SUPPLEMENTAL MATERIAL

List of investigators and participating centres

Main Investigators

Hugo ten Cate, MD, PhD (Chair)	Maastricht University Medical Centre
Cornelis H. A. Wittens, MD, PhD	Maastricht University Medical Centre
Arina J. ten Cate-Hoek, MD, PhD	Maastricht University Medical Centre
Pascale Notten, MD, PhD	Maastricht University Medical Centre

Data Safety Monitoring Board

Karly Hamulyak, MD, PhD (Chair)	Maastricht University Medical Centre
Roger J.M.W. Rennenberg, MD, PhD	Maastricht University Medical Centre
Martinus H. Prins, MD, PhD	Maastricht University Medical Centre

CAVA Clinical Centres

- **Maastricht University Medical Centre (n = 51)*:** Hugo ten Cate– site PI.
- **Maasstad Hospital (n = 23)*:** Andre de Smet – site PI.
- **Maxima Medical Centre (n = 21):** Lidwine Tick – site PI.
- **Laurentius Hospital (n = 16):** Marlene van de Poel – site PI.
- **Nij Smellinghe Hospital (n = 12)*:** Marald Wikkeling – site PI.
- **Vie Curi Medical Centre (n = 11):** Ad Koster – site PI.
- **Haga Hospital (n = 11)*:** Louis-Jean Vleming – site PI.
- **Zuyderland Medical Centre (n = 10):** Guy Mostard – site PI.
- **Elkerliek Hospital (n = 7):** Esther Jacobs – site PI.
- **Amsterdam University Medical Centres, location VUmc (n = 6)*:** Harm Ebben – site PI.
- **Amsterdam University Medical Centres, location AMC (n = 5)*:** Michiel Coppens – site PI.
- **St. Jans Gasthuis Hospital (n = 3):** Antoni Gajic – site PI.
- **St. Antonius Hospital Nieuwegein (n = 3):** Jeroen Vincent – Site PI.
- **Catharina Hospital Eindhoven (n = 3):** Wim Peters – Site PI.
- **St. Anna Hospital (n = 2):** Alexander Stork – site PI.

* Participating interventional centre, performing ultrasound-accelerated catheter-directed thrombolysis and eventual adjunctive interventions.

Table S1. Inclusion and exclusion criteria.

Inclusion Criteria
• Age 18 – 85 years; • Objectively documented iliofemoral deep-vein thrombosis (complete or partial thrombosis of the common femoral vein or more cranial vein segments); • Acute stage iliofemoral deep-vein thrombosis: onset of symptoms < 14 days; • Life expectancy > 6 months; • First deep-vein thrombosis in the index leg.
Exclusion Criteria
• Previous thrombosis of the affected limb; • Varicosities/ Venous insufficiency CEAP classification C3 or higher; [30] • History of gastro-intestinal bleeding within the previous 12 months; • History of cerebrovascular accident or central nervous system disease within the previous 12 months; • Severe hypertension (systolic >180 mmHg or diastolic > 100 mmHg); • Active malignancy (metastatic, progressive, or treated within the last 6 months); • Increased alanine transaminase levels (> 3 times normal range*); • Renal failure (estimated GFR < 30 mL/min); • Major surgery within the previous 6 weeks; • Pregnancy • Immobility (wheelchair dependent).

* The normal range of alanine transaminase levels is 34 international units/liter (IU/L) for women and 45 IU/L for men.

Table S2. Schedule of study assessments.

What:	How:	Who/ Where:
Prior to study inclusion		
Objectify deep vein thrombosis	Diagnostic process according to international guidelines at least including a 2-point compression ultrasound	Treating physician
Check eligibility for study participation	Check inclusion and exclusion criteria	Treating physician
Inform patient on the CAVA-trial	Inform the patient on the CAVA-trial, the possibility to participate, and ask if patient is interested in participating	Treating physician
Refer patient for participation in CAVA-trial	Contact the study coordinator (MUMC)	Treating physician
Including patient	Contact/Visit the patient to inform them on the purpose and content of the study, check eligibility, and ask if they are willing to participate	Study coordinator (MUMC)
Obtain informed consent	Provide the patient with patient information and an informed consent form. Written informed consent was obtained after a prespecified reflection period	Study coordinator (MUMC)
Standard post-thrombotic care (applicable to both treatment groups)		
Provide standard post-thrombotic care	*Post-thrombotic care according to international guidelines including early anticoagulation therapy, compression therapy, and mobilisation.*	*Treating physician*
Randomisation		
Randomisation	Randomisation using TENALEA	Study coordinator (MUMC)
Communication	Participation is confirmed but **not** treatment allocation by mail/letter to the patient's treating physician and general practitioner. Allocated treatment is **communicated to the patient directly**. All patients would visit the intervention centre nearest to their homes for additional imaging and other study related assessments. If allocated to the intervention group, the interventional physician at the intervention centre nearest to the patient's home was informed by the study coordinator and asked to initiate treatment.	Study coordinator (MUMC)
Baseline (All patients)		
Clinical consultation and physical examination	Obtaining baseline characteristics and VCSS	Study personnel (interventional centres)
Assessment of Health-related Quality of Life	Hand out and take in patient-reported Health-related Quality of life questionnaires: - SF36v2 - EQ5D - Pain Disability Index - VEINES-QOL/Sym	Study personnel (interventional centres)
Imaging of the vein segments of the affected leg	Obtaining an extended duplex ultrasound of the affected leg (from the popliteal vein up to the diaphragm) and a Magnetic Resonance Venography or APG if available	Independent radiologist and/or registered vascular technologists (interventional centres)

Thrombolytic treatment (Only applicable to patients allocated to the intervention group)		
Thrombolysis (including adjunctive stenting)	Thrombolysis using Urokinase and the Ekos Endowave®-system. For details see the protocol/Supplementary Appendix.	Radiologists and/or vascular surgeons (interventional centres)
Care after venous stenting (2 and 6 weeks after thrombolytic treatment)	Clinical consultation and physical examination. Check for complications of the intervention, and symptom relief.	Study personnel or vascular surgeon that performed the intervention (interventional centres)
Imaging of the vein segments of the affected leg	Obtaining an extended duplex ultrasound to assess the result of the intervention.	Independent radiologist and/or registered vascular technologists (interventional centres)
Follow-up visit at 3 months all patients (All patients)		
Clinical consultation and physical examination	Obtaining treatment characteristics (anticoagulation, adherence to compression therapy), adverse events, and Villalta-score	Local study personnel or treating physician (interventional and contributing centres)
Assessment of Health-related Quality of Life	Hand out and take in patient-reported Health-related Quality of life questionnaires: - SF36v2 - EQ5D - Pain Disability Index - VEINES-QoL/Sym	Local study personnel or treating physician (interventional and contributing centres)
Follow-up visit at 6 months all patients (All patients)		
Clinical consultation and physical examination	Obtaining treatment characteristics (anticoagulation, adherence to compression therapy), adverse events, and Villalta-score	Local study personnel or treating physician (interventional and contributing centres)
Assessment of Health-related Quality of Life	Hand out and take in patient-reported Health-related Quality of life questionnaires: - SF36v2 - EQ5D - Pain Disability Index - VEINES-QoL/Sym	Local study personnel or treating physician (interventional and contributing centres)
Follow-up visit at 12 months (All patients)		
Clinical consultation and physical examination	Obtaining treatment characteristics (anticoagulation, adherence to compression therapy), adverse events, Villalta-score and VCSS	Study personnel (interventional centres)
Assessment of Health-related Quality of Life	Hand out and take in patient-reported Health-related Quality of life questionnaires: - SF36v2 - EQ5D - Pain Disability Index - VEINES-QoL/Sym	Study personnel (interventional centres)
Imaging of the vein segments of the affected leg	Obtaining an extended duplex ultrasound of the affected leg (from the popliteal vein up to the diaphragm) and a Magnetic Resonance Venography or Air PlethysmoGraphy if available.	Independent radiologist and/or registered vascular technologists (interventional centres)
Final follow-up visit (All patients)		
Clinical consultation and physical examination	Obtaining treatment characteristics (anticoagulation, adherence to compression therapy), adverse events, Villalta-score and VCSS	Study personnel (interventional centres)

Assessment of Health-related Quality of Life	Hand out and take in patient-reported Health-related Quality of life questionnaires: - SF36v2 - EQ5D - Pain Disability Index - VEINES-QoL/Sym	Study personnel (interventional centres)
Imaging of the vein segments of the affected leg	Obtaining an extended duplex ultrasound of the affected leg (from the popliteal vein up to the diaphragm).	Registered vascular technologist (interventional centres)

EQ5D = EuroQoL 5D-3L questionnaire. SF36v2 = Short Form 36-Health Survey version 2. MUMC = Maastricht University Medical Centre. VCSS = Venous Clinical Severity Score. VEINES QOL/Sym = VEnous INsufficiency Epidemiological and Economic Study - Quality of Life questionnaire.