Rapid Resource

Anticoagulation FORUM | ANTICOAGULATION Centers of Excellence

Management of Unusual Site Thrombosis – Splanchnic, Cerebral, Ovarian & Renal Veins

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Background: Venous thrombosis involving splanchnic, cerebral, renal and ovarian veins are uncommon compared to lower extremity DVT and PE. High quality evidence is lacking on best treatment. Medical management with AC remains the therapeutic mainstay. Patients should be evaluated for hereditary or acquired risk factors that may be playing a role. Multidisciplinary approach is key to improving patient outcomes.

SVT AND CVT - BOTTOM LINE

	DO[1,3]	DON'T[3,4]	CONSIDER[3,5,6,7]	CAUTION
SVT	Order Doppler ultrasound for PVT and BCS as first line In patients with cirrhosis/HCC exclude tumor thrombus with CT-A or MRI. Tumor thrombus does not benefit from AC Order CT angiography or MRI for SpVT and MVT as first line Use AC in patients with acute SVT (including incidental & cirrhosis patients) if no CI	Order liver biopsy in BCS as imaging is sufficient for diagnosis Use antiplatelets as alternative to AC for those who need long term treatment of SVT[4]	Early endovascular intervention if progression despite AC or if signs of bowel ischemia[7] DOAC > VKA in non-cirrhotic PVT For malignancy-associated SVT use LMWH or DOAC Start early AC if no active bleeding. If high risk for bleed, consider individualized dose reduction. If poor prognosis, consider withholding AC. Untreated gastroesophageal varices are CI to AC After primary treatment when AC may be discontinued (e.g. provoked CVT), consider thrombophilia screening to guide further AC duration	Prior to starting AC, address modifiable risk factors for bleeding (e.g. endoscopic and/or medical treatment of esophageal varices in patients with or at high risk of portal HTN) and ensure no immediate need for surgical intervention (e.g. for intestinal infarction)
CVT	MR Venography (gold standard) or CTA for diagnosis depending on availability Early AC with LMWH or UFH unless contraindicated (ICH is not considered an absolute contraindication)	Use thrombolysis in those with acute CVT & low risk of poor outcomes Use antiplatelet agents as alternative to AC for those who need long term treatment of CVT	Thrombolysis in patients with severe CVT or with worsening neurological symptoms despite therapeutic AC Using DOAC following clinical stability and improvement on imaging After primary treatment when AC may be discontinued (e.g. provoked SVT), consider thrombophilia screening to guide further AC duration	Address modifiable risk factors for bleeding prior to starting AC

Table 1. Facts about SVT & CVT[1,2,8-11]

- Unprovoked SVT/CVT is less common than unprovoked DVT/PE; a thorough evaluation is recommended for provoking factors (Table 2)
- Thrombosis in unusual location (40%) may be initial presenting manifestation of prothrombotic disorder (malignancy, PNH, APLS)
- Inherited thrombophilia (e.g. Factor V Leiden) are more prevalent for clots in unusual locations compared to clots in common locations (DVT/PE)
- CVT occurs more commonly in females (75% of cases), while SVT in males (66%)
- Therapeutic aims of AC for acute SVT: prevent intestinal ischemia/infarction and achieve vessel recanalization to reduce splanchnic HTN and associated bleeding risk
- Therapeutic aims of AC for acute CVT: prevent thrombus progression, reduce risk of hemorrhage from venous congestion, and prevent neurologic decline
- Duration of AC is not well studied and most data is extrapolated from DVT/PE
- Minimal high-quality data for DOACs in SVT & CVT
- Recent guidelines suggest a strategy of using thrombophilia screening to guide duration of AC for some patients[2]

Clinical Presentation of SVT and CVT

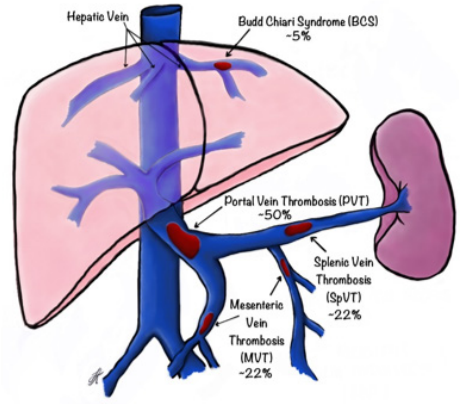
SVT [8]

- Most common symptom is abdominal pain
- 30% are asymptomatic and found incidentally on imaging (esp in cirrhosis & malignancy patients)
- Acute MVT can cause intestinal infarction (pain out of proportion to physical exam findings)
- BCS can present with fulminant liver failure (triad of abdominal pain, ascites, and hepatosplenomegaly)
- Portal HTN seen in chronic MVT, PVT & BCS
- SVT may present with esophageal varices
- SpVT can present as acute splenomegaly, especially following abdominal surgery

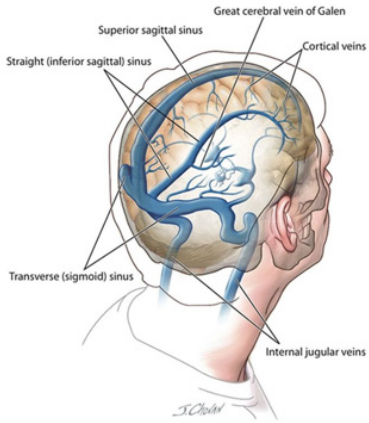
CVT [9,12]

- Most common symptom is headache (present in 85% of cases, only symptom in 25% of cases)
- Neurological deficits (1% of stroke caused by CVT)
- 33% present with ICH
- Chronic CVT presents with signs of intracranial HTN
- Seizures (20% of cases)
- Encephalopathy and coma

Splanchnic Veins



Cerebral Veins



Moll, Stephan, and Beth Waldron. "Cerebral and sinus vein thrombosis." Circulation vol. 130,8 (2014): e68-70. doi:10.1161/CIRCULATIONAHA.113.008018

Table 2. Risk Factors of Splanchnic Vein Thrombosis / Cerebral Vein Thrombosis[8,9]

	ACQUIRED		INHERITED[8]
	Persistent[8,9,13]	Transient[8,9]	
SVT	• Cirrhosis (25%) • Myeloproliferative neoplasms [JAK2V617 mutation] • Solid tumor malignancies (eg liver & pancreatic) • Inflammatory bowel disease • Antiphospholipid syndrome • Autoimmune disease • Paroxysmal nocturnal hemoglobinuria	• Intra-abdominal infections • Intra-abdominal trauma • Abdominal surgery • Estrogen hormone therapy • Pregnancy/puerperium (~15%) • Heparin induced thrombocytopenia	Factor V Leiden mutation Prothrombin G20210A mutation Protein C or S deficiency Antithrombin deficiency
CVT	• CNS malignancies • Antiphospholipid syndrome • Myeloproliferative neoplasms [JAK2V617 mutation] • Autoimmune disease • Paroxysmal nocturnal hemoglobinuria • CNS disorders (AVM or dural fistulae) (<5%)	• Pregnancy/puerperium (~15%) • Heparin induced thrombocytopenia • Infections: Head & Neck and COVID-19 • Neurosurgical trauma or infections • COVID-19 vaccination/VITT (adenovirus-vector ChAdOx1 nCov-19 and Ad26.COV2.S) - Rare • Medications: – Chemotherapy (L-asparaginase, ATRA) – Estrogen therapy (~50%)	

CVT and SVT are unprovoked in 15-30% of cases

Treatment Algorithm For SVT

Anticoagulation

1. Acute Symptomatic OR Incidental
2. Chronic SVT (case by case)
3. BCS - indefinite

Progression despite above treatment

Endovascular Intervention

1. Thrombolysis
2. Endovascular stenting
3. Angioplasty
4. TIPS (in BCS)

Progression in cases of BCS despite above treatment

Liver Transplant in BCS

SVT AND CVT Continued

Table 3. Duration of AC for SVT[14-17, 26]

	Cirrhotic	Non-Cirrhotic	Chronic SVT	Incidental SVT
2024 ISTH	6 months at minimum	N/A	N/A	6 months at min. if thrombus progression. Extended duration if awaiting transplant
2020 ISTH	≥ 3-6 months. Consider longer/indefinite if thrombus progression or recurrence after treatment discontinuation, unprovoked or persistent risk factors		Case by case	≥3-6 months
2020 ACG	6 months if complete main PVT or MVT	6 months if transient risk factors	Indefinite if thrombophilia, MVT, bowel ischemia, or awaiting transplant	N/A
2020 ASH	Cancer + SVT: suggests short term AC or observation			
2019 ASCO	Case by case basis considering potential risk and benefits			

Duration of AC for CVT[18-21]

2024 AHA	Parenteral heparin followed by transition to oral VKAs for 3 to 12 months, indefinitely if thrombophilia or recurrent VTE; DOACs appear safe and effective
2023 ASH	Consider thrombophilia screening to guide duration of AC in patients who would otherwise discontinue AC after primary treatment
2021 CHEST	At least 3 months
2021 ESC	LMWH acute phase (5-15 days) then dabigatran or VKA for long-term treatment (6 months)
2017 ESO	Variable duration ranging from 3 – 12 months Can be prolonged with recurrent VTE or persistent prothrombotic conditions *Recommendations made prior to newer studies exploring DOAC (RE-SPECT trial)

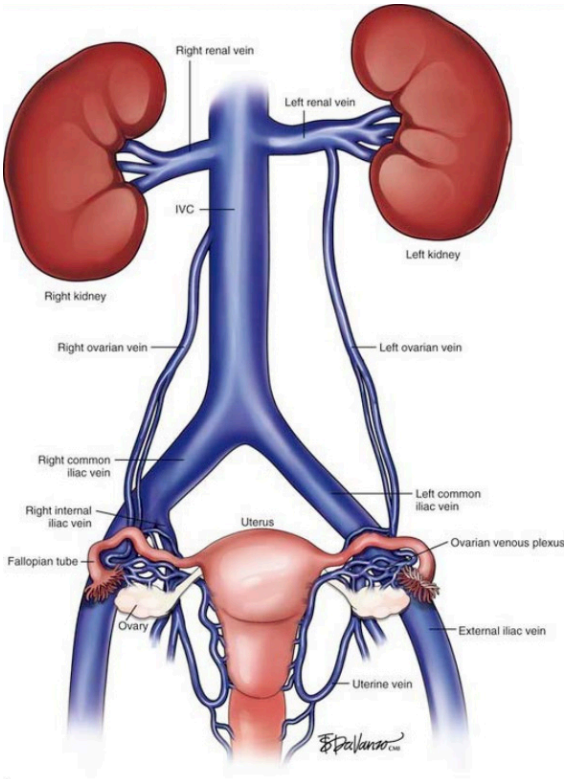
Table 4. DOAC Considerations in CVT and SVT

Avoid Use	• Drug-drug interactions: Strong Pgp and Cyp 3A4 inducers • Child-Pugh class C (rivaroxaban if Child-Pugh classes B-C) • CrCl < 15 mL/min (dabigatran if CrCl < 30 mL/min)
Caution	• CVT associated with CNS malignancies, infections, trauma (not enough evidence to support or refute use of DOACs) • Luminal GI cancer (except apixaban) • MVT complicated bowel ischemia • Untreated gastroesophageal varices – as with any therapeutic AC • Platelet count < 50,000 (consider reduced dose AC)
Use Considerations	• Rates of SVT recanalization are improved with DOACs and LMWH compared with VKA[1] • Dabigatran and warfarin both efficacious in preventing recurrence of venous thrombotic events in RCT of 120 patients with CVT[22] • In CVT, DOACs have similar efficacy and bleeding risk as warfarin in a systematic review/meta-analysis[23]

Renal and Ovarian Vein Thrombosis

Table 5. Renal Vein Thrombosis and Ovarian Vein Thrombosis

	Renal Vein Thrombosis[24]	Ovarian Vein Thrombosis[25]
Epidemiology	• Limited data • High variability in prevalence (5% to 60% of patients with nephrotic syndrome may have RVT)	• Rare; limited data • Occurs in less than 0.2% of pregnancies • Incidence higher after C-section (0.1%) than after vaginal delivery (0.02%) • Age: 30s to 60s • Right ovarian vein commonly involved (~75%), bilateral (10%)
Risk Factors	• 12% unprovoked • Nephrotic syndrome • Malignancy (RCC) • Surgery • Abdominal trauma • Infections	• Pelvic infections - related to septic pelvic thrombophlebitis • Pregnancy or post partum period • Malignancy (ovarian & uterine) • Recent abdomen-pelvic surgery • Inherited thrombophilia • Idiopathic
Presentation	• Triad of flank pain, hematuria, and AKI. Often asymptomatic, and incidentally discovered on imaging	• Abdominal pain • Palpable cord-like abdominal mass • Nausea, vomiting • Anorexia, malaise, Ileus • Triad of fever, pelvic pain, abdominal mass -> septic pelvic thrombophlebitis
Diagnosis	• Renal venography – gold standard • CT angiography – test of choice due to feasibility (sensitivity & specificity ~100%) • MR venography (if AKI) – equal sensitivity as CT	•Doppler Ultrasound – first line •Contrast-enhanced CT or CT venography •MR venography (highest sensitivity/specificity)
Complications	• Propagation into IVC, CKD, HTN, and PE	• Rare complications Including thrombus extension to the IVC or rarely PE
Treatment	• Start LMWH (renally dosed) or UFH followed by VKA with INR goal 2-3 • Consider degree of renal function when choosing anticoagulant • Duration of treatment: 6 – 12 months, longer if nephrotic syndrome • Systemic thrombolysis NOT recommended due to bleeding risk • Local thrombolytic therapy with or without thrombectomy for acute bilateral RVT and acute renal failure	• Parenteral antibiotics are mainstay of therapy due to underlying infectious etiology • Asymptomatic OVT may not need treatment • LMWH, VKAs, or DOACs (latter if not breastfeeding) can be used for treatment **Duration** • Optimal duration of AC is unclear • 3 months of AC is reasonable especially if provoked by postpartum state or other prothrombotic risk factor • Longer duration can be considered in patients with persistent risk factors • Subset of patients may do well with shorter duration (2-6 weeks)



A. https://www.stepwards.com/?page_id=12016

BCS: Budd Chiari Syndrome **CVT**: Cerebral vein thrombosis
MVT: Mesenteric vein thrombosis **PVT:** Portal vein thrombosis
SpVT: Splenic vein thrombosis **SVT:** Splanchnic vein thrombosis
VKA: Vitamin K antagonist

References: 1. Blood. 2021;137(9):1233-1240. 2. Blood Advances vol. 7 (2023): 7101 – 7138. 3. Blood vol. 135,5 (2020): 326-334. 4. Hematology Am Soc Hematol Educ Program. 2020;2020(1):634-641. 5. Blood Adv. 2020;4(4):655-666 6. Journal of thrombosis and thrombolysis vol. 41,1 (2016): 129-43. 7. Vasc Med. 2017;22(6):529-540. 8. Vascular health and risk management vol. 15 449-461. 22 Oct. 2019. 9. Journal of clinical medicine vol. 9,3 743. 10 Mar. 2020 10. J Thromb Haemost. 2021;19(4):983-991. 11. The Lancet. Haematology vol. 3,6 (2016): e267-75. 12. Stroke. 2007;38(2):337-342. 13. Blood. 2013;121(25):4985-5105. 14. J Clin Oncol. 2020;38(5):496-520. 15. Blood Adv. 2021 Apr 13;5(7):1953]. Blood Adv. 2021;5(4):927-974. 16. J Thromb Haemost. 2020;18(7):1562-1568. 17. Am J Gastroenterol. 2020;115(1):18-40. 18. Eur Heart J. 2018 Mar 1;39(9):763-816. 19. Eur J Prev Cardiol. 2022 May 27;29(8):1248-1263. 20. Stevens SM, et al. CHEST. 2021;160(6):2247-59. 21. Stroke. 2024;55(3):e77-e90. 22. JAMA Neurol. 2019;76(12):1457-1465. 23. J Thromb Thrombolysis. 2020;50(3):724-731. 24. StatPearls Publishing, 21 June 2022. 25. Hamostaseologie vol. 41,4 (2021): 257-266. 26. Thromb Haemost. 2024 Sep;22(9):2653-2669.

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