Non-Cirrhotic Portal Vein Thrombosis: Perspectives in 2015

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Non-Cirrhotic Portal Vein Thrombosis: Perspectives in 2015

Dominique-Charles Valla

I have no conflicts of interest to disclose

Non-cirrhotic, non-malignant PVT Perspectives in 2015

- Causes and risk factors
- Treatment

Risk factors for deep vein thrombosis

PC, PS, AT deficiency
FV Leiden, FII Leiden
Fibrinogen levels
Factor VIII levels

Overall hypofibrinolysis
PAI-1
TAFI

Antiphospholipid antibodies
Non-O blood groups
Hormonal factors

Immobilization
Malignancy
Surgery
Obesity

Myeloproliferative neoplasms
PNH
Behçet disease
Other autoimmune diseases

Local inflammation

Adapted from Smalberg. Arteriosclr Thromb Vasc Biol 2010

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Adapted from Smalberg. Arteriosclr Thromb Vasc Biol 2010

Central obesity and portal vein thrombosis

PVT N	with causes	idiopathic	*P*
BM			004
W			1
P			
T2 D			NS
Triglyceri		0.6	NS
HDL cholesterol *g/L*	0.5 ± 0.39	0.5 ± 0.3	NS

- Obesity associated overproduction of procoagulant microparticles and increased thrombin generation
- Independent from metabolic syndrome

Campello. Thromb Haemost 2015

Bureau. J Hepatol 2015 (accepted for publication)

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Adapted from Smalberg. Arteriosclr Thromb Vasc Biol 2010

PVT after laparoscopic bariatric surgery

- Incidence of symptomatic cases ~ 1%
  on prophylactic anticoagulation

RR > 100

- Previous deep vein thrombosis in ~ 50%
  Prothrombotic condition in ~ 50%
- Recanalization on anticoagulation in ~ 40%
- Intestinal infarction uncommon ?

Rottenstreich, Surg Obes Related Dis 2014.
Goitein, JAMA/Surg 2013. Salinas, Surg Endosc 2014.

Rajani, APT 2010

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Local inflammation
Idiopathic portal hypertension

Adapted from Smalberg. Arteriosclr Thromb Vasc Biol 2010

Idiopathic portal hypertension
A high risk factor for PVT

Extrahepatic PVT (5 yrs) 18-50%

Blood stasis in portal vein?

Underlying prothrombotic conditions?

Primary alterations of portal venous wall?

Hillaire, Gut 2005. Matsutani, Liver Int 2005. Cazals-Hatem J Hepatol 2011. Schouten APT 2012. Siramolpiwat, Hepatology 2014

Causes and risk factors for PVT – 2015

- The impact of recognizing causes
- How to improve the recognition of causes ?

The impact of recognizing the causes for PVT

- An explanation for the location
- A determinant of outcome
- An indication for cause-specific therapy

Non-cirrhotic, non-malignant PVT

Risk factors for venous thrombosis

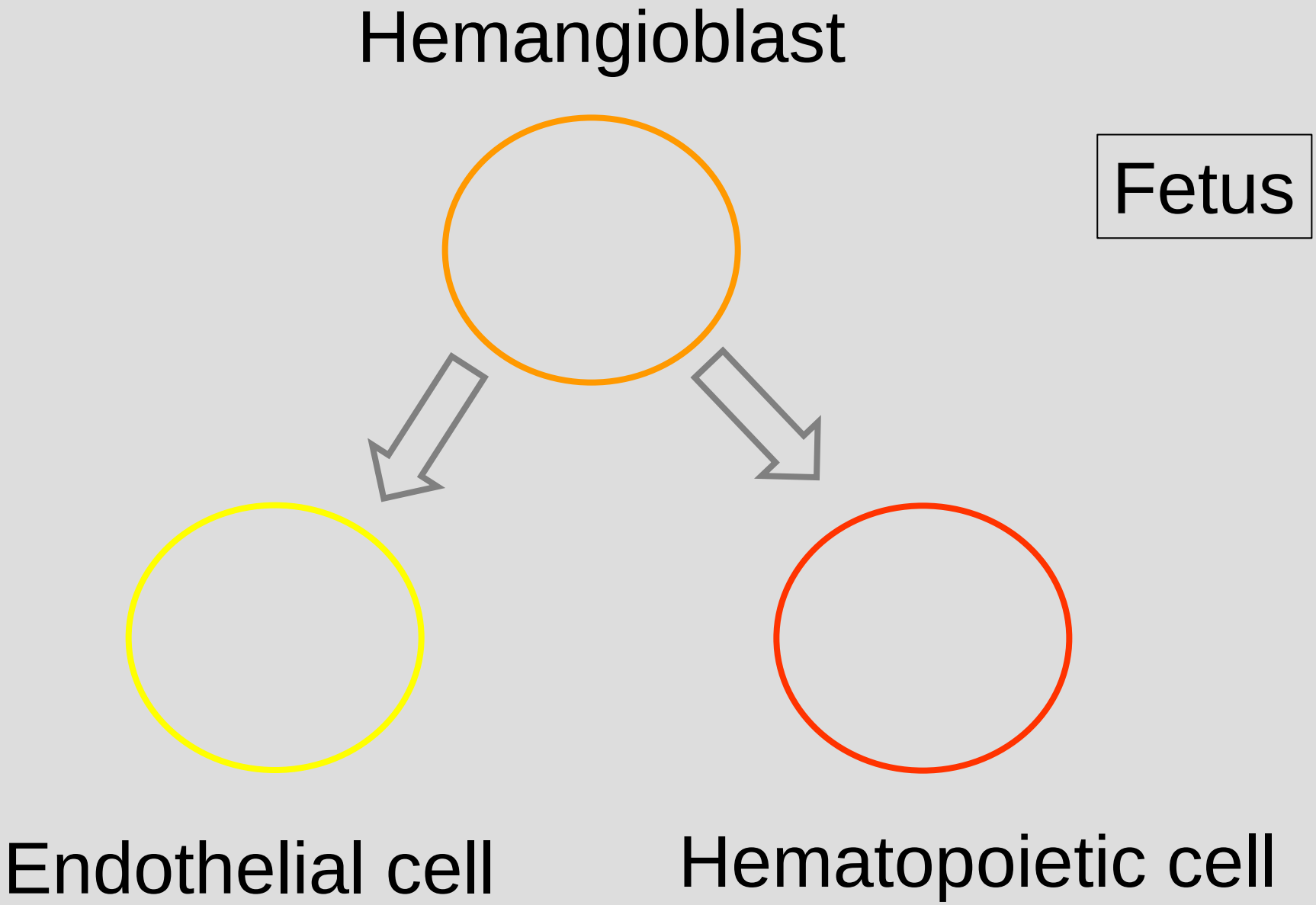
- At least one 67%
- Multiple 18%
- Local factor 21%
- No local factor 79%

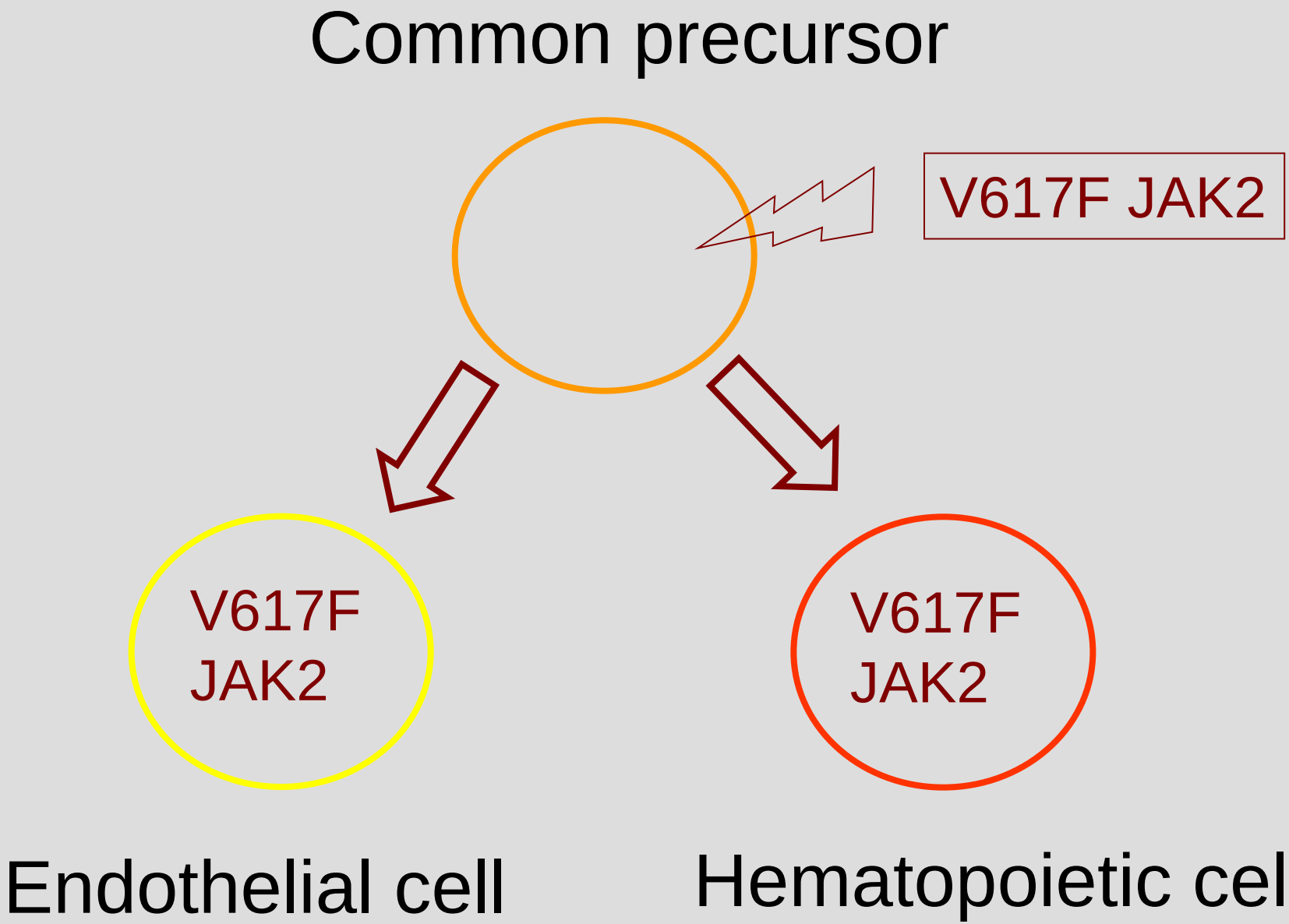
Plessier. Hepatology 2010. N = 102

Site specificity for thrombosis in MPN

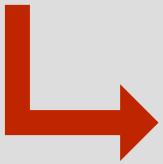
	V617F *JAK2*
Hepatic vein thrombosis	35-50%
Portal vein thrombosis	20-35%
Extra-splanchnic thrombosis	2%
General population	0.2%

Mercier, NEJM 2007. Pardanani, Leukemia 2007. Plessier, Hepatology 2009. Kiladjian, Blood 2008, Dentali, Blood 2009. Smalberg, Blood 2012


Hemangioblast
Fetus
Endothelial cell
Hematopoietic cell


Common precursor
V617F JAK2
V617F
JAK2
V617F
JAK2
Endothelial cell
Hematopoietic cell

MPN/G-JAK2^{V617F} 42/31

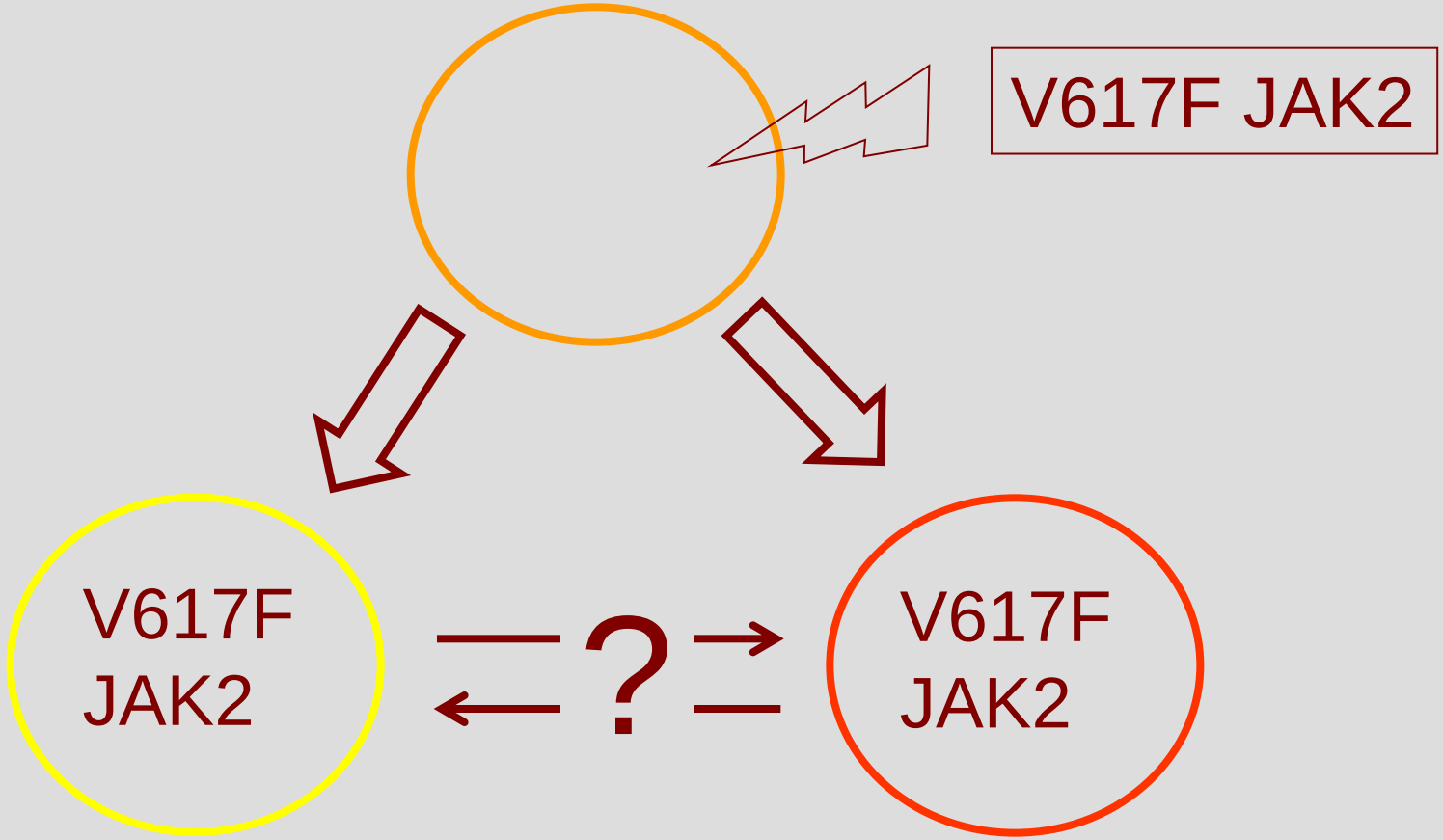


E-CFCs/G-JAK2^{V617F} 22/17

E-CFCs-JAK2^{V617F} 5

Teofili, Blood 2011

Common precursor

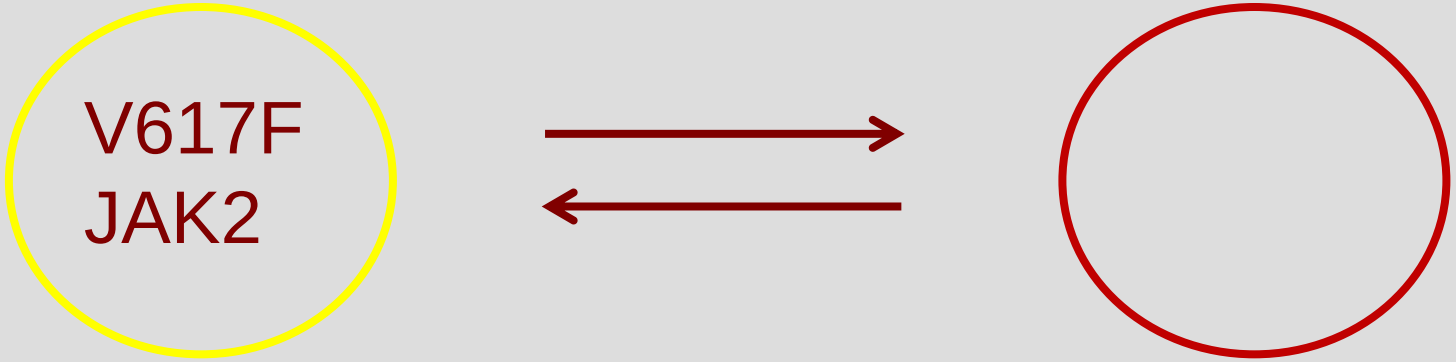


Endothelial cell

Hematopoietic cell

Circulating endothelial cell progenitors

Mononuclear cells



- Increased activation of JAK/STAT pathways
- Increased proficiency to adhere to mononuclear cells
- High granulocyte counts, high V617F-JAK2 load

Teofili, Blood 2011

MPN/G-JAK2^{V617F} 42/31

E-CFCs/G-JAK2^{V617F} 22/17

E-CFCs-JAK2^{V617F} 5

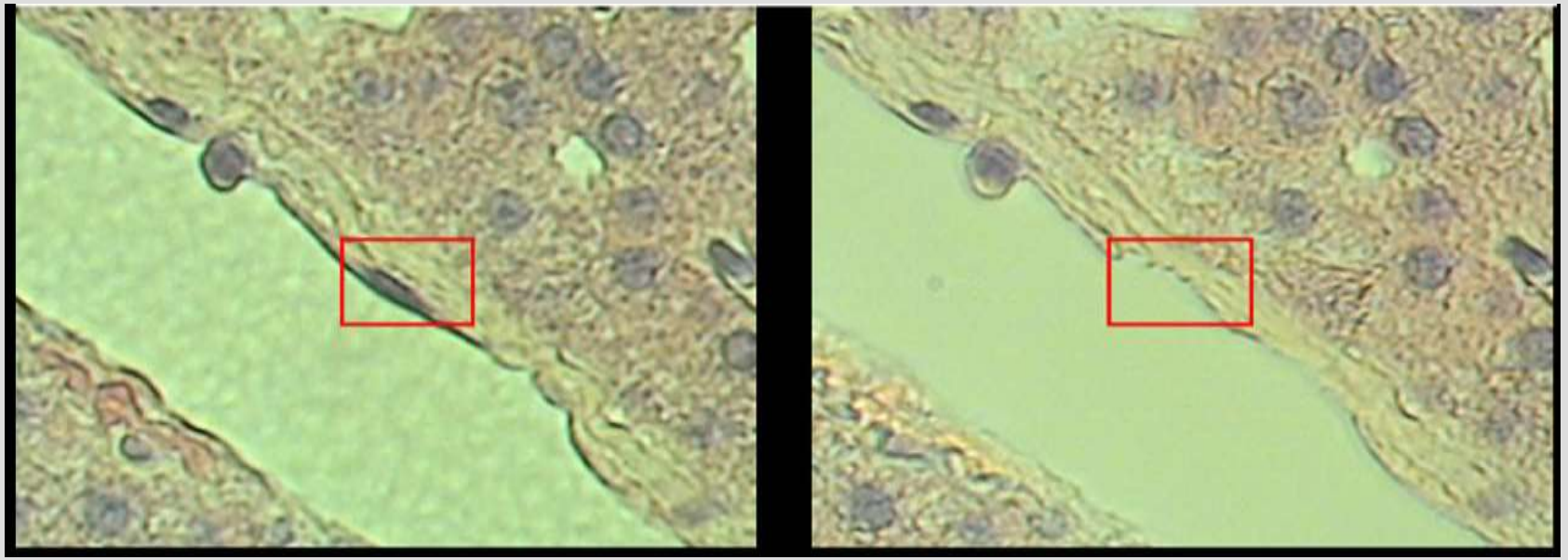
Thrombosis 5

BCS	1
PVT	1
IPH	1

Teofili, Blood 2011

V617F JAK2 mutation and liver endothelium

- Laser capture microdissection
  HV endothelial cells, hepatocytes, blood cells.
- Nested PCR for *JAK2*^{V617F}

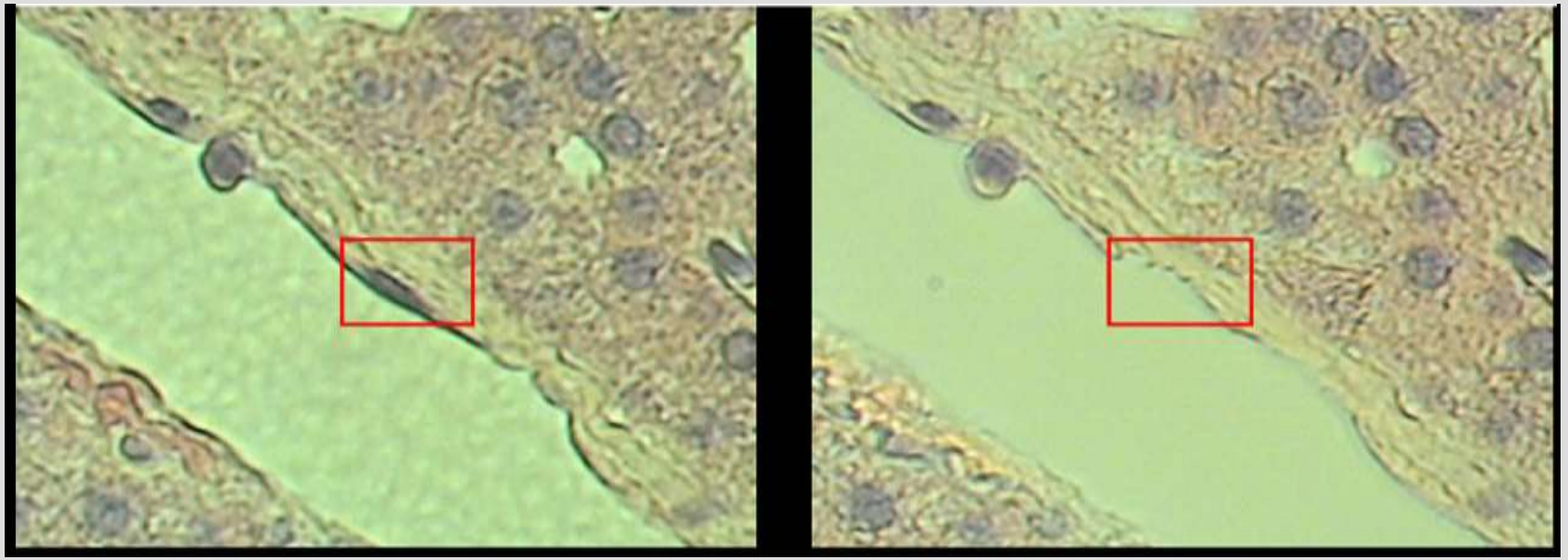


Sozer. Blood 2009

V617F JAK2 mutation and liver endothelium

2 of 3 BCS patients with *JAK2*^{V617F} Polycythemia Vera

0 of 2 OPV controls without Polycythemia Vera



Sozer. Blood 2009

The impact of recognizing the causes for PVT

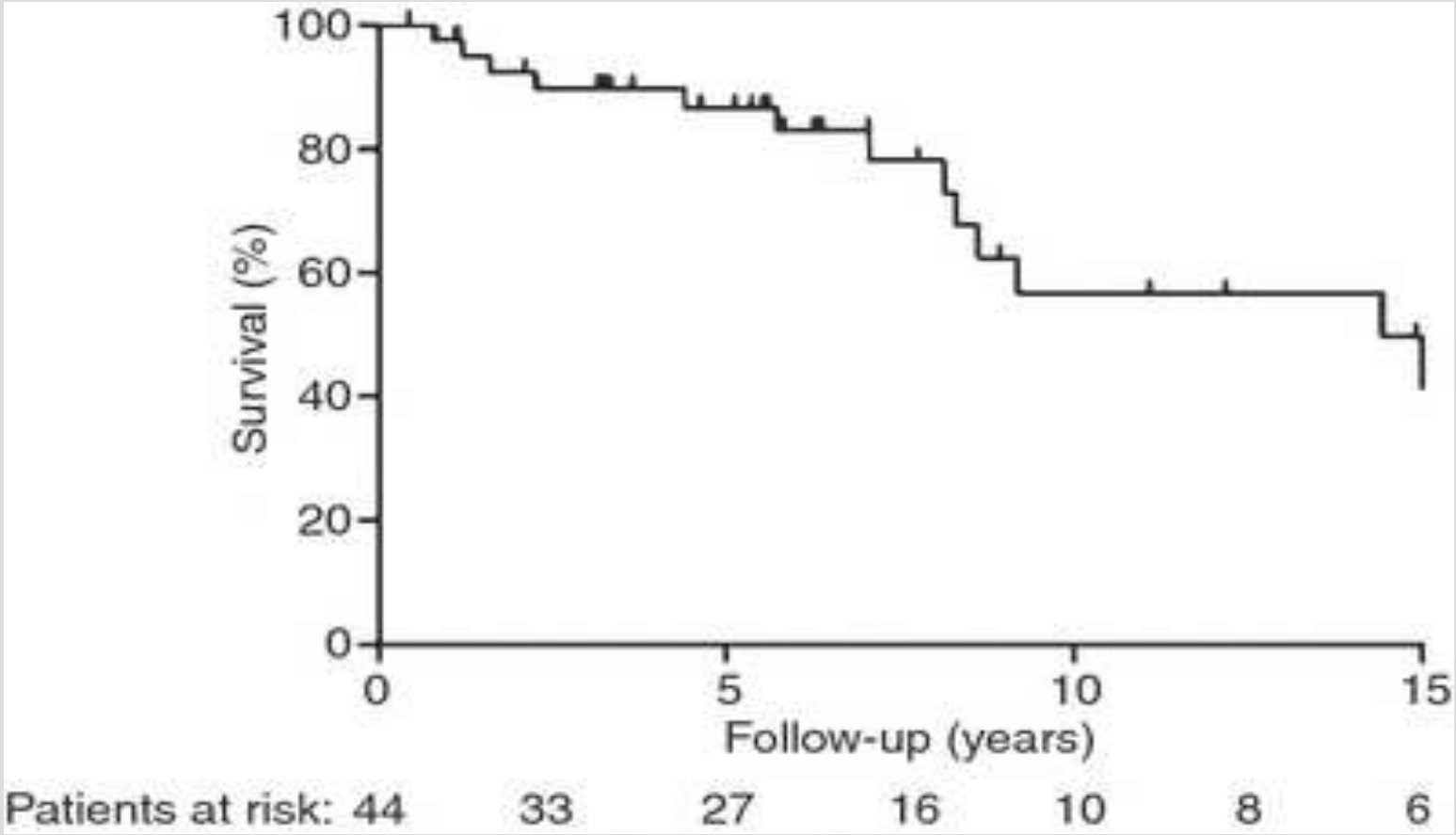
- An explanation for the location
- A determinant of outcome
- An indication for cause-specific therapy

Causes of death in PVT patients

	PVT	PVT/MPN
Number	120	44
F-u - *months*	66	70
Non liver-related - *N*	29	17
MPN - *N*	6	8
Bleeding - *N*	5	0
Thrombosis - *N*	3	3
Other/Unknown - *N*	15	6

Spaander, JTH 2011a. Spaander, JTH 2011b

Portal vein thrombosis and MPN



Mean age at diagnosis 48 years – Hoekstra, JTH 2011

The impact of recognizing the causes for PVT

- An explanation for the location
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Splanchnic vein thrombosis and MPN
Impact of treatment for MPN

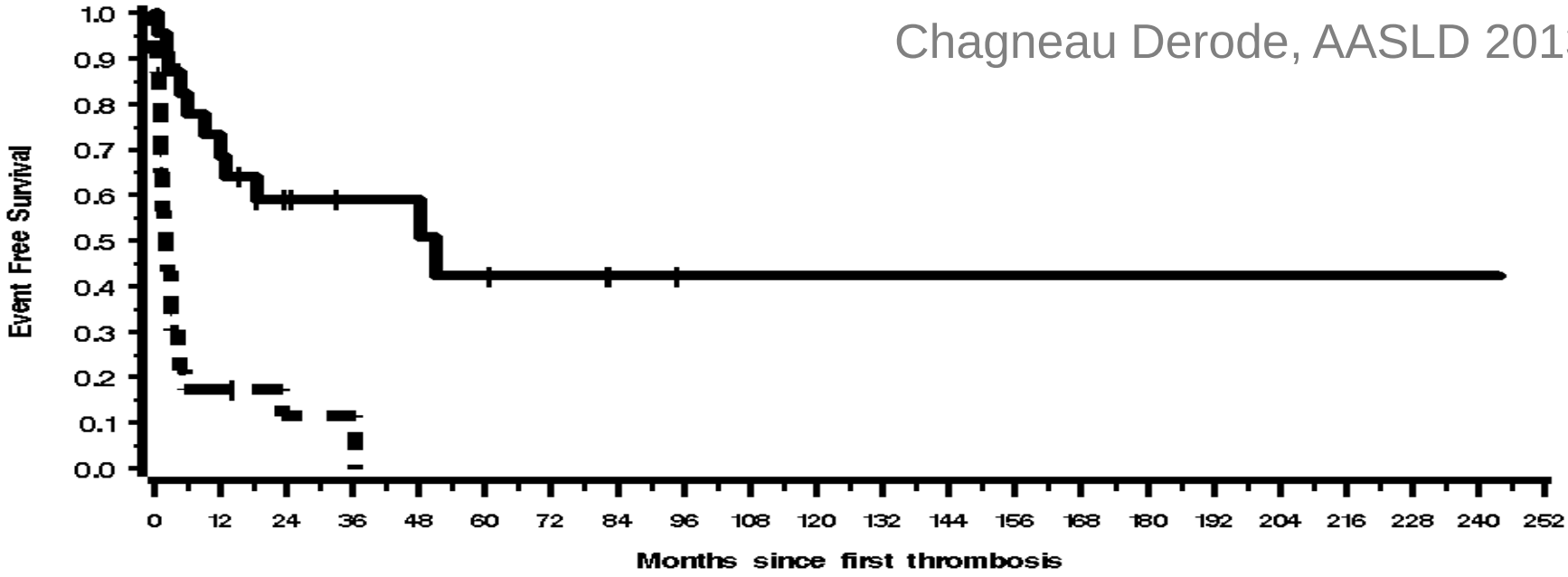
Budd-Chiari syndrome (N = 46)	Portal vein thrombosis (N = 63)
↓	↓
Major events (N =33)	Major events (N =26)

Only independent factor: absence of cytoreductive therapy after SVT diagnosis

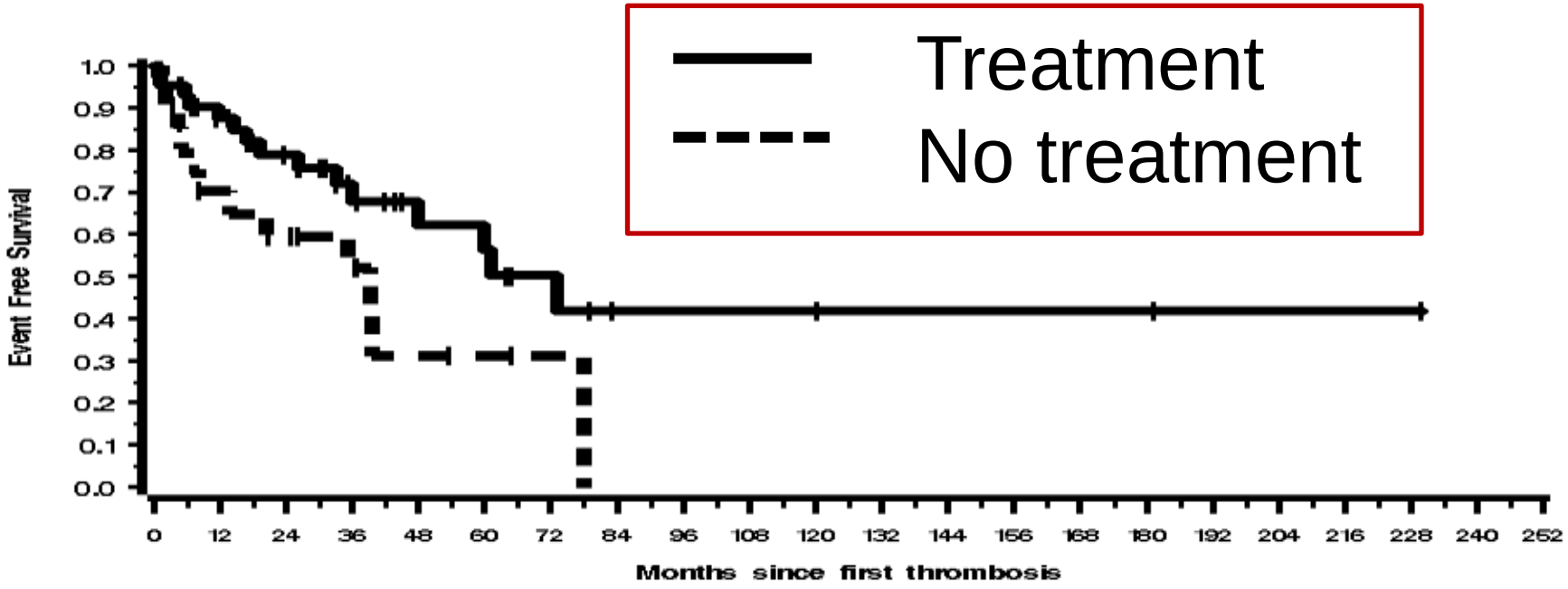
Major vascular or liver-related events:
thrombosis, hemorrhage, refractory ascites, hepatorenal syndrome, encephalopathy, death or liver transplantation

Chagneau Derode, AASLD 2013

BCS



PVT



The impact of recognizing the causes for PVT

- Causes and risk factors may explain the location of thrombosis.
- Underlying causal disease is a major determinant of long term outcome.
- Cause-specific therapy could impact overall outcome.

Causes and risk factors for PVT – 2015

- The impact of recognizing causes
- How to improve the recognition of causes ?

Risk factors for portal vein thrombosis

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Non-O blood groups
~~Hormonal factors~~

Immobilization
Malignancy
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Myeloproliferative neoplasms
~~PNH~~
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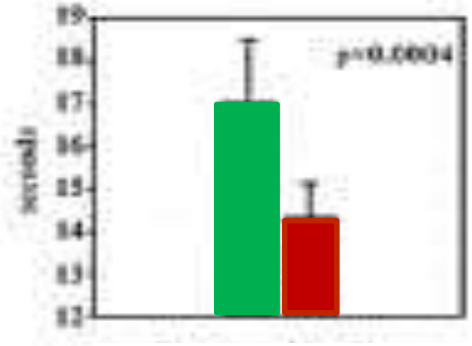
~~Other autoimmune diseases~~

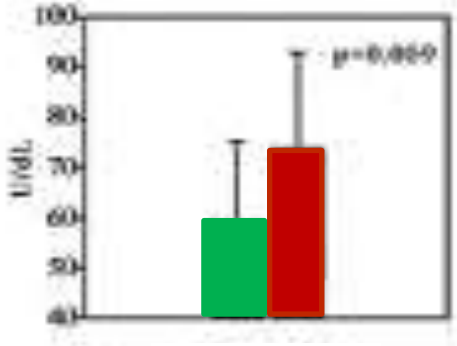
Local inflammation
Idiopathic portal hypertension

Adapted from Smalberg. Arteriosclr Thromb Vasc Biol 2010

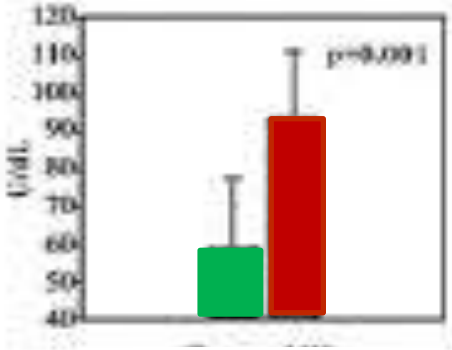
Coagulation inhibitors and PVT



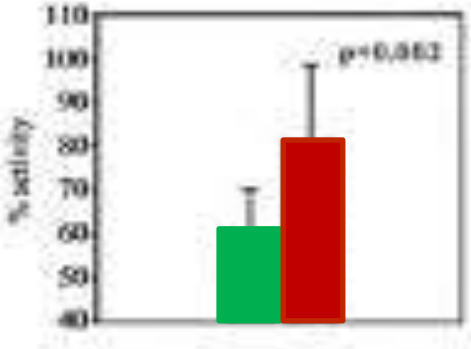
Prothrombin Time



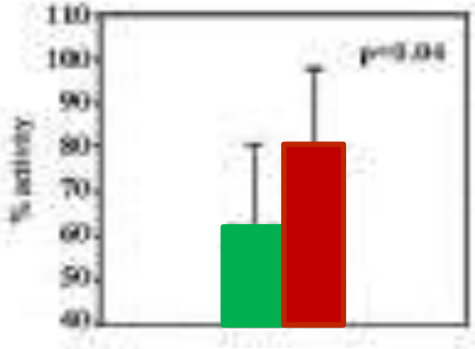
Factor V



Factor VII



Protein C



Protein S

Prior to Rex shunt

1 yr after Rex shunt

Mack, J Pediatr 2003

PVT patients with protein C deficiency (n=18)

PROC	PC %	Other	History
F118V	59		low PC (father & daughter)
N389K/type II	38		No
R194 C	57		No
R40C	58	MPN	Past DVT
R57W	33	APLS	No

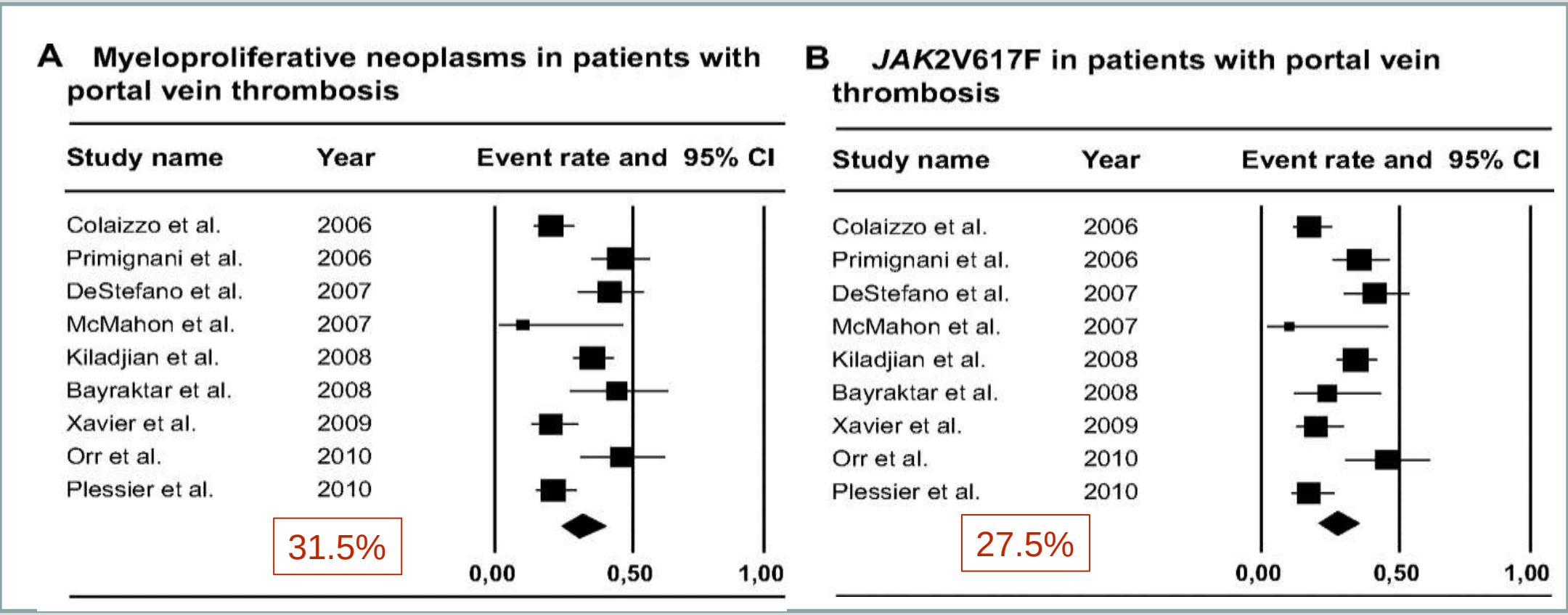
Plessier, EASL 2014. 150 PVT patients

PVT patients with protein S deficiency (n=17)

PROS1	PS %	Other	History
R40L	43	APLS	No
N258S	19		PVT (brother)
V510M/type II	43	HIV	No
R101 C	28		No

Plessier, EASL 2014. 150 PVT patients

Myeloproliferative neoplasms and portal vein thrombosis

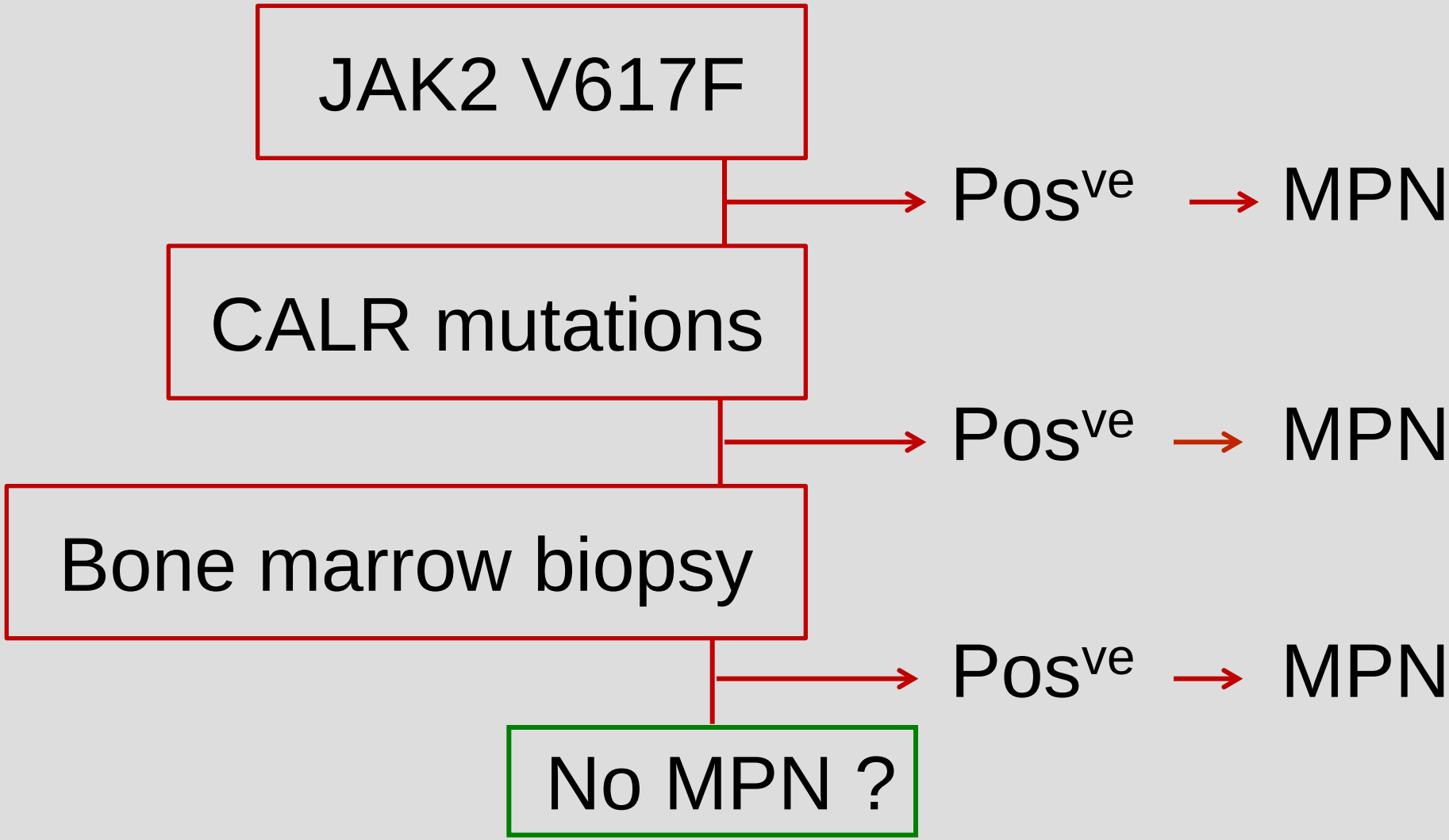


Smalberg. Blood 2012

Other MPN mutations in splanchnic vein thromboses

JAK2 exon 12	0/268
MPL515	3/305
CALR	8/361

Smalberg. Blood 2012. Turon J Hepatol 2014.
Plompen Hematologica 2015. Rautou J EASL ILC 2015


JAK2 V617F
Pos^ve → MPN
CALR mutations
Pos^ve → MPN
Bone marrow biopsy
Pos^ve → MPN
No MPN ?

Causes and risk factors for PVT – 2015

- The impact of recognizing causes
- How to improve recognition ?

High throughput biology
Genetics
Metabolomics

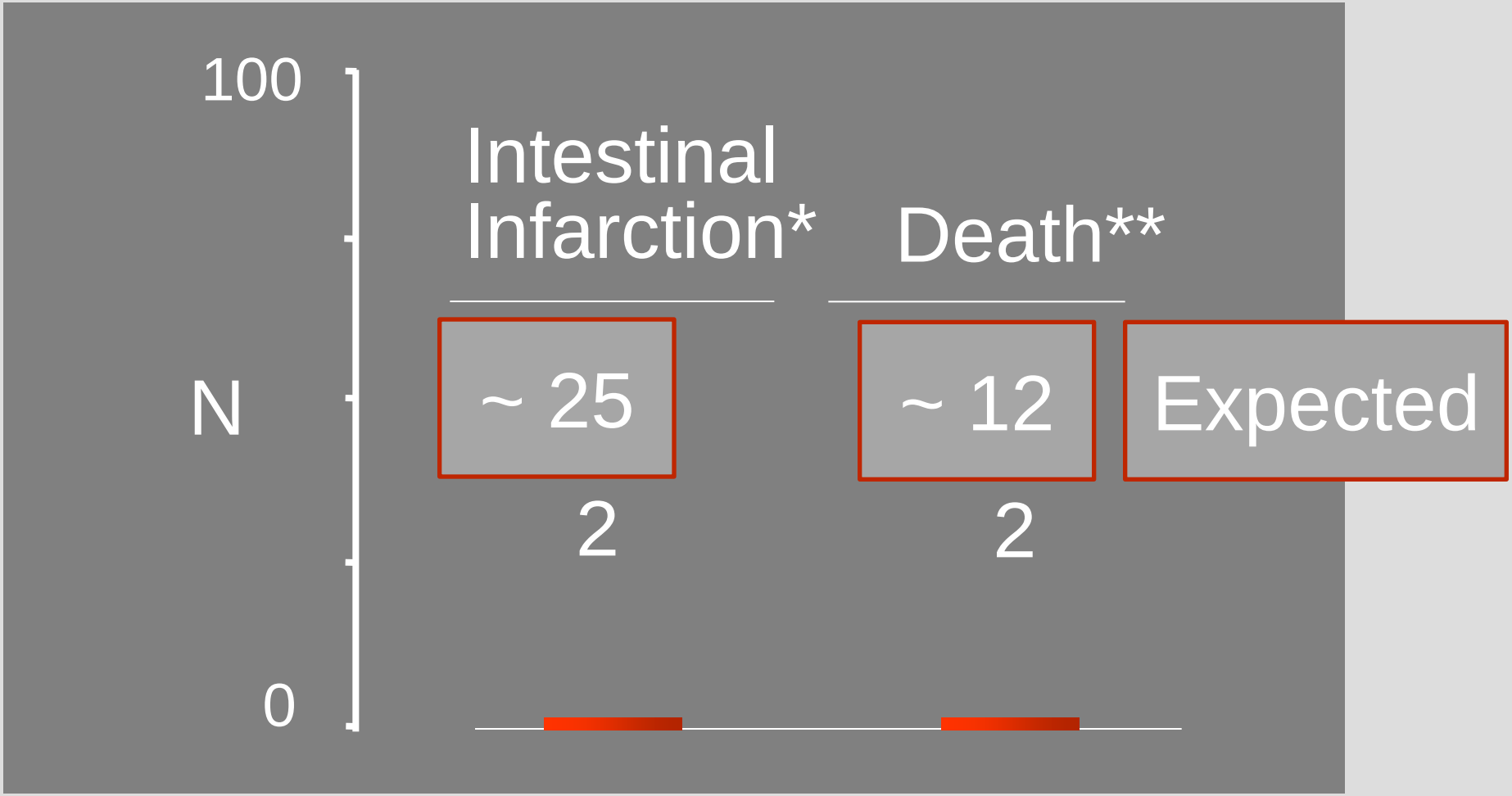
Non-cirrhotic, non-malignant PVT Perspectives in 2015

- Causes and risk factors
- Treatment

Non-cirrhotic, non-malignant PVT Treatment

- Cure/control underlying disorders
- Prevent potentially lethal complications
    - Intestinal infarction
    - Recurrent thrombosis
    - Portal hypertension

Recent PVT. Anticoagulation in 95 Patients



*Limited intestinal resection. Both survived. **Malignancy 1. Sepsis 1

Plessier. Hepatology 2010. Hmoud, J Clin Exp Hepatol 2014

Non-cirrhotic, non-malignant PVT Treatment

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- Prevent potentially lethal complications
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  - Portal hypertension

PVT – Anticoagulation and thrombosis

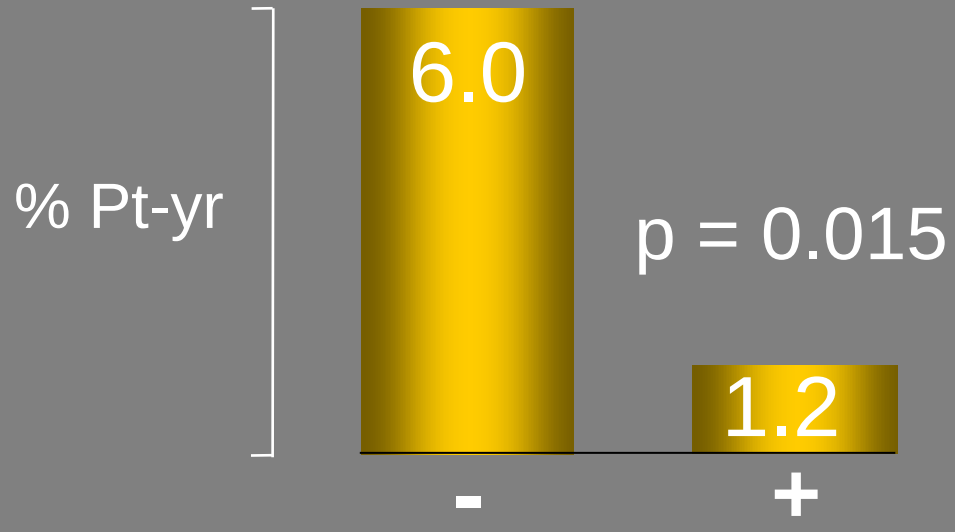
3

HR 0.2, p = 0.1

Spaander, JTH 2013

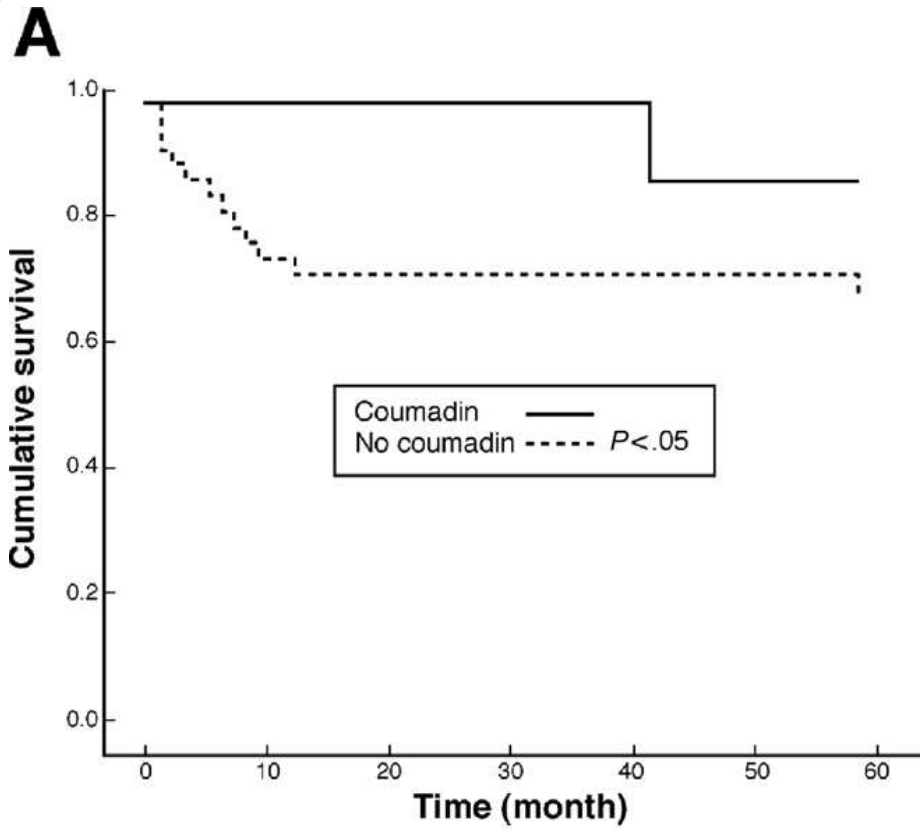
1

New thrombosis



Condat, Gastroenterology 2001

2



Orr, CGH 2007

PVT : Prevention of recurrent thrombosis

Unresolved issues

- Benefit/risk of permanent anticoagulation therapy?
- Which criteria for a precision medicine ?
  - Status of portal venous system
  - Causes and risk factors
  - Personal or familial history
  - Biology

Non-cirrhotic, non-malignant PVT Treatment

- Cure/control underlying disorders
- Prevent potentially lethal complications
  - Intestinal infarction
  - Recurrent thrombosis
  - Portal hypertension

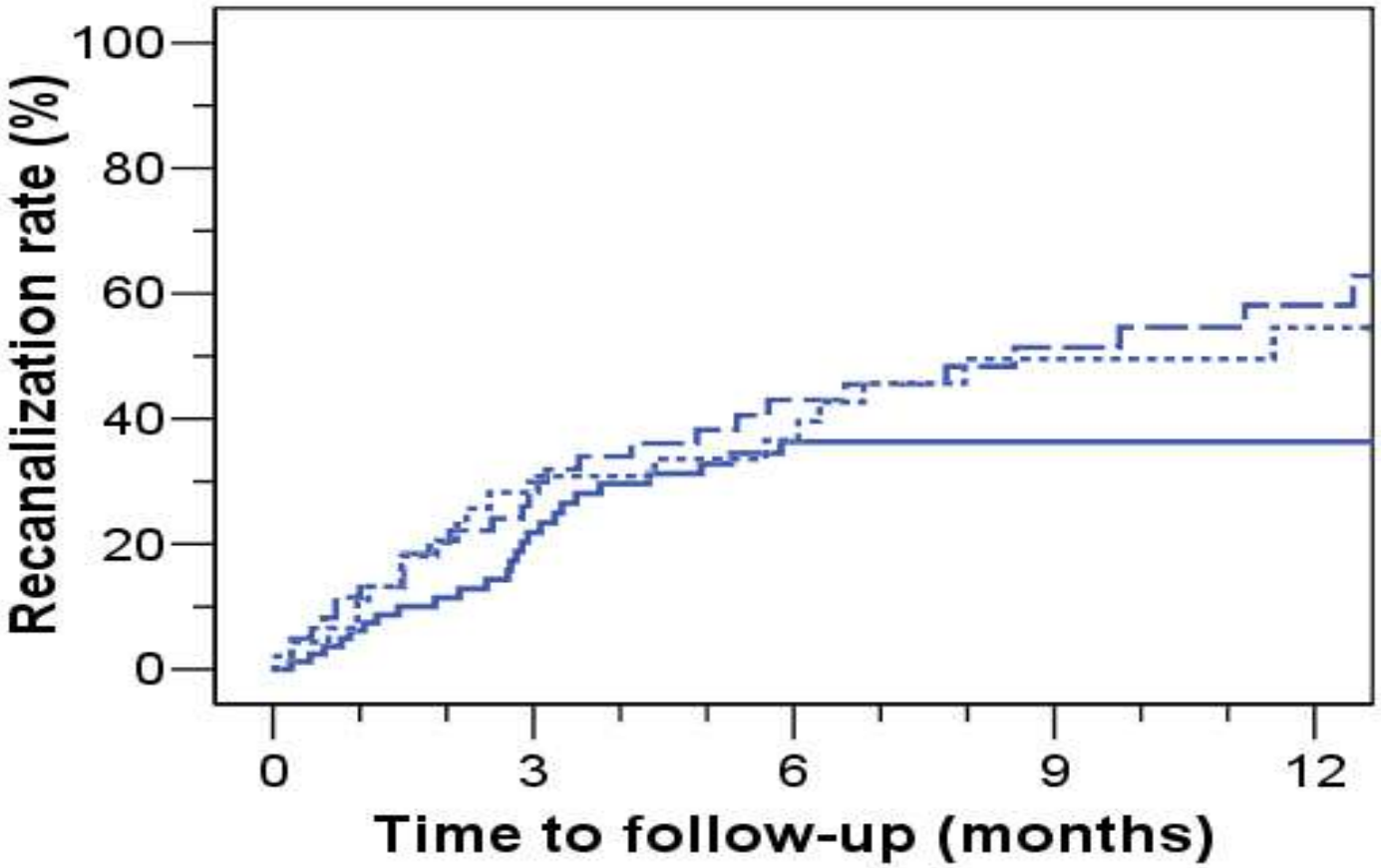
Anticoagulation for recent (acute) PVT

Anticoagulation		No anticoagulation
Complete recanalization	Partial recanalization	Recanalization
38.3%	14.0%	< 17%

Hall. World J Surg 2011

Recent PVT: EN-Vie Cohort

EN-Vie Cohort: 95 anticoagulated patients



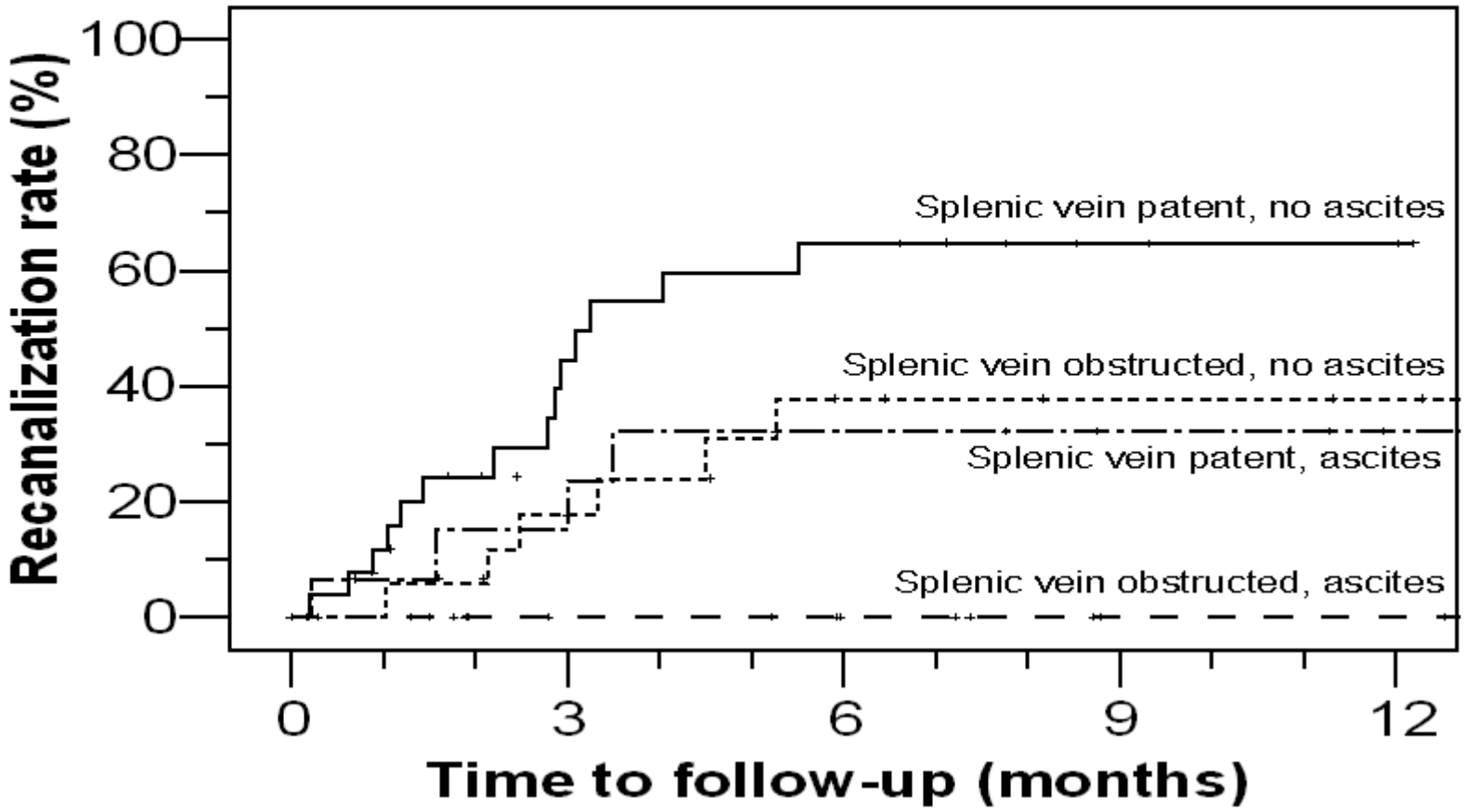
Sup. mesenteric
Splenic
Portal

Plessier. Hepatology 2011.

Hall. Hepatogastroenterol 2013

Recent PVT: EN-Vie Cohort

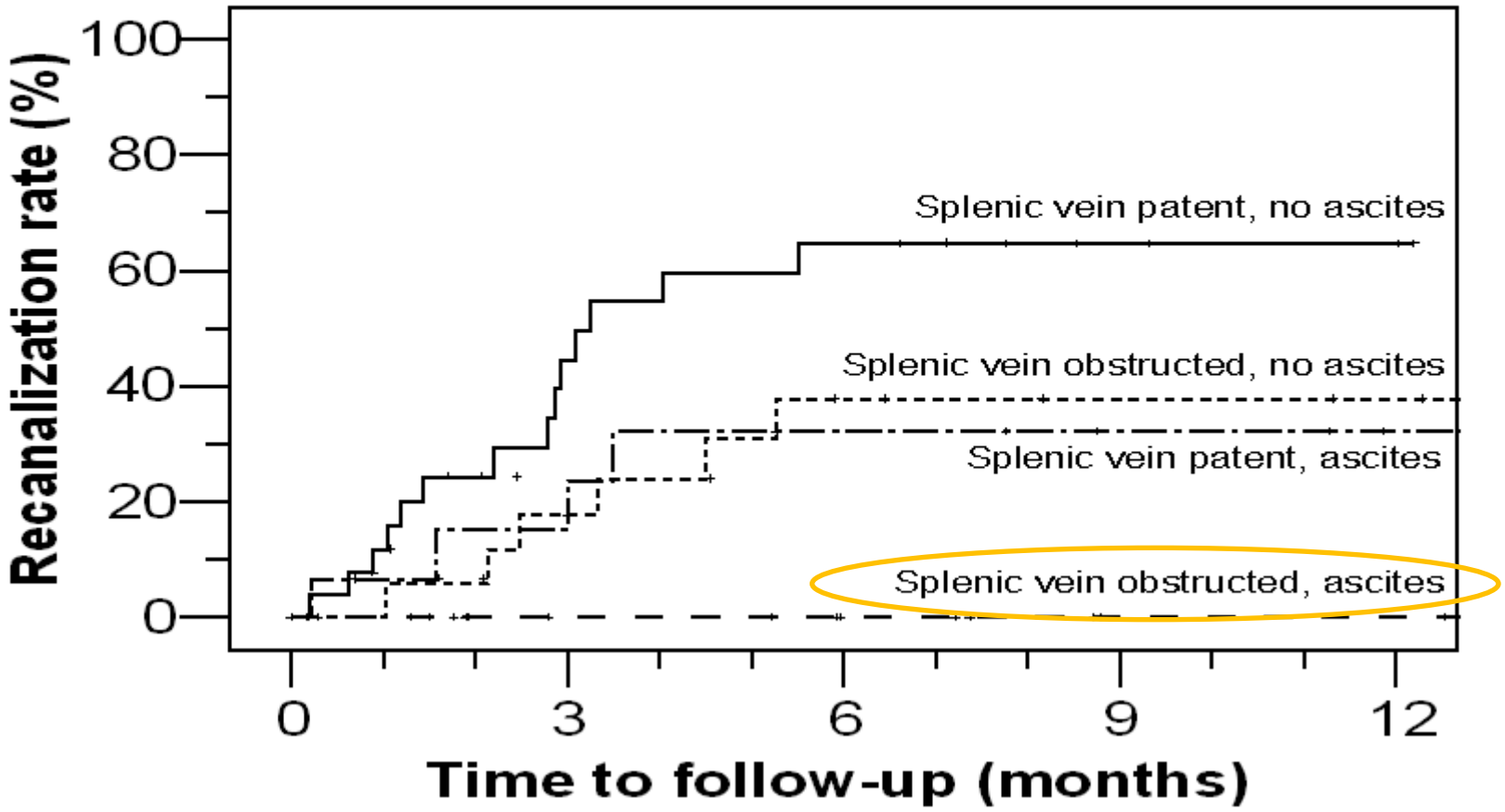
Predictive Factors for Portal Vein Recanalization



Plessier. Hepatology 2010.

Recent PVT: EN-Vie Cohort

Alternative therapy ?



Recent PVT: Alternatives to anticoagulation

Reports of selected case or small case-series

- Pharmacological thrombolysis
- Mechanical/pharmacological thrombolysis
- Transjugular or transcapsular approach
- With or without portosystemic shunting

Hall, World J Surg 2011. Hmoud, J Clin Exp Hepatol 2014

Treatment for recent PVT

	Complete recanalization	Partial recanalization
Anticoagulation	38.3%	14.0%
Thrombolysis	40.8%	45.1

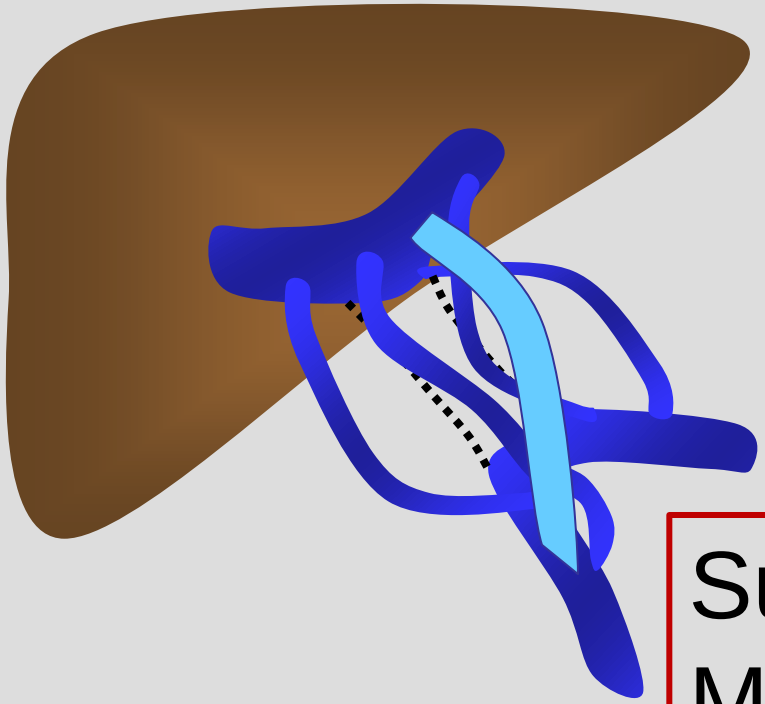
Major complications in > 60% of patients with pharmacological thrombolysis

Prophylaxis for bleeding in adults with PVT

- Beta blockers
- Endoscopic therapy
- Portosystemic shunting/Devascularization
- Recanalization/Mesentericoportal bypass

Sarin Gastroenterology 2010. Plessier J Hepatol 2012. Khanna J Hepatol 2014

Mesenterico-left portal vein bypass (Meso-Rex)



Successfull bypass	60-100%
Mortality	0%
Encephalopathy	0%
Bleeding	0%

Reviewed in Khanna and Sarin J Hepatol 2014. Guérin, Br J Surg 2013

PVT - Severity of Bleeding

No impact of anticoagulation therapy on

Hemoglobin (g/dL)

Length of stay (days)

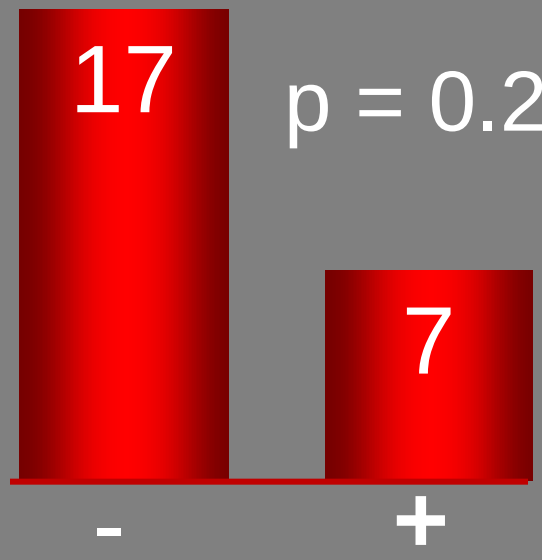
Transfusion (N units)

Condat, Gastroenterology 2001. Spaander, JTH 2013. Christol, ILC 2012

PVT – Anticoagulation and bleeding

1

Bleeding



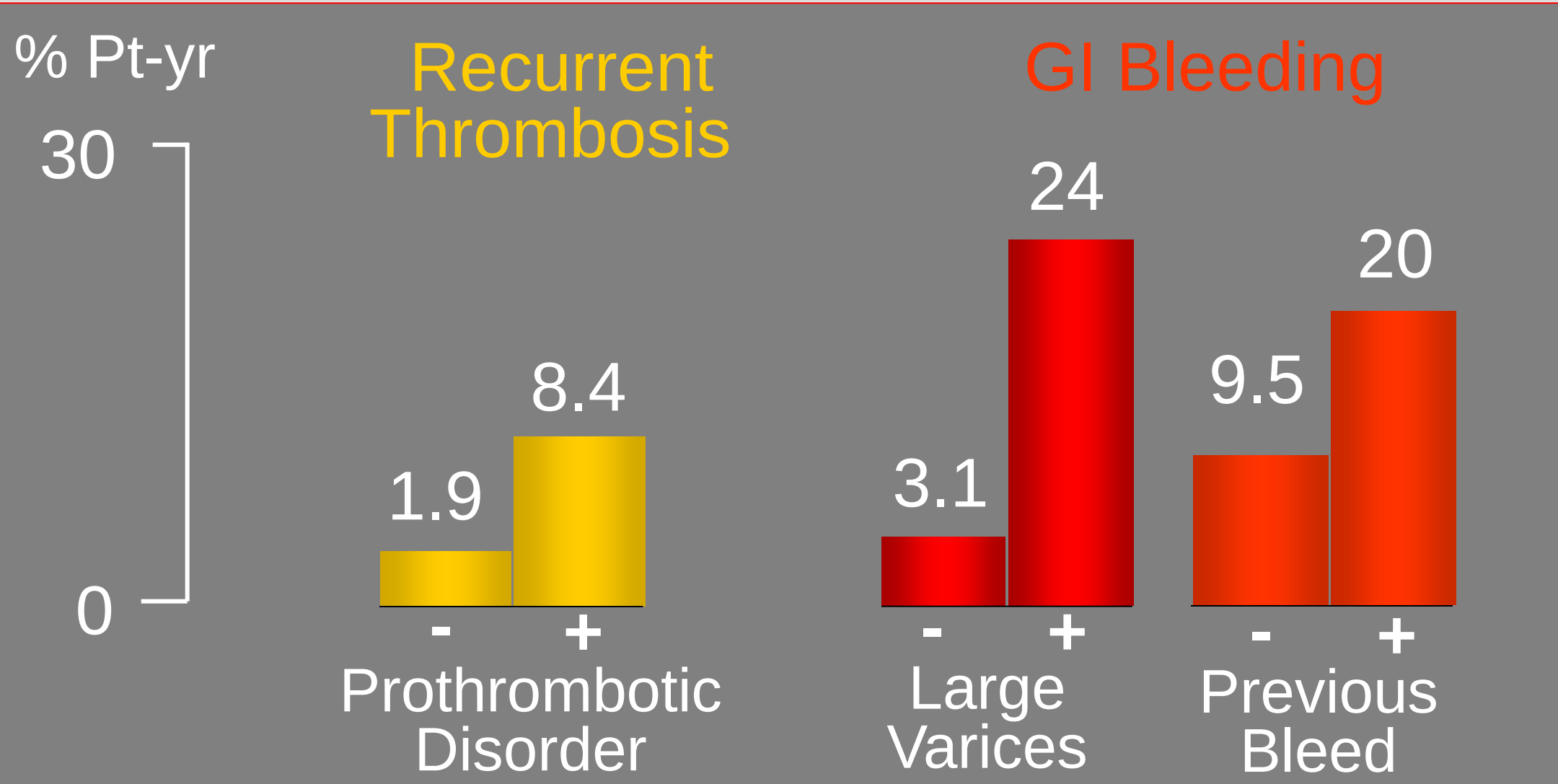
Condat, Gastroenterology 2001

2

	HR	*P*
Bl GI bleed	2.1	<.01
Bl ascites	2.0	=.01
Anticoagulant	2.1	<.01

Spaander, JTH 2013

Portal Vein Thrombosis – Prognosis



p = 0.04, 0.07 and 0.004

Condat, Gastroenterology 2001

Non-cirrhotic, non-malignant PVT
Prognosis

N of Patients	23 to 136
Period	1980 to 2008
Median follow-up	3-5,5 years
Mortality	7-25%
Prognosis	SMV involvement Associated conditions

Merkel, J Hepatol 1992. Condat, Gastroenterology 2001. Janssen, Gut 2001.
Orr, Hepatology 2005. Sogaard, BMC Gastro 2007. Amitrano AJG 2007. Spaander, JTH 2011

Noncirrhotic portal vein thrombosis Conclusions

- A manifestation of underlying blood disorders, whose treatment influences overall outcome.
- Complications controlled by early anticoagulation and treatment for portal hypertension.
- Benefit/risk ratio of long-term anticoagulation in the absence of strongly prothrombotic conditions is unknown. RCT needed.
- Overall outcome determined by associated conditions and extent of thrombosis

Non-cirrhotic PVT: Perspectives for 2015

- Recent PVT
  - Prognosing recanalization
  - Alternatives to anticoagulation therapy
- Cavernoma
  - Permanent anticoagulation for all ?
  - Meso-Rex shunt

Epidemiology of portal vein thrombosis

Country	Sweden	Sweden
Registries	Autopsy	Inpatients Outpatients
Period	1970-1982	1995-2004
Prevalence *per* 10^5	1000	3.7

Ogren. WJG 2006. 23,796 autopsies. Rajani, APT 2010

Portal vein obstruction – Causal factors

Malignancy – *diverse mechanisms**	1/3
Cirrhosis – *thrombosis*	1/3
Others – *thrombosis, malformation***	1/3

** Invasion or encasement or thrombosis*
*** Malformation in children with cavernoma*

Janssen Blood 2000. Ogren WJG 2006. Rajani APT 2010

Prothrombotic disorders in PVT

Myeloproliferative neoplasms %	35
Inherited disorders %	35
Antiphospholipid syndrome %	15
Others (IBD, …) %	10
Any of the above %	65
Any combination %	15

From Janssen, HLA Blood 2000. Denninger, MH Hepatology 2000. Primignani, Hepatology 2006. Plessier, Hepatology 2010

Prothrombotic Disorders
Diagnostic Pitfalls

1. Liver dysfunction decreases PC, PS and AT plasma levels

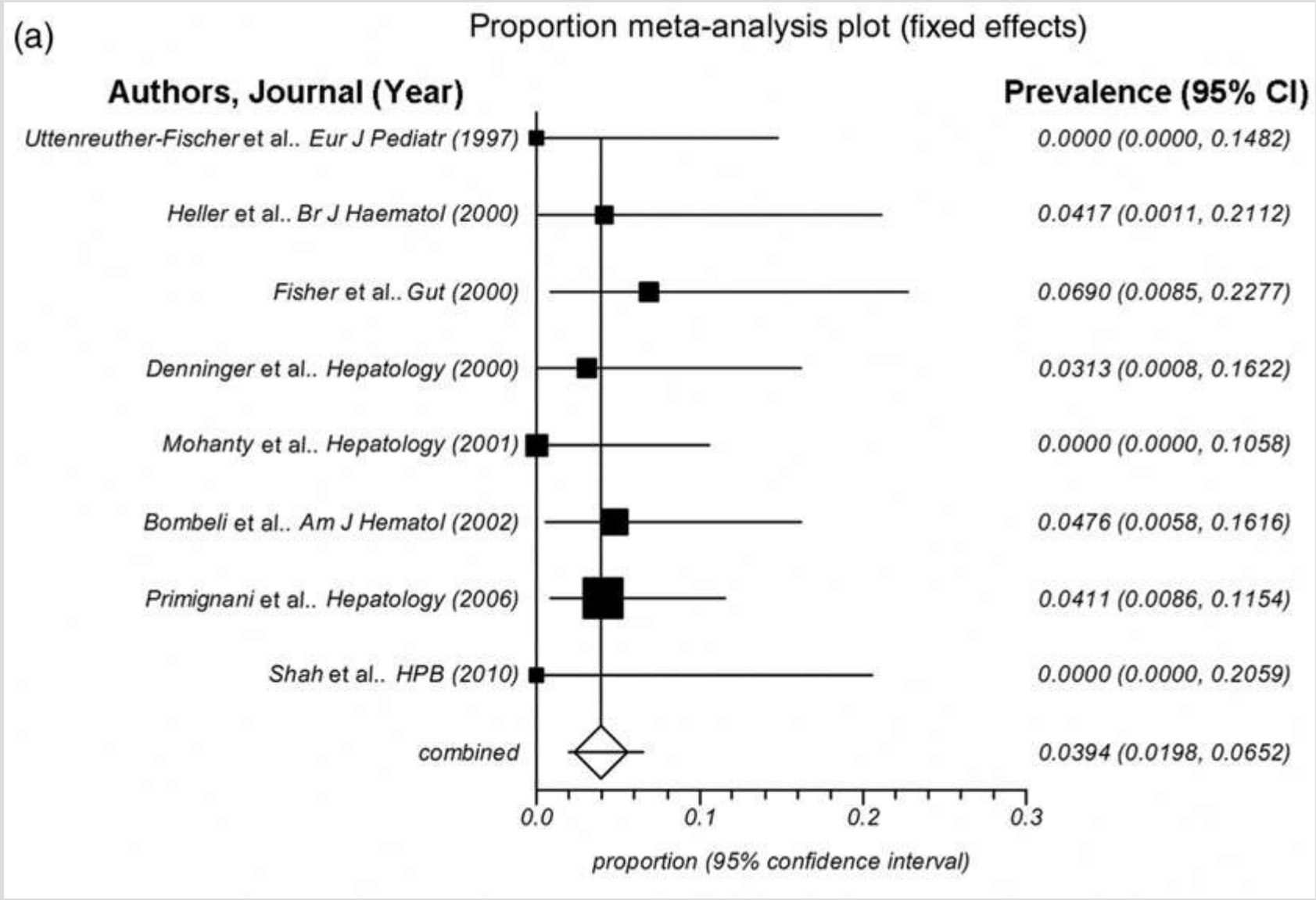
→ *Molecular analyses*

2. Portal hypertension masks MPN. Hypersplenism decreases blood cell counts.

→ *V617F JAK2 mutation (blood granulocytes)*

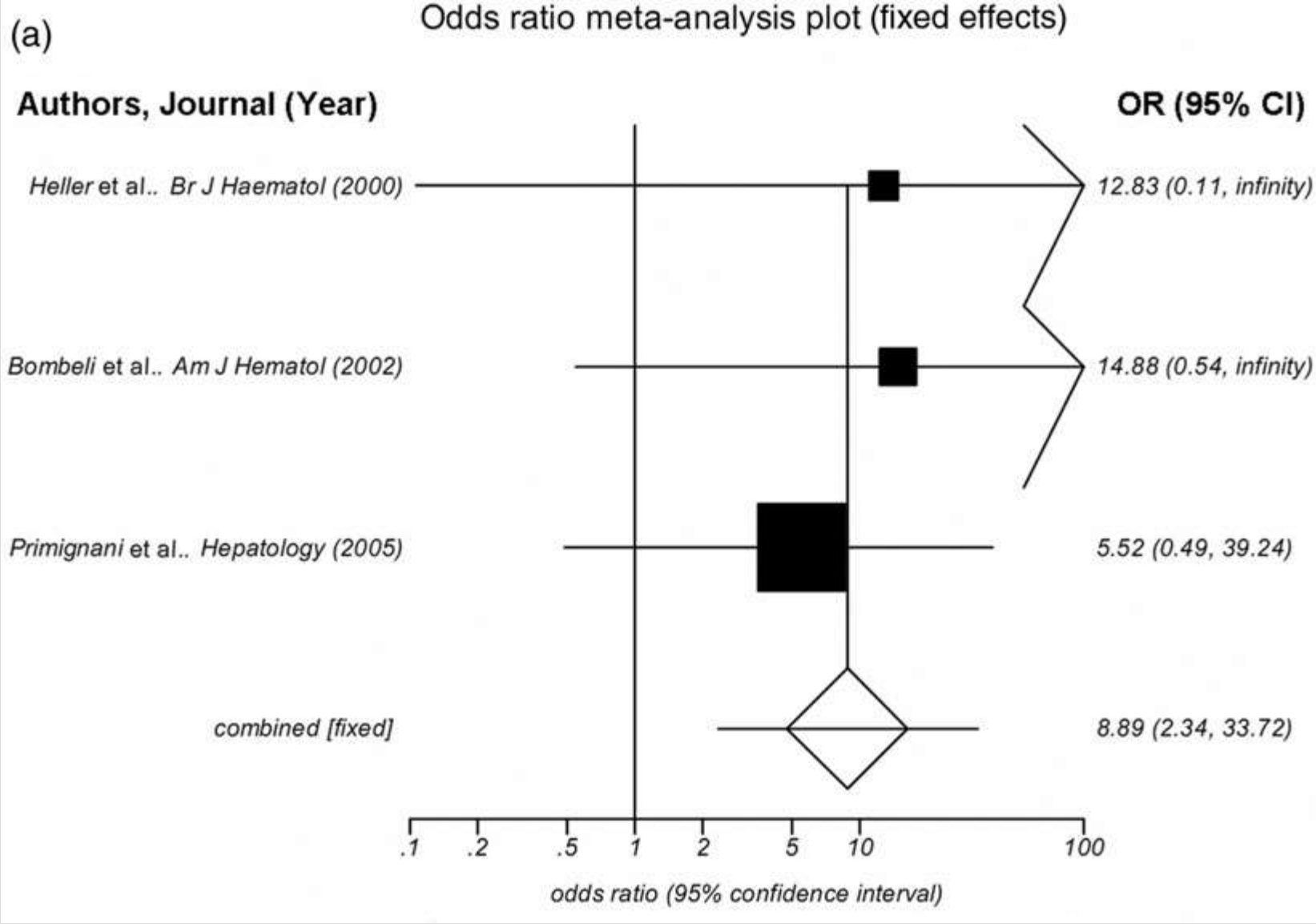
→ *Clusters of dystrophic megacaryocytes (BMB)*

Antithrombin and PVT



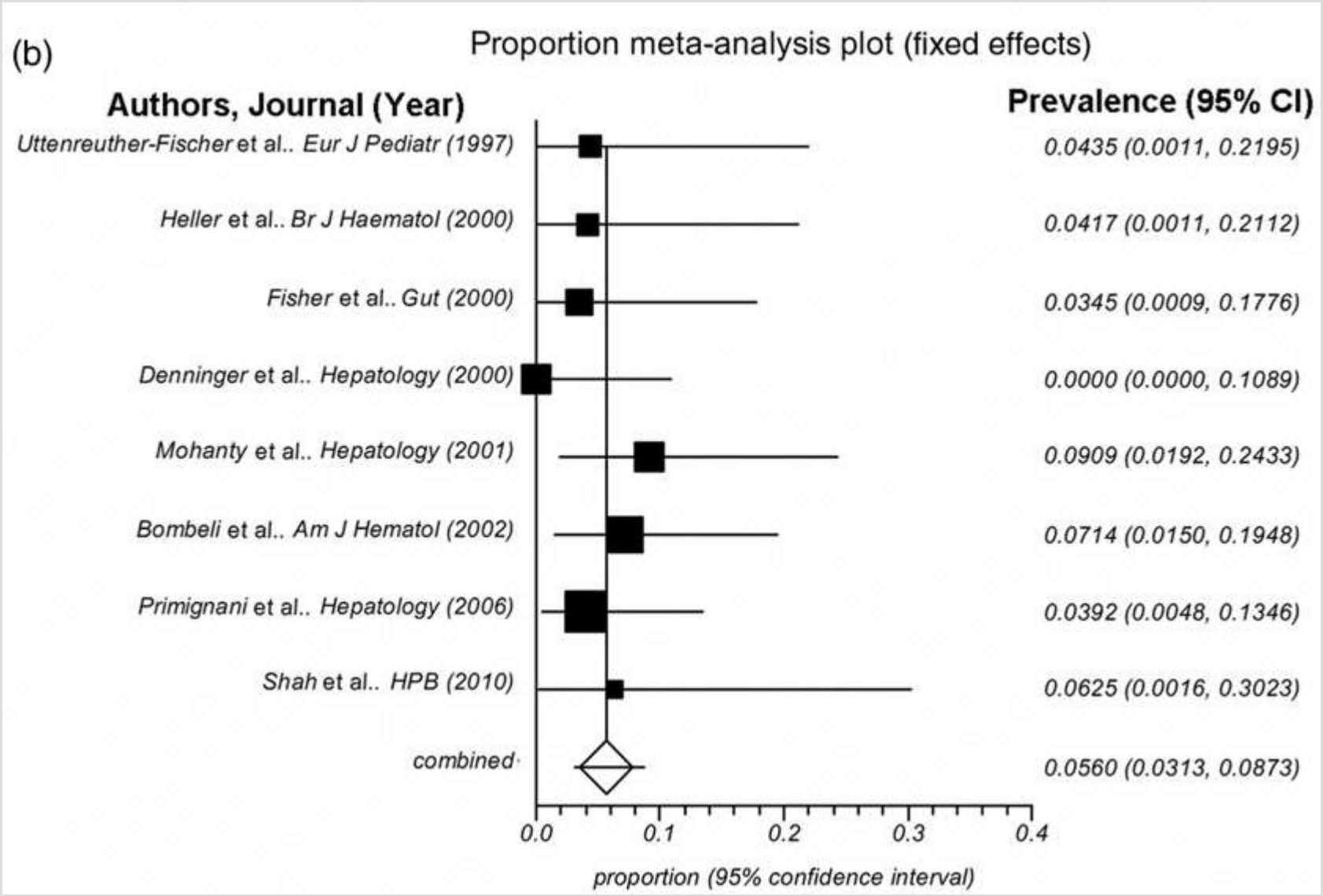
Qi. J Gastroenterol Hepatol 2013

Antithrombin and PVT



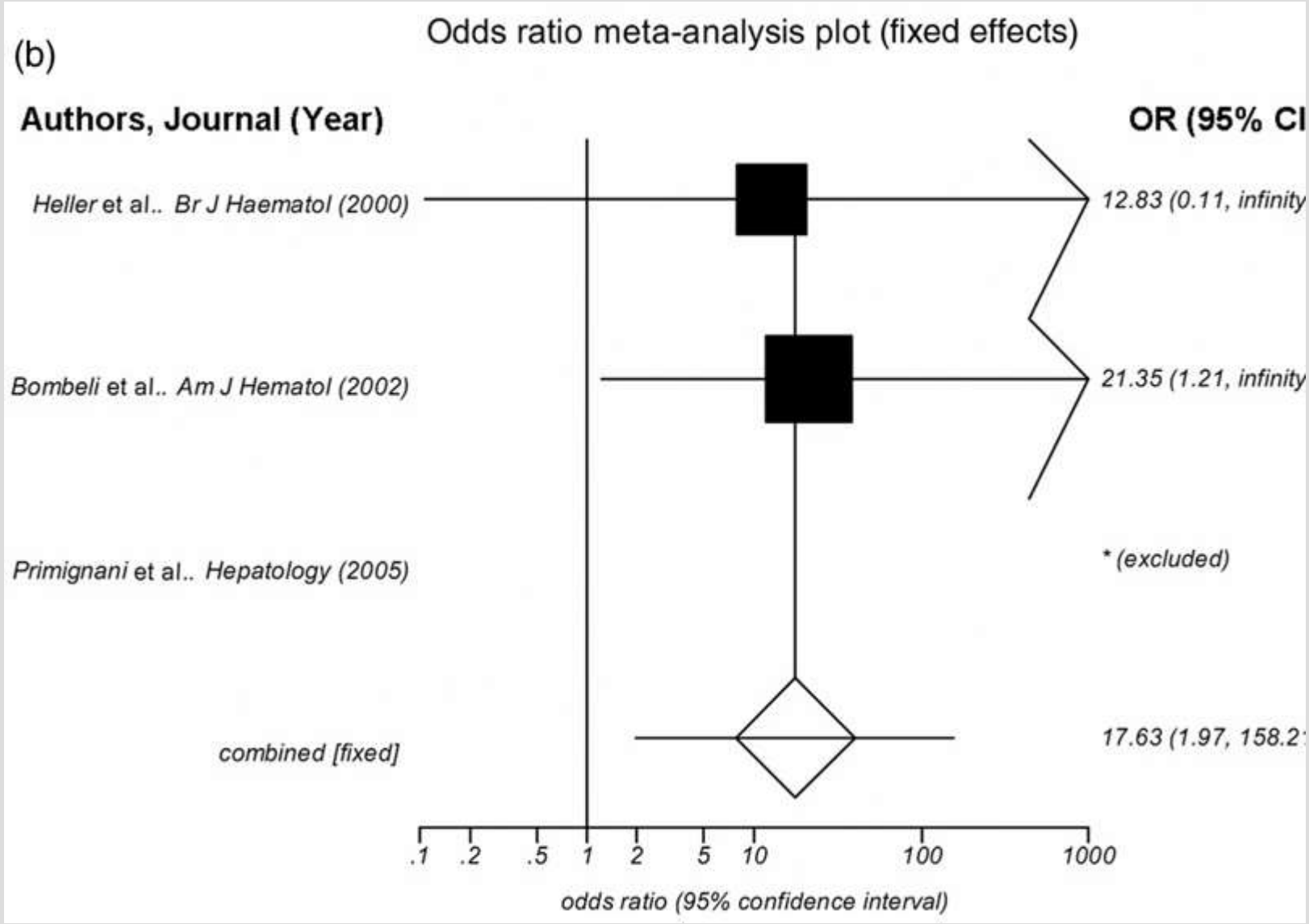
Qi. J Gastroenterol Hepatol 2013

Protein C and PVT



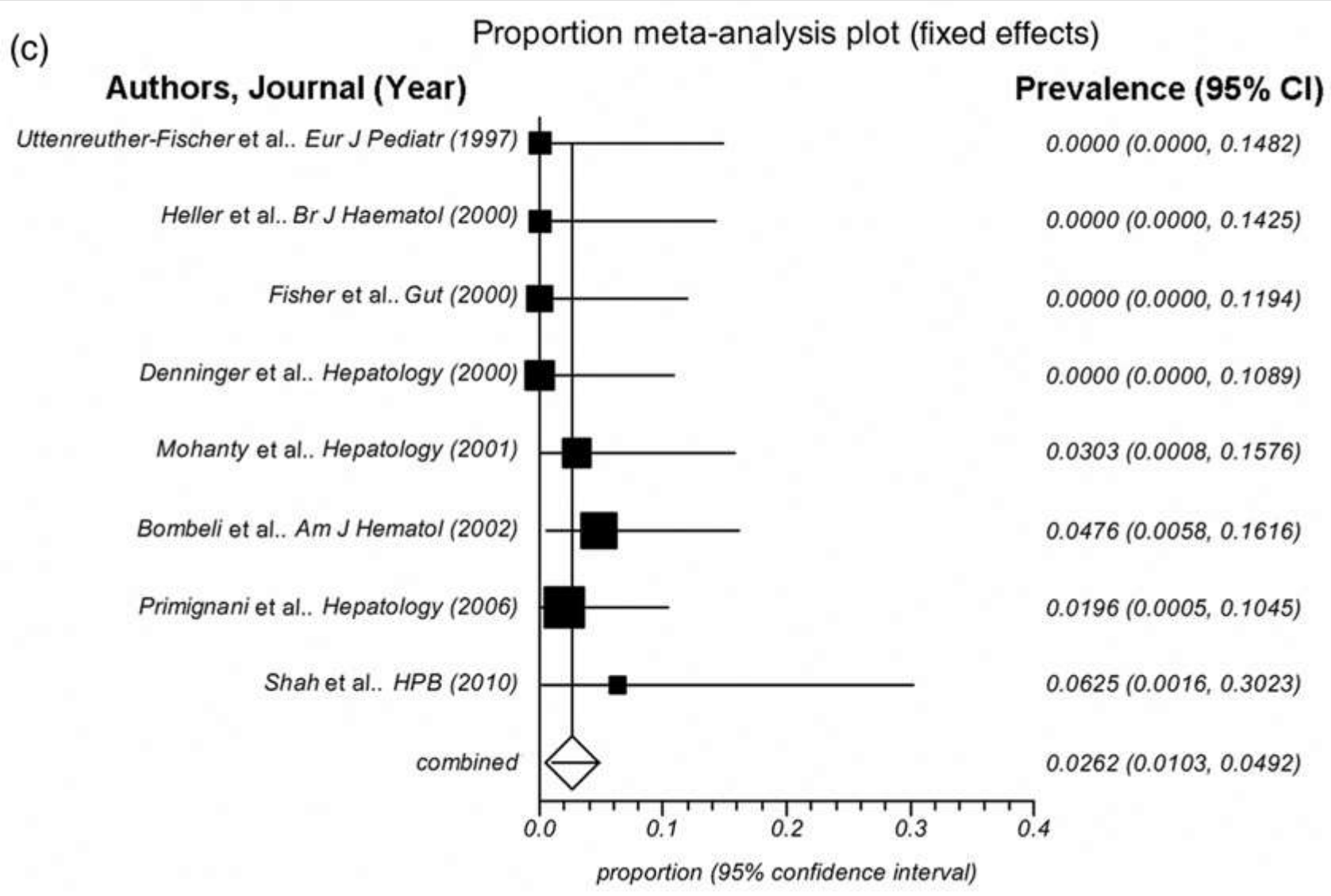
Qi. J Gastroenterol Hepatol 2013

Protein C and PVT



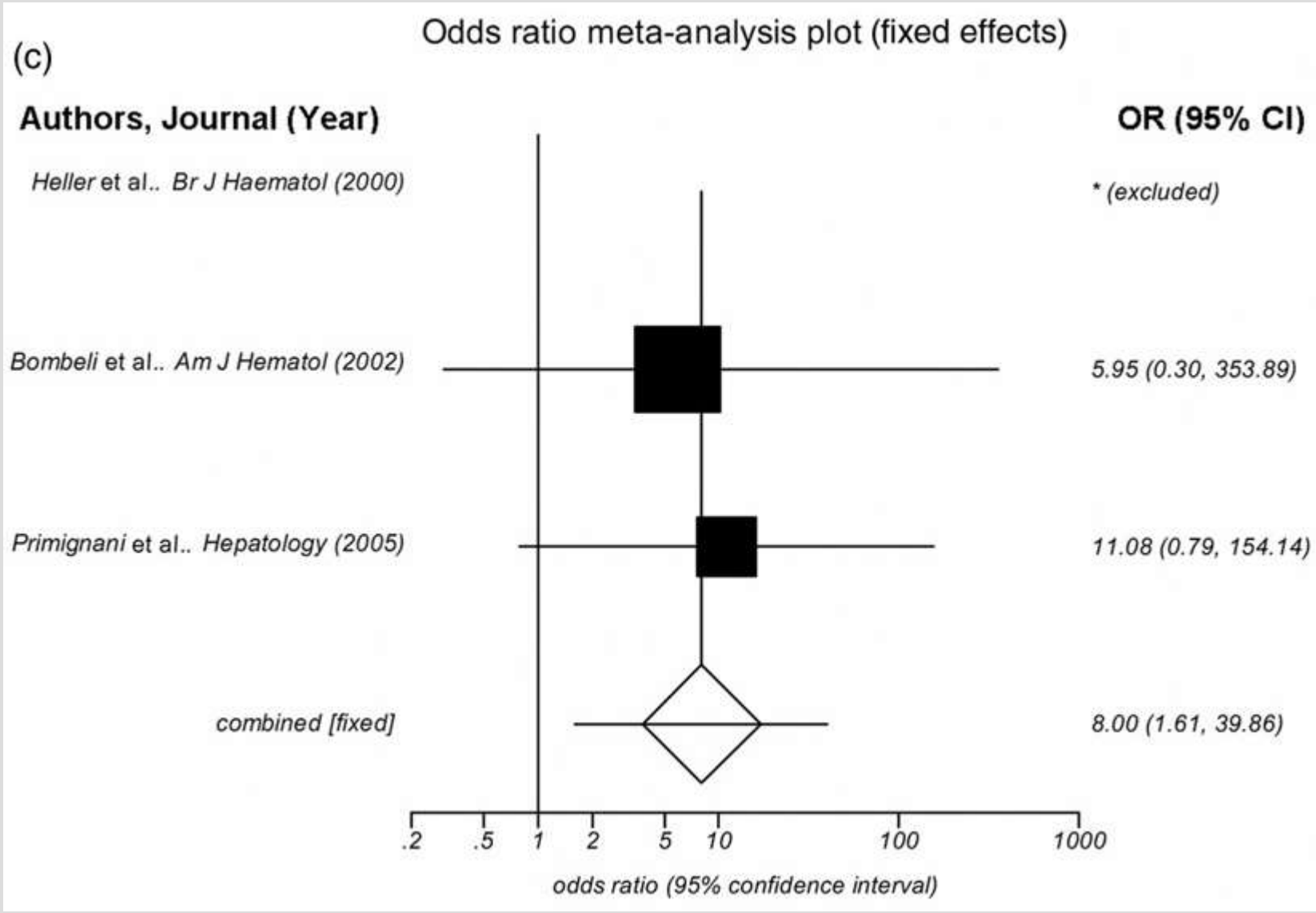
Qi. J Gastroenterol Hepatol 2013

Protein S and PVT



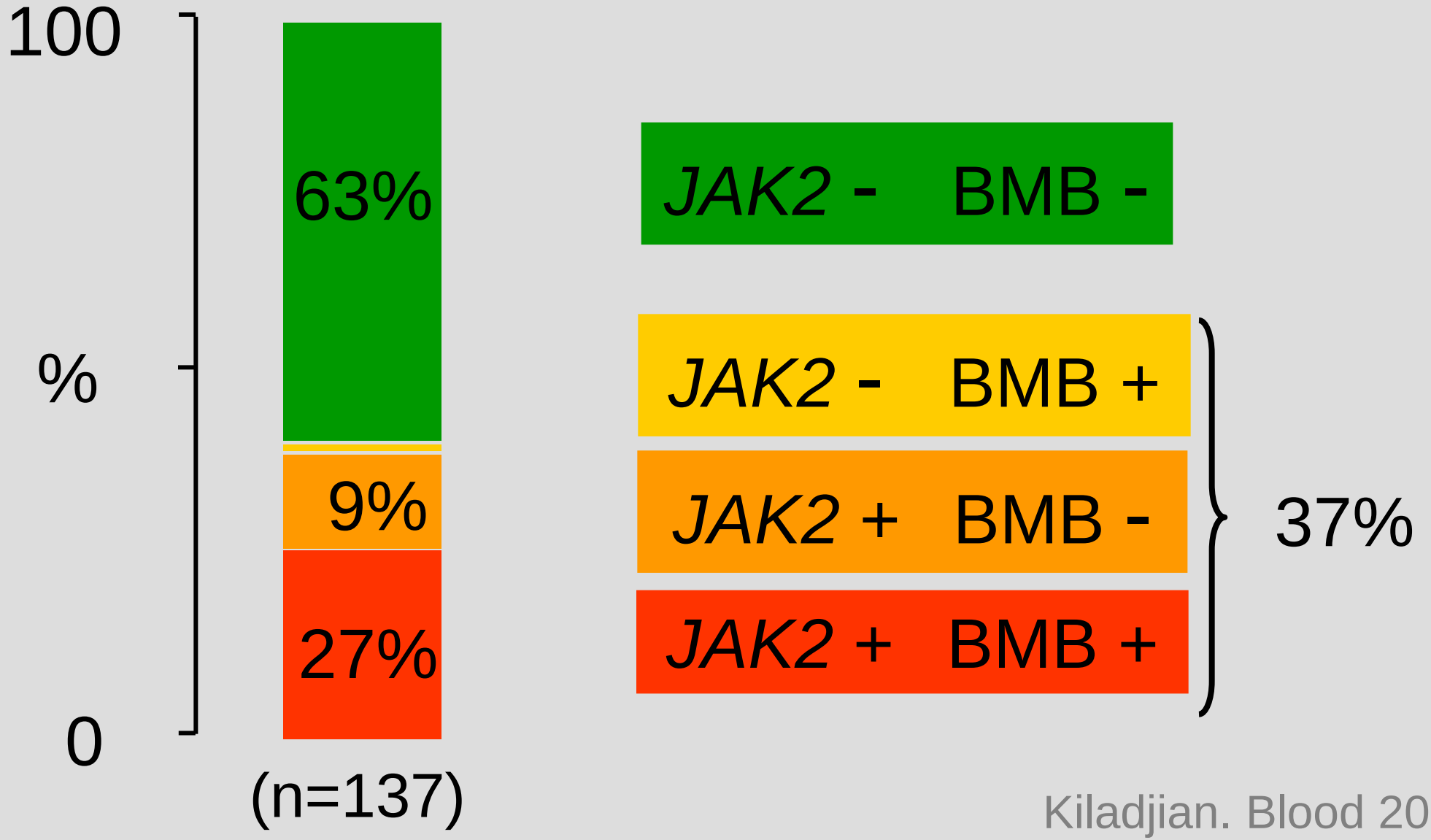
Qi. J Gastroenterol Hepatol 2013

Protein S and PVT



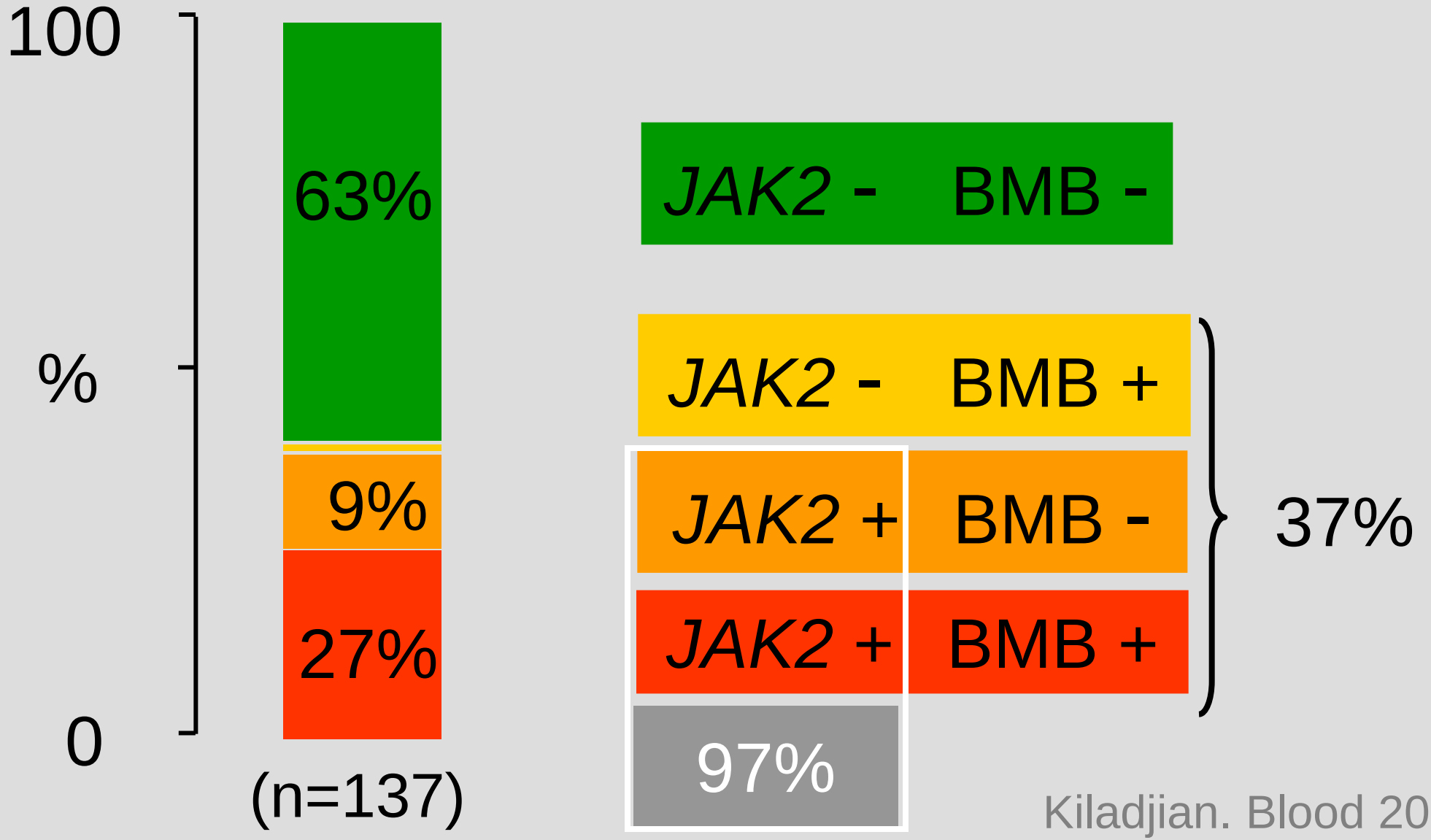
Qi. J Gastroenterol Hepatol 2013

Myeloproliferative neoplasms and PVT



Kiladjian. Blood 2008

Myeloproliferative neoplasms and PVT

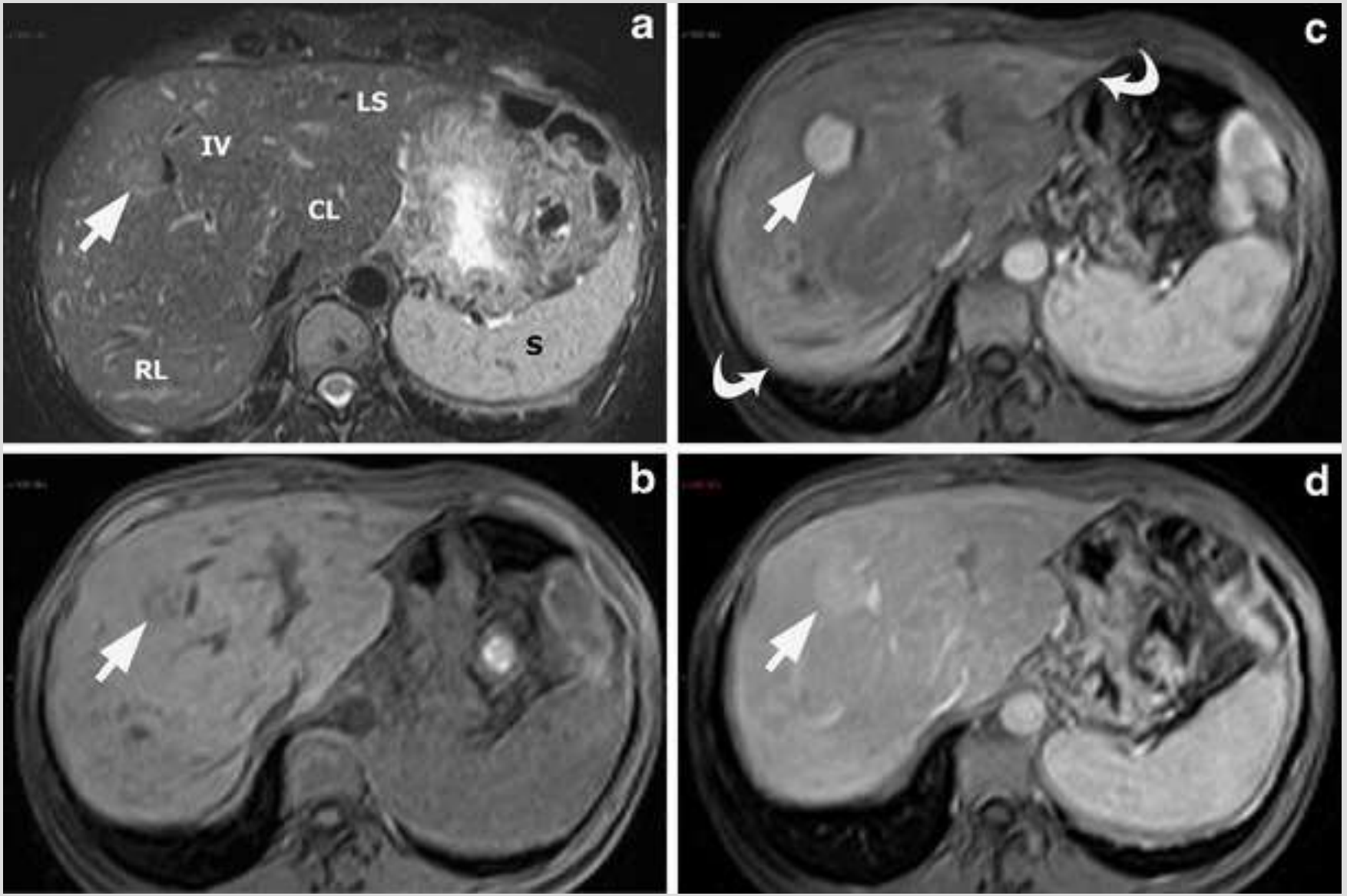


Kiladjian. Blood 2008

CALR mutations in Splanchnic Vein Thromboses

	PVT		BCS	
	N	*N* CALR +ve	*N*	*N* CALR +ve
All patients	140	2	69	2
MPN	35	2	39	2
JAK2 +ve	30	0	31	0
JAK2 -ve	5	2	8	2

Turon, J Hepatol 2014

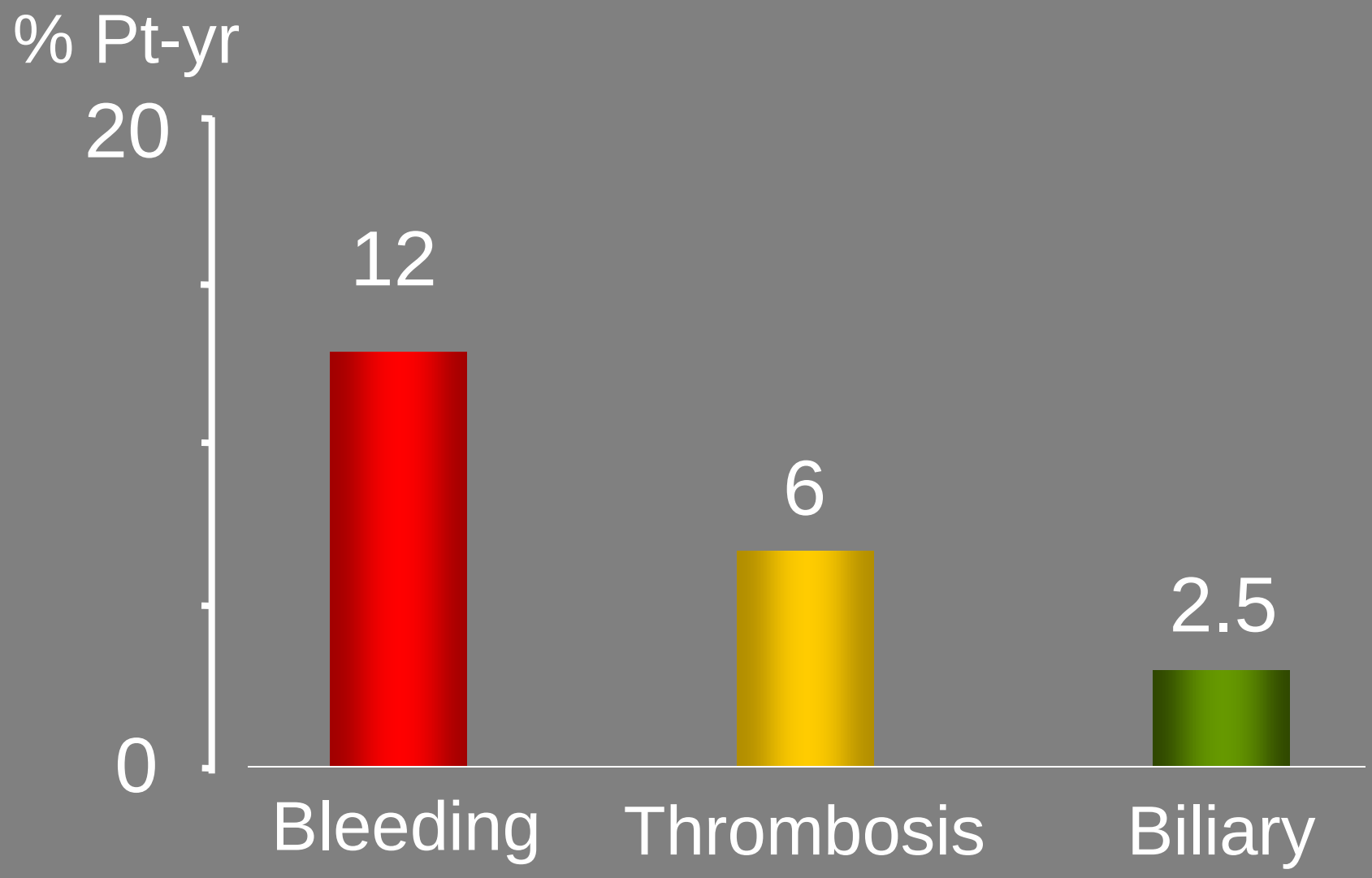

a
LS
IV
CL
S
RL
c
b
d

Hepatocellular nodules in PVT patients

Portal cavernoma 58 Pts	M/F 32/26 mean age 53/51
FNH-like nodules 12 Pts	79% Imaging + follow-up 21% Percutaneous LBx
	36 lesions Ø: 1.3 cm (0.5-4.2 cm)
Stable course 9 Pts	30 lesions
Progressive course 3 Pts	8 lesions

Marin, Eur Radiol 2011

Chronic PVT - Complications



Condat. Gastroenterology 2001 & Hepatology 2003. Chait Br J Haematol 2005

Causes of death in PVT patients

120 patients (1985-2008)

Death	29
Progressive MPN	6 (20%)
Bleeding	5
Thrombosis	3
Infection	3
Other/unknown causes	12

Follow-up 5.5 years (range 0.1–32.5 years) Spaander, JTH 2011

Causes of Death in BCS En-Vie Cohort

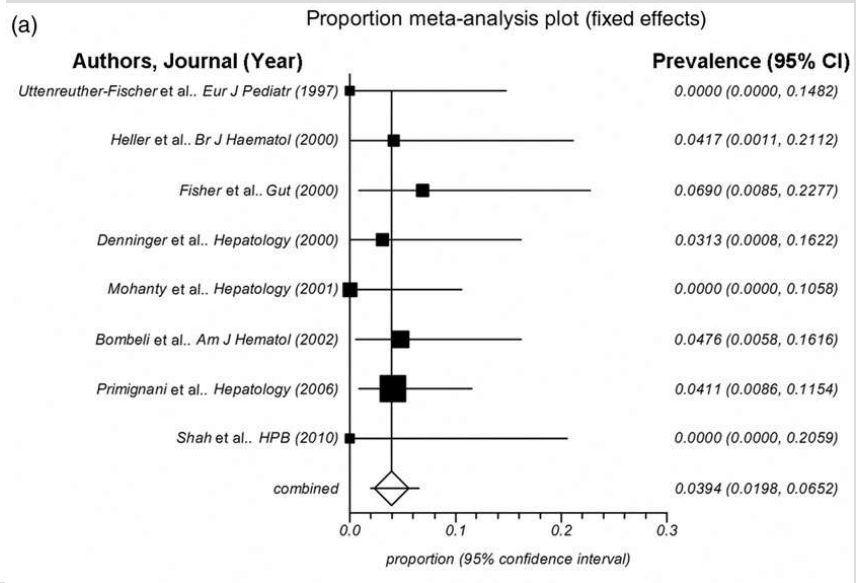
Table 2. Causes of Death

Related or Probably Related Liver Deaths (n = 30)	Non-Liver-Related Deaths (n = 6)
Liver failure (n = 12)	Extrahepatic malignancy (n = 1);
Multiorgan failure (n = 4)	Complication/progression of hematological disease (n = 4);
GI bleeding (n = 2)	Intracraneal hemorrhage (n = 1)
Sepsis (n = 4)	
Hepatobiliary malignancy (n = 2)	
Unknown (n = 6)	

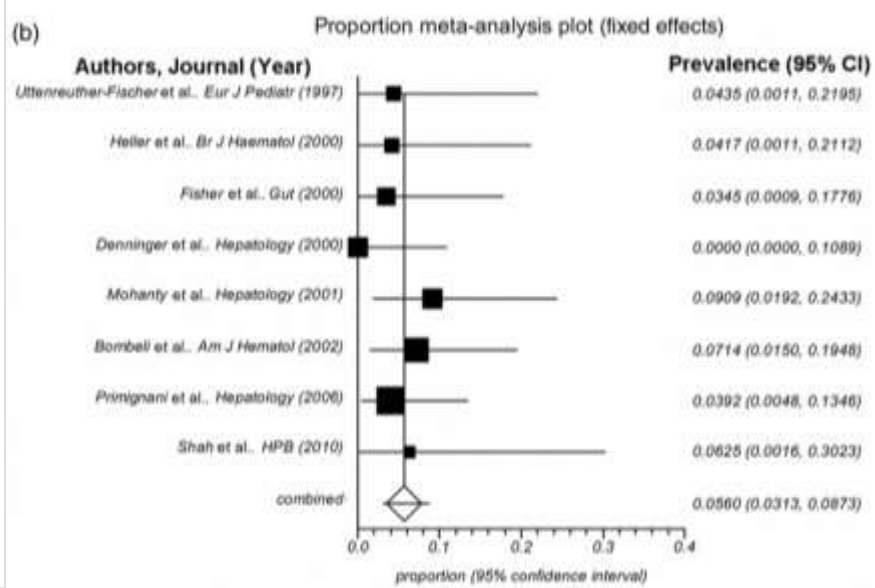
Seijo, Hepatology 2013

Coagulation Inhibitors and PVT

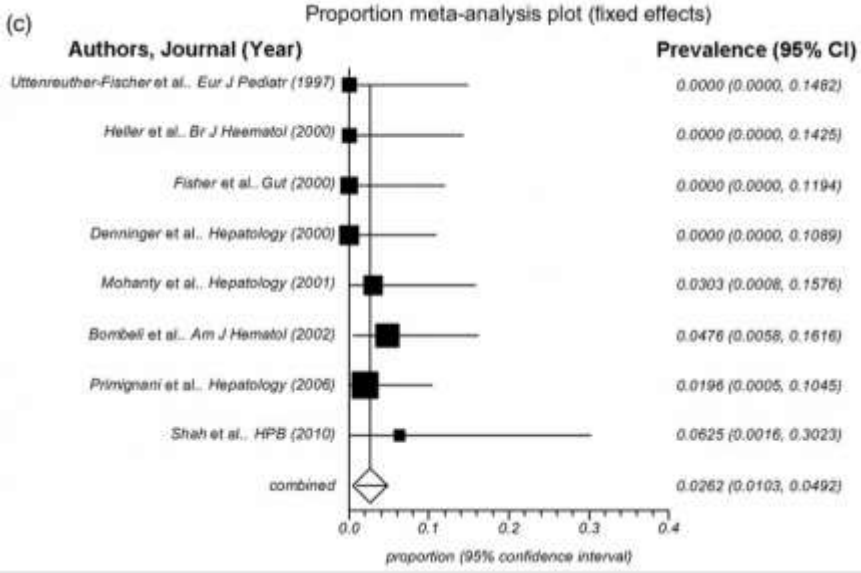
Antithrombin



Protein C



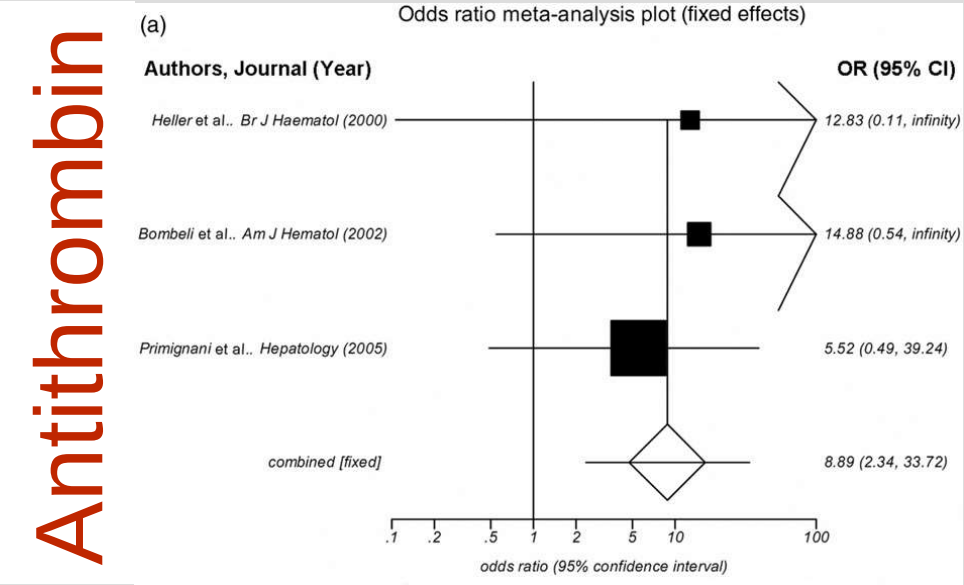
Protein S



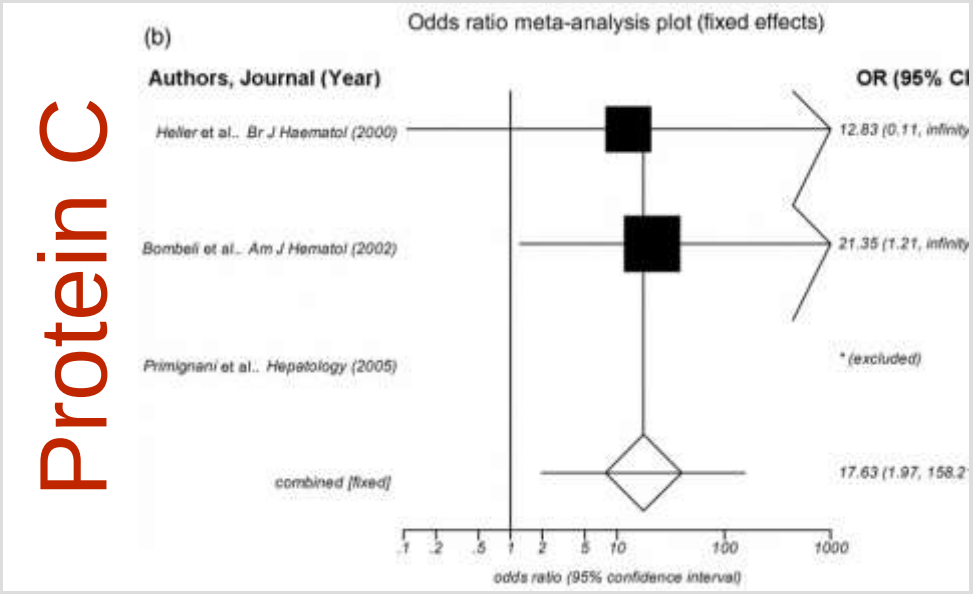
Qi. J Gastroenterol Hepatol 2013

Coagulation Inhibitors and PVT

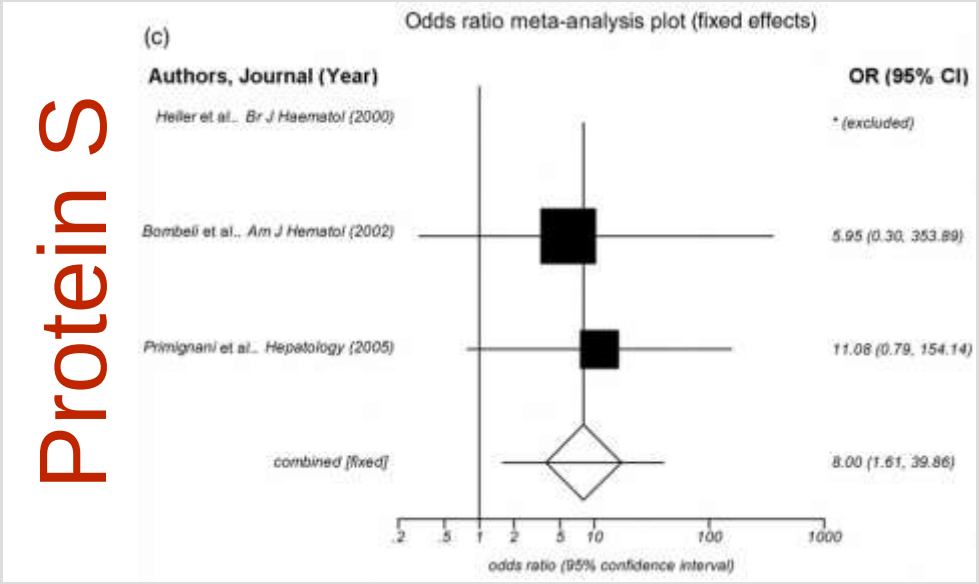
Antithrombin



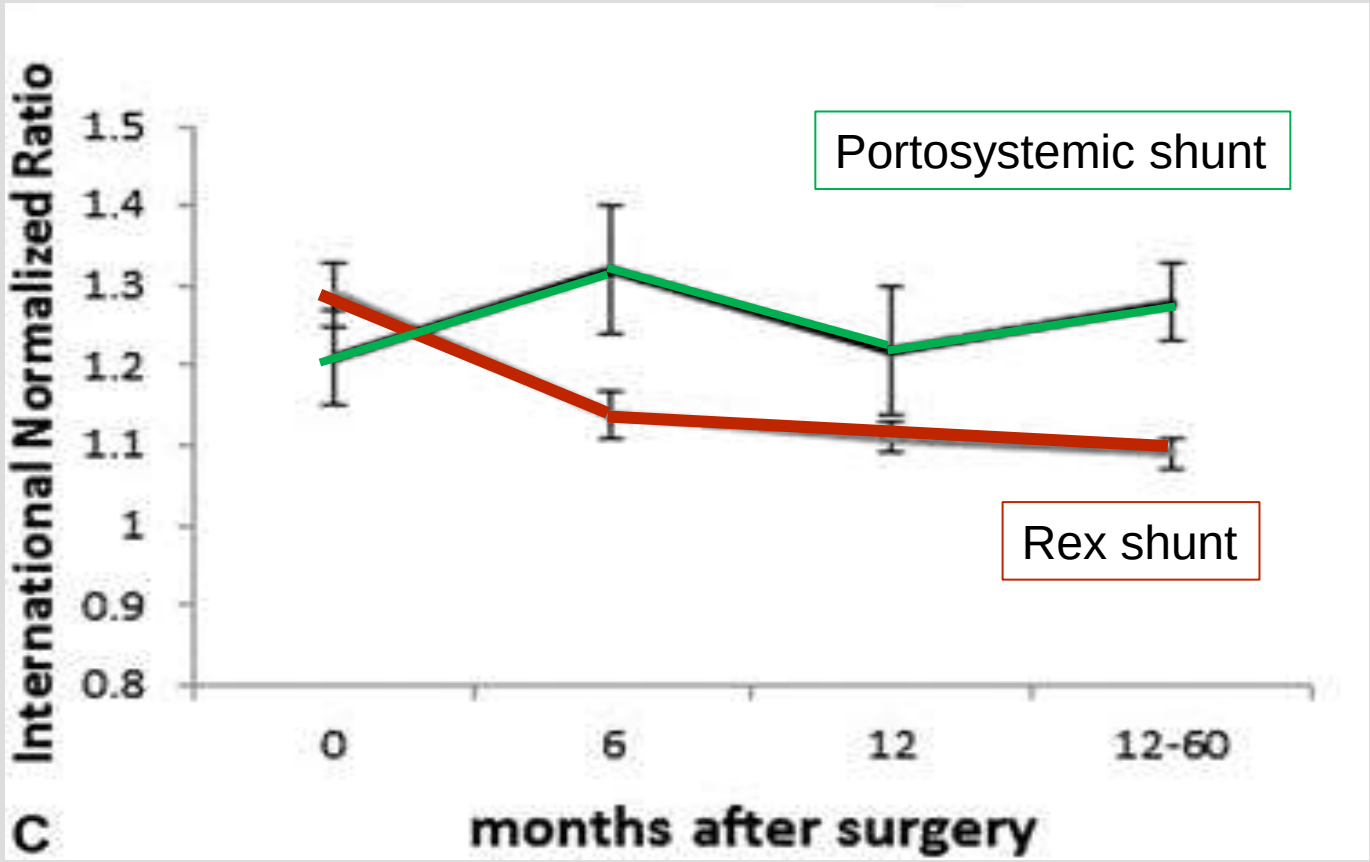
Protein C



Protein S

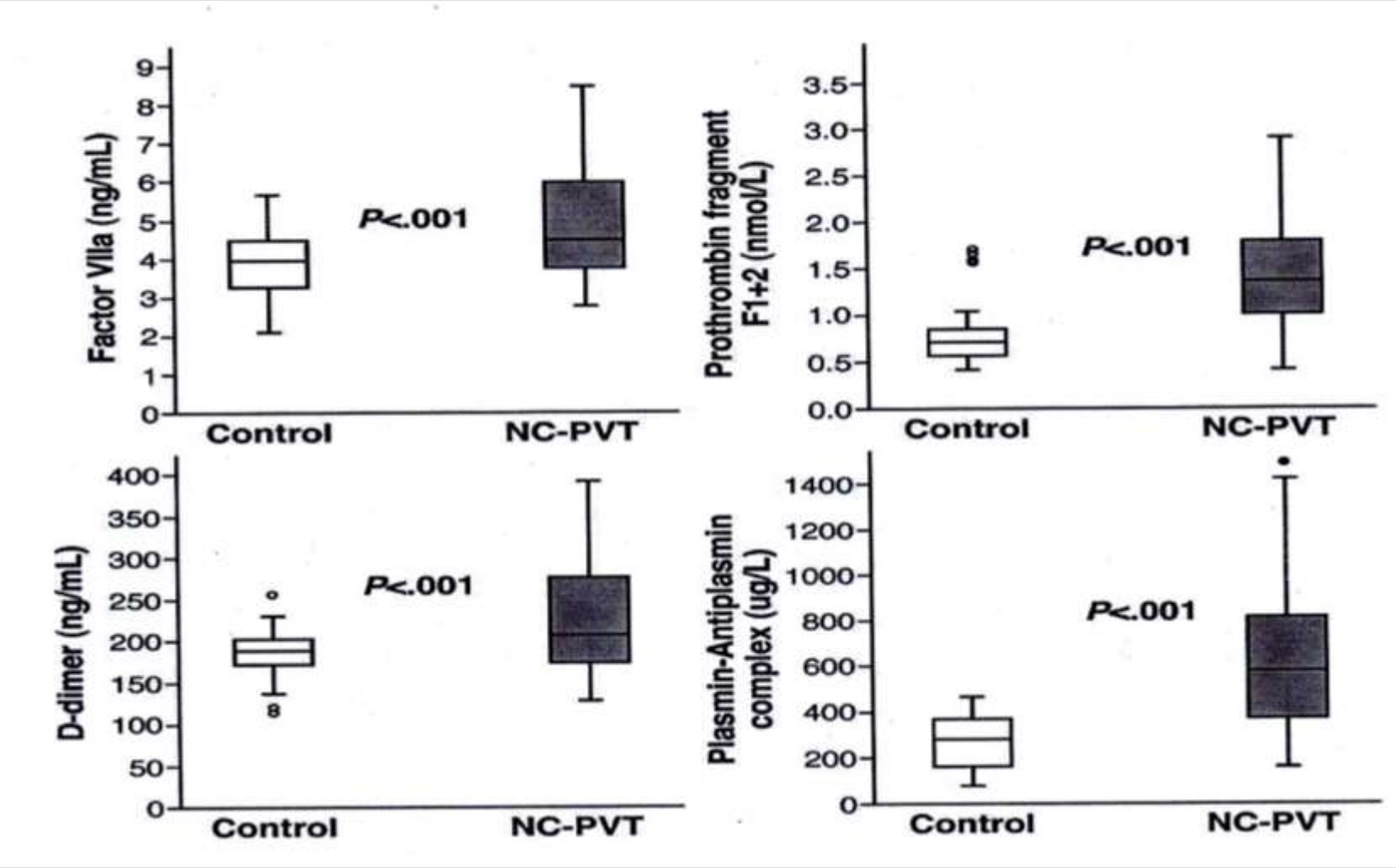


Qi. J Gastroenterol Hepatol 2013



Laut. J Am J Coll Surg 2013.

Hypercoagulability in patients with PVT



Raffa. Clin Hepatol Gastroenterol 20

Hypercoagulability in patients with PVT

PT and aPTT	Increased	20%
Coagulation factors		
II, V, VII, IX-XII	Decreased	8-30%
Anticoagulant factors	Decreased	17-27%
Factor VIII, vWF	Increased	20-40%
ADAMTS-13	Decreased	20%
ETP without TM	Unchanged	NS
ETP with TM	Increased	18%

Raffa. Clin Gastroenterol Hepatol 2012

Recent symptomatic PVT - Natural history

	%
• Spontaneous recanalization[1-3]	0
• Complications:	
- Intestinal ischemia [4-7]	
- Pure PVT	0
- SMV thrombosis	50
- Mortality rate	50
- Portal hypertension [8]	100

[1] Baril, Am J Surg 1996. [2] Condat, Hepatology 2000. [3] Turnes, Clin Gastroenterol Hepatol 2008
[4] Harnik, Vascular Med 2010. [5] Kumar, NEJM 2001. [6] Morasch J Vasc surg 2001.
[7] Brunaud, J vasc surg 2001. [8] Plessier, Hepatology 2011

*

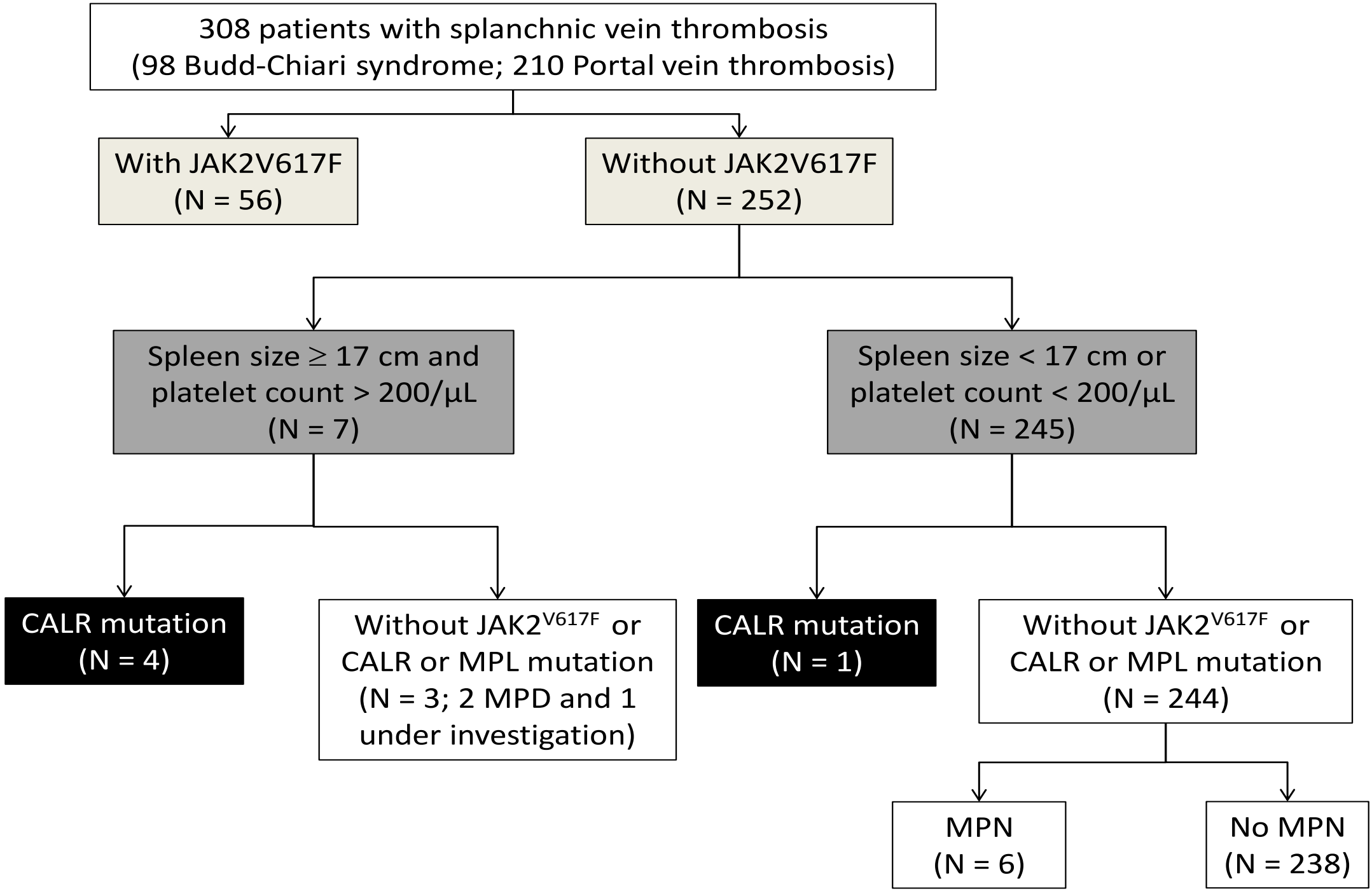
Chronic PVT/Portal cavernoma
Natural history

- Related to portal hypertension
  - Gastrointestinal bleeding
  - Portosystemic encephalopathy
- Related to cavernoma
  - Portal cavernoma cholangiopathy
- Related to prothrombotic conditions
  - New thrombosis

Plessier, J Hepatol 2012. Khanna and Sarin. J Hepatol 2014

Non-cirrhotic, non-malignant PVT
Local factors

- Inflammation: Splanchnic organs
- Cancer: Gastrointestinal
- Venous injury: Splenectomy
- Venous stasis: Obliterative portal venopathy


308 patients with splanchnic vein thrombosis
(98 Budd-Chiari syndrome; 210 Portal vein thrombosis)
With JAK2V617F
(N = 56)
Without JAK2V617F
(N = 252)
Spleen size ≥ 17 cm and
platelet count > 200/µL
(N = 7)
Spleen size < 17 cm or
platelet count < 200/µL
(N = 245)
CALR mutation
(N = 4)
Without JAK2V617F or
CALR or MPL mutation
(N = 3; 2 MPD and 1
under investigation)
CALR mutation
(N = 1)
Without JAK2V617F or
CALR or MPL mutation
(N = 244)
MPN
(N = 6)
No MPN
(N = 238)

Extrahepatic Portal Hypertension
Elective (central) PS Shunts

	Orloff *n=200*	Pande *n=94*	Warren *n=29*
Operative death - *%*	0	1	2
Follow-up - *yr*	~15	~5	~7
Rebleeding - *%*	2.5	10	10
Overall mortality - *%*	5	10	0

Orloff, J Am Coll surg 2002. Pande, BMJ 1987. Warren Ann Surg 1988

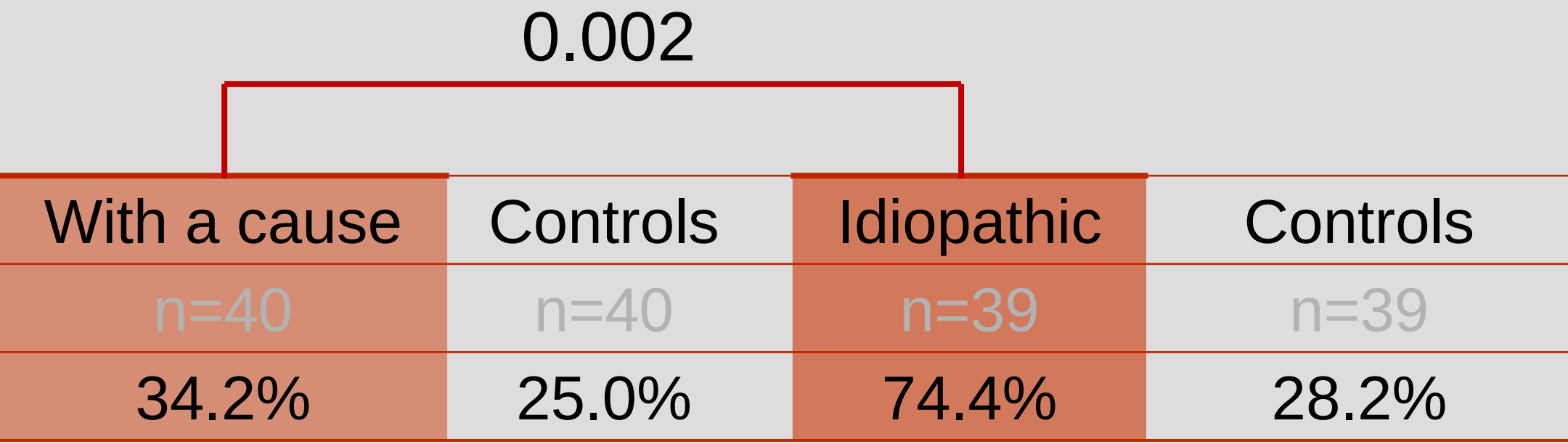
Similar results in Pal, J Gastro Hepato 2013, for primary prophylaxis

Waist circumference in PVT patients
men > 102 cm, woman > 88 cm

With a cause	Controls	Idiopathic	Controls
n=40	n=40	n=39	n=39
34.2%	25.0%	74.4%	28.2%
P = 0.58		*P* = 0.001	

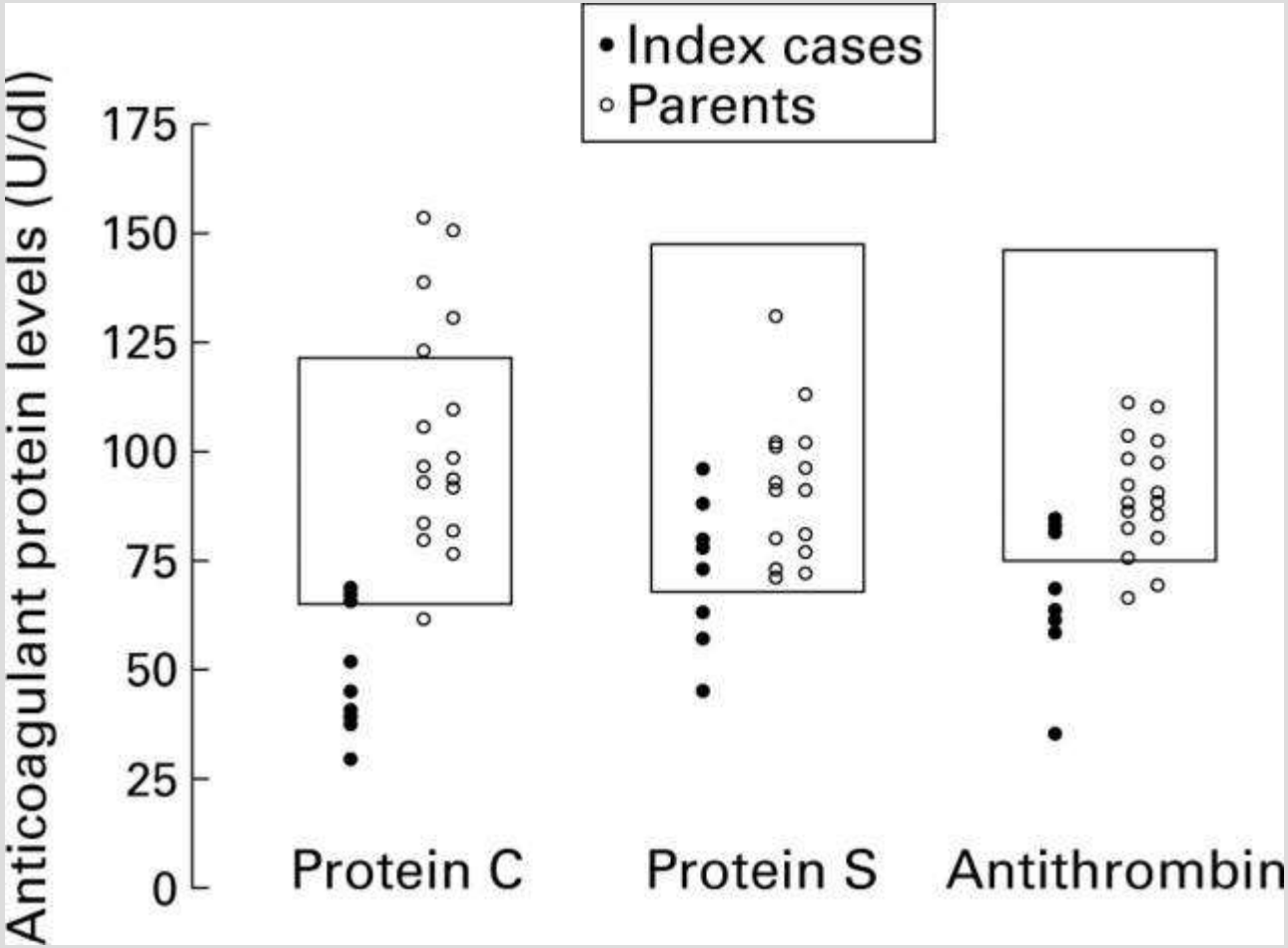
Bureau, J Hepatol 2015 (accepted)

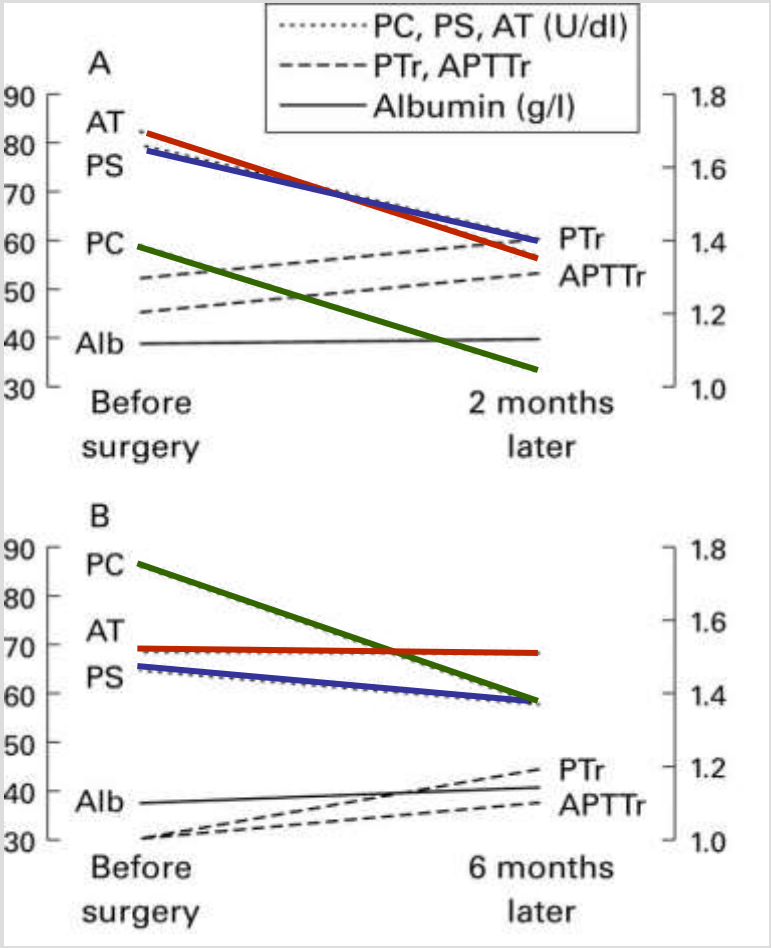
Waist circumference in PVT patients
men > 102 cm, woman > 88 cm



Bureau, J Hepatol 2015 (accepted)

Coagulation Inhibitors and PVT



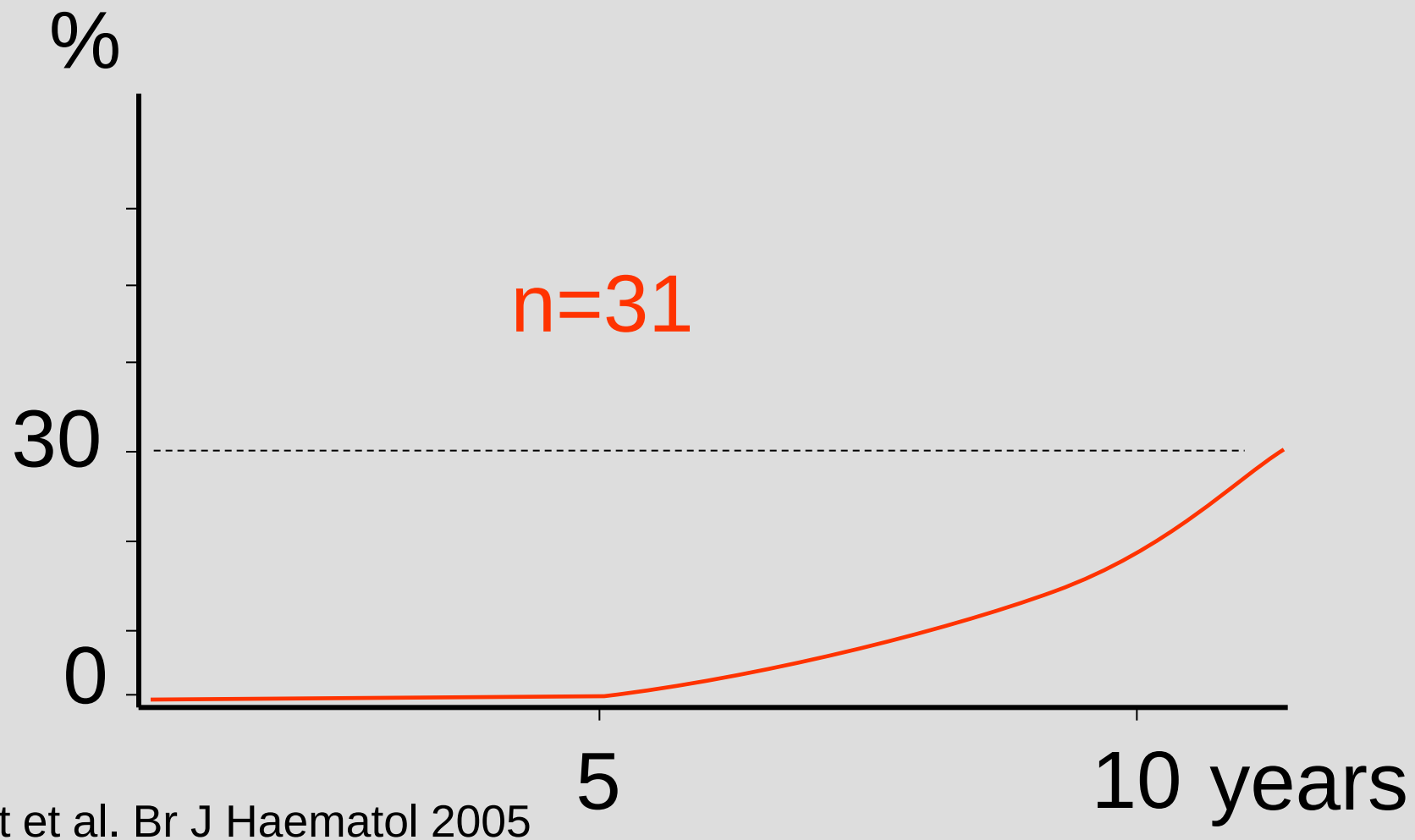


Fisher et al. Gut 2000

Site specificity for thrombosis in prothrombotic disorders

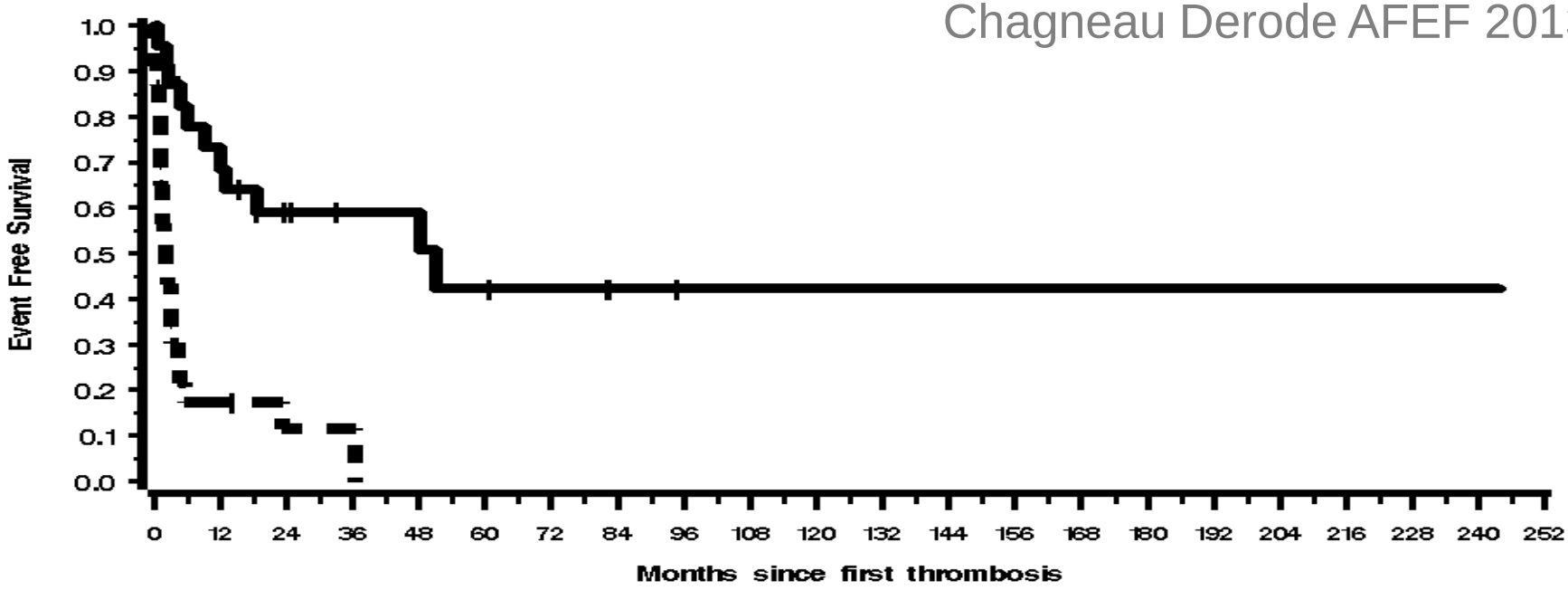
	HVT	PVT
Myeloproliferative neoplasms	+++++	+++
PNH	++++++	
Oral contraceptives	++	
Factor V Leiden	+++	+
Factor II gene mutation		++
Local factor *Central obesity*		+++

Transformation of MPN in patients with splanchnic vein thrombosis

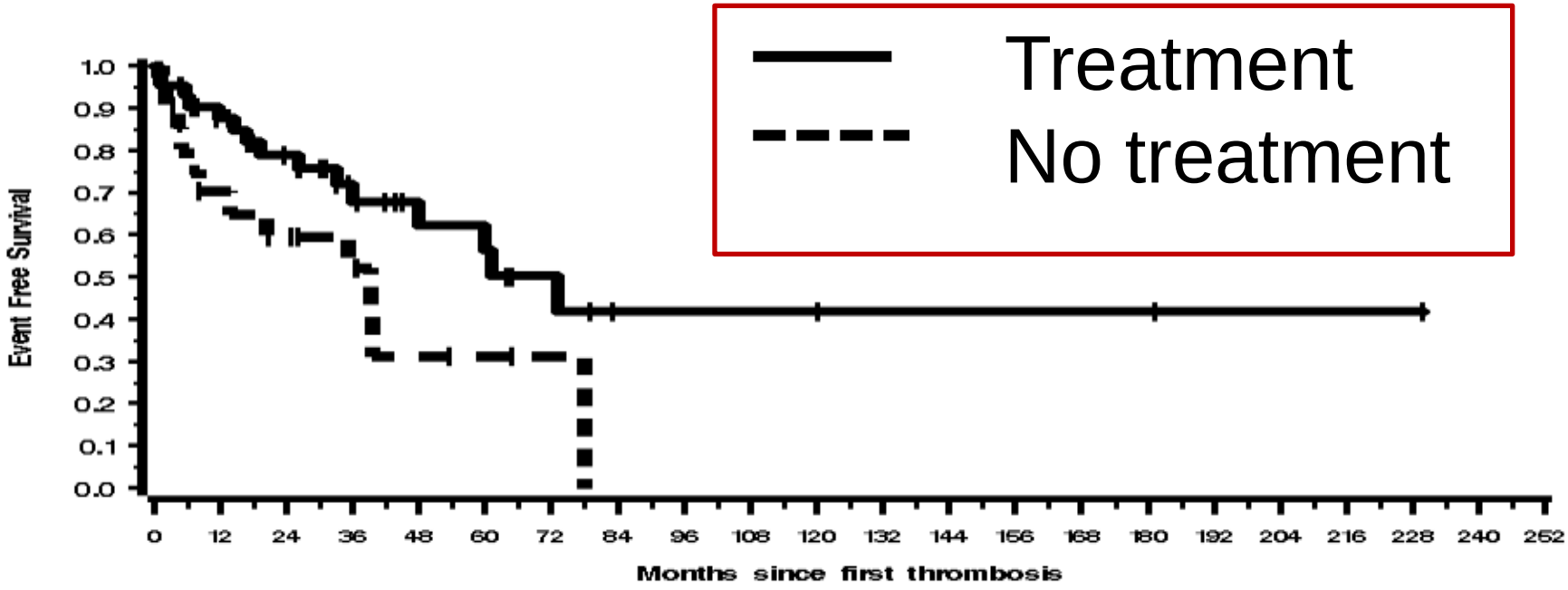


Chaït et al. Br J Haematol 2005

BCS


Event Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240 252
Months since first thrombosis

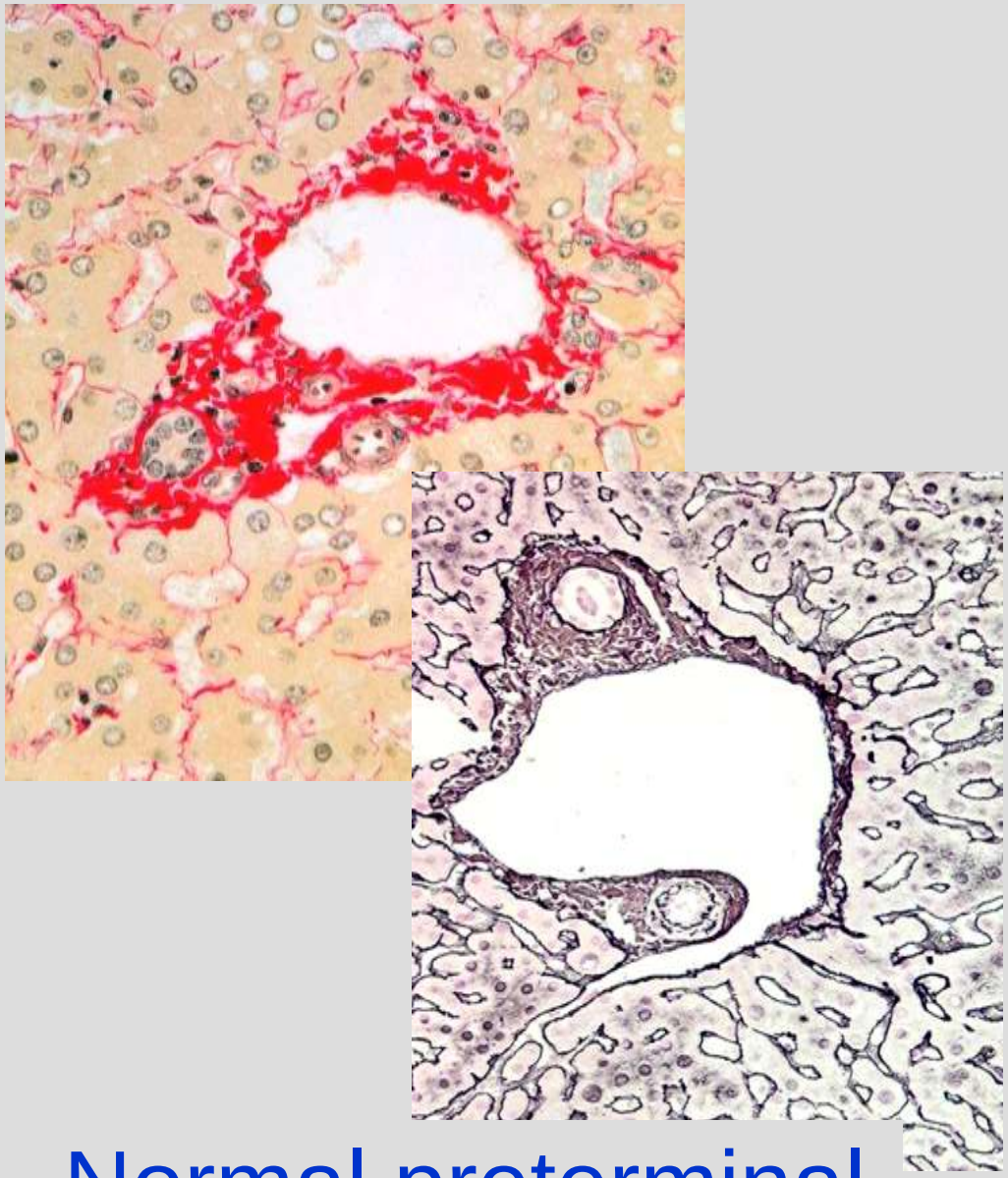
PVT


Event Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240 252
Months since first thrombosis
Treatment
No treatment

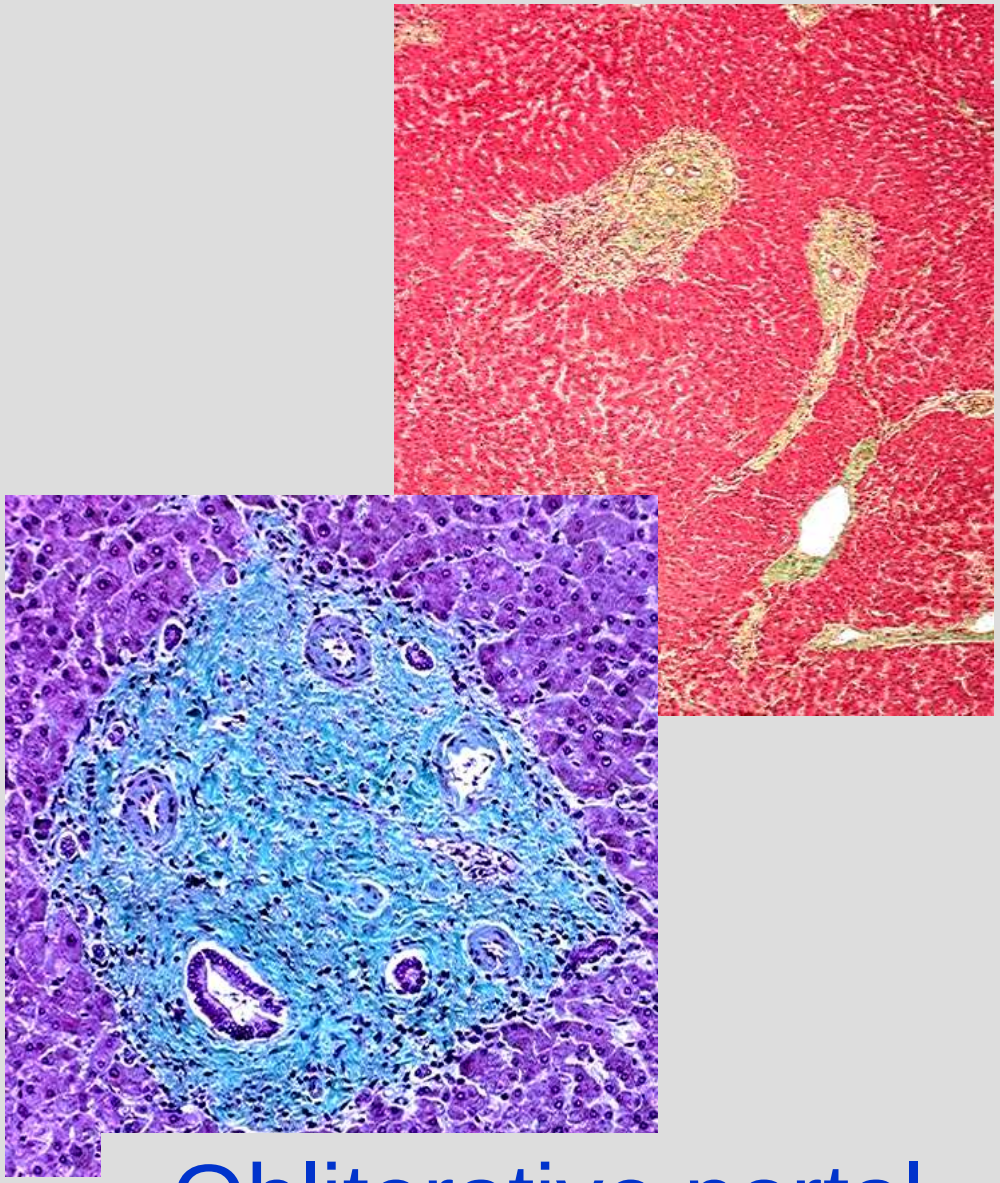
Portal Cavernoma Cholangiopathy

- Gross bile duct alterations almost constant, but rarely symptomatic (up to 20%).
- Biliary ectasias predictive for symptoms.
- In anticoagulated patients, severe forms develop within a year or do not. In non-anticoagulated patients, a late complication.
- Manage symptomatic patients with endoscopic sphincterotomy and protheses; consider porto-systemic shunting; consider surgical bypass.

Condat, Hepatology 2003. Llop, Gut 2011.
Dhiman, J Clin Exp Hepatol 2014

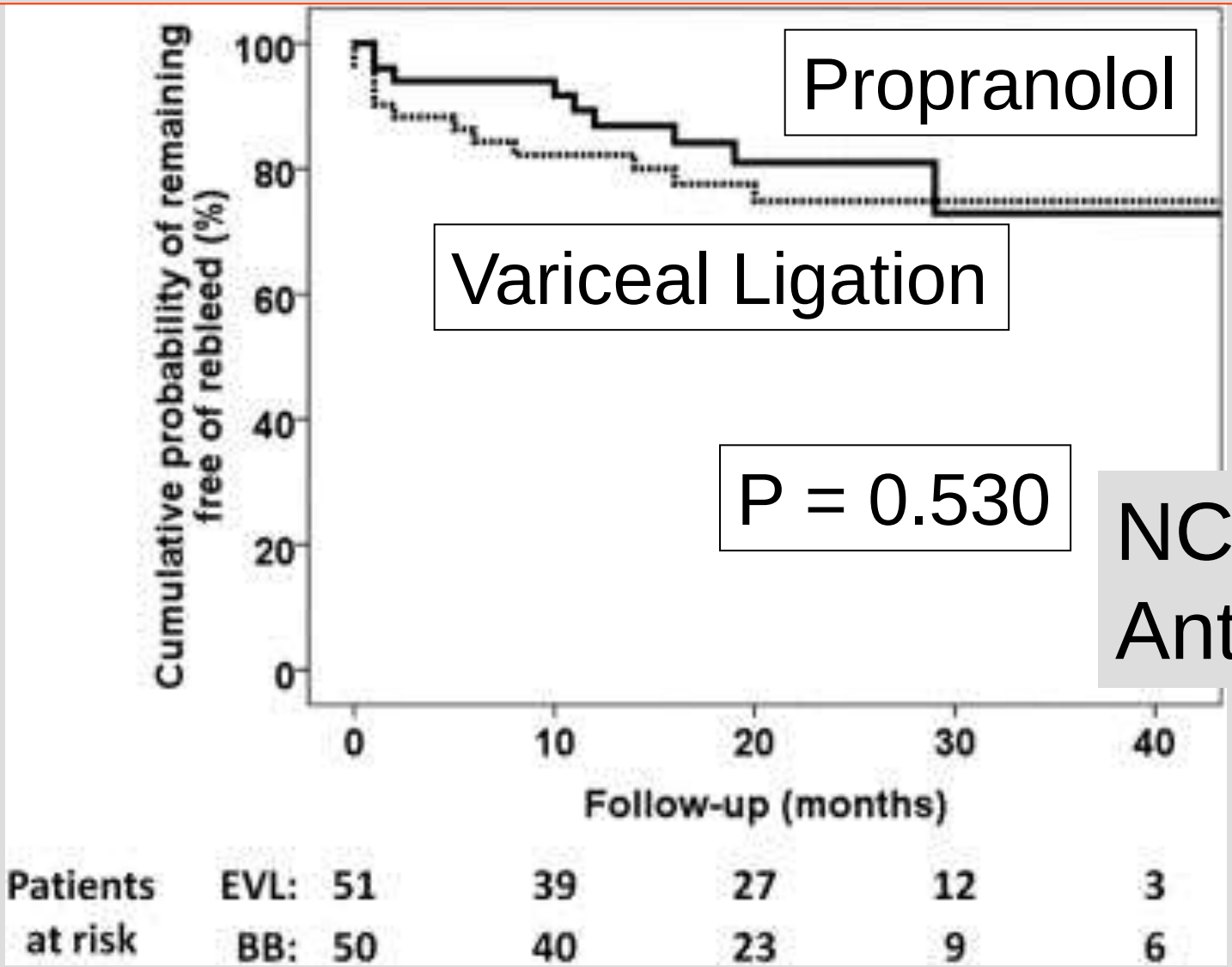


Normal preterminal portal venules



Obliterative portal venopathy

Secondary prophylaxis for PHT Bleeding



~ 20% at 2 yr

NCIPHT
Anticoagulation=0

Sarin. Gastro 2010

EVL and anticoagulation

	PVT & VKA	PVT no VKA
EVL proc.	121	130
Bleeding	7%	5%
Eradication	71 %	85 %
N. procedures	5,6	5,8

Christol. ILC 2012. 75% secondary prophylaxis

EVL, bleeding and anticoagulation

	PVT & VKA	PVT no VKA
Hospitalisation	75 %	69 %
Days in hospital	7,4	11
Days in USI	2,3	0,6
Blood units	3,2 ± 1,9	4,2 ± 2,2

Portal vein thrombosis and MPN

- 137 PVT patients (47 $JAK2^{V617F}$)
- Mean follow-up 5.5 years

→ No impact of $JAK2^{V617F}$ on OS or EFS

Kiladjian Blood 2008

Causes of death in SVT patients

Vascular disease	BCS	SVT	PVT
Number	156	128	120
F-u - *months*	50	72	66
Non liver-related - *N*	24	14	29
MPN - *N*	4	3	6
Bleeding - *N*	3	NA	5
Thrombosis - *N*	0	NA	3
Other/Unknown - *N*	17	NA	15

Seijo, Hepatology 2013. Chait, Br J Haematol 2005. Spaander, JTH 2011a. Spaander, JTH 2011b

Causes of death in SVT patients

Vascular disease	BCS	SVT	PVT	PVT/MPN
Number	156	128	120	44
F-u - *months*	50	72	66	70
Non liver-related - *N*	24	14	29	17
MPN - *N*	4	3	6	8
Bleeding - *N*	3	NA	5	0
Thrombosis - *N*	0	NA	3	3
Other/Unknown - *N*	17	NA	15	6

Seijo, Hepatology 2013. Chait, Br J Haematol 2005. Spaander, JTH 2011a. Spaander, JTH 2011b

PVT Causes of Death

120 patients (1985-2008)

Follow-up 5.5 years (range 0.1–32.5 years)

Death	29
Bleeding (EV)	5 (2)
Thrombosis	3
Progressive MPN	6
Infection	3
Other/unknown causes	12

Spaander, JTH 2011