Erasmus MC
Universitair Medisch Centrum Rotterdam

Behandeling van veneuze trombose met bijzondere locatie

LMWH/VKA

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Debate Dutch Thrombosis Academy

Disclosure belangen spreker: Frank Leebeek

Erasmus MC

Dutch Thrombosis Academy – 30 juni 2022

(potentiële) Belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Ja
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk:	CSL Behring, uniQure, Sobi, Takeda Takeda, CSL Behring, Novo Nordisk, uniQure (naar ErasmusMC) Roche (DSMB) Nee Nee

prevents

Erasmus MC

4.1 Therapeutic indications

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients).

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Veneuze trombose: bijzondere locatie

- Diep Veneuze Trombose/ Longembolie wordt gezien als een zelfde aandoening (CBO 2008 / AR 2014)
  - DOAC voorkeur, langdurige behandeling

- Veneuze trombose op **atypische locatie** is een **andere** ziekte
  - Andere etiologie
  - Andere korte termijn morbiditeit en mortaliteit
  - Ander / Hoger risico op recidief
  - Ander / Hoger risico op bloedingen

Dit vraagt om een specifieke behandeling en wetenschappelijke onderbouwing van effectiviteit en veiligheid

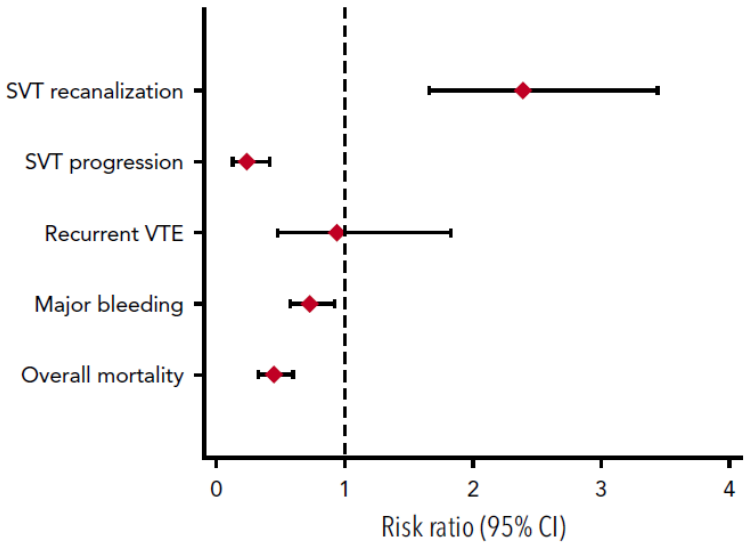
Antistollingsbehandeling Buikvene trombose

Geen gerandomiseerde studies

Meeste richtlijnen gebaseerd op expert opinies

- Case series, retrospectieve observaties

Antistolling voor buikvene trombose



Outcome	Anticoagulated: events (n/N, %)	Untreated: events (n/N, %)	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)

Figure 4. Radiological and clinical outcomes in treated vs untreated patients.

Valeriani E, et al Blood 2021

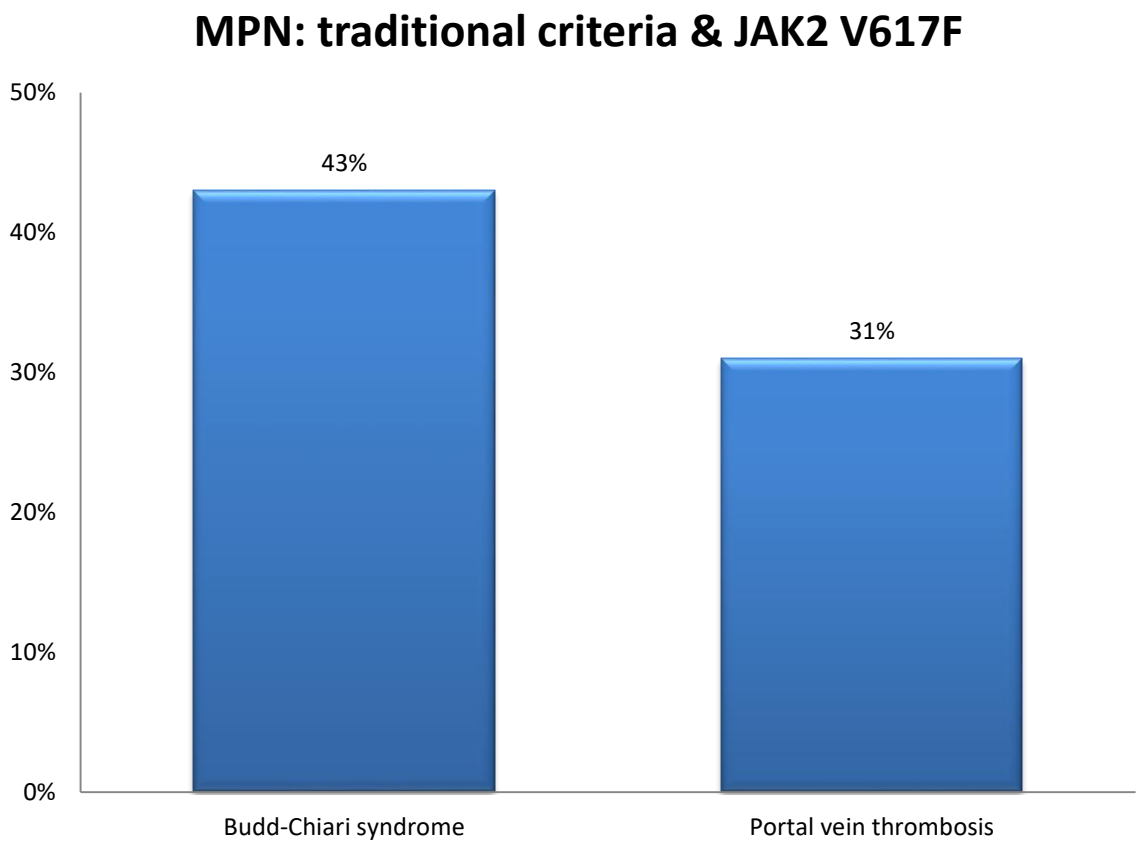
Onderliggende oorzaken buikvene trombose

- Cirrose
  - Leverfunctiestoornissen

- Niet-cirrotische oorzaken
  - Myeloproliferatieve Neoplasie (MPN)
  - Antifosfolipide antistoffen (APS)
  - Paroxysmale Nocturnale Hemoglobinurie (PNH)
  - Zwangerschap
  - Erfelijke trombofilie
  - Combinatie van factoren

Murad et al, Ann Int Med 2009; Plessier et al. Hepatology 2009

Frequentie MPN in buikvene trombose: meta-analyse



$P < 0.001$

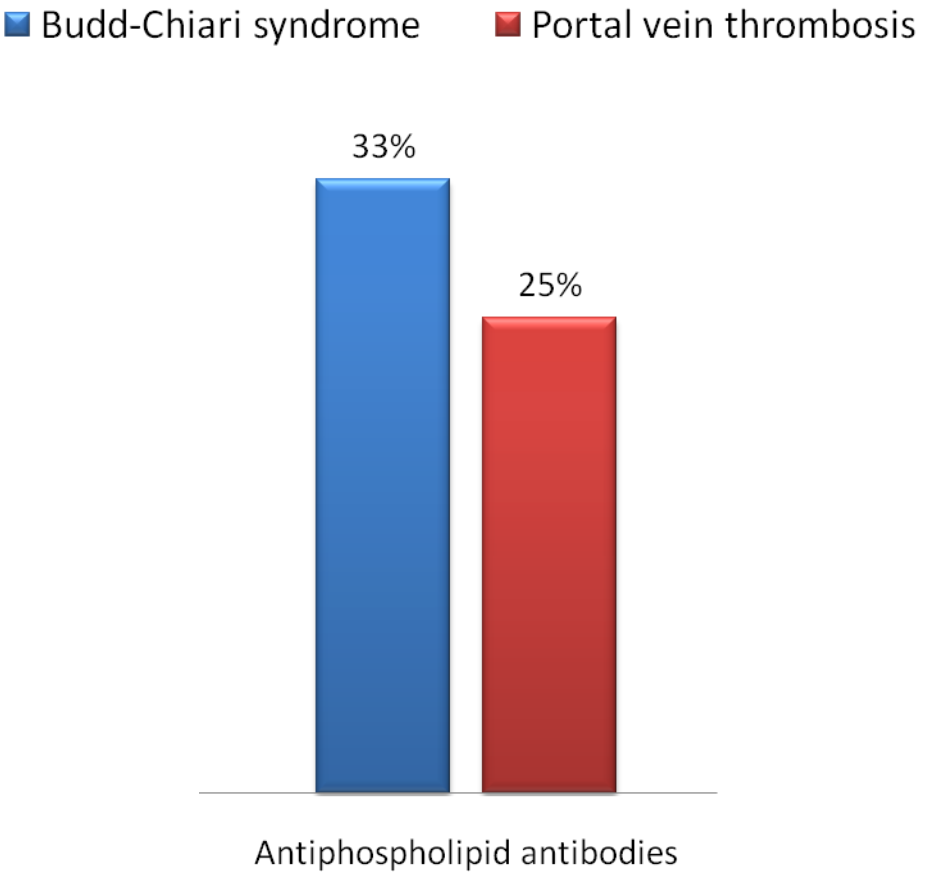
Smalberg, JH et al. Blood 2012

Meta-analyse: MPN –geassocieerde trombose

Recurrent thrombosis per type of oral anticoagulant			
VKA only	39/106	36.8	
VKA + cytoreduction	55/313	17.6	0.51 (0.23-1.14); 62.2%
DOAC only	3/14	21.4	
DOAC + cytoreduction	5/63	7.9	0.21 (0.08-0.60); 16.9%
VKA + antiplatelet therapy	4/11	36.4	
VKA + antiplatelet + cytoreduction	9/37	24.3	0.43 (0.16-1.15); 0%
DOAC + antiplatelet therapy	0/5	0%	—

Hamulyak E, et al. Blood Advances 2021

Antiphospholipide antistoffen bij buikvene trombose



Murad et al, Ann Int Med 2009; Plessier et al. Hepatology 2009

ISTH guideline voor APS-geassocieerde VTE

Budd-Chiari syndrome

Portal vein th

5 GUIDANCE STATEMENTS ON THE USE OF DOACs IN APS PATIENTS

The guidance below is based on expert consensus opinion following review of all available published evidence, to provide clinical guidance. All authors agreed on the following statements:

For patient management

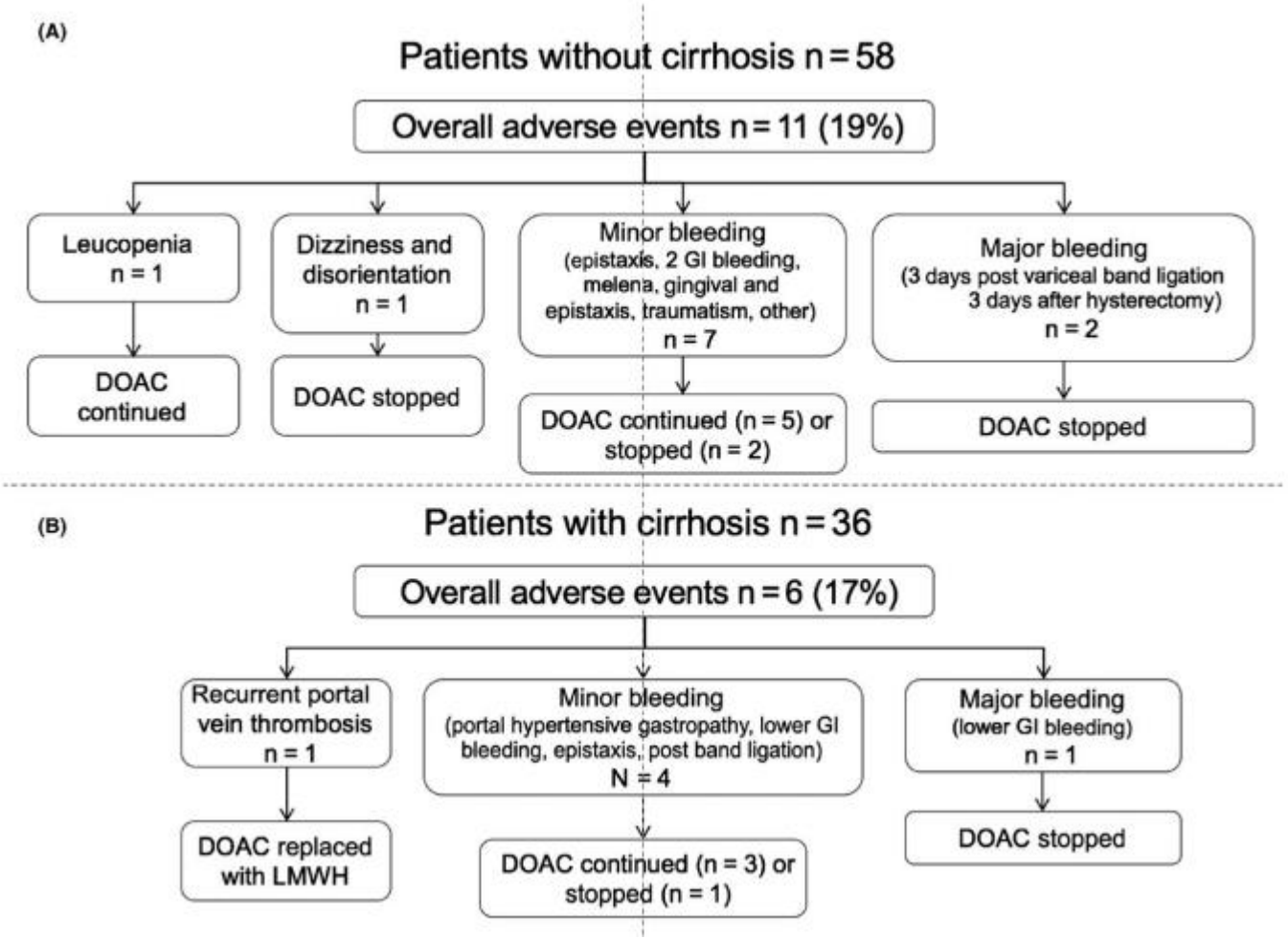
1. We recommend that for the treatment of thrombotic APS among patients with any of the following (termed "high-risk" APS patients):
   a. triple positivity,
   b. arterial thrombosis,
   c. small vessel thrombosis or organ involvement
   d. heart valve disease according to Sydney criteria[5]

VKA should be used instead of DOACs

Antiphospholipid antibodies

ZuillyS, et al. JTH 2021

Bewijs voor DOACs in buikvene trombose is beperkt



De Gottardi A, et al. Liver Int 2017

Behandeling buikvene trombose: meta-analyse prospectieve studies (individuele patient-data)

	Overall cohort Patient-years = 1975	Never treated Patient-years = 376	Treated, on treatment Patient-years = 1132	Treated, off treatment[a] Patient-years = 467
Recurrent venous thromboembolism	N events = 104	N events = 35	N events = 38	N events = 31
	5.3 (5.1, 5.5)	9.3 (8.4, 10.3)	3.4 (3.2, 3.6)	6.6 (6.0, 7.2)
Major bleeding	N events = 86	N events = 24	N events = 35	N events = 27
	4.4 (4.2, 4.6)	6.4 (5.8, 7.1)	3.1 (2.9, 3.3)	5.8 (5.3, 6.4)
All-cause mortality	N events = 136	N events = 82	N events = 65	N events = 109
	13.0 (12.4, 13.6)	21.8 (19.7, 24.1)	5.7 (5.4, 6.0)	23.3 (21.3, 25.3)

Candeloro M, et al. Blood Adv 2022

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Anticoagulant therapy, n (%)	
None	325 (19.8)
LMWH[d] alone	521 (31.9)
VKAs[e] alone	416 (25.4)
DOACs[f] alone	27 (1.7)

Candeloro M, et al. Blood Adv 2022

Cerebrale trombose VKA of DOAC?

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BJHaem

ORIGINAL PAPER

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Open access Original research

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Study or Subgroup	DOAC Events	DOAC Total	Standard Therapy Events	Standard Therapy Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
1.1.1 Randomized Controlled Trial								
Ferro 2019	0	60	0	60		Not estimable	2019	
Subtotal (95% CI)		**60**		**60**		**Not estimable**		
Total events	0		0					

Ferro, et al JAMA Neurol 2019

Cerebrale vene trombose

- Onderliggende factoren
  - APS
  - Hormonale therapie/zwangerschap
  - ALL

- Open vragen
  - Wanneer starten; direct of na LMWH
  - Duur van de behandeling 6 maanden of langer?
  - Alleen dabigatran of ook Factor Xa remmers ?
  - Minder bloedingen met DOAC?

Noodzaak voor additionele RCTs (VKA vs DOAC)

Conclusie

- Er is geen bewijs dat DOACs effectief en veilig zijn bij trombose op bijzondere locaties (Buikvene / Cerebrale trombose)
- LMWH/VKA zijn vooralsnog de therapie van keuze
- Gebruik DOAC voor de geregistreerde indicaties