



SIEMENS



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# Diabetes and the Cardiorenal Syndrome

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Answers for life.

## Learning Objectives

Discuss the nature of Cardiorenal Syndrome and its pathophysiology connection with diabetes

Review the prevalence of diabetes and kidney diseases in the U.S.

Examine the latest guidelines from leading research groups on this topic

Apply learnings to Cardiorenal Syndrome case studies

## Topics Covered

<b>Overview</b>	<ul style="list-style-type: none"><li>• What is cardiorenal syndrome?</li><li>• Pathophysiology of how diabetes can impact cardiorenal syndrome</li></ul>
<b>The Stats</b>	<ul style="list-style-type: none"><li>• Diabetes in the U.S.</li><li>• Chronic kidney disease in the U.S.</li></ul>
<b>Cardiorenal Syndrome</b>	<ul style="list-style-type: none"><li>• Diabetes complications: kidney disease</li><li>• Diabetes complications: cardiovascular disease</li></ul>
<b>Guidelines</b>	<ul style="list-style-type: none"><li>• American Diabetes Association (ADA)</li><li>• American Heart Association/American College of Cardiology (AHA/ACC)</li><li>• National Kidney Foundation</li></ul>
<b>Case Studies</b>	<ul style="list-style-type: none"><li>• Utilizing what we've learned</li></ul>

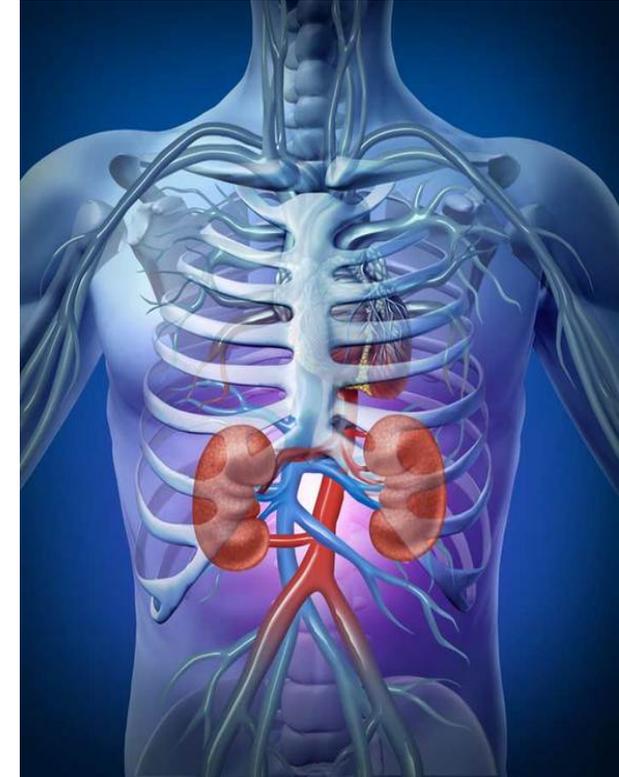
## What Is Cardiorenal Syndrome?

There are many interactions between the heart and kidney.

The interaction is **bidirectional**.

This interaction can induce acute or chronic dysfunction:

1. Heart and kidneys, or
2. In either organ

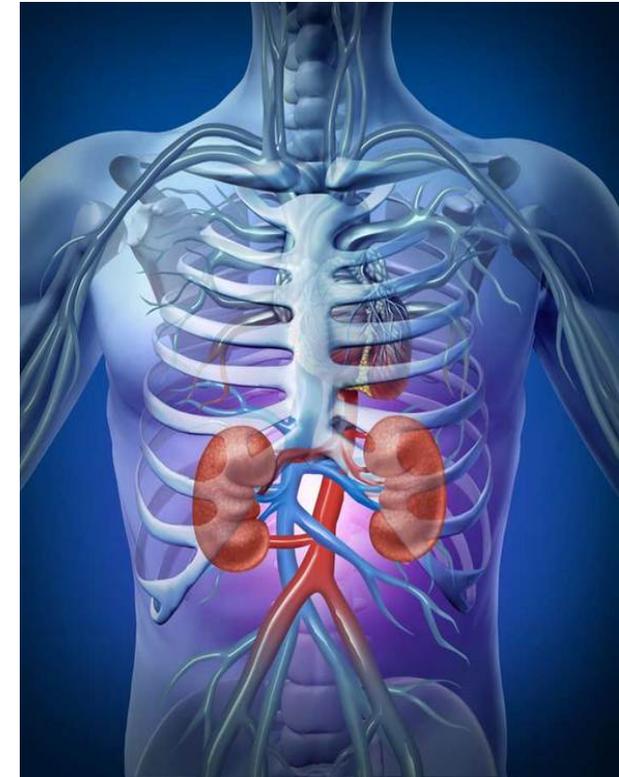


## What Is Cardiorenal Syndrome?

There are many interactions between heart disease and kidney disease.

The clinical importance of such relationships is illustrated by the following observations:

- Mortality is increased in patients with heart failure (HF) who have a reduced glomerular filtration rate (GFR).
- Patients with chronic kidney disease (CKD) have an increased risk of both atherosclerotic cardiovascular disease and heart failure.
- Acute or chronic systemic disorders can cause both cardiac and renal dysfunction.

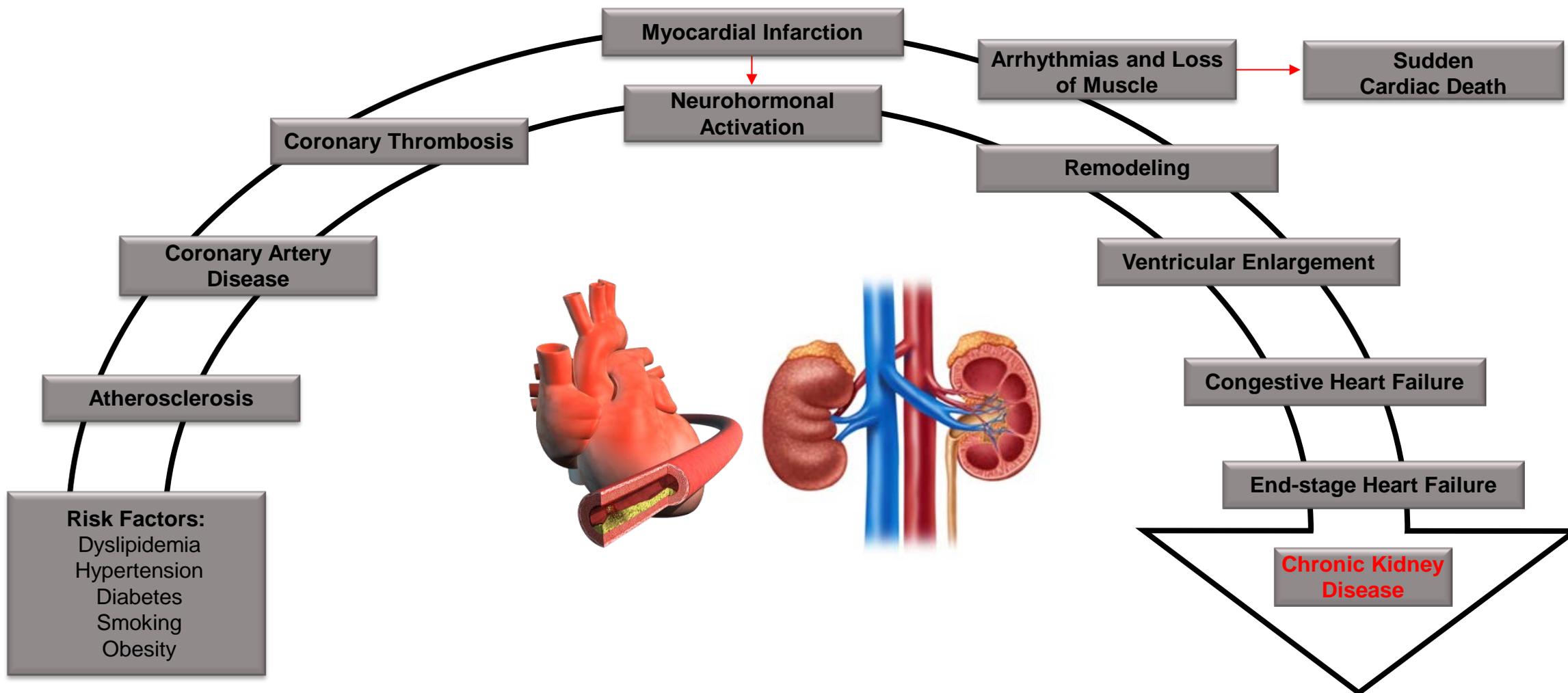


## Understanding the Five Types of Cardiorenal Syndrome

The different interactions that can occur led to the following classification of CRS that was proposed by Ronco et al.:

<b>TYPE 1</b>	Acute heart failure (HF) results in acute kidney injury (previously called acute renal failure).
<b>TYPE 2</b>	Chronic cardiac dysfunction (e.g., chronic HF) causes progressive chronic kidney disease (CKD); <i>previously called chronic renal failure</i> .
<b>TYPE 3</b>	Abrupt and primary worsening of kidney function due, for example, to renal ischemia or glomerulonephritis causes acute cardiac dysfunction, which may be manifested by HF.
<b>TYPE 4</b>	Primary CKD contributes to cardiac dysfunction, which may be manifested by coronary disease, HF, or arrhythmia.
<b>TYPE 5</b>	Acute or chronic systemic disorders (e.g., sepsis or diabetes mellitus) that cause both cardiac and renal dysfunction.

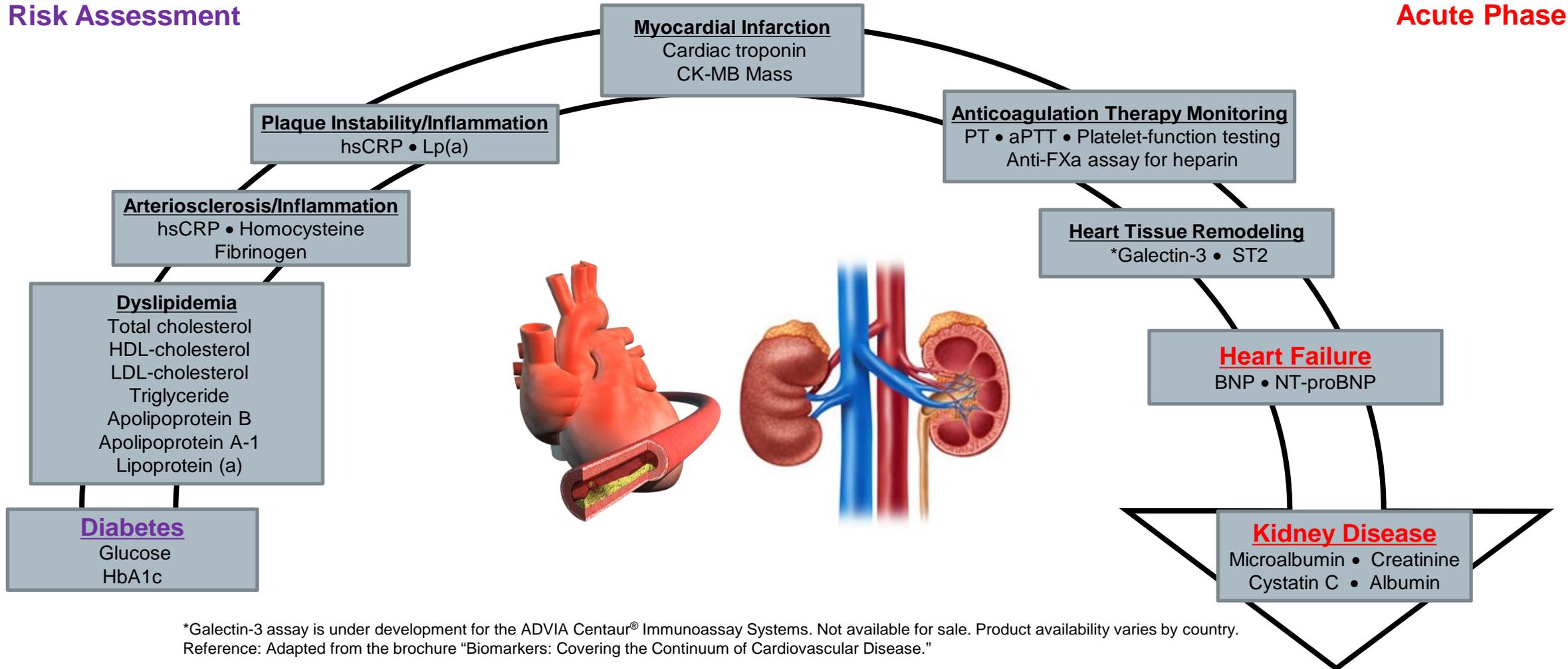
# Cardiorenal Syndrome in the Context of Cardiovascular Disease



# Cardiorenal Syndrome CVD Context: The Important Role of Laboratory Testing

## Risk Assessment

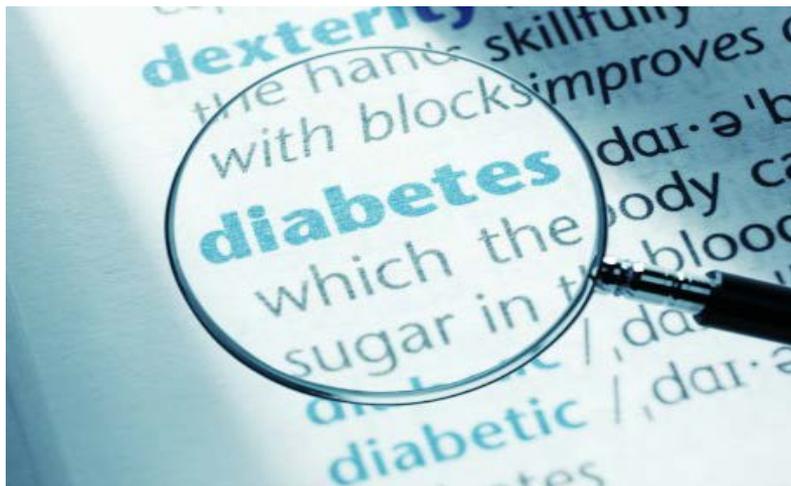
## Acute Phase



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# Diabetes Mellitus



- A metabolic disease in which the body's blood glucose levels become extremely elevated
- Develops when the body either:
  - Stops responding to insulin, or
  - Stops producing enough insulin
- Types of diabetes:
  - Type 1 and type 2
  - Gestational diabetes
  - Other (e.g., genetic defects in  $\beta$ -cell function, genetic defects in insulin action, diseases of the exocrine pancreas such as cystic fibrosis, drug- or chemically induced)

## U.S. Statistics for Diabetes Mellitus Are Staggering

# Did you know?

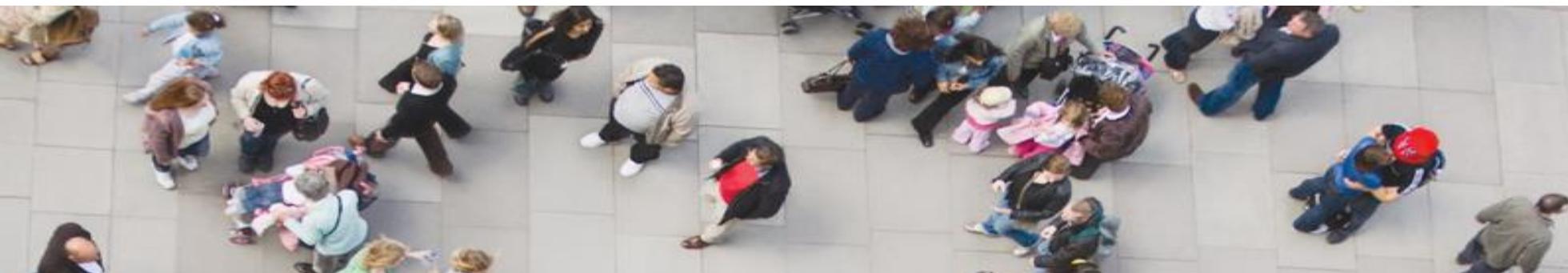
**29.1 million** people have diabetes.

...a **3.3 million increase** in  
3 years since 2011 CDC report.

**21.0 million** people diagnosed.

...and **8.1 million** people  
undiagnosed—don't know they have it.

We **spend \$245 billion** total on direct  
and indirect diabetes costs.



## Chronic Kidney Disease (CKD)

- When kidneys lose their ability to filter effectively, toxic metabolites build up and cause multi-organ damage.
- End-stage renal disease (ESRD) is very serious. A person with ESRD needs to have a kidney transplant or dialysis treatments.
- The two major forms of dialysis are hemodialysis and peritoneal dialysis.



## Mortality of Patients on Renal Replacement (Dialysis and Kidney Transplant)

- Among dialysis patients age 65 and older, **mortality is twice as high as for patients who have diabetes.**
- Rates of mortality in the prevalent population have declined nearly 25% over the last two decades and 19% since 1999.
- However, today only **50% of dialysis patients**, and 82% of those who receive a preemptive transplant, are **still alive 3 years after the start of ESRD therapy**, illustrating the extreme vulnerability of these patients when compared to the general population.

## Kidney Disease: “Kidneys Don’t Hurt”



- Patients with kidney disease do not exhibit overt symptoms.
- Physicians typically do not see signs during an exam until the disease is advanced.
- We need IVD tests to diagnose kidney disease and resolve the “silence.”

## Evidence of Kidney Disease: The Symptoms

- Changes in urination
- Swelling of extremities or face
- Fatigue
- Skin rash or itching
- Metallic taste in mouth/ammonia breath
- Nausea and vomiting
- Shortness of breath
- Feeling cold
- Dizziness and trouble concentrating
- Leg/flank pain



## Also Staggering—the U.S. Statistics for Chronic Kidney Disease

# Did you know?

**26 million Americans** have kidney disease and don't know.

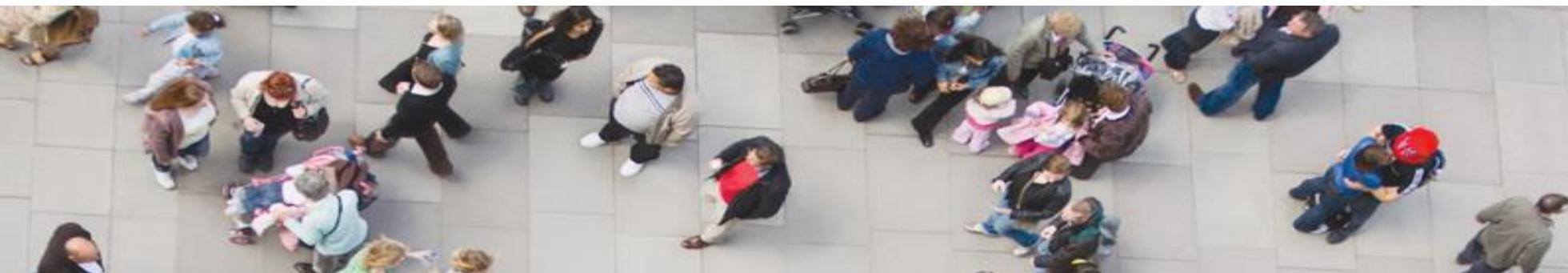
**One in three American adults** are at risk of developing kidney disease.

Medicare spending rose 5.2% in 2012 to **\$507 billion**.

**Diabetes** is listed as the primary cause of kidney failure in 44% of all new cases.

**49,677** people began treatment for kidney failure due to diabetes.

**28,924** people with kidney failure due to diabetes are **living on chronic dialysis** or with a kidney transplant.



## Learning Objectives

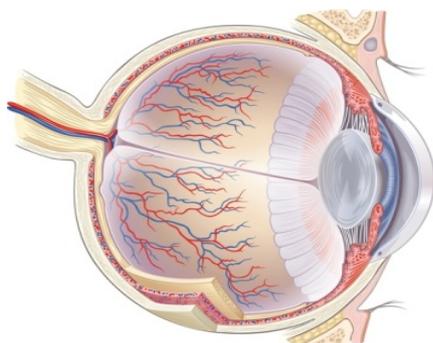
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## Overall, What Are the Potential Complications of Diabetes?

- Many diabetics already have some of the complications associated with diabetes at the time of diagnosis.
- Major organs of concern:

### Eye

Diabetic retinopathy



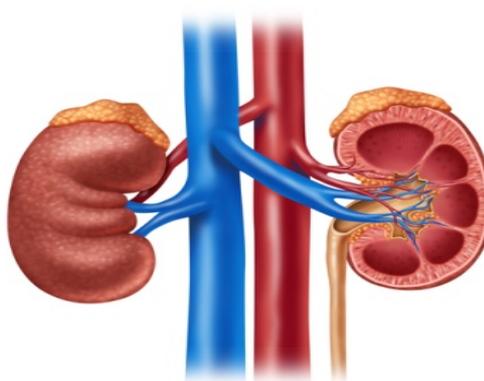
### Nerves

Diabetic neuropathy



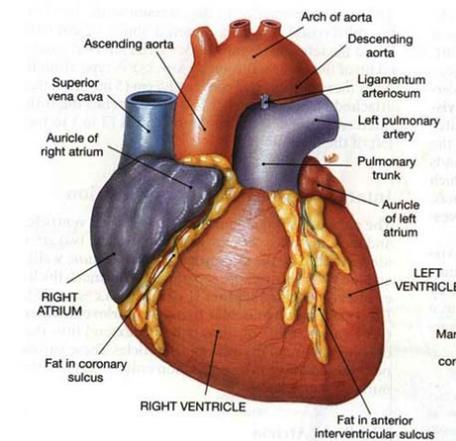
### Kidney

Diabetic nephropathy

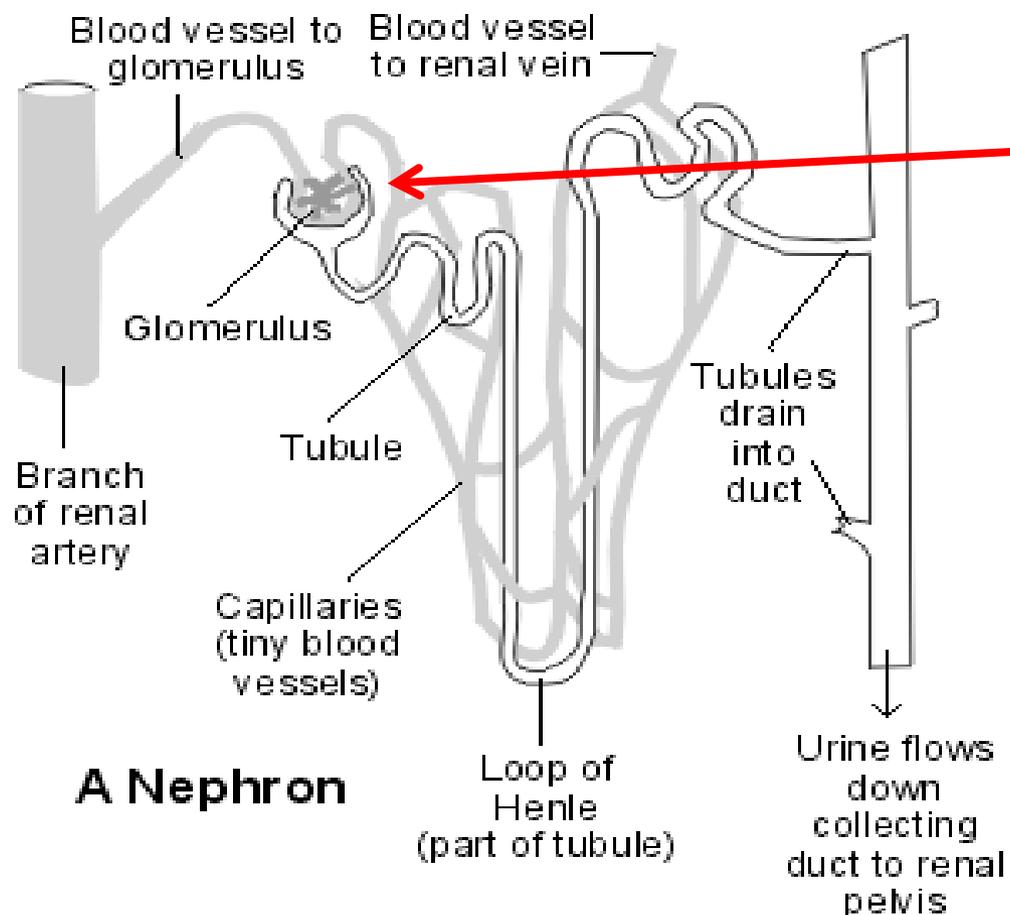


### Heart and Blood Vessels

Atherosclerosis, hypertension, cardio- and cerebrovascular disease



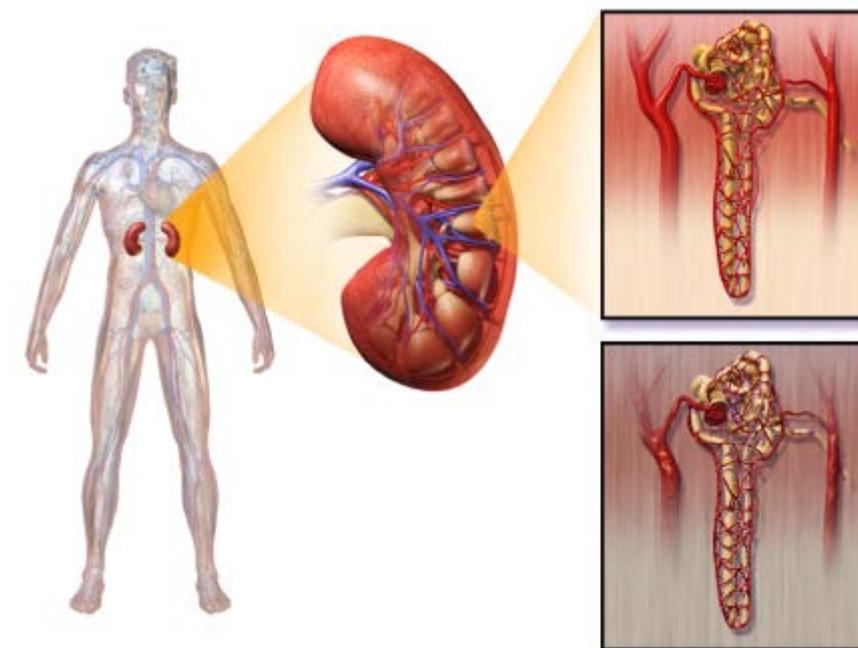
## How Does Diabetes Cause Kidney Disease?



- In high-risk groups, the **glomerulus** of the kidney is damaged, causing increased porosity, which eventually prevents them from filtering blood effectively.
- The gradual failing of kidney function results in end-stage kidney failure (ESRD).

## How Does Diabetes Cause Kidney Disease?

- Consistent hyperglycemia causes abnormal glycosylation of cellular proteins, forming advanced glycation end-products (AGEs).
- AGEs induce abnormal changes in the glomerulus, affecting kidney filtration.
- Abnormalities in extracellular proteins damaging the glomerular basement membrane and capillary loops also occur.
- Formation of oxygen radicals can further damage cells.
- Linkage of proteins in the glomeruli triggers localized scarring, preventing the kidney from effectively filtering blood.



## An Epidemic—the U.S. Statistics for CKD and Diabetes

# Did you know?

**55.1 million Americans** afflicted with CKD and diabetes.

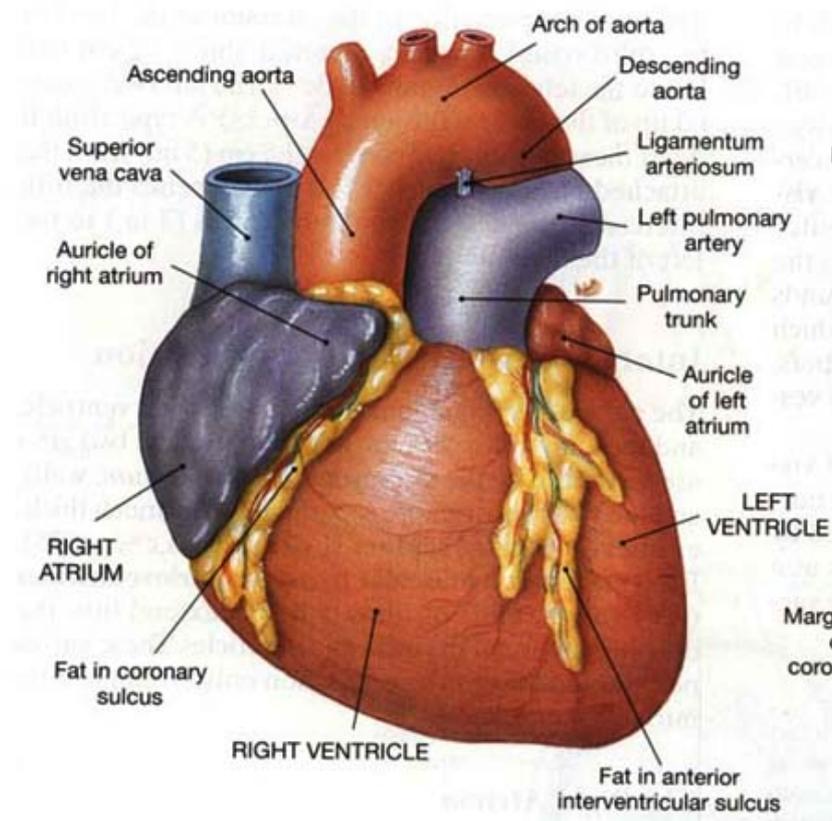
**One in three American adults** are at risk of developing kidney disease.

We spend **\$752 billion total** on CKD and diabetes, and growing annually.

**One out of three people** with Type 2 diabetes do not know they have it.



## Diabetic Complications: Heart Disease and Stroke



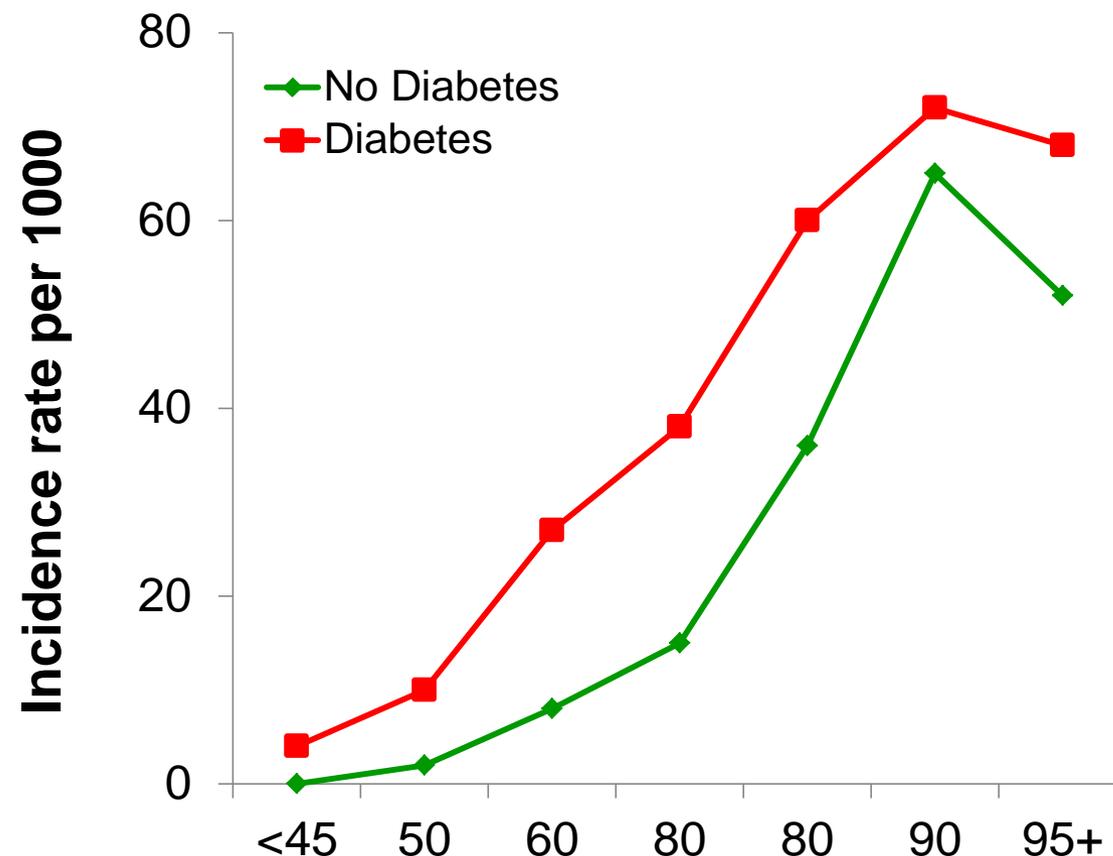
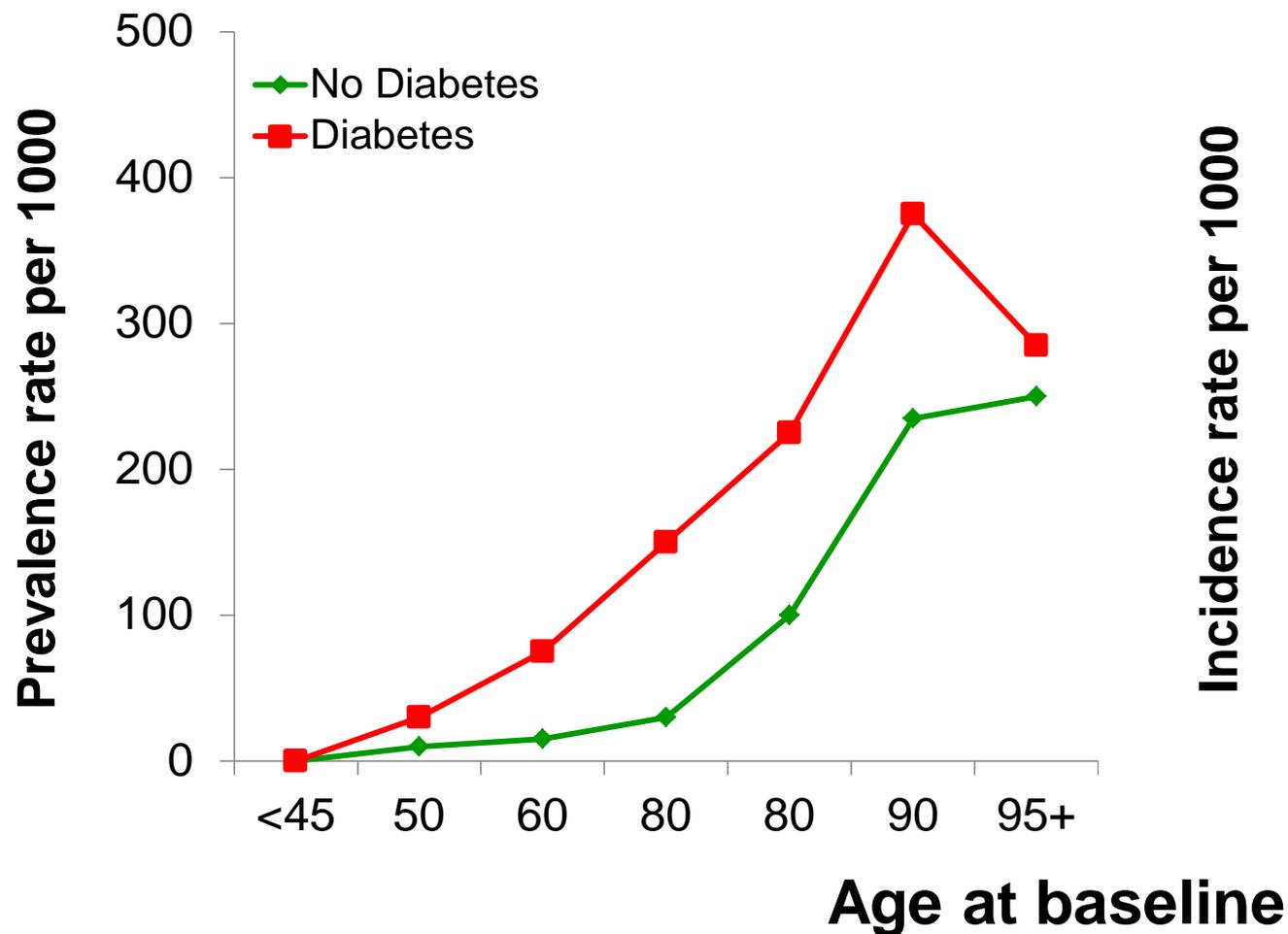
### Comparison of Diabetic to General Population

- Heart-disease death rates: **2 to 4x higher**
- Risk of stroke: **2 to 4x higher**
- 75% of diabetics treated for high blood pressure
- 68% of diabetes-related death certificates in 2004 noted heart disease for those >65 years old
- 16% of diabetes-related death certificates in 2004 noted stroke for those >65 years old

## Diabetes and Heart Failure: Current Knowledge

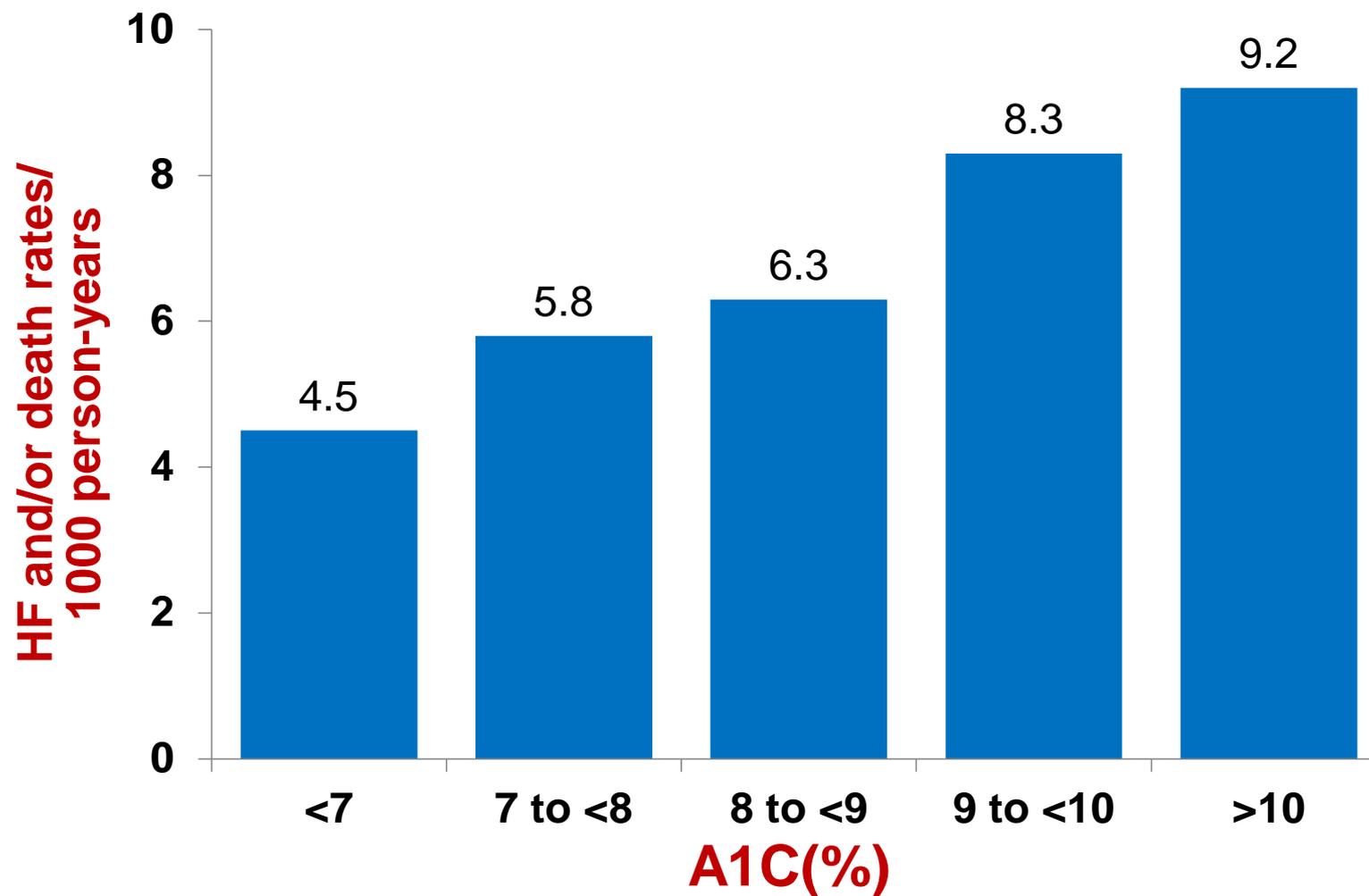
- Numerous trials (e.g., SOLVD, HOPE, and CHS) have identified diabetes as a major risk for development of heart failure.
- Diabetes can cause overt heart failure, independent of atherosclerosis or hypertension, via the development of a *diabetic cardiomyopathy*.
- There is *indirect evidence* that diabetes frequently causes abnormal heart function, even in the absence of other risk factors.
- Multiple mechanisms have been implicated in the causation of heart failure.

# Heart Failure Is More Common in Patients with Type 2 Diabetes



## Glycemic Control and Risk of Development of HF in Diabetes

HF = heart failure



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## First, Why So Many Guidelines?

### **In 2011, the Institute of Medicine (IOM) defined clinical practice guidelines:**

*“Statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.”*

### **Trustworthy guidelines should:**

- Be based on a systematic evidence review developed by a panel of multidisciplinary experts.
- Provide a clear explanation of the logical relationships between alternative care options and health outcomes.
- Provide ratings of both the quality of evidence and the strength of the recommendations.

Source: [www.nhlbi.nih.gov/guidelines/about.htm](http://www.nhlbi.nih.gov/guidelines/about.htm)

# May 2014 National Kidney Foundation KDOQI Commentary: Guidelines for the Evaluation and Management of CKD

- **Spot/untimed urine sample—early morning void.**
  - **No need for 24-hour collections**
- Tests to be performed in preferred order:
  - **Albumin:creatinine ratio (ACR)**
    - Semiquantitative results using urinalysis strip
    - Reflex quantitative
    - If ACR positive, confirm ACR  $\geq 30$  mg/g ( $\geq 3$  mg/mmol) on a random urine using an early morning collection
  - Protein:creatinine ratio (PCR)
    - *Total protein (automated reading)*
    - *Total protein (manual reading)*
- Assess GFR and albuminuria at least annually for patients with CKD and more often for those at higher risk of progression.
- Test cystatin C in adults with eGFR 45–50 mL/min/1.74 m<sup>2</sup> who do not have markers of kidney damage, if CKD confirmation is required.

## AJKD

KDOQI Commentary

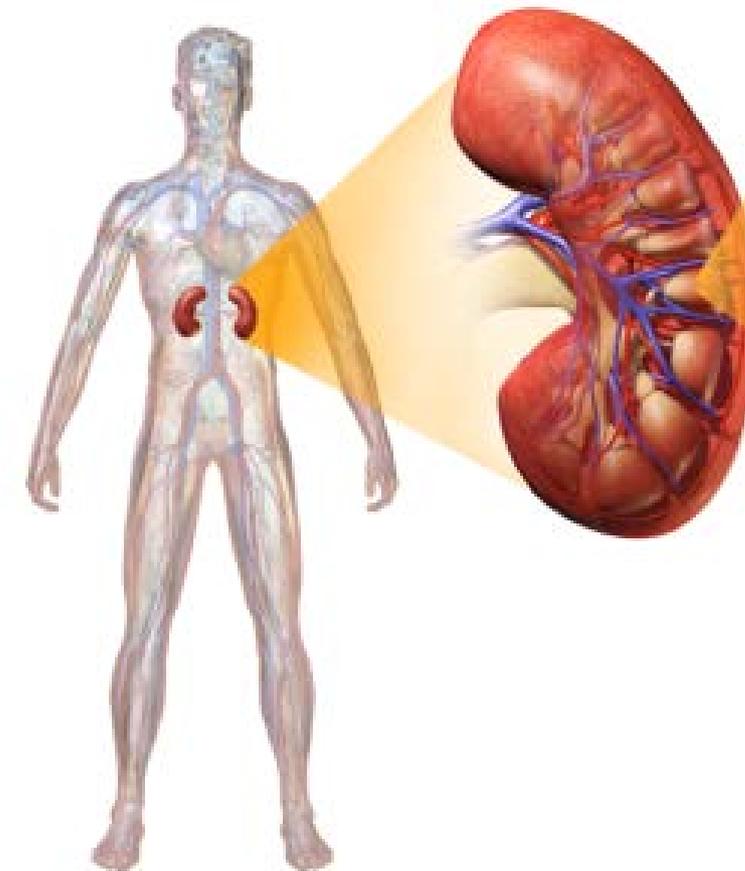
### KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD

Lesley A. Inker, MD,<sup>1</sup> Brad C. Astor, PhD,<sup>2</sup> Chester H. Fox, MD,<sup>3</sup> Tamara Isakova, MD,<sup>4</sup> James P. Lash, MD,<sup>5</sup> Carmen A. Peralta, MD,<sup>6</sup> Manjula Kurella Tamura, MD,<sup>7</sup> and Harold I. Feldman, MD, MSCE<sup>8</sup>

The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline for evaluation, classification, and stratification of chronic kidney disease (CKD) was published in 2002. The KDOQI guideline was well accepted by the medical and public health communities, but concerns and criticisms arose as new evidence became available since the publication of the original guidelines. KDIGO (Kidney Disease: Improving Global Outcomes) recently published an updated guideline to clarify the definition and classification of CKD and to update recommendations for the evaluation and management of individuals with CKD based on new evidence published since 2002. The primary recommendations were to retain the current definition of CKD based on decreased glomerular filtration rate or markers of kidney damage for 3 months or more and to include the cause of kidney disease and level of albuminuria, as well as level of glomerular filtration rate, for CKD classification. NKF-KDOQI convened a work group to write a commentary on the

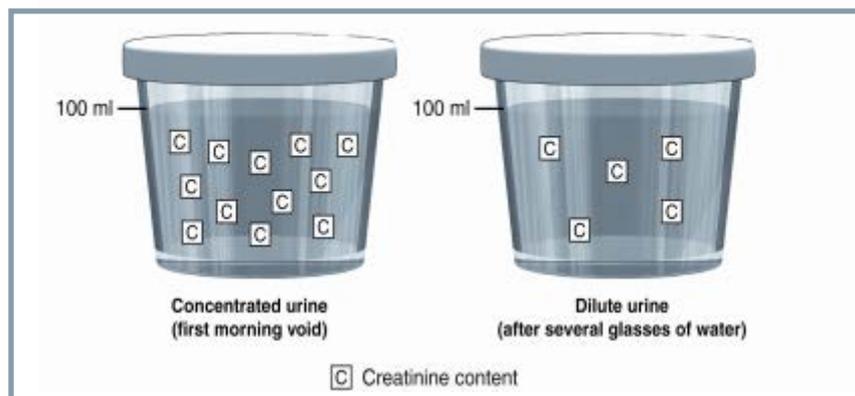
## Chronic Kidney Disease Guidelines

	<b>ROLE OF:</b>
<b>CKD</b>	Remove need for 24-hour urine collection
	Preferred urinalysis testing: ACR ratio
<b>CKD and Diabetes</b>	Microalbumin testing



## Why Is ACR Preferred over PCR and Total Protein?

- Albumin:creatinine ratio (ACR) is:
  - The most sensitive and specific measure of kidney damage
  - An accurate predictor of kidney and cardiovascular risk
  - A sound tool to show progression of CKD
  - More precise at low, diagnostically important concentrations
- There are ongoing standardization efforts; protein is difficult to standardize.
- Untimed collections are difficult to standardize; hence results could be misleading.
- **First morning void is preferred**; concentration correlates well with 24-hour excretion and has low intra-individual variability.
- Ratios utilizing creatinine account for the variability of urine albumin or protein concentrations due to urine concentration.



**Unlike albumin or protein, creatinine is excreted into urine at a constant rate.**

**Value of a ratio test: Accounts for urine concentration or dilution.**

## NKF Education on Microalbuminuria in Line with KDOQI

### Screening for Microalbuminuria in Patients with Diabetes

		Albuminuria		
GFR (mL/min)	CKD Stage*	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
>60	1 + 2	At risk <sup>†</sup>	Possible DKD	DKD
30–60	3	Unlikely DKD <sup>‡</sup>	Possible DKD	DKD
<30	4 + 5	Unlikely DKD <sup>‡</sup>	Unlikely DKD	DKD

\*Staging may be confounded by treatment because RAS blockade could render microalbuminuric patients normoalbuminuric and macroalbuminuric patients microalbuminuric. Thus, although staging is done according to the current level of albuminuria for practical reasons, the implication of the staging undoubtedly is affected by past history. Therefore, when available, data before the initiation of therapy should be considered for classification purposes.

<sup>†</sup>Because patients with diabetes often have elevated GFR in the early years after diagnosis, GFR less than 90 mL/min may represent a significant loss of function. Kidney biopsy in these patients can show histological evidence of DKD. Patients with diabetes at increased risk of DKD include those with poor glycemic control, longer duration, hypertension, retinopathy, high-normal albuminuria, nonwhite race, family history of hypertension, CVD, type 2 diabetes, and DKD.

<sup>‡</sup>Reduction in GFR in patients with diabetes and normoalbuminuria is well described in both type 1 and type 2 diabetes; kidney biopsy in such patients often shows evidence of diabetic glomerulopathy. However, in the absence of histological evidence, these patients should be considered to have diabetes and CKD, which may require further investigation.

**Abbreviations:** DKD = diabetic kidney disease; RAS = renin-angiotensin system; CVD = cardiovascular disease.

## American Diabetes Association (ADA): 2015 Diabetes Diagnostic Criteria

	Hemoglobin A1c (A1C)	Fasting Plasma Glucose Test (FPG)	2-Hour Oral Glucose Challenge
<b>Acceptable</b>	≤5.6%	Below 100 mg/dL	Below 140 mg/dL
<b>Prediabetes</b>	5.7–6.4%	100–125 mg/dL (IFG)	140–199 mg/dL (IGT)
<b>Diabetes*</b>	≥6.5%	<b>126 mg/dL or above</b>	<b>200 mg/dL or above</b>

\*Or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

Source: American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In Standards of Medical Care in Diabetes-2015. Diabetes Care. 2015;38(Suppl. 1):S8-S16.

# AHA Recommendations

Treatment Locations	WHY?	Recommended Guidelines
Hospitalized Acute	DIAGNOSIS	Should be Performed
	PROGNOSIS	
Outpatient POC	THERAPY DECISIONS	Reasonable to be Performed
	POTENTIAL USE	May be Considered to be Performed

## AHA Recommendations: Hospitalized/Acute

WHY?	Recommended Guidelines
DIAGNOSIS	<p><b>Class I (Should be Performed)</b> Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis.</p>
PROGNOSIS	<p>Measurement of BNP or NT-proBNP and/or cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF.</p>
POTENTIAL USE	<p><b>Class IIb (May be Considered to be Performed)</b> The usefulness of BNP- or NT-proBNP-guided therapy for acutely decompensated HF is not well established.</p> <p>Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with acutely decompensated HF.</p>

## AHA Recommendations: Outpatient/Point-of-care Treatment

WHY?	Recommended Guidelines
<b>DIAGNOSIS</b>	<p><b>Class I (Should be Performed)</b></p> <p>In ambulatory patients with dyspnea, measurement of BNP or NT-proBNP is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty.</p>
<b>PROGNOSIS</b>	<p>Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.</p>
<b>THERAPY DECISIONS</b>	<p><b>Class IIa (Reasonable to be Performed)</b></p> <p>BNP- or NT-proBNP-guided HF therapy can be useful to achieve optimal dosing of guideline-directed medical therapy (GDMT) in select clinically euvolemic patients followed in a well-structured HF disease management program.</p>
<b>POTENTIAL USE</b>	<p><b>Class IIb (May be Considered to be Performed)</b></p> <p>The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established.</p>
	<p>Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF.</p>

## AHA and ADA Guidelines: CVD Prevention in Type 2 Diabetes



**A1C (Hemoglobin A1C, HbA1c)**  
<7% is optimal

**Blood Pressure**  
130/80 to 140/90 mm Hg

**Cholesterol (Lipids, HDL, LDL)**  
accent shifted to management of LDL

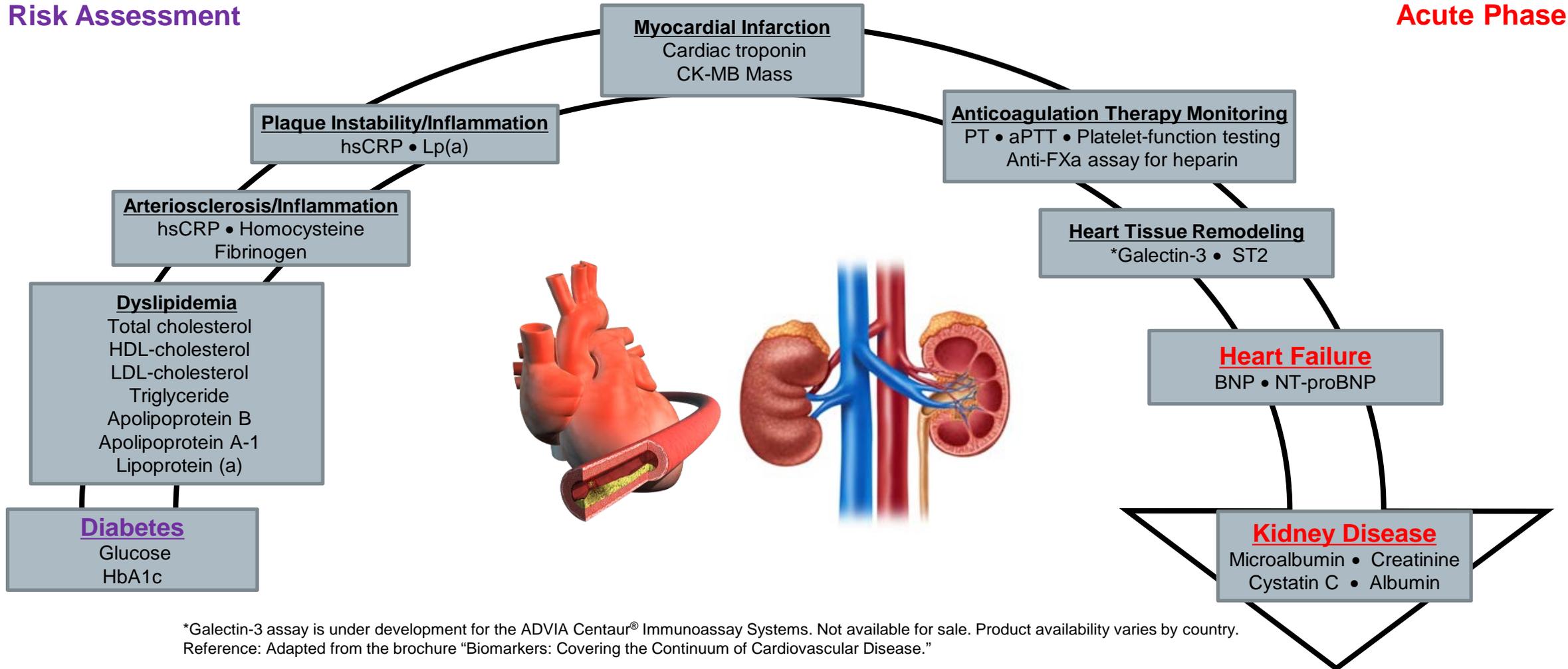
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# Cardiorenal Syndrome CVD Context: The Important Role of Laboratory Testing

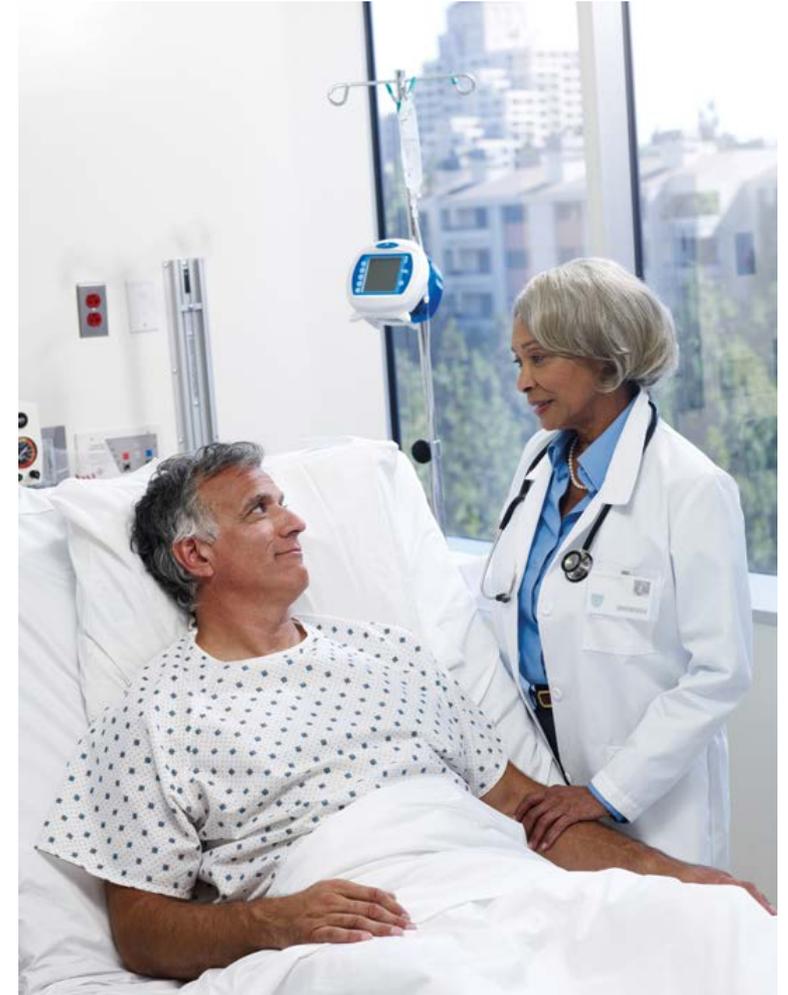
## Risk Assessment

## Acute Phase



## Case Study: In-hospital Patient

- A 58-year-old, nonsmoking, obese man presents for the treatment of heart failure.
- Past medical history includes type 2 diabetes, hypertension, and dyslipidemia. Treatment is prescribed in accordance with current conditions.
- Physical exam: blood pressure (BP) 152/92 mm Hg, P 68/min and regular, and body mass index 33.
- Jugular venous pressure is not visible. There is +1 peripheral edema.



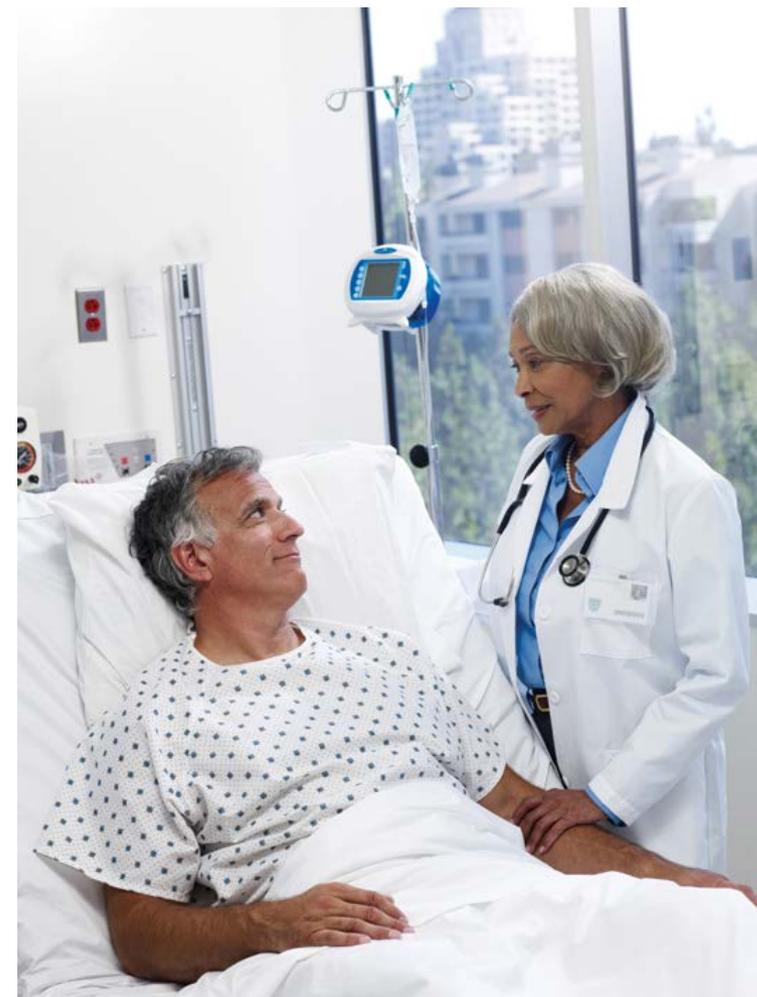
Reference: Bakris G, et al. National Kidney Foundation consensus conference on cardiovascular and kidney and disease risk: an integrated therapeutic approach to reduce events. International Society of Nephrology. 2010.

## Case Study: In-hospital Patient

### Diagnostic Testing

- HbA1c
- BNP/NT-proBNP
- Troponin for risk stratification may be considered
- Albumin:creatinine ratio (ACR)
- eGFR/creatinine/cystatin C

Reference: Bakris G, et al. National Kidney Foundation consensus conference on cardiovascular and kidney and disease risk: an integrated therapeutic approach to reduce events. International Society of Nephrology. 2010.



## Case Study: Ambulatory Geriatric Patient

### ABOUT THE PATIENT:

- 92-year-old male discharged after acute heart failure episode with CKD
- History of hypertension
- Five-part CABG 40 years in the past
- History of diabetes; no smoking or no hyperlipidemia

**What testing would you do to follow up on this patient?**



Hb**A**1c

NT-pro**B**NP

**A**CR

(Albumin, Creatinine, Albumin:Creatinine Ratio)

## Case Study: Ambulatory Geriatric Patient

**What is the goal of treatment?**

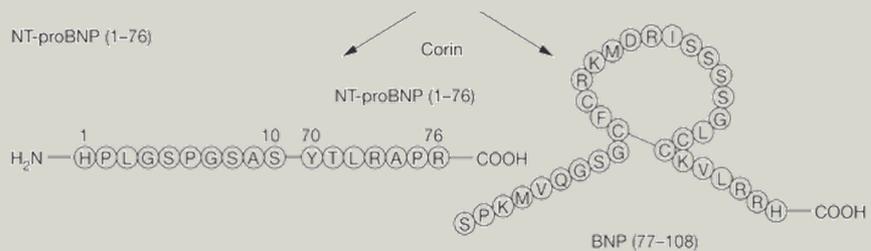
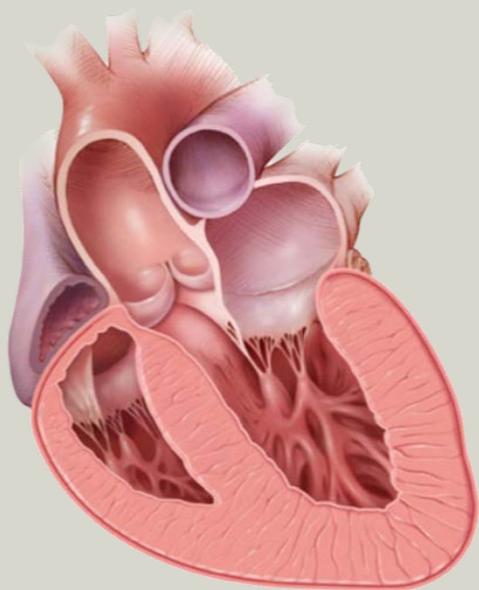
**Balance of kidneys and heart function**



## Topics We Covered

<b>Overview</b>	<ul style="list-style-type: none"><li>• What is cardiorenal syndrome?</li><li>• Pathophysiology of how diabetes can impact cardiorenal syndrome</li></ul>
<b>The Stats</b>	<ul style="list-style-type: none"><li>• Diabetes in the U.S.</li><li>• Chronic kidney disease in the U.S.</li></ul>
<b>Cardiorenal Syndrome</b>	<ul style="list-style-type: none"><li>• Diabetes complications: kidney disease</li><li>• Diabetes complications: cardiovascular disease</li></ul>
<b>Guidelines</b>	<ul style="list-style-type: none"><li>• American Diabetes Association (ADA)</li><li>• American Heart Association/American College of Cardiology (AHA/ACC)</li><li>• National Kidney Foundation</li></ul>
<b>Case Studies</b>	<ul style="list-style-type: none"><li>• Utilizing what we've learned</li></ul>

Thank You!



Q & A