

Supplemental Table 1:

	Pharmacologic stress (n=8,272)	Exercise stress (n=5,744)	P-value
Rest shape index(%), mean±SD	64.9 ± 8.0	63.1 ± 6.9	<0.001
Stress shape index(%), mean±SD	64.9 ± 7.8	61.4 ± 6.3	<0.001
Post-stress change in shape index(%), mean±SD	0.2 ± 4.1	-1.7 ± 3.9	<0.001
Rest eccentricity index(%), mean±SD	80.4 ± 4.7	81.9 ± 4.3	<0.001
Stress eccentricity index(%), mean±SD	80.3 ± 4.8	82.4 ± 3.9	<0.001
Post-stress change in eccentricity index(%), mean±SD	-0.1 ± 3.0	0.5 ± 2.6	<0.001
Resting TPD, mean±SD	2.4 ± 6.2	1.2 ± 4.2	<0.001
Stress TPD, mean±SD	5.7 ± 8.0	3.7 ± 5.8	<0.001
Ischemic TPD, mean±SD	3.2 ± 3.4	2.5 ± 3.0	<0.001
Resting LVEF, mean±SD	61.9 ± 14.0	62.5 ± 10.8	<0.001
Stress LVEF, mean±SD	60.8 ± 13.6	62.4 ± 10.4	0.003
Change in LVEF, mean±SD	-1.1 ± 7.3	-0.1 ± 7.2	<0.001
Resting LVEDV, mean±SD	73.7 ± 40.8	70.7 ± 27.5	<0.001
Stress LVEDV, mean±SD	75.5 ± 42.2	67.5 ± 26.8	<0.001
Change in LVEDV, mean±SD	1.8 ± 10.0	-3.2 ± 8.6	<0.001
Transient ischemic dilation, n(%)	353 (4.3)	202 (3.5)	0.046

Imaging Characteristics stratified by mode of stress. LVEDV – left ventricular end diastolic

volume, LVEF – left ventricular ejection fraction, MACE – major adverse cardiovascular event,

SD – standard deviation, TPD – total perfusion deficit

Supplemental Table 2: Unadjusted and Adjusted Associations with major adverse cardiovascular events (MACE) in a non-parsimonious model

Variable	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Rest shape index (per 10%)	1.16(1.09 – 1.22)	<0.001	1.06(0.95 – 1.18)	0.301
Stress shape index (per 10%)	1.40(1.33 – 1.47)	<0.001	*	*
Post-stress change in shape index (per 10%)	2.01(1.82 – 2.22)	<0.001	1.31(1.13 – 1.53)	<0.001
Rest eccentricity index (per 10%)	0.82(0.75 – 0.89)	<0.001	1.02(0.85 – 1.23)	0.828
Stress eccentricity index (per 10%)	0.63(0.58 – 0.69)	<0.001	*	*
Post-stress change in eccentricity index (per 10%)	0.52(0.46 – 0.59)	<0.001	0.81(0.66 – 0.99)	0.041
Age (per 10 years)	1.52(1.47 – 1.58)	<0.001	1.31(1.26 – 1.37)	<0.001
Male	1.62(1.48 – 1.78)	<0.001	1.25(1.12 – 1.40)	<0.001
Body mass index	0.98(0.97 – 0.99)	<0.001	0.98(0.97 – 0.99)	0.002
Hypertension	1.82(1.65 – 2.01)	<0.001	1.20(1.07 – 1.33)	0.001
Diabetes	1.87(1.72 – 2.04)	<0.001	1.37(1.25 – 1.51)	<0.001
Dyslipidemia	1.64(1.49 – 1.81)	<0.001	1.02(0.92 – 1.13)	0.676
Current smoker	0.95(0.83 – 1.06)	0.385	1.00(0.89 – 1.12)	0.975
PVD	1.82(1.63 – 2.01)	<0.001	1.05(0.94 – 1.18)	0.399
Prior MI	2.40(2.18 – 2.65)	<0.001	1.20(1.07 – 1.36)	0.002
Prior revascularization	2.87(2.63 – 3.12)	<0.001	1.61(1.45 – 1.79)	<0.001
Family history of CAD	0.73(0.66 – 0.82)	<0.001	0.90(0.81 – 1.00)	0.047
Typical angina	1.37(1.16 – 1.61)	<0.001	1.20(1.02 – 1.41)	0.031

Systolic BP (per 10 mmhg)	1.04(1.02 – 1.07)	<0.001	1.05(1.02 – 1.08)	<0.001
Diastolic BP (per 10 mmhg)	0.85(0.82 – 0.89)	<0.001	0.84(0.80 – 0.89)	<0.001
Heart Rate (per 10 bpm)	1.07(1.04 – 1.10)	<0.001	1.14(1.10 – 1.17)	<0.001
Exercise stress	0.44(0.40 – 0.48)	<0.001	0.66(0.60 – 0.74)	<0.001
Resting TPD	1.05(1.04 – 1.05)	<0.001	0.99(0.99 – 1.00)	0.086
Stress TPD	1.05(1.04 – 1.05)	<0.001	*	*
Ischemic TPD	1.12(1.11 – 1.13)	<0.001	1.05(1.03 – 1.06)	<0.001
Resting LVEF	0.97(0.97 – 0.98)	<0.001	0.99(0.98 – 0.99)	<0.001
Stress LVEF	0.97(0.96 – 0.97)	<0.001	*	*
Change in LVEF	0.98(0.97 – 0.99)	<0.001	0.98(0.98 – 0.99)	<0.001
Resting LVEDV	1.01(1.01 – 1.01)	<0.001	1.00(0.99 – 1.00)	0.199
Stress LVEDV†	1.01(1.01 – 1.01)	<0.001	*	*
Change in LVEDV†	1.02(1.02 – 1.02)	<0.001	1.00(1.00 – 1.00)	0.639
Transient ischemic dilation	1.23(1.01 – 1.50)	0.043	0.90(0.73 – 1.11)	0.328

Unadjusted and Adjusted Associations with major adverse cardiovascular events (MACE) in a non-parsimonious model. *- variable excluded due to inclusion of rest and change in variables.

†Multivariable results similar when considering left ventricular end-systolic volume in place of left ventricular end-diastolic volume (LVEDV). CAD – coronary artery disease, HR – hazard ratio, LVEDV – left ventricular end-diastolic volume, LVEF – left ventricular ejection fraction, MI – myocardial infarction, PVD – peripheral vascular disease, TID – transient ischemic dilation.

Supplemental Table 3: Summary of Reclassification

Variable	Event reclassification	Non-event reclassification	Continuous net reclassification
Rest shape index	-0.057 (-0.085 – 0.081)	0.044 (-0.032 – 0.066)	-0.013 (-0.065 – 0.061)
Stress shape index	-0.014 (-0.044 – 0.021)	0.093 (0.066 – 0.116)	0.079 (0.028 – 0.130)
Post-stress change in Shape Index	0.080 (0.051 – 0.118)	0.074 (0.048 – 0.098)	0.154 (0.108 – 0.209)
Rest eccentricity index	-0.056 (-0.082 – 0.094)	0.037 (-0.089 – 0.116)	-0.018 (-0.069 – 0.076)
Stress eccentricity index	-0.066 (-0.093 to -0.024)	0.127 (0.104 – 0.150)	0.061 (0.016 – 0.116)
Post-stress change in eccentricity index	0.061 (0.028 – 0.098)	0.056 (0.027 – 0.087)	0.117 (0.069 – 0.174)

Summary of Reclassification for inclusion of shape index and eccentricity variables.

Multivariable models adjusted for all variables other than shape index and eccentricity outlined in Table 3 including stress and ischemic TPD.

Supplemental Table 4: Comparison of Prognostic Accuracy

Variable	Threshold method	Abnormal threshold	Annualized MACE abnormal	Annualized MACE normal	PPV	NPV
Rest shape index	ROC	>64.21	3.6%	3.2%	16.2%	85.8%
	95 th Percentile	>77.07	4.7%	3.3%	21.5%	85.2%
Stress shape index	ROC	>63.83	4.2%	2.7%	18.5%	87.5%
	95 th Percentile	>76.62	6.1%	3.2%	27.1%	85.5%
Post-stress change in shape index	ROC	>0.236	4.5%	2.6%	19.5%	88.0%
	95 th Percentile	>5.65	5.0%	3.3%	23.3%	85.3%
Rest eccentricity index	ROC	<81.47	3.1%	3.7%	16.4%	86.1%
	95 th Percentile	<72.63	3.8%	3.4%	18.1%	85.0%
Stress eccentricity index	ROC	<81.32	4.1%	2.8%	18.1%	87.4%
	95 th Percentile	<73.04	5.6%	3.3%	24.8%	85.4%
Post-stress change in eccentricity index	ROC	< -0.18	4.1%	2.8%	18.1%	87.2%
	95 th Percentile	< -3.97	4.7%	3.2%	22.5%	85.3%

Comparison of prognostic accuracy for abnormal thresholds derived using the Youden index

from receiver-operating characteristic (ROC) curves or as the 95th percentile. MACE – major

adverse cardiovascular events, NPV – negative predictive value, PPV – positive predictive value.

Supplemental Table 5: Thresholds for Abnormal Change in Shape Index

	ROC AUC (95% CI)	Abnormal threshold	Annualized MACE negative	Annualized MACE positive
Overall	0.597 (0.584 – 0.610)	>0.236	2.6%	4.5%
Site held out				
Assuta	0.620 (0.603 – 0.637)	>0.263	4.4%	5.3%
BW	0.597 (0.584 – 0.610)	>0.236	0.6%	3.7%
CSMC	0.592 (0.577 – 0.607)	>0.236	2.4%	4.1%
Oregon	0.587 (0.572 – 0.601)	>0.236	1.8%	4.7%
Ottawa	0.587 (0.573 – 0.6010)	>0.358	2.0%	3.3%

Thresholds for abnormal change in shape index in the overall population and in a leave one site out approach. In the leave one site out approach, receiver-operating characteristic (ROC) curves were generated from the remaining sites and the optimal ROC thresholds were then tested in the held-out site. AUC – area under the curve, BW – Brigham and Women’s, CI – confidence interval, CSMC – Cedars-Sinai Medical Center, MACE – major adverse cardiovascular event.

Supplemental Table 6:

	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	P-value
Rest shape index	1.31 (1.23 – 1.40)	<0.001	1.27 (1.12 – 1.45)	<0.001
Stress shape index	1.58 (1.49 – 1.67)	<0.001	*	*
Post-stress change in Shape Index	2.18 (1.93 – 2.46)	<0.001	1.59 (1.34 – 1.88)	<0.001
Rest eccentricity index	0.65 (0.59 – 0.72)	<0.001	1.09 (0.87 – 1.36)	0.455
Stress eccentricity index	0.52 (0.47 – 0.57)	<0.001	*	*
Post-stress change in eccentricity index	0.53 (0.45 – 0.62)	<0.001	1.05 (0.82 – 1.34)	0.713

Associations with all-cause mortality. Multivariable model included the same variables outlined in Table 3. *- variable excluded due to inclusion of rest and change in variables. HR – hazard ratio

Supplemental Table 7:

	Mean \pm SD	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	P-value
Exercise stress (n=5,744)					
Rest shape index	63.1 \pm 6.9	0.90 (0.80 – 1.02)	0.095	0.74 (0.55 – 0.98)	0.036
Stress shape index	61.4 \pm 6.3	1.19 (1.04 – 1.36)	0.009	*	*
Post-stress change in shape index	-1.7 \pm 3.9	2.31 (1.85 – 2.90)	<0.001	1.14 (0.80 – 1.63)	0.477
Rest eccentricity index	81.9 \pm 4.3	1.07 (0.88 – 1.30)	0.520	0.57 (0.36 – 0.92)	0.022
Stress eccentricity index	82.4 \pm 3.9	0.74 (0.60 – 0.90)	0.003	*	*
Post-stress change in Eccentricity Index	0.5 \pm 2.6	0.40 (0.29 – 0.56)	<0.001	0.44 (0.25 – 0.77)	0.004
Pharmacologic stress (n=8,272)					
Rest shape index	64.7 \pm 8.0	1.16 (1.10 – 1.23)	<0.001	1.14 (1.01 – 1.27)	0.030
Stress shape index	64.9 \pm 7.8	1.29 (1.22 – 1.36)	<0.001	*	*
Post-stress change in shape index	0.2 \pm 4.1	1.53 (1.36 – 1.72)	<0.001	1.41 (1.22 – 1.63)	<0.001
Rest eccentricity index	80.4 \pm 4.7	0.87 (0.79 – 0.96)	0.007	1.08 (0.89 – 1.31)	0.437
Stress eccentricity index	80.3 \pm 4.8	0.74 (0.67 – 0.81)	<0.001	*	*
Post-stress change in eccentricity index	-0.1 \pm 3.0	0.65 (0.56 – 0.75)	<0.001	0.90 (0.73 – 1.11)	0.329

Associations between shape index and eccentricity index in patients undergoing exercise stress

and pharmacologic stress. Mean of all parameters was significantly different between exercise and pharmacologic stress. Multivariable models are the same as outlined for Table 3. Formal interaction testing was not significant for change in shape index (p=0.066) or change in eccentricity index (p=0.119). *- variable excluded due to inclusion of rest and change in variables.

Supplemental Table 8:

	Mean \pm SD	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	P-value
Preserved LVEF ($\geq 40\%$) (n=13,283)					
Rest shape index	63.7 \pm 7.4	1.07 (1.01 – 1.14)	0.019	1.01 (0.89 – 1.13)	0.928
Stress shape index	63.1 \pm 7.2	1.32 (1.25 – 1.40)	<0.001	*	*
Post-stress change in shape index	-0.6 \pm 4.1	2.03 (1.83 – 2.26)	<0.001	1.35 (1.16 – 1.57)	<0.001
Rest eccentricity index	81.2 \pm 4.5	0.89 (0.81 – 0.98)	0.015	0.90 (0.74 – 1.10)	0.322
Stress eccentricity index	81.3 \pm 4.5	0.67 (0.61 – 0.73)	<0.001	*	*
Post-stress change in eccentricity index	0.2 \pm 2.8	0.50 (0.44 – 0.58)	<0.001	0.73 (0.59 – 0.90)	0.004
Reduced LVEF (<40%) (n=733)					
Rest shape index	69.4 \pm 8.7	1.14 (0.99 – 1.31)	0.065	1.39 (1.07 – 1.81)	0.014
Stress shape index	69.9 \pm 8.8	1.22 (1.07 – 1.40)	0.003	*	*
Post-stress change in shape index	0.5 \pm 4.5	1.35 (1.05 – 1.73)	0.020	1.66 (1.18 – 2.34)	0.004
Rest eccentricity index	78.2 \pm 5.3	0.91 (0.73 – 1.14)	0.402	1.69 (1.07 – 2.66)	0.024
Stress eccentricity index	78.1 \pm 5.1	0.86 (0.68 – 1.08)	0.186	*	*
Post-stress change in eccentricity index	-0.2 \pm 3.3	0.86 (0.59 – 1.25)	0.436	1.61 (0.92 – 2.81)	0.093

Associations between shape index and eccentricity index in patients with preserved or reduced

LVEF. Mean of all parameters was significantly different between reduced and preserved LVEF.

Multivariable models are the same as outlined for Table 3. Interaction testing was not significant

for post-stress change in shape index (p=0.279) or post-stress change in eccentricity index

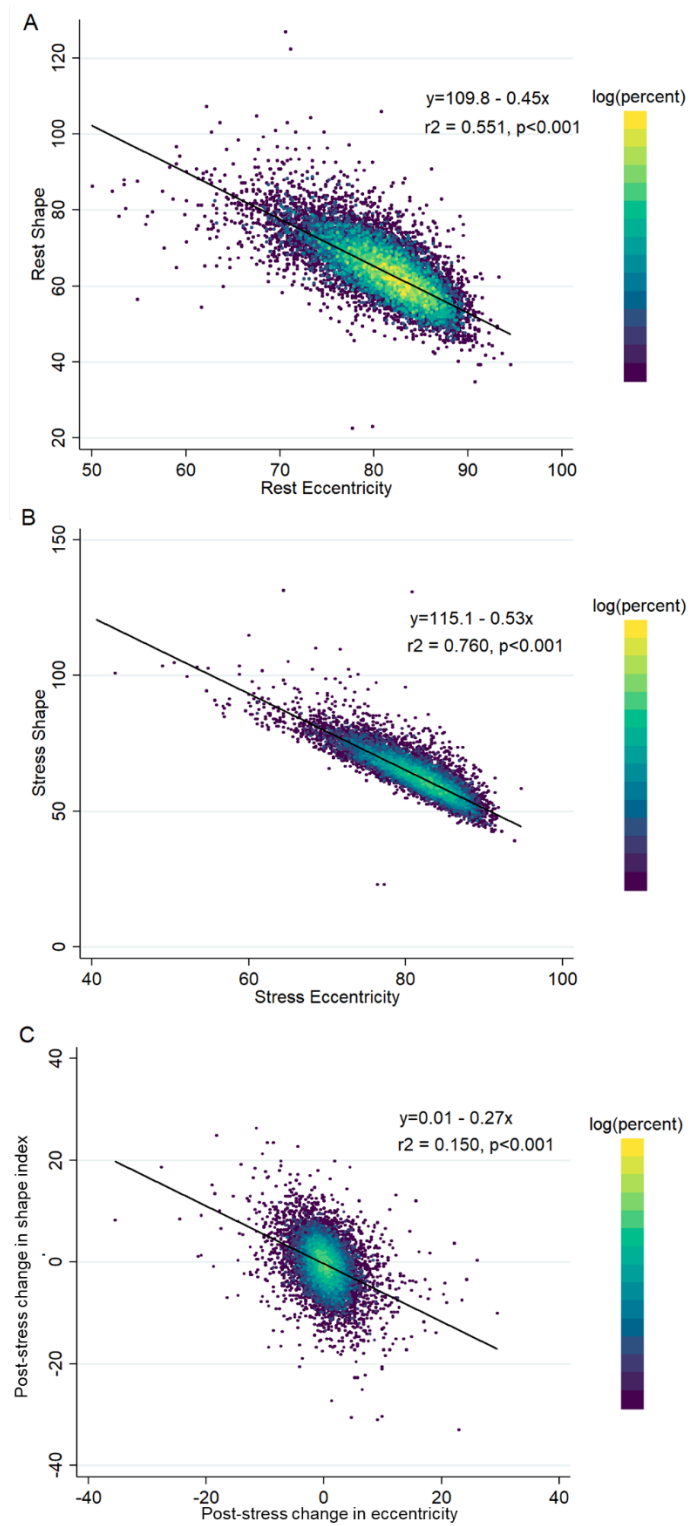
(p=0.084). *- variable excluded due to inclusion of rest and post-stress change in variables.

Supplemental Table 9:

	Mean \pm SD	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	P-value
DSPECT (n=5,660)					
Rest shape index	64.7 \pm 8.6	1.23 (1.14 – 1.34)	<0.001	1.20 (1.05 – 1.37)	0.006
Stress shape index	63.9 \pm 8.3	1.41 (1.32 – 1.50)	<0.001	*	*
Post-stress change in shape index	-0.7 \pm 4.9	1.88 (1.60 – 2.21)	<0.001	1.61 (1.36 – 1.91)	<0.001
Rest eccentricity index	80.7 \pm 5.3	0.73 (0.63 – 0.83)	<0.001	1.19 (0.94 – 1.50)	0.153
Stress eccentricity index	81.0 \pm 5.1	0.59 (0.52 – 0.67)	<0.001	*	*
Post-stress change in eccentricity index	0.3 \pm 3.8	0.39 (0.30 – 0.51)	<0.001	0.96 (0.76 – 1.22)	0.761
GE530 (n=8,356)					
Rest shape index	63.6 \pm 6.9	1.13 (1.05 – 1.22)	0.001	0.95 (0.80 – 1.12)	0.530
Stress shape index	63.2 \pm 6.7	1.43 (1.33 – 1.55)	<0.001	*	*
Post-stress change in shape index	-0.4 \pm 3.5	2.11 (1.86 – 2.40)	0.020	1.24 (1.00 – 1.53)	0.049
Rest eccentricity index	81.2 \pm 4.1	0.86 (0.76 – 0.96)	0.009	0.74 (0.56 – 0.97)	0.031
Stress eccentricity index	81.3 \pm 4.1	0.64 (0.57 – 0.71)	0.186	*	*
Post-stress change in eccentricity index	0.1 \pm 2.0	0.55 (0.47 – 0.64)	0.436	0.65 (0.46 – 0.93)	0.017

Associations between shape index and eccentricity index in patients imaged with DSPECT or GE530 cameras. Multivariable models are the same as outlined for Table 3. Interaction testing was not significant for post-stress change in shape index (p=0.113) or post-stress change in eccentricity index (p=0.687). *- variable excluded due to inclusion of rest and post-stress change in variables.

Supplemental Figure 1: Correlation between shape index and eccentricity index

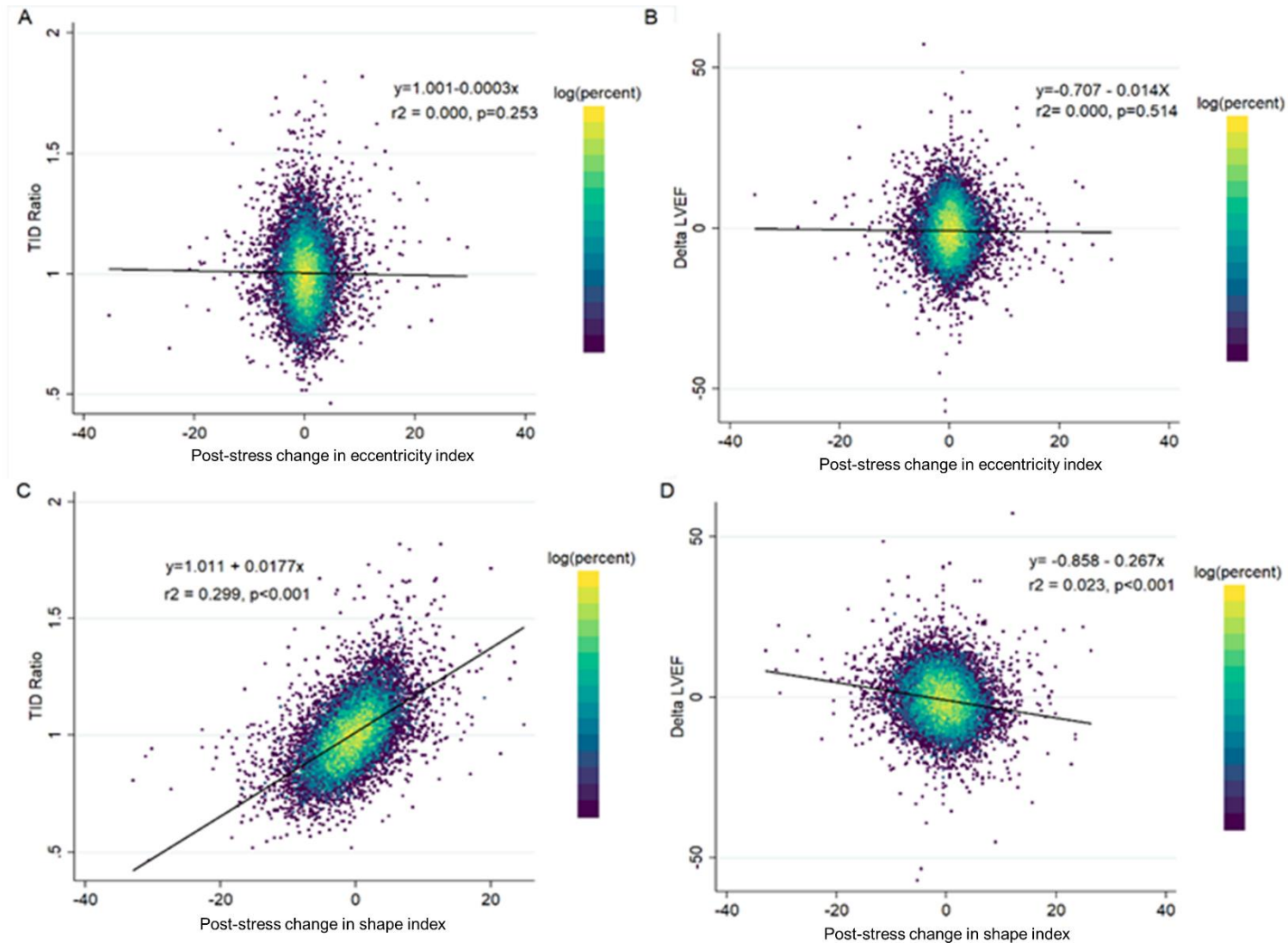


Supplemental Figure 1: Correlation gradient plots between shape index and eccentricity index.

Rest (A), stress (B) and post-stress change in (C) values were all significantly correlated

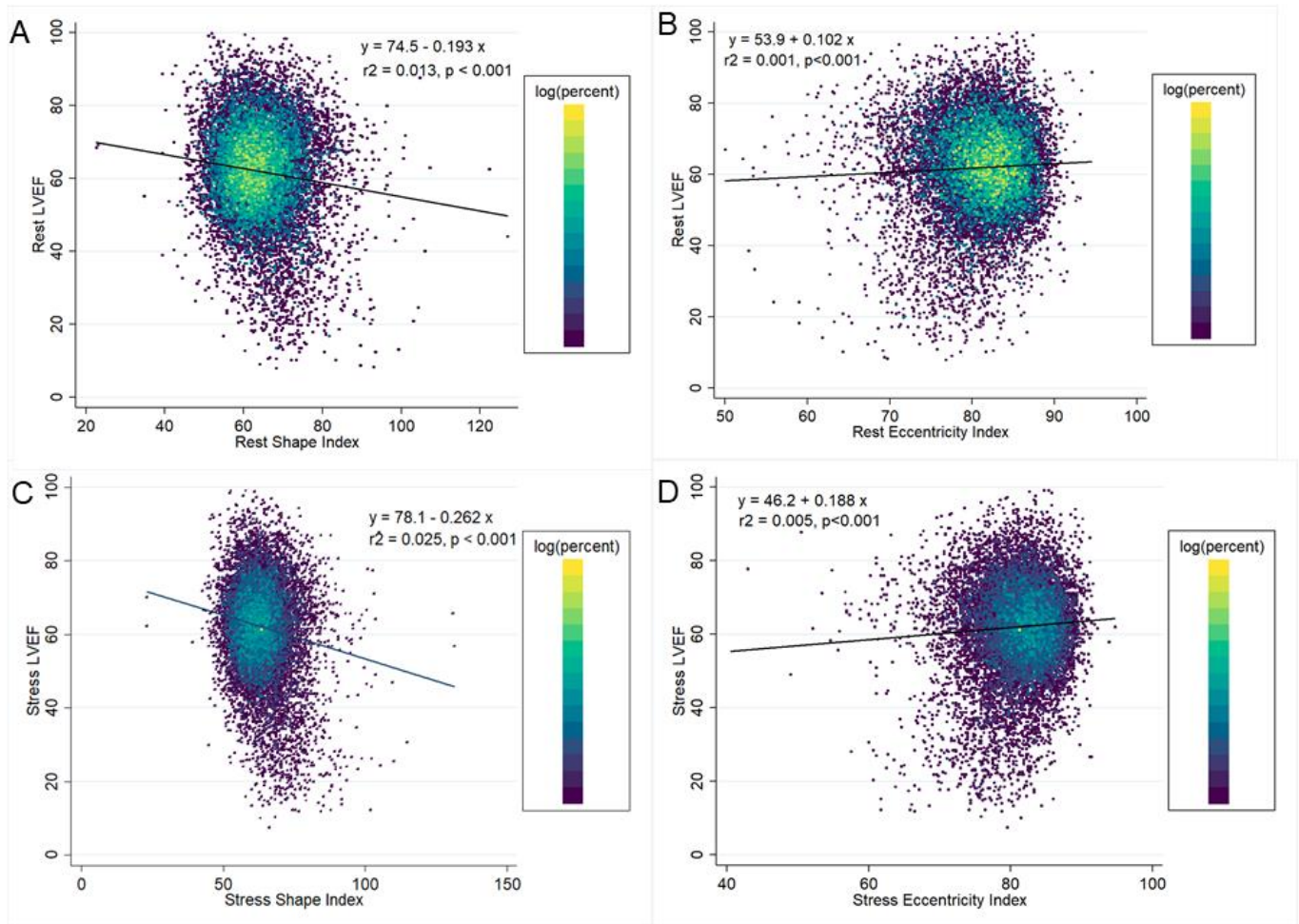
($p < 0.001$).

Supplemental Figure 2 Correlation gradient plots between change in shape index and eccentricity index with transient ischemic dilation ratio and change in left ventricular ejection fraction



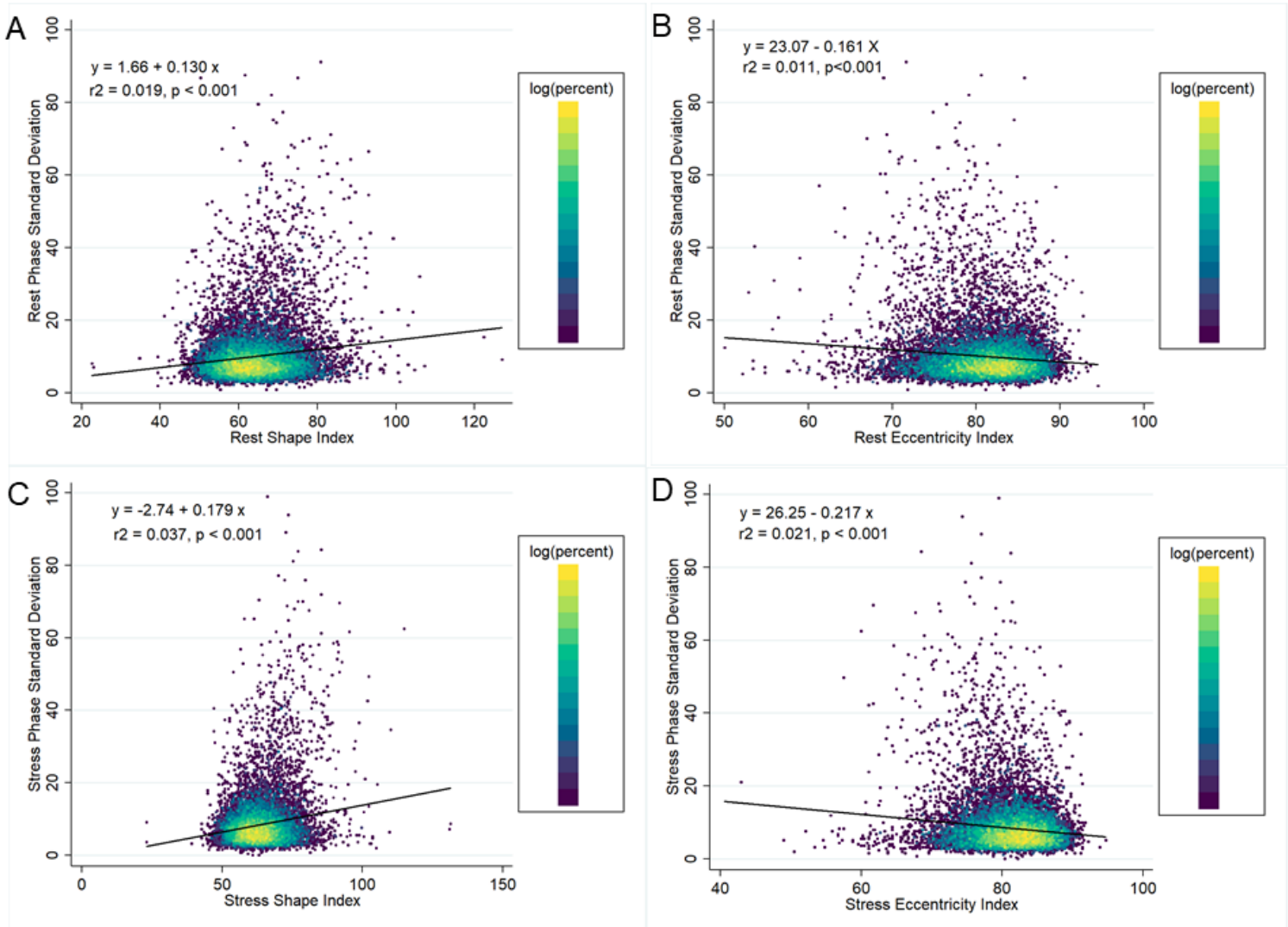
Correlation gradient plots between post-stress change in shape index and eccentricity index with transient ischemic dilation (TID) ratio and post-stress change in left ventricular ejection fraction (LVEF). There was no correlation between post-stress change in eccentricity index and TID (A) or change in LVEF (B). There was poor correlation between post-stress change in shape index and TID (C) and post-stress change in LVEF (D).

Supplemental Figure 3: Correlation between Shape Index and Eccentricity Index with Left Ventricular Ejection Fraction.



Correlation between shape index and eccentricity index with left ventricular ejection fraction (LVEF). Correlation shown for rest LVEF and rest shape index (panel A), rest LVEF and rest eccentricity index (panel B), stress LVEF and stress shape index (panel C), and stress LVEF and stress eccentricity index (panel D).

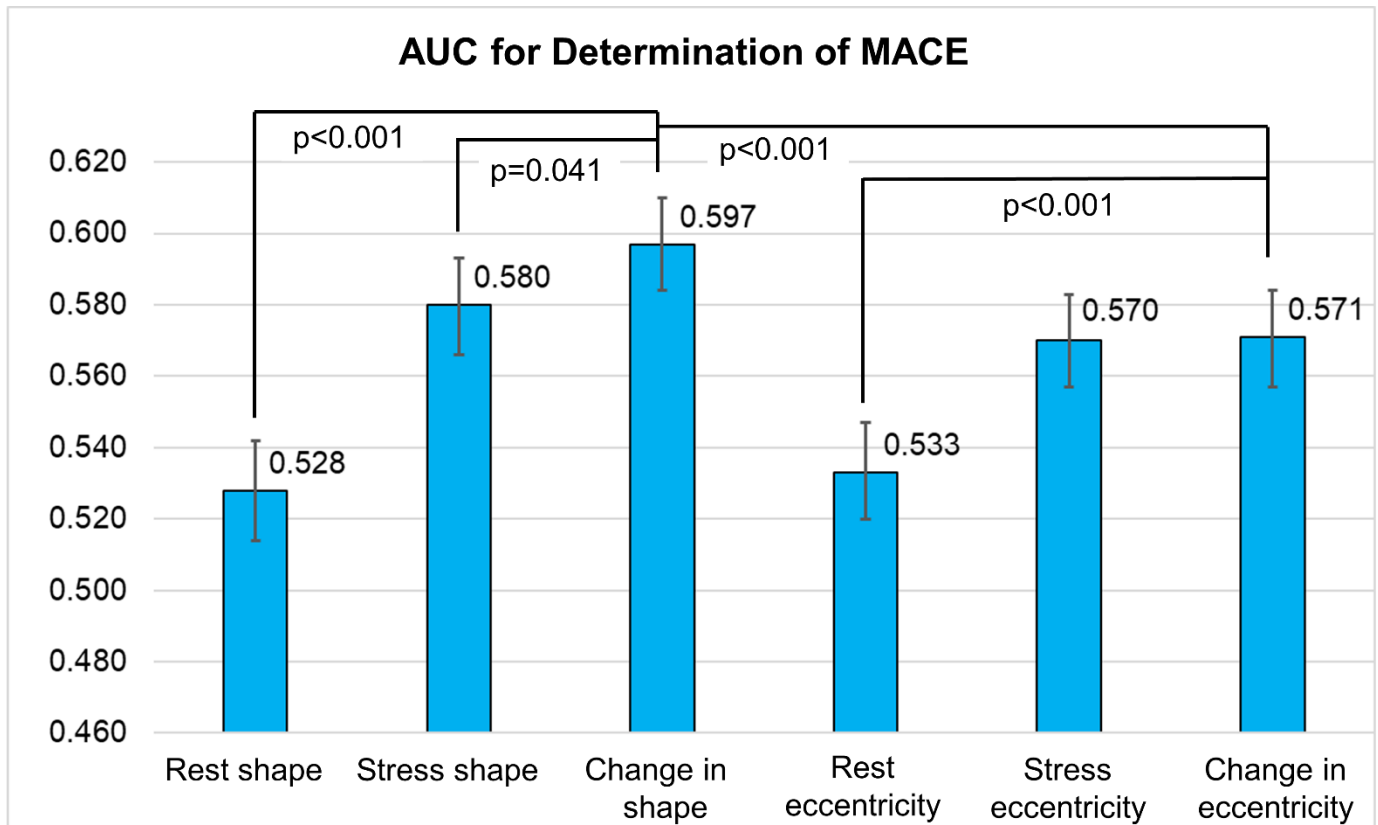
Supplemental Figure 4:



Correlation between Shape Index and Eccentricity Index with phase standard deviation (SD).

Correlation shown for rest phase SD and rest shape index (panel A), rest phase SD and rest eccentricity index (panel B), stress phase SD and stress shape index (panel C), and stress phase SD and stress eccentricity index (panel D).

Supplemental Figure 5: Comparison of area under the curve for eccentricity index and shape index variables



Comparison of receiver operating characteristic (ROC) area under the curve (AUC) of eccentricity index and shape index variables for MACE. Post-stress change in shape index had significantly higher AUC compared to all other measures. There was no significant difference in discrimination between stress eccentricity index and post-stress change in eccentricity index.

MACE – major adverse cardiovascular event.