Risk Stratification in Non-Compaction Cardiomyopathy. Who Should Get an ICD or CRT-D?

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University Hospital - Favaloro Foundation
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First recognised in 1932 by Bellet S. et al. as "hipertrabeculation of the LV", Non-Compaction Cardiomyopathy (NCC) was officially described by Chin TK et al. in 1990.

It is a rare disorder, classified as a primary genetic cardiomyopathy by the AHA and as an unclassified cardiomyopathy by The ESC Working Group on Myocardial and Pericardial Diseases (2008).

Non-Compaction Cardiomyopathy

Pathoanatomical Features

- NCC is characterized by:
  - An altered myocardial wall with prominent trabeculae and deep intertrabecular recesses with a thickened myocardium and two layers consisting of compacted and noncompacted myocardium.
  - Continuity between the left ventricular cavity and the deep intratrabecular recesses, which are filled with blood from the ventricular cavity.
  - Decreased coronary flow reserve in most segments that show wall motion abnormalities.
The embryonal myocardium consists of a “spongy” meshwork of trabecular fibers and intertrabecular recesses that communicate with the cavity to receive their blood supply.

During the 5th to 8th week of fetal life, the development of the coronary vasculature establishes a permanent nutrient supply. The “spongy” meshwork gradually becomes “compacted”, advancing, in parallel with coronary development, from the base to the apex and from the epicardium to the endocardium.

In the mature, normal heart only a few residual trabeculations remain, typically more in the RV than in the LV.
Non-Compaction Cardiomyopathy

Cardiac embryology and pathogenesis

Two hypotheses are proposed to explain a primary genetic disease:

- **Non-Compaction hypothesis:**
  - It revolves around the notion that compaction of the embryogenic, hypertrabeculated myocardium is arrested or impaired because of a primary genetic defect.
  - The severity of the phenotype will depend on the timing of the insult that forestalls further maturation.

- **Compensation hypothesis:**
  - A genetic defect impairs ventricular morphology or function.
  - Non-Compaction arises as an adaptive reaction.
Two hypotheses are proposed to explain a secondary non-genetic disease:

- **Hemodynamic/ischemic hypothesis:**
  - It is thought that microcirculatory dysfunction or metabolic disorders give rise to myocardial ischemia or microinfarcts which induce a hypertrabeculation reaction.

- **Myocarditis hypothesis:**
  - The presence of subendocardial fibrosis in some cases suggested that myocarditis may be the cause of some of them.
Non-Compaction Cardiomyopathy

Genetics

- NCC can be either sporadic or familial.
  - Genetics disorders are identified in only half of the patients.
  - The genetic heterogeneity is evident from the few mutations identified, with implications of sarcomeric, cytoskeletal, Z-line and mitochondrial proteins in its pathogenesis.
  - This profound heterogeneity implies that the pathogenetic behind NCC must be equally diverse, with no single pathological model to fit and suit all cases.
Non-Compaction Cardiomyopathy

Diagnosis

- Doppler Echocardiography

Chin et al. Echocardiographic criteria:

- The presence of $X/Y \leq 0.5$:
  - $X$ is the distance from the epicardial surface to the trough of the trabecular recess.
  - $Y$ is the distance from the epicardial surface to the peak of trabeculation.

This criteria is applied to trabeculae at the left ventricular apex on parasternal or apical four-chamber views at end-diastole.

Non-Compaction Cardiomyopathy

**Diagnosis**

- Doppler Echocardiography

- Jenni et al. Echocardiographic criteria:
  - Left ventricular wall consisting of two layers: a thin compacted epicardial layer and a markedly thickened endocardial layer with numerous and prominent trabeculations and deep recesses with a maximum ratio of noncompacted to compacted myocardium **> 2:1** at end-systole in the parasternal short-axis view.
  - Trabeculations must be localized in the LV apex or midventricular segments.
  - Color Doppler evidence of flow within the deep intertrabecular recesses.
  - Absence of coexisting cardiac structural abnormalities.

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Non-Compaction Cardiomyopathy

Diagnosis

- Stöllberger et al Echocardiographic criteria:
  - More than three trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in a single image plane.

Stöllberger et al. Am J Cardiol 2002;90:899-902
Non-Compaction Cardiomyopathy

**Diagnosis**

- **Cardiac MRI criteria:**
  
  The best distinguishing feature is a ratio in diastole of noncompacted to compacted myocardial thickness > 2.3 as assessed in three long-axis views or > 2.5 in short-axis and four-chamber views.
Non-Compaction Cardiomyopathy

**Diagnosis**

- Cardiac MRI criteria

**Short-axis view**

**Short-axis and four-chamber view**
Non-Compaction Cardiomyopathy

**Diagnosis**

- **MSCT 64 rows criteria:** The same used for MRI.
Non-Compaction Cardiomyopathy

Clinical Features

Its natural history is diverse and still unresolved.

Includes:

- LV systolic dysfunction and heart failure (HF).
- Thromboembolic events.
- Arrhythmias (AF/AT - VT/FV) and sudden cardiac death.
Non-Compaction Cardiomyopathy

Management

- Mild and asymptomatic patients: Close follow-up seems to be sufficient.
- Patients with mild to moderate heart failure: Medical treatment seems appropriate.
- Patients with AF, severe LV dysfunction or intracardiac thrombi: Anticoagulation seems mandatory.
- Advanced heart failure: Resynchronization therapy and heart transplantation seem to be the only viable alternatives.
- Patients recovered from cardiac arrest or VT/FV: The ICD (secondary prevention) is accepted.
Non-Compaction Cardiomyopathy

Management

### Outcome in Children

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Pts (n)</td>
<td>8</td>
<td>27</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Mean age</td>
<td>7 years</td>
<td>5 years</td>
<td>9 years</td>
<td>3.9 years</td>
</tr>
<tr>
<td>Men</td>
<td>63%</td>
<td>56%</td>
<td>89%</td>
<td>40%</td>
</tr>
<tr>
<td>Follow-up</td>
<td>&gt; 5 years</td>
<td>&gt; 17 years</td>
<td>&gt; 5 years</td>
<td>&gt; 16 years</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>63%</td>
<td>30%</td>
<td>55%</td>
<td>54%</td>
</tr>
<tr>
<td>Embolic Events</td>
<td>38%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Death</td>
<td>38%</td>
<td>7%</td>
<td>22%</td>
<td>14%</td>
</tr>
<tr>
<td>Heart Transplantation</td>
<td>0%</td>
<td>4%</td>
<td>0%</td>
<td>9%</td>
</tr>
<tr>
<td>VT</td>
<td>38%</td>
<td>0%</td>
<td>0%</td>
<td>15%</td>
</tr>
</tbody>
</table>
# Non-Compaction Cardiomyopathy

## Management

### Outcome in Adults

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Pts (n)</td>
<td>34</td>
<td>32</td>
<td>45</td>
<td>65</td>
<td>86</td>
</tr>
<tr>
<td>Mean age</td>
<td>40 years</td>
<td>49 years</td>
<td>37 years</td>
<td>47 years</td>
<td>52 years</td>
</tr>
<tr>
<td>Men</td>
<td>74%</td>
<td>53%</td>
<td>62%</td>
<td>37%</td>
<td>76%</td>
</tr>
<tr>
<td>Follow-up</td>
<td>&gt; 11 years</td>
<td>&gt; 15 years</td>
<td>&gt; 3 años</td>
<td>&gt; 8 years</td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>68%</td>
<td>62,5%</td>
<td>62%</td>
<td>61%</td>
<td>70%</td>
</tr>
<tr>
<td>Embolic Events</td>
<td>21%</td>
<td>4%</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>35%</td>
<td>2%</td>
<td>10%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Heart Transplantation</td>
<td>12%</td>
<td>-</td>
<td>14%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>41%</td>
<td>20%</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dr. Nestor O. Galizio*

[www.fundacionfavaloro.org](http://www.fundacionfavaloro.org)  
División Electrofisiología
Non-Compaction Cardiomyopathy

Management

- The first series of any new recognized disease are dominated by cases with advanced phenotypes.

- Over time, it was observed that, probably, due to their genetic and pathogenetic heterogeneity, NCC is associated with a wide spectrum of presentation and variable outcomes.

- It seems inappropriate to issue a general recommendation for primary prevention of SCD.
In the absence of information from randomized studies or registries, the ACC/AHA/HRS 2008 guidelines recommended primary prophylactic implantation of ICD in pts with NCC, as a strategy to reduce the risk of SCD (Class IIb Level C).

Non-Compaction Cardiomyopathy

Management

ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities

3.2.6. Noncompaction of the Left Ventricle

Ventricular arrhythmias and sudden death are among the major complications of this disorder. Sudden death can occur at any age, and there are currently no techniques clinically useful for risk stratification for life-threatening ventricular arrhythmias with noncompaction. Although there is no impairment of systolic function, ventricular arrhythmias are frequent in noncompaction. Approximately 40% of children with noncompaction demonstrate complex ventricular arrhythmias. Available clinical data indicate that sudden death is the most common cause of mortality. Although there are no prospective trials or registry data, there are sufficient observational data to indicate that placement of an ICD as a strategy to reduce the risk of sudden death is a reasonable clinical strategy (410,413–421).

Non-Compaction Cardiomyopathy

OBJECTIVE

- **COMPAS** (COMparación de estrategias de Prevención de Arritmias Sostenidas) is a prospective registry of pts with ICD and CRT-D implantation for primary and secondary prevention of SCD.

- We investigated the outcome of pts with NCC according to some selection criteria for risk stratification of SCD, to guide ICD and CRT-D indications.
Non-Compaction Cardiomyopathy

METHODS

- From January 1997 to November 2010, 87 consecutive pts with NCC were analyzed.
- Mean age was 42±18 years, 56 men.
- Mean follow up was 28.3±33 months.
- Thirty five pts (40.2%) received an ICD.

Diagnosis:
It was established according to the accepted Echocardiographic, Cardiac MRI or Multislide Computed Tomography (MSCT) criteria.
Non-Compaction Cardiomyopathy

RESULTS

Basal characteristics

Total population: 87 pts.

. Age 42±18 years
. Gender 56 men.
. NYHA Class II-IV 35 pts
. Previous SCD 3 pts
. SVT 3 pt
. NSVT 16 pts
. Syncope 10 pts
. Stroke 3 pts
## RESULTS

Basal characteristics of pts with or without ICD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non ICD group (n= 52)</th>
<th>ICD group (n= 35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>41±18 years</td>
<td>42±17 years</td>
<td>NS</td>
</tr>
<tr>
<td>Gender</td>
<td>33 men (63.5%)</td>
<td>23 men (65.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA FC III-IV</td>
<td>10 pts (19.2%)</td>
<td>11 pts (31.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>SCD</td>
<td>-</td>
<td>3 pts (8.5%)</td>
<td>0.0617</td>
</tr>
<tr>
<td>Syncope</td>
<td>3 pts (5.7%)</td>
<td>7 pts (20%)</td>
<td>0.0371</td>
</tr>
<tr>
<td>SVT</td>
<td>-</td>
<td>3 pts (8.6%)</td>
<td>0.0617</td>
</tr>
<tr>
<td>NSVT</td>
<td>4 pts (7.7%)</td>
<td>12 pts (34.3%)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Mean LVEF</td>
<td>42.6 ± 14 %</td>
<td>31 ± 12 %</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean follow-up</td>
<td>20.3±26 months</td>
<td>37.4±32 months</td>
<td>0.0075</td>
</tr>
</tbody>
</table>
# Results

Reasons for ICD Implantation

**ICD Group (n=35)**

<table>
<thead>
<tr>
<th>Secondary Prevention (n=4)</th>
<th>Primary Prevention (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCD</strong></td>
<td>LVEF ≤ 30%</td>
</tr>
<tr>
<td></td>
<td>21 pts (60%)</td>
</tr>
<tr>
<td><strong>SVT/FV</strong></td>
<td>LVEF ≤ 30% + FH of SCD</td>
</tr>
<tr>
<td></td>
<td>4 pts (11.4%)</td>
</tr>
<tr>
<td><strong>SVT</strong></td>
<td>LVEF ≤ 30% + syncope</td>
</tr>
<tr>
<td></td>
<td>2 pts (5.7%)</td>
</tr>
<tr>
<td></td>
<td>LVEF ≤ 30% + NSVT</td>
</tr>
<tr>
<td></td>
<td>6 pts (14.3%)</td>
</tr>
<tr>
<td></td>
<td>NSVT + Syncope</td>
</tr>
<tr>
<td></td>
<td>4 pts (11.4%)</td>
</tr>
<tr>
<td></td>
<td>NSVT + FH of SCD</td>
</tr>
<tr>
<td></td>
<td>2 pt (5.7%)</td>
</tr>
<tr>
<td></td>
<td>NSVT with SVT at EP study</td>
</tr>
<tr>
<td></td>
<td>1 pt (2.8%)</td>
</tr>
</tbody>
</table>

- SCD: 3 pts (8.6%)
- SVT/FV: 3 pts
- SVT: 1 pt (2.8%)
- LVEF ≤ 30%
- LVEF ≤ 30% + FH of SCD
- LVEF ≤ 30% + syncope
- LVEF ≤ 30% + NSVT
- NSVT + Syncope
- NSVT + FH of SCD
- NSVT with SVT at EP study
Outcomes of pts with or without ICD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Non ICD group (n=52)</th>
<th>ICD group (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up</td>
<td>20.3±26 months</td>
<td>37.4±32 months</td>
</tr>
<tr>
<td>Death (advanced HF)</td>
<td>1 pt (1.9 %)</td>
<td>none</td>
</tr>
<tr>
<td>Heart transplantation</td>
<td>3 pts (5.7 %)</td>
<td>2 pts (5.7 %)</td>
</tr>
<tr>
<td>(advanced HF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDT (&gt; 20 J)</td>
<td></td>
<td>4 pts (11%)</td>
</tr>
<tr>
<td>Appropriate shoks</td>
<td></td>
<td>3 pts (8.6%)</td>
</tr>
<tr>
<td>(VT/VF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappropriate shocks</td>
<td></td>
<td>5 pts (14.2%)</td>
</tr>
<tr>
<td>(AF-AT-ST)</td>
<td></td>
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</tbody>
</table>

**RESULTS**

Outcome of pts with or without ICD

- **Non-Compaction Cardiomyopathy**
Non-Compaction Cardiomyopathy

CONCLUSIONS

- In our study population, ICD was implanted in 40% of the pts with NCC.

**ICD group:**
- Most of the pts received an ICD for primary prevention (88%) due to low LVEF or ≥ 2 risk factors.
- The rate of appropriate shocks was low and similar to that reported in previous trials about ischemic or non-ischemic cardiomyopathy.
- There was no death.
- HTX was due to heart failure progression.
Non-Compaction Cardiomyopathy

CONCLUSIONS

- Non-ICD group.
  - There was no SCD.
  - Death and HTX were due to heart failure progression.

This registry suggests that pts with non-compaction cardiomyopathy might be stratified to select those at a higher risk of sudden cardiac death who could benefit from ICD therapy.
### Outcome in Adults

<table>
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<tbody>
<tr>
<td>Pts (n)</td>
<td>34</td>
<td>32</td>
<td>45</td>
<td>65</td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>mean age</td>
<td>40 years</td>
<td>49 years</td>
<td>37 years</td>
<td>47 years</td>
<td>52 years</td>
<td>42 years</td>
</tr>
<tr>
<td>Men</td>
<td>74%</td>
<td>53%</td>
<td>62%</td>
<td>37%</td>
<td>76%</td>
<td>56%</td>
</tr>
<tr>
<td>Follow-up</td>
<td>&gt; 11 years</td>
<td>&gt; 15 years</td>
<td>&gt; 3 años</td>
<td>&gt; 8 years</td>
<td>&gt; 2 years</td>
<td></td>
</tr>
<tr>
<td>H. Failure</td>
<td>68%</td>
<td>62,5%</td>
<td>62%</td>
<td>61%</td>
<td>70%</td>
<td>40.2%</td>
</tr>
<tr>
<td>Embolic events</td>
<td>21%</td>
<td>4%</td>
<td>5%</td>
<td>3.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>35%</td>
<td>2%</td>
<td>10%</td>
<td>22%</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>H. Transplantation</td>
<td>12%</td>
<td>-</td>
<td>14%</td>
<td>1%</td>
<td>5.7%</td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>41%</td>
<td>20%</td>
<td>6%</td>
<td>3.5%</td>
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</tbody>
</table>
Recently, Stöllberger and Finsterer proposed a complementary set of criteria for the diagnosis:

- **Definitive:** If both Stöllberger and Jenni’s criteria were satisfied.
- **Probably:** Fulfilment of only one set of diagnosis criteria.
- **Possible:** Cases with fewer than four trabeculations or a NC/C ratio less than 2.

Finsterer J, Stöllberger et al. In J Cardiol 2008;123:175-176
Non-Compaction Cardiomyopathy

METHODS

- Statistical analysis
  - Continuous data with normal distribution are reported as mean and standard deviation.
  - The comparisons between the two groups were established by 2-tailed Student’s t tests.
  - For testing independence of dichotomous or ordinal variables, the data were arranged in contingency tables and the statistical significance was established by using the Fisher exact test.
  - P values less than 0.05 were considered statistically significant.