Supplemental Material

Supplemental Results

The baseline patient characteristics for all subgroups analyzed are shown in Table S1. Tables S2-S6 demonstrate the association between ECG metrics and cardiovascular death (CVD) in the validation cohort and low-risk subgroups, adjusting by TRS, LVEF and BNP as appropriate. None of the ECG metrics were significantly associated with CVD in a higher-risk subgroup (TRS≥5, Table S7).

Supplemental Tables

Table S1: Baseline patient characteristics for whole dataset (MERLIN placebo) and subpopulations. *: statistically significant difference (at the 5% level) compared to the validation cohort.

	Validation Cohort (LVEF & BNP)	TRS≤4	TRS≥5	Lower Risk-1 (LVEF>40 & TRS≤4)	Lower Risk-2 (BNP≤80 & TRS≤4)	Lower Risk-3 (BNP≤80 & LVEF>40 & TRS≤4)
N	1082	864	218	776	538	503
CV Deaths	45(4.5%)	22(2.7%)*	23(12.0%)*	17(2.3%)*	8(1.6%)*	6(1.3%)*
Age, years, median (IQR)	63(55-71)	61(54-69)*	69(65-74)*	61(54-69)*	58(53-66)*	59(53-66)*
Female (%)	37	37	39	39	36	38
BMI, median (IQR)	28(25-32)	29(26-32)	28(25-32)	29(26-32)	29(26-33)	29(26-32)
Diabetes mellitus (%)	35	32	48*	32	34	34
Hypertension (%)	78	75	91*	75	76	77
Current smoker (%)	24	26	20	26	26	26
Previous MI (%)	36	28*	71*	26*	27*	25*
Index event (%)						
Unstable angina	52	52	50	53	64*	64*
Myocardial infarction	48	48	50	47	36*	36*
ST depression ≥1mV (%)	39	35*	58*	35*	27*	27*
TIMI risk score (%)						
Group 1 Low(1-2)	25	31*	0*	32*	35*	35*
Group 2 Moderate(3-4)	55	69*	0*	68*	65*	65*
Group 3 High(5-7)	20	0*	100*	0*	0*	0*
LVEF measured (%)	100	100	100	100	100	100
LVEF <40% (%)	12	10	21*	0*	7*	0*
BNP measured (%)	100	100	100	100	100	100
BNP >80 (%)	42	38	57*	35*	0*	0*

Table S2: Multivariable models consisting of LVEF≤40%, TRS≥5, BNP>80pg/ml, and a single ECG metric, as assessed on the validation cohort (MERLIN Placebo population with both LVEF and BNP measurements). There are 45 CVD in 1082 patients (4.5%). Hazard ratios are computed relative to the upper quartile value in this population unless otherwise indicated. Metrics with significant hazard ratios are in bold.

Risk Metric	Multivariable 1-year hazard ratio (adjusted for LVEF,BNP,TRS)	95% CI	p
MV>52.5	**3.31**	**(1.80,6.09)**	**0.000**
MV	**2.62**	**(1.43,4.81)**	**0.002**
DC≤2.5 (vs >4.5)	**2.39**	**(1.00,5.73)**	**0.050**
DC	**2.26**	**(1.22,4.17)**	**0.009**
HRV-LFHF	**2.21**	**(1.20,4.09)**	**0.011**
MVB	**2.11**	**(1.15,3.89)**	**0.016**
DC≤4.5	**2.07**	**(1.12,3.85)**	**0.021**
MVB>2.9	**1.90**	**(1.04,3.50)**	**0.038**
DC≤2.5	1.77	(0.82,3.84)	0.148
HRV-SDANN	1.53	(0.83,2.81)	0.171
HRT12	1.39	(0.75,2.58)	0.299
HRV-HRVI	1.12	(0.59,2.13)	0.728
HRV-ASDNN	1.09	(0.58,2.07)	0.790
HRV-SDNN	1.03	(0.54,1.98)	0.925
HRT2 (vs 0)	0.88	(0.33,2.36)	0.805
TWA	0.82	(0.39,1.71)	0.597
HRT2	0.77	(0.32,1.89)	0.574
HRV-PNN50	0.76	(0.37,1.58)	0.459
HRV-RMSSD	0.75	(0.35,1.61)	0.452
SAF	0.68	(0.24,1.97)	0.481

Table S3: Multivariable models consisting of LVEF≤40%, BNP>80pg/ml, and a single ECG metric, as assessed on patients with TRS≤4. There are 22 CVD in 864 patients (2.7%). Hazard ratios are computed relative to the upper quartile value in this population unless otherwise indicated. Metrics with significant hazard ratios are in bold.

Risk Metric	Multivariable 1-year hazard ratio (adjusted for LVEF,BNP)	95% CI	p
MV>52.5	**5.29**	**(2.22,12.64)**	**0.000**
MV	**3.67**	**(1.53,8.79)**	**0.003**
MVB	**2.99**	**(1.25,7.15)**	**0.014**
MVB>2.9	**2.85**	**(1.19,6.80)**	**0.018**
HRV-LFHF	2.32	(0.98,5.53)	0.057
DC≤4.5	2.03	(0.85,4.84)	0.110
DC≤2.5 (vs >4.5)	2.00	(0.58,6.88)	0.272
DC	1.97	(0.82,4.73)	0.132
HRT2 (vs 0)	1.91	(0.54,6.70)	0.313
HRT2	1.85	(0.60,5.74)	0.284
DC≤2.5	1.82	(0.59,5.65)	0.300
HRT12	1.71	(0.69,4.21)	0.247
SAF	1.59	(0.45,5.65)	0.474
HRV-SDANN	1.43	(0.59,3.45)	0.423
HRV-SDNN	1.41	(0.59,3.40)	0.442
HRV-ASDNN	1.18	(0.48,2.91)	0.726
HRV-PNN50	0.93	(0.34,2.53)	0.890
HRV-HRVI	0.72	(0.26,1.98)	0.526
HRV-RMSSD	0.68	(0.23,2.00)	0.480
TWA	0.63	(0.21,1.88)	0.411

Table S4: Multivariable models consisting of BNP>80pg/ml and a single ECG metric, as assessed on patients with Lower-Risk-1 subpopulation (TRS≤4 and LVEF>40%). There are 17 CVD in 776 patients (2.3%). Hazard ratios are computed relative to the upper quartile value in this population unless otherwise indicated.

Risk Metric	Multivariable 1-year hazard ratio (adjusted for BNP)	95% CI	p
MV>52.5	**4.83**	**(1.85,12.62)**	**0.001**
MVB	**3.84**	**(1.45,10.15)**	**0.007**
MV	**2.95**	**(1.13,7.72)**	**0.027**
MVB>2.9	**2.67**	**(1.02,6.97)**	**0.045**
HRV-LFHF	1.55	(0.57,4.20)	0.389
HRT12	1.43	(0.52,3.97)	0.488
HRV-SDNN	1.43	(0.53,3.88)	0.486
HRV-SDANN	1.42	(0.52,3.86)	0.490
DC<=4.5	1.37	(0.50,3.75)	0.541
DC	1.34	(0.49,3.67)	0.570
HRV-ASDNN	1.10	(0.39,3.13)	0.861
HRV-PNN50	0.94	(0.31,2.90)	0.920
HRT2 (vs 0)	0.82	(0.10,6.60)	0.851
HRT2	0.69	(0.09,5.28)	0.722
HRV-RMSSD	0.64	(0.19,2.24)	0.490
TWA	0.64	(0.19,2.24)	0.490
HRV-HRVI	0.59	(0.17,2.05)	0.406
SAF	0.00	(0.00,Inf)	0.994
DC<=2.5	0.00	(0.00,Inf)	0.993
DC≤2.5 (vs >4.5)	0.00	(0.00,Inf)	0.994

Table S5: Multivariable models consisting of LVEF≤40% and a single ECG metric, as assessed on the LowerRisk-2 subpopulation (TRS≤4 and BNP≤80pg/ml). There are 8 CVD in 538 patients (1.6%). Hazard ratios are computed relative to the upper quartile value in this population unless otherwise indicated.

Risk Metric	Multivariable 1-year hazard ratio (adjusted for LVEF)	95% CI	p
MVB	**7.81**	**(1.52,40.09)**	**0.014**
MVB>2.9	**5.08**	**(1.15,22.41)**	**0.032**
MV>52.5	**4.91**	**(1.20,20.17)**	**0.027**
MV	**4.42**	**(1.04,18.86)**	**0.044**
HRT2 (vs 0)	4.29	(0.44,41.95)	0.211
DC≤2.5 (vs >4.5)	3.86	(0.42,35.67)	0.233
HRT12	3.09	(0.69,13.85)	0.140
DC<=2.5	3.05	(0.37,24.85)	0.297
HRT2	2.94	(0.35,24.72)	0.320
DC<=4.5	2.71	(0.62,11.87)	0.184
DC	2.39	(0.55,10.30)	0.243
HRV-LFHF	1.67	(0.40,7.01)	0.484
HRV-PNN50	1.02	(0.20,5.03)	0.985
TWA	0.98	(0.20,4.88)	0.984
HRV-ASDNN	0.90	(0.18,4.47)	0.893
HRV-RMSSD	0.39	(0.05,3.21)	0.383
HRV-SDANN	0.38	(0.05,3.09)	0.364
HRV-SDNN	0.37	(0.04,3.03)	0.354
SAF	0.00	(0.00,Inf)	0.995
HRV-HRVI	0.00	(0.00,Inf)	0.994

Table S6: Univariate 1-year hazard ratios for risk metrics, as assessed on the LowerRisk-3 subpopulation (BNP≤80pg/ml and LVEF>40% and TRS≤4). There are 6 CVD in 503 patients (1.3%). Hazard ratios are computed relative to the upper quartile value in this population unless otherwise indicated. Metrics with significant hazard ratios are in bold.

Risk Metric	1-year Hazard Ratio	95% CI	p
MVB	**14.92**	**(1.74,127.71)**	**0.014**
MVB>2.9	**8.24**	**(1.51,45.02)**	**0.015**
MV>52.5	**6.13**	**(1.24,30.36)**	**0.026**
MV	**5.92**	**(1.08,32.33)**	**0.040**
HRT2 (vs 0)	5.49	(0.50,60.52)	0.165
HRT2	3.72	(0.42,33.28)	0.240
HRT12	3.26	(0.54,19.48)	0.196
DC	2.99	(0.60,14.79)	0.180
DC≤4.5	2.02	(0.37,11.05)	0.416
TWA	1.55	(0.28,8.46)	0.615
HRV-PNN50	1.49	(0.27,8.14)	0.645
HRV-ASDNN	1.47	(0.27,8.04)	0.655
HRV-LFHF	1.46	(0.27,7.98)	0.662
HRV-SDNN	0.59	(0.07,5.09)	0.635
HRV-SDANN	0.59	(0.07,5.06)	0.632
HRV-RMSSD	0.59	(0.07,5.04)	0.629
DC≤2.5	0.00	(0.00,Inf)	0.995
SAF	0.00	(0.00,Inf)	0.997
DC≤2.5 (vs >4.5)	0.00	(0.00,Inf)	0.997
HRV-HRVI	0.00	(0.00,Inf)	0.995

Table S7: Multivariable models consisting of LVEF≤40%, BNP>80pg/ml, and a single ECG metric, as assessed on patients with TRS≥5. There are 23 CVD in 218 patients (12.0%). Hazard ratios are computed relative to the upper quartile value in this population unless otherwise indicated. None of the metrics have significant hazard ratios.

Risk Metric	Multivariable 1-year hazard ratio (adjusted for LVEF,BNP)	95% CI	p
DC≤2.5 (vs >4.5)	3.14	(0.93,10.59)	0.066
MV	2.19	(0.91,5.25)	0.080
DC≤4.5	2.12	(0.88,5.09)	0.093
HRV-LFHF	2.10	(0.88,5.01)	0.093
MVB>2.9	2.07	(0.87,4.94)	0.101
MV>52.5	2.07	(0.87,4.94)	0.101
DC≤2.5	1.74	(0.60,5.02)	0.306
DC	1.53	(0.63,3.73)	0.345
HRV-SDANN	1.30	(0.53,3.17)	0.568
MVB	1.46	(0.60,3.58)	0.407
HRT12	1.17	(0.51,2.72)	0.709
HRV-ASDNN	1.08	(0.42,2.76)	0.872
HRV-SDNN	1.07	(0.42,2.73)	0.895
HRV-HRVI	0.99	(0.38,2.56)	0.978
TWA	0.93	(0.34,2.52)	0.885
HRV-RMSSD	0.69	(0.23,2.06)	0.511
HRV-PNN50	0.65	(0.22,1.92)	0.439
HRT2 (vs 0)	0.41	(0.09,1.99)	0.271
HRT2	0.35	(0.08,1.53)	0.164
SAF	0.25	(0.03,1.93)	0.185

Table S8: Correlation of MVB and MV with other risk metrics across the placebo population. To normalize for the different numerical ranges of the different metrics, continuous risk metrics are dichotomized at the upper quartile in the placebo population. For categorical risk metrics with more than two categories, the highest risk categories are used: HRT=2 and TRS≥5.

Risk Metric	MVB	MV
MV	**0.745**	1.000
HRV-SDNN	0.095	0.007
HRV-SDANN	0.146	0.078
HRV-ASDNN	0.083	0.018
HRV-RMSSD	-0.088	-0.125
HRV-PNN50	-0.128	-0.148
HRV-HRVI	0.139	0.071
HRV-LFHF	0.400	0.419
HRT	0.180	0.184
DC	0.382	0.370
SAF	0.204	0.213
TWA	0.044	0.051
BNP80	0.166	0.155
TRG	0.069	0.059
LVEF40	0.177	0.174

Table S9: Correlation of MVB and MV with baseline characteristics across the placebo population. To normalize for the different numerical ranges of the variables, continuous variables are dichotomized at the upper quartile in the placebo population unless otherwise indicated.

Variable	MVB	MV
AGE≥65	0.148	0.188
Gender	0.022	0.003
BMI>30	0.054	0.018
Diabetes Mellitus	0.086	0.067
Hypertension	0.046	0.055
Smoker	-0.067	-0.086
Previous MI	0.003	0.016
PCI	0.001	-0.004
CHF	0.03	0.041
Ventricular Arrhythmia	0.058	0.052
Resuscitation	0.042	0.056
Creatine Clearance <60	0.106	0.113
Index Event	0.094	0.068
ST depression	0.069	0.071
Prior Angiography	0.000	-0.001
Aspirin	-0.086	-0.068
B-Blocker	-0.042	-0.047
Statin	0.002	0.015
Heart Rate	0.361	0.284

Table S10: AUC and Category-free Net Reclassification Index (cfNRI) comparing addition of MVB to models incorporating TRS, LVEF, and BNP as appropriate. Since meaningful improvements in discrimination can be masked by small changes in AUC,[1] the statistical difference in the model was quantified by reclassification. 95% confidence intervals (CI) were computed using a nonparametric stratified bootstrap approach with 2000 repeats. *The small number of events in this population made it difficult to reach convergence in the logistic regression models.

Population	# patients (CVD rate)	Reference Model	AUC of Model Including MVB (Reference Model)	cfNRI_event (95% CI)	cfNRI_nonevent (95% CI)	cfNRI (95% CI)
Entire placebo	1082 (4.5%)	TRS,LVEF, BNP	0.761 (0.735)	-6.67 (-33.3,28.9)	52 (45.4,57.2)	45.3 (12.9,75.7)
TRS≤4	864 (2.7%)	LVEF,BNP	0.725 (0.661)	9.09 (-27.3,54.5)	51.5 (44.9,57.5)	60.6 (16.7,103)
TRS≤4,LVEF>40	776 (2.3%)	BNP	0.762 (0.651)	17.6 (-29.4,64.7)	51.5 (44.9,57.6)	69.2 (21.6,115)
TRS≤4,BNP≤80*	538 (1.6%)	LVEF	0.801 (0.594)	50 (-5.83e-15,100)	51.7 (43.8,58.9)	102 (29.3,155)

Table S11: Evaluation of calibration of models incorporating TRS, LVEF, BNP, and MVB as appropriate (as per Table S10). Since all variables are dichotomized (Methods), categories were chosen corresponding to unique probabilities instead of deciles (16,8,4,4 categories respectively). P-values were computed using the Hosmer-Lemeshow goodness of fit test[2].

Population	# patients (CVD rate)	Model	p
Entire placebo	1082 (4.5%)	TRS,LVEF, BNP,MVB	0.74
TRS≤4	864 (2.7%)	LVEF,BNP, MVB	0.43
TRS≤4,LVEF>40	776 (2.3%)	BNP,MVB	0.14
TRS≤4,BNP≤80	538 (1.6%)	LVEF,MVB	0.13

Table S12: Discrimination performance of MVB using segments of the ECG. The ECG signal is first pre-processed as per the steps in MVB. Next, the beat-to-beat morphologic distance time series is computed. The distance attributed to each quarter of the ECG segment is then computed, resulting in 4 values for each original MD value: MD1, MD2, MD3, and MD4; MD=MD1+MD2+MD3+MD4. This results in 4 new time series which summarize the variability in partial segments of the ECG. The remaining steps of conversion to the frequency domain, summing the energy in the range every 2 to 7 heartbeats, and taking the 90th percentile are identical. The AUC for MVB computed using the entire segment is the highest, suggesting that the variability measured by MVB can occur in any part of the cardiac cycle across different patients.

Quarter-segment	AUC for MVB
1	0.6078
2	0.6293
3	0.6443
4	0.6868
Entire Segment	0.7253

Supplementary Figures

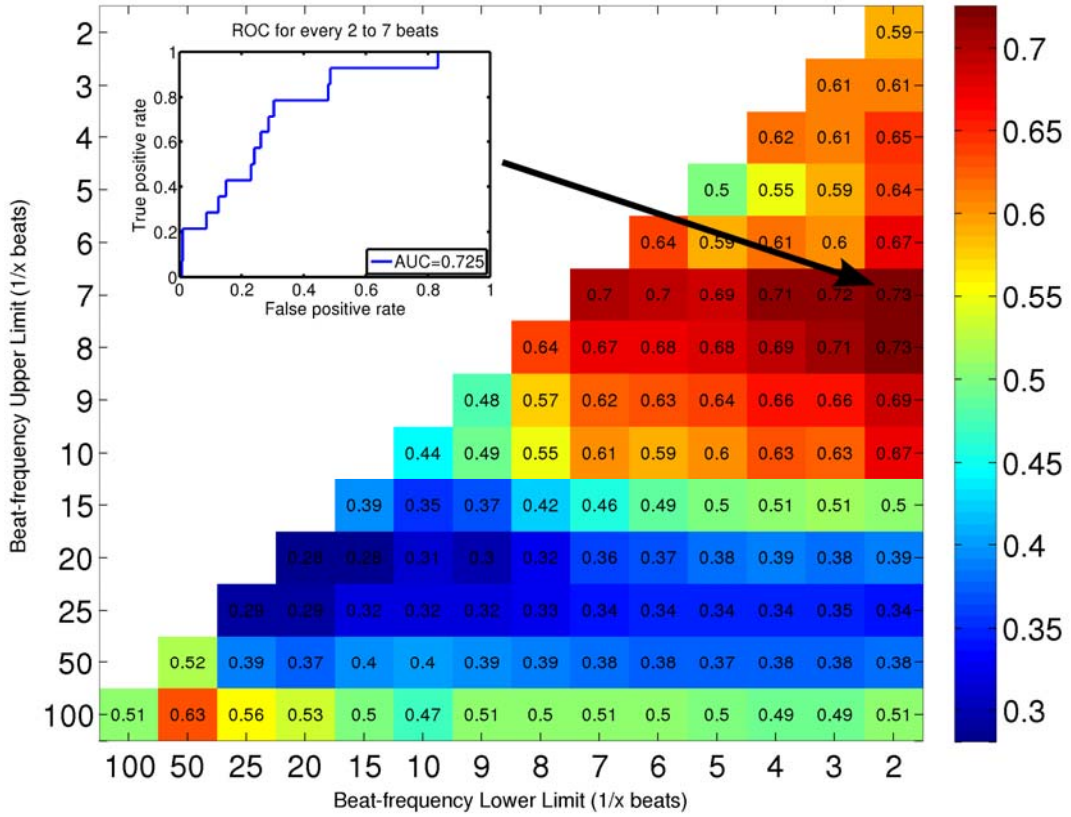

Figure S1: Optimizing the diagnostic beat-frequency for maximum AUC in the derivation cohort (DISPERSE2-TIMI 33 clinical trial, N=764). Figure 2 summarizes the procedure for computing Morphologic Variability in Beatspace (MVB). The input ECG signal converted into a beat-to-beat difference time series termed the Morphologic Distance (MD) time series. The MD time series is then segmented into 5-minute windows, transformed into the beat-frequency domain, and the energy in the diagnostic beat-frequency range is summed for each window. The 90th percentile of these energies over all 5-minute windows in 24 hours is termed the MVB for the patient. This figure illustrates the procedure of optimizing the diagnostic beat-frequency. Each point represents the AUC for death within 90 days, computed using a diagnostic beat-frequency with lower and upper limits defined by the x-y axes. For example, the value of 0.73 (indicated by the arrow) means that a diagnostic beat-frequency of every 2 to 7 beats results in an AUC of 0.73. This is also the peak AUC; thus we define the optimal diagnostic beat-frequency to be every 2 to 7 beats. The inset illustrates the Receiver Operating Characteristic (ROC) curve for this optimal diagnostic beat-frequency.

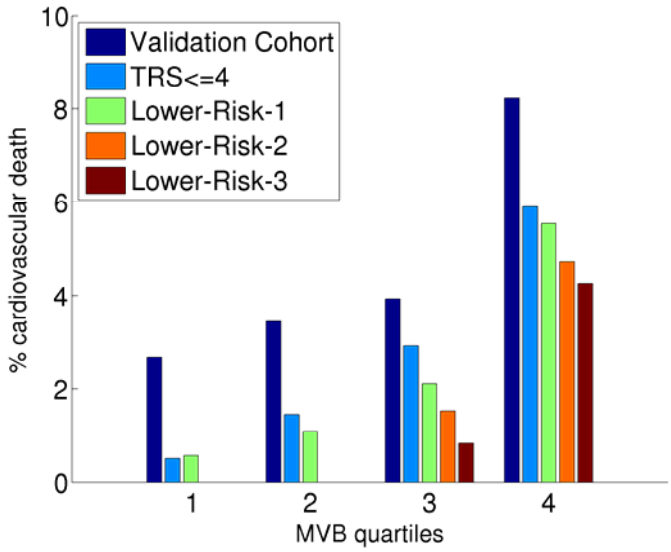

Figure S2: Rate of cardiovascular death by quartiles of MVB. Population definitions and baseline characteristics are stated in Table S1. Briefly, Lower-Risk-1 indicates TRS≤4 and LVEF>40%, Low-Risk-2 indicates BNP≤80pg/ml and TRS≤4, and Lower-Risk-3 indicates BNP≤80pg/ml and LVEF>40% and TRS≤4. “missing” bars in the bottom two quartiles for the lower-risk-2 and lower-risk-3 populations indicate no deaths occurred in those populations.

Supplemental Material References

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2. Hosmer DW, Lemesbow S. Goodness of fit tests for the multiple logistic regression model. *Communications in Statistics-Theory and Methods*. 1980;9:1043-1069