Anti-
THrombosis with 
Enoxaparin in 
iNtubated 
Adolescents

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ATHENA Trial
Research question, central hypothesis and primary aim

- **Research Question**
  - Should we provide pharmacologic prophylaxis against VTE in critically ill adolescents?

- **Central Hypothesis**
  - Pharmacologic prophylaxis safely reduces the risk of VTE in critically ill adolescents

- **Primary Aim**
  - Determine the efficacy of enoxaparin in reducing the risk of radiologically diagnosed lower extremity DVT in mechanically ventilated adolescents
Secondary aims

- **Secondary Aim 1**
  - Assess the effect of enoxaparin on the
    - Risks of any VTE, clinically apparent VTE, CVC-associated DVT and composite of VTE or mortality
    - Risks of clinically relevant bleeding, any bleeding and heparin-induced thrombocytopenia
  
in mechanically ventilated adolescents

- **Secondary Aim 2**
  - Assess the net clinical benefit of prophylaxis with enoxaparin in mechanically ventilated adolescents
    - Number needed to treat to prevent clinically apparent VTE
    - Number needed to harm to cause clinically relevant bleeding

- **Secondary Aim 3**
  - Assess the efficacy of enoxaparin on the risk of radiologically diagnosed lower extremity DVT in mechanically ventilated adolescents based on
    - Sex
    - Presence of obesity
    - Presence of lower extremity CVC
Study design

- Bayesian adaptive, Goldilocks phase III RCT
- Multicenter superiority, pragmatic, parallel-cohort design
- Open label, non-placebo controlled but with blinded endpoint
- Ethical concerns with use of placebo
  - Pain without direct benefit
- Active radiologic surveillance of DVT
  - Centralized blinded adjudication
- 1:1 block stratified randomization
  - Lower extremity CVC
- 6 interim analyses
Eligibility criteria

**Inclusion**
- 13 to < 18 years old
- Anticipated invasive mechanical ventilation $\geq 48$H

**Exclusion**
- Presence of or at high risk of clinically relevant bleeding
  - Post-surgical
  - Trauma
  - Renal failure
  - Coagulopathy
- Receiving or anticipated to receive an antithrombotic agent
- Presence of pre-existing VTE
- FDA approval for enoxaparin
- Less likely to benefit from prophylaxis
Detailed exclusion criteria

- Radiologic diagnosis of VTE during enrollment period
- Radiologic diagnosis of lower extremity DVT in prior 6 weeks
- On or anticipated to be on therapeutic anticoagulation
- On prophylactic UFH or LMWH for >24 hours, except UFH at doses to maintain patency of a catheter
- On any other antithrombotic agent, including aspirin
- Presence of clinically relevant bleeding, i.e., hemoglobin decreased ≥2 g/dl in 24 hours, required medical or surgical intervention to restore hemostasis, or in a critical organ system, in the prior 60 days
- Surgery in the prior 7 days
- Major trauma in the prior 7 days
- Presence of renal failure, i.e., creatinine clearance <30 mL/min/m²
- Presence of coagulopathy, i.e., international normalized ratio >2.0, activated partial thromboplastin time >50 seconds or platelet count <50,000/mm³
- Known allergy to heparin or any of its components, including pork
- Diagnosis of HIT confirmed with a positive serotonin release assay
- Current pregnancy or lactation
- Presence of an epidural catheter
- Limitation of care
- Previous enrollment in the ATHENA Trial
Trial arms

- **Treatment arm**
  - Enoxaparin
  - Mechanical prophylaxis
  - Ultrasound on day of ICU discharge
  - Followed until hospital discharge
    - Maximum of 28 days

- **Control arm**
  - Mechanical prophylaxis
  - Ultrasound on day of ICU discharge
  - Followed until hospital discharge
    - Maximum of 28 days

- **Observation arm**
  - Waiver of consent
  - Usual care
  - Followed for clinically apparent VTE until day of ICU discharge
    - Maximum of 28 days
Enoxaparin

• Regimen (FDA approval)
  – 40 mg SQ q 24H for ≥45 kg
  – 0.5 mg/kg SQ q12H for <45 kg
  – 30 mg SQ q12H for BMI ≥40 kg/m²

• Start of treatment
  – <6H after enrollment

• End of treatment
  – Mobile AND NO femoral CVC
  – Only while in the ICU

• Mobility
  – Braden Q scale q12H nursing shift
  – Score of 4 in the mobility subscale (*i.e.*, no limitations), or ≥3 in the activity subscale (*i.e.*, walks occasionally) for ≥2 consecutive shifts
  – Back to baseline mobility and activity subscale scores for ≥2 consecutive shifts
### Discontinuation of enoxaparin

#### Permanent
- Lower extremity DVT is radiologically diagnosed by the clinical team
- Therapeutic anticoagulation or another antithrombotic agent is started
- Clinically relevant bleeding develops
- HIT is diagnosed with a positive serotonin release assay
- Renal failure develops
- Discharge from the ICU
- 28 days after randomization

#### Temporary
- Coagulopathy develops
- 12 hours before surgery or invasive procedure
- In cases of suspected HIT

#### Restart enoxaparin
- 24 hours after coagulopathy is corrected
- 24 hours after surgery or procedure
- After exclusion of HIT (i.e., negative serotonin release assay)
Mechanical prophylaxis

• **Regimen**
  - SCD preferred
  - ≥18H per day

• **Start of treatment**
  - <6H after enrollment

• **End of treatment**
  - Mobile AND NO femoral CVC, OR
  - Earlier when the following occurs
    • Lower extremity DVT is radiologically diagnosed by the clinical team
    • Discharge from the ICU
    • 28 days after randomization
Radiologically diagnosed lower extremity DVT

- Minimizes ascertainment bias
  - Clinical suspicion not sensitive nor specific
  - Recommended by ISTH
- Direct and immediate consequence of enoxaparin
  - Causal pathway to clinically apparent VTE
- Parallels a similar reduction in clinically apparent VTE
- Primary outcome in critically ill adult RCTs
  - Match for Bayesian analysis
- Basis for FDA approval for enoxaparin
Ultrasound

- **Timing**
  - Within 48H of day of ICU discharge, OR
  - Earlier when the following occurs
    - Lower extremity DVT is radiologically diagnosed by the clinical team
    - Therapeutic anticoagulation or another antithrombotic agent is started
    - 28 days after randomization

- **Anatomic site**
  - Bilateral lower extremities, AND
  - Upper extremity if with CVC within 3 days of start of mechanical ventilation

- **Read**
  - Local for clinical purposes (site co-I radiologist)
    - Relay to clinical team for treatment management
  - Centralized blinded adjudication for trial purposes

- **Transmission to DCC**
  - Electronic through Medidata Medical Imaging
Secondary outcome measures

- Any VTE
  - Lower extremity DVT
  - Upper extremity CVC-associated DVT
  - Clinically apparent VTE
- Clinically apparent VTE
- CVC-associated DVT
- VTE or death
- Clinically relevant bleeding
- Any bleeding
- HIT
Safety assessment

- Bleeding
  - Bleeding assessment tool
  - Defined by ISTH
  - Daily

- Blood draw
  - CBC, creatinine, ALT and AST
    - On enrollment and weekly ± 2 days
  - Serotonin release assay
    - If suspicious for HIT
  - Stool guaiac test
    - As per clinical team
Statistical considerations

- Interim analysis
  - Minimum of 100 patients
  - Every 50 patients
  - Maximum sample size of 400 patients

- Early termination
  - Efficacy
  - Futility

- Final analysis
  - Intent to treat analysis
  - $H_0$: RR = 1 vs. $H_a$: RR < 1
Local research team

- PI
- Pharmacist
- Radiologist
- Nurse
- Research coordinator
Proposed budget

- Treatment arm (6 patients)
  - $6,000 per patient
  - Enoxaparin, ultrasound, other study-related tests
  - Personnel support
  - Indirect cost

- Control arm (6 patients)
  - $2,500 per patient
  - Ultrasound, other study-related tests
  - Personnel support
  - Indirect cost

- Observation arm (8 patients)
  - $250 per patient
  - Personnel support (limited data collection)
  - Indirect cost

- Additional support
  - $4,000 start up cost in Year 1
  - $1,200 maintenance cost in Years 2-4
  - $1,500 closing cost in Year 5