THE NATURAL HISTORY OF DILATED CARDIOMYOPATHY (DCM)

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DEFINITION OF DILATED CARDIOMYOPATHY

“The presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment”.

Elliot P et al. EHJ 2008
# CAUSES OF DCM

## Major causes of dilated cardiomyopathy

<table>
<thead>
<tr>
<th>Infectious diseases</th>
<th>Medications</th>
<th>Inflammatory/autoimmune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>Chemotherapeutic agents</td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Adenovirus</td>
<td>Anthracyclines</td>
<td>Dermatomyositis</td>
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<tr>
<td>Coxsackie virus</td>
<td>Cyclophosphamide</td>
<td>Scleroderma</td>
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<td>Cytomegalovirus</td>
<td>Trastuzumab</td>
<td>Rheumatoid arthritis</td>
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<td>HIV</td>
<td>Antiretroviral drugs</td>
<td>Sarcoidosis</td>
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<tr>
<td>Influenza virus</td>
<td>Zidovudine</td>
<td>Hypersensitivity myocarditis</td>
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<tr>
<td>Varicella</td>
<td>Didanosine</td>
<td>Other autoimmune myocarditis</td>
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<tr>
<td>Hepatitis</td>
<td>Zalcitabine</td>
<td>Giant cell arteritis</td>
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<td>Epstein-Barr</td>
<td>Phenothiazines</td>
<td>Kawasaki disease</td>
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<tr>
<td>Echovirus</td>
<td>Chloroquine</td>
<td></td>
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<tr>
<td>Parvovirus</td>
<td>Clozapine</td>
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<tr>
<td>Other</td>
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</table>

<table>
<thead>
<tr>
<th>Bacterial</th>
<th>Toxins</th>
<th>Endocrinologic disorders</th>
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<tbody>
<tr>
<td>Streptococci-rheumatic fever</td>
<td>Ethanol</td>
<td>Thyroid hormone excess or deficiency</td>
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<tr>
<td>Typhoid fever</td>
<td>Cocaine</td>
<td>Growth hormone excess or deficiency</td>
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<td>Diphtheria</td>
<td>Amphetamines</td>
<td>Diabetes mellitus</td>
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<td>Brucellosis</td>
<td>Cobalt</td>
<td>Cushing’s syndrome</td>
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<tr>
<td>Psitticosis</td>
<td>Lead</td>
<td>Pheochromocytoma or other catecholamine excess</td>
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<td>Mycobacteria</td>
<td>Lithium</td>
<td></td>
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<tr>
<td>Rickettsial</td>
<td>Mercury</td>
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<tr>
<td>Spirochetal</td>
<td>Carbon monoxide</td>
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<td>Leptospirosis</td>
<td>Beryllium</td>
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<tr>
<td>Syphilis</td>
<td>Methysergide</td>
<td></td>
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<tr>
<td>Lyme disease</td>
<td>Electrolyte and renal abnormalities</td>
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<tr>
<td>Fungal</td>
<td>Hypocalcemia</td>
<td>Genetically or without neuromuscular disease</td>
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<tr>
<td>Histoplasmosis</td>
<td>Hypophosphatemia</td>
<td>Familial (and sporadic), genetic cardiomyopathies</td>
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<td>Cryptococcosis</td>
<td>Uremia</td>
<td>Duchenne’s muscular dystrophy</td>
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<td>Parasitic</td>
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<td>Myotonic dystrophy</td>
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<td>Toxoplasmosis</td>
<td>Nutritional deficiencies</td>
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<td>Trypanosoma cruzi</td>
<td>Thiamine</td>
<td>Friedreich’s ataxia</td>
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<tr>
<td>(Chagas disease)</td>
<td>Selenium</td>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
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<tr>
<td>Shistosomiasis</td>
<td>Carnitine</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Trichinosis</td>
<td>Niacin (pellagra)</td>
<td>Penicillamine cardiomyopathy</td>
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<table>
<thead>
<tr>
<th>Deposition diseases</th>
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<tr>
<td>Hemochromatosis</td>
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<td>Tachycardia</td>
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<tr>
<td>Amyloidosis</td>
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<td>Heat stroke</td>
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<td></td>
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<td>Hypothermia</td>
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<td></td>
<td></td>
<td>Sleep apnea</td>
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<td></td>
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<td>Radiation</td>
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<td></td>
<td></td>
<td>(Calcium overload)</td>
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<td></td>
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<td>(Oxygen free radical damage)</td>
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<tr>
<td></td>
<td></td>
<td>Differential diagnosis</td>
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<tr>
<td></td>
<td></td>
<td>Ischemic heart disease</td>
</tr>
</tbody>
</table>
CAUSES OF DCM IN PATIENTS WITH INITIALLY UNEXPLAINED CARDIOMYOPATHY

Felker et al NEJM 2000
EPIDEMIOLOGY OF IDCM

- **ANNUAL INCIDENCE**: 5-8/100,000
- **PREVALENCe**: 36/100,000
- **INCREASED RISK ASSOCIATED WITH**:
  - **MALE GENDER**
  - **BLACK RACE**
  - **CHRONIC BETA-AGONIST USE**

Dec GW, Fuster V. NEJM 1994;331:1564-75
FAMILIAR DCM

- Over 20-50% of patients with IDCM
- Over 30 genes responsible have been discovered

**GENES**
- Lamin A/C
- \(\delta\)-sarcoglycan
- Dystrophin
- Desmin
- Vinculin
- Titin
- Troponin-T
- \(\alpha\)-tropomyosin
- \(\beta\)-myosin heavy chain
- Actin
- Mitochondrial DNA mutations

Fatkin D, et al. NEJM 1999;341
LAMINOPATHIES

- 6% of all DCM patients
- 7.5% of familiar forms
- 33% of DCM patients with conduction disturbances

CLINICAL PRESENTATION OF DCM

- Heart failure symptoms 75%-85%
- Chest angina 8%-20%
- Emboli (systemic or pulmonary) 1%-4%
- Syncope <1%
- Sudden cardiac death <1%

Dec GW, Fuster V. NEJM 1994;331:1564-75
DCM EVALUATION

- Detailed family history and screening of first degree relatives if necessary
- Complete blood count
- Metabolic panel
- Thyroid function tests
- Cardiac biomarkers
- B-type natriuretic peptide assay
- Chest radiography
- Echocardiography
- Cardiac magnetic resonance imaging (MRI)
- Electrocardiography (ECG)
- Endomyocardial biopsy may be useful in case of:
  - Recent onset of rapidly deteriorating cardiac function
  - Patients receiving chemotherapy with doxorubicin
  - Patients with systemic diseases with possible cardiac involvement (eg, hemochromatosis, sarcoidosis, amyloidosis, Löffler endocarditis, endomyocardial fibroelastosis)
NATURAL HISTORY OF DCM

HEART FAILURE AND FUNCTIONAL STATUS

Asymptomatic
100%

Mild
< 5%

Severe
0

Moderate
10%

20 - 30%

30 - 80%

ANNUAL MORTALITY

CAUSE OF DEATH

SUDDEN DEATH 40%
CONGESTIVE HEART FAILURE 40%
OTHER CAUSES 20%

Acute event

CAUSES OF DEATH BASED ON NYHA CLASS

Modes of death based on heart failure severity

**NYHA II**
- CHF: 64%
- Other: 24%
- Sudden death: 12%

**NYHA III**
- CHF: 59%
- Other: 15%
- Sudden death: 26%

**NYHA IV**
- CHF: 33%
- Other: 11%
- Sudden death: 56%

As the severity of heart failure symptoms worsens, the mode of death is less likely to be arrhythmic sudden cardiac death and more likely to be due to heart failure.

DIFFERENCES IN NATURAL HISTORY OF DCM ETIOLOGIES

Outcome with a cardiomyopathy is related to the etiology

![Graph showing survival rates for different etiologies of cardiomyopathy.]

- Peripartum
- Idiopathic
- Doxorubicin
- Ischemic heart disease
- Infiltrative myocardial disease
- HIV infection

Felker et al NEJM 2000
SURVIVAL IN IDCM VERSUS MYOCARDITIS

Grogan, et al JACC 1995
SURVIVAL IN IDCM VERSUS ALCOHOLIC DCM

![Graph showing survival rates over time for ACM and IDCM with a p-value of 0.002.](image)

SURVIVAL IN IDCM VERSUS SARCOIDOSIS CARDIOMYOPATHY

NATURAL HISTORY OF LAMINOPATHIES

- Age related penetrance with early onset atrial arrhythmias followed by conduction disease, often with mild LV dilatation and systolic dysfunction.
- Over 60% of patients experience cardiovascular death or major cardiovascular events by the age of 45
- 46% of mortality of carriers due to sudden death

PROGNOSTIC FACTORS OF DCM

▶ ECHOCARDIOGRAPHIC FINDINGS
  ▶ Degree of impairment in LVEF
  ▶ Extent of left ventricular enlargement
  ▶ Diastolic dysfunction
  ▶ Coexistent right ventricular dysfunction

▶ CLINICAL FINDINGS
  ▶ Favorable prognosis: NYHA < IV, younger age, female sex
  ▶ Poor prognosis: Syncope, persistent S3 gallop, right-sided heart failure, atrial fibrillation, AV or bundle branch block, hyponatremia, troponin elevation, increased BNP, maximum oxygen uptake < 12 mg/kg/min
AHA/ACC 2013 AND ESC 2015 INDICATIONS FOR ICD IMPLANTATION IN DCM

Predictors of SCD used in the guidelines also predict overall mortality and simply reflect severity of disease.
45 studies. 6088 DCM patients enrolled

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Studies</th>
<th>Events/n (%)</th>
<th>Calculated 3-Yr Event Rate (%)</th>
<th>Prov. (%)</th>
<th>Sens. (%)</th>
<th>Spec. (%)</th>
<th>PPA (%)</th>
<th>NPA (%)</th>
<th>RR (95% CI)</th>
<th>OR (95% CI)</th>
<th>p Value</th>
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<tbody>
<tr>
<td><strong>Autonomic</strong></td>
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<tr>
<td>BRS</td>
<td>2</td>
<td>48/359 (13.4)</td>
<td>17.0</td>
<td>52.9</td>
<td>64.6</td>
<td>48.9</td>
<td>16.3</td>
<td>89.9</td>
<td>1.80 (0.63-5.16)</td>
<td>1.98 (0.60-6.59)</td>
<td>0.23</td>
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<tr>
<td>HRT</td>
<td>3</td>
<td>66/434 (15.2)</td>
<td>18.6</td>
<td>32.3</td>
<td>47.0</td>
<td>70.4</td>
<td>22.1</td>
<td>88.1</td>
<td>2.12 (0.77-5.83)</td>
<td>2.57 (0.64-10.36)</td>
<td>0.16</td>
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<tr>
<td>HRV</td>
<td>4</td>
<td>83/630 (13.2)</td>
<td>15.6</td>
<td>43.1</td>
<td>55.4</td>
<td>58.8</td>
<td>16.9</td>
<td>89.7</td>
<td>1.52 (0.84-2.75)</td>
<td>1.72 (0.80-3.73)</td>
<td>0.13</td>
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<tr>
<td><strong>Functional</strong></td>
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<tr>
<td>LVEDD</td>
<td>4</td>
<td>62/427 (14.5)</td>
<td>17.1</td>
<td>42.9</td>
<td>66.1</td>
<td>61.1</td>
<td>22.4</td>
<td>91.4</td>
<td>2.85 (1.70-4.79)</td>
<td>3.47 (1.90-6.35)</td>
<td>0.014</td>
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<td>LVEF</td>
<td>12</td>
<td>293/1,804 (16.2)</td>
<td>16.9</td>
<td>53.1</td>
<td>71.7</td>
<td>50.5</td>
<td>21.9</td>
<td>90.2</td>
<td>2.34 (1.85-2.96)</td>
<td>2.87 (2.09-3.95)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Arrhythmia</strong></td>
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<tr>
<td>EPS</td>
<td>15</td>
<td>146/936 (15.6)</td>
<td>21.5</td>
<td>15.4</td>
<td>28.8</td>
<td>87.1</td>
<td>29.2</td>
<td>86.9</td>
<td>2.09 (1.30-3.35)</td>
<td>2.49 (1.40-4.40)</td>
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<td>NSVT</td>
<td>18</td>
<td>403/2,746 (14.7)</td>
<td>15.7</td>
<td>45.5</td>
<td>64.0</td>
<td>57.7</td>
<td>20.7</td>
<td>90.3</td>
<td>2.45 (1.90-3.16)</td>
<td>2.92 (2.17-3.93)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Depolarization</strong></td>
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<tr>
<td>QRS/LBBB</td>
<td>10</td>
<td>262/1,797 (14.6)</td>
<td>14.7</td>
<td>35.7</td>
<td>45.4</td>
<td>65.9</td>
<td>18.5</td>
<td>87.6</td>
<td>1.43 (1.11-1.83)</td>
<td>1.51 (1.13-2.01)</td>
<td>0.010</td>
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<td>SAECG</td>
<td>10</td>
<td>152/1,119 (13.6)</td>
<td>19.9</td>
<td>36.9</td>
<td>51.3</td>
<td>65.4</td>
<td>18.9</td>
<td>89.5</td>
<td>1.84 (1.18-2.88)</td>
<td>2.11 (1.18-3.78)</td>
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<td>Frag. QRS</td>
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<td>65/652 (10.0)</td>
<td>11.8</td>
<td>25.6</td>
<td>61.5</td>
<td>78.4</td>
<td>24.0</td>
<td>94.8</td>
<td>5.16 (3.17-8.41)</td>
<td>6.73 (3.85-11.76)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Repolarization</strong></td>
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<tr>
<td>QRS-T</td>
<td>1</td>
<td>97/455 (21.3)</td>
<td>25.0</td>
<td>62.2</td>
<td>74.2</td>
<td>41.1</td>
<td>25.4</td>
<td>85.5</td>
<td>1.75* (1.16-2.65)</td>
<td>2.01* (1.22-3.31)</td>
<td>0.006*</td>
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<tr>
<td>TWA</td>
<td>12</td>
<td>177/1,631 (10.9)</td>
<td>15.8</td>
<td>66.8</td>
<td>91.0</td>
<td>36.2</td>
<td>14.8</td>
<td>97.0</td>
<td>3.25 (2.04-5.16)</td>
<td>4.66 (2.55-8.53)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Syncopal events imply a higher risk of SCD regardless of the proven etiology of the syncope.

These patients with ICD implantation receive similar clinical benefits to secondary prevention cases.
LATE GADOLINIUM ENHANCEMENT

A. All-cause mortality

No. at risk
No fibrosis 330 318 260 136 51
Fibrosis 142 122 99 39 13

B. Cardiovascular mortality or transplantation

No. at risk
No fibrosis 330 316 184 93 26
Fibrosis 142 120 79 28 10

C. Sudden cardiac death or aborted sudden cardiac death

No. at risk
No fibrosis 330 314 180 92 25
Fibrosis 142 111 67 24 7

D. Heart failure death, hospitalization, or transplantation

No. at risk
No fibrosis 330 297 172 85 25
Fibrosis 142 110 71 24 9
LAMINOPATHIES

- **RISK FACTORS FOR MAJOR EVENTS IN 269 PATIENTS**
  - Baseline LVEF < 45%
  - Non-sustained ventricular tachycardia
  - Male gender

van Rijssingen IA, et al. JACC 2012
- 373 patients with an evaluation consistent with IDC or myocarditis
- Fewer than 6 months of symptom duration

<table>
<thead>
<tr>
<th></th>
<th>All (n = 373)</th>
<th>Men (n = 230)</th>
<th>Women (n = 143)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>45 ± 14</td>
<td>46 ± 14</td>
<td>43 ± 14</td>
<td>0.01</td>
</tr>
<tr>
<td>Black</td>
<td>21.5</td>
<td>19.1</td>
<td>25.2</td>
<td>0.19</td>
</tr>
<tr>
<td>NYHA functional class I/II/III/IV</td>
<td>18/46/29/7</td>
<td>20/45/27/7</td>
<td>15/48/31/6</td>
<td>0.53</td>
</tr>
<tr>
<td>LVEF baseline</td>
<td>0.24 ± 0.08</td>
<td>0.23 ± 0.08</td>
<td>0.24 ± 0.08</td>
<td>0.09</td>
</tr>
<tr>
<td>LVEF at 6 months</td>
<td>0.40 ± 0.12</td>
<td>0.39 ± 0.12</td>
<td>0.43 ± 0.12</td>
<td>0.004</td>
</tr>
<tr>
<td>BP systolic</td>
<td>112 ± 19</td>
<td>113 ± 20</td>
<td>111 ± 17</td>
<td>0.27</td>
</tr>
<tr>
<td>BP diastolic</td>
<td>71 ± 13</td>
<td>71 ± 13</td>
<td>71 ± 13</td>
<td>0.97</td>
</tr>
<tr>
<td>Heart rate</td>
<td>83 ± 17</td>
<td>83 ± 17</td>
<td>83 ± 16</td>
<td>0.86</td>
</tr>
<tr>
<td>Therapy at entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>82.3</td>
<td>84.3</td>
<td>79.0</td>
<td>0.21</td>
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<tr>
<td>Aldosterone receptor antagonist</td>
<td>27.4</td>
<td>29.1</td>
<td>24.5</td>
<td>0.34</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>82.0</td>
<td>80.9</td>
<td>83.9</td>
<td>0.49</td>
</tr>
</tbody>
</table>

McNamara D et al. JACC 2011
LVEF IMPROVEMENT IN IDCM AFTER OMT (IMAC2 STUDY)

- Solid bars: Lvedd < 6.00 cm
- Shaded bars: Lvedd 6.00 to 7.00 cm
- Open bars: Lvedd > 7.00 cm

- 70% demonstrated an increase of 10 ejection fraction units,
- 39% demonstrated an increase of 20 U or more.
- In 25% the LVEF had normalized (0.50 or more).
LVEF IMPROVEMENT IN ALCOHOLIC DCM

LVEF IMPROVEMENT IN CHEMOTHERAPY INDUCED DCM

Cardinale D, et al JACC 2010
LVEF IMPROVEMENT IN CARDIAC SARCOIDOSIS

Chou CZ, et al. Am J Cardiol 2004
ROLE OF LVEF IMPROVEMENT ON THE NATURAL HISTORY OF DCM

Steimle AE, et al. JACC 1994;23:553-9
SURVIVAL IN IDC M (1975-2000)

- 25-30% annual mortality
- 50% five-year mortality

Dec GW, Fuster V. NEJM 1994;331:1564-75
94% transplant free survival at 1st year
88% at 4 years
603 patients with IDCM

- 4 enrollment periods:
  - 1977-1984: pre ACEI
  - 1985-1990: ACEI introduction
  - 1991-2000: B-blockers introduction
  - 2001-2011: Devices introduction
CHANGES IN MANAGEMENT OF DCM

A. ACE-i/ARBs

B. Beta-blockers

C. MRA

D. Diuretics
CHANGES IN MANAGEMENT OF DCM

CARDIOVASCULAR AND HEART FAILURE MORTALITY REDUCTION

- HF mortality decreased:
  - 53% for period 2
  - 74% for period 3
  - 90% for period 4
  compared to period 1

- 5 year event-free rate:
  - 62% for period 1
  - 74% for period 2
  - 84% for period 3
  - 93% for period 4

SUDDEN DEATH RATE REDUCTION

- 87% risk reduction in period 2000-2010 compared to period 1977-1984

AHEPA CARDIOMYOPATHIES CENTER COHORT

- 183 DCM patients

![Bar chart showing various causes of DCM with percentages: Idiopathic 37.7%, Familial 24%, Myocarditis 10.4%, Alcoholic 9.8%, Chemotherapy 0.5%, Other 17.6%.]
AHEPA CARDIOMYOPATHIES CENTER COHORT

- 183 DCM patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEI/ARB</td>
<td>77.6</td>
</tr>
<tr>
<td>B-Blocker</td>
<td>75.4</td>
</tr>
<tr>
<td>Diuretics</td>
<td>64.5</td>
</tr>
<tr>
<td>MRA</td>
<td>44.3</td>
</tr>
</tbody>
</table>
After a mean follow up of 6±4 years, 9.8% died

NYHA class and LVEF were independent predictors
1.6% suffered SCD
18% of the patients received ICD
21% of ICD patients received appropriate interventions.
CONCLUSIONS

- DCM is an heterogeneous disease with variable natural history.
- The natural history of DCM has changed substantially over the last decades.
- The prognostic factors of DCM, especially for SCD, still remain a subject of controversy.
THANK YOU

WHAT'S NEXT?