Πνευμονική Εμβολή
Αντιπηκτική αγωγή 2018 (και στο μέλλον)

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Disclosures

Lecture & Consultancy Honoraria: Actelion, Bayer HealthCare, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Pfizer – Bristol-Myers Squibb, Biocompatibles Group UK

Institutional research support: Bayer HealthCare, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Pfizer, Actelion
1) Prolonged primary prevention of VTE in hospitalized medically ill patients: the end of the road?

2) Contemporary anticoagulation for acute VTE: Benefits for all patients, and for specific patient groups

3) Extended anticoagulation for secondary prevention: A change of paradigm
Trials on prolonged VTE prophylaxis for hospitalized patients - 1

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Enoxaprin</td>
<td>Apixaban</td>
<td>Rivaroxaban</td>
<td>Betrixaban</td>
</tr>
<tr>
<td><strong>Primary efficacy outcome</strong></td>
<td><strong>Asymptomatic proximal DVT and symptomatic VTE through Day 28</strong>&lt;br&gt; Enoxaparin: 2.5 %&lt;br&gt; Placebo: 4 %</td>
<td><strong>Idem through Day 30</strong>&lt;br&gt; Apixaban: 2.7 %&lt;br&gt; Enox/placebo: 3.1 %</td>
<td><strong>Idem at d10 and d35</strong>&lt;br&gt; Rivaroxaban: 4.4 % on d35&lt;br&gt; Enoxaparin/placebo: 5.7 % on d35</td>
<td><strong>Idem through d35</strong>&lt;br&gt; Betrixaban: 6.9 %&lt;br&gt; Enox/placebo: 8.5 %&lt;br&gt; <em>(P=0.054 in cohort 1, D-dimers only)</em></td>
</tr>
<tr>
<td><strong>Principal safety outcome</strong></td>
<td><strong>Major bleeding</strong>&lt;br&gt; Enoxaparin: 0.8 %&lt;br&gt; Placebo: 0.3 %</td>
<td>Apixaban: 0.5 % <em>major</em>, 2.7 % CRNM&lt;br&gt; Enox/placebo: 0.2% <em>major</em>, 2.1 % CRNM</td>
<td>Major/CRNM bleeding, d35&lt;br&gt; Rivaroxaban: 4.1 %&lt;br&gt; Enox/placebo: 1.7 %</td>
<td>Major bleeding&lt;br&gt; Betrixaban: 0.7 %&lt;br&gt; Enox/placebo: 0.6 %&lt;br&gt; <em>(P=0.55 in overall population)</em></td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>5,963</td>
<td>6,758</td>
<td>8,101</td>
<td>6,850</td>
</tr>
</tbody>
</table>

### Trials on prolonged VTE prophylaxis for hospitalized patients - 2

<table>
<thead>
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<tbody>
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<td><strong>Drug</strong></td>
<td>Enoxaprin</td>
<td>Apixaban</td>
<td>Rivaroxaban</td>
<td>Betrixaban</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>40 mg o.d.</td>
<td>2.5 mg b.i.d.</td>
<td>10 mg o.d.</td>
<td>80 mg o.d.</td>
</tr>
<tr>
<td><strong>Dose ▼ in selected pts</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes (CrCl 15-30 ml/min, P-gp)</td>
</tr>
<tr>
<td><strong>Timing of Rx</strong></td>
<td>In hospital</td>
<td>In hospital</td>
<td>In hospital</td>
<td>In hospital</td>
</tr>
<tr>
<td><strong>RAM for eligibility</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>D-dimers for eligibility</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Treatment duration</strong></td>
<td>28±4 d after initial 10±4 d</td>
<td>30 d</td>
<td>35±4 d</td>
<td>35-42 d</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Placebo</td>
<td>Enoxaparin ≥6 d</td>
<td>Enoxaparin 10±4 d</td>
<td>Enoxaparin 6-14 d</td>
</tr>
<tr>
<td><strong>Double-blind design</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
VTE prevention in the medically ill: Rivaroxaban (MARINER)

**Official study title:** Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thromboembolism Risk

**Objective:** efficacy and safety of rivaroxaban in reducing post-discharge VTE risk in high-risk medically ill patients

**Population:** Medically ill patients at risk of VTE after hospital discharge

**Short design:** Multicentre, prospective, randomized, double-blind, placebo-controlled, event-driven study

**Indication:** VTEp Med Ill

**FPFV:** Q2-14

**LPLV:** Q1-17

*Patients with CrCl 30–49 ml/min

www.clinicaltrials.gov/ct2/show/NCT02111564

MARINER vs previous VTE prophylaxis studies

- Validated VTE risk score for hospitalized patients
- Combination with D-dimer levels
- Randomization at hospital discharge
- 45-day treatment period
- Efficacy outcome includes only symptomatic VTE
- Rivaroxaban dosage reduction (7.5 mg od) in renal impairment

Modified IMPROVE VTE score

<table>
<thead>
<tr>
<th>VTE Risk Factor</th>
<th>VTE Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>3</td>
</tr>
<tr>
<td>Known thrombophilia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>Current lower limb paralysis or paresis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>History of cancer&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>ICU/CCU stay</td>
<td>1</td>
</tr>
<tr>
<td>Complete immobilisation&lt;sup&gt;d&lt;/sup&gt; ≥ 1 day</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>1</td>
</tr>
</tbody>
</table>

Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score ≥4, or a score of 2 or 3 plus elevation of D-dimer levels >2x ULN

MARINER results

A Symptomatic VTE or VTE-Related Death

Hazard ratio, 0.76 (95% CI, 0.52–1.09)

P = 0.14

B VTE-Related Death

Hazard ratio, 0.93 (95% CI, 0.62–1.42)

C Death from Any Cause

Hazard ratio, 0.80 (95% CI, 0.58–1.09)

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Clinical suspicion of PE

Shock / Hypotension?

Yes
- Diagnostic algorithm as for suspected high-risk PE
  - PE confirmed

No
- Diagnostic algorithm as for suspected not high-risk PE
  - PE confirmed
    - Assess clinical risk (PESI or sPESI)
      - PESI Class III-V or sPESI ≥1
        - Intermediate risk
          - RV function (echo or CT)
            - Laboratory testing
              - One positive or both negative
                - Intermediate-low risk
                  - A/C; hospitalization
              - Both positive
                - Intermediate-high risk
                  - A/C; monitoring: consider rescue reperfusion
        - Intermediate risk
          - Consider further risk stratification
      - PESI Class I-II or sPESI = 0
        - Low risk
          - A/C; consider early discharge and home treatment, if feasible
  - PE confirmed

Intermediate risk

High risk
- A/C; Primary reperfusion

Intermediate-high risk
- A/C; monitoring: consider rescue reperfusion

Intermediate-low risk
- A/C; hospitalization

Low risk
- A/C; hospitalization

Current (2018) anticoagulation regimens for PE and DVT

Initial treatment schemes with non-VKA oral anticoagulants

**Single drug approach**
- **Rivaroxaban**: 15 mg bid × 21 days, then 20 mg od
- **Apixaban**: 10 mg bid × 7 days, then 5 mg bid

**Initial parenteral anticoagulation**
- **Dabigatran**: 150 mg bid OR **Edoxaban**: 60 mg od

**Traditional approach**
- **UFH, LMWH, fondaparinux**, ≥5 days
- **VKA (INR 2.0–3.0)**, ≥3 months

**Acute**
- **Overlap**

**Prevention**
- **Extended use**

- **Long-term secondary prevention**
  - **VKA (INR 2.0–3.0)**, indefinite with periodic assessment

ESC Guidelines, European Heart Journal 2014; doi:10.1093/eurheartj/ehu283
# Efficacy and safety of F Xa inhibitors in VTE

## Meta-analysis

### Efficacy and safety: rivaroxaban/apixaban/edoxaban

<table>
<thead>
<tr>
<th></th>
<th>Xa inhibitors n/N (%)</th>
<th>VKA n/N (%)</th>
<th>Risk ratio (95% CI)</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrent VTE</strong></td>
<td>211/10,877 (1.9)</td>
<td>246/10,888  (2.3)</td>
<td></td>
<td>0.86</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.72–1.03)</td>
<td></td>
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<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>111/10,924 (1.0)</td>
<td>187/10,927  (1.7)</td>
<td></td>
<td>0.56</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.36–0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>13/10,924 (0.1)</td>
<td>38/10,927   (0.3)</td>
<td></td>
<td>0.35</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.19–0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>6/10,924 (0.1)</td>
<td>20/10,927   (0.2)</td>
<td></td>
<td>0.32</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.13–0.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major GI</td>
<td>48/10,924 (0.4)</td>
<td>61/10,927   (0.6)</td>
<td></td>
<td>0.69</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.36–1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically relevant</td>
<td>755/10,924 (6.9)</td>
<td>937/10,927  (8.6)</td>
<td></td>
<td>0.80</td>
<td>0.13</td>
</tr>
<tr>
<td>non-major</td>
<td></td>
<td></td>
<td>(0.59–1.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net clinical benefit</td>
<td>327/10,877 (3.0)</td>
<td>431/10,888  (4.0)</td>
<td></td>
<td>0.76</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.65–0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>269/10,924 (2.5)</td>
<td>277/10,927  (2.5)</td>
<td></td>
<td>0.97</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.81–1.16)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial anticoagulation</th>
<th>ACCP recommendation</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute DVT or haemodynamically stable PE and no cancer</td>
<td>NOAC preferred to LMWH/VKA</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>LMWH/VKA preferred to LMWH alone</td>
<td>2C</td>
</tr>
<tr>
<td>PE with hypotension</td>
<td>Thrombolytic therapy (systemic rather than catheter-directed unless bleeding risk is high)</td>
<td>2B (2C)</td>
</tr>
<tr>
<td>DVT or PE with cancer</td>
<td>LMWH suggested over NOAC or VKA</td>
<td>2C</td>
</tr>
</tbody>
</table>

Kearon C et al, Chest 2016;149:315–352
Specific subgroups: **Low-risk PE**

Single oral drug and early discharge -> home treatment

- Haemodynamically stable patient admitted with clinically suspected PE:
  - **Start parenteral anticoagulation**
  - **Confirm PE within 24 hours of admission** (Chest CT, V/Q scan or pulmonary angiogram)
  - Enrolment after eligibility criteria verified and informed consent
  - **First dose of rivaroxaban in-hospital**
  - Additional baseline tests (echocardiography, CUS of leg veins)
    - recommended, not compulsory
  - **Discharge within 48 hours**

**3-month follow-up**

**Additional baseline tests (echocardiography, CUS of leg veins)**
- recommended, not compulsory

**CUS, compression ultrasound**

**HoT-PE**

EudraCT Nr. 2013-001657-28

++ Absence of RV dilatation/dysfunction
Absence of RA or RV thrombi

CUS, compression ultrasound
Specific subgroups: PE and cancer (Guidelines)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental PE in patients with cancer should be managed in the same manner as</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>symptomatic PE.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative D-dimer levels have the same negative diagnostic value as in non-cancer</td>
<td>Iia</td>
<td>B</td>
</tr>
<tr>
<td>patients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be</td>
<td>Iia</td>
<td>B</td>
</tr>
<tr>
<td>considered for the first 3 to 6 months.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with PE and cancer, extended anticoagulation (beyond the first</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>3 to 6 months) should be considered for an indefinite period or until the cancer</td>
<td></td>
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<tr>
<td>is cured.</td>
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</tbody>
</table>

Specific subgroups: Recent Hokusai VTE Cancer trial

Recurrent VTE (mITT, n=1046)

Major bleeding (mITT, n=1046)

Specific subgroups: Recent select-d trial

*15 mg bid for 21 days followed by 20 mg od; for patients with CrCl 30–49 ml/min dosing recommendations as in rivaroxaban SmPC; if a patient’s platelet counts falls to <50,000/mm³, rivaroxaban should be discontinued until the platelet count recovers to above 50,000/mm³. *200 IU/kg od for the first 30 days of treatment followed by 150 IU/kg od; if a patient’s platelet count falls to 50,000–100,000/mm³ the daily dose of dalteparin should be reduced by 2500 IU until platelet count returns to ≥100,000/mm³; if a patient’s platelet count falls to <50,000/mm³, dalteparin should be discontinued until the platelet count recovers to above 50,000/mm³

IIR, Investigator Initiated Research; FU, follow-up; R, randomization; RVT, residual vein thrombosis

http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/cancer/select-d/; EudraCT number: 2012-005589-37

Young AM, et al. J Clin Oncol 2018; Epub ahead of print
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## Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>In patients who receive extended anticoagulation, the risk-benefit ratio of continuing such treatment should be reassessed at regular intervals.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prophylaxis.</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

High risk of VTE recurrence – highly effective prevention by VKA

Cumulative incidence of VTE recurrence over time


**BUT:** Bleeding frequent and potentially dangerous while on chronic VKA treatment

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Clinical Impact of Bleeding in Patients Taking Oral Anticoagulant Therapy for Venous Thromboembolism
A Meta-Analysis

Lori Ann Linkins, MD, FRCPC; Peter T. Choi, MD, MSc, FRCP(C); and James D. Douketis, MD, FRCP(C)

33 studies; 10,757 patients; 4,374 patient-years of OAC

**After** the first 3 months of OAC:
- Major bleeding rate: **2.74%/yr**
- Intracranial bleeding: **0.65%/yr**
- Fatal bleeding rate: **0.63%/yr**
- Case fatality rate: **9.1%**

Recurrence versus bleeding risk (in the VKA era): What is done in clinical practice?

RIETE Registry (N=6944)

Safety and efficacy of extended prophylaxis with *half-dose* apixaban: AMPLIFY-EXT

- Two doses of apixaban (2.5 mg and 5 mg, twice daily) versus placebo
- Pts with VTE who had completed 6-12 months of anticoagulation
- study drugs were given for 12 months
- 2482 pts included in ITT
- **Primary EP:** 8.8% in placebo vs. 1.7% in EACH apixaban dose

**Major / CRNM bleeding:**
2.7% vs. 3.2% (2.5 mg) vs. 4.3% (5 mg)

Safety and efficacy of extended prophylaxis with standard-dose vs half-dose rivaroxaban: EINSTEIN Choice

Efficacy*

<table>
<thead>
<tr>
<th></th>
<th>Cumulative incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 20 mg od vs ASA</td>
<td>17/1107 (1.5%) vs 50/1131 (4.4%)</td>
</tr>
<tr>
<td>Rivaroxaban 10 mg od vs ASA</td>
<td>13/1127 (1.2%) vs 50/1131 (4.4%)</td>
</tr>
<tr>
<td>HR=0.34 (95% CI 0.20–0.59), p=0.001</td>
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</table>

Major bleeding#

<table>
<thead>
<tr>
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<th>Cumulative incidence (%)</th>
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<td>HR=0.34 (95% CI 0.20–0.59), p=0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Intention-to-treat analysis; #safety analysis; ‡no events after Day 360 up to Day 480

STOP after 3 months:
PE provoked by a **strong reversible** risk factor
- Major, especially orthopaedic surgery (anaesthesia > 30 min)
- Major trauma with/without surgical treatment
- Immobilisation in hospital for acute severe illness

CONTINUE: All other transient or permanent factors
- More than one VTE event (without strong reversible factor)
- Cancer
- Antiphospholipid syndrome **(only VKA)!**
- Inflammatory bowel disease
- Active autoimmune disease
- Family history of VTE, or major hereditary thrombophilia
- Minor surgery (anaesthesia < 30 min), or (leg) trauma
- Long-haul flight
- Oestrogen contraception or replacement therapy
- Male sex
- Age
- Obesity (BMI > 30 kg/m²)
- Location of index VTE: PE or proximal DVT (not distal DVT)
- **No identifiable risk factor!**
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.

For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.

Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.

In patients who receive extended anticoagulation, the risk-benefit ratio of continuing such treatment should be reassessed at regular intervals.

In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prophylaxis.

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Future targets of anticoagulants?
Targeting coagulation factor XI and XII


Targeting coagulation factor XI

- Patients with congenital F XI deficiency protected from VTE and ischemic stroke
- Subjects with higher levels of F XI at greater risk for VTE and ischemic stroke than those with lower levels
- Levels of factor XI correlate with stroke risk in women taking oral contraceptives

- 300 patients for elective primary TKA to of FXI-ASO (200 mg or 300 mg) or 40 mg of enoxaparin once daily
- Tx with FXI-ASO initiated 36 days before surgery: three s.c. doses on days 1, 3, and 5; once-weekly doses on days 8, 15, 22, and 29. On day 36, the day of surgery, one dose 6 hours postoperatively; a final dose on day 39
- **Primary efficacy outcome**: VTE by mandatory bilateral venography or symptomatic: 27% vs 4% vs 30%
- **Principal safety outcome**: major or clinically relevant nonmajor bleeding: 3% vs 3% vs 8%

Weitz JI. *Thromb Res* 2017;140 (Suppl 2):S40-S45

Potential indications for targeting coagulation factor XI or XII

- Elective knee arthroplasty *(proof of principle)*
- Secondary prevention of venous thromboembolism *(safety, convenience)*
- Stroke prevention in atrial fibrillation patients with end stage renal disease on dialysis *(unmet medical need for efficacy and safety!)*
- Extracorporeal membrane oxygenation, left ventricular assist devices or mechanical heart valves -> F XII *(unmet medical need in the NOAC era!)*