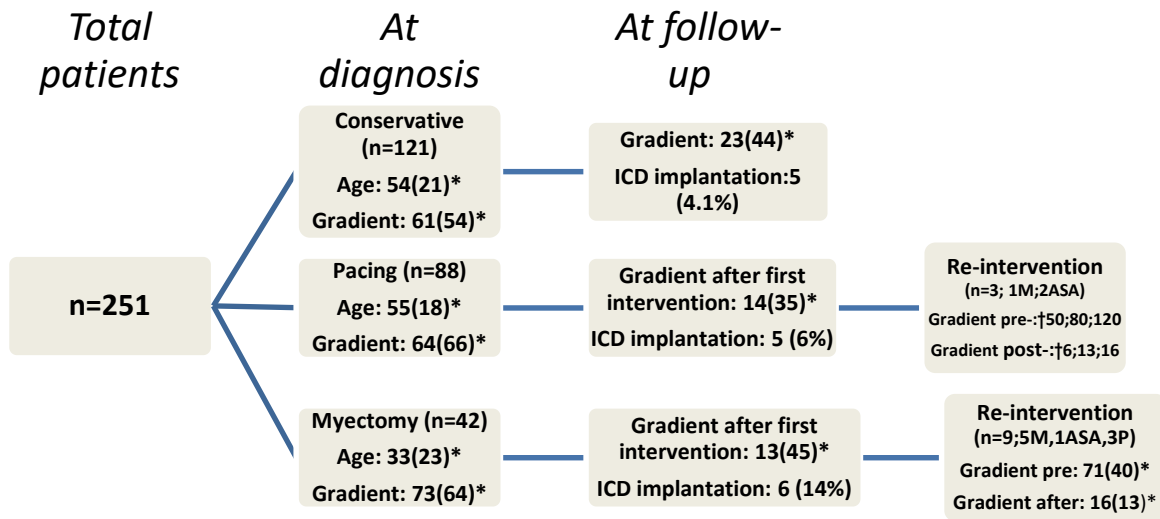
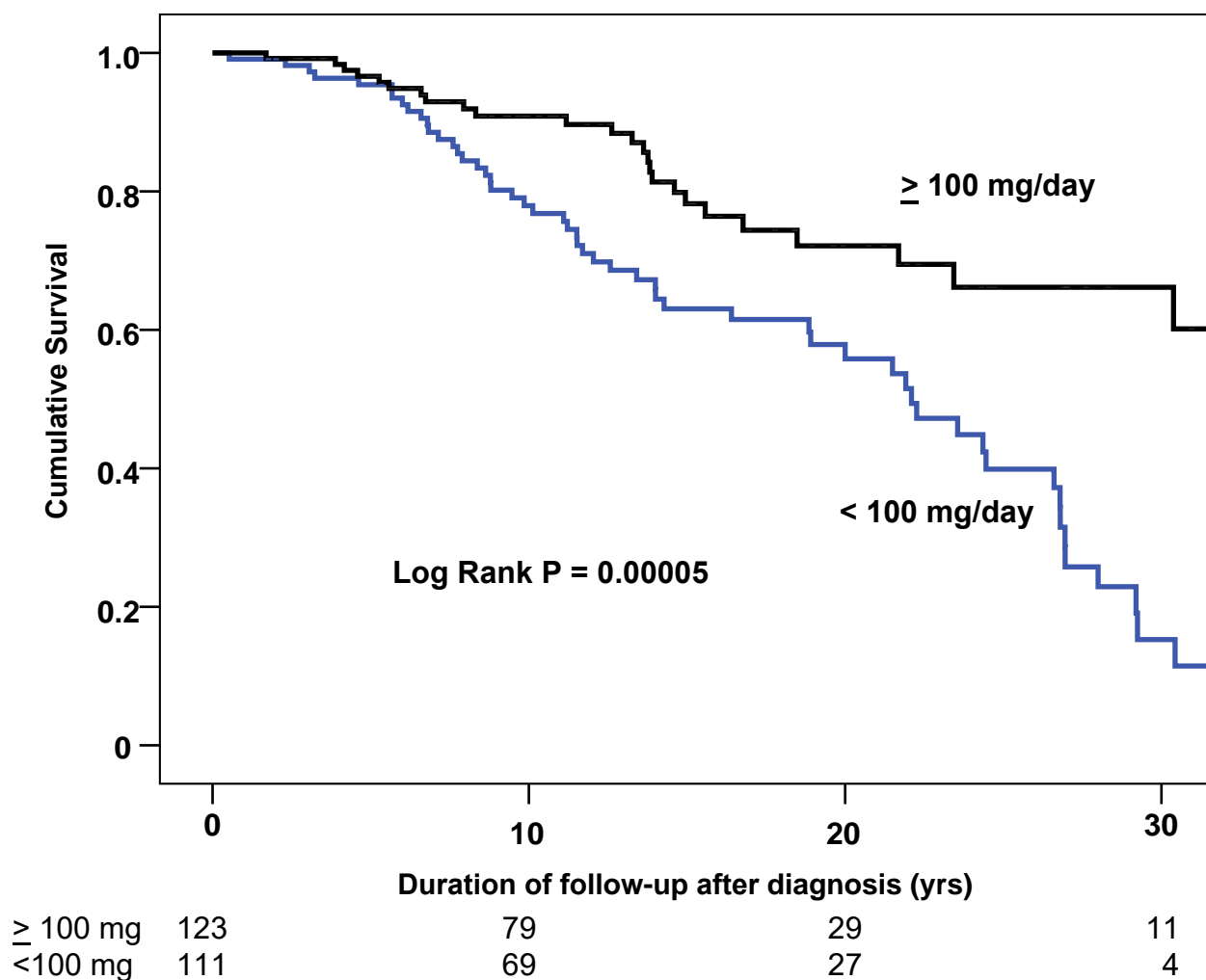


Supplementary Figure S1. Flow chart of the total HOCM cohort



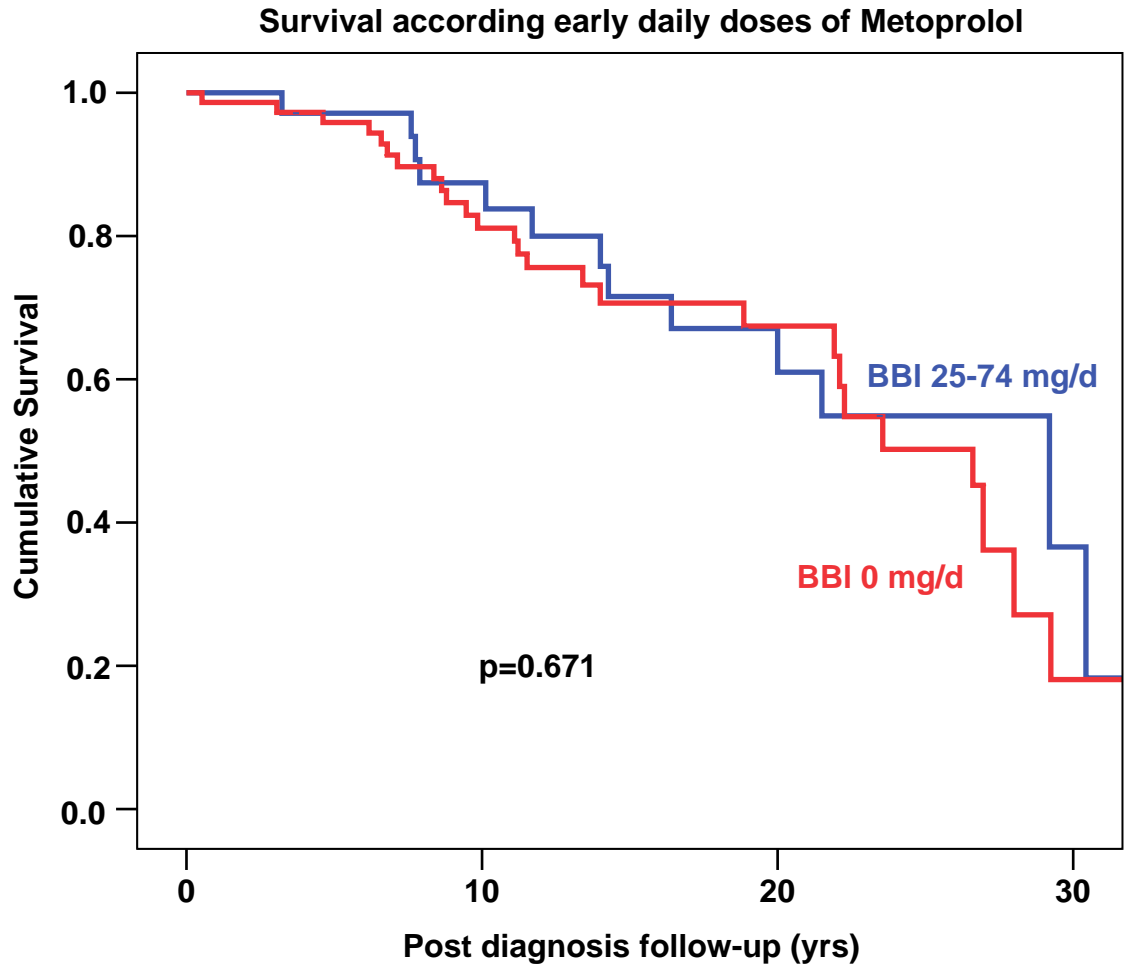
Flow chart: *= Median (IQR), †= individual value, M= Myectomy, ASA= Alcohol septal ablation, P=Pacing

Suppl. Figure S2



Supplementary Figure S2. Kaplan-Meier survival curves with all-cause mortality, according to daily dose of metoprolol equivalents

Figure S3



Supplementary Figure S3. Kaplan-Meier survival curves showing freedom from disease-related death in patients according to treatment started at the time of diagnosis. Patients receiving no beta-blockers at all are shown in red, and those receiving low doses of 25-74 mg/kgBW/day in metoprolol-equivalents are shown in blue.

SUPPLEMENTARY FILES

Supplementary Table S1 Medical therapy split between treatment groups							
Group	<i>Total cohort n=251</i>	<i>Conservative n=121</i>	<i>Pacing n=88</i>	<i>Myectomy n=42</i>	<i>Con v PM p-value</i>	<i>Con v Myect p-value</i>	<i>PM v Myect p-value</i>
Therapy at diagnosis:							
Beta-blockers use (%)	71.3	72.7	67.0	76.2	0.36	0.84	0.39
Verapamil/diltiazem use (%)	12.4	11.6	15.9	7.0	0.45	0.41	0.18
Therapy at latest FU: Yes vs No							
Beta-blocker use (%)	86.1	87.6	85.2	83.3	1.0	0.62	0.79
Verapamil/diltiazem use (%)	12.7	12.4	17.0	4.8	0.34	0.24	0.057
Any calcium-blocker use (%)	31.9	23.1	48.9	23.8	<0.001	0.95	0.005
Amiodarone use (%)	11.8	13.2	10.3	11.9	0.56	0.85	0.79
Disopyramide use (%)	11.8	12.2	6.9	20.9	0.21	0.16	0.18
ACE-inhibitor use (%)	25.5	28.1	22.7	23.8	0.49	0.61	0.97
Spironolacton use (%)	15.5	14.0	18.2	14.3	0.34	0.95	0.52

Abbreviations: Con=Conservative=only medical therapy, PM=pacemaker, Myect= Myectomy, FU=follow up, Calcium-channel blockers (inclusive Verapamil, Felodipine, Amlodipine, Nifedipine, Diltiazem). P-value= Mann-Whitney/Chi-square/Fisher exact test used as appropriate.

Supplementary Table S2: Risk-factors/protective factors at diagnosis for total mortality on Cox hazard regression

<i>Variable</i>	<i>B</i>	<i>SE</i>	<i>Exp(B)</i>	<i>95% CI Exp(B)</i>	<i>p-value</i>
Univariate Cox hazard analysis					
Female sex	0.812	0.221	2.253	1.461-3.474	<0.001
Age at diagnosis	0.055	0.008	1.057	1.041-1.073	<0.001
NYHA class ≥III vs ≤II	0.236	0.213	1.266	0.834-1.922	0.267
Body mass index	-0.045	0.028	0.956	0.906-1.009	0.105
Systemic hypertension Yes vs No	0.368	0.326	1.445	0.762-2.739	0.259
Diabetes mellitus Yes vs No	0.783	0.373	2.188	1.053-4.544	0.036
Coronary artery disease Yes vs No	1.469	0.434	4.343	1.855-10.167	0.001
Atrial fibrillation Yes vs No	0.431	0.721	1.539	0.375-6.320	0.550
Chronic kidney disease	0.330	0.728	1.392	0.334-5.792	0.650
Chronic Obstructive Pulmonary Disease	0.624	0.337	1.866	0.965-3.609	0.064
Family history of SCD Yes vs No	0.297	0.183	1.346	0.941-1.926	0.104
History of syncope Yes vs No	0.212	0.132	1.236	0.954-1.602	0.109
History of chest pain Yes vs No	-0.004	0.107	0.996	0.807-1.228	0.967
Septum (mm)	-0.033	0.024	0.968	0.923-1.015	0.174
Septum:cavity ratio	-1.528	0.935	0.217	0.035-1.357	0.102
Left Ventricle wall:cavity ratio	-1.336	1.504	0.263	0.014-5.016	0.375
Max.wall thickness (mm)	-0.032	0.024	0.969	0.924-1.016	0.187
Max.wall thickness ≥30 vs <30mm	0.591	0.716	1.806	0.444-7.355	0.409
Left Ventricle posterior wall (mm)	-0.002	0.040	0.998	0.922-1.080	0.961
Initial LVEDD	0.008	0.014	1.008	0.980-1.037	0.566
Initial Ejection Fraction (%)	-0.675	0.951	0.509	0.079-3.285	0.478
Left Atrium diameter (mm)	0.015	0.014	1.016	0.989-1.043	0.258
LVOT gradient at rest (mmHg)	0.002	0.003	1.002	0.997-1.007	0.402
LVOT-gradient at rest ≥30 vs <30 (mmHg)	0.570	0.301	1.767	0.979-3.190	0.059
LVOT-gradient at rest ≥50 vs <50 (mmHg)	0.561	0.239	1.752	1.096-2.799	0.019
12-lead QRS product	0.003	0.105	1.003	0.816-1.233	0.974
Sokolow -Lyon index (mm)	0.007	0.006	1.007	0.996-1.018	0.200
QRS-duration (ms)	0.004	0.004	1.004	0.995-1.013	0.368
QTC (ms)	0.007	0.003	1.007	1.002-1.012	0.009
Beta-blocker Yes vs No	-0.785	0.215	0.456	0.299-0.696	<0.001
Beta-blocker dose mg/day	-0.006	0.001	0.994	0.991-0.997	<0.001
Beta-blocker ≥100mg vs <100mg	-0.925	0.235	0.397	0.250-0.628	<0.001
Verapamil,Diltiazem use Yes vs No	1.115	0.252	3.051	1.863-4.995	<0.001
Verapamil,Diltiazem daily dose, mg/day	0.004	0.001	1.004	1.002-1.006	<0.001
Statin treatment Yes vs No	-0.624	0.402	0.536	0.244-1.179	0.121
Multivariate Cox hazard analysis					
Female sex	0.805	0.252	2.237	1.367-3.663	0.001
Age	0.050	0.008	1.051	1.035-1.068	<0.001
LVOT-gradient at rest ≥50 vs <50 (mmHg)	0.708	0.257	2.029	1.226-3.58	0.006
Beta-blocker dose mg/day	-0.003	0.001	0.997	0.995-1.000	0.064

Abbreviations: NYHA=New York Heart Association Class, SCD=Sudden Cardiac Death, LVEDD= Left Ventricle End Diastolic Diameter, LVOT=Left Ventricular outflow tract. Significant negative values of B suggest reduction in risk

Supplementary Table S3: Risk-factors/protective factors at diagnosis for heart failure death on Cox hazard regression

Variable	B	SE	Exp(B)	95% CI Exp(B)	p-value
Univariate Cox hazard analysis					
Female sex	0.752	0.328	2.121	1.116-4.034	0.022
Age at diagnosis	0.065	0.013	1.067	1.041-1.094	<0.001
NYHA class ≥III vs ≤II	0.323	0.320	1.382	0.739-2.586	0.312
Body mass index	0.009	0.046	1.009	0.922-1.105	0.842
Systemic hypertension Yes vs No	0.488	0.488	1.629	0.626-4.241	0.317
Diabetes mellitus Yes Vs No	0.268	0.731	1.307	0.312-5.471	0.714
Coronary artery disease Yes vs No	0.537	1.025	1.710	0.230-12.742	0.600
Atrial fibrillation Yes vs No	0.840	0.734	2.316	0.550-9.760	0.252
Chronic kidney disease	0.238	1.036	1.269	0.166-9.671	0.818
Chronic Obstructive Pulmonary Disease	0.740	0.481	2.097	0.817-5.384	0.124
Family history of SCD Yes vs No	0.100	0.236	1.105	0.697-1.753	0.670
History of syncope Yes vs No	0.151	0.195	1.163	0.794-1.704	0.439
History of chest pain Yes vs No	0.089	0.164	1.093	0.792-1.508	0.587
Septum (mm)	-0.024	0.036	0.976	0.909-1.048	0.508
Septum:cavity ratio	-0.411	1.411	0.663	0.042-10.535	0.771
Left ventricle wall:cavity ratio	1.319	2.109	3.738	0.060-233.099	0.532
Max.wall thickness (mm)	-0.024	0.036	0.976	0.909-1.048	0.504
Max.wall thickness ≥30 vs <30mm	-0.314	0.729	0.730	0.175-3.050	0.666
Left ventricle posterior wall (mm)	0.001	0.063	1.001	0.884-1.132	0.991
Initial LVEDD	-0.006	0.021	0.994	0.954-1.037	0.787
Initial Ejection Fraction (%)	-1.641	1.403	0.194	0.012-3.032	0.242
Left atrium diameter (mm)	-0.008	0.022	0.992	0.951-1.035	0.712
LVOT gradient at rest (mmHg)	0.002	0.004	1.002	0.995-1.010	0.554
LVOT-gradient at rest ≥30 vs <30 (mmHg)	0.738	0.480	2.092	0.817-5.357	0.124
LVOT-gradient at rest ≥50 vs <50 (mmHg)	0.514	0.355	1.672	0.833-3.356	0.148
12-lead QRS product	0.009	0.157	1.009	0.742-1.373	0.954
Sokolow -Lyon index (mm)	0.009	0.008	1.009	0.994-1.026	0.246
QRS-duration (ms)	0.005	0.007	1.005	0.991-1.018	0.483
QTC (ms)	0.007	0.004	1.007	0.999-1.016	0.096
Beta-blocker Yes vs No	-0.813	0.326	0.443	0.234-0.840	0.013
Beta-blocker dose mg/day	-0.008	0.003	0.992	0.986-0.992	0.002
Beta-blocker ≥100mg vs <100mg	-1.187	0.375	0.305	0.146-0.636	0.002
Verapamil,Diltiazem use Yes vs No	0.940	0.408	2.561	1.151-5.699	0.021
Verapamil,Diltiazem daily dose, mg/day	0.004	0.002	1.004	1.001-1.007	0.008
Statin treatment Yes vs No	-0.035	0.153	0.966	0.716-1.303	0.819

Abbreviations: NYHA=New York Heart Association Class, SCD=Sudden Cardiac Death, LVEDD= Left Ventricle End Diastolic Diameter, LVOT=Left Ventricular outflow tract. Significant negative values of B suggest reduction in risk.

Supplementary Table S4: Characterization and co-morbidity at diagnosis according to early beta-blocker dose, as median (IQR) unless otherwise specified (n=234, in 17 patients initial dose unknown).

	0-99 mg (n=111)	≥100mg (n=123)	P-value
Female (%) Male (%)	55 45	43 57	0.070 F/M
Age at diagnosis	60 (25)	52 (32)	<0.001
NYHA class (Mean±SD)	2.2 (0.76)	2.1 (0.76)	0.90
NYHA class ≥III (%)	40	41	0.90
LVOT-gradient(mm Hg)	65 (50)	58 (66)	0.30
LVOT ≥50 mmHg (%)	70	59	0.076
Max wall thickness	19 (6)	20 (6)	0.41
Body mass index	26 (5)	26 (7)	0.555
Systemic hypertension (%)	15.3	11.4	0.442
Atrial fibrillation (%)	0.9	0.8	1.000
Statin therapy (%)	5.4	10.6	0.15
Diabetes mellitus (%)	6.3	4.9	0.63
Coronary artery disease (%)	4.5	2.4	0.48
Chronic kidney disease (%)	1.8	0.8	0.61
Chronic pulmonary obstructive disease (%)	7.2	7.3	0.96

Abbreviations: IQR=interquartile range, NYHA=New York Heart Association Class. LVOT= Left Ventricular Outflow Tract, P-value= Mann-Whitney/Chi-square/Fisher exact test used as appropriate.

Supplementary Table S5: Predictive-factors/protective factors at latest follow-up for heart failure death on Cox hazard regression

<i>Variable</i>	<i>B</i>	<i>SE</i>	<i>Exp(B)</i>	<i>95% CI Exp(B)</i>	<i>p-value</i>
Univariate Cox hazard analysis					
Female sex	0.752	0.328	2.121	1.116-4.034	0.022
Age	0.034	0.011	1.035	1.012-1.057	0.002
NYHA class ≥III vs ≤II	0.554	0.462	1.740	0.704-4.304	0.230
Body mass index	0.000	0.014	1.000	0.973-1.028	0.997
Systemic hypertension Yes vs No	0.772	0.318	2.164	1.160-4.038	0.015
Diabetes mellitus Yes Vs No	0.219	0.532	1.245	0.439-3.533	0.680
Coronary artery disease Yes vs No	0.173	0.445	1.189	0.497-2.842	0.697
Atrial fibrillation Yes vs No	0.263	0.321	1.301	0.693-2.443	0.412
Chronic kidney disease	0.507	0.741	1.659	0.389-7.088	0.494
Chronic Obstructive Pulmonary Disease	0.774	0.446	2.168	0.905-5.194	0.083
Septum (mm)	-0.053	0.042	0.948	0.873-1.030	0.208
Septum:cavity ratio	1.903	1.610	6.722	0.286-157.840	0.237
Left ventricle wall:cavity ratio	1.802	1.267	6.060	0.506-72.600	0.155
Max.wall thickness (mm)	-0.012	0.041	0.988	0.912-1.070	0.761
Left ventricle posterior wall (mm)	0.068	0.066	1.071	0.940-1.219	0.303
LVEDD	-0.041	0.028	0.960	0.908-1.015	0.149
Ejection Fraction (%)	0.200	1.239	1.221	0.108-13.851	0.872
Left atrium diameter (mm)	-0.009	0.028	0.991	0.938-1.047	0.742
LVOT gradient at rest (mmHg)	0.012	0.004	1.012	1.004-1.019	0.002
LVOT-gradient at rest ≥30 vs <30 (mmHg)	0.021	0.006	1.022	1.009-1.034	0.001
LVOT-gradient at rest ≥50 vs <50 (mmHg)	0.021	0.006	1.022	1.009-1.034	<0.001
12-lead QRS product	-3.215	3.795	0.040	0.000-68.231	0.397
Sokolow -Lyon index (mm)	-0.537	0.960	0.584	0.089-3.839	0.576
QRS-duration (ms)	-1.26	1.21	0.000	0.000-9.652	0.301
QTC (ms)	-0.042	0.035	0.959	0.894-1.028	0.234
Myectomy	0.231	0.203	1.237	0.831-1.841	0.295
Pacemaker therapy	0.014	0.163	1.014	0.737-1.395	0.933
Beta-blocker Yes vs No	-0.526	0.368	0.591	0.287-1.216	0.153
Beta-blocker dose mg/day	-0.004	0.002	0.996	0.992-0.999	0.015
Beta-blocker ≥100mg vs <100mg	-0.648	0.319	0.523	0.280-0.977	0.042
Verapamil,Diltiazem use Yes vs No	1.030	0.389	2.801	1.306-6.008	0.008
Verapamil,Diltiazem daily dose, mg/day	0.004	0.002	1.004	1.000-1.007	0.040
Disopyramide Yes vs No	-1.707	1.013	0.181	0.025-1.322	0.092
ACE-I Yes vs No	-0.241	0.162	0.786	0.572-1.081	0.139
Spirolactone Yes vs NO	-0.108	0.193	0.898	0.616-1.310	0.577
Statin treatment Yes vs No	-0.833	0.528	0.435	0.154-1.233	0.115

Abbreviations: NYHA=New York Heart Association Class, LVEDD= Left Ventricle End Diastolic Diameter, LVOT=Left Ventricular outflow tract. Significant negative values of B suggest reduction in risk.

Supplementary Table S6 : Predictor factors/protective factors for total mortality on Cox hazard regression as recorded at latest follow-up

Variable	B	SE	Exp(B)	95% CI expB	P-value
Univariate Cox hazard analysis					
Female sex	0.812	0.221	2.253	1.461-3.474	<0.001
Age at follow-up	0.026	0.007	1.026	1.012-1.040	<0.001
NYHA class ≥III vs ≤II	0.760	0.290	2.137	1.210-3.775	0.009
Body mass index	0.000	0.004	1.000	0.991-1.009	0.993
Systemic hypertension Yes vs No	0.417	0.214	1.518	0.999-2.308	0.051
Diabetes mellitus Yes Vs No	0.025	0.313	1.025	0.556-1.893	0.936
Coronary artery disease Yes vs No	0.546	0.265	1.726	1.027-2.901	0.039
Chronic kidney disease	0.074	0.432	1.077	0.462-2.512	0.864
Atrial fibrillation Yes vs No	0.389	0.213	1.475	0.972-2.238	0.068
Chronic Obstructive Pulmonary Disease	0.537	0.323	1.710	0.908-3.221	0.097
Septum (mm)	0.017	0.027	1.017	0.966-1.072	0.520
Septum:cavity ratio	1.211	1.002	3.357	0.471-23.936	0.227
Max wall thickness (mm)	0.043	0.026	1.044	0.992-1.099	0.097
Left ventricle posterior wall(mm)	0.034	0.047	1.035	0.944-1.135	0.469
Left ventricle wall:cavity ratio	1.241	1.004	3.457	0.483-24.727	0.217
LVEDD (mm)	-0.029	0.018	0.972	0.938-1.007	0.117
Ejection fraction (%)	0.848	0.861	2.336	0.433-12.612	0.324
Left atrium diameter (mm)	-0.014	0.017	0.986	0.954-1.019	0.397
LVOT gradient (mmHg)	0.012	0.002	1.012	1.008-1.017	<0.001
LVOT gradient at rest ≥30 vs <30 (mm Hg)	0.015	0.005	1.016	1.005-1.026	0.003
LVOT-gradient at rest ≥50 vs <50 (mmHg)	0.015	0.005	1.016	1.005-1.026	0.002
Myectomy	0.176	0.135	1.193	0.916-1.553	0.190
Pacemaker therapy	-0.054	1.07	0.948	0.769-1.169	0.617
QTC (ms)	-0.002	0.004	0.998	0.990-1.007	0.669
Beta-blocker dose mg/day	-0.003	0.001	0.997	0.995-0.999	0.003
Verapamil/Diltiazem use Yes vs No	0.983	0.254	2.672	1.625-4.394	<0.001
Verapamil/Diltiazem dose mg/day	0.003	0.001	1.003	1.001-1.006	0.002
Amiodarone use Yes vs No	-0.269	0.271	0.764	0.449-1.299	0.320
Disopyramide use Yes vs No	-0.539	0.394	0.587	0.269-1.264	0.172
ACE-inhibitor use Yes vs No	-0.085	0.126	0.919	0.575-1.468	0.723
Spirolacton use Yes vs No	0.001	0.136	1.001	0.766-1.0307	0.995
Statin treatment Yes vs No	-0.962	0.371	0.382	0.185-0.791	0.010
Implantable Cardioverter Defibrillator (ICD)	-1.511	0.592	0.221	0.069-0.704	0.011
Multivariate Cox hazard analysis (98% complete data)					
Female sex	1.131	0.284	3.099	1.777-5.406	<0.001
Age	0.019	0.008	1.019	1.003-1.035	0.017
LVOT-gradient at rest ≥50 vs <50 (mmHg)	0.052	0.015	1.053	1.023-1.083	<0.001
Max wall thickness (mm)	0.071	0.030	1.074	1.013-1.139	0.017
Beta-blocker dose mg/day	-0.004	0.001	0.996	0.993-0.999	0.008

Abbreviations: NYHA=New York Heart Association Class, LVEDD=Left Ventricle end-diastolic diameter, LVOT=Left Ventricular outflow tract, ACE=angiotensin-converting-enzyme. Significant negative values of B suggest reduction in risk.

Supplementary Table S7: Characterization and comorbidity at diagnosis and at latest follow-up according to post-interventional daily beta-blocker dosage 25-99mg vs ≥100mg in interventional groups (n=108).			
	25-99 mg (n=24)	≥100mg (n=84)	P-value
Female (%)	46	49	0.821(M/F)
Male (%)	54	51	
Age at intervention (Mean±SD)	56.0 (24.7)	54.1(20.0)	0.691
NYHA class (Mean±SD)			
Diagnosis	2.2 (0.75)	2.1 (0.66)	0.699
FU	1.8 (0.61)	1.7 (0.70)	0.590
NYHA class ≥III (%)			
Diagnosis	46	41	0.647
FU	9	9	0.987
LVOT mmHg (Median/IQR)			
Diagnosis	67 (47)	65 (66)	0.952
FU	12 (31)	13 (30)	0.882
LVOT ≥50 mmHg (%)			
Diagnosis	79	69	0.445
FU	25	17	0.356
Max wall thickness, mm (Median/IQR)			
Diagnosis	19 (8)	20 (6)	0.963
FU	17 (6)	18 (6)	0.833
Body mass index (Median/IQR)			
Diagnosis	26 (7)	27 (6)	0.024
FU	25 (12)	29 (7)	0.026
Systemic hypertension (%)			
Diagnosis	12.5	8.3	0.689
FU	37.5	39.3	1.000
Atrial fibrillation (%)			
Diagnosis	4.2	2.4	0.533
FU	29.2	40.5	0.351
Statin treatment (%)			
Diagnosis	4.2	7.1	1.000
FU	8.3	19.0	0.352
Diabetes mellitus (%)			
Diagnosis	16.7	4.8	0.071
FU	20.8	16.7	0.761
Coronary artery disease (%)			
Diagnosis	4.2	4.8	1.000
FU	25.0	14.3	0.225
Chronic kidney disease (%)			
Diagnosis	4.2	1.2	0.397
FU	8.3	6.0	0.650
Chronic pulmonary obstructive disease (%)			
Diagnosis	0.0	9.5	0.195
FU	0.0	11.9	0.113

Abbreviations: IQR=interquartile range, NYHA=New York Heart Association Class. LVOT= Left Ventricular Outflow Tract, FU= follow up, P= Mann-Whitney/Chi-square/Fisher exact test used as appropriate.

Supplementary Table S8. Characterization of co-morbidities in total cohort at diagnosis and at latest follow-up: comparison between survivors and disease-related (“cardiac”) and non-cardiac deaths. Values as median (IQR) unless otherwise specified

	Survivors (S) (n=161)	Cardiac deaths (CD) (n=65)	Non- cardiac deaths (NCD) (n=25)	P-value S/CD,S/NCD, CD/NCD	
				Diagnosis	Follow-up (FU)
Body mass index (Median+IQR)				0.024/	0.039/
Diagnosis	27 (6)	25 (6)	25 (5)	0.11/	FV/
FU	27 (7)	23 (8)	FV*	0.99	FV
Systemic hypertension (%)				0.95/	0.17/
Diagnosis	14.3	13.8	8.0	0.54/	0.65/
FU	34.2	44.6	40.0	0.72	0.81
Statin therapy (%)				0.91/	0.011/
Diagnosis	8.7	9.2	4.0	0.75/	0.011/
FU	26.1	10.8	4.0	0.81	0.44
Diabetes mellitus (%)				0.21/	0.97/
Diagnosis	3.7	7.7	12.0	0.10/	0.91/
FU	13.7	13.8	12.0	0.68	0.85
Coronary artery disease (%)				0.11/	0.06/
Diagnosis	1.9	6.2	8.0	0.13/	0.031/
FU	9.3	18.5	24.0	0.67	0.56
Chronic kidney disease (%)				0.20/	0.12/
Diagnosis	0.6	3.1	0.0	0.91/	0.52/
FU	2.5	7.7	4.0	0.45	0.65
Chronic obstructive pulmonary disease (%)				0.15/	0.32/
Diagnosis	4.3	9.2	16.0	0.04/	0.12/
FU	6.8	10.8	16.0	0.46	0.49

Abbreviations: Cardiac deaths= disease-related deaths, IQR=Interquartile Range, NYHA=New York Heart Association Class, *FV= Few Values, P-values=Mann-Whitney/Chi-square/Fisher exact test used as appropriate.