Echocardiographic Detection of Increases in Ejection Fraction in Patients with Heart Failure Receiving the Selective Cardiac Myosin Activator, CK-1827452

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Abstract

Purpose: Ejection fraction (EF) remains a standard measure of left ventricular function in heart failure. Stroke volume by Doppler interrogation of the left ventricular outflow tract (LVOT SV) is more accurately measured than EF by the standard 2D image-derived Method of Discs (MoD), but it is not as familiar as EF. CK-1827452 (CK-452) increases LVOT SV in heart failure patients by prolonging systolic ejection time (SET). We compared EF changes calculated by "hybrid" methods (employing both Doppler and 2D data) to EF changes calculated by MoD for patients receiving CK-452.

Methods: Using echos obtained before, during and after infusion of the selective cardiac myosin activator, CK-452, EF was assessed by MoD and by Doppler derived LVOT SV as a percentage of ventricular volumes assessed by MoD.

Results: EF by MoD did not increase significantly; hybrid EFs increased significantly at [CK-452] >300 ng/mL. Correlation (r-square) of change from baseline in EF vs. change from baseline in SET was 0.73 (p=0.02) for EF by MoD, 0.77 (p<0.0001) for the hybrid EF based on left ventricular end-diastolic volume (LVEDV) and 0.83 (p<0.0001) for the hybrid EF based on left ventricular end-systolic volume (LVESV).

Conclusions: Hybrid EF calculations relating Doppler-derived LVOT SV to a 2D image-derived ventricular volume may be more sensitive to increases in systolic function than assessments of EF based entirely on 2D imaging.

Placebo Corrected Changes from Baseline

[CK-452] (ng/mL)		1-100	>100-200	>200-300	>300-400	>400-500	>500-883	
(n per range)		(69)	(50)	(32)	(19)	(30)	(20)	
	Baseline							P-value for Correlation vs. [CK-452]
SET (ms)	318	3 ± 4	24 ± 5‡	54 ± 5‡	65 ± 7‡	72 ± 8‡	98 ± 7‡	< 0.0001
LVOT SV (mL)	68	1 ± 2	1 ± 2	6 ± 2*	12 ± 3‡	14 ± 3‡	14 ± 3‡	< 0.0001
LVESV (mL)	174	0 ± 5	-1 ± 5	-3 ± 6	-12 ± 7	-16 ± 8	-8 ± 7	< 0.05
LVEDV (mL)	251	0 ± 6	2 ± 6	0 ± 7	-13 ± 9	-16 ± 10	-4 ± 9	NS
EF-A (%)	32	0 ± 1	0 ± 1	1 ± 1	1 ± 1	1 ± 1	2 ± 1	< 0.05
EF-B (%)	30	1 ± 1	1 ± 1	1 ± 2	7 ± 2†	8 ± 2†	5 ± 2#	< 0.0001
EF-C (%)	30	0 ± 1	0 ± 1	1 ± 1	5 ± 1†	6 ± 2‡	3 ± 1#	< 0.0001

p < 0.05, *p ≤ 0.01. †p < 0.001, ‡p < 0.0001, EF-A = ([LVEDV-LVESV]/LVEDV)*100 (MoD), EF-B = (LVOT SV/LVEDV)*100 (Doppler, MoD), EF-C = (LVOT SV/[LVESV + LVOT SV])*100 (Doppler, MoD)

Introduction

Ejection fraction (EF) remains a standard measure of left ventricular function in heart failure. Stroke volume assessed by Doppler interrogation of the left ventricular outflow tract (LVOT SV) is likely a more accurate measurement than is EF assessed by the standard 2D image-derived Method of Discs (MoD), but it is not as familiar as EF. The selective cardiac myosin activator, CK-452, has been demonstrated to increase various echocardiographically-assessed indices of systolic function in heart failure patients by prolonging systolic ejection time (SET)[1].

Objectives

In patients receiving CK-452

- To compare EF changes calculated by "hybrid" methods (employing both Doppler and 2D data) to EF changes calculated by MoD
- To explore whether the hybrid EF employing left ventricular end-systolic volume (LVESV) by MoD performs better than the hybrid EF employing left ventricular end-diastolic volume (LVEDV) by MoD

Methods

This first Phase II trial of CK-452 was a multi-center, double-blind, randomized, placebo-controlled study in heart failure patients treated with an ACE inhibitor (or ARB) and a beta-blocker, ± diuretics. In Cohorts 1-4, patients each received four treatments; three escalating doses of CK-452 and one placebo treatment which was randomized into the dosing sequence to maintain blinding. Each of the four treatments was at least one week apart. In Cohort 5, patients received two 72-hour treatments, CK-452 and placebo, in a double-blind crossover fashion. The dosing scheme is shown in the table below.

From across the five cohorts, a total of 564 echocardiograms and coincident plasma samples for measurement of CK-452 concentrations were obtained before, during and after infusion CK-452. EF was assessed by MoD and by each of two "hybrid" methods that employed both Doppler-derived LVOT SV and ventricular volumes assessed by MoD:

$$EF_{HYB\text{-}EDV} = (LVOT\ SV/LVEDV) \times 100$$

$$EF_{HYB\text{-}ESV} = (LVOT\ SV/[LVESV + LVOT\ SV]) \times 100$$

Dosing Scheme

	Loading Dose mg/kg/hr		Maintenance Dose mg/kg/hr	Entry EF and Cohort Features
Cohort 1 1 hr + 1hr n = 8	0.125 0.25 0.5	→	0.0625 0.125 0.25	EF < 40%, investigator verified Echos at Baseline, 1.5, 24 hours Four treatment sessions/patient*
Cohort 2 1 hr + 1hr n = 9	0.5 0.75 1.0	→	0.25 0.375 0.5	EF < 40%, investigator verified Echos at Baseline, 1.5, 24 hours Four treatment sessions/patient*
Cohort 3 1hr + 23hr n = 10	0.25 0.5 1.0	→	0.025 0.05 0.1	EF < 40%, investigator verified Echos at Baseline, 1.5, 24, 48 hours Four treatment sessions/patient*
Cohort 4 1hr + 1hr + 22hr n = 8	0.25/0.125 0.5/0.25 1.0/0.5	→	0.025 0.05 0.1	EF ≤ 30%, core lab verified Echos at Baseline, 1.5, 24, 48 hours Three women required Four treatment sessions/patient*
Cohort 5 1hr + 1hr + 70hr n = 10	1.0/0.5 or 0.75/0.375	→	0.1 0.075	EF < 40%, core lab verified Echos at Baseline, 1.5, 24, 72, 96 hours Two period crossover Dose reduction in last 2 patients

* Each patient receives double-blind placebo randomly interspersed in dosing order

Results

Demographics and Baseline Characteristics

	Cohorts 1-5 (n=45)	
	Mean	(min-max)
Age (yrs)	58	30 – 77
Weight (kg)	78	52 – 115
Systolic BP (mmHg)	124	96 – 183
Diastolic BP (mmHg)	75	57 – 117
Heart Rate (bpm)	69	48 – 96
Ejection Fraction (%)	33	20 – 55

Cohorts 1-5	
39 Men	6 Women
29 IHD	16 DCM

Results (contd.)

Echo PK/PD Relationship: Pooled Analysis

[CK-1827452] (ng/mL)		1-100	>100-200	>200-300	>300-400	>400-500	>500	Correlation versus [CK-1827452] (p value)
Variable	Mean Baseline	Placebo Corrected Changes from Baseline Difference of Least Squares Means ± SEM						
SET (msec)	316	1 ± 4 NS	18 ± 4 p < 0.0001	47 ± 5 p < 0.0001	58 ± 6 p < 0.0001	59 ± 6 p < 0.0001	80 ± 5 p < 0.0001	<0.0001
LVOT SV (mL)	69	0 ± 2 NS	1 ± 2 NS	5 ± 2 p = 0.01	11 ± 3 p < 0.0001	9 ± 3 p = 0.001	10 ± 2 p < 0.0001	<0.0001
LVOT CO (mL/min)	4423	-32 ± 116 NS	52 ± 123 NS	180 ± 141 NS	408 ± 173 p = 0.02	400 ± 189 p = 0.03	330 ± 142 p = 0.02	0.0005
LVOTHR (bpm)	66	0 ± 1 NS	0 ± 1 NS	-2 ± 1 p = 0.06	-4 ± 2 p = 0.005	-2 ± 2 NS	-4 ± 1 p = 0.001	0.0003
EF_{MOD} (%)	33	0 ± 1 NS	0 ± 1 NS	1 ± 1 NS	1 ± 1 NS	0 ± 1 NS	2 ± 1 p = 0.02	0.009
$EF_{HYB\text{-}EDV}$ (%)	32	0 ± 1 NS	1 ± 1 NS	3 ± 2 P = 0.07	8 ± 2 p < 0.0001	7 ± 2 p = 0.0009	10 ± 1 p < 0.0001	<0.0001
$EF_{HYB\text{-}ESV}$ (%)	31	0 ± 1 NS	1 ± 1 NS	2 ± 1 p = 0.03	5 ± 1 p < 0.0001	5 ± 1 p < 0.0001	6 ± 1 p < 0.0001	<0.0001
LVESV (mL)	168	1 ± 4 NS	3 ± 4 NS	-5 ± 5 NS	-11 ± 6 p = 0.08	-13 ± 7 p = 0.06	-15 ± 5 p = 0.003	<0.0001
LVEDV (mL)	243	1 ± 5 NS	5 ± 5 NS	-2 ± 6 NS	-14 ± 8 p = 0.07	-15 ± 8 p = 0.07	-16 ± 6 p = 0.01	0.0005

p < 0.05

Ejection Fraction versus Systolic Ejection Time

Variable	Correlation (r^2)*	P-value**
EF_{MOD} (%)	0.80	0.0006
$EF_{HYB\text{-}EDV}$ (%)	0.83	< 0.0001
$EF_{HYB\text{-}ESV}$ (%)	0.89	< 0.0001

* Generalized r^2 is calculated using ejection fraction by the indicated method versus systolic ejection time treating patients as random effect

** P-value is computed using ANOVA analysis based on the following model: ejection fraction by the indicated method = systolic ejection time + Error, treating patients as random effect

p < 0.05

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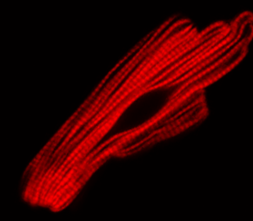
References

1 Malik FI, Saikali KG, Clarke CP, Teerlink JR, Wolff AA. Systolic Ejection Time is a Sensitive Indicator of Left Ventricular Systolic Function During Treatment with the Selective Cardiac Myosin Activator, CK-1827452. 2007 Annual Heart Failure Society of America Meeting, Washington, DC. September, 2007.



Conclusions

- CK-452 increases systolic ejection time, stroke volume, cardiac output, and ejection fraction in a concentration-dependent manner
- While ejection fraction by all three methods increased with the plasma concentration of CK-452, increases of greater magnitude were observed with the hybrid methods
- As expected, ejection fraction assessed by hybrid methods that employ a measurement of stroke volume based on Doppler interrogation of the left ventricular outflow tract correlates much better with systolic ejection time (a measurement also based on Doppler interrogation of the left ventricular outflow tract) than does ejection fraction assessed by the Method of Discs
- Ejection fraction by the hybrid method based on left ventricular end-systolic volume was slightly better correlated with systolic ejection time than the hybrid EF based on left ventricular end-diastolic volume

CYTOKINETICS