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Cardiac resynchronization therapy in chronic heart failure with moderately reduced left ventricular ejection fraction: Lessons from the Multicenter InSync Randomized Clinical Evaluation MIRACLE EF study

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ABSTRACT

Background: The benefits of CRT for symptomatic heart failure (HF) patients with a wide QRS and reduced left ventricular ejection fraction (LVEF ≤35%), are well established .Post-hoc subgroup analyses suggest that CRT benefit may extend to patients with LVEF >35%.
Methods: The MIRACLE EF was a prospective, randomized, controlled, double-blinded study to evaluate CRT-P in NYHA II–III HF patients with LBBB and with LVEF of 36%–50% and no previous pacing or ICD. The primary endpoint was a composite of time to first HF event or death. All patients were implanted with a CRT-P and randomized 2:1 to CRT-P ON or CRT-P OFF groups. The minimum follow up time was 24 months.
Results: The MIRACLE EF study was stopped for enrollment futility after 13 months and enrolling only 44 patients. The main difficulties in recruiting patients were lack of eligible patients, previous ICD implants, and the reluctance of institutions, patients or physicians to enroll in the study which included a potential 5 year CRT OFF period.
Conclusion: Despite a careful design, identification and randomization of eligible patients were challenging and a trial to assess morbidity and mortality trial was not feasible. The MIRACLE EF experience illustrates the difficulties of designing a scientifically robust but feasible study to assess potential new indications for implantable devices. Smaller randomized studies with surrogate endpoints may therefore be more reasonable, although the potential impact of such studies on clinical practice, guidelines, and reimbursement remain to be determined.

1. Introduction

The benefits of Cardiac Resynchronization Therapy (CRT) have been firmly established in heart failure (HF) patients who remain in New York Heart Association (NYHA) Classes II–III despite optimal medical therapy and have a wide QRS and reduced left ventricular ejection fraction (LVEF) (≤35%) [1–6]. Subgroup analyses suggest that the benefits are larger in patients with wider QRS durations and/or left bundle branch block (LBBB) [7–9] and this has been recognized in current guidelines [10,11]. Recently, it has been suggested that CRT may also be beneficial in patients LVEF >35% [12–14] by results of post hoc subgroup analysis from the PROSPECT [12], MADIT-CRT [13], and REVERSE [14] trials. Patients with NYHA II–III HF with LVEF 36–50% remain at high risk of mortality/morbidity, but have few established treatments, and their prognosis is worse in the presence of bundle branch

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block [15,16]. Therefore, the aim of the MIRACLE EF study was to test the hypothesis that CRT prolongs time to death or HF event in patients with NYHA Classes II–III HF, LVEF of 36–50%, and LBBB. This paper describes the process of creating the study protocol, the influence of the U.S. Food and Drug Administration (FDA) on trial design, challenges in effectively recruiting patients, and lessons learned.

2. Methods

MIRACLE EF aimed to evaluate CRT pacemaker (CRT-P) devices in symptomatic HF patients with LVEF 36–50% and to compare CRT-P ON to optimal medical therapy alone CRT-P OFF over at least 24 months of post-implant follow-up. We hypothesized that CRT would improve the combination of morbidity and mortality, improve health-related Quality of Life (QoL), and reduce healthcare costs. The study was expected to require approximately 2900 enrolled patients in order to reach approximately 2300 implanted subjects, across up to 275 centers in the US, Canada, Europe, Asia, Africa, Latin America, Australia and the Middle East.

2.1. Study design

The MIRACLE EF study was a prospective, randomized, controlled, double-blinded, global multi-center, cardiac resynchronization therapy (CRT) in heart failure (HF) clinical study. Inclusion and exclusion criteria are listed in Table 1. At baseline, eligibility was to be verified. All patients with LVEF 36–40% were required to be on optimal HF medication including beta-blockers and ACE-inhibitors or angiotensin II receptor-blockers with or without aldosterone-antagonists on stable doses for at least one month. For patients with LVEF >40%, where evidence and guideline recommendations for use of neurohormonal antagonist therapy as treatments for HF is lacking, optimal medical therapy depended on co-morbidity such as ischemic heart disease, hypertension, diabetes or atrial fibrillation.

Table 1
Inclusion and exclusion criteria in the MIRACLE EF study.

Inclusion criteria
Chronic heart failure >90 days in duration
LVEF between 36% to 50%
LBBB with QRS ≥130 ms
Patient is either
A. NYHA Class III OR
B. NYHA Class II, with hospitalization for HF in the last 12 months OR
C. NYHA Class II, without hospitalization for HF, but with BNP ≥250 pg/ml or NT-proBNP >1000 pg/ml
Sinus rhythm at time of enrollment
Sinus rhythm at time of enrollment
Optimal medical therapy per guidelines for Heart Failure, Ischemic Heart Disease (IHD), Hypertension and Atrial Fibrillation, as applicable
No change in non-diuretic heart failure medical therapy within prior 30 days
Able to receive pectoral implant
Able to receive pectoral implant
Signed and dated informed consent
Expected to remain available for follow-up visits
Willing and able to comply with the Clinical Investigation Plan
Exclusion criteria
Requires permanent cardiac pacing
Indicated for implantable cardioverter defibrillator (ICD)
CRT-P, pacemaker, ICD or CRT-D device implanted previously or currently
Mechanical tricuspid heart valve
Unstable angina or an acute MI within past 40 days
Coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) within the past 90 days
Chronic (permanent) atrial arrhythmias
Cardioversion for atrial fibrillation within the past 30 days
Primary valvular disease, indicated for valve repair or replacement.
Treatable pericardial constraint
Restrictive (infiltrative) cardiomyopathies, such as amyloidosis, sarcoidosis, or hemochromatosis or other restrictive, hypertrophic, or reversible cardiomyopathy
Enrolled in a concurrent study, with exception of an approved observational study (e.g. registries)
Life expectancy of less than 24 months due to non-cardiac conditions
<18 years of age
Female patient who is pregnant, or of childbearing potential and not on a reliable form of birth control
Heart transplant, or is currently on a heart transplant list
Significant renal dysfunction, (serum creatinine level >2.5 mg/dl or ≥275 μmol/L or estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2)
Significant hepatic dysfunction (hepatic function panel (serum) > 3 times upper limit of normal)
Chronic or treatment-resistant severe anemia (hemoglobin <10.0 g/dL)
Patient is on intravenous inotropic drug therapy

Subjects meeting all eligibility criteria would undergo a CRT-P implant. All successfully implanted patients would be randomized to CRT-P ON or CRT-P OFF in a 2:1 ratio and then remain in their randomized assignment for at least 24 months and up to 60 months or until the study was stopped. An enrollment rate of 0.33 patients/center/month was estimated based on average performance in previous CRT studies. Stopping rules defined enrollment futility as a recruitment <0.1/center/month in at least 30 centers over 6 months.

2.2. Study procedures and data collection

Potentially eligible study subjects were to be screened within 30 days of signing informed consent to establish eligibility and collect baseline data. Subjects were then implanted within 14 days of enrollment and randomized within 14 days of successful implant. Following successful implant, subjects were randomized in a 2:1 ratio to either CRT-P ON or CRT-P OFF. For patients programmed to CRT OFF, the device was conservatively programmed to provide anti-bradycardia right ventricular pacing if spontaneous heart rate was below 40 bpm. Comprehensive follow-up visits would occur at 6 and 24 months, while limited follow-up would occur at 1, 3, 12, 18, 30, and every 6 months thereafter up until 60 months (Fig. 1, Table 2). Data collected at baseline included an echocardiogram, BNP or NT proBNP, 12-lead ECG, physical examination, 6 minute hall walk, quality of life (QOL), medical history and cardiovascular (CV) medications. QOL was assessed by the Kansas City Cardiomyopathy Questionnaire [18] and EuroQol [19] and the latter was used to perform the Health Economic analysis. Data collected at follow-ups included an echocardiogram, 12-lead ECG, BNP or NT proBNP, quality of life, CV medications, device evaluation, NYHA class. System modifications, adverse events and health care utilizations were collected as they occurred throughout the study. All study subjects were to be followed to a common study closing date after the pre-specified number of events had occurred, or the trial was stopped.

NYHA class was determined by a blinded heart failure specialist or nurse while the electro-physiologists un-blinded to therapy allocation checked the device. There were core labs for both ECG and echocardiography. The ECG core lab verified the presence of LBBB and prolonged QRS duration. An Echocardiographic Core Lab determined the LVEF and left ventricular end systolic volume (LVESV) measures at baseline and during follow-up, these measurements were used in determining whether a subject experienced secondary endpoints such as worsening systolic function after 6 and 24 months. The 24 month evaluation was chosen since it was anticipated from previous trials that the maximal extent of reverse remodeling would have been reached within that time and then sustained [17]. The LVEF for inclusion was based on the investigational center's assessment to mimic what would happen in normal practice after the trial. The echo core lab tested the proficiency of the center sonographer prior to their activation on the study.

2.3. Study objectives

The primary efficacy endpoint of MIRACLE EF was a composite endpoint similar to other CRT studies in HF patients (CARE-HF [3], MADIT-CRT [5], RAFT [6]) and drug studies in HF such as the EMPHASIS-HF study [20] and would assess time to first event. The composite endpoint consisted of all-cause mortality or a HF event, defined as either an in-patient hospitalization for HF, or an outpatient event requiring invasive clinical intervention and management for HF (i.e. IV diuretics, ultrafiltration, or equivalent) and overnight stay. The classification of all HF events was to be adjudicated by a blinded Endpoint Adjudication Committee (EAC) of qualified clinicians.

The primary safety endpoint of MIRACLE EF was freedom from system-related complications of greater than 80% in randomized subjects as of 6 months post implant to demonstrate the safety of CRT-P devices in this population.

The six secondary endpoints were: (1) mortality, (2) secondary composite objective, (3) recurrent HF events, (4) QoL, (5) healthcare system cost effectiveness and (6) changes in LVEF and LVESV. Mortality, a component of the primary endpoint, would be assessed separately for comparison between the study groups.

The secondary composite endpoint would include the following components: all-cause mortality, HF event, defined as either an in-patient hospitalization for HF, or an outpatient event requiring invasive clinical intervention and management for HF (i.e. IV diuretics, ultrafiltration, or equivalent) and overnight stay, or worsening systolic function meeting an ICD/CRT-D indication, defined as a drop in LVEF to 35% or below, with an absolute decrease of ≥10% after maximum tolerated doses of guideline HF medications had been established.

It was anticipated that subjects whose systolic function worsened during the course of the study might experience a drop in LVEF to 35% or below resulting in an ICD or CRT-D indication, as well as an increased risk of morbidity and mortality. These events were therefore, included in the secondary composite endpoint. The determination of worsening LVEF meeting an ICD indication would be made using a standard of care echocardiogram initiated by a blinded clinician because of clinical worsening or as deemed necessary for management of the subject. The LVEF would then be adjudicated by the Echo Core Lab and the EAC would then adjudicate for inclusion as a study endpoint, including review of medications to confirm all requirements. Use of LVEF changes in the endpoint could not be determined using the protocol-defined echo data (at 6 and 24 months), unless