VŠEOBECNÁ FAKULTNÍ NEMOCNICE V PRAZE

1. LÉKAŘSKÁ FAKULTA
Univerzita Karlova

Antikoagulační medikace po žilní trombóze / PE

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KOMPLEXNÍ KARDIO VASKULÁRNÍ CENTRUM
VFN Praha

Cíle léčby trombembolické nemoci

včasnou diagnostikou, promptním zahájením adekvátní léčby a správnou délkou antikoagulační medikace bráníme:

- v akutní fázi fatálním komplikacím,
- maximální rekanalizací dlouhodobým následkům – PTS, CTEPH,
- recidivě trombembolické příhody
- optim. bez navození nežádoucích účinků léčby – bez velkého krvácení

FÁZE LÉČBY ŽILNÍ TROMBEMBOLIE

- **INICIÁLNÍ** (7-21 DNŮ)
- **ZÁKLADNÍ** (3-6 MĚSÍCŮ)
- **EXTENDOVANÁ** (> 6 MĚSÍCŮ)

Klasifikace VTE (**V**enous **T**hrombembolic **E**vent)
– základní vodítko pro akutní léčbu a délku následné medikace

vyvolávající faktor	provokovaná (sekundární), **neprovokovaná** (idiopatická)
klinická forma různé závažnosti	**PE high – intermediate -** low risk **DVT – „masívní“ (flegmázie)** asymptomatické formy
lokalizace	**proximální** – distální **atypické** povrchová trombóza
počet příhod	první / **recidiva**
následky	**CTEPH /** PTS

dilema 1:

ENDOVASKULÁRNÍ INTERVENCE

TROMBOLÝZA? MECHANICKÁ TROMBEKTOMIE? KOMBINACE?

Kontraindikace podání trombolytika

ABSOLUTNÍ

- **aktivní krvácení nebo DIC**
- **neurovaskulární příhoda (<3 měs.)**
- **mozkový tumor**

RELATIVNÍ

- **velká „událost“ v posl. 7-10 d. (operace, porod, trauma, ..)**
- **neurologické postižení**
- **nekontrolovaná hypertense >180/ >110**
- **velké GI krvácení v posl. 3 měs.**
- **alergie na kontrastní látku, trombolytikum**
- **těžká trombocytopenie**
- **pravo-levý nebo plicní zkrat, trombus levé komory**
- **těžká renální a hepatální dysfunkce**
- **těhotenství a laktace**
- **infekční endokarditis**
- **diabetická hemoragická retinopatie**

Trombolytická a antikoagulační medikace při CDTL:

- bolus tPA: 7.5 - 10 mg
- altepláza kontin.: 0.5–1.0 mg/h
  + heparin: 300–500 IU/h s APTT < 1,5
- PTA / stenting
- LMWH
- DOAC, ev. warfarin

Techniky katétrem vedené trombektomie/trombolýzy

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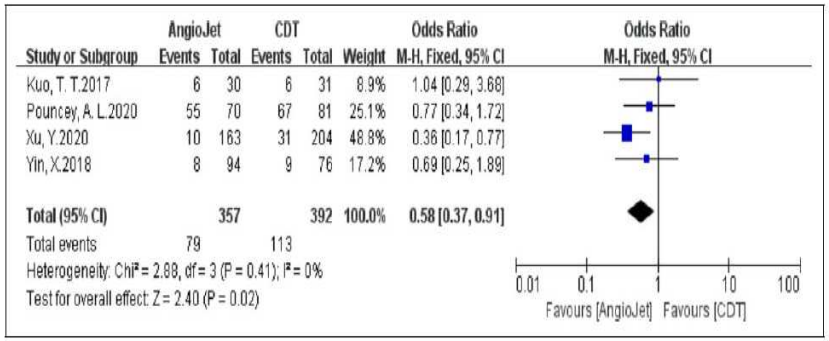
AngioJet Thrombectomy Versus Catheter-Directed Thrombolysis for Lower Extremity Deep Vein Thrombosis: A Meta-Analysis of Clinical Trials

Guan Qiang Li, MD[1,2], Lei Wang, MD[2], and Xi Cheng Zhang, MD[2,3]

Abstract

Early catheter-directed thrombolysis (CDT) for lower extremity deep vein thrombosis (LEDVT) can reduce post-thrombotic morbidity and the AngioJet thrombectomy is a new therapy that can be selected for the treatment of LEDVT. We performed a systematic review and meta-analysis of clinical trials comparing AngioJet versus CDT to assess the efficacy and safety of AngioJet thrombectomy. We systematically searched PubMed and Embase for clinical trials that published before November 1, 2020 and compared AngioJet thrombectomy and CDT in the treatment of LEDVT. We meta-analyzed effective rate of treatment, serious complications, PTS, Villalta score, duration of treatment and drug dose. AngioJet does not result in a significant difference in the effective rate (OR 1.00, CI 0.73-1.36, $P = 0.98$; $I^2 = 0\%$) and complications (OR 1.16 CI 0.84-1.61, $P = 0.36$; $I^2 = 39\%$) compare to CDT. And there was a statistically significant decrease in incidence of PTS (OR 0.58 CI 0.37-0.91, $P = 0.02$; $I^2 = 0\%$) and Villalta score (OR −1.86 CI −3.49 to −0.24, $P = 0.02$; $I^2 = 34\%$) for AngioJet compared to CDT. In addition, there was a statistically significant decrease in duration of the treatment (OR −2.45 CI −2.75 to −2.15, $P < 0.0001$; $I^2 = 95\%$) and drug dose (OR −3.15 CI −3.38 to −2.93, $P < 0.0001$; $I^2 = 98\%$) between AngioJet and CDT. AngioJet results in a low severity of PTS compared to CDT therapy. Moreover, the average duration of treatment and thrombolysis time was shorter in the AngioJet group compared to the CDT group. However, the AngioJet group was not significantly different in effective rate of treatment and serious complications compared to the CDT group.



CDTL - **catheter directed thrombolysis -** nižší dávka trombolytika, menší systémový účinek, lepší disoluce trombu

- **AngioJet -** metoda reolytické trombektomie – fragmentace trombu a rychlé odsátí

➢ v dané meta-analýze kratší doba léčby oproti běžné CDT, nižší dávka TL a nižší procento výskytu PTS

➢ nebyly rozdíly v účinnosti a míře komplikací

Arrow-Trerotola PTD (Arrow), AngioJet (Boston Scientific), Hydrolyser (Cordis), EKOS (Ekos Corporation)...

Farmakologická a reperfúzní strategie VTE

	Systemic thrombolysis for acute PE (approved regimens)	
	Dose regimen	**Practical issues or device used for reperfusion**
Thrombolytic agent		
Recombinant tissue-type plasminogen activator	100 mg over 2 hours or 0.6 mg/kg over 15 minutes (maximum dose, 50 mg)	Absolute contraindications: History of hemorrhagic stroke, stroke at ≤6 months, central nervous system tumor, major trauma, surgery, or head injury at ≤3 weeks, bleeding diathesis, active bleeding Relative contraindications: Transient ischemic attack at ≤6 months, oral anticoagulation, pregnancy or first postpartum week, non-compressible puncture sites, traumatic resuscitation, refractory hypertension (systolic blood pressure >180 mmHg), advanced liver disease, infective endocarditis, active peptic ulcer
Streptokinase	250 000 IU loading dose over 30 minutes, followed by 100 000 IU/h over 12 to 24 hours; accelerated regimen: 1.5 million IU over 2 hours	
Urokinase	4400 IU/kg loading dose over 10 minutes followed by 4400 IU/kg per hour over 12 to 24 hours; accelerated regimen: 3 million IU over 2 hours	
Catheter interventions		
With thrombolysis for acute PE		
Catheter-directed thrombolysis	Alteplase 25 mg	UniFuse, Cragg-McNamara
Ultrasound-assisted catheter-directed thrombolysis	Alteplase 24 mg (1 mg/h for 24 hours if unilateral; 1 mg/h via catheter for 12 hours if bilateral)	EkoSonic 5.2F 12-cm treatment zone device
Rheolytic thrombectomy plus catheter-directed thrombolysis	4 to 12 mg alteplase per lung and infusion duration from 2 to 6 hours	AngioJet thrombectomy with Power Pulse thrombolysis
Combined techniques	Urokinase 250 000 to 500 000 U or alteplase 25 mg	Pigtail fragmentation plus AngioJet thrombectomy
Without thrombolysis for acute PE		
Aspiration thrombectomy (suction pump or manual)	Start UFH bolus and delay continuous infusion until the completion of the procedure (additional unfractionated heparin boluses to be given during the procedure at the physician's discretion)	Angiovac suction cannula: Indigo Mechanical Sheath with detachable hemostatic valve, multipurpose guide catheter, aspiration syringe.
Mechanical thrombectomy		Flowtriever, AngioJet catheter, Pigtail catheter
Rheolytic thrombectomy		
Thrombus fragmentation combined techniques		
With thrombolysis for acute DVT		
Catheter-directed thrombolysis	Alteplase 0.5-1.0 mg/h or 0.01 mg/kg per hour	AngioJet device
Ultrasound-assisted catheter-directed thrombolysis	Concomitant intravenous infusion of unfractionated heparin at subtherapeutic levels	EkoSonic treatment zone device
Isolated thrombolysis power pulse technique	Need for vena cava filter insertion debated	Trellis Peripheral Infusion System, Angiojet Rheolytic Thrombectomy Catheter

Becattini C, Agnelli G.Blood. 2020 Jan 30;135(5):305-316. doi: 10.1182/blood.2019001881.

Akutní žilní trombóza – co zvažujeme?

TYP PACIENTA

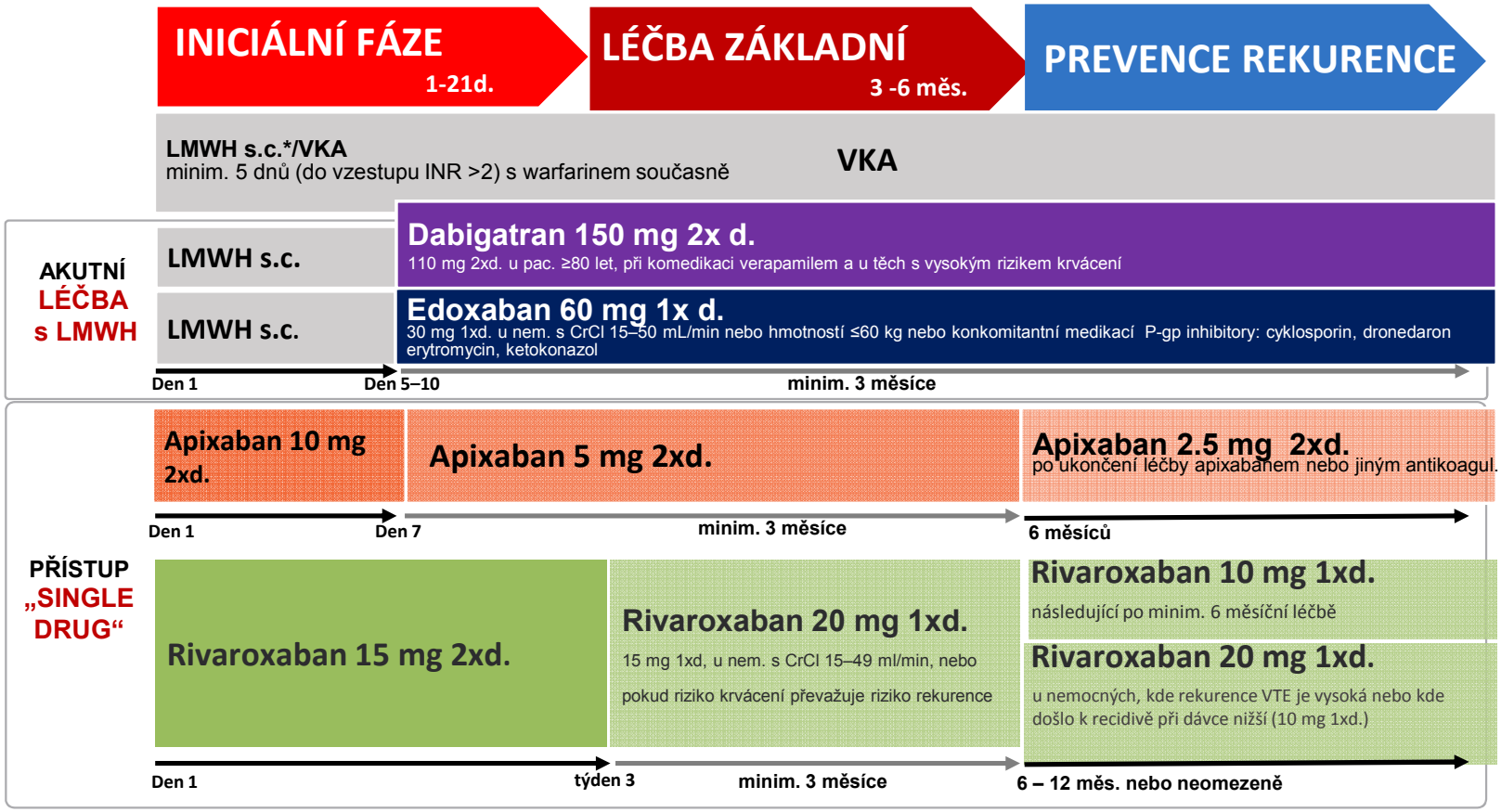
- ✓senioři (polyfarmakoterapie)
- ✓těhotné
- ✓nem. s aktivním nádorem
- ✓renální selhání
- ✓velmi rizikoví pro krvácení

ROZSAH TROMBOT. PŘÍHODY

- ✓stabilita / instabilita (PE)
- ✓flegmázie
- ✓ostatní formy: femoro-popliteální, subklaviální
- ✓ atypické
- ✓izolovaná distální trombóza
- ✓subsegmentální PE – sympt./asympt.

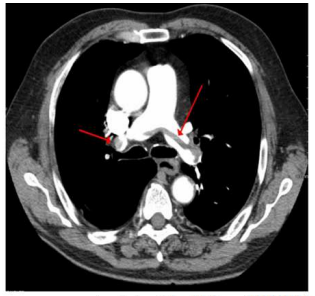
dilema 2:
JAKÝ ORÁLNÍ ANTIKOAGULAČNÍ PŘÍPRAVEK

DOAC – strategie moderní léčby



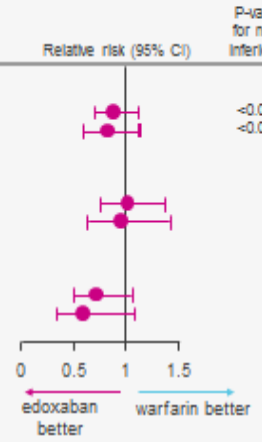
Apixaban SmPC; 2. Rivaroxaban SmPC; 3. Dabigatran SmPC; 4. Edoxaban SmPC. www.ema.europa.eu.

Edoxaban – HOKUSAI VTE



Primary efficacy outcome in pre-specified subgroups according to presenting diagnosis

Outcome	Edoxaban (N=4,118)	Warfarin (N=4,122)	P-value for non-inferiority
All patients, n (%)			
Overall study period	130 (3.2)	146 (3.5)	<0.001
On-treatment period	66 (1.6)	80 (1.9)	<0.001
Patients with Index DVT, n (%)	2,468 (59.9)	2,453 (59.5)	
Overall study period	83 (3.4)	81 (3.3)	
On-treatment period	48 (1.9)	50 (2.0)	
Patients with Index PE, n (%)	1,650 (40.1)	1,669 (40.5)	
Overall study period	47 (2.8)	65 (3.9)	
On-treatment period	18 (1.1)	30 (1.8)	



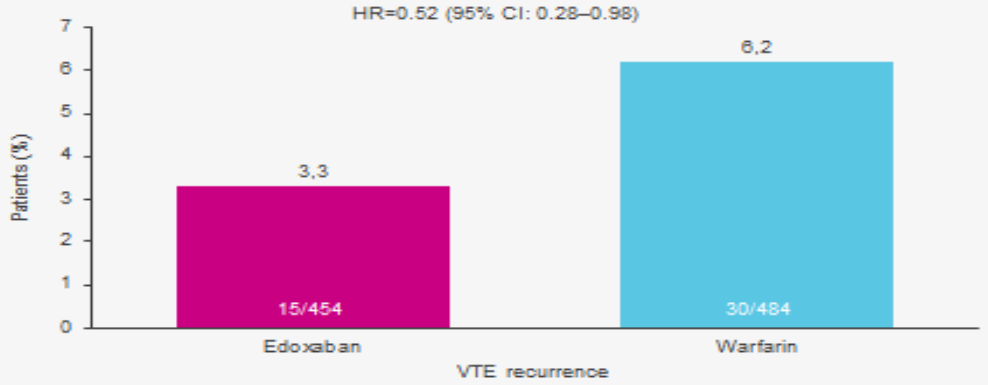
Principal safety outcomes

HokusaiVTE

Outcome	Edoxaban (N=4,118)	Warfarin (N=4,122)	Relative risk (95% CI)
First major or clinically relevant non-major bleeding, %	8.5	10.3	0.81 (0.71–0.94)*
Major bleeding, %	1.4	1.6	
Fatal	<0.1	0.2	0.84
Non-fatal in critical sites	0.3	0.6	(0.59–1.21)*
Non-fatal in non-critical sites	1.0	0.8	
Clinically relevant non-major bleeding, %	7.2	8.9	0.80 (0.68–0.93)*
Any bleeding, %	21.7	25.6	0.82 (0.75–0.90)*

Subgroup analysis in PE patients with NT-proBNP ≥500 pg/mL

HokusaiVTE



- HOKUSAI-VTE: největší studie s DOAC v léčbě VTE
- široké spektrum pacientů (8 292), včetně „submasívní“ PE
- testovány 2 dávky edoxabanu: 60 mg a 30 mg
  (CrCl 30-50 ml/min., hmotn.≤60 kg nebo komedikace P-Gp inh.)
- flexibilní doba medikace: 3-12 m., vyhodn. ve 12 měs.

Raskob et al. J Thromb Haemost 2013;11:1287–1294
The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406–1415

Individualizace léčby VTE

- **DVT: mladší, bez rizika krvácení, flegmázie – katétrem řízená farmakomechanická trombolýza → LMWH → DOAC**
- **PE s hospit.: celk. TL nebo LMWH** → dabigatran (Pradaxa) nebo edoxaban (Lixiana) …. po LMWH lze převést i na jiný xaban

- **ambulantní** nem.: preference - **xabany** (= Eliquis, Xarelto)
- pokročilá **renální insuf.: xabany** > dabigatran (vždy redukce dávek)
- vyšší **riziko krvácení**, zejm. do GIT: **apixaban** (Eliquis)
- medikace v režimu **1x denně: rivaroxaban** (Xarelto) nebo **edoxaban** (Lixiana)
- **starý, fragilní nemocný:** volba nižších dávek po 6 měs. (apixaban, rivaroxaban)
- **onkologický pacient: LMWH;** solidní tumory (cave GIT, urogenit…) – **DOAC / apixaban, edoxaban nebo rivaroxaben**
- **renální selhání: warfarin**
- **těhotné: LMWH, kojící: LMWH / warfarin**
- **antifosfolipidový syndrom: LMWH nebo warfarin**

V indikaci VTE a nutnosti přechodného vysazení antikoagulancia - **nepřemosťovat pomocí LMWH !**

Individualizace léčby

Clinical setting	Patients subgroups	Limitations	Recommended strategies
Renal function	Stage I-II KDOQI (GFR ≥60) Stage III KDOQI (GFR 59-30) Stage IV KDOQI (GFR 29-15) Dialysis	None Dose reduction not tested in VTE Avoid DOACs Avoid DOACs & LMWH	DOACs DOACs VKAs or halved-dose LMWH VKAs
Elderly	Over 75 years	Very limited data available Comorbidities & concomitant therapies Consider bleeding risk	DOACs Adapt accordingly Consider to avoid thrombolysis
Polypharmacotherapy	Strong inhibitors/competitors Strong inducers/competitors Moderate inhibitors/inducers Dual antiplatelet	Potential DOACs overdosing Potential DOACs underdosing Consider potential interactions Consider to stop ≥1 antiplatelet	Consider to avoid DOACs Consider to avoid DOACs Consider DOACs at standard dose Consider DOACs (with ASA)
Pregnancy & breast-feeding	Pregnancy I trimester Pregnancy II-III trimesters Breast-feeding	Avoid DOACs & VKAs Avoid DOACs Avoid DOACs & VKAs	LMWH LMWH LMWH
Cancer	Oral route not feasible Gastrointestinal cancer On chemotherapy	Avoid DOACs Avoid DOACs Assess for DOACs interactions	LMWH LMWH (DOACs second choice) Edoxaban/rivaroxaban or LMWH
Isolated Distal DVT	Asymptomatic DVT Cancer or previous VTE All symptomatic distal DVT	Limited data available Treat as proximal Limited observational data with DOACs	Consider US surveillance LMWH or VKAs (or DOACs) LMWH or VKAs (or DOACs)
Isolated Subsegmental PE	Asymptomatic incidental PE Concomitant cancer Symptomatic PE	Limited data available Treat as PE Treat as PE	Consider clinical surveillance or DOACs Edoxaban/rivaroxaban or LMWH DOACs
Vena cava filter	Absolute contraindications for anticoagulant treatment	Limited data available with DOACs	Start anticoagulant treatment as soon as possible

Becattini C, Agnelli G. Blood. 2020 Jan 30;135(5):305-316. doi: 10.1182/blood.2019001881.

dilema 3:
JAK DLOUHO LÉČIT

Nestrašíme se vysokým rizikem rekurence VTE?

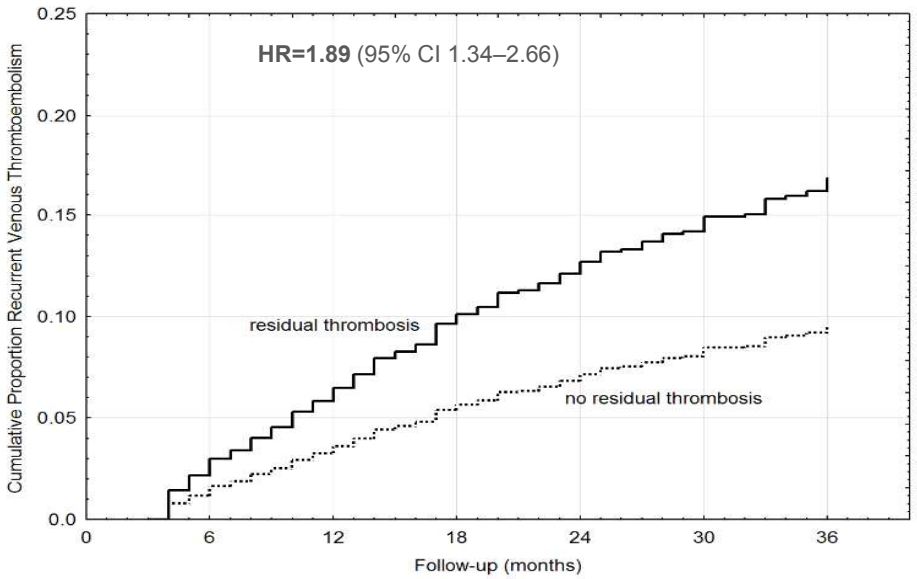
Variable	Studie s VKA vs placebo: Incidence[a] (Per 100 Patient Years [95% CI]) VKA	Studie s VKA vs placebo: Incidence[a] (Per 100 Patient Years [95% CI]) Placebo	Studie s VKA vs placebo: NNT/NNH (Patient Years [95% CI])[a]	Studie s DOAC vs placebo: Incidence[a] (Per 100 Patient Years [95% CI]) DOAC	Studie s DOAC vs placebo: Incidence[a] (Per 100 Patient Years [95% CI]) Placebo	Studie s DOAC vs placebo: NNT/NNH (Patient Years [95% CI])[a]
All-cause mortality	1.42 (0.43-4.68)	1.88 (0.74-4.74)	NA	0.52 (0.34-0.79)	0.84 (0.41-1.70)	≈196 (112-833)
VTE-related mortality	1.63 (0.73-3.65)	0.78 (0.22-2.11)	NA	0.20 (0.09-0.42)	0.46 (0.21-1.03)	≈278 (164-833)
Cardiovascular mortality	1.55 (0.52-4.55)	1.74 (0.56-5.45)	NA	0	0	NA
VTE recurrence	2.45 (1.32-4.55)	11.46 (9.13-14-38)	≈8 (5-12)	1.49 (1.17-1.88)	7.94 (5.36-11.76)	≈14 (10-24)
Major bleeding[b]	2.89 (1.80-4.63)	1.66 (0.78-3.52)	[69 (34-infinite)][c]	0.48 (0.27-0.85)	0.35 (0.17-0.72)	NA[d]
Net clinical benefit[e]	4.43 (3.09-6.36)	11.32 (8.48-15.12)	≈16 (10-51)	1.91 (1.55-2.35)	8.16 (2.97-11.04)	≈15 (11-26)

Mai V, et al. Chest 2019

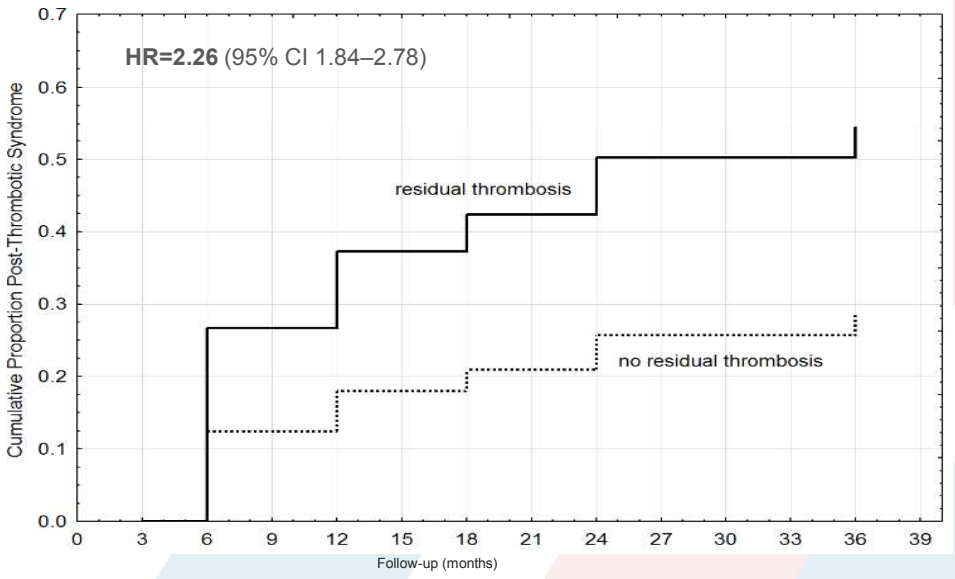
Recidiva stavu a reziduální žilní trombóza může vést k těžké chronické žilní nemoci (PTS)

869 nemocných, 3 měsíce po akutní žilní trombóze

Rekurence VTE



Reziduální obstrukce - potrombotický syndrom



Vznik PTS lze dle sympt. a zejména klin. znaků konstatovat až po 6 měs. od akutní trombózy

Prandoni *et al. Semin Thromb Haemost* 2015;41:133–140.

Faktory vzniku <=> Faktory rekurence

Strong risk factors (OR >10)
Fracture of lower limb
Previous VTE
Spinal cord injury
Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)
Hip or knee replacement
Major trauma
Myocardial infarction (within previous 3 months)

Moderate risk factors (OR 2–9)	Moderate risk factors (cont'd)
Arthroscopic knee surgery	In vitro fertilization
Autoimmune diseases	Oral contraceptive therapy
Blood transfusion	Postpartum period
Central venous lines	Infection (specifically pneumonia, urinary trac
Intravenous catheters and leads	Inflammatory bowel disease
Chemotherapy	Cancer (highest risk in metastatic disease)
Congestive heart failure or respiratory failure	Paralytic stroke
Erythropoiesis-stimulating agents	Superficial vein thrombosis
Hormone replacement therapy (depends on formulation)	Thrombophilia

Weak risk factors (OR <2)
Bed rest >3 days
Diabetes mellitus
Arterial hypertension
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy
Varicose veins

anatomické odchylky (May-Thurnerův syndrom, anomálie dolní duté žíly, aneur. vény)

persistence velkého (klin. významného) faktoru – př.: maligní proces,

systémový zánět (IBD, revmatologické procesy) a související léčba

orgánové dysfunkce (zejména srdeční a plicní funkce. ...)

omezená mobilita celková, končetiny – paresy / plegie

habitus (BMI > 30)

pohlaví - mužské, věk nad 65

reziduální venózní obstrukce (RVO)

Estimated risk for long-term recurrence	Risk factor category for index PE	Examples
High (>8% per year)		•Active cancer •One or more previous episodes of VTE in the absence of a major transient or reversible factor •Antiphospholipid antibody syndrome

VTE = venous thromboembolism.

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Modely predikce rekurence VTE

Model name	Vienna prediction model[18]	DASH score[19]	Rodger or men continue and HER DOO2 score[20]
Number of patients	929	1,818	646
Design	Prospective cohort study	Patient-level meta-analysis	Prospective cohort study
Predictive variables	Male > female. PE > proximal DVT > distal DVT. Elevated D-dimer after AC	D-dimer abnormal after cessation of AC (2 points). Age ≤50 years (1 point). Sex – male (1 point). Hormonal use at VTE onset (–2 points)	Men continue. Hyperpigmentation (1 point). Edema (1 point). Redness (1 point). D-dimer ≥250 µg/L during AC (1 point). Obesity (BMI ≥30 kg/m²) (1 point). Old (age ≥65 years) (1 point)
Total score	0 to 350	–2 to 4	0 to 6
Annual risk of recurrence	2%–15% depending on total score (nomogram)	Score of ≤1: 3.1% Score of 2: 6.4% Score of ≥3: 12.3%	Women with score of ≤1: 1.6% Women with score of ≥2: 14.1% Men: 13.7%

Fahrni J, et al. Vascular Health and Risk Management 2015:11 451–459

- Nízké riziko rekurence: < 3% /1.rok
- Střední riziko: 3-8% / 1. rok
- Vysoké riziko: > 10% / 1. rok

významná (velká) DVT/PE
muž
perzistence zvýšených D-dimerů
obezita s BMI >30
věk > 65

ZÁKLADNÍ DOBA (3 měs.-6)

- **operace**
- **trauma**
- **imobilizace / hospitalizace** pro akutní onemocnění s upoutáním na lůžko nad 3 dny

- **izolovaná distální DVT** dolní končetiny
- **izolovaná subsegmentální PE**

EXTENDOVANÁ LÉČBA

- **idiopatické stavy**
- **aktivní maligní procesy**
- **systémová autoimunitní a zánětlivá onemocnění**
- **chronické orgánové dysfunkce**
- **chronická „trombogenní“ farmakoterapie**
- **lab. významná trombofilie**
- **recidivy stavů, s následky: PTS, CTEPH**
- **zejména u mužů, obézních, nad 65 let**

V KONTEXTU INDIVIDUÁLNÍHO RIZIKA KRVÁCENÍ, TYPOLOGIE PACIENTA - PROFESE, ….

Table 14 Risk factors for long-term VTE recurrence (1)

ESC
European Society of Cardiology

Estimated risk for long-term recurrence	Risk factor category for index PE	Examples
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	•Surgery with general anaesthesia for >30 min •Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness •Trauma with fractures

VTE = venous thromboembolism.

Table 14 Risk factors for long-term VTE recurrence (2)

ESC
European Society of Cardiology

Estimated risk for long-term recurrence	Risk factor category for index PE	Examples
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	•Minor surgery (general anaesthesia for <30 min) •Admission to hospital for <3 days with an acute illness •Oestrogen therapy/contraception •Pregnancy or puerperium •Confined to bed out of hospital for ≥3 days with an acute illness

VTE = venous thromboembolism.

Table 14 Risk factors for long-term VTE recurrence (3)

ESC
European Society of Cardiology

Estimated risk for long-term recurrence	Risk factor category for index PE	Examples
	Non-malignant persistent risk factors	• Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight • Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	

VTE = venous thromboembolism.

Estimated risk for long-term recurrence	Risk factor category for index PE	Examples
High (>8% per year)		•Active cancer •One or more previous episodes of VTE in the absence of a major transient or reversible factor •Antiphospholipid antibody syndrome

VTE = venous thromboembolism.

dilema 4:
JE EXTENZE ANTIKOAGULACE BEZPEČNÁ?

Klíčová otázka:

Je zvýšené riziko krvácení?

- **věk** (>75 let)
- recentní **krvácení spont. nebo při antikoagulaci**
- **anémie** (Hb < 100 g/l)
- **trombocytopenie** < 100 x 10^9/l
- **renální nedostatečnost (CrCl <50 ml/min.)**
- **koagulopatie**
- **polymorbidita a fragilita**
- **komedikace** zvyšující riziko krvácení, abusus alkoholu
- **maligní nemoc** – některé formy

Idiopatické trombózy léčíme vždy déle než 3 měs.,

pokud není vysoké riziko krvácení

- žádný rizikový faktor vzniku v době diagnostiky akutního stavu není zřejmý
- v průběhu léčby může dojít k jeho odhalení
- nejběžněji se jedná buď o hereditární trombofilní stav nebo o skrytě probíhající maligní proces – nutnost zákl. vyšetření i u ambulantních nem.!
- riziko rekurence u neprovokované – idiopatické trombózy zvýšeno

	Roční riziko recidivy TEN	Roční riziko velkého krvácení
Provokovaná TEN		
Přechodný RF	**4,2 %** (HŽT 2,3 %, PE 1,9 %)	**VKA** 1 - **3 %**
Trvalý/chronický RF (kromě nádorů)	**9,7 %** (HŽT 5,3 %, PE 4,4 %)	
Neprovokovaná TEN	**7,4 %** (HŽT 4,1 %, PE 3,3 %)	**DOAC** 0,7 - 2,1 %
Recidivující neprovokovaná TEN	**12 %** (HŽT 6,6 %, PE 5,4 %)	

Ortel T et al., ASH 2020 Blood Adv 2020; 4 (19): 4693–4738

Meta-analýza 16 studií s 12 458 nem.,

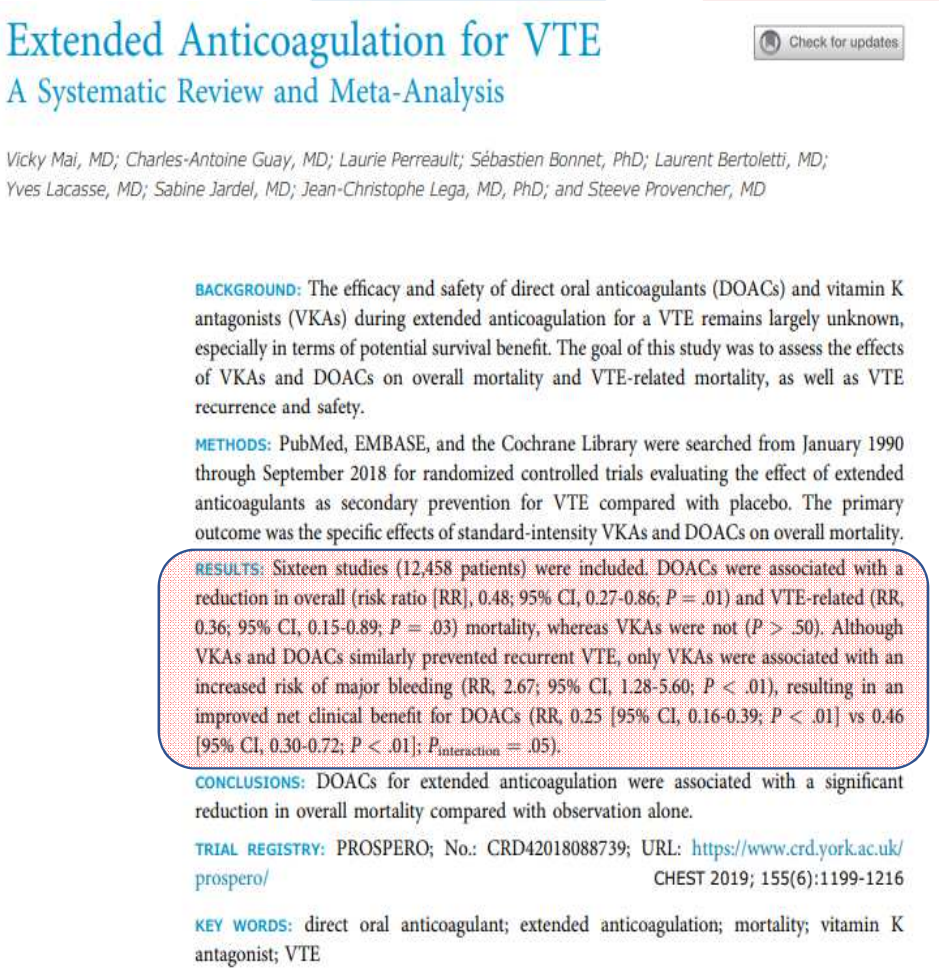
porovnání VKA vs placebo

a DOAC vs placebo

v extenzi léčby:

Vliv prodloužené antikoagulační léčby:

- **na rekurenci VTE**
- **na mortalitu na VTE a celkovou**
- **s ohledem na bezpečnost**



Extended Anticoagulation for VTE

A Systematic Review and Meta-Analysis

Check for updates

Vicky Mai, MD; Charles-Antoine Guay, MD; Laurie Perreault; Sébastien Bonnet, PhD; Laurent Bertoletti, MD; Yves Lacasse, MD; Sabine Jardel, MD; Jean-Christophe Lega, MD, PhD; and Steeve Provencher, MD

BACKGROUND: The efficacy and safety of direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) during extended anticoagulation for a VTE remains largely unknown, especially in terms of potential survival benefit. The goal of this study was to assess the effects of VKAs and DOACs on overall mortality and VTE-related mortality, as well as VTE recurrence and safety.

METHODS: PubMed, EMBASE, and the Cochrane Library were searched from January 1990 through September 2018 for randomized controlled trials evaluating the effect of extended anticoagulants as secondary prevention for VTE compared with placebo. The primary outcome was the specific effects of standard-intensity VKAs and DOACs on overall mortality.

RESULTS: Sixteen studies (12,458 patients) were included. DOACs were associated with a reduction in overall (risk ratio [RR], 0.48; 95% CI, 0.27-0.86; $P = .01$) and VTE-related (RR, 0.36; 95% CI, 0.15-0.89; $P = .03$) mortality, whereas VKAs were not ($P > .50$). Although VKAs and DOACs similarly prevented recurrent VTE, only VKAs were associated with an increased risk of major bleeding (RR, 2.67; 95% CI, 1.28-5.60; $P < .01$), resulting in an improved net clinical benefit for DOACs (RR, 0.25 [95% CI, 0.16-0.39; $P < .01$] vs 0.46 [95% CI, 0.30-0.72; $P < .01$]; $P_{interaction} = .05$).

CONCLUSIONS: DOACs for extended anticoagulation were associated with a significant reduction in overall mortality compared with observation alone.

TRIAL REGISTRY: PROSPERO; No.: CRD42018088739; URL: https://www.crd.york.ac.uk/prospero/

CHEST 2019; 155(6):1199-1216

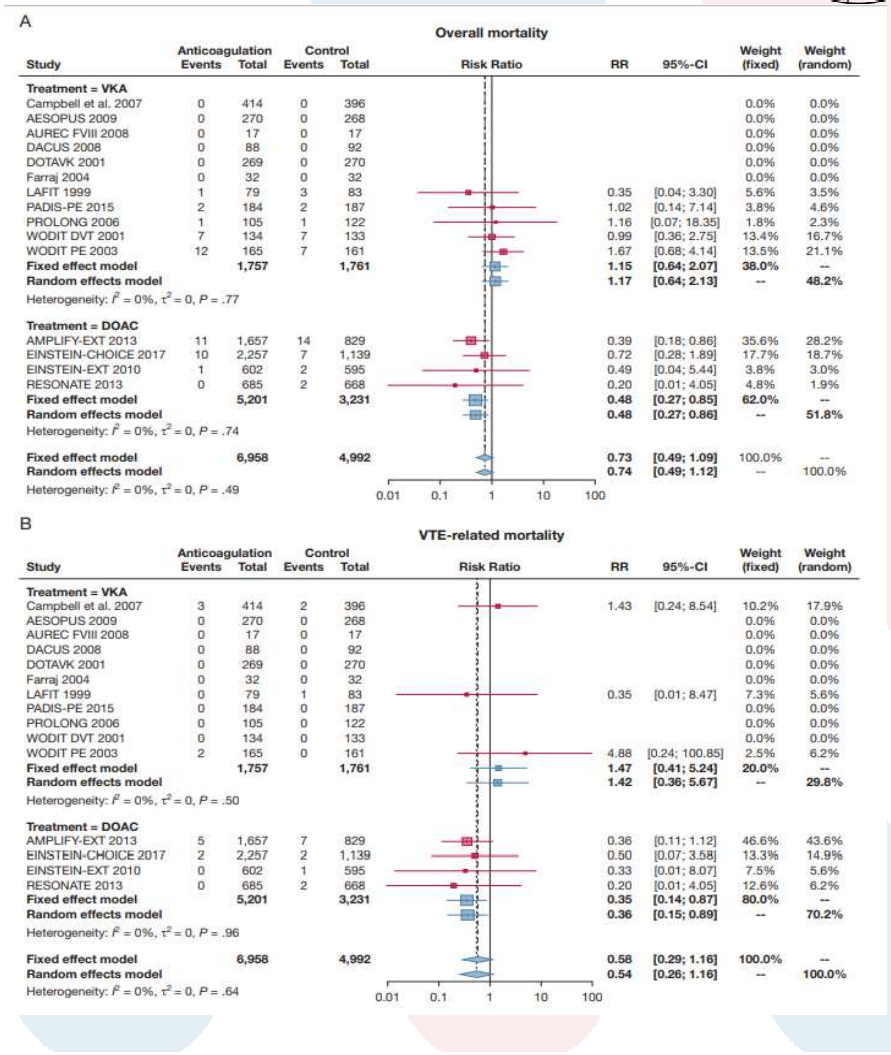
KEY WORDS: direct oral anticoagulant; extended anticoagulation; mortality; vitamin K antagonist; VTE

Extenze antikoagulační medikace cestou DOAC je spojena se snížením mortality na VTE (o 65%), i mortality celkové (o 50%)

- DOAC i VKA snížilo riziko rekurence o 80%

- čistý zisk při léčbě DOAC vyšší než u VKA (↑velké krvácení u warfarinu).

- limitace analýzy: data z registračních studií s NOAC, kam většinou zařazováni nemocní s nízkým rizikem krvácení
- kalkulována jen velká krvácení
- výsledky warfarinu – studie z doby, kdy byla hůře kontrolována art. hypertense, bylo více KV příhod pro nedostatečnou korekci RF celkově

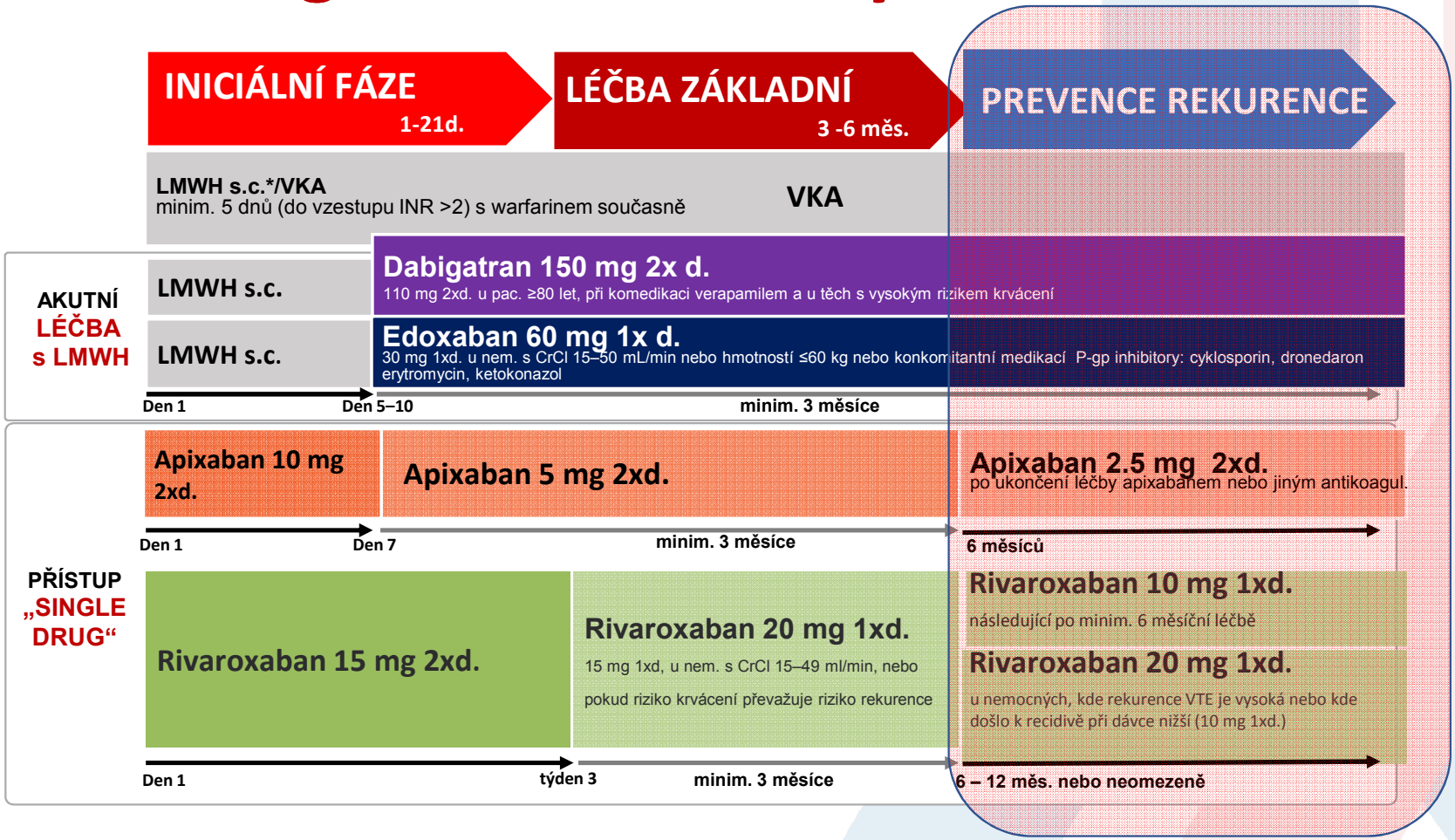


Studie farmakoprofylaxe VTE při extensi léčby

Lék / studie		Pokles rekurence (%)
Rivaroxaban 20 mg vs placebo	EINSTEIN EXT	82%
Apixaban 2x 2.5 mg vs placebo	AMPLIFY EXT	81%
Dabigatran 2x 150 mg vs placebo	RE-SONATE	92%
Dabigatran 2x 150 mg vs warfarin	RE-MEDY	účinnost - noninferiorita 46% RR velkých + význ. krvácení
ASA 100 mg	ASPIRE WARFASA	26% 42%
Sulodexid	SURVET	50%

Schulman S, et al; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013 Feb 21;368(8):709-18. doi: 10.1056/NEJMoa1113697. PubMed PMID: 23425163. *Romualdi et al ;EINSTEIN-extension study; Expert Rev Cardiovasc Ther. 2011 Jul;9(7):841-4. doi: 10.1586/erc.11.62. PubMed PMID: 21809964. Agnelli G et al; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013 Feb 21;368(8):699-708. doi: 10.1056/NEJMoa1207541. Epub 2012 Dec 8. PubMed PMID: 23216615.* Hokusai-VTE Investigators, Bu¨ller HR, De´cousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369:1406– 1415. [14] Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuu¨nemann HJ, American College of Chest Physicians Antithromboti

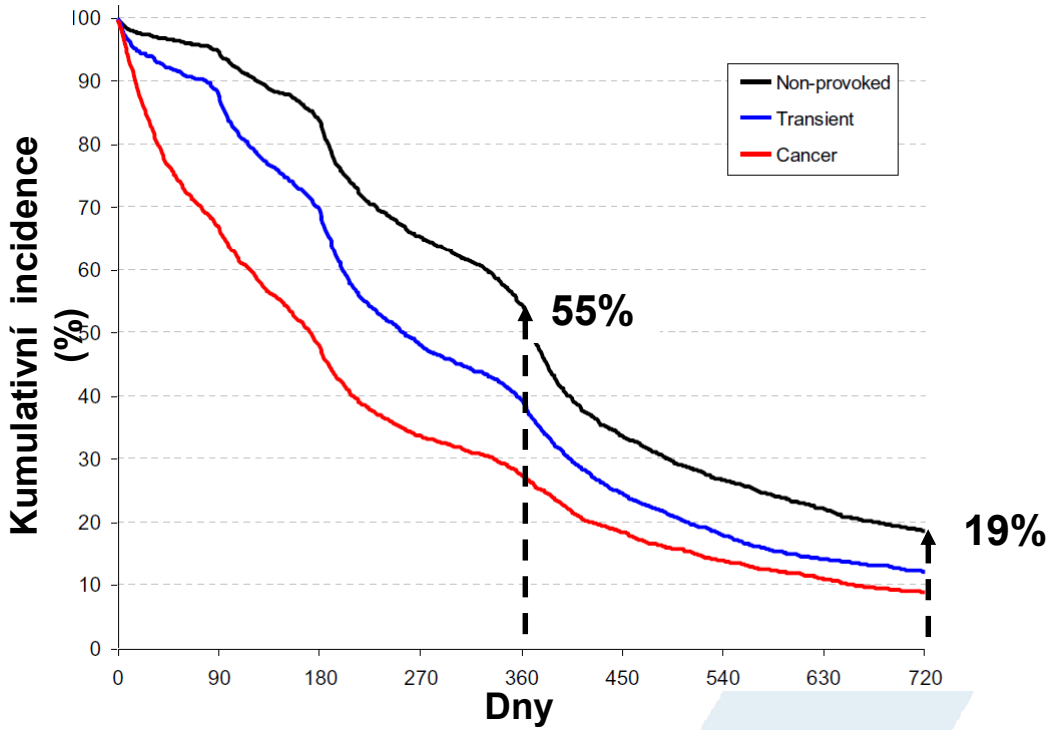
DOAC – strategie moderní léčby



Apixaban SmPC; 2. Rivaroxaban SmPC; 3. Dabigatran SmPC; 4. Edoxaban SmPC. www.ema.europa.eu.

Délka antikoagulační léčby v reálné praxi dle registru RIETE (n=6 944)

55% pacientů s neprovokovanou trombózou je léčeno déle než 12 měsíců



Ageno W *et al. Thromb Res* 2015;135:666–672.

Akutní žilní trombóza v různých subkategoriích nem.

- ✓senioři (fragilní, polymorbidní - polyfarmakoterapie)
- ✓těhotné (a kojící)
- ✓**nem. s aktivním nádorem**
- ✓renální selhání
- ✓významné trombofilie / APS
- ✓velmi rizikoví pro krvácení

Hokusai-VTE Cancer

- edoxaban vs dalteparin
- 1046 pac., 12 měsíců
- noninferiorita edoxabanu (Lixiana®) v rekurenci VTE / počtu velkých krvácení

Edoxaban for the Treatment of Cancer–Associated Venous Thromboembolism

Abstract

Background: Low-molecular-weight heparin is the standard treatment for cancer-associated venous thromboembolism. The role of treatment with direct oral anticoagulant agents is unclear.

Methods: In this open-label, noninferiority trial, we randomly assigned patients with cancer who had acute symptomatic or incidental venous thromboembolism to receive either low-molecular-weight heparin for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily (edoxaban group) or subcutaneous dalteparin at a dose of 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kilogram once daily (dalteparin group). Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, regardless of

SELECT-D

- rivaroxaban vs dalteparin
- 406 nemocných, 6 měsíců
- noninferiorita v účinnosti
- nárůst CRNMB u rivaroxabanu

Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT–D)

Abstract

Purpose Venous thromboembolism (VTE) is common in patients with cancer. Long-term daily subcutaneous low molecular weight heparin has been standard treatment for such patients. The purpose of this study was to assess if an oral factor Xa inhibitor, rivaroxaban, would offer an alternative treatment for VTE in patients with cancer. Patient and Methods In this multicenter, randomized, open-label, pilot trial in the United Kingdom, patients with active cancer who had symptomatic pulmonary embolism (PE), incidental PE, or symptomatic lower-extremity proximal deep vein thrombosis (DVT) were recruited. Allocation was to dalteparin (200 IU/kg daily during month 1,

Caravaggio Study

- apixaban vs dalteparin
- 1155 nem., 6 měs.
- noninferiorita apixabanu v rekurenci VTE
- srovnatelný počet velkých krvácení (3,8% vs 4,0%)

Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer

Abstract

Background: Recent guidelines recommend consideration of the use of oral edoxaban or rivaroxaban for the treatment of venous thromboembolism in patients with cancer. However, the benefit of these oral agents is limited by the increased risk of bleeding associated with their use.

Methods: This was a multinational, randomized, investigator-initiated, open-label, noninferiority trial with blinded central outcome adjudication. We randomly assigned consecutive patients with cancer who had symptomatic or incidental acute proximal deep-vein thrombosis or pulmonary embolism to receive oral apixaban (at a dose of 10 mg twice daily for the first 7 days, followed by 5 mg twice daily) or subcutaneous dalteparin (at a dose of 200 IU per kilogram of body weight once daily for the first month, followed by 150 IU per kilogram once daily). The treatments were administered for 6 months. The primary outcome was objectively confirmed recurrent venous thromboembolism during the trial period. The principal safety outcome was major bleeding.

Results: Recurrent venous thromboembolism occurred in 32 of 576 patients (5.6%) in the apixaban group and in 46 of 579 patients (7.9%) in the dalteparin group (hazard ratio, 0.63; 95% confidence interval [CI], 0.37 to 1.07; P<0.001 for noninferiority). Major bleeding occurred in 22 patients (3.8%) in the apixaban group and in 23 patients (4.0%) in the dalteparin group (hazard ratio, 0.82; 95% CI, 0.40 to 1.69; P = 0.60).

Conclusions: Oral apixaban was noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism without an increased risk of major bleeding. (Funded by the Bristol-Myers Squibb–Pfizer Alliance; Caravaggio ClinicalTrials.gov number, NCT03045406.).

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LÉČBA A PROFYLAXE ŽILNÍ TROMBÓZY A PLICNÍ EMBOLIE U ONKOLOGICKÝCH NEMOCNÝCH

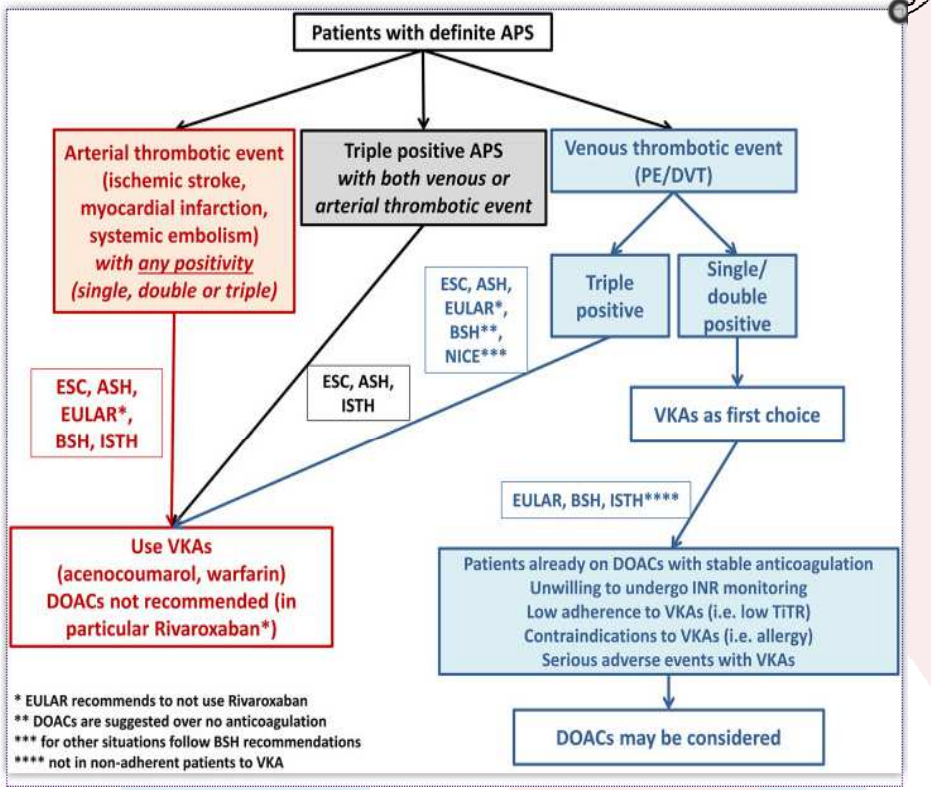
- v léčbě DOAC etablovány / Modrá kniha

cave: tumory GIT (a uro-genit.)
interakce s chemoterapií

Antifosfolipidový syndrom (APS)

TABLE 2 | Characteristics of studies enrolling patients with APS treated with DOACs.

Author (year)	Design	Follow up (months)	Triple positive (%)	Study sample	Anticoagulant	Women (%)	Age (mean)	Index event	Safety endpoint	Efficacy endpoint
RE-COVER(R), RE-COVER II, RE-MEDY (2016) (27)	*Post-hoc* RCTs	NR	NR	151	Dabigatran: 71 VKA: 80	36.4	47.6	VTE	MB (ISTH criteria), CRB and any bleeding **Results:** Similar MB and CRBs. Less any bleeding with dabigatran (HR 0.50, 95%CI 0.26–0.95)	Recurrent VTE/VTE-related death **Results:** Similar VTE between dabigatran and warfarin (HR 0.43, 95%CI 0.08–2.38)
RAPS (2016) (28)	RCT	7.0	28.0	116	Rivaroxaban: 57 VKA: 59	72.4	48.5	VTE	MB, CRB, and minor bleedings **Results:** No MB or CRB occurred	Thromboembolism **Results:** No thrombotic events occurred
TRAPS (2018) (29)	RCT	20.4	100.0	120	Rivaroxaban: 59 VKA: 61	64.2	46.3	Arterial, venous, and/or biopsy-proven micro-thrombosis.	Arterial or venous thromboembolic events, MB, and vascular death **Results:** 13 total events (7 thrombotic and 6 MB): 11 (19%) in the rivaroxaban and 2 (3%) in the warfarin group Rivaroxaban: 4 IS and 3 MI, and 4 (7%) MB Warfarin: no thrombotic events and 2 (3%) MB. No death reported	
Ordi-Ros et al. (30)	RCT	36.0	60.5	190	Rivaroxaban: 95 VKA: 95	63.7	49.0	Arterial or venous thrombosis	MB **Results:** MB occurred in 6 patients (6.3%) in the rivaroxaban group and 7 (7.4%) in the VKA group (RR 0.86, 95%CI 0.30–2.40)	Venous and arterial thrombosis **Results:** 11 recurrent thrombosis in the rivaroxaban and 6 in the VKA group (RR 1.83, 95%CI, 0.71–4.70) More IS with rivaroxaban (RR 19.00, 95%CI, 1.12–321.9)
Malec et al. (31)	P Case series	22.0	28.6	56	Rivaroxaban: 49 Dabigatran: 4 Apixaban: 3	78.6	52.0	VTE	MB according to ISTH criteria **Results:** 2 severe bleedings	VTE **Results:** 6 (10.7%) VTE (5.8%/year)
Malec et al. (32)	P	51.0	26.1	176	Rivaroxaban: 36 Dabigatran: 4 Apixaban: 42 VKA: 94	83.0	44.5	VTE or arterial thrombosis	MB or CRB **Results:** DOACs increased risk of MB or CRNMB if menstrual bleeding were included (HR 3.63, 95%CI 1.53–8.63) GI bleeds and MB or CRNMB other than menstrual bleeding were similar between groups	Composite of VTE, cerebrovascular ischemic events or MI **Results:** Increased thrombosis with DOACs (HR 3.98, 95%CI 1.54–10.28) and recurrent VTE (HR 3.69, 95%CI 1.27–10.68) compared with VKAs
Legault et al. (33)	P	19.0	0.0	82	Rivaroxaban	47.6	53.4	VTE	MB Minor bleeding **Results:** There were no MB but 23 minor bleeding occurred	VTE, myocardial infarction, IS, and cardiovascular death **Results:** 4 thrombotic events (2 cerebrovascular and 2 VTE)



Exkluzívní užívání VKA u nemocných s arteriálním APS a triple pozitivitou.
Evidence o nutnosti preference VKA u „venózního trombembolismu“ při APS je slabá (zvláště u single nebo double positivit).

Front Cardiovasc Med. 2021; 8: 715878.

Výběr optimálního přípravku k extendované léčbě

INDIVIDUALIZACE LÉČBY

- **DOAC u většiny jako lék volby**, volba ev. snížené dávky (od 6. měsíce)
- **LMWH** u malé části nemocných – v případě malignity s vyšším rizikem krvácení, případně u nemocných ve vyšetřovacím procesu pro susp. nádorové onemocnění, nebo u těhotných
- **Warfarin** při arteriálním APS, při renálním selhání, event. atypických lokalizacích trombózy, u kojících
- **Sulodexid** u nemocných s permanentním rizikem rekurence VTE a současně vysokým rizikem krvácení
- **ASA** jako prevence rekurence – žilní trombembolie a současně i prevence arteriální trombózy (KV onemocnění)

otázka délky léčby: porovnání rizika rekurence *versus* riziko krvácení

Nejasnosti: perzistence malých rizik, atypické trombózy – déle?

Které hereditární trombofilie jsou skutečně významné?

Proč u mužů je riziko recidivy vyšší?

Řídit se D-dimery?


„Jiří, přišel mi dopis od Elona Muska, asi poletíme do vesmíru.“
„No... ehm...“
e·on

Recommendations for the regimen and duration of anticoagulation after PE in patients *without* cancer (3)

ESC
European Society of Cardiology

Recommendations	Class	Level
Patients in whom extension of anticoagulation beyond 3 months should be considered		
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and no identifiable risk factor.	IIa	A
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a persistent risk factor other than the antiphospholipid antibody syndrome.	IIa	C
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a minor transient or reversible risk factor.	IIa	C

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Recommendations for the regimen and duration of anticoagulation after PE in patients *without* cancer (4)

ESC
European Society of Cardiology

Recommendations	Class	Level
NOAC dose in extended anticoagulation		
If extended oral anticoagulation is decided after PE in a patient without cancer, a reduced dose of the NOACs apixaban (2.5 mg *b.i.d.*) or rivaroxaban (10 mg *o.d.*) should be considered after 6 months of therapeutic anticoagulation.	IIa	A
Extended treatment with alternative antithrombotic agents		
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin or sulodexide may be considered for extended VTE prophylaxis.	IIb	B

NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); VTE = venous thromboembolism.

Recommendations for the regimen and duration of anticoagulation after PE in patients *without* cancer (5)

ESC
European Society of Cardiology

Recommendations	Class	Level
Follow-up of the patient under anticoagulation		
In patients who receive extended anticoagulation, it is recommended to reassess drug tolerance and adherence, hepatic and renal function, and the bleeding risk at regular intervals.	I	C

Recommendations for the regimen and the duration of anticoagulation after PE in patients with active cancer (1)

ESC
European Society of Cardiology

Recommendations	Class	Level
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 6 months over VKAs.	IIa	A
Edoxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.	IIa	B
Rivaroxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.	IIa	C

LMWH = low molecular weight heparin; VKA(s) = vitamin K antagonist(s).

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Recommendations for the regimen and the duration of anticoagulation after PE in patients with active cancer (2)

ESC
European Society of Cardiology

Recommendations	Class	Level
For patients with PE and cancer, extended anticoagulation (beyond the first 6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	B
In patients with cancer, managing incidental PE in the same manner as symptomatic PE should be considered, if it involves segmental or more proximal branches, multiple subsegmental vessels, or a single subsegmental vessel in association with proven DVT.	IIa	B

DVT = deep vein thrombosis

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Co zvažujeme:

Ukončení léčby

3 měsíce
primární léčby

Pokračovat v léčbě

Riziko krvácení

Riziko recidivy

Preference pacienta / životní prognóza

Ukončení léčby

3 měsíce
primární léčby

Pokračovat v léčbě

Riziko recidivy ↑↑

Riziko krvácení

Možnosti farmakoprofylaxe VTE při extensi léčby

Lék / studie		Pokles rekurence (%)
Rivaroxaban 20 mg vs placebo	EINSTEIN EXT	82%
Apixaban 2x 2.5 mg vs placebo	AMPLIFY EXT	81%
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ASA 100 mg	ASPIRE WARFASA	26% 42%
Sulodexid	SURVET	50%

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Ukončení léčby

3 měsíce
primární léčby

Pokračovat v antikoagul. léčbě? NE

Riziko recidivy nízké

Riziko krvácení ↑↑↑

Ukončení léčby

3 měsíce
primární léčby

Pokračovat v léčbě

Riziko krvácení ↑↑

Riziko recidivy ↑↑

Koho léčit sulodexidem a koho ASA?

SULODEXID (Vessel due F 2x2 tob.)

- glykosaminoglykan s mírným antitrombotickým účinkem, endotelprotektivní
- snížení rizika rekurence o 51%
- četnost krvácení obd. jako u placeba
- vhodný ve stř. riziku rekurence a zvýšeném riziku krvácení, alternativa při neschválení DOAC (úhrada 2 roky po VTE)
- **indikace – při vysokém riziku krvácení, komplikacích antikoagulační léčby, odmítnutí (intoleranci) antikoagulační léčby**

ASA 100 mg

- snížení rizika rekurence asi o 30%
- standardní formy ASA (Anopyrin, Godasal, …)
- vhodný u nemocných ve středním riziku rekurence VTA a současné přítomnosti atero-trombotických komplikací

- **Acetylsalicylová kyselina (ASA) levný lék pro nemocné se souč. KV onem.**

Aspirin for Extended Prevention of VTE

- **WARFASA**[a]
  - Aspirin 100 mg vs placebo for ≥24 months (N = 402)

Observed VTE Reduction	Major Bleeding (Aspirin)	Major Bleeding (Placebo)	Major or CRNM Bleeding (Aspirin)	Major or CRNM Bleeding (Placebo)
40%	0.3%*	0.3%*	1%*	1%*

ASA stand.

- **ASPIRE**[b]
  - Aspirin 100 mg vs placebo for up to 4 years (N = 822)

Observed VTE Reduction	Major Bleeding (Aspirin)	Major Bleeding (Placebo)	Major or CRNM Bleeding (Aspirin)	Major or CRNM Bleeding (Placebo)
26%	0.9%*	0.7%*	1.1%*	0.6*

ASA enterosolv.

*Per patient year.

ASPIRE = Aspirin to Prevent Recurrent Venous Thromboembolism; WARFASA = The Warfarin and Aspirin Study

a. Becattini C, et al. *N Engl J Med*. 2012;366(21):1959-1967.
b. Brighton T, et al. *N Engl J Med*. 2012;367(21):1979-1987.

Medscape EDUCATION

+ metaanalýza **INSPIRE:** snížení rizika rekurence **32%**, velké krvácení **0,5% / rok**

Sulodexid s účinností vyšší než ASA a nižší než DOAC
bezpečný lék pro nemocné s vyšším rizikem krvácení

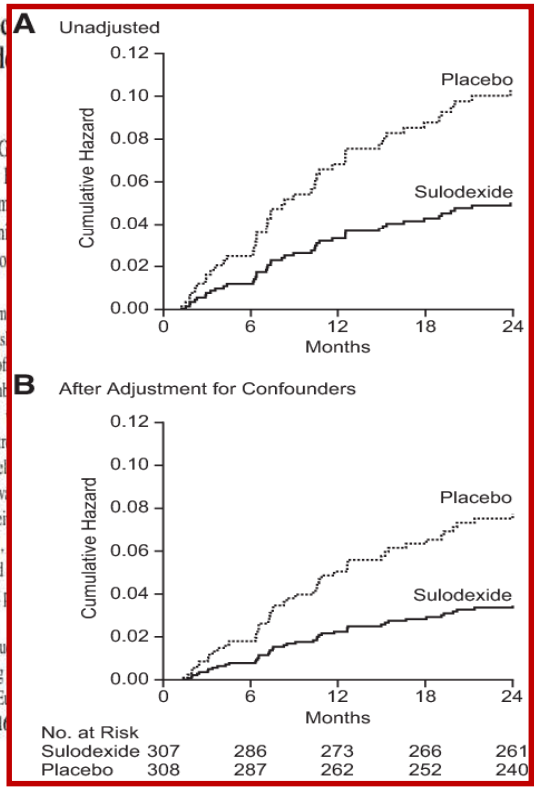
Sulodexide for the Prevention of Recurrent Venous Thromboembolism

The Sulodexide in Secondary Prevention of Rec… Thrombosis (SURVET) Study: A Multicenter, Rand… Placebo-Controlled Trial

Giuseppe M. Andreozzi, MD; Angelo A. Bignamini, PhD; G…
Gualtiero Palareti, MD; Jiří Matuška, MD; Martin …
Katarzyna Pawlaczyk-Gabriel, MD; Andrej Džupina, MD; Germ…
Yury P. Didenko, MD; Laurentia D. Andrei, MD; Gianfranco Lessian…
on behalf of the SURVET Study Investigato…

Background—Patients with a first episode of unprovoked venous thromboembolism… discontinuation of anticoagulant therapy. Extending anticoagulation reduces the ris… increased bleeding. Sulodexide, a glycosaminoglycan, exerts antithrombotic and prof… risk when administered orally, but its benefit for preventing recurrent venous thromb…
Methods and Results—In this multicenter, double-blind study, 615 patients … thromboembolism who had completed 3 to 12 months of oral anticoagulant tr… sulodexide 500 lipasemic units twice daily or placebo for 2 years, in addition to el… outcome was recurrence of venous thromboembolism. Major or clinically relev… outcome. Venous thromboembolism recurred in 15 of the 307 patients who recei… patients who received placebo (hazard ratio, 0.49; 95% confidence interval [CI], … which lost to follow-up was assigned to failure yielded a risk ratio among treated … confidence interval, 0.35–0.85; *P*=0.009). No major bleeding episodes occurred; 2 p… clinically relevant bleeding episode. Adverse events were similar in the 2 groups.
Conclusion—Sulodexide given after discontinuation of anticoagulant treatment redu… with unprovoked venous thromboembolism, with no apparent increase of bleeding…
Clinical Trial Registration—URL: https://www.clinicaltrialsregister.eu/. Identifier: E…

(*Circulation*. 2015;132:1891-1897. DOI: 10.1161/CIRCULATIONAHA.115.01…



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The Efficacy of Sulodexide in the Prevention of Postthrombotic Syndrome

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Potrombotický syn.

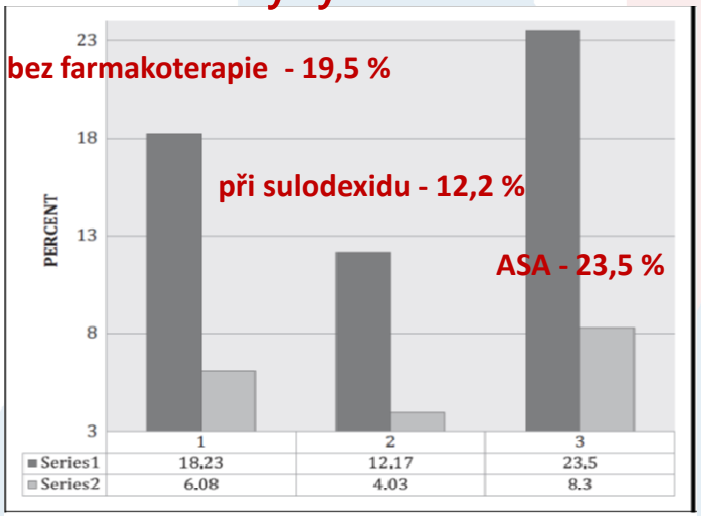

Figure 1. Percentage of patients with postthrombotic limbs (black) or… recurrent DVT (gray) at 54 Months: Group 1: standard management… (SM); group 2: SM + sulodexide; group 3: SM + ASA. DVT indicates… deep venous thrombosis; ASA, aspirin.

Predicting anticoagulant-related bleeding in patients with venous thromboembolism: a clinically oriented review

Frederikus A. Klok[1], Judith Kooiman[2], Menno V. Huisman[2], Stavros Konstantinides[1] and Mareike Lankeit[1]

Riziko velkého krvácení - akutní léčba

TABLE 2 Overview of bleeding risk in the phase 3 clinical trials with non-vitamin K dependent anticoagulants for the initial treatment of venous thromboembolism

Trial [ref.]	Design	Treatment	Duration months	Patients	Incidence of major bleeding
RE-COVER [3]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg twice daily) *versus* enoxaparin/warfarin	6	2539 patients with acute DVT and/or PE	1.6% under dabigatran *versus* 1.9% under warfarin
RE-COVER II [8]				2568 patients with acute DVT and/or PE	1.2% under dabigatran *versus* 1.7% under warfarin
EINSTEIN-DVT [4]	Open label	Rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily) *versus* enoxaparin/warfarin	3, 6, or 12	3449 patients with acute DVT	0.8% under rivaroxaban *versus* 1.2% under warfarin
EINSTEIN-PE [5]				4832 patients with acute PE	1.1% under rivaroxaban *versus* 1.2% under warfarin
AMPLIFY [6]	Double-blind, double-dummy	Apixaban (10 mg twice daily for 7 days, then 5 mg twice daily) *versus* enoxaparin/warfarin	6	5395 patients with acute DVT and/or PE	0.6% under apixaban *versus* 1.8% under warfarin
Hokusai-VTE [7]	Double-blind, double-dummy	LMWH/edoxaban (60 mg once daily) *versus* UFH or LMWH/warfarin	3–12	8240 patients with acute DVT and/or PE	1.4% under edoxaban *versus* 1.6% under warfarin

DVT: deep vein thrombosis; PE: pulmonary embolism; LMWH: low molecular weight heparin; UFH: unfractionated heparin.

Riziko velkého krvácení - extense

TABLE 3 Overview of bleeding risk in the phase 3 clinical trials with non-vitamin K dependent anticoagulants for the continued treatment of venous thromboembolism

Trial	Design	Treatment	Duration months	Patients	Incidence of major bleeding
RE-SONATE [9]	Double-blind	Dabigatran (150 mg twice daily) *versus* placebo	6	1343 patients after uneventful initial treatment for acute DVT and/or PE	0.3% under dabigatran *versus* 0% under placebo
RE-MEDY [9]	Double-blind, double-dummy	Dabigatran (150 mg twice daily) *versus* warfarin	18–36	2856 patients after uneventful initial treatment for acute DVT and/or PE	0.9% under dabigatran *versus* 1.8% under warfarin
EINSTEIN-EXT [4]	Double-blind	Rivaroxaban (20 mg once daily) *versus* placebo	6–12	1196 patients after uneventful initial treatment for acute DVT and/or PE	0.7% under rivaroxaban *versus* 0% under placebo
AMPLIFY-EXT [10]	Double-blind	Apixaban (2.5 mg twice daily or 5 mg twice daily) *versus* enoxaparin/warfarin	12	2482 patients after uneventful initial treatment for acute DVT and/or PE	0.2% under apixaban 2.5 mg twice daily *versus* 0.1% under apixaban 5 mg twice daily *versus* 0.5% under placebo

DVT: deep vein thrombosis; PE: pulmonary embolism.

Otázky?

… s díky dkare@lf1.cuni.cz

Rizikové faktory vzniku PTS

- Žilní trombóza v oblasti ilických a femorálních vén
- Nedostatečná léčba / reziduální trombóza
- Recidiva trombózy
- Obezita (BMI > 30-35)
- Preexistující chron. žilní onemocnění, zejména stav po operaci varixů
- Vyšší věk

Rizikové faktory vzniku PTS
– můžeme je ovlivnit?

- Žilní trombóza v oblasti ilických a femorálních vén („flegmázie“) → **profylaxe vzniku, maximální disoluce trombu**
- Recidiva trombózy → **délka antikoagulační medikace, optimální přípravek a volba správné dávky**
- Obezita (BMI > 30-35) → **redukce hmotnosti**
- Preexistující chron. žilní onemocnění, zejména stav po operaci varixů
- Věk