Therapeutic Approach to the Management of DMD-Associated Cardiomyopathy

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HeartWare Inc: Consultant
PhaseBio Inc: Member of the Scientific Advisory Committee
Overview

- Brief overview of DMD.
- Plasticity of the human heart.
- 2016 standard of care in the management of heart failure.
- Management of DMD-associated cardiomyopathy, including LVAD therapy.
Duchenne Muscular Dystrophy
## Examples of Monogenic Myopathies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>Dystrophin</td>
</tr>
<tr>
<td>X-linked Myotubular Myopathy</td>
<td>MTM1</td>
</tr>
<tr>
<td>Centronuclear Myopathy</td>
<td>DNM2 and BIN1</td>
</tr>
<tr>
<td>Central Core Disease</td>
<td>Ryanodine receptor 1</td>
</tr>
<tr>
<td>Multiminicore Disease</td>
<td>RYR1 and SEPN1</td>
</tr>
<tr>
<td>Desmin Myopathy</td>
<td>Desmin and CRYAB</td>
</tr>
<tr>
<td>Nemaline Myopathy</td>
<td>Thin filament genes</td>
</tr>
<tr>
<td>ISCU Myopathies</td>
<td>Iron-sulphur cluster assembly gene</td>
</tr>
<tr>
<td>Laminopathies</td>
<td>α-type laminin</td>
</tr>
<tr>
<td>Myofibrillar Myopathy</td>
<td>Contractile proteins</td>
</tr>
<tr>
<td>Danon Disease</td>
<td>LAMP2</td>
</tr>
<tr>
<td>Myotonic Dystrophy (type 1)</td>
<td>DMPK</td>
</tr>
<tr>
<td>Myotonic Dystrophy (type 2)</td>
<td>ZNF9</td>
</tr>
</tbody>
</table>

The future of medicine, today.
Duchenne Muscular Dystrophy

- X-linked dystrophinopathy.
- 1 in 3,500 to 5,000 boys.
- No cure.
- In 2016, development of cardiomyopathy and arrhythmias are the primary mode of death in DMD patients.
Dystrophin and Muscular Dystrophy

The Dystrophin Gene

Extracellular matrix
Sarcolemma
Cytoplasm
Actin filaments
Dystrophin

Sarcoglycan complex
Sarcospan
nNOS binding sites
α-Dystrobravin

αDG
βDG

Laminin 2
α2
β1
γ1

Syntrophins
β1
β2

The future of medicine, today.

Nature Reviews | Genetics
Novel Approaches to Treating Duchenne Muscular Dystrophy

- Dystrophin-like gene delivery by viral vectors.
- Read-through of translation stop codons by drugs.
- Exon-skipping oligonucleotides.
- Increased expression of the compensatory utrophin gene.
- Transplantation of normal myoblasts or stem cells.
- Genome editing via CRISPR-Cas9.
Survival Rates in DMD Patients in 2016

Kamdar et al.
JACC 2016 67:2533-2546
Plasticity of the Human Heart
Standard Approach to Treating Heart Failure in 2016
### ACC/AHA Heart Failure Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High risk of developing HF, but no structural heart disease or HF.</td>
<td>HTN, CAD, Diabetes, family history of cardiomyopathy.</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease, but no signs of heart failure (Asymptomatic HF).</td>
<td>Prior MI, LV systolic dysfunction, Valvular disease, RV hypertrophy.</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with signs of heart failure (Symptomatic HF).</td>
<td>Dyspnea, fatigue, exercise intolerance, orthopnea, PND.</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF despite maximal medical therapy.</td>
<td>Marked symptoms at rest despite maximal therapy.</td>
</tr>
</tbody>
</table>

Hunt et al. *JACC* 2001
Heart Failure Management: Standard of Care in 2016

Treatment of advanced heart failure:
- Beta-Blockers (Coreg or Toprol XL)
- ACEI vs. ARB
- Aldosterone Inhibitors (Spironolactone or Eplerenone)
- ARNI (ARB + inhibitor of neprilysin)
- Ivabradine
- BiDil (or Isordil/Hydralazine)
- Diuretics (only if volume overloaded)
- Digoxin
- AICD vs. BiV/AICD (QRS>120msec and/or cardiac dyssynchrony noted by ECHO)
- LVAD and/or Heart Transplantation
# Effect of ACE Inhibitors on Mortality Reduction in Patients With Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>ACEI</th>
<th>Controls</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic CHF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS I</td>
<td>39%</td>
<td>54%</td>
<td>0.56 (0.34–0.91)</td>
</tr>
<tr>
<td>SOLVD (Treatment)</td>
<td>35%</td>
<td>40%</td>
<td>0.82 (0.70–0.97)</td>
</tr>
<tr>
<td>SOLVD (Prevention)</td>
<td>15%</td>
<td>16%</td>
<td>0.92 (0.79–1.08)</td>
</tr>
<tr>
<td><strong>Post-MI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE</td>
<td>20%</td>
<td>25%</td>
<td>0.81 (0.68–0.97)</td>
</tr>
<tr>
<td>AIRE</td>
<td>17%</td>
<td>23%</td>
<td>0.73 (0.60–0.89)</td>
</tr>
<tr>
<td>TRACE</td>
<td>35%</td>
<td>42%</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>23%</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>
Major Placebo Controlled Trials of β-Blockade in Heart Failure

US Carvedilol Trials\(^1\)

- Carvedilol (n=696)
- Placebo (n=398)

65% ↓
\(P<.001\)

Probability of Event-free Survival

Cumulative Mortality (%)

Metoprolol CR/XL (n=1990)

Placebo (n=2001)

\(34\% \downarrow\)
\(P=.0062\) (adjusted)

Days

Survival (% of Patients)

CIBIS-II\(^3\)

- Bisoprolol (n=1327)
- Placebo (n=1320)

34% ↓
\(P<.0001\)

Survival (% of Patients)

COPERNICUS\(^4\)

- Carvedilol (n=1156)
- Placebo (n=1133)

35% ↓
\(P=.00013\)

Days

---


Mortality Benefit of $\beta$-Blockers and ACE-Inhibitors in HF Trials

- SOLVD (1991)
  - 15.6
  - 7.8

McMurray et al. Heart 1999
Aldosterone Blockade in Heart Failure
RALES: Randomized Aldactone Evaluation Study

Pitt B et al.
NEJM 1999

Probability of Survival (%)

Follow-up (months)

RR 0.70 (0.60–0.82)

P < .001
Heart Failure Management: Standard of Care in 2016

<table>
<thead>
<tr>
<th></th>
<th>ACE-I or ARB</th>
<th>Beta Blocker</th>
<th>Aldosterone Antagonist</th>
<th>CRT</th>
<th>AICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improves Functional Status</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Promotes Changes in LV Structure</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Reduces Hospitalization</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Decreases Mortality</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

The future of medicine, today.
Reverse Cardiac Remodeling in Human Cardiomyopathy: 33% Rule

The future of medicine, today.
Treatment of DMD-Associated Cardiomyopathy

The future of medicine, today.

Jessup et al. NEJM 2003
Medical Management of DMD-Associated Cardiomyopathy
Dilemma in the Management of DMD-Associated Cardiomyopathy

- Failure to include DMD and other muscular dystrophy patients in the majority of the large clinical heart failure trials.

- Limited number of well controlled randomized clinical trials to guide management of DMD-associated cardiomyopathy.

- Lack of guidelines for CV care of DMD patients by the major cardiovascular organizations.
UTSW Adult Neuromuscular Cardiomyopathy Clinic

- Established in 2010.
- Directed and managed by an adult heart failure/transplant cardiologist.
- One of six Adult NM CHF Clinics in the US and one of the largest.
- 400 patient referrals to date.
- 2-4 new DMD/DMD Carrier patient referrals per month.

The future of medicine, today.
UTSW Neuromuscular Cardiomyopathy Clinic: The Vision

UTSW Neuromuscular Cardiomyopathy Clinic

Translational Research

Stem Cell Biology & Genome Editing

Small Molecules: Induction of cardiac & muscle regeneration

State-of-the Art Cardiovascular Care

The future of medicine, today.

UT Southwestern Medical Center
UTSW Neuromuscular Cardiomyopathy Clinic: Patient Referral Patterns

UTSW Adult Neuromuscular Cardiomyopathy Clinic

UTSW Pediatric MDA Clinic

UTSW Adult MDA Clinic

Neurologists & Cardiologists in North Texas

Assessment & Management of CV Status in NMD (& DMD) Patients

The future of medicine, today.
UTSW Neuromuscular Cardiomyopathy Clinic: Initial CV Assessment of Patients

Assessment & Management of CV Status in NMD (including DMD) Patients

Clinical & Molecular Phenotyping

Cardiac Electrical Assessment: EKG & Holter

Cardiac Imaging: Cardiac MRI
Heart Failure Management in DMD Patients in 2016

Treatment of heart failure in DMD:
* Beta-Blockers (Coreg or Toprol XL)
* ACEI vs. ARB
* Aldosterone Inhibitors (Spironolactone or Eplerenone)
* Steriods ??
* ARNI (ARB + inhibitor of neprilysin) ??
* Ivabradine ??
* BiDil (or Isordil/Hyndralazine) ??
* Diuretics (only if volume overloaded)
* Digoxin ??
* AICD vs. BiV/AICD ??
* LVAD and/or Cardiac Transplantation ??
Role of Perindopril in Preventing LV Dysfunction DMD-Associated Cardiomyopathy

Duboc et al. JACC 2004 45:855-857
# Role of Eplerenone and ACEI in DMD-Associated Cardiomyopathy

Raman et al.  
*Lancet Neurology* 2015 14:153-161

## Table: Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone (N=20)</th>
<th>Placebo (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>14.5 (12.0-18.5)</td>
<td>15.0 (11.0-19.0)</td>
</tr>
<tr>
<td><strong>White ethnic background</strong></td>
<td>18 (90%)</td>
<td>20 (91%)</td>
</tr>
<tr>
<td><strong>Ambulatory</strong></td>
<td>10 (50%)</td>
<td>8 (36%)</td>
</tr>
<tr>
<td><strong>Ventilatory support</strong></td>
<td>7 (35%)</td>
<td>6 (27%)</td>
</tr>
<tr>
<td><strong>Dystrophin mutation type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon deletion</td>
<td>17 (85%)</td>
<td>14 (64%)</td>
</tr>
<tr>
<td>Exon duplication</td>
<td>1 (5%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Point mutation</td>
<td>2 (10%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Intron splice mutation</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td><strong>Left ventricular ejection fraction</strong></td>
<td>56.1% (5.6)</td>
<td>57.9 (7.1)</td>
</tr>
<tr>
<td><strong>Left ventricular strain</strong></td>
<td>-16.3% (2.3)</td>
<td>-16.9 (2.1)</td>
</tr>
<tr>
<td><strong>LGE</strong></td>
<td>0.30 (0.09)</td>
<td>0.27 (0.10)</td>
</tr>
</tbody>
</table>

## Blood pressure, mm Hg

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone (N=20)</th>
<th>Placebo (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic</strong></td>
<td>107.1 (12.2)</td>
<td>107.5 (15.0)</td>
</tr>
<tr>
<td><strong>Diastolic</strong></td>
<td>64.4 (10.6)</td>
<td>68.2 (12.6)</td>
</tr>
</tbody>
</table>

## Heart rate, beats per min

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone (N=20)</th>
<th>Placebo (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>91.2 (14.0)</td>
<td>91.3 (12.3)</td>
<td></td>
</tr>
</tbody>
</table>

## Weight, kg

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone (N=20)</th>
<th>Placebo (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53.5 (15.6)</td>
<td>52.1 (19.0)</td>
<td></td>
</tr>
</tbody>
</table>

## Serum potassium, mmol/L

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone (N=20)</th>
<th>Placebo (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0 (0.3)</td>
<td>4.0 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>

## Background medical therapy at enrolment

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone (N=20)</th>
<th>Placebo (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACEI</strong></td>
<td>18 (90%)</td>
<td>20 (91%)</td>
</tr>
<tr>
<td><strong>ARB</strong></td>
<td>2 (10%)</td>
<td>2 (9)</td>
</tr>
<tr>
<td><strong>ACEI or ARB duration, years</strong></td>
<td>1.7 (1.7)</td>
<td>1.5 (1.5)</td>
</tr>
<tr>
<td><strong>β-blocker</strong></td>
<td>8 (40%)</td>
<td>9 (41%)</td>
</tr>
<tr>
<td><strong>β-blocker duration, years</strong></td>
<td>1.9 (0.9)</td>
<td>1.2 (0.4)</td>
</tr>
<tr>
<td><strong>Steroid</strong></td>
<td>17 (85%)</td>
<td>18 (82%)</td>
</tr>
<tr>
<td><strong>Prednisone</strong></td>
<td>10 (59%)</td>
<td>13 (72%)</td>
</tr>
<tr>
<td><strong>Deflazacort</strong></td>
<td>7 (41%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td><strong>Steroid duration, years</strong></td>
<td>5.5 (2.8)</td>
<td>5.4 (2.9)</td>
</tr>
</tbody>
</table>

## 12-month change in LV strain (%)

- **Eplerenone**: Median 0 (IQR -5 to 10)  
- **Placebo**: Median 0 (IQR -5 to 10)  

## 12-month change in LV EF (%)

- **Eplerenone**: Median 0 (IQR -10 to 10)  
- **Placebo**: Median 0 (IQR -10 to 10)  

---

Raman et al.  
*Lancet Neurology* 2015 14:153-161
Role of Steroids in DMD-Associated Cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 86)</th>
<th>Steroid Therapy (n = 63)</th>
<th>No Steroid Therapy (n = 23)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial cardiac evaluation, yrs</td>
<td>9.1 ± 3.5</td>
<td>8.5 ± 2.9</td>
<td>10.8 ± 4.3</td>
<td>0.0267</td>
</tr>
<tr>
<td>Age at initiation of RAASa, yrs</td>
<td>12.9 ± 4.3</td>
<td>12.0 ± 3.4</td>
<td>15.1 ± 5.5</td>
<td>0.0162</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>74 (86)</td>
<td>54 (86)</td>
<td>20 (87)</td>
<td>0.8830</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>35 (41)</td>
<td>28 (44)</td>
<td>7 (30)</td>
<td>0.2418</td>
</tr>
<tr>
<td>ACE inhibitor and ARB</td>
<td>23 (27)</td>
<td>19 (30)</td>
<td>4 (17)</td>
<td>0.2364</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>53 (62)</td>
<td>41 (65)</td>
<td>12 (52)</td>
<td>0.2160</td>
</tr>
<tr>
<td>Digoxin</td>
<td>22 (26)</td>
<td>12 (19)</td>
<td>10 (43)</td>
<td>0.0215</td>
</tr>
<tr>
<td>Diuretic agents</td>
<td>8 (9)</td>
<td>3 (5)</td>
<td>5 (22)</td>
<td>0.0164</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>58 ± 6</td>
<td>59 ± 5</td>
<td>56 ± 8</td>
<td>0.1704</td>
</tr>
<tr>
<td>Normal</td>
<td>61 (76)</td>
<td>47 (77)</td>
<td>14 (73)</td>
<td></td>
</tr>
<tr>
<td>Mildly impaired</td>
<td>17 (21)</td>
<td>14 (23)</td>
<td>3 (16)</td>
<td></td>
</tr>
<tr>
<td>Moderately impaired</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>2 (11)</td>
<td></td>
</tr>
<tr>
<td>Severely impaired</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>LV shortening fraction, %</td>
<td>32 ± 4</td>
<td>32 ± 3</td>
<td>30 ± 5</td>
<td>0.1486</td>
</tr>
<tr>
<td>Normal</td>
<td>78 (98)</td>
<td>61 (100)</td>
<td>17 (90)</td>
<td></td>
</tr>
<tr>
<td>Mildly abnormal</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Moderately abnormal</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Severely abnormal</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>41 ± 5</td>
<td>40 ± 3</td>
<td>43 ± 7</td>
<td>0.0956</td>
</tr>
<tr>
<td>z-score LV end-diastolic dimension</td>
<td>0.89 ± 1.11</td>
<td>0.91 ± 1.04</td>
<td>0.80 ± 1.34</td>
<td>0.7220</td>
</tr>
<tr>
<td>LV end-systolic dimension, mm</td>
<td>28 ± 5</td>
<td>27 ± 3</td>
<td>30 ± 8</td>
<td>0.1471</td>
</tr>
<tr>
<td>PR interval, ms*</td>
<td>116 (108, 120)</td>
<td>115 (108, 120)</td>
<td>120 (114, 120)</td>
<td>0.3716</td>
</tr>
<tr>
<td>QRS duration, ms*</td>
<td>80 (80, 88)</td>
<td>80 (80, 88)</td>
<td>80 (70, 80)</td>
<td>0.1537</td>
</tr>
<tr>
<td>Corrected QT interval, ms*</td>
<td>404 (400, 416)</td>
<td>404 (400, 418)</td>
<td>404 (390, 410)</td>
<td>0.5112</td>
</tr>
</tbody>
</table>
Role of Steroids in DMD-Associated Cardiomyopathy

Schram et al.
JACC 2013 61:948-954
UTSW Clinical Algorithm to Treating DMD-Associated Cardiomyopathy

Cardiac MRI: Preferred imaging tool to assess cardiac structure and function

- Normal LVEF (-) DE
  - ACEI (or ARB)
  - + Aldosterone Receptor Antagonist

- Normal LVEF (+) DE
  - ACEI (or ARB)
  - + Aldosterone Receptor Antagonist

- Abnormal LVEF (-) DE
  - Beta-Blocker
  - + ACEI (or ARB)
  - + Aldosterone Receptor Antagonist

- Abnormal LVEF (+) DE
  - Beta-Blocker
  - + ACEI (or ARB)
  - + Aldosterone Receptor Antagonist
UTSW Experience: Reverse Cardiac Remodeling in DMD Cardiomyopathy

7/43 patients expired in 5 years

14/43

27/43

2/43
Role of LVADs in DMD-Associated Cardiomyopathy
Use of LVADs in Advanced Cardiomyopathy Patients

HeartMate I

HeartMate II

HeartWare

The future of medicine, today.

UT SOUTHWESTERN Medical Center
Mechanical VAD Support for Patients with Advanced Heart Failure

- Immediate stabilization of hemodynamics.
- Favorable alterations in cellular/organ geometry.
- Reduces wall stress.
- Improves overall cardiomyocyte function.

Purpose of VADs
- Bridge to recovery.
- Bridge to transplantation.
- Destination therapy (permanent device).
- Bridge to decision.
Complications Related to Mechanical VAD Support

- Infection.
- Bleeding.
- Strokes.
- Device Malfunction
  - Mechanical pump failure.
  - LVAD Thrombosis.
  - Fractures in drive line.
Key Points: Take Home Messages

- Development of a cardiomyopathy is the primary mode of death in DMD patients in 2016.
- Initiate ACEI and aldosterone inhibitors early in DMD patients irrespective of LV function.
- Beta-blockers appear to improve cardiac function in DMD patients with heart failure.
- Benefits of AICD and BiV-AICD are not clear.
- Consideration of LVADs in select DMD patients refractory to medical therapy.
Acknowledgements
UTSW CHF/VAD/Transplant Team

UTSW Transplant Cardiologists
Alpesh Amin, MD
Faris Araj, MD
Mark H. Drazner, MD
Pradeep P.A. Mammen, MD
Robert Morlend, MD
Jenny Thibodeau, MD

UTSW Transplant Surgeons
Pietro Bajona, MD
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Acknowledgements

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Duchenne Muscular Dystrophy Clinical Symposium

Friday, August 26, 2016 9:30am-3:30pm

William P. Clements Jr. University Hospital
William T. and Gay F. Solomon Education Center Auditorium
6201 Harry Hines Blvd
Dallas TX 75390

Reservation Needed
Space is Limited
R.S.V.P. by July 30th to
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