Variabele expressie en verminderde penetrantie: klinische uitdagingen en oplossingen

VERENIGING KLINISCHE GENETICA NEDERLAND

J. Peter van Tintelen MD, PhD
clinical geneticist

UMC Utrecht

CARDIOGENETICA

meestal gaat het goed……

-structurele hartafwijkingen

-ritme- en geleidingsstoornissen

-cardiomyopathieën

-dyslipidemieën

-aortapathologie

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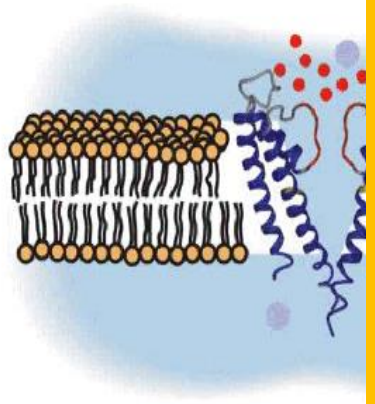
elektrische hartziekten

- LQTS
- SQTS
- Brugada syndro
- Cathecholamine
  polymorfe vent
  tachcardieen



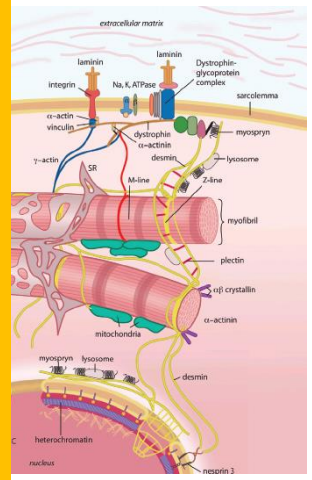
cardiomyopathieen

ardiomyopathie
diomyopathie
iomyopathie
ardiomyopathie
ardiomyopathie

Hartritmestoornissen
(te snel/ te langzaam)

-hartkloppingen
-overslagen
(duizeligheid)
-plotse dood

pompfalen
-vocht vasthouden
-kortademigheid



aortapathologie

dyslipidemieen

Hoe zit het nu met de

PENETRANTIE/VARIABILITEIT?

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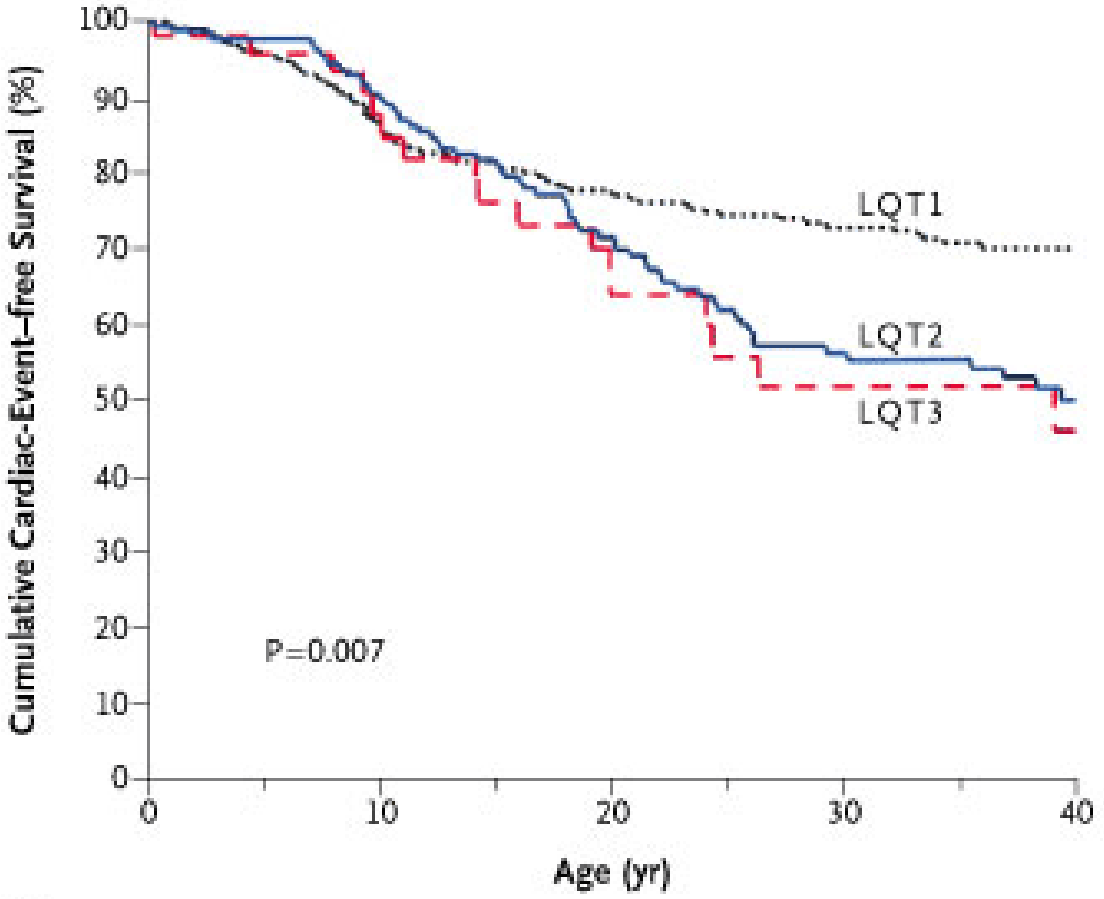
Lange QT syndroom



No. at Risk					
LQT1	355	249	192	146	100
LQT2	176	130	187	57	34
LQT3	49	30	20	9	7

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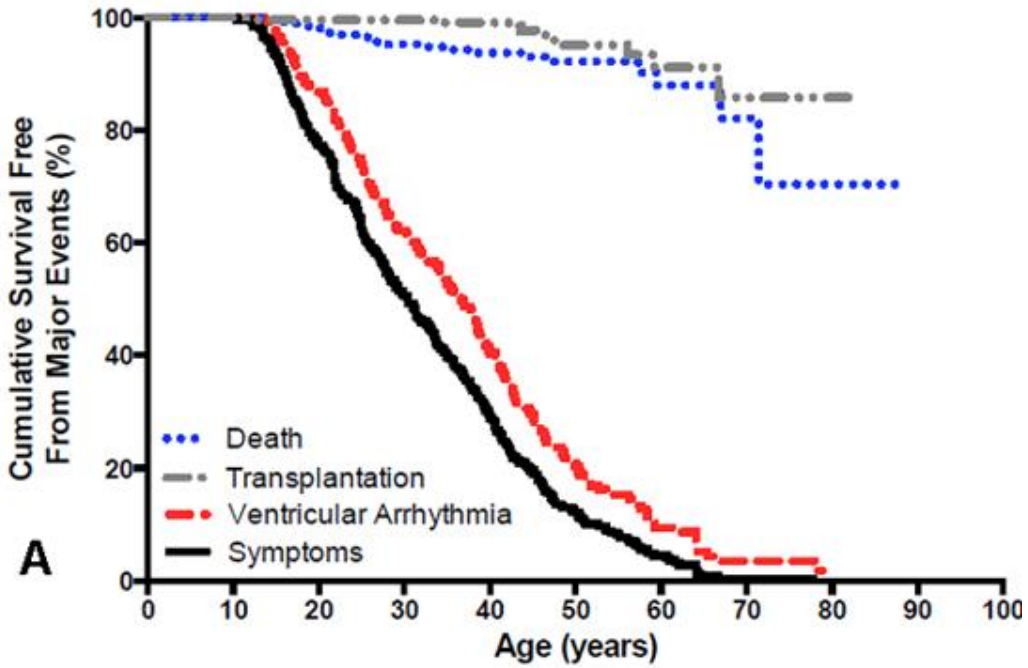
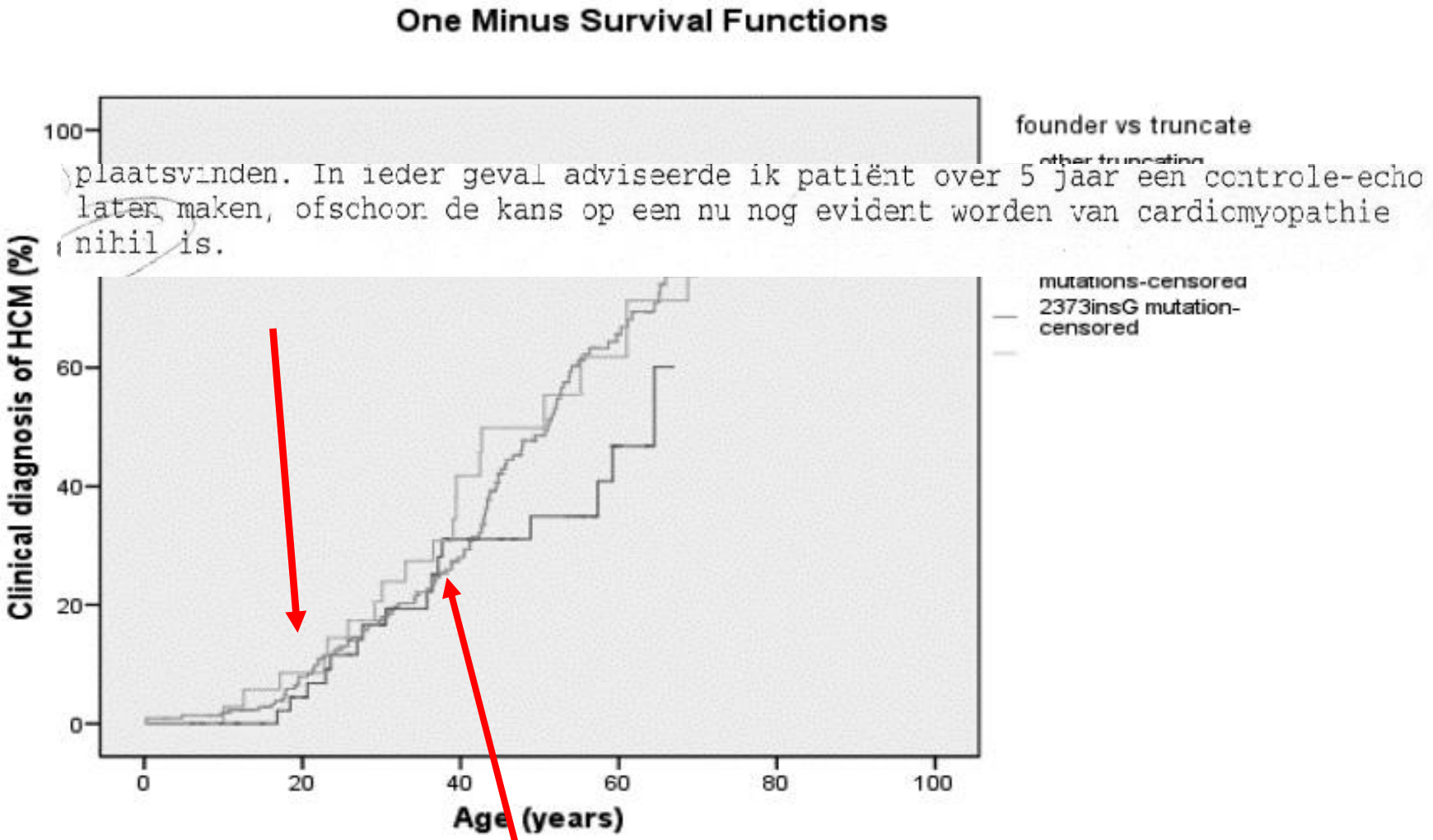
Aritmogene RV cardiomyopathie

Probands with pathogenic variant (N=276)



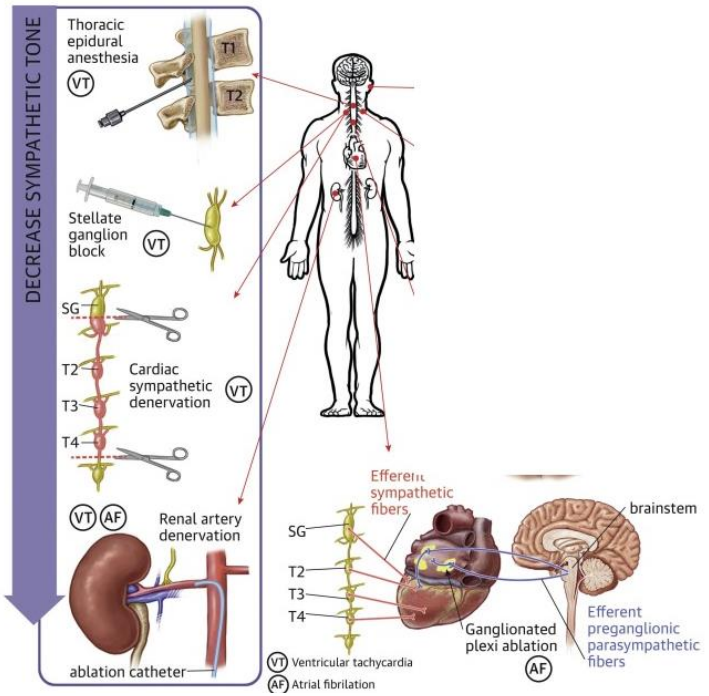
Number at risk											
Death	264	264	253	209	161	94	35	8	1	0	0
Transplantation	264	264	253	209	161	94	35	8	1	0	0
Ventricular arrhythmia	264	264	229	159	99	44	13	2	0	0	0
Symptoms	264	264	206	137	79	33	11	1	0	0	0

Groeneweg et al. Circ Cardiovasc Genet 2015

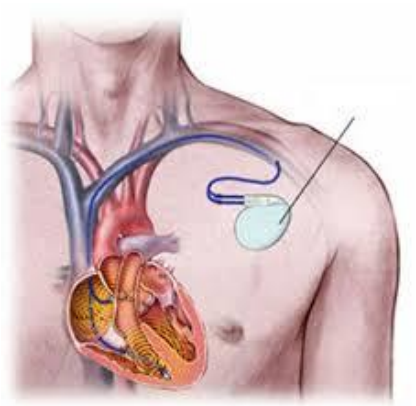


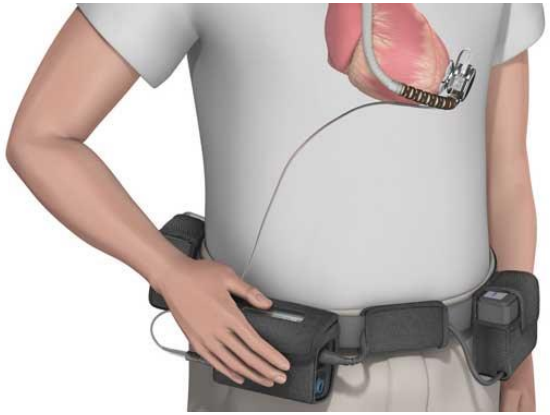
Bespreking: geen aanwijzingen voor cardiale pathologie. Patiënte werd gerustgesteld. Gee
cardiologische controle.

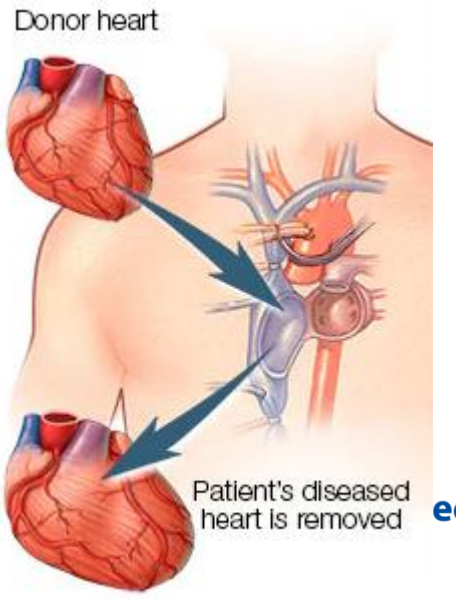
Christiaans et al Neth H J 2010



Zhu, C. et al. J Am Coll Cardiol EP. 2019;5(8):881-96.







echt

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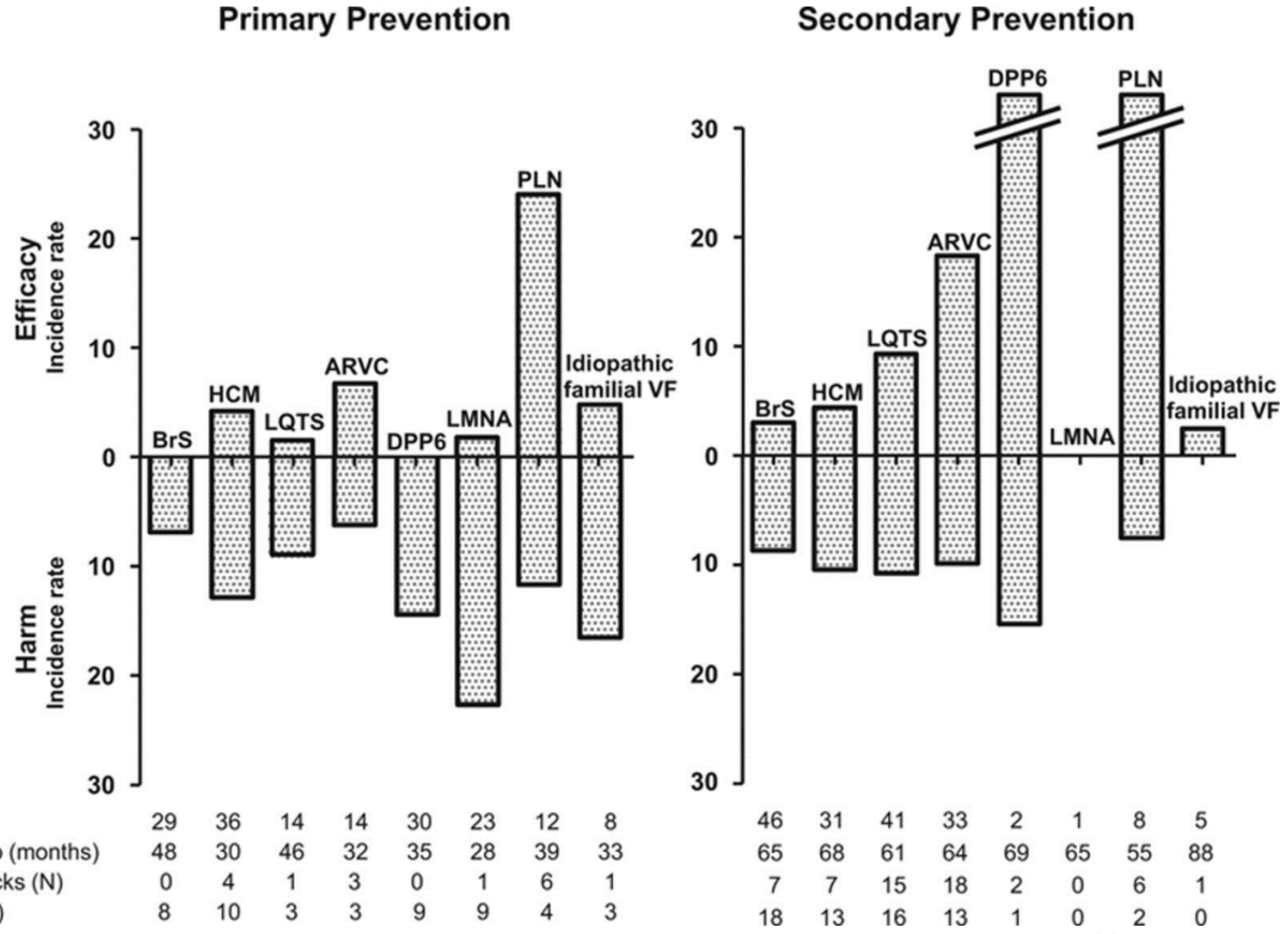

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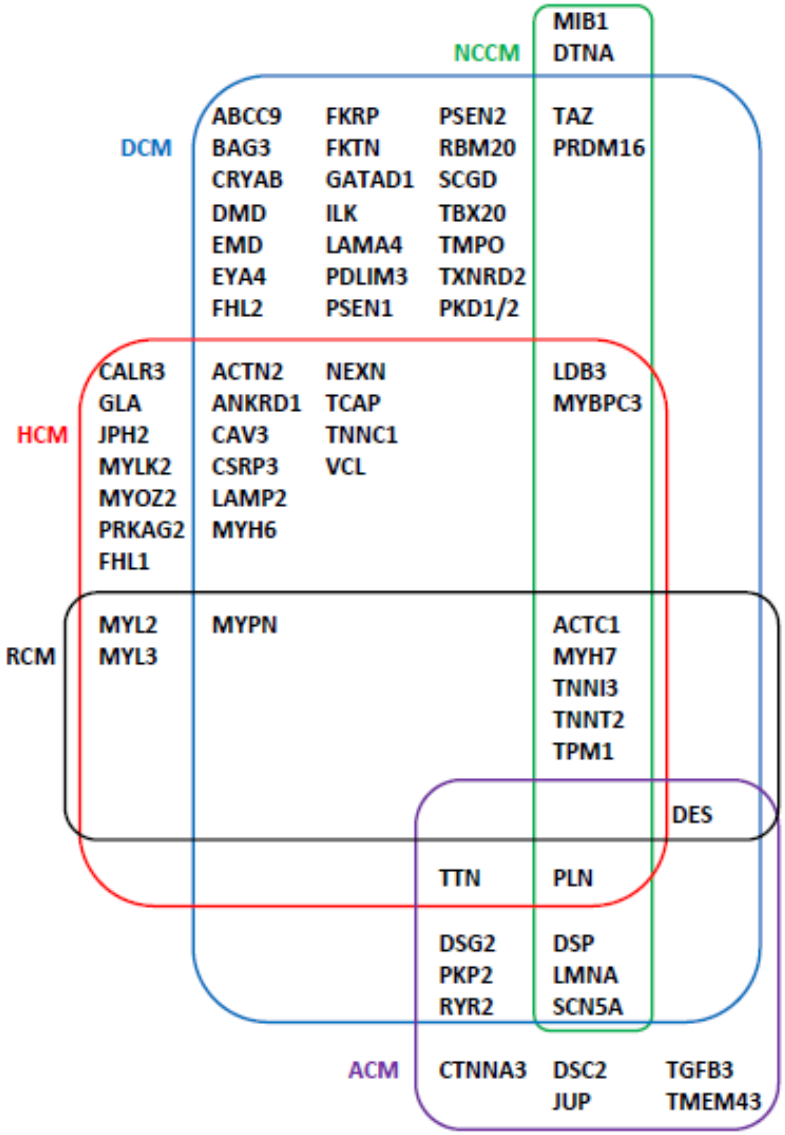
Olde Nordkamp L et al. Circ Arrhythm Electrophysiol 2013;6:91-100

Cardiomyopathieen: genetisch heterogeen



Jongbloed et al
Expert Opinion on Med Diagnostics

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Recommendations for reporting of secondary findings

Ehlers-Danlos syndrome, vascular type	130050	20301667	Child/adult	*COL3A1*	120180	AD	KP and EP
Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	154700 609192 608967 610168 610380 613795 611788	20301510 20301312 20301299	Child/adult	*FBN1* *TGFBR1* *TGFBR2* *SMAD3* *ACTA2* *MYH11*	134797 190181 190182 603109 102620 160745	AD	KP and EP
Hypertrophic cardiomyopathy, dilated cardiomyopathy	115197 192600 601494 613690 115196 608751 612098 600858 301500 608758 115200	20301725	Child/adult	*MYBPC3* *MYH7* *TNNT2* *TNNI3* *TPM1* *MYL3* *ACTC1* *PRKAG2* *GLA* *MYL2* *LMNA*	600958 160760 191045 191044 191010 160790 102540 602743 300644 160781 150330	AD XL AD	KP and EP KP KP and EP KP KP and EP (hemi, het, hom) KP KP and EP
Catecholaminergic polymorphic ventricular tachycardia	604772			*RYR2*	180902	AD	KP
Arrhythmogenic right ventricular cardiomyopathy	609040 604400 610476 607450 610193	20301310	Child/adult	*PKP2* *DSP* *DSC2* *TMEM43* *DSG2*	602861 125647 125645 612048 125671	AD	KP and EP KP KP and EP
Romano-Ward long-QT syndrome types 1, 2, and 3, Brugada syndrome	192500 613688 603830 601144	20301308	Child/adult	*KCNQ1* *KCNH2* *SCN5A*	607542 152427 600163	AD	KP and EP
Familial hypercholesterolemia	143890 603776	No GeneReviews entry	Child/adult	*LDLR* *APOB* *PCSK9*	606945 107730 607786	SD SD AD	KP and EP KP

European Journal of Human Genetics (2019) 27:325–330
https://doi.org/10.1038/s41431-018-0284-2

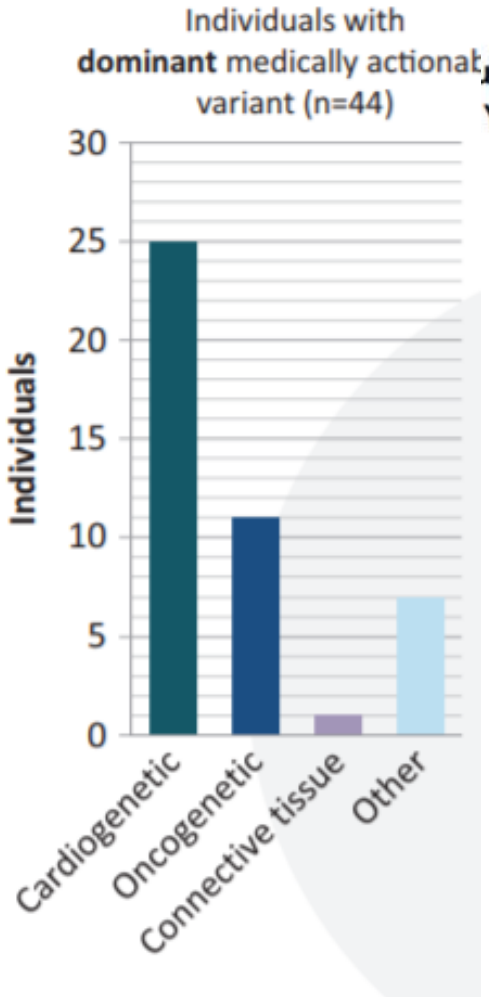
ESHG

ARTICLE

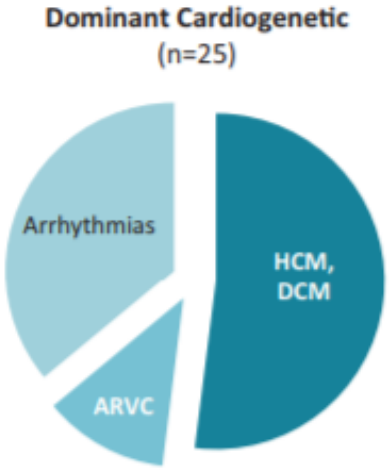
1 in 38 individuals at risk of a dominant medically actionable disease

N=1640

CARDIOGENETIC		
Phenotype disease	***Gene***	**Individuals**
Hypertrophic cardiomyopathy, dilated cardiomyopathy	*MYBPC3*	7
	MYH7	2
	TNNT2	
	TNNI3	1
	TPM1	
	MYL3	
	ACTC1	
	PRKAG2	
	GLA[a]	2
	MYL2	1
	LMNA	
Catecholaminergic polymorphic ventricular tachycardia	*RYR2*	
Arrhythmogenic right ventricular cardiomyopathy	*PKP2*	
	DSP	3
	DSC2	
	TMEM43	
	DSG2	
Romano-Ward long QT syndromes 1, 2 and 3, Brudaga syndrome	*KCNQ1*	3
	KCNH2	1
	SCN5A	5



ılto-van Silfhout[1] ·
Yntema[1]



+ 1 vEDS, 4FH (1:55)

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MYBPC3	AD	NM_000256.3	c.1831G>A	p.Glu611Lys	3	Likely pathogenic	PM1	PM2	PP2	PP3	PP5
			c.1468G>A	p.Gly490Arg	3	Likely pathogenic	PM1	PM2	PP2	PP3	PP5
			c.442G>A	p.Gly148Arg	1	Likely pathogenic	PM1	PM2	PP2	PP5	
MYH7	AD	NM_000257.3	c.2644C>T	p.Gln882* [d.]	1	Likely pathogenic	PVS1	PM2			
			c.2389G>A	p.Ala797Thr	1	Pathogenic	PS3	PS4	PM5	PP1	PP2
TNNT2	AD	NM_001276346.1									
TNNI3	AD	NM_000363.4	c.354del	p.Thr119fs [d.]	1	Likely pathogenic	PVS1	PM2			
TPM1	AD	NM_001018008.1									
MYL3	AD	NM_000258.2									
ACTC1	AD	NM_005159.4									
PRKAG2	AD	NM_016203.3									
GLA	XLD	NM_000169.2	c.427G>A	p.Ala143Thr	2	Likely Pathogenic	PS3	PM2	PM5	PP5	
MYL2	AD	NM_000432.3	c.403-1G>C	r.spl?	1	Pathogenic	PVS1	PS3	PM2		
LMNA	AD	NM_170707.3									
RYR2	AD	NM_001035.2									
PKP2	AD	NM_004572.3									
DSP	AD	NM_001008844.2	c.85G>T	p.Glu29* [d.]	1	Likely pathogenic	PVS1	PM2			
			c.4518del	p.Arg1506fs [d.]	1	Likely pathogenic	PVS1	PM2			
			c.6336del	p.Asn2114fs [d.]	1	Likely pathogenic	PVS1	PM2			
DSC2	AD	NM_024422.4									
TMEM43	AD	NM_024334.2									
DSG2	AD	NM_001943.4									
KCNQ1	AD	NM_000218.2	c.961C>T	p.Gln321* [d.]	1	Likely pathogenic	PVS1	PM2			
			c.1066C>T	p.Gln356*	1	Likely pathogenic	PVS1	PM2			
			c.1124_1127del	p.Ile375fs	1	Likely pathogenic	PVS1	PM2			
KCNH2	AD	NM_000238.3	c.2254C>T	p.Arg752Trp	1	Likely pathogenic	PS3	PM1	PM2	PP2	
SCN5A	AD	NM_198056.2	c.4999G>A	p.Val1667Ile	1	Likely pathogenic	PM1	PM2	PP1	PP2	PP3
			c.4978A>G	p.Ile1660Val	1	Pathogenic	PS3	PM1	PM2	PP1	PP2
			c.3956G>T	p.Gly1319Val	1	Pathogenic	PS3	PM1	PM2	PP1	PP2
			c.3911C>T	p.Thr1304Met	1	Pathogenic	PS3	PM1	PM2	PP1	PP2
			c.80G>A	p.Arg27His	1	Pathogenic	PS3	PM1	PM2	PP1	PP2

Hoe zit het nu ***echt*** met de

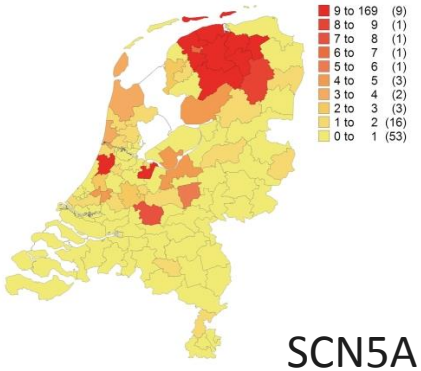
PENETRANTIE/VARIABILITEIT?

Median age of (50%) event free survival

ORIGINAL ARTICLE

Effect of Ascertainment Bias on Estimates of Patient Mortality in Inherited Cardiac Diseases

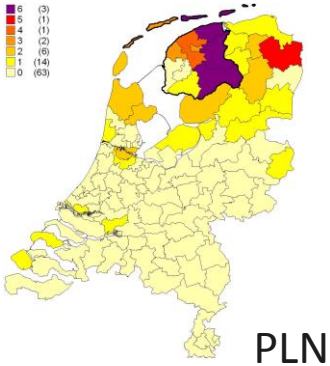
Nannenberg E et al. Circ Genom Precis Med. 2018;11:e001797



SCN5A

1999
56.1 yr (48-64)

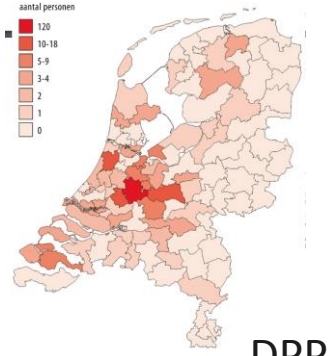
2009
70 yr (61-78)



PLN R14del

2010
63.5 (59-68)

2012
65.2 (62-68)

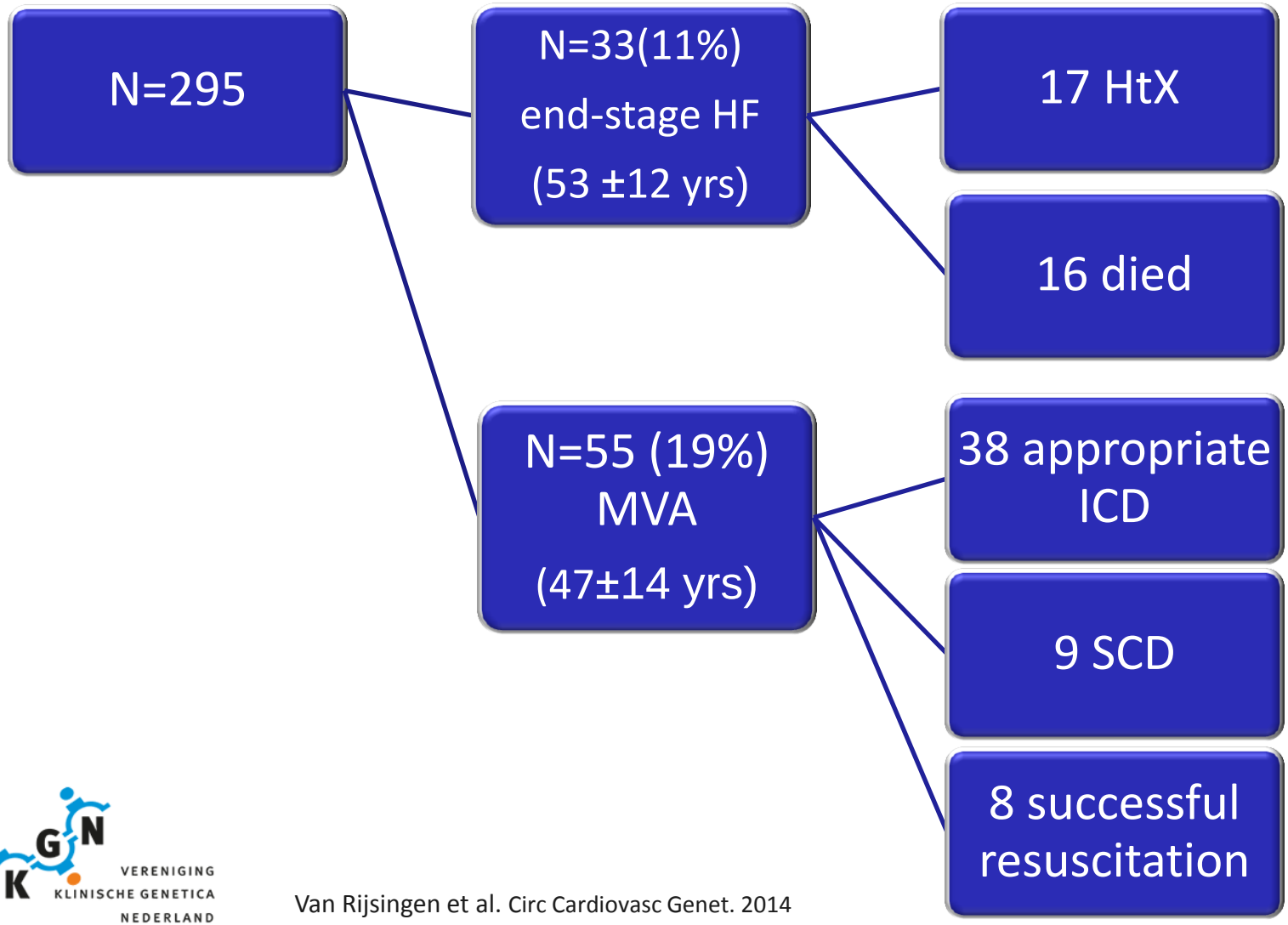


DPP6

2008
44.6(37-52)

2012
68.2 (64-72)

Cardiac outcomes PLN R14del



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Van Rijsingen et al. Circ Cardiovasc Genet. 2014

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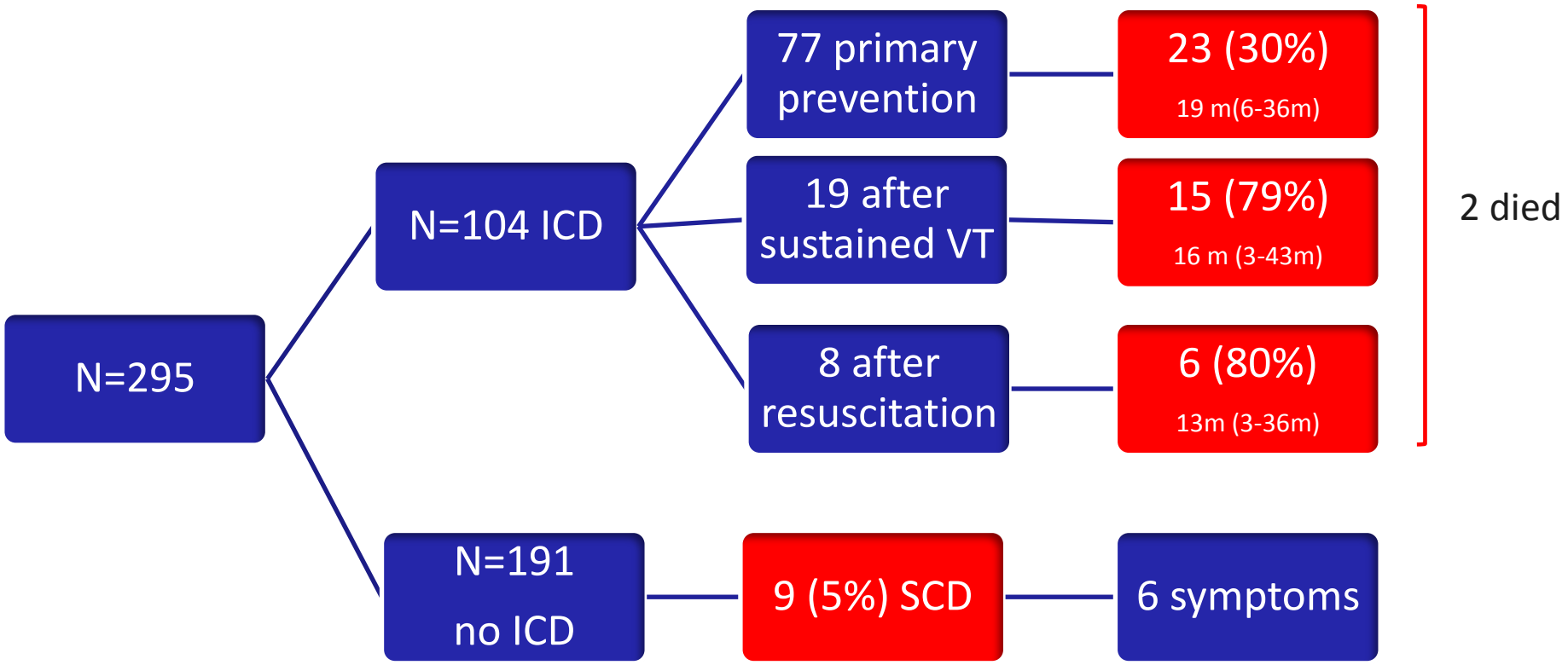
Cardiac outcomes/ ICD therapy: PLN R14del



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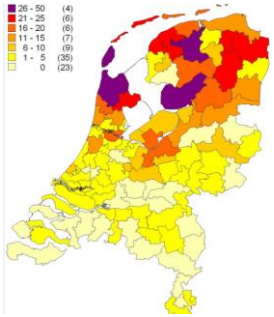
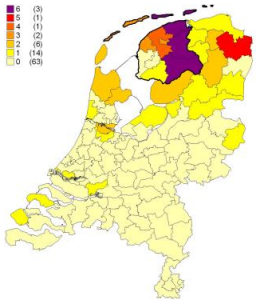
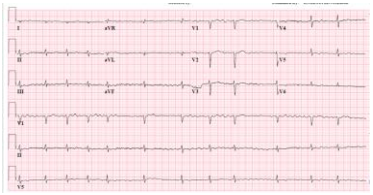
Van Rijsingen et al. Circ Cardiovac Genet 2014

PLN R14del: low penetrance?







PLN R14del

Van der Zwaag PA et al Neth Heart J 2013;21:286-93.

1:1000 Dx DCM/ARVC

10% PLN R14del: 1:10,000

5.6 million➔ n=11,000/NL

Registry n=1000

1/473
1/225
1/1300
1/440

=1 in 500

Low penetrance (10%) dominant pathogenic variant?

Susceptibility?

Van der Zwaag PA et al Eur J Heart Fail. 2012;14:1199-207
Milano A te al Circ Cardiovasc Genet 2016;9:147-53.

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Methods

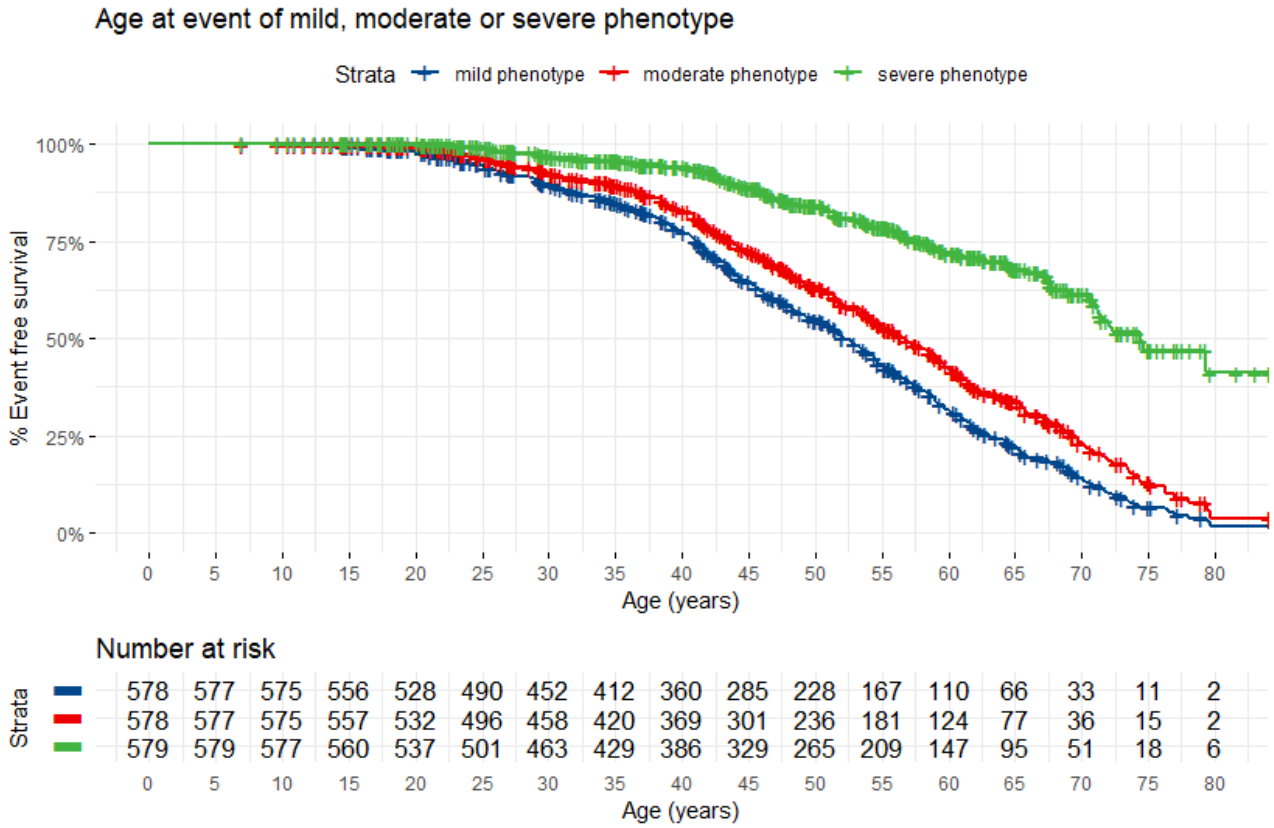
Outcome measurements:

- **Mild phenotype:** microvoltages or repolarization disturbances or >500 PVC on holter
- **Moderate phenotype:** NSVT, fibrosis on MRI, LVEF <45% or NYHA>2
- **Severe phenotype:** CPR at presentation, VT or VF, heart transplantation or LVAD, hospitalisation for heart-failure, appropriate ICD shock, cardiac death

- **Arrhythmic event:** minor (>500 PVC, NSVT), major (sust VT, appropriate ICD shock or ATP, cardiac death due to arrhythmia)
- **Heart-failure event:** minor (LVEF <45% or NYHA >2), major (HTx or LVAD, hospitalisation for heart-failure or cardiac death due to pump failure)

Results- kaplan-meier plots

Mild phenotype	
Age	**% penetrance**
20 yrs	2,2
40 yrs	22,7
60 yrs	68,7
80 yrs	98,1
Moderate phenotype	
20 yrs	1,1
40 yrs	17,2
60 yrs	58
80 yrs	96,1
Severe phenotype	
20 yrs	0
40 yrs	6,1
60 yrs	28
80 yrs	58,8



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Tom Verstraelen et al.

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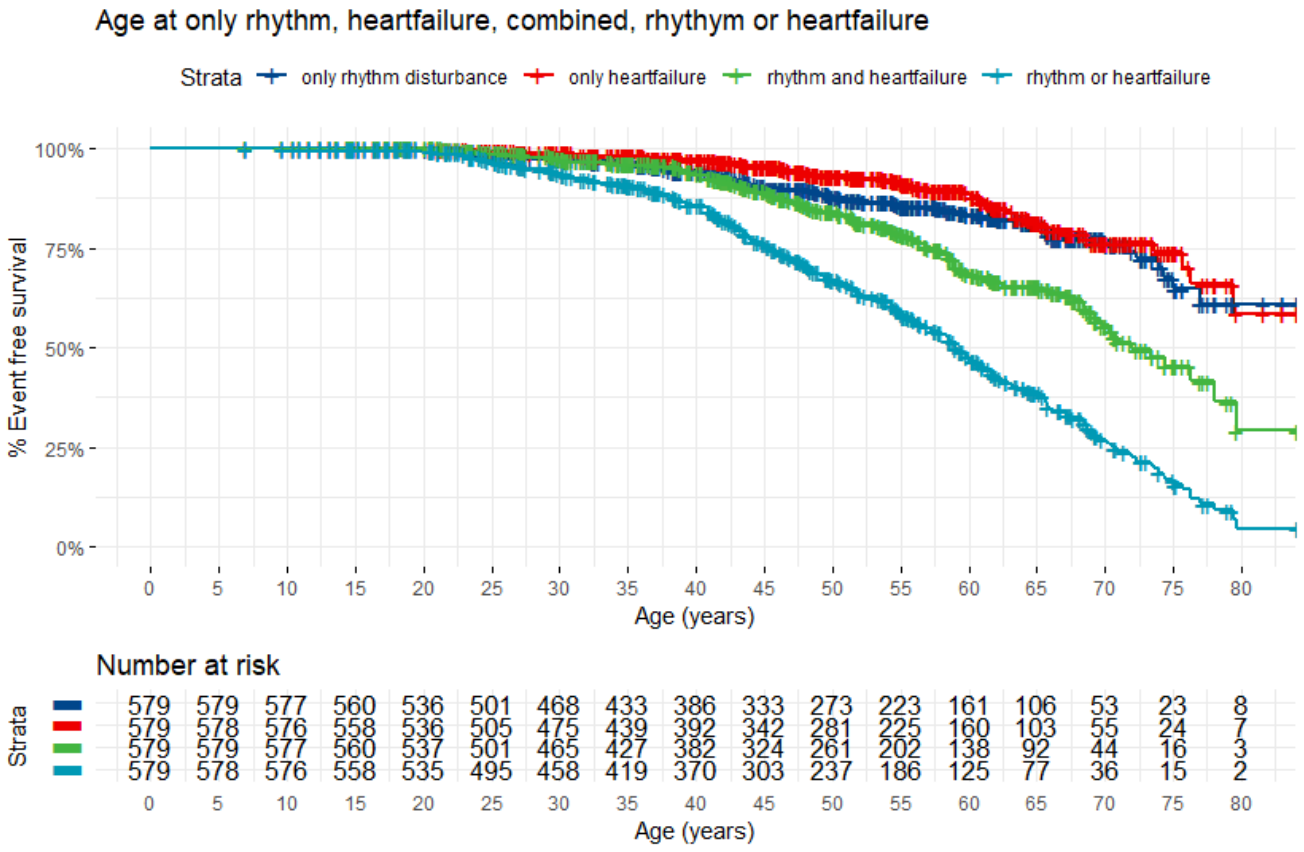
Results- kaplan-meier plots

Only rhythm	
Age	**% penetrance**
20 yrs	0,2
40 yrs	5,9
60 yrs	16,6
80 yrs	39
Only heartfailure	
20 yrs	0,5
40 yrs	2,9
60 yrs	11,6
80 yrs	41,4
Rhythm AND heartfailure	
20 yrs	0
40 yrs	6,1
60 yrs	31,8
80 yrs	70,9
Rhythm OR heartfailure	
20 yrs	0,5
40 yrs	14,3
60 yrs	53,1
80 yrs	95,3



Echter: dit zijn indexen + familieleden!

ARVC verschil in familieleden?

Approach to family screening in arrhythmogenic right ventricular dysplasia/cardiomyopathy

Anneline S.J.M. te Riele[1,2], Cynthia A. James[1], Judith A. Groeneweg[2,3],

European Heart Journal (2016) 37, 755–763

Siblings had a three-fold-increased risk of ARVD/C diagnosis compared with parents and children (odds ratio 3.11, P. 0.001)

One-third of first-degree relatives develop manifest ARVD/C. Siblings have highest risk of disease, even after correcting for age and sex

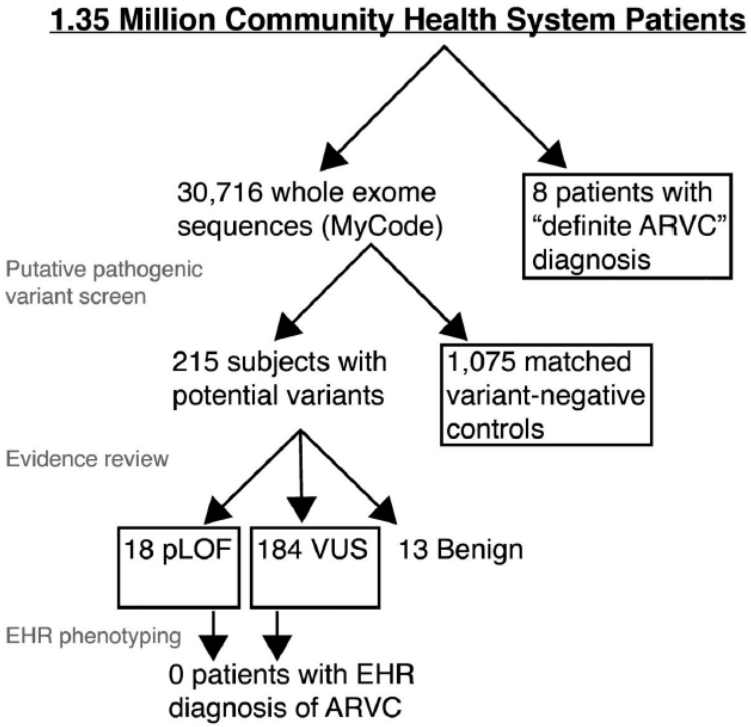
VERENIGING KLINISCHE GENETICA NEDERLAND

Electronic Health Record Phenotype in Subjects with Genetic Variants Associated with Arrhythmogenic Right Ventricular Cardiomyopathy: A Study in 30,716 Subjects with Exome Sequencing:

Genotype-Phenotype Association in Incidental ARVC Genetic Findings

Christopher M. Haggerty, PhD[1], Cynthia A. James, ScM, PhD[2], Hugh Calkins, MD[2], Crystal Tichnell, MGC[2], Joseph B. Leader, BA[3], Dustin N. Hartzel, BS[3], Christopher D. Nevius, BT[1],

Genet Med. 2017 Nov;19(11):1245-1252



Geen verschillen in de groepen qua:
-diagnostische criteria ARVC
-cardiomyopathie
-ICD
-pompfunctie etc

N=14 ECGs
1 minor criterion

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Circulation: Genomic and Precision Medicine

RESEARCH LETTER

Phenotypic Characterization of Indi
With Variants in Cardiovascular Ger
the Absence of a Primary Cardiovas
Indication for Testing

The rapid uptake of clinical genomic sequencing has exposed patients to the unanticipated identification of variants in genes associated with cardiovas-

Robyn

N=33 patienten verwezen:
22 varianten (14 SF, 8 PF)
Classificatie: 10 P/LP
ACMG classificatie: 1 P/ 3 LP (geen cardiol phenotype!)

Managing Secondary Ge
Associated With Arrhyth
Ventricular Cardiomyopa

Case Studies and Proposal for Clinica

DNA variants that are expected to confer risk for arrhythm
tricular cardiomyopathy (ARVC) are recommended as ret
findings from clinical genomic sequencing. However, ARVC presents several

PhD
Brittney Murray, MS

PKP2 c.1237C>T; p.(Arg413*) 67 jr m
PKP2 c.2146-1G>C 38 jr v
PKP2 c.2509delA; p.(Ser837Valfs*94) 8 jr v HCM en vader
DSP c.478C>T; p.(Arg2160*) 25 jr M en vader 59 jr

VKGN VERENIGING KLINISCHE GENETICA NEDERLAND

UMC Utrecht

Circulation: Genomic and Precision Medicine

ORIGINAL ARTICLE

Prevalence and Electronic Health Record-Based Phenotype of Loss-of-Function Genetic Variants in Arrhythmogenic Right Ventricular Cardiomyopathy-Associated Genes

BACKGROUND: Arrhythmogenic right ventricular cardiomyopathy

Eric D. Carruth. PhD

Circ Genom Precis Med. 2019;12:e002579.

N=61000 WES

PENETRANTIE 6%
(ipv 40-60%)

.23%

Geen Dx ARVC; % cardiol afw = controles

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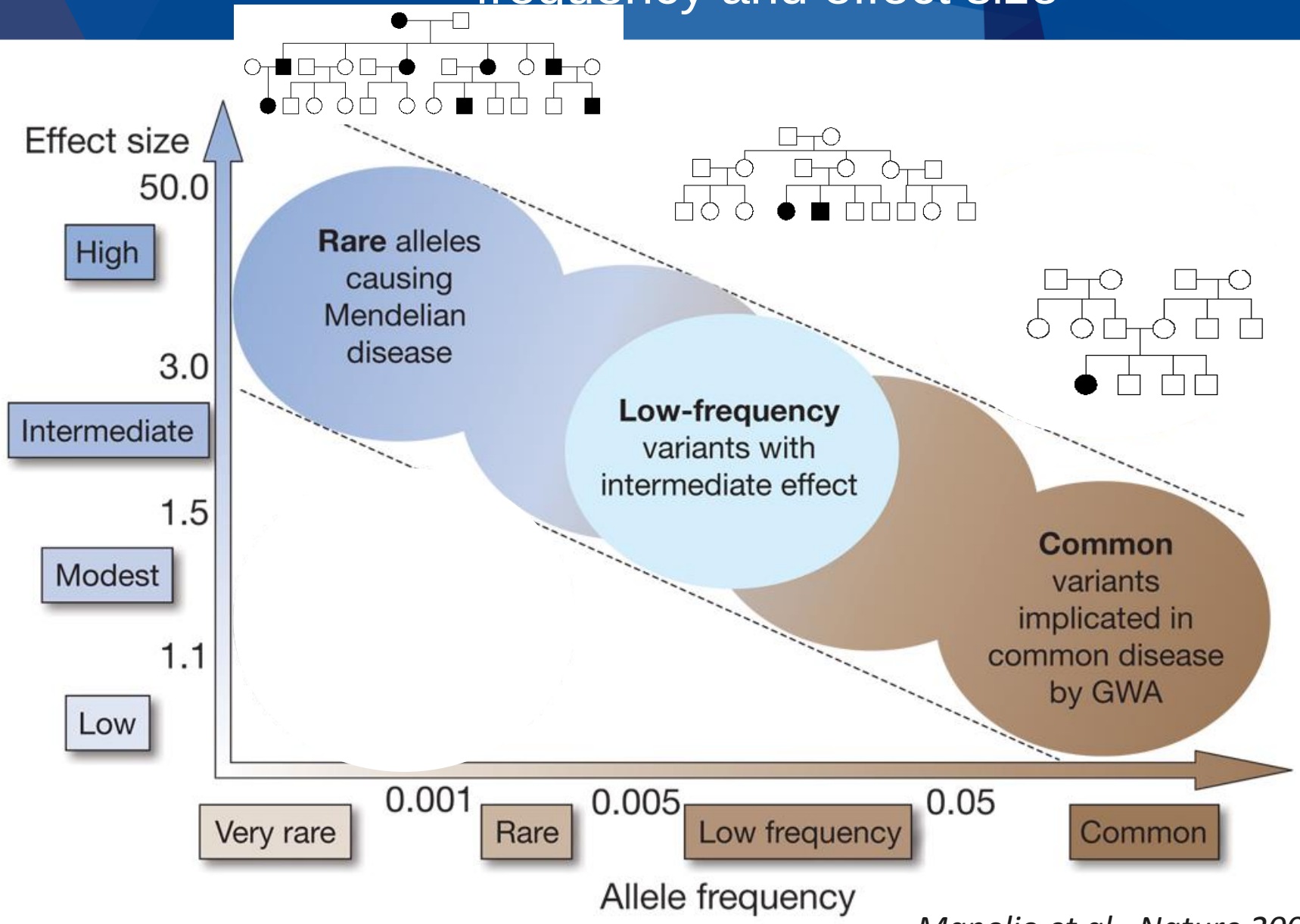
Utrecht

Genetic variants occuring in the general population:
- frequency and effect size -



Manolio et al., Nature 2009

WAT DRAAGT BIJ AAN PENETRANTIE/VARIABILITEIT

Non-genetic modifiers

PKP2 + exercise = earlier Dx ARVC

Exercise Increases Age-Related Penetrance and Arrhythmic Risk in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Associated Desmosomal Mutation Carriers

Cynthia A. James, ScM, PhD, Aditya Bhonsale, MD, Crystal Tichnell, MGC, Brittney Murray, MS, Stuart D. Russell, MD, Harikrishna Tandri, MD, Ryan J. Tedford, MD, Daniel P. Judge, MD, and Hugh Calkins, MD

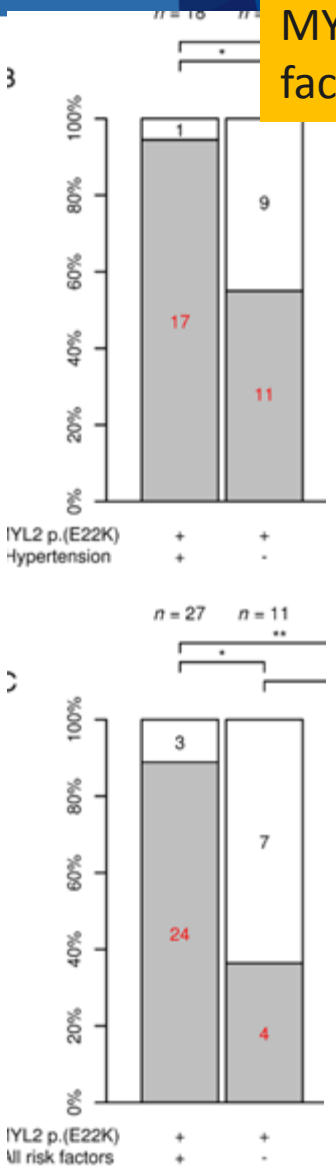
Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members

Jørg Saberniak[1,2], Nina E. Hasselberg[1,2], Rasmus Borgquist[3], Pyotr G Platonov[3], Sebastian I. Sarvari[1,2], Hans-Jørgen Smith[4], Margareth Ribe[1,2], Anders G. Holst[5], Thor Edvardsen[1,2], and Kristina H. Haugaa[1,2]*

Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy

Anne-Christine Ruwald , Frank Marcus , N.A. Mark Estes III, Mark Link , Scott McNitt , Bronislava Polonsky , Hugh Calkins , Jeffrey A. Towbin , Arthur J. Moss , Wojciech Zareba

MYL2 + risk factors= Dx HCM



Claes et al. Eur Heart J. 2015;37:1815-22.

ALCOHOL + GENETICS

PHENOTYPE	
Alcoholic Cardiomyopathy (ACM)	**Dilated Cardiomyopathy (DCM)**
Prevalence of rare genetic variants in cardiomyopathy genes: ACM: 13.5% Controls: 2.9% $P_{Fisher} = 0.000012$	LVEF according to titin truncating variant (TTNtv) status and alcohol intake: no TTNtv or excess alcohol intake: 39.6 ± 12.2% TTNtv only: 39.8 ± 13.2% excess alcohol intake only: 37.8 ± 11.8% TTNtv AND excess alcohol intake: 27.7 ± 12.7% $P_{Multivariate} = 0.007$

Ware, J.S. et al. J Am Coll Cardiol. 2018;71(20):2293-302.

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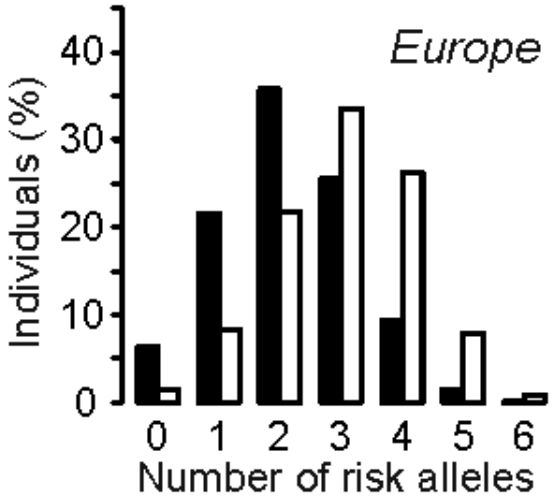
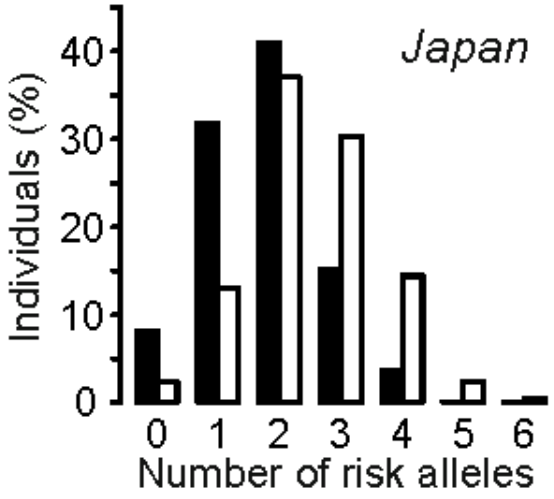
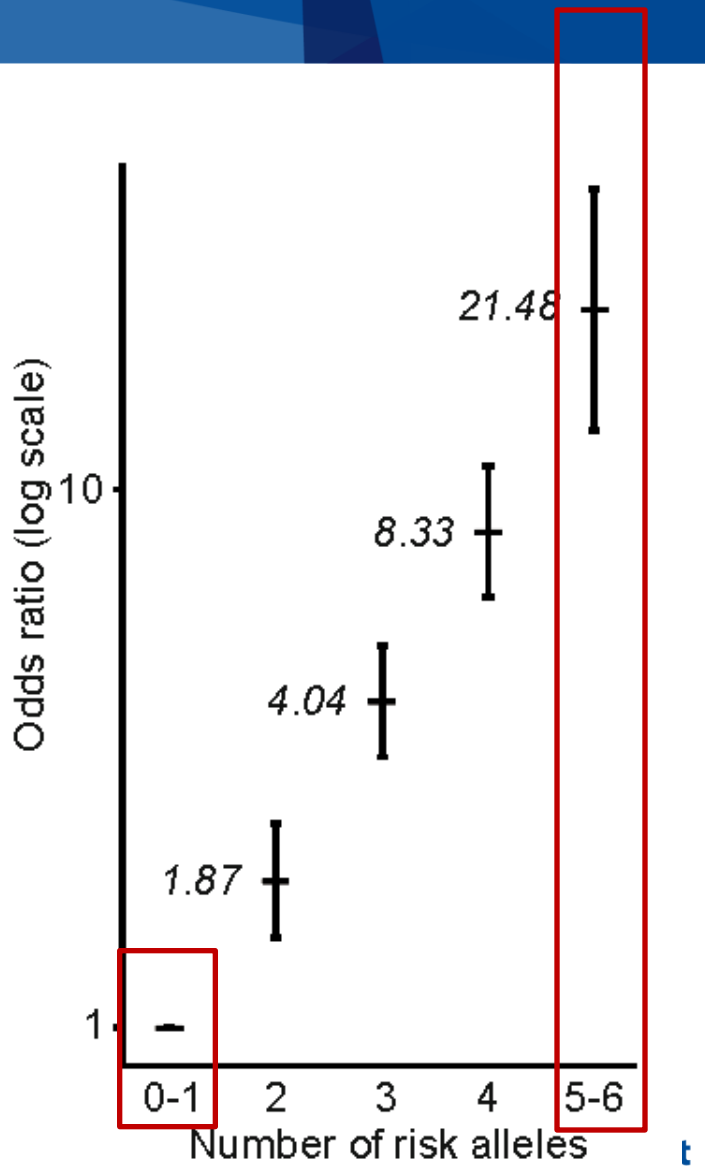
Cumulative effect of alleles at the three loci on susceptibility to Brugada Syndrome

Controls

BrS cases







Bezzina et al., *Nat Genet* 2013

VERENIGING KLINISCHE GENETICA NEDERLAND

Klinische uitdagingen en oplossingen

Bezzina et. al., Circ Res 2015

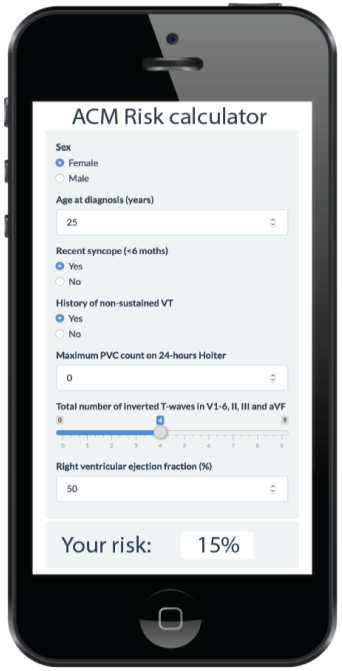
-Controle frequentie
-Behandeling
-Leefregels (sport)

VERENIGING KLINISCHE GENETICA NEDERLAND

CVON eDETECT/ CUREPLaN

- Betere risico-inschatting (grotere series)
- Betere inschatting penetrantie/variabiliteit (grotere series)
- Studies naar additionele factoren

(genetisch, niet-genetisch, epigenetisch)



Cadrin/Bosman*, ….,
Te Riele/James*. Eur Heart J 2019

VKGN VERENIGING KLINISCHE GENETICA NEDERLAND

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Aanpassen controle-intervallen

asymptomatic

Late manifestation

Early manifestation

VERENIGING KLINISCHE GENETICA NEDERLAND

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CONCLUDEREND

- Penetrantie/ernstige fenotypen overschat
- Genetics loads the gun, other factors pull the trigger

  =inspanning, risicofact HVZ, alcohol, infecties,

  2e mutatie/SNPs, zwangerschap, chemotherapie=
- Risico-inschatting in individuele patient (ICD)/ G+/P-schiet tekort
- Kalm aan doen met secondary findings in ACMG genen
- van wasstraat naar maatwerk

UMC Utrecht

Dank voor jullie aandacht

ERFELIJKE Hartziekten.nl

ZonMw

STICHTING GENETISCHE HARTSPIERZIEKTE PLN

CURE-PLaN

Hartstichting

CVON Cardio Vasculair Onderzoek Nederland