14th DHC 2020
January 22-23-24
Papendal, Arnhem

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Dutch Hematology Congress

Unusual Site Venous Thromboembolism; Epidemiology and Treatment

Moderator
Dr. E.A.M. Beckers

Speaker
Dr. M.N. Lauw

Belangenverklaring

In overeenstemming met de regels van de Inspectie van de Gezondheidszorg (IGZ)

Naam: *Dr. M.N. Lauw*

Organisatie: *Erasmus MC, Rotterdam*

☑ Ik heb geen 'potentiële' belangenverstrengeling

☐ Ik heb de volgende mogelijke belangenverstrengelingen:

Type van verstrengeling / financieel belang	**Naam van commercieel bedrijf**
Ontvangst van subsidie(s)/research ondersteuning:	
Ontvangst van honoraria of adviseursfee:	
Lid van een commercieel gesponsord ‘speakersbureau’:	
Financiële belangen in een bedrijf (aandelen of opties):	
Andere ondersteuning (gelieve te specificeren):	
Wetenschappelijke adviesraad:	

Erasmus MC
University Medical Center Rotterdam

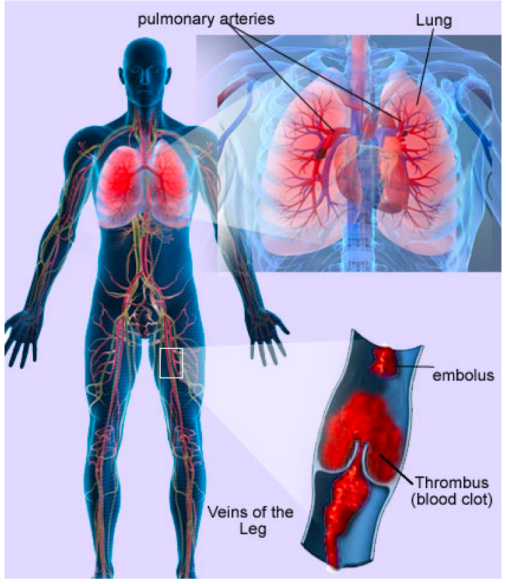
Unusual Site Venous Thromboembolism; Epidemiology and Treatment

Mandy N. Lauw, MD PhD
Dept. of Hematology
Erasmus MC, Rotterdam, The Netherlands

Venous thromboembolism (VTE)

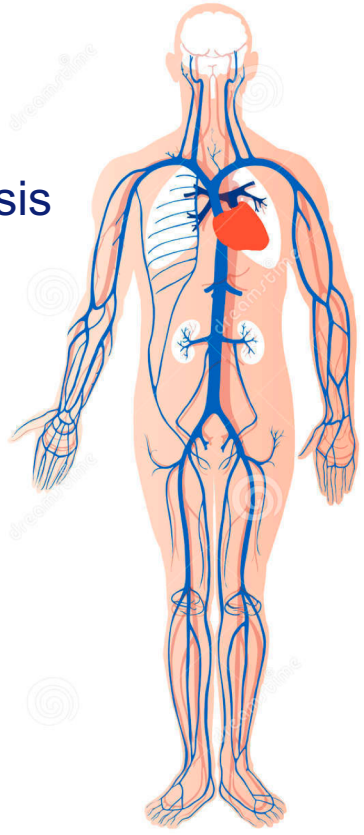
“Usual site”

- Deep vein thrombosis of the leg
- Pulmonary embolism

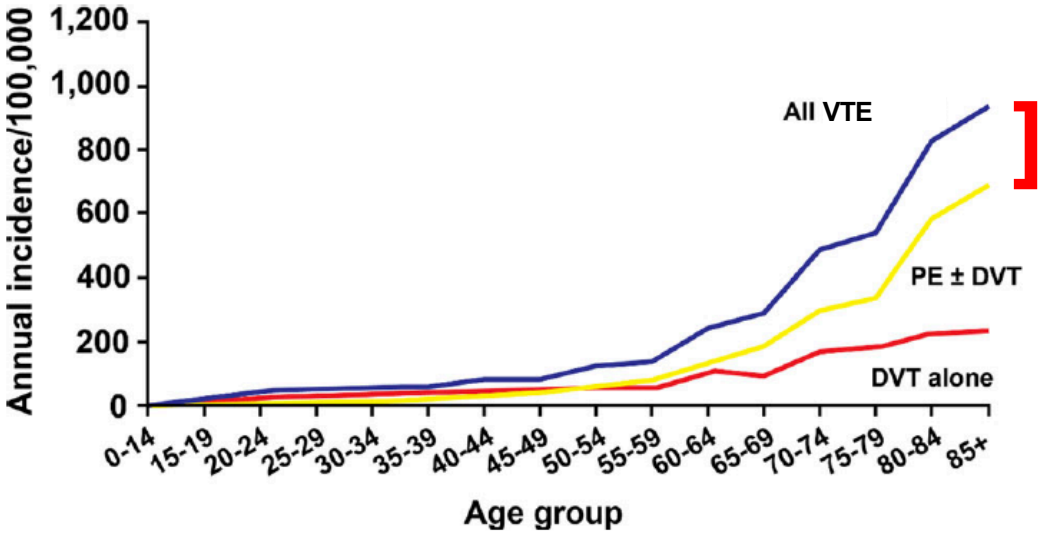


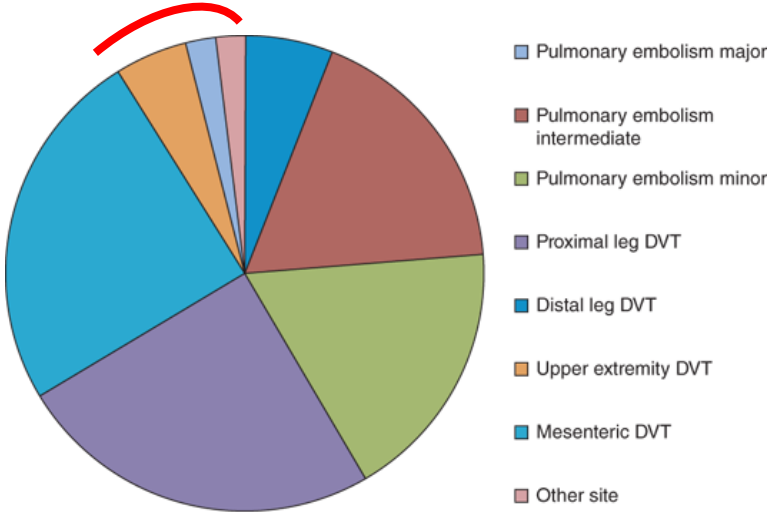
“Unusual site”

- Cerebral vein thrombosis
- Splanchnic vein thrombosis
- Arm vein thrombosis
- … vein thrombosis



Incidence of Unusual Site VTE





Heit et al. J Thromb Thrombolysis 2016

Unusual vs. Usual site VTE

- Less common
  - Fewer data
  - Fewer or no trials (diagnosis, management)
- More often provoked / secondary to other disease
- Heterogeneous in clinical presentation and management

Cerebral vein thrombosis
Splanchnic vein thrombosis

1. Epidemiology
2. Etiology and risk factors
3. Management
4. Conclusions and Future directions

Cerebral vein thrombosis (CVT)

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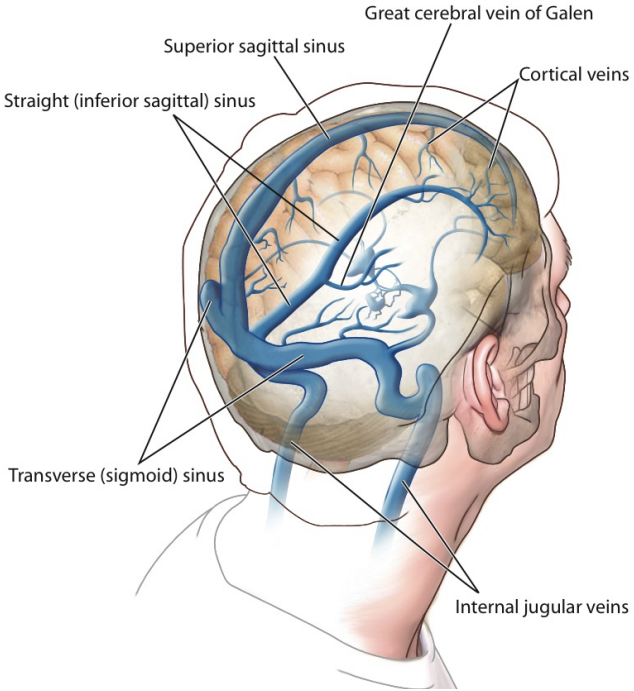
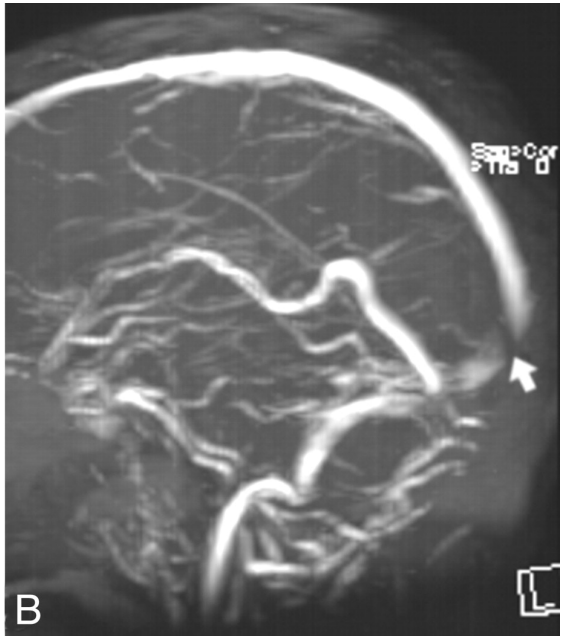
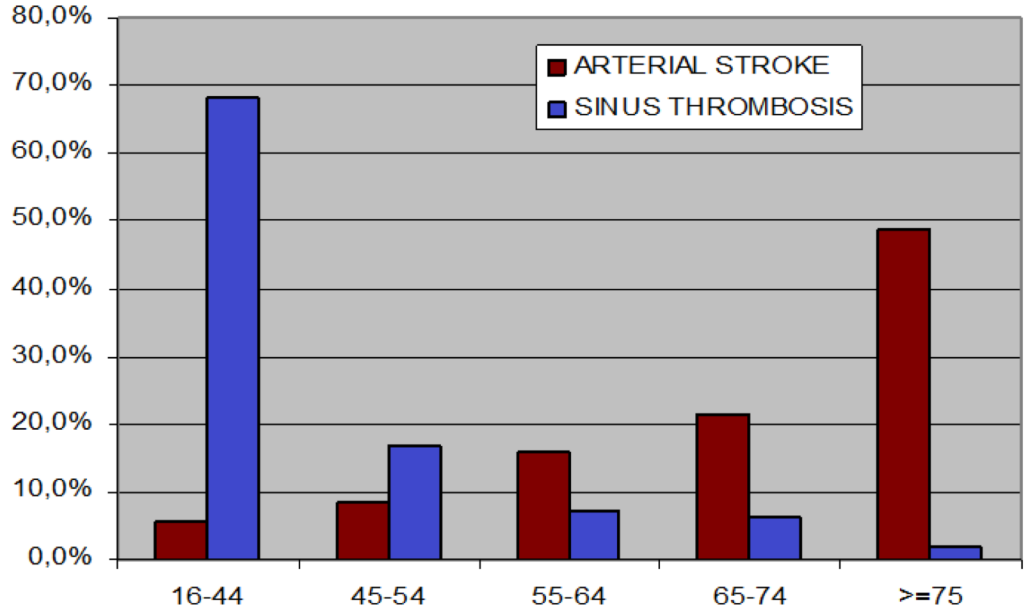
Cerebral sinus or sinovenous thrombosis





Epidemiology of CVT

- Annual incidence 1.3 / 100 000 individuals
- Specific age distribution
- Median age 37 years



Ferro et al. Stroke 2004
Dentali et al. J Thromb Haemost 2012
Devasagayam et al. Stroke 2016

Epidemiology of CVT

- 75% female
- Male : female ratio 1 : 3 during reproductive years
- Sex-distribution more equal in children and > 65 years group

Population	Incidence Year^{-1} 100 000^{-1}
Overall adult incidence	1.32 (1.06–1.61)
Subgroups	
Women	1.86 (1.44–2.36)
Men	0.75 (0.49–1.09)
Age 18–30 y	1.64 (1.05–2.44)
Age 31–50 y	1.71 (1.26–2.27)
Age ≥51 y	0.77 (0.48–1.16)
Women age 31–50 y	2.78 (1.98–3.82)
Men age 31–50 y	0.64 (0.29–1.21)

deVeber et al. NEJM 2001
Ferro et al. Stroke 2005
Coutinho et al. Stroke 2009
Coutinho et al. Stroke 2012

Etiology and risk factors of CVT

Vraag 1

Welk aanvullend onderzoek vraagt u aan bij een patiënt met een niet-uitgelokte, non-maligne sinustrombose?

A. Antifosfolipiden antistoffen
B. Trombofilie screening
C. MPN-screening (JAK2)
D. Alle bovenstaande
E. Geen

Etiology and risk factors of CVT

- 60-85% of CVT provoked or with underlying condition

- Risk factors partially overlap with ‘usual’ VTE risk factors
  - Sex-specific
  - Hereditary thrombophilia
  - Systemic disease (paroxysmal nocturnal hemoglobinuria)
  - Cancer (hematological)
  - Local infections
  - Lumbar punctures

Ferro et al. Stroke 2004
Dentali et al. J Thromb Haemost 2012
Ziakas et al. J Thromb Haemost 2007

Etiology and risk factors of CVT

Sex-specific risk factors for CVT

- Explanatory for higher risk in reproductive women

Risk factor	Prevalence[a]	Strength of association	Type of studies
Sex-specific risk factors			
Oral contraceptives	54 to 71%[b]	OR = 5.59	Case–control
Pregnancy and puerperium	11 to 59%b	NA	Cohort
Hormone replacement therapy	4%[b]	NA	Case reports

Silvis et al. Semin Thromb Hemost 2016

Etiology and risk factors of CVT

Thrombophilia and CVT

- Risks similar as in DVT or PE
- Limited impact on recurrence risk

Risk factor	Prevalence[a]	Strength of association	Type of studies
Hereditary thrombophilia	34 to 41%		
Factor V Leiden	9 to 13%	OR = 2.89	Case–control
Prothrombin G20210A mutation	9 to 21%	OR = 6.05	Case–control
Antithrombin deficiency	3%	OR = 3.75	Case–control
Protein S deficiency	2 to 3%	OR = 8.35	Case–control
Protein C deficiency	2 to 5%	OR = 6.45	Case–control

Lauw et al. Semin Thromb Hemost 2013

Etiology and risk factors of CVT

Systemic disease and CVT

- Limited number of cohort studies
- Association with hematological cancers, particularly ALL

Risk factor	Prevalence[a]	Strength of association	Type of studies
Systemic diseases			
Cancer	7%	NA	Cohort
Myeloproliferative neoplasms	2 to 3%	NA	Cohort
Inflammatory bowel disease	2 to 3%	NA	Cohort
Behçet disease	1%	NA	Cohort
Thyroid disease	2%	NA	Case reports
Systemic lupus erythematosus	1%	NA	Case series
Antiphospholipid antibodies	6 to 17%	NA	Cohort

Silvis et al. Semin Thromb Hemost 2016

Recurrence after CVT

- Recurrent VTE: 2.0-4.1 per 100 person-years
- Recurrent CVT: 0.5-1.5 per 100 person-years

- Recurrence after PE / DVT: 10.3 per 100 person-years

- Risk factors:
  - Male sex: HR 2.7 (95% CI 1.4-5.3)
  - Polycythemia / thrombocythemia: HR 4.9 (95% CI 1.7-14.0)

Miranda et al. Stroke 2010
Martinelli et al. Circulation 2010
Dentali et al. J Thromb Haemost 2012
Khan et al. BMJ 2019

Management of CVT

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Vraag 2

Welk type antistolling gebruikt u voor behandeling van een sinustrombose?

A. VKA
B. LMWH monotherapie
C. DOAC
D. Anders

Management of CVT

- **Acute phase**
  - Anticoagulation modality
  - Endovascular intervention
- **Long-term**
  - Duration
- CVT not included in all VTE guidelines

Management of CVT

Anticoagulation in acute phase

- Two guidelines: AHA/ASA 2011, ESO 2017

- LMWH preferred in ESO guideline (based on 1 RCT and 1 cohort study)
  - regardless of presence of intracerebral hemorrhage at baseline

Saposnik et al. AHA Guideline Stroke 2011
Ferro et al. ESO guideline 2017
Coutinho et al. Stroke 2010
Coutinho et al. Cochrane Database Syst Rev 2011
Afshari et al. Neurosciences 2015
Misra et al. Eur J Neurol 2012

Management of CVT

Endovascular intervention

- **TO-ACT trial**: Thrombolysis Or Anticoagulation for severe CVT
- Primary outcome: clinical outcome (mRS 0-1 after 12 months)

- RCT stopped after 1st interim analysis due to futility

Conclusion: no indication for endovascular intervention

Coutinho et al. Int J Stroke 2013
NCT 01204333

Management of CVT

Long-term anticoagulation

- VKA after initial LMWH
- Duration:
  - 3-6 months for transient risk factor
  - 6-12 months for unprovoked CVT (indefinite?)
  - Indefinite with severe thrombophilia, permanent risk factors or recurrent VTE

- **EXCOA-CVT:** multicenter cluster-RCT (N=1428)
  - short (3-6 mo) vs. long-term (12 mo) anticoagulation

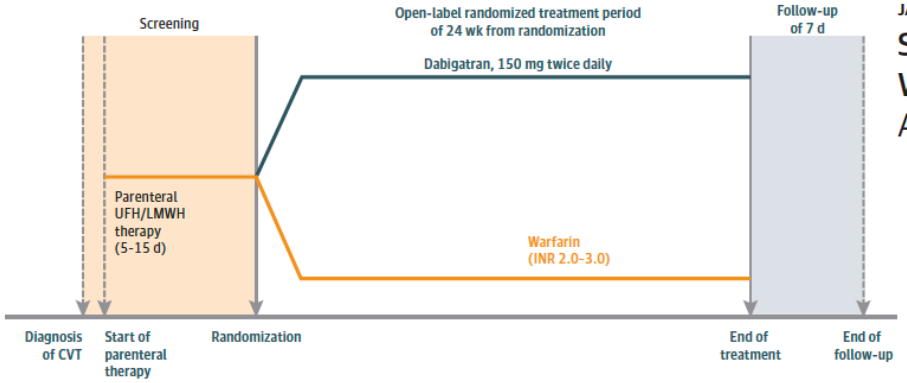
Saposnik et al. AHA Guideline Stroke 2011
Ferro et al. ESO guideline 2017
Miranda et al. Int J Stroke 2018

Management of CVT

2019: RE-SPECT CVT

- Dabigatran vs. warfarin (INR 2.0-3.0) after initial heparin
- N=120; no active malignancy, no CNS trauma or infection
- **RESULTS:** No recurrent VTE
- Major bleeding: dabigatran 1.7% vs. warfarin 3.3%

- **Conclusion:** dabigatran safe and effective (non-inferior) for CVT



JAMA Neurology | Original Investigation

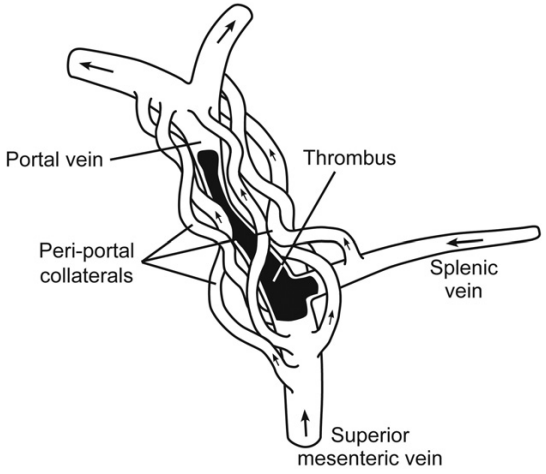
Safety and Efficacy of Dabigatran Etexilate vs Dose-Adjusted Warfarin in Patients With Cerebral Venous Thrombosis

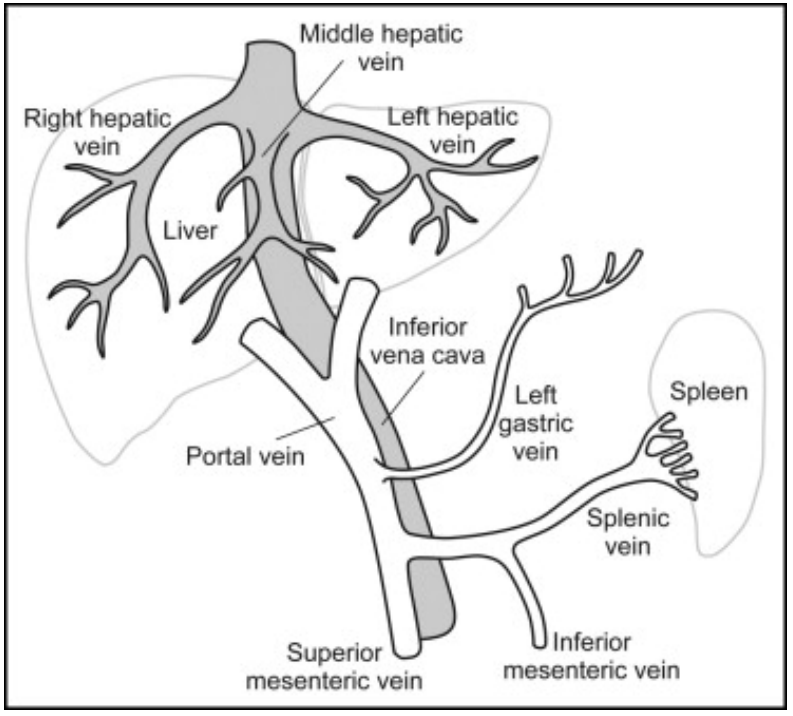
A Randomized Clinical Trial

Ferro et al. JAMA Neurol 2019

Splanchnic vein thrombosis (SVT)

- Portal vein
- Splenic vein
- Mesenteric veins
- Hepatic veins => Budd-Chiari syndrome





Epidemiology of SVT

- **Portal vein thrombosis (non-cirrhotic)**
  - Most common SVT
  - 3-5 / 1.000.000 / year
  - More frequent in males
- **Budd-Chiari syndrome (BCS)**
  - 1-2 / 1.000.000 / year
  - More frequent in females
- Only ~1% of all VTE

Riva & Ageno. Vascular Med 2017
Hernandez-Gea et al. J Hepatol 2019

Etiology and risk factors of SVT

Vraag 3

Welk aanvullend onderzoek vraagt u aan bij een patiënt met een non-maligne, non-cirrotische portatrombose?

A. Antifosfolipiden antistoffen
B. Trombofilie screening
C. MPN-screening (JAK2)
D. Alle bovenstaande
E. Geen

Etiology and risk factors of SVT

- >60% associated with underlying disease
  - ~50% liver cirrhosis and abdominal cancer (HPB, gastrointestinal)

- Specific risk factors for SVT
  - Local abdominal (infection, trauma, pregnancy)
  - Myeloproliferative neoplasms (MPN)
  - Paroxysmal nocturnal hemoglobinuria

Ziakas et al. J Thromb Haemost 2007
Ageno et al. Semin Thromb Hemost 2014
Riva & Ageno. Vascular Med 2017
Hernandez-Gea et al. J Hepatol 2019

Etiology and risk factors of SVT

Specific risk factors for non-cirrhotic SVT

Underlying condition	NCPVT n = 432		BCS n = 168	
	n tested	% positive	n tested	% positive
Acquired conditions				
Myeloproliferative neoplasms	432	21%	168	41%
JAK2^{V617F}	432	16%	168	35%
Antiphospholipid syndrome	429	6%	165	10%
PNH	386	0.3%	152	7%
External factors				
Recent pregnancy	353	2%	168	1%
Recent oral contraceptive use	353	14%	168	22%
Systemic disease*	432	3%	168	6%
Inflammatory intra-abdominal lesions**	432	11%	168	2%
Intra-abdominal surgery	432	10%	168	1%
Abdominal trauma	292	4%	168	2%
>1 risk factor	432	14%	168	19%

Murad et al. Ann Int Med 2009
Plessier et al. Hepatology 2009
Hernandez-Gea et al. J Hepatol 2019

MPN in SVT

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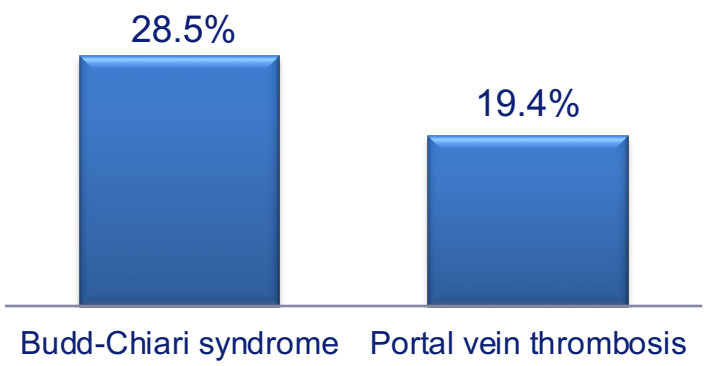
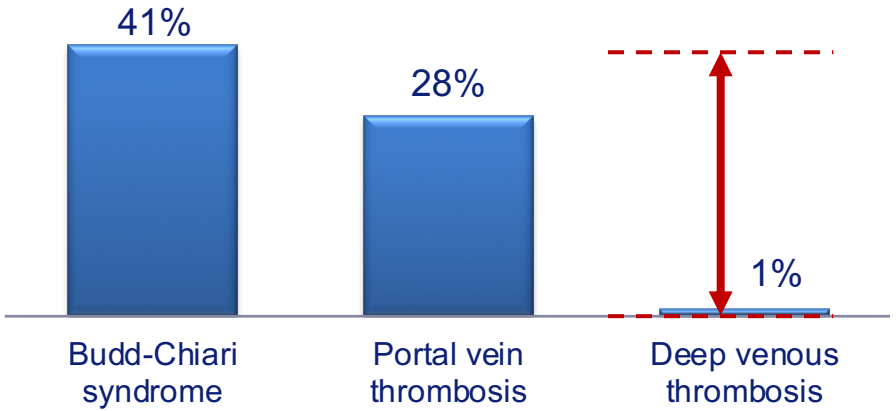
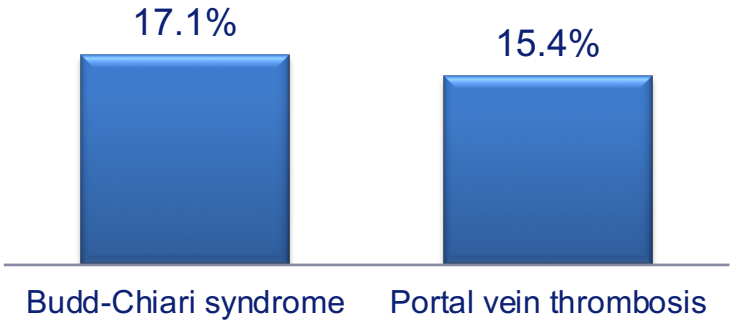
Classical MPN



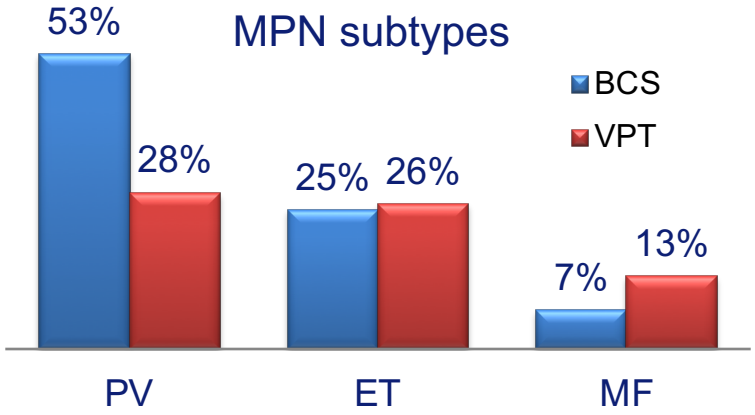
JAK2 mutation



Occult MPN



MPN subtypes



Smalberg et al. Blood 2012

Recurrence of VTE / SVT after SVT

- Recurrent VTE: 7.3 per 100 person-years
  - Without anticoagulation: 10.5 per 100 person-years
- Recurrent SVT: 1.6 per 100 person-years

- Recurrence after PE / DVT: 10.3 per 100 person-years

- Risk factors:
  - Liver cirrhosis
  - Non-transient risk factors

Ageno et al. JAMA Int Med 2015
Riva et al. Gastroenterol Res Pract 2015
Ageno et al. J Thromb Thrombolysis 2016
Tufano et al. Thromb Res 2018
Khan et al. BMJ 2019
Sant'Antonio et al. Am J Hematol 2020

Management of SVT

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Vraag 4

Welk type antistolling gebruikt u voor behandeling van een non-maligne portatrombose?

A. VKA
B. LMWH monotherapie
C. DOAC
D. Anders

Management of SVT

- **Acute phase management**
  - Anticoagulation modality
- **Long-term management**
  - Duration?
  - Secondary prevention in MPN
- No RCTs, observational studies only
- SVT not included in all VTE guidelines

Management of SVT

3 guidelines: ACCP 2012, AASLD 2009, Baveno VI consensus 2015

Anticoagulation in acute phase

- Symptomatic SVT: treat with anticoagulation
- Asymptomatic SVT less clear
  - Heterogeneous populations
  - GI bleeding and esophageal varices common problem
- Dependent on underlying condition

Ageno et al. Semin Thromb Hemost 2014
Riva & Ageno. Vascular Med 2017
DeLeve et al. Hepatology 2009
De Franchis et al. J Hepatol 2015
Kearon et al. Chest 2012

Management of SVT

Long-term anticoagulation

- VKA after initial LMWH
  - Except for malignancy, severe liver dysfunction or thrombocytopenia

- Optimal duration unknown
  - 3-6 months for transient risk factor
  - Indefinite if unprovoked, permanent risk factors or recurrence

Ageno et al. J Thromb Haemost 2017
Riva & Ageno. Vascular Med 2017
Hernandez-Gea et al. J Hepatol 2019

Management of SVT in MPN

Acute phase anticoagulation

- VKA after initial LMWH
- DOACs?

Long-term anticoagulation:

- Cytoreduction
- Combined with VKA or ASA (or DOACs)
  - Most effective combination unclear
  - Duration unclear
  - Need for OAC after normalization Ht / Plts?

Ageno et al. J Thromb Haemost 2017
Riva & Ageno. Vascular Med 2017
De Stefano et al. Blood Cancer J 2018
Hernandez-Gea et al. J Hepatol 2019
Hamulyak et al. DHC 2020

Management of SVT

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DOACs in SVT; 2 ongoing trials

- RIPORT; N=296
  - Rivaroxaban vs. no treatment for prevention of recurrent thrombosis in patients with chronic portal vein thrombosis

- RIVASVT-100; N=100
  - Prospective pilot cohort study investigating treatment of acute portal, mesenteric, and splenic vein thrombosis with rivaroxaban

Retrospective cohort studies and case series

RIPORT: NCT 02555111
RIVASVT-100: NCT 02627053
De Gottardi et al. Liver Int 2017
Hum et al. Eur J Haematol 2017
Janczak et al, Mayo Clin Proc 2018

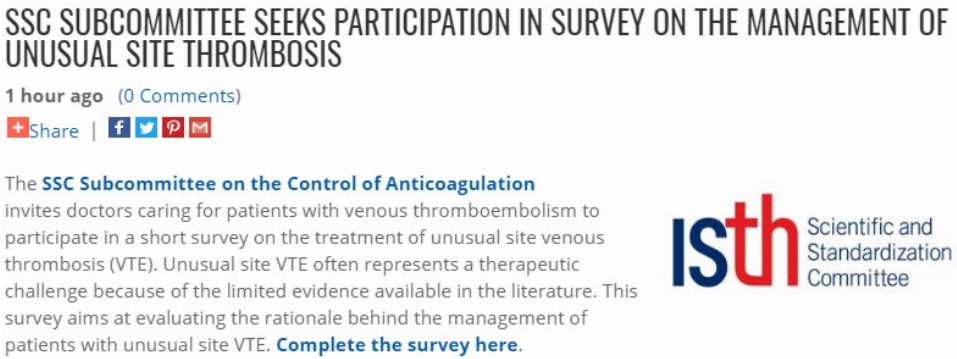
Conclusions / Take home messages

- Unusual site VTE: uncommon but not unimportant
- Often underlying disease ((hematological) malignancy, MPN)
- Less evidence on diagnosis and management

- Current guidelines for management:
  - Initial therapy: (LMW)heparin
  - Long-term therapy: VKA
  - Trials with DOACs ongoing or just published, seem safe

Future directions

- (Inter)national collaborations needed for unusual site VTE
  - Registries
  - Trials (diagnosis, management)
  - DOACs (efficacy, safety)
  - Recurrence, bleedingcombinations, duration



SSC SUBCOMMITTEE SEEKS PARTICIPATION IN SURVEY ON THE MANAGEMENT OF UNUSUAL SITE THROMBOSIS

1 hour ago (0 Comments)

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The **SSC Subcommittee on the Control of Anticoagulation** invites doctors caring for patients with venous thromboembolism to participate in a short survey on the treatment of unusual site venous thrombosis (VTE). Unusual site VTE often represents a therapeutic challenge because of the limited evidence available in the literature. This survey aims at evaluating the rationale behind the management of patients with unusual site VTE. **Complete the survey here**.

ISTH Scientific and Standardization Committee

Acknowledgements

- Saskia Middeldorp
- Suzanne Silvis
- Yvonne Zuurbier
- Jonathan Coutinho
- Jan Stam
- Stefano Barco
- Eva Hamulyak
- Frank Leebeek
- Sarwa Darwish Murad
- Jasper Smalberg
- Jildou Hoekstra
- Moniek de Maat
- Walter Ageno
- Nicoletta Riva

14th DHC 2020
January 22-23-24
Papendal, Arnhem

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