Online Supplement

Heart rate variability on 10-second ECG and risk of acute exacerbation of COPD: a secondary analysis of BLOCK COPD

Authors

David MacDonald[1,2], Takudzwa Mkorombindo[3], Sharon X. Ling[4], Selcuk Adabag[5], Richard Casaburi[6], John Connett[4], Erika S. Helgeson[4], Janos Porszasz[6] , Harry Rossiter[6], William Stringer[6], Helen Voelker[4]

Dongxing Zhao[7], Mark Dransfield[3], and Ken Kunisaki[2.1]

1. Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, University of Minnesota, Minneapolis, MN, USA
2. Pulmonary Section, Minneapolis VA Health Care System, Minneapolis, MN, USA
3. Lung Health Center, University of Alabama at Birmingham, Birmingham, AL, USA
4. Division of Biostatistics, University of Minnesota, Minneapolis, MN, USA
5. Cardiology Section, Minneapolis VA Health Care System, Minneapolis, MN, USA
6. Lundquist Institute for Biomedical Innovation at Harbor–UCLA Medical Center, Torrance, CA, USA
7. Division of Respiratory & Critical Care Physiology & Medicine, National Clinical Research Center for Respiratory Disease, Guangzhou, China

Contents of online data supplement

e-Figure 4: Scatterplots and Spearman correlations between SDNN and RMSSD versus FEV_1 percent predicted and total SGRQ score.

e-Table 1: Tests for interactions between SDNN and treatment assignment (metoprolol vs placebo) on time to AECOPD. Hazard ratios for the relationship between SDNN and time to acute exacerbation of COPD stratified by treatment assignment are also presented. Interaction terms test whether associations between SDNN and time to AECOPD vary by treatment group and represent the ratio of hazard ratios in those assigned to metoprolol vs. placebo. Higher values represent lower risk of AECOPD in the placebo group compared to the metoprolol group. Hazard ratios represent the change in risk for each 10 ms increase in SDNN. Visualizations of the adjusted analyses are included in the main text (**Figure 2**).

	Unadjusted			**Adjusted[1]**		
	Metoprolol HR, (95% CI)	Placebo HR, (95% CI)	Ratio of HRs, (95% CI), p-value	Metoprolol HR, (95% CI)	Placebo HR, (95% CI)	Ratio of HRs, (95% CI), p-value
Baseline SDNN						
Any AECOPD	0.949 (0.882 to 1.022)	0.963 (0.886 to 1.047)	0.986 (0.882 to 1.101), p=0.798	0.956 (0.882 to 1.035)	0.977 (0.895 to 1.067)	0.978 (0.868 to 1.102), p=0.713
Severe AECOPD[2]	0.944 (0.844 to 1.057)	0.942 (0.783 to 1.132)	1.003 (0.808 to 1.244), p=0.979	0.957 (0.844 to 1.085)	0.909 (0.737 to 1.121)	1.053 (0.825 to 1.344), p=0.679
Time varying SDNN						
Any AECOPD	0.973 (0.916 to 1.035)	0.97 (0.899 to 1.048)	1.003 (0.91 to 1.106), p=0.95	0.975 (0.911 to 1.042)	0.943 (0.867 to 1.026)	1.033 (0.928 to 1.15), p=0.547
Severe AECOPD[2]	0.96 (0.87 to 1.059)	0.748 (0.569 to 0.985)	1.283 (0.958 to 1.717), p=0.094	0.988 (0.895 to 1.09)	0.751 (0.569 to 0.991)	1.316 (0.981 to 1.766), p=0.067

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; SDNN, standard deviation of normal RR intervals; HR, hazard ratio, CI, confidence interval

1: Adjusted models include treatment assignment (metoprolol vs placebo), SDNN , age at baseline, sex, Black race, forced expiratory volume in 1-second percent predicted, history of coronary artery disease, smoking status, and long-acting muscarinic antagonist use as covariates and were stratified by center.

2: Severe AECOPD are defined as those that require hospitalization, with or without mechanical ventilation.

e-Table 2: Tests for Interactions between RMSSD and treatment assignment (metoprolol vs placebo) on time to acute exacerbations of COPD. Hazard ratios for the relationship between RMSSD and time to acute exacerbation of COPD stratified by treatment assignment are also presented. Interaction terms test whether associations between RMSSED and time to AECOPD vary by treatment group and represent the ratio of hazard ratios in those assigned to metoprolol vs. placebo. Higher values represent lower risk of AECOPD in the placebo group compared to the metoprolol group. Hazard ratios represent the change in risk for each 10 ms increase in RMSSD. Visualizations of the adjusted analyses are included in the main text (**Figure 3**).

	Unadjusted			**Adjusted[1]**		
	Metoprolol HR, (95% CI)	Placebo HR, (95% CI)	Ratio of HRs, (95% CI), p-value	Metoprolol HR, (95% CI)	Placebo HR, (95% CI)	Ratio of HRs, (95% CI), p-value
Baseline RMSSD						
Any AECOPD	0.984 (0.927 to 1.044)	0.954 (0.883 to 1.03)	1.031 (0.936 to 1.137), p=0.534	0.983 (0.922 to 1.048)	0.966 (0.894 to 1.044)	1.017 (0.92 to 1.125), p=0.737
Severe AECOPD[2]	0.999 (0.921 to 1.082)	0.901 (0.742 to 1.094)	1.109 (0.898 to 1.368), p=0.336	1.006 (0.921 to 1.099)	0.858 (0.691 to 1.065)	1.173 (0.928 to 1.483), p=0.181
Time varying RMSSD						
Any AECOPD	0.985 (0.944 to 1.027)	0.961 (0.897 to 1.03)	1.024 (0.945 to 1.111), p=0.559	0.986 (0.942 to 1.032)	0.944 (0.877 to 1.016)	1.045 (0.959 to 1.139), p=0.318
Severe AECOPD[2]	0.983 (0.92 to 1.049)	0.719 (0.533 to 0.97)	1.366 (1.006 to 1.856), p=0.046	0.996 (0.933 to 1.063)	0.705 (0.517 to 0.961)	1.412 (1.029 to 1.938), p=0.032

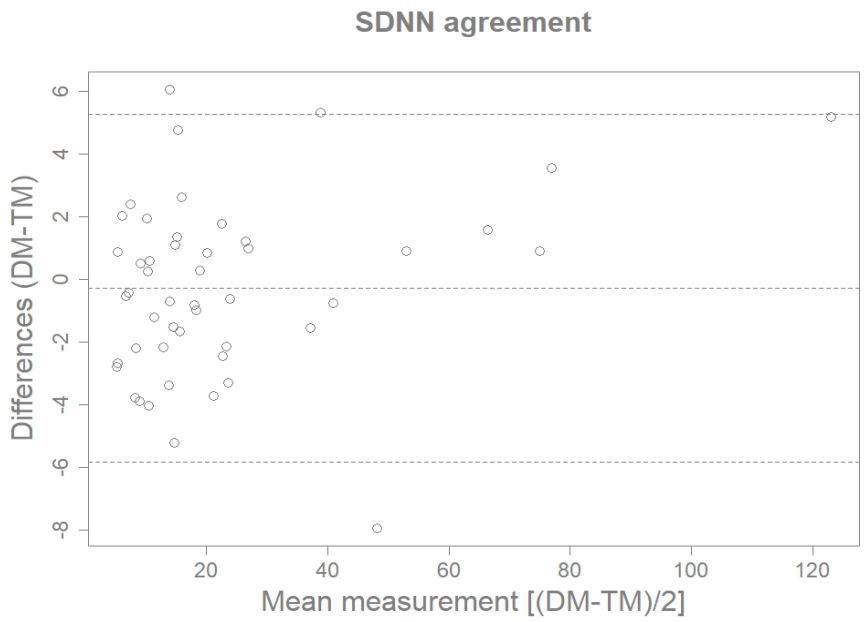
AECOPD, acute exacerbations of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; RMSSD, root mean square of successive normal RR intervals. HR, hazard ratio, CI, confidence interval

1: Adjusted models include treatment assignment (metoprolol vs placebo), RMSSD, age at baseline, sex, Black race, forced expiratory volume in 1-second percent predicted, history of coronary artery disease, smoking status, and long-acting muscarinic antagonist use as covariates and were stratified by center.

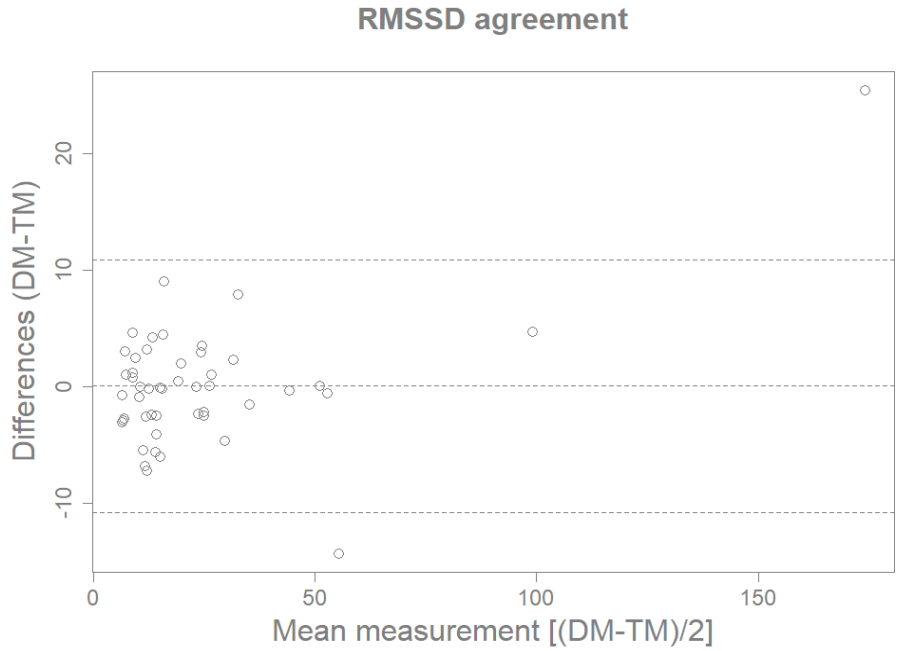
2: Severe AECOPD are defined as those that require hospitalization, with or without mechanical ventilation

e-Figure 1: Bland-Altman plots for the agreement in heart rate variability measures between ECG readers. RR intervals on 48 ECGs were read independently by authors DMM and TM and SDNN and RMSSD were calculated as described in the methods section. Bland-Altman plots are shown for agreement in SDNN (a) and RMSSD (b).

(a)

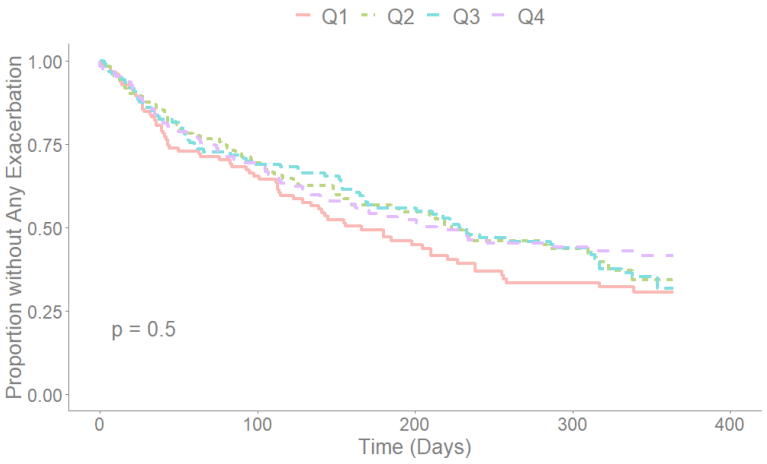


(b)

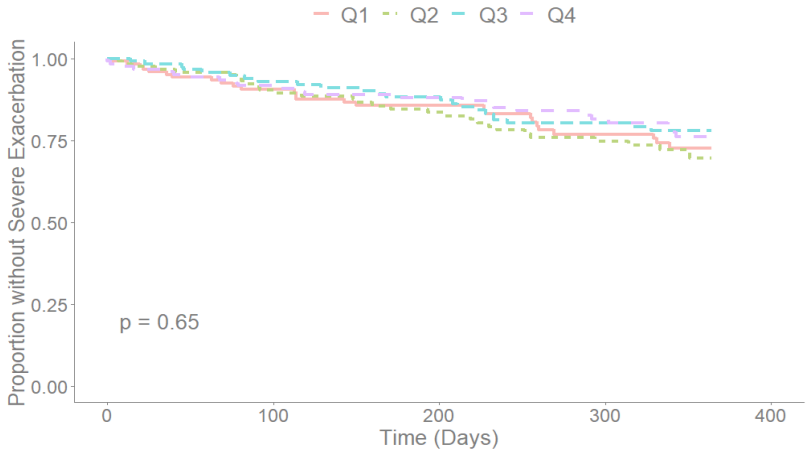


e-Figure 2: Kaplan-Meier estimates (figures) for freedom from acute exacerbation of COPD and Cox proportional hazards models (tables) for time to acute exacerbation of COPD by SDNN quartile for (a) any exacerbation, and (b) severe exacerbation. There was no significant difference detected between quartiles for any acute exacerbation of COPD (logrank p-value 0.50, adjusted omnibus p-value 0.43) or severe exacerbations of COPD (logrank p-value 0.65, adjusted omnibus p-value 0.35). Adjusted models include treatment assignment (metoprolol vs placebo), age, sex, Black race, FEV_1 percent predicted, history of coronary artery disease, smoking status, and long-acting muscarinic antagonist use as covariates and were stratified by center.

(a)



(b)



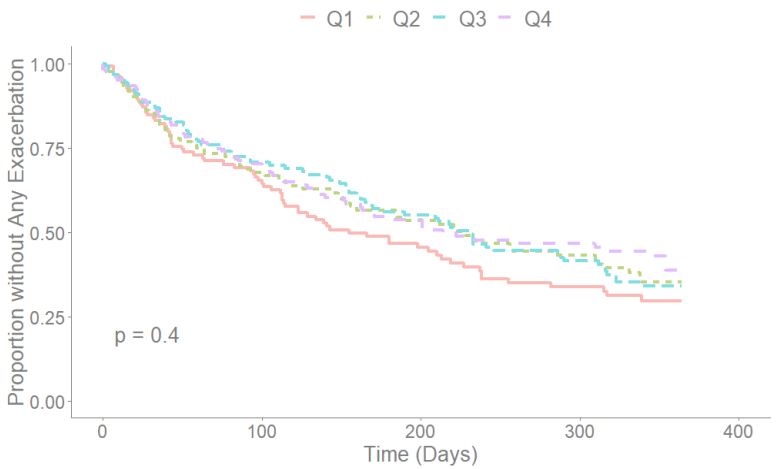
Cox proportional hazards models for time to any AECOPD by SDNN quartile					
Quartile RMSSD range	Q1 ≤11	Q2 > 11 and ≤18	Q3 >18 and ≤29	Q4 >29	Omnibus p-value
Unadjusted HR	1.00 (ref)	0.84 (0.60 to 1.17)	0.84 (0.61 to 1.17)	0.78 (0.56 to 1.09)	0.51
Adjusted HR	1.00	0.82	0.80	0.751	0.43

	(ref)	(0.57 to 1.17)	(0.56 to 1.13)	(0.53 to 1.07)	

Cox proportional hazards models for time to severe AECOPD by SDNN quartile					
Quartile RMSSD range	Q1 ≤11	Q2 > 11 and ≤18	Q3 >18 and ≤29	Q4 >29	Omnibus p-value
Unadjusted HR	1.00 (ref)	1.07 (0.63 to 1.82)	0.79 (0.45 to 1.38)	0.83 (0.48 to 1.45)	0.65
Adjusted HR	1.00 (ref)	1.01 (0.58 to 1.77)	0.687 (0.38 to 1.24)	0.688 (0.38 to 1.24)	0.35

e-Figure 3: Kaplan-Meier estimates (figures) for freedom from acute exacerbation of COPD and Cox proportional hazards models (tables) for time to acute exacerbation of COPD by RMSSD quartile for (a) any exacerbation, and (b) severe (hospitalized) exacerbation. There was no significant difference detected between quartiles for any acute exacerbation of COPD (logrank p-value 0.40, adjusted omnibus p-value 0.37) or severe exacerbations of COPD (logrank p-value 0.58, adjusted omnibus p-value 0.33). Adjusted models include treatment assignment (metoprolol vs placebo), age, sex, Black race, FEV_1 percent predicted, history of coronary artery disease, smoking status, and long-acting muscarinic antagonist use as covariates and were stratified by center.

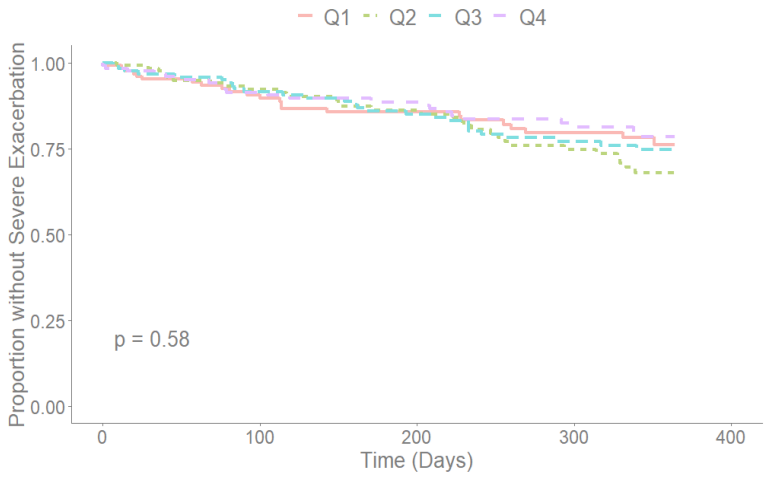
(a)



Number at risk

Q1	124	68	40	27	0
Q2	123	71	50	36	0
Q3	123	81	57	40	0
Q4	124	78	55	40	0

(b)



Number at risk

Q1	124	95	76	62	0
Q2	123	97	80	60	0
Q3	123	104	87	71	0
Q4	124	100	89	68	0

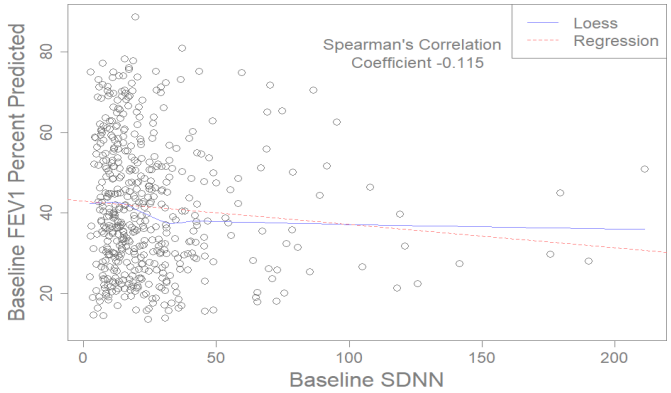
Cox proportional hazards models for time to severe AECOPD by RMSSD quartile

Cox proportional hazards models for time to any AECOPD by RMSSD quartile					
Quartile RMSSD range	Q1 ≤11	Q2 > 11 and ≤18	Q3 >18 and ≤29	Q4 >29	Omnibus p-value
Unadjusted HR	1.00 (ref)	0.84 (0.60 to 1.17)	0.83 (0.60 to 1.15)	0.75 (0.54 to 1.05)	0.41
Adjusted HR	1.00 (ref)	0.85 (0.59 to 1.21)	0.766 (0.55 to 1.07)	0.755 (0.53 to 1.08)	0.37

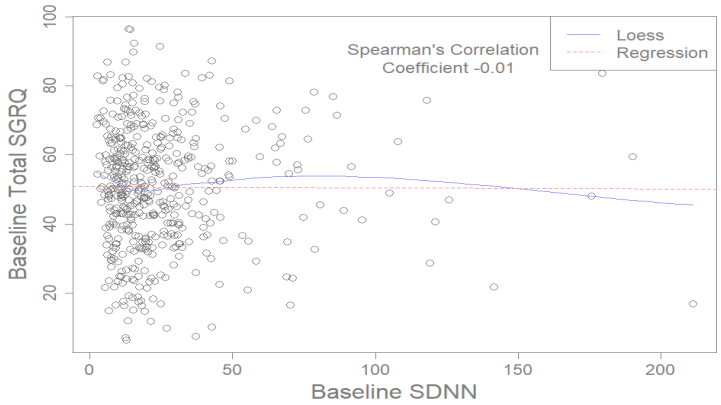
Quartile RMSSD range	Q1 ≤11	Q2 > 11 and ≤18	Q3 >18 and ≤29	Q4 >29	Omnibus p-value
Unadjusted HR	1.00 (ref)	1.30 (0.76 to 2.24)	1.06 (0.61 to 1.85)	0.90 (0.50 to 1.61)	0.59
Adjusted HR	1.00 (ref)	1.38 (0.77 to 2.46)	0.936 (0.52 to 1.67)	0.82 (0.44 to 1.52)	0.34

e-Figure 4: Associations between baseline (a) SDNN and FEV_1 percent predicted, (b) SDNN and total SGRQ scores, (c) RMSSD and FEV_1 percent predicted, and (d) RMSSD and total SGRQ scores. Blue lines represent locally estimated scatterplot smoothing (LOESS) lines and red lines represent simple linear regression.

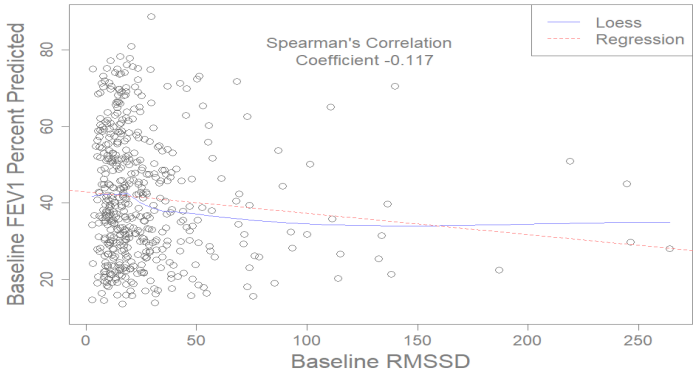
(a)



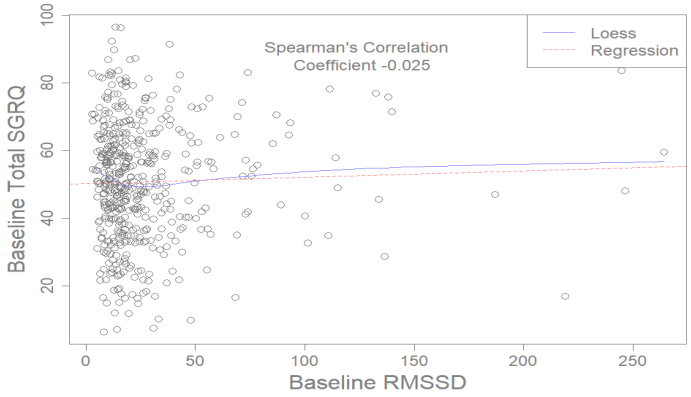
(b)



(c)


Spearman's Correlation
Coefficient -0.117
Loess
Regression
Baseline FEV1 Percent Predicted
Baseline RMSSD
20
40
60
80
0
50
100
150
200
250

(d)


Spearman's Correlation
Coefficient -0.025
Loess
Regression
Baseline Total SGRQ
Baseline RMSSD
20
40
60
80
100
0
50
100
150
200
250