Left Ventricular Reverse Remodeling, Device-Related Adverse Events, and Long-Term Outcome After Cardiac Resynchronization Therapy in the Elderly

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Background—Limited data are available on efficacy, safety, and long-term prognosis after cardiac resynchronization therapy (CRT) in elderly patients. We aimed at evaluating the effect of CRT, device-related adverse events, and long-term outcome after CRT among elderly patients.

Methods and Results—A total of 798 CRT recipients (208 elderly: age, ≥75 years; 590 nonelderly: age, <75 years) underwent clinical and echocardiographic evaluation at baseline and 6-month follow-up. Elderly patients had similar improvements in clinical symptoms, left ventricular function, and left ventricular reverse remodeling as their counterparts. Similar rates of device-related in-hospital (within 24 hours; \( P=0.552 \)), early (within 30 days; \( P=0.984 \)), and long-term adverse events (entire follow-up; hazard ratio, 0.90; \( P=0.620 \)) were observed between groups. During long-term follow-up (median, 38.6 months; interquartile range, 22.5–61.8 months), all-cause mortality rate was significantly higher among the elderly patients. However, the differences in cumulative event rates started after 4 years of follow-up (\( P=0.013 \)), and the cause of death was mainly noncardiac (29% in the elderly versus 19% in nonelderly; \( P<0.001 \)). Diabetes mellitus (hazard ratio, 2.322; \( P=0.019 \)), impaired renal function (hazard ratio, 0.975; \( P=0.006 \)), and reduced 6-minute walk distance (hazard ratio, 0.996; \( P<0.019 \)) were independently associated with all-cause mortality in elderly patients.

Conclusions—CRT efficacy and device-related adverse events in elderly patients were comparable with that of nonelderly patients. However, after 4 years of follow-up, elderly patients showed worse survival and the cause of death was mainly noncardiac. Diabetes mellitus, impaired renal function, and reduced 6-minute walk distance were independently associated with all-cause mortality of elderly patients. (Circ Cardiovasc Qual Outcomes. 2014;7:00-00.)

Key Words: aged ■ cardiac resynchronization therapy ■ heart failure ■ prognosis

The incidence and prevalence of heart failure increase significantly with aging, and older patients often present with more advanced heart failure when compared with younger patients.1,2 Patients aged ≥75 to 80 years are often under-represented in heart failure therapy trials, including the ones involving cardiac resynchronization therapy (CRT). The mean age of patients in the large CRT trials was ranged between 62 and 67 years, whereas the mean age of patients included in large registries was higher with nearly one third of patients being ≥75 years old.3-5 Device-related adverse events, efficacy, and long-term outcome after CRT implantation in the elderly are, therefore, unknown.5 The present study aimed at evaluating (1) the effect of CRT on clinical and echocardiographic parameters in the elderly, (2) the effect of age on left ventricular (LV) reverse remodeling after CRT, (3) device-related adverse events after CRT and finally, and (4) the long-term prognosis of elderly CRT recipients.

Patient Population

Patients included between June 2000 and July 2010 in an ongoing CRT registry from the Department of Cardiology of the Leiden University Medical Center (Leiden, The Netherlands) were evaluated in the present analysis.7 Patients underwent CRT device implantation according to the presence of LV ejection fraction (EF) ≤35%, a QRS duration ≥120 ms, and New York Heart Association (NYHA) functional class II to IV heart failure symptoms, despite optimal medical therapy.8 The cause of heart failure was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and a history of myocardial infarction or revascularization. Patients with decompensated heart failure before the implantation or recent myocardial infarction (<3 months) were excluded.

All patients underwent extensive clinical evaluation and transthoracic 2-dimensional (2D) echocardiography before and 6 months after CRT implantation. All patients were scheduled for regular visits to the outpatient clinic at 6 months of follow-up. To evaluate the association between age and CRT outcomes, patients were dichotomized

Methods

Patient Population

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Original Article
WHAT IS KNOWN

- In patients with heart failure, cardiac resynchronization therapy (CRT) can improve left ventricular systolic function and survival independently from age.
- Early CRT-related adverse events are not different between older and younger patients.

WHAT THE STUDY ADDS

- CRT implantation in elderly patients was not associated with higher rates of acute and long-term adverse events than in younger patients.
- Older and younger patients treated with CRT had comparable rates of ventricular arrhythmias requiring appropriate implantable cardioverter-defibrillator therapy together with ventricular arrhythmic death. However, older patients had worse survival than younger patients but only 4 years after CRT implantation and mainly because of noncardiac causes.
- Among older patients undergoing CRT implantation, diabetes mellitus, impaired renal function, and reduced 6-minute walk distance were independently associated with all-cause mortality.

Device-Related Adverse Events

To evaluate the safety of CRT implantation, device-related adverse events requiring invasive treatment or resulting in serious injury within 30 days after CRT implantation were registered. Pneumothorax, pericardial effusion, coronary sinus dissection or perforation, LV lead dislodgement, pocket hematoma requiring pocket exploration, or prolonged hospitalization with and without change in antiocoagulation regimen and device infection/device extraction were considered as device-related adverse events. On the basis of the timing of the event, we compared device-related adverse events between the 2 age groups, within 24 hours after the procedure (defined as device-related in-hospital) and after 24 hours but within 30 days after the procedure (defined as device-related early adverse events). Device-related adverse events occurring 30 days after the procedure (lead fracture and replacement, pocket hematoma requiring pocket exploration, device infection, and replacement) were defined as long-term device-related adverse events.17,18

Long-Term Outcome

Long-term follow-up was performed by medical chart review, outpatient clinical visits, and telephone contact. The primary end point was all-cause mortality. The secondary end points included combination of all-cause mortality together with heart failure hospitalization or ventricular arrhythmias requiring appropriate implantable cardioverter-defibrillator (ICD) therapy (antitachycardia pacing and defibrillator shocks) and ventricular arrhythmic death.19 Heart failure hospitalizations were adjudicated by the cardiologist responsible for the management of the patients during admission, whereas the appropriate ICD therapy was adjudicated by trained pacemaker technicians (and confirmed by a cardiologist) after device interrogation. Furthermore, the mode of death was compared between the 2 age groups. Death was categorized as cardiac, noncardiac, or unknown. Cardiac death included deaths caused by the progression of heart failure, sudden cardiac death, myocardial infarction, ventricular arrhythmias, or other cardiac cause.20

Statistical Analysis

Continuous variables with normal distribution are presented as mean and SD, non-normally distributed data as median with interquartile range, and dichotomous data as numbers and percentages. Student t test was used to compare continuous variables and χ² tests to compare categorical variables. Wilcoxon signed-rank test was used for the comparison changes in nominal data at follow-up. Generalized estimating equations were used to compare changes in clinical and echocardiographic parameters within and between the age groups at follow-up (interaction). Linear scale response was used for normally distributed data and ordinal logistic response for the nominal data.

Device-related in-hospital and device-related early adverse events were compared with the construction of Kaplan–Meier curves. To account for the effect of multiple device-related long-term adverse events, the long-term adverse events data were analyzed using the Frailty Model in R package.21 The log-rank tests were used to compare the difference in Kaplan–Meier curves for the survival free from the primary and secondary end points between the age groups. The cumulative incidences of cardiac and noncardiac death were calculated using competing risks analysis, and the mode of death was compared by Cox regression analysis.22 Furthermore, the predictors of the primary end point within the elderly group were evaluated with the Cox proportional hazards model: all clinical and echocardiographic relevant predictors and the variables that showed a significant effect (P<0.15) at the univariable analysis were introduced in the multivariable model. In case of collinearity, only 1 of these variables was entered in the multivariable model. All statistical tests were 2 sided and for all tests, a value of P<0.05 was considered statistically significant.
Follow-Up Clinical and Echocardiographic Characteristics

In the overall population, a significant improvement in functional and echocardiographic parameters was observed at 6-month follow-up when compared with baseline. NYHA functional class decreased from 3 (interquartile range, 3–3) to 2 (interquartile range, 2–2; Z score, –19.927; Wilcoxon, $P<0.001$), quality of life score decreased from 34±19 to 23±18 ($P<0.001$), and 6-minute walked distance increased from 300±118 to 373±122 m ($P<0.001$). Furthermore, LV end-diastolic volume index decreased from 112±40 to 100±38 mL/m$^2$ ($P<0.001$), LVESV index decreased from 84±36 to 70±33 mL/m$^2$ ($P<0.001$), and LVEF increased from 26±8% to 32±9% ($P<0.001$).

A comparable magnitude of improvement in clinical and echocardiographic characteristics was observed in elderly and nonelderly patients at 6-month follow-up (Table 2, interaction $P$ value). Of interest, the incidence of response to CRT (defined as reduction of ≥15% in LVESV) was not significantly different between both age groups (53% in the nonelderly versus 58% in the elderly; $P=0.202$).

Device-Related Adverse Events

Table 3 summarizes the incidence of device-related in-hospital and device-related early adverse events in elderly versus nonelderly patients. There were no differences between elderly and nonelderly patients and only a trend toward a slightly higher incidence of pneumothorax and pocket hematoma was observed among elderly patients. During a median of 38.6 months, elderly patients were exposed to similar risk of the device-related long-term adverse events: lead fractures/replacements (Frailty Model hazard ratio, 0.56; 95% confidence interval [CI], 0.31–1.01; $P=0.055$) and device infections/extraction when compared with nonelderly patients (Frailty Model hazard ratio, 1.86; 95% CI, 0.82–4.21; $P=0.140$). Moreover, the Frailty Model demonstrated a significant higher risk of pocket hematomas among elderly patients (Frailty Model hazard ratio, 6.23; 95% CI, 1.07–36.33; $P=0.042$). However, the total number of device-related long-term adverse events was similar between the 2 groups (Frailty Model hazard ratio, 0.90; 95% CI, 0.58–1.38; $P=0.620$).

Long-Term Outcome

During long-term follow-up (median, 38.6 months; interquartile range, 22.5–61.8 months), a total of 274 patients (34%) died of which 84 (40%) were elderly patients and 190 (32%) were nonelderly patients. The cumulative incidence of the primary end point was significantly higher in elderly patients (log rank, $P=0.013$). Of note, survival difference was statistically significant only after 4-year follow-up with a survival rate of 72% in the nonelderly (95% CI, 68%–76%) versus 60% in the elderly (95% CI, 52%–68%; log rank $P=0.013$; Figure 1).

About the cause of death (Table 4), 61 patients (22%) died from a noncardiac and 176 patients (64%) from a cardiac (mainly progression of heart failure, 79%). In 34 patients (12%), the mode of death was unknown. A higher rate of noncardiac cause of death was observed among elderly patients (Table 4). Moreover, as depicted in Figure 2,
cumulative incidence of noncardiac death between the 2 groups was significantly different, which suggests that noncardiac mortality is the determinant of the survival difference between elderly and nonelderly patients (Figure 1; log-rank \( P < 0.001 \)).

About the secondary end points, similar event rates for the combination of all-cause mortality or heart failure hospitalizations were observed between the age groups (survival free from events, 45%; 95% CI, 40%–51%) in the elderly versus (53%; 95% CI, 50%–56%) in the nonelderly (log-rank \( P = 0.099 \)). Furthermore, the cumulative incidence rates of ventricular arrhythmias requiring appropriate ICD therapy and ventricular arrhythmic death were comparable between the 2 groups (survival free from events, 47%; 95% CI, 51%–63%) in the elderly versus (42%; 95% CI, 22%–62%) in the nonelderly (log-rank \( P = 0.792 \)).

Predictors of the Primary End Point in the Elderly

Univariable analysis performed in the elderly population indicated that NYHA functional class, quality-of-life score, 6-minute walked distance, glomerular filtration rate, LVESV index, and LVEF were significantly related to all-cause mortality (primary end point). These variables together with other clinical and echocardiographic relevant characteristics (age, ischemic cause, atrial fibrillation, and diabetes mellitus) were included in the multivariable model (Table 5). The multivariate analysis showed that the presence of diabetes mellitus, impaired renal function (lower glomerular filtration rate values), and reduced 6-minute walked distance at baseline were independently associated with the primary end point among elderly CRT recipients (Table 5).

**Discussion**

The present evaluation shows that elderly patients benefit from CRT similar to nonelderly patients, with comparable improvements in clinical symptoms and LV function and similar rates of in-hospital and early device-related adverse events. However, elderly patients had significantly higher 4-year mortality rate, specifically with higher rate of noncardiac mortality. Diabetes mellitus, reduced 6-minute walk distance, and impaired renal function were independently associated with all-cause mortality among elderly patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age &lt;75 Y (n=590)</th>
<th>Age ≥75 Y (n=208)</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class (IQR)</td>
<td>3 (3–3)</td>
<td>2 (2–3)*</td>
<td>0.311</td>
</tr>
<tr>
<td>Quality-of-life score</td>
<td>35±19</td>
<td>23±18*</td>
<td>0.019†</td>
</tr>
<tr>
<td>6-min walked distance, m</td>
<td>314±117</td>
<td>388±120</td>
<td>0.687</td>
</tr>
<tr>
<td>LVESVi, mL/m²</td>
<td>114±42</td>
<td>102±40*</td>
<td>0.406</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>26±8</td>
<td>32±10*</td>
<td>0.662</td>
</tr>
</tbody>
</table>

Values are mean±SD or median and (IQR). IQR indicates interquartile range; LVESVi, left ventricular end-systolic volume index; and NYHA, New York Heart Association.

*P<0.001, baseline vs follow-up.
†P values are statistically significant.

**Table 3. Device-Related In-Hospital and Early Adverse Events After Cardiac Resynchronization Therapy Implantation in the Total Patient Population and Compared With Elderly and Nonelderly Patients**

<table>
<thead>
<tr>
<th></th>
<th>Total n=798 n (%)</th>
<th>Age &lt;75 Y n (%)</th>
<th>Age ≥75 Y n (%)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital adverse events</td>
<td>23 (2.9)</td>
<td>16 (2.7)</td>
<td>7 (3.4)</td>
<td>0.552</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>6 (0.8)</td>
<td>3 (0.5)</td>
<td>3 (1.4)</td>
<td>0.158</td>
</tr>
<tr>
<td>Pocket hematoma</td>
<td>4 (0.5)</td>
<td>2 (0.3)</td>
<td>2 (1.0)</td>
<td>0.250</td>
</tr>
<tr>
<td>Sinus coronarius dissection, lead perforation, or pericardial effusion</td>
<td>2 (0.3)</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td>0.563</td>
</tr>
<tr>
<td>LV lead dislodgement</td>
<td>11 (1.4)</td>
<td>10 (1.7)</td>
<td>1 (0.5)</td>
<td>0.218</td>
</tr>
<tr>
<td>24 h to 30 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early adverse events</td>
<td>20 (2.5)</td>
<td>15 (2.5)</td>
<td>5 (2.4)</td>
<td>0.984</td>
</tr>
<tr>
<td>Pocket hematoma</td>
<td>2 (1)</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td>0.418</td>
</tr>
<tr>
<td>LV lead dislodgement</td>
<td>14 (1.8)</td>
<td>11 (1.9)</td>
<td>3 (1.4)</td>
<td>0.748</td>
</tr>
<tr>
<td>Device infections/explantation</td>
<td>4 (0.5)</td>
<td>3 (0.5)</td>
<td>1 (0.5)</td>
<td>0.995</td>
</tr>
</tbody>
</table>

LV indicates left ventricular.

*Based on log-rank test comparison.
Effect of Age on LV Reverse Remodeling After CRT

CRT induces favorable LV reverse remodeling and improvement in LV systolic function. These favorable effects have been shown independent of age. For example, the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE) and MIRACLE-ICD trials showed that patients randomized to CRT-ON group had important reductions in LV end-diastolic diameters across all age groups.\(^2^5\) Similarly, the subanalysis of the InSync/InSync ICD Italian Registry demonstrated significant reductions in LV volumes at 6- and 12-month follow-up independent of age.\(^1^2\) In line with these observations, subanalysis of the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) comparing the magnitude of LVESV change at 12-month follow-up among patients <60, 60 to 74, and ≥75 years reported no significant differences between age groups.\(^1^3\) The present results provide more evidence on the beneficial effects of CRT on LV structure and function and would support the appropriateness of implanting CRT in old patients with heart failure.

Device-Related Adverse Events

Despite the technical challenges associated with CRT implantation, the overall perioperative complications rates have significantly decreased during the past decades (from 28% in earlier trials to 4% in recent trials).\(^1^0\) The relationship between age and CRT implantation-related adverse events remains controversial. Data from the InSync registry, MADIT-CRT, MIRACLE, and MIRACLE-ICD trial subanalyses demonstrated that the incidence of device-related adverse events was not influenced by age.\(^1^2,1^3,2^5\) However, a recent study including 26,887 recipients of ICD or CRT devices has shown a significant higher frequency of acute device-related adverse event among elderly patients, women, and black race/ethnicity.\(^2^6\) Similar to the results of the InSync, MADIT-CRT, MIRACLE, and MIRACLE-ICD studies, the present evaluation showed that the rates of early adverse events were not different between young and elderly patients. About the long-term CRT-related complications, the data are scarce. Especially in the elderly patients, this evaluation is important considering potential effect of device-related adverse events on the quality of life.\(^2^7\) In the present study, we observed only a significant difference in the proportion of pocket hematomas after device-related interventions between the 2 groups, which probably could be explained by the higher percentage of anticoagulant therapy among elderly patients. However, the Frailty Model analysis showed for total number of all device-related long-term adverse events that the safety of CRT in the elderly is similar to the nonelderly.

Long-Term Prognosis After CRT

Subgroup analyses of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION), MIRACLE, and MIRACLE-ICD trials reported no significant difference in survival between elderly and nonelderly patients (≥75 years) after cardiac resynchronization therapy.
patients. The results were probably limited by the relative short-term follow-up (≤12 months). Remarkably, the MADIT-CRT trial, evaluating CRT efficacy versus ICD in patients with mild or nonsymptomatic heart failure, reported significant reduction in heart failure hospitalization or mortality rates only among patients ≥60 years. In the present study, which reflects a real-world evaluation of patients with CRT, we demonstrated that the survival difference between elderly and nonelderly patients became significant after 4 years of follow-up. This difference was mainly because of an increase rate of noncardiac death among elderly patients. An age-related increase in noncardiac mortality was also reported in the InSync ICD Italian Registry.

In addition, we evaluated 2 important end points for the elderly population. First, our study showed an equal proportional incidence of heart failure hospitalizations combined with all-cause mortality between the age groups, suggesting a comparable effect of CRT on clinical symptoms and quality of life. Second, we observed a comparable incidence rate of ventricular arrhythmias requiring appropriate ICD therapy.

### Table 5. Cox Regression Survival Analysis for the Primary End Point in the Elderly (Age ≥75 Years) Patients With Heart Failure After Cardiac Resynchronization Therapy Implantation

<table>
<thead>
<tr>
<th></th>
<th>Univariable Model</th>
<th>Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age, per y</td>
<td>1.022</td>
<td>0.950–1.100</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.340</td>
<td>0.754–2.383</td>
</tr>
<tr>
<td>Ischemic cause</td>
<td>1.709</td>
<td>1.031–2.832</td>
</tr>
<tr>
<td>QRS duration, per ms</td>
<td>1.000</td>
<td>0.993–1.008</td>
</tr>
<tr>
<td>NYHA functional class II (reference)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>
| NYHA functional class III | 1.550             | 0.795–3.025        | 0.199   | ... | ... | ...
| NYHA functional class IV | 3.349             | 1.349–8.313        | 0.009*  | ... | ... | ...
| Atrial fibrillation    | 1.472             | 0.912–2.378        | 0.114   | 1.543 | 0.869–3.106 | 0.166 |
| Diabetes mellitus      | 1.810             | 0.999–3.279        | 0.050   | 2.322 | 0.979–4.178 | 0.019* |
| Quality-of-life score (per point) | 1.024             | 1.010–1.037        | 0.001*  | ... | ... | ...
| 6-min walked distance, per m | 0.995             | 0.993–0.998        | <0.001* | 0.996 | 0.993–0.998 | 0.001* |
| GFR, per mL/min per 1.73 m² | 0.976             | 0.962–0.989        | 0.001*  | 0.975 | 0.959–0.995 | 0.006* |
| β-blocker use          | 0.828             | 0.535–1.282        | 0.398   | 0.828 | 0.535–1.282 | 0.398 |
| Oral anticoagulants use | 0.532             | 0.231–1.226        | 0.139   | 0.532 | 0.231–1.226 | 0.139 |
| LVEDVi, per mL/m²      | 1.005             | 0.998–1.011        | 0.156   | 1.005 | 0.998–1.011 | 0.156 |
| LVESVi, per mL/m²      | 1.009             | 1.002–1.016        | 0.015*  | 1.009 | 1.002–1.016 | 0.015* |
| LVEF, per %            | 0.942             | 0.913–0.971        | <0.001* | 0.942 | 0.913–0.971 | <0.001* |
| Frailty score ≥3 points, n (%) | 1.520             | 0.859–2.691        | 0.150   | 1.520 | 0.859–2.691 | 0.150 |

CI indicates confidence interval; GFR, glomerular filtration rate estimated according Cockcroft-Gault equation; HR, hazard ratio; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; and NYHA, New York Heart Association.

*P values are statistically significant.
together with ventricular arrhythmic death. This suggests that elderly patients do benefit equally to nonelderly patients from CRT-D.

**Limitations**

Several limitations of the current study should be mentioned. First, the study design was retrospective and reported the experience of a single center. Therefore, these findings should be confirmed in larger prospective multicenter studies. Second, atrial fibrillation was more often present in elderly patients. Finally, the majority of the study population (95%) received a CRT-D system and a comparison with a CRT-P system could not be performed.

**Conclusions**

CRT efficacy and device-related adverse events in elderly patients were comparable with that in nonelderly patients. However, after 4 years of follow-up, elderly patients showed worse survival and the cause of death was mainly noncardiac. Diabetes mellitus, impaired renal function, and reduced 6-minute walk distance were independently associated with all-cause mortality of elderly patients.

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**Disclosures**

None.

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