NOVITÀ IN COAGULAZIONE
attraverso i centri emostasi e trombosi
Torino, 12-13 novembre 2021

Trombosi in sedi atipiche

Francesco Dentali

Dipartimento di Emergenza ad Alta Specialità e Medical Center

ASST Setteleghi– Fondazione Macchi - Varese

Conflitti di Interesse

Letture
Protocolli di Ricerca
Advisory Boards

- Bayer
- BMS/Pfizer
- Boheringer
- Daiichi
- Sanofi
- Alfa Wasserman

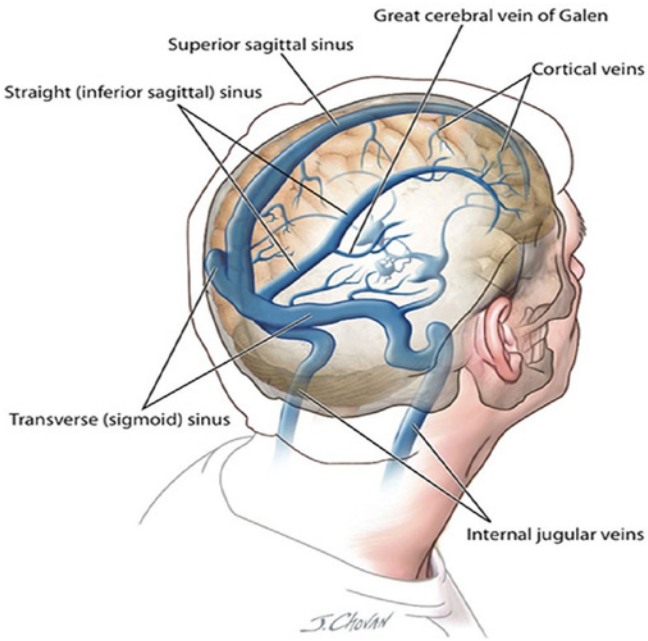
Mini-Agenda

- Trombosi Venose Cerebrali
- Trombosi Venose Splancniche
- Altro

American Heart Association.

Trombosi venosa cerebrale

The anatomy and terminology of the cerebral and sinus veins.



Moll and Waldron; Circulation. 2014

Incidenza

Populati		100 000^{-1}
Overall adult in		-1.61)
Subgroups		
Women		-2.36)
Men		-1.09)
Age 18–30 y		-2.44)
Age 31–50 y		-2.27)
Age ≥51 y		-1.16)
Women age		-3.82)
Men age 31-		-1.21)

Incidence ra 5% CIs in parentheses.

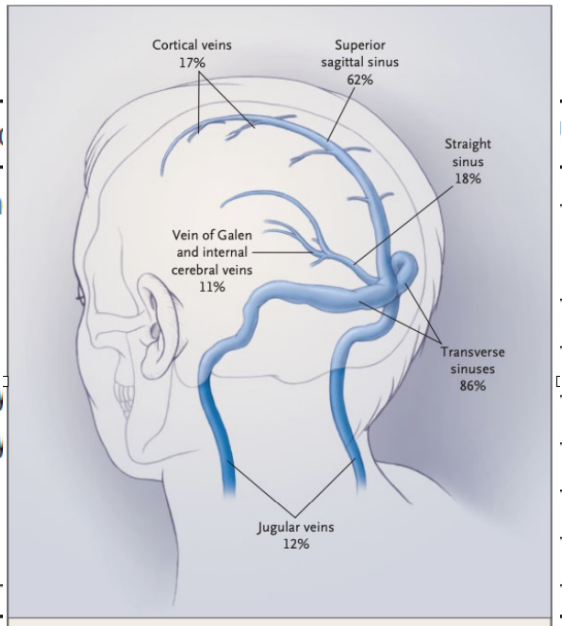


Figure 1. Frequency of Thrombosis of the Major Cerebral Veins and Sinuses.
The frequencies of thrombosis in the various sinuses are given as percentages and are based on data from the International Study on Cerebral Vein and Dural Sinus Thrombosis.[1] In most patients, thrombosis occurs in more than one sinus.

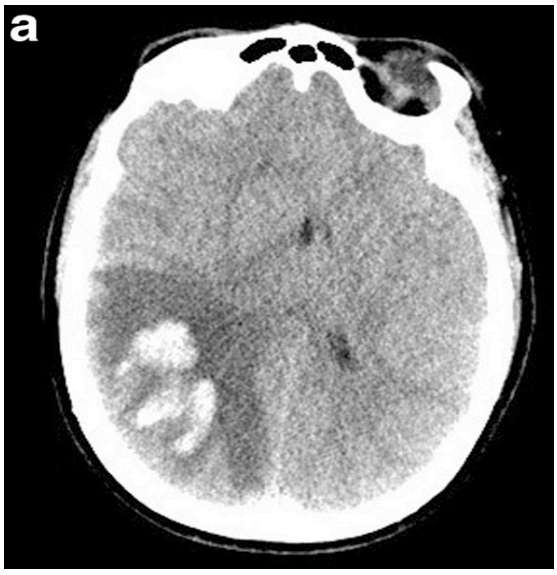
Coutinho et al; Stroke 2012

ORIGINAL ARTICLE

Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study

F. DENTALI*, D. POLI†, U. SCODITTI‡, M. N. D. DI MINNO§, V. D. STEFANO¶, S. SIRAGUSA**, M. KOSTAL††, G. PALARETI‡‡, M. T. SARTORI§§, E. GRANDONE¶¶, M. C. VEDOVATI***, W. AGENO* and FOR THE CEVETIS (CEREBRAL VEIN THROMBOSIS INTERNATIONAL STUDY) INVESTIGATORS[1]

Total number, *n*	706
Male gender, *n* (%)	186 (26.3)
Mean age, years (± SD)	40.0 (16.3)
Principal sites of thrombosis, *n* (%)	Superior sagittal sinus 267 (37.8) Left lateral sinus 281 (39.8) Right lateral sinus 225 (31.9)
Concomitant intracranial hemorrhage, *n* (%)	197 (27.9)
Risk factors at first CVT, *n* (%)	Infections 59 (8.3) Trauma 18 (2.5) OC or HRT 278 (39.4) Pregnancy/puerperium 55 (7.8) Cancer or MPD 52 (7.4) Thrombophilic abnormalities (one at least) 290 (41.1) Severe thrombophilic abnormalities 83 (11.7) Unprovoked 312 (44.2)
Personal history of VTE, *n* (%)	54 (7.6)
Family history of VTE, *n* (%)	109 (15.4)



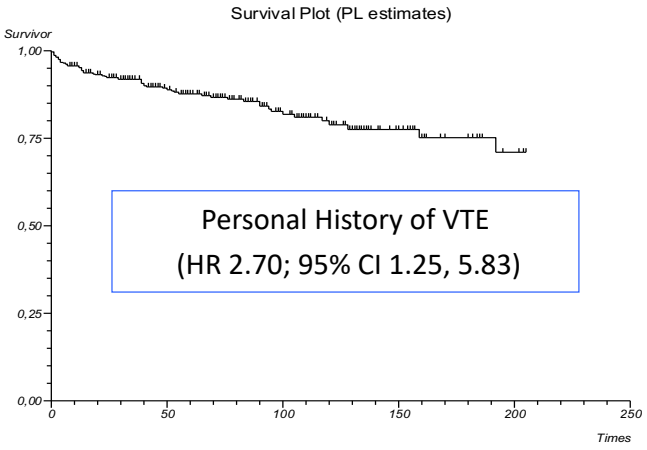
Recidiva

19 studies; 1488 patients

2.8% (range 0-11.7%) had a CVT recurrence during follow up

3.7% (range 0-8.6%) had a VTE (other than CVT) during follow up

706 patients



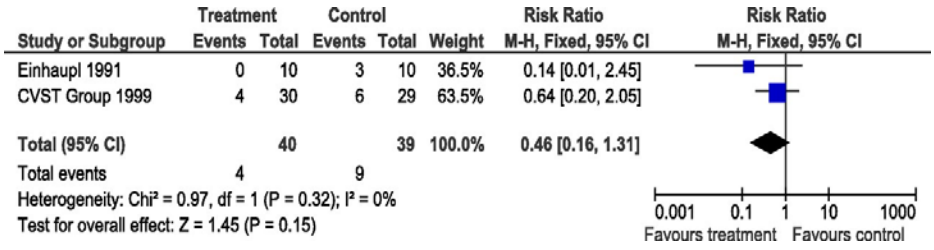
Personal History of VTE
(HR 2.70; 95% CI 1.25, 5.83)

Dentali, Ageno et al; Blood 2006
Dentali, Ageno et al; JTH 2012

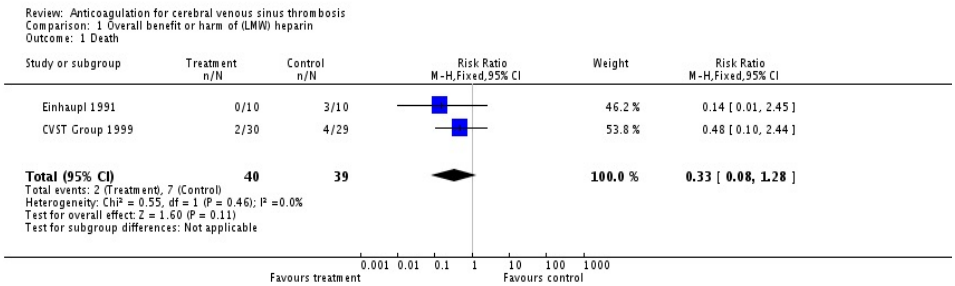
Anticoagulation for Cerebral Vein Sinus Thrombosis (LMWH or UFH?)

THE COCHRANE COLLABORATION®

Death or Dependency



Death



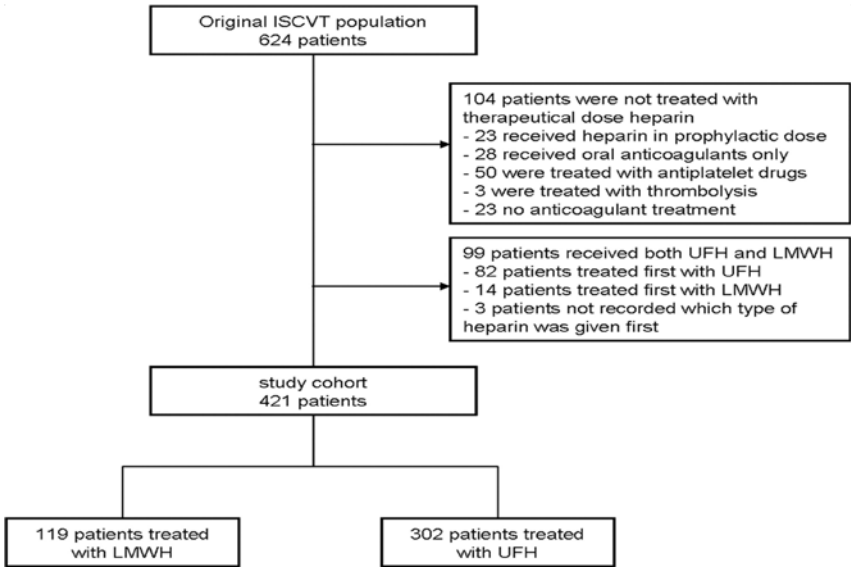
Trattamento Fase Acuta

ISCVT		CEVETIS	
UFH	64%	UFH	21.9%
LMWH	34.9%	LMWH	62.7%
Antiplatelets	5.9%	Antiplatelets	0%
Thrombolysis	2.1%	Thrombolysis	1.5%

Dentali et al; JTH 2012
Ferro et al; Stroke 2004

Unfractionated or Low–Molecular Weight Heparin for the Treatment of Cerebral Venous Thrombosis

Jonathan M. Coutinho, MD; José M. Ferro, MD, PhD; Patrícia Canhão, MD, PhD; Fernando Barinagarrementeria, MD; Marie-Germaine Bousser, MD, PhD; Jan Stam, MD, PhD; for the ISCVT Investigators



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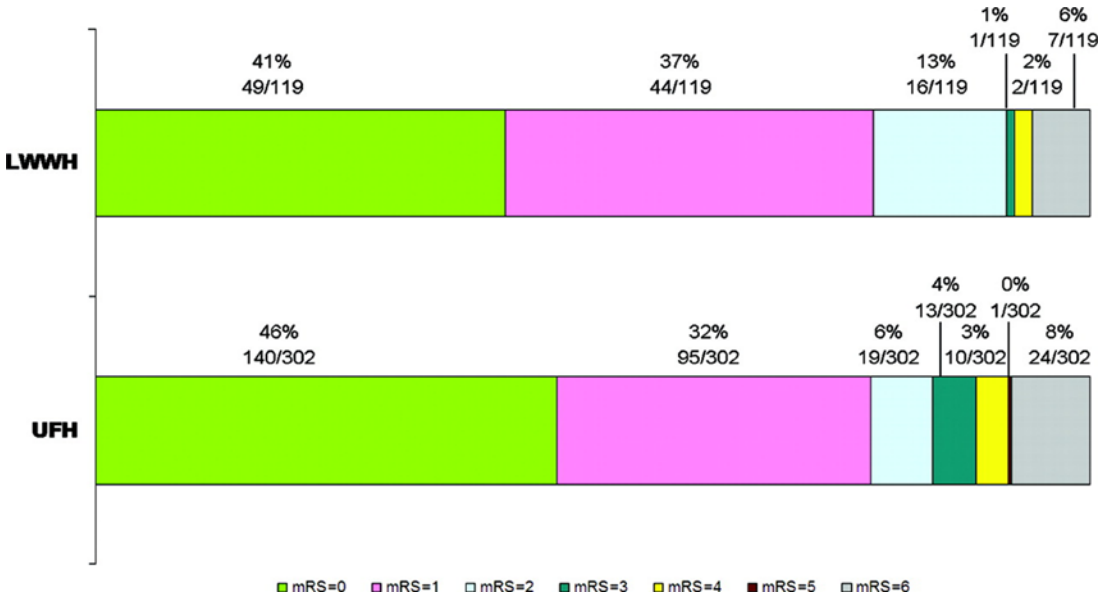

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	LMWH n=119	UFH n=302	Univariate Analysis Unadjusted OR (95% CI)	*P* Value	Multivariate Analysis† Adjusted OR (95% CI)	*P* Value
Primary end point						
Independency (mRS 0–2)	92%	84%	2.1 (1.0–4.2)	0.04	2.4 (1.0–5.7)	0.04
Secondary end points						
Complete recovery (mRS 0 or 1)	78%	78%	1.0 (0.61–1.7)	0.94	0.94 (0.55–1.9)	0.94
Mortality	6%	8%	0.72 (0.30–1.7)	0.47	0.81 (0.29–2.3)	0.70
New intracranial hemorrhage*	10%	16%	0.61 (0.22–1.7)	0.35	0.29 (0.07–1.3)	0.10

*The percentages of patients who underwent repeated CT or MRI are given.
†*P* value for Hosmer–Lemeshow test was >0.20 and <0.85 for each of the multivariate analyses.

EUROPEAN STROKE ORGANIZATION GUIDELINE ON CEREBRAL VENOUS THROMBOSIS

José M Ferro[1,2], Marie-Germaine Bousser[3], Patrícia Canhão[1,2], Jonathan M Coutinho[4], Isabelle Crassard[3], Francesco Dentali[5], Matteo di Minno[6], Alberto Maino[7], Ida Martinelli[7], Florian Masuhr[8], Diana Aguiar de Sousa[1], Jan Stam[4]

Recommendation: we recommend treating adult patients with acute cerebral venous thrombosis with heparin in therapeutic dosage. This recommendation also applies to patients with an intracerebral hemorrhage at baseline. No recommendation can be given on the treatment of children with CVT.

Quality of evidence: moderate

Strength of recommendation: strong

Recommendation: we suggest treating patients with acute cerebral venous thrombosis with low-molecular weight heparin instead of unfractionated heparin. This recommendation does not apply to patients with a contraindication for LMWH (e.g. renal insufficiency) or situations where fast reversal of the anticoagulant effect is required (e.g. patients who have to undergo neurosurgical intervention).

Quality of evidence: low

Strength of recommendation: weak

Recommendation. We suggest using oral anticoagulants (vitamin K antagonists) for a variable period (3-12 months) after CVT to prevent recurrent CVT and other venous thromboembolic events

Quality of evidence: very low

Strength of recommendation: weak

ARTICLE

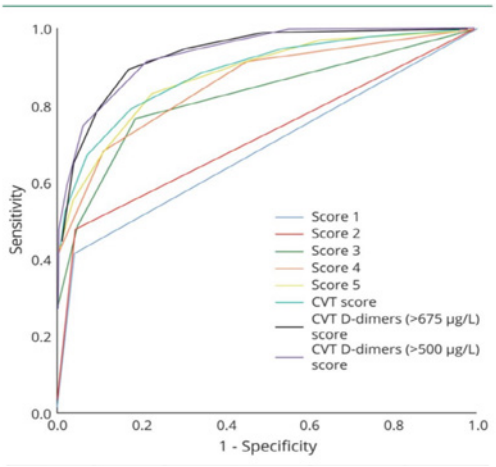
Prediction of cerebral venous thrombosis with a new clinical score and D-dimer levels

	Score 1	Score 2	Score 3	Score 4	Score 5	CVT score
AUC	0.687	0.718	0.823	0.857	0.879	0.889
95% CI	0.617-0.757	0.649-0.786	0.767-0.879	0.809-0.905	0.837-0.922	0.847-0.930
	Seizure(s)	Seizure(s)	Seizure(s)	Seizure(s)	Seizure(s)	Seizure(s)
		Thrombophilia	Thrombophilia	Thrombophilia	Thrombophilia	Thrombophilia
			Oral contraception	Oral contraception	Oral contraception	Oral contraception
				Duration of symptoms >6 days	Duration of symptoms >6 days	Duration of symptoms >6 days
					Worst headache ever	Worst headache ever
						Focal neurologic deficits

Subitems	Regression coefficient	Points	*p* value	Odds ratio (95% CI)
Seizure(s)	3.871	4	<0.0001	48.01 (15.25-151.12)
Thrombophilia	3.509	4	0.002	33.42 (3.55-315.03)
Oral contraception	1.870	2	<0.0001	6.49 (3.16-13.30)
Duration of symptoms >6 days	1.496	2	<0.0001	4.46 (2.18-9.14)
Worst headache ever	1.218	1	0.001	3.38 (1.655-6.69)
Focal neurologic deficits	1.103	1	0.003	3.01 (1.45-6.25)

Subitems and scores	Regression coefficient	Points	*p* value	Odds ratio (95% CI)
D-dimers (>675µg/L)	2.453	3	<0.0001	11.63 (6.62-20.42)
D-dimers (>500µg/L)	2.810	3	<0.0001	16.61 (8.220-33.57)
CVT D-dimers (>675µg/L) score	AUC 95% CI : 0.934 (0.906-0.961)			
CVT D-dimers (>500µg/L) score	AUC 95% CI : 0.937 (0.910-0.963)			

CVT = cerebral venous thrombosis; ROC = receiver operating characteristics.



Heldner et al. Neurol 2020

Table 1. Studies evaluating the use of the direct oral anticoagulants in patients with cerebral vein thrombosis.

Author (year)	Study Design	No. Patients	Demographics	Treatment	Treatment Duration	Safety and Efficacy Outcomes
Geisbüsch (2014) [36]	Retrospective	7	Age (median): 31 years Female/male 7:0	Rivaroxaban (15 mg BID, followed by 20 mg OD, or directly 20 mg OD), both preceded by heparin	8 months (median)	Excellent outcome (mRS 0–1): *n* = 7 (100%) Recanalization (partial or complete): *n* = 7 (100%) Recurrent VTE: *n* = 0 (0%) Major bleeding: *n* = 0 (0%) Minor bleeding: *n* = 2 (28.6%)
		9	Age (median): 43 years Female/male 6:3	Phenprocoumon (INR target range 2.0–3.0), preceded by heparin	9 months (median)	Excellent outcome (mRS 0–1): *n* = 8 (88.9%) Recanalization (partial or complete): *n* = 9 (100%) Recurrent VTE: *n* = 0 (0%) Major bleeding: *n* = 0 (0%) Minor bleeding: *n* = 1 (11.1%)
Mendonça (2015) [37]	Retrospective	15	Age (median): 38 years Female/male 12:3	Dabigatran (110 or 150 mg BID), preceded by heparin/VKA	6 months (median)	Excellent outcome (mRS 0–1): *n* = 13 (86.7%) Recanalization: *n* = 12 (80%) Recurrent VTE: *n* = 0 (0%) Major or minor bleeding: *n* = 0 (0%)
Anticoli (2016) [38]	Retrospective	6	Age (mean): 36.5 years Female/male 6:0	Rivaroxaban (15 mg BID, followed by 20 mg OD, or directly 20 mg OD), the latter preceded by heparin/VKA	11 months (median)	Excellent outcome (mRS 0–1): *n* = 6 (100%) Recanalization (partial or complete): *n* = 6 (100%) Recurrent VTE: *n* = 0 (0%) Major or minor bleeding: *n* = 0 (0%)
Herweh (2017) [39]	Retrospective	13	Age (median): 38 years * Female/male 81:18 *	DOAC (unspecified), preceded by heparin	7 months (median) *	Recanalization (partial or complete): *n* = 11 (84.6%) Recurrent CVT: *n* = 0 (0%) Major bleeding: *n* = 0 (0%)
		86	Age (median): 38 years * Female/male 81:18 *	Phenprocoumon (INR target range 2.0-3.0), preceded by heparin (*n* = 83), or LMWH only (*n* = 3)	7 months (median) *	Recanalization (partial or complete): *n* = 75 (87.2%) Recurrent CVT: *n* = 0 (0%) Major bleeding: *n* = 0 (0%)
Shankar Iyer(2018) [41]	Prospective	20	Age (mean): 34.1 years Female/male 4:16	Rivaroxaban (15 mg BID, followed by 20 mg OD), without heparin	6 months (mean)	Excellent outcome (mRS 0–1): *n* = 19 (95%) Recanalization (partial or complete): *n* = 20 (100%) Recurrent VTE: *n* = 0 (0%) Major or minor bleeding: *n* = 0 (0%)
Covut (2019) [40]	Retrospective	9	Age (median): 56 years Female/male 7:2	Apixaban or rivaroxaban, preceded by heparin/VKA	12 months (median)	Recanalization (partial or complete): *n* = 5 (55.6%) Recurrent VTE: *n* = 0 (0%) Major or minor bleeding: *n* = 0 (0%)
Ferro (2019) RE-SPECT CVT [44]	Randomized controlled trial	60	Age (mean): 45.2 years Female/male 33:27	Dabigatran (150 mg BID), preceded by heparin	5.1 months (mean)	Excellent outcome (mRS 0–1): *n*/*N* = 54/59 (91.5%) Recanalization (partial or complete): *n*/*N* = 33/55 (60%) Recurrent VTE: *n* = 0 (0%) Major bleeding: *n* = 1 (1.7%) Clinically-relevant non-major bleeding: *n* = 0 (0%) Any bleeding: *n* = 12 (20%)
		60	Age (mean): 45.2 years Female/male 33:27	Warfarin (INR target range 2.0–3.0), preceded by heparin	5.3 months (mean)	Excellent outcome (mRS 0–1): *n*/*N* = 53/58 (91.4%) Recanalization (partial or complete): *n*/*N* = 35/52 (67.3%) Recurrent VTE: *n* = 0 (0%) Major bleeding: *n* = 2 (3.3%) Clinically-relevant-non-major bleeding: *n* = 1 (1.7%) Any bleeding: *n* = 12 (20%)
Rusin (2019) [42]	Prospective	36	Age (mean): 40.3 years Female/male 21:15	Apixaban (5 mg BID), dabigatran (110 or 150 mg BID), rivaroxaban (20 mg OD), all preceded by heparin	8.5 months (median)	Excellent outcome (mRS 0–1): *n* = 24 (66.7%) Recanalization (partial or complete): *n* = 34 (94.4%) Recurrent CVT: *n* = 2 (5.6%)—off anticoagulation Deep vein thrombosis: *n* = 2 (5.6%)—off anticoagulation Major bleeding: *n* = 3 (8.3%)
Wasay (2019) [43]	Prospective	45	Age (mean): 36.5 years Female/male 27:18	Dabigatran (75–150 mg BID), rivaroxaban (15–20 mg OD), 80% preceded by heparin	8 months (median)	Excellent outcome (mRS 0–1): *n*/*N* = 25/39 (64.1%) Recurrent VTE: *n* = 0 (0%) Major bleeding: *n* = 1 (2.2%) Any bleeding: *n* = 2 (4.4%)
		66	Age (mean): 41.3 years Female/male 37:29	Warfarin (INR target range 2.0–3.0), 65% preceded by heparin	8 months (median)	Excellent outcome (mRS 0–1): *n*/*N* = 35/56 (62.5%) Recurrent VTE: *n* = 0 (0%) Major bleeding: *n* = 1 (1.5%) Any bleeding: *n* = 4 (6.1%)

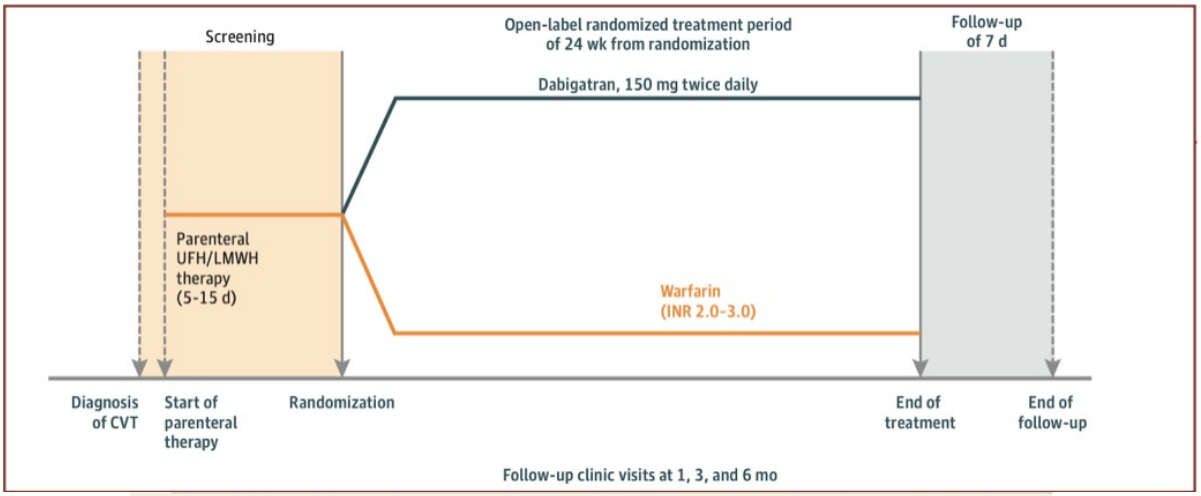
DOAC?

Riva et al, J Clin Med 2020

JAMA Neurology | Original Investigation

Safety and Efficacy of Dabigatran Etexilate vs Dose-Adjusted Warfarin in Patients With Cerebral Venous Thrombosis

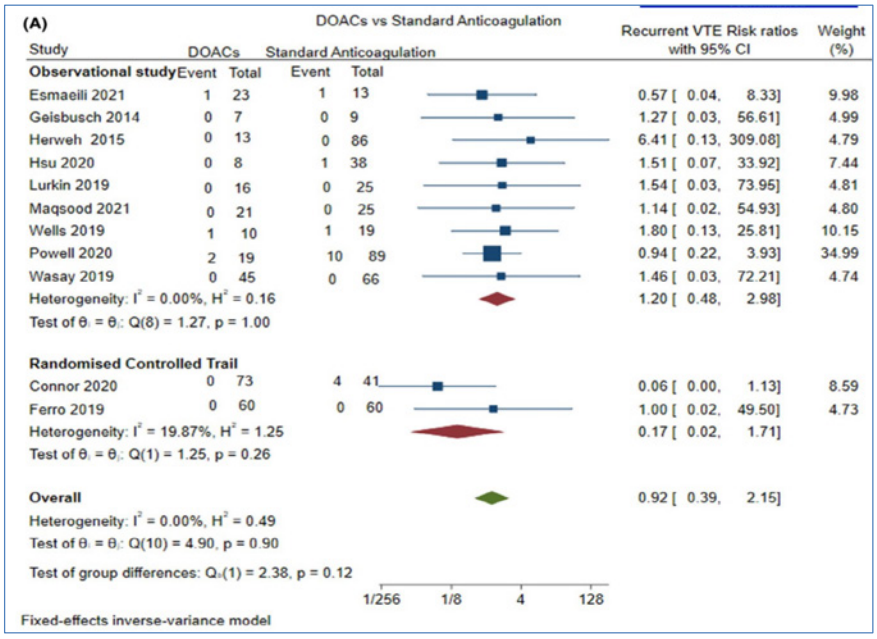
A Randomized Clinical Trial



Major bleeding event	1 (1.7) [0.0-8.9]	2 (3.3) [0.4-11.5]
Clinically relevant non-major bleeding event	0 [0.0-0.6]	1 (1.7) [0.0-8.9]

Ferro, Dentali et al. JAMA Neurol 2019

Safety and efficacy of Direct Oral Anticoagulants in cerebral venous thrombosis: A meta-analysis



Nepal et al, Acta Neur Scand 2020

Recanalization after cerebral venous thrombosis. A randomized controlled trial of the safety and efficacy of dabigatran etexilate versus dose-adjusted warfarin in patients with cerebral venous and dural sinus thrombosis

International Journal of Stroke
0(0) 1–9

DOI: 10.1177/17474930211006303
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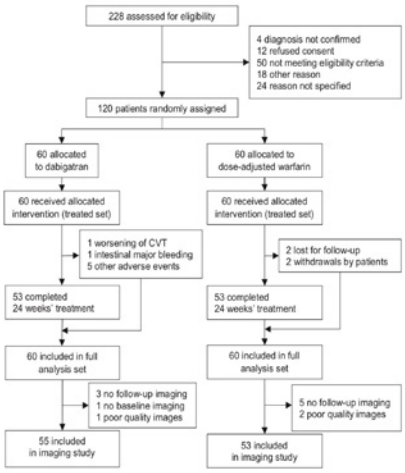
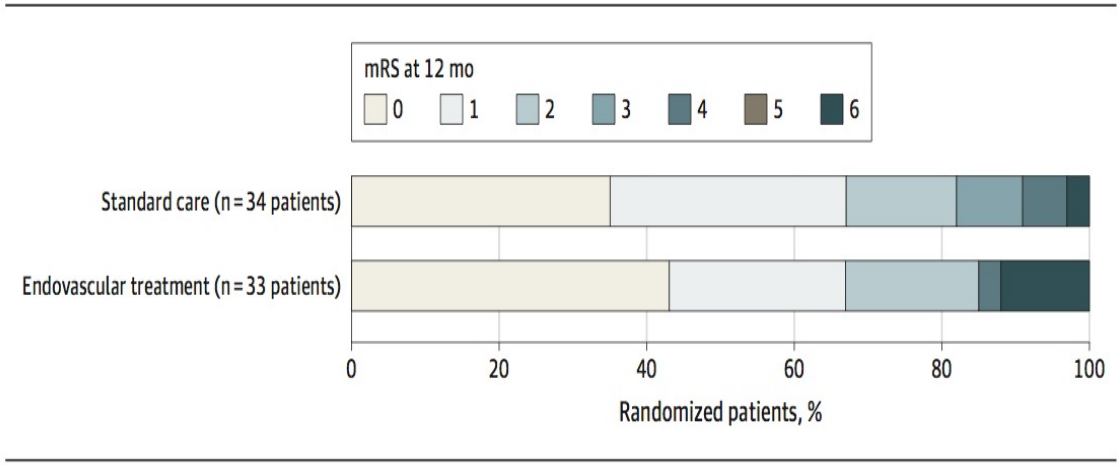


	Dabigatran	Warfarin
Cerebral venous occlusion score	55 patients	52 patients*
Improved	33 (60.0%)	35 (67.3%)
No change	22 (40.0%)	17 (32.7%)
Modified Qureshi score	55 patients	53 patients
Full recanalization	24 (43.6%)	19 (35.8%)
Partial recanalization	23 (41.8%)	26 (49.1%)
No recanalization	8 (14.5%)	8 (15.1%)

Ferro et al, Int Journ Stroke 2021

JAMA Neurology | Original Investigation

Effect of Endovascular Treatment With Medical Management vs Standard Care on Severe Cerebral Venous Thrombosis
The TO-ACT Randomized Clinical Trial

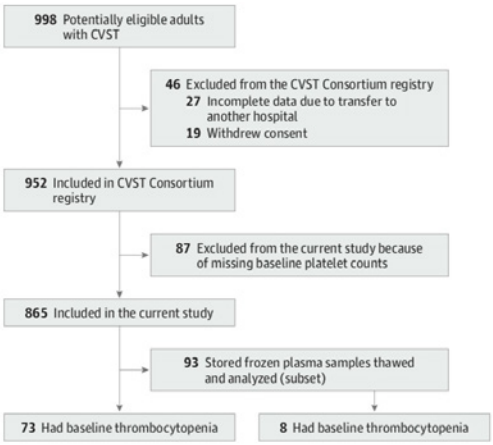


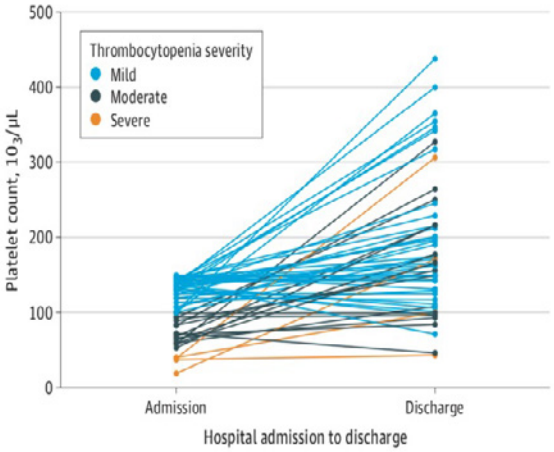
Coutinho et al; JAMA Neurol 2020

DURATA?

JAMA | Original Investigation

Frequency of Thrombocytopenia and Platelet Factor 4/Heparin Antibodies in Patients With Cerebral Venous Sinus Thrombosis Prior to the COVID-19 Pandemic





Sanchez Van Kammen et al, JAMA 2021

Characteristics and Outcomes of Patients With Cerebral Venous Sinus Thrombosis in SARS-CoV-2 Vaccine–Induced Immune Thrombotic Thrombocytopenia

Variable	Group, No./total No. (%) TTS (n = 78)	No TTS (n = 38)
SARS-CoV-2 vaccine[a]		
ChAdOx1 nCov-19	76/78 (97)[b]	20/38 (53)
Ad26.COV2.S	1/78 (1)	0
BNT162b2	1/78 (1)	15/38 (40)[c]
mRNA-1273	0	1/38 (3)
CoronaVac	0	2/38 (5)
Time from vaccination to CVST symptom onset, median (IQR), d[d]	9 (7-10)	7 (3-16)
Previous COVID-19 infection	1/72 (1)	4/36 (11)
Confirmed[e]	0	4/36 (11)
Suspected	1/72 (1)	0
Thrombocytopenia details		
Platelet count at admission, median (IQR), $\times 10^3/\mu L$	45 (25-71)	272 (224-319)
Platelet count nadir, median (IQR), $\times 10^3/\mu L$	30 (14-53)[f]	NA
Positive for PF4 antibodies	63/69 (91)[g]	NA
Positive findings on platelet activation assays	36/36 (100)	NA
Positive for antiphospholipid antibodies	8/56 (14)[h]	0[i]

Sanchez Van Kammen et al, JAMA Neurology 2021

Characteristics and Outcomes of Patients With Cerebral Venous Sinus Thrombosis in SARS-CoV-2 Vaccine–Induced Immune Thrombotic Thrombocytopenia

Characteristic	Group, No./total No. (%)		
	TTS (n = 78)	No TTS (n = 38)	Control (n = 207)
Demographic characteristics			
Age, mean (SD), y	45 (14)	55 (20)	42 (16)
Sex			
Female	63/78 (81)	30/38 (79)	145/207 (70.0)
Male	15/78 (19)	8/38 (21)	62/207 (30.0)
Race			
Asian	4/77 (5)	2/38 (5)	ND
Black	0	1/38 (3)	ND
White	73/77 (95)	35/38 (92)	ND
CVST risk factors			
Any conventional CVST risk factor	19/78 (24)	16/38 (42)	110/172 (64.0)
Oral contraceptives[a]	11/63 (17)	9/30 (30)	61/144 (42.4)
Hormone therapy among women[a]	2/63 (3)	1/30 (3)	0
Pregnancy[a]	0	0	14/145 (9.7)
Recent delivery[a]	0	1/30 (3)	4/145 (2.8)
Any infection	5/78 (6)	0	19/206 (9.2)
Previous thromboembolism	1/78 (1)[b]	1/38 (3)[c]	17/202 (8.4)
Known thrombophilia	1/78 (1)[d]	1/38 (3)[e]	17/181 (9.4)
Cancer	3/78 (4)	3/38 (8)	20/207 (9.7)
Clinical presentation of CVST			
Time from symptom onset to CVST diagnosis, median (IQR), d	3 (2-4)	3 (0-8)	5 (2-11)
Headache	75/78 (96)	30/38 (79)	185/207 (89.4)
Focal neurologic deficits	41/78 (53)	14/38 (37)	128/206 (62.1)
Seizure	8/78 (10)	13/38 (34)	62/205 (30.2)
Coma	18/75 (24)	1/37 (3)	10/207 (4.8)

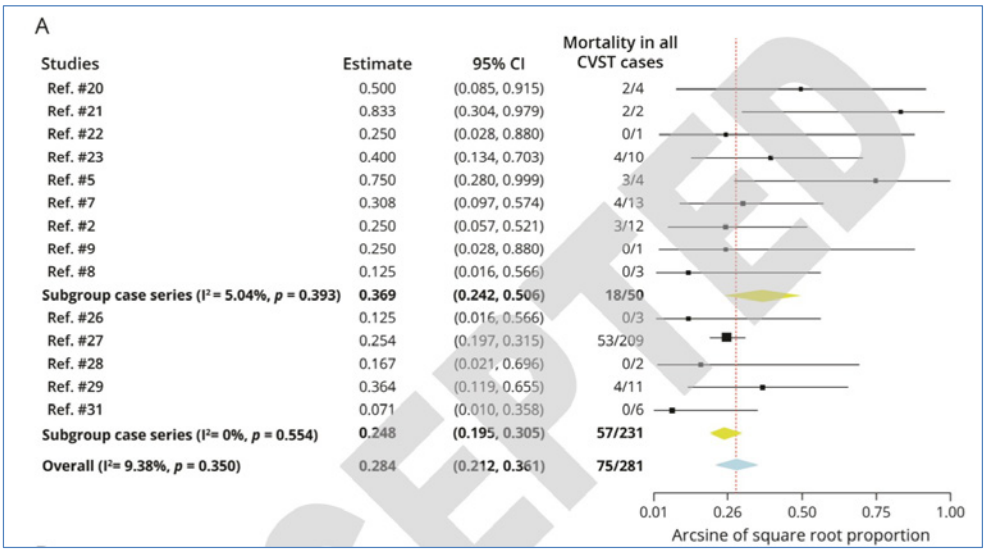
Sanchez Van Kammen et al, JAMA Neurology 2021

Characteristics and Outcomes of Patients With Cerebral Venous Sinus Thrombosis in SARS-CoV-2 Vaccine–Induced Immune Thrombotic Thrombocytopenia

Treatment and outcome	Group, No./total No. (%)		
	TTS (n = 78)	No TTS (n = 38)	Control (n = 207)
CVST treatment			
Any anticoagulant treatment	67/78 (86)[a]	38/38 (100)	200/206 (97.1)
Intensive care unit admission	60/74 (81)	8/38 (21)	32/179 (17.9)
Endovascular treatment	16/77 (21)	1/38 (3)	1/207 (0.5)
Hemicraniectomy	23/77 (30)	1/38 (3)	10/207 (4.8)
Immunomodulation treatment			
Any immunomodulation treatment	52/78 (67)	NA	NA
Intravenous immunoglobulins	47/78 (60)	NA	NA
Plasma exchange	6/78 (8)	NA	NA
Corticosteroids	25/78 (32)	NA	NA
Eculizumab	2/78 (3)	NA	NA
Rituximab	1/78 (1)	NA	NA
Platelet transfusion	20/78 (26)	NA	NA
Because of neurosurgical intervention	13/78 (17)	NA	NA
Outcomes			
Any concomitant thromboembolism	25/70 (36)	2/35 (6)	10/206 (4.9)
Splanchnic vein thrombosis	10/70 (14)	1/35 (3)	0
Deep vein thrombosis	6/70 (9)	0	3/206 (1.5)
Pulmonary embolism	16/70 (23)	0	3/206 (1.5)
Pelvic vein thrombosis	6/70 (9)	1/35 (3)	0
Other thrombosis	6/70 (9)[b]	1/35 (3)[c]	1/206 (0.5)
Any major bleeding complication[d]	9/76 (12)	3/37 (8)	9/206 (4.4)
New intracranial hemorrhage	8/76 (11)	3/37 (8)	ND
Other major bleeding	4/76 (5)[e]	0	ND
Mortality at discharge	36/76 (47)	2/37 (5)	8/207 (3.9)

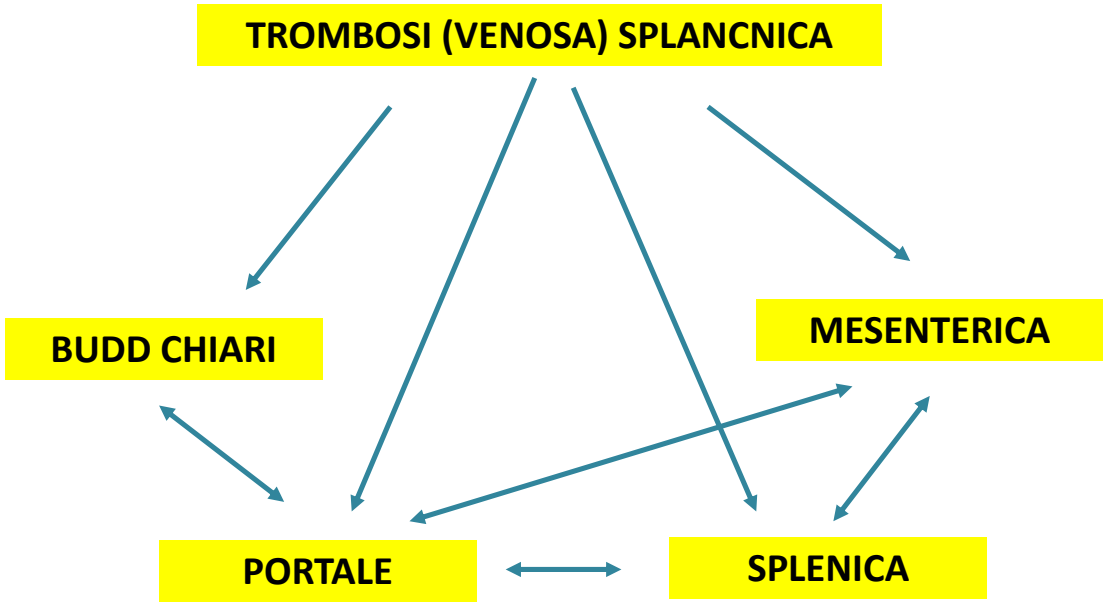
Sanchez Van Kammen et al, JAMA Neurology 2021

Cerebral Venous Sinus Thrombosis and Thrombotic Events After Vector-Based COVID-19 Vaccines: A Systematic Review and Meta-analysis



Palaiodimou et al, Neurology 2021

Trombosi venosa splancnica



AP&T Alimentary Pharmacology and Therapeutics

The epidemiology and clinical features of portal vein thrombosis: a multicentre study

R. Rajani*†, E. Björnsson‡, A. Bergquist§, Å. Danielsson¶, A. Gustavsson**, O. Grip††, T. Melin‡‡, P. Sangfelt§§, S. Wallerstedt¶¶ & S. Almer†

*Department of Medicine, Ryhov Hospital, Jönköping, Sweden.
†Division of Gastroenterology & Hepatology, Department of Clinical and Experimental Medicine/IKE, Linköping University, Linköping, Sweden.
‡Department of Medicine, Sahlgrenska University Hospital, Göteborg, Sweden.
§Department of Gastroenterology & Hepatology, Karolinska University Hospital, Huddinge, Sweden.
¶Department of Medicine, University Hospital, Umeå, Sweden.
**Department of Medicine, University Hospital, Örebro, Sweden.
††Department of Medicine, University Hospital, Malmö, Sweden.
‡‡Division of Gastroenterology & Hepatology, University Hospital, Lund, Sweden.
§§Division of Gastroenterology & Hepatology, University Hospital, Uppsala, Sweden.
¶¶Department of Medicine, Östra Hospital, Göteborg, Sweden.

Correspondence to:
Dr S. Almer, Division of Gastroenterology & Hepatology, University Hospital, SE-581 85 Linköping, Sweden.
E-mail: sven.almer@liu.se

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SUMMARY

Background
Reliable epidemiological data for portal vein thrombosis are lacking.

Aims
To investigate the incidence, prevalence and survival rates for patients with portal vein thrombosis.

Methods
Retrospective multicentre study of all patients registered with the diagnosis of portal vein thrombosis between 1995 and 2004.

Results
A total of 173 patients (median age 57 years, 93 men) with portal vein thrombosis were identified and followed up for a median of 2.5 years (range 0–9.7). The mean age-standardized incidence and prevalence rates were 0.7 per 100 000 per year and 3.7 per 100 000 inhabitants, respectively. Liver disease was present in 70 patients (40%), malignancy in 27%, thrombophilic factors in 22% and myeloproliferative disorders in 11%. Two or more risk factors were identified in 80 patients (46%). At diagnosis, 65% were put on anticoagulant therapy. Thrombolysis, TIPS, surgical shunting and liver transplantation were performed in 6, 3, 2 and 8 patients, respectively. The overall survival at 1 year and 5 years was 69% and 54%. In the absence of malignancy and cirrhosis, the survival was 92% and 76%, respectively.

Conclusions
The incidence and prevalence rates of portal vein thrombosis were 0.7 per 100 000 inhabitants per year and 3.7 per 100 000 inhabitants, respectively. Concurrent prothrombotic risk factors are common. The prognosis is variable and highly dependent on underlying disease.

Aliment Pharmacol Ther 2010; 32: 1154–1162

Una o più patologie?

IRSVT

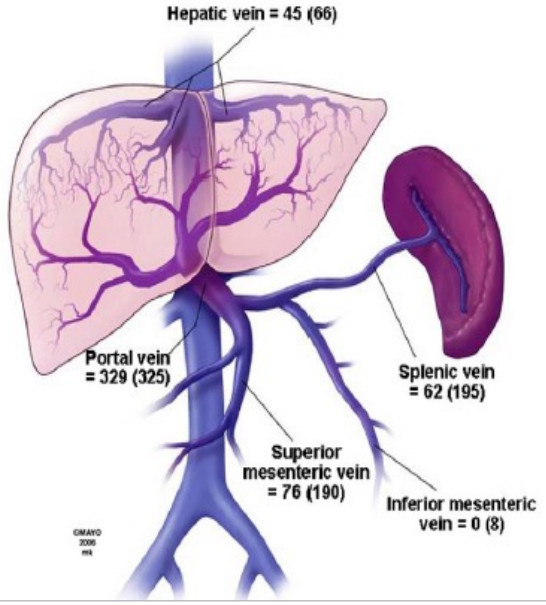
33 centres 613 pazienti

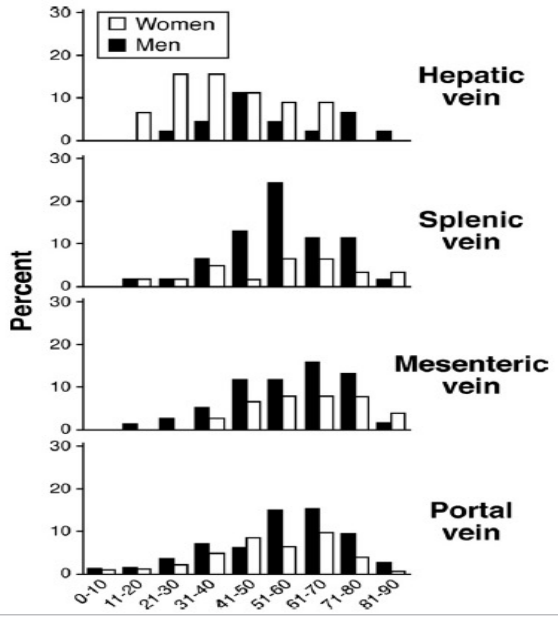
- **Isolated PVT** **246/613 (40.1%)**
- **Isolated MVT** **61/613 (10.0%)**
- **Isolated SpVT** **19/613 (3.1%)**
- **Budd Chiari** **49/613 (8.0%)**
- **Multiple sites** **238/613 (38.8%)**

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





Causes of splanchnic vein thrombosis in the largest published cohort from Mayo Clinic

Number	832
Idiopathic	15%
Cirrhosis	24%
Solid cancer (liver, pancreas)	27%
Infectious diseases	10%
Pancreatitis	13%
IBD	6%
Surgical (liver transplant, splenectomy)	10%
Myeloproliferative neoplasms	11%
Leukemias – lymphomas	5%
Oral contraceptives	6%
Autoimmune disorders	6%

Thatipelli et al Clin Gastroenterol Hepatol 2010

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:200–205

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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)

Efficacy and safety of VKA therapy after PVT in non-cirrhotics

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

GI bleeding	**12.5 (95% CI 10-15) 100 pt/y**
Independent predictors	
➢ Esophageal varices (RR 3.1)	
Recurrent thrombosis	**5.5 (95% CI 3.8-7.2) 100 pt/y**
Independent predictors	
➢ Prothrombotic state (RR 4.6)	
➢ No VKA (RR 3.3)	

Condat et al Gastroenterology 2001

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

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.

Research

Original Investigation

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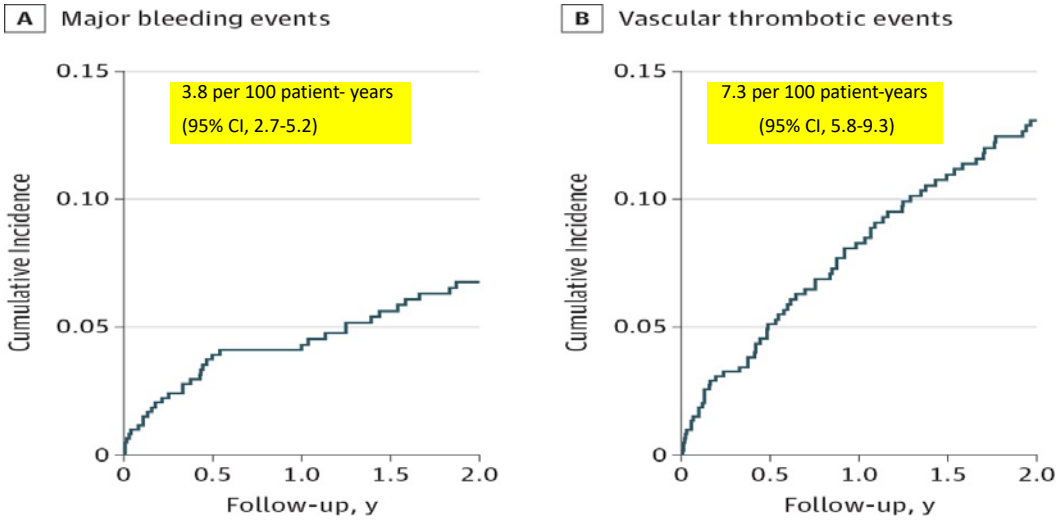

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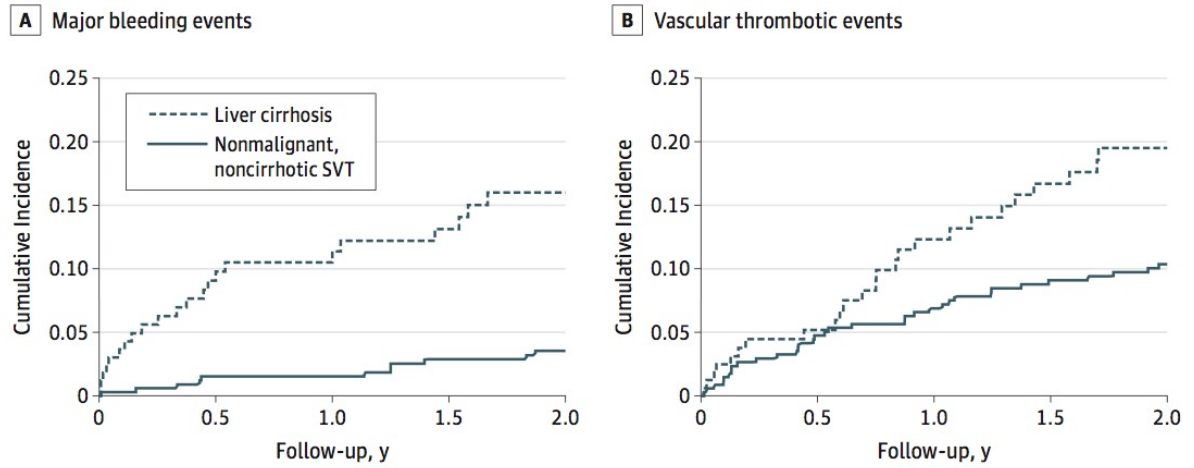


Clinical history of incidentally detected SVT in the ISTH registry

Number	177
Median follow-up	2 years
Major bleeding	3.3/100 pt-yrs (95% CI 1.7-6.3)
Thrombotic events	8.0/100 pt-yrs (95% CI 5.2-12.1)
Major bleeding on treatment	3.2/100 pt-yrs (95% CI 1.2-8.4)
Thrombosis off-treatment	11.9/100 pt-yrs (95% CI 5.0-28.7)

Riva et al Lancet Haemat 2016

Clinical history of incidentally detected SVT in the ISTH registry

	Liver cirrhosis (n:82)	Solid cancer (n:62)	Non-malignant non-cirrhotic SVT (n:57)
Major bleeding	6.1/100 pt-yrs (95% CI 2.9-12.8)	1.2/100 pt-yrs (95% CI 0.2-8.2)	1.8/100 pt-yrs (95% CI 0.5-7.4)
Thrombotic events	14.8/100 pt-yrs (95% CI 9.2-23.8)	8.1/100 pt-yrs (95% CI 3.9-17.0)	2.8/100 pt-yrs (95% CI 0.9-8.6)
Mortality	9.9/100 pt-yrs (95% CI 5.9-16.7)	21.7/100 pt-yrs (95% CI 14.0-33.6)	0 events

Riva et al Lancet Haemat 2016

ISTH International registry on SVT: therapeutic strategies

None	**22.0%**
UFH	**10.4%**
LMWH or fondaparinux	**66.4%**
VKA	**48.5%**
Surgery	**3.1%**
Thrombolysis	**1.5%**

Ageno et al STH 2014

Treated vs untreated patients

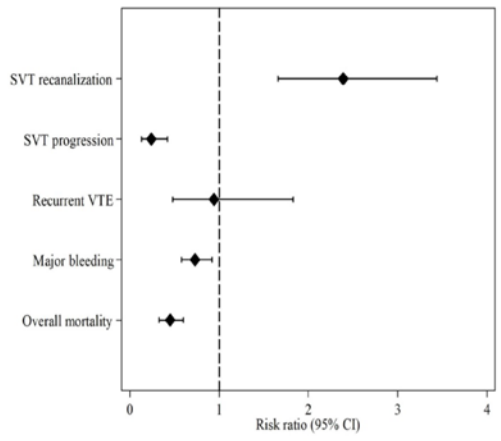
	No treatment	Treated	p
N	135	471	
Previous VTE (%)	3.8	13.5	0.003
Incidental (%) *	49.6	23.7	<0.0001
GI bleeding (%)	15	7.1	0.008
Single vein (%)	77.8	55.8	<0.0001
Cancer (%)	31.3	20.1	0.009
MPN (%)	1.5	10.0	0.003
Surgery (%)	1.5	11.1	0.001
Cirrhosis (%)	49.3	21.4	<0.0001
PLT (mean)	151.7	240.8	<0.0001

*110/176 patients with incidental VTE received treatment

Ageno et al STH 2014

Anticoagulant therapy for splanchnic vein thrombosis: A systematic review and meta-analysis

blood



Outcome	Anticoagulated: events (no./No., %)	Untreated: events (no./No., %)	Studies (n)	I^2 (%)	RR (95% CI)
SVT recanalization	381/667 (57.1)	158/710 (22.3)	25	74	2.39 (1.66-3.44)
SVT progression	16/454 (3.5)	55/383 (14.4)	20	0	0.24 (0.13-0.42)
Recurrent VTE	140/1350 (10.3)	55/498 (11.0)	18	75	0.91 (0.44-1.87)
Major bleeding	287/1927 (14.9)	154/967 (15.9)	28	0	0.73 (0.58-0.92)
Overall mortality	221/1789 (12.2)	204/913 (22.6)	39	28	0.45 (0.33-0.60)

Valeriani et al Blood 2021

CHEST Supplement
ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

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)

CHEST Supplement
ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

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.

Table 2. Studies evaluating the use of the direct oral snticoagulants in patients with splanchnic vein thrombosis.

Author (year)	Study Design	No. Patients	Demographics	Treatment	Treatment Duration	Safety and Efficacy Outcomes
Intagliata (2016) [98]	Retrospective	20 (but only 12 SVT)	Age (median): 57 years * Female/male 10:10 * All liver cirrhosis	Apixaban (2.5–5 mg BID), rivaroxaban (10–20 mg OD)	8.8 months (median) *	Major bleeding: *n* = 1 (5%) * Any bleeding: *n* = 4 (20%) *
		19 (but only 6 SVT)	Age (median): 60 years * Female/male 7:12 * All liver cirrhosis	LMWH and/or VKA (INR target range not reported)	15.7 months (median) *	Major bleeding: *n* = 2 (10.5%) * Any bleeding: *n* = 3 (15.8%) *
De Gottardi (2017) [97]	Retrospective	94 (but only 69 SVT)	Age (mean): 55.4 years * Female/male 44:50 * 62% liver cirrhosis *	Dabigatran (110–220 mg daily), apixaban (2.5–10 mg daily), rivaroxaban (5–20 mg daily)	10.5 months (median) in patients without cirrhosis * 7.0 months (median) in patients with cirrhosis *	Recurrent SVT: *n* = 1 (1.1%) * Major bleeding: *n* = 3 (3.2%) * Minor bleeding: *n* = 11 (11.7%) *
Janczak (2018) [103]	Prospective	36 (but only 25 SVT)	Age (mean): 53.6 years * Female/male 23:13 * No liver cirrhosis	Apixaban, rivaroxaban	10.8 months (mean) *	Recurrent VTE: *n* = 2 (5.6%) * Major bleeding: *n* = 2 (5.6%) * Clinically relevant non major bleeding: *n* = 1 (2.8%) *
		23 (but only 17 SVT)	Age (mean): 59.8 years * Female/male 6:17 * No liver cirrhosis	LMWH	10.8 months (mean) *	Recurrent VTE: *n* = 3 (13.0%) * Major bleeding: *n* = 3 (13.0%) * Clinically relevant non major bleeding: *n* = 2 (8.7%) *
Nagaoki (2018) [99]	Retrospective	20	Age (median): 69 years Female/male 7:13 All liver cirrhosis	Edoxaban (30–60 mg OD), preceded by danaparoid	6 months	Recanalization (partial or complete): *n* = 18 (90%) Significant gastrointestinal bleed: *n* = 3 (15%)
		30	Age (median): 67 years Female/male 13:17 All liver cirrhosis	Warfarin (INR target range 1.5–2.0), preceded by danaparoid	6 months	Recanalization (partial or complete): *n* = 9 (30%) Significant gastrointestinal bleed: *n* = 2 (6.7%)
Hanafy (2019) [104]	Randomized controlled trial	40	Age (mean): 46 years Female/male 8:32 All liver cirrhosis	[illegible]	Not reported	[illegible]lization (partial or complete): *n* = 40 (100%) Recurrent SVT: *n* = 0 (0%) Major bleeding: *n* = 0 (0%)
		40	Age (mean): 41.3 years Female/male 5:35 All liver cirrhosis	[illegible]	[illegible]	[illegible]analization (partial or complete): *n* = 18 (45%) Recurrent SVT: *n* = 4 (10%) Severe upper gastrointestinal bleed: *n* = 17 (42.5%)
Sharma (2019) [100]	Retrospective	36	Age (median): 29.5 years Female/male 17:19 All BCS patients following endovascular intervention	Dabigatran (150 mg BID), preceded by heparin and/or VKA	10.5 months (mean)	Restenosis: *n* = 4 (11.1%) Major bleeding: *n* = 1 (2.8%) Any bleeding: *n* = 6 (16.7%)
		62	Age (median): 28 years Female/male 24:38 All BCS patients following endovascular intervention	Acenocoumarol (INR target range 2–2.5), preceded by heparin	14.1 months (mean)	Restenosis: *n* = 4 (6.5%) Major bleeding: *n* = 3 (4.8%) Any bleeding: *n* = 7 (11.3%)
Salim (2019) [101]	Retrospective	22	Age (median): 57.5 years Female/male 7:15 All MVT patients	Apixaban, dabigatran, rivaroxaban	Not reported	Recanalization (partial or complete): *n*/*N* = 11/16 (68.8%) Major bleeding: *n* = 2 (9.1%) Recurrent SVT: *n* = 0 (0%)
		56	Age (median): 56 years Female/male 21:35 All MVT patients	VKA (INR target range not reported)	Not reported	Recanalization (partial or complete): *n*/*N* = 29/41 (70.7%) Major bleeding: *n* = 8 (14.3%) Recurrent SVT: *n* = 0 (0%)
		22	Age (median): 65 years Female/male 11:11 All MVT patients	LMWH	Not reported	Recanalization (partial or complete): *n*/*N* = 6/12 (50%) Major bleeding: *n* = 4 (18.2%) Recurrent SVT: *n* = 0 (0%)
Naymagon (2020) [102]	Retrospective	93	Age (mean): 47.1 years Female/male 46:47 No liver cirrhosis	Apixaban, dabigatran, rivaroxaban	> 3 months	Recanalization (complete): *n*/*N* = 61/93 (65.6%) Major bleeding: *n*/*N* = 2/93 (2.2%)
		108	Age (mean): 50.4 years Female/male 51:57 No liver cirrhosis	Warfarin (INR target range 2.0–3.0)	> 3 months	Recanalization (complete): *n*/*N* = 33/108 (30.6%) Major bleeding: *n*/*N* = 26/108 (24.1%)
		70	Age (mean): 51.4 years Female/male 43:27 No liver cirrhosis	LMWH (enoxaparin)	> 3 months	Recanalization (complete): *n*/*N* = 40/70 (57.1%) Major bleeding: *n*/*N* = 10/70 (14.3%)

DOAC?

Riva et al, J Clin Med 2020