DECLARATION OF CONFLICT OF INTEREST

The Role of Ventricular Electrical Delay to Predict Left Ventricular Remodeling With Cardiac Resynchronization Therapy

Results from the SMART-AV Trial

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DECLARATION OF CONFLICT OF INTEREST

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FINANCIAL DISCLOSURE:

Research Grants: Medtronic, Boston Scientific, St. Jude, Sorin

Honoraria / Consulting: Medtronic, Boston Scientific, St. Jude, Sorin

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Introduction

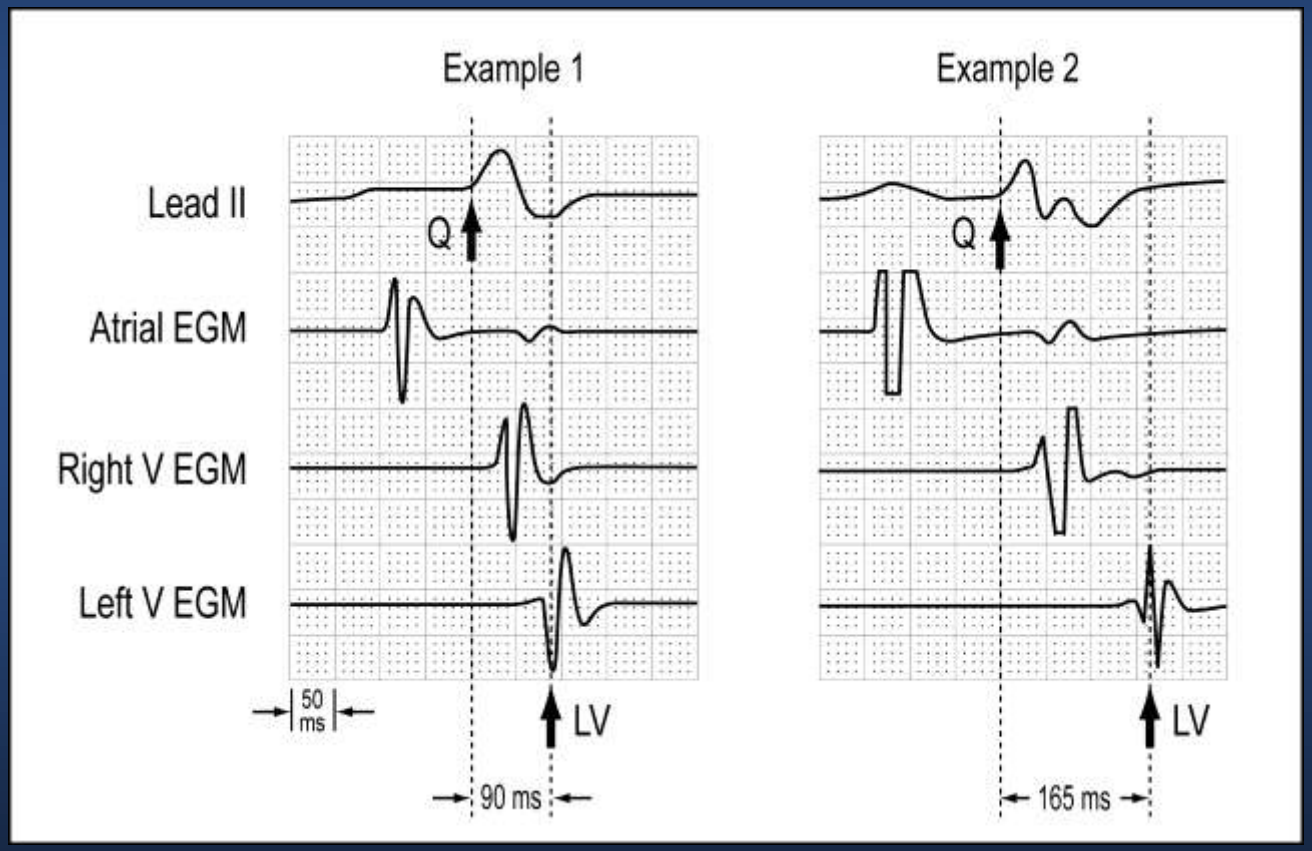
- Prospective, randomized trials have demonstrated that cardiac resynchronization therapy (CRT) improves quality of life, exercise capacity, LV systolic function and decreases hospitalizations for heart failure (HF)
- Subgroup analyses have identified QRS duration and QRS morphology as independent predictors of CRT outcomes
- This suggests that electrical delay or electrical dyssynchrony is an important factor for predicting benefit from CRT
- Identifying the electrical delay at the LV stimulation site may quantify the amount of resynchronization that occurs with CRT and thus predict response more accurately

Objective

- To investigate the relationship between the intrinsic electrical delay at the LV stimulation site and clinical endpoints in a prospectively designed substudy of the SMART-AV Trial
  - Electrical delay was defined by the time interval from the first QRS deflection on a surface ECG to local intrinsic activation at the LV stimulation site ("Q-LV")

QLV Interval Measurement

The QLV interval was measured in sinus rhythm and in the absence of ventricular pacing as the interval from the onset of QRS from the surface ECG to the first large positive or negative peak of the LV EGM during a cardiac cycle



Description of SMART-AV Trial

SMART-AV Inclusion

- NYHA class III or IV
- EF ≤ 0.35
- QRS ≥120ms
- Expected to be in sinus rhythm at the time of implant
- Receiving optimal pharmacologic therapy
- Randomized: N = 980

Primary Endpoint:

- LVESV at 6 months

Secondary Endpoints:

- 6 min walk, EF, NYHA Class, LVEDV, LVEF, QOL (MLWHF)

SMART-AV Exclusion

- Complete heart block or unable to tolerate pacing at VVI-40-RV for up to 14 days
- Previously received CRT

Stein KM et al. *Pacing Clin Electrophysiol* (2010)
Ellenbogen KA et al. *Circulation* (2011)

Substudy Patient Characteristics

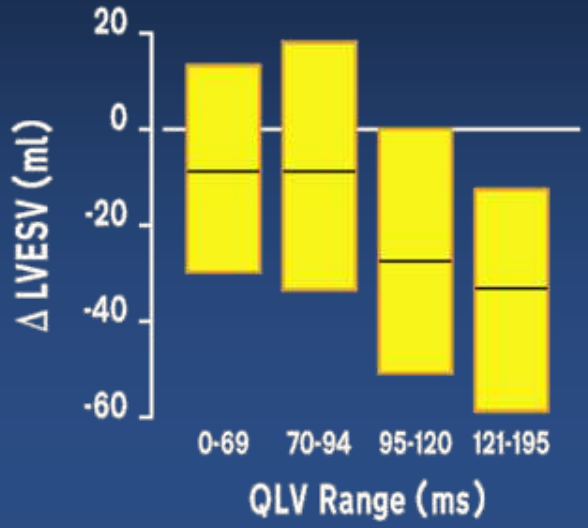
N =	426
Age, years	66 ±11
Gender (%Male)	66%
Ischemic heart disease	59%
LV ejection fraction (%)	26 ± 7
NYHA functional class	
I	0%
II	3%
III	94%
IV	3%
Cardiac medications	
ACE/ARB	84%
Beta-blocker	92%
Diuretic	82%
ECG characteristics	
QRS duration (ms)	151 ± 19
LBBB (%)	75%

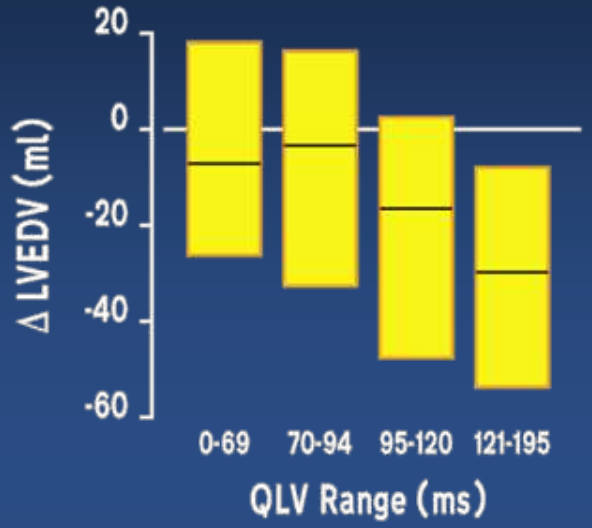
All values were similar to the larger full cohort (n=980) enrolled in the SMART-AV trial, except a slightly shorter mean QRS duration in the substudy cohort

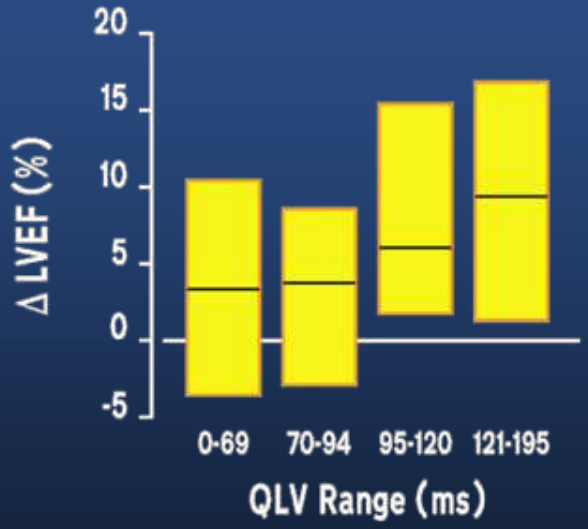
QRS: 151±19 vs. 154±21 ms (p<0.05)

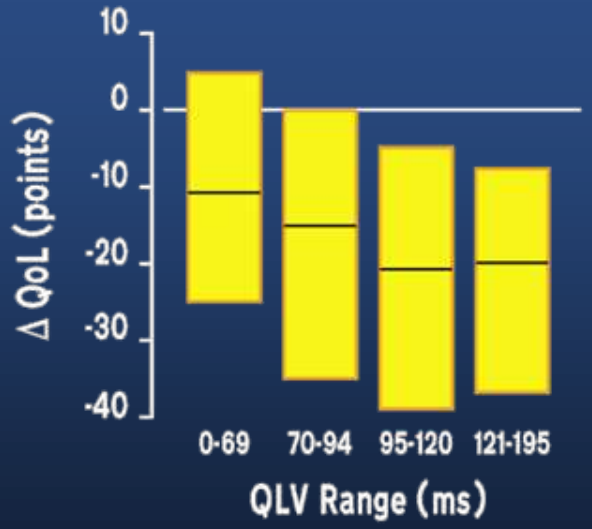
Values expressed as mean ± SD

Results: CRT Response By QLV Quartiles









All p<0.001
Kruskal-Wallis test

Data presented as median ± inter-quartile range

Results: CRT Response Rates at 6 Months by QLV Quartile

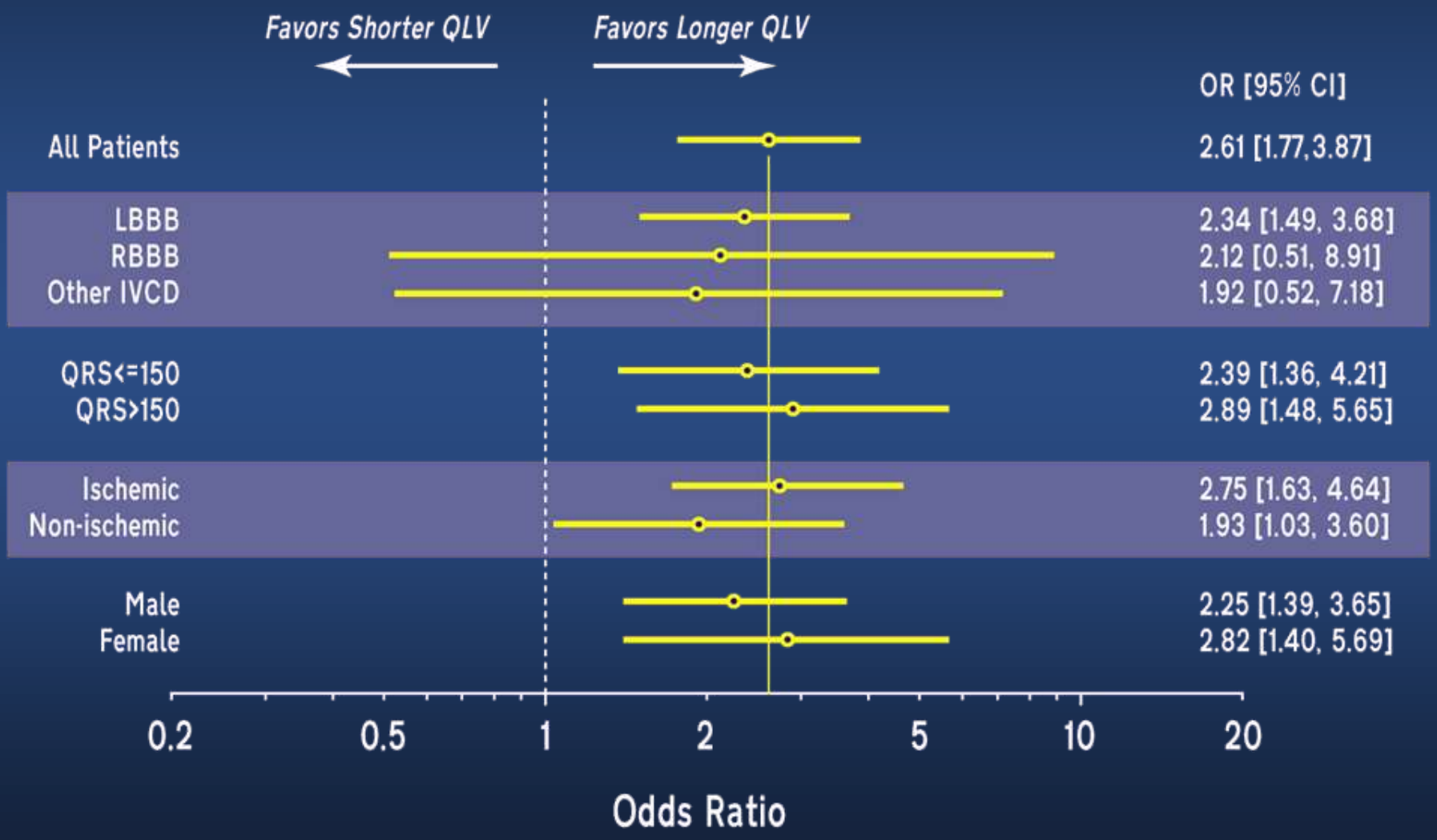
QLV	LVESV Response Rate (>15% reduction)	QOL Response Rate (>10 point reduction)
0-70 ms	**39%**	**50%**
70-95 ms	**40%**	**55%**
95-120 ms	**58%**	**65%**
120-195 ms	**68%**	**72%**
Pearson Chi-sq	<.001	.004

Results: Clinical Secondary Outcomes

	QLV Quartiles						
	Q1: 0 - 70 ms	Q2: 70 - 95 ms	Q3: 95 - 120 ms	Q4: 120 - 195 ms	Total:	Overall p-value	Q4 vs. Q1 p-value
Patients w/ HF events	12.1%	7.1%	6.4%	6.3%	8.2%	0.37	0.17
ΔSix minute walk distance	52 ± 118	68 ± 91	50 ± 104	70 ± 93	59 ± 103	0.36	0.13
NYHA Class							
Improved	89 (73.0%)	79 (80.6%)	76 (71.0%)	77 (83.7%)	321 (76.6%)	0.04	0.04
No Change	33 (27.1%)	16 (16.3%)	30 (28.0%)	14 (15.2%)	93 (22.2%)		
Worsened	0 (0%)	3 (3.1%)	1 (.9%)	1 (1.1%)	5 (1.2%)		

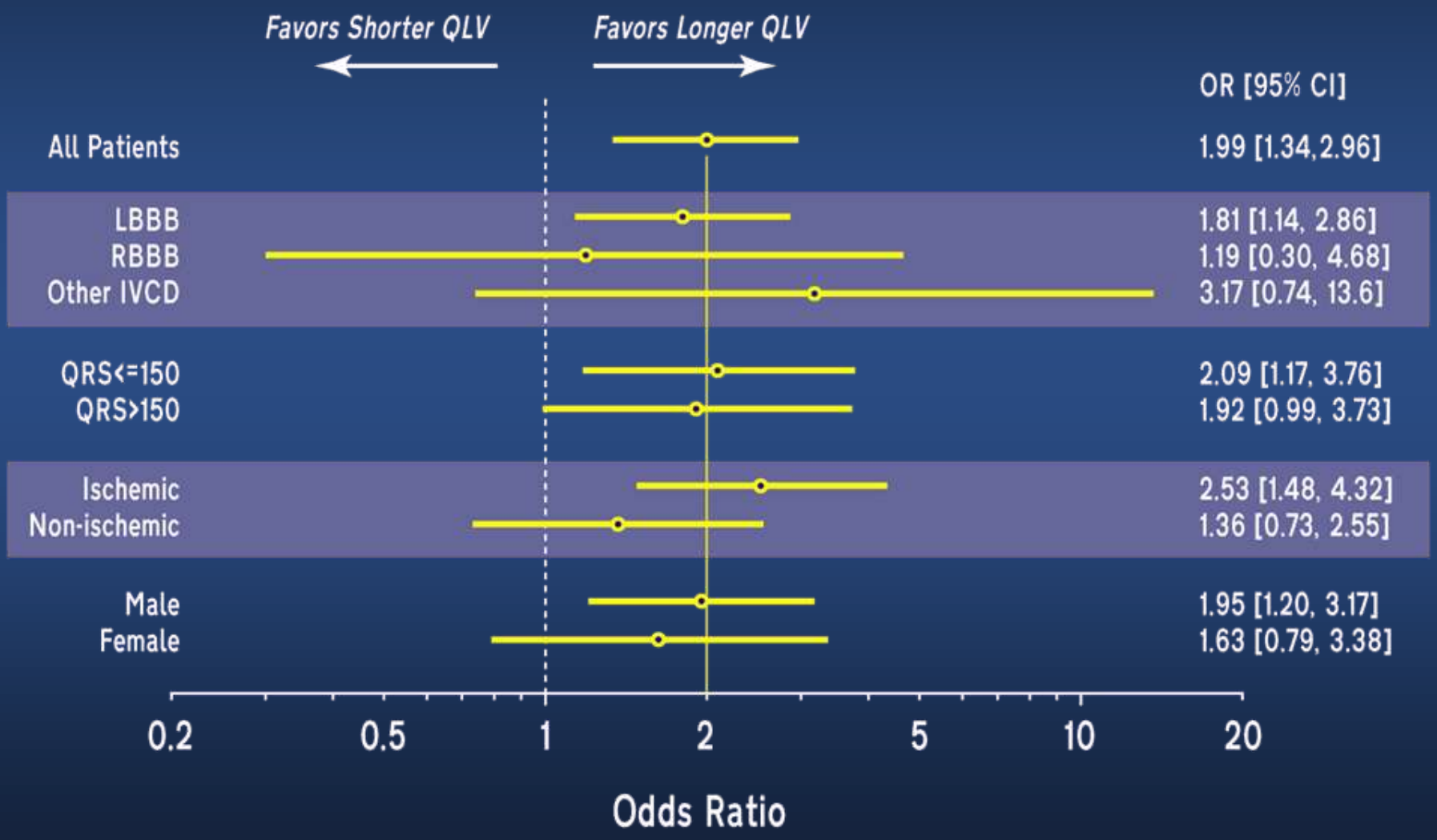
LVESV Response by Subgroup

Univariate Logistic Regression Results



QOL Response by Subgroup

Univariate Logistic Regression Results



Odds Ratio of CRT Response
Multivariate Logistic Regression

QLV	Odds Ratio (95% CI), p-value	
	LVESV response	QOL response
2nd quartile vs. 1st quartile	1.10 (.62 - 1.95), .74	1.30 (.75 - 2.26), .35
3rd quartile vs. 1st quartile	1.86 (1.04 - 3.31), .04	1.86 (1.05 - 3.31), .03
4th quartile vs. 1st quartile	3.21 (1.58 - 6.50), .001	2.73 (1.35 - 5.54), .005

* Adjusted for baseline EF, LVESV, Etiology of HF, LBBB, Gender, NYHA, QRS and age

Summary

In the SMART-AV QLV Substudy:

- When stratified by QLV duration quartiles, CRT response rates at 6 months increased:
  - Reverse remodeling (>15% reduction of LV end systolic volume) response increased from 39% to 68%
  - QOL (>10 points reduction) response increased from 50% to 72%.
- Patients in the highest quartile of QLV had a ~3x fold increase in their odds of a ESV and QOL response after correcting for QRS duration, BBB type and clinical characteristics

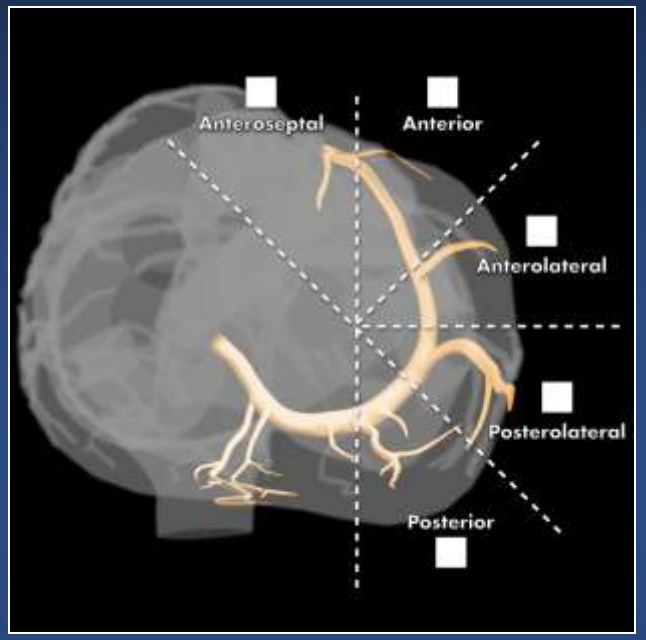
Conclusions

- Electrical dyssynchrony, as measured by QLV, was a strong and independent predictor of outcomes with CRT
- The best improvements in ESV, EDV, EF and QOL were observed with a QLV > 95 ms, so this cutoff should be considered when selecting LV lead position at the time of CRT implantation
- Further study is warranted to assess the value of using QLV rather than anatomic location to guide lead positioning to improve response rates with CRT

Backup

Relationship between Electrical Intervals and Anatomical Locations

- The location of the LV lead was not controlled in this study
  - Most leads were placed in the anterolateral or posterolateral veins, as reported by the implanting physicians
- 46 of 426 (11%) had apical leads
- 13 of 426 (3%) had anterior or septal leads
- These small numbers preclude any meaningful analysis of the impact of lead location on QLV or response rate
- However, even in similar vein locations, there was marked variation in QLV
  - Mid-anterolateral (n=89): QLV range = 10 – 195 ms
  - Mid-posterolateral (n=230): QLV range = 15 – 195 ms



Odds Ratio of CRT Response
Multivariate Logistic Regression

	Odds Ratio (95% CI), p-value	
Covariate	LVESV response	QOL response
QLV: 2nd quartile vs. 1st quartile	1.10 (.62 - 1.95), .74	1.30 (.75 - 2.26), .35
QLV: 3rd quartile vs. 1st quartile	**1.86 (1.04 - 3.31), .04**	**1.86 (1.05 - 3.31), .03**
QLV: 4th quartile vs. 1st quartile	**3.21 (1.58 - 6.50), .001**	**2.73 (1.35 - 5.54), .005**
Age (per 1 year increase)	1.00 (.98 - 1.02), .80	.99 (.97 - 1.01), .21
LVEF (per 1% increase)	.98 (.94 - 1.01), .19	1.00 (.96 - 1.03), .83
Ischemic vs. non-Ischemic	**.58 (.37 - .91), .02**	1.05 (.67 - 1.64), .85
QRS (>150 ms vs. ≤ 150 ms)	.86 (.53 - 1.40), .54	.88 (.55 - 1.43), .61
LBBB vs. non-LBBB	1.20 (.72 - 2.01), .48	1.17 (.71 - 1.93), .53
Male vs. Female	**.53 (.33 - .85), .01**	**.56 (.34 - .91), .02**
NYHA class IV vs. I-III	1.67 (.44 - 6.29), .45	3.41 (.69 - 16.92), .13
LVESV (per 1ml increase)	1.00 (.99 - 1.01), .98	1.00 (.99 - 1.00), .68

Odds > 1 indicates increased likelihood of response

Odds Ratio of CRT Response

Multivariate Logistic Regression

(after adjustment for QLV)

	Odds Ratio (95% CI), p-value	
Covariate	LVESV response	QOL response
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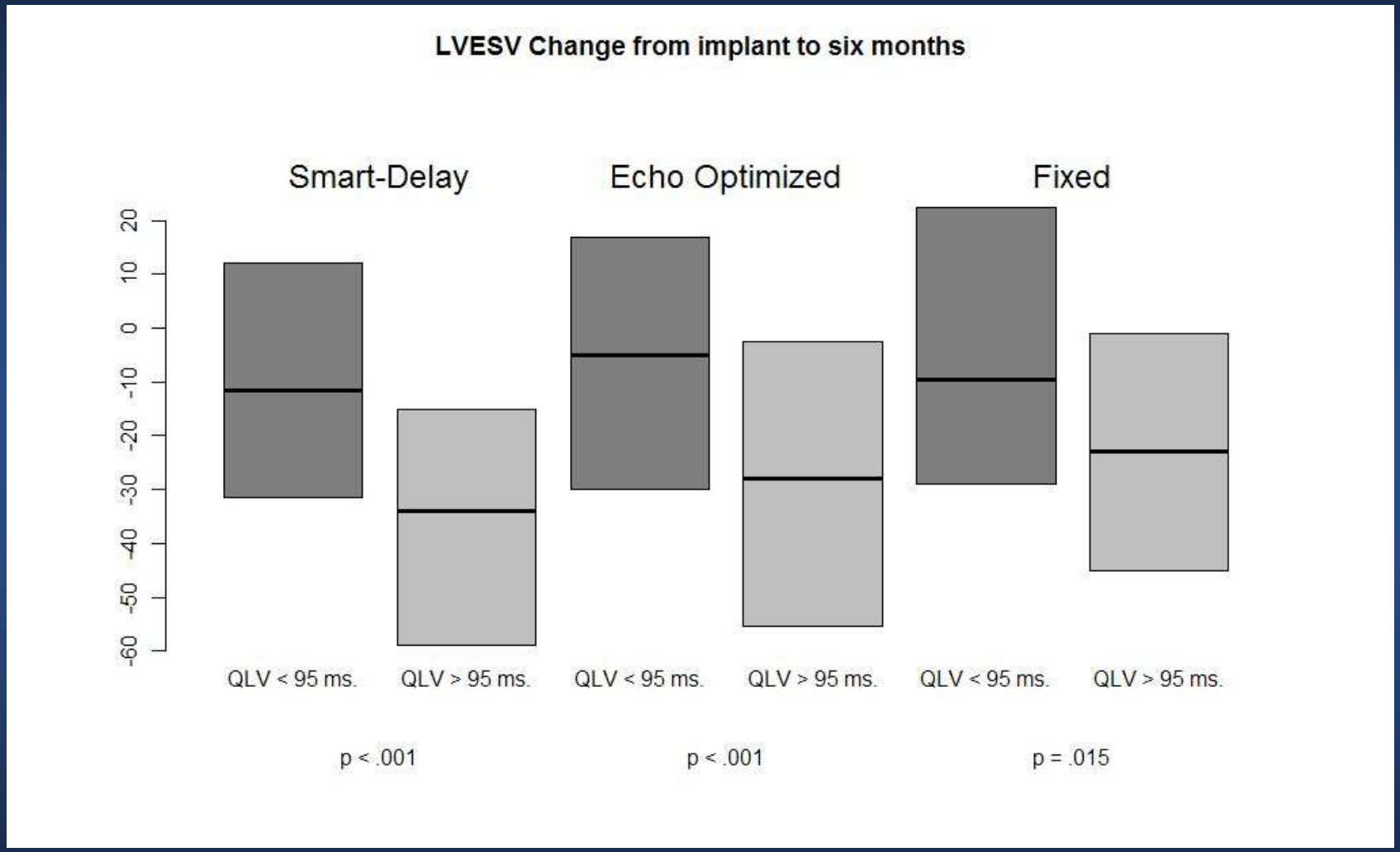
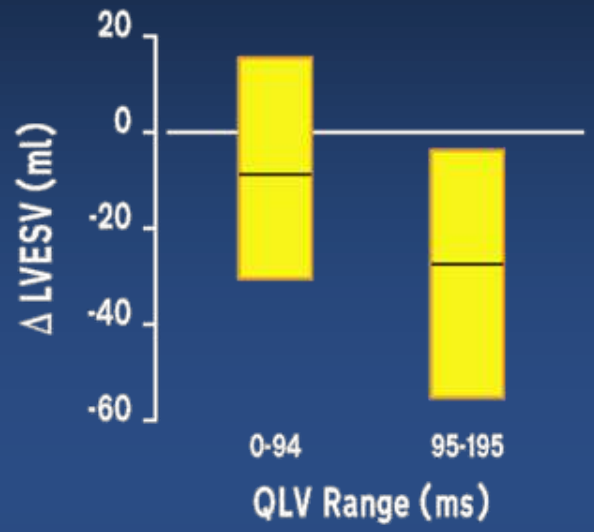
LVESV Response by Median QLV For 3 Smart-AV Study Arms

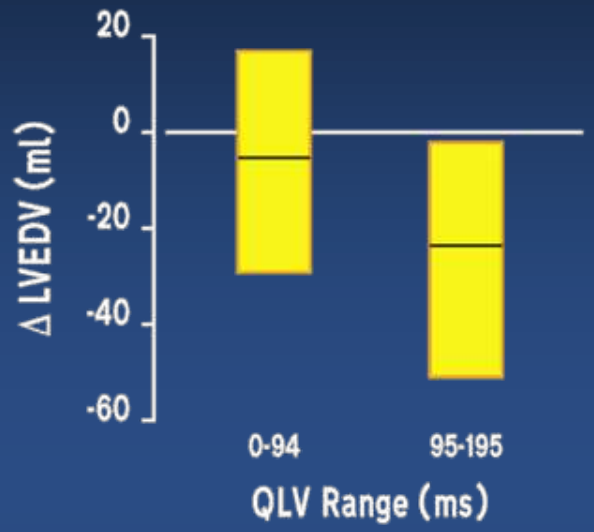


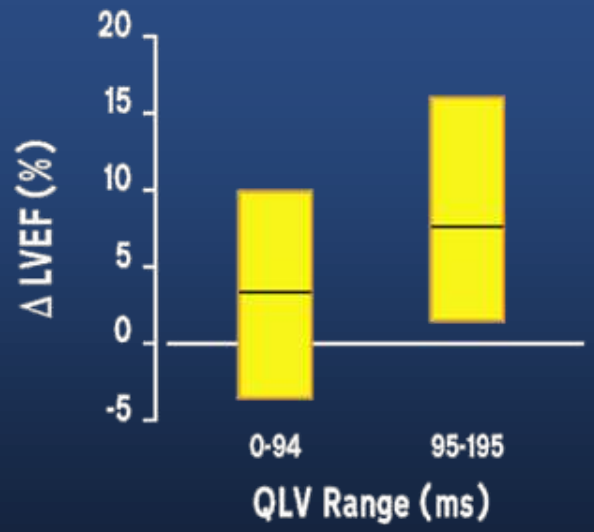
P-value for Fixed_AV*QLV_quartile interaction (from MV logistic model) = .077
--- for pooled (echo + smart-delay) vs. Fixed.

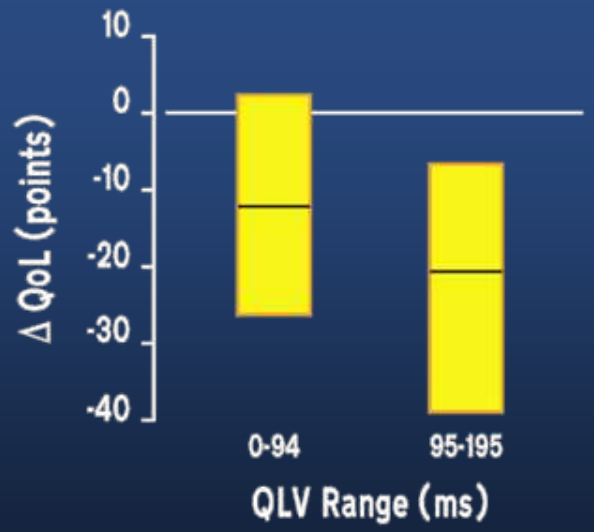
Results: CRT Response By Median QLV

Implant to 6 Months









All p<0.001
Wilcoxon test

Data presented as median ± inter-quartile range