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Treatment Strategies for the Prevention of Heart Failure

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Abstract

With the astounding morbidity and mortality associated with heart failure (HF), preventive approaches have been explored. Controlling hypertension to prevent HF is well-established, especially with sodium restriction and thiazide-based antihypertensive therapies showing potential advantages. Control of dyslipidemia with aggressive statin therapy is particularly beneficial in preventing HF in the setting of acute coronary syndrome. The HOPE study also established the benefit of ACE inhibitors in the prevention of HF in high-risk subjects. Meanwhile old data supporting tight glycemic control in preventing HF have not been confirmed, suggesting the complexity of diabetic cardiomyopathy. Avoiding tobacco use and other known cardiotoxins are likely helpful. While there has been substantial development in identifying biomarkers predicting future development of HF, therapeutic interdiction guided by biomarker levels have yet to be established even though it offers hope in modulating the natural history of the development of HF in at risk individuals.

Keywords

heart failure; prevention; beta-blocker; angiotensin converting enzyme inhibitor; angiotensin receptor blocker; thiazide diuretic; left ventricular hypertrophy; left bundle branch block; diabetes mellitus; troponin; brain natriuretic peptide; cardiomyopathy; statins; biomarkers; coronary artery disease; hypertension; obesity; hyperlipidemia; insulin resistance

INTRODUCTION

Heart failure (HF) is an increasingly prevalent condition characterized by elevated filling pressures within the heart and the decline in the heart's efficiency to pump blood to the rest of the body. Estimates from 2010 suggest that approximately 6.6 million United States adult citizens have HF. Projections suggest that this number will increase by an additional 3 million by year 2030. [1] For men and women, the lifetime risk of developing HF is 20% at 40 years of age and, despite decreasing life expectancy, this risk remains until the eighth decade.

There are currently well established therapies for treating HF. The use of beta-blockers (BB), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), implantable cardiac defibrillators (ICD), and cardiac resynchronization therapy (CRT) have all improved outcomes in patients

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with established chronic HF. Additionally, the advents of orthotopic heart transplantation and left ventricular devices (LVAD) have improved outcomes in patients with end stage heart failure (HF). However, despite continued improvements in survival after a diagnosis of HF [2], the death rate remains unacceptably high. Therefore, there needs to be more emphasis on preventing HF.

Heart failure itself is not an isolated disease process, but rather the latter stages of a continuum of cardiac risk to those with structural heart disease, symptomatic HF and end-stage cardiomyopathy. The first step in this endeavor is identifying those at heightened risk on this scale for developing HF that may potentially benefit from both earlier and more intensive medical therapy. However, this is not an easy task. Therefore, recognizing and treating the sub-clinical phases of HF is essential. This review will elaborate on both traditional and more recently described high-risk phenotypes of those at risk for HF, and review the latest supportive evidence and approaches, including a summary of the recently published clinical practice guideline recommendations on this topic.

I. TARGETING AT-RISK CONDITIONS

Traditionally, HF prevention has focused on targeting optimal management of traditional cardiovascular risk factors. Table 1 summarizes the latest guideline recommendations once structural heart disease has been detected (so-called "Stage B" HF), but a more important goal is to preemptively target at-risk conditions ("Stage A") before structural alterations ensue[3].

1. Hypertension

Hypertensive heart disease is a prevalent and well-described risk factor for the development of HF. [4] Commonly, hypertension can lead to the development of concentric or eccentric hypertrophy which then can manifest as the clinical syndrome of HF either with a preserved or with a decreased left ventricular ejection fraction. Furthermore, hypertension may progress directly to HF in the absence of any hypertrophy or via the development of myocardial ischemia and/or infarction (MI).

Preventing HF with hypertension control has some of the best supportive evidence over the past decades with the publication of several landmark clinical trials. Non-pharmacologic therapy has been well-established in treating this condition. Current guidelines recommend lifestyle changes including maintaining a normal body mass index (18.5–24.9 kg/m^2), adopting the DASH (Dietary Approaches to Stop Hypertension) eating plan and reducing dietary sodium to 2.4 g. [5] In a Swedish cohort of 36,019 women, the top quartile of subjects whose diets most closely resembled the DASH diet had a 37% lower rate of HF at seven years when compared to the least compliant quartile. [6] Hence, sodium restriction likely has a beneficial effect in prevention of HF, and this effect seems to be likely mediated by the reduction in blood pressure and protection of renal function.

a. Thiazide Diuretics for Hypertension—Despite a wealth of effective drugs, hypertension is often underdiagnosed and under-treated. The latest clinical guidelines recommended a thiazide diuretic as first-line drug therapy for Stage I HF (systolic blood pressure 140–150 or diastolic blood pressure 90–99 mm Hg) in subjects without HF, previous MI, high coronary disease risk, chronic kidney disease (CKD), and recurrent stroke prevention. [5] This recommendation is based primarily on the landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). [7] Over 33,000 patients over the age of 55 years with hypertension and at least one other coronary heart disease risk factor were randomized to chlorthalidone, amlodipine, or lisinopril. Chlorthalidone had lower 6 year rates of HF when compared to the other medications, and

reduced HF hospitalization or death when compared to amlodipine (but not when compared to lisinopril). In another study involving a large cohort of octogenarians, indapamide, another thiazide diuretic, was shown to reduce the secondary endpoint of HF, but not death from HF. [8] Taken together, thiazide diuretics should be considered the first-line drug therapy from the perspectives of HF prevention.

b. The role of beta-blockade and angiotensin converting enzyme inhibitors/ angiotensin receptor blockers—It is important to point out that with the exception of α-blockers, any anti-hypertensive regimen can reduce the risk of HF as long as blood pressure is adequately controlled. [9] In ALLHAT, the cumulative event rates of HF and hospitalized plus fatal HF in subjects taking lisinopril approached that of chlorthalidone at seven years. It is therefore conceivable that the effects of ACEI and ARBs in preventing HF may not be evident for years after the initiation of therapy. The data is less clear when prescribing beta-blockers in efforts to prevent the progression towards symptomatic HF, even though beta-blockers have consistently been shown to reduce mortality in patients with asymptomatic LV dysfunction. [32] When compared to other anti-hypertensive medications in a meta-analysis, beta-blockade does not seem to confer additional benefit towards the prevention of developing HF. [10] Notably, many of the trials in the results in the aforementioned meta-analysis were based upon older drugs such as atenolol, oxprenolol, pindolol and metoprolol tartrate. [11–22] None of these studies utilized more contemporary beta-blockers that are currently recognized to improve outcomes in patients in HF (metoprolol succinate, carvedilol, or bisoprolol). [23–26] Therefore it remains unclear whether these newer-generation drugs would offer any benefit for primary prevention of HF beyond their blood pressure-lowering effects.

2. Coronary Artery Disease and Myocardial Infarction

a. The role of ACEIs/ARBS—Coronary artery disease (and myocardial infarction) remains an important cause of HF. Neurohormonal antagonists remain the mainstay of post-MI care based on well-established clinical evidence with major adverse cardiac events as the primary endpoint. Most clinical outcome studies involving ACEI or ARBs have utilized HF or hospitalization for HF as secondary outcomes. In a post-hoc analysis of the HOPE (Heart Outcomes Prevention Evaluation) trial with HF being the primary outcome, ramipril significantly reduced the incidence of HF by a relative risk reduction of 23% when compared to placebo. [27] Additionally, a Japanese trial involving a cohort with cardiovascular disease on standard therapy observed a 47% decreased relative risk for HF with valsartan at approximately 3 years. [19] However, not all studies showed the same magnitude of benefit. The EUROPA (European trial on reduction of cardiac events with perindopril in stable coronary artery disease) trial, a large randomized controlled trial, demonstrated that patients with previous MI, previous coronary revascularization, angiographic evidence of coronary artery disease, or positive stress testing without apparent HF treated with perindopril versus placebo suggested a trend toward decreased risk of HF requiring hospitalization. [28] Of note, out of 12,218 patients entered in EUROPA, only 63/6110 (1%) patients in the perindopril group and 103/6108 (1.4%) patients in the placebo group developed HF. Similarly, the PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) Trial corroborated similar results suggesting that, in addition to standard therapy with, ACEI may not add any benefit of cardiovascular outcomes. [17] Combination therapies have also been disappointing. In ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial), which enrolled higher risk patients (those with coronary, peripheral, cerebrovascular disease, or diabetes with evidence with end organ damage), no advantage of combination therapy with telmisartan and ramipril over ramipril alone was observed. [16].

b. The role of beta-blockade—Beta-adrenergic blockers have been known to improve survival, relieve cardiac ischemia, decrease the risk of recurrent MI, and attenuate myocardial remodeling after an MI. [25–27] In the REVERT trial (The Reversal of Ventricular Remodeling with Toprol-XL Trial), treatment with metoprolol succinate has been shown to ameliorate remodeling in asymptomatic patients with LV dysfunction when compared to placebo. However it is important to recognize that published contemporary data in post-MI HF prevention with beta-blockers are relatively sparse, and even in the latest guidelines in chronic stable angina the benefits of beta-blockers have largely been endorsed up to two years following cardiac events.

3. Diabetes Mellitus and Insulin Resistance

Currently 8.3% of the population has diabetes mellitus (DM) and the prevalence is increasing. [29] Several epidemiologic studies have shown DM and insulin resistance (IR) to be a known predictor of HF. [30, 31] When compared to controls, DM has a doubled incidence of HF. [32] Additionally, DM not only confers an increased prevalence and incidence, but also predicts higher risk in those with HF. [33] Aside from the common coincident conditions of LVH and CHD, several mechanisms have been postulated for the increased risk of HF in patients with DM. For instance, there are perturbations in free fatty acid metabolism and glucose metabolism in cardiomyocytes; there is increased free fatty acid accumulation; and the function of peroxisome-proliferator-activator receptor alpha activity is altered. [34]. Although the underlying mechanisms are not well understood, patients with DM and increased hemoglobin A1c (HBA1c) percentages may have increased HF risk. [35] However, there is likely competing risk as the development of HF may be more related to cardiac dysfunction than to other risk factors. But what cannot be ignored, is that DM does play a prominent role in affecting clinical outcomes. [36] Therefore, understanding the potential cardiovascular implications of treating DM has been and will be essential.

a. The control of hyperglycemia—The UK prospective diabetes study (UKPDS) revealed that reduction in glycemia is associated with a decreased incidence of myocardial infarction and the development of HF when compared to higher levels.[37] However, several recent randomized trials have challenged this notion. In a large trial of 10,251 patients with a median HBA1c of 8.1% randomized to either intensive anti-hyperglycemic therapy (targeting a HBA1c of <6.0%) versus targeting a HBA1c of 7–7.9%, there was a higher mortality at 3.5 years and no advantage in preventing HF. [38] Yet, another large randomized trial involving patients with DM to either undergo intensive glucose control with gliclazide plus other anti-hyperglycemic medications targeting a HBA1c of <6.5 versus standard therapy did show a 10% relative risk reduction in macrovascular complications. [39] A later study involving 1,791 military veterans with poorly controlled DM (median HBA1c 9.4%) randomized to intensive or standard glucose control revealed that intensive glucose control did not affect the rates of major cardiovascular events. [40] Based on these results, the beneficial effects of intensive glucose control with HF prevention are unclear and could potentially be harmful. However, many of these studies have a relatively low number of HF incidence in their outcomes and it is difficult to extrapolate these results to HF prevention.

b. Metformin and heart failure—Metformin, a biguanide, decreases gluconeogenesis in the liver, augments glucose uptake and utility with improvement in insulin sensitization. [41] Metformin use has been shown to be safe, and is associated with improved outcomes in observational cohorts of patients with DM and HF. [42, 43]. These improved outcomes with metformin usage may stem from chronic activation of AMP-activated protein kinase, which has beneficial effects in myocardial structure and function in murine models of HF. [44]

Metformin has also been shown to prevent the development of chronic HF in a genetic model of spontaneously hypertensive, insulin-resistant rats, [45] presumably due to activation of AMP-activated protein kinase, endothelial nitric oxide synthase, and vascular endothelial growth factor. Additionally, metformin reduced expression of tumor necrosis factor-α and myocyte apopotosis. However, in humans these effects are less clear and further work is needed to address the hypothesis that metformin usage decreases the risk for developing HF.

c. Renin angiotensin aldosterone system blockade—Drugs antagonizing the renin angiotensin aldosterone system are likely important in the setting of DM in HF prevention. Interestingly, in studies with non-cardiac patients such as in those with diabetic nephropathy, losartan usage significantly reduced the risk first hospitalization for HF when compared to placebo. [14] The HOPE trial also demonstrated benefits of ramipril in subset of diabetic subjects. [46, 47] In those with underlying cardiac dysfunction and history of DM even in the absence of HF symptoms following myocardial infarction in the EPHESUS study, add-on eplerenone provided significant clinical benefits. [48]

4. Obesity

Obesity is a well recognized risk factor for the development of HF. [49] Although, classically, obesity is described as a body mass index (BMI) ≥30 kg/m^2, measures of body mass index likely do not completely classify those at higher risk for developing HF. Central obesity, as measured by waist-hip ratio, identifies those at higher risk for myocardial infarction [50] and incident HF. [51] Aside from the complications that are typically associated with obesity such as LVH, obstructive sleep apnea, and increasing levels of metabolic demands, increased adiposity may confer an increased inflammatory state predisposing to HF. [52] It is conceivable that weight loss may not only prevent HF through more traditional pathways like reducing the incidence of sleep apnea and more traditional cardiac risk factors, but may also independently affect the myocardium directly. However, direct supporting evidence and optimal treatment goals are not well established since the majority of data linking obesity to adverse HF outcomes were from epidemiologic studies.

5. Hyperlipidemia

In a large randomized cohort of patients with obstructive coronary artery disease and without previous symptoms of HF, treatment with simvastatin reduced the incidence of HF over 5 years after randomization. [53] However, a recurring criticism of the studies of statins in patients with coronary artery disease assessing HF as an endpoint is that the lowered incidence of HF may be more related to the reduction of vascular complications. Data from the Heart Protection Study revealed an association with simvastatin usage in high-levels of NT-proBNP and 14% reduction in the HF. [54] This observation suggests a benefit over treatment with statins towards prevention of HF. Yet, there is still uncertainty in the setting of established HF. Two prospective randomized trials with patients with chronic symptomatic HF (NYHA II-IV) found no benefit with the usage of rosuvastatin towards reduction in clinical outcomes. [55, 56] In post-hoc analyses, however, there was a hint linking potential benefits in those with lower rather than higher NT-proBNP levels. [57] Data from the Physicians' Health Study also found no association with total and high density lipoprotein levels and incident HF. [58] Although this cohort is relatively healthy and there was a low incidence of HF (222 out of over 10,000 subjects), it would still be reasonable to assume that statins may, in fact, be protective in a higher risk population, namely those with obstructive coronary artery disease, towards the development of HF. It is likely that, once HF has developed and progressed, any influence of statins on outcomes may be negligible.

II. TARGETING AT-RISK PHENOTYPES

1. Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) is an increase in cardiomyocyte mass in response to increased load that often leads to increased wall thickness, increased cavity size, or both. It is a well described possible intermediate step in the transition from hypertension to clinical HF manifested either as left ventricular systolic or diastolic dysfunction [59]. The presence of LVH is often associated with worsening outcomes and may lead to HF independent of MI. [60, 61] There are additional alterations in the extracellular matrices with accumulation of fibrotic tissue and abnormalities in intramyocardial blood flow. [62] Conditions that are well known predictors of HF such obesity, diabetes mellitus, and coronary artery disease [63] are also well described predictors for LVH and may also affect the pattern of hypertrophic response in the setting of hypertension.

Although the presence of LVH is an intermediary towards the development of symptomatic HF, not all patients with LVH will develop symptomatic LV systolic or diastolic dysfunction. [64] Therefore, describing a high risk LVH phenotype is crucial towards preventing the development of HF. For instance, sex and racial disparity may affect the end stage determinants of LVH. Middle aged men with LVH have an increased tendency towards developing coronary heart disease, in contrast to middle aged women with LVH have tendencies towards HF. [65] In the general population, African Americans have higher LV mass as compared to whites with a 2–3 higher prevalence of LVH despite controlling for risk factors or adjustment for body habitus. [66] One longitudinal study found that out of 1,024 patients with LVH only 13% had developed systolic dysfunction after a mean follow-up of 33+/−22 months. [67] Interestingly, those that developed systolic dysfunction had either myocardial infarction, QRS prolongation (>120 ms), or increased arterial impedance on follow-up (>4 mmHg/ml/m^2) suggesting the presence of more malignant phenotypes of LVH. Recently, the Dallas Heart Study identified that elevated cardiac troponin T (cTnT) and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) in subjects with LVH detectable via magnetic resonance imaging (MRI) identify a higher risk phenotype for developing HF and for increased cardiovascular mortality. [68] At some point in the transition from LVH to HF there must be an intermediary at which disarray in the extracellular matrix begins. Compared to 141 subjects with LVH and no HF, a study of 61 subjects with LVH and HF had elevated levels of matrix metalloproteinases and tissues inhibitors of metalloproteinases. [69]

A further mechanism, less well described, is that mechanical interventricular dyssynchrony may also mark one of the transitions from LVH to clinical HF with preserved ejection fraction (HFpEF). In a trial comparing 47 patients with HFpEF and 34 hypertensive patients with LVH after dobutamine stress echocardiography, the HFpEF group had stress-induced changes in dynamic dyssynchrony and impaired myocardial longitudinal functional reserve. [70] Chronic changes in LV filling pressure lead to left atrial dilatation that may also be an important determinant towards the development of clinical HF. [71]

Clinically, all of these proposed mechanisms manifest themselves as increased diastolic pressures which are pivotal in the transition from both HF with preserved ejection fraction and decreased ejection fraction to acute decompensated HF. [72] LVH is an important intermediary to developing both HF and cardiovascular disease because it can regress. A meta-analysis of 80 double-blind, randomized trials revealed that anti-hypertensive treatment does decrease LV mass with treatment. [73] Reduction in LVH with treatment has favorable prognostic outcomes as well. In the Losartan Intervention for Endpoint Reduction in Hypertension randomized controlled trial, 941 patients with both hypertension and LVH

followed for a mean of 4.8 years, decreased measures of LV mass were associated with lower cardiovascular and all-cause mortality. [74]

2. Abnormal Cardiac Biomarkers

a. Brain natriuretic peptides—B-type natriuretic peptide (BNP) and amino-terminus BNP (NT-proBNP) are formed from a prohormone of BNP in the setting of myocardial hemodynamic stress. The prohormone BNP is cleaved by proteases into an inactive 76 amino acid peptide, NT-proBNP and a biologically active 32 amino acid peptide, BNP.[75] BNP opposes the pathophysiological derangements of HF. It counteracts the sympathetic nervous system, renin-angiotensin-aldosterone system, while it vasodilates the arterial bed, and also increases both diuresis and natriuresis. Levels of all natriuretic peptides are elevated in the setting of renal dysfunction, and have found to be higher in the elderly and in women (likely a as a function of progressive renal dysfunction and changes in body composition over time). [76, 77]

Natriuretic peptide testing has greatly assisted in both the diagnosis and prognosis of HF. BNP levels have greatly increased the accuracy of diagnosing acute HF in patients presenting to the emergency department with dyspnea, [78, 79] as well as being a significant predictor of in-hospital mortality. [80] In chronic HF, BNP levels have been implicated to both guide management and predict outcomes. [75, 81, 82] Data supporting its use as screening for HF have been less robust. In high risk populations, such as advanced age, elevated blood pressure, diabetes mellitus, asymptomatic coronary heart disease, or detection of the cardiotoxic effects of chemotherapy, natriuretic peptides may also be useful in screening for HF. [75, 83] BNP concentration identifies patients at high risk for adverse left-ventricular remodeling, lowered ejection fraction, and HF after a myocardial infarction. [84, 85] This prognostic role of BNP concentration levels are also extended to the general population as well. [86] Although increasing BNP levels may be associated with asymptomatic LV dysfunction, these levels must be interpreted with consideration of gender and age. Female sex and increased age are predictors of BNP and NT-proBNP.[87] Although elevated concentrations of natriuretic peptides in the general population predict poor cardiovascular outcomes [88], the yield of measuring natriuretic peptides in addition to conventional screening may be relatively low.[89] It seems as though the utility of measuring natriuretic peptides as methods of screening may rely more on populations that are at increased risk for HF. NT-proBNP concentrations were shown in a study of asymptomatic subject with hypertension and/or diabetes mellitus to have an excellent negative predictive value (100%) at ruling our asymptomatic left ventricular dysfunction. [90]. However, guiding therapy based on elevated BNP levels have not resulted in improvement in long-term outcomes in those without overt HF. [91]

b. Cardiac troponin levels—Troponin is an intracellular protein essential in the regulation of muscular contraction. Increases in circulating cTnI and cTnT are highly specific for ongoing myocardial damage, and have been utilized for the past two decades as markers for defining myocardial infarction [92] and may also be elevated in both acute and chronic HF [93, 94]. Here, one possible explanation for elevated cardiac troponins in HF may arise from reversible or irreversible myocardial supply and demand mismatch. [95] Here, cTn release may be caused by both acute and chronic myocardial stress, as well as chronic sub-clinical sub-endocardial ischemia or directly related to cardiomyocyte injury. [96] This release of troponin may also signify increased cardiomyocyte turnover in the setting of progressing myocardial dysfunction.[97] Therefore, it is reasonable to assume that troponin levels would be related to subclinical myocardial stress indicative of a subclinical state of myocardial dysfunction, thus creating a situation whereby early or intensive medical therapy may prevent clinical HF. In the general population, elevated cTnT marks subclinical

cardiac injury [98] and elevations of cTnT quantified via high sensitivity assays mark an increased risk for structural heart disease and all-cause mortality. [99] Interestingly, circulating levels measured by newer-generation, highly-sensitive cTn assays are frequently detectable and detectable cTn using these assays is independently associated with all-cause mortality, cardiovascular mortality, and incident HF in the general population, despite controlling for renal function, amino terminus pro-B-type natriuretic peptide (NT-proBNP), and high-sensitivity C-reactive protein (CRP). [68, 99–101] Interestingly, a recent analysis of high sensitivity cTnI in the Framingham Offspring Study found an association with HF, but not with incident myocardial infarction. [102] Meanwhile, changes in cTnT levels over time also correlate with HF risk. After adjusting for baseline high sensitivity cTnT and other risk factors, elderly subjects followed for 2–3 years in Cardiovascular Health Study with high sensitivity cTnT 50% or higher from baseline were found at increased risk for developing HF. [100] To date, it is unknown whether intensifying medical therapy based on elevated cTn improves outcomes.

3. Left Bundle Branch Block

Left bundle branch block (LBBB) has long been suspected to be a hallmark of the beginnings of structural heart disease and increased risk of cardiovascular mortality in the general population. [103] LBBB is a marker of interventricular depolarization delay. The Framingham population has posed that the development of LBBB over time is associated with the coincident development of HF or coronary artery disease. [104, 105] Additionally, in individuals with a normal baseline ECG the appearance of an exercise related LBBB also marks higher risk for both mortality and cardiac events. [106] The presence of LBBB in patients with cardiovascular disease or diabetes marks an independent risk for the development of HF. [107] Additionally, patients with chronic HF as LBBB marks an increased mortality [108] and is one of the hallmarks for which ventricular resynchronization is based. Recently, data from the Women's Health Initiative Study has revealed that LBBB with a QRS >140 ms is a strong independent predictor of incident HF. [109] It is clear that other ECG abnormalities besides LBBB may hold subtle clues to underlying risks in the development HF and may warrant further investigations.

CONCLUSION

Heart failure is becoming more and more prevalent and projections suggest even higher numbers in the future. Currently, we have both traditional and advanced therapies that have not only improved outcomes, but also change the course and natural history of the disease. Yet, strategies for preventing HF are still evolving, especially in the identification of those at increased risk. We currently have a wealth of pharmacologic therapies to test hypotheses in HF prevention. The burden of proof for clinical adoption of HF prevention approaches relies heavily on supportive data from prospective clinical trials that test interventional strategies with HF as a clinical endpoint, rather than simply relying on epidemiologic descriptions of HF risk profiles. It is conceivable that targeting high risk patients with reliable measures of subclinical myocardial dysfunction as surrogates to prevent HF provides new exciting opportunities towards preventing the heavy burden of HF.

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Table 1

ACC/AHA Clinical Guideline Recommendations for Treatment of Stage B HF

Recommendations	Class of Recommendation	Level of Evidence
In patients with a history of MI and low EF, ACE inhibitors or ARBs should be used to prevent HF	I	A
In patients with MI and low EF, evidence-based beta blockers should be used to prevent HF	I	B
In patients with MI, statins should be used to prevent HF	I	A
Blood pressure should be controlled to prevent symptomatic HF	I	A
ACE inhibitors should be used in all patients with a reduced EF to prevent HF	I	A
Beta blockers should be used in all patients with a reduced EF to prevent HF	I	C
An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT	IIa	B
Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF	III: Harm	C

Abbreviations: ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

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