

DRAFT Panel Questions

Circulatory System Devices Panel Meeting
October 8, 2013

P010015 / S205 & P010031/S381

Expanded Indications for Medtronic Cardiac Resynchronization Therapy Devices Based on the Block HF Study

Question #1: Interpretation of Study Outcome Considering LVESVI

The Block HF study used a composite endpoint of first time to one of the following:

- All-cause mortality
- Heart failure urgent care visit
- Increase in Left Ventricular End Systolic Volume Index (LVESVI) of $\geq 15\%$

The pre-specified Bayesian analysis of this composite endpoint indicates that BiV pacing resulted in a 27% reduction in risk for developing a first primary composite endpoint event compared to RV pacing. The primary objective was met with a posterior probability that the hazard ratio is less than one of 0.999. The data used in analyzing the primary objective of the Block HF study are provided below.

Objective	Number of Subjects (% Subjects)				Hazard Ratio (95% CI)			Posterior Probability of Hazard Ratio of <1
	CRT-P (N= 484)		CRT-D (N= 207)		CRT-P (N= 484)	CRT-D (N=207)	All Subjects (N=691)	
	BiV Arm (N=243)	RV Arm (N=128)	BiV Arm (106)	RV Arm (N=101)				
Primary Objective	109 (44.9%)	128 (53.1%)	51 (48.1%)	63 (62.4%)	0.72 (0.57, 0.90)	0.74 (0.56, 1.00)	0.73 (0.59, 0.89)	0.999
LVESVI	55 (22.6%)	78 (32.4%)	30 (28.3%)	36 (35.6%)				
HF Urgent Care Event	40 (16.5%)	39 (16.2%)	16 (15.1%)	23 (22.8%)				
Death	14 (5.8%)	11 (4.6%)	5 (4.7%)	4 (4.0%)				

However, the following were noted regarding the ability to interpret clinical meaning of LVESVI:

- FDA's Cox-Regression analysis (shown below) of the predictive value of LVESVI with regard to future death or death/heart failure urgent care events showed evidence that there is no consistent evidence that LVESVI events predict future death or heart failure urgent care events in the BiV or RV arm.

Category		Predictability for Death/Heart Failure Urgent Care Event			
		Total Number	Number of Death/HF Urgent Care Event (%)	Hazard Ratio**	95% CI
RV	LVESVI event observed before death or HF urgent care event	125*	48 (38.4%)	1.74	(1.15, 2.65)
	No LVESVI event observed before death or HF urgent care event	143*	45 (31.5%)		
BiV	LVESVI event observed before death or HF urgent care event	89*	26 (29.2%)	1.00	(0.63, 1.59)
	No LVESVI event observed before death or HF urgent care event	210*	68 (32.4%)		

*Number of patients with at least one non-missing echo evaluation before the first death or heart failure urgent care event.

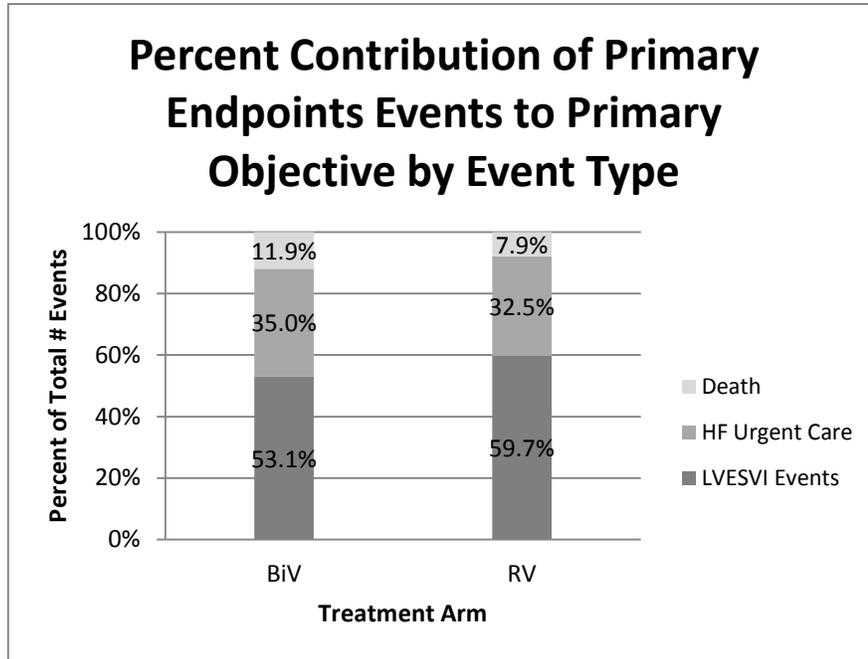
**For this analysis, hazard ratios greater than one suggest that LVESVI events predict future death or heart failure urgent care events. A hazard ratio of one suggests no predictive value.

- Of the 252 subjects who met an LVESVI endpoint, approximately 50% of subjects did so within 6 months of being programmed to their final therapy and 75% of subjects did so within 12 months.

QUESTION 1A: Please describe what, if any, clinically relevant information changes in LVESVI provide with regard to heart failure status.

The following were noted regarding the contribution of LVESVI to the success of the Block HF study:

- LVESVI events accounted for 53.1% of the BiV events used in the primary analysis and 59.7% of the RV events. A breakdown of the events contributing to the primary analysis is provided below.



- The estimated hazard ratio when LVESVI events are excluded from the analysis of the composite endpoint was calculated using a Bayesian and Frequentist approach. The magnitude of benefit observed is smaller (particularly with the Frequentist approach) when LVESVI events are excluded.

Events Included in Analysis	Hazard Ratio	
	Bayesian Approach	Frequentist Approach
Death/HF Urgent Care/LVESVI events	0.729	0.675
Death/HF Urgent Care	0.738	0.796

- The annualized rates for mortality and heart failure urgent care events were calculated using a Frequentist approach. The results indicate that the absolute difference in treatment effect is seen predominantly in year one. The absolute benefit seen for mortality at one year is 1.0% and the absolute benefit seen for heart failure urgent care events at one year is 7.9%.

Annualized Mortality Rate

Arm		Annualized Mortality Rate		
		up to 1 year	1-2 years	2-3 years
BiV	Proportion	20	18	11
	# Evaluable	349	305	234
	Proportion	6.0%	6.6%	5.7%
	95% CI	(3.5%, 8.5%)	(3.6%, 9.5%)	(2.4%, 8.9%)
RV	# Dead	23	16	10
	# Evaluable	342	298	237
	Proportion	7.0%	5.9%	4.7%
	95% CI	(4.3%, 9.7%)	(3.1%, 8.7%)	(1.9%, 7.6%)
Treatment Effect	absolute difference in proportion	-1.0%	0.7%	0.9%

Annualized Rate for Heart Failure Urgent Care Events

Arm		Annualized Heart Failure Urgent Care Event Rate		
		up to 1 year	1-2 years	2-3 years
BiV	# Heart Failure Urgent Care Event	34	21	13
	# Evaluable	349	284	206
	Proportion	10.1%	8.2%	7.1%
	95% CI	(6.9%, 13.3%)	(4.8%, 11.5%)	(4.9%, 12.1%)
RV	# Heart Failure Urgent Care Event	59	20	13
	# Evaluable	342	256	189
	Proportion	18.0%	8.5%	8.1%
	95% CI	(13.8%, 22.1%)	4.9%, 12.1%)	(3.8%, 12.3%)
Treatment Effect	absolute difference in proportion	-7.9%	-0.3%	-1.0%

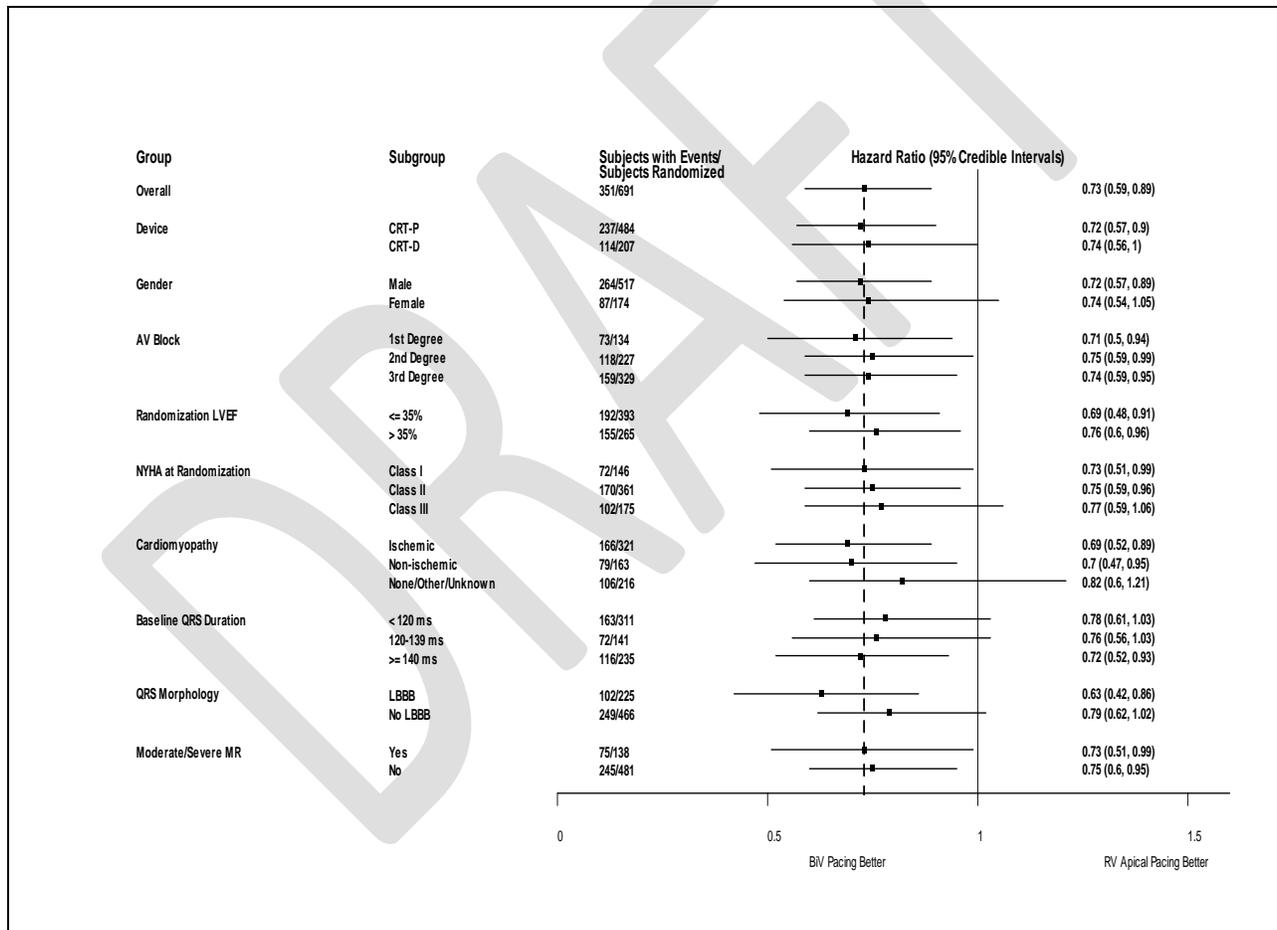
QUESTION 1B: Please indicate whether the contribution of LVESVI to the success of the Block HF study impacts your assessment of whether the study as a whole provides reasonable assurance that BiV pacing is effective in the studied patient population. Specifically, please indicate if a clinically meaningful benefit is observed when the contribution of LVESVI is excluded.

Question #2: Treatment Effect across Subgroups

The Block HF study enrolled patients with a variety of baseline demographics. Exploratory analyses indicated that there may not be a significant difference in results among a variety of subgroups, but overall rates of all-cause mortality and heart failure urgent care visits were somewhat low and the number of subjects available for subgroups analyses was also somewhat low. The following subgroups were assessed:

- Subjects who received a CRT-P and those who receive a CRT-D
- Subjects with and without Left Bundle Branch Block (LBBB)
- Male and female subjects
- Subjects with randomization LVEF $\leq 35\%$ and subjects with LVEF $> 35\%$
- NYHA Class I subjects, NYHA Class II subjects, and NYHA Class III subjects
- Heart Failure Stage A/B and Heart Failure Stage C/D subjects
- Subjects with randomization LVESVI $> 40 \text{ mL/m}^2$ and subjects with LVESVI $\leq 40 \text{ mL/m}^2$
- Subjects with and without Mitral Regurgitation (MR) benefitted from BiV pacing.

The below forest plot summarized the results of the subgroup analyses.



QUESTION 2: Please indicate if any specific subgroups would be expected to benefit more or less from BiV pacing compared to RV pacing.

Question #3: Proposed Indicated Population

The sponsor has proposed to expand the indications for use statements for their CRT-P and CRT-D devices by including patients who meet the following criteria:

- Class I or Class IIa indications for pacemaker implantation in accordance with ACC/AHA/HRS guidelines, have NYHA functional Class I, II or III, LVEF \leq 50% and are diagnosed with at least one of the following:
 - Third degree AV block
 - Second degree AV block
 - First degree AV block with symptoms similar to pacemaker syndrome
 - Documented Wenckebach or PR interval > 300ms when paced at 100 ppm

FDA notes the following regarding the extent of LV dysfunction and heart failure symptoms in the enrolled population:

- 581 out of 691 (84.1%) randomized subjects were NYHA Class II or III
- 606 out of 691 (87.7%) randomized subjects had heart failure symptoms at randomization (Heart Failure Stages C or D).
- Most randomized subjects had significant LV dysfunction:
 - o 393 out of 658 (59.71%) of randomized subjects had an LVEF less than 35% at randomization (echo read by the core lab).
 - o 547 out of 691 (79.1%) of randomized subjects had an LVESVI greater than 40 mL/m² at randomization (also read by the core lab).

QUESTION 3: Considering the characteristics of the subjects studied in the Block HF investigation, please comment on whether the proposed indicated population is adequately supported by the Block HF study findings. In particular, please comment on whether NYHA Class I subjects should be included in the indicated population considering the level of LV dysfunction and heart failure in the randomized population. Please also comment on whether there are any other elements of the indications statement that you find are not adequately supported by the Block HF study.

Question #4: Overall Benefit-Risk Assessment

When the absolute benefit in terms of mortality and heart failure urgent care events is analyzed by calculating the annualized event rates seen in the Block HF study, the benefit of BiV pacing is seen predominantly in year one and in heart failure urgent care events only; the absolute benefit up to year one for heart failure urgent care events is 7.9%. In contrast, the addition of the left ventricular lead needed to provide BiV pacing was observed to add complications requiring invasive intervention in 51 out of 809 subjects (6.3%).

Question 4: Based on the Block HF study results and additional analyses presented, please discuss whether the overall benefits of expanding the indications for use of CRT-P and CRT-D devices outweigh the risks in the intended patient population. Please discuss all key factors that influence your assessment.

Question #5: Post Approval Study

The Block HF study evaluated the impact of BiV pacing compared to RV pacing for patients with AV block, left ventricular ejection fraction $\leq 50\%$, and NYHA functional class I, II, or III. Based on exploratory analyses of annualized rate for mortality and mortality or heart failure urgent care events, the treatment effect is predominantly seen in 12 months. Based on exploratory analyses of subgroups, the relevant subgroups appear to have similar treatment effects. Please address the following under the assumption that approval of the requested expansion in indications for use statement for CRT is granted.

QUESTION 5: Please comment on whether data should be collected postmarket in a broader patient population. If so, please specifically discuss the duration of follow-up needed to assess long-term effectiveness, the endpoints that should be included such as mortality and heart failure events, and the appropriate patient subgroups to be evaluated.

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