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Cardiac Resynchronization Therapy

State of the Art Review For the 25th Anniversary of Cardiac Resynchronization Therapy

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Patients with heart failure (HF) have a significant morbidity and mortality that competes with those of many cancers. In HF patients with a severely depressed left ventricular function, and a wide QRS reflecting left ventricular dyssynchrony, cardiac resynchronization therapy (CRT) has been shown to improve functional capacity, HF symptoms, and quality of life. Since the first case reports were published in 1994, there have been a large number of randomized controlled clinical trials conducted that have proven the efficacy of CRT in diverse HF populations showing a significant reduction in HF hospitalization and improved survival. CRT has, over the past 25 years, become a guideline-indicated, evidence-based device therapy for mild and advanced HF patients with severely reduced left ventricular function, and a wide QRS. Nevertheless, there are a number of factors negating beneficial response to CRT, and multiple unresolved questions to this day. This review article summarizes current available knowledge on CRT in HF patients from randomized clinical trials and other relevant studies, discusses important determinants of CRT response, and provides a selected overview of unresolved questions with future directions for research.

Keywords: Cardiac Resynchronization Therapy, Left Ventricular Dyssycnhrony, Clinical Outcomes, Clinical Trials, Future Directions

Mechanism of Cardiac Resynchronization Therapy in the Failing Heart

Patients with HF often present with an electrical conduction delay, resulting in dyssynchronous left ventricular activation, impaired left ventricular systolic function, mitral regurgitation, and a significantly reduced cardiac output (1). An electrical conduction delay is manifested either as a left bundle branch block (LBBB), right bundle branch block (RBBB), or as an intraventricular conduction delay (IVCD). Electrical activation of the ventricles in patients with LBBB and RBBB has been previously described by Fantoni et al. (2). Patients with LBBB typically have multiple right ventricular (RV) breakthrough sites in the septum as compared to RBBB with a single RV breakthrough site. Transseptal activation time, activation time of the RV, and total activation time is significantly longer in RBBB as compared to LBBB. In patients with LBBB or RBBB, there is a slow left ventricular (LV) electrical activation from the septal or anterior breakthrough sites to the apical and lateral regions. Most typically, the postero-lateral basal region is the latest activated LV area in both LBBB and RBBB, providing the rationale for biventricular pacing with an LV lateral, posterolateral lead in this population. Although patients with RBBB exhibit a more advanced conduction tissue disease than LBBB that is often less amenable to CRT.

Cardiac resynchronization therapy (CRT) or biventricular pacing is delivered using a 3-lead pacing/defibrilla-

tor system that delivers electrical stimuli to the right atrium, right ventricle, and left ventricle to synchronize the dyssynchronous LV activation in patients with conduction tissue disease and a severely reduced LV function. CRT was developed to restore the physiological atrial and ventricular contraction in the failing heart and correct atrioventricular dyssynchrony, as well as interventricular dyssynchrony and intraventricular dyssynchrony. Atrioventricular dyssynchrony, or PR-prolongation is often observed in HF patients linked to worse clinical outcomes (3). The pathophysiology of a prolonged-PR interval is primarily based on the atrial systole (A) occurring early in diastole and therefore, it is superimposed on the early left ventricular filling phase (E), subsequently leading to the fusion of the diastolic E and A waves, shortening effective diastolic LV filling time, and decreasing cardiac output. The early atrial systole uncouples the mitral valve closure from LV systole resulting in diastolic pre-systolic mitral regurgitation, decreased preload, and decreased forward stroke volume, further worsening LV function. Following CRT implantation, normalization of the PR-interval restores the physiologic AV-sequence, eliminating the pathologic E and A fusion, and diastolic pre-systolic mitral regurgitation. Restoration of interventricular and intraventricular dyssynchrony via synchronized left ventricular (LV) and right ventricular (RV) pacing, or most often, LV pre-excitation additionally results in an immediate decrease of intra- and interventricular dyssynchrony, a decrease in mitral regurgitation, and an increase in LV contractility (4). Long-term CRT use is linked to a reduction in LV end-diastolic (LVEDV) and LV end-systolic volume (LVESV), and improvement in LV ejection fraction (LVEF), described as LV reverse remodeling (5, 6) *(Figure 1)*. Eliminating LV dyssynchrony, reducing LV volumes, and increasing LVEF is the hallmark of cardiac resynchronziation therapy that is associated with beneficial clinical outcomes (7) *(Figure 2)*.

Randomized Clinical Trials in Cardiac Resynchronization Therapy

There have been a large number of randomized controlled clinical trials to ascertain the safety and efficacy of CRT or CRT-D to improve quality of life, HF symptoms, functional capacity, and clinical outcomes. These studies are summarized below in *Table 1*. As it has been evidenced in the early studies enrolling 50-100 patients, implantation of CRT resulted in a significant improvement in HF symptoms, functional capacity, and quality of life in HF patients with advanced HF symptoms (NYHA class III-IV), reduced LVEF≤35% and a prolonged QRS duration (QRS≥120 ms) (8–10). The first double-blind randomized controlled comparison of CRT was conducted in the MIRACLE trial, enrolling 453 patients, confirming in a larger cohort of HF patients that CRT improves New York Heart Association (NYHA) class, quality of life, 6 minute walk test, and also reduces left ventricular volumes, and improves left ventricular ejection fraction, coupled with improvements in clinical symptoms.
Subsequent well-designed, randomized, controlled large clinical trials, Cardiac Resynchronization-Heart Failure (CARE-HF), and Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) have shown, for the first time, that CRT also improves survival in patients with advanced HF symptoms (NYHA

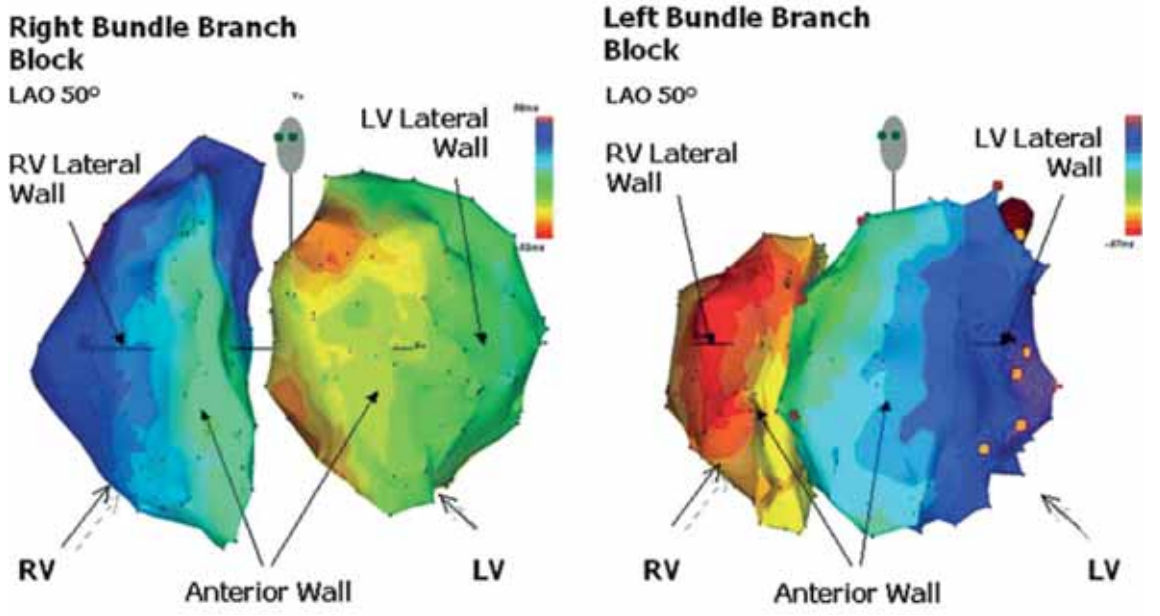

FIGURE 1. Electrical activation of the left and right ventricle in patients with right bundle branch block and left bundle branch block (2)

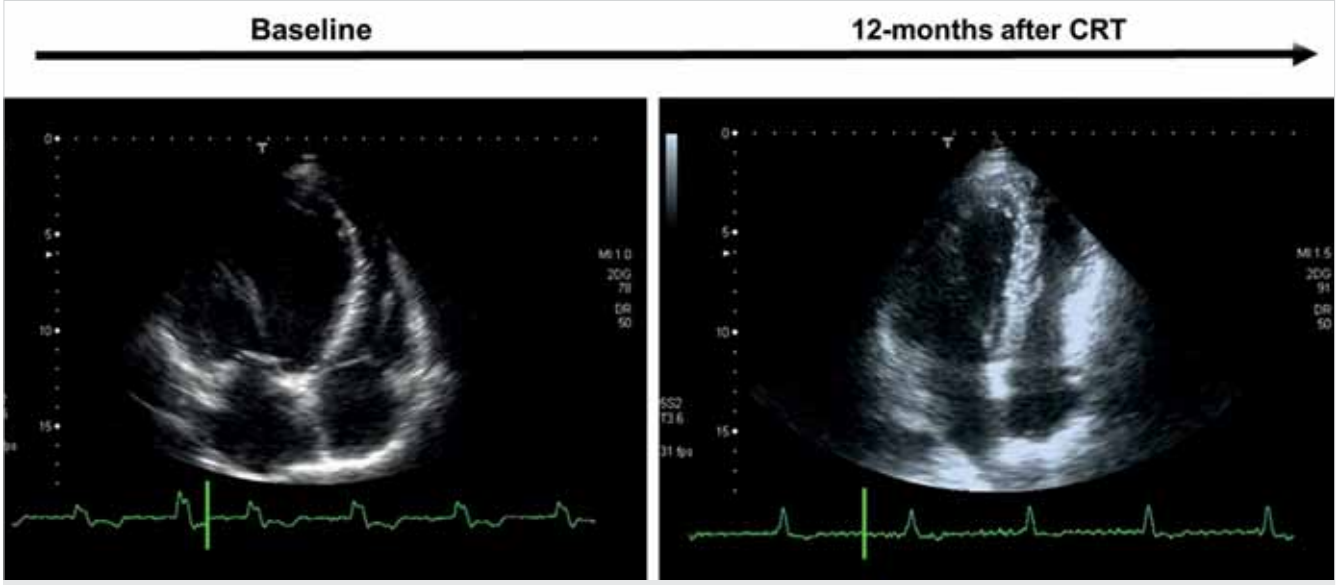

FIGURE 2. Electrical activation of the left and right ventricle in patients with right bundle branch block and left bundle branch block (2)

class III-IV), reduced LVEF≤35% and a prolonged QRS duration (QRS≥120 ms) (9, 10). Altogether, these studies provided the basis for current guideline-based indications for CRT in advanced HF patients with NYHA Class III or IV (11). Today, tens of thousands of advanced HF patients are implanted with CRT in Hungary, in Europe, and worldwide (12). A meta-analysis of CRT trials in advanced HF showed an overall 29% risk reduction in all-cause mortality, and a 38% risk reduction in mortality due to progressive HF (13).

Following the success of CRT in advanced HF patients, subsequent clinical trials focused on broadening the indication of CRT to patients with mild HF. The Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT), the Resynchronization-Defibrillation in Ambulatory Heart Failure Trial (RAFT) and Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trials enrolled patients primarily with mild HF, presenting with NYHA class I and II HF symptoms (14, 15). These studies have shown a significant reduction in HF events and improvement in clinical symptoms, as well as significant LV reverse remodeling. The subsequently published long-term follow-up of MADIT-CRT, and REVERSE studies confirmed sustained benefit of CRT in mild HF patients up to 5 years with reduction in HF events and a significant reduction in mortality (16, 17).

Modifying Factors of Response to Cardiac Resynchronization Therapy

Despite the overall beneficial effects of cardiac resynchronization therapy shown in numerous large clinical trials, nearly one third of the patients demonstrate a lack of echocardiographic or clinical response to CRT, they are so-called non-responders. Non-response has been the major focus of CRT research the past 25 years to optimize use, delivery, and care of CRT patients to optimize outcomes. Non-response to CRT is multifactorial, including baseline clinical charcteristics linked to unfavorable outcomes through CRT delivery, and post-implant factors, such as arrhythmias and CRT programming.

Baseline Clinical Characteristics

There have been a number of clinical factors associated with poor clinical response to CRT including diabetes, renal dysfunction, and ischemic cardiomyopathy (18). On the contrary, a superior response to CRT is predicted by female sex, non-ischemic etiology of cardiomyopathy, left bundle branch block, wide QRS, and a less dilated left ventricle (19). The amount of scar has been shown to negatively correlate with outcomes in patients with CRT and warrant further investigation. It is plausible that advanced scar formation might not be amenable to CRT and on the contrary, might be arrhythmogenic, especially if LV pacing occurs near a scar region as shown by previous studies. Important gender differences in CRT outcomes might be linked to the fact that women often present with non-ischemic cardiomyopathy and LBBB, a substrate that is the most responsive to biventricular pacing (20).

QRS morphology and QRS duration

Although CRT has been shown to be beneficial in HF patients with a low LVEF and a wide QRS, several early studies noted differences in response by QRS duration, and by the underlying ECG pattern at baseline, befo-

TABLE 1. Randomized Past and *Ongoing Controlled Trials of Cardiac Resynchronization Therapy. Abbreviations: 6MWT, 6-min walk test; CARE-HF, Cardiac Resynchronization-Heart Failure; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; HF, heart failure; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MADITCRT, Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MIRACLE ICD, Multicenter InSync Implantable Cardioverter Defibrillator trial; MR, mitral regurgitation; MUSTIC, Multisite Simulation in Cardiomyopathies; NYHA, New York Heart Association; PATH-CHF, Pacing Therapies in Congestive Heart Failure trial; QOL, quality-of-life score; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction; VO_2, volume of oxygen

Clinical Trial	Patients (n)	Primary end points	Secondary end points	LVEF (%)	QRS (ms)
MUSTIC-SR	58	6MWT	NYHA, QOL, Peak VO_2, MR, LV, Hosp, Mortality	23±7	174
MUSTIC-AF	64	6MWT	NYHA, QOL, Peak VO_2, Hosp, Mortality	26±0	206
PATH-CHF 2	41	6MWT, peak VO2	NHYA class, QOL, Hospitalizations	21±7	175
PATH-CHF-II: (Europe)	86	6MWT, peak VO2	NHYA class, QOL, Hospitalizations	21±7	175
MIRACLE	453	6MWT, NHYA, QOL	Peak VO2, LVEF, LVEDD, MR, Clin Response	22±6	166
COMPANION	1520	All-cause mortality or hospitalization	All-cause mortality and cardiac mortality	21	159
CARE-HF	814	All-cause mortality	NYHA, QOL, LVEF, LVESV, Hospitalization for heart failure	25	160
REVERSE	610	HF clinical composite score	LVESVi	27±7	153
MADIT-CRT	1820	HF or death	LVESV, LVEDV change, multiple HF events	24±5	162
RAFT	1798	All-cause mortality or HF hospitalization	All-cause mortality, cardiac mortality, HF hospitalization	23±5	158
RAFT AF*	412	HF hospitalization or death	Mortality, HF hosp, QoL, 6MWT,	n.a.	n.a.
BUDAPEST CRT Upgrade*	360	HF hospitalization, death, or lack of LV remodeling	Mortality, HF hospitalization	n.a.	n.a.

re CRT implantation. The first large randomized trials designed to evaluate the effect of CRT on all-cause mortality, Cardiac Resynchronization-Heart Failure (CARE-HF), and Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION), enrolled only 6% and 29% of their patients with non-LBBB, respectively. The REVERSE study enrolled 38% of patients with non-LBBB, and MADIT-CRT enrolled 30% (21), allowing us with an opportunity to analyze response by QRS morphology.

Patients with a LBBB ECG pattern before device implantation have been suggested to derive a significant benefit from CRT-D, while those with non-LBBB ECG pattern were shown to derive less or no benefit, and our sub-study from MADIT-CRT suggested potential harm (22). Subsequent studies confirmed an association between QRS duration and outcomes in the REVERSE trial (23). A sub-analysis from the RAFT trial confirmed a link between QRS morphology, QRS duration and outcomes in LBBB, and no benefit in non-LBBB patients (24), similarly to a large U.S. nationwide registry, the National Cardiovascular Database Registry (NCDR) ICD Registry (25). Based on these observations, CRT today is a Class I or Class IIa indication for CRT in symptomatic HF patients with LBBB ≥120 ms with a Class I indication for those with a QRS ≥150 ms. For patients with non-LBBB, CRT is a Class IIa indication for a QRS duration ≥150 ms, and a Class IIb indication for a QRS duration of 120 to 149 ms (26).

The previously conducted and published ECHO-CRT (27) and RethinQ (28) studies assessed CRT indication for HF patients with a narrow QRS complex <120 ms but failed to demonstrate a benefit. Therefore, CRT is currently not indicated for patients with a narrow QRS complex, unless they require frequent ventricular pacing (>40%) to treat bradycardia, an indication tested in the BLOCK-HF study (29).

Prolonged PR-interval

A prolonged PR-interval may result in atrioventricular dyssynchrony, with altered transmitral left ventricular filling and possible serious adverse clinical consequences as discussed above (3), and it could potentialy-ly be another important determinant of CRT response. We have previously shown in a sub-study of the MADIT-CRT trial that HF patients with non-LBBB ECG

pattern and a prolonged PR-interval ≥230 ms derive a significant clinical benefit from CRT-D as compared to ICD (30), with a 73% risk reduction in HF or death, and an 81% risk reduction in all-cause mortality. Non-LBBB patients with a normal PR-interval <230 ms were however exposed to a harm from CRT-D with a more than two-fold increase in mortality when compared to ICD-only (interaction p-value<0.001) (30). We subsequently confirmed in the MADIT-CRT long-term follow-up sub-study suggesting a sustained clinical benefit during a median follow-up of 5.6 years (31). A prior study showed similar associations from COMPANION with a prolonged PR-interval in more advanced HF patients (32), and in those with a narrow QRS enrolled in RethinQ (33). However, more recent studies challenged these findings using data from the NCDR ICD Registry, however, this cohort lacked randomization (34). Further studies are needed in this cohort.

Controversies in CRT and Future Directions

Frequent Right Ventricular Pacing and CRT

The underlying concept for the benefit of physiologic, AV-sequential pacing in HF patients with a prolonged PR-interval is well known. Previously reported case series on right ventricular (RV) DDD pacing with shorter AV-delay in HF patients and low ejection fraction in the 1990's reported an improvement in HF symptoms (35). It has been previously shown that frequent apical right ventricular pacing has deleterious effects (36, 37), especially in patients with a depressed left ventricular duntion. In this population, upgrading the pacing or ICD device to CRT could potentially improve outcomes. There have been a few retrospective studies evaluating the effects of CRT upgrade in patients with frequent RV apical pacing showing improvements in reverse remodeling, and functional capacity, however, none of these studies were randomized or had an appropriate control group (38). A large, randomized controlled clinical trial, the BUDAPEST CRT Upgrade study is currently ongoing to prospectively evaluate the effects of CRT upgrade from conventional PM or ICD therapy in patients with intermittent or permanent right ventricular (RV) septal/apical pacing, reduced LVEF, and symptomatic HF. This prospective, randomized, multicentre, investigator-sponsored clinical trial will enroll a total of 360 subjects with LVEF ≤35%, NYHA functional class II-IVa, paced QRS ≥150 ms, and RV pacing ≥20%. Patients will be randomized to CRT-D vs. ICD in a 3:2 ratio and they will be followed for 12 months. The primary composite endpoint is all-cause mortality, or a HF event, or less than 15% reduction in LV end-systolic volume at 12 months *(Table 2).* Secondary endpoints are all-cause mortality, all-cause mortality or HF event, and LV volume reduction at 12 months (https://clinicaltrials.gov/ct2/show/NCT02270840).

Use of CRT-Defibrillator vs. CRT-Pacemaker

It has been a long debate whether CRT with a defibrillator (CRT-D) is superior to CRT with a pacemaker (CRT-P) and whom should be implanted with a CRT-D vs. a CRT-P device. There have been no studies directly comparing the benefit of CRT-D to CRT-P in unselected patients in a randomized fashion. Patients with non-ischemic cardiomyopathy, those with LBBB, women, are at a significantly lower risk of ventricular arrhythmias and derive significant LV reverse remodeling from CRT, all negating the potential need and benefit of an added defibrillator (39). In addition, defibrillator leads are associated with a higher risk of complications, lead fractures, and infections. Currently, CRT-P use is common in Europe due to the financial constraints of many countries (40). Our very own, single-center, high volume registry data additionally suggested that selected non-ischemic patients who were more often women, and older, did not have an improved survival with CRT-D as compared to CRT-P (41). Further studies are currently underway to prospectively evaluate outcomes of CRT-D vs. CRT-P in a randomized fashion in both ischemic and non-ischemic patients.

Left Ventricular Lead Location and CRT Programming

Several previous studies highlighted the importance of LV lead location for CRT outcomes. Early studies suggested that lateral or posterolateral LV lead location is associated with better outcomes while studies from MADIT-CRT and REVERSE highlighted the importance of avoiding apical LV lead locations to reduce the risk of HF or death (42). A subsequent analysis also suggested that anterior LV lead placement is linked to an increased risk of ventricular arrhythmias and should be avoided (43). Several attempts have been made to individually optimize LV lead placement and target the latest activated area identified by imaging studies (44, 45) however, despite initial promising findings none of these techniques are currently employed in routine clinical practice. A recent study focusing on CRT non-responder non-LBBB patients to optimize lead placement using LV electrical delay measured by Q-LV, also failed to meet its primary end point (https://clinicaltrials.gov/ct2/show/NCT01983293). Newer technical advancements, such as quadripolar LV leads with multipoint pacing, and individually optimized pacing sequences are currently studied to further improve outcomes of CRT non-responders.

Optimal CRT programming is a cornerstone of beneficial CRT outcomes, with several studies suggesting that the higher the biventricular pacing percentage is, the better the outcomes. Ruwald et al. (46) showed that >97% of biventricular pacing was linked with improved survival in MADIT-CRT. Prior studies assessing optimal CRT programming and outcomes using echocardiography optimization vs. "out of the box" device settings

vs. dynamic optimization techniques have been however unsuccessful in de novo CRT recipients (47–49), but showed some benefits in CRT non-responders (50).

Atrial Fibrillation

HF patients with atrial fibrillation have been shown to have adverse outcomes with an implanted CRT. In CRT recipients, lack of biventricular pacing and abrogation of the remodeling process are of particular concern. Many randomized clinical trials also excluded patients with persistent/permanent atrial fibrillation, significantly limiting our understanding of CRT outcomes in this cohort. A currently ongoing randomized clinical trial, RAFT-AF (https://clinicaltrials.gov/ct2/show/NCT01420393) is evaluating the role of catheter ablation with PV antral isolation and LA substrate ablation vs. rate control in CRT recipients, hopefully shedding more lights on treatment outcomes in this difficult to treat patient population.
Another prospective, randomized clinical trial of 80 patients, JAVA-CRT is assessing the role of AV-junctional ablation in CRT patients with high burden of atrial fibrillation to improve outcomes (https://clinicaltrials.gov/ct2/show/NCT02946853).

Conclusions

Cardiac resynchronization therapy has evolved as a mainstream therapy for heart failure in patients with mild to advanced heart failure symptoms, severely depressed left ventricular ejection fraction, and a wide QRS. Short- and long-term outcomes have been favorable, nevertheless influences by various clinical characteristics, and comorbidities. Tailored LV lead implantation or CRT programming does not further improve outcomes however further studies are currently underway. The utility of CRT upgrade in patients with chronic RV apical/septal pacing, rhythm control/AV junctional ablation in patients with atrial fibrillation, and the appropriate use of CRT-D vs. CRT-P are currently unresolved issues that need further investigation to optimize outcomes.

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