Risk stratification for VT Sudden cardiac death in ACHD

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The Korean Heart rhythm
COI Disclosure

The authors have no financial conflicts of interest to disclose concerning the presentation

Epidemiology of SCD in ACHD

- **SCD is one of the leading cause of death in ACHD**
  - along with progressive heart failure, peri-operative mortality
  - account for **20~25% of death in ACHD population**
- **Incidence rate : 0.3-2.7 / 1,000 PYs (20~30-fold higher than general population)**
- **Highest incidence in mid-30s to 40s** (cf. after 50s in simple forms of CHD)
- **Risk of SCD increases with complexity of the disease**
  - highest risk : ToF, TGA, cyanotic heart disease, Ebstein anomaly, Fontan circulation
  - mild disease still have a non-negligible risk of SCD
- **ACHD patients were younger and more often had a shockable initial rhythm**

Khairy P *et al*. EHJ 2022 (PMID 35302168)

Vehmeijer JT *et al*. Int J Cardiol. 2019 (PMID 30414749)

ACHD-ICD recommendations

-Based on expert opinion, observational data, and extrapolation from other patient groups (eg. acquired NICMP)

	PACES/HRS 2014	ESC 2015	ACC/AHA/HRS 2017	EHRA 2018	ESC 2020	PACES 2021
Sudden cardiac arrest due to VF/VT after evaluation to define cause and exclude reversible triggers	I	I	I	I	I	I
Unstable VT after electrophysiologic and hemodynamic evaluation	I	I	I	I	I	I
LVEF <35% with biventricular physiology and NYHA Classes II–III	I	I	IIb	I	IIa	
Unexplained syncope with LVEF <35% or VT/VF at EPS	IIb	IIa	IIa	II	IIa	IIa
Tetralogy of Fallot with clinical VT or multiple risk factors	IIa	IIa	IIa	II	IIa	
Single/systemic right ventricular dysfunction with NSVT, NYHA Classes II–III	IIb	IIb	IIb	II	IIb	IIb
Non-hospitalized CHD awaiting transplant	IIb			II		
Life expectancy ,1 year; Incessant VT/VF; NYHA Class IV; severe psychiatric illness	III		III	III		III

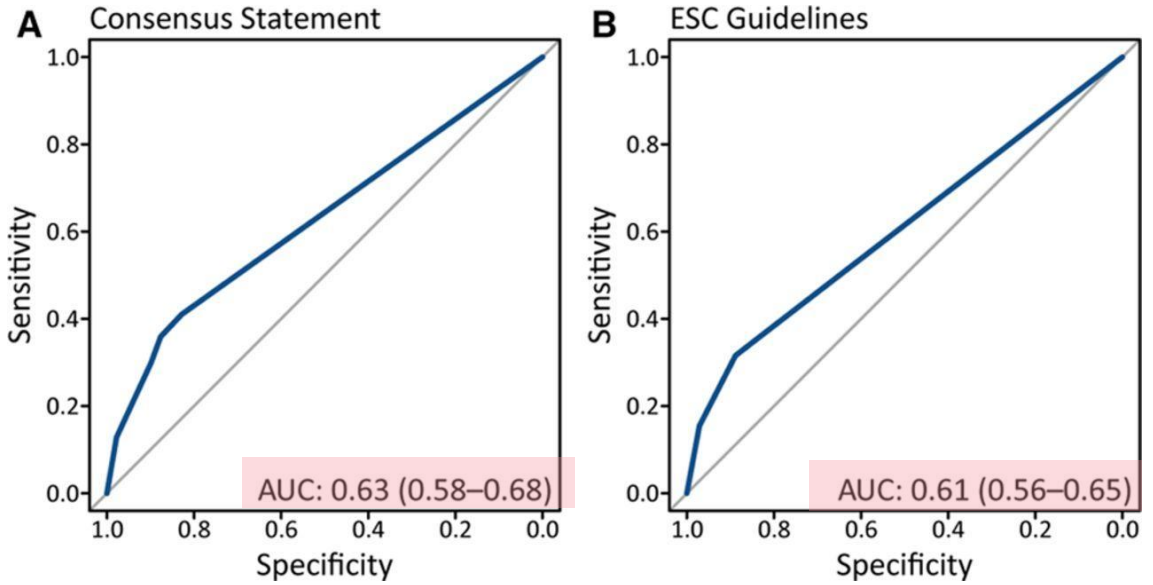
Khairy P *et al*. EHJ 2022 (PMID 35302168)

Can ACHD-ICD guidelines predict SCD? : Suboptimal discrimination of SCD

Study subjects	25,790 ACHD patients from CONCOR / TCCCA / UZ Leuven registry → 157 SCD cases (arrhythmic death) & matched controls by age, sex, congenital defect, surgical repair
Objectives & Method	To validate ACHD-ICD guidelines (2014 PACE/HRS consensus statement, 2015 ESC guidelines) → Assessed diagnostic accuracy of primary prevention ICD recommendations in case-control design

ICD Indications	2014 PACE/HRS		2015 ESC	
	Sensitivity	Specificity	Sensitivity	Specificity
Class I	12 (7–19)	98 (95–99)	15 (10–21)	97 (94–99)
Class IIa	39 (22–59)	76 (63–86)	34 (18–54)	73 (60–84)
Class IIb (1)	16 (10–24)	92 (88–95)	15 (10–22)	92 (88–95)
Class IIb (2)	35 (26–44)	86 (81–91)	NA	NA
Any indication	41 (32–51)	83 (77–88)	35 (27–43)	85 (80–89)

% (95% CI)



Guideline recommendations are not sufficiently risk prediction tools

Vehmeijer JT *et al*. Circ Arrhythm Electrophysiol. 2017 (PMID 28696220)

Why does ACHD-ICD guidelines have poor discriminative ability?

- **Scarcity of data on SCD in ACHD patients**
  - Lack of RCTs
  - ACHD-ICD guideline recommendations are based on expert opinion, observational data, and extrapolation from other patient groups (eg. acquired NICMP)

- **SCD in ACHD population include marked heterogeneity**
  - Prognostic value of any given factor vary widely according to the type of CHD
  - eg. inducible sustained VT in EPS
  - : x5 higher risk of clinical VT or SCD in ToF *vs* no prognostic value in TGA with arterial switch
  - Constant flux from evolving surgical / percutaneous interventions and medical therapies

Khairy P *et al*. EHJ 2022 (PMID 35302168)

Risk score model of SCD in ACHD : PREVENTION-ACHD

Risk model development

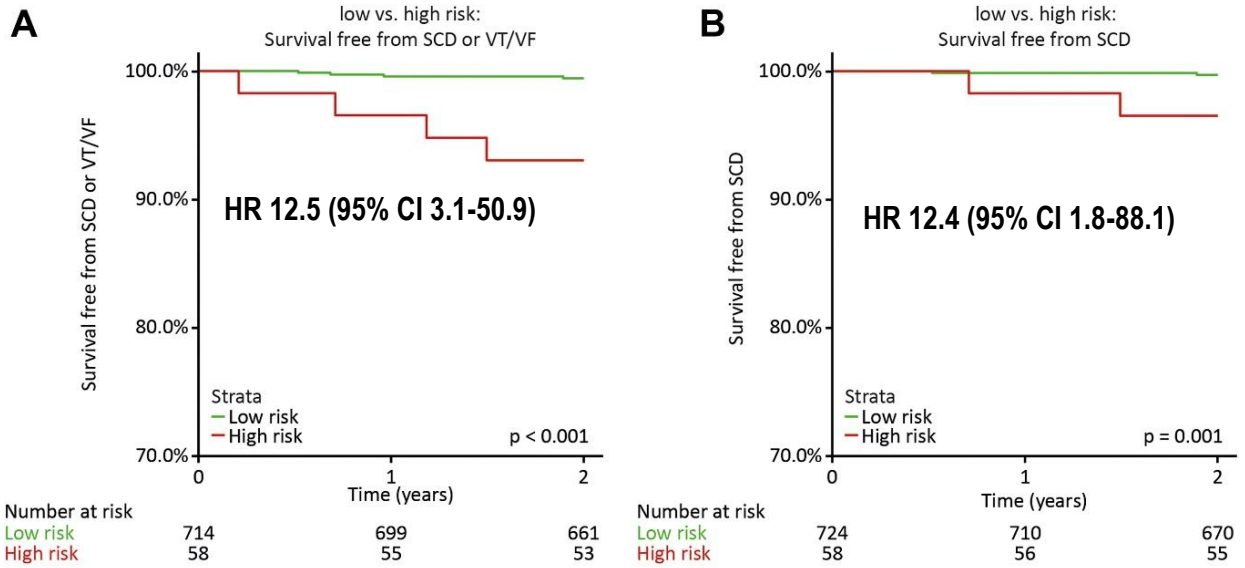
Diagnosis	Annual risk of SCD: <1%	1-2%	3-4%	5-10%	11-25%	>25%
Eisenmenger syndrome	4	8	16	>25	>25	>25	>25
Cyanotic non-Eisenmenger	3	7	15	>25	>25	>25	>25
Ebstein anomaly	1	2	5	11	23	>25	>25
Fontan circulation	<1	2	5	10	20	>25	NA*
TGA Mustard/Senning repair	<1	2	4	8	17	>25	>25
Congenitally corrected TGA	<1	<1	2	4	9	18	>25
Left sided lesions	<1	<1	2	3	7	15	>25
Tetralogy of Fallot	<1	<1	1	3	6	14	>25
Closed ASD	<1	<1	1	2	5	10	22
	1	2	3	4	5	6	7

Number of risk factors

- High risk: annual SCD risk ≥ 3%
- Low risk: annual SCD risk < 3%

(1-2%: intermediate risk, <1%: very-low risk)

Model validation



Model performance

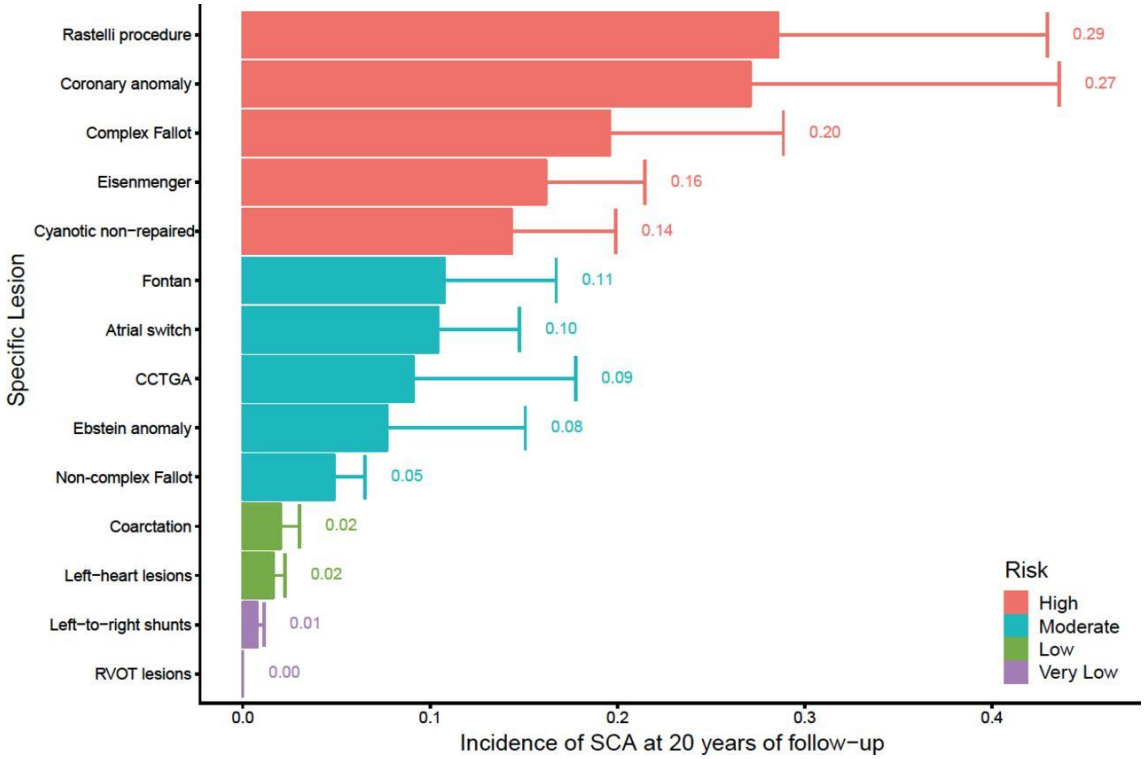
Sensitivity : 0.5 (0.25*)
Specificity : 0.93 (0.98*)
C-statistics : 0.75(95% CI 0.59-0.92) (0.61*)
KM estimates
- High risk : 7.0%
- Intermediate risk : 0.8%
- Low-risk : 0.3%

* Consensus statement

Vehmeijer JT *et al*. Heart Rhythm 2021 (PMID 33465514)

Risk Prediction model of SCD in ACHD : SPANISH ACHD

Risk model development

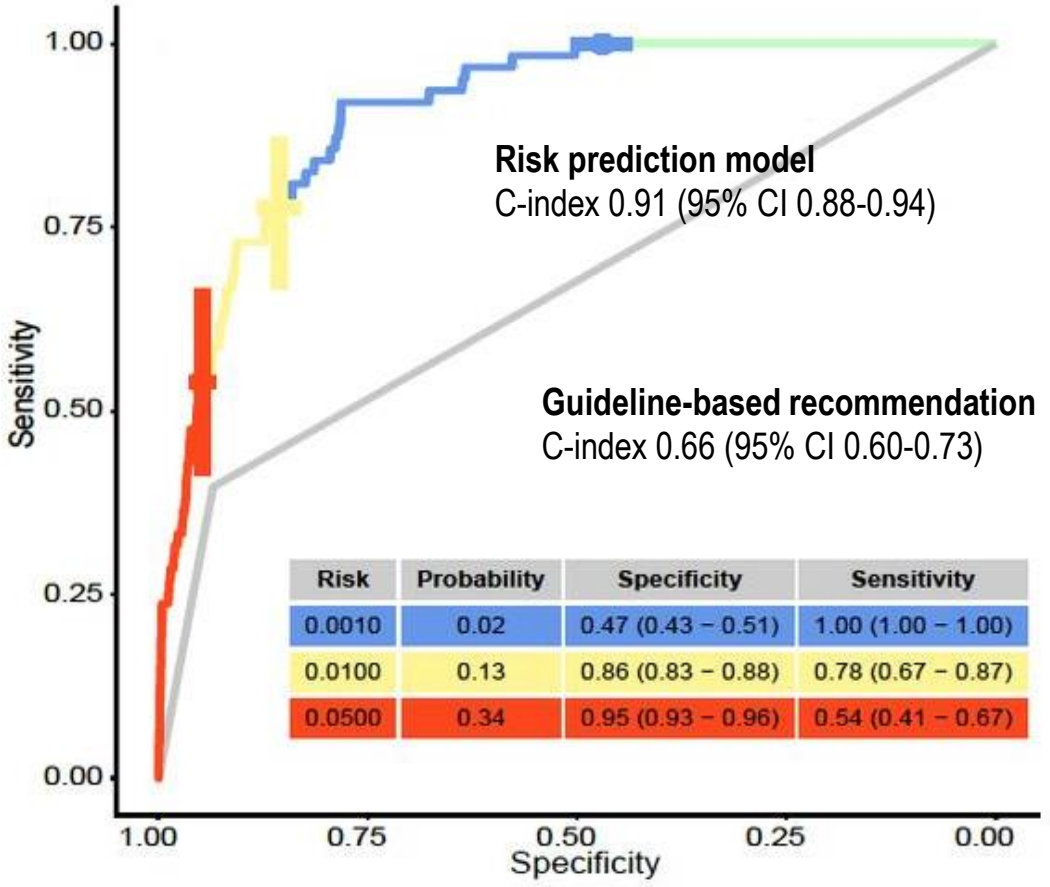


Type of CHD

20 year cumulative SCD/SCA incidence

- High-risk > 12%
- Intermediate-risk 4-12%
- Low-risk 1-4%
- Very-low risk < 1%

Model performance: Discrimination



Risk	Probability	Specificity	Sensitivity
0.0010	0.02	0.47 (0.43 – 0.51)	1.00 (1.00 – 1.00)
0.0100	0.13	0.86 (0.83 – 0.88)	0.78 (0.67 – 0.87)
0.0500	0.34	0.95 (0.93 – 0.96)	0.54 (0.41 – 0.67)

Compared with current guidelines approach,
sensitivity increases 29%
with less than 1% change in specificity

Oliver JM *et al*. Heart 2021 (PMID 32546506)

Comparision of ACHD risk score model

PREVENTION-ACHD

Annual risk of SCD

Diagnosis	<1%	1-2%	3-4%	5-10%	11-25%	>25%
Eisenmenger syndrome	4	8	16	>25	>25	>25	>25
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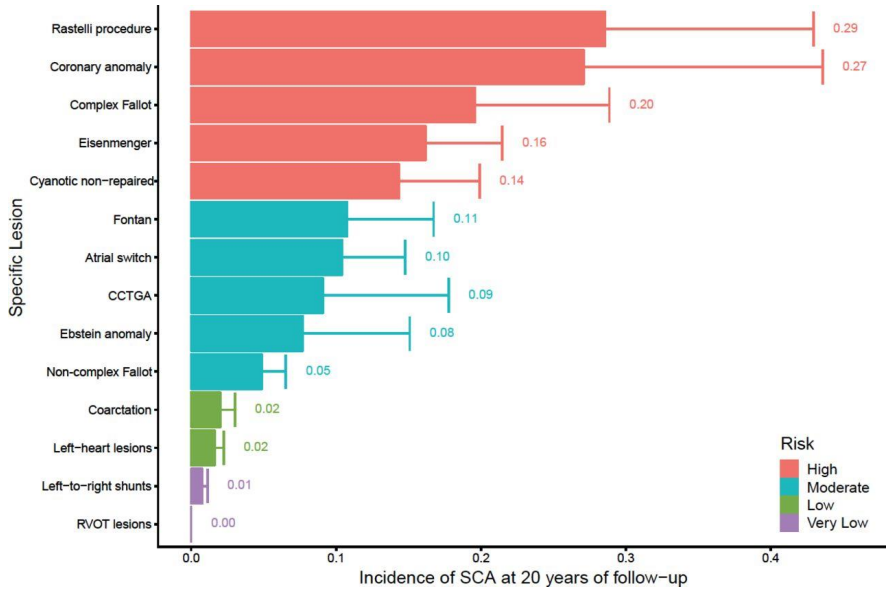
Number of risk factors

- **Type of CHD**
- Coronary artery disease
- NYHA II/III heart failure
- Supraventricular tachycardia
- Systemic ejection fraction <40%
- Sub-pulmonary ejection fraction <40%
- QRS duration ≥120ms
- QT dispersion ≥70ms

SPANISH ACHD



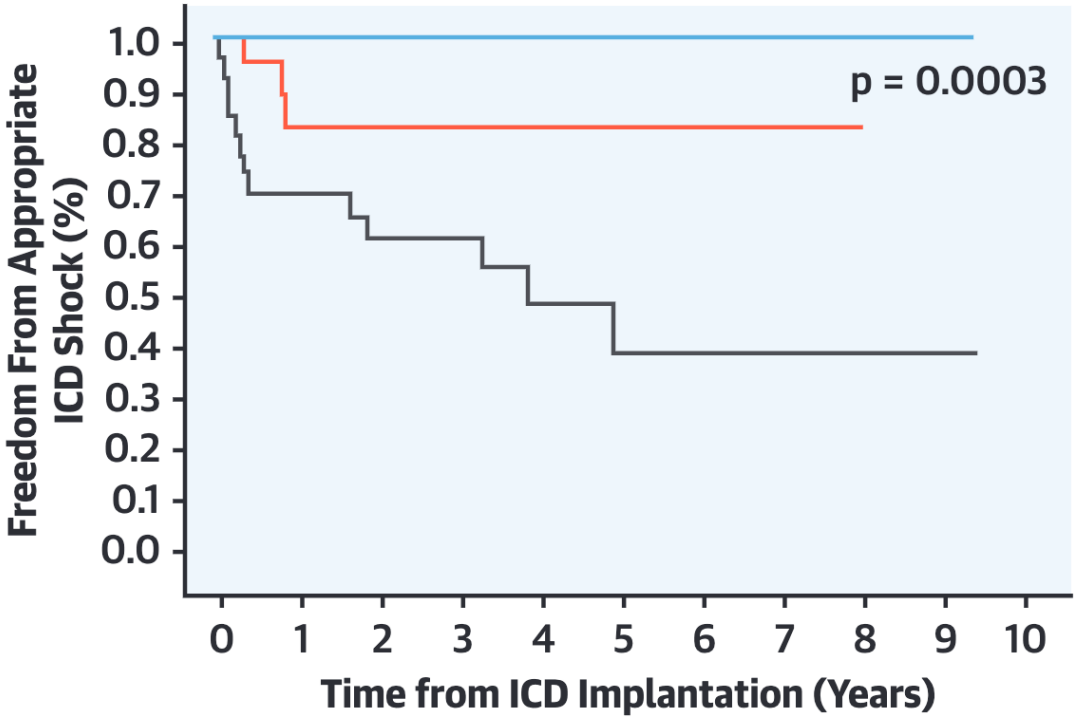
- **Type of CHD**
- Younger age
- Male sex
- Unexplained syncope
- Symptomatic ischemic heart disease
- Non-life threatening ventricular arrhythmia
- QRS duration
- Mod–sev systemic ventricular hypertrophy
- Mod–sev sub-pulmonary ventricular hypertrophy
- Mod–sev dysfunction of either ventricle (EF < 45%)

SCD risk stratification in Tetralogy of Fallot

- 1/3 of late deaths in ToF patients occurs due to VA with a prevalence of 2% to 8%

ToF is the largest subgroup of ICD recipients with CHD
Yet, overall low incidence of SCD within a population: 0.15% /year

→ identifying high-risk patients continues to be a major challenge



Clinical Risk Score for SCD in ToF

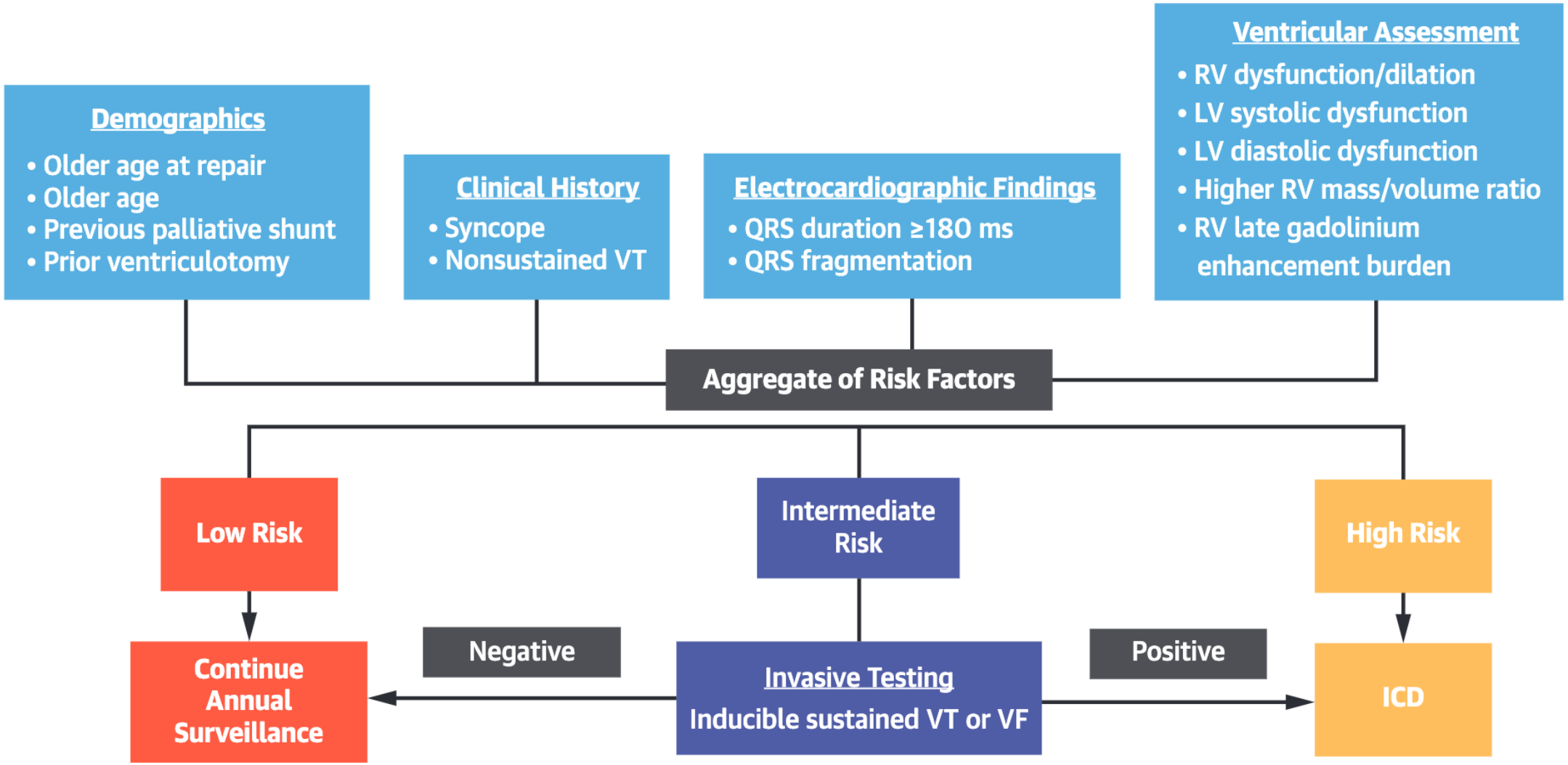
	Exp (B)	Point Attributed
Prior palliative shunt	3.2	2
Inducible sustained ventricular tachycardia	2.6	2
QRS >180 ms	1.4	1
Ventriculotomy incision	3.4	2
Nonsustained ventricular tachycardia	3.7	2
Left ventricular end-diastolic pressure ≥12 mm Hg	4.9	3
TOTAL POINTS		0-12

Risk Score	Risk Category	N	Annualized Rate of Appropriate Shocks
0-2	Low	18	0.0%
3-5	Intermediate	24	3.8%
6-12	High	26	17.5%

Khairy P *et al*. Circulation 2008 (PMID 18172030)

Cohen *et al*. JACC 2021 (PMID 33573746)

SCD risk stratification in Tetralogy of Fallot



Cohen *et al*. JACC 2021 (PMID 33573746

EPS role in SCD risk stratification

Tetralogy of Fallot

Study subjects

Multicenter, observational cohort

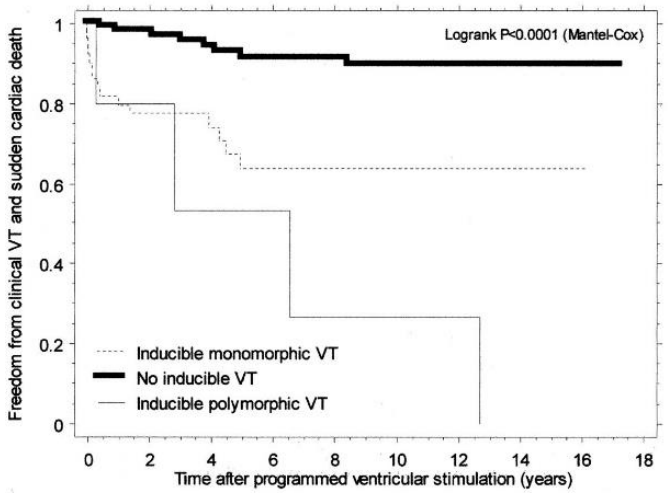
252 rToF patients underwent EPS

Results

Inducible sustained VT was a predictor of VT / SCD

Relative risk of inducible VT (vs non-inducible)

: 5.0 for monomorphic VT, 12.9 for polymorphic VT



PPV: 55.2±5.3%

NPV: 91.5±2.2%

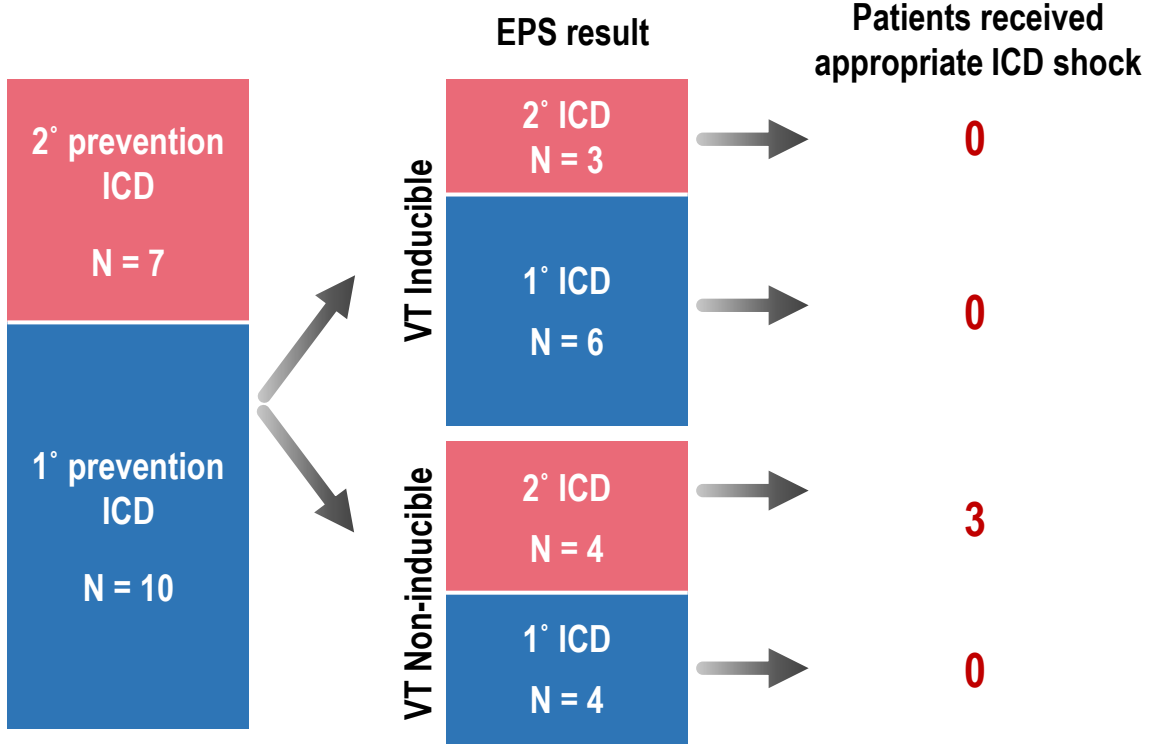
Khairy P *et al*. Circulation 2004 (PMID 15051640)

Transposition of Great Arteries with atrial switch

Study subjects

37 ICD recipients for primary/secondary prevention

17 patients underwent EPS



Khairy P *et al*. Circ Arrhythm Electrophysiol. 2008 (PMID 19808416)

SCD risk stratification in TGA

- SCD rate of 10% was found in d-TGA patients after the Mustard operation after 15 years of follow-up
- In d-TGA patients after Arterial switch, SCD is an infrequent event with a prevalence of approximately 1%

Atrial switch operation	Arterial switch operation
• Leave RV as lifelong systemic ventricle : systemic ventricular failure • Create surgical scar in atrium (substrate for flutter) : atrial arrhythmia or sinus node dysfunction	Reduced late SCD events in repaired D-TGA
Suggested risk factors • Longer duration of follow up • History of syncope or rapid palpitation • Atrial tachycardia • Systemic RV dysfunction	Mechanism of SCD • Denervated coronary arteries • Rare events of ventricular dysfunction

Walsh. Heart rhythm 2014 (PMID 25046858)

SCD risk stratification in single ventricle

- **Lack of evidence d/t population heterogeneity & small number of ICD recipients**
- **Major challenges from limited access when ICD therapy is contemplated**
- **Supraventricular tachycardias are poorly tolerated & may be linked to VA/SCD**
  - Macroreentrant atrial tachycardia is the most common arrhythmia (~50% with old AP Fontan)
  - surgical modifications (lateral tunnel / extra-cardiac conduit) decreased AT incidence <10%

Suggested risk factors of VA/SCD in patients with Fontan circulation
- longer duration of follow-up - history of syncope or rapid palpitation - older Fontan technique (atriopulmonary connection) - atrial tachycardia - severely reduced single ventricular function

Walsh. Heart rhythm 2014 (PMID 25046858)

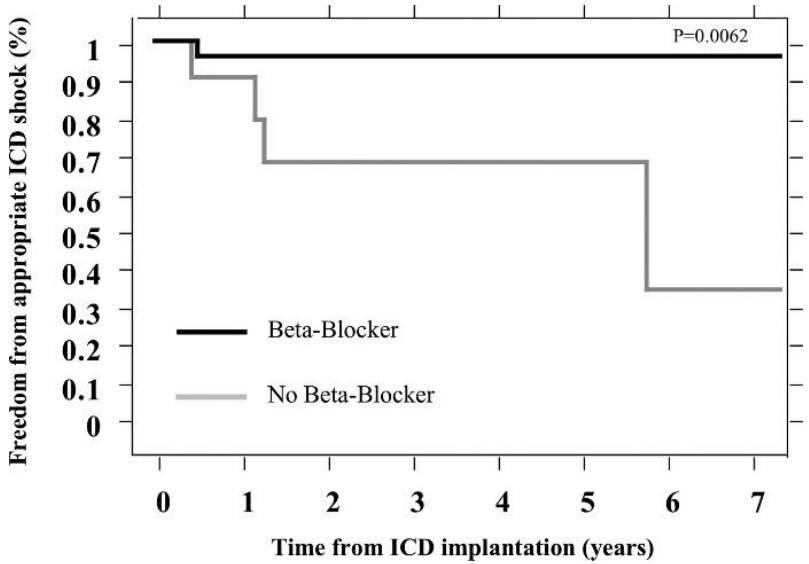
SVT control

SVTs play a role in at least some of SCDs in ACHD

- A potent trigger for thrombus formation
- Poorly tolerated in ACHD, particularly in TGA, Fontan, Ebstein anomaly
- precede or coexist with ventricular tachycardia or trigger to ventricular arrhythmia

Aggressive therapy for SVT should be considered in ACHD

- β-blockers decreased SCD after Mustard/Senning repair of TGA [2)]
- catheter ablation could be useful in some cases



[1)] Rhodes LA *et al*. PACE 1995 (PMID 7659551)

[2)] Khariy P *et al*. Circ Arrhythm Electrophysiol. 2008 (PMID 19808416)

Summary

- **SCD risk stratification in ACHD is a multidisciplinary mission**
  - SCD is a terminal event with diverse causes and triggers
  - Considerable heterogeneity from diverse congenital defects and operation methods
  - RCTs and large population studies are missing in ACHD population
  - Results from acquired heart diseases are often not conferrable
  - We should try to develop and validate risk score model that can predict SCD more accurately
- **Remarkable progress in EP understanding of VT has been made in ToF**
  - Many risk factors was suggested (age, surgical factors, QRS, ventricular dysfunction)
  - Invasive risk stratification including substrate mapping and ablation can be helpful
- **Atrial arrhythmia plays a crucial role in VA/SCD in TGA and many other ACHDs**

Thank you for your attention

Is ICD helpful in preventing SCD in ACHD?

- < 30% of sudden death are d/t shockable ventricular arrhythmia in general population
- Proportion of shockable SCD is uncertain in ACHD population
- ACHD patients were younger than controls and more often had a shockable initial rhythm

- ICD-related complication are higher in the ACHD.
- Consider ICD-related cost.

CONCOR & TCCCA registry

N = 25,790

213 sudden death (among 1,189 overall death)

Arrhythmic death		**Non-arrhythmic death**	
171 (80%)		42 (20%)	
Rhythm documentation in 37(22%)			
VF and/or VT	31(84%)	Aortic disease	19(9%)
SVT	3(8%)	CVA	8(4%)
brady-arrhythmia	3(8%)	PE / hemorrhage	8(4%)
		MI	4(2%)
		GI bleeding	3(1%)

<15% of SCD had shockable rhythm

Koyak Z *et al*. Circulation 2012 (PMID 22991410)

CONCOR (ACHD) *vs* ARREST (general)

N = 17,868

Characteristics of ACHD OHCA patients and OHCA cases without ACHD.

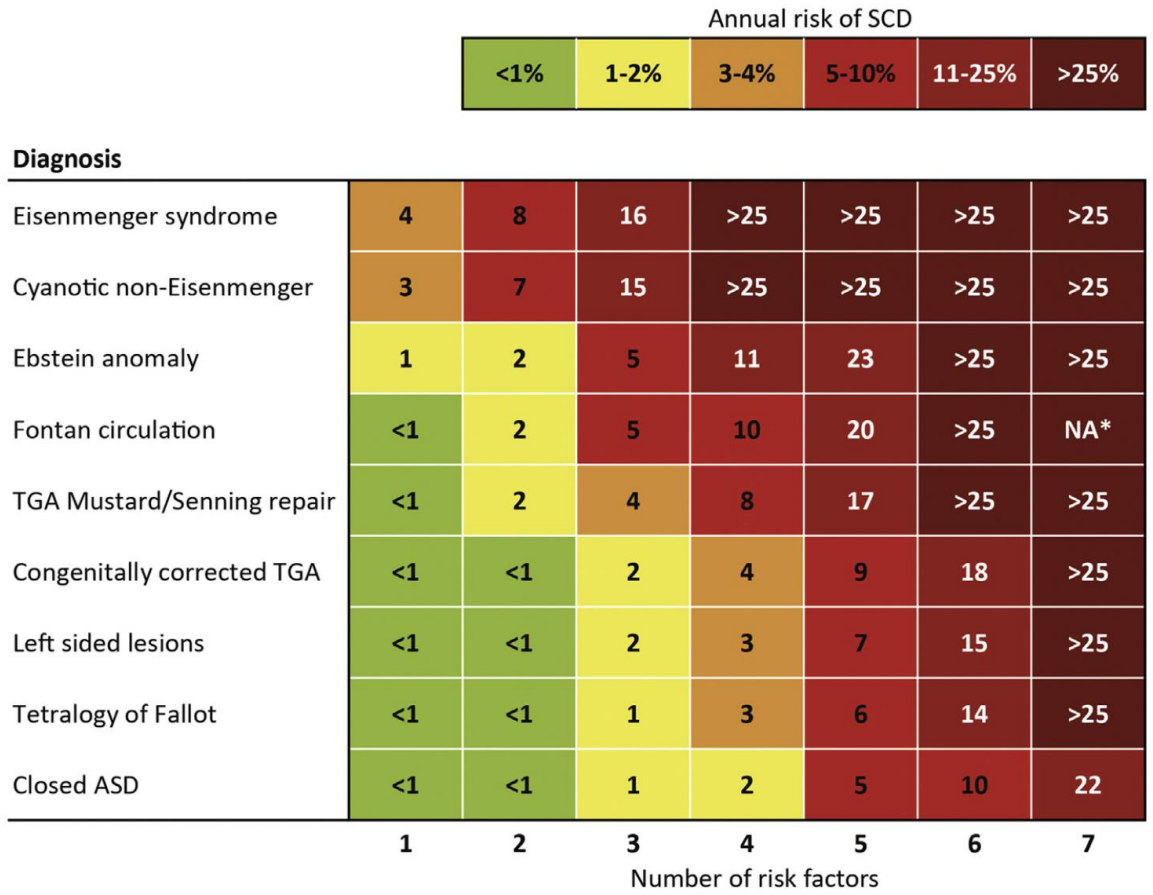
	ACHD	No ACHD	p
	n = 62	n = 11,624	
Age, mean ± SD	47 ± 17	66 ± 15	<0.001
Male gender, n (%)	41 (66)	8308 (71)	0.416
Initial rhythm, n (%)			0.001
Ventricular fibrillation/tachycardia	40 (65)	4653 (40)	
Pulseless electric activity	11 (18)	3050 (26)	
Asystole	7 (11)	3208 (28)	
Undefined, not-shockable/unknown	4 (6)	713 (6)	
Cause of OHCA, n (%)			0.026
Cardiac	47 (76)	6320 (54)	
Trauma	0 (0)	351 (3)	
Respiratory or other non-cardiac	5 (8)	1289 (11)	
Unknown	10 (16)	3664 (32)	

Vehmeijer JT *et al*. Int J Cardiol. 2019 (PMID 30414749)

Risk score model of SCD in ACHD

PREVENTION-ACHD

Study design	Risk score model development by retrospective multicenter case–control study
Outcome	SCD or VT/VF
Subjects / N of events	Model design: 25,790 patients / 165 events
Variables in final model	• **Type of CHD** • Coronary artery disease • NYHA II/III heart failure symptom • Supraventricular tachycardia • Systemic ejection fraction <40% • Sub-pulmonary ejection fraction <40% • QRS duration ≥120ms • QT dispersion ≥70ms



- High risk: annual SCD risk ≥ 3%
- Low risk: annual SCD risk < 3%

  (1-2%: intermediate risk, <1%: very-low risk)

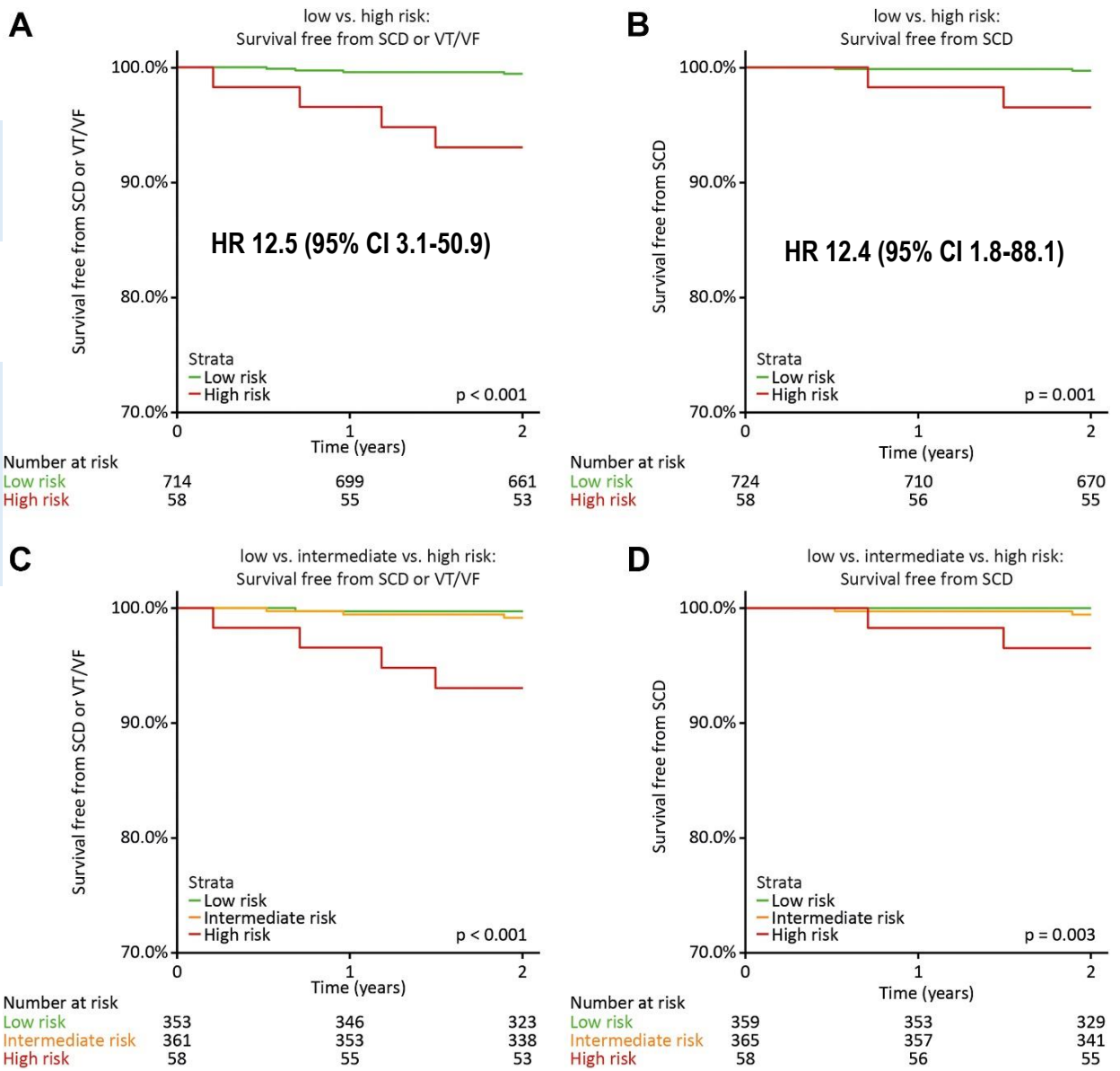
Vehmeijer JT *et al*. Heart Rhythm 2021 (PMID 33465514)

Prospective validation of PRVENTION-ACHD risk score

PREVENTION-ACHD

Study design	Prospective validation by single center f/u
Outcome	SCD or VT/VF (primary), SCD alone (secondary)
Subjects / N of events	738 patients, 2 years / 8 events High-risk (annual SCD risk ≥3%): 58 Intermediate-risk (1-2%): 365 Low-risk (<1%): 359
Model performance	Sensitivity : 0.5 (0.25*) Specificity : 0.93 (0.98*) C-statistics : 0.75(95% CI 0.59-0.92) (0.61*) KM estimates - High risk : 7.0% - Intermediate risk : 0.8% - Low-risk : 0.3%

* Consensus statement

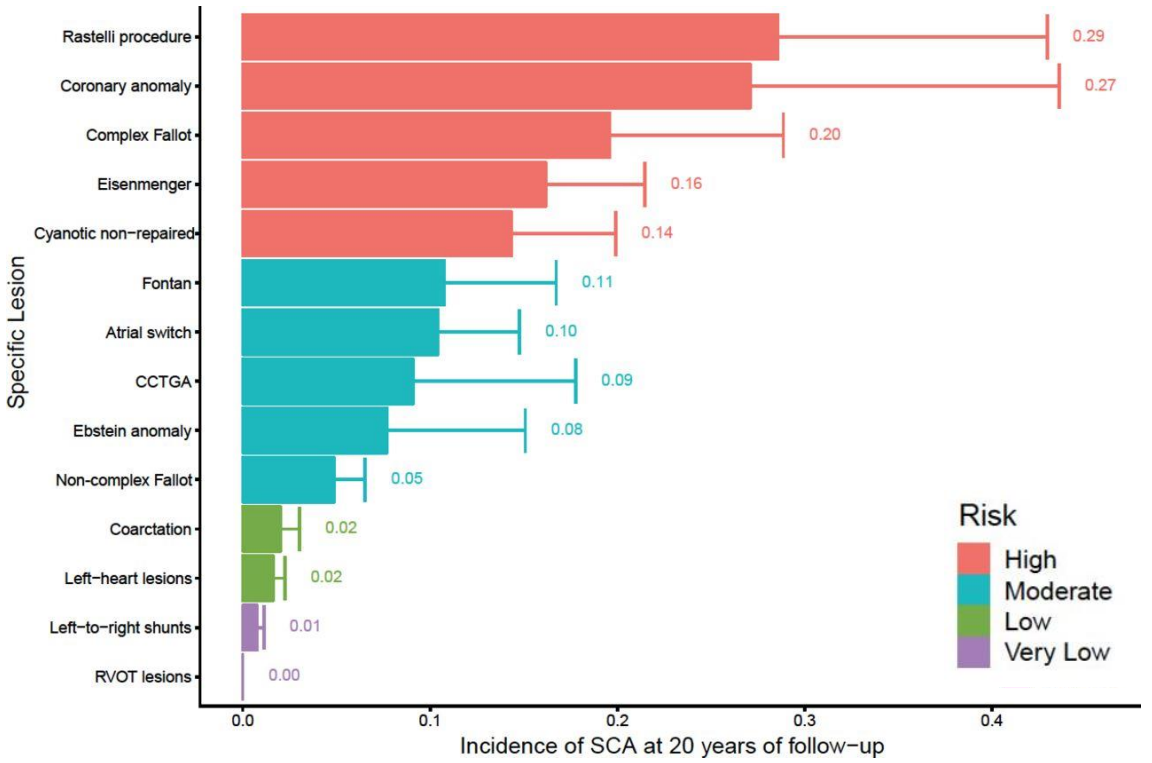


Vehmeijer JT *et al*. Heart Rhythm 2021 (PMID 33465514)

Risk Prediction model of SCD in ACHD : SPANISH ACHD

SPANISH ACHD

Study design	**Lesion stratification** from single-center cohort Risk score development and validation from multicenter case-control study
Outcome	SCD or non-fatal SCA
Subjects / N of events	Stratification: 3,311 patients / 71 events Model develop: 144 cases /1,501 controls Validation: 63 cases / 786 controls
Variables in final model	• **Type of CHD (clustered into four groups)** • Younger age • Male sex • Unexplained syncope • Symptomatic ischemic heart disease • Non-life threatening ventricular arrhythmia • QRS duration • Mod–severe systemic ventricular hypertrophy • Mod–severe sub-pulmonary ventricular hypertrophy • Mod–severe dysfunction of either ventricle (EF < 45%)



Type of CHD

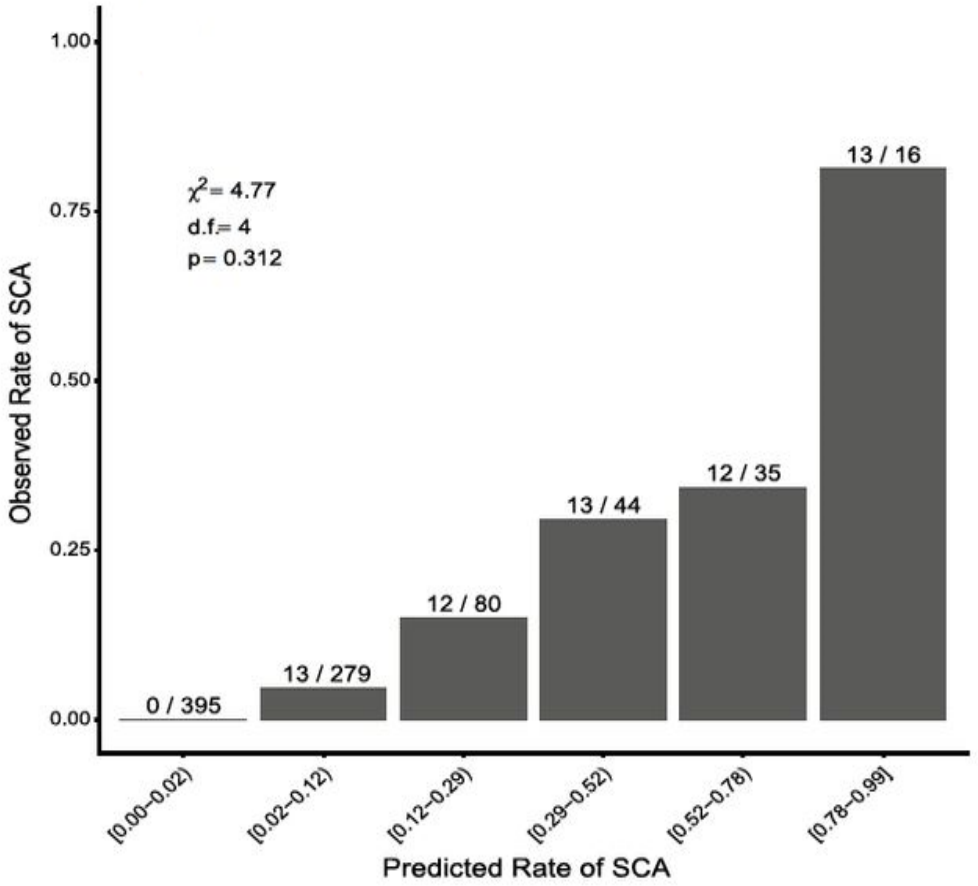
20 year cumulative SCD/SCA incidence

- High-risk > 12%
- Intermediate-risk 4-12%
- Low-risk 1-4%
- Very-low risk < 1%

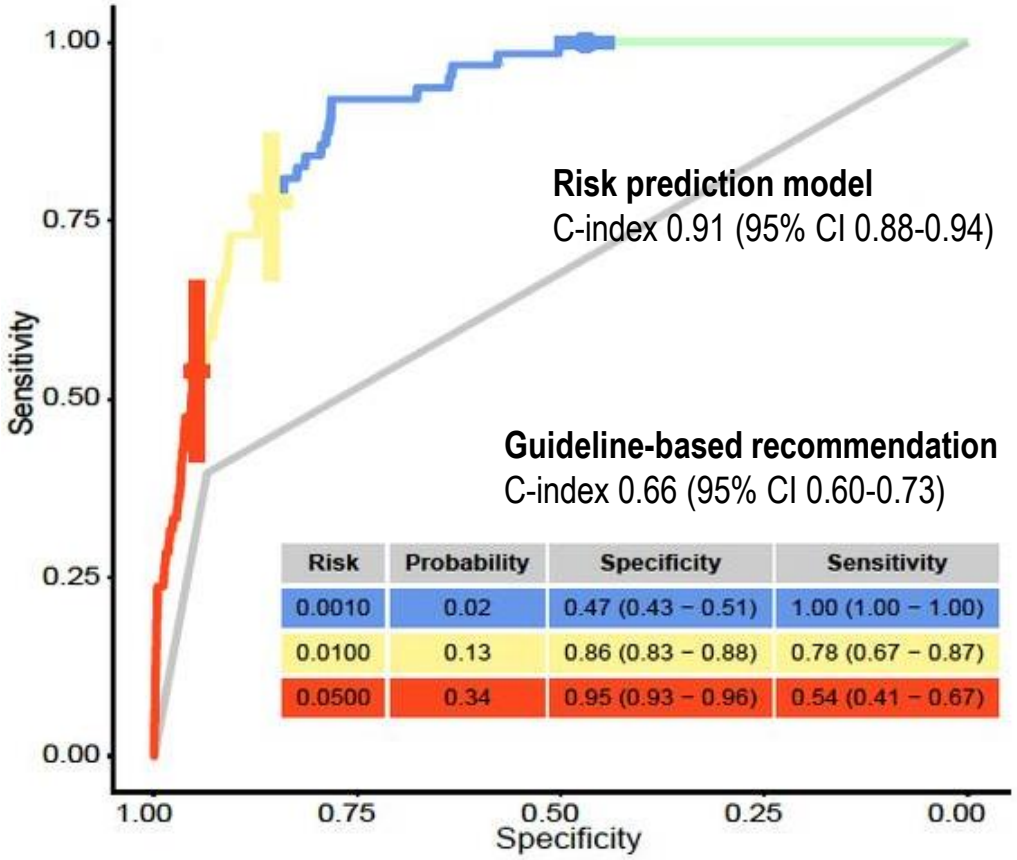
Oliver JM *et al*. Heart 2021 (PMID 32546506)

Performance of SPANISH ACHD risk score

Callibration



Discrimination



Risk	Probability	Specificity	Sensitivity
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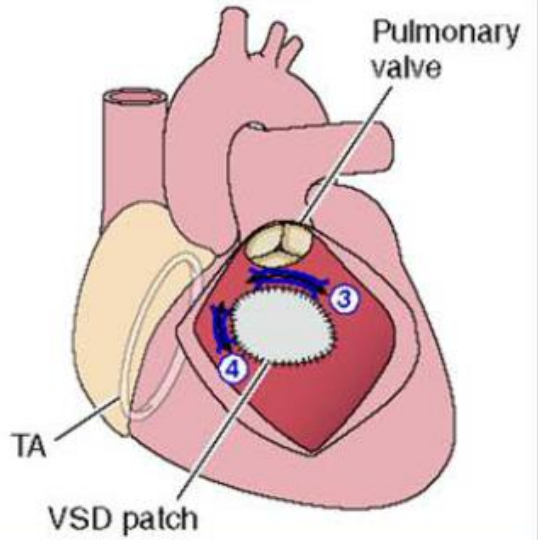
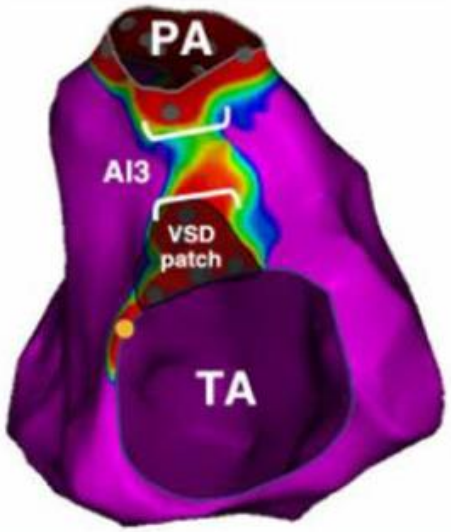
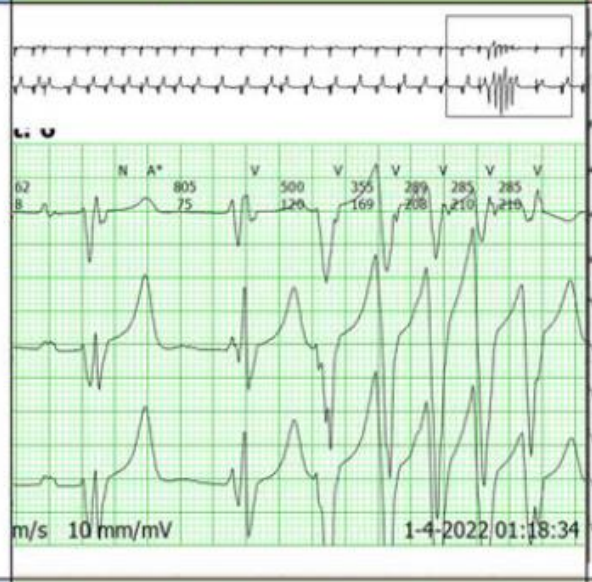
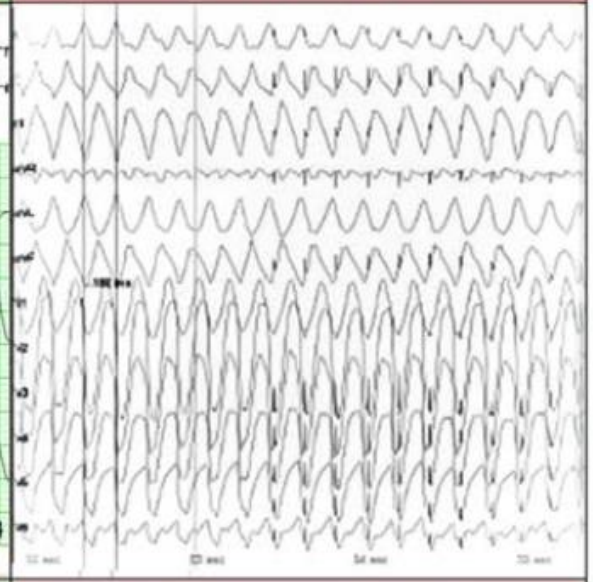
Compared with current guidelines approach,
sensitivity increases 29%
with less than 1% change in specificity

Oliver JM *et al*. Heart 2021 (PMID 32546506)

VT mechanism in TOF

Substrate	Slow conduction	Triggers	Ventricular tachycardia
			
Determined by initial anatomy and surgical repairs.	Caused by fibrosis from volume or pressure overload, dilation, hypertrophy, and aging. Associated with QRS prolongation.	Triggers (PVCs, NSVT) facilitated by diffuse fibrosis and abnormal hemodynamics. Triggers coupled with susceptible substrate can trigger VT.	Typically monomorphic and fast. Hemodynamic tolerance depends on cycle length and ventricular function.

- **Great progress in defining the mechanisms contributing to SCD in patients with repaired TOF**
  - Isthmus dependent monomorphic VT between identified anatomic barriers
  - Can be target for effective catheter or surgical ablation

Kriger *et al*. Circ Arrhythm Electrophysiol. 2022 (PMID 18172030)

Incidence* of SCD in ACHD

	Silka *et al.*	**Gallego** *et al.*	**van der Velde** *et al.*	**Moore** *et al.*	**Lynge** *et al.*
Study population	Repaired CHD N = 3,589	Repaired CHD ≥18 years N = 936	Repaired / unrepaired CHD N = 4,252	Repaired / unrepaired CHD ≥16 years N = 2,935	Repaired / unrepaired CHD 0–35 years Nationwide
Study period	1958–1996	1990–2010	2001–2004	2000–2015	2000–2009
Overall	**0.9**	**2.6**	**2.7**	**0.4**	**0.3**
Repaired tetralogy of Fallot	1.5	1.4	1.3	1.0	0.9
Complete TGA	4.9	9.5	4.6	-	1.7
Atrial switch	-	-	3.7	2.4	-
Arterial switch	-	-	5.4	-	-
Congenitally corrected TGA	-	25.0	1.8	2.1	-
Cyanotic heart disease	-	5.4	16.6	-	-
Eisenmenger syndrome	-	-	17.3	4.8	-
Non-Eisenmenger	-	5.4	15.5	-	-
Fontan circulation	-	2.8	4.4	2.1	1.9
Left-sided lesions	-	-	1.4	-	-
Ebstein anomaly	-	-	5.1	0.7	5.0
Ventricular septal defect	0.2	3.6	-	0.2	0.1
Aortic coarctation	1.3	2.1	-	0.4	0.5
Atrioventricular septal defect	0.9	1.8	-	1.8	1.0
Aortic stenosis	5.4	0.0	-	0.0	-
Pulmonary stenosis	0.3	0.0	-	-	0.3
Patent ductus arteriosus	0.0	0.0	-	-	-
Atrial septal defect	0.0	0.0	1.0	0.2	-

* per 1,000 patient-years

VA/SCD according to type of CHD

	Supraventricular arrhythmias			Ventricular arrythmias and SCD		Bradycardia			
						SND		AV block	
Type of CHD	AVRT	IART/ EAT	AF	Sustained VT	SCD	Congenital	Acquired	Congenital	Acquired
Secundum ASD		++	++			(+)	+		(+)
Superior sinus venosus defect		++	+				+		
AVSD/primum ASD		++	++	(+)		(+)		(+)	++
VSD		+	(+)	+	(+)[a]				+
Ebstein anomaly	+++	++	+	(+)	++[b]		++		
TOF		++	++	++	++		+		+
TGA									
Atrial switch		+++	+	++[c]	+++[b]		+++		+
Arterial switch		+		+[c]	(+)		(+)		
ccTGA	++	+	+	(+)	++[b]			+	++
Fontan operation									
Atriopulmonary connection		+++	++		+[b]		++		
Intracardiac lateral tunnel		++	+		+[b]		++		
Extracardiac conduit		+	+		+[b]		+		
Eisenmenger physiology Incompletely palliated CHD		++	++		++[d]				