**Journal Club Outline**

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| ***Background and Overview*** | | |
| **Study Citation** | Smith LM et al. Angiotensin II for the treatment of refractory shock: a matched analysis | |
| **Purpose/Background** | Patients with refractory shock have a high mortality (50% 30 day all-cause mortality) and current management typically consists of epinephrine/norepinephrine and vasopressin. Recent research has focused on additional agents to augment standard therapy for patients with refractory shock. Angiotensin II (AT II) directly agonizes angiotensin receptors in the vasculature, leading to calcium influx and vasoconstriction.  The ATHOS-3 trial was a multicenter RCT evaluating the use of AT II (20 ng/kg/min) in patients with high-output shock requiring high doses of vasopressors. The dose was titrated to achieve a MAP of ≥ 75 mmHg. The primary outcome was a MAP ≥ 75 mmHg or 10 mmHg higher than baseline without an increase in vasopressors. There were several secondary outcomes.  Primary – 69.9% (tx) vs. 23.4% (ctrl): OR 7.95 (95%CI 4.76-13.3, p < 0.001)  Secondary – decreased cardio component of SOFA score and lower rates of AEs. No difference in mortality or total SOFA (not adequately powered for these outcomes).  Other data:  Retrospective study of real-world patients showed no mortality difference.  Higher renin levels in patients with refractory shock are predictive of mortality.  Patients prescribed ARBs no not respond to AT II as well as patients prescribed ACEIs.  Potential benefit with starting at lower doses of vasopressors (post-hoc exploratory) and in patients with vasoplegia after cardiac surgery w/bypass.  C/E ration (based on ATHOS 3) of $12,843 QALY and likely below $50,000 per QALY (86%).  It is unknow if AT II has a mortality benefit when administered in addition to vasopressors in patients with refractory shock. | |
| **Study Objective** | To determine if AT II improves 30-day and 90-day mortality in patients with refractory shock. | |
| **PICO Question** | In adult patients with refractory shock does AT II in addition to standard therapy, as compared to standard therapy alone, decrease mortality? | |
| ***Methods*** | | |
| **Study design** | Things to consider -   * Retrospective matched cohort * Single center * Control arms: 1) historical - received vasopressors before AT II was available, 2) concurrent – received vasopressors (not AT II) after it was available * Matching: the total NE dose (converted from all vasopressors) at the start of AT II was used to match each patient to a historical and concurrent control. If there were multiple matches then one was selected at random. Historical/concurrent control groups were combined. | |
| **Population** | **Inclusion Criteria** | **Exclusion Criteria** |
| * Adults (≥ 18 years) * Vasopressor tx: NE, epi, dopamine, AT II * ICU admission | AT II started in OR |
| **Funding** | No funding reported, no conflicts of interested reported. | |
| **IRB Approval** | IRB approved with waiver of consent. | |
| **RCT-Related Methods** | n/a | |
| **Observational Study-Related Methods** | Quality: similar groups recruited from same population, similar measures for both groups, valid patient-oriented outcome, confounders identified and adjusted, no AT II prior to study enrollment, reasonable follow up time, follow up complete, appropriate stats.  Overall high quality retrospective cohort study. | |
| **Intervention** | Initiation of AT II in addition to vasopressors. | |
| **Outcomes** | Primary – 30-day all cause mortality (POEM)  Secondary – 90-day mortality (POEM), RRT (POEMish), mech vent (POEM), MA-SOFA (DOE), thrombotic events (POEM), vent free days (DOE) | |
| **Statistical Analysis** | Primary outcome – 30-day mortality was compared using a GEE including several variables: basic demographics, NE equivalent dose, time to study enrollment (AT2 initiation or time to the same NE equivalent dose in the non-AT2 patients), number of vasopressors, comorbidities, laboratory values, SOFA score calculated at study enrollment, cultures, type of sepsis, and processes of care.  SMDs > 0.1 or < -0.1 = clinically significant  p-value < 0.05 = statistical significance  Power – based on ATHOS 3 (8% mortality difference at 7 days) the authors estimated that 198 patients in the treatment arm and 396 matched controls would be needed to have a 90% power to detect an 8% mortality difference.  (Observational studies) Was confounding controlled for? | |
| ***Results*** | | |
| **Sample** | **Sample size** | **Baseline characteristics** |
| Tx: 271 vs. Ctrl: 542 | Gender – 65% vs. 61% male  Race – 71% vs. 77% White  Post-Op – 62% vs. 49%\*  Sepsis – 83% vs. 75%\*  Epi – 77% vs. 68%\*  Vasopressin – 86% vs. 78%\*  Glucocorticoids – 77% vs 70%\*  NE dose – similar  SOFA – 12 vs. 10\*  MAP – 69 vs. 73\*  TTE – 5 hrs vs. 29 hrs\*  Lactate – 8.5 vs 5.9\* |
| **Results** | 30-day mortality: 60% vs. 56% (SDiff – 0.079, p = 0.292)  90-day mortality: 65% vs. 63% (SDiff – 0.058, p = 0.440)  Similar thrombotic events (29 vs. 27%).  Higher MA-SOFA at baseline with similar daily changes.  No difference in MAP by day 5.  30-day mortality (adjusted): OR 0.95 (95% CI 0.61-1.48, p = 0.827)  Similar findings for 90-day mortality, KRT, mech vent, AEs, and other secondary outcomes.  Be sure to include the results of the primary and secondary endpoints, statistical significance (e.g., p-value, confidence interval, etc.), and clinical significance (e.g., HR, RR, NNT).  Address noteworthy adverse event rates (if applicable). | |
| ***Discussion*** | | |
| **Evaluation of Study Quality** | Quality – matched controls w/concurrent and historical cohort, appropriately powered, confounders identified and adjusted, POEMs. | |
| **Authors Discussion/Conclusion** | According to the authors, the use of AT II did not improve mortality or secondary outcomes in ICU patients with refractory shock. | |
| **Strengths** | What strengths did the authors identify? What additional strengths did you identify (e.g., external validity, patient-oriented outcomes)? | |
| **Limitations** | Treatment group was generally more critically ill than the control group, consistent with practice of using AT II as salvage therapy.  No accounting for previous ACEI or ARB use.  Questionable methodology for power analysis. | |
| **Your analysis** | The findings of this study support previous literature that although AT II can improve DOEs (e.g., MAP) it has not demonstrated a clear benefit for improving patient-oriented outcomes (e.g., mortality). Based on the findings of this study the role of AT II in the poisoned patient should be limited to cases with a known overdose involving an ACEI. Otherwise AT II has no role in managing patients with refractory hypotension secondary to drug overdose (e.g., CCBs, BB, ARBs).  It would be helpful to have a prospective study evaluating AT II powered to detect mortality in patients with refractory shock. Additionally, a retrospective cohort study matching for additional factors that predict mortality (e.g., lactate, MAP, SOFA) or in a cohort where AT II is used earlier in patient care. | |
| **Application to patient** | In patients with refractory shock, including drug induced shock, the use of AT II is not recommended and does not reduce mortality. It is reasonable to consider AT II in patients with ACEI overdose. | |