CHAPTER 6

EFFECT OF AV- AND VV-DELAY OPTIMIZATION ON CLINICAL AND ECHOCARDIOGRAPHIC OUTCOMES OF PATIENTS TREATED WITH CARDIAC RESYNCHRONIZATION THERAPY: A META-ANALYSIS

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ABSTRACT

Optimization of atrio-ventricular (AV) and ventriculo-ventricular (VV) delays of cardiac resynchronization therapy (CRT) devices maximizes left ventricular (LV) filling and stroke volume. However, the incremental value of these optimizations over empiric device programming remains unclear. The objective of this analysis was to perform a systematic review and meta-analysis of the effects of AV and VV delay optimization on clinical and echocardiographic end points of heart failure patients treated with CRT.

A standardized search strategy was performed and identified 12 trials comparing AV and/or VV delay optimization and conventional CRT device programming and their effects on various clinical and echocardiographic outcomes. Pooled odds ratios were analyzed using random effect meta-analysis with Mantel-Haenszel method.

Combined data from a total of 4356 heart failure patients treated with CRT showed no differences in clinical or echocardiographic outcomes between patients who underwent AV and/or VV optimization and patients who underwent empiric device programming (Mantel-Haenszel odds ratio=0.86 [95% confidence interval 0.68-1.09], P value for overall effect =0.21 by intention-to-treat analysis).

The current literature suggests that routine AV and/or VV delays optimization has a neutral effect on clinical and echocardiographic outcomes based on pooled data from randomized and non-randomized studies. Standardization of patient selection and optimization timing and method may help to further define the role of CRT device optimization.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is indicated in heart failure patients with New York Heart Association (NYHA) functional class II-IV symptoms despite adequate medical therapy, left ventricular ejection fraction (LVEF) ≤35% and QRS complex width ≥120ms.[1] This therapy has been shown to reduce mortality and to induce left ventricular (LV) reverse remodeling while improving clinical status (improvement in NYHA functional class, 6 minute walk distance test [6MWT] and quality of life [QoL]).[2, 3] Furthermore, late generation devices permit adjustment of the atrio-ventricular (AV) and ventriculo-ventricular (VV) delays to further improve LV performance. Non-echocardiographic parameters of LV performance (invasive dP/dT and cardiac output, impedance cardiography, intracardiac electrograms) as well as echocardiographic indices (left ventricular outflow tract velocity-time integral [LVOT VTI], cardiac output) are influenced by changes in AV and/or VV delays.[4] Accordingly, optimization of CRT device settings has been proposed to further improve the clinical and echocardiographic benefits of CRT. However, randomized and non-randomized trials evaluating the effects of AV and/or VV delays optimization on various clinical or echocardiographic outcomes at mid or long-term follow-up have not clearly defined whether CRT optimization provides incremental benefit over empiric device programming.[4-12] Furthermore, there is no consensus on when, how and in which patients CRT optimization should be performed. Consequently, although device optimization was included in the study protocols of several landmark CRT trials,[13-15] no recommendation has been established on the pertinence of AV and/or VV delay optimization in CRT patients. Therefore, the objective of this study was to perform a systematic review and meta-analysis of the effects of AV and VV delay optimization in heart failure patients treated with CRT.

METHODS

Data sources and searches

The present meta-analysis has been developed and reported according to the Prefered Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations' checklist.[16] Randomized and non-randomized controlled trials evaluating the effect of optimization of the AV and/or VV delays on clinical status and/or LV function of heart failure patients treated with CRT were sought. Electronic and manual literature searches were conducted including studies published from January 1, 2004 through

December 1, 2012. First, databases inquiries of MEDLINE (www.nlm.nih.gov/pubmed), EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and U.S. Clinical Trials databases (clinicaltrials.gov) were performed using the key terms "cardiac resynchronization therapy", "biventricular", "optimization", "atrioventricular delay", and "interventricular delay". No limits of language, publication status or date were applied to the present search. References from reviews already published on optimization of CRT were additionally screened. Additional studies were identified by searching abstracts presented at the American Heart Association and American College of Cardiology Scientific Sessions, the European Society of Cardiology congress, at the Heart Rhythm Society, at Europace and Cardiostim).

Study selection

Studies identified by the pre-specified search strategy were independently reviewed by two readers. Inclusion criteria were:

1) randomized and non-randomized controlled trials comparing the clinical and/or echocardiographic outcomes of heart failure patients treated with CRT who underwent AV and/or VV delay optimization performed in resting conditions versus patients who remained with an empiric programming of the device, and
2) with ≥3 months follow-up period after AV and/or VV delay optimization.

No further exclusion criteria were applied.

Abstraction of the data

From each article, the following data were derived: year of publication, study design, number of patients included, baseline demographic characteristics of patients, AV and/or VV delay optimization method and timing, CRT device settings, follow-up durations and definition of response to CRT (improvement in clinical and echocardiographic outcomes at follow-up). For each study, the group of patients who underwent AV and/or VV delay optimization was identified as the optimized group whereas the group of patients in whom the device was programmed empirically formed the control group. Importantly, data obtained from studies which compared more than two groups were treated to generate one optimized group and one control group.[8, 9, 4] Similarly, patients who received CRT but who did not undergo AV and/or VV delay optimization

were considered control group.[2] Moreover, data from patients who underwent AV and/or VV delay optimization by 2 different methods were combined to form one treatment group.[9] Dichotomous clinical and echocardiographic outcomes were recorded for the AV and/or VV delay optimization group and the control group according to the intention-to-treat principle and for available cases analysis. Finally, data from patients who were randomized to LV pacing alone were not included.[10]

Statistical analysis

The primary outcome of the present meta-analysis was the lack of clinical or echocardiographic improvement at follow-up. Clinical improvement was defined as amelioration in either one of the following outcomes: survival or survival free of cardiac transplantation, heart failure hospitalizations, NYHA functional class, QoL, 6MWT, or study-defined combined clinical outcome. Echocardiographic improvement was defined as an absolute increase ≥10% in LVEF. Dichotomous outcome data were consequently pooled and analyzed as odds ratios (OR) with 95% confidence intervals. Fixed effects meta-analyses were performed using the Mantel-Haenszel method. Heterogeneity was assessed by using the I^2 statistic. If heterogeneity was observed ($I^2 \geq 50\%$), random effects meta-analysis using the Mantel-Haenszel method were additionally performed. Both fixed and random effects models were also conducted as a sensitivity analysis. Intention to treat and available cases analysis were also conducted for sensitivity analysis purposes. Data were analyzed using the Comprehensive Meta Analysis™ program (www.meta-analysis.com, access date: March 2011). Review Manager, version 5.1 (Cochrane Collaboration, Copenhagen, Denmark) was used to obtain the forest plots. Two-sided P values <0.05 were considered statistically significant.

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RESULTS

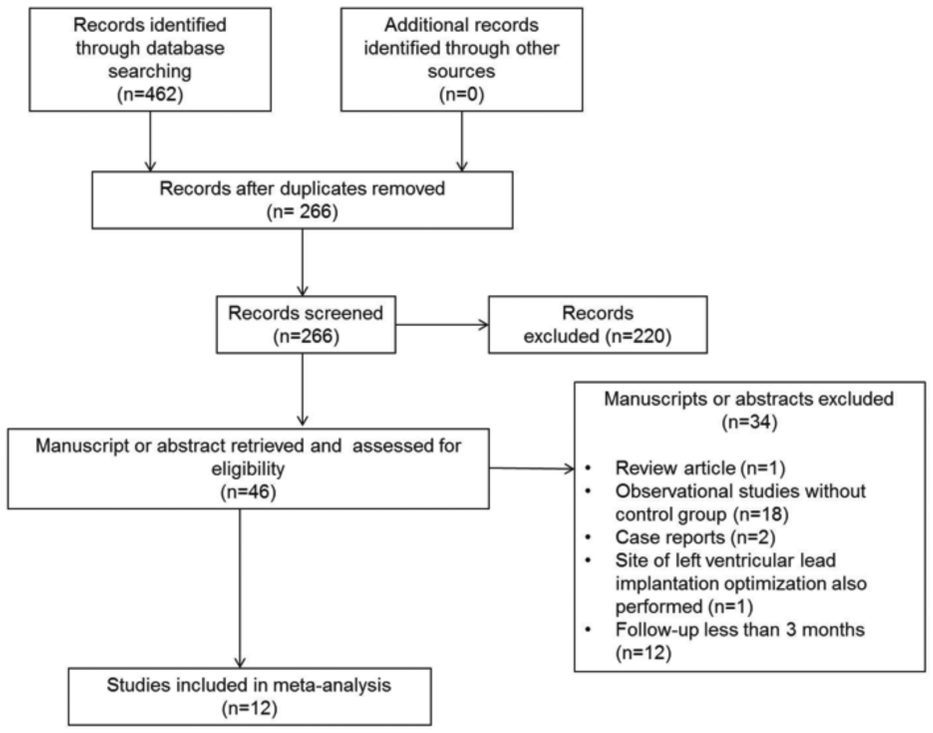
Search results

The results of the search strategy are displayed in ***Figure 1***. A total of 462 records were obtained through database searches. Among the primarily screened references, 196 duplicates were identified and

removed from the selection. Consequently, an additional 220 records were excluded for not fulfilling inclusion criteria based on studies' titles. Subsequently, 46 manuscripts or abstracts were retained for full-text evaluation. After review, 34 manuscripts or abstracts were excluded for not fulfilling the inclusion criteria. In particular, one study was excluded because of concomitant optimization of the implantation site of the LV lead.[17] Accordingly, 12 studies were selected for the final analysis.[5, 7-12, 18-22]

Figure 1. **Search strategy, study inclusion and exclusion flow chart.**

Abbreviations: none



Data from included studies

The studies included in the current meta-analysis comprised 8 randomized trials, 3 prospective cohort studies and one retrospective case-control study. The results of 2 studies were only available in abstract format.[20, 21] However, these records had complete data to be included in the meta-analysis. The data extracted from the selected studies are presented in ***Table 1***. Noticeably, 4 studies reported on the prognostic

impact of AV delay optimization of CRT,[5, 9, 11, 19] 5 studies reported on the effect of VV delay optimization on clinical or echocardiographic outcomes,[7, 8, 10, 12, 20] and 3 studies evaluated the effect of AV and VV delay optimization on clinical or echocardiographic outcome of heart failure patients treated with CRT.[18, 21, 22] In 8 studies, the optimization intervention was performed on one occasion.[5, 7, 10-12, 18-20] Conversely, repeated optimizations were performed in 4 studies.[8, 9, 21, 22] Moreover, AV and VV delay optimization were performed by echocardiography in the majority of studies, whereas other trade-marked algorithms were used in 5 studies.[9, 10, 20-22]

A total of 4,356 patients were included in the final analysis. The mean age and standard deviation (SD) of the participants ranged from 59.8±12.1 years to 73±9.9 years. The mean QRS complex duration ranged from 145±27 ms to 176±22 ms and the mean LVEF ranged from 21.6±6.9% to 28.0±9%. The prevalence of ischemic heart failure varied in the different studies (from 31.0% to 63.3% of patients). Most patients were in NYHA functional class III at the time of AV and/or VV delay optimization. Importantly, the timing of AV and/or VV delay optimization was variable ranging from 1 day to 3 months after CRT implantation. In addition, the RESPONSE-HF trial was conducted exclusively in patients who did not respond to CRT (defined as the lack of improvement in NYHA functional class and ≤10% increase in the 6MWT 3 months after device implantation).[20]

Table1. Data from included studies

	Morales et al. 2006[5]	Sawhney et al. 2004[19]	Response-HF[20]	RHYTHM ICD II[7]
Study design	Prospective cohort	Randomized, single blinded, controlled	Randomized	Randomized, multicenter, single-blind
Number of patients	41	40	65	121
Intervention				
AV/VV delay optimization	AV	AV	VV	VV
Timing	3.4 months (range 2-4 months) after CRT	1 day after CRT	3 months after CRT in non-responders	Before discharge
Optimization method	dP/dt by Doppler echocardiography	Aortic VTI by Doppler echocardiography	Echocardiography or QuickOPT®	Doppler LVOT VTI
Device settings in control group	AV delay=120ms	AV delay=120ms	VV delay=0ms	AV optimized-iterative VV delay=0ms
Follow-up period	6 months (range 5.3-7.1 months)	3 months	9 months	6 months
Patients' characteristics				
Age (years)	69 (53-90)	59.8±12.1	66±12	67.0±8.6
Ischemic cardiomyopathy	31%	45%	59%	63%
NYHA functional class	87% in NYHA III	3.1±0.5	NYHA III	92.6% in NYHA III
QRS duration (ms)	163±4	176±22	145±27	175±22
LVEF (%)	24.8±0.8	25.6±5.4	24.8±0.8	24.2±5.8
Outcome	No ≥1 NYHA functional class improvement	No ≥1 NYHA functional class improvement	No improvement in composite end point (≥1 NYHA functional class improvement and increase ≥10% in 6MWT)	No ≥1 NYHA functional class improvement

Abbreviations: AV=atrio-ventricular; CRT=cardiac resynchronization therapy; HFH=hospitalization for heart failure; NA=not available; NYHA=New York Heart Association; Qol=quality of life; Response-HF=Response of Cardiac Resynchronization Therapy Optimization With Ventricle to Ventricle Timing in Heart Failure Patients; RHYTMH= Resynchronization for the Hemodynamic Treatment of Heart Failure Management; VV=ventriculo-ventricular; 6MWT=6 minute walking test.

Table 1. Data from included studies (continued)

	Vidal et al. 2007[18]	Adlbrecht et al. 2010[11]	DECREASE-HF[10]	Abraham et al. 2012[12]
Study design	Prospective cohort	Retrospective case-control	Randomized, double-blind	Randomized, double-blind
Number of patients	100	205	205	238
Intervention				
AV/VV delay optimization	AV+VV	AV	VV	VV
Timing	3 days after CRT	NA	7 days after CRT	12 days after device implant
Optimization method	AV: iterative followed by VV: TDI best synchrony and best Doppler LVOT VTI	Iterative	AV and VV by Expert Ease® (Boston, Guidant, Indianapolis, IN)	VV: best synchrony based on M-Mode AV: iterative method
Device settings in control group	AV delay=120ms and VV delay=0ms	Initial settings	AV by expert ease, VV delay=0ms	VV delay=0ms, AV: iterative method
Follow-up period	6 months	mean 32 months	6 months	6 months
Patients' characteristics				
Age (years)	70±8	64.2±11.6	66.7±10.6	67.1±10.4
Ischemic cardiomyopathy	47%	47%	63.3%	74.7%
NYHA functional class	3.0±0.6	84% in NYHA III	98% in NYHA III	84.5% NYHA III
QRS duration (ms)	175±26	156±33	167±95	156±22
LVEF (%)	24±1.2	28.0±9	22.7±6.8	23.8±6.7
Outcome	No improvement in composite end point (survival+freedom from heart transplant +≥10% increase in 6MWT)	Death or cardiac hospitalization	Absolute LVEF gain<10%	No improvement in clinical composite heart failure score

Abbreviations: AV=atrio-ventricular; CRT=cardiac resynchronization therapy; DECREASE-HF=Device Evaluation of Contak Renewal 2 and Easytrak 2; NA=not available; LVOT=left ventricle outflow tract; NYHA=New York Heart Association; VTI=velocity-time integral; VV=ventriculo-ventricular; 6MWT=6 minute walking test.

Table 1. Data from included studies (continued)

	CLEAR[22]	In-Sync III[8]	SMART-AV[9]	FREEDOM[21]
Study design	Randomized, multicenter, single-blind	Prospective cohort	Randomized, multicenter, double-blind	Randomized, multicenter
Number of patients	268	397	980	1647
Intervention				
AV/VV delay optimization	AV+VV	VV	AV	AV+VV
Timing	AV: weekly VV: Discharge and at 3 and 6 months	Discharge, 3 and 6 months	1 to 14 days device implant repeated at 3 months in SmartDelay® group	14 days after device implant and every 3 months
Optimization method	SonR® (Sorin Milano, Italy)	AV: Ritter's method followed by VV: Doppler LVOT VTI	SmartDelay® (n=332) Iterative (n=323)	QuickOPT®
Device settings in control group	Standard clinical practice	CRT MIRACLE	AV delay=120ms	Standard clinical practice
Follow-up period	12 months	6 months	5.8±1.6 months	12 months
Patients' characteristics				
Age (years)	73.1±9.9	65.8±10.8	66.1±11.0	66.7±11.2
Ischemic cardiomyopathy	39%	46.2%	57%	NA
NYHA functional class	3.0±0.3	91.6% in NYHA III	95% in NYHA III	93.8% in NYHA III
QRS duration (ms)	160.1±22.0	164±22	154±20	152±27
LVEF (%)	27.1±8.1	21.5±6.9	24.3±6.9	24.3±7.0
Outcome	No improvement in composite end point (survival+freedom HF hospitalization +≥10% increase in quality-of-life +≥1 NYHA functional class improvement)	No ≥1 NYHA functional class improvement	No ≥1 NYHA functional class improvement	No improvement in clinical HF composite score

Abbreviations: AV=atrio-ventricular; CLEAR=Clinical Evaluation of Advanced Resynchronization; CRT=cardiac resynchronization therapy; FREEDOM=Frequent Optimization Study Usingt the QuickOpt Method; HF=heart failure; In-Sync III=Cardiac Resynchronization With Sequential Biventricular Pacing for the Treatment of Moderate-to-Severe Heart Failure; LVOT=left ventricle outflow tract; NA=not available; NYHA=New York Heart Association; SMART-AV=Comparison of AV Optimization Methods Used in Cardiac Resynchronization Therapy; VTI=velocity-time integral; VV=ventriculo-ventricular.

Effect of AV and VV optimization on clinical or echocardiographic outcome

According to the intention-to-treat principle, pooled data from 4,356 patients showed that AV and/or VV delay optimization had a neutral effect on clinical or echocardiographic outcome of patients treated with CRT (Mantel-Haenszel odds ratio=0.96 [95% confidence interval 0.84-1.10], P value for overall effect =0.56, I^2 statistic=54%). Moreover, available cases analysis performed on a total of 3,821 patients confirmed the neutral effect of AV and/or VV delay optimization on clinical or echocardiographic outcome (Mantel-Haenszel odds ratio 0.88 [0.77-1.02], P=0.08, I^2 statistic=54%). Random effect meta-analysis revealed similar results according to the intention-to treat principle (Mantel-Haenszel odds ratio=0.86 [0.68-1.09], P=0.21) and the available cases analysis (Mantel-Haenszel odds ratio=0.82 [0.63-1.06], P=0.13). ***Figures 2 and 3*** show the forest plots of random-effect meta-analysis for the intention-to-treat analysis and for the efficacy subset analysis respectively.

Similar results were observed by separate subgroup analysis including only non-randomized studies (Mantel-Haenszel odds ratio=0.88 [0.67, 1.17], P=0.38) and randomized studies (Mantel-Haenszel odds ratio=0.99 [0.85, 1.14], P=0.85). Subgroup analysis performed with studies reporting on the clinical or echocardiographic outcome after isolated AV delay optimization (Mantel-Haenszel odds ratio= 0.87 [0.74-1.25], P=0.77) (***Figure 4***), isolated VV delay optimization (Mantel-Haenszel odds ratio= 1.01 [0.79-1.29], P=0.94) (***Figure 5***), any AV optimization (isolated AV optimization or combined to VV optimization: Mantel Haenszel odds ration=0.94 [0.81-1.10], P=0.46) (***Figure 6***) and any VV optimization (isolated VV delay optimization or combined to AV delay optimization: Mantel-Haenszel odds ratio=0.96 [0.83-1.12], P=0.62) (***Figure 7***) revealed similar neutral effect.

Figure 2. **Forest plot of the included studies' data collected according to the intention-to-treat principle. The meta-analysis was performed with a random effect model.**

Abbreviations: CI=confidence interval; CLEAR=Clinical Evaluation of Advanced Resynchronization; DECREASE-HF=Device Evaluation of Contak Renewal 2 and Easytrak 2; FREEDOM=Frequent Optimization Study Using the QuickOpt Method; In-Sync III=Cardiac Resynchronization With Sequential Biventricular Pacing for the Treatment of Moderate-to-Severe Heart Failure; M-H=Mantel Haenszel; OPT=optimization; Response-HF=Response of Cardiac Resynchronization Therapy Optimization With Ventricle to Ventricle Timing in Heart Failure Patients; RHYTMH-II= Resynchronization for the Hemodynamic Treatment of Heart Failure Management; SMART-AV=Comparison of AV Optimization Methods Used in Cardiac Resynchronization. Therapy.

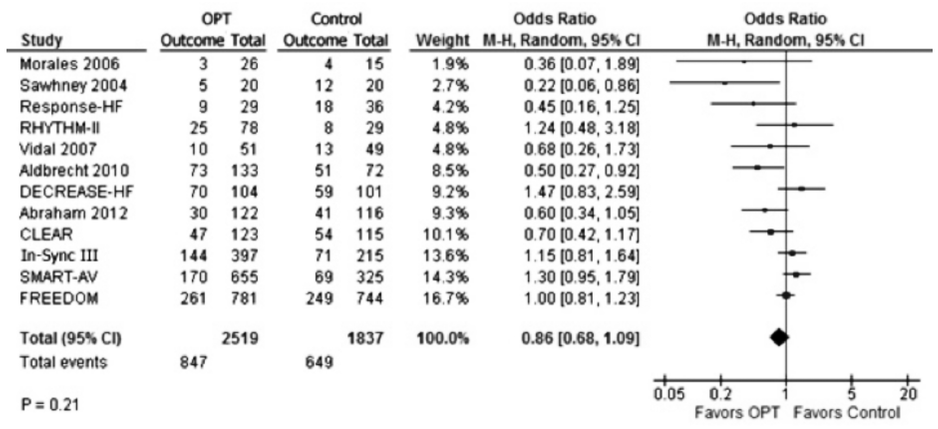


Figure 3. **Forest plot of the included studies' data collected for available cases efficacy subset analysis. The meta-analysis was performed with a random effect model.**

Abbreviations: CI=confidence interval; CLEAR=Clinical Evaluation of Advanced Resynchronization; DECREASE-HF=Device Evaluation of Contak Renewal 2 and Easytrak 2; FREEDOM=Frequent Optimization Study Using the QuickOpt Method; In-Sync III=Cardiac Resynchronization With Sequential Biventricular Pacing for the Treatment of Moderate-to-Severe Heart Failure; M-H=Mantel Haenszel; OPT=optimization; RHYTMH-II= Resynchronization for the Hemodynamic Treatment of Heart Failure Management. SMART-AV=Comparison of AV Optimization Methods Used in Cardiac Resynchronization.

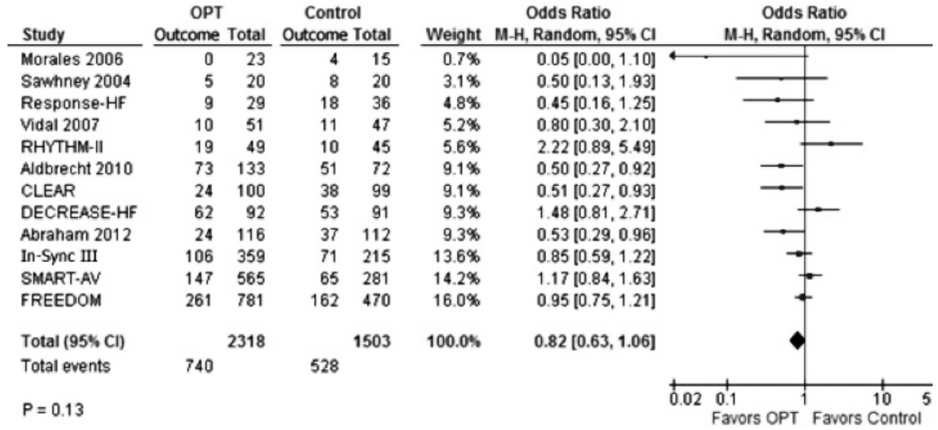


Figure 4. **Forest plot of the isolated AV delay optimization studies' data collected according to the intention-to-treat principle. The meta-analysis was performed with a fixed effect model.**

Abbreviations: CI=confidence interval; M-H=Mantel Haenszel; OPT=optimization; SMART-AV=Comparison of AV Optimization Methods Used in Cardiac Resynchronization.

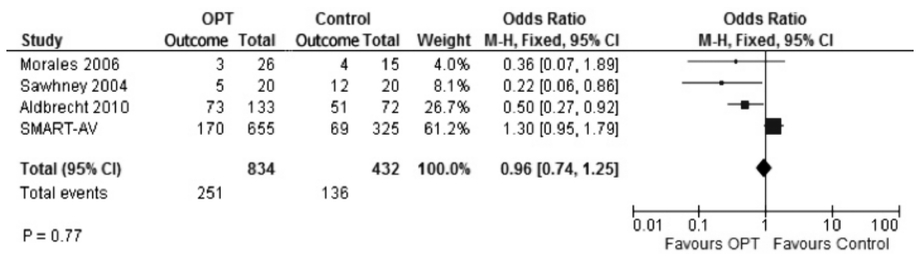


Figure 5. **Forest plot of the isolated VV delay optimization studies' data collected according to the intention-to-treat principle. The meta-analysis was performed with a fixed effect model.**

Abbreviations: CI=confidence interval; DECREASE-HF=Device Evaluation of Contak Renewal 2 and Easytrak 2; In-Sync III=Cardiac Resynchronization With Sequential Biventricular Pacing for the Treatment of Moderate-to-Severe Heart Failure; M-H=Mantel Haenszel; OPT=optimization; Response-HF=Response of Cardiac Resynchronization Therapy Optimization With Ventricle to Ventricle Timing in Heart Failure Patients; RHYTMH-II= Resynchronization for the Hemodynamic Treatment of Heart Failure Management.

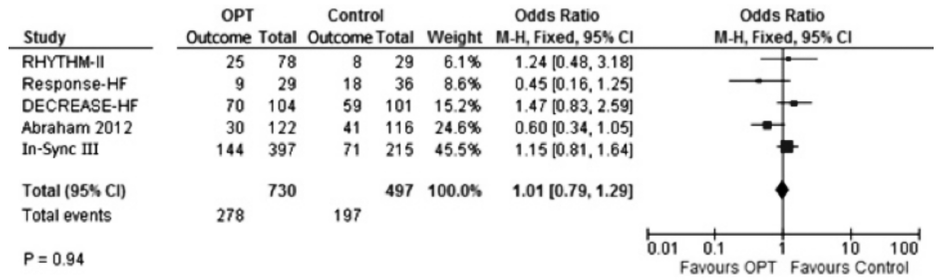


Figure 6. **Forest plot of the optimization studies' data on any AV delay optimization (isolated AV optimization and combined AV and VV delay optimizations) collected according to the intention-to-treat principle. The meta-analysis was performed with a fixed effect model.**

Abbreviations: CI=confidence interval; CLEAR=Clinical Evaluation of Advanced Resynchronization; M-H=Mantel Haenszel; OPT=optimization; FREEDOM=Frequent Optimization Study Using the QuickOpt Method; OPT=optimization; SMART-AV=Comparison of AV Optimization Methods Used in Cardiac Resynchronization.

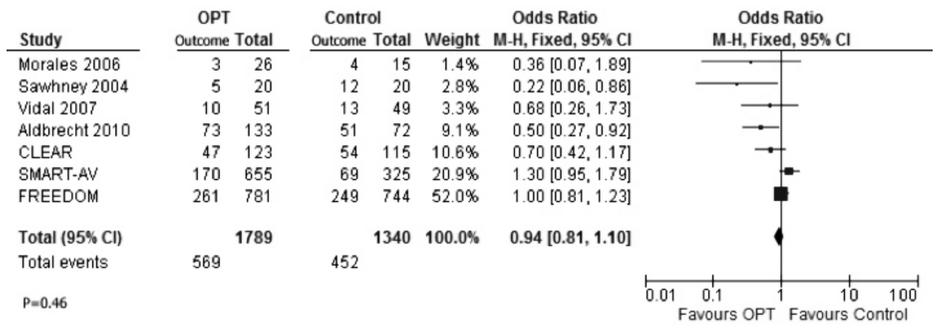
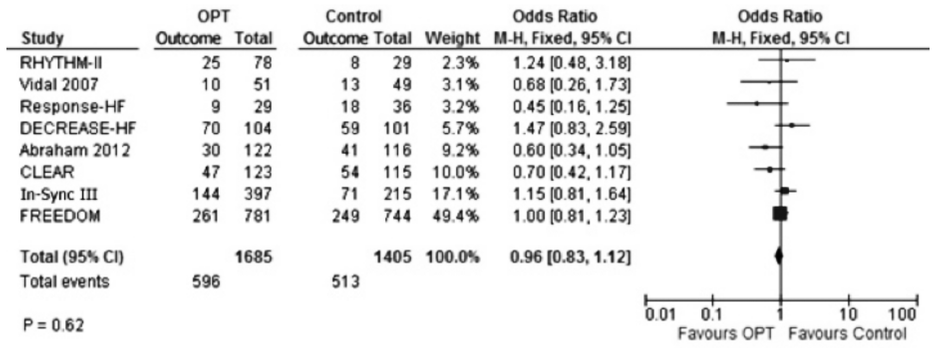


Figure 7. **Forest plot of the optimization studies' data on any VV delay optimization (isolated VV optimization and combined AV and VV delay optimizations) collected according to the intention-to-treat principle. The meta-analysis was performed with a fixed effect model.**

Abbreviations: CI=confidence interval; CLEAR=Clinical Evaluation of Advanced Resynchronization; DECREASE-HF=Device Evaluation of Contak Renewal 2 and Easytrak 2; FREEDOM=Frequent Optimization Study Using the QuickOpt Method; In-Sync III=Cardiac Resynchronization With Sequential Biventricular Pacing for the Treatment of Moderate-to-Severe Heart Failure; M-H=Mantel Haenszel; OPT=optimization; Response-HF=Response of Cardiac Resynchronization Therapy Optimization With Ventricle to Ventricle Timing in Heart Failure Patients; RHYTMH-II=Resynchronization for the Hemodynamic Treatment of Heart Failure Management.



DISCUSSION

The present meta-analysis combining the results from randomized and non-randomized studies does not establish whether routine AV and/or VV delays optimization influences clinical and echocardiographic outcomes in heart failure patients undergoing CRT implantation.

Reasons for non-response to CRT and potential role of device optimization

Clinical and echocardiographic outcomes have been commonly used over the last decade to define response to CRT.[23, 24] According to the definition used, the level of non-response may reach 40% of patients treated with CRT.[23, 24] Among several factors that may contribute to non-response (i.e., extensive myocardial scar tissue or suboptimal LV lead position) inappropriate AV and/or VV delay programming has been shown to play a significant role. Mullens et al. recently conducted a study evaluating the different determinants of non-response to CRT.[25] In their series of 75 heart failure patients treated with CRT who experienced sub-optimal response at least 6 months after CRT implantation, inadequate AV delay was identified in 47% of patients and persistence of LV mechanical dyssynchrony in 16% of

patients.[25] Furthermore, inadequate LV lead location was reported in 21% of patients.[25] Therefore, strategies aiming at reducing the non-response rate may include AV and VV delay and LV lead location optimization to enhance LV performance and improve clinical symptoms.[26]

Effect of AV and/or VV delay optimization on LV performance

AV delay optimization acutely improves LV performance by allowing adequate diastolic filling of the LV and increasing stroke volume.[4] Furthermore, optimization of the AV delay reduces the incidence of diastolic mitral regurgitation, a condition attributable to dyssynchronous AV coupling.[4, 27] Auricchio et al. demonstrated in 39 heart failure patients treated with CRT that maximal hemodynamic benefit is reached at the AV interval that simultaneously provides an optimal LV diastolic filling without decreasing LV preload.[27] Subsequently, several single centre trials have reported on the beneficial effects of AV optimization on LV hemodynamics.[4, 6]

In addition, several prospective studies have demonstrated the benefits of VV delay optimization. Bordachar et al. analyzed the effect of different VV intervals on LV dyssynchrony (assessed by tissue Doppler imaging) and LV performance in 41 heart failure patients treated with CRT.[28] Synchronous LV contraction, maximized cardiac output, and significant reduction of mitral regurgitation were observed after VV interval optimization.[28]

However, these beneficial acute effects of AV and VV delay optimization have not been consistently found in subsequent larger randomized and non-randomized trials. As demonstrated in the present meta-analysis, AV and/or VV delay optimization do not seem to provide a clear incremental clinical or echocardiographic benefit over empirical device programming.

Effect of AV/VV delay optimization on clinical and echocardiographic outcomes

The neutral effect of CRT optimization observed in the current meta-analysis may have resulted from significant heterogeneity between the included studies as indicated by the I^2 statistic value (I^2 statistics 56% and 64% for the intention-to-treat analysis and for the efficacy subset analysis respectively).[29] Various sources of statistical and clinical heterogeneity can be identified in the present meta-analysis. First, AV and/or VV delay optimization were mainly performed in an unselected population of patients treated with CRT. Only one study evaluated specifically the effect of AV and VV delay optimization in non-responder patients (the RESPONSE-HF trial).[20] In this study, 65 patients who did not show response to CRT at 3 months of follow-up (i.e., absence of improvement in NYHA functional class or increase <10% in 6MWT) were randomized to VV delay optimization with echocardiography or a device-based algorithm (QuickOpt®, St. Jude Medical, Sylmar, CA, USA).[20] At follow-up, VV delay optimization showed a trend towards improved composite clinical end point (≥1 NYHA functional class improvement and increase ≥10% in 6MWT) as compared to the non-optimization strategy (Mantel-Haenszel odds ratio 2.22 [0.80-6.18]). Consequently, further studies evaluating the impact of device optimization on larger populations of non-responders to CRT are warranted.

In addition, AV and VV delay optimizations algorithms were not consistent throughout the studies. Indeed, the present meta-analysis included studies in which CRT optimization was either performed by echocardiography or device-based algorithms. To date, the reference methodology to optimize AV and/or VV delays has not been established. Whereas AV and/or VV delay optimization guided by echocardiography may be more time consuming and requires a certain local expertise, device-based or ECG-guided optimizations may be more accessible. The various echocardiographic methods to optimize CRT may also have discordant feasibility and inter- and intra-observer variability. For example, Thomas et al. observed that the measurement of the LVOT VTI with pulsed wave Doppler echocardiography performed best (feasibility >90% and coefficient of variation <20%) when compared to other LV performance indices (interventricular mechanical delay, LV dyssynchrony, diastolic filling…).[30] Interestingly, some data show that echocardiographic and ECG or device-based algorithm may be equivalent in identifying the ideal AV and/or VV delay in CRT patients. In a series including 106 patients treated with CRT, Bertini et al. showed a good agreement between ECG and pulsed wave Doppler echocardiography of the LVOT to optimize the VV delay.[31] The SMART-AV study also evaluated the comparative effect of AV optimization by the echocardiographic iterative method and a device-based algorithm, the SmartDelay® trade-marked method (Boston Scientific, Natick, MA, USA).[9] Notably, this study did not demonstrate any superiority of device based algorithms or echocardiographic method of AV optimization over a fixed AV delay of 120ms (OR 1.3 [0.95-1.79]).[9] Consequently, whether the optimization method could further influence patients' outcome after the adjustments of AV or VV delays remains presently unclear.

Limitations

A number of limitations can be identified in the present meta-analysis. First, the present work includes data from unpublished studies derived from cardiology conferences abstracts.[20, 21] Secondly, significant heterogeneity exists between the different studies.[29] Whereas some of the studies performed AV and/or VV optimization using echocardiography,[5, 7, 8, 11, 18, 19] some studies used device built-in algorithms.[9, 10, 21, 22] Furthermore, repeated optimizations were performed in 4 studies, [8, 9, 20, 22] whereas optimization was performed only once in 7 studies. [5, 7, 10, 11, 18-20] The baseline characteristics of the studied populations differed across the studies. While the majority of the studies was performed in an unselected population of CRT patients, one study specifically included patients that were non-responders to CRT after 6 months of treatment.[20] Finally, heterogeneous outcomes have been studied. Whereas some of the studies aimed at a single clinical outcome,[5, 7-9, 19] some studies have used a combined clinical outcome,[11, 12, 18, 20-22] or an echocardiographic outcome.[10] These discrepancies in the trial designs may explain the statistical heterogeneity observed in the present meta-analysis. However, the results of the present meta-analysis provide a complete and objective evaluation of the current literature on AV and VV delay optimization. Thus, the present findings may guide the elaboration of future trials.

CONCLUSION

The current literature suggests that routine AV and/or VV delays optimization has a neutral effect on clinical and echocardiographic outcomes based on pooled data from randomized and non-randomized studies. The heterogeneous populations and optimization methodologies of the included studies preclude strong recommendations on AV and/or VV delays optimization in patients treated with CRT. The results observed in studies performing routine CRT device setting optimization may be applicable to patients with suboptimal response to CRT and vice versa. Standardization of patient selection and optimization timing and method may help to further define the role of CRT device optimization.

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