DIASTOLIC HEART FAILURE CLINICAL TRIALS

Karla M. Kurrelmeyer, M.D.

From Methodist DeBakey Heart & Vascular Center, Houston, Texas

INTRODUCTION

Congestive heart failure (CHF) affects nearly five million Americans, and more than 550,000 new cases are diagnosed each year.1 The leading cause for hospitalization in those over 65 years of age, CHF accounts for more than 800,000 hospital visits each year and carries a 20-30% risk of death in the year following the first visit.1 CHF may occur in the setting of either reduced ejection fraction (LVEF), systolic heart failure (SHF) or normal LVEF, diastolic heart failure (DHF). Although DHF is also known as heart failure with preserved or normal LVEF, for the purposes of this review it will simply be referred to as DHF.

Community based epidemiology studies have demonstrated that more than 50% of people living with CHF have DHF.2,3 The Cardiovascular Health Study demonstrated that DHF is even more prevalent in individuals over 65 years of age. In this study, 69% of men and 90% of women with CHF had DHF defined as current heart failure symptoms and EF greater than 45%.4 In fact, the prevalence of DHF has been increasing since 1986 and is attributed to a combination of factors, including an increase in the elderly population, increased awareness of the condition, increased detection due to the development of non-invasive echocardiography diagnostic techniques, and improvements in the treatment of coronary artery disease and other cardiovascular diseases that has resulted in preservation of LVEF.

DHF MULTICENTER, RANDOMIZED CONTROLLED TRIALS

Very few multicenter, randomized controlled trials have been completed to date. Most of the drugs that have been or are currently being studied are those that have been found to be useful in SHF. These drugs were targeted first since they have been shown to reverse some of the underlying pathophysiologic mechanisms of impaired diastology. The specific mechanisms that are targeted by these drugs include reduction in afterload, calcium homeostasis, reduction in the extracellular matrix/fibrosis, and blockade of neurohormonal activation (i.e., renin-angiotensin-aldosterone system, sympathetic nervous system, endothelin, nitric oxide, natriuretic peptides).

Digitalis Ancillary Trial. The first completed multicenter, randomized, placebo-controlled trial for diastolic heart failure was the Digitalis Investigation Group (DIG) ancillary trial **that** investigated the effects of digoxin on CHF hospitalization and CHF mortality (Table 1).[1] A total of 988 subjects with LVEF >45% were randomly assigned to digoxin (n = 492) or placebo (n = 496). The mean age was 67 years, 41% were women, median LVEF was 53%, and 86% were taking angiotensin-converting enzyme inhibitors (ACEI)(Table 1).[5] After a mean follow-up of 37 months, there was no difference in CHF mortality or all-cause mortality between the group assigned to placebo and the group assigned to digoxin. Likewise, there was no difference between the groups with respect to all-cause or cardiovascular hospitalizations. There was a trend that did not reach statistical significance for decreased hospitalizations for CHF in those assigned to digoxin; however, this was offset by an increase in hospitalizations for unstable angina in this group. Therefore, the investigators concluded that digoxin is not helpful in treating patients who have mild to moderate chronic DHF and are in normal sinus rhythm.[1]

CHARM Preserved. Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) was the second completed multicenter, randomized, placebo-controlled trial for DHF.[6] CHARM Preserved was one of three components of the CHARM program that studied the effects of candesartan, an angiotensin receptor blocker (ARB), on CHF hospitalization and cardiovascular death. Subjects with LVEF s 40% who were intolerant of ACEI were assigned to the CHARM Alternative trial. Those with LVEF s 40% and receiving ACEI therapy were assigned to the CHARM Added trial. Those with LVEF > 40% regardless of ACEI therapy were assigned to the CHARM Preserved rrial.[6] The CHARM Preserved trial enrolled a total of 3,025 subjects with a mean age of 67 years, 40% women, mean LVEF 54%, previous hospitalization for CHF 69%, and just 19% receiving ACEI therapy (Table 1).[6] Unlike the CHARM trials with moderately and severely reduced LVEF (CHARM Alternative, CHARM Added), the CHARM Preserved trial demonstrated no difference in cardiovascular deaths between the group assigned to placebo and the group

assigned to candesartan. There was a trend in decreased hospitalization for CHF in those assigned to candesartan that reached statistical significance only after adjustments for covariates (age, sex, New York Heart Association [NYHA] class, medical history, drugs other than spironolactone). Therefore, the investigators concluded that since candesartan appears to decrease CHF hospitalizations, it is o fmoderate benefit in treating individuals with DHF.[6]

Because of its very large size, the CHARM program database allowed baseline characteristic comparisons between subjects with SHF and DHF. Individuals with DHF tended to be older, more likely to have a history of hypertension, and less likely to have a history of myocardial infarction. They were also more likely female and in NYHA class II. Hean failure signs and symptoms were indistinguishable between the two groups except for increased prevalence of 53 and cardiomegaly by chest X-ray in those with SHF.[6]

PEP-CHF. The Perindopril in Elderly People with Chronic Heart Failure study was the third completed multicenter, randomized, placebo-controlled trial that enrolled subjects with DHF and studied the effects of perindopril, an ACEI, on all-cause death and hospitalization for CHF.- Unlike the former two trials, inclusion criteria mandated enrolled subjects to be;,, 70 years o fage, be taking diuretics, have had a previous hospitalization for cardiovascular disease within six months of enrollment, and to fulfill certain clinical and echocardiographic criteria.- The PEP-CHF trial enrolled 850 subjects with a mean age of 76 years, 55% women, mean LVEF 65%, and none receiving background ACEI or ARB therapy (Table 1).- After a mean follow-up of 26 months, there was no difference in all-cause mortality between the group assigned to placebo and the group assigned to perindopril. Likewise, there was no difference between the groups with respect to CHF hospitalizations.7 However, some of the secondary endpoints were met. Specifically, subjects taking perindopril who were admitted to the hospital had shorter hospital stays and were more likely to have improvements in their NYHA class. Other measures that were examined but not prespecified included CHF hospitalizations, 6-min corridor walk distance, and plasma concentrations ofNTproBNP at a mean follow-up of one year. Subjects assigned to perindopril demonstrated decreased CHF hospitalizations and greater 6-min corridor walk distance, and they tended to have lower NTproBNP levels, though the latter measure did not reach statistical significance.[7]

The investigators concluded that the primary endpoints were not reached because of lower-than-anticipated enrollment and event rates and low adherence rate to the assigned study drug. Approximately 30% of subjects in both groups (perindopril, placebo) stopped their assigned study drug and initiated open-label ACEI after one year.7 Since some of the secondary endpoints and other measures that were not pre-specified were obtained yet the primary endpoint was not, the study concluded that perindopril was of uncertain benefit in subjects with DHF.

	Ancillary Digitalis Trial	CHARM-Preserved	PEP-CHF	SENIORS
Patients (no.)	988	3022	850	2128
Women(%)	40	40	54	36
LVEF (%)	>45	>40	>40	N/A
Inclusion criteria				
Mean LVEF (%)	>50	54	65	36
Prior EF <40%	Included	Included	Excluded	Excluded
Mean Age (years)	67	67	76	76
Study Drug	Digitalis	Candesartan	Perindopril	Nebivolol
Other Inclusion Criteria	Symptomatic CHF	Symptomatic CHF	CV hosp within six months, Symptomatic CHF, Echo Criteria	Symptomatic CHF and CHF hosp within 12 months or LVEF s35%
Study Primary Endpoint	CHF death and CHF hosp	CV death and CHF hosp	All-cause death and CHF hosp	All-cause death and CV hosp

Table 1. Inclusion criteria, baseline characteristics, and primary endpoint comparisons between the completed multicenter, randomized, controlled trials in DHF5-B

SENIORS. The Study of the Effects of Nebivolol Intervention on Out-

comes and Rehospitalizacion in Seniors with Heart Failure examined the effects of nebivolol, a 131-selective vasodilating -blocker, on mortality and cardiovascular hospitalizations in elderly patients with heart failure.[8] It was not an exclusive trial for DHF. In fact, the 2,128 subjects enrolled in this trial collectively had a mean LVEF of just 36%. Approximately 65% had an LVEF :.;35% and 35% had an LVEF >35%. The number of subjects that had an LVEF 50% was a little more than 300.[8] Inclusion criteria mandated an age 70 years, a hospital admission for CHF within the previous year, or a known ejection fraction :s:35%.[8] After a mean follow-up of 21 months, those treated with nebivolol were less likely to have died or been hospitalized for a cardiovascular event (P <0.04).[8] When an LVEF subgroup analysis was performed with a cut-off point of 35%, the favorable effect of nebivolol was still seen in both groups (LVEF s35%, LVEF >35%), which lead the authors to conclude that nebivolol was beneficial regardless of LVEF. However, it should be noted that due to the small numbers of patients with normal LVEF, if the above analysis was done with a cut-off point of 50%, a statistically significant beneficial effect would not be seen in those with LVEF 50%. Therefore, additional multicenter, randomized, placebo-controlled trials with -blockers will need to be performed to confirm a beneficial role in the treatment of DHF.[8]

PENDING MULTJCENTER, RANDOMIZED CONTROLLED TRIALS

Table 2 lists several multicenter, randomized controlled trials that are either currently enrolling or undergoing statistical analysis. I-Preserve (lrbesartan in heart failure with Preserved Systolic Function) will be examining the effects of irbesartan, an ARB, on all-cause mortality and cardiovascular hospitalizations in 4,128 subjects.[9] Inclusion criteria included NYHA class II-IV, LVEF 45%, age 60 years, hospitalization for CHF within six months of enrollment or corroborative evidence of CHF or cardiac substrate for LV dysfunction from electrocardiogram (ECG), echocardiogram, or chest X-ray.[9] Enrollment was completed in 2005. Mean follow-up is anticipated to be approximately four years.[10]

The effects of sitaxsentan, an endothelin-A (ET-A) receptor blocker on treadmill exercise time, quality

Trial	Drug	Size	Criteria	Primary Endpoint
I-PRESERVE	Irbesartan	4128	EF >45%, CHF hosp within six months or substrate for CHF	Death/CV hosp
ET-A Blockade	Sitaxsentan	150	Clinical and Echo Criteria, LVEF >50%	Treadmill time, Echo, QOL
TOPCAT	Spironolactone	4500	EF >45%, CHF hosp within 12 months or elevated BNP or NTproBNP	CV death, aborted cardiac arrest, CHF hosp

Table 2. Comparison of the different study characteristics of the pending multicenter, randomized, controlled trials in DHF.[9,11,12]

Recommendation	Class	Level of Evidence
Control systolic and diastolic hypertension	1	A
Control ventricular rate in patients with atrial fibrillation	1	C
Use diuretics to control pulmonary congestion and peripheral edema	1	C
Coronary revascularization in symptomatic and demonstrable myocardial ischemia if judged to be the cause of DHF	IIa	C
Restoration and maintenance of sinus rhythm in patients with atrial fibrillation	IIb	C
Use of j3-blockers, AGEi, ARB, or calcium antagonist in patients with controlled hypertension	IIb	C
Use of digitalis to minimize symptoms of CHF is not well established	IIb	C

Table 3. ACC/AHA Guidelines for Treatment of Patients with DHF.[13]

of life, NYHA functional class, and diastology parameters measured using echocardiography will be studied in 150 patients with DHF}[1] In this study, DHF is defined as NYHA class II or III symptoms, LVEF 2:50%, and echocardiography evidence of diastolic dysfunction.[11]

TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone an Tagonist) will be examining the effects of spironolactone, an aldosterone antagonist, on cardiovascular death, aborted cardiac arrest, and CHF hospitalizations in 4,500 subjects.12 lnclusion criteria include age c::50 years, LVEF :45%, heart failure symptoms and signs, plus one of the following: CHF hospitalization within 12 months of enrollment, BNP JOO pg/ml, or NTproBNP 2:360 pg/ml. A mean follow-up of 3.25 years is anticipated.11

TREATMENT

Due to the disappointing results of the completed DHF trials, the ACC/AHA guidelines have changed very little in the last seven years.13 As outlined in Table 3, the ACC/AHA Class I guidelines focus on controlling blood pressure without mandating a specific class of agents, controlling tachycardia in atrial fibrillation, and using diuretics to treat pulmonary congestion and peripheral edema. Il Class Ila guidelines include coronary revascularization if ischemia is thought to be causing diastolic dysfunccion.13 Class Ilb guidelines include: I) restoration and maintenance of sinus rhythm in patients with atrial fibrillation, and 2) addition of the following agents if blood pressure is already controlled: ACEI/ARB, -blockers, and calcium blockers. They also state that the usefulness of digitalis is not well established.[13] Hopefully, as more multicenter trials are completed, a better understanding of the best treatment for DHF will emerge.

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