

PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA

Centro Congressi
di Confindustria

**Auditorium
della Tecnica**

9^a Edizione

30 Settembre

1 Ottobre

2022



Cardiomiopatia Aritmogena – What's New?

STRATIFICAZIONE DEL RISCHIO ARITMICO E INDICAZIONE AD ICD: DALLE LINEE GUIDA AI NUOVI SCORE DI RISCHIO

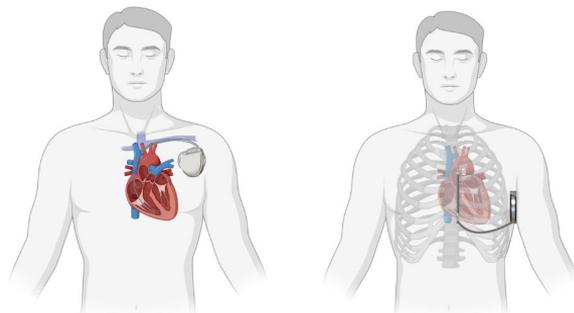
Alessio Gasperetti, MD





ICD & ARVC

A clinical dilemma



Avoid sudden
cardiac death
(SCD)



Avoid implantable
cardioverter
defibrillator (ICD)
Complications



ARVC Predictors and ICD recommendations

Level of ICD recommendation

I
Recommended

ITFC 2015

Cardiac arrest
Sustained VT
RVEF or LVEF \leq 35%

ACC/AHA/HRS 2017

Cardiac arrest
Sustained VT
RVEF or LVEF \leq 35%

HRS 2019

Cardiac arrest
Unstable Sustained VT
LVEF \leq 35% + NYHA II-III

ESC 2022

Cardiac arrest
Unstable Sustained VT

IIa
Should be considered

Cardiac Syncope
NSVT
RVEF < 40%
LVEF < 45%

Cardiac Syncope

Stable sustained VT
Cardiac syncope
LVEF < 35% + NYHA I
Multiple risk factors †
3 major
2 major + 2 minor
1 major + 4 minor

Stable sustained VT
Cardiac Syncope
RVEF or LVEF \leq 35%
RVEF < 40% / LVEF < 45%
+ NSVT or VT at PVS

IIb
May be considered

Other minor risk factors*

Multiple risk factors †
2 major
1 major + 2 minor
4 minor

Corrado, Circulation, 2015
 Al-Khatib, JACC, 2018
 Zeppenfeld, ESC, 2022
 Towbin, Heart Rhythm, 2019



Risk prediction models in ARVC

Primary Prevention & ICD



An arrhythmic risk prediction model for ARVC



Why?

- **Improve risk prediction** over a single risk factor-based approach
 - Predictors have different weight/interactions/additive value
 - Allows use of continuous predictors
 - Consensus not prospectively validated/mostly based on small studies
- Provide an **absolute risk** to inform shared decision-making process



European Heart Journal (2022) 00, 1–9
<https://doi.org/10.1093/eurheartj/ehac180>

CLINICAL RESEARCH

Arrhythmia/electrophysiology

A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy

Julia Cadrin-Tourigny^{1,2†}, Laurens P. Bosman^{3,4†}, Anna Nozza⁵, Weijia Wang¹, Rafik Tadros², Aditya Bhonsale¹, Mimount Bourfiss⁴, Annik Fortier⁵, Øyvind H. Lie^{6,7}, Ardan M. Saguner⁸, Anneli Svensson⁹, Antoine Andorin², Crystal Tichnell¹, Brittney Murray¹, Katja Zeppenfeld¹⁰, Maarten P. van den Berg¹¹, Folkert W. Asselbergs^{3,4,12}, Arthur A.M. Wilde¹³, Andrew D. Krahn¹⁴, Mario Talajic², Lena Rivard², Stephen Chelko¹, Stefan L. Zimmerman¹⁵, Ihab R. Kamel¹⁵, Jane E. Crosson¹, Daniel P. Judge¹, Sing-Chien Yap¹⁶, Jeroen F. van der Heijden⁴, Harikrishna Tandri¹, Jan D.H. Jongbloed¹⁷, Marie-Claude Guertin⁵, J. Peter van Tintelen^{3,18}, Pyotr G. Platonov¹⁹, Firat Duru⁸, Kristina H. Haugaa^{6,7}, Paul Khairy², Richard N.W. Hauer^{3,4}, Hugh Calkins¹, Anneline S.J.M. te Riele^{3,4‡}, and Cynthia A. James^{1*‡}



Cadrin-Tourigny



Bosman



te Riele



James



5-yr risk prediction for any sustained VA

Population:

Definite ARVC , Primary prevention
 USA, Netherlands, Canada, Switzerland,
 Norway, Sweden

	N (%)
	528
Male sex	236 (45)
Age at diagnosis (years)	38 ± 15
Proband status	263 (50)
Pathogenic mutation	340 (64)
Plakophilin 2 (PKP2)	258 (49)
Recent syncope	48 (9)
RVEF (%)	44 ± 10
LVEF <50%	67 (13)
ICD at baseline	218 (41)
	146 (28)
	4.83 y

Candidate Predictors

Male Sex
 Younger age
 Recent Cardiac syncope
 Non sustained VT (NSVT)
 PVC count/24h Hours
 ECG Leads with T-wave
 inversion anterior + inferior (per
 lead increase)
 RVEF
 LVEF

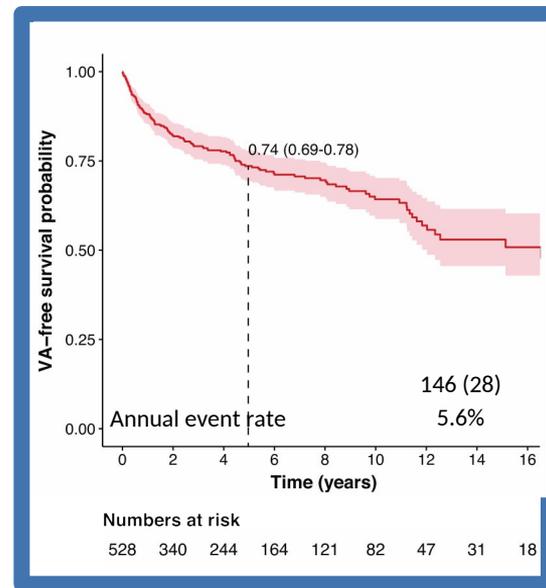
Outcome:

Sustained Ventricular arrhythmias (VA)

SCD/Aborted SCD

Sustained VT/VF

VT/VF treated by ICD



Model performance



Predictors	Multivariate	
	HR (95% CI)	p-value
Male sex	1.61 (1.14-2.27)	0.006
Age (per year increase)	0.98 (0.97-0.99)	< 0.001
Recent cardiac syncope	1.95 (1.20-3.15)	0.007
Prior NSVT	2.27 (1.48-3.48)	< 0.001
24 h. PVC count (ln)*	1.17 (1.03-1.33)	0.013
Leads with T-wave inversion	1.12 (1.03-1.22)	0.010
RVEF (per % decrease)	1.03 (1.01-1.04)	0.001
LVEF (per % decrease)	(Not included in the model)	



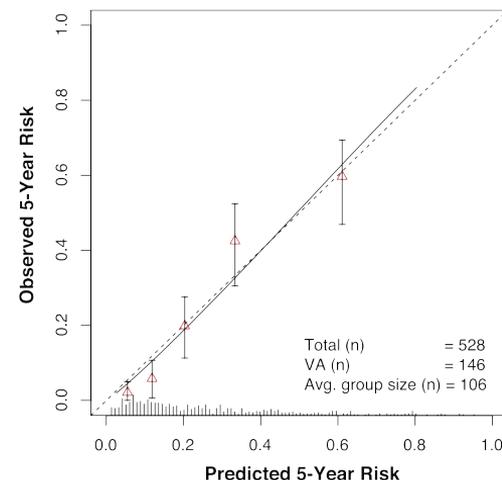
ARVCrisk.com

Discrimination:

C-statistic: 0.77

Internal validation:

Calibration slope: 0.93





2 Large external validation studies


 ESC
 European Heart Journal (2022) 00, 1–12
<https://doi.org/10.1093/eurheartj/ehac289>

 CLINICAL RESEARCH
Arrhythmias

Arrhythmic risk prediction in arrhythmogenic right ventricular cardiomyopathy: external validation of the arrhythmogenic right ventricular cardiomyopathy risk calculator

Paloma Jordà^{1,2,3†}, Laurens P. Bosman^{4†}, Alessio Gasperetti⁵, Andrea Mazzanti^{6,7,8}, Jean-Baptiste Gourraud⁹, Brianna Davies¹⁰, Tanja Charlotte Frederiksen^{11,12}, Zoraida Moreno Weidmann¹³, Andrea Di Marco¹⁴, Jason D. Roberts^{15,16,17}, Ciorsti MacIntyre¹⁸, Colette Seifer¹⁹, Antoine Delinière²⁰, Wael Alqarawi²¹, Deni Kukavica^{6,7,8}, Damien Minois⁹, Alessandro Trancuccio^{6,7,8}, Marine Arnaud⁹, Mattia Targetti²², Annamaria Martino²³, Giada Oliviero²³, Daniel C. Pipilas²⁴, Corrado Carbuicchio²⁵, Paolo Compagnucci²⁶, Antonio Dello Russo²⁶, Iacopo Olivotto²², Leonardo Calò²³, Steven A. Lubitz²⁴, Michael J. Cutler²⁸, Philippe Chevalier²⁰, Elena Arbelo^{2,3,29,30}, Silvia Giuliana Priori^{6,7,8}, Jeffrey S. Healey^{15,16}, Hugh Calkins⁵, Michela Casella²⁷, Henrik Kjærulf Jensen^{11,12}, Claudio Tondo^{25,31}, Rafik Tadros¹, Cynthia A. James⁵, Andrew D. Krahn¹⁰, and Julia Cadrin-Tourigny^{1*}


 ESC
 European Society of Cardiology
 European Heart Journal (2022) 43, 3053–3067
<https://doi.org/10.1093/eurheartj/ehac235>

 CLINICAL RESEARCH
Heart failure and cardiomyopathies

Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator

Alexandros Protonotarios^{1,2*}, Riccardo Bariani³, Chiara Cappelletto^{4,5}, Menelaos Pavlou⁶, Alba García-García⁷, Alberto Cipriani³, Ioannis Protonotarios⁸, Adrian Rivas⁹, Regitze Wittenberg¹⁰, Maddalena Graziosi¹¹, Zafeirenia Xylouri⁸, José M. Larrañaga-Moreira¹², Antonio de Luca⁴, Rudy Celeghin³, Kalliopi Pilichou³, Athanasios Bakalakis^{1,2}, Luis Rocha Lopes^{1,2,13}, Konstantinos Savvatis^{1,2,13}, Davide Stolfo^{4,5}, Matteo Dal Ferro⁴, Marco Merlo⁴, Cristina Basso³, Javier Limeres Freire^{13,14,15}, Jose F. Rodriguez-Palomares^{13,14,15}, Toru Kubo¹⁶, Tomas Ripoll-Vera¹⁷, Roberto Barriaes-Villa^{12,13}, Loizos Antoniadis¹⁸, Jens Mogensen¹⁹, Pablo Garcia-Pavia^{9,13,15}, Karim Wahbi²⁰, Elena Biagini¹¹, Aris Anastasakis²¹, Adalena Tsatsopoulou^{8,21}, Esther Zorio^{15,22}, Juan R. Gimeno^{7,13,15}, Jose Manuel Garcia-Pinilla^{15,23}, Petros Syrris¹, Gianfranco Sinagra⁴, Barbara Baucé³, and Perry M. Elliott^{1,2,13}

Large external validation (1)



- Canada
 - Paloma Jorda
 - Jeff Healey
 - Jason Roberts
 - Brianna Davis
 - Wael Alqarawi
 - Ciorsti Malntyre
 - colette seifer
 - Rafik Tadros
 - Andrew Krahn
 - Julia Cadrin Tourigny
- USA
 - Cindy James
 - Hugh Calkins
 - Steve Lubitz
 - Michael Cutler
- Italy
 - Alessio Gasperetti
 - Silvia Priori
 - Andrea Mazzanti
 - Iacopo Olivotto
 - Leonardo Calo
 - Michele Casella
- Spain
 - Elena Arbelo
 - Zoraida Moreno Weidmann
 - Andrea di Marco
- Denmark
 - Henrik Jenssen
 - Tanja Charlotte Frederiksen
- France
 - Jean Baptiste Gourraud
 - Antoine Delinière
 - Philippe Chevalier

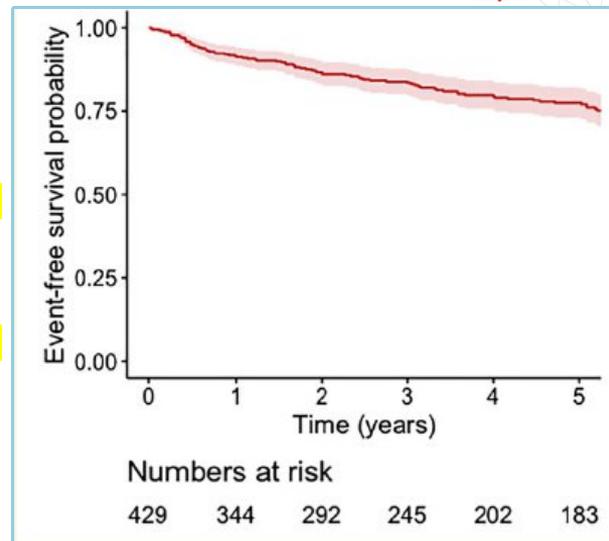


Jorda & Bosman ...Cadrin-Tourigny European Heart Journal 2022

Baseline Characteristics



	Overall (n=429)	No sustained VA (n=326)	Sustained VA (n=103)	P value
Demographics and genetics				
Age at diagnosis (years)	43.1 ±15.8	44.1±15.7	40.1±16.0	0.025
Male sex	235 (54.8)	159 (48.8)	76 (73.8)	<0.001
Proband status	278 (64.8)	197 (60.4)	81 (78.6)	0.001
(Likely) pathogenic variants (n=282)	198 (46.2)	150 (46.0)	48 (46.6)	0.480
Genotype				0.302
PKP2	111 (25.6)	84 (25.8)	27 (26.2)	
DSP	38 (8.9)	33 (10.1)	5 (4.9)	
DSG2	27 (6.3)	22 (6.7)	5 (4.9)	
DSC2	3 (0.7)	1 (0.3)	2 (1.9)	
JUP	0 (0.0)	0 (0.0)	0 (0.0)	
TMEM43	10 (2.3)	4 (1.2)	6 (5.8)	
PLN	3 (0.7)	3 (0.9)	0 (0.0)	
Recent cardiac syncope (n=424)	37 (8.6)	16 (4.9)	21 (20.4)	<0.001
ECG/continuous ECG monitoring				
PVC count (n=324)	1434 [439-3601]	1354 [400-3719]	1676 [602-3492]	0.160
Imaging				
RVEF (%) (n=410)	45 [36-53]	47 [38-53]	40 [35-48.5]	<0.001
LVEF (%) (n=404)	57 [51-60]	57 [51-61]	57 [50-60]	0.049
ICD at baseline	175 (40.8)	113 (34.7)	62 (60.2)	<0.001



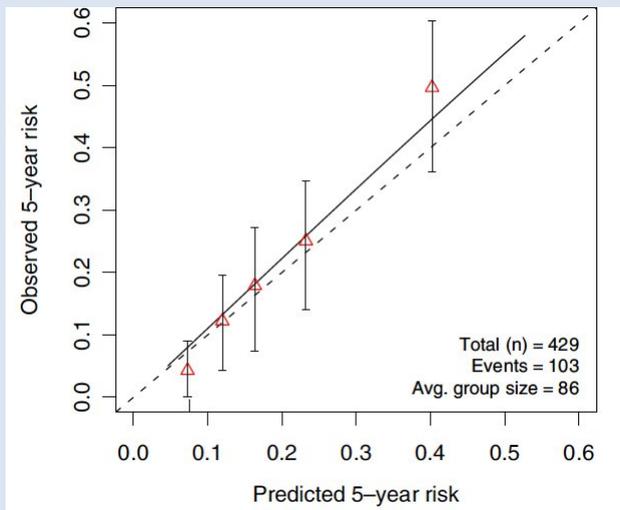
Event rate 4.83/year
Follow-up 5.02 y

Jorda & Bosman ...Cadrin-Tourigny
 Eur Heart J 2022



Large external validation (1)

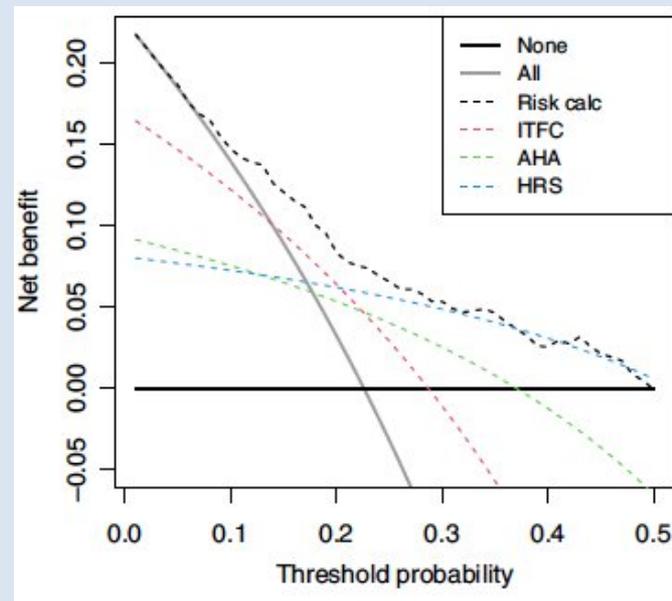
Performance



C-statistic=0.70

No advantage in updating the model

Comparison



Works better than other single factor based approaches



Large external validation (2)



ESC

European Society
of CardiologyEuropean Heart Journal (2022) 43, 3053–3067
<https://doi.org/10.1093/eurheartj/ehac235>

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Table 1 Demographic, genetic, and clinical characteristics of patients according to the occurrence of the primary endpoint

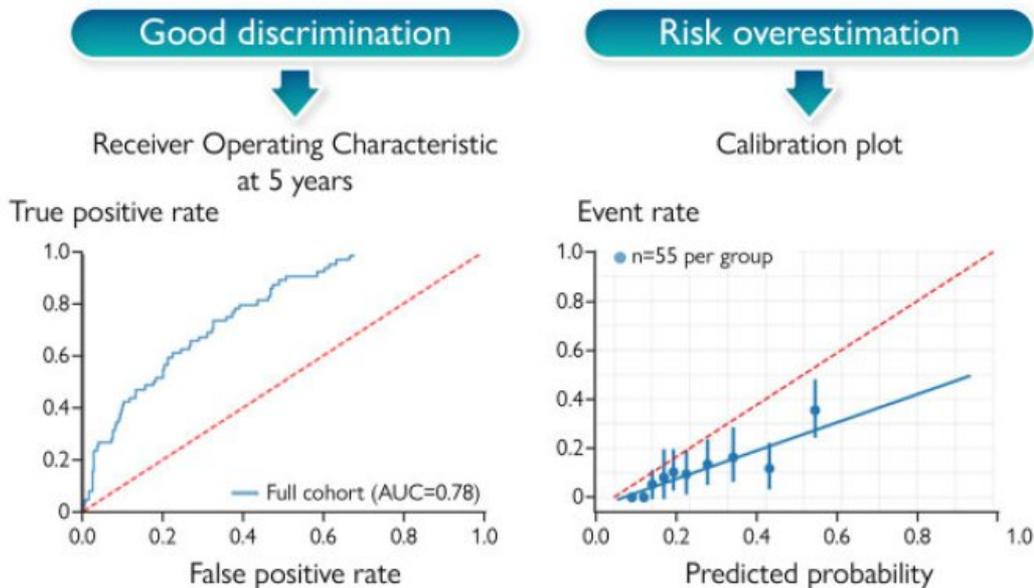
	NA	Overall (n = 554)	No VA (n = 454)	VA (n = 100)	P-value
Baseline					
Age (years)	0	41.0 (27.2,53.1)	42.8 (29.0,54.0)	37.0 (21.0,49.0)	0.002
Male sex	0	302 (54.5)	231 (50.9)	71 (71.0)	<0.001
Genotype	0				0.136
Gene elusive		157 (28.3)	138 (30.4)	19 (19.0)	
DES		5 (0.9)	4 (0.9)	1 (1.0)	
DSC2		11 (2.0)	9 (2.0)	2 (2.0)	
DSG2		27 (4.9)	24 (5.3)	3 (3.0)	
DSP		79 (14.3)	68 (15.0)	11 (11.0)	
FLNC		10 (1.8)	10 (2.2)		
JUP		21 (3.8)	16 (3.5)	5 (5.0)	
Multiple		13 (2.3)	8 (1.8)	5 (5.0)	
Not performed		104 (18.8)	79 (17.4)	25 (25.0)	
PKP2		118 (21.3)	91 (20.0)	27 (27.0)	
PLN		3 (0.5)	2 (0.4)	1 (1.0)	
RBM20		1 (0.2)	1 (0.2)		
TMEM43		2 (0.4)	1 (0.2)	1 (1.0)	
Proband status	0	304 (54.9)	234 (51.5)	70 (70.0)	0.001
PVCs (per 24 h)	77	1232.0 (382,3044)	1126.5 (273,3022)	1695.0 (983,3315)	0.004
RVEF (CMR)	263	46.0 (39.0,55.0)	48.0 (41.0,56.0)	39.0 (35.0,45.0)	<0.001
LVEF (CMR)	253	57.0 (48.0,63.0)	56.5 (47.0,63.0)	58.0 (52.0,62.5)	0.308
Follow-up					
ICD implantation	0	263 (47.5)	185 (40.7)	78 (78.0)	<0.001

100 events
Event rate 2.6%/year
Follow-up 6 years

Protonotarios, Eur H J, 2022



Large external validation (2)

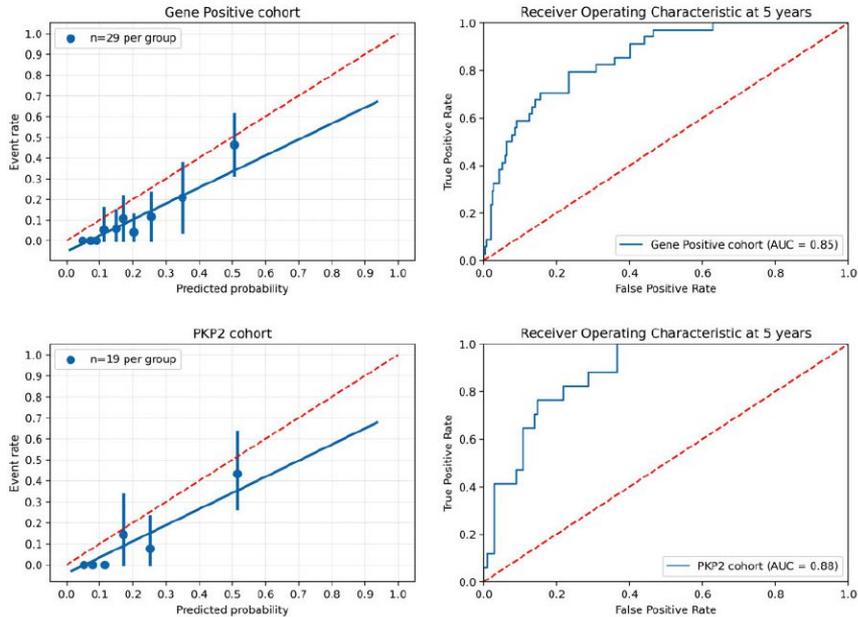




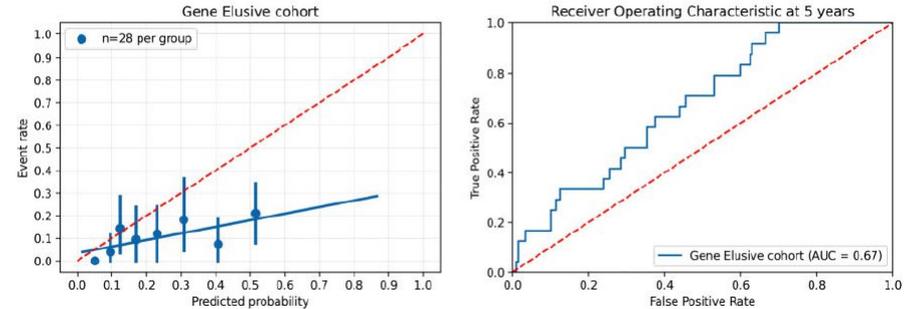
The model in subgroups

Gene +/PKP2

Gene Elusive

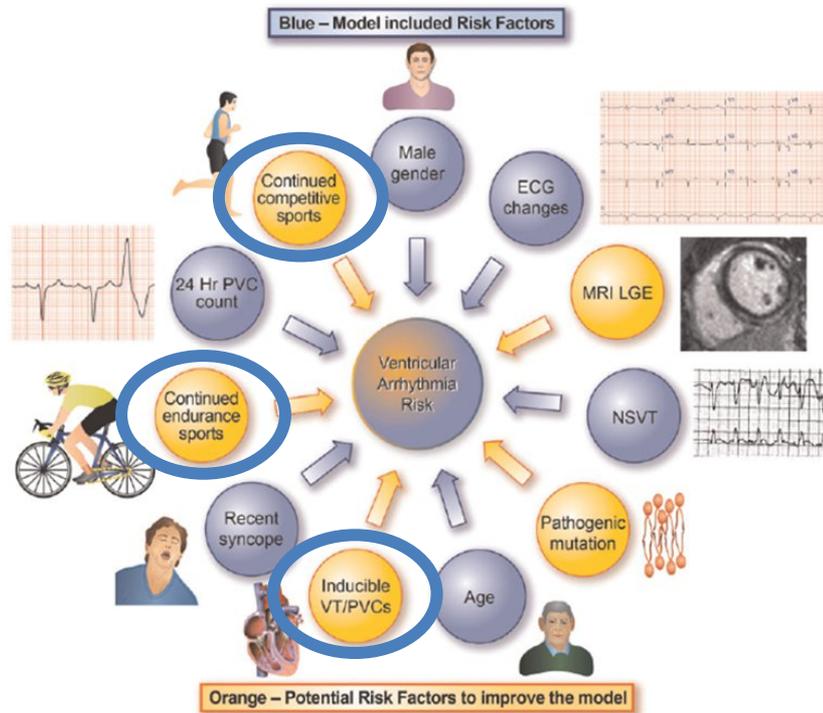


VS





IMPROVING THE RISK SCORE



McKenna et al. Eur Heart J 2019

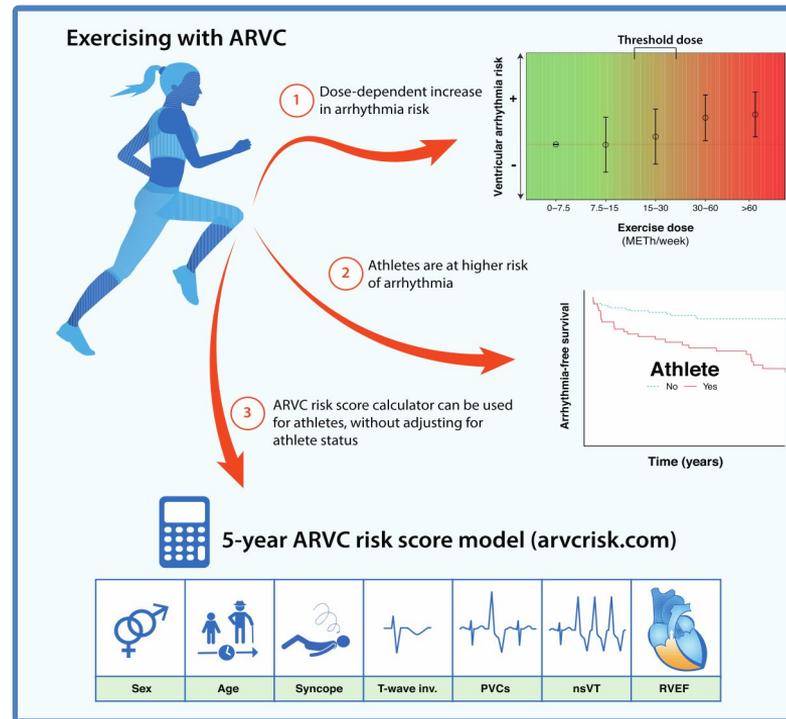


Exercise + Calculator

Context: Exercise in ARVC increases the Risk of ventricular arrhythmia

N=22 from Italian cohort (Gasperetti... Dello Russo)
 N=176 from initial cohort (Bosman... James)

Exercise does not impact the calculator
Not an independent predictor





Time + Risk Calculator

Rationale:

- ARVC risk calculator developed with variables at baseline= time of Dx
- How does the risk prediction **change through time?**
 - Should we **use time dependent variables?**
 - Should we **update the model?**

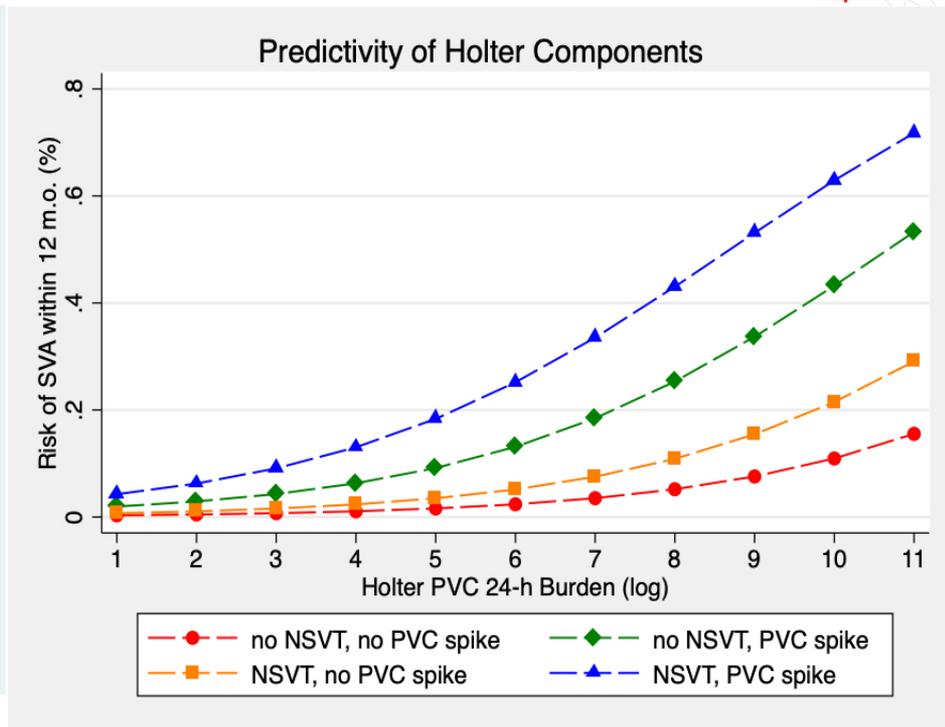
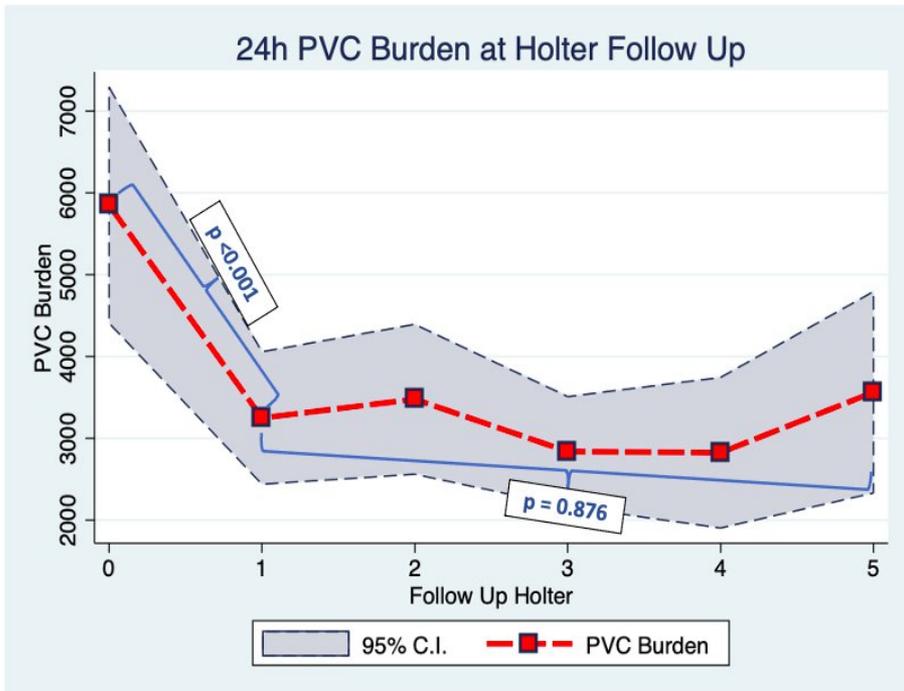
Population:

- N=408, Johns Hopkins/Netherlands
- Definite diagnosis
- Primary prevention



Carrick...James Accepted for publication Circ AE, Aug 2022

Dynamic Arrhythmic Risk Re-Evaluation by PVC variation



Holter has a strong predictivity for VA events at follow
 C statistic 0.891 (0.853 – 0.929)

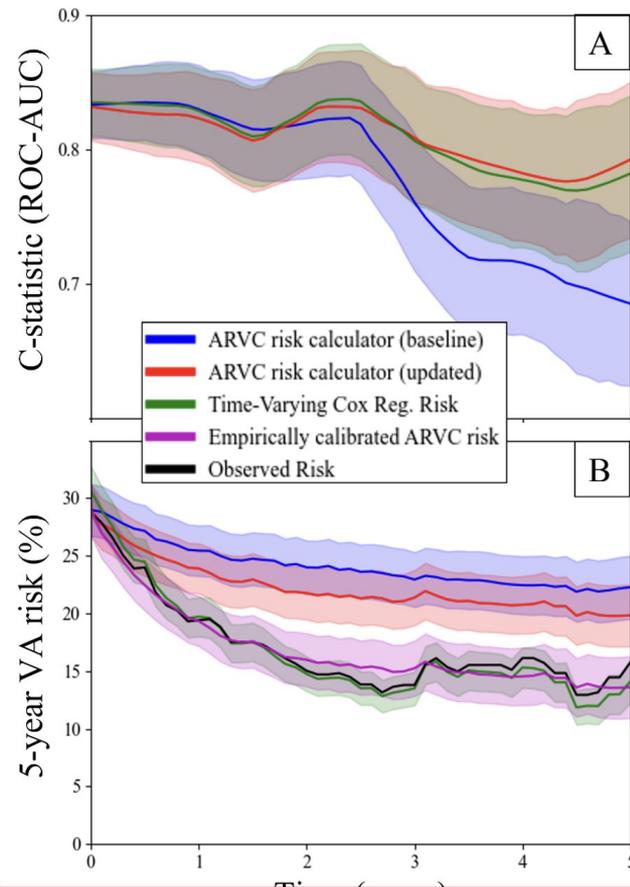
Gasperetti A... Calkins H; JAMA Cardiology



Time + Calculator

Main Findings

- 1- NSVT/PVC decrease with time
- 2- Model can be improved by either:
 - Time-varying cox regression
 - Updating the model at each visit**





EPS + Risk Calculator

Context: Conflicting information about programmed ventricular stimulation in ARVC

Question: 1-Is PVS an independent predictor of VA in ARVC?

2-Is PVS still useful now that we have a complete risk calculator?

Population: 288 patients

1-With definite Dx of ARVC

2-Without a prior history of sustained VT

3-190 part of ARVC cohort (+Italian centers)

Findings: 1-PVS predicts VA (Uni HR=4.2)

2-PVS predicts VA over the risk calculator HR=2.5

C-Stat PVS+Risk calc: 0.75, PVS alone=0.68, Risk Calc: 0.72, LLR $p < 0.001$

“Bayesian approach”



5-year risk from ARVC calculator PVS result Updated VA Risk

5%	PVS +	11.2%
	PVS -	2.2%
10%	PVS +	21.1%
	PVS -	4.5%
15%	PVS +	29.8%
	PVS -	6.9%
20%	PVS +	37.5%
	PVS -	9.5%
25%	PVS +	44.4%
	PVS -	12.3%
30%	PVS +	50.7%
	PVS -	15.3%
35%	PVS +	56.4%
	PVS -	18.4%
40%	PVS +	61.5%
	PVS -	21.9%
45%	PVS +	66.3%
	PVS -	25.6%
50%	PVS +	70.6%
	PVS -	29.6%
55%	PVS +	74.6%
	PVS -	33.9%
60%	PVS +	78.3%
	PVS -	38.7%

As measured by cardiac MRI.

Calculate

Risk of sustained ventricular arrhythmia

37.1% within 5 years

24.2% within 2 years

15.7% within 1 year

Optional: programmed ventricular stimulation (PVS)

- Positive
 Negative
 Not performed

Positive is defined as induction of sustained monomorphic VT lasting >30s or with hemodynamic compromise

Calculate

Risk of sustained ventricular arrhythmia (adjusted for PVS)

19.9% within 5 years

11.8% within 2 years

7.3% within 1 year

Reset



ARVCrisk.com



Conclusions

- ICD for ARVC patients is almost always recommended in secondary prevention
- Recent algorithm for ICD placement in primary prevention outperforms guidelines indication
- The ARVCrisk calculator is a validate tool to help ICD placement in primary prevention through a shared decision model



[ARVCrisk.com](https://www.arvcrisk.com)



Future Directions

- Risk stratification for left sided ARVC
- Genotype First Approach (FLN-C, PLN, DSP, DSG-2)

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Julia Cadrin-Tourigny



Ardan Saguner



Hari Tandri



Richard Carrick



Cindy James



Brittney Murray



Crystal Tichnell



Claudio Tondo



Hugh Calkins



Firat Duru



Anneline te Riele



Paolo Compagnucci



Michela Casella



Antonio Dello Russo



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The Campanella Family

The Patrick J. Harrison Family

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Bernstein Cardiac Arrhythmia Center

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Peter and Leonie Wild Foundation

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and families who
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possible.



GRAZIE PER L'ATTENZIONE