Transjugular intrahepatic portosystemic shunt in the treatment of symptomatic portal hypertension

KERSTIN ROSENVIST
Portal hypertension (PHT) is a condition with serious complications, such as variceal bleeding, refractory ascites and bowel ischemia. The cause of PHT may be pre-, intra- or post-hepatic. Initial treatment is pressure-reducing drugs and the treatment of acute symptoms.

Ten patients presented with severe abdominal pain and acute portomesenteric venous thrombosis. Their response to systemic anticoagulation was insufficient. Treatment with primary continuous thrombolysis by a transhepatic or transjugular approach in four patients resulted in major complications, incomplete recanalization and a 75% survival rate. Treatment with repeated transjugular thrombectomy (TT) combined with the creation of a transjugular intrahepatic portosystemic shunt (TIPS) achieved near complete recanalization, prompt symptom relief and 100% survival in five patients treated with this method as the primary intervention. In one patient, treated with TT and TIPS secondary to surgical thrombectomy and bowel resection, the outcome was fatal.

Nineteen patients with portal vein thrombosis presented with acute or threatening variceal bleeding or refractory ascites. TIPS was feasible in 16 of the 18 patients in whom it was attempted and symptom relief was achieved in the majority of them.

In 14 patients with Budd-Chiari syndrome, 13 patients were treated with TIPS, four of them after previous liver vein angioplasty. The 5-year transplantation-free survival rate was 100% in patients treated with primary TIPS.

In 131 patients with variceal bleeding treated with TIPS, the survival at 12 months in patients with and without cirrhosis was 70% and 100% respectively and in accordance with previous studies. A high Child-Pugh score prior to TIPS and severe HE within 12 months after TIPS was related to an increased mortality. The occurrence of HE after TIPS did not correlate with the PSG after TIPS. Re-bleeding within 12 months after TIPS occurred in 10 patients and was associated with TIPS dysfunction.

In conclusion, endovascular intervention, mainly TIPS, seems to be safe and effective for treating patients with complications of PHT, regardless of the underlying cause of disease and site of venous blood flow obstruction. HE may occur more frequently after TIPS than medical and endoscopic treatment, but is often mild and easily treated. In selected patients with PHT, TIPS may improve survival.

Keywords: Portal hypertension, TIPS, transjugular, portal venous thrombosis, mesenteric venous thrombosis, liver cirrhosis, interventional radiology

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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<td>CP</td>
<td>Child-Pugh</td>
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<td>CT</td>
<td>Computer tomography</td>
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<td>GAVE</td>
<td>Gastric antral vascular ectasia</td>
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<td>HCC</td>
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<td>INR</td>
<td>International normalized ratio</td>
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<td>IVC</td>
<td>Inferior vena cava</td>
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<td>MELD</td>
<td>Model for end-stage liver disease</td>
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<td>NAFLD</td>
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<td>PSC</td>
<td>Primary sclerosing cholangitis</td>
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<td>PSG</td>
<td>Portosystemic gradient</td>
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<td>PTFE</td>
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<td>PV</td>
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<td>PVT</td>
<td>Portal vein thrombosis</td>
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<td>SMV</td>
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<td>TIPS</td>
<td>Transjugular intrahepatic portosystemic shunt</td>
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<td>PMVT</td>
<td>Portomesenteric venous thrombosis</td>
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<td>WHVP</td>
<td>Wedged hepatic venous pressure</td>
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</tbody>
</table>
Introduction

Portal hypertension (PHT) is a serious condition with complications such as variceal bleeding, refractory ascites and hepatorenal syndrome (1). Recently, treatment strategies for severe PHT have shifted from mainly pharmacological, with surgery as rescue, to pharmacological combined with endoscopic and methods of interventional radiology (2–5). The presented papers evaluate the outcome of interventional radiology, mainly with the creation of a transjugular intrahepatic portosystemic shunt (TIPS), in patients with symptomatic portal hypertension at Uppsala University Hospital. Papers I and III discuss patients with portal vein thrombosis (PVT) and Paper II discusses patients with Budd-Chiari syndrome (BCS). Paper IV presents the results in patients with variceal bleeding.
Background

Portal hypertension

PHT is defined as an increased difference in the pressure gradient between the portal vein and the hepatic veins. The most common cause of PHT, liver cirrhosis, impairs the intrahepatic portal blood flow and can be induced by many different entities including abundant alcohol intake, viral infections and autoimmune disease (6). Pre-hepatic obstruction of the portal vein, caused by portal vein thrombosis, tumour vein invasion or mechanical obstruction, is less common. Post-hepatic obstruction of hepatic venous outflow (BCS) is a rare cause of PHT.

When the hepatic venous pressure gradient (HVPG) reaches 10 mmHg or more, PHT is considered to be clinical significant (7). In cirrhotic patients gastro–oesophageal varices develop at a gradient of 10–12 mmHg, and at a gradient of >12 mmHg there is a high risk of variceal bleeding (8), associated with a 6-week mortality rate of 10–20% (9). Other consequences of PHT are ascites, hepatic encephalopathy (HE) and jaundice (6).

The HVPG represents the pressure difference between the portal vein (PV) and the inferior vena cava (IVC) (10). To avoid the transhepatic puncture required to reach the PV, the preferred method of obtaining the HVPG is to compare the indirect wedged hepatic venous pressure (WHVP) with the pressure in the IVC. The WHVP is obtained, via a transjugular access, by catheterising a small hepatic vein as far as possible, to occlude the vein before measuring the pressure, which then represents the pressure in the hepatic sinusoids (10). The WHVP has been shown to accurately reflect the portal pressure in alcoholic and hepatitis C virus cirrhosis (11) but may underestimate the pressure in the PV in pre-hepatic induced PHT (12).

In the papers presented in the thesis, the true PV pressure has been measured and the gradient obtained by comparison with the pressure in the right atrium, namely the portosystemic gradient (PSG). While this is a frequently used method, the pressure in the right atrium may differ slightly from the pressure in the IVC, and the PSG and the HVPG cannot be considered completely equal (10). Recently, it has been reported that general anaesthesia can affect the gradient between the PV and the IVC, the portal pressure gradient (PPG), and
that a repeated PPG in the same patients when awake is slightly higher (13). Hence, several factors affect the measurement and the different techniques used make it difficult to compare results related to the pressure gradient from different studies.

Liver cirrhosis

Liver cirrhosis is the irreversible final stage of chronic liver disease. Even though liver cirrhosis is both common and associated with high mortality the pathophysiology is not fully understood (14). The major causes are abundant alcohol intake, chronic hepatitis B and C and non-alcoholic fatty liver disease (NAFLD) (1). A daily intake of 30-80 gram of alcohol (2-5 glasses of wine) is associated with a risk of developing liver cirrhosis (15). In patients with alcohol-induced liver cirrhosis the prognosis is poor if abundant alcohol intake is continued, with a five year survival rate of around 35% (15). In liver cirrhosis due to hepatitis C infection the five-year survival is 85-91% and if the cirrhosis is decompensated it is 51% (16). The prevalence of NAFLD has increased in recent years and NAFLD is now the most common cause of chronic liver disease in the US (17). The prevalence of NAFLD worldwide is around 20% and it is considered the hepatic manifestation of metabolic syndrome (18).

When liver disease progresses, blood flow in the intrahepatic portal veins is impaired, due to both structural (fibrosis and regenerative nodules) and dynamic (increased hepatic vascular tone) changes (19). With the increased portal pressure, compensated (asymptomatic) liver cirrhosis turns into decompensated cirrhosis (with symptoms of portal hypertension) (6). Patients with decompensated liver cirrhosis have an expected survival of about two years (6).

To predict mortality, several prognostic models have been suggested; the most widely used are the Child-Pugh (CP) classification (20) and the model for end-stage liver disease (MELD) score (21). In the CP classification, the level of bilirubin, albumin, international normalized ratio (INR), ascites and HE are converted into points and the sum of the five components form the total score. A higher score correlates to more severe liver disease. A score of 5-6 points is considered CP class A, 7-9 points CP class B and 10-15 points CP class C. The prognosis for patients in CP class C is poor with a one year mortality of around 50% (22). Even though different prognostic models have proved better in selected patients, the CP score is still a robust and dependable method for predicting mortality in patients with liver cirrhosis (23). The MELD score is based on the three variables of bilirubin, creatinine and INR and was initially developed to estimate survival prognosis after the creation of a transjugular intrahepatic portosystemic shunt (TIPS) (21). Since then, it has proven to be a
dependable prognostic tool for estimating survival in end stage liver disease (24).

The primary treatment in cirrhosis is of the underlying disease, which is alcohol abstinence, anti-viral treatment and metabolic control. Complications of decompensated liver cirrhosis are treated accordingly. In patients with refractory ascites, diuretics are the first line treatment and non-selective beta blockers may be used with careful monitoring, with TIPS recommended as secondary prophylaxis (7). The treatment of variceal bleeding is discussed in detail below. Occurrence of hepatocellular carcinoma (HCC) is strongly associated with liver cirrhosis, mainly with cirrhosis due to chronic hepatitis C and B (25). HCC is the most common malignant primary liver tumour and the third leading cause of all cancer-related deaths worldwide (25).

Variceal bleeding

As the pressure in the portal vein system increases in advanced PHT, pre-existing portosystemic collaterals dilate into variceal veins (26). In cirrhosis, the most common sites are oesophageal and gastric, but variceal veins can develop at any site along the gastrointestinal tract (27). Bleeding occurs in about one fourth of patients with cirrhosis and variceal veins, and the risk of bleeding is associated with the size of the varices, degree of liver dysfunction, and presence of red wale marks (red spots on the varices, visible at endoscopy) (28). The mortality rate six weeks after variceal bleeding has been estimated at around 10-20% (7).

First line treatment for an acute episode of variceal bleeding is medical (vasoactive drugs and antibiotics) in combination with the endoscopic band ligation of varices (7). In patients where the initial treatment fails, a TIPS should be considered (7). Early TIPS, i.e. performed within 72 hours of the onset of the primary bleeding episode, has recently shown to improve survival in patients at high risk of treatment failure (29,30) and this has been incorporated into the current guidelines (7,31). More than 130 patients with variceal bleeding have been treated with TIPS at Uppsala University Hospital since 2002.

Portal and mesenteric vein thrombosis

The PV originates at the confluence of the superior mesenteric vein (SMV) and the splenic vein, and accounts for the main blood supply to the liver. Obstruction of the PV leads to PHT and the formation of portosystemic collaterals in gastric, oesophageal, duodenal and jejune veins. Chronic obstruction
leads to fibrotic transformation of the PV with multiple small surrounding ve-
nous collateral veins, a portal cavernoma (32). The national prevalence of
PVT is reported to be 1% (33) but can, in patients with cirrhosis, be as high as
25% (34). The aetiology for PVT is often local, as liver cirrhosis, hepatobiliary
malignancies, infections and inflammatory conditions; it is less commonly
systemic, as congenital and acquired myeloproliferative disorders (33).

Patients with PVT may be asymptomatic if the thrombus is partial and the
onset gradual, but acute PVT with the involvement of mesenteric veins is
rarely asymptomatic (35–38). How the disease develops depend on the exten-
sion of PVT, whether it is occlusive or partial and the degree of recanalization
(36,39–43). Spontaneous recanalization is rare (44,45) and systemic anticoag-
ulation is the first line of treatment (7). Further treatment is based on the symp-
toms and the calculated risk of complications, but symptomatic patients with
insufficient response to medical treatment, or who are unsuitable for antico-
agulation, often need invasive intervention (45,46). PVT has, until recently,
been considered a contraindication for TIPS. However, an increasing number
of studies show that TIPS is a valuable and safe intervention in both cirrhotic
and non-cirrhotic patients with PVT (41,47–52).

Acute extensive portomesenteric venous thrombosis (PMVT) can be a life-
threatening condition due to the risk of developing bowel ischemia in the acute
setting (38,42,53). The risk of developing complications is higher if PMVT
recanalization is not achieved (36) and the mortality rate is 20-50% (54,55).
PMVT is a rare condition (56) which makes it difficult to collect larger series
for study. With systemic anticoagulation as the primary treatment, recanaliza-
tion is achieved in less than half of the patients (45,46). Reports of invasive
treatment are often in very limited study populations (57–61). Thrombolysis
by direct (transhepatic and transplenic) or indirect (via the superior mesenteric
artery) routes may be associated with fatal complications (35,59,62).
Transjugular thrombectomy (TT) in combination with the creation of a TIPS
seems very effective for recanalization and symptom relief (57,58,61,63), but
there are only a few reported cases and the method needs to be further investi-
gated.

**Budd-Chiari syndrome**

BCS is defined as hepatic venous outflow obstruction at any level from the
small hepatic veins to the junction of the IVC and the right atrium, regardless
of the cause (64). It is a rare disease with local variation in aetiology. In the
western hemisphere, hepatic vein obstruction is the predominant cause while
obstruction of the IVC is more common in the eastern hemisphere (47). In
Sweden, the incidence is 0.8 per million per year and the most common aetiology is myeloproliferative disorder (65). Clinical presentation may vary from asymptomatic to liver failure. Common symptoms are abdominal pain, hepatomegaly and ascites (66). Untreated, the prognosis for symptomatic BCS is poor with an estimated 3-year survival of only 10% (67).

For many years, the treatment of BCS has been mainly medical, with anticoagulation, and orthopic liver transplantation (OLT) as a rescue treatment. The current treatment recommendations are to follow a step-wise approach including anticoagulation, angioplasty/thrombolysis, TIPS and OLT. TIPS should be attempted in patients with insufficient response to anticoagulation where angioplasty of liver veins is not feasible, but not in patients with a high risk of TIPS failure according to the Budd-Chiari syndrome prognostic index (BCS-PI) (7). However, in a multi-centre study of BCS the intervention-free 5-year survival was only 29% (68) and in a previous national study in which patients were mainly treated medically the 1- and 5-year transplantation-free survival rates were 47% and 28%, respectively (65). The survival rates are higher in studies of patients with BCS treated with interventional radiology methods, 78-87% (69–71). It has been suggested that earlier intervention with the creation of a TIPS may lead to improved results and possibly prevent further ischemic liver damage (72).

Endovascular interventional radiology

Angiography, the visualization of blood vessels, is now a standard procedure in most radiological departments. With magnetic resonance imaging (MRI) or computer tomography (CT), blood vessels can be detected even without contrast media. For intervention, however, the blood vessel must still be reached by surgery or from the inside by endovascular techniques.

It is almost 90 years since the development of clinical arteriography in the late 1920s. The initial technique required a large needle for the transcutaneous puncture to allow a catheter to be threaded through the needle into the vessel. A contrast medium was then injected through the catheter and vessels visualized with plain radiography. The use of large needles limited the method to large vessels and led to a high risk of bleeding (73). In 1953, the Swedish radiologist Sven-Ivan Seldinger introduced a new technique in which a thin metal wire was inserted through the needle, the needle removed and a catheter threaded onto the wire and inserted into the artery (74). This method, which allowed smaller needles and could be used in almost any vessel, is known as the Seldinger Technique and is used worldwide.
The use of the Seldinger Technique and the development of flexible catheters, guide wires, stents, stent grafts and embolization material, means that a major part of vascular surgery is now performed using the endovascular approach. Small catheters also allow the injection of oncologic agents into selected tumour-feeding vessels. There is currently rapid development of endovascular treatment in the field of oncology.

TIPS

The aim of the creation of a TIPS is to establish an efficient outflow from the portal vein and thus reduce PHT. An example is provided in Fig.1. The first report of human TIPS procedures was presented in 1983 (75) and the use of stents to keep the shunt patent was introduced in 1988 (76). In the early years, the frequency of procedure-related complications and shunt dysfunction was high, but as reports showed lower morbidity and mortality after TIPS than with the previous surgical shunts the method started to spread in the early 1990s (77). The first TIPS procedure was performed in Uppsala in 1993, but it would take nine years until the procedure was repeated.

Fig.1. Venography moments after a transjugular intrahepatic portosystemic shunt (TIPS) has been inserted. The blood from the main portal vein passes through the TIPS stent (black arrow) into the hepatic veins.
As knowledge and technical skills have improved, TIPS has proven to be a very safe method with low procedure-related mortality (78). The rate of shunt patency improved dramatically with the introduction of stents covered with polytetrafluoroethylene (PTFE) (79,80) and the number of TIPS procedures increased rapidly. In the last ten years, about 260 TIPS procedures have been performed in Uppsala alone. The outcome after TIPS depends mainly on the aetiology of PHT (78). TIPS may improve survival and symptom-relief in selected patients with liver cirrhosis and variceal bleeding (30) and refractory ascites (81,82), but the effects in hepatorenal and the hepatopulmonary syndromes are less well defined (78). In patients with PVT and BCS, TIPS is not only feasible, it may improve long-term survival (35,79,83).

HE is a frequent complication in liver cirrhosis and a significant predictor of death (6). The incidence of HE is correlated to the severity of liver deficiency. However, the incidence of HE after TIPS is higher than in patients with liver cirrhosis in general (84) and can be as high as 51% (82). As HE is associated with the cause, as well as the treatment, of PHT in patients with liver cirrhosis it is hard to identify risk factors, but a high MELD score, a low PSG after TIPS, a big reduction in PSG, shunt stenosis and a previous history of HE have all been suggested as being associated with a higher risk of HE after TIPS (85–87).

Registry of interventional radiology in portal hypertension

Following ethical approval in 2012, patients with PHT treated with interventional radiology at Uppsala University Hospital were registered in a database specifically created for this purpose. The aim was to gather information about the clinical status prior to, and after, intervention, as well as the type of intervention, complications and number of re-interventions. The registry was set up on the hospital’s internal server and secured with individual passwords acquired only by physicians in the hepatology department and the radiologists who performed the procedures. Patients were informed of the database and possible inclusion in studies, retrospectively if they had already been treated.
To date, the database includes about 325 patients, aged 16-78, more than two-thirds males. The number of patients treated each year is presented in Fig. 2. The methods included in the database are transjugular liver biopsy, PSG measurement, recanalization and angioplasty of veins (liver veins, PV and SMV), TIPS, dilatation of shunt stenosis, reduction of shunt diameter and embolization of collateral veins. Indications for interventions are presented in Fig. 3 and aetiologies of PHT are presented in Fig. 4.
Fig. 3. Indications for intervention in patients in the registry of portal hypertension. Other includes portal vein thrombosis, Budd-Chiari syndrome and pre-surgical investigations.
Fig. 4. Aetiology of portal hypertension (PHT) in patients in the registry of portal hypertension. Other includes primarily inflammatory bowel disease. NAFLD=non-alcoholic fatty liver disease.
Aims

The general aim was to evaluate the procedure-related safety of interventional radiology in patients with symptomatic PHT by: reporting the frequency of technical success and re-interventions; to evaluate the long-term effects in terms of disease progression, survival rate, post-procedure complications, and the recurrence of symptoms; to roughly compare results in Uppsala with international results; and to find areas for improvement in the techniques used.

Paper I
To report the results of endovascular treatment of portal venous thrombosis at Uppsala University Hospital.

Paper II
To assess the safety and efficiency of endovascular treatment of symptomatic patients with BCS and to compare mortality with symptomatic BCS patients in the same region treated with only sporadic endovascular techniques.

Paper III
To retrospectively evaluate the efficacy and safety of repeated TT through a TIPS, created in the same session, in patients with acute PMVT.

Paper IV
To evaluate the safety and efficacy of TIPS in patients with portal hypertension and variceal bleeding in a clinical setting. End-points were re-bleeding, survival, TIPS-dysfunction and adverse events.
Materials and methods

Patients and study designs

Paper I

A retrospective review of the log of radiology interventions from January 2002 to February 2013 identified a total of 21 patients (15 men, 6 women; mean age 53 years; range 20–75 years) with PVT treated with endovascular procedures. Clinical data were collected from the medical records. In patients with cirrhosis, liver function was assessed using the CP score (20). Diagnostic CT scans were reviewed to estimate the extent and onset of thrombosis. Acute PVT was defined by the absence of collaterals and the rapid onset of abdominal pain, intestinal ischemia, and/or infarction within 14 days of the diagnosis. Chronic PVT was defined as a decrease in intra-luminal density in the portal vein, a replacement of the original main portal vein (MPV) with a fibrotic cord, or a portal cavernoma. Threatening variceal bleeding was defined as very large varicose veins combined with previous episodes of gastrointestinal bleeding, thrombocytopenia, and/or need of surgery. Patients with variceal bleeding were treated with current standard methods, such as band ligation, vasoactive drugs, and antibiotics prior to intervention.

The patients were selected for intervention because of an insufficient response to conservative treatment. The aim of intervention was to reduce portal hypertension by the creation of a TIPS and/or recanalization of the portal vein. Informed consent was obtained from the patients included in the study.
**Paper II**

A retrospective review of the intervention log January 2003 to May 2015 identified a total of 14 patients with BCS, six men and eight women, who were treated with interventional radiology. Clinical data, including aetiology, time from onset, presenting symptoms, method of intervention, PSG, complications, recurrence of symptoms, re-interventions, occurrence of OLT, clinical status at latest follow-up and survival, were collected from medical records. The degree of liver function was assessed and followed using the CP score (20). Prognostic indices before TIPS were calculated: the Rotterdam score \((1.27 \times \text{encephalopathy} + 1.04 \times \text{ascites} + 0.72 \times \text{INR} + 0.004 \times \text{bilirubin})\) (88) and the BCS-TIPS PI score \([\text{age (years)}] \times 0.08 + \text{bilirubin (mg/dl)} \times 0.16 + \text{INR} \times 0.63\) (69). Dysfunction of TIPS was defined as the need for revision. The aim of the intervention was to reduce the PHT by recanalizing an obstructed liver vein or by creating a shunt between the PV and the IVC.

**Paper III**

Between September 2014 and May 2016, six consecutive patients (all men, aged 39 to 51) with acute extensive PMVT were treated with repeated TT through a TIPS created in the same session. Data was collected retrospectively from medical records and from the radiology information system. CT scans and venograms were reviewed. Clinical baseline information is presented in Table 1. All 6 patients had acute onset of severe abdominal pain \((\leq 2 \text{ weeks})\). The CT scans demonstrated extensive PMVT and mesenteric stranding and/or bowel wall oedema. The venograms verified extensive thrombosis of the SMV including several branches and partial or complete thrombosis of the portal vein. The splenic vein was complete or partially occluded in three patients. All patients received systemic anticoagulation therapy (heparin or low molecular weight heparin) immediately at diagnosis, but without symptom relief.
Table 1. Clinical data prior to transjugular thrombectomy in combination with creation of a transjugular intrahepatic portosystemic shunt.

<table>
<thead>
<tr>
<th>Pt No</th>
<th>Age (in years) /sex</th>
<th>Aetiology</th>
<th>Indication for intervention</th>
<th>Time from symptoms to diagnosis</th>
<th>Time from diagnosis to transjugular thrombectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/M</td>
<td>Unknown</td>
<td>Worsening abdominal pain despite anticoagulation</td>
<td>7 days</td>
<td>1 day</td>
</tr>
<tr>
<td>2</td>
<td>51/M</td>
<td>Heterozygote mutation Factor V</td>
<td>Persistent abdominal pain despite anticoagulation</td>
<td>4</td>
<td>3 days</td>
</tr>
<tr>
<td>3</td>
<td>49/M</td>
<td>ITP, liver cirrhosis</td>
<td>Persistent abdominal pain despite anticoagulation</td>
<td>14 days</td>
<td>1 day</td>
</tr>
<tr>
<td>4</td>
<td>48/M</td>
<td>Unknown</td>
<td>Persistent abdominal pain despite anticoagulation</td>
<td>11 days</td>
<td>2 days</td>
</tr>
<tr>
<td>5</td>
<td>58/M</td>
<td>Cirrhosis, previous liver transplantation</td>
<td>Persistent abdominal pain despite anticoagulation + kidney failure</td>
<td>4 days</td>
<td>2 days</td>
</tr>
<tr>
<td>6</td>
<td>39/M</td>
<td>AT III deficiency</td>
<td>Worsening abdominal pain despite surgical thrombectomy and resection of necrotic bowel</td>
<td>14 days</td>
<td>4 days</td>
</tr>
</tbody>
</table>

Pt no= patient number, M=male, ITP=Idiopathic thrombocytopenic purpura, AT III deficiency=Antithrombin III deficiency,

Paper IV

All patients with variceal bleeding treated with TIPS January 2002-May 2016 were reviewed retrospectively using the local PHT database. One patient was lost in follow-up, the remaining 131 patients were included. 116 patients had liver cirrhosis. In patients with cirrhosis, the degree of liver disease was assessed according to CP score (20) and MELD score (89). End-points were re-bleeding, survival, TIPS dysfunction and adverse events. Re-bleeding was defined as hematemesis or melena together with transfusion of two or more units of blood. TIPS dysfunction was defined as stenosis or occlusion of the TIPS. HE was considered mild when it subdued with treatment of the percipient factor and/or with laxatives, and severe when recurrent or permanent (84). StatView 5.0.1 (SAS Institute, Cary, North Carolina) was used for statistical analyses. The significance level was set at 0.05 in all analyses.
Methods of interventional radiology

Portal venography

Access to a right sided portal venous branch was achieved by transcutaneous and transhepatic puncture with a 0.9 mm needle, guided by ultrasound. A GOLD® introducer set (Cook Medical, Bloomington, IN, USA) with a 0.46 mm (0.018 inch) guide wire and a 1.67 mm (5 French) catheter was placed in the PV or the SMV. Venography was performed with iodinated contrast media (240 mgI/ml).

Portal and mesenteric vein angioplasty (paper I)

A 0.89 mm (0.035 inch) guide wire was used to pass through PV and SMV thrombosis and concurrent stenosis. The affected parts of the PV and SMV were dilated with 8–10 mm balloons and, when needed, self-expanding bare metal stents (LUMINEXX® Bard Peripheral Vascular, Inc, TempeAZ, USA) were used to keep the lumen patent.

TIPS

A 0.46 mm guide wire was left in an intrahepatic portal venous branch to visualize the portal vein during the TIPS procedure. A TIPS set (Cook Medical, Bloomington, IN, USA) was used for the rest of the procedure. The 3.3 mm (10 French) sheath was inserted through the right jugular vein and positioned in the right atrium for pressure measurements, as the PSG was obtained by comparing the pressures of the right atrium and the portal vein. When possible, a liver vein was catheterized (possible in all patients except four with BCS) and the shunt was created by aiming the TIPS needle towards the guide wire in a portal branch. When no liver vein could be re-canalized, the shunt was created between the IVC and an intrahepatic portal branch. The parenchymal canal was dilated and PTFE-covered stents (GORE® VIATORR® Tips Endoprothesis Gore Medical, W. L. Gore & Associates, Inc, Flagstaff AZ, USA) were inserted to keep the shunt open. Stent diameter was 10 mm and stents were dilated to 8-10 mm. Blood flow through the shunt was confirmed using portal venography. The TIPS procedures were performed under general anaesthesia.

Liver vein dilatation and stent for BCS (paper II)

Liver vein venography was performed using a transjugular approach. When possible, a liver vein was re-canalized and dilated with balloons. If needed, stents were used to keep the lumen patent. Haemostasis of the jugular puncture site was obtained by manual compression.
Transhepatic thrombolysis in PVT (paper I)
In extensive acute PVT, an infusion catheter (Uni-fuse™, AngioDynamics, Latham NY, USA) was positioned through the thrombus, with the distal end in open lumen in the MPV or SMV. A bolus dose of 2-8 mg of Alteplase (Actilyse® Boehringer Ingelheim, Ingelheim am Rhein, Germany), was injected and followed by infusion with 1-2 mg per hour until the next venography. In addition to medical thrombolysis, over-the-wire mechanical thrombectomy catheters were used in two patients, Rotarex (Straub Medical, Wangs, Switzerland) in one and Aspirex (Straub Medical, Wangs, Switzerland) in one. Thrombolysis was discontinued when no further recanalization was achieved or if major complications with haemorrhaging occurred.

Transjugular thrombectomy in PMVT (paper III)
After creation of a TIPS, TT was performed. A pharmacomechanical thrombectomy system (AngioJetTM Boston Scientific Corporation, Quinzy, MA, USA) with active aspiration and pulse delivery of 5-22 mg Alteplase (Actilyse®) was used in four of the patients. Residual thrombotic material was removed with a rotational thrombectomy device system (Cleaner 15, Argon medical device, Plano, USA) in all patients. TT, with or without pulse delivered Alteplase, was performed until recanalization was achieved in the main venous branches. The MPV and SMV were dilated with 8-10 mm balloons to compress remaining thrombi and in one case a 10 mm bare metal stent (Protege™ EverFlex+™ Self-Expanding stent, Medtronics, Minneapolis, MN) was positioned in the SMV to maintain an open lumen.

Interventional procedures were repeated under local anaesthesia 0-2 times within 24-72 hours, to maximize the clearance of thrombotic material and blood flow through the MPV, SMV and TIPS. Between the procedures there was a continuous infusion of heparin in four patients. To facilitate the control venograms, a central venous catheter was left in the jugular vein in four patients.

Embolization of the cutaneous transhepatic canal
Embolization with NESTER® embolization coils (Cook Medical, Bloomington, IN, USA) ended the procedures. A single dose of antibiotic (cefotaxim) was administered intravenously before interventions.
Ethics

Informed consent was collected and the retrospective study of logs and charts was approved by the ethical committee on 7 November 2012 (Dnr2012/134) and 27 July 2016 (Dnr2016/288).
Results

Paper I

Eleven patients had liver cirrhosis; one of them also had a thrombogenic disorder. In the 10 non-cirrhotic patients, the underlying cause of the PVT was thrombogenic (n=7), post-inflammatory (n=1), post-surgical (n=1) or unknown (n=1). The use of systemic anticoagulation after diagnosis varied due to different symptoms, thrombophilic states and the referring hospital.

Four non-cirrhotic patients with extensive PVT and SMV involvement and symptoms of bowel ischemia were treated with continuous local thrombolysis, three transhepatic and one transjugular through a TIPS created in the same session. Interventions and outcome in these patients is presented in table 2. Partial recanalization was achieved but thrombolysis had to be discontinued prematurely in three patients due to severe haemorrhages that required blood transfusion; re-occlusion occurred early in all patients. Despite renewed thrombolysis combined with TIPS in two patients, the recanalization and TIPS remained patent in only one of the four patients. Apart from haemorrhages, complications were septicaemia in two patients and stenosis of the jejunum that required surgery in one patient. Three of the patients recovered and one patient died six weeks after intervention due to progressive liver failure.
Table 2. Venous involvement, interventions and outcome in the four non-cirrhotic patients with acute PMVT treated with continuous local thrombolysis.

<table>
<thead>
<tr>
<th>No</th>
<th>Venous involvement</th>
<th>Intervention</th>
<th>Recanalization</th>
<th>Complications</th>
<th>Re-intervention</th>
<th>TIPS and recanalization patency</th>
<th>Clinical status at endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PV, SMV, IMV</td>
<td>TIPS and continuous local thrombolysis for 42 hours</td>
<td>Partial in MPV, SMV and IMV, none in IHPV</td>
<td>Hemothoma, sepsis</td>
<td>None</td>
<td>Occlusion</td>
<td>Dead (6 weeks after intervention)</td>
</tr>
<tr>
<td>2</td>
<td>PV, SMV, SV</td>
<td>Transhepatic continuous local thrombolysis for 48 hours</td>
<td>Partial in MPV and SMV, complete in SV</td>
<td>Infection</td>
<td>TIPS and continuous thrombolysis for 72 hours, TIPS dilatation</td>
<td>Patent</td>
<td>No recurrent symptoms</td>
</tr>
<tr>
<td>3</td>
<td>PV, SMV, SV</td>
<td>Transhepatic continuous local thrombolysis for 96 hours</td>
<td>Partial in PV, SMV and SV</td>
<td>Hemothorax</td>
<td>None</td>
<td>Occlusion</td>
<td>No recurrent symptoms</td>
</tr>
<tr>
<td>4</td>
<td>PV, SMV, SV</td>
<td>Transhepatic continuous local thrombolysis for 48 hours</td>
<td>Partial in PV and SMV, none in SV</td>
<td>Hemothoma x 2</td>
<td>Coiling of hepatic artery x 2, TIPS and continuous thrombolysis for 72 hours</td>
<td>Occlusion</td>
<td>No recurrent symptoms</td>
</tr>
</tbody>
</table>

No=patient number, PV=portal vein, SMV=superior mesenteric vein, IMV= inferior mesenteric vein, TIPS=transjugular intrahepatic portosystemic shunt, IHPV=inhahepatic portal vein, SV=splenic vein
Fig. 5. Non-cirrhotic patient with Waldenström’s macroglobulinemia, chronic portal vein thrombosis and recurrent variceal bleeding. CT (a) showed cavernous transformation of the main portal vein (MPV) (white arrow) and classic signs of portal hypertension with large collateral veins (black arrow), ascites (white arrowheads), diffuse mesenteric stranding and splenomegaly (*). A portal venogram (b) confirmed the finding of a cavernous MPV (white arrow). Venogram (c) after partial recanalization and an established connection between liver vein and the portal vein showed reversed blood flow into large collaterals (black arrow). Venogram (d) after stent insertion showed good flow through the transjugular intrahepatic portosystemic shunt (blank arrow) and reduced flow into collateral veins (black arrow).
Six non-cirrhotic patients presented with acute/threatening variceal bleeding and chronic PVT (table 3). In three of them, the recanalization of the MPV and TIPS was successful and PSG was normalized after intervention. An example is demonstrated in Fig 5. The TIPS stayed patent in these three patients, although one of them had variceal re-bleeding and transient episodes of HE. In one of the six patients, complete recanalization of the MPV was achieved with PTA and a stent, but the PV re-occluded and blood flow could not be restored. Recanalization failed in the last two patients. All these six patients were free of symptoms at follow-up.

Table 3. Indication and outcome in six non-cirrhotic patients with chronic portal vein thrombosis

<table>
<thead>
<tr>
<th>No</th>
<th>Indication</th>
<th>Intervention</th>
<th>Complications</th>
<th>Reintervention</th>
<th>TIPS and recanalization</th>
<th>Re-bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Large varices, previous bleeding</td>
<td>TIPS</td>
<td>HE</td>
<td>TIPS dilation</td>
<td>Patent</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Acute variceal bleeding</td>
<td>Portal venography</td>
<td>No</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Large varices pre surgery</td>
<td>TIPS</td>
<td>No</td>
<td>Not applicable</td>
<td>Patent</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Large varices and previous bleeding</td>
<td>Portal venography</td>
<td>No</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Large varices, thrombocytopenia</td>
<td>Recanalization, portal PTA and stent</td>
<td>No</td>
<td>Recanalization</td>
<td>Occlusion</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Previous variceal bleeding</td>
<td>Recanalization, TIPS</td>
<td>No</td>
<td>No</td>
<td>Patent</td>
<td>No</td>
</tr>
</tbody>
</table>

No=patient number, TIPS=transjugular intrahepatic portosystemic shunt

The eleven cirrhotic patients presented with acute/threatening variceal bleeding (n=10) or refractory ascites (n=1). The clinical presentation, PVT extension, interventions and outcome are presented in table 4. Recanalization of the MPV and primarily successful TIPS were achieved in all. PSG was normalized post-intervention in the seven patients in whom the gradient was obtained. Three patients had variceal re-bleeding: one due to TIPS occlusion; one patient due to progressive liver failure; and one patient due to gastric antral vascular ectasia (GAVE). Five patients had re-interventions. In eight of the 11 patients, the TIPS was patent at the 12-month follow-up or until death. Two patients (with patent shunts) had a liver transplant. Three of the patients with a patent shunt died. The survival rate in patients with liver cirrhosis was 73% at 12 months and all five deaths during follow-up were due to progressive liver failure.
Table 4. Clinical presentation, interventions, and outcome in the 11 patients with liver cirrhosis. No = patient number, A = acute, C = chronic, SMV = Superior mesenteric vein, PV=portal vein, TIPS=transjugular intrahepatic porto-systemic shunt, HE=hepatic encephalopathy, GAVE=gastric antral vascular ectasia.

<table>
<thead>
<tr>
<th>No</th>
<th>Indication</th>
<th>SMV involvement</th>
<th>Intervention in addition to re-canalization of the MPV</th>
<th>Complications</th>
<th>Re-intervention</th>
<th>TIPS patency</th>
<th>Re-bleeding/death</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>A Large varices, thrombocytopenia</td>
<td>No</td>
<td>TIPS</td>
<td>Mild HE</td>
<td>No</td>
<td>Yes</td>
<td>No/No</td>
</tr>
<tr>
<td>12</td>
<td>A Acute variceal bleeding</td>
<td>No</td>
<td>TIPS</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No/No</td>
</tr>
<tr>
<td>13</td>
<td>C Acute variceal bleeding</td>
<td>No</td>
<td>TIPS</td>
<td>Occult hematoma</td>
<td>No</td>
<td>Yes</td>
<td>No/Yes</td>
</tr>
<tr>
<td>14</td>
<td>C Acute variceal bleeding</td>
<td>Yes</td>
<td>Portal PTA</td>
<td>No</td>
<td>TIPS</td>
<td>No</td>
<td>No/No</td>
</tr>
<tr>
<td>15</td>
<td>C Refractory ascites</td>
<td>Yes</td>
<td>TIPS</td>
<td>Sepsis, mild HE</td>
<td>No</td>
<td>No</td>
<td>No/Yes</td>
</tr>
<tr>
<td>16</td>
<td>C Acute variceal bleeding</td>
<td>No</td>
<td>TIPS, portal stent</td>
<td>Cutaneous infection, mild HE Mild HE</td>
<td>No</td>
<td>No</td>
<td>No/Yes</td>
</tr>
<tr>
<td>17</td>
<td>C Acute variceal bleeding</td>
<td>No</td>
<td>TIPS, portal stent</td>
<td>Liver capsule hematoma Pulmonary embolism</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes/yes</td>
</tr>
<tr>
<td>18</td>
<td>C Acute variceal bleeding</td>
<td>No</td>
<td>TIPS</td>
<td>Embolization of collaterals</td>
<td>Yes</td>
<td>No</td>
<td>Yes/No</td>
</tr>
<tr>
<td>19</td>
<td>C Acute variceal bleeding GAVE</td>
<td>Yes</td>
<td>TIPS, Portal stent</td>
<td>Recanalization, TIPS dilatation, embolization of collaterals</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes/No</td>
</tr>
<tr>
<td>20</td>
<td>C Acute variceal bleeding</td>
<td>No</td>
<td>Trans-splenic TIPS</td>
<td>No</td>
<td>Yes</td>
<td>Yes /No</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>C Large varices, previous liver transplant</td>
<td>No</td>
<td>TIPS, portal stent</td>
<td>No</td>
<td>Yes</td>
<td>No/No</td>
<td></td>
</tr>
</tbody>
</table>

33
Paper II
The time from symptom to diagnosis of BCS varied from one day to three months. The median time from diagnosis to intervention was one month, but varied from one day to 8½ years. Indications for the primary intervention were recurrent ascites with insufficient response to medical treatment with diuretic drugs and anticoagulation.

The five patients treated in 2003 to 2008 had a liver vein angioplasty as the primary intervention, and the nine patients treated in 2009 to 2015 had TIPS as the primary intervention. In total, 6/14 patients had some sort of re-intervention. The 1-, 3- and 5-year transplantation-free survival was 100%, 100% and 93%, respectively. One patient died due to liver failure, 12 years after the primary intervention and 8 months after TIPS. The median follow-up time from primary intervention was 4 years.

Overall results of TIPS
In total, 13 patients had TIPS, all with technical success. The primary TIPS patency rate was 85% at 1 year and 67% at 2 years. The rate of TIPS dysfunction was lower than expected, as the risk of TIPS failure according to BCS-TIPS PI was high (>7 points) in 12 patients and low (<7 points) in one patient.

All four patients with TIPS dysfunction had stenosis in the distal end of the stent and they all had stents that did not fully extend to the IVC. De novo episodes of HE occurred in three patients. Risk of death or OLT according to the Rotterdam score was intermediate or high in ten patients, but only one patient died and one patient had an OLT. The median follow-up time for TIPS procedures was 3 years. Results for each patient are presented in Table 5.

Results of primary TIPS
Nine patients had TIPS as the primary intervention. The only immediate complication was transient liver ischemia in one patient. Late complications were de novo episodes of HE in three patients and the recurrence of ascites in three patients, associated with TIPS occlusion in two. Primary patency rates at 3 months, 1 and 2 years were 100%, 83% and 67%, respectively. The 1-, 3- and 5-year transplantation-free survival rate was 100%.
Table 5. Results of transjugular intrahepatic portosystemic shunt (TIPS) in patients with Budd-Chiari syndrome.

<table>
<thead>
<tr>
<th>ID</th>
<th>Previous Angio-plasty</th>
<th>BCS-PI &gt;7</th>
<th>TIPS-dysfunction</th>
<th>Ascites</th>
<th>GI-bleeding</th>
<th>De novo HE</th>
<th>Follow-up/endpoint, in months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes x 2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>Yes x 7</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>Yes x 3</td>
<td>Yes x 3</td>
<td>Yes*</td>
<td>Yes*</td>
<td>No</td>
<td>No</td>
<td>8 Dead</td>
</tr>
<tr>
<td>4</td>
<td>Yes x 9</td>
<td>Yes x 1</td>
<td>Yes*</td>
<td>Yes*</td>
<td>No</td>
<td>No</td>
<td>45 OLT</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>55</td>
</tr>
<tr>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>Yes</td>
<td>Yes x 1</td>
<td>Yes*</td>
<td>No</td>
<td>No</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>47</td>
</tr>
<tr>
<td>9</td>
<td>No</td>
<td>Yes x 2</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>38</td>
</tr>
<tr>
<td>11</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>26</td>
</tr>
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<td>12</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>7</td>
</tr>
<tr>
<td>13</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>48</td>
</tr>
</tbody>
</table>

ID=patient study ID, BCS-PI=Budd-Chiari syndrome prognostic index, * at TIPS dysfunction, GI = gastro-intestinal, HE = hepatic encephalopathy, OLT = orthotopic liver transplant, ?=of unknown number.

Results of liver vein angioplasty/stent

Five patients had liver vein angioplasty/stenting as the primary intervention. Angioplasty was the only intervention in one of the patients, with no recurrent symptoms. In another patient, the liver vein re-occluded within one week of stent angioplasty and, after a TIPS procedure and three episodes of TIPS dysfunction, the patient eventually had an OLT. The third patient had had liver vein dilatation of an unknown number and surgical resection of thrombotic liver veins at another hospital nine years previously and was referred to our hospital with progressing liver failure. A TIPS procedure was performed and the patient has now remained asymptomatic for almost three years. The fourth and fifth patients were treated in the acute setting with angioplasty and stents. Both experienced repeated dysfunction and had multiple re-interventions before receiving TIPS several years after the primary intervention. One of them had occlusion of the TIPS and died six weeks later. This patient had severe liver disease with cirrhosis and HE prior to TIPS and was one of the two patients with a high risk of death according to the Rotterdam score.
Patients were treated with TT combined with TIPS as primary intervention (n=5) or secondary to surgical thrombectomy and bowel resection (n=1). TT was repeated 0-2 times within 3-14 days. Blood flow was restored in the MPV and the SMV in all six patients. Recanalization of the MPV and the SMV were complete in the patients who had TT and TIPS as the primary intervention, and it was partial in the patient who had had previous surgical treatment. An example is displayed in Fig. 6. Main procedure-related data and outcomes are presented in table 6.

In one patient with primary TT, extensive re-thrombosis and occlusion of the TIPS occurred within 36 hours. Only partial recanalization was achieved with repeated mechanical thrombolysis. Alteplase was thus infused through an indwelling catheter in the SMV and MPV. After 24 hours of Alteplase infusion recanalization was complete, and it persisted at second-look after 48 hours.

The patient who had had a surgical thrombectomy and bowel resection prior to TT and TIPS never recovered. Even though blood flow was restored after repeated TT, bowel necrosis extended. Further surgery and bowel resection were performed, but the patient died of multi-organ failure eight months after admittance.

Three of the four patients treated with Alteplase had transient episodes of haematuria between interventions. Four of the five patients with primary TT and TIPS improved promptly and could be discharged within two weeks of admission. The fifth patient suffered from persistent mild abdominal pain for two weeks and was hospitalized for seven weeks due to recurrent septicaemia originating in the urinary tract. To prevent re-thrombosis, all patients were prescribed systemic anticoagulation which was continued for at least six months.

Follow-up was 8-23 months. The two patients with liver cirrhosis had one episode each of transient HE, at 1 and at 4 months after the TIPS insertion respectively. HE was concurrent with obstipation in both patients and it was successfully treated with laxatives. None of the surviving patients experienced any PMVT relapse and all were free of symptoms.
**Fig. 6.** Coronal computed tomography image showing acute extensive portomesenteric vein thrombosis (PMVT) with bowel wall oedema in a 48-year-old man (A) and transhepatic portal venogram showing PMVT prior to (B) and restored blood flow after (C) mechanical transjugular thrombolysis in combination with the establishment of a transjugular portosystemic shunt in the same patient.
Table 6. Interventional details and outcome of transjugular thrombectomy (TT) through a transjugular intrahepatic portosystemic shunt (TIPS) created in the same session.

<table>
<thead>
<tr>
<th>No</th>
<th>Administration of Actilyse</th>
<th>No of re-interventions</th>
<th>Restored blood flow in the MPV and the SMV</th>
<th>Complications</th>
<th>In-hospital time</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>1</td>
<td>Yes</td>
<td>None</td>
<td>12 days</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>At primary, and at the two repeated, interventions</td>
<td>2</td>
<td>Yes</td>
<td>Transient hematuria</td>
<td>11 days</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>At primary intervention</td>
<td>1</td>
<td>Yes</td>
<td>Transient hematuria, transient encephalopathy</td>
<td>5 days</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>At primary intervention + delayed continuous infusion</td>
<td>2</td>
<td>Yes</td>
<td>Transient hematuria</td>
<td>10 days</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>At primary intervention</td>
<td>0</td>
<td>Yes</td>
<td>DVT, transient encephalopathy</td>
<td>7 weeks</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>2</td>
<td>Yes</td>
<td>Not related to TIPS or TT</td>
<td>8 months</td>
<td>Yes</td>
</tr>
</tbody>
</table>

No=patient number, MPV=main portal vein, SMV=superior mesenteric vein, DVT=deep venous thrombosis.
Paper IV

One hundred sixteen of the 131 patients had liver cirrhosis and the most common causes of cirrhosis were alcohol and viral disease. In patients with liver cirrhosis the majority had severe liver disease prior to treatment with TIPS, 90% were classified as CP B or C and the mean MELD score was 13 (range 5-30). The most common cause of PHT in the 15 non-cirrhotic patients were PVT, idiopathic liver trauma and inflammatory bowel disease.

The site of bleeding was oesophageal in close to 80% of the patients and gastric, stomal, rectal or caput medusa in the rest. All patients had pharmacologic and endoscopic treatment prior to TIPS and more than half of the patients had had repeated episodes of variceal bleeding. Covered stent grafts, 10 mm in diameter, were used in all patients. After TIPS the mean PSG dropped from 18 mmHg to 5 mmHg. The mean follow-up was 35 months (range 4-108 months).

Of the 131 patients, 58 were treated with TIPS after or during their first variceal bleeding, and 24 of them within 72 hours from bleeding onset. Fifty of the patients were treated within 72 hours from bleeding onset regardless of whether it was their first bleeding episode or not. There were no significant differences in 1-year, 2-year or overall mortality, or in the frequency of re-bleeding, between any of these subsamples. Neither was there a significant difference in patients with or without liver cirrhosis nor in a subsample of patients with Child-Pugh B and C treated with TIPS later than 72 hours after the variceal bleeding.

Overall survival in patients with liver cirrhosis was 92%, 70% and 57% at 6 weeks, 1 year and 2 years, respectively (Fig. 7) and 100% at 2 years in non-cirrhotic patients. None of the patients in CP class A, or non-cirrhotic patients, died of a liver-related cause while the majority of patients with more severe liver disease died of causes related to the liver disease.
In a simple unadjusted analysis, an increased overall mortality was associated with having a higher Child-Pugh score, a higher MELD score, with having liver cirrhosis and with the occurrence of severe HE within 12 months from TIPS. These associations remained for Child-Pugh, MELD, and HE when adjusted for age, but nor for liver cirrhosis. In a multiple regression analysis of these parameters, a higher Child-Pugh score and having severe HE within 12 months from TIPS were independently related to an increased mortality (Table 7). There was no difference in mortality in patients with a MELD score above 18 compared to in those with a MELD score below 18.

**Fig. 7.** Probability of survival in patients with liver cirrhosis, divided into Child-Pugh classes.
Table 7. Simple and multiple regression analysis of factors associated with overall mortality in patients treated with transjugular intrahepatic portosystemic shunt (TIPS).

<table>
<thead>
<tr>
<th></th>
<th>Alive (n=73)</th>
<th>Deceased (n=58)</th>
<th>p-value (simple analysis)</th>
<th>p-value (multiple analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (years)</td>
<td>53 ± 14</td>
<td>62 ± 8</td>
<td>0.0002</td>
<td>0.015</td>
</tr>
<tr>
<td>Child-Pugh, mean ± SD</td>
<td>8 ± 2</td>
<td>9 ± 2</td>
<td>0.0006</td>
<td>0.025</td>
</tr>
<tr>
<td>MELD score, mean ± SD</td>
<td>12 ± 5</td>
<td>14 ± 5</td>
<td>0.021</td>
<td>0.74</td>
</tr>
<tr>
<td>Confirmed liver cirrhosis, number (%)</td>
<td>60 (82)</td>
<td>56 (97)</td>
<td>0.01</td>
<td>-</td>
</tr>
<tr>
<td>Severe HE within 12 months from TIPS</td>
<td>2 (3)</td>
<td>10 (17)</td>
<td>0.004</td>
<td>0.02</td>
</tr>
</tbody>
</table>

MELD= model of end-stage liver disease. HE= hepatic encephalopathy

Re-bleeding occurred in five patients (4%) within 6 weeks and in 10 patients (8%) within 12 months after TIPS. Re-bleeding was associated with TIPS dysfunction and occurred less frequently in patients with a post-TIPS PSG below 5 mmHg than in patients with a post-TIPS PSG of 5 mmHg or above.

Overall, 13 patients had one or more episodes of TIPS dysfunction, the majority within 12 months (n=10). The TIPS could be restored at re-intervention in 11 of the 13 patients. When the TIPS procedure images were reviewed, the dysfunction appeared to be caused by the TIPS stent being too short, not fully reaching the vena cava, in 10 of the 13 patients.

Overall, 47 (40%) of the patients had HE within 12 months after TIPS, the majority had mild HE (79%). Severe HE after TIPS occurred more frequently in patients that had a history of HE prior to TIPS than in those without HE prior to TIPS. In four of the 10 patients with severe HE after TIPS the diameter of the shunt was reduced in an attempt to treat HE. Two of the four patients died within a month of the shunt diameter reduction (of progressive liver failure) and the other two had a liver transplant within 12 months. Severe HE after TIPS was associated with increased mortality. There were no correlations between the pre-TIPS MELD score, diameter of the TIPS, or the post TIPS PSG and the reduction of PSG, and severe HE within 12 months after TIPS. Apart from HE, eight patients (6%) had major procedure-related complications. These were septicemia (n=2), pneumonia (n=3), pulmonary embolism (n=1) and transient liver ischemia (n=2). None of these complications was fatal and all could be treated without sequel.
Discussion

Interventional radiology in portal vein thrombosis (PVT)

In patients with PVT endovascular intervention and TIPS may be effective in recanalization and the reduction of portal hypertension (50). The risk of complications with more aggressive techniques (such as continuous thrombolysis) must be balanced with the risk of the disease with its complications such as variceal bleeding, ascites, and intestinal ischemia. The different aetiology, onset and extension of the thrombi made the study population very heterogeneous, so to make the results a bit more comprehensible we chose to present them divided into sub-groups with somewhat more uniformity.

Chronic portal vein thrombosis

Patients with chronic PVT may present with abdominal pain, but the thrombosis may also be an incidental finding in patients with liver cirrhosis induced PHT (48,50,90). Patients with complications of PHT may benefit from a TIPS irrespective of the presence of specific thrombosis symptoms (91). Extensive thrombi is a negative predictor for complete recanalization and long-term prognosis (50), and due to the fibrotic transformation of vessels it is hard to completely differentiate vessels from thrombogenic tissue.

Due to post-thrombotic changes in the vessels, recanalization may be difficult, but when successful it may lead to clinical improvement (90). In paper I, the decompression of varices with the use of a TIPS was achieved with great technical success in patients with chronic PVT. This was in spite of including patients with acute variceal bleeding, for whom high procedure-related mortality has been reported (92). Of the 13 patients in whom a shunt was attempted, the procedure failed in only two, both non-cirrhotic patients with extensive chronic PVT. This supports earlier studies showing that TIPS can be a safe method for decompressing varices in both cirrhotic and non-cirrhotic patients with PVT (48–50). In the present study, the cirrhotic sub-group had a lower survival rate than patients without liver cirrhosis (73% vs 100% at 12 months). However, both overall survival and survival in patients with liver cirrhosis improved compared to a national multicentre study with less interventional
treatment (39). The results suggest that TIPS is a safe procedure and may prolong survival in patients with chronic PVT.

Acute portomesenteric venous thrombosis (PVMT)

In paper I, four non-cirrhotic patients with acute PVMT had signs of insipient bowel ischemia. Treatment with primary continuous local thrombolysis, in three of them in combination with TIPS, achieved only partial recanalization and re-occlusion soon followed. However, thrombolysis was discontinued prematurely in three of the patients, due to complications with haemorrhaging, which may have affected the degree of recanalization, as well as delaying post-interventional anticoagulation treatment. Whether the aggressive treatment had any impact on the disease’s progress remains unclear, but three patients recovered clinically and were alive more than six years after intervention. Even though symptom relief was achieved in the surviving patients with acute PMVT treated with primary continuous thrombolysis in paper I, the rate of complications was very high and one patient died. Another treatment regime was called for, but in the literature there was no perfect choice.

Continuous thrombolysis through the transhepatic and transcolic route may be associated with risk of bleeding (59,62). Treatment with indirect thrombolysis through the SMV has been successful in some studies (93–95), but recanalization may be limited because combined thrombectomy cannot be performed (59,62). Transjugular thrombectomy (TT) and continuous thrombolysis are effective for symptom relief, but may be associated with a high risk of bleeding and recanalization may only be partial (96–98). There are studies of TIPS combined with TT and primary continuous thrombolysis with few complications (57,61,99–102), but recanalization is not always achieved (57,100,101).

The best option seemed to be a combination of creating a TIPS and TT, which has been associated with effective symptom relief and low rates of complications, but not always complete recanalization. Very few cases are reported and the method varies slightly in the case reports (57,58,61,63).

The study of six patients with acute PMVT (paper IV) demonstrates that it is possible to effectively recanalize extensive PMVT with repeated TT through a TIPS. This method was effective for recanalization, symptom relief and survival in five patients with TIPS and TT as the primary intervention. In the sixth patient, TT was performed after surgical thrombectomy and bowel resection and although recanalization was achieved the disease’s progress could not be stopped and the patient eventually died of multi-organ failure. The results, with near complete recanalization and few complications in the majority
of patients, are in agreement with the previously reported cases using similar techniques (57,58,61,63).

Primary continuous thrombolysis was avoided because of the risk of haemorrhage previously experienced in similar patients who were treated with transhepatic and transjugular thrombolysis (35,59). In the present study, no procedure-related haemorrhage occurred. Therefore, the use of pulse-spray injections of Alteplase instead of continuous infusion during the primary procedure seems to be effective and have less risk of haemorrhaging. This might be because the half-life of Alteplase in plasma is short (4-5 min) and so it was already eliminated by the time the patients left the endovascular theatre.

In addition to less haemorrhaging, the time to symptom relief and in-hospital time in the five patients with TIPS and TT as the primary intervention was reduced compared to patients treated with the method described in paper I. This implies that repeated mechanical TT through the TIPS was a more effective way of recanalization than primary continuous thrombolysis. The long-term patency of TIPS, and absence of re-thrombosis, may be partly explained by the fact that an unconstrained outflow of blood is achieved through the TIPS, allowing thrombi to be eliminated more effectively. The TIPS also provides easy transjugular access to the portal vein, allowing repeated procedures without further trauma to the liver parenchyma. This reduces the need for general anaesthetics during repeated interventions. Adding systemic corticosteroids, in order to reduce the inflammatory reaction, (103) to the treatment regime could be discussed.

The patient who had TIPS and TT secondary to surgical thrombectomy and bowel resection presented with thrombus extension similar to that of the other patients. As in all other patients, the initial treatment was heparin. However, three weeks after admission he was diagnosed with antithrombin III insufficiency, and was thus resistant to heparin. The inadequate anticoagulation and prolonged time to effective treatment may partly explain treatment failure in this patient. Although there are case reports of successful transjugular mesenteric vein recanalization secondary to resection of necrotic intestines and surgical thrombectomy (100), the patient in the present study may have benefitted from having an earlier TT through a TIPS before surgery was attempted.

A potential risk with TT through a TIPS is embolization to the pulmonary arteries. However, there were no clinical signs of pulmonary embolism in any of the patients treated with this method.
To the best of our knowledge, the regime used in paper III of creating a TIPS, performing repeated TT through a maintained transjugular access with constant heparin infusion between the TT sessions to treat acute PMVT has not been described before.

**Budd-Chiari Syndrome**

BCS is a rare but serious condition with poor prognosis if not treated (67). The present study reports 14 patients with BCS treated with interventional radiology. The overall 1- and 5-year transplantation-free survival was 100% and 93%, respectively.

In the primary TIPS group, both the 1- and 5-year transplantation-free survival was 100%. In a previous national study in which patients were mainly treated medically, the 1- and 5-year transplantation-free survival rates were 47% and 28%, respectively (65). The dramatic improvement in transplantation-free survival in the present study clearly demonstrates the value of combining medical treatment with endovascular intervention.

The outcome after TIPS in patients with BCS may be estimated using the BCS-TIPS PI score (69) and the Rotterdam score (88). In the present study, 11 and 12 (of the 13 patients treated with TIPS) had an intermediate to high risk of death or OLT according to the Rotterdam score and BCS-TIPS PI score respectively. However, very high survival rates were achieved. Although the only patient who died in our study had a high BCS-TIPS score, all of the other 11 patients with high scores survived. Whether these prognostic indexes should be used to estimate the value of treatment with TIPS or not needs further evaluation.

Although the study population was very limited, the results indicate better patency and less mortality with a primary TIPS procedure than with primary angioplasty. Survival rates were higher than the 78-87% shown in larger similar studies (69–71). Post-TIPS occurrence of HE was as expected (69,104). The results of better efficiency with primary TIPS than with liver vein angioplasty, and much lower mortality than with only medical treatment, support the recent suggestions of early TIPS in symptomatic BCS patients (72). There may be reasons to reconsider the present recommendations (7) for a step-wise approach in the treatment of patients with BCS.
TIPS in variceal bleeding

Variceal bleeding is a serious condition with poor outcome and high mortality (7). TIPS has proven to be an efficient complementary treatment with less re-bleeding than endoscopic and pharmacological methods (52,105,106). Overall survival rates of 70% and 57% at 1 and 2 years respectively in patients with liver cirrhosis and 100% at 2 years in patients without cirrhosis in the present study, are comparable with other cohorts treated with TIPS (52,105,107–109). As expected, the Child-Pugh score was correlated to survival.

Early TIPS, within 72 hours of onset of primary oesophageal variceal bleeding, has been shown to improve survival and reduce the rate of re-bleeding in patients with a high risk of treatment failure (29,30). In the present study there was no difference in survival or re-bleeding between patients who were treated with early TIPS compared to those who were treated with TIPS later, nor after multiple bleeding episodes. These results suggest that receiving a TIPS at all may be of greater importance than receiving it within 72 hours or at the first bleeding episode.

A MELD score of 18 or above has been associated with higher mortality after TIPS than a lower MELD score (89,110–112). In the present study, the MELD score did not correlate with mortality in the multivariate analyse. In addition, the outcome in the surviving patients with a MELD score of 18 or above was good, none had re-bleeding or TIPS dysfunction (mean follow-up 12 months). This implies that some patients with a high MELD score may benefit from treatment with TIPS.

A pressure gradient of 12 mmHg after TIPS is often recommended to avoid HE (113,114). However, as variceal bleeding occurs at pressure gradients above 12 mmHg (8) the interval of the optimal pressure gradient is very limited. In the present study of TIPS in 131 patients with variceal bleeding, the mean post TIPS PSG was lower than what is usually recommended. On the other hand, the rate of re-bleeding (8% at 12 months) was lower than what could have been expected with conventional treatment (52,105) and the occurrence of HE after TIPS was not associated with the PSG. Re-bleeding was associated with TIPS dysfunction which is discussed below.

With the aim to further reduce re-bleeding TIPS is sometimes combined with embolization of varices (107,115). There are studies reporting less re-bleeding with the combination of TIPS and variceal embolization compared to TIPS alone (116) but other studies report no difference in re-bleeding rates (117). In the present study of variceal bleeding (paper IV) embolization of collaterals
was performed in only one patient, this patient was one of the few that experienced re-bleeding (when the TIPS occluded). Whether embolization of varices is effective or not remains uncertain.

In patients with gastric variceal bleeding a treatment option is balloon-occluded retrograde transvenous obliteration (BRTO) of the varices. There are reports of BRTO being as effective as TIPS in preventing re-bleeding, and with less occurrence of post procedural HE, in patients with isolated gastric variceal bleeding (118,119). However, when the gastric varices are occluded there is a potential risk of developing oesophageal variceal bleeding (120). To combine BRTO and TIPS in patients with gastric variceal bleeding may be more effective than embolization alone (121), or TIPS alone (122), but the combination may prolong the procedures and increase the risk of complications (123) without affecting survival (121).

TIPS dysfunction

In the early years of treatment with TIPS the rate of TIPS dysfunction was very high due to neointimal proliferation which reduced the diameter of the uncovered stents (108) but the occurrence of TIPS dysfunction dropped markedly with the introduction of covered stents (106,124,125). Dysfunction in TIPS with covered stents has been associated with severe inflammation in the liver tissue and a high MELD score (85) and stenosis in the distal (hepatic venous) end of the stent (126).

When the TIPS procedures of the presented studies were reviewed, the major causes of TIPS dysfunction were re-thrombosis in patients with PVT prior to TIPS, and stenosis of the distal end of the TIPS stent graft. In 18/19 patients with stent stenosis the stent appeared to be too short, not fully reaching the IVC. An example is provided in Fig.8. TIPS dysfunction due to stents not reaching the IVC has been reported by others (127). These observations suggest that the rate of TIPS dysfunction might be lowered if the TIPS stent definitely reaches all the way to the confluence of the hepatic veins and the IVC or into the IVC. As a consequence, as re-bleeding was associated with TIPS dysfunction (paper IV), the rate of re-bleeding might be further reduced.
Fig. 8. To the left: a transjugular intrahepatic portosystemic shunt (TIPS) at insertion. The fully expanded TIPS stent (black arrow) does not reach the confluence to the inferior vena cava (IVC) (thin white arrow). To the right: in-stent stenosis in the same patient in the distal end of the stent (thick white arrow).

Hepatic encephalopathy

Hepatic encephalopathy after TIPS is a dreaded complication as it is associated with higher risk of death (84), occurred at the expected rate in all four papers (50–52,91,107). The majority of patients had mild HE and could be treated easily, but severe HE after TIPS was associated with higher mortality in paper IV.

Treatment with TIPS is considered a risk factor for HE, but as HE can be induced by liver cirrhosis and portal hypertension per se (6,84), the TIPS cannot be the sole explanation. In a recent study of patients with refractory ascites, there was no difference in the occurrence of HE in patients treated with TIPS and patients treated with pharmacological and endoscopic methods (81). In one study of variceal bleeding there was an initial difference in the frequency of HE in patients treated with TIPS and patients treated with pharmacological and endoscopic methods, but this difference diminished after 12 months (107).

It has been suggested that a post-TIPS pressure gradient of 12 mmHg or lower is associated with HE (86,87,128). However, there was no correlation between the post-TIPS PSG, nor the diameter or length of the stent graft, and
HE in the largest study population in the presented papers (paper IV). Further studies are needed to determine the optimal post-TIPS pressure gradient.

As reported previously (87), patients with episodes of HE prior to TIPS were at higher risk of severe HE after TIPS. However, as in paper IV, not all patients with HE before TIPS had recurrent episodes after TIPS. In a life-threatening situation with extensive variceal bleeding or insipient bowel ischemia, treatment with TIPS may be worth a chance even in patients with a history of HE.

Importance and limitations of the portal pressure gradient

The portal pressure gradient is used to determine the degree of PHT and to estimate the risk of complications (7,8) and as such, is considered a key to treating patients with PHT. The gradient has, as discussed above, been associated with the development of HE after TIPS (86,87,128) and great care is taken not to reduce the gradient too much when creating a TIPS. However, in the present study of variceal bleeding (paper IV) a low post TIPS PSG seemed favourable in order to avoid re-bleeding while there were no correlation between the PSG and HE at all.

Several factors have been suggested to affect the gradient; it may differ depending on the measurement technique (10) and whether the measurement was obtained during general anaesthesia or sedation (13) (as described in the background section of the thesis). Recently, it has also been suggested that stent grafts used for the TIPS procedure may expand over time, possibly resulting in a reduction of the gradient (129,130). It remains uncertain whether these possible changes to the PSG are of any clinical importance. However, more uniformity in procedures when measuring the gradient may possibly facilitate the search for the optimal gradient for avoiding HE, as well as the recurrence of PHT related symptoms, after TIPS.

Limitations

The biggest limitation in all the studies is the retrospective format. The first three studies were also limited by the small number of patients. Since both BCS and PMVT are rare conditions, the number of patients that can be collected is limited, making it difficult to effectively study these conditions.
Future work

The major clinical concern with TIPS is the occurrence of post-intervention HE. A review of all patients treated with TIPS in the PHT registry, irrespective of clinical presentation, might reveal one or more common factors in patients that develop HE after TIPS. A prospective study of patients with refractory ascites considered for treatment with TIPS has also been initiated to try to identify risk factors for HE. The importance of the method used to obtain the gradient between the portal vein and the systemic venous pressure needs further evaluation.

Recently, Swedish centres that perform TIPS have started to register their patients in the PHT registry. This may improve national treatment uniformity and facilitate further studies of patients with rare conditions such as BCS and PMVT. Since the short-term results of the recently introduced treatment regime in acute PMVT were very promising, further patients may be treated with the same method and follow-up should continue.
Conclusions

Interventional radiology, mainly TIPS, seems to be safe and effective for the treatment of patients with complications of PHT, regardless of the underlying causes of disease and sites of venous blood flow obstruction. HE may occur more frequently after TIPS than medical and endoscopic treatment, but is often mild and easily treated. In selected patients with PHT, TIPS may improve survival.

Paper I
In patients with PVT and threatening symptoms of portal hypertension, endovascular recanalization and TIPS should be considered. TIPS can be accomplished in a safe and effective way to decompress portal hypertension, even in challenging cases with PVT, which reduces the risk of life-threatening complications like variceal bleeding and bowel ischemia.

Paper II
TIPS seems to be a safe and effective treatment for symptomatic BCS and there is an obvious improvement in transplantation-free survival compared to conservative medical treatment. It should therefore be considered early, as a first-line intervention, in patients with insufficient response to medical treatment.

Paper III
TT in combination with TIPS seems to be safe and effective for primary recanalization and symptom-relief in cirrhotic, as well as non-cirrhotic, patients with acute extensive PMVT and insufficient response to systemic anticoagulation therapy. The TIPS allows an effective outflow of blood and access for repeated procedures. This treatment strategy can reduce the complication rate and the in-hospital time compared to continuous transhepatic thrombolysis.

Paper IV
TIPS was safe and effectively prevented re-bleeding in patients with variceal bleeding, regardless of occurrence of liver cirrhosis; Child-Pugh class; of how
soon after bleeding onset the TIPS procedure was performed; and of the di-
ameter and the length of the TIPS stent A post-TIPS PSG below 5 mmHg was
associated with a decreased risk for re-bleeding and there was no correlation
between the post-TIPS PSG and the occurrence of HE. Effective treatment,
and reduced risk of stenosis, may be obtained by assuring that the TIPS stent
reaches the IVC and allowing a low PSG. This might invalidate the need for
collateral embolization.
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References


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)