Supplemental materials to the manuscript: Randomized controlled trial of individualized dialysate cooling for cardiac protection in hemodialysis patients by Odudu et al.

Supplemental Methods:

Follow-up data imputation

As per the intention-to-treat principle, follow-up CMR data were imputed for 10 patients to avoid the biased treatment outcome estimates that are associated with listwise deletion of study dropouts (1). With the exception of younger age, the intention-to-treat cohort was not significantly different from the complete-case cohort (Supplemental Table 1). Multiple imputations used Markov Chain Monte Carlo estimation methods available in SPSS version 21. Twelve simulated data sets were created with 10,000 iterations to derive pooled parameter estimates using Rubin's rules (2). The variables used for the imputation were study centre, age, sex, smoking history, age, diabetes status, ischemic heart disease status, vascular access and all baseline observed variables. The complete-case analysis did not change our findings (Supplemental Table 2).

Supplemental Table 1: Baseline characteristics stratified by study completion.
Abbreviations; RAAS= Renin Angiotensin Aldosterone System.

	Completed the Study(n=44)	Did not complete the study (n=10)	P val
Age (y)	59(22)	49(28)	0.03
Female (%)	13(30)	2(20)	0.7
Body Mass Index (kg/m^2)	29±6	25±4	0.2
Body Surface Area (m^2)	1.9±0.2	1.9±0.2	0.5
Systolic blood pressure (mmHg)	140(27)	144(61)	0.6
Diastolic blood pressure (mmHg)	74(17)	87(22)	0.08
Pulse pressure (mmHg)	62(30)	56(39)	0.6
Medical history			
HD vintage (d)	135±69	122±69	0.8
Tunnelled catheter (%)	12(27)	2(20)	1
Arteriovenous fistula (%)	32(73)	8(80)	1
Diabetes mellitus (%)	12(27)	2(20)	1
Ischemic heart disease (%)	4(9)	3(40)	0.1
Current/Ex-smoker (%)	21(48)	4(40)	0.7
Peripheral vascular disease (%)	7(16)	0(0)	0.3
Medication			
Treated hypertension (%)	35(80)	7(10)	0.7
RAAS antagonist (%)	11(25)	3(30)	0.7
β-blocker (%)	15(34)	4(40)	0.7
Statin use (%)	20(46)	3(30)	0.5
Phosphate binder			
Calcium-containing (%)	13(30)	2(20)	0.7
Non-calcium (%)	12(27)	2(20)	1
Erythropoiesis Stimulating Agent (%)	31(71)	8(80)	0.7
Vitamin D analogue (%)	24(55)	7(70)	0.5
Laboratory values			
Hemoglobin g/dl	11.0±1.6	12.3±0.5	0.06
Calcium (mg/dl)	9.2±0.8	9.6±0.4	0.2
Phosphate (mg/dl)	4.6(1.5)	4.3 (1.5)	0.8
Albumin (g/dl)	3.6±0.3	3.8±0.4	0.2
Total Cholesterol (mg/dl)	135.1(27)	158.3(34.8)	0.3
Ultrafiltration per session (L)	2.0±0.8	2.2±1.0	0.5

Supplemental Table 3: Trial outcomes in the complete-case cohort with no missing data (n=44, 23 control, 21 intervention). Table annotations are identical to Table 2 in the main manuscript.

[a]Endpoint	Treatment	Baseline	12 months	[b]Treatment difference between groups
EF (%)	control	59.5±6.7	61±11	0.7(-5.5,6.9)
	intervention	60±13.7	62.3±11	
LV mass (g)	control	143.9±58	147.6±58	-15.5(-28.9, -2.1)
	intervention	160.1±44.9	148.3±39.4	
LV mass indexed to BSA (g/m^2)	control	73±23.5	76±23.5	-8.2(-15.4, -1.1)
	intervention	81.9±17.4	76.6±17.4	
Global peak-systolic strain (%)[c]	control	-16.2±3.8	-13.3±17.7	-2.6(-4.6, -0.5)
	intervention	-15.9±4.6	-15.6±5	
[d]Global peak-systolic strain rate (s^{-1})	control	-0.99±0.2	-0.87±0.2	-0.22(-0.40, -0.04)
	intervention	-1.04±0.3	-1.01±0.2	
[e]Global peak-diastolic strain rate (s^{-1})	control	1.01±0.2	0.86±0.3	0.23(0.03, 0.43)
	intervention	1.04±0.3	0.96±0.3	
LV end-diastolic volume (ml)	control	146±45.1	147.3±40.8	-19.4(-38.2,-0.46)
	intervention	149.7±39.9	134.0±29.8	
LV end-diastolic volume indexed to BSA (ml/m^2)	control	75.3±22.1	76.7±19.7	-9.4(-18.7,-0.03)
	intervention	76.9±18.3	69.7±16	
[f]Aortic Distensibility ($mmHg^{-1}\times10^{-3}$)	control	5.5±2.9	2.5±2.9	2.8(0.6,5.0)
	intervention	3.7±2.7	3.4±2.7	

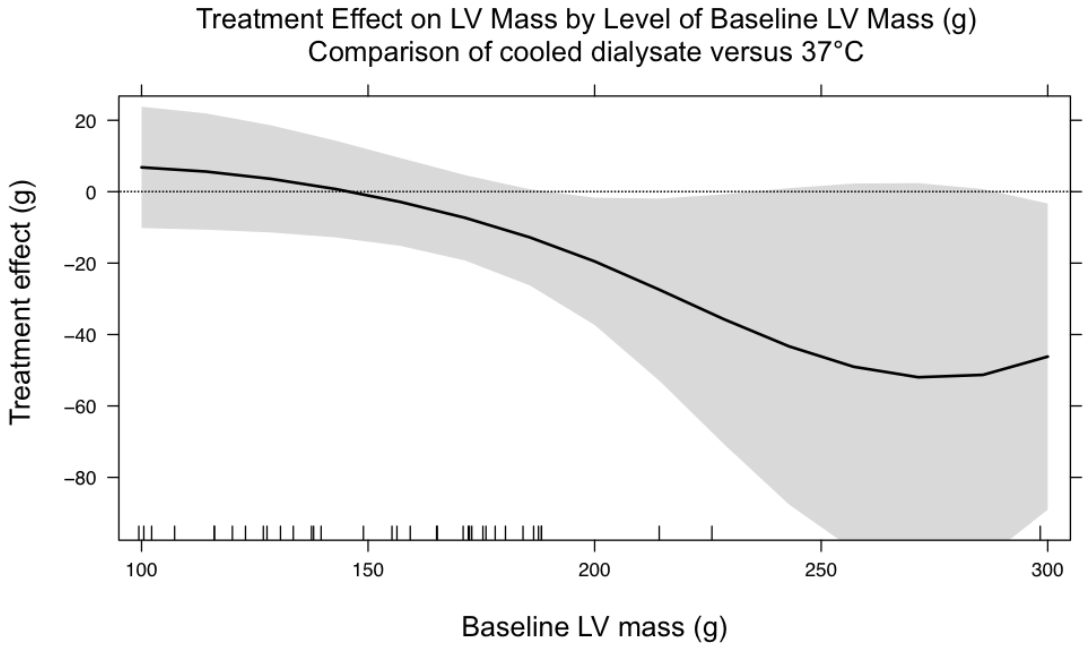
Post-hoc explanatory analyses

The intervention group had a non-significantly greater LV mass at baseline (Supplemental Table 3). The mixed-model accounted for baseline differences in a similar fashion to ANCOVA. However, to explore if the baseline LV mass modified the reported effects on LV mass, a linear regression of the treatment effect on baseline LV mass was made with natural cubic splines by three equally spaced knots as previously described (Supplemental Figure 1) (3). Higher baseline LV mass was modestly correlated to greater reductions in LV mass at follow-up (adjusted R^2 of 0.17, p=0.005) but the effects were not significantly different between groups (p value for the interaction 0.65). There were no significant between-group differences in body composition by bioimpedance (Supplemental Table 4), interdialytic weight gain or pre-dialysis mean arterial blood pressure (Supplemental Figures 2 and 3).

Supplemental Table 3: Extended Baseline characteristics. Values are mean±SD or median(interquartile range)

CMR parameters	Control Dialysate temperature 37°C (n=28)	Individualised Cooled Dialysate temperature (n=26)	p val
EF (%)	58.7±8.5	57.4±15.3	0.9
LV mass(g)	140.3±48.7	157.9±50.5	0.2
LV mass indexed to BSA (g/m^2)	72.4±21.7	80.7±17.8	0.1
Global peak-systolic strain (%)	-16.3±3.7	-15.9±0.9±4.6	0.7
Global peak-systolic strain rate (1/s)	-0.97±0.2	-1.02±0.3	0.6
Global peak-diastolic strain rate (1/s)	1.05±0.3	1.12±0.4	0.7
LV end-diastolic volume (ml)	150.3±37	162.9±39.8	0.3
LV end-diastolic volume indexed to BSA (ml/m^2)	78.8±21.2	83.5±27	0.5
Aortic Distensibility ($mmHg^{-1}\times10^{-3}$)	2.6(3.3)	2.6(1.5)	1.0

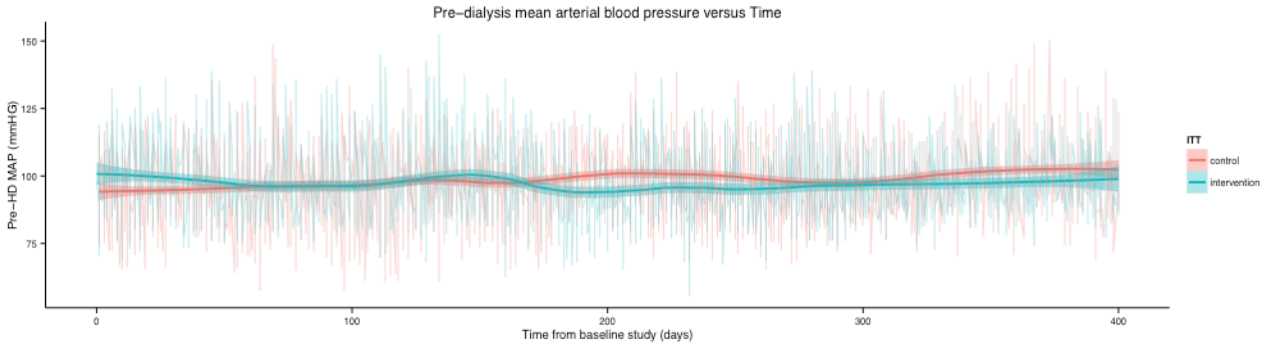
Supplemental Figure 1: The effect of baseline left ventricular mass on the change in left ventricular mass in the dialysate cooling trial. A linear regression with a cubic spline and 3 equally spaced knots of mean and 95% CI of treatment effect on baseline LV mass (adjusted R^2 of 0.17, p=0.005). There was no significant difference between treatment groups (p value for the interaction 0.65).



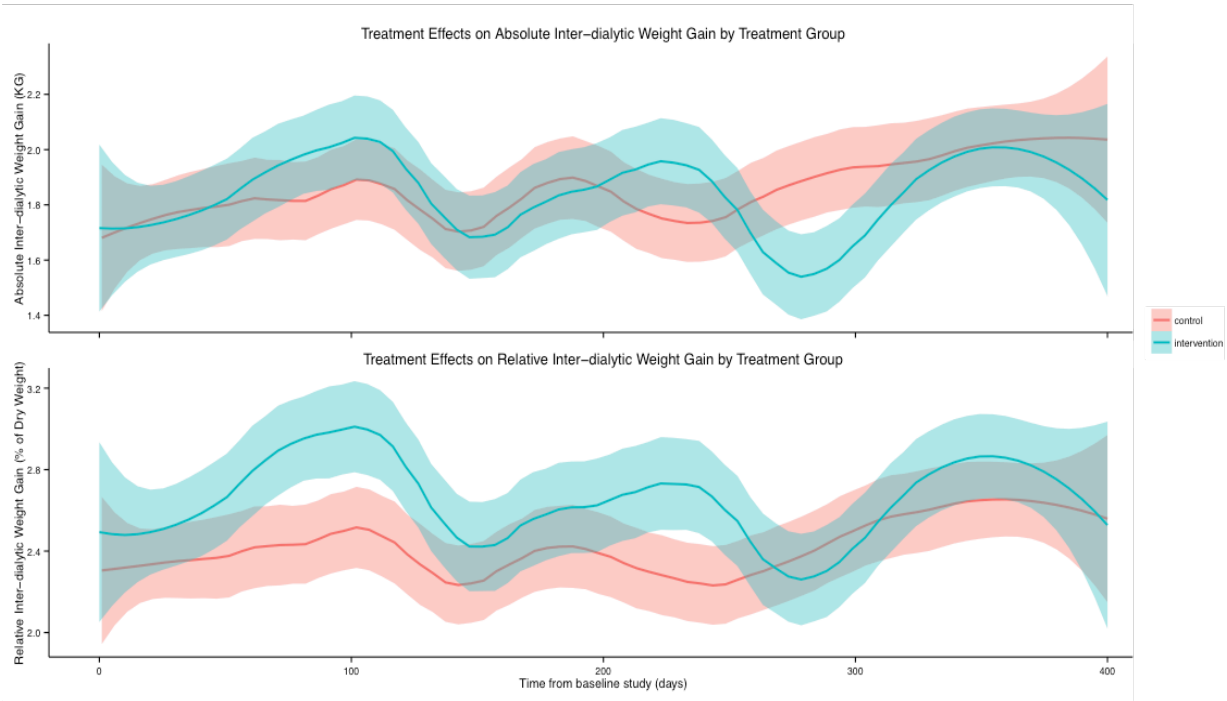
Supplemental Table 1 Body volume status by multiple frequency bioimpedance in the dialysate cooling trial. Treatment differences are mean(95%CI)

Variable	**Treatment group**	**Baseline**	**12 months**	**Treatment difference between groups**
Total Body Water (L)	control	41.3±6.1	40.6±6.2	0.4(-1.7,2.5)
	intervention	44±5.6	43.7±5.9	
Extracellular Water (L)	control	16.2±2.7	16.0±2.7	0(-0.8,0.8)
	intervention	17.7±2.5	17.5±2.6	
Intracellular Water (L)	control	25.1±3.7	24.6±3.8	0.4(-0.9,1.6)
	intervention	26.2±3.5	26.2±3.6	
Extracellular Water/Total Body Water	control	0.39±0.02	0.39±0.02	0(0,0)
	intervention	0.40±0.02	0.40±0.02	

Supplemental Figure 2: Repeated measures of pre-dialysis mean arterial blood pressure by treatment group. The red and green lines and their respective shaded bands lines represent adjusted means and standard error by locally weighted-regression (loess) for the control and intervention group respectively across the study period. A linear mixed model showed no significant between group differences with time.



Supplemental Figure 3: Repeated measures of inter-dialytic weight gain by treatment group. The red and green lines and their respective shaded bands represent the adjusted means and standard error by locally weighted-regression (loess) for the control and intervention group respectively. A linear mixed model showed no significant between group differences with time.



References

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2. Rubin DB, Schenker N: Multiple imputation in health-care databases: an overview and some applications. *Stat Med,* 10**:** 585-598, 1991
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