

# VTE prevention and COVID-19

**Dr Susie Shapiro**

Consultant Haematologist

Oxford University Hospitals NHS Foundation Trust

# Overview

- UK standard thromboprophylaxis for medical inpatients (pre-COVID era)
  - VTE risk and standard LMWH dosing
  - Weight adjusted LMWH dosing
  - Extended thromboprophylaxis
  - Role of mechanical thromboprophylaxis
- The concern with COVID – is this enough?
  - Rate of VTE in patients with COVID
- Interim guidelines
  - Risk stratification

# LMWH prophylaxis in medical inpatients

Trial	TP	VTE (%)	Bleeding (%)
MEDENOX <sup>1</sup>	Enoxaparin 40mg v placebo	<b>14.9 v 5.5</b> <b>RRR 63%</b> P<0.001	1.7 v 1.1
PREVENT <sup>2</sup>	Dalteparin 5000u v placebo	<b>5.0 v 2.8</b> <b>RRR 49%</b>	0.49 v 0.16 p=0.15

<sup>1</sup>Samama MM *et al. N Engl J Med* 1999;341:793–800

<sup>2</sup>Leizorovicz A *et al. J Circulation* 2004;110:874–9

# LMWH prophylaxis in ICU

- Higher baseline VTE
  - 28% without LMWH <sup>1</sup>
  - risk varies: reasons for admission to ICU, recent surgery, chronic disease
- Higher risk of bleeding
  - up to 80% of ICU patients have 1 or more episodes of bleeding though 95% is minor<sup>2</sup>
  - risk of major bleeding 2.7%, in the untreated arm of prophylaxis in ICU<sup>3</sup>

<sup>3</sup> ACCP Prevention of VTE in non-surgical patients 2012

<sup>2</sup> Arnold et al 2007 Clin Invest Med

<sup>1</sup> Fraisse et al 2000 Am J Respir Crit Care Med

# LMWH prophylaxis in ICU

Trial	TP	VTE (%)	Major Bleeding (%)
<p><b>PROTECT<sup>1</sup></b></p> <p>3764 patients</p> <p>Exclusions incl major trauma + orthopaedic surgery</p> <p>Incl USS screening</p> <p>F/u until discharge from hospital or 28 days</p>	<p>Dalteparin 5000u od</p> <p>v</p> <p>heparin 5000iu bd</p>	<p><b>Overall ~10%</b></p> <p>Proximal DVT 5.1 v 5.8</p> <p>PE 1.3 v 2.3 p=0.01</p> <p>Catheter related thrombosis 2.3 v 2.1</p> <p>85% VTE occurred on ICU</p>	<p><b>5.5 v 5.6</b></p>

# Weight based dosing for VTE prevention

- LMWH SPCs – fixed dose
- Inverse correlation between antiXa levels and body weight after a prophylactic dose
- Bariatric surgery
  - antiXa more likely in range and lower incidence of VTE with adjustments for body weight

# Extended thromboprophylaxis for medical inpatients

- EXCLAIM            enoxaparin 40mg 28days
  - ADOPT             apixaban 2.5mg bd 30days
  - MAGELLAN        rivaroxaban 10mg od 30days
  - APEX              betrixaban 80mg od 35-42days
  - MARINER         rivaroxaban
- 
- Reduction in symptomatic VTE or VTE death
    - 0.8% vs 1.2%     $p=0.002$
  - Increased ISTH major or fatal bleeding
    - 0.6% v 0.3 %     $p<0.001$

# MARINER - rivaroxaban

- RCT, 12024 patients
- 10mg rivaroxaban for 45 days v placebo at hospital discharge
- Eligibility:
  - Medical inpatients, > 40 years, hospitalised 3-10 days with significant medical illness
  - Additional VTE risk factors as indicated by modified Improve score of  $\geq 4$  or Improve score  $\geq 2$  + ddimer  $> 2 \times \text{ULN}$

	<b>Symptomatic VTE or death from VTE</b>	<b>Major bleeding</b>	<b>Clinically relevant non major bleeding</b>
Placebo	1.10%	0.15%	0.85%
Rivaroxaban	0.83% <b>RR 0.76</b> P=0.14	0.28% <b>RR 1.88</b>	1.42% <b>RR 1.66</b>



# Mechanical thromboprophylaxis

- GCS and elective surgical patients<sup>1</sup>
  - RCT 1905 patients
  - LMWH alone non-inferior to LMWH +GCS
- IPC and ICU<sup>2</sup>
  - RCT 2003 patients
  - Adjunctive IPC did not significantly reduce DVT/VTE v LMWH alone
- IPC and stroke<sup>3</sup>
  - RCT 2876 patients
  - Significantly reduced DVT (12.1% to 8.5%)

<sup>1</sup> GAPS: Shalhoub et al BMJ 2020; 369:m1309

<sup>2</sup> Arabi et al NEJM 2019 380:1305

<sup>3</sup> CLOTS3: Dennis et al Lancet 2013 382:1020

**VTE rate in COVID**

# Cohort studies in COVID-19 - ICU alone

Study	Key points	Thrombosis rate (VTE+arterial)
<p>Klok et al Netherlands</p> <p>April 2020 Throm Res</p>	<p><b>184 patients</b></p> <p>100% received TP: at least standard dose, dose increased over time</p> <p>Median f/u 14 days</p> <p>35% still hospitalised</p>	<p>31% @ 7 days</p> <p><b>41% @14 days</b> <b>35% PE</b> <b>2% other VTE</b> <b>4% arterial</b></p>
<p>Helms et al France</p> <p>April 2020 Intensive Care Medicine</p>	<p><b>150 patients</b></p> <p>100% received TP: 70% prophylactic, 30% therapeutic</p> <p>Median f/u not stated</p> <p>67% still intubated</p>	<p><b>42.6%</b></p> <p><b>PE 16.7%</b> <b>DVT 2%</b> 2.7% arterial 18.7% RRT filter clotting 2.7% major bleed</p> <p>Comparison to historical non-covid ARDS: more PEs 11.7 v 2.1%</p>

# Cohort studies in COVID-19: ICU and non-ICU

Study	Key points	Thrombosis rate
<p>Middledorp et al Netherlands May 2020 JTH</p> <p>Standard dose TP doubled for ICU during study, not associated with reduced risk of VTE</p>	<p><b>ICU/non-ICU 75/123</b></p> <p>USS screening in 25%</p> <p>95% received TP</p> <p>Median f/u 7 days (ICU 15; ward 4 days)</p> <p>8% still hospitalised</p>	<p>All VTE 20% Symptomatic VTE 13%</p> <p><b>PE 6.6%</b> <b>DVT 13%</b></p> <p>ICU v ward HR 3.9</p> <p>VTE was associated with death HR 2.3</p> <p>Bleeding data not described</p>
<p>Lodigiani et al Italy Thromb Res May 2020</p>	<p><b>ICU/non-ICU 61/327</b></p> <p>TP:100% ICU, 75% ward (standard, intermediate, therapeutic)</p> <p>Median f/u 10 days</p> <p>7% patients still hospitalised</p>	<p>In closed cases, <b>ICU: VTE 8.3%</b> <b>Ward: VTE 3.8%</b></p> <p><b>Half of VTE diagnosed within 24 hours of admission</b></p>

If we increase intensity/duration/lower threshold for thromboprophylaxis, will we:

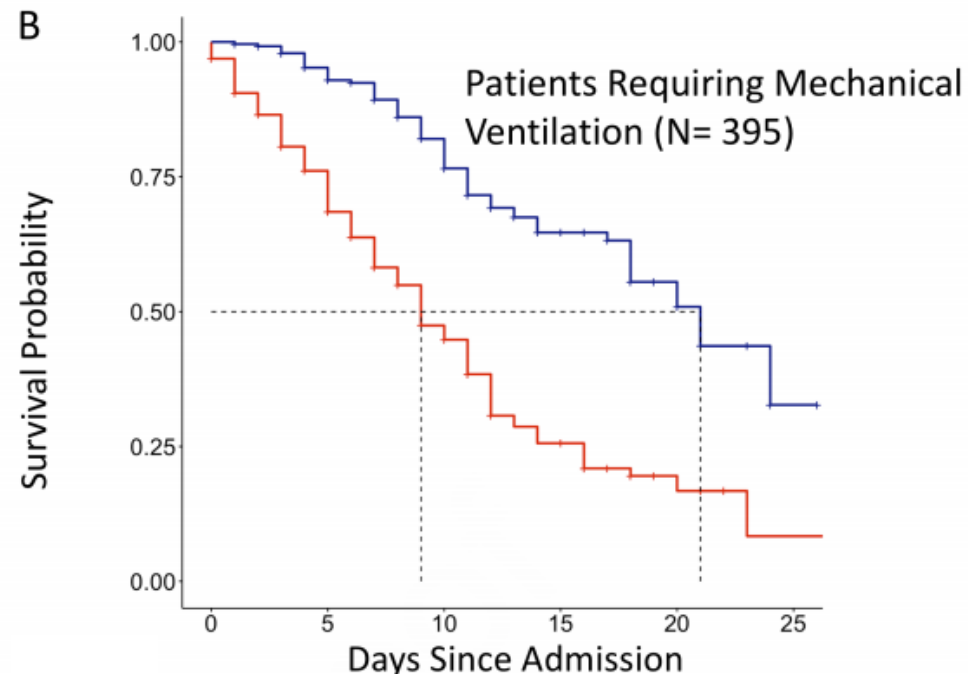
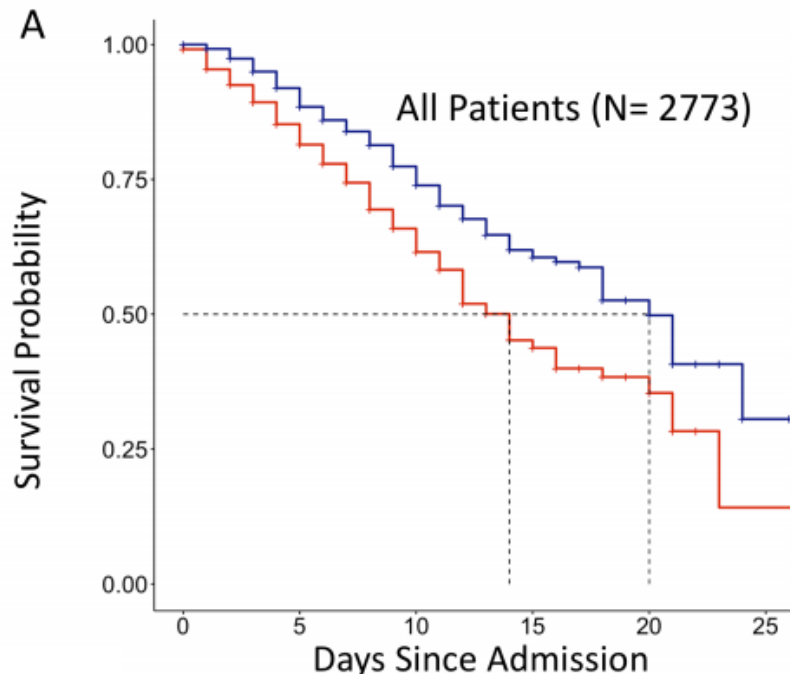
- reduce risk of VTE?
- reduce risk of death?
- and what is risk/benefit with likely increased bleeding risk?

# Prophylactic LMWH associated with reduced mortality

- Retrospective observational analysis
- 449 patients
- 22% of patients received thromboprophylaxis
  - (95% 40-60mg enoxaparin; 5% therapeutic)
- 28 day mortality 30%
  - Overall no difference in mortality between patients given heparin and not
- In patients with ddimers  $>6x$  ULN or SIC score  $\geq 4$ , heparin was associated with reduced mortality
  - mortality 64.2% to 40% (40% RRR)

# Therapeutic anticoagulation associated with reduced mortality?

■ No in-hospital anticoagulation    ■ Received treatment-dose anticoagulation during hospitalization



2773 patients, 28% received systemic AC  
Unknown indication for AC  
Median duration of AC 3 days (IQR 2-7)  
MB 3% v 1.9% (7.5% in intubated patients)

# Bleeding risk

- Anecdotal – patients with Covid-19 aren't bleeding
- Retrospective ICU audit (unpublished)
  - 12% bleeding, 7% major bleeding
- In UK we are set up to capture VTE risk, but not bleeding rates



Interim guidelines?

Possible risk stratification

# Risk stratification (1)

## Data from Wuhan, mortality and ddimers

- Retrospective observational studies
- Tang et al<sup>1</sup>
  - 183 patients, overall mortality 11.5%
  - On admission, non-survivors had significantly higher ddimers compared to survivors
  - During admission, 71.4% of non-survivors v 0.6% of survivors met the criteria for DIC during stay
- Zhou et al<sup>2</sup>
  - 191 adults, overall mortality 28%
  - Increased risk of death associated with:
    - admission ddimer >1000µg/ml, OR 18
    - higher SOFA score, OR 5.65

<sup>1</sup> Tang et al JTH Feb 2020 18(4):844-847

<sup>2</sup> Zhou et al Lancet Mar 2020

# Risk stratification (2)

## European data – thrombosis and mortality

- Higher rates of thrombosis associated with ICU admission
- Higher rates of mortality associated with ICU admission, particularly ventilation

# Risk stratification (3)

- Traditional VTE risk factors
  - Previous VTE but not on long-term anticoagulation
  - Active cancer
- Community
  - Hospital assessed ambulatory patients
  - Community

# Interim COVID-19 thromboprophylaxis guidelines

- VTE risk assess everyone on admission
- Dose-adjusted standard LMWH whilst an inpatient
- Remaining questions
  - Increase dose LMWH?
  - Extended thromboprophylaxis?
  - Hospital-assessed ambulatory patients?
  - High risk patients in the community?

# Obligations

- RCTs
- Audit – thrombosis and bleeding risk, ideally prospectively
- Regularly review ‘interim’ guidance