Approach to Family Screening in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

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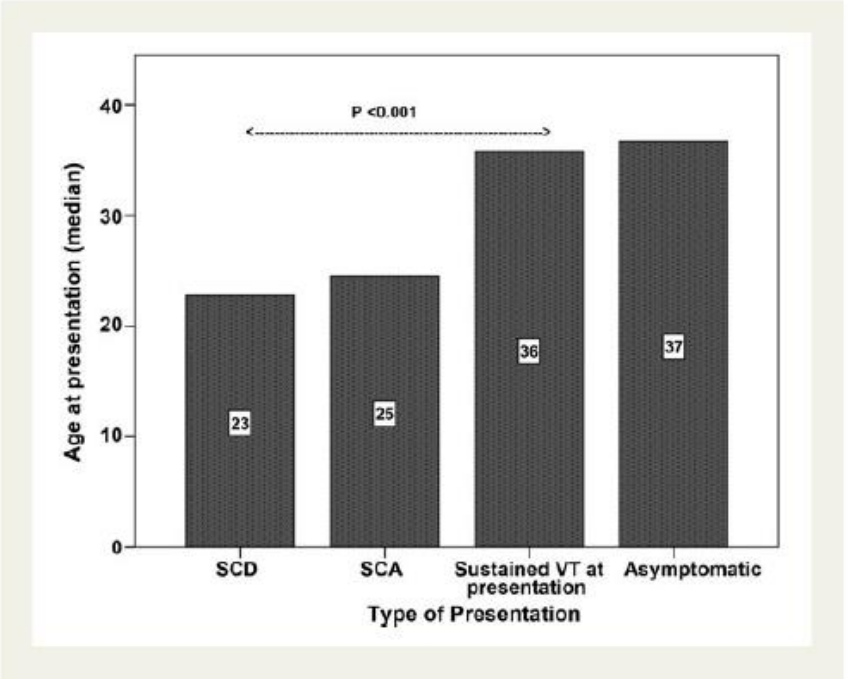
ARVD/C

- Inherited cardiomyopathy
- Desmosomal mutations
- RV dysfunction
- Ventricular arrhythmias
- Sudden cardiac death
  - Risk of sudden cardiac death is highest early in disease course[1]



1. Bhonsale, .., **Te Riele**, et al. Eur Heart J 2015;36:847-55

Rationale and Objectives

- Autosomal dominant inheritance with variable expressivity
- Family screening is recommended
  - Prior studies only evaluated disease penetrance[1,2]
  - No guidelines on screening strategy or risk stratification

- Objective:
  - Determine predictors of ARVD/C diagnosis
  - Optimize arrhythmic risk stratification among relatives of ARVD/C patients

1. Dalal et al. Circulation 2005;112:3823-32.
2. Groeneweg, …., **Te Riele**, et al. Circ Cardiovasc Genet 2015;8:437-46.

Study Design

- Population: 274 first-degree relatives of ARVD/C patients who underwent comprehensive cardiologic evaluation
  - ICIN and Johns Hopkins Hospital
  - 36.5 ± 18.9 years, 46% male
  - Grouped as parents (n=68), siblings (n=120), or children (n=86)

- Primary outcome:
  - ARVD/C diagnosis as per 2010 diagnostic Task Force Criteria (TFC)
    - Also ascertained TFC independent of family history

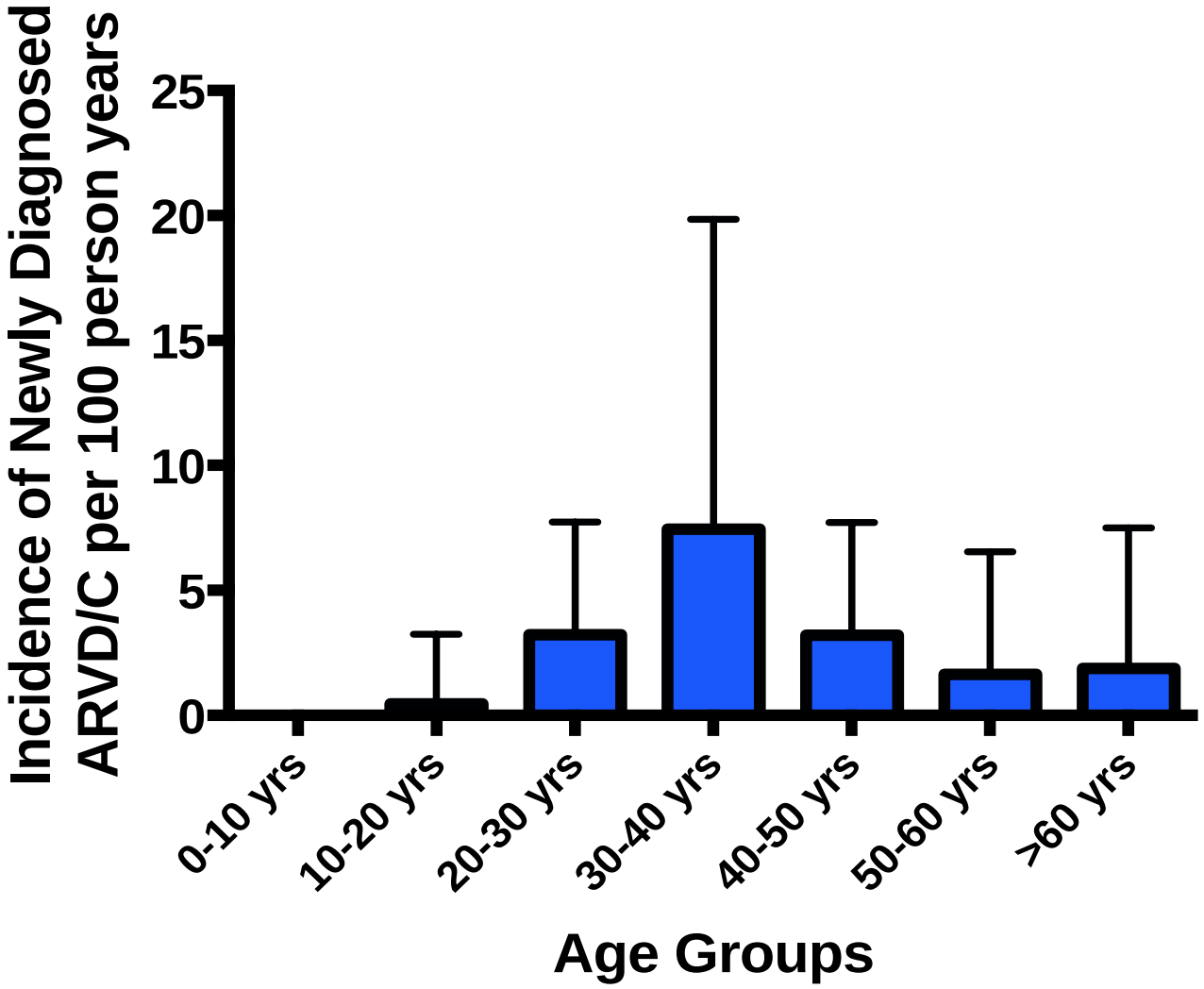
- Secondary outcome:
  - Composite of life-threatening ventricular arrhythmia

Results – ARVD/C diagnosis

- 96/274 (35%) relatives fulfilled 2010 TFC of ARVD/C by last follow-up

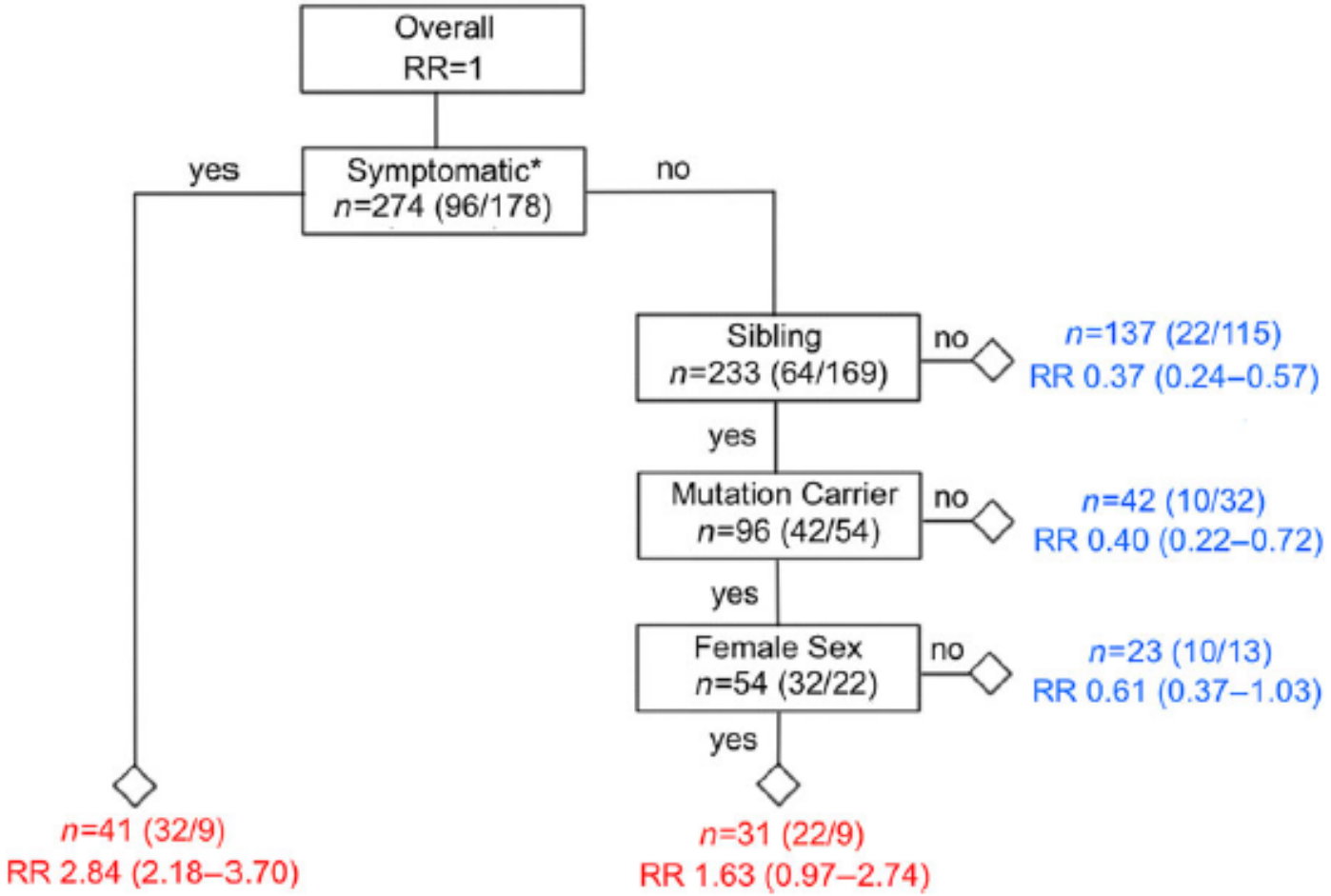
	ARVD/C (n=96)
Male	32 (33)
Age at diagnosis (yrs)	36.3 ± 14.6
Symptomatic	32 (33)
Syncope	11 (12)
Presyncope	7 (7)
Palpitations	27 (27)
Pathogenic mutation	75 (78)
Generation	
Sibling	61 (63)
Child	19 (20)
Parent	16 (17)

Results – Incidence of new ARVD/C diagnosis



Results – Predictors of ARVD/C Diagnosis

	Univariate		Multivariate	
	OR	**p-value**	**OR**	**p-value**
Age at presentation (compared to 18-35 year age group)				
<18 years	0.19 (0.09-0.44)	<0.001	0.37 (0.14-0.93)	0.036
35-50 years	0.57 (0.30-1.10)	0.093	0.74 (0.34-1.60)	0.443
>50 years	0.29 (0.14-0.61)	0.001	0.51 (1.65-5.88)	0.122
Male gender	0.44 (0.26-0.73)	0.002	0.45 (0.25-0.83)	0.010
Symptomatic at presentation	9.39 (4.25-20.76)	<0.001	7.84 (3.23-19.06)	<0.001
Pathogenic mutation	3.26 (1.85-5.75)	<0.001	3.81 (1.96-7.40)	<0.001
Sibling	3.52 (2.09-5.91)	<0.001	3.11 (1.65-5.88)	<0.001
Malignant family history	1.70 (0.97-2.96)	0.061	-	-



Model statistics:
Accuracy 78% (95% CI 73–83%)

Results – Risk Stratification

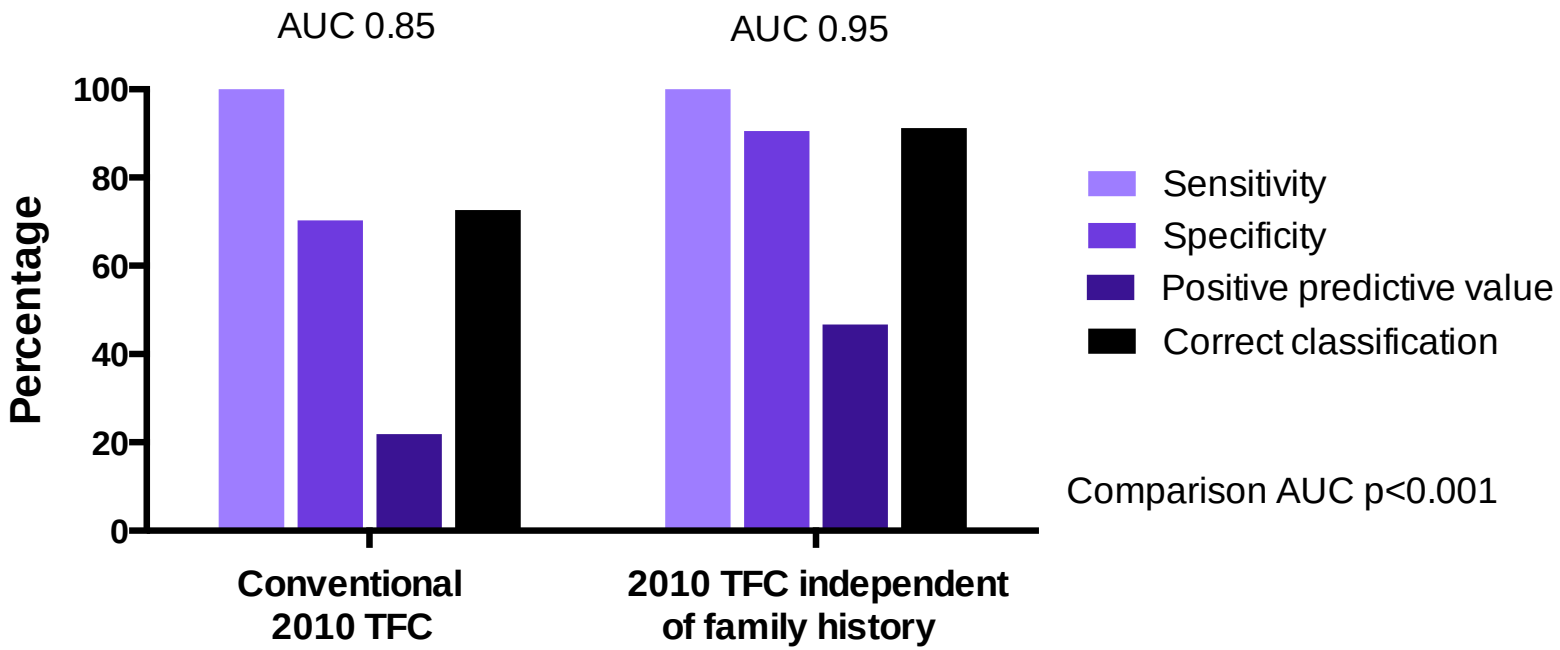
- Once diagnosis is made, most important management decision is whether to implant an ICD
  - 2008 ACC/AHA/HRS guidelines (updated 2012): fulfilling TFC is class IIa indication for ICD implantation[1]

- Revised 2010 TFC:
  - First-degree relatives get major criterion for family history
  - Many ARVD/C relatives are diagnosed at an early stage with unknown SCD risk

1. Tracy, Epstein et al. Heart Rhythm 2012;9(10):1737-53.

Results – Risk Stratification

- 21 (8%) subjects experienced an arrhythmic event
  - Mean follow-up 6.7 ± 3.8 years
  - 35.0 ± 14.7 years, 11 (52%) male
  - All diagnosed 4.2 (IQR 1.1-7.4) years prior to the event
    - All fulfilled 2010 TFC independent of family history



Conclusion

- One-third of first-degree relatives develop ARVD/C
  - Siblings are at highest risk of disease
  - Highest yield of screening in 20-40 year age range
- A combination of symptoms, being a sibling, pathogenic mutation, and female gender accurately predicts manifest ARVD/C
- Fulfillment of TFC independent of family history is superior to conventional TFC for risk stratification purposes

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Family Screening – Predictors of Events

- 21 (8%) subjects experienced an arrhythmic event
  - Mean follow-up 6.7 ± 3.8 years

	Overall (n=96)	No ventricular arrhythmia (n=75)	Ventricular arrhythmia (n=21)	p-value
Male	32 (33)	21 (28)	11 (52)	0.036
Age at presentation	36.3 ± 14.6	36.7 ± 14.7	35.0 ± 14.7	0.652
Symptomatic	32 (33)	18 (24)	14 (67)	<0.001
Mutation	75 (78)	56 (75)	19 (91)	0.121
Generation Sibling Parent Child	 61 (64) 16 (17) 19 (20)	 47 (63) 15 (20) 13 (17)	 14 (67) 1 (5) 6 (29)	0.185
Malignant family history	31 (32)	26 (34)	5 (24)	0.347

Clinical Implications

- Optimize ARVD/C family screening regimens
  - Specific age range for screening
  - Focus on siblings
  - Characteristics that are independently associated with ARVD/C
  - Hierarchically cluster these variables in a risk stratification paradigm

- Improved risk stratification in at-risk subjects
  - Identify subgroup that may benefit from prophylactic ICD implantation