CONCERT-HF

- **CONDITION**: Ischemic Cardiomyopathy
- **PI**: Jay Traverse, MD
- **CONTACT INFO**: Jane Fox | jane.fox@allina.com   ph: 612-863-6289
- **DESCRIPTION**: Phase II, randomized, placebo-controlled clinical trial designed to assess feasibility, safety, and effect of investigational autologous bone marrow-derived mesenchymal stem cells (MSCs) and c-kit+ cardiac stem cells (CSCs) both alone and in combination (Combo), compared to placebo as well as each other, administered by NOGA injection in subjects with ischemic cardiomyopathy.

- **CRITERIA LIST/ QUALIFICATIONS**:
  - NYHA Class II-III Ischemic Heart Failure; EF ≤ 40% by cMRI.
  - Myocardial injury defined as > 5% LV involvement and any subendocardial involvement by cMRI.
  - Receiving guideline driven medical therapy for Ischemic Heart Failure.

- **SPONSORS**: National Institutes of Health/The University of Texas Health Science Center (CCTRN Data Coordinating Center)
Vasodilator Strategies for the Treatment of Cardiogenic Shock

David Miranda
Cardiology Fellow

• No disclosures
Case Presentation

- 66 year old male, with a history of ischemic cardiomyopathy
- 2 weeks of progressive shortness of breath, lower extremity edema and increase on abdominal girth.
- Vitals:
  - BP: 95/77 mmHg
  - HR: 92 bpm
- Exam: elevated JVP, bilateral crackles, systolic murmur, pitting lower extremity edema, cool extremities

Echocardiogram
Right Heart Catheterization

- Heart Rate: 92 bpm
- Systemic Blood pressure: 95/77 mmHg
- Right atrial pressure: 20 mmHg
- Pulmonary Artery Pressure: 56/30 mean 46
- Pulmonary Capillary Wedge Pressure: 36 mmHg
- SvO2: 49%  SaO2: 100%
- Estimated Fick Cardiac Index: 1.85
- SVR: 1456 dynes·sec·cm⁻⁵
Admitted to CCU in Cardiogenic Shock

- PA-Catheter Guided Therapy:
  - Started on Furosemide drip
  - Started on Sodium Nitroprusside drip
  - Prior to admission Beta blocker and ACE inhibitor held

### CCU Course

<table>
<thead>
<tr>
<th>Time admission (Hrs)</th>
<th>CVP mmHg</th>
<th>PCWP mmHg</th>
<th>MAP mmHg</th>
<th>CI L/min/m²</th>
<th>Sodium Nipride Dose (mcg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>36</td>
<td>82</td>
<td>1.85</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>24</td>
<td>80</td>
<td>2.0</td>
<td>1.5</td>
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<tr>
<td>12</td>
<td>12</td>
<td>20</td>
<td>78</td>
<td>2.8</td>
<td>2.5*</td>
</tr>
<tr>
<td>18</td>
<td>8</td>
<td>16</td>
<td>75</td>
<td>2.8</td>
<td>1.5</td>
</tr>
<tr>
<td>22</td>
<td>8</td>
<td>16</td>
<td>72</td>
<td>2.8</td>
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</tr>
</tbody>
</table>
Objectives

- Review of the Treatment of Acute Decompensated Heart Failure (ADHF)
- Acute Heart Failure Management – Vasodilators
- IV Sodium Nitroprusside for cardiogenic shock
- Oral vasodilator protocol

Clinical Characteristics of ADHF

<table>
<thead>
<tr>
<th>ADHERE¹</th>
<th>Euro-HF²</th>
<th>OPTIMIZE-HF³</th>
</tr>
</thead>
<tbody>
<tr>
<td>105,388 patients</td>
<td>11,327 patients</td>
<td>48,612 patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ADHERE¹</th>
<th>Euro-HF²</th>
<th>OPTIMIZE-HF³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y</td>
<td>75</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;50%</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>Hx of CAD/MI</td>
<td>60%</td>
<td></td>
<td>SBP &gt;140 mm Hg</td>
</tr>
<tr>
<td>Hx of hypertension</td>
<td>70%</td>
<td></td>
<td>SBP 90-140 mm Hg</td>
</tr>
<tr>
<td>Hx of diabetes</td>
<td>40%</td>
<td></td>
<td>SBP &lt;90 mm Hg</td>
</tr>
</tbody>
</table>

Outcomes During and After AHF

- 5.2 Day Mean length of stay<sup>1</sup>
- 20% 30 day readmission rate<sup>2</sup>
- 11.6% Mortality at 30 Days<sup>3</sup>

Hemodynamic Profiles of ADHF

“Dry Out”
- Diuretics and Ultrafiltration
- Vasodilators:
  - Nitroglycerin
  - Nitroprusside
  - Nesiritide

“Warm up” and “Dry Out”
- Warm & Wet
  - Warm & Dry
  - Cold & Wet

ADHF – Treatment Goals

- Improve Symptoms
- Optimize volume status
- Identify etiology
- Identify and address precipitating factors
- Optimize chronic drug and device therapy
Main Approaches of Treatment for ADHF

- Diuretics/Ultrafiltration
- Vasodilators
- Inotropes

AHA/ACC Practice Guidelines 2013

- Vasodilators:
  
  – If symptomatic hypotension is absent, IV NTG, Nitroprusside, or Nesiritide may be considered an adjuvant to diuretic therapy for relief of dyspnea in patients admission with acutely decompensated HF. (Class IIb, Level of Evidence: A)

IV Vasodilators in the treatment of ADHF

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Nitroprusside</th>
<th>Nitroglycerin</th>
<th>Nesiritide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective studies in HF</td>
<td>-</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Hemodynamic effect</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Need for dose titration</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Tolerance</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
</tbody>
</table>

- Decrease Preload
- Decrease Afterload
- Decrease Oxygen demand and increase Oxygen Supply to the Myocardium

ADHF: Management at MHI by Advanced HF Team

- One of the Unique, HF team approach is utilization of Swan-guided therapy for patients on cardiogenic shock and low EF
- That entitles assessment of hemodynamics every 4 – 6 hours with the titration of vasoactive drips
- End result in <24 hours you can efficiently hemodynamic reconstitute patients in cardiogenic shock
Swan Guided Therapy: Hemodynamic targets

– Pulmonary Capillary Wedge Pressure ≤ 18 mmHg
– Central Venous Pressure ≤ 8 mmHg
– Cardiac Index ≥ 2.2 L/min/m²
– Mean Arterial Pressure ≥ 65 – 75 mmHg

CCU Course

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VMAC Trial: Demonstrated that Vasodilators can rapidly decrease Pulmonary Capillary Wedge Pressure

†P < .05 vs placebo  *P < .05 vs NTG


IV NTG in the Tx of ADHF
Relationship Between Dose and Effect on PCWP
Prevention of Nitrate Tolerance with Hydralazine in Patients with Heart Failure

![Graph showing percent change from baseline over hours with NTG and NTG + HYD](image)

*P<0.05 vs 0 hours.

Gogia H, Elkayam U. JACC 1995;26:575

Patients with low EF have better outcomes when treated with IV Vasodilators

![Graph showing freedom from all cause mortality](image)

Mullens W et al. JACC 2008;52:200
Sodium Nitroprusside: Chemical composition

Limitations of Nitroprusside

- Development of resistance
- Patients can develop tolerance
- Lack of long-term data on efficacy or mortality
- Only available IV
- Expensive
Sodium Nitroprusside Cost at Allina Hospital

- SNP daily cost depends:
  - patient weight
  - infusion rate
  - dynamic drug pricing of SNP over the past 5 years

- Healthcare cost considerations:
  - nursing time for close monitoring
  - need for ICU admission
  - continued RHC monitoring until SNP is off to assess hemodynamics after conversion to orals, etc.

For an 80 kg patient running at 2.5 mcg/kg/min the estimated daily drug cost is:

<table>
<thead>
<tr>
<th>Year</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>~$250</td>
</tr>
<tr>
<td>2014</td>
<td>~$4,700</td>
</tr>
</tbody>
</table>

Source: Matt Lillyblad
Rationale for an Oral Vasodilator Protocol

- Facilitate the transition
- Decreased length of stay in the ICU
- Decreased overall use of nipride (avoiding toxicity)
- Decreased cost - $$$

Oral Vasodilator Protocol: Objectives

- Assess and describe the hemodynamic response and tolerance to aggressive oral vasodilator up-titration after intravenous vasodilator therapy in advanced decompensated heart failure (ADHF)
  - Decreased length of stay in ICU
  - Decrease 30 day readmission
  - Decreased overall use of nitroprusside (avoiding toxicity)
  - “Aggressive” up-titration will result in higher outpatient doses of vasodilators.
Methods: Inclusion Criteria

– Admitted to CCU
– PA catheter placement
– Received IV Vasodilator agent
– Primary diagnosis of ADHF between January 2013 and December of 2017
– Age > 18
– EF ≤35%

Results: Distribution

  ICU Admissions N=559
    EF ≤35% N=92
  Total N = 92

Pts w/ ADHF - SNP between 2013-2017 N=1444

  ICU Admissions N=661
    EF ≤35% N=157
  Total N = 155

  ICU Admissions 139
    EF ≤35% N=58
  Total N = 57

Total of 307 patients
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total Population</th>
<th>Before protocol</th>
<th>After protocol</th>
<th>p-value</th>
<th>Off protocol</th>
<th>On protocol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, n</td>
<td>307 (100)</td>
<td>92 (30)</td>
<td>215 (70)</td>
<td></td>
<td>157 (73)</td>
<td>58 (27)</td>
<td></td>
</tr>
<tr>
<td>Sex - %</td>
<td>235 (77)</td>
<td>72 (78)</td>
<td>163 (76)</td>
<td>0.75</td>
<td>123(78)</td>
<td>40(69)</td>
<td>0.21</td>
</tr>
<tr>
<td>Age - Mean</td>
<td>61 (63)</td>
<td>60 (63)</td>
<td>62 (64)</td>
<td>0.13</td>
<td>63 (65)</td>
<td>60 (63)</td>
<td>0.35</td>
</tr>
<tr>
<td>EF Within 120 Days</td>
<td>21 (20)</td>
<td>21 (20)</td>
<td>20 (20)</td>
<td>0.38</td>
<td>21 (20)</td>
<td>19 (20)</td>
<td>0.23</td>
</tr>
<tr>
<td>CAD</td>
<td>224 (73)</td>
<td>69 (75)</td>
<td>155 (72)</td>
<td>0.67</td>
<td>115 (73)</td>
<td>40 (69)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

- No difference of medication use among the groups.
- Medications were very appropriate – CAD
- Most of the patients were on guideline medical therapy
- Sick population - 38% of patients on inotropes upon admission.

## Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total Population</th>
<th>Before protocol</th>
<th>After protocol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>60(20)</td>
<td>22(24)</td>
<td>38(18)</td>
<td>0.21</td>
</tr>
<tr>
<td>Aspirin</td>
<td>219(71)</td>
<td>70(76)</td>
<td>149(69)</td>
<td>0.27</td>
</tr>
<tr>
<td>Statin</td>
<td>200(65)</td>
<td>59(64)</td>
<td>141(66)</td>
<td>0.91</td>
</tr>
<tr>
<td>Warfarin</td>
<td>144(47)</td>
<td>42(46)</td>
<td>102(47)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>55(18)</td>
<td>14(15)</td>
<td>41(19)</td>
<td>0.52</td>
</tr>
<tr>
<td>Isosorbide</td>
<td>29(9)</td>
<td>6(7)</td>
<td>23(11)</td>
<td>0.29</td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>259(84)</td>
<td>79(86)</td>
<td>180(84)</td>
<td>0.73</td>
</tr>
<tr>
<td>Mineral Corticoid Receptor Antagonist</td>
<td>145(47)</td>
<td>47(51)</td>
<td>98(46)</td>
<td>0.45</td>
</tr>
<tr>
<td>Intravenous Inotrope</td>
<td>116(38)</td>
<td>39(42)</td>
<td>77(36)</td>
<td>0.3</td>
</tr>
<tr>
<td>Renin Angiotensin Blocker</td>
<td>146(48)</td>
<td>49(53)</td>
<td>97(45)</td>
<td>0.24</td>
</tr>
<tr>
<td>Beta Adrenergic Blocker</td>
<td>262(85)</td>
<td>83(90)</td>
<td>179(83)</td>
<td>0.16</td>
</tr>
</tbody>
</table>
### Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Total Population</th>
<th>Before protocol</th>
<th>After protocol</th>
<th>p-value</th>
<th>Off protocol</th>
<th>On protocol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission MAP</td>
<td>90 (89)</td>
<td>89 (88)</td>
<td>91 (89)</td>
<td>0.34</td>
<td>89 (87)</td>
<td>95 (94)</td>
<td>0.02</td>
</tr>
<tr>
<td>MAP Onset of Protocol</td>
<td>85 (84)</td>
<td>86 (84)</td>
<td>85 (82)</td>
<td>0.31</td>
<td>87 (84)</td>
<td>80 (80)</td>
<td>0.002</td>
</tr>
<tr>
<td>Admission CVP</td>
<td>14 (13)</td>
<td>13 (13)</td>
<td>13 (13)</td>
<td>0.77</td>
<td>13 (13)</td>
<td>13 (13)</td>
<td>0.63</td>
</tr>
<tr>
<td>Instant CVP</td>
<td>11 (12)</td>
<td>12 (12)</td>
<td>11 (11)</td>
<td>0.85</td>
<td>11 (11)</td>
<td>11 (11)</td>
<td>0.76</td>
</tr>
<tr>
<td>Admission – PCWP</td>
<td>26 (26)</td>
<td>26 (26)</td>
<td>25 (25)</td>
<td>0.45</td>
<td>25 (24)</td>
<td>26 (26)</td>
<td>0.27</td>
</tr>
<tr>
<td>Instant – PCWP</td>
<td>23 (23)</td>
<td>24 (23)</td>
<td>23 (22)</td>
<td>0.61</td>
<td>23 (22)</td>
<td>24 (23)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

### Multivariate Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Estimate</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>On protocol vs off protocol</td>
<td>0.22</td>
<td>-0.13</td>
<td>0.73</td>
</tr>
<tr>
<td>Post protocol vs Pre protocol</td>
<td>0.14</td>
<td>-0.43</td>
<td>1.27</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th></th>
<th>Total Population</th>
<th>Before protocol</th>
<th>After protocol</th>
<th>p-value</th>
<th>Off protocol</th>
<th>On protocol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Length of Stay - Days</td>
<td>3.0 (1.8, 5.3)</td>
<td>3.8 (2.2, 6.2)</td>
<td>2.8 (1.6, 4.8)</td>
<td>0.16</td>
<td>2.6 (1.3, 4.4)</td>
<td>3.0 (2.0, 5.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Total Nipride Use - Hours</td>
<td>71.0</td>
<td>78.5</td>
<td>67.0</td>
<td>0.21</td>
<td>60.0</td>
<td>76.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Readmit 30 Day (%)</td>
<td>63 (22)</td>
<td>20 (23)</td>
<td>43 (22)</td>
<td>0.88</td>
<td>33 (23)</td>
<td>10 (18)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

### Underutilization of Oral Vasodilator Protocol

Protocol uptake by providers per month - %

Mean use of 28%/month

Percentage of Use

Month and Year
Discussion points about under utilization

- Patient is too "tenuous" for a rapid oral dose escalation
- It may not be used for patients on “low dose” of SNP – easy to titrate off.
- Angiotensin Receptor Antagonists
- Forget of the protocol if not in formal rounds.

Oral vasodilator protocol: Conclusions

AHF is a complex syndrome representing a broad spectrum of conditions rather than a single disease.

1) Continued education of providers and nursing
2) Heterogeneous use by provider
3) Optimal timing of transition is not clear
4) Given the variations within the single population it is unlikely that a single (same) therapy would be efficacious in all patients.
Discussion about oral vasodilator protocol

- Protocol only addresses the time it takes to wean off – only a small fraction of the total time on SNP
- Weaning without the protocol allows for provider discretion
- Avoidance of the protocol for “easy” weans. i.e rates <1 mcg/kg/min, so only reserve for high doses weans.
- Protocol execution errors by nursing were included in the protocol arm
- Provider aborting the protocol were included in the protocol arm

Conclusions

- IV vasodilators are the mainstay of therapy of acute HF
- Oral vasodilators are in important part of chronic HF therapy
- Strategies to increase utilization of protocol:
  - Education
  - Providers should be aware of cost
  - Development of protocols for optimization of care
Special Thanks

- Dr. Bennett and Dr. Bradley – Mentors
- Matt Lillyblad – PharmD (Minneapolis Heart Institute and Allina Hospital).
- All the MHI Advanced Heart Failure Section – Physicians and APPs.
- Larissa Stanberry, PhD – Statistician (Minneapolis Heart Institute).
- Chelsey Thomas – Clinical Data Analyst (Allina Performance Resources)
- MHI Center for Healthcare Delivery Innovation
- MHI Foundation

Questions?

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