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Stage A: Can Heart Failure Be Prevented?

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Abstract: Heart failure (HF) is an epidemic associated with significant morbidity and mortality, affecting over 5 million people in the United States and 1-2% of the population worldwide. Observational studies have suggested that a healthy lifestyle can reduce HF risk. Although no clinical trials have targeted the prevention of HF as a primary endpoint, many have evaluated outcomes associated with the development of symptomatic disease (i.e., progression to HF, HF hospitalization or death) as secondary endpoints. Blood pressure treatment represents the most effective strategy in preventing heart failure; each 5 mm Hg decrease in systolic blood pressures reduces the risk of HF development by 24%. Thiazide diuretics appear to be the most efficacious agents in patients with hypertension. Angiotensin converting enzyme inhibitors and angiotensin-II receptor blockers are first line agents for patients with chronic atherosclerosis, diabetes, or chronic kidney disease. Beta blockers appear less effective as single agents and cardioselective agents are preferred. Calcium channel blockers, specifically non-dihydropyridines, should be avoided and alpha blockers should not be used to reduce HF risk.

Keywords: ACE inhibitors, diet, diuretics, heart failure, hypertension, lifestyle, prevention, stage A.

INTRODUCTION

Heart failure (HF) is an epidemic affecting approximately 1-2% of the population worldwide and 5.1 million people in the United States (US) [1, 2]. It is projected that by 2030 the prevalence of this condition will increase by 25% [2]. The lifetime risk of developing HF is 1 in 5 at 40 years of age for both men and women in the US [1]. Aggressive treatment of patients at high risk for developing HF is therefore critical. In 2001, the AHA/ACC HF Guideline introduced the concept of HF stages and provided goals of therapy [3]. Table **1** outlines the characteristics and treatment of patients with stage A, individuals considered at high risk for the development of HF. Although no clinical trials have targeted the HF prevention as a primary endpoint, many have evaluated outcomes associated with the development of symptomatic disease (i.e., progression to HF, HF hospitalization or death) as secondary endpoints. This article updates two reviews on primary prevention of HF [4, 5], discusses modifiable risk factors, highlights pivotal trials, and reviews recent meta-analyses targeting the pharmacologic management of stage A patients.

MODIFIABLE LIFESTYLE RISK FACTORS

The association between six modifiable risk factors and incidence of new HF was studied in a prospective cohort of 20,900 men in the Physician's Health Study [6]. Overall, lifetime risk of HF was 13.8% (95% CI, 12.9–14.7%) at age 40 years and remained constant through age 70 years. Factors individually associated with a lower lifetime risk of HF included body mass index < 25 kg/m^2, never smoking, regular exercise at least five times per week, moderate alcohol intake with at least five drinks per week, consumption of breakfast cereal at least one serving per week, and fruits and vegetables at least four servings per day. There was an inverse and graded relationship between the number of healthy lifestyle factors and lifetime risk of HF. The lifetime risk for HF was approximately one in five among men adhering to none of the desirable lifestyle factors, compared to one in 10 among those adhering to four or more healthy lifestyle factors. An additional analysis of this cohort demonstrated a positive and graded association between red meat consumption and incidence of HF [7].

A prospective observational study of 36,019 women in the Swedish Mammography Cohort investigated the relationship of the dietary approaches to stop hypertension (DASH) diet to the incidence of HF [8]. The DASH diet features high intake of fruits, vegetables, low-fat dairy products, and whole grains, resulting in high potassium, magnesium, calcium, fiber, moderately high protein, and low total and saturated fat consumption. During seven years of follow up, 443 women (1.2%) developed HF. There was a graded relationship between event rate and quartile; women in the top quartile (most adherent to the DASH diet) had a 37% lower rate of HF events compared with the bottom quartile (least adherent).

These studies demonstrate a significant and graded relationship between the incidence of HF events and modifiable lifestyle factors.

HIGH-RISK PATIENTS

Several trials have studied the impact of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin-II receptor blockers (ARB) on major adverse cardiovascular events

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Table 1. Stage A Heart Failure.

Patients at Risk for Heart Failure	Therapies for Stage A Heart Failure Patients
Hypertension Diabetes mellitus Atherosclerotic disease Obesity Metabolic syndrome History of use of cardiotoxins Family history of cardiomyopathy	Goals Healthy lifestyle Prevent CAD, vascular disease Prevent cardiac structural abnormalities Therapies ACE-I/ARB: atherosclerosis diabetes hypertension with associated CV risk factors Thiazide diuretics in hypertension Statins in appropriate patients

ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CAD: coronary artery disease; CV: cardiovascular.

including HF. In the Heart Outcomes Prevention Evaluation Study (HOPE), development of HF was reduced by 23% among high-risk patients ≥ 55 years receiving ramipril versus placebo (risk ratio (RR) 0.77, p<0.001) [9]. High risk was defined as patients with coronary artery disease (CAD), peripheral vascular disease, history of stroke, or diabetes with one other cardiovascular risk factor (i.e., hypertension, elevated total cholesterol, low high density cholesterol, cigarette smoking, or microalbuminuria).

In the European Trial on Reduction Of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease (EUROPA) [10], heart failure hospitalization was reduced by 39% (p=0.002) in patients with CAD but without HF who were randomized to perindopril. Heart failure hospitalization or death was significantly reduced in patients 50 years or older with stable CAD and left ventricular ejection fraction >40% randomized to trandolapril (hazard ratio (HR) 0.75, p=0.02) in the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial [11]. Furthermore, perindopril ± indapamide reduced the risk of HF by 26% (p=0.02) compared to placebo in patients with a history of stroke or transient ischemic attack in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial [12].

Three trials have not demonstrated a superior benefit with ARB therapy. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) randomized patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage to telmisartan, ramipril, or both [13]. After a median follow-up of 4.7 years, the three treatment arms were found to be equivalent in terms of the primary composite outcome of cardiovascular death, myocardial infarction (MI), stroke, or hospitalization for HF. However, there were more adverse events with the combination of ACE-I and ARB including renal impairment, symptomatic hypotension, and hyperkalemia. In contrast, telmisartan compared to placebo did not significantly reduce the same primary endpoint or secondary endpoints in the Telmisartan Randomised Assessment Study in ACE Intolerant subjects (TRANSCEND) trial [14]. Additionally, in contrast to PROGRESS, no clinical benefit of ARB therapy was demonstrated in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial which randomized patients with history of recent ischemic stroke to telmisartan or placebo [15]. Possible explanations include greater blood pressure reduction with perindopril compared to telmisartan and the nearly 37% utilization of ACE-Is in the placebo arm of PRoFESS.

Based on these studies, ACE-I should remain the medication class of choice for high risk patients with atherosclerosis, with ARBs reserved for ACE-I intolerant individuals. The combination of ACE-I and ARB therapy is not recommended.

TREATMENT OF HYPERTENSION

An estimated 33% of US adults ≥ 20 years of age have hypertension [2]. Among hypertensive adults, approximately 78% are aware of their condition and 68% are using antihypertensive medication, but only 64% are controlled to target levels. Treatment of hypertension is the most effective strategy for preventing HF, as each 5 mm Hg reduction in systolic blood pressure (SBP) reduces overall risk of HF by 24% [16].

Multiple trials have demonstrated improved cardiovascular outcomes, including HF, associated with blood pressure reduction. The Systolic Hypertension in the Elderly Program (SHEP) randomized patients with isolated systolic hypertension to chlorthalidone or placebo [17]. After 4.5 years, SBP in the treatment arm decreased to 144/67.7 mm Hg versus 155.1/71.1 mm Hg in the placebo group. The incidence of total stroke was reduced by 36% (p=0.003) and HF was reduced by 54% in the treatment arm (95% confidence interval (CI) 0.33-0.65). SHEP represented the first trial to demonstrate a significant improvement in cardiovascular outcomes associated with the treatment of isolated systolic hypertension.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) randomized 42,418 patients ≥ 55 years with hypertension and at least one additional cardiovascular risk factor to chlorthalidone, amlodipine, lisinopril, or doxazosin [18-21]. The doxazosin arm was terminated early after a 20% increase in risk of combined cardiovascular events and 80% increase in risk of HF was observed during interim analysis. No significant dif-

ference was observed for the primary endpoint of fatal coronary heart disease or non-fatal MI among the other groups. In a validation study of all hospitalized HF events, chlorthalidone was superior in reducing the risk of HF with reduced ejection fraction compared to amlodipine (HR 0.74, p=0.013) but was similar to lisinopril (HR 1.07, p=0.596) [20]. Chlorthalidone significantly reduced the risk of HF with preserved ejection fraction compared to amlodipine (HR 0.69, p=0.009) and lisinopril (HR 0.74, p=0.032). In a post-trial follow-up of ALLHAT, hypertensive patients were stratified by baseline estimated glomerular filtration rate (eGFR, measured in mL/min/1.73 m^2) [21]. Chlorthalidone was superior to amlodipine in preventing HF in the overall population (HR 1.12, 95% CI 1.02-1.22), but no difference was identified between chlorthalidone and lisinopril. Based on the results of ALLHAT, calcium channel blockers (CCB) should not be preferred for treatment of hypertension in patients at high risk for developing HF, and alpha blockers should be avoided for this indication in high-risk individuals.

In addition to the pivotal SHEP trial, the importance of treating hypertension in the elderly was addressed in the Hypertension in the Very Elderly Trial (HYVET), which randomized 3,845 patients over the age of 80 years with SBP between 160 and 199 mm Hg and diastolic blood pressure less than 110 mm Hg to indapamide (with the addition of perindopril if needed to achieve a goal blood pressure of less than 150/80 mm Hg) or placebo [22]. After 2.1 years, blood pressure in the treatment group was lower by 15/6.1 mm Hg compared to placebo with approximately 73% of patients receiving indapamide and perindopril. The incidence of fatal and non-fatal HF was reduced by 64% (HR 0.36, p<0.001) and all-cause mortality was decreased by 21% (p=0.02) in the treatment arm. Separation in the cumulative event rates for development of HF became evident within the first year and remained separate throughout the duration of the study.

META-ANALYSES

Since 2008, seven meta-analyses have evaluated various classes of anti-hypertensive medications on cardiovascular outcomes including HF.

The first meta-analysis by Bangalore *et al*. [23] evaluated the impact of beta blocker therapy on development of HF in hypertensive patients with or without cardiovascular disease across 12 trials. In placebo-controlled trials, beta blockers were associated with a nonsignificant 23% reduction in HF (p=0.055). In drug comparator-controlled trials, no difference was observed between beta blockers and other anti-hypertensive medications. However, beta blockers were associated with an increased the risk of stroke, 19%, when compared with other anti-hypertensive agents, particularly in patients ≥ 60 years old (RR 1.19, p<0.0001).

In a meta-analysis by Law *et al*. [24], the risk of HF development was analyzed across 64 blood pressure difference trials and 31 comparator-treatment studies. Cardioselective beta blockers significantly decreased the risk of HF by 23%, whereas non-cardioselective or vasodilating beta blockers did not prevent HF. In placebo-controlled trials, CCBs decreased the incidence of HF by 19%. However, CCBs increased the risk of HF by 22% compared to other agents. Overall, drugs other than calcium channel blockers and non-selective beta blockers were associated with a 24% reduction in HF.

A meta-analysis by Costanza *et al*. [25] specifically investigated the impact of CCBs on long-term outcomes in patients with hypertension or CAD across 27 trials. All-cause mortality was reduced with CCBs (odds ratio (OR) 0.96, 95% CI 0.93-0.99); however, the benefit was only observed with dihydropyridine CCBs (i.e., amlodipine, felodipine, nifedipine) but not with non-dihydropyridines (i.e., diltiazem and verapamil). Whereas CCBs decreased the risk of HF by 28% compared to placebo more benefit was derived from ACE-Is (OR 1.19, 95% CI 1.08-1.31) and beta blockers/diuretics (OR 1.26, 95% CI 1.16-1.36) compared to CCBs. These findings are consistent with previous meta-analyses and illustrate a potential difference between dihyropyridine and non-dihydropyridine CCBs. The negative inotropic properties combined with an increased neuroendocrine response to non-dihydropyridine CCBs may be potential mechanisms which increase the risk of heart failure with reduced ejection fraction (HFrEF). Similar effects have not been observed with amlodipine and felodipine, which are not associated with increased mortality among patients with HFrEF.

A meta-analysis by Verdecchia *et al*. [16] evaluated the influence of renin-angiotensin system (RAS) antagonists on prevention of HF in patients with hypertension or high cardiovascular risk but without HF. A total 31 trials were analyzed. In placebo-controlled trials, ACE-Is were associated with a 21% reduction in HF, whereas no significant effect was observed for ARBs or CCBs. In comparator-controlled trials, ACE-Is were not different from beta blockers/diuretics, while CCBs increased risk of HF by 18% compared to beta blockers/diuretics. Each 5 mm Hg reduction in SBP decreased risk of HF by 24% (p<0.001). A meta-regression analysis demonstrated that independent of a blood pressure differences, ACE-I/ARB therapy decreased the risk of HF by 19% compared to CCBs (P<0.001) and 16% in studies of patients without multiple cardiovascular risk factors (p<0.001).

In contrast to the previous meta-analysis, which grouped beta blockers and diuretics together, a meta-analysis by Sciarretta *et al*. [26] compared individual classes in patients with hypertension or high cardiovascular risk. Diuretics were found to be more effective than all other classes of anti-hypertensive medications in preventing HF, followed by ACE-Is and ARBs. Beta blockers were less effective compared to diuretics and CCBs were less effective compared to diuretics and RAS antagonists.

A meta-analysis by Roush *et al*. [27], based on nine trials, compared hydrochlorothiazide (HCTZ) and chlorthalidone on mortality or at least one cardiovascular event. Each of the included trials required HCTZ or chlorthalidone to be the sole step one drug. In a drug-adjusted network meta-analysis, chlorthalidone reduced the incidence of HF by 23% and cardiovascular events by 21% compared to HCTZ. In addition, an 18% reduction in cardiovascular events was observed with chlorthalidone for any given difference in mean achieved office systolic blood pressure compared to HCTZ.

The meta-analysis by Fretheim *et al*. [28] examined a healthier population, excluding most trials where more than half of participants had a history of MI, stroke or other significant cardiovascular event as well as studies performed in select subgroups of patients with hypertension (e.g., individuals with diabetes or microalbuminuria). Overall, mixed results were observed with no one drug class being superior to another across clinical outcomes. However, diuretics were superior in preventing HF compared to beta blockers (RR 0.73, 95% credibility interval (CrI) 0.54-0.96), CCBs (RR 0.83, 95% CrI 0.62-0.84), and alpha blockers (RR 0.51, 95% CrI 0.40-0.64), but had a higher incidence of diabetes compared to ACE-Is (RR 1.43, 95% CrI 1.12-1.83) and CCBs (RR 1.27, 95% CrI 1.05-1.57). ACE-Is were superior to CCBs (RR 0.82, 95% CrI 0.69-0.94) in HF prevention.

These meta-analyses confirm the importance of blood pressure control overall, as well as advantages of ACE-Is and ARBs that are independent of blood pressure lowering effects. Thaizide diuretics, particularly chlorthalidone, should be considered first line agents to prevent HF in patients with hypertension followed by ACE-Is and ARBs. Beta blockers are less effective, especially non-cardioselective agents. CCBs are not recommended in hypertensive patients if other classes of anti-hypertensive drugs remain options. If used, dihydropyridine CCBs (i.e., amlodipine, felodipine) are preferred. Table **2** outlines recommendations for stage A patients.

DIABETES MELLITUS

No studies have shown that tight glucose control prevents HF. In fact, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study found that intensive glucose control (glycated hemoglobin level [HbA_{1c}] < 6%) compared with standard therapy (HbA_{1c} 7-7.9%) increased mortality and did not significantly reduce major cardiovascular events, including HF [29].

Several trials have investigated the effect of BP control in diabetics. The UK Prospective Diabetes Study Group (UKPDS) trial randomized hypertensive patients with newly diagnosed diabetes to "tight blood" pressure control (goal <150/85 mm Hg) or less tight blood pressure control (goal < 180/105 mm Hg) [30]. Patients allocated to the tight blood pressure control arm received either captopril or atenolol. After 8.4 years, the incidence of HF was reduced by 56% in the tight control arm (p=0.0043). In the ACCORD trial, lowering blood pressure below currently recommended levels (SBP < 120 mm Hg) did not reduce the primary outcome of cardiovascular death, MI, or stroke or the secondary outcome of prevention of HF [31].

These studies indicate that while the optimal blood pressure goal in patients with diabetes remains unknown, a goal of less than 140/80 mm Hg appears reasonable in most patients.

DIABETES AND RENAL DISEASE

Two trials have reported the influence of ARBs on the risk of HF in patients with diabetes and nephropathy. In the Reduction of Endpoints in NIDDM with the Angiotensin II antagonist Losartan (RENAAL) study, losartan compared to placebo, reduced first hospitalization for HF by 32% in patients with type II diabetes and macroalbuminuria [32]. The benefit of losartan exceeded its expected antihypertensive effect. Additionally, losartan reduced the incidence of end stage renal disease by 28% (p=0.002) and doubling of serum creatinine by 25% (p=0.006).

Similar results were observed in the Irbesartan Diabetic Nephropathy Trial (IDNT), where irbesartan reduced HF hospitalization by 23% compared to placebo in patients with hypertension, diabetes, and proteinuria [33]. The risk of doubling in serum creatinine concentration was 33% lower in the irbesartan group compared to placebo (p=0.003) and 37% lower compared to amlodipine (p<0.001).

These findings extend the evidence of benefit with RAS antagonists, specifically ARBs, to patients with diabetes and chronic kidney disease, illustrating that their benefits are often independent of blood pressure effects.

STATINS

A recent Cochrane review analyzed 18 randomized controlled trials of statins versus placebo or usual care control in 56,934 adults of whom 10% or less had a history of cardiovascular disease [34]. Fourteen trials recruited patients with specific conditions (hyperlipidemia, diabetes, hypertension, microalbuminuria). Included studies had minimum treatment duration of one year and follow-up of six months. Statins reduced all-cause mortality by 24%, combined fatal and non-fatal cardiovascular disease by 25%, stroke by 22%, and revascularization by

Table 2. Choice of Medications for Stage A Heart Failure[1].

Most Effective	Less Effective	Not Preferred	Do Not Use
Thiazide Diuretic*	Beta blocker‡	Calcium channel blocker†	Alpha blocker
ACE-I			
Angiotensin Receptor Blocker¶			

[1]Concomitant disease states and conditions (e.g., atherosclerotic disease, diabetes, chronic kidney disease) should guide drug therapy selection
*Especially chlorthalidone
¶Use if ACE-inhibitor intolerant
‡Cardioselective beta blockers are preferred
†If calcium channel blockers are utilized, dihydropyridines (e.g., amlodipine, felodipine) are preferred
ACE-I: angiotensin converting enzyme inhibitor

38%. There was no evidence of any serious harm of statins reported. The Treating to New Targets (TNT) trial randomized patients 35 to 75 years of age with stable CAD (58% with previous myocardial infarction) and LDL concentration of < 130 mg/dL to atorvastatin 10 mg or 80 mg daily [35]. After a median follow-up of 4.9 years, a 22% reduction in the first occurrence of a major cardiovascular event was observed in the high-dose arm (HR 0.78, p<0.001) including a 26% decrease in hospitalization for HF (HR 0.76, p=0.01). Based on this data, appropriate stage A patients should receive statin therapy.

ADHERENCE

The impact of adherence to anti-hypertensive medications on the development of HF was evaluated in a cohort of 82,320 Canadian patients without cardiovascular disease who were 45 to 85 years of age with newly treated hypertension [36]. After a mean follow-up of 2.7 years, the development of HF was reduced by 11% in patients with high adherence (defined as ≥ 80%; mean 95%) compared with low adherence (defined as < 80%; mean 60%) to anti-hypertensive therapy (RR 0.89, CI 0.9-0.99). When the endpoint was further expanded to include HF and death, the risk reduction increased to 20% (RR 0.8, CI 0.73-0.86). The improvement in these clinical endpoints became evident after one year of being on anti-hypertensive therapy. The broad diversity of patients included in this study increase the generalizability of these findings to contemporary clinical practice.

The impact of adherence to statins was investigated in a cohort of 111,481 Canadian patients without cardiovascular disease who initiated treatment [37]. High adherence was associated with a 19% reduction (95% CI 0.71-0.91) in the development of HF compared to low adherence. Similar to anti-hypertensive treatment, the benefit of adherence to statins became evident after one year of therapy.

CONCLUSION

Living a healthy lifestyle and treating hypertension are the best strategies for reducing HF risk in stage A patients. Overall, thiazide diuretics represent the drug class of choice in patients with hypertension, while ACE-Is and ARBs are first line agents for patients with atherosclerotic disease, diabetes, and diabetes plus chronic kidney disease. Beta blockers are less effective and cardioselective agents are preferred. Calcium channel blockers, specifically non-dihydropyridines (i.e., diltiazem, verapamil), should not be used to decrease HF risk if alternatives are available, and alpha blockers should be avoided altogether. Medication adherence is critical in reducing the risk of HF.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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