Supplementary Online Content

Gasperetti A, Cappelletto C, Carrick R, et al. Association of premature ventricular contraction burden on serial Holter monitoring with arrhythmic risk in patients with arrhythmogenic right ventricular cardiomyopathy. *JAMA Cardiol*. Published online February 23, 2022. doi:10.1001/jamacardio.2021.6016

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Final Model Performance

The following tables reports the final model performance if the following definition of a PVC spike is used:
- a) an absolute increase in PVC burden ≥5000 PVCs and/or
- b) a relative % increase ≥50% from the preceding Holter, with an absolute increase of at least 1000 PVCs.

Holter predictors of an SVA event in the upcoming 12 months			
Fixed Effects			
	OR	C.I.	p
24-h PVC burden (log)	1.532	[1.128–2.082]	**0.006**
Presence of a PVC Spike	5.343	[2.387–11.962]	**<0.001**
Presence of nsVT	2.223	[1.103–4.479]	**0.025**
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.889	0.343	[0.418–1.893]

C-statistic: 0.889 [0.850–0.927]

The following tables reports the final model performance if the following definition of a PVC spike is used:
- a) an absolute increase in PVC burden ≥5000 PVCs and/or
- b) a relative % increase ≥100% from the preceding Holter, with an absolute increase of at least 1000 PVCs.

Holter predictors of an SVA event in the upcoming 12 months			
Fixed Effects			
	OR	C.I.	p
24-h PVC burden (log)	1.557	[1.151–2.106]	**0.004**
Presence of a PVC Spike	5.189	[2.352–11.447]	**<0.001**
Presence of nsVT	2.213	[1.108–4.422]	**0.024**
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.837	0.342	[0.376–1.864]

Harrel's C: 0.880 [0.840–0.920]

eTable 1. Characteristics at Disease Diagnosis by Presence of PVC Spikes

	ARVC patients with PVC spikes (n = 67)	ARVC patients without PVC spikes (n = 102)	p
Age (years), mean±s.d.	37.5±14.9	35.5±15.0	0.381
Male sex, n (%)	37 (55.2)	58 (56.9)	0.834
Proband Status, n (%)	54 (80.6)	74 (72.6)	0.233
Pathogenic/Likely Pathogenic Variant, n (%)	33 (49.2)	52 (51.0)	0.826
Recent cardiac syncope, n (%)	13 (19.4)	11 (10.8)	0.116
TWI, median [IQR]	3 [2–4]	3 [2–4]	0.755
nsVT at diagnosis, n (%)	29 (43.9)	32 (32.0)	0.118
24-h PVC count, median [IQR]	3851 [1241–9979]	1553 [366–7000]	**0.011**
History of SVT at diagnosis, n (%)	19 (28.4)	28 (27.5)	0.898
RVEF at CMR (%), mean±s.d.	44.9±12.7	46.8±11.8	0.338

eTable 2. Characteristics at Disease Diagnosis by Presence of Ventricular Arrhythmia Events During Follow-up

Characteristics at Disease Diagnosis			
	ARVC patients with VA events (n = 57)	ARVC patients without VA event (n = 112)	p
Age (years), mean±s.d.	34.0±14.4	37.4±15.1	0.166
Male sex, n (%)	35 (51.4)	60 (53.6)	0.332
Proband Status, n (%)	49 (85.9)	79 (70.5)	**0.027**
Recent cardiac syncope, n (%)	11 (9.8)	13 (22.8)	**0.022**
TWI, median [IQR]	4 [3 – 5]	3 [2 – 4]	**0.002**
nsVT at diagnosis, n (%)	27 (48.2)	34 (30.9)	**0.029**
24-h PVC count, median [IQR]	5000 [2240 – 8000]	1437 [333 – 6047]	**<0.001**
History of SVT at diagnosis, n (%)	20 (35.1)	27 (24.1)	0.132
RVEF at CMR (%), mean±s.d.	43.7±10.2	47.2±12.9	0.102
LVEF at CMR (%), mean±s.d.	53.4±8.1	55.1±8.2	0.247

eTable 3. Association of PVC on Holter Finding With Occurrence of a Sustained Ventricular Arrhythmia Event

Per Holter Event Predictor			
Fixed Effects			
	OR	C.I.	p
PVC at Holter (log)	2.189	[1.636–2.929]	**<0.001**
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.760	0.343	[0.313–1.842]

eTable 4. Association of PVC Spike on Holter Finding With Occurrence of a Sustained Ventricular Arrhythmia Event

Per Holter Event Predictor			
Fixed Effects			
	OR	C.I.	p
PVC Spike	13.071	[6.036–28.307]	**<0.001**
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.890	0.350	[0.413–1.919]

eTable 5. Association of NSVT on Holter Finding With Occurrence of a Sustained Ventricular Arrhythmia Event

Per Holter Event Predictor			
Fixed Effects			
	OR	C.I.	p
NSVT	4.110	[2.333–7.240]	**<0.001**
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.441	0.420	[0.068–2.852]

eTable 6. Association of Use of β-Blockers During Holter Examination With Occurrence of a Sustained Ventricular Arrhythmia Event

Per Holter Event Predictor			
Fixed Effects			
	OR	C.I.	p
Use of BB-blockers	1.010	[0.574–1.773]	0.973
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.570	0.358	[0.166–1.952]

eTable 7. Association of Use of Class III AADs During Holter Examination With Occurrence of a Sustained Ventricular Arrhythmia Event

Per Holter Event Predictor			
Fixed Effects			
	OR	C.I.	p
Use of ClassIII AADs	1.191	[0.630–2.253]	0.590
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.554	0.365	[0.153–2.012]

eTable 8. Association of Male Sex at Holter Examination With Occurrence of a Sustained Ventricular Arrhythmia Event

Per Holter Event Predictor			
Fixed Effects			
	OR	C.I.	p
Male sex	1.042	[0.585–1.856]	0.888
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.574	0.357	[0.169–1.942]

eTable 9. Results of Final Model

Holter predictors of an SVA event in the upcoming 12 months			
Fixed Effects			
	OR	C.I.	p
24-h PVC burden (log)	1.498	[1.104–2.034]	**0.010**
Presence of a PVC spike	6.196	[2.743–13.993]	**<0.001**
Presence of NSVT	2.289	[1.100–4.514]	**0.026**
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.882	0.347	[0.408–1.907]

eTable 10. Final Model in Primary Prevention Patients With ARVC (n = 122)

Holter predictors of an SVA event in the upcoming 12 months			
Fixed Effects			
	OR	C.I.	p
24-h PVC burden (log)	1.388	[0.955–2.017]	0.086
Presence of a PVC Spike	8.276	[2.663–25.715]	**<0.001**
Presence of nsVT	2.297	[0.907–5.818]	0.080
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.893	0.499	[0.299–2.669]

eTable 11. Final Model in Secondary Prevention Patients With ARVC (n = 47)

Holter predictors of an SVA event in the upcoming 12 months			
Fixed Effects			
	OR	C.I.	p
24-h PVC burden (log)	1.673	[0.986–2.839]	*0.056*
Presence of a PVC Spike	4.150	[1.159–14.863]	**0.029**
Presence of nsVT	2.171	[0.712–6.621]	0.173
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.884	0.507	[0.287–2.718]

**eTable 12. Final Model Performance in Patients With ARVC and No ICD at Baseline (n = 96)**

Holter predictors of an SVA event in the upcoming 12 months			
Fixed Effects			
	OR	C.I.	p
24-h PVC burden (log)	1.504	[0.954–2.375]	*0.079*
Presence of a PVC Spike	7.835	[2.127–28.858]	**0.002**
Presence of nsVT	2.191	[0.692–6.940]	0.182
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.689	0.436	[0.081–5.834]

eTable 13. Final Model Performance in Patients With ARVC Implanted With ICD at Baseline (n = 73)

| Holter predictors of an SVA event in the upcoming 12 months			
Fixed Effects			
	OR	C.I.	p
24-h PVC burden (log)	1.600	[1.033–2.479]	**0.035**
Presence of a PVC Spike	4.472	[1.527–13.099]	**<0.001**
Presence of nsVT	2.056	[0.835–5.059]	0.117
Random Effects			
	Estimate	Standard Error	C.I.
Patient	0.806	0.436	[0.279–2.326]

eFigure 1. PVC Burden Modification During Follow-up Stratifying Patients by β-Blocker Therapy

No significant difference in the trend of reduction of the PVC burden was observed between patients on and off beta-blocker therapy.
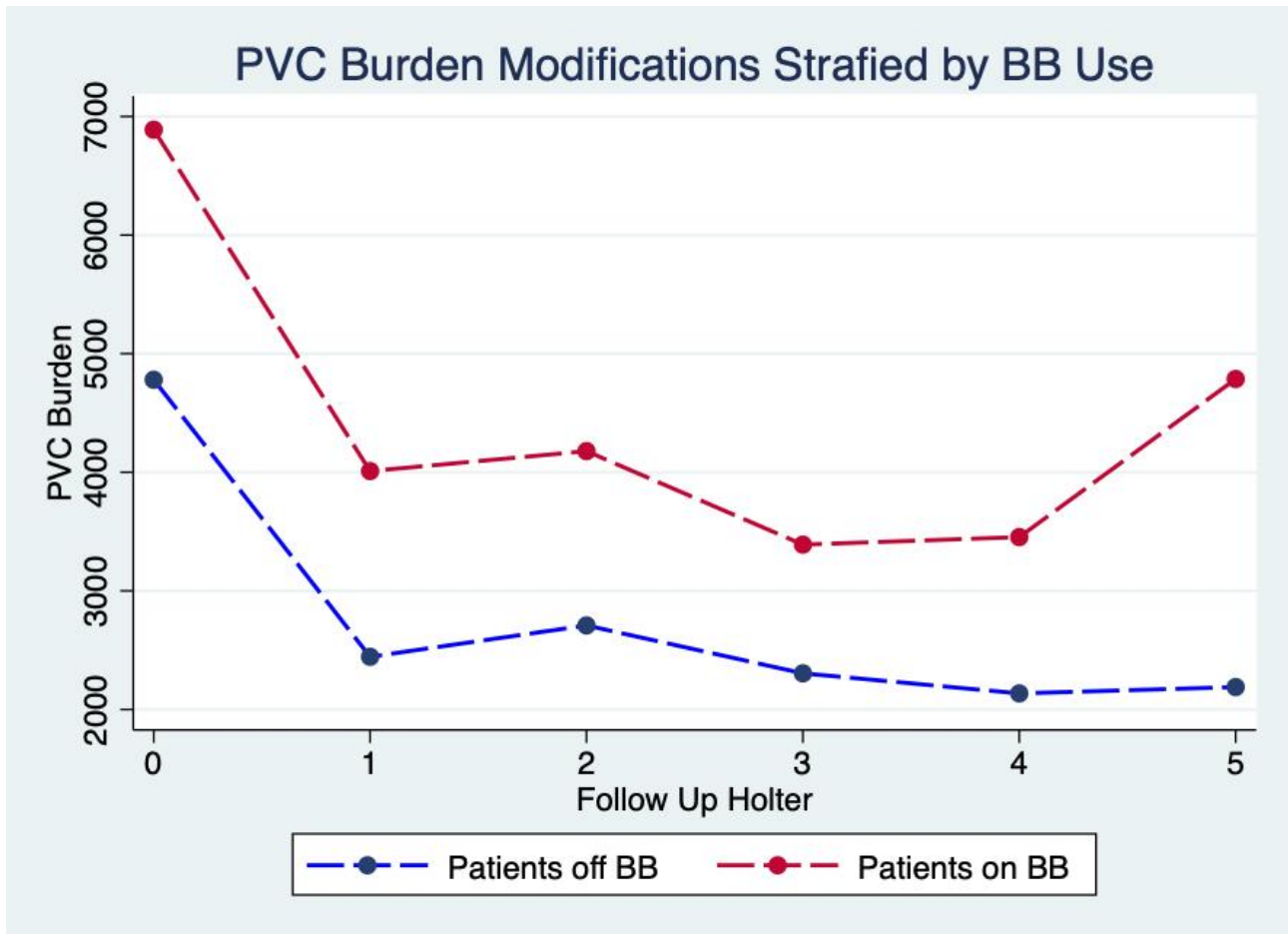
eFigure 2. Calibration Plots for Final Model

- A) Final model, using the PVC spike definition from the main manuscript;
- B) Final model, using a PVC spike definition with 50% increase as % increase threshold;
- C) Final model, using a PVC spike definition with 100% increase as % increase threshold;
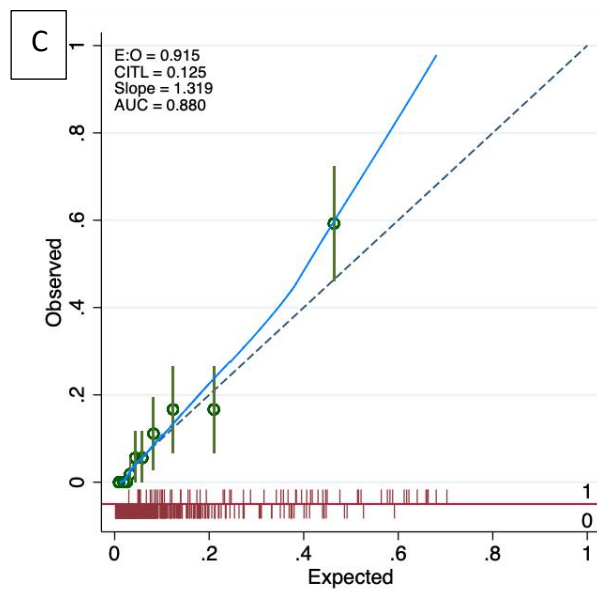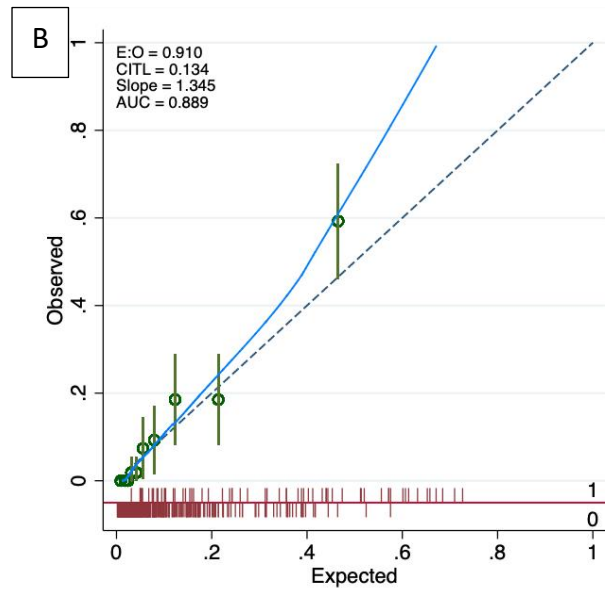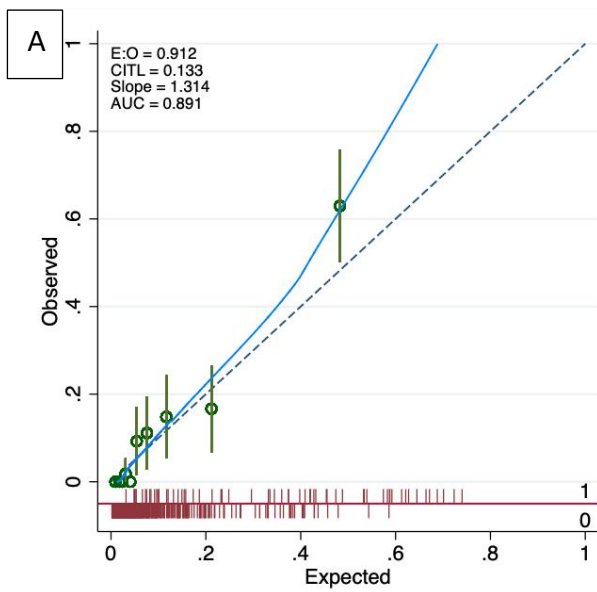
The overall results of the 3 model are comparable, both in overall significance and in with the model included in the manuscript using a 75% increase as a percentage cut-off presenting a slightly superior discrimination.