ECHO Diabetes

Diabetes & Heart Failure

Overview of Consensus Report from the ADA

December 15, 2022

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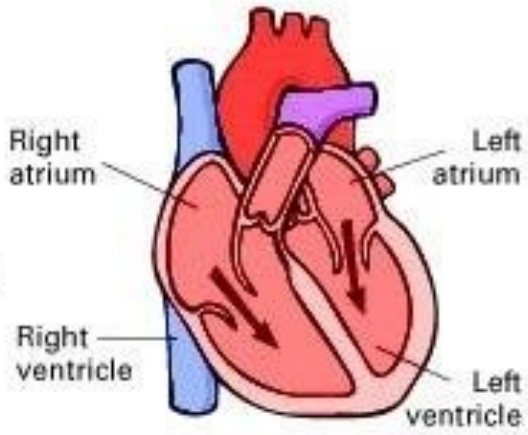
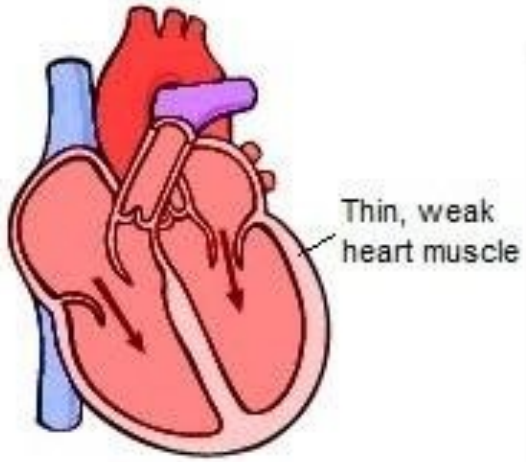
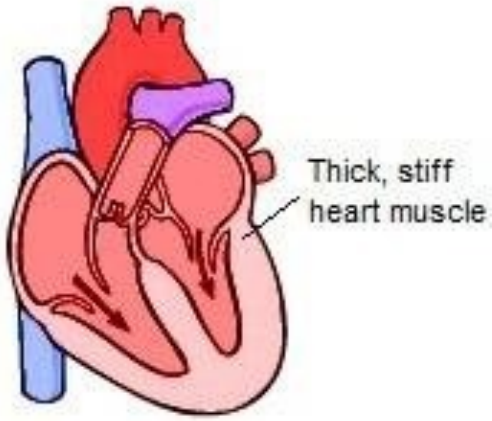
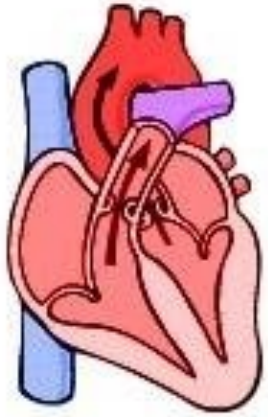
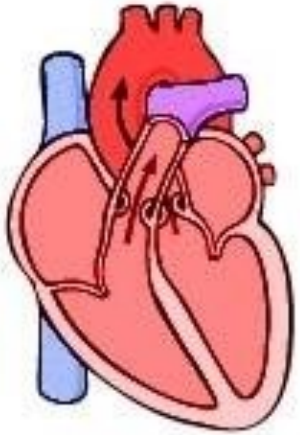
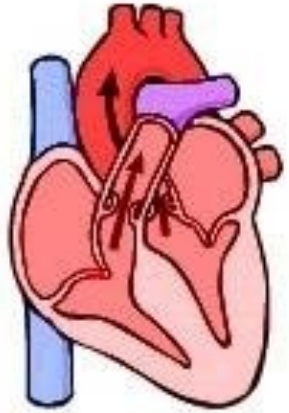
Pre-Question – which statement is accurate

- Heart failure (HF) in people with diabetes
  - Is more common in people with type 2 diabetes than in those with type 1 diabetes
  - Is more common in men than women
  - Is almost always a late complication of diabetes
  - Can progress rapidly from “pre-HF” to symptomatic HF and death

Background – Terminology

- **Ejection fraction (EF) -** describes how well the heart chambers (the left or right ventricles) can pump blood to the body to deliver oxygen and nutrients. (e.g., an EF of 65% means that *65% of the amount of blood in the left ventricle is pumped out with each contraction of the heart*.)
  - A **normal ejection fraction** ranges from ~50% to 70% (55-75%)
  - **HFrEF** - An ejection fraction below 40 percent is classified as ***heart failure with a reduced ejection fraction (HFrEF)***
    - a left ventricular EF (LVEF) between 41% and 49% is referred to as “mildly reduced” EF
  - **HFpEF** – ***heart failure with a preserved, or normal, ejection fraction (HFpEF)*** occurs when the left ventricle doesn’t relax properly (diastolic dysfunction) and holds a lower volume of blood (often because thick or stiff heart tissue effectively *shrinks ventricle size*)
    - the *proportion* of blood pumped out is normal (>50%), but the *amount* of blood pumped out isn’t enough to meet the needs of the body.

	Normal Heart	Systolic Heart Failure (HFrEF)	Diastolic Heart Failure (HFpEF)
Filling (Diastole)	 Ventricles relax and expand to fill with blood	 Enlarged ventricles fill with blood	 Thickened and stiff ventricles fill with blood less than normal
Pumping (Systole)	 Ventricles contract and pump out between 50% and 60% of the blood	 Stretched ventricles are weaker, pumping out less blood than normal	 Thickened ventricles contract normally, but have less blood to pump out

Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association

Diabetes Care 2022;45(7):1670–1690

Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association | Diabetes Care | American Diabetes Association (diabetesjournals.org)

The scope of this consensus report is to provide clear guidance to practitioners on the best approaches for screening and diagnosing HF in individuals with diabetes or prediabetes, with the goal to ensure access to optimal, evidence-based management for all and to mitigate the risks of serious complications

“Detection of people at high risk for HF (stage A) or those with stage B HF would permit earlier implementation of effective strategies to prevent or delay the progression to advanced HF in individuals with diabetes”

Improve outcomes and quality of life

Heart Failure as a Complication of Diabetes

- Traditionally, the prevention and management of chronic complications in individuals with type 1 (T1D) and type 2 (T2D) diabetes have been focused on *nephropathy, retinopathy, neuropathy, and atherosclerotic cardiovascular disease (ASCVD)* (including ischemic heart disease, stroke, and peripheral vascular disease).

However, **Heart failure (HF)**

- has been recognized as a ***common complication of diabetes***, with a prevalence of up to 22% in individuals with diabetes
  - This recognition stems in part from trials focused on cardiovascular safety of newer drugs to treat diabetes.
- represents a ***major cardiovascular complication*** in this vulnerable population - it may develop in individuals with diabetes *even in the absence of hypertension, coronary heart disease, or valvular heart disease*
- may be the ***first presentation of cardiovascular disease*** in many individuals with diabetes

Heart Failure & Diabetes

- People with ***diabetes or prediabetes*** have a **two- to fourfold increased risk of HF** compared with those without
  - T2D is an independent risk factor for incident HF and increased HF-associated morbidity and mortality
- HF may be even **more prevalent among men and women with T1D** than among those with T2D
  - Men and women with T1D have a two to five times higher incidence rate of HF hospitalization and mortality compared with those without diabetes and higher prevalence of diastolic dysfunction
- The deleterious relationship between diabetes and HF persists after adjustment for age and relevant comorbidities.
  - "Both-and" - a *longer duration of diabetes* is linked to higher risk for HF and HF is observed even in individuals with *recent-onset diabetes or younger age*.
  - Glycemic control and insulin resistance are strongly associated with risk for incident HF, suggesting a ***continuous relationship*** between ***any blood glucose abnormality and HF risk*** and HF prognosis

Diabetes and HF has a Unique Bidirectional Association

- Insulin resistance is prevalent in people with HF (found in >60% of individuals with HF and new-onset diabetes with HF)
- A heightened risk for diabetes in those with HF
  - Data indicate a high prevalence of dysglycemia in people with HF, with prevalence of
    - 20% in community-based cohorts
    - ~34% in pharmacological intervention trials for systolic HF
    - up to 47% in acute decompensated HF
    - 47–56% for Black, Hispanic, and Native American individuals with HF
  - In a study of hospitalized individuals with HF, prevalence of diabetes was ~40% among both HFrEF and HFpEF patients

Updated ADA & EASD Guidelines

As ***first-line*** therapy
Can then add metformin
And/or GLP1 RA if needed

Key Points from the Consensus Report

- Both T1D and T2D increase the risk of developing HF across the entire range of glucose levels, but HF may be more prevalent in people with T1D compared with T2D.

- There is increased incidence rate of HF among people with diabetes even after adjustment for age and comorbidities.

- HF may be the first presenting cardiovascular complication in individuals with diabetes.

Risk Factors for HF in both T2D and T1D

- Risk Factors
  - The risk factors for HF in both T2D and T1D include
    - diabetes duration
    - poor glycemic control
    - uncontrolled hypertension
    - hyperlipidemia
    - higher BMI
    - albuminuria
    - renal dysfunction
    - ischemic heart disease
    - peripheral artery disease
  - Attention to the modifiable risk factors needs to be emphasized

Pathophysiology of HF in people with Diabetes

- The pathophysiology of HF in individuals with diabetes is complex
  - reflects the interactions of multiple risk factors acting in concert with dysregulated subcellular pathways that extend beyond the consequences of diabetes-associated hyperglycemia, all leading to functional and structural changes in the diabetic heart

- For HFrEF - predominant mechanisms can be direct myocardial injury due to associated CAD or hypertension *(weak heart muscle)*
- For HFpEF – mechanisms likely include endothelial and microvascular dysfunction → left ventricular stiffness *(limited volume)*

- There are shared HF mechanisms between T1D and T2D - these include:
  - **cardiovascular autonomic neuropathy** - associated with impaired left ventricle diastolic relaxation in both people with T2D and people with T1D
  - **coronary microvascular dysfunction -** associated with functional and/or structural abnormalities of the coronary microvasculature resulting in myocardial perfusion impairment

“Diabetic cardiomyopathy”
direct effects of diabetes on the heart muscle

- Defined as - ***ventricular dysfunction in the absence of coronary artery disease (CAD) and hypertension***
  - Several potential mechanisms contribute to the development of HF in diabetes:
    - renin-angiotensin-aldosterone system (RAAS) activation
    - mitochondrial dysfunction
    - oxidative stress
    - inflammation
    - changes in intracellular calcium homeostasis
    - increased formation of advanced glycation end products
    - myocardial energy substrate alterations resulting in decreased cardiac efficiency
      - derangements in myocardial lipid and glucose metabolism (***“Bioenergetic failure”)*** are increasingly recognized as an early event in the deterioration of diabetes-related cardiac function → maladaptive fibrosis, microvascular rarefaction, lipotoxicity, and decreased nitric oxide availability, leading to further cardiovascular dysfunction.

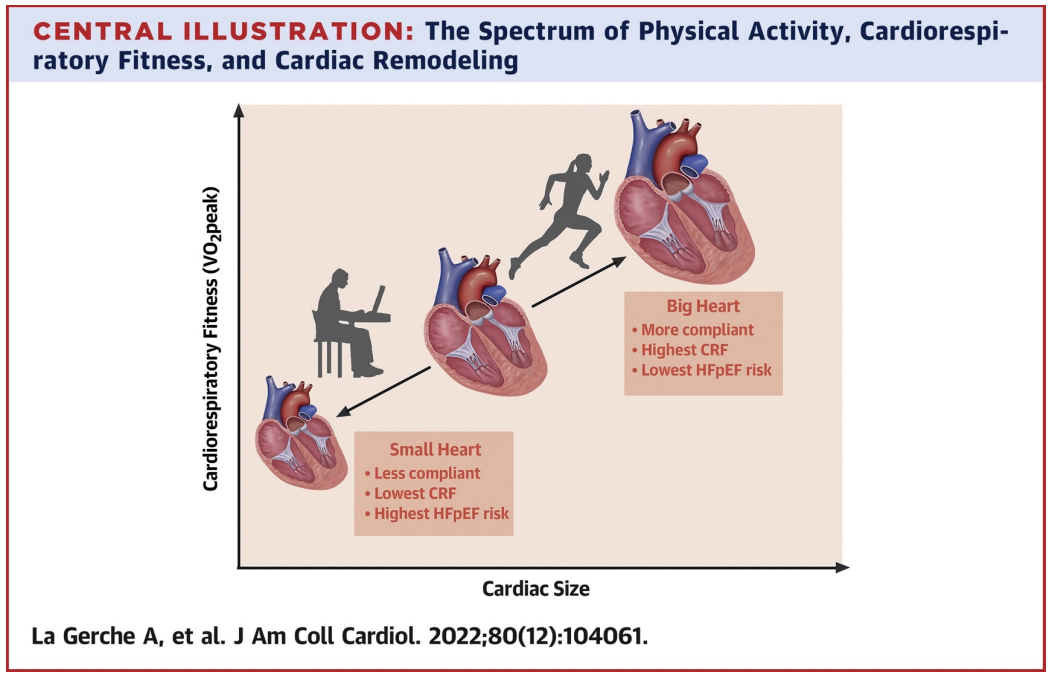
Increased Risk of Diabetic Cardiomyopathy & HF in Women with Diabetes

- Compared to men with diabetes, evidence shows that women with diabetes exhibit greater
  - endothelial abnormalities
  - coronary microvascular abnormalities
  - diastolic abnormalities

- Underlying mechanisms for the increased risk of HF in women with diabetes are not entirely clear, but sex hormones, a different spectrum of cardiovascular risk factors, and/or differences in prescription patterns between men and women may play a role

Exercise deficiency is a major risk factor for HFpEF

- Chronic lack of exercise — dubbed ***"exercise deficiency"*** — is associated with cardiac atrophy, reduced cardiac output and chamber size, and diminished cardiorespiratory fitness (CRF) in a *subgroup* of patients with heart failure with preserved ejection fraction (HFpEF)
  - Increasing physical activity is associated with greater cardiac mass, stroke volumes, cardiac output, and peak oxygen consumption



Key Points from the Consensus Report

- Individuals with diabetes may develop “diabetic cardiomyopathy,” defined as left ventricular systolic or diastolic dysfunction in the absence of other causes (such as CAD or hypertension), with excess risk in women.

- Both HFpEF and HFrEF may be present in diabetes.

- The pathophysiology of HF in individuals with diabetes reflects complex interactions between numerous pathways with deleterious effects on myocardial remodeling and muscle function.

From: **Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association**

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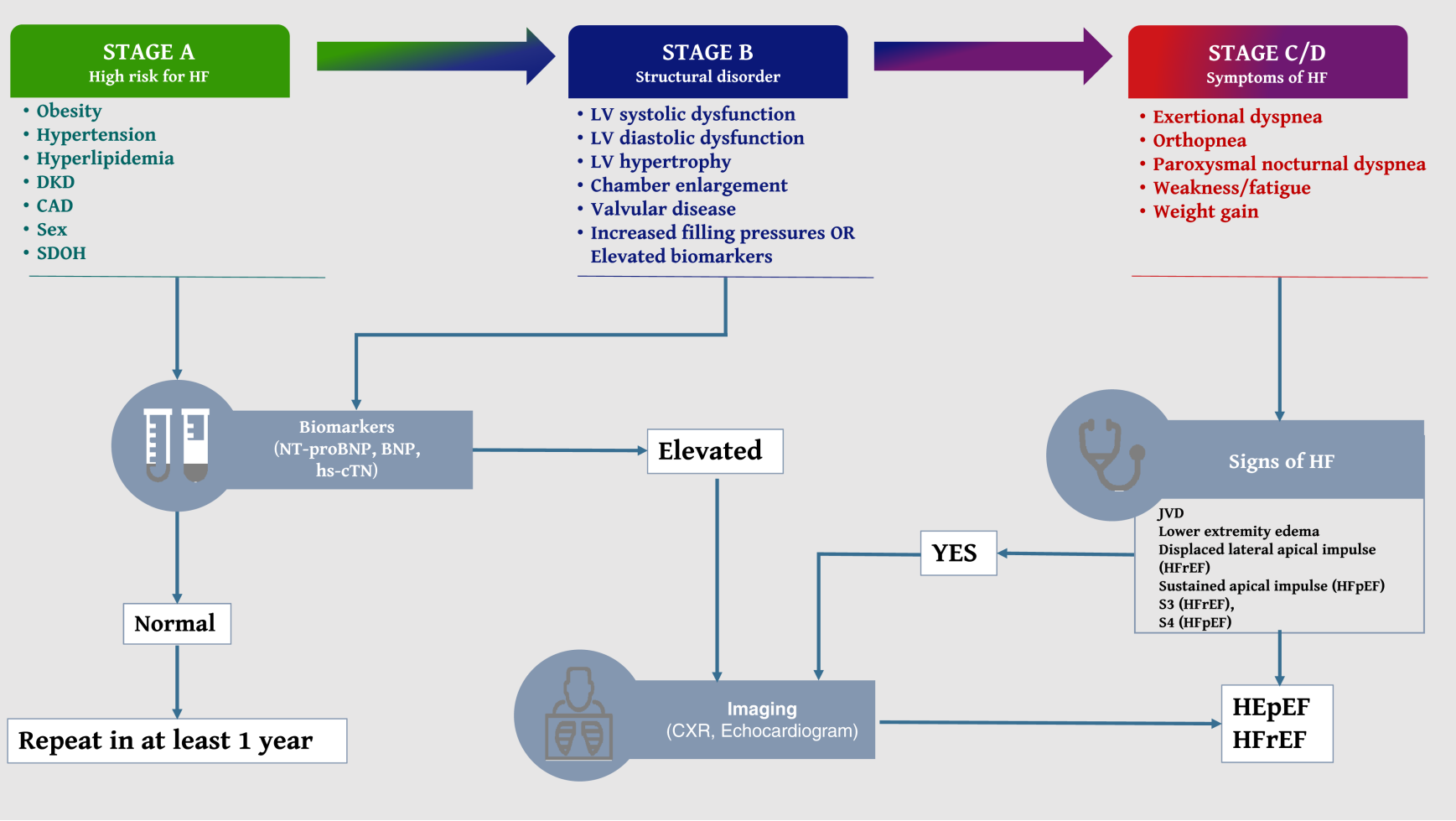
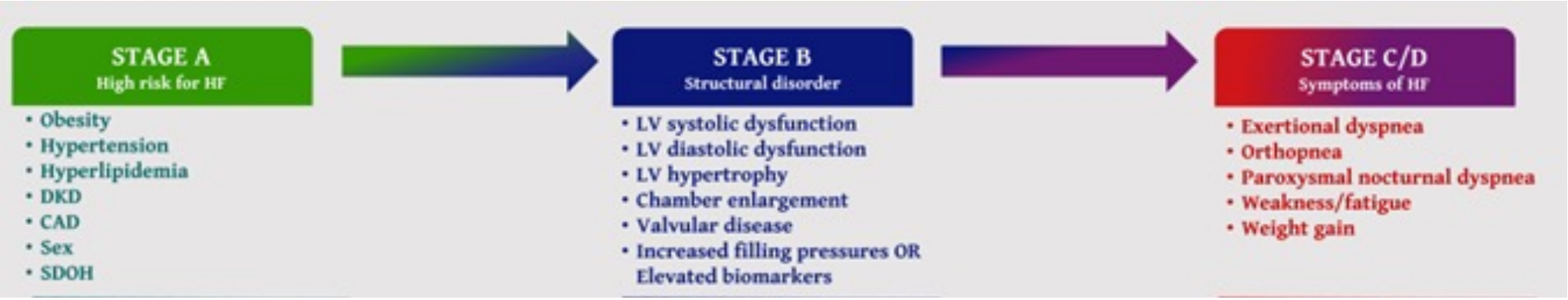


Figure Legend:

Stepwise approach for screening and diagnosis across HF stages. CXR, chest X-ray; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-cTN, high-sensitivity cardiac troponin; JVD, jugular vein distension; LV, left ventricle.

Diagnosis and Clinical Stages

- HF represents a *continuum* of cardiac structural abnormality and dysfunction and associated cardiovascular risk



Stage A: Individuals at risk for HF

- The presence of established diabetes indicates that an individual is at risk for HF, and these patients should be considered in the stage A category and at heightened risk for progression to later stages of HF.
  - In this stage, the achieved control of glycemia and other risk factors may modify (or instead amplify) risk for clinical HF.

- Key Points - Anyone with a diagnosis of diabetes and the listed risk factors is in the stage A category of HF.

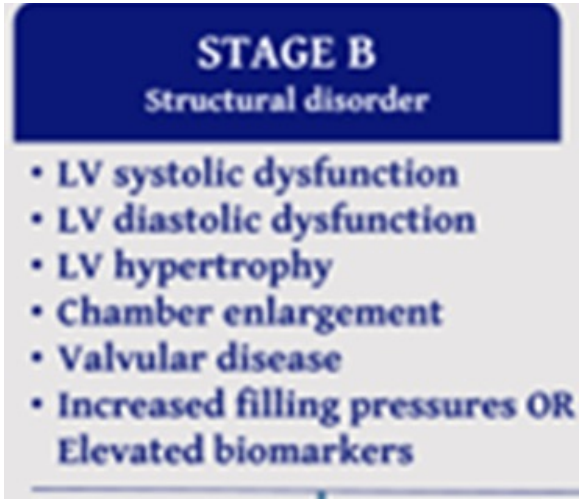
Stage B: Pre-HF/Early Detection

- Stage B includes *asymptomatic* individuals with at least one of the following:

  1) evidence of structural heart disease

  2) abnormal cardiac function

  3) elevated natriuretic peptide levels or elevated cardiac troponin levels



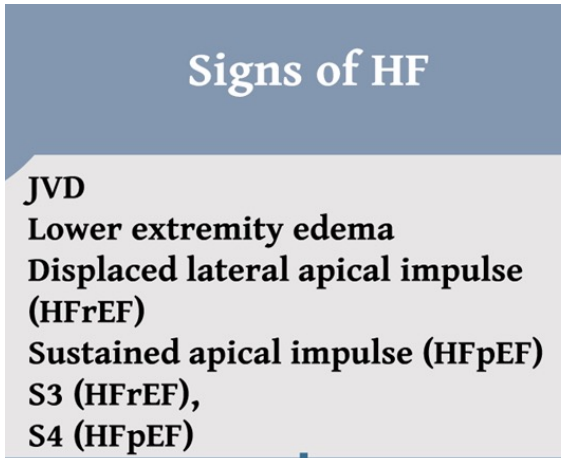
- Stage B HF is linked to
  - increased risks of cardiovascular and all-cause mortality
  - progression to more advanced stages of overt HF
  - may be referred to as ***"pre-HF."***
  - *can progress rapidly to symptoms & death*

Many individuals with diabetes can be classified in stage B

Stages C & D: Symptomatic HF in Individuals With Diabetes

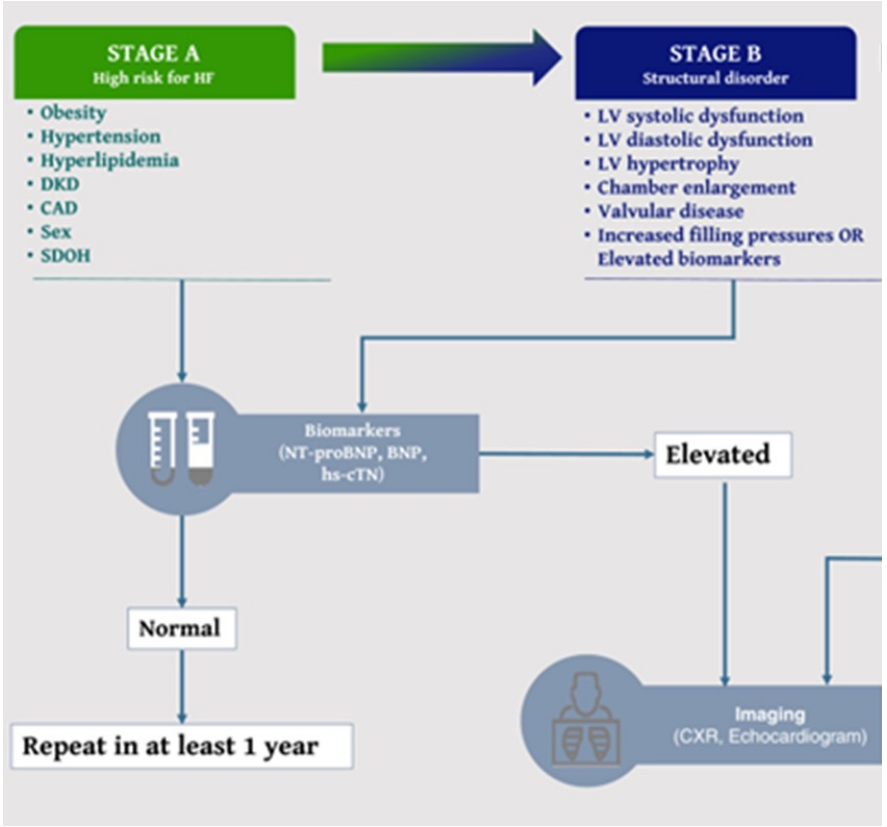
- Stages C – symptomatic HF with prior or current symptoms
- Stage D – advanced HF (refractory – end stage)

- Symptoms & Signs of HF:
  - key for making a clinical diagnosis of HF
  - reflect fluid retention and congestion, or low cardiac output.
  - individuals with HFpEF present with symptoms similar to those of individuals with HFrEF, most commonly
    - exertional dyspnea
    - fatigue
    - edema



Recommendations for Detection of Subclinical HF in Individuals With Diabetes

- Among individuals with diabetes, measurement of a natriuretic peptide or high-sensitivity cardiac troponin is recommended on at least a yearly basis to identify the earliest HF stages and implement strategies to prevent transition to symptomatic HF.



This recommendation is based on data indicating:

- the ability of these biomarkers **to identify those in stage A or B at highest risk of progressing to symptomatic HF or death**
- evidence that **the risk in such individuals may be lowered** through targeted intervention or multidisciplinary care
    - More intensive interventions in those with higher levels of natriuretic peptide **reduce risk for LV dysfunction, newly diagnosed HF, or HF hospitalization**

Recommendations for Detection of Subclinical HF in Individuals With Diabetes

- Based on aggregate population and clinical trial data, the biomarker thresholds for clinical use include
  - BNP ≥50 pg/mL and
  - NT-proBNP ≥125 pg/mL
  - high-sensitivity cardiac troponin a value >99th percentile for a healthy patient population (the usual upper reference limit for high-sensitivity assays).

- One natriuretic peptide or troponin measurement may provide important prognostic insights - *serial* measurements to detect rising values increase sensitivity for identifying those at highest risk for incident HF
  - As an example, in individuals with T2D in the EXAMINE trial, *two NT-proBNP* measurements spaced *6 months apart* were able to identify those at
    - highest risk (both elevated)
    - rising risk (baseline low, follow-up higher)
    - lower risk (6-month measurement lower)

Key Points from the Consensus Report

- Many people with diabetes have stage B HF, defined as asymptomatic with at least one of the following: 1) evidence of structural heart disease, 2) abnormal cardiac function, or 3) elevated natriuretic peptide levels or elevated cardiac troponin levels.

- Early diagnosis of HF could enable targeted treatment to prevent adverse outcomes.

- Measurement of a natriuretic peptide or high-sensitivity cardiac troponin on at least a yearly basis is recommended to identify the presence of stage B HF and to determine risk for progression to symptomatic HF.

- Useful cutoff values for BNP (50 pg/mL), NT-proBNP (125 pg/mL), or high sensitivity cardiac troponin (>99th percentile upper reference limit) to determine HF risk are based on population-based data and/or clinical trials.

- The identification of an abnormal natriuretic peptide or high-sensitivity cardiac troponin should be part of individualized management decision plans.

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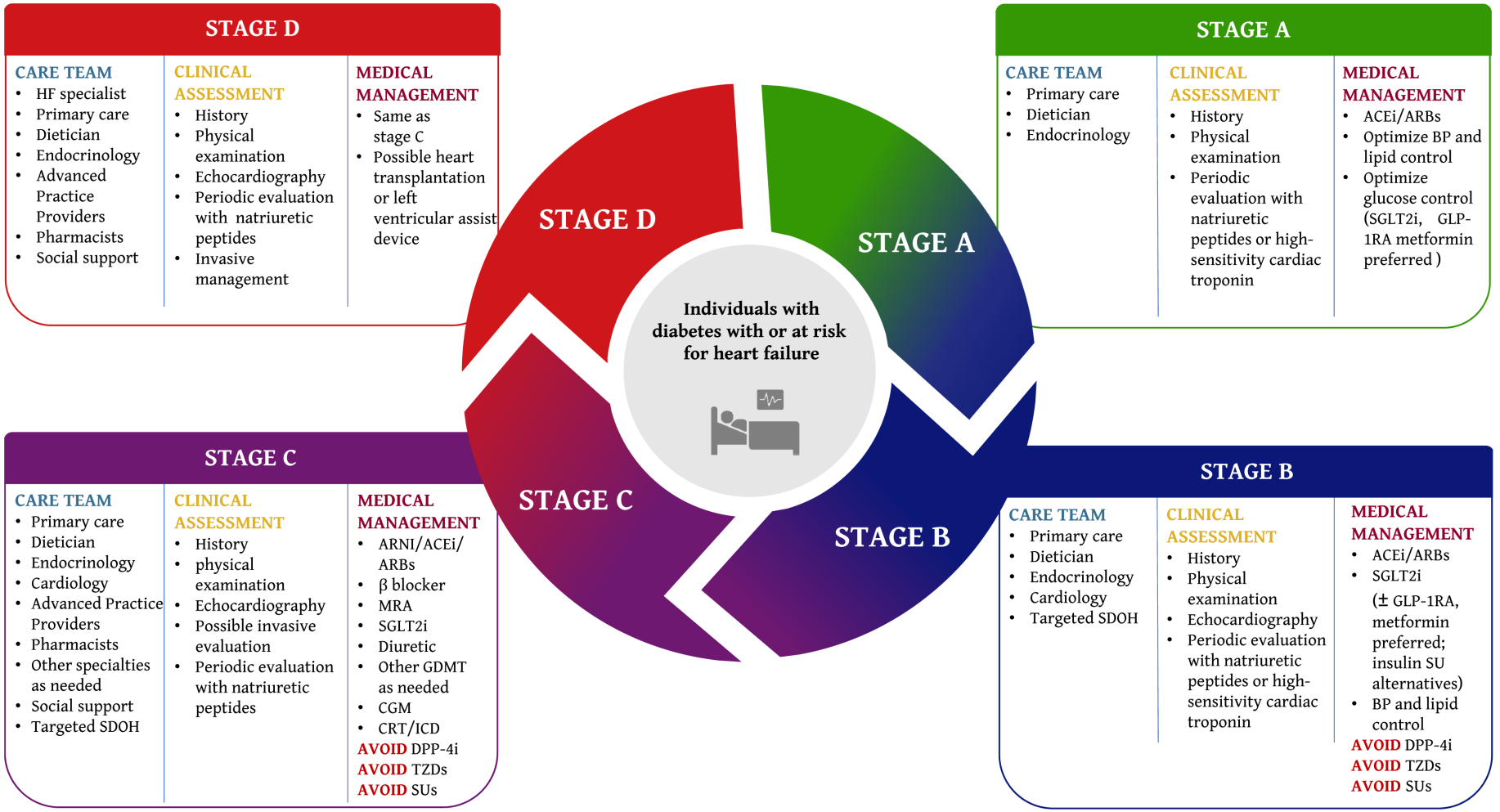

Figure Legend:

Multidisciplinary personalized care for in individuals with HF and diabetes. DPP-4i, DPP-4 inhibitors; SUs, sulfonylureas.

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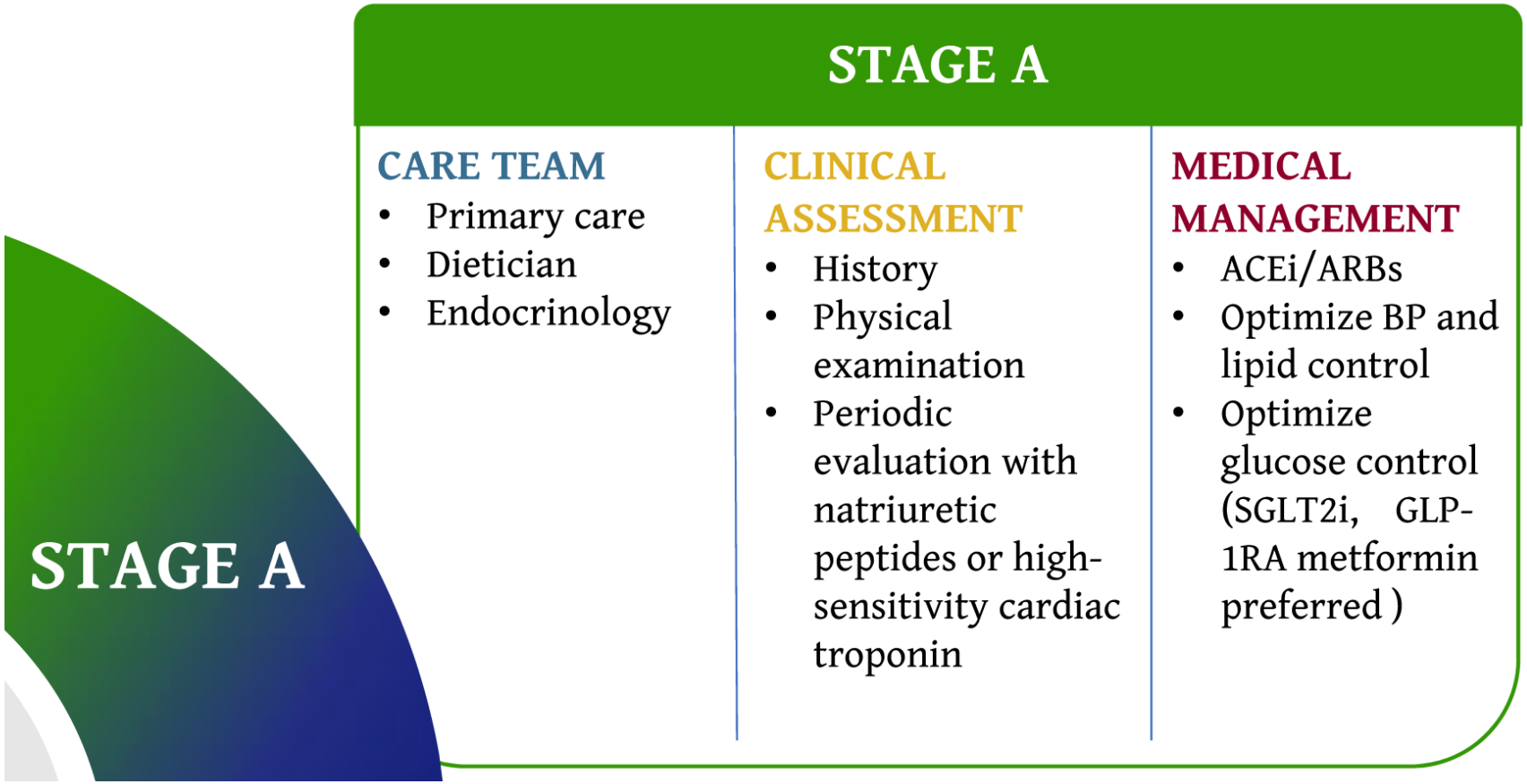

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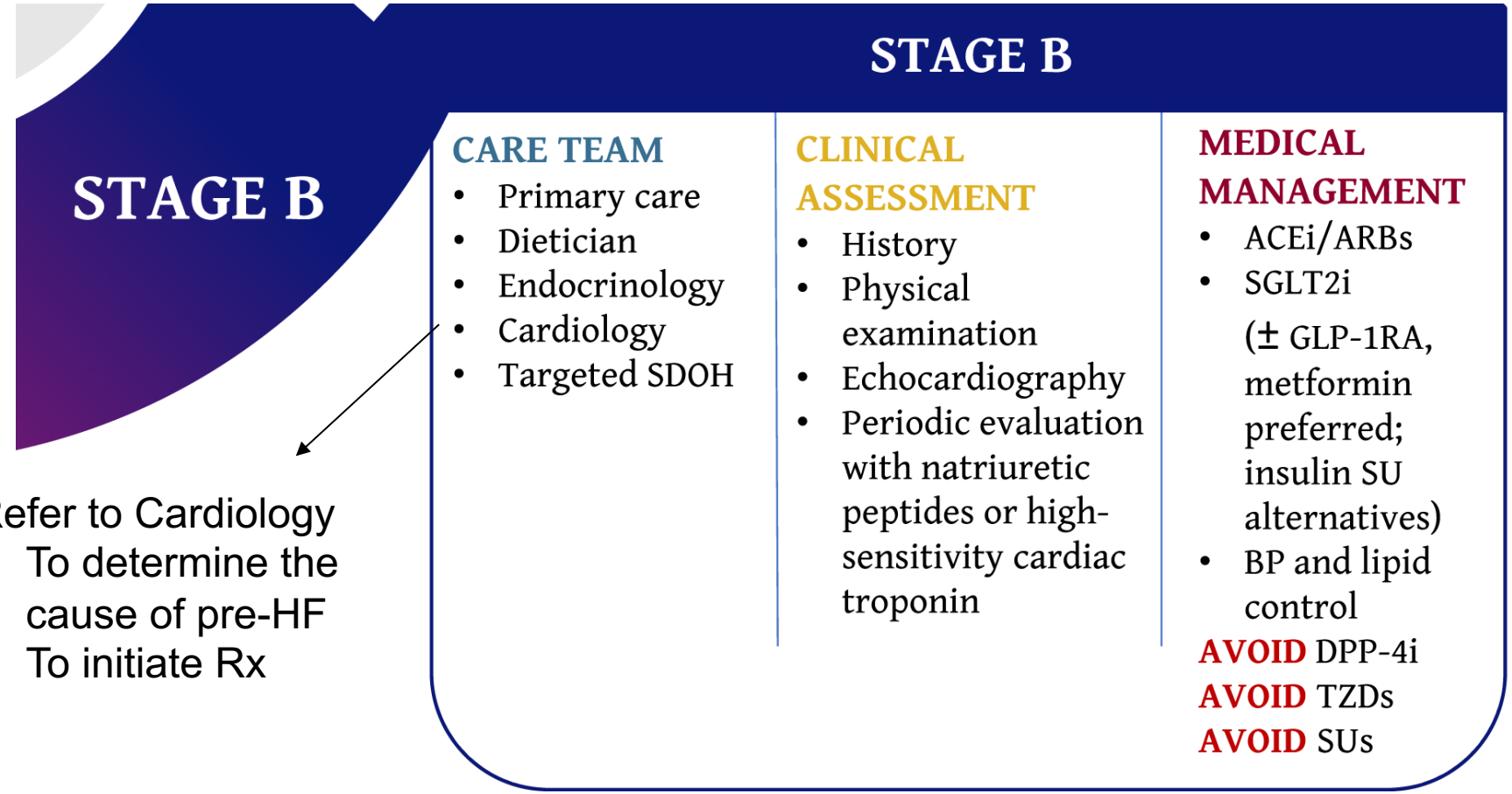

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Multidisciplinary personalized care for in individuals with HF and diabetes. DPP-4i, DPP-4 inhibitors; SUs, sulfonylureas.

Summary – Heart Failure (HF) in People with Diabetes

- HF is more common and higher risk (for poor outcomes) in people with diabetes – and diabetes is more common in people with HF
- HF is more common in women than men with diabetes
- HF is more common in people with T1D than T2D
- HF can be an early complication of diabetes
- HF can occur without CAD or HTN – i.e., as a direct effect of diabetes on the heart muscle (“diabetic cardiomyopathy”)
- Anyone with diabetes is at risk for HF – the more additional risk factors, the higher the risk
- ADA & ACC recommend use of biomarkers to help stratify risk in patients with stage A (at risk) and B (pre-HF) status
- Early intervention can improve outcomes
  - Attention to how you manage the diabetes – preferred meds/ meds to avoid

Post-Question – which statement is accurate

- Heart failure (HF) in people with diabetes
  - Is more common in people with type 2 diabetes than in those with type 1 diabetes
  - Is more common in men than women
  - Is almost always a late complication of diabetes
  - Can progress rapidly from “pre-HF” to symptomatic HF and death

Extra Slides

HFpEF vs Diastolic Dysfunction

- Heart failure with preserved ejection fraction (HFpEF) occurs when the left ventricle is not able to fill properly with blood during the diastolic (filling) phase. The amount of blood pumped out to the body is less than normal. It is also called diastolic heart failure.
  - Heart failure is a clinical syndrome characterized by symptoms and signs of increased tissue/organ water and decreased tissue/organ perfusion.
  - When heart failure is accompanied by a predominant or isolated abnormality in diastolic function, this clinical syndrome is called diastolic heart failure.

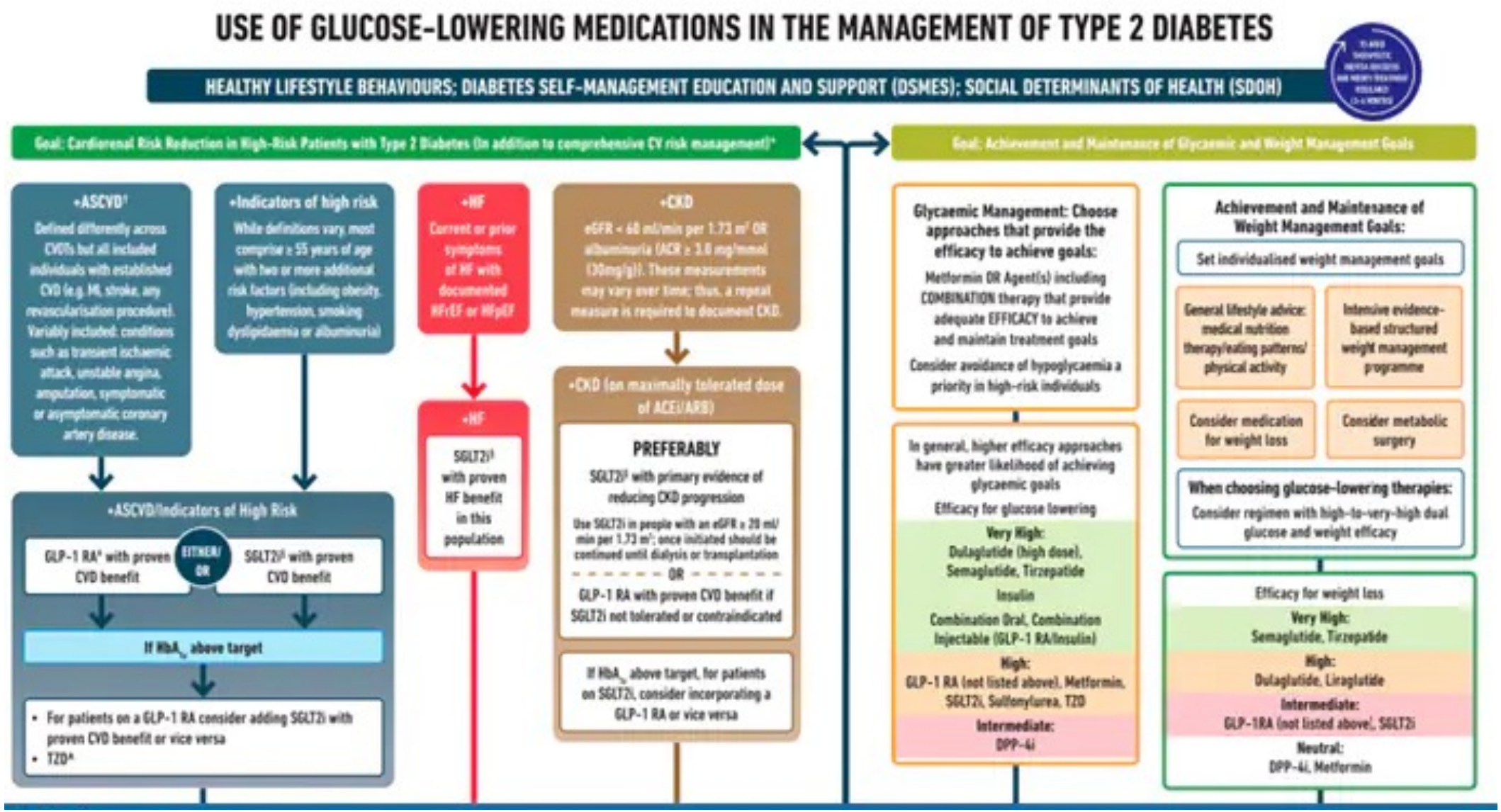
- Patients without signs and symptoms of HF but who have evidence of diastolic dysfunction on echocardiography do not meet the criteria for HFpEF.
  - Diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole. Abnormalities in diastolic function can occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal systolic function. Therefore, whereas diastolic dysfunction describes an abnormal mechanical property, diastolic heart failure describes a clinical syndrome.

Impact of adding annual biomarker testing

- Biomarker testing itself is not medically harmful, there is the potential for cascade testing following recognition of an abnormal result to increase costs and complexity of existing diabetes care recommendations.
  - However, a substantial gap in diagnosis and treatment of HF exists and the preponderance of accumulating evidence suggests that detection of a signal of HF risk would increase intervention with treatments to reduce the potential for development of symptomatic HF.
  - It is therefore impossible to understate the importance of early recognition of HF at a time when intervention might be expected to be even more impactful
- Normal BNP and NT-proBNP levels have **high negative predictive value**, and thus can be used to exclude a diagnosis of HF & such a finding would preclude pursuing further diagnostics or treatment.
- An abnormal natriuretic peptide or high-sensitivity cardiac troponin result should be individualized to the patient but might include
  - further diagnostic studies,
  - *avoidance of treatments that might increase HF risk (TZDs, DPP4 inhibitors, Sulfonyl Ureas)*
  - introduction of therapies with proven usefulness to prevent HF in this vulnerable population.
- While no precedent data exist to suggest specific populations of those with diabetes more likely to benefit from testing of natriuretic peptides or high-sensitivity cardiac troponins, certain ***higher-risk populations*** such as those with long-standing diabetes, CKD, or microalbuminuria are particularly likely to be a group with a higher yield from testing

Use of Biomarkers – confounding issues

- Using biomarkers to identify and in turn reduce risk for HF should always be done within the context of a thoughtful clinical evaluation, supported by all information available, and with an understanding regarding the known confounders that may reduce reliability of testing for natriuretic peptides or troponin.
  - Increased levels of natriuretic peptide with atrial fibrillation
  - Increased levels of natriuretic peptide levels can be associated with several *noncardiac causes*, including
    - advanced age, anemia, renal failure, obstructive sleep apnea, pulmonary hypertension, critical illness, and sepsis, as well as severe burns
    - The diagnostic accuracy of natriuretic peptides appears to be unaffected by the presence of diabetes.
    - Diagnostic evaluation for HIV, rheumatological diseases, amyloidosis, or pheochromocytoma may be indicated if there is high clinical suspicion
  - obesity may *lower natriuretic peptide concentrations* even in the presence of significant HF risk.



ADA and EASD – updated standards for management of hyperglycemia 2022

Cardiac Imaging for Elevated Biomarker &/or Clinical HF

- Chest X-ray
  - A chest X-ray may be used to assess heart size and pulmonary congestion and evaluate for alternative causes of dyspnea.
  - Cardiomegaly and pulmonary redistribution are among the most commonly observed findings in individuals with HF
  - The sensitivity of chest X-ray for making a diagnosis is poor - one of five individuals with acute HF has no signs of congestion on a chest X-ray
- Transthoracic two-dimensional echocardiography with Doppler assessment
  - Is the key diagnostic test in establishing the initial diagnosis and cause of clinical HF,
  - Provides information on cardiac structural and functional changes and etiology, and
  - Will differentiate between HFpEF and HFrEF
- Given the associations between diabetes and risk for ASCVD, when an individual with diabetes is diagnosed with HF, subsequent evaluation for obstructive CAD is strongly advisable in the absence of contraindication

Initial Laboratory Testing for Suspected or Confirmed HF

- guidelines recommend initial laboratory testing:
  - complete blood count
  - urinalysis
  - serum electrolytes
  - blood urea nitrogen &serum creatinine
  - glucose &HbA1c
  - fasting lipid profile
  - liver function tests
  - iron studies
  - thyroid-stimulating hormone
- In addition, a 12-lead electrocardiogram is recommended
  - may identify a specific cause of HF (i.e., myocardial ischemia, uncontrolled arrhythmia) and
  - may provide information to guide management strategies (e.g., rhythm abnormalities, QRS width for consideration of resynchronization therapy)*

Clinical examination

- For most individuals, clinical signs may include weight gain and lower extremity edema. As part of the clinical examination (Fig. 1), vital signs and volume status should be assessed, including current weight and recent changes in weight and assessment for physical findings consistent with congestion such as pulmonary rales.
- During cardiac examination, a laterally displaced apical impulse and a third heart sound may be helpful in evaluating chamber dilation and left ventricular filling pressures, respectively, and cardiac murmurs may be detected.
- In more advanced HF, the extremities may be cool due to increased systemic vascular resistance; this finding is most common among individuals in stage D.

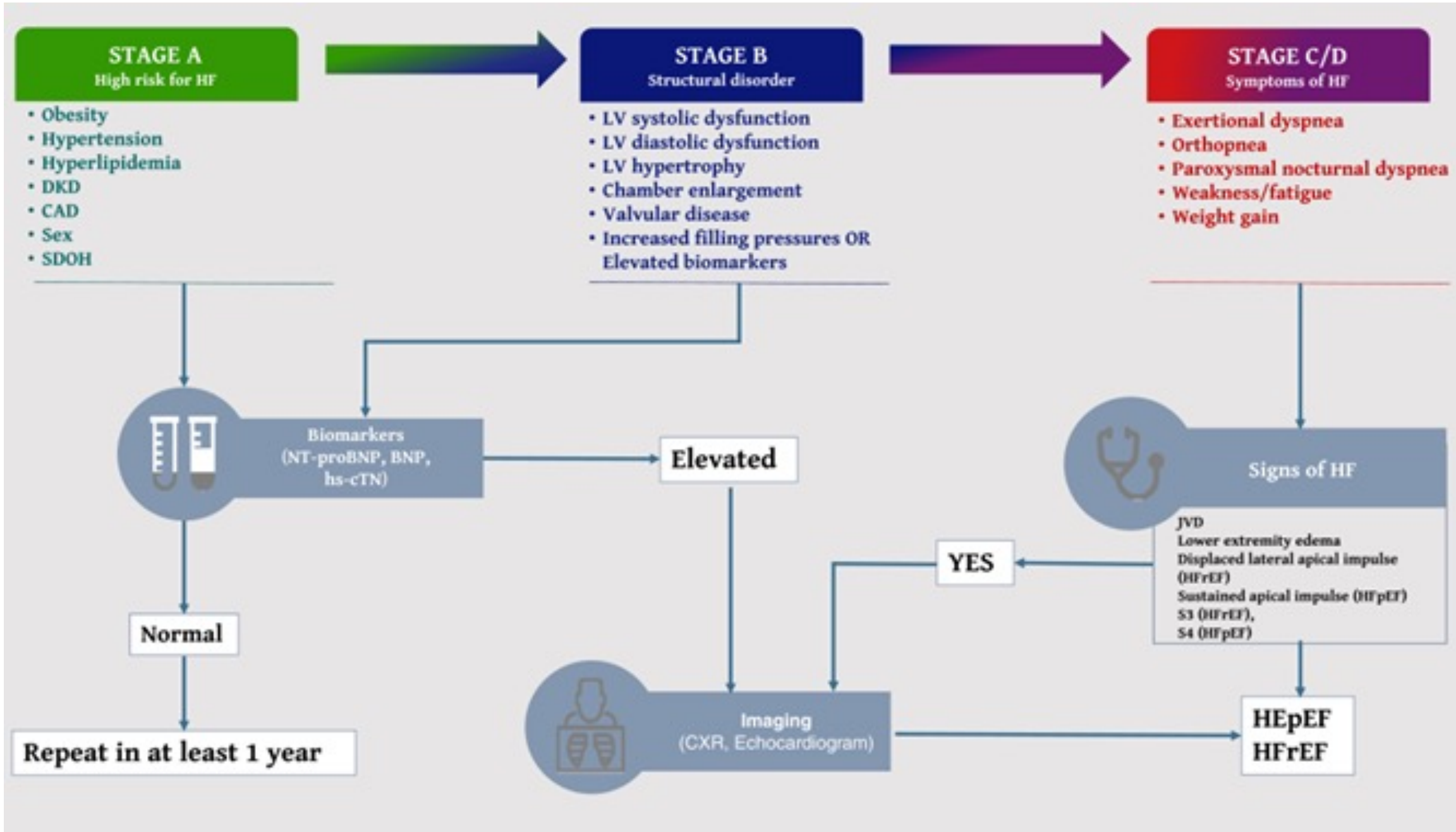
Key Points

- Clinicians should be aware of the multiple symptoms, signs, and physical findings in patients with HF.

- Recommended laboratory evaluations for patients with HF include natriuretic peptide, complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function, and thyroid-stimulating hormone. A chest X-ray and 12-lead electrocardiogram are also recommended.

- Imaging studies such as transthoracic echocardiography will add meaningful information to the evaluation of a patient with suspected or proven HF.

- When HF is diagnosed in individuals with diabetes, clinicians should evaluate for evidence of obstructive CAD as the cause.


STAGE A
High risk for HF
• Obesity
• Hypertension
• Hyperlipidemia
• DKD
• CAD
• Sex
• SDOH
STAGE B
Structural disorder
• LV systolic dysfunction
• LV diastolic dysfunction
• LV hypertrophy
• Chamber enlargement
• Valvular disease
• Increased filling pressures OR Elevated biomarkers
STAGE C/D
Symptoms of HF
• Exertional dyspnea
• Orthopnea
• Paroxysmal nocturnal dyspnea
• Weakness/fatigue
• Weight gain
Biomarkers (NT-proBNP, BNP, hs-cTN)
Elevated
Normal
Repeat in at least 1 year
Signs of HF
JVD
Lower extremity edema
Displaced lateral apical impulse (HFrEF)
Sustained apical impulse (HFpEF)
S3 (HFrEF),
S4 (HFpEF)
YES
Imaging (CXR, Echocardiogram)
HEpEF
HFrEF

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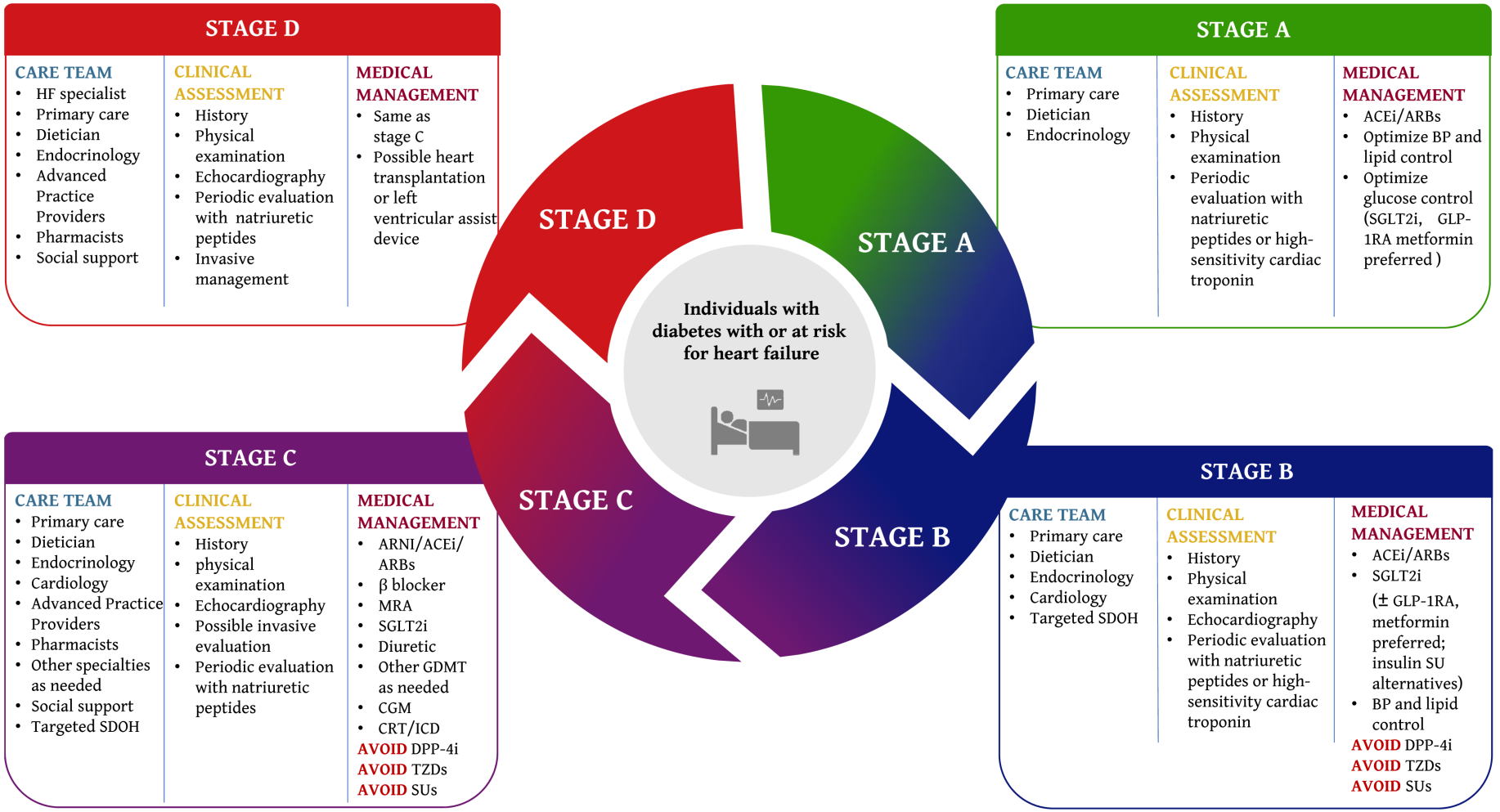

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American Heart Association (AHA) said: A new scientific statement from the American Heart Association summarized the efficacy and safety of complementary and alternative medicine (CAM) therapies in the setting of heart failure (HF).

The statement was aimed at patients, the public, all health care professionals directly or indirectly managing patients with HF, and those who use alternative therapeutic approaches and nontraditional medicine in practice. The writing group, composed of cardiologists, scientists, pharmacists, and a nurse practitioner with expertise on CAM in the setting of acute and chronic HF, reviewed the evidence of efficacy and safety of these kinds of therapy, including interactions with HF treatment and adverse effects on HF progression. The group looked at data from primary literature, review articles, consensus documents, and abstracts of landmark studies published before November 2021. The scientific statement was published Dec. 8 by Circulation.

- The statement strongly encouraged health care professionals to ask their patients about CAM use at every clinical visit; currently, they rarely ask patients about CAM or document its use in the medical record, it noted. Clinicians should also consider discussing the interactions, benefits, and adverse effect profiles of CAM and guideline-directed medical therapy with patients using a shared decision-making model, according to the statement. Both clinicians and patients should be aware of the current lack of federal oversight and regulation of CAM therapies, since the manufacturing process is not overseen by the FDA, the statement said.
- Among CAM agents, omega-3 polyunsaturated fatty acids have the strongest evidence for clinical benefit in patients with HF and are safe when used in moderation, the statement said. Other potentially beneficial CAM therapies were coenzyme Q10, D-ribose, and L-carnitine. Patients can use yoga and tai chi as adjunctive wellness approaches to guideline-directed medical therapy to improve exercise tolerance and quality of life, the statement added. On the other hand, potentially harmful CAM therapies identified in the statement included ginkgo biloba (may increase bleeding risk in patients on anticoagulation), devil's claw (may increase blood pressure), and grapefruit juice (can cause worsening arrhythmias in patients with cardiomyopathy at doses >1,000 mL). In patients with HF who use CAM therapies, a multidisciplinary team with pharmacist involvement can improve drug therapy management and safety, according to the statement.
- “More research and well-powered randomized controlled trials are warranted to further evaluate CAM efficacy and adverse effects in this population,” the authors concluded. “Education, communication, and collaboration between patients, multidisciplinary health care professionals, and nontraditional practitioners are encouraged in patients with HF to promote transparency and improve outcomes.”