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ORIGINAL RESEARCH

The ADOPT trial (Assessment of Efficacies of Cardiac Resynchronization Therapies (CRT-P/D) for Heart Failure Patients in China): rationale, design, and end-points

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Background: Cardiac resynchronization therapy (CRT) is a novel nonpharmacological treatment for patients with chronic heart failure (CHF). Some clinical trials conducted in Western countries have demonstrated that CRT could improve CHF patients' symptoms and reduce mortality. However, due to the differences in economic and social conditions as well as inconsistencies in CHF etiologies between China and Western countries, there is an urgent need to conduct a large-scale CRT clinical study in Chinese patients with CHF. The ADOPT Trial (Assessment of Efficacies of Cardiac Resynchronization Therapies (CRT-P/D) for Heart Failure Patients in China) is designed to observe whether CRT can further improve syptoms and reduce mortality in Chinese patients in addition to optimal pharmalogical therapy.

Methods: The ADOPT study is a prospective, nested, case-controlled, open-label clinical trial. About 40 centers across China participate in this study with a planned 800 Chinese cases to be enrolled. All patients will receive optimal medical treatment. Patients who have successful CRT-P/D implant will be assigned to the CRT group. According to the baseline evaluation, matched cases will be selected from the enrolled optimal pharmaceutical therapy alone group (Group for Selection). After successful match, the cases in Group for Selection enter into follow-up and become the control group. The unmatched cases in the Group for Selection will be removed. If patients agree, after re-evaluation of the baseline situation, they may enter into Group for Selection again. Since patients know they already have a device implant and the examiners are aware of the grouping of the patients after seeing the incision scar and post-implant electrocardiogram, this study is of open-label design; however the executive committee will be kept blind when making event-adjudication.

Results: Prospectively defined primary end-points for the study include combined all-cause mortality and hospitalizations. A variety of secondary end-points will further define the efficacy and mechanism(s) of action of CRT in CHF. The last date of the study shall be the day after 24 months of follow-up of the last enrolled patient. Recruitment is expected to be completed at the end of 2011 and the study should close at the beginning of 2014.

Conclusion: The ADOPT trial will evaluate the effects of CRT on Chinese CHF patients and provide related research data for Chinese CHF patients who may need CRT.

Keywords: heart failure, clinical trial, biventricular pacing, cardiac device

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Introduction

Chronic heart failure (CHF) is a difficult therapeutic challenge in cardiology, and may incapacitate a patient and have a high morbidity and mortality. Epidemiology data have demonstrated that the total number of patients with CHF has reached 22.5 million worldwide, with 2 million new cases annually.[1–3] A CHF epidemiology survey conducted in

China in 2003 indicated that CHF prevalence was 0.9% among the Chinese adult population aged between 35 and 74 years.[4] The mortality from CHF is related to the severity of the disease: in moderate and severe CHF, the mortality may be as high as 30% to 50% within 5 years.[5] Meanwhile the medical costs of CHF are enormous.[6]

Over the past decades, with the increasing use of angiotensin-converting enzyme inhibitors (ACEI) (or angiotensin receptor blockers), beta-blockers, and aldosterone antagonists, great progress has been made in the treatment of CHF, but many patients still respond poorly to these therapies.[7,8] Cardiac resynchronization therapy (CRT) is a novel nonpharmacological treatment for CHF.[9] In order to confirm the effect of CRT as well as provide detailed and solid evidence for drafting and revising CRT guidelines, a series of clinical trials was initiated and conducted in Western developed countries. The PATH-CHF,[10] InSync,[11] MUSTIC,[12,13] and MIRACLE[14] studies all demonstrated that long-term treatment with CRT could improve cardiac function, increase 6-minute walk distance and peak O_2 consumption, improve quality of life and symptoms, reduce hospitalization, and reverse left ventricular remodeling. A meta-analysis,[15] the COMPANION study[16] in 2003, and the CARE-HF study[17] in 2005 found that CRT not only improved the symptoms of CHF patients and reduced hospitalization, but also significantly reduced their mortality. Based on these studies, in 2005 both the European Society of Cardiology and American College of Cardiology/American Heart Association heart failure guidelines placed CHF with ventricular dysynchrony as the Class I indication for CRT.[18]

In China CRT was first used in clinical practice in 1999, and until 2005 total implants numbered only about 800 cases.[19–22] Many factors contributed to this situation, such as high treatment cost, complex implant procedures, and lack of awareness of CRT for CHF among clinical physicians. With the progress of large overseas clinical trials, the application of CRT in clinical practice has increased. In recent years, the number of CRT implants has risen gradually and annual implants in China have now surpassed 500 cases. Because of China's economic and social conditions, the clinic-visit time-point and CRT implant time-point differ between Chinese patients and Western patients. In the COMPANION study, the average course of heart failure was about 3.5 years in Western patients who received CRT, but the course of the disease in Chinese patients was longer, about 5.3 years. Meanwhile, the disease spectrum causing CHF also differs between China and Western countries. In the MIRACLE, COMPANION, and CARE-HF studies, ischemic cardiomyopathy was detected in 50% of Western patients with CRT, whereas it was detected in about 30% of Chinese CRT patients.[23] Thus, the clinical results obtained from overseas trials may not be wholly applicable to Chinese practice. A large clinical study evaluating the effect of CRT on Chinese CHF patients is urgently needed. This kind of study has the following important aims: first, to evaluate the effects of CRT on Chinese CHF patients and provide related research data for Chinese CHF patients who may need CRT; second, to enhance the awareness and knowledge of CRT among clinical physicians as well among CHF patients and further advance the adoption of CRT in clinical practice; third, to provide demographic data of Chinese CHF patients with CRT device implant.

Since a large proportion of the population in China is not covered by health insurance, many CHF patients cannot afford CRT, and thus have to choose optimal pharmaceutical therapy (OPT) instead of CRT. For this reason therefore, we designed the trial as a case-control study instead of a randomized study. At the same time, the number of CHF patients who will receive OPT is much greater than that of CHF patients who will receive CRT. Because the enrolled OPT-alone group will be larger than the CRT group, we chose a nested case-control design. We hope the method can decrease the systematic bias and increase statistical efficiency.

Methods

Study purpose

The ADOPT Trial (Assessment of Efficacies of Cardiac Resynchronization Therapies (CRT-P/D) for Heart Failure Patients in China) was designed to evaluate whether CRT can further reduce mortality, improve CHF symptoms, and enhance quality in addition to OPT compared with OPT alone in Chinese CHF patients.

Study design

The ADOPT study is a prospective, nested, case-controlled, open-label clinical trial. About 40 centers across China participate in this study with a planned 800 cases to be enrolled, of which 400 cases will be CRT-P/D patients while the other 400 cases will be in the control group. Patients who meet the inclusion/exclusion criteria will be enrolled after signing written information consent. All patients will receive OPT. Patients who have a successful CRT-P/D implant will be assigned to the CRT group. According to the baseline evaluation, matched cases will be selected from the enrolled OPT-alone group (Group for Selection). After successful matching, the Group for Selection enters into follow-up and becomes the control group. The unmatched cases in the Group for Selection will be removed. If patients agree, after re-evaluation of the baseline situation,

they may enter into Group for Selection again. Since patients know they already have a device implant and the examiners are aware of the grouping of the patients after seeing the incision scar and post-implant electrocardiogram, this study is of open-label design; however the executive committee will be kept blind when making event-adjudication. The last date of the study shall be the day after 24 months of follow-up of the last enrolled patient. All cases were collected in 2010 and study results will be reported in 2012. Figure 1 shows the study scheme.

Inclusion and exclusion criteria

To participate in the study, patients must meet the 'Guideline for cardiac resynchronization therapy in patients with chronic heart failure' in China.[24] Patients must meet all the following criteria for inclusion: ischemic or nonischemic cardiomyopathy; New York Heart Association (NYHA) classes III–IV despite OPT; normal sinus rhythm; left ventricular ejection fraction (LVEF) ≤35%; LV end-diastolic diameter ≥55 mm; and wide QRS complex ≥120 milliseconds (ms) at the time of enrollment. Patients who do not meet each of the following criteria will be excluded: potentially reversible forms of cardiomyopathy; cardiac surgery, percutaneous coronary intervention, cardiomyoplasty, myocardial infarction, unstable or severe angina or stroke within 6 weeks before randomization; in-patients requiring continuous intravenous therapy for heart failure; life expectancy <1 year for disease unrelated to heart failure; mechanical tricuspid valve; anticipated problem with compliance; participation in another trial; aged younger than18 years; women who are pregnant or not using medically acceptable birth control.

End-points

Primary end-point

The primary end-point in the ADOPT study is the composite of all-cause mortality or unplanned cardiovascular hospitalization using a time to first event analysis (Table 1). Deaths occurring at any time after randomization will count towards the primary end-point, even if they occur prior to device implantation. Patients who undergo emergency heart transplantation due to end-stage heart failure will be counted as deaths. Patients who undergo elective heart transplantation are censored 7 days post-transplant. Patients who undergo transplantation will have their vital status assessed for the duration of the study. Hospitalization means admission to a hospital involving an overnight stay or resulting in death. Cardiovascular hospitalization includes hospitalization for or with worsening heart failure, angina, myocardial infarction, syncope, arrhythmia, stroke, transient ischemic attack, acute peripheral vascular emergencies, pulmonary embolism, or other cardiovascular events. Hospitalization for or with worsening heart failure includes heart failure induced by infection, supraventricular or ventricular arrhythmias, acute coronary syndromes or renal dysfunction due to drug effects or worsening cardiac function.

Admissions for initial device implantation are planned and do not count towards the primary endpoint. Re-admissions within the first 10 days for device-related re-interventions are considered as part of the same episode of care. In order to avoid bias in favor of the device, hospitalizations within 10 days of randomization regardless of the treatment arm will be recorded, but will not contribute to the primary end-point. Planned admissions for diagnostic procedures, revascularization, or nonemergency arrhythmia management or nonemergency transplantation will be recorded but will not count towards the primary end-point. Readmission for lead displacement that has not precipitated a cardiac emergency will be considered planned. All data will be adjudicated by an end-points committee in a blinded fashion.

Secondary end-points[1,25–27]

All-cause mortality is the outcome least subject to bias. Death will be classified according to place (in-hospital,

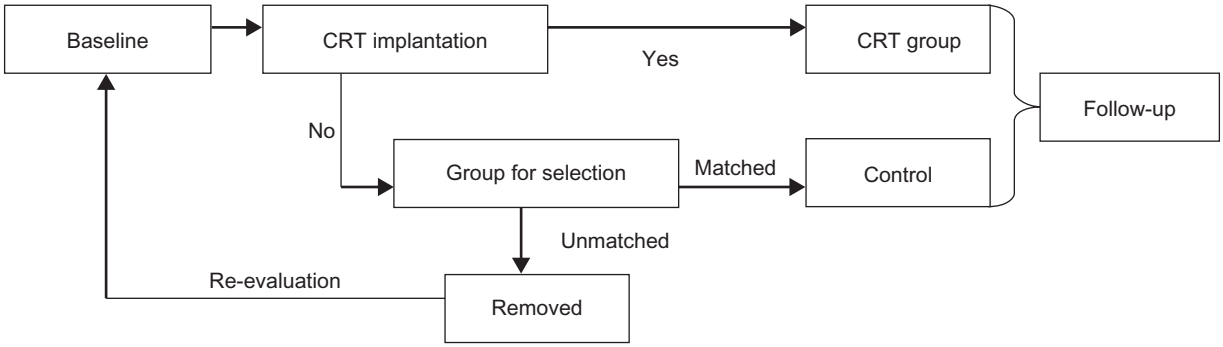

Figure 1 Study scheme.
Abbreviation: CRT, cardiac resynchronization therapy.

Table 1 Clinical end-point

Primary clinical end-point
The composite of all-cause mortality or unplanned cardiovascular hospitalization
Secondary clinical end-points in hierarchical order
All-cause mortality
The composite of all-cause mortality or unplanned hospitalization for or with heart failure
Days alive and not in hospital for unplanned cardiovascular cause during the minimum period of follow-up
Days alive and not in hospital for any reason during the minimum period of follow-up
New York Heart Association classification at 90 days
Quality of life at 90 days
Patient status at the end of study

out-of-hospital, and in-transit to hospital), mode (eg, sudden, circulatory failure, stroke), and relationship to preceding events (eg, myocardial infarction, unstable angina, persistent NYHA class IV heart failure, renal failure, stroke, device-related complication, cardiovascular procedure, cancer). Sudden death is defined as death within 1 hour of the onset of symptoms or unwitnessed death without any other obvious cause.

For each hospital admission for or with worsening heart failure, the investigator will be requested to state whether or not the patient experienced worsening heart failure a) at the time of admission or b) during the admission, and, if so, whether or not this was the primary reason for admission or secondary to an obvious precipitating factor such as infection, myocardial infarction, or atrial fibrillation. The investigator will also be asked to state whether or not the patient received a) intravenous medication for heart failure (including diuretics, vasodilators, or inotropic agents) or b) a substantial increase in oral diuretic therapy for heart failure, defined as an increase of furosemide ≥40 mg or equivalent, or the addition of a thiazide to a loop diuretic. Patients are generally expected to be on ACEI and beta-blockers at baseline and will often be receiving spironolactone; therefore, these therapies, directed principally at the improvement of prognosis rather than symptoms, are not used as supportive evidence of worsening heart failure. Only patients who are reported to have worsening heart failure and who have also undergone an intensification of therapy as outlined above will be deemed to have worsening heart failure. Patients who have an exacerbation of heart failure secondary to supraventricular or ventricular arrhythmia, myocardial ischemia, myocardial infarction, renal dysfunction, or infection may be included in this end-point. Final classification of hospital admission for or with heart failure will be made by a blinded end-points committee.

The end-point of days alive and not in hospital for unplanned cardiovascular cause over the first 500 days of follow-up uses the definitions for all-cause mortality and unplanned cardiovascular hospitalizations set out previously. In this analysis, each patient has the same exposure to risk and a maximum possible score of 500. The number of days 'lost' due to death or days in hospital for unplanned cardiovascular cause will be deducted from this maximum score. Admission days will be counted by the number of midnights in hospital. The whole period of any admission that fulfils the definition of the 'unplanned cardiovascular hospitalization' component of the primary end-point will be counted as days in hospital. The end-point of days alive and not in hospital for any reason over the first 500 days is similar to the above, but includes noncardiovascular hospitalization, planned admissions, and admissions for device implantation or revision.

Patients lost to follow-up will be assumed to have died on the day after they were last known to be alive. These types of analyses take into account the competing effects of mortality, duration of hospital stay and frequency of hospital admission. In order to prevent the confounding effects of a possible difference in long-term mortality between groups, the effect of therapy on symptoms will be assessed principally at 90 days. Symptoms will be assessed using the NYHA classification. The worst status within the last week will be counted. Patients who have died will be assumed to be in NYHA class IV. Patients and investigators are aware of their treatment allocation. Accordingly, the patients rather than the investigators will decide which NYHA class most closely resembles their current status. Long-term effects on symptoms may be best gauged by composite measures including need for intensification of therapy and frequency and duration of hospitalization for heart failure.

Quality of life, for the above reasons, will also be assessed at 90 days using 3 quality-of-life tools, 2 of which are completed by the patients and 1 by the investigator. Changes from baseline to 90 days will be assessed. The Minnesota Living with Heart Failure questionnaire is a well-validated but highly disease-specific tool that may be poorly responsive to change. It is completed by the patient. The EuroQoL is a simple, general quality-of-life tool that is completed by the patient. The EuroHeart Failure questionnaire is designed to assess both general and disease-specific quality-of-life in patients with heart failure. The investigator asks the patient a series of questions and records the answers given. It is currently undergoing validation.

Patients' symptoms may follow a fluctuating clinical course. Increasing diuretic therapy may alleviate symptoms

and mask progressive deterioration. Some patients may fair badly at first, but show late improvement. For these reasons, the long-term clinical status is of interest and will be evaluated at the end of the study. Patients who are alive, in the same NYHA class (or better) as at the start of the study, and who are not receiving a substantial increase in diuretic therapy (see previous page) will be deemed to have benefited. Patients who do not fulfill all of these criteria will be deemed to have deteriorated. As status may be confounded by differences in the duration of follow-up, this analysis will also be assessed at 18 months for all patients.

Study conduct

Patients were enrolled from 44 clinical centers through an Internet-based system. Each center, with a unique account, registered patients from a computer connected to the Internet. The study committee prescribed that 11 variables should be included and balanced. As shown in Table 2, all 11 variables were ranked to 2 to 3 levels. Five variables, including sex, NYHA class, ischemic/nonischemic heart disease, rhythm, and QRS duration, must be identical between treatment and control groups. Six other variables, including age, heart failure duration, LVEF, left ventricular end-diastolic dimension, heart rate, and medicine therapy, were matched by a sum weighted unbalanced score.

The unbalanced score Z_{mj} is defined as the amount of variation of all 6 variables between 2 quasi-matching patients (patient *m* in the CRT group and patient *j* in the control group) from 2 different groups.

$$Z_{mj} = \sum_{i=1}^{6} w_i * v_i$$

(w_i is the weight of variable *i*, v_i is the absolute difference of rank score of variable *i* between 2 groups).

If the score is less than the threshold value initially appointed, they are matched. Once matched, the patient can

Table 2 Variables and matching method

Characteristic	Match regulation	Score weight	Levels	Rank
Sex	full match	–	Male	1
			Female	2
NYHA class	full match	–	I–II	1
			III	2
			IV	3
Ischemic or not	full match	–	Ischemic heart disease	1
			Nonischemic heart disease	2
Rhythm type	full match	–	sinus rhythm	1
			atrial fibrillation	2
QRS duration	full match	–	<120 ms	1
			120–150 ms	2
			>150 ms	3
Age	by score	1	<40 years old	1
			40–60 years old	2
			>60 years old	3
HF duration	by score	1	<1 year	1
			1–5 years	2
			>5 years	3
LVEF	by score	2	<20%	1
			20%–30%	2
			30%–35%	3
LVEDD	by score	2	55–80 mm	1
			80–100 mm	2
			>100 mm	3
Heart rate	by score	1	<60 bpm	1
			60–80 bpm	2
			>80 bpm	3
Medicine therapy	by score	1	neither ACEI/ARB nor beta-blocker	1
			ACEI/ARB or beta-blocker	2
			ACEI/ARB and beta-blocker	3

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; bpm, beats per minute; HF, heart failure; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; ms, millisecond; NYHA, New York Heart Association.

no longer be matched again with others. And once the patient had been enrolled for more than 4 weeks, they were outdated and no longer eligible for matching. The matching was running automatically once a day at every midnight.

Clinical follow-up starts at the time when the patient is enrolled into study. Follow-up will be made for all patients at the third month (±14 days), sixth month (±14 days), then 6 months each till the end of the 24th month of last enrolled patient. If patients in the CRT group need optimization of cardiac resynchronization, related information should be documented. The follow-up procedure is shown in Figure 2.

Statistical power

Because of the increased initial risk of a primary event in the intervention group, because of the hazard associated with implantation, ADOPT provides particular challenges for design and analysis. From the study result of MIRACLE[14] and CARE HF,[17] we assume a hazard ratio in the first month of 2.5, attributable to the intervention, a subsequent hazard ratio of 0.69 for the remaining months of follow-up, and power (1-β) of 0.8. A cross-over rate of 1.8% is assumed for the control group for the overall period of the trial. Similarly, a failure to implant successfully of 20% is assumed. A 14% reduction in the risk of a primary event is expected and considered clinically significant.[28] With one-tailed type one error $\alpha = 0.025$, a total sample of 400 is required to achieve 80% power.

Statistical analysis plan

The statistical analysis for the primary outcome, and other 'time to event' outcomes, is by log rank test. The analyses for the continuous variables is by standard methods, unless there is good evidence of important deviation from assumptions of normality, in which case nonparametric bootstrap methods will be used to generate confidence intervals. An exploratory analysis considering a limited number of potentially important predictive factors will be examined through a Cox proportional hazards model, accounting for the negative effects of implantation as a time dependent covariate.

Timelines

The first patient was randomized in December 2008. At the time of writing, 100 patients have been randomized. Recruitment is expected to be completed at the end of 2011 and the study should close at the beginning of 2014.

Study organization

The study organization for ADOPT includes a Steering Committee, Adverse Event and End-Point Committee, Data Safety Monitoring Board, Independent statistician, and a contract research organization for field monitoring and data management.

Summary

ADOPT has been developed as an open-label, prospective, multicenter, case-controlled study, as were the MIRACLE and CARE HF studies in China. ADOPT has been designed to evaluate whether CRT can further reduce mortality, improve CHF symptoms, and enhance quality of life in addition to OPT compared with OPT alone in Chinese CHF patients. ADOPT has the following important and useful aims: first, to evaluate the effects of CRT on Chinese CHF patients and provide related research data for Chinese CHF patients who may need CRT; second, to enhance the awareness and knowledge of CRT among clinical physicians as well among CHF patients, and further advance the adoption of CRT in clinical practice; third, to provide demographic data of Chinese CHF patient with CRT device implant.

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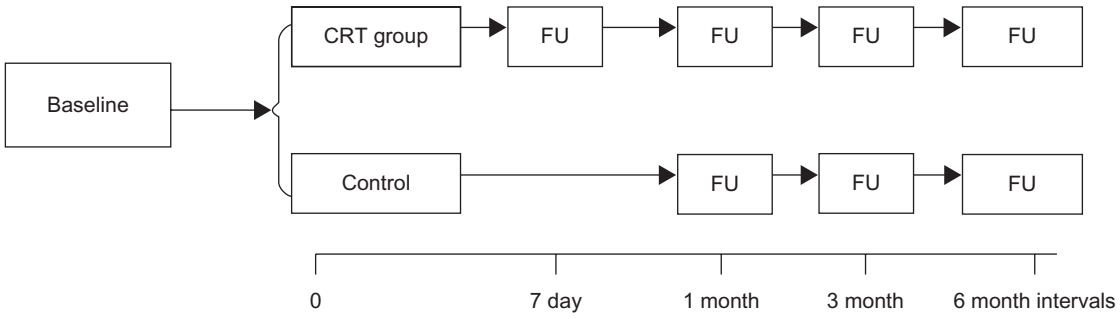

Figure 2 Follow-up testing.
Abbreviations: CRT, cardiac resynchronization therapy; FU, follow-up.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005;112:e154–e235.
2. Adams KF Jr. New epidemiologic perspectives concerning mild-to-moderate heart failure. *Am J Med*. 2001;110 Suppl 7A:6S–13S.
3. Cleland JG, Alamgir F, Nikitin NP, Clark AL, Norell M. What is the optimal medical management of ischemic heart failure?. *Prog Cardiovasc Dis*. 2001;43:433–455.
4. Gu D, Huang G, Wu X, et al. Investigation of prevalence and distributing feature of chronic heart failure in Chinese adult population. *Chinese Journal of Cardiology*. 2003;31:3–6.
5. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001–2007.
6. O'Connell JB. The economic burden of heart failure. *Clin Cardiol*. 2000;23:III6–III10.
7. Khand A, Gemmel I, Clark AL, Cleland JG. Is the prognosis of heart failure improving? *J Am Coll Cardiol*. 2000;36:2284–2286.
8. Cleland JG, Clark AL. Delivering the cumulative benefits of triple therapy to improve outcomes in heart failure: too many cooks will spoil the broth. *J Am Coll Cardiol*. 2003;42:1234–1237.
9. Cleland JG, Freemantle N. Cardiac resynchronization for progressive heart failure. *JAMA*. 2003;290:36–37; Author reply 37–38.
10. Stellbrink C, Breithardt OA, Franke A, et al. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J Am Coll Cardiol*. 2001;38:1957–1965.
11. Gras D, Mabo P, Tang T, et al. Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc. InSync Study. *Pacing Clin Electrophysiol*. 1998;21:2249–2255.
12. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001;344:873–880.
13. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol*. 2002;40:111–118.
14. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845–1853.
15. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA*. 2003;289:730–740.
16. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140–2150.
17. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549.
18. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26:1115–1140.
19. Wang F, Zhang S, Hua W, et al. Clinical application of biventricular pacing to treat congestive heart failure. *Chin J Cardiac Arrhyth*. 1999;3:245–248.
20. Hua W, Wang F, Zhang S, et al. The hymodynamic observation on patients with congestive heart failure treated by biventricular pacing. *Chin J Cardiac Arrhyth*. 2000;4:90–93.
21. Shen F, Huang Y, Shen Y, et al. Clinical application of biventricular pacing. *Chin J Cardiac Arrhyth*. 2000;4:94–96.
22. Wang S, Huang D, Wen S, Wang H. Reproducibility of head up tilt testing results in patients with cardioinhibitory vasovagal syncope. *Chin J Cardiac Arrhyth*. 2000;4:270–272.
23. Hua W, Niu HX, Wang FZ, Zhang S, Chen KP, Chen X. Short-term effect of cardiac resynchronization therapy in patients with ischaemic or nonischaemic cardiomyopathy. *Chin Med J (Engl)*. 2006;119:1507–1510.
24. Wang F, Zhang S, Huang D, et al. Guideline for cardiac resynchronization therapy in patients with chronic heart failure. *Chin J Cardiac Arrhyth*. 2006;10:90–102.
25. Bristow MR, Feldman AM, Saxon LA. Heart failure management using implantable devices for ventricular resynchronization: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. COMPANION Steering Committee and COMPANION Clinical Investigators. *J Card Fail*. 2000;6:276–285.
26. Abraham WT. Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *J Card Fail*. 2000;6:369–380.
27. Cleland JG, Daubert JC, Erdmann E, et al. The CARE-HF study (CArdiac REsynchronisation in Heart Failure study): rationale, design and end-points. *Eur J Heart Fail*. 2001;3:481–489.
28. Shih JH. Sample size calculation for complex clinical trials with survival endpoints. *Control Clin Trials*. 1995;16:395–407.