Contributory Risk and Management of Comorbidities of Hypertension, Obesity, Diabetes Mellitus, Hyperlipidemia, and Metabolic Syndrome in Chronic Heart Failure

A Scientific Statement From the American Heart Association

Biykem Bozkurt, MD, PhD, FAHA, Chair
David Aguilar, MD, FAHA
Anita Deswal, MD, MPH, FAHA
Sandra B. Dunbar, RN, PhD, FAHA
Gary S. Francis, MD, FAHA
Tamara Horwich, MD, MS, FAHA
Mariell Jessup, MD, FAHA
Mikhail Kosiborod, MD, FAHA
Allison M. Pritchett, MD
Kumudha Ramasubbu, MD
Clive Rosendorff, MD, PhD, DScMed, FAHA
Clyde Yancy, MD, MSc, FAHA
On behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; Council on Hypertension; and Council on Quality and Outcomes Research

The comorbidities of hypertension, diabetes mellitus, obesity, hyperlipidemia, and metabolic syndrome are common in patients with heart failure (HF) and affect clinical outcomes.[1–3] Interestingly, although these comorbidities are associated with the development of incident HF in the general population, in patients with established HF, their contributory roles to clinical outcomes are not predictable, and their management is quite challenging. Recent American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines have addressed the role of lifestyle modification,[4] treatment of blood cholesterol,[5] and management of overweight and obesity[6] in the general population and in patients with increased cardiovascular risk, and a recent report from the Eighth Joint National Committee addressed the management of hypertension.[7] However, these guidelines did not specifically address the management of such comorbidities in patients with HF. Similarly, the most recent ACCF/AHA HF practice guidelines[8] in 2013 addressed the overall management of comorbidities in patients with HF in broad terms, but again, specific and detailed recommendations on how to manage hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome are lacking. The intent of this AHA scientific statement is to summarize data relevant to contributory risk and to provide guidance on the management of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in the development and prognosis of HF to provide recommendations (Table 1) and to foster communication between physicians and other healthcare professionals and patients on the management of these comorbidities. Recommendations in this document are based on published studies and the multidisciplinary expertise of the writing group and harmonized with published practice guidelines from the ACC/AHA[4–6,8–12] and other organizations.[7,13–15]

HYPERTENSION AND HF

Hypertension is a worldwide epidemic; in many countries, 50% of the population >60 years of age has hypertension. Hypertension is defined as a repeatedly elevated blood pressure (BP) exceeding 140/90 mm Hg. The prevalence of hypertension is steadily increasing, even with the expanded use of antihypertensive medications.[16] It is widely recognized that hypertension is associated with increased cardiovascular and all-cause mortality independently of other risk factors.[14,17] Specific HF mortality attributable to hypertension is probably underreported because of the competing adjudication for stroke or myocardial infarction (MI) at the end of the spectrum of hypertensive cardiovascular death.

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ comorbidity ■ diabetes mellitus ■ heart failure ■ hyperlipidemia ■ hypertension ■ obesity ■ risk factors

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/ administered/ other is not useful/ beneficial/ effective COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Hypertension Plays a Significant Role in the Development of HF

Elevated levels of diastolic BP and especially systolic BP (SBP) are major risk factors for the development of HF.[18,19] One of the most impactful observations from the Framingham cohort was that the cumulative incidence of HF was significantly higher in patients with hypertension[18,19] (Figure 1) Among 5143 patients, 91% of the patients with HF had hypertension antedating the development of HF, underlining that in the majority of patients with HF, hypertension was a contributing cause. The hazard ratios (HRs) for developing HF in hypertensives compared with normotensives were 2-fold higher in men and 3-fold higher in women.[18,19] It should be noted that the risk associated with hypertension may be accentuated through its confounding effect on ischemic heart disease and other cardiovascular outcomes such as stroke. Furthermore, these studies predate current HF management strategies and guidelines and may no longer reflect the risk in the current population treated for hypertension. However, they underscore the importance of hypertension as a cause of HF when left untreated. The residual lifetime risk for hypertension for middle-aged and elderly

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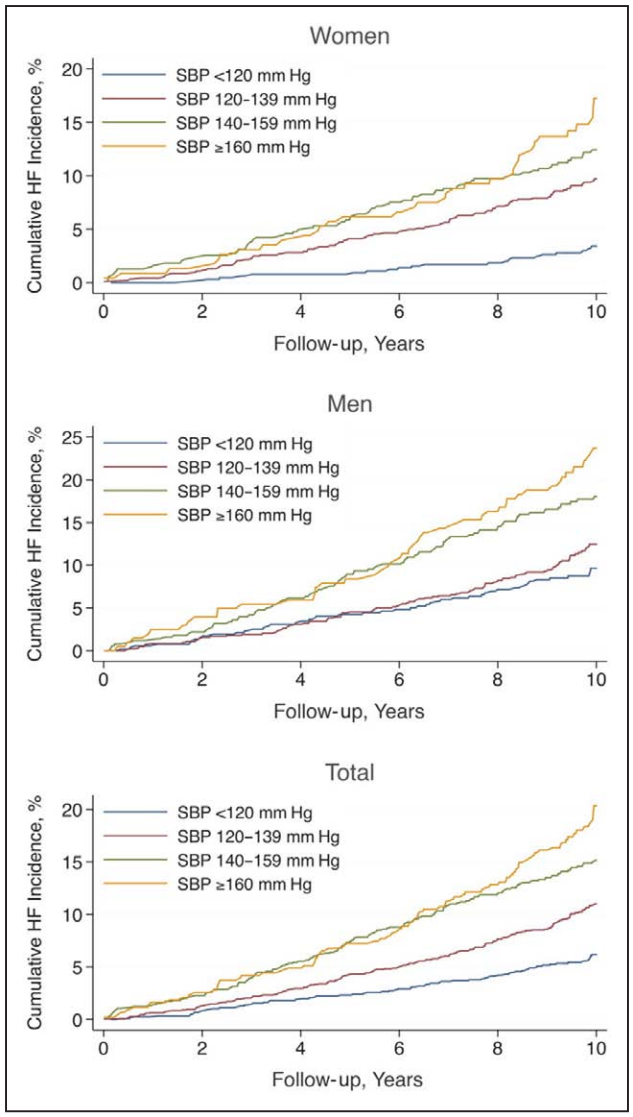

Figure 1. Cumulative incidence of heart failure, adjusted for death as a competing risk, by baseline systolic blood pressure (SBP) categories of <120, 120 to 139, 140 to 159, and ≥160 mm Hg for women (top), men (middle), and the overall population (bottom).
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individuals in the United States is 90%, indicating a huge public health burden[20] and defining the importance of strategies to control hypertension to prevent HF.

Treatment of Hypertension Prevents the Development of HF

Long-term treatment of both systolic and diastolic hypertension has been shown to reduce the risk of HF.[21,22] With treatment of hypertension, the risk of developing HF is reduced by 30% in younger populations,[23] by 50% in the elderly,[22,24] and by almost 80% among the elderly with history of MI.[22] A meta-analysis of long-term hypertension treatment trials[25] and a number of large, controlled studies[26] have uniformly demonstrated that optimal BP control decreases the risk of new HF by ≈50%. In placebo-controlled trials, although the relative risks of total major cardiovascular events were reduced by regimens based on angiotensin-converting enzyme (ACE) inhibitors (22%) or calcium antagonists (18%), the risk for developing HF was reduced significantly by ACE inhibitors but not calcium antagonists.[27] Greater risk reductions were produced by treatment regimens that targeted lower BP goals than those targeting relatively higher BP goals.[28]

Table 2. Recommendation for the Treatment of Hypertension in Stage A HF: Asymptomatic Patients at Risk for HF

Recommendation	COR	LOE	Referenced Guideline	References
Hypertension should be controlled in accordance with contemporary guidelines to lower the risk of development of HF.	I	A	7–9	14, 21–28, 30, 31

COR indicates Class of Recommendation; HF, heart failure; and LOE, Level of Evidence.

Treatment

Treatment of Hypertension in Patients at Risk for Developing HF

Goals of Treatment of Hypertension to Prevent HF

Patients with hypertension are at high risk for developing HF (stage A), and their BP should be controlled in accordance with contemporary guidelines to lower the risk of HF (Level of Evidence A[8]; Table 2). According to the recently published 2014 evidence-based guidelines for the management of high BP in adults,[7] the goal for treatment of BP has been identified as <140/90 mm Hg for patients who are <60 years of age or for adult patients with chronic kidney disease or diabetes mellitus and as <150/90 mm Hg for patients ≥60 years of age in the general population. It should be noted that this last recommendation of a higher target for patients ≥60 years of age has been controversial and debated in the literature.[32–34] There is evidence that the initiation of antihypertensive treatment for the above thresholds is associated with a reduction of HF and other cardiovascular events and overall mortality among hypertensive adults ≥30 years of age in the general population or in hypertensive patients ≥18 years of age with chronic kidney disease or diabetes mellitus.[7] Similar targets were quoted in the 2002 "AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke," which identified a general goal of <140/90 mm Hg for the treatment of

hypertension in HF.[9] Ongoing trials are intended to specifically address the question of goal BP reduction, and a new ACCF/AHA Guideline Writing Committee has been convened to address the management of hypertension.

Medication Choices for the Treatment of Hypertension to Prevent HF

For antihypertensive regimens in patients without established HF, optimal control of BP should remain the primary goal. The most recent 2014 evidence-based guideline for the management of high BP in adults recommends that in the general nonblack population, including those with diabetes mellitus, the initial antihypertensive treatment should include a thiazide-type diuretic, a calcium channel blocker, an ACE inhibitor, or an angiotensin receptor blocker (ARB).[7] Each of these 4 drug classes recommended by the writing group yielded comparable effects on overall mortality, cardiovascular (excluding HF), cerebrovascular, and kidney outcomes. However, the effects of these drug classes on HF differ.

Treatment with a thiazide-type diuretic or an ACE inhibitor has been shown to be more effective than treatment with a calcium channel blocker in improving HF outcomes.[7] Although the writing committee recognized that improved HF outcome was an important finding that should be considered in the selection of a drug for initial therapy for hypertension, the panel did not conclude that it was compelling enough to preclude the use of the other drug classes for initial therapy. The panel also acknowledged that the evidence supported BP control, rather than a specific agent used to achieve that control, as the most relevant consideration for their recommendation.[7] Supporting this, historically, most antihypertensive drugs have demonstrated comparable cardiovascular efficacy and safety.[35] Specifically, diuretic-based antihypertensive therapies have been shown to prevent HF in a wide range of target populations as first-line therapy.[27,35–39] Additionally, low-dose diuretics have been shown to be more effective as a first-line treatment for preventing the development of HF compared with ACE inhibitors, β-blockers, or calcium channel blockers by meta-analysis.[38] It should also be noted that most of the original trials used the longer-acting chlorthalidone rather than hydrochlorothiazide. ACE inhibitors have also been shown to be very effective in the prevention of HF,[14,27,35,40] even more significantly in patients with left ventricular (LV) systolic dysfunction or patients after MI.[41,42] Likewise, ARBs have been shown to reduce the incidence of HF, especially in patients with hypertension and type 2 diabetes mellitus and nephropathy.[43,44] However, calcium channel blockers appear to be somewhat less efficacious than the above agents for preventing HF.[8,27] There are inadequate data to determine whether this is true only for dihydropyridine calcium channel blockers or whether it is true of the entire class of drugs.[26] Regarding α-blockers, in the ALLHAT trial (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial), doxazosin was inferior to chlorthalidone for the prevention of HF and was associated with the doubling of HF risk compared with chlorthalidone.[45,46] The "2013 ACCF/AHA Guideline for the Management of Heart Failure" indicated that the role of calcium antagonists or α-blockers is less clear for reducing the risk for incident HF, and the choice of antihypertensive therapy should follow the contemporary guidelines.[8] In addition to medications, patients with hypertension should be advised on healthy lifestyle modification; weight reduction; reduction of sodium intake; increased consumption of fruits, vegetables, and low-fat dairy products; and moderation of alcohol intake.[7,9,14]

In patients with stage B HF with structural heart disease or LV dysfunction but without HF symptoms, there is benefit with ACE inhibitors, ARBs, or β-blockers (Table 3). Thus, in patients with a recent or remote history of MI or acute coronary syndrome and reduced ejection fraction (EF), ACE inhibitors[49–51] (or ARBs if the patient is ACE inhibitor intolerant[30,52]) prevent symptomatic HF and reduce mortality. Similarly, in patients with a recent or remote history of MI or acute coronary syndrome and reduced EF, β-blockers reduce mortality.[53–55] In patients with a reduced EF but without any history of MI or symptoms of HF, ACE inhibitors prevent symptomatic HF,[51,56] and β- blockers can improve symptoms, ameliorate LV

Table 3. Recommendations for the Treatment of Hypertension in Stage B HF: Patients With Cardiac Structural Abnormalities or Remodeling Who Have Not Developed HF Symptoms

Recommendations	COR	LOE	Referenced Guideline	References
In patients with structural cardiac abnormalities, including LV hypertrophy, BP should be controlled in accordance with clinical practice guidelines for hypertension to prevent symptomatic HF.	I	A	7–9, 29	14, 22, 31, 35, 47
Nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF. α-Adrenergic blockers such as doxazosin should be avoided and might be used only if other drugs for the management of hypertension and HF are inadequate to achieve BP control at maximum tolerated doses.	III: Harm	C	8, 29, 48	46

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BP, blood pressure; COR, Class of Recommendation; HF, heart failure; LOE, Level of Evidence; LV, left ventricular; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

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remodeling, and improve LV function.[57,58] Although these beneficial effects of ACE inhibitors, ARBs, and β-blockers are not specific for patients with hypertension or for treatment of BP, a significant proportion of patients in these trials (40%–60%) had a history of hypertension, and the beneficial effects could be generalized to the hypertensive population.

Treatment of Hypertension in Patients With Established HF

How Aggressively to Treat BP in Patients With HF?

There have not been compelling data to justify a single BP target in treating hypertension in patients with established HF. Former guidelines and position papers differ significantly in such threshold definitions and lack strong evidence for treatment targets of hypertension in HF.[9,14,48,59] Therefore, the optimal BP target for the treatment of hypertension in patients with HF is not firmly established. The 2007 AHA scientific statement on the treatment of hypertension in the prevention and management of ischemic heart disease recommended a target BP of <130/80 mm Hg in patients with HF.[48] Similarly, the 2002 "AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke"[9] identified the BP treatment goal as <130/85 mm Hg if HF was present. However, these recommendations were empirical, not supported by trial evidence.[9,48] Furthermore, there is concern about potential adverse outcomes with BP lowering that is too aggressive, which was further supported by the change to a higher BP threshold of 140/90 mm Hg in patients <60 years of age and <150/90 mm Hg in patients ≥60 years of age in the 2014 evidence-based guideline for the management of high BP in adults.[7] It should be noted, however, that the writing committee did not address BP treatment targets in patients with established HF. The lack of definitive BP targets in patients with existing HF notwithstanding, treatment of HF is usu-

Table 4. Recommendations for the Treatment of Hypertension in Stage C HF: Patients With Cardiac Structural Abnormalities or Remodeling With Prior or Current Symptoms of HF

Recommendations	COR	LOE	Referenced Guideline	References
Patients with previous or current symptoms of HFrEF should be treated with GDMT, including diuretics, ACE inhibitors (or ARBs if ACE inhibitor intolerant), β-blockers, and aldosterone receptor antagonists, which have been proven to improve outcomes for patients with HF and can lower BP in hypertensive patients with HFrEF.	I	A for clinical outcomes, B for BP control	8, 29	50, 63–68
Addition of hydralazine/isosorbide dinitrate to the background treatment with ACE inhibitor or ARB and β-blocker in self-described black patients with HFrEF and persistent NYHA class III or IV HF symptoms is beneficial to reduce morbidity and mortality and can lower BP in hypertensive patients with HFrEF.	I	A for reduction in morbidity and mortality in HF, B for BP control	8, 29	69, 70
The treatment of hypertension in patients with HF should include behavioral modification such as sodium restriction and a closely monitored exercise program. Weight reduction in overweight or obese, an appropriate diet, and moderation of alcohol intake are recommended in patients with hypertension.	I	C	7, 9, 14, 48	
Thiazide or thiazide-like diuretics can be useful for BP control and to reverse mild volume overload and associated symptoms in symptomatic patients with HF with volume overload. Loop diuretics, which are the preferred agents for treatment of congestion in symptomatic patients with HF, are less effective than thiazide or thiazide-like diuretics in lowering BP.	IIa	C	7, 8, 48	
Addition of hydralazine isosorbide to the background therapy with ACE inhibitor or ARB and β-blocker may be beneficial for BP control in nonblack patients with HFrEF and hypertension.	IIa	C	8	71
Drugs to avoid in patients with HF and hypertension include nondihydropyridine calcium channel blockers (eg, verapamil and diltiazem) and moxonidine. An attempt should be made to avoid α-adrenergic blockers such as doxazosin; they might be used only if other drugs for the management of hypertension and HF are inadequate to achieve BP control at maximum tolerated doses.	III: Harm	C	8, 14, 29, 48	

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; COR, Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LOE, Level of Evidence; and NYHA, New York Heart Association.

ally the main focus of the initial treatment of patients with established HF, and the standard treatment of HF usually lowers BP. This is supported by the observation that SBP has usually been lowered to a normal range of 110 to 130 mm Hg in most successful HF treatment trials with HF medications.[48] After optimization of HF treatment, if BP is not controlled, further treatment strategies targeting both BP and HF can be used. It should also be noted that the BP-lowering effects of HF medications may relate to the baseline BP; that is, there may be a greater BP-lowering effect in patients with a higher baseline BP. However, the beneficial effects of the HF medications are usually independent of the baseline BP or changes in BP and do not vary according to baseline BP or reductions in SBP levels.[60–62]

Medication Choices for the Treatment of Hypertension in Patients With HF

Currently, there are no randomized, large-scale trials comparing the effectiveness of different antihypertensive medications targeting optimal treatment of BP solely in patients with hypertension and established HF. Thus, most evidence comes from hypertension clinical trials that have not excluded patients with a history of HF. In patients with established HF, drugs that have been shown to improve outcomes for patients with HF generally also lower BP. Thus, the emphasis should be on initiating and optimizing guideline-directed medical treatment of HF, which will likely help control BP at target doses. Therefore, patients with hypertension and HF with reduced EF (HFrEF) are treated with diuretics, ACE inhibitors (or ARBs if ACE inhibitor intolerant), β-blockers, and aldosterone antagonists unless contraindicated[8] (Table 4).

Although thiazide or thiazide-like diuretics are usually recommended for the treatment of hypertension,[7] in patients with current or prior symptoms of HF who have evidence of fluid retention, loop diuretics are usually used[8] (Table 4). It should be noted, however, that loop diuretics are usually less effective than thiazide or thiazide-like diuretics in lowering BP[8] and thus should be used for the management of hypertension in patients with symptomatic HF with congestion. For patients with stage C HFrEF, ACE inhibitors (or ARBs in ACE inhibitor–intolerant patients), β-blockers, and aldosterone antagonists are titrated to target doses as tolerated. BP is frequently within the target range or lower after careful titration of these agents. In those for whom BP remains in the hypertensive range, further increases of the recommended agents may be considered. Reasonable next steps would be the addition of other medications with proven benefit in HF populations such as ARBs or aldosterone antagonists or the addition of nitrates or hydralazine.

Treatment of Refractory Hypertension in HF

Most patients with advanced stage C or D HF do not manifest hypertension and may actually develop hypotension resulting from pump failure and an inability to raise the BP. However, if a patient with HFrEF has refractory hypertension, there are no definitive studies to provide guidance on the efficacy and safety of additional antihypertensive approaches when recommended HF therapies are inadequate to treat BP. Nondihydropyridine calcium channel blockers (diltiazem, verapamil) are used to treat hypertension, but they are not recommended as routine treatment for patients with HFrEF.[8] Amlodipine and felodipine neither improve nor worsen the survival of patients with HF[72,73]; therefore, a dihydropyridine group of calcium channel blockers could be used to control hypertension only after other medications have failed. There are few data assessing the efficacy and safety of other medications or of specific combinations of ≥3 drugs for hypertension in the HF population.[74] Accordingly, the recommendation of specific multidrug combinations is largely empirical or anecdotal. Intuitively, it seems most appropriate to continue to combine agents of different mechanisms of action. In that regard, a triple-drug regimen of an ACE inhibitor or ARB, a calcium channel blocker, and a thiazide diuretic is effective and can be well tolerated.[74] It should be kept in mind that carvedilol, 1 of the 3 β-blockers proven to reduce mortality in HF, is more effective in reducing BP than metoprolol succinate or bisoprolol because of its combined α_1 β_1 β_2-blocking properties and may be the β-blocker of choice among β-blockers in patients with HFrEF with refractory hypertension. Evidence with other β-blockers with vasodilatory properties such as nebivolol[75] and labetolol[76] is very limited, and they are not the β-blocker of choice for the treatment of HFrEF according to HF guidelines.[8] Experience with older-generation antihypertensive medications such as prazosin, an α-receptor blocker,[77] or clonidine, a centrally acting agent,[78,79] is again very limited and precedes the evidence with standard HF therapies. Furthermore, studies suggest potential adverse outcomes with these classes of agents that are elaborated below in the Drugs to Avoid in Patients With HF section.

In addition to medication choices, the evaluation of patients with resistant hypertension should be directed toward confirming true treatment resistance, accurate assessment of treatment adherence and use of good BP measurement techniques to exclude pseudo-resistance, and identification of causes contributing to treatment resistance, including secondary causes of hypertension. In most cases, treatment resistance is multifactorial in origin, with obesity, excessive dietary sodium intake, obstructive sleep apnea (OSA), and chronic kidney disease being particularly common factors in patients with HF.

New antihypertension treatment strategies such as renin inhibition with aliskiren failed to improve clinical outcomes in patients with HF,[80] and catheter-based renal artery denervation (SYMPLICITY HTN-3 trial [A Controlled Trial of Renal Denervation for Resistant Hypertension])

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failed to show a significant reduction of SBP in patients with resistant hypertension.[81] Other strategies such as targeting excessive sympathetic nerve activity by carotid body denervation are awaiting clinical validation in the hypertension and HF populations.

Drugs to Avoid in Patients With HF

Several classes of drugs should be avoided in patients with HFrEF with a history of hypertension. Because of their negative inotropic properties and the increased likelihood of worsening HF symptoms, the nondihydropyridine calcium channel blockers such as diltiazem and verapamil should be avoided.[8] The dihydropyridine calcium channel blocker amlodipine appeared to be safe in patients with severe HFrEF in the PRAISE trial (Prospective Randomized Amlodipine Survival Evaluation),[82] as was felodipine.[73] In the current 2013 HF guidelines, most calcium channel–blocking drugs except amlodipine are not recommended.[8] Although clonidine is an effective antihypertensive agent, a similar centrally acting drug, moxonidine, was associated with increased mortality in patients with HF; thus, centrally acting norepinephrine-depleting agents may need to be avoided or used with caution in patients with HFrEF.[83] In the ALLHAT trial, the α-blocker doxazosin arm of the trial was discontinued because of a 2-fold increase in the risk of developing HF compared with chlorthalidone treatment.[45] Although the ALLHAT study excluded patients with established HF and there are caveats about extrapolating these data to the management of hypertension in patients with established HF, the safety and efficacy of α-blockers in the management of patients with HF with hypertension are currently unclear. Potent direct-acting vasodilators such as minoxidil should also be avoided because of their renin-related salt and fluid-retaining effects. Nonsteroidal anti-inflammatory agents should be used with caution in these patients, given their effects on BP, volume status, and renal function.

Treatment of Hypertension in Patients With HF With Preserved LVEF

Most patients with HF and preserved LVEF (HFpEF), especially elderly women, have hypertension. A significant proportion of these patients also have evidence of LV hypertrophy, and some may have atrial dilatation, cardiac enlargement, and wall motion abnormalities without LV systolic dysfunction. Patients with HFpEF may respond particularly well to the treatment of hypertension with regression of hypertrophy[84] and improvement in filling pressures.[84,85] Most patients with HFpEF require treatment with cardiac medications for the comorbidities of hypertension, diabetes mellitus, coronary artery disease, and atrial fibrillation. The 2013 HF guidelines suggest that the use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control BP in patients with HFpEF.[8] The use of ARBs might also be considered to decrease hospitalizations for patients with HFpEF.[8]

Recommendations Harmonized With Existing Guidelines for the Recognition and Treatment of Patients With HF With Hypertension

See Tables 2 through 4 for a summary of these recommendations.

Stage A HF

For patients with hypertension who are at high risk for developing HF in the future but with no functional or structural cardiac disorder at present time, the following is recommended:

1. **Hypertension should be controlled in accordance with contemporary guidelines to lower the risk of developing HF *(Class I; Level of Evidence A)*.[7–9,21–28,30,31]**

Stage B HF

For patients with hypertension, with cardiac structural abnormalities or remodeling who have not developed HF symptoms, the following is recommended:

1. **In patients with structural cardiac abnormalities, including LV hypertrophy, BP should be controlled in accordance with clinical practice guidelines for hypertension to prevent symptomatic HF *(Class I; Level of Evidence A)*.[7–9,14,22,29,31,35,47]**

Stage C HF

For patients with hypertension and previous or current symptoms of HF in the context of an underlying structural heart problem, the following are recommended:

1. **Patients with HFrEF should be treated with guideline-directed medical therapy, including diuretics, ACE inhibitors or ARBs if ACE inhibitor intolerant, β-blockers, and aldosterone receptor antagonists, which have been proven to improve outcomes for patients with HF (*Class I; Level of Evidence A*) and can lower BP in hypertensive patients with HFrEF (*Class I; Level of Evidence B*).[8,29,50,63–68]**
2. **The addition of hydralazine/isosorbide dinitrate to the background regimen of a diuretic, an ACE inhibitor or ARB, and a β-blocker treatment in self-described black patients with HFrEF and with persistent New York Heart Association (NYHA) class III or IV HF symptoms is beneficial to reduce morbidity and mortality (*Class I; Level of Evidence A*) and can lower BP in hypertensive patients with HFrEF (*Class I; Level of Evidence B*).[8,69,70]**
3. **The treatment of hypertension in patients with HF should include behavioral modification such as sodium restriction and a closely monitored exercise program.[48] Weight reduction in obese or overweight, a heart-healthy diet, and moderation of alcohol intake in**

individuals with ≥140 mm Hg SBP or 90 mm Hg diastolic BP are recommended (*Class I; Level of Evidence C*).[7,9,14,48]

4. **Thiazide or thiazide-like diuretics can be useful for BP control and to reverse mild volume overload and associated symptoms in symptomatic patients with HF with volume overload. Loop diuretics, which are the preferred agents for treatment of congestion in symptomatic patients with HF, are less effective than thiazide or thiazide-like diuretics in lowering BP (*Class IIa; Level of Evidence C*).[7,8,48]**
5. **The addition of hydralazine/isosorbide dinitrate to the background treatment with an ACE inhibitor or ARB and a β-blocker may be beneficial in nonblack patients with HFrEF and hypertension *(Class IIa; Level of Evidence C)*.[8,71]**
6. **Drugs to avoid in patients with HF and hypertension are nondihydropyridine calcium channel blockers (eg, verapamil and diltiazem) and moxonidine (*Class III: Harm; Level of Evidence C*). α-Adrenergic blockers such as doxazosin should be avoided and might be used only if other drugs for the management of hypertension and HF are inadequate to achieve BP control at maximum tolerated doses *(Class III: Harm; Level of Evidence C)*.[8,14,29,48]**

Paradox: Once HFrEF Is Manifest, Higher BP Is Associated With Better Prognosis

An epidemiological paradox exists in the HF-hypertension relationship. Although hypertension results in the development of HF, once advanced HFrEF is manifest, lower BP is associated with a worse prognosis, and similarly, a higher BP is associated with a better prognosis. This is attributable to a loss of myocardial contractility in advanced HF, which suggests a poor prognosis. In these patients, the higher SBP may be a marker of the ability of the ventricle to generate a SBP or better cardiac output. However, it should be noted that the BP ranges demonstrated to have an association with mortality in retrospective analyses were not defined or validated as targets in prospective, controlled trials and should not be accepted as a target for BP control in patients with HF. In the Digitalis Investigation Group trial database, mortality was significantly higher for patients in the lowest SBP group (<100 mm Hg) than in the reference group of patients with an SBP of 130 to 139 mm Hg (HR, 1.65; 95% confidence interval [CI], 1.25–2.17; P<0.001).[86] Similar results were reported by the Valsartan Heart Failure Trial (Val-HeFT), in which patients in the lowest quartile of SBP (SBP ≤110 mm Hg) had more severe HF and a significantly increased mortality (HR, 1.21; 95% CI, 1.03–1.43; P=0.02) and hospitalization for HF (HR, 1.45; 95% CI, 1.22–1.73; P<0.001) than patients in the upper 3 quartiles of baseline SBP (mean SBP, 130 mm Hg[60]; Figure 2). Similar findings are noted in patients with acute decompensated HF.[87–90]

In a meta-analysis of 10 studies of a total population of 8088 subjects, higher SBP resulted in better outcomes in patients with established HF.[91] Studies included in this analysis had a maximum SBP of 158 mm Hg. The decrease in mortality rates associated with a 10–mm Hg higher SBP was 13.0% in the HF population. In a recent study by Ather et al[92] incorporating data from 2 large cohorts of ambulatory patients with chronic HF, it was noted that the relationship of BP and mortality is different in patients with mild and those with severe LV systolic dysfunction. In patients with mild to moderate LV systolic dysfunction, SBP was found to have a nonlinear U-shaped association with increased all-cause mortality at both the lower and upper ranges of SBP (Figure 3A). It should be noted, however, that these numbers were defined to have an association with mortality in a retrospective analyses, were not defined or validated targets in a prospective, controlled trial, and thus should not be accepted as a target for BP control in patients with HF. In the same study, in patients with severe LV systolic dysfunction with LVEF <30%, SBP was found to have a linear association, with lower SBP being associated with worse mortality (Figure 3B), similar to what has been described in other HF studies. Nuñez et al[93] also noted a differential prognostic effect of SBP on mortality according to LV function in patients with acute decompensated HF. These results suggest that the association of SBP with mortality may vary with LV function severity. In patients with HF with preserved or mildly depressed LV function, SBP appears to have a nonlinear U-shaped relationship, with increased mortality at both ends of low or high BP. In patients with HF with severe LV systolic dysfunction

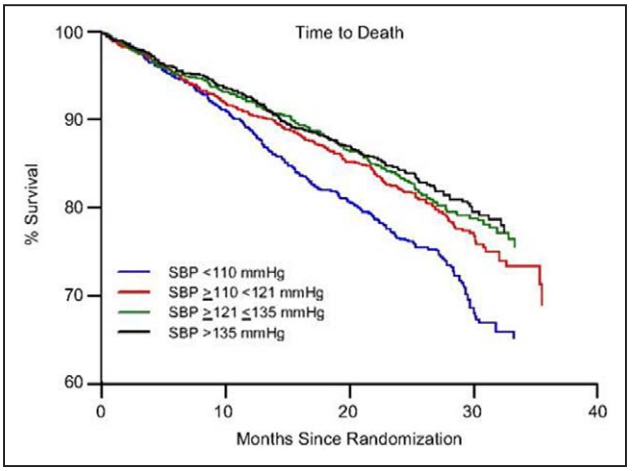

Figure 2. Effect of baseline systolic blood pressure (SBP) in all-cause mortality in the Valsartan Heart Failure Trial.
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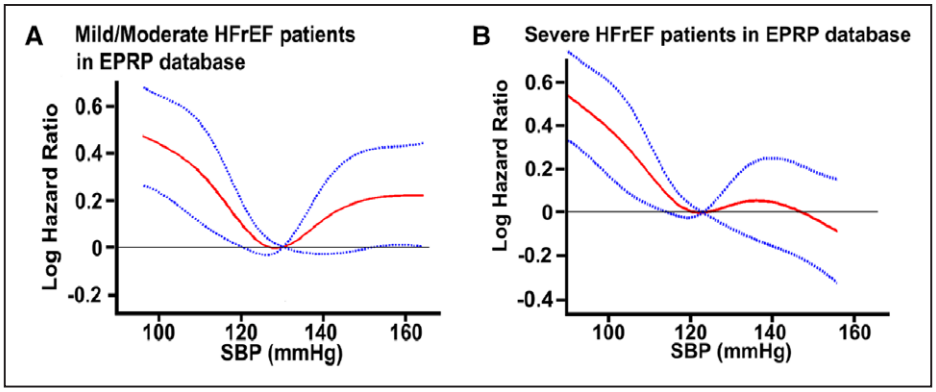

Figure 3. Restricted cubic spline analysis for Cox proportional hazards model.
A, In patients with heart failure (HF) with mild to moderate left ventricular systolic dysfunction (left ventricular ejection fraction ≥30% and <50%) showing a nonlinear U-shaped association of systolic blood pressure (SBP) with increased all-cause mortality at both the lower and upper ranges of SBP. The red line represents the estimated logarithmic hazard ratio (HR) of all-cause mortality; the blue lines represent the 95% pointwise confidence bands. **B**, In patients with HF with severe left ventricular systolic dysfunction (left ventricular ejection fraction <30%) showing a relatively linear association of SBP with all-cause mortality. The red line represents the estimated logarithmic HR of all-cause mortality; the blue lines represent the 95% pointwise confidence bands. HFrEF indicates heart failure with reduced ejection fraction; and EPRP, Veterans Affairs External Peer Review Program. Reprinted from Ather et al[92] with permission from Elsevier. Copyright © 2011, Mosby, Inc.

(EF <30%), SBP has a linear association with mortality, with higher SBP being associated with better survival and lower SBP being associated with worse mortality.

DIABETES MELLITUS AND HF

Association of Diabetes Mellitus With the Development of Incident HF

Multiple observational studies have demonstrated that diabetes mellitus is associated with an increased risk for the development of HF.[94–98] In the Framingham Heart Study, diabetes mellitus was associated with a nearly 2-fold greater risk of HF in men and a nearly 4-fold increased risk of HF in women independently of the presence of hypertension, coronary artery disease, LV hypertrophy, and valvular heart disease.[95] In the NHANES (National Health and Nutrition Examination Survey) Epidemiologic Follow-Up Study, diabetes mellitus was independently associated with an 80% increased risk of HF.[94] In the Framingham Heart Study, the population-attributable risk for HF associated with diabetes mellitus was 6% in men and 12% in women.[18,19]

Studies have also demonstrated that milder elevations in glucose and abnormalities in insulin resistance, even in the absence of overt diabetes mellitus, are associated with an increased risk for HF.[99,100] In individuals without known diabetes mellitus or HF at baseline in the ARIC study (Atherosclerosis Risk in Communities), the risk of incident HF was higher in individuals with hemoglobin A1c (HbA1c) of 6.0% to 6.4% (HR,1.40; 95% CI, 1.09–1.79) and HbA1c of 5.5% to 6.0% (HR,1.16; 95% CI, 0.98–1.37) compared with those with an HbA1c of 5.0% to 5.4%[100] (Table 5).

The mechanisms contributing to the greater degree of HF in individuals with diabetes mellitus are likely multifactorial and include the commonly shared HF risk factors of hypertension, coronary artery disease, renal

Table 5. Recommendations for the Treatment of Diabetes Mellitus in Stage A HF: Asymptomatic Patients at Risk for HF

Recommendations	COR	LOE	Referenced Guideline	References
For patients with diabetes mellitus (who are all at high risk for developing HF), blood sugar should be controlled in accordance with contemporary guidelines.	I	C	8, 29	
ACE inhibitors or ARBs can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors.	IIa	A for ACE inhibitor, B for ARBs for prevention of HF	8	25, 27, 40, 49

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; COR, Class of Recommendation; HF, heart failure; and LOE, Level of Evidence.

dysfunction, and obesity. In addition, diabetes mellitus may independently contribute to cardiac dysfunction in the absence of these risk factors (ie, diabetic cardiomyopathy). Potential pathogenic factors contributing to cardiac dysfunction in patients with diabetes mellitus include the direct and indirect effects of hyperglycemia and advanced glycation end products, autonomic dysfunction, microangiopathy, subclinical myocardial necrosis,[101] macrovessel (coronary) disease, mitochondrial dysfunction, lipotoxicity, and potential genetic abnormalities.[102–105]

Association of Diabetes Mellitus With Outcomes in Patients With Established HF

Diabetes mellitus is commonly present in patients with HF. It is estimated that ≈12% to 30% of patients with symptomatic HF have previously diagnosed diabetes mellitus.[104] Between 1995 and 1999 in Olmsted County, Minnesota, the prevalence of diabetes mellitus in patients with incident HF was 25%.[106] The prevalence of diabetes mellitus appears to be even greater in patients hospitalized with acute decompensated HF, with registries demonstrating a prevalence of 40% to 44%.[107,108] Similarly, in a registry of individuals with HFpEF, diabetes mellitus was present in 46% of patients.[109] Systematic assessment with oral glucose tolerance testing in patients with HF without a previous diagnosis of diabetes mellitus may also identify a large proportion (18%) of patients with newly diagnosed diabetes mellitus.[110]

The presence of diabetes mellitus in patients with HF is associated with increased morbidity and mortality.[104,111–116] In the CHARM Program (Candesartan Heart Failure Assessment of Reduction), rates of HF hospitalization in patients with diabetes mellitus were approximately twice the rates of those without diabetes mellitus.[113] In SOLVD (Studies of Left Ventricular Dysfunction), the adjusted relative risk of HF hospitalization for subjects with diabetes mellitus was 1.386 (95% CI, 1.138–1.689; P=0.001) and 1.835 (95% CI, 1.387–2.427; P<0.001) in the treatment and prevention trials, respectively.[116] The association of increased mortality with diabetes mellitus in patients with HF appears to be limited to or more apparent in patients with an ischemic than in those with a nonischemic pathogenesis.[112,117] Diabetes mellitus has also been independently associated with increased mortality in patients with HF in multiple observational studies and clinical trials.[104,106,111,113,114]

Treatment: Current Evidence of HF Risk Reduction With the Treatment of Diabetes Mellitus in Patients With HF

Given the increased morbidity and mortality associated with diabetes mellitus and HF, efforts for preventing HF are increasingly important. These efforts include the treatment and prevention of coronary artery disease and adequate treatment of hypertension in patients with diabetes mellitus.

An important risk factor for the development of HF in patients with diabetes mellitus is abnormal glucose control.[118–121] In a large cohort study of nearly 50 000 diabetic patients without HF at baseline, each 1% increase in HbA1c was associated with an 8% increased risk of HF.[118] In a similar study of patients with diabetes mellitus enrolled in the ARIC study, the adjusted HR of HF for each 1% higher HbA1c was 1.17 (95% CI, 1.11–1.25) for individuals without coronary heart disease at baseline and 1.20 (95% CI, 1.04–1.40) for those with coronary heart disease at baseline.[119] The increased risk for the development of HF with increasing HbA1c in ARIC was also present in patients in the absence of incident coronary heart disease (HR,1.20; 95% CI, 1.11–1.29).[119] In the CHS (Cardiovascular Health Study), elevated fasting glucose among older adults with diabetes mellitus was also independently associated with incident HF.[121]

Despite the epidemiological data linking worse glycemic control to greater rates of HF in observational studies and clinical trials, data from randomized, controlled, clinical trials of more intensive glucose control have not demonstrated a benefit in HF reduction with intensive glycemic control. In a meta-analysis of 8 randomized, controlled trials (that included a total of 37 229 patients) comparing more with less intensive glucose-lowering strategies, the risk of HF-related events did not differ significantly between more intensive regimens and standard therapy despite achieving an average HbA1c difference of 0.9% (odds ratio, 1.20; 95% CI, 0.96–1.48).[122] In subgroup analyses limited to clinical trials specifically designed to compare strategies targeting more intensive and standard glycemic control (VA-CSDM [Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes] Feasibility, UKPDS [United Kingdom Prospective Diabetes Study], ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation], ACCORD [Action to Control Cardiovascular Risk in Diabetes], and VADT [Veterans Affairs Diabetes Trial]), intensive glucose-lowering strategies were not associated with a reduced risk of HF compared with standard regimens (odds ratio, 1.02; 95% CI, 0.88–1.20).[122]

Glycemic Control and Outcomes in Patients With Established HF

In patients with established HF at baseline, the relationship between glycemic control and outcomes has not been clearly defined. Some observational data have demonstrated a potential U-shaped or inverse relationship between glycemic levels (HbA1c) and mortality in individuals with established HF and diabetes mellitus.[123–125] In a study of 5815 ambulatory patients with HF receiving

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medical treatment for diabetes mellitus treated at Veterans Affairs medical centers, individuals with modest glycemic control (HbA1c >7.1%–7.8%) had lower mortality compared with individuals with either higher or lower HbA1c levels (Figure 4).[123] In another cohort of 123 diabetic individuals with advanced HFrEF referred to a single academic medical center, patients with an HbA1c ≤7.0% had significantly increased mortality compared with those with an HbA1c >7.0% (adjusted HR, 2.3; 95% CI, 1.0–5.2).[124] In a similar study of 358 patients with advanced HFrEF and diabetes mellitus, the relationship between HbA1c levels and 2-year mortality or need for urgent transplantation was assessed with the use of quartiles of HbA1c (quartile 1, ≤6.4%; quartile 2, 6.5%–7.2%; quartile 3, 7.3%–8.5%; and quartile 4, ≥8.6%). Two-year event-free survival was 61% and 65% in quartiles 3 and 4 compared with 48% and 42% in quartiles 1 and 2 (P=0.005).[125] The reasons for this paradoxical relationship have not been well established, and given the observational nature of these analyses, these studies do not necessarily imply that glucose lowering causes adverse events. The nature of the association between glucose control and outcomes in patients with HF has also not been consistent in all HF cohorts. In a subset of individuals enrolled in the CHARM trial who had HbA1c available, the relationship between HbA1c and outcomes was assessed in 2412 participants (of whom 907 participants had known diabetes mellitus).[126] In the total CHARM cohort, increasing levels of HbA1c were associated with increased risk of total mortality, HF hospitalization, and a composite outcome of cardiovascular death or HF hospitalization. Of note, the graded relationship between HbA1c and mortality was more pronounced in the nondiabetic patients enrolled in CHARM and did not reach statistical significance for the outcomes of cardiovascular death (P for heterogeneity=0.04) and total mortality (P for heterogeneity=0.008) in the cohort of HF patient with diabetes mellitus.[126] Among patients hospitalized with HF, hyperglycemia is commonly observed in both patients with and those without recognized diabetes mellitus. In a large, nationally representative study of >50 000 elderly patients hospitalized with HF, elevated glucose was found in nearly half of patients and was associated with greater HF severity.[127] However, in sharp contrast to patients hospitalized with acute coronary syndromes, there was no significant association between glucose values on admission and either short- or long-term mortality, regardless of their diabetes mellitus status. Given these findings and the absence of data from clinical trials of targeted glucose control in this patient population, there is insufficient evidence to recommend specific glucose thresholds or glucose treatment targets in patients hospitalized with HF.

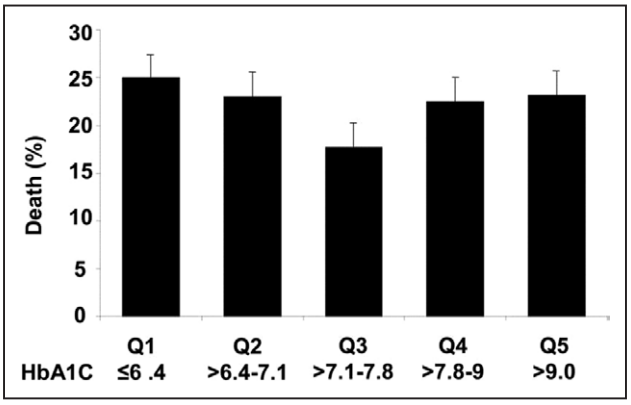

Figure 4. The U-shaped association between the proportion of patients who died at the 2-year follow-up according to quintiles (Q) of hemoglobin A1c (HbA1c) in diabetic patients with heart failure, with the lowest risk of death in those patients with modest glucose control (7.1%<HbA1c≤7.8%).
Global χ^2 P=0.001. Error bars indicate 95% confidence intervals. Reprinted from Aguilar et al[123] with permission from the American College of Cardiology Foundation. Copyright © 2009, American College of Cardiology Foundation.

To date, no randomized, clinical trials of more versus less intensive glucose control have been performed specifically in patients with HF. Until such trials are completed, the ideal glucose targets in patients with established HF remain uncertain. Prospective data from subgroups of clinical trials assessing optimal glycemic targets in patients with HF also are limited. In VADT, which examined an intensive glycemic control strategy compared with standard care, individuals with NYHA class III to IV HF were excluded,[128] and the outcomes of subsets of diabetic individuals who may have less advanced HF have not been reported separately.[129] In the ACCORD trial, which examined whether a therapeutic strategy targeting normal HbA1c (ie, <6.0%) would reduce the rate of cardiovascular events compared with a strategy targeting HbA1c levels from 7.0% to 7.9% in diabetic patients with established cardiovascular disease (CVD) or high CVD risk, ≈5% of individuals (n=494) had HF at baseline.[130] In ACCORD, there was an unexpected finding of increased mortality in the intensive treatment arm compared with the standard therapy arm.[130] This increased hazard was not statistically different in patients with and without HF at baseline (interaction P=0.71).[131]

Safety and Efficacy of Antihyperglycemic Drugs in Patients With Established HF and Diabetes Mellitus

The optimal hyperglycemic therapy in patients with HF with diabetes mellitus has not been well defined, and some antihyperglycemic drugs may pose challenges for patients with HF.

In diabetes, metformin is currently recommended as first-line therapy in patients with type 2 diabetes mellitus in the absence of contraindications.[132,133] Metformin

was previously contraindicated in individuals with HF because of potential concerns about lactic acidosis.[133] Subsequent analyses and reviews have suggested that the risk of lactic acidosis associated with metformin is extremely low in patients with type 2 diabetes mellitus and may not be higher than in diabetic patients not receiving metformin therapy.[134–136] In addition, multiple observational studies in patients with diabetes mellitus and established HF have suggested that metformin not only may be safe but also may be associated with improved survival in patients with diabetes mellitus and HF.[137–145] Animal studies in HF models have also demonstrated potential cardioprotective effects of metformin therapy on the progression of HF via activation of AMP-activated protein kinase pathways,[146–149] inhibition of cardiac fibrosis,[148,150] and modulation of cardiomyocyte autophagy.[147] It is important to note that prospective, large outcome trials assessing the safety and efficacy of metformin in patients with established HF have not been performed. Nonetheless, the contraindication to metformin use in patients with HF has been removed.[151] Metformin, which is excreted by the kidneys, remains contraindicated in patients with renal insufficiency, a comorbid condition particularly relevant in patients with HF. The package insert states that metformin should not be used in men with serum creatinine levels ≥1.5 mg/dL and in women with levels ≥1.4 mg/dL,[152] but the exact level of renal insufficiency precluding metformin use remains controversial.[153] In the United Kingdom, National Institute for Health and Clinical Excellence guidelines suggest that metformin can be used to an estimated glomerular filtration of 30 mL·min^{-1}·1.73 m^{-2} (with a dose reduction advised at an estimated glomerular filtration rate <45 mL·min^{-1}·1.73 m^{-2}).[154] Given these concerns, metformin should be used cautiously (or avoided) in patients at risk for worsening renal dysfunction (eg, acute decompensated HF). Further prospective human studies are necessary to assess the potential benefits and safety of metformin in patients with diabetes mellitus and HF.

Thiazolidinediones have been associated with fluid retention and increased rates of HF in randomized, controlled trials of patients predominantly free of HF at baseline.[155–158] The exact mechanisms contributing to increased HF events with thiazolidinediones are not known, but the predominant proposed mechanism relates to thiazolidinedione-associated volume expansion resulting from increased renal sodium reabsorption[159] rather than a direct effect on myocardial structure and function.[160] Prospective, randomized, controlled studies specifically in patients with established HF and diabetes mellitus have demonstrated increased rates of edema, a need for increased HF medications, and increased HF hospitalization in patients treated with thiazolidinediones compared with patients treated with placebo or sulfonylurea.[161,162] Given these findings, caution is urged for the use of thiazolidinediones in all patients with signs and symptoms of HF, and initiation of either agent is contraindicated in patients with NYHA class III to IV HF[155,163] (Table 6).

Sulfonylureas are commonly used in diabetic patients with HF. In a study of >16 000 Medicare recipients who had been discharged with a diagnosis of HF, approximately half of the patients were treated with sulfonylureas.[140] In that observational study, sulfonylurea was not associated with increased mortality (HR, 0.99; 95% CI, 0.91–1.08).[140] Some observation studies have suggested improved survival with metformin compared with sulfonylurea.[138,141] Prospective, randomized, controlled trials on sulfonylurea use in patients with HF have not been performed. Important adverse effects relevant to patients with HF include the risk of hypoglycemia and weight gain associated with sulfonylurea therapy. The new-generation sulfonylureas (eg, glyburide, gliclazide, glipizide, glimepiride) have largely replaced the first-generation agents (eg, acetohexamide, chlorpropamide, tolazamide, tolbutamide) in routine use because they are more potent, can be administered in lower doses, and can be given on a once-daily basis. A few studies based on older-generation sulfonylureas have led to conflicting results for cardiovascular risk. Some evidence suggests greater risk of mortality with first-generation sulfonylureas[164] compared with more recent ones that have been implicated in marginal cardiovascular benefit.[165] These older studies have been criticized for flaws in clinical trial design.[166] Although no certain cardioprotective effect or beneficial effect in HF can be attributed to sulfonylureas, newer-generation compounds have not been associated with adverse cardiovascular outcomes.[165] Mechanistic differences exist between sulfonylureas. Impairment of

Table 6. Recommendations for the Treatment of Diabetes Mellitus in Stage C HF: Patients With Cardiac Structural Abnormalities or Remodeling With Prior or Current Symptoms of HF

Recommendations	COR	LOE	Referenced Guideline	References
Physicians should control diabetes mellitus in patients with HF in accordance with recommended guidelines	I	C	8, 29	
Caution is urged for the use of thiazolidinediones in all patients with signs and symptoms of congestive HF. Initiation of these agents is contraindicated in patients with class III or IV HF.	III: Harm for NYHA class III–IV HF	C	8, 155, 163	

COR indicates Class of Recommendation; HF, heart failure; LOE, Level of Evidence; and NYHA, New York Heart Association.

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cardiac ischemic preconditioning has been implicated as a reason for the potential detrimental cardiovascular effect of older-generation sulfonylureas on the basis of nonselective effects of these agents on pancreatic and cardiac K-ATPase channels. Impairment of cardiac ischemic preconditioning does not seem to occur with more selective and newer-generation sulfonylureas.[166]

The incretin-based therapies (glucagon-like peptide-1 [GLP-1] agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) have emerged as a new class of hyperglycemic medications. The side-effect profile of these medications when used as monotherapy (less risk of hypoglycemia and association with modest weight loss with GLP-1 agonists) represents potential benefits, but the safety and efficacy of DPP-4 inhibitors and GLP-1 agonists have not been studied extensively in patients with established HF. Human studies of DPP-4 inhibitors or GLP-1–based therapies have also been limited by HF not being identified as a prospective primary outcome, and these limited studies in patients with HF have yielded mixed results in cardiovascular versus HF outcomes.[167–170] Although there were no significant changes with the use of DPP-4 inhibitors in cardiovascular outcomes in large-scale clinical studies,[171,172] the SAVOR-TIMI 53 trial (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction), reported by Scirica et al,[172] showed a 27% increase in hospitalization for HF among patients with diabetes mellitus who received saxagliptin compared with placebo. In this trial, 12.8% of patients had a history of HF at baseline. The composite risk of cardiovascular events and hospitalization for HF was similar for patients with history of HF compared with patients without a history of HF with the use of saxagliptin.[173] A recent meta-analysis of available studies suggests that DPP-4 inhibitor use is associated with an increased risk of HF, without any clear evidence of differences among drugs of that class.[174] Additional studies are being conducted to assess the cardiovascular efficacy of DPP-4 inhibitors and GLP-1–based therapies, with HF being measured as a secondary outcome. These studies may provide insights into the safety and efficacy of incretin-based therapies with primary outcomes of HF, especially in patients with diabetes mellitus and established HF.

Many patients with diabetes mellitus and HF will require insulin therapy either as monotherapy or in combination with other agents to achieve adequate glycemic control. Insulin is associated with hypoglycemia and weight gain. Some observational studies have demonstrated that insulin use may be associated with a greater risk of developing incident HF in patients with diabetes mellitus.[175] In diabetic patients with established HF, observational studies have also demonstrated an association between insulin use and increased mortality,[114,176,177] although these findings are potentially limited by unmeasured confounding factors, and not all observational studies have demonstrated this increased hazard.[140] Given that individuals who require insulin for type 2 diabetes mellitus are more likely to have a longer diabetes mellitus duration and severity, the use of insulin may be a marker of more advanced disease and a high-risk group rather than a direct contributor to increased HF events and increased mortality in patients with HF. In a recent large, randomized, controlled trial of 12 537 patients with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes mellitus and cardiovascular risk factors, patients were randomized to insulin glargine or standard care.[178] In this prospective study, rates of cardiovascular outcomes (including HF events) were similar in the insulin-glargine and standard care groups.[178]

Sodium-glucose cotransporter 2 inhibitors are a newer class of glucose-lowering medications with several compounds currently approved for diabetes mellitus management.[179] Sodium-glucose cotransporter 2 inhibitors promote the renal excretion of glucose, thereby causing osmotic diuresis. In a recent trial in patients with diabetes and cardiovascular risk, empagliflozin, an inhibitor of sodium–glucose cotransporter 2, when added to standard care, was shown to reduce cardiovascular death, all-cause mortality, and HF hospitalizations. Hospitalization for HF was reduced by 35%; 10% of the patients had pre-existing HF. Consistent effects of empagliflozin were observed across subgroups defined by baseline characteristics, including patients with versus without HF. But among patients with HF, improvement in clinical outcomes including reductions in mortality, cardiovascular death, or HF hospitalizations did not reach significance. There was no measure of LVEF or natriuretic peptides in the trial. Currently, other ongoing large, cardiovascular outcome trials of several sodium-glucose cotransporter 2 inhibitors (and other novel glucose-lowering medications with potentially favorable cardiovascular effects such as glucagon-like peptide-1 agonists) will provide additional valuable data, especially in patients with established HF, in this regard.

Recommendations Harmonized With Existing Guidelines for the Recognition and Treatment of Patients With HF With Diabetes Mellitus

See Tables 5 through 7 for summary of these recommendations.

Stage A HF

1. **For patients with diabetes mellitus (who are all at high risk for developing HF), blood sugar should be controlled in accordance with contemporary guidelines (*Class I; Level of Evidence C*).[8]**
2. **ACE inhibitors can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular**

Table 7. Glycemic Goals in Patients With Diabetes Mellitus and HF

Recommendations	COR	LOE	Referenced Guideline	References
Lowering HbA1c to <7% or ≈7% is reasonable for many nonpregnant adults with HF.	IIa	A to reduce microvascular complications, B to reduce macrovascular complications	13, 181	28, 122, 128–131, 182
More stringent HbA1c goals (eg, <6.5%), if can be achieved without significant hypoglycemia or other adverse effects of treatment, might be considered for patients with a short duration of diabetes mellitus, a long life expectancy, and no significant CVD.	IIb	C	13	
Less stringent HbA1c goals (eg, <8%) may be reasonable for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions and those with long-standing diabetes mellitus in whom the general goal is difficult to attain despite diabetes mellitus self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents, including insulin.	IIb	B	13, 181	130, 183–187

COR indicates Class of Recommendation; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HF, heart failure; and LOE, Level of Evidence.

disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors (*Class IIa; Level of Evidence A*).

3. **ARBs can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors (*Class IIa; Level of Evidence B*).**

Stages B and C HF

Management of Hyperglycemia: Glycemic Goals in Patients With Diabetes Mellitus and HF

Current American Diabetes Association (ADA) guidelines[13] and the AHA/ACC statement on intensive glycemic control and the prevention of cardiovascular events[181] provide the following:

The following recommendations are from the ADA Standards of Medical Care (2015)[13]:

(1) Lowering A1c to approximately 7% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes, it is associated with long-term reduction in macrovascular disease. Therefore, a reasonable A1c goal for many nonpregnant adults is <7%. (B)[13,181]

(2) Providers might reasonably suggest more stringent A1c goals (such as <6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, and no significant CVD. (C)[13,181]

(3) Less-stringent A1c goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose lowering agents including insulin. (B)[13,181]

The following recommendations are from "Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a Position Statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association"[181]:

1. *Microvascular disease: lowering A1c to below or approximately 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. Therefore, the A1c goal for nonpregnant adults in general is <7%. ADA, A-level recommendation; ACC/AHA, Class I recommendation (Level of Evidence A).*
2. *Macrovascular disease: in type 1 and type 2 diabetes, randomized controlled trials of intensive versus standard glycemic control have not shown a significant reduction in CVD*

outcomes during the randomized portion of the trials. However, long-term follow-up of the DCCT and UKPDS cohorts suggests that treatment to A1c targets below or near 7% in the years soon after the diagnosis of diabetes is associated with long-term reduction in risk of macrovascular disease. Until more evidence becomes available, the general goal of <7% appears reasonable. ADA, B-level recommendation; ACC/AHA, Class IIb recommendation (Level of Evidence A).

3. *For some patients, individualized glycemic targets other than the above general goal may be appropriate:*
   a. *Subgroup analyses of clinical trials such as the DCCT and UKPDS and the microvascular evidence from the ADVANCE trial suggest a small but incremental benefit in microvascular outcomes with A1c values closer to normal. Therefore, for selected individual patients, providers might reasonably suggest even lower A1c goals than the general goal of <7% if it can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients might include those with short duration of diabetes, long life expectancy, and no significant CVD. ADA, B-level recommendation; ACC/AHA, Class IIa recommendation (Level of Evidence C).*
   b. *Conversely, less stringent A1c goals than the general goal of <7% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions or those with long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents, including insulin. ADA, C-level recommendation; ACC/AHA, Class IIa recommendation (Level of Evidence C).*

   There are no compelling data to suggest that tight glycemic control improves outcomes in patients with HF. Observational studies suggest a potential hazard associated with lower glycemic HbA1c levels (<7%), but this may be confounded by baseline comorbid conditions. Prospective data are available only from ACCORD. There is not enough evidence to suggest that HbA1c targets should be different from the targets described above. Particularly relevant to patients with HF is that less stringent goals of HbA1c <7% may be more appropriate, particularly in patients with conditions that are difficult to control (hypoglycemia, adverse effects of medications, variable blood glucose).

Antihyperglycemic Medications in Patients With HF and Diabetes Mellitus

Metformin

Randomized, clinical trials of metformin therapy, including a subset of the UKPDS 34 study[182] and a trial of 390 diabetic patients receiving background insulin therapy,[188] have demonstrated metformin-associated reductions in macrovascular events, including MI and all-cause mortality. A potential reduction in macrovascular events in patients with ischemic HF may improve outcomes in a high-risk population. However, no prospective studies assessing the safety and efficacy of metformin in patients with HF have been published. A large number of observational data support its safety and potential benefit, but residual confounding may be present (ie, patients with advanced illness do not receive metformin). The American Diabetes Association Standards of Medical Care in Diabetes statement has specified, "In patients with stable CHF, metformin may be used if renal function is normal but should be avoided in unstable or hospitalized patients with HF."[13] One of the concerns about the use of metformin in patients with HF is the potential risk of developing lactic acidosis, which may be particularly relevant in patients with renal disease. Current US prescribing guidelines state that metformin should not be used in men with a creatinine level ≥1.5 mg/dL and in women with a creatinine level ≥1.4 mg/dL because metformin is renally eliminated. The threshold of renal insufficiency at which to restrict metformin is controversial. In the United Kingdom, National Institute for Health and Clinical Excellence guidelines suggest that metformin can be used down to an estimated glomerular filtration of 30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ (with a dose reduction advised at an estimated glomerular filtration <45 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$).[154]

Thiazolidinedione

Current ACC/AHA guidelines for the management of heart failure recommend that thiazolidinediones be avoided or discontinued in patients with HF (Class III Recommendation: Harm; Level of Evidence B). Similarly, scientific advisories caution against the use of rosiglitazone or pioglitazone in all patients with signs and symptoms of HF. Initiation of either agent is contraindicated in patients with class III to IV HF.

Other Medications

There are inadequate data to make recommendations on other diabetic agents.

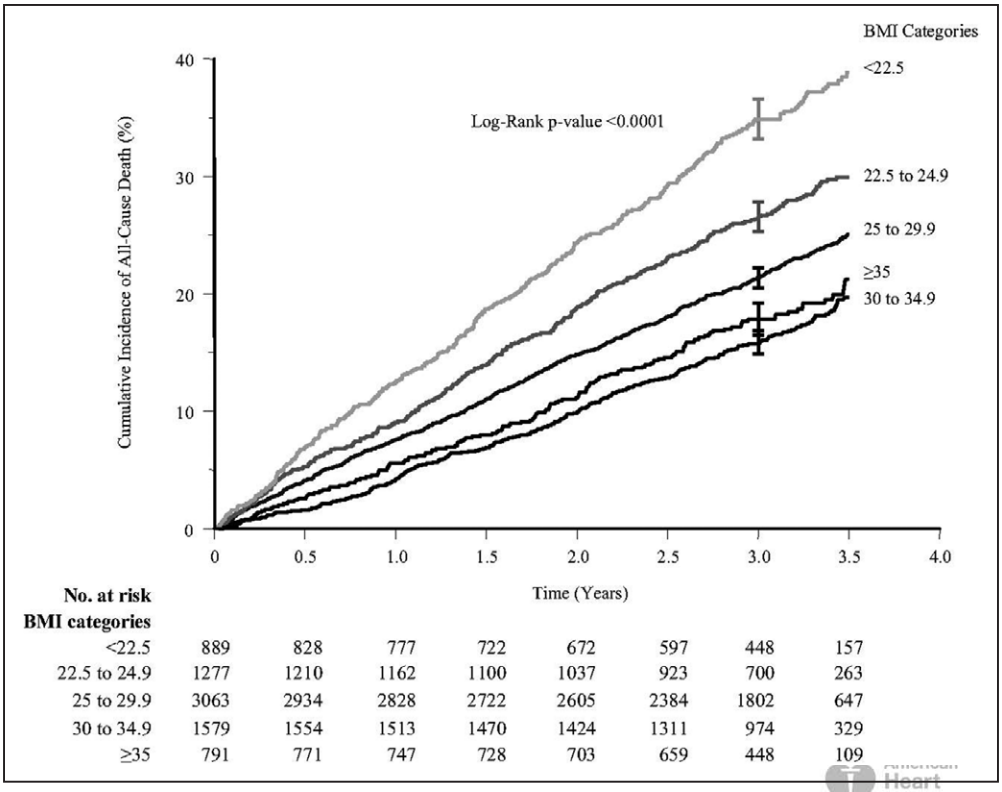

Figure 5. Cumulative incidence curves for all-cause death according to category of body mass index (BMI) at the baseline examination.

Vertical bars indicate standard errors of the incidence estimates at 3 years of follow-up. Data shown are truncated at 3.5 years. Reprinted from Kenchaiah et al.[201] Copyright © 2007, American Heart Association, Inc.

OBESITY AND HF

Obesity and Incident HF

Multiple studies have established obesity as a risk factor for the development of HF. Although the concept of cardiomyopathy relating to obesity has been described previously,[189–191] the strong, independent, incremental relationship between obesity as indexed by body mass index (BMI) and HF incidence was only more recently established. In a study of 5881 participants in the Framingham Heart Study, the increase in the risk of HF per 1-unit BMI increase was 5% for men and 7% for women, even after adjustment for demographics and known risk factors of MI, diabetes mellitus, hypertension, and cholesterol.[192] The continuous gradient between higher BMI and risk of HF has been confirmed in larger prospective, cohort studies.[193,194] In addition to BMI, other anthropometric indexes of obesity, including waist circumference, waist-to-hip ratio, and waist-to-height ratio, have been independently associated with incident HF in large, population-based studies; however, indexes such as waist circumference and waist-to-hip ratio have not been shown to perform better than BMI as predictors of HF.[194–196] Although the relationship between overweight/obesity and incident HF may be associated with hemodynamic and anatomic cardiac changes related to excess body mass,[197] recent evidence suggests that the relationship is also mediated by obesity-related metabolic, inflammatory, and hormonal changes. Obesity is highly correlated with insulin resistance, which may in part potentiate the link between obesity and HF. In the Uppsala study, insulin sensitivity, but not anthropometric indexes of obesity, was independently predictive of HF risk.[99] In a cohort study from Greece, individuals with normal BMI and metabolic syndrome were at substantially higher risk of HF at 6 years compared with obese individuals without metabolic syndrome.[198] Analyses from MESA (Multi-Ethnic Study of Atherosclerosis) suggest that inflammation may potentiate the link between obesity and the risk of developing HF. Although the risk of HF was 83% higher in obese compared with nonobese subjects after adjustment for traditional risk factors, the relationship between obesity and incident HF was no longer significant after adjustment for the inflammatory biomarkers.[199,200]

Obesity and Outcomes in Patients With Established HF: The Obesity Paradox

Overweight and obesity are exceedingly prevalent in HF, although the prevalence may vary depending on the population studied. However, recent studies have shown that 29% to 40% of patients with HF are overweight and 30% to 49% are obese, with a significantly higher prevalence

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of obesity in patients with HFpEF compared with patients with HFrEF.[1,201–203]

Although obesity is well established as a risk factor for CVD and incident HF, as described above, obesity, as measured by BMI or other anthropometric indexes, is not a risk factor for adverse outcomes in patients with established HF. This reversal of traditional epidemiology, or the obesity paradox, has now been well documented in numerous studies in the HF medical literature. Given the high prevalence of obesity not only in the general population but also in HF populations, discussion of obesity and its treatment is highly relevant.

In an initial study of 1203 patients with advanced HF followed up at a single university HF referral center, obesity, as defined by BMI, was not associated with worsened outcomes.[204] A subsequent analysis of the Digitalis Investigation Group database of 7788 patients with chronic, stable HF also revealed lower risk-adjusted mortality rates in the overweight and obese compared with normal-weight patients.[205] Similarly, in a substudy of the CHARM program, including 7599 subjects with symptomatic HF with a wide range of LVEF, higher BMI was incrementally associated with lower mortality. Furthermore, a BMI ≥35.0 kg/m^2 was not associated with excess risk, and the group with the highest mortality rates was the group of patients with BMI <22.5 kg/m^2 (Figure 5). The association between higher BMI and improved outcomes was seen in patients with HFrEF and with HFpEF.[201] A meta-analysis of 9 observational studies of BMI and outcomes in HF (n=28 209 HF subjects) revealed that overweight (BMI, 25.0–9.9 kg/m^2) was associated with reduced relative risk of cardiovascular mortality of 0.81 (95% CI, 0.72–0.92) and that obesity (BMI ≥30 kg/m^2) was associated with an even lower risk (relative risk, 0.60; 95% CI, 0.53–0.69).[206] Lastly, the protective effect of obesity was also noted in patients with acute decompensated HF; patients in the highest quartile of BMI had the lowest risk of in-hospital mortality in the Acute Decompensated Heart Failure National Registry.[207]

BMI, because of its general acceptance and ease of use, is the primary tool for assessing obesity or body fatness in clinical practice; however, BMI does not discriminate between fat and lean mass and furthermore cannot assess the distribution of body fat.[204,208] Waist circumference has been shown to be associated with improved outcomes in both men and women with advanced HF.[205,206,209,210] Furthermore, in a study of patients with advanced HF that assessed body fat percentage using the skin-fold technique, patients with HF in the highest body fat quintile (mean, 37.7%) had the lowest rate of death and urgent heart transplantation (5%) compared with an event rate of 22% in the patients in the lowest body fat quintile (mean, 16.4%).[211] A study of community HF clinic patients in the United Kingdom assessed multiple measures of body mass, including weight, height, body surface area, BMI, and bioelectrical impedance data, and found that the larger the patient's size was, the lower the risk of mortality was. In a multivariable model, the single best predictor of outcome was body surface area[212]

Epicardial adipose tissue is a visceral fat depot of variable volume around the heart that is biochemically active in terms of free fatty acid release and the production of adipokines.[213] In the general population, epicardial adipose tissue is known to be associated with metabolic syndrome and coronary artery disease risk.[210,214] However, preliminary studies have demonstrated low epicardial adipose tissue in patients with HF compared with healthy subjects.[215] Furthermore, a recent study found low epicardial adipose tissue in HF to be associated with increased HF mortality, possibly representing a novel component of the obesity paradox in HF.[212,216] Taken as a whole, these data suggest that higher body mass, whether fat or lean mass, is associated with improved outcomes in the syndrome of HF. The underlying explanatory reasons for this counterintuitive relationship between obesity and improved HF outcomes are not fully understood, although several plausible hypotheses have been put forth.[213,214,217,218] Importantly, HF is known to be a catabolic state,[215,219] and thus, obesity and increased fat or lean mass likely represent a beneficial greater metabolic reserve in HF. It is also well recognized that cardiac cachexia or unintentional weight loss is associated with advanced HF state and increased mortality.[217,220] In trials that included underweight patients, when patients with obesity were compared with nonobese patients, the detrimental role of underweight status or cachexia may have confounded the analysis of nonobesity toward an adverse outcome. This is supported by the U-shaped association of BMI and mortality in patients with HF, with increased mortality being observed in patients with a BMI <18.5 kg/m^2. In addition to direct effects of cachexia on mortality, this reverse epidemiology may be explained partly by decreased levels of lipoprotein molecules and adipocytes in the setting of cachexia distorting their endotoxin-scavenging role, predisposing patients with HF with cachexia to inflammatory consequences of endotoxemia.[221]

It is also interesting to note that brain natriuretic peptide levels are significantly lower in overweight and obese patients with HF compared with lean patients.[222–224] A potential important explanation includes the increase in the clearance of active natriuretic peptides by means of an increased expression of clearance receptors on adipocytes.[225] Furthermore, obese subjects are frequently treated for hypertension and coronary artery disease. Pharmacological treatment reduces plasma levels of cardiac natriuretic peptides, and this effect may explain, in part, the lower brain natriuretic peptide levels of some asymptomatic subjects with increased BMI values. Diminished activation of natriuretic peptides, enhanced protection against endotoxin or inflammatory cytokines, and increased nutritional and metabolic reserve may explain some aspects of reverse epidemiology with obesity and mortality in patients with HF. Still, it is important to

note that although obese patients have lower levels of brain natriuretic peptide than nonobese patients, brain natriuretic peptide levels predict worse symptoms, impaired hemodynamics, and higher mortality in any BMI category, even in obese patients.[222] It has also been proposed that obese patients may simply have less advanced illness, earlier diagnosis, or competing diagnoses with excess symptoms such as fatigue and dyspnea caused part by their excess body weight.

Treatment of Obesity in Patients Without Established HF and Potential Beneficial Effects to Prevent HF

There are multiple beneficial effects of weight reduction in obesity on the cardiovascular system, including decreasing LV mass, decreased arterial pressure, decreased filling pressures of the left and right sides of the heart, and improvement in indexes of diastolic and systolic cardiac function.[218,226] The role of intentional weight loss in obesity as a means of preventing CVD has been the subject of multiple previous studies and reviews[218,219,222,226–229] and is beyond the scope of this document. The recent 2013 AHA/ACC/The Obesity Society "Guideline for the Management of Overweight and Obesity in Adults" underlines the importance of the prevention and treatment of overweight and obesity on risk factors for CVD and type 2 diabetes mellitus, as well as CVD morbidity and mortality, but did not have specific comments on the prevention of HF or treatment of obesity in patients with HF.[6] Given the strong association between obesity and incident HF discussed above, it is plausible that intentional weight loss via dietary intervention, physical activity, approved pharmacotherapy, or surgery may reduce the incidence of HF, although there are no prospective studies of weight loss specifically studying clinical HF as an outcome (Table 8).

Treatment of Obesity in Patients With Established HF

Although obesity is not associated with impaired survival in HF, patients with obesity and HF may wish to lose weight for a variety of reasons, including but not limited to improving their quality of life (QOL), improving other medical conditions such as diabetes mellitus or sleep apnea, or in those with advanced disease, improving their candidacy for aggressive therapies such as heart transplantation or ventricular assist device placement (Table 9). The long-term effect of intentional weight loss in obese patients with HF has not been well studied prospectively. However, a few notable, small, short-term studies of interventions to achieve weight loss, including dietary intervention, physical activity, pharmacotherapy, and surgery, have been performed in populations of obese patients with HF.

Table 8. Recommendation for Obesity in Stage A HF: Asymptomatic Patients at Risk for HF

Recommendation	COR	LOE	Referenced Guideline	References
Obesity should be controlled or avoided to prevent the development of HF along with other CVDs.	I	C	6	

COR indicates Class of Recommendation; CVD cardiovascular disease; HF, heart failure; and LOE, Level of Evidence.

Dietary Intervention

Pilot studies have assessed the safety and feasibility of dietary intervention to achieve weight loss in HF. Evangelista et al[239] randomized 14 symptomatic patients with HFrEF (NYHA class II–III) with type 2 diabetes mellitus and BMI ≥27 kg/m^2 to 12 weeks of a high-protein diet, standard-protein diet, or control. Although patients in both intervention groups achieved weight loss, more weight loss with greater decreases in waist circumference and percentage body fat was seen with the high-protein diet.[226,239] Furthermore, there was a significant improvement in HF symptoms and QOL associated with weight loss. There was, however, no change in cardiac structure or function.[226,239] Recently, Pritchett et al[240] studied 20 obese patients with HFrEF randomized for 3 months to standard therapy (control) versus lifestyle modification, including a portion-controlled diet with meal replacements and an unsupervised walking program. In this study, the intervention group did not have weight loss, and there was no significant difference between the intervention and control groups in terms of metabolic, biomarker, or functional parameters.[227,240] In both studies, the intervention groups had a mean BMI >35 kg/m^2. Neither study reported adverse events, however, suggesting that monitored, healthy dietary intervention programs aiming to achieve weight loss are safe in obese patients with HF. These small studies highlight the need to further investigate the effects of various dietary compositions on body composition, metabolic risk factors, and long-term outcomes in patients with HF.

Physical Activity

The major study of exercise intervention in HF, HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), demonstrated that aerobic exercise training in patients with HFrEF (n=2331) was associated with a nonsignificant trend toward a reduction in mortality or hospitalization and a substantial improvement in health status.[228–230,241] In a subanalysis of HF-ACTION, obese (BMI >30 kg/m^2) patients had a slightly greater degree of weight loss with exercise intervention compared with the control groups, although the changes in weight were minimal, with a median weight change <1 kg. Furthermore, nonsignificant reductions in the composite end

Table 9. Recommendations for the Treatment of Obesity in Stages B and C HF: Patients With Cardiac Structural Abnormalities or Remodeling With or Without HF Symptoms

Recommendations	COR	LOE	Referenced Guideline	References
Purposeful weight loss via healthy dietary intervention and physical activity for the purposes of improving health-related QOL or managing comorbidities such as diabetes mellitus, hypertension, or sleep apnea may be reasonable in obese patients with HF.	IIb	C	6, 8, 29	202, 228, 230–236
Sibutramine and ephedra weight loss preparations may contribute to the development of HF and should be avoided.	III: Harm	C	8	237, 238

COR indicates Class of Recommendation; HF, heart failure; LOE, Level of Evidence; and QOL, quality of life.

point of all-cause mortality/hospitalization across a broad range of BMI categories were seen.[39] Improvement in QOL was also seen in all the BMI ranges. Thus, data from HF-ACTION suggest that physical activity as part of an exercise program is safe in obese patients with HF and may improve QOL, although its effectiveness at inducing weight loss has not been shown (Table 9). The section on the metabolic syndrome gives further information on exercise as part of lifestyle modification.

Medications

Currently, only 3 weight-loss medications are approved by the US Food and Drug Administration for the long-term treatment of overweight and obesity (BMI ≥27 kg/m^2) in the US general population: orlistat, the recently approved lorcaserin,[231,242–244] and the combination pill of phentermine and topiramate.[245] Orlistat, a lipase inhibitor, has been tested in a small population of obese patients with HF.[241,246] Twenty-one patients with HF with a BMI ≥30 kg/m^2 and LVEF <40% were randomized to orlistat plus dietary counseling versus dietary counseling alone. Those randomized to orlistat for 12 weeks had significantly more weight loss (–4.65±9.8 kg) compared with the control group (4.39±7.4 kg; P=0.04). Furthermore, the orlistat group had more improvement in 6-minute walk distance and in NYHA class compared with the control group. The safety of lorcaserin, an agonist of the 5-hydroxytryptamine (serotonin) receptor 2C, in patients with HF is unknown, and the initial US Food and Drug Administration approval includes a provision mandating postmarketing studies to assess for adverse cardiovascular effects. The combination of phentermine and topiramate has been approved for use in adults with a BMI >30 kg/m^2 and at least 1 weight-related condition such as hypertension, type 2 diabetes mellitus, or dyslipidemia, but there are no data on patients with HF. The US Food and Drug Administration's statement also includes a notation that the drug can increase heart rate and should not be used in those with unstable heart disease,[245] and the sponsor is required to perform a long-term postmarketing study of cardiovascular outcomes associated with the drug.

Ephedra, which has been used for the purposes of athletic performance enhancement and weight loss, has been linked to a high rate of serious adverse outcomes, including LV systolic dysfunction, the development of HF,[237] and cardiac deaths, ultimately resulting in ban of this agent by the US Food and Drug Administration. There has also been concern about the use of sibutramine in HF because of reports of the development of cardiomyopathy, and this medication is contraindicated in patients with HF[238] (Table 9).

Bariatric Surgery in HF

Obesity surgery, or bariatric surgery, is recommended for class 2 obesity or above (BMI ≥35 kg/m^2) and possibly in individuals with a BMI of 30 to 34.9 kg/m^2 when associated with comorbid conditions such as diabetes mellitus, sleep apnea, and systemic hypertension, but the safety and efficacy of bariatric surgery in patients with HF have not been ascertained. Bariatric surgery has been shown to improve cardiovascular risk factors, including sustainable weight loss, reversal of diabetes mellitus, improvements in lipid profiles and inflammation, and a reduction in the frequency of apnea in those with OSA.[228,247] In the Utah Obesity Study, a large retrospective cohort of 423 severely obese patients who underwent gastric bypass surgery compared with a control group of 733 severely obese subjects who did not have surgery, gastric bypass surgery was associated with a large reduction in BMI (–15.4 ± 7.2 versus –0.03 ± 4.0 kg/m^2; P<0.0001) and improved LV systolic function, as assessed by fractional midwall shortening, and improved diastolic function, as assessed by E/E' ratio.[230,232] Furthermore, in a long-term follow-up of the SOS study (Swedish Obesity Surgery), patients in the surgery group compared with obese patients without surgery were more likely to have normal diastolic function and improved systolic function as defined by a slightly improved systolic myocardial velocity. In both studies, the LVEFs of the surgery and control groups were normal at baseline and similar at follow-up.[231,248]

Although severe HF or systolic dysfunction is considered a general contraindication to bariatric surgery,[228,249] a few notable studies have investigated its safety and efficacy in obese patients with HF.[232,243,244,250] In a retrospective study of 14 patients with HFrEF who underwent bariatric surgery (10 with laparoscopic Roux-en-Y gastric bypass) and had a

decrease in mean BMI from 50.8 ± 2.04 to 36.8 ± 1.72 kg/m^2, significant improvement in LVEF from 23±2% to 32±4% (P=0.04) was noted at 6 months.[250] Similarly, in another retrospective report, 12 obese patients with HFrEF who underwent bariatric surgery had improvement in LVEF from 21.7±6.5% to 35.0±14.8% (P<0.01).[243] In both of these reports, patients also had improvements in NYHA functional class. Clearly, further prospective studies are needed to better define which patients can be safely referred for bariatric surgery, the optimal surgical techniques, and the effects on long-term outcomes.

QOL and Obesity in Patients With HF

Recent studies have suggested that health-related QOL is lower in obese patients with HF.[230,251] Evangelista et al[251] evaluated the effect of obesity on QOL (measured by the Minnesota Living With Heart Failure Questionnaire) in an ambulatory cohort of 358 patients followed up at an HF clinic. Obesity was associated with decreasing QOL, including both physical health and emotional well-being. In addition, of note, overweight women reported more impaired QOL than men, consistent with other studies that obese women have more impaired health-related QOL than obese men.[252] High body weight is a modifiable risk factor, and proper weight management could potentially improve the low QOL of obese patients with HF.

Our understanding of changes in QOL with exercise in obese and overweight patients with HF was enhanced by a secondary analysis of the HF-ACTION program.[202] HF-ACTION enrolled patients with NYHA class II to IV HFrEF who were able to exercise.[230] At baseline, QOL as measured by the Kansas City Cardiomyopathy Questionnaire was lower in the obese (not overweight) categories. Aerobic exercise training was associated with a significant improvement in QOL across all BMI categories, with a slightly greater degree of improvement in QOL with exercise in the more obese patients (BMI ≥35 kg/m^2).[202] Thus, exercise therapy may be a strategy to improve the QOL of obese patients with HF. Because adherence to exercise programs has been shown to be difficult in patients with HF and home-based exercise programs may be more practical and less expensive to implement, adherence to the programs may need to be monitored with heartrate monitors, exercise diaries, and pedometers.[253,254]

Obesity is even more prevalent in patients with HFpEF. Although no study has specifically examined exercise training and QOL in obese patients with HFpEF, >50% of patients enrolled in studies of exercise training in HFpEF are obese (mean BMI >30 kg/m^2).[255–257] A meta-analysis of 228 individuals with HFpEF enrolled in studies that examined exercise training demonstrated a significantly greater improvement in exercise capacity and QOL in patients in the exercise training arm compared with the control arms with no serious adverse events related to exercise.[258]

Taken together, the above data suggest that exercise therapy may be safe in obese patients with HFrEF and HFpEF and may be associated with improvement in both QOL and exercise capacity.

Sleep Apnea, Obesity, and HF

OSA, obesity, and HF have a complex interaction.[259] In the Sleep Heart Health Study, OSA was detected in 37% of patients with HF, with a higher prevalence of OSA in men than in women.[260] In men, the main risk factor for OSA was obesity, whereas in women, it was older age. Studies have reported a prevalence of OSA of 11% to 26% in patients with HFrEF and 40% to 50% in patients with HFpEF.[261–263] The greater associations of HFpEF with obesity and of hypertension with both OSA and obesity may be factors in the higher prevalence of OSA in this patient population. Although no randomized trials have been performed to evaluate the effect of treatment of OSA on longer-term outcomes of mortality and morbidity in patients with HF, smaller short-term studies have suggested that treatment of OSA with continuous positive airway pressure is associated with an improvement in EF, dyspnea, and QOL in patients with HFrEF[233,234] and in BP, diastolic function, and cardiac remodeling in patients without HF.[235,236,259] Whether weight loss in obese patients with HF will result in improvements in OSA and associated cardiovascular abnormalities and, more important, in longer-term outcomes in patients with OSA and HF (in HFpEF and HFrEF) remains an area for future research.

Recommendations Harmonized With Existing Guidelines

There are no specific recommendations for weight loss in the 2013 ACCF/AHA focused update guidelines on HF,[8] but the guidelines acknowledge that obesity and insulin resistance are important risk factors for the development of HF and that there are no large-scale studies on the safety or efficacy of weight loss with diet, exercise, or bariatric surgery in obese patients with HF. In addition, the writing committee cautions against the use of ephedra, sibutramine, and other weight-loss preparations because they may contribute to the development of HF and should be avoided.[8]

Currently, given the above concerns and the lack of evidence on intentional weight loss in HF, the 2009 AHA scientific statement on promoting self-care in individuals with HF suggests weight loss only if the BMI is >40 kg/m^2.[249] If the BMI is <30 kg/m^2, weight loss is not encouraged.

In the 2010 Heart Failure Society of America guidelines, for both obesity cardiomyopathy and obesity-hypoventilation syndromes, weight loss is recommended to improve symptoms and prognosis. Realizing that there is a paucity of data, the guidelines authors suggest that

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caloric restriction may be reasonable in severely obese patients with the goal of weight stabilization or reduction.[29] The authors also acknowledge that for patients with HF with a BMI >35 kg/m^2, gastrointestinal surgery may be an option. Additionally, in patients with diabetes mellitus, dyslipidemia, or severe obesity, specific dietary instructions are recommended (Level of Evidence B).

Recommendations for the Recognition and Treatment of Obesity in Patients at Risk for or With Established HF

See Tables 8 and 9 for a summary of these recommendations.

Stage A HF

1. **Obesity should be controlled or avoided to prevent the development of HF along with other CVDs *(Class I; Level of Evidence C).***

Stages B and C HF

1. **Purposeful weight loss via healthy dietary intervention or physical activity for the purposes of improving health-related QOL or managing comorbidities such as diabetes mellitus, hypertension, or sleep apnea may be reasonable in obese patients with HF *(Class IIb; Level of Evidence C).***
2. **Sibutramine or ephedra weight loss preparations are contraindicated in HF. Use of ephedra weight-loss preparations may contribute to the development of HF and should be avoided *(Class III: Harm; Level of Evidence C).***

No Data

Weight reduction, including with bariatric surgery or weight-loss drugs such as orlistat, has not been proven to reduce the incidence or severity of HF or mortality in HF.

HYPERLIPIDEMIA AND HF

Hyperlipidemia and Its Paradoxical Association With Clinical Outcomes in HF

In the general population and in patients with atherosclerotic CVD, hypercholesterolemia has consistently been shown to be associated with worse outcomes, including mortality, cardiovascular events, and the development of HF.[264,265] In contrast, in patients with established HF, several analyses have now demonstrated an inverse relationship between cholesterol levels and outcome. That is, low cholesterol levels have been shown to be independently associated with increased mortality and higher cholesterol levels with improved survival. In patients with chronic HF, this inverse relationship has been demonstrated in patients with HF of ischemic and nonischemic origin with a cutoff for total cholesterol at 190 to 200 mg/dL.[266–268] This inverse relationship also held true in a large cohort of patients admitted with acute decompensated HF.[269] It is currently unclear whether low cholesterol levels play a causative role in the worse outcome of patients with HF or whether low cholesterol levels merely reflect an advanced disease state. Moreover, the question of whether there is a difference between intrinsically low cholesterol and low cholesterol as a result of treatment remains unanswered.

Treatment of Hyperlipidemia in HF for the Indication of HF Alone

Numerous retrospective analyses and small, prospective trials have demonstrated the beneficial effects of statins in patients with HF with respect to mortality and worsening HF.[270,271] Furthermore, retrospective analyses of trials in patients with coronary artery disease but without a history of HF demonstrated a reduction in the risk of development of HF and HF hospitalizations in patients taking statins.[272] However, 2 large, prospective, randomized trials failed to confirm these beneficial effects of statins in patients with established HF. CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) randomized 5011 patients (age ≥60 years) with NYHA class II to IV ischemic HF to 10 mg rosuvastatin versus placebo. In this trial, treatment with rosuvastatin did not confer a significant benefit with respect to the primary end point, a composite of death resulting from cardiovascular causes, nonfatal MI, or nonfatal stroke, or several secondary end points, including all-cause mortality, coronary events, and worsening HF, despite a significant decrease in low-density lipoprotein cholesterol and C-reactive protein. Interestingly, rosuvastatin reduced the total number of hospitalizations for cardiovascular causes and hospitalizations for HF, raising the possibility that the drug could have prevented the development of acute coronary disease that would have contributed to such episodes.[273] The second trial, GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure), randomized 4574 patients with NYHA class II to IV chronic HF regardless of pathogenesis to rosuvastatin 10 mg or placebo; 40% of the patients had ischemic cardiomyopathy. The 2 coprimary end points, time to death and time to death or admission to hospital for cardiovascular reasons, were not significantly different between the rosuvastatin- and placebo-treated patients. Similarly, the rates of secondary outcomes, which included cardiovascular death, ischemic end points, and admissions for HF, were not different between the 2 groups.[274] However, similar to CORONA, treatment with rosuvastatin was shown to be safe in patients with HF.

In summary, low cholesterol levels are associated with increased mortality in patients with chronic HF and in those presenting with acute decompensated

Table 10. Recommendations for the Treatment of Hyperlipidemia in Stages A and B HF: Asymptomatic Patients at Risk for HF or With Structural Heart Disease

Recommendations	COR	LOE	Referenced Guideline	References
In patients with a recent or remote history of MI or ACS, statins should be used to prevent cardiovascular events.	I	A		282–285
Lipid disorders should be controlled in accordance with contemporary guidelines.	IIa	B	8	5, 52, 272, 286

ACS indicates acute coronary syndrome; COR, Class of Recommendation; HF, heart failure; LOE, Level of Evidence; and MI, myocardial infarction.

HF of ischemic and nonischemic origin. Despite retrospective analyses and small trials demonstrating beneficial effects of statins in patients with HF, 2 large, well-executed, prospective, randomized trials revealed that statin treatment does not confer significant clinical benefit in patients with HF of either ischemic or nonischemic origin. Thus, the routine use of statins to treat HF of any type is not indicated outside the current practice guidelines for the primary and secondary prevention of atherosclerotic vascular disease.[8,275,276] Similarly, according to the "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults,"[5] statin therapy is not routinely recommended for individuals with NYHA class II to IV HF (Table 10). That said, patients with ischemic cardiomyopathy who are already on statins may be continued on them. Moreover, because of the established effect of statins on lowering the rate of ischemic events and improving survival in patients with ischemic heart disease, statins should strongly be considered in patients with HF presenting with acute ischemic events or with evidence of significant myocardial ischemia (Table 10). In light of the observed inverse relationship between cholesterol levels and mortality in patients with HF, it is unknown whether the cholesterol treatment goals recommended for the general population and patients with atherosclerotic CVD apply to patients with HF and remain to be determined. The 2013 ACC/AHA guideline for the treatment of blood cholesterol makes no recommendations for the initiation or discontinuation of statins in patients with NYHA class II to IV ischemic HFrEF.[5]

Treatment With n-3 Polyunsaturated Fatty Acids in Patients With HF

The use of a different type of lipid therapy, n-3 polyunsaturated fatty acids (PUFAs), has also been investigated in the treatment of HF. Use of PUFA gained interest in HF on the premise that primary and secondary prevention trials in patients with coronary heart disease demonstrated a 10% to 20% relative risk reduction in fatal and nonfatal cardiovascular events with PUFA supplementation.[280] Furthermore, in clinical and preclinical studies, PUFA use has been associated with antiarrhythmic effects, with a beneficial impact on sudden cardiac death.[277,281] Thus, in the GISSI-HF trial, 6975 patients with NYHA class II to IV chronic HF were randomized to therapy with 1 g PUFA daily or placebo.[278] Of note, ≈50% of patients had ischemic cardiomyopathy and <10% had HFpEF. Treatment with PUFA was associated with a significant decrease in the primary end points of time to death and time to death or admission to hospital for cardiovascular reasons.[277–279] The number needed to treat was 56 patients with chronic HF for a median duration of 3.9 years to avoid 1 death

Table 11. Recommendations for the Treatment of Hyperlipidemia in Stage C HF: Patients With Cardiac Structural Abnormalities or Remodeling With Prior or Current Symptoms of HF

Recommendations	COR	LOE	Referenced Guideline	References
PUFA supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II–IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.	IIa	B	8	277–279
Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications, and routine use of statins for the treatment of HF is not indicated outside of current practice guidelines for the primary and secondary prevention of atherosclerotic vascular disease.	III: No benefit	B	5, 8, 275	273, 274, 276

COR indicates Class of Recommendation; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LOE, Level of Evidence; NYHA, New York Heart Association; and PUFA, n-3 polyunsaturated fatty acid.

or 44 to avoid 1 event such as death or admission to hospital for cardiovascular reasons. Although the benefit is statistically modest, it was incremental to background HF therapy. Moreover, use of PUFA was found to be safe in patients with HF. Thus, the use of PUFA is reasonable in patients with HFrEF regardless of type and lipid profile.

Recommendations Harmonized With Existing Guidelines for the Treatment of Hyperlipidemia in Patients at Risk for and With Established HF

See Tables 10 and 11 for a summary of these recommendations.

Stage A HF

1. **Lipid disorders should be controlled in accordance with contemporary guidelines[5,52,272,286] (*Class IIa; Level of Evidence B*).**

Stage B HF

1. **In patients with a recent or remote history of MI or acute coronary syndrome, statins should be used to prevent cardiovascular events[5,282–285] (*Class I; Level of Evidence A*).**

Stages C and D HF

1. **PUFA supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II to IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations[8,277–279] *(Class IIa; Level of Evidence B).***
2. **Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications, and routine use of statins for the treatment of HF is not indicated outside of current practice guidelines for the primary and secondary prevention of atherosclerotic vascular disease[5,8,273–276] *(Class III: No benefit; Level of Evidence A).***

METABOLIC SYNDROME AND HF: CLUSTERING RISK WITH COMORBIDITIES

The Metabolic Syndrome and Incremental Risk in HF

In the earlier sections of this document, the independent roles of hypertension, diabetes mellitus, and obesity in the development of HF and their effect on outcomes in patients with HF are reviewed. In this section, we review whether there is incremental risk when these comorbidities cluster as the metabolic syndrome in patients with HF. The metabolic syndrome constitutes a clustering of risk factors that include elevated glucose, hypertension, central obesity, and dyslipidemias, namely hypertriglyceridemia and low high-density lipoprotein.[287] Although the underlying cause of the syndrome remains poorly understood, insulin resistance and central obesity are thought to play a key role. A variety of organizations have proposed definitions for the metabolic syndrome,[288–291] and there are some caveats in the application of the various definitions of the metabolic syndrome. The risk factors included in the metabolic syndrome are continuous and may impart varying degrees of risk across the spectrum of values. Instead, the definitions have been used in a dichotomous manner with risk assessed as above or below a cut point. In addition, each criterion of the definition is given equal weight toward the diagnosis of the metabolic syndrome. Lastly, unmeasured or related conditions such as chronic inflammation, prothrombotic milieu, polycystic ovary syndrome, nonalcoholic steatohepatitis, cholesterol gallstones, and sleep apnea may be associated with the metabolic syndrome.

Impact of the Metabolic Syndrome on Incident HF

A number of studies have demonstrated that the presence of the metabolic syndrome translates into an increased risk of developing HF. NHANES III (Third National Health and Nutrition Examination Survey; 1988–1994) reported an association between the metabolic syndrome and HF.[292] Participants with the metabolic syndrome were twice as likely to report HF. The prevalence of HF increased with the number of components of the metabolic syndrome. However, when the homeostasis model assessment was included in the multivariate model, the odds ratio of the metabolic syndrome was no longer significant, suggesting that 90.7% of the association between the metabolic syndrome and HF was attributed to insulin resistance. Interestingly, the strength of this association varied among ethnic groups, with the homeostasis model assessment explaining 85.7% of the association in whites, 95.7% in Mexican Americans, and only 32.7% in blacks.

The first prospective study to confirm that the metabolic syndrome is a significant predictor of incident HF comes from the Uppsala Longitudinal Study of Adult Men.[293] A cohort of 2314 men (age, 50 years) without HF, MI, or valvular disease at baseline was followed up for ≈20 years. With the application of a modified version of the ATP III (Adult Treatment Panel III) criteria (BMI >29.4 kg/m^2 was used instead of waist circumference), the risk of incident HF was 5.3 per 1000 person-years for those with the metabolic syndrome versus 1.7 per 1000 person-years for those without the metabolic syndrome. The metabolic syndrome increased the risk of developing HF >3-fold and remained significant after adjustment for established risk factors for HF. The incidence of HF in those with the metabolic syndrome began

diverging from those without the syndrome at ≈10 years of follow-up, suggesting that long-term follow-up may be necessary to truly estimate the impact of the metabolic syndrome.

The increased risk of HF with the metabolic syndrome has consistently been demonstrated in other populations. In assessments of the contribution of the individual metabolic syndrome components to incident HF, the results vary slightly between studies, but overall, obesity, hypertension, and an increased fasting glucose most strongly predicted incident HF. These risk factors had HRs similar to that of the metabolic syndrome as a whole, suggesting that the metabolic syndrome does not predict HF better than its individual components. Wang et al[294] applied the World Health Organization, National Cholesterol Education Program, International Diabetes Federation, and AHA/National Heart, Lung, and Blood Institute definitions to a population of elderly Finns and found that each of them was predictive of incident HF. Both MESA[199] and this study demonstrated that the metabolic syndrome predicts HF independently of MI, suggesting that it is also associated with nonischemic HF.

CHS[295] and MESA[199] also demonstrate the important contribution of other typically unmeasured components of the metabolic syndrome, including inflammation and microalbuminuria (included in the World Health Organization definition), to the development of HF. In CHS, a C-reactive protein level ≥3 mg/L and interleukin-6 level ≥2.21 pg/mL were significant predictors of incident HF and provided additive information when combined with the metabolic syndrome in predicting the development of HF.[294] Moreover, in MESA, C-reactive protein, interleukin-6, fibrinogen, and microalbuminuria levels were significantly associated with incident HF. Although obesity (BMI ≥30 kg/m^2) was also an independent risk factor for the development of HF, its results were attenuated with the addition of interleukin-6 or C-reactive protein to the model, suggesting that the effects of obesity may be partially mediated through inflammatory pathways.[199]

Role of the Metabolic Syndrome in Patients With Established HF

The prevalence and effects of the metabolic syndrome in the established HF population are less well studied. Because the metabolic syndrome is an independent risk factor for the development of HF, it is not surprising that its prevalence in the HF population is higher than in the general adult population. The 2 studies from the United States, 1 study done in a hospitalized HF population (without restriction of EF with modified ATP III using BMI ≥30 kg/m^2)[296] and the other focused on an outpatient population with HFrEF,[297] reported a prevalence of 68.3% and 40%, respectively. The prevalence of the metabolic syndrome in a Japanese HF cohort was 37%, which is more than double the prevalence found in the general Japanese population.[298] Lastly, a small Turkish study of HFrEF reported a prevalence of 51%.[299] These studies uniformly found a higher prevalence of the metabolic syndrome in women than in men. Hispanics had the highest prevalence of the metabolic syndrome (78.8%) followed by whites (69.5%) and blacks (60.9%).[296] In the 2 studies that did not restrict EF, the prevalence of HFpEF was higher in those with the metabolic syndrome.

The effect of the metabolic syndrome on mortality in the HF population has been assessed in 2 studies with discrepant results. Hassan et al[296] reported a lower mortality in patients with HF with compared with those without the metabolic syndrome (43.8% versus 57.6%) in a retrospective cohort of patients (n=625) admitted with HF. There was a nonlinear decrease in mortality with an increasing number of metabolic syndrome criteria: 68.2% in those with no criteria to 37.0% in those with all 5 criteria. Conversely, a prospective cohort of 865 outpatients with HFrEF (EF <40%) demonstrated a mortality of 24% in those with the metabolic syndrome compared with 16% in those without at 2.6 years of follow-up.[297] The Kaplan-Meier curves were similar for up to 4 years of follow-up for both groups and diverged thereafter with higher mortality in the metabolic syndrome group.

As described for obesity, hypertension, and diabetes mellitus, a similar paradoxical effect may exist with respect to the metabolic syndrome: Although obesity, higher BP, and elevated cholesterol are risk factors for the development of HF and mortality in the general adult population, these factors are associated with improved survival in patients with established HF. The metabolic syndrome is associated with higher all-cause and cardiovascular mortality in the general adult population,[300–302] but as suggested by Hassan et al,[296] the metabolic syndrome may exert an inverse association with improved survival in the HF population. Further studies are warranted to confirm and better understand this paradox.

Treatment of the Metabolic Syndrome

Given that overweight and obesity, physical inactivity, and an atherogenic diet contribute to the development of the metabolic syndrome, the institution of lifestyle modification is first-line therapy. Lifestyle modification involves the institution of changes in diet, exercise, and behavior to gradually achieve a modest degree of intentional weight loss.[289,302] In the general population, a realistic weight loss goal is a 7% to 10% reduction in baseline weight over 6 to 12 months. Even if this degree of weight loss does not achieve a normal BMI, it imparts significant metabolic benefits.

In general, the diet should be low in saturated fats, *trans* fats, cholesterol, and simple sugars and incorporate an increased intake of fruits, vegetables, and whole grains.

Exercise is an important factor in initiating and maintaining weight loss. A minimum of 30 minutes of moderate-intensity physical activity is recommended on most days of the week, with further increases in exercise imparting greater benefits. Implementation of the above lifestyle recommendations to achieve a gradual, modest weight loss has significant benefits in the general population. These include a significant reduction in BP, total cholesterol, triglycerides, and fasting glucose. In addition, there is a 58% reduction in the development of diabetes mellitus.[303]

A slightly different dietary approach to the metabolic syndrome may be the implementation of a Mediterranean-style diet. In general, the traditional Mediterranean diet consists of a high intake of monounsaturated fatty acids, primarily from olives and olive oil, and PUFAs, particularly α-linoleic acid from nuts, as well as increased consumption of fruits, vegetables, whole grains, legumes, and fish, along with moderation in alcohol intake and limited red meats (Table 12). Kastorini et al[305] performed a meta-analysis demonstrating that the Mediterranean diet exerts favorable effects on the components of the metabolic syndrome, namely reducing waist circumference, triglycerides, SBP, diastolic BP, glucose, and insulin resistance measured by homeostatic model assessment, and increases high-density lipoprotein levels.

Table 12. Mediterranean Diet Used in the Primary Prevention of Cardiovascular Disease With a Mediterranean Diet Trial

Mediterranean Diet	
Recommended	
Olive oil*	≥4 tbsp/d
Tree nuts and peanuts	≥3 servings/wk
Fresh fruits	≥3 servings/d
Vegetables	≥2 servings/d
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sauce made with tomato and onion, slowly simmered with olive oil	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (socially, with moderation)	5–7 glasses/wk
Discouraged	
Soda drinks	<1 drink/d
Commercial bakery goods, sweets, and pastries	<3 servings/wk
Spread fats	<1 serving/d
Red and processed meats	<1 serving/d

CVD indicates cardiovascular disease.

*The amount of olive oil includes oil used for cooking and salads and oil consumed in meals eaten outside the home. In the group assigned to the Mediterranean diet with extravirgin olive oil, the goal was to consume ≥50 g (≈4 tbsp) per day of the polyphenol-rich olive oil supplied, instead of the ordinary refined variety, which is low in polyphenols.

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LIFESTYLE MODIFICATIONS AND HF

Multifactorial Lifestyle Modification Interventions

Does Multifactorial Lifestyle Modification Prevent HF?

A healthful lifestyle appears to reduce the risk of developing HF. The Physicians Health Study (1982–2008) demonstrated that participants with the healthiest lifestyles had the lowest lifetime risk of developing HF.[306] Six healthy lifestyle factors were assessed: BMI <25 kg/m^2, not smoking, regular exercise ≥5 times/wk, moderate drinking (5–14 times/wk), consumption of breakfast cereal, and consumption of fruits and vegetables (≥4 servings/d). During 22.4 years of follow-up in 20 900 men, 1200 (5.7%) developed HF. A higher number of healthy lifestyle characteristics was associated with a lower risk of developing HF. The lifetime risk for HF in those without any of the above healthy lifestyle factors was 21.2% compared with only 10.1% in those with ≥4 lifestyle factors.

There are limited data to determine whether the implementation of lifestyle modification in at-risk patients can translate into a reduced risk of HF. The Steno-2 study[307] (Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria) reported a reduced risk of CVD in patients with type 2 diabetes mellitus who participated in an intensive, multifactorial intervention that included quarterly clinic visits; a low-fat diet; 30 minutes of exercise 3 to 5 times/wk; prescription of an ACE inhibitor, a multivitamin, and aspirin; and a step-wise approach to pharmacological therapy for diabetes mellitus, hypertension, and hyperlipidemia. After a mean follow-up of 7.8 years, the intensive therapy group experienced a significant risk reduction in a combined end point that included cardiovascular mortality, nonfatal MI, coronary artery bypass surgery, percutaneous coronary intervention, nonfatal stroke, amputation, or vascular surgery for peripheral atherosclerotic disease (HR, 0.47; 95% CI, 0.24–0.73; *P*=0.008). Because the Steno-2 trial used an aggressive lifestyle and pharmacological approach to improving the metabolic risk factors, the study could not assess the contributions of the individual treatment components and specific reduction in HF. In the Look-AHEAD trial (Action in Health in Diabetes), intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes mellitus.[308,309] Participants (n=5145) were randomized to conventional therapy or an intensive lifestyle modification program that included a hypocaloric, low-fat diet; use of

Table 13. Recommendation for Lifestyle Modifications in Stages A and B HF: Asymptomatic Patients at Risk for HF or With Structural Heart Disease

Recommendation	COR	LOE	Referenced Guideline	References
Exercise or regular physical activity is beneficial in prevention of cardiovascular disease and HF.	I	B		193, 311–316

COR indicates Class of Recommendation; HF, heart failure; and LOE, Level of Evidence.

meal replacement products; 175 min/wk of physical activity; and frequent visits with study personnel. Weight loss was greater in the intervention group than in the control group throughout the study (8.6% versus 0.7% at 1 year; 6.0% versus 3.5% at study end). The intensive lifestyle intervention produced greater reductions in glycated hemoglobin and greater initial improvements in fitness and all cardiovascular risk factors except for low-density-lipoprotein cholesterol levels but did not have a significant impact on cardiovascular events[308–310] (Table 13).

Does Multifactorial Lifestyle Modification Improve Outcomes in Patients With Established HF?

There are few data on the application of a lifestyle modification program in the HF population. A small pilot study (n=20) randomized patients with HFrEF (EF <50%) and the metabolic syndrome to a lifestyle modification program modeled after the Look-AHEAD trial.[240] At 3 months, the lifestyle group had not lost significantly more weight than the control group (−0.56±3.7 kg for the control group versus −1.2±4.1 kg for the lifestyle group; *P*=0.71). Thus, there were no significant alterations in metabolic or functional parameters and biomarkers. Importantly, the intervention, which included a hypocaloric diet with meal replacement products and a home walking program, was not associated with adverse events related to weight loss or exercise.

Current approaches for lifestyle modifications for a HF patient include a variety of approaches such as losing or maintaining normal weight, tracking daily fluid intake, avoiding alcohol, avoiding or limiting caffeine, eating a heart-healthy diet, being physically active, exercising, managing stress, keeping track of and monitoring BP, getting adequate rest, developing support, avoiding flu and pneumonia with vaccinations, and implementing other dietary interventions[8] (Table 14). Given their importance in lifestyle modification, in the next sections, we focus on specific dietary interventions and exercise regimen.

Dietary Lifestyle Interventions in HF

Evidence for the effects of dietary patterns among patients with HF is limited. Current dietary recommendations for patients with HF are based largely on data from populations without HF.

Dietary Interventions for the Prevention of HF

The DASH (Dietary Approaches to Stop Hypertension) diet, which includes high intakes of fruits, vegetables, low-fat dairy, and whole grains, resulting in high potassium, magnesium, calcium, and fiber, moderately high protein, and low total and saturated fat, effectively reduces BP. Current data suggest that the DASH diet is effective in preventing HF.[321,322] In a prospective, observational study of 36 019 participants without baseline HF, diabetes mellitus, or MI in Sweden, the DASH diet was associated with lower rates of incident HF.[321] Similarly, in 38 987 participants in a cohort of Swedish men 45 to 79 years of age, the DASH diet was associated with lower rates of HF and HF events.[322]

The Mediterranean diet emphasizes high consumption of olive oil and a high intake of vegetables, fruits, whole grains, legumes, fish, and nuts and limits unhealthy fats. It has been shown to prevent cardiovascular events.[323] The PREDIMED study (Prevención con Dieta Mediterránea), a multicenter, randomized trial to assess the effects of the Mediterranean diet (components listed in Table 12) on the primary prevention of CVD, randomized

Table 14. Recommendations for Lifestyle Modifications in Stage C HF: Patients With Cardiac Structural Abnormalities or Remodeling With Prior or Current Symptoms of HF, Especially With Clustering Risk or Several Comorbidities at the Same Time

Recommendations	COR	LOE	Referenced Guideline	References
Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status.	I	A	8, 29, 317, 318	230, 319, 320
Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms. Otherwise, there are no specific recommendations for caloric intake or dietary composition.	IIa	C	4, 8, 29	

COR indicates Class of Recommendation; HF, heart failure; and LOE, Level of Evidence.

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7447 participants to 1 of 3 groups: the Mediterranean diet with extravirgin olive oil, the Mediterranean diet with 30 g of mixed nuts daily, or a control group with low-fat diet.[304] Participants had either type 2 diabetes mellitus or at least 3 major risk factors of smoking, hypertension, increased low-density lipoprotein cholesterol, low high-density lipoprotein levels, overweight/obesity, or a family history of premature coronary heart disease. After a median follow-up of 4.8 years, there was a significant reduction in the primary end point (a composite of MI, stroke, or death resulting from cardiovascular causes) in both Mediterranean diet groups compared with the control group with a low-fat diet. When the components of the primary end point were assessed individually, there was a significant reduction in the rate of stroke but no significant impact on the risk of MI or mortality (from cardiovascular or all-cause). Although there are no data specifically addressing the impact of the Mediterranean diet on the development of HF or established HF, both Mediterranean diets in the PREDIMED diet resulted in significant decreases in plasma N-terminal pro-brain natriuretic peptide levels, suggesting mitigation against HF risk.[323]

Similarly, the Lyon Diet Heart Study, a small, randomized, secondary prevention trial of the Mediterranean diet performed in patients after first MI (n=423),[324] showed that the Mediterranean diet group had fewer cardiac deaths, nonfatal MIs, or HF development compared with the control group after a mean follow-up of 46 months. Although these data are provocative, the Mediterranean diet has not been widely implemented or incorporated into the metabolic syndrome guidelines and needs to be further studied in the HF population.

Diet in Patients With Established HF

Among Women's Health Initiative participants, higher DASH diet scores were associated with modestly lower mortality rates in women with HF.[325] Similarly, there was a trend toward an inverse association between Mediterranean diet scores and lower mortality rates among women with HF.[325] In a cross-sectional study of 372 consecutive patients with HF, the Mediterranean diet was associated with beneficial effects on biventricular systolic and diastolic function.[326]

These data provide support for the concept that dietary recommendations developed for other cardiovascular conditions or general populations may also be appropriate in patients with HF.

Similarly, in patients with HFpEF with treated hypertension, the sodium-restricted DASH diet has been shown to reduce systemic BP, arterial stiffness, and oxidative stress[327] and to improve diastolic function, arterial elastance, and ventricular-arterial coupling.[328]

Data on the role of the Mediterranean diet in patients with HF are very limited. Among postmenopausal women enrolled in the Women's Health Initiative trial, there was a nonsignificant trend toward an inverse association between Mediterranean diet scores and mortality in women with HF.[325] It should be noted that the major and distinctive components of the Mediterranean diet may not have been captured by the food frequency questionnaire used in this study and may have contributed to these nonsignificant results.[329]

It is also interesting to note that the DASH-type diet is similar to the Mediterranean diet in its components. Both are high in fruits, vegetables, whole grains, and nuts, and especially when reduced in sodium intake, both seem to be a reasonable nutritional model in HF.[329] The above studies related to the DASH and Mediterranean diets provide support for the concept that dietary recommendations developed for other cardiovascular conditions or general populations may also be appropriate in patients with HF.

Experimental studies have demonstrated inconsistent results with a high-protein diet in patients with HF. In some models, a high-protein diet (30% of energy intake) compared with a standard diet with 18% of energy intake from protein failed to affect cardiac mass, LV volumes, LVEF, or myocardial mitochondrial oxidative capacity or did not improve survival.[330] A few early clinical studies, on the other hand, demonstrated that a high-protein diet can result in moderate weight loss and reduced adiposity in overweight and obese patients with HF, and these changes were associated with improvements in functional status, lipid profiles, glycemic control, and QOL.[239] However, these preliminary findings need to be confirmed in studies with more participants and long follow-up.[331]

Exercise Training and Physical Activity as Lifestyle Intervention in HF

Exercise and Physical Activity for the Prevention of HF

Physical activity and physical fitness have been associated with a lower incidence of HF in several population-based studies and large-scale cohorts.[193,311–315] On the other hand, a sedentary lifestyle and physical inactivity have been associated with an increased risk of the development of HF regardless of BMI category, baseline hypertension status, and prevalent coronary heart disease.[314] Although current HF guidelines focus on the role of exercise training (or regular physical activity) in patients with established HF, the beneficial role of physical activity and exercise in cardiovascular health is clear and supported for the prevention of HF[193,311–315] (Table 13).

Exercise Training and Physical Activity in Patients With Established HF

Of the components of lifestyle modification, exercise is the most studied in HF. Exercise training (or regular physical activity) is recommended by guidelines as

safe and effective for patients with HF who are able to participate to improve functional status.[8,29,317] Exercise has been described to exert the following physiological benefits in HF: decreased plasma norepinephrine levels and inflammation; increased heart rate variability, endothelial vasodilatation, coronary blood flow reserve, and anaerobic threshold; and changes in skeletal muscle metabolism.[332] Meta-analyses and a large, randomized, clinical trial have demonstrated the beneficial effects of an exercise program in patients with established HFrEF.[230,241,319,333] The ExTraMATCH (Exercise Training Meta Analysis of Trials in Chronic Heart Failure Patients) meta-analysis of 9 prospective studies (n=801) demonstrated a reduction in overall mortality with exercise that translated into a number needed to treat of 17 to prevent 1 death.[333] As mentioned in the obesity section, the HF-ACTION trial randomized 2331 outpatients with HF (EF <35%) to an exercise program or usual care.[230,241] The exercise regimen consisted of 36 supervised sessions over 3 months followed by home-based training. All-cause mortality and hospitalization were not different between the 2 groups. The Cochrane Database recently published a meta-analysis of 19 trials (including the above-mentioned HF-ACTION trial; total n=3647) that assessed the effects of exercise training in HFrEF.[319] Exercise interventions reduced HF hospitalizations (relative risk, 0.72; 95% CI, 0.52–0.99) and improved QOL but did not affect all-cause mortality. Interestingly, when HF-ACTION was excluded, mortality was improved with exercise (relative risk, 0.91; 95% CI, 0.39–0.98; Table 14).

Types of Exercise Training Recommended in HF

Aerobic exercise training regimens in HF have varied among studies from a low level to a more moderate intensity. Interval training at various intensities (50%, 70%, and 80% of maximal capacity) has shown to be beneficial, but training intensity does not seem to directly influence the magnitude of the increase in exercise tolerance.[334] The exercise training regimen varied from general exercise to isolated muscle training involving major muscle groups; the setting has varied from supervision to home training; the modality has also been variable, more commonly treadmill or bicycle ergometry; and the length of training program has been as short as several weeks to as long as a year.[335] Therefore, agreement on a universal exercise prescription for HF population does not exist, and an individualized approach with guidance of the AHA exercise standards for testing and training statement is recommended.[335,336] Gas exchange measurements can offer an objective assessment of functional capacity and can be used when feasible to derive the exercise prescription and to monitor changes in functional status.[335,337] The most frequently used exercise intensity range is 70% to 80% of peak $\dot{V}O_2$, usually determined from a symptom-limited exercise test.[335] Common exercise regimens include jogging, calisthenics, walking, use of a treadmill, rowing, use of an arm ergometer, step aerobics, or cycling at 60% to 80% of $\dot{V}O_2$max or maximum work capacity for 30 to 40 minutes 3 to 4 times/wk.[335] Very debilitated patients or those who are not accustomed to aerobic activity may need to initiate the program at a lower intensity (60% or 65% of peak $\dot{V}O_2$) and perform interval training with periods of rest.[335] The most commonly used exercise duration is 20 to 30 minutes at the desired intensity.[335] Progression should be built into the prescription to adjust the exercise intensity as the patient becomes better conditioned. Duration of exercise should include an adequate warm-up period, with this period being longer in the most debilitated patients. Most studies have used 3 to 5 times/wk as the optimal training frequency.[335] The need for monitoring has not been systematically studied, but telemetry monitoring is recommended initially.[337] Home training can follow this early supervised period for patients not demonstrating any hemodynamic or rhythm instability. It would be prudent, however, to monitor patients who have demonstrated exercise-induced arrhythmias and those patients with advanced HF.[335]

Although the safety and efficacy of resistance training have not been established in this population,[335] resistance training can offer the opportunity to strengthen individual muscle groups and has been shown to be effective without safety issues in small trials with patients with HF.[338,339] Small free weights (1, 2, or 5 lb), elastic bands, or repetitive isolated muscle training can be used,[340] but the safety of resistance training in patients with HF needs to be further established in larger trials.[335]

Recommendations Harmonized With Existing Guidelines

See Tables 13 and 14 for a summary of these recommendations.

Dietary Guidelines in Patients With HF

Typical dietary guidelines for the HF population state that sodium restriction or fluid restriction in patients with severe HF with congestion and with hyponatremia is reasonable.[8] Otherwise, there are no specific recommendations for caloric intake or dietary composition included in the current AHA/ACCF, Heart Failure Society of America, or European Society of Cardiology HF guidelines[8,29,317] other than nutritional supplements not being recommended as treatment of HF in patients with current or prior symptoms of HFrEF.[8]

Guideline Recommendations for Exercise

With the above background, the Heart Failure Society of America, European Society of Cardiology, ACC, and AHA recommend exercise training or regular physical activity in patients with HF,[8,29,249,317,318] but these guidelines have

not addressed the beneficial role of exercise in prevention of HF, which we tried to address by adding a recommendation stating the beneficial role of exercise or physical activity for patients with stage A or B HF.

In the Heart Failure Society of America guidelines, it is recommended that patients with HF undergo exercise testing before enrollment in an exercise training program to determine suitability for exercise training and to assess for ischemia or arrhythmias. If deemed safe, exercise training should be considered for patients with HF. Initially, exercise should be supervised to educate the patient on heart rate response and level of exercise and to gradually increase exercise duration and intensity. The exercise goal is 30 minutes of moderate activity 5 d/wk with warm-up and cool-down periods (Strength of Evidence B).[29]

In the European Society of Cardiology guidelines, it is recommended that regular aerobic exercise be encouraged to improve functional capacity and symptoms.[317]

The 2013 ACCF/AHA HF guidelines indicate that exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status[8,230,319,320] (Level of Evidence A).

Stage A or B HF

1. **Exercise or regular physical activity is beneficial in prevention of CVD and HF *(Class I; Level of Evidence B)*.[193,311–316]**

Stage C HF

1. **Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status[8,230,319,320] *(Class I; Level of Evidence A).***

SUMMARY AND FUTURE DIRECTIONS

As addressed in the earlier sections, lifestyle modification and the management of comorbidities remain challenging in patients with HF. Despite intensive lifestyle and medical interventions, the prevention and optimal treatment of hypertension, diabetes mellitus, obesity, and metabolic syndrome have often proved difficult in patients with HF.

- These comorbidities are highly prevalent and are associated with the development of incident HF in the general population.
- However, in patients with established HF, their contributory roles to clinical outcomes are paradoxical; that is, patients with HF with diabetes mellitus, obesity, and hypertension usually are associated with better outcomes than patients without those comorbidities individually, making their management targets and treatment reasons quite challenging.
- Participants in clinical trials receive maximally supportive and evidence-based interventions, yet adherence to standard guideline-directed HF therapy in real-world patients may be limited by the coexistence of chronic HF and comorbid conditions.
- Self-care strategies are limited by HF itself and these competing comorbidities and usually require coordination and different care models.[249,341]
- Treatment options of these chronic comorbidities in HF are limited and usually without large-scale or definitive clinical trial evidence of improved outcomes in patients with HF.
- Treatment of these comorbidities may be associated with adverse outcomes resulting from overtreatment or side effects of treatment modalities.
- It should be kept in mind that even modest changes in the prevention of comorbidities and risk factors for HF can greatly affect the development of and outcomes in HF.
- These underline the importance of prevention strategies, which probably are the most effective approaches to reduce the burden of HF.
- Furthermore, in recent years, focus has moved from control of a single risk factor to reducing overall cardiovascular risk.[342] Greater benefit may be realized by combining a healthy lifestyle with BP lowering; prevention of diabetes mellitus, insulin resistance, obesity, and ischemic events; and avoidance of cardiotoxic exposure (alcohol, cardiotoxic drugs, and chemotherapy) rather than any single approach alone.[343] Although this approach is likely to be valid, it requires evaluation in well-designed trials.
- New innovative initiatives such as the Life's Simple 7 developed by the AHA emphasize the prevention of CVD and aim to empower individuals on self-care and prevention by concise yet thorough explanation of the AHA's recommendations for healthy living, including guidance on how (1) to get active, (2) to control cholesterol, (3) to eat better, (4) to manage BP, (5) to lose weight, (6) to reduce blood sugar, and (7) to stop smoking.[344] The emphasis on prevention is one of the most effective strategies for the 2020 goal of the AHA, defined as "to improve the cardiovascular health of all Americans by 20 percent while reducing deaths from CVDs and stroke by 20 percent by the year 2020."[345] Such initiatives with emphasis on prevention are critical in reducing the burden of HF.

FOOTNOTES

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete

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Biykem Bozkurt	Baylor College of Medicine	None	None	None	None	None	None	None
David Aguilar	Baylor College of Medicine	National Heart, Lung, Blood Institute*	None	None	None	None	Bristol Myers Squibb*	
Anita Deswal	Michael E. DeBakey VA Medical Center/Baylor College of Medicine	NIH†	None	AHA Heart Failure Spotlight Series*; Aurora Health Care Inc.*	None	None	None	None
Sandra B. Dunbar	Emory University	None	None	None	None	None	None	None
Gary S. Francis	University of Minnesota	NIH*	None	None	None	None	Novartis*; Amgen*	None
Tamara Horwich	UCLA	None	None	None	None	None	None	None
Mariell Jessup	University of Pennsylvania	None	None	None	None	None	None	None
Mikhail Kosiborod	Mid America Heart Institute	Gilead†; Genentech†; Sanofi Aventis†; AstraZeneca†	None	Amgen*	None	None	AstraZeneca†; Eli Lilly*; Boehringer Ingelheim†; ZS Pharma†; Sanofi-Aventis†; Amgen†; GSK*; Merck*; Novo Nordisk*	Gilead (other research support)†
Allison M. Pritchett	Baylor College of Medicine	None	None	None	None	St. Jude*	None	None
Kumudha Ramasubbu	New York Methodist Hospital	None	None	None	None	None	None	None

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Clive Rosendorff	James J. Peters VA Medical Center	None	None	None	None	None	None	None
Clyde Yancy	Northwestern University	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Maya Guglin	University of South Florida	None	None	None	None	None	None	None
Douglas Mann	Washington University School of Medicine	None	None	None	None	None	None	None
Lynne Stevenson	Brigham and Women's Hospital	None	None	None	None	None	None	None
W.H. Wilson Tang	Cleveland Clinic Foundation	NIH*	None	None	None	None	None	None

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*Significant.

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