Microaxial Flow Pump Use and Renal Outcomes in Infarct-Related Cardiogenic Shock – a Secondary Analysis of the DanGer Shock Trial

SUPPLEMENTAL MATERIAL

The DanGer Shock Study Protocol: Renal Section

Guidance on initiation for renal replacement therapy and treatment target in the DanGer Shock protocol (the full DanGer Shock study protocol is available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa2312572/suppl_file/nejmoa2312572_protocol.pdf

- Normal renal function: furosemide infusion: 5-40 mg/h iv if diuresis <1 ml/kg/h.
- Fluid balance is adjusted to secure adequate CVP (10-12 mmHg) but avoid volume overload (negative fluid balance)
- Renal impairment before or during hospitalization results in CRRT by the following indications:
    - Renal insufficiency (s-creatinine > 300-400 mmol/l)
    - Hyperkalemia (s-potassium > 6,5 mmol/l)
    - Treatment-resistant metabolic acidosis (pH <7.30)
    - Volume overload (pulmonary edema) or TD <50 ml for 6 consecutive hours
- Loop diuretics may be supplemented with metolazone 2.5-10 mg/day orally.
- Dialysis catheters are recommended placed in Jugular / subclavia veins.
- CRRT is implemented according to the individual center's own guidelines.

Supplemental Table 1: Baseline characteristics of patients undergoing RRT in both study arms.

Characteristic	All			Standard			mAFP		
	No RRT, N = 233	**RRT**, N = 122	**p-value**	**No RRT**, N = 129	**RRT**, N = 47	**p-value**	**No RRT**, N = 104	**RRT**, N = 75	**p-value**
Age in years, median (IQR)	70 (61, 77)	67 (57, 74)	0.007	70 (62, 76)	67 (57, 72)	0.063	70 (59, 77)	66 (57, 74)	0.082
Male sex, no. (%)	175 (75%)	106 (87%)	0.009	100 (78%)	39 (83%)	0.43	75 (72%)	67 (89%)	0.005
Hypertension, no. (%)	129 (55%)	54 (44%)	0.047	72 (56%)	22 (47%)	0.29	57 (55%)	32 (43%)	0.11
Diabetes, no. (%)	48 (21%)	32 (26%)	0.23	32 (25%)	15 (32%)	0.35	16 (15%)	17 (23%)	0.22
History of Myocardial infarction, no. (%)	43 (18%)	14 (11%)	0.089	22 (17%)	6 (13%)	0.49	21 (20%)	8 (11%)	0.088
History of Heart failure, no. (%)	16 (6.9%)	12 (9.8%)	0.23	10 (7.8%)	4 (8.5%)	>0.99	6 (5.8%)	8 (11%)	0.10
History of Chronic kidney disease, no. (%)	23 (9.9%)	12 (9.8%)	>0.99	14 (11%)	4 (8.5%)	0.78	9 (8.7%)	8 (11%)	0.65
Endotracheal intubation before arrival at cath lab, no. (%)	39 (17%)	24 (20%)	0.49	21 (16%)	7 (15%)	0.82	18 (17%)	17 (23%)	0.37
Systolic blood pressure at randomization, median (IQR)	81 (70, 91)	84 (74, 92)	0.39	81 (73, 90)	83 (71, 95)	0.72	80 (70, 91)	85 (75, 90)	0.46
Resuscitation before randomization, no. (%)	50 (21%)	22 (18%)	0.45	27 (21%)	6 (13%)	0.22	23 (22%)	16 (21%)	0.90
Mean arterial blood pressure at randomization, median (IQR)	63 (55, 71)	64 (56, 72)	0.46	64 (55, 71)	64 (55, 73)	0.88	62 (54, 71)	64 (57, 72)	0.38
Heart rate at randomization, median (IQR)	95 (75, 107)	95 (79, 120)	0.040	95 (74, 110)	96 (80, 121)	0.16	91 (77, 104)	95 (78, 118)	0.10
LVEF at randomization (%), median (IQR)	25 (20, 35)	20 (15, 29)	<0.001	25 (15, 30)	20 (13, 25)	0.002	29 (20, 35)	20 (15, 30)	0.004
Lactate concentration at randomization, median (IQR)	4.3 (3.2, 6.6)	5.2 (3.5, 8.0)	0.019	4.3 (3.1, 6.0)	5.3 (3.5, 8.9)	0.034	4.30 (3.30, 7.10)	4.90 (3.60, 7.00)	0.24

Characteristic	All			Standard			mAFP		
	No RRT, N = 233	**RRT**, N = 122	**p-value**	**No RRT**, N = 129	**RRT**, N = 47	**p-value**	**No RRT**, N = 104	**RRT**, N = 75	**p-value**
pH at randomization, median (IQR)	7.30 (7.18, 7.39)	7.26 (7.16, 7.33)	0.012	7.30 (7.20, 7.39)	7.26 (7.17, 7.32)	0.057	7.29 (7.17, 7.39)	7.26 (7.15, 7.35)	0.12
Hemoglobin admission, median (IQR)	8.70 (7.52, 9.50)	9.10 (7.85, 9.70)	0.043	8.70 (7.60, 9.40)	9.10 (8.10, 9.80)	0.089	8.60 (7.50, 9.58)	9.05 (7.70, 9.60)	0.29
Creatinine at admission, µmol/L, median (IQR)	104 (84, 130)	114 (94, 156)	0.001	105 (85, 139)	116 (95, 155)	0.11	100 (81, 123)	113 (94, 160)	0.001
eGFR, mL/min/1.73 m2, median (IQR)	64 (48, 82)	60 (40, 76)	0.034	61 (43, 79)	55 (41, 71)	0.26	65 (52, 87)	62 (40, 77)	0.031
C-reactive protein (CRP) at admission, mg/L, median (IQR)	5 (2, 22)	5 (3, 22)	0.35	5 (2, 25)	5 (4, 21)	0.52	5 (2, 19)	5 (2, 19)	0.33
SCAI stage at admission, n (%)			0.009			0.007			0.23
SCAI C	141 (61%)	56 (46%)		79 (61%)	18 (38%)		62 (60%)	38 (51%)	
SCAI D or E	92 (39%)	66 (54%)		50 (39%)	29 (62%)		42 (40%)	37 (49%)	
Anterior myocardial infarction, no. (%)	164 (70%)	91 (75%)	0.40	95 (74%)	34 (72%)	0.86	69 (66%)	57 (76%)	0.16
Multivessel, no. (%)	167 (72%)	89 (73%)	0.80	91 (71%)	38 (81%)	0.17	76 (73%)	51 (68%)	0.46
Time of randomization, n (%)			0.75			>0.99			0.57
Randomization performed before revascularization	130 (56%)	71 (58%)		75 (58%)	27 (57%)		55 (53%)	44 (59%)	
Randomization performed in the catheterization laboratory but after revascularization	66 (28%)	30 (25%)		35 (27%)	13 (28%)		31 (30%)	17 (23%)	
Randomization performed ≤12 hr after departure from the catheterization laboratory	37 (16%)	21 (17%)		19 (15%)	7 (15%)		18 (17%)	14 (19%)	

eGFR denotes estimated glomerular filtration rate; mAFP denotes microaxial flow pump; LVEF denotes left ventricular ejection fraction; RRT denotes renal replacement therapy.

Supplemental Table 2: Trajectories of VIS, pH, base excess and MAP

Parameter	Group	Rand	ICU	1h	3h	6h	12h	24h	48h
VIS	Standard		8.0 (5.5 - 10.6)	10.9 (7.8 - 14.0)	15.9 (12.2 - 19.6)	19.3 (15.2 - 23.4)	16.1 (12.3 - 19.8)	13.6 (10.0 - 17.2)	9.9 (7.0 - 12.8)
	mAFP		5.7 (3.6 - 7.8)	8.1 (5.6 - 10.7)	10.9 (8.0 - 13.8)	12.6 (9.5 - 15.7)	12.2 (9.1 - 15.3)	14.7 (11.3 - 18.2)	14.1 (10.9 - 17.3)
Difference			2.3 (-1.0 - 5.7)	2.8 (-1.2 - 6.7)	5.0 (0.3 - 9.7)	6.6 (1.5 - 11.8)	3.9 (-1.0 - 8.7)	-1.1 (-6.1 - 3.8)	-4.2 (-8.4 - 0.1)
pH	Standard	7.27 (7.25 - 7.29)	7.26 (7.24 - 7.28)	7.29 (7.27 - 7.31)	7.33 (7.31 - 7.35)	7.35 (7.33 - 7.37)	7.38 (7.37 - 7.40)	7.42 (7.40 - 7.43)	7.43 (7.42 - 7.44)
	mAFP	7.26 (7.24 - 7.29)	7.29 (7.27 - 7.32)	7.31 (7.30 - 7.33)	7.33 (7.32 - 7.35)	7.34 (7.32 - 7.37)	7.37 (7.35 - 7.38)	7.39 (7.38 - 7.40)	7.41 (7.40 - 7.42)
Difference		0.00 (-0.03 - 0.04)	-0.03 (-0.06 - 0.00)	-0.02 (-0.05 - 0.00)	0.00 (-0.03 - 0.02)	0.01 (-0.02 - 0.04)	0.01 (-0.01 - 0.03)	0.02 (0.01 - 0.04)	0.02 (0.00 - 0.03)
Base excess	Standard		-6.4 (-7.5 - -5.4)				-2.1 (-2.9 - -1.4)	0.1 (-0.6 - 0.9)	1.0 (0.1 - 1.9)
	mAFP		-5.7 (-6.7 - -4.6)				-2.8 (-3.5 - -2.1)	-1.6 (-2.3 - -0.9)	-0.2 (-1.0 - 0.6)
Difference			-0.8 (-2.2 - 0.7)				0.7 (-0.4 - 1.7)	1.7 (0.7 - 2.8)	1.2 (0.0 - 2.4)
MAP	Standard	64.7 (62.7 - 66.7)	76.1 (73.0 - 79.1)	71.9 (69.0 - 74.9)	74.5 (71.8 - 77.2)	70.7 (68.2 - 73.2)	70.0 (67.9 - 72.1)	71.1 (69.0 - 73.3)	72.4 (70.2 - 74.6)
	mAFP	64.1 (62.1 - 66.1)	79.8 (76.9 - 82.8)	79.0 (76.2 - 81.7)	75.1 (72.6 - 77.6)	74.0 (71.7 - 76.2)	73.2 (71.3 - 75.1)	70.0 (68.1 - 72.0)	69.9 (68.0 - 71.9)
Difference		0.6 (-2.3 - 3.4)	-3.8 (-8.0 - 0.5)	-7.0 (-11.0 - -3.0)	-0.6 (-4.3 - 3.1)	-3.3 (-6.6 - 0.1)	-3.2 (-6.0 - -0.4)	1.1 (-1.8 - 4.0)	2.5 (-0.5 - 5.4)

Estimated geometric means of the parameters on the left (with 95% confidence intervals) for each time point, calculated from linear mixed models.

Supplemental Table 3: Stimulation of diuresis and prior use of ACE inhibitor or angiotensin I receptor blocker in both study arms

	Standard care	**Impella**	**P value**
Stimulation of diuresis within f*irst 24 hours of ICU admission*			
Furosemide bolus	48 (36.9%))	59 (38.6%)	P=0.78
Furosemide infusion	38 (29.2%)	43 (28.1%)	P=0.84
Metolazone	7 (5.4%)	7 (4.6%)	P=0.75
Stimulation of diuresis *24 – 48 hours after ICU admission*			
Furosemide bolus	35 (28.9%)	39 (27.1%)	P=0.74
Furosemide infusion	28 (23.1%)	27 (18.8%)	P=0.38
Metolazone	5 (4.1%)	5 (3.5%)	P=0.78
Treatment before admission			
ACE inhibitor or angiotensin II receptor blocker	49 (28.3%)	57 (32.0%)	P=0.45

Supplemental Table 4: Stimulation of diuresis and prior use of ACE inhibitor or angiotensin I receptor blocker in patients with and without AKI/RRT

	No AKI	**AKI no RRT**	**AKI and RRT**	**P value**
Stimulation of diuresis within f*irst 24 hours of ICU admission*				
Furosemide bolus	40 (33.6%)	28 (53.8%)	39 (34.8%)	**P=0.03**
Furosemide infusion	28 (23.5%)	15 (28.8%)	38 (33.9%)	P=0.21
Metolazone	3 (2.5%)	3 (5.8%)	8 (7.1%)	P=0.26
Stimulation of diuresis *24 – 48 hours after ICU admission*				
Furosemide bolus	37 (32.7%)	17 (38.6%)	20 (18.5%)	**P=0.01**
Furosemide infusion	22 (19.5%)	12 (27.3%)	21 (19.4%)	P=0.51
Metolazone	3 (2.7%)	3 (6.8%)	4 (3.7%)	P=0.45
Treatment before admission				
ACE inhibitor or angiotensin II receptor blocker	50 (30.3%)	22 (33.3%)	34 (28.3%)	P=0.78

Supplemental Table 5: Univariable predictors of RRT in both study arms.

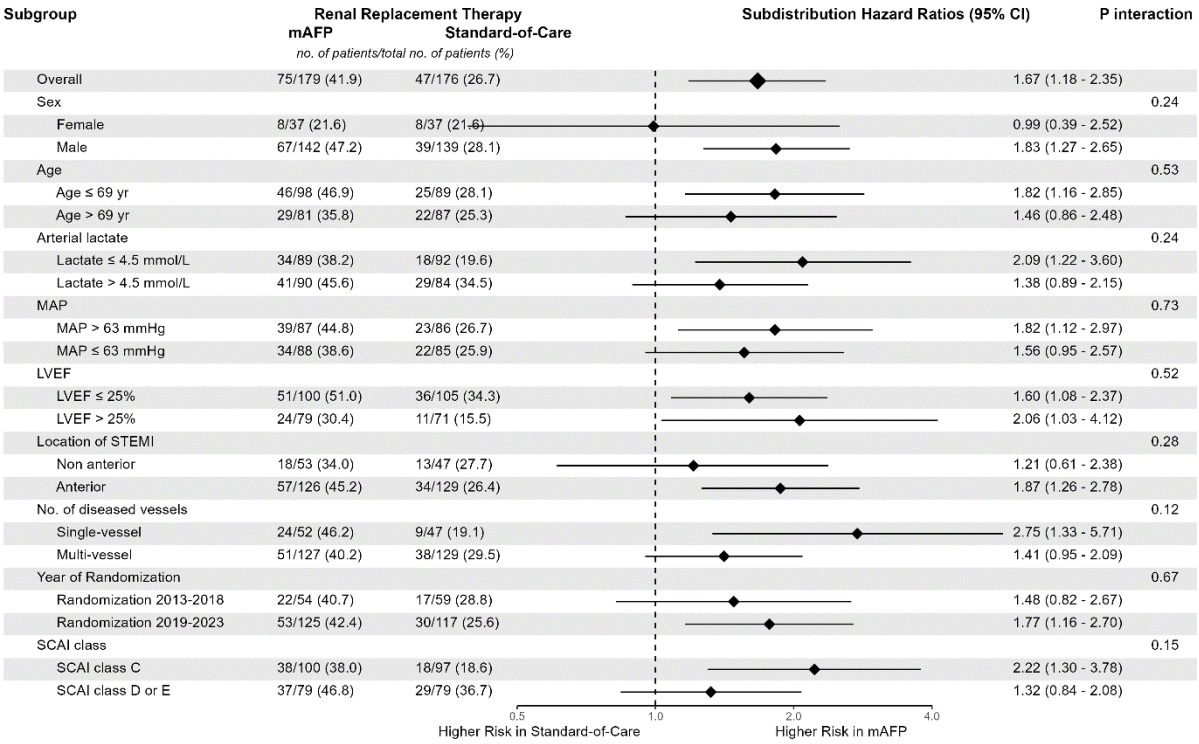
	Standard (RRT: n=47/176)		**mAFP (RRT: n=75/179)**	
Covariate	**SHR (95% CI)**	**P**	**SHR (95% CI)**	**P**
Age	0.98 (0.96 - 1.00)	0.06	0.99 (0.97 - 1.00)	0.10
Gender	1.29 (0.61 - 2.73)	0.50	2.40 (1.18 - 4.89)	0.02
Lactate at admission, by 10% increase	1.06 (1.01 - 1.11)	0.02	1.03 (0.99 - 1.08)	0.16
LVEF at randomization (%)	0.96 (0.94 - 0.99)	< 0.01	0.97 (0.95 - 0.99)	< 0.01
Heart rate at randomization	1.01 (1.00 - 1.02)	0.04	1.01 (1.00 - 1.01)	0.09
Creatinine at admission, by 10% increase	1.06 (1.01 - 1.12)	0.02	1.06 (1.02 - 1.09)	< 0.001
eGFR at admission	0.99 (0.98 - 1.00)	0.21	0.99 (0.98 - 1.00)	0.02
Bleeding				
No Bleeding	Ref		Ref	
BARC 3-5	4.23 (2.54 - 7.03)	< 0.001	1.75 (1.17 - 2.62)	< 0.01
Bilirubin at 24 hours, by 10% increase	1.13 (1.06 - 1.19)	< 0.001	1.06 (1.03 - 1.09)	< 0.001
SCAI classification				
SCAI C	Ref		Ref	
SCAI D or E	2.19 (1.25 - 3.84)	< 0.01	1.32 (0.87 - 1.99)	0.19
Highest plasma free hemoglobin at day 1-3 by 10 % increase	1.00 (0.96 - 1.05)	0.89	1.00 (1.01 - 1.04)	< 0.01
Fluid balance at 24 hours				
Neutral fluid balance (±0.5 L) Ref)	Ref		Ref	

Supplemental Table 5: Univariable predictors of RRT in both study arms.

	Standard (RRT: n=47/176)		**mAFP (RRT: n=75/179)**	
Covariate	**SHR (95% CI)**	**P**	**SHR (95% CI)**	**P**
Negative fluid balance	0.89 (0.30 - 2.64)	0.83	0.96 (0.38 - 2.45)	0.93
Positive fluid balance < 2.5 L	1.54 (0.66 - 3.57)	0.32	1.27 (0.69 - 2.32)	0.44
Positive fluid balance > 2.5 L	2.01 (0.83 - 4.83)	0.12	1.39 (0.78 - 2.48)	0.27
Escalation to veno-arterial ECMO	3.30 (1.94 - 5.62)	< 0.001	2.06 (1.34 - 3.16)	< 0.01
Suction			2.67 (1.77 - 4.03)	< 0.001
P level at 6 hours				
Low - Medium (1-6)			Ref	
High (7-9)			1.86 (1.17 - 2.95)	< 0.01

RRT: Renal replacement therapy, SHR: Subdistribution hazard ratio. Values for creatinine, plasma free hemoglobin, lactate, and bilirubin were log-transformed prior to regression analysis.

Supplemental Figure 1: Risk of RRT in mAFP versus standard of care groups, stratified by prespecified subgroups



Appendix

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