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SACUBITRIL/VALSARTAN VERSUS ENALAPRIL IN ISCHEMIC AND NONISCHEMIC HEART FAILURE (PARADIGM-HF SUBGROUP ANALYSIS)

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ABSTRACT

Background: We compared the angiotensin receptor–neprilysin inhibitor (LCZ696 or sacubitril/valsartan) with enalapril in patients who had ischemic and nonischemic heart failure with a reduced ejection fraction. **Methods:** In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes. **Results:** The trial was stopped early, after a median follow up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. The ischemic patients were 5036 (60%) patients and non-ischemic patients were 3363 (40%) patients. In ischemic and in nonischemic group the LCZ696 was superior to enalapril for reduce primary outcome and cardiovascular death (CV) death (P< 0.001). In LCZ696 group: the primary outcome had occurred in 339 patients (20.16 %) in the non-ischemic group and 575 patients (22.9 %) in the ischemic group (P: 0.03). A total of 199 patients (11.8%) in non-ischemic group and 359 patients in ischemic group (14.3%) died from cardiovascular causes (P: 0.01). in patient who receive enalapril no significant difference between CV death and primary outcome in the ischemic and nonischemic patients. **Conclusions:** LCZ696 was superior to enalapril in reducing the risks of cardiovascular death and hospitalization for heart failure in ischemic and nonischemic heart failure. LCZ696 also was superior to reducing the risks of cardiovascular death and hospitalization for heart failure in nonischemic than ischemic heart failure.

INTRODUCTION

A ngiotensin-converting–enzyme (ACE) inhibitors have been the cornerstone of the treatment for heart failure and a reduced ejection fraction for nearly 25 years, since enalapril was shown to reduce the risk of death in two trials. Long-term treatment with enalapril decreased the relative risk of death by 16% among patients with mild-to-moderate symptoms. The effect of angiotensin-receptor blockers (ARBs) on mortality has been inconsistent, and thus, these drugs are recommended primarily for patients who have unacceptable side effects (primarily cough) while receiving ACE inhibitors. Subsequent studies showed that the use of beta-blockers and mineralocorticoid receptor antagonists, when added to ACE inhibitors, resulted in incremental decreases in the risk of death of 30 to 35% and 22 to 30%, respectively.

LCZ696 is the first of a new class of drugs known as angiotensin receptor neprilysin inhibitors. In the pivotal PARADIGM-HF trial (Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure), (1) published in 2014, patients with heart failure (HF) and reduced ejection fraction were randomized to receive either sacubitril/valsartan or enalapril.

Patients in the LCZ696 group had a 20% relative risk reduction in the primary outcome cardiovascular death or HF hospitalization. Regarding the mode of death, most deaths in the study (1587; 80.9%) were because of cardiovascular factors, with sudden death being the most common cause of cardiovascular death (44.8%), followed by worsening HF (26.5%).The reduction in mortality with LCZ696 was similar for sudden death and pump failure (20% and 21% relative risk reduction, respectively).

In PRADIGM-HF trial , A 8442 patients (mean age 63.8±11.4 years) with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy.

Both groups received optimal medical therapy (93% on a beta blocker, 56.6 % on a mineralocorticoid antagonist) and 21.6 % of both groups receiving CRT or ICD. Over a median follow-up of 27 months. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure. The trial was stopped early, according to prespecified rules, after a median follow up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (P<0.001). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (P<0.001). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P = 0.001). the causes of heart failure in this trial was 60% ischemic and 40% non- ischemic. (1).

The non-ischemic causes were idiopathic (N:1595), hypertension (N:968), invective/viral (N:185) , alcoholic (N:158), valvular (N:110), Diabetic (N:66), drug related (N:30), Peripartum -related (N:14) and others (N:237). (2).

METHOD

In this article we analysis the the primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure and cardiovascular death between ischemic and non-ischemic patients in PARADIGM Trial. And we compared the efficacy of LCZ696 in ischemic and nonischemic heart failure.

RESULT

The ischemic patients were 5036 (60%) patients and non-ischemic patients were 3363 (40%) patients. In ischemic and in non ischemic group the sacubitril/valsartan was superior to enalapril for reduce primary outcome and Cardiovacsular death death. (figure 1).

Figure. 1: Primary outcome in ischemic and nonischemic heart failure.

	Ischemic (5036)			Non-Ischemic (3363)		
	Enalapril (2530)	LCZ696 (2506)	p	Enalapril (1682)	LCZ 696 (1681)	P
Primary outcome	697 (27.55%)	575 (22.94%)	0.0002	420 (24.97%)	339 (20.16%)	0.0008
CV Death	430 (16.99%)	359 (14.32%)	0.008	263(15.64%)	199 (11.84%)	0.001

In a follow-up of 27 months the number needed to treat to prevent primary end points was 22 patients and to prevent one CV death was 37 patients in ischemic group In non-ischemic group the number needed to treat to prevent primary end points was 21 patients and to prevent one CV death was 26 patients.

In LCZ696 group: the primary outcome had occurred in 339 patients (20.16 %) in the non-ischemic group and 575 patients (22.9 %) in the ischemic group (P: 0.03). A total of 199 patients (11.8%) in non-ischemic group and 359 patients in ischemic group (14.3%) died from cardiovascular causes (P: 0.01). and no significant difference between in CV death and primary outcome in enalapril group in the ischemic and nonischemic patients. (Figure 2).

Figure. 2: LCZ696 and Enalapril in ischemic and nonischemic heart failure.

	LCZ696 Group			Enalapril Group		
	Ischemic	nonischemic	P value	Ischemic	Nonischemic	P Value
Primary outcome	575 (22.94%)	339 (20.16%)	0.03	697 (27.55%)	420 (24.97%)	0.07
CV death	359 (14.32%)	199 (11.84%)	0.01	430 (16.99%)	263 (15.64%)	0.2

In subgroup analysis of LCZ696 in ischemic and idiopathic nonischemic heart failure (N:1595): the primary outcome had occurred in 150 patients (19%) in the non-ischemic group and 575 patients (22.9 %) in the ischemic group (P: 0.021). A total of 91 patients (11.5%) in non-ischemic group and 359 patients in ischemic group (14.3%) died from cardiovascular causes (P: 0.045). figure 3.

Figure. 3: LCZ696 and Enalapril in ischemic and idiopathic nonischemic heart failure.

	LCZ696 Group		
	Ischemic	Nonischemic	P value
Primary outcome	575 (22.94%)	150 (19%)	0.021
CV death	359 (14.32%)	91 (11.5%)	0.045

DISCUSSION

These results are more compelling if we take into account that the vast majority of patients in the PARADIGM-HF trial received optimal guideline-based medical therapy with drugs that have already been shown to reduce overall mortality and sudden death; 93% of patients were taking β-blockers and 55% were taking a mineralocorticoid receptor antagonist. The reduction in cardiovascular death and sudden death with LCZ696 was independent of protection with implantable cardioverter defibrillators (ICDs), present in only 15% of enrolled patients.

In this study involving patients with nonischemic and ischemic chronic heart failure and a reduced ejection fraction, the inhibition of both the angiotensin II receptor and neprilysin with LCZ696 was more effective in reducing the risk of death from cardiovascular causes or hospitalization for heart failure than enalapril. But LCZ696 more effective in nonischemic than ischemic heart failure group.

There is some preliminary clinical evidence of the antiarrhythmic effects of sacubitril/valsartan. de Diego and colleagues (3) showed that, in patients with HF with a reduced ejection fraction (82% ischemic) who had an implanted ICD with remote monitoring capability, treatment with sacubitril/valsartan was associated with lower premature ventricular contraction burden, less nonsustained ventricular arrhythmias, and appropriate ICD shocks compared with previous therapy with an angiontensin-convertin enzyme inhibitor or an angiotensin receptor blocker.

Current guidelines recommend prophylactic ICD in patients with HF and an ejection fraction ≤35%. This recommendation is based on evidence from clinical trials conducted >10 years ago. More recent trials, such as DANISH, which included patients with nonischemic HF and optimal medical therapy according to more recent standards, failed to show a mortality benefit from the use of ICDs except in the younger patient subgroup.

In this new era of nonischemic HF management, we may need to reassess the role of ICDs in primary prevention for patients with nonischemic HF in the context of angiotensin receptor neprilysin inhibitor therapy added to β-blockers and mineralocorticoid receptor antagonists, especially if evidence continues to suggest antiarrhythmic effects of sacubitril/valsartan.

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