Management of Heart Failure in Older Adults – New Data, New Guidelines, New Challenges

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Assistant Professor of Medicine
Cardiovascular Director Amyloidosis Program
DISCLOSURES

- Advisory Board for Alnylam Pharmaceutical
CONTENTS

NEW DATA, NEW GUIDELINES
1. Heart Failure with Reduced Ejection Fraction (HFrEF)
2. Heart Failure With Preserved Ejection Fraction (HFpEF)

NEW CHALLENGES
3. Focus in Cardiac Amyloidosis
AGE DISTRIBUTION OF HF ADMISSIONS 2003-2005

(a) N = 3924
Mean (SD) 77.1 (11.2)
Median (IQR) 79.0 (71.0–84.5)

Established Management of HFrEF in older adults

- Angiotensin Converting Enzyme Inhibitors (ACE-I)
- Angiotensin Receptor Blockers (ARBs)
- Beta blockers
- Aldosterone Receptor Blockers
ACEI - MECHANISM
ACEI – CONSENSUS STUDY

- Mean Age 71 yo
- 253 patients
- Class IV HF
- Conventional treatment
- Enalapril 5 mg BID vs Placebo
- Protocol modified for hypotension and renal insufficiency.
ACEI – SOLVD STUDY

- Mean age 61 yo
- 2,568 patients
- Class II-III HF
- LVEF < 35%
- Enalapril 2.5 mg BID vs Placebo
- Mean dose ~ 10 mg BID
- 4% excluded in the initial period for hypotension and renal failure.
BETA BLOCKERS – MECHANISM
BETA BLOCKERS – BLACK BOX

Beta blockers were contraindicated in patients with heart failure.

Cardiac Output = Heart Rate x Stroke Volume
The New England Journal of Medicine

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Volume 334  MAY 23, 1996  Number 21

THE EFFECT OF CARVEDILOL ON MORBIDITY AND MORTALITY IN PATIENTS WITH CHRONIC HEART FAILURE

MILTON PACKER, M.D., MICHAEL R. BRISTOW, M.D., PH.D., JAY N. COHN, M.D., WILSON S. COLECCI, M.D., MICHAEL B. FOWLER, M.B., B.S., EDWARD M. GILBERT, M.D., AND NEIL H. SHUSTERMAN, M.D., FOR THE U.S. CARVEDILOL HEART FAILURE STUDY GROUP®
BB – US CARVEDILOL STUDY

Mean age 58 yo

Class II-III HF

LVEF < 35%

Carvedilol 3.125 mg or 6.25 mg BID vs Placebo

Mean dose ~ 25 mg BID

Risk reduction = 65%

p<0.001
BB – MERIT-HF STUDY

Mean age 64 yo

Class II-IV HF
LVEF < 40%
Metoprolol XL 12.5 mg vs Placebo
Mean dose ~ 25 mg BID

CAN BB BE USED IN CLASS IV PATIENTS?
BB – COPERNICUS STUDY

- Mean age 63 yo
- Class IV HF
- LVEF < 25%
- Carvedilol 3.125 mg or 6.25 mg BID vs Placebo

Krum H et al. JAMA 2003;289:754-6
### DO OLDER ADULTS HAVE SAME BB BENEFIT?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Risk ratio (95% CI)</th>
<th>N</th>
<th>Age group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copernicus</td>
<td>0.75 (0.58–0.98)</td>
<td>1102</td>
<td>≥65</td>
</tr>
<tr>
<td>Carvedilol US</td>
<td>0.45 (0.24–0.86)</td>
<td>554</td>
<td>≥59</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>0.70 (0.49–0.99)</td>
<td>539</td>
<td>≥71</td>
</tr>
<tr>
<td>Merit-HF</td>
<td>0.70 (0.52–0.95)</td>
<td>1330</td>
<td>upper tertile</td>
</tr>
<tr>
<td>BEST</td>
<td>0.91 (0.78–1.05)</td>
<td>1092</td>
<td>≥65</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>0.76 (0.64–0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>P = 0.002</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALDOSTERONE RECEPTOR ANTAGONIST - MECHANISM

Krum H et al. JAMA 2003;289:754-6
SPIRONOLACTONE – RALES STUDY

- Mean age 65 yo
- Class III-IV HF
- LVEF < 35%
- Aldactone 3.125 mg or 6.25 mg BID vs Placebo
- Mean dose ~ 25 mg daily

Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study

David N. Juurlink, M.D., Ph.D., Muhammad M. Mamdani, Pharm.D., M.P.H., Douglas S. Lee, M.D., Alexander Kopp, B.A., Peter C. Austin, Ph.D., Andreas Laupacis, M.D., and Donald A. Redelmeier, M.D.
Hospital Death
Hyperkalemia

Is there a benefit in NYHA II Patients?

Is there a benefit on Top of ACEI And BB?
EPLERENONE – EMPHASIS-HF STUDY

- Mean age 69 yo
- Class II HF
- LVEF < 30%
- ACEI + BB
- Eplerenone 25 mg vs Placebo
- Mean dose ~ 50 mg daily

### STANDARD OF CARE - HFrEF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial daily dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisinopril</td>
<td>2.5 mg once</td>
<td>20-40 mg daily</td>
</tr>
<tr>
<td>Losartan</td>
<td>25 mg daily</td>
<td>100 mg daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice</td>
<td>25 mg twice</td>
</tr>
<tr>
<td>Metoprolol succinate XL</td>
<td>12.5 to 25 mg once</td>
<td>150 to 200 mg once</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5 mg daily</td>
<td>25 mg daily</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg daily</td>
<td>50 mg daily</td>
</tr>
</tbody>
</table>
STANDARD OF CARE – IN OLDER ADULTS


Age-related differences in GWTG-HF quality indicators.
WHAT IS NEW IN – HFrEF?
MORE NEUROHORMONAL BLOCKADE?
LCZ696 – A first-in-class Angiotensin Receptor Neprilysin Inhibitor (ARNI)

Vasoactive Peptide System

Heart Failure

Renin Angiotensin System

Sacubitril (AHU377)

Angiotensinogen (liver secretion)

Angiotensin I

Angiotensin II

AT1 receptor

Neprilysin

Inactive fragments

LCZ696 is a novel crystalline complex consisting of the molecular moieties of valsartan and sacubitril in an equimolar ratio

Provided by M.D. Scott Solomon

Vasodilation
+ blood pressure
+ sympathetic tone
+ aldosterone levels
+ fibrosis
+ hypertrophy
Natriuresis/Diuresis

Vasoconstriction
+ blood pressure
+ sympathetic tone
+ aldosterone
+ fibrosis
+ hypertrophy
SACUBITRIL/VALSARTAN – PARADIGM

- Mean age 64 yo
- Class II-IV HF
- LVEF < 35%
- Able to tolerate ACEI/ARBs
- Optimal Medical Therapy (BB, Spironolactone)
  - Enalapril vs Sacubitril/Valsartan

2017 Guidelines

## PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th>Prospectively identified adverse events</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>588</td>
<td>388</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181</td>
<td>236</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139</td>
<td>188</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474</td>
<td>601</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>449</td>
<td>516</td>
<td>0.02</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>29</td>
<td>59</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial
WHAT ELSE IS NEW IN – HFrEF?
HEART RATE AS A TARGET?

Thollon. Brit J Pharmacol 1994;112:37
IVABRADINE – SHIFT TRIAL

- Mean 60 yo
- 6,500 subjects
- Class II-IV HF
- LVEF < 35%
- ACEI/ARB, BB, Aldo antagonists
- Sinus rhythm with HR > 70 bpm
- Ivabradine vs Placebo

Swedber Lancet. 2010. 376(10):875-885
WHAT IS COMING IN – HFrEF?
NITRIC OXIDES GC-CGMP PATHWAY STIMULATION
VERICIGUAT – VICTORIA STUDY

Population: Subjects with heart failure with reduced ejection fraction

N~4,900

Starting dose of 2.5 mg taken orally once daily with food, on a background of standard of care. Dose will be uptitrated to 5 mg and to 10 mg.

Vericiguat

Event-driven study

Placebo

Starting dose of placebo equivalent to 2.5 mg taken orally once daily with food, on a background of standard of care. Dose will be sham uptitrated to 5 mg and to 10 mg placebo equivalent.

Primary End Point:
Time to First Occurrence of Composite Endpoint of Cardiovascular (CV) Death or Heart Failure Hospitalization
ANYTHING NEW IN DEVICES?
DEFIBRILLATORS – SCD-HeFT TRIAL

2,521
Class II-III HF
LVEF < 35%
Optimal medical therapy vs...
DEFIBRILLATORS – IN OLDER ADULTS

DANISH TRIAL

LVEF < 35%
Nonischemic cardiomyopathy
ICD vs conventional therapy

OTHER DEVICES

• Left Ventricular Assist Devices
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IS NEUROHORMONAL ACTIVATION PRESENT IN HFpEF?

ARB – CHARM-PRESERVED TRIAL

- Mean age 67 yo
- 1,514 subjects
- Class II-IV
- LVEF > 40%
- Candesartan vs Placebo

ACEI – PEP TRIAL

- Mean age 76 yo
- 850 subjects
- More than 70 yo
- LVEF > 50%
- Perindopril vs Placebo

ARB – I-PRESERVE TRIAL

- Mean age 72 yo
- 4,128 subjects
- Class II-IV
- LVEF > 45%
- Irbesartan vs Placebo

Massie et al. NEJM 2008.
PHOSPHODIESTERASE INHIBITORS RELAX TRIAL

Redfield et al. Cir Heart Fail 2013

- Mean age 69 yo
- 216 subjects
- LVEF > 50%
- Sildenafil vs Placebo

Change in Peak VO₂

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>94 (91%)</td>
<td>91 (80%)</td>
</tr>
</tbody>
</table>

Redfield et al. Cir Heart Fail 2013
NITRATES - NEAT-HFpEF TRIAL

- Mean age 69 yo
- 110 subjects
- LVEF > 50%
- Isosorbide mononitrate vs Placebo

Redfield et al. 2015;373;2314

2017 Guidelines
Treatment with spironolactone was associated with
- increased serum creatinine levels and
- doubling of the rate of hyperkalemia (18.7%, vs. 9.1% in the placebo group)

REGIONAL VARIATION – TOPCAT TRIAL

Pfeffer et al. Circulation 2015
WHAT IS COMING IN – HFpEF?
SACUBITRIL/VALSARTAN PARAGON-HF TRIAL

Target patient population: ~4300 patients with symptomatic HF (NYHA Class II–IV) and LVEF ≥45%

Active run-in period

- Screening
- Valsartan 80mg BID
- LCZ696 100mg BID

Double-blind treatment period

- LCZ696 200mg BID
- Randomisation 1:1
- Valsartan 160mg BID

On top of optimal background medications for co-morbidities (excluding ACEis and ARBs)

- Up to 2 weeks
- 3–8 weeks
- ~240 weeks

Primary outcome: CV death and total (first and recurrent) HF hospitalisations (anticipated ~1721 primary events)

Pfeffer et al. Circulation 2015
WHAT ELSE IS COMING IN – HFpEF?
TREATING DIABETES IN HFpEF?

Diastolic Dysfunction in HF With Preserved Systolic Function (EF >40%): Results From the CHARM Echocardiographic Substudy CHARMES

Major predictors of severity of echo-derived diastolic dysfunction were age, diabetes, previous HF, and atrial fibrillation.
DAPAGLIFLOZIN INHIBITS SUBTYPE 2 OF THE SODIUM-GLUCOSE TRANSPORT PROTEINS (SGLT2)
DAPAGLIFLOZIN  PRESERVED-HF TRIAL

Objectives:
Evaluate the impact of dapagliflozin, as compared with placebo, on heart failure, disease specific biomarkers, symptoms, health status and quality of life.

Subjects:
Type 2 diabetes or prediabetes
Chronic heart failure with preserved systolic function (LVEF > 45%).

Pfeffer et al.  Circulation 2015
HOW ABOUT HYPERTENSION?

9.5.2 Treating Hypertension in Stage C HFpEF: Recommendation.

Recommendation for Hypertension in Stage C HFpEF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>Patients with HFpEF and hypertension should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg (191).</td>
<td>NEW: Recommendation has been adapted from recent clinical trial data but not specifically tested per se in a randomized trial of patients with HF.</td>
</tr>
</tbody>
</table>

9.5.3 Treating Hypertension in Stage C HFpEF: Recommendation.

Recommendation for Hypertension in Stage C HFpEF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-LD</td>
<td>Patients with HFpEF and persistent hypertension after management of volume overload should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg (167,169,170,194-199).</td>
<td>NEW: New target goal blood pressure based on updated interpretation of recent clinical trial data.</td>
</tr>
</tbody>
</table>

Pfeffer et al. Circulation 2015
CONTENTS

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WIILD TYPE ATTR AMYLOIDOSIS – DISEASE OF THE ELDERLY

Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System

Martha Grogan, MD, Christopher G. Scott, MS, Robert A. Kyle, MD, Steven R. Zeldenrust, MD, PhD, Morie A. Gertz, MD, Grace Lin, MD, Kyle W. Klarich, MD, Wayne L. Miller, MD, PhD, Joseph J. Maleszewski, MD, Angela Dispenziere, MD

TABLE 1 Baseline Characteristics of Patients With Antemortem Diagnosis of ATTRwt (N = 360)

<table>
<thead>
<tr>
<th>Age, yrs</th>
<th>n or n (%)</th>
<th>Median (Q1, Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>5 (1.3)</td>
<td></td>
</tr>
<tr>
<td>61-70</td>
<td>61 (17)</td>
<td></td>
</tr>
<tr>
<td>71-80</td>
<td>177 (49)</td>
<td></td>
</tr>
<tr>
<td>80-90</td>
<td>114 (32)</td>
<td></td>
</tr>
<tr>
<td>&gt; 90</td>
<td>3 (1)</td>
<td></td>
</tr>
</tbody>
</table>

82% >70 yo
Worst survival with AL amyloidosis

\[ \text{Survival time, months} \]

- Wild Type TTR: 100%
- Mutant TTR: 92%
- AL amyloidosis: 25%

Dubrey, Falk et al. Heart 1997;78:74-82
Ng, Falk et al. Arch Intern Med 2005;165:1425
Organ Involvement

AL

mutant TTR

wild type TTR

Dubrey, et al. Heart 2011;97:75e84
WILD TYPE ATTR IS UNDERDIAGNOSED

- People aged over 85 Years ~ 25% (1)
- Aortic Surgical Valve Replacement ~ 6% (2)
- Transcatheter Aortic Valve Replacement ~ 16% (3)
- Patients with HFpEF~12% (4)

Pathology
Cardiovascular Evaluation

12 Lead ECG

Pseudoinfarct 88%
Low voltage 50%
AV block 22%

Pseudo infarction + low voltage:
Sensitivity: 28%
Specificity: 98%

Echocardiography
Cardiac MRI

sensitivity 88%

specificity 90%

positive predictive value 88%

negative predictive value 90%
Phyrophosphate Scan

IMPRESSION:

1. Findings consistent with TTR cardiac amyloidosis, with a heart to contralateral lung ratio of 2.5:1.
### PYP Scan Validation

**Multicenter Study of Planar Technetium 99m Pyrophosphate Cardiac Imaging**

Predicting Survival for Patients With ATTR Cardiac Amyloidosis

Adam Castano, MD, MS; Muhammad Haq, MD; David L. Narotsky, MD; Jeff Goldsmith, PhD; Richard L. Weinberg, MD, PhD; Rachelle Morgenstern, MPH; Ted Pozniakoff, ARRT; Frederick L. Ruberg, MD; Edward J. Miller, MD, PhD; John L. Berk, MD; Angela Dispensieri, MD; Martha Grogan, MD; Geoffrey Johnson, MD, PhD; Sabahat Bokhari, MD; Mathew S. Maurer, MD

#### 1-h Incubation

<table>
<thead>
<tr>
<th></th>
<th>ATTR+</th>
<th>ATTR-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive scan  ≥1.5</td>
<td>89</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>Negative scan &lt;1.5</td>
<td>8</td>
<td>28</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
<td>29</td>
<td>126</td>
</tr>
</tbody>
</table>

Sensitivity = 92%

Specificity = 97%

AUC, 0.971 (95% CI, 0.940-0.992)

*Castano, et al. JAMA 2016*
Non-Invasive Approach for Screening

Heart Failure

Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis

Julian D. Gillmore, MD, PhD; Mathew S. Maurer, MD; Rodney H. Falk, MD; Giampaolo Merlini, MD; Thibaud Damy, MD; Angela Dispenzieri, MD; Ashutosh D. Wechalekar, MD, DM; John L. Berk, MD; Candida C. Quarta, MD, PhD; Martha Grogan, MD; Helen J. Lachmann, MD; Sabahat Bokhari, MD; Adam Castano, MD; Sharmila Dorbala, MD, MPH; Geoff B. Johnson, MD, PhD;

Table 4. Combined Radionuclide ‘Bone’ Scintigraphy and Monoclonal Protein Studies

<table>
<thead>
<tr>
<th>Grade 2 or 3 Radionuclide Scan+Absence of Clone vs ATTR Amyloid Deposits on EMB (n=374)</th>
<th>Grade 2/3 Scan+No Clone, n</th>
<th>Grade 0/1 Scan or Clone, n</th>
<th>Sensitivity and Specificity (CI), %</th>
<th>PPV and NPV (CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac ATTR amyloid deposits</td>
<td>182</td>
<td>79</td>
<td>70 (64–75) sensitive</td>
<td>NPV, 59 (52–66)</td>
</tr>
<tr>
<td>No cardiac ATTR amyloid deposits</td>
<td>0</td>
<td>113</td>
<td>100 (96–100) specific</td>
<td>PPV, 100 (98–100)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; EMB, endomyocardial biopsy; NPV, negative predictive value; and PPV, positive predictive value.

Screening Evaluation
Utah Amyloidosis Program

Clinical Suspicion
- Heart failure and neuropathy
- Heart failure with preserved ejection fraction
- Echo suggestive of infiltrative pattern
- MRI suggestive of restrictive cardiomyopathy

Non Invasive Approach
- Pyrophosphate Scan
- Serum kappa/lambda light chains
- Serum protein electrophoresis

Invasive Approach
- Endomyocardial Biopsy
- Serum kappa/lambda light chains
- Serum protein electrophoresis
EMERGING THERAPIES FOR ATTR AMYLOIDOSIS

Heart Failure
- Diuretics (torsemide)
- Heart Transplantation
- Mechanical support

Suppression of TTR
- TTR Silencers

TTR Stabilizers
- Tafamidis
- Diflunisal

TTR Degraders
- Doxycycline/TUDCA
- Green Tea
MECHANICAL CIRCULATORY SUPPORT

• Left Ventricular Assist Devices
ATTR DEGRADERS

- Doxycycline
- Green Tea

Degradation of TTR aggregates and amyloid
TTR STABILIZERS

• Tafamidis
• Diflunisal

Stabilization of TTR proteins

Liver, Transthyretin, Dissociation, misfolding, amyloidosis fibrils
TAFAMIDIS FOR ATTRAMYLOIDOSIS

https://www.scripps.edu/newsandviews/e_20120604/tafamidis.html
• Tafamidis Randomized Clinical Trial
  - Mutant ATTR and Wild-Type ATTR.
  - Placebo vs Tafamidis 20 mg vs Tafamidis 80 mg.
  - Fully enrolled and is anticipated to be completed in the first half of 2018.
  - June 6, 2017 Received FDA Fast Track Designation
TTR STABILIZERS

• Tafamidisi

• Diflunisal
DIFLUNISAL FOR ATTR AMYLOIDOSIS

- NonSteroidal Anti-inflammatory
- ATTR Stabilizer
- 250 mg twice daily
# DIFLUNISAL FOR ATTR AMYLOIDOSIS

## Table II. Biochemical and Echocardiographic Characteristics (N=13)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.7±0.3</td>
<td>14.0±0.4</td>
<td>.55</td>
</tr>
<tr>
<td>Platelets, 10^9/L</td>
<td>179±12</td>
<td>168±11</td>
<td>.81</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>22±2</td>
<td>27±3</td>
<td>.7</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.2±0.1</td>
<td>1.2±0.1</td>
<td>.7</td>
</tr>
<tr>
<td>eGFR, ml/min</td>
<td>82±8</td>
<td>77±8</td>
<td>.35</td>
</tr>
<tr>
<td>Troponin I, ng/mL</td>
<td>0.04±0.01</td>
<td>0.07±0.02</td>
<td>.08</td>
</tr>
<tr>
<td>BNP, pg/ml</td>
<td>388±92</td>
<td>481±102</td>
<td>.52</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>4.1±0.1</td>
<td>4.0±0.1</td>
<td>.33</td>
</tr>
<tr>
<td>Modified BMI, kg g/m²/dl</td>
<td>100±4</td>
<td>95±4</td>
<td>.21</td>
</tr>
<tr>
<td><strong>Echocardiographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>50±3</td>
<td>48±6</td>
<td>.61</td>
</tr>
<tr>
<td>LV end-diastolic diameter, cm</td>
<td>4.4±0.1</td>
<td>4.5±0.1</td>
<td>.33</td>
</tr>
<tr>
<td>Interventricular septal thickness, cm</td>
<td>1.8±0.1</td>
<td>1.6±0.1</td>
<td>.25</td>
</tr>
<tr>
<td>LV posterior wall thickness, cm</td>
<td>1.6±0.1</td>
<td>1.5±0.2</td>
<td>.50</td>
</tr>
<tr>
<td>LA diameter, cm</td>
<td>4.6±0.2</td>
<td>4.5±0.2</td>
<td>.80</td>
</tr>
<tr>
<td>LV mass, g/m³</td>
<td>384±37</td>
<td>331±65</td>
<td>.36</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; BNP, B-type natriuretic peptide; BUN, serum urea nitrogen; eGFR, estimated glomerular filtration rate; LA, left atrial; LV, left ventricular. *Means±standard error at baseline and follow-up, change, and P value from Kruskal-Wallis test are shown.

Congest Heart Fail. 2012;18:315–319
DIFLUNISAL UTAH PROTOCOL

Screen for Side Effects

- GI bleeding
- Renal insufficiency
- Worsening heart failure

Initiation
Diflunisal 250 mg twice daily

1 Week
• Hemoglobin
• Creatinine
• Weight/swelling

2 Weeks
• Hemoglobin
• Creatinine
• Weight/swelling

Monthly
• Hemoglobin
• Creatinine
• Weight/swelling
TTR SILENCERS/GENE THERAPY

• Patisaran

• IONIS-TTRRx
PATISARAN FOR ATTR AMYLOIDOSIS

Transthyretin Silencer - Small Interfering RNA

The RNAi Therapeutic Mechanism

A. Direct-tethering RNA (siRNA) designed to cognate to gene target
B. siRNA synthesized with drug-like properties, stability, and conjugation for delivery
C.Modified siRNA penetrates the cell membrane and harnesses the RNAi mechanism for gene silencing
D. siRNA silencing enzymes at therapeutically effective levels
PATISARAN FOR ATTR AMYLOIDOSIS

Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: a phase II multi-dose study

EMERGING THERAPIES FOR ATTR AMYLOIDOSIS

Heart Failure
• Diuretics (torsemide)
• Heart Transplantation
• Mechanical support

Suppression of TTR
• TTR Silencers

TTR Stabilizers
• Tafamidis
• Diflunisal

TTR Degraders
• Doxycycline/TUDCA
• Green Tea
CONTENTS

NEW DATA, NEW GUIDELINES
1. Heart Failure with Reduced Ejection Fraction (HFrEF)
2. Heart Failure With Preserved Ejection Fraction (HFpEF)

NEW CHALLENGES
3. Focus in Cardiac Amyloidosis
CONCLUSIONS

HFrEF

1. ACEI/ARB, BB, Aldo antagonists have class I indication
2. Sacubitril/Valsartan has class I indication
3. Ivabridine has class IIa indication
4. Watch for vericiguat (VICTORIA Trial)
CONCLUSIONS

HFpEF
1. ACEI/ARB, BB, Aldo antagonists have no indication
2. Isosorbide has class III indication
3. Sildenafil has class III indication
4. Aldo antagonist has class IIb indication
5. Watch for Sacubitril/Valsartan (PARAGON Trial)
6. Watch for dapagliflozin (PRESERVED-HF Trial)
CONCLUSIONS

OLDER ADULTS WITH HEART FAILURE

1. Think about ATTR Amyloidosis    You will find it.