HHS Public Access

Author manuscript

Circ Heart Fail. Author manuscript; available in PMC 2022 February 04.

Published in final edited form as:

Circ Heart Fail. 2021 February ; 14(2): e007761. doi:10.1161/CIRCHEARTFAILURE.120.007761.

A Risk-Based Approach for the Prediction and Prevention of Heart Failure

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Abstract

Targeted prevention of heart failure (HF) remains a critical need given the high prevalence of HF morbidity and mortality. Similar to risk-based prevention of atherosclerotic cardiovascular disease, optimal HF prevention strategies should include quantification of risk in the individual patient. In this review, we discuss incorporation of a quantitative risk-based approach into the existing HF staging landscape and the clinical opportunity that exists to translate available data on risk estimation to help guide personalized decision making. We first summarize the recent development of key HF risk prediction tools that can be applied broadly at a population level to estimate risk of incident HF. Next, we provide an in-depth description of the clinical utility of biomarkers to personalize risk estimation in select patients at the highest risk of developing HF. We also discuss integration of genomics-enhanced approaches (e.g. *TTN)* and other risk enhancing features to reclassify risk with a precision medicine approach to HF prevention. While sequential testing is very likely to identify low and high-risk individuals with excellent accuracy, whether or not interventions based on these risk models prevent HF in clinical practice requires prompt attention including randomized placebo-controlled trials of candidate therapies in risk-enriched populations. We conclude with a summary of unanswered questions and gaps in evidence that must be addressed to move the field of HF risk assessment forward.

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Disclosures:

Dr. Shah has received research grants from Actelion, AstraZeneca, Corvia, Novartis, and Pfizer; and has received consulting fees from Abbott, Actelion, AstraZeneca, Amgen, Axon Therapeutics, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Cardiora, CVRx, Cytokinetics, Eisai, GSK, Ionis, Ironwood, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Regeneron, Sanofi, Shifamed, Tenax, and United Therapeutics.

Keywords

Heart Failure; Risk Prediction; Biomarkers; Genetics

Introduction

The high lifetime risk of heart failure (HF) in the US population is well established and estimates range from 20–46%.[1,2] More than 8 million US adults are expected to have HF by 2030.[3] Therefore, it is crucial to develop strategies focused on HF prevention that can be implemented broadly across populations and within health systems. The current construct of HF stages defined by the American Heart Association (AHA) and the American College of Cardiology (ACC) categorizes asymptomatic individuals at risk of developing HF as Stage A or B. An analysis of the Coronary Artery Risk Development in Young Adults (CARDIA) cohort showed that the prevalence of Stage A/B increased from 21% between the ages of 22 and 37 to 68% between the ages of 47 and 62 (Figure 1).[4] However, there is substantial heterogeneity of risk within HF Stage A/B, and there remain specific groups that are not included in the current HF staging schema but are nonetheless at increased risk for symptomatic HF.

To-date, much of the focus in HF has been on prevalent, symptomatic Stage C patients. Numerous risk prediction models using different methodologies including machine learning have been developed to estimate prognosis in symptomatic HF.[5–7] In spite of significant advances in pharmacological, device, and surgical interventions for HF,[8, 9] overall morbidity and mortality remain high and quality of life remains poor once symptomatic HF has developed.[3, 10, 11] Thus, the focus needs to shift upstream to Stages 0 through B to prevent or delay the onset of symptomatic HF (Figure 2). The availability of management strategies (e.g. lifestyle modification,[12–14] intensive blood pressure lowering[15]) and novel therapies (e.g. sodium glucose co-transporter 2 [SGLT2] inhibitors[16]) that can prevent or delay onset of symptomatic HF provides a compelling basis for the need to transform towards a risk-based paradigm in HF prevention. Specifically, earlier detection of high-risk individuals within Stage A or those with subclinical disease in Stage B who may derive the greatest benefit will inform a targeted approach to preventive interventions as has been demonstrated in biomarker-based trials for HF prevention.[17, 18] Finally, identifying high-risk individuals may be utilized in clinical trial screening to study novel therapies in a risk-enriched population.

In order to match the intensity of prevention efforts with the absolute risk of the individual, a comprehensive understanding of HF risk prediction, reclassification, and personalization is needed. We aim to summarize the relevant data and create a framework for refining risk prediction within the heterogeneity of the current classification system to inform interventions focused on risk-based prevention of HF. In this review, we describe (1) available HF risk prediction models to calculate risk; (2) use of biomarkers to reclassify HF risk; (3) novel risk enhancers including genetics to personalize risk; (4) selective use of noninvasive imaging to identify subclinical dysfunction; and (5) unanswered questions and

gaps in evidence that must be addressed in order to move the field of HF risk assessment forward.

Clinical Risk Prediction Models for Incident HF

The primary goal of a risk prediction model is to accurately quantify risk in the general population using readily available clinical variables. As HF can be caused by a wide array of etiologies, from familial dilated cardiomyopathy to ischemic heart disease, a single risk prediction model will not capture all of those at risk. This highlights the need to incorporate non-traditional risk enhancers in HF risk assessment to account for the heterogeneity within HF. However, traditional cardiovascular risk factors remain the predominant contributors to the population burden of HF.[19, 20] Thus, the risk prediction model, which can ideally be used in the primary care setting for a large fraction of the general population, should be focused on the major cardiovascular risk factors. Herein, we restricted our discussion to risk prediction models that use factors readily available to primary care clinicians, specifically clinical history, routine lab values from lipid and metabolic panels, and/or electrocardiogram findings. In order to identify risk prediction scores that were generalizable, we focused on models derived from population-based cohorts free of baseline HF with external validation in a separate population-based cohort.

Criteria for evaluating risk prediction models have been previously described and most commonly include discrimination and calibration.[21, 22] Discrimination is the ability of the model to distinguish those who will get the disease from those who will not and is assessed by determining the area under the receiver-operating-characteristic curve (AUC). The AUC incorporates both sensitivity and specificity of the prediction model with a value of 0.5 representing no discrimination and a value of 1.0 representing perfect discrimination. Calibration refers to the agreement between predicted and observed risks across the spectrum of baseline risk. Calibration is commonly measured using the Hosmer-Lemeshow χ^2 or Greenwood-Nam-D'Agostino (GND) statistics, with a p-value >0.05 representing no significant difference. We report the AUC and calibration statistic, when available, for each of the models discussed here.

The utility of an easy to use risk calculator that clinicians can incorporate into their clinical visits has been well demonstrated with the Pooled Cohort Equations (PCE), a 10-year risk prediction model for atherosclerotic cardiovascular disease (ASCVD). The current AHA/ACC guidelines for primary prevention of ASCVD use the PCE to personalize and guide both cholesterol and blood pressure management.[23, 24] Development of a validated HF risk calculator comprised of clinical variables that can be easily obtained during a clinic visit may similarly allow for targeted implementation of preventive therapies.

General Population-Based Cohort Risk Models of Incident HF

HF risk prediction models from population-based cohort studies with published external validation are summarized in Table 1. If available, we also included in Table 1 the risk prediction models derived in the cohorts that were used for external validation. One of the earliest HF risk prediction scores was developed in the Framingham Heart Study (FHS) cohort. This 10-year risk model included a mix of clinical risk factors such as age, systolic

blood pressure (SBP), heart rate (HR), T2DM, body mass index (BMI), left ventricular hypertrophy (LVH) on electrocardiogram, coronary artery disease (CAD), and significant valvular disease on auscultation.[25] In this cohort, CAD was the strongest predictor of incident HF. External validation of the FHS HF risk score was attempted in both the Atherosclerosis Risk in Communities (ARIC) and the Health Aging and Body Composition (ABC) study cohorts. It did not perform well in the ARIC cohort with an AUC of only 0.61.[26] In the Health ABC study cohort, the FHS HF risk score was adapted to provide a 5-year HF risk prediction.[27] The risk score discriminated better in men (AUC 0.74) than in women (AUC 0.68). The overall poor performance of the FHS risk score was likely due to differences in the age and racial composition of the cohorts. These findings underscore the need for external validation of risk predictions scores in multiple cohorts with diverse populations.

The HF risk score developed in the Health ABC study cohort consisted of age, SBP, HR, smoking status, LVH, CAD as well as routine laboratory values such as serum creatinine, glucose, and albumin.[27] Since the baseline age was older (70–79 years) for this cohort, the HF risk score was based on a 5-year risk prediction model. Prevalent CAD was again the strongest predictor of incident HF. The Health ABC HF model had an AUC of 0.72 by internal validation and good calibration (χ^2 6.24, p = 0.62). The Health ABC HF risk score was externally validated in the ARIC cohort and performed well with respect to discrimination (AUC 0.79).[26] It was also externally validated in the Cardiovascular Health Study (CHS) cohort and performed relatively well with good discrimination (AUC 0.74) and calibration (χ^2 14.72, p = 0.14).[28]

Both the FHS and Health ABC HF risk scores are inherently limited in generalizability as they are derived from single cohorts focused on specific population subgroups. A pooled study of participants from the FHS, PREVEND (Prevention of Renal and Vascular End-stage Disease), and CHS cohorts developed risk prediction models specific for HF subtypes (heart failure with persevered ejection fraction, HFpEF and heart failure with reduced ejection fraction, HFrEF).[29] The HFpEF specific model included age, sex, SBP, BMI, antihypertensive treatment, and previous myocardial infarction (MI). The model was applied to a validation sample and had an AUC of 0.79 with good calibration (χ^2 9.02, p = 0.34) The HFrEF specific model additionally included smoking, LVH, left bundle branch block (LBBB), and T2DM. In the validation sample, the model had an AUC of 0.80 with reasonable calibration (χ^2 14.19, p = 0.08). Both models were then externally validated in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. Both models performed well with good discrimination (HFpEF AUC 0.76, HFrEF AUC 0.76) and good calibration (HFpEF χ^2 4.54, p = 0.81, HFrEF χ^2 7.56, p = 0.48). However, over 95% of the discovery cohort was white, limiting generalizability. Furthermore, one global HF risk score, may make clinical implementation easier and is more clinically relevant given shared risk factors between HFrEF and HFpEF.

The prediction models discussed so far were developed in cohorts that included individuals with prevalent CAD. Their applicability is limited in the context of identifying high risk individuals for targeted primary prevention as individuals with CAD or MI should already be considered at high risk for HF and be on preventive therapies. An optimal derivation cohort

for development of incident HF prediction model should exclude individuals with baseline ASCVD. The Pooled Cohort equations to Prevent HF (PCP-HF) were developed using pooled individual participant-level data free of ASCVD from 5 diverse cohorts, including ARIC, CARDIA (Coronary Artery Risk Development in Young Adults), CHS, FOF (Framingham Offspring Study), and MESA.[30] Pooling across multiple contemporary cohorts allowed for a large enough sample size to generate race- and sex-specific models. The variables in the risk score included age, sex, race, SBP, hypertension treatment, fasting plasma glucose, T2DM treatment, BMI, smoking status, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and QRS duration (optional). Among white men and women, and Black men and women in the internal validation sample, the AUC in each race-sex group was 0.79, 0.71, 0.85, and 0.78, respectively. The equations had good calibration in the internal validation sample as assessed by GND statistic ($p > 0.05$ for all). The models were then externally validated in white participants from the PREVEND cohort and in Black participants from the Jackson Heart Study (JHS) with good discrimination (AUC ranging from 0.71 to 0.88) and strong calibration. The models have been further validated in a diverse cohort from a single integrated health system leveraging electronic health record data.[31] Limitations of this risk score include the use of cohorts from earlier time periods and unclear applicability to other racial/ethnic ancestry groups such as Latinx or Asian.

Similar to the PCE for ASCVD, a tool such as the PCP-HF score can provide a quick and easy method for initial risk stratification to identify individuals at high risk for developing symptomatic HF. For example, a threshold of >5% predicted 10-year risk, which represents the top 10th percentile of the US population, could be proposed to categorize individuals at high risk who may benefit from enhanced surveillance with sequential risk stratification and application of preventive therapies and behavioral interventions aimed at preventing HF. Further studies are needed to examine different risk thresholds for interventions.

An important limitation in the studies discussed here is the difference in the definition of HF between cohorts. For example, most cohorts only reviewed hospitalizations while certain cohorts such as FHS, CHS, and MESA reviewed study and clinic examinations in addition to hospitalizations to determine HF events. HF events in the ARIC cohort were identified using administrative diagnosis codes from HF hospitalizations and death certificates, while the other cohorts had independent adjudication of using a combination of symptoms, physical exam findings, and imaging.

Clinical Risk Prediction Models for Incident HF in T2DM

A HF risk prediction model specifically for individuals with T2DM is of considerable interest given the strong association of T2DM with HF and the emergence of SGLT2 inhibitors, which can reduce HF in patients with T2DM by 23%.[16, 32] Incident HF is also the most common initial cardiovascular presentation in patients with T2DM and given the rising prevalence of T2DM, stratifying HF risk in this population is of importance.[33, 34]

The predictors and performance characteristics of HF risk prediction models specific to T2DM that have been externally validated are described in Table 2. A 10-year HF risk prediction score (QDiabetes) was developed in individuals free from HF from the QResearch cohort, a patient-level database of over 1000 general practices covering a population >20

million patients in England.[35] The risk score performed well with good discrimination and calibration in the internal validation dataset as well as in an external validation cohort of 357 separate general practices in England. T2DM-specific HF risk scores have also been developed using clinical trial populations. The WATCH-DM score was created using participants free from HF at baseline from the ACCORD (Action to Control Cardiovascular Risk in T2DM) trial and validated in individuals with T2DM from ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial).[36] Similarly, a clinical risk score was developed using participants randomized to placebo in SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with T2DM Mellitus-Thrombolysis in Myocardial Infarction 53) and externally validated in the placebo arm of DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58).[37]

However, these diabetes-specific risk scores have limitations. The QDiabetes risk score was developed and derived in databases that used diagnostic codes, which may lead to ascertainment bias. The clinical trial-based scores clearly cannot be generalized at a population level since trial inclusion criteria creates significant selection bias. In addition, the risk models included participants with established ASCVD or very high baseline cardiovascular risk. Therefore, it is unclear whether these risk scores would be useful in discriminating HF risk in the broader population of those with diabetes without underlying ASCVD. It is unknown whether they improve risk classification compared with the more generalizable HF risk scores discussed in the prior section.

HF Risk Reclassification

While clinical risk scores can be broadly applied to a general primary prevention population and are a key first step in risk assessment, validated biomarkers can further personalize risk estimates and minimize misclassification in Stage A/B HF patients. Net reclassification index (NRI) is an important, clinically relevant measure that helps quantify how well a new marker reclassifies patients when added to the existing the model.[38] It is a sum of the proportion of patients that are correctly up-classified and down-classified with the introduction of a new marker. We limit our discussion primarily to widely available biomarkers such as B-type natriuretic peptide (BNP) and troponin, which can be readily adopted in clinical practice. We also briefly discuss the role of a multi-biomarker approach.

Natriuretic Peptide System

In response to ventricular myocardial wall stretch, pre-proBNP is synthesized and processed to pro-BNP, which is further processed into the biologically inactive N terminal-proBNP (NT-proBNP) and the biologically active BNP. The BNP pathway plays a fundamental role in cardiovascular remodeling and volume homeostasis and has been extensively studied in diagnosis of clinical HF, HF risk stratification, and as a pharmaceutical target for HF treatment.[39, 40]

A few studies have evaluated the improvement in HF risk prediction, as measured by categorical NRI, when BNP or NT-proBNP is added to the model. In the MESA cohort, addition of NT-proBNP significantly improved the HF risk prediction model (categorical

NRI = 0.37). The improvement was primarily due to upward reclassification of individuals who subsequently developed HF.[41] In the ARIC cohort, NT-proBNP was added to three separate HF risk prediction models.[26] The addition of NT-proBNP significantly improved the FHS, Health ABC, and ARIC HF risk prediction models, as measured using categorial NRI, by 0.18, 0.12, and 0.13, respectively. The addition of NT-proBNP to the Health ABC HF risk score was also assessed in the CHS cohort.[42] NRI was observed in 11% of the individuals with participants classified as intermediate risk by the clinical model deriving the greatest benefit. Similarly, in the Malmo Diet and Cancer Study, a community-based cohort in southern Sweden, NRI was observed in 16% of individuals with the addition of NT-proBNP to conventional risk factors.[43] Again, this was mostly due to substantial upward reclassification to a higher risk category.

High-Sensitivity Troponin

High sensitivity (hs)-troponin is another commonly used biomarker that has been shown to be associated with incident HF and represents subclinical myocardial damage from underlying nonischemic etiology.[44, 45] A prospective cohort of elderly individuals from CHS illustrated a 2.5-fold higher risk of HF in participants with the highest level of hs-troponin T (>12.94 pg/mL) compared to those with an undetectable level of hs-troponin T (<3 pg/mL).[46] The higher risk did not attenuate even after further adjustment for BNP. In those who had repeat measures during follow-up, a rising trajectory was associated with a greater risk of HF while a declining trajectory was associated with a lower risk of HF. However, the addition of troponin T to a clinical risk model led to a modest NRI of 0.04. In the ARIC cohort, addition of hs-troponin I to the PCE led to a NRI of 0.09 for incident HF.[47]

Multi-biomarker Approach

A multi-biomarker approach is an appealing way to incorporate information from different pathways implicated in HF development. In the FOF cohort, the strength of association of soluble ST2, growth differentiation factor-15, and hs-troponin I with HF was similar to that of BNP.[48] When these biomarkers were added to C-reactive protein and BNP to create a multi-biomarker score, individuals with scores in the highest quartile had a 6-fold higher risk of HF. Addition of the multi-biomarker score to the best-fit clinical model for HF led to a categorical NRI of 0.13. Another study in the FOF cohort demonstrated urinary albumin-to-creatinine ratio (UACR) to be a key predictor of HF.[49] Addition of UACR and BNP to a clinical risk model led to NRI of 0.13. Higher UACR has been associated with impaired endothelial dysfunction in different patient populations[50, 51], which is increasingly recognized as an important pathway in HF.[52] Findings from these two studies suggest a modest additive value of incorporating multiple biomarkers beyond BNP in HF risk prediction models. Additional research is needed to determine which individuals may benefit from sequential multi-biomarker screening.

Risk Enhancers for Incident HF

HF risk prediction models based on traditional cardiovascular risk factors can perform well, but they likely underestimate risk in individuals with non-traditional risk factors. Specifically, genetic susceptibility for HF is identified as a key risk enhancer (Stage A) and

will be the focus of this section to personalize risk stratification. Additional risk enhancing features also need to be considered to better identify individuals at high risk for HF. These include a myriad of comorbidities outlined in Table 3 and include chronic kidney disease, chronic liver disease, adverse pregnancy outcomes, chronic inflammatory diseases, radiation therapy, and history of cardiotoxic chemotherapy exposure.

Genetic or Inherited Cardiomyopathies

Nearly one-fifth of the community burden of HF can be attributed to heritable factors.[71] Both Mendelian (single gene) and non-Mendelian (common variants) genetic underpinnings of HF have been well-described. For the single gene mutations, there is a well described complexity of variable penetrance and expressivity of the genetic mutations which typically follow autosomal dominant inheritance patterns. In some gene mutations like *TTN* (titin) and certain arrhythmogenic right ventricular cardiomyopathy gene mutations, earlier or more severe manifestation of the phenotype may occur with concomitant exposure to environmental insults (e.g. hypertension), providing an opportunity for more intensive prevention strategies.[72] The range of genetic contribution to HF is starting to be better understood, from rare pathogenic variants involved in inherited cardiomyopathies (development of dilated [DCM] and hypertrophic [HCM] cardiomyopathies) to more prevalent genetic variants that are increasingly being recognized as potential risk enhancers for HF.

Conservative estimates place the prevalence of DCM and HCM at 1 in 250 and 1 in 500, respectively. Currently, nearly 30% of DCM cases and over 50% of HCM cases have an identified genetic cause.[73] The genes in which DCM-associated pathogenic variants most commonly occur include *TTN*, lamin A/C (*LMNA*), and β-myosin heavy chain (*MYH7*).[73] In HCM, mutations in *MYH7* and cardiac myosin binding protein-c (*MYBPC3*) account for 80% of inherited cases. The age of onset of DCM and HCM associated with specific mutations varies from adolescence to early middle-age or even later for DCM mutations. Therefore, it is crucial to obtain a targeted three-generation family history to identify potential asymptomatic individuals who are at significantly higher risk than their clinical HF risk score would otherwise suggest. An underlying genetic cardiomyopathy should be considered when two or more family members have been reported to have HF or a first-degree relative has had a premature sudden cardiac death without a well-defined cause.[74] A positive family history should lead to cascade clinical assessment of the patient with ECG, echocardiography, and possibly heart rhythm monitoring.

Broadening the Role of Genetic Testing in HF

While cascade testing is essential for asymptomatic individuals with family history, family history is often an insensitive tool in identifying individuals with a genetic component to their HF.[75] Even in individuals with isolated LV dysfunction without HCM or DCM, nearly 1 in 6 individuals without family history had a pathogenic mutation in DCM-related genes.[76] Similarly, there is evidence that certain pathogenic mutations, primarily in *TTN*, create a genetic predisposition to HF due to other causes such as alcohol, chemotherapy and peripartum cardiomyopathy.[77–79] Given the emerging understanding of this interaction between genetics and other etiologies of HF, a more broad and systematic approach to

genetic testing should be considered in individuals with HF.[80] Determining a potential genetic component is important for subsequent family screening, which would lead to identification of asymptomatic individuals at risk, as well as to inform life-saving changes to management (e.g. implantable cardioverter defibrillator) and prognostication.[81]

Furthermore, a genomics-informed (or genomics-first) approach may be used for certain genetic variants that have a high enough prevalence in certain population subgroups and may serve to guide risk reduction strategies. As genetic risks can be identified at birth, earlier diagnosis and initiation of preventive therapies may be a possibility. In this setting, such gene variants are considered risk alleles for HF and do not necessarily represent monogenic causes of HF. Examples of such genetic variants include titin truncating variants (TTNtv) in individuals with European ancestry, a transthyretin (*TTR*) variant in African Americans, and a *MYBPC3* variant in south Asians. While nearly 15–20% of patients with DCM have a TTNtv, we have only recently started to understand the significance of TTNtv in the general population. The prevalence of TTNtv was approximately 0.5% in individuals with European ancestry and was associated with a 4.1-fold higher risk of incident HF.[82] Similarly, the variant leading to valine to isoleucine amino acid substitution at position 122 (V122I) of transthyretin is present in nearly 4% of the African American population.[83] Multiple studies have shown that the presence of the V122I *TTR* variant increases the risk of incident HF by approximately 1.5-fold.[84, 85] The frequency of a 25 base-pair deletion in the *MYBPC3* gene is 4% in south Asians. This deletion is associated with a nearly 7-fold higher risk of HF.[86] Therefore, current strategies incorporating genetics into HF prevention should focus on screening for common variants with clear underlying pathophysiology in race-specific subgroups.

Refining Risk with Detailed Phenotyping of Cardiac Mechanics

Identification of high-risk Stage 0/A HF patients with quantitative risk assessment and sequential testing with biomarkers (including possible genetic risk and other risk enhancers) can help create an enriched pool that would achieve the greatest benefit from direct myocardial imaging to aid in early detection of Stage B HF. Classically, Stage B HF refers to structural heart disease such as prior MI, LVH, reduced left ventricular ejection fraction (LVEF), and valvular disease. Data from the Olmsted County, Minnesota cohort found the prevalence of systolic dysfunction, as defined by LVEF ≤ 50%, to be 6% and the prevalence of moderate or severe diastolic dysfunction with normal LVEF to be 5.6%.[87] The prevalence of Stage B HF, encompassing a wide range of structural abnormalities, was estimated to be 34% in a cross-sectional study of Olmsted County residents.[88] In the more recent analysis from the CARDIA cohort, 26% of middle-aged adults had Stage B HF.[4] Individuals with Stage B HF and especially a decreased EF are at a significantly greater risk of developing HF, estimated to be near 10% risk over 10 years.[89]

As demonstrated in the SOLVD prevention trial, early identification of asymptomatic LV dysfunction in patients can lead to implementation of beneficial preventive therapies, such as beta-blockers and angiotensin converting enzyme inhibitors, that help reduce progression to Stage C HF.[90, 91] In addition to medical therapy, multiple studies have demonstrated the importance of lifestyle in HF prevention. Specifically, physical activity, defined as ≥150

min/week of moderate intensity or ≥75 min/week of high intensity activity, has been associated with a lower risk of HF.[12–14] While direct evidence of a specific diet reducing HF risk is lacking, different types of diet have been effective in preventing HF risk factors such as T2DM, hypertension, and ASCVD.[92–94] Since these lifestyle changes are directly tied to social determinants of health, they need to be addressed by health systems and public health institutions via broader policy changes. Whether other therapies effective for treatment of Stage C HFrEF, such as mineralocorticoid receptor antagonists (MRA), angiotensin receptor-neprilysin inhibitor, and SGLT2 inhibitors, are also of benefit for the prevention of HF in patients with asymptomatic left ventricular dysfunction warrants further investigation. Furthermore, the use of more sensitive imaging markers such as LV global longitudinal strain (LV-GLS) may also better identify individuals at risk that can be intervened upon earlier to prevent HF.[95, 96]

Risk Based HF Prevention Trials

Our discussion on risk assessment, reclassification, and personalization identifies a pathway for selecting high-risk individuals for intervention trials focused on HF prevention. There have been two landmark studies that have evaluated the effect of BNP-based screening on HF prevention. The STOP-HF trial included adults with at least one HF risk factor and no evidence of systolic dysfunction or symptomatic HF with a mean age of 65 years.[17] The participants randomized to the BNP-guided group had 45% lower development of LV dysfunction with or without HF over a 4-year period compared with those randomized to routine primary care. Along with more diagnostic interventions, there was a greater use of RAAS modifying therapies in the BNP-guided group. The PONTIAC trial was a similar study in patients with T2DM and no history of HF, who had an NT-proBNP level greater than 125 pg/mL. The participants randomized to the intensive therapy group were treated with up-titration of RAAS antagonists and beta-blockers, which resulted in a 5-fold lower incidence of hospitalization for HF compared with the routine care group.[18]

These two trials led to the class IIB recommendation of BNP screening in patients at high risk for HF in the 2017 AHA/ACC HF guidelines.[97] However, it remains unclear how to identify these high-risk individuals, thus highlighting the need for a readily available risk score to appropriately select an enriched population that would benefit from biomarker testing, as opposed to shotgun screening. While 40% of the BNP-guided arm in STOP-HF had a BNP value above the threshold, nearly 25% of the treatment group had known ASCVD including prior MI. In a broader population without underlying ASCVD or prior MI, indiscriminate BNP screening is likely to be of low yield. Therefore, measuring BNP as a secondary testing strategy to reclassify individuals with an intermediate clinical risk score is likely to be of more value, while keeping in mind BNP-deficient states associated with higher BMI and African ancestry where the clinical utility of high sensitivity troponin and other biomarkers may be greater.[98–100]

Future Directions

The next phase in HF prevention research must be focused on examining efficacy of novel therapies in reducing incident HF in populations at greatest risk (Table 4). Risk-based trials

utilizing risk scores, such as the race- and sex-specific PCP-HF tool, are needed to investigate the benefits of a management strategy guided by the PCP-HF risk score followed by sequential biomarker testing and cardiac imaging in high-risk individuals compared with usual care. The risk-based management strategy should evaluate a variety of interventions, including disease modifying therapies (e.g. RAAS agents), targeted uptake of SGLT2 inhibitors in those with or without DM, intensive risk factor modification, and lifestyle education. In addition, longitudinal studies are needed to determine how a genomics-enhanced approach with highly prevalent risk alleles for HF can best be translated into actionable clinical interventions. Specifically, it is not clear whether these risk alleles have synergy with HF risk factors and thus carriers may benefit from aggressive risk factor modification earlier in life. Novel therapies targeted at certain culprit genes such as *TTR* need to be studied in the context of HF prevention in carriers of risk alleles who have Stage B HF.

Conclusions

Given the growing burden of HF on the healthcare system, a systematic approach to risk assessment of HF is necessary to inform personalized clinical approaches for precision prevention in those at highest risk for developing HF. We advocate for an easy-to-use clinical risk tool that can be applied broadly in the US population to estimate risk of HF. Risk for HF can be further reclassified using biomarkers such as BNP and UACR. Risk enhancing features including genetic risk also must be considered when determining an individual's risk of HF. Those at high risk should undergo echocardiography to evaluate for structural heart disease and adverse cardiac mechanics, which may help refine risk and identify those who would benefit most from preventive strategies. In order to create this paradigm shift in HF prevention towards a risk-based approach, randomized clinical trials in risk-enriched populations are needed to generate the evidence base to support that this structured approach can decrease incident HF by focusing preventive strategies on those with the highest risk.

Acknowledgements:

The funding sponsors did not contribute to design and conduct of the study, collection, management, analysis, or interpretation of the data or preparation, review, or approval of the manuscript. The authors take responsibility for decision to submit the manuscript for publication. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding:

Dr. Arjun Sinha is supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number T32HL069771. Dr. Sadiya Khan is supported by grants from the National Institutes of Health/ National Heart, Lung, and Blood Institute (KL2TR001424) and the American Heart Association (#19TPA34890060). Research reported in this publication was supported, in part, by the National Institutes of Health's National Center for Advancing Translational Sciences, Grant Number KL2TR001424. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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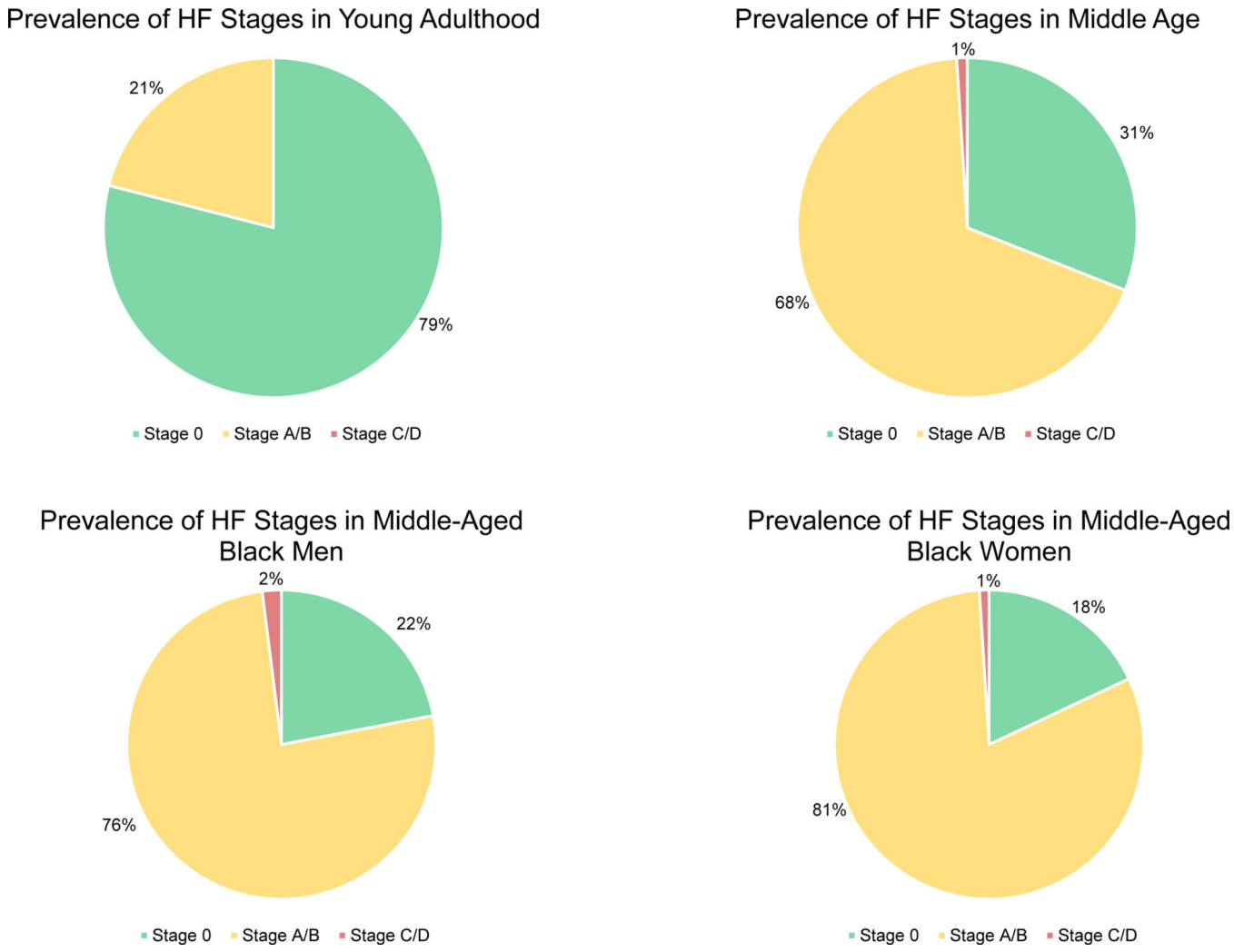

Figure 1.

Prevalence of asymptomatic and symptomatic American Heart Association/American College of Cardiology Stages of Heart Failure (adapted from the Coronary Artery Risk Development in Young Adults study)[4]

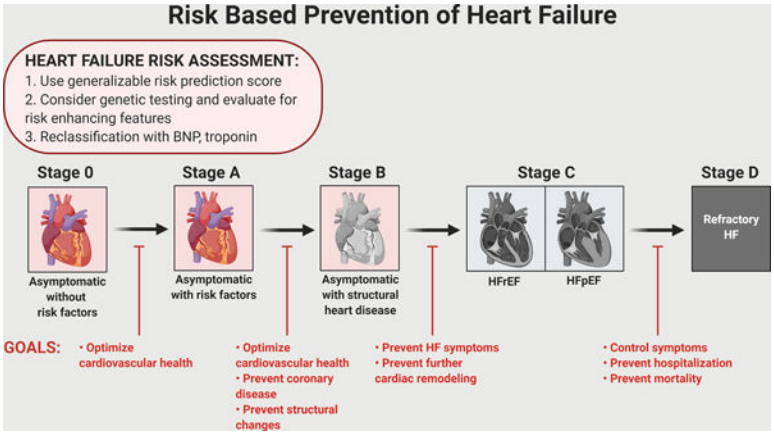

Figure 2.

Overarching conceptual diagram of heart failure prevention (primordial, primary, and secondary) across the American Heart Association/ American College of Cardiology Stages

Table 1.

Incident heart failure risk prediction models from population-based cohorts

Study Cohort	Demographics	HF Predictors	Internal Validation	External Validation
Free of CVD from Population-Based Cohorts				
Pooled Cohort Equations to Prevent Heart Failure (ARIC, CARDIA, CHS, FOF, MESA)	Ages: 30–79 White: 78%, Black: 22% Follow-up: 12 years	Age, race, sex, smoking status, SBP, HTN medication, glucose, diabetes medication, TC, HDL-C, LDL-C, QRS duration	Whites Men – AUC: 0.79; Calibration: p = 0.06 Women – AUC: 0.85; Calibration: p = 0.14 Blacks Men – AUC: 0.71; Calibration: p = 0.78 Women – AUC: 0.78; Calibration: p = 0.33	PREVEND (Whites) Men – AUC: 0.80; Calibration: p = 0.03 Women – AUC: 0.87; Calibration: p = 0.30 JHS (Blacks) Men – AUC: 0.74; Calibration: p = 0.75 Women – AUC: 0.76; Calibration: p = 0.06
MESA	Ages: 45–84 White: 39%, Black: 28%, Hispanic: 22%, Chinese: 12% Follow-up: 5 years	Age, sex, smoking status, BMI, SBP, HR, DM, creatinine	AUC: 0.87	--
Inclusion of Participants with Prior CVD from Population-Based Cohorts				
Framingham	Ages: 45–94 White: 100%, Black: 0% Follow-up: 38 years	Age, SBP, HR, LVH, CAD, DM, valvular disease, BMI	AUC: NR Calibration: NR	ARIC – AUC: 0.614; Calibration: NR Health ABC – AUC: 0.735 (men), AUC 0.684 (women); Calibration: NR
ARIC	Ages: 45–64 White: 73%, Black: 27% Follow-up: 15 years	Age, race, sex, CAD, SBP, HTN medication, DM, smoking status, HR, BMI	AUC: 0.797 Calibration: NR	--
Health ABC	Ages: 70–79 White: 59%, Black: 41% Follow-up: 6 years	Age, SBP, HR, smoking status, LVH, CAD, creatinine, glucose, albumin	AUC: 0.72 Calibration: p=0.62	ARIC – AUC: 0.785; Calibration: NR CHS – AUC: 0.74; Calibration: p = 0.14
International Collaboration of HF subtypes (FHS, CHS, PREVEND)	Ages: 30–79 22048 White: 95%, Black: 5% Follow-up: 13 years	HFpEF: age, SBP, BMI, HTN medication, prior MI HFrEF: age, sex, SBP, BMI, HTN medication, prior MI, LVH, LBBB, DM	HFpEF – AUC: 0.79; Calibration: p = 0.34 HFrEF – AUC: 0.80; Calibration: p = 0.08	MESA HFpEF – AUC: 0.76; Calibration: p = 0.81 HFrEF – AUC: 0.76; Calibration: p = 0.48

Table 2.

Incident heart failure risk prediction models in clinical trial populations with Type 2 diabetes mellitus

Study Cohort	Demographics	HF Predictors	Internal Validation	External Validation
ACCORD Trial (WATCH-DM)	Ages: 55–79 White: 63%, Black: 19%, Hispanic: 7%, Others: 11% Follow-up: 5 years	Age, BMI, SBP, DBP, glucose, creatinine, HDL-C, QRS duration, prior MI, prior CABG	AUC: 0.72 Calibration: p = 0.23	ALLHAT Trial AUC: 0.74 Calibration: p = 0.20
SAVOR-TIMI 53	Ages: 55–75 White: 75%, Hispanic: 22% Other: 3% Follow-up: 2 years	Atrial fibrillation, CAD, GFR, UACR	AUC: 0.81 Calibration: NR	DECLARE-TIMI 58 AUC: 0.78 Calibration: p = 0.20
QResearch	Ages: 25–84 White: 83% South Asian: 9% Black: 4% Other: 4%	Age, BMI, SBP, TC/HDL-C ratio, HbA1c, material deprivation, ethnicity, smoking, duration of diabetes, atrial fibrillation, CVD, chronic kidney disease	Men – AUC: 0.764; Calibration: NR Women – AUC: 0.770; Calibration: NR	CPRD Men – AUC: 0.769; Calibration: NR Women – AUC: 0.783; Calibration: NR

Table 3.

Summary of cardiac dysfunction and heart failure risk secondary to risk-enhancing features

Risk Enhancing Feature	HF and Cardiac Dysfunction Risk	Disease-specific Risk Factors
Chronic Kidney Disease[53–55]	1. 2-fold increase with eGFR <60 ml/min/1.73m^2 2. 1.5 to 5-fold increase with increasing levels of albuminuria	Anemia, insulin resistance, inflammation
Chronic Liver Disease[56]	1. Prevalence of cirrhotic cardiomyopathy as high as 40%	Hyperdynamic circulation, inflammation
Chronic Inflammatory Diseases[57]	1. RA: 1.3 to 2-fold increase[58, 59] 2. SLE: 3-fold increase[60] 3. SSc: 3 to 7-fold increase[61] 4. Psoriasis: 1.2 to 1.5-fold increase[62] 5. HIV: 1.5 to 2-fold increase[63, 64]	1. RA: +RF, elevated ESR, severe extraarticular manifestations 2. SLE: disease severity especially nephritis 3. SSc: diffuse cutaneous subtype, positive SSc specific serology, peripheral myositis[65] 4. Psoriasis: disease severity 5. HIV: low nadir CD4, low current CD4, high viral load
Cardiotoxic Chemotherapy[66]	1. Anthracyclines: 2–20% incidence rate of cardiac dysfunction 2. HER2 inhibitors: 3% incidence rate of cardiac dysfunction 3. Alkylating agents: 22% incidence rate of cardiac dysfunction 4. Taxanes: 0.7% incidence rate of cardiac dysfunction 5. VEGF inhibition: 0.2–20% incidence rate of cardiac dysfunction 6. Immune checkpoint inhibitors: 0.06 to 1% incidence rate of myocarditis	Advanced age, female sex, CAD, cardiovascular risk factors, prior history of chest radiation, concurrent or sequential use of multiple cardiotoxic chemotherapies
Radiation Therapy[67]	1. Decreased LVEF in 7–15% with anterior radiation 2. Diastolic dysfunction in 22% of survivors of childhood cancer	CVD risk factors, concomitant anthracycline use, anterior or left chest irradiation
Adverse Pregnancy Outcomes[68–70]	1. Pre-term birth: 1.6-fold increase 2. Pre-eclampsia: 2.2-fold increase 3. Maternal placental syndromes: 1.5-fold increase	Hypertension, older age at pregnancy

Table 4.

Future directions and unmet needs

Question	Significance	Future Directions
Does using a HF risk score to identify individuals for preventive interventions reduce incident HF?	Important to identify patients that will gain the greatest benefit from early use of emerging preventive therapies	Trials comparing a clinical risk score-based strategy of management including subsequent use of biomarkers, imaging, and interventions focused on HF prevention compared with usual care
Does intensive lifestyle intervention in high-risk adults reduce incident HF?	Programs like the diabetes prevention program have shown significant benefits for risk factor management, and a similar framework needs to be explored with HF prevention	Creation and implementation of an intensive lifestyle program focused on adults at high-risk for HF with longitudinal follow-up to determine efficacy
When should biomarker or imaging-based screening be started in individuals with highly prevalent risk alleles to identify subclinical cardiac dysfunction?	The V122I *TTR* variant and the *MYBPC3* deletion variant are present in nearly 4% of the African American and South Asian populations, respectively	Longitudinal cohort studies of young to middle-aged African American and South Asian adults with genetic data and contemporary cardiac imaging
In adults with *TTR* risk alleles, does initiation of TTR-specific therapies or aggressive risk factor modification during the subclinical phase prevent onset of HF?	Interaction of *TTR* risk alleles with clinical risk factors is not known; rationale for early use of TTR-specific therapies is based on the underlying pathophysiology and may significantly reduce morbidity and mortality	Large longitudinal cohorts studies to evaluate the interaction between *TTR* risk alleles and clinical risk factors; clinical trials of TTR-specific therapies in patients with *TTR* risk alleles and Stage B HF
How should HF risk be assessed in individuals with different risk enhancing features?	Clinical risk scores validated in the general population have not been specifically evaluated in these populations and disease-specific characteristics may need to be added to the score to improve its performance	Use of multicenter registries, specialized cohort studies, and electronic health record data to identify large enough cohorts for these more rare risk enhancing diseases