HEparin Low-dose Protocol versus therapeutic dose heparin in patients on veno-venous Extra Corporeal Membrane Oxygenation-the HELP-ECMO trial

Prof Jamie Cooper on behalf of the HELP-ECMO Investigators
Bleeding and thrombosis are common in VV-ECMO

- Bleeding (16-56%)
- Thrombosis (7-50%)
- Anticoagulation
- Invasive procedures
- SIRS
- SIRS - Hypercoagulable state
- Interaction blood/membrane -circuit
- Coagulopathy

Therapeutic anticoagulation with heparin

- Unfractionated heparin = the most common anticoagulation used on ECMO

- *ELSO anticoagulation guidelines 2014* recommend therapeutic anticoagulation

- **International variability** in level of anticoagulation and monitoring - although limited data in adults

- **Australia** - therapeutic anticoagulation is standard practice in VV-ECMO according to a recent survey of the 10 most active ECMO centres

*Bembea MM et al, Pediatr Crit Care Med (2013):14;e77-84*
Bleeding major cause of morbidity and mortality

- Reported bleeding rates range from 16% to 60%\(^1,2\)
- Bleeding is independent predictor of mortality in ECMO patients\(^1\)
- In 2009 Influenza A (H1N1) pandemic – of non-surviving ECMO patients\(^3\)
  - 40% had intracranial haemorrhage
  - 70% had bleeding as a primary cause contributing to death
- Intensity of anticoagulation is a risk factor for bleeding in ECMO\(^1\)

\(^1\)Aubron et al, Annals of Intensive Care, 2016
\(^3\)ANZ ECMO Influenza investigators, JAMA, 2009; 302(17):1888-1895
Low dose heparin in VV-ECMO

- Use of heparin bonded circuits questions the need for therapeutic anticoagulation\(^1\)
- Low dose heparin is already standard practice in some international referral centres
- Experience of prolonged VV-ECMO with low dose or no heparin and low thrombosis rates
- Without heparin in trauma\(^2\)
- Prophylactic subcutaneous heparin\(^3\)

\(^1\)Luyt CE et al. Intensive Care Medicine (2016):5;897-907
\(^2\)Muellenbach RM et al. J Trauma Acute Care Surg (2012):7;647-52
\(^3\)Krueger K et al. Artificial Organs (2017):41;186-92
Existing evidence for anticoagulation in VV-ECMO

- Available evidence = 19 observational, retrospective studies in VV-ECMO\(^1,2\)
- Studies that targeted low range aPTT
  - lower bleeding rates (8% vs 56%)
  - higher thrombosis rate (32% vs 7%), but mostly circuit-related and of uncertain clinical significance

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th>Number of patients</th>
<th>Bleeding</th>
<th>All thrombosis</th>
<th>Patient arterial/venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>High target aPTT(^1)</td>
<td>43</td>
<td>56%</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Low target aPTT(^1)</td>
<td>156</td>
<td>8%</td>
<td>32%</td>
<td>6%</td>
</tr>
<tr>
<td>Minimal/no anticoagulation(^1,2)</td>
<td>167</td>
<td>NR</td>
<td>42%</td>
<td>6%</td>
</tr>
</tbody>
</table>

\(^1\) Sklar et al, Annals American Thoracic Society (2016);13:2242-50
\(^2\) Krueger K et al. Artificial Organs (2017):41;186-92
Existing evidence for anticoagulation in VV-ECMO

Only randomised study comparing different anticoagulation protocols in ECMO is the HELP-ECMO Pilot study:

- Alfred Hospital (Melbourne), Royal Prince Alfred (Sydney)
- Enrolled 32 patients: 9 VA and 23 VV ECMO
- Primary Aim: To determine the feasibility of randomising ECMO patients to therapeutic or lower intensity anticoagulation and whether this leads to a significant difference in mean daily heparin dose, aPTT and anti Xa levels
Eligible patients

Low dose heparin
- aiming for aPTT < 45sec
- maximum 12,000 IU/24h

Therapeutic heparin
- aiming for aPTT 50 - 70 sec

Bleeding: stop heparin (at the discretion of clinician)
New indication for therapeutic anticoagulation: increase to therapeutic dose (or continue)
aPTT and anti Xa performed at least once /day
HELP-ECMO Pilot results

117 patients assessed for eligibility

Not eligible (N=73)
- 50: indication for therapeutic anticoagulation
- 18: contra indication to heparin or therapeutic anticoagulation

44 eligible patients
- 9: Refusals/unable to obtain
- 3: missing

32 enrolled patients
- 23 VV ECMO, 9 VA ECMO

VV-ECMO
- 67% screened eligible, 50% enrolled
Pilot results – treatment separation all patients

- **Heparin dose**: 20710 IU/day vs 11742 IU/day, p=0.001
- **aPTT**: 55.5 sec vs 48.1 sec, p=0.04
- **Anti-Xa**: 0.27 vs 0.11, p=0.01

![Graph showing daily mean anti-Xa levels](image)

- Therapeutic heparin
- Low dose heparin

*p = 0.01*
Pilot results – treatment separation VV-ECMO

- **Heparin daily dose:** 22,906 IU/day vs 8816 IU/day, p<0.001
- **aPTT:** 54.3 sec vs 45.3 sec, p<0.001
- **anti-Xa:** 0.25 vs 0.10, p=0.02

![Graph showing Anti-Xa VV ECMO levels over time for therapeutic and low dose heparin, with marked significance p<0.001.]
## Pilot results – bleeding and thrombosis – VV-ECMO

<table>
<thead>
<tr>
<th>Event</th>
<th>Low dose (n=11)</th>
<th>Standard care (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bleeding</td>
<td>27%</td>
<td>50%</td>
</tr>
<tr>
<td>Major bleeding*</td>
<td>18%</td>
<td>42%</td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>64%</td>
<td>92%</td>
</tr>
<tr>
<td>Circuit thrombosis</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>Patient arterial/venous thrombosis</td>
<td>18%</td>
<td>25%</td>
</tr>
</tbody>
</table>

*Major bleeding defined by site (Intracranial, intrathoracic, retroperitoneal) or if required ≥2RBC/24hours and/or drop in Hb >20g/L AND required intervention (e.g. surgery, endoscopy)
Pilot results - conclusions

- Allocation of ECMO patients to low dose or therapeutic heparin protocol resulted in
  - Less heparin administered (half the dose)
  - Clinically meaningful and statistically significant differences in aPTT and anti-Xa
  - Trend to less bleeding in low-dose group and no signal of increased thrombosis in VV-ECMO

- Results support feasibility of a larger phase III study to evaluate the safety and efficacy of low-dose heparin compared to therapeutic anticoagulation in patients receiving VV ECMO
Hypothesis:
*In patients supported with VV-ECMO, low dose heparin will decrease the proportion of patients who experience major bleeding, compared to standard care therapeutic dose anticoagulation, without increasing thrombosis.*

Aims:
- To evaluate the effect of low dose heparin during treatment with VV-ECMO on the proportion of patients experiencing major bleeding compared to patients receiving standard care.
- Other outcomes including thrombosis and all-cause mortality will be also be evaluated.
Participants

- Inclusion criteria: Intensive care patients who require VV-ECMO
- Exclusion criteria:
  - <16yo
  - Contraindication to heparin (e.g. HITTS)
  - Pre-existing indication for therapeutic anticoagulation (e.g. PE)
  - >48hours ECMO support prior to enrolment
  - Treating clinician deems it not in patient’s best interest
Standard care

Heparin 10,000 units IV at ECMO insertion

- No bleeding
  - Heparin infusion
  - aPTT 50-70 sec (or equivalent)

- Bleeding
  - As per local bleeding management protocol
Intervention – low dose heparin

Heparin 10,000 units IV at ECMO insertion

No bleeding

No indication for therapeutic anticoagulation

aPTT >45 sec
Repeat aPTT 6 hourly

aPTT <45 sec
Fixed dose heparin:
Wt <50kg: 8,000 U/24h
Wt 50-70kg: 10,000 U/24h
Wt >70kg: 12,000 U/24h

New indication for therapeutic anticoagulation arisen since enrolment

Heparin infusion:
Aim aPTT 50-70 sec (or equivalent)

Bleeding

As per local bleeding management protocol
Primary outcome

Major bleeding defined as any of the following

- Intracranial haemorrhage
- Retroperitoneal bleeding
- Intrathoracic bleeding
- Bleeding from any site that:
  1. Requires ≥ 2 RBC in 24/hr OR associated with a drop in Hb of >20g/L in 24hr AND
  2. Requires an intervention for treatment (includes surgical, radiological and endoscopic interventions)
- Death due to bleeding (as determined by blinded, independent adjudication committee)
Secondary outcomes

1. All-cause mortality at 90-days post randomisation
2. Venous or arterial thrombosis up to 28-days post randomisation
3. Circuit-thrombosis up to 28-days post randomisation
4. Intracranial haemorrhage up to 28-days post randomisation
5. Proportion of patients who experience major bleeding or arterial/venous thrombosis up to 28-days post randomisation
6. Time to first bleeding event
7. Daily and total red blood cell requirements up to 28-days post randomisation
8. Daily SOFA score
9. Health status using EQ5D-5L at 180 days
Sample size:

200 patients will provide 90% power to detect a 22% difference in major bleeding (42% vs. 20%).

To account for loss to follow up (5%) and early deaths within 14 days (9%), the sample size will be inflated to total of 230 patients.

Thrombosis – this sample size will provide 80% power to detect absolute difference 20% in patient arterial/venous thrombosis.

Primary outcome based on:

- Pilot data major bleeding: 42% vs. 18%
- Systematic review in VV-ECMO: 56% vs 8%1
- Our observational data: Standard care 47% in VV-ECMO2

1Aubron et al, Annals of Intensive Care, 2016
Conclusion

• HELP-ECMO will be the first RCT comparing different anticoagulation protocols in ECMO powered for patient outcomes

• Good evidence for safety of low dose heparin in observational studies, but insufficient to change standard care

• Inexpensive and simple intervention – and if successful has potential to improve patient outcomes

• Important to define optimal ‘standard care’ with heparin
HELP-ECMO investigators

- Prof C Aubron
- Ms J Board
- Ms H Buhr
- Dr B Cartwright
- Prof DJ Cooper
- Prof J Fraser
- Ms A Higgins
- A/Prof C Hodgson
- Dr M Dennis
- A/Prof P Forrest
- Dr J Josephs
- Dr D McIlroy
- Dr Z McQuilten
- Ms L Murray
- Dr P Nair
- Dr V Pellegrino
- A/Prof D Pilcher
- Ms J Sheldrake
- Ms S Vallance
- A/Prof H Tran
• Questions?