Supplementary Online Content

Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury. *JAMA*. doi:10.1001/jama.2016.5828.

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable S1: Advanced inclusion criteria for dialysis initiation

	Early (n=112)	**Delayed (n=119)**	**Absolute difference Early - Delayed [95% CI]**	**p-value**
Severe Sepsis, No. (%)	34 (30.4)	41 (34.5)	-4.1% [-16.2%, 8.0%]	0.51
Catecholamines > 0.1 µg/kg/min, No. (%)	96 (85.7)	108 (90.8)	-5.0% [-13.4%, 3.3%]	0.23
Fluid overload or worsening pulmonary edema, No. (%)	82 (73.2)	93 (78.2)	-4.9% [-16.0%, 6.1%]	0.38
Non renal SOFA Score > 2, No. (%)	102 (91.1)	112 (94.1)	-3.1% [-9.8%, 3.7%]	0.38
Number of advanced inclusion critera, No. (%)				0.50
1	10 (8.9)	7 (5.9)	3.1% [-3.7%, 9.8%]	0.38
2	28 (25.0)	23 (19.3)	5.7% [-5.0%, 16.4%]	0.30
3	48 (42.9)	55 (46.2)	-3.4% [-16.2%, 9.5%]	0.61
4	26 (23.2)	34 (28.6)	-5.4% [-16.6%, 5.9%]	0.35

eTable S2: Sub-group analysis of the delayed group (n=119)

	Delayed (n=91)	**Absolute indication*** (n=17)	**p-value**
Time from KDIGO 2 to RRT, median (Q1, Q3), hours	25.0 (19.0, 40.0)	27.0 (14.0, 41.0)	0.97
Primary endpoint			
90-day all cause mortality, No. (%)	53 (58.3)	9 (52.9)	0.91
Key secondary endpoints			
Duration of RRT, median (Q1, Q3), days[1]	36 (7, -)	12 (5, 71)	0.91
ICU stay, median (Q1, Q3), days	17.0 (9.8, 29.0)	9.0 (3.5, 39.0)	0.63
Hospital stay, median (Q1, Q3), days	43.0 (25.5, 80.3)	38.0 (4.0, 92.5)	0.55

* Absolute indication for RRT: serum urea > 100 mg/dl; serum potassium > 6 mmol/l or with ECG abnormalities; serum magnesium > 4mmol/l d); urine production < 200 ml/12h or anuria (without diuretics, according to the KDIGO recommendations); and organ edema in the presence of AKI resistant to diuretic treatment (one attempt with loop diuretics prior to randomization)

[1] Duration of RRT was censored at patients' date of death or at day 90 where applicable, whatever occurred first.

eTable S3: Characteristics of renal replacement therapy

	Early (n=112)	Delayed (n=119)	Absolute difference Early - Delayed [95% CI]
Received RRT, No.	112	108	
Blood flow per session, mean ± SD, ml/h	110.15 ± 3.19	110.57 ± 5.27	-0.43 [-1.60, 0.75]
Effluent volume per session, mean ± SD, ml/kg/h	26.6 ± 4.7	26.6 ± 5.8	0.0 [-1.5, 1.6]
Session duration per day, mean ± SD, hours	22.6 ± 1.7	22.4 ± 2.1	0.2 [-0.3, 0.8]
Pre filter BUN, mean ± SD	31.64 ± 11.53	39.54 ± 17.54	-7.91 [-11.86, -3.95]
Effluent UN, mean ± SD	30.06 ± 10.95	37.57 ± 16.66	-7.51 [-11.27, -3.75]
FUN/BUN-ratio, median (Q1, Q3)	0.96 (0.95, 0.97)	0.95 (0.95, 0.97)	0.05 [0.00, 0.01]
Urea mass removal rate [mg/min], median (Q1, Q3)	9.90 (7.42, 13.04)	11.82 (8.56, 16.60)	-1.76 [-3.22, -0.31]
Complications, Number of Individuals (%)			
Air embolism	0 (0)	0 (0)	0%
Catheter insertion complication	4 (3.57)	2 (1.85)	1.72% [-2.56%, 5.99%]
Hypotension	2 (1.79)	1 (0.93)	0.86% [-2.19%, 3.91%]
Iatrogenic fluid or electrolyte Disturbance	2 (1.79)	0 (0)	1.79% [-0.67%, 4.24%]
Bleeding	0 (0)	0 (0)	0%
Seizures	0	0	0%

	(0)	(0)	
New onset of arrhythmia	1 (0.89)	0 (0)	0.89% [-0.85%, 2.63%]
Hypocalcemia (ionized calcium < 1.0 mmol/L)	75 (66.96)	71 (65.74)	1.22% [-11.27%, 13.71%]
Transition to other RRT modalities			
No RRT, No./Total No. patients (%)	0 / 112 (0)	11 / 119 (9.2)	-9.2% (-14.5%, -4.0%)
RRT w/o Transition to SLEDD/IHD, No./Total No. patients who received RRT (%)	80 / 112 (71.4)	66 / 108 (61.1)	10.3% (-2.1%, 22.8%)
Transition to SLEDD alone, No./Total No. patients who received RRT (%)	25 / 112 (22.3)	32 / 108 (29.6)	-7.3% (-18.9%, 4.3%)
Transition to IHD alone, No./Total No. patients who received RRT (%)	2 / 112 (1.8)	2 / 108 (1.9)	-0.1% (-3.6%, 3.5%)
Transition to SLEDD + IHD, No./Total No. patients who received RRT (%)	5 / 112 (4.5)	8 / 108 (7.4)	-2.9% (-9.2%, 3.3%)

eTable S4: Analysis of pro- and anti-inflammatory markers

		Early, d0 (n=112)	Delayed, d0 (n=119)	Absolute difference Early - Delayed [95% CI]	p-value	Early, d1 (n=112)	Delayed, d1 (n=119)	Absolute difference Early - Delayed [95% CI]	p-value
MIF, (Q1, pg/ml	median Q3),	18471.6 (8423.4, 48146.4)	16675.2 (10155.6, 38407.2)	-98.4 [-4465.2, 4647.6]	0.79	14388.0 (6393.3, 28118.7)	15346.2 (7362.9, 30125.7)	-1132.2 [-4747.2, 2564.4]	0.89
IL-6, (Q1, pg/ml	median Q3),	1218.3 (435.6, 2142.0)	871.1 (217.5, 1778.4)	224.9 [30.4, 467.9]	0.41	399.4 (116. 5, 901.1)	989.3 (190.9, 2012.8)	-310.9 [-663.2, -93.3]	**0.02**
IL-8, (Q1, pg/ml	median Q3),	344.0 (145.5, 568.1)	222.6 (71.8, 480.5)	73.0 [10.4, 143.5]	0.08	65.7 (28.0, 162.5)	215.5 (67.3, 373.7)	-105.9 [-160.6, -52.7]	**0.001**
IL-18, (Q1, pg/ml	median Q3),	552.1 (270.7, 1137.7)	605.6 (309.7, 1386.1)	-49.4 [-178.8, 77.3]	0.46	518.4 (351.0, 1056.8)	603.9 (316.0, 1379.8)	-27.3 [-185.3, 101.9]	0.28
IL-10, (Q1, pg/ml	median Q3),	51.6 (20.2, 211.2)	45.0 (17.2, 159.9)	3.9 [-7.9, 19.0]	0.68	27.0 (12.4, 73.1)	30.7 (13.0, 67.5)	-0.9 [-9.0, 6.5]	0.72

Day 0: blood samples were withdrawn at the time of randomization; day 1: blood samples were withdrawn 24 hours after randomization

eTable S5: Cox regression analysis of over-all mortality by cytokines

	Hazard Ratio	95% CI	p-value
Day 1 interleukin 6, per 1000pg/ml increase	1.24	1.04-1.48	0.02
Day 1 interleukin 8, per 1000pg/ml increase	2.01	1.34-3.00	< 0.001