

## **A novel role for cytochrome P450 epoxygenase metabolites in septic shock – supplementary material**

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## Supplementary Methods

### VANISH study inclusion and exclusion criteria

Adult patients who require vasopressors for the management of sepsis despite adequate fluid resuscitation fulfilling these criteria:

Inclusion criteria:

- Fulfil 2/4 of the systemic inflammatory response syndrome criteria (1) due to known or suspected infection within the previous 24 hours.
- Hypotension despite adequate intravenous fluid resuscitation.

Exclusion Criteria

- Patient has received a continuous infusion of vasopressors previously during this ICU admission (other than vasopressors used as emergency treatment [for less than six hours] to stabilize the patient during this episode). Vasopressors include norepinephrine, epinephrine, vasopressin, dopamine, metaraminol, phenylephrine, and (intermittent) terlipressin.
- Regular systemic corticosteroid therapy within the previous three months (this does not include inhaled steroid therapy). Known adrenal dysfunction / insufficiency. End-stage renal failure (i.e. requiring long term dialysis)
- Physician and team are not committed to full active care.
- Patient is known to be pregnant.
- Patient has known acute mesenteric ischemia.
- Patient is known to have Raynaud's phenomenon, systemic sclerosis or other vasospastic diseases.
- Patient has been enrolled in another clinical trial of an investigational medicinal product within 30 days or is enrolled in another interventional study that might

interact with the study drugs.

- Patient has a history of anaphylaxis or hypersensitivity to any study drug.

## References

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*. 1992;101(6):1644–55.

**Supplementary Table 1:** 43 oxylipins and 5 precursor PUFAs (polyunsaturated fatty acids) measurable with the ultrahigh-performance liquid chromatography-electrospray ionization triple quadrupole mass spectrometry (UHPLC-MS) assay. The table shows the precursor polyunsaturated fatty acid and the enzymic pathway producing each. Lower (LLOQ) and upper (ULOQ) limits of quantification are shown along with the number and percentage, brackets, of samples taken at each time point (TP) during the study. Oxylipins in bold are those where there were quantifiable in at least 10% values at baseline (TP0). (LOX, lipoxygenase; CYP450, cytochrome P450, COX, cyclooxygenase, TP0=baseline, TP1=~24h, TP2=~48h, TP3=~96h)

Class	Oxylipin	PUFA precursor	Main pathway	LLOQ (fg/μL)	ULOQ (fg/μL)	TP0 (n=152)		TP1 (n=115)		TP2 (n=79)		TP3 (n=58)	
						Patients with levels below the LLOQ	Patients with levels above the ULOQ	Patients with levels below the LLOQ	Patients with levels above the ULOQ	Patients with levels below the LLOQ	Patients with levels above the ULOQ	Patients with levels below the LLOQ	Patients with levels above the ULOQ
Precursor PUFA	C18:2 Linoleic acid (LA)	-	-	25000	5000000	1 (0.7)	151 (99)	0 (0)	115 (100)	1 (1.3)	78 (99)	0 (0)	58 (100)
	<b>C20:3 Dihomo-γ-linolenic acid (DGLA)</b>	-	-	5000	2500000	1 (0.7)	6 (4)	0 (0)	3 (3)	1 (1.3)	2 (3)	0 (0)	1 (2)
	C20:4 Arachidonic acid (AA)	-	-	2500	5000000	1 (0.7)	148 (97)	0 (0)	115 (100)	1 (1.3)	78 (99)	0 (0)	57 (98)
	<b>C20:5 Eicosapentaenoic acid (EPA)</b>	-	-	2500	2500000	1 (0.7)	39 (26)	0 (0)	30 (26)	1 (1.3)	17 (22)	0 (0)	9 (16)
	C22:6 Docosahexaenoic acid (DHA)	-	-	2500	2500000	1 (0.7)	139 (91)	0 (0)	108 (94)	1 (1.3)	71 (90)	0 (0)	52 (90)
Hydroxy PUFA - HODE	<b>9-Hydroxyoctadecadienoic acid (9(S)-HODE)</b>	C18:2 (LA)	LOX	2.5	5000	1 (0.7)	4 (3)	0 (0)	1 (1)	1 (1.3)	1 (1)	0 (0)	0 (0)
	<b>13(S)-Hydroxyoctadecadienoic acid (13(S)-HODE)</b>	C18:2 (LA)	LOX	250	500000	1 (0.7)	4 (3)	0 (0)	1 (1)	1 (1.3)	1 (1)	0 (0)	0 (0)
Hydroxy PUFA - HEPE	<b>12 (S)-Hydroxyeicosapentaenoic acid (12(S)-HEPE)</b>	C20:5 (EPA)	LOX	500	500000	66 (43)	0 (0)	55 (48)	0 (0)	40 (51)	0 (0)	23 (40)	0 (0)
	15(S)-Hydroxyeicosapentaenoic acid (15(S)-HEPE)	C20:5 (EPA)	LOX	250	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
EET	<b>5,6-Epoxyeicosatrienoic acid (5,6-EET)</b>	C20:4 (AA)	CYP450	250	500000	118 (78)	0 (0)	93 (81)	0 (0)	62 (78)	0 (0)	49 (84)	0 (0)
	8,9- Epoxyeicosatrienoic acid (8,9-EET)	C20:4 (AA)	CYP450	500	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	<b>11,12- Epoxyeicosatrienoic acid (11,12-EET)</b>	C20:4 (AA)	CYP450	250	500000	109 (72)	0 (0)	85 (74)	0 (0)	59 (75)	0 (0)	41 (71)	0 (0)
	14,15- Epoxyeicosatrienoic acid (14,15-EET)	C20:4 (AA)	CYP450	1000	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
DHET	5,6-Dihydroxyeicosatrienoic acid (5,6-DHET)	C20:4 (AA)	CYP450	250	250000	139 (91)	0 (0)	108 (94)	0 (0)	76 (96)	0 (0)	50 (86)	0 (0)

	<b>8,9-Dihydroxyeicosatrienoic acid (8,9-DHET)</b>	C20:4 (AA)	CYP450	250	250000	123 (81)	0 (0)	97 (84)	0 (0)	74 (94)	0 (0)	46 (79)	0 (0)
	<b>11,12-Dihydroxyeicosatrienoic acid (11,12-DHET)</b>	C20:4 (AA)	CYP450	250	500000	116 (76)	0 (0)	93 (81)	0 (0)	66 (84)	0 (0)	46 (79)	0 (0)
	<b>14,15-Dihydroxyeicosatrienoic acid (14,15-DHET)</b>	C20:4 (AA)	CYP450	250	500000	82 (54)	0 (0)	79 (69)	0 (0)	63 (80)	0 (0)	42 (72)	0 (0)
<b>Hydroxy PUFA - HETE</b>	<b>5(S)-Hydroxyeicosatetraenoic acid (5(S)-HETE)</b>	C20:4 (AA)	LOX	500	250000	7 (5)	0 (0)	4 (3)	0 (0)	7 (9)	0 (0)	2 (3)	0 (0)
	<b>8(S)-Hydroxyeicosatetraenoic acid (8(S)-HETE)</b>	C20:4 (AA)	LOX	250	500000	60 (39)	0 (0)	54 (47)	0 (0)	39 (49)	0 (0)	25 (43)	0 (0)
	<b>11(R)-Hydroxyeicosatetraenoic acid (11(R)-HETE)</b>	C20:4 (AA)	COX	250	250000	37 (24)	0 (0)	35 (30)	0 (0)	24 (30)	0 (0)	19 (33)	0 (0)
	<b>12(R)-Hydroxyeicosatetraenoic acid (12(R)-HETE)</b>	C20:4 (AA)	LOX	250	500000	1 (0.7)	0 (0)	1 (0.9)	0 (0)	4 (5)	0 (0)	0 (0)	0 (0)
	<b>15(S)-Hydroxyeicosatetraenoic acid (15(S)-HETE)</b>	C20:4 (AA)	LOX	250	250000	3 (2)	0 (0)	1 (0.9)	0 (0)	2 (3)	0 (0)	0 (0)	0 (0)
	<b>16(R)-Hydroxyeicosatetraenoic acid (16(R)-HETE)</b>	C20:4 (AA)	CYP450	50	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
<b>Hydroxy PUFA - HDoHE</b>	<b>14-hydroxydocosahexaenoic acid (14-HDoHE)</b>	C22:6 (DHA)	LOX	500	250000	11 (7)	0 (0)	10 (9)	0 (0)	9 (11)	0 (0)	10 (17)	0 (0)
	<b>17-hydroxydocosahexaenoic acid (17(S)-HDoHE)</b>	C22:6 (DHA)	LOX	500	250000	99 (65)	0 (0)	83 (72)	0 (0)	59 (75)	0 (0)	42 (72)	0 (0)
	<b>10(S),17(S)-dihydroxydocosahexaenoic acid (10(S),17(S)-DiHDoHE)</b>	C22:6 (DHA)	LOX	50	500000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
<b>ETE</b>	<b>5-Oxo-eicosatetraenoic acid (5-oxo-ETE)</b>	C20:4 (AA)	LOX	250	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	<b>12-Oxo-eicosatetraenoic acid (12-oxo-ETE)</b>	C20:4 (AA)	LOX	250	500000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
<b>Leukotrienes</b>	<b>Leukotriene B4 (LTB4)</b>	C20:4 (AA)	LOX	250	500000	124 (82)	0 (0)	100 (87)	0 (0)	68 (86)	0 (0)	53 (91)	0 (0)
	<b>12-oxo-Leukotriene B4 (12-oxo-LTB4)</b>	C20:4 (AA)	LOX	500	500000	133 (88)	0 (0)	101 (88)	0 (0)	67 (85)	0 (0)	46 (79)	0 (0)
	<b>Leukotriene C4 (LTC4)</b>	C20:4 (AA)	LOX	100	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	<b>Leukotriene D4 (LTD4)</b>	C20:4 (AA)	LOX	50	500000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	<b>Leukotriene E4 (LTE4)</b>	C20:4 (AA)	LOX	100	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)

<b>Prostaglandins and thromboxanes</b>	15-Deoxy- $\Delta$ -12,14-Prostaglandin J2 (15dPGJ2)	C20:4 (AA)	COX	500	250000	151 (99)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	tetranor-PGDM	C20:4 (AA)	COX	500	500000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	tetranor-PGEM	C20:4 (AA)	COX	2500	500000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	tetranor-PGFM	C20:4 (AA)	COX	5000	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	Prostaglandin D2 (PGD2)	C20:4 (AA)	COX	250	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	Prostaglandin E2 (PGE2)	C20:4 (AA)	COX	50	500000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	Prostaglandin F2 $\alpha$ (PG F2 $\alpha$ )	C20:4 (AA)	COX	50	250000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	6-keto-Prostaglandin F1 $\alpha$ (6-keto-PGF1 $\alpha$ )	C20:4 (AA)	COX	500	500000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	8-iso-Prostaglandin F2 $\alpha$ (8-iso-PGF2 $\alpha$ )	C20:4 (AA)	COX	100	250000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	<b>Thromboxane (TXB2)</b>	C20:4 (AA)	COX	250	500000	50 (33)	0 (0)	49 (43)	0 (0)	28 (35)	1 (1)	16 (28)	0 (0)
11-dehydro thromboxane (11-dehydro TXB2)	C20:4 (AA)	COX	50	250000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)	
<b>Resolvins</b>	Resolvin D1	C22:6 (DHA)	LOX	10	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	Resolvin D2	C22:6 (DHA)	LOX	100	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
<b>Lipoxins</b>	Lipoxin A4	C20:4 (AA)	LOX	250	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)
	Lipoxin B4	C20:4 (AA)	LOX	1000	1000000	152 (100)	0 (0)	115 (100)	0 (0)	79 (100)	0 (0)	58 (100)	0 (0)

**Supplementary Table 2:** Time independent (baseline) and time dependent (daily) clinical variables included in the mixed-effects logistic models. (APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; IV, intravenous).  
<sup>a</sup>Additional vasopressors refers to the need for supplementary vasopressor in addition to those under investigation in the original trial (norepinephrine vs vasopressin), this could be additional open label norepinephrine.

<b>Time independent variables (baseline data)</b>	<b>Time dependent variables (daily data)</b>
<b><i>Physiological Variables</i></b>	
Mean arterial pressure	Lowest mean arterial pressure
Heart rate	Highest heart rate
Lactate	Highest lactate
PaO <sub>2</sub> :FiO <sub>2</sub> ratio	Lowest PaO <sub>2</sub> :FiO <sub>2</sub> ratio
Creatinine	Highest creatinine
Bilirubin	Highest bilirubin
Platelet count	Lowest platelet count
Glasgow Coma Score	Average urine output per kg per hour
<b><i>Organ Support</i></b>	
Mechanical ventilation	Mechanical ventilation
Renal replacement therapy	Renal replacement therapy
Volume of IV fluid administered in the 4h prior to enrolment	Total volume of IV fluids administered in 24h
Need for supplementary vasopressors on enrolment <sup>a</sup>	Total norepinephrine equivalent dose of vasopressors
Dose of additional norepinephrine	
<b><i>Measures of disease severity</i></b>	
APACHE II Score	Total SOFA score
<b><i>Chronic Disease</i></b>	
Ischemic heart disease	
Chronic obstructive pulmonary disease	
Chronic kidney disease	
Cirrhosis	
Cancer	
Immunosuppression	
Diabetes	
<b><i>Source of infection</i></b>	
Lung	
Abdomen	
Soft tissue or line	
Other	
<b><i>Other variables</i></b>	
Time from onset of shock to study enrolment	

**Supplementary Table 3:** Clinical comparison of those patients included in the current analysis with those that were not. Continuous variables are given as medians and inter-quartile range (IQR). Categorical variables are given as number over total and percentage. P-values in bold are those <0.05. (BMI, body mass index; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Score; IV, intravenous)

	Patients included in oxylipin analysis	Patients not included in oxylipin analysis	p-value
n	152	257	-
Age median (IQR), years	66 (54-77)	66 (55-76)	0.63
Men, No./total (%)	96/152 (63)	142/257 (55)	0.12
Weight, median (IQR), kg	75 (62-90)	74 (63-86)	0.48
BMI, median (IQR)	25.8 (22.5-31.3)	25.2 (22.4-30)	0.43
Caucasian ethnicity, No./total (%)	126/152 (83)	223/257 (87)	0.28
Recent surgical history, No./total (%)	25/152 (16)	48/257 (19)	0.57
APACHE II score, median (IQR)	24 (19-30)	24 (19-30)	0.80
<b>Pre-existing conditions, No./total (%)</b>			
Ischemic heart disease	25/152 (16)	37/257 (14)	0.58
Severe COPD	10/152 (7)	5/257 (2)	<b>0.03</b>
Chronic kidney failure	7/152 (5)	20/257 (8)	0.30
Cirrhosis	10/152 (7)	5/257 (2)	<b>0.03</b>
Cancer	19/152 (13)	28/257 (11)	0.62
Immunocompromised	8/152 (5)	20/257 (8)	0.42
Diabetes	36/152 (24)	54/257 (21)	0.53
<b>Organ failure, No./total (%)</b>			
Respiratory	56/150 (37)	93/252 (37)	0.93
Kidney	31/152 (20)	54/256 (21)	0.87
Liver	11/134 (8)	9/245 (4)	0.09
Hematological	9/147 (6)	13/251 (5)	0.82
Neurological	53/145 (37)	75/240 (31)	0.28
<b>Physiological variables, median (IQR)</b>			
Mean arterial pressure, mmHg	69 (62-75)	70 (62-78)	0.27
Heart rate, beats/min	94 (80.5-110)	99 (86.5-110)	<b>0.04</b>
Central venous pressure, mmHg	13 (9-19)	12 (9-16)	0.19
Lactate, mmol/L	2.2 (1.5-3.8)	2.4 (1.4-4.4)	0.73
PaO <sub>2</sub> /FiO <sub>2</sub> , kPa	15.6 (18.1-41.4)	24.7 (14.7-39.2)	0.19
Creatinine, mg/dL	1.3 (0.9-2.1)	1.4 (0.8-2.5)	0.40
Bilirubin, mg/dL	0.9 (0.5-1.8)	0.9 (0.5-1.6)	0.49
Platelets, x10 <sup>3</sup> /μL	188 (118-278)	187 (124-294)	0.84
GCS	14 (3-15)	14 (5-15)	0.22
Mechanical ventilation, No./total (%)	83/152 (55)	153/257 (60)	0.33
Renal replacement therapy, No./total (%)	4/152 (3)	7/257 (3)	1.00
Volume of IV fluid in previous 4 h, median (IQR), mL	1041 (542-1952)	1244.5 (752.25-2149.75)	<b>0.03</b>
Patients receiving open-label vasopressor at randomization, No./total (%)	130/152 (86)	218/257 (85)	0.85
Time from onset of shock to receiving first study drug, median (IQR), h	3.6 (2-5)	3.5 (1.5-5.3)	0.45
norepinephrine dose at randomization in those requiring open-label vasopressors, median (IQR), μg/kg/min	0.14 (0.08-0.25)	0.19 (0.12-0.35)	<b>0.002</b>
<b>Source of infection, No./total (%)</b>			
Lung	66/149 (44)	99/251 (39)	0.34
Abdomen	33/149 (22)	60/251 (24)	0.69
Soft tissue or line	4/149 (3)	15/251 (6)	0.15
Other	46/149 (31)	77/251 (31)	0.97
<b>Outcome</b>			
28-Day Mortality, No./total (%)	39/152 (26)	80/256 (31)	0.23

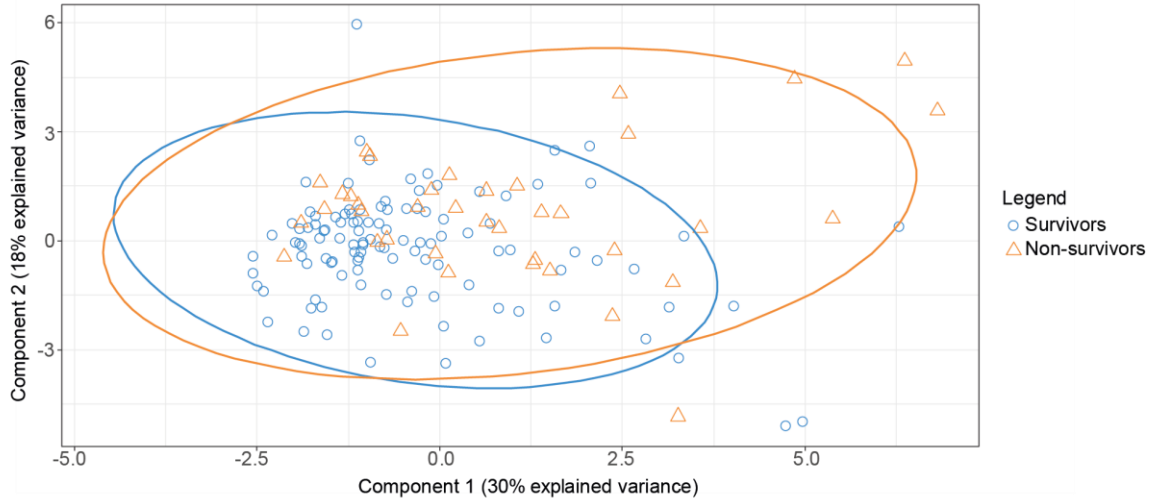


**Supplementary Table 4:** Clinical comparison of those patients who survived and did not survive to day 28 within those included in the current study. Continuous variables are given as medians and inter-quartile range (IQR). Categorical variables are given as number over total and percentage. P-values in bold are those <0.05. (BMI, body mass index; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Score; IV, intravenous)

	Day-28 Survivors	Day-28 non-survivors	p-value
n	113	39	
Age median (IQR), years	65 (52-77)	67 (58-80)	0.13
Men, No./total (%)	74/113 (65)	22/39 (56)	0.31
Weight, median (IQR), kg	75 (62-90)	73 (61-94)	0.88
BMI, median (IQR)	26 (22-31)	27 (22-32)	0.57
Caucasian ethnicity, No./total (%)	93/113 (82)	33/39 (85)	0.74
Recent surgical history, No./total (%)	20/113 (18)	5/39 (13)	0.62
APACHE II score, median (IQR)	23 (18-29)	28 (23-35)	<b>&lt;0.001</b>
<b>Pre-existing conditions, No./total (%)</b>			
Ischemic heart disease	16/113 (14)	9/39 (23)	0.22
Severe COPD	8/113 (7)	2/39 (5)	1.00
Chronic kidney failure	5/113 (4)	2/39 (5)	1.00
Cirrhosis	7/113 (6)	3/39 (8)	0.72
Cancer	14/113 (12)	5/39 (13)	1.00
Immunocompromised	5/113 (4)	3/39 (8)	0.42
Diabetes	30/113 (27)	6/39 (15)	0.19
<b>Organ failure, No./total (%)</b>			
Respiratory	35/111 (32)	21/39 (54)	<b>0.01</b>
Kidney	16/113 (14)	15/39 (38)	<b>0.001</b>
Liver	8/97 (8)	3/37 (8)	1.00
Hematological	7/108 (6)	2/39 (5)	1.00
Neurological	35/108 (32)	18/37 (49)	0.08
<b>Physiological variables, median (IQR)</b>			
Mean arterial pressure, mmHg	68 (62-75)	69 (63-81)	0.51
Heart rate, beats/min	92 (80-110)	95 (83-112)	0.62
Central venous pressure, mmHg	13 (9-18)	15 (10-20)	0.19
Lactate, mmol/L	2 (1.4-3.5)	2.5 (1.7-4.7)	0.06
PaO <sub>2</sub> /FiO <sub>2</sub> , kPa	30.4 (20-42.8)	20.7 (13.1-27.4)	<b>&lt;0.001</b>
Creatinine, mg/dL	1.2 (0.8-1.9)	1.7 (1.0-3.1)	<b>0.045</b>
Bilirubin, mg/dL	0.8 (0.5-1.8)	1.0 (0.6-2.3)	0.49
Platelets, ×10 <sup>3</sup> /μL	177 (111-256)	208 (129-335)	0.11
GCS	14 (6-15)	10 (3-14)	<b>0.01</b>
Mechanical ventilation, No./total (%)	60/113 (53)	23/39 (59)	0.53
Renal replacement therapy, No./total (%)	2/113 (2)	2/39 (5)	0.27
Volume of IV fluid in previous 4 h, median (IQR), mL	1047 (588-1949)	1000 (492-2000)	0.58
Patients receiving open-label vasopressor at randomization, No./total (%)	97/113 (86)	33/39 (85)	0.85
Time from onset of shock to receiving first study drug, median (IQR), h	3.7 (2-5)	3.5 (2-5.1)	0.98
norepinephrine dose at randomization in those requiring open-label vasopressors, median (IQR), μg/kg/min	0.13 (0.08-0.2)	0.22 (0.14-0.35)	<b>0.002</b>
<b>Source of infection, No./total (%)</b>			
Lung	44/111 (40)	22/38 (58)	0.05
Abdomen	29/111 (26)	4/38 (11)	0.07
Soft tissue or line	4/111 (4)	0/38 (0)	0.57
Other	34/111 (31)	12/38 (32)	0.91

**Supplementary Figure 1:** Partial least squared discriminant analysis (PLS-DA) of all oxylipins measurable at baseline comparing 28-day survivors and non-survivors (R2X 0.48, R2Y 0.15, Q2 0.04). A) 2-component PLS-DA scores plots (orange triangle, non-survivors and blue circles, survivors; ellipses 95% Hotelling's ellipses). B) Plot showing the weights of each oxylipin in predicting non-survivors C) Variable importance in projection (VIP) for the PLS-DA models. VIP>1.0 show the variable important in separating the two classes and those >1.5 are the most important.

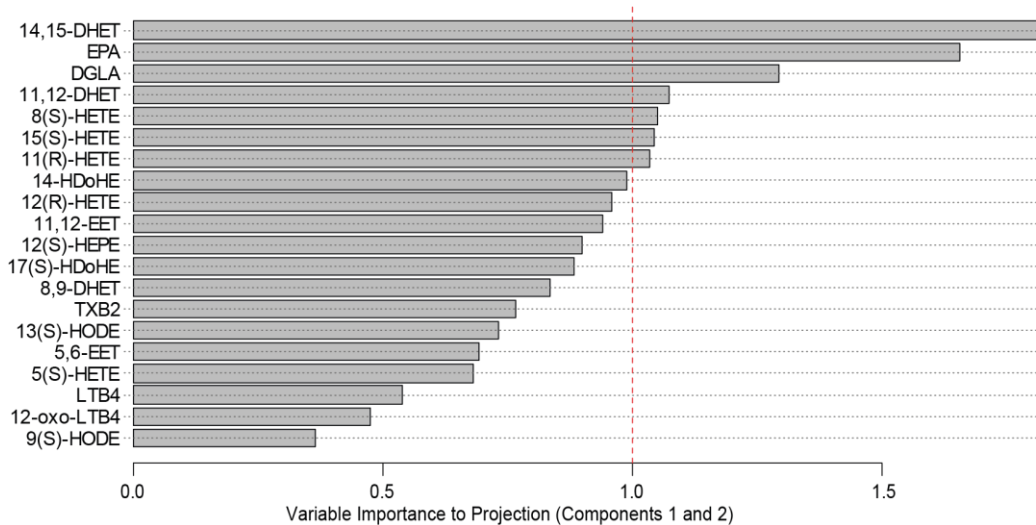
A



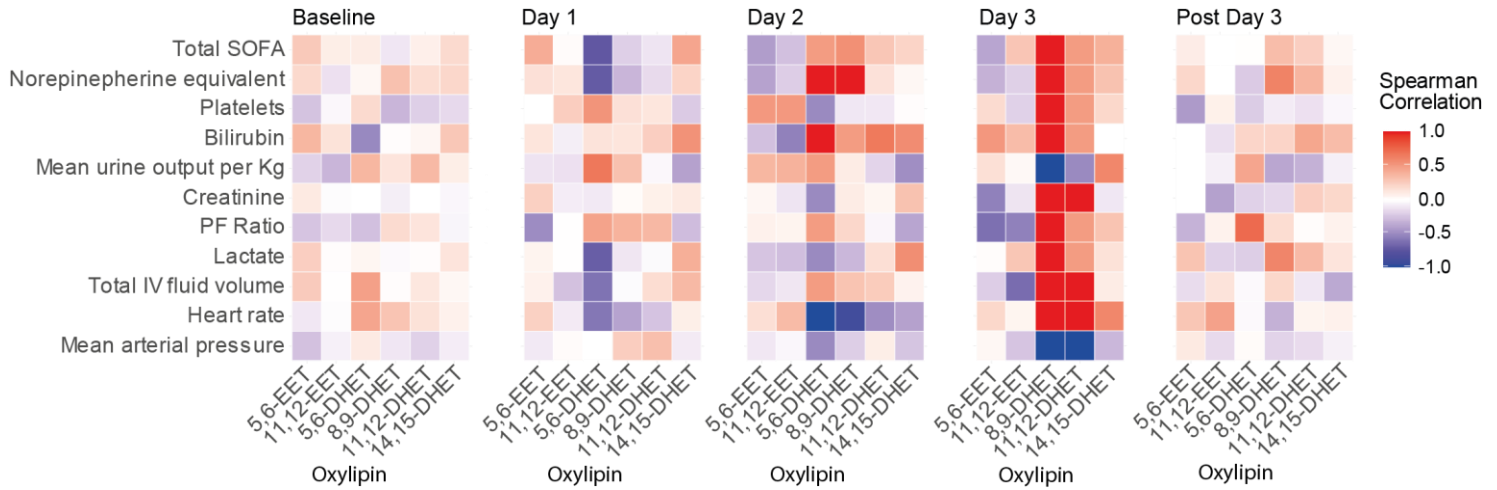
B



C



**Supplementary Figure 2:** Correlation matrices showing the Spearman's rho correlation coefficients for oxylipin concentrations of the dihydroxyeicosatrienoic acids (DHETs) and their precursor epoxyeicosatrienoic acids (EETs) for samples with concentrations above the lower limit of quantification. Data are displayed by day of sampling in relation to baseline (baseline samples (TP0), day 1,2 and 3 post baseline and samples taken on the final sampling time point (day 4-6 post baseline)). Samples are matched to continuous clinical data taken on the same date as samples were drawn. On day 3 there were insufficient samples with quantifiable 5,6-DHET to perform analysis, so this oxylipin has been omitted from this plot. (PF, PaO<sub>2</sub>:FiO<sub>2</sub> ratio; SOFA, sequential organ failure assessment score; IV, intravenous).



**Supplementary Figure 3:** Box plots showing the total sequential organ failure assessment (SOFA) score and its component parts comparing patients in whom levels of dihydroxyeicosatrienoic acids (DHETs) were either below (blue boxes) or above (yellow boxes) the lower limit of quantification. Data are displayed by day of sampling in relation to baseline (baseline samples (TP0), day 1,2 and 3 post baseline and samples taken on the final sampling time point (day 4-6 post baseline)). The neurological component was not recorded due to difficulties in its measurement in sedated patients. The highest possible SOFA score for each component was 4 and the highest total SOFA score possible was 20.

