APPROPRIATE ICD THERAPY IN DILATED CARDIOMYOPATHY DEPENDING ON ITS AETIOLOGY

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INFLUENCE of LEFT VENTRICULAR EJECTION FRACTION DYNAMICS on FREQUENCY of ICD SHOCKS (I)

Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Trial, Chicago, 449 patients

Objective:

to evaluate the effect of LVEF change on outcome in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial

Inclusion criteria:

✓ nonischemic cardiomyopathy with LVEF<36%
✓ history of symptomatic heart failure
✓ presence of significant ventricular ectopic activity

Results:

✓ patients whose LVEF improved had reduced mortality compared to patients whose LVEF decreased (HR 0.09; 95% CI 0.02-0.39; p = 0.001)
✓ survival free of appropriate shocks was not significantly related to LVEF improvement during follow-up at least 90 days (90 – 730 days)

INFLUENCE of LEFT VENTRICULAR EJECTION FRACTION DYNAMICS on FREQUENCY of ICD SHOCKS (II)

123 patients with DCM, mean LV EF 23 ± 6% (9-35%)
mean follow-up 74 month

Aims: to assess the incidence and prognostic significance of left ventricular (LV) function improvement in patients with non-ischaemic dilated cardiomyopathy (DCM) and prophylactic implantable cardioverter-defibrillator (ICD).

Criteria of LV function improvement:

✓ increase of LV ejection fraction of more than 5% to more than 35%
✓ decrease LV end-diastolic diameter of at least 5 mm

Results:

✓ LV function improvement after prophylactic ICD implant was found in 24%, recent onset DCM with symptoms ≤9 months as the only significant predictor of LV function improvement [OR: 6.89; 95%CI: 2.43-21.99, p = 0.0002]

✓ total mortality was higher in patients without vs. with LV function improvement [HR: 3.75; 95%CI: 1.14-12.31, p = 0.0034], while the incidence of appropriate ICD therapies was similar in both groups (HR: 1.15; 95% CI: 0.57-2.33, p = 0.70)

✓ the incidence of appropriate ICD therapies decreased to ~1% per year after LV function improvement had occurred

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

7.1.2.1 Trials of implantable cardioverter defibrillator therapy in dilated cardiomyopathy

A number of trials have compared ICD therapy alone or in combination with CRT against placebo or amiodarone in patients with DCM. Most were conducted in an era when best medical therapy evolved to include ACE inhibitors, beta-blockers and MRAs. The first RCTs of ICD therapy were underpowered to detect clinically meaningful differences in survival, and in some cases (e.g. DEFINITE) the overall mortality rate was lower than anticipated before enrolment. Follow-up was relatively short in some studies and, as in other settings, the relation of appropriate shocks to prognosis is still uncertain. No study has prospectively investigated the benefit of ICDs in specific aetiological subgroups of DCM.
OBJECTIVE

to study the frequency and causes of appropriate ICD/CRT-D shocks in patients with dilated cardiomyopathy (DCM) depending on its aetiology
STUDY GROUP (I)

dilated cardiomyopathy as a syndrome

✓ LV end-diastolic diameter more than 5.5 cm
✓ LV ejection fraction less than 35%

exclusion criteria

● Myocardium infarction or acute coronary syndrome
● Congenital and valvular heart diseases (except nonsignificant atrial septal defect)
  ● Infective endocarditis
  ● Thyrotoxicosis
● LV hypertrophy >14 mm, hypertrophic cardiomyopathy
  ● Systemic autoimmune diseases and vasculitis
    ● Verified amyloidosis, sarcoidosis
  ● Storage diseases
    ● Lymphoproliferative diseases
  ● Chemotherapy with anthracyclines
● Heart surgery last two months (including angioplasty and RF ablation)
  ● Patient failure
METHODS

- medical history, clinical examination
- standard blood examination (including thyroid function)
- ECG
- Holter monitoring
- Echo-CG
- measurement of the anti-heart antibodies (ELISA):
  - antigen-specific anti-nuclear antibodies
  - IgG to the antigens of endothelial cell
  - IgG to the antigens of cardiomyocyte
  - IgG to the antigens of smooth muscle
  - IgG to the antigens of conduction heart system

- viral genome detection in the blood (real-time PCR)
- endomyocardial biopsy of the RV/ intraoperative LV biopsy (n=36)
  - virus detection (real-time PCR)
  - morphological study with hematoxylin-eosin, Van Gieson, PAS staining, congo red
  - immunohistochemistry in some cases

- myocardial scintigraphy with $^{99}$Tc-MIBI (n=10)
- multi-slice computed tomography of the heart (MSCT, n=64)
- magnet resonance imaging of the heart (MRI, n=16)
- coronary angiography (n=41)
- geneticist, DNA-diagnostic
STUDY GROUP (II)

mean follow-up 18.5 [6.0; 31.5] month

ICD/ CRTD group
- 32 patients (21 male)
- mean age 47.3±12.3 years

<table>
<thead>
<tr>
<th>Device</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD</td>
<td>19</td>
<td>59.4%</td>
</tr>
<tr>
<td>CRT-D</td>
<td>13</td>
<td>40.6%</td>
</tr>
</tbody>
</table>

29 patients (90.6%) – primary prevention of SCD

Comparison group
(DCM with LV EF < 35%)
- 65 patients (44 male)
- mean age 45.6±13.1 years

no patients with history of sustained VT/ VF

<table>
<thead>
<tr>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>15.6%</td>
</tr>
<tr>
<td>8</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

n=5 reconstructive surgery with mitral valve replacement
<table>
<thead>
<tr>
<th></th>
<th>STUDY GROUP (III)</th>
<th>comparison group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD / CRT-D</td>
<td>parameters</td>
<td></td>
</tr>
<tr>
<td>2.7±0.8</td>
<td>NYHA class</td>
<td>3.0±0.9</td>
</tr>
<tr>
<td>6.7±0.8 cm</td>
<td>LV end-diastolic diameter</td>
<td>6.9±0.9 cm</td>
</tr>
<tr>
<td>204.9±104.2 ml</td>
<td>LV end-diastolic volume</td>
<td>219.4±83.9 ml</td>
</tr>
<tr>
<td>156.6±88.3 ml</td>
<td>LV end-systolic volume</td>
<td>169.3±73.4 ml</td>
</tr>
<tr>
<td>24.8±10.0%</td>
<td>LV ejection fraction</td>
<td>24.2±7.7%</td>
</tr>
<tr>
<td>609.1±175.7 Hg mm</td>
<td>dp/dt</td>
<td>765.3±405.0 Hg mm</td>
</tr>
<tr>
<td>11.0±4.2 cm</td>
<td>VTI</td>
<td>9.5±4.0 cm</td>
</tr>
<tr>
<td>110.1±35.9 ml</td>
<td>LA volume</td>
<td>109.3±54.7 ml</td>
</tr>
<tr>
<td>90.0±38.6 ml</td>
<td>RA volume</td>
<td>84.0±51.0 ml</td>
</tr>
<tr>
<td>3.4±0.7 cm</td>
<td>RV diameter</td>
<td>3.1±0.7 cm</td>
</tr>
<tr>
<td>50.4±14.7 Hg mm</td>
<td>PA systolic pressure</td>
<td>46.3±16.3 Hg mm</td>
</tr>
</tbody>
</table>
VENTRICULAR ARHYTHMIAS in TWO GROUPS

ICD / CRT-D

<table>
<thead>
<tr>
<th>Category</th>
<th>ICD / CRT-D</th>
<th>Comparison Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1000 PVBs/day</td>
<td>38%</td>
<td>33%</td>
</tr>
<tr>
<td>1000-4999 PVBs/day</td>
<td>29%</td>
<td>59%</td>
</tr>
<tr>
<td>5000-9999 PVBs/day</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>≥ 10,000 PVBs/day</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>No VT</td>
<td>55%</td>
<td>56%</td>
</tr>
<tr>
<td>Unsustained VT</td>
<td>16%</td>
<td>44%</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>29%</td>
<td></td>
</tr>
</tbody>
</table>

- 71.4% amiodarone
- 81.5% β-blockers
- 51.7% β-blockers + amiodarone
- 55.4% amiodarone
- 72.3% β-blockers
- 35.4% β-blockers + amiodarone
AETIOLOGY of DILATED CARDIOMYOPATHY

ICD / CRT-D

- definite myocarditis: 53%
- probable myocarditis: 9%
- genetic cardiomyopathy: 10%
- genetic cardiomyopathy + myocarditis: 17%
- idiopathic DCM: 11%

comparison group

- 40%
Immediate causes of appropriate ICD/ CRTD shocks (sustained VT/ VF)

- the myocarditis development in patients with previously stable (noncompaction) cardiomyopathy (n=2)
  - urgent abdominal surgery (n=1)
- unjustified cancel amiodarone, its replacement by digoxin (n=2)
  - amiodarone-associated thyrotoxicosis (n=1)
  - terminal stage of heart failure (n=2)
APPROPRIATE ICD/ CRTD SHOCKS DEPENDING on DCM AETIOLOGY

- Genetic forms of DCM
  - Unverified (n=4)
  - Family dilated cardiomyopathy (n=1)
  - TTR amyloidosis (n=1)
  - Emery-Dreifuss muscular dystrophy (n=1)
  - Unverified muscular dystrophy (n=1)
  - Left ventricular noncompaction syndrome (n=11)
RESULTS of ENDOMYOCARDIAL BIOPSY in PATIENTS with CLINICAL DIAGNOSIS ARVD

ARVD diagnosis according diagnostic criteria (1998), EMB od right ventricle, Italy, Padova

30 patients (17 female, 47±17 years)

ARVD (n=15)  active myocarditis (n=15)

13 ICD  1 ICD

follow-up 21±8 month

ICD shocks in 47%  no arrhythmia

INITIAL PARAMETERS in ICD/CRT-D PATIENTS WITH DIFFERENT ETIOLOGY of DCM

<table>
<thead>
<tr>
<th>Medical Condition / Parameter</th>
<th>Appropriate Shocks</th>
<th>No Appropriate Shocks</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>genetic DCM</td>
<td>100%</td>
<td>41.7%</td>
<td>0.013</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.2±0.9</td>
<td>2.9±0.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>31.8±11.5%</td>
<td>22.8±7.9%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>a poor response to therapy</td>
<td>37.5%</td>
<td>46.7%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>(LV EF increasing &lt; 5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a good response (&gt;10%)</td>
<td>12.5%</td>
<td>41.7%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>nonsustained / sustained VT</td>
<td>75.0% / -</td>
<td>58.3% / 8.3%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>β-blockers</td>
<td>75.0%</td>
<td>85.0%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>amiodarone</td>
<td>75.0%</td>
<td>71.4%</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Factors depending on frequency of appropriate shocks.
## CLINICAL CASES

**Case №1:** male 50 y., active viral myocarditis, no shocks

**Case №2:** male 58 y., hypernephroma, idiopathic DCM, 2 appropriate shocks

<table>
<thead>
<tr>
<th>Patient №1</th>
<th>parameters</th>
<th>Patients №2</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 month</td>
<td>follow-up after CRT-D</td>
<td>13 month</td>
</tr>
<tr>
<td>3</td>
<td>NYHA class</td>
<td>1-2</td>
</tr>
<tr>
<td>2 years</td>
<td>duration of DCM</td>
<td>1 year</td>
</tr>
<tr>
<td>7,5 cm/ 408 ml</td>
<td>LV end-diastolic diameter/ volume</td>
<td>6,3 cm/ 171 ml</td>
</tr>
<tr>
<td>17%</td>
<td>LV EF (initially)</td>
<td>25%</td>
</tr>
<tr>
<td>from 30 to 10%</td>
<td>LV EF (during of treatment)</td>
<td>42%</td>
</tr>
<tr>
<td>700 PVBs/day</td>
<td>PVBs/ VT</td>
<td>no (initially)</td>
</tr>
<tr>
<td>paroxismal</td>
<td>atrial fibrillation</td>
<td>paroxismal</td>
</tr>
<tr>
<td>betaxolol 20 mg/day</td>
<td>β-blockers</td>
<td>bisoprolol 2,5 mg/day</td>
</tr>
<tr>
<td>200 mg/ 0,25 mg</td>
<td>amiodarone/ digoxin</td>
<td>200 mg/ no (initially)</td>
</tr>
</tbody>
</table>
MORTALITY in TWO GROUPS

21.9% (ICD/CRT-D) vs 33.8% (p = 0.228)
21.9% vs 40.0% (death + heart transplantation, p=0.148)

immediate causes of death

study group

62%

comparison group

51%

- terminal heart failure
- sudden arrhythmic death
- death in the early postoperative period
- hepatic failure
- stroke (ischemic, hemorrhagic)
- pulmonary embolism
- pneumonia
- myocardial infarct
- stomach cancer
CONCLUSIONS

in patients with different forms of DCM ICD/ CRTD implantation is reasonable and effective for prevention of sudden cardiac death (appropriate shocks in 25% by follow-up 18.5 month, incl. 24% in primary prevention group)

***

the mortality in the patient with DCM who have indication to ICD (NYHA class 2-3, LV EF < 35%) was higher than in similar patients with ICD/ CRTD (33.8% vs 21.9%, p = 0.228)

***

the patients with association of genetic DCM and myocarditis had a maximal rate of ICD/ CRTD appropriate shocks, the patients with isolated myocarditis - minimal

***

the aetiology of DCM is a more important predictor of shocks than the LV ejection fraction and NYHA class

***

immediate causes of appropriate shocks were the myocarditis development in patients with previously stable cardiomyopathy, unjustified cancel amiodarone, its replacement by digoxin, amiodarone-associated thyrotoxicosis, terminal stage of heart failure