

## Meeting Coverage

# Angiotensin II Promising for Vasodilatory Shock

— Treatment tied to lower catecholamine requirements

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WASHINGTON -- Treatment with angiotensin II was associated with clinically relevant blood pressure increases in critically ill patients with vasodilatory shock who failed to respond to high doses of conventional vasopressors, researchers reported here.

According to findings from the [ATHOS-3 trial](#), patients with catecholamine-resistant hypotension treated with angiotensin II (LJPC-501) had a three-fold greater incidence of achieving target blood pressure at hour 3 than placebo treated patients, according to Rinaldo Bellomo, MD, of the University of Melbourne, and colleagues.

They also had lower requirements for catecholamines, the authors reported at the [American Thoracic Society](#) meeting and in the [New England Journal of Medicine](#).

Vasodilatory shock can quickly progress to irreversible organ failure if blood pressure is not restored. Vasopressors are used when IV fluid resuscitation fails to do this, but not all patients respond.

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Both classes of vasopressors currently available -- catecholamines, including the first-line drug norepinephrine, and vasopressin -- have substantial toxicities at high doses.

"It is often the case that patients reach the maximum doses of both of these drugs very soon and are no longer responding," said co-author Ashish Khanna, MD, of the Cleveland Clinic, to *MedPage Today*. "When this happens things start spiralling out of control very quickly."

Khanna said angiotensin II targets a novel mechanism for maintaining blood pressure known as the renin-angiotensin-aldosterone system (RAAS).

In a [recent pilot study](#), which ultimately led to the phase III trial, the addition of intravenous human angiotensin II to catecholamine and vasopressin increased mean arterial pressure in patients with vasodilatory shock, allowing reductions in catecholamine dosages.

The current multinational, randomized trial included 321 patients with vasodilatory shock who were receiving more than 0.2 µg of norepinephrine per kg of body weight per minute, or the equivalent dose of another vasopressor. The patients were randomized to receive either angiotensin II (n=163) or placebo (n=158).

The primary endpoint was a response with respect to mean arterial pressure at hour 3 after the start of infusion. Response was defined as an increase from baseline of at least 10 mmHg or an increase to at least 75 mmHg without an increase in the dose of background vasopressors.

The authors reported that 69.9% of angiotensin II patients and 23.4% of placebo patients reached the primary endpoint (OR 7.95, 95% CI 4.76-13.3,  $P < 0.001$ ).

At 48 hours, the mean improvement in the cardiovascular Sequential Organ Failure Assessment (SOFA) score was greater in the angiotensin II group (-1.75 vs -1.28,  $P = 0.01$ ).

Also, serious adverse events were reported in 60.7% of the patients in the angiotensin II group and 67.1% of the patients in the placebo group.

At day 28, 46% of the patients receiving angiotensin II died compared with 54% of the placebo-treated patients (HR 0.78 95% CI, 0.57-1.07,  $P = 0.12$ ).

Patients treated with angiotensin II had lower requirements for catecholamines than placebo-treated patients, the authors noted.

"In a finding consistent with this result, cardiovascular SOFA scores, which quantify catecholamine use, were significantly lower in the angiotensin II group than in the placebo group at 48 hours," the researchers wrote.

Discontinuation of treatment due to adverse events occurred in 14.1% of angiotensin II-treated patients and 21.5% of placebo-treated patients. The most common adverse events leading to discontinuation were similar in the two treatment groups, and included septic shock, multi-organ failure, cardiogenic shock, and cardiac arrest.

Pending FDA approval, Khanna said the drug could be available for the treatment of shock patients as early as next year.

"This is a new drug in our armamentarium to manage patients dying of catecholamine-resistant hypotension, while achieving a decrease in drugs like norepinephrine and vasopressin that do more harm than good at very high doses," he said. "It can essentially buy the patient some time to fix the primary problem causing the hypotension."

**The ATHOS-3 trial was funded by La Jolla Pharmaceuticals. Some co-authors were company employees.**

**Bellomo disclosed no relevant relationships with industry. Khanna disclosed a relevant relationships with La Jolla Pharmaceuticals.**

**Co-authors disclosed multiple relevant relationships with industry including La Jolla Pharmaceuticals.**

**Primary Source**

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