

ESM Table 1: Effects of Intervention on Measures of Regional [¹¹C]HED RI, Endothelial Function, Myocardial Blood Flow, and Measures of Peripheral Neuropathy

		Placebo (N=22 baseline) (N=18 follow up)	Anti-Oxidant (N=22 baseline) (N=13 follow up)	p-value	Anti-oxidant effect (95% confidence interval)
[¹¹C]HED RI (blood/min/ml tissue)					
Global [¹¹ C]HED RI	Baseline	0.073±0.016	0.081±0.017	0.32	
	24 mo.	0.074±0.016	0.070±0.018	0.045	-0.010 (-0.020,-0.001)
Regional [¹¹C]HED RI (blood/min/ml tissue)					
Apical	Baseline	0.062±0.016	0.070±0.017	0.32	
	24 mo.	0.062±0.016	0.059±0.016	0.22	-0.006 (-0.017,0.004)
Distal Inferior	Baseline	0.071±0.018	0.083±0.019	0.19	
	24 mo.	0.070±0.022	0.072±0.020	0.20	-0.007 (-0.018,0.004)
Distal Lateral	Baseline	0.074±0.017	0.081±0.020	0.54	
	24 mo.	0.075±0.016	0.068±0.021	0.054	-0.011 (-0.023,0.001)
Distal Anterior	Baseline	0.083±0.020	0.086±0.019	0.94	
	24 mo.	0.083±0.018	0.072±0.021	0.043	-0.012 (-0.024,-0.001)
Distal Septal	Baseline	0.082±0.018	0.090±0.020	0.35	
	24 mo.	0.078±0.025	0.080±0.019	0.61	-0.004 (-0.019,0.011)
Proximal Inferior	Baseline	0.077±0.018	0.083±0.016	0.47	
	24 mo.	0.076±0.017	0.073±0.018	0.13	-0.008 (-0.019,0.002)
Proximal Lateral	Baseline	0.076±0.019	0.081±0.019	0.79	
	24 mo.	0.079±0.019	0.069±0.020	0.043	-0.013 (-0.025,-0.001)
Proximal Anterior	Baseline	0.085±0.022	0.088±0.018	0.88	
	24 mo.	0.085±0.020	0.074±0.020	0.030	-0.014 (-0.026,-0.001)
Proximal Septal	Baseline	0.079±0.017	0.085±0.015	0.33	

	24 mo.	0.081±0.017	0.079±0.017	0.27	-0.007 (-0.019,0.005)
Coronary Flow Reserve (CFR)					
Global CFR	Baseline	2.94±1.70	2.95±1.32	0.52	
	24 mo.	3.22±0.85	3.02±1.52	0.82	0.08 (-0.67,0.84)
Regional CFR					
Apical	Baseline	3.21±1.87	3.21±1.37	0.56	
	24 mo.	3.41±1.15	3.25±1.62	0.56	0.28 (-0.69,1.24)
Distal Inferior	Baseline	2.88±1.80	2.73±0.89	0.89	
	24 mo.	2.96±0.87	2.92±1.58	0.66	0.20 (-0.73,1.14)
Distal Lateral	Baseline	2.88±2.26	3.34±3.26	0.26	
	24 mo.	3.02±0.76	2.77±1.56	0.72	0.13 (-0.63,0.90)
Distal Anterior	Baseline	2.88±2.19	2.83±1.68	0.65	
	24 mo.	3.12±1.39	2.79±1.44	0.95	-0.02 (-0.83,0.78)
Distal Septal	Baseline	3.07±1.79	2.66±0.96	0.58	
	24 mo.	3.25±1.19	3.24±1.87	0.61	0.28 (-0.81,1.36)
Proximal Inferior	Baseline	2.46±1.06	2.56±0.88	0.48	
	24 mo.	2.97±0.95	2.96±1.40	0.72	0.15 (-0.69,0.98)
Proximal Lateral	Baseline	2.87±1.39	3.14±2.01	0.22	
	24 mo.	3.28±1.50	2.62±1.27	0.42	-0.35 (-1.23,0.53)
Proximal Anterior	Baseline	2.97±2.21	2.94±1.54	0.53	
	24 mo.	3.37±1.88	3.02±1.71	0.92	-0.05 (-1.14,1.03)
Proximal Septal	Baseline	2.80±1.54	2.69±1.09	0.81	
	24 mo.	3.29±1.26	3.25±2.09	0.56	0.27 (-0.67,1.21)
Resting Perfusion					
Global MBF	Baseline	0.82±0.23	0.86±0.30	0.71	
	24 mo.	0.69±0.13	0.79±0.19	0.21	0.06 (-0.04,0.16)
Regional MBF					
Apical	Baseline	0.59±0.16	0.57±0.18	0.12	
	24 mo.	0.48±0.13	0.55±0.14	0.40	0.04 (-0.06,0.15)

Distal Inferior	Baseline	0.86±0.26	0.87±0.3	0.50	
	24 mo.	0.73±0.13	0.80±0.22	0.45	0.04 (-0.07,0.16)
Distal Lateral	Baseline	0.86±0.24	0.90±0.39	0.69	
	24 mo.	0.72±0.14	0.85±0.29	0.22	0.08 (-0.05,0.22)
Distal Anterior	Baseline	0.84±0.26	0.92±0.39	0.89	
	24 mo.	0.71±0.16	0.85±0.30	0.26	0.09 (-0.07,0.24)
Distal Septal	Baseline	0.85±0.31	0.98±0.40	0.67	
	24 mo.	0.77±0.18	0.83±0.22	0.73	0.02 (-0.11,0.15)
Proximal Inferior	Baseline	0.96±0.29	0.97±0.29	0.82	
	24 mo.	0.77±0.13	0.86±0.18	0.15	0.07 (-0.03,0.17)
Proximal Lateral	Baseline	0.91±0.32	0.96±0.42	0.98	
	24 mo.	0.78±0.19	0.91±0.27	0.22	0.10 (-0.06,0.25)
Proximal Anterior	Baseline	0.95±0.29	0.98±0.40	0.64	
	24 mo.	0.82±0.23	0.92±0.30	0.64	0.04 (-0.13,0.20)
Proximal Septal	Baseline	0.95±0.30	1.03±0.39	0.98	
	24 mo.	0.80±0.21	0.91±0.24	0.44	0.05 (-0.09,0.20)
Stress Perfusion					
Global MBF	Baseline	2.03±0.44	2.12±0.46	0.48	
	24 mo.	2.05±0.39	1.99±0.50	0.53	-0.08 (-0.35,0.19)
Regional MBF					
Apical	Baseline	1.61±0.40	1.58±0.40	0.75	
	24 mo.	1.49±0.38	1.48±0.42	0.72	0.05 (-0.22,0.31)
Distal Inferior	Baseline	2.14±0.64	2.17±0.62	0.84	
	24 mo.	2.01±0.76	2.03±0.57	0.74	0.09 (-0.46,0.63)
Distal Lateral	Baseline	2.08±0.50	2.19±0.43	0.41	
	24 mo.	2.05±0.39	1.95±0.47	0.79	-0.04 (-0.39,0.30)
Distal Anterior	Baseline	1.96±0.39	2.14±0.50	0.23	
	24 mo.	2.04±0.52	1.96±0.43	0.43	-0.10 (-0.36,0.16)
Distal Septal	Baseline	2.20±0.58	2.34±0.71	0.62	
	24 mo.	2.34±0.72	2.31±0.82	0.85	-0.05 (-0.55,0.46)

Proximal Inferior	Baseline	2.14±0.54	2.29±0.61	0.40	
	24 mo.	2.16±0.59	2.25±0.66	0.66	0.11 (-0.38,0.59)
Proximal Lateral	Baseline	2.23±0.50	2.41±0.45	0.19	
	24 mo.	2.27±0.49	2.08±0.36	0.08	-0.28 (-0.58,0.03)
Proximal Anterior	Baseline	2.22±0.57	2.39±0.58	0.22	
	24 mo.	2.39±0.67	2.25±0.53	0.21	-0.21 (-0.54,0.12)
Proximal Septal	Baseline	2.32±0.71	2.47±0.79	0.46	
	24 mo.	2.46±0.72	2.46±1.01	0.63	-0.11 (-0.58,0.36)
Nerve Conduction Studies					
Sural Amplitude, (uV)	Baseline	4.4±3.8	4.7±4.1	0.93	
	24 mo.	6.0±5.0	3.4±3.6	0.11	-3.07 (-6.92,0.78)
Sural Conduction Velocity (m/s)	Baseline	32.6±20.0	27.7±19.8	0.50	
	24 mo.	39.1±16.5	28.1±24.4	0.28	-9.04 (-25.8,7.7)
Peroneal Motor Amplitude (uV)	Baseline	3.9±2.7	2.7±2.1	0.054	
	24 mo.	3.7±3.3	4.5±4.2	0.2	1.12 (-0.6,2.9)
Peroneal Motor, F-wave	Baseline	34.4±24.8	31.4±24.9	0.79	
	24 mo.	26.8±27.7	45.8±21.2	0.13	-14.4 (-33.5,4.7)
Ulnar Sensory Amplitude (uV)	Baseline	12.1±9.1	12.6±10.2	0.57	
	24 mo.	12.4±11.7	11.8±8.1	0.58	-1.55 (-7.2,4.1)
Ulnar Sensory Conduction Velocity (m/s)	Baseline	41.6±14.9	41.8±15.4	0.69	
	24 mo.	43.5±17.7	46.0±16.0	0.69	2.3 (-9.3,14.0)
QSART and QST					
Proximal Leg Total Sweat Volume (ul)	Baseline	1.01±1.36	1.21±1.18	0.6	
	24 mo.	1.41±1.29	0.92±0.83	0.33	-0.41 (-1.26,0.43)

Distal Leg Total Sweat Volume (ul)	Baseline	0.99±1.28	0.82±0.96	0.85	
	24 mo.	0.96±1.14	1.52±1.21	0.029	0.73 (0.08,1.37)
Foot Total Sweat Volume (ul)	Baseline	0.80±0.81	0.65±0.84	0.91	
	24 mo.	0.68±0.95	1.08±1.38	0.27	0.50 (-0.42,1.42)
Cold Perception Threshold (ND)	Baseline	1.93±0.53	1.71±0.96	0.78	
	24 mo.	1.66±0.67	2.03±0.35	0.10	0.39 (-0.06,0.84)
Vibration Perception Threshold (ND)	Baseline	1.81±0.74	1.62±0.90	0.43	
	24 mo.	0.91±1.52	1.71±0.69	0.18	0.72 (-0.36,1.80)
Intraepidermal nerve fibre density (fibres/mm)					
Distal Leg IENFD	Baseline	1.64±2.01	2.72±2.31	0.35	
	24 mo.	1.57±1.94	1.86±1.99	0.19	-0.58 (-1.48,0.31)
Proximal Thigh IENFD	Baseline	5.12±3.79	7.53±6.36	0.25	
	24 mo.	6.86±4.80	5.76±3.15	0.47	-0.92 (-3.54,1.70)

All data shown as mean ± SD; P-value computed using general linear model (GLM) adjusted for age strata, sex and HbA1c if baseline and for baseline value, age strata, sex and HbA1c if 24 mo.; nerve conduction studies were also adjusted for temperature of the limb (see Methods). Anti-oxidant effect is the adjusted mean difference between the anti-oxidant group and the placebo group when the p-value is <0.05.

CFR: coronary flow reserve, MBF: myocardial blood flow; QSART: quantitative sudomotor axon reflex testing; QST: quantitative sensory testing; ND: normal deviates; IENFD: Intraepidermal nerve fibre density