Come trattare i pazienti con trombosi venose splancniche

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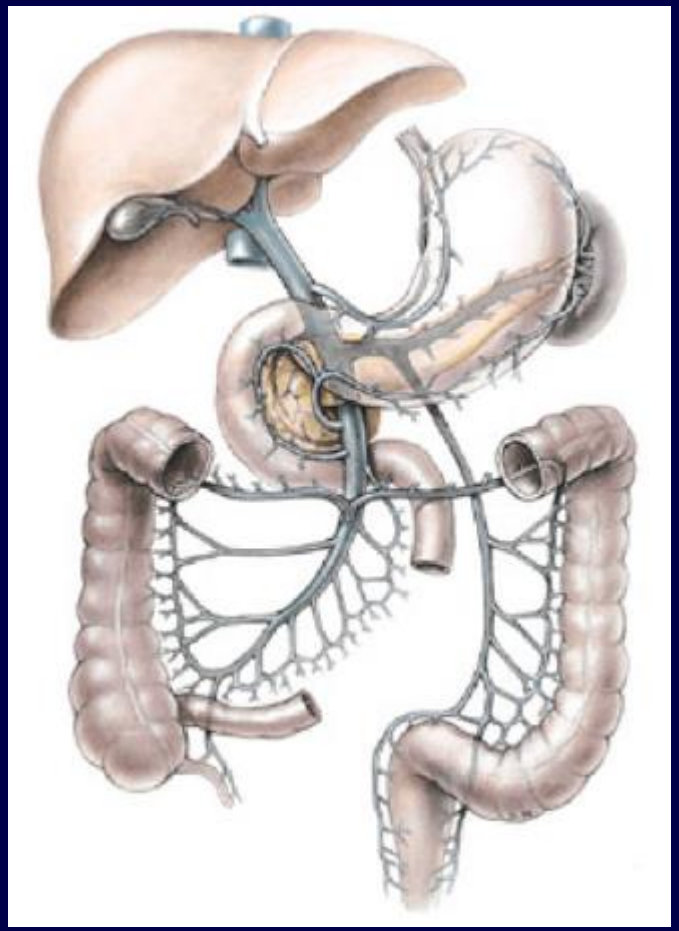
Splanchnic vein thrombosis (SVT)

Unusual site venous thromboembolism

- Portal vein
- Splenic vein
- Mesenteric veins (superior / inferior)
- Budd-Chiari syndrome



De Stefano et al, Intern Emerg Med. 2010

SVT : unusual site VTE

- Usual site VTE (DVT/PE) :
  - incidence 70-100 cases per 100,000 person-years

- PVT : - incidence 0.7 per 100,000 person-years
  - prevalence at autopsy 1%
- MVT : - incidence 2.7 per 100,000 person-years
- BCS : - incidence < 1 per million person-years

- Incidental SVT : - 1.7% of abdominal CT scans

White, Circulation. 2003; Rajani et al, Aliment Pharmacol Ther. 2010; Ogren et al, World J Gastroenterol 2006; Acosta et al, Br J Surg. 2008; Rajani et al, Liver Int. 2009; Ageno et al, J Thromb Haemost. 2012

SVT prognosis

- MVT
  - Associated with intestinal infarction in ⅓ of patients
  - 30-day mortality rate 20% *Acosta et al, Br J Surg. 2008*

- PVT and BCS
  - Development of portal hypertension → thrombocytopenia, ascites (30-70%), esophageal varices (20-35%), GI bleeding (10-30%) *Thatipelli et al, Clin Gastroenterol Hepatol. 2010*

- SVT
  - Worse survival compared to leg DVT (60% vs 68%, p= 0.024) *Thatipelli et al, Clin Gastroenterol Hepatol. 2010*

SVT as a marker of occult cancer

- In the first 3 months after SVT diagnosis: 8.0% cancer
  (risk of liver cancer 3.5%, risk of pancreatic cancer 1.5%)
- 3-month survival after cancer diagnosis
  - Liver cancer: 44% prior SVT vs. 55% no prior SVT
  - Pancreatic cancer: 35% prior SVT vs. 53% no prior SVT

Søgaard et al, Blood. 2015

- SVT as first clinical manifestation of MPN
  - Prevalence MPN 40.9% of BCS, 31.5% of PVT
  - Prevalence *JAK2V617F* 41.4% of BCS , 27.7% of PVT
  - In ≈74% of patients SVT developed prior to MPN diagnosis

Smalberg et al, Blood. 2012

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)

Thatipelli et al, Clin Gastroenterol Hepatol. 2010;8:200-5

Clinical onset of SVT

	Hepatic (n = 45)	Portal (n = 329)	Mesenteric (n = 76)	Splenic (n = 62)	Total (n = 512)
Asymptomatic	15%	21%	10%	17%	18%
Abdominal pain	64%	40%	63%	57%	48%
Nausea	13%	16%	16%	23%	16%
Diarrhea	2%	8%	7%	8%	7%
Fever	9%	13%	8%	10%	12%
Gastrointestinal bleed	11%	28%	20%	29%	26%
Ascites	71%	31%	11%	11%	29%
Jaundice	16%	13%	4%	11%	11%
Anorexia	24%	8%	4%	8%	9%
Acute abdomen	4%	12%	47%	15%	17%
Encephalopathy	9%	9%	3%	7%	8%
Asterixis	16%	0%	0%	0%	1%
Gastroesophageal varices	18%	35%	7%	18%	27%

Thatipelli et al, Clin Gastroenterol Hepatol. 2010;8:200-5

Therapeutic options

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CHEST 2012; 141(2)(Suppl):e419S–e494S

10.1. In patients with symptomatic splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we recommend anticoagulation over no anticoagulation (Grade 1B).

10.2. In patients with incidentally detected splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we suggest no anticoagulation over anticoagulation (Grade 2C).

11.1. In patients with symptomatic hepatic vein thrombosis, we suggest anticoagulation over no anticoagulation (Grade 2C).

11.2. In patients with incidentally detected hepatic vein thrombosis, we suggest no anticoagulation over anticoagulation (Grade 2C).

- Consider anticoagulation in incidentally detected SVT if acute extensive thrombosis, progression of thrombosis, active cancer

- LMWH may be preferred over VKA if there is active malignancy, liver disease, or thrombocytopenia

Treatment duration

AMERICAN COLLEGE OF CHEST PHYSICIANS®

CHEST 2012; 141(2)(Suppl):e419S–e494S

- 3 months duration

if presence of a reversible provoking factor for SVT (such as intra-abdominal sepsis, recent surgery or oral contraceptives)

- Extended anticoagulant therapy

if absence of a reversible risk factor (e.g. “unprovoked” thrombosis or presence of a persistent risk factor, such as myeloproliferative disease) and a low risk of bleeding

AASLD PRACTICE GUIDELINES

HEPATOLOGY, Vol. 49, No. 5, 2009

Vascular Disorders of the Liver

Laurie D. DeLeve,[1] Dominique-Charles Valla,[2] and Guadalupe Garcia-Tsao[3]

- Start with LMWH, in order to achieve rapid anticoagulation, and shift to VKA when the patient is stabilized (acute PVT and BCS)
- If gastro-esophageal varices, initiate anticoagulation after adequate prophylaxis (chronic PVT)

- Anticoagulation therapy for at least 3 months
- Long-term anticoagulation
  - Acute or chronic PVT with permanent thrombotic risk factors or thrombus extension distal into the mesenteric veins
  - BCS without major contraindication

Expanding consensus in portal hypertension
Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension

Roberto de Franchis*, on behalf of the Baveno VI Faculty†

Journal of Hepatology **2015** vol. 63 | 743–752

- Anticoagulation should be given for at least 6 months
- Long-term anticoagulation
  - Acute or chronic EHPVO with persistent documented prothrombotic state
  - Recurrent thrombosis
  - Intestinal infarction
  - All patients with BCS
- Anticoagulation should be started after adequate portal hypertensive bleeding prophylaxis has been initiated

Current Outcome of Portal Vein Thrombosis in Adults: Risk and Benefit of Anticoagulant Therapy

GASTROENTEROLOGY 2001;120:490–497

BERTRAND CONDAT,* FABIENNE PESSIONE,* SOPHIE HILLAIRE,* MARIE–HELENE DENNINGER,† MARIE–CLAUDE GUILLIN,† MARC POLIQUIN,* ANTOINE HADENGUE,* SERGE ERLINGER,* and DOMINIQUE VALLA*

- Retrospective cohort 136 non-malignant non-cirrhotic PVT
- 84 (62%) treated with anticoagulation (UFH, LMWH, VKA)
- Enrollment years 1983-1998; median follow-up 46 months

	Incidence rate	
GI bleeding	**12.5 per 100 pt-y**	
• Anticoagulant therapy NO	13.3 per 100 pt-y	
• Anticoagulant therapy YES	9.0 per 100 pt-y	**RR 0.9 (p = 0.8)**
A/V thrombotic events	**5.5 per 100 pt-y**	
• Anticoagulant therapy NO	6.3 per 100 pt-y	
• Anticoagulant therapy YES	3.8 per 100 pt-y	**RR 0.3 (p = 0.04)**

Survival and Recurrence in Patients With Splanchnic Vein Thromboses

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:200–205

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

- Retrospective cohort 832 patients with SVT (28% warfarin)
- Enrollment years 1980-2000; mean follow-up 27 (± 41) months

- Recurrent venous thrombosis **3.5 per 100 pt-y**
- Hormonal therapy HR 2.2 (95% CI, 1.09-4.45; p=0.02)
- ***Warfarin therapy*** did not improve recurrence-free survival

- Major bleeding events **6.9 per 100 pt-y**
- Gastroesophageal varices HR 2.63 (95% CI, 1.72-4.03, p<0.001)
- ***Warfarin therapy*** HR 1.91 (95% CI, 1.25-2.92, p=0.003)

Anticoagulant therapy in patients with non-cirrhotic portal vein thrombosis: effect on new thrombotic events and gastrointestinal bleeding

J Thromb Haemost 2013; 11: 452–9.

M. C. W. SPAANDER,* J. HOEKSTRA,* B. E. HANSEN,*† H. R. VAN BUUREN,* F. W. G. LEEBEEK‡ and H. L. A. JANSSEN*

- Retrospective cohort 120 non-malignant non-cirrhotic PVT
- 66 (55%) treated with anticoagulation (VKA, LMWH, UFH)
- Enrollment years 1985-2008; median follow-up 5.5 years

- Recurrent thrombosis: **3% at 1y, 8% at 5 y, 24% at 10y**
- Anticoagulant therapy HR 0.2 (95% CI, 0.0-1.9; p=0.1)

- GI bleeding: **33% at 1y, 43% at 5y, 46% at 10y**
- Anticoagulant therapy HR 1.7 (95% CI, 1.1-2.7; p=0.03)
- No significant effect on the severity of GI bleeding

ISTH registry: treatment options

- No anticoagulant treatment 22%

- Any anticoagulant drug 77%

  mean (SD) duration 13.9 (9.2) months

  – 62.4% started VKA treatment

  mean (SD) duration 16.7 (8.5) months

  – 37.6% parenteral treatment only

  mean (SD) duration 8.2 (7.7) months

- Other: ASA, thrombolysis, surgery, interventional procedures

Ageno et al, JAMA Intern Med. 2015;175(9):1474-80

ISTH registry: treatment vs. no treatment

- Use of **anticoagulant drugs**
  - Previous VTE — p = 0.002
  - MPN — p = 0.002
  - Recent abdominal surgery — p = 0.001
  - Hormonal therapy — p = 0.044

- **No treatment**
  - Incidental SVT diagnosis — p < 0.001
  - Single vein thrombosis — p < 0.001
  - GI bleeding at onset — p = 0.009
  - Solid cancer — p = 0.010
  - Hepatic cirrhosis — p < 0.001
  - Thrombocytopenia (PLT ≤ 100.000) — p < 0.001

Ageno et al, Semin Thromb Hemost. 2014;40(1):99-105

ISTH registry: heparin vs. VKA

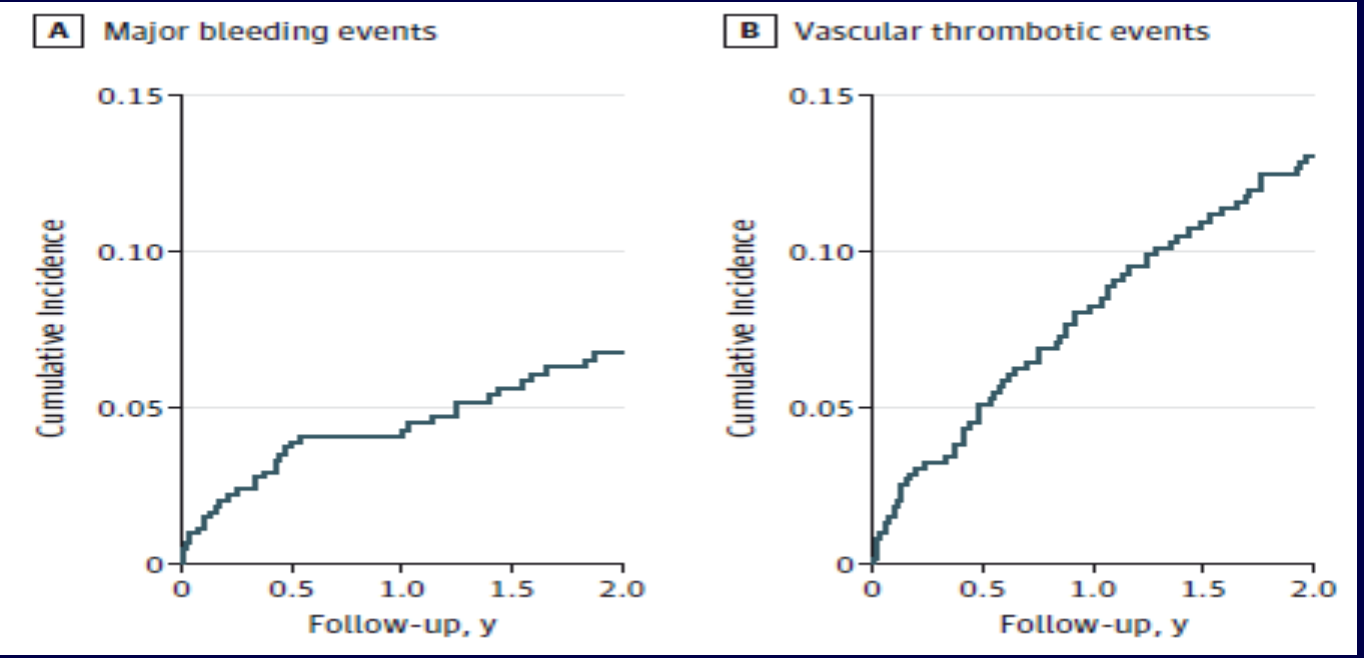
- Long-term use of **parenteral anticoagulation**
  - Incidental SVT diagnosis — p = 0.001
  - Solid cancer — p < 0.001
  - Hepatic cirrhosis — p < 0.001
  - Thrombocytopenia (PLT ≤ 100.000) — p < 0.001
  - Anaemia (Hb ≤ 10 g/dL) — p = 0.019

- Use of **vitamin K antagonists**
  - Younger age (median 50 vs. 58 y) — p < 0.001
  - Multiple veins thrombosis — p = 0.009
  - Unprovoked SVT — p < 0.001
  - MPN — p = 0.021

Ageno et al, Semin Thromb Hemost. 2014;40(1):99-105

ISTH registry: long-term clinical outcome

2-year follow-up



35 major bleeding
incidence rate **3.8 per 100 pt-y**
(95% CI, 2.7-5.2)
CFR 5.7%

68 thrombotic events
incidence rate **7.3 per 100 pt-y**
(95% CI, 5.8-9.3)
CFR 13.2%

Ageno et al, JAMA Intern Med. 2015;175(9):1474-80

ISTH registry: long-term clinical outcome

- Major bleeding events
  - 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

Ageno et al, JAMA Intern Med. 2015;175(9):1474-80

ISTH registry: long-term clinical outcome

- Vascular 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

	Hazard Ratio	*95% confidence interval*	*p value*
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

Ageno et al, JAMA Intern Med. 2015;175(9):1474-80

ORIGINAL ARTICLE

Safety of vitamin K antagonist treatment for splanchnic vein thrombosis: a multicenter cohort study

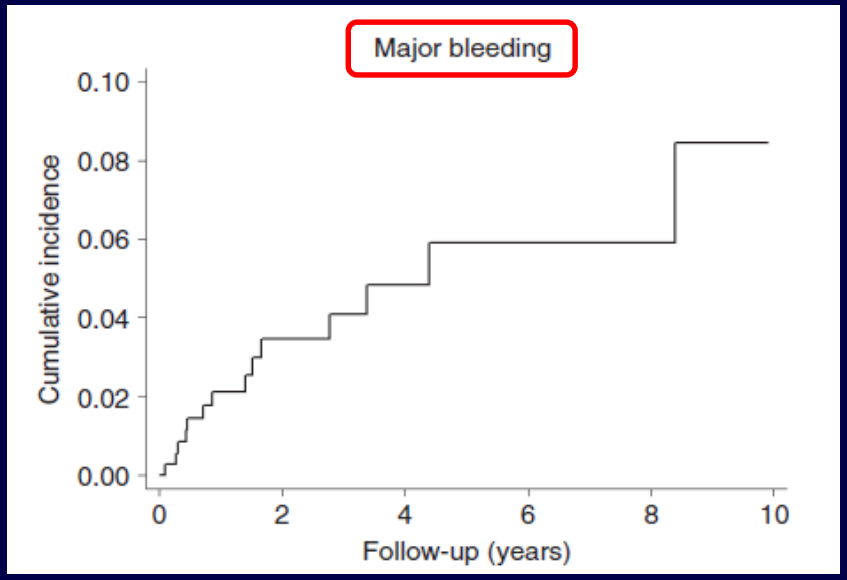
N. RIVA,* W. AGENO,* D. POLI,† S. TESTA,‡ S. RUPOLI,§ R. SANTORO,¶ T. LEREDE,** A. PIANA,†† M. CARPENEDO,‡‡ A. NICOLINI,§§ P. M. FERRINI¶¶ and A. TOSETTO,*** FOR THE ITALIAN FEDERATION OF ANTICOAGULATION CLINICS (FCSA)[1]

J Thromb Haemost 2015; **13**: 1019–27.

- 375 SVT patients treated with VKA and followed by 37 Italian Anticoagulation Clinics (FCSA)

- Time of warfarin inception median 0.5 (IQR 0.1–1.6) months after the acute event
- Warfarin treatment duration median 1.98 y (IQR 0.91–4.10)
- INR target range 2.0-3.0 (94.1%)
- Median TTR 69% (IQR 58–79%)

During VKA treatment



MB (ISTH definition)

15 events

Incidence **1.24 per 100 pt-y**

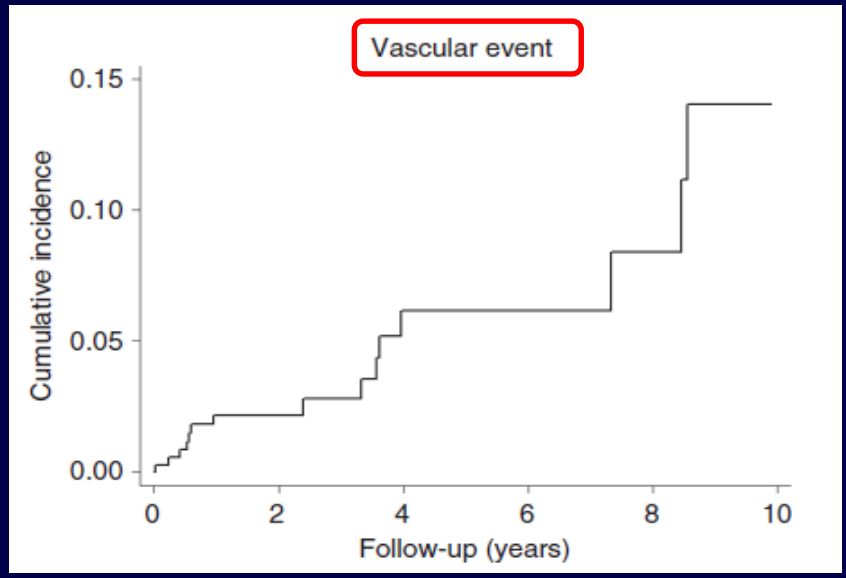
(95% CI, 0.75-2.06)

Vascular events (venous and arterial)

16 events

Incidence **1.37 per 100 pt-y**

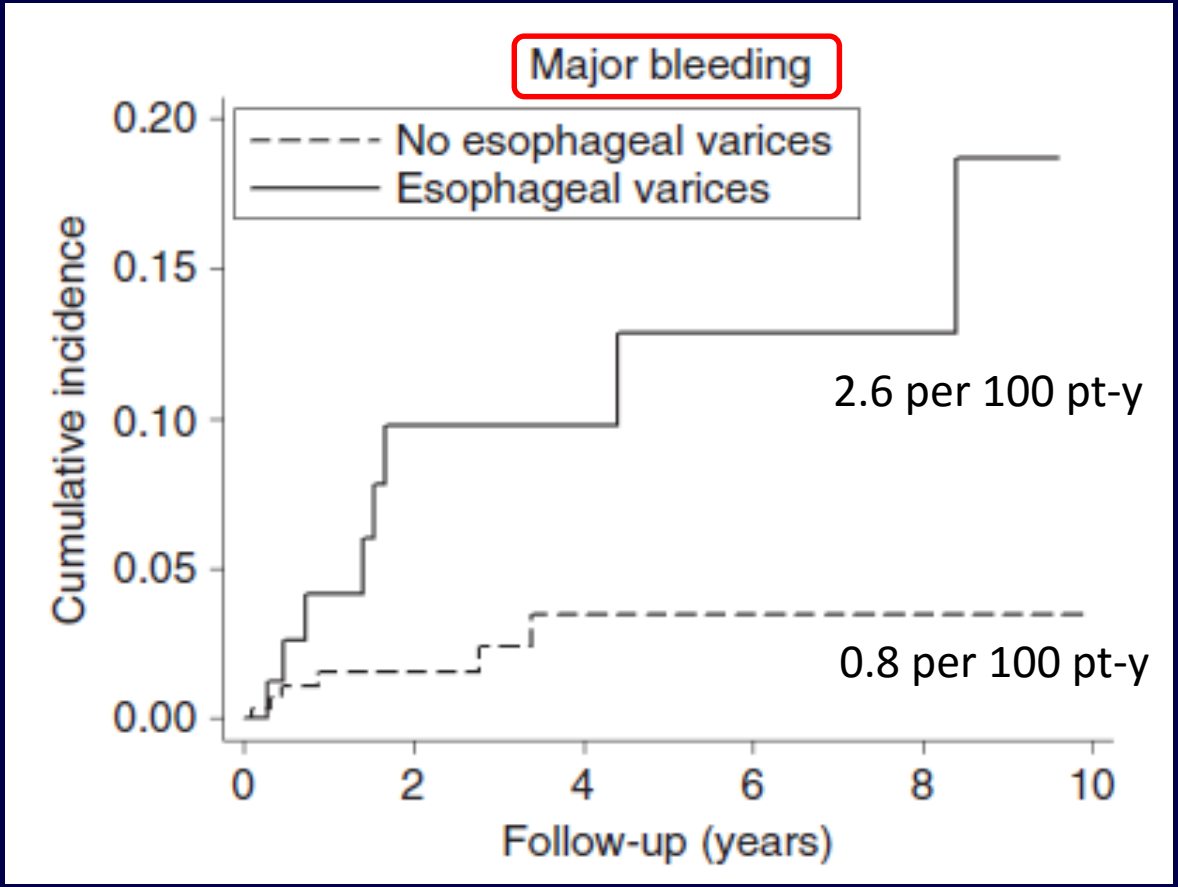
(95% CI, 0.84–2.23)



Riva et al, J Thromb Haemost. 2015;13(6):1019-27

During VKA treatment

Esophageal varices HR 5.4 (95% CI, 1.4–21.1)



Riva et al, J Thromb Haemost. 2015;13(6):1019-27

After VKA discontinuation

- 90 patients discontinued VKA (for reasons other than a major bleeding complication) and did not receive any other anticoagulant drug
  - VKA treatment duration

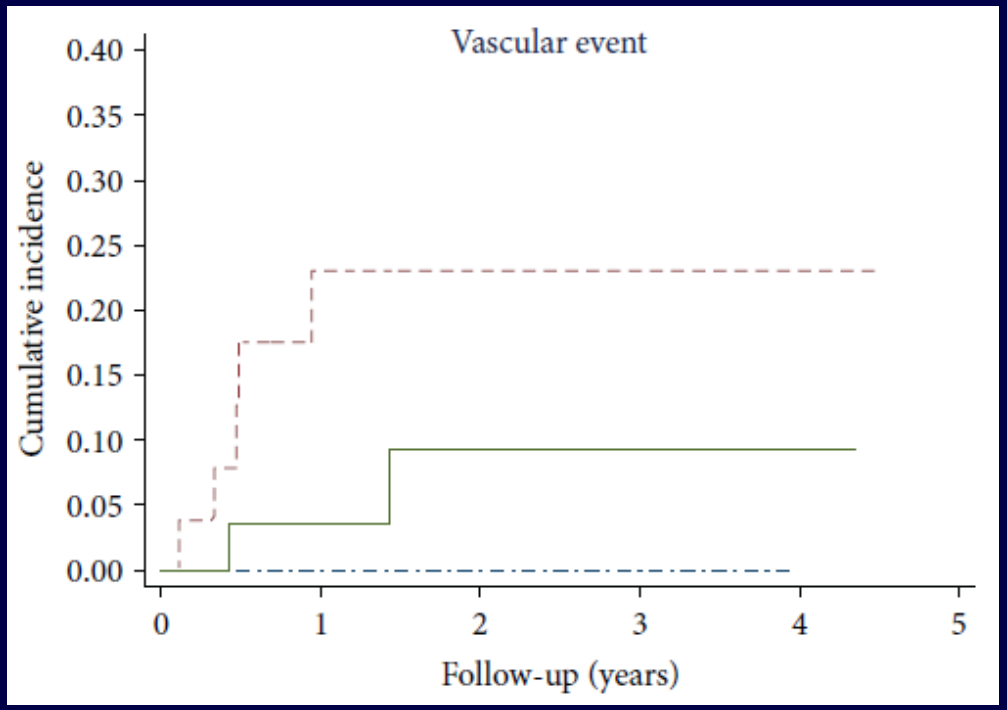
< 3 months	7.8%
3-6 months	11.1%
6-12 months	24.4%
> 12 months	56.7%

- Follow-up median 1.6 y (IQR 0.5-3.3)
- 7 recurrent thrombotic events

  incidence rate 3.3 per 100 pt-y (95% CI, 1.6-6.9)

Riva et al, Gastroenterol Res Pract. 2015;2015:620217

After VKA discontinuation



Secondary to permanent risk factors
10.2 per 100 pt-y

Unprovoked SVT
2.4 per 100 pt-y

Secondary to transient risk factors
0 events

Liver cirrhosis HR 7.9 (95% CI, 1.8–35.9)

Riva et al, Gastroenterol Res Pract. 2015;2015:620217

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)

Table 1
An overview of study characteristics.

First author (year)	Publication form	Region	Enrollment period	Design	Population	Anticoagulants	No. Pts with cirrhotic PVT receiving anticoagulants
Amitrano (2010)	Full text	Naples, Italy	2005.6–2006.12	Non-comparative	Cirrhotic patients with non-neoplastic PVT	Enoxaparin 200 U/kg/day for at least 6 months	28
Delgado (2012)	Full text	Barcelona, Spain	2003.6–2010.9	Multi-center, non-comparative	Cirrhotic patients with non-neoplastic PVT (1 underwent liver resection for HCC)	LMWH and/or VKA	55
Dell'Era (2014)	Full text	Milan, Italy	1995.2–2009.2	Retrospective, non-comparative	Cirrhotic patients with PVT treated with endoscopic variceal ligation (HCC was excluded)	LMWH	10
Francoz (2005)	Full text	Clichy, France	1996.1–2001.12	Comparative	Cirrhotic patients with PVT listed for LT (HCC with one nodule <5 cm or 2–3 nodules each <3 cm was not excluded; malignant vascular invasion was ruled out)	Nadroparin (5700 UI/day subcutaneously) followed by acenocoumarol (INR: 2–3)	19
Naeshiro (2014)	Full text	Hiroshima, Japan	2011.12–2013.4	Retrospective, non-comparative	Cirrhotic patients with PVT (9 had HCC)	Danaparoid sodium 2 weeks	26
Senzolo (2012)	Full text	Padua, Italy	2007.1–2008.1	Prospective, comparative	Cirrhotic patients with non-malignant PVT (HCC was excluded)	Therapeutic dose: nadroparin (95 antiXa U/kg body weight td); Prophylactic dose: nadroparin (3800 anti-Xa U daily) for 6 months	33
Werner (2013)	Full text	Phoenix, USA	2005.1–2011.11	Retrospective, non-comparative	Cirrhotic patients with PVT awaiting LT (advanced HCC was excluded; HCC within Milan criteria were not excluded)	Warfarin (INR 2–3)	28

Is there a role for the DOACs?

Successful treatment of acute portal vein thrombosis with rivaroxaban

Sven Pannach[1]; Jana Babatz[1]; Jan Beyer-Westendorf[2]

[1]Division Gastroenterology, Medical Clinic I, Dresden University Hospital "Carl Gustav Carus", Dresden, Germany; [2]Center for Vascular Diseases and Medical Clinic III, Dresden University Hospital "Carl Gustav Carus", Dresden, Germany

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

Authors K. Lenz[1], B. Dieplinger[2], R. Buder[1], P. Piringer[1], M. Rauch[3], M. Voglmayr[1]

Affiliations

CLINICAL OBSERVATIONS IN HEPATOLOGY

Treatment of Acute Portal Vein Thrombosis by Nontraditional Anticoagulation

Melissa Martinez,[1] Anand Tandra,[2] and Raj Vuppalanchi[1]

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

Conclusions

- SVT is an uncommon manifestation of VTE, but also a potentially life-threatening disease

- Anticoagulant treatment appears to be safe and effective in most patients with SVT. Selected SVT patients followed by anticoagulation clinics for the management of VKA treatment show a low rate of major bleeding and vascular events.

- Most patients with SVT have a substantial long-term risk of thrombotic events. The incidence rate was particularly remarkable in patients with permanent risk factors (such as liver cirrhosis)