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著者	Birnie David, Hudnall Harrison, Lemke Bernd, Aonuma Kazutaka, Lee Kathy Lai-Fun, Gasparini Maurizio, Gorcsan John, Cerkenik Jeffrey, Martin David O.
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Continuous optimization of cardiac resynchronization therapy reduces atrial fibrillation in heart failure patients: Results of the Adaptive Cardiac Resynchronization Therapy Trial



David Birnie, MD, MB, ChB,* Harrison Hudnall, BS,[†] Bernd Lemke, MD,[‡] Kazutaka Aonuma, MD, PhD,[§] Kathy Lai-Fun Lee, MBBS,[¶] Maurizio Gasparini, MD,^{||} John Gorcsan III, MD,[#] Jeffrey Cerkevnik, MS,[†] David O. Martin, MD, MPH**

From the *University of Ottawa Heart Institute, Ottawa, Canada, [†]Medtronic, Mounds View, Minnesota, [‡]Lüdenscheid Clinic, Lüdenscheid, Germany, [§]Tsukuba University Hospital, Tsukuba, Japan, [¶]University of Hong Kong, Hong Kong, China, ^{||}Istituto Clinico Humanitas Mirasole–Humanitas Research Hospital, Rozzano, Italy, [#]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, and **Cleveland Clinic Foundation, Cleveland, Ohio.

BACKGROUND Data from randomized trials have suggested a modest or no effect of conventional cardiac resynchronization therapy (convCRT) on the incidence of atrial fibrillation (AF). AdaptivCRT (aCRT, Medtronic, Mounds View, MN) is a recently described algorithm for synchronized left ventricular (LV) pacing and continuous optimization of cardiac resynchronization therapy (CRT).

OBJECTIVE We compared the long-term effects of aCRT with convCRT pacing on the incidence of AF.

METHODS The Adaptive CRT trial randomized CRT-defibrillator (CRT-D)-indicated patients (2:1) to receive either aCRT or convCRT pacing. The aCRT algorithm evaluates intrinsic conduction every minute, providing LV-only pacing during normal atrioventricular (AV) conduction and AV and ventriculoventricular timing adjustments during prolonged AV conduction. The primary outcome of this subanalysis was an episode of AF >48 consecutive hours as detected by device diagnostics.

RESULTS Over a follow-up period with a mean and standard deviation of 20.2 ± 5.9 months, 8.7% of patients with aCRT and 16.2% with convCRT experienced the primary outcome (hazard ratio [HR] = 0.54; 95% confidence interval [CI] = 0.31–0.93;

$P = .03$). In patients with prolonged baseline AV, the incidence of the primary outcome was 12.8% in patients randomized to aCRT compared with 27.4% in convCRT patients (HR = 0.45; 95% CI = 0.24–0.85; $P = .01$). Also, patients with AF episodes adjudicated as clinical adverse events were less common with aCRT (4.3%) than with convCRT (12.7%) (HR = 0.39; 95% CI = 0.19–0.79; $P = .01$).

CONCLUSION Patients receiving aCRT had a reduced risk of AF compared with those receiving convCRT. Most of the reduction in AF occurred in subgroups with prolonged AV conduction at baseline and with significant left atrial reverse remodeling.

KEYWORDS Atrial fibrillation; AV conduction; Cardiac resynchronization therapy; Clinical outcome; Heart failure; LV pacing

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Introduction

Atrial fibrillation (AF) is a common comorbidity among heart failure (HF) patients and is associated with an increased risk of hospitalization, stroke, and death.^{1–4} The prevalence of AF reported in recent HF studies and registries ranges from 10% to 15% in mild-to-moderate chronic HF and up to approximately 50% in patients with severe HF.^{5–7} According to the Framingham Heart study, 20% of HF patients develop AF within 4 years.⁵

In numerous trials, cardiac resynchronization therapy (CRT) consistently improved quality of life, reduced HF hospitalizations, and reduced risk of death.^{8–10} However, the

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effect of CRT on AF is less clear. Many observational studies have suggested that CRT reduces the risk of AF.^{11–16} Yet, data from 3 large clinical trials have shown conflicting results; 1 study found no benefit,¹⁷ another found benefit only in patients with significant left atrial (LA) remodeling,¹⁸ and a third found a trend toward an increased incidence of AF.¹⁹

The AdaptiveCRT algorithm (aCRT, Medtronic, Mounds View, MN) was designed to continually adjust CRT to the patient's intrinsic atrioventricular (AV) conduction. The algorithm adjusts AV and interventricular pacing intervals and withholds right ventricular (RV) pacing when normal AV conduction exists—fusing the left ventricular (LV) stimulation to intrinsic conduction. During periods of prolonged AV conduction, the algorithm continuously optimizes AV and ventriculoventricular (VV) intervals. The algorithm is noninferior to conventional CRT (convCRT) pacing and may increase responder rates and improve clinical outcomes.^{20–22}

RV pacing has been shown to increase the risk of AF in patients with sinus node dysfunction.^{23–25} As aCRT significantly reduces RV pacing, we hypothesized that the incidence of AF would be reduced with the algorithm. This study examines the long-term effects of aCRT on the incidence of AF using data from the Adaptive CRT trial.

Methods

The aCRT algorithm

The aCRT algorithm aims to provide fusion pacing by evaluating intrinsic conduction every minute. During normal AV conduction (≤ 200 ms), synchronized LV-only pacing is provided by preempting the atrial to RV sense interval by ≥ 40 ms. During prolonged AV conduction (> 200 ms), aCRT pacing is provided with adjustment to the AV and VV timing based on intervals of atrial to RV sense, atrial to P-wave end, and RV sense to QRS end.^{26,27}

The Adaptive CRT trial

The trial design and primary results of the Adaptive CRT trial have been previously published, and the protocol was approved by the ethics committee at each participating institution and associated national and local regulatory agencies.^{22,26} The Adaptive CRT was a noninferiority study to test the performance of aCRT vs convCRT. Patients implanted with CRT with defibrillation therapy (CRT-D) for clinical indications of New York Heart Association functional class III or IV HF symptoms, LV ejection fraction $\leq 35\%$, and QRS duration ≥ 120 ms were randomized in a 2:1 ratio to receive aCRT or echo-optimized convCRT pacing. Patients and clinicians were both blinded to the assigned treatment. Primary objectives were met, demonstrating the algorithm's safety and effectiveness of improving the patient clinical composite mean score by 6 months at a rate similar to that of the control arm.

AF substudy

Atrial arrhythmia information was extracted from the device diagnostics report for all patients at each study visit. Contin-

uous data were available from randomization through to the end of the follow-up period. As a post hoc analysis, the primary outcome was defined as time to ≥ 2 consecutive days of ≥ 23 hours of device-detected AF (ie, > 48 consecutive hours of AF). This outcome was chosen because of its relationship with thromboembolic risk.²⁸

Additional outcomes and analyses

To explore the relationship between the 2 components of the aCRT algorithm, we examined the incidence of the primary end point in subgroups of patients with normal AV conduction and prolonged AV conduction at randomization. In patients with normal baseline AV conduction (defined as intrinsic AV ≤ 200 ms when in sinus rhythm or AV ≤ 250 ms when receiving atrial pacing), the expectation is that much of the time they will receive synchronized LV pacing. In patients with prolonged AV conduction, the expectation is that most of the time the patient will receive biventricular pacing with optimized AV and VV intervals.

In addition to the primary end point of 48 hours of AF, the time to the first occurrence of other shorter and longer durations of AF was analyzed. Also, we examined the incidence of the primary end point in a number of additional subgroups. In addition, the incidence of AF episodes that met the protocol definition of new or worsening adverse event, including all deaths and all hospitalizations, were compared. Such adverse events were collected prospectively and defined as any untoward medical occurrence in a participant. All adverse events were reviewed and adjudicated by a blinded independent committee for relatedness and severity. We also examined incidence of persistent AF (defined as continuous episode > 7 days). Finally, we assessed baseline and change (after 6 months) in LA area by 2-dimensional echocardiography measured by a blinded core laboratory at the University of Pittsburgh. For this latter analysis patients were classified as LA responders (LA area decreased $> 20\%$ between baseline and 6 months) or LA nonresponders (LA area decreased $< 20\%$ or increased between baseline and 6 months).¹⁸

Statistical analysis

Continuous variables are reported as mean plus or minus standard deviation (SD). Cumulative incidence curves are based on the Kaplan–Meier method, with time 0 being the date of randomization unless otherwise specified. Comparisons are made using the log-rank test. Cox proportional hazard methods are used to compare subgroups, with the *P* value of the interaction between randomization and the subgroup reported. Adverse event rates were compared using Kaplan–Meier methods and the log-rank test. A multivariable Cox proportional hazards model was used to examine whether aCRT was still significant after adjusting for other variables. Variables known or suspected to affect AF were chosen for the model. Because these variables affect AF, the full model

was used, even if the individual factor was not statistically significant in this study.

Results

Patients and follow-up

The baseline characteristics of the patients (N = 478) are shown in Table 1. Two patients with permanent AF were excluded from this analysis. Also, 18% had a history of AF but were in sinus rhythm at randomization and thus were included in analysis. Patients were followed for an average of 20.2 ± 5.9 months. Total ventricular pacing ($95.0\% \pm 8.5\%$) was similar between groups; however, LV-only pacing was used $35.3\% \pm 37.1\%$ of the time in the aCRT patients, whereas convCRT patients were always paced biventricularly when ventricular paced.

Primary outcome

During the follow-up period, 8.7% of patients with aCRT and 16.2% of patients with convCRT experienced the primary outcome of an AF event of >48 hours, which was a 46% reduced risk with aCRT (hazard ratio [HR] = 0.54; 95% confidence interval [CI] = 0.31–0.93; $P = .03$) compared with convCRT patients (Figure 1). The multivariable analysis (Table 2) demonstrated that aCRT had a significant independent effect (HR = 0.51; 95% CI = 0.29–0.91; $P = .02$) on the primary outcome even after adjusting for variables that affect the incidence of AF.

Incidence of AF stratified by baseline AV conduction

The incidence of AF was stratified by baseline AV conduction interval. In patients with normal baseline AV conduction,

Table 1 Baseline demographics

Patient characteristic	Adaptive CRT (n = 318)	Conventional CRT (n = 160)
Age, y, mean \pm SD	65.4 \pm 11.2	66.2 \pm 9.7
Male, %	69	68
NYHA class III, %	94	96
LVEF, %, mean \pm SD	24.7 \pm 6.6	24.9 \pm 6.5
QRS, ms, mean \pm SD	154.3 \pm 20.9	155.7 \pm 21.4
LBBB, %	75	80
AV block: first, second, third degree, %	25, 2, 4	23, 3, 3
Ischemic, %	45	51
Beta-blockers, %	91	91
ACE-i/ARB, %	86	89
History of AF, %	18	19
Antiarrhythmic drug, %	17	16
Oral anticoagulation, %	19	23
Left atrial area, cm ² , mean \pm SD	22.8 \pm 6.4	23.3 \pm 6.6

ACE-i/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AF = atrial fibrillation; AV = atrioventricular; CRT = cardiac resynchronization therapy; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation.

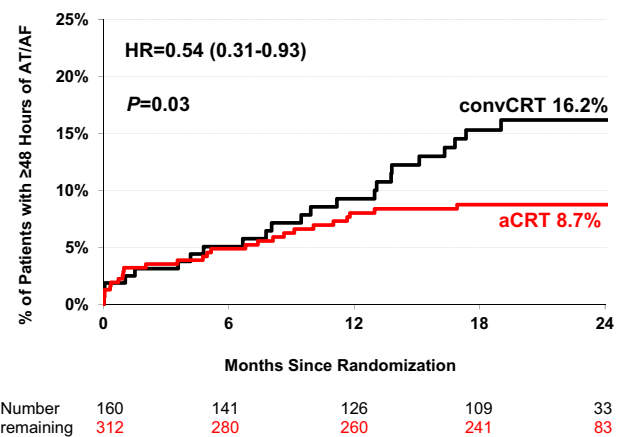


Figure 1 Incidence of primary end point (≥ 48 consecutive hours of atrial fibrillation).

aCRT patients received synchronized LV pacing $58.6\% \pm 33.9\%$ of the time over the course of the study. The incidence of the primary outcome (AF >48 hours) was 4.2% in aCRT patients compared with 7.4% in convCRT (HR = 0.60; 95% CI = 0.19–1.85; $P = .37$). In contrast, in patients with prolonged baseline AV conduction (in aCRT, LV-only pacing is used only when the AV interval is <200 ms), aCRT patients received synchronized LV pacing $14.4\% \pm 25.7\%$ of the time. The incidence of the primary outcome was 12.8% in aCRT patients compared with 27.4% in convCRT patients (HR = 0.45; 95% CI = 0.24–0.85; $P = .01$).

Additional outcomes

Subgroup analysis showed consistent effect favoring the aCRT patients except for patients with LA area ≤ 18.5 mm² or on antiarrhythmic medication at baseline. As shown in Figure 2, the HR point estimates favor aCRT; however, note confidence intervals overlapping with the line of no effect. No significant interaction effect was detected across subgroups.

AF episodes adjudicated as clinical adverse events were less common with aCRT; 4.3% of patients in the aCRT compared with 12.7% in the convCRT therapy arm (HR = 0.39; 95% CI = 0.19–0.79; $P = .01$). We investigated additional measures of AF. Table 3 shows that aCRT does not seem to affect short duration AF, but it does affect longer duration episodes as evidenced by similar HRs from 1 full day to 30 consecutive days or more. For example, 7.7% of patients with aCRT and 11.3% of patients with convCRT had developed an episode of persistent AF (>7 days) by the 24-month follow-up visit (HR = 0.68; 95% CI = 0.19–1.03; $P = .23$).

LA remodeling

Similar proportions of patients were LA responders; 70 of 256 (27.3%) of the aCRT group compared with 38 of 124 (30.7%) in the convCRT group ($P = .50$). In the LA-responder patients, risk of AF was 82% lower with aCRT beyond the 6-month follow-up visit (HR = 0.18; 95% CI = 0.37–0.91; $P = .02$). In patients with no observed reverse remodeling, there was a trend for a reduced risk of AF

Table 2 Multivariable predictors of primary end point (episode of atrial fibrillation >48 hours) using the Cox proportional hazards model

Variable	Units/level	Hazard ratio (95% CI)	P value
Randomization	Adaptive CRT	0.51 (0.29–0.91)	.02
History of AF	Yes	3.31 (1.76–6.24)	.0002
Left atrial area	Per 2 mm ²	1.12 (1.03–1.22)	.007
Age	Per 10 y	1.62 (1.12–2.34)	.01
QRS morphology	LBBB	0.50 (0.26–0.95)	.03
Etiology	Ischemic	0.53 (0.29–1.00)	.05
AV interval	Normal AV	0.54 (0.26–1.09)	.09
LVEF	Per 5%	0.85 (0.67–1.07)	.16
Antiarrhythmic	On drug	1.45 (0.73–2.90)	.29
QRS	Per 10 ms	0.96 (0.84–1.10)	.53
Race	Nonwhite	0.91 (0.38–2.17)	.84
Sex	Female	0.97 (0.49–1.93)	.94

AF = atrial fibrillation; AV = atrioventricular; CI = confidence interval; CRT = cardiac resynchronization therapy; LBBB = left bundle branch block.

in the aCRT arm beyond the 6-month follow-up visit (HR = 0.66; 95% CI = 0.29–1.48; P = .30).

Discussion

In this study, we found that patients who received an adaptive therapy that continuously optimizes CRT experienced a 46% reduced incidence of AF episodes lasting >48 hours at up to 2 years of follow-up. We found that most of the reduction in AF occurred in subgroups with prolonged AV conduction at baseline and in patients with significant LA reverse remodel-

ing. These data build on previously reported evidence of the aCRT algorithm increasing responder rates and improving clinical outcomes.²²

Although many observational studies have suggested that CRT reduces the risk of AF,^{11–16} data from 3 large clinical trials have shown conflicting results. In the Cardiac Resynchronization in Heart Failure (CARE-HF) trial, after a mean follow-up period of 29 months, AF occurred in 16% of patients in the CRT group compared with 14% of those who received medical therapy only (P = .79).¹⁷ There was no difference in the time until first onset of AF between groups. Mortality was higher in patients who developed AF; however, CRT improved the outcome regardless of whether AF developed. It should be noted that AF was detected by means of electrocardiography during scheduled and adverse events and not from device diagnostics, and hence the incidence of AF is likely underestimated.

In the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) trial, CRT-D and implantable cardioverter-defibrillator (ICD) patients showed similar 3-year cumulative probabilities of device-detected atrial arrhythmias (7% vs 9%, respectively; P = .63).¹⁸ However, if CRT led to LA remodeling, defined as >20% reduction in LA volume at 1 year post implant, then there was a reduction in atrial arrhythmia with CRT-D.

In the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT), electrocardiography-detected or device-detected AF episodes (defined as AF lasting ≥30 seconds) occurred in 45% of patients randomized to ICD and 50% randomized to CRT-D >41 months.¹⁹ After adjusting for competing risk of death, randomization to CRT-D was associated with a 20% increased risk of AF (P = .045).¹⁹ Among those with ≥1 episode of device-detected AF, 16% and 15% of patients subsequently developed persistent and permanent AF forms, respectively, with no significant between-group differences.¹⁹

The explanation for the observed reduction in AF with aCRT is likely multifactorial and is not fully understood. We found that most of the reduction occurred in patients with prolonged AV conduction at baseline. Patients who

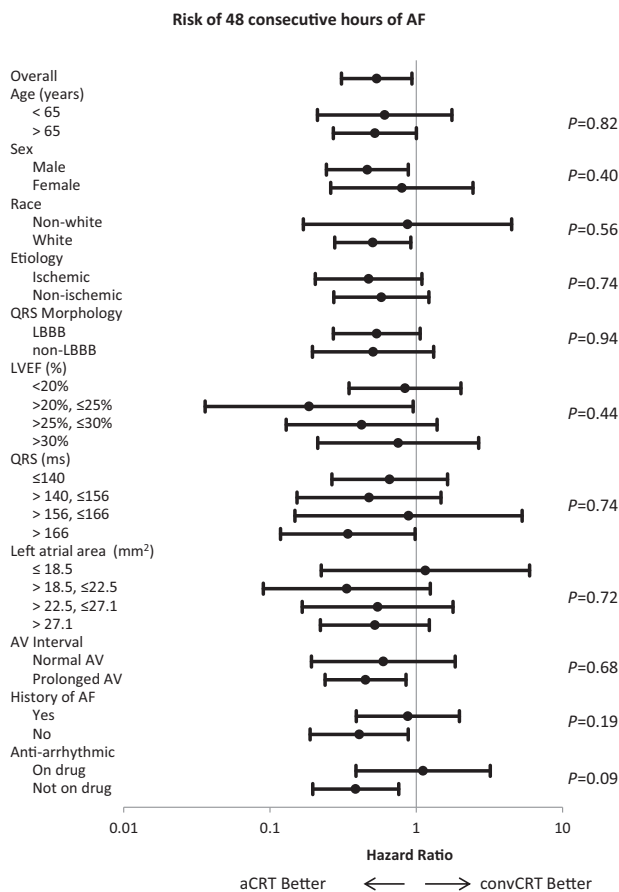


Figure 2 Incidence of primary end point in subgroups.

Table 3 Incidence of atrial fibrillation at 24 mo

Minimum AF duration	Incidence at 24 mo*		Hazard ratio	P value [†]
	Adaptive CRT (n = 312), %	Conventional CRT (n = 160), %		
6 min in 1 d	35.8	38.9	0.98	.93
1 d of >23 h	10.9	18.1	0.60	.05
2 consecutive days of >23 h	8.7	16.2	0.54	.03
7 consecutive days of >23 h	7.7	11.3	0.68	.23
30 consecutive days of >23 h	5.3	8.7	0.53	.10

AF = atrial fibrillation; CRT = cardiac resynchronization therapy.

*Kaplan–Meier estimate.

[†]AF rates compared by log-rank tests; AF burden categories compared by the Fisher exact test; and the mean AF burden compared by the Wilcoxon rank-sum test.

were randomized to aCRT received synchronized LV pacing 14% of the time and biventricular pacing 81% of the time. Thus, the major mechanism of benefit is likely not due to a reduction in RV pacing. In patients with prolonged AV interval, the aCRT algorithm continuously assesses the patient's P-wave conduction interval, AV conduction, and QRS conduction interval, resulting in minute-to-minute dynamic adjustments to AV and VV pacing intervals. Thus, more physiological AV intervals may in part explain the benefit of the algorithm. Note that the RAFT investigators postulated that overly short programming of AV intervals may explain their observation of increased AF with CRT.¹⁹ Additional research should focus on elucidating the mechanism of benefit. Such research would have potential clinical relevance to additional patient populations. Other device algorithms for optimization of CRT have been described.^{29–31} To our knowledge, however, the current report is the first to describe a reduction in AF.

Another observation of our study was the relationship between LA remodeling (reduction in LA area) and AF. Similar proportions of patients were LA responders at the 6-month follow-up visit; 27% of the aCRT group compared with 31% of patients with convCRT. In the LA-responder patients, risk of AF was 82% lower with aCRT beyond the 6-month follow-up visit. In patients with no observed reverse remodeling, there was a nonsignificant trend for a reduced risk of AF beyond the 6-month follow-up visit. These data are similar to results from MADIT-CRT. In that study, if CRT was associated with LA remodeling, then there was a reduction in atrial arrhythmia with CRT (3%) compared with that in nonresponders to CRT (9%) and ICD-only patients (7%) ($P = .03$).¹⁸ The relationship between LA remodeling and lesser incidence in AF also likely explains our observation that the Kaplan–Meier curves diverge at 12 months (Figure 1).

Limitations

The primary limitations of this study are that it is a post hoc analysis with modest sample size, and the effect of aCRT on AF should be investigated in a larger study. The AdaptResponse Clinical Trial is a prospective study of 3000 patients randomized to aCRT or convCRT (NCT02205359); the incidence of AF is a prespecified secondary end point in that trial.

Conclusion

In conclusion, aCRT is a recently described algorithm for synchronized LV pacing and continuous optimization of CRT. In the current study, we found patients receiving aCRT experienced a reduced risk of AF compared with convCRT. We found that most of the reduction in AF occurred in patients with prolonged AV conduction at baseline and in patients with LA remodeling.

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Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2017.08.017>.

References

- Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;82(8A):2N–9N.
- Hannon N, Sheehan O, Kelly L, et al. Stroke associated with atrial fibrillation—incidence and early outcomes in the north Dublin population stroke study. *Cerebrovasc Dis* 2010;29(1):43–49.
- Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98(10):946–952.
- Rienstra M, Lubitz SA, Mahida S, Magnani JW, Fontes JD, Sinner MF, Van Gelder IC, Ellinor PT, Benjamin EJ. Symptoms and functional status of patients with atrial fibrillation: state of the art and future research opportunities. *Circulation* 2012;125(23):2933–2943.
- Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;107(23):2920–2925.
- Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003;91(6A):2D–8D.
- Rienstra M, Damman K, Mulder BA, Van Gelder IC, McMurray JJ, Van Veldhuisen DJ. Beta-blockers and outcome in heart failure and atrial fibrillation: a meta-analysis. *JACC Heart Fail* 2013;1(1):21–28.
- Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Cardiac Resynchronization-Heart Failure Study Investigators. The

- effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352(15):1539–1549.
9. Abraham WT, Fisher WG, Smith AL, et al. MIRACLE Study Group; Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346(24):1845–1853.
 10. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350(21):2140–2150.
 11. Gasparini M, Auricchio A, Metra M, Regoli F, Fantoni C, Lamp B, Curmis A, Vogt J, Klersy C, Multicentre Longitudinal Observational Study Group. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. *Eur Heart J* 2008;29(13):1644–1652.
 12. Gasparini M, Auricchio A, Regoli F, Fantoni C, Kawabata M, Galimberti P, Pini D, Ceriotti C, Gronda E, Klersy C, Fratini S, Klein HH. Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. *J Am Coll Cardiol* 2006;48(4):734–743.
 13. Gasparini M, Steinberg JS, Arshad A, Regoli F, Galimberti P, Rosier A, Daubert JC, Klersy C, Kamath G, Leclercq C. Resumption of sinus rhythm in patients with heart failure and permanent atrial fibrillation undergoing cardiac resynchronization therapy: a longitudinal observational study. *Eur Heart J* 2010; 31(8):976–983.
 14. Khadjooi K, Foley PW, Chalil S, Anthony J, Smith RE, Frenneaux MP, Leyva F. Long-term effects of cardiac resynchronisation therapy in patients with atrial fibrillation. *Heart* 2008;94(7):879–883.
 15. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, Djiane P, Mabo P, Levy T, Gadler F, Bailleul C, Daubert JC. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002;23(22):1780–1787.
 16. Molhoek SG, Bax JJ, Bleeker GB, Boersma E, van Erven L, Steendijk P, van der Wall EE, Schalij MJ. Comparison of response to cardiac resynchronization therapy in patients with sinus rhythm versus chronic atrial fibrillation. *Am J Cardiol* 2004;94(12):1506–1509.
 17. Hoppe UC, Casares JM, Eiskjaer H, Hagemann A, Cleland JG, Freemantle N, Erdmann E. Effect of cardiac resynchronization on the incidence of atrial fibrillation in patients with severe heart failure. *Circulation* 2006;114(1):18–25.
 18. Brenyo A, Link MS, Barsheshet A, Moss AJ, Zareba W, Wang PJ, McNitt S, Huang D, Foster E, Estes M 3rd, Solomon SD, Goldenberg I. Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). *J Am Coll Cardiol* 2011; 58(16):1682–1689.
 19. Wilton SB, Exner DV, Wyse DG, Yetisir E, Wells G, Tang AS, Healey JS. Frequency and outcomes of postrandomization atrial tachyarrhythmias in the Resynchronization/Defibrillation in Ambulatory Heart Failure Trial. *Circ Arrhythm Electrophysiol* 2016;9(5):e003807.
 20. Birnie D, Lemke B, Aonuma K, et al. Clinical outcomes with synchronized left ventricular pacing: analysis of the adaptive CRT trial. *Heart Rhythm* 2013; 10(9):1368–1374.
 21. Singh JP, Abraham WT, Chung ES, Rogers T, Sambelashvili A, Coles JA Jr, Martin DO. Clinical response with adaptive CRT algorithm compared with CRT with echocardiography-optimized atrioventricular delay: a retrospective analysis of multicentre trials. *Europace* 2013;15(11):1622–1628.
 22. Martin DO, Lemke B, Birnie D, et al. Adaptive CRT Study Investigators. Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: results of the adaptive CRT trial. *Heart Rhythm* 2012;9(11):1807–1814.
 23. Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D, Sheldon T, Lamas GA, Search AV, Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACE) Trial. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. *N Engl J Med* 2007; 357(10):1000–1008.
 24. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen AK. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. *Lancet* 1997; 350(9086):1210–1216.
 25. Lamas GA, Lee KL, Sweeney MO, Silverman R, et al. Mode Selection Trial in Sinus-Node Dysfunction. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med* 2002;346(24):1854–1862.
 26. Krum H, Lemke B, Birnie D, Lee KL, Aonuma K, Starling RC, Gasparini M, Gorcsan J, Rogers T, Sambelashvili A, Kalmes A, Martin D. A novel algorithm for individualized cardiac resynchronization therapy: rationale and design of the adaptive cardiac resynchronization therapy trial. *Am Heart J* 2012;163(5):747–752.e1.
 27. Daoud GE, Houmsse M. Cardiac resynchronization therapy pacemaker: critical appraisal of the adaptive CRT-P device. *Med Devices (Auckl)* 2016;9:19–25.
 28. January CT, Wann LS, Alpert JS, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; 64(21):e1–e76.
 29. Stein KM, Ellenbogen KA, Gold MR, Lemke B, Lozano IF, Mittal S, Spinale FG, Van Eyk JE, Waggoner AD, Meyer TE. SmartDelay determined AV optimization: a comparison of AV delay methods used in cardiac resynchronization therapy (SMART-AV): rationale and design. *Pacing Clin Electrophysiol* 2010;33(1):54–63.
 30. Brugada J, Brachmann J, Delnoy PP, Padeletti L, Reynolds D, Ritter P, Borri-Brunetto A, Singh JP. Automatic optimization of cardiac resynchronization therapy using SonR-rationale and design of the clinical trial of the SonRtip lead and automatic AV-VV optimization algorithm in the paradigm RF SonR CRT-D (RESPOND CRT) trial. *Am Heart J* 2014;167(4):429–436.
 31. Abraham WT, Gras D, Yu CM, Guzzo L, Gupta MS, Committee FS. Rationale and design of a randomized clinical trial to assess the safety and efficacy of frequent optimization of cardiac resynchronization therapy: the Frequent Optimization Study Using the QuickOpt Method (FREEDOM) trial. *Am Heart J* 2010; 159(6):944–948.e1.