## Background and Overview

### Article

### Background
Mortality in the ICU due to shock remains unacceptably high (>50%)
- The use of high doses of catecholamines in patients with severe hypotension is associated with poor outcomes (increased mortality risk of >50%)
- Angiotensin II may effectively treat hypotension in patients suffering from vasopressor resistant shock and has been safely studied in patient with a variety of comorbidities

### Objective
To determine whether the addition of angiotensin II to background vasopressors would improve blood pressure in patients with catecholamine-resistant vasodilatory shock

## Methods

### Study design
Multi-center (74 centers in 9 countries), randomized, double-blind, placebo-controlled trial

### Funding
La Jolla Pharmaceutical Company

### Inclusion Criteria
- Vasodilatory shock despite intravenous volume resuscitation with at least 25 mL/kg of body weight over the previous 24 hours and administration of high-dose vasopressors

### Exclusion Criteria
- Burns covering more than 20% of the total body-surface area, acute coronary syndrome, bronchospasm, liver failure, mesenteric ischemia, active bleeding, abdominal aortic aneurysm, absolute neutrophil count less than 1000 per cubic millimeter, receiving venoarterial extracorporeal membrane oxygenation, or treatment with high-dose glucocorticoids

### Interventions
A total of 344 patients were assigned to one of two regimens; 321 received a study intervention
- Angiotensin II: N = 163 (10 excluded did not receive study drug)
- Placebo: N= 158 (13 excluded never received placebo)

### Outcome Measures
**Primary Endpoint**
- Response with respect to mean arterial pressure at hour 3 defined as a mean arterial pressure of 75 mm Hg or higher or an increase in mean arterial pressure from baseline of at least 10 mm Hg without an increase in the dose of background vasopressors

**Secondary Endpoints**
- Changes in cardiovascular SOFA score between baseline measurement and hour 48
- Changes in total SOFA score between baseline measurement and hour 48

**Safety**
- Rate of serious adverse events, adverse event-related to drug discontinuations, all adverse events, and all-cause mortality at 7 days and 28 days
### Statistical Analysis
- Sample size of 150 participants per treatment group would provide more than 90% power to show superiority of angiotensin II over placebo
- Logistic regression with two-sided alpha level 0.05
- Modified intention-to-treat analysis; last observation carried forward

### Results

#### Baseline Characteristics
- Median age: 64 (IQR = 52-75), mostly males (60.7%)
- Region: United States or Canada (73.5%), Europe (10.3%), Australia or New Zealand (16.2%)
- BMI ≥ 30: 140/316 (44.3%)
- MAP Median: 66.3 (IQR = 63.7-68.7)
- Apache II Score median: 28 (IQR = 22-33)
- Median vasopressor dose in $\mu$g/kg/min: 0.34 (IQR = 0.23-0.56)
- Cause of shock: Sepsis (80.7%), Other/potentially sepsis (9.7%), multifactorial (3.1%)

#### Primary/Secondary Endpoints

<table>
<thead>
<tr>
<th>End point</th>
<th>Angiotensin II (N=163)</th>
<th>Placebo (N=158)</th>
<th>Odds or Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary End Point</strong></td>
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<tr>
<td>MAP response at hour 3 – no. (%)</td>
<td>114 (69.9)</td>
<td>37 (23.4)</td>
<td>Odds ratio, 7.95 (4.786-13.3)</td>
<td>&lt;0.001</td>
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<td><strong>Secondary End Points</strong></td>
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<tr>
<td>Mean change in cardiovascular SOFA score at hour 48</td>
<td>-1.75±1.77</td>
<td>-1.28±1.65</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Mean change in total SOFA score at hour 48</td>
<td>1.05±5.50</td>
<td>0.04±5.34</td>
<td></td>
<td>0.49</td>
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<tr>
<td><strong>Additional End Points</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean change in norepinephrine-equivalent dose from baseline to hour 3</td>
<td>-0.03±0.10</td>
<td>0.03±0.23</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause mortality at day 7 – no. (%)</td>
<td>47 (29)</td>
<td>55 (35)</td>
<td>Hazard ratio, 0.78 (0.53-1.16)</td>
<td>0.22</td>
</tr>
<tr>
<td>All-cause mortality at day 28 – no. (%)</td>
<td>75 (46)</td>
<td>85 (54)</td>
<td>Hazard ratio, 0.78 (0.57-1.07)</td>
<td>0.12</td>
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</tbody>
</table>

#### Safety Endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Angiotensin II (N=163)</th>
<th>Placebo (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event of any grade</td>
<td>142 (87.1)</td>
<td>145 (91.8)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation</td>
<td>23 (14.1)</td>
<td>34 (21.5)</td>
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</tbody>
</table>

### Discussion and Conclusion

#### Author’s Conclusions
- Angiotensin II administered intravenously increased blood pressure and allowed catecholamine dose reductions in patients with vasodilatory shock who were receiving high-dose vasopressors
- Larger trials with longer duration of follow-up are warranted to address mortality and long-term side effects as well as direct comparisons of angiotensin II with other vasopressors

#### My Conclusions
- This study was powered to statistically reflect changes in MAP due to angiotensin II
- Larger studies powered for clinically meaningful endpoints such as organ dysfunction and mortality are needed

#### Application
- Angiotensin II may be a last-line option in patients with shock who have not responded to therapy with fluids, vasopressors, and vasopressin therapy
References:
