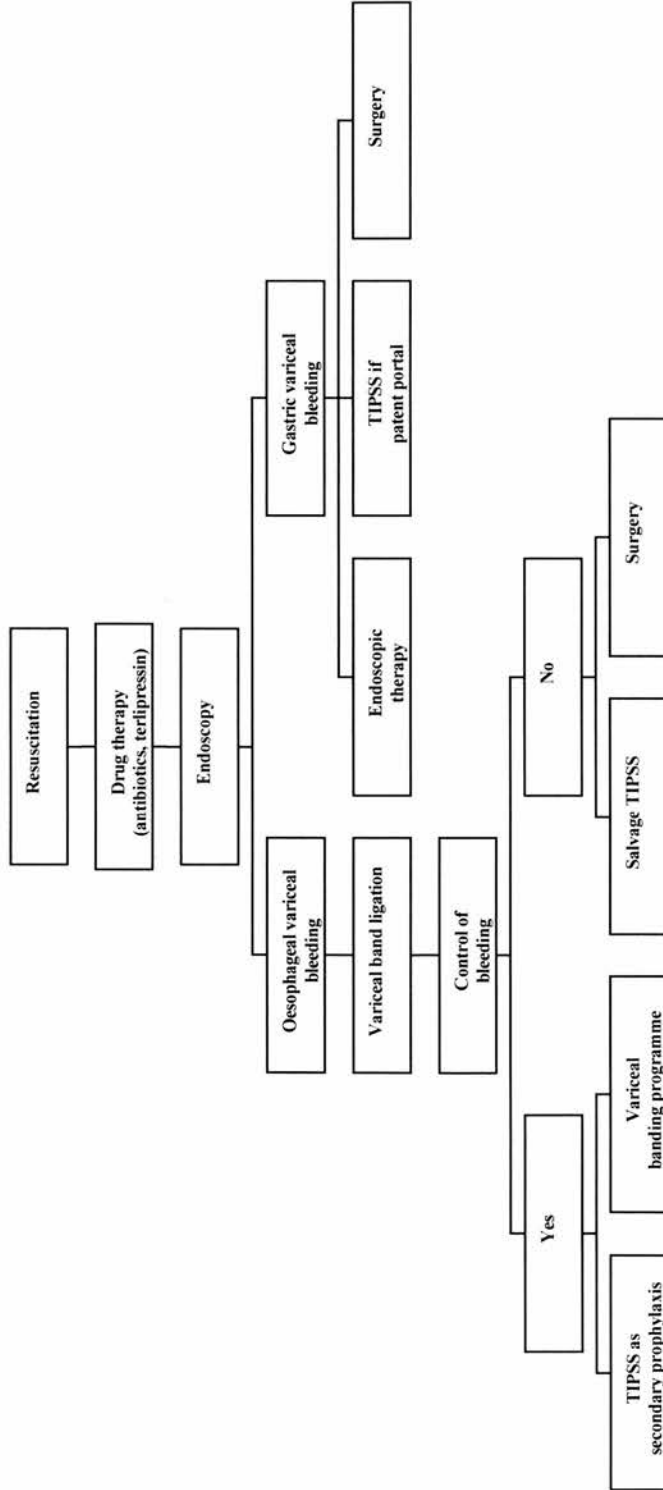
Figure 3: Kaplan Meier graph of primary patency of standard stents used for TIPSS (Tripathi and others 2004)



1.5.4 The role of TIPSS in the management of variceal haemorrhage.

Variceal haemorrhage is a life threatening complication of portal hypertension with an in-hospital mortality between 30-60% depending on severity of liver disease (Jalan and Hayes 2000). There has been much research in recent years aimed at finding the best possible therapy to prevent and treat variceal haemorrhage. In most centres endoscopic therapy is instituted as first line therapy, with pharmacological therapy such as terlipressin having an important role (Ferguson and others 2003). Broad spectrum antibiotics should be administered to all patients with cirrhosis following gastrointestinal haemorrhage, as this has been shown to improve survival (Ferguson and others 2003). In refractory cases or where the risk of variceal rebleeding is high, TIPSS is utilised (Figure 4). It terminates variceal haemorrhage in over 90% of patients, and prevents rebleeding 80-90% of patients (Stanley and others 1996). The availability of TIPSS still remains restricted to large teaching hospitals, but its use appears to be growing. Despite the increasing use of TIPSS, the number of controlled studies involving the use of TIPSS in the management of variceal haemorrhage is rather limited. At the present time there is no evidence to support the use of TIPSS in the prevention of the first variceal bleed, so TIPSS cannot be recommended for primary prophylaxis.

Figure 4: Algorithm for the management of variceal bleeding



Management of acute variceal bleeding

The role of TIPSS in the management of acute variceal haemorrhage as “salvage” therapy is well established. In such cases patients have been treated with endoscopic therapy and/or pharmacological therapies without success. Many clinicians would attempt a second endoscopic procedure prior to referring the patient to specialized centres for a TIPSS, but this will depend on the severity of the acute bleed. In severe cases where balloon tamponade is needed to control bleeding, a TIPSS may be indicated at an earlier stage. Prior to the introduction of TIPSS patients would have been referred for a surgical procedure such as oesophageal transection, which is associated with a high mortality in this setting (Jalan and others 1995b). Studies indicate that TIPSS results in control of acute variceal bleeding in over 90% of cases (Haag and others 1993; Helton and others 1993; Laberge and others 1993; Le Moine and others 1994; Rubin and others 1995; Jalan and others 1995b; Jabbour and others 1996; Sanyal and others 1996; Perarnau 1997; Gerbes and others 1998; Chau and others 1998; Banares and others 1998; Barange and others 1999; Azoulay and others 2001; Bizollon and others 2001) (Table 9). However, the mortality is high and reflects the severity of liver disease at the time of TIPSS insertion. Overall rebleeding rate is 18% and mortality is 38%, with most deaths occurring early (Burroughs and Patch 1999).

The rather dismal statistics prompted investigators to identify clinical and haemodynamic variables that could predict poor outcome. Early studies from our unit identified Child-Pugh score, hyponatraemia, pre-TIPSS encephalopathy, and pre TIPSS PPG > 16 (in alcoholic cirrhotics) to predict

mortality post TIPSS (Jalan and others 1995a; Stanley and others 1998b). The role of portal pressure as a predictor of mortality was reinforced by recent studies (Patch and others 1999; Moitinho and others 1999a). Others have suggested a greater role of the model of end stage liver disease (MELD) as a predictor of early mortality (Salerno and others 2002). There still remains some controversy regarding the best prognostic model following a recent study which failed to identify any single variable to predict mortality following salvage TIPSS (Azoulay and others 2001). The utility of such models is limited as many clinicians even knowing the likely poor outcome would proceed with salvage therapy.

Table 9: Studies utilising TIPSS as “rescue” therapy for variceal bleeding.

Author	No. Patients	% patients with Pugh Class C disease	Previous endoscopic treatment	Initial haemostasis (%)	Rebleeding (%)	Mortality (%)
LaBerge et al, 1993	32	N/a	ES	97	N/a	N/a
Haag et al, 1993	19	68	N/a	100	11	26 (30 days)
Helton et al, 1993	23	78	ES	N/a	N/a	56 (in hospital)
Le Moine et al, 1994	4	N/a	ES	N/a	N/a	75 (30 days)
Rubin et al, 1995	12	N/a	ES/VBL	75	N/a	N/a
Jalan et al, 1995	19	68	ES	100	16	42 (30 days)
Jabbour et al, 1996	25	48	ES	96	N/a	44 (30 days)
Sanyal et al, 1996	30	73	ES	100	7	40 (6 weeks)
Perarnau et al, 1997	48	56	ES	92	9	25 (30 days)
Banares et al, 1998	56	41	ES	95	14	15 (30 days)
Gerbes et al, 1998	11	64	ES/VBL	91	27	27 (30 days)
Chau et al, 1998	112	71	ES	96	OV 13	37 (30 days)
	(OV 84, GV 28)	(OV 75, GV 61)			GV 14	(OV 34, GV 42)
Barange et al, 1999	32	47	ES	90	14	25 (30 days)
Bizzollon et al, 2001	28	61	ES/VBL	96	8	25 (40 days)
Azoulay et al, 2001	58	81	ES	90	6	29 (30 days)

ES – endoscopic sclerotherapy; VBL – variceal band ligation; OV – oesophageal varices; GV – gastric varices.

Prevention of variceal rebleeding

Endoscopic therapies versus TIPSS

There are 13 trials comparing endoscopic therapies (usually injection sclerotherapy) with TIPSS for the management of variceal bleeding and especially rebleeding (Table 10) ([Anon] 1995; Cabrera and others 1996; Cello and others 1997; Rossle and others 1997; Jalan and others 1997a; Sauer and others 1997a; Sanyal and others 1997d; Merli and others 1998; Garcia-Villarreal and others 1999; Sauer and others 2000; Narahara and others 2001; Pomier-Layrargues and others 2001; Gulberg and others 2002). One of these studies has been published in abstract form ([Anon] 1995). In most trials TIPSS was also used to rescue refractory bleeders in the endoscopic therapy arm (Cabrera and others 1996; Cello and others 1997; Rossle and others 1997; Sanyal and others 1997a; Jalan and others 1997a; Merli and others 1998; Garcia-Villarreal and others 1999; Sauer and others 2000; Narahara and others 2001; Pomier-Layrargues and others 2001; Gulberg and others 2002).

The variceal rebleeding rate of 19% in the TIPSS arm compares favourably with 47% in the endoscopic therapy arm (Papatheodoridis and others 1999). Taking all the 13 trials together the number needed to prevent one variceal rebleeding episode is 4 (Burroughs and Vangeli 2002). A reduced rate of rebleeding is demonstrated by all but 2 studies which showed similar efficacy of TIPSS and endoscopic therapy (Sanyal and others 1997b; Gulberg and others 2002). The rate of rebleeding appears to be related to the Pugh score, although the results with surgical shunts are better (Rosemurgy and others 1996). The majority of rebleeding episodes are related to shunt

insufficiency, which is reflected in the high early rebleeding rates in most trials.

However, there appears to be no benefit of TIPSS over endoscopic therapy in overall rates of mortality (27.3% versus 26.5% respectively) (Papatheodoridis and others 1999). The risk of rebleeding and death was highest in the trials with $\geq 40\%$ patients in Pugh class C. A recent retrospective study over an 11-year period in our unit identified this group to have a lower mortality than those treated with endoscopic therapy for variceal haemorrhage (Jalan and others 2002). We currently do not use TIPSS to prevent rebleeding in Child Pugh A patients. The cost of endoscopic therapy and TIPSS is similar because TIPSS is so much more effective in reducing rebleeding and the potential need for very expensive intensive care unit bed.

Table 10: Studies comparing TIPSS versus endoscopic therapy for the prevention of variceal rebleeding.

Trial	% with Child C disease	ET arm	Variceal rebleeding		Death		Encephalopathy	
			TIPSS	ET	TIPSS	ET	TIPSS	ET
Cabrera, 1996	9.5	Sclerotherapy	7/31	16/32	6/31	5/32	10/31	4/32
Rosle, 1997	18.3	Sclerotherapy or VBL + propranolol	9/61	29/65	8/61	8/65	18/61	9/65
Sanyal, 1997	48.8	Sclerotherapy	9/41	8/39	12/41	7/39	12/41	5/39
Cello, 1997	N/A	Sclerotherapy	3/24	12/25	8/24	8/25	12/24	11/25
Sauer, 1997	24.1	Sclerotherapy + propranolol	6/42	21/41	12/42	11/41	14/42	3/41
Jalan, 1997	48.3	VBL	3/31	15/27	13/31	10/27	5/31	3/27
Merli, 1998	12.3	Sclerotherapy	7/38	17/43	9/38	8/43	21/38	10/43
Garcia-Villareal, 1999	30.4	Sclerotherapy	2/22	12/24	3/22	8/24	5/22	6/24
GEAII, 1995	100	Sclerotherapy + propranolol	13/32	20/33	16/32	14/33	Not available	Not available
Pomier-Layrargues, 2001	53.8	VBL	8/41	22/39	17/41	16/39	15/41	16/39
Gulberg, 2002	11.1	VBL	7/28	7/26	4/28	4/26	2/28	1/28
Narahara, 2001	NA	Sclerotherapy	7/38	13/40	11/38	7/40	13/38	6/40
Sauer, 1998	NA	VBL	7/43	18/42	11/43	12/42	16/43	9/42

ET – Endoscopic therapy. VBL – variceal band ligation.

Pharmacological agents compared with TIPSS.

The only publication is a study recently published, which randomised patients to either TIPSS only (n = 47) or propranolol plus ISMN combination therapy (n = 44) (Escorsell and others 2002). The TIPSS arm had significantly fewer episodes of rebleeding (13% vs. 39%, $p = 0.007$), but encephalopathy was significantly higher in the shunted group (38% vs. 14%, $p = 0.007$). Mortality was similar for both groups. The cost of TIPSS was more than twice that of drug therapy. Interestingly, the drug treated arm has more frequent improvement in the Pugh score during follow up. This finding is not fully explained by the authors, and it would have been useful to know how many of the patients with alcoholic liver disease remained abstinent in each arm.

It should be emphasised that the addition of propranolol to endoscopic therapy does to confer any benefit over endoscopic therapy alone, although the incidence of encephalopathy is less (Rossle and others 1997; Sauer and others 1997a; Sauer and others 2002). However, outside of clinical trials it is unlikely that most patients will comply fully with follow up banding sessions and drug therapy particularly those patients with alcoholic cirrhosis.

TIPSS versus surgery

The use of surgical shunts is limited by the very high mortality rates in patients with advanced liver disease. Early experience strongly favored the use of TIPSS over oesophageal transection, with the latter associated with a

higher mortality and rate of infection (Jalan and others 1995b), despite similar efficacy as TIPSS in the prevention of variceal rebleeding. This probably reflects the fact that most patients referred for a TIPSS had advanced liver disease, thus making such major surgery particularly hazardous. The only randomised controlled study comparing shunt surgery using a portocaval H-graft with TIPSS revealed more episodes of variceal rebleeding in the TIPSS arm (11% versus 0%), although the technical success of the TIPSS procedure was poorer than with most other series (Rosemurgy and others 1996). It is also noteworthy that the average portal pressure following TIPSS insertion was high at 25 ± 7.5 mm Hg. Others have looked at distal splenorenal shunt (DSRS) surgery versus TIPSS in a non-randomised study of cirrhotic patients in Pugh class A & B (Khaitiyar and others 2000). The results were in favor of surgery with lower rates of rebleeding (6.3% vs. 25.7%), encephalopathy ((18.8% vs. 42.9%), and shunt dysfunction (6.3% vs. 68.6%). There was no difference in survival (6.2% versus 5.7%). From the limited data it appears that surgery may be better suited to patients in Pugh class A to B, with TIPSS being used in patients with more severe liver disease who would not normally be candidates for shunt surgery.

TIPSS for the management of gastric variceal bleeding

The management of bleeding gastric varices has been a particular challenge to clinicians. The risk of bleeding from gastric varices is less than that of oesophageal varices, the outcome once bleeding has occurred is worse, particularly for isolated gastric varices (IGV) (Sarin and others 1992).

Historically the management of gastric variceal bleeding has been sub optimal. Endoscopic measures have met with varying degrees of success (Ramond and others 1986; Gimson and others 1991), although current UK guidelines recommend endoscopic treatment as the first line in the management of the acute gastric variceal bleed (Jalan and Hayes 2000). Iatrogenic complications such as embolic phenomena and the potential for equipment damage may limit the use of tissue adhesives (See and others 1986; Lee and others 2000). Thrombin seems to be promising (Przemioslo and others 1999), but large multi centre controlled trials have yet to emerge (Williams and others 1994; Yang and others 2002). Two of the previous studies have used bovine thrombin which has the potential risk of prion transmission (Williams and others 1994; Przemioslo and others 1999). Surgical shunts may be of value in patients with early liver disease (Thomas and D'Cruz 1994), but have the disadvantage of high mortality in patients with advanced liver disease particularly in the emergency setting.

Due to gastric variceal haemorrhage being relatively uncommon, there are relatively few studies looking at the efficacy of TIPSS in bleeding gastric varices, and no controlled studies. Previous work has demonstrated that TIPSS was equally effective in the management of bleeding from either gastric or oesophageal varices (Stanley and others 1997a). The complications of TIPSS such as encephalopathy and shunt dysfunction were also similar. TIPSS has recently been studied in the management of refractory variceal bleeding either from gastric alone (Barange and others 1999) or gastric compared with oesophageal varices (Chau and others 1998). The results suggest that TIPSS is effective in the arresting

haemorrhage from and prevention of rebleeding from gastric varices. Chau and colleagues also found that portal pressure in patients who had early rebleeding before 7 days was lower in patients with GVB (Chau and others 1998).

1.5.5 New developments.

TIPSS in combination with other therapies

One of the limitations of TIPSS is the high incidence of shunt insufficiency and the need for lifelong invasive portography and intervention. There have been two recent studies investigating the effect of adjuvant drug therapy in patients with an insufficient TIPSS (Brensing and others 2002; Bellis and others 2003). The administration of intravenous propranolol in the presence of an insufficient TIPSS resulted in a significant reduction in the PPG of 30%, although the effect was not so pronounced in those patients with severe shunt insufficiency. A second study confirmed these findings with propranolol, although no effect was seen with nitrates. Both these studies were uncontrolled, and no data was available on the incidence of variceal bleeding. If controlled studies are favourable, the addition of drug therapy to reduce the need for shunt surveillance sounds attractive. However, it is likely only to be of temporary benefit. In addition, the side effect profile of propranolol is not favorable in our experience, and compliance could be a major problem (Luo and others 1998).

Covered stents

The idea of covering the stent to reduce clotting and intimal hyperplasia, comes from cardiovascular medicine where it has been successful. Early results with covered TIPSS using Dacron were rather disappointing, possible due to its non-biocompatible nature (Otal and others 1999). Subsequent studies using polytetrafluoroethylene (PTFE) have been more successful. The Viatorr endoprosthesis is made of titanium, which supports a reduced permeability expanded PTFE graft with a bile resistant membrane. It comprises a 2cm unlined distal section, and a lined section available in 4-8 cm lengths, separated by a radio opaque marker (Figure 5a). It is available in 8, 10, and 12mm diameters. Unlike uncovered stents (Figure 5b), the length of the tract is determined prior to stent deployment. This is measured using a catheter with markings at 1 cm intervals. The aim is to cover the entire tract from the portal vein entry point to the inferior vena cava. This is likely to favor the patency of the Viatorr stents by reducing the risk of hepatic vein stenosis. Encouraging results in animals (Nishimine and others 1995; Haskal and others 1997) have been reproduced in humans in small uncontrolled studies (Saxon and others 1997; Haskal 1999; Cejna and others 1999; Andrews and others 1999; Rose and others 2001; Cejna and others 2002; Otal and others 2002). Overall the results are impressive, with primary patency rates between 80-100%. Our results on a 100 patients with the Viatorr endoprosthesis showed a primary patency of 92%, and variceal rebleeding rate of 9.5% over an average follow up period of 10 months (Barkell et al, Abstract in press). The rates of encephalopathy were comparable to standard uncovered TIPSS. The main reasons for shunt insufficiency seem to be inadequate covering of the tract

in the hepatic vein, resulting in hepatic vein stenosis. In some cases we had to use an uncovered stent to extend the tract to the hepatic vein, and this was another source of shunt insufficiency. However, the absence of shunt thrombosis in our series is remarkable. Interim results of a randomised controlled trial also show excellent shunt patency (Bureau and others 2002b). Clearly if in the final analysis the results are favorable, there may be much reduced need for long-term portographic surveillance.

A potential complication of PTFE covered stents is the development of segmental hepatic ischaemia, which has been reported in a small number of patients (Bureau and others 2002a; Laberge and Kerlan 2003). This arises from extending the tract to the hepatic vein almost as far the IVC, resulting in a partial Budd Chiari like syndrome. Some patients reported abdominal pain, and were found to have abnormalities on the CT scan. In all cases patients were managed conservatively, and did not have long-term complications. We have had experience of one asymptomatic patient who was noted to have an abnormal area of low attenuation in a CT scan. These changes resolved on further scanning 3 months later, probably as a result of collaterals. It is therefore important to bear in mind this complication, particularly since there is the need to extend the tract to the hepatic vein to ensure good patency.

Figure 5a: Viatorr Gore type of covered stent

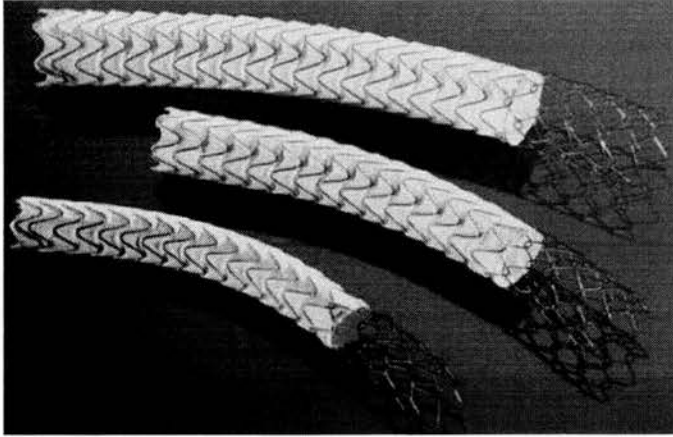
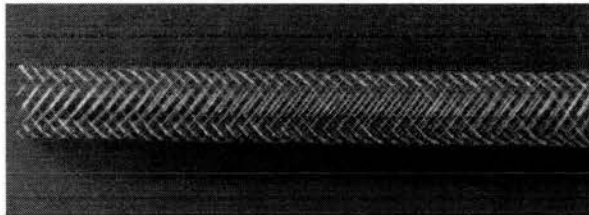


Figure 5b: Standard Wallstent



Chapter 2

Methods

2.1 Methods of haemodynamic monitoring.

All haemodynamic measurements are performed under controlled conditions with the patient in the supine position using fluoroscopic guidance. The following measurements are performed:

2.1.1 Hepatic venous pressure gradient (HVPG).

After infiltration with 10ml 2% lignocaine a 7 FG venous introducer (Cordis, USA) is inserted into the right femoral vein using the Seldinger technique. Under fluoroscopic guidance either a Swann Ganz catheter (Baxter Healthcare Corporation, USA) or the Sidewinder II torque balloon catheter (Cordis Corporation, USA) is inserted through the main right hepatic vein for the measurement of the free and wedged hepatic venous pressures (FHVP and WHVP). The HVPG is derived from these values as the WHVP minus FHVP. All haemodynamic measurements are taken in triplicate, with the mean of these values being used for analysis.

2.1.2 Systemic and cardiac haemodynamics.

The same standard Swann Ganz catheter is used to measure the right atrial pressure, the cardiac output, and pulmonary artery pressures. The cardiac output is measured using the standard thermodilution technique. The mean arterial pressure (MAP) was measured using an automatic sphygmomanometer (Hewlett Packard series 54 model 78339A) and was calculated as $(\text{Pulse Pressure}/3) + \text{Diastolic blood Pressure}$. The systemic vascular resistance (SVR) is calculated as $(79.96 ((\text{MAP} - \text{RAP (right atrial pressure)}) / \text{CO (cardiac output)}))$.

2.1.3 Hepatic blood flow.

Hepatic blood flow (HBF) was derived from measurements of the indocyanine green (ICG, Akorn) clearance and extraction. ICG was infused at the beginning of the study as a 10mg intravenous bolus via a peripheral cannula followed by an infusion of 0.2mg/min ICG (Caesar and others 1961). After an equilibration time of 40 minutes three samples were taken simultaneously from the right hepatic vein and femoral vein. The peripheral and hepatic samples were centrifuged at 1500g for 20 minutes, and the optical density of the supernatant determined. The value for optical density was then plotted on a standard graph and the % concentration extrapolated (Figure 6). The following formula was next used to calculate HBF:

$$\begin{aligned} \text{HBF} &= (\text{ICG Clearance} / \text{ICG Extraction}) / (1 - \text{Haematocrit}) \\ &= (Q / (C_p - C_h)) / (1 - \text{Haematocrit}) \end{aligned}$$

Q is the infusion rate of ICG at 0.2 mg/min. C_p and C_h are peripheral and hepatic % concentrations of ICG derived as above. The final value for HBF has to be multiplied by a factor of 100 to derive HBF in ml/min. This method cannot be used if $C_p - C_h$ is less than 10% i.e. hepatic excretion less than 10%.

2.1.4 Analyses of neurohumeral agents.

Venous blood was sampled after the patient was in the supine position for 30 mins for baseline biochemical and haematological measurements. Ten ml was admixed with 0.5 ml of 0.45% O-phenanthroline/4.65% disodium

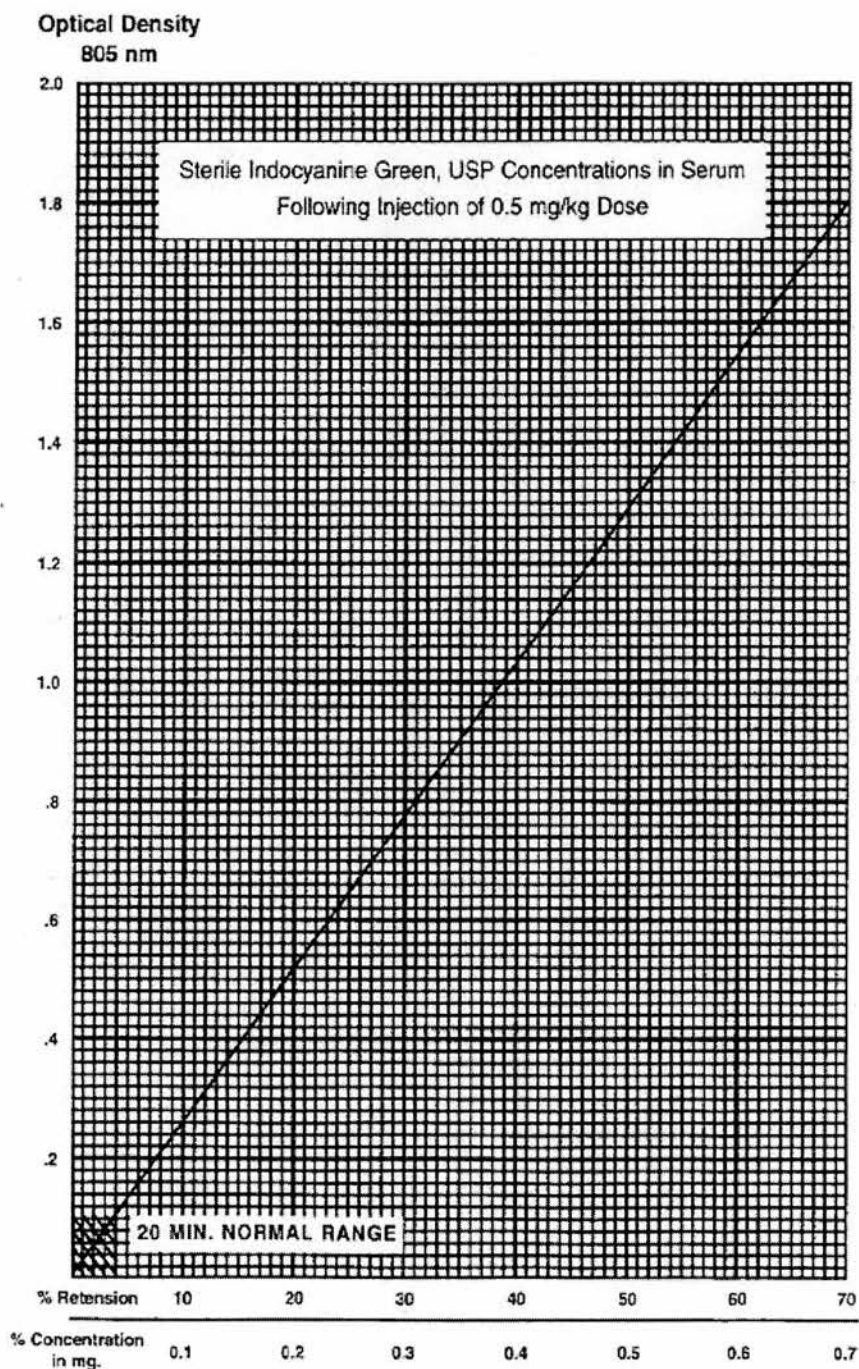
EDTA for measuring ANG II concentration, and 1 ml of 1% disodium EDTA and 1000 KIU aprotinin (Bayer AG, Leverkusen, Germany) for measuring plasma renin activity (PRA). The samples were placed on ice and immediately centrifuged at 1500g for 20 minutes. Plasma was frozen and stored at -80°C until assayed. Plasma ANG II concentrations were measured by radioimmunoassay following extraction using Bond Elut columns (Varian, Harbor City, CA) as previously described (Morton and Webb 1985). PRA was measured under standard conditions through the generation of ANG I using radioimmunoassay as previously described (Haber and others 1969). Aldosterone levels were obtained from samples of plasma analysed from frozen with a commercial radioimmunoassay (Peninsula Laboratories, California, USA) using a technique previously described (Demers and others 1976).

2.1.5 Assessment of renal function.

Urine was collected over a 24-hour period to measure creatinine clearance and urinary sodium excretion. 24 hour creatinine clearance in mL/min was calculated as:

$$(\text{Urine creatinine} \times \text{urine volume in 24 hours}) / (\text{serum creatinine} \times 1440)$$

Figure 6: Graph used to extrapolate % concentration of indocyanine green (ICG, Akorn) from optical density of the supernatant from samples of peripheral and hepatic blood after infusion of ICG.



2.2 Transjugular intrahepatic portosystemic stent-shunt (TIPSS).

2.2.1 Insertion of TIPSS.

TIPSS is a non-surgical means of diverting blood from the portal circulation through the hepatic parenchyma to the systemic circulation, thereby creating a portosystemic shunt (Chalmers and others 1992). The internal jugular vein is first entered percutaneously, and a catheter is passed through the superior vena cava, right atrium, inferior vena cava, and in most cases the right hepatic vein under fluoroscopic guidance. A needle is inserted through the catheter to puncture the hepatic parenchyma, creating a tract to link the hepatic vein and usually right portal vein. This tract is kept patent by using an expandable metal stent. These stents included Palmaz stents (Johnson & Johnson, Norderstedt, Germany) , the newer covered stents (Wallgraft, Boston Scientific, Boston, Mass or Jostent, Jomed, Zurich, Switzerland or the latest Viatorr Gore PTFE stents), and Wallstents (Boston Scientific, Boston, Mass, USA). All patients had intravenous Cefotaxime 1 hour pre- and for 48 hours post-procedure.

2.2.2 Follow up and shunt surveillance.

Doppler ultrasound was performed at 1 week. Urgent portography was carried out if there was Doppler evidence of shunt dysfunction, or if there was clinical evidence of shunt dysfunction, such as variceal rebleeding or increased ascites. Intervention at portography includes balloon angioplasty, shunt extension, or insertion of a parallel shunt. All subjects are followed up

at 4-6 month intervals with full clinical, haematological and biochemical assessment, until death, liver transplantation, or loss to follow up. Routine portography was performed six monthly where possible, or at other times if there was clinically indicated.

2.2.3 Definitions.

Variceal rebleeding

Any subsequent haematemesis or melaena with a 20 g/L reduction in haemoglobin requiring an unscheduled endoscopy. Non-variceal causes of rebleeding were also documented.

Early mortality

Death within 6 weeks of the index variceal bleed.

Shunt insufficiency

An increase in the portal pressure gradient (PPG) to > 12 mm Hg or an increase in the PPG > 20% from the post-TIPSS value where the pre-TIPSS value is < 12 mm Hg. (Jalan and others 1997b). The Doppler criteria for shunt insufficiency is a peak velocity of ≤ 90 cm/s (Ferguson and others 1995; Jalan and others 1998).

Primary patency

The absence of shunt insufficiency without intervention during TIPSS surveillance.

Secondary assisted patency

The absence of shunt insufficiency with intervention.

Successful portal pressure reduction

PPG immediately post-TIPSS of < 12 mm Hg (where PPG pre-TIPSS > 12 mm Hg) or a > 20% reduction in the PPG pre-TIPSS (where PPG pre-TIPSS < 12 mm Hg).

CHAPTER 3

**Haemodynamic effects of low dose carvedilol, a vasodilating
beta-blocker in patients with cirrhosis and portal
hypertension.**

3.1 Introduction.

Carvedilol is a non-selective beta-blocker with vasodilating properties as a result of weak α_1 antagonism and calcium channel antagonism. Its effect on portal hypertension has been studied in several clinical studies as previously mentioned, with the main findings being of a reduction of the HVPG of between 20 – 28%, at the expense of systemic side effects on account of the significant reduction in the MAP (Forrest and others 1996a; Stanley and others 1999; Banares and others 1999). Lower doses have also produced a significant portal hypotensive effect, although a short follow up limited the assessment of the tolerability of Carvedilol (De and others 2002).

The aim of this study was to investigate the acute and chronic effects at a low dose of 12.5 mg per day of carvedilol on portal and systemic haemodynamics. Patient tolerability was also assessed at this dose over a 4 week period.

3.2 Patients and methods.

10 patients, 7 male and 3 female with a mean age of 53 ± 4.0 years, were recruited, all of whom had biopsy proven or clinical, biochemical and ultrasonographic evidence of cirrhosis. Eight patients had alcoholic liver disease, one patient had primary biliary cirrhosis, and one hepatitis C virus related cirrhosis. Seven patients had Child-Pugh grade B disease, 1 grade A, and 2 grade C. Six patients had ascites at the time of the study or in the past. All patients had gastroesophageal varices, with none having bled. All patients gave informed consent and the study was approved by the Lothian Medicine and Oncology Ethics Committee. The study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

All patients had baseline haemodynamic measurements performed following an overnight fast. They were then administered 12.5mg of oral carvedilol (Roche Pharmaceuticals) and haemodynamic measurements were repeated after one hour. After completion of the acute study, patients were instructed to take 12.5mg of carvedilol daily at 09:00 for four weeks, after which time the haemodynamic measurements were repeated before and one hour following the administration of 12.5mg of carvedilol as per initial protocol. There was no change in the observed alcohol consumption for the duration of the study. There were no detectable serum ethanol levels prior to each study or during follow up.

3.2.1 Haemodynamic study protocol.

Haemodynamic measurements were performed with the patient in the supine position. The HVPG, MAP, RAP and HBF were measured using the techniques mentioned earlier. The CO was measured using the standard thermodilution technique. SVR was derived from these measurements.

3.2.2 Statistical analysis.

All results are expressed as mean \pm SEM. Parametric data were analysed using the paired Student *t*-test and the Pearson's correlation. Wilcoxon signed rank test and Spearman correlation were used for non-parametric data. Significance was taken at the 5% level. Microsoft Excel 2000 and SPSS packages (version 9, Chicago, Illinois, USA) were used for statistical analysis.

3.3 Results.

Nine patients completed both the acute and chronic studies. One male patient with Child's C disease who had a hypotensive reaction to acute dosing with carvedilol, and developed an alcoholic hepatitis, completed only the acute phase of the study.

3.3.1 Portal haemodynamics.

Following acute administration of carvedilol, there was a 23.9% reduction in the HVPG (from 16.37 ± 2.14 to 12.56 ± 3.91 mmHg; $p < 0.05$), due principally to a reduction in WHVP (from 22.03 ± 1.28 to 16.86 ± 1.15 mmHg; $p < 0.01$) with no significant change in the FHVP (Table 11).

Chronic administration resulted in a sustained and even greater fall in the HVPG from the baseline average value of 16.37 ± 0.71 to a predosing value following chronic dosing of 9.27 ± 1.40 mmHg ($p < 0.001$, -43.4%). In all cases except one there was a $\geq 20\%$ reduction in the HVPG after chronic dosing. There was no additional effect on the HVPG following rechallenge with carvedilol (Figures 7, 8, 9, 10).

3.3.2 Hepatic blood flow.

ICG clearance and extraction was measured in five patients (Table 11). In the acute phase of the study, there was a significant reduction in HBF from 1725 ± 435 to 718 ± 179 mL/min ($p < 0.05$, $n=5$) following acute administration. Following chronic dosing one patient had an initial ICG extraction $< 10\%$, therefore HBF could not be calculated. There was no further significant reduction in the HBF following chronic administration or rechallenge with carvedilol ($n = 4$).

3.3.3 Systemic haemodynamics.

The MAP fell acutely from 90.33 ± 4.95 to 81.56 ± 5.84 mmHg ($p < 0.01$), but with chronic administration and rechallenge there was no additional change. The CO also fell acutely with no additional effect after chronic dosing or rechallenge. The heart rate (HR) fell acutely and with chronic dosing, but was unaffected following rechallenge with carvedilol. The RAP fell acutely and following rechallenge. SVR was unaffected. The changes in HVPG did not correlate with changes in the MAP, CO, HR or RAP.

3.3.4 Effect on hepatic and renal function.

The serum ALT, bilirubin, creatinine and clotting parameters were unaffected by chronic administration.

3.3.5 Tolerability.

No side effects were reported except in 1 patient who experienced palpitations, and no patients were withdrawn because of side effects. The patient who became hypotensive after acute dosing experienced a fall in the MAP from 64mm/Hg to 57 mm/Hg. He successfully completed the acute study and remained asymptomatic. His blood pressure normalised after 3 hours and following colloid administration.

There were 6 patients with a history of ascites although only 4 had ascites at the time of the study, which limited valid statistical analysis. These patients exhibited a similar reduction in HVPG following acute and chronic dosing of 26.41% and 38.38% respectively. There was no significant reduction in

the MAP (-1.23%). No patients experienced deterioration in ascites or renal function during follow up.

Table 11: Haemodynamic data following acute and chronic dosing of carvedilol. The first baseline refers to measurements performed before drug administration. The second baseline refers to measurements performed after 4 weeks administration of 12.5 mg/day carvedilol. +60 mins refers to the measurements performed 60 minutes following administration of 12.5 mg carvedilol at the index visit, and following rechallenge after chronic drug administration.

	ACUTE DOSING		AFTER CHRONIC DOSING	
	Baseline	+60mins	Baseline	+60mins
HVPG (mmHg)	16.37 ± 0.71 ^a	12.56 ± 1.30*	9.27 ± 1.40 ^b	10.27 ± 1.16
WHVP (mmHg)	22.03 ± 1.28	16.86 ± 1.15 [‡]	16.92 ± 1.65	16.98 ± 1.47
FHVP (mmHg)	5.67 ± 1.03	4.3 ± 0.56	7.59 ± 0.93	6.64 ± 1.00 [‡]
HR (bpm)	88.33 ± 5.81	79.11 ± 4.93 [‡]	71.78 ± 4.62	71.89 ± 4.93
MAP (mmHg)	90.33 ± 4.95	81.56 ± 5.84 [‡]	85.67 ± 4.29	83.22 ± 3.76
CO (l/min)	7.11 ± 0.93	6.29 ± 0.75*	6.72 ± 0.77	6.74 ± 0.84
RAP (mm/Hg)	3.22 ± 1.02	1.22 ± 0.57*	6.00 ± 1.22	3.33 ± 1.18 [‡]
SVR (dyn.Cm)	1111 ± 138	1118 ± 131	1151 ± 112	1156 ± 164
HBF (mL/min)	1725 ± 435	718 ± 179* [†]	539 ± 99	720 ± 203 [∇]

Mean ± SE.

MAP: mean arterial pressure. HR: heart rate. WHVP: Wedged hepatic venous pressure. FHVG: Free hepatic venous pressure HVPG: hepatic venous pressure gradient. CO: cardiac output. SVR: systemic vascular resistance. RAP: right atrial pressure. HBF: hepatic blood flow.

N = 9 unless otherwise stated

α - β - $p < 0.001$

[‡] - $p < 0.01$ compared to baseline

* - $p < 0.05$ compared to baseline

[†] - n=5 ∇ - n=4

Figure 7: Effect on hepatic venous pressure gradient following chronic dosing of carvedilol. Baseline refers to measurements at the index visit prior to drug administration. Chronic 1 refers to measurements after 4 weeks administration of 12.5 mg/day of carvedilol before rechallenge with the drug.

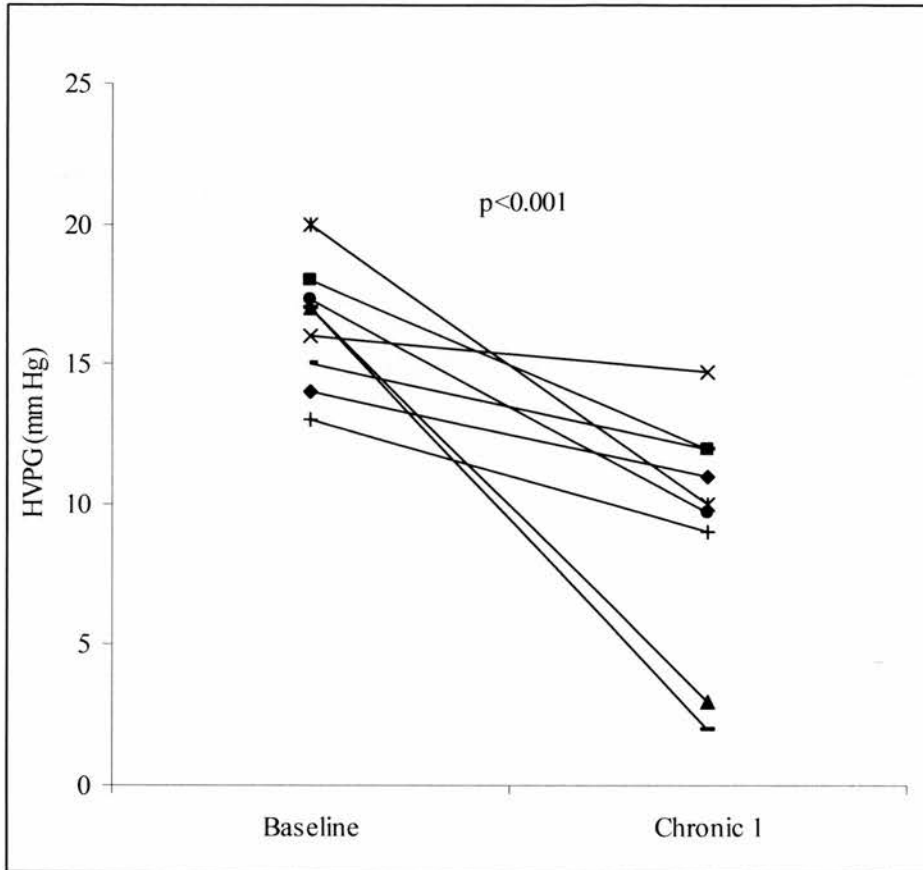


Figure 8: Overall effect of carvedilol on hepatic venous pressure gradient. Baseline refers to the index value prior to drug administration. Acute refers to + 60 minutes after first dose. Chronic 1 and chronic 2 refer to measurements after 4 weeks administration of 12.5 mg/day of carvedilol before and after rechallenge with the drug.

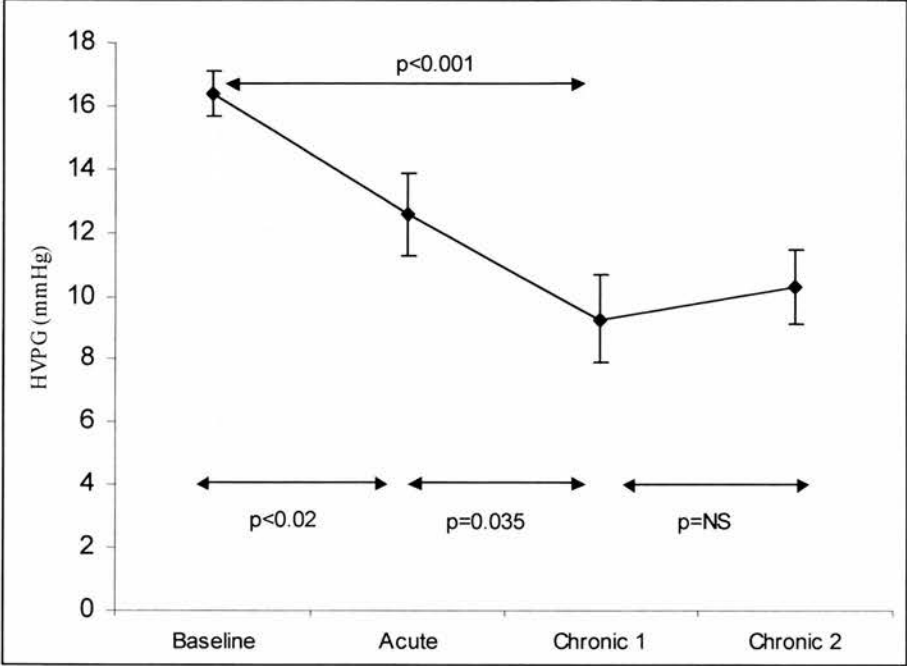


Figure 9: Acute haemodynamic effects of carvedilol. The values represent % change 60 minutes following administration of 12.5 mg of carvedilol at the index visit. MAP: mean arterial pressure. HR: heart rate. HVPG: hepatic venous pressure gradient. CO: cardiac output. SVR: systemic vascular resistance.

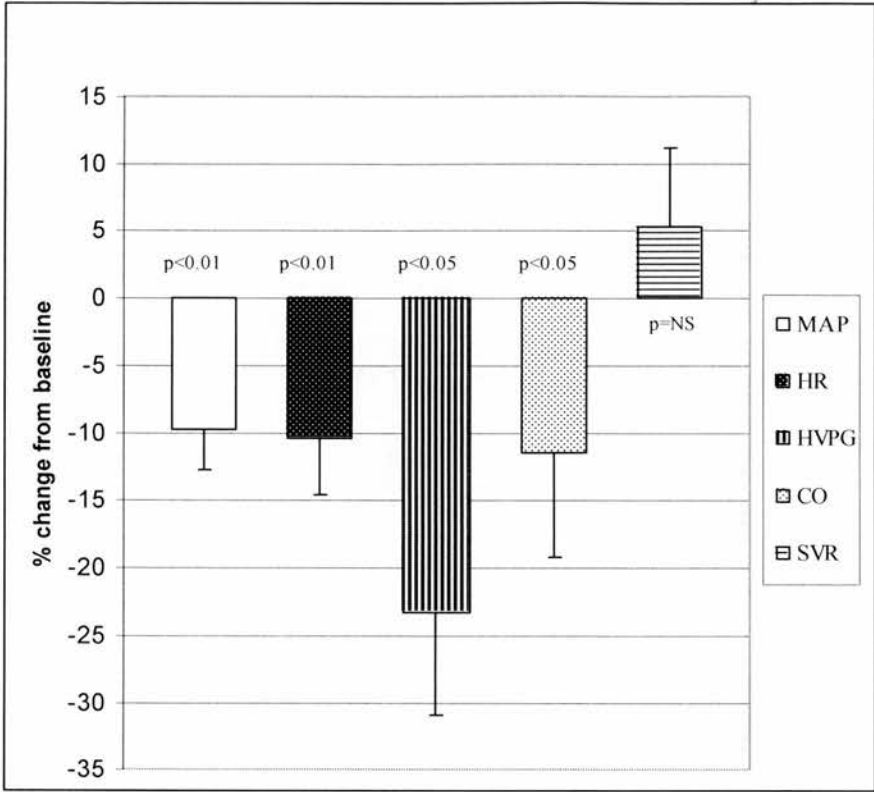
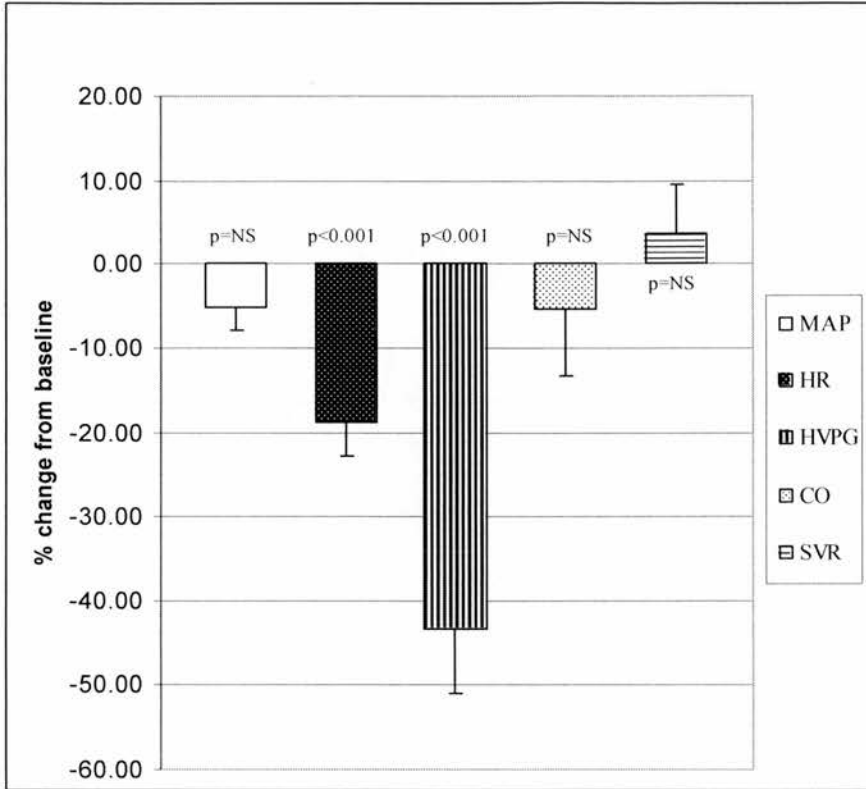


Figure 10: Haemodynamic effects of carvedilol following chronic dosing. The values represent % change of measurements at the index visit prior to drug administration and at the second visit following 4 weeks of 12.5 mg/day of carvedilol prior to rechallenge i.e. % difference between baseline and chronic 1 as in Figure 8. MAP: mean arterial pressure. HR: heart rate. HVPG: hepatic venous pressure gradient. CO: cardiac output. SVR: systemic vascular resistance.



3.4 Conclusions.

This study demonstrates the significant portal hypotensive effect of low dose carvedilol, which compares favourably with propranolol. This effect is achieved with minimal detrimental effects on the systemic circulation.

Carvedilol should be considered for use in large randomised controlled trials for the prevention of the first variceal bleed.

CHAPTER 4

Haemodynamic effects of losartan, an angiotensin II receptor antagonist, in patients with cirrhosis and portal hypertension.

4.1 Introduction.

Plasma ANG II concentrations are elevated in cirrhosis and have been implicated as a cause of portal hypertension. There is conflicting evidence regarding the efficacy and tolerability of losartan, a specific AT1 receptor antagonist with no agonist activity, in patients with cirrhosis and portal hypertension (Schneider and others 1999; Gonzalez-Abraldes and others 2001). We aimed to study both the systemic and portal haemodynamics and tolerability after chronic administration of losartan in patients with pre-ascitic cirrhosis.

4.2 Patients and methods.

Twelve patients with biopsy, radiological, biochemical or clinical evidence of cirrhosis were recruited. The baseline characteristics are summarised in Table 12. All the patients were pre-ascitic, and were on no diuretics or other vasoactive medication prior to and throughout the study period. Seven patients had oesophageal varices, 6 had Grade II and 1 had Grade III varices, with none having variceal bleeding in the past. All patients gave written informed consent, and the study was approved by the local research ethics committee. The study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki.

Baseline haemodynamic measurements were performed at 09:00 following an overnight fast. The patients were then instructed to take 25mg of losartan (Cozaar, Merck Sharp & Dohme Limited, NJ, USA) at 21:00 hours for four weeks. Schneider and colleagues (Schneider and others 1999) demonstrated a significant effect on portal hypertension with the 25 mg dose, hence the

use of this dose. Patients were followed up at 2 weeks in the clinic for assessment of side effects, blood pressure, serum creatinine and liver function. After 4 weeks of treatment, the haemodynamic measurements were repeated as in the initial protocol. There was no change in the observed alcohol consumption for the duration of the study. There were no detectable serum ethanol levels prior to each study or during follow up.

4.2.1 Haemodynamic study protocol.

All blood sampling and haemodynamic measurements were performed in the hepatic haemodynamics suite in the supine position. The MAP, HVPG, RAP and HBF were measured according to methods mentioned earlier. The CO was measured using the standard thermodilution method. SVR was derived from these measurements as mentioned earlier.

4.2.2 Blood sampling and analysis.

Venous blood was sampled after the patient was in the supine position for 30 mins for baseline biochemical and hematological measurements. In addition, ANG II concentration, plasma renin activity (PRA), and aldosterone levels were measured by techniques described previously.

4.2.3 Assessment of renal function.

Prior to the first dose of losartan, urine was collected over a 24-hour period to measure creatinine clearance and urinary sodium excretion. After four weeks of administration of losartan, the urinary measurements were repeated.

4.2.4 Statistical Analysis.

All results are expressed as mean \pm SEM. Parametric data were analysed using the paired Student *t*-test and the Pearson's correlation. Wilcoxon signed rank test and Spearman correlation were used for non-parametric data. Significance was taken at the 5% level. The SPSS package (version 9, Chicago, Illinois, USA) was used for statistical analysis.

Table 12: Baseline characteristics.

Characteristic (n = 12)	
Sex (M/F)	7/5
Age (years)	53 ± 3
Child's class (A/B)	9/3
Child's Score	5.8 ± 0.3
Aetiology	
Alcoholic cirrhosis	5
Hepatitis C/B	3/1
Primary biliary cirrhosis	3

4.3 Results

All patients completed the study.

4.3.1 Hepatic haemodynamics and function.

After administration of losartan for 4 weeks there was no significant reduction in the HVPG (15.4 ± 1.5 to 13.6 ± 1.6 mm Hg, -11.7 %, $p = 0.1$), despite a significant reduction in the WHVP (20.3 ± 1.8 to 17.3 ± 1.8 mm Hg, -14.8 %, $p < 0.05$) (Table 11). In 5 cases there was a > 20 % reduction in the HVPG, while in 3 cases there was a reduction in the HVPG to ≤ 12 mm Hg in patients with a HVPG of > 12 mm Hg at baseline ($n = 10$). (Figure 11) In the first 3 patients repeat haemodynamic measurements performed at 60 minutes post dosage did not demonstrate any acute effect on the HVPG.

It was not possible to calculate the hepatic blood flow in 3 patients where the hepatic extraction of ICG was < 10%. In the remainder there was no change in the hepatic blood flow (552.5 ± 72.9 to 559.7 ± 106.6 mL/min, $n = 9$, $p = \text{NS}$).

The liver function tests in all patients were unaffected.

4.3.2 Systemic haemodynamics.

There was a significant reduction in the MAP (97 ± 3 to 89 ± 4.0 mm Hg, -7.8%, $p = 0.02$). There was no change in the heart rate, CO or SVR (Table 13).

4.3.3 Renal function.

The creatinine clearance was unaffected (90 ± 14 to 93 ± 19 mL/min, $P =$ NS, $n = 7$), as was the 24-hour urinary sodium excretion (154 ± 61 to 122 ± 36 mmol/day, $P =$ NS, $n = 5$).

4.3.4 Effect on the renin-angiotensin system.

There was a significant increase in the serum plasma renin activity from 2.7 ± 0.4 to 5.2 ± 1.1 ng/mL/hr after chronic dosing ($p < 0.05$) confirming activation of the renin-angiotensin system. There was a strong trend towards increased serum ANG II levels (8.0 ± 1.8 to 24.2 ± 8.5 pg/mL, $p = 0.08$). Serum aldosterone levels were unaffected (Table 13).

4.3.5 Tolerability.

One patient experienced symptomatic hypotension after the first dose of losartan, but elected to continue with the study and experienced no further symptoms. During follow up he was noted to have a 35% reduction in the MAP from 122 to 79 mm Hg. This patient was found subsequently to have systemic hypertension and commenced on drug therapy. There were no other side effects reported during follow up.

Table 13: Effects on haemodynamic and humoral mediators following chronic dosing

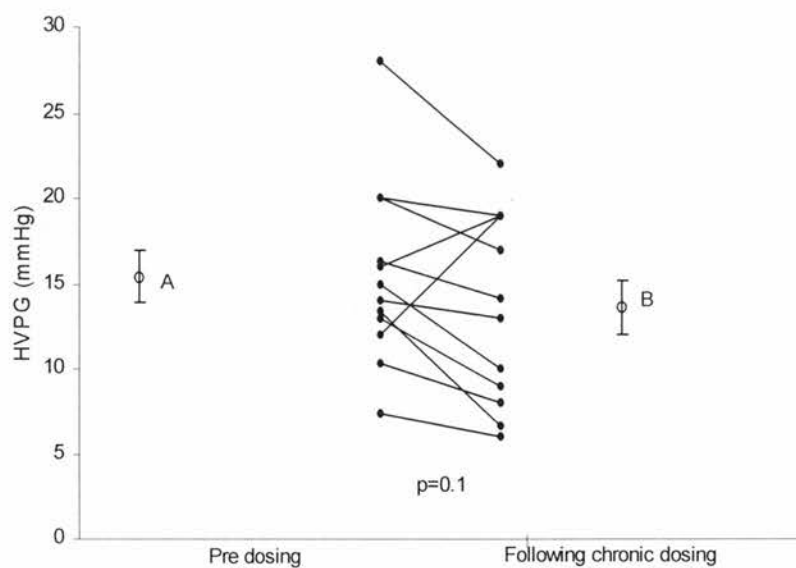
	Baseline	After 4 weeks
HVPG (mm Hg)	15.4 ± 1.5	13.6 ± 1.6
WHVP (mm Hg)	20.3 ± 1.8	17.3 ± 1.8*
FHVP (mm Hg)	4.9 ± 0.6	3.7 ± 0.7
HR (bpm)	88.3 ± 5.8	79.1 ± 4.9
MAP (mm Hg)	97 ± 3	89 ± 4*
CO (l/min)	5.8 ± 0.3	5.7 ± 0.3
SVR (dyn.Cm)	1324 ± 48	1240 ± 97
PRA (ng/mL/hr)	2.7 ± 0.4	5.2 ± 1.1*
ANG II (pg/mL)	8.0 ± 1.8	24.2 ± 8.5**
Aldosterone (pg/mL)	52.5 ± 12.8	77.5 ± 27.4

* : P < 0.05 compared with baseline.

** : P = 0.08 compared with baseline

HVPG: Hepatic venous pressure gradient. WHVP: Wedged hepatic venous pressure gradient. FHVP: Free hepatic venous pressure gradient, HR: Heart rate, MAP: Mean arterial pressure. CO: Cardiac output. SVR: Systemic vascular resistance. PRA: Plasma renin activity

Figure 11: Effect on hepatic venous pressure gradient following chronic dosing.



A: mean HVPG \pm SEM pre dosing

B: mean HVPG \pm SEM post chronic dosing

Values in the centre of the chart refer to individual patient data.

4.4 Conclusions.

Losartan, at the 25mg dose, appears to be well tolerated in patients with pre-ascitic cirrhosis. However, chronic administration did not result in a significant reduction in the HVPG. Therefore, losartan is unlikely to be effective for the prevention of variceal bleeding.

CHAPTER 5

**Transjugular intrahepatic portosystemic stent-shunt
for the management of variceal bleeding: clinical and
haemodynamic correlations.**

5.1 Introduction.

The management of gastric variceal bleeding remains a clinical challenge. Endoscopic treatments with sclerotherapy (Gimson and others 1991) have resulted in good initial haemostasis, but were marred by a high rebleeding rate. Recent evidence on the use of tissue adhesives (Zimmer and others 1998; Akahoshi and others 2002; Sarin and others 2002) and thrombin (Yang and others 2002; Heneghan and others 2002) for bleeding gastric varices are more promising.

TIPSS has been used extensively for the treatment for bleeding varices, with recent meta-analyses confirming its superior efficacy over endoscopic methods in preventing oesophageal variceal rebleeding, although mortality was unaffected and the rates of hepatic encephalopathy are higher with TIPSS (Papatheodoridis and others 1999; Burroughs and Vangeli 2002). There are relatively few studies on the use of TIPSS for bleeding gastric varices, although the available evidence is encouraging with the efficacy of TIPSS in preventing gastric variceal rebleeding as good as for oesophageal variceal bleeding (Stanley and others 1997a; Barange and others 1999; Albillos and Ruiz 1999).

Despite reports that varices bleed almost exclusively at portal pressures > 12 mmHg (Groszmann and others 1990), it has been shown that patients with directly measured PPG < 12mm Hg remain at risk of variceal bleeding (Jalan and others 1995c). Furthermore, it is recognised that gastric varices

occur at lower portal pressures than oesophageal varices (Watanabe and others 1988).

The aim of this study is to compare retrospectively the clinical outcome of patients who have bled from gastric and oesophageal varices requiring a TIPSS procedure. Haemodynamic and clinical correlations were made, and the patients who bled at PPG of < 12 mmHg were studied to identify whether they differed from the group who bled at higher portal pressures with regard to site of variceal bleed, rebleeding and survival.

5.2 Patients and methods.

Over a 9-year period, 436 patients underwent a TIPSS procedure in our centre. In 377 patients the primary indication was variceal haemorrhage with the remainder having ascites (n = 44) or portal hypertensive gastropathy (n = 9) or other indication (n = 6). Patients were excluded if the TIPSS procedure had failed (n = 24), if they had participated in a trial comparing TIPSS versus TIPSS and banding and were randomised to the TIPSS and banding arm (where TIPSS angiographic surveillance was performed for the first year after TIPSS only, n = 40), or if there was insufficient data (n = 21). After exclusions there were a total of 292 patients from which the study populations were selected.

In the eligible patients 40 had a TIPSS performed for gastric variceal bleeding (GVB), 232 for oesophageal variceal bleeding (OVB) alone, 12 for both gastric and oesophageal variceal bleeding and 8 for ectopic variceal bleeding. All varices were thought to have arisen because of portal hypertension secondary to parenchymal liver disease. In 38 cases of GVB bleeding was believed to have been from varices in the fundus or cardia, and 2 cases from varices along the lesser curve. Table 14 illustrates the baseline characteristics of these patients. There were more patients with cryptogenic cirrhosis in the OVB group.

Table 14: Baseline characteristics.

	Gastric varices (n = 40)	Oesophageal varices (n = 232)	Gastric & Oesophageal varices (n=12)	Ectopic varices (n=8)
Age	50.9 ± 1.6	53.6 ± 0.8	45.4 ± 5.4	52.5 ± 4.0
Sex				
Male	22 (55.0%)	150 (64.7%)	6 (50%)	4 (50%)
Female	18 (45.0%)	82 (35.3%)	6 (50%)	4 (50%)
Aetiology				
Alcoholic liver disease	28 (70.0%)	140 (60.3%)	5 (41.8%)	5 (62.5%)
Primary biliary cirrhosis	1 (2.5%)	28 (12.1%)	1 (8.3%)	0
Hepatitis C	1 (2.5%)	16 (6.9%)	2 (16.7%)	0
Cryptogenic cirrhosis	7 (17.5%)	18 (7.8%)**	1 (8.3%)	1 (12.5%)
Autoimmune	1 (2.5%)	8 (3.4%)	0	0
Cystic fibrosis	0	5 (2.2%)	1 (8.3%)	0
Primary sclerosing cholangitis	1 (2.5%)	4 (1.7%)	1 (8.3%)	2 (25%)
Hepatitis B	1 (2.5%)	4 (1.7%)	1 (8.3%)	0
Others	0	9 (3.9%)	0	0
Child Pugh Score	9.3 ± 0.5	9.8 ± 0.2	9.3 ± 0.7	10.9 ± 0.9
Portal Pressure Gradient (mm Hg)				
Pre TIPSS	15.8 ± 0.8	21.4 ± 0.5**	22.5 ± 3.0*	15.6 ± 2.5
Post TIPSS	6.7 ± 0.6	7.2 ± 0.3	7.1 ± 1.4	6.9 ± 1.9
Reduction post TIPSS	9.2 ± 0.8	14.2 ± 0.5**	15.4 ± 3.5*	8.8 ± 2.1
Median follow up (months)	36.7 ± 5.1	19.8 ± 1.3**	16.8 ± 5.1	8.1 ± 4.9*

* : p < 0.05 compared with gastric varices

** : p < 0.001 compared with gastric varices

Table 15: Patient characteristics depending on the portal pressure gradient at the time of TIPSS.

	Group 1 (n = 38)	Group 2 (n = 254)	P-value
Age (years)	54.9 ± 1.9	52.5 ± 0.8	N.S.
Sex			
Male	25 (65.8%)	157 (61.8%)	N.S.
Female	13 (34.2%)	97 (38.2%)	N.S.
Aetiology			
Alcoholic liver disease	27 (71.1%)	151 (59.4%)	N.S.
Primary biliary cirrhosis	3 (7.9)	27 (10.6%)	N.S.
Hepatitis C	0	20 (7.9%)	N.S.
Cryptogenic cirrhosis	5 (13.2%)	23 (9.1%)	N.S.
Autoimmune	1 (2.6%)	8 (3.1%)	N.S.
Cystic fibrosis	0	6 (2.4%)	N.S.
Primary sclerosing cholangitis	1 (2.6%)	7 (2.8%)	N.S.
Hepatitis B	1 (2.6%)	3 (1.2%)	N.S.
Others	0	9 (3.5%)	N.S.
Portal Pressure Gradient (mm Hg)			
Pre TIPSS	9.8 ± 0.4	22.1 ± 0.4	< 0.001
Post TIPSS	4.2 ± 0.5	7.6 ± 0.3	< 0.05
Reduction post TIPSS	5.6 ± 0.5	14.6 ± 0.5	< 0.001
Child Pugh Score	9.1 ± 0.5	9.9 ± 0.2	N.S.
Indication			
Oesophageal variceal bleeding	20 (52.6%)	212 (83.5%)	< 0.001
Gastric variceal bleeding	14 (36.8%)	26 (10.2%)	< 0.001
Gastric and oesophageal variceal bleeding	2 (5.3%)	10 (3.9%)	N.S.
Ectopic variceal bleeding	2 (5.3%)	6 (2.4%)	N.S.

Group 1: all patients with PPG ≤12 mmHg.

Group 2: all patients with PPG >12 mmHg.

In order to make haemodynamic and clinical correlations the patients were further divided into 2 groups according to the direct PPG at the time of index TIPSS. In addition to the patients in Table 14, these groups also incorporated those patients who bled from both oesophageal and gastric varices (n=12) and from ectopic varices (n=8). Group 1 included those patients with PPG \leq 12 mm Hg (n = 38), and group 2 those patients with PPG $>$ 12 mm Hg (n = 254). The baseline characteristics of these patients are detailed in Table 15. There was no difference in the age, sex, aetiology of liver disease or Child Pugh score of the two groups.

5.2.1 TIPSS procedure.

All patients were referred for a TIPSS from within the Royal Infirmary of Edinburgh, or from other hospitals within Scotland. Our unit operates a 24-hour facility for emergency TIPSS insertion. TIPSS insertion was performed by an experienced radiologist using an established technique (Chalmers and others 1992). Where the original pressure was $>$ 12 mm Hg the aim was to reduce the portal pressure gradient to below 12 mmHg. The patency of the TIPSS shunt was assessed by Doppler ultrasound within a week of insertion, and by portograms at 3 months then 6 monthly thereafter or whenever there were clinical features suggestive of shunt insufficiency.

5.2.2 Follow up.

The patients were followed up clinically at 3 monthly intervals to assess their clinical condition with emphasis being placed on any episodes of encephalopathy and variceal rebleeding. Early mortality, variceal rebleeding, and shunt insufficiency were defined as stated in chapter 2.

Follow up time was defined as the time interval in months between the initial TIPSS insertion to the most recent clinic review, liver transplantation, or death.

5.2.3 Statistical analysis.

All results are expressed as mean \pm standard error of mean (S.E.M) or percentage where indicated. Statistical significance for parametric data was determined using Students *t*-tests, and for non-parametric data using Chi Squared and Mann Whitney *U*-test. The Kaplan-Meier method was used to analyse patient survival, and cumulative rebleeding risk, with comparison between the two groups determined by the log rank test. Univariate and multivariate relations between survival and variables of interest in those patients who bled from gastric varices and oesophageal varices at PPG > 12 mm Hg was performed using Cox Regression analysis. These variables were: aetiology of cirrhosis (alcoholic or non-alcoholic), site of bleeding (from gastric or oesophageal varices), sex and age of patients, encephalopathy, ascites, bilirubin, prothrombin time, albumin, and the time interval between the index bleed and TIPSS insertion. Significance was taken at $p < 0.05$ for all tests. All statistical analysis was performed using the SPSS package (Version 10, SPSS Inc., Chicago, IL).

5.3 Results.

5.3.1 PPG pre and post TIPSS.

The PPG pre-TIPSS was significantly higher in patients with OVB compared with GVB (21.4 ± 0.5 versus 15.8 ± 0.8 mm Hg, $p < 0.001$).

Following TIPSS insertion all patients who had bled from gastric varices had the PPG reduced to < 12 mmHg, while in 22 (9.5%) patients who bled from oesophageal varices the post-TIPSS PPG was >12 mmHg. However, the mean PPG post-TIPSS was similar in the GVB and OVB groups. (Table 14)

5.3.2 Rebleeding.

The mean follow up period was 19.8 ± 1.3 and 36.7 ± 5.1 months in the OVB and GVB groups respectively ($p < 0.01$). The longer follow up time in the GVB group may reflect the greater proportion of patients recruited in or prior to 1995 compared with the OVB group (62.5% versus 29.7%, $p < 0.001$). In this time, 34 (14.7%) of the patients in the OVB group rebled, and 8 (20%) of the patients in the GVB group rebled. The cumulative risk of rebleeding was similar in both groups. (Figure 12) In 31 (73.5%) cases of variceal rebleeding there was evidence of TIPSS dysfunction.

5.3.3 Mortality.

During the follow up period there was a significant difference in the cumulative risk of death in favour of the GVB group ($p < 0.05$ by Kaplan-Meier method). This was true for 30 day mortality (15% versus 23.8%), 1 year mortality (30.7% versus 38.6%) and 5 year mortality (49.5% versus 74.9%). (Figure 13) There was no significant difference in the time interval

to TIPSS from the variceal bleed (5.4 ± 0.9 days versus 4.9 ± 0.4 days for GVB and OVB groups respectively, $p = \text{N.S.}$). The principal cause of death was similar in both groups, with liver failure or sepsis accounting for 82 (64.1%) deaths in the OVB group and 12 (75%) deaths in the GVB group.

5.3.4 Encephalopathy.

The rate of encephalopathy prior to TIPSS insertion was similar in the OVB and GVB groups (27.6% versus 30.0%, $p = \text{NS}$). There was no significant difference in the episodes of new or worsening encephalopathy in the oesophageal and gastric varices groups (16.35% versus 17.5% respectively, $p = \text{NS}$) All episodes of encephalopathy were managed initially with lactulose and protein reduction. In 3 cases the shunt was reduced in size, and in 8 cases it was necessary to block the shunt with a filter \pm coils.

5.3.5 Shunt insufficiency.

There was no difference in the overall incidence of shunt insufficiency in the study period between the two groups (42.67% versus 55% in the OVB and GVB groups respectively). In 1 patient in the GVB group problems with maintaining TIPSS patency resulted in elective surgery with the creation of a distal spleno-renal shunt.

5.3.6 Orthotopic liver transplantation.

Twenty-one patients required an orthotopic liver transplantation, 19 (8.2%) in the oesophageal varices group and 2 (5%) in the gastric varices group ($p = \text{NS}$).

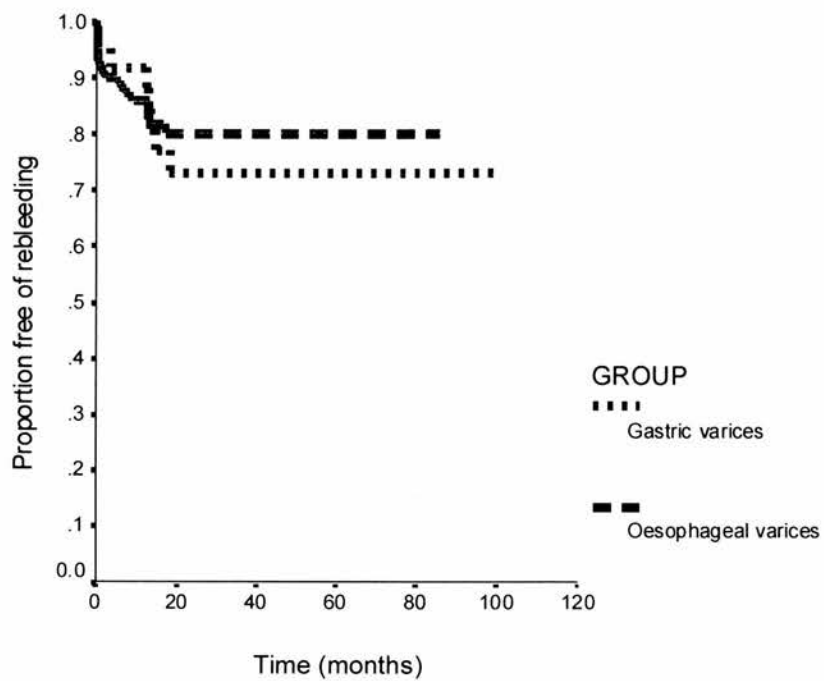
5.3.7 Correlations between portal pressure and clinical outcome.

When patients with a pre-TIPSS PPG ≤ 12 mmHg were analysed it was clear that gastric variceal bleeding accounted for significantly more cases than for those patients who bled at PPG > 12 mmHg (36.8% vs 10.2%, $p < 0.001$, Table 15). However, there was no overall difference in the rebleeding rate and mortality in the 2 groups. Rates of shunt insufficiency and encephalopathy were also similar in the two groups. In group 1 the final PPG post-TIPSS is similar in those patients that rebled ($n = 9$) compared with those that do not rebleed ($n = 29$) of 5.1 ± 0.1 mmHg and 3.9 ± 0.5 mmHg respectively ($p = 0.2$). In group 2 the PPG post-TIPSS is significantly higher in patients who rebled post-TIPSS ($n = 35$) compared with those that do not rebleed ($n = 219$) of 9.4 ± 0.8 mmHg and 7.3 ± 0.3 mmHg respectively ($p < 0.005$). In addition 75% of the patients in group 2 who rebled had a PPG post-TIPSS of > 7 mmHg.

When patients who bled from either oesophageal varices or gastric varices with PPG pre-TIPSS of > 12 mmHg were analysed, there was a significant difference in mortality in favour of gastric varices ($p = 0.02$ by Kaplan-Meier method). 30 day mortality (12% versus 24.2%), 1 year mortality (33.8% versus 40.4%), and 5 year mortality (39.4% versus 79.1%) were all significantly better in the gastric varices group (Figure 14). Univariate analysis showed that the following variables were associated with higher mortality in the patients who bled from gastric or oesophageal varices at PPG > 12 mm Hg : increasing age ($p < 0.01$); bleeding from oesophageal varices ($p = 0.04$); high prothrombin time ($p < 0.05$); high bilirubin ($p < 0.001$), low albumin ($p = 0.001$); presence of ascites ($p < 0.001$); and

encephalopathy ($p < 0.05$). Multivariate analysis of these variables revealed that greater age of patients ($p < 0.05$), high bilirubin ($p < 0.05$) and a low albumin ($p < 0.001$) were independent variables predicting mortality. There was no difference in the rebleeding rate. The mortality and rebleeding rates were similar in the GVB and OVB groups who bled at $\text{PPG} \leq 12$ mmHg.

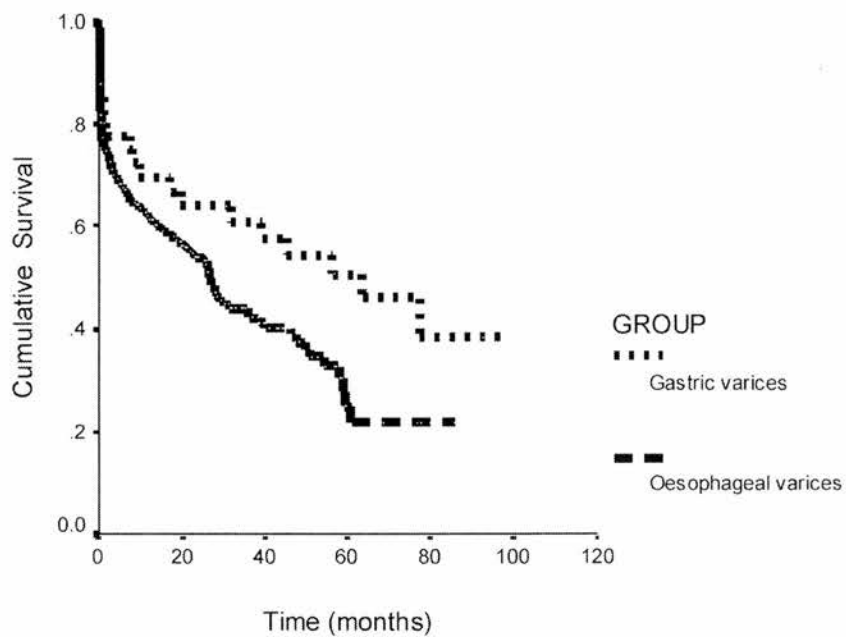
Figure 12: Kaplan Meier graph of rebleeding for all patients who bled from gastric and oesophageal varices treated with a TIPSS



p = 0.2

	0	10	20	30	40	50	60
		months	months	months	months	months	months
Gastric varices	40	25	17	17	15	14	9
Oesophageal varices	232	114	85	52	37	22	6

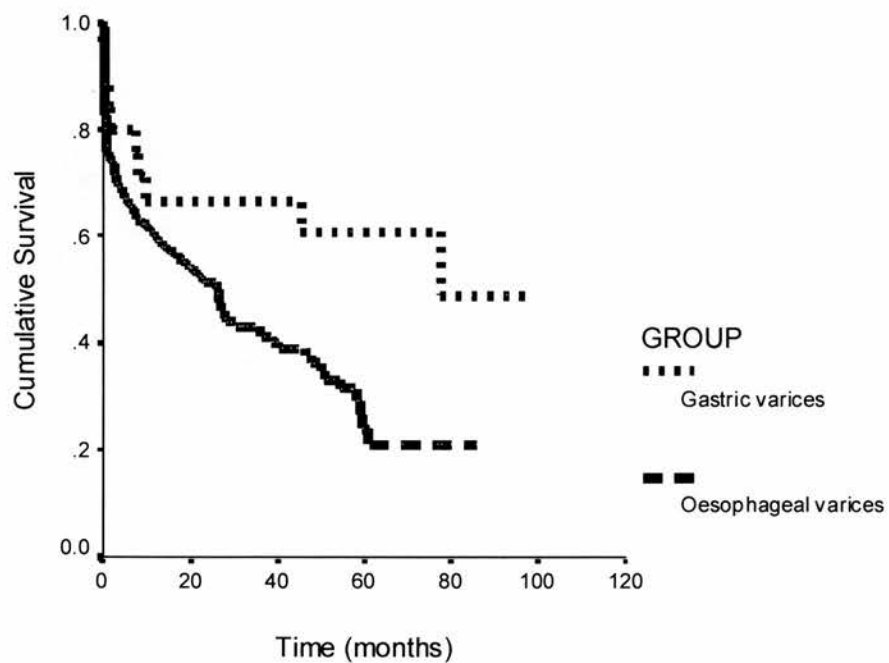
Figure 13: Kaplan Meier graph of survival for all patients who bled from gastric and oesophageal varices treated with a TIPSS



p=0.046

Time (months)	0	10 months	20 months	30 months	40 months	50 months	60 months
Gastric varices	40	25	22	20	18	16	11
Oesophageal varices	232	128	101	60	40	25	8

Figure 14: Kaplan Meier graph of survival for all patients who bled from gastric and oesophageal varices at a portal pressure gradient of > 12 mmHg



p=0.02

Time (months)	0	10 months	20 months	30 months	40 months	50 months	60 months
Gastric Varices	26	14	14	14	12	11	8
Oesophageal Varices	212	114	87	54	37	23	8

5.4 Conclusions.

This study demonstrates that TIPSS is equally effective in the prevention of gastric or oesophageal variceal rebleeding. In addition, mortality is significantly better in the GVB group who bled at PPG > 12 mmHg, and warrants further study. The findings also highlight the significant number of patients with gastric varices who bled at PPG \leq 12 mmHg, and challenge the use of this cut off value as a treatment goal particularly in such patients. Our results also suggest that clinicians should aim for a PPG post TIPSS of < 7 mmHg for patients who have variceal bleeding at PPG > 12 mmHg. TIPSS therefore has a major role in the management of GVB, which can be very difficult to control by other measures. Further long-term prospective studies would assist in clarifying the effect of TIPSS on mortality in the GVB group compared with OVB.

CHAPTER 6

**Randomised controlled trial of VBL versus standard
TIPSS surveillance following TIPSS insertion for the
prevention of oesophageal variceal rebleeding**

6.1 Introduction.

Long term patency of TIPSS is a major clinical problem. Studies indicate that without regular TIPSS surveillance and intervention, approximately 50% of stents will occlude after a year (Lind and others 1994; Haskal and others 1994; Stanley and others 1997b; Jalan and others 1997b; Latimer and others 1998; Jalan and others 1998). Regular invasive portographic surveillance, which is essential for maintaining shunt patency is not available in all centres, and places an additional burden on resources. Moreover, non-invasive methods of assessing TIPSS patency such as Doppler ultrasound are not as sensitive as regular portography (Ferguson and others 1995), and lead to a higher rebleeding rate (Papatheodoridis and others 1999). In any case, Doppler ultrasound does not allow for interventions, such as balloon angioplasty and re-stenting or the measurement of portal pressures.

VBL has replaced injection sclerotherapy in most centres as the favoured endoscopic treatment for the prevention of variceal rebleeding. VBL is associated with a high rate of rebleeding particularly in the month following the index variceal bleed (Jalan and others 1997a). However, once the varices have been eradicated, VBL may be as effective as a patent TIPSS in preventing variceal rebleeding. Thus, following variceal eradication in a patient with a TIPSS, it may not be necessary to continue TIPSS surveillance to maintain TIPSS patency. It is not known whether terminating angiographic TIPSS surveillance following successful VBL will compromise the variceal rebleeding rate.

We hypothesise that combining VBL and TIPSS with short-term portographic surveillance will be as effective as a TIPSS alone with long-term surveillance in the prevention of oesophageal variceal rebleeding. Patients in the former group could benefit from the reduced need for angiographic surveillance, and incidence of hepatic encephalopathy as the TIPSS is allowed to occlude following variceal eradication. There may also be cost advantages in using VBL instead of long-term TIPSS surveillance.

Therefore, the aim of this randomised controlled trial was to compare the efficacy of TIPSS *plus* VBL without long-term surveillance, with TIPSS and long-term surveillance in the secondary prevention of oesophageal variceal rebleeding. Other potential differences such as mortality, encephalopathy, and costs were also explored.

6.2 Methods.

The trial was undertaken with the approval of the local research ethics committee, written informed consent of each subject, and in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

6.2.1 Patients selection.

Between December 1995 and August 2000, a total of 303 patients were referred for TIPSS insertion from centres throughout Scotland. All TIPSS procedures were performed in the Royal Infirmary, Edinburgh. All patients presenting with bleeding oesophageal varices were considered for inclusion into the trial. Exclusion criteria are as follows: 1) technical failure of TIPSS insertion; 2) age < 18 or > 85; 3) bleeding gastric or ectopic varices; 4) portal vein thrombosis; 5) Budd-Chiari Syndrome; 6) ascites as a primary indication for TIPSS; 7) advanced cardiopulmonary disease; 8) malignancy with prognosis that will affect study outcome; 9) inability to give informed consent; 10) previous variceal haemorrhage; 11) pregnancy or women of childbearing potential not taking contraception. Patients were recruited after haemodynamic stabilisation.

6.2.2 Randomisation and treatments.

Prior to TIPSS, all patients were resuscitated with fluids and blood or blood products, and underwent endoscopy with VBL or sclerotherapy using 5% ethanolamine oleate if there was active bleeding. In some patients, pharmacological intervention with octreotide or terlipressin was undertaken.

Randomisation was performed following TIPSS insertion and only after initial control of bleeding and haemodynamic stabilisation. Patients were allocated to either Group 1 or Group 2 by the sealed envelope method (Peto and others 1977).

Group 1: TIPSS alone (n = 39)

At the time of index endoscopy active variceal bleeding was noted in 23 patients. VBL was performed in 13 patients, VBL and sclerotherapy in 1 patient, and sclerotherapy in 6 patients. In 3 patients it was not possible to control bleeding with endoscopic therapies requiring the use of balloon tamponade. In 16 patients there was stigmata of recent bleeding but no active bleeding, with 3 patients having VBL and 1 both VBL and sclerotherapy. The remainder proceeded straight to TIPSS. All TIPSS procedures in the recruited patients were performed or closely supervised by a skilled interventional radiologist using a standard technique described earlier. All patients were administered broad spectrum antibiotics pre- and for 48 hours post-procedure. Ten to 14 mm diameter expandable metal stents (Wallstent, Schneider, Switzerland) were used, with the aim of reducing the PPG to < 12 mm Hg or by $\geq 20\%$. This was achieved in 36 (92%) and 37 (93%) patients in groups 1 and 2 respectively. Two or more stents were used, if necessary, to cover the entire length of the tract between the hepatic vein and the portal vein.

Following creation, TIPSS function was assessed at one week by colour Doppler ultrasound. Routine portographic follow up with intervention, if required, to maintain shunt patency was undertaken at six monthly intervals thereafter. However, additional TIPSS portography was also performed

where there was clinical suspicion of TIPSS insufficiency such as rebleeding.

Group 2: TIPSS plus VBL (n=40)

At the time of index TIPSS 28 patients were actively bleeding from varices. Eighteen patients required VBL, 2 patients VBL and sclerotherapy, and 4 sclerotherapy. Four patients failed endoscopic therapy requiring balloon tamponade and urgent TIPSS. In 12 patients there were stigmata of recent bleeding but not active bleeding, with 6 patients having VBL, and the remainder proceeding to TIPSS. TIPSS procedure was performed as above. Following satisfactory haemodynamic stabilisation, VBL was undertaken or closely supervised by an experienced endoscopist. One of two banding devices was used (Speedbander, Boston Scientific, Herts or 6-Shooter Saeed Multi-Band Ligator, Cook, Ireland), deploying 5 or 6 bands respectively. Varices just above the gastro-oesophageal junction were banded using a single band at a time. A varix was considered eradicated if the column had disappeared, or if they could not be sucked into the banding device. It should be noted that in patients with a patent TIPSS the varices often appear collapsed, and therefore require suction for their size to be appreciated and VBL to be performed.

Repeat endoscopy \pm VBL was performed within a week of TIPSS insertion and at two weekly intervals until variceal eradication. Intervals were extended to 3 and 6 months thereafter. Shunt function was assessed as previously mentioned. Portographic follow up was continued for up to 12

months following TIPSS insertion in all patients, but was discontinued earlier in patients where variceal eradication was achieved.

6.2.3 Follow up.

All subjects were followed up until death, liver transplantation, or lost to follow up. A specialist research nurse coordinated clinical follow up, with full clinical examination and biochemical profile at 6 weeks post randomisation and 4 monthly thereafter.

6.2.4 Outcomes.

The outcomes were assessed at 6, 12 and 24 months. The primary outcome of the study was variceal rebleeding. Secondary outcomes were mortality, incidence of encephalopathy, and orthotopic liver transplantation (OLT).

6.2.5 Sample size calculation.

Sample size was calculated to show that both treatments were equally effective in preventing rebleeding (Blackwelder 1982). Assuming that both treatments were expected to have a 10% variceal rebleeding rate, and with a type I error (α) of 0.05 and type II error (β) of 0.2, 38 patients would be required in each arm to demonstrate equivalence (assumed as < 17% difference) of the two treatments. Once sufficient numbers were reached in each arm, recruitment stopped and the study was terminated 4 months after the last patient was recruited.

6.2.6 Calculation of costs of treatment.

Data regarding the time spent by each patient in a general, intensive care, or high-dependency ward during the follow up period were retrieved. The costs were based on data from the National Health Service, our Department of Radiology, and our Endoscopy Unit. The costs are expressed as cost per patient and also the cost per month survival. The latter is the overall cost per patient divided by the follow up time in months (Table 4).

Costs of ward beds

The cost per day in a general ward was £350, high-dependency ward was £500 and an intensive care ward was £1200. These costs include staff and consumables.

Cost of the TIPSS procedure and follow up

The consumable cost of the TIPSS procedure is £1679. Follow up costs are as follows; routine portography (£205), balloon angioplasty (£371), shunt reduction (£753), insertion of a caval filter and coils for the purposes of occluding the shunt (£785), shunt extension (£927), and insertion of parallel shunt (£1462).

Cost of VBL

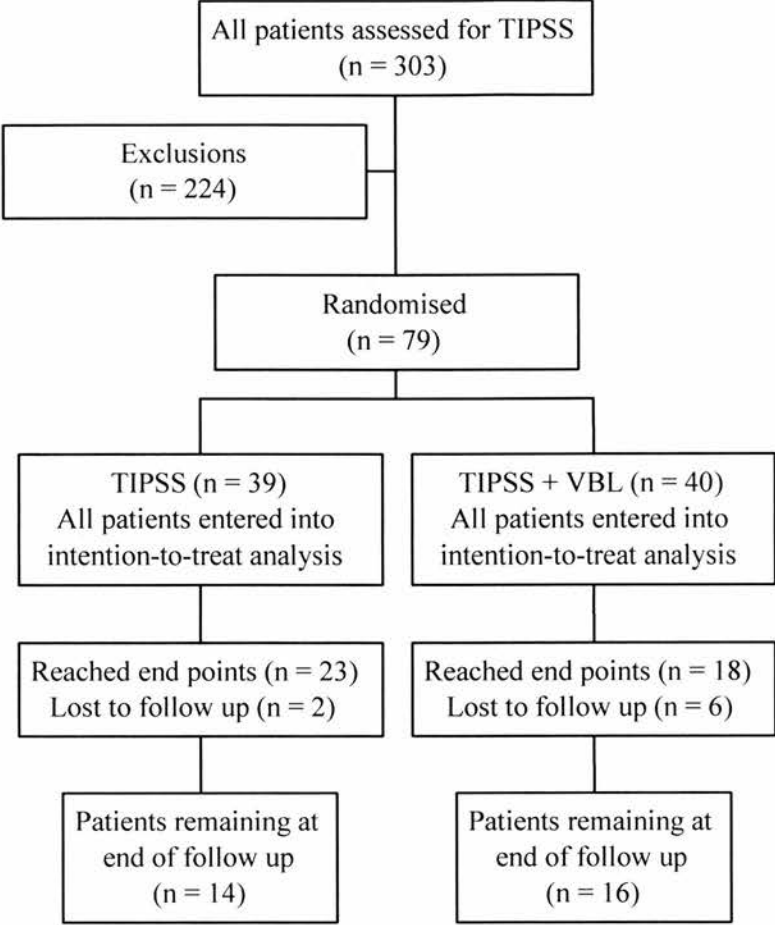
The cost of the endoscopy session is £250. Where VBL is also required, the overall cost increases to £350.

6.2.7 Statistical analysis.

Data was analysed on an intention-to-treat basis. Baseline characteristics were described in the 2 groups using summary statistics. Chi squared test

was used to compare non-parametric data, and Student *t*-test was used to compare parametric data. Kaplan-Meier graphs and log-rank tests were applied to survival, rebleeding, encephalopathy, and shunt insufficiency. Cox regression analysis was used to control of gender and PPG pre-TIPSS. Significance was taken at the 5% level. The SPSS statistics package (version 9, Chicago, Illinois, USA) was used for all statistical analyses.

Figure 15: Flow diagram of patient recruitment. See text for exclusion criteria. Patients who reached the end points after randomisation and withdrawn from the trial had one of the following events: 1) Death; 2) Liver transplantation; or 3) Variceal rebleeding.



6.3 Results.

6.3.1 Patients recruited.

79 patients met the inclusion criteria, with 39 randomised to group 1 and 40 to group 2 (Figure 15). There were no patients excluded from the trial after randomisation. The mean follow up period was 22.5 ± 17.2 (range 0.1 to 58.9) and 26.6 ± 18.1 (range 0.3 to 64.1) months for Groups 1 and 2 respectively.

6.3.2 Baseline characteristics.

There were more male patients and the PPG pre-TIPSS was higher in the TIPSS alone arm. Clinical parameters of the 2 groups are shown in Table 16.

6.3.3 Procedures.

TIPSS insertion was complicated by an intraperitoneal bleed in 1 patient in Group 1. In another patient in Group 2, there was a biliary leak leading to a percutaneous fistula and suprahepatic abscess. This patient developed respiratory failure and staphylococcal septicaemia requiring antibiotics, vasoconstrictor therapy, and ventilation. The suprahepatic abscess was drained percutaneously. The patient then made an uneventful recovery. In 73 (92%) patients, there was reduction in the PPG following TIPSS insertion to < 12 mm Hg, and in all patients except one there was a $> 20\%$ reduction in the PPG post-TIPSS. The mean diameter of the stents was similar in the 2 groups.

VBL post-TIPSS insertion was performed successfully in 38 patients in Group 2. One patient rebled before VBL could take place, and another refused banding. A total of 176 endoscopies were performed during the follow up period. VBL was required in 69 endoscopies, with 47 (68%) procedures performed in the first 3 sessions. Successful eradication of varices was achieved in 28 patients following an average of 2.8 ± 0.3 sessions. Four patients rebled prior to eradication and were entered into a regular long-term TIPSS surveillance program instead of regular VBL. Two patients died before eradication could take place. Another 6 patients did not complete the banding program either because they were lost to follow up, or because they refused further banding. Post-banding ulceration occurred in 12 (30%) patients.

Table 16: Characteristics of the 2 groups at baseline. Figures are mean \pm SD unless stated otherwise.

Characteristic	TIPSS (n = 39)	TIPSS & VBL (n = 40)
Mean age (years), min to max	53.9 \pm 11.2 (32 to 74)	55.9 \pm 11.4 (30 to 82)
Male sex <i>n</i> (%)	30 (77%)	22 (55%)*
Child-Pugh Score (at baseline)	9.2 \pm 2.1	8.7 \pm 2.3
Aetiology		
<i>Alcoholic n</i> (%)	28 (72)	35 (88)
<i>Abstained from alcohol n</i> (%)	8 (29)	10 (29)
<i>Non-alcoholic n</i> (%)	11 (25)	5 (13)
PPG (mm Hg)		
<i>Pre-TIPSS</i>	25.2 \pm 6.6	20.1 \pm 6.1**
<i>Post-TIPSS</i>	7.2 \pm 4.0	6.6 \pm 4.4
Requirement for mechanical ventilation <i>n</i> (%)	5 (13%)	6 (15%)
Time from index bleed to randomisation (days)	8.1 \pm 6.8	6.3 \pm 5.5
Time from TIPSS insertion to randomisation (days)	3.3 \pm 2.9	2.9 \pm 3.3
Blood transfusion at randomisation (units)	3.5 \pm 4.2	2.7 \pm 2.6
Hypotensive at randomisation <i>n</i> (%)	6 (15%)	4 (10%)

PPG: Portal pressure gradient.

* : $p = 0.040$

** : $p < 0.001$

6.3.4 Rebleeding.

In Group 1, 3 episodes of variceal rebleeding occurred in 3 patients (8%) during follow up, 2 with Child C and 1 with Child B disease (Table 17). In 2 patients rebleeding proved to be rapidly fatal, whilst in the third case the shunt was insufficient with a PPG of 18 mm Hg, and evidence of hepatic vein stenosis requiring shunt extension. This patient did not have a further rebleed and made a satisfactory recovery. In addition, there were 4 patients who rebled from non-variceal sources (2 from banding ulceration, 1 from oesophagitis, and another from a Mallory Weiss Tear).

In Group 2 there were 9 episodes of variceal rebleeding in 6 patients (15%) during follow up, 2 with Child A and 4 with Child C disease (Table 17). Varices were eradicated in only two patients. In all cases there was evidence of TIPSS insufficiency requiring re-stenting or balloon angioplasty. In all cases except one, variceal rebleeding was controlled. One patient who rebled from gastric varices initially responded to thrombin injection and balloon angioplasty of the TIPSS. This patient had gastric varices at randomisation. However, he rebled again within 24 hours from gastric varices, despite a patent TIPSS. He unfortunately died from oesophageal rupture secondary to balloon tamponade. Three patients rebled from non-variceal sources (1 from oesophagitis, 1 from a duodenal ulcer, and another from severe portal hypertensive gastropathy).

There was no significant difference in the cumulative risk of variceal rebleeding by Kaplan Meier analysis ($p = 0.440$; relative hazard 0.58; 95%

CI 0.15 to 2.33; Figure 16 and Table 17). The 2 groups were similar even after controlling for PPG pre-TIPSS and gender (Table 17).

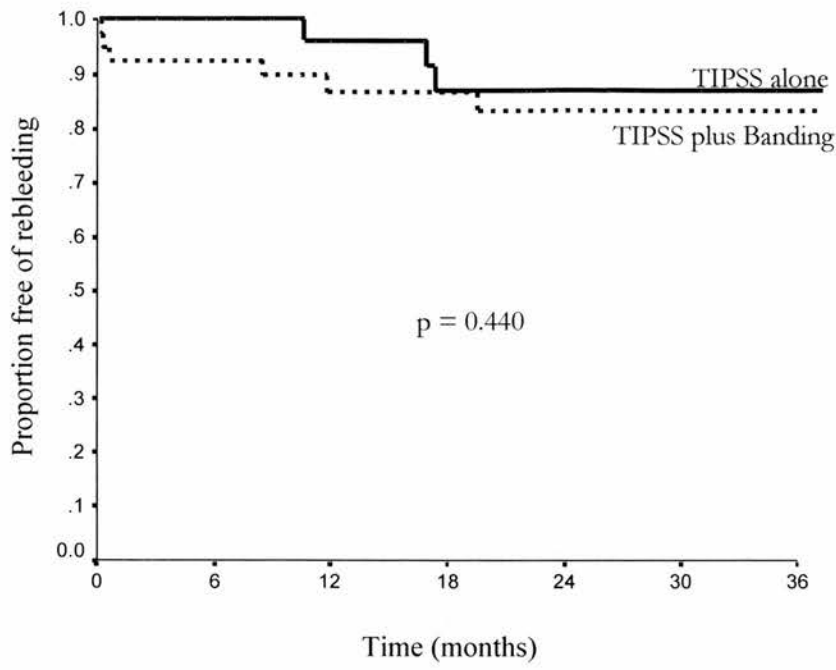
Table 17: Details of trial outcomes.

	TIPSS	TIPSS + VBL	TIPSS / TIPSS + VBL relative hazard over entire follow-up (95% CI)*	P value*
Mortality n (%)				
6 month	5 (13%)	2 (5%)	1.31 (0.66 to 2.61) /	0.434 / 0.803
12 month	8 (21%)	6 (15%)	1.10 (0.53 to 2.28)	
24 month	14 (36%)	11 (28%)		
Variceal rebleeding n (%)				
6 month	0	3 (8%)	0.58 (0.15 to 2.33) /	0.440 / 0.221
12 month	1 (3%)	5 (13%)	0.39 (0.09 to 1.77)	
24 month	3 (8%)	6 (15%)		
Hepatic encephalopathy n (%)				
6 month	5 (13%)	3 (8%)	2.63 (1.11 to 6.25) /	0.023** / 0.136
12 month	10 (26%)	3 (8%)	2.10 (0.79 to 5.58)	
24 month	14 (26%)	7 (18%)		

* : TIPSS versus TIPSS + VBL. The first value refers to uncontrolled analysis. The second value refers to analysis controlled for gender and pre-TIPSS portal pressure gradient.

** : p = 0.386 for comparisons in the first 6 months of follow up only.

Figure 16: Kaplan Meier analysis of variceal rebleeding.



Time (months)	0	6	12	18	24	30	36
TIPSS alone (n)	39	27	23	19	13	11	9
TIPSS <i>plus</i> VBL (n)	40	34	28	26	20	13	10

6.3.5 Mortality.

In Group 1, there were 17 deaths (44%) in total during follow up (Table 17). Early mortality occurred in 2 patients from multiorgan failure resulting from the variceal bleed. The other causes of death were renal failure secondary to gentamicin therapy for a presumed shunt infection (n = 1), cerebrovascular accident (n = 2), liver failure following non-variceal rebleeding (n = 4), and for the remainder multiorgan failure and sepsis.

In Group 2, there were 15 deaths (38%) in total during follow up (Table 17). One patient died within 6 weeks of the index bleed from aspiration pneumonia. The causes of death were liver failure following variceal rebleeding (n = 2), oesophageal rupture following insertion of a Sengstaken tube (n = 1), sepsis after a colectomy (n = 1), cerebrovascular accident (n = 2), multiorgan failure (n = 7), and pneumonia (n = 1).

There was no statistically significant difference in the cumulative survival by the Kaplan Meier method between the two groups (p = 0.434; relative hazard 1.31; 95% CI 0.66 to 2.61; Figure 17 and Table 17). The two groups were similar even after controlling for PPG pre-TIPSS and gender (Table 17).

6.3.6 Encephalopathy

In Group 1, 15 patients (39%) in total developed encephalopathy during follow up (Table 17). Four patients experienced deterioration of pre-existing

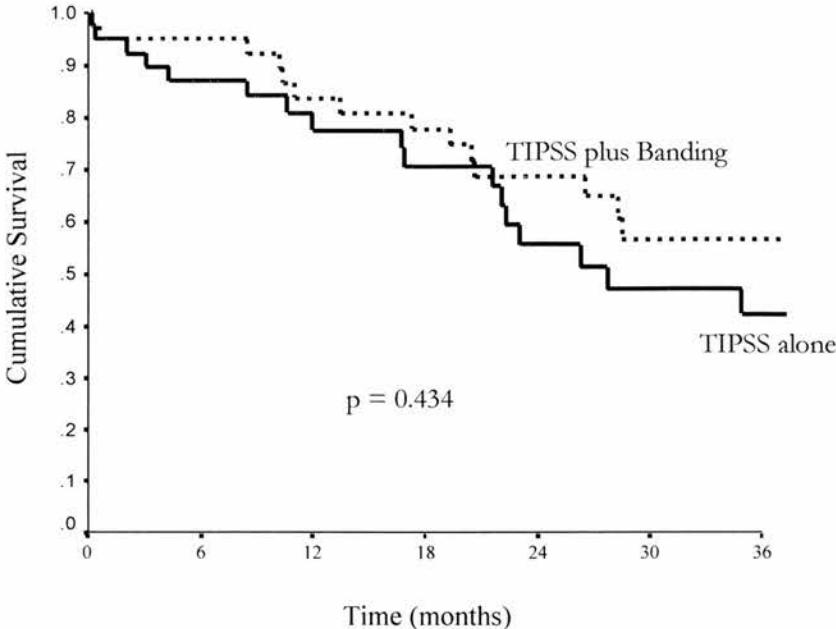
encephalopathy. Two patients responded to conservative therapy with lactulose and protein restriction, whilst the other 2 patients died with severe encephalopathy and liver failure. The remainder (28%) had *de-novo* encephalopathy. These patients were treated conservatively, with 2 patients requiring occlusion of the shunt with a filter, and subsequent entry into a banding program.

In Group 2, 8 patients (20%) in total developed encephalopathy during follow up (Table 17). Two patients were encephalopathic prior to TIPSS. Both responded to conservative therapy. The remainder (15%) had *de-novo* encephalopathy. Four responded to conservative therapy, and two required occlusion of the shunt.

There was a significance difference (relative hazard 2.63; 95% CI 1.11 to 6.25; $p = 0.023$) in favour of group 2, in the cumulative risk of being free of encephalopathy during the follow up period (Figure 18 and Table 17). This difference did not maintain statistical significance after controlling for gender and PPG pre-TIPSS ($p = 0.136$; Table 17). The cumulative risk of developing *de-novo* encephalopathy was also significantly less in Group 2 ($p = 0.041$). Further analysis revealed that there was no statistical difference ($p = 0.386$) in the incidence of hepatic encephalopathy in the first 6 months in the 2 groups, the period when the number of portograms was similar in groups 1 and 2 (25 *versus* 27 respectively). However, the difference in hepatic encephalopathy in favour of Group 2 remained statistically significant ($p = 0.028$) when analysis was confined to the period from the

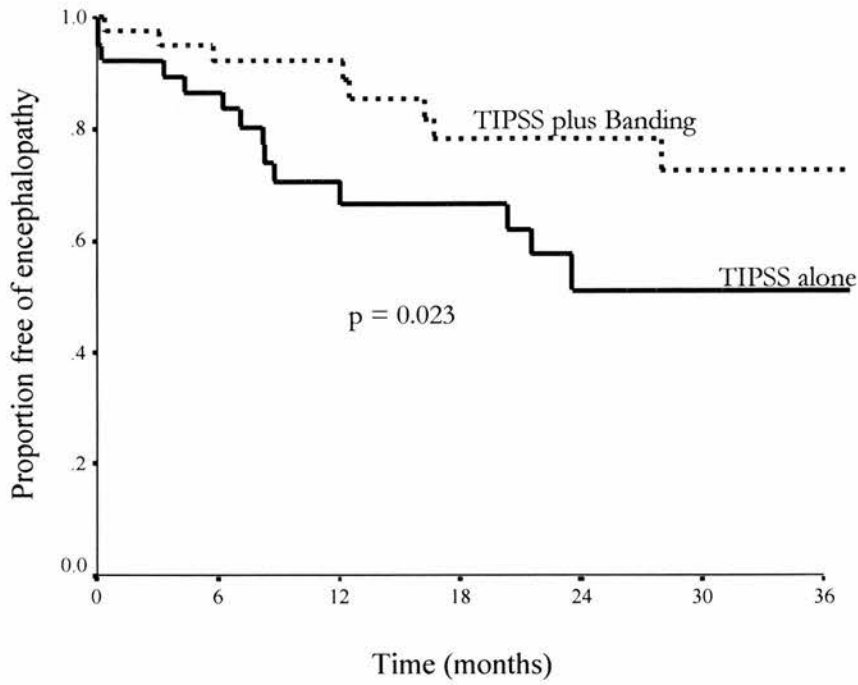
end of the first 6 months follow up, when there were far fewer portograms performed in Group 2 (10 *versus* 21).

Figure 17: Kaplan Meier analysis of cumulative survival.



Time (months)	0	6	12	18	24	30	36
TIPSS alone (n)	39	32	23	19	13	11	9
TIPSS plus VBL (n)	40	34	28	26	20	13	10

Figure 18: Kaplan Meier analysis of encephalopathy.



Time (months)	0	6	12	18	24	30	36
TIPSS alone (n)	39	29	17	15	8	6	5
TIPSS plus VBL (n)	40	33	27	22	17	11	8

6.3.7 Shunt function in the first year.

Since TIPSS portography was performed only for up to a year following TIPSS insertion in Group 2, valid comparisons of shunt function between the 2 groups can only be made for 12 months following TIPSS insertion.

In group 1, a total of 46 TIPSS portograms were performed in the first year, with 54% of these performed in the first 6 months. A total of 16 (41%) patients developed shunt insufficiency. In the first 12 months, 59% of shunt interventions were performed within the first 6 months following TIPSS insertion.

In Group 2, a total of 37 TIPSS portograms were performed in the first year, with 73% of these in the first 6 months. There were 17 (43%) cases of shunt insufficiency in the first 12 months. There was no difference in the cumulative risk of shunt insufficiency in the 2 groups by the Kaplan Meier Method (Figure 19).

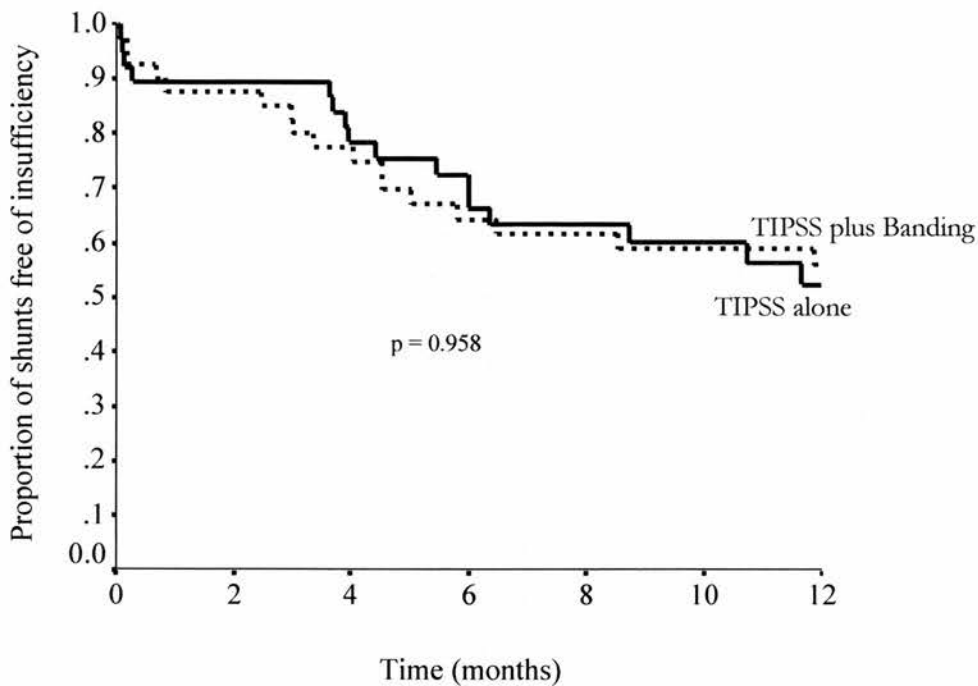
6.3.8 Orthotopic liver transplantation (OLT).

Four patients, all from Group 1, underwent OLT during the follow-up period, between 9.1 and 40.4 months after TIPSS creation. Most patients in both groups were unsuitable for OLT on account of the high incidence of continued alcohol consumption (Table 16).

6.3.9 Duration of hospital stay.

Total requirements for in-patient care were similar in the two groups during follow up: 46.5 ± 54.5 versus 58.0 ± 65.2 days in Groups 1 and 2 respectively ($p = 0.396$). There was also no difference in the intensive care or high dependency care requirements (Table 18).

Figure 19: Kaplan Meier analysis of 12 month shunt insufficiency.



Time (months)	0	2	4	6	8	10	12
TIPSS alone (n)	39	33	28	23	20	17	12
TIPSS plus VBL (n)	40	35	30	24	23	22	18

Table 18: Days spent in hospital during follow up.

Ward	Days in hospital per patient	
	TIPSS (n = 39)	TIPSS & VBL (n = 40)
General Ward	43.9 ± 54.0	55.0 ± 64.2
HDU	1.8 ± 1.4	1.9 ± 1.9
ITU	0.8 ± 2.1	1.1 ± 3.3
Total	46.5 ± 54.5	58.0 ± 65.2

Mean ± SD

ITU: Intensive care unit.

HDU: High dependency unit.

No statistical difference was detected between the two groups.

6.3.10 Costs of treatment.

Table 19 details the costs incurred in both groups following randomisation.

The difference in the total cost per patient did not reach statistical significance (£19560 ± 19146 *versus* £24738 ± 24299, $p = 0.297$, in Groups 1 and 2 respectively).

6.3.11 Severity of liver disease at the end of follow up.

The Child-Pugh score did not change significantly at the end of follow up (8.9 ± 2.6 *versus* 9.2 ± 2.2, $p = 0.609$, Groups 1 and 2 respectively).

Table 19: Costs of treatments following randomisation in both groups.

Procedures	Cost per patient (£)	
	TIPSS (n = 39)	TIPSS & VBL (n = 40)
TIPSS surveillance	877 ± 930	805 ± 969
VBL	-	1270 ± 985
Ward treatment	17004 ± 19154	20983 ± 23823
Total cost	19560 ± 19146	24738 ± 24299
Cost per patient free of rebleeding	20633 [‡]	24520 ^a
Cost per surviving patient	15922 [‡]	20127 ^{**}
Cost per month survived*	4576	6024

Mean ± SD.

[‡]: n = 36. ^a: n = 34. [‡]: n = 22. ^{**}: n = 24.

*: Total cost per patient divided by the follow up time in months.

There was no statistical difference in the costs between the two groups.

6.4 Conclusions

TIPSS *plus* VBL without long-term surveillance is effective in preventing oesophageal variceal rebleeding, and has the potential for low rates of encephalopathy. Therefore, VBL with short-term TIPSS surveillance is a suitable alternative to long-term TIPSS surveillance in the prevention of oesophageal variceal rebleeding.

Chapter 7

Discussion

The clinical studies presented in this thesis aim to clarify the following questions:

1. The systemic and portal haemodynamic effects and patient tolerability of 2 novel pharmacological agents:
 - a. Is low dose carvedilol, a non-cardioselective vasodilating beta-blocker, as effective in reducing portal pressure and better tolerated than higher doses?
 - b. Does modification of the renin-angiotensin system by using losartan, an angiotensin I receptor antagonist, result in reduction of portal pressure in patients with pre-ascitic cirrhosis?

2. Is there any difference in the efficacy of TIPSS for the management of gastric and oesophageal variceal haemorrhage? What is the role of portal pressure in determining clinical outcomes following TIPSS?

3. Can variceal band ligation replace long-term portographic surveillance following a TIPSS for the management of oesophageal variceal bleeding?

7.1 The role of low dose carvedilol in cirrhotic portal hypertension.

Our results clearly show that carvedilol at a dose of 12.5mg per day is a potent portal hypotensive agent and is well tolerated. Its acute administration significantly reduces portal pressure, an effect which is maintained following chronic dosing. In all cases except 1 there was a reduction in the HVPG of > 20%, and in 7 out of 9 patients the HVPG was \leq 12mmHg with chronic administration. The reduction in portal pressure observed in this study is one of the largest reported in literature to date, and is comparable to that seen following the insertion of a transjugular intrahepatic portosystemic stent-shunt (TIPSS).

7.1.1 Effects of carvedilol on portal and systemic haemodynamics.

The reductions in the HVPG, CO, and MAP which we observed following acute dosing are consistent with that observed in previous studies performed in our unit using 25 mg of carvedilol (Forrest and others 1996a). We also demonstrated a reduction in the HBF in a small number of patients, a finding that was noted in one the previous studies (Banares and others 1999). These haemodynamic findings would be consistent with non-selective β -blockade as has been demonstrated with propranolol (Lebrec and others 1982). In comparison with propranolol, carvedilol has less effect on CO and HR compared with its effect on HBF, suggesting that the degree of β_1 blockade is less than propranolol, at least acutely (Banares and others 1999). However, chronic administration did not lead to a further significant

fall in the CO and MAP despite a reduction in the HR. These findings are similar to those previously demonstrated in our centre (Stanley and others 1999). Alpha-1 receptor antagonism and hence reduced intra-hepatic resistance are likely to have contributed to the marked reduction in the HVPG following chronic dosing. A reduction in the hepatic blood flow noted in the small group of patients could have had an additional effect.

The acute haemodynamic effects of low dose carvedilol have been investigated in 3 previous studies (Banares and others 1999; De and others 2002). A 10mg dose significantly reduced the HVPG by 15% at 60 minutes and by 17% after 90 minutes in 10 patients, although only 50% of patients had a greater than 20% reduction in the HVPG (Sekiyama and others 1997). The 12.5 mg dose has been studied in a further smaller study, which did not demonstrate an effect on the portal or systemic haemodynamics, although there was a tendency to reduced HVPG and MAP (Banares and others 1999). A similar dose of carvedilol has been studied alongside propranolol, in a recent study by De and colleagues (De and others 2002). Following acute administration of 25 mg carvedilol, there was a 27.7% reduction in the HVPG, compared with 23.0% for 80 mg propranolol ($p=NS$). The effect on portal pressure was sustained after 7 days administration of once daily 12.5mg of carvedilol, and 80 mg propranolol. There was a significant reduction in the MAP, with just 1 ascitic patient in the carvedilol arm suffering symptomatic hypotension necessitating withdrawal from the trial. An important finding in the study was the strong predictive value of the

acute response to carvedilol in determining those that will respond after chronic dosing.

A recent study showed that the reduction in the HVPG, MAP, HR, and CO was greater with chronic administration of carvedilol than with propranolol (Banares and others 2002). Hepatic blood flow was unchanged with carvedilol, but decreased with propranolol. The authors expressed concern about the significant reduction in the MAP. The dose of carvedilol used was significantly greater than the dose used in our study (31 mg vs 12.5 mg per day), which may have been because Banares and colleagues titrated the dose against HR. It is doubtful whether such high doses are required because we have demonstrated in this and a previous study (Stanley and others 1999) that a lower fixed dose can result in a similar magnitude of portal pressure reduction with minimal side effects. These findings were mirrored in a randomised study comparing carvedilol with propranolol over a mean follow up of 11 weeks (Banares and others 2002). In addition, carvedilol and propranolol both reduced the azygous blood flow with no effect on renal function.

7.1.2 Bioavailability of carvedilol.

Concerns have been expressed regarding the effect of carvedilol on systemic haemodynamics, in particular blood pressure, in patients with liver disease. This stems from the fact that the bioavailability is very variable in patients with hepatic impairment. Carvedilol undergoes extensive stereoscopic first pass metabolism in the liver (Morgan 1994). The stereoisomer R-carvedilol

has equal β and α_1 antagonism while S-carvedilol has only non-selective β antagonism (Ruffolo and others 1990). In healthy individuals R-carvedilol has twice the bioavailability of S-carvedilol, whereas patients with liver disease have equal and increased availability of both stereoisomers (Neugebauer and others 1990; Neugebauer and others 1992). This means that β antagonism is greater in patients with liver disease, which could result in undesirable systemic effects. These effects appear to be dose related and our results indicate that despite the greater bioavailability, patients with advanced liver disease experienced minimal systemic hypotension. In particular patients with ascites, despite exhibiting similar reductions in HVPG compared with patients without ascites, did not experience significant systemic hypotension. Clearly this reinforces the need to adhere to lower dose regimens in such patients, especially as we have demonstrated carvedilol can still have a marked portal hypotensive effect at these doses. In heart failure carvedilol should be started from such a low dose as 3.125mg bd for two weeks and titrated according to patient tolerance (Frishman 1998). Our results indicate that the first dose of carvedilol had a greater effect on systemic haemodynamics than subsequent doses. It would therefore seem logical to introduce carvedilol in a stepwise fashion in patients with liver disease with the dose titrated according to patient tolerability, aiming for a target daily dose of 12.5mg.

7.1.3 Effects of carvedilol on renal function.

Previous studies have shown that carvedilol does not affect the renal blood flow (Forrest and others 1996a), and our findings confirm that the renal

function remains unaffected following chronic dosing with no evidence of increased ascites formation. Therefore, it seems that additional non-selective β -blockade helps to maintain renal blood flow and function. This may be explained by previous observations of non-cardioselective beta-blockers suppressing the increase in plasma renin activity and plasma aldosterone that occurs following alpha blockade (Albillos and others 1995). Although not included in our present study, we have previously shown that carvedilol at a dose of 25mg has no effect on creatinine clearance, urine volume or natiuresis (Stanley and others 1999). This is consistent with the observation that none of the patients with ascites suffered from increased fluid retention.

7.1.4 Carvedilol in clinical practice.

These findings and the earlier observation that carvedilol appears to have superior portal hypotensive effects than propranolol (Banares and others 1999), suggests that carvedilol should be assessed in large randomised controlled trials for the primary prevention of variceal haemorrhage. If the finding that more patients respond to carvedilol than propranolol holds true, then it is plausible that carvedilol could be used as secondary prophylaxis against variceal rebleeding or even during acute variceal haemorrhage as is the case with terlipressin.

7.2 Haemodynamic effects of chronic administration of losartan.

The present study demonstrates that in patients with preascitic cirrhosis, oral dosing of 25 mg losartan did not result in a significant reduction in the HVPG despite a significant fall in the WHVP. Losartan significantly reduced the MAP with one patient experiencing mild symptoms after the first dose, a phenomenon that has been reported previously with ACE inhibitors (Hodsman and others 1983).

7.2.1 Effect on systemic and portal haemodynamics: Comparison with other studies.

The literature appears to be divided on the efficacy of Losartan in portal hypertension. Schneider and colleagues reported a significant reduction in the portal pressure approaching 45%, the largest reported to date for any pharmacological agent. This is particularly impressive considering the minimal effect on blood pressure, with only 1 patient experiencing symptomatic hypotension. A recent paper, however, does not support the observation by Schneider (Gonzalez-Abraldes and others 2001). This randomised study revealed that propranolol produced a significantly greater reduction in the HVPG than losartan following a variceal haemorrhage (10% vs 2%). A concerning observation was a significant reduction in the glomerular filtration rate in Childs B patients taking losartan. Adverse effects related to therapy were similar in both groups. However, a recent randomised

study demonstrated better efficacy with 25mg losartan compared to propranolol even in non-ascitic patients (De and others 2003) . The 80% response rate in the losartan arm is also noteworthy.

Our results contrast with those of Schneider and colleagues (Schneider and others 1999) , but are in keeping with that of Gonzalez-Abraldes et al (Gonzalez-Abraldes and others 2001). This is despite using the same dose of losartan that resulted in activation of the renin-angiotensin system, as evidenced by a significant increase in PRA. Our study design differs in a number of ways from that of Schneider et al. First, we studied preascitic cirrhotic patients. This was to minimise the potential risk of systemic hypotension with ANG II blockade in patients with more advanced cirrhosis (Arroyo and others 1981). Second, significant proportions of patients in Schneider's study were on diuretics, both in the treatment and control groups. Clearly, this will have an effect on circulating volume, and the degree of activation of the renin-angiotensin system. Third, the timing of the haemodynamic measurements is different. Schneider et al. performed the measurements at 4 hours post dosing compared with 12 hours for our study. It is known, however, that the pharmacological actions of losartan last up to 24 hours (Christen and others 1991). Losartan is a pro drug that is converted to the active metabolite E-3174, whose maximum plasma levels are obtained after 3–4 hours. This may explain why we saw no effect on the HVPG in the 3 patients in whom we repeated measurements 60 min after acute dosing. The half-life of E-3174 is 6–9 hours and the levels in plasma in cirrhotics are 1.7 times those of healthy individuals (McIntyre and others 1997). This may

partly explain the difference in the results, but for a drug to be considered for therapy it must have a sustained chronic effect on portal hypertension. The third point also applies to the study by De and colleagues, in addition to the fact that there were no assays of renin, angiotensin II or aldosterone. It is therefore not clear the degree of activation of the renin angiotensin system nor the effect of losartan. In the study by Gonzalez-Abraldes the timing of the measurements is also not clear (Gonzalez-Abraldes and others 2001). Finally, our sample size is smaller, and a larger sample size may have resulted in a significant difference. Our study shows that the drug is biologically active in cirrhotic patients as evidenced by a significant decrease in the MAP, and increase in the renin activity. Although we cannot rule out that the inclusion of more patients may result in a statistically significant effect on HVP, we feel it is unlikely to show greater clinical effect. One could argue that the dosing may be inadequate, but our dosage was the same as used in the Schneider study and was enough to cause sufficient blockage of ANG II receptors as demonstrated by the significant increase in ANG II levels following chronic dosing. Higher doses may not prove to be more effective, and are likely to significantly increase the risk of adverse systemic side effects as demonstrated by Gonzalez-Abraldes and colleagues (Gonzalez-Abraldes and others 2001).

7.2.2 Effect of on renal function.

Girgrah et al. have recently studied the renal effects of losartan in preascitic cirrhotics (Girgrah and others 2000). This study demonstrated that the renin-angiotensin system is activated even in early cirrhosis, a finding that is in

keeping with that of our recent study (Helmy and others 2000). It was suggested by the authors that losartan, at a dose of 7.5 mg per day, improved natriuresis by blocking the sodium-retaining actions of ANG II proximal to the distal tubule. Our findings are not in keeping with this observation, but the sample size of the patients in whom the 24-hour sodium excretion was measured was small. Our study also examined the chronic rather than acute effect of losartan, and the dietary intake of sodium was not so strictly regulated. Creatinine clearance was unaffected, suggesting that at this dose in preascitic cirrhotic patients losartan appears to have no adverse renal effects. In other patients with more severe liver disease, and especially those on potassium-sparing diuretics, problems with renal function and electrolyte imbalance may occur as demonstrated by Gonzalez-Abraldes and colleagues (Gonzalez-Abraldes and others 2001).

7.2.3 Clinical implications of losartan therapy.

Our results suggest that although low-dose losartan appears to be well tolerated and has no adverse renal effects, there is no significant reduction in HVPG following chronic dosing with losartan in well compensated cirrhotic patients. Losartan therefore is unlikely to have a place in the management of patients with cirrhosis and portal hypertension who are at risk of variceal haemorrhage.

7.3 The efficacy of TIPSS in the management of gastric and oesophageal varices: Clinical and haemodynamic correlations.

Our findings show that TIPSS is equally effective in the prevention of rebleeding from gastric and oesophageal variceal haemorrhage. Incidence of shunt insufficiency and encephalopathy were similar in both groups. These results are similar to that of an earlier study in our unit (Stanley and others 1997a). We have adopted a policy of referring patients with bleeding gastric varices and a patent portal vein directly for TIPSS insertion. A further finding is the significant numbers of patients that bleed at PPG of <12 mmHg, and gastric varices accounting for a sizeable proportion of this group.

7.3.1 Portal pressure of gastric varices.

It has been reported that patients with large gastric varices have a lower portal pressure than those with oesophageal varices (Chao and others 1993), which may be as a result of the development of gastro-renal porto-systemic shunts (GRS) (Watanabe and others 1988). Portography at the time of index TIPSS insertion was primarily performed in order to identify varices, and not specifically to look for the presence of GRS, although the splenic vein was visualised if not always in its entirety. Given these limitations, we have looked at the portograms of over 400 patients who have had a TIPSS for any cause, and identified shunts in 18.3%. A wider portographic review and a prospective MR angiography study will assist in identifying all those patients with GRS. Watanabe and colleagues also demonstrated increased collateral flow at the expense of reduced portal venous flow in patients with gastric

varices. The authors proposed that reduced portocollateral resistance may account for the latter finding. It is however unclear as to why patients bleed at portal pressures of < 12 mmHg. Other factors such as the presence of red spots, variceal size and that of gastritis may be important. Therefore particularly in patients with gastric varices it would not be safe to regard reducing the portal pressure gradient of < 12 mmHg as a therapeutic goal. Indeed, for patients who bleed at $PPG \leq 12$ mmHg our results demonstrate that PPG post TIPSS is not statistically different in patients who rebleed compared with those that do not. However for patients who bleed at $PPG > 12$ mmHg, the post TIPSS PPG is greater for patients who rebleed with most of these patients having a PPG post TIPSS of greater than 7 mmHg. These results suggest that in group 2 i.e. predominantly oesophageal variceal bleeders a therapeutic goal of a post TIPSS $PPG < 7$ mmHg would be reasonable.

7.3.2 TIPSS as salvage therapy in bleeding gastric varices.

TIPSS has recently been studied in the management of refractory variceal bleeding either from gastric alone (Barange and others 1999) or gastric compared with oesophageal varices (Chau and others 1998; Rees and others 2000). Our rebleeding rates are comparable to these studies. Chau and colleagues also found that portal pressure in patients who had early rebleeding before 7 days was lower in patients with GVB (Chau and others 1998). Rees et al did not demonstrate significant differences in the PPG prior to TIPSS which was >20 mmHg in both groups (Rees and others 2000). This study was limited by small number of patients and a short follow up period.

7.3.3 Survival following TIPSS: Gastric versus oesophageal varices.

An interesting finding in the present study is that of significantly better survival in the GVB group, compared with the OVB group, despite the 2 groups being matched for age of patient, aetiology of liver disease, Child Pugh score, and pre TIPSS encephalopathy. We have previously shown the latter 2 parameters to strongly predict mortality post TIPSS (Jalan and others 1995a). It has also been observed that the mortality following a variceal haemorrhage is highest in the first few days after the index bleed (Smith and Graham 1982). Both the OVB and GVB groups were matched for the time of intervention with TIPSS after the variceal bleed, thus there was no undue selection of patients in either group who were likely to have a better survival. The difference in mortality between the two groups appears to be confined to patients who bleed at a portal pressure gradient of >12 mmHg, and is particularly striking for long-term mortality. Older age of patient, high bilirubin and low albumin in keeping with more advanced liver disease were independent predictors of mortality. The causes of death in both groups were predominantly liver failure and sepsis. The earlier study in our unit (Stanley and others 1997a) had demonstrated a trend towards improved survival amongst the GVB group. The present study has a greater number of patients and a longer follow up period, which may account for the now significant findings. The longer follow up period in the GVB is likely to be as a result the combination of reduced mortality and larger number of patients recruited before or in 1995.

7.3.4 Role of portal pressure in determining clinical outcome.

It is important to highlight the observation of a significantly higher PPG prior to TIPSS insertion in patients with OVB. We have previously shown that a HVPG of >16 mmHg predicted mortality in patients with alcoholic cirrhosis (Stanley and others 1998b). This finding was reinforced in a later study by Patch and colleagues (Patch and others 1999). HVPG measurements made within the first or second week had the greatest predictive value. Nearly all our patients had their portal pressures measured at the time of TIPSS within the first 2 weeks of the index variceal bleed. A recent study by Moitinho and colleagues (Moitinho and others 1999b) assessed the prognostic value of early portal pressure measurements following an acute variceal bleed. The striking finding in this study was that patients with a HVPG of >20 mmHg had a 1 year mortality of 64% compared with that of 20% for patients with HVPG <20 mmHg ($p < 0.004$). In our group all the patients who bled from oesophageal varices had a mean PPG > 21 mmHg. It is therefore plausible that the difference in PPG between the OVB and GVB groups may account for the difference in the observed mortality, although the reason why PPG affects mortality is not understood. We have not shown a difference in rebleeding rates as the rebleeding rate is so low in both groups following TIPSS insertion that much larger numbers may be needed to show any differences. This illustrates the impressive efficacy of TIPSS in preventing variceal rebleeding.

7.3.5 Clinical implications.

Our study demonstrates that TIPSS is very effective in the prevention of variceal rebleeding irrespective of whether patients have had an OVB or a GVB. Mortality is significantly better in the GVB group who bleed at PPG > 12 mmHg, and warrants further study. The findings also highlight the significant role of GVB in patients who bleed at PPG \leq 12mmHg, and challenges the use of this cut off value as a treatment goal particularly in patients with gastric varices. Our results also suggest that clinicians should aim for a PPG post TIPSS of < 7 mmHg for patients who have variceal bleeding at PPG > 12 mmHg. TIPSS therefore has a major role in the management of GVB, which can be very difficult to control by other measures. Further long-term prospective studies would assist in clarifying the effect of TIPSS on mortality in the GVB group compared with OVB.

7.4 Variceal band ligation versus long-term surveillance following TIPSS insertion for the prevention of oesophageal variceal rebleeding.

TIPSS has now become accepted as a method of treating variceal bleeding refractory to endoscopic methods, and for the prevention of variceal rebleeding. We have shown for the first time that VBL can replace long-term TIPSS surveillance for patients who have required a TIPSS for bleeding oesophageal varices.

7.4.1 Comparison of variceal rebleeding.

The rebleeding rates in the two groups were not significantly different even after adjustment for gender and portal pressure, and are consistent with that from previous trials (Papatheodoridis and others 1999). Although the absolute cumulative risk of variceal rebleeding was higher in Group 2 (15% *versus* 8%), this did not reach statistical significance. The lack of statistical difference needs to be interpreted with caution in view of the wide confidence intervals, and the fact that the power calculations allow for large differences in the 2 groups. However, it must be emphasised that the absolute risk of variceal rebleeding in Group 2 appears less than that seen with VBL alone as demonstrated in a recent study performed in our unit (Jalan and others 1997a).

7.4.2 Comparison of mortality.

Likewise, mortality was not different in the two groups even after adjusting for the difference in gender and portal pressure at baseline, and is in keeping with most of the previous studies comparing TIPSS and endoscopic modalities ([Anon] 1995; Cabrera and others 1996; Cello and others 1997; Rossle and others 1997; Jalan and others 1997a; Sauer and others 1997a; Sauer and others 1997b; Sanyal and others 1997c; Merli and others 1998; Sauer and others 1998; Papatheodoridis and others 1999; Luca and others 1999; Garcia-Villarreal and others 1999; Pomier-Layrargues and others 2001). The 2 groups were well matched for degree of liver disease, age, alcoholic aetiology, requirement for mechanical ventilation, time to randomisation from the index bleed, and encephalopathy pre-TIPSS; all variables which our unit and others have shown to predict mortality post-TIPSS (Smith and Graham 1982; Jalan and others 1995a; Tyburski and others 1997; Williams and others 1998). (Smith and Graham 1982; Tyburski and others 1997; Williams and others 1998)

7.4.3 Comparison of hepatic encephalopathy.

Encephalopathy, both overall and *de novo*, was significantly less in the Group 2 and is similar to that seen with VBL alone when used for secondary prophylaxis of variceal haemorrhage (Papatheodoridis and others 1999). This difference is maintained when the first 6 months of follow up is excluded, following which time there are fewer interventions in Group 2 to maintain shunt patency. However, in the first 6 months following TIPSS insertion, the period of maximum and equivalent shunt interventions in both groups, there was no difference in the incidence of hepatic encephalopathy. Since the shunt patency in Group 1 was maintained by regular portographic surveillance and intervention throughout the study period, the fact this group had greater episodes of encephalopathy would be expected. The rate of encephalopathy (39%) seen in Group 1 is similar to that published in recent literature (Papatheodoridis and others 1999), with *de-novo* encephalopathy being significantly less frequent (Blackwelder 1982). The majority of the patients responded to conservative measures with just 4 (5%) patients in total requiring blockage of the TIPSS. The statistically significant difference in encephalopathy was not maintained after controlling for PPG pre-TIPSS and gender. However, there did not appear to be any detrimental effects of TIPSS combined with VBL, and this treatment modality certainly has the potential to reduce the rate of hepatic encephalopathy.

7.4.4 Change in Child-Pugh score during follow up.

The severity of liver disease, quantified by the Child-Pugh score, did not change significantly in both groups during follow up. This may be explained by the fact that most patients had alcoholic liver disease, with most patients continuing to consume alcohol. A recent study demonstrated an improvement in the Child-Pugh score following TIPSS (Escorsell and others 2002), but there were fewer patients with alcoholic cirrhosis and it is not clear how many people abstained.

7.4.5 Shunt function and surveillance.

We have shown that the rates of shunt insufficiency in the first year are similar in the two groups, with most episodes occurring in the first six months following TIPSS creation. This important observation suggests that portographic follow up is of most value for the first few months following TIPSS insertion and may not be required for 1 year. However, at the time of study design, we were more conservative with respect to TIPSS surveillance. In all cases of variceal rebleeding, where portography was performed, there was evidence of shunt insufficiency.

7.4.6 Cost implications.

There was a trend to higher costs in the TIPSS + VBL group, the lack of statistical significance being due to high standard deviation in costs, and the small sample size. With longer follow up, the costs differences may lessen since the patients in the TIPSS and VBL group will only be followed up by endoscopy and VBL if required. One could even put forward a case for no surveillance at all in Group 2, provided every attempt was made to eradicate varices early. This could significantly reduce the costs, and increase the use of TIPSS since follow up after TIPSS insertion can occur in any hospital with endoscopy and banding facilities.

7.4.7 Clinical implications.

Our findings suggest that VBL can replace long-term TIPSS surveillance, and still maintain low rates of variceal rebleeding with the potential to reduce the rates of post-TIPSS encephalopathy. Therefore, in patients who have bled from oesophageal varices, combining TIPSS and short-term surveillance with VBL is a suitable alternative to TIPSS with long-term surveillance in the prevention of variceal rebleeding. The recent introduction of covered stents promises excellent patency without the need for long-term surveillance, but controlled trials are lacking.

Epilogue

What of the future?

The studies comprising this thesis have important implications for further research. These are briefly summarised:

The role of haemodynamic measurements in cirrhosis

The measurement of HVPG remains an important research tool. Clearly as demonstrated in chapter 5, the haemodynamic goals of therapy for portal hypertension may have to be revised particularly for patients who bleed from gastric varices. It is worth noting that the measurement of HVPG is not so widely available and is invasive. Future research should focus on non-invasive means of measuring portal pressure.

Pharmacological agents for portal hypertension

Clearly of the 2 drugs studied, carvedilol appears to be more effective. The excellent tolerability is particularly impressive, since up to a third of patients on propranolol withdraw due to side effects. We are currently running a randomised controlled trial comparing carvedilol with VBL in the primary prevention of variceal haemorrhage.

Transjugular intrahepatic portosystemic stent-shunt

Despite TIPSS being utilised for the management of the complications of portal hypertension for almost 15 years, there are relatively few controlled studies. In this thesis, we have shown that TIPSS can effectively be

combined with VBL to reduce invasive portography and potentially reduce hepatic encephalopathy. The hot topic at the moment is the introduction of PTFE covered stents, with the potential for excellent shunt patency. There are few studies at the moment using these stents, but early data from our unit is very encouraging. We hope to publish these soon. The studies so far have not demonstrated any survival benefit of TIPSS over endoscopic therapies in the management of variceal bleeding. The potential superiority of PTFE covered stents over standard stents leads one to ask whether these stents would not only lead to reduced variceal rebleeding, but also improved survival when compared with endoscopic therapies. Therefore, it would be very interesting to compare PTFE covered stents with VBL for the prevention of variceal bleeding in a controlled trial.

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APPENDIX

Publications resulting from studies presented in this thesis

1. Tripathi D, Hayes PC. *Review article: A drug therapy for the prevention of variceal haemorrhage*. ALIMENTARY PHARMACOLOGY & THERAPEUTICS. 2001 Mar;15(3):291-310.
2. Tripathi D, Therapondos G, Lui HF, Stanley AJ, Hayes PC. *Haemodynamic effects of acute and chronic administration of low dose carvedilol, a vasodilating β -blocker in patients with cirrhosis and portal hypertension*. ALIMENTARY PHARMACOLOGY & THERAPEUTICS. 2002 Mar;16(3):373-80.
3. Tripathi D, Therapondos G, Jackson E, Redhead DN, Hayes PC. *The role of the transjugular intrahepatic portosystemic stent-shunt (TIPSS) in the management of bleeding gastric varices: Clinical and haemodynamic correlations*. GUT. 2002 Aug; 51(2):270-4. (This paper is also the feature article for a selected summary in GASTROENTEROLOGY reference: Heneghan MA, Rockey DC. Is tips shunt effective for secondary prophylaxis of gastric variceal hemorrhage? GASTROENTEROLOGY 125 (1): 263 July 2003.)
4. Tripathi D, Lui HF, Helmy A, Dabos K, Forrest E, Stanley AJ, Jalan R, Redhead DN, Hayes PC. *Randomized controlled trial of long-term portographic follow-up versus variceal band ligation following transjugular intrahepatic portosystemic stent-shunt for preventing oesophageal variceal rebleeding*. GUT. 2004 Mar;53(3):431-7.
5. Tripathi D, Therapondos G, Lui HF, Johnston N, Webb DJ, Hayes PC. *Chronic Administration of Losartan, an Angiotensin II Receptor Antagonist, is not Effective in Reducing Portal Pressure in Patients with Preascitic Cirrhosis*. AMERICAN JOURNAL OF GASTROENTEROLOGY. 2004 Feb;99(2):390-4.
6. Tripathi D, Helmy A, Macbeth K, Balata S, Lui HF, Stanley AJ, Redhead DN, Hayes PC. *Ten years follow up of 472 patients following transjugular intrahepatic portosystemic stent-shunt insertion at a single centre*. EUROPEAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY. 2004 Jan;16(1):9-18.

Manuscripts in the process of peer review

1. Tripathi D, Hayes PC, Redhead DN, Jalan R. TIPSS: *Technical considerations and clinical utility in the management of variceal haemorrhage*.
(Book chapter for “Clinical Gastroenterology”).
2. Balata S, Helmy A, Tripathi D, Lui HF, Redhead DN, Hayes PC. *Role of technical variables in early shunt insufficiency following TIPSS for the treatment of portal hypertension*.
(Submitted to Journal of Vascular and Interventional Radiology and undergoing revision)
3. Tripathi D, Ferguson JW, Barkell H, Macbeth K, Ireland H, Redhead DN, Hayes PC. *Transjugular intrahepatic portosystemic stent-shunt utilising PTFE covered stents: Improved survival and shunt patency*.
(Submitted to the American Journal of Gastroenterology)

Abstracts and meetings

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Review article: a drug therapy for the prevention of variceal haemorrhage

D. TRIPATHI & P. C. HAYES

Liver Unit, Department of Medicine, Royal Infirmary, Edinburgh, UK

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SUMMARY

The development of varices is a major complication of cirrhosis, and variceal haemorrhage has a high mortality. There have been major advances in the primary and secondary prevention of variceal haemorrhage over the last 20 years involving endoscopic, radiological and pharmacological approaches. This review concentrates principally on drug therapy, particularly on the numerous haemodynamic studies. Many of these drugs have not been studied in clinical trials, but provide data

about the underlying pathogenesis of portal hypertension.

Also covered in this review are the randomized controlled trials and meta-analyses that involve a large number of patients. These trials involve relatively few drugs such as non-selective beta-blockers and nitrates. Correlations between haemodynamic and clinical parameters are discussed.

Despite the recent increase in the use of alternative endoscopic therapies, an effective and well tolerated drug remains a clinically important research goal.

INTRODUCTION

Cirrhosis is the main cause of portal hypertension in North America and Europe. Common causes include alcohol abuse, hepatitis C, primary biliary cirrhosis and autoimmune disease. The major life threatening complication of portal hypertension is the development of gastro-oesophageal varices that have the potential to bleed torrentially. At the time of diagnosis of cirrhosis varices are present in 30% of compensated and 60% of decompensated patients.¹ In a third of these patients the varices will bleed, with an inhospital mortality of approximately 50%. Seventy to one-hundred per cent of survivors will re-bleed over 1–2 years, with a 20% mortality for each survivor that re-bleeds.² These dismal statistics have led to the search for primary prophylaxis against variceal bleeding, and secondary prophylaxis against re-bleeding. Although a variety of strategies

including surgical and endoscopic techniques have been proposed, drug therapy has been the strategy most explored. Bearing in mind that the majority of patients will not bleed, pharmacological agents, especially for primary prophylaxis, seem to be the most attractive option. This review aims to present the evidence for the current use of drug therapy in patients with portal hypertension and varices (Table 1). The treatment of an acute variceal haemorrhage will not be covered. Prophylaxis against the formation of varices has been little studied and does not appear to be promising.³

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION

Propranolol was the first drug used to reduce portal pressure in 1981 by Didier Lebrec. Since then an improved understanding of the mechanisms behind portal hypertension has led to the use of a variety of pharmacological agents that act by altering portal haemodynamics favourably.

Normal portal pressure is between 1 and 4 mmHg. The cirrhotic liver leads to an increase in resistance to

Correspondence to: Dr D. Tripathi, Liver Unit, Department of Medicine, Royal Infirmary, Lauriston Place, Edinburgh, EH3 9YW, UK.
E-mail: d.tripathi@ed.ac.uk

Table 1. Drugs used in portal hypertension

β -blockers	
	Propranolol
	Nadolol
	Timolol
	Atenolol
	Metoprolol
	ICI 11855
	Mepindolol
	Carvedilol
Nitrates	
	Isosorbide dinitrate
	Isosorbide-5-mononitrate
Drugs acting on α adrenergic receptors	
	Prazosin
	Clonidine
Drugs acting on the renin-angiotensin system	
	Losartan
	Irbesartan
Drugs acting on serotonin S ₂ receptors	
	Ketanserin
	Ritanserin
Drugs affecting plasma volume	
	Spironolactone
Combination therapy	
	Isosorbide-5-mononitrate and β -blockers
	Prazosin and β -blockers or isosorbide-5-mononitrate

sinusoidal blood flow, which in turn leads to the development of collaterals that should decompress the portal system and minimize portal hypertension. However increased inflow in the splanchnic circulation leads to increased portal inflow, which maintains portal pressure.

Many studies have looked at the hepatic vein pressure gradient (HVPG) as a prognostic marker and as a guide to the efficacy of pharmacological agents. The HVPG is the difference between the wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP). The HVPG correlates with the true portal pressure in patients with alcoholic cirrhosis,⁴ hepatitis B⁵ and hepatitis C,⁶ but underestimates the true portal pressure in conditions such as primary biliary cirrhosis and chronic active hepatitis.⁴

The aim of pharmacological therapy is to prevent or reduce the risk of variceal bleeding and because this is unusual if the HVPG is less than 12 mmHg this has been adopted as a haemodynamic target.⁷ A reduction in the portal pressure of greater than 20% has also been proposed as a therapeutic goal.⁸ In clinical practice it is also important to combine drug efficacy with tolerability.

HAEMODYNAMIC STUDIES

β -blockers

A number of β -blockers have been studied in patients with portal hypertension and varices, although only propranolol and nadolol have been studied in large randomized trials.

Propranolol. In 1982 Lebec and colleagues investigated the portal hypotensive effect of propranolol in a placebo controlled haemodynamic study in alcoholic cirrhotic patients.⁹ Other studies have corroborated these findings reporting reductions in the HVPG of between 10 and 31% (Table 2). The fall in portal pressure is produced by a combination of reduced cardiac output (β_1 antagonism) and reduced splanchnic blood flow (β_2 antagonism). Changes in portal blood flow are probably mainly a result of β_1 blockade.¹⁰ It was also observed by others that propranolol consistently reduced azygous blood flow, which was elevated in patients with portal hypertension.¹¹ It has been postulated that a reduction in collateral flow, indirectly measured by azygous blood flow, might be an important mechanism of action in reducing variceal bleeding risk.

Others have found that there appeared to be a reciprocal relationship between severity of liver disease and response to propranolol.²¹ It seemed that although all patients with liver disease responded to propranolol, the response of the collateral circulation to propranolol administration in Child's C patients was significantly diminished. Child's C patients had higher baseline azygous blood flow, and despite a fall in the azygous blood flow, a higher fraction of the cardiac output was distributed to the azygous venous bed following propranolol administration. This was described as a pooling of blood in the collateral circulation, and the authors suggest stratification of patients according to the degree of liver disease. This is not universally supported.¹¹ Most of the haemodynamic studies have included predominantly Child's A and B patients, possibly because Child's C patients were less tolerant of the drug or were too unwell to be included in such studies.

The first paper to examine the effect of chronic administration of propranolol on portal pressure was published by Vorobioff and colleagues.¹³ Here the acute and chronic effects on alcoholic cirrhotics with oesophageal varices were studied over an average of 106 days. A portal hypotensive effect of 25% was maintained chronically. However 30% of patients failed to

Table 2. The effect of propranolol on portal and systemic haemodynamics

Study	Dose	Child's Class	Acute/chronic study	Mean arterial pressure (MAP)*	Cardiac output/cardiac index*	Hepatic venous pressure gradient (HVPG)*	Estimated hepatic blood flow*	Azygous blood flow
Lebrec <i>et al.</i> ⁹	40 mg	All A	Acute	Not stated	31	23	12	Not stated
Bosch <i>et al.</i> ¹¹	83 mg	Not stated	Acute	2	22.6	11.5	13.4	34.2
Mastai <i>et al.</i> ¹²	10 mg i.v.	A/B/C: 9/3/0	Acute	NS	17	10	NS	31
Vorobioff <i>et al.</i> ¹³	40 mg	Not stated	Acute	NS	21	17.6	Not stated	Not stated
	158† mg	Not stated	Chronic	NS	27	22.5	Not stated	Not stated
Westaby <i>et al.</i> ¹⁴	> or =2 mg i.v.	A/B: 2/7	Acute	Not stated	13	31	21	Not stated
Braillon <i>et al.</i> ¹⁵	10 mg i.v.	Mean score: 5.3	Acute	NS	26	15	NS	36
Garcia-Pagan <i>et al.</i> ¹⁶	i.v. 0.1 mg/kg bolus 2 mg/h 30 min infusion	A/B/C: 9/10/1	Acute	NS	24	13	12.8	38
Groszmann <i>et al.</i> ⁷	132 mg†	Mean score: 8	Chronic	NS	22	29	Not stated	NS
Garcia-Pagan <i>et al.</i> ¹⁷	†(actual doses not stated)	Mean score: 6.9	Chronic	NS	10	10	25	29
Bendtsen <i>et al.</i> ¹⁸	160 mg†	A/B/C: 7/5/2	Chronic	NS	20	24	39	47
Aramaki <i>et al.</i> ¹⁹	90 mg	A/B/C: 7/4/0	Chronic	NS	14	12	NS	Not stated
Vorobioff <i>et al.</i> ²⁰	140 mg†	Mean score: 7	Chronic	NS	38	12.5	Not stated	Not stated

*Measured as the percentage decrease from the baseline.

†Dose required to reduce the mean pulse to 25% of baseline.

NS - not significant.

respond after chronic dosing. This paper highlighted the considerable non-response rate of portal pressure to propranolol confirmed by later studies. This may be explained by a portal hypertensive model demonstrating that a rise in the portocollateral resistance accompanies the reduction in portal blood flow thus reducing the overall portal hypotensive response to propranolol.²² It has been shown that in healthy subjects S-propranolol, which is the haemodynamically active component, is present in higher concentrations than R-propranolol on account of reduced first pass metabolism.²³ In patients with liver disease the concentration of the S-propranolol is greatly elevated. Stereoisomer concentrations, however, do not appear to predict the haemodynamic response to propranolol, and there is no difference in the relative concentrations of both stereoisomers in propranolol responders and nonresponders.²⁴

Another chronic study with a longer follow-up period of 1 year failed to demonstrate a sustained fall in portal pressure gradient when propranolol was compared with placebo, despite significant reductions in hepatic blood flow, azygous blood flow and cardiac index.¹⁸ The investigators suggested that the splanchnic hyperdynamic

circulation observed in cirrhotics might be partly reversible in some patients, without drug therapy. This may be explained by the fact that patients in the second study were clinically better and had reduced sympathetic tone, but probably more importantly all had stopped drinking alcohol. Patients who were not studied after 1 year due to bleeding episodes or death could introduce selection bias despite the initial haemodynamic parameters being comparable to that of the group who were studied. The findings add weight to the hypothesis that reduction in collateral blood flow and therefore variceal blood flow is the mechanism behind the beneficial effect of propranolol in preventing bleeding. Feu and colleagues investigated the concept of reduced variceal flow using a non-invasive pressure sensitive endoscopic technique.²⁵ Their findings suggested that even in patients in whom the HVPG did not fall significantly there appeared to be a fall in variceal pressure, of similar magnitude to those patients that responded to propranolol.

Groszmann and associates looked at a larger number of patients in a randomized double-blind placebo-controlled trial to investigate whether lowering the HVPG with propranolol protects against a variceal bleed over a 2-year follow-up period.⁷ They found that a

HVPG of less than 12 mmHg protected patients from variceal haemorrhage and improved survival. It is of note that in this study almost all patients bled within the first year and that treatment with propranolol did not result in a greater portal pressure reduction than placebo after 3 months of treatment, suggesting propranolol had a protective effect earlier on. The authors did point out that this might have been due to a greater drop-out rate of patients with the highest pressures in the placebo group from terminating events such as variceal bleed and death. Fifty-one patients were studied in both groups and after 24 months the final number was nine and 12 in the placebo and propranolol groups respectively. It is questionable whether these small numbers allow meaningful analysis. Values for HVPG were higher in the patients who dropped out of the placebo group at 3–12 months. However recent papers by McCormick *et al.*²⁶ and Stanley *et al.*²⁷ have supported this observation. The latter study concluded that the HVPG was the only haemodynamic parameter that predicted death or bleeding. Interestingly it has been demonstrated that bleeding may occur at pressures below the threshold level of 12 mmHg,²⁸ although the numbers quoted in this study are quite small.

Nadolol. Nadolol is also a non-selective β -blocker, which was first studied by Gatta and colleagues.^{29–32} These studies suggested a similar mechanism of action and efficacy to propranolol. Nadolol, unlike propranolol, has low hepatic metabolism and lipid solubility resulting in a longer half life. The main chronic effects at a dose that reduced the heart rate by 25% were of significant reductions in HVPG (19–22%), cardiac output and effective hepatic blood flow. Mean arterial pressure, liver function and renal function were unaffected. Recent studies also suggest that nadolol therapy results in a significant reduction in portal blood flow.³³ This paper also suggested that nadolol results in a slight fall in renal blood flow.

Timolol. This is a non-selective β -blocker that has only been studied in one haemodynamic study.³⁴ The mean reduction in the portal pressure gradient was 20%, which is comparable to the that of propranolol and nadolol. The drug has not been studied in any clinical trials.

Atenolol. Hillon and colleagues, in a comparative haemodynamic study with propranolol, first investigated atenolol, a selective β_1 receptor antagonist in portal

hypertensive patients with cirrhosis.³⁵ They found a 16% reduction in HVPG, which significantly correlated with cardiac output. Propranolol produced a greater reduction of portal pressure, although the reduction in cardiac output was similar to that of atenolol. It was postulated that the extra cardiac effects of propranolol were responsible for the difference.

Another comparative study looked at the effect of atenolol, propranolol and prazosin (α blocker) on portal haemodynamics in a chronic study with an 8-week follow-up period.³⁶ Atenolol resulted in a non-significant 15% reduction in HVPG compared with a significant 25% reduction in HVPG with propranolol. The findings again suggested a significant correlation between cardiac output and portal pressure with atenolol but not with propranolol. Both β blockers were well tolerated.

Atenolol therefore appears less effective at reducing portal pressure than propranolol, which suggests that the β_2 receptor blockade has a major role to play in the mechanism of action propranolol.

Metoprolol. Metoprolol is another β_1 selective β -blocker. Initial haemodynamic studies suggested that it was of equal efficacy to propranolol in reducing portal pressure.³⁷ The study also demonstrated significant falls in cardiac output in both groups, but a reduced hepatic blood flow only in the propranolol group. The latter finding led the authors to conclude that metoprolol may even be preferable to propranolol in patients with advanced liver disease. It has, however, been little studied.

β_2 receptor antagonists. ICI 11855 is a selective β_2 antagonist, which was studied by Bihari *et al.* in 17 patients.³⁸ There was a significant reduction in the portal pressure 60 min following administration of the drug, which was accompanied by significant reductions in the heart rate and cardiac index, both of which were not related to the fall in the portal pressure.

Another selective β_2 antagonist mepindolol was compared with intravenous propranolol in patients with cirrhosis and portal hypertension by Brallion and colleagues.³⁹ The effect on the HVPG and systemic circulation was similar to that of propranolol, but at the expense of significantly reduced hepatic blood flow, which was not the case with propranolol. Clearly both these drugs have a significant effect on the systemic circulation, and mepindolol offers no benefit over

propranolol in reducing portal pressure. This may explain why they have not been studied further.

Carvedilol. Carvedilol is a novel vasodilating non-selective β -blocker with weak α_1 receptor antagonism and calcium channel antagonism. It has a rapid onset of action with 2–4 times greater β -blocking action than propranolol.

Forrest and colleagues performed the first acute haemodynamic study on cirrhotic patients using 25 mg oral carvedilol.⁴⁰ A 20% fall in HVPG from 17 to 14 mmHg was achieved mainly due to a fall in wedge hepatic venous pressure. A significant fall in MAP of 10% was noted particularly in ascitic patients. Hepatic blood flow, azygous blood flow and renal blood flow were unaffected. This effect of carvedilol on HVPG was similar to that of propranolol as demonstrated in previous studies (Table 2).

The chronic effect of carvedilol was investigated by Stanley *et al.*⁴¹ A 21% drop in HVPG was maintained chronically. The fall in HVPG was mainly as a result of a significant drop in the wedge hepatic venous pressure. There was no change in renal function or hepatic blood flow. Poor tolerability was noted in three out of the 17 patients who experienced dizziness, breathlessness or hypotension.

A recent study compared carvedilol with intravenous propranolol and placebo.⁴² Carvedilol at a dose 25 mg was used and resulted in a 21% drop in the HVPG. A lower dose of 12.5 mg carvedilol did not lead to a significant drop in the portal pressure in this series. Propranolol in this study was not as effective in lowering HVPG with only a 13% reduction. Both drugs significantly reduced cardiac output, hepatic blood flow and azygous blood flow. Once again carvedilol caused a significant reduction in the mean arterial pressure of 17% compared with 3.4% with propranolol.

A lower dose of carvedilol has been studied in our center and the findings were published in abstract form.⁴³ The acute and chronic effects of 12.5 mg of carvedilol were studied in six patients. A significant 40% reduction in the HVPG was noted. The drug was very well tolerated.

All these studies seemed to suggest that carvedilol has a portal hypotensive effect greater than propranolol, and that lower doses may avoid significant systemic effects. To date there are no clinical studies looking at the effect of carvedilol in preventing variceal bleeding.

Nitrates

Isosorbide-5-mononitrate is a long acting organic nitrate. The mononitrate, either as native drug or formed from the denitration of isosorbide dinitrate in the liver,⁴⁴ is the active component, and undergoes minimal first class pass metabolism unlike isosorbide dinitrate,⁴⁵ thus assisting in appropriate dosing for patients with liver disease and portal shunting. Isosorbide mononitrate reaches peak concentrations within an hour of oral dosing, and has a half-life of approximately 5 h. Only 1–2% of an orally administered dose is excreted unchanged in the urine, with the remainder being eliminated as inactive metabolites. Its pharmacokinetic properties are unchanged in the elderly and in patients with renal failure, or liver cirrhosis.⁴⁶ It is therefore preferred to isosorbide dinitrate in such patients. To date it is the only nitrate to be used in large randomized controlled trials for preventing variceal bleeding.

The molecular mechanism of action of nitrates is uncertain. It is thought the vasodilatory actions may be a result of enhanced production of intrahepatic nitric oxide or cyclic-GMP.⁴⁷

There have been a number of haemodynamic studies using isosorbide-5-mononitrate in patients with portal hypertension (Table 3). All the studies with the exception of one,⁴⁹ which included predominantly Childs A patients, demonstrated significant reductions in the HVPG. This appears to have been achieved by a fall in the HVWP. Three studies looking at the chronic effects show that the effect of reduced portal pressure is sustained.^{51–53} Indeed the portal hypotensive effect seemed to be amplified after rechallenge following chronic dosing, confirming lack of tolerance.

Pronounced effects on other parameters may help to explain the mechanism underlying the fall in HVPG, which is comparable to that of propranolol. Early studies⁴⁸ noted that the hepatic blood flow fell acutely, and this along with an increase in systemic vascular resistance index (SVRI) suggested that a baroreceptor-mediated splanchnic vasoconstriction may be responsible for the fall in portal pressure rather than portal venous dilation. However recent work⁵⁵ demonstrated a significant fall in the portal pressure gradient without affecting the portal blood flow in patients with a transjugular intrahepatic portosystemic stent shunt (TIPSS). It was clear, therefore, that in the study group of patients reflex baroreceptor-mediated vasoconstriction

Table 3. The effect of isosorbide-5-mononitrate on portal and systemic haemodynamics

Study	Number of patients	Dose	Child's Class	Acute/chronic study	Mean arterial pressure*	Cardiac output*	Hepatic venous pressure gradient*	Estimated hepatic blood flow*	Azygous blood flow*	Systemic vascular resistance index*
Hayes <i>et al.</i> ⁴⁸	11	20 mg-60 mins	A/B/C: 0/6/5	Acute	NS	-12.0	-8.8	-15.5	Not stated	+10.9
Tsai <i>et al.</i> ⁴⁹	10	20 mg-60 mins	A/B: 9/1	Acute	-10.9	NS	NS	Not stated	Not stated	NS
	6	40 mg-1 week		Chronic	NS	NS	NS	Not stated	Not stated	NS
Navasa <i>et al.</i> ⁵⁰	10	20 mg-60 mins	A/B/C: 6/16/1	Acute	-8.0	-15.0	-9.8	+12.7	NS	+10.6
	9	40 mg-60 mins		Acute	-20.5	-13.5	-19.1	NS	-16.2	NS
Garcia-Pagan <i>et al.</i> ⁵¹	11	80 mg-3 months		Chronic	-7.6	NS	-7.5	+14.4	NS	NS
Grose <i>et al.</i> ⁵²	21	20 mg-60 mins	A/B/C: 6/4/11	Acute	-10.1	Not stated	-10.3	Not stated	NS	Not stated
	8	40 mg-1 month		Chronic	NS	Not stated	-15.8	Not stated	-38.9	Not stated
Jones <i>et al.</i> ⁵³	12	10 mg-60 mins	Mean: 8 ± 0.6	Acute	-5.4	Not stated	-21.9	NS	NS	Not stated
	13	20 mg-1 month		Chronic	NS	Not stated	-31.3	NS	NS	Not stated
		40 mg-60 mins	Mean: 8.1 ± 0.6	Acute	-8.7	Not stated	-23.8	-22.3	NS	Not stated
		80 mg-1 month		Chronic	NS	Not stated	-29.9	NS	NS	Not stated
Escorsell <i>et al.</i> ⁵⁴	12	40 mg-40 min	Mean: 5.8 ± 1	Acute	-14.3	-15	-10	NS	-10.6	Not stated
Forrest <i>et al.</i> ⁵⁵	8	20 mg-60 mins	A/B: 1/7	Acute	-5.8	Not stated	-15.7	Not stated	NS	Not stated

*Measured as the percentage difference from the baseline.

NS = not significant.

tion of the splanchnic bed could not be the case and that any vasoconstrictive effect to account for the rise in SVRI was limited to the periphery. The observed findings were attributed to reduced intrahepatic vascular resistance rather than a reduction in the liver blood flow (which would be undesirable). Chronic administration resulted in no change or even an increase in the hepatic blood flow^{50, 51} and may reflect the buffer response of hepatic artery blood flow to a decrease in portal flow.⁵⁶

Isosorbide-5-mononitrate also reduces the cardiac preload and hence the cardiac output, at least acutely. Significant correlation between the reduction in portal pressure gradient and cardiac output suggests that this may partly be responsible for the reduced portal blood flow observed in this study.⁴⁸ In all cases the mean arterial pressure fell acutely. It is interesting to note that chronic administration does not appear to have a significant effect on cardiac output or mean arterial pressure.

Azygous blood flow has already been demonstrated as a useful indicator of variceal blood flow in patients with

cirrhosis.⁵⁷ Azygous blood flow responds in a variable fashion to isosorbide-5-mononitrate. Jones and colleagues⁵³ demonstrated no significant change in the azygous blood flow in response to varying doses of nitrates, both acutely and following chronic dosing. However, a relationship was noted between baseline azygous blood flow and the response to nitrates, with those patients with a high azygous blood flow responding by reducing their flow and vice versa. The dose did not seem to influence the azygous blood flow.

Nitrate tolerance is clearly documented in cardiovascular medicine.^{58, 59} However, of the studies looking at the chronic effects of isosorbide-5-mononitrate therapy only one has reported partial tolerance in five out of 11 patients,⁵¹ with others reporting no tolerance.^{52, 53} The exact mechanism behind why patients with cirrhosis do not develop nitrate tolerance is unknown. It has been suggested that patients with cirrhosis may not be able to develop compensatory mechanisms that are necessary to bring about nitrate tolerance.⁵³

An important observation with nitrate monotherapy has been the deleterious effect on renal function.⁶⁰

Activation of the renin-angiotensin system was felt to be a major factor. In particular, patients with ascites suffered from a reduced glomerular filtration rate, sodium excretion and renal plasma flow. It is interesting that combination therapy with other portal hypotensive agents abolished these undesirable renal effects. The combination therapies will be covered later.

Drugs acting on alpha adrenergic receptors

Prazosin. Prazosin is an α_1 receptor blocker, which was initially studied by Mills and colleagues³⁶ in a comparative haemodynamic study with propranolol and atenolol over an 8-week follow-up period. An 18% reduction of the hepatic venous pressure gradient was obtained with prazosin compared with 25% with propranolol. Prazosin did not affect the cardiac index or hepatic blood flow, and had no effects on renal function or sodium handling. It acts by reducing intra-hepatic resistance. In a recent study⁶¹ impressive results were obtained with acute and chronic reductions in the HVPG of 25.7% and 19.1% respectively, which are comparable to propranolol. However this was accompanied by a significant fall in the MAP and systemic vascular resistance. An important finding in this study was the tendency to increased ascites and oedema as a result of a reduction in sodium excretion and expansion of the plasma volume. Tolerance was also felt likely to have occurred following chronic administration. Hepatic blood flow and liver function, as quantified by indocyanine green clearance and galactose elimination, were noted to have improved. These findings were mirrored in a subsequent study⁶² and thus the use of prazosin in clinical practice was not an attractive proposition. There are at present no clinical trials using prazosin in primary or secondary prophylaxis of variceal haemorrhage.

Clonidine. Clonidine is a centrally acting α_2 agonist that acts by reducing peripheral noradrenaline outflow and thus the sympathetic tone in patients with cirrhosis.⁶³⁻⁶⁵ A fall in the hepatic venous wedge pressure was believed to occur secondary to reduced post sinusoidal hepatic vascular resistance. Azygous blood flow was reduced, but hepatic blood flow remained unaffected. The change in hepatic haemodynamic parameters was unrelated to changes in the systemic haemodynamics, where there was a reduction in the cardiac output and mean arterial pressure. The hepatomesenteric circulation was more sensitive to the actions of clonidine in

cirrhotic patients compared with healthy controls. Clonidine resulted in a greater fall in the portal pressure compared with propranolol⁶⁶ and a recent study looking at the effects of clonidine and propranolol in cirrhotic patients found that only propranolol or a combination of propranolol and clonidine resulted in a fall in the portal blood flow.⁶⁷ Despite these results, there are no randomized clinical trials using clonidine for primary or secondary prophylaxis in patients with varices. The effect on systemic haemodynamics may limit its use.

Drugs acting on the renin-angiotensin system

Losartan. This is an angiotensin II receptor antagonist that is used in the treatment of systemic hypertension. In cirrhotic patients it is known that the levels of angiotensin II are elevated⁶⁸ and *in vitro* studies have shown that angiotensin II can cause a rise in the portal pressure.⁶⁹ The only published human study demonstrated impressive reductions in the portal pressure of over 20% in response to Losartan⁷⁰ with minimal effects on the systemic circulation.

Irbesartan. This is another angiotensin II receptor antagonist that has been studied by Debernardi-Venon and colleagues with the results published in abstract form.⁷¹ A mean reduction in portal pressure of 20.7% after 2 months in 10 patients is similar to that demonstrated with Losartan. One patient experienced symptomatic hypotension. There was no adverse effect on renal function.

If other studies corroborate these findings, and they were proved not to have deleterious effects on renal function, sodium handling and systemic haemodynamics, angiotensin II receptor antagonists could be ideal agents for use in large randomized clinical trials. Caution is necessary however, because of the deleterious effect on renal function demonstrated in the past with captopril.⁷²

Drugs acting on the serotonin 5₂ receptors

It has been shown in an experimental model that portal hypertensive animals are more sensitive to the vasoconstrictor effects of serotonin on mesenteric veins, and that administration of ketanserin, a 5HT₂ receptor blocker with α adrenergic antagonist activity, resulted in significant reductions in the portal venous inflow and portal pressure.⁷³ The reduction in portal pressure

caused by ketanserin was due mainly to a decrease in portal venous inflow secondary to a decreased cardiac output, which was only seen in portal hypertensive rats. This would be consistent with venous dilatation and pooling of blood in the portal venous system secondary to 5HT₂ receptor blockade. These findings led to human studies investigating the effect of 5HT₂ receptor blockade on portal pressure.

Early trials in cirrhotic patients demonstrated a significant reduction of 23% in the HVPG following ketanserin administration, which was accompanied by reductions in the azygous blood flow and mean arterial pressure with the hepatic blood flow remaining unaffected.⁷⁴ Subsequent studies corroborated these findings.^{75, 76} The chronic administration of ketanserin was associated with a sustained drop in the portal pressure of 14.6%, a reduction in the cardiac index, and a drop in the mean arterial pressure.⁷⁶ This study also demonstrated that 50% of patients developed reversible portosystemic encephalopathy. Hypotension probably results from α receptor blockade.

Combination treatments have also been studied. Ketanserin in combination with propranolol, both administered intravenously, has been shown to reduce the HVPG in patients who did not initially respond to propranolol.⁷⁷ Ritanserin, a more selective serotonin S₂ blocker, was combined with propranolol in a study investigating the haemodynamic effects of the chronic dosing of these agents.⁷⁸ An initial reduction in the portal pressure was noted, but this effect was not sustained during follow up.

These agents have not been studied in randomized controlled trials for the prevention of variceal bleeding or for the treatment of variceal bleeding. The high incidence of encephalopathy observed with monotherapy, and the potential for systemic hypotension may limit their clinical use. Combination therapy with non-selective β -blockers seems more promising.

Drugs affecting plasma volume

The expansion of plasma volume leading to increased cardiac index is believed to play a major role in sustaining portal hypertension.⁷⁹ Thus diuretics or a low sodium diet may in theory help to reduce portal pressure. Early studies suggested that spironolactone had the potential to be as potent a portal hypotensive agent as propranolol.⁸⁰ A significant reduction in the portal pressure of between 10 and 15% was shown to be

accompanied by reductions in plasma volume, cardiac output, mean arterial pressure and azygous blood flow.^{81–83} Hepatic blood flow was unaffected. Although there was no significant correlation between the plasma volume and HVPG, a significant inverse relationship between post treatment serum aldosterone levels and the HVPG was noted, thus confirming the mode of action of aldosterone.⁸¹ The reductions in the HVPG following spironolactone administration were not affected by dietary sodium content suggesting that a low sodium diet alone is not sufficient to reduce the portal pressure.^{82, 83} In clinical practice the use of spironolactone, like propranolol, may be limited by its side effects, particularly painful gynaecomastia which was present in 55% of male patients in one series.⁸⁴ There are no published clinical trials assessing the efficacy of spironolactone in preventing variceal bleeding, although an ongoing study is comparing nadolol monotherapy with nadolol and spironolactone combination therapy in the primary prevention of variceal bleeding.⁸⁵ Initial results show no differences in the bleeding rate in the two groups.

Combination therapy

Combination therapy was first used for the treatment of portal hypertension using nitrates and vasopressin.^{86, 87} Enhancement of the portal hypotensive effect was observed. Studies using propranolol, as already discussed, have revealed that 30% of patients failed to reduce portal pressure.¹³ This observation and the fact that nitrate monotherapy consistently reduced portal pressure led to studies to investigate the effect of combined nitrate and β -blocker therapy (Table 4), a combination that was first investigated *in vitro* by Kroeger and Groszmann.⁸⁸ In general there is an enhanced portal hypotensive effect of the combination therapy using isosorbide-5-mononitrate leading to a further 13–16% fall in the HVPG. This effect is particularly striking in those patients who did not respond to a β -blocker alone.¹⁶ The mechanism proposed has been that of a decrease in the outflow resistance.⁹¹ It is of note that 1 year after combination therapy with nadolol there did not seem to be any additional effect of the nitrate either in the hepatic or systemic haemodynamics⁹³ despite there being a sustained effect after 3 months of therapy. This may be partly explained by a study by Bendsten and associates who demonstrated that placebo treatment had an equal

Table 4. The effect of combination therapy on portal and systemic haemodynamics

Study	Number of patients	Drug(s)/dose	Child's Class/score	Acute/chronic study#	Mean arterial pressure†#	Cardiac output†#	Hepatic venous pressure gradient†#	Estimated hepatic blood flow†#	Azygous blood flow†#	Systemic vascular resistance index†#
Garcia Pagan <i>et al.</i> ¹⁶	20	Propranolol i.v. (0.1 mg/kg bolus 2 mg/h 30 min infusion) + ISMN 20/40 mg	A/B/C: 9/10/1	Acute	-22(-22)	-36(-11.5)	-27(-13.3)	-28.3(-15.5)	-38(0)	+15(-7)
	8	Propranolol + ISMN 20 mg	A/B: 7/1	Acute*	-12	-22	-10	-23	-10.8	NS
Garcia Pagan <i>et al.</i> ¹⁷	21	Propranolol + ISMN 80 mg - 3 months	Mean - 6.6	Chronic	NS	-23(-13)	-19(-9)	NS	-37(-8)	+16
Morillas <i>et al.</i> ⁸⁹	15	Propranolol 114 mg + ISMN 68 mg - 3 months	Mean - 7.6	Chronic	-10, n = 20	-24	-19	Not Stated	-31	+25
Merkel <i>et al.</i> ⁹⁰	46	Nadolol 69 mg + ISMN 34 mg - 6 months	Mean - 7.9	Chronic	-5.2(-0.6)	Not Stated	-30, n = 6 (-15)	Not Stated	Not Stated	Not Stated
Merkel <i>et al.</i> ⁹¹	9	Nadolol 80 mg + ISMN 40 mg - 3 months ^o	Mean - 6	Chronic	NS	Not Stated	-26(-16.8)	Not Stated	Not Stated	Not Stated
Albillos <i>et al.</i> ⁹²	28	Propranolol + ISMN - 3 months	Mean - 6	Chronic	-6.4	-21	-16	NS	Not stated	+21
Merkel <i>et al.</i> ⁹³	11	Nadolol 80 mg + ISMN 60 mg - 3 months ^o	Mean - 6.9	Chronic	NS(NS)	Not Stated	-27(-16)	NS(NS)	Not Stated	Not Stated
	7	Nadolol 80 mg + ISMN 60 mg - 1 year	Mean - 6.9	Chronic	NS(NS)	Not Stated	-18(NS)	NS(NS)	Not Stated	Not Stated

*ISMN administered following 3-12 months of propranolol therapy. average maintenance dose of 85 mg.

oMean maintenance dose.

†Measured as the percentage difference from the baseline.

#Results in brackets represent the additional effect of adding nitrate therapy.

^oFollowing 1 month treatment with Nadolol.

NS = not significant.

effect to propranolol after 1 year suggesting that portal hypertension improves spontaneously in some patients.¹⁸ Although studies looking at the short term effect of nitrates failed to demonstrate tolerance,^{52, 53} nitrate tolerance could still be an explanation for the lack of effect due to a longer follow-up period in this study.⁹³

The hepatic blood flow and liver metabolic activity are unaffected, but the azygous blood flow decreased in most cases with the effect being less pronounced with longer duration of treatment. Mean arterial blood pressure and cardiac output both fell, again with the effect most pronounced following acute administration.

Renal function and ascites formation have been the focus of some of the studies,^{89, 90, 92} particularly as isosorbide-5-mononitrate has been associated with deteriorating renal function.⁶⁰ The findings suggest that the combination of isosorbide-5-mononitrate with either propranolol or nadolol had no detrimental effect on renal function in patients with or without ascites, despite significant effects on hepatic haemodynamics. These encouraging findings have led to a number of clinical trials using such combinations.

Other combination therapies have also been studied, but none of them have been studied in large clinical trials. One combination therapy worth noting is that of prazosin and propranolol.⁹² This study showed a greater portal hypotensive effect of prazosin and propranolol than isosorbide-5-mononitrate and prazosin, with no effect on hepatic or renal function. Undesirable systemic effects unfortunately offset the impressive hepatic haemodynamic results with more patients experiencing symptomatic hypotension in the prazosin arm of the study, thus limiting its use in clinical practice.

CLINICAL APPLICATION OF DRUGS IN PORTAL HYPERTENSION

Primary prophylaxis

β-blockers versus placebo. Propranolol and nadolol have been compared with placebo in nine randomized controlled trials in patients with varices (Table 5), although two of these were published in abstract form.^{99, 100} Another large trial involving 319 patients treated with either placebo or propranolol is not comparable with the other trials.¹⁰³ Here patients were unselected with regard to the presence of cirrhosis and varices. This accounts for the low event rate with just 11 patients bleeding and probably explains why no difference was found in the two groups.

The results of meta-analyses of these trials¹⁰⁴⁻¹⁰⁶ are very favourable for the treatment group, with reductions in the number of bleeding episodes approaching 50%. Overall deaths due to bleeding were significantly reduced by 45% in one of these studies and overall deaths by 22% ($P = 0.052$).¹⁰⁴ The other two analyses did not show any benefit on overall survival, although in one mortality from bleeding episodes was reduced by 50%.¹⁰⁵ This analysis also demonstrated that the presence of ascites was associated with greater mortality and bleeding risk. One of the main problems with many of the trials is the low number of patients, resulting in insufficient power to detect a reduction in bleeding risk and especially mortality. The study by Colman *et al.*¹⁰⁰ is unique in showing an increase in bleeding rate in the treatment group. However the sample size of this study is low and the very low event rate in the control group suggests that patient selection may have been responsible.

Table 5. Beta-blocker therapy in the primary prophylaxis of variceal haemorrhage

Trial	Drug	Number of patients		Follow up (months)	Bleeding rate (%)		Death rate (%)	
		Control	Treatment		Control	Treatment	Control	Treatment
Pascal <i>et al.</i> ⁹⁴	Propranolol	112	118	24	61	26	49	28
Italian ⁹⁵	Propranolol	89	85	42	41	26	49	41
Conn <i>et al.</i> ⁹⁶	Propranolol	51	51	16	22	4	22	16
PROVA ⁹⁷	Propranolol	72	68	15	18	18	19	10
Anreani <i>et al.</i> ⁹⁸	Propranolol	41	42	24	39	6	46	34
Strauss <i>et al.</i> ⁹⁹	Propranolol	16	20	24	25	20	44	35
Colman <i>et al.</i> ¹⁰⁰	Propranolol	25	23	24	8	35	28	26
Ideo <i>et al.</i> ¹⁰¹	Nadolol	49	30	24	30	6	18	10
Lebrec <i>et al.</i> ¹⁰²	Nadolol	53	53	12	20	17	19	19

A recent trial by Calès and colleagues involving 206 patients with no or only small (< 5 mm) varices was performed to investigate whether propranolol prevents the development of varices.³ One-hundred and four patients were randomized to receive placebo and 102 to receive long acting propranolol (160 mg/day). After a 2-year follow-up period 31% of patients in the propranolol arm and 14% of patients taking placebo developed large varices ($P < 0.05$). There was no difference in the rate of bleeding or mortality in the two groups. The low bleeding rate in the placebo group may reflect the small numbers of patients in Child's C class (13%). However the high incidence of the development of varices in the propranolol group is striking. The authors postulated that above a certain portal pressure the development of varices is not directly related to portal pressure and other 'non-haemodynamics' play a part. Another mechanism proposed was that of increased vascular resistance in the collateral circulation following propranolol administration, although it is not clear what the relationship between collateral resistance and the development of varices is. Clearly further studies would assist in elucidating the exact mechanisms. This may involve the measurement of portal pressure in the two groups. Until further studies are performed it is not recommended that propranolol be prescribed for the prevention of the development of varices and bleeding in cirrhotic patients with small or no varices.

Studies have shown propranolol to be safe in long term use in patients with cirrhosis, but up to a third of patients are intolerant of the side effects resulting in discontinuation of the drug.²³ The dosage in most of the studies is that required to reduce the resting heart rate by 25%. This usually means starting therapy with a dose 40 mg twice daily and working up to an average maintenance dose of 160 mg/day. Nadolol is typically administered at a dose of 80 mg/day. Fatigue is the most important side effect. Compliance can be a major problem, especially in patients with alcoholic liver disease.

Isosorbide-5-mononitrate. There is only one published randomized controlled trial comparing ISMN with placebo.¹⁰⁷ Forty-two cirrhotic patients were randomized to either ISMN ($n = 23$) or placebo ($n = 19$). Both groups were followed up for an average of 43–49 weeks. There was a tendency towards reduced bleeding

and death in the ISMN group, although the results did not reach statistical significance. It is also of note ISMN was well tolerated.

A recent randomized double-blinded study published in abstract form comparing ISMN (in patients intolerant of β -blockers) with placebo in 133 consecutive cirrhotic patients with gastro-oesophageal varices, reported a higher first bleeding rate in the treatment group (29%) than in the placebo group (14%) following a 2-year follow-up period.¹⁰⁸ There was no significant difference in survival. The presence of ascites, larger variceal size and red signs were associated with a greater incidence of the first bleed. A greater withdrawal from the study because of side effects was noted in the ISMN group.

There was no effect on the development of new ascites or worsening of existing ascites in the treatment arm. The incidence of bleeding in the placebo group was lower than in most other studies. The full paper will need to be published before conclusions can be made from this study.

Others have compared ISMN with propranolol.¹⁰⁹ This was a large randomized trial over a 7-year follow-up period involving 118 patients. The probability of bleeding was identical in both the groups. Mortality was significantly greater in the nitrate group, but this was only in patients above 50 years of age.

A smaller study demonstrated that ISMN was less effective than nadolol in preventing bleeding in 30 patients with ascites.¹¹⁰ Mortality was unaffected, but sodium excretion was reduced by almost 50% in the nitrate group. The small size of this study makes it difficult to draw conclusions from the findings.

It appears that ISMN is at least as effective as propranolol in the prevention of gastrointestinal haemorrhage. However the reduced mortality seen with propranolol is not present in the nitrate group. Caution is needed in prescribing nitrate monotherapy on account of the potential for deterioration in renal function and the increased mortality seen in the older age group.¹⁰⁹ This may explain why there are not so many trials using nitrate monotherapy and many more looking at combination therapy.

Combination therapy. As discussed earlier, combination therapy has been shown to be effective in producing a sustained portal hypotensive response. The only combination that has been studied in large randomized trials is that of nitrates and β -blockers.

Nadolol monotherapy has been compared with nadolol and ISMN dual therapy by Merkel and colleagues with the results of long-term follow-up published recently.^{111, 112} Initial results following a 30-month follow-up period in 146 patients demonstrated a significant reduction of greater than 50% in the cumulative risk of variceal bleeding in the combination treatment group compared with nadolol alone. There was a non-significant trend towards reduced mortality in the combination therapy group. However there was a high incidence of side effects in the combination group (51%), which were severe enough to cause withdrawal from the study in 11% of patients. This compares with 4% in the nadolol only group.

Long-term follow-up of these patients over 7 years has revealed a sustained effect of combination therapy in preventing variceal haemorrhage.¹¹² Survival was unaffected. A larger sample size would be required to show up any survival differences. Two significant findings are of note. First, long-term administration did not result in further side-effects leading to withdrawal from the study. Thus side-effects usually occur early, after the initial doses for nitrates, and in the first few months in the case of β -blockers. Second, there was no significant effect on the occurrence of *de novo* ascites in the two groups. Previous studies have shown a deleterious effect on renal function and sodium handling when using nitrate monotherapy.⁶⁰

Another two double-blind placebo-controlled randomized studies have been published in abstract form.^{113, 114} The first of these compared propranolol and placebo with propranolol and ISMN in 349 patients of whom 57% had > 5 mm size varices.¹¹³ Low bleeding rates at 2 years in both the groups were 13% and 10% respectively. The bleeding rates were similar in patients with only large varices. Mortality was similar in both groups, but there were significantly more side-effects in the combination group (36.5% vs. 24.7%, $P < 0.05$). Development of ascites and renal function were unaffected.

The second study¹¹⁴ involved fewer patients. Patients with large oesophageal varices and red colour signs were randomized to either nadolol and placebo ($n = 27$) or nadolol and ISMN ($n = 30$). There was no significant difference in the bleeding rate or mortality following a 2-year follow-up. Side-effects were significantly more common in the combination group (53% vs. 26%, $P = 0.03$) with 40% in the combination group withdrawing as a result, compared with 15% in the nadolol monotherapy group ($P = 0.034$). However the study

was terminated early on account of excess mortality in patients treated with nadolol and ISMN in a parallel trial for the prevention of rebleeding.¹¹⁵ Thus it is not appropriate to make valid conclusions based on this trial.

Beta-blocker and ISMN combination therapy, in particular nadolol and ISMN, appears to be more effective than nadolol monotherapy in preventing the first variceal bleed. Until further studies are performed there does not appear to be any advantage in adding ISMN to propranolol. The side-effect profile of combination therapy is considerably worse, and this is likely to limit its clinical application. Outside of clinical trials patients and clinicians may not be so vigilant in continuing therapy that leads to so many side-effects when alternatives such as endoscopic treatments are available.

Pharmacological agents compared with endoscopic treatments. Sclerotherapy has been compared with placebo and propranolol in two studies^{97, 98} and the efficacy of sclerotherapy and propranolol combination therapy assessed in one of these and a further study.^{97, 116} One study revealed that bleeding from a portal hypertensive source was significantly less in the propranolol group than the sclerotherapy group (4.7% vs. 21.4%, $P < 0.003$).⁹⁸ None of the studies showed differences in variceal bleeding or mortality when propranolol was compared with sclerotherapy.

A recent trial, which selected patients with high intra-oesophageal variceal pressures, randomized patients to propranolol (42 patients) or to propranolol plus sclerotherapy (44 patients).¹¹⁶ After a 2-year follow-up period, 23% of the patients in the combination group bled due to varices or congestive gastropathy as compared with 14% in the propranolol group (not significant). Fifty-two per cent in the combination group developed complications as compared with 19% in the propranolol group ($P = 0.002$). The mortality rate was similar in both groups. The findings are similar to those in an earlier study where patients were unselected with regard to the characteristics of varices.⁹⁷

Endoscopic band ligation is a recent technique that has been compared with sclerotherapy in a meta-analysis,¹¹⁷ and was found to be superior to sclerotherapy in the secondary prophylaxis against variceal rebleeding with fewer complications and quicker eradication of varices. Band ligation has been compared with propranolol for the primary prophylaxis of variceal bleeding in two published trials^{118, 119} and also a recent abstract from our center.¹²⁰ In the first study,¹¹⁸ 30 patients

with grade III or higher varices were studied over a 17-month follow-up period. There was no difference in the bleeding rate in the two groups. Sarin and colleagues¹¹⁹ studied 89 patients with greater than 5 mm varices and observed that over a 17-month period the probability of bleeding was 43% in the propranolol group and 15% in the ligation group ($P = 0.04$). There was no difference in mortality. The very high bleeding rate in the propranolol group contrasts with that observed in other trials. The dose of propranolol was also lower than in other trials. A recent multicenter trial involving 172 patients compared propranolol, ISMN and band ligation over a mean follow up of 20 months.¹²⁰ Banding was superior to ISMN but similar to propranolol in preventing the first bleed. There was no difference in the overall mortality in the three groups. A very significant proportion of patients had to withdraw from drug therapy as result of side-effects.

Clearly, of the two modes of endoscopic treatments, banding is preferable to sclerotherapy because there are fewer iatrogenic complications and it has been shown to be at least as good as if not better than propranolol. Banding is particularly useful where patients are intolerant of drug therapy. Sclerotherapy combined with propranolol does not offer any further benefit over propranolol monotherapy. It remains to be seen whether this is also the case with banding. It therefore appears that banding is at least as good as propranolol in the primary prevention of variceal bleeding and will probably be widely employed, because of its lack of dependence on compliance and the attraction of eradicating oesophageal varices.

Secondary prophylaxis

It is clear that secondary prevention following a variceal bleed is essential in view of the high rate of rebleeding without intervention.² There is a greater choice of endoscopic, pharmacological, radiological and surgical therapies for secondary prophylaxis than for primary prophylaxis.

β -blockers versus placebo. There were several trials in the 1980s, and a meta-analysis of these performed in our center revealed significant benefits of propranolol therapy.¹⁰⁴ In a population of 1080 patients there was a 39% reduction in rebleeding episodes, a 40% reduction in deaths from bleeding and a 25% reduction in total mortality in the propranolol groups. Heterogeneity was significant for rebleeding episodes, but not when deaths from bleeding or overall mortality were assessed. Although not all of these trials were randomized or placebo controlled, further analysis of selected trials that met more strict criteria, and in those where there was no significant heterogeneity, demonstrated significant benefits from propranolol therapy in the reduction of bleeding and improved mortality rates.

There are 12 published randomized controlled trials comparing β -blockers with placebo against variceal rebleeding (Table 6). Propranolol was assessed in 11, nadalol in one and atenolol in one study which also included propranolol.¹²⁸ The latter study found atenolol to be less effective than propranolol at reducing rebleeding and improving patient survival. A meta-analysis of these trials¹⁰⁶ demonstrated a significant

Table 6. β -blocker therapy in the secondary prophylaxis against variceal rebleeding

Trial	Drug	Number of patients		Follow up (months)	Rebleeding rate (%)		Death rate (%)	
		Control	Treatment		Control	Treatment	Control	Treatment
Burroughs <i>et al.</i> ¹²¹	Propranolol	22	26	21	59	54	23	15
Lebrec <i>et al.</i> ¹²²	Propranolol	36	38	24	64	21	22	8
Villeneuve <i>et al.</i> ¹²³	Propranolol	37	42	24	81	76	38	45
Carbelaud <i>et al.</i> ¹²⁴	Propranolol	50	50	24	78	40	33	26
Queuniet <i>et al.</i> ¹²⁵	Propranolol	48	51	18	64	57	21	23
Gatta <i>et al.</i> ¹²⁶	Nadalol	12	12	33	67	25	25	8
Kobe <i>et al.</i> ¹²⁷	Propranolol	28	26	16	46	38	32	23
Colombo <i>et al.</i> ¹²⁸	Propranolol	30	32	11	47	25	23	12
Colombo <i>et al.</i> ¹²⁹	Atenolol	30	32	11	47	31	23	9
Sheen <i>et al.</i> ¹³⁰	Propranolol	18	18	24	55	28	11	0
Garden <i>et al.</i> ¹³¹	Propranolol	43	38	24	77	47	44	37
Colman <i>et al.</i> ¹³²	Propranolol	26	26	24	50	35	4	4
Rossi <i>et al.</i> ¹³³	Propranolol	27	27	19	63	48	33	26

reduction in the rebleeding rate from 66% in the placebo group to 44% in the treatment group (pooled odds ratio of 0.4). There was no significant effect of drug therapy on survival, which may reflect the heterogeneity of the study populations, particularly with respect to aetiology, severity of the liver disease and the time to treatment from the index bleed. Only two of these studies included a significant proportion of Child's C patients,^{123, 131} and benefit for the Child's C patients was seen in one.¹³¹

A recent meta-analysis also revealed that there was a significantly greater reduction in the variceal rebleeding rate in the β -blocker treated patients than in the placebo group (20% mean improvement rate, $P < 0.001$).¹³⁴ However this study also demonstrated that there was a significant improvement in the survival rate in the treatment group with a mean improvement of 5.5% ($P = 0.05$), with this being more marked in patients with more advanced liver disease. The methods of analysis did not reveal any significant heterogeneity amongst the trials. It would therefore seem appropriate that β -blocker therapy for secondary prophylaxis can be recommended for patients regardless of the degree of liver disease. Although the prevalence of adverse events was significantly higher in the treatment group, because adverse events were only mentioned in some of the studies it remains somewhat unclear of the impact of this on practice.

Combination therapy. There is only one published trial assessing the effect of combination drug therapy in preventing variceal rebleeding.¹³⁵ In this randomized study involving 95 patients, after a 2-year follow-up period, overall rebleeding and survival was not improved by the addition of ISMN to propranolol compared with propranolol alone. However there was a significant reduction in the risk of rebleeding when patients were stratified according to age, i.e. less than 50 years old versus over 50 year olds or by adding an extra year of follow up. It is also of note that more patients experienced side-effects leading to discontinuation of medication with the combination therapy. However no adverse events concerning renal function or effect on ascites was observed with the combination therapy.

Another two studies published in abstract form reinforce the findings of the above study that combining β -blockers with ISMN offers no additional benefit in reducing the overall rebleeding rate and mortality.^{136, 137}

In fact one of these studies reported greater mortality in patients treated with nadolol and ISMN than nadolol alone (32% vs. 14%, $P = 0.02$).¹³⁶ Clearly the full paper would need to be published and analysed before firm conclusions can be made.

It seems, therefore, that combination therapy may have a role in secondary prophylaxis, but adverse side-effects may limit its clinical use. Further studies are necessary before confident recommendations can be made.

Pharmacological agents compared with endoscopic treatments. There have been several trials comparing sclerotherapy with β -blockers alone or β -blockers combined with sclerotherapy. Meta-analysis of these studies¹⁰⁴ demonstrated a small benefit of sclerotherapy over propranolol on the rebleeding rate but no effect on survival. Sclerotherapy was associated with a greater number and severity of complications. Propranolol combined with sclerotherapy was found to be better than sclerotherapy in reducing the rebleeding rate, but there was no difference in survival. The rationale being that the addition of propranolol reduces the risk of rebleeding in the first few months before the varices are completely eradicated. However the meta-analysis revealed significant heterogeneity in all these trials, which makes firm conclusions difficult. A recent abstract found that propranolol and sclerotherapy were significantly more effective at reducing the rebleeding rate than sclerotherapy alone (11/35 vs. 16/30 patients, $P < 0.001$).¹³⁸ It is interesting that most of the difference was accounted for by a greater incidence of bleeding from gastric varices and congestive gastropathy in the sclerotherapy only group.

Propranolol in combination with sclerotherapy was found to be superior, in terms of rebleeding rate and survival, to propranolol alone based on the results of two studies. In the meta-analysis the odds ratios for rebleeding in the above trial comparisons were not as low as that when comparing propranolol with placebo. The trials comparing the latter were also of a higher quality with a longer follow-up period. Another meta-analysis comparing propranolol with sclerotherapy mirrors these findings in that sclerotherapy was more effective at reducing variceal rebleeding, but was associated with more iatrogenic adverse events.¹³⁹ Survival was similar in the two groups.

The combination of nadolol and ISMN was found to be superior to sclerotherapy in a recent trial.¹⁴⁰ Rebleeding

rate and treatment related complications were significantly lower than in sclerotherapy. Overall survival was, however, identical in the two groups. It is interesting that patients in whom the hepatic venous wedge pressure fell by 20% or more had far fewer episodes of rebleeding.

Banding has been compared with β -blocker and ISMN combination therapy in preventing recurrent variceal bleeding in three studies all published in abstract form.¹⁴¹⁻¹⁴³ The results suggest that drug therapy is better than band ligation in reducing the risk of rebleeding, although there was no effect on mortality. The full report of these trials is awaited.

It seems, therefore, that further trials with a longer follow-up and including banding combined with propranolol are necessary before combination drug or endoscopic therapy can be recommended for the secondary prophylaxis against variceal rebleeding.

Pharmacological agents compared with transjugular intra-hepatic portosystemic shunt (TIPSS). The only publication is a study published in abstract form that randomized patients to either TIPSS only ($n = 47$) or propranolol and isosorbide-5-mononitrate combination therapy ($n = 44$).¹⁴⁴ The TIPSS arm had significantly fewer episodes of rebleeding (11% vs. 32%, $P = 0.02$), but encephalopathy was significantly higher in the shunted group (38% vs. 11%, $P = 0.004$). Mortality was similar for both groups. The cost of TIPSS was more than twice that of drug therapy. Full publication of the report is awaited.

There is no doubt that TIPSS is very effective at reducing rebleeding and has been demonstrated in a recent meta-analysis to be more effective than endoscopic therapy, although overall survival is similar.¹⁴⁵ Encephalopathy often responds to simple measures and in most cases improves or resolves over time.¹⁴⁶ There is now more of a case for TIPSS to be used early in the secondary prevention of variceal bleeding in patients with more advanced disease. Further studies with drug therapy are needed before conclusions can be made about its efficacy compared with TIPSS in the prevention of variceal rebleeding.

CONCLUSIONS

There have been many studies investigating the effect of pharmacological agents on portal hypertension with varying results. Of these agents non-selective β -blockers

and isosorbide-5-mononitrate alone and in combination seem to be the most promising. The haemodynamic response to drug therapy also has been shown to correlate with the risk of bleeding, and monitoring the haemodynamic response to medical therapy may assist in appropriate dosing and choice of agent. Newer preparations such as carvedilol and losartan deserve further study following very encouraging initial results.

Large randomized clinical trials remain the gold standard for testing the efficacy of these agents in preventing the initial variceal bleed and rebleeding. The first choice for primary prevention are non-selective β -blockers, although recent evidence suggests a role for β -blockers in combination with isosorbide-5-mononitrate. Endoscopic variceal ligation also compares favourably with drug therapy especially where drugs are not tolerated.

For secondary prevention non-selective β -blockers are also effective and similar to sclerotherapy. As band ligation replaces sclerotherapy the relative efficacy of drug therapy versus band therapy should be studied. Following initial encouraging results further studies looking at combination therapy for secondary prevention are needed. TIPSS is also very effective at reducing the rebleeding rate compared with endoscopic therapy, and has a place in the management of patients with more advanced liver disease. It is currently unclear how TIPSS compares with pharmacological agents.

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Haemodynamic effects of acute and chronic administration of low-dose carvedilol, a vasodilating β -blocker, in patients with cirrhosis and portal hypertension

D. TRIPATHI, G. THERAPONDOS, H. F. LUI, A. J. STANLEY & P. C. HAYES

Liver Unit, Department of Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK

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SUMMARY

Background: Carvedilol is a non-selective vasodilating β -blocker with weak α_1 receptor antagonism. Recent studies have demonstrated its potential as a portal hypotensive agent.

Aim: To assess the haemodynamic effects and patient tolerability of the acute and chronic administration of low-dose carvedilol.

Methods: Haemodynamic measurements were performed in ten cirrhotic patients before and 1 h after the administration of 12.5 mg oral carvedilol. The study was repeated 4 weeks after daily administration of 12.5 mg carvedilol.

Results: After acute administration of carvedilol, there was a 23% reduction in the hepatic venous pressure

gradient from 16.37 ± 2.14 to 12.56 ± 3.91 mmHg ($P < 0.05$), with significant falls in the heart rate, mean arterial pressure and cardiac output. Chronic administration resulted in a further fall in the hepatic venous pressure gradient from a baseline of 16.37 ± 0.71 to 9.27 ± 1.40 mmHg ($P < 0.001$) with the mean arterial pressure being unaffected. The drug was well tolerated with only one patient experiencing asymptomatic hypotension.

Conclusions: The results show that low-dose carvedilol is an extremely potent portal hypotensive pharmacological agent, and is worthy of further investigation in large randomized trials to assess its effect in preventing variceal haemorrhage.

INTRODUCTION

The haemodynamic effects of propranolol have been well studied. Lebrech *et al.* demonstrated a greater than 20% reduction in the hepatic venous pressure gradient (HVPG) following the acute administration of propranolol,¹ but up to one-third of patients do not exhibit a portal hypotensive response.² This may be explained by a portal hypertensive model demonstrating that a rise in the portocollateral resistance accompanies the reduc-

tion in portal blood flow, thus reducing the overall portal hypotensive response to propranolol.³ Current evidence suggests that the goal of pharmacotherapy in reducing the risk of variceal haemorrhage is to achieve a fall in the HVPG to ≤ 12 mmHg⁴ or a 20%⁵ reduction from baseline values.

The role of non-selective β -blockers in the primary prevention of variceal haemorrhage has been extensively studied.^{6–14} Meta-analysis of these trials has clearly shown the benefit of these drugs when compared with placebo.¹⁵ However, many patients are intolerant to drug side-effects.^{10, 13}

α_1 antagonism has been investigated in three haemodynamic studies.^{16–18} Impressive reductions in the HVPG were achieved and these were comparable with

Correspondence to: Dr D. Tripathi, Department of Medicine, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh, EH3 9YW, UK.
E-mail: d.tripathi@ed.ac.uk

those of propranolol. It was postulated that prazosin exerted its effect by reducing the intrahepatic resistance. However, patients suffered from symptomatic hypotension and a worsening of renal function and ascites. Prazosin in combination with propranolol was found to achieve a greater reduction in the portal pressure than a combination of propranolol and isosorbide-5-mononitrate.¹⁹ It is interesting that the combination of an α blocker and a non-selective β -blocker had no effect on renal function. A drug which combines the properties of these two agents is worth investigating.

Carvedilol is a vasodilating non-selective β -blocker with weak α_1 receptor and calcium channel antagonism. It has a rapid onset of action with 2–4 times greater β -blocking action than propranolol.²⁰ Studies have shown that carvedilol at a dose of 25 mg daily is effective in reducing the HVPG in cirrhotic subjects,^{21, 22} both acutely and after chronic use. A recent study has demonstrated that carvedilol is more effective in reducing the portal pressure than intravenous propranolol or placebo when administered acutely.²³ However, all of these studies reported a significant incidence of systemic hypotension, which was dose related, whilst renal function was unaffected. A 15% fall in HVPG was reported following the acute administration of 10 mg carvedilol, but to date there has been no investigation of the haemodynamic effects of low-dose carvedilol following chronic administration.²⁴ The aim of this study was to investigate the acute and chronic effects of low-dose carvedilol on portal and systemic haemodynamics and the patient tolerability at this dose.

PATIENTS AND METHODS

Ten patients, seven male and three female, with a mean age of 53 ± 4.07 years, were recruited, all of whom had either biopsy-proven or clinical, biochemical and ultrasonographic evidence of cirrhosis. Eight patients had alcoholic liver disease, one patient had primary biliary cirrhosis and one patient had hepatitis C virus-related cirrhosis. Seven patients had Child–Pugh grade B disease, one grade A and two grade C. Six patients had ascites at the time of the study or in the past. All patients had gastro-oesophageal varices, with none having bled. All patients gave informed consent and the study was approved by the Lothian Medicine and Oncology Ethics Committee. The study protocol was in

accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

All patients had baseline haemodynamic measurements performed following an overnight fast. They were then given 12.5 mg of oral carvedilol (Roche Pharmaceuticals) and haemodynamic measurements were repeated after 1 h as per our previous protocols using this drug.^{21, 22} After completion of the acute study, patients were instructed to take 12.5 mg of carvedilol daily at 09.00 h for 4 weeks, after which time the haemodynamic measurements were repeated before and 1 h after the administration of 12.5 mg carvedilol as per the initial protocol. There was no change in the observed alcohol consumption for the duration of the study. There were no detectable serum ethanol levels prior to each study or during follow-up.

Haemodynamic study protocol

All measurements were performed in the Liver Haemodynamics Suite. Blood for baseline biochemical and haematological measurements was obtained from a peripheral vein. All haemodynamic measurements were performed in the supine position. After infiltration with 10 mL 2% lignocaine (lidocaine), a 7 FG venous introducer (Cordis, USA) was inserted into the right femoral vein using the Seldinger technique. Under fluoroscopic guidance, a Swan–Ganz catheter (Baxter Healthcare Corporation, USA) was inserted through the introducer to measure cardiac output (CO) and right atrial pressure (RAP) in the standard manner. Using the same catheter, or a Sidewinder II torque balloon catheter (Cordis Corporation, USA), the main right hepatic vein was then catheterized for the measurement of the free (FHVP) and wedge (WHVP) hepatic venous pressures. The HVPG was derived from WHVP – FHVP. All haemodynamic measurements were taken in triplicate, with the mean of the values being used for analysis. The mean arterial pressure (MAP) was measured using an automatic sphygmomanometer (Hewlett Packard series 54 model 78339A) and was calculated as (pulse pressure/3) + diastolic blood pressure. The systemic vascular resistance (SVR) was calculated as $(79.96 (MAP - RAP)/CO)$.

The hepatic blood flow (HBF) was derived from measurements of the indocyanine green (Akorn) clearance and extraction. Indocyanine green was infused at the beginning of the study as a 10 mg

intravenous bolus via a peripheral cannula, followed by an infusion of 0.2 mg/min indocyanine green. After an equilibration time of 40 min, three samples were taken simultaneously from the right hepatic vein and femoral vein. The HBF was calculated using the following equation (provided that the hepatic excretion exceeded 10%):

$$\text{HBF} = (\text{indocyanine green clearance} / \text{indocyanine green extraction}) / (1 - \text{haematocrit})$$

Statistical analysis

All results are expressed as the mean \pm S.E.M. Parametric data were analysed using the paired Student's *t*-test and Pearson's correlation. The Wilcoxon signed rank test and Spearman correlation were used for non-parametric data. Significance was taken at the 5% level. Microsoft Excel 2000 and SPSS packages (version 9, Chicago, IL, USA) were used for statistical analysis.

RESULTS

Nine patients completed both the acute and chronic studies. One male patient with Child's C disease, who had a hypotensive reaction to acute dosing with

carvedilol and developed an alcoholic hepatitis, completed only the acute phase of the study.

Portal haemodynamics

Following the acute administration of carvedilol, there was a $23.9 \pm 5.6\%$ reduction in HVPG (from 16.37 ± 2.14 to 12.56 ± 3.91 mmHg; $P < 0.05$), due principally to a reduction in WHVP (from 22.03 ± 1.28 to 16.86 ± 1.15 mmHg; $P < 0.01$) with no significant change in FHVP (Table 1). Chronic administration resulted in a sustained and even greater fall in HVPG from the baseline average value of 16.37 ± 0.71 to a pre-dosing value following chronic dosing of 9.27 ± 1.40 mmHg ($P < 0.001$, $43.4 \pm 9.2\%$). In all cases except one, there was a $\geq 20\%$ reduction in HVPG after chronic dosing. There was no additional effect on HVPG following re-challenge with carvedilol (Figures 1–4).

Hepatic blood flow

Indocyanine green clearance and extraction were measured in five patients (Table 1). In the acute phase of the study, there was a significant reduction in HBF from 1725 ± 435 to 718 ± 179 mL/min ($P < 0.05$, $n = 5$) following acute administration. Following chronic dosing, one patient had an initial indocyanine

Table 1. Haemodynamic data for acute and chronic studies

	Acute dosing		After chronic dosing	
	Baseline	+ 60 min	Baseline	+ 60 min
HVPG (mmHg)	$16.37 \pm 0.71\alpha$	$12.56 \pm 1.30^*$	$9.27 \pm 1.40\beta$	10.27 ± 1.16
WHVP (mmHg)	22.03 ± 1.28	$16.86 \pm 1.15\ddagger$	16.92 ± 1.65	16.98 ± 1.47
FHVP (mmHg)	5.67 ± 1.03	4.3 ± 0.56	7.59 ± 0.93	$6.64 \pm 1.00\ddagger$
HR (b.p.m.)	88.33 ± 5.81	$79.11 \pm 4.93\ddagger$	71.78 ± 4.62	71.89 ± 4.93
MAP (mmHg)	90.33 ± 4.95	$81.56 \pm 5.84\ddagger$	85.67 ± 4.29	83.22 ± 3.76
CO (L/min)	7.11 ± 0.93	$6.29 \pm 0.75^*$	6.72 ± 0.77	6.74 ± 0.84
RAP (mmHg)	3.22 ± 1.02	$1.22 \pm 0.57^*$	6 ± 1.22	$3.33 \pm 1.18\ddagger$
SVR (dyn/sec/cm ⁻⁵)	1111 ± 138	1118 ± 131	1151 ± 112	1156 ± 164
HBF (mL/min)	1725 ± 435	$718 \pm 179^*\ddagger$	539 ± 99	$720 \pm 203\§$

CO, cardiac output; FHVP, free hepatic venous pressure; HBF, hepatic blood flow; HR, heart rate; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; RAP, right atrial pressure; SVR, systemic vascular resistance; WHVP, wedge hepatic venous pressure.

$n = 9$ unless otherwise stated.

α vs. β : $P < 0.001$.

* $P < 0.05$ compared to baseline.

$\ddagger n = 5$.

$\ddagger P < 0.01$ compared to baseline.

$\§ n = 4$.

green extraction of < 10%, and therefore HBF could not be calculated. There was no further significant reduction in HBF following chronic administration or re-challenge with carvedilol ($n = 4$).

Systemic haemodynamics

MAP fell acutely from 90.33 ± 4.95 to 81.56 ± 5.84 mmHg ($P < 0.01$), but with chronic administration and re-challenge there was no additional change. CO also fell acutely with no additional effect after

chronic dosing or re-challenge. The heart rate fell with acute and chronic dosing, but was unaffected following re-challenge with carvedilol. RAP fell acutely and following re-challenge. SVR was unaffected. The changes in HVPG did not correlate with changes in MAP, CO, heart rate or RAP.

Liver function tests and renal function

The serum alanine aminotransferase, bilirubin, creatinine and clotting parameters were unaffected by chronic administration.

Tolerability

No side-effects were reported, except in one patient who experienced palpitations, and no patients were withdrawn because of side-effects. The patient who became hypotensive after acute dosing experienced a fall in MAP from 64 to 57 mmHg. He successfully completed the acute study and remained asymptomatic. His blood pressure normalized after 3 h and following colloid administration.

There were six patients with a history of ascites, although only four had ascites at the time of the study, which limited valid statistical analysis. These patients exhibited a similar reduction in HVPG following acute and chronic dosing of 26.41% and 38.38%, respectively. There was no significant reduction in MAP (-1.23%). No patients experienced

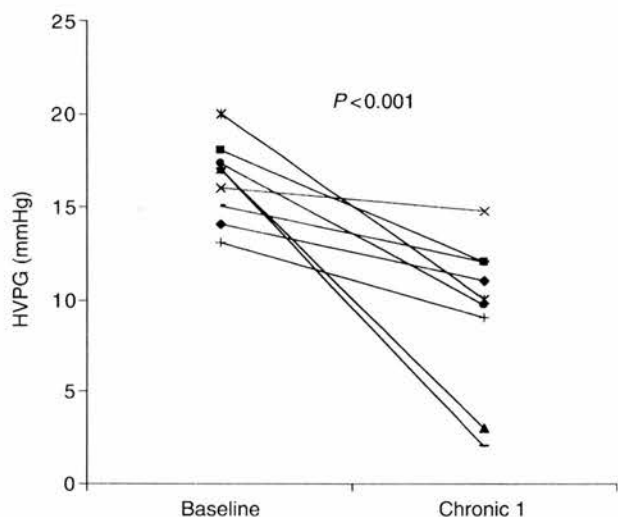


Figure 1. Effect on hepatic venous pressure gradient (HVPG) following chronic dosing. Each patient is represented by a symbol.

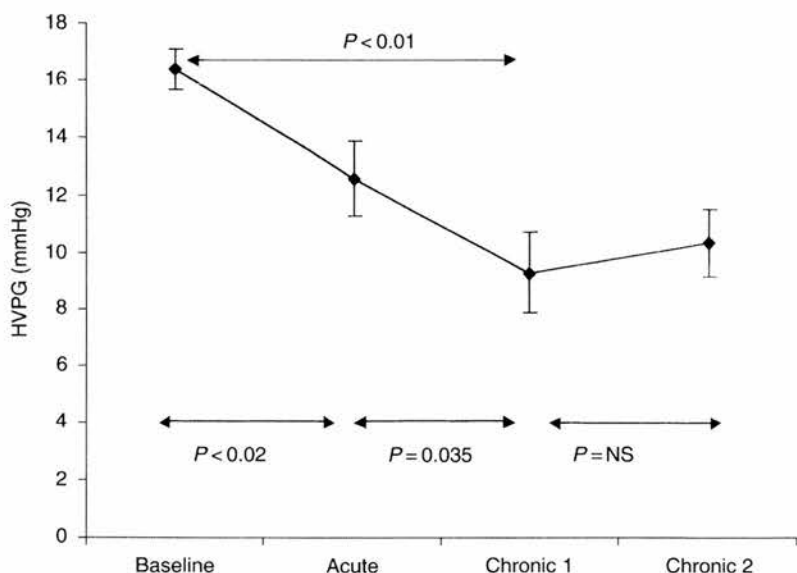


Figure 2. Overall effect on hepatic venous pressure gradient (HVPG).

deterioration in ascites or renal function during follow-up.

DISCUSSION

These results clearly show that carvedilol, at a dose of 12.5 mg/day, is a potent portal hypotensive agent and is well tolerated. Its acute administration significantly reduces portal pressure, an effect which is maintained following chronic dosing.

The acute haemodynamic effect of low-dose carvedilol has been investigated in two previous studies.^{23, 24} A 10 mg dose significantly reduced HVPG by 15% after 60 min and by 17% after 90 min in 10 patients, although only 50% of patients had a greater than 20% reduction in HVPG.²⁴ The 12.5 mg dose has been investigated in a smaller study, which did not demonstrate an effect on the portal or systemic haemodynamics, although there was a tendency to reduce HVPG and MAP.²³ The reductions in HVPG, CO and MAP observed following acute dosing in this study are consistent with those observed in previous studies performed in our unit using 25 mg of carvedilol.^{21, 22} We also demonstrated a reduction in HBF in a small number of patients, a

finding that was noted in one of the previous studies.²³ These haemodynamic findings are consistent with non-selective β -blockade, as demonstrated with propranolol.¹ In comparison with propranolol, carvedilol has less of an effect on CO and heart rate compared with its effect on HBF, suggesting that the degree of β_1 blockade is less than that of propranolol, at least acutely.²³ However, chronic administration did not lead to a further significant fall in CO and MAP despite a reduction in the heart rate. These findings are similar to those previously demonstrated in our centre.²² α_1 receptor antagonism, and hence reduced intrahepatic resistance, is likely to have contributed to the marked reduction in HVPG following chronic dosing. A reduction in HBF noted in a small group of patients could have had an additional effect.

A recent abstract has shown that the reduction in HVPG, MAP, heart rate and CO is greater with chronic administration of carvedilol than with administration of propranolol.²⁵ HBF was unchanged with carvedilol, but decreased with propranolol. The authors expressed concern about the significant reduction in MAP. The dose of carvedilol used was significantly greater than that used in our study (31 vs. 12.5 mg/day), which

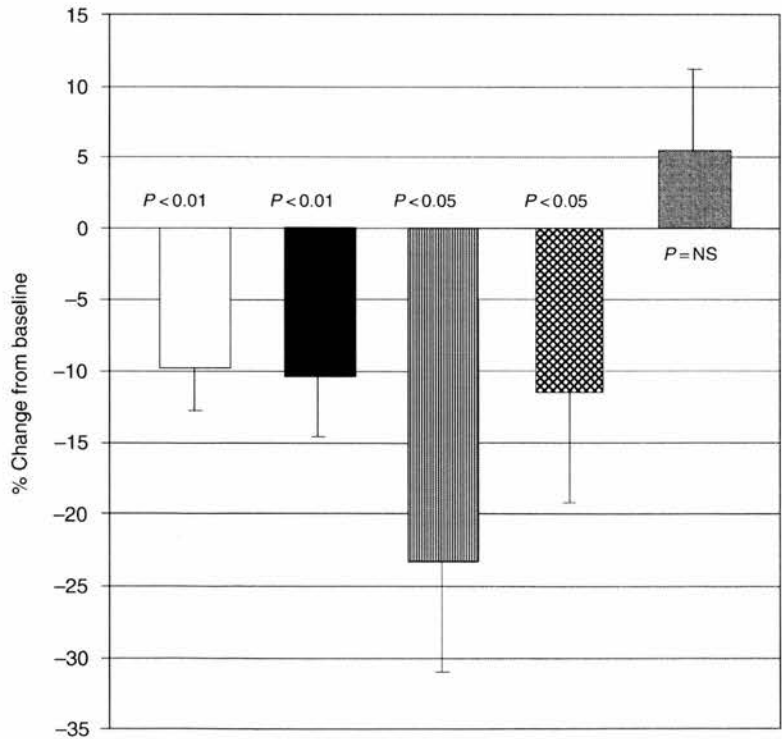


Figure 3. Acute haemodynamic effects of carvedilol. CO, cardiac output; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; PR, pulse rate; SVR, systemic vascular resistance. Bars (left to right): MAP, PR, HVPG, CO, SVR.

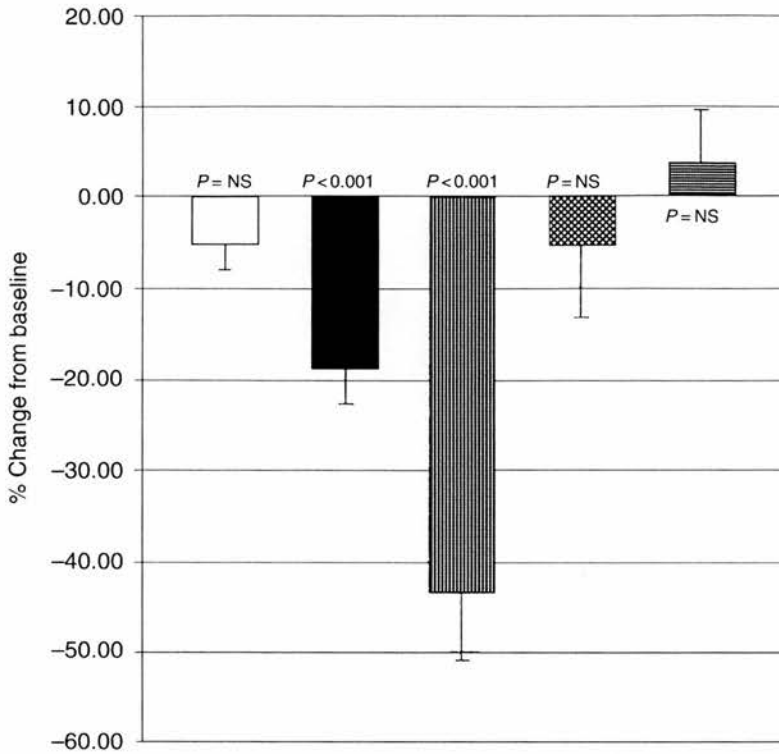


Figure 4. Haemodynamic effects of carvedilol following chronic dosing. CO, cardiac output; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; PR, pulse rate; SVR, systemic vascular resistance. Bars (left to right): MAP, PR, HVPG, CO, SVR.

may have been because Banares *et al.* titrated the dose against the heart rate. It is doubtful whether such high doses are required, because we have demonstrated in this and a previous study²² that a lower fixed dose can result in a similar magnitude of portal pressure reduction with minimal side-effects. Prazosin has been shown to have detrimental effects on sodium handling, resulting in an increased tendency to ascites formation.¹⁶ However, combination therapy with propranolol did not affect renal function.¹⁹ Previous studies have shown that carvedilol does not affect the renal blood flow,²¹ and our findings confirm that the renal function remains unaffected following chronic dosing, with no evidence of increased ascites formation. Therefore, it seems that additional non-selective β -blockade helps to maintain renal blood flow and function. This may be explained by previous observations that non-cardioselective β -blockers suppress the increase in plasma renin activity and plasma aldosterone that occurs following α blockade.¹⁷ Although not included in our present study, we have previously shown that carvedilol at a dose of 25 mg has no effect on creatinine clearance, urine volume or natriuresis.²² This is consistent with the observation that none of the

patients with ascites suffered from increased fluid retention.

Concerns have been expressed regarding the effect of carvedilol on systemic haemodynamics, in particular blood pressure, in patients with liver disease. This stems from the fact that the bioavailability is very variable in patients with hepatic impairment. Carvedilol undergoes extensive stereoscopic first-pass metabolism in the liver.²⁶ The stereoisomer R-carvedilol has equal β and α_1 antagonism, while S-carvedilol has only non-selective β antagonism.²⁷ In healthy individuals, R-carvedilol has twice the bioavailability of S-carvedilol, whereas patients with liver disease have equal and increased availability of both stereoisomers.^{28, 29} This means that β antagonism is greater in patients with liver disease, which could result in undesirable systemic effects. These effects appear to be dose related and our results indicate that, despite the greater bioavailability, patients with advanced liver disease experience minimal systemic hypotension. In particular, patients with ascites, despite exhibiting similar reductions in HVPG compared with patients without ascites, do not experience significant systemic hypotension. Clearly, this reinforces the need to adhere to

lower dose regimens in such patients, especially as we have demonstrated that carvedilol can still have a marked portal hypotensive effect at these doses. In heart failure, carvedilol should be started from a low dose, such as 3.125 mg b.d., for 2 weeks and titrated according to patient tolerance.³⁰ Our results indicate that the first dose of carvedilol has a greater effect on systemic haemodynamics than subsequent doses. It would therefore seem logical to introduce carvedilol in a stepwise fashion in patients with liver disease, with the dose titrated according to patient tolerability, aiming for a target daily dose of 12.5 mg.

In conclusion, our study demonstrates that low-dose carvedilol leads to a significant reduction in portal pressure with minimal effects on systemic haemodynamics. In all cases except one, there was a reduction in HVPG of > 20%, and in seven out of nine patients HVPG was \leq 12 mmHg with chronic administration. The reduction in portal pressure observed in this study is one of the largest reported in the literature to date, and is comparable to that seen following the insertion of a transjugular intrahepatic portosystemic stent-shunt. These findings, and the earlier observation that carvedilol appears to have superior portal hypotensive effects to propranolol,²³ suggest that carvedilol should be assessed in large randomized controlled trials for the primary prevention of variceal haemorrhage.

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LIVER DISEASE

The role of the transjugular intrahepatic portosystemic stent shunt (TIPSS) in the management of bleeding gastric varices: clinical and haemodynamic correlations

D Tripathi, G Therapondos, E Jackson, D N Redhead, P C Hayes

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Background: The transjugular intrahepatic portosystemic stent shunt (TIPSS) is effective in the management of both oesophageal and gastric variceal bleeding. Although it has been reported that gastric varices can bleed at pressures of ≤ 12 mm Hg, this phenomenon has been little studied in the clinical setting.

Aims: To assess the efficacy of TIPSS on rebleeding and mortality following gastric and oesophageal variceal bleeding, and the importance of portal pressure in both groups.

Methods: Forty eligible patients who had bled from gastric varices and 232 from oesophageal varices were studied. Patients were also subdivided into those whose portal pressure gradients (PPG) prior to TIPSS were ≤ 12 mm Hg (group 1) and >12 mm Hg (group 2).

Results: There was no difference in Child-Pugh score, age, sex, or alcohol related disease between patients bleeding from gastric or oesophageal varices. Patients who bled from gastric varices had a lower PPG pre-TIPSS (15.8 (0.8) v 21.44 (0.4) mm Hg; $p < 0.001$). There was no difference in the rebleeding rate (20.0% v 14.7%; NS). There was a significant difference ($p < 0.05$) in favour of the gastric varices group in the one year mortality (30.7% v 38.7%) and five year mortality (49.5% v 74.9%), particularly in those patients in group 2. Gastric variceal bleeding accounted for significantly more cases in group 1 than in group 2 (36.8% v 10.2%; $p < 0.001$). Most patients in group 2 who rebled had a PPG post-TIPSS of >7 mm Hg.

Conclusions: TIPSS is equally effective in the prevention of rebleeding following gastric and oesophageal variceal bleeding. A significant proportion of gastric varices bleed at a PPG ≤ 12 mm Hg. The improved mortality in patients with gastric variceal bleeding is seen only in those that bleed at a PPG >12 mm Hg, and warrants further study.

See end of article for authors' affiliations

Correspondence to: D Tripathi, Department of Medicine, Royal Infirmary of Edinburgh, 1 Lauriston Place, Edinburgh EH3 9YW, UK; d.tripathi@ed.ac.uk

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Variceal haemorrhage is a major cause of mortality and morbidity in patients with cirrhosis and portal hypertension.¹ Studies have reported an association between portal pressure and the risk of variceal bleeding.^{2,3} It has been reported that varices rarely bleed if the portal pressure gradient (PPG) is less than 12 mm Hg and many advocate this as a therapeutic goal.⁴

The management of bleeding gastric varices has been a particular challenge to clinicians. It is known that the natural history of bleeding gastric varices differs from that of oesophageal varices. Although the risk of bleeding from gastric varices is less than that of oesophageal varices, the outcome once bleeding has occurred is worse, particularly for isolated gastric varices.⁵ Various endoscopic methods, including standard sclerotherapy⁶ and injection of tissue adhesives,⁷ have resulted in good initial haemostasis but are limited by a high rebleeding rate. Results using thrombin are more promising in uncontrolled studies.^{8,9} The use of a transjugular intrahepatic portosystemic stent shunt (TIPSS) has been studied extensively for oesophageal variceal bleeding (OVB) and more recently for the management of gastric variceal bleeding (GVB). We have previously shown TIPSS to be equally effective in the management of gastric varices, a finding which has been confirmed by other centres, particularly in emergency or refractory GVB.¹⁰⁻¹²

Despite reports that varices bleed almost exclusively at portal pressures of greater than 12 mm Hg,⁴ we have shown previously that a minority of patients with directly measured PPG < 12 mm Hg remain at risk of variceal bleeding.¹¹ Furthermore, it is recognised that gastric varices occur at lower portal pressures than oesophageal varices.¹¹

The aim of this study was to analyse retrospectively the clinical outcome of patients who have bled from gastric varices and in whom a TIPSS procedure was undertaken. These patients were compared with a group of patients who bled from oesophageal varices. Haemodynamic and clinical correlations were made, and patients who bled at a PPG of ≤ 12 mm Hg were studied to identify whether they differed from the group who bled at higher portal pressures with regard to site of variceal bleed, rebleeding, and survival.

PATIENTS AND METHODS

Patients

During the period between September 1991 and August 2000, 436 patients underwent a TIPSS procedure in our centre. In 377 patients the primary indication was variceal haemorrhage with the remainder having ascites ($n=44$), portal hypertensive gastropathy ($n=9$), or other indication ($n=6$). Patients were excluded if the TIPSS procedure had failed ($n=24$), if they had participated in a trial comparing TIPSS versus TIPSS and banding and were randomised to the TIPSS and banding arm (where TIPSS angiographic surveillance was performed for the first year after TIPSS only, $n=40$), or if there were insufficient data ($n=21$). After exclusions there were a total of 292 patients from which the study populations were selected.

Abbreviations: TIPSS, transjugular intrahepatic portosystemic stent shunt; PPG, portal pressure gradient; GVB, gastric variceal bleeding; OVB, oesophageal variceal bleeding; HVPG, hepatic venous pressure gradient.

Table 1 Baseline characteristics of the patients

	Gastric varices (n=40)	Oesophageal varices (n=232)	Gastric and oesophageal varices (n=12)	Ectopic varices (n=8)
Age (y)	50.9 (1.6)	53.6 (0.8)	45.4 (5.4)	52.5 (4.0)
Sex				
Male	22 (55.0%)	150 (64.7%)	6 (50%)	4 (50%)
Female	18 (45.0%)	82 (35.3%)	6 (50%)	4 (50%)
Aetiology				
Alcoholic liver disease	28 (70.0%)	140 (60.3%)	5 (41.8%)	5 (62.5%)
Primary biliary cirrhosis	1 (2.5%)	2 (12.1%)	1 (8.3%)	0
Hepatitis C	1 (2.5%)	16 (6.9%)	2 (16.7%)	0
Cryptogenic cirrhosis	7 (17.5%)	18 (7.8%)**	1 (8.3%)	1 (12.5%)
Autoimmune	1 (2.5%)	8 (3.4%)	0	0
Cystic fibrosis	0	5 (2.2%)	1 (8.3%)	0
Primary sclerosing cholangitis	1 (2.5%)	4 (1.7%)	1 (8.3%)	2 (25%)
Hepatitis B	1 (2.5%)	4 (1.7%)	1 (8.3%)	0
Other	0	9 (3.9%)	0	0
Child-Pugh score	9.3 (0.5)	9.8 (0.2)	9.3 (0.7)	10.9 (0.9)
Portal pressure gradient (mm Hg)				
Pre-TIPSS	15.8 (0.8)	21.4 (0.5)**	22.5 (3.0)*	15.6 (2.5)
Post-TIPSS	6.7 (0.6)	7.2 (0.3)	7.1 (1.4)	6.9 (1.9)
Reduction post-TIPSS	9.2 (0.8)	14.2 (0.5)**	15.4 (3.5)*	8.8 (2.1)
Median follow up (months)	36.7 (5.1)	19.8 (1.3)**	16.8 (5.1)	8.1 (4.9)*

TIPSS, transjugular intrahepatic portosystemic stent shunt; PPG, portal pressure gradient.
*p<0.05, **p<0.001 compared with gastric varices.

Table 2 Patient characteristics depending on the portal pressure gradient (PPG) at the time of transjugular intrahepatic portosystemic stent shunt (TIPSS)

	Group 1 (n=38)	Group 2 (n=254)	p Value
Age (y)	54.9 (1.9)	52.5 (0.8)	NS
Sex			
Male	25 (65.8%)	157 (61.8%)	NS
Female	13 (34.2%)	97 (38.2%)	NS
Aetiology			
Alcoholic liver disease	27 (71.1%)	151 (59.4%)	NS
Primary biliary cirrhosis	3 (7.9)	27 (10.6%)	NS
Hepatitis C	0	20 (7.9%)	NS
Cryptogenic cirrhosis	5 (13.2%)	23 (9.1%)	NS
Autoimmune	1 (2.6%)	8 (3.1%)	NS
Cystic fibrosis	0	6 (2.4%)	NS
Primary sclerosing cholangitis	1 (2.6%)	7 (2.8%)	NS
Hepatitis B	1 (2.6%)	3 (1.2%)	NS
Other	0	9 (3.5%)	NS
PPG (mm Hg)			
Pre-TIPSS	9.8 (0.4)	22.1 (0.4)	<0.001
Post-TIPSS	4.2 (0.5)	7.6 (0.3)	<0.05
Reduction post-TIPSS	5.6 (0.5)	14.6 (0.5)	<0.001
Child-Pugh score	9.1 (0.5)	9.9 (0.2)	NS
Indication			
Oesophageal variceal bleeding	20 (52.6%)	212 (83.5%)	<0.001
Gastric variceal bleeding	14 (36.8%)	26 (10.2%)	<0.001
Gastric and oesophageal variceal bleeding	2 (5.3%)	10 (3.9%)	NS
Ectopic variceal bleeding	2 (5.3%)	6 (2.4%)	NS

Group 1, all patients with PPG ≤12 mm Hg; group 2, all patients with PPG >12 mm Hg.

In the eligible patients, 40 patients had a TIPSS performed for GVB, 232 for OVB alone, 12 for both GVB and OVB, and eight for ectopic variceal bleeding. All varices were thought to have arisen because of portal hypertension secondary to parenchymal liver disease. In 38 cases of GVB, bleeding was believed to have been from varices in the fundus or cardia, and two cases from varices along the lesser curve. Table 1 illustrates the baseline characteristics of these patients. There were more patients with cryptogenic cirrhosis in the OVB group.

In order to make haemodynamic and clinical correlations, patients were further divided into two groups according to the direct PPG at the time of TIPSS. Group 1 included those patients with PPG ≤12 mm Hg (n=38) and group 2 those

patients with a PPG >12 mm Hg (n=254). The baseline characteristics of these patients are detailed in table 2. There was no difference in the age, sex, aetiology of liver disease, or Child-Pugh score between the two groups.

TIPSS procedure

All patients were referred for TIPSS from within the Royal Infirmary, Edinburgh, or from other hospitals within Scotland. Our unit operates a 24 hour facility for emergency TIPSS insertion. TIPSS insertion was performed by an experienced radiologist using an established technique.¹⁵ Where the original pressure was >12 mm Hg, the aim was to reduce the PPG to below 12 mm Hg. The patency of the TIPSS shunt was assessed by Doppler ultrasound within a week of insertion,

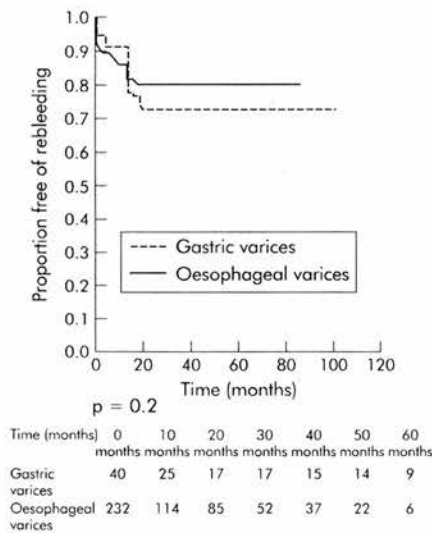


Figure 1 Kaplan Meier graph of rebleeding for all patients who bled from gastric and oesophageal varices treated with a transjugular intrahepatic portosystemic stent shunt.

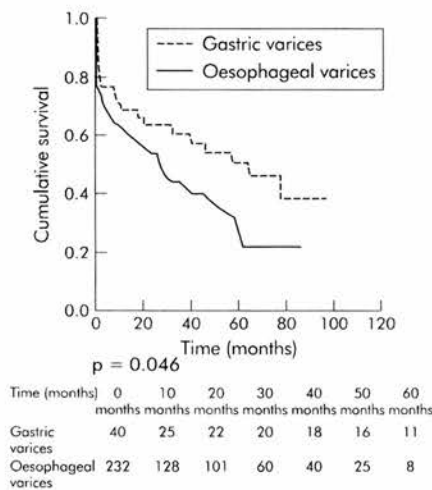


Figure 2 Kaplan Meier graph of survival for all patients who bled from gastric and oesophageal varices treated with a transjugular intrahepatic portosystemic stent shunt.

and by portogram at three months then six monthly thereafter or whenever there were clinical features suggestive of shunt insufficiency.

Follow up

Patients were followed up clinically at three monthly intervals to assess their clinical condition with emphasis being placed on any episodes of encephalopathy and variceal rebleeding. Early mortality was defined as death within four weeks of the variceal haemorrhage. Variceal rebleeding was defined as subsequent variceal bleeding manifested by haematemesis and/or melaena, requiring an unscheduled endoscopy, and accompanied by a reduction in haemoglobin concentration by 20 g/l or more. Shunt insufficiency (defined as an increase in PPG ≥12 mm Hg or a 20% rise above the immediate post-TIPSS PPG) was assessed based on the results of routine follow up angiographic surveillance. Any episodes of shunt insufficiency were treated by balloon angioplasty, shunt extension, or parallel shunt placement, as required to maintain patency. Follow up

time was defined as the time interval in months between the initial TIPSS insertion to either the most recent clinic review, liver transplantation, or death.

Statistical analysis

All results are expressed as mean (SEM) or percentage, where indicated. Statistical significance for parametric data was determined using Student *t* tests, and for non-parametric data using the χ^2 and Mann Whitney *U* tests. The Kaplan-Meier method was used to analyse patient survival, and cumulative rebleeding risk, with comparison between the two groups, was determined by the log rank test. Univariate and multivariate relations between survival and variables of interest in those patients who bled from gastric varices and oesophageal varices at a PPG >12 mm Hg was performed using Cox regression analysis. These variables were: aetiology of cirrhosis (alcoholic or non-alcoholic), site of bleeding (from gastric or oesophageal varices), sex and age of the patients, encephalopathy, ascites, bilirubin, prothrombin time, albumin, and the time interval between the index bleed and TIPSS insertion. Significance was taken at $p < 0.05$ for all tests. All statistical analysis was performed using the SPSS package (version 10; SPSS Inc., Chicago, Illinois, USA).

RESULTS

PPG before and after TIPSS

PPG pre-TIPSS was significantly higher in patients who bled from oesophageal varices compared with GVB (21.4 (0.5) v 15.8 (0.8) mm Hg; $p < 0.001$). Following TIPSS insertion, all patients who had bled from gastric varices had PPG reduced to <12 mm Hg, while in 22 (9.5%) patients who bled from oesophageal varices the post-TIPSS PPG was >12 mm Hg. However, mean PPG post-TIPSS was similar in the GVB and OVB groups (table 1).

Rebleeding

The mean follow up period was 19.8 (1.3) and 36.7 (5.1) months in the OVB and GVB groups, respectively ($p < 0.01$). The longer follow up time in the GVB group may reflect the greater proportion of patients recruited in or prior to 1995 compared with the OVB group (62.5% v 29.7%; $p < 0.001$). In this time, 34 (14.7%) patients in the OVB group rebled and eight (20%) patients in the GVB group rebled. The cumulative risk of rebleeding was similar in both groups (fig 1). In 31 (73.5%) cases of variceal rebleeding there was evidence of TIPSS dysfunction.

Mortality

During this follow up period there was a significant difference in the cumulative risk of death in favour of the GVB group ($p < 0.05$ by Kaplan-Meier method). This was true for 30 day mortality (15% v 23.8%), one year mortality (30.7% v 38.6%), and five year mortality (49.5% v 74.9%) (fig 2). There was no significant difference in the time interval to TIPSS from the variceal bleed (5.4 (0.9) days v 4.9 (0.4) days for the GVB and OVB groups, respectively; NS). The principal cause of death was similar in both groups, with liver failure or sepsis accounting for 82 (64.1%) deaths in the OVB group and 12 (75%) deaths in the GVB group.

Encephalopathy

The rate of encephalopathy prior to TIPSS insertion was similar in the OVB and GVB groups (27.6% v 30.0%; NS). There was no significant difference in episodes of new or worsening encephalopathy in the oesophageal and gastric varices groups (16.35% v 17.5% respectively; NS). All episodes of encephalopathy were managed initially with lactulose and protein reduction. In three cases the shunt was reduced in size, and in eight cases it was necessary to block the shunt with a filter with or without coils.

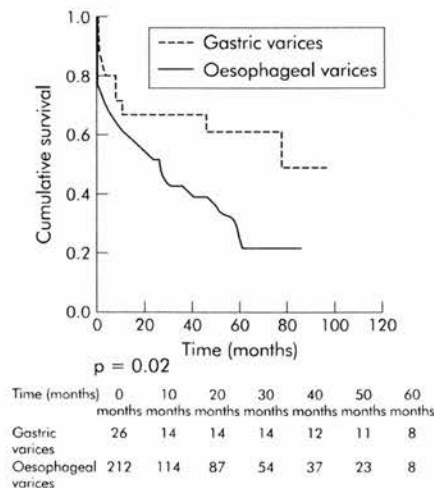


Figure 3 Kaplan Meier graph of survival for all patients who bled from gastric and oesophageal varices at a portal pressure gradient of greater than 12 mm Hg.

Shunt insufficiency

There was no difference in the incidence of shunt insufficiency between the two groups (42.67% v 55% in the OVB and GVB groups, respectively). In one patient in the GVB group problems with maintaining TIPSS patency resulted in elective surgery with the creation of a distal splenorenal shunt.

Orthotopic liver transplantation

Twenty one patients required an orthotopic liver transplantation, 19 (8.2%) in the oesophageal varices group and two (5%) in the gastric varices group (NS).

Correlations between portal pressure and clinical outcome

When patients with a pre-TIPSS PPG ≤ 12 mm Hg were analysed, it was clear that GVB accounted for many more cases than for those patients who bled at a PPG > 12 mm Hg (36.8% v 10.2%; $p < 0.001$) (table 2). However, there was no overall difference in the rebleeding rate and mortality in the two groups. Rates of shunt insufficiency and encephalopathy were also similar in the two groups. In group 1, the final PPG post-TIPSS was similar in those patients that rebled ($n=9$) compared with those that did not rebleed ($n=29$) (5.1 (0.1) mm Hg and 3.9 (0.5) mm Hg, respectively; $p=0.2$). In group 2, PPG post-TIPSS was significantly higher in patients who rebled post-TIPSS ($n=35$) compared with those that did not rebleed ($n=219$) (9.4 (0.8) mm Hg and 7.3 (0.3) mm Hg, respectively; $p < 0.005$). In addition, 75% of patients in group 2 who rebled had a PPG post-TIPSS of > 7 mm Hg.

When patients who bled from either oesophageal varices or gastric varices with a PPG pre-TIPSS of > 12 mm Hg were analysed, there was a significant difference in mortality in favour of gastric varices ($p=0.02$ by Kaplan-Meier method). Thirty day mortality (12% v 24.2%), one year mortality (33.8% v 40.4%), and five year mortality (39.4% v 79.1%) were all significantly better in the gastric varices group (fig 3). Univariate analysis showed that the following variables were associated with higher mortality in patients who bled from gastric or oesophageal varices at a PPG > 12 mm Hg: increasing age ($p < 0.01$), bleeding from oesophageal varices ($p=0.04$), high prothrombin time ($p < 0.05$), high bilirubin ($p < 0.001$), low albumin ($p=0.001$), presence of ascites ($p < 0.001$), and encephalopathy ($p < 0.05$). Multivariate analysis of these variables revealed that older age of patients ($p < 0.05$), high bilirubin ($p < 0.05$), and a low albumin ($p < 0.001$) were independent variables predicting mortality. There was no differ-

ence in the rebleeding rate. Mortality and rebleeding rates were similar in the GVB and OVB groups who bled at a PPG ≤ 12 mm Hg.

DISCUSSION

Historically, the management of GVB has been suboptimal. Endoscopic measures have met with varying degrees of success⁶ although current UK guidelines recommend endoscopic treatment as the first line in the management of the acute gastric variceal bleed.^{7-9 16 17} Iatrogenic complications such as embolic phenomena and the potential for equipment damage may limit the use of tissue adhesives.^{18 19} Thrombin seems to be promising but large multicentre controlled trials have yet to emerge. Previous studies have used bovine thrombin which has the potential risk of prion transmission^{8 9} although our experience with human thrombin has been promising so far.²⁰ Surgical shunts may be of value in patients with early liver disease²¹⁻²³ but have the disadvantage of high mortality in patients with advanced liver disease, particularly in the emergency setting.²⁴

Our findings show that TIPSS is equally effective in the prevention of rebleeding from gastric and oesophageal variceal haemorrhage. Incidences of shunt insufficiency and encephalopathy were similar in both groups. These results are similar to those of an earlier study in our unit.¹³ We have adopted a policy of referring patients with bleeding gastric varices and a patent portal vein directly for TIPSS insertion. A further finding is the significant numbers of patients that bleed at a PPG of < 12 mm Hg, and gastric varices account for a sizeable proportion of this group.

It has been reported that patients with large gastric varices have a lower portal pressure than those with oesophageal varices,²⁵ which may be as a result of the development of gastro-renal porto-systemic shunts.¹⁴ Watanabe *et al* also demonstrated increased collateral flow at the expense of reduced portal venous flow in patients with gastric varices. The authors proposed that reduced portocollateral resistance may account for the latter finding. It is however unclear as to why patients bleed at portal pressures of < 12 mm Hg. Other factors such as the presence of red spots, variceal size, and that of gastritis may be important. Therefore, particularly in patients with gastric varices, it would not be safe to regard reducing a PPG of < 12 mm Hg as a therapeutic goal. Indeed, for patients who bleed at a PPG ≤ 12 mm Hg, our results demonstrate that PPG post-TIPSS is not statistically different in patients who rebled compared with those that do not. However, for patients who bleed at a PPG > 12 mm Hg, the post-TIPSS PPG is greater for patients who rebled, with most of these patients having a PPG post-TIPSS of > 7 mm Hg. These results suggest that in group 2 (that is, predominantly oesophageal variceal bleeders) a therapeutic goal of a post-TIPSS PPG < 7 mm Hg would be reasonable.

TIPSS has recently been studied in the management of refractory variceal bleeding either from gastric alone¹¹ or gastric compared with oesophageal varices.^{26 27} Our rebleeding rates are comparable with these studies. Chau *et al* also found that portal pressure in patients who had early rebleeding before seven days was lower in patients with GVB.²⁶ Rees and colleagues²⁷ did not demonstrate significant differences in PPG prior to TIPSS which was > 20 mm Hg in both groups. This study was limited by a small number of patients and a short follow up period.

An interesting finding in the present study is that of significantly better survival in the GVB group compared with the OVB group, despite the two groups being matched for age, aetiology of liver disease, Child-Pugh score, and pre-TIPSS encephalopathy. We have previously shown the latter two parameters to strongly predict mortality post-TIPSS.²⁴ It has also been observed that mortality following a variceal haemorrhage is highest in the first few days after the index

bleed.²⁹ Both the OVB and GVB groups were matched for the time of intervention with TIPSS after the variceal bleed and thus there was no undue selection of patients in either group who were likely to have a better survival. The difference in mortality between the two groups appears to be confined to patients who bleed at a PPG >12 mm Hg, and is particularly striking for long term mortality. Older age of the patient, high bilirubin, and low albumin in keeping with more advanced liver disease were independent predictors of mortality. The causes of death in both groups were predominantly liver failure and sepsis. The earlier study in our unit¹² had demonstrated a trend towards improved survival among the GVB group. The present study had a greater number of patients and a longer follow up period, which may account for the now significant findings. The longer follow up period in the GVB group is likely to be a result of the combination of reduced mortality and larger numbers of patients recruited before or in 1995.

It is important to highlight the observation of a significantly higher PPG prior to TIPSS insertion in patients with OVB. We have previously shown that a hepatic venous pressure gradient (HVPG) of >16 mm Hg predicted mortality in patients with alcoholic cirrhosis.³⁰ This finding was reinforced in a later study by Patch and colleagues.¹¹ HVPG measurements made within the first or second week had the greatest predictive value. Nearly all of our patients had their portal pressures measured at the time of TIPSS within the first two weeks of the index variceal bleed. A recent study by Moitinho and colleagues³¹ assessed the prognostic value of early portal pressure measurements following an acute variceal bleed. The striking finding in this study was that patients with a HVPG of >20 mm Hg had a one year mortality of 64% compared with 20% for that of patients with HVPG <20 mm Hg (p<0.004). In our group, all patients who bled from oesophageal varices had a mean PPG >21 mm Hg. It is therefore plausible that the difference in PPG between the OVB and GVB groups may account for the difference in the observed mortality, although the reason why PPG affects mortality is not understood. We have not shown a difference in rebleeding rates as the rebleeding rate was so low in both groups following TIPSS insertion that much larger numbers may be needed to show any differences. This illustrates the impressive efficacy of TIPSS in preventing variceal rebleeding.

In conclusion, our study demonstrates that TIPSS is very effective in the prevention of variceal rebleeding irrespective of whether patients have had an OVB or a GVB. Mortality is significantly better in the GVB group who bleed at a PPG >12 mm Hg, and warrants further study. The findings also highlight the significant role of GVB in patients who bleed at a PPG ≤12 mm Hg, and challenges the use of this cut off value as a treatment goal, particularly in patients with gastric varices. Our results also suggest that clinicians should aim for a PPG post-TIPSS of <7 mm Hg for patients who have variceal bleeding at a PPG >12 mm Hg. TIPSS therefore has a major role in the management of GVB, which can be very difficult to control by other measures. Further long term prospective studies would assist in clarifying the effect of TIPSS on mortality in the GVB group compared with OVB.

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Authors' affiliations

D Tripathi, G Therapondos, P C Hayes, Centre for Liver and Digestive Disorders and Department of Medicine, Royal Infirmary of Edinburgh, UK
E Jackson, Medical School, University of Edinburgh, UK
D N Redhead, Department of Radiology, Royal Infirmary, Edinburgh, UK

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LIVER

Randomised controlled trial of long term portographic follow up versus variceal band ligation following transjugular intrahepatic portosystemic stent shunt for preventing oesophageal variceal rebleeding

D Tripathi, H F Lui, A Helmy, K Dabos, E Forrest, A J Stanley, R Jalan, D N Redhead, P C Hayes

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Background/aims: Transjugular intrahepatic portosystemic stent shunt (TIPSS) is effective in the prevention of variceal rebleeding but requires invasive portographic follow up. This randomised controlled trial aims to test the hypothesis that combining variceal band ligation (VBL) with TIPSS can obviate the need for long term TIPSS surveillance without compromising clinical efficacy, and can reduce the incidence of hepatic encephalopathy.

Patients/methods: Patients who required TIPSS for the prevention of oesophageal variceal rebleeding were randomised to either TIPSS alone (n=39, group 1) or TIPSS plus VBL (n=40, group 2). In group 1, patients underwent long term TIPSS angiographic surveillance. In group 2, patients entered a banding programme with TIPSS surveillance only continued for up to one year.

Results: There was a tendency to higher variceal rebleeding in group 2 although this did not reach statistical significance (8% v 15%; relative hazard 0.58; 95% confidence interval (CI) 0.15-2.33; p=0.440). Mortality (47% v 40%; relative hazard 1.31; 95% CI 0.66-2.61; p=0.434) was similar in the two groups. Hepatic encephalopathy was significantly less in group 2 (20% v 39%; relative hazard 2.63; 95% CI 1.11-6.25; p=0.023). Hepatic encephalopathy was not statistically different after correcting for sex and portal pressure gradient (p=0.136).

Conclusions: TIPSS plus VBL without long term surveillance is effective in preventing oesophageal variceal rebleeding, and has the potential for low rates of encephalopathy. Therefore, VBL with short term TIPSS surveillance is a suitable alternative to long term TIPSS surveillance in the prevention of oesophageal variceal rebleeding.

See end of article for authors' affiliations

Correspondence to: Dr D Tripathi, Liver Unit, Royal Infirmary, 51 Little France Crescent, Edinburgh EH16 4SU, UK; d.tripathi@ed.ac.uk

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Variceal bleeding is a serious complication of portal hypertension with in-hospital mortality of 30-50% depending on the severity of liver disease.¹ Mortality following variceal rebleeding is as high as 78% in patients with advanced hepatic decompensation.² Transjugular intrahepatic portosystemic stent shunt (TIPSS) is superior to variceal band ligation (VBL) in the prevention of variceal rebleeding although patients are more likely to develop hepatic encephalopathy and patient survival is unaffected.³⁻¹¹ Long term patency of TIPSS is also a clinical problem. Studies indicate that without regular TIPSS surveillance and intervention, approximately 50% of stents will occlude after one year.¹²⁻¹⁷ Regular invasive portographic surveillance, which is essential for maintaining shunt patency, is not available in all centres, and places an additional burden on resources. Moreover, non-invasive methods of assessing TIPSS patency such as Doppler ultrasound are not as sensitive as regular portography,¹⁸ and lead to a higher rebleeding rate.³ In any case, Doppler ultrasound does not allow for interventions, such as balloon angioplasty and re-stenting, or for measurement of portal pressures.

VBL has replaced injection sclerotherapy in most centres as the favoured endoscopic treatment for the prevention of variceal rebleeding. VBL is associated with a high rate of rebleeding, particularly in the month following the index variceal bleed.⁷ However, once the varices have been eradicated, VBL may be as effective as a patent TIPSS in preventing variceal rebleeding. Thus following variceal eradication in a patient with a TIPSS, it may not be necessary to continue TIPSS surveillance to maintain TIPSS patency. It

is not known whether terminating angiographic TIPSS surveillance following successful VBL will compromise the variceal rebleeding rate.

We hypothesised that combining VBL and TIPSS with short term portographic surveillance would be as effective as TIPSS alone with long term surveillance in the prevention of oesophageal variceal rebleeding. Patients in the former group could benefit from the reduced need for angiographic surveillance and incidence of hepatic encephalopathy as TIPSS is allowed to occlude following variceal eradication. There may also be cost advantages in using VBL instead of long term TIPSS surveillance.

Therefore, the aim of this randomised controlled trial was to compare the efficacy of TIPSS plus VBL without long term surveillance, with TIPSS and long term surveillance in the secondary prevention of oesophageal variceal rebleeding. Other potential differences such as mortality, encephalopathy, and costs were also explored.

METHODS

The trial was undertaken with the approval of the local research ethics committee, written informed consent of each subject, and in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Abbreviations: PPG, portal pressure gradient; TIPSS, transjugular intrahepatic portosystemic stent shunt; VBL, variceal band ligation; OLT, orthotopic liver transplantation

Patients selection

Between December 1995 and August 2000, a total of 303 patients were referred for TIPSS insertion from centres throughout Scotland. All TIPSS procedures were performed at the Royal Infirmary, Edinburgh. All patients presenting with bleeding oesophageal varices were considered for inclusion into the trial. Exclusion criteria are as follows: (1) technical failure of TIPSS insertion; (2) age <18 or >85 years; (3) bleeding gastric or ectopic varices; (4) portal vein thrombosis; (5) Budd-Chiari syndrome; (6) ascites as a primary indication for TIPSS; (7) advanced cardiopulmonary disease; (8) malignancy with prognosis that will affect study outcome; (9) inability to give informed consent; (10) previous variceal haemorrhage; and (11) pregnancy or women of childbearing potential not taking contraception. Patients were recruited after haemodynamic stabilisation.

Randomisation and treatments

Prior to TIPSS, all patients were resuscitated with fluids and blood or blood products, and underwent endoscopy with VBL or sclerotherapy using 5% ethanalamine oleate if there was active bleeding. In some patients, pharmacological intervention with octreotide or terlipressin was undertaken. Randomisation was performed following TIPSS insertion and only after initial control of bleeding and haemodynamic stabilisation. Patients were allocated to either group 1 or group 2 using the sealed envelope method.¹⁹

Group 1: TIPSS alone

At the time of the index endoscopy, active variceal bleeding was noted in 23 patients. VBL was performed in 13 patients, VBL and sclerotherapy in one patient, and sclerotherapy in six patients. In three patients it was not possible to control bleeding with endoscopic therapies requiring the use of balloon tamponade. In 16 patients there were stigmata of recent bleeding but no active bleeding, with three patients having VBL and one both VBL and sclerotherapy. The remainder proceeded straight to TIPSS. All TIPSS procedures in recruited patients were performed or closely supervised by a skilled interventional radiologist using a standard technique described elsewhere.²⁰ All patients were administered broad spectrum antibiotics pre- and for 48 hours post-procedure. Ten to 14 mm diameter expandable metal stents (Wallstent, Schneider, Switzerland) were used with the aim of reducing the portal pressure gradient (PPG) to <12 mm Hg or by $\geq 20\%$. This was achieved in 36 (92%) and 37 (93%) patients in groups 1 and 2, respectively. Two or more stents were used, if necessary, to cover the entire length of the tract between the hepatic vein and portal vein.

Following creation, TIPSS function was assessed at one week by colour Doppler ultrasound. Routine portographic follow up with intervention, if required, to maintain shunt patency was undertaken at six monthly intervals thereafter. However, additional TIPSS portography was also performed where there was clinical suspicion of TIPSS insufficiency, such as rebleeding.

Group 2: TIPSS plus VBL

At the time of the index TIPSS, 28 patients were actively bleeding from varices. Eighteen patients required VBL, two patients VBL and sclerotherapy, and four sclerotherapy. Four patients failed endoscopic therapy requiring balloon tamponade and urgent TIPSS. In 12 patients there were stigmata of recent bleeding but not active bleeding, with six patients having VBL, and the remainder proceeding to TIPSS. The TIPSS procedure was performed as above. Following satisfactory haemodynamic stabilisation of the patient, VBL was undertaken or closely supervised by an experienced endoscopist. One of two banding devices was used (Speedbander,

Boston Scientific, Herts, UK; or 6-Shooter Saeed Multi-Band Ligator, Cook, Ireland), deploying 5 or 6 bands, respectively. Varices just above the gastro-oesophageal junction were banded using a single band at a time. A varix was considered eradicated if the column had disappeared or if they could not be sucked into the banding device. It should be noted that in patients with a patent TIPSS, varices often appear collapsed and therefore require suction for their size to be appreciated and VBL to be performed.

Repeat endoscopy with or without VBL was performed within a week of TIPSS insertion and at two weekly intervals until variceal eradication. Intervals were extended to three and six months thereafter. Shunt function was assessed as previously mentioned. Portographic follow up was continued for up to 12 months following TIPSS insertion in all patients but was discontinued earlier in patients where variceal eradication was achieved.

Follow up

All subjects were followed up until death, liver transplantation, or lost to follow up. A specialist research nurse coordinated clinical follow up, with full clinical examination and biochemical profile at six weeks post-randomisation and four monthly thereafter.

Outcomes

Rebleeding

Rebleeding was defined as subsequent haematemesis or melaena with a 20 g/l reduction in haemoglobin requiring an unscheduled endoscopy.

Early mortality

This was defined as death within six weeks of the index variceal bleed.

Hepatic encephalopathy

This was assessed prior to and during follow up, as already mentioned, and was classified as de novo or deterioration of pre-existing encephalopathy using the criteria of Parson-Smith and colleagues.²²

Shunt insufficiency

This was defined as an increase in PPG to >12 mm Hg or an increase in PPG of more than 20% of the immediate post-TIPSS value.¹⁴

Outcomes were assessed at 6, 12, and 24 months. The primary outcome of the study was variceal rebleeding. Secondary outcomes were mortality, incidence of encephalopathy, and orthotopic liver transplantation (OLT).

Sample size calculation

Sample size was calculated to show that both treatments were equally effective in preventing rebleeding.²¹ Assuming that both treatments were expected to have a 10% variceal rebleeding rate, and with a type I error (α) of 0.05 and a type II error (β) of 0.2, 38 patients would be required in each arm to demonstrate the equivalence (assumed as <17% difference) of the two treatments. Once sufficient numbers were reached in each arm, recruitment stopped and the study was terminated four months after the last patient was recruited.

Calculation of costs of treatment

Data regarding the time spent by each patient in a general, intensive care, or high dependency ward during the follow up period were retrieved. Costs were based on data from the National Health Service, our Department of Radiology, and our Endoscopy Unit. Costs are expressed as cost per patient and also the cost per month survival. The latter is the overall

Table 1 Characteristics of the two groups at baseline

Characteristic	TIPSS (n = 39)	TIPSS+VBL (n = 40)
Age (y) (range)	53.9 (11.2) (32-74)	55.9 (11.4) (30-82)
Male sex (n (%))	30 (77%)	22 (55%)*
Child-Pugh score (at baseline)	9.2 (2.1)	8.7 (2.3)
Aetiology (n (%))		
Alcoholic	28 (72%)	35 (88%)
Abstained from alcohol	8 (29%)	10 (29%)
Non-alcoholic	11 (25%)	5 (13%)
PPG (mm Hg)		
Pre-TIPSS	25.2 (6.6)	20.1 (6.1)**
Post-TIPSS	7.2 (4.0)	6.6 (4.4)
Requirement for mechanical ventilation (n (%))	5 (13%)	6 (15%)
Time from index bleed to randomisation (days)	8.1 (6.8)	6.3 (5.5)
Time from TIPSS insertion to randomisation (days)	3.3 (2.9)	2.9 (3.3)
Blood transfusion at randomisation (units)	3.5 (4.2)	2.7 (2.6)
Hypotensive at randomisation (n (%))	6 (15%)	4 (10%)

Values are mean (SD) unless stated otherwise.
 TIPSS, transjugular intrahepatic portosystemic stent shunt; VBL, variceal band ligation; PPG, portal pressure gradient.
 *p = 0.040; **p < 0.001.

cost per patient divided by the follow up time in months (table 4).

Costs of ward beds

The cost per day in a general ward is £350, high dependency ward is £500, and an intensive care ward is £1200. These costs include staff and consumables.

Cost of TIPSS procedure and follow up

The consumable cost of the TIPSS procedure is £1679. Follow up costs are as follows: routine portography (£205), balloon angioplasty (£371), shunt reduction (£753), insertion of a caval filter and coils for the purposes of occluding the shunt (£785), shunt extension (£927), and insertion of a parallel shunt (£1462).

Cost of VBL

The cost of the endoscopy session is £250. Where VBL is also required, the overall cost increases to £350.

Statistical analysis

Data were analysed on an intention to treat basis. Baseline characteristics were described in the two groups using summary statistics. The χ^2 test was used to compare non-parametric data, and the Student's *t* test was used to compare parametric data. Kaplan-Meier graphs and log rank tests were applied to survival, rebleeding, encephalopathy, and shunt insufficiency. Cox regression analysis was used to control for sex and PPG pre-TIPSS. Significance was taken at the 5% level. The SPSS statistics package (version 9; Chicago, Illinois, USA) was used for all statistical analyses.

RESULTS

Patients recruited

Seventy nine patients met the inclusion criteria, with 39 were randomised to group 1 and 40 to group 2 (fig 1). There were no patients excluded from the trial after randomisation. Mean follow up period was 22.5 (17.2) months (range 0.1-58.9) and 26.6 (18.1) months (range 0.3-64.1) in groups 1 and 2, respectively.

Baseline characteristics

There were more male patients and PPG pre-TIPSS was higher in the TIPSS alone arm. Clinical parameters of the two groups are shown in table 1.

Procedures

TIPSS insertion was complicated by an intraperitoneal bleed in one patient in group 1. In another patient in group 2, there was a biliary leak leading to a percutaneous fistula and suprahepatic abscess. This patient developed respiratory failure and staphylococcal septicaemia requiring antibiotics, vasoconstrictor therapy, and ventilation. The suprahepatic abscess was drained percutaneously. The patient then made an uneventful recovery. In 73 (92%) patients there was a reduction in PPG following TIPSS insertion to <12 mm Hg, and in all patients except one there was a >20% reduction in PPG post-TIPSS. Mean diameter of the stents was similar in the two groups.

VBL post-TIPSS insertion was performed successfully in 38 patients in group 2. One patient rebled before VBL could take place and another refused banding. A total of 176 endoscopies were performed during the follow up period. VBL was required in 69 endoscopies, with 47 (68%) procedures performed in the first three sessions. Successful eradication

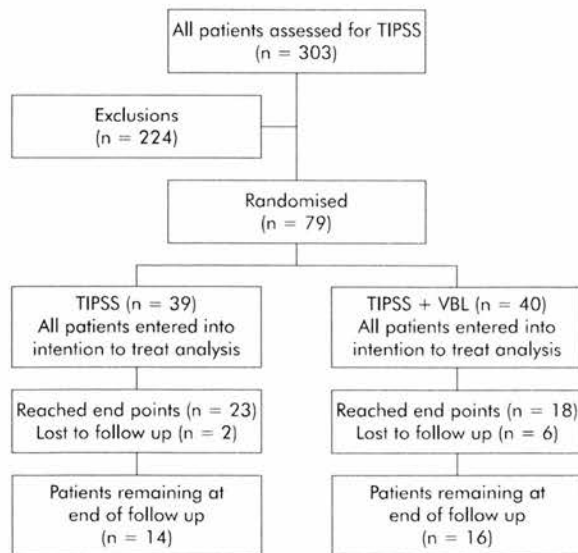


Figure 1 Flow diagram of patient recruitment (see text for exclusion criteria). Patients who reached the end points after randomisation and withdrew from the trial had one of the following events: (1) death; (2) liver transplantation; or (3) variceal rebleeding.

Table 2 Details of trial outcomes

	TIPSS	TIPSS+VBL	TIPSS/TIPSS+VBL relative hazard over entire follow up (95% CI)*	p Value*
Mortality (n (%))			1.31 (0.66–2.61)/1.10 (0.53–2.28)	0.434/0.803
6 month	5 (13%)	2 (5%)		
12 month	8 (21%)	6 (15%)		
24 month	14 (36%)	11 (28%)		
Variceal rebleeding (n (%))			0.58 (0.15–2.33)/0.39(0.09–1.77)	0.440/0.221
6 month	0	3 (8%)		
12 month	1 (3%)	5 (13%)		
24 month	3 (8%)	6 (15%)		
Hepatic encephalopathy (n (%))			2.63 (1.11–6.25)/2.10 (0.79–5.58)	0.023**/0.136
6 month	5 (13%)	3 (8%)		
12 month	10 (26%)	3 (8%)		
24 month	14 (26%)	7 (18%)		

*TIPSS versus TIPSS+VBL. The first value refers to uncontrolled analysis. The second value refers to analysis controlled for sex and pre-TIPSS portal pressure gradient.

**p=0.386 for comparisons in the first six months of follow up only.

of varices was achieved in 28 patients following an average of 2.8 (0.3) sessions. Four patients rebled prior to eradication and were entered into a regular long term TIPSS surveillance programme instead of regular VBL. Two patients died before eradication could take place. Another six patients did not complete the banding programme either because they were lost to follow up or because they refused further banding. Post-banding ulceration occurred in 12 (30%) patients.

Rebleeding

In group 1, three episodes of variceal rebleeding occurred in three patients (8%) during follow up, two with Child C and one with Child B disease (table 2). In two patients rebleeding proved to be rapidly fatal while in the third case the shunt was insufficient with a PPG of 18 mm Hg and evidence of hepatic vein stenosis requiring shunt extension. This patient did not have a further rebleed and made a satisfactory recovery. In addition, there were four patients who rebled from non-variceal sources (two from banding ulceration, one from oesophagitis, and another from a Mallory Weiss tear).

In group 2 there were six episodes of variceal rebleeding in six patients (15%) during follow up, two with Child A and four with Child C disease (table 2). Three of these patients had one further episode of variceal rebleeding during follow up. Varices were eradicated in only two patients. In all cases there was evidence of TIPSS insufficiency requiring re-stenting or balloon angioplasty. In all cases except one, variceal rebleeding was controlled. One patient who rebled from gastric varices initially responded to thrombin injection and balloon angioplasty of TIPSS. This patient had gastric varices at randomisation. However, he rebled again within 24 hours from gastric varices, despite a patent TIPSS. He unfortunately died from oesophageal rupture secondary to balloon tamponade. Three patients rebled from non-variceal sources (one from oesophagitis, one from a duodenal ulcer, and another from severe portal hypertensive gastropathy).

There was no significant difference in the cumulative risk of variceal rebleeding by Kaplan-Meier analysis ($p=0.440$; relative hazard 0.58; 95% confidence interval (CI) 0.15–2.33) (fig 2, table 2). The two groups were similar even after controlling for PPG pre-TIPSS and sex (table 2).

Mortality

In group 1, there were 17 deaths (44%) in total during follow up (table 2). Early mortality occurred in two patients from multiorgan failure resulting from the variceal bleed. The other causes of death were renal failure secondary to gentamicin therapy for a presumed shunt infection ($n=1$), cerebrovascular accident ($n=2$), liver failure following

non-variceal rebleeding ($n=4$), and for the remainder, multiorgan failure and sepsis.

In group 2, there were 15 deaths (38%) in total during follow up (table 2). One patient died within six weeks of the index bleed from aspiration pneumonia. The causes of death were liver failure following variceal rebleeding ($n=2$), oesophageal rupture following insertion of a Sengstaken tube ($n=1$), sepsis after a colectomy ($n=1$), cerebrovascular accident ($n=2$), multiorgan failure ($n=7$), and pneumonia ($n=1$).

There was no statistically significant difference in the cumulative survival by the Kaplan-Meier method between the two groups ($p=0.434$; relative hazard 1.31; 95% CI 0.66–2.61) (fig 3, table 2). The two groups were similar even after controlling for PPG pre-TIPSS and sex (table 2).

Encephalopathy

In group 1, 15 patients (39%) in total developed encephalopathy during follow up (table 2). Four patients experienced deterioration of pre-existing encephalopathy. Two patients responded to conservative therapy with lactulose and protein restriction while the two other patients died with severe encephalopathy and liver failure. The remainder (28%) had de novo encephalopathy. These patients were treated conservatively, with two patients requiring occlusion of the shunt with a filter and subsequent entry into a banding programme.

In group 2, eight patients (20%) in total developed encephalopathy during follow up (table 2). Two patients were encephalopathic prior to TIPSS. Both responded to conservative therapy. The remainder (15%) had de novo encephalopathy. Four responded to conservative therapy and two required occlusion of the shunt.

There was a significance difference (relative hazard 2.63; 95% CI 1.11–6.25; $p=0.023$) in favour of group 2 in the cumulative risk of being free of encephalopathy during the follow up period (fig 4, table 2). This difference did not maintain statistical significance after controlling for sex and PPG pre-TIPSS ($p=0.136$; table 2). The cumulative risk of developing de novo encephalopathy was also significantly less in group 2 ($p=0.041$). Further analysis revealed that there was no significant difference ($p=0.386$) in the incidence of hepatic encephalopathy in the first six months in the two groups, the period when the number of portograms was similar in groups 1 and 2 (25 v 27, respectively). However, the difference in hepatic encephalopathy in favour of group 2 remained statistically significant ($p=0.028$) when the analysis was confined to the period from the end of the first six months of follow up,

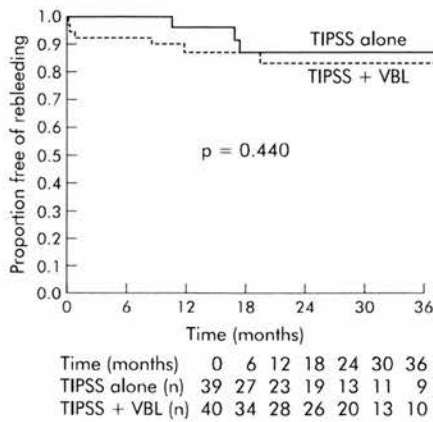


Figure 2 Kaplan-Meier analysis of variceal rebleeding in the transjugular intrahepatic portosystemic stent shunt (TIPSS) alone group and in the TIPSS plus variceal band ligation group (TIPSS+VBL).

where there were far fewer portograms performed in group 2 (10 v 21).

Shunt function in the first year

As TIPSS portography was performed only for up to one year following TIPSS insertion in group 2, valid comparisons of shunt function between the two groups can only be made for the 12 months following TIPSS insertion.

In group 1, a total of 46 TIPSS portograms were performed in the first year, with 54% of these performed in the first six months. A total of 16 (41%) patients developed shunt insufficiency. In the first 12 months, 59% of shunt interventions were performed within the first six months following TIPSS insertion.

In group 2, a total of 37 TIPSS portograms were performed in the first year, with 73% of these in the first six months. There were 17 (43%) cases of shunt insufficiency in the first 12 months. There was no difference in the cumulative risk of shunt insufficiency in the two groups by the Kaplan-Meier Method (fig 5).

Orthotopic liver transplantation (OLT)

Four patients, all from group 1, underwent OLT during the follow up period, between 9.1 and 40.4 months after TIPSS creation. Most patients in both groups were unsuitable for

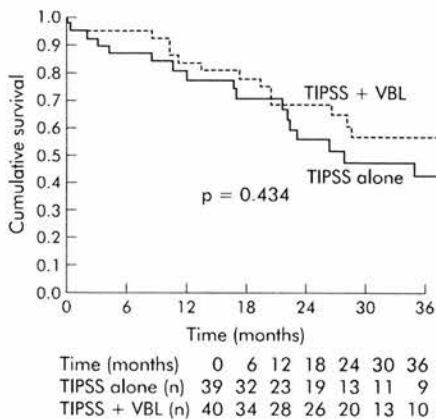


Figure 3 Kaplan-Meier analysis of cumulative survival in the transjugular intrahepatic portosystemic stent shunt (TIPSS) alone group and in the TIPSS plus variceal band ligation group (TIPSS+VBL).

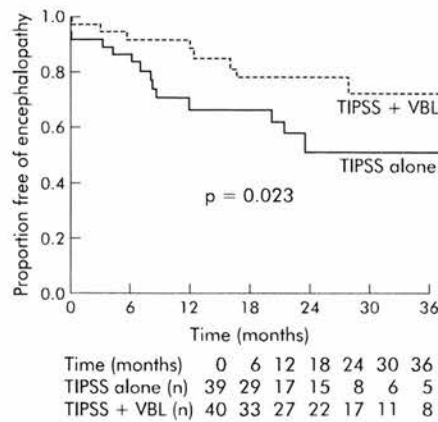


Figure 4 Kaplan-Meier analysis of encephalopathy in the transjugular intrahepatic portosystemic stent shunt (TIPSS) alone group and in the TIPSS plus variceal band ligation group (TIPSS+VBL).

OLT on account of the high incidence of continued alcohol consumption (table 1).

Duration of hospital stay

Total requirements for inpatient care were similar in the two groups during follow up: 46.5 (54.5) versus 58.0 (65.2) days in groups 1 and 2, respectively (p = 0.396). There was also no difference in intensive care or high dependency care requirements (table 3).

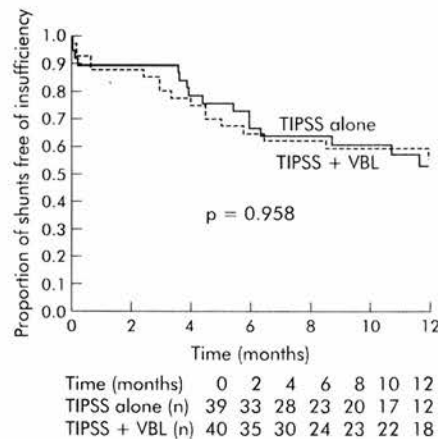


Figure 5 Kaplan-Meier analysis of 12 month shunt insufficiency in the transjugular intrahepatic portosystemic stent shunt (TIPSS) alone group and in the TIPSS plus variceal band ligation group (TIPSS+VBL).

Table 3 Days spent in hospital during follow up

Ward	Days in hospital per patient	
	TIPSS (n = 39)	TIPSS+VBL (n = 40)
General ward	43.9 (54.0)	55.0 (64.2)
HDU	1.8 (1.4)	1.9 (1.9)
ITU	0.8 (2.1)	1.1 (3.3)
Total	46.5 (54.5)	58.0 (65.2)

Values are mean (SD). TIPSS, transjugular intrahepatic portosystemic stent shunt; VBL, variceal band ligation; ITU, intensive care unit; HDU, high dependency unit. No significant difference was detected between the two groups.

Table 4 Costs of treatments following randomisation in both groups

Procedure	Cost per patient (£)	
	TIPSS (n = 39)	TIPSS+VBL (n = 40)
TIPSS surveillance	877 (930)	805 (969)
VBL	—	1270 (985)
Ward treatment	17 004 (19154)	20 983 (23823)
Total cost	19 560 (19146)	24 738 (24299)
Cost per patient free of rebleeding	20 633†	24 520‡
Cost per surviving patient	15 922§	20 127¶
Cost per month survived*	4576	6024

Values are mean (SD).

*Total cost per patient divided by the follow up time in months.

†n = 36; ‡n = 34; §n = 22; ¶n = 24.

There was no significant difference in costs between the two groups.

Costs of treatment

Table 4 details the costs incurred in both groups following randomisation. The difference in total cost per patient did not reach statistical significance (£19 560 (19 146) v £24 738 (24 299), $p = 0.297$, in groups 1 and 2, respectively).

Severity of liver disease at the end of follow up

The Child-Pugh score did not change significantly at the end of follow up (8.9 (2.6) v 9.2 (2.2), $p = 0.609$, groups 1 and 2, respectively).

DISCUSSION

TIPSS has now become accepted as a method of treating variceal bleeding refractory to endoscopic methods, and for the prevention of variceal rebleeding. We have shown for the first time that VBL can replace long term TIPSS surveillance for patients who have required a TIPSS for bleeding oesophageal varices.

The rebleeding rates in the two groups were not significantly different, even after adjustment for sex and portal pressure, and are consistent with previous trials.¹ Although the absolute cumulative risk of variceal rebleeding was higher in group 2 (15% v 8%), this did not reach statistical significance. The lack of statistical difference needs to be interpreted with caution in view of the wide confidence intervals (table 2), and the fact that the power calculations allow for large differences in the two groups. However, it must be emphasised that the absolute risk of variceal rebleeding in group 2 appears less than that seen with VBL alone, as demonstrated in a recent study performed in our unit.⁷

Likewise, mortality was not different in the two groups, even after adjusting for differences in sex and portal pressure at baseline, and is in keeping with most of the previous studies comparing TIPSS and endoscopic modalities.^{9-11 23-26} The two groups were well matched for degree of liver disease, age, alcoholic aetiology, requirement for mechanical ventilation, time to randomisation from the index bleed, and encephalopathy pre-TIPSS; all variables which our unit and others have shown to predict mortality post-TIPSS.²⁷⁻³⁰

Encephalopathy, both overall and de novo, was significantly less in group 2 and is similar to that seen with VBL alone when used for secondary prophylaxis of variceal haemorrhage (fig 4).¹ This difference is maintained when the first six months of follow up is excluded, following which time there are fewer interventions in group 2 to maintain shunt patency. However, in the first six months following TIPSS insertion, the period of maximum and equivalent shunt interventions in both groups, there was no difference in the incidence of hepatic encephalopathy. As shunt patency

in group 1 was maintained by regular portographic surveillance and intervention throughout the study period, the fact that this group had greater episodes of encephalopathy would be expected. The rate of encephalopathy (39%) seen in group 1 is similar to that published in the recent literature,¹ with de novo encephalopathy being significantly less frequent.²⁰ The majority of patients responded to conservative measures, with only four (5%) patients in total requiring blockage of the TIPSS. The significance of the difference in encephalopathy was not maintained after controlling for PPG pre-TIPSS and sex (table 2). However, there did not appear to be any detrimental effects of TIPSS combined with VBL, and this regimen certainly has the potential to reduce the rate of hepatic encephalopathy.

The severity of liver disease, quantified by the Child-Pugh score, did not change significantly in both groups during follow up. This may be explained by the fact that most patients had alcoholic liver disease, with most patients continuing to consume alcohol. A recent study demonstrated improvement in Child-Pugh score following TIPSS¹¹ but there were fewer patients with alcoholic cirrhosis and it is not clear how many people abstained.

We have shown that the rates of shunt insufficiency in the first year were similar in the two groups, with most episodes occurring in the first six months following TIPSS creation. This important observation suggests that portographic follow up is of most value for the first few months following TIPSS insertion and may not be required for one year. However, at the time of the study design, we were more conservative with respect to TIPSS surveillance. In all cases of variceal rebleeding, where portography was performed, there was evidence of shunt insufficiency.

There was a trend towards higher costs in the TIPSS+VBL group, the lack of statistical significance being due to a high standard deviation in costs (table 4) and the small sample size. With longer follow up, the costs differences may lessen as patients in the TIPSS+VBL group will only be followed up by endoscopy and VBL if required. One could even put forward a case for no surveillance in group 2, provided every attempt was made to eradicate varices early. This could significantly reduce costs and increase the use of TIPSS as follow up after TIPSS insertion can occur in any hospital with endoscopy and banding facilities.

In conclusion, for the first time, our findings suggest that VBL can replace long term TIPSS surveillance and still maintain low rates of variceal rebleeding with the potential to reduce the rates of post-TIPSS encephalopathy. Therefore, in patients who have bled from oesophageal varices, combining TIPSS and short term surveillance with VBL is a suitable alternative to TIPSS with long term surveillance in the prevention of variceal rebleeding.

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Authors' affiliations

D Tripathi, H F Lui*, A Helmy†, K Dabos, E Forrest‡, A J Stanley‡, R Jalan§, P C Hayes, Liver Unit, The Royal Infirmary, Edinburgh, UK
D N Redhead, Department of Radiology, The Royal Infirmary, Edinburgh, UK

Present addresses:

*Singapore General Hospital, Outram Rd, Singapore
†Department of Gastroenterology and Tropical Medicine, Assiut University Hospital, Assiut, 71111, Egypt
‡Department of Gastroenterology, Glasgow Royal Infirmary, 84 Castle St, Glasgow G4 OSF, UK
§Institute of Hepatology, University College London, 69-75 Cheynes Mews, London WC1E 6HX, UK

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Chronic Administration of Losartan, an Angiotensin II Receptor Antagonist, is not Effective in Reducing Portal Pressure in Patients with Preascitic Cirrhosis

Dhiraj Tripathi, M.R.C.P., George Therapondos, M.R.C.P., Hock F. Lui, M.R.C.P., Neil Johnston, MSc, F.I.B.M.S., David J. Webb, F.R.C.P, M.D., D.Sc., and Peter C. Hayes, F.R.C.P., M.D., Ph.D. *Liver Unit, Department of Medicine, Royal Infirmary, Edinburgh; and Clinical Pharmacology Unit, Department of Medical Sciences and Centre for Cardiovascular Science, The University of Edinburgh, Western General Hospital, Edinburgh, UK*

- OBJECTIVES:** Plasma angiotensin II (ANG II) concentrations are elevated in cirrhosis and have been implicated as a cause of portal hypertension. We aimed to study both the systemic and portal hemodynamics, and tolerability after chronic administration of losartan, an ANG II receptor antagonist.
- METHODS:** Twelve patients with preascitic cirrhosis were studied: mean age of 53.8 ± 3.3 yr; average Child-Pugh score of 5.8 ± 0.3 ; alcohol etiology (5), hepatitis B/C (1/3), primary biliary cirrhosis (3). No patients were on diuretics or vasoactive medication. Hemodynamic measurements were performed at baseline and 4 weeks after daily administration of 25 mg losartan.
- RESULTS:** There was no significant change in the hepatic venous pressure gradient (15.4 ± 1.5 to 13.6 ± 1.6 mmHg, -11.7% , $p = \text{NS}$), despite a significant reduction in the wedge hepatic venous pressure (20.3 ± 1.8 to 17.3 ± 1.8 mmHg, -14.8% , $p < 0.05$). Cardiac output, hepatic blood flow, systemic vascular resistance, creatinine clearance, and natriuresis were unaffected. The plasma renin activity increased significantly from 2.7 ± 0.4 to 5.2 ± 1.1 ng/ml/h ($p < 0.05$). There was a significant reduction in the mean arterial pressure from 96.9 ± 3.3 to 89.3 ± 3.5 mmHg, $-7.8 \pm 3.0\%$ ($p = 0.02$), with 1 patient experiencing symptomatic hypotension.
- CONCLUSIONS:** Chronic administration of low-dose losartan does not lead to a significant reduction in the portal pressure gradient. Losartan is unlikely to be useful in the management of patients with early cirrhosis, who are at risk of variceal bleeding.

INTRODUCTION

Portal hypertension is a serious complication of cirrhosis, and can result in life-threatening variceal hemorrhage with an in-hospital mortality of between 30% and 40% despite current therapeutic interventions (1). There have been many studies investigating the effects of pharmacological agents on portal hypertension in cirrhotic patients (2). Non-cardio-selective beta-blockers remain the drugs of choice in preventing variceal hemorrhage and have been studied in several randomized controlled trials (3–6). However, up to a third of the patients do not respond to these drugs (7), and a similar proportion are intolerant due to side effects (8). There has been increasing interest in alternative agents, which act via different pathways and promise better efficacy and tolerability.

The renin-angiotensin system has been the focus of several studies in patients with cirrhosis. It is known that the system is activated in cirrhosis and portal hypertension, and that the degree of activation increases with the severity of portal hypertension (9).

Angiotensin II (ANG II), acting via AT1 receptors, may cause portal hypertension by increasing intrahepatic resistance, portocollateral resistance, and portal blood flow (10–12). We have also shown ANG II to play an important role in mediating peripheral vascular tone, particularly in advanced cirrhosis (13). Inhibiting the actions of ANG II at any of these sites may result in a reduction of portal pressure, thus offering a therapeutic alternative for the treatment of portal hypertension.

Losartan is a specific AT1 receptor antagonist with no agonist activity (14). It is licensed for the treatment of systemic hypertension. Schneider and colleagues studied the effects of losartan in patients with varying degrees of portal hypertension, and demonstrated an impressive and significant portal hypotensive response in excess of 40% (15). This was accomplished with minimal effects on the systemic circulation. Irbesartan, another AT1 receptor antagonist with no agonist activity but a longer half-life, was also found to have significant portal hypotensive effects (16, 17). However, a recent study failed to confirm the findings of Schneider in a large

Table 1. Baseline Characteristics

Characteristic (n = 12)	
Sex (M/F)	7/5
Age (yr)	53 ± 3
Child's class (A/B)	9/3
Child's score	5.8 ± 0.3
Etiology	
Alcoholic cirrhosis	5
Hepatitis C/B	3/1
Primary biliary cirrhosis	3

group of cirrhotic patients, and also reported significant side effects with losartan (18). Therefore, there remains some uncertainty about the efficacy and tolerability of such agents in cirrhosis.

The aim of the current study is to investigate the effect of the chronic dosing of losartan in patients with cirrhosis and portal hypertension. The patients, unlike those in previous studies, all had early cirrhosis and were not on vasoactive medication or diuretics, thus the activation of the renin-angiotensin system was minimal.

PATIENTS AND METHODS

Twelve patients with biopsy, radiological, biochemical, or clinical evidence of cirrhosis were recruited. The baseline characteristics are summarized in Table 1. All the patients were preascitic, and were on no diuretics or other vasoactive medication prior to and throughout the study period. Of the 7 patients who had esophageal varices, 6 had Grade II and 1 had Grade III varices, with none having bled in the past. All patients gave written informed consent, and the local research ethics committee approved the study. The study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki.

Baseline hemodynamic measurements were performed at 09:00 hours following an overnight fast. The patients were then instructed to take 25 mg of losartan (Cozaar, Merck Sharp & Dohme Ltd, NJ, USA) at 21:00 hours for 4 weeks. Schneider and colleagues (15) demonstrated a significant effect on portal hypertension with the 25 mg dose, hence the use of this dose. Patients were followed up at 2 wk in the clinic for the assessment of side effects, blood pressure, serum creatinine, liver function, and compliance from the history. After 4 wk of treatment, the hemodynamic measurements were repeated as in the initial protocol. There was no change in the observed alcohol consumption for the duration of the study. There were no detectable serum ethanol levels prior to each study or during follow-up.

Hemodynamic Study Protocol

All measurements were performed in the hepatic hemodynamics suite. All hemodynamic measurements and blood sampling were performed in the supine position. After in-

filtration with 10 ml 2% lidocaine a 7FG venous introducer (Cordis, USA) was inserted into the right femoral vein using the Seldinger technique. Under fluoroscopic guidance a Swann Ganz catheter (Baxter Healthcare Corporation, USA) was inserted through the introducer to measure cardiac output (CO) and right atrial pressure (RAP) in the standard manner. Using the same catheter or a Sidewinder II torque balloon catheter (Cordis Corporation, USA) the main right hepatic vein was then catheterized for the measurement of the free and wedge hepatic venous pressures (FHVP and WHVP). The hepatic venous pressure gradient (HVPG) was derived from these values as [WHVP–FHVP]. All hemodynamic measurements were taken in triplicate. The mean arterial pressure (MAP) was measured using an automatic sphygmomanometer (Hewlett Packard series 54 model 78339A) and was calculated as (pulse pressure/3) + diastolic blood pressure. The systemic vascular resistance (SVR) was calculated as (79.96 (MAP–RAP)/CO).

Measurement of Hepatic Blood Flow

Hepatic blood flow (HBF) was derived from measurements of the indocyanine green (ICG, Akorn, IL) clearance and extraction (19). ICG was infused at the beginning of the study as a 10 mg intravenous bolus via a peripheral cannula followed by an infusion of 0.2 mg/min ICG. After an equilibration time of 40 min three samples were taken simultaneously from the right hepatic vein and femoral vein. Hepatic blood flow was calculated using the following equation (provided the hepatic excretion exceeded 10%):

$$\text{HBF} = (\text{ICG Clearance} / \text{ICG Extraction}) / (1 - \text{Hematocrit})$$

Blood Sampling and Analysis

Venous blood was sampled after the patient was in the supine position for 30 min for baseline biochemical and hematological measurements. In addition, ANG II concentration and plasma renin activity (PRA) were measured by techniques described previously (13). Aldosterone levels were also measured by radioimmunoassay (20).

Assessment of Renal Function

Prior to the first dose of losartan, urine was collected over a 24-h period to measure creatinine clearance and urinary sodium excretion. After 4 wk of administration of losartan, the urinary measurements were repeated.

Statistical Analysis

All results are expressed as mean ± SEM. Parametric data were analyzed using the paired Student's *t*-test and the Pearson's correlation. Wilcoxon signed rank test and Spearman correlation were used for nonparametric data. Significance was taken at the 5% level. The SPSS package (version 9, Chicago, IL) was used for statistical analysis.

Table 2. Effects on Hemodynamic and Humoral Mediators Following Chronic Dosing

	Baseline	After 4 wk
HVPG (mmHg)	15.4 ± 1.5	13.6 ± 1.6
WHVP (mmHg)	20.3 ± 1.8	17.3 ± 1.8*
FHVP (mmHg)	4.9 ± 0.6	3.7 ± 0.7
HR (bpm)	88.3 ± 5.8	79.1 ± 4.9
MAP (mmHg)	97 ± 3	89 ± 4*
CO (l/min)	5.8 ± 0.3	5.7 ± 0.3
SVR (dyn.Cm)	1324 ± 48	1240 ± 97
PRA (ng/ml/h)	2.7 ± 0.4	5.2 ± 1.1*
ANG II (pg/ml)	8.0 ± 1.8	24.2 ± 8.5**
Aldosterone (pg/ml)	52.5 ± 12.8	77.5 ± 27.4

* $p < 0.05$ compared with baseline, ** $p = 0.08$ compared with baseline.

HVPG: Hepatic venous pressure gradient; WHVP: Wedge hepatic venous pressure; FHVP: Free hepatic venous pressure; HR: Heart rate; MAP: Mean arterial pressure; CO: Cardiac output, SVR: Systemic vascular resistance, PRA: Plasma renin activity.

RESULTS

All patients completed the study.

Hepatic Hemodynamics and Function

After administration of losartan for 4 wk there was no significant reduction in the HVPG (15.4 ± 1.5 to 13.6 ± 1.6 mmHg, -11.7% , $p = 0.1$), despite a significant reduction in the WHVP (20.3 ± 1.8 to 17.3 ± 1.8 mmHg, -14.8% , $p < 0.05$) (Table 2). In five cases there was a $>20\%$ reduction in the HVPG, while in three cases there was a reduction in the HVPG to ≤ 12 mmHg in patients with a HVPG of >12 mmHg at baseline ($n = 10$). (Fig. 1) There were two patients, one with ALD and the other with hepatitis C, in whom the HVPG increased. These patients had similar baseline characteristics compared with the rest of the group. Patients with ALD, despite a higher baseline HVPG, experienced a similar reduction in the HVPG from 19.8 ± 1.8 to 17.4 ± 2.1 mmHg (-12.1% , $p = \text{NS}$, $n = 5$) compared with patients with other etiologies (12.3 ± 1.1 to 10.8 ± 1.8 mmHg, -12.2% , $p = \text{NS}$, $n = 7$). In the first three patients repeat hemodynamic measurements performed at sixty min post dosage did not demonstrate any acute effect on the HVPG.

It was not possible to calculate the hepatic blood flow in three patients where the hepatic extraction of ICG was $<10\%$. In the remaining patients there was no change in the hepatic blood flow (552.5 ± 72.9 to 559.7 ± 106.6 ml/min, $n = 9$, $p = \text{NS}$).

The liver function tests in all patients were unaffected

Systemic Hemodynamics

There was a significant reduction in the MAP (97 ± 3 to 89 ± 4.0 mmHg, $-7.8 \pm 3.0\%$, $p = 0.02$). There was no change in the heart rate, CO, or SVR (Table 2).

Renal Function

The creatinine clearance was unaffected (90 ± 14 to 93 ± 19 ml/min, $p = \text{NS}$, $n = 7$), as was the 24-hour urinary sodium

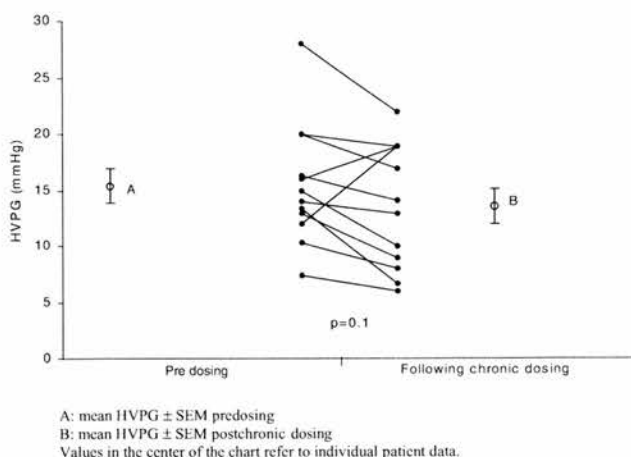


Figure 1. Effect on HVPG following chronic dosing.

excretion (154 ± 61 to 122 ± 36 mmol/day, $p = \text{NS}$, $n = 5$).

Effect on the Renin-Angiotensin System

There was a significant increase in the serum plasma renin activity from 2.7 ± 0.4 to 5.2 ± 1.1 ng/ml/h after chronic dosing ($p < 0.05$) confirming activation of the renin-angiotensin system. There was a strong trend toward increased serum ANG II levels (8.0 ± 1.8 to 24.2 ± 8.5 pg/ml, $p = 0.08$). Serum aldosterone levels were unaffected (Table 2).

Tolerability

One patient experienced symptomatic hypotension after the first dose of losartan, but elected to continue with the study and experienced no further symptoms. During follow-up he was noted to have a 35% reduction in the MAP from 122 to 79 mmHg. This patient was subsequently diagnosed as having systemic hypertension and commenced on drug therapy. There were no other side effects reported during follow-up.

DISCUSSION

The present study demonstrates that in patients with preascitic cirrhosis, oral dosing of 25 mg losartan did not result in a significant reduction in the HVPG despite a significant fall in the WHVP. Losartan significantly reduced the MAP with one patient experiencing mild symptoms after the first dose, a phenomenon that has been reported previously with ACE inhibitors (21).

The interest in ANG II receptor antagonism stems from the observation that there is activation of the renin-angiotensin system in cirrhosis, the degree of which is proportional to the severity of cirrhosis, and portal hypertension (9). Studies have shown that ANG II has a direct effect on portal pressure, via AT1 type receptors (11). Animal models demonstrate that ANG II mediates vasoconstriction of the

portosystemic collaterals leading to increased portocollateral resistance (11), and to have diminished vasoconstrictive effects on the splanchnic circulation leading to increased portal blood flow (10). Recent interest has concentrated on the role of the activated hepatocyte stellate cells (HSC), particularly in light of the finding that AT1-type receptors on human-activated HSC mediate the vasoconstrictive and mitogenic actions of ANG II (12, 22). Blockade of the AT1 receptor may therefore result in relaxation of the activated HSC and reduced intrahepatic resistance and portal pressure. This selective blockade may also result in the unopposed action of ANG II on AT2 type receptors, leading to endothelium-mediated vasodilatation, further enhancing the pharmacological effects of such agents (23).

Initial attempts at ANG II receptor blockade were hindered by pronounced systemic hypotension (24), although the latter was not seen at higher doses possibly due to the partial agonist effect of saralasin at such doses, leading to vasoconstriction and potentially hypertension (23). Newer agents such as losartan and irbesartan, which have no intrinsic agonist activity, have resulted in greater success (15, 17). Losartan was used at a dose of 25 mg in 45 patients with cirrhosis, and either moderate or severe portal hypertension in a study by Schneider and colleagues (15). Both acutely after 4 h and following chronic administration there was a significant reduction in the portal pressure approaching 45%, the largest reported to date for any pharmacological agent. This is particularly impressive considering the minimal effect on blood pressure, with only one patient experiencing symptomatic hypotension.

A recent paper, however, does not support the observation by Schneider (18). This study randomized 25 patients to losartan following a variceal hemorrhage, and compared the portal hypotensive effect of 6 wk therapy with that of propranolol ($n = 15$). Propranolol produced a significantly greater reduction in the HVPG (10% vs 2%), despite the fact that losartan had a significant effect on MAP (-8%), which was not seen with propranolol. There was a significant reduction in the glomerular filtration rate in Childs B patients taking losartan, with propranolol having no detrimental effect on renal function. Adverse effects related to therapy were similar in both groups.

Our results contrast with those of Schneider and colleagues (15), but are in keeping with that of Gonzalez-Abraldes *et al.* (18). This is despite using the same dose of losartan that resulted in activation of the renin-angiotensin system, as evidenced by a significant increase in PRA. Our study design differs in a number of ways from that of Schneider *et al.* First, we studied preascitic cirrhotic patients. This was to minimize the potential risk of systemic hypotension with ANG II blockade in patients with more advanced cirrhosis (24). Second, significant proportions of patients in Schneider's study were on diuretics, both in the treatment and control groups. Clearly, this will have an effect on circulating volume, and the degree of activation of the renin-angiotensin system. Third, the timing of the hemodynamic measurements is different.

Schneider *et al.* performed the measurements at 4 h post dosing compared with 12 h for our study. It is known, however, that the pharmacological actions of losartan last up to 24 h (25). Losartan is a pro drug that is converted to the active metabolite E-3174, whose maximum plasma levels are obtained after 3–4 h. This may explain why we saw no effect on the HVPG in the three patients in whom we repeated measurements sixty min after acute dosing. The half-life of E-3174 is 6–9 h and the levels in plasma in cirrhotics are 1.7 times those of healthy individuals (26). This may partly explain the difference in the results, but for a drug to be considered for therapy it must have a sustained chronic effect on portal hypertension. In the study by Gonzalez-Abraldes (18) the timing of the measurements is not clear. Finally, our sample size is smaller, and a larger sample size may have resulted in a significant difference. Our study shows that the drug is biologically active in cirrhotic patients as evidenced by a significant decrease in the MAP and increase in the renin activity. Although we cannot rule out that the inclusion of more patients may result in a statistically significant effect on HVPG, we feel it is unlikely to show greater clinical effect. One could argue that the dosing may be inadequate, but our dosage was the same as used in the Schneider study and was enough to cause sufficient blockade of ANG II receptors as demonstrated by the significant increase in ANG II levels following chronic dosing. Higher doses may not prove to be more effective, and are likely to significantly increase the risk of adverse systemic side effects as demonstrated by Gonzalez-Abraldes and colleagues (18).

Girgrah *et al.* have recently studied the renal effects of losartan in preascitic cirrhotics (27). This study demonstrated that the renin-angiotensin system is activated even in early cirrhosis, a finding that is in keeping with that of our recent study (13). It was suggested by the authors that losartan, at a dose of 7.5 mg per day, improved natriuresis by blocking the sodium-retaining actions of ANG II proximal to the distal tubule. Our findings are not in keeping with this observation, but the sample size of the patients in whom the 24-h sodium excretion was measured was small. Our study also examined the chronic rather than acute effect of losartan, and the dietary intake of sodium was not so strictly regulated. Creatinine clearance was unaffected, suggesting that at this dose in preascitic cirrhotic patients losartan appears to have no adverse renal effects. In other patients with more severe liver disease, and especially those on potassium-sparing diuretics, problems with renal function and electrolyte imbalance may occur as demonstrated by Gonzalez-Abraldes and colleagues (18).

In conclusion, although low-dose losartan appears to be well tolerated in this group of patients, and has no adverse renal effects, we have not shown a significant reduction in HVPG following chronic dosing with losartan in well-compensated cirrhotic patients. Losartan therefore is unlikely to have a place in the management of patients with cirrhosis and portal hypertension who are at risk of variceal hemorrhage.

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Reprint requests and correspondence: Dr. Dhiraj Tripathi, Liver Unit, Royal Infirmary, 51 Little France Crescent, Edinburgh, UK.

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Ten years' follow-up of 472 patients following transjugular intrahepatic portosystemic stent-shunt insertion at a single centre

Dhiraj Tripathi^a, Ahmed Helmy^a, Kim Macbeth^a, Sherzad Balata^a, Hock F. Lui^a, Adrian J. Stanley^a, Doris N. Redhead^b and Peter C. Hayes^a

Background Transjugular intrahepatic portosystemic stent-shunt (TIPSS) is increasingly used for the management of portal hypertension. We report on 10 years' experience at a single centre.

Methods Data held in a dedicated database was retrieved on 497 patients referred for TIPSS. The efficacy of TIPSS and its complications were assessed.

Results Most patients were male (59.4%) with alcoholic liver disease (63.6%), and bleeding varices (86.8%). Technical success was achieved in 474 (95.4%) patients. A total of 13.4% of patients bled at portal pressure gradients ≤ 12 mmHg, principally from gastric and ectopic varices. Procedure-related mortality was 1.2%. The mean follow-up period of surviving patients was 33.3 ± 1.9 months. Primary shunt patency rates were 45.4% and 26.0% at 1 and 2 years, respectively, while the overall secondary assisted patency rate was 72.2%. Variceal rebleeding rate was 13.7%, with all episodes occurring within 2 years of TIPSS insertion, and almost all due to shunt dysfunction. The overall mortality rate was 60.4%, mainly resulting from end-stage liver failure (42.5%). Patients who bled from gastric varices had lower mortality than those from

oesophageal varices (53.9% versus 61.5%, $P < 0.01$). The overall rate of hepatic encephalopathy was 29.9% (*de novo* encephalopathy was 11.5%), with pre-TIPSS encephalopathy being an independent predicting variable. Refractory ascites responded to TIPSS in 72% of cases, although the incidence of encephalopathy was high in this group (36.0%).

Conclusions TIPSS is effective in the management of variceal bleeding, and has a low complication rate. With surveillance, good patency can be achieved. Careful selection of patients is needed to reduce the encephalopathy rate. *Eur J Gastroenterol Hepatol* 16:9–18
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Keywords: TIPSS, portal hypertension, variceal haemorrhage, refractory ascites, encephalopathy

^aLiver Unit and ^bDepartment of Radiology, The Royal Infirmary, Edinburgh, UK.

Correspondence to Dhiraj Tripathi, Liver Unit, Royal Infirmary, 51 Little France Crescent, Edinburgh EH16 4SU, UK.
Tel: +44 131 242 1625; fax: +44 131 242 1633; e-mail: d.tripathi@ed.ac.uk

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Introduction

Transjugular intrahepatic portosystemic stent-shunt (TIPSS) has improved the management of the complications of portal hypertension, and has largely replaced surgical treatment modalities in patients with advanced cirrhosis and variceal bleeding [1]. Randomized controlled trials [2–10] and meta-analyses [11,12] confirm the superiority of TIPSS over endoscopic treatments in controlling variceal bleeding and preventing rebleeding. In addition, TIPSS is effective in the management of gastric variceal bleeding [13] and refractory ascites [14,15]. Furthermore, TIPSS can be successfully used as a 'bridge' to liver transplantation without any detrimental effects [16,17].

The principal disadvantages of TIPSS are the development of shunt insufficiency and hepatic encephalopathy. Up to 50% of shunts will become insufficient within 1 year of insertion [18–20]. Current

surveillance portography, and intervention if required, ensures excellent secondary assisted patency rates [21,22], and explains the very low rates of rebleeding. The use of new covered stents promises superior patency rates, but current evidence is limited to small series with a short follow-up [11,23–26]. Hepatic encephalopathy occurs in approximately one-third of patients with TIPSS, and results in a significant reduction in the quality of life and increased hospital admissions [12].

Most studies are small and do not indicate an improvement in the mortality rates following TIPSS insertion [12]. However, we have previously shown that TIPSS can result in a favourable outcome in patients with Child class C cirrhosis with variceal bleeding, when compared with endoscopic methods [27]. Most randomized controlled trials do not have the statistical power to demonstrate difference in survival.

We report our experience of TIPSS in almost 500 patients over a 10-year period, the second largest series reported to date, with emphasis on assessing its clinical efficacy and complications.

Methods

Patient selection

Between July 1991 and July 2001, 497 patients were referred for TIPSS. The TIPSS was successfully inserted in 474 patients (95.4%). Data was collected on all these patients prospectively, and entered into a dedicated database. Two patients required a TIPSS following orthotopic liver transplantation (OLT) and were excluded from the analysis, leaving 472 patients for the final analysis. In another 40 patients in a clinical trial, angiographic surveillance was continued only for up to 1 year post-TIPSS insertion, with variceal band ligation started following TIPSS insertion and continued indefinitely [28]. These patients were excluded for analysis of variceal rebleeding, mortality, shunt function, and hepatic encephalopathy. Patient consent and ethics committee approval were not necessary for a retrospective audit such as this.

Procedures

TIPSS insertion was performed as previously reported [29,30]. The index TIPSS was created using Palmaz stents (Johnson and Johnson, Norderstedt, Germany) in 20 patients, the newer covered stents (Wallgraft; Boston Scientific, Boston, MA, USA or Jostent; Jomed, Zurich, Switzerland) in 35 patients, and Wallstents (Boston Scientific) in the remainder, with eight of these cases requiring re-stenting with a covered stent during follow-up. All patients had intravenous Cefotaxime 1 h pre-procedure and for 48 h post-procedure. Doppler ultrasound was performed at 1 week. Urgent portography was carried out if there was Doppler evidence of shunt dysfunction, or if there was clinical evidence of shunt dysfunction, such as variceal rebleeding or increased ascites.

Follow-up

All subjects were followed up at 4–6 month intervals with full clinical, haematological and biochemical assessment, until death, liver transplantation, or loss to follow-up. Routine portography was performed every 6 months where possible, or at other times if there was clinical evidence of shunt dysfunction such as rebleeding or increased ascites.

Definitions

Variceal rebleeding

Any subsequent haematemesis or melaena confirmed endoscopically. Non-variceal causes of rebleeding were also documented.

Early mortality

Death within 6 weeks of the index variceal bleed.

Shunt insufficiency

An increase in the portal pressure gradient (PPG) to > 12 mmHg or an increase in the PPG $> 20\%$ from the post-TIPSS value where the post-TIPSS value is < 12 mmHg [31]. The Doppler criteria for shunt insufficiency is a peak velocity of ≤ 90 cm/s [20,32].

Primary patency

The absence of shunt insufficiency, without intervention during TIPSS surveillance.

Secondary assisted patency

The absence of shunt insufficiency with intervention.

Successful portal pressure reduction

A PPG immediately post-TIPSS of < 12 mmHg (where PPG pre-TIPSS > 12 mmHg) or a $> 20\%$ reduction in the PPG pre-TIPSS (where PPG pre-TIPSS < 12 mmHg).

Statistical analysis

Data were analysed using the SPSS statistics package (version 9; SPSS Inc., Chicago, Illinois, USA), and expressed as means \pm standard error of the mean. Data for mortality, encephalopathy and rebleeding were analysed using the Kaplan–Meier method and log-rank test. The chi-squared test and the Student *t*-test were used to compare unpaired data. Cox regression analysis was performed to determine independent variables predicting variceal rebleeding, survival, and shunt insufficiency. Significance was taken at the 5% level.

Results

Baseline patient characteristics are presented in Table 1. The most common indication for TIPSS insertion was oesophageal variceal haemorrhage ($n = 313$, 66.3%), and most patients had Child C disease ($n = 246$, 52.1%) of alcoholic origin ($n = 300$, 63.6%). There were 22 patients (4.7%) who were lost to follow-up.

TIPSS procedure

Technical success

Technical success was achieved in 472 (95%) patients, and was not possible in the remainder due to: (1) portal vein thrombosis ($n = 4$); (2) intraperitoneal bleeding from the portal vein ($n = 2$); (3) death during the procedure from cardiovascular instability ($n = 1$); and (4) the inability to access the hepatic or portal circulation due to the patient's anatomy ($n = 16$).

Successful portal pressure reduction

This was achieved in 354 (83.9%) patients. Patients with gastric variceal bleeding had lower PPGs pre-TIPSS compared with oesophageal variceal bleeding

Table 1 Baseline characteristics of subjects

Characteristic	n = 472
Mean age (years)	54.1 ± 0.6
Sex (male/female)	280/192
Child-Pugh score	9.7 ± 0.1
Etiology [n (%)]	
Alcoholic cirrhosis	300 (63.6)
Cryptogenic cirrhosis	42 (8.9)
Viral hepatitis	39 (8.3)
Primary biliary cirrhosis	38 (8.1)
Autoimmune hepatitis	13 (2.8)
Primary sclerosing cholangitis	12 (2.5)
Cystic fibrosis	8 (1.7)
Other ^a	20 (4.2)
Indication [n (%)]	
Oesophageal variceal bleeding	313 (66.3)
Gastric variceal bleeding	65 (13.8)
Refractory ascites	50 (10.6)
Oesophageal and gastric variceal bleeding	21 (4.4)
Ectopic variceal bleeding	12 (2.5)
Portal hypertensive gastropathy	7 (1.5)
Other	4 (0.9)
Mean follow-up period (months)	
Overall	19.9 ± 1.1
For surviving patients	33.3 ± 1.9

Values expressed as mean ± standard error of the mean.

^aIncludes nodular regenerative hyperplasia (n = 3), congenital hepatic fibrosis (n = 3), haemochromatosis (n = 4), Budd-Chiari syndrome (n = 2), myelofibrosis (n = 2), alpha 1 antitrypsin deficiency (n = 1), hepatic amyloid (n = 1), secondary biliary cirrhosis from choledocholithiasis and stenting of common bile duct (n = 1), chronic granulomatous hepatitis (n = 1), cholangiocarcinoma (n = 1), and Poems' syndrome (n = 1).

(Table 2). Fifty-five patients (13.4% of all variceal bleeders) bled at PPG ≤ 12 mmHg, with gastric varices accounting for most of these cases (Table 3).

Procedure-related mortality

There were six deaths (1.2%) during or as a direct result of the TIPSS procedure. These were due to intraperitoneal haemorrhage (n = 2) and perforation of the gallbladder leading to overwhelming sepsis (n = 1). Three patients died during the procedure as a result of cardiac arrest (pulseless electrical activity in two

Table 2 Haemodynamic data for patients (n = 472) who had successful transjugular intrahepatic portosystemic stent-shunt (TIPSS) insertion

Characteristic	
PPG Pre-TIPSS (mmHg)	
All cases	20.7 ± 0.3
Oesophageal variceal bleeding	21.5 ± 0.4 ^A
Gastric variceal bleeding	16.1 ± 0.9 ^B
PPG Post-TIPSS (mmHg)	
All cases	7.2 ± 0.2
Oesophageal variceal bleeding	7.5 ± 0.3 ^C
Gastric variceal bleeding	6.2 ± 0.4 ^D
Successful PPG reduction [n (%)] ^a	354 (83.9)

Values expressed as mean ± standard error of the mean. PPG, Portal pressure gradient.

^A versus ^B P < 0.001, ^C versus ^D P < 0.05.

^aDefined as a PPG post-TIPSS of < 12 mmHg (where PPG pre-TIPSS > 12 mmHg) or a > 20% reduction in the PPG pre-TIPSS (where PPG pre-TIPSS < 12 mmHg).

Table 3 Subgroup analysis of patients who bled at portal pressure gradient (PPG) ≤ 12 mmHg

Source of variceal bleed	Patients who bled at PPG ≤ 12 mmHg [n (%)]
Oesophageal varices (n = 313)	24 (7.7)
Gastric varices (n = 65)	25 (38.5)
Gastric and oesophageal varices (n = 21)	2 (9.5)
Ectopic varices (n = 12)	4 (33.3)

patients and asystole in one patient). Other non-fatal procedure-related complications are presented in Table 4.

Shunt function

Most cases of shunt insufficiency occurred within the first year (Fig. 1), particularly the first 6 months following index TIPSS insertion (31.4%). Intimal hyperplasia was the most common abnormality (Table 5). Of the 387 episodes of shunt insufficiencies in the first 2 years post-TIPSS insertion, 46 (11.9%) were associated with variceal rebleeding. This compares with 96 episodes of shunt insufficiencies in 53 patients after 2 years, where there was just one episode associated with variceal rebleeding (1%, P < 0.001). The majority of these patients (92.5%, n = 49) had successful portal pressure reduction at the time of index TIPSS insertion. In patients who had at least one portogram during follow-up (n = 295), the overall secondary assisted patency rate is 72.2%. Of the variables assessed (age and sex of patient, Pugh score, prothrombin time, stent diameter, requirement for ventilation, PPG pre-TIPSS and post-TIPSS, PPG reduction post-TIPSS, successful PPG reduction post-TIPSS, and alcoholic aetiology), none independently predicted shunt insufficiency on multivariate analysis.

Variceal rebleeding

Of the 371 patients selected for analysis, variceal rebleeding occurred in 51 (13.7%) patients. In total

Table 4 Non-fatal procedure-related complications

Complication	Number of patients affected
Portal vein thrombosis ^a	5
Intraperitoneal haemorrhage	5
Portal vein to bile duct fistula	2
Neck haematoma from central line insertion	4
Local collection between gallbladder and liver	2
Central line sepsis	2
Shunt migration	2
Presumed shunt sepsis	2
Tension pneumothorax from central line insertion	1
Right atrial clot ^b	1
Haematoma around TIPSS	1

TIPSS, transjugular intrahepatic portosystemic stent-shunt.

^aThree cases were successfully evacuated and two required thrombolysis with streptokinase.

^bNoted at follow-up portography, which was aspirated via a 10 Fg sheath, and seen later at echocardiography pre-orthotopic liver transplantation.

Fig. 1

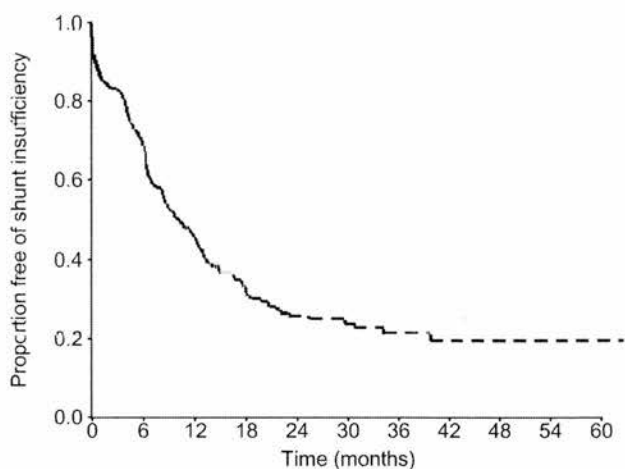
Kaplan-Meier analysis of cumulative shunt insufficiency ($n = 432$).

Table 5 Causes of shunt insufficiency during follow-up

Abnormality on portography	Number of episodes	Number of patients affected
Intimal hyperplasia	289	157
Hepatic vein stenosis	100	72
Thrombosis within shunt	31	28
Occluded shunt	60	46
Portal vein thrombosis	3	3

there were 59 episodes of variceal rebleeding, with oesophageal variceal rebleeding in 41 episodes (74.6%), gastric variceal rebleeding in 13 episodes (22.0%), and both gastric and oesophageal variceal rebleeding in two episodes (3.4%). Following five episodes of variceal rebleeding, patients died rapidly from hepatic decompensation before TIPSS portography could take place. Following the other 54 episodes (91.5% of all episodes of variceal rebleeding), portography revealed evidence of shunt insufficiency in 46 (85.2%) episodes. Shunt intervention at the time of portography resulted in successful shunt function in 41 (89.1%) episodes of shunt insufficiency. In the other five cases where it was not possible to re-establish shunt function, principally due to unsuccessful attempts at insertion of a parallel stent, two patients were entered successfully into a banding programme, one patient was treated successfully with thrombin for bleeding gastric varices, and two patients underwent surgery. One of these patients required oesophageal transection and splenectomy, and the other patient splenectomy and underpinning of veins following gastric variceal rebleeding.

The 1 year and 2 year cumulative rebleeding rates are 14.5% and 18.37% respectively (Fig. 2a). There was only one patient who had an episode of variceal rebleeding 2 years after TIPSS insertion associated with shunt dysfunction. In this patient it was not possible to

bring the PPG post-TIPSS to below 12 mmHg after the index TIPSS insertion, thus resulting in an insufficient shunt. The following variables were entered into multivariate analysis: (1) age and sex of patient; (2) alcohol aetiology; (3) Pugh score; (4) gastric and oesophageal variceal bleeding as an indication; (5) requirement for ventilation; (6) successful portal pressure reduction following TIPSS. Cox regression analysis revealed that the Pugh score of greater than 7 ($P = 0.01$), requirement for ventilation ($P < 0.05$), and failure to achieve successful portal pressure reduction following index TIPSS insertion ($P < 0.05$) independently predicted variceal rebleeding (Table 6 and Fig. 2b,c).

There were 21 additional episodes of non-variceal rebleeding with the causes as follows: (1) banding/sclerotherapy induced ulceration ($n = 11$); (2) peptic ulceration ($n = 6$); (3) Mallory-Weiss tear ($n = 2$); (4) oesophagitis ($n = 1$); and (5) arterial bleeding ($n = 1$). There were 11 documented rebleeding episodes where the source of the bleed was not identified at endoscopy, or the patient did not have an endoscopy.

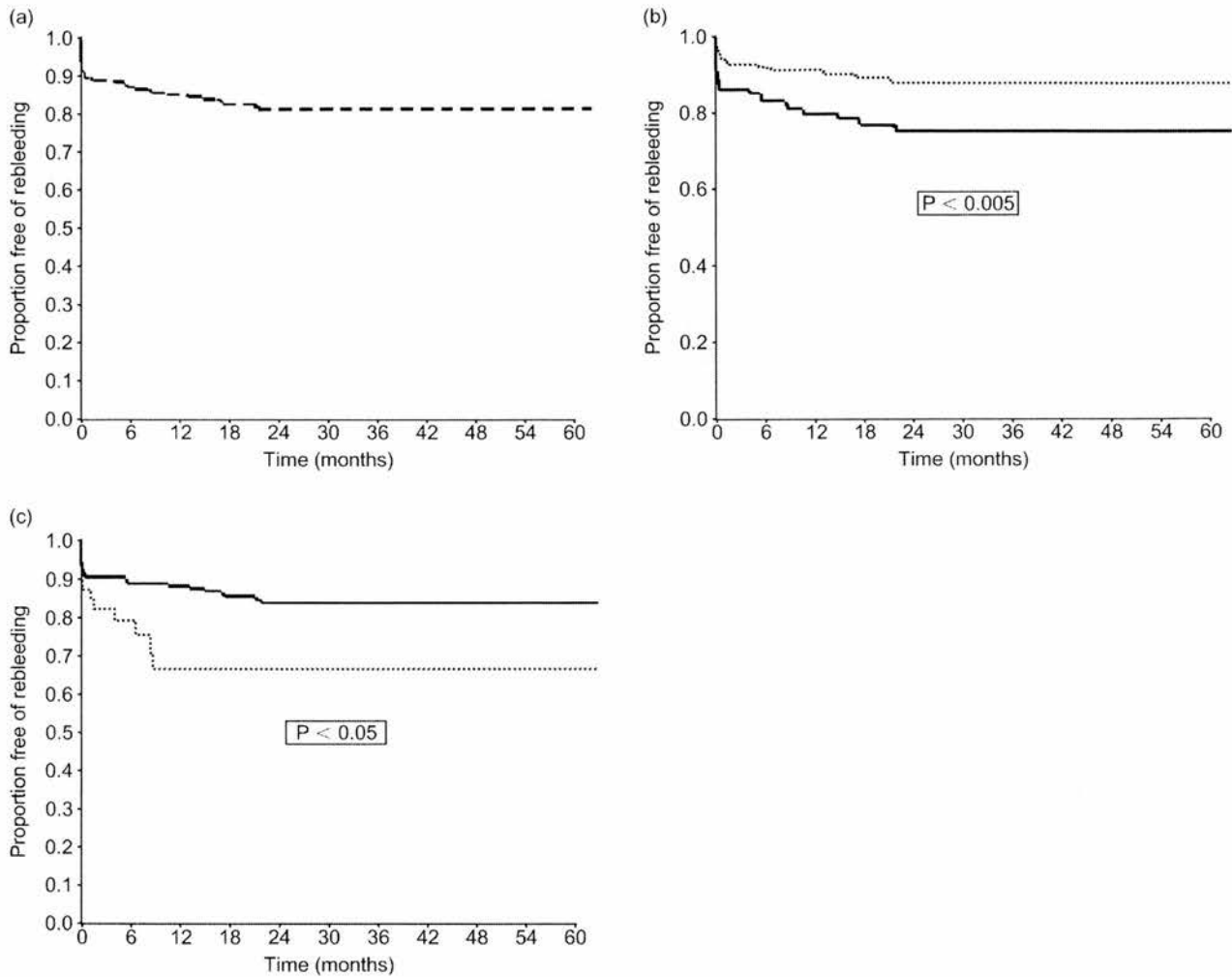
Mortality

There were 261 deaths (60.4%) in the 432 patients selected for this analysis (Table 7). The early mortality rate was 27.2%, and 1 year, 2 year and 5 year cumulative survival rates are 55.2%, 45.8% and 27.0%, respectively (Fig. 3a). The following variables were entered into multivariate analysis: (1) age and sex of patient; (2) alcohol aetiology; (3) gastric or oesophageal variceal bleeding, and ascites as an indication for TIPSS; (4) Pugh score; (5) requirement for ventilation; (6) PPG pre-TIPSS; and (7) successful portal pressure reduction post-TIPSS. Multivariate regression analysis revealed the Pugh score, age of patient, requirement for mechanical ventilation at index TIPSS insertion, and oesophageal variceal bleeding or ascites as an indication for TIPSS, to be independent factors predicting mortality (Table 6). Patients in Child Pugh class C had significantly higher cumulative mortality (Fig. 3b), with a 5 year survival rate of 18.2% compared with 37.2% for patients in Child class A and Child class B ($P < 0.001$). Further analysis of patients with Pugh score > 12 revealed an early mortality rate of 54.2%, with 1 year and 2 year survival of 33.7% and 31.4%, respectively. Figure 3c illustrates the difference in mortality in favour of patients who required a TIPSS for gastric variceal bleeding compared with oesophageal variceal bleeding. Figure 3d illustrates the detrimental effect of ascites on mortality when compared with other indications for TIPSS.

Orthotopic liver transplantation

Of the population in whom a TIPSS was successfully inserted ($n = 472$), there were 43 patients (9.1%) who

Fig. 2



Kaplan-Meier analyses of cumulative variceal rebleeding: (a) in all subjects ($n = 371$); (b) in Pugh class A/B (····, $n = 168$) versus class C (—, $n = 203$) patients; and (c) in patients with successful portal pressure gradient (PPG) reduction (—, $n = 313$) versus unsuccessful PPG reduction (····, $n = 58$).

Table 6 Variables independently predicting poor clinical outcome following transjugular intrahepatic portosystemic stent-shunt (TIPSS)

Clinical outcome	Variable	P value
Mortality	High Pugh score	< 0.001
	Increasing age	< 0.01
	Requirement for mechanical ventilation	< 0.01
	Oesophageal variceal bleeding	< 0.05
	Ascites	< 0.05
Variceal rebleeding	High Pugh score	< 0.01
	Requirement for mechanical ventilation	< 0.05
	Failure to achieve successful portal pressure gradient reduction following TIPSS insertion	< 0.05
	Pre-TIPSS encephalopathy	< 0.05
Hepatic encephalopathy	Pre-TIPSS encephalopathy	< 0.05

underwent OLT at 13.8 ± 2.7 months following TIPSS insertion. There were no adverse complications or mortality directly as a result of the presence of a TIPSS.

Hepatic encephalopathy

Hepatic encephalopathy was classified into *de novo* or a deterioration of pre-existing encephalopathy using the Parson-Smith criteria [31]. In the 432 patients included

Table 7 Mortality data ($n = 261$) following transjugular intrahepatic portosystemic stent-shunt (TIPSS) insertion

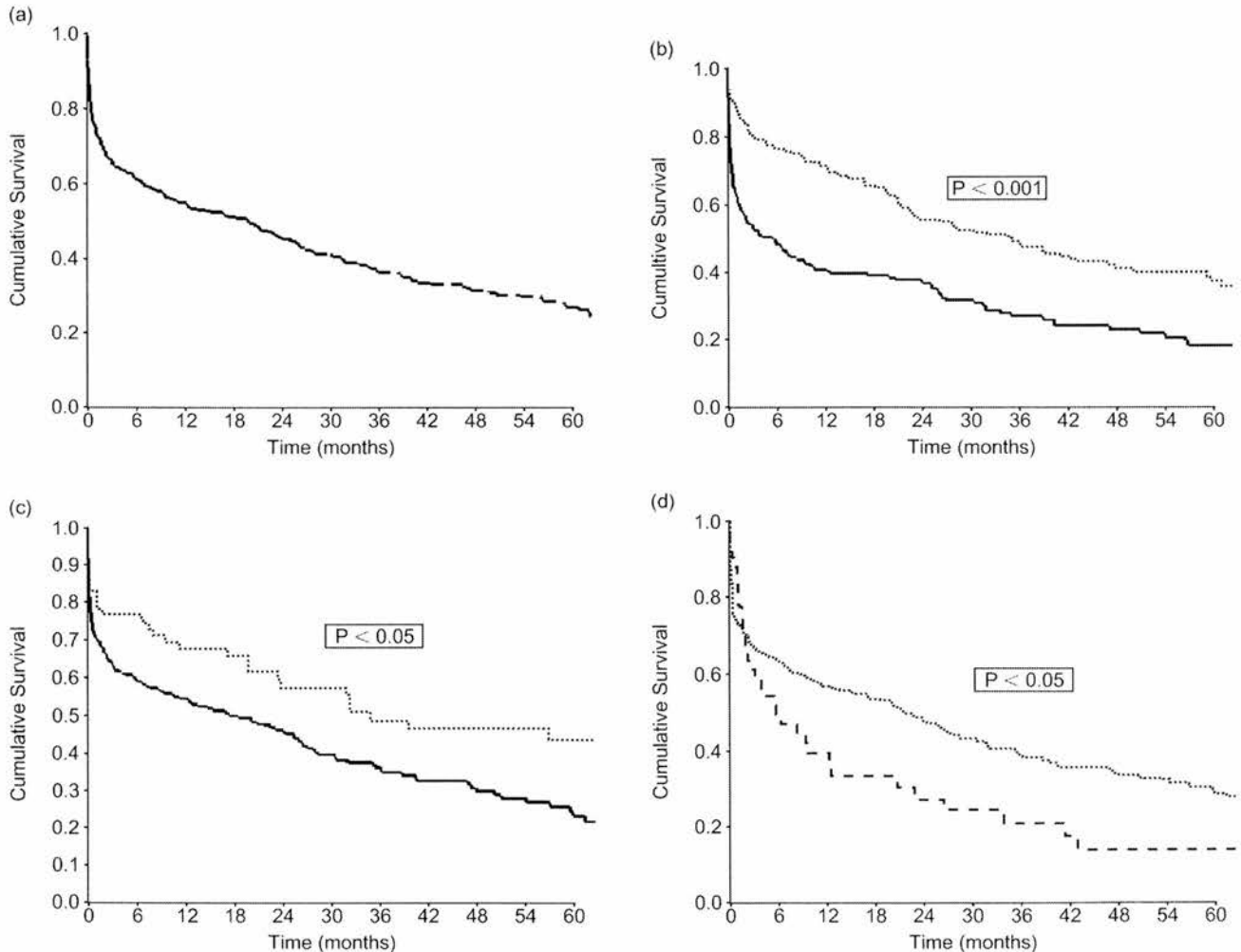
Cause of death	n (%)
Liver failure	111 (42.5)
Sepsis	60 (23.0)
Variceal rebleed	34 (13.0)
Hepatoma	11 (4.2)
Cerebrovascular accident	9 (3.5)
Non-variceal rebleed	5 (2.3)
TIPSS procedure related ^a	6 (2.3)
Other	24 (9.2)

^aProcedure related mortality for the entire study population is 1.2%.

for analysis, there were 137 (31.7%) patients who were encephalopathic prior to TIPSS insertion (38.0% with Grade I, 26.3% with Grade II, 21.2% with Grade III, 14.5% with Grade IV). One hundred and twenty nine

(29.9%) patients developed encephalopathy during follow-up. Of these 48 (11.1%) patients were encephalopathic prior to TIPSS insertion and had the following outcomes: (1) deterioration of encephalopathy managed by therapeutic occlusion of the shunt ($n = 6$) or reduction in stent diameter ($n = 1$), OLT ($n = 3$), or termination of portographic surveillance, with the shunt allowed to become insufficient and the patient entered into a banding program ($n = 1$); (2) rapid resolution of hepatic encephalopathy following the initial variceal bleed without recurrence ($n = 12$), or with recurrence due to rebleeding ($n = 1$), or with spontaneous 'de novo' recurrence ($n = 2$); (3) death shortly following TIPSS due to liver/multi-organ failure ($n = 8$), variceal rebleeding ($n = 4$), or sepsis ($n = 3$); and (4) improvement in encephalopathy with persistent mild episodes easily amenable to dietary protein restriction and lactulose ($n = 7$).

Fig. 3



Kaplan-Meier analyses of cumulative survival: (a) in all subjects ($n = 432$); (b) in Pugh class A/B (·····, $n = 202$) versus class C (—, $n = 230$) patients; (c) in oesophageal (—, $n = 272$) versus gastric variceal bleeding (·····, $n = 65$) patients; and (d) in patients with ascites (·····, $n = 50$) versus other primary indications for transjugular intrahepatic portosystemic stent-shunt (—, $n = 382$).

The remaining 81 (18.9%) patients were not encephalopathic prior to TIPSS insertion and had the following outcomes: (1) development of 'de novo' hepatic encephalopathy requiring therapeutic intervention with occlusion of the shunt ($n = 13$), reduction in the stent diameter ($n = 1$), or OLT ($n = 6$); (2) development of 'de novo' hepatic encephalopathy that resolved with conservative therapy with no shunt intervention required ($n = 24$), or persisted with the patient subsequently dying from severe end stage liver failure ($n = 4$); (3) hepatic encephalopathy due to rebleeding that improved after satisfactory management of the bleed ($n = 9$), or persisted with the patient subsequently dying from end-stage liver failure ($n = 22$); and (4) hepatic encephalopathy related to sepsis that improved following antimicrobial therapy ($n = 1$), or led to severe hepatic decompensation and death ($n = 1$).

Multivariate regression analysis of variables of interest (indication for TIPSS, sex, age, Pugh score, alcoholic aetiology, pre-TIPSS encephalopathy, PPG post-TIPSS, diameter of the index TIPSS, and the requirement for mechanical ventilation) revealed the presence of pre-TIPSS encephalopathy ($P < 0.01$) to independently predict post-TIPSS encephalopathy (Table 6).

Ascites

In 50 (10.6%) patients, refractory ascites was the primary indication for TIPSS, with none of these patients experiencing variceal bleeding at the time of TIPSS insertion. All patients had failed to respond to repeated paracentesis or diuretic therapy, with two patients having had unsuccessful surgical peritoneo-venous shunts (Denver and La Veen). Two patients had Budd–Chiari syndrome. Thirty-six (72.0%) patients responded to the TIPSS, but in 10 (27.8%) of these patients there was recurrence of ascites due to shunt insufficiency ($n = 5$), renal impairment ($n = 2$), progressive liver failure despite a patent TIPSS ($n = 2$), or therapeutic occlusion of the TIPSS to treat intractable hepatic encephalopathy ($n = 1$). Fourteen (28%) patients did not respond to the TIPSS due to inability to maintain adequate shunt function ($n = 5$), worsening renal function ($n = 4$), spontaneous bacterial peritonitis ($n = 2$), hepatoma and tumour thrombus ($n = 1$), rapidly deteriorating liver function ($n = 1$), or other malignancy ($n = 1$). In total, six patients underwent OLT. In the patients with Budd–Chiari syndrome, one required decompressive surgery following failure to overcome a blocked TIPSS, and the other patient died as a result of an intracranial haemorrhage while on anticoagulant therapy. The average stent diameter of 10.6 ± 0.3 mm was similar in the groups that did and did not respond. The mortality was higher ($P < 0.05$) where ascites was the primary indication for TIPSS compared with other indications (Fig. 3d). The incidence of hepatic encephalopathy also appeared higher in the ascitic popu-

lation (36.0%) compared with those that required a TIPSS for variceal bleeding (25.6%), although this just failed to reach statistical significance ($P = 0.08$).

Discussion

TIPSS has established itself to have a major role in the management of portal hypertension, and with better expertise and additional indications is likely to be increasingly used. It is clear that TIPSS is effective in the prevention of variceal rebleeding, although current data from most randomized controlled trials do not suggest an improvement in mortality [12]. Our experience reflects 10 years of TIPSS in a single centre, and mirrors that of most other units with an overall success rate of 95.4%, and a procedure-related mortality of 1.2%. Both these figures are likely to improve in the future with increasing expertise.

Our findings confirm the efficacy of TIPSS in the prevention of variceal rebleeding, with an overall rebleeding rate of 13.7%, with most episodes occurring early during follow-up and almost always related to shunt dysfunction. Intervention to correct shunt insufficiency was very effective, with only five cases where TIPSS intervention failed. An interesting observation was of just one variceal rebleeding episode after 2 years, despite shunt dysfunction. The fact that 92.5% of patients who experienced shunt insufficiency after 2 years had successful PPG reduction at the time of index TIPSS insertion may partly explain this, since we have identified haemodynamic success to independently predict varices rebleeding. Perhaps most of these patients had also selected themselves as being in the better prognostic group as they had survived beyond 2 years, and thus less likely to bleed. In keeping with our previous findings, the severity of liver disease prior to TIPSS insertion has a profound effect on rebleeding rates (Fig. 2b) [22], but even in those patients with Child class C disease the efficacy of TIPSS in preventing variceal rebleeding has previously been shown to be better than endoscopic modalities [6]. The Pugh score, requirement for ventilation, and failure to achieve successful PPG reduction at the index TIPSS independently predicted variceal rebleeding.

There is some controversy regarding the therapeutic haemodynamic goals for TIPSS insertion, with some advocating a reduction in the PPG of 20–50% rather than simply a reduction in the PPG to < 12 mmHg [33]. Using the latter criteria has its limitations, particularly in those patients that bled at $\text{PPG} \leq 12$ mmHg, of which there are a considerable number in our population (13.4% of all cases of variceal haemorrhage), in contrast to previous studies (Tables 2 and 3) [34]. Our criteria for successful portal pressure reduction apply to all patients. We have shown previously that patients

with gastric varices frequently bleed at lower portal pressures [35], and that achieving pressures much lower than 12 mmHg following TIPSS insertion may be necessary to prevent rebleeding [36]. A possible explanation for the lower portal pressure in patients with gastric varices could be the development of spontaneous spleno-renal porto-systemic shunts, or reduced portocollateral resistance [37]. It is unclear why gastric varices bleed at lower pressures, but fundal varices may bleed as a result of increased variceal wall tension owing to their large size, since variceal wall tension plays an important role in determining the risk of variceal bleeding [38].

Shunt insufficiency occurred frequently, with most episodes being easily treated resulting in good secondary assisted patency. The observation noted earlier of just one episode of shunt dysfunction after 2 years associated with variceal rebleeding, brings into question the rationale of continuing invasive portographic follow-up beyond this time. The introduction of covered stents, and very promising patency rates reported in uncontrolled series [26,39], may reduce the need for TIPSS surveillance in the future.

Mortality in the TIPSS population remains high, despite correction of portal hypertension in the vast majority, with most deaths due to liver failure and/or sepsis. The Pugh score, presence of ascites, and requirement for mechanical ventilation are independent factors predicting mortality. Around one-half of all deaths occur within the first year (Fig. 3a). This reflects the underlying liver disease, and particularly in our population, the fact that most patients continue to consume alcohol. A trend towards reduced mortality in patients with gastric variceal bleeding compared with oesophageal variceal bleeding has previously been noted [35], and this is confirmed in the present study. It is probable that the reduced portal pressure in the former group (Table 2), both pre-TIPSS insertion and post TIPSS insertion, makes a significant contribution. Our unit and others have demonstrated the significance of portal pressure on mortality, particularly if measured shortly after a variceal bleed [40,41].

Post-TIPSS hepatic encephalopathy remains a controversial topic. It is important to separate the encephalopathy related to the variceal bleed or other precipitants such as sepsis from that occurring *de novo*, as seen in some trials. In our population, the overall encephalopathy rate of 29.9% is similar to the literature, but only 11.6% of patients developed *de novo* encephalopathy. The only independent variable predicting post TIPSS encephalopathy was pre-TIPSS encephalopathy, a finding that we have previously reported [21]. One has to question the use of TIPSS in severely encephalopathic patients, but in clinical practice the severity of encephalopathy is related to the severity of the variceal bleed and liver disease, and TIPSS is often used as a salvage procedure in such patients, where clearly it is preferable to surgical treatment.

Initial enthusiasm for TIPSS in refractory ascites was dampened by results published by Lebrec *et al.*, where patients randomly assigned to TIPSS had worse 1 year and 2 year survival compared with repeated paracentesis [42]. However, this study had very small numbers in the TIPSS arm ($n = 13$), and the findings have been challenged by a recent publication by Rössle and colleagues [14]. The latter study included 29 patients randomly assigned to TIPSS, and showed convincingly an improved survival and a reduced incidence of recurrent ascites compared with paracentesis, with improvement in renal function and no difference in the incidence of hepatic encephalopathy. Two recent randomized studies comparing TIPSS versus paracentesis plus albumin [43], and TIPSS plus medical therapy versus medical therapy [44], reinforce the efficacy of TIPSS in the prevention of recurrent ascites and development of hepato renal syndrome. However, survival is unaffected, with hepatic encephalopathy and costs greater in the TIPSS arms. The better survival for patients in the TIPSS arm in the study by Rössle *et al.* may have been due to patients in the paracentesis arm not routinely receiving albumin, thus resulting in greater circulatory instability [45]. The survival of our patients is worse than that for the other studies mainly due to our unselected patients having more advanced liver disease. Our findings demonstrate a definite response to TIPSS, although in a significant number ascites recurred. These findings are consistent with that of other uncontrolled series [46–50], with two studies showing renal function to predict the response to TIPSS [46,47]. In over one-half of these cases the reason for TIPSS failure was shunt insufficiency, with one patient having had an occlusion of the shunt due to encephalopathy. In experienced centres, TIPSS appears to be a valuable addition to the management of refractory ascites in those patients who have failed to respond to other therapies, but careful selection of patients and rigorous TIPSS surveillance is needed to minimize failure.

In our population only 9.1% of patients had an OLT. This reflects the high proportion of patients who have alcoholic liver disease, and the fact that most of them continue to drink, and are therefore not transplant candidates. There have been several studies investigating the use of TIPSS as a bridge to OLT, including some from our unit [16,17,25]. There is little evidence that TIPSS has any detrimental effect on the liver transplant or subsequent patients and graft survival. Careful selection of patients is required on account of the potential of a TIPSS to cause deterioration in any

pre-existing hepatic encephalopathy. Since the TIPSS used in the present study extend from the portal vein to the inferior vena cava, there is the potential to interfere with OLT. However, studies performed in our unit so do not show any greater operative time or transfusion requirements [16,17]. The present study also illustrates the use of TIPSS post-OLT, although the outcome in the two patients was not favourable. Studies looking at TIPSS post-OLT have been limited in size, and it is not possible to make valid conclusions [24]. Another unusual indication in our population is Budd–Chiari syndrome, with once again rather poor results, although we only had two cases. These patients are inherently difficult to manage, with some having an underlying coagulation disorder resulting in increased risk of TIPSS thrombosis despite the use of anti-coagulation. Others have reported greater success [51], but it is important to bear in mind that these patients may be more suitable for surgical shunts or in cases of cirrhosis OLT.

In conclusion, our experience with TIPSS over a 10 year period confirms the efficacy of TIPSS in the management of portal hypertension, particularly variceal bleeding. The mortality rate following TIPSS is related to the severity of liver disease, and mortality is greater in patients with refractory ascites. Patients with gastric variceal bleeding are particularly suited to TIPSS, a finding that has been demonstrated by others [13,15,35]. Careful selection of patients is needed to reduce post-TIPSS encephalopathy. The high incidence of shunt insufficiency post-TIPSS can easily be overcome by regular surveillance, but contributes to reduced efficacy in the management of refractory ascites. In the future polytetrafluoroethylene-covered stents, if shown to have better patency rates in controlled studies, may reduce the need for TIPSS surveillance.

Conflict of interest

None declared.

Authors' contributions

Dhiraj Tripathi: major role in writing and revising manuscript, statistical analysis, data collection, clinical follow-up; role in technical revisions to TIPSS database, and application of computing skills analysing the data. Ahmed Helmy: major role in writing manuscript, and statistical analysis; role in data collection and entry, and clinical follow-up of patients. Kim Macbeth: contribution to text of manuscript; major role in data collection, and clinical follow-up of patients. Sherzad Balata: contribution to text of manuscript; assistance with data collection. Hock F Lui: major role in data collection and clinical follow-up. Adrian J Stanley: original design of TIPSS database; significant role in early data collection and clinical follow-up; major contribution to the text of manuscript. Doris N Redhead: interventional radiologist with strong interest in TIPSS; all TIPSS procedures performed by her or under her direct supervision; major contributor to the text, particularly technical aspects. Peter C Hayes: Professor of Hepatology; major contributions to all aspects of manuscript design and textual content; involved in clinical follow-up and treatment of patients.

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