# Trombosi in sedi atipiche

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# Trombosi Venose in Sedi Inusuali

- Occlusioni venose retinche
- Trombosi venose cerebrali (CVT)
- Trombosi venose addominali – splancniche (SVT)
- Trombosi venose profonde degli arti Superiori

# Malattie eterogenee

- Different provoking mechanisms
- – Gender related risk factors for CVT
- – Myeloproliferative neoplasms for SVT
- – Cardiovascular risk factors for RVO

- Severity of clinical outcomes
- – Residual neurological impairment/epilepsy
- – Liver cirrhosis
- – Portal hypertension
- – Blindness

# Malattie rare ?

- Rarity
- – Cerebral vein thrombosis 3-6 cases/1 million adults/year
- – Portal vein thrombosis 4 cases/1 million adults/year
- – Superior mesenteric vein thrombosis 3 cases/100,000/year
- – Budd Chiari syndrome 1 case/2.5 million adults/adults
- – Retinal vein occlusion 0.5-1.5 cases/1,000 adults/year

- Challenging clinical presentations
- – Intraparenchimal bleeding (approx. 25%)
- – Gastrointestinal bleeding (approx. 25%)
- – Retinal bleeding
- – Heterogeneous clinical pictures

# Trombosi Venose in Sedi Inusuali

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# Trombosi venose degli arti superiori

- Trombosi venosa dell'arto superiore ( T.V. a.s.) Fino a 25 aa fa costituiva un "case report" della letteratura ( 2 % di tutte le trombosi)
- La maggior parte riconducibili a situazioni «benigne», PRIMITIVE
- - sindrome di Paget von Schroetter, T.V. succlavio-ascellare idiopatica insorta in soggetti giovani, prevalentemente a destra.
- - T.V. da sforzo dopo attività sportive (tennis, polo, sollevamento pesi) o in rapporto a lavori particolarmente gravosi si associano alla sindrome dello stretto toracico superiore.
- - Post traumatiche
- SECONDARIE:
- Associate a patologia neoplastica (compressione e/o invasione, trombofiilia)
- Da introduzione di cateteri venosi o pace-maker

# TV Correlate a catetere

- Theiss e collaboratori hanno rinominato il 1980 come “l’anno del viraggio”. In una serie di  casi si è passati dal 14 al 60 % di T.V. secondarie dopo l’introduzione di cateteri venosi o pace-maker.
- Il Center for Disease Control di Atlanta (USA) ha valutato 7503 pazienti portatori di c.v. Nel 34,5 % dei casi il c.v. era sede di colonizzazione batterica con sepsi nel 3 – 6 % dei casi (tromboflebite settica).
- La stima di embolizzazione settica polmonare è del 20 % (principale concausa la tossicodipendenza).
- L’applicazione di pace-maker ha una incidenza di T.V. delle grosse vene nello 0,6 – 35 %, quasi sempre asintomatiche.
- Nei soggetti neoplastici con c.v.c. la frequenza è del 10 – 13 %.

# Caso clinico 1

- Uomo di 67anni, ottime condizioni, unica co morbilità ipertensione arteriosa
- Agosto 2017 : asportazione sarcoma tessuti molli spalla dx
- Avviato a chemioterapia adiuvante ad ottobre, paziente potenzialmente guarito
- Somministrato I° ciclo CT (Idarubicina ifosfamide), dopo 7 giorni febbre resistente ad antibioticoterapia orale protratta  per 5 giorni
- IN PS: Neutropenia febbrile ed edema caldo, dolente dell intero aa sup dx
- GB 700, GN 100, PLT 21000, Hb 11.9 PCR 36 RX Torace nn. Trombosi ascellare succlavia dx
- Emocolture, antibioticoterapia (Vancomicina Ceftazidime) filgrastim

# Caso clinico 1

- A 48 ore: febbre ridotta, persistenza edema infiammatorio Arto superiore dx
- GB 350 N 50 Plt 17000 PCR 28. 3 emocolture (2 da PICC) pos Staphilo. Aureus metilcillinosensibile
- Avviata terapia battericida (Oxacillina 3gx4, Rifampicina 900) fatta TC Torace: noduli polmonari diffusi bilaterali da embolizzazione settica, conferma estesa trombosi ascellare succlavia. ECOCARDIO nn
- A 4 GIORNI: sfebbrato ,condizioni migliorate edema ridotto- GB 2300 GN 1600 Plt 76000 PCR 24: inizia terapia anticoagulante: Clexane 8000x2
- A 7 GIORNI EMOCROMO NORMALE, MIGLIORATO, PCR SEMPRE 14 PICC FUNZIONANTE, NON PIU'USATO

- DEVE RIMUOVERE PICC? SE SI QUANDO?

# Caso clinico 1

- Linee guida :
- CHEST ACCP 2012 e 2016:  Iniziare terapia anticoagulante

Mantenere  dispositivo se funzionante,necessario, non infetto, senza sintomatologia, senza convolgimento vene prossimali Altrimenti rimozione dopo tre mesi di terapia anticoagulante NON specificato come comportarsi se dispositivo infetto

- EHJ  ESC 2014: idem
- SISET 2012 :  Rimozione precoce  in caso di sepsi

PRO RIMOZIONE: Paziente migliorato ma con edema residuo importante e PCR stabilizzata 12. Difficile ulteriore miglioramento e risoluzione definitiva infezione. NECESSITA' DI PROSEGUIRE ANTIBIOTICOTERAPIA EV IN AMBITO DI RICOVERO PROTRATTO

CONTRO: RISCHIO EMBOLIA POLMONARE

ASSENZA DI SEPSI

NECESSITA' DI NUOVO DISPOSITIVO

# Caso clinico 1

- RIMOSSO  PICC A 13 GIORNI  DOPO DIECI GIORNI DI TERAPIA ANTICOAGULANTE
- NESSUNA COMPLICAZIONE, DIMESSO DOPO 14 GG  DI TERAPIA ANTIBIOTICA EV, PCR 1, IN TAO E INDICAZIONI  A CONTROLLI DOPO  10 GG
- COMMENTO PAZIENTE: PICC RIMOSSO IN TRE MINUTI. CI VOLEVA TANTO?

# Splanchnic vein thrombosis

- Splanchnic vein thrombosis (SVT) encompasses Budd–Chiari syndrome, portal vein thrombosis, mesenteric vein thrombosis, and splenic vein thrombosis. Of all symptoms, abdominal pain is the most frequent. Other clinical manifestations may be associated with the underlying disorder and/or may represent the consequence of the acute thrombosis, such as in the case of gastrointestinal bleeding and ascites
- . Systemic risk factors such as hematologic disorders, autoimmune diseases and the use of hormonal therapy are the most common risk factors associated with Budd–Chiari syndrome, whereas local precipitating factors such as solid abdominal cancer, liver cirrhosis, intraabdominal inflammatory conditions, and surgery are the most common risk factors associated portal and mesenteric vein thrombosis
- . Thus, a careful imaging of the abdominal organs often identifies underlying predisposing pathologies in these patients. Myeloproliferative neoplasms have emerged as a leading systemic cause of SVT, and screening for the JAK2V617F mutation should be considered in patients without a known major underlying provocative factor

# Splanchnic vein thrombosis

- Overall survival after long-term follow up is lower than in patients with deep vein thrombosis of the lower limbs, and depends on the location of thrombosis and on underlying diseases .
- Long-term sequelae include, among others, portal hypertension and liver cirrhosis
- . Bleeding is commonly reported during follow up, and may be related to underlying diseases, esophageal varices and anticoagulant treatment
- The annual incidence of recurrent thrombosis was reported to be about 2.5/100 patient years

# Cause di trombosi venosa viscerale

- Cirrosi
- • Sindromi trombofiliche
- • Neoplasie addominali (epatiche, pancreatiche, MTS epatiche)
- • Sepsi (locale o sistemica)
- • Schistosomiasi/aspergillosi
- • Pancreatiti
- • Post-chirurgiche (trapianto fegato, splenectomia)
- • Contraccettivi orali
- • Gravidanza/puerperio
- • IBD
- • Sindrome di Bechet

# Caso Clinico 2

- Uomo di 60 anni, ex fumatore iperteso buone condizioni generali
- 2014:Riscontro di modesti edemi, aumento peso e dimensioni addominali
- HT 59, GB 23000, PLT 104000 .
- ETG: epato splenomegalia (16 cm) modesta ascite. TROMBOSI PORTA VV SPLENICHE E MESENTERICHE
- Inizia salassoterapia E TAO . Dopo riscontro di Mutazione gene JAK2 DIAGNOSI DI MALATTIA MIELOPROLIFERATIVA CRONICA TIPO POLICITEMIA VERA ASSOCIATA AD ESTESA TROMBOSI SPLANCINCA. Inizia ONCOCARBIDE, PROSEGUE TAO LONG TERM e salassoterapia l bisogno per mantenere HT < 45%
- Miglioramento generale, scomparsa ascite, ricanalizzate vene splenica e mesenterica, sviluppo cavernoma portale e ipertensione portale con varici

# Caso clinico 2

- Paziente sospende oncocarbide per leucopiastrinopenia  modesta, (!) prosegue salassi e tao con controlli accettabili  dell'Ht  e INR
- 2015: Episodo di gastroenterite acuta, disidratazione: Ht 55, GB 18000 plt 88000: nuova trombosi mesenterica, infarto intestinale sottoposto in urgenza a resezione ileale e terapia anticoagulante + ASA nel post operatorio, con pronta ripresa delle condizioni generali
- In decima giornata enterorragia e shok emorragico  con ressi arteriosa in sede di intervento : salvato da posizionamento microspirale in corso di procedura angiografica
- Stabilizzato e dimesso dopo 8 giorni, ripresa TAO e salassi poi sospesi per nuovo episodio emorragico (ematochezia, diverticolosi) a fine 2015
- Il Paziente è stato avviato a terapia con fondaparinux a dosi intermedie per la difficoltà a mantenre INR nel range e salassi al bisogno

# Caso clinico 2

- Controllo a 18 mesi: Cavernoma portale invariato, ipertensione portale con modesta ascite, varici F1, epatosplenomegalia invariata
- GB 29000, Ht variabile, mantenuto < 45% con rari salassi, PLT 102000.
- Proposta Oncocarbide , rifiutata
- Proposta rivalutazione del midollo per ev trattamento con Ruxolitinib rifiutato
- Prosegue Fondaparinux e controlli

# **ISTH registry on splanchnic vein** thrombosis

| | Total | Women | Men |
|---|---|---|---|
| Patients | 424 | 160 (37.7%) | 264 |
| Age (mean) | 52.6 | 52.9 | 52.5 |
| PVT | 40.5% | | |
| MVT | 11.9% | | |
| BCS | 7.5% | | |
| Multiple | 36.4% | | |
| Cancer | 24.1% | 23.6% | 24.4% |
| MPN | 15.4% | 17.1% | 14.3% |
| Cirrhosis | 23.1% | 17.7% | 26.5% |
| OC/HRT | 10.5% | | |
| Pregnancy | 1.2% | | |

# International registry on splanchnic vein thrombosis www.svt.altervista.org

- 25 centers
- 7 countries (Europe, Asia, North America)
- 530 patients
- 40.5% portal vein thrombosis
- 11.9% mesenteric vein thrombosis
- 7.5% Budd Chiari Syndrome
- 36.4% multiple segments
- 56.9% treated with UFH/LMWH – OAT
- 30.8% treated with UFH/LMWH only

# Antithrombotic treatment of splanchnic vein thrombosis: results of an international registry. Ageno et al; IRSVT study group; Semin Thromb Hemost. 2014 Feb;40(1):99-105

- Treatment of splanchnic vein thrombosis (SVT) is a clinical challenge due to heterogeneity of clinical presentations, increased bleeding risk, and lack of evidences from clinical trials. We performed an international registry to describe current treatment strategies and factors associated with therapeutic decisions in a large prospective cohort of unselected SVT patients. A total of 613 patients were enrolled (mean age 53.1 years, standard deviation ± 14.8); 62.6% males; the majority (468 patients) had portal vein thrombosis. Most common risk factors included cirrhosis (27.8%), solid cancer (22.3%), and intra-abdominal inflammation/infection (11.7%); in 27.4% of patients, SVT was idiopathic. **During the acute phase, 470 (76.7%) patients received anticoagulant drugs, 136 patients (22.2%) remained untreated**.. Decision to start patients on vitamin K antagonists after an initial course of parenteral anticoagulation was significantly associated with younger age, symptomatic onset, multiple veins involvement, and unprovoked thrombosis. **Although a nonnegligible proportion of SVT patients did not receive anticoagulant treatment, the majority received the same therapies recommended for patients with usual sites thrombosis, with some differences driven by the site of thrombosis and the pathogenesis of the disease.**

# Long-term Clinical Outcomes of Splanchnic Vein Thrombosis: Results of an International Registry. Ageno W. et al; JAMA Intern Med. 2015 Sep;

- RESULTS: Of the 604 patients (median age, 54 years; 62.6% males), 21 (3.5%) did not complete follow-up. The most common risk factors for SVT were liver cirrhosis (167 of 600 patients [27.8%]) and solid cancer (136 of 600 [22.7%]); the most common sites of thrombosis were the portal vein (465 of 604 [77.0%]) and the mesenteric veins (266 of 604 [44.0%]). Anticoagulation was administered to 465 patients in the entire cohort (77.0%) with a mean duration of 13.9 months; 175 of the anticoagulant group (37.6%) received parenteral treatment only, and 290 patients (62.4%) were receiving vitamin K antagonists. The incidence rates (reported with 95% CIs) were 3.8 per 100 patient-years (2.7-5.2) for major bleeding, 7.3 per 100 patient-years (5.8-9.3) for thrombotic events, and 10.3 per 100 patient-years (8.5-12.5) for all-cause mortality. During anticoagulant treatment, these rates were 3.9 per 100 patient-years (2.6-6.0) for major bleeding and 5.6 per 100 patient-years (3.9-8.0) for thrombotic events. After treatment discontinuation, rates were 1.0 per 100 patient-years (0.3-4.2) and 10.5 per 100 patient-years (6.8-16.3), respectively. The highest rates of major bleeding and thrombotic events during the whole study period were observed in patients with cirrhosis (10.0 per 100 patient-years [6.6-15.1] and 11.3 per 100 patient-years [7.7-16.8], respectively); the lowest rates were in patients with SVT secondary to transient risk factors (0.5 per 100 patient-years [0.1-3.7] and 3.2 per 100 patient-years [1.4-7.0], respectively).

- CONCLUSIONS AND RELEVANCE: Most patients with SVT have a substantial long-term risk of thrombotic events. In patients with cirrhosis, this risk must be balanced against a similarly high risk of major bleeding. Anticoagulant treatment appears to be safe and effective in most patients with SVT.

# InheritedThrombophilic Abnormalities and the Risk of PVT

## Dentali et al Thromb Haemost 2008

| | |
|---|---|
| Patients, n | 77 |
| Mean age, years (SD) | 49.2 (11.9) |
| Male sex, n (%) | 45 (58.4) |
| Previous VTE, n (%) | 13 (17) |
| Thrombophilic abnormalities, n | – 7 V Leiden<br>– 7 II G2010A<br>– 9 LAC or ACL<br>– 4 Hyperhomocysteinemia<br>– 2 Antithrombin deficiency<br>– 3 Protein C deficiency<br>– 2 Protein S deficiency |
| Risk factors, n | – 12 MPD<br>– 10 Abdominal surgery<br>– 8 Inflammatory bowel disease<br>– 6 Cirrhosis<br>– 5 Cancer<br>– 5 OC/HRT use |

# Trombofilia, mutazione JAK2 e trombosi venosa portale

**Primignani M et al Hepatology 2006**

- Numero 73
- Età media (anni) 42
- Maschi 39%
- Fattori di rischio transitori (traumi, chirurgia) 15.1%
- Fattore V Leiden 2.7%
- Protrombina G20210A 20.5%
- Deficit inibitori 10.0%
- Anticorpi antifosfolipidi 10.9%
- Iperomocisteinemia 10.9%
- JAK2 V617F 35.6%
- Sindrome mieloproliferativa 53%

# JAK2 and splanchnic vein thrombosis 16 studies (831 pts)

**Dentali et al Blood 2009**

- 280 of 831 SVT patients were JAK2+:

  mean prevalence 32.7% (95%CI 25.5, 35.9%).

- Mean prevalence of JAK2 mutation in patients with idiopathic SVT :49.0% (95%CI 32.9, 65.1%)

The mean prevalence of MPD at the time of SVT diagnosis was 59.5% (95%CI 51.3, 67.5%)

• Five studies evaluated the rate of MPD

diagnosis during the follow-up in JAK2+ patients without a diagnosis of MPD at the time of SVT diagnosis: mean rate 52.4% (95%CI

38.0, 66.5%).

# Splanchnic vein thrombosis and myeloproliferative neoplasms: molecular-driven diagnosis and long-term treatment.

**Thromb Haemost. 2016 Jan;115(2):240-9** **De Stefano V[1], Qi X, Betti S, Rossi E.**

- Splanchnic vein thrombosis (SVT) encompasses Budd-Chiari syndrome (BCS), extrahepatic portal vein obstruction (EHPVO), and mesenteric vein thrombosis. Philadelphia-negative myeloproliferative neoplasms (MPNS) are the leading systemic cause of non-cirrhotic and non-malignant SVT and are diagnosed in 40% of BCS patients and one-third of EHPVO patients. In SVT patients the molecular marker JAK2 V617F is detectable up to 87% of those with overt MPN and up to 26% of those without. In the latter, other MPN molecular markers, such as mutations in JAK2 exon 12, CALR and MPL genes, are extremely rare. Immediate anticoagulation with heparin is used to treat acute patients. Upon clinical deterioration, catheter-directed thrombolysis or a transjugular intrahepatic portosystemic shunt is used in conjunction with anticoagulation. Orthotopic liver transplantation is the only reliable option in BCS patients with a lack of a response to other treatments, without contraindication due to MPN. Long-term oral anticoagulation with vitamin K-antagonists (VKA) is recommended in all SVT patients with the MPN-related permanent prothrombotic state; the benefits of adding aspirin to VKA are uncertain. Cytoreduction is warranted in all SVT patients with an overt MPN, but its appropriateness is doubtful in those with molecular MPN without hypercythaemia.

## Myeloproliferative neoplasms in Budd-Chiari syndrome and portal vein thrombosis: a meta-analysis.

Smalberg JH et al Blood. 2012 Dec 13;120(25):4921-8

- Myeloproliferative neoplasms (MPNs) are the most common cause of Budd-Chiari syndrome (BCS) and nonmalignant, noncirrhotic portal vein thrombosis (PVT). In this meta-analysis, we determined the prevalence of MPNs and their subtypes as well as JAK2V617F and its diagnostic role in these uncommon disorders. MEDLINE and EMBASE databases were searched. Prevalence of MPNs, JAK2V617F, and MPN subtypes were calculated using a random-effects model. A total of 1062 BCS and 855 PVT patients were included. In BCS, mean prevalence of MPNs and JAK2V617F was 40.9% (95% CI, 32.9%-49.5%) and 41.1% (95% CI, 32.3%-50.6%), respectively. In PVT, mean prevalence of MPNs and JAK2V617F was 31.5% (95% CI, 25.1%-38.8%) and 27.7% (95% CI, 20.8%-35.8%), respectively. JAK2V617F and MPNs were more frequent in BCS compared with PVT (P = .03 and P = .09, respectively). Polycythemia vera was more prevalent in BCS than in PVT (P = .001). JAK2V617F screening in splanchnic vein thrombosis (SVT) patients without typical hematologic MPN features identified MPN in 17.1% and 15.4% of screened BCS and PVT patients, respectively. These results demonstrate a high prevalence of MPNs and JAK2V617F in SVT patients and show differences in underlying etiology between these disorders. Furthermore, these results validate routine inclusion of JAK2V617F in the diagnostic workup of SVT patients.

# Prevalence of incidentally detected SVT
# Ageno et al,

- Retrospective review of abdominal CT scans from September 1st 2009 to March 31st 2010
- Total number 2619
- CT scan and no suspected SVT 2592
- Age (mean) 65
- Males (%) 59.2
- Incidentally detected SVT 50 (1.93%, 1.45-2.56)
- Indipendent predictors Cancer and liver cirrhosis

# Guidance for the management of venous thrombosis in unusual sites

Walter Ageno, Jan Beyer-Westendorf, David A. Garcia, Alejandro Lazo-Langner, Robert D. McBane, and Maurizio Paciaroni
J Thromb Thrombolysis. 2016; 41: 129–143

- Splanchnic vein thrombosis

- (1) Should all patients with SVT receive anticoagulant treatment?
- (2) Is gastrointestinal bleeding at the time of diagnosis a contraindication to anticoagulant therapy?
- (3) Is the standard treatment regimen used for patients with deep vein thrombosis of the lower limbs (i.e. heparins for approximately 5–7 days and warfarin possibly started on the first treatment day) applicable to all treatable patients?
- (4) What factors should be considered before starting anticoagulant treatment in a patient with liver cirrhosis?
- (5) Is there a role for thrombolysis?
- (6) What are the factors driving treatment duration?
- (7) Is there a role for the direct oral anticoagulants?

# 1.Should all patients with SVT receive anticoagulant treatment?

- The American College of Chest Physicians guidelines recommend anticoagulation for symptomatic SVT patients, and no anticoagulation for asymptomatic patients with incidentally detected events [37]. Anticoagulation for patients with acute and chronic portal vein thrombosis and Budd Chiari syndrome is recommended by the American Association for the Study of Liver Diseases [38].
- However, patients with SVT may present with active gastrointestinal bleeding or with a very high risk of bleeding due to concomitant underlying disorders. In these patients, the risks associated with anticoagulation may offset its benefits. ***In a prospective study aimed at describing treatment strategies for SVT patients in real life, more than 20 % of patients did not receive anticoagulant treatment [39]. Factors associated with no treatment included gastrointestinal bleeding at presentation, thrombocytopenia, cancer, hepatic cirrhosis, and incidental diagnosis of SVT [39].***
- **Guidance Statement**

***Anticoagulant treatment should be considered for all patients with symptomatic SVT and no evidence of active bleeding. The decision to administer anticoagulants to patients with incidentally detected, asymptomatic SVT should be made on an individual basis, carefully balancing the presence of risk factors for recurrence (e.g. underlying prothrombotic conditions) and the risk of bleeding***.

# Is gastrointestinal bleeding at the time of diagnosis a contraindication to anticoagulant therapy?

- ***Gastrointestinal bleeding may be present at the time of SVT diagnosis in up to 25 % of patients [8]. It is in most cases associated with esophageal varices, but it can also occur after intestinal infarction in patients with mesenteric vein thrombosis***. Active gastrointestinal bleeding represents a contraindication to anticoagulant treatment, but anticoagulation should be considered in patients with previous bleeding, in particular when at high risk of thrombus extension or recurrence. However, the optimal timing for starting anticoagulant therapy is unknown and it should be decided on an individual basis taking into account the management of bleeding sources and the presence of additional risk factors for bleeding. For example, in some cases, it may make sense to start anticoagulation only after the high pressure due to venous obstruction has been relieved
- ***Guidance Statement :*** *In the presence of active bleeding, anticoagulant treatment should be initiated only when the bleeding source has been successfully treated and the patient is clinically stable. The decision to start anticoagulant treatment should be driven by the presence of major risk factors for recurrence, the ability to address the underlying cause for bleeding, and by the location and extent of thrombosis.*

# Is the standard treatment regimen used for patients with deep vein thrombosis applicable to all treatable patients?

- SVT is associated with solid cancer in approximately 22–27 % of patients [6, 39]. LMWH has been shown to be more effective than warfarin in patients with cancer-associated deep vein thrombosis of the lower limbs or pulmonary embolism and, for this reason, LWMH is the current treatment of choice at least for the first 3–6 months in this population [37]. Although no studies comparing LMWH with warfarin are available in SVT patients, it is plausible that the clinical benefit of LMWH is similar also in this setting

- **Guidance Statement**

*This treatment regimen may not be appropriate for patients with cancer-associated SVT or for patients with major risk factors for bleeding (e.g. liver cirrhosis and/or known esophageal varices, thrombocytopenia), for whom an initial course of treatment with LMWH (3–6 months for cancer patients) is preferable. In patients with thrombocytopenia, reduced doses of LMWH should be used (prophylactic or half therapeutic dose) according to the platelet count and to the concomitant presence of additional risk factors for bleeding. For all other patients, the introduction of warfarin should be considered only when the patient is clinically stable. In patients at very high risk of bleeding or possibly requiring invasive procedures the use of UFH may be preferred over LMWH.*

# What factors should be considered before starting anticoagulant treatment in a patient with cirrhosis?

- Approximately 24–28 % of SVT patients have known liver cirrhosis [6, 39]. In these patients, bleeding risk associated with the **presence of portal hypertension needs to be carefully assessed**. ***Esophageal varices*** have been consistently reported to be associated with an increased risk of bleeding in SVT patients [6, 9], **but their presence does not represent an absolute contraindication to anticoagulant therapy, because treatment of SVT may improve the portal hypertension**. However, before starting anticoagulants, routine endoscopic screening of esophageal varices and prophylactic treatment of variceal bleeding, if indicated, may be warranted
- Anticoagulation with LMWH was started ***not earlier than 15 days after the last banding session***. One episode of variceal bleeding was reported in this study. In another study, 55 cirrhotic patients with portal vein thrombosis were treated with either warfarin or LMWH and the main study outcome was the rate of complete recanalization of the portal vein [41]. Of interest, initiation of anticoagulant treatment within the first 2 weeks after diagnosis was the only predictive factor for complete recanalization. The majority of these patients (78 %) received beta-blockers for prophylaxis of variceal bleeding.
- **Guidance Statement** ***: Routine endoscopic screening of esophageal varices and prophylactic treatment of variceal bleeding should be considered for all cirrhotic patients with SVT. In patients who are not actively bleeding, anticoagulant treatment should be started as soon as possible with initially reduced doses of LMWH (either prophylactic doses or half therapeutic doses also according to the platelet count). Full doses of LMWH should be started only after the completion of the banding treatment.***

# What is the optimal duration of anticoagulant therapy after a first episode of SVT?

- The American Association for the Study of Liver Diseases recommends anticoagulant therapy for at least 3 months for all patients with acute portal vein thrombosis, and long-term anticoagulation for patients with concomitant mesenteric vein thrombosis or patients with permanent thrombotic risk factors [38]. ***The majority of SVT patients have underlying prothrombotic risk factors, which in most cases are permanent***. Recurrent thrombosis may be severe since in about one fourth of cases it occurs as hepatic, mesenteric, or splenic infarctions [9]. Anticoagulant treatment is effective in preventing recurrence, but bleeding rates reported in SVT patients appear to be higher than those reported in patients with deep vein thrombosis of the lower limbs. However, in the study on patients with MVT only, case-fatality rate of thrombosis was significantly higher than that of gastrointestinal bleeding [11]. Whether patients with SVT plus a symptomatic myeloproliferative syndrome with positive JAK2 V617F mutation can safely transition from anticoagulation to aspirin therapy once they have started cytoreductive therapy or JAK2 inhibitors (e.g. with hydroxyurea or interferon) is not known.
- **Guidance Statement ：** *Anticoagulant treatment should be administered for a minimum of 3 months to all SVT patients. It appears safe to discontinue anticoagulant treatment in the presence of major transient risk factors, such as surgery or infections. For all other patients, including patients with cirrhosis, cancer including myeloproliferative neoplasms, or autoimmune disorders, indefinite treatment duration should be considered with periodic careful assessment of the risks and benefits.*

# Is there a role for the direct oral anticoagulants?

- No SVT patients have ***been enrolled in phase III clinical trials of the direct oral anticoagulants. We found only two published case reports of PVT or MVT patients treated with rivaroxaban [48, 49]. Al***though direct oral anticoagulants represent important alternatives to LMWH and warfarin also in this setting, the reported increased risk of gastrointestinal bleeding in phase III clinical trials, at least with some molecules, remains a matter of concern. Furthermore, the direct oral anticoagulants are contraindicated in patients with acute or chronic severe liver impairment as a result of their partial metabolism through the CYP 3A4 system [50]. Thus, additional evidence is needed; pending such evidence, we can neither recommend for or against the use of direct oral anticoagulants in the management of SVT patients**.**

- **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.***

# Summary of therapeutic interventions for Splanchnic vein thrombosis

- **Without active bleeding**
- LMWH (UFH) recommended for all pts. with symptomatic SVT
- In asymptomatic (incidental) SVT, treatment decision need to balance risk of thromboembolic and bleeding complications
- LMWH: 200 aXa/kg/day; UFH: 2.5-fold PTT
- VKA: INR 2–3
- **At least 3 months for all pts.**
- **Discontinuation in pts. with transient risk factors (surgery, infections)**
- Long-term in pts. in all other pts (including cirrhosis, solid cancer, myeloproliferative neoplasms, severe thrombophilia (antithrombin, protein C or protein S deficiency; APS; homozygous factor V Leiden or prothrombin gene mutation or combined heterozygous mutation; PNH)
- In cirrhotic patients limited search for underlying conditions, but screening for esophageal or fundus varices (and prophylactic treatment)
- **In non-cirrhotic patients search for solid cancers, PNH (if suggested by concomitant signs of hemolysis), JAK-2 mutation, myeloproliferative neoplasms**
- Autoimmune disease
- Intraabdominal infections
- Thrombophilia
- Steroid use/abuse
- Selected cases: - Patients with mesenteric vein thrombosis and intestinal ischemia
- - Deterioration despite adequate anticoagulant therapy

# Conclusion

- The treatment of venous thrombosis occurring in unusual sites is particularly challenging because of the lack of evidence from clinical trials. The prescription of standard therapeutic regimens that are usually recommended for patients with deep vein thrombosis of the lower limbs or pulmonary embolism needs to be carefully assessed on an individual basis, because the optimal timing of introduction, the optimal duration, and the dosages of anticoagulant drugs may need to be adapted according to the clinical presentation and to the presence of underlying disorders.
- In patients with SVT presenting with concomitant gastrointestinal bleeding the use of any anticoagulant can only be considered when the bleeding source is treated and the patient is stable. Not uncommonly, SVT patients do not receive anticoagulation because the risk of bleeding is perceived to persistently outweigh the risk of recurrence.
- ***SVT is frequently associated with major permanent risk factors such as liver cirrhosis or cancer, which place patients at a high long-term risk of recurrence. Thus, for the majority of patients, with the exclusion of those with SVT secondary to surgery or an acute infection, indefinite treatment duration is suggested.***