Risk score in HCM is it enough?

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Table 7 **Major clinical features associated with an increased risk of sudden cardiac death in adults**

Risk Factor	Comment
Age	• The effect of age on SCD has been examined in a number of studies[73,82,99,208,244,372–374] and two have shown a significant association, with an increased risk of SCD in younger patients.[73,99] • Some risk factors appear to be more important in younger patients, most notably, NSVT,[69] severe LVH[375] and

The HCM Risk-SCD formula is as follows: ProbabilitySCD at 5 years 1⁄4 1 – 0.998exp(Prognostic index) where Prognostic index 1⁄4 [0.15939858 x maximal wall thickness (mm)] 2 [0.00294271 x maximal wall thickness2 (mm2)]+ [0.0259082 x left atrial diameter (mm)] + [0.00446131 x maximal (rest/Valsalva) left ventricular outflow tract gradient (mm Hg)] + [0.4583082 x family history SCD]+[0.82639195 x NSVT]+ [0.71650361 x unexplained syncope] 2 [0.01799934 x age at clinical evaluation (years)].

Left ventricular outflow tract obstruction	• A number of studies have reported a significant association with LVOTO and SCD.[73,82,83,246,372,380] Several unanswered questions remain, including the prognostic importance of provocable LVOTO and the impact of treatment (medical or invasive) on SCD.
Exercise blood pressure response	• Approximately one third of adult patients with HCM have an abnormal systolic blood pressure response to exercise characterised by progressive hypotension or a failure to augment the systolic blood pressure that is caused by an inappropriate drop in systemic vascular resistance and a low cardiac output reserve.[241,381] • Various definitions for abnormal blood pressure response in patients with HCM have been reported[69,83,246,377]; for the purposes of this guideline an abnormal blood pressure response is defined as a failure to increase systolic pressure by at least 20 mm Hg from rest to peak exercise or a fall of >20 mm Hg from peak pressure.[237] • Abnormal exercise blood pressure response is associated with a higher risk of SCD in patients aged ≤40 years,[237] but its prognostic significance in patients >40 years of age is unknown.

HCM = hypertrophic cardiomyopathy; LA = left atrium; LVH = left ventricular hypertrophy; LVOTO = left ventricular outflow tract obstruction; NSVT = non-sustained ventricular tachycardia; SCD = sudden cardiac death; TTE = transthoracic echocardiography.

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HCM Risk-SCD Calculator

Age	44 **Years**	*Age at evaluation*
Maximum LV wall thickness	30 **mm**	*Transthoracic Echocardiographic measurement*
Left atrial size	35 **mm**	*Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation*
Max LVOT gradient	45 **mmHg**	*The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernouilli equation: Gradient= $4V^2$, where V is the peak aortic outflow velocity*
Family History of SCD	○ No ◉ Yes	*History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).*
Non-sustained VT	◉ No ○ Yes	*3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.*
Unexplained syncope	◉ No ○ Yes	*History of unexplained syncope at or prior to evaluation.*

Risk of SCD at 5 years (%):	**3.6**
ESC recommendation:	**ICD generally not indicated ****

*** ICD not recommended unless there other clinical features that are of potential prognostic importance and when the likely benefit is greater than the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.*

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HCM Risk-SCD Calculator

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Unexplained syncope	● No	○ Yes	*History of unexplained syncope at or prior to evaluation.*

Risk of SCD at 5 years (%):	**8.03**
ESC recommendation:	**ICD should be considered**

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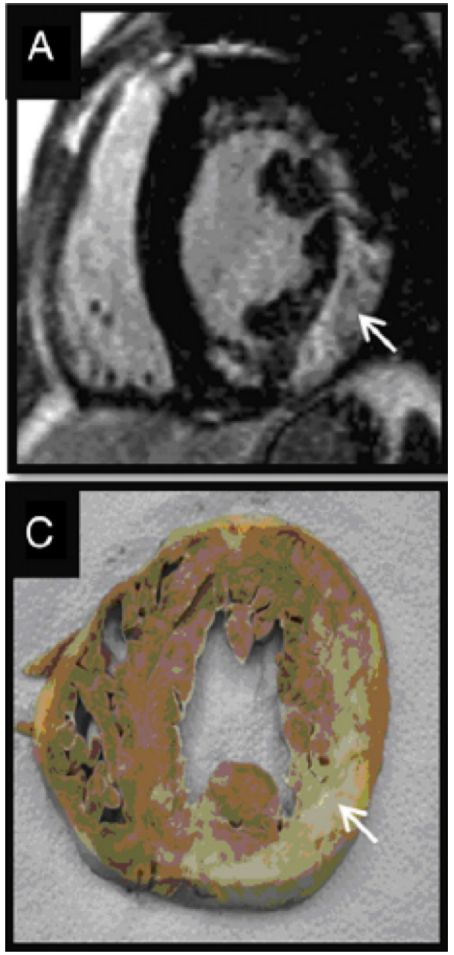
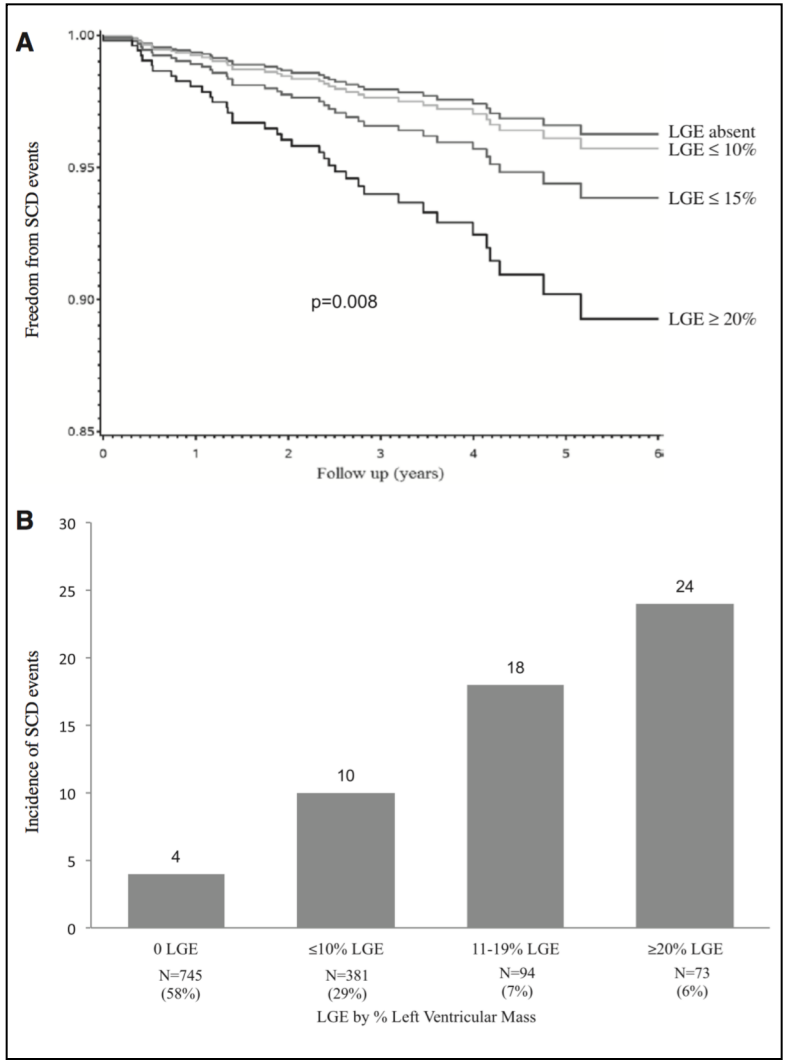
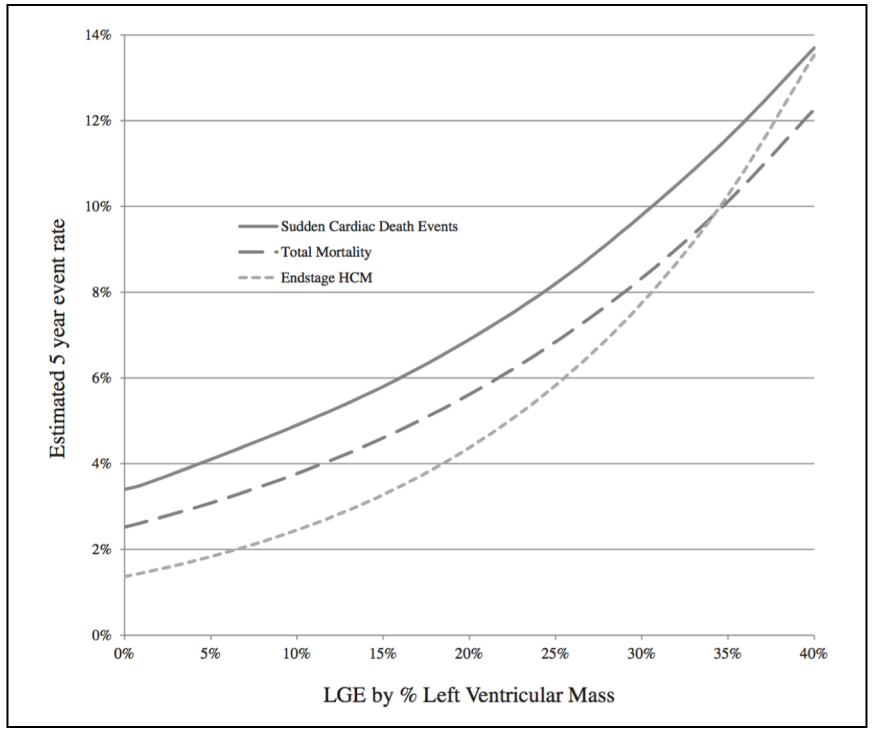
Relation between extent of late gadolinium enhancement (LGE) and sudden cardiac death (SCD) events in 1293 patients with hypertrophic cardiomyopathy.







Chan and Maron et al, Circulation 2014

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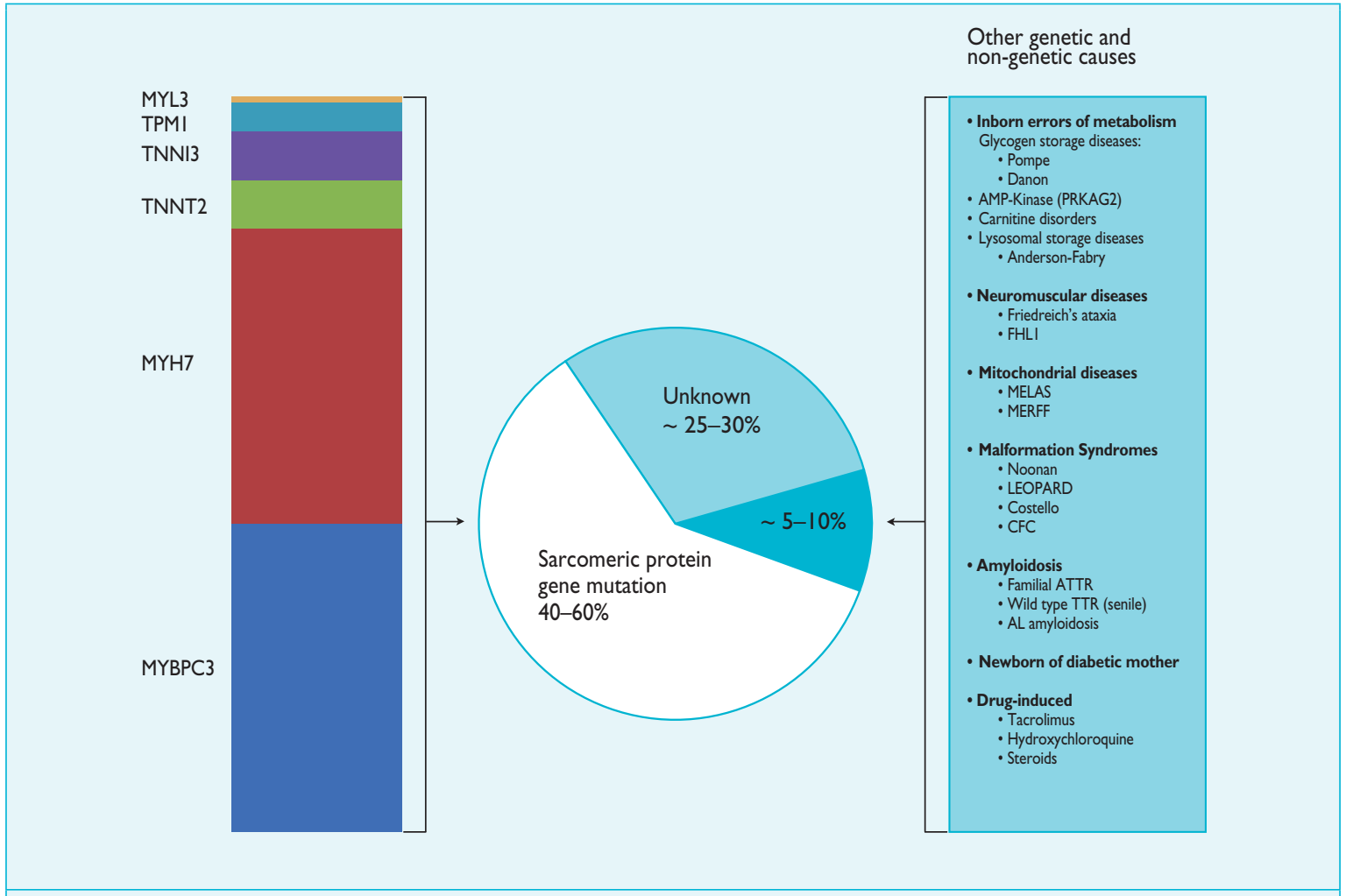
Gene	Chromosomal position[a]	Protein	HCM-associated mutations[a]	Location or function[b]
ACTA1	1q42.13–q42.2	Actin, alpha 1	1	Sarcomere, skeletal muscle
ACTC1	15q11–q14	Actin, alpha, cardiac muscle 1	25	Sarcomere, cardiac muscle
ACTN2	1q42–q43	Actinin, alpha 2	5	Z-disk
ANKRD1	10q23.33	Ankyrin repeat domain 1	3	Z-disk and nucleus (transcription factor)
BRAF	7q34	v-Raf murine sarcoma viral oncogene homolog B1	1	Cytoplasmic serine/threonine kinase
COA5	2q11.2	Cytochrome c oxidase assembly factor 5	1	Mitochondrial
CALM3	19q13.2–q13.3	Calmodulin 3 (phosphorylase kinase, delta)	1	Calcium sensor and signal transducer
CALR3	19p13.11	Calreticulin 3	2	Endoplasmic reticulum chaperone
CASQ2	1p13.3–p11	Calsequestrin 2	1	Sarcoplasmic reticulum; calcium storage
CAV3	3p25	Caveolin 3	1	Plasma membrane
COX15	10q24	Cytochrome c oxidase assembly homolog 15	2	Mitochondrial respiratory chain
CSRP3	11p15.1	Cysteine and glycine-rich protein 3	15	Z-disk
DES	2q35	Desmin	1	Intermediate filament
FHL1	Xq26	Four and a half LIM domains 1	3	Biomechanical stress sensor
FHOD3	18q12	Formin homology 2 domain containing 3	1	Actin-organizing protein
FXN	9q13–q21.1	Frataxin	1	Mitochondrial iron transport and respiration
GLA	Xq22	Galactosidase, alpha	765	Lysosome
JPH2	20q13.12	Junctophilin 2	6	Junctional membrane complexes; calcium signaling
KLF10	8q22.2	Kruppel-like factor 10	6	Transcriptional repressor; inhibits cell growth

MAP2K1	15q22.1–q22.33	Mitogen-activated protein kinase kinase 1	1	MAP kinase kinase; signal transduction
MAP2K2	19p13.3	Mitogen-activated protein kinase kinase 2	1	MAP kinase kinase; signal transduction
MRPL3	3q21–q23	Mitochondrial ribosomal protein L3	1	Mitochondrial ribosomal protein
MTO1	6q13	Mitochondrial tRNA translation optimization 1	2	Mitochondrial tRNA modification
MYBPC3	11p11.2	Myosin binding protein C, cardiac	506	Sarcomere
MYH6	14q12	Alpha-myosin heavy chain	3	Sarcomere
MYH7	14q12	Beta-myosin heavy chain	491	Sarcomere
MYL2	12q23–q24.3	Ventricular myosin regulatory light chain	20	Sarcomere
MYL3	3p21.3–p21.2	Myosin light chain 3	16	Sarcomere
MYLK2	20q13.31	Myosin light chain kinase 2	2	Calcium/calmodulin-dependent kinase
MYO6	6q13	Myosin VI	1	Actin-based reverse-direction motor protein
MYOM1	18p11.31	Myomesin 1	1	Sarcomere
MYOZ2	4q26–q27	Myozenin 2	2	Z-disk
MYPN	10q21.3	Myopalladin	8	Z-disk
NDUFAF1	15q11.2–q21.3	NADH dehydrogenase (ubiquinone) complex I, assembly factor 1	2	Mitochondrial chaperone
NDUFV2	18p11.31–p11.2	NADH dehydrogenase (ubiquinone) flavoprotein 2	1	Mitochondrial respiratory chain
NEXN	1p31.1	Nexilin	2	Z-disk
OBSCN	1q42.13	Obscurin	1	Sarcomere
PDLIM3	4q35	PDZ and LIM domain 3	1	Z-disk
PRKAG2	7q36.1	5′-AMP-activated protein kinase subunit gamma-2	7	Energy sensor protein kinase
PLN	6q22.1	Phospholamban	7	Sarcoplasmic reticulum; regulates Ca^{2+}-ATPase

RAF1	3p25	v-Raf-1 murine leukemia viral oncogene homolog 1	1	Serine/threonine-protein kinase; signal transduction
SLC25A3	12q23	Solute carrier family 25, member 3	1	Phosphate carrier protein (cytosol to mitochondria)
SLC25A4	4q35	Solute carrier family 25, member 4	2	Adenine nucleotide translocator (cytosol/mitochondria)
SOS1	2p22–p21	Son of sevenless homolog 1	1	Guanine nucleotide exchange factor for RAS proteins; signal transduction
SRI	7q21.1	Sorcin	2	Calcium-binding; modulates excitation-contraction coupling
TCAP	17q12	Telethonin	7	Z-disk
TNNC1	3p21.3–p14.3	Troponin C	14	Sarcomere
TNNI3	19q13.4	Troponin I	70	Sarcomere
TNNT2	1q32	Troponin T	90	Sarcomere
TPM1	15q22.1	Alpha-tropomyosin	38	Sarcomere
TRIM63	1p34–p33	Tripartite motif-containing 63	3	Sarcomere; regulates protein degradation
TTN	2q31	Titin	6	Sarcomere
VCL	10q22.1–q23	Vinculin	1	Sarcomere



The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes. AL = amyloid light chain; ATTR=amyloidosis, transthyretin type. CFC = cardiofaciocutaneous; FHL-1=Four and a half LIM domains protein 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF = myoclonic epilepsy with ragged red fibres; MYL3 = myosin light chain 3; MYBPC3 = myosin-binding protein C, cardiac-type; MYH7 = myosin, heavy chain 7; TNNI3 = troponin I, cardiac; TNNT2 = troponin T, cardiac: TPM1 = tropomyosin 1 alpha chain; TTR = transthyretin.

Distinct mutation cannot be the sole factor that dictates clinical phenotype

- “malignant” MYH7-R403Q mutation: no SCD
- “benign” MYH7-V606M mutation: 50% of SCD
- “malignant” TNNT2-I79N mutation: no SCD

Role of genomic other mutations, genetic modifier and epigenetic on disease expression

Watkins H. *Hum Mol Genet*. 1995
Menon S, *Clin Genet*. 2008

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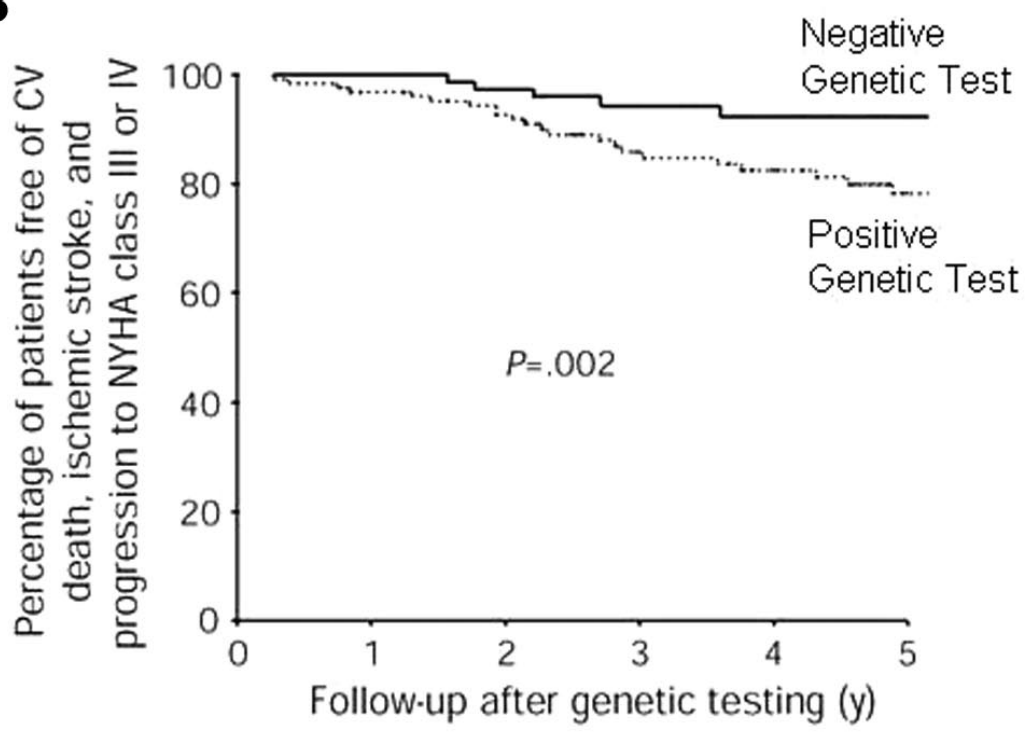
Positive genetic test leads to a more severe prognosis

A

Characteristic	Positive	Negative	P-Value
Age at Dx (yr)	36±17	45±19	<0.001
MLVWT (mm)	23±7	21±6	0.002
FH of HCM	68%	59%	<0.001
ICD	25%	10%	<0.001

Characteristic	HR	95% CI	P-Value
Positive Test	4.3	1.5-12.5	0.008
Age (per yr)	1.03	1.01-1.06	0.017
LVOTO (≥30mmHg)	1.33	0.7-2.7	0.43
Atrial Fibrillation	1.67	0.7-3.8	0.22

B



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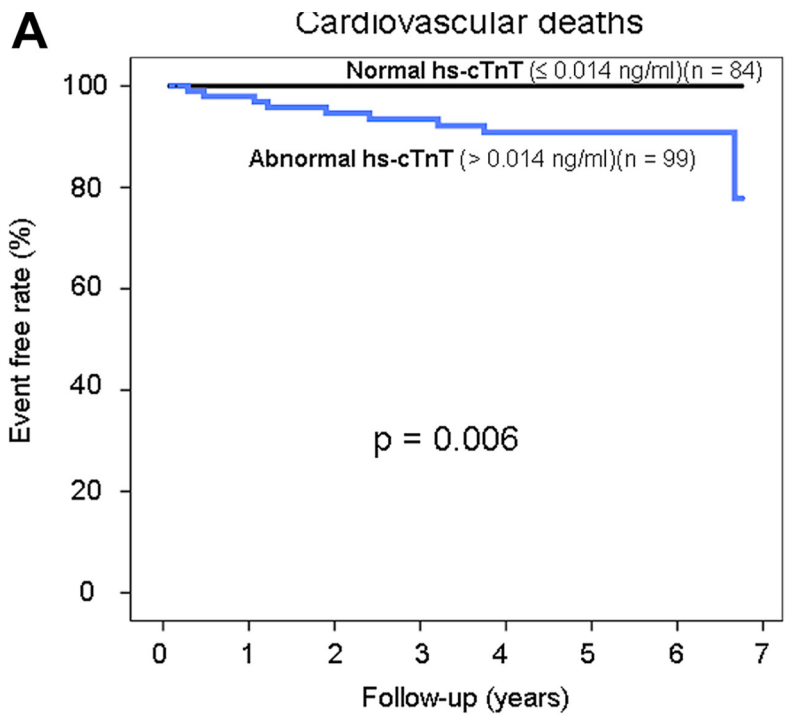
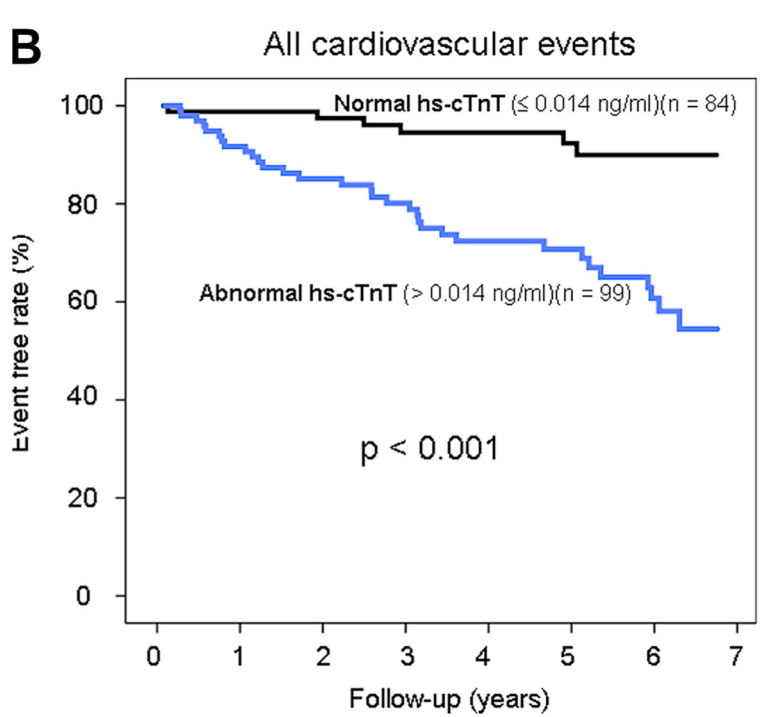
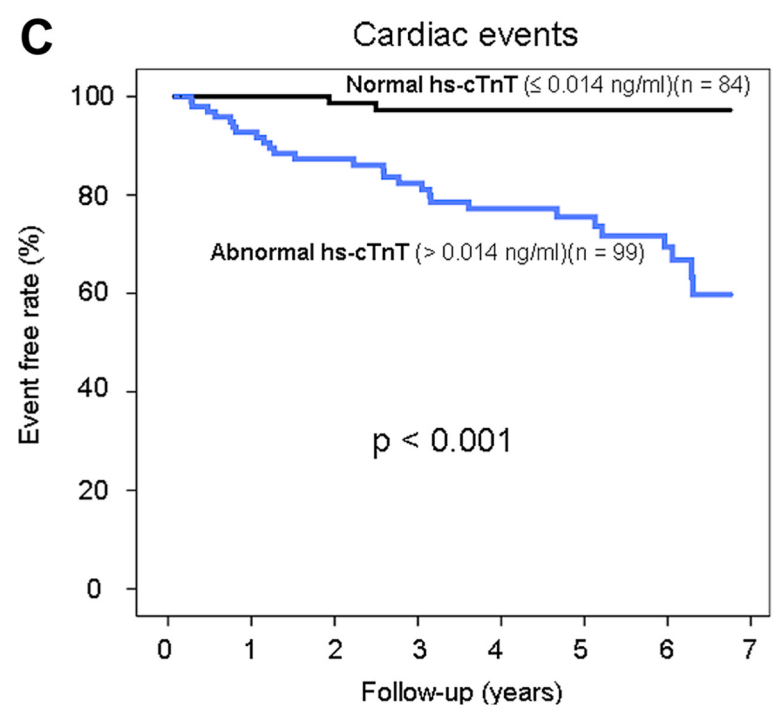
Landstrom, Circulation , 2010

Hs TNT







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Conclusion

- MRI and most specifically LGE seems to be helpful for the the arrhythmic risk classification of the patients
- HsTNT
- Genetic is not helpful most of the time with the exception of patients carriers of multiple mutations

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Evaluation of the arrhythmic risk remains a probabilistic evaluation!!!

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