Cardio-Renal Complications of Type 2 Diabetes Mellitus: Focus on Heart Failure

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Cardio-Renal Complications of Type 2 Diabetes Mellitus: Focus on Heart Failure

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Disclosures

• Ralph J. Riello III
  – Janssen, Johnson & Johnson, Portola, and AstraZeneca: consultant

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Learning Objectives

- Recognize the causative role of type 2 diabetes mellitus (TD2M) in the development of cardiovascular and renal disease
- Define the prevalence, pathophysiology, and healthcare burden of heart failure (HF) in the United States
- Discuss the risk of HF as an underappreciated complication of T2DM
- Describe the progression of chronic kidney disease (CKD) as a common comorbidity of T2DM

T2DM: Cardio-Renal Complications
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T2DM Epidemiology

- **50%** Die from cardiovascular (CV) disease
- **75%** Had BP ≥140/90 mmHg or on antihypertensive medications
- **25%** Of CKD is attributable to diabetes
- **50%** At risk of developing HF

30.3 million


American Diabetes Association. Diabetes Care. 2019;42(Suppl 1);S103-S123.

T2DM Pathophysiology

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T2DM and CVD Pathophysiology

Diabetes mellitus → Metabolic Disturbances (Hyperglycemia, Hyperinsulinemia, Insulin Resistance, Dyslipidemia, Obesity) → Oxidative stress, Glycation → Autonomic neuropathy → Activation of Reticular Activating System (RAS) → Inflammation → Cardiac fibrosis, Cardiac dysfunction → Endothelial dysfunction, Atherosclerotic CVD (ASCVD) → Heart Failure → Coronary Artery Disease (CAD)


T2DM and HF Pathophysiology

Diabetes → Impaired glucose handling, insulin resistance → Oxidative Stress → Inflammation → Hypertension → Atherosclerosis → Fibrosis → ↓ Perfusion, CAD

↓ Compliance → Diastolic Dysfunction, Systolic Dysfunction → Myocardium → Diabetic HF

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Cardiorenal T2DM Complications

- Diabetes affects the PUMP
- Diabetes affects the PLUMBING
- Diabetes affects the FILTER

HF as a T2DM Complication

- T2DM causes ischemic HF by increasing CAD and hypertension risk
- T2DM directly induces myocardial structural and functional changes

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HF is more likely than myocardial infarction or stroke to be the first cardiovascular complication of type 2 diabetes?

a. True  
b. False
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**Epidemiology**

- **6.5 million** adults with HF  
  - Increase 46% by 2030
- **960,000** new cases diagnosed annually
- **46%** five-year survival rate after diagnosis  
  - 1 in 9 deaths attributed to HF
- **$30.7 billion** in healthcare costs per year
- **#1** hospitalization cause among age >65 y/o  
  - 25% readmitted within 30 days


**Pathophysiology**

- Heart is unable to pump blood at a rate commensurate with tissue demand or only can with high filling pressures

**Impaired left ventricular (LV) filling**
- During diastole, LV fills with blood
- Improper relaxation reduces stroke volume

**Impaired blood ejection**
- During systole, LV ejects blood
- Improper ejection reduces cardiac output

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Classification

- LV ejection fraction (EF) is key HF measurement
  - Portion of blood pumped from heart with each beat
    - ≥50% is normal
  - HF with reduced EF (HFrEF)
    - ≤40% or systolic HF
  - HF with preserved EF (HFpEF)
    - ≥50% or diastolic HF

Echocardiography

- Gold standard assessment of cardiac function
  - Diagnostic ultrasound measurement of LVEF, cardiac volume, mass
  - Characterizes structural, flow abnormalities
  - Reveals subclinical HF
    - Predict future CV risk

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Biomarker

- **N-terminal pro-B-type natriuretic peptide (NT-proBNP)**
- Counterregulatory, vasoactive hormone
  - Myocytes release during ventricular wall stress
  - Elevated levels indicate HF, rise with severity
- Assay identifies T2DM patients at risk for HF

Kaplan-Meier Analysis of 631 T2DM Patients Using NT-proBNP at Cutoff of 125 pg/mL

- NT-proBNP >125 pg/mL (n=358)
- NT-proBNP <125 pg/mL (n=273)

Death or Unplanned CV Hospitalization

- P <0.0001

Classification

<table>
<thead>
<tr>
<th>HFrEF (Systolic HF)</th>
<th>HFP EF (Diastolic HF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Systolic LV dysfunction</td>
<td>• Diastolic LV dysfunction</td>
</tr>
<tr>
<td>• LV dilation</td>
<td>• No LV dilation</td>
</tr>
<tr>
<td>• Eccentric LV remodeling</td>
<td>• Concentric LV remodeling</td>
</tr>
<tr>
<td>• Due to loss of systolic function, typically after an acute cardiac event</td>
<td>• Due to pro-inflammatory CV and non-CV co-existing conditions</td>
</tr>
<tr>
<td>• Associated with coronary artery disease risk factors (eg, hypertension, diabetes, advanced age, smoking, dyslipidemia)</td>
<td>• Associated with hypertension, obesity, diabetes, metabolic syndrome, lung disease, smoking, and iron deficiency</td>
</tr>
<tr>
<td>• Accounts for nearly 50% of all HF cases</td>
<td>• Accounts for &gt;50% of all HF cases</td>
</tr>
</tbody>
</table>

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Staging

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF</th>
<th>NYHA Functional Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At high risk for HF but without structural heart disease or symptoms of HF</td>
<td>None</td>
</tr>
<tr>
<td>B Structural heart disease but without signs or symptoms of HF</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause symptoms* of HF.</td>
</tr>
</tbody>
</table>
| C Structural heart disease with prior or current symptoms of HF | I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.  
II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.  
III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.  
IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest. |
| D Refractory HF requiring specialized interventions | IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest. |

The ACCF/AHA stages progressively worsen such that patients cannot revert to an earlier stage. NYHA functional classes can progress in either direction.


Presentation

- Ascites
- Pulmonary Edema
- Pleural Effusion
- Trouble Sleeping
- Difficulty breathing at night when recumbent
- Swelling in Feet and Ankles
- Edema and Fluid Retention
  Sudden weight gain 2-3 lbs in 24 hours
- Loss of Appetite
- Dry Cough
- Dyspnea
- Fatigue
- Exercise Intolerance

Mayo Clinic Cardiology. 2012:858-63.
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Disease Progression

- Cardiac function progressively declines after acute HF hospitalization
- Exacerbations more frequent after HF diagnosis
  - >60% readmission rate within 1 year

Mortality After Acute HF

- Atherosclerosis Risk in Communities (ARIC) Study
  - 10% Day 30
  - 22% Year 1
  - 42% Year 5

- US Acute Care Study
  - 31% 2000
  - 31% 2002
  - 30% 2004
  - 28% 2006
  - 30% 2008

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HF Hospitalization Rates by EF

<table>
<thead>
<tr>
<th>Year</th>
<th>HFrEF</th>
<th>HFPF</th>
<th>40-50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>52%</td>
<td>33%</td>
<td>15%</td>
</tr>
<tr>
<td>2006</td>
<td>51%</td>
<td>35%</td>
<td>14%</td>
</tr>
<tr>
<td>2007</td>
<td>50%</td>
<td>36%</td>
<td>14%</td>
</tr>
<tr>
<td>2008</td>
<td>51%</td>
<td>35%</td>
<td>14%</td>
</tr>
<tr>
<td>2009</td>
<td>49%</td>
<td>38%</td>
<td>13%</td>
</tr>
<tr>
<td>2010</td>
<td>47%</td>
<td>39%</td>
<td>14%</td>
</tr>
</tbody>
</table>


HF Rehospitalization Risk by Time

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Which of the following patient characteristics is associated with an increased risk of heart failure hospitalization?

a. No prior hospitalization for acute decompensated heart failure
b. Reduced N-terminal pro-B-type natriuretic peptide level
c. Presence of comorbid type 2 diabetes mellitus
d. Absence of comorbid chronic kidney disease

HF as a Complication of T2DM
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T2DM and HF Risk

Patients with T2D are **2.5x more likely** to develop HF than people without diabetes

Risk of hospitalization from heart failure was **33% higher** in patients with diabetes

The prevalence of HF in US patients with T2DM is **as high as 22%**

Even with optimal glycemic management, patients with T2D and HF have a high risk of morbidity and mortality


HF Risk by T2DM Control

<table>
<thead>
<tr>
<th>Hemoglobin A1C (%)</th>
<th>Rates of HF Hospitalization or Death per 1000 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>4.5</td>
</tr>
<tr>
<td>7 to &lt;8</td>
<td>5.8</td>
</tr>
<tr>
<td>8 to &lt;9</td>
<td>6.3</td>
</tr>
<tr>
<td>9 to &lt;10</td>
<td>8.3</td>
</tr>
<tr>
<td>≥10</td>
<td>9.2</td>
</tr>
</tbody>
</table>

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HF Risk by T2DM Control

HF risk increases linearly above an A1c 5.0%


HF Risk by T2DM and Age


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HF and T2DM Share Risk Factors

- Hypertension
- Obesity
- Dyslipidemia
- Advanced Age
- Coronary Heart Disease
- Chronic Kidney Disease

**RISK FACTORS FOR HF**

All are associated with diabetes

Risk of T2DM Complications

- MI (prior MI)
- PVD
- Stroke (prior MI)
- MI (no prior MI)
- Death
- Stroke (no prior MI)
- Pancreatitis
- End Stage Renal Disease
- Blindness


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Risk of T2DM Complications

- Initial CV event presentations of 6,137 events in T2DM cohort, %
  - PAD: 16%
  - Heart Failure: 14%
  - Nonfatal MI: 12%
  - Stroke: 10%
  - CV death: 4%

LV Dysfunction Precedes HF in T2DM

- 68% of T2DM patients had LV dysfunction (LVD) 5 years after diagnosis
- LVD was without evidence of inducible ischemia by stress testing at baseline

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Undiagnosed HF is Common in T2DM

- High risk subsets
  - BMI $\geq 30$ kg/m$^2$
  - Hypertension
  - Age $>65$ y/o
  - Female
  - Fatigue
  - Dyspnea

T2DM Patients Previously Undiagnosed with HF ($n=581$)

- HFpEF 23%
- HFrEF 5%
- No HF 72%


T2DM Worsens HF Hospitalization Risk

Risk of HF hospitalization was 33% higher in T2DM patients

- No Diabetes
  - 5.9%
- Diabetes
  - 9.4%

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**Comorbid T2DM and HF Worsens Survival**

![Graph showing survival data](image)

- Diabetes without HF
  - (n=69,083)
- Diabetes with incident HF
  - (n=46,720)

HF significantly decreased survival in T2DM patients

*P*<0.001

**T2DM Worsens Overall CV Risk**

![Graph showing cumulative incidence](image)

- T2DM increased CV morbidity and mortality, irrespective of EF

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Relative to patients without type 2 diabetes mellitus, which complication occurs most commonly?

a. End stage renal disease
b. Myocardial infarction
c. Heart failure
d. Stroke

CKD as a Complication of T2DM
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CKD is a Common T2DM Complication

- ~26% of T2DM patients have diabetic nephropathy
  - Persistent albuminuria, reduced glomerular filtration rate (GFR), or both

High CKD Prevalence Among T2DM

Prevalence of CKD is 3 times higher in T2DM

<table>
<thead>
<tr>
<th>Year</th>
<th>Without Diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1994</td>
<td>4.1</td>
<td>14.3</td>
</tr>
<tr>
<td>2011-2012</td>
<td>5.3</td>
<td>19.1</td>
</tr>
</tbody>
</table>

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CKD Progression in T2DM

Cardio-Renal T2DM Connection

Diabetes

Na⁺ Retention
Hypervolemia
RAAS activation
Neurohumoral

Activation
Inflammation
Ischemia
Altered Energetics

Consider cardio-renal systems together

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**CKD Increases HF Risk**

Higher incidence rates of HF among CKD patients

**CKD Progression Worsens CV Risk**

Reduced GFR increases risk of major adverse CV events

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Which of the following statements describing diabetic nephropathy is true?

a. Prevalence of CKD is equivalent with and without diabetes
b. Risk of HF decreases with progressive renal dysfunction
c. Proteinuria and GFR increase with the progression to ESRD
d. Decreased GFR correlates with risk for adverse CV events

Summary
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Summary

• T2DM is associated with multiple cardio-renal comorbidities, worse outcomes, and increased healthcare costs
• Both HF and T2DM prevalence are increasing
• Diabetes increases risk for HF, CVD, and CKD
• Earlier identification and management of T2DM patients at risk for HF is critical

Potential Action Items

• Evaluate type 2 diabetes mellitus (T2DM) patients for risk of cardiovascular and renal complications
• Collaborate with a multidisciplinary team of endocrinology, cardiology, and nephrology specialists early in the diabetes care continuum
• Help develop a T2DM management algorithm prioritizing antihyperglycemic agents with demonstrated cardiorenal benefits
• Optimize individual T2DM treatment plans to reduce heart failure hospitalization rates among at risk patients
• Champion discussion of diabetes as a risk equivalent for heart failure among pharmacy, nursing, and medical colleagues
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Selected Resources


Thank you for joining us

- On-demand activity coming March 2020
- Related topics in this series coming soon
  www.ashpadvantage.com/t2dheartfailure/