A Long-term Prospective Randomized Controlled Study Using Repetitive Education at Six-Month Intervals and Monitoring for Adherence in Heart Failure Outpatients – The REMADHE Study

Short title: Repetitive Education and Monitoring HF Trial

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Word Count : Manuscript 4478 words + references 1281 words = 5759 words
Appendix 967 words
Abstract

Background  The effectiveness of heart failure (HF) disease management programs (DMP) in patients under cardiologists’ care over long-term follow-up is not established.

Methods  We investigated the effects of a DMP with repetitive education and telephone monitoring on primary (combined death or unplanned first hospitalization, and quality of life changes) and secondary end-points (hospitalization, death, and adherence). REMADHE is a long-term randomized, prospective, parallel trial designed to compare intervention versus control. 117 patients were randomized to usual care, and 233 to additional intervention.

Results  The mean follow-up was 2.47±1.75 years with 54% adherence to the program. In the intervention group, the primary endpoint composite of death or unplanned hospitalization was reduced (hazard ratio 0.64, CI 0.43 to 0.88, p=0.008), driven by reduction in hospitalization. The quality of life questionnaire score improved only in the intervention group (p.000). Mortality was similar in both groups. Number of hospitalizations (1.3±1.7 versus 0.8±1.3, p<0.0001), total hospital days over the follow-up (19.9±51 versus 11.1±24 days, p<0.0001), and the need for emergency visits (4.5±10.6 versus 1.6±2.4, p<0.0001) were lower in the intervention group. Beneficial effects were homogeneous for sex, race, diabetes and no diabetes, age, functional class, and etiology.

Conclusions  Over longer follow-up than previous studies, this HF DMP model in patients already cared for by a cardiologist is associated with reduction in
unplanned hospitalization, total hospital days and need for emergency care, as well as improved quality of life, despite modest program adherence over time.

Keywords:

heart failure, education, disease program management, case management, controlled clinical trials
Recent disease management program (DMP) meta-analyses have reported reductions in mortality and hospitalization of heart failure (HF) patients. However, important issues in DMP for HF remain to be resolved. For example, few investigations include non high-risk HF for early hospitalization managed by cardiologists or reported long-term results. No studies have reported the long-term effects of a repetitive-cyclic reeducation program. Most DMPs have been tested in high-risk HF patients discharged from the hospital, and it has been suggested that DMPs are less effective when patients are already being treated by an HF specialist. Improved survival is associated with cardiologist care and with multidisciplinary teams providing specialized follow-up. Whether both together could benefit HF is not well defined.

We tested whether a DMP consisting of a long-term repetitive multidisciplinary education program and telephone monitoring could benefit HF outpatients in usual ambulatory care already under the care of a cardiologist with experience in HF.

**Methods**

**Study Design (Figure 1)**

REMADEHE was a prospective, randomized, single-center open parallel trial controlled by nonintervention simple randomization and designed to compare intervention versus control.
The first patient was randomized on October 05, 1999 and the last on January 18, 2005 in the Heart Institute of the São University Medical School. At least 18-month follow-up from the last patient inclusion was planned to initiate the trial analysis. Referred patients with no exclusion criteria were randomized in a 2:1 ratio between the intervention and control parallel groups, respectively. A computer-generated randomization list was drawn up by the statistician. The randomization 2:1 was used based on the previous published benefit of DMP in HF. The 2:1 randomization sequence was developed in blocks of 3 including 2 interventions and 1 control. The order of interventions and control within each block was also randomly assigned. To avoid the deduction of the next treatment allocation and for arrangement of education classes researches were blinded for block size; and each randomization included a number of patients multiple of three with at least 15 eligible participants except for the last group. The order of subjects in each group was randomized using a computer program. For allocation concealment it was used sequential, numbered, opaque, and sealed envelopes. Investigators ensured that the envelopes were opened sequentially and only after the participant’s names were written on the appropriate envelope. The nurse involved in the education/monitoring enrolled the patients and assigned participants to their groups. The participants, the nurse and multidisciplinary team were not blinded to group assignment. Those assessing the outcomes were blinded to group assignment and endpoints (except for quality of life and adherence) that were determined by unanimous decision.
The research staff did not participate in intervention decisions. Hospitalizations, deaths, modes of death, need for emergency treatment, procedures, and events were obtained from patient self-reported data at medical visits, in telephone calls, and in a review of hospital records. At the time of enrollment and at 6-month intervals, scripted questionnaires were administered addressing heart-failure quality of life (The Minnesota Living with Heart Failure Questionnaire), and adherence score.

Standard follow-up medical visits for the intervention and control groups were performed during the study period by the same ambulatory cardiology team, which was not informed of the randomization. The scheduled interval between routine ambulatory evaluations was 3-4 months. Also, the ambulatory team did not participate in any step of the study. The ambulatory cardiology team was oriented to follow Brazilian Guidelines and standard treatment of the Heart Failure Clinics in the management of patients. Complementary follow-up visits were carried out, depending on each patient’s needs and on the decision of the attending cardiologist. When nurses detected noncompliance or worsening of the clinical condition, an unscheduled visit to the patient’s attending cardiologist could be proposed. It was not permitted use of any telemanagement by cardiologists or in-home technology, such as electronic blood pressure monitoring, ECG, or finger pulse oximeter.

**Study Population Selection**
Patients under the care of a cardiologist with experience in heart failure were consecutively recruited from a tertiary referral center. The study was carried out in the Heart Failure Clinics. Eligible ambulatory care patients were aged 18 years or older with irreversible chronic heart failure of at least 6-months duration.

Exclusion criteria included: the patients’ inability to attend educational sessions and researchers’ inability to monitor patients because of the patients’ lack of transportation, living too far away, or social or communication barriers; myocardial infarction or unstable angina within 6 months before randomization; cardiac surgery or angioplasty within 6 months of randomization; hospitalized patients or recently hospital discharged patients; severe renal/hepatic/neurological/pulmonary or any systemic disease that could confuse the interpretation of results and impair expected survival; planned surgical procedure or other procedure that could influence follow-up, and pregnant women or women of childbearing potential.

Disease Program Management (Figure 1) (Table 1)

This disease program management protocol was designed to have the following characteristics: inclusion of outpatients; intervention through education for patients and caregivers; medication management with optimized therapy based on guidelines, and remote monitoring; delivery personnel with nurses, cardiologists, pharmacists, social workers, dietitians, dentists, and psychologists; face-to-face individual/group communication, and telephone in-person. The intensity/complexity was long-term follow-up with repetitive education at 6-month
intervals. The environment was hospital outpatient; and the outcomes measured were clinical, quality of life, and adherence. A daily telephone number was provided to patients for emergencies or questions about HF management except on weekends.

**Evaluation of Adherence**

Adherence was monitored during the follow-up by using a self-reporting specific questionnaire (Appendix).

**Objectives**

The prespecified primary endpoints were (1) combined death secondary to any cause or unplanned first hospitalization and (2) quality of life changes. The prespecified secondary endpoints were (1) feasibility of this repetitive DMP, based on the percentage of referred patients who were excluded and on the percentage of patients randomized for intervention who did not attend more than one educational session; (2) death from any cause; (3) unplanned total hospitalizations; (4) unexpected death at home and death during hospitalization; (5) need for unplanned emergency care; (6) total days of hospitalization, (7) number of days of each hospitalization, (8) adherence after DMP, and (9) subgroup analysis. The study protocol was submitted initially to the Heart Institute Ethical Committee in 1999 and received the number 827/99. The local ethical committees approved the study. All patients gave informed consent for participation in the study. The study was registered at http://clinicaltrials.gov.
(Identifier NCT 00505050). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Statistical Analysis**

Descriptive statistical analysis was composed of simple distribution of frequencies, calculation of proportions, means, and their respective standard deviations (SD) or standard errors (SE). Continuous variables were expressed as mean ± SD or SE, and categorical variables were expressed as percentages. For effects of group comparison the $t$ test was used for normal distribution. The Mann-Whitney test was used to compare variables without normal distribution. For analysis of quality of life and adherence we used a two-way analysis of variance (ANOVA) with repeated measures on time (follow-up) (two factors: group – intervention and control; and time – T0, T1,..Tn). For categorical variables, the chi-square test or the Fisher exact test was applied. Patient survival, hospitalization, and event rate were described using Kaplan-Meier estimates and survival graphs. Differences between the curves were tested for significance by log-rank statistics using a Cox proportional-hazards regression model and Breslow’s test. We analyzed all major outcomes by time to first event. Statistical analysis was performed according to the intention-to-treat principle for combined endpoints, death, and all data. The analysis was follow-up driven instead of event-driven. In the analysis, data on patients were censored at the
time of cardiac transplantation. Differences between treatment groups in post randomization measures or events were evaluated by analysis of variance and with the chi-square test. The planned sample size of 350 patients was designed to provide around 90% power, and 5% significance to detect a 20% relative reduction in the primary outcome combined death secondary to any cause or unplanned first hospitalization, assuming an annual event rate of 30%.

Proportions of patients responding were compared between treatment subgroups (sex, race, age, functional class I/II and III/IV, diabetes/non diabetes, and ischemic/non ischemic etiology) with the Mantel-Haenszel Chi-squared test, adjusted for the stratification variable, intervention procedure. Also, participant characteristics (prognostic variables) were adjusted for by using Cox multiple regression analysis. All analyses and graphs were performed with SPSS statistical software version 11.5 and Graphpad Prism software version 4.02.

Results

Population Baseline Demographic Data and Feasibility of DMP (Table 2)

From October 5, 1999 to February 8, 2005, 529 outpatients were referred for treatment. (Figure 1 and 2) The control and intervention groups were similar in all baseline characteristics (Table 2). The mean follow-up was 2.47±1.75 years for all patients, 2.44±1.7 years for the control group, and 2.48±1.79 years for the intervention group (p=ns). Five patients (4.3%) of the control group and four (1.7%) patients of the intervention group were lost to follow-up. The interval from
the result analysis to first randomization and last randomization were 2543 days and 611 days respectively. The number of monitoring calls was 15±10 per patient with intervals of 74±30 days between them. In 25% of calls it was observed modification of water and sodium restriction; and in 2% additional cardiologist evaluation necessity. In 95% of additional visits to cardiologist there were changes in medication. During the follow-up in 5% of patients the doses of diuretics were changed by calls.

**Prespecified Primary Endpoints (Figure 2 and 3)**

In the intention-to-treat analysis, the intervention group had a statistically significant risk reduction in the estimated combined end-point first hospitalization or mortality (p=0.008, hazard ratio 0.64, CI 0.43 to 0.88) in comparison with controls (Figure 2). In the intervention group, the cumulative proportion event-free estimates (SE) at 1-, 3-, and 5-year follow-up were 71%(6), 53%(7), and 37%(9), respectively, whereas in the control group, they were 60% (9), 32%(9), and 21%(11), respectively. At 2½-year follow-up, the DMP intervention resulted in a reduction of 17% in the absolute risk of the combined event and 27% reduction in the relative risk.

The intervention group had smaller sequential Minnesota Quality of Life Questionnaire scores compared with control group scores during the follow-up (Figure 3). The mean scores in the intervention group from baseline to follow-up reduced -25±20 whereas in the intervention group the means scores reduced -2.2±24 (p=0.000, intervention versus control). The initial reduction in the
intervention group remained during the follow-up. The sequential questionnaire values (SD) in the intervention group at 1, 3, and 5 years were 29±20, 26±19, and 32±19. In the control group, the scores (SD) were 39±22, 29±18, and 48±32.

Secondary End-Points

The feasibility of our HF DMP study was 54%. In the intention-to-treat analysis, no difference occurred in estimated total mortality between intervention and control groups (p=ns, hazard ratio 0.80, 95%CI 0.55 to 1.13) (Figure 5). Also, no statistical differences between the groups were verified for death during hospitalization (p=ns, hazard ratio 0.86, 95%CI 0.53 to 1.41), and unexpected death at home (p=ns, hazard ratio 0.83, 95% CI 0.47 to 1.46) (Table 3). The number of unplanned hospitalizations from any cause, the total days of hospitalization, and the need for emergency care were smaller in the intervention group than in the control group (Table 3).

The sequential HF adherence index values were higher in the intervention group compared with those in the control group (Figure 6). The initial increment in the intervention group remained during the follow-up. The mean adherence scores at baseline and during follow-up in the control group were 36.4±9.95 and 39.9±7.9 (p=ns), whereas in the intervention group, they were 30.8±11 and 51.8±5.8 (p<0.0001). The sequential score values in the intervention group at 1, 3, and 5 years were 52±8, 52±6, and 51±7, respectively, whereas, in the control group the scores were 42±10, 39±11, and 40±8.
Subgroup Analysis (Figure 7)

The beneficial effects on the composite outcome were consistently observed among predefined subgroups: women and men; Caucasian (white) and afro-Brazilian descendents; diabetes and no diabetes; age < 52 years and > 52 years; New York Heart Association functional class II/II and III/IV; ischemic and non ischemic etiology. On Cox multiple regression analysis the functional class was indentified as the unique independent predictor of combined outcome (p <0.000, corrected relative risk 0.51, confidence interval 0.38-0.68).

Discussion

To our knowledge our HF DMP trial is unique in the long-term repetitive employment of high intensive education through interviewers and education classes in HF outpatients. Also, the study provides new sequential long-term data using an adherence index to improve the knowledge of mechanisms explaining DMP benefits.

Our HF DMP consisting of repetitive education at 6-month intervals and monitoring improved outpatient status in long-term follow-up in patients already being treated by cardiologists. The beneficial effects of the combined end-point on subgroup analysis were homogeneous for sex, race, diabetes and non diabetes, age, functional class, and etiology. Particularly noteworthy was the effectiveness in younger patients, no ischemic causes, and in patients with less severe disease in New York functional class I-II. The calculated number of HF
patients who needed this DMP intervention to prevent one combined event (hospitalization or death) until 2½ years of follow-up was 6 patients.

Our beneficial effects in outpatients indicate that the spectrum of patients who would have long-term benefit from DMP is quite broad including patients with non advanced heart failure, or those under ambulatory care. In fact, most patients in a community setting of HF in a beta-blocker era are in functional class I and II, and could become a target for DMP application. The DMP indication for non advanced HF under ambulatory care might prevent deterioration to a stage that requires hospitalization. Our results differ from those of previous trials that included non advanced heart failure, and were different in design, DMP intensity and complexity, time of follow-up, and sociodemographic characteristics. Our findings are in accordance with the first report of DMP success in high-risk HF patients for early hospitalization, and with the DIAL trial that had shorter follow-up.

Our results support the role of our DMP design of long-term follow-up with high-intensity repetitive education and monitoring in the management of non advanced HF outpatients already being treated by cardiologists. Our results disagree with the idea that DMP of medium duration (3-6 months) follow-up is more consistently associated with success compared with long-duration programs. Also, our results do not support the concept that long-term, intensive post discharge follow-up is unnecessary, especially in non advanced HF under ambulatory care, providing that the patient has immediate access to specialist service in the event of suspected deterioration. However, our
results are in accordance with the long-term benefit of DMP reported recently regarding heart failure clinics, and home-based intervention for HF patients after hospital discharge.23,24,25,26

REMADHE is a unique study with sequential quality of life results on long-term follow-up in non advanced HF outpatients. The repetitive education could be a factor contributing to persistence of the early benefit. Persistent effects on quality of life can have important clinical implications, because the conventional step-up medication approach in HF may have a positive impact on survival or morbidity, but not on quality of life.27 HF DMP effects on quality of life are controversial or the beneficial effects have not been sustained.1,3,28 In general, trials that include quality of life assessment had short follow-up, and the evaluation was at the end of the study.3,5,20,29,30 Our results agree with results from a previous trial developed in South America in different clinical settings that resulted in improved end-study quality of life.5 However, our results do not agree with long-term quality of life results after hospital discharge in older patients, or a reported unsustained effect.18,28 Also, our quality of life improvement was higher than that reported in a meta-regression analysis.29

Our understanding of the potential underlying mechanisms for improving outcomes with DMP remains limited.23,31,32,33,34,35,36,37 Based on the persistent initial improvement in sequential adherence results, reported for the first time in our study, a role for adherence improvement in mechanisms determining long-term HF DMP success may be suggested. The hypothesis that adherence would be monitored in long-term follow-up as an additional mechanism to prevent the
A reduction in late positive effects is attractive. Also, the intervention has no underlying psychosocial theory but was designed with methods of support that have worked well in these medical settings.

**Prespecified Subgroup Analysis**

Our investigation is the first to suggest the HF DMP can have long-term effects in Caucasian-Brazilians as in African-Brazilians. As a consequence, this HF DMP can be proposed for use in black populations as it is for the general population. It attractive to test this DMP design also in African-Americans because they are at a higher risk of HF, and the age of onset is significantly younger in comparison with whites. However, the functional class was an independent predictor of combined outcome.

**Limitations**

Inherent main limitations of the protocol include the open design, and the absence of blinding to the treatment assignment. The unblinded design could allow a certain degree of co-intervention by nurses or doctors to compensate for patients not being in the DMP group, or to optimize the situation of the intervened subjects to better illustrate the effectiveness of the DMP. Also, control patients could learn about the intervention. However, the researches provided different schedules for control and intervention groups concerning ambulatory care to avoid any contamination. Despite of the cardiology team was not informed of patient allocations, a blind care is not completely warranted. However, all
nonpharmacological trials have these limitations. Furthermore, the REMADHE study can be accepted as of very high quality according the CLEAR NPT checklist developed for nonpharmacological trial. Perception of quality of life may be better because patients in intervention group have the comfort of knowing that they have a knowledgeable health care professional that they will talk to frequently; however, this comfort is essential component of the intervention. The included population was composed of relatively fewer older patients in comparison with reported data. However, less aged patients may represent a significant absolute number of HF hospitalized patients in general not included in DMP trials. There are limitations in obtaining self report data and hospital records because of unreliable answers and hospitalizations in non accessible distant hospitals. However, all deaths, hospitalizations, and needs for emergency treatment were confirmed by documentation. One additional limitation of our HF DMP is the initial low feasibility of the intervention influenced by social conditions, however, its long-term indication for selected patients seems to be a realistic objective.

Conclusions and Clinical Implications

Over longer follow-up than previous studies, this HFDMP model in patients already cared for by a cardiologist is associated with reduction in unplanned hospitalization, total hospital days and need for emergency care, as well as improved quality of life, despite modest program adherence over time.
Disclosures

None.
References


Legend of Figures

Figure 1. Study design

Figure 2. Flow Diagram of the REMADHE Trial

Figure 3. Survival free of hospitalization or death in control and intervention groups according to intention-to-treat analysis.

Figure 4. Quality of Life Minnesota Questionnaire results during the follow-up in the control and intervention groups according intention-to-treat analysis.

Figure 5. Survival free of death in control and intervention groups according to the intention-to-treat analysis.

Figure 6. The Sequential Adherence Index results in control and intervention groups during the follow-up.

Figure 7. Subgroup analysis comparing control and intervention groups.
Table 1. Interventions of the Disease Program Management

Interviewers and Education Classes

Interviewers
- Duration: 30 minutes with any multidisciplinary component
- Personnel: nurses, pharmacists, social workers, dietitians, psychologists
- Design: face-to-face including all randomized intervention patients
- Schedule: Early After Randomization

Education Classes:
- Duration: 60 minutes
- Personnel: multidisciplinary (nurse, pharmacist, social worker, dietitian, dentist, and psychologist)
- Design: group class including all randomized intervention patients
- Schedule: early after randomization (four times) and during the follow-up
- Intervals: one week between the 1st and 2nd; one month between the 2nd, 3rd (1st reinforcement), and 4th (2nd reinforcement); and after at 6 months intervals

Content of Interviewers and Education Classes:
- Basic principles related to heart failure (HF)
- Causes and pathophysiology of HF; causes of volume overload
- Rationale for pharmaceutical and no pharmaceutical therapy
- Importance of drug adherence, mechanisms of drug action
- Role of sodium, fluid restriction, and diet (unless otherwise specified by the patient’s physician)
- Rationale for self-care behaviors, daily weight monitoring
- Avoidance of alcohol intake, cigarette smoking, and anti-inflammatory drugs
- Instruction about exercise, work, and daily physical activities
- Signs of the onset of HF exacerbation
- Appropriate reaction to signs and symptoms (in special for syncope, tachycardia, hemoptyses, ascites, edema, fever, worsened dyspnea, chest pain, paroxysmal nocturnal dyspnea, nocturnal cough, new orthopnea, oliguria, anorexia, abdominal pain)
- Instruction about what to do if symptoms worsened or with a new symptom
- Potential drugs that can worse HF (estrogen, corticosteroids, calcium antagonists, antiarrhythmic agents, etc)

Monitoring

Telephone calls
- Initiation: after the 2nd group education class
- Intervals: scheduled at 14-day frequency (more or less according nurse’s decision about necessity)
- Personnel: nurse trained in HF management
- Content: predetermined questionnaire
- Objective: to reinforce the education
  - Monitor compliance/adherence, signs/symptoms of worsening HF, self-control mechanisms
  - Adjustment of diuretic dosage by nurse if necessary
- To recommend unscheduled medical or emergency visit if worsening HF or noncompliance
### TABLE 2. BASELINE CHARACTERISTICS OF CONTROL AND INTERVENTION GROUPS

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CONTROL N=117</th>
<th>INTERVENTION=233</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>AGE (YEARS)</strong></td>
<td>52 ± 11</td>
<td>50 ± 19</td>
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</tr>
<tr>
<td><strong>MALE SEX (%)</strong></td>
<td>64.1%</td>
<td>71.2%</td>
<td>NS</td>
</tr>
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<td><strong>RACE: WHITE/BLACK/MULATTO/YELLOW (%)</strong></td>
<td>59/22/19/1</td>
<td>50/28/21/0.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>RADIOISOTOPIC LVEF (%)</strong></td>
<td>30 ± 8.9</td>
<td>28 ± 11</td>
<td>NS</td>
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<tr>
<td><strong>RADIOISOTOPIC RVEF (%)</strong></td>
<td>35 ± 9</td>
<td>30 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td><strong>LVEDD (IN CM) BY ECHO</strong></td>
<td>7.0 ± 1</td>
<td>7 ± 1</td>
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</tr>
<tr>
<td><strong>BMI (BODY MASS INDEX)</strong></td>
<td>26 ± 4.7</td>
<td>26.3 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>NY. F. C. III/IV (%)</strong></td>
<td>23/34/29/14</td>
<td>19/45/25/11</td>
<td>NS</td>
</tr>
<tr>
<td><strong>SYSTOLIC HF (LVEF &lt; 45%)</strong></td>
<td>80%</td>
<td>81.6%</td>
<td>NS</td>
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<tr>
<td><strong>LEFT BRANCH BLOCK</strong></td>
<td>14.5%</td>
<td>19.7%</td>
<td>NS</td>
</tr>
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<td><strong>CAUSE (IN %)</strong></td>
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<td>NS</td>
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<tr>
<td><strong>ISCHEMIC/ ALCOHOLIC/ CHAGASIC</strong></td>
<td>22/8/21</td>
<td>28/4/16</td>
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<td><strong>HYPERTENSIVE/IDIOPATHIC/VALVAR/OTHER</strong></td>
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<td>18/17/3/14</td>
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<td><strong>ATRIAL FIBRILLATION OR FLUTTER</strong></td>
<td>14.5%</td>
<td>9.8%</td>
<td>NS</td>
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<tr>
<td><strong>HF PHARMACOTHERAPY (%)</strong></td>
<td></td>
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<tr>
<td><strong>AMIODARONE</strong></td>
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<td><strong>ARA</strong></td>
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<td><strong>ACEI</strong></td>
<td>80%</td>
<td>85%</td>
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<td><strong>B-BLOCKER</strong></td>
<td>71%</td>
<td>61%</td>
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<td><strong>SPIRONOLACTONE</strong></td>
<td>58.1%</td>
<td>53.6%</td>
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<td><strong>HYDRAZINE</strong></td>
<td>9.4%</td>
<td>3.4%</td>
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<td><strong>NITRATES</strong></td>
<td>11.1%</td>
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<tr>
<td><strong>DIGOXIN</strong></td>
<td>58.1%</td>
<td>68.2%</td>
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<td><strong>DIURETICS</strong></td>
<td>82.9%</td>
<td>80.5%</td>
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<td><strong>FUROSEMIDE</strong></td>
<td>72%</td>
<td>80.5%</td>
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<tr>
<td><strong>RESYNCHRONIZATION</strong></td>
<td>2.6%</td>
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<td><strong>STATIN</strong></td>
<td>15.8%</td>
<td>10.1%</td>
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<tr>
<td><strong>OTHER PHARMACOTHERAPY (%)</strong></td>
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<td></td>
<td>NS</td>
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<tr>
<td><strong>ORAL ANTIDIABETIC THERAPY</strong></td>
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<td>3.4%</td>
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<td><strong>ORAL THYROID HORMONE</strong></td>
<td>5.1%</td>
<td>3.4%</td>
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<tr>
<td><strong>SERUM SODIUM, MEQ/L</strong></td>
<td>139 ± 6</td>
<td>139 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td><strong>% LEUCOCYTES</strong></td>
<td>28 ± 9</td>
<td>27 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HEMOGLOBIN (G/L)</strong></td>
<td>13.8±2.1</td>
<td>13.9±1.6</td>
<td>NS</td>
</tr>
<tr>
<td><strong>SERUM CREATININE, MG/DL</strong></td>
<td>1.4±1</td>
<td>1.2±5</td>
<td>NS</td>
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<tr>
<td><strong>LDL CHOLESTEROL</strong></td>
<td>124 ± 47</td>
<td>125 ± 38</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HDL CHOLESTEROL</strong></td>
<td>45 ± 15</td>
<td>43 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td><strong>V02 PEAK (IN ML/KG/MIN)</strong></td>
<td>16.9 ± 6.8</td>
<td>17.5 ± 6.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>FASTING Glucose LEVELS</strong></td>
<td>109±30</td>
<td>111±37</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HF DURATION (MONTHS)</strong></td>
<td>87±169</td>
<td>84±155</td>
<td>NS</td>
</tr>
<tr>
<td><strong>NO. OF HOSPITALIZATIONS (PREVIOUS 12 MO)</strong></td>
<td>0.42±1.06</td>
<td>0.39±1.09</td>
<td>NS</td>
</tr>
<tr>
<td><strong>IMPLANTED CARDIOVERTER-DEFIBRILLATOR</strong></td>
<td>0.85%</td>
<td>0.43%</td>
<td></td>
</tr>
<tr>
<td><strong>COMORBIDITIES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DIABETES</strong></td>
<td>18.1%</td>
<td>16.6%</td>
<td></td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>3.4%</td>
<td>1.28%</td>
<td></td>
</tr>
<tr>
<td><strong>PREVIOUS 12 MONTHS NON HOSPITALIZED (%)</strong></td>
<td>82.9%</td>
<td>82.4%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HYPTERTHYROIDISM</strong></td>
<td>7.7%</td>
<td>7.3%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HYPERHYPERTHYROIDISM</strong></td>
<td>0.8%</td>
<td>1.7%</td>
<td>NS</td>
</tr>
</tbody>
</table>

LVEF means left ventricular ejection fraction; RVEF, right ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; N.Y.H.A., New York Heart Association; HF, heart failure; ARA, angiotensin receptor antagonist; ACEI, angiotensin-converting enzyme inhibitor; V02 peak, maximal oxygen consumption in treadmill exercise; No., number of; mo, month; COPD, chronic obstructive pulmonary disease
### TABLE 3. COMPARISON BETWEEN FOLLOW-UP OF INTERVENTION GROUP VERSUS CONTROL GROUP (INTENTION-TO-TREAT ANALYSIS)

<table>
<thead>
<tr>
<th></th>
<th>CONTROL N = 117</th>
<th>INTERVENTION N = 233</th>
<th>RR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY COMBINED END-POINT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up until event</td>
<td>1.63 years</td>
<td>3.19 years</td>
<td>0.64 (0.46 to 0.85)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Median follow-up until death</td>
<td>3.7 years</td>
<td>5.15 years</td>
<td>0.79 (0.55 to 1.12)</td>
<td>0.192</td>
</tr>
<tr>
<td>Median follow-up until 1st hospitalization</td>
<td>2.06 years</td>
<td>4.21 years</td>
<td>0.62 (0.42 to 0.85)</td>
<td>0.0041</td>
</tr>
<tr>
<td>SECONDARY END-POINTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total mortality (n) (%)</td>
<td>50 (42.7%)</td>
<td>84 (36%)</td>
<td>0.92 (0.76 to 1.11)</td>
<td>NS</td>
</tr>
<tr>
<td>Unexpected home death</td>
<td>20 (17%)</td>
<td>33 (14%)</td>
<td>0.97 (0.88 to 1.07)</td>
<td>NS</td>
</tr>
<tr>
<td>Intrahospital death</td>
<td>26 (22%)</td>
<td>46 (18%)</td>
<td>0.97 (0.86 to 1.09)</td>
<td>NS</td>
</tr>
<tr>
<td>Unknown cause or place</td>
<td>4 (3.4%)</td>
<td>5 (2.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>1.26±1.74</td>
<td>0.81±1.34</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>(from 0 to 8)</td>
<td>(from 0 to 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total days</td>
<td>19.9±51</td>
<td>11.09±24.01</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Need for emergency treatment</td>
<td>4.55±10.61</td>
<td>1.60±2.42</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Surgical/invasive procedures</td>
<td>13 (11%)</td>
<td>45 (19.3%)</td>
<td>1.10 (1.01 to 1.21)</td>
<td>0.052</td>
</tr>
<tr>
<td>Transplantation (n) (%)</td>
<td>5 (4.3%)</td>
<td>16 (6.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacing-resynchronization</td>
<td>3 (2.6%)</td>
<td>6 (2.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial revascularization</td>
<td>1 (0.8%)</td>
<td>6 (2.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD or VAD</td>
<td>3 (2.6%)</td>
<td>3 (1.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td>0</td>
<td>3 (1.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve surgery</td>
<td>0</td>
<td>8 (3.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other procedures</td>
<td>1 (0.8%)</td>
<td>3 (1.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Need for emergency treatment means any treated emergency during <24 hours; unplanned hospitalization, hospital admission >24 hours; ICD, implantable cardioverter-defibrillator; PCA, percutaneous coronary angioplasty; VAD, ventricular Assist Device; RR, relative risk; CI, confidence intervals.
Figure 1.

Pts Referred to DMP
N=529

Exclusion Criteria (n=179)

Randomized Pts
N=350

DMP Intervention Group
N=233

Months
1
2
3
6

Monitoring by Phone
Nurse-based

1st Multidisciplinary Education

2nd Multidisciplinary Education

1st Education Reinforcement

2nd Education Reinforcement

6 Month Interval Education Reinforcement

Baseline Data

Sequential Evaluations:
Mortality
Hospitalization
Quality of life each 6 mo
Adherence each 6 mo

Control Group
N=117
Figure 3.

Survival free of unplanned hospitalization

years of follow-up

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>233</td>
<td>156</td>
</tr>
<tr>
<td>117</td>
<td>69</td>
</tr>
<tr>
<td>102</td>
<td>41</td>
</tr>
<tr>
<td>59</td>
<td>21</td>
</tr>
<tr>
<td>35</td>
<td>13</td>
</tr>
<tr>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

p = 0.002
Figure 4.
Figure 5.
Figure 6.
Figure 7.
### Appendix

**Questionnaire for Adherence in Patients with Heart Failure**

Questions and Possible Answers with Respective Score

1. **Medications**
   1.1. Did you take the medications in the last 15 days according to the medical prescription?
   - 0 - Never (0%)
   - 1 - Almost never (from 1 to 2 days or from 7% to 13%)
   - 2 - Few times (during 3 or 4 days or from 20% to 27%)
   - 3 - Sometimes (from 5 to 7 days or from 33% to 47%)
   - 4 - Frequently (from 8 to 11 days or from 53% to 73%)
   - 5 - Almost ever (from 12 to 14 days or from 80% to 93%)
   - 6 - Ever (during 15 days or 100%)

2. **Food and Fluids**
   2.1. Did you measure your weight daily?
   - 0 - Never (0%)
   - 1 - Almost never (from 1 to 2 days or from 7% to 13%)
   - 2 - Few times (during 3 or 4 days or from 20% to 27%)
   - 3 - Sometimes (from 5 to 7 days or from 33% to 47%)
   - 4 - Frequently (from 8 to 11 days or from 53% to 73%)
   - 5 - Almost ever (from 12 to 14 days or from 80% to 93%)
   - 6 - Ever (during 15 days or 100%)

   2.3. Did you restrict the addition of salt to foods?
   - 0 - Never (0%)
   - 1 - Almost never (from 1 to 2 days or from 7% to 13%)
   - 2 - Few times (during 3 or 4 days or from 20% to 27%)
   - 3 - Sometimes (from 5 to 7 days or from 33% to 47%)
   - 4 - Frequently (from 8 to 11 days or from 53% to 73%)
   - 5 - Almost ever (from 12 to 14 days or from 80% to 93%)
   - 6 - Ever (during 15 days or 100%)

   2.4. Did you add spices, sauce, and other manufactured foods with normal salt to your meals?
   - 0 - Ever (during 15 days or 100%)
   - 1 - Almost ever (from 12 to 14 days or from 80% to 93%)
   - 2 - Frequently (from 8 to 11 days or from 53% to 73%)
   - 3 - Sometimes (from 5 to 7 days or from 33% to 47%)
   - 4 - Few times (during 3 or 4 days or from 20% to 27%)
   - 5 - Almost never (from 1 to 2 days or from 7% to 15%)
   - 6 - Never (0%)

   2.5. Did you have meals or foods intake out of the home without salt restriction?
   - 0 - Ever (during 15 days or 100%)
   - 1 - Almost ever (from 12 to 14 days or from 80% to 93%)
   - 2 - Frequently (from 8 to 11 days or from 53% to 73%)
   - 3 - Sometimes (from 5 to 7 days or from 33% to 47%)
   - 4 - Few times (during 3 or 4 days or from 20% to 27%)
   - 5 - Almost never (from 1 to 2 days or from 7% to 15%)
   - 6 - Never (0%)

   2.6. Did you have meals with or intake soups, ice-cream, gelatin, jelly, juice, milk, tea, coffee, soft-drinks, etc without considering the quantity of liquid?
   - 0 - Ever (during 15 days or 100%)
   - 1 - Almost ever (from 12 to 14 days or from 80% to 93%)
   - 2 - Frequently (from 8 to 11 days or from 53% to 73%)
   - 3 - Sometimes (from 5 to 7 days or from 33% to 47%)
   - 4 - Few times (during 3 or 4 days or from 20% to 27%)
   - 5 - Almost never (from 1 to 2 days or from 7% to 15%)
   - 6 - Never (0%)

   2.8. Did you restrict fluid ingestion according to medical or nurse instruction?
   - 0 - Never (0%)
   - 1 - Almost never (from 1 to 2 days or from 7% to 13%)
   - 2 - Few times (during 3 or 4 days or from 20% to 27%)
   - 3 - Sometimes (from 5 to 7 days or from 33% to 47%)
   - 4 - Frequently (from 8 to 11 days or from 53% to 73%)
   - 5 - Almost ever (from 12 to 14 days or from 80% to 93%)
   - 6 - Ever (during 15 days or 100%)

   2.9. Did you ingest fruits with higher quantities of fluids without considering the liquid, such as oranges, melons, watermelon, pineapple, coconut water, etc.?
   - 0 - Ever (during 15 days or 100%)
   - 1 - Almost ever (from 12 to 14 days or from 80% to 93%)
   - 2 - Frequently (from 8 to 11 days or from 53% to 73%)
   - 3 - Sometimes (from 5 to 7 days or from 33% to 47%)
   - 4 - Few times (during 3 or 4 days or from 20% to 27%)
   - 5 - Almost never (from 1 to 2 days or from 7% to 13%)
   - 6 - Never (0%)

   2.10. Did you ingest any alcoholic beverages?
   - 0 - Ever (during 15 days or 100%)
   - 1 - Almost ever (from 12 to 14 days or from 80% to 93%)
   - 2 - Frequently (from 8 to 11 days or from 53% to 73%)

22
3 - Sometimes (from 5 to 7 days or from 33% to 47%)
4 - Few times (during 3 or 4 days or from 20% to 27%)
5 - Almost never (from 1 to 2 days or from 7% to 13%)
6 - Never (0%)

4. Medical Appointments
4.1. Did you miss any medical or nurse appointments, or scheduled exams?
0 - Ever (during 15 days or 100%)
1 - Almost ever (from 12 to 14 days or from 80% to 93%)
2 - Frequently (from 8 to 11 days or from 53% to 73%)
3 - Sometimes (from 5 to 7 days or from 33% to 47%)
4 - Few times (during 3 or 4 days or from 20% to 27%)
5 - Almost never (from 1 to 2 days or from 7% to 13%)
6 - Never (0%)
A Long-term Prospective Randomized Controlled Study Using Repetitive Education at Six-Month Intervals and Monitoring for Adherence in Heart Failure Outpatients: The REMADHE Study

Edimar A Bocchi, Fátima Cruz, Guilherme Guimarães, Luiz Felipe Pinho Moreira, Victor Sarli Issa, Silvia Moreira Ayub Ferreira, Paulo Roberto Chizzola, Germano Emilio Conceição Souza, Sara Brandão and Fernando Bacal

Circ Heart Fail. published online January 1, 2008;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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