Emergency TIPS ?

The role of transjugular intrahepatic portosystemic shunt (TIPS) in management of cirrhotic patients

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EF Clif
EUROPEAN FOUNDATION FOR THE STUDY OF CHRONIC LIVER FAILURE

Disclosures

- Speaker Fees
  - Gore Medical
  - MSD
  - Gilead
  - Bayer
  - Sequana Medical
  - Alexion
  - AOP Orphan Pharmaceuticals AG

Agenda

What patients benefit from TIPS?

Why to TIPS?

When to TIPS?

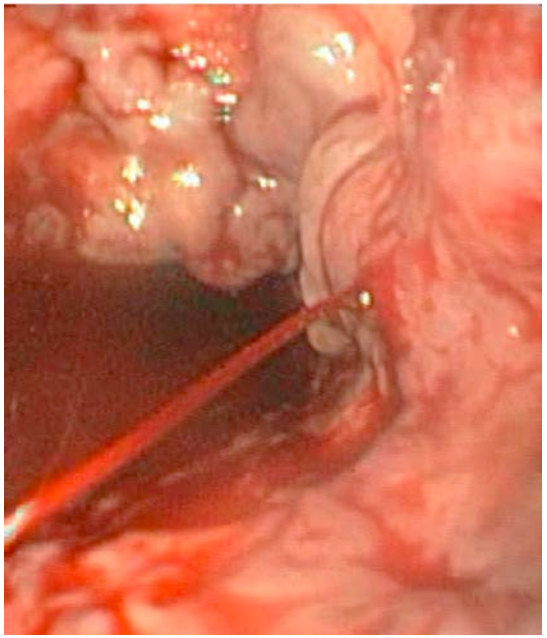
How to TIPS?

WHAT patients benefit from TIPS?

Complications of portal hypertension

Complications of portal hypertension

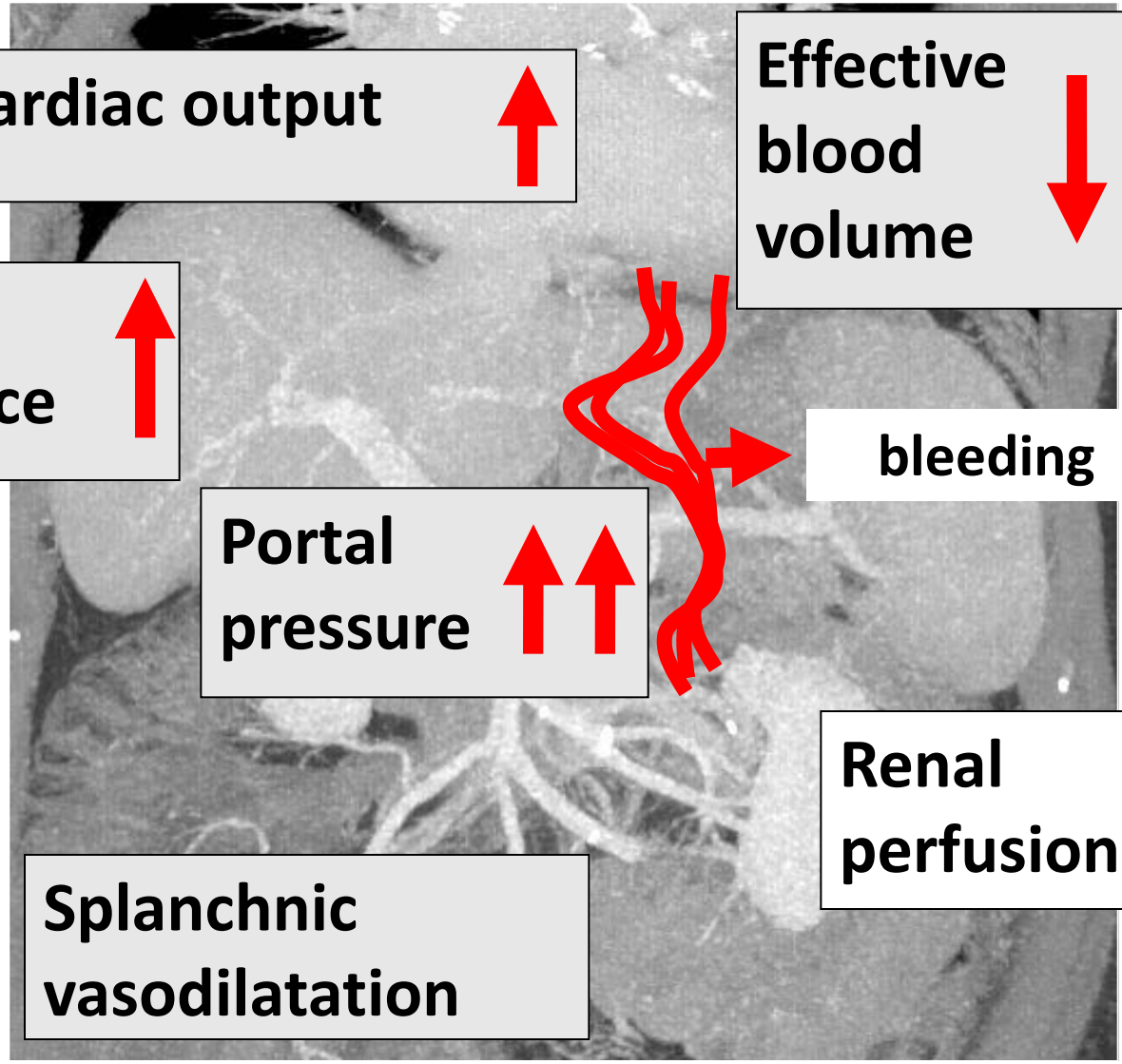
Gastrointestinal Bleeding



Renal dysfunction with ascites

WHY benefit patients from TIPS?

Pathophysiology of portal hypertension



Cardiac output ↑

Effective blood volume ↓

Hepatic resistance ↑

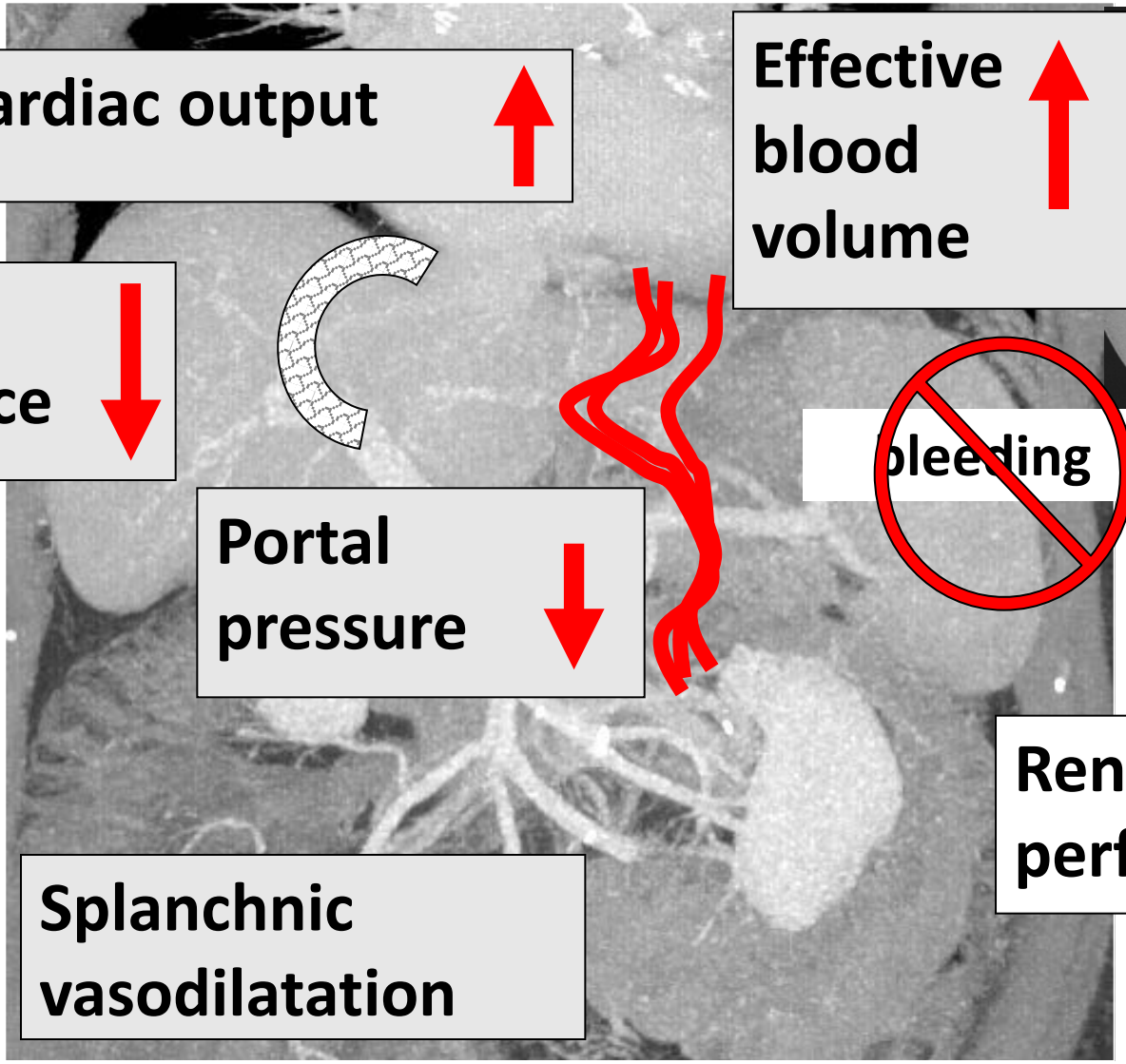
bleeding

Portal pressure ↑↑

Renal perfusion ↓ → Renal dysfunction

Splanchnic vasodilatation

TIPS for portal hypertension



Cardiac output ↑

Effective blood volume ↑

Hepatic resistance ↓

Portal pressure ↓

Bleeding

Renal perfusion ↑

Splanchnic vasodilatation

Renal dysfunction

WHEN benefit patients from TIPS?

Acute variceal bleeding

5% in 10 years in patients with cirrhosis

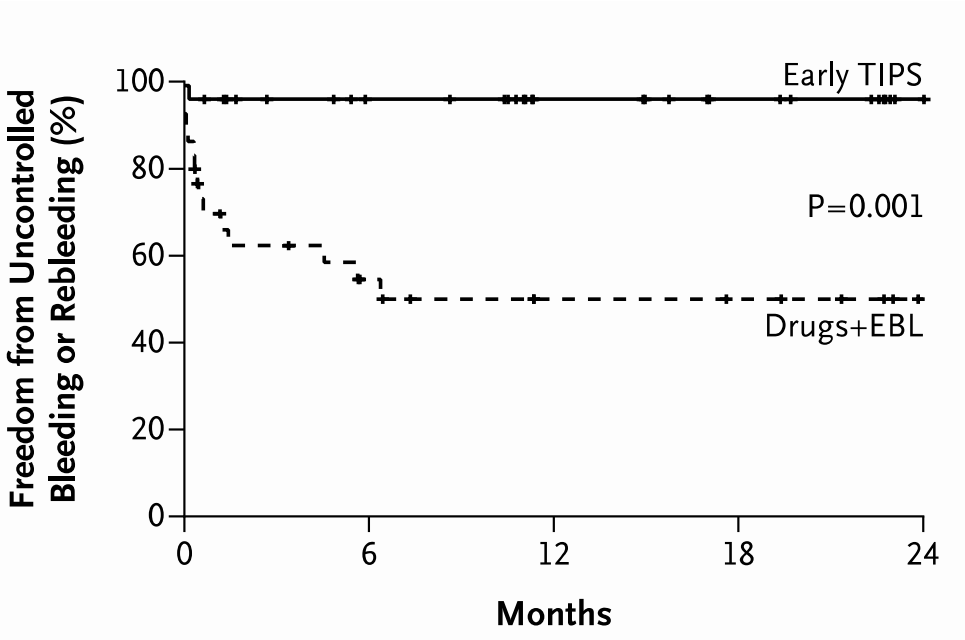
Ca. 10% in 2 years under primary prophylaxis

Sanyal et al. Ann Intern Med 1997;
Sauer et al Endoscopy 2002;
Vilanueva et al. NEJM 2001
De la Pena et al. Hepatology 2005
Benvegnu et al. Gut 2004
Shah et al. J Hepatol 2013

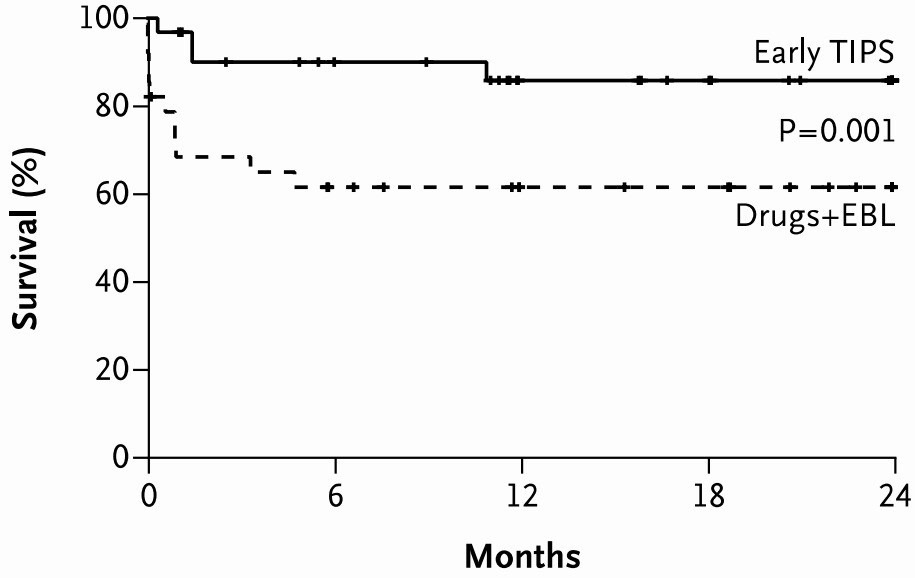
Early TIPS for variceal bleeding

Within 72 h in patients with Child C (<14) or Child B and active bleeding at endoscopy

Rebleeding



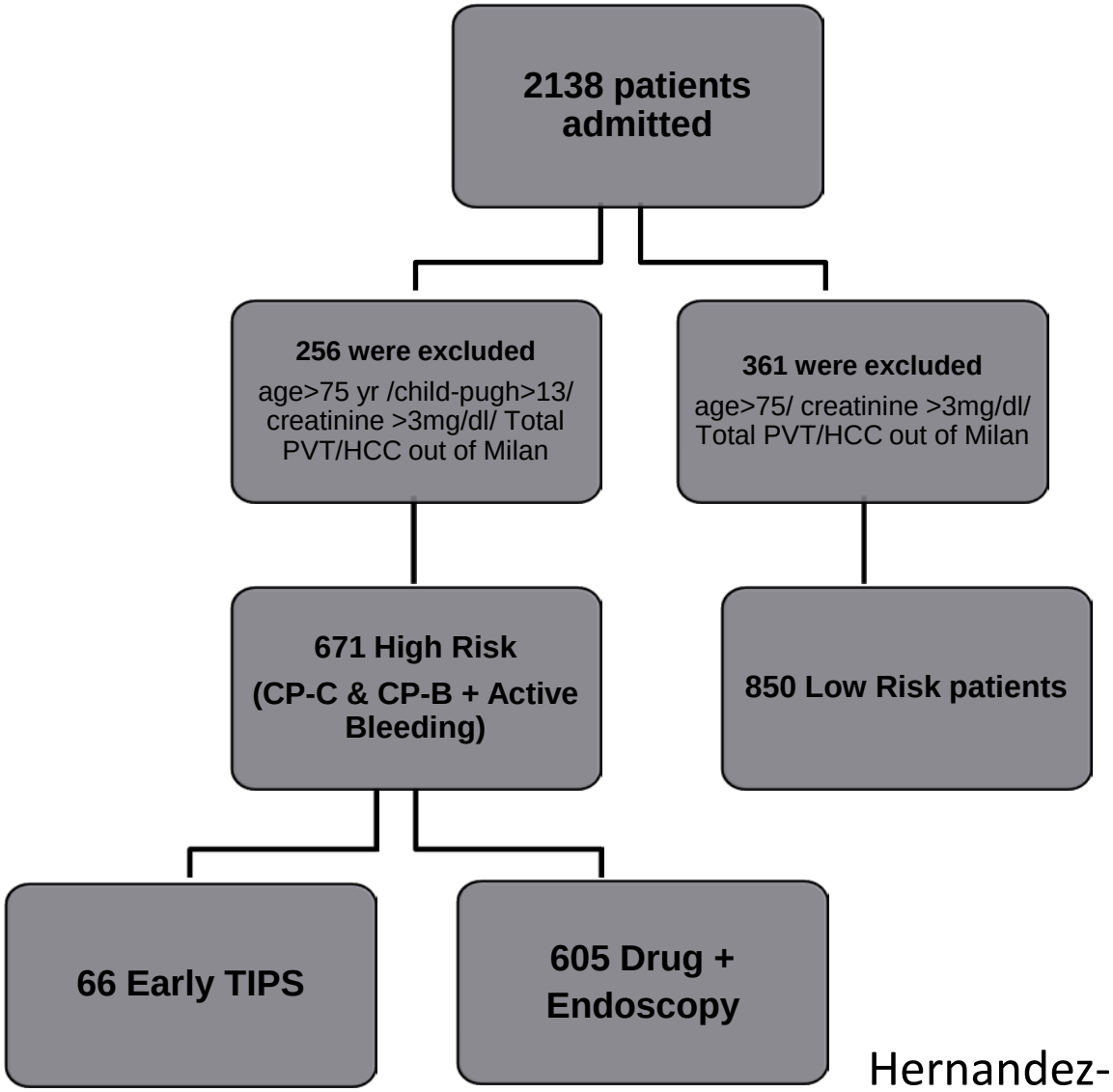
Survival



Garcia-Pagan et al. NEJM 2010
Garcia-Pagan et al. J Hepatol 2013

„Early TIPS“ in real life

International Variceal Bleeding Observational Study Group

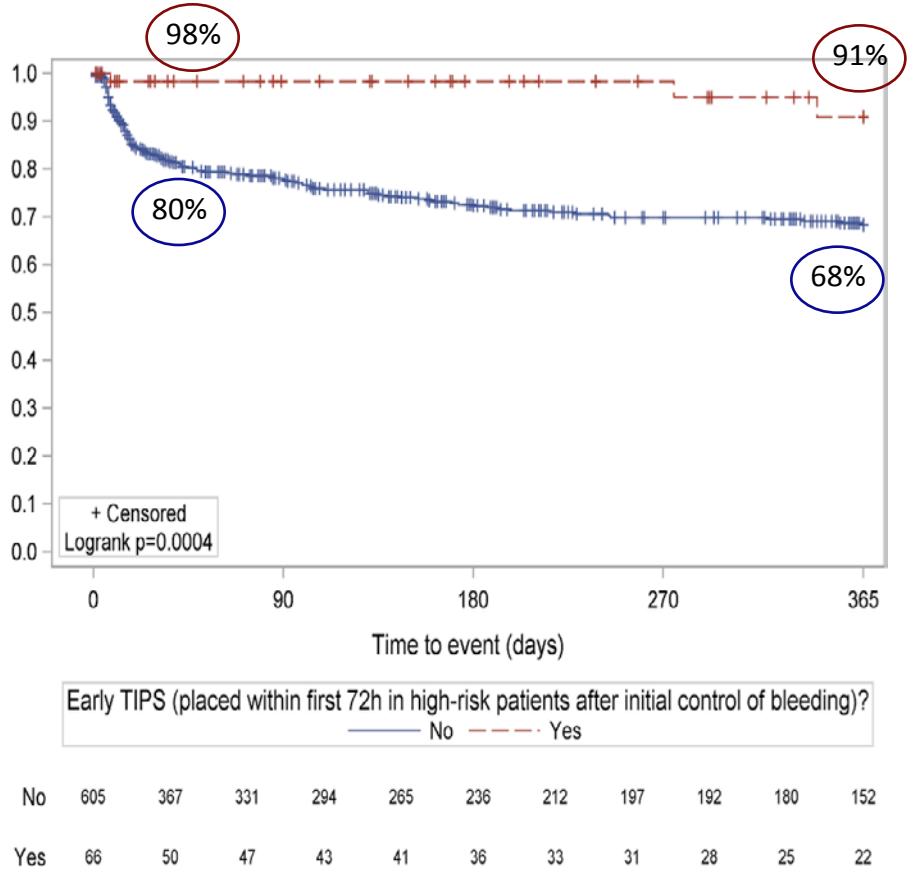


Hernandez-Gea et al. AASLD 2016

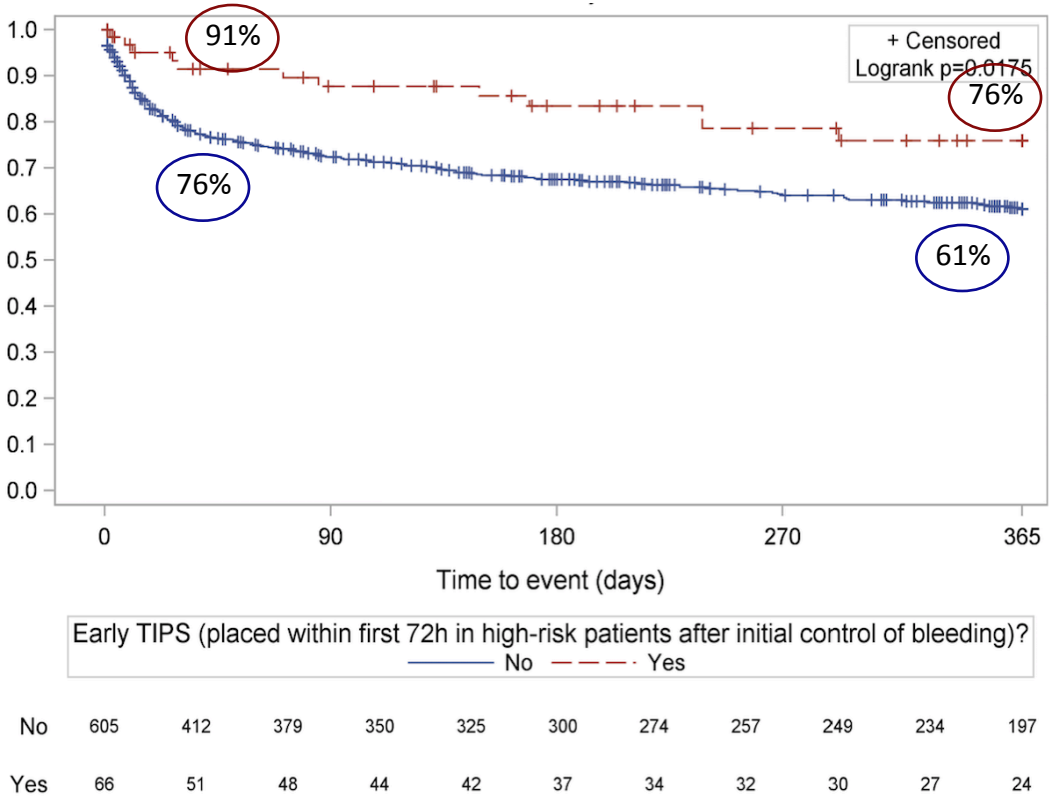
Early (preemptive) TIPS in real life

International Variceal Bleeding Observational Study Group

Failure & Rebleeding



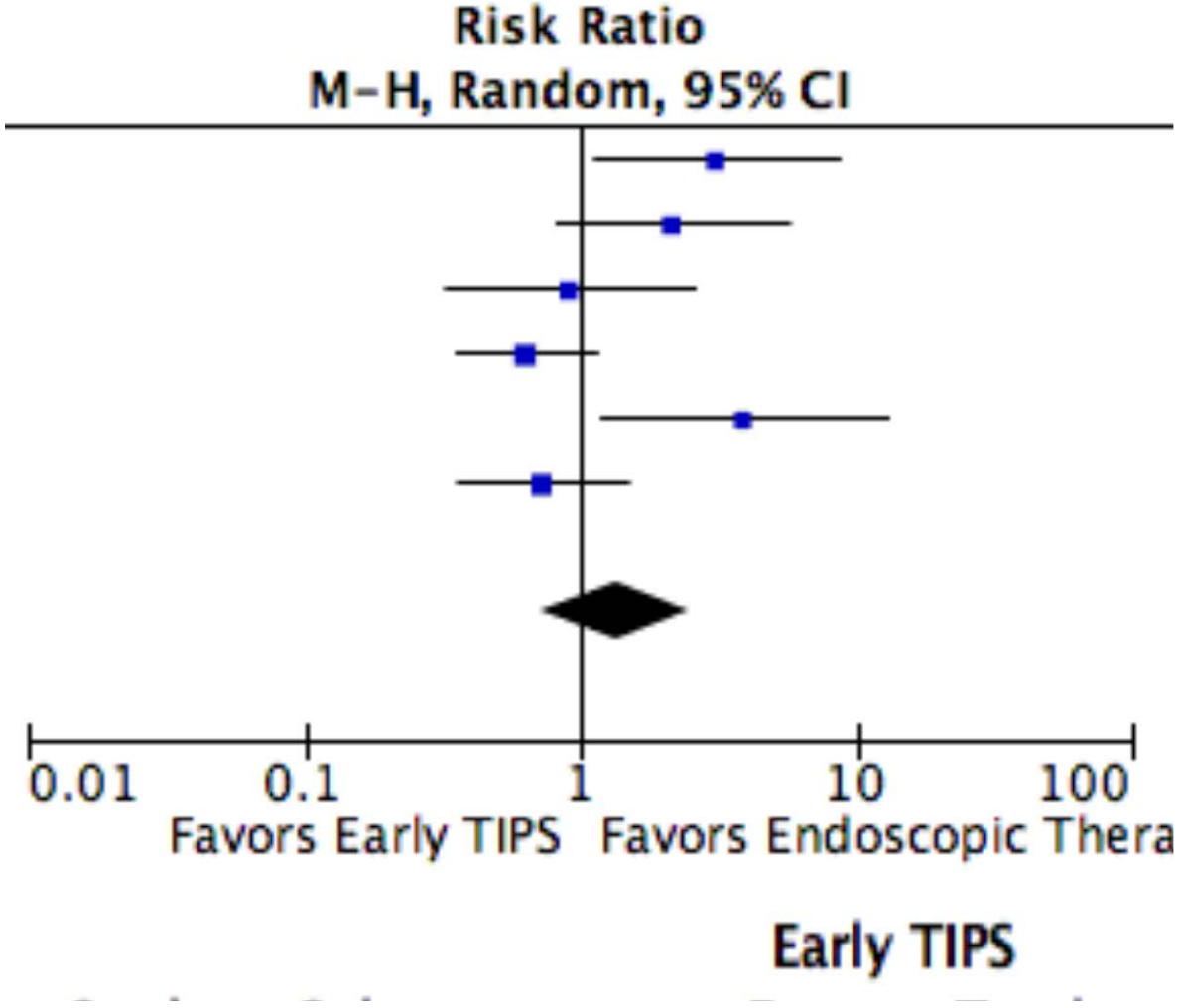
Transplant-free Survival



Hernandez-Gea et al. AASLD 2016

Early TIPS is not associated with more HE

Hepatic Encephalopathy



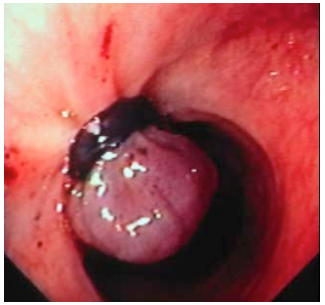
Halabi et al. J Gastroenterol Hepatol 2016

Rebleeding prophylaxis is mandatory

without therapy 60-70% rebleeding and 40% mortality

First line

Band ligation



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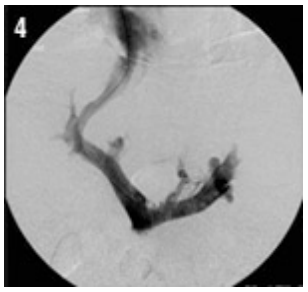
NSBB

40-50% rebleeding

20-35% mortality

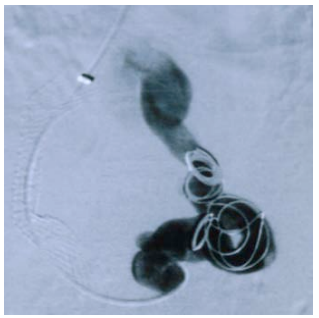
Second line

TIPS



+

evtl. embolisation



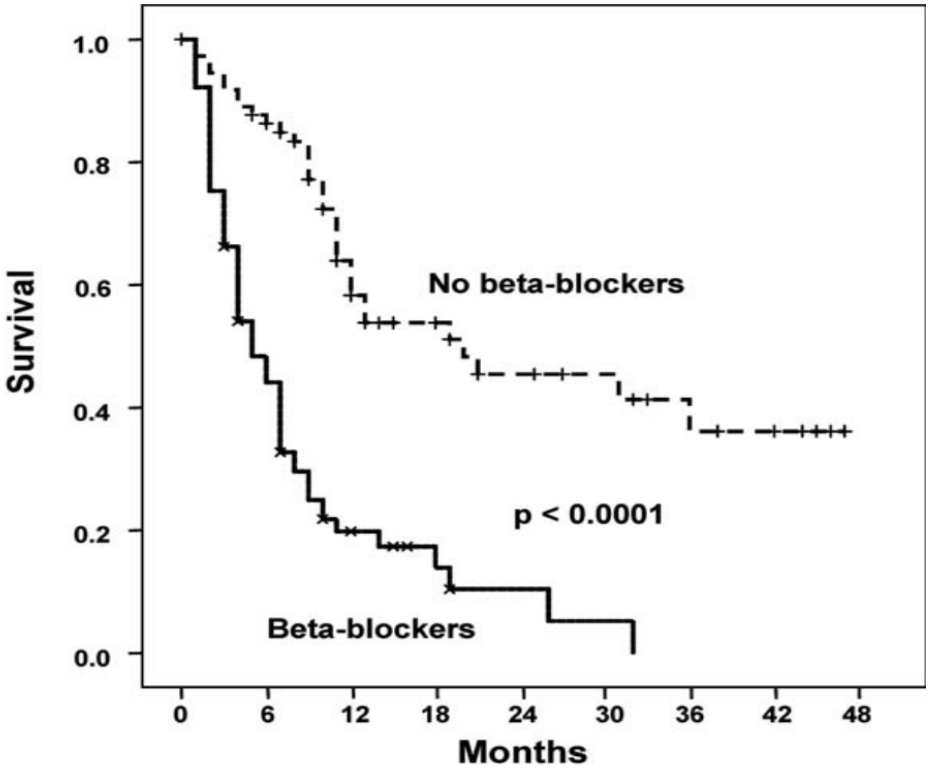
10-20% rebleeding

20-30% mortality

BUT,

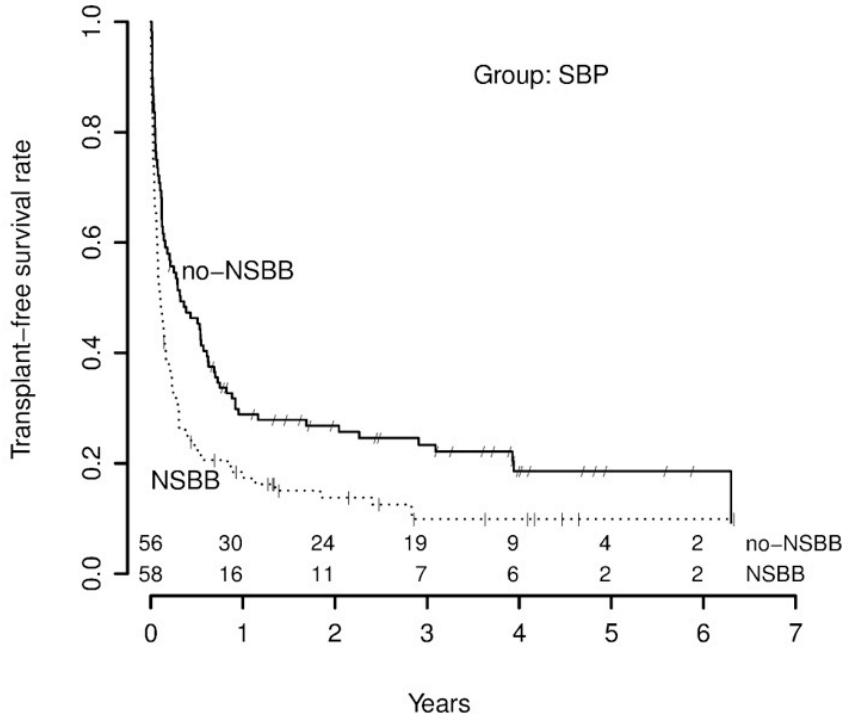
BAVENO VI. *J Hepatol* 2015

NSBB might be dangerous in ...



refractory ascites

Serste et al, Hepatology 2011



spontaneous bacterial peritonitis

Mandorfer et al, Gastroenterology 2014

NSBB in refractory ascites, when to TIPS?

Indication for NSBB

↓

Moderate Dose → *Liver vein catheterization (HVPG)*

↓

SBP

↓

Stop NSBB

Liver vein catheterization (HVPG) →

↓

Non-responder Bleeding

↓

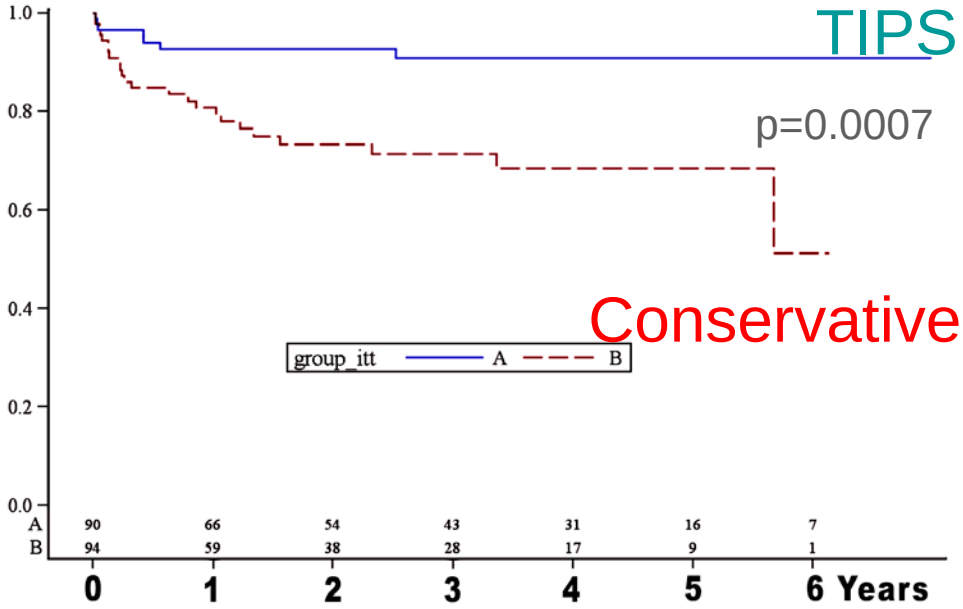
TIPS

Baveno VI J Hepatol 2015

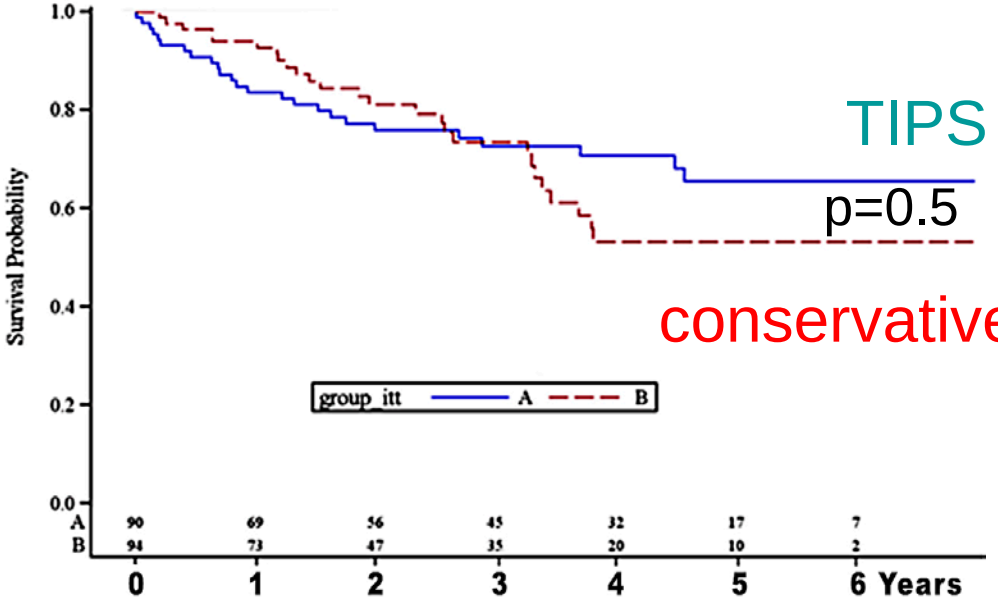
WHY not use TIPS as first line always after bleeding?

8mm TIPS vs. NSBB or EVL

rebleeding



survival



Conservative arm (NSBB or EVL):

- **more early rebleeding**
- **non-responder**

2-year survival: ca. 80 %
5-year survival: ca. 60 %

Hepatic encephalopathy:

- **TIPS: 18%** **vs.** **conservative: 8%**

Sauerbruch, et al. Gastroenterology 2015

10mm TIPS vs. NSBB + Endo

Early HE (one year)

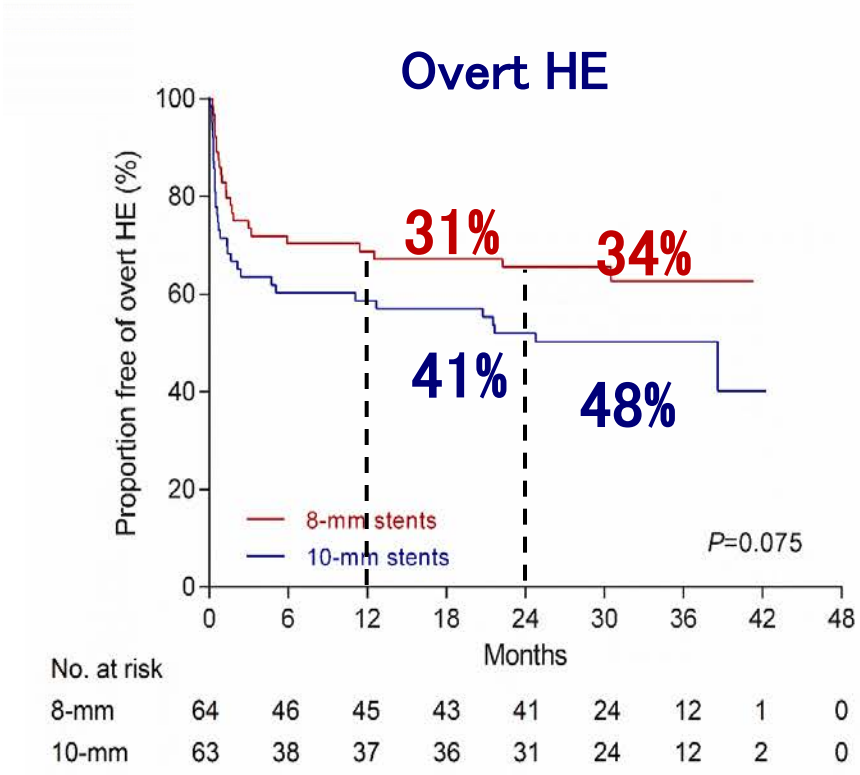
TIPS: 35%

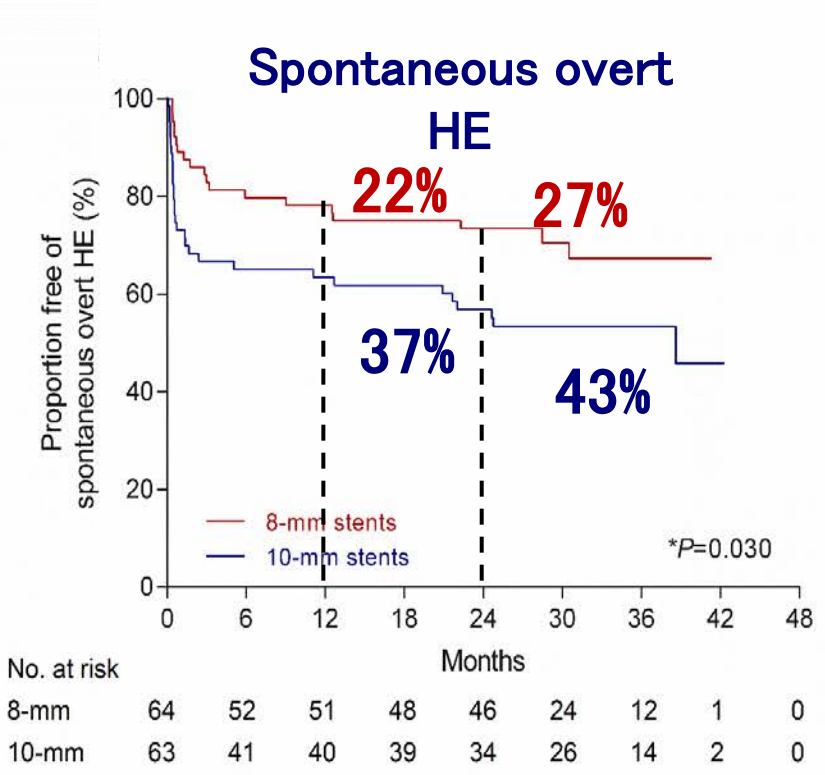
vs.

NSBB+EVL:14%;

Holster et al. Hepatology 2016

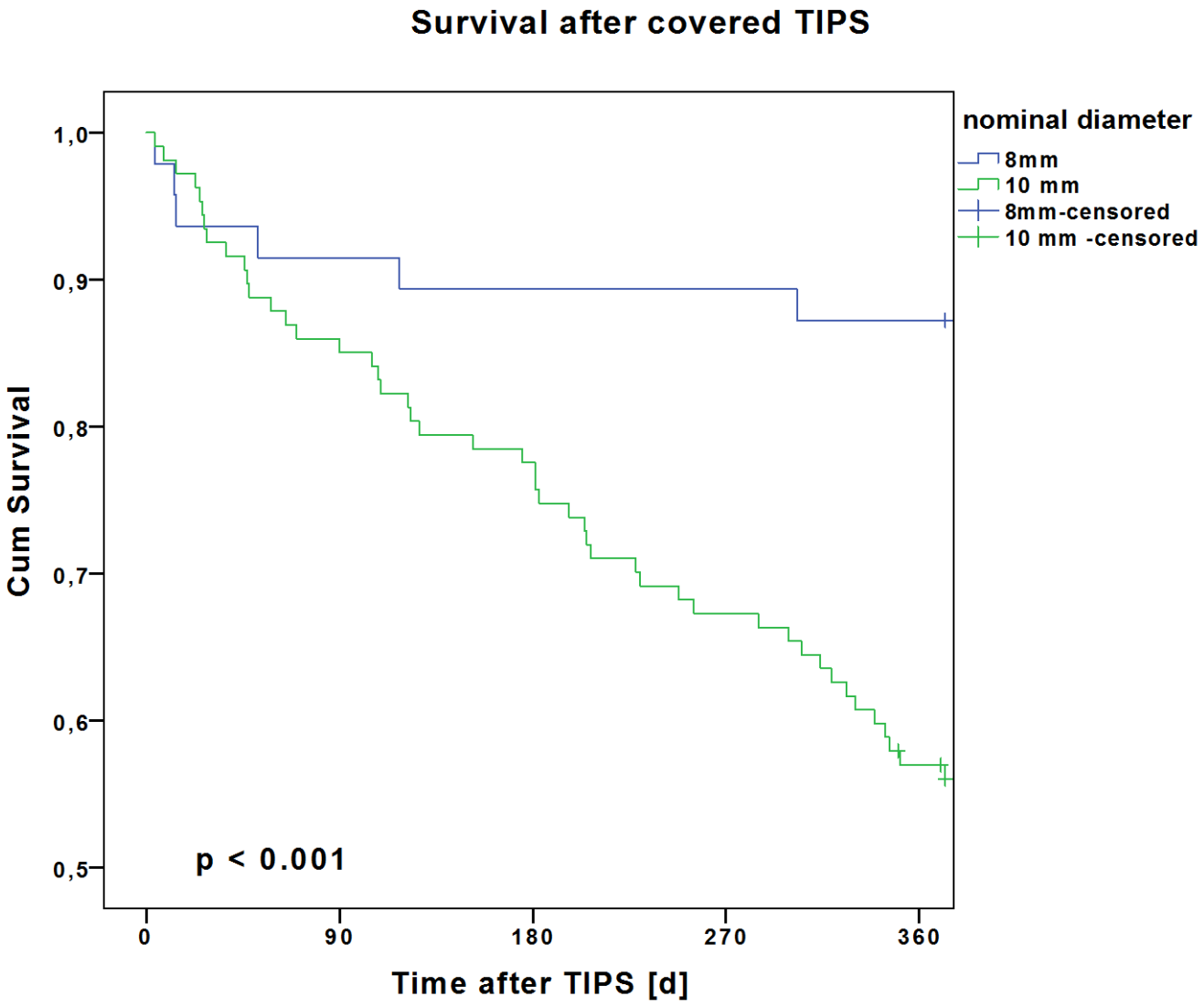
What TIPS? 8 mm vs 10mm





Wang et al. J Hepatology in press

What TIPS? 8 mm vs 10mm



Trebicka, Sauerbruch, Rössle. unpublished

TIPS for bleeding

Early TIPS improves survival of patients without increased rate of hepatic encephalopathy.

TIPS for secondary prophylaxis is very effective, and smaller TIPS might reduce hepatic encephalopathy.

Consider TIPS in secondary prophylaxis and refractory ascites, or after episodes of SBP.

Emergency TIPS in ascites?

Therapy of ascites

Max. 5g NaCl/d
Max. fluids 1,5l/d

Aldosteron antagonists
(e.g. Spironolacton)
max. 300mg/d

Loop diuretics
e.g. Furosemid
max. 160mg/d

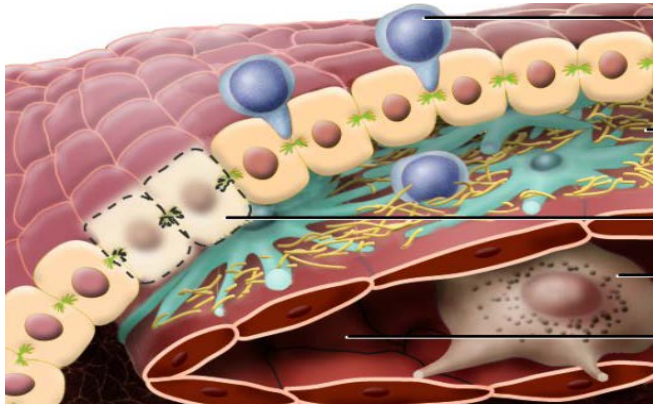
If urine-Na < 20mmol/d
or serum-Na < 125mmol/l
no effect of diuretics is expected!

Refractory ascites!
Then „emergency“ TIPS!

Why should we treat it without loosing time?

Gines & Guevara Hepatology 2008; Moore et al Hepatology 2003

Bacterial translocation increased in refractory ascites



cytokines

Riordan et al. Hepatology 2003
Kitamura et al. Lab invest 2002
Tarrats et al. Hepatology 2011
Wiest et al. JCI 1999

Systemic
Vasodilation

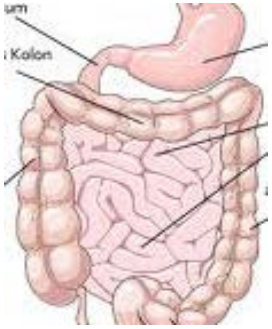
Apoptosis

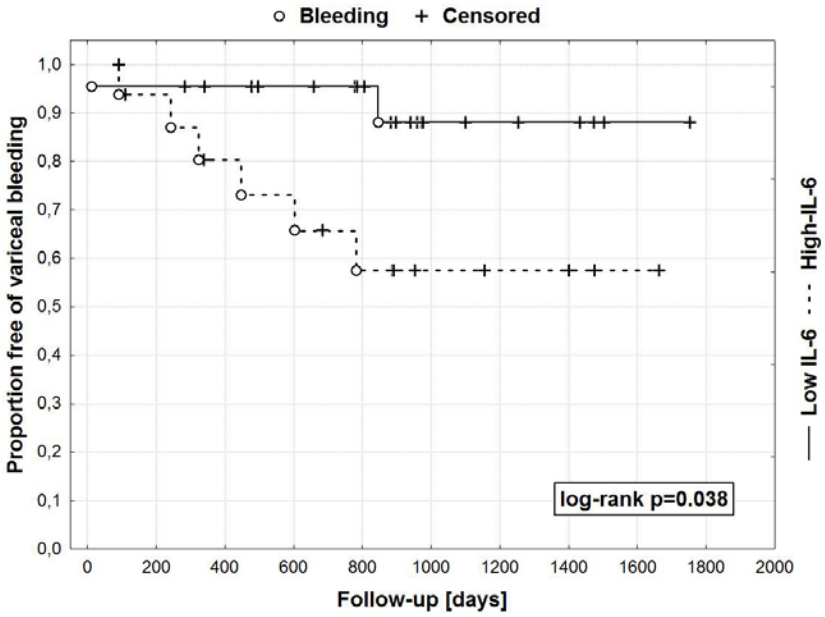
Inflammation

Fibrosis

Endotoxin

Bacterial translocation



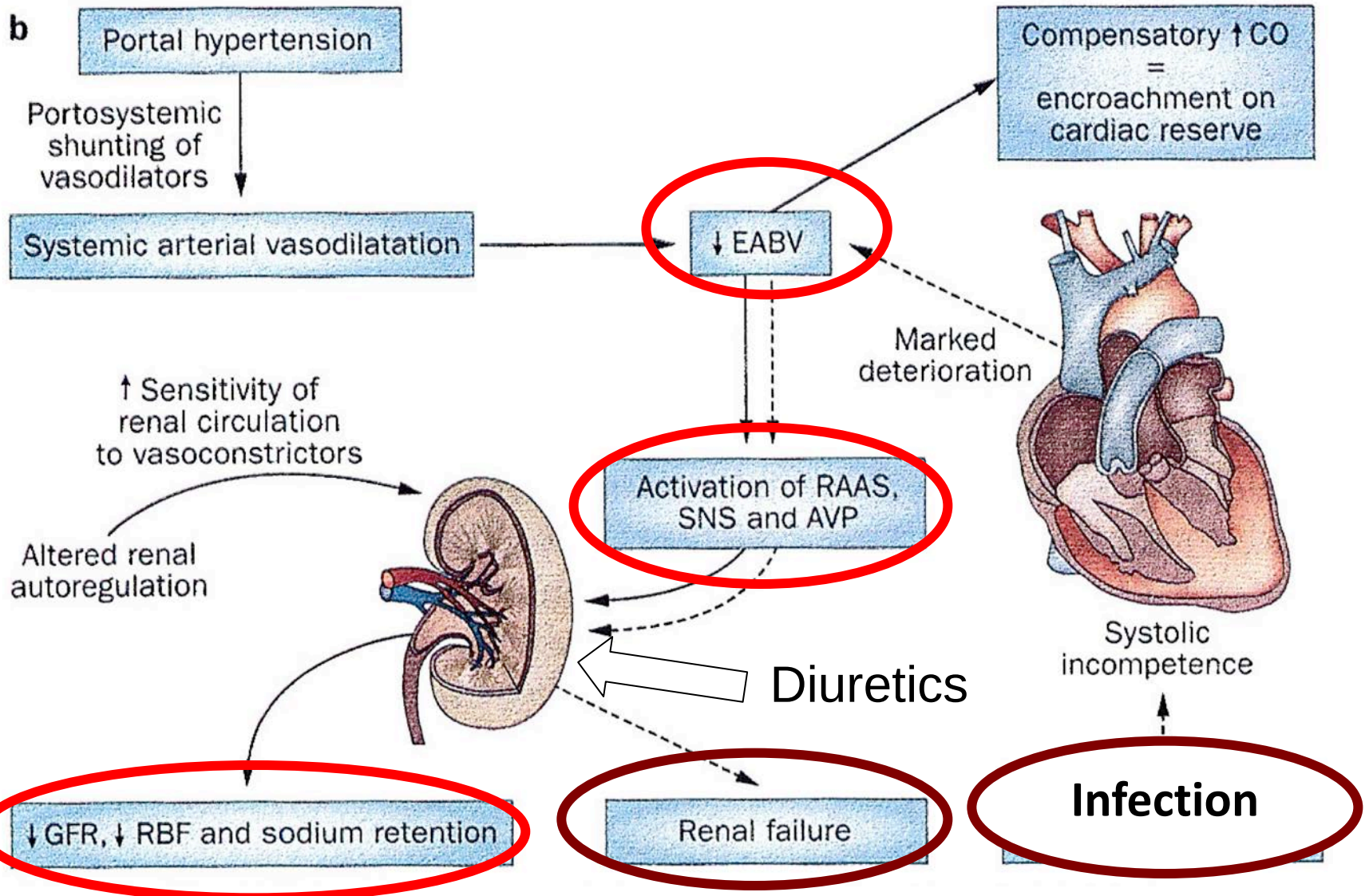


Reiberger et al. J Hepatol 2013

Trebicka et al. Eur J Gastro Hepatol 2011
Trebicka et al. PlosOne 2013

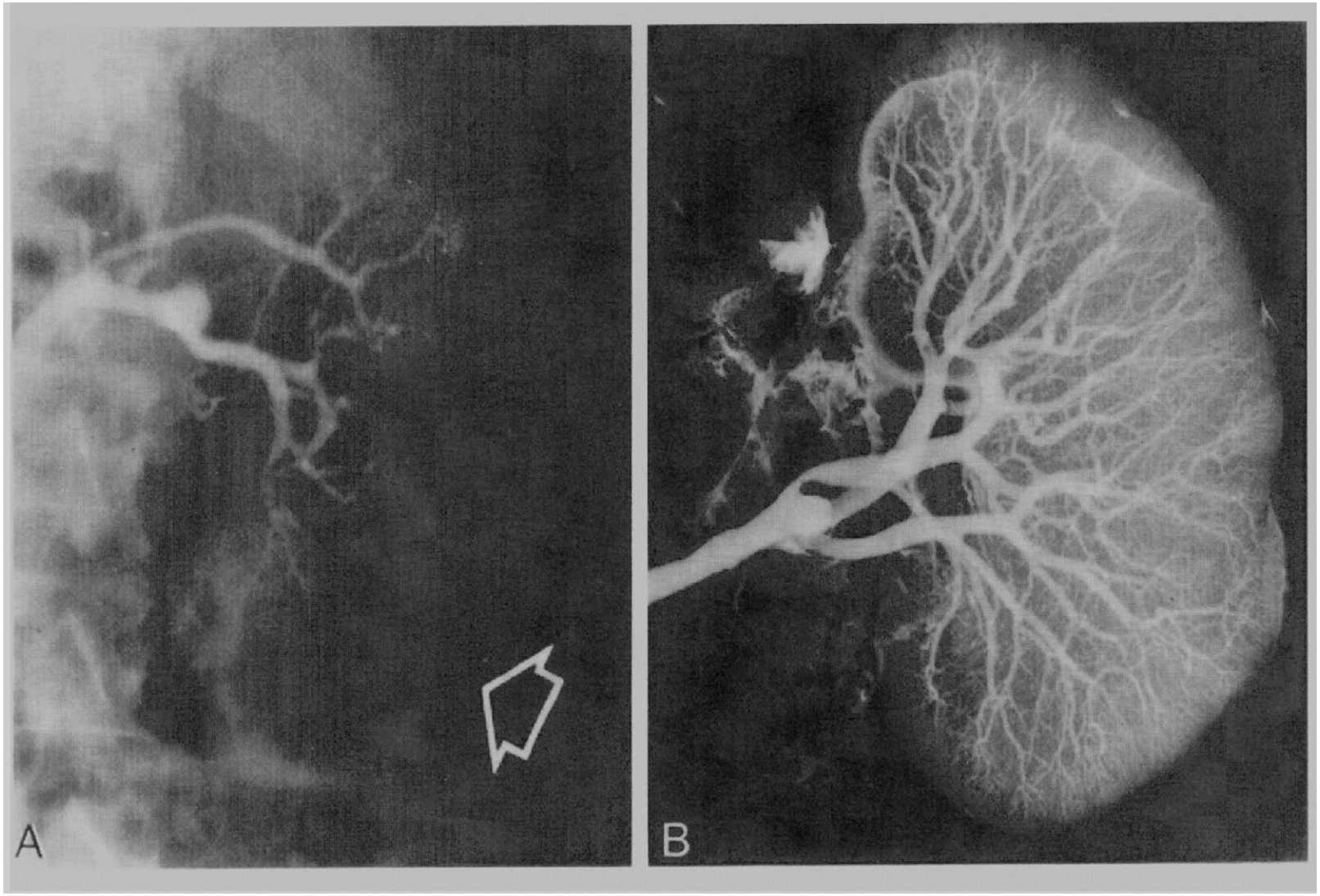
Berres, [...], Trebicka. J Hepatol 2015,
Berres, [...], Trebicka. Liver International 2016
Nielsen, [...], Trebicka. Dig Dis Sci 2015

Hepatorenal Syndrome (HRS)



Wong F, Nat Rev Gastroenterol Hepatol 2012

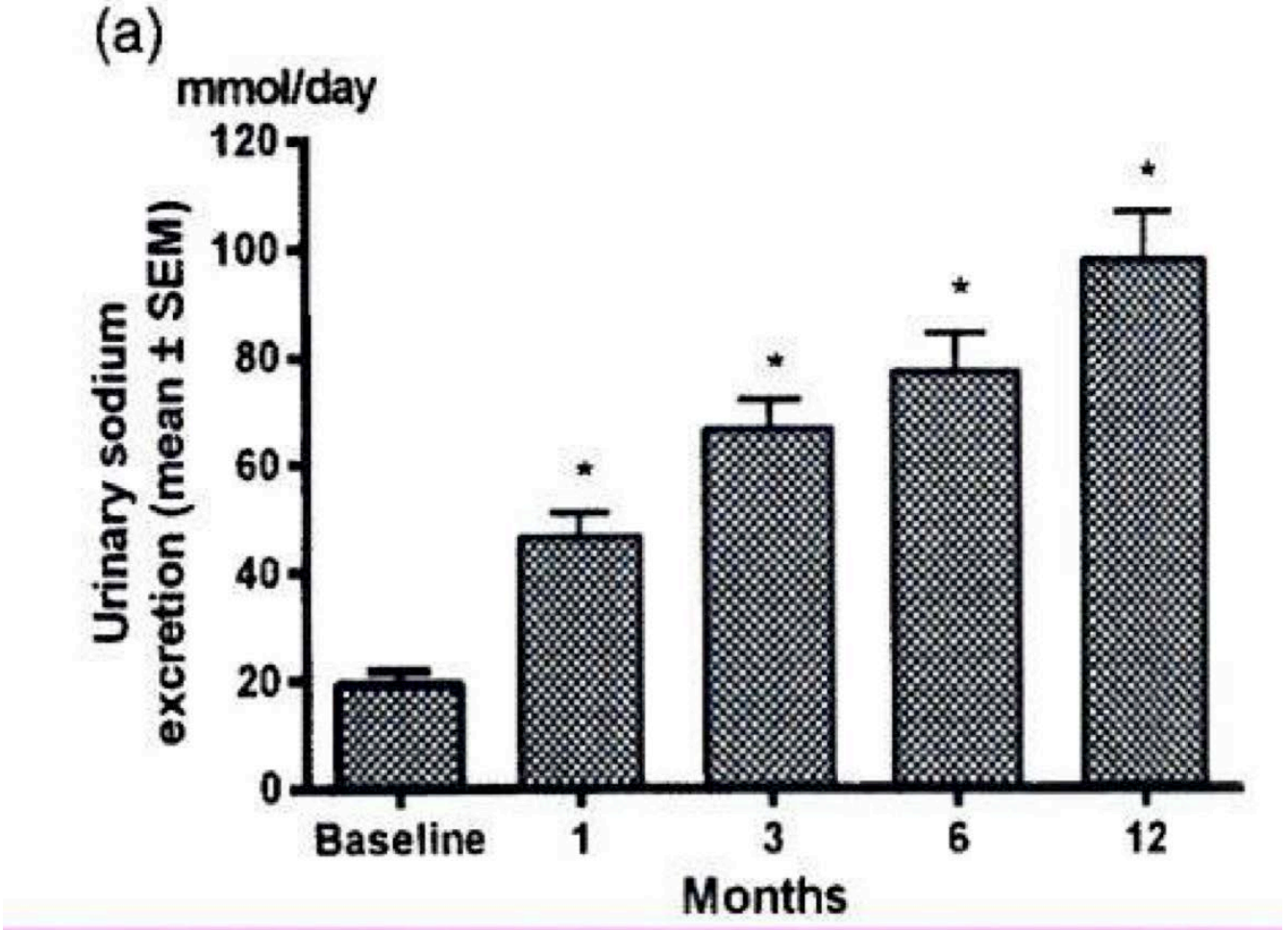
Hepatorenal Syndrome



Hepatorenal Syndrome **post mortem**

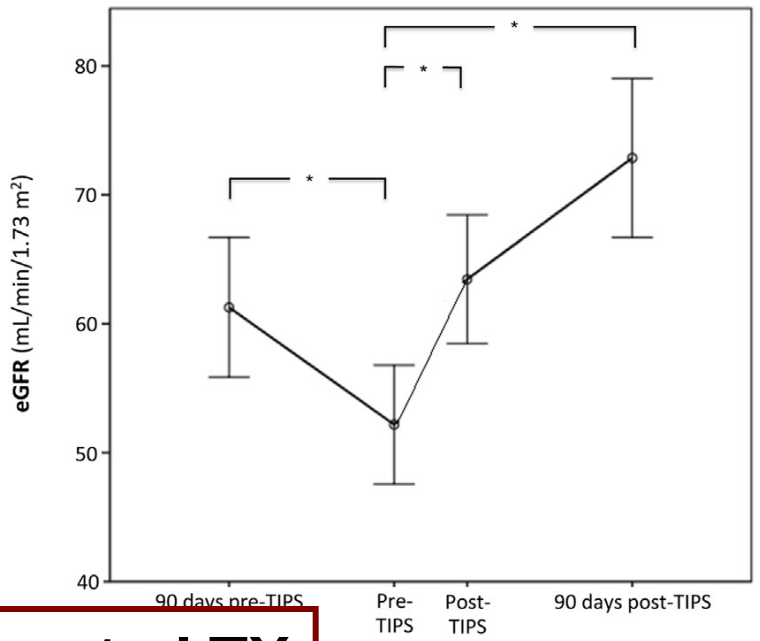
Refractory ascites

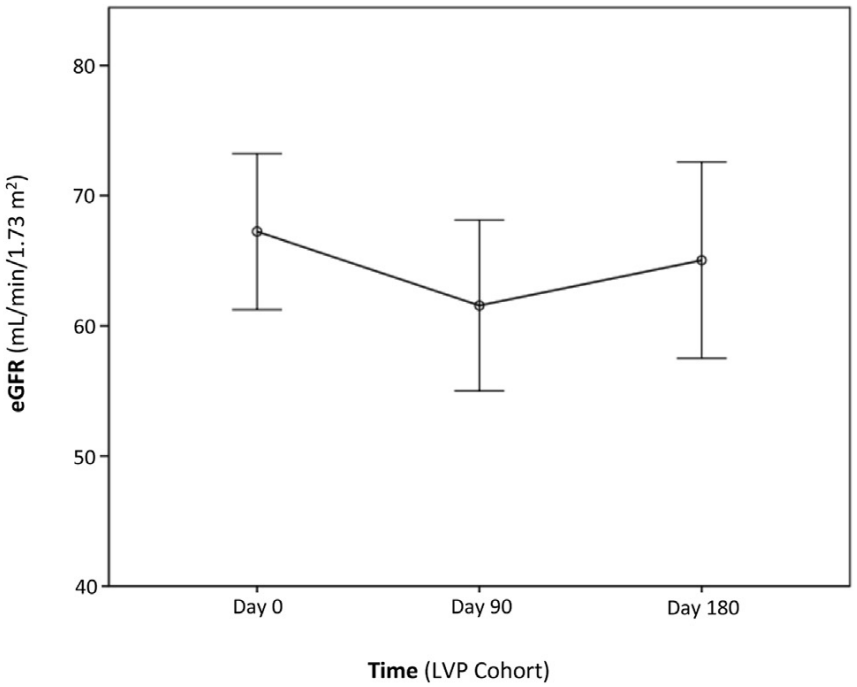
TIPS controlls ascites



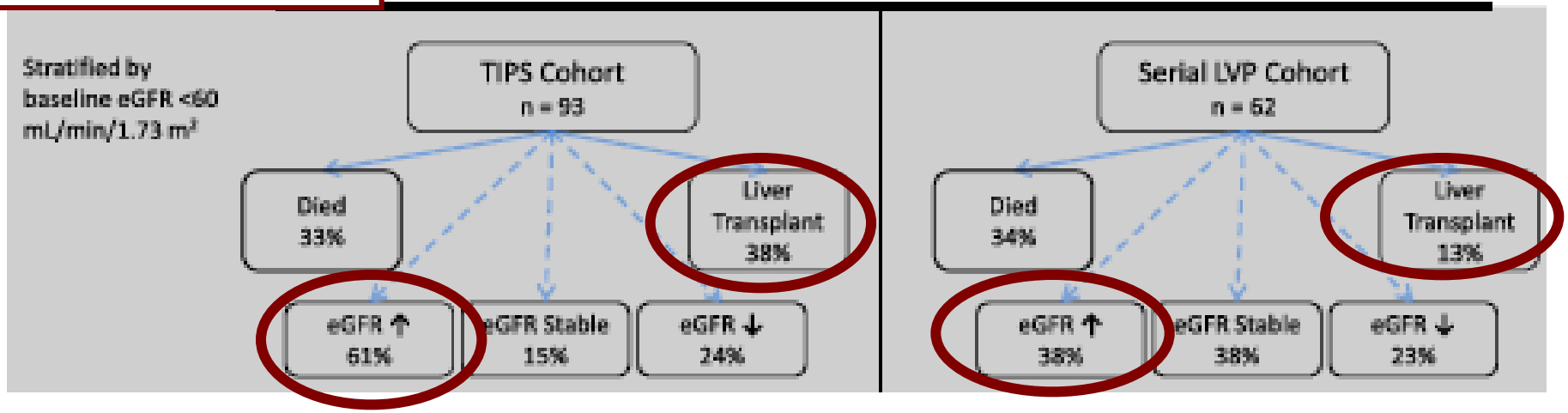
Tan et al. J Gastroenterology and Hepatology 2015

TIPS improves kidney function



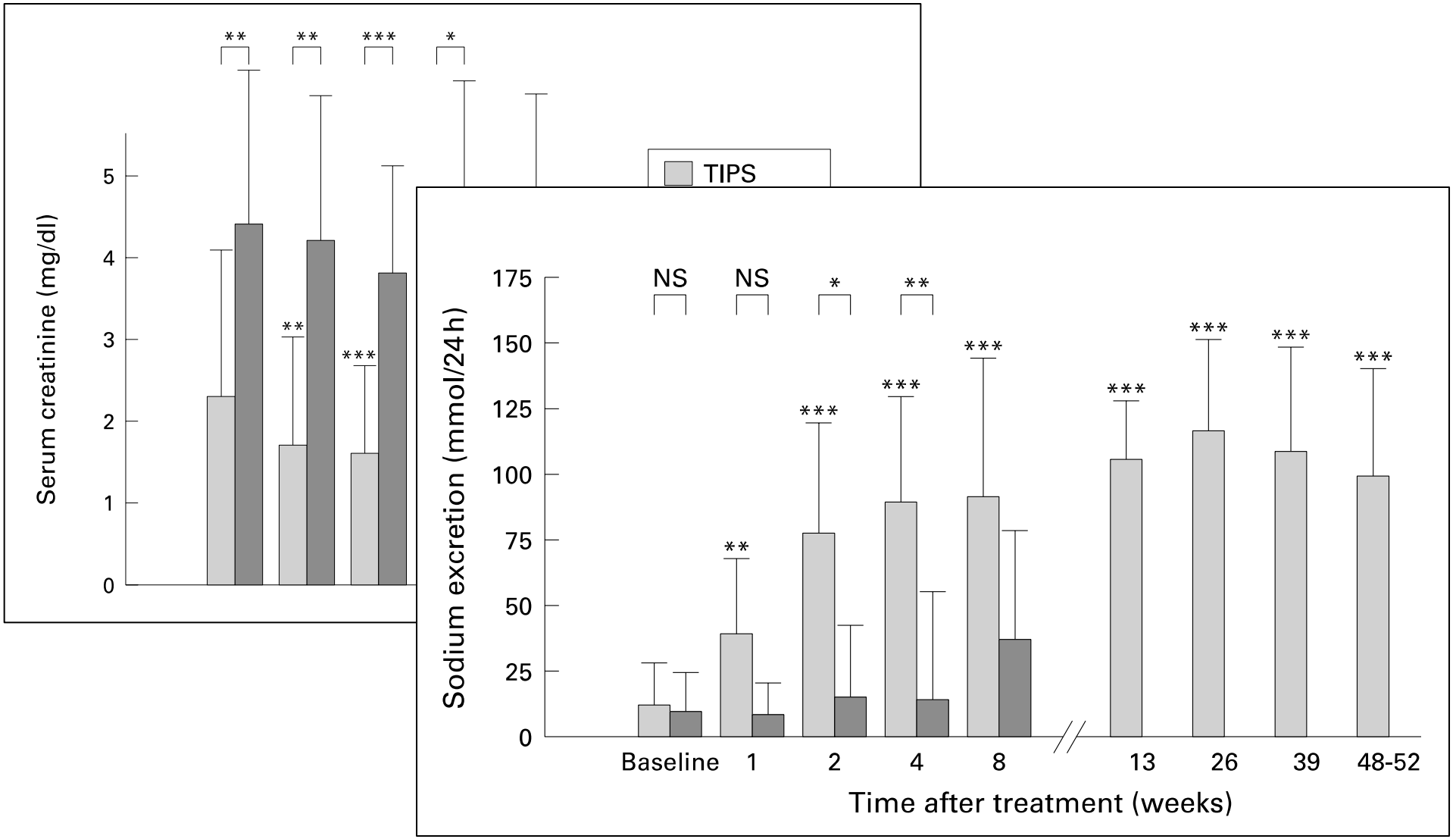


Bridging to LTX



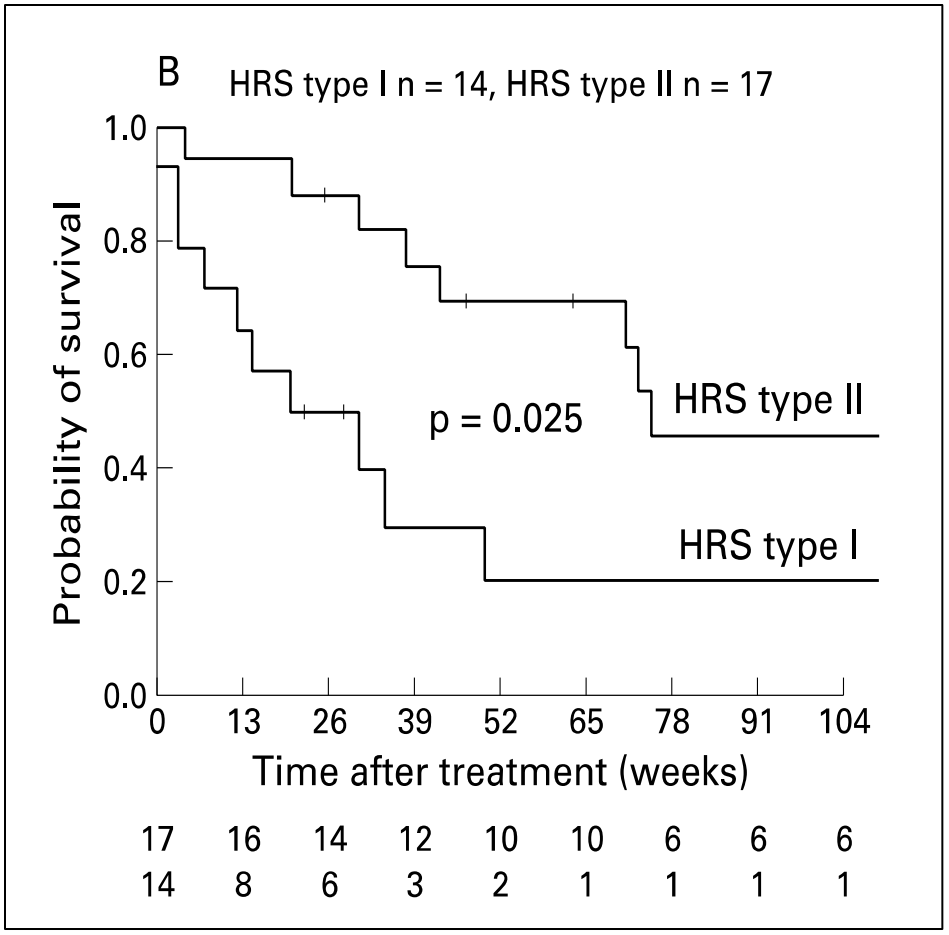
Allegretti et al. Am J Kidney Disease 2016

TIPS improves renal function in HRS!



Brensing et al. Gut 2000

TIPS for HRS



contraindications for TIPS:

-bilirubin > 5 mg/dl

-diastolic dysfunction

-ongoing bacterial infection

-severe hepatic encephalopathy

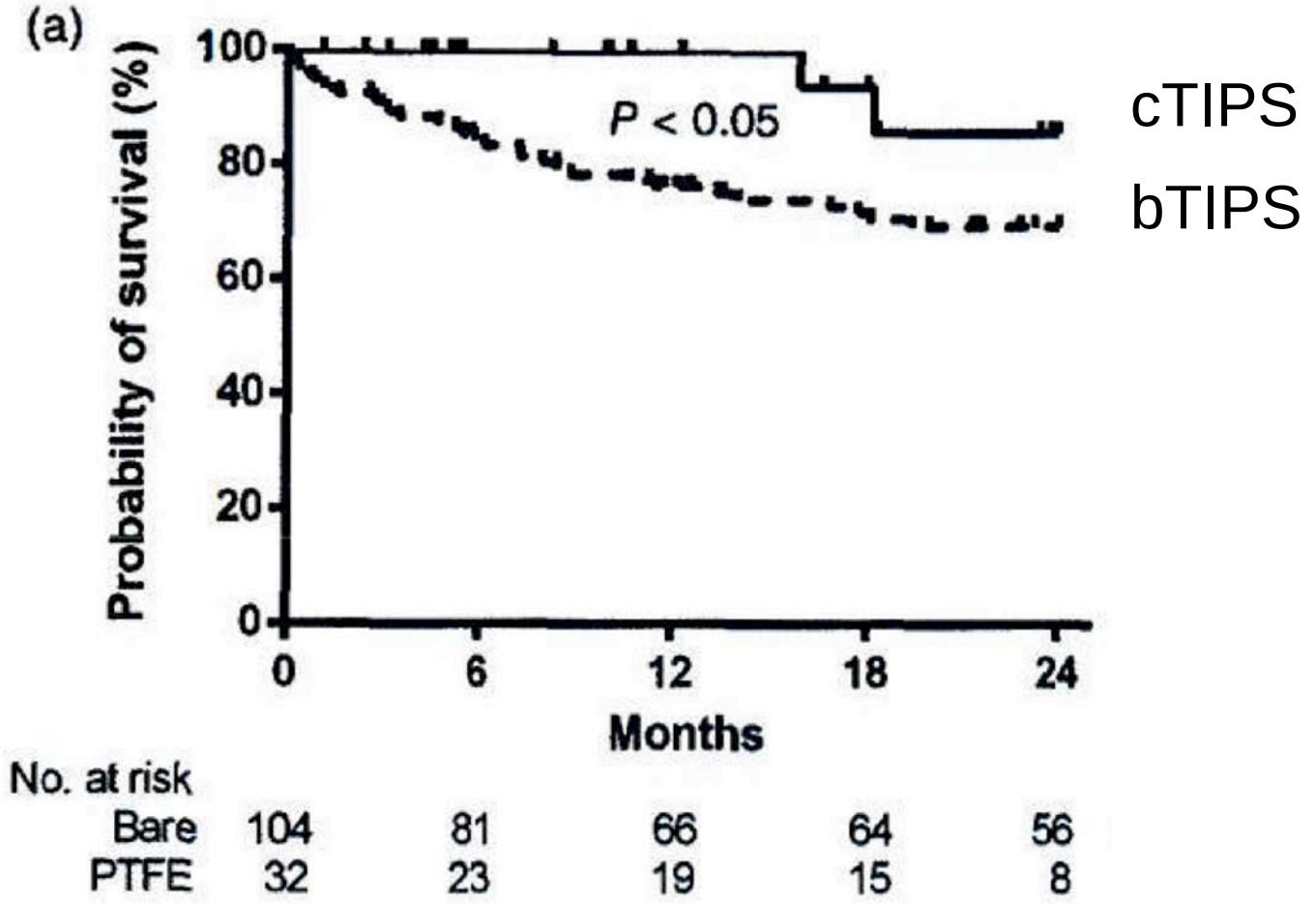
Brensing, et al. Gut 2000

Platelets and bilirubin

Bureau et al. Journal of Hepatology 2011

How to TIPS?

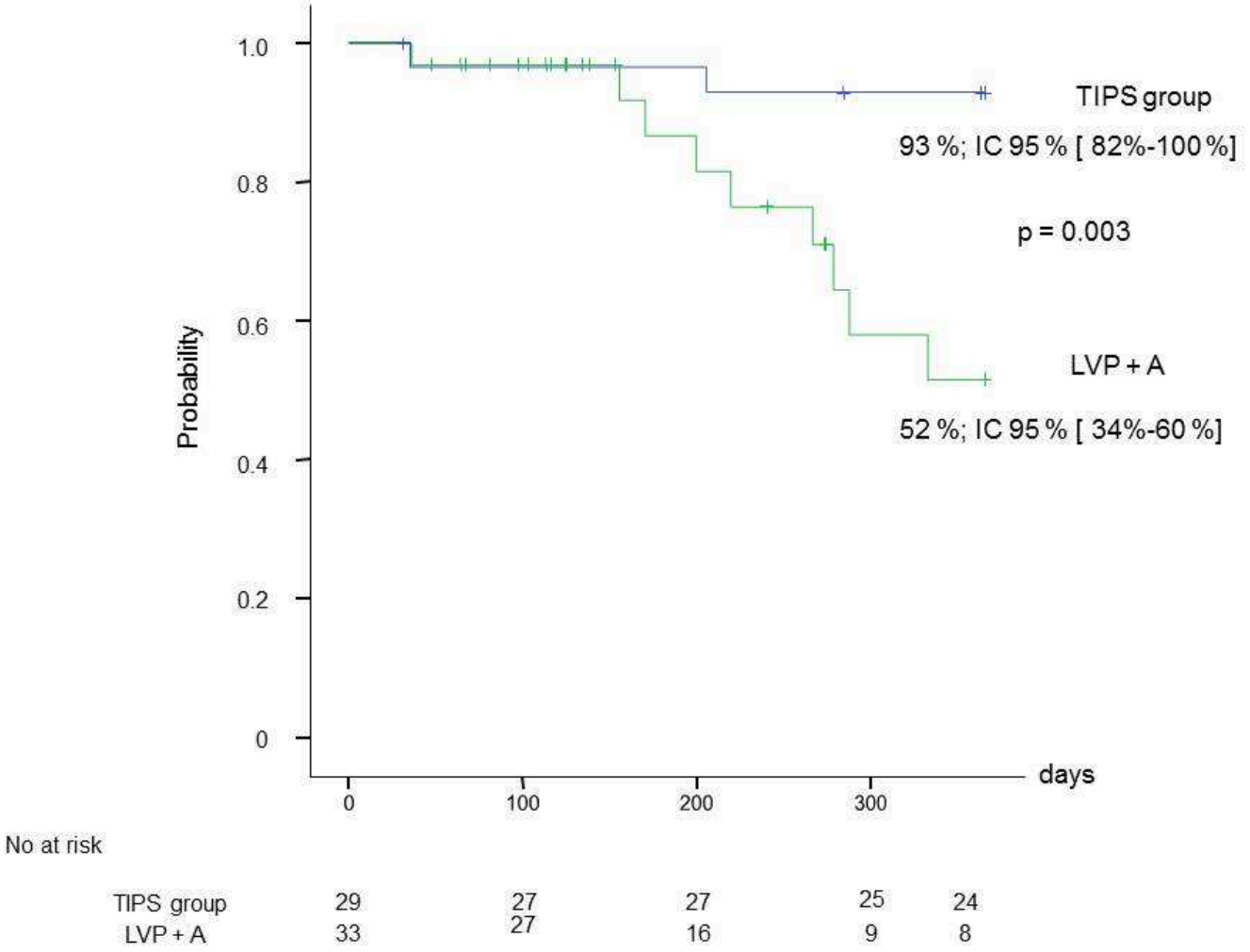
cTIPS is better than bTIPS



Tan et al. J Gastroenterology and Hepatology 2015

Refractory ascites

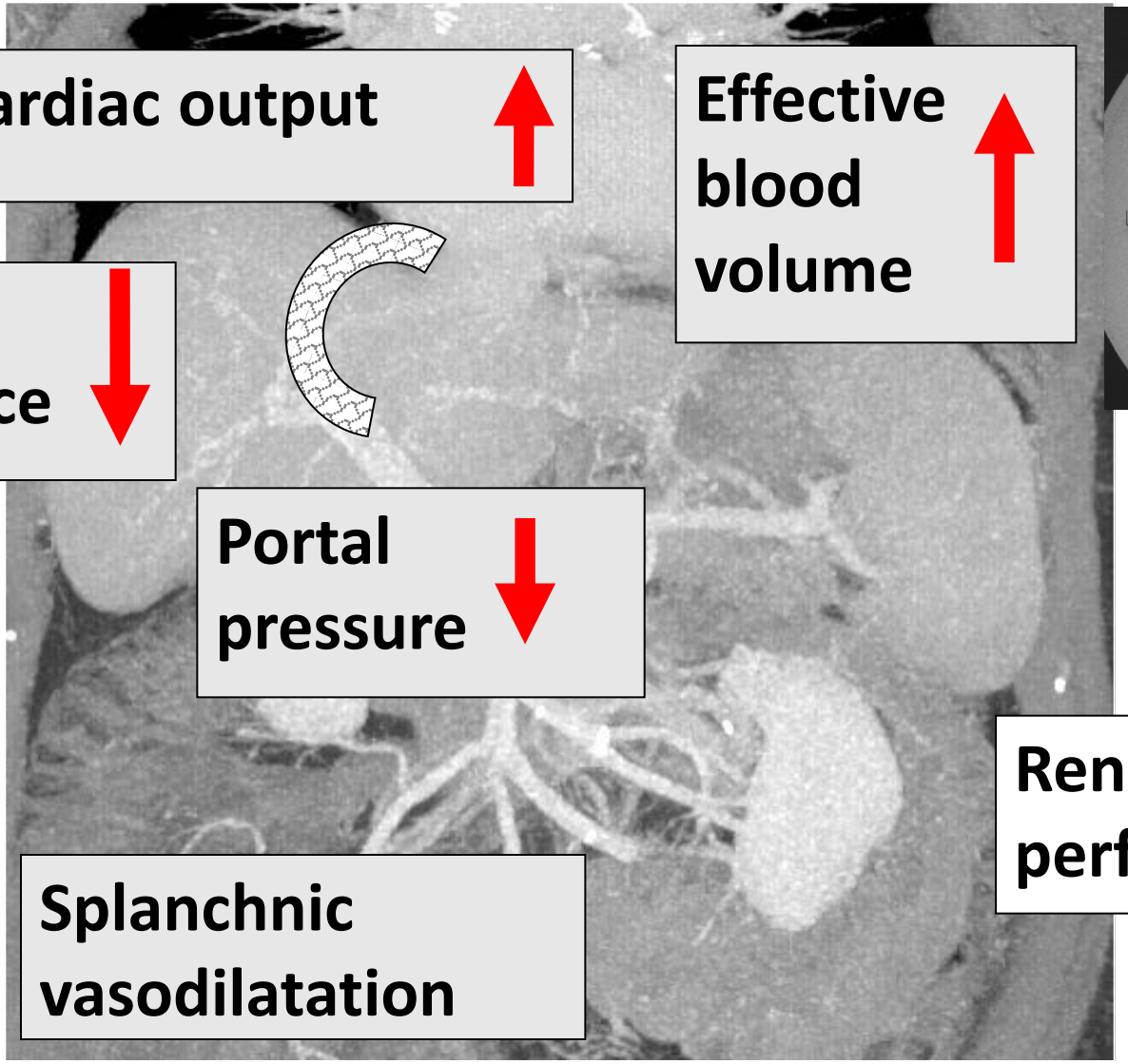
CTIPS improves survival



Bureau et al. Gastroenterology 2017

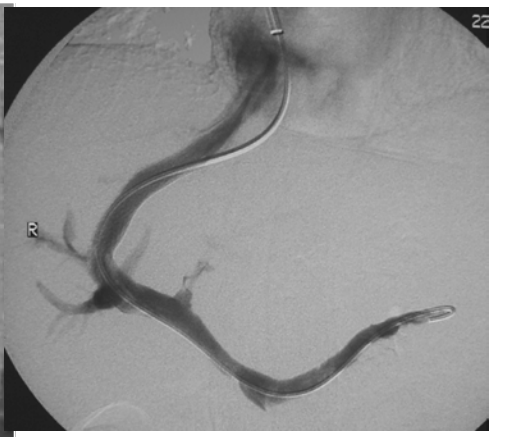
BUT,...

High volume shunting might deteriorate clinics



Cardiac output ↑

Effective blood volume ↑



Hepatic resistance ↓

Portal pressure ↓

Renal perfusion ↑

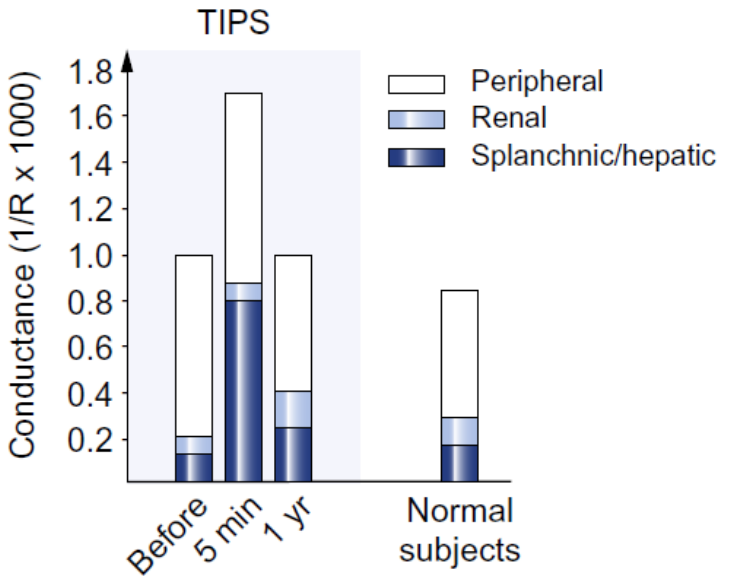
Splanchnic vasodilatation

Trebicka. J Hepatol 2017

TIPS increases cardiac output and flow

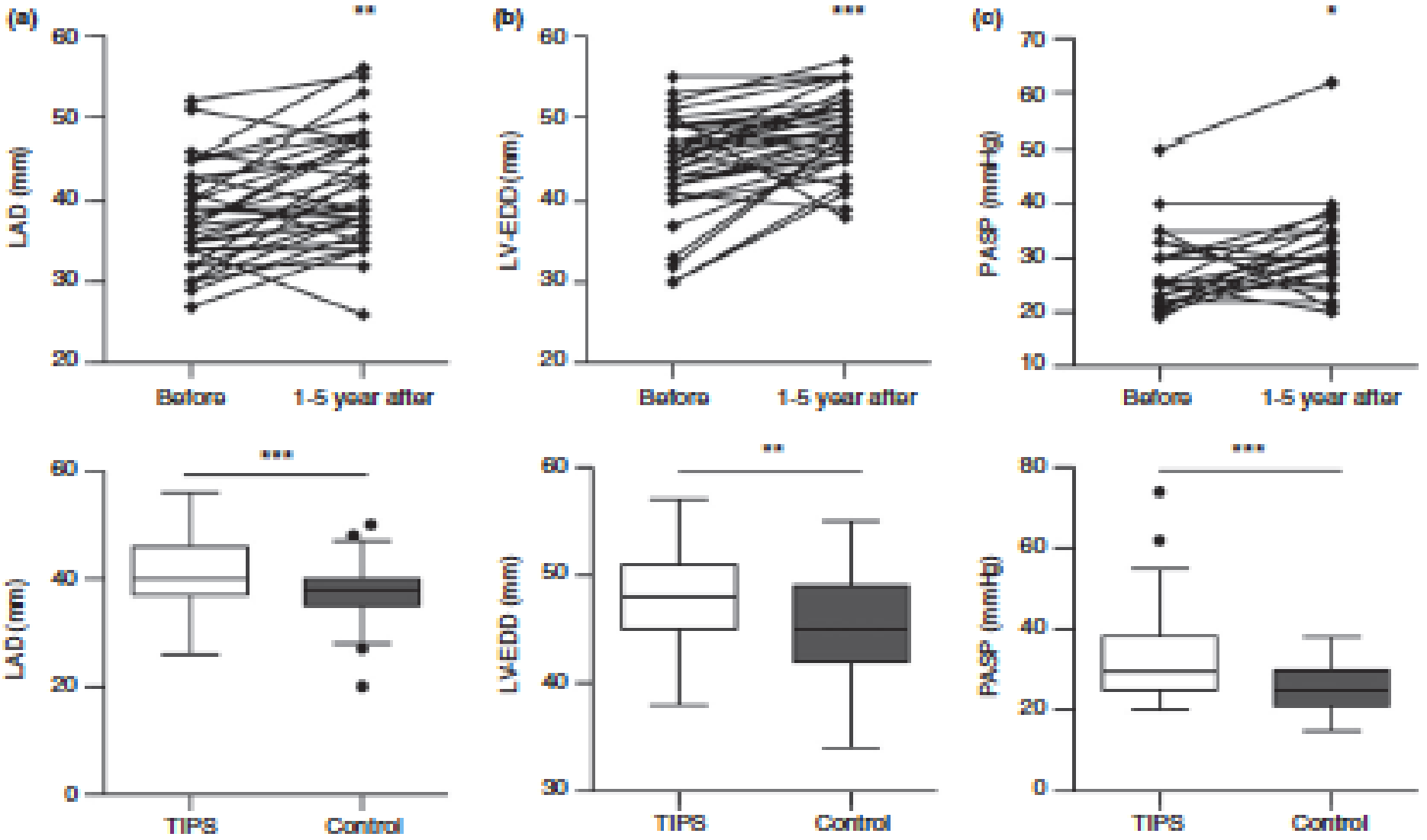
Variable	Before TIPS	Change from Baseline at Day 1	Change from Baseline at 1 Month
Cardiac output, *L/min*	6.83 (5.31 to 8.16)	+1.61 (+0.74 to +2.49)†	+4.03 (+2.03 to +6.03)†
Right pulmonary vascular volume, mL/m^2	181 (98 to 264)	+20 (−3 to +43)	+35 (+16 to +53)
Left pulmonary vascular volume, mL/m^2	183 (117 to 249)	+27 (−7 to +60)	+33 (−1 to +68)
Cardiac and central vascular volume, mL/m^2	886 (582 to 1191)	+49 (−41 to +139)	+260 (+96 to +423)

* Values are expressed as mean (95% CI). TIPS = transjugular intrahepatic portosystemic shunt.
† $P < 0.05$ compared with baseline using analysis of variance.



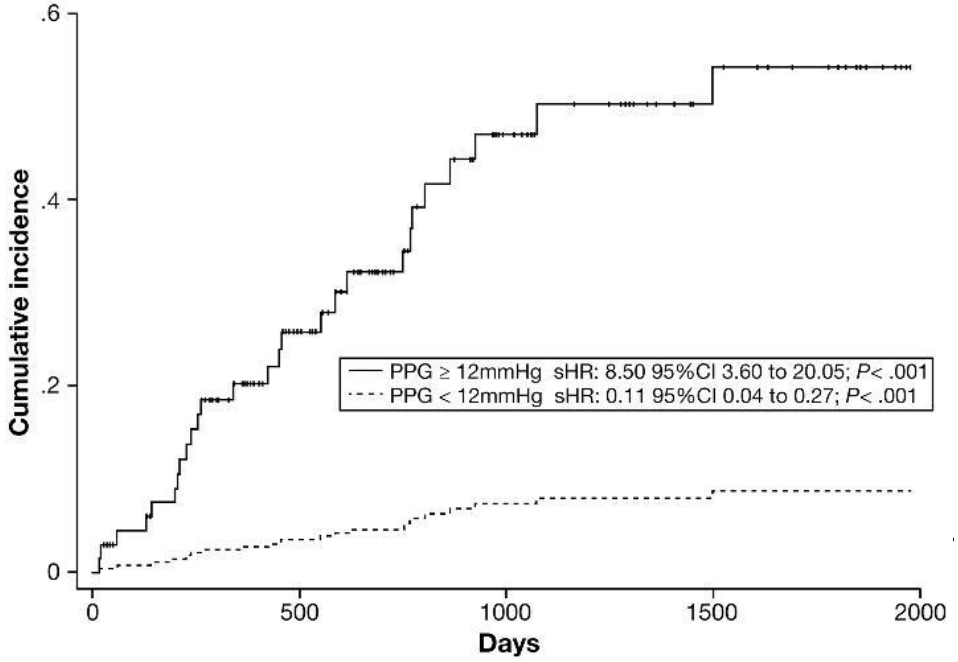
Wong et al. Ann Int Med 1995, Rössle J Hepatol 2013

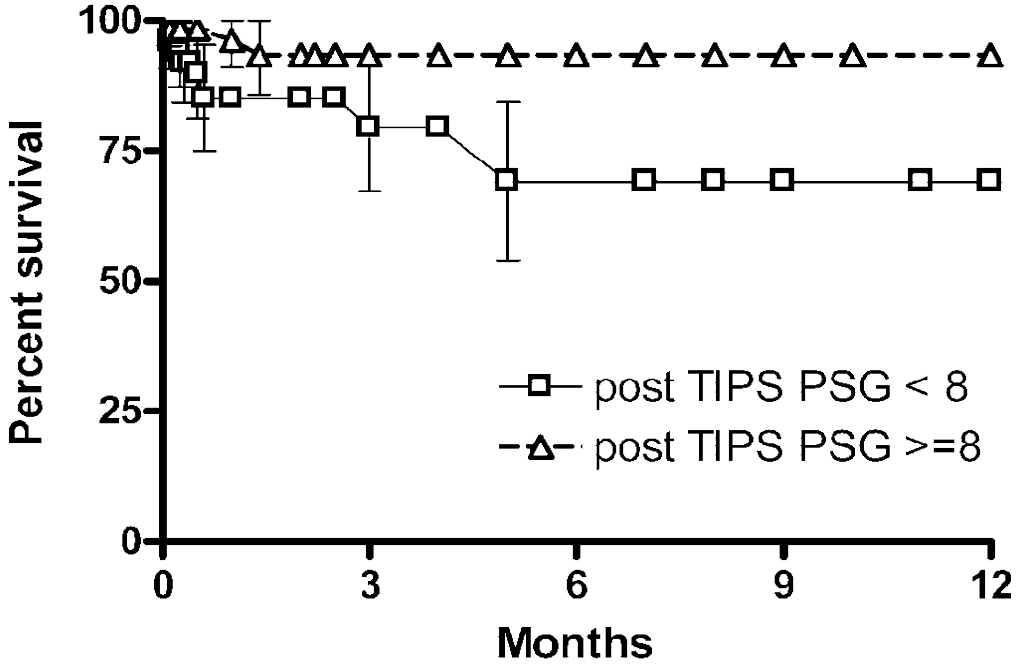
Cardiac function worsens after TIPS



Wahnhoff et al. AP&T 2016

Post TIPS gradient is prognostic important





Silva-Junior et al. Gastroenterology 2017

Harrod-Kim et al. J Vasc Interv Radiol 2006

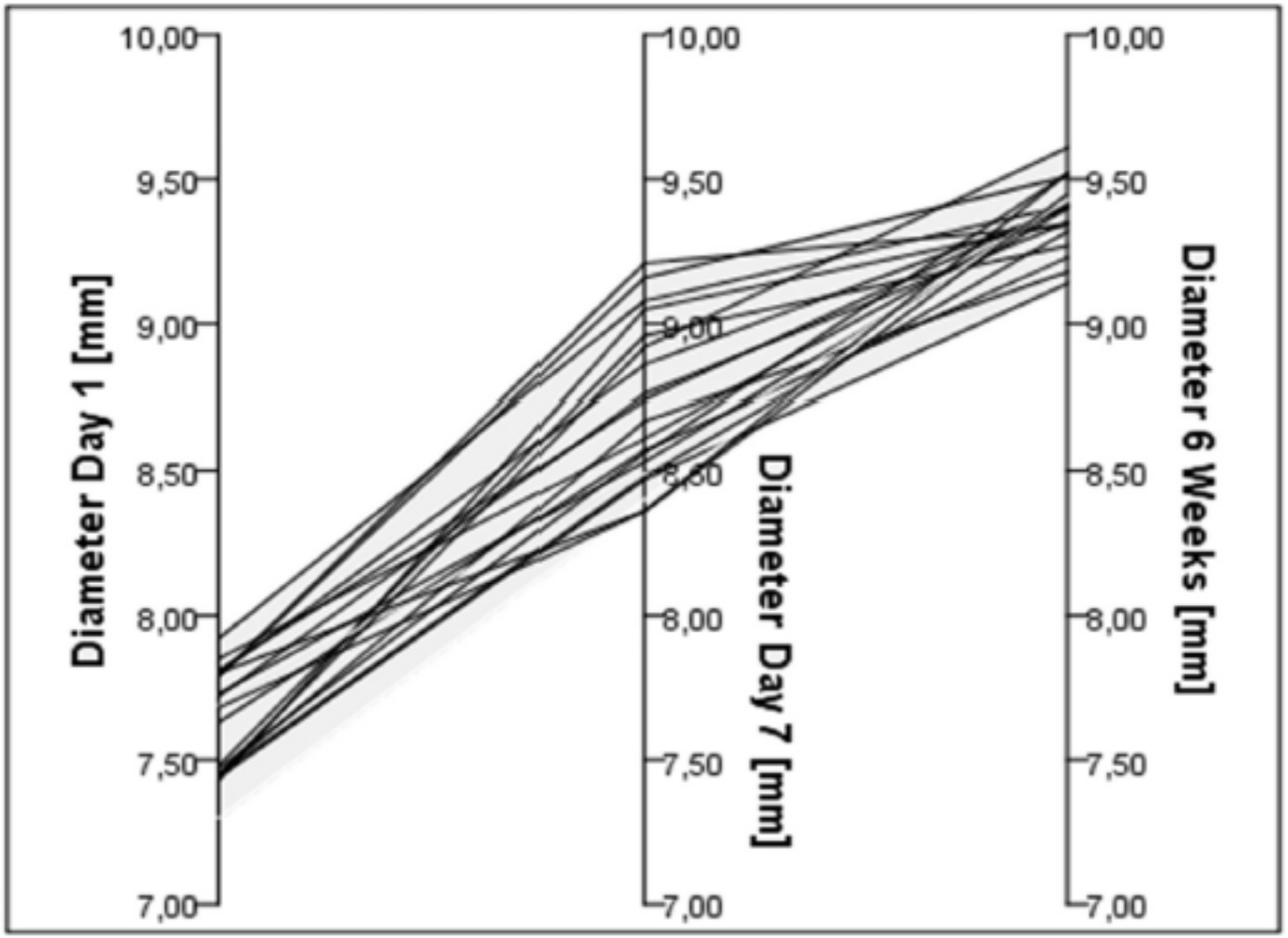
But the gradient decreases after TIPS?

Immediate	early PPG (range 1-6 days)	
12±4	10.5±4 mmHg	p=0.010

Why?

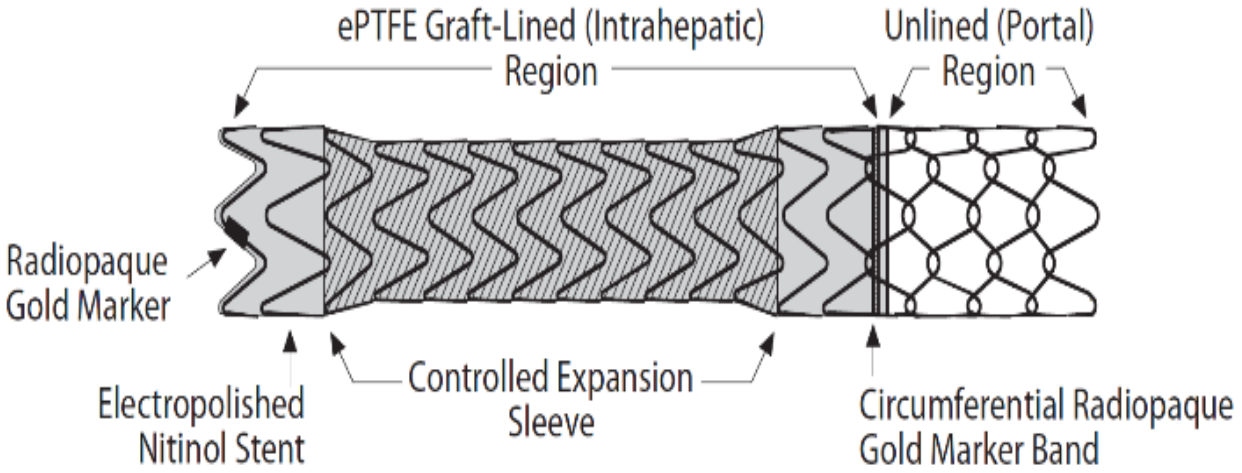
Silva-Junior et al. Gastroenterology 2017

Passive expansion of the stent



Pieper et al. JVIR 2016

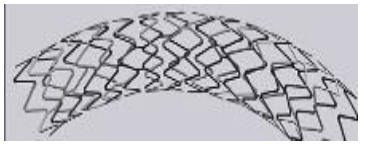
GORE® VIATORR® Controlled Expansion



Case control study

Viatorr controlled expansion
VTX

Viatorr stent
VTS



bare metal stent
BMS

Praktiknjo et al. EASL 2017

Baseline characteristics

Parameter	VTX	VTS	BMS
10 mm stents dilated to 8 mm	**n=30**	**N=34**	**N=14**
sex (male/female)	17/13	20/14	19/17
age	56(29-72)	59(30-78)	58(27-74)
etiology of cirrhosis			
(alcohol / non-alcohol)	16 / 14	17 / 16	8 / 6
indication for TIPS (bleeding/ascites)	10/20	9/25	7/7

No difference

Praktiknjo et al. EASL 2017

Controlled expansion Viatorr controls PSPG!

	Immediate	later PSPG	
Silva-Junior et al.	12±4	10.5±4 mmHg	p=0.010
Praktiknjo et al.	**10.4±1**	**10.6±1 mmHg**	**p=0.805**

Silva-Junior et al. Gastroenterology 2017

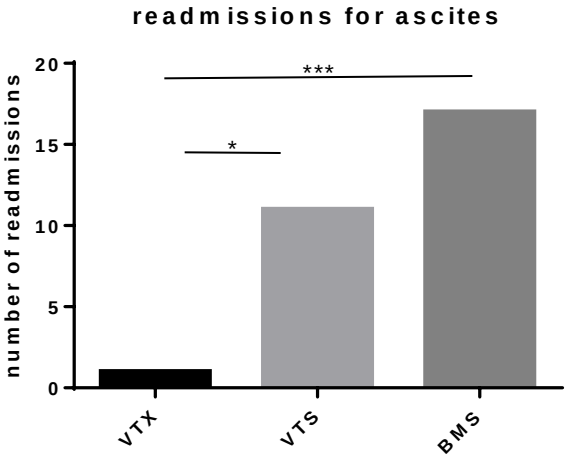
Controlled expansion Viatorr controls shunting and HE!

	nominal ø	dilated ø	rate of OHE
Sauerbruch et al.	8 mm	8 mm	18%
Holster et al.	10 mm	8 mm	38%
Wang et al.	**10 mm**	**10 mm**	**37%**
	8 mm	**8 mm**	**22%**
Praktiknjo et al.	**10 mm (VTS)**	**8 mm**	**38%**
	10 mm (VTX)	**8 mm**	**23%**

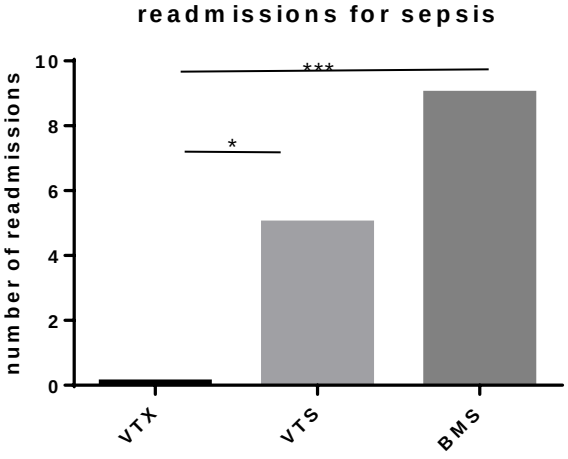
Controlled Expansion Stent improves HE!

Sauerbruch et al. Gastroenterology 2015
Holster et al. Hepatology 2016
Wang et al. J Hepatology in press

Hospital readmission at follow up



VTX reduces readmissions for ascites

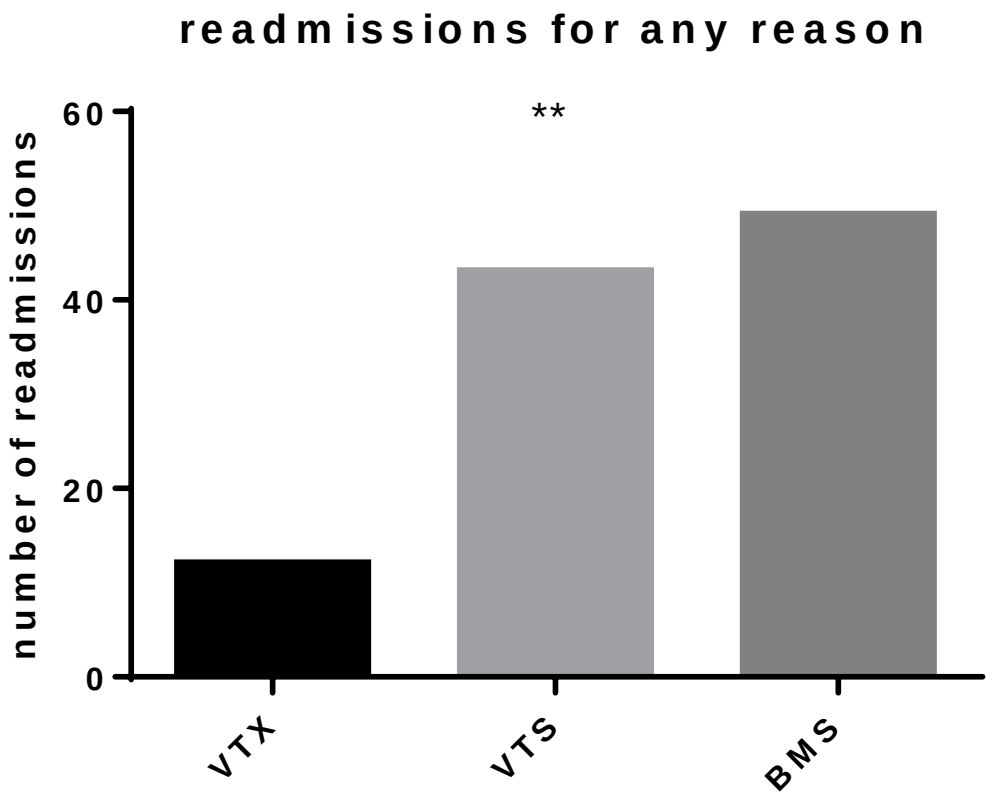


VTX reduces readmissions for sepsis

* $p < 0.05$
*** $p < 0.001$

Praktiknjo et al. EASL 2017

Hospital readmission at follow up



VTX reduces readmissions overall

Praktiknjo et al. EASL 2017

Summary

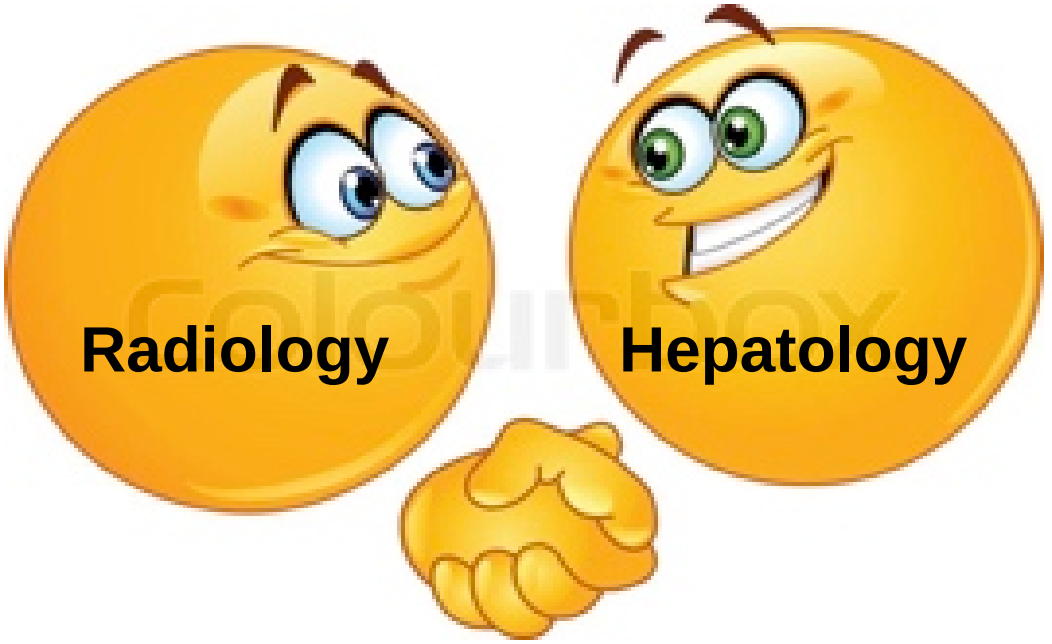
What to TIPS?
Complications of portal hypertension.

WHY to TIPS?
TIPS stops bleeding, prevents rebleeding, improves kidney function, treats refractory ascites and improves survival

When to TIPS:
Within 72 hours in Child B and active bleeding, or Child C <14p
for secondary prophylaxis, if NSBB unappropriate;
when refractory ascites or HRS establishes

How to TIPS?
Covered, smaller (8mm) TIPS might improve survival.
The control expansion stents might prevent decompensation.

Carsten Meyer,
Guido Kukuk,
Claus Pieper,
Julian Luetkens,
Daniel Thomas,
Stefan Fischer,
Daniel Küting,
Hans Schild,
Holger Strunk,
...



Tilman Sauerbruch,
Michael Praktiknjo,
Christian Jansen,
Jennifer Lehmann,
Alessandra Pohlmann,
Christian Strassburg,
Nadine Köstlmaier,
Teresija Bosnic,
Julia Groffy,
...

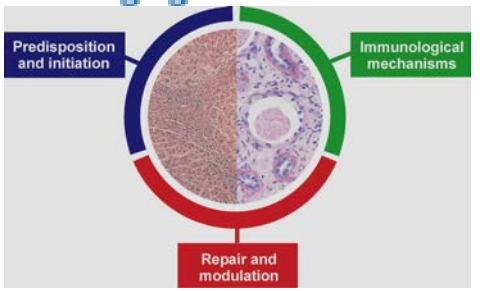
European Commission

EF Clif
EUROPEAN FOUNDATION FOR THE STUDY OF CHRONIC LIVER FAILURE

PREDICT

LiF-PHyt-Bonn
Laboratory for Liver Fibrosis and Portal Hypertension Bonn

DFG Deutsche Forschungsgemeinschaft



Thank you !

Summary

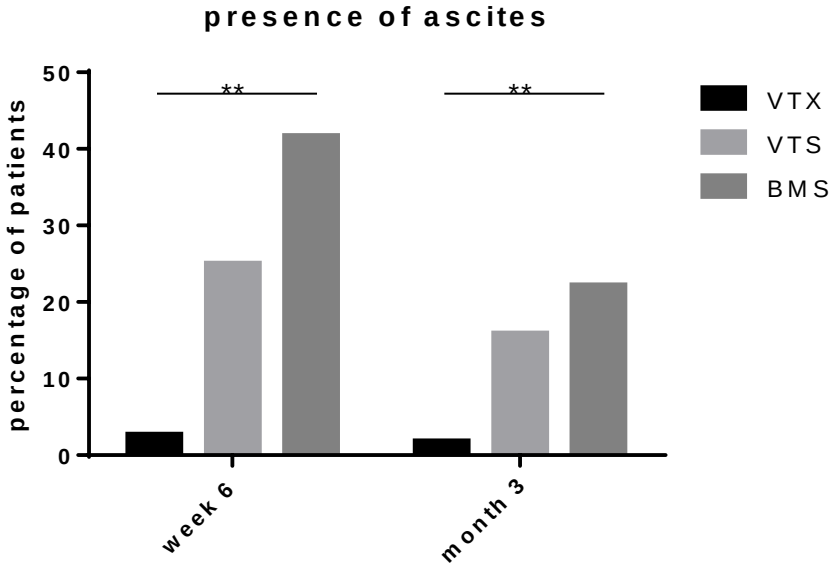
TIPS improves kidney function and might brigde to LTX.

TIPS improves survival in refractory ascites.

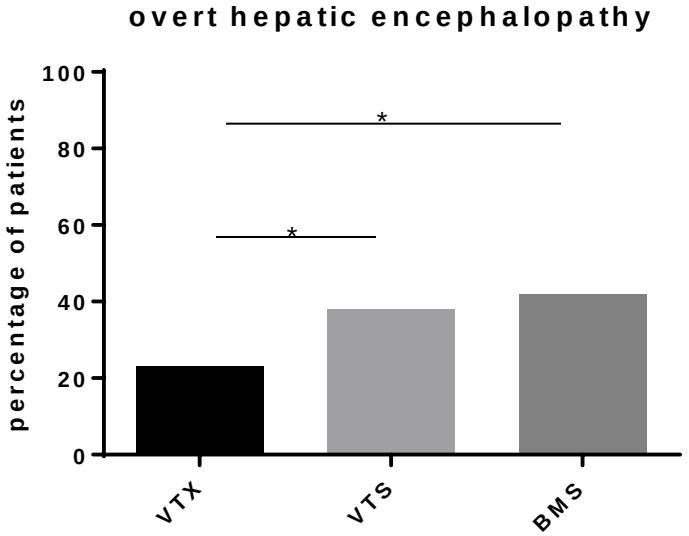
Low bilirubin levels and high platelets predict better outcome after TIPS for refractory ascites.

New biomarkers for long-term survival (e.g. CXCL9, CXCL11, Elastin, etc.).

Ascites and hepatic encephalopathy at follow up



Ascites in VTX is reduced compared to VTS and BMS



Episodes of overt HE in VTX are reduced compared to VTS and BMS

* $p < 0.05$
** $p < 0.01$

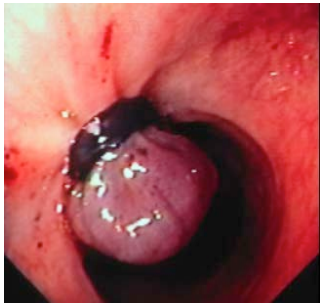
Praktiknjo et al. EASL 2017

What patients to TIPS for refractory ascites?

Rebleeding prophylaxis is mandatory

without therapy 60-70% rebleeding and 40% mortality

Band ligation



First line

+

NSBB

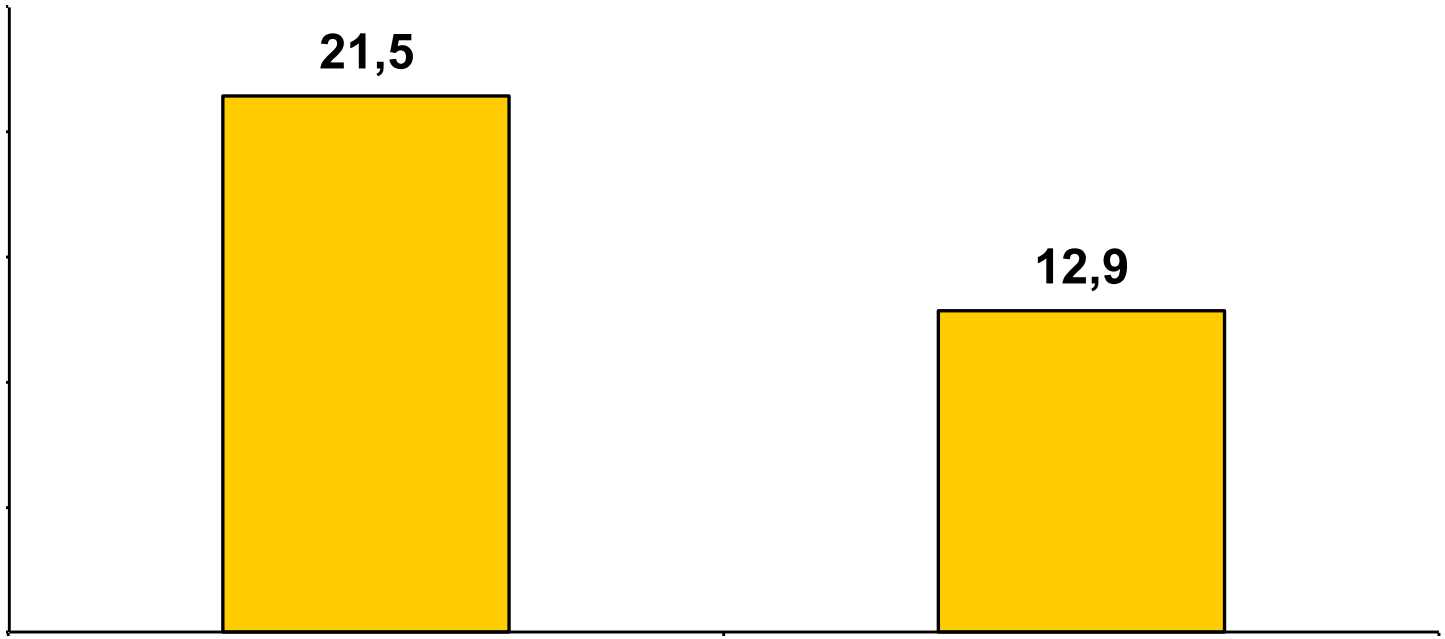
40-50% rebleeding

20-35% mortality

BUT,

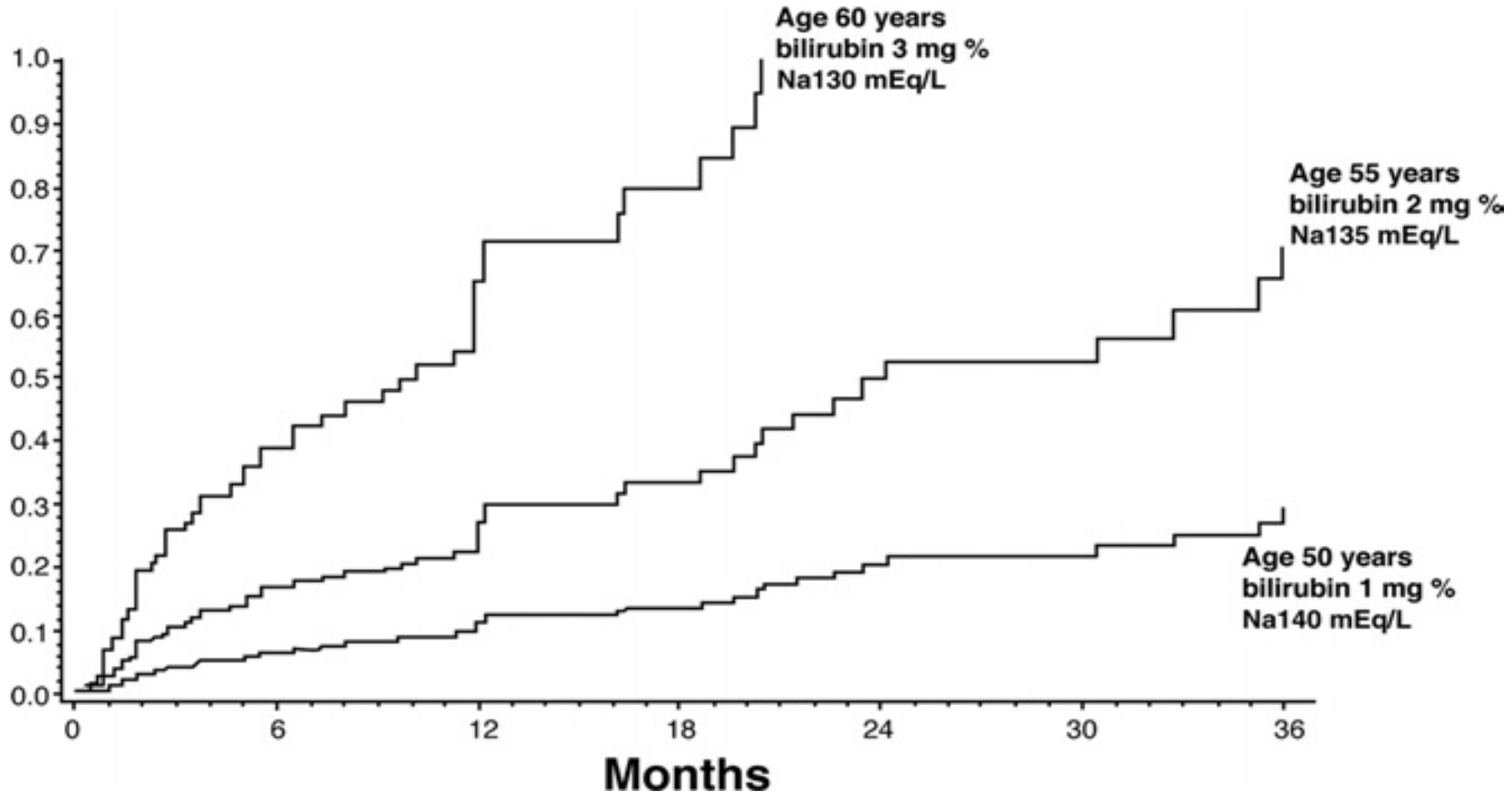
BAVENO VI. *J Hepatol* 2015

„Early TIPS“ in real life (France)



Thabut et al. AASLD 2014

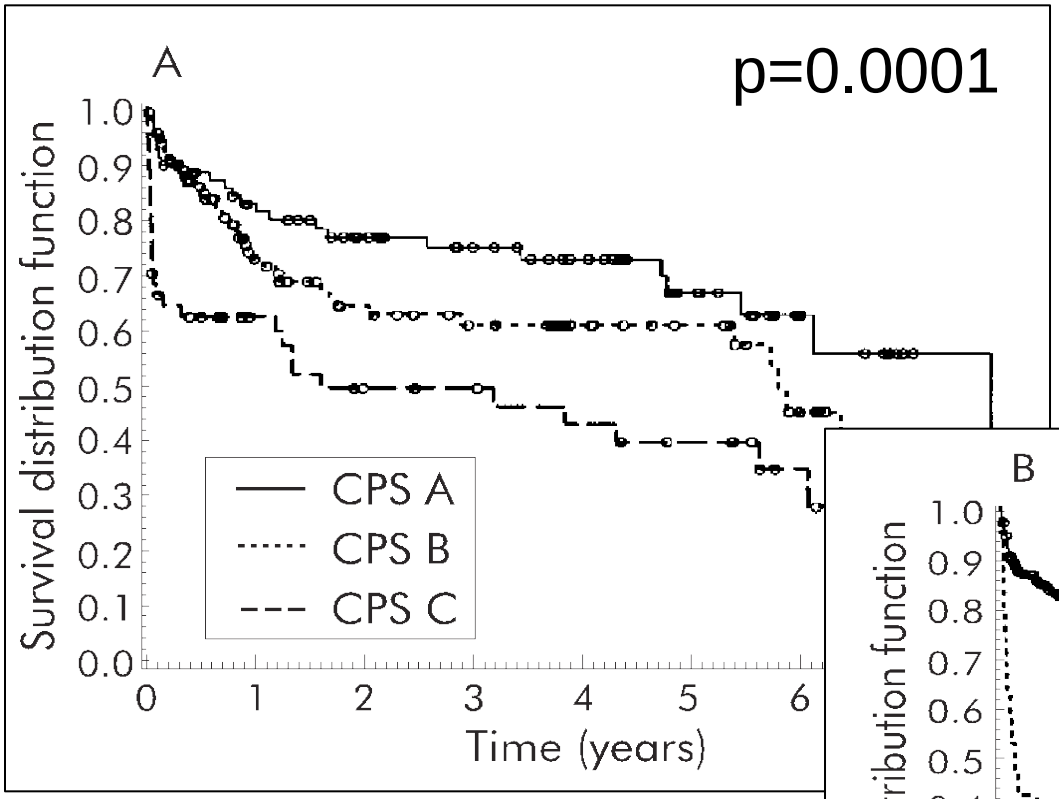
Age, bilirubin and sodium



n=305

Salerno et al. Gastroenterology 2007

Child-Pugh-Score and MELD-score



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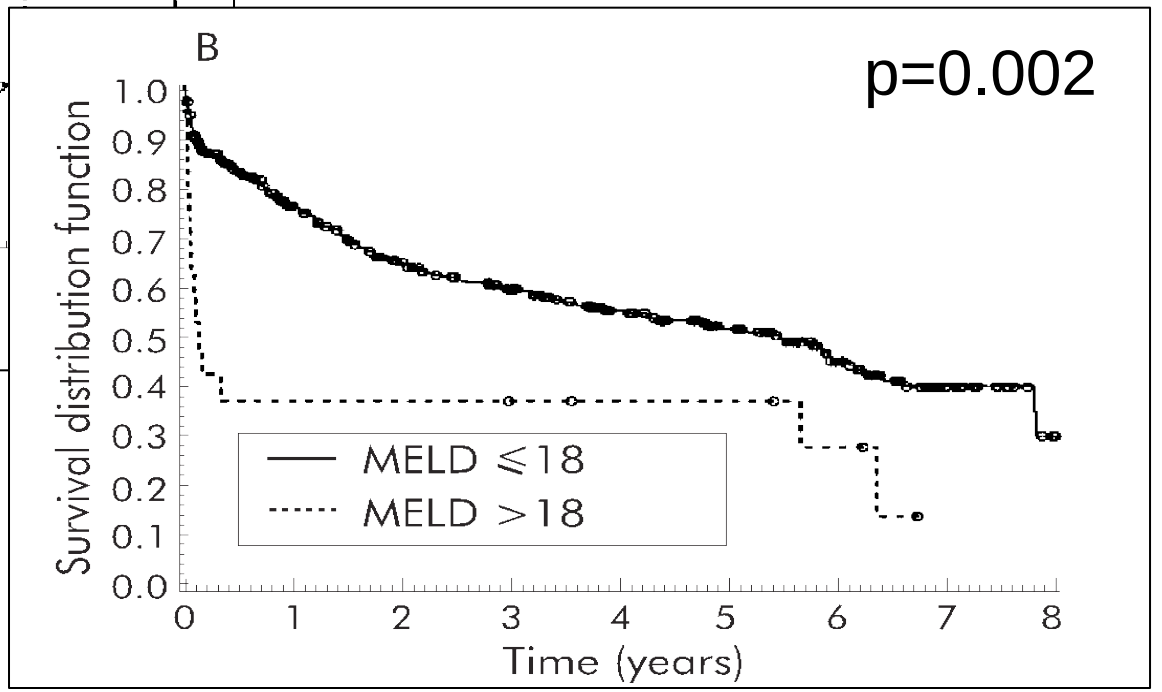


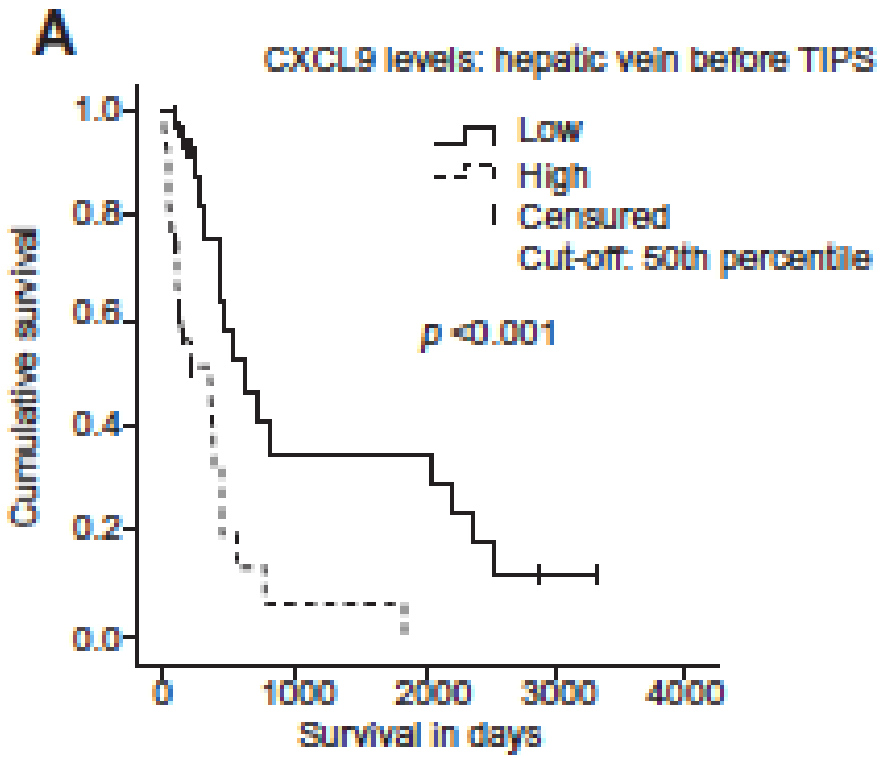
CPS > 11 or MELD > 14

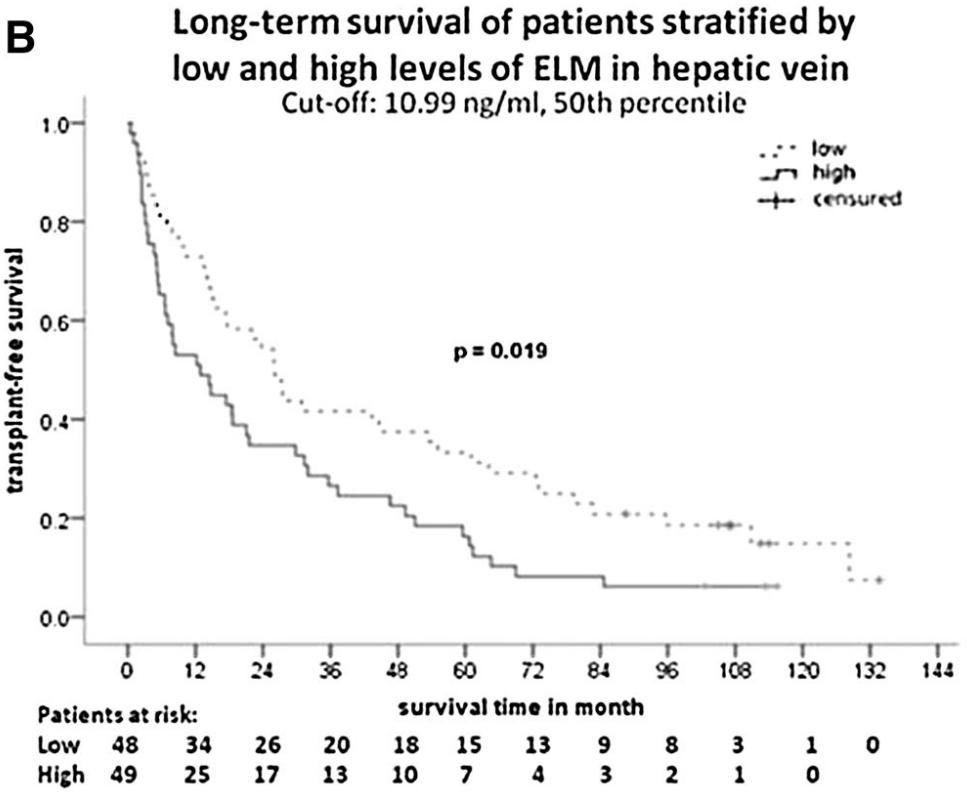
Specificity ca. 95%

Sensitivity ca. 35%

Angermayr et al. Gut 2003

Biomarker

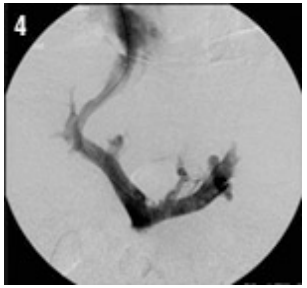




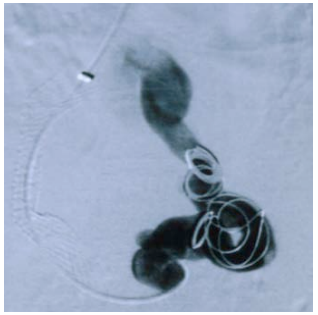
Berres, [...], Trebicka. J Hepatol 2015,
Berres, [...], Trebicka. Liver International 2016
Nielsen, [...], Trebicka. Dig Dis Sci 2015

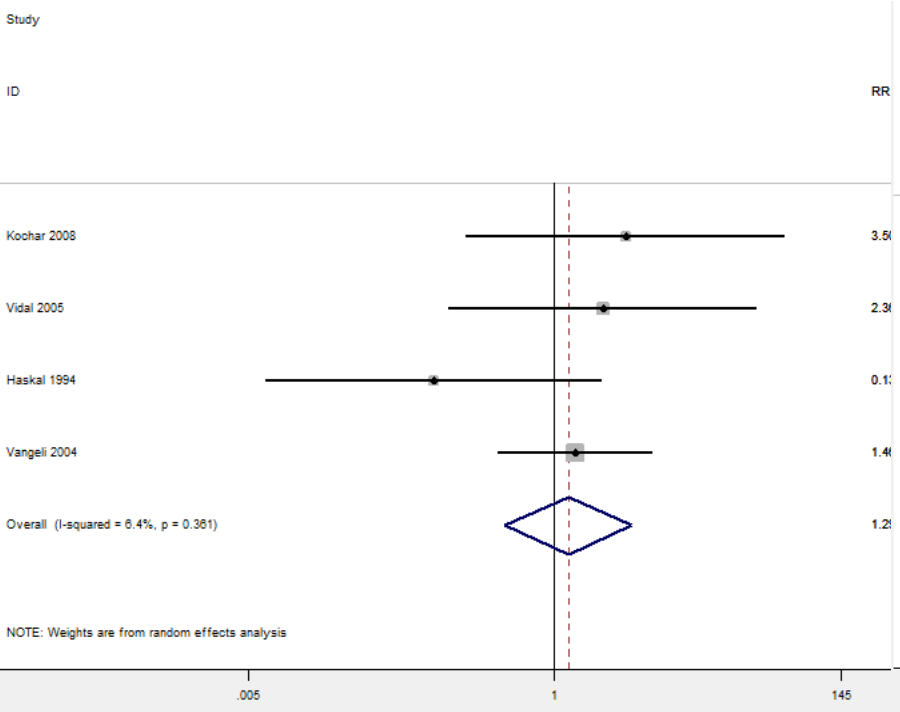
Variceal embolisation

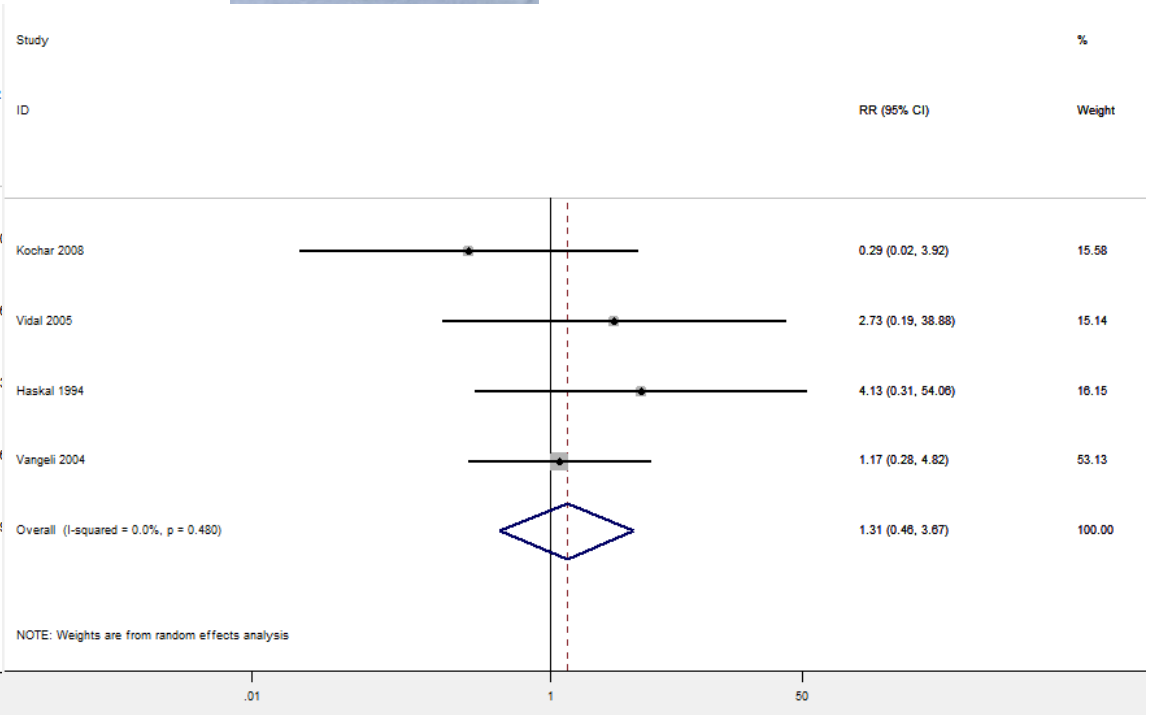
TIPS



embolisation



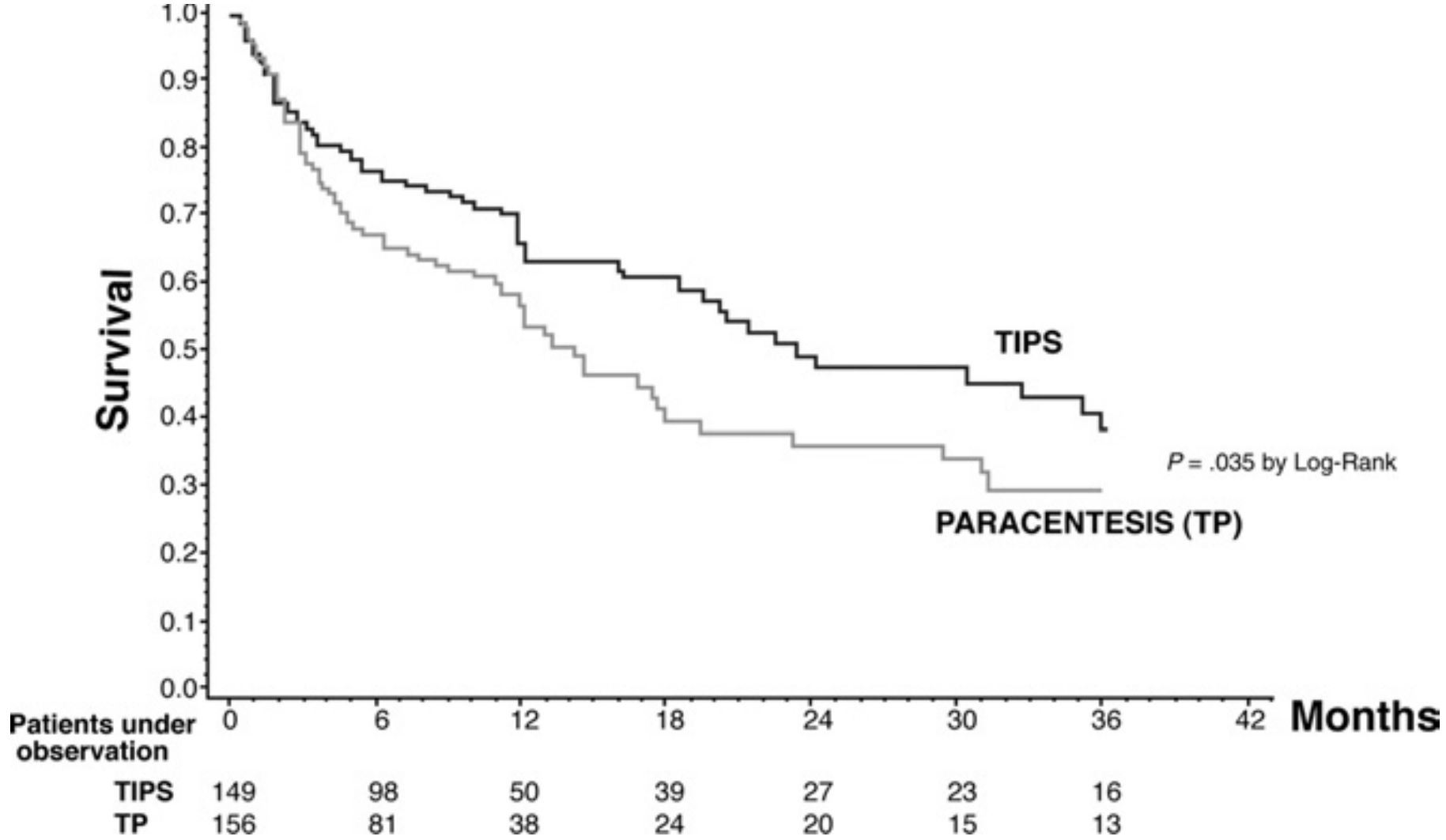




Trebicka et al. *J Hepatol* 2017
Trebicka et al. J Hepatol in press

Why to TIPS in refractory ascites?

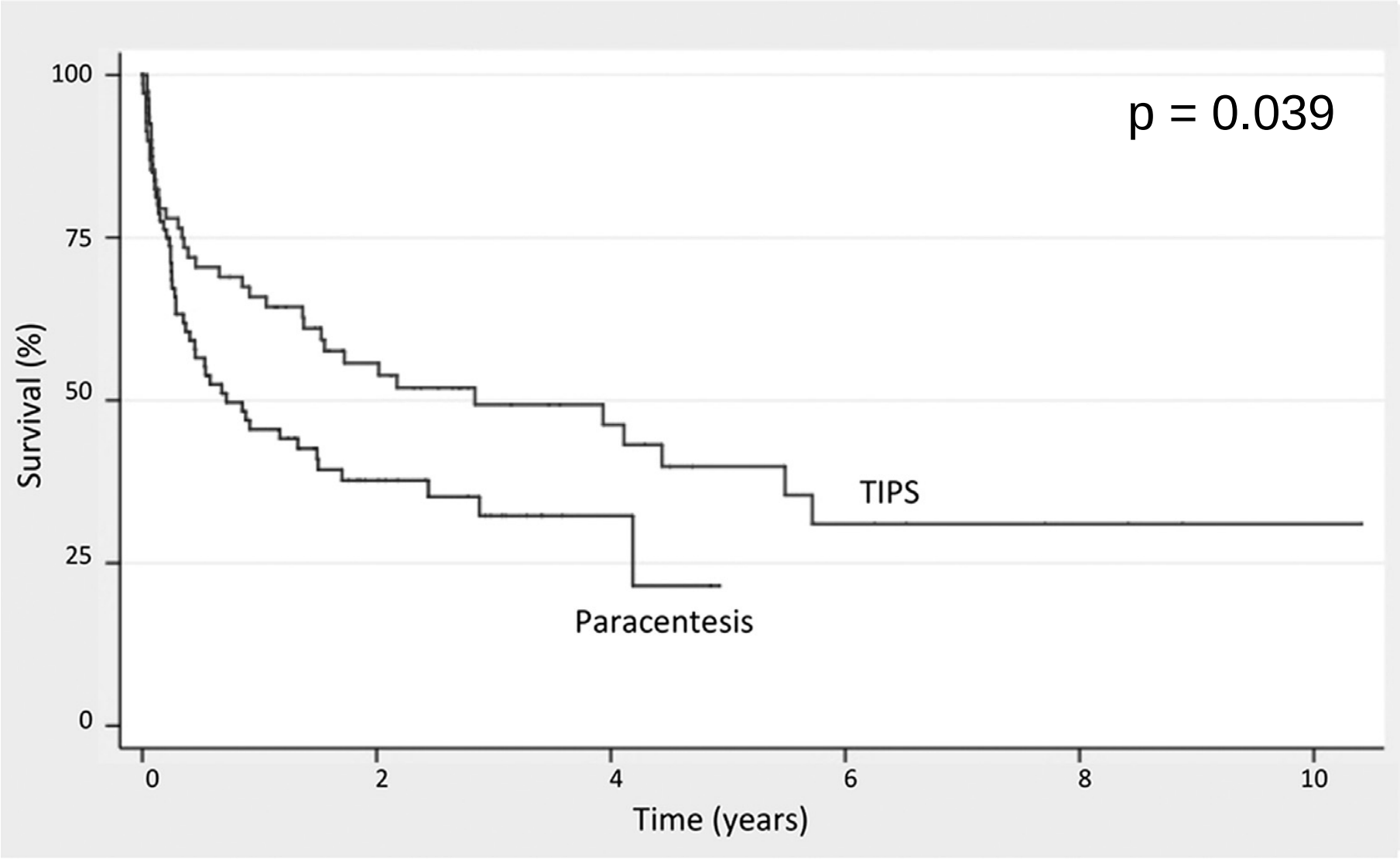
TIPS improves survival



Salerno et al. Gastroenterology 2007

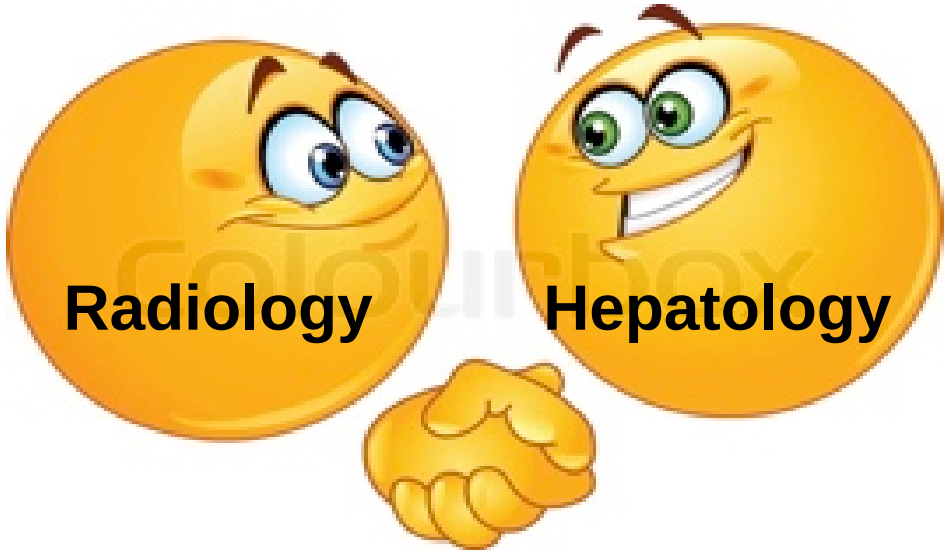
Refractory ascites

cTIPS improves survival



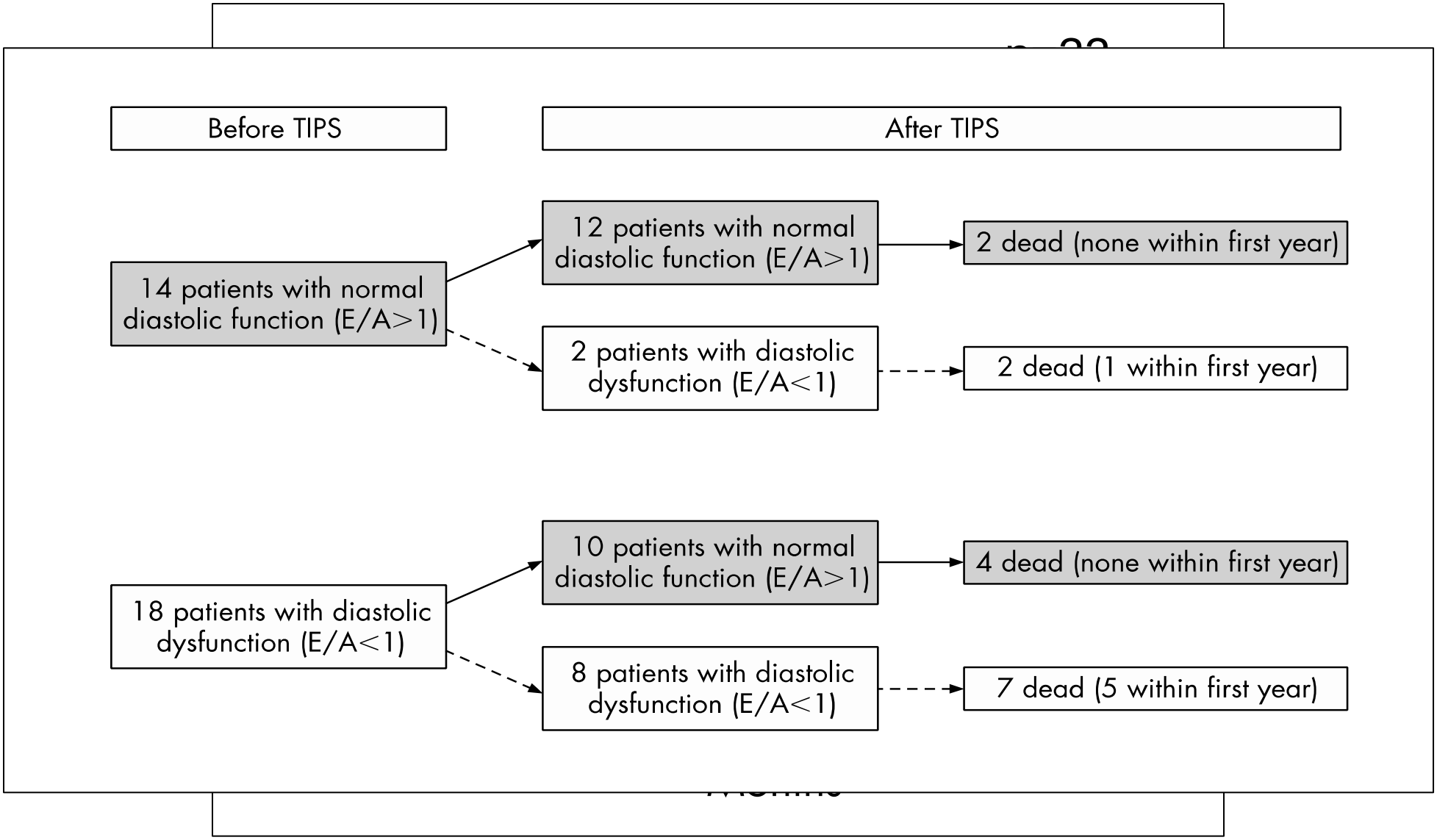
Gaba et al. Clinical Radiology 2015

Follow up after TIPS is very important, since the evolution of the patients might be different!



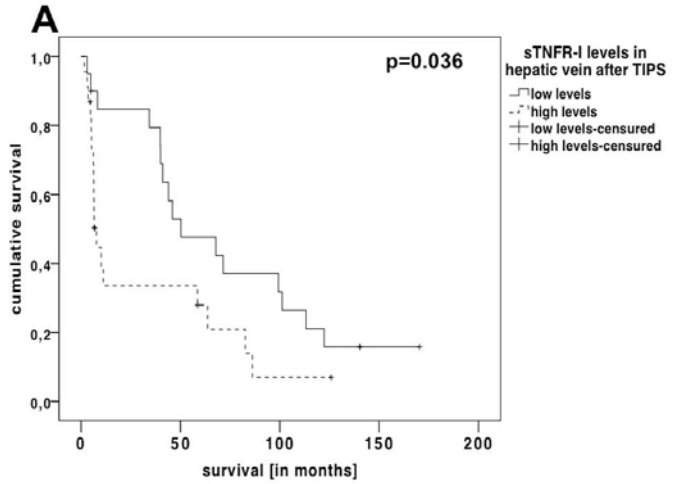
Thank you !

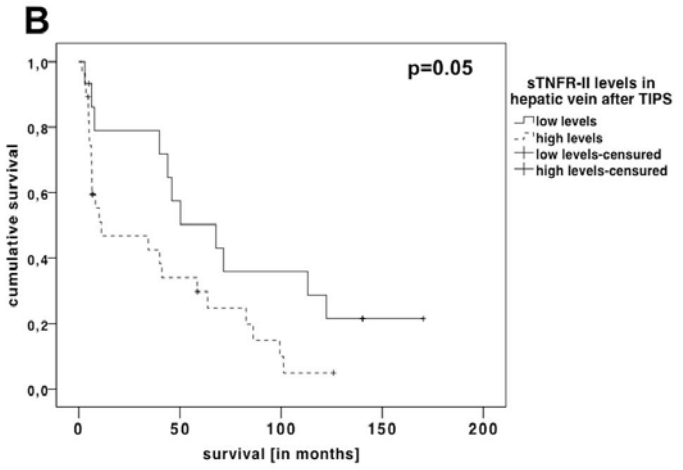
Cardiac function

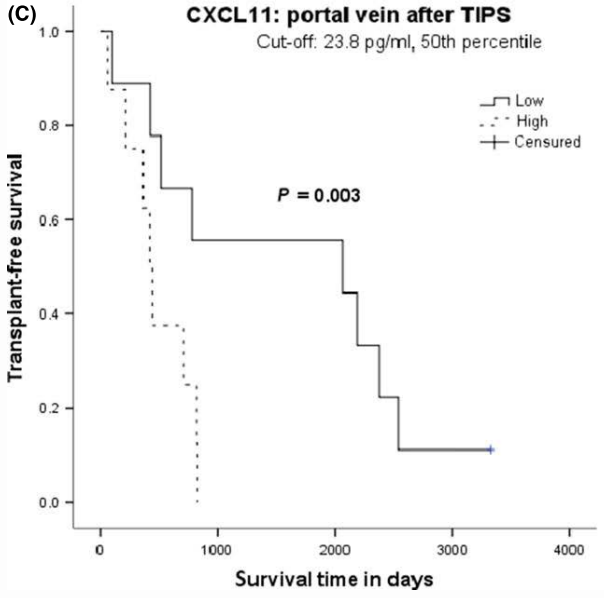


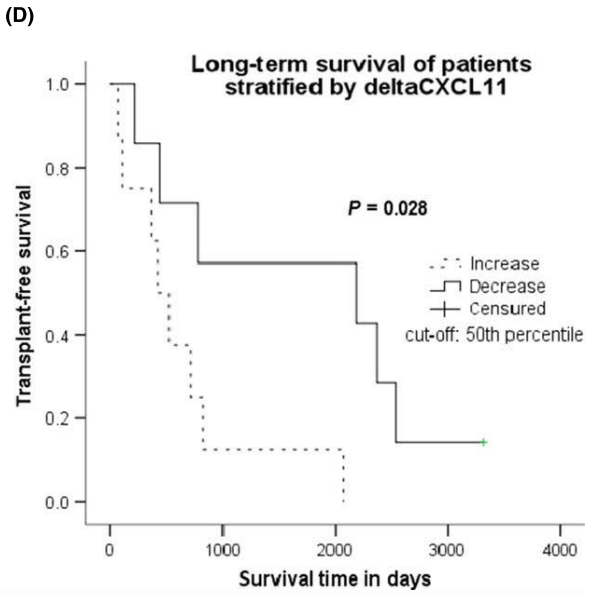
Cazzaniga et al. Gut 2007

Follow up of Biomarker









Trebicka et al. PLoS One 2013

Berres, [...], Trebicka. Liver International 2016

Refractory ascites

TIPS improves survival

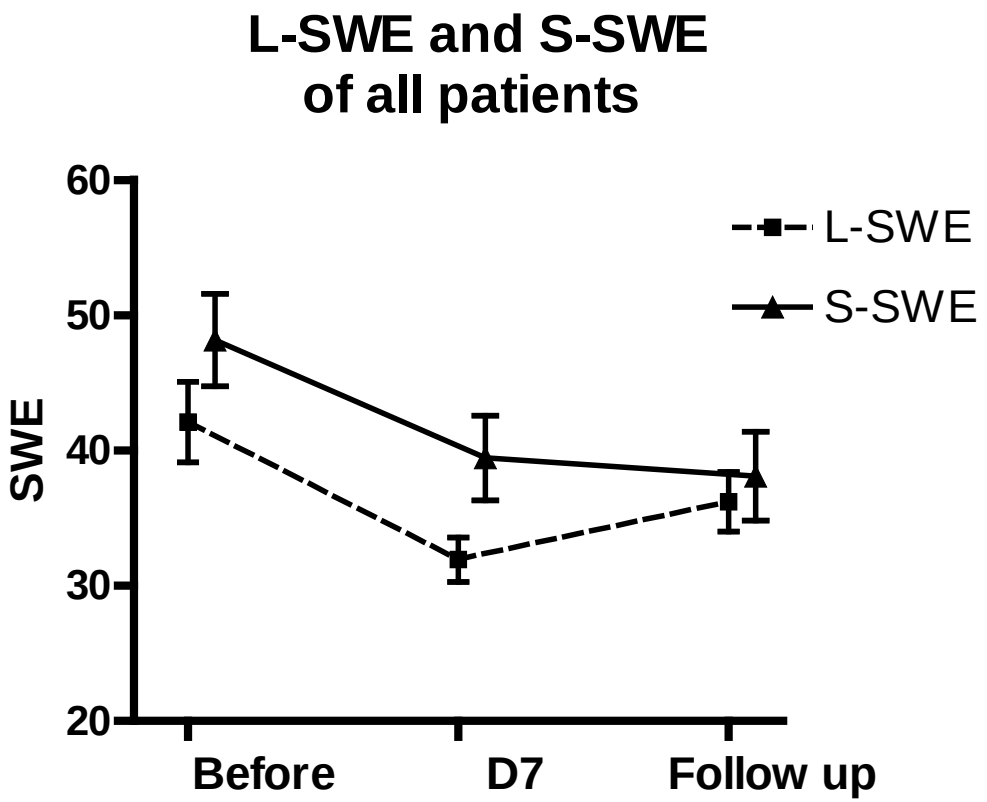
cTIPS

c + bTIPS

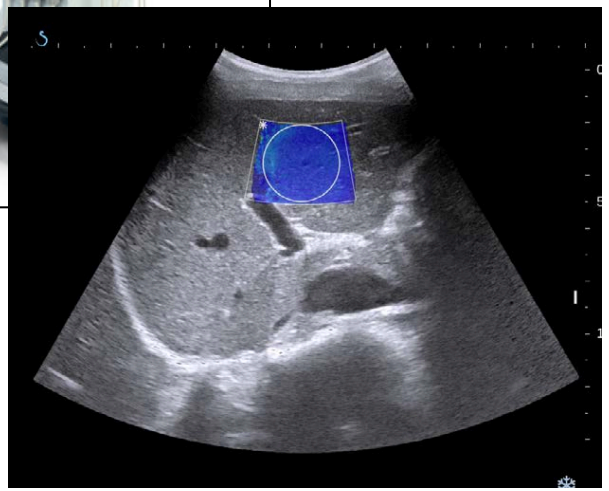
Bai et al. WJG 2015

Clinical Follow up

TIPS decreases liver and spleen stiffness (Aixplorer)

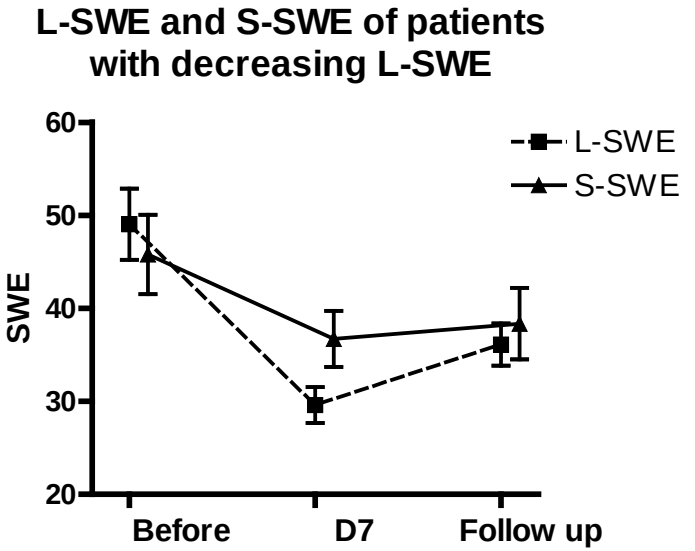


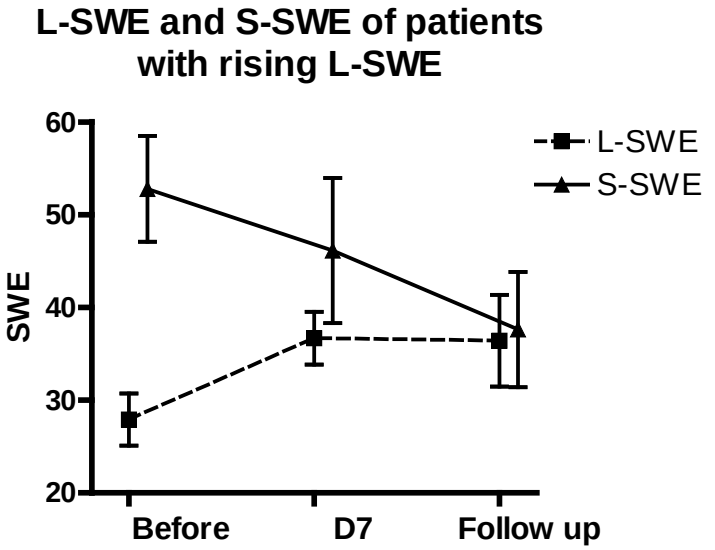
Real-time Shear-Wave

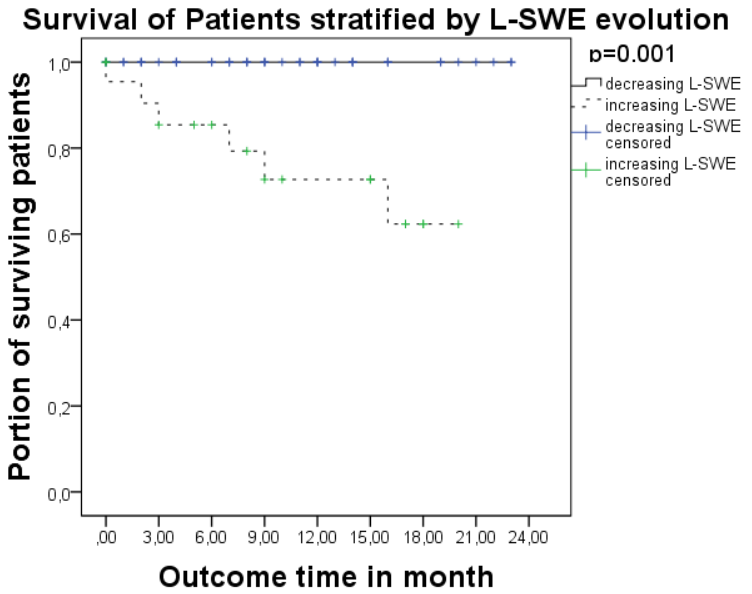


Jansen, [...], Trebicka. In preparation

Clinical Follow up

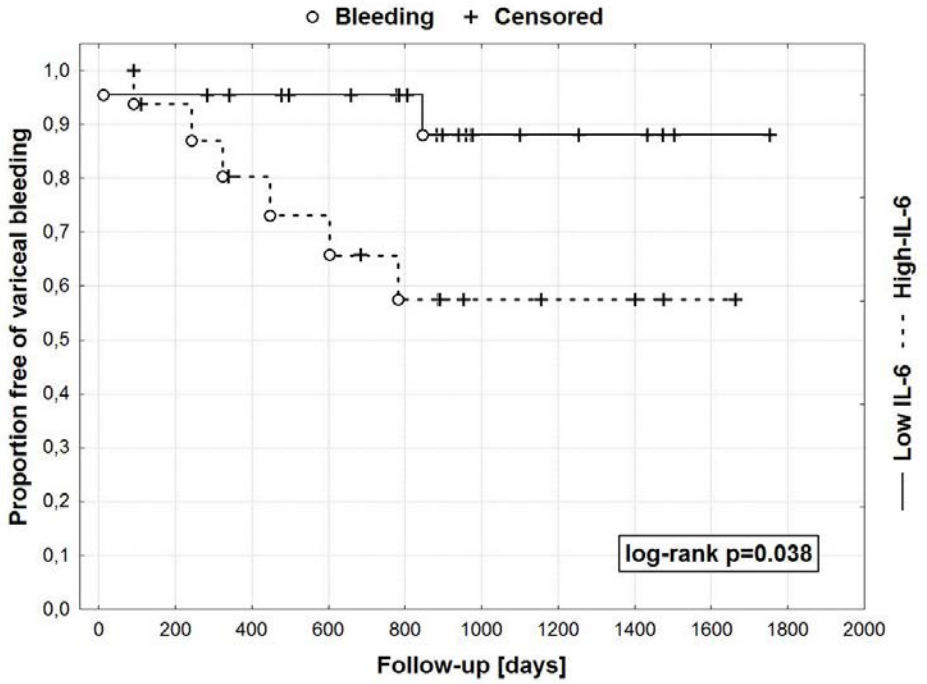




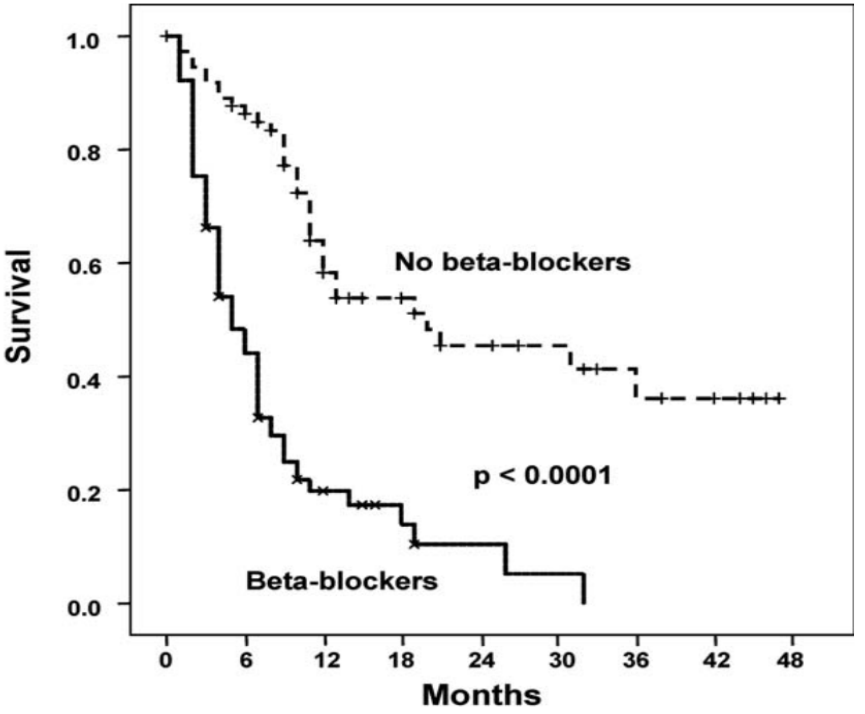


Jansen, [...], Trebicka. In preparation

Bakterielle Translokation führt zu Varizenblutung



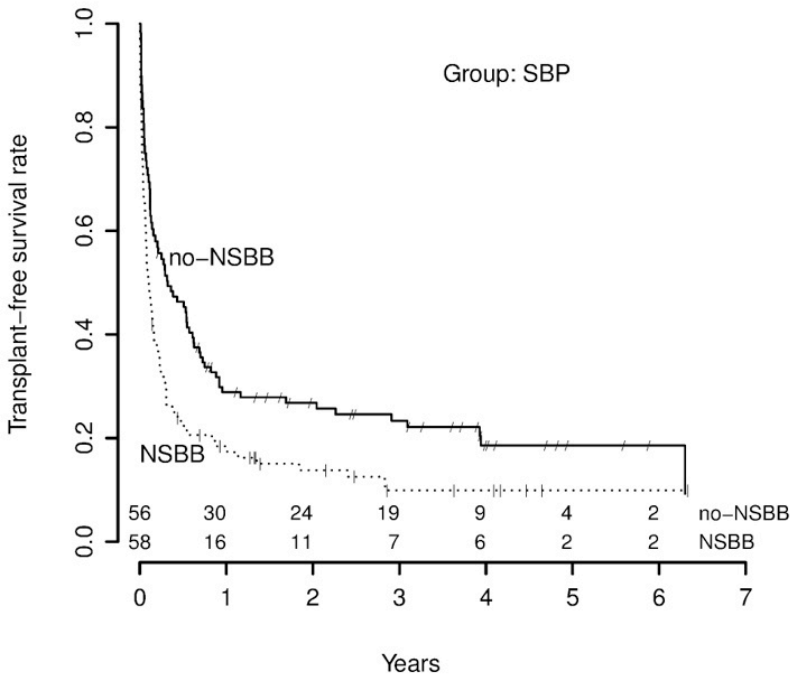
Rezidivprophylaxe mit NSBB

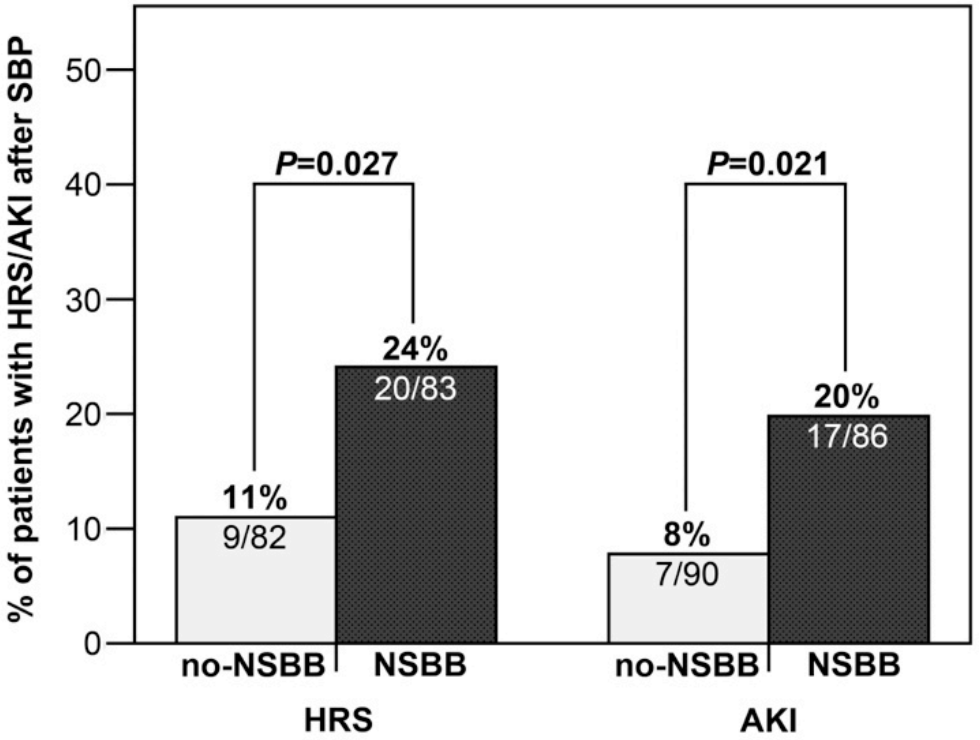


Reiberger et al. J Hepatol 2013

Serste et al, Hepatology 2011

Nach einer SBP Betablocker absetzten





Mandorfer et al, Gastroenterology 2014

Hepatorenales Syndrom

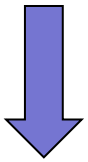
HRS Typ 2
(1,5 < Krea < 2,5 mg/dl)

- **Midodrin (Gutron) 3 X 7.5-12.5 mg/d**
- **+ Albumin 20-40 g/d i.v.**
- **+ Octreotid (Sandostatin) 3 X 200µg**

Therapieversagen oder
HRS Typ 1
(Krea > 2,5 mg/dl)

- **Terlipressin (2-12 mg/d)**
- **+ Albumin 20-40 g/d**

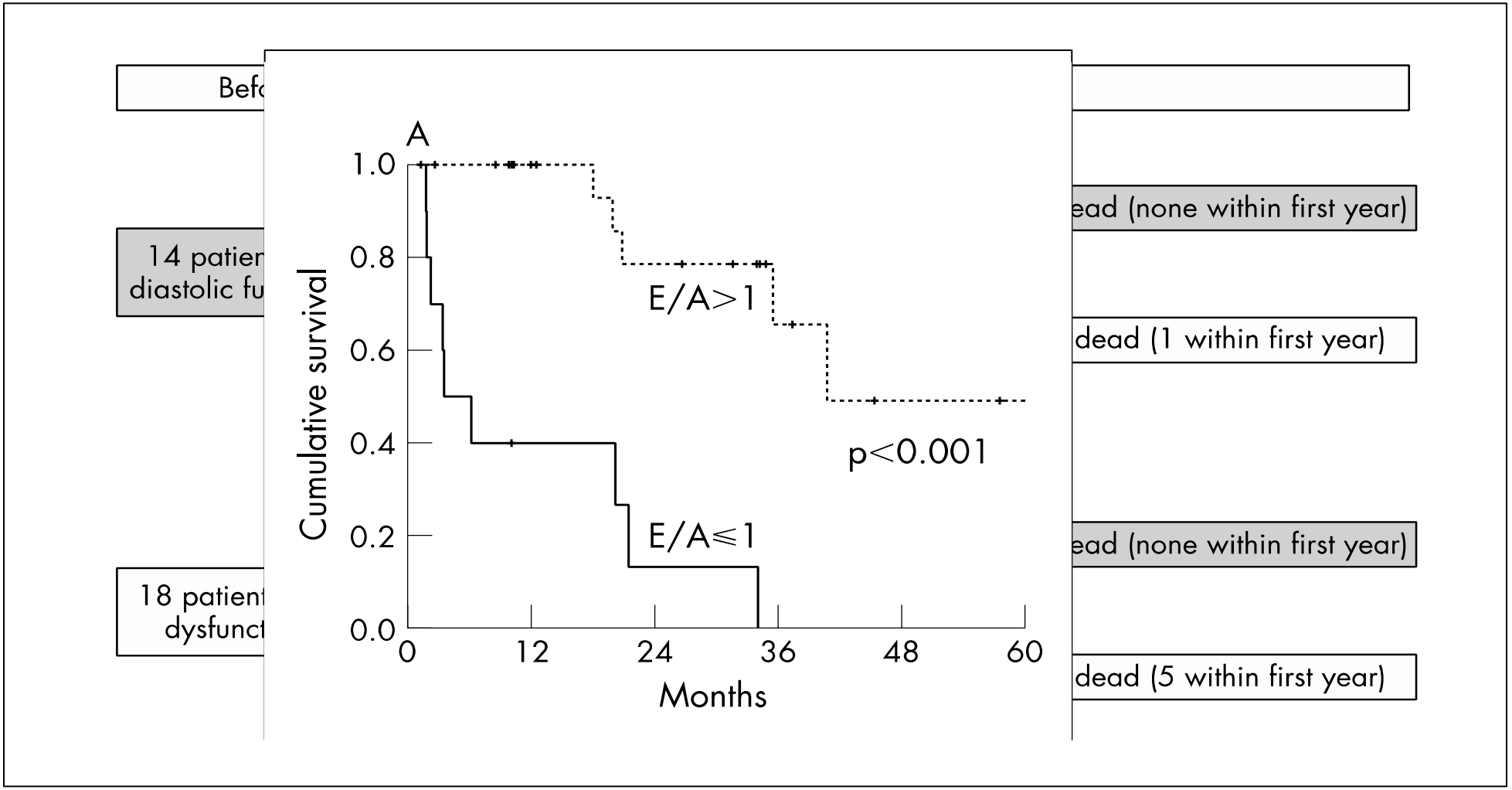
LTX/TIPS-Evaluation



evtl. Midodrin als Erhaltung

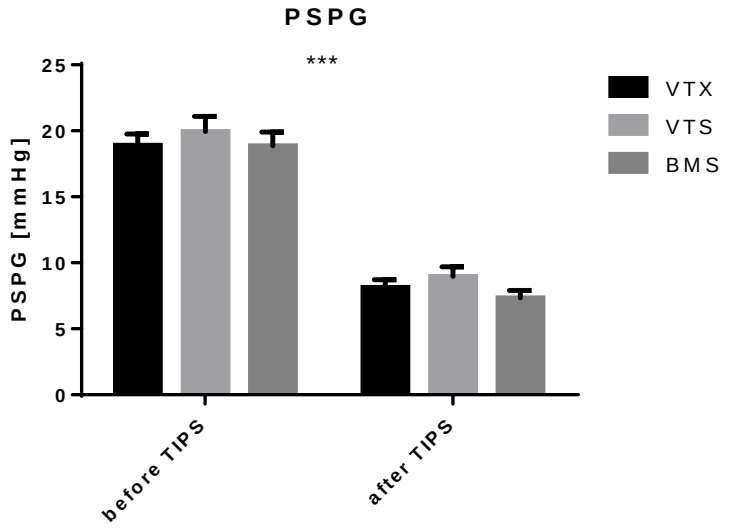
Gerbes et al. Z Gastroenterol 2011

Cardiac function might deteriorate after TIPS

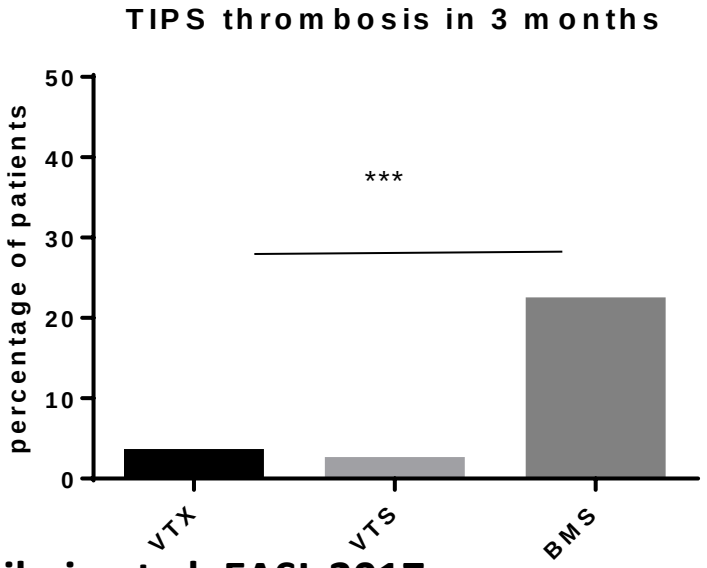


Cazzaniga et al. Gut 2007

Shunt viability



PSPG is not different immediately after TIPS



VTX and VTS much less thrombosis compared to BMS

Praktiknjo et al. EASL 2017

*/#/+ p<0.05; **/##/++ p<0.01; ***/###/+++ p<0.001

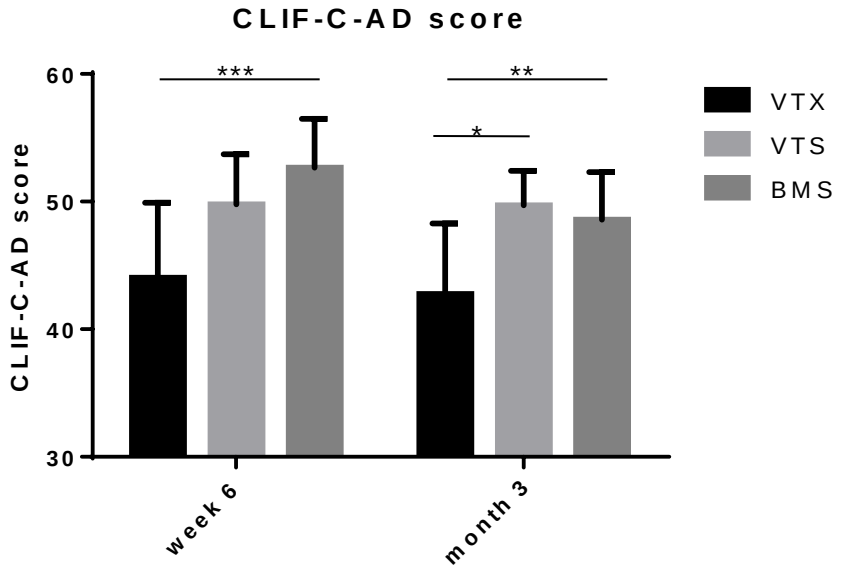
3 months follow up

Parameter	VTX	VTS	BMS
MELD-Na	11(5-22)*##	12(6-27)	15(5-40)
Sodium mmol/l	140(136-151)**##	138(127-145)	136(124-144)
Creatinine mg/dl	0.8(0.5-2.3)*#	0.8(0.6-4.0)	1.1(0.7-3.7)
gGT U/l	108(9-484)*	126(28-2063)	276(36-1696)
Albumin g/l	36.2(21.4-44.7)*	32.9(18.6-43)	30.9(21.8-45.3)
MELD	11(6-20)	11(6-21)	13(7-40)
Child-Pugh-Score	6(5-10)	7(5-11)	7(5-10)
Bilirubin mg/dl	1.5(0.5-4.2)	1.3(0.4-7.9)	1.5(0.3-24.1)
INR	1.1(1-2.5)	1.2(1-1.6)	1.2(1-5.4)
CRP mg/l	**3.9(0.6-107) §**	**6.3(0.9-50.5)**	**7.8(0.9-55.8)**

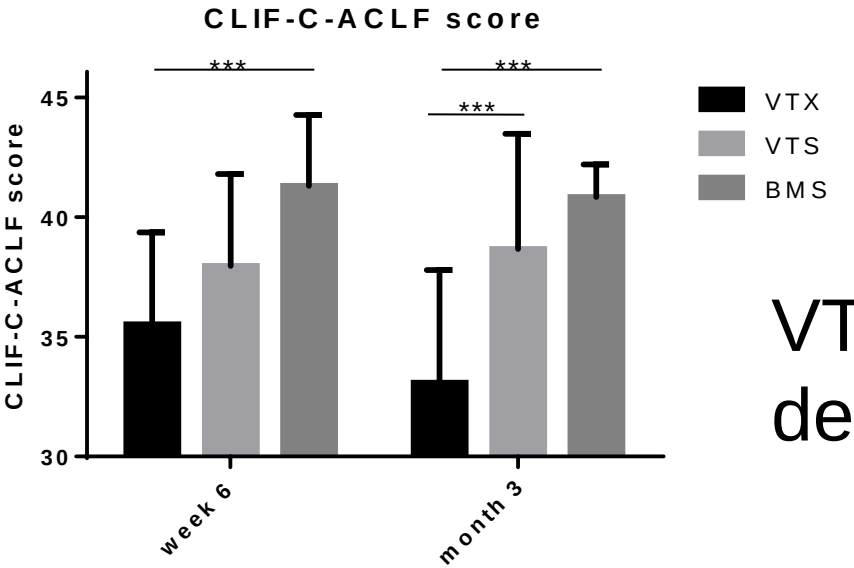
* P < 0.05 all groups
# P<0.05 VTX vs. BMS
§ p<0.05 after 6w

Praktiknjo et al. EASL 2017

AD and ACLF at follow up



VTX group has lower risk of acute decompensation and ACLF



VTX group has lower risk of developing severe ACLF and death

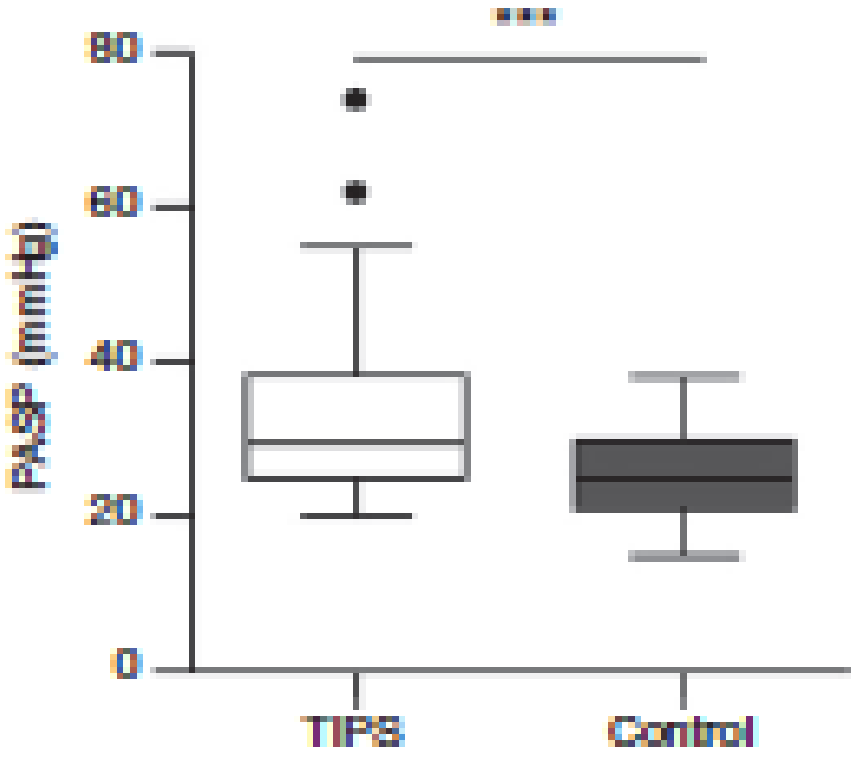
Praktiknjo et al. EASL 2017

Cardiac reserve decreases after TIPS

Variable	Before TIPS	Change from Baseline at Day 1	Change from Baseline at 1 Month
Cardiac output, *L/min*	6.83 (5.31 to 8.16)	+1.61 (+0.74 to +2.49)†	+4.03 (+2.03 to +6.03)†
Right pulmonary vascular volum			+35 (+16 to +53)
Left pulmonary vascular volume			+33 (−1 to +68)
Cardiac and central vascular vol			+260 (+96 to +423)

* Values are expressed as mean (

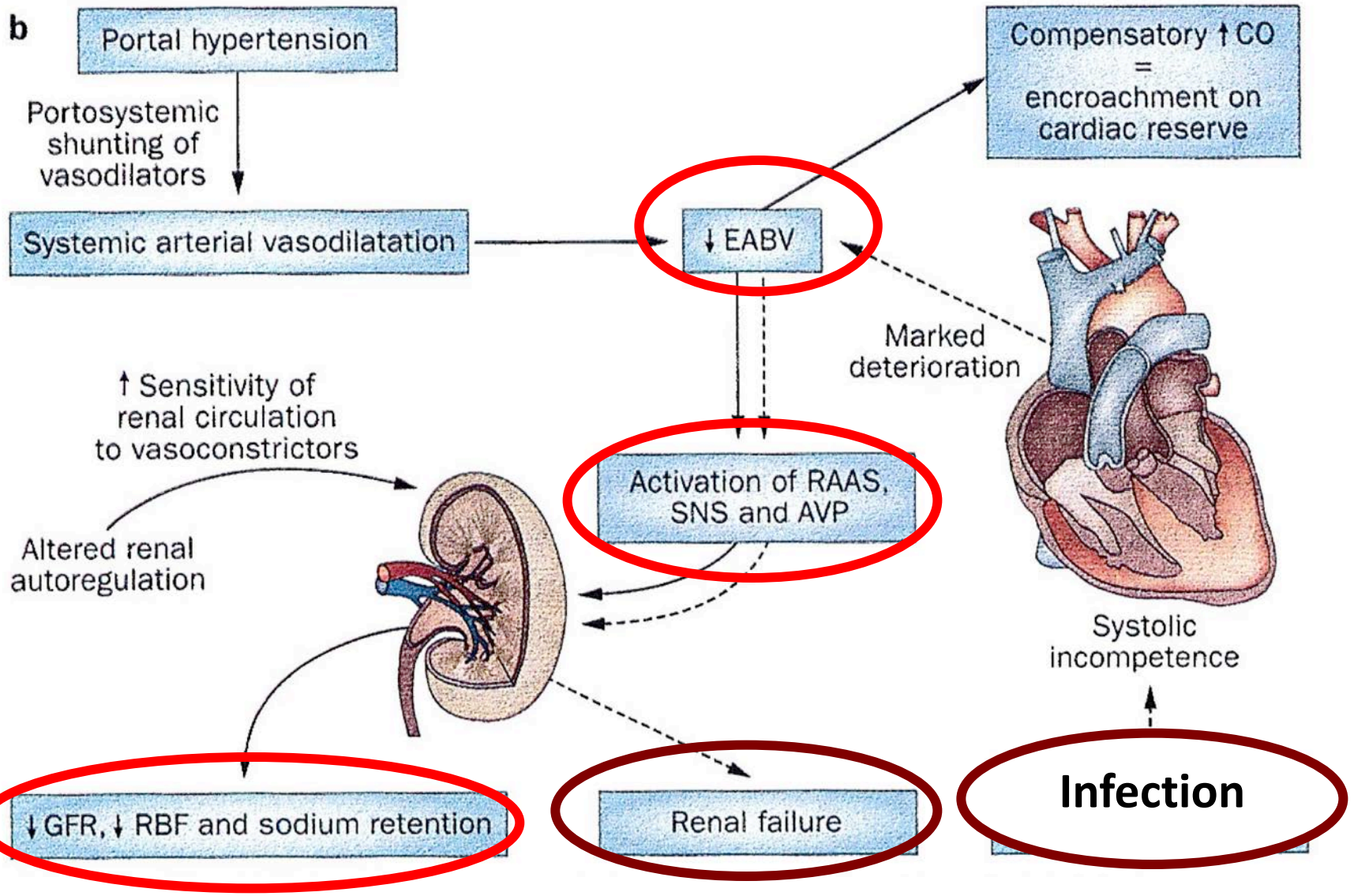
† $P < 0.05$ compared with baselin



Wong et al. Ann Int Med 1995,

Wahnhoff et al. AP&T 2016

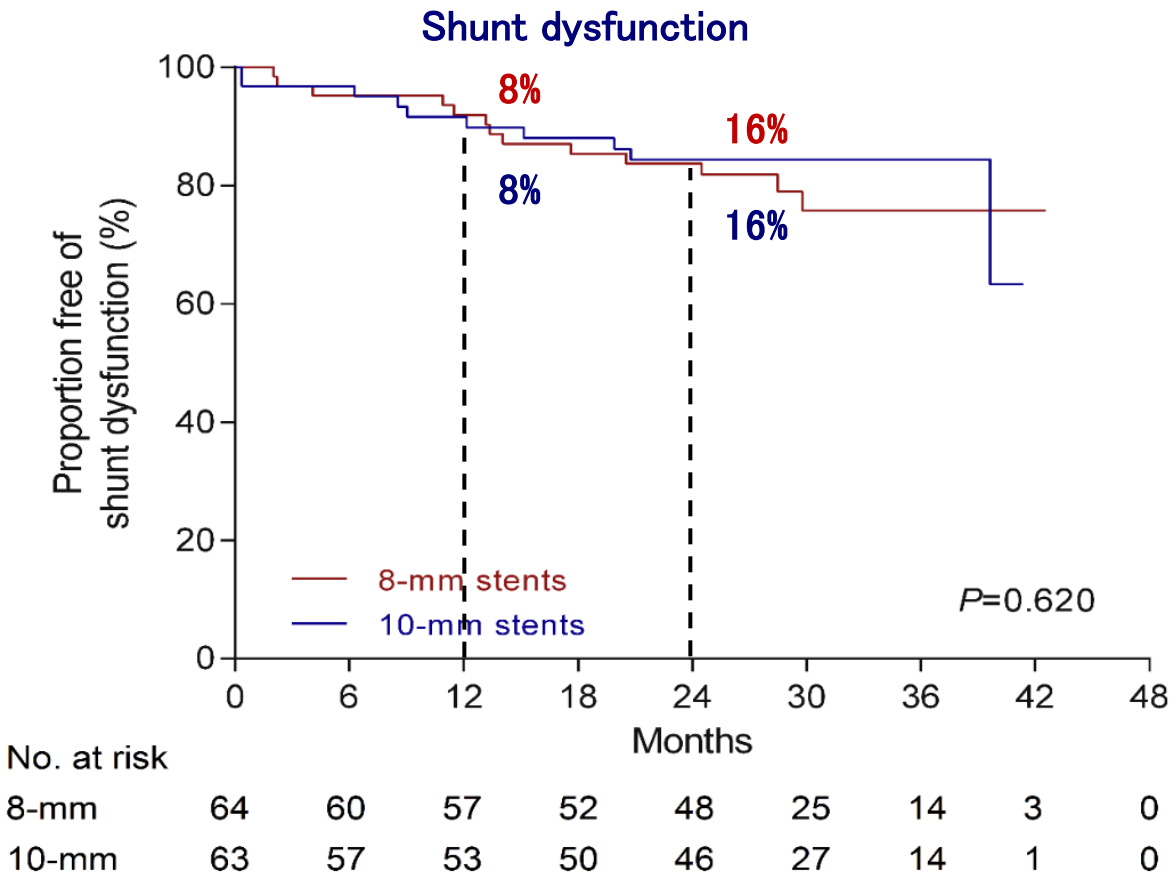
Cardiac reserve is needed!



Wong F, Nat Rev Gastroenterol Hepatol 2012

Controlled expansion Viatorr might save cardiac reserve and prevent further decompensation.

TIPS 8 mm vs 10mm for variceal bleeding



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