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Shock prediction with dipeptidyl peptidase-3 and renin (SPiDeR) in hypoxemic patients with COVID-19

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ABSTRACT

Background: Plasma dipeptidyl peptidase-3 (DPP3) and renin levels are associated with organ dysfunction and mortality. However, whether these biomarkers are associated with the subsequent onset of shock in at-risk patients is unknown.

Abbreviations: ACTIV-4, fourth Accelerating COVID-19 Therapeutic Interventions and Vaccines Host Tissue platform trial; CI, confidence interval; DPP3, plasma dipeptidyl peptidase-3; HR, hazard ratio; ICU, intensive care unit; IRB, institutional review board; NIH, National Institutes of Health; OR, odds ratio; RAS, renin-angiotensin system; SHR, subdistribution hazard ratio.

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Dipeptidyl peptidase-3
Clinical trial registered on June 10, 2021, on www.clinicaltrials.gov (NCT04924660).

Methods: Using plasma samples collected from participants enrolled in the fourth Accelerating COVID-19 Therapeutic Interventions and Vaccines Host Tissue platform trial, we measured DPP3 and renin in 184 subjects hospitalized with acute hypoxemia from COVID-19 without baseline vasopressor requirement. We calculated the odds ratio of development of shock (defined as the initiation of vasopressor therapy) by Day 28 based on Day 0 DPP3 and renin levels.

Results: Subjects with DPP3 above the median had a significantly higher incidence of vasopressor initiation within 28 days (28.4 % vs. 16.7 %, $p = 0.031$) and higher 28-day mortality (25.0 % vs. 6.7 %, $p < 0.001$). After adjusting for covariables, DPP3 above the median was associated with shorter time to vasopressor initiation, greater 28-day mortality, fewer vasopressor-free days, and greater odds of a hypotensive event over 7 days. Significant associations were not observed for renin.

Conclusions: In patients hospitalized with COVID-19 and hypoxemia without baseline hypotension, higher baseline plasma levels of DPP3 but not renin were associated with increased risk of subsequent shock and death.

1. Background

Shock is a life-threatening state of acute circulatory failure, characterized by decreased tissue perfusion and inadequate cellular oxygen utilization, and carries a mortality rate of up to 40–50 % [1,2]. The most common cause of shock is sepsis, which hospitalizes approximately 1.7 million patients in the U.S. annually and carries a 15 % mortality rate, translating into >250,000 deaths per year [2-4]. Protocolized management of septic shock consists of fluid resuscitation, appropriate and timely antibiotics, source control, and vasopressor support. High-quality evidence supports early identification of those needing vasopressor therapy to maintain adequate perfusion pressure when outcomes are potentially modifiable [5]. Unfortunately, shock is typically addressed only after an observable decrement in systemic blood pressure (i.e., a mean arterial pressure < 65 mmHg or a systolic blood pressure < 90 mmHg) when significant tissue injury may have already occurred. Despite its incorporation into the most recent definition of septic shock, lactate has limited utility in early detection, often only becoming significantly elevated in the setting of frank tissue hypoperfusion or sepsis-induced tissue dysfunction [6-8]. Presently, there is a paucity of validated biomarkers to recognize impending shock.

The circulating enzymes dipeptidyl peptidase-3 (DPP3) and renin are two candidate biomarkers that may prove useful in the early identification of patients with septic shock. Both are components of the renin-angiotensin system (RAS) (Supplementary Fig. A1). DPP3 is a zinc-dependent aminopeptidase that is released from dying cells. DPP3 cleaves a variety of biologically active oligopeptides, including both angiotensin II and angiotensin- [1-7], the major effector molecules of the classical RAS and alternative RAS, respectively [9-13]. Renin is secreted by the juxtaglomerular apparatus of the kidney in response to hypotension or sympathetic stimulation and is responsible for the conversion of angiotensinogen to angiotensin I. Elevations in DPP3 and renin have been found to have significant prognostic value in critically ill patients with established shock, predicting organ dysfunction and death in patients with septic shock, cardiogenic shock, and severe burns; following cardiac surgery; and in mixed intensive care unit (ICU) populations [13-29]. Moreover, both DPP3 and renin have been shown in observational studies to outperform lactate in predicting short-term mortality in critically ill patients [17,22,27,30]. However, in virtually all these studies patients already had established shock at the time of DPP3 and renin measurement. Whether elevations of these biomarkers are associated with the subsequent onset of shock in at-risk patients is unknown. Therefore, using plasma samples collected in a recently completed multicenter trial, we sought to investigate whether DPP3 and renin would be associated with the subsequent need for vasopressor support and death in a cohort of patients with acute hypoxemia from COVID-19 who were not in shock but were at risk of developing shock.

2. Methods

2.1. Study design

This study is a post-hoc analysis of DPP3 and renin levels from biospecimens collected from two of the randomized trials completed within the fourth Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-4) Host Tissue trial (NCT04924660), a randomized shared-placebo platform trial evaluating multiple therapies in patients hospitalized for COVID-19 [31]. In ACTIV-4 Host Tissue, patients aged ≥18 years hospitalized with COVID-19 with positive SARS-CoV-2 molecular or antigen test and diagnosed with new-onset or acute-on-chronic hypoxemia were recruited from 35 hospitals across the U.S. and included in one of two trials running in parallel with a shared placebo arm to investigate the RAS-modulating agents TXA-127, a synthetic angiotensin- [1-7], and TRV-027, an angiotensin II type 1 receptor-biased ligand. The full protocol is published as a supplement to the primary trial manuscript [31]. (The ACTIV-4 Host Tissue platform included a third non-RAS agent, fostamatinib, the study of which contributed to the shared placebo; however, none of the fostamatinib active comparator subjects were included in this analysis, as that trial, as of writing, has yet to be finalized.) All participants provided written informed consent, and the study was approved by the institutional review board (IRB) of Vanderbilt University Medical Center, which oversaw the trial, with appropriate local IRB reliance at participating sites. Neither RAS agent studied was found to improve oxygen-free days (primary outcome), and both trials met prespecified stopping criteria. Approximately 20 % of patients in the parent studies experienced hypotension, which was defined as low arterial blood pressure leading to one of three interventions: [1] initiation or increase in vasopressor therapy, [2] administration of a fluid bolus of ≥500 mL, or [3] dose reduction or discontinuation of the study drug. Notably, though these RAS modulators could theoretically induce hypotension and for this reason we carried out analyses stratified by treatment arm including analyses restricted to the placebo group, the observed rates of hypotension in the active treatment and placebo arms were similar for both agents in the parent study [31]. Given that our primary outcome was the development of shock, patients requiring vasopressor support on or prior to study Day 0 were excluded.

2.2. Outcome measures

In the current analysis, we used the initiation of vasopressor agents as a surrogate for shock onset. Specifically, we measured the cumulative incidence of vasopressor initiation by Day 28 (primary endpoint) based on Day 0 (at time of randomization) DPP3 and renin. Secondary endpoints included 28-day mortality, vasopressor-free days within 28 days, and incident hypotension (as defined in the parent trial above) within 7 days.

2.3. Biospecimen collection

Plasma samples from ACTIV-4 Host Tissue participants were obtained from the ACTIV Biorepository and shipped on dry ice to investigators (LWB, CTL) at Emory University. The ACTIV Biorepository is a central web-based virtual biorepository portal providing a readily searchable systematic inventory of the samples and associated metadata to the public. This biorepository was derived from trials under the public-private COVID-19 therapeutic partnership between the National Institutes of Health (NIH) and pharmaceutical companies. Samples were originally collected as part of the ACTIV-4 Host Tissue parent study on Day 0 (at the time of randomization) among participants drawn from all three study arms (TXA127, TRV-027, or shared placebo).

2.4. DPP3 and renin quantification

Plasma samples in EDTA were received on dry ice and stored at −80 °C until ready for processing. Upon thawing, samples were separated into two aliquots (300 μL and 50 μL. The 300-μL sample was immediately analyzed at Emory University using the direct renin chemiluminescent immunoassay (LIAISON XS, DiaSorin Molecular LLC., Cypress, California). The 50-μL sample was re-frozen to −80 °C and shipped to 4TEEN4 Pharmaceuticals GmbH (Hennigsdorf, Germany) for DPP3 measurement using a sandwich-type luminometric immunoassay. The assay for DPP3 exhibits stability for up to 15 days and 6 freeze-thaw cycles [13].

2.5. Statistical analysis

In our primary analysis, we estimated the association of higher DPP3 and renin at study Day 0 with time to vasopressor therapy initiation while accounting for death as a competing risk using cumulative incidence curves with Gray's test and multivariable Fine-Gray subdistribution hazards models. DPP3 and renin were evaluated both as dichotomous variables according to sample median split and as continuous variables with distributions normalized by $\log_2$ transformation. Thus, subdistribution hazard ratio (SHR) estimates and 95 % confidence intervals (CI) for vasopressor initiation are presented in reference to participants with values below the sample median or per two-fold increment in DPP3 or renin, respectively. Multivariable Fine-Gray models were adjusted for age, sex assigned at birth, baseline shock index (heart rate/systolic blood pressure), baseline level of oxygen support according to the WHO ordinal COVID-19 scale [32], and ACTIV-4 Host Tissue study treatment arm (TRV-027, TXA-127, or placebo).

Secondary outcomes included 28-day all-cause mortality, vasopressor-free days over 28 days, and the occurrence of a hypotensive event requiring intervention during the first 7 days of the study as defined and reported in the parent study and outlined above. Associations of DPP3 and renin with mortality were evaluated using Cox proportional hazards models, and associations with 7-day incident hypotension were assessed with logistic regression. Vasopressor-free days were modeled as an ordered categorical variable, interpreted as a count of days free from vasopressor therapy between study time of randomization (Day 0) and Day 28, similar to the modeling of the oxygen-free days in the parent trial [31,33]. As in the parent trial and similar to other recent trials using organ support as an outcome [34,35], participants who died during this period were coded as −1 regardless of vasopressor use during their time alive; thus, vasopressor-free days could take any integer value between −1 and 28, with a value of 28 representing alive without any need for vasopressor support during the study period. Associations of DPP3 and renin with vasopressor-free days were assessed via proportional odds logistic regression, with resulting odds ratios (OR) <1.0 representing fewer days free of vasopressor therapy. All analyses included adjustments for the covariates described above. To assess the consistency of results across the placebo, TRV-027, and TXA-127 arms, in a supplemental analysis we stratified results by treatment group and assessed for interaction between the outcomes and treatment arms. Analyses were completed in R 4.2.3 (2023) with a two-sided type 1 error rate (α) of 0.05.

3. Results

3.1. Baseline characteristics and clinical outcomes

Among 510 patients in the two included ACTIV-4 Host Tissue trials, circulating DPP3 and/or renin were assayed in a total of 199 participants (39.0 %) at the time of study randomization (Day 0). Fifteen participants (7.5 %) received vasopressor therapy on or before Day 0 and were thus excluded from the analysis, leaving a total analytic sample size of 184, among which there were 178 with measured DPP3 and 176 participants with measured renin.

Mean (standard deviation) age was 54.3 (13.9) years and 63.0 % were male (Table 1). The treatment arm distribution was: placebo, $n = 65$ (35.3 %); TRV-027, $n = 53$ (28.8 %); and TXA-127, $n = 66$ (35.9 %). Median [interquartile range] plasma values were 40.9 [28.4–59.8] ng/mL for DPP3 ($n = 193$) and 12.7 [5.4–35.3] pg/mL for renin ($n = 191$). A total of 40 participants (21.7 %) developed a vasopressor requirement by day 28 (16 in the placebo arm; 14 in the TRV-027 arm; and 10 in the TXA-127 arm), with a median [interquartile range] time to initiation of 7 [3−11] days. A total of 28 deaths (15.2 %) occurred within 28 days of randomization (median time to death = 12 [8–15] days; Table 1): 10 deaths in the placebo arm; 12 in the TRV-027 arm; and 6 in the TXA-127 arm. Six deaths occurred without the initiation of vasopressor therapy.

The baseline characteristics and clinical outcomes of the 184 subjects included in this sub-study were similar to that of the entire ACTIV-4 Host Tissue trial population (**Supplementary Table A1**).

3.2. Primary outcome: association between baseline DPP3 and renin levels and vasopressor initiation

Participants with higher circulating DPP3 (i.e., ≥median) had a significantly higher cumulative incidence of vasopressor initiation compared to those with DPP3 below the median (28.4 % vs. 16.7 %, respectively; $p = 0.031$; unadjusted SHR [95 % CI] = 2.00 [1.08, 3.74]; Fig. 1A and Table 2). In contrast, there was no significant difference in cumulative incidence of vasopressor initiation between groups dichotomized by the overall sample median renin concentration (26.5 % in those with renin ≥median vs. 18.3 % in those with renin <median; $p = 0.25$; unadjusted SHR [95 % CI] = 1.44 [0.77, 2.71]; Fig. 1B and Table 2). After adjustment for age, sex, baseline shock index, baseline level of oxygen support, and treatment arm, the results were largely consistent, with no signal for renin, whereas participants with DPP3 above the median had shorter time to vasopressor initiation (adjusted SHR [95 % CI] = 1.99 [1.00, 3.97]; Table 2). Results for DPP3 and renin as $\log_2$-normalized continuous variables were consistent with those dichotomized by median split, with an adjusted SHR of 1.46 [1.01, 2.13] for time to vasopressor initiation per two-fold increment in DPP3, but no significant signal for renin (Table 2). When stratified by treatment arm, the association of DPP3 with vasopressor initiation appeared to be most strongly driven by the TRV-027 arm (adjusted SHR [95 % CI] = 5.10 [1.64, 15.88]) rather than the TXA-127 arm (adjusted SHR [95 % CI] = 1.23 [0.36, 4.15]) or placebo arm (adjusted SHR [95 % CI] = 1.51 [0.48, 4.71]), though the interaction was not statistically significant (p for interaction = 0.106; **Supplementary Table A2**).

3.3. Secondary outcomes

Secondary outcomes followed a similar pattern. Higher DPP3 was associated with significantly greater 28-day mortality (adjusted HR [95 % CI] = 4.33 [1.72, 10.96]; per two-fold increment = 1.84 [1.20, 2.82]), whereas renin values were not significantly associated with 28-day

Table 1
Baseline characteristics and primary outcomes of 184 patients with measured circulating DPP3 or renin from the ACTIV-4 Host Tissue trial.

	Total Sample (N = 184)	DPP3 < median (40.9 ng/mL)	DPP3 ≥ median	Renin < median (12.7 pg/mL)	Renin ≥ median
Age, years, mean (SD)	54.3 (13.9)	53.9 (14.8)	54.6 (13.3)	54.5 (14.1)	54.0 (13.9)
Age group, n (%)					
18–30 years	11 (6.0)	7 (7.8)	4 (4.5)	6 (6.5)	4 (4.8)
31–64 years	128 (69.6)	61 (67.8)	62 (70.5)	65 (69.9)	58 (69.9)
≥65 years	24 (24.5)	22 (24.4)	22 (25.0)	22 (23.7)	21 (25.3)
Sex assigned at birth, n (%)					
Female	68 (37.0)	34 (37.8)	33 (37.5)	42 (45.2)	24 (28.9)
Male	116 (63.0)	56 (62.2)	55 (62.5)	51 (54.8)	59 (71.1)
Race/ethnicity, n (%)					
Non-Hispanic Black	32 (17.4)	14 (15.6)	16 (18.2)	23 (24.7)	8 (9.6)
Non-Hispanic White	101 (54.9)	49 (54.4)	50 (56.8)	43 (46.2)	54 (65.1)
Hispanic of any race	35 (19.0)	20 (22.2)	14 (15.9)	21 (22.6)	14 (16.9)
Other or prefer not to answer	16 (8.7)	7 (7.8)	8 (9.1)	6 (6.5)	7 (8.4)
Obesity (body mass index ≥30 kg/m^2), n (%)	120 (65.2)	58 (64.4)	58 (65.9)	59 (63.4)	56 (67.5)
Hypertension, n (%)	85 (46.2)	39 (43.3)	44 (50.0)	40 (43.0)	39 (47.0)
Diabetes, n (%)	52 (28.3)	27 (30.0)	25 (28.4)	24 (25.8)	25 (30.1)
Chronic kidney disease (not undergoing kidney replacement therapy), n (%)	14 (7.6)	8 (8.9)	6 (6.8)	10 (10.8)	4 (4.8)
Medication use prior to COVID-19, n (%)					
Angiotensin converting enzyme inhibitor	12 (6.5)	5 (5.6)	7 (8.0)	2 (2.2)	9 (10.8)
Angiotensin receptor blocker	6 (3.3)	4 (4.4)	2 (2.3)	3 (3.2)	2 (2.4)
Predominant SARS-CoV-2 variant in the US					
Delta (enrolled prior to and including Dec. 26, 2021)	173 (94.0)	86 (95.6)	81 (92.0)	89 (95.7)	77 (92.8)
Omicron (enrolled after Dec. 26, 2021)	11 (6.0)	4 (4.4)	7 (8.0)	4 (4.3)	6 (7.2)
Receipt of ≥ 1 COVID-19 vaccine dose	48 (26.1)	25 (27.8)	22 (25.0)	27 (29.0)	20 (24.1)
Baseline level of oxygen support according to World Health Organization COVID-19 clinical progression scale,* assessed at randomization					
Level 4: hospitalized and receiving supplemental oxygen by nasal prongs or mask	118 (64.1)	63 (70.0)	51 (58.0)	65 (69.9)	49 (59.0)
Level 5: hospitalized and receiving high-flow nasal oxygen or noninvasive ventilation	64 (34.8)	26 (28.9)	36 (40.9)	26 (28.0)	34 (41.0)
Level 6 or 7: hospitalized and receiving invasive mechanical ventilation alone or with other organ support	2 (1.1)	1 (1.1)	1 (1.1)	2 (2.2)	0 (0.0)
Shock index,† (beats / min) / mm Hg, mean (SD)	0.64 (0.15)	0.64 (0.16)	0.65 (0.13)	0.61 (0.14)	0.69 (0.14)
Treatment arm assignment, n (%)					
Placebo	65 (35.3)	25 (27.8)	34 (38.6)	34 (36.6)	26 (31.3)
TRV-027	53 (28.8)	32 (35.6)	21 (23.9)	27 (29.0)	25 (30.1)
TXA-127	66 (35.9)	33 (36.7)	33 (37.5)	32 (34.4)	32 (38.6)
Vasopressor use within 28 days of randomization,‡ n (%)	40 (21.7)	15 (16.7)	25 (28.4)	17 (18.3)	22 (26.5)
Days to vasopressor initiation, median [interquartile range]	7 [3–11]	11 [8–13]	4 [2–8]	7 [4–10]	7 [2–12]
Vasopressor-free days,§ mean (SD)	26.9 (4.1)	27.1 (3.5)	26.6 (5.0)	26.8 (4.6)	27.1 (3.4)
Hypotensive event within 7 days of randomization, n (%)	22 (12.0)	5 (5.6)	17 (19.3)	9 (9.7)	13 (15.7)
Death within 28 days of randomization,‖ n (%)	28 (15.2)	6 (6.7)	22 (25.0)	12 (12.9)	15 (18.1)
Days to death, median [interquartile range]	13 [9–28]	13 [11–18]	11 [7–14]	12 [8–16]	10 [7–14]

* Patients meeting criteria for Levels 4–7 of the 8-level ordinal scale were eligible for the parent trial. Other levels included: Level 1, ambulatory and not hospitalized with no limitation in activities; Level 2, ambulatory and not hospitalized with some limitation of activities or receiving home oxygen therapy; Level 3, hospitalized with mild disease and not receiving supplemental oxygen; Level 8, dead.

† Heart rate divided by systolic blood pressure.

‡ Includes any vasopressors or inotropes (e.g., dobutamine, dopamine, epinephrine, milrinone, norepinephrine, phenylephrine, and vasopressin).

§ Among those alive at Day 28 (n = 156).

‖ 6 deaths occurred without vasopressor initiation.

mortality in unadjusted or adjusted Cox models (Table 3). Likewise, higher DPP3 was associated with fewer vasopressor-free days (adjusted OR [95 % CI] = 0.33 [0.14, 0.74]; per two-fold increment = 0.61 [0.39, 0.94]), but higher renin was not (Table 4). Finally, DPP3 higher than the median was associated with greater odds of a hypotensive event over the first 7 days (adjusted OR [95 % CI] = 4.00 [1.21, 13.18]), and, similarly, a two-fold increment in DPP3 was associated with increased odds of hypotension (adjusted OR [95 % CI] = 1.73 [1.01, 2.98], Table 5).

Results for each secondary outcome stratified by treatment arm are presented in **Supplementary Tables A3-A5**. Notably, higher DPP3 remained significantly associated with greater mortality among participants in the TXA-127 arm (adjusted HR [95 % CI] per two-fold increment = 2.63 [1.21, 5.71]; **Supplementary Table A3**), and with fewer vasopressor-free days in both the placebo (adjusted HR [95 % CI] vs. <median = 0.25 [0.06, 0.88]) and TXA-127 (adjusted HR [95 % CI] per two-fold increment = 0.49 [0.22, 0.97]) arms **(Supplementary Table A4)**.

4. Discussion

4.1. Major findings

In this post-hoc analysis of two randomized controlled trials of novel

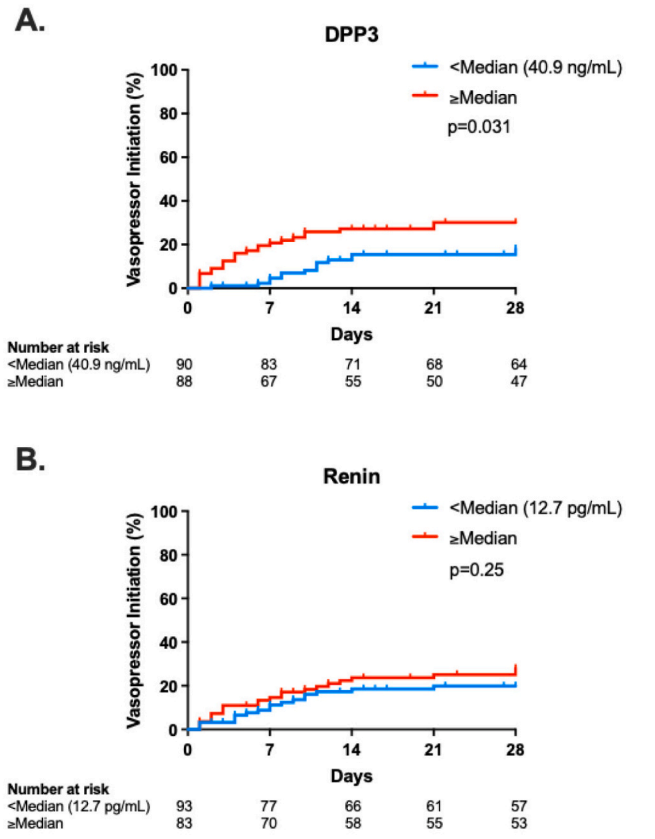

Fig. 1. Cumulative incidence curves for initiation of vasopressor support according to sample median split of (A) DPP3 and (B) renin. *P*-values are derived from Gray's test with death treated as a competing risk. DPP3, dipeptidyl peptidase 3.

Table 2
Association of baseline DPP3 and renin with time to initiation of vasopressor therapy over 28 days among 184 ACTIV-4 Host Tissue trial participants hospitalized with COVID-19 and new-onset hypoxemia.

	Subdistribution Hazard Ratio (95 % CI)*	
	Unadjusted	Adjusted†
DPP3 ≥ median, vs. <median (40.9 ng/mL)	2.00 (1.08, 3.74)	1.99 (1.00, 3.97)
Log_2[DPP3]	1.35 (0.98, 1.87)	1.46 (1.01, 2.13)
Renin ≥ median, vs. <median (12.7 pg/mL)	1.44 (0.77, 2.71)	1.11 (0.54, 2.28)
Log_2[renin]	1.08 (0.94, 1.25)	0.97 (0.80, 1.18)

ACTIV-4, fourth Accelerating COVID-19 Therapeutic Interventions and Vaccines platform; CI, confidence interval; DPP3, dipeptidyl peptidase 3.
* Estimated via Fine-Gray subdistribution hazards models with 28-day mortality as a competing risk.
† Adjustments included age, sex assigned at birth, baseline shock index, baseline level of oxygen support, and treatment arm.

RAS modulators within the ACTIV-4 Host Tissue multicenter platform trial, we found that higher DPP3 was associated with subsequent vasopressor requirement, hypotensive events, and mortality over 28 days. The association of higher DPP3 with mortality was especially strong, with an adjusted hazard ratio of 4.3. The association of DPP3 with subsequent hemodynamic deterioration was reproduced using multiple definitions of hypotension, including time to vasopressor initiation within 28 days, vasopressor-free days within 28 days, and development of incident hypotension requiring intervention over 7 days. Likewise, our results were reproduced when DPP3 was dichotomized (≥median vs. <median) or was treated as a continuous (log_2-transformed) variable. In contrast, we observed no statistically significant associations between baseline renin levels and incident hypotension or mortality. Notably, the median DPP3 level observed in our cohort of 40.9 ng/mL is similar to the cutoffs (40 ng/mL) previously shown to have prognostic value for predicting shock or shock outcomes in multiple settings [17-19,30,36,37].

Table 3
Association of baseline DPP3 and renin with mortality over 28 days among 184 ACTIV-4 Host Tissue trial participants hospitalized with COVID-19 and new-onset hypoxemia.

	Hazard Ratio (95 % CI)*	
	Unadjusted	Adjusted†
DPP3 ≥ median, vs. <median (40.9 ng/mL)	4.34 (1.76, 10.71)	4.33 (1.72, 10.96)
Log_2[DPP3]	1.56 (1.08, 2.24)	1.84 (1.20, 2.82)
Renin ≥ median, vs. <median (12.7 pg/mL)	1.37 (0.64, 2.92)	0.95 (0.39, 2.31)
Log_2[renin]	1.02 (0.83, 1.24)	0.89 (0.71, 1.13)

ACTIV-4, fourth Accelerating COVID-19 Therapeutic Interventions and Vaccines platform; CI, confidence interval; DPP3, dipeptidyl peptidase 3.
* Estimated via Cox proportional hazards models.
† Adjustments included age, sex assigned at birth, baseline shock index, baseline level of oxygen support, and treatment arm.

Table 4
Association of baseline DPP3 and renin with days free of vasopressor support over 28 days among 184 ACTIV-4 Host Tissue trial participants hospitalized with COVID-19 and new-onset hypoxemia.

	Odds Ratio (95 % CI)*	
	Unadjusted	Adjusted†
DPP3 ≥ median, vs. <median (40.9 ng/mL)	0.41 (0.20, 0.81)	0.33 (0.14, 0.74)
Log_2[DPP3]	0.69 (0.48, 0.99)	0.61 (0.39, 0.94)
Renin ≥ median, vs. <median (12.7 pg/mL)	0.63 (0.31, 1.23)	1.01 (0.42, 2.45)
Log_2[renin]	0.91 (0.77, 1.09)	1.03 (0.82, 1.31)

ACTIV-4, fourth Accelerating COVID-19 Therapeutic Interventions and Vaccines platform; CI, confidence interval; DPP3, dipeptidyl peptidase 3.
* Estimated via proportional odds logistic regression. An odds ratio < 1.0 indicates fewer days free of vasopressor support.
† Adjustments included age, sex assigned at birth, baseline shock index, baseline level of oxygen support, and treatment arm.

Table 5
Association of baseline DPP3 and renin with hypotension occurring during the first 7 study days among 184 ACTIV-4 Host Tissue trial participants hospitalized with COVID-19 and new-onset hypoxemia.

	Odds Ratio (95 % CI)*	
	Unadjusted	Adjusted†
DPP3 ≥ median, vs. <median (40.9 ng/mL)	4.07 (1.43, 11.58)	4.00 (1.21, 13.18)
Log_2[DPP3]	1.68 (1.07, 2.63)	1.73 (1.01, 2.98)
Renin ≥ median, vs. <median (12.7 pg/mL)	1.73 (0.70, 4.29)	1.45 (0.46, 4.59)
Log_2[renin]	1.23 (0.98, 1.55)	1.27 (0.93, 1.75)

ACTIV-4, fourth Accelerating COVID-19 Therapeutic Interventions and Vaccines platform; CI, confidence interval; DPP3, dipeptidyl peptidase 3.
* Estimated via logistic regression.
† Adjustments included age, sex assigned at birth, baseline shock index, baseline level of oxygen support, and treatment arm.

4.2. Interpretation of results in context of prior studies and ongoing research

Though the classical RAS was discovered over a century ago [38], its potential role in septic shock pathophysiology and treatment has only

recently become a focus of critical care research. Furthermore, though the results of this and other studies [13-18,20,30] suggest significant promise for DPP3 as a biomarker in critical illness, much of the RAS is complex and remains relatively poorly understood. For example, DPP3 inactivates angiotensin II, a primary effector molecule of the classical RAS. Consequently, pharmacologic DPP3 inhibition to enhance angiotensin II activity has been proposed as a treatment for shock, with data from animal models available to support this approach and a phase I trial of a DPP3 inhibitor (procizumab) currently underway (NCT06331884) [14,39,40]. Likewise, DPP3 has been proposed as a biomarker that may identify patients with septic shock and relative angiotensin II deficiency who may benefit from targeted vasopressor therapy with exogenous angiotensin II [40,41]. However, DPP3 also inactivates angiotensin- [1-7], the primary effector molecular of the counterbalancing alternative RAS (Supplementary Fig. A1). In contrast to angiotensin II, which has vasoconstrictive, proinflammatory, prothrombotic, and profibrotic effects, angiotensin- [1-7] has vasodilatory, anti-inflammatory, antithrombotic, and antifibrotic properties [42,43]. Therefore, the net hemodynamic effect of DPP3 inhibition in humans may be difficult to predict, and prospective data are required to better define the prognostic and therapeutic meaning of DPP3 levels in human sepsis.

The lack of statistically significant association between renin levels and the development of shock or mortality in most of our analyses appears to run contrary to multiple recent studies [21-29]. One possible explanation is simply a type II error, as most of the point estimates for the associations between renin levels and outcomes were in the expected direction but did not achieve statistical significance. Another possibility is differences in timing of renin measurement. In our study, we excluded patients requiring vasopressor therapy prior to randomization and our median time to vasopressor initiation was 7 days. In contrast, either all [21,23,26] or the majority [22,24,25,27,28] of patients in the prior studies reporting an association between renin and mortality or organ dysfunction were experiencing shock and requiring vasopressor support at the time of evaluation. In the context of these prior studies, our findings are consistent with DPP3 as a pre-shock biomarker, renin as an early shock biomarker, and lactate as an established shock biomarker. However, additional data are required to evaluate this hypothesis.

4.3. Study strengths and limitations

This investigation has a number of strengths. All biospecimen samples were collected within the context of a rigorously executed double-blind, randomized, placebo-controlled trial across 35 hospitals. Furthermore, the parent study had broad inclusion criteria and limited exclusion criteria, suggesting our findings may generalize to other populations. In addition, unlike prior studies of DPP3 and renin that focused on patients with or at imminent risk of developing shock, our study population excluded patients requiring vasopressor therapy at time of randomization. Finally, our primary finding that higher DPP3 was associated with subsequent shock was robust to multiple definitions and timeframes of hypotension and was reproduced when we analyzed DPP3 levels as a continuous (rather than dichotomized) variable.

There are also several limitations to this study. Approximately two-thirds of our cohort received modulators of the RAS which could theoretically influence the development of the outcome of interest, hypotension. Importantly, however, hypotension was a prespecified adverse event in the parent platform trial and no significant differences in the rates of hypotension at Day 7 or day 28 were observed with either agent [31]. Stratifying our analyses by treatment arm did yield a few statistically significant results, but a consistent discernable pattern was not observed. Moreover, we did not detect any statistically significant treatment interaction in our analyses. Furthermore, when restricting our analyses to placebo-treated subjects, the effect sizes of the associations between baseline DPP3 level and our primary and secondary outcomes were largely preserved despite the loss of statistical power. Finally, any biologic rationale for how treatment with TXA-127 or TRV-027 could influence the relationship between DPP3 levels and risk of shock remains speculative.

Among other limitations, the limited sample size, as previously noted, may potentially explain the lack of a significant signal for renin. Furthermore, all included patients were hospitalized with acute hypoxic respiratory failure from COVID-19, which limits generalizability to lower acuity patients or other infections. Prior studies of DPP3 in COVID-19 are limited [30-33], and no prior studies of the prognostic value of renin in COVID-19 have been published. Moreover, this is a post-hoc analysis, which increases the risk of unmeasured confounding and renders causative inference difficult. Next, while we had planned to evaluate the association of sequential DPP3 and renin levels with shock, the number of specimens collected beyond Day 0 precluded such an analysis. In multiple prior studies including several in which baseline levels carried no prognostic significance, *changes* in renin were found to be associated with organ dysfunction and death [14,16,17,22,24-29,36]. Similarly, we had hoped to analyze lactate in comparison to both DPP3 and renin, but lactate measurement was not protocolized in the parent study and lactate levels were unavailable for the majority of the participants. Furthermore, though observational studies often use vasopressor use as a surrogate of shock [44-46], it is an imperfect surrogate as not all patients with hypotension requiring vasopressor therapy have shock (i.e., hypotension from sedation), and we were unable to clinically adjudicate this. However, the strong relationship found between higher DPP3 and mortality suggests that the hypotension we observed in patients was clinically relevant. Finally, prospective external validation will be vital to confirm these findings.

5. Conclusion

In this post-hoc analysis of two large randomized controlled trials within the ACTIV-4 Host Tissue platform, higher baseline DPP3 levels were associated with the subsequent development of shock. In contrast, within the limitations of our study, we failed to observe a relationship between renin and the multiple definitions of hypotension assessed or mortality, while DPP3 levels were strongly and independently associated with 28-day mortality. Though hypothesis-generating, these data reinforce the rationale for future prospective research on the use of DPP3 as a prognostic biomarker or a biomarker to guide therapy in patients with sepsis or in other critically ill patients at risk of shock.

Ethics approval and consent to participate

The study was approved by the institutional review board (IRB) of Vanderbilt University Medical Center, which oversaw the trial, with appropriate local IRB reliance at participating sites. All participants provided written informed consent.

Availability of data and materials

Deidentified, patient-level data with a supporting data dictionary from the parent ACTIV-4 trial are publicly available via the National Heart, Lung, and Blood Institute (NHLBI) BioData Catalyst; information on how to obtain permission to access the data from the NIH is available at https://biodatacatalyst.nhlbi.nih.gov/. A systematic inventory of the samples analyzed in this study and the associated meta-data are available via the ACTIV Biorepository; information on how to obtain access to the biospecimens is available at https://activ-biorep.org/.

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Declaration of competing interest

All authors completed and submitted the ICMJE form for disclosure of potential conflicts of interest.

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Appendix A. Supplementary data

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