

11th HEMOSTASIS SEMINAR

1-2 OCTOBER 2019

Ramada Plaza by
Wyndham Bucharest



Gemelli



Splanchnic vein thrombosis : diagnosis and management

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Valerio De Stefano - Disclosures

Amgen	Honorarium	Speaker
Novartis		Advisory Board
Celgene	Honorarium	Speaker
Grifols	Honorarium	Advisory Board
Janssen	Honorarium	Speaker

Definition

Budd Chiari Syndrome (BCS)

Occlusion of hepatic veins, from the small hepatic veins to the entrance of the right atrium

Extra Hepatic Portal Vein Obstruction (EHPVO)

Obstruction of the extrahepatic portal vein:

- With or without thrombosis of the intrahepatic portal veins
- With or without thrombosis of the splenic or superior mesenteric veins

Mesenteric vein thrombosis

Splenic vein thrombosis

Epidemiology

Budd Chiari Syndrome (BCS)

Annual incidence 0.4-0.8 per million individuals in Western countries

Extra Hepatic Portal Vein Obstruction (EHPVO)

Annual incidence 0.7 per 100,000 individuals

1 per cent of autopsies (one-third non-malignant and non-cirrhotic EHPVO)

Superior Mesenteric Vein Thrombosis

Annual incidence 2.7 per 100,000 individuals

Reviewed in Martinelli & De Stefano et al, Thromb Haemost 2010; 103:1136

Risk factors for SVT

Variable (%)	Total (n = 832)	Hepatic (n = 45)	Portal (n = 329)	Mesenteric (n = 76)	Splenic (n = 62)
Age (mean ± SD)	53 ± 17	45 ± 17	54 ± 18	59 ± 16	56 ± 16
Female (%)	42	67	38	37	29
Idiopathic	15	9	16	22	5
Cancer	27	13	31	20	36
Myeloproliferative	11	22	5	5	5
Leukemia/lymphoma	5	0	6	4	2
Inflammatory bowel disease	6	11	8	3	2
Pancreatitis	13	4	9	12	45
OCP/HRT	6	13	4	7	5
Cirrhosis	24	16	34	8	10
Surgery	10	11	9	12	5
Infection	10	7	13	18	5
Connective tissue disease	6	9	5	5	2
Thrombophilia					
No. positive (no. tested)	105 (319)	10 (25)	20 (86)	22 (43)	4 (12)

Long-term Clinical Outcomes of Splanchnic Vein Thrombosis

Results of an International Registry

Characteristic	Patients With SVT, No./Total No. (%) (n = 604)
Age, median (IQR), y	54 (43-64)
Male sex	378/604 (62.6)
Asian ethnicity	137/604 (22.7)
Risk factors	
Unprovoked	163/600 (27.2)
Hepatic cirrhosis	167/600 (27.8)
Solid cancer	136/600 (22.7)
Myeloproliferative neoplasm	49/600 (8.2)
Inflammatory bowel disease	11/600 (1.8)
Other intra-abdominal inflammations or infections	60/600 (10.0)
Abdominal surgery	54/600 (9.0)
Hormonal therapy	25/226 (11.1)
Pregnancy or puerperium	8/226 (3.53)

	Budd-Chiari syndrome	Portal vein thrombosis
Local risk factors (%)		
● Acquired		
Cancer	6–7	13–24
Cirrhosis	8–14	17–18
Abdominal infection	7	10
Liver abscess	2	3–5
Inflammatory bowel diseases	3–8	1–4
Pancreatitis	-	6–19
Cholecystitis	-	2–7
Appendicitis	-	1
Tuberculous lymphadenitis	-	3
Membranous web	1–4 (West) – 30 (East)	-
Neonatal omphalitis	-	1–6
● Circumstantial		
Abdominal surgery	2–23	10–30
Splenectomy	2	7
Cholecystectomy	-	3–12
Gastrectomy	-	3
Liver transplantation	-	2
Abdominal trauma	10	1–3

Martinelli & De Stefano, Thromb Haemost 2010;103:1136

	Budd-Chiari syndrome	Portal vein thrombosis
Systemic risk factors (%)		
● Inherited		
Antithrombin deficiency	2–5	1–2
Protein C deficiency	2–9	1–9
Protein S deficiency	3–7	1–5
Factor V Leiden	4–26	3–8
Prothrombin G20210A	3–8	3–22
● Acquired		
Myeloproliferative neoplasms	23–49	6–33
JAK2 V617F (with overt myeloproliferative neoplasms)	57–100	78–100
JAK2 V617F (without overt myeloproliferative neoplasms)	44	27
Antiphospholipid antibodies	1–11	3–13
Behcet disease	4–9	
Autoimmune diseases	10–13	1–4
Paroxysmal nocturnal haemoglobinuria	2–19	1–2
● Circumstantial*		
Oral contraceptives	15–50	15–30
Hormone replacement therapy	14	3
Pregnancy or puerperium	4–16	2–3
* percentage calculated on the number of women.		

Martinelli & De Stefano, Thromb Haemost 2010

MPN are frequent in non-cirrhotic and non malignant SVT

Reference	Type of SVT	Patients (n)	JAK2 V617F %	Overt MPN %¶	JAK2 V617F %¶		
					All patients ¶	MPN patients¶	No-MPN patients¶
Dentali et al. 2009 [38], meta-analysis	not specified	831	280/831 32.7%	77/131 59.5%	N/A	N/A	N/A
Qi et al. 2011 [39], meta-analysis	BCS + PVT + not specified	1697 §	427/1697 § 25.1%	280/1063 26.3%	343/1063 32.2%	213/280 76.1%	120/783 15.3%
	BCS	555	177/555 31.8%	77/242 31.8%	106/242 43.8%	62/77 80.5%	44/165 26.6%
	PVT	858	250/858 29.1%	86/532 16.1%	136/532 25.5%	75/86 87.2%	61/446 13.6%
Smalberg et al. 2012 [19], meta-analysis	BCS	1062	159/401 41.1%	180/440 40.9%	188/440 42.7%	144/180 80.3%	44/260 17.1%
	PVT	855	166/595 27.7%	188/615 31.5%	228/615 37.0%	162/188 86.6%	66/427 15.4%

¶ including only patients with non-cirrhotic and non-malignant SVT who received a complete diagnostic work-up for MPN. § including 91 patients with cirrhosis, 5 of them JAK2V617-positive. N/A: not available.

De Stefano et al, Thromb Haemost 2016;115:240

JAK2 V617F is frequent in SVT

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De Stefano et al, Thromb Haemost 2016;115:240

CALR mutations are not frequent in SVT

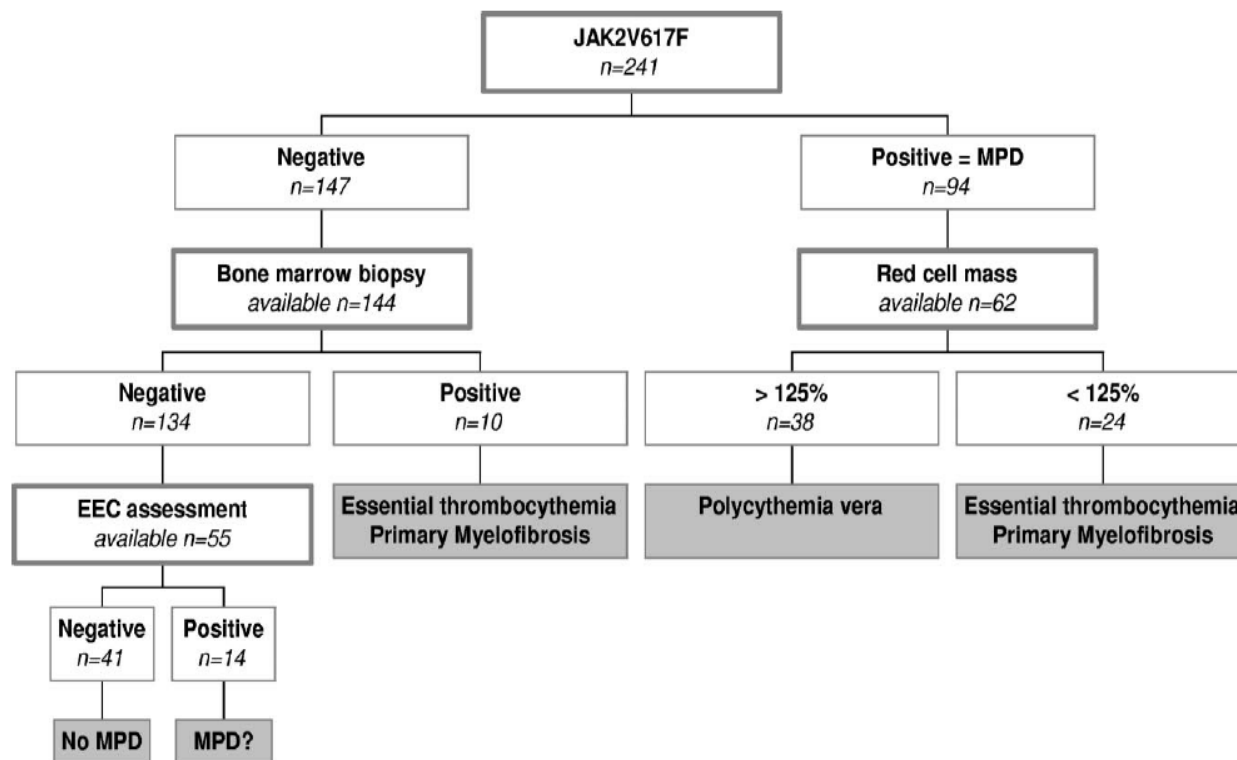
Reference	SVT patients, n	CALR mutations, n (%)	CARL-mutated patients	
			Type of MPN	Type of SVT
Turon et al. 2015 [48]	209	4 (1.9%)	ET= 3 PMF= 1	BCS=2, PVT=2
Marzac et al. 2015 [49]	308	5 (2%)	ET= 1 PMF= 4	PVT=5
Haslam et al, 2015 [50]	144	0	N/A	N/A
Roques et al. 2015 [51]	66	1 (1.5%)	not specified	not specified
Castro et al. 2015 [52]	40	0	N/A	N/A
Iurlo et al. 2015 [53]	29	0	N/A	N/A
Plompen et al. 2015 [54]	141	1 (0.7%)	PMF	PVT
Colaizzo et al. 2015 [55]	132	0	N/A	N/A
Total	1,066	10 (0.9%)	ET= 4 PMF= 6	BCS= 2, PVT= 8

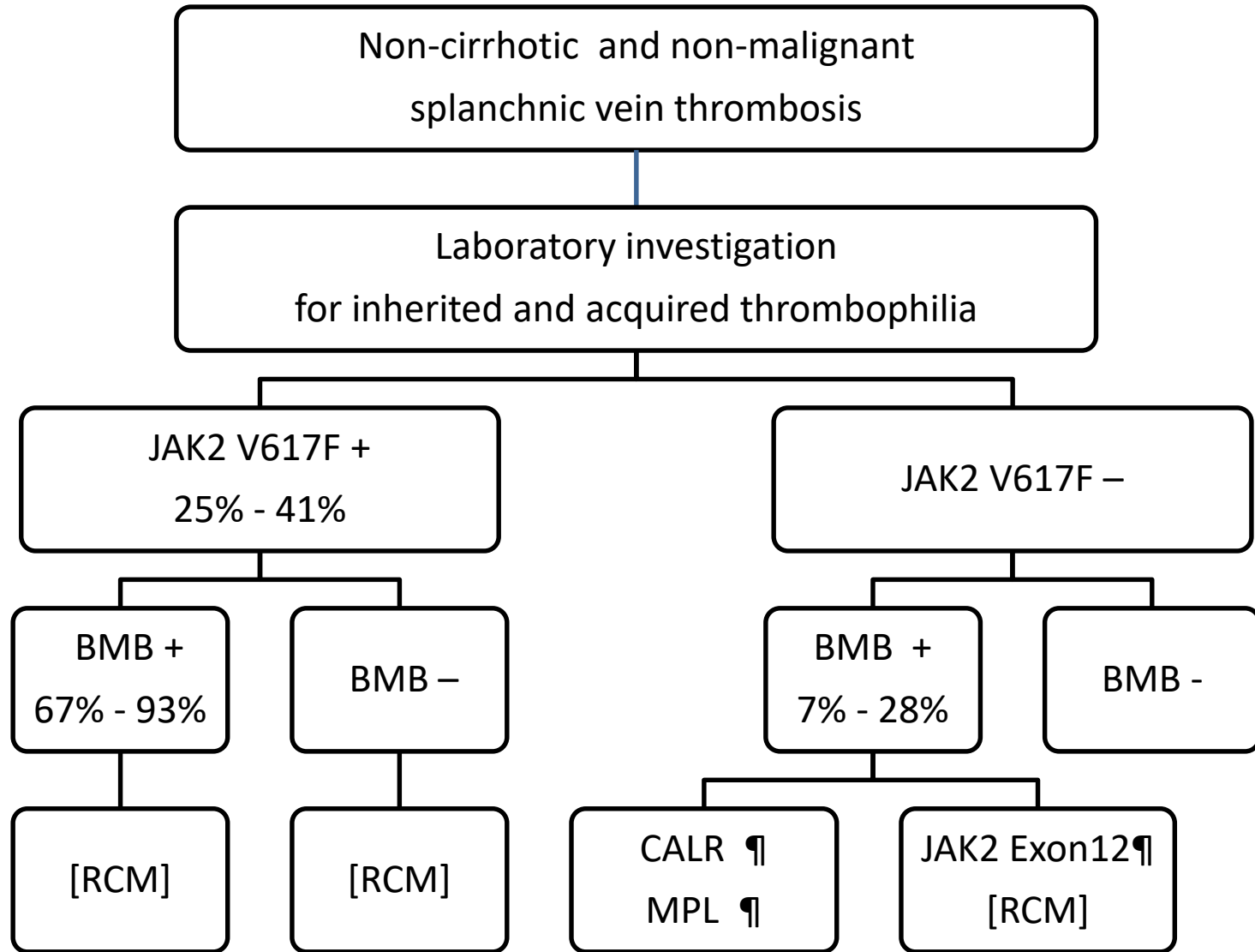
ET: essential thrombocythaemia; N/A: not available; PMF: primary myelofibrosis.

De Stefano et al, Thromb Haemost 2016;115:240

The impact of JAK2 and MPL mutations on diagnosis and prognosis of splanchnic vein thrombosis: a report on 241 cases

Jean-Jacques Kiladjian, Francisco Cervantes, Franck W. G. Leebeek, Christophe Marzac, Bruno Cassinat, Sylvie Chevret, Dominique Cazals-Hatem, Aurélie Plessier, Juan-Carlos Garcia-Pagan, Sarwa Darwish Murad, Sebastian Raffa, Harry L. A. Janssen, Claude Gardin, Sophie Cereja, Carole Tonetti, Stéphane Giraudier, Bertrand Condat, Nicole Casadevall, Pierre Fenaux and Dominique C. Valla





Outcomes

- Recurrent thrombosis
- Bleeding
- Evolution to MPN

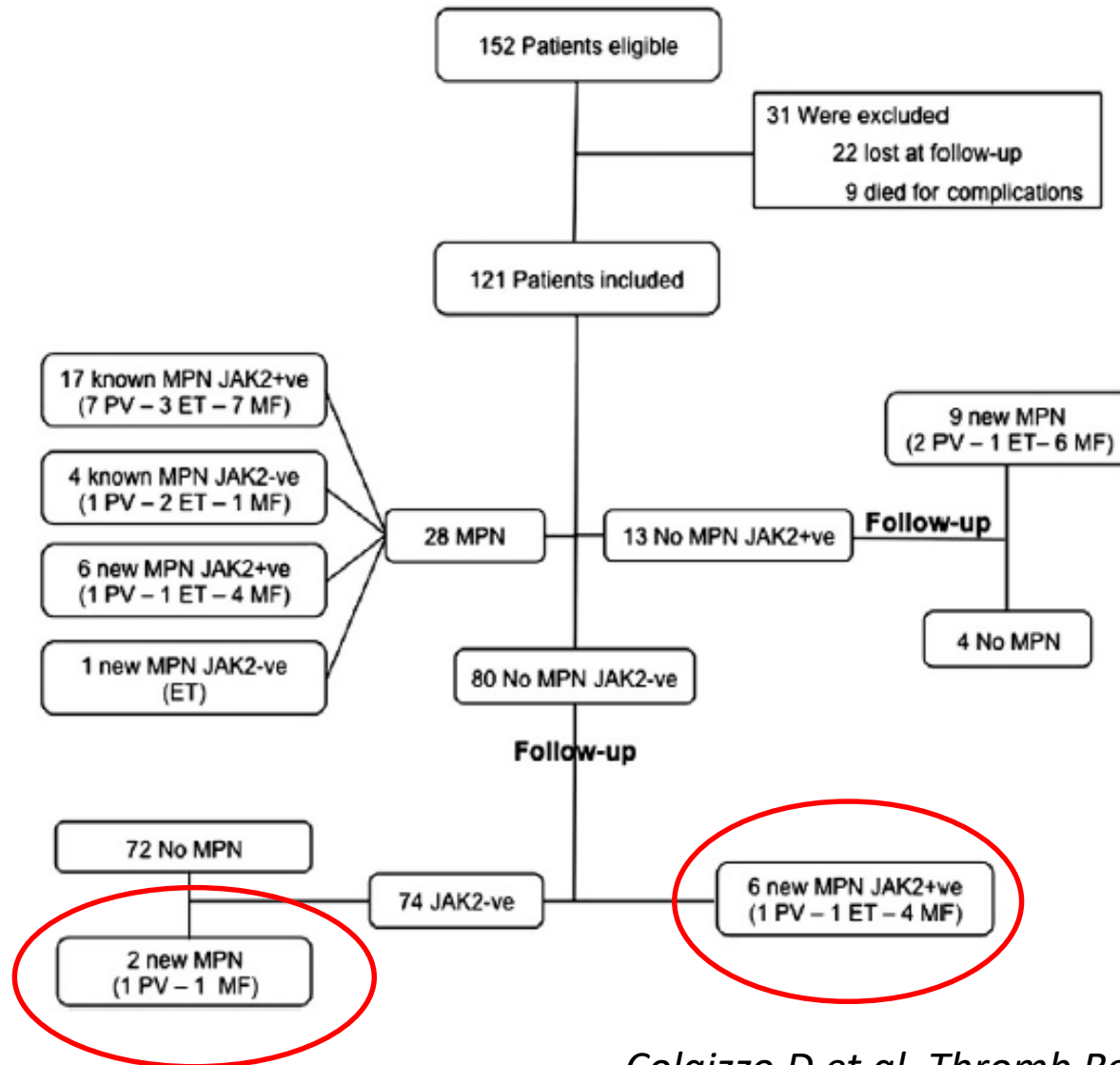
SVT predicts MPN during the follow-up

280 of 831 patients with SVT had the *JAK2V617F* mutation, for a mean prevalence of 33.7%

Five studies provided data on development of MPN during follow-up in patients with JAK2 mutation and without an overt MPN at the time of SVT diagnosis (21 of 41 patients, 51.2%, developed overt MPN)

Dentali et al, Blood 2009;113:5617

SVT predicts MPN during the follow-up



SVT predicts MPN during the follow-up

Table 3. SIRs for cancer in 1191 patients with SVT

Cancer site	Observed cancers and SIRs (95% CI)							
	0 to <3 months		3 to <12 months		12+ months		Overall	
Any	95	33 (27-40)	18	2.7 (1.6-4.3)	70	2.1 (1.6-2.6)	183	4.2 (3.6-4.9)
Liver	41	1805 (1295-2449)	5	92 (30-215)	2	7.4 (0.9-27)	48	138 (101-182)
Myeloproliferative neoplasms	8	764 (329-1505)	3	119 (25-348)	12	88 (45-153)	23	133 (85-200)
Pancreas	17	256 (149-409)	0	—	3	4.0 (0.8-12)	20	21 (13-32)
Hodgkin malignant lymphoma	1	172 (4.3-956)	0	—	0	—	1	9.7 (0.3-54)
Gallbladder or biliary tract	2	132 (16-476)	1	28 (0.7-155)	0	—	3	14 (2.9-41)
Metastases and nonspecified cancer in lymph nodes	5	86 (28-201)	0	—	0	—	5	6.3 (2.0-15)
MDS	1	75 (1.9-415)	0	—	1	6.8 (0.2-38)	2	11 (1.3-38)
Kidney	2	47 (5.6-168)	0	—	0	—	2	3.0 (0.4-11)
Leukemia	2	38 (4.6-138)	0	—	1	1.7 (0.0-9.3)	3	3.9 (0.8-11)
Non-Hodgkin malignant lymphoma	3	34 (7.0-99)	0	—	1	0.9 (0.0-5.3)	4	3.0 (0.8-7.5)
Lung, bronchi, or trachea	4	13 (3.6-34)	1	1.4 (0.0-8.0)	7	2.0 (0.8-4.2)	12	2.7 (1.4-4.7)
Colon	2	9.5 (1.1-34)	1	2.1 (0.1-12)	3	1.3 (0.3-3.8)	6	2.0 (0.7-4.4)
Breast	1	3.6 (0.1-20)	0	—	4	1.2 (0.3-3.2)	5	1.2 (0.4-2.8)
Bladder	0	—	2	6.1 (0.7-22)	6	3.8 (1.4-8.3)	8	3.9 (1.7-7.7)
Stomach	0	—	1	9.8 (0.3-55)	3	6.1 (1.3-18)	4	6.3 (1.7-16)
Rectum	0	—	0	—	2	1.6 (0.2-5.8)	2	1.3 (0.2-4.5)
Uterus	0	—	1	8.9 (0.2-50)	0	0	1	1.5 (0.0-8.4)
Prostate	0	—	1	1.6 (0.0-8.7)	5	1.4 (0.4-3.2)	6	1.3 (0.5-2.9)

Danish National Health Service 1994-2011 [Sogaard K et al, Blood 2015;126:957]

Survival and Recurrence in Patients With Splanchnic Vein Thromboses

MALLIKARJUN R. THATIPELLI,* ROBERT D. MCBANE,*‡ DAVID O. HODGE,§ and WALDEMAR E. WYSOKINSKI*‡

**Division of Cardiovascular Medicine, ‡Division of Hematology, and §Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota*

1847 patient-years of follow up (28% treated with warfarin)

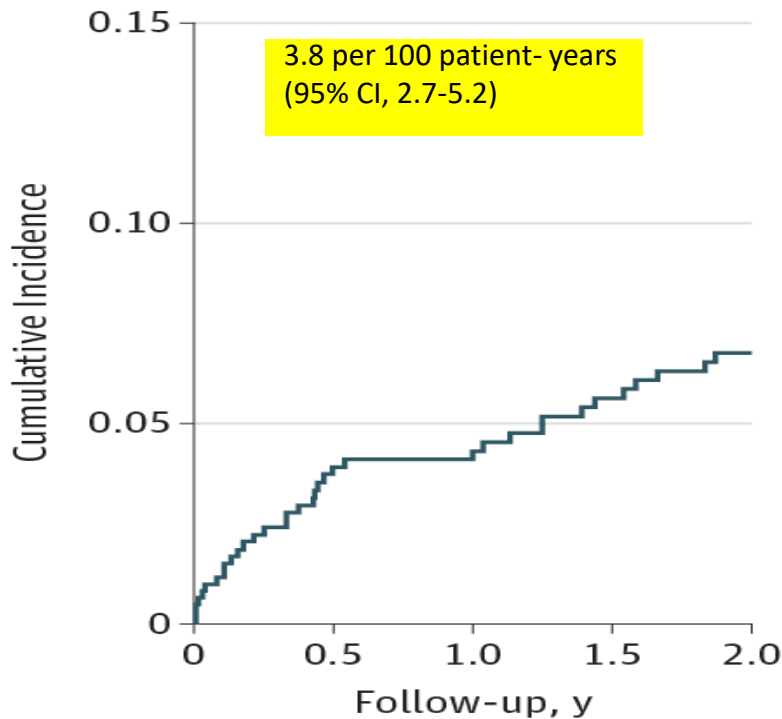
Major bleeding	6.9/100 patient-years
Independent predictors	
➤ Esophageal varices	HR 2.63 (95% CI 1.72-4.03)
➤ Warfarin	HR 1.91 (95% CI 1.25-2.92)
Recurrent thrombosis	3.5/100 patient-years
Independent predictors	
➤ Oral contraceptives	HR 2.2 (95% CI 1.09-4.45)

Original Investigation

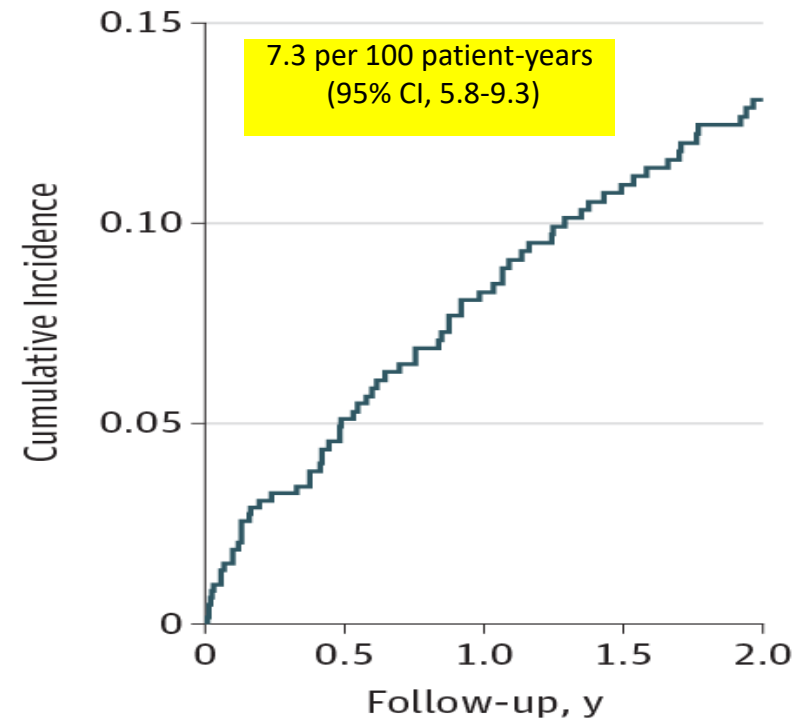
Long-term Clinical Outcomes of Splanchnic Vein Thrombosis Results of an International Registry

Walter Ageno, MD; Nicoletta Riva, MD; Sam Schulman, MD; Jan Beyer-Westendorf, MD; Soo Mee Bang, MD; Marco Senzolo, MD; Elvira Grandone, MD; Samantha Pasca, MD; Matteo Nicola Dario Di Minno, MD; Rita Duce, MD; Alessandra Malato, MD; Rita Santoro, MD; Daniela Poli, MD; Peter Verhamme, MD; Ida Martinelli, MD; Pieter Kamphuisen, MD; Doyeun Oh, MD; Elbio D'Amico, MD; Cecilia Becattini, MD; Valerio De Stefano, MD; Gianpaolo Vidili, MD; Antonella Vaccarino, MD; Barbara Nardo, MD; Marcello Di Nisio, MD; Francesco Dentali, MD

A Major bleeding events



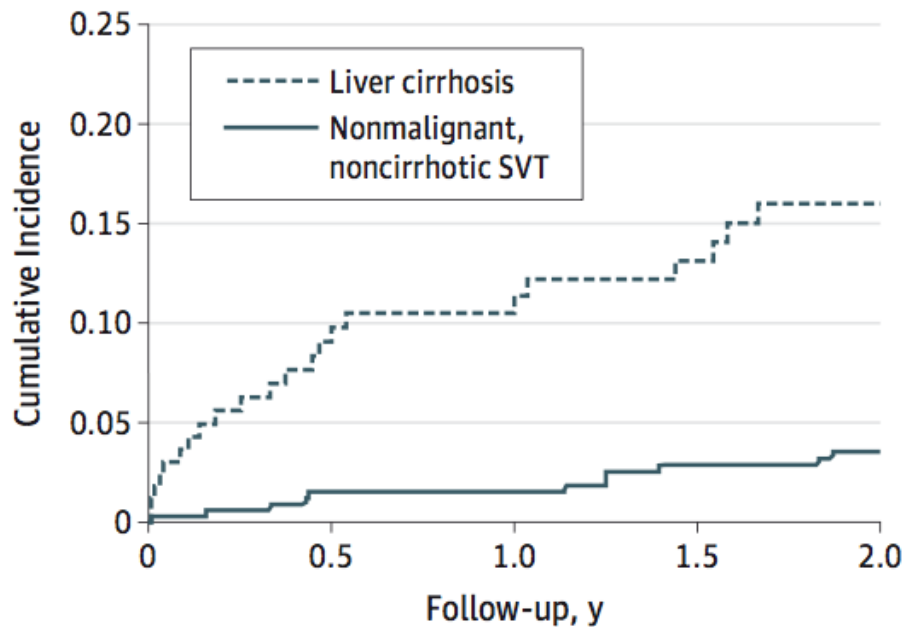
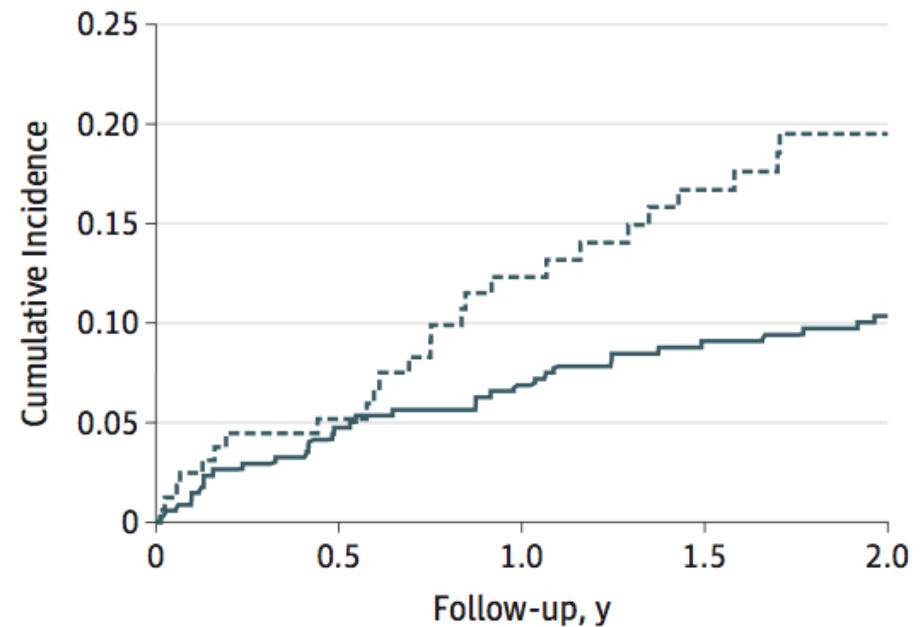
B Vascular thrombotic events



Original Investigation

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A Major bleeding events**B** Vascular thrombotic events

Original Investigation

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Outcome	Liver Cirrhosis (n = 167)	Solid Cancer (n = 136)	Myeloproliferative Neoplasm (n = 49)	Unprovoked SVT (n = 163)	Transient Risk Factors ^b (n = 105)
Major bleeding events	22 Events; 10.0 per 100 patient-years (6.6-15.1)	7 Events; 4.4 per 100 patient-years (2.1-9.3)	3 Events; 3.6 per 100 patient-years (1.1-11.1)	5 Events; 1.7 per 100 patient-years (0.7-4.2)	1 Event; 0.5 per 100 patient-year (0.1-3.7)
Thrombotic events	25 Events; 11.3 per 100 patient-years (7.7-16.8)	12 Events; 7.6 per 100 patient-years (4.3-13.3)	5 Events; 5.9 per 100 patient-year (2.5-14.3)	18 Events; 6.3 per 100 patient-year (4.0-10.0)	6 Events; 3.2 per 100 patient-year (1.4-7.0)
Mortality	45 Events; 16.8 per 100 patient-year (12.5-22.4)	67 Events; 39.5 per 100 patient-years (31.1-50.1)	3 Events; 3.4 per 100 patient-year (1.1-10.4)	7 Events; 2.3 per 100 patient-years (1.1-4.8)	5 Events; 2.5 per 100 patient-years (1.1-6.1)

Abbreviation: SVT, splanchnic vein thrombosis.

^a Some patients had more than 1 risk factor.

^b Transient risk factors included recent surgery, intra-abdominal infection, use of hormone therapy, pregnancy/puerperium, and abdominal trauma.

ISTH International registry on SVT: Therapeutic strategies according to the site of thrombosis

Treatment	BCS (n: 51)	PVT (n:244)	MVT (n: 67)	SpVT (n: 19)	Multiple site (n:232)
No treatment	31.4%	33.2%	9.0%	15.8%	12.9%
UFH	15.7%	4.9%	9.0%	0	16.4%
LMWH/fonda parinux	49%	58.6%	83.6%	84.2%	71.8%
VKA	47.1%	31.6%	61.2%	63.2%	60.8%
Thrombolysis	3.9%	0	1.5%	0	2.6%

Efficacy and safety of VKA therapy after portal vein thrombosis in non-cirrhotics

136 patients, median follow-up 46 months (84 on VKA), retrospective cohort study

GI bleeding 12.5 (95% CI 10-15) 100 pt/y

Recurrent venous thrombosis 5.5 (95% CI 3.8-7.2) 100 pt/y

ISTH registry: long-term clinical outcome

• **Thrombotic events**

- **On treatment** **5.6 per 100 pt-y (95% CI, 3.9-8.0)**
- **After discontinuation** **10.5 per 100 pt-y (95% CI, 6.8-16.3)**
- **Never treated** **9.2 per 100 pt-y (95% CI, 5.7-15.1)**

eTable 3. Multivariate Analysis for Thrombotic Events

	<i>Hazard Ratio</i>	<i>95% confidence interval</i>	<i>p value</i>
Whole study cohort			
• Age (year)	1.028715	1.003079 - 1.055007	0.028
• Male sex	4.097299	1.680863 - 9.987643	0.002
• Time on anticoagulant treatment (months)	.8876051	.8414891 - .9362483	< 0.001

ISTH registry:
long-term clinical outcome

- **On treatment** **3.9 per 100 pt-y (95% CI, 2.6-6.0)**
- **After discontinuation** **1.0 per 100 pt-y (95% CI, 0.3-4.2)**
- **Never treated** **5.8 per 100 pt-y (95% CI, 3.1-10.7)**

eTable 2. Multivariate Analysis for Major Bleeding

	Hazard Ratio	95% confidence interval	p value
Whole study cohort			
• Liver cirrhosis with ascites	13.37157	3.259943 - 54.84727	< 0.001
• Liver cirrhosis without ascites	4.844619	1.499181 - 15.65543	0.008
• Ascites without liver cirrhosis	4.891776	.8804843 - 27.17762	0.070
• Time on anticoagulant treatment (months)	.8981033	.8363653 - .9643986	0.003

Safety of VKAs for SVT: multicenter retrospective cohort study

Demographic characteristics	Patients with SVT
Number	375
Age (years), median (IQR)	53 (43-63)
Males	54.7%
Unprovoked SVT	37.1%
Haematologic cancer	21.6%
Cirrhosis	15.2%
Solid cancer	10.7%
Recent surgery	8.0%
Inflammation/infection	6.7%

Esophageal varices: 23.2%

Safety of VKAs for SVT: multicenter retrospective cohort study

Time-point	Cumulative number of events	Incidence rate of major bleeding (95% CI)
6 months	5	2.85 per 100 pt-y (1.18-6.84)
1 year	7	2.18 per 100 pt-y (1.04-4.56)
2 years	10	1.83 per 100 pt-y (0.99-3.41)
5 years	13	1.41 per 100 pt-y (0.82-2.44)
End of follow-up	15	1.24 per 100 pt-y (0.75-2.06)

Predictors of bleeding: esophageal varices (HR 4.9, 1.4-17.1), IBD (HR 15.2, 0.99-233.1)

Anticoagulation for the treatment of portal vein thrombosis in liver cirrhosis: A systematic review and meta-analysis of observational studies

Xingshun Qi ^{a,b,1}, Valerio De Stefano ^{c,2}, Hongyu Li ^{a,3}, Junna Dai ^{a,4}, Xiaozhong Guo ^{a,*}, Daiming Fan ^{b,**}

European Journal of Internal Medicine 26 (2015) 23–29

- **16 observational studies**
- **Complete portal vein recanalization in anticoagulated pts 41.5%**
(95% CI, 29.2-54.5; $I^2 = 82.2\%$, $p < 0.0001$)
Anticoagulation OR 4.16 (95% CI, 1.88-9.20, $p = 0.0004$)
- **Thrombus progression in anticoagulated pts 5.7%**
(95% CI, 2.0-11.3; $I^2 = 48.6\%$, $p = 0.0698$)
Anticoagulation OR 0.061 (95% CI, 0.019-0.196, $p < 0.0001$)
- **Anticoagulation-related bleeding complications 3.3%**
(95% CI, 1.1-6.7; $I^2 = 53.5\%$, $p = 0.018$)



Antithrombotic Therapy for VTE Disease

- Symptomatic splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses): anticoagulation over no anticoagulation (Grade 1B)
- Incidentally detected splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses): no anticoagulation over anticoagulation (Grade 2C)



Antithrombotic Therapy for VTE Disease

- LMWH may be preferred over VKA if there is active malignancy, liver disease, or thrombocytopenia.
- The presence of a reversible provoking factor for splanchnic vein thrombosis, such as intraabdominal sepsis or recent surgery, supports stopping anticoagulant therapy after 3 months.
- Absence of a reversible risk factor (eg, “unprovoked” thrombosis or presence of a persistent risk factor, such as myeloproliferative disease) and a low risk of bleeding support extended anticoagulant therapy.

ISTH Guidance statements

In patients with incidental splanchnic vein thrombosis (AND CANCER), we suggest anticoagulant therapy in patients with thrombosis that appears to be acute, shows progression or extension over time, and in those who are not actively bleeding nor have a very high risk of bleeding.

Revising consensus in portal hypertension: Report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension

Roberto de Franchis*, On behalf of the Baveno V Faculty¹

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Treatment: recent EHPVO: anticoagulation

- Recent EHPVO rarely resolves spontaneously.
- In non-cirrhotic patients with symptomatic recent EHPVO, low molecular weight heparin should be started immediately followed by oral anticoagulant therapy (2b;B). In asymptomatic patients, anticoagulation should be considered.
- Anticoagulation should be given for at least three months, unless an underlying persistent prothrombotic state has been documented, in which case life-long anticoagulation is recommended (5;D).

Vascular Disorders of the Liver

Laurie D. DeLeve,¹ Dominique-Charles Valla,² and Guadalupe Garcia-Tsao³

- Minimum duration of treatment 3 months
- Discontinue when secondary to surgery or infections
- Indefinite treatment duration when secondary to cirrhosis, cancer (including MPN), autoimmune disorders, thrombus extension into the mesenteric veins

MPN or absence of VKA are risk factors for recurrence after SVT

REFERENCE	Amitrano et al, 2007	Thatipelli et al, 2009	Spaander et al, 2013	Colaizzo et al, 2013	Riva et al, 2015	Agno et al, 2015	De Stefano et al, 2015 [unpublished]
Patients (n)	121 (follow-up in 95)	832	120	121	375	604	154
Exclusion criteria	cirrhosis solid cancer	None	Only PVT without cancer, cirrhosis, liver Tx, BCS	Only PVT without cancer, cirrhosis, liver Tx, BCS	SVT without VKA	None	cirrhosis solid cancer
Recurrent thrombosis (patients %)	4.2 arterial 10.5 venous	7.8 venous	15.8 (either arterial and venous)	18.1 venous	1.8 arterial 2.4 venous	2.3 arterial 8.9 venous	1.9 arterial 14.2 venous
Recurrent thrombosis (% pt-years)	not available	3.5 venous	approx. 2.4 (either arterial and venous)	5.7 (either arterial and venous)	0.60 arterial 0.77 venous	1.5 arterial 5.8 venous	0.4 arterial 2.9 venous
Risk factors for thrombosis	Overt MPN No VKA	Hormonal therapy Multiple veins involved	No VKA	MPN	Solid cancer MPN	Cirrhosis Unprovoked SVT Permanent risk factors No VKA	Male gender Age >45 yrs No VKA JAK2 V617F

Splanchnic vein thrombosis in myeloproliferative neoplasms: risk factors for recurrences in a cohort of 181 patients

	<i>Events, n (%)</i>	<i>Incidence rate per 100 pt-years (95% CI)</i>
Thrombotic events	31 (17.1)	4.2 (2.9–5.9)
<i>Venous thrombosis</i>	19 (10.5)	2.5 (1.6–4.0)
Recurrent SVT		1.9 (1.1–3.1)
Hepatic vein thrombosis	3 (1.7)	
Portal vein thrombosis	4 (2.2)	
Mesenteric vein thrombosis	6 (3.1)	
Splenic vein thrombosis	1 (0.6)	
Venous thrombosis at other sites		0.6 (0.2–1.5)
DVT	2 (1.1)	
PE	2 (1.1)	
Cerebral vein thrombosis	1 (0.6)	
<i>Arterial thrombosis</i>	10 (5.5)	1.3 (0.7–2.4)
Unstable angina	1 (0.6)	
Myocardial infarction	2 (1.1)	
Ischaemic stroke	3 (1.7)	
Peripheral artery thrombosis	3 (1.7)	
Retinal artery thrombosis	1 (0.6)	
Not specified	2 (1.1)	

VKA were prescribed in 85% of patients and the recurrence rate was 3.9 per 100 pt-years, whereas in the small fraction (15%) not receiving VKA more recurrences (7.2 per 100 pt-years) were reported.

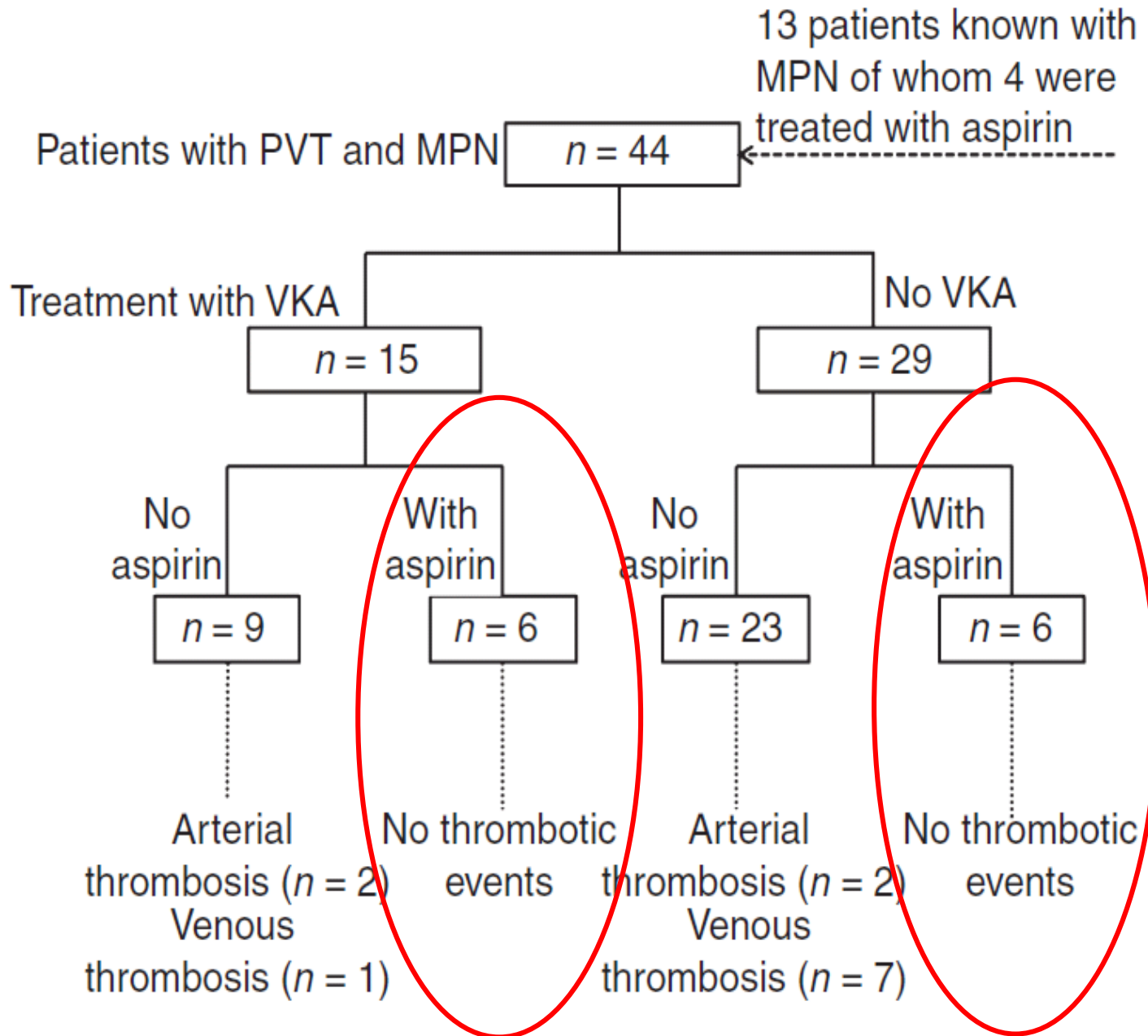
Events, n (%) Incidence rate, % pt-yrs (95% C.I.)	Index Budd-Chiari (n=31)	Other index SVT (n=150)	p-value
On VKA treatment, n (%)	10 (32)	17 (11)	0.003
Thrombotic events	11 (35) 7.5 (4.0-14.0)	20 (13) 3.2 (2.0-5.0)	0.003 0.020
Venous thrombosis	7 (23) 4.9 (2.3-10.3)	12 (8) 1.9 (1.1-3.4)	0.016 0.028
Arterial thrombosis	3 (10) 1.9 (0.6-5.8)	7 (5) 1.1 (0.5-2.3)	0.266 0.454
Major bleeding	3 (10) 1.2 (0.3-4.8)	13 (9) 1.6 (0.9-3.0)	0.740 0.788
Deaths	2 (6) 1.2 (0.3-4.6)	12 (8) 1.8 (1.0-3.1)	0.558 0.550

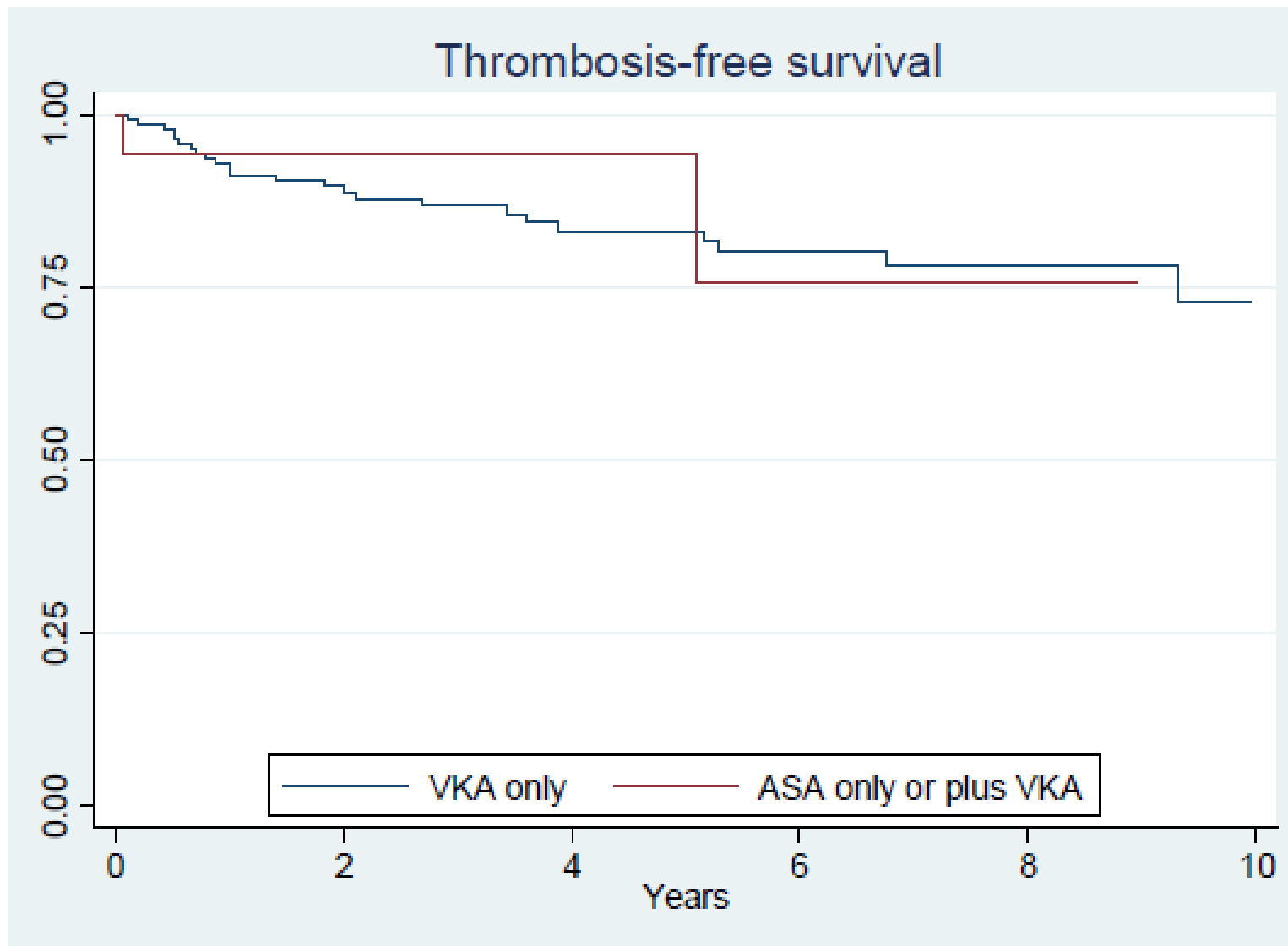
Significant risk factors associated with incidence of thrombosis after SVT index by stepwise selection (complete multivariate model included age > 60 years, thrombosis history, CV risk factors, Hb > 15g/dL, Hct > 45%, WBC > 14x10⁹/L, Plt > 500x10⁹/L, splenomegaly, unprovoked event, hepatic event vs other splenic events, VKA treatment, other treatments).

Risk factor for Thrombosis	Hazard ratio (95%CI)	Risk factor for Bleeding	Hazard ratio (95%CI)
WBC > 14x10 ⁹ /L	2.88 (1.32 – 6.28)	WBC > 14x10 ⁹ /L	5.01 (1.43 – 17.56)
Thrombotic history	3.62 (1.22 – 10.78)	CV risk factors	9.92 (2.54 – 38.73)
Budd-Chiari	3.03 (1.37-6.69)		
Splenomegaly	2.66 (1.06 – 6.64)		

- BCS is confirmed to be the more severe event among SVT
- Splenomegaly should be likely considered either as an index of portal hypertension and proliferation
- The role of leukocytosis as a risk factor for recurrence and bleeding calls for cytoreduction

Are MPN patients with SVT candidates to a combined treatment of VKA plus aspirin ?





Aspirin does not give any advantage over VKA

Are MPN patients with SVT candidates to
cytoreduction ?

Pooled analysis of 1500 cases – GIMEMA / ELN cohorts 2008-2018

Table 1 Clinical features of the cohort at the index thrombosis (N = 1500)

Diagnosis	Total – N (%)
PV	590 (39.3%)
ET	761 (50.8%)
PMF	149 (9.9%)
Total	1500 (100%)
Male/female	652/848 (43.4%)
Age at thrombosis—median (range)	65 (19–90)
> = 60 years	848 (56.5%)
Type of index thrombosis	
<i>Arterial thrombosis (N = 935)</i>	
Acute coronary syndrome	107 (7.1%)
TIA	302 (20.1%)
Ischemic stroke	486 (32.5%)
Other arterial thromboses	40 (2.7%)
<i>Venous thrombosis (N = 565)</i>	
DVT of the legs and/or pulmonary embolism	293 (19.5%)
Budd–Chiari syndrome	38 (2.5%)
Portal–mesenteric venous thrombosis	180 (12.0%)
Cerebral vein thrombosis	40 (2.7%)
Other venous thromboses	14 (0.9%)

Pooled analysis of 1500 cases – GIMEMA / ELN cohorts 2008-2018

Table 3 Effect of long-term treatments on the risk of recurrences after the index thrombosis in the entire patient cohort (multivariable analysis).

	Overall recurrent thromboses (HR, 95% CI)		Arterial recurrent thrombosis (HR, 95% CI)*	<i>p</i>	Venous recurrent thrombosis (HR, 95% CI)*	<i>p</i>
Age > 60 years	1.23 (0.99–1.52)	0.06	1.18 (0.89–1.57)	0.23	1.28 (0.91–1.79)	0.15
Male sex	0.94 (0.76–1.17)	0.60	0.97 (0.73–1.28)	0.99	0.91 (0.65–1.28)	0.61
Antiplatelet treatment	0.58 (0.43–0.79)	0.0005	0.54 (0.35–0.82)	0.003	0.64 (0.40–1.03)	0.07
Oral anticoagulation (VKA or DOACs)	0.58 (0.41–0.81)	0.001	0.58 (0.35–0.96)	0.03	0.60 (0.37–0.95)	0.03
Hydroxyurea	0.75 (0.57–1.00)	0.05	0.67 (0.46–0.98)	0.04	0.87 (0.56–1.33)	0.52
Cytoreduction with agents other than hydroxyurea [#]	1.04 (0.74–1.45)	0.80	0.94 (0.61–1.46)	0.80	1.22 (0.72–2.04)	0.44

HR hazard ratio

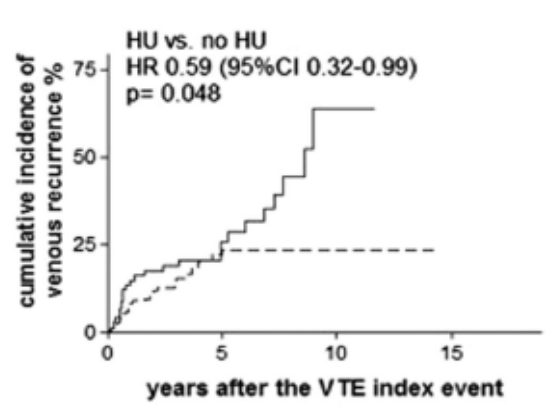
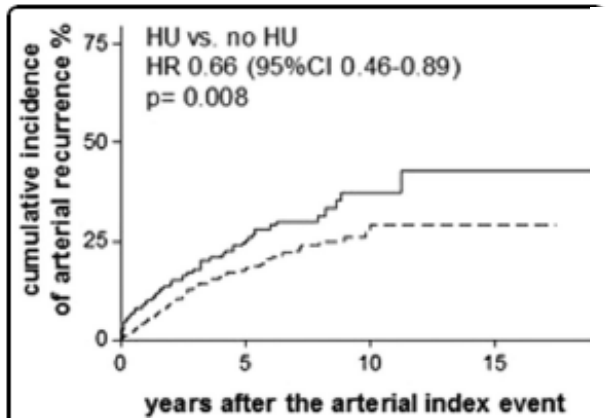
*Multivariable analysis adjusted for the arterial or venous site of the first thrombosis

[#]Anagrelide, interferon, pipobroman, busulfan, and ruxolitinib

Bold values are those with statistical significance

De Stefano et al, Blood Cancer Journal 2018; 8: 112

Pooled analysis of 1500 cases – GIMEMA / ELN cohorts 2008-2018



De Stefano et al, Blood Cancer Journal 2018; 8: 112

Recurrence after splanchnic vein thrombosis is prevented only by VKA, whereas HU has no effect. In this setting HU is suggested only in the presence of hypercythemia or in the case of progressive disease.

The direct oral anticoagulants for the treatment of splanchnic vein thrombosis

Successful treatment of acute portal vein thrombosis with rivaroxaban

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Treatment of Acute Portal Vein Thrombosis by Non-traditional Anticoagulation

Melissa Martinez,¹ Anand Tandra,² Raj Vuppalanchi¹

Successful Treatment of Partial Portal Vein Thrombosis (PVT) with Low Dose Rivaroxaban

Authors

K. Lenz¹, B. Dieplinger², R. Buder¹, P. Piringer¹, M. Rauch³, M. Voglmayr¹

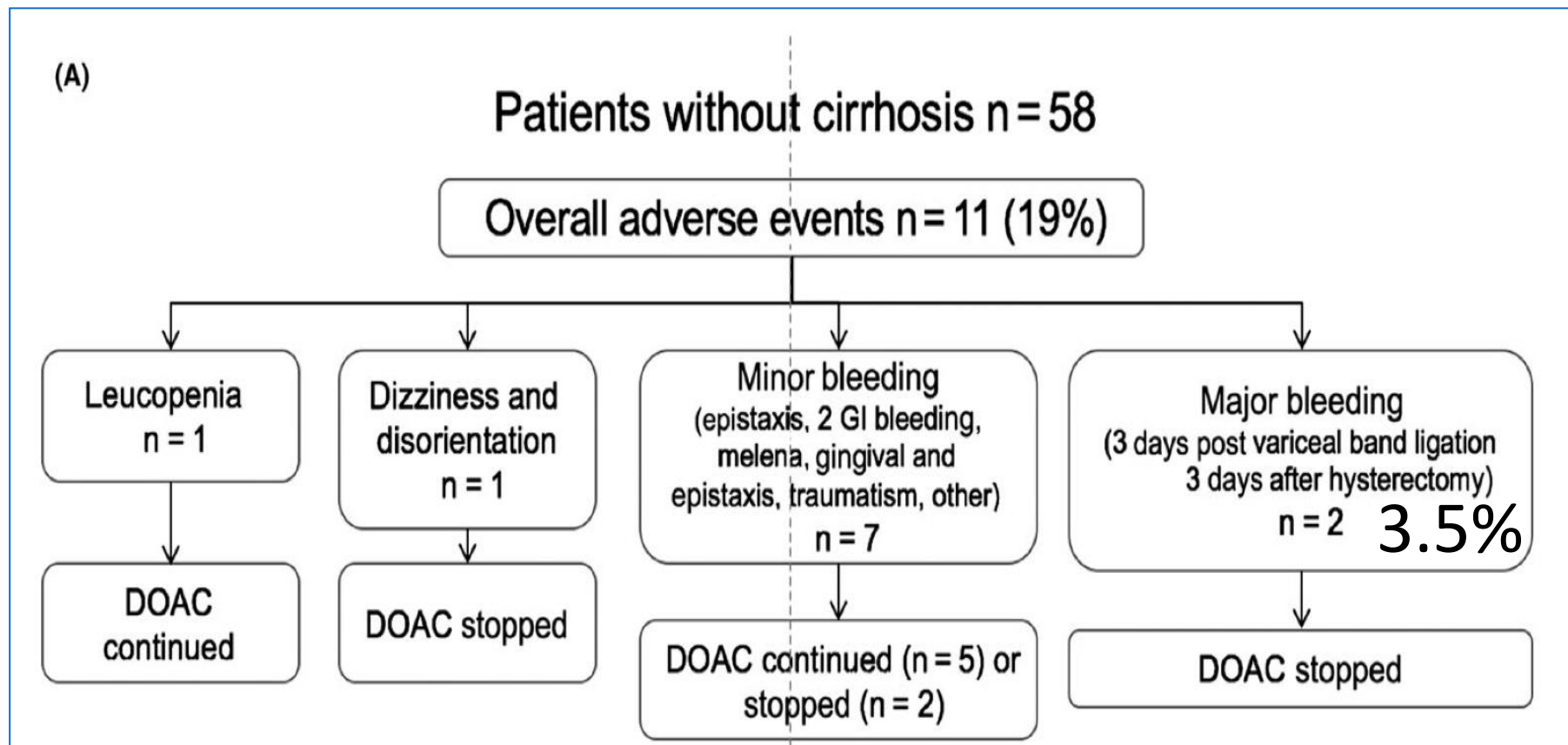
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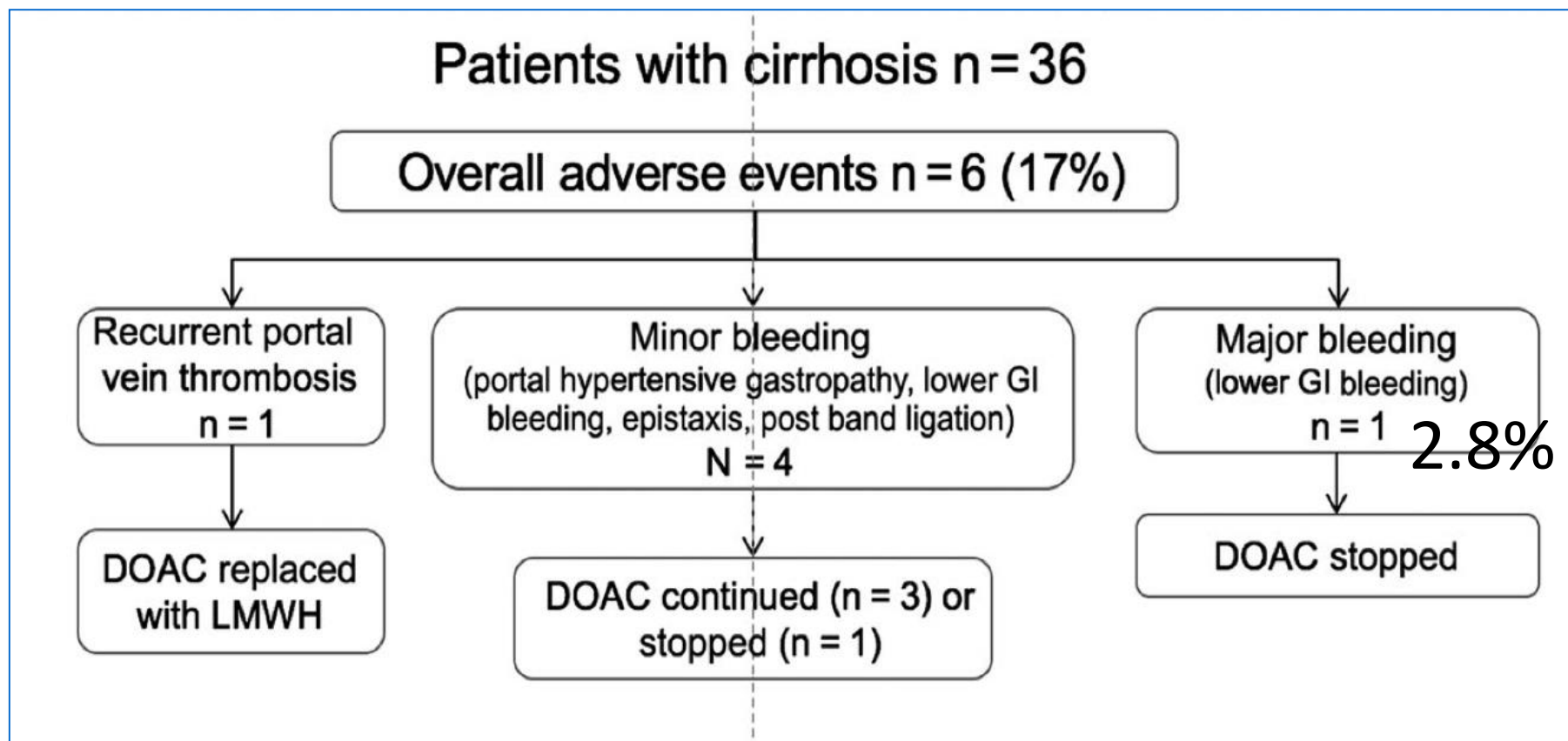
Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis

	Patients without cirrhosis (n=58)	Patients with cirrhosis (n=36)
Age (Y)	49.5 (range 16-82)	64.9 (range 32-82)
Gender	29 F-29 M (50%-50%)	15 F-21 M (42%-58%)
Aetiology of cirrhosis		
Alcohol	–	10 (28%)
HCV	–	6 (17%)
NAFLD/NASH	–	8 (22%)
Other	–	12 (33%)
Oesophageal or gastric varices:		
Total	24 (41%)	23 (64%)
Large	15 (62%)	7 (30%)
Previous variceal bleeding	17 (70%)	9 (39%)
Presence of ascites	13 (22%)	12 (33%)
Indication for anticoagulation		
Portal vein thrombosis	38 (65%)	22 (61%)
Budd-Chiari Syndrome	4 (7%)	5 (14%)
Cardiac arrhythmia	12 (21%)	5 (14%)
Peripheral deep vein thrombosis	–	2 (5%)
Other	6 (10%) ^a	2 (5%) ^b
DOAC used and median daily dose		
Rivaroxaban	49 (84%), 20 mg (range 10-20 mg)	30 (83%), 15 mg (range 5-20 mg)
Apixaban	6 (10%), 7.5 mg (range 5-10 mg)	4 (11%), 5 mg (range 2.5-10 mg)
Dabigatran	3 (5%), 220 mg (range 150-220 mg)	2 (5%), 165 mg (range 110-220 mg)

Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis



Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis



The direct oral anticoagulants for the treatment of splanchnic vein thrombosis

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Xarelto Versus no Treatment for the Prevention of Recurrent Thrombosis in Patients With Chronic Portal Vein Thrombosis. (RIPORT)

This study is currently recruiting participants. (see [Contacts and Locations](#))

ClinicalTrials.gov Identifier:
NCT02555111

Treatment of portal, mesenteric, and splenic vein thrombosis with rivaroxaban. A pilot, prospective cohort study

Rivaroxaban for the treatment of SVT: RIVASVT100 study

Inclusion criteria

- **Symptomatic, objectively diagnosed portal, mesenteric or splenic vein thrombosis**

Exclusion criteria

- **Liver cirrhosis, ALT >3 times ULN, BCS, history of variceal bleeding, portal vein cavernoma, creatinine clearance <30 mL/min, platelet count <100,000/mm³, therapeutic doses of anticoagulants >7 days**

Anticoagulation Forum guidance for the management of venous thrombosis in unusual sites

Guidance Statement: Given the absence of clinical experience with the use of the direct oral anticoagulants in this setting, there is no evidence for or against their use in the management of patients with SVT.

If a decision to use these agents is made, their use should be considered off label and careful patient counselling and clinical monitoring should follow. Ideally, patients receiving direct oral anticoagulants should be included in prospective cohort studies aimed to fill this knowledge gap.