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Biomarkers for the Diagnosis of Heart Failure in People with Diabetes: A Consensus Report from Diabetes Technology Society

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Abbreviations: ACC, American College of Cardiology; ADA, American Diabetes Association; AGE, advanced glycation end product; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; AHA/ACC/HFSA Guideline, American Heart Association/American College of Cardiology/Heart Failure Society of America Guideline for the Management of Heart Failure; AI, artificial intelligence; AMR, analytical measurement range; ANP, atrial natriuretic peptide; ARB, angiotensin II receptor blocker; ARIC, Atherosclerosis Risk in Communities; ARNI, angiotensin receptor/neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; CANVAS, canagliflozin cardiovascular assessment study; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; CMP, cardiomyopathy; CPX, cardiopulmonary exercise test; CRR, clinical reportable range; CVD, cardiovascular disease; DTS, Diabetes Technology Society; ECG, electrocardiogram; EDIC, Epidemiology of Diabetes Interventions and Complications; EF, ejection fraction; EMR, electronic medical record; FDA, United States Food and Drug Administration; GDMT, guideline-directed medical therapy; HbA1c, hemoglobin A1c; HF, heart failure; HFA, Heart Failure Association; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; HR, hazard ratio; hs-cTn, high sensitivity cardiac troponin; IGFBP7, insulin-like growth factor binding protein 7; ILI, intensive lifestyle intervention; KDIGO, Kidney Disease Improving Global Outcomes; LA, left atrium; LDL, low-density lipoprotein; LLD, lower limit of detection; LoD, limit of detection; LoQ, limit of quantitation; LV, left ventricular; LVH, left ventricular hypertrophy; MRA, mineralocorticoid receptor antagonist; NPR-A, natriuretic peptide-A receptor; NPV, negative predictive value; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; O-GlcNAcylation, O-linked-*N*-acetylglucosaminylation; PASP, pulmonary artery systolic pressure; PONTIAC, PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease; POCT, point-of-care testing; PPV, positive predictive value; PWD, people with diabetes; QALY, quality-adjusted life years; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; RCV, relative change value; RF, risk factor; RRR, relative risk ratio; RR, risk ratio; STOP-HF, sSt. Vincent"s Screening to Prevent Heart Failure; sST2, soluble suppression of tumorigenesis-2; T1D, type 1 diabetes; T2D, type 2 diabetes; TR, tricuspid regurgitation; TTD, transthoracic echocardiography; URL, upper reference limit; US, United States; Universal Statement, Universal Definition and Classification of Heart Failure Consensus Statement; VHD, valvular heart disease; VSMC, vascular smooth muscle cells.

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ABSTRACT

Diabetes Technology Society assembled a panel of clinician experts in diabetology, cardiology, clinical chemistry, nephrology, and primary care to review the current evidence on biomarker screening of people with diabetes (PWD) for heart failure (HF), who are, by definition, at risk for HF (Stage A HF). This consensus report reviews features of HF in PWD from the perspectives of 1) epidemiology, 2) classification of stages, 3) pathophysiology, 4) biomarkers for diagnosing, 5) biomarker assays, 6) diagnostic accuracy of biomarkers, 7) benefits of biomarker screening, 8) consensus recommendations for biomarker screening, 9) stratification of Stage B HF, 10) echocardiographic screening, 11) management of Stage A and Stage B HF, and 12) future directions. The Diabetes Technology Society panel recommends 1) biomarker screening with one of two circulating natriuretic peptides (B-type natriuretic peptide or N-terminal prohormone of B-type natriuretic peptide), 2) beginning screening five years following diagnosis of type 1 diabetes (T1D) and at the diagnosis of type 2 diabetes (T2D), 3) beginning routine screening no earlier than at age 30 years for T1D (irrespective of age of diagnosis) and at any age for T2D, 4) screening annually, and 5) testing any time of day. The panel also recommends that an abnormal biomarker test defines asymptomatic preclinical HF (Stage B HF). This diagnosis requires follow-up using transthoracic echocardiography for classification into one of four subcategories of Stage B HF, corresponding to risk of progression to symptomatic clinical HF (Stage C HF). These recommendations will allow identification and management of Stage A and Stage B HF in PWD to prevent progression to Stage C HF or advanced HF (Stage D HF).

Contents

Introduction

Heart failure (HF) has been recently defined in two multi-expert consensus statements. One was a clinical practice guideline, which was the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Failure Society of America (HFSA) Guideline for the Management of Heart Failure (AHA/ACC/HFSA Guideline) in 2021.[1] The other was a Universal Definition and Classification of Heart Failure Consensus Statement (Universal Statement) by the HFSA, the Heart Failure Association of the European Society of Cardiology, and Japanese Heart Failure Society[2] with endorsement by the Canadian Heart Failure Society, the Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association in 2022.[3]

The AHA/ACC/HFSA Guideline defines HF as a clinical syndrome with symptoms and signs that result from structural heart disease, increased filling pressures, or increased levels of natriuretic peptides. This definition excludes people with asymptomtaic structural heart disease who are considered to be at-risk for HF.[1] The Universal Statement defines HF as a clinical syndrome with signs and/or symptoms caused by a structural and/or functional cardiac abnormality that is corroborated by elevated natriuretic peptides and/or objective evidence of pulmonary or systemic congestion.[2,3]

According to both guidelines, all people with diabetes (PWD) are considered to be at increased risk of developing HF and are therefore classified as having Stage A HF.[1–3] Furthermore, many PWD have asymptomatic structural heart disease or increased filling pressures and are then defined to be in Stage B HF. Subsequently, with the development of symptoms, the diagnostic stage becomes Stage C HF. This can progress to advanced disease interfering with daily life, which is classified as Stage D HF. According to both guidelines, asymptomatic preclinical Stage B HF can be diagnosed by biomarker screening with measurements of natriuretic peptides, including either B-type natriuretic peptide (BNP) or N-terminal prohormone of B-type natriuretic peptide (NT-proBNP).

Recently in 2022, a consensus on HF was published by the American Diabetes Association (ADA) with designated representation from the ACC. This document included guidance in support of annual biomarker testing for PWD to assess risk of HF; specifically, "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.".[4]

Based on recent interest in identifying PWD with asymptomatic HF by way of biomarker screening related to this recent guidance, Diabetes Technology Society (DTS) organized a panel of experts in diabetology, cardiology, clinical chemistry, nephrology, and primary care to generate practical advice on biomarker screening. The purpose of the panel was to: 1) provide PWD (who are in Stage A HF by definition) with information to identify development of preclinical Stage B HF and 2) prevent progression of asymptomatic Stage B HF to symptomatic Stage C HF or Stage D HF.

Epidemiology

HF is a frequent complication of both type 1 diabetes (T1D) and type 2 diabetes (T2D). PWD are automatically classified as being in Stage A HF, which is defined as being at risk for HF.[5,6] In people with T2D, 9–27% have been reported to be affected by HF,[7–9] which corresponds to a 2–5 times higher prevalence of HF in PWD than in people without diabetes.[10–13] In the Health ABC observational study, among a cohort of 2896 participants (mean age of 74 years with 34.6% having diabetes at onset), the incident HF rate was 2.5% per 100 person-years in those with diabetes and 1.5% in those without diabetes (hazard ratio [HR] 1.66, 95% CI 1.39–1.99) after an average follow-up of 11.4 years.[14]

The risk of developing HF is higher in people with T1D than with T2D.[15–18] A number of registry-based and population-based studies have reported elevated risk for more advanced HF, including hospitalization for HF and HF-associated deaths by 2–6 fold for people with T1D compared to people without diabetes or people with T2D (Table 1).

In people with T1D or T2D, risk factors for HF include female sex,[19] cumulative exposure to hyperglycemia,[20–22] and other cardiovascular disease (CVD) risk factors, such as hypertension, hyperlipidemia, obesity,[23] and smoking. While these risk factors are frequently associated with macrovascular disease in T2D, microvascular disease (MVD) is also a risk factor for HF. In studies of T1D[24] and T2D,[24,25] an approximate two-fold increased risk of HF was noted in the presence of retinopathy, peripheral neuropathy, and chronic kidney disease (CKD). Finally, social determinants of health can also contribute to the risk of developing HF (Table 2).[26]

Classification of HF Stages

Both the recent AHA/ACC/HFSA HF Guideline[1] and Universal Statement[2,3] have classified HF as occurring in four stages (Fig. 1). PWD are, by definition, in Stage A HF and are at risk for HF but do not have current or previous signs and/or symptoms of HF. Individuals with Stage A HF are defined as not having structural or functional heart disease or evidence of abnormal serum biomarkers.[1,3] PWD with Stage B (preclinical) HF also have no current or previous signs and/or symptoms of HF but do have evidence of structural heart disease, abnormal heart function, or elevated cardiac biomarkers indicative of myocardial stretch or cell damage. In Stage C (symptomatic) HF, PWD do have current or prior signs and/or symptoms of HF associated with structural and/or functional cardiac abnormalities.[1,3] Finally, Stage D (advanced) HF is defined as having severe signs and/or symptoms of HF, even at rest.[1,3] Five-year survival with a diagnosis of HF has been reported to be: Stage A 97%, Stage B 96%, Stage C 75%, and Stage D 20%.[27] Therefore, early identification and initiation of treatment to delay or prevent progression of preclinical to clinical HF are important public health objectives.

Pathophysiology of HF in Diabetes

Diabetes can cause myocardial dysfunction leading to HF by processes that promote atherosclerosis and coronary disease, but also by mechanisms that directly affect the myocardium. Diabetic cardiomyopathy (or diabetic heart disease) refers to a distinct structural and functional disorder of the myocardium, characterized by cardiac hypertrophy and myocardial stiffness not directly related to coronary artery disease, atherosclerosis, or hypertension.[28,29] Diabetic cardiomyopathy, first reported in 1972,[30] is characterized by distinct functional, morphological, and structural impairments.[28,29] Early asymptomatic pathophysiological changes in diabetic cardiomyopathy, including inflammation, cardiac fibrosis, stiffness, left ventricular (LV) hypertrophy and subclinical diastolic dysfunction, may progress to eventual systolic dysfunction and symptoms of HF.[31] Ten potential mechanisms contributing to diabetic cardiomyopathy are illustrated in Fig. 2.

Biomarkers for Diagnosing HF

Natriuretic peptides, BNP and NT-proBNP, which are recognized surrogates for intracardiac volumes and filling pressures, are currently considered to be the best biomarkers for prevention, diagnosis, and prognostications of HF.[32–35] The first natriuretic hormone identified was atrial natriuretic peptide (ANP), followed by BNP.[33] ANP and BNP originate from myocardial cells and induce natriuresis, vasodilation, anti-mitogenesis, inhibition of the renin-angiotensin-aldosterone system (RAAS), and inhibition of growth of vascular smooth muscle cells (VSMC) and endothelial cells. BNP is synthesized as pre-proBNP and then is cleaved to proBNP. Cleavage of the 108 amino acid proBNP results in BNP (amino acids 77–108) and NT-proBNP (amino acids 1–76) (Fig. 3).

Table 1
T1D study populations in registry-based or population-based risk studies published since 2013. In two studies[15,105] people with T2D were also compared. Four studies[20,101,102,104] contain overlapping data from the Swedish National Diabetes Register. Abbreviations: BMI = body mass index, BP = blood pressure, CI = confidence interval, CKD = chronic kidney disease, CVD = cardiovascular disease, EDIC = Epidemiology of Diabetes Interventions and Complications, EMR = electronic medical record, HbA1c = hemoglobin A1c, HFpEF = heart failure with preserved ejection fraction, HF = heart failure, HR = hazard ratio, LDL = low-density lipoprotein, RR = risk ratio, T1D = type 1 diabetes, T2D = type 2 diabetes, US = United States.

First author	Year	Study Design	Duration of follow-up (years)	Mean age at baseline (years)	Sample size	Risk for Heart Failure	Remarks
Konduracka[100]	2013	Prospective cohort study	Up to 7	58.7	393 T1D	Prevalence of HF was 3.7% (85% HFpEF) Incidence 0.02% per year.	
Rosengren[101]	2015	Swedish National Diabetes Registry between Jan 1, 1998 and Dec 31, 2011	Mean of 7.9	35 T1D Age-matched controls	33,402 T1D 166,228 controls	HR for hospitalization for HF 4.69 (95% CI 3.64–6.04).	Albuminuria and glycemic control were two major risk factors for HF.
Rawshani[102*]	2017	Swedish National Diabetes Register between Jan 1, 1998 and Dec 31, 2014	Mean of 10.4	32.3 Age-matched controls	33,333 T1D 166,529 controls For ancillary analysis: (9465 T1D, 47,302 controls)	HR for HF for T1D (despite all five risk factors controlled) was higher than controls [1.97 (95% CI, 1.04–3.73)].	The risk for CVD (including HF) was lower among those with all five risk factors (HbA1c, BP, albuminuria, smoking, LDL) under control compared to those with uncontrolled.
Conway[103]	2018	Southern Community Cohort Study in the US (12 southeastern states)	Mean of 9.5	50.2 childhood-onset T1D 49.7 young-adulthood-onset T1D 51.6 controls	162 childhood-onset T1D 313 young-adulthood-onset T1D 65,266 controls	Compared to controls, adjusted mortality due to HF among childhood-onset T1D [HR 7.3, CI 4.2–12.7] was higher than young-adulthood-onset T1D [HR 5.4, CI 3.3–8.9].	Cumulative mortality was higher among childhood onset T1D than young-adulthood-onset or controls.
Larsson S et al.[15]	2018	Population-based study from Sweden	Up to 17	57.2 T1D 63.2 T2D 59.9 controls	247 T1D 2130 T2D 69,106 controls	HR in T1D 2.68 (1.76–4.09) HR in T2D 1.69 (1.5–1.9)	Small sample size for T1D.
McAllister[6]	2018	National Scottish Registers	Over 10-years	50.0 T1D 65.0 T2D 52.9 controls	18,240 T1D 136,042 T2D 3,066,253 controls	The crude incidence rate for HF hospitalization was 5.6, 12.4, and 2.4 per 1000 person-years for T1D, T2D, and controls, respectively.	
Rawshani et al.[20*]	2018	The Swedish National Diabetes Register between Jan 1, 1998 and Dec 31, 2012	Median of 10	28.9 T1D 28.8 controls	27,195 T1D 135,178 matched controls	5- to 12-fold increased risk for HF compared to controls depending on age at T1D onset.	T1D disease onset at young age (before 10 years) and female sex were two major risk factors for CVD in this study.
Edqvist et al.[104]	2019	The Swedish National Diabetes Registry between Jan 1, 1998 and Dec 31, 2012	Median of 10.9	33.3 Not reported for controls	26,125 T1D Not reported for controls	Overall crude incidence rate per 1000 person-years for hospitalization of HF was 2.22 (2.04–2.041).	Higher BMI was a risk factor for HF in this cohort.
Lee[105]	2019	Korean National Health Insurance datasets	Mean of 4.6	56.2 T1D 57.8 T2D 45.9 controls	9397 T1D 1,913,503 T2D 18,500,151 controls	HR for hospitalization for HF was higher in T1D compared with T2D [2.105 (1.901–2.330)] and compared with controls [3.024 (2.730–3.350)].	
Shah[106]	2020	US T1D Exchange Clinic Registry	Mean of 4.6	Median of 33	8727 T1D	Overall 0.4% had HF. 10% of CVD events were due to HF.	Young age and shorter duration of follow-up. Data is based on EMR, so underreporting is possible.
Harjutsalo[107]	2021	Retrospective, nationwide, registry-based cohort study; Finnish Care Register for Health Care between Jan 1, 1965 and Dec 31, 1999	Median of 29.6	Not reported	11,766 T1D	17.5% had HF events.	
Kristófi R[16]	2021	Secondary analysis from Sweden and Norwegian studies	Mean of 2.6 years	45.8 T1D 64.1 T2D	59,331 T1D 484,241 T2D	Prevalence of HF at baseline was 3.1% in T1D vs 7.5% in T2D After age 65, event rates for HF was significantly higher in T1D compared to T2D.	Event rates were low for age < 40 years Higher CVD events may be confounded due to higher CKD prevalence in T1D vs T2D
Parente EB[108]	2021	Finnish Diabetic Nephropathy Study Cohort	Median of 16.4	36.6	4668 T1D	The HF hospitalization incidence was 6.6%.	HbA1c, albuminuria, and central obesity were major risk factors.

Table 1 (*continued*)

First author	Year	Study Design	Duration of follow-up (years)	Mean age at baseline (years)	Sample size	Risk for Heart Failure	Remarks
Guo[83]	2022	Pittsburgh Epidemiology of Diabetes Complications (EDC)	Up to 25	27	655 with T1D	6.6% had HF. The incident rates for any HF were 3.4/1000 person-years.	

Both the AHA/ACC/HFSA Guideline[1] and Universal Statement[2,3] specified that for biomarker screening for HF in patients at high risk of HF, either of the two natriuretic peptide biomarkers, if elevated, would make a diagnosis of Stage B HF. The recent ADA report also identified troponin, using a highly sensitive assay, as being useful for screening HF in PWD with Stage A HF.[4] Although elevated troponin concentrations are associated with development of HF, troponin indicates myocardial injury through any mechanism, which decreases its specificity for HF when used as a screening tool. On the other hand, BNP and NT-proBNP are indicators of cardiac myocyte stretch, wall stress, and volume overload, and they have a strong mechanistic link to HF. Elevated natriuretic peptide levels in the absence of competing causes identifies Stage B HF.

Biomarker Assays

Several antibody-based immunoassays with variable performance characteristics, that are either large laboratory-based or point-of-care testing (POCT) instruments are commercially available (Table 3). Additional assays are under evaluation and/or are available outside of the United States (US) markets. Although both laboratory-based and POCT devices are available, for mass screening of PWD, it does not make economic sense to use POCT devices. In general, laboratory-based assays have wider measurement and reportable ranges than POCT devices. Thus, laboratory-based assays are best-suited for diagnostic testing, and POCT devices are best-suited for monitoring responses to therapy. For NT-proBNP, some assays record up to 100 pg/mL as the upper cutoff value whereas others use the recommended 125 pg/mL cutoff value. For the assays presented in Table 3, sensitivities and specificities ranged from 74%–88% and from 87%–98%, respectively, when provided.

Lack of standardization of cardiac biomarker assays has resulted in variation of results among various assays and thus limits interchangeable use of different assays.[36] The assays are calibrated against pure synthetic NT-proBNP and BNP by mass. However, because NT-proBNP availability is restricted to certain manufacturers (Roche and QuidelOrtho), this lends some degree of standardization that supports commutability and transferability of results. This is not necessarily the case for BNP, which is available from many manufacturers, and consequently, values vary significantly between different manufacturers' systems (Table 3).

Studies have shown that natriuretic peptides, over a period of weeks to months, exhibit high biological variation, resulting in reference change values (RCV) of 100% or more.[37] Assays must also be free from interference by common interferants, such as hemolysis and drugs. Examples of physiologic factors that can influence the concentrations of natriuretic peptides are shown in Table 4. BNP, but not NT-proBNP, is also a substrate for neprilysin, which breaks down BNP. Treatment of HF with an angiotensin receptor/neprilysin inhibitor (ARNI) drug, such as sacubitril/valsartan (the only FDA approved drug in this class), can result in a sustained decrease in NT-proBNP concentrations, suggesting less myocardial stress.[38] However, BNP concentrations may temporarily increase initially because of neprilysin inhibition, and then as HF improves, BNP concentrations may decrease compared to baseline.[39] NT-proBNP, however, is not degraded by neprilysin and may be preferred for screening in a setting of ARNI therapy particularly within 8 to 10 weeks.[40] Sample hemolysis negatively interferes with natriuretic peptide assays. Biotin (Vitamin B7 or Vitamin H) is used to conjugate antibodies employed in immunoassays and can produce assay interferences when present as a supplement.[41] The interpretation of biomarker concentrations may also be confounded in the setting of kidney dysfunction. See Table 5 for examples of such considerations.[42–45]

Diagnostic Accuracy of Biomarkers

The ADA report identified the abnormal biomarker thresholds for clinical use: BNP ≥50 pg/mL and NT-proBNP ≥125 pg/mL.[4] This BNP cutoff for defining Stage B HF is higher than that in the two heart association documents, which recommended ≥35 pg/mL as meeting the definition of Stage B HF due to structural heart disease or increased filling pressure. The two heart association documents established the same cutoffs for NT-proBNP (≥125 pg/mL). No statistically significant difference in diagnostic accuracy has been observed between the two natriuretic peptides.[46]

Clinical Value of BNP

BNP is released in response to established cardiovascular damage[47] and LV stretching or wall tension.[48] The diagnostic cutoff for BNP for HF is 100 pg/mL.[49] The St. Vincent's Screening to Prevent Heart Failure (STOP-HF) Study used BNP to screen people without HF and applied a cutpoint of 50 pg/mL.[47] In this trial, the 50 pg/mL cutpoint was chosen because of an earlier study about elevated BNP levels in a cohort of asymptomatic individuals with preserved systolic function,[50] which had a median BNP concentration of 50 pg/mL. This cutpoint of BNP

Table 2
Examples of social determinants of health and how they impact risk of heart failure. Abbreviations: HF = heart failure, HR = hazard ratio.

Social Determinant of Health	First author	Year	Finding
Neighborhood Greenness	Wang[109]	2019	Neighborhoods with the higher amounts of greenness (top third), compared with neighborhoods with lower amounts of greenness (bottom third), were associated with reduced odds of HF by 16%.
Low Income	Hung[110]	2021	HF readmission is less likely in high-income individuals, compared with low-income individuals (HR 1.36) and median-income individuals (HR 1.12).
Race	Osei[111], Bank IEM,[112] Choi[113]	2017	Black people have a twofold higher prevalence of HF than White people.[111] An increased incidence of diabetes in Asian adults with HF compared to White people with HF may[112] or may not[113] be present.
Food Access	Ziliak JP[114]	2014	Among older adults, those with versus without food insecurity were 57% more likely to have HF than food secure seniors.

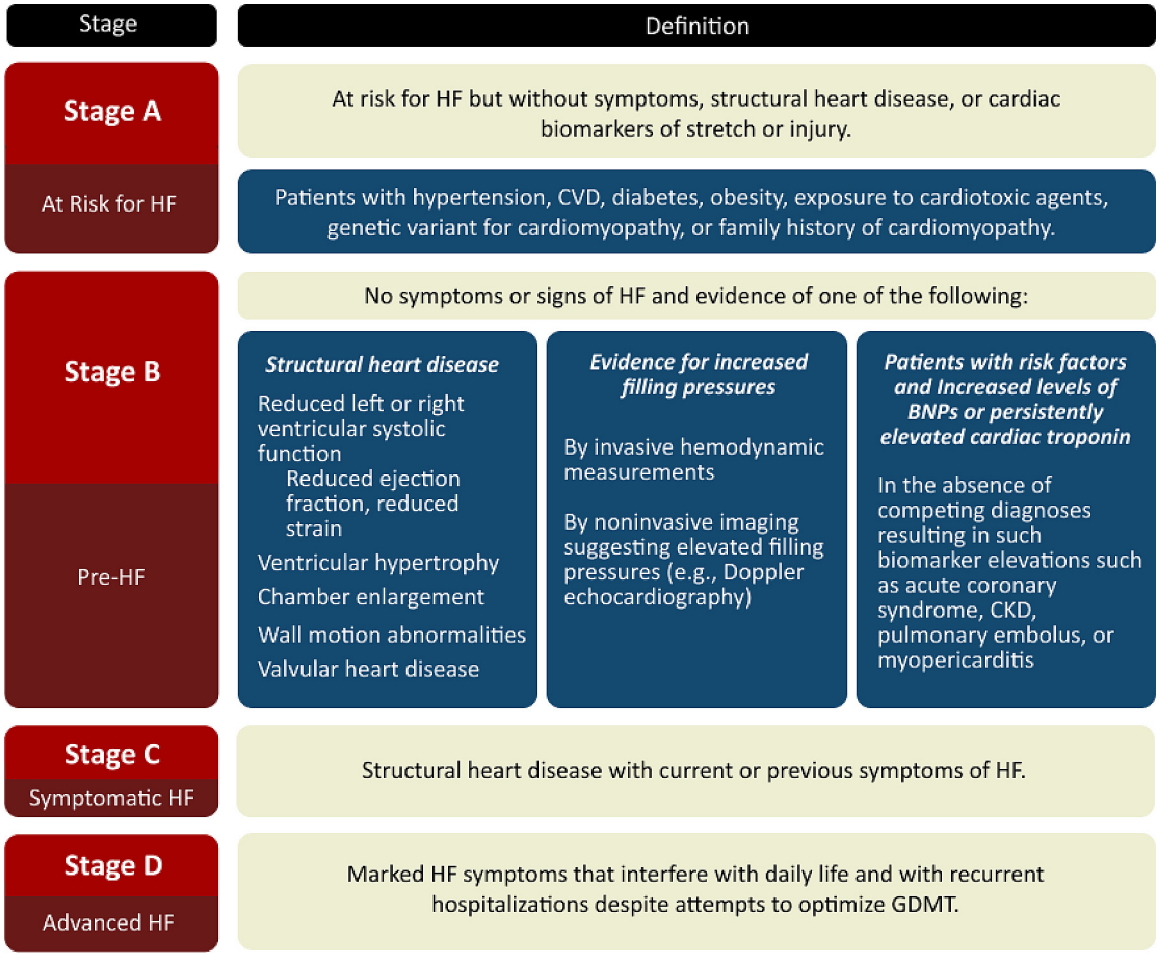

Fig. 1. The definitions and criteria of the four stages of heart failure per the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. [1] Source: American Heart Association, Inc. Abbreviations: ACC = American College of Cardiology, AHA = American Heart Association, BNP = B-type natriuretic peptide, CKD = chronic kidney disease, CVD = cardiovascular disease, GDMT = guideline-directed medical therapy, HF = heart failure, HFSA = Heart Failure Society of America.

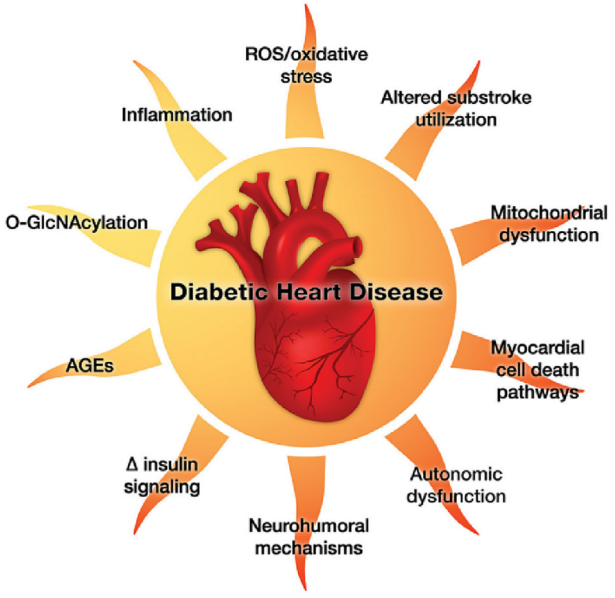

Fig. 2. Ten potential mechanisms contributing to diabetic cardiomyopathy. Abbreviations: AGEs = advanced glycation end products, O-GlcNAcylation = O-linked-*N*-acetylglucosaminylation, ROS = reactive oxygen species. Figure reproduced with permission from Ritchie et al. [29].

≥50 pg/mL was also chosen by ADA as their cutoff.[4] The STOP-HF randomized clinical trial recruited 1374 participants in Ireland who were older than 40 years and had at least one risk factor for HF (Stage A HF). Participants were assigned 1:1 either to a control group (routine primary care physician management) or to an intervention group (screening with BNP testing). Participants in the intervention group who had BNP ≥50 pg/mL underwent echocardiography and received collaborative care between their primary care physician and a cardiologist. Individuals with a BNP concentration above the 50 pg/mL cutpoint had significantly more admissions for major CVD outcomes.[50] Outcomes and results of STOP-HF are shown in Table 6. The STOP-HF study confirmed that treating individuals with Stage B HF diagnosed by the BNP cutpoint of ≥50 pg/mL decreases progression to Stage C HF and LV dysfunction. Stage C HF was defined as symptoms of HF requiring emergency hospitalization.

Clinical Value of NT-proBNP

NT-proBNP is indicative of the presence and severity of CVD burden.[51] A normal concentration of NT-proBNP is considered to be below 125 pg/mL for adults <75 years and below 450 pg/mL for adults ≥75 years[52–54] whereas the European Society of Cardiology[55] and Canadian Cardiovascular Society[56] guidelines specify a cutpoint of normal up to 125 pg/mL for NT-proBNP. The stated cutpoints for screening for Stage B HF differ from those using NT-proBNP for diagnosing acute HF and are based on outcomes from various epidemiological studies.

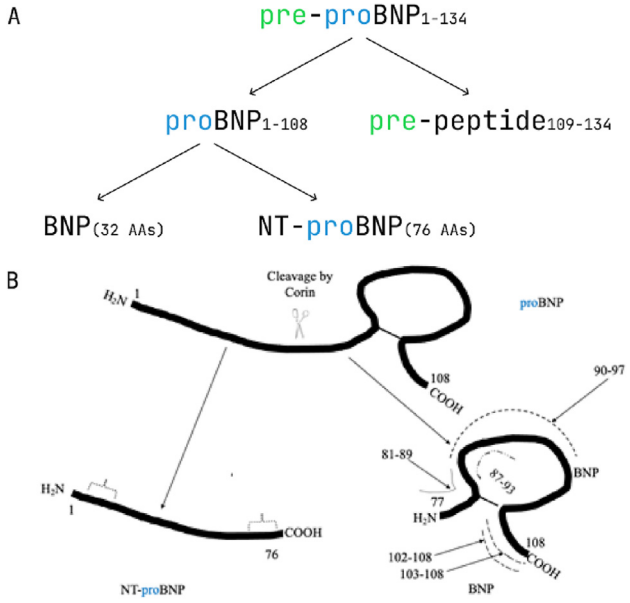

Fig. 3. Production of BNP and NT-proBNP from pre-proBNP. A) Schematic showing the products at each intermediate step. B) Primary structure of natriuretic peptides and assays related to molecular detection and target epitopes. Dotted lines indicate opposite target regions of the common assays' antibodies. Figure adapted from Semenov et al. [99] under the Creative Commons license: https://creativecommons.org/licenses/by-nc/3.0/. Abbreviations: BNP = B-type natriuretic peptide, NT-proBNP = N-terminal proBNP.

However, clinical assessment is required when interpreting laboratory data, especially when evaluating higher values of NT-proBNP. A cutpoint of NT-proBNP of 125 pg/mL was chosen for biomarker screening by ADA[4] in reference to two studies: (1) the NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease (PONTIAC) study[51] and (2) the Canagliflozin Cardiovascular Assessment Study (CANVAS).[57]

The objective of the PONTIAC study was to see whether neurohumoral therapy would be effective for preventing CVD events in high-risk patients with T2D who met the current definition of Stage B HF and who were selected based on elevated NT-proBNP. A threshold of NT-proBNP >125 pg/mL was selected by the PONTIAC study based on a previous study[58] that evaluated the predictive value of NT-proBNP for PWD. In this previous study, PWD had their NT-proBNP levels measured and were followed for an observation period of 12 months for unplanned hospitalization for CVD events or death, which were the primary endpoints of the study.[58] A Kaplan-Meyer analysis demonstrated significant differences in these endpoints between patients above and below a NT-proBNP value of 125 pg/mL (Fig. 4).

The CANVAS Program enrolled participants with T2D and high CVD risk. Participants received either canagliflozin or placebo and were

Table 4
Physiological factors influencing the interpretation of BNP or NT-proBNP concentrations. [115–118] Abbreviations: BNP = B-type natriuretic peptide, NT-proBNP = N-terminal proBNP.

Factors that decrease [BNP/NT-proBNP]	Factors that increase [BNP/NT-proBNP]
• Obesity • Constrictive pericarditis	• Left ventricular dysfunction • Chronic kidney disease and acute kidney injury • Atrial tachyarrhythmias (e.g., atrial fibrillation) • Cardiotoxic drugs • Significant pulmonary disease • Advanced age • Female at birth • Renal dysfunction • Anemia • Burns • Stroke • High cardiac output states (e.g. sepsis, anemia, thyrotoxicosis)

Table 3
Characteristics of selected BNP and NT-proBNP assays available in routine clinical use.

Instrument	POCT				Laboratory Based						
Characteristics	A	B	#C	D	E	#F	G	H	I	J	K
BNP	X	X							X	X	X
NT-proBNP			X	X	X	X	X	X			
LLD (pg/mL)	5	15		34	5	20	11	<20	1.7	2.4	1
LoQ (pg/mL)	5	15	48	57	50 at CV < 20%.	33	20		20	2.5	1
AMR (pg/mL)	5–5000	15–5000	20–35,000	18–35,000	10–35,000		20–30,000			2.0–5000	1–5000
CRR	5–5000	15–5000			10–70,000						1–10,000
Diagnostic threshold (pg/mL)	100	<100	<125[c]	<125[c] <450[e]	<125 (All patients age, <450 for >75 years old: Exclude) <450[a] <900[b] <1800[d]	125[c] 450[e]	125[c] 450[e]	125[c] 450[e]	100	<100	<100
Sensitivity (%)	80	74.2	88	95.4	83		91.5	93.7	85		82
Specificity (%)	98	91.5	87	90.7	83		76.9	85	92		98
Imprecision (%)	9.1	11.1	15	10.3	5.2	5.9	4.0	5.1	4.2	2.4	5.8
RCV (%)	83	84.9	49.5	39.4	30.1	31.9	29.6	30.8	80.1	79.6	80.1

A: Triage BNP, Beckman Coulter, Quidel Cardiovascular Inc., CA, USA (limited availability as the assay is being transitioned to Beckman from QUIDEL), B: iSTAT POCT, Abbott Diagnostics, IL, USA, #C: Triage NT-proBNP, QuidelOrtho Corporation Inc., CA, USA, D: RAMP NT-proBNP Response, Response Biomedical, BC, Canada, E: Roche NT-proBNP, Roche Diagnostics, IN, USA), #F: NT-proBNP, Siemens (Atellica), Siemens Healthineers, PA, USA, G: NT-proBNP II, VITROS, Ortho Clinical Diagnostics, Rochester, NY, USA, H: BioMerieux/Vidas/NTproBNP bioMerieux Inc., MO, USA, I: BNP, Abbott Diagnostics, IL, USA, J: Siemen ATELLICA BNP, Siemens Medical Solutions USA Inc., PA, USA, K: Beckman Coulter Triage-QUIDEL, Quidel Cardiovascular Inc., CA, USA.
#: Not available for sale in the USA market.
Adapted from the published assays characteristics, International Federation of Clinical Chemistry and Laboratory Medicine—Clinical Applications of Cardiac Bio-Markers Updated tables (https://www.ifcc.org/media/477653/point-of-care-cardiac-troponin-i-and-t-assay-analytical-characteristics-designated-by-manufacturer-v012019.pdf), and from Cullen, Collinson, and Giannitsis (2022).
Abbreviations: POCT = point-of-care testing, LLD = lower limit of detection, LoQ = limit of quantitation, AMR = analytical measurement range, CRR = clinical reportable range (extended AMR range following sample dilution), RCV = relative change value (combined analytical and biological variability).
[a] <50 years old.
[b] 50–70 years old.
[c] <75 years old.
[d] >70 years old.
[e] >75 years old.

Table 5
Features of Biomarker Concentrations in Patients With Kidney Dysfunction. [42–45]
Abbreviations: HF = heart failure, NP = natriuretic peptide.

Features of Biomarker Concentrations in Patients With Kidney Dysfunction
NP concentrations may be elevated because of volume overload and left ventricular hypertrophy.
NP concentrations may also be elevated because of impaired clearance.
There is insufficient data indicating appropriate elevated cutoff concentrations for NP biomarker screening.
NP concentrations can be used to exclude HF if they are below the cutoff.
Elevated troponin concentrations have shown promise as a biomarker for heart disease in this setting.

followed to compare their incidence of CVD events.[59,60] Baseline concentrations of NT-proBNP were non-significantly higher in those with a history of HF compared to those without. Baseline NT-proBNP >125 pg/mL predicted new HF, CVD death, and all-cause death. Canagliflozin reduced NT-proBNP concentrations, but no significant interaction between biomarker concentration and treatment outcome was observed after a mean follow-up period of 188 weeks.[57]

A concentration of NT-proBNP below 125 pg/mL was shown to have a high negative predictive value (NPV), and a value above 125 pg/mL was shown to have a low positive predictive value (PPV) in diagnosing Stage B HF in the PROBE-HF trial, such that a test result below the cutoff was highly suggestive that HF was not present.[61] Overall, in PWD with Stage A HF (at risk for HF), a screening test with a high NPV is useful for establishing the absence of the condition being screened for and providing reassurance after a negative result.

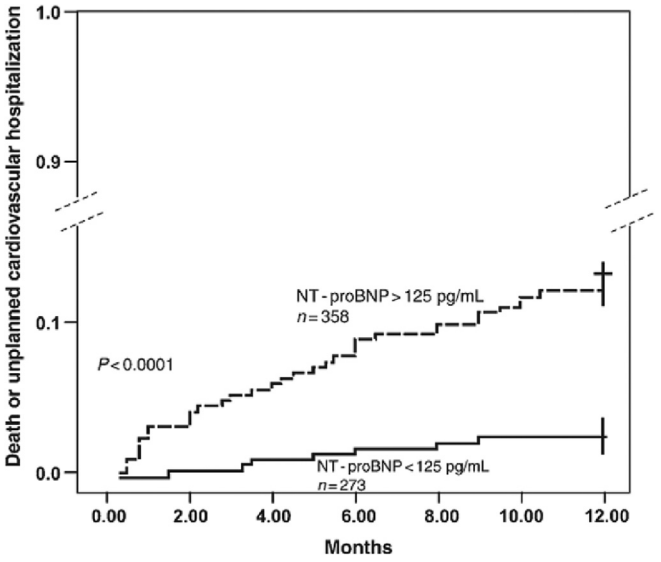

Fig. 4. Kaplan-Meier curves of all-cause mortality or unplanned cardiovascular hospitalizations in 631 PWD according to plasma-levels of NT-proBNP at baseline in the PONTIAC study. Solid line: patients with NT-proBNP levels below cut-off (<125 pg/mL). Dashed line: patients with NT-proBNP levels above cut-off (>125 pg/mL). Log-rank test for overall difference, $P < 0.0001$. Reproduced from Huelsmann et al. [58] with permission from Oxford University Press. Abbreviations: NT-proBNP = N-terminal proBNP, PONTIAC = PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease, PWD = people with diabetes.

Benefits of Biomarker Screening

Public Health Benefits

Features of a clinically actionable biomarker screening program for an asymptomatic condition are presented in Table 7. In some individuals, biomarker screening for HF will be abnormal even before an echocardiogram shows structural or functional abnormalities.[62] Screening allows opportunities for the early use of treatments to arrest the progression of preclinical HF (Stage A or B) to clinical HF (Stage C and D) and decrease CVD mortality.[63]

Biomarker screening for HF in PWD is a sensible public health practice because both the disease and the available screening tests meet the criteria of a sound screening program for identifying asymptomatic HF.[64,65] Table 8 presents features of a target disease and a screening test in a sound screening program, and biomarker screening for HF in PWD meets these features. A pharmacist-led HF sceening program based on elevated NT-proBNP concentrations has been reported for patients with Stage A HF and either diabetes or hypertension.[66]

Screening for Chronic Kidney Disease

Multiple shared risk factors and pathways contribute to the development of HF and CKD in PWD.[4,67,68] There is a similar pathophysiology between HF and CKD in diabetes and a similar need to identify preclinical disease before organ dysfunction evolves into symptomatic and/or debilitating disease. Like the need to identify early HF, there is a critical need for routine screening and early identification of CKD in PWD, given the high degree of unawareness of this complication (i.e., nine out of ten individuals with CKD are unaware of having this condition[69]). For both complications, there is a great potential impact of early therapeutic interventions in avoiding or delaying the progression to further stages.

Consensus Recommendations for Biomarker Screening for HF

Diabetes Technology Society Screening Recommendations

The DTS Panel addressed five practical topics related to biomarker screening for HF for PWD. These included: 1) Which age should biomarker testing begin? 2) What duration of diabetes should occur before initial testing? 3) With what frequency should testing be repeated? 4) Which biomarkers should be tested? and 5) When should biomarker testing be performed (such as during fasting conditions or at any particular time of day)?

The DTS Panel recommends the same screening schedule of PWD for HF as that recommended for CKD screening by the 2023 ADA Standards of Care[70] and Kidney Disease Improving Global Outcomes (KDIGO).[71]

Table 6
Results of the STOP-HF study [47] after a mean follow-up period of 4.2 years after initial assessment. Abbreviations: BNP = B-type natriuretic peptide, HF = heart failure, LV = left ventricular.

End point	Control group (n = 677)	Intervention Group (n = 697)	p-value
LV dysfunction or HF	8.7% (59/677)	5.3% (37/697)	0.007
	*18.7% (44/677)	*9.5% (25/697)	*0.005
Asymptomatic LV dysfunction	6.6% (45/677)	4.3% (30/697)	0.02
	*13.6% (32/677)	*7.6% (20/697)	*0.02
HF	2.1% (14/677)	1.0% (7/697)	0.17
	*5.1% (12/677)	*1.9% (5/697)	*0.15
Major adverse cardiovascular events	10.5% (71/677)	7.3% (51/697)	0.08
	*19.1% (45/677)	*13.3% (35/697)	*0.13

* only out of patients with BNP ≥50 pg/mL.

Table 7
Features of a clinically actionable serum biomarker. [115,119–121].

- An objective and reproducibly measurable biological observation
- Substitutes for or predicts a relevant clinical endpoint or intermediate outcome that may be difficult to observe otherwise
- Provides information other than what is already available by routine physical examination (however, vital signs are considered to be biomarkers)
- Adds to clinical judgment for understanding diagnosis, prognosis, management, and/or prevention of a disease

These two guidelines specify CKD screening at least annually. For people with T1D, screening for CKD should begin five years following diagnosis, and for people with T2D, screening for CKD should begin at the time of initial diagnosis.[67,70]

Regarding the age for initial screening, duration of diabetes, and testing frequency, the DTS Panel recommends screening annually for HF in: people with T1D at age ≥ 30 years beginning five years following diagnosis (but no earlier than age 30 years) and people with T2D at any age beginning at the time of initial diagnosis.

Regarding the optimal biomarkers, the DTS Panel recommends using natriuretic peptides (BNP and NT-proBNP) for HF screening in PWD. Other cardiac biomarkers such as high-sensitivity troponin also have prognostic evidence for development of HF, and troponin is a promising biomarker for future use as a complementary test to order along with natriuretic peptides.[72,73] Regarding testing circumstances, we recommend that testing occur any time irrespective of food intake. We recommend using the same laboratory testing platform every time if possible. Our consensus recommendations for routine biomarker screening for HF in PWD with Stage A HF are presented in Table 9. We do not yet have evidence that this recommended screening strategy results in better clinical outcomes or more effective prevention of HF. This will require large randomized controlled trials. It should also be noted that screening programs generate both false positives and false negatives.

Evidence

Age

In a review of 21 studies of 507,637 subjects with T2D about the age of onset for HF (mean age at study onset of 62 years, mean follow-up period of 4.8 years), the mean annual incidence of HF was 2.2%. There was a significant association between each 5-year increment in age and development of HF (hazard ratio 1.47; 1.25–1.73).[74] This study demonstrated that HF can occur in early adulthood during the same age range as T2D diagnosis and supports screening for HF at the age of diabetes diagnosis for people with T2D. In a cohort of 1.1 million people with T2D from the Australian diabetes registry, an increasing incidence of HF was noted by duration of diabetes and age at diagnosis (starting at age 30 years) (Fig. 5).[75] In a cohort of 100,878 individuals with T2D in the Swedish National Diabetes Register, a progressively increasing incidence of new onset HF with increasing age was noted.[76] In a population of 150,582 adults (who did not necessarily have diabetes) from the Hillingdon Health Authority in West London, England, between an age range of 45–54 years and 55–64 years, the incidence of HF increased considerably from 0.3 to 1.7 new cases per 1000 persons per year.[77]

Table 8
Features of a target disease and a screening test in a sound screening program. [64,65].

The disease must have:
• a significant public health impact • a readily available treatment that provides significant benefit (e.g., fewer complications, longer survival, less deployment of medical resources, or greater quality of life) which increases with early detection and deployment
The screening test for the disease must be:
• mechanistically linked to the pathophysiology of the disease • capable of accurately detecting a disease • safe to administer • minimally uncomfortable • reasonable in cost • associated with evidence of improved health outcomes • widely available • capable of a high yield if high-risk people are targeted for screening • highly sensitive in detecting the disease

Table 9
DTS consensus recommendations for routine biomarker screening for HF in PWD with Stage A HF. Abbreviations: BNP = B-type natriuretic peptide; DTS = Diabetes Technology Society, HF = heart failure, NT-proBNP = N-terminal prohormone of B-type natriuretic peptide, T1D = type 1 diabetes, T2D = type 2 diabetes, PWD = people with diabetes.

Screening Program Feature	Timing
Which age to begin testing	T1D: Age 30 years T2D: At any age of diagnosis
What duration of diabetes before initial screening	T1D: Five years following diagnosis (but no earlier than age 30 years) T2D: At the time of diagnosis
What frequency	Annually
Which biomarkers	BNP or NT-proBNP
When to test	Any time of day

Duration of Diabetes

Diabetes duration is an important feature of screening because Stage B HF progresses to Stage C HF if left untreated. For PWD with Stage B HF due to LV diastolic dysfunction (compared to without diabetes), the probability of developing Stage C HF after 5 years has been reported to be 36.9% compared to 16.8%.[78] For a diabetes population with LV systolic dysfunction, the probability of developing HF after 3 years of living with diabetes has been reported to be significantly higher than those without diabetes with a HR of 1.53.[79] Hamo and colleagues studied the incidence of Stage B HF among 9052 adults with diabetes from four US population centers in the Atherosclerosis Risk in Communities (ARIC) study. In cohorts of various diabetes duration, they compared the incidence of increased plasma high sensitivity cardiac troponin T, (defined as ≥14 ng/L), which is a measure of Stage B HF and which had previously been shown to be strongly associated with incident CVD and mortality. As the duration of diabetes increased, from no diabetes to diabetes for 0–5 years, the relative risk ratio also increased (Fig. 6).[80]

Three studies reported data regarding the amount of time passed before Stage B HF developed into Stage C HF, which support screening for HF at the time of diabetes diagnosis. In the Rochester Epidemiology Project,[81] among all residents of Olmsted County, MN, over three years, 11.6% of patients with Stage B HF progressed to Stage C HF. In the CHART-2 study in Japan,[82] 415 of 4005 (10%) of a cohort of

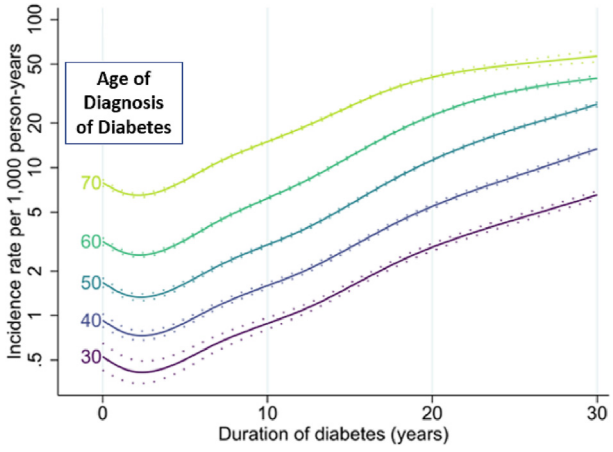

Fig. 5. The incidence of heart failure by duration of diabetes, stratified by age at diagnosis of diabetes (ages 30, 40, 50, 60, and 70 years). 95% confidence intervals are represented by dotted lines. Figure modified with permission from Morton et al. [75].

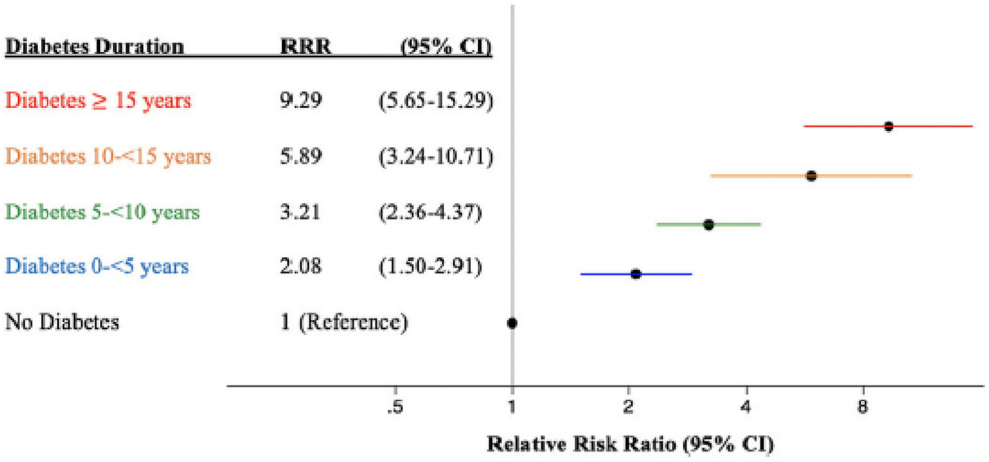

Fig. 6. Relative risk ratios (95% CIs) for increased high-sensitive cardiac troponin T by categories of diabetes duration. Regression model adjusted for age, sex, race per study centersite included in the study, smoking, alcohol, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, triglycerides and estimated glomerular filtration rate. Figure reproduced with permission from Hamo et al. [80] Abbreviations: CI = confidence interval, RRR = relative risk ratio.

asymptomatic patients with Stage B HF developed Stage C HF within one year after baseline assessment. There was a 3.4% increase in incidence of HF per additional decade of age (starting with age 27 years) in a T1D cohort in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study.[83]

Frequency of Screening

While annual cardiac biomarker screening seems reasonable, as recommended in the recent ADA guidance[4], the clinical usefulness and cost-effectiveness of this approach applied to the entire population might eventually dictate a different frequency for some groups of PWD.[84,85] Additional studies are needed to determine the extent to which aggressive medical management of PWD who have Stage A or B HF will delay or prevent the development of Stage C HF.

Which Test to Use

The two natriuretic peptides, BNP and NT-proBNP, were recommended as the sole screening biomarkers for HF by the AHA/ACC/HFSA HF Guideline[1] and Universal Statement.[2,3] These two biomarkers were recommended as being useful to support clinical judgment for the diagnosis of HF by The Diabetes & Cardiovascular Disease Study group of the European Association for the Study of Diabetes.[63] Troponin is being increasingly measured as a circulating biomarker for diagnoses other than HF.[86] This protein and other circulating biomarkers have shown promise for future use in screening for HF.[4,87] Multimarker panel-based risk scores incorporating multiple biomarker levels have demonstrated good model performance for HF risk prediction.[88,89]

Circumstances Around Testing

Circumstances around measuring biomarkers for diagnosis of HF in PWD need to be validated in future prospective studies.[90] Food intake or meal timing do not affect concentrations of circulating natriuretic peptides in PWD.[91] Chronic dietary modifications associated with a decreased risk of HF can decrease natriuretic peptide concentrations.[92]

Stratification of Stage B HF

Among adults with Stage B HF, the risk of downstream HF grows with increasing burden of subclinical abnormalities in cardiac structure, function, and biomarker levels. Accordingly, we propose a further stratification of Stage B HF into four subcategories based on the prevalent cardiac abnormalities (Fig. 7). Isolated elevations in cardiac biomarkers without abnormalities in cardiac structure or function (Stage B1) are associated with an increased risk of Stage C HF.[78] Concurrent abnormalities in cardiac structure (LV hypertrophy [LVH] or adverse remodeling) with elevation in cardiac biomarker levels (Stage B2) portends an even higher risk of Stage C HF. Stage B3 HF identifies individuals with elevated cardiac biomarker levels and abnormalities in cardiac structure and function (diastolic dysfunction, elevated right ventricular systolic pressure, E/e', and/or increased left atrium [LA] size). Individuals with Stage B3 HF warrant evaluation for underlying subclinical HF with assessment of HF symptoms and cardiopulmonary exercise (CPX) testing. Finally, a subset of patients may have depressed LVEF and/or significant valvular abnormalities (Stage B4) who may be at the highest risk of Stage C HF and need dedicated cardiac evaluation and consideration for initiation of specific therapies for heart failure with reduced ejection fraction (HFrEF), even in the absence of clinical symptoms of HF.

Screening for HF with Echocardiography

All asymptomatic PWD with biomarker results above the recommended cutpoints should follow biomarker testing with transthoracic echocardiography (TTE) to further confirm and characterize their diagnosis of Stage B.[55] TTE can identify abnormalities in cardiac structure and function. Key parameters obtained by echocardiography that provide important prognostic data include morphologic changes, systolic function, and diastolic function. Specifically, increased LV size and LA size are strong predictors for the development of HF.[93]

Elevated concentrations of cardiac biomarkers may precede development of abnormalities in cardiac structure and function and guide echocardiographic assessment of Stage B HF. Sex-specific thresholds of LV mass indexed to body size are used to identify LVH. The presence of LVH in a setting of elevated cardiac biomarkers identifies a high-risk intermediate phenotype, meaning that they are asymptomatic with subclinical abnormalities in cardiac structure and function and are at an increased subsequent risk of Stage C HF.[94] The relationship between LVH and relative LV wall thickness can further classify the LVH as concentric versus eccentric, which has prognostic implications for the development of HF subtypes: HF with preserved versus reduced ejection fraction, respectively.[95] In addition to ejection fraction, LV strain is also a sensitive marker of systolic function that can identify abnormalities even within the normal range of LV ejection fraction. Furthermore, diastolic dysfunction may be present in advance of any abnormality in systolic function. Diastolic function encompasses the passive and active phases of LV filling that precede ejection.[96] This is a complex process assessed non-invasively by two-dimensional and Doppler echocardiography. In the STOP-HF trial, a serial testing strategy was examined that

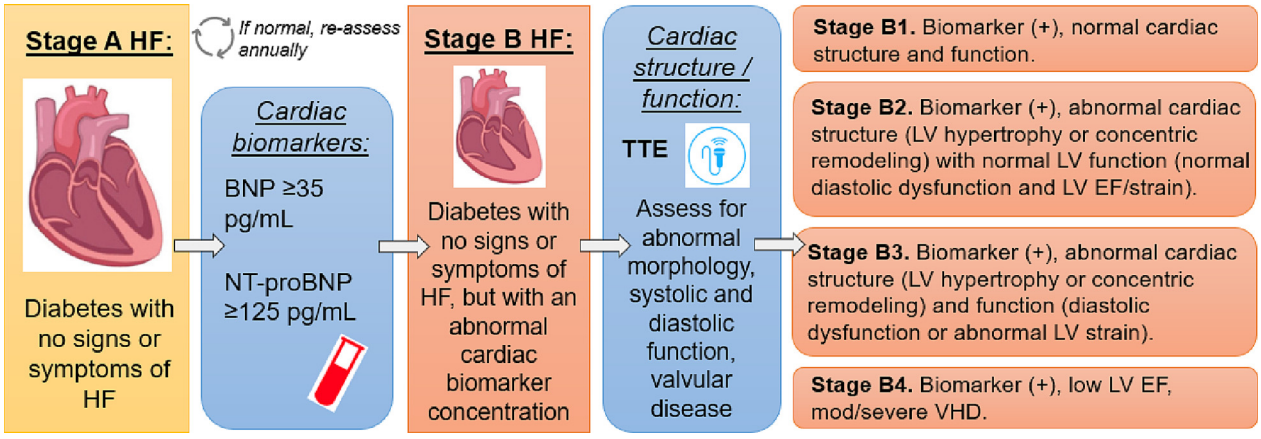

Fig. 7. Assessment of cardiac biomarkers and transthoracic echocardiogram to identify subclinical HF (Stage B) and subcategories of Stage B in PWD at high risk for developing HF. Cardiac structure and function parameters include the following: morphology = LV mass, LV wall thickness, relative wall thickness, LA volume; systolic function = LV EF, LV global longitudinal strain; diastolic function = E/e' (a non-invasive estimate of LA filling pressure and diastolic function), septal e' (the early diastolic wave on the septal side of the mitral annulus), lateral e' (the early diastolic wave on the lateral side of the mitral annulus), TR velocity, estimated PASP. Abbreviations: BNP = brain natriuretic peptide, E/e' = early mitral inflow velocity/mitral annular early diastolic velocity, EF = ejection fraction; HF = heart failure, LA = left atrium, LV = left ventricular, NT-proBNP = N-terminal proBNP, PASP = pulmonary artery systolic pressure, PWD = people with diabetes, TR = tricuspid regurgitation, TTE = transthoracic echocardiogram, VHD, valvular heart disease.

included BNP testing followed by an initial echocardiogram that was repeated annually. This approach effectively reduced a composite progression from Stage A to Stage B HF plus Stage C HF. Thus, stepwise testing of cardiac biomarkers followed by echocardiography among those with elevated biomarker concentrations represents an evidence-based approach for assessment of Stage B HF.

While cardiac biomarker testing as a screening strategy for Stage B HF is recommended based on existing evidence, it may not be pragmatic and feasible to screen all PWD with biomarker testing. Among people with T2D who are high-risk based on a clinical HF risk score,[97] echocardiography can be considered directly without requiring cardiac biomarker assessment. The presence of abnormal cardiac structure and function among people with T2D with high-risk factor burden, even in the absence of biomarker testing, would identify Stage B HF and warrant aggressive risk modification approaches as detailed below. Such strategies for HF risk stratification and prevention need to be validated and confirmed in prospective clinical trials to establish their clinical effectiveness.

Management of Stage A and Stage B HF

Lifestyle and Pharmacologic Therapy

As depicted in Table 10, management of Stage A and Stage B HF is focused on prevention of the development of clinical Stage C HF and can be divided into non-pharmacologically-based intensive lifestyle interventions (ILIs) (such as nutrition, physical activity, smoking cessation) and aggressive risk factor modification with evidence-based pharmacotherapies.

Economics

No economic analysis has been reported on a biomarker screening program for asymptomatic PWD. Given the limited amount of outcomes data to date for the exact benefits of identifying Stage B HF and preventing Stage C HF through biomarker screening, it is not clear who will pay for screening tests and whether public/private insurance or patients themselves will ultimately be responsible for the cost.

Future Directions

More clinical trial data is needed to increase confidence in the value of biomarker screening of PWD for HF prevention to promote clinician adoption of this procedure into their practices. Furthermore, some clinicians might have questions about specific steps to properly screen for and treat Stage B HF that were not covered in prior consensus statements. A list of types of additional information needed to increase clinician awareness and interest in biomarker screening for prevention of HF in PWD is presented in Table 11. This data and information will help clinicians understand the rationale behind the recommendations for biomarker screening and the proper way to screen.

Table 10
Assessment schedule and treatment plan for PWD in Stage A or Stage B HF's four subcategories as defined in this article. GDMT consists of ACEI or ARB plus beta-blocker plus SGLT2i for Stage B4 with reduced LV ejection fraction. Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CPX = cardiopulmonary exercise test, GDMT = guideline-directed medical therapy, HFrEF = heart failure with reduced ejection fraction, ILI = intensive lifestyle intervention, MRA = mineralocorticoid receptor antagonist, RF = risk factor, SGLT2i = Sodium-glucose cotransporter-2 inhibitor, T2D = type 2 diabetes, TTE = transthoracic echocardiogram.

		Stage A	Stage B1	Stage B2	Stage B3	Stage B4
Assessment	Repeat TTE 1–3 years		Y	Y	Y	
	Consider CPX				Y	
Plan	ILI	Y	Y	Y	Y	Y
	RF modification	Y	Y	Y	Y	Y
	GDMT for LV dysfunction					Y
	Refer to cardiology					Y
	In T2D, consider the initiation of SGLT2i therapy or other cardioprotective therapies (ACEI/ARB, beta blockers, MRA)		Y	Y	Y	Y

Table 11
Future directions for discovering additional information to improve clinician awareness and interest in biomarker screening for prevention of HF in PWD. Abbreviations: HF = heart failure, PONTIAC = PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease, PWD = people with diabetes, STOP-HF = St. Vincent's Screening to Prevent Heart Failure, T1D = type 1 diabetes, T2D = type 2 diabetes.

1. The likelihood of screening various types of Stage A (high risk) PWD and finding Stage B HF individuals (in addition to data from the PONTIAC [51] and STOP-HF [47] trials, ongoing studies such as PONTIAC II [NCT02817360] [122] and the ADOPT trial [NCT04286399] [123] will provide more guidance in this regard.)
2. The spectrum and frequencies of abnormalities on echocardiogram in PWD with Stage B HF. [124]
3. Determination of best treatments and strategies to prevent transition from Stage B to Stage C HF and identifying who should deliver the treatments. [125]
4. Global outcomes (e.g., quality of life, morbidity, and mortality) of biomarker screening programs intended to assess people with Stage A HF and prevent further progression from Stage A to Stage C and D HF.
5. The role of additional biomarkers, multiplex panels, clinical risk models, composite scores, circulating biomarkers [126] and artificial intelligence analyses of electrocardiograms. [127] as well as further clarification of the role of cardiac imaging studies for diagnosing types of Stage B HF.
6. The optimal cutpoints for biomarker concentrations to diagnose Stage B HF in PWD of various groups according to race/ethnicity/sex/age as well as PWD who also have kidney dysfunction, obesity, or natriuretic peptide deficiency.
7. The optimal biomarker rescreening frequency, including the implications of serial screening more or less frequently than annually.
8. The differences (if any) in benefits of biomarker screening between T1D and T2D patients.
9. Economic analyses of biomarker screening for HF in various populations with Stage A HF, including people with T1D and T2D.
10. Patient reported outcomes for preferences in screening tests [128]

Conclusions

This consensus report regarding the use of biomarkers for the diagnosis of HF in PWD presents specific diagnostic pathways leading to the characterization of four subcategories of Stage B HF (called B1 through B4). Each subcategory can be managed to decrease the risk of progression to Stage C and Stage D HF. The report is based on five features of HF in PWD: 1) HF is common in PWD, 2) if HF is not treated, then it can lead to serious complications and death, 3) subclinical asymptomatic HF can be diagnosed with biomarker screening in PWD who are, by definition, at high risk (and are said to be in Stage A HF) and who in some cases are actually at an early undetected preclinical stage of HF (called Stage B HF), 4) natriuretic peptides (BNP and NT-proBNP) are appropriate biomarkers to screen for preclinical Stage B HF, and 5) new treatments provide opportunities to prevent the progression of HF from preclinical to clinical stages.[98] Further research is needed to more specifically define the efficacy and economic implications of various screening and treatment programs. In summary, biomarker screening of HF for PWD should be considered as a best practice and part of routine care.

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Declaration of Competing Interests

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