Table 1 of the supplementary data. Full list of the 213 genes related to inherited cardiac diseases included in the next-generation sequencing panel

Gene name	Codified protein
AARS2	Alanine--tRNA ligase, mitochondrial
ABCC9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9
ACAD9	Acyl-CoA dehydrogenase family member 9, mitochondrial
ACADM	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial
ACADVL	Very long-chain specific acyl-CoA dehydrogenase, mitochondrial
ACTA1	Actin, alfa 1, skeletal muscle
ACTA2	Actin, aortic smooth muscle
ACTC1	Actin, alpha cardiac muscle 1
ACTN2	Alpha-actinin-2
ACVRL1	Serine/threonine-protein kinase receptor R3
ADAMTSL4	ADAMTS-like protein 4
AGK	Acylglycerol kinase, mitochondrial
AGL	Glycogen debranching enzyme
AGPAT2	1-acyl-sn-glycerol-3-phosphate acyltransferase beta
AKAP9	A-kinase anchor protein 9
ALMS1	Alstrom syndrome protein 1
ANK2	Ankyrin 2
ANK3	Ankyrin-3
ANKRD1	Ankyrin repeat domain-containing protein 1
APOA5	Apolipoprotein A-V
APOB	Apolipoprotein B-100
APOC3	Apolipoprotein C-III
ATPAF2	ATP synthase mitochondrial F1 complex assembly factor 2
BAG3	BAG family molecular chaperone regulator 3
BMPR1B	Bone morphogenetic protein receptor type-1B
BMPR2	Bone morphogenetic protein receptor type II
BRAF	Serine/threonine-protein kinase B-raf

BSCL2	Seipin
CACNA1C	Voltage-dependent L-type calcium channel subunit alpha-1C
CACNA1D	Voltage-dependent L-type calcium channel subunit alpha-1D
CACNA2D1	Voltage-dependent calcium channel subunit alpha-2/delta-1
CACNB2	Voltage-dependent L-type calcium channel subunit beta-2
CALM1	Calmodulin
CALM2	Calmodulin
CALR3	Calreticulin 3
CAPN3	Calpain-3
CASQ2	Calsequestrin-2
CAV1	Caveolin-1
CAV3	Caveolin-3
CBL	E3 ubiquitin-protein ligase CBL
CBS	Cystathionine beta-synthase
CETP	Cholesteryl ester transfer protein
COL1A1	Collagen alpha-1(I) chain
COL1A2	Collagen alpha-2(I) chain
COL3A1	Collagen alpha-1(III) chain
COL5A1	Collagen alpha-1(V) chain
COL5A2	Collagen alpha-2(V) chain
COQ2	4-hydroxybenzoate polyprenyltransferase, mitochondrial
COX15	Cytochrome c oxidase assembly protein COX15 homolog
COX6B1	Cytochrome c oxidase subunit 6B1
CRELD1	Cysteine-rich with EGF-like domain protein 1
CRYAB	Alpha-crystallin B chain
CSRP3	Cysteine and glycine-rich protein 3
CTF1	Cardiotrophin 1
CTNNA3	Catenin alpha-3
DES	Desmin
DLD	Dihydrolipoyl dehydrogenase, mitochondrial

DMD	Dystrophin
DNAJC19	Mitochondrial import inner membrane translocase subunit TIM14
DOLK	Dolichol kinase
DSC2	Desmocollin 2
DSG2	Desmoglein 2
DSP	Desmoplakin
DTNA	Dystrobrevin alpha
ELN	Elastin
EMD	Emerin
ENG	Endoglin
EYA4	Eyes absent homolog 4
FAH	Fumarylacetoacetase
FBN1	Fibrillin 1
FBN2	Fibrillin 2
FHL1	Four and a half LIM domains protein 1
FHL2	Four and a half LIM domains 2
FHOD3	FH1/FH2 domain-containing protein 3
FKRP	Fukutin-related protein
FKTN	Fukutin
FLNA	Filamin-A
FLNC	Filamin-C
FOXD4	Forkhead box protein D4
GAA	Lysosomal alpha-glucosidase
GATA4	Transcription factor GATA-4
GATA6	Transcription factor GATA-6
GATAD1	GATA zinc finger domain-containing protein 1
GDF2	Growth/differentiation factor 2
GFM1	Elongation factor G, mitochondrial
GJA1	Gap junction alpha-1 protein
GJA5	Gap junction alpha-5 protein

GLA	Alpha-galactosidase A
GLB1	Beta-galactosidase
GNPTAB	N-acetylglucosamine-1-phosphotransferase subunits alpha/beta
GPD1L	Glycerol-3-phospate dehydrogenase 1-like protein
GUSB	Beta-glucuronidase
HCN4	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4
HFE	Hereditary hemochromatosis protein
HRAS	GTPase HRas
JAG1	Jagged-1
JPH2	Junctophilin 2
JUP	Junction plakoglobin
KCNA5	Potassium voltage-gated channel subfamily A member 5
KCND3	Potassium voltage-gated channel subfamily D member 3
KCNE1	Potassium voltage-gated channel subfamily E member 1
KCNE1L	Potassium voltage-gated channel subfamily E member 1-like protein
KCNE2	Potassium voltage-gated channel subfamily E member 2
KCNE3	Potassium voltage-gated channel subfamily E member 3
KCNH2	Potassium voltage-gated channel subfamily H member 2
KCNJ2	Inward rectifier potassium channel 2
KCNJ5	G protein-activated inward rectifier potassium channel 4
KCNJ8	ATP-sensitive inward rectifier potassium channel 8
KCNK3	Potassium channel subfamily K member 3
KCNQ1	Potassium voltage-gated channel subfamily KQT member 1
KLF10	Krueppel-like factor 10
KRAS	GTPase KRas
LAMA2	Laminin subunit alpha-2
LAMA4	Laminin subunit alpha-4
LAMP2	Lysosome-associated membrane glycoprotein 2
LDB3	LIM domain-binding protein 3

LDLR	Low density lipoprotein receptor
LIAS	Lipoyl synthase, mitochondrial
LMNA	Prelamin-A/C
LRP6	Low-density lipoprotein receptor-related protein 6
MAP2K1	Dual specificity mitogen-activated protein kinase kinase 1
MAP2K2	Dual specificity mitogen-activated protein kinase kinase 2
MIB1	E3 ubiquitin-protein ligase MIB1
MLYCD	Malonyl-CoA decarboxylase, mitochondrial
MRPL3	39S ribosomal protein L3, mitochondrial
MRPS22	28S ribosomal protein S22, mitochondrial
MTO1	Protein MTO1 homolog, mitochondrial
MURC	Muscle-related coiled-coil protein
MYBPC3	Myosin-binding protein C, cardiac-type
MYH11	Myosin-11
MYH6	Myosin-6
MYH7	Myosin-7
MYL2	Myosin regulatory light chain 2, ventricular/cardiac muscle isoform
MYL3	Myosin light chain 3
MYLK	Myosin light chain kinase, smooth muscle
MYLK2	Myosin light chain kinase 2, skeletal/cardiac muscle
MYOT	Myotilin
MYOZ2	Myozenin 2
MYPN	Myopalladin
NEBL	Nebulette
NEXN	Nexilin
NKX2-5	Homeobox protein Nkx-2.5
NOTCH1	Neurogenic locus notch homolog protein 1
NOTCH3	Neurogenic locus notch homolog protein 3
NPPA	Atrial natriuretic factor
NRAS	GTPase NRas

OBSL1	Obscurin-like protein 1
PCSK9	Proprotein convertase subtilisin/kexin type 9
PDHA1	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial
PDLIM3	PDZ and LIM domain protein 3
PHKA1	Phosphorylase b kinase regulatory subunit alpha, skeletal muscle isoform
PITX2	Pituitary homeobox 2
PKP2	Plakophilin 2
PLN	Cardiac phospholamban
PLOD1	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1
PMM2	Phosphomannomutase 2
PRDM16	PR domain zinc finger protein 16
PRKAG2	5'-AMP-activated protein kinase subunit gamma-2
PRKG1	cGMP-dependent protein kinase 1
PSEN1	Presenilin-1
PSEN2	Presenilin 2
PTPN11	Tyrosine-protein phosphatase non-receptor type 11
RAF1	RAF proto-oncogene serine/threonine-protein kinase
RANGRF	Ran guanine nucleotide release factor
RBM20	Probable RNA-binding protein 20
RYR2	Ryanodine receptor 2
SCN10A	Sodium channel protein type 10 subunit alpha
SCN1B	Sodium channel subunit beta-1
SCN2B	Sodium channel subunit beta-2
SCN3B	Sodium channel subunit beta-3
SCN4B	Sodium channel subunit beta-4
SCN5A	Sodium channel protein type 5 subunit alpha
SGCA	Alpha-sarcoglycan
SGCB	Beta-sarcoglycan
SGCD	Delta-sarcoglycan

SHOC2	Leucine-rich repeat protein SHOC-2
SKI	Ski oncogene
SLC22A5	Solute carrier family 22 member 5
SLC25A4	ADP/ATP translocase 1
SLC2A10	Solute carrier family 2, facilitated glucose transporter member 10
SLMAP	Sarcolemmal membrane-associated protein
SMAD1	Mothers against decapentaplegic homolog 1
SMAD3	Mothers against decapentaplegic homolog 3
SMAD4	Mothers against decapentaplegic homolog 4
SMAD9	Mothers against decapentaplegic homolog 9
SNTA1	Alpha-1-syntrophin
SOS1	Son of sevenless homolog 1
SPRED1	Sprouty-related, EVH1 domain-containing protein 1
SURF1	Surfeit locus protein 1
TAZ	Tafazzin
TBX1	T-box transcription factor TBX1
TBX20	T-box transcription factor TBX20
TBX5	T-box transcription factor TBX5
TCAP	Telethonin
TGFB2	Transforming growth factor beta-2
TGFB3	Transforming growth factor, beta 3
TGFBR1	TGF-beta receptor type-1
TGFBR2	TGF-beta receptor type-2
TMEM43	Transmembrane protein 43
TMEM70	Transmembrane protein 70, mitochondrial
TMPO	Thymopoietin
TNNC1	Troponin C, slow skeletal and cardiac muscles
TNNI3	Troponin I, cardiac muscle
TNNT2	Troponin T, cardiac muscle
TPM1	Tropomyosin alpha-1 chain

TRDN	Triadin
TRIM63	E3 ubiquitin-protein ligase TRIM63
TRPM4	Transient receptor potential cation channel subfamily M member 4
TSFM	Elongation factor Ts, mitochondria
TTN	Titin
TTR	Transthyretin
TXNRD2	Thioredoxin reductase 2, mitochondrial
VCL	Vinculin

Table 2 of the supplementary data. Full list of the reasons for referral to the inherited cardiac disease unit

Reason for referral	No. (%)
Symptoms	245 (46)
Family screening	133 (25)
ECG abnormalities	41 (8)
Casual finding on echocardiography	41 (8)
Family history	39 (7)
Abnormal physical examination	27 (5)
Others	4 (1)
TOTAL	530 (100)

Table 3 of the supplementary data. List of described genetic variants in our cohort of patients with excessive trabeculation of the left ventricle

	Pathogenic or likely pathogenic genetic variants in probands (n = 88)	Pathogenic or likely pathogenic genetic variants in probands and relatives (n = 176)	All described genetic variants (including nonpathogenic variants and variants of unknown significance) (n = 247)
Complex genotype	**18**	23	36
MYH7	**16**	38	46
TTN	**11**	16	23
ACTC1	**10**	49	49
MYBPC3	**10**	18	20
DSP	**3**	3	5
LDB3	**3**	3	4
BAG3	**2**	2	3
Notch1	**2**	2	3
ACTN2	**1**	1	1
DMD	**1**	1	1
HCN4	**1**	6	8
TBX20	**1**	5	5
FHOD3	**0**	0	3
MIB1	**0**	0	2
FLNC	**1**	1	3
JPH2	**0**	0	1
TNNT2	**1**	1	2

NKX2-5	**1**	1	2
FHL1	**1**	1	1
JUP	**1**	1	1
RBM20	**1**	1	1
TNNC1	**1**	1	1
TNNI3	**1**	1	1
TPM1	**1**	1	1
RYR2	**0**	0	6
MYH6	**0**	0	1
CASQ2	**0**	0	2
JAG1	**0**	0	2
NKX2-6	**0**	0	1
DMN1L	**0**	0	1
KCNJ2	**0**	0	1
KRAS	**0**	0	1
MYOT	**0**	0	1
MYPN	**0**	0	1
PDLIM3	**0**	0	1
PMM2	**0**	0	1
SCN5A	**0**	0	1
TGFBR2	**0**	0	1
TMEM43	**0**	0	1
TXNRD2	**0**	0	1
MAP2K1	**0**	0	1

Table 4 of the supplementary data. Baseline characteristics and major adverse cardiovascular events

	All (N = 530)	MACE (n = 106)	No MACE (n = 424)	Crude HR (95%CI)	*P*
Clinical characteristics					
Age at diagnosis, y	44.1 ± 19.4	50.5 ± 17.0	42.5 ± 19.7	1.02 (1.01-1.03)	< .001
Female sex	235 (44.3)	39 (36.8)	196 (46.2)	0.72 (0.48-1.07)	.102
Proband	391 (73.8)	91 (85.8)	300 (70.8)	2.65 (1.53-4.58)	.001
Positive family screening, n (% of probands)	98 (43)	21 (46)	77 (41)	1.00[a] (0.55-1.80)	.994
Positive genotype, n (% of genetic tests in probands)	88 (40.7)	26 (49.1)	62 (38.0)	1.59[b] (0.93-2.74)	.090
Medical history					
Hypertension	115 (22.4)	37 (36.6)	78 (18.9)	2.43 (1.62-3.66)	< .001
Dyslipidemia	122 (23.9)	38 (38.0)	84 (20.5)	2.10 (1.40-3.15)	< .001
Diabetes mellitus	40 (7.8)	18 (18.0)	22 (5.4)	2.63 (1.57-4.38)	< .001
Smoking	69 (18.9)	18 (22.0)	51 (18.0)	1.58 (0.93-2.68)	.088
BMI, kg/m^2	25.3 (4.9)	26.7 (5.8)	24.9 (4.6)	1.06 (1.02-1.10)	.002
Electrocardiogram					
Atrial fibrillation	39 (7.8)	23 (24.0)	16 (4.0)	3.70 (2.33-5.88)	< .001
QRS, ms	103.2 (27.1)	120.0 (30.6)	99.4 (24.7)	1.02 (1.01-1.03)	< .001
QRS ≥120 ms	132 (33.0)	43 (53.1)	89 (27.9)	2.22 (1.43-3.45)	< .001
LBBB	68 (17.0)	19 (23.5)	49 (15.4)	1.37 (0.81-2.33)	.237
Echocardiography (n = 530, 100%)					
LVEF, %	49.3 ± 16.2	38.2 ± 15.6	52.0 ± 15.1	0.96 (0.94-0.97)	< .001

LVEDDi, mm/m^2	29.2 ± 5.1	32.0 ± 5.4	28.5 ± 4.7	1.11 (1.08-1.15)	< .001
LVESDi, mm/m^2	20.1 ± 5.7	24.3 ± 7.1	19.4 ± 5.1	1.13 (1.09-1.17)	< .001
TAPSE, mm	21.5 ± 4.6	19.6 ± 5.2	21.9 ± 4.4	0.92 (0.87-0.97)	.002
PASP, mmHg	32.2 ± 11.0	36.3 ± 11.5	30.8 ± 10.5	1.03 (1.01-1.06)	.004
LA diameter, mm	38.1 ± 8.2	42.2 ± 8.9	37.1 ± 7.7	1.06 (1.04-1.09)	< .001
Follow-up LVEF, %	50.1 ± 14.4	38.7 ± 15.6	52.9 ± 12.6	-	-
LVEF decline	29 (5.5)	14 (13.2)	15 (3.5)	3.71 (2.10 – 6.53)	< .001
Cardiovascular magnetic resonance (n = 403, 76%)					
LVEF, %	51.5 ± 15.0	40.8 ± 18.0	53.6 ± 13.5	0.95 (0.93-0.96)	< .001
LVEDVi, mL/m^2	89.8 ± 38.5	111.9 ± 49.4	85.8 ± 34.8	1.02 (1.01-1.02)	< .001
LVESVi, mL /m^2	45.6 ± 32.3	66.5 ± 44.9	42.0 ± 28.3	1.02 (1.01-1.02)	< .001
LVSVi, mL/m^2	43.6 ± 15.4	41.7 ± 15.8	43.9 ± 15.3	0.99 (0.97-1.01)	.339
RVEF, %	54.5 ± 11.6	52.4 ± 15.8	55.0 ± 10.5	0.98 (0.95-1.01)	.280
RVEDVi, mL/m^2	78.2 ± 26.7	75.6 ± 26.5	78.7 ± 26.8	1.00 (0.98-1.02)	.877
RVESVi, mL/m^2	37.0 ± 17.9	40.9 ± 22.2	36.3 ± 17.0	1.02 (1.00-1.05)	.107
LGE	66 (16.4)	20 (28.6)	46 (13.8)	2.46 (1.46-4.13)	.001
Medical treatment[c]					
Beta-blockers	291 (52)	106 (85)	185 (46)	-	-
ACE inhibitor/ARB	263 (50)	85 (68)	178 (44)	-	-
Sacubitril-valsartan	28 (5)	18 (14)	10 (3)	-	-
MRAs	149 (28)	69 (55)	80 (20)	-	-
Ivabradine	39 (8)	14 (13)	25 (6)	-	-
Diuretics	135 (26)	70 (56)	65 (16)	-	-
OAC	143 (27)	70 (57)	73 (18)	-	-

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; HR, hazard ratio; LA, left atrium; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LVEDDi, left ventricular end-diastolic diameter indexed by body surface area (BSA); LVEDVi, left ventricular end-diastolic volume indexed by BSA; LVEF, left ventricular ejection fraction; LVESDi, left ventricular end-systolic diameter indexed by BSA; LVESVi, left ventricular end-systolic volume indexed by BSA; MACE, major adverse cardiovascular events; MRA, mineralocorticoid receptor antagonist; OAC, oral anticoagulation; PSAP, pulmonary systolic artery pressure; RVEDVi, right ventricular end-diastolic volume indexed by BSA; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume indexed by BSA; TAPSE, tricuspid annular systolic excursion.

Unless otherwise indicated, the data are expressed as No. (%) or mean ± standard deviation.

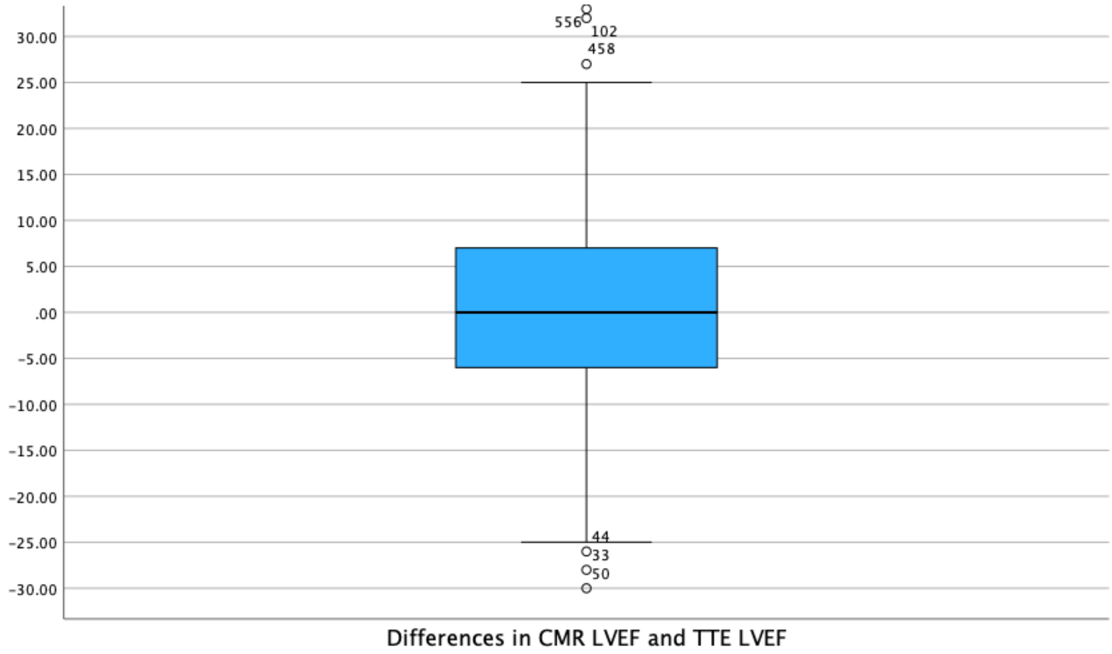
[a] Among probands who underwent family screening.
[b] Among probands who underwent genetic testing.
[c] Time of treatment prescription was not available so HR were not analyzed.

Table 5 of the supplementary data. Multivariate analysis of hard MACE

Variable	Adjusted HR (95%CI)	*P*
Atrial fibrillation	2.68 (1.63-4.38)	< .001
QRS ≥ 120 ms	2.79 (1.67-4.65)	< .001
LVEF (%)	0.94 (0.92-0.96)	< .001
LVEF decline	2.42 (1.26-4.67)	.008

LVEF, left ventricular ejection fraction.

Figure 1 of the supplementary data. Box-plot for the difference between CMR LVEF and TTE LVEF

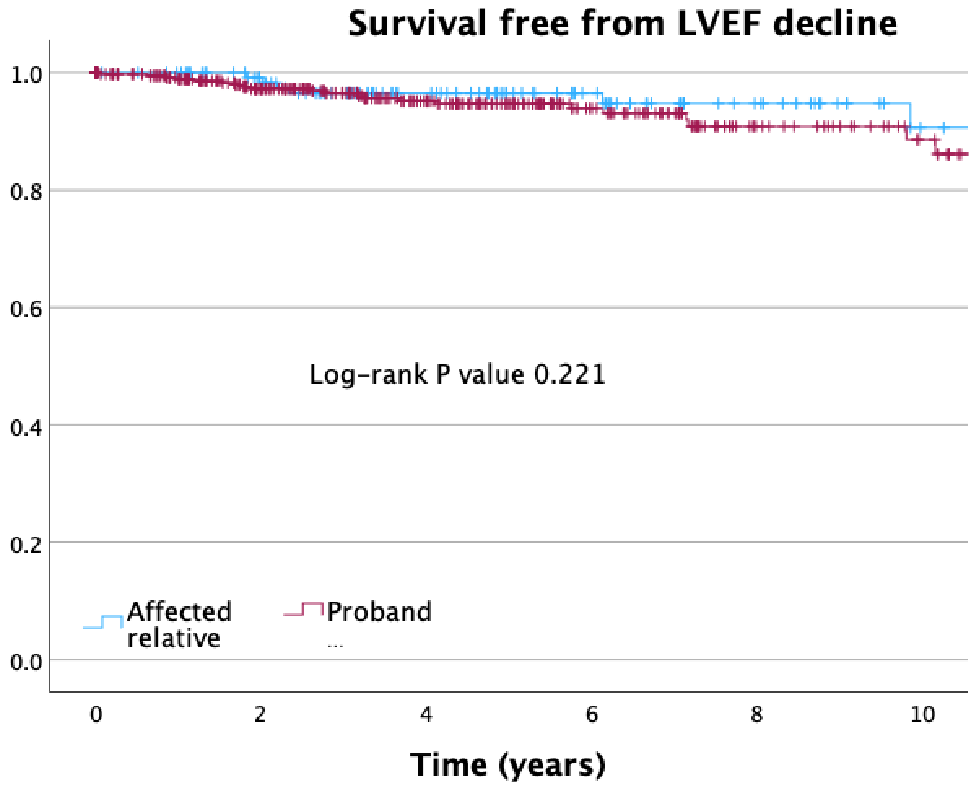


CMR LVEF, cardiag magnetic resonance; LVEF, left ventricular ejection fraction, TTE, transthoracic echocardiography

Difference between CMR LVEF and TTE LVEF: 0.6 ± 10% (mean ± SD).

Intraclass correlation coefficient between CMR LVEF and TTE LVEF: 0.88 (95%CI 0.85-0.90).

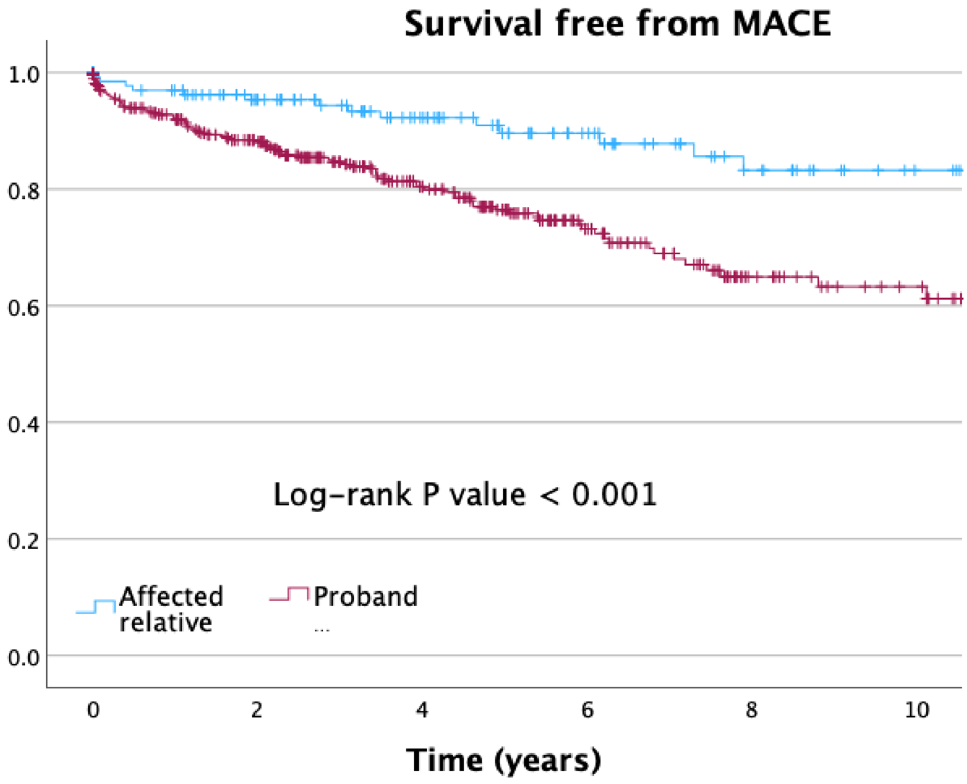
Figure 2 of the supplementary data. Event-free survival rates



Kaplan Meier curves for LVEF decline stratified by proband status.

LVEF, left ventricular ejection fraction.

Figure 3 of the supplementary data. Event-free survival rates



Kaplan Meier curves for MACE stratified by proband status.

MACE, major adverse cardiovascular event.