Cardiac resynchronization therapy improves psycho-cognitive performance in patients with heart failure

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Background
Reduced cognitive performance and high prevalence of depression have been reported in patients with congestive heart failure (CHF) and severe left ventricular dysfunction. However, effects of contemporary device therapy on cognitive performance and depression symptoms have not been studied thoroughly.

Methods
Seventy-four consecutive CHF patients—45 receiving a biventricular defibrillator (CRT-D) and 29 receiving an implantable single or dual-chamber defibrillator (ICD) as a control group—were enrolled in this investigator-initiated, prospective, controlled, and investigator-blinded study. A set of neuropsychological tests (mini-mental state examination, DemTect, age–concentration test, and Beck depression inventory) was performed before, at 3 and at 6 months after device implantation.

Results
DemTect-score improved significantly ($F = 7.8; P = 0.007$) after CRT-D-implantation compared with ICD. Age–concentration test revealed better concentration ability after CRT-D-implantation ($F = 8.3; P = 0.005$) compared with ICD. Under CRT-D mini-mental state examination showed a significant improvement ($F = 4.2; P = 0.043$). CRT with defibrillator therapy also improved depression revealed by beck depression inventory ($F = 14.7; P < 0.001$) compared with ICD.

Conclusion
This prospective study is the first to demonstrate psycho-cognitive improvement by resynchronization therapy in CHF patients with severe left ventricular dysfunction. In contrast to ICD therapy, the beneficial effect of CRT-D on psycho-cognitive performance might be attributed to improved cardiac function and haemodynamics.

Keywords
Heart failure • Cerebrovascular circulation • Cardiac resynchronization therapy • Cognitive function

Introduction
Congestive heart failure associated with systolic left ventricular dysfunction is one of the leading causes of morbidity and mortality in western countries. Impaired psycho-cognitive function is highly prevalent in patients with congestive heart failure (CHF) and has been linked to the degree of left ventricular dysfunction.1 Besides depression blunted concentration and memory have been reported previously in heart failure patients.2 Cerebral hypoperfusion and hypoxemia along with metabolic alterations consecutive to hepatic and renal malfunction due to heart failure may be pathophysiological responsible.3,4

Pharmacological intervention with β-blockers, ACE-inhibitors/angiotensin receptor blockers and mineralocorticoid receptor antagonists is established to improve outcome in heart failure patients. Additionally, a significant proportion of patients shows ventricular dysynchrony and conduction disturbances consistent with bundle branch block. Cardiac resynchronization therapy (CRT) on top of optimal pharmacological therapy has been shown not only to reduce symptoms but also to reduce mortality in patients with heart failure symptoms, severe left ventricular dysfunction and left bundle branch block.

Patients in end-stage heart failure were shown to improve in several cognitive functions after heart transplantation,5 as well as...
after implantation of ventricular assist devices.1 Cardiac resynchron-
ization therapy ameliorates left ventricular systolic function and has
been shown to improve cerebral perfusion.6 Previously, two
reports with a small number of patients have shown improvement
of cognitive measures over a short follow-up period of 3 months
after CRT.7,8 However, controlled data over a longer follow-up
period are still lacking. We therefore aimed to investigate the
effects of CRT on cognitive function in patients either receiving
CRT with defibrillator therapy (CRT-D) or defibrillator therapy
(ICD) alone.

Methods
The present study is a prospective single-centre investigator-initiated
controlled investigator-blinded study. Between July 2010 and July 2011
consecutive patients receiving CRT-D or ICD for primary prophylactic
indications according to international guidelines at the Hannover
Medical School, Germany, were screened. In brief, study enrolment cri-
teria consisted of (i) CHF NYHA functional class II–IVA; (ii) ejection frac-
tion (EF) ≤ 35% within 3 months prior to device implantation; (iii) patients
on maximally tolerated and guideline-adherent medical therapy consist-
ing of β-blockers, ACE-inhibitors/angiotensin receptor blockers,
and mineralocorticoid receptor antagonists. Patients receiving CRT-D
needed to have a complete left bundle branch block with a QRS-duration
of ≥ 130 ms. Only native German speakers were enrolled in order to
exclude confounding of psycho-cognitive data. Patients with an indication
for ICD/CRT-D but with aborted cardiac arrest, history of stroke,
epilepsy, head injury, major psychiatric disorder, current untreated
major depression, or known dementia were excluded. The study
excluded confounding of psycho-cognitive data. Patients with an indication
for ICD/CRT-D but with aborted cardiac arrest, history of stroke,
epilepsy, head injury, major psychiatric disorder, current untreated
major depression, or known dementia were excluded. The study
design was approved by the local ethics committee. Patients were
given the opportunity to decline participation. All patients participating
in the study provided written informed consent.

Data acquisition
A research associate (K.F.) supervised by a working psychiatrist (M.D.),
both blinded to the type of device implanted, performed a set of psycho-
cognitive tests after enrolment prior to device implantation, at 3 and 6
months post successful device implantation. At the same time-points,
data about NYHA functional class and device-interrogation data were
collected and a 6-min hallway walk-test was performed. The Minnesota
Living with Heart Failure Questionnaire (MLHFQ), a widely used ques-
tionnaire for assessing quality of life in patients with heart failure was
filled out by the participants at enrolment and during 3- and 6-month
follow-up.

Functional and psycho-cognitive tests
Mini-mental state examination
The mini-mental state examination (MMSE) is the most widely used
instrument to assess cognitive status in adults. It consists of 11 items
that assess domains of orientation, short-term memory, attention, and
visual spatial skills, and is scored on a 30-point scale. It has a sensitivity
of 71–92% and specificity of 56–96% for diagnosing dementia and has
been used for many years to assess cognitive function in heart failure
patients. Mini-mental state examination was used to preliminary rule
out undiagnosed dementia.

DemTect
DemTect is a highly sensitive test in detecting dementia and mild cognitive
impairment independent of age and education. It consists of five subtests
covering a broad range of cognitive abilities including immediate and
delayed recall of verbal information, working memory, language and
number processing, and executive functioning. A score of <12 points
is generally considered to show cognitive impairment.

Alterskonzentrationstest—age–concentration test
Alterskonzentrationstest is a well-established non-visual psychometric
test to investigate selective attention and concentration ability in patients
aged 55 years and older. For this test, subjects have to mark 20 symbols
of 55 similar-looking patterns within a maximum time limit of 30 s. After
an initial training session, three consecutive test sessions are performed.
The total value (G-value), the time required for each subject to complete
the test sessions, and the amount of mistakes (faults %) is averaged and
interpreted comparatively.

Beck depression inventory
Beck depression inventory is one of the most widely used questionnaires
for reliably measuring the severity of depression. The National Heart,
Lung, and Blood Institute Working Group recommended the use of this
inventory for assessment of depression in patients with cardiovascular
disease. Higher scores in Beck depression inventory indicate more
severe depressive symptoms. A score of at least 10 depicts mild depression.

EQ-SD-3L
EQ-SD-3L is a widespread questionnaire for assessment of health-related
quality of life in different cohorts of patients and has been extensively used
in patients with cardiovascular disease. EQ-SD-3L comprises five dimen-
sions, i.e. mobility, self-care, usual activities, pain/discomfort, and anxiety/
depression. Each dimension has three levels: no problems, some problems,
or extreme problems, which are reported by the patient. The test contains
an additional visual analogue scale, which enables the patient to rate his
current health state on a range from 0 (worst imaginable health state) to
100 (best imaginable health state).

Statistics
Statistical analyses were performed using IBM SPSS Statistics version 20
(IBM Corp., Chicago, IL, USA). Continuous variables are presented as
mean ± standard error of the mean. Baseline differences between ICD
and CRT-D group were analysed using Student’s t-test for continuous
variables or χ² test for categorical variables, respectively.

The primary goal of this study was to describe the effect of CRT
therapy on different psycho-cognitive functions compared with the
control group of ICD patients. Therefore, to analyse differences
between the ICD and CRT-D group over time, the mean of the 3- and
6-month value of each parameter was calculated and then used as
dependent variable in an analysis of covariance. Since patient age at inclu-
sion was the only significant difference between ICD and CRT-D group
at baseline (see Table 1), age was used as a covariate in this model. Further-
more, since this was not a randomized trial, the model for each parameter
was corrected for the baseline score to correct for differences in baseline
variances. Group affiliation (ICD or CRT-D) was defined as a factor.

Missing data points were imputed according to the last-observation-
carried-forward method. A P-value of <0.05 was considered statistically
significant.

Results
Study population
A total of 101 ICD and 71 CRT-D patients were screened. Forty-five
patients fulfilled the criteria for inclusion in the CRT-D arm and 29
patients in the ICD arm, which served as a control group. Baseline
characteristics are shown in detail in Table 1. Patients were predominantly male, CRT-D recipients being significantly older (65 ± 10 years vs. 58 ± 11 years; P = 0.008). Underlying heart disease was ischemic heart disease in 51% vs. 52%, non-ischemic cardiomyopathy in 42% vs. 41% of CRT-D and ICD recipients, respectively. Ninety-six per cent of CRT-D patients and 90% of ICD patients suffered from heart failure NYHA functional class II or III. Left ventricular EF was comparable in both groups. All patients underwent successful device implantation.

Follow-up
At 3 months, follow-up was missed in five CRT-D patients and none of the ICD patients. At 6 months, data of three patients in each group were lost to follow-up. Overall, >95% data at all three time-points were acquired.

Functional status and Minnesota living with heart failure questionnaire
Patients with CRT therapy showed a significant improvement in NYHA functional class after 6 months compared with baseline (2.5 ± 0.6 vs. 2.1 ± 0.5; baseline vs. 6 months follow-up; P < 0.001). Walking distance improved in ICD patients from 403.8 ± 18.8 to 424.69 ± 17.1 m, whereas this improvement was more pronounced in CRT patients from 415.13 ± 15.2 to 487.29 ± 10.3 m. During follow-up, patients with a CRT-D showed a significant

### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>ICD</th>
<th>CRT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>58 ± 11.2</td>
<td>64.8 ± 10.2</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>24 (82.8%)</td>
<td>37 (82.2%)</td>
<td>0.953</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>28 ± 6.2</td>
<td>28 ± 4.3</td>
<td>0.978</td>
</tr>
<tr>
<td><strong>Cardiomyopathy</strong></td>
<td></td>
<td></td>
<td>0.997</td>
</tr>
<tr>
<td>ICM</td>
<td>15 (51.7%)</td>
<td>23 (51.1%)</td>
<td></td>
</tr>
<tr>
<td>DCM</td>
<td>12 (41.4%)</td>
<td>19 (42.2%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (6.9%)</td>
<td>3 (6.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>NYHA</strong></td>
<td>2.38 ± 0.68</td>
<td>2.49 ± 0.59</td>
<td>0.464</td>
</tr>
<tr>
<td>I</td>
<td>3 (10.3%)</td>
<td>1 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>12 (41.4%)</td>
<td>22 (48.9%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>14 (48.3%)</td>
<td>21 (46.7%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>1 (2.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>EF (%)</strong></td>
<td>29.9 ± 4.9</td>
<td>28.1 ± 6.7</td>
<td>0.376</td>
</tr>
<tr>
<td><strong>Arterial hypertension</strong></td>
<td>10 (34.5%)</td>
<td>33 (73.3%)</td>
<td>0.473</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>19 (65.5%)</td>
<td>12 (26.7%)</td>
<td>0.473</td>
</tr>
<tr>
<td><strong>Atrial rhythm</strong></td>
<td></td>
<td></td>
<td>0.366</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>25 (86.2%)</td>
<td>35 (77.8%)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (13.8%)</td>
<td>10 (22.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td>77.3 ± 13.4</td>
<td>73.7 ± 16.5</td>
<td>0.348</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTproBNP (ng/L)</td>
<td>2369.3 ± 6473.6</td>
<td>2641.8 ± 2790.1</td>
<td>0.810</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>143.6 ± 197.6</td>
<td>99.7 ± 27.1</td>
<td>0.244</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>13.5 ± 1.9</td>
<td>13.8 ± 1.4</td>
<td>0.540</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>23 (79.3%)</td>
<td>24 (53.3%)</td>
<td>0.023</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>6 (20.7%)</td>
<td>3 (6.7%)</td>
<td>0.072</td>
</tr>
<tr>
<td>Oral anticoagulation</td>
<td>4 (13.8%)</td>
<td>11 (24.4%)</td>
<td>0.266</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>29 (100%)</td>
<td>44 (97.8%)</td>
<td>0.419</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>27 (93.1%)</td>
<td>40 (88.9%)</td>
<td>0.545</td>
</tr>
<tr>
<td>Diuretics</td>
<td>21 (72.4%)</td>
<td>36 (80%)</td>
<td>0.521</td>
</tr>
<tr>
<td>Minelocorticoide receptor antagonist</td>
<td>12 (41.4%)</td>
<td>19 (42.2%)</td>
<td>0.943</td>
</tr>
<tr>
<td>Statin</td>
<td>19 (65.5%)</td>
<td>23 (51.1%)</td>
<td>0.222</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>2 (6.9%)</td>
<td>5 (11.1%)</td>
<td>0.545</td>
</tr>
<tr>
<td>Digitals</td>
<td>5 (17.2%)</td>
<td>7 (15.6%)</td>
<td>0.848</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>0</td>
<td>1 (2.2%)</td>
<td>0.419</td>
</tr>
<tr>
<td>Class Ic</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; EF, ejection fraction; ACEI/ARB, ACE inhibitor/angiotensin receptor blocker; ±, standard error of the mean.
improvement in 6-min walk-test compared with ICD patients ($F = 12.3; P = 0.001$). Cardiac resynchronization therapy with defibrillator therapy significantly improved total MLHFQ-Score compared with ICD ($F = 6.6; P = 0.012$). Both physical ($F = 4.4; P = 0.039$) and emotional ($F = 8.1; P = 0.006$) sub-dimensions of MLHFQ improved significantly over the 6 months after CRT compared with ICD therapy (Table 2).

**Functional and psycho-cognitive tests**

**Mini-mental state examination**
The average MMSE score at enrolment among CRT-D recipients was 28.5 ± 1.1 vs. 28.7 ± 1.0 in ICD patients revealing normal cognitive function among both groups, since a score of <25 is generally considered abnormal. As shown in Figure 1, over the follow-up period, CRT-D patients showed a statistically significant improvement of cognitive scores compared with ICD recipients ($F = 4.3; P = 0.043$).

**DemTect**
Cardiac resynchronization therapy with defibrillator therapy patients had a mean DemTect score of 13.6 ± 3.3 vs. 14.6 ± 3.3 in the ICD group revealing cognitive abilities in the normal range in our patient cohort. However, during the follow-up period, DemTect scores improved significantly in the CRT-D group compared with the ICD group ($F = 7.8; P = 0.007$) (Figure 1). At enrolment, 24% of CRT-D and 14% of ICD patients had a DemTect score of <12 indicating cognitive impairment. At 6 months follow-up, only 5% of CRT-D patients still had a pathological score compared with 8% in the ICD group.

**AKT—age—concentration test**
At enrolment, patients receiving a CRT-D achieved a total score of 53.44 ± 1.74 compared with 53.93 ± 1.41 in the ICD group. During follow-up, concentration ability in CRT-D patients evolved towards significantly ($F = 8.3; P = 0.005$) better scores (54.29 ± 0.87) compared with ICD patients (53.41 ± 1.92).

**Beck depression inventory**
At enrolment, mean BDI score was comparable between both groups (7.87 ± 6.6 vs. 9.24 ± 8.65). In the CRT-D group, the proportion of patients with at least mild depression decreased from 30% at enrolment to 5% at 6 months. On the other hand, 39% of ICD patients had at least mild depressive symptoms at enrolment and still 20% at 6 months follow-up. During follow-up, we observed a significant reduction of depressive symptoms in CRT-D patients compared with ICD patients ($F = 14.8; P < 0.001$).

**EQ-5D-3L**
The results of the five dimensions of the EQ-5D were dichotomized to ‘reporting no problem’ or ‘reporting a problem’. No significant differences between CRT-D and ICD therapy were measurable in the dimensions mobility, self-care, and usual activities. Sixty per cent of CRT-D patients reported having problems in the dimension pain/discomfort at enrolment, which declined to 44% after 6 months. However, in the ICD group 52% reported having problems in the dimension pain/discomfort at enrolment and 48% at 6 months. The difference over time was significant in favour of CRT-D therapy ($F = 4.2; P = 0.043$). Twenty-four per cent of CRT-D patients reported depressive symptoms at enrolment. After 6 months of CRT, we observed a significant reduction with only 2.2% of CRT-D patients still reporting being depressed. However, 31% of ICD patients reported being depressive at enrolment and 21% after 6 months ($F = 19.1; P < 0.001$). Similarly, patients reporting on their health status in the EQ-5D visual analogue scale improved significantly after CRT-D therapy over the follow-up period compared with ICD therapy ($F = 4.6; P = 0.035$).

**Discussion**
This study is the first prospective controlled study demonstrating significant psycho-cognitive improvement in heart failure patients consecutive to CRT in combination with an ICD compared with ICD therapy alone. Cognitive functioning, concentration ability besides reduction in depressive symptoms and quality of life was significantly better after CRT-D compared with ICD in heart failure patients.

Cognitive impairment, unfortunately often underestimated, is present in up to 85% of patients with heart failure. A meta-analysis by Vogels et al. demonstrated that CHF is associated with generalized cognitive impairment including primarily memory, attention, mental flexibility, and global cognitive deficits. Festa et al. recently reported an association between verbal memory function and left ventricular EF in heart failure patients. Previously, Zuccalà et al. found lower MMSE scores in heart failure patients with lower EF. Furthermore, cognitive impairment is associated with poor outcome in patients with heart failure. Zuchallà et al. found that cognitive impairment is an independent prognostic marker for in-hospital mortality in patients hospitalized for heart failure.

The pathophysiology of cognitive decline secondary to heart failure is not fully understood. However, cerebral and systemic haemodynamics seem to play a crucial role. Alves et al. reported on reduced cerebral perfusion in heart failure patients and could show a link to cognitive impairment. Alósco et al. recently showed that reduced cerebral perfusion is associated with greater white matter hyperintensities in patients with heart failure. Interestingly, van Bommel et al. observed an increase in cerebral blood flow following CRT, which may explain the cognitive improvement reported in our study.

Several pharmacological interventions have been attempted to improve cognitive function in heart failure. However, only Zuccala et al. reported an improvement in cognitive function after therapy with ACE inhibitors in heart failure patients. In patients with severe left ventricular dysfunction, Zimpfer et al. found an improvement of cognitive functions following implantation of ventricular assist devices. Ultimately, it has previously been demonstrated that cognition often improves following cardiac transplantation, and that this improvement is associated with increased cerebral perfusion as measured by transcranial Doppler assessments of middle cerebral arterial flow and cerebral SPECT.

A further major finding of our study is that we additionally provide data showing a significant reduction of depressive symptoms in heart failure patients after CRT-D compared with ICD therapy. A strong body of evidence has been published in the last years underlining the negative impact of depression as an independent predictor of mortality in heart failure patients. Unfortunately, often underestimated in heart failure patients, reduction of depressive symptoms is of immense clinical significance since it may be associated with
better self-care and adherence to therapy. However, data on effects of heart failure therapy on depression are scarce. Recently, Knackstedt et al. failed to show any effect of CRT on depressive symptoms in their patients. However, only 22 patients with CRT were studied, a presumably too small sample size to study these effects. The fact that even quality of life remained unimproved after CRT in their cohort

Table 2 Parameters during follow-up ICD vs. CRT

<table>
<thead>
<tr>
<th>parameter</th>
<th>Inclusion 3 months</th>
<th>Inclusion 6 months</th>
<th>CRT vs. ICD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class</td>
<td>2.38 ± 0.13</td>
<td>2.18 ± 0.12</td>
<td>2.17 ± 0.11</td>
<td>1.342</td>
</tr>
<tr>
<td>ICD</td>
<td>2.35 ± 0.10</td>
<td>2.11 ± 0.09</td>
<td>2.07 ± 0.74</td>
<td>0.251</td>
</tr>
<tr>
<td>CRT</td>
<td>2.49 ± 0.09</td>
<td>2.11 ± 0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>403.8 ± 18.8</td>
<td>428.8 ± 18.2</td>
<td>424.69 ± 17.1</td>
<td>12.279</td>
</tr>
<tr>
<td>ICD</td>
<td>415.13 ± 15.2</td>
<td>449.93 ± 17.6</td>
<td>487.29 ± 10.3</td>
<td>0.001</td>
</tr>
<tr>
<td>CRT</td>
<td>428.72 ± 0.19</td>
<td>28.81 ± 0.18</td>
<td>28.55 ± 0.22</td>
<td>0.043</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.47 ± 0.16</td>
<td>28.86 ± 0.13</td>
<td>28.91 ± 0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>CRT</td>
<td>14.62 ± 0.61</td>
<td>14.93 ± 0.49</td>
<td>15.38 ± 0.57</td>
<td>0.007</td>
</tr>
<tr>
<td>ICD</td>
<td>13.56 ± 0.49</td>
<td>15.31 ± 0.34</td>
<td>16.16 ± 0.29</td>
<td>0.005</td>
</tr>
<tr>
<td>AKT G-value</td>
<td>53.93 ± 0.26</td>
<td>53.83 ± 0.25</td>
<td>53.41 ± 0.36</td>
<td>0.13</td>
</tr>
<tr>
<td>ICD</td>
<td>54.44 ± 0.26</td>
<td>54.22 ± 0.17</td>
<td>54.29 ± 0.13</td>
<td>0.039</td>
</tr>
<tr>
<td>CRT</td>
<td>31.45 ± 4.37</td>
<td>24.76 ± 4.26</td>
<td>22.93 ± 4.61</td>
<td>0.012</td>
</tr>
<tr>
<td>MLHFQ</td>
<td>29.36 ± 3.02</td>
<td>12.84 ± 1.29</td>
<td>16.18 ± 2.00</td>
<td>0.039</td>
</tr>
<tr>
<td>ICD</td>
<td>29.84 ± 1.05</td>
<td>11.55 ± 1.86</td>
<td>10.86 ± 1.98</td>
<td>0.006</td>
</tr>
<tr>
<td>MMSE</td>
<td>15.24 ± 2.14</td>
<td>11.55 ± 1.86</td>
<td>10.86 ± 1.98</td>
<td>0.006</td>
</tr>
<tr>
<td>MLHFQ physical sub-dimension</td>
<td>15.24 ± 1.55</td>
<td>6.53 ± 0.85</td>
<td>8.44 ± 1.28</td>
<td>0.039</td>
</tr>
<tr>
<td>ICD</td>
<td>14.78 ± 1.55</td>
<td>6.53 ± 0.85</td>
<td>8.44 ± 1.28</td>
<td>0.039</td>
</tr>
<tr>
<td>CRT</td>
<td>5.72 ± 1.05</td>
<td>4.52 ± 1.10</td>
<td>4.55 ± 1.16</td>
<td>0.006</td>
</tr>
<tr>
<td>MLHFQ emotional sub-dimension</td>
<td>4.76 ± 0.67</td>
<td>1.93 ± 0.26</td>
<td>2.31 ± 0.31</td>
<td>0.006</td>
</tr>
<tr>
<td>ICD</td>
<td>7.87 ± 0.98</td>
<td>3.36 ± 0.43</td>
<td>3.20 ± 0.44</td>
<td>0.006</td>
</tr>
<tr>
<td>BDI</td>
<td>14.24 ± 1.61</td>
<td>7.31 ± 1.49</td>
<td>6.59 ± 1.31</td>
<td>0.006</td>
</tr>
<tr>
<td>CRT</td>
<td>7.87 ± 0.98</td>
<td>3.36 ± 0.43</td>
<td>3.20 ± 0.44</td>
<td>0.006</td>
</tr>
<tr>
<td>EQ-SD mobility</td>
<td>14 (48.3%)</td>
<td>12 (41.4%)</td>
<td>10 (34.5%)</td>
<td>0.326</td>
</tr>
<tr>
<td>ICD</td>
<td>16 (35.6%)</td>
<td>12 (26.7%)</td>
<td>12 (26.7%)</td>
<td>0.326</td>
</tr>
<tr>
<td>CRT</td>
<td>3 (10.3%)</td>
<td>2 (6.9%)</td>
<td>2 (6.9%)</td>
<td>0.252</td>
</tr>
<tr>
<td>EQ-SD self-care</td>
<td>2 (4.4%)</td>
<td>0</td>
<td>1 (2.2%)</td>
<td>0.252</td>
</tr>
<tr>
<td>ICD</td>
<td>18 (62.1%)</td>
<td>9 (31%)</td>
<td>7 (24.1%)</td>
<td>0.309</td>
</tr>
<tr>
<td>CRT</td>
<td>19 (42.2%)</td>
<td>7 (15.6%)</td>
<td>8 (17.8%)</td>
<td>0.309</td>
</tr>
<tr>
<td>EQ-SD usual activities</td>
<td>15 (51.7%)</td>
<td>14 (48.3%)</td>
<td>14 (48.3%)</td>
<td>0.43</td>
</tr>
<tr>
<td>ICD</td>
<td>27 (60%)</td>
<td>21 (46.7%)</td>
<td>20 (44.4%)</td>
<td>0.43</td>
</tr>
<tr>
<td>CRT</td>
<td>15 (51.7%)</td>
<td>14 (48.3%)</td>
<td>14 (48.3%)</td>
<td>0.43</td>
</tr>
<tr>
<td>EQ-SD pain/discomfort</td>
<td>11 (24.4%)</td>
<td>1 (2.2%)</td>
<td>1 (2.2%)</td>
<td>0.252</td>
</tr>
<tr>
<td>ICD</td>
<td>11 (24.4%)</td>
<td>1 (2.2%)</td>
<td>1 (2.2%)</td>
<td>0.252</td>
</tr>
<tr>
<td>CRT</td>
<td>5.91 ± 3.46</td>
<td>59.83 ± 3.70</td>
<td>65.97 ± 3.15</td>
<td>0.035</td>
</tr>
<tr>
<td>EQ-SD VAS</td>
<td>53.67 ± 3.05</td>
<td>66.36 ± 2.90</td>
<td>66.07 ± 2.39</td>
<td>0.035</td>
</tr>
<tr>
<td>ICD</td>
<td>53.67 ± 3.05</td>
<td>66.36 ± 2.90</td>
<td>66.07 ± 2.39</td>
<td>0.035</td>
</tr>
<tr>
<td>CRT</td>
<td>53.67 ± 3.05</td>
<td>66.36 ± 2.90</td>
<td>66.07 ± 2.39</td>
<td>0.035</td>
</tr>
</tbody>
</table>

6MWT, 6-min walk-test; MMSE, mini-mental state examination; AKT, age–concentration test; MLHFQ, Minnesota Living with Heart Failure Questionnaire; BDI, beck depression inventory; EQ-SD VAS, EQ-SD visual analogue scale; ± standard error of the mean.
supports this hypothesis, since large clinical trials have already conclusively shown significant improvement in quality of life and reduction in depression after CRT.\textsuperscript{19–21}

**Limitations**

Even if this study included more patients than previous ones, the number of patients included remains relatively low.

Echocardiographic data post CRT implantation were not studied. Therefore, it remains unresolved if the effects of CRT are different in responders vs. non-responders. Nevertheless, since significant psycho-cognitive improvement was seen in all CRT patients in our study, the effects might be even more pronounced in echocardiographic CRT responders. Beyond that, our limited sample size did not allow any subgroup analyses within the CRT group.

Furthermore, clinical significance of changes of the absolute values of test results implemented remains unclear. No data on clinical significance of changes in this range are available. Nevertheless, a set of different neuro-cognitive tests was implemented, most showing an at least statistically significant improvement in CRT patients. Taking all these improvements together, we therefore believe that even slight changes in the test results represent the clinical benefit from CRT concerning neuro-cognitive functional status.

**Figure 1** Significant improvement in cognitive function and reduction of depressive symptoms after CRT (red bars) compared with ICD (turquoise bars) in heart failure patients. MMSE, mini-mental state examination; AKT, age–concentration test; BDI, Beck depression inventory.
Conclusions

This is the first prospective single-centre, investigator-initiated, and controlled study showing significant improvement in cognitive function in heart failure patients receiving CRT-D compared with ICD. Additionally, our data show significant improvement in depressive symptoms and in quality of life after CRT. These findings are of clinical significance since cognitive decline and depression are common in heart failure patients and are associated with poor outcome.

Conflict of interest: D.D. received lecture honoraria and travel support from Zoll and received traveling and accommodation costs and participation fees from St Jude Medical, Biotronik, Medtronic, and BioControl Medical. T.K. received traveling and accommodation costs and participation fees from Biotronik, Boston Scientific, and Medtronic and received honoraria as advisor from Biotronik. G.K. received honoraria as advisor, proctor and for lectures from St Jude Medical, Biotronik, Boston Scientific, Medtronic, Bayer Healthcare, and Boehringer Ingelheim. H.O. received honoraria as advisor, proctor and for lectures St Jude Medical, Biotronik, Medtronic, Sanofi, and Sorin. A.G. received traveling and accommodation costs and participation fees from Sanofi and received honoraria as advisor from Medtronic.

References