MULTICENTER STUDY OF THE SURVIVAL IMPACT OF CARDIAC RESYNCHRONIZATION THERAPY IN PEDIATRIC AND CONGENITAL HEART DISEASE

Authors
Henry Chubb MA MBBS PhD[1,2], Douglas Mah MD[3], Maully Shah MD[4], Kimberly Y Lin MD[4], David Peng MD[5], David Bradley MD[5], Benjamin Hale MD[5], Lindsay May MD[6], Susan Etheridge MD[6], Doff B McElhinney MD[1,2], Anne M Dubin MD[1]

Author Affiliations
[1]Division of Pediatric Cardiology, Department of Pediatrics, Stanford University, CA, USA
[2]Division of Pediatric Cardiothoracic Surgery, Department of Cardiothoracic Surgery, Stanford University, CA, USA
[3] Department of Cardiology, Boston Children's Hospital; Department of Pediatrics, Harvard Medical School; Boston MA, USA
[4] Department of Cardiology, Children's Hospital of Philadelphia, Philadelphia, PA, USA
[5] Division of Cardiology, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI, USA
[6] Department of Cardiology, Primary Children's Hospital, University of Utah, Salt Lake City, UT, USA

Corresponding Author
Henry Chubb, Clinical Assistant Professor, Department of Pediatrics, Stanford University School of Medicine, 750 Welch Road, Stanford, CA 94304
Telephone: 650 721 2121
mhchubb@stanford.edu

Objectives
Evidence for the efficacy of cardiac resynchronization therapy (CRT) in pediatric and congenital heart disease (CHD) has been limited to surrogate outcomes. This study aimed to assess the impact of CRT upon the risk of transplant or death in a retrospective, high risk, controlled cohort at five large quaternary referral centers.

Methods
Both CRT subjects and controls were <21 years or had CHD; had systemic ventricular ejection fraction <45%; symptomatic heart failure; and had significant electrical dyssynchrony (defined as QRS duration z-score>3 or single site Vp>40%) at enrollment. Patients with CRT were matched with controls without CRT by 1:1 propensity-score matching (PSM) using 21 comprehensive baseline indices for risk stratification. Controls were retrospectively enrolled at the time of the outpatient clinical encounter where inclusion criteria were met. CRT subjects were enrolled at time of CRT implantation.

Results
In total, 324 eligible controls and 167 eligible CRT recipients were identified across the 5 centers. The mean follow-up was 4.2 ($\pm$3.7) years and was similar in CRT and control cohorts (HR for loss to follow-up in CRT cohort 0.98 [95% CI 0.78-1.22, p=0.86]). Upon propensity score matching, 139 matched pairs were identified with no significant differences across all 21 baseline indices (10 of 21 indices are presented in Table 1).

Of the 139 matched pairs, 52 (37%) controls and 31 (22%) CRT reached the primary endpoint of transplant or death. On univariable analysis, HR for the primary endpoint was 0.53 ([0.34-0.83], p=0.005). (Figure 1) On multivariable Cox Regression, the reduction in risk associated with CRT remained significant (HR 0.456 [0.29-0.717], p=0.001). The presence of a biventricular circulation, CHD, prior ventricular pacing (Vp>40%), absence of heart transplant listing, absence of prior VT and lower number of HF medications were also all associated with significant reduction in risk.

Conclusions
In pediatric and CHD patients with symptomatic systolic heart failure and electrical dyssynchrony, CRT was associated with improved heart transplant-free survival.

	All Subjects (n=491)			Propensity Score Matched Subjects (n=278)		
	Controls (n=324)	CRT (n=167)	p-value (Standard difference, %)	Controls (n=139)	CRT (n=139)	p-value (Standard difference, %)
Age (years)	13.5 [4.7-22.6]	12 [4.3-20]	0.94 (-0.7)	14.9 [6.9-22.5]	12.8 [4.9-20]	0.51 (-8.3)
Weight (kg)	44 [15-65]	36 [16-70]	0.66 (4.2)	49 [19-67]	38 [17-68]	0.82 (-2.6)
Systemic Ventricle EF (%)	34 +/-6.7	31.2 +/-8.8	0 (-35.8)	32.6 +/-7.4	32.3 +/-8.2	0.72 (-4.4)
Biventricular Circulation (n)	209 (64.5%)	145 (86.8%)	0 (53.8)	114 (82%)	118 (84.9%)	0.52 (6.9)
Systemic LV (n)	228 (70.4%)	141 (84.4%)	0 (34)	117 (84.2%)	115 (82.7%)	0.75 (-3.5)
Congenital Heart Disease (n)	260 (80.2%)	122 (73.1%)	0.07 (-17)	102 (73.4%)	103 (74.1%)	0.89 (1.7)
Prior pacing (Vp>40%)	89 (27%)	105 (63%)	0 (75.9)	73 (53%)	78 (56%)	0.55 (7.7)
QRS duration z-score	5.9 +/-2.4	7.4 +/-2.7	0 (59.3)	7 +/-2.7	7.1 +/-2.6	0.66 (5.6)
Listed for Heart Transplant (n)	17 (5.2%)	7 (4.2%)	0.61 (-5)	3 (2.2%)	6 (4.3%)	0.31 (10.2)
Number of HF Medications (n)	2.3 +/-1.5	2.5 +/-1.3	0.05 (19)	2.5 +/-1.5	2.4 +/-1.3	0.39 (-10.2)

Table 1. Summary of 10 (out of total 21) baseline indices at the date of enrollment, for the whole cohort (left) and propensity score-matched cohort (right). HR: Hazard ratio. EF: ejection fraction, LV: left ventricle, Vp: percentage of beats ventricularly paced, HF: heart failure.
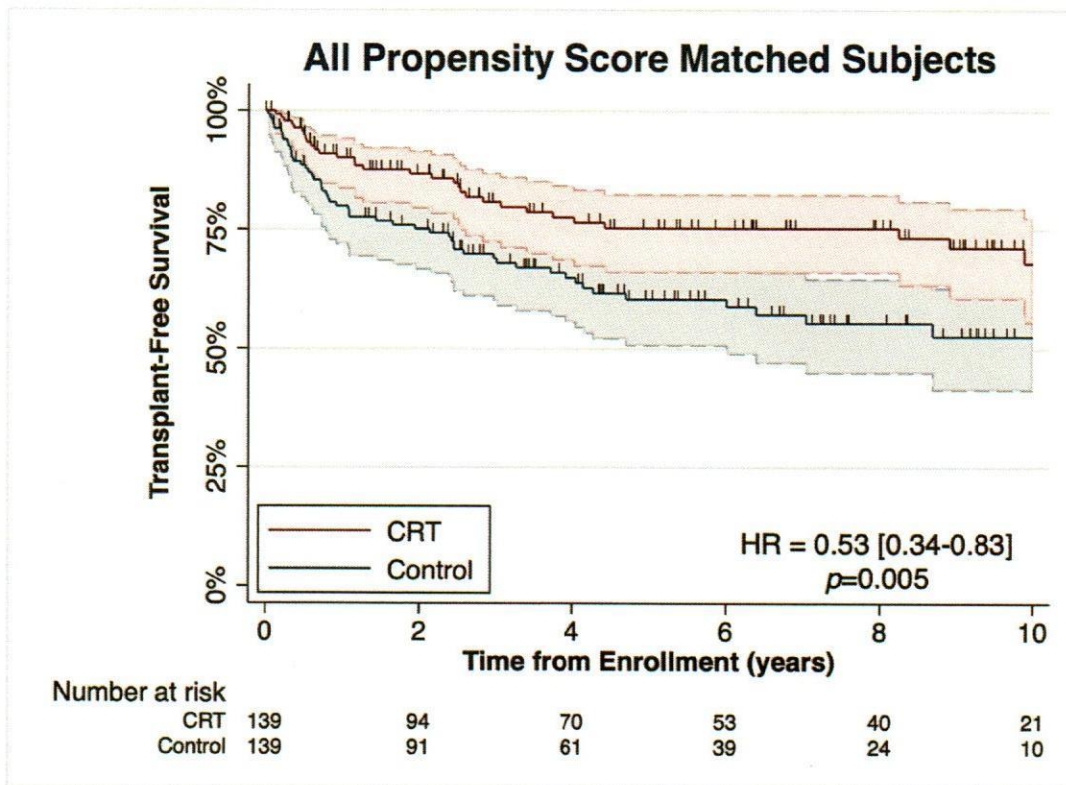

Figure 1. Kaplan Meier plot: Survival free from Heart Transplant. All Propensity Score Matched subjects.