Cardiac Health: Understanding Cardiac Medications

Larry W. Markham, MD
Professor, Department of Pediatrics and Medicine
Chief, Division of Pediatric Cardiology
lwmarkha@iu.edu
Outline

• Implications of cardiac involvement
  – What is the risk?
  – Defining a treatment strategy: Prevention vs Rescue

• Medical treatment options
  – Beneficial in DMD
Duchenne Cardiomyopathy Natural History

What are we treating?

LV EF < 55% Percent

- < 5 years: 1%
- 5-10 yrs: 5%
- 10-15 yrs: 25%
- 15-20 yrs: 45%
- > 20 yrs: 75%
A picture is worth 1000 words...
Why are we treating?

Impact Survival

N = 83
LVFS < 25% or LVEF < 50%
Average age: 18 years

Corrado G et al; Am J Cardiol 2002;89:838
Prevention vs Rescue

**Prevention**
- Low toxicity
- Low risk
- Long-term use
- Potential benefit
- Low cost
- Treat a large number to prevent disease
Prevention vs Rescue

Rescue
- Accept more toxicity
- Accept more side effects
- Length = response
- Definite benefit
- Cost?
- Treat smaller number with disease
Angiotensin Converting Enzyme Inhibitors
captopril, enalapril, lisinopril, perindopril

• Action:
  – Blocks the activity of ACE which decreases the production of angiotensin II
  – Relaxes blood vessels (vasodilator); anti-fibrosis

• Role:
  – Prevention and Rescue: Everyone - shown to be beneficial; Age?

• Side effects:
  – Generally well tolerated
  – Allergic reaction, cough, elevated potassium, lower blood pressure

• References:
  – Duboc JACC 2005;45:855 Effect of Perindopril on the Onset and Progression…
  – Duboc Am Heart J 2007;154:596 Perindopril preventive treatment ...
Angiotensin Receptor Blockers
candesartan, losartan, valsartan

• Action:
  – Blocks angiotensin II from its receptor; blocks TGFβ
  – Relaxes blood vessels (vasodilator); anti-fibrosis

• Role:
  – Prevention and Rescue: Largely for those intolerant of ACEi

• Side effects:
  – Generally well tolerated
  – Allergic reaction, less cough, elevated potassium, lower blood pressure

• References:
  – Allen H PLoS Curr. 2013 Dec 12;5 Comparison of lisinopril and losartan
Aldosterone Receptor Antagonists
eplerenone, spironolactone

• Action:
  – Weak diuretic; blocks aldosterone from its receptor
  – Anti-fibrosis

• Role:
  – Prevention: Developing role
  – Rescue: Role in congestion and moderate-severe

• Side effects:
  – Allergy; medication interactions; elevated potassium

• References:
  – Rafael-Fortney JA Circulation 2011 Aug 2;124(5):582-8. Early treatment ... in DMD mice
  – Raman SV Lancet Neurol. 2015 Feb;14(2):153-61 Eplerenone for early cardiomyopathy
β-blockers
bisoprolol, carvedilol, metoprolol

• Action:
  – Blocks adrenaline from its receptor
  – Anti-fibrosis ? carvedilol > metoprolol

• Role:
  – Prevention: Uncertain role
  – Rescue: Benefit shown; consider in all with abnormal LVEF

• Side effects:
  – Generally well tolerated, more side effect potential
  – Altered mood, depression, lower heart rate/lower blood pressure, nightmares

• References:
  – Rhodes Pediatric Cardiology 2008;29:343 - Safety and Efficacy of Carvedilol Therapy for DCM...
  – Ogata J of Cardiology 2009;53:72 - Beneficial effect of b-blockers and ACEi in DMD
Cardiac glycoside
digoxin

- **Action:**
  - Increase in intracellular calcium
  - Secondary neurohormonal effects

- **Role:**
  - Prevention: No role; may actually be harmful
  - Rescue: May play a role in severe HF and low BP; theoretic arrhythmia risk

- **Side effects:**
  - Side effect potential with other drugs
  - Need to monitor levels and electrolytes
    - Higher plasma concentration but rapid clearance; may have higher levels if combined with spironolactone

- **References:**
  - Tateishi Am J of Therapeutics 1994;1:144-149 *Pharmacokinetics in DMD*
  - Konstantinou Cardiology 2016;134:311-319 *Review of digoxin in HF*
Diuretics
furosemide, chlorothiazide, metolazone

• Action:
  – Promotes loss of fluid through urine

• Role:
  – Prevention: No role
  – Rescue: Fluid retention and congestion associated with heart failure

• Side effects:
  – Side effect potential with other drugs
  – Electrolyte imbalance (low potassium), dehydration

• References:
Diagnosis of DMD:

- Comprehensive cardiac evaluation – Hx/PE, ECG, Imaging

Findings:
- Normal LV size and function plus no fibrosis

Treatment:
- Multi-disciplinary care – Neuro/Pulm; Education re: risk, signs, and symptoms;
  - Discuss pros/cons ACEi or ARB +/- ARA

Follow-up:
- Q12 months until age 10 years, then consider Q6 months given risk at Stage B

Stage A
- Risk of CM due to DMD

Findings:
- Normal LV size and function plus no fibrosis

Treatment:
- Multi-disciplinary care – Neuro/Pulm; Education re: risk, signs, and symptoms;
  - Discuss pros/cons ACEi or ARB +/- ARA

Follow-up:
- Q12 months until age 10 years, then consider Q6 months given risk at Stage B

Stage B
- Age > 10 years
- Structural disease
- Borderline Fxn
- No Symptoms

Findings:
- LVE or Fibrosis or Borderline SF 28-30%/EF 50-55%

Treatment:
- If not already, definite initiation of therapy – ACEi or ARB +/- ARA
  - Consider β-blocker if elevated heart rate or decreased HRV

Follow-up:
- Q6 months, repeat Imaging

Stage C
- Structural disease
- Abnormal Fxn
- No Symptoms

Findings:
- LVE or Fibrosis and Abnormal Fxn (SF<28%, EF<50%)

Treatment:
- Maximize dose of ACEi or ARB; add ARA and β-blocker if not already; titrate to HR/BP

Follow-up:
- As needed until stable doses, then Q6 months

Stage D
- Abnormal Fxn
- Symptoms

Findings:
- LVE or Fibrosis or Abnormal Fxn

Treatment:
- Guided by severity of symptoms – ACEi or ARB, ARA, β-blocker, Diuretics, Digoxin

Consider:
- Arrhythmia: Meds vs device; Inotropes

Follow-up:
- As needed

Proactive Strategy
Collaborators:

Riley
   JJ Parent, MD

Vanderbilt
   Jon Soslow, MD
   Basic Science
   Cristi Galindo, PhD
   Erica Carrier, PhD

Maine
   Doug Sawyer, MD, PhD

Texas A&M
   Joe Kornegay, DVM, PhD
   Candice Brinkmeyer-Langford, PhD

Nationwide/OSU
   Linda Cripe, MD
   Kan Hor, MD
   May Ling Ammons, MD

Wisconsin
   D. Woodrow Benson, MD, PhD