

## SUPPLEMENTARY DATA

**Table S1.** Distribution of pathogenic/likely pathogenic variants according to functional gene groups in the overall cohort

Functional gene groups	Frequency	Percent
Cytoskeleton/Z-disk genes ( <i>DMD, FLNC, JHP2</i> )	30	9.87
Desmosomal genes ( <i>DSC2, DSG2, DSP, PKP2</i> )	32	10.53
Nuclear envelope genes ( <i>EMD, LMNA, TMEM43</i> )	40	13.16
Motor sarcomeric genes ( <i>ACTC1, MYBPC3, MYH7, TNNI3, TNNT2, TPM1</i> )	46	15.13
<i>TTN</i> gene	107	35.20
Others ( <i>BAG3, PLN, RBM20, PRDM16, NKX2-5, FKTN</i> )	49	16.12
Total	304	100.00

Functional gene groups	Frequency	Percent	
Cytoskeleton/ Z-disk genes	30	9.87	
	<i>DMD</i>	13	4.28
	<i>FLNC</i>	16	5.26
	<i>JPH2</i>	1	0.33
Desmosomal genes	32	10.53	
	<i>DSC2</i>	1	0.33

	<i>DSG2</i>	3	0.99
	<i>DSP</i>	27	8.88
	<i>PKP2</i>	1	0.33
Nuclear envelope genes		40	13.16
	<i>EMD</i>	1	0.33
	<i>LMNA</i>	36	11.84
	<i>TMEM43</i>	3	0.99
Motor sarcomeric genes		46	15.13
	<i>MYBPC3</i>	11	3.62
	<i>MYH7</i>	11	3.62
	<i>TNNT2</i>	13	4.28
	<i>TPM1</i>	7	2.30
	<i>ACTC1</i>	1	0.33
	<i>TNNI3</i>	3	0.99
<i>TTN</i> gene		107	35.20
Others		49	16.12
	<i>BAG3</i>	23	7.57
	<i>RBM20</i>	22	7.24
	<i>PLN</i>	1	0.33

	<i>PRDM16</i>	1	0.33
	<i>NKX2-5</i>	1	0.33
	<i>FKTN</i>	1	0.33
Total		304	100.00

**Table S2.** Medical treatment and dose according to left ventricular reverse remodeling at mid-term (n = 711)

	Total (n=711)	With LVRR (n = 307)	Without LVRR (n = 404)	P
<i>Baseline</i>				
β-blocker	583 (83.29)	265 (86.32)	318 (80.92)	.057
Half dose	255 (43.74)	108 (40.75)	147 (46.23)	.185
ACE inhibitor/ARB	579 (82.71)	246 (80.13)	333 (84.73)	.110
Half dose	257 (44.39)	118 (47.97)	139 (41.74)	.136
Sacubitril/valsartan	50 (7.14)	32 (10.42)	18 (4.58)	.003
Half dose	13 (26.00)	8 (25.00)	5 (27.78)	.830
MRA	314 (44.86)	161 (52.44)	153 (38.93)	<.001
Half dose	297 (94.59)	153 (95.03)	144 (94.12)	.721
<i>Mid-term</i>				
β-blocker	617 (90.60)	282 (93.69)	335 (88.16)	.014
Half dose	368 (59.64)	184 (65.25)	184 (54.93)	.009
ACE inhibitor/ARB	524 (77.06)	215 (71.67)	309 (81.32)	.003

Half dose	307 (58.70)	140 (65.12)	167 (54.22)	.013
Sacubi- tril/valsartan	122 (17.99)	74 (24.67)	48 (12.70)	<.001
Half dose	85 (69.67)	55 (74.32)	30 (62.50)	.165
MRA	413 (61.00)	199 (66.33)	214 (56.76)	.011
Half dose	401 (97.09)	193 (96.98)	208 (97.20)	.898

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; MRA, mineralcorticoid receptor antagonist.

Values are expressed as No. (%). Half dose= percentage of patients achieving at least 50% of target dose

**Table S3.** Medical treatment and dose at mid-term according to functional gene group

	Total (n = 703)	Negative genotype (n = 399)	Cyto-skeleton/Z-disk (n = 30)	Desmo-somal (n = 32)	Nuclear envelope (n = 40)	Motor sarco-mer (n = 46)	TTN (n = 107)	Other genes (n = 49)	P
β-blocker	613 (90.68)	356 (92.71)	28 (93.33)	28 (87.50)	28 (75.68)	38 (88.37)	96 (93.20)	39 (82.98)	.010
Half dose	366 (59.71)	219 (61.52)	13 (46.43)	14 (50.00)	11 (39.29)	24 (63.16)	65 (67.71)	20 (51.28)	.054
ACE inhibitor/ARB	520 (77.04)	293 (76.50)	26 (86.67)	26 (81.25)	28 (75.68)	33 (76.74)	78 (75.73)	36 (76.60)	.910
Half dose	306 (58.96)	187 (64.04)	17 (65.38)	7 (26.92)	10 (35.71)	19 (57.58)	44 (56.41)	22 (61.11)	.002
Sacubitril/valsartan	121 (17.98)	77 (20.16)	3 (10.00)	4 (12.50)	2 (5.41)	6 (13.95)	21 (20.39)	8 (17.39)	.236
Half dose	84 (69.42)	58 (75.32)	3 (100)	3 (75.00)	2 (100)	2 (33.33)	11 (52.38)	5 (62.50)	.114
MRA	409 (60.86)	231 (60.47)	16 (55.17)	18 (56.25)	17 (45.95)	30 (69.77)	69 (66.99)	28 (60.87)	.301

Half	397	223	16 (100)	18 (100)	17 (100)	30 ( 100)	65	28 (100)	.480
dose	(97.07)	(96.54)					(94.20)		

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; MRA, mineralcorticoid receptor antagonist.

Values are expressed as No. (%). Half dose= percentage of patients achieving at least 50% of target dose (target dose recommended in 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure).<sup>15</sup>

**Table S4.** Outcomes and Events during follow-up according to left ventricular reverse remodeling at mid-term (n = 711)

	Total (n = 711)	With LVRR (n =307)	Without LVRR (n = 404)	P
New onset AF	71 (12.59)	27 (10.67)	44 (14.15)	.216
Stroke	26 (3.66)	7 (2.28)	19 (4.70)	.088
Sustained ventricular arrhythmia	51 (7.17)	11 (3.58)	40 (9.90)	.001
Appropriate ICD therapy	47 (6.61)	11 (3.58)	36 (8.91)	.005
Aborted SCD	7 (1.00)	1 (0.33)	6 (1.50)	.120
Heart transplant	70 (9.85)	10 (3.26)	60 (14.85)	<.001
LVAD implantation	19 (2.67)	5 (1.63)	14 (3.47)	.133
Composite MACE	156 (21.94)	35 (11.40)	121 (29.95)	<.001
Composite ESHF	97 (13.64)	17 (5.54)	80 (19.80)	<.001
Composite MVA	79 (11.11)	19 (6.19)	60 (14.85)	<.001

AF, atrial fibrillation; ESHF, end-stage heart failure; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; MACE, major adverse cardiovascular events; MVA, malignant ventricular arrhythmia; SCD, sudden cardiac death.

Values are expressed as No. (%).

**Table S5.** Outcomes and events according to left ventricular reverse remodeling at long-term

	Total (n = 284)	Persistent recovery (n = 211)	Worsening LVEF (n = 73)	P
New onset AF	27 (11.54)	16 (8.94)	11 (20.00)	.025
Stroke	7 (2.46)	3 (1.42)	4 (5.48)	.054
Sustained ventricular arrhythmia	11 (3.87)	4 (1.90)	7 (9.59)	.003
Appropriate ICD therapy	11 (3.87)	4 (1.90)	7 (9.59)	.003
Aborted SCD	1 (0.36)	0 (0.00)	1 (1.37)	.091
Heart transplant	9 (3.17)	1 (0.47)	8 (10.96)	<.001
LVAD implantation	5 (1.76)	1 (0.47)	4 (5.48)	.005
Composite MACE	33 (11.62)	15 (7.11)	18 (24.66)	<.001
Composite ESHF	16 (5.63)	3 (1.42)	13 (17.81)	<.001
Composite MVA	18 (6.34)	9 (4.27)	9 (12.33)	.015

AF, atrial fibrillation; ESHF, end-stage heart failure; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; MACE, major adverse cardiovascular events; MVA, malignant ventricular arrhythmia; SCD, sudden cardiac death.

Values are expressed as No. (%). Events from mid-term echocardiogram to last follow-up.

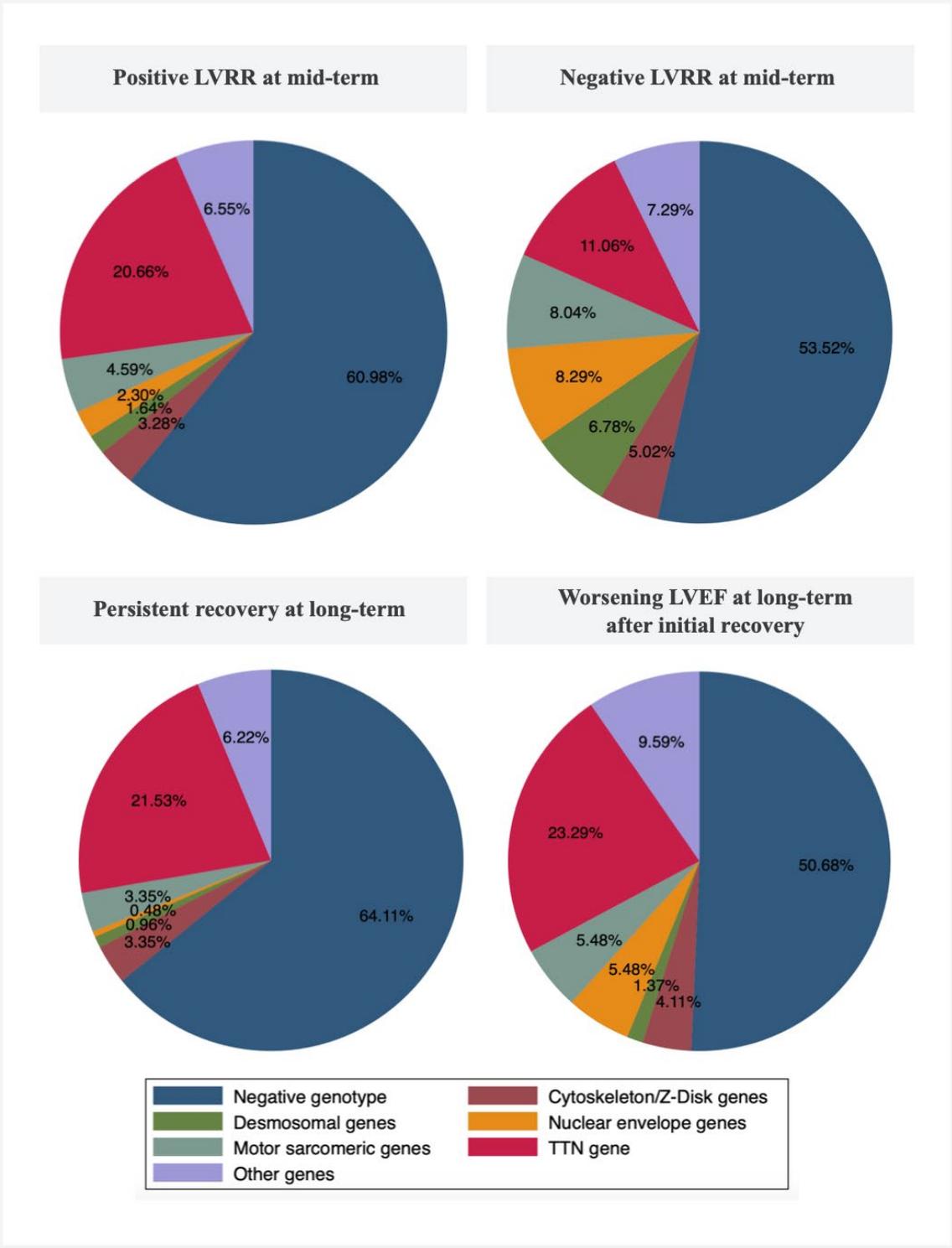
**Table S6.** Outcomes and events according to left ventricular reverse remodeling at mid- and long-term

	Total (n = 688)	No recovery (n = 404)	Transient re- covery (n = 73)	Persistent recovery (n = 211)	<i>P</i>
New onset AF	71 (13.03)	44 (14.15)	11 (20.00)	16 (8.94)	.069
Stroke	26 (3.78)	19 (4.70)	4 (5.48)	3 (1.42)	.093
Sustained ventricular arrhythmia	51 (7.41)	40 (9.90)	7 (9.59)	4 (1.90)	.001
Appropriate ICD therapy	47 (6.83)	36 (8.91)	7 (9.59)	4 (1.90)	.003
Aborted SCD	7 (1.03)	6 (1.50)	1 (1.37)	0 (0.00)	.209
Heart transplant	69 (10.03)	60 (14.85)	8 (10.96)	1 (0.47)	<.001
LVAD implantation	19 (2.76)	14 (3.47)	4 (5.48)	1 (0.47)	.032
Composite MACE	154 (22.38)	121 (29.95)	18 (24.66)	15 (7.11)	<.001
Composite ESHF	96 (13.95)	80 (19.80)	13 (17.81)	3 (1.42)	<.001
Composite MVA	78 (11.34)	60 (14.85)	9 (12.33)	9 (4.27)	<.001

AF, atrial fibrillation; ESHF, end-stage heart failure; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; MACE, major adverse cardiovascular events; MVA, malignant ventricular arrhythmia; SCD, sudden cardiac death.

Values are expressed as No. (%). Events from mid-term echocardiogram to last follow-up.

**Figure S1.** Distribution of genes according to the functional gene group and left ventricular reverse remodelling at mi-d and long-term.



**Figure S2.** Distribution of genes according to the functional gene group in patients with an initial complete recovery

