Kearon trained as a respirologist and obtained a Ph.D. from McMaster University for studies relating to respiratory and exercise physiology. He is a Professor in the Department of Medicine, an Associated Member in the Department of Health Research Methods, Evidence, and Impact at McMaster University, Career Investigator of the Heart and Stroke Foundation of Ontario, Program Director of the Clinician Investigator Program, and holds the Jack Hirsh Professorship in Thromboembolism at McMaster University. He has received awards from the Canadian Institutes of Health Research for providing mentorship in the design and conduct of randomized controlled trials, and the International Society on Thrombosis and Haemostasis’ 14th Biennial Investigator Recognition Award.

OBJECTIVES:
Participants should be better able to:

1. Understand how clinical controversy arises
2. Appreciate the limitations of age-adjusted D-dimer interpretation
3. Have a strategy for deciding with subsegmental PE should be treated
4. Understand indications for thrombolysis in patients with PE
5. Understand the evolving role of DOAC therapy for cancer associated thrombosis

SATURDAY, MARCH 24, 2018   11:15 AM
Controversies in Thromboembolic Disease

NAMDRC 2018, Carlsbad
22 March 2018

Clive Kearon, McMaster University, Canada

Relevant Disclosures

| Research Support/P.I.                     | CIHR  
|                                          | NIH 
|                                          | Bayer Inc.  
| Employee                                 | No relevant  
| Consultant                               | Bayer  
|                                          | BMS  
|                                          | Stago  
| Major Stockholder                        | No relevant  
| Speakers Bureau                          | No relevant  
| Honoraria                                | No relevant  
| Scientific Advisory Board                | No relevant  

“Intellectual COIs”

Primary research

• Diagnostic testing for VTE
• Treatment of VTE

ACCP VTE treatment guidelines

Controversy

“A state of prolonged public dispute or debate, usually concerning a matter of conflicting opinion”
Controversy

“A state of prolonged public dispute or debate, usually concerning a matter of conflicting opinion”

“Resulting in important differences in practices“

Question 1

Most important reason for Clinical Controversy is:

A. Differences in treatment resources
B. Lack of good evidence
C. Finely balanced risk and benefits of alternatives
D. Differences in patient's values and preferences
Clinical Controversy

No clear benefit of “A” vs. “B”

(“B” may be “control” or “another active therapy”)
Clinical Controversy

No clear benefit of “A” vs. “B”

(“B” may be “control” or “another active therapy”)

Usually: Low quality evidence

Occasionally: High quality evidence but risks & benefits are finely balanced and “different physician philosophies”

Grading of Recommendations
Grading of Recommendations

**Strength (For or Against)**

**Grade 1: STRONG**
*(stated as: “We recommend…”)*
- clear benefit
- applies to most
- “just do it”

**Grade 2: WEAK**
*(stated as: “We suggest…”)*
- not large benefit or
- uncertain benefit

Decision strongly influenced by:
- clinical differences
- patient preference

---

“Conditional”
or
“Discretionary”
Grading of Recommendations

Strength *(For or Against)*

**Grade 1: STRONG**
*(stated as: “We recommend…”)*
- clear benefit
- applies to most
- “just do it”

Apply to ≥ 90%

**Grade 2: WEAK**
*(stated as: “We suggest…”)*
- not large benefit or
- uncertain benefit

Decision strongly influenced by:
- clinical differences
- patient preference

Apply to 67-90%

“*my interpretation*”
*(not GRADE or ACCP!)*

---

**Areas of controversy**
### Grading of Recommendations

#### Strength *(For or Against)*

**Grade 1: STRONG**

*(stated as: "We recommend…")*
- clear benefit
- applies to most
- “just do it”

**Grade 2: WEAK**

*(stated as: "We suggest…")*
- not large benefit or
- uncertain benefit

Decision strongly influenced by:
- clinical differences
- patient preference

#### Quality of Evidence

**Grade A (High)**
Randomized Trials
- Precise (narrow CIs) and
- Bias very unlikely and
- Consistent

**Grade B (Moderate)**
Randomized Trials
- Less precise (wider CIs) or
- Bias likely but not major or
- Inconsistent

**Grade C (Low)**
Randomized Trials
- Major limitations
Observational Studies (only)
- not very strong or exceptional

---

### Guidelines & Controversial Topics

*should make “weak recommendations”*
My perspective

ACCP Guidelines
• Treatment and no major new evidence

Personal perspective
• Treatment and major new evidence
• Diagnostic testing for VTE

Controversial topics

Diagnosis
• Age adjusted D-dimer interpretation

Treatment
• Subsegmental PE treatment
• Systemic lysis for intermediate risk PE
• Catheter directed thrombolysis for PE
• IVC filters for severe PE
• DOACS for cancer associated VTE
Age Adjusted D-dimer for exclusion of VTE

Question 2

Age Adjusted D-Dimer interpretation for PE:
A. Is safe
B. Reduces the need for CT scanning
C. Is non-specific and may be suboptimal
D. All of the above
To get more out of D-dimer

Subgroups in which VTE excluded using a higher D-dimer threshold
(higher specificity, but Negative PV preserved)
To get more out of D-dimer

Subgroups in which VTE excluded using a higher D-dimer threshold
(higher specificity, but Negative PV preserved)

Two ways proposed

“Age-adjusted” D-dimer threshold

Theory: Because D-dimer increases with age, can use higher threshold in elderly
“Age-adjusted” D-dimer threshold

**Theory:** Because D-dimer increases with age, can use higher threshold in elderly

- ≤50 years
  - Threshold 500ug/L
- >50 years
  - Threshold = age x 10 ug/L
  - e.g. 78 years x 10 = 780ug/L

---

**D-dimer Threshold According to Age**

![Graph showing age-adjusted D-dimer threshold according to age](image-url)
“Age-adjusted” D-dimer threshold

Supported by:
Many retrospective analyses for DVT and PE

“Non-high C-PTP” & “D-dimer 500 to Age x 10”
• Prevalence: 337/3346 (10.1%)
• VTE at 3 mo: 1/331 (0.3%, 95%CI 0.1 – 1.7)

Righini for ADJUST-PE JAMA 2014
“Age-adjusted” D-dimer threshold

Sounds logical (superficially)

But illogical

- lower specificity doesn’t justify lower sensitivity
- prevalence of VTE increases with age

D-dimer Threshold According to Age

(mean D-dimer cut-off designed to be the same for the 3 strategies [640])
“Age-adjusted” D-dimer threshold

Sounds logical (superficially)

But illogical
- lower specificity doesn’t justify lower sensitivity
- prevalence of VTE increases with age

Comppared to:
- Standard (<500 in everyone): Better
- Mean for age-adjusted in everyone: Same
- Opposite of age-adjusted: Same
- Clinical probability-adjusted: Worse

Takash Lapner J Tromb Haemost 2016 and Thromb Haemost 2017

Second way to “get more out of” D-dimer

Which we believe is better than “age-adjusted” interpretation
“C-PTP-adjusted” D-dimer threshold

Theory: Because less VTE with low C-PTP, can exclude VTE with much higher D-dimer
Predictive value of different D-dimer levels

Trend p = 0.009

Takach Lapner ASH poster 2013
Predictive value of different D-dimer levels

Trend $p = 0.009$

Likelihood ratio

Prevalence %

D-Dimer (μg/L)

~1,300
Predictive value of different D-dimer levels

```
<table>
<thead>
<tr>
<th>Prevalence %</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low C-PTP</td>
<td>Threshold 1,000ug/L</td>
</tr>
<tr>
<td>Moderate C-PTP</td>
<td>Threshold 500ug/L</td>
</tr>
</tbody>
</table>
```

**Theory:** Because less VTE with low C-PTP, can exclude VTE with much higher D-dimer

- **Low C-PTP:** Threshold 1,000ug/L
- **Moderate C-PTP:** Threshold 500ug/L

2-fold difference
“C-PTP-adjusted” D-dimer threshold

Supported by:

Some retrospective analyses for DVT and PE

One randomized trial in suspected DVT

“Low C-PTP CPTP” & “D-dimer 500 to 999”

• Prevalence in outpatients: 169/1422 (11.9%)
• VTE at 3 mo: 0/169 (0%, 95%CI 0.0 – 2.2)
• RCT comparison: -0.3% (95%CI -1.8 to 0.8)

Linkins for SELECT Ann Intern Med 2013
Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study

Van der Hulle for YEARS, Lancet 2017

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other more likely diagnosis</td>
<td>3</td>
</tr>
<tr>
<td>Signs &amp; Symptoms of DVT (tender/swelling)</td>
<td>3</td>
</tr>
<tr>
<td>Active cancer</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization / Surgery &lt;4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Heart rate &gt; 100/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
</tbody>
</table>

Total points

**Clinical Assessment:**

- Low or Unlikely: < 4.5
- Moderate: 4.5-6
- High: > 6

*Wells, Thromb Haemost 2000*
<table>
<thead>
<tr>
<th>Clinical Items*</th>
<th>Clinical Prob.</th>
<th>D-dimer Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs of DVT</td>
<td>0 = Low</td>
<td>1,000 ug/L</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1-3 = Not Low</td>
<td>500 ug/L*</td>
</tr>
<tr>
<td>PE most likely</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Dropped from Wells Rule:
HR >100; Surgery <4 wks;
Hx VTE; Cancer

* even if High C-PTP

3616 pts: 86% outpatients; 10% Hx. VTE

Van der Hulle for YEARS, Lancet 2017
Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study

3616 pts: 86% outpatients; 10% Hx. VTE

**Clinical Items**
- Signs of DVT
- Haemoptysis
- PE most likely

**Clinical Prob.**
- 0 = Low
- 1-3 = Not Low

**D-dimer Cutoff**
- 1,000 ug/L
- 500 ug/L*

* Dropped from Wells Rule:
  - HR >100; Surgery <4 wks;
  - Hx VTE; Cancer

* even if High C-PTP

Van der Hulle for YEARS, Lancet 2017

**Results – YEARS study**

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<th>Low C-PTP</th>
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<td>1743 (50%)</td>
<td>1722 (50%)</td>
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Van der Hulle for YEARS, Lancet 2017
**Results – YEARS study**

**Low C-PTP**
- 1743 (50%)

**D-dimer <1,000**
- 1320 (76%)

**4 VTE**
- 0.3% (0.1 - 0.8)

**Not-Low C-PTP**
- 1722 (50%)

---

**Results – YEARS study**

**Low C-PTP**
- 1743 (50%)

**D-dimer <500**
- 331 (19%)

**3 VTE***
- 1.2% (0.5 – 3.1)

*baseline violation

---

*Van der Hulle for YEARS, Lancet 2017*
Results – YEARS study

Low C-PTP
1743 (50%)

D-dimer <1,000
1320 (76%)

4 VTE
0.3% (0.1 - 0.8)

Not-Low C-PTP
1722 (50%)

D-dimer <500
331 (19%)

3 VTE*
1.2% (0.5 – 3.1)

7 VTE
0.4% (0.2 - 0.9)

*baseline violation

Van der Hulle for YEARS, Lancet 2017

13% PE
scheduled testing

scheduled testing
Subsegmental PE (SSPE)

Question 3

Subsegmental PE:
A. Are usually incidental findings on CT scans
B. Should not be treated
C. Must have proximal DVT excluded if not treating
D. Should be treated
Subsegmental PE (SSPE)

Should these patients be anticoagulated?
SSPE on CT

~15% of PE

Accuracy of CT for SSPE
Sensitivity: ~50%  Specificity: uncertain
PPV: ~25-33%

Cause of “SSPE”
• Symptomatic PE (true-positives)
• Artifacts (false-positives)
• Incidental asymptomatic PE

Routine CTPA 24-36hrs after Knee or Hip Replacement

Gandhi J Arthroplasty 2012
Routine CTPA 24-36hrs after Knee or Hip Replacement

<table>
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<td>Knee (n=27)</td>
<td>41%</td>
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<tr>
<td>Hip (n=21)</td>
<td>5%</td>
</tr>
</tbody>
</table>

Most proximal
- Main (1)
- Lobar (5)
- Segmental (5)
- Subsegmental (0)

No patient with incidental PE was:
- Treated for PE
- Had PE/DVT diagnosed in next 3 mo

Symptoms and signs same in PE +ve vs. –ve patients

Gandhi J Arthroplasty 2012
Routine CTPA 24-36hrs after Knee or Hip Replacement

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Most proximal
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No patient with incidental PE was:
- Treated for PE
- Had PE/DVT diagnosed in next 3 mo

Symptoms and signs same in PE +ve vs. –ve patients

Many PE after knee surgery are incidental/unimportant!

Subsegmental PE (SSPE)

( must exclude proximal DVT if not anticoagulating)
Subsegmental PE (SSPE)
*(must exclude proximal DVT if not anticoagulating)*

ACCP recommendations based primarily on assessment of risk of recurrence without anticoagulation

SSPE & Recurrence Risk

**Convincing for SSPE**
- good quality CTPA
- surrounded by contrast
- multiple
- larger (≥1 image/projection)
- Symptomatic, high CPTP

  D-dimer elevated (marked, unexplained)
### SSPE & Recurrence Risk

**Convincing for SSPE**
- good quality CTPA
- surrounded by contrast
- multiple
- larger (≥1 image/projection)
- Symptomatic, high CPTP

D-dimer elevated (marked, unexplained)

**Higher risk for progression**
- hospitalized/immobile
- active cancer
- no reversible RF

**Others that favor no anticoagulation**
- High bleeding risk;
- Good cardiopulmonary reserve
- Patient preference
SSPE & Recurrence Risk

**Convincing for SSPE**
- good quality CTPA
- surrounded by contrast
- multiple
- larger (≥1 image/projection)
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D-dimer elevated (marked, unexplained)

**Higher risk for progression**
- hospitalized/immobile
- active cancer
- no reversible RF

**Others that favor no anticoagulation**
High bleeding risk; Good cardiopulmonary reserve
Patient preference

Subsegmental PE (SSPE)
*(must exclude proximal DVT if not anticoagulating)*

**Lower Risk Recurrence**
Clinical surveillance over anticoagulation  
*Grade 2C*  
*(may repeat proximal US at 1 ± 2 wks)*

**Higher Risk Recurrence**
Anticoagulation over clinical surveillance  
*Grade 2C*
Systemic lysis for intermediate risk PE

Thrombolysis for PE

Balancing Rapid Resolution and Bleeding
Indications for Lytic Therapy in PE

**Lysis indicated**
- Impending cardiac arrest

**Lysis not indicated**
- PE is not severe
  - symptoms not severe
  - vital signs are normal
  - no signs of right heart failure
  - clinically well perfused
  - not “massive PE” on imaging

~5% of patients

Risk:Benefit Uncertain
- Severity of PE
- Risk of Bleeding

~50% of patients
PE Severity and Mortality

Sudden death
Cardiac arrest
Shock

Mortality (%)

Emboli size
Cardiopulmonary status

Wood KE. Chest 2002

Uncertain if sick enough for lytic Rx?
PE and Systemic Thrombolysis

AT9

No hypotension (BP ≥90 mmHg)  No Lysis  Grade 1C
Hypotension & Not High Bleeding Risk  Lysis  Grade 2B

Fibrinolysis for Intermediate-Risk PE

- RVD (echo or CTPA)  +  Myocardial injury (troponin I or T)
- 1006 patients (tenecteplase ~0.5 mg or 100 U/kg)

<table>
<thead>
<tr>
<th>7 days</th>
<th>Tenect.</th>
<th>Placebo</th>
<th>Diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>6</td>
<td>9</td>
<td>-6</td>
</tr>
<tr>
<td>PE</td>
<td>1</td>
<td>7</td>
<td>-6</td>
</tr>
<tr>
<td>Bleeding</td>
<td>5</td>
<td>0</td>
<td>+5</td>
</tr>
<tr>
<td>Non-fatal Strokes</td>
<td>7</td>
<td>1</td>
<td>+6</td>
</tr>
<tr>
<td>Major Bleeds</td>
<td>58</td>
<td>12</td>
<td>+46</td>
</tr>
<tr>
<td>Cardio Decomp.</td>
<td>8</td>
<td>25</td>
<td>-17</td>
</tr>
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Meyer, PEITHO, NEJM 2014
### Fibrinolysis for Intermediate-Risk PE

- **RVD** (echo or CTPA) + **Myocardial injury** (troponin I or T)
- **1006 patients** (tenecteplase ~0.5 mg or 100 U/kg)

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</tr>
</tbody>
</table>

*Meyer, PEITHO, NEJM 2014*
Mortality with Thrombolysis vs. Anticoagulation alone for PE

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>No. of Patients</th>
<th>OR (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>URETSG, 1970</td>
<td>6</td>
<td>92</td>
<td>7</td>
<td>78</td>
<td>0.80 (0.26-2.43)</td>
<td>20.2</td>
</tr>
<tr>
<td>Triburt et al., 1974</td>
<td>0</td>
<td>13</td>
<td>1</td>
<td>17</td>
<td>0.17 (0.00-0.94)</td>
<td>1.6</td>
</tr>
<tr>
<td>Le et al., 1978</td>
<td>1</td>
<td>14</td>
<td>2</td>
<td>11</td>
<td>0.37 (0.03-1.90)</td>
<td>4.5</td>
</tr>
<tr>
<td>Marin et al., 1988</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>10</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Lavine et al., 1990</td>
<td>1</td>
<td>33</td>
<td>0</td>
<td>25</td>
<td>5.80 (1.11-32.40)</td>
<td>1.6</td>
</tr>
<tr>
<td>PROPEL, 1990</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>4</td>
<td>4.34 (0.56-36.30)</td>
<td>1.4</td>
</tr>
<tr>
<td>Delta-Vento et al., 1992</td>
<td>2</td>
<td>20</td>
<td>1</td>
<td>16</td>
<td>1.61 (0.15-16.82)</td>
<td>4.7</td>
</tr>
<tr>
<td>Goldhaber et al., 1993</td>
<td>0</td>
<td>46</td>
<td>2</td>
<td>55</td>
<td>0.16 (0.01-2.57)</td>
<td>3.3</td>
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<tr>
<td>Jerges-Sanchez et al., 1995</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>0.03 (0.00-0.40)</td>
<td>3.8</td>
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<tr>
<td>Kostas et al., 2002</td>
<td>4</td>
<td>118</td>
<td>3</td>
<td>138</td>
<td>1.58 (0.35-7.00)</td>
<td>11.4</td>
</tr>
<tr>
<td>TIPS, 2010</td>
<td>0</td>
<td>28</td>
<td>1</td>
<td>30</td>
<td>0.14 (0.00-7.31)</td>
<td>1.7</td>
</tr>
<tr>
<td>Fusillo et al., 2011</td>
<td>0</td>
<td>37</td>
<td>6</td>
<td>35</td>
<td>0.11 (0.02-0.58)</td>
<td>9.3</td>
</tr>
<tr>
<td>NOPEET, 2012</td>
<td>1</td>
<td>61</td>
<td>3</td>
<td>60</td>
<td>0.35 (0.05-2.57)</td>
<td>6.5</td>
</tr>
<tr>
<td>ULMADD, 2013</td>
<td>0</td>
<td>30</td>
<td>1</td>
<td>29</td>
<td>0.11 (0.00-5.95)</td>
<td>1.7</td>
</tr>
<tr>
<td>TOPCAT, 2014</td>
<td>1</td>
<td>40</td>
<td>1</td>
<td>43</td>
<td>1.68 (0.07-17.51)</td>
<td>3.3</td>
</tr>
<tr>
<td>PEITHO, 2014</td>
<td>6</td>
<td>506</td>
<td>9</td>
<td>499</td>
<td>0.66 (0.24-1.82)</td>
<td>24.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>23</td>
<td>1001</td>
<td>41</td>
<td>1034</td>
<td>0.33 (0.32-0.88)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 36.51, P = 0.001, I^2 = 51$
Overall effect: $z = 2.45, P = 0.01$

16 studies; 3176 patients; heterogeneity P=0.28
Risk: Low = 10%; Moderate = 71%; High = 1.5%; uncertain =18%

OR 0.53 (0.32, 0.88)

Other findings of note

**Major Bleeding** OR 2.7 (9.2% vs. 3.4%)

**Intracranial Bleeds** OR 4.6 (1.5% vs. 0.2%)

**Recurrent VTE** OR 0.40 (1.2% vs. 3.0%)

“**Net clinical benefit**” 0.8% better for lytics

**Subgroups** Overall, possibly better if <65yrs

**Sensitivity analyses** Robust

Chatterjee JAMA 2014
PE and Systemic Thrombolysis

AT10

No hypotension (BP ≥90 mmHg) No Lysis Grade 1B
Hypotension & Not High Bleeding Risk Lysis Grade 2B

Selected patients who deteriorate but not yet hypotensive & low bleeding risk (with qualifying remark) Lysis Grade 2C
Can CDT achieve the benefits of systemic thrombolysis with a lower risk of bleeding?
Fibrinolysis for Intermediate-Risk PE

- RVD (echo or CTPA) + Myocardial injury (troponin I or T)
- 1006 patients (tenecteplase ~0.5 mg or 100 U/kg)

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<td>Death</td>
<td>6</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>1</td>
<td>7</td>
<td>-6</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>5</td>
<td>0</td>
<td>+5</td>
<td></td>
</tr>
<tr>
<td>Non-fatal Strokes</td>
<td>7</td>
<td>1</td>
<td>+6</td>
<td></td>
</tr>
<tr>
<td>Major Bleeds</td>
<td>58</td>
<td>12</td>
<td>+46</td>
<td></td>
</tr>
<tr>
<td>Cardio Decomp.</td>
<td>8</td>
<td>25</td>
<td>-17</td>
<td></td>
</tr>
</tbody>
</table>

Meyer, PEITHO, NEJM 2014
If yes

High risk PE
• CDT preferred over systemic lysis

Intermediate risk PE
• CDT preferred over anticoagulation alone

CDT for PE: RCT vs. No CDT

Kucher for ULTIMA Circ 2014
CDT for PE: RCT vs. No CDT

59 pts; 8 centers;
Main or lobar PE; RV/LV >1.0

IV UFH for all

**US-assisted CDT (EKOS)**

rtPA per lung: 1 mg/h x 5h, 0.5 mg/h x 10h
rtPA total: 10mg or 20 mg (1 or 2 lungs)

*Kucher for ULTIMA Circ 2014*

---

**Results - ULTIMA**

<table>
<thead>
<tr>
<th></th>
<th>CDT</th>
<th>No CDT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RV/LV decrease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hours</td>
<td>0.30</td>
<td>0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>90 days</td>
<td>0.35</td>
<td>0.24</td>
<td>0.07</td>
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<td>11.6</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Cardio decomp. 90d</strong></td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Major Bleeds 90d</strong></td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Minor Bleeds 90d</strong></td>
<td>3</td>
<td>1</td>
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CDT for PE: Before/After comparison

150 pts; Main or lobar PE; RV/LV >0.9
Hypotensive/syncope in 31 (21%); 22 centers;

**US-assisted CDT (EKOS)**
rtPA 24 mg
over 12h (2 lungs; 86%) or 24h (1lung; 14%)
IVC Filter in 16%

*Piazza for SEATTLE II JACC CI 2015*
Results – SEATTLE II

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV/LV (48h; n=115)</td>
<td>1.55</td>
<td>1.13</td>
<td>-0.42 (27%)*</td>
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<tr>
<td>PAP(\text{mean}) (post &amp; 48h)</td>
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<td>37</td>
<td>-14 (28%)*</td>
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<tr>
<td>Miller Index (48h; n=115)</td>
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<td>16</td>
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<tr>
<td>Major Bleeds (transfused; &lt;72h)</td>
<td>15</td>
<td></td>
<td>(10%)</td>
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Death from PE: 1 pre and 1 post * P=<0.0001
### Results – SEATTLE II

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<td>No ICB or fatal</td>
</tr>
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Death from PE: 1 pre and 1 post  
* P=<0.0001

### Role of CDT for PE
Role of CDT for PE

Systemic Thrombolysis vs. CDT

If lysis, systemic over CDT  Grade 2C

CDT (or other catheter surgical removal) if:

- High bleeding risk
- Failed thrombolysis
- Impending death

&

- Expertise available
- Resources available

Grade 2C
IVC Filters for DVT or PE

Anticoagulated         No Filter*   Grade 1B
Not Anticoagulated   Filter        Grade 1B

(* may not apply to PE with hypotension)
IVC Filters for DVT or PE

**Anticoagulated**  
No Filter*  
Grade 1B

**Not Anticoagulated**  
Filter  
Grade 1B

(* may not apply to PE with hypotension)

But:  
PREPIC 2 suggests benefit is unlikely in this subgroup of PE patients

---

**IVCF vs. No IVCF if anticoagulated**  
PE + DVT + ≥1 severity factor (RVD in 2/3)

Studies: 1  
Participants: 399  
F-U & Temp IVCF: 3 mo

<table>
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<th>Qual Evid (GRADE)</th>
<th>Hazard Ratio</th>
<th>Difference Per 1,000</th>
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<td><strong>PE-sympt</strong>*</td>
<td>Mod</td>
<td>2.0 (0.51, 7.9)</td>
<td>+15 (-7, +104)</td>
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<td><strong>Mj Bleeding</strong></td>
<td>Mod</td>
<td>0.80 (0.32, 2.0)</td>
<td>-10 (-34, +49)</td>
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<tr>
<td><strong>Mortality</strong></td>
<td>Mod</td>
<td>1.25 (0.60, 2.6)</td>
<td>+15 (-24, +96)</td>
</tr>
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* Fatal PE: 6/6 vs 2/3  
Mismetti, PREPIC 2, JAMA 2015
## IVCF vs. No IVCF if anticoagulated

PE + DVT + ≥1 severity factor (RVD in 2/3)

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* Fatal PE: 6/6 vs 2/3  

Mismetti, PREPIC 2, JAMA 2015

### Choice of anticoagulant
Use of a DOAC for cancer associated thrombosis is NOT influenced by:

A. Patient preference
B. Presentation as PE vs. DVT
C. Presence of a GI malignancy
D. Drug costs
Choice of anticoagulant

No Cancer

Cancer (CAT)

Kearon et al. 10th ACCP Chest 2016

Choice of anticoagulant

No Cancer

NOAC over VKA  Grade 2B
VKA over LMWH  Grade 2C
### Choice of anticoagulant

**No Cancer**

<table>
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<tr>
<td>VKA over LMWH</td>
<td>2C</td>
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</table>

- similar efficacy
- ~2/3 major bleeding, ~1/2 ICB
- easier for patients

**Cancer**

<table>
<thead>
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<tr>
<td>LMWH over VKA</td>
<td>2B</td>
</tr>
<tr>
<td>over DOAC</td>
<td>2B</td>
</tr>
</tbody>
</table>
Choice of anticoagulant

- More effective
- Possibly safer

Cancer
LMWH over VKA  Grade 2B
over DOAC  Grade 2C

Choice of anticoagulant

- Probably (we thought) more effective
- Uncertain safety of NOACs in patients with active cancer

Cancer
LMWH over VKA  Grade 2B
over NOAC  Grade 2C
Choice of anticoagulant

Not Grade 1 for LMWH because:
- VKA/DOAC often reasonable (eg, no chemo, remission, non-metastatic, later)

Cancer
- LMWH over VKA Grade 2B
- over DOAC Grade 2B

Choice of anticoagulant

• Probably (we thought) more effective
• Uncertain safety of NOACs in patients with active cancer

Cancer
- LMWH over VKA Grade 2B
- LMWH over NOAC Grade 2C
**Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism**

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators

Edoxaban 60mg & LMWH 7d vs. Dalteparin 200/150 IU/kg

1050 patients; PE 63%; Symptomatic 68%; Metastatic 53%

Anticoagulated: 6 to 12 mo (Edox 211 vs. Dalt 184; P=0.01)

Follow-up ~12 mo

*Raskob & Hokusai VTE Cancer NEJM 2017*

---

**Recurrent VTE**

![Recurrent VTE graph](image)

RR 0.70 (0.45, 1.02)

Dalteparin 11.3%

Edoxaban 7.9%

*Raskob & Hokusai VTE Cancer NEJM 2017*
Major Bleeding

RR 1.72 (1.02, 2.91)

Edoxaban 6.9%
Dalteparin 4.0%

Days

0 30 60 90 120 150 180 210 240 270 300 330 360

Raskob & Hokusai VTE Cancer NEJM 2017

Major Bleeding

RR 1.72 (1.02, 2.91)

Edoxaban 6.9%
Dalteparin 4.0%

Days

0 30 60 90 120 150 180 210 240 270 300 330 360

Cancer type | Edoxaban | Dalteparin
--- | --- | ---
GI cancer (25%) | 13.2% | 2.4%
No GI cancer (75%) | 4.7% | 4.5%

P= 0.02 for difference

Raskob & Hokusai VTE Cancer NEJM 2017
Major Bleding

![Graph showing Major Bleding percentage over time for Edoxaban and Dalteparin.](image)

**Cancer type** | Edoxaban | Dalteparin | P-value
---|---|---|---
GI cancer (25%) | 13.2% | 2.4% | 0.02
No GI cancer (75%) | 4.7% | 4.5% |

**Rivaroxaban vs. LMWH for CAT**

**SELECT-D Study**

Rivaroxaban 15 BID / 20 OD vs. Dalteparin 200/150 /kg

406 patients; symptomatic 47%; metastatic 59%

Follow-up: 6 mo

*Young et al: ASH 2017; [clinical trialresults.org/slides/SELECT-D_young.pdf](https://clinicaltrialresults.org/slides/SELECT-D_young.pdf)*
<table>
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<tr>
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<th>LMWH n=203</th>
<th>RR (95% CI)</th>
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<td><strong>VTE Recurrence</strong></td>
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<td>9%</td>
<td>0.4 (0.2 - 1.0)</td>
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<tr>
<td><strong>Major Bleeds</strong>*</td>
<td>5%</td>
<td>3%</td>
<td>1.8 (0.7 - 4.9)</td>
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<td><strong>Major &amp; CRNM Bl.</strong></td>
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* Most bleeds were GI
Amended to exclude upper GI cancers late in study
## Results: SELECT-D

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* Most bleeds were GI  
Protocol amended to exclude upper GI cancers late in study

## DOACS for CAT: conclusions

**Edoxaban or Rivaroxaban vs. LMWH**

- at least as effective as LMWH
- higher risk of bleeding  
  (but appears confined to patients with GI lesions)

“*Very acceptable alternative to LMWH if no GI lesions*”
**Take Home Messages**

**AADD:** Okay but (probably) not optimal

**SSPE:** Treat some but not all

**Systemic Lysis:**
- generally preferred over CDT
- if hypotensive (or impending)

**IVCF:** Not if anticoagulated

**CAT:** DOACS often a good alternative to LMWH