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Abstract

Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder. The incidence of heart failure (HF) in ARVC has been reported at 5-13%. We aimed to define the genotype and disease progression of ARVC patients with HF. Methods: Patients with a definite diagnosis of ARVC who underwent genetic testing were consecutively recruited. Detailed clinical data was collected at baseline and during follow up. Clinical endpoint was a composite of heart transplantation and death due to HF. Results: 135 patients were included. 8 (5.9%) patients reached the endpoint. Patients reaching the endpoint were significantly more likely to carry a Plakophilin 2 mutation than patients without HF, and 50% had multiple variants, however only one patient had 2 pathogenic mutations. Conclusions: HF is a rare but significant outcome of patients with a definite diagnosis of ARVC. Patients with HF predominantly carried Plakophilin 2 mutations and often had multiple variants. RV dysfunction appears to be a determinant of heart transplantation and death.

Keywords	arrhythmogenic right ventricular cardiomyopathy; heart failure; Plakophilin 2; genotype; heart Transplantation; follow-up
Taxonomy	Transplantation, Heart Failure, Myocardial Disease, Genetics
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Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
Data will be made available on request

HIGHLIGHTS

- Genotype and phenotype in arrhythmogenic right ventricular cardiomyopathy
- Focus on patients with heart transplantation or heart failure death
- A Plakophilin 2 mutation was present in most patients reaching the endpoint
- 50% had multiple mutations
- RV dysfunction is a determinant of heart transplantation and heart failure death

ABSTRACT:

Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder. The incidence of heart failure (HF) in ARVC has been reported at 5-13%. We aimed to define the genotype and disease progression of ARVC patients with HF.

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Conclusions: HF is a rare but significant outcome of patients with a definite diagnosis of ARVC. Patients with HF predominantly carried Plakophilin 2 mutations and often had multiple variants. RV dysfunction appears to be a determinant of heart transplantation and death.

HEART FAILURE IN PATIENTS WITH ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY:

GENETIC CHARACTERISTICS

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Foundation Trust receives a proportion of funding from the Department of Health's NIHR Biomedical Research Centre funding scheme.

Declaration of interest: none

Heart Failure in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy: Genetic Characteristics

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ABSTRACT:

Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder. The incidence of heart failure (HF) in ARVC has been reported at 5-13%. We aimed to define the genotype and disease progression of ARVC patients with HF.

Methods: Patients with a definite diagnosis of ARVC who underwent genetic testing were consecutively recruited. Detailed clinical data was collected at baseline and during follow up. Clinical endpoint was a composite of heart transplantation and death due to HF.

Results: 135 patients were included. 8 (5.9%) patients reached the endpoint. Patients reaching the endpoint were significantly more likely to carry a Plakophilin 2 mutation than patients without HF, and 50% had multiple variants, however only one patient had 2 pathogenic mutations.

Conclusions: HF is a rare but significant outcome of patients with a definite diagnosis of ARVC. Patients with HF predominantly carried Plakophilin 2 mutations and often had multiple variants. RV dysfunction appears to be a determinant of heart transplantation and death.

INTRODUCTION:

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder characterised by disruption of the myocytic architecture resulting in electrical instability and increased risk for life-threatening ventricular arrhythmias in some patients[1-3]. Disease causing mutations have been reported in genes encoding for desmosomal and more rarely non-desmosomal proteins[4-13].

However, arrhythmias are only one possible outcome for patients with ARVC. Heart failure (HF) is a rare, but important outcome for patients with ARVC. In a large cohort of patients with definite ARVC, the incidence of HF was reported 13%, with 4% of patients proceeding to heart transplantation (HTx)[14]. Another study reported death due to chronic HF in 11% of patients, with the age at onset being significantly higher than in patients presenting with arrhythmia[15]. In a cohort of patients carrying an ARVC-associated gene mutation, the incidence of HF has been reported at 5%[16]. Patients with multiple mutations are thought to develop a more

severe phenotype[16-18] and patients with a desmoplakin (DSP) mutation to more likely develop HF[16].

Aim of our study was to define the genotype and disease progression of patients with HTx or death due to HF with arrhythmogenic right ventricular cardiomyopathy.

METHODS:

Patients referred to the Inherited Cardiovascular Disease Unit at The Heart Hospital in London, and to St Georges Hospital, London (before 2003), with a suspicion for ARVC, or with a premature sudden cardiac death (SCD) and/or known ARVC in the family (with the initial family member not checked at our hospitals), and who had undergone genetic testing, were consecutively recruited. Only patients who fulfilled diagnostic criteria according to the 2010 task force criteria[1] at any time throughout the course of their disease were included. Family members were excluded in order to study those patients with the most complete phenotype [19]; therefore, all patients were unrelated.

Detailed clinical and genetic data was collected at baseline and during follow up.

CLINICAL DATA:

Clinical evaluation included personal and family history, 12 lead electrocardiogram (ECG), signal averaged ECG (SAECG) and 24h-ECG, 2D-echocardiography, and cardiopulmonary exercise test (CPEX).

Follow up visits were performed as clinically necessary, usually every 6-12 months. Patients who had not been seen for at least 2 years were contacted by telephone in January 2015. Using a structured questionnaire, information about current medication, ICD implantation/discharges, hospitalisations, comorbidities and new

cases of ARVC in the family was collected.

Paper prints of the ECGs were evaluated with regard to electrical axis, QRS duration in leads V1 and V6, duration of terminal activation measured from the nadir of the S wave to the end of the QRS in leads V1 and V2, presence of T wave inversions in all leads, presence of Q waves in all leads, presence of low voltage, presence of delayed R progression, presence of left or right bundle branch block, presence and configuration of ventricular ectopics.

Automated interpretation of SAECGs was analysed with regard to filtered QRS duration, duration of the terminal QRS, low-amplitude signal duration (LAS), root-mean-square voltage of the terminal 40 ms (RMS), the same parameters in only the Z axis, the number of beats analysed and the documented noise. SAECGs with a noise ≥ 0.5 µV and <300 beats were excluded.

Automated interpretation of 24h-ECGs was utilized for the number of ventricular ectopics, couplets, triplets, tachycardias, and supraventricular ectopics and tachycardias and prevalence of atrial fibrillation, and full disclosure was available if needed.

CPEX was performed using a standard Bruce protocol. Maximal oxygen consumption (VO2max), its percentage of predicted, peak heart rate and its percentage of predicted, respiratory quotient, minutes of exercise (always rounded down to the next lower), achieved power in Watts, occurring arrhythmias and current medication were taken from the standardised reports.

All echocardiographic measurements were taken from the standardised reports. Information on decreased right ventricular function, dilatation and wall motion abnormalities were also taken from the written reports, unless there were conflicting reports, in which case three cardiologists with a special interest in cardiomyopathies reviewed the images independently (ASV, SC, AP).

In all above mentioned investigations the last available was used as the follow up examination.

Genotyping was performed using next generation sequencing as described previously for hypertrophic cardiomyopathy[20]. Sequence variants were classified according to the American College of Medical Genetics (ACMG) guidelines[21].

Endpoint:

Clinical endpoint was a composite endpoint of HTx and death caused by HF. HF was defined as signs and symptoms of HF without documentation of arrhythmias. Patients were then divided into two groups, one consisting of those patients reaching the composite endpoint, the other of the remainder.

Statistical analysis:

Continuous variables were compared between the groups with mean ± SD and categorical variables as number (percentages) of all cases using independent sample T test and Fisher's exact test. Parameters were evaluated using Odds Ratios (OR) and their Area Under the Curve (AUC) to assess their accuracy to discriminate between patients with and without heart failure. All data were analysed with SPSS Version 22 for Mac. An alpha level of 0.05 and p-values of < 0.05 were considered as statistically significant.

Results:

ARVC diagnosis was definite in 135 patients. Of these, 8 patients (5.9%) reached the composite endpoint of death caused by HF or HTx during a mean follow-up of 83.6 ± 31.5 months. The patients not reaching the endpoint were followed for 112.5 ± 65.8 months. HTx was performed in 5 patients, one of which died due to a dilated cardiomyopathy developing in the transplanted heart. The remaining 3 died due to HF. Of the latter, two

were considered for HTx at some point throughout the course of their disease. Of those two patients, one declined HTx, and the other improved initially, however later died due to HF. All patients with HF had RV dysfunction at some point throughout the course of their disease, but only 4 (50%) had LV dysfunction (Table 1).

BASELINE

HF patients either presented because of cardiac symptoms (4 patients, 50%) or VT/VF (4 patients, 50%). No patients were referred due to family screening or incidental findings. Among the 8 patients with HF, 5 (62.5%) had a pathogenic desmosomal gene mutation in comparison to 57 patients (44.9%) without heart failure (p 0.469). Four HF-patients had a single desmosomal pathogenic mutation, 1 had 2 desmosomal mutations (Table 1). A pathogenic Plakophilin-2 mutation was identified in 5 HF-patients (62.5%), a significantly higher percentage of patients compared to 34 (26.8%) patients in the control group (p 0.045, OR 4.56, AUC 0.68) (Table 2, Appendix Tables A.1 and A.2, Figure 1).

At presentation, 4 patients (50%) who developed HF, reported dyspnea (19 patients (15.8%) in the control group, p 0.034) (Table 3, Appendix Table A.3~~2~~).

With regard to ECG, patients with heart failure showed more extensive T wave inversions in the precordial leads. They also had more inverted and flattened T waves in leads I and aVL. Also, they presented more often with a complete or incomplete RBBB (37.5% vs. 9.0%, p 0.041, OR 6.06) (Table 3, Appendix Table A.4~~3~~).

As for SAECG, patients with a HF outcome presented with a trend towards a longer filtered QRS duration (140.8 ± 31.0 ms vs. 115.9 ± 21.1 ms, p 0.050), lower RMS of the last 40 ms (4.7 ± 1.1 µV vs. 24.5 ± 19.0 µV, p

0.076) and longer LAS duration (67.2 ± 25.2 ms vs. 41.9 ± 20.0 ms, p 0.036) (Table 3, Appendix Table A.54).

In their baseline echocardiograms, 7 patients (87.5%) presented with a reduced RV function and all of them had RV dilatation as reported by the echocardiographer. In accordance to this, they had a larger RVOT diameter. No patients with HF showed dyskinesia or bulging of the RV. The left ventricular posterior wall was thinner in patients with HF (Table 3, Appendix Table A.87).

There was only a very small number of 24h-ECGs available in patients with HF (Appendix Table A.65).

FOLLOW UP

During follow-up 5 patients (62.5%, vs. 16 patients (18.0%), p 0.011) reported dyspnea. Among the 8 patients with HF, 4 patients (50%) underwent an electrophysiological study, 7 patients (87.5%) were implanted with an ICD (e-component Table 1, Appendix Table A.98).

All patients with HF were medically treated during follow-up (e-component Table 1, Appendix Table A.109).

On their follow-up ECGs, patients with HF showed more T wave flattening and more complete left bundle branch blocks (e-component Table 1, Appendix Table A.110).

There was only one follow up signal averaged ECG available of the patients with HF (e-component Table 1, Appendix Table A.121).

Only 2 CPEX investigations were available from patients with HF (e-component Table 1, Appendix Table A.143).

All patients with HF showed RV dysfunction, dilatation and regional wall motion abnormalities in their follow-up echocardiograms. Patients with HF had a lower LVEF at the time of follow up (e-component Table 1, Appendix Table A.154).

DISCUSSION:

HF is a rare outcome for patients with ARVC. The prevalence varies highly depending on the definition of HF in previous studies[15, 16]. About 1% of patients undergoing heart transplantations have ARVC as their underlying disease[22]. In our cohort, 5.9 % of patients with definite ARVC were either transplanted and/or died of HF. Pathogenic mutations in Plakophilin 2 were significantly more prevalent in patients reaching the HF endpoint. Half of the patients with HF had multiple gene mutations, however only one of them had multiple pathogenic mutations. Also, most of them presented with RV failure early on in the course of the disease and all of them signs of RV failure during their last follow-up examination.

To our knowledge, this is first complete analysis of genetic mutations in the era of next generation sequencing in patients with HF in the context of definite ARVC and specifically in recipients of heart transplantation for heart failure. One short report was published by Tedford et al, however the rate of patients genetically tested was not disclosed. In those patients who were genetically tested, PKP2 mutations were predominant, similarly to our study[23]. Similar results were reported by a recently published study on HTx in patients with ARVC, taken from a registry, [24]. However, genetic results were available in only about half of the patients undergoing HTx, but again PKP2 mutations were predominant [24]. There was no information on genetic results in the largest cohort of ARVC patients undergoing HTx reported to date [25].

Bhonsale et al[16] reported that patients with Desmoplakin mutations had a four-fold increased incidence of LV dysfunction and heart failure in comparison to Plakophilin 2 carriers. However, LV dysfunction was defined as LVEF <55% and HF as "evidence of structural heart disease including RV abnormalities and symptoms directly attributed to heart failure" and therefore differ completely from our definition of a hard endpoint as HTx and death due to heart failure. In the tables in the named study, it appears that only patients with Plakophilin 2 mutations died or underwent heart transplantation. The percentage of patients dying or undergoing HTx out of all patients is smaller than ours, however in this study family members were included, which are generally thought to have a better prognosis. Loss of Plakophilin 2 in knockdown zebra fish has shown a loss of desmosomal proteins and hence cell adhesion, resulting in cardiac oedema and blood pooling, which can be interpreted as signs of HF[26].

RV dilatation and dysfunction are a component of the diagnostic criteria for ARVC[1]. Their occurrence has been reported to be a predictor of an adverse outcome[27, 28]. The reason for the bad prognosis due to RV failure may lie in the difficulty of drug therapy. Medical treatment for RV failure is limited, with the usual therapeutic options used for LV failure remaining without success. So far the best data exists for phosphodiesterase type 5 inhibitors, but also this treatment is not fully developed[29]. Right ventricular assist devices and biventricular assist devices are generally only indicated in patients eligible for transplantation[30], however we are not aware of any reports in ARVC patients. As only half of the patients had LV dysfunction, but all of them had RV dysfunction, it appears that RV dysfunction is the major contributor to the development of heart failure leading to transplantation or death.

We were unable to demonstrate an age difference between patients with and without HF in contrast to was has been previously reported[15]. However, numbers of patients with HF were small in both studies, which can significantly influence this result.

LIMITATIONS:

This is a retrospective study. The outcome of HF was very rare, therefore we were unable to find predictors by multivariable analysis.

CONCLUSION:

Heart transplantation or death due to HF occurred in about 6% of patients with a definite diagnosis of ARVC. Most patients with HF in ARVC had a genetic mutation in Plakophilin 2. Half the patients have multiple mutations. RV dysfunction appears to be a marker of heart transplantation or death due to HF.

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DISCLOSURES:

The authors declare that there is no conflict of interest.

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TABLE 1: PATIENTS WITH HEART FAILURE OUTCOME.

No	Presentation	Age at first presentation	LV dysfunction	RV dysfunction	ICD	Endpoint	Variant	MAF	ARVD/C Genetic Variants Database classification and variant ID	ACMG classification	GenomAD MAF
1	Cardiac symptoms	16	+	+	+	HTx, † fatal stroke	DSG2 c.3G>C; p.Met1Ile		Pathogenic; 7537 [31]	VUS	Not reported
							DSG2 c.998T>C; p.Ile333Thr		VUS; 8230 [19]	VUS	Not reported
2	VT	6	-	+	-	Declined HTx, † HF	PKP2 c.2197_2202delinsG; p.His733AlafsX8		Pathogenic; 7495 [32]	Pathogenic	2.12E-05
							PKP2 c.1941T>G; p.Cys647Trp		-	VUS	2.12E-05
3	VT	50	+/-	-/+	+	Considered for HTx, then improved, † HF	No variants				
4	VT	55	-	+	+	† HF	PKP2 c.1613G>A; p.Trp538X		Pathogenic; 7468 [19]	Pathogenic	1.59E-05
							JUP c.1159-2A>T		-	Pathogenic	Not reported

5	Cardiac symptoms	16	-	+	+	HTx	PKP2 c.775G>T; p.Glu259X	Pathogenic; 8227 [19]	Pathogenic	Not reported
6	Cardiac symptoms	59	-	+	+	HTx	PKP2 c.2197_2202delinsG; p.His733AlafsX8del	Pathogenic; 7495 [32]	Pathogenic	2.12E-05
7	Cardiac symptoms	56	+	+	+	HTx, † HF (DCM in transplanted heart)	PKP2 c.419C>T; p.Ser140Phe	Pathogenic; 7446 [33]	Likely benign	2.29E-03
							LMNA c.725C>T; p.Ala242Val	-	Likely Pathogenic	7.954E-06
8	VT	49	+	+	+	HTx, early primary graft dysfunction	PKP2 c.184C>A; p.Gln62Lys	VUS; 7441 [34]	VUS	1.68E-04
							PKP2 c.1237C>T; p.Arg413X	Pathogenic; 7462 [32]	Pathogenic	1.42E-05

714 Table 1: Patients with heart failure outcome. Sequence variants identified in ARVC cases were cross referenced to the updated version of the ARVD/C Genetic Variants Database
715 (https://molgenis07.gcc.rug.nl/# - accessed on 15 October 2018)[35] Classification of identified variants was according to the American College of Medical Genetics (ACMG)
716 guidelines for the interpretation of sequence variants. [21]Missense variants were evaluated using the InterVar bioinformatics software tool (http://wintervar.wglab.org/) [36]
717 and the pathogenicity of nonsense, frameshift and splice site variants was determined with the online Genetic Variant Interpretation Tool provided by the University of Maryland,
718 School of Medicine at http://www.medschool.umaryland.edu/Genetic_Variant_Interpretation_Tool1.html/. [37]

719 LV: left ventricular, RV: right ventricular, VT: ventricular tachycardia, ICD: implantable cardioverter defibrillator, HTx heart transplantation, HF: heart failure, †: death, DSG:
720 desmoglein, PKP2: Plakophillin 2, JUP: junctional Plakoglobin, LMNA: Lamin A/C, VUS: variant of unknown significance

TABLE 2: BASELINE CHARACTERISTICS

		HF	No HF	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Baseline characteristics (n=8/127)	Age at diagnosis	38.4 ± 21.7	41.1 ± 14.2	0.611	0.99 (0.94-1.04; 0.608)	0.52 (0.27-0.77; 0.868)
	Time of follow up (months) at THH	83.6 ± 31.5	112.5 ± 65.8	0.222	0.99 (0.98-1.01; 0.221)	0.63 (0.49-0.77; 0.228)
	Male sex	5 (62.5%)	77 (60.6%)	1.000	1.08 (0.25-4.73; 0.916)	0.51 (0.30-0.72; 0.929)
	Caucasians	8 (100%)	119 (95.2%)	1.000	108603347 (0.00-NA; 0.999)	0.52 (0.33-0.72; 0.820)
	Family history SCD	2 (25.0%)	56 (48.3%)	0.281	0.36 (0.07-1.84; 0.219)	0.62 (0.43-0.81; 0.272)
	Multiple family members with SCD	0 (0.0%)	12 (9.6%)	1.000	0.00 (0.00-NA; 0.999)	0.55 (0.36-0.74; 0.650)
Genetics (n=8/127)	Desmosomal pathogenic gene mutation	7 (87.5%)	74 (58.3%)	0.144	5.01 (0.60-41.97; 0.137)	0.65 (0.48-0.82; 0.166)
	Plakophilin2 pathogenic mutation	5~~6~~ (62.5~~75.0~~%)	3~~4~~7 (26.8~~29.1~~%)	**0.0451~~3~~**	**4.56~~7.30~~ (1.03~~4~~1~~37.82~~20.12; 0.018)**	**0.~~73 68~~ (0.55-0.91; 0.030)**
	2 desmosomal mutations, same gene	3 (37.5%)	8 (6.3%)	**0.018**	**8.93 (1.80-44.22; 0.007)**	0.66 (0.43-0.88; 0.140)
	JUP pathogenic mutation	1 (12.5%)	1 (0.8%)	0.115	**18.00 (1.02-318.87; 0.049)**	0.56 (0.34-0.78; 0.579)

Diagn. Crite (n=8/1:	Structural major criterion	8 (100%)	63 (50.0%)	**0.007**	205139656 (0.00-NA; 0.997)	**0.75 (0.63-0.87; 0.018)**
Reason for screening (n=8/124)	Family history as reason for screening	0 (0.0%)	42 (33.1%)	0.057	0.00 (0.00-NA; 0.998)	0.67 (0.52-0.81; 0.117)
	VT/VF as reason for screening	4 (50.0%)	38 (29.9%)	0.255	2.34 (0.56-9.86; 0.246)	0.60 (0.39-0.81; 0.342)
	Cardiovascular symptoms as reason for screening	4 (50.0%)	40 (31.5%)	0.437	2.18 (0.52-9.14; 0.289)	0.59 (0.38-0.80; 0.381)
	Incidental findings as reason for screening	0 (0.0%)	4 (3.1%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.31-0.72; 0.881)

Table 2:

Baseline characteristics. HF: heart failure; CI: confidence interval; AUC: area under the curve; THH: The Heart Hospital

TABLE 3: SIGNIFICANT PARAMETERS AT BASELINE

	Baseline parameters	HF	No HF	pvalue	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Symptoms at presentation (n=8/124)	Dyspnea	4 (50.0%)	19 (15.8%)	**0.034**	**5.32 (1.22-23.12; 0.026)**	0.67 (0.46-0.89; 0.106)
ECG at baseline (n=8/122)	Negative T wave V4	7 (87.5%)	46 (37.7%)	**0.008**	**11.57 (1.38-97.03; 0.024)**	**0.75 (0.60-0.90; 0.019)**
	Positive T wave I	2 (25.0%)	91 (74.6%)	**0.007**	**0.11 (0.02-0.59; 0.010)**	**0.75 (0.57-0.93; 0.019**
	Positive T wave aVL	1 (12.5%)	72 (59.0%)	**0.021**	**0.10 (0.01-0.83; 0.033)**	**0.73 (0.58-0.89; 0.028)**
	RBBB (complete and incomplete)	3 (37.5%)	11 (9.0%)	**0.041**	**6.06 (1.27-28.80; 0.024)**	0.64 (0.42-0.87; 0.178)
SAECG at baseline (n=3/90)	QRS duration	140.8 ± 31.0	115.9 ± 21.1	0.050	1.04 (1.00-1.09; 0.073)	0.76 (0.49-1.00; 0.123)
	QRS duration ≥ 140 ms	2 (66.7%)	10 (11.1%)	**0.043**	**16.00 (1.33-192.76; 0.029)**	0.78 (0.46-1.00; 0.103)
	RMS	4.7 ± 1.1	24.5 ± 19.0	0.076	0.60 (0.34-1.05; 0.072)	**0.95 (0.90-1.00; 0.009)**
	RMS ≤ 6 uV	3 (100%)	8 (8.9%)	**0.001**	605803060 (0.00-NA, 0.996)	0.96 (0.91-1.00; 0.007)
	LAS	67.2 ± 25.2	41.9 ± 20.0	**0.036**	1.04 (1.00-1.09; 0.057)	0.83 (0.651.000; 0.056)
CPEX at baseline (n=6/113)	Arrhythmias at rest	6 (100.0%)	43 (38.4%)	**0.004**	225415093 (0.00-NA; 0.997)	**0.81 (0.70-0.91; 0.011)**
	NSVT during recovery	1 (16.7%)	1 (0.9%)	0.100	**22.2 (1.21-408.76; 0.037)**	0.58 (0.32-0.84; 0.516)
	%VO2max	51.0 ± 19.9	81.0 ± 23.9	**0.003**	**0.93 (0.89.0.98; 0.007)**	**0.84 (0.70-0.99; 0.005)**
	VO2 max (ml/min/1.73m2)	14.3 ± 3.1	24.3 ± 7.4	**0.001**	**0.74 (0.59-0.93; 0.009)**	**0.88 (0.80-0.97; 0.002)**

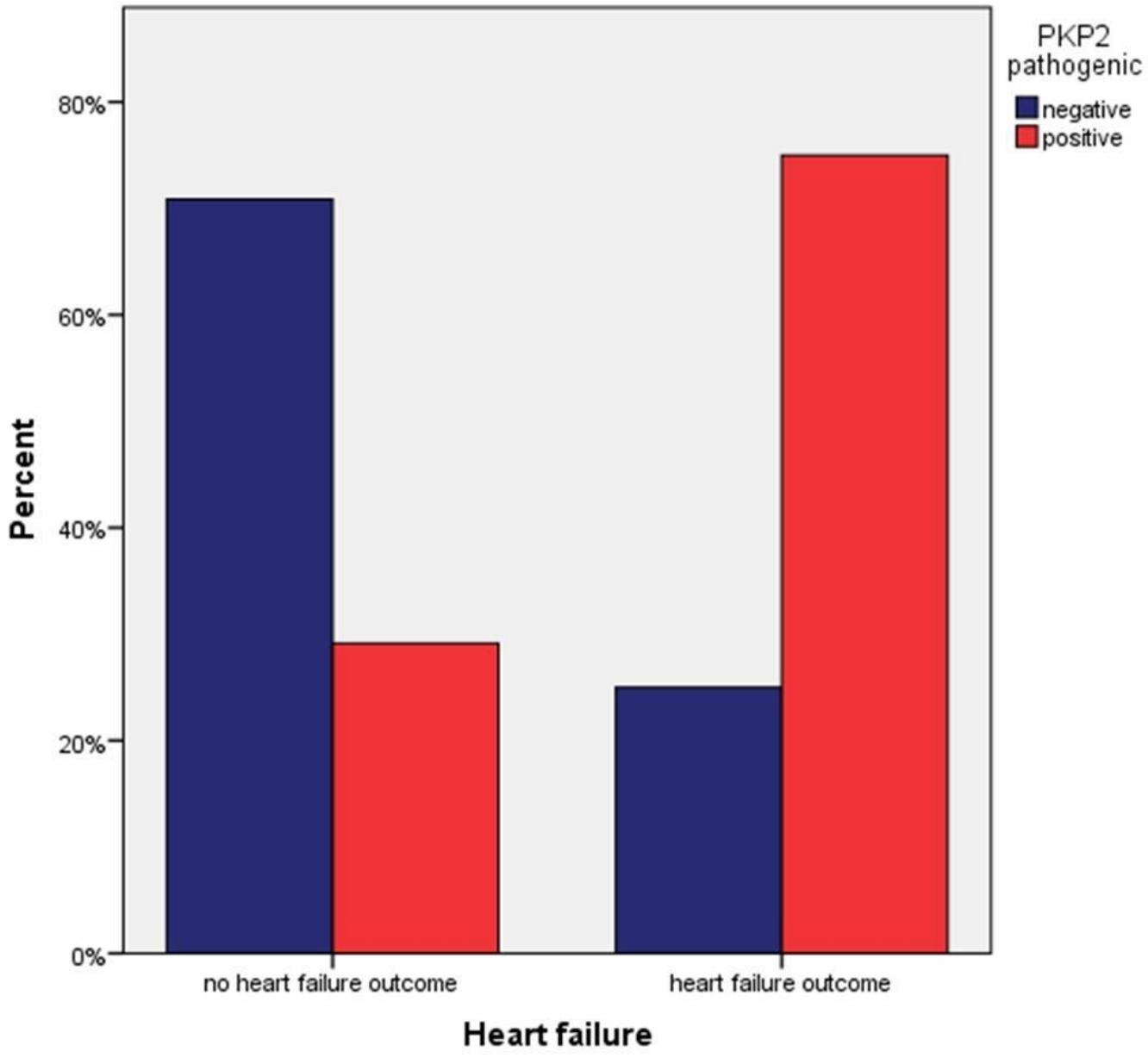
	Min	6.2 ± 0.8	8.6 ± 2.4	**0.016**	**0.641 (0.44-0.94; 0.022)**	**0.84 (0.76-0.92; 0.005)**
	Watts	74.0 ± 21.3	152.8 58.1	± **0.003**	**0.97 (0.94-0.99; 0.010)**	**0.91 (0.83-0.99; 0.002)**
Echo at baseline (n=8/124)	Reduced RV function (incl borderline)	7 (87.5%)	55 (44.4%)	**0.026**	**8.78 (1.05-73.53; 0.045)**	**0.72 (0.56-0.87; 0.041)**
	Reduced RV function (excl borderline)	7 (87.5%)	54 (43.5%)	**0.024**	**9.07 (1.08-75.99; 0.042)**	**0.72 (0.56-0.88; 0.038)**

	RV dilatation (excl upper normal)	8 (100%)	73 (58.9%)	**0.023**	177038337 (0.00-NA; 0.997)	0.71 (0.57-0.84; 0.052)
	RVOT PLAX (cm)	4.6 ± 1.1	3.6 ± 0.7	**0.000**	**4.53 (1.69-12.14; 0.003)**	**0.79 (0.60-0.99; 0.011)**
	RVOT PLAX ≥ 4.4 cm	4 (57.1%)	8 (9.1%)	**0.004**	**13.33 (2.53-70.41; 0.002)**	**0.74 (0.51-0.97; 0.035)**
	RVOT PLAX/BSA	2.6 ± 0.6	1.8 ± 0.3	**0.000**	10.03 (0.15-691.65; 0.286)	0.78 (0.46-1.00; 0.197)
	RVOT PLAX/BSA ≥ 2.0	4 (80.0%)	13 (19.1%)	**0.009**	**16.9 (1.74-164.32; 0.015)**	**0.80 (0.59-1.00; 0.024)**
	RVOT PSAX/BSA	2.2 ± 0.3	1.6 ± 0.3	**0.017**	15.18 (0.02-10230.20; 0.413)	0.75 (0.20-1.00; 0.439)
	Posterior LV wall	0.7 ± 0.2	0.8 ± 0.2	**0.044**	0.00 (0.00-1.03; 0.051)	0.72 (0.52-0.93; 0.034)
	EF	48.8 ± 18.4	58.4 ± 11.6	**0.030**	**0.95 (0.90-1.00; 0.038)**	0.66 (0.46-0.85; 0.136)

Table 3: Significant parameters at baseline. HF: heart failure; CI: confidence interval; AUC: area under the curve; ECG: electrocardiogram; RBBB: right bundle branch block; SAECG: signal averaged ECG; RMS 40: root-mean square of the last 40 ms; LAS: low amplitude signal duration; VPB: ventricular premature complexes; SVE: supraventricular ectopics; CPEX: cardiopulmonary exercise testVO2max: maximal oxygen uptake; %VO2max: VO2max, % of predicted; RV: right ventricle/ventricular; RVOT: right ventricular outflow tract; PLAX: parasternal long axis view; BSA: body surface area; PSAX: parasternal short axis view; RVIT: right ventricular inflow tract; LV: left ventricle/ventricular; LVEF: left ventricular ejection fraction.

FIGURE LEGENDS:

Figure 1: Prevalence of Plakophilin 2 mutations


PKP2 pathogenic
negative
positive
80%
60%
40%
20%
0%
Percent
no heart failure outcome
heart failure outcome
Heart failure

Author Agreement Form – International Journal of Cardiology

Manuscript Title: Heart Failure in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy: Genetic characteristics

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E-COMPONENT TABLE 1: SIGNIFICANT PARAMETERS AT FOLLOW-UP

	FU parameters	HF	No HF	pvalue	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Symptoms FU (n=8/122)	Dyspnea	5 (62.5%)	23 (18.9%)	**0.012**	**7.17 (1.60-32.20; 0.010)**	**0.72 (0.520.92; 0.039)**
Medication FU (n=8/125)	Diuretics	4 (50.0%)	21 (16.8%)	**0.041**	**4.95 (1.15-21.39; 0.032)**	0.67 (0.45-0.88; 0.116)
	Digoxin	2 (25.0%)	1 (1.6%)	**0.018**	**20.50 (2.45-171.54; 0.005)**	0.62 (0.390.85; 0.268)
ECG at FU (n=6/103)	Time to follow up ECG	42.7 ± 25.0	76.1 ± 43.0	0.063	0.98 (0.95-1.00; 0.070)	**0.74 (0.590.89; 0.047)**
	Flat T wave V1	4 (66.7%)	22 (21.4%)	**0.028**	**7.36 (1.27-42.87; 0.026)**	0.73 (0.50-0.95; 0.063)
	Complete LBBB	2 (33.3%)	4 (3.9%)	**0.035**	**12.38 (1.73-88.72; 0.012)**	0.65 (0.380.91; 0.227)
	Complete + incomplete LBBB	3 (37.5%)	8 (6.6%)	**0.020**	**24.75 (3.75-163.31; 0.001)**	0.73 (0.470.99; 0.058)
SAECG FU (n=1/38)	LAS	82.0	44.3 ± 15.6	**0.022**	2.695E+10 (0.00-NA; 0.967)	1.00 (1.001.00; 0.091)
CPEX FU (n=2/31)	vO2	12.8 ± 3.5	24.3 ± 7.3	**0.035**	0.54 (0.26-1.13; 0.541)	**0.96 (0.881.00; 0.031)**
	Min	5.0 ± 0	8.9 ± 2.2	**0.016**	0.00 (0.00-NA; 0.993)	**0.99 (0.96-1.00; 0.021)**
	Watts	52.5 ± 24.7	154.2 ± 51.8	**0.010**	0.06 (0.005.823E+131; 0.986)	**1.00 (1.001.00; 0.019)**
	Any arrhythmias at rest	6 (100.0%)	46 (41.4%)	**0.007**	210714104 (0.00-NA; 0.997)	**0.79 (0.680.91; 0.016)**
Echo at FU (n=5/78)	Any RV dysfunction (incl borderline)	8 (100.0%)	69 (57.0%)	**0.021**	187301416 (0.00-NA; 0.997)	**0.72 (0.590.84; 0.042)**

Any RV dysfunction (excl borderline)	8 (100.0%)	67 (55.4%)	**0.020**	192892505 (0.00-NA; 0.997)	**0.72 (0.60-0.85; 0.035)**
RVOTlax/BSA	2.4 ± 0.2	1.9 ± 0.4	0.054	35.74 (0.57-2254; 0.091)	**0.93 (0.831.00; 0.044)**
LVESD	4.6 ± 2.5	3.6 ± 0.7	**0.016**	**2.20 (1.01-4.78; 0.047)**	0.57 (0.270.87; 0.629)
Posterior LV wall	0.7 ± 0.1	0.8 ± 0.2	0.062	0.00 (0.00-1.07; 0.052)	**0.81 (0.640.98; 0.035)**
LVEF	43 ± 20	56 ± 12	**0.027**	**0.94 (0.89-1.00; 0.041)**	0.72 (0.500.94; 0.100)

Table 4: Significant parameters at follow-up. FU: follow-up; HF: heart failure; CI: confidence interval; AUC: area under the curve; ECG: electrocardiogram; LBBB: left bundle branch block; SAECG: signal averaged ECG; RMS 40: root-mean-square of the last 40 ms; LAS: low amplitude signal duration; Z: Z-vector; CPEX: cardiopulmonary exercise testVO2max: maximal oxygen uptake; %VO2max: VO2max, % of predicted; RQ: respiratory quotient; BSA: body surface area; RV: right ventricle/ventricular; RVOT: right ventricular outflow tract; PLAX: parasternal long axis view; PSAX: parasternal short axis view; RVIT: right ventricular inflow tract; LV: left ventricle/ventricular; RWMA: regional wall motion abnormalities; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction.

APPENDIX

TABLE A.1: GENERAL CHARACTERISTICS.

	HF n = 8	No HF n = 127	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Age at diagnosis	38.4 ± 21.7	41.1 ± 14.2	0.611	0.99 (0.94-1.04; 0.608)	0.52 (0.27-0.77; 0.868)
Time of follow up (months)	83.6 ± 31.5	112.5 ± 65.8	0.222	0.99 (0.98-1.01; 0.221)	0.63 (0.49-0.77; 0.228)
Male sex	5 (62.5%)	77 (60.6%)	1.000	1.08 (0.25-4.73; 0.916)	0.51 (0.30-0.72; 0.929)
Caucasians	8 (100%)	119 (95.2%)	1.000	108603347 (0.00-NA; 0.999)	0.52 (0.33-0.72; 0.820)
Family history SCD	2 (25.0%)	56 (48.3%)	0.281	0.36 (0.07-1.84; 0.219)	0.62 (0.43-0.81; 0.272)
Multiple family members with SCD	0 (0.0%)	12 (9.6%)	1.000	0.00 (0.00-NA; 0.999)	0.55 (0.36-0.74; 0.650)
Desmosomal pathogenic gene variant	5 (62.5%)	57 (44.9%)	0.469	2.05 (0.47-8.93; 0.341)	0.59 (0.39-0.79; 0.404)
Single desmosomal pathogenic variant	4 (50%)	54 (42.5%)	0.725	1.35 (0.32-5.65; 0.679)	0.54 (0.33-0.75; 0.723)
Desmoplakin pathogenic variant	0 (0.0%)	14 (11.0%)	1.000	0.46 (0.02-8.40; 0.601)	0.45 (0.26-0.63; 0.602)
Plakophilin2 pathogenic mutation	5 (62.5%)	34 (26.8%)	**0.045**	**4.56 (1.03-20.11; 0.045)**	0.68 (0.48-0.88; 0.091)
Desmoglein pathogenic mutation	0 (0.0%)	6 (4.7%)	1.000	1.10 (0.06-21.21; 0.950)	0.48 (0.28-0.68; 0.823)
Desmocollin2 pathogenic mutation	0 (0.0%)	3 (2.4%)	1.000	2.09 (0.10-43.90; 0.635)	0.49 (0.29-0.69; 0.911)

JUP pathogenic mutation	1 (12.5%)	1 (0.8%)	0.115	**18.00 (1.02-318.87; 0.049)**	0.56 (0.34-0.78; 0.579)
2 desmosomal variants	1 (12.5%)	3 (2.4%)	0.219	5.90 (0.54-64.30; 0.145)	0.55 (0.33-0.77; 0.631)
Structural major criterion	8 (100%)	63 (50.0%)	**0.007**	205139656 (0.00-NA; 0.997)	**0.75 (0.63-0.87; 0.018)**
Structural minor criterion	0 (0.0%)	17 (13.5%)	0.595	0.00 (0.00-NA; 0.998)	0.57 (0.39-0.75; 0.523)
Tissue major criterion	1 (12.5%)	4 (3.2%)	0.270	4.32 (0.43-43.97; 0.216)	0.55 (0.33-0.77; 0.660)
Tissue minor criterion	0 (0.0%)	0 (0.0%)	NA	NA	NA
Repolarisation major criterion	4 (50.0%)	61 (48.4%)	1.000	1.07 (0.26-4.45; 0.931)	0.51 (0.30-0.72; 0.940)
Repolarisation minor criterion	0 (0.0%)	17 (13.5%)	0.595	0.00 (0.00-NA; 0.998)	0.57 (0.39-0.75; 0.523)
Depolarisation major criterion	0 (0.0%)	7 (5.6%)	1.000	0.00 (0.00-NA; 0.999)	0.53 (0.33-0.73; 0.793)
Depolarisation minor criterion	2 (25.0%)	18 (14.3%)	0.341	2.00 (0.37-10.69; 0.418)	0.55 (0.34-0.77; 0.612)
Arrhythmias major criterion	6 (75.0%)	65 (52.0%)	0.283	2.77 (0.54-14.25; 0.223)	0.62 (0.43-0.81; 0.276)
Arrhythmias minor criterion	2 (25.0%)	35 (28.2%)	1.000	0.85 (0.16-4.40; 0.844)	0.52 (0.31-0.72; 0.879)
Family history major criterion	7 (87.5%)	91 (72.8%)	0.680	2.62 (0.31-22.05; 0.377)	0.57 (0.39-0.76; 0.487)
Family history minor criterion	0 (0.0%)	4 (3.2%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.32-0.72; 0.880)

Table A.1: General characteristics. HF: heart failure; AUC: area under the curve; CI: confidence interval; THH: The Heart Hospital; SCD: sudden cardiac death.

TABLE A.2: PATHOGENIC PKP2 VARIANTS IN PATIENTS WITHOUT HEART FAILURE OUTCOME

No	Gene	Type of variant	Variant	GnomAD MAF	ARVD database classification	ACMG classification
13	PKP2	splicing	ENST00000070846:exon12:c.2146-1G>C	3.18E-05	Pathogenic	Pathogenic
26	PKP2	frameshift deletion	ENSG00000057294:ENST00000070846:exon11:c.2198_2202del:p.733_734del	2.12E-05	Pathogenic	Pathogenic
29	PKP2	stopgain SNV	ENSG00000057294:ENST00000070846:exon10:c.2027G>A:p.Trp676X	not reported	not classified	Pathogenic
34	PKP2	splicing	ENST00000070846:exon13:c.2489+1G>A	2.83E-05	Pathogenic	Pathogenic
41	PKP2	splicing	ENST00000070846:exon12:c.2146-1G>C	3.18E-05	Pathogenic	Pathogenic
61	PKP2	splicing	ENST00000070846:exon12:c.2146-1G>C	3.18E-05	Pathogenic	Pathogenic
74	PKP2	stopgain SNV	ENSG00000057294:ENST00000070846:exon5:c.1237C>T:p.Arg413X	1.42E-05	Pathogenic	Pathogenic
92	PKP2	frameshift deletion	ENSG00000057294:ENST00000070846:exon1:c.148_151del:p.50_51del	not reported	Pathogenic	Pathogenic
97	PKP2	splicing	ENST00000070846:exon13:c.2489+1G>A	2.83E-05	Pathogenic	Pathogenic
104	PKP2	splicing	ENST00000070846:exon12:c.2146-1G>C	3.18E-05	Pathogenic	Pathogenic
108	PKP2	splicing	ENST00000070846:exon12:c.2146-1G>C	3.18E-05	Pathogenic	Pathogenic
110	PKP2	splicing	ENST00000070846:exon12:c.2146-1G>C	3.18E-05	Pathogenic	Pathogenic
114	PKP2	splicing	ENST00000070846:exon13:c.2489+1G>A	2.83E-05	Pathogenic	Pathogenic
118	PKP2	stopgain SNV	ENSG00000057294:ENST00000070846:exon5: c.1237C>T:p.Arg413X	1.42E-05	Pathogenic	Pathogenic
152	PKP2	splicing	ENST00000070846:exon12:c.2146-1G>C	3.18E-05	Pathogenic	Pathogenic
244	PKP2	splicing	ENST00000070846:exon12:c.2146-1G>C	3.18E-05	Pathogenic	Pathogenic
265	PKP2	frameshift deletion	ENSG00000057294:ENST00000070846:exon8:c.1799delA:p.Asp600fs	not reported	Pathogenic	Pathogenic
274	PKP2	frameshift deletion	ENSG00000057294:ENST00000070846:exon3:c.968_972del:p.323_324del	not reported	Pathogenic	Pathogenic
279	PKP2	splicing	ENST00000070846:exon12:c.2146-1G>C	3.18E-05	Pathogenic	Pathogenic

283	PKP2	splicing	ENST00000070846:exon13:c.2489+1G>A	2.83E-05	Pathogenic	Pathogenic
298	PKP2	frameshift deletion	ENSG00000057294:ENST00000070846:exon1:c.14delG:p.Gly5fs	not reported	not classified	Pathogenic
301	PKP2	frameshift deletion	ENSG00000057294:ENST00000070846:exon11:c.2198_2202del:p.733_734del	2.12E-05	Pathogenic	Pathogenic
308	PKP2	splicing	ENST00000070846:exon12:c.2146-1G>C	3.18E-05	Pathogenic	Pathogenic

319	PKP2	splicing	ENST00000070846:exon13:c.2489+1G>A	2.83E-05	Pathogenic	Pathogenic
324	PKP2	stopgain SNV	ENSG00000057294:ENST00000070846:exon2:c.235C>T:p.Arg79X	3.98E-06	Pathogenic	Pathogenic
325	PKP2	frameshift deletion	ENSG00000057294:ENST00000070846:exon11:c.2198_2202del:p.733_734del	2.12E-05	Pathogenic	Pathogenic
328	PKP2	stopgain SNV	ENSG00000057294:ENST00000070846:c.2071C>T:p.Arg691X	not reported	not classified	Pathogenic
340	PKP2	splicing	ENST00000070846:exon13:c.2489+1G>A	2.83E-05	Pathogenic	Pathogenic
355	PKP2	stopgain SNV	ENSG00000057294:ENST00000070846:exon3:c.582T>G:p.Tyr194X	not reported	not classified	Pathogenic
364	PKP2	splicing	ENST00000070846:exon12:c.2146-1G>C	3.18E-05	Pathogenic	Pathogenic
366	PKP2	splicing	ENST00000070846:exon13:c.2489+1G>T	not reported	Pathogenic	Pathogenic
382	PKP2	frameshift deletion	ENSG00000057294:ENST00000070846:exon4:c.1075_1091del:p.359_364del	not reported	not classified	Pathogenic
388	PKP2	frameshift deletion	ENSG00000057294:ENST00000070846:exon2:c.314delC:p.Pro105fs	not reported	not classified	Pathogenic
392	PKP2	frameshift deletion	ENSG00000057294:ENST00000070846:exon9:c.1903delC:p.Arg635fs	not reported	not classified	Pathogenic

Table A.2: Pathogenic PKP2 variants in patients without heart failure outcome. No: patient number; GnomAD MAF: genome Aggregation Database minor allele frequency; ARVD: arrhythmogenic right ventricular dysplasia; ACMG: American College of Medical Genetics and Genomics; SNV: single nucleotide variant

TABLE A.32: CLINICAL SYMPTOMS AT BASELINE.

Symptoms at initial presentation	HF n = 8	No HF n = 124	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Family history as reason for screening	0 (0.0%)	42 (33.1%)	0.057	0.00 (0.00-NA; 0.998)	0.67 (0.52-0.81; 0.117)
VT/VF as reason for screening	4 (50.0%)	38 (29.9%)	0.255	2.34 (0.56-9.86; 0.246)	0.60 (0.39-0.81; 0.342)

Cardiovascular symptoms as reason for screening	4 (50.0%)	40 (31.5%)	0.437	2.18 (0.52-9.14; 0.289)	0.59 (0.38-0.80; 0.381)
Incidental findings as reason for screening	0 (0.0%)	4 (3.1%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.31-0.72; 0.881)
Dyspnea	4 (50.0%)	19 (15.8%)	**0.034**	**5.32 (1.22-23.12; 0.026)**	0.67 (0.46-0.89; 0.106)
Chest pain	0 (0.0%)	16 (13.3%)	0.595	0.00 (0.00-NA; 0.999)	0.57 (0.38-0.75, 0.529)
Palpitations	3 (37.5%)	49 (40.8%)	1.000	0.87 (0.20-3.81; 0.853)	0.52 (0.31-0.72; 0.875)
Presyncope	1 (12.5%)	32 (26.7%)	0.679	0.393 (0.05-3.32; 0.391)	0.57 (0.38-0.76; 0.503)
Syncope	5 (62.5%)	39 (32.5%)	0.122	3.46 (0.79-15.23; 0.100)	0.65 (0.45-0.85; 0.156)

Table A.3~~2~~: Clinical symptoms at baseline. HF: heart failure; AUC: area under the curve; CI: confidence interval; VT: ventricular tachycardia; VF: ventricular fibrillation

TABLE A.4~~3~~: ECG CHARACTERISTICS AT BASELINE.

ECG at baseline	HF n = 8	No HF n = 122	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
QRS duration V1	98.75 ± 26.96	95.42 ± 18.36	0.632	1.01 (0.97-1.05; 0.629)	0.51 (0.30-0.72; 0.923)
QRS duration V6	85.00 ± 15.12	79.57 ± 19.17	0.435	1.02 (0.98-1.06; 0.432)	0.59 (0.41-0.78; 0.371)
S upstroke duration V1	34.29 ± 12.72	40.26 ± 13.70	0.263	0.97 (0.91-1.02; 0.257)	0.68 (0.47-0.89, 0.114)
S upstroke duration V2	37.14 ± 11.13	44.69 ± 15.68	0.213	0.97 (0.92-1.02; 0.204)	0.69 (0.49-0.89; 0.094)
Abnormal axis	3 (37.5%)	25 (20.8%)	0.371	2.28 (0.51-10.19; 0.281)	0.58 (0.37-0.80; 0.431)

Negative T wave V1	5 (62.5%)	88 (72.1%)	0.687	0.64 (0.15-2.84; 0.561)	0.55 (0.34-0.76; 0.649)
Negative T wave V2	5 (62.5%)	71 (58.2%)	1.000	1.20 (0.27-5.24; 0.811)	0.52 (0.32-0.73; 0.839)
Negative T wave V3	6 (75.0%)	60 (49.2%)	0.274	3.10 (0.60-15.97; 0.176)	0.63 (0.44-0.82; 0.222)
Negative T wave V4	7 (87.5%)	46 (37.7%)	**0.008**	**11.57 (1.38-97.03; 0.024)**	**0.75 (0.60-0.90; 0.019)**
Negative T wave V5	4 (50.0%)	30 (24.6%)	0.205	3.07 (0.72-13.02; 0.129)	0.63 (0.42-0.84; 0.230)
Negative T wave V6	3 (37.5%)	20 (16.4%)	0.149	3.06 (0.68-13.85; 0.146)	0.61 (0.39-0.83; 0.318)
Negative T wave I	1 (12.5%)	6 (4.9%)	0.366	2.76 (0.29-26.21; 0.376)	0.54 (0.32-0.76; 0.720)
Positive T wave I	2 (25.0%)	91 (74.6%)	**0.007**	**0.11 (0.02-0.59; 0.010)**	**0.75 (0.57-0.93; 0.019**
Negative T wave II	1 (12.5%)	16 (13.1%)	1.000	0.95 (0.11-8.21; 0.960)	0.50 (0.30-0.71 (0.977)
Positive T wave II	2 (25.0%)	68 (55.7%)	0.143	0.27 (0.05-1.36; 0.112)	0.65 (0.47-0.84; 0.146)
Negative T wave III	3 (37.5%)	42 (34.4%)	1.000	1.14 (0.26-5.02; 0.860)	0.52 (0.31-0.72; 0.884)
Positive T wave III	1 (12.5%)	36 (29.5%)	0.439	0.34 (0.04-2.88; 0.323)	0.59 (0.40-0.77; 0.421)
Negative T wave aVR	3 (37.5%)	81 (66.4%)	0.130	0.30 (0.07-1.33; 0.114)	0.64 (0.44-0.85; 0.172)
Positive T wave aVR	0 (0.0%)	13 (10.7%)	1.000	0.00 (0.00-NA; 0.999)	0.55 (0.37-0.74; 0.614)
Negative T wave aVL	0 (0.0%)	14 (11.5%)	0.598	0.00 (0.00-NA; 0.999)	0.56 (0.37-0.74; 0.587)
Positive T wave aVL	1 (12.5%)	72 (59.0%)	**0.021**	**0.10 (0.01-0.83; 0.033)**	**0.73 (0.58-0.89; 0.028)**

Negative T wave aVF	2 (25.0%)	25 (20.5%)	0.671	1.29 (0.25-6.80; 0.761)	0.52 (0.31-0.73; 0.831)
Positive T wave aVF	2 (25.0%)	56 (45.9%)	0.297	0.39 (0.08-2.02; 0.264)	0.61 (0.41-0.80; 0.323)
Any Q wave V1	1 (12.5%)	2 (1.7%)	0.176	8.50 (0.69-105.49; 0.096)	0.55 (0.33-0.78; 0.608)
Any Q wave V2	1 (12.5%)	1 (0.8%)	0.121	17.14 (0.97-303.76; 0.053)	0.56 (0.34-0.78; 0.581)
Any Q wave V3	1 (12.5%)	1 (0.8%)	0.121	17.14 (0.97-303.76; 0.053)	0.56 (0.34-0.78; 0.581)
Any Q wave V4	1 (12.5%)	5 (4.1%)	0.324	3.31 (0.34-32.36; 0.303)	0.54 (0.32-0.76; 0.692)
Any Q wave V5	2 (25.0%)	21 (17.4%)	0.632	1.59 (0.30-8.42; 0.587)	0.54 (0.32-0.75; 0.718)
Any Q wave V6	2 (25.0%)	27 (22.3%)	1.000	1.16 (0.22-6.08; 0.860)	0.51 (0.30-0.72; 0.899)
Any Q wave I	2 (25.0%)	20 (16.5%)	0.624	1.68 (0.32-8.95; 0.541)	0.54 (0.33-0.76; 0.689)
Any Q wave II	1 (12.5%)	23 (19.0%)	1.000	0.61 (0.07-5.19; 0.650)	0.53 (0.33-0.73; 0.76)
Any Q wave III	2 (25.0%)	25 (20.7%)	0.673	1.28 (0.24-6.73; 0.771)	0.52 (0.31-0.73; 0.838)
Any Q wave aVR	2 (25.0%)	13 (10.7%)	0.234	2.77 (0.51-15.17; 0.240)	0.57 (0.35-0.79; 0.500)
Any Q wave aVL	1 (12.5%)	22 (18.2%)	1.000	0.64 (0.08-5.50; 0.687)	0.53 (0.33-0.73; 0.788)
Any Q wave aVF	2 (25.0%)	23 (19.0%)	0.652	1.42 (0.27-7.50; 0.679)	0.53 (0.32-0.74; 0.777)
Left bundle branch block (comp +incom)	1 (12.5%)	6 (4.9%)	0.366	2.76 (0.29-26.21; 0.376)	0.54 (0.32-0.76; 0.720)
Complete LBBB	0 (0.0%)	3 (2.5%)	1.000	0.00 (0.00-NA; 0.999)	0.51 (0.31-0.72; 0.907)

Right bundle branch block (“)	3 (37.5%)	11 (9.0%)	**0.041**	**6.06 (1.27-28.80; 0.024)**	0.64 (0.42-0.87; 0.178)
Complete RBBB	1 (12.5%)	3 (2.5%)	0.227	5.67 (0.52-61.73; 0.155)	0.55 (0.33-0.77; 0.635)
Low voltage	4 (50.0%)	28 (23.0%)	0.102	3.36 (0.79-14.29; 0.101)	0.64 (0.42-0.85; 0.201)
Poor R wave progression	2 (25.0%)	42 (35.6%)	0.712	0.60 (0.12-3.12; 0.547)	0.55 (0.35-0.75; 0.617)

Table A.43: ECG characteristics at baseline. HF: heart failure; AUC: area under the curve; CI: confidence interval; LBBB: left bundle branch block; RBBB: right bundle branch block

TABLE A.54: SIGNAL AVERAGED ECG MEASUREMENTS AT BASELINE.

SAECG at baseline	HF n = 3	No HF n = 90	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
QRS duration	140.8 ± 31.0	115.9 ± 21.1	0.050	1.04 (1.00-1.09; 0.073)	0.76 (0.49-1.00; 0.123)
QRS duration ≥ 140 ms	2 (66.7%)	10 (11.1%)	**0.043**	**16.00 (1.33-192.76; 0.029)**	0.78 (0.46-1.00; 0.103)
RMS	4.7 ± 1.1	24.5 ± 19.0	0.076	0.60 (0.34-1.05; 0.072)	**0.95 (0.90-1.00; 0.009)**
RMS ≤ 6 uV	3 (100%)	8 (8.9%)	**0.001**	605803060 (0.00-NA, 0.996)	0.96 (0.91-1.00; 0.007)
LAS	67.2 ± 25.2	41.9 ± 20.0	**0.036**	1.04 (1.00-1.09; 0.057)	0.83 (0.65-1.000; 0.056)
LAS ≥ 44	3 (100.0%)	34 (37.8%)	0.060	142541899 (0.00-NA; 0.997)	0.81 (0.67-0.95; 0.068)
All 3 parameters positive	2 (61.1%)	35 (38.9%)	0.561	3.14 (0.28-35.97; 0.357)	0.64 (0.32-0.96; 0.415)
Z QRS duration	114.2 ± 9.9	109.9 ± 18.9	0.703	1.01 (0.96-1.07; 0.699)	0.63 (0.45-0.81; 0.455)
Z RMS	9.8 ± 4.7	18.4 ± 16.5	0.371	0.90 (0.73-1.10; 0.297)	0.69 (0.47-0.90; 0.271)
Z LAS	51.0 ± 7.3	45.7 ± 18.3	0.619	1.01 (0.96-1.08; 0.614)	0.62 (0.44-0.80; 0.478)
Number of beats	418 ± 228	338 ± 182	0.460	1.00 (1.00-1.01; 0.462)	0.63 (0.36-0.89; 0.461)
Fnoise	0.407 ± 0.083	0.382 ± 0.063	0.496	1496.5 (0.00-1.618E+12)	0.59 (0.23-0.95; 0.598)

Table A.54: Signal averaged ECG (SAECG) measurements at baseline. HF: heart failure; AUC: area under the curve; CI: confidence interval; RMS: Root-mean-square voltage of the terminal 40 ms; LAS: low amplitude signal < 40 µV duration; Z: Z-vector

A.65: HOLTER RESULTS AT BASELINE.

Holter at baseline	HF n = 1	No HF n = 85	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Number of VPB	1016	2475 ± 4543	0.750	1.00 (1.00-1.00; 0.734)	0.55 (0.45-0.66; 0.856)
VPB present	1 (100.0%)	81 (95.3%)	1.000	19944133.9 (0.00-NA; 0.999)	0.52 (0.00-1.00; 0.936)
≥ 1000 VPB	1 (100.0%)	39 (45.9%)	0.465	41422432.2 (0.00-NA; 0.998)	0.77 (0.50-1.00; 0.354)
Number of couplets	18	174 ± 384	0.686	0.99 (0.95-1.04; 0.756)	0.60 (0.50-0.71; 0.726)
Couplets present	1 (100.0%)	53 (63.9%)	1.000	30480657.5 (0.00-NA; 0.998)	0.68 (0.31-1.00; 0.536)
≥ 15 couplets	1 (100.0%)	36 (43.4%)	0.440	44874301.2 (0.00-NA; 0.998)	0.78 (0.52-1.00; 0.332)
Number of triplets	0	14 ± 39	0.731	0.00 (0.00-NA; 0.980)	0.71 (0.37-1.00; 0.473)
Triplets present	0 (0.0%)	34 (41.5%)	1.000	0.00 (0.00-NA; 0.998)	0.71 (0.36-1.00; 0.478)
Polymorphic VPBs	1 (100.0%)	43 (59.7%)	1.000	37569182.6 (0.00-NA; 0.998)	0.70 (0.35-1.00; 0.491)
VT present	1 (50.0%)	21 (25.3%)	0.453	2.95 (0.18-49.32; 0.451)	0.62 (0.21-1.00; 0.552)
Number of VT	1	2 ± 13	0.840	0.95 (0.47-1.90; 0.874)	0.60 (0.21-0.99; 0.639)
Max beats VT	0	3 ± 5	0.184	0.01 (0.00-NA; 0.997)	0.71 (0.37-1.00; 0.464)

TABLE

Max HR VT	123	149 ± 47	0.604	0.99 (0.96-1.03; 0.589)	0.80 (0.63-0.98; 0.322)
Number SVE	0	364 ± 1474	0.807	0.01 (0.00-1.310E+24; 0.877)	0.84 (0.64-1.00; 0.248)
AF present	0 (0.0%)	2 (2.4%)	1.000	0.00 (0.00-NA; 1.000)	0.51 (0.00-1.00; 0.967)
SVT present	0 (0.0%)	6 (7.2%)	1.000	0.00 (0.00-NA; 0.999)	0.54 (0.00-1.00; 0.902)

Table A.6~~5~~: Holter results at baseline. HF: heart failure; AUC: area under the curve; CI: confidence interval; VPB: ventricular premature beats; VT: ventricular tachycardia; HR: heart rate; SVE: supraventricular ectopics; AF: atrial fibrillation; SVT: supraventricular tachycardia

A.7~~6~~: RESULTS FROM CARDIOPULMONARY EXERCISE TEST (CPEX) AT BASELINE.

CPEX at baseline	HF n = 6	No HF n = 113	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Betablockers	4 (66.7%)	59 (52.2%)	0.683	1.83 (0.32-10.40; 0.495)	0.57 (0.34-0.80; 0.552)
Calcium channel blockers	0 (0.0%)	1 (0.9%)	1.000	0.00 (0.00-NA; 1.000)	0.50 (0.27-0.74; 0.971)
Sotalol	1 (16.7%)	10 (8.9%)	0.452	2.04 (0.22-19.22; 0.533)	0.54 (0.29-0.79; 0.750)
Amiodarone	1 (16.7%)	6 (5.4%)	0.313	3.53 (0.36-35.21; 0.282)	0.56 (0.30-0.81; 0.642)
Antiarrhythmics	0 (0.0%)	9 (8.0%)	1.000	0.00 (0.00-NA; 0.999)	0.54 (0.32-0.76; 0.743)
Arrhythmias at rest	6 (100.0%)	43 (38.4%)	**0.004**	225415093 (0.00-NA; 0.997)	**0.81 (0.70-0.91; 0.011)**
Arrhythmias during exercise	4 (66.7%)	67 (59.9%)	1.000	1.34 (0.24-7.65; 0.739)	0.53 (0.30-0.77; 0.778)
NSVT during exercise	0 (0.0%)	7 (6.3%)	1.000	0.00 (0.00-NA; 0.999)	0.53 (0.31-0.76; 0.797)
Arrhythmias during recovery	3 (50.0%)	50 (44.7%)	1.000	1.24 (0.24-6.41; 0.797)	0.53 (0.29-0.77; 0.825)
NSVT during recovery	1 (16.7%)	1 (0.9%)	0.100	**22.2 (1.21-408.76; 0.037)**	0.58 (0.32-0.84; 0.516)
%VO2max	51.0 ± 19.9	81.0 ± 23.9	**0.003**	**0.93 (0.89.0.98; 0.007)**	**0.84 (0.70-0.99; 0.005)**
VO2 max (ml/min/1.73m2)	14.3 ± 3.1	24.3 ± 7.4	**0.001**	**0.74 (0.59-0.93; 0.009)**	**0.88 (0.80-0.97; 0.002)**
RQ	1.06 ± 0.19	1.10 ± 0.09	0.445	0.03 (0.00-234.11; 0.442)	0.60 (0.25-0.95; 0.448)

TABLE

Min		6.2 ± 0.8	8.6 ± 2.4	**0.016**	**0.641 (0.44-0.94; 0.022)**	**0.84 (0.76-0.92; 0.005)**	
Watts		74.0 ± 21.3	152.8 ± 58.1	**0.003**	**0.97 (0.94-0.99; 0.010)**	**0.91 (0.83-0.99; 0.002)**	
Max HR	130.7 ± 30.5	142.0 ± 28.5	0.348			0.99 (0.96-1.01; 0.347)	0.62 (0.38-0.87; 0.309)
Predicted max HR	150 ± 54	156 ± 44	0.772			1.00 (0.978-1.02; 0.770)	0.58 (0.31-0.84; 0.559)

Table A.7~~6~~: Results from cardiopulmonary exercise test (CPEX) at baseline. HF: heart failure; AUC: area under the curve; CI: confidence interval; NSVT: nonsustained VT; VO2max: maximal oxygen uptake; %VO2max: VO2max, % of predicted; RQ: respiratory quotient; HR: heart rate

A.8~~7~~: ECHO CHARACTERISTICS AT BASELINE.

Echo at baseline	HF n = 8	No HF n = 124	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Reduced RV function (incl borderline)	7 (87.5%)	55 (44.4%)	**0.026**	**8.78 (1.05-73.53; 0.045)**	**0.72 (0.56-0.87; 0.041)**
Reduced RV function (excl borderline)	7 (87.5%)	54 (43.5%)	**0.024**	**9.07 (1.08-75.99; 0.042)**	**0.72 (0.56-0.88; 0.038)**
RV dilatation (incl upper normal)	8 (100%)	85 (68.5%)	0.104	152044683 (0.00-NA; 0.998)	0.66 (0.51-0.81; 0.137)
RV dilatation (excl upper normal)	8 (100%)	73 (58.9%)	**0.023**	177038337 (0.00-NA; 0.997)	0.71 (0.57-0.84; 0.052)
RVOT PLAX (cm)	4.6 ± 1.1	3.6 ± 0.7	**0.000**	**4.53 (1.69-12.14; 0.003)**	**0.79 (0.60-0.99; 0.011)**
RVOT PLAX ≥ 4.4 cm	4 (57.1%)	8 (9.1%)	**0.004**	**13.33 (2.53-70.41; 0.002)**	**0.74 (0.51-0.97; 0.035)**
RVOT PLAX/BSA	2.6 ± 0.6	1.8 ± 0.3	**0.000**	10.03 (0.15-691.65; 0.286)	0.78 (0.46-1.00; 0.197)
RVOT PLAX/BSA ≥ 2.0	4 (80.0%)	13 (19.1%)	**0.009**	**16.9 (1.74-164.32; 0.015)**	**0.80 (0.59-1.00; 0.024)**
RVOT PSAX (cm)	4.0 ± 0.6	3.2 ± 0.6	0.090	3.21 (0.09-114.18; 0.522)	0.75 (0.20-1.00; 0.439)
RVOT PSAX/BSA	2.2 ± 0.3	1.6 ± 0.3	**0.017**	15.18 (0.02-10230.20; 0.413)	0.75 (0.20-1.00; 0.439)
RVIT (cm)	4.5 ± 1.0	3.8 ± 0.9	0.067	1.12 (0.24-5.22; 0.884)	0.50 (0.01-0.99; 1.000)
RV/LV	1.5 ± 0.9	1.0 ± 0.6	0.103	0.62 (0.06-6.58; 0.691)	0.75 (0.20-1.00; 0.439)
RV regional wall motion abnormalities	7 (87.5%)	67 (54.5%)	0.137	923128605 (0.00-NA; 1.000)	0.56-0.22-0.91; 0.734)

TABLE

Akinesia or dyskinesia RV	3 (37.5%)	29 (23.8%)	0.406	1.92 (0.43-8.54; 0.390)	0.57 (0.35-0.78; 0.516)
Dyskinesia RV	0 (0.0%)	18 (14.8%)	0.599	0.00 (0.00-NA; 0.998)	0.57 (0.39-0.75; 0.485)
Bulge RV	0 (0.0%)	16 (13.3%)	0.595	0.00 (0.00-NA; 0.999)	0.57 (0.38-0.75; 0.529)
RV aneurysm	1 (12.5%)	14 (11.7%)	1.000	1.08 (0.12-9.46; 0.943)	0.50 (0.30-0.71; 0.969)
LVEDD	5.1 ± 1.1	5.1 ± 0.6	0.796	0.85 (0.25-2.89; 0.795)	0.60 (0.33-0.87; 0.359)
LVESD	3.9 ± 1.4	3.5 ± 0.6	0.117	1.87 (0.84-4.18; 0.127)	0.52 (0.27-0.78; 0.834)
IVS	0.7 ± 0.2	0.9 ± 0.2	0.059	0.01 (0.00-1.17; 0.057)	0.70 (0.51-0.88; 0.065)
Posterior LV wall	0.7 ± 0.2	0.8 ± 0.2	**0.044**	0.00 (0.00-1.03; 0.051)	0.72 (0.52-0.93; 0.034)
Left atrium	3.7 ± 0.8	3.7 ± 0.6	0.822	1.14 (0.36-3.63; 0.820)	0.54 (0.30-0.78; 0.705)
EF	48.8 ± 18.4	58.4 ± 11.6	**0.030**	**0.95 (0.90-1.00; 0.038)**	0.66 (0.46-0.85; 0.136)
EF < 55%	4 (50.0%)	39 (31.5%)	0.437	2.18 (0.52-9.17; 0.288)	0.59 (0.38-0.80; 0.380)
LV regional wall motion abnormalities	3 (37.5%)	26 (21.1%)	0.374	2.24 (0.50-9.99; 0.291)	0.58 (0.37-0.80; 0.439)
LV akinesia or dyskinesia	2 (25.0%)	7 (5.7%)	0.095	5.52 (0.94-32.52; 0.059)	0.60 (0.37-0.82; 0.361)
LV dyskinesia	1 (12.5%)	5 (4.1%)	0.320	3.37 (0.35-32.91; 0.296)	0.54 (0.32-0.76; 0.690)
LV aneurysm	0 (0.0%)	3 (2.5%)	1.000	0.00 (0.00-NA; 0.999)	0.51 (0.31-0.72; 0.906)

Table A.8~~7~~: Echo characteristics at baseline. HF: heart failure; AUC: area under the curve; CI: confidence interval; RV: right ventricle/ventricular; RVOT: right ventricular outflow tract; PLAX: parasternal long axis view; BSA: body surface area; PSAX: parasternal short axis view; RVIT: right ventricular inflow tract; LV: left ventricle/ventricular;

LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; IVS: interventricular septum thickness; LVEF: ejection fraction

A.98: CLINICAL SYMPTOMS AT FOLLOW UP.

FU clinical	HF n = 8	No HF n = 122	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Dyspnea	5 (62.5%)	23 (18.9%)	**0.012**	**7.17 (1.60-32.20; 0.010)**	**0.72 (0.52-0.92; 0.039)**
Improvement of NYHA	1 (12.5%)	14 (12.0%)	1.000	1.05 (0.12-9.19; 0.964)	0.50 (0.29-0.71; 0.980)
Deterioration NYHA	3 (37.5%)	17 (14.5%)	0.116	3.53 (0.77-16.15; 0.104)	0.62 (0.39-0.84; 0.278)
Chest pain	0 (0.0%)	8 (6.6%)	1.000	0.00 (0.00-NA; 0.999)	0.53 (0.34-0.73; 0.755)
Palpitations	2 (25.0%)	22 (18.2%)	0.642	1.50 (0.28-7.93; 0.633)	0.53 (0.32-0.75; 0.747)
Pre-Syncope	2 (25.0%)	10 (8.3%)	0.162	3.70 (0.55-20.79; 0.137)	0.58 (0.36-0.81; 0.429)
Syncope	0 (0.0%)	7 (5.8%)	1.000	0.00 (0.00-NA; 0.999)	0.53 (0.33-0.73; 0.785)
EPS	4 (50.0%)	48 (38.4%)	0.711	1.60 (0.38-6.72; 0.518)	0.56 (0.35-0.77; 0.583)
ICD	7 (87.5%)	83 (66.4%)	0.436	3.54 (0.42-29.75; 0.244)	0.61 (0.43-0.79; 0.318)

Table A.98: Clinical symptoms at follow-up. HF: heart failure; AUC: area under the curve; CI: confidence interval; NYHA: New York Heart Association functional class.

TABLE

A.109: MEDICATION AT FOLLOW-UP

Medication at last FU	HF n = 8	No HF n = 125	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Any medication	8 (100.0%)	112 (89.6%)	1.000	115391040 (0.00-NA; 0.999)	0.55 (0.36-0.74; 0.623)
Beta blockers	5 (62.5%)	74 (59.2%)	1.000	1.15 (0.26-5.02; 0.854)	0.52 (0.31-0.72, 0.876)
Amiodarone	2 (25.0%)	13 (10.4%)	0.223	2.87 (0.53-15.72; 0.224)	0.57 (0.35-0.79; 0.490)
Sotalol	1 (12.5%)	21 (16.8%)	1.000	0.71 (0.08-6.06; 0.752)	0.52 (0.32-0.72; 0.839)
ACE inhibitors	4 (50.0%)	45 (36.0%)	0.466	1.78 (0.42-7.45; 0.431)	0.57 (0.36-0.78; 0.508)
ARB	0 (0.0%)	14 (11.2%)	1.000	0.00 (0.00-NA; 0.999)	0.56 (0.37-0.74; 0.596)
Diuretics	4 (50.0%)	21 (16.8%)	**0.041**	**4.95 (1.15-21.39; 0.032)**	0.67 (0.45-0.88; 0.116)
Digoxin	2 (25.0%)	1 (1.6%)	**0.018**	**20.50 (2.45-171.54; 0.005)**	0.62 (0.39-0.85; 0.268)
Antiarrhythmics	0 (0.0%)	11 (8.8%)	1.000	0.00 (0.00-NA; 0.999)	0.54 (0.35-0.74; 0.677)

Table A.109: Medication at follow-up (FU). HF: heart failure; AUC: area under the curve; CI: confidence interval; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

A.110: ELECTROCARDIOGRAPHIC CHARACTERISTICS AT FOLLOW-UP

ECG FU	HF n = 6	No HF n = 103	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Time to follow up ECG	42.7 ± 25.0	76.1 ± 43.0	0.063	0.98 (0.95-1.00; 0.070)	**0.74 (0.59-0.89; 0.047)**
Change in axis	0 (0.0%)	14 (14.1%)	1.000	0.00 (0.00-NA; 0.999)	0.57 (0.36-0.78; 0.562)
QRS V1	100 ± 0.0	97 ± 20	0.808	1.01 (0.96-1.06; 0.805)	0.63 (0.49-0.76; 0.462)
(QRS $V1_{FU}$)-(QRS $V1_{baseline}$)	10 ± 10	1 ± 20	0.425	1.02 (0.97-1.08; 0.420)	0.69 (0.51-0.88; 0.256)
Shorter QRS V1	0 (0.0%)	33 (35.1%)	0.549	0.00 (0.00-NA; 0.998)	0.68 (0.45-0.90; 0.302)
Longer QRS V1	2 (66.7%)	31 (33.0%)	0.266	4.07 (0.36-46.57; 0.260)	0.67 (0.35-0.98; 0.322)
Stable QRS V1	1 (33.0%)	30 (31.9%)	1.000	1.07 (0.09-12.23; 0.959)	0.51 (0.17-0.84; 0.967)
QRS V6	107 ± 23	86 ± 22	0.119	1.04 (0.99-1.08; 0.135)	0.76 (0.49-1.00; 0.129)
(QRS $V6_{FU}$)-(QRS $V6_{baseline}$)	23 ± 6	5 ± 23	0.175	1.04 (0.99-1.09; 0.177)	0.80 (0.70-0.90; 0.080)
Shorter QRS V6	0 (0.0%)	27 (28.7%)	0.558	0.00 (0.00-NA; 0.998)	0.64 (0.40-0.89; 0.399)
Longer QRS V6	3 (100.0%)	42 (44.7%)	0.096	115391061 (0.00-NA; 0.997)	0.78 (0.62-0.94; 0.104)
Stable QRS V6	0 (0.0%)	25 (26.6%)	0.567	0.00 (0.00-NA; 0.998)	0.63 (0.38-0.88; 0.435)
S upstroke V1	40 ± 40	48 ± 19	0.493	0.98 (0.92-1.04; 0.481)	0.57 (0.14-1.00; 0.667)

TABLE

(Sup $V1_{FU}$)-(Sup $V1_{baseline}$)	10 ± 42	7 ± 22	0.873	1.01 (0.95-1.07; 0.871)	0.51 (0.00-1.00; 0.969)
Shorter S upstroke V1	1 (50.0%)	24 (26.1%)	0.463	2.83 (0.17-47.09; 0.468)	0.62 (0.20-1.00; 0.564)

Longer S upstroke V1	1 (50.0%)	49 (53.3%)	1.000	0.88 (0.05-14.46; 0.927)	0.52 (0.11-0.92; 0.937)
Stable S upstroke V1	0 (0.0%)	19 (20.7%)	1.000	0.00 (0.00-NA; 0.998)	0.60 (0.28-0.93; 0.619)
S upstroke V2	57 ± 21	48 ± 19	0.493	1.02 (0.97-1.08; 0.415)	0.64 (0.34-0.94; 0.417)
(Sup $V2_{FU}$)-(Sup $V2_{baseline}$)	15 ± 35	2 ± 20	0.873	1.03 (0.97-1.08; 0.377)	0.61 (0.12-1.00; 0.595)
Shorter S upstroke V2	1 (50.0%)	32 (34.4%)	1.000	1.91 (0.12-31.49; 0.652)	0.58 (0.17-0.99; 0.578)
Longer S upstroke V2	1 (50.0%)	39 (41.9%)	1.000	1.39 (0.08-22.82; 0.820)	0.54 (0.13-0.95; 0.846)
Stable S upstroke V2	0 (0.0%)	22 (23.7%)	1.000	0.00 (0.00-NA; 0.998)	0.62 (0.30-0.93; 0.568)
New T wave inversion V1	0 (0.0%)	3 (3.0%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.28-0.75; 0.902)
Flat T wave V1	4 (66.7%)	22 (21.4%)	**0.028**	**7.36 (1.27-42.87; 0.026)**	0.73 (0.50-0.95; 0.063)
Loss of T wave V1	1 (16.7%)	17 (17.0%)	1.000	0.98 (0.11-8.90; 0.983)	0.50 (0.26-0.74; 0.989)
New T wave inversion V2	0 (0.0%)	3 (3.0%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.28-0.75; 0.902)
Flat T wave V2	2 (33.3%)	16 (15.7%)	0.261	2.69 (0.45-15.93; 0.276)	0.59 (0.34-0.84; 0.469)
Loss of T wave V2	1 (16.7%)	12 (12.4%)	0.565	1.42 (0.15-13.18; 0.760)	0.52 (0.28-0.77; 0.860)
New T wave inversion V4	0 (0.0%)	8 (8.0%)	1.000	0.00 (0.00-NA; 0.999)	0.54 (0.32-0.76; 0.743)
Flat T wave V4	2 (33.3%)	20 (19.4%)	0.599	2.08 (0.36-12.14; 0.418)	0.57 (0.32-0.82; 0.568)

TABLE

New T wave inversion V3	0 (0.0%)	7 (7.0%)	1.000	0.00 (0.00-NA; 0.999)	0.54 (0.31-0.76; 0.774)
Flat T wave V3	2 (33.3%)	10 (9.7%)	0.130	4.65 (0.76-28.65; 0.098)	0.62 (0.36-0.88; 0.332)
Loss of T wave V3	0 (0.0%)	7 (7.0%)	1.000	0.00 (0.00-NA; 0.999)	0.54 (0.31-0.76; 0.774)

Flat T wave II	3 (50.0%)	32 (31.1%)	0.383	2.22 (0.42-11.56; 0.345)	0.60 (0.35-0.84; 0.437)
			1.000		

Loss of T wave II	0 (0.0%)	13 (13.0%)		0.00 (0.00-NA; 0.999)	0.57 (0.35-0.78; 0.594)
Loss of T wave V4	1 (16.7%)	14 (14.0%)	1.000	1.23 (0.13-11.31; 0.856)	0.51 (0.27-0.76; 0.913)
New T wave inversion V5	0 (0.0%)	2 (2.0%)	1.000	0.00 (0.00-NA; 0.999)	0.51 (0.28-0.75; 0.935)
Flat T wave V5	3 (50.0%)	26 (25.2%)	0.190	2.96 (0.56-15.59; 0.200)	0.62 (0.38-0.87; 0.309)
Loss of T wave V5	2 (33.3%)	18 (17.8%)	0.312	2.31 (0.39-13.57; 0.356)	0.59 (0.33-0.83; 0.525)
New T wave inversion V6	1 (16.7%)	2 (2.0%)	0.162	0.98 (0.76-127.17; 0.081)	0.57 (0.31-0.83; 0.547)
Flat T wave V6	2 (33.3%)	26 (25.2%)	0.646	1.48 (0.26-8.56; 0.661)	0.54 (0.30-0.79; 0.740)
Loss of T wave V6	1 (16.7%)	14 (14.0%)	1.000	1.23 (0.13-11.31; 0.856)	0.51 (0.27-0.76; 0.913)
Precordial new T wave inversion	1 (16.7%)	17 (17.0%)	1.000	0.98 (0.11-8.90; 0.983)	0.50 (0.26-0.74; 0.989)
Flat T wave any precordial lead	5 (83.3%)	62 (60.2%)	0.403	3.31 (0.37-29.34; 0.283)	0.62 (0.41-0.83; 0.342)
Flat T wave in >1 precordial lead	3 (50.0%)	30 (29.1%)	0.364	2.43 (0.47-12.74; 0.293)	0.60 (0.36-0.85; 0.391)
Loss of T wave in any precordial lead	5 (83.3%)	45 (44.6%)	0.096	0.62 (0.70-55.19; 0.101)	0.69 (0.50-0.89; 0.112)
Loss of T wave in >1 precordial lead	1 (16.7%)	20 (19.8%)	1.000	0.81 (0.09-7.33; 0.851)	0.52 (0.28-0.75; 0.898)
New T wave inversion I	0 (0.0%)	2 (2.0%)	1.000	0.00 (0.00-NA; 0.999)	0.51 (0.28-0.75; 0.935)
Flat T wave I	4 (66.7%)	28 (27.2%)	0.060	5.36 (0.93-30.89; 0.060)	0.70 (0.47-0.92; 0.105)
			1.000		

Loss of T wave I	2 (33.3%)	16 (16.0%)	0.269	2.63 (0.44-15.56; 0.288)	0.59 (0.33-0.84; 0.477)
New T wave inversion II	0 (0.0%)	1 (1.0%)	1.000	0.00 (0.00-NA; 1.000)	0.51 (0.27-0.74; 0.967)

1.000

Any Flat T	6 (100.0%)	97 (94.2%)	1.000	99926303.2 (0.00-NA; 0.999)	0.53 (0.30-0.76; 0.811)
			1.000		

Flat T in >1 lead	4 (66.7%)	70 (68.0%)		0.94 (0.16-5.41; 0.947)	0.51 (0.27-0.75; 0.958)
New T wave inversion III	0 (0.0%)	5 (5.0%)	1.000	0.00 (0.00-NA; 0.999)	0.53 (0.30-0.75; 0.838)
Flat T wave III	3 (50.0%)	44 (42.7%)	1.000	1.34 (0.26-6.96; 0.727)	0.54 (0.30-0.78; 0.765)
Loss of T wave III	1 (16.7%)	26 (26.0%)	1.000	0.57 (0.06-5.10; 0.615)	0.55 (0.32-0.77; 0.702)
New T wave inversion aVR	0 (0.0%)	2 (2.0%)	1.000	0.00 (0.00-NA; 0.999)	0.51 (0.28-0.75; 0.935)
Flat T wave aVR	4 (66.7%)	36 (35.0%)	0.189	3.72 (0.65-21.314; 0.140)	0.66 (0.43-0.88; 0.193)
Loss of T wave aVR	1 (16.7%)	21 (21.0%)	1.000	0.75 (0.08-6.79; 0.800)	0.52 (0.29-0.76; 0.859)
New T wave inversion aVL	0 (0.0%)	0 (0.0%)	NA	NA	NA
Flat T wave aVL	3 (50.0%)	44 (42.7%)	1.000	1.34 (0.26-6.96; 0.727)	0.54 (0.30-0.78; 0.765)
Loss of T wave aVL	1 (16.7%)	23 (23.0%)	1.000	0.67 (0.07-6.03; 0.720)	0.53 (0.30-0.76; 0.795)
New T wave inversion aVF	0 (0.0%)	4 (4.0%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.29-0.75; 0.870)
Flat T wave aVF	3 (50.0%)	43 (41.7%)	0.696	1.40 (0.27-7.25; 0.692)	0.54 (0.30-0.78; 0.735)
Loss of T wave aVF	1 (16.7%)	19 (19.0%)	1.000	0.85 (0.09-7.73; 0.887)	0.51 (0.28-0.75; 0.924)
New T wave inversion extremity leads	0 (0.0%)	10 (10.0%)	1.000	0.00 (0.00-NA; 0.999)	0.55 (0.33-0.77; 0.682)
Any new T wave inversion	1 (16.7%)	22 (22.0%)	1.000	0.71 (0.08-6.39; 0.759)	0.53 (0.30-0.76; 0.827)
			1.000		

Flat T wave any extremity lead	5 (83.3%)	91 (88.3%)	0.542	0.66 (0.07-6.13; 0.714)	0.53 (0.28-0.77; 0.837)
Flat T in > 1 extremity lead	3 (50.0%)	51 (49.5%)	1.000	1.02 (0.20-5.29; 0.982)	0.50 (0.26-0.74; 0.984)
Loss of T any extremity lead	3 (50.0%)	57 (57.0%)	1.000	0.75 (0.15-3.92; 0.738)	0.54 (0.30-0.77; 0.774)
Loss of T wave in >1 extremity lead	1 (16.7%)	27 (27.0%)	1.000	0.54 (0.06-4.84; 0.582)	0.55 (0.33-0.78; 0.672)
Any loss of T wave	6 (100.0%)	74 (73.3%)	0.334	130984433 (0.00-NA; 0.998)	0.63 (0.45-0.82; 0.273)
Loss of T wave in >1 lead	2 (33.3%)	44 (43.6%)	0.698	0.65 (0.11-3.70; 0.625)	0.55 (0.32-0.78; 0.675)
Epsilon wave V1	0 (0.0%)	7 (6.8%)	1.000	0.00 (0.00-NA; 0.999)	0.53 (0.31-0.76; 0.780)
Epsilon wave V2	0 (0.0%)	3 (2.9%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.28-0.75; 0.905)
Epsilon wave V3	0 (0.0%)	2 (1.9%)	1.000	0.00 (0.00-NA; 0.999)	0.51 (0.28-0.74; 0.936)
Epsilon wave II	0 (0.0%)	3 (2.9%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.28-0.75; 0.905)
Epsilon wave III	0 (0.0%)	5 (4.9%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.30-0.75; 0.842)
Epsilon wave aVF	0 (0.0%)	3 (2.9%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.28-0.75; 0.905)
Q wave V1	0 (0.0%)	4 (3.9%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.29-0.75; 0.873)
New Q wave V1	0 (0.0%)	3 (3.0%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.28-0.75; 0.902)
Q wave V2	0 (0.0%)	1 (1.0%)	1.000	0.00 (0.00-NA; 1.000)	0.51 (0.27-0.74; 0.968)
			1.000		

New Q wave V2	0 (0.0%)	1 (1.0%)	1.000	0.00 (0.00-NA; 1.000)	0.51 (0.27-0.74; 0.968)
Q wave V3	0 (0.0%)	0 (0.0%)	NA	NA	NA
New Q wave V3	0 (0.0%)	0 (0.0%)	NA	NA	NA
Q wave V4	0 (0.0%)	6 (5.9%)	1.000	0.00 (0.00-NA; 0.999)	0.53 (0.30-0.76; 0.811)
New Q wave V4	0 (0.0%)	5 (5.0%)		0.00 (0.00-NA; 0.999)	0.53 (0.30-0.75; 0.838)

1.000

Q wave V5	0 (0.0%)	24 (23.3%)	0.335	0.00 (0.00-NA; 0.998)	0.62 (0.43-0.81; 0.339)
New Q wave V5	0 (0.0%)	12 (12.0%)	1.000	0.00 (0.00-NA; 0.999)	0.56 (0.35-0.77; 0.623)
Q wave V6	1 (16.7%)	40 (38.8%)	0.406	0.00 (0.00-NA; 0.999)	0.64 (0.47-0.82; 0.245)
Pathological Q wave V6	1 (16.7%)	1 (1.9%)	0.158	10.10 (0.78-131.03; 0.077)	0.57 (0.31-0.83; 0.545)
New Q wave V6	0 (0.0%)	21 (21.0%)	0.596	0.00 (0.00-NA; 0.998)	0.61 (0.41-0.80; 0.389)
Precordial new Q wave	0 (0.0%)	26 (26.0%)	0.332	0.00 (0.00-NA; 0.998)	0.63 (0.45-0.81; 0.286)
Q wave I	1 (16.7%)	22 (21.4%)	1.000	0.87 (0.29-2.63; 0.804)	0.52 (0.29-0.76; 0.852)
New Q wave I	0 (0.0%)	11 (11.0%)	1.000	0.00 (0.00-NA; 0.999)	0.56 (0.34-0.77; 0.652)
Q wave II	0 (0.0%)	22 (21.3%)	0.345	0.00 (0.00-NA; 0.998)	0.61 (0.41-0.80; 0.381)
New Q wave II	0 (0.0%)	10 (10.0%)	1.000	0.00 (0.00-NA; 0.999)	0.55 (0.33-0.77; 0.682)
Q wave III	1 (16.7%)	24 (23.3%)	1.000	0.93 (0.28-3.09; 0.905)	0.53 (0.29-0.76; 0.837)
New Q wave III	1 (16.7%)	14 (14.0%)	1.000	1.23 (0.13-11.31; 0.856)	0.51 (0.27-0.76; 0.913)
Q wave aVR	0 (0.0%)	0 (0.0%)	NA	NA	NA
New Q aVF	0 (0.0%)	15 (15.0%)	0.591	0.00 (0.00-NA; 0.999)	0.58 (0.37-0.78; 0.538)
New Q extremity	1 (16.7%)	46 (46.0%)	0.224	0.24 (0.03-2.08; 0.193)	0.65 (0.44-0.85; 0.229)

TABLE

Q wave aVL	0 (0.0%)	35 (34.0%)	0.174	0.00 (0.00-NA; 0.997)	0.67 (0.50-0.84; 0.163)
New Q aVL	0 (0.0%)	25 (25.0%)	0.332	0.00 (0.00-NA; 0.998)	0.63 (0.44-0.81; 0.305)
Q wave aVF	1 (16.7%)	25 (24.3%)	1.000	0.82 (0.27-2.51; 0.722)	0.54 (0.31-0.77; 0.770)
Any new Q	1 (16.7%)	57 (57.0%)	0.089	0.15 (0.02-1.34; 0.090)	0.70 (0.51-0.89; 0.098)
Complete LBBB	2 (33.3%)	4 (3.9%)	**0.035**	**12.38 (1.73-88.72; 0.012)**	0.65 (0.38-0.91; 0.227)
Complete + incomplete LBBB	3 (37.5%)	8 (6.6%)	**0.020**	**24.75 (3.75-163.31; 0.001)**	0.73 (0.47-0.99; 0.058)
Complete RBBB	1 (16.7%)	8 (7.8%)	0.411	2.38 (0.25-22.88; 0.454)	0.54 (0.29-0.80; 0.715)
Complete + incomplete RBBB	3 (37.5%)	16 (13.1%)	0.092	1.67 (0.18-15.65; 0.652)	0.53 (0.28-0.78; 0.806)
Low voltage	4 (66.7%)	33 (32.0%)	0.177	4.24 (0.74-24.34; 0.105)	0.67 (0.45-0.90; 0.155)
Any low voltage	6 (75.0%)	49 (40.2%)	0.070	4.47 (0.87-23.06; 0.074)	0.67 (0.49-0.86; 0.100)
Poor R progression	3 (50.0%)	29 (28.2%)	0.356	2.55 (0.49-13.38; 0.268)	0.61 (0.37-0.85; 0.370)
Any poor R progression	4 (50.0%)	56 (45.9%)	1.000	1.18 (0.28-4.93; 0.822)	0.52 (0.31-0.73; 0.846)

Table A.11~~10~~: Electrocardiographic (ECG) characteristics at follow-up (FU). HF: heart failure; AUC: area under the curve; CI: confidence interval; LBBB: left bundle branch block; RBBB: right bundle branch block

A.12~~1~~: SIGNAL AVERAGED ECG MEASUREMENTS AT FOLLOW-UP

SAECG FU	HF n = 1	No HF n = 38	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)

Time to follow up SAECG	7.00	44.82 ± 28.56	0.199	0.00 (0.00-NA; 0.999)	1.00 (1.00-1.00; 0.091)
QRS duration	158.0	120.7 ± 21.4	0.094	1.08 (0.96-1.20; 0.192)	0.92 (0.84-1.00; 0.155)
QRS duration positive (≥114ms)	1 (100%)	23 (60.5%)	1.000	70238037 (0.00-NA; 0.999)	0.70 (0.33-1.00; 0.505)
Change positivity QRS duration	0 (0.0%)	7 (18.4%)	1.000	0.00 (0.00-NA; 0.999)	0.59 (0.11-1.00; 0.756)
Difference QRS duration	16.5	8.1 ± 14.2	0.566	1.03 (0.93-1.14; 0.566)	0.82 (0.69-0.94; 0.286)
RMS 40	2.1	22.3 ± 18.7	0.295	0.18 (0.00-14.46; 0.447)	0.97 (0.92-1.00; 0.110)
RMS 40 positive	1 (100%)	25 (65.8%)	1.000	64618993.6 (0.00-NA; 0.999)	0.67 (0.28-1.00; 0.564)
Change positivity RMS 40	0 (0.0%)	10 (26.3%)	1.000	0.00 (0.00-NA; 0.999)	0.63 (0.19-1.00; 0.657)
Difference RMS40	-1.9	-5.8 ± 15.4	0.805	1.02 (0.86-1.21; 0.800)	0.61 (0.45-0.76; 0.722)
LAS	82.0	44.3 ± 15.6	**0.022**	2.695E+10 (0.00-NA; 0.967)	1.00 (1.00-1.00; 0.091)
LAS positive ≥ 38	1 (100%)	25 (65.8%)	1.000	64618993.5 (00-NA; 0.999)	0.67 (0.28-1.00; 0.564)
Change positivity LAS	0 (0.0%)	9 (23.7%)	1.000	0.00 (0.00-NA; 0.999)	0.62 (0.17-1.00; 0.689)
All 3 parameters positive FU	1 (100%)	20 (52.6%)	1.000	80773742.1 (0.00-NA; 0.998)	0.74 (0.41-1.00; 0.424)
Any SAECG positive	2 (66.7%)	61 (76.3%)	0.568	0.62 (0.05-7.26; 0.706)	0.55 (0.20-0.89; 0.779)
Difference LAS	18.5	4.7 ± 16.6	0.419	1.06 (0.93-1.20; 0.389)	0.84 (0.73-0.96; 0.248)

TABLE

ZQRS duration	158.0	121.8 ± 36.0	0.335	1.02 (0.98-1.06; 0.360)	0.88 (0.74-1.00; 0.212)
ZRMS40	1.5	17.1 ± 18.7	0.420	0.50 (0.17-1.46; 0.205)	0.96 (0.88-1.00; 0.127)
ZLAS	104.5	59.6 ± 55.0	0.432	1.01 (0.99-1.03; 0.463)	0.92 (0.81-1.00; 0.166)
Nbeats	307	279 ± 105	0.796	1.00 (0.98-1.02; 0.788)	0.82 (0.69-0.94; 0.286)
fnoise	0.355	0.374 ± 0.067	0.778	0.02 (0.00-1.271E+10; 0.771)	0.68 (0.54-0.83; 0.534)

Table A.12~~11~~: Signal averaged ECG (SAECG) measurements at follow-up. HF: heart failure; AUC: area under the curve; CI: confidence interval; RMS: Root-mean-square voltage of the terminal 40 ms; LAS: low amplitude signal < 40 µV duration; Z: Z-vector

A.13~~2~~: HOLTER RESULTS AT FOLLOW-UP

Holter FU	HF n = 0	No HF n = 37	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Time to FU Holter	NA	65.7 ± 37	NA	NA	NA
Number of VPB	NA	1675 ± 3251	NA	NA	NA
Prevalence VPB FU	NA	34 (94.4%)	NA	NA	NA
Prevalence VPB BL+FU	1 (100.0%)	82 (96.5%)	1.000	19700912.8 (0.00-NA; 0.999)	0.52 (0.00-1.00; 0.952)
Number of couplets	NA	69 ± 168	NA	NA	NA
Prevalence couplets FU	NA	21 (56.8%)	NA	NA	NA
Prevalence couplets BL+FU	1 (100.0%)	56 (67.5%)	1.000	28847765.2 (0.00-NA, 0.998)	0.66 (0.27-1.00; 0.578)
Number of triplets	NA	25 ± 135	NA	NA	NA
≥ 7 triplets FU	NA	4 (10.8%)	NA	NA	NA
Prevalence triplets FU	NA	5 (14.7%)	NA	NA	NA
Prevalence triplets BL+FU	0 (0.0%)	33 (40.2%)	1.000	0.00 (0.00-NA; 0.998)	0.70 (0.35-1.00 0.491)
Polymorphic VPBs	NA	17 (58.6%)	NA	NA	NA
Number of VTs	NA	0.2 ± 0.8	NA	NA	NA

TABLE

Prevalence VT FU	NA	2 (5.4%)	NA	NA	NA
Prevalence VT BL+FU	1 (50.0%)	22 (26.5%)	0.470	2.77 (0.17-46.26; 0.478)	0.62 (0.20-1.00; 0.572)
Max beats VT	NA	9 ± 2	NA	NA	NA
Max HR VT	NA	142	NA	NA	NA
Number SVE	NA	252 ± 1085	NA	NA	NA
Prevalence AF FU	NA	3 (7.7%)	NA	NA	NA
Prevalence AF BL+FU	0 (0.0%)	3 (3.6%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.00-1.00; 0.951)
Prevalence SVT FU	NA	3 (8.1%)	NA	NA	NA
Prevalence SVT BL+FU	0 (0.0%)	9 (10.8%)	1.000	0.00 (0.00-NA; 0.999)	0.55 (0.04-1.00; 0.853)

Table A.13~~12~~: Holter results at follow-up (FU). HF: heart failure; AUC: area under the curve; CI: confidence interval; VPB: ventricular premature beats; BL: baseline; VT: ventricular tachycardia; HR: heart rate; SVE: supraventricular ectopics; AF: atrial fibrillation; SVT: supraventricular tachycardia

A.14~~13~~: RESULTS FROM CARDIOPULMONARY EXERCISE TEST AT FOLLOW-UP

CPEX FU	HF n = 2	No HF n =42	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Time to FU CPEX	19.0 ± 11.3	55.0 ± 50.3	0.323	0.94 (0.82-1.06; 0.307)	0.79 (0.55-1.00; 0.176)
Betablockers	1 (50.0%)	25 (59.5%)	1.000	0.68 (0.04-11.63; 0.790)	0.55 (0.13-0.96; 0.822)
Calcium channel antagonists	0 (0.0%)	0 (0.0%)	NA	NA	NA
Sotalol	0 (0.0%)	7 (16.7%)	1.000	0.00 (0.00-NA; 0.999)	0.58 (0.23-0.94; 0.693)
Amiodarone	0 (0.0%)	7 (16.7%)	1.000	0.00 (0.00-NA; 0.999)	0.58 (0.23-0.94; 0.693)
Antiarrhythmics	0 (0.0%)	2 (4.8%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.13-0.92; 0.910)
%vO2	50.0 ± 2.8	79.6 ± 23.4	0.087	0.91 (0.80-1.03; 0.122)	0.89 (0.78-1.00 0.067)
Difference %vO2	-12.0 ± 14.1	0.1 ± 14.5	0.259	0.93 (0.83-1.06; 0.269)	0.74 (0.45-1.00; 0.258)
vO2	12.8 ± 3.5	24.3 ± 7.3	**0.035**	0.54 (0.26-1.13; 0.541)	**0.96 (0.88-1.00; 0.031)**
Difference vO2	-3.0 ± 3.1	-1.6 ± 5.7	0.744	0.96 (0.74-1.24; 0.733)	0.61 (0.34-0.88; 0.597)
RQ	1.0 ± 0.1	1.1 ± 0.1	0.149	0.00 (0.00-195.6; 0.166)	0.77 (0.48-1.00; 0.200)
Difference RQ	0.0	0.0 ± 0.1	0.984	0.78 (0.00-4.493E+9; 0.983)	0.52 (0.33-0.71; 0.949)
Min	5.0 ± 0	8.9 ± 2.2	**0.016**	0.00 (0.00-NA; 0.993)	**0.99 (0.96-1.00; 0.021)**

TABLE

Difference min	-1.5 ± 0.7	0.0 ± 3.0	0.491	0.82 (0.48-1.40; 0.474)	0.72 (0.58-0.86; 0.299)
Watts	52.5 ± 24.7	154.2 ± 51.8	**0.010**	0.06 (0.00-5.823E+131; 0.986)	**1.00 (1.00-1.00; 0.019)**
Difference Watts	-22.5 ± 38.9	-12.5 ± 33.0	0.491	0.989 (0.94-1.04; 0.674)	0.56 (0.09-1.00; 0.776)
MaxHR	152.5 ± 31.8	137.1 ± 23.0	0.366	1.03 (0.97-1.10; 0.370)	0.67 (0.29-1.00; 0.430)
Difference MaxHR	-9.5 ± 14.8	-8.8 ± 21.5	0.962	1.00 (0.93-1.07; 0.961)	0.50 (0.22-0.78; 1.000)
Predicted HR	166 ± 6	175 ± 13	0.342	0.94 (0.82-1.07; 0.343)	0.74 (0.56-0.93; 0.249)
Arrhythmias at rest FU	2 (100.0%)	17 (40.5%)	0.181	190055859 (0.00-NA; 0.998)	0.80 (0.61-0.99; 0.159)
Any arrhythmias at rest	6 (100.0%)	46 (41.4%)	**0.007**	210714104 (0.00-NA; 0.997)	**0.79 (0.68-0.91; 0.016)**
Arrhythmias during exercise FU	2 (100.0%)	20 (47.6%)	0.488	161547477 (0.00-NA; 0.998)	0.76 (0.54-0.98; 0.215)
Any arrhythmias during exercise	5 (83.3%)	69 (62.2%)	0.412	3.04 (0.34-26.95; 0.317)	0.61 (0.40-0.82; 0.384)
Arrhythmias during recovery FU	2 (100.0%)	21 (50.0%)	0.489	153854743 (0.00-NA; 0.998)	0.75 (0.52-0.98; 0.237)
Any arrhythmias during recovery	4 (66.7%)	54 (48.6%)	0.439	2.11 (0.37-12.00; 0.399)	0.59 (0.36-0.82; 0.458)

Table A.14~~13~~: Results from cardiopulmonary exercise test (CPEX) at follow-up (FU). HF: heart failure; AUC: area under the curve; CI: confidence interval; NSVT: nonsustained VT; VO2max: maximal oxygen uptake; %VO2max: VO2max, % of predicted; RQ: respiratory quotient; HR: heart rate

A.154: ECHO CHARACTERISTICS AT FOLLOW-UP

Echo FU	HF n = 5	No HF n = 107	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)

Time to FU Echo	47.8 ± 20.1	79.1 ± 39.2	0.079	0.98 (0.95-1.00; 0.094)	0.74 (0.60-0.88; 0.070)
BSA FU	1.9 ± 0.0	2.0 ± 0.2	0.366	0.01 (0.00-108.62; 0.330)	0.71 (0.58-0.84; 0.327)
BMI FU	27.4 ± 3.8	27.6 ± 5.5	0.955	0.99 (0.74-1.32; 0.954)	0.57 (0.13-1.00; 0.757)
Any RV dysfunction (incl borderline)	8 (100.0%)	69 (57.0%)	**0.021**	187301416 (0.00-NA; 0.997)	**0.72 (0.59-0.84; 0.042)**
Any RV dysfunction (excl borderline)	8 (100.0%)	67 (55.4%)	**0.020**	192892505 (0.00-NA; 0.997)	**0.72 (0.60-0.85; 0.035)**
Any RV dilatation (incl upper normal)	8 (100.0%)	96 (79.3%)	0.353	134622901 (0.00-NA; 0.998)	0.60 (0.43-0.77; 0.329)
Any RV dilatation (excl upper normal)	8 (100.0%)	86 (71.1%)	0.107	150276729 (0.00-NA, 0.998)	0.65 (0.49-0.80; 0.172)
RVOTlax	4.2 ± 0.6	3.7 ± 0.7	0.277	2.24 (0.51-9.86; 0.284)	0.72 (0.51-0.93; 0.194)
RVOTlax/BSA	2.4 ± 0.2	1.9 ± 0.4	0.054	35.74 (0.57-2254; 0.091)	**0.93 (0.83-1.00; 0.044)**
Difference RVOTlax	0.5 ± 0.6	0.2 ± 0.5	0.475	2.45 (0.22-27.85; 0.470)	0.66 (0.28-1.00; 0.437)
RVOTsax	4.2	3.8 ± 0.6	0.454	4.40 (0.11-182.59; 0.435)	0.80 (0.69-0.91; 0.308)
RVOTsax/BSA	2.2	1.9 ± 0.3	0.167	3330.06 (0.01-1.407E+9; 0.220)	0.95 (0.85-1.00; 0.137)
Difference RVOTsax	-0.2	0.3 ± 0.6	0.413	0.15 (0.00-12.64; 0.405)	0.92 (0.76-1.00; 0.181)
RVIT	5.0 ± 1.3	4.4 ± 0.9	0.217	1.87 (0.68-5.16; 0.225)	0.68 (0.32-1.00; 0.286)
Difference RVIT	1.2 ± 1.7	0.6 ± 0.7	0.216	3.70 (0.44-31.46; 0.231)	0.60 (0.04-1.00; 0.637)

TABLE

RV/LV	1.0 ± 0.4	0.9 ± 0.2	0.326	23.98 (0.04-14466.92; 0.331)	0.63 (0.16-1.00; 0.557)
Difference RV/LV	0.3	-0.2 ± 0.6	0.507	1766.71 (0.00-6.505E+9; 0.332)	0.94 (0.83-1.00; 0.148)
RV regional wall motion abnormalities	5 (100.0%)	54 (50.5%)	0.059	149581006 (0.00-NA, 0.997)	0.75 (0.60-0.89; 0.062)
Any RV RWMA	7 (87.5%)	68 (57.1%)	0.140	5.25 (0.63-44.02; 0.126)	0.65 (0.48-0.82; 0.152)
RV dyskinesia	1 (12.5%)	20 (16.9%)	1.000	0.70 (0.08-6.01; 0.745)	0.52 (0.32-0.72; 0.834)
RV akinesia or dyskinesia	4 (50.0%)	25 (21.2%)	0.081	3.72 (0.87-15.93; 0.077)	0.64 (0.43-0.86; 0.174)
Bulge	0 (0.0%)	18 (17.0%)	0.590	0.00 (0.00-NA; 0.998)	0.59 (0.37-0.81; 0.522)
Any bulge	0 (0.0%)	28 (23.5%)	0.198	0.00 (0.00-NA; 0.998)	0.62 (0.45-0.78; 0.266)
RV aneurysm	1 (20.0%)	11 (10.4%)	0.442	2.16 (0.22-21.08; 0.508)	0.55 (0.27-0.82; 0.717)
Any RV aneurysm	1 (12.5%)	22 (18.5%)	1.000	0.63 (0.07-5.39; 0.673)	0.53 (0.33-0.73; 0.777)
LVEDD	5.7 ± 1.8	5.1 ± 0.6	0.106	2.39 (0.80-7.14; 0.120)	0.52 (0.20-0.85; 0.879)
Difference LVEDD	0.2 ± 0.6	-0.1 ± 0.4	0.300	3.87 (0.31-48.01; 0.293)	0.56 (0.18-0.93; 0.696)
LVESD	4.6 ± 2.5	3.6 ± 0.7	**0.016**	**2.20 (1.01-4.78; 0.047)**	0.57 (0.27-0.87; 0.629)
Difference LVESD	0.3 ± 0.9	0.1 ± 0.4	0.260	3.25 (0.42-25.39; 0.262)	0.54 (0.18-0.91; 0.772)
IVS	0.8 ± 0.2	0.9 ± 0.2	0.264	0.03 (0.00-13.49; 0.268)	0.68 (0.45-0.90; 0.233)

Difference IVS	0.0 ± 0.1	0.1 ± 0.2	0.447	0.15 (0.00-20.59 0.447)	0.65 (0.46-0.84; 0.306)
Posterior LV wall	0.7 ± 0.1	0.8 ± 0.2	0.062	0.00 (0.00-1.07; 0.052)	**0.81 (0.64-0.98; 0.035)**

Difference posterior LV wall	-0.1 ± 0.2	0.0 ± 0.2	0.131	0.01 (0.00-3.83; 0.136)	0.73 (0.51-0.96; 0.115)
LA	4.1 ± 0.9	3.7 ± 0.5	0.161	4.33 (0.54-34.99; 0.169)	0.70 (0.31-1.00; 0.173)
Difference LA	0.1 ± 0.5	0.0 ± 0.5	0.874	1.18 (0.15-9.19; 0.872)	0.50 (0.22-0.79; 0.985)
LV regional wall motion abnormalities	3 (60.0%)	30 (28.0%)	0.151	3.85 (0.61-24.20; 0.151)	0.66 (0.40-0.92; 0.228)
Any LV RWMA	5 (62.5%)	43 (35.8%)	0.150	2.98 (0.68-13.10; 0.147)	0.63 (0.43-0.83; 0.208)
LV dyskinesia	2 (25.0%)	8 (6.9%)	0.126	4.50 (0.78-26.00; 0.093)	0.59 (0.37-0.82; 0.393)
LV aneurysm	0 (0.0%)	5 (4.7%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.28-0.77; 0.859)
Any LV aneurysm	0 (0.0%)	8 (6.7%)	1.000	0.00 (0.00-NA; 0.999)	0.53 (0.34-0.73; 0.751)
LVEF	43 ± 20	56 ± 12	**0.027**	**0.94 (0.89-1.00; 0.041)**	0.72 (0.50-0.94; 0.100)
Difference LVEF	-8 ± 11	-3 ± 9	0.249	0.95 (0.86-1.04; 0.251)	0.67 (0.41-0.92; 0.212)

Table A.15~~14~~: Echo characteristics at follow-up (FU). HF: heart failure; AUC: area under the curve; CI: confidence interval; BSA: body surface area; BMI: body mass index; RV: right ventricle/ventricular; RVOT: right ventricular outflow tract; PLAX: parasternal long axis view; PSAX: parasternal short axis view; RVIT: right ventricular inflow tract; RWMA: regional wall motion abnormalities; LV: left ventricle/ventricular; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; IVS: interventricular septum thickness; LVEF: left ventricular ejection fraction.