Renin, Angiotensin II, and the Journey to Evidence-based Individual Treatment Effects

Randomized trials, the most reliable method for determining the effect of a treatment on patient outcomes, have traditionally reported the average effect of a treatment across the whole study population. Bedside clinicians have long recognized that a given treatment can benefit some patients while conveying no benefit (or even harm) to other patients with the same illness ("heterogeneity of treatment effect") (1, 2). Ideally, clinicians would be able to make decisions using estimates of treatment effect that were both *1*) evidence-based and *2*) personalized to the individual patient. If "evidence-based individual treatment effects" are the promised land, how can critical care get there?

In this issue of the *Journal*, Bellomo and colleagues (pp. 1253–1261) demonstrate an important early step in this journey (3). In a secondary analysis of the ATHOS-3 (Angiotensin II for the Treatment of High-Output Shock) trial (4), they examine how biologic measures along the proposed mechanistic pathway for angiotensin II infusion modify the effect of the treatment on outcomes, posing the question, "Can bedside measurement of serum renin levels identify which patients will benefit from treatment with angiotensin II?"

The original ATHOS-3 trial randomized 344 patients with catecholamine-resistant vasodilatory shock to infusion of angiotensin II or placebo. Angiotensin II increased mean arterial pressure at 3 hours (the primary outcome). Although 28-day mortality was numerically lower in the angiotensin II group, the difference was not statistically significant (hazard ratio, 0.78; 95% confidence interval, 0.57–1.07; $P = 0.12$).

The ATHOS-3 trial derived from the hypothesis that decreased angiotensin-converting enzyme activity in shock produces a relative deficiency of angiotensin II and resultant elevations in renin and angiotensin I. The hypothesis of this secondary analysis, that angiotensin II infusion might be more effective among patients with higher serum renin levels (as a surrogate for decreased angiotensin converting enzyme activity, decreased angiotensin II, and increased angiotensin I), was a natural next step in striving to understand which patients with shock benefit from treatment with angiotensin II (5).

To test this hypothesis, the authors analyzed specimens from the ATHOS-3 trial obtained from 255 patients at the time of randomization and from 200 patients at 3 hours after initiation of the study drug. The authors found that *1*) most patients had elevated renin levels, *2*) renin levels correlated moderately with angiotensin I levels and weakly with the ratio of angiotensin I to angiotensin II, and *3*) renin levels at randomization appeared to potentially modify the effect of angiotensin II infusion on mortality.

The investigators are to be applauded for incorporating into a rigorous randomized trial the collection of specimens in a manner that allowed the evaluation of the mechanism of action and heterogeneity of the treatment effect. These results are critical to understanding the mechanistic effects of angiotensin II infusion in shock and to planning future research.

As for the enticing question, "Can bedside measurement of serum renin levels identify which patients will benefit from angiotensin II?", the answer is "not yet." Like all *post hoc* analyses, these results require prospective validation. Because the original ATHOS-3 trial was not stratified by baseline renin levels (which were unavailable at randomization), the apparent differences in mortality between angiotensin II and placebo in the higher-renin subgroup may result from chance imbalances in baseline characteristics. For example, in this subgroup, patients assigned to placebo had numerically greater norepinephrine receipt, Model for End-Stage Liver Disease scores, and prevalence of acute respiratory distress syndrome and acute kidney injury at baseline. Furthermore, the primary analysis dichotomized patients with "high" versus "low" renin levels using the median renin level for the trial population. This arbitrary cut point does not represent a biologically meaningful threshold. When the authors examined the effect of angiotensin II versus placebo across the full range of baseline renin levels as a continuous variable, the baseline renin level did not appear to modify the effect of angiotensin II on mortality (*see* Figure 4 in Reference 3). Finally, the effect of angiotensin II on mortality has been proposed to be mediated through blood pressure—the primary outcome of the ATHOS-3 trial. In the current study, baseline renin level did not modify the effect of angiotensin II infusion on mean arterial blood pressure.

Designing randomized trials to assess for heterogeneity of treatment effect by biologic measures of the proposed mechanistic pathway is one important step toward evidence-based individual treatment effects, but it is not the only step. Bellomo and colleagues (3) apply a traditional "one-variable-at-a-time" approach to evaluating for heterogeneity of treatment effect (6). A complete understanding of how individual patients will respond to treatment, however, may require simultaneous consideration of the interaction among multiple related variables (e.g., intravascular volume, left ventricular ejection fraction, tissue oxygen saturation, and exogenous catecholamine receipt). For example, euvolemic patients with "inappropriately" high renin levels might benefit from angiotensin II infusion, whereas hypovolemic patients with "appropriately" high renin levels might be harmed by angiotensin II infusion. The number of potential effect modifiers and their theoretical combinations may outpace traditional methods for analyzing randomized trials (7).

Building the tools clinicians need to make evidence-based treatment decisions for individual patients will require investment on multiple fronts. In the long term, we believe randomized trials in critical care should:

Originally Published in Press as DOI: 10.1164/rccm.202007-2731ED on August 4, 2020

1. Be large enough to estimate, with adequate statistical power, treatment effects for individuals or small groups of patients, rather than average treatment effects.
2. Enroll broad and representative enough patient populations to estimate treatment effects for the full range of individuals who might be exposed to an intervention in practice. Specifically, trials should only exclude patients for whom an incontrovertible pathophysiologic rationale suggests they will not respond to the treatment (e.g., absence of the molecular target) (8). This approach allows a comprehensive understanding of which patients do and do not benefit from a treatment and avoids inappropriately depriving patients of a treatment from which they would have benefited in cases in which the treatment's mechanism is multimodal or incompletely understood.
3. Extract data automatically from the electronic health record to generate large volumes of granular data on physiology and response to treatment (9) and develop innovative, inexpensive approaches to targeted assessment of mechanistic biomarkers.
4. Address in design, analysis, and dissemination the complex patterns of covariates and interactions that determine the effects of treatment on outcomes for individual patients. Analysis of randomized trials using advanced approaches to regression analysis or machine learning may inform both mechanistic understanding and treatment decisions (10, 11). Computerized clinician decision-support tools may help translate increasingly sophisticated estimates of individual treatment effect into clinical care.

In summary, we thank Bellomo and colleagues (3) for their informative analysis of how hormone levels along the renin–angiotensin–aldosterone system may help identify which patients benefit from angiotensin II infusion. We challenge future randomized trials in critical care to innovate robust approaches to generating the evidence-based estimates of treatment effect for individual patients that clinicians and patients need to make informed, personalized treatment decisions. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Jonathan D. Casey, M.D., M.Sc.
Matthew W. Semler, M.D., M.Sc.
Division of Allergy, Pulmonary, and Critical Care Medicine
Vanderbilt University School of Medicine
Nashville, Tennessee

ORCID ID: 0000-0002-7664-8263 (M.W.S.).

References

1. Prescott HC, Calfee CS, Thompson BT, Angus DC, Liu VX. Toward smarter lumping and smarter splitting: rethinking strategies for sepsis and acute respiratory distress syndrome clinical trial design. *Am J Respir Crit Care Med* 2016;194:147–155.
2. Iwashyna TJ, Burke JF, Sussman JB, Prescott HC, Hayward RA, Angus DC. Implications of heterogeneity of treatment effect for reporting and analysis of randomized trials in critical care. *Am J Respir Crit Care Med* 2015;192:1045–1051.
3. Bellomo R, Forni LG, Busse LW, McCurdy MT, Ham KR, Boldt DW, *et al*.; ATHOS-3 Investigators. Renin and survival in patients given angiotensin II for catecholamine-resistant vasodilatory shock: a clinical trial. *Am J Respir Crit Care Med* 2020:202:1253–1261.
4. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, *et al*.; ATHOS-3 Investigators. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 2017;377:419–430.
5. Bellomo R, Wunderink RG, Szerlip H, English SW, Busse LW, Deane AM, *et al*. Angiotensin I and angiotensin II concentrations and their ratio in catecholamine-resistant vasodilatory shock. *Crit Care* 2020;24:43.
6. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine: reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007;357:2189–2194.
7. Gershman B, Guo DP, Dahabreh IJ. Using observational data for personalized medicine when clinical trial evidence is limited. *Fertil Steril* 2018;109:946–951.
8. Center for Drug Evaluation and Research. Enrichment strategies for clinical trials to support approval of human drugs and biological products. Silver Spring, MD: U.S. Food and Drug Administration; 2019 [updated 2019 Mar 15; accessed 2020 Jul 9]. Available from: http://www.fda.gov/regulatory-information/search-fda-guidance-documents/enrichment-strategies-clinical-trials-supprt-approval-human-drugs-and-biological-products.
9. Harhay MO, Casey JD, Clement M, Collins SP, Gayat É, Gong MN, *et al*. Contemporary strategies to improve clinical trial design for critical care research: insights from the First Critical Care Clinical Trialists Workshop. *Intensive Care Med* 2020;46:930–942.
10. Shah FA, Talisa V, Angus DC, Kennedy J, DeMerle KM, Seymour CW, *et al*. A novel ensemble learning approach to understand heterogeneity of treatment effect in critical care trials [abstract]. *Am J Respir Crit Care Med* 2020;201:A1644.
11. Biswas A, Parikh CR, Feldman HI, Garg AX, Latham S, Lin H, *et al*. Identification of patients expected to benefit from electronic alerts for acute kidney injury. *Clin J Am Soc Nephrol* 2018;13:842–849.