Advancing Complex Innovative Trial Designs to Accelerate Drug Development in Pediatric Patients

FDA Workshop Sept 2021

Case Study in Assessing Disease Similarity: Heart Failure in Adult and Pediatric Patients

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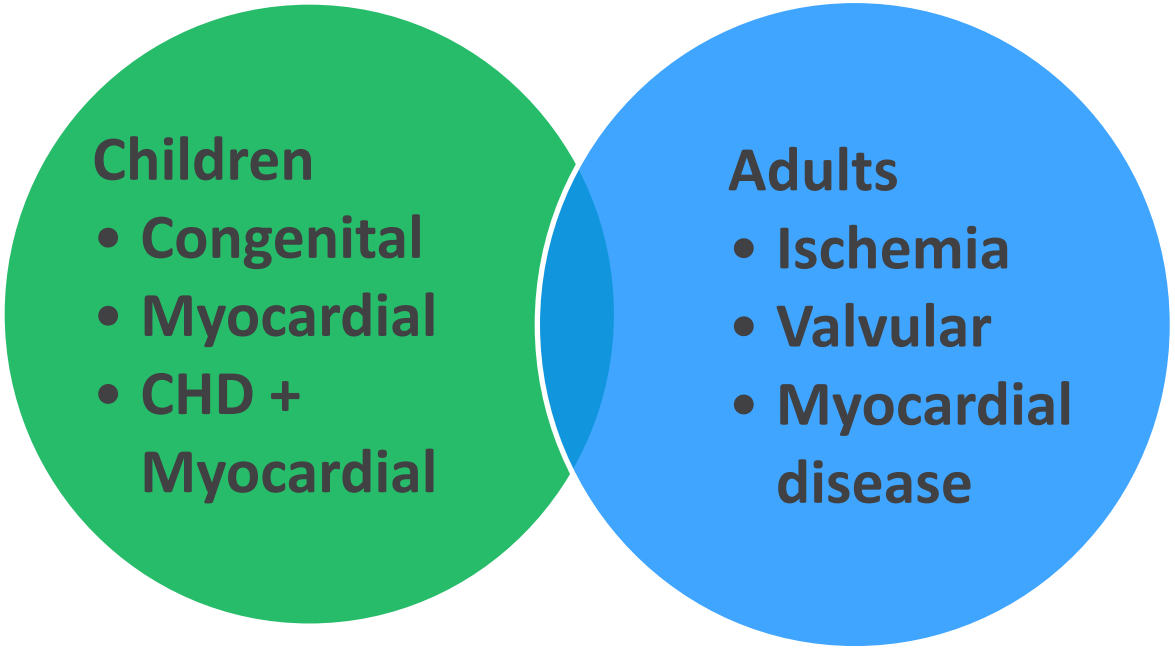
Montefiore DOING MORE℠

Disease Characteristics

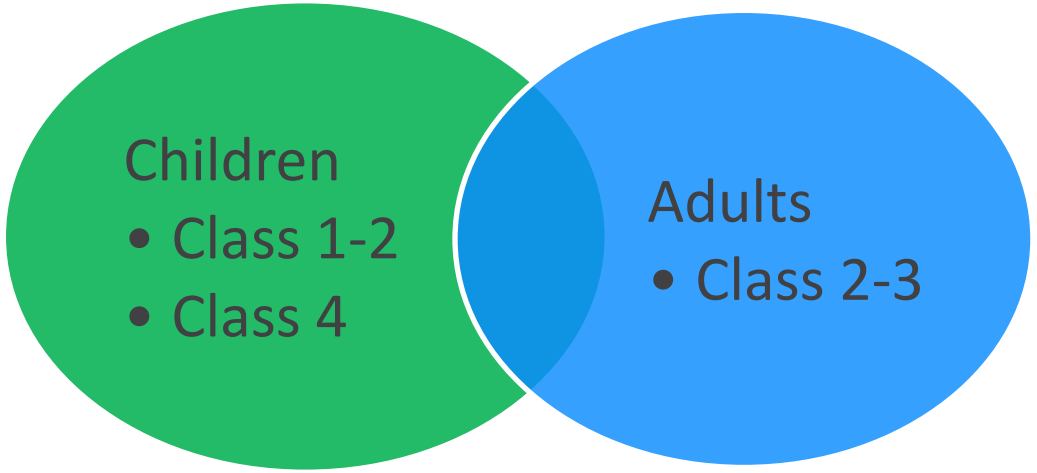
- Underlying etiology or mechanism of disease
- Clinical phenotype
  - Symptoms
  - Laboratory findings
    - Blood
    - Imaging
- Patient characteristics
  - Non-cardiac manifestations
  - Co-morbidities
- Outcomes

Characteristics of Chronic Heart Failure: Children vs. Adults

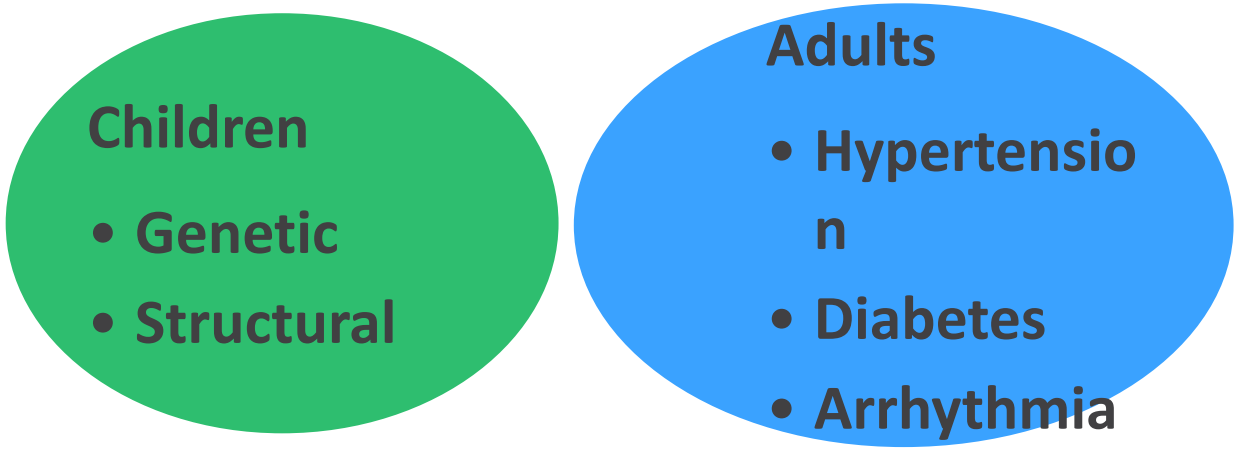
ETIOLOGY



CLINICAL PHENOTYPE



PATIENT CHARACTERISTICS



Etiologies of Pediatric Heart Failure

Definition: Inadequate cardiac output to meet demand

- **Normal myocardial function**
  - **Too much demand: Volume overload in congenital heart disease**
  - **Not enough supply: Structural impediments to adequate blood flow**
- **Decreased myocardial function**
  - **Systolic dysfunction with primary myocardial disease or following insult to myocardium in CHD**
  - **Diastolic dysfunction**

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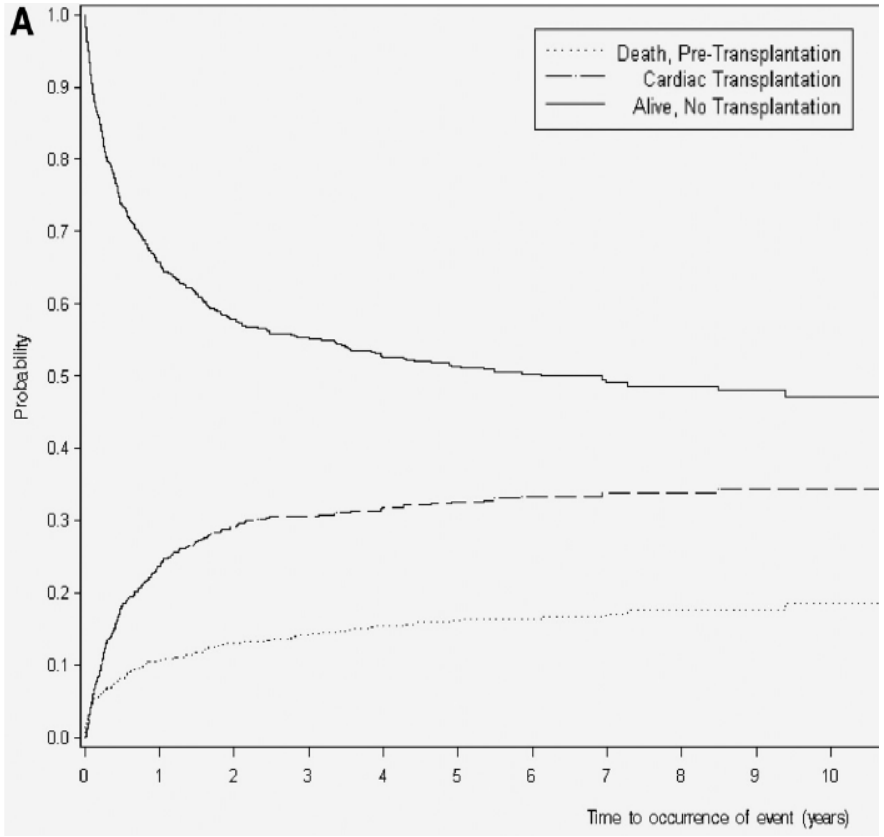
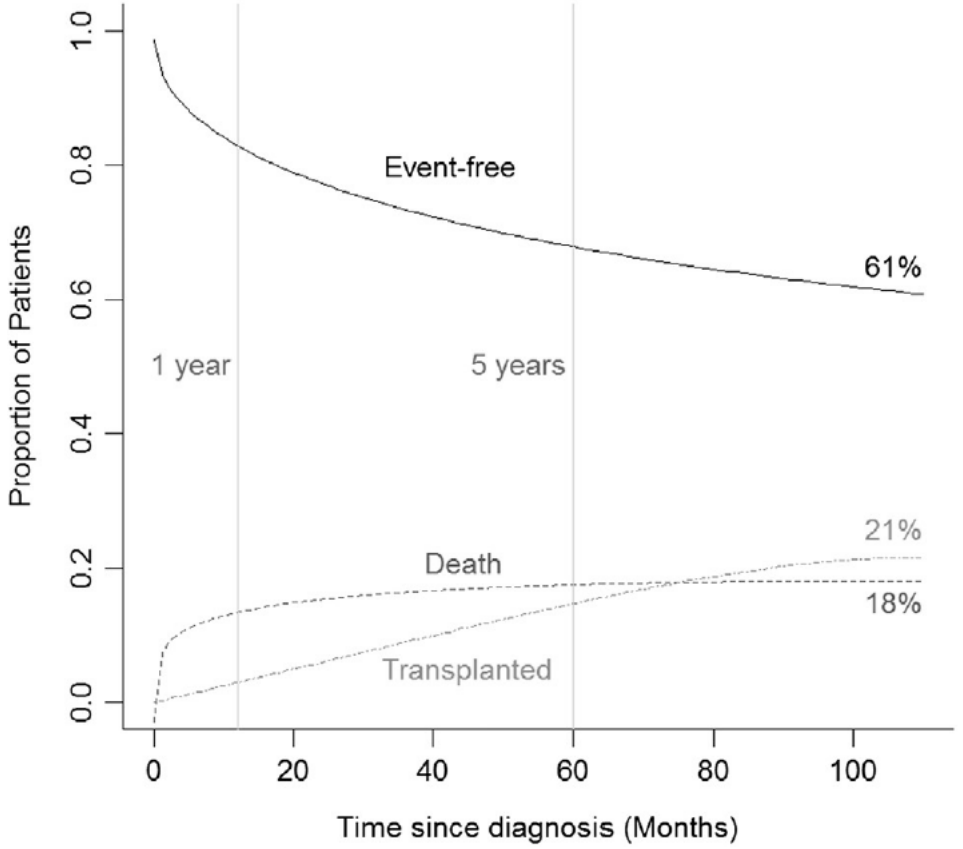
Chronic Heart Failure Therapies and Outcome Transplantation vs. Medical Therapy in DCM 2006 vs. 2016



- ACE-I 65%
- Beta-blocker 15%

Towbin et al JAMA 2006;296:1867-1876



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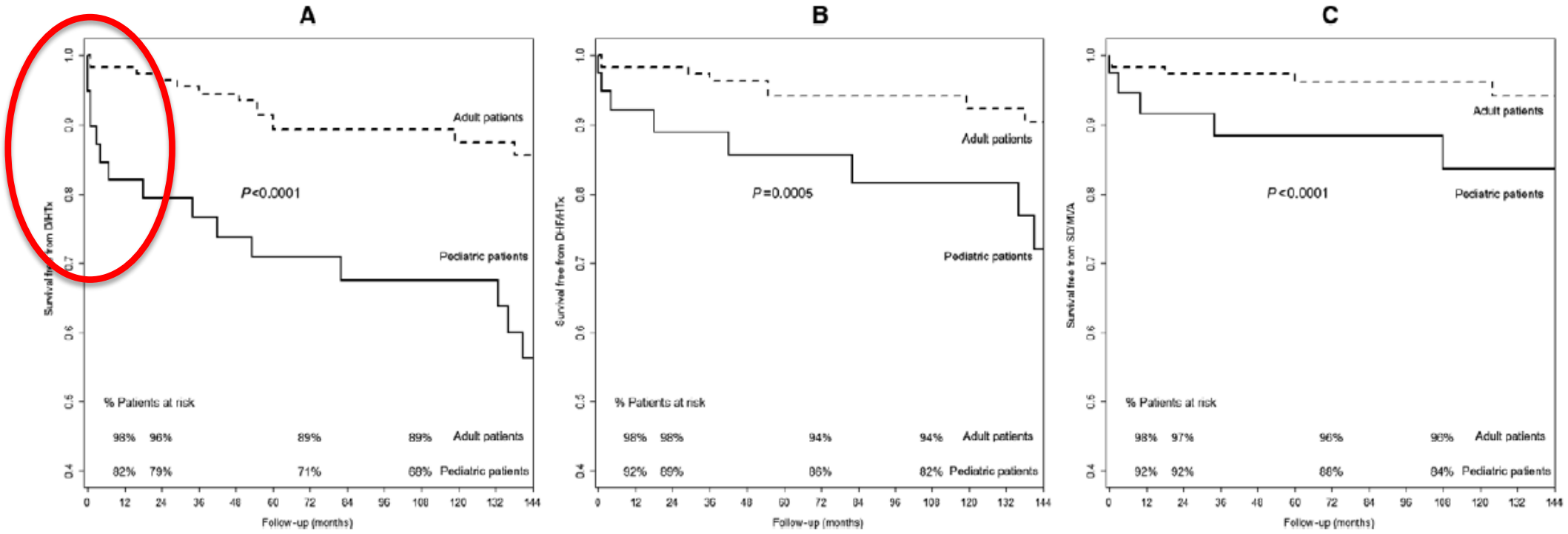
den Boer et al J Heart Lung Transplant 2016;34:963-969

Outcomes of CM and HF in children compared to adults



- 1 year survival without death or transplant
  - Children: 82%
  - Adults: 98%
- Sudden death/malignant arrhythmias were also more common in children

J Am Heart Assoc. 2016;5:e003450 doi: 10.1161/JAHA.116.003450

PARADIGM vs. PEDIATRIC CARVEDILOL TRIAL

	PARADIGM	Carvedilol in Children
	8399	161
Age at Enrollment	64 years	3 years
Diagnosis	Ischemic 60%	LV 74%, CHD Non-LV 26%
Duration HF > 1 yr	67%	< 10%
Class IV HF	Class II-III	Class II-III
Vent function	LVEF 30%	LVEF 26%
Hypertension Diabetes Atrial fibrillation	71% 35% 36%	0% 0% 0%

PARADIGM vs. PEDIATRIC CARVEDILOL TRIAL

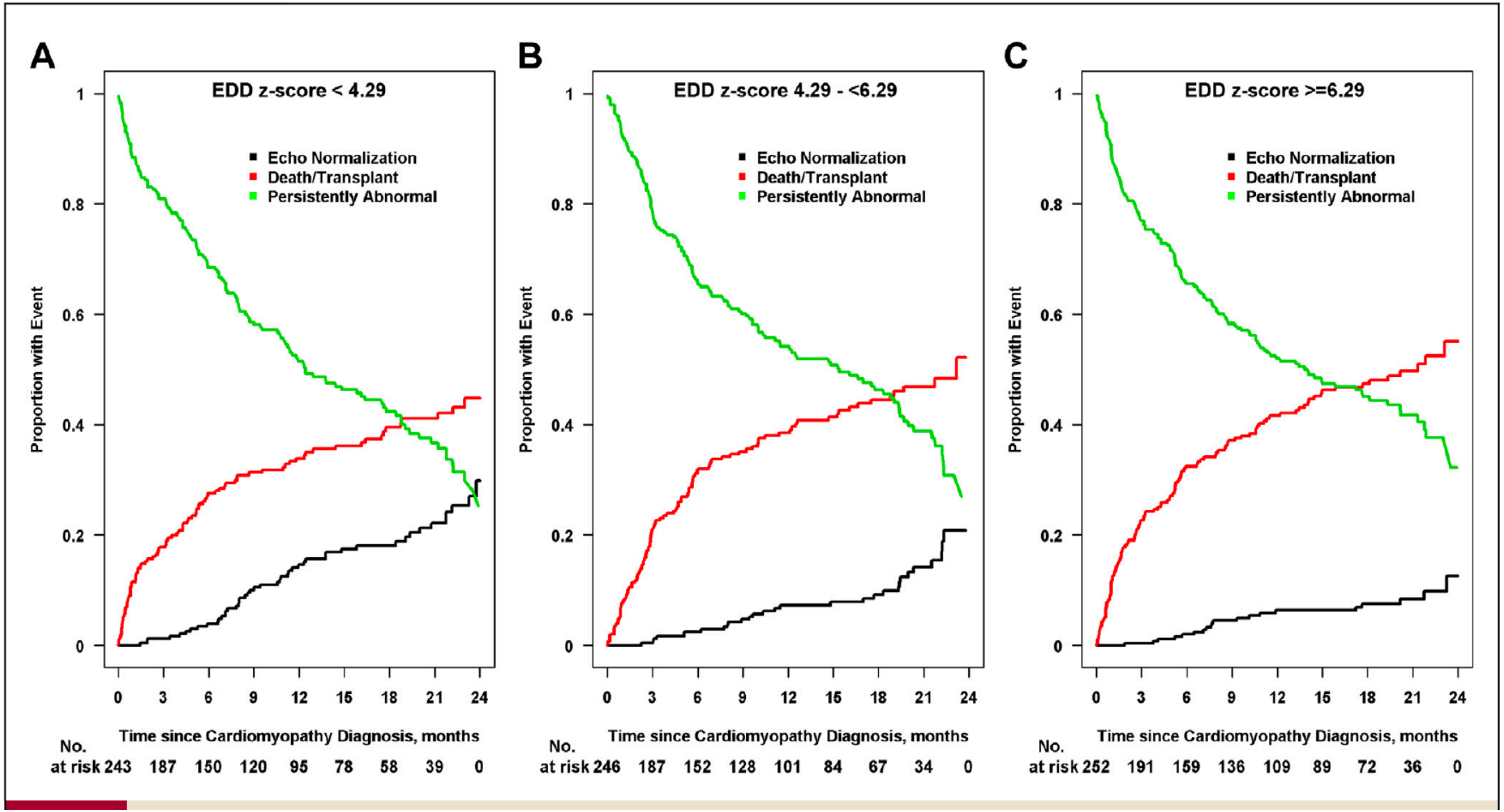
	PARADIGM	Carvedilol in Children
	8399	161
All cause death/HF	26.5% enalapril 21.8% LCZ646	17% placebo 16% carvedilol
Death	16.5% enalapril 13.3% LCZ646	6% placebo 5.6% carvedilol
LVEF at end study	N/A	34.9% placebo 39-41% carvedilol
BNP at enrollment pg/ml	225	116
BNP at end study	N/A	49 placebo 35-43 carvedilol
Non LV at end study		No difference in LVEF Carvedilol: worse composite endpoint

Echocardiographic Measurements and Outcome

	Normalized (n = 96)	Death or Transplantation (n = 317)	Persistently Abnormal (n = 328)	p Value
LV dimension, mean ± SD, *z*-score				
EDD	4.56 ± 1.87	5.70 ± 2.06	5.41 ± 2.06	<0.001
ESD	6.39 ± 2.03 (n = 87)	7.69 ± 1.95 (n = 287)	7.20 ± 2.09 (n = 293)	<0.001
LVFS				
Mean ± SD, *z*-score	−9.21 ± 2.86 (n = 90)	−10.28 ± 2.28 (n = 297)	−9.34 ± 2.81 (n = 313)	<0.001
Mean ± SD, %	15.4 ± 6.9	11.4 ± 4.9	14.7 ± 6.3	<0.001

Everitt et al. J Am Coll Cardiol 2014;63:1405–13

LV EDD and Outcome



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Pediatric vs Adult Dilated Cardiomyopathy

Similarities

- **Nonischemic CM**
- **Younger age**
- **Few co-morbidities**
- **LV size and dimension**
- **BNP**
- Genetics?

Differences

- Heart failure class
- Recovery potential
- Age-related differences
- Pharmacology

Study Design of Adult and Pediatric HF trials

- Specify enrollment of a cohort with patient and disease characteristics similar to the pediatric population
- Collect surrogate outcome data to be used for extrapolation
  - LVEF
  - LV dimensions
  - BNP/pro-BNP
- Validate heart failure and quality of life scores in children
- Obtain data from chronic heart failure patients with systolic dysfunction to determine differences in clinical characteristics and outcomes