Supplementary Information

Premature Ventricular Contraction Characteristics that Predict Incident Congestive Heart Failure in a Community-based Population

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Figure Legends

Supplementary Figure I: Correlation between PVC frequency and coupling interval heterogeneity. Scatter plot between PVC frequency and $\log_{10}$ of the coupling interval heterogeneity (correlation coefficient - 0.00234, p-value 0.97).

Supplementary Figure II: Predictors of incident CHF accounting for death as a competing factor. Adjusted hazards ratio of incident CHF. BMI denotes body mass index (by 10 kg/m^2); the reference for former and current smoker is never smoker; Antiarrhythmics include Vaughan-Williams class Ia, Ib, Ic, II, and IV antiarrhythmics; PVC frequency is per 0.1 %; PVC duration is per 100 ms; Coupling interval is per 100 ms; Coupling interval heterogeneity is $\log_{10}$ transformed.

Supplementary Table I: Baseline characteristics of participants excluded from the analyses because of existing borderline/abnormal LVEF and CHF at baseline.

	Excluded participants (n=39)
Mean age	74.1 ± 5.5
Female sex	13 (33%)
Race	
- white	38 (97%)
- black	1 (3%)
Mean BMI (kg/m^2)	27.5 ± 4.5
Diabetes	5 (13%)
Hypertension	25 (64%)
History of myocardial infarction	15 (38%)
Smoking	
- non-smoker	18 (46%)
- ex-smoker	16 (41%)
- current smoker	5 (13%)
Taking class Ia, Ib, and Ic antiarrhythmics	5 (13%)
Taking class II antiarrhythmics	0 (0%)
Taking class III antiarrhythmics	0 (0%)
Taking class IV antiarrhythmics	3 (8%)
Median PVC frequency	0.22 %
Mean PVC duration (ms)	158.9 ± 20.3
Mean coupling interval (ms)	519.7 ± 90.0
Mean coupling interval heterogeneity	0.12 ± 0.07

BMI denotes Body Mass Index

Supplement Table II: Number of participants with LVEF in normal, borderline, and abnormal ranges at baseline and at the 5-year follow up

	LVEF at 5-year follow up			
Baseline LVEF	Normal	Borderline	Abnormal	Total
Normal	180	19	10	209
Borderline	0	0	0	0
Abnormal	1	3	1	5
Total	181	22	11	214

Supplementary Table III: Unadjusted and adjusted odds ratio of predictors of LVEF reduction

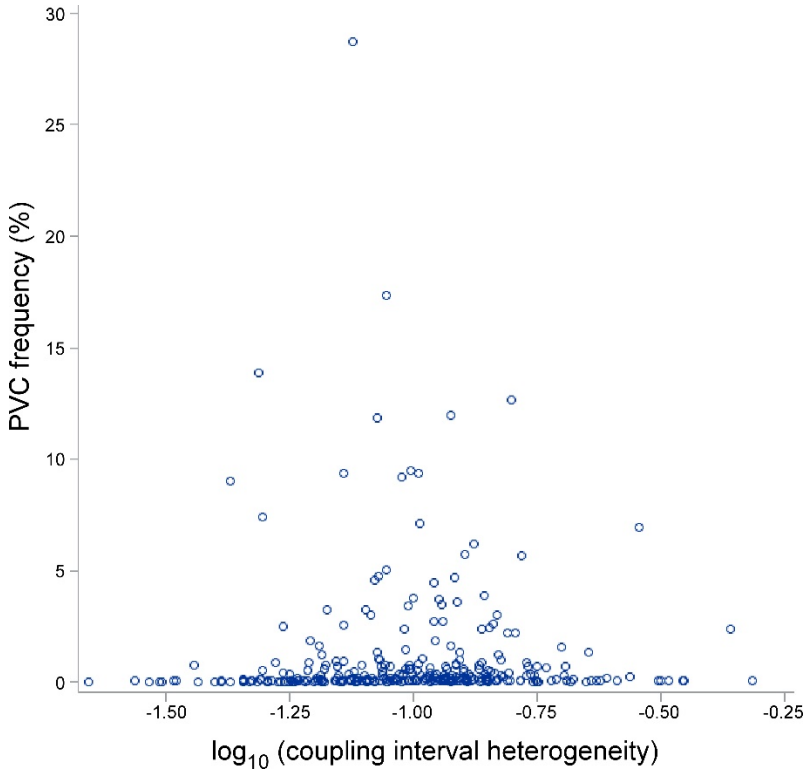
	Unadjusted Model				Adjusted Model			
	OR	**Confidence Interval**		**p-value**	**OR**	**Confidence Interval**		**p-value**
Age	1.04	0.96	1.14	0.315	1.06	0.95	1.17	0.36
Male Sex	1.71	0.73	4.01	0.218	1.61	0.63	4.12	0.30
Non-white Race	1.22	0.15	10.19	0.852	2.25	0.21	24.39	0.41
BMI	2.24	0.87	5.75	0.094	2.77	0.82	9.36	0.15
Diabetes	2.14	0.77	5.9	0.143	2.32	0.74	7.29	0.10
Hypertension	1.17	0.52	2.64	0.708	1.09	0.44	2.66	0.92
Myocardial Infarction	2.04	0.62	6.72	0.243	1.97	0.51	7.70	0.05
Ex-smoker	1.16	0.49	2.77	0.736	0.88	0.33	2.31	0.77
Current Smoker	1.29	0.32	5.19	0.722	1.56	0.34	7.09	0.67
PVC Frequency	1.91	0.67	5.45	0.225	1.54	0.46	5.18	0.48
PVC width	0.83	0.13	5.37	0.845	0.77	0.09	7.05	0.62
Coupling Interval	1.47	0.89	2.43	0.130	1.32	0.70	2.52	0.36
Coupling interval Heterogeneity	17.58	2.58	119.66	**0.003**	15.14	1.93	118.73	**0.004**

Age is per year; BMI denotes body mass index (by 10 kg/m^2); the reference for former and current smoker is never smoker; PVC frequency is per 0.1 %; PVC duration is per 100 ms; Coupling interval is per 100 ms; Coupling interval heterogeneity is $\log_{10}$ transformed.

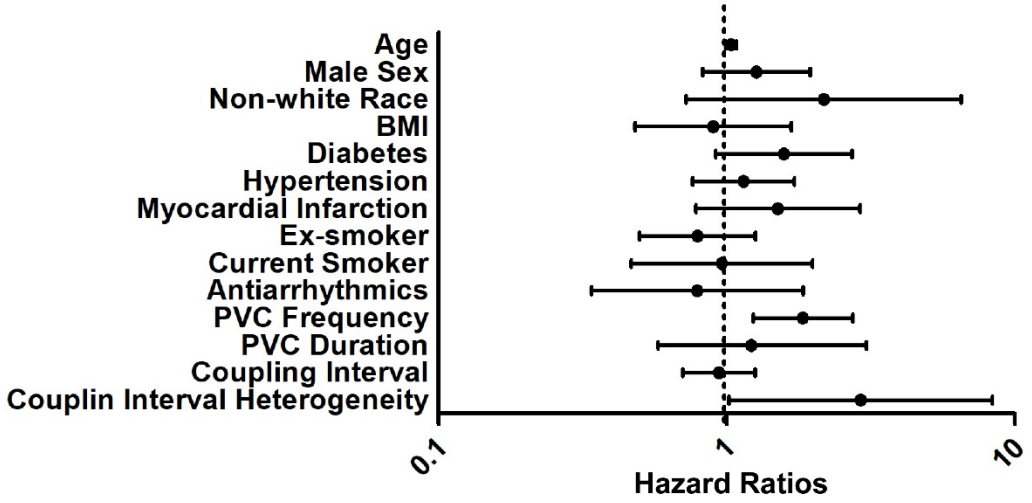
Supplementary Table IV: Unadjusted and adjusted hazard ratio of predictors of incident CHF

	Unadjusted Model				Adjusted Model			
	HR	**Confidence Interval**		**p-value**	**HR**	**Confidence Interval**		**p-value**
Age	1.09	1.05	1.13	**< 0.001**	1.08	1.03	1.12	**< 0.001**
Sex	1.78	1.19	2.64	**0.005**	1.47	0.96	2.25	0.08
Non-white Race	1.42	0.52	3.84	0.496	1.65	0.39	1.25	0.34
BMI	0.76	0.47	1.23	0.258	0.70	0.93	1.25	0.23
Diabetes	1.83	1.14	2.93	**0.012**	1.80	1.08	3.00	**0.02**
Hypertension	1.27	0.86	1.87	0.225	1.19	0.79	1.79	0.40
Myocardial Infarction	1.88	1.13	3.13	**0.015**	1.94	1.11	3.40	**0.02**
Ex-smoker	1.18	0.78	1.76	0.434	1.12	0.73	1.73	0.61
Current Smoker	1.14	0.59	2.20	0.704	1.13	0.56	2.29	0.74
Antiarrhythmics	0.54	0.20	1.47	0.226	0.44	0.15	1.27	0.13
PVC Frequency	2.10	1.30	3.38	**0.002**	2.04	1.23	3.38	**0.006**
PVC width	1.73	0.78	3.86	0.178	1.45	0.61	3.46	0.40
Coupling Interval	1.03	0.81	1.32	0.787	0.95	0.71	1.25	0.69
Coupling interval Heterogeneity	2.12	0.88	5.14	0.095	2.98	1.13	7.84	**0.03**

Age is per year; BMI denotes body mass index (by 10 kg/m^2); the reference for former and current smoker is never smoker; Antiarrhythmics include Vaughan-Williams class Ia, Ib, Ic, II, and IV antiarrhythmics; PVC frequency is per 0.1 %; PVC duration is per 100 ms; Coupling interval is per 100 ms; Coupling interval heterogeneity is $\log_{10}$ transformed.



Supplementary Figure I: Correlation between PVC frequency and coupling interval heterogeneity. Scatter plot between PVC frequency and $\log_{10}$ of the coupling interval heterogeneity (correlation coefficient - 0.00234, p-value 0.97).



Supplementary Figure II: Predictors of incident CHF accounting for death as a competing factor. Adjusted hazards ratio of incident CHF. BMI denotes body mass index (by 10 kg/m^2); the reference for former and current smoker is never smoker; Antiarrhythmics include Vaughan-Williams class Ia, Ib, Ic, II, and IV antiarrhythmics; PVC frequency is per 0.1 %; PVC duration is per 100 ms; Coupling interval is per 100 ms; Coupling interval heterogeneity is $\log_{10}$ transformed.

Supplementary Note I: Logistic Regression Model Characteristics

To assess the adequacy of the multivariable logistic model for change in LVEF, we first tested for interactions among all 13 covariates (potential 78 interactions) and did not find any that reached statistical significance after taking multiple testing into account.

In addition, we also tested for non-linearity of the associations of five continuous covariates with change in LVEF using a 3-knot restricted cubic spline transformation, then calculating the p-value of the second spline component, which captures any non-linearity, and found that none violates linearity assumption (p-value ≥ 0.05).

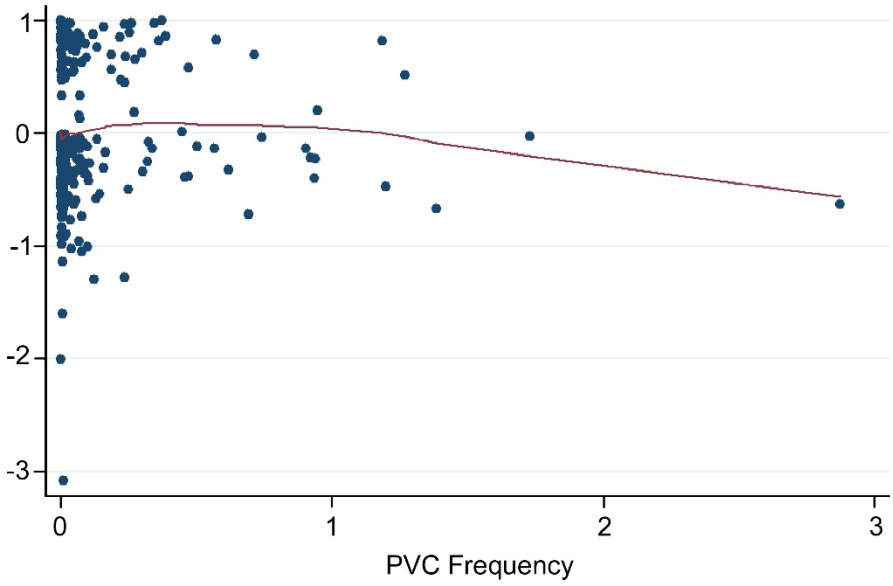
For logistic regression analysis of a binary outcome such as LVEF reduction, residual vs. predictor plots using either Pearson or deviance residuals can be difficult to interpret, in contrast to linear regression. Alternatively, smoothing the binary outcome against the predictor, then logistically transforming the result, does not take into account of covariate effects [1]. Therefore, we opted to test for non-linearity using the spline approach as opposed to running residual analysis on this model.

Supplementary Note II: Multivariable Cox Proportional Hazard Model Characteristics

We assessed the adequacy of the multivariable cox proportional hazard model for incident CHF. We have tested for interactions among 13 covariates (potential 78 interactions) and only found six statistically significant interactions (7.7%, 3 more than might be expected by chance) between the following covariates:

Interaction Pairs	p-value
PVC duration vs. age	0.025
PVC duration vs. antiarrhythmic usage	0.039
Coupling interval duration vs. history of hypertension	0.015
Coupling interval heterogeneity vs. history of hypertension	0.015
Male sex vs. history of diabetes	0.022
History of myocardial infarction vs. antiarrhythmic usage	0.035

In addition, we assessed non-linearity of the six continuous covariates using Martingale residual vs predictor plots [2], followed by statistical assessment using restricted cubic spline transformation. This analysis detected non-linearity only in the association of PVC frequency (p-value = 0.015) with time to CHF (shown below).



Lastly, we assessed the proportional hazards assumption using scaled Schoenfeld residuals [3]. This showed that while two individual covariates violate proportionality (age, p-value = 0.032; history of myocardial infarction, p-value = 0.005), the model overall does not (p-value = 0.095).

Supplementary References

1 Vittinghoff E, Shiboski SC, Glidden DV, MuCulloch CE. Regression Methods in Biostatistics, 2nd Edition. New York: Springer 2012:192-5.

2 Therneau TM GP, Fleming TR. Martingale-based residuals for survival models. *Biometrika* 1990;**77**:147-60.

3 Grambsch P, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994;**81**:515-26.