Novel Strategies in the Management of Heart Failure in Pediatrics

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Heart Failure
Therapeutic Options

- Medications
- Mechanical support
- Heart transplantation
- Cell therapy

Pediatric Heart Failure
Program Structure
Medications

- Ivabradine
- LCZ696 (Entresto)
• No direct myocardial contractility effect
• No direct blood pressure effect
Systolic Heart failure treatment with the *If* inhibitor ivabradine Trial (SHIFT)

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine group (n=3241)</th>
<th>Placebo group (n=3264)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death or</td>
<td>793 (24%)</td>
<td>937 (29%)</td>
<td>0.82 (0.75–0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>hospital admission for</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>worsening heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mortality endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>503 (16%)</td>
<td>552 (17%)</td>
<td>0.90 (0.80–1.02)</td>
<td>0.092</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>449 (14%)</td>
<td>491 (15%)</td>
<td>0.91 (0.80–1.03)</td>
<td>0.128</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>113 (3%)</td>
<td>151 (5%)</td>
<td>0.74 (0.58–0.94)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Other endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause hospital</td>
<td>1231 (38%)</td>
<td>1356 (42%)</td>
<td>0.89 (0.82–0.96)</td>
<td>0.003</td>
</tr>
<tr>
<td>admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admission for</td>
<td>514 (16%)</td>
<td>672 (21%)</td>
<td>0.74 (0.66–0.83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>worsening heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cardiovascular</td>
<td>977 (30%)</td>
<td>1122 (34%)</td>
<td>0.85 (0.78–0.92)</td>
<td>0.0002</td>
</tr>
<tr>
<td>hospital admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death,</td>
<td>825 (25%)</td>
<td>979 (30%)</td>
<td>0.82 (0.74–0.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>or hospital admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>for non-fatal myocardial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are number of first events (%), hazard ratio (HR; 95% CI), and p values.

*Table 3: Effects on primary and major secondary endpoints*

Swedberg et al. Lancet 2011
Patients with primary composite endpoint (%)

- Placebo (937 events)
- Ivabradine (793 events)

HR 0.82 (95% CI 0.75–0.90), p<0.0001
Ivabradine - Indications

Diuretics to relieve symptoms/signs of congestion^a

ACE inhibitor (or ARB if not tolerated)^b

ADD a beta-blocker^b

Still NYHA class II–IV?

ADD a MR antagonist^b,d

Still NYHA class II–IV?

LVEF ≤35%?

Sinus rhythm and HR ≥70 beats/min?

ADD ivabradine^a
## TABLE 1  Incidence of Selected Adverse Drug Reactions Occurring on Ivabradine Versus Placebo in the SHIFT Trial

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine (n = 3,232)</th>
<th>Placebo (n = 3,260)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>2,439 (75)</td>
<td>2,423 (74)</td>
<td>0.303</td>
</tr>
<tr>
<td>Heart failure</td>
<td>804 (25)</td>
<td>937 (29)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>150 (5)</td>
<td>32 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>184 (6)</td>
<td>48 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AF</td>
<td>306 (9)</td>
<td>251 (8)</td>
<td>0.012</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>89 (3)</td>
<td>17 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>17 (1)</td>
<td>7 (&lt;1)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Values are n (%). Adapted with permission from Swedberg et al (9).

AF = atrial fibrillation; SHIFT = Systolic Heart failure treatment with the \( l_f \) Inhibitor ivabradine Trial

Koruth et al. JACC 2017
LCZ696 (Entresto)
<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Substrates for Human Neprilysin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardio-renal</td>
<td>ANP, BNP, and CNP; angiotensins 1, 2, 3, 1-9; endothelin-1, -2, and -3; adrenomedullin; bradykinin</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Amyloid-beta (1-40), (1-42); enkephalins (met and leu); alpha-endorphin, gamma-endorphin; alpha-neoendorphin; beta-neoendorphin; nociceptin; corticotrophin-releasing factor; luteinizing hormone-releasing hormone; oxytocin; arginine vasopressin; neurotensin; neuropeptide Y; neurokinin A</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Gastrin-releasing peptide; gastric inhibitory peptide; vasoactive intestinal peptide; cholecystokinin</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Substance P, other tachykinins</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Glucagon; glucagon-like peptide; beta-lipotropin; insulin B-chain; secretin; CGRP; somatostatin</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Chemotactic peptide; interleukin 1-beta</td>
</tr>
<tr>
<td>Multisystem/other</td>
<td>Substance P</td>
</tr>
</tbody>
</table>

ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CGRP = calcitonin gene-related peptide; CNP = C-type natriuretic peptide.
LCZ696: A First-in-Class Angiotensin Receptor Neprilysin Inhibitor

**Natriuretic Peptide System**
- pro BNP
- BNP
- NT-pro BNP
- Inactive fragments
- Neprilysin

**Renin-Angiotensin System**
- Angiotensinogen (liver secretion)
- Angiotensin I
- Angiotensin II
- AT₁ receptor

**Vasodilation**
- ↓ blood pressure
- ↓ sympathetic tone
- ↓ aldosterone levels
- ↓ fibrosis
- ↓ hypertrophy
- ↓ natriuresis/diuresis

**Vasoconstriction**
- ↑ blood pressure
- ↑ sympathetic tone
- ↑ aldosterone
- ↑ fibrosis
- ↑ hypertrophy

Heart Failure

AHU377
 LBQ657
 Valsartan
**Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.**

Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).
Entresto - Indications

U.S.: Symptomatic adults with HFrEF should **switch** from a stable regimen of ACEi or ARB to LCZ

Less consensus on whether to start ACEi or LCZ *de novo*
Development of Therapeutics for Heart Failure

Developing New Treatments for Heart Failure
Focus on the Heart

Mihai Gheorghiade, MD; Christopher J. Larson, PhD; Sanjiv J. Shah, MD; Stephen J. Greene, MD; John G.F. Cleland, MD, PhD; Wilson S. Colucci, MD; Preston Dunnmon, MD; Stephen E. Epstein, MD; Raymond J. Kim, MD; Ramin V. Parsey, MD, PhD; Norman Stockbridge, MD, PhD; James Carr, PharmD; Wilfried Dinh, MD; Thomas Krahn, PhD; Frank Kramer, PhD; Karin Wahlander, MD, PhD; Lawrence I. Deckelbaum, MD; David Crandall, PhD; Shunichiro Okada, MD; Michele Senni, MD; Sergey Sikora, PhD; Hani N. Sabbah, PhD; Javed Butler, MD, MPH, MBA

Table 1. Summary Points

<table>
<thead>
<tr>
<th>Point 1: Lack of therapies for WCHF and HFpEF continues to be a huge unmet need</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality and morbidity among patients with stable systolic dysfunction has improved by modulating neurohormonal abnormalities, but the long-term clinical outcomes are still poor. We have thus far failed to improve outcomes in WCHF and HFpEF.</td>
</tr>
</tbody>
</table>
Point 2: The macroscopic and microscopic structural abnormalities of the heart should be the focus of HF research and drug development.

Structural cardiac abnormalities represent the proximal causes of HF, but interventions often target issues secondary to the failing heart. Most patients die with considerable dysfunctional viable myocardium, unlike end-stage renal disease or liver failure/cirrhosis where residual tissue viability (i.e., tissue capital) is minimal at the point of clinical organ failure.
HEART FAILURE WITH REDUCED EF

RECOVERY
"Normal" Structure and Function

Enhanced Phenotyping of Myocardial Substrate

Components of DVM
1) Myocyte
2) Interstitium
3) Microcirculation
4) Abnormal mitochondria
5) Metabolic abnormalities

NON-VIABLE TISSUE

Vulnerable Myocardium
Dysfunctional Myocyte
Dysfunctional Myocardium
Novel Therapeutics in Heart Failure

Von Lueder and Krum Nat Rev Cardiol 2015
What About Us Kids???
Increased Heart Rate is Independently Associated with Worse Survival in Pediatric Patients with Dilated Cardiomyopathy: a Multicenter Study From the Pediatric Cardiomyopathy Registry

Joseph W. Rossano, Paul F. Kantor, Robert E. Shaddy, James D. Wilkinson, John L. Jefferies, Christophe Depre, Heidi Wirtz, Steven E. Lipshultz
Multivariable Analysis

Increased heart rate independent association

Death (adjusted hazard ratio HR=2.6; IQR 1.55, 4.36; p<0.001)
Death or transplant (adjusted HR 1.5; IQR 1.1, 2.1; p=0.01)
Ivabradine in Children With Dilated Cardiomyopathy and Symptomatic Chronic Heart Failure

Damien Bonnet, MD, PhD, a Felix Berger, MD, b Eero Jokinen, MD, c Paul F. Kantor, MD, d Piers E.F. Daubney, DM e

**FIGURE 2** Heart Rate at Rest

![Graph showing heart rate at rest over time.](image)

Mean resting heart rate began decreasing with ivabradine almost immediately upon administration.
Figure 1. Study design in paediatric HF

Part 1

Sacubitril/valsartan single dose PK/PD

N = 6
0.8* mg/kg

N = 6
3.1* mg/kg

N = 6
0.8* mg/kg

Part 2

Group 1
6 to <18 years

Group 2
1 to <6 years

Group 3
1 month to <1 year

*Sacubitril/valsartan bid N = 180

*Enalapril bid N = 180

Time (Weeks)

Screening
First PK dose
Second PK dose
Screening
PreRandomisation
Double-blind period

1 All available data will be reviewed from Group 1 prior to enrolment in Group 2 and Groups 1 and 2 all available data review prior to enrolment in Group 3
**Table 3. Primary endpoint algorithm using ranked analysis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategory</th>
<th>Description</th>
<th>Ranking algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>Death; UNOS status 1A listing for heart transplant or equivalent; VAD/ECMO/mechanical ventilation requirement for life support at end of study</td>
<td>Rank within this category by time-to-first event. All Category 1 events are considered equal</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>Worsening HF with HFH-ICU</td>
<td>Patients will be ranked first by event subcategory and subsequently by number of events within each subcategory. Further ranking by time-to-first event in the worst subcategory</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>Worsening HF with hospitalisation but without intensive care unit stay (HFH-No ICU)</td>
<td>Rank by combination of NYHA/Ross and PGIS degree of change. If the degree of change is same, further rank by change in PedsQL</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
<td>Worsening HF without hospitalisation</td>
<td>Worst baseline combination of NYHA/Ross functional class and PGIS without change is ranked worse. Within a group of the same baseline NYHA/Ross and PGIS, further rank by change in PedsQL</td>
</tr>
<tr>
<td>3</td>
<td>E</td>
<td>Worsened NYHA/Ross (Table 2) or PGIS based on the last available assessment compared with baseline</td>
<td>Rank by combination of NYHA/Ross and PGIS degree of change. If the degree of change is same, further rank by change in PedsQL</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>Unchanged NYHA/Ross and unchanged PGIS based on the last available assessment compared with baseline</td>
<td>Rank by combination of NYHA/Ross and PGIS degree of change. If the degree of change is same, further rank by change in PedsQL</td>
</tr>
<tr>
<td>5</td>
<td>G</td>
<td>Improved NYHA/Ross or PGIS (neither can be worse) based on the last available assessment compared with baseline</td>
<td>Rank by combination of NYHA/Ross and PGIS degree of change. If the degree of change is same, further rank by change in PedsQL</td>
</tr>
</tbody>
</table>
PANORAMA-HF

FDA Approval
To Continue

LCZ696 PK/PD

N=6

0.8 mg/kg

N=6

3.1 mg/kg

N=6

0.8 mg/kg

9 subjects enrolled
7 observations in each dose
enrollment complete

LCZ696 b.i.d

N = 180

Group 1
6 to < 18 year

Group 2
1 to < 8 year

6 subjects enrolled
1 subject in screening
1 subject screen failed

Enalapril b.i.d

N = 180

Part 1

Visit

101 102 103 to 120

199 201 202 203 to 220

299 301 401 402 403 404 405 406 407 411

Time (Weeks)

och Screening Period 1 First PK dose

Period 2 Second PK dose

Screening PreRand

Double-blind
# Pharma Pediatric HF/Cardiovascular Trials

<table>
<thead>
<tr>
<th>Sponsor, Drug, Reference</th>
<th>Enrollment Period (months)</th>
<th># Sites</th>
<th># Pts</th>
<th>Countries</th>
<th>Completed / Ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis / aliskiren*</td>
<td>50 mo</td>
<td>71</td>
<td>267</td>
<td>US, EU, LATAM</td>
<td>Completed</td>
</tr>
<tr>
<td>Novartis / serelaxin*</td>
<td>21 mo</td>
<td>19</td>
<td>36</td>
<td>US, EU</td>
<td>Completed</td>
</tr>
<tr>
<td>GSK / carvedilol</td>
<td>55 mo</td>
<td>26</td>
<td>161</td>
<td>US</td>
<td>Completed Neutral</td>
</tr>
<tr>
<td>Servier/ Ivabradine</td>
<td>24 mo</td>
<td>(20 countries)</td>
<td>90</td>
<td>EU, Russia, Brazil, India</td>
<td>Completed Positive</td>
</tr>
<tr>
<td>BMS/ clopidogrel</td>
<td>~39 m</td>
<td>134</td>
<td>906</td>
<td>US, EU, LATAM, Asia</td>
<td>Completed Neutral</td>
</tr>
<tr>
<td>Novartis LCZ696</td>
<td>~38 mo (Pt 1,2)</td>
<td>(29 countries)</td>
<td>360</td>
<td>US, EU, Russia, LATAM, Asia</td>
<td>Enrolling</td>
</tr>
</tbody>
</table>

* Different indication: aliskerin – HTN; serelaxin – ADHF; clopidogrel- Sys/PA shunt
STEM CELL DEPOT

PARTS DEPT.

YA' GOT A FEMUR FOR A '57 CAUCASIAN?
Transcoronary infusion of cardiac progenitor cells in hypoplastic left heart syndrome: Three-year follow-up of the Transcoronary Infusion of Cardiac Progenitors in Congenital Heart Disease (TICC) study.

ABSTRACT

Objectives: Our objective was to determine whether transcoronary infusions of cardiosphere-derived cells (CDCs) improve right ventricular function in patients with hypoplastic left heart syndrome (HLHS) during the first 3 years after surgery.

Methods: In this single-center, prospective, investigator-initiated, open-label, phase IIb registry study, we evaluated 11 HLHS patients allocated to receive transcoronary CDC infusions. The primary outcome was to assess prospectively the impact of CDCs on changes in right ventricular ejection fraction and heart failure status through 36-month follow-up.

Results: No complications, including tumor formation, were reported within 1 year of infusion. Follow-up right ventricular ejection fraction (52.2% ± 9.3% vs. 51.8% ± 7.3%; r = 0.91, P = 0.005) and heart failure status (New York Heart Association (NYHA) improved from 1.6 ± 0.6 to 0.7 ± 0.4; P < 0.001).
Intracoronary Cardiac Progenitor Cells in Single Ventricle Physiology

The PERSEUS (Cardiac Progenitor Cell Infusion to Treat Univentricular Heart Disease) Randomized Phase 2 Trial

Shuta Ishigami,* Shinichi Ohtsuki, Takahiro Eitoku, Daiki Ousaka, Maiko Kondo, Yoshihiko Kurita, Kenta Hirai, Yosuke Fukushima, Kenji Baba, Takuya Goto, Naohiro Horio, Junko Kobayashi, Yosuke Kuroko, Yasuhiro Kotani, Sadahiko Arai, Tatsuo Iwasaki, Shuhei Sato, Shingo Kasahara, Shunji Sano, Hidemasa Oh*

Circulation Research     March 31, 2017
110 patients with single ventricle physiology undergoing surgical reconstruction

34 excluded due to 1st palliative procedure
13 had Norwood (RV-PA shunt)
11 had pulmonary artery banding
10 had modified BT shunt

76 met initial eligibility criteria

35 excluded due to EF > 60% at initial screening

41 were eligible and randomly assigned

Study A

18 were randomly allocated to receive standard care

1 excluded EF > 60%

Study B

23 were randomly allocated to receive CDCs

6 excluded
3 had EF > 60%
1 had infectious endocarditis
2 withdrew consent

17 controls patients with 3 months of follow up and late CDC infusion

17 CDC-treated patients with 3 months of follow up

17 CDC-treated patients with 3 months of follow up

17 CDC-treated patients with 12 months of follow up

17 CDC-treated patients with 12 months of follow up
Same findings with Echo and Ventriculography
A randomized study of autologous bone marrow–derived stem cells in pediatric cardiomyopathy

E. Sian Pincott, PhD, MRCPCH, Deborah Ridout, MSc, Margaret Brocklesby, BSc, Angus McEwan, FRCA, Vivek Muthurangu, MD, MRCPCH, and Michael Burch, MD, FRCP, FRCPCH

From the "Department of Cardiology, Great Ormond Street Hospital, London, United Kingdom; Population Policy and Practice Programme, UCL Institute of Child Health, London, United Kingdom; and the "Bone Marrow Laboratory, Great Ormond Street Hospital, London, United Kingdom."

The Journal of Heart and Lung Transplantation, Vol 36, No 8, August 2017
<table>
<thead>
<tr>
<th></th>
<th>Before stem cells</th>
<th>Before stem cells</th>
<th>Before stem cells</th>
<th>Before stem cells</th>
<th>After stem cells</th>
<th>After stem cells</th>
<th>After stem cells</th>
<th>After stem cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>Mean 1,318</td>
<td>132.6</td>
<td>79.5</td>
<td>40</td>
<td>1,371</td>
<td>122.24</td>
<td>74.31</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Range 180–6,285</td>
<td>81.33–283.78</td>
<td>43.69–165.59</td>
<td>33–49</td>
<td>22–4,055</td>
<td>77.73–275.73</td>
<td>41.76–173.41</td>
<td>46–53</td>
</tr>
<tr>
<td>Before placebo</td>
<td>Before placebo</td>
<td>Before placebo</td>
<td>Before placebo</td>
<td>After placebo</td>
<td>After placebo</td>
<td>After placebo</td>
<td>After placebo</td>
<td>After placebo</td>
</tr>
<tr>
<td>Mean 1,325</td>
<td>128.9</td>
<td>78.96</td>
<td>39</td>
<td>1,433</td>
<td>129.30</td>
<td>80.99</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

NT-proBNP, N-terminal prohormone brain natriuretic peptide; EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume.

*a* Patient with Duchenne muscular dystrophy was excluded from statistical analyses.

*b* Reached statistical significance.
# Summary of Pediatric CV Cell Therapy Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Design</th>
<th>Sponsor and Collaborators</th>
<th>Cell Type</th>
<th>Route</th>
<th>Timing</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>TICAP (Transcoronary Infusion of Cardiac Progenitor Cells in Patients With Single Ventricle Physiology)</td>
<td>2011</td>
<td>Nonrandomized, controlled phase I</td>
<td>Okayama University</td>
<td>CPC (autologous)</td>
<td>IC</td>
<td>Stage II or III operation</td>
<td>Reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>National Cerebral and Cardiovasc. Ctr. (Japan)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Can we better structure our Pediatric Heart Failure Programs?
1990’s

Pediatric Heart Transplantation and Heart Failure
2000’s

Pediatric Heart Transplant

Pediatric Heart Failure

Arrows indicate a relationship or comparison between pediatric heart transplant and pediatric heart failure during the 2000’s.
Pediatric Cardiomyopathy and Heart Failure
MDs, NPs, RNs
Social Work, Pharmacology
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

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Developed in Collaboration with the American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation

ACC/AHA Task Force Members, see page e150
Summary

New drugs are here and more are coming

We need to study these new drugs in children

New targets are needed

Cell therapy has as yet unrealized potential

Pediatric Heart Failure Program Structure is important