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Title: 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.

Article Type: Original Article

Keywords: Heart failure, cardiac resynchronization therapy, Left ventricular ejection fraction, LBBB, mortality

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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 was 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.

Suggested Reviewers:

Cover Letter

Stockholm 12 June, 2015

To the Editor in Chief

Professor Andrew Coats
International Journal of Cardiology

Dear Professor Coats,

We hereby re-submit the paper: 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 by Cecilia Linde, Anne B. Curtis, Gregg C. Fonarow, Kerry Lee, William Little, Anthony Tang, Francisco Levya, Shin-ichi Momomura, Christopher Manrodt ,Tracy Bergemann and Martin R Cowie after revision.

We are grateful for the valuable input from the reviewers and have answered all comments and adjusted the manuscript when appropriate. All named authors have seen and approved the final version of the manuscript. We hope that the paper will now be suitable for publication.

Best wishes

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Author Agreement Form – International Journal of Cardiology

Manuscript Title: **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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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology.*

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

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***Detailed Response to Reviewers**

Comments from the editors and reviewers:
Reviewer #1: Title: 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. - Linde et al.

Reviewer #1 : In this interesting paper the authors describe the challenges met with conducting a prospective, randomized, controlled, double-blinded study, MIRACLE EF, 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 study was stopped due to issues with recruitment, and the reluctance of institutions, patients or physicians to enroll in the study which included a potential 5 year CRT OFF period.
The following are my comments:

Questions from Reviewer 1.

Question 1.The authors must highlight the "ethical" component of subjecting patients to surgical procedures which bear significant risks to acute and chronic complications, including death.
The authors claim to "careful design" of the trial is incorrect, as was proven to be far from it by lack of acceptance by so many IRBs, and importantly the patients and the referring physicians.
The negative experience should provide opportunities to learn and feel humbled, for which the authors should be commended!

Answer to Question 1 :
We are aware of the ethical component of our study protocol, subjecting our study patients to possibly 5 years of CRT implanted but programmed off. Accordingly, we have added this ethical discusion of risk and benefit to section 3.1.2 of the manuscript.

In our initial IDE application to the FDA, we proposed a different study protocol that had a control arm with no device implanted. But in correspondance with FDA, they recommended that the study use a control arm with an implanted device to achieve blinding. The main concern of having a control arm without a device implant was that the lack of blinding may lead to differing treatment decisions regarding admissions for HF hospitalization and subsequent ascertainment bias for these events. Although we did not strictly have to comply to these recommendations according to current FDA rules, the steering committee and the sponsor did.

We also believed an implanted control arm was ethical because the study design used an event driven approach such that not all study subjects would need to be followed for five years and required follow-up could be as low as 24 months depending on observed event rate in the study. We had previous experience with a 24 months blinded period in the European part of the REVERSE study (Daubert el al. J Am Coll Cardiol 2009; 54: 1837-1846) in which all patients were implanted with a device and then randomized to CRT ON or OFF. For patients randomized to the control arm, once activated to CRT ON they experienced the same magnitude of benefit as those initially randomized to CRT ON, Leclercq et al 2015 in preparation). The overall complication rate related to the LV lead was 10%.

It is correct that a minority of the IRBs that were submitted to did not accept this protocol for safety reasons (4 IRB rejections), as did some study physicians and patients.

As stated in Subsection 3.1.2 of the manuscript, there were 90 unique site submissions for IRB/Ethics review: 72 approvals, 4 rejections, 14 in process at the time the study stopped. To provide more detail on this process: 35 of the approvals required a 2nd submission after initially being "tabled" or "denied with the opportunity to resubmit. 26 of the 37 approvals without a second submission were Western IRB, which is a central IRB that some US hospitals out-source their ethics approvals through. Once

WIRB has given their first approval, each subsequent site was approved as an expansion of the original approval to cover each additional site.

Patient and physician refusals were also observed during the screening process, as noted in Figure 2 of the manuscript, constituting about 3% of screen failures. Furthermore, there were 81 sites (45%) out of 180 approached that declined to participate in the study, with the status of 39 sites pending at the time of study closure.

Question 2. What is the clinical follow-up of the patients that were enrolled? Has any interim analyses been made on the endpoints on data gathered so far? If the devices were not beneficial, and not used i.e. not even utilized for regular pacing, should they be removed, or should the generator be not replaced at the time of battery depletion?

Answer to Question 2 :
Twenty-six patients were successfully implanted with a CRT pacemaker and randomized (19 CRT, 7 Control). Of these patients, 10 (7 CRT, 3 Control) completed the 6-month visit with paired echocardiographic data before the study was stopped. Results of echo parameters will be presented at the ESC 2015 conference. A 28 % reduction in LVESV after 6 months of CRT compared to baseline was seen in the CRT ON group with no change in the control group. The difference in the LVESV reduction between groups was borderline significant (p=0.05), but the differences in LVESVi and LVEF were not. These results, although by no means conclusive given the small sample size, underline that the hypothesis for the study is worth further exploration.

Management of CRT-P devices in implanted patients after study exit was left to the discretion of their attending study physician. At study close, instructions were sent to participating sites to that effect. None of the implanted devices were explanted before study close. This information about study closure instructions have been added to the manuscript, at the end of the first paragraph of the Results section.

Reviewer #2: 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 planned to be 24 months.
On the basis of a series of statistical assumptions, 609 events were considered to be observed in approximately 2,300 randomized subjects over the length of the study. Results:
The MIRACLE EF study was stopped for enrollment futility after 13 months and at that time it had enrolled only 44 patients.
In this manuscript is reported that the study was stopped for futility but usually futility refers to a specific statistical analysis which was planned before study initiation, after a predefined number of enrollments (at an interim analysis).
Here the discrepancy between planned and enrolled pts is so high that probably the reason for interrupting the study was not a true futility analysis but a general judgment dictated by only 44 pts enrolled in one year of study period. So it was a decision not based on statistical analysis resulting in futility but on a general evaluation of recruitments. This should be clarified because futility usually refers to the results of an interim , preplanned analysis. In the manuscript the role of the sponsor in taking this decision should be also discussed.

Answer :

We thank the reviewer for underlining the true meaning of futility. Indeed the study was not stopped based on the statistical analysis of the study endpoints according to pre-specified futility guidelines. Rather, the study was stopped due to enrollment futility, based on the fact that we truly failed to find study patients. In the study protocol we prespecified a stopping guideline for enrollment futility. The text in the study protocol states that_ "Medtronic may stop the study due to lack of enrollment, if less than 0.1 patients are enrolled per center per month in at least 30 activated centers over any 6 consecutive months". In the paper we describe this stopping guideline on page 4. In the paper we discuss the possible reasons for lack of enrollment. It is very likely that patient recruitment was not done at the correct level of care which can be expected in order to find HF patients with mid range LVEF and LBBB.The sponsor also clearly had a decisive role in interrupting the study after it was demonstrated that enrollment fell way below the stopping guidelines stipulated in the CIP. The manuscript has been edited so that it is consistently clarified that the study was stopped due to enrollment futility and not due to statistical futility based on interim analyses of effect sizes.

Reviewer #3: This is an interesting report on lessons drawn from the MIRACLE EF randomized study. Authors described the protocol of the study, challenges in recruitment of study population, discussed in depth why the trial was stopped as well as provided directions how the future studies should be designed. Despite the trial was ended early the knowledge presented in the article might have have research and study design implications.

Answer :
We thank this reviewer for commending us on our effort to correctly describe the fate of the MIRACLE EF study.

Highlights

1. CRT benefits may extend to heart failure patients with less depressed left ventricular function.
2. MIRACLE EF trial aimed to assess CRT benefits in HF patients with LVEF 36-50% and LBBB.
3. The study was stopped early for futility and a trial on morbidity and mortality trial not feasible.
4. We discuss the difficulties of study design to assess new indications for implantable devices.
5. Smaller RCTs with surrogate endpoints may be more reasonable than morbidity mortality studies.

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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 was 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.

Key words,

Heart failure, cardiac resynchronization therapy, Left ventricular ejection fraction, LBBB, mortality

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) Class 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)[7,8,9] 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%[12,13,14] 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 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 Class 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 2,900 enrolled patients in order to reach approximately 2,300 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 neuro-hormonal 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.

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 (**Figure 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 $\geq$ 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 the patient was

symptomatic at the scheduled visit and approval was granted by the study team to un-blind echo results for that subject.

Recurrent HF events would be compared between the study groups and be tracked by the recording of admission and discharge dates for both inpatient hospitalizations and outpatient events that required overnight stay, and were determined by adjudication from the EAC. QOL would be compared between the study groups by two validated instruments, the EQ-5D and the Kansas City Cardiomyopathy Questionnaire, with changes from baseline assessed through 24 months. Healthcare system cost-effectiveness of CRT-P would be evaluated through the use of standard and accepted economic methods. Mortality, healthcare utilization and the utility index from the EQ-5D would be used in this evaluation. LVEF and LVESV would be assessed at baseline, 6 months and 24 months and a comparison of the longitudinal changes between treatment groups was to be made. Progression of HF in the control group was hypothesized, including worsening of LVEF. In previous CRT studies, reverse remodeling was observed by measuring changes in the non-paced LVEF at follow-up.

2.4 Sample Size Calculation

The estimated mortality rate was calculated from the CHARM study which included patients with similar disease states.[21] The MIRACLE EF study was event driven, comparing the hazard rate of first events from the composite primary efficacy endpoint. The number of required events was estimated in order to observe statistical significance with an assumed hazard ratio of 0.75 or less. Four interim analyses were pre-specified, and the sample size requirement assumed a type I error rate of 0.039 based on the nominal value derived from an O'Brien-Fleming alpha spending function and a power of 0.9 for the final analysis. Based on published analyses,[21] it was projected that the primary endpoint would be reached in 10% of CRT-P OFF arm subjects and 7.5% of CRT-P ON arm subjects per year. The sample size calculations further assumed a hazard ratio of 0.75 before cross-over, a loss-to-follow-up rate of 2% per year, a total cross-over rate between study arms of 15% (with one half contributing to the primary endpoint prior to cross-over), three years of enrollment and a minimum of two years of follow-up. The allocation of study arm would be according to a 2:1 randomization schedule. Under these assumptions, 609 events would be observed in approximately 2,300 randomized subjects over the length of the study.

3.RESULTS

The MIRACLE EF steering committee was assembled in 2011 to review the literature, assemble available information, and subsequently draft a proposed protocol. Following discussion with the FDA addressing details of the study protocol including their recommendation of a double-blinded design or

a robust blinded endpoint, the MIRACLE EF protocol received an Investigational Device Exemption (IDE) from the FDA on November 1, 2012. The first subject was enrolled on January 3, 2013. On February 18, 2014, the study was stopped due to enrollment futility. At that time, 72 active clinical study sites from 5 countries had enrolled 44 subjects and randomized a total of 26 subjects. All 26 subjects had received CRT-P implants and were alive at the time of study closure. Management of CRT-P devices in these implanted patients after study exit was left to the discretion of their attending study physician. None of the implanted devices were explanted before study close.

The MIRACLE EF study sought to enroll a new population of patients for CRT therapy. While this has been a challenge to many clinical studies of new indications, the majority of the active sites in MIRACLE EF had previous experience enrolling new indication device trials, and yet >50 of these sites failed to enroll even one eligible subject. The MIRACLE EF trial was burdened with two major challenges to enrollment: 1) identification of eligible patients; and 2) patient and clinician acceptance of the long-term double-blinded design requiring a non-indicated implantable device in the control arm.

3.1.1 Patient Identification

Based on available national HF registries, we estimated that 4-5% of HF patients have both LBBB and an EF 35-50%, compared to 10-13% of HF patients with LVEF < 35%.[10,11] However, screening of databases or file screening within high-volume HF centers participating in the study did not reach these expectations. Many otherwise eligible patients already were implanted with primary prevention ICDs. Moreover, many of the patients successfully screened for the MIRACLE EF study were determined ineligible based on the baseline procedures, meaning that patients´ records did not contain the information necessary to determine eligibility (**Figure 2**). Twenty five study centers reported screening a total of 60,372 patients to find 5,754 potentially eligible patients for the study to enroll 44 and randomize 26 patients. The most common reasons for not being eligible for the study were the following: absence of LBBB (35%), QRS too narrow (15%), ongoing device therapy (16%; most often an ICD), or NYHA II HF without prior hospitalization or with low BNP or NT proBNP (14%). This observation is consistent with the IMPROVE HF registry, which showed that for each patient with an LVEF <35% identified through chart review to be eligible for CRT, more than four others with LVEF < 35% were indeterminate because of missing information, such as the QRS duration or NYHA class.[22]

3.1.2.Patient, Investigator and Institution Acceptance

A randomized, double-blinded study was proposed for two main reasons: (1) optimal medical therapy for HF is required under current indications for CRT, and is required in CRT studies to demonstrate

benefit over standard of care. However, the majority of patients in the study population (LVEF >40%) do not have HF medication recommendations in the current guidelines.[23,24] We believed that an unblinded trial would introduce too great a risk of selective medication management, potentially creating bias in the primary outcome (2) Study endpoints were expected to be primarily HF interventions, where knowledge of the treatment group assignment could impact decision-making.

Using a blinded trial design required an evaluation of the study risks and benefits to participants. A blinded trial meant exposing control arm patients to the risks of surgical intervention. Based on an analysis of the results from the REVERSE and the MIRACLE trials, the six month risk of system-related complications is approximately 15%. This risk is juxtaposed with the potential benefits to the patient population should the MIRACLE EF trial have successfully demonstrated efficacy. Given the risks of hospitalization and death observed in this population in the CHARM study, the morbidity and mortality were considered potentially significant enough to offset the risk of device implantation. Further, because the statistical design was event-driven, not all study subjects would need to be followed for five years and required follow-up could be as low as 24 months before devices in the control arm could be re-programmed to pacing.

Unfortunately, some investigators and subjects declined to participate because the double-blinded parallel design required a surgical intervention with a potentially long follow-up with only back up pacing in the control group (Figure 2). At the time the study was stopped there were 72 Ethics committee´s approvals out of 90 submissions, 35 of which had required a 2nd submission, 4 rejections and 14 applications still in process.

4.DISCUSSION

We wanted to test the hypothesis that CRT-P would be beneficial in HF patients with LVEF 36-50% for the combined endpoint of mortality and HF hospitalizations since these patients have high mortality and morbidity, especially in the presence of left bundle branch block.

The most important finding from the MIRACLE EF study was the difficulty in finding study patients fulfilling the inclusion criteria. The main reasons were 1) number of eligible patients for the study was far less than anticipated from the literature, especially regarding LBBB; 2) institutions, investigators and patients were reluctant to participate in a study that contained a five year inactive randomization arm (CRT-OFF); or 3) eligible patients already had an ICD, which was an exclusion criteria.

The LVEF criterion for CRT indications in current guidelines[10,11] is an LVEF of 30%[5,6] or 35%[1-4] based on previous CRT studies. Such patients also have an indication for an ICD. In contrast, HF patients with LVEF > 40% are not indicated for primary prevention ICDs or CRTs and also lack indications for evidence-based HF medications. [23,24] LVEF is recognized as a risk predictor for morbidity and mortality in HF patients.[21,25] While the risk of hospitalization and/or death declines as LVEF increases, an LVEF in the range of 36% to 45% still confers a significant risk of adverse outcomes, whereas a higher LVEF does not further contribute to mortality.[21,25] Moreover, while the proportion of HF patients with reduced ejection fraction has decreased, that of HF patients with relatively preserved LVEF has increased, probably due to better management of acute myocardial infarctions and an aging population.[26] Taken together, these facts illustrate the need for therapies in this increasing population with mildly reduced LVEF.

In the CHARM studies performed nearly 10 years ago, the risk of death and hospitalizations was still high in patients with LVEF > 40% and even greater in the presence of LBBB.[16.] Data from the Swedish National Heart failure Registry[15] based on 25,171 patients indicate that 25% of HF patients with LVEF 40-45% had wide QRS $\geq$ 120 ms, and wide QRS was linked to a greater mortality risk independently of LVEF. We assumed that LBBB would be encountered in about 4-5% of NYHA II-III HF and LVEF 36-50%.

Results of post-hoc analyses of randomized controlled trials of CRT reported comparable CRT benefits in patients with an LVEF > 35%[12,13,14] as in patients with LVEF $\leq$ 35%. In a sub-study from the PROSPECT[12] trial that included NYHA III-IV HF patients, Chung et al. reported similar benefits from CRT regarding the clinical composite response by Packer and reverse remodeling in patients with LVEF>35% compared to those with LVEF < 35%.

In the MADIT CRT trial with NYHA I-II patients, 38% had a baseline LVEF above the inclusion criteria of LVEF $\leq$ 30% when evaluated by the echocardiographic-core-lab.[13] In these patients there was a significant reduction in risk for HF hospitalizations or death compared to ICD alone. Moreover, the patients with LVEF >30% experienced greater extent of reverse remodeling than subjects with lower EF. Similar results were obtained in the REVERSE study[14] in which blinded echo core lab analysis revealed that almost 24% patients had LVEF >30%. After 24 month follow-up time, CRT in patients with LVEF >30% resulted in a significant 74% relative risk reduction in time to HF hospitalizations or death compared to 42% in the group with LVEF $\leq$30%. There were also modest reductions in LV end systolic volume index and LV mass in LVEF >30% patients although not to the same extent as in those with LVEF < 30%. We therefore, designed the MIRACLE EF trial to prospectively study CRT effects in HF patients with LBBB and LVEF in the range36-50%, to potentially establish new treatment in this underserved population. There are many lessons learned

from the MIRACLE EF experience.

4.1 Study design

The steering committee initially planned a CRT arm compared to optimal medical therapy (OMT) alone since patients in this study lacked an indication for a device. FDA questioned this design due to lack of blinding. The double-blinded, parallel design with an implanted control-arm programmed to CRT OFF may be more scientifically rigorous, but the consequence proved unappealing to patients, who declined the prospect of a CRT-P implant programmed OFF except for anti-bradycardia pacing for up to five years. It is our belief that patients´ willingness to participate would have been greater with a control arm of OMT with no device. Understandably, the risks of surgery without the benefits of therapy (even an ICD) were not embraced by many patients, and some clinicians managing eligible patients, as well as some Institutional Review Boards and Medical Ethics Committees. In the MADIT CRT[5] and RAFT[6] studies, the patients in the control group received an ICD. Since MIRACLE EF study patients did not fulfill an indication for a primary prevention ICD we could not provide such a control arm.

4.1. 2 *Placebo effects* are powerful in device studies[27] and may exaggerate or mimic treatment effects. Improvements may also be related to improved baseline care, fluid and nutritional guidance and better adherence to medical therapy. In a recent meta-analysis of 150 consecutive CRT studies the incremental symptomatic response to CRT was only 16%[28] when calculated as deducting the placebo effects in the control arm from the treatment effects in the CRT arm. It has also been suggested that a controlled study with a sham procedure may be particularly justified in device studies focusing on a patient group with no guideline indicated therapy[29] such as the Miracle EF study population. We therefore believed it was justified to plan to subject our patients to CRT implantation and with randomization to CRT ON or OFF in order to separate a therapy effect from placebo in a new HF population. Moreover, patients were randomized 2:1 CRT ON versus CRT OFF to increase the probability of receiving therapy and patients assigned to CRT OFF would have been offered to be programmed to CRT ON once a benefit had been established.

Previous trials have used non-implanted control arms to demonstrate CRT efficacy, including CARE HF[3] and COMPANION[30]. More recently, however, it has been suggested that studies with only objective endpoints such as mortality[31] or changes in echocardiographic parameters may not need an inactive control arm but this reasoning to our knowledge has not yet been applied in device studies.

4.1. 3 *Study duration*: In the MIRACLE study, the use of surrogate endpoints including change in Six Minute Hall-walk, quality of life, and NYHA class allowed for a short-duration of follow-up (6-months) with cross-over. More recent CRT trials, such as REVERSE[4], MADIT-CRT[5] and RAFT[6],

were conducted in HF populations already indicated for other rhythm device therapy. Lessons from these trials are that the milder disease states (NYHA II) demanded much longer observation times to prove mortality benefits. RAFT was the only one of these trials with a long enough observation time of 40 months to demonstrate a mortality benefit by CRT compared to control.[6] The MIRACLE EF study planned to include both NYHA II-III patients with an anticipated low event rate both regarding mortality and HF morbidity. Therefore, a long study follow up time was required to observe a sufficient number of events.

At the time of study closure, the MIRACLE EF Steering Committee could not reconcile the theoretical equipoise based on the scientific literature with the reality of the situation within the clinical and patient community. Our experience of designing and running the study raises important points for the choice of endpoints in future device studies with populations not already indicated for devices. Today, the commonly used endpoint for HF trials is the combination of HF hospitalization and mortality[20] or the combination of HF hospitalization and CV mortality.[32] In a population with decreasing events rates due to improvements in HF and other cardiovascular medication and invasive treatments it may prove extremely hard to calculate an accurate event rate in a long term RCT study. Therefore introduction of additional endpoints – more upstream in HF pathophysiology - such as reverse remodeling (in the study group) or adverse remodeling[4] in the control group[33] have been introduced. An alternative is to choose reverse remodeling *as primary endpoint* or to power the study for reverse remodeling. REVERSE[4] did not reach its primary endpoint of percent worsening in the control arm by the clinical composite endpoint[33] but did reach the powered secondary of drop in LV end-systolic volume index. If the CCS would have been used in the common way[34] i.e. with its entire distribution of scores, the REVERSE study would have reached its primary endpoint, as in previous CRT studies such as the MIRACLE ICD.[35] Although considered a surrogate endpoint, reverse remodeling is linked to improved morbidity and mortality both in device[36-37] and drug studies.[31] Gold et al recently reported that significant reverse remodeling by CRT at 6 months in REVERSE was associated with a 68% mortality reduction.[36] Similar observations were made in RCTs on HF medication such as most recently with ivabradine in the SHIFT trial.[32] In recent meta-analysis comprising 30 mortality studies, 25 drug/device therapies and 88 remodeling trials short term LV remodeling was associated with lower mortality[37] with more pronounced mortality effects among patients with greater reductions in left ventricular volumes. Importantly, the MADIT_ASIA trial that was also terminated early due to poor enrollment did have reverse remodeling as its primary endpoint. [38]

4.2 Study Population. MIRACLE EF initially targeted patients with LVEF in the range 36-50% and wide QRS. Broadly, this group would have better survival and lower morbidity than patients already indicated for CRT and would have been expected to contain a larger proportion of women. So, a subgroup with greater potential for benefit was selected. All subjects were required to have LBBB,

and also must have either NYHA Class III symptoms or NYHA Class II with additional risk-factor(s). LBBB is linked to greater benefit by CRT in substudies[7,8,9] and registry studies.[39] This higher-risk group was selected to promote detecting a benefit and to demonstrate cost-effective use of CRT in a reasonable sample size and follow-up duration

The electronic medical record (EMR) has become standard in many countries. EMR was to be considered a valuable tool for both the identification of potential subjects for study outside existing indications if they may be used for such a purpose by patient privacy reasons. To have the possibility to search for HF patients with LBBB and LVEF 36-50% would have been helpful for recruitment in MIRACLE EF. However, it was not possible to perform such search in most hospitals by patient privacy reasons or for operational reasons with the EMRs.

For future studies such issues may determine recruitment success since patients may be outside of in-hospital Cardiology units and seen by private cardiologists, internists or general practitioners who do not refer patients to heart failure specialists or to physicians implanting CRT and would be even less likely to do so in milder disease states. Pre-trial feasibility assessments may reduce the risk of subsequent early closure of studies ~~for futility reasons~~due to enrollment futility. Nonetheless, we believe that the major reason for not finding patients for the MIRACLE EF was not solely such technical difficulties but might also have been due to the low number of patients fulfilling inclusion criteria, in particular LBBB, than anticipated and the poor patient and physician acceptance of the study design. In a recent registry of patients with HF with preserved LVEF (defined as LVEF > 45%)[40] LBBB was only found in 3.5 %. Amongst our screened patients it was even lower. It is clear that we overestimated the presence of LBBB in our study emphasizing that the true prevalence of LBBB in our LVEF HF range remains unknown. Future trials would need to account for different referral patterns and prevalence of HF with LVEF 36-50%, as well as investigate the distribution of QRS widths and prevalence of co-existing LBBB in these patients, in order to optimize the trial design.

4.3 Lessons for the future. The fact remains that heart failure patients with electrical dyssynchrony and less severe LV dysfunction may benefit from CRT. Our experience demonstrates that although scientifically justifiable, a large mortality and morbidity study with double blinding with a long randomized follow up time of therapy turned OFF is unlikely to be feasible. A smaller parallel randomized study (CRT or no device) with reverse LV remodeling as the primary endpoint appears more realistic. Potentially it can be accompanied by a long term follow up comparing the mortality with that expected by the use of a predictive model. One such model, the MAGGIC[41], is based on established independent predictors of mortality. The MAGGIC meta-analysis included individual data

on 39 372 patients with HF, both reduced and preserved left ventricular ejection fraction (EF), from 30 cohort studies, six of which were clinical trials. It remains to be seen if such meta-analysis and use of predictive models will influence clinical practice, practice guidelines, and reimbursement strategies.

5.Conclusion

The MIRACLE EF trial raises questions of how to study new therapies in HF patients. These include choice of study population and primary endpoints. The more we move into lower risk HF populations the harder it will be to demonstrate morbidity and mortality improvements on top of existing medical therapy. Since the greater life-long benefits are to be found with preventive rather than therapeutic approaches, the ideal study design for such therapy remains to be established. The difficulties of implementing scientifically robust long-term studies in lower risk populations are substantial, and further discussions between trialists, regulators, patients, industry and physicians are essential: more reliance may be required on surrogate endpoints or on a combination of the clinical composite endpoint with surrogate endpoints followed by registry-type long term up.

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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 ≥130ms
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
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
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 m2)
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

Table 2. Data collection Overview

Data Collection Overview

Study Requirement	Baseline	CRT-P Implant	PHD*	Wound Check	3 Months	6 Months	12 and 18 Months	24 Months	30, 36, 42, 48, 54 and 60 Months	66, 72, 78 Months, etc.
Patient informed consent	X									
Inclusion/exclusion assessment	X									
Physical exam	X				X	X	X	X	X	
Echo	X**					X		X		
12-Lead ECG	X**					X		X		
Blood tests	X**									
BNP or NT-proBNP	X**					X		X		
CV medications	X				X	X	X	X	X	
Medical history	X									
Device check		X	X	X	X	X	X	X	X	
Randomization			X							
NYHA assessment	X**				X	X	X	X	X	
6-minute hall walk	X					X		X		
Quality of life and utility measures (KCCQ and EQ-5D)	X				X	X	X	X		
Blinding assessment								X		
LV lead implant assessment		X								
Telephone contact										X

*Pre-hospital Discharge visit

**Unless done within 30 days prior to enrollment

CRT-P cardiac resynchronization therapy pacemaker, CV= cardiovascular, Echo= echocardiography, EuroQoL, European Quality of Life Questionnaire [19], NYHA= New York Heart Association Functional Class, KCCQ= Kansas City Cardiomyopathy Questionnaire [18]LV=left ventricular, PHD= pre hospital discharge

Legends

Figure 1. Study design and flow diagram

Figure 2. Patients screened for participation in the study and the reasons for their ineligibility

Figure 1. Study design flow diagram

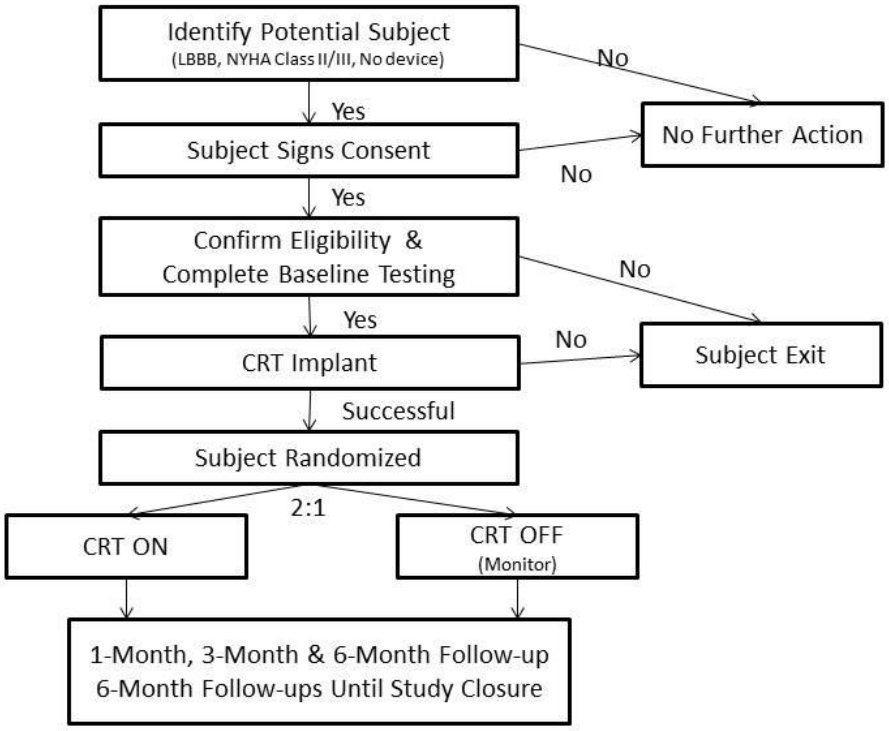

Figure 2. Screening log