The prevalence of the combination of diabetes and both systolic and diastolic heart failure is increasing independent of coronary associated artery disease. Patients with heart failure and diabetes have higher rates of hospitalizations and worse outcomes compared to heart failure patients without diabetes. Patients with diabetes and heart failure have several pathophysiologic abnormalities that may contribute to progressive cardiac dysfunction. In the past decade new data has expanded our understanding of the importance of glucose control and the impact classes of old and new diabetic medications on the risk of heart failure complications.

References:

4. Margulies KB et al. Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA, 2016 Aug 2; Vol. 316 (5), pp. 500-8
Congestive Heart Failure: The Complication that Gets No Respect

Richard J Katz, MD
George Washington University

In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

Richard Katz, MD
Disclosed no conflict of interest.

Relationship Between DM and HF

Diabetes Mellitus
Heart Failure

Six-year CHF incidence per 1000 person-years by Age Group

<table>
<thead>
<tr>
<th>Age</th>
<th>Diabetic patients</th>
<th>Nondiabetic patients</th>
<th>Rate ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45 years</td>
<td>4.5</td>
<td>0.4</td>
<td>11.0</td>
<td>5.6-21.8</td>
</tr>
<tr>
<td>45-54 years</td>
<td>11.9</td>
<td>1.4</td>
<td>8.6</td>
<td>6.4-11.4</td>
</tr>
<tr>
<td>55-64 years</td>
<td>23.6</td>
<td>5.0</td>
<td>4.7</td>
<td>3.0-5.8</td>
</tr>
<tr>
<td>65-74 years</td>
<td>38.7</td>
<td>13.7</td>
<td>2.8</td>
<td>2.4-3.3</td>
</tr>
<tr>
<td>75-84 years</td>
<td>63.9</td>
<td>34.7</td>
<td>1.8</td>
<td>1.6-2.2</td>
</tr>
<tr>
<td>85-94 years</td>
<td>92.8</td>
<td>78.8</td>
<td>1.2</td>
<td>0.9-1.8</td>
</tr>
<tr>
<td>95+ years</td>
<td>30.5</td>
<td>110.4</td>
<td>0.3</td>
<td>0.1-2.2</td>
</tr>
<tr>
<td>All</td>
<td>50.9</td>
<td>12.4</td>
<td>2.5</td>
<td>2.3-2.7</td>
</tr>
</tbody>
</table>

Insulin Resistance, Hyperglycemia, and Heart Failure

- Hyperglycemia
  - oxidative stress
  - altered intracellular signaling
  - decreased vascular endothelial growth factor
  - altered gene expression
- Insulin
  - Myocardial hypertrophy
- Advanced Glycation Endproduct (AGEs)
  - sconopeplasmin/endoplasmin reticulum Ca²⁺ ATPase
  - collagen cross-linking and reduce ventricular distensibility and vascular compliance
- Myocardial metabolism may become more dependent on free fatty acids
  - uncoupling of oxidative phosphorylation

<table>
<thead>
<tr>
<th>Slide 4</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>k1</td>
<td>katz, 2/8/2017</td>
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<tr>
<td>k2</td>
<td>katz, 2/8/2017</td>
</tr>
</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>k4</td>
<td>katz, 2/8/2017</td>
</tr>
</tbody>
</table>
Diabetic Cardiomyopathy: Potential Mechanisms

- Hyperglycemia → ↑ oxidative stress, ↓ vascular endothelial growth factor, and alter gene expression
- Insulin → myocardial hypertrophy
- ↑ FFA concentration → ↑ FFA oxidation and ↓ glucose oxidation
- ↑ Mitochondrial dysfunction → ↓ ATP
- ↓ Ca++ homeostasis → ↓ contractility
- ↑ Protein kinase activation → ↓ NO and ↑ ET → hypertrophy+fibrosis
- ↑ AGE formation → cross-link AGEs and proteins → fibrosis, coronary microangiopathy
- ↑ Activation RAS → apoptosis, oxidative stress → fibrosis

Diabetes and HFPEF

Diastolic Heart Failure and DM

- Subclinical HfPEF detected on 2D echo by speckle tracking
- 30-40% patients with HfPEF have DM
- HfPEF patients with DM have 70-70% increased mortality and hospitalization

Poor Glycemic Control in DM is Independently Associated with Increased HF Risk

Diabetes and HF Prognosis
Antihyperglycemic Agents and Heart Failure

1. Glucose control
2. Metformin
3. Thiazolidinediones (PPAR gamma agonists)
4. Insulin
5. Dipeptidyl peptidase 4 (DPP-4) Inhibitors
6. Glucagon-like peptide 1 (GLP-1) Receptor Agonists
7. Sodium-glucose co-transporter 2 (SGLT2) Inhibitors

Effect of More vs Less-Intensive Control of Glucose on Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPIDone</td>
<td>1.41 (1.14–1.78)</td>
<td>32.8</td>
</tr>
<tr>
<td>ACCORD</td>
<td>1.23 (0.91–1.67)</td>
<td>25.16</td>
</tr>
<tr>
<td>Subgroup 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VADT</td>
<td>0.53 (0.37–0.72)</td>
<td>10.3</td>
</tr>
</tbody>
</table>

Mortality with Metformin in Patients with Heart Failure and Diabetes

<table>
<thead>
<tr>
<th>Days</th>
<th>No Insulin Sensitizer</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.99</td>
<td>0.96</td>
</tr>
<tr>
<td>100</td>
<td>0.78</td>
<td>0.75</td>
</tr>
<tr>
<td>200</td>
<td>0.68</td>
<td>0.66</td>
</tr>
<tr>
<td>300</td>
<td>0.61</td>
<td>0.60</td>
</tr>
<tr>
<td>400</td>
<td>0.57</td>
<td>0.56</td>
</tr>
<tr>
<td>500</td>
<td>0.53</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Conclusions: Diabetes and HF

- The two disease entities are highly co- prevalent
- Diabetes contributes to disease progression in HF and is associated with worse prognosis
- Standard HF therapies (ARNI, ACEI, or ARB, BB, MRA, ICD/CRT) should be instituted in eligible HF patients with DM
- The optimal glucose-lowering regimen in diabetic HF patients requires further investigation
- More needs to be done to prevent HF in patients with diabetes
# Antihyperglycemic Agents and Heart Failure

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## Thiazolidinediones Compared with Other Treatments
### for All Cause Mortality

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds ratio (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aguilar 2007</td>
<td>146/818</td>
<td>1192/4760</td>
<td>31.87 (0.63 to 0.91)</td>
<td>6.0</td>
<td>31.87 (0.63 to 0.91)</td>
</tr>
<tr>
<td>Dangle 2007</td>
<td>8/119</td>
<td>3/114</td>
<td>1.89 (0.34 to 5.46)</td>
<td>0.3</td>
<td>1.89 (0.34 to 5.46)</td>
</tr>
<tr>
<td>Inzucchi 2005</td>
<td>92/255</td>
<td>760/2186</td>
<td>23.36 (0.79 to 0.76)</td>
<td>33.0</td>
<td>23.36 (0.79 to 0.76)</td>
</tr>
<tr>
<td>Massin 2005</td>
<td>670/2256</td>
<td>3436/1326</td>
<td>44.88 (0.69 to 0.86)</td>
<td>32.0</td>
<td>44.88 (0.69 to 0.86)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>34/95</td>
<td>19/67</td>
<td>100.00 (0.71 to 0.97)</td>
<td>12.0</td>
<td>100.00 (0.71 to 0.97)</td>
</tr>
</tbody>
</table>

### Risk of Heart Failure with TZD Use

- Rosiglitazone
- Pioglitazone

### Product Labeled Heart Failure Cautions for Diabetes Medications

- Metformin
- No longer contraindicated with heart failure (as of 11/2006)

- Thiazolidinediones
- Observe for signs/symptoms of heart failure
- Caution for use with any HF (NYHA Class I-IV)
- Initiation contraindicated in Class III-IV

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Altered gene expression genes reduce FFA uptake and metabolism (solid red arrows) and cardiac myocyte insulin resistance reduces glucose uptake via the transporters GLUT1 and GLUT4 (dotted red arrows) impairing uptake and utilization of both substrates for ATP generation via oxidative phosphorylation. Glucagon-like peptide 1 (GLP-1) or degradation-resistant GLP-1 agonists reduce insulin resistance and increase cardiac myocyte glucose uptake via signaling through the GLP-1R receptor that induces phosphorylation (activation) of AMP-activated protein kinase (AMPK), (green arrows).

Lixisenatide in Patients with Type 2 Diabetes and ACS: Heart Failure Hospitalization

Pfeffer M et al. NEJM 2015;373:2247

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes: Hospitalization for Heart Failure

Marso SP et al. NEJM 2016;375:22-33

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Margulies KB et al. JAMA 2016;316:500-8
Antihyperglycemic Agents and Heart Failure

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EMPA-REG OUTCOME: Death from Cardiovascular Causes

EMPA-REG OUTCOME: Hospitalization for Heart Failure

Sodium-glucose co-transporter 2 (SGLT2) Inhibitors: Metabolic and Hemodynamic Mechanisms

SUMMARY

- Antihyperglycemic therapies/strategies may influence risk for heart failure
  - Increased risk
    - Intensification of glucose control
    - Thiazolidinediones
    - Saxaglaptin and alogliptin
  - Neutral / Safe
    - Dulaglutide, sitagliptin, liraglutide, exenatide, exenatide
  - Decreased risk
    - Empagliflozin; perhaps metformin
- Effects on HF risk of selected therapies appear independent of glycemic effects
  - TZDs, saxaglaptin, alogliptin
  - Empagliflozin (and SGLT2i's?)