CO MORBIDITIES & HEART FAILURE

Maria Nikolaou
Cardiologist
Co•mor•bid•i•ty

• Any *distinct additional entity* that has existed or may occur during the clinical course of a patient who has the *index disease* under study.


• Two or more *coexisting* medical conditions or disease processes that are additional to an initial diagnosis.

HF & comorbidities: co-incidence OR disease interactions?

Cardiac Comorbidities

Heart Failure

• Cancer
• Prostate Hyperplasia
• Arthritis
• Thyroid Disorder
• Diabetes Mellitus
• Renal Dysfunction
• Anemia
• Lung Disease COPD- SAS
• Cognitive Dysfunction Depression

•••••
Non-cardiac comorbidities

• may provoke similar symptoms
e.g. dyspnea by COPD

• may result from HF treatment
e.g. RAAS blockade & Anemia
  Diuretics & Renal Dysfunction

• may require “harmful” treatment
e.g. NSAIDS for Arthritis
  B agonists, steroids for COPD

• may worsen prognosis
e.g. Renal Dysfunction, Anemia, Depression, Diabetes Mellitus...

• may represent treatment target
clinical trials ≠ real world
### Summary of comorbidities in CHF

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Prevalence (%)</th>
<th>Mortality Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>37</td>
<td>YES</td>
</tr>
<tr>
<td>Cerebral dysfunction</td>
<td>28-58</td>
<td>YES</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>50-60</td>
<td>YES</td>
</tr>
<tr>
<td>COPD</td>
<td>10-60</td>
<td>YES</td>
</tr>
<tr>
<td>Depression</td>
<td>22</td>
<td>YES</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6-44</td>
<td>YES</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60-70</td>
<td>YES</td>
</tr>
<tr>
<td>Iron Deficiency</td>
<td>50-60</td>
<td>YES</td>
</tr>
<tr>
<td>Kidney dysfunction</td>
<td>55</td>
<td>YES</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>30-60</td>
<td>YES</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>60</td>
<td>YES</td>
</tr>
<tr>
<td>Stroke</td>
<td>5</td>
<td>YES</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>85</td>
<td>YES</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>-</td>
<td>YES</td>
</tr>
</tbody>
</table>

*Van Deursen et al. Heart Fail Rev 2012*
The additive impact on survival

Nikolaou M, Parissis J, ...Filippatos G. ESC 2011
The additive impact on QoL

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>≥3</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>KCCQ-fs</td>
<td>48±19</td>
<td>44±23</td>
<td>30±16</td>
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<td>0.007</td>
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<tr>
<td>KCCQ-os</td>
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<td></td>
<td></td>
<td>58±31</td>
<td>0.003</td>
</tr>
<tr>
<td>DASI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zung score</td>
<td>34±19</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 MWT</td>
<td>419±98</td>
<td>340±132</td>
<td>287±120</td>
<td>200±143</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Nikolaou M, Parissis J, ...Filippatos G. ESC 2011
Important Differences in the Mode of Death in HF-PEF versus HF-REF

<table>
<thead>
<tr>
<th>Mode of Death</th>
<th>I-Preserve</th>
<th>HF-REF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden Death</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Heart failure</td>
<td>14</td>
<td>45</td>
</tr>
<tr>
<td>Sudden/HF deaths</td>
<td>1.9</td>
<td>0.6</td>
</tr>
<tr>
<td>MI</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Non-Cardiovascular</td>
<td>30</td>
<td>15</td>
</tr>
</tbody>
</table>

Zile et al. Circulation 2010
<table>
<thead>
<tr>
<th>Variable</th>
<th>HFpEF (n = 2,843)</th>
<th>HFrEF (n = 6,599)</th>
<th>p Value</th>
<th>Age-Adjusted p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>44.9</td>
<td>40.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypertension</td>
<td>70.5</td>
<td>62.2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>27.5</td>
<td>27.8</td>
<td>0.76</td>
<td>0.42</td>
</tr>
<tr>
<td>CVA</td>
<td>21.0</td>
<td>21.3</td>
<td>0.76</td>
<td>0.48</td>
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<tr>
<td>Atrial fibrillation</td>
<td>35.0</td>
<td>35.4</td>
<td>0.73</td>
<td>0.22</td>
</tr>
<tr>
<td>Past MI</td>
<td>27.1</td>
<td>40.4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>48.8</td>
<td>51.9</td>
<td>0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>33.2</td>
<td>28.4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>33.9</td>
<td>26.6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>51.0</td>
<td>34.7</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1.7</td>
<td>1.7</td>
<td>1.00</td>
<td>0.81</td>
</tr>
<tr>
<td>Cancer</td>
<td>21.6</td>
<td>18.6</td>
<td>0.001</td>
<td>0.01</td>
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<tr>
<td>AIDS</td>
<td>0.3</td>
<td>0.3</td>
<td>1.00</td>
<td>0.84</td>
</tr>
<tr>
<td>Dementia</td>
<td>3.0</td>
<td>2.6</td>
<td>0.31</td>
<td>0.56</td>
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<tr>
<td>Psychiatric disorders</td>
<td>27.8</td>
<td>22.8</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rheumatological disorders</td>
<td>4.4</td>
<td>3.8</td>
<td>0.20</td>
<td>0.22</td>
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<tr>
<td>Peptic ulcer disease</td>
<td>8.1</td>
<td>6.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey

<table>
<thead>
<tr>
<th>Condition</th>
<th>HFrEF (LVEF &lt;40%)</th>
<th>HFPpEF (LVEF ≥40%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease</td>
<td>541 (41)</td>
<td>383 (39)</td>
<td>0.381</td>
</tr>
<tr>
<td>Anaemia</td>
<td>349 (28)</td>
<td>306 (30)</td>
<td>0.130</td>
</tr>
<tr>
<td>Diabetes</td>
<td>470 (30)</td>
<td>343 (28)</td>
<td>0.191</td>
</tr>
<tr>
<td>COPD</td>
<td>255 (16)</td>
<td>173 (14)</td>
<td>0.101</td>
</tr>
<tr>
<td>Stroke</td>
<td>166 (11)</td>
<td>129 (10)</td>
<td>0.892</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>69 (4)</td>
<td>49 (4)</td>
<td>0.578</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>152 (10)</td>
<td>96 (8)</td>
<td>0.062</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>54 (4)</td>
<td>32 (3)</td>
<td></td>
</tr>
</tbody>
</table>
Renal Dysfunction

• 55% of CHF patients have eGFR <60 ml/min

• Independent prognostic marker for mortality (HR 2)

• Vicious Cycle known as CR(A)S

• Mechanisms
  - hypotension
  - venous congestion
  - sympathetic activation, vasoconstriction
  - inflammation, endothelial dysfunction
  - HF drugs (β-blockers, ACE-I, diuretics), other drugs (antibiotics)

• Kidney injury provokes Acute HF decompensation
  - Diuretic Resistance
Worsening Renal Function

**Graph:**
- Cumulative survival (death or HF admission) over follow-up time (days) for WRF in-hospital, WRF 0–6 months, and WRF 6–12 months.
- Two curves are shown: one for No WRF and another for WRF.

**Source:**
Damman K. Eur J Heart Fail 2009
Worsening Renal Function - the role of congestion
Renal Dysfunction in Patients With Heart Failure With Preserved Versus Reduced Ejection Fraction

- eGFR ≥90
- eGFR 60-89.9
- eGFR 45-59.9
- eGFR 30-44.9
- eGFR 15-29.9
- eGFR <15

HF r EF

HF p EF

Mc Alister Circ Heart Failure 2012
Treatment

- avoid nephrotoxic drugs

- while up-titrating ACE-I/ARB/MRA
  monitor closely renal markers, K

- while decompensating- NO EVIDENCE BASED THERAPIES
  (diuretic resistance, need for inotropes, ultrafiltration)
Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

Bradley A. Hart, M.D., Steven R. Goldsmith, M.D., Kerry L. Lee, Ph.D., Michael M. Gragert, M.D., Christopher W. Connor, M.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Anita Dewald, M.D., M.P.H., Jean L. Roumie, M.D., Martin L. Zierler, M.D., Elizabeth D. Ollis, M.D., M.P.H., Lynne W. Simeone, M.D., Marc C. Sennett, M.D., G. Michael Felker, M.D., Herm H. Chen, M.D., Adrian F. Hernandez, M.D., Kevin J. Antman, Ph.D., Steven E. McNally, M.S., Eric L. Velazquez, M.D., Jenny C. Huang, R.N., M.S.N., Alice M. Mascette, M.D., and Eugene Braunwald, M.D., for the Heart Failure Clinical Research Network

ABSTRACT

BACKGROUND
Ultrafiltration is an alternative strategy to diuretic therapy for the treatment of patients with acute decompensated heart failure. Little is known about the efficacy and safety of ultrafiltration in patients with acute decompensated heart failure complicated by persistent congestion and worsened renal function.

METHODS
We randomly assigned a total of 168 patients with acute decompensated heart failure, worsened renal function, and persistent congestion to a strategy of stepped pharmacologic therapy (94 patients) or ultrafiltration (94 patients). The primary end point was the binary change from baseline in the serum creatinine level and body weight, assessed 96 hours after random assignment. Patients were followed for 66 days.

RESULTS
Ultrafiltration was inferior to pharmacologic therapy with respect to the binary end point of the change in the serum creatinine level and body weight 96 hours after randomization (P=0.008), owing primarily to an increase in the creatinine level in the ultrafiltration group. At 96 hours, the mean change in the creatinine level was +0.006 [9.3 mg per deciliter (0.37 mmol per liter) in the pharmacologic therapy group, as compared with +0.012 [9.8 mg per deciliter (0.45 mmol per liter) in the ultrafiltration group (P=0.008). There was no significant difference in weight loss 96 hours after randomization between patients in the pharmacologic therapy group and those in the ultrafiltration group in 5.5±2.1 kg [12.1±4.6 lb] and 5.2±2.0 kg [11.6±4.5 lb], respectively (P=0.58). A higher percentage of patients in the ultrafiltration group than in the pharmacologic therapy group had a serious adverse event (24% vs. 9%, P=0.06).

CONCLUSIONS
In a randomized trial involving patients hospitalized for acute decompensated heart failure, worsened renal function, and persistent congestion, the use of a stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 hours, with a similar amount of weight loss with the two approaches. Ultrafiltration was associated with a higher rate of adverse events. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00984891)
Renal Replacement Therapy

Ultrafiltration may be considered for patients with obvious volume overload to alleviate congestive symptoms and fluid weight.

Ultrafiltration may be considered for patients with refractory congestion not responding to medical therapy.
Anemia
Relation of Low Hemoglobin and Anemia to Morbidity and Mortality in Patients Hospitalized With Heart Failure (Insight from the OPTIMIZE-HF Registry)

Young JB et al. Am J Cardiol 2008
Patients with CRAS have a 2-year Mortality Rate of ~46%

- 1,136,201 patients in the 5% Medicare database
  - Anemia, CKD and CHF contribute significantly to mortality rates

Potential Causes of Anemia in HF

LV dysfunction

RAS & SNS activation

↓ EPO Secretion

Kidney

↓ Perfusion RAS activation

↑ Sympathetic tone

ACE inhibitor therapy

RAS & SNS activation

Bone marrow

↑ TNF-α

↓ Perfusion

Malnutrition

↓ EPO resistance

Anemia

↓ RBC production

Hemodilution

Plasma Volume expansion


RAS, renin-angiotensin system

SNS, sympathetic nervous system
Iron deficiency for erythropoiesis: 64%

Defective endogenous EPO production: 76%

Anemia of Chronic Disease (ACD) – the Most Frequent Cause of Anemia in HF

All Cause Death

Selected Adverse Events of Interest

<table>
<thead>
<tr>
<th>Event</th>
<th>Darbepoeitin alfa (N = 1133)</th>
<th>Placebo (N = 1140)</th>
<th>Risk difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic cerebrovascular conditions</td>
<td>51 (4.5)</td>
<td>32 (2.8)</td>
<td>1.7 (0.2, 3.2)</td>
<td>0.031</td>
</tr>
<tr>
<td>Embolic and thrombotic events</td>
<td>153 (13.5)</td>
<td>114 (10.0)</td>
<td>3.5 (0.9, 6.1)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Causes of anemia

- Iron deficient anemia: 73.0%
- Anemia of chronic disease: 18.9%
- Hemodilution: 5.4%
- Drug induced: 2.7%
Prevalence of Iron Deficiency in Patients with CHF and CKD

- Patients can be iron deficient with and without anemia
- 21% of hospitalized patients with CHF and anemia are iron deficient\(^1\)
- Iron deficiency in patients with CHF and anemia is >70% (determined by bone marrow biopsy)\(^2\)
- Iron deficiency in CKD: \(^3\)
  - Almost 70% have TSAT <20% OR ferritin <100 ng/mL
  - Almost 30% have TSAT <20% AND ferritin <100 ng/mL

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Correction of Iron Deficiency – a Promising Option for CRAS Patients?

- **FAIR-HF: Primary Endpoints**

  FCM improved NYHA functional class at week 24 (OR for ↑ by 1 class: 2.40, p<0.001)

  FCM improved self-reported PGA scores at week 24 (OR for better rank: 2.51; p<0.001)

Anker SD et al. NEJM 2009; 361:2436–2448
Summary of the American College of Physicians Guideline on
Treatment of Anemia in Patients With Heart Disease

Anemia and heart disease
Internists, family physicians, and other clinicians
Adult patients with symptomatic CHF (with or without reduced systolic function) or CHD (acute coronary syndrome, postacute coronary syndrome, or a history of MI or angina) and anemia or iron deficiency
Red blood cell transfusion, ESAs with or without iron (including erythropoietin and darbepoetin), and intravenous iron
Mortality (all-cause and disease-specific): cardiovascular events (MI, CHF exacerbation, arrhythmia, or cardiac death); exercise tolerance (any metric, most commonly NYHA class, 6-min walk test); quality of life; hospitalization (all-cause and

**Recommendation 1:** ACP recommends using a restrictive red blood cell transfusion strategy (trigger hemoglobin threshold of 7–8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease. (Grade: weak recommendation; low-quality evidence)

**Recommendation 2:** ACP recommends against the use of erythropoiesis-stimulating agents in patients with mild to moderate anemia and congestive heart failure or coronary heart disease. (Grade: strong recommendation; moderate-quality evidence)

Red blood cell transfusion: no benefits shown when comparing liberal to restrictive transfusion
ESAs: no benefit
Intravenous iron: increased exercise tolerance, improved quality of life

Patients with heart disease may have anemia because of iron deficiency, use of ACE inhibitors, renal insufficiency, and poor nutrition.

Presence of anemia is associated with increased mortality and morbidity. However, it is uncertain if anemia is an independent risk factor for poor outcomes or if it is a marker of more severe illness.

The impact of oral administration of iron and how it compares with IV iron for treating anemic patients with heart disease is unknown.
Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure

Maria Nikolaou, John Parissis, M. Birhan Yilmaz, Marie-France Seronde, Matti Kivikko, Said Laribi, Catherine Paugam-Burtz, Danlin Cai, Pasi Pohjanjoulu, Pierre-François Laterre, Nicolas Deye, Pentti Poder, Alain Cohen Solal, and Alexandre Mebazaa

Figure 2 Kaplan–Meier curves of mortality based on (A) abnormal or normal alkaline phosphate at baseline, or (B) abnormal or normal transaminases. ALT, alanine transaminase; AST, aspartate transaminase.

Eur Heart J 2012
COPD

- Prevalence not well described, large range (9-52%)

  *Hawkins NM. EJHF 2009*

- Similar symptoms
- Up to 20% of HF exacerbations is upon lung infections

- COPD is the main reason for BB underuse, ...although the contraindication is for asthma

- Steroid therapy may cause sodium and water retention- Inhaled steroids permitted
B-B reduce mortality in COPD

<table>
<thead>
<tr>
<th></th>
<th>Any BB</th>
<th>Selective</th>
<th>Non selective</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.64 (0.52-0.77)</td>
<td>0.63 (0.51-0.77)</td>
<td>0.80 (0.60-1.05)</td>
</tr>
</tbody>
</table>

Rutten Arch Intern Med 2010
Depression

• Prevalence

Joynt et al. J Cardiac Failure 2004

• Impact on prognosis

RR 2.1 (CI 1.71-2.58) for mortality/CV events

Rutledge et al. JACC 2006
Safety and Efficacy of Sertraline for Depression in Patients With Heart Failure

Results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) Trial

Table 3: Fatal and Nonfatal Events Through 12 Weeks

<table>
<thead>
<tr>
<th>Event</th>
<th>Sertraline (n = 234)</th>
<th>Placebo (n = 235)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>18 (7.7)</td>
<td>15 (6.8)</td>
<td>0.58</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>16 (6.8)</td>
<td>10 (4.3)</td>
<td>0.59</td>
</tr>
<tr>
<td>Nonfatal cardiovascular event</td>
<td>47 (20.1)</td>
<td>55 (23.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1 (0.4)</td>
<td>0</td>
<td>0.31</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4 (1.7)</td>
<td>6 (2.6)</td>
<td>0.53</td>
</tr>
<tr>
<td>Cardiac syncope</td>
<td>0</td>
<td>1 (0.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>2 (0.8)</td>
<td>1 (0.4)</td>
<td>0.56</td>
</tr>
<tr>
<td>Exacerbation of heart failure</td>
<td>19 (8.1)</td>
<td>30 (12.8)</td>
<td>0.1</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>7 (3.0)</td>
<td>5 (2.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Other nonfatal cardiovascular event</td>
<td>14 (6.0)</td>
<td>12 (5.1)</td>
<td>0.68</td>
</tr>
<tr>
<td>All-cause mortality or nonfatal cardiovascular event</td>
<td>65 (29.4)</td>
<td>70 (29.8)</td>
<td>0.63</td>
</tr>
<tr>
<td>Heart failure hospitalization or death</td>
<td>37 (15.8)</td>
<td>45 (19.2)</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Clinical Investigation

Effects of Sertraline on Circulating Markers of Oxidative Stress in Depressed Patients With Chronic Heart Failure: A Pilot Study

CHRISTOS A. MICHALAKEAS, MD,1 JOHN T. PARISSIS, MD,1 ATHANASIOS DOUZENIS, MD,2 MARIA NIKOLAOU, MD,1 CHRISTOS VAROUNIS, MD,1 IOANNA ANDREADOU, PhD,3 NIKOLAOS ANTONELLOS, MS,3 SOPHIA MARKANTONIS-KIROUDIS, PhD,3 IOANNIS PARASKEVADIS, MD,1 IGNATIOS IKONOMIDIS, MD,1 EVANGELOS LYKOURAS, MD,2 AND DIMITRIOS KREMASTINOS, MD1

F = 4.657, p = 0.037

J Cardiac Failure 2011
Effects of Exercise Training on Depressive Symptoms in Patients With Chronic Heart Failure
The HF-ACTION Randomized Trial

Context  Depression is common in patients with cardiac disease, especially in patients with heart failure, and is associated with increased risk of adverse health outcomes. Some evidence suggests that aerobic exercise may reduce depressive symptoms, but to our knowledge the effects of exercise on depression in patients with heart failure have not been evaluated.

Objective  To determine whether exercise training will result in greater improvements in depressive symptoms compared with usual care among patients with heart failure.

Design, Setting, and Participants  Multicenter, randomized controlled trial involving 2322 eligible patients treated for heart failure at 82 medical centers in the United States, Canada, and France. Patients who had a left ventricular ejection fraction of 35% or lower, had New York Heart Association class I to IV heart failure, were hospitalized in the usual care group compared with 739 (32%) in the aerobic exercise group (hazard ratio [HR], 0.89; 95% CI, 0.81 to 0.99; P = .03). The median BDI-II score at study entry was 8, with 28% of the sample having BDI-II scores of 14 or higher. Compared with usual care, aerobic exercise resulted in lower mean BDI-II scores at 3 months (aerobic exercise, 8.95; 95% CI, 8.61 to 9.29 vs usual care, 9.70; 95% CI, 9.34 to 10.06; difference, –0.76; 95% CI, –1.22 to –0.29; P = .002) and at 12 months (aerobic exercise, 8.86; 95% CI, 8.67 to 9.24 vs usual care, 9.54; 95% CI, 9.15 to 9.92; difference, –0.68; 95% CI, –1.20 to –0.16; P = .01).

Conclusions  Compared with guideline-based usual care, exercise training resulted in a modest reduction in depressive symptoms, although the clinical significance of this improvement is unknown.

Trial Registration  clinicaltrials.gov Identifier: NCT00047437
Thyroid dysfunction

- ft3 (2.0-4.4 pg/ml)
- ft4 (0.8-2.0 ng/dl)
- TSH (0.27-4.2 μIU/ml)

19% normal
12% low
19% high

19%
Thyroid Dysfunction

Survival Functions

Prevalence 20%

Log rank p<0.001
Diabetes Mellitus

- Prevalence 20-30% in HF trials
- HF treatment does not affect diabetic profile
- Avoid the azolidinediones
- Withdraw metformin in case of contrast/hypoxia/renal deterioration

Wei et al. Cardiovasc Diabet 2012
Key Secondary Endpoint in non-DM Patients
CV Death or HF Re-hospitalization Within 12 Months

Kaplan-Meier estimate of cumulative event rate (%)

- Aliskiren (148/489 patients with events; 30.3%)
- Placebo (165/464 patients with events; 35.6%)

HR: 0.80 (95% CI: 0.64-0.99) p = 0.04

<table>
<thead>
<tr>
<th>Event</th>
<th>Aliskiren n (%)</th>
<th>Placebo n (%)</th>
<th>HR (95% CI)</th>
<th>p-value (two-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>64 (13.1)</td>
<td>85 (18.3)</td>
<td>0.63 (0.45-0.87)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HF re-hospitalization</td>
<td>104 (21.3)</td>
<td>116 (25.0)</td>
<td>0.79 (0.61-1.04)</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Take Home Messages

• HF is related to multiple comorbid conditions
• Comorbidities affect QoL, morbidity & mortality both in HFrEF & HFrEF
• Screening is essential for identifying a patient’s profile
• Target therapies are under investigation