123I-mIBG assessed cardiac sympathetic activity: standardizing towards clinical implementation
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Cardiac $^{123}$I-$m$IBG scintigraphy predicts freedom of appropriate ICD therapy in stable chronic heart failure patients

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GA Somsen
HJ Verberne
ABSTRACT

Aim
Chronic heart failure (CHF) is a life-threatening disease, partly due to sudden cardiac death (SCD). Implantable cardioverter defibrillators (ICD) for primary prevention of SCD have improved overall survival of CHF patients. However, a high percentage of patients never receives appropriate ICD therapy. This prospective multicentre study evaluated whether cardiac sympathetic activity assessed by planar $^{123}$I-mIBG scintigraphy could optimize selection for ICD implantation.

Materials and Methods
135 stable CHF subjects (age 64.5 ± 9.3 years, 79% male, LVEF 25 ± 6%) referred for ICD implantation for primary prevention in 13 European institutions were enrolled. All subjects underwent planar and SPECT $^{123}$I-mIBG scintigraphy. Planar images were acquired at 15 minutes (early) and 4 hours (late) after administration of $^{123}$I-mIBG. Early and late heart-to-mediastinum (H/M) ratio, $^{123}$I-mIBG washout (WO) and late summed scores were calculated. Cross-calibrated phantom study-data were used to correct for different gamma camera-collimator use. The primary endpoint was appropriate ICD therapy. The secondary endpoint was the combined endpoint of all first cardiac events: appropriate ICD therapy, progression of heart failure (HF) and cardiac death.

Results
During a median follow-up of 30 months (6 - 68 months), 24 subjects (17.8%) experienced a first cardiac event (appropriate ICD therapy [12], HF progression [6], cardiac death [6]). The combination of late H/M ratio (HR 0.461 [0.281 - 0.757]) and LVEF (HR 1.052 [1.021 - 1.084]) was significantly associated with freedom of appropriate ICD therapy ($p < 0.001$). Late H/M ratio was independently associated with the combined endpoint (HR 0.135 [0.035 - 0.517], $p = 0.001$).

Conclusion
Planar myocardial $^{123}$I-mIBG-derived late H/M ratio and LVEF were associated with freedom of appropriate ICD therapy. In addition there was a significant association between late H/M ratio and the combined endpoint. Therefore, $^{123}$I-mIBG scintigraphy seems to be able to optimize the selection of CHF subjects who might benefit from ICD implantation.
INTRODUCTION

Despite therapeutic improvements the prognosis of chronic heart failure (CHF) remains unfavorable partly due to sudden cardiac death (SCD). The introduction of implantable cardioverter defibrillators (ICD) has improved overall survival of CHF patients.¹,² Based on large randomized trials, current European guidelines recommend ICD implantation for primary prevention of fatal arrhythmias in subjects with a left ventricular ejection fraction (LVEF) < 35% and symptomatic CHF with NYHA class ≥ 2 under optimal pharmacological therapy.³ ICDs applied for primary or secondary prevention of SCD reduce the relative risk of death by 20%. However, the MADIT II (Second Multicenter Automated Defibrillator Implantation Trial) has shown that the absolute reduction of fatal events was only 5.6% (mortality was 19.8% in the control and 14.2% in the ICD group during a mean follow-up of 20 months).¹ In addition, the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study showed that the annual number of ICD shocks was 7.1%. However, the number of inappropriate ICD shocks was 2.0%. The cumulative number of appropriate shocks increased to 21% in the 5th year post-implantation.⁴ Conversely, three years after ICD implantation for primary prevention, a remarkably high percentage (65%) of patients had never received appropriate ICD therapy.⁴ Moreover, the risk of malfunction, (post)operative complications⁵ and the relatively high cost of these devices urges for optimization of current ICD selection criteria for primary prevention.

Cardiac sympathetic activity can non-invasively be assessed with meta-iodobenzylguanidine (¹²³I-mIBG).⁶ The past decades, myocardial ¹²³I-mIBG scintigraphy has been shown to predict prognosis in CHF patients.⁷,⁸ A late heart-to-mediastinum (H/M) ratio < 1.6 has been suggested to be a predictor of ventricular arrhythmia.⁹ Furthermore, decreased ¹²³I-mIBG uptake and increased wash-out (WO) are associated with increased incidence of SCD or appropriate ICD therapy.¹⁰-¹² Most of these studies have been conducted in various populations, both with primary and secondary prevention of SCD. In addition, extrapolation of the obtained data is hampered by the fact that the data were not corrected for differences in gamma camera-collimators.¹³ Therefore, the aim of this prospective study was to evaluate whether increased cardiac sympathetic activity (i.e., cross-calibrated decreased H/M ratio, increased ¹²³I-mIBG WO) assessed by planar and SPECT ¹²³I-mIBG scintigraphy could identify high-risk CHF patients most likely to experience appropriate ICD therapy for primary prevention of SCD.
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METHODS

Thirteen institutions in Europe (see “Appendix” for list of all participating institutions) participated. The study was approved by the local institutional review boards and conducted according to the principles of the International Conference on Harmonization–Good Clinical Practice. All subjects provided written informed consent before participation. The study was registered on www.trialregister.nl (registration number NTR2735).

Design

All included patients underwent cardiac $^{123}$I-mIBG scintigraphy within 2 weeks prior to ICD implantation and were followed for the occurrence of the primary and secondary endpoints. The primary endpoint for this study was appropriate ICD therapy: ICD therapy to overcome potentially fatal ventricular arrhythmias: i.e. anti-tachycardia pacing (ATP) or shock triggered by ventricular tachycardia or fibrillation. The secondary endpoint was defined as the combined endpoint of all first cardiac events: appropriate ICD therapy, progression of heart failure (HF) and cardiac death.

Subjects

Patients with stable CHF (ischaemic or non-ischaemic) who were referred for ICD implantation for primary prevention of SCD were enrolled between July 2010 - October 2015. The inclusion criteria were: 1. LVEF < 35%, 2. New York Heart Association (NYHA) functional class II or III, 3. Pacemaker-naive, 4. Stable and treated with optimal medical therapy for at least 3 months according to the European HF guidelines. Exclusion criteria were: 1. History of defibrillation to treat a previous ventricular arrhythmic event, 2. History of acute myocardial infarction within the previous 30 days. As part of the workup for ICD implantation all subjects underwent complete clinical evaluation including echocardiography and blood sample analysis.

$^{123}$I-mIBG scintigraphy acquisition and analysis

To block uptake of free $^{123}$I by the thyroid gland, subjects were pretreated with 250 mg oral potassium iodide 30 min before intravenous (IV) injection of 185 MBq $^{123}$I-mIBG (Adreview®, GE, Healthcare). Fifteen minutes (early acquisition) and 4 hours (late acquisition) after administration of $^{123}$I-mIBG, 10-min planar images were acquired from an anterior thoracic view (256 × 256 matrix) with the subjects in supine position. A 20% window was centered at 159 KeV. Additional SPECT $^{123}$I-mIBG images, without attenuation correction, were acquired after the late planar acquisitions (128 × 128 matrix).

All $^{123}$I-mIBG data were anonymized and sent to the study coordinating centre (Academic Medical Center, Amsterdam, the Netherlands). Planar data were analysed by one experienced observer (D.O.V.) blinded to patient data using post-processing software. Heart-to-mediastinum (H/M) ratio was calculated from planar $^{123}$I-mIBG images using a manually drawn region-of-interest (ROI) over the heart and a fixed rectangular
mediastinal ROI. To correct for differences in gamma camera-collimator combination, institutional early and late planar H/M ratios were converted to standardized values by using conversion coefficients from our previous 123I-mIBG cross-calibrated phantom study. The washout (WO) was defined by:

\[ WO = \left( \frac{\text{early H/M ratio} - \text{late H/M ratio}}{\text{early H/M ratio}} \right) \times 100 \]

All late SPECT 123I-mIBG images were analysed by two experienced observers (B.L.v.E.S. and H.J.V.) blinded to patient data according a previous published protocol. Summed scores (range 0–68) were derived by the standard 17-segment model and 5-point scoring method.

**ICD implantation**

After myocardial 123I-mIBG imaging transvenous or subcutaneous ICDs were implanted in the participating institutions. Testing of sensing, pacing and defibrillation thresholds was performed according to local protocols. In case of patient eligibility for cardiac resynchronization therapy (CRT), a combined CRT-D device was implanted. Settings for detection of ventricular tachycardias or fibrillation were at the discretion of the implanting physician.

**Clinical follow-up and event adjudication**

Follow-up was based on telephone interviews (D.O.V.) and medical records. All subjects received standard clinical care and were followed up until: 1. subjects death was confirmed by medical records of the general practitioner; 2. the trial was terminated (30th of April 2016). The Clinical Adjudication Committee, whose members were unaware of the scintigraphy data, reviewed all data from case record forms and source documents to confirm occurrence of cardiac events, specifically: 1. HF progression: increase in symptomatic status from NYHA functional class II to III or IV, or increase from NYHA class III to class IV; 2. potentially life-threatening arrhythmic event, including documented episode of spontaneous sustained (30 s) ventricular tachyarrhythmia, resuscitated cardiac arrest, or appropriate ICD therapy: ATP or defibrillation; or 3. cardiac death (further classified as due to terminal heart failure and SCD).

**Comparison with a historical Japanese CHF cohort**

To compare the mortality rate of our study population with other published data we used a risk model, based on a historical Japanese CHF cohort. This model estimates the 2-years mortality risk based on four variables (NYHA class, age, LVEF and standardized late H/M ratio). Using the median 2-year mortality of 9%, patients were divided into 2 groups: mortality rate < 9% and ≥ 9%. Since the Japanese risk model was made using data from 1990, the effect of ICD therapy was not included and...
# Table 1. Patients characteristics with subgroups appropriated ICD therapy, combined endpoint (CE) and no CE.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Appropriated ICD discharge</th>
<th>CE</th>
<th>No CE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 135)</td>
<td>(n = 12)</td>
<td>(n = 24)</td>
<td>(n = 111)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.5 ± 9.3</td>
<td>65.8 ± 6.9</td>
<td>66.4 ± 7.1</td>
<td>64.1 ± 9.6</td>
<td>0.471</td>
</tr>
<tr>
<td>Male (%)</td>
<td>106 (79)</td>
<td>10 (83)</td>
<td>21 (88)</td>
<td>85 (77)</td>
<td>0.462</td>
</tr>
<tr>
<td>Ischaemic heart disease (%)</td>
<td>80 (59)</td>
<td>9 (75)</td>
<td>16 (67)</td>
<td>64 (58)</td>
<td>0.409</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.308</td>
</tr>
<tr>
<td>II</td>
<td>104 (77)</td>
<td>8 (67)</td>
<td>16 (67)</td>
<td>88 (79)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>31 (23)</td>
<td>4 (33)</td>
<td>8 (33)</td>
<td>23 (21)</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25.0 ± 6.2</td>
<td>26.2 ± 5.8</td>
<td>25.4 ± 6.3</td>
<td>25.0 ± 6.2</td>
<td>0.787</td>
</tr>
<tr>
<td>BMI</td>
<td>27.9 ± 4.7</td>
<td>28.1 ± 3.9</td>
<td>29.1 ± 6.0</td>
<td>27.7 ± 4.3</td>
<td>0.364</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127 ± 19</td>
<td>129 ± 18</td>
<td>125 ± 16</td>
<td>128 ± 19</td>
<td>0.828</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>73 ± 12</td>
<td>77 ± 12</td>
<td>76 ± 10</td>
<td>75 ± 12</td>
<td>0.852</td>
</tr>
<tr>
<td>QRS time (msec)</td>
<td>125 ± 21</td>
<td>125 ± 21</td>
<td>117 ± 18</td>
<td>132 ± 32</td>
<td>0.209</td>
</tr>
<tr>
<td>ICD type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous (%)</td>
<td>7 (5)</td>
<td>2 (17)</td>
<td>2 (8)</td>
<td>3 (3)</td>
<td>0.065</td>
</tr>
<tr>
<td>CRT (%)</td>
<td>56 (41)</td>
<td>3 (25)</td>
<td>10 (42)</td>
<td>45 (41)</td>
<td>0.980</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>39 (29)</td>
<td>5 (42)</td>
<td>10 (42)</td>
<td>29 (26)</td>
<td>0.330</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>76 (56)</td>
<td>7 (58)</td>
<td>13 (54)</td>
<td>63 (57)</td>
<td>0.965</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>56 (42)</td>
<td>7 (58)</td>
<td>12 (50)</td>
<td>44 (40)</td>
<td>0.465</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>34 (25)</td>
<td>3 (25)</td>
<td>11 (46)</td>
<td>23 (21)</td>
<td>0.633</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>112 (83)</td>
<td>11 (92)</td>
<td>18 (75)</td>
<td>94 (85)</td>
<td>0.379</td>
</tr>
<tr>
<td>CCB (%)</td>
<td>12 (9)</td>
<td>25 (25)</td>
<td>4 (17)</td>
<td>8 (7)</td>
<td>0.081</td>
</tr>
<tr>
<td>ACE-I/ARB (%)</td>
<td>126 (93)</td>
<td>11 (92)</td>
<td>22 (92)</td>
<td>104 (94)</td>
<td>0.917</td>
</tr>
<tr>
<td>Loop diuretic (%)</td>
<td>88 (65)</td>
<td>10 (83)</td>
<td>20 (83)</td>
<td>68 (61)</td>
<td>0.051</td>
</tr>
<tr>
<td>MRA(%)</td>
<td>64 (47)</td>
<td>7 (58)</td>
<td>13 (54)</td>
<td>51 (48)</td>
<td>0.594</td>
</tr>
<tr>
<td>Asperin (%)</td>
<td>64 (47)</td>
<td>5 (42)</td>
<td>10 (42)</td>
<td>54 (49)</td>
<td>0.770</td>
</tr>
</tbody>
</table>
**123I-mIBG scintigraphy helpful for prophylactic ICD implantation?**

Continuation table 1.

<table>
<thead>
<tr>
<th></th>
<th>All (n = 135)</th>
<th>Appropriate ICD discharge (n = 12)</th>
<th>CE (n = 24)</th>
<th>No CE (n = 111)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statine (%)</td>
<td>86 (64)</td>
<td>9 (75)</td>
<td>15 (63)</td>
<td>71 (64)</td>
<td>0.733</td>
</tr>
<tr>
<td><strong>Planar 123I-mIBG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early H/M ratio</td>
<td>2.04 ± 0.39</td>
<td>2.09 ± 0.27</td>
<td>2.00 ± 0.26</td>
<td>2.06 ± 0.42</td>
<td>0.721</td>
</tr>
<tr>
<td>Late H/M ratio</td>
<td>1.79 ± 0.38</td>
<td>1.74 ± 0.20</td>
<td>1.66 ± 0.24</td>
<td>1.82 ± 0.40</td>
<td>0.131</td>
</tr>
<tr>
<td><strong>123I-mIBG WO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>123I-mIBG Early</td>
<td>12.4 ± 9.2</td>
<td>16.2 ± 8.0</td>
<td>16.6 ± 9.2</td>
<td>11.5 ± 8.9</td>
<td>0.017*</td>
</tr>
<tr>
<td>123I-mIBG Late</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summed score</td>
<td>39.4 ± 15.5</td>
<td>34.9 ± 13.1</td>
<td>37.4 ± 14.7</td>
<td>39.8 ± 15.7</td>
<td>0.516</td>
</tr>
<tr>
<td>Predicted 2-year mortality risk (%)</td>
<td>12.4 ± 9.4</td>
<td>14.3 ± 9.5</td>
<td>16.1 ± 11.0</td>
<td>11.6 ± 11.0</td>
<td>0.036</td>
</tr>
</tbody>
</table>

* = difference between CE and no CE, p = 0.005. NYHA: New York Heart Association, LVEF: left ventricular ejection fraction; BMI: body mass index; ICD: implantable cardioverter defibrillator, CRT: cardiac resynchronization therapy; CCB: calcium channel blocker; ACE-I: angiotensin converting enzyme-inhibitor; ARB: angiotensin II receptor blockers; MRA: mineral receptor blocker.

therefore appropriate ICD therapy was scored as a fatal event. As this mortality risk model assumes complete 2-year follow-up, patients who had a follow-up < 2 years and were alive were excluded for this analysis.

**STATISTICAL ANALYSIS**

All continuous variables are expressed as mean ± standard deviation. Difference between groups for continuous data we compared using analysis of variance (ANOVA) with post-hoc Bonferroni. Efficacy analysis used univariate and multivariate Cox proportional regression hazards models using age, NYHA class, LVEF, early and late H/M ratio, 123I-mIBG WO and SPECT summed score as variables. Forward elimination determined the combination of variables that most influenced the time-over-event model. The overall goodness-of-fit for each model was expressed as the adjusted R². The F-test was used to assess whether a model explained a significant proportion of the variability. A p-value <0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed with SPSS, release 22.0 (SPSS Inc., Chicago, IL, USA 2003).
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Figure 1. Frequency of combined endpoint per tertile late H/M ratio.

Figure 2. Kaplan Meier curves of appropriated ICD therapy in patients with (blue line) and without (red line) ischaemic heart disease.
**RESULTS**

**Subjects**
A total of 135 stable CHF patients (79% men, age 64.5 ± 9.3) were enrolled. Baseline characteristics of the study population are shown in Table 1. Almost 60% of the patients had ischaemic heart disease. Mean NYHA class was 2.2 ± 0.4 and mean LVEF was 25.0 ± 6.2%. The mean early H/M ratio was 2.05 ± 0.39, the late H/M ratio was 1.79 ± 0.38 and $^{123}$I-mIBG WO was 12.4 ± 9.2%. The mean SPECT summed score was 39.4 ± 15.5.

**Predictor of appropriate ICD therapy and cardiac events**
Follow-up was complete for all 135 patients with a median follow-up of 30 months (6 - 68 months). In total 34 patients experienced 43 events during the course of the study. Death from all causes occurred in 15 patients (11.1%). Of these, 9 were cardiac deaths (6.7%), of which 5 were SCD and 4 due to terminal heart failure. Seventeen patients (12.6%) received ICD therapy of whom 12 patients received appropriate therapy (i.e., ATP in 8 patients and ICD shocks in 4 patients). Furthermore 6 patients had progression of HF.

For the analysis of the primary and secondary endpoint 24 patients (17.8%) experienced a first cardiac event during the course of the study: appropriate ICD therapy ($n = 12$), progression of CHF ($n = 6$), cardiac death ($n = 6$), consisting of SCD ($n = 5$) and terminal heart failure ($n = 1$) (Figure 1). Kaplan Meier curves for appropriate ICD therapy in patients with and without ischaemic heart disease was not significantly different (Figure 2).

Six patients (4.4%) experienced more than one cardiac event. One patient experienced inappropriate ICD therapy more than once. Pocket revision due to hematoma post-implantation was needed in 2 patients and ICD replacement due to end of life of the battery was performed in 3 patients.

A total of 98 patients had complete follow-up at 2 years. There was agreement between the estimated and the actual events (2 vs. 3 in the group with risk of < 9% and 10 vs. 8 in the group with risk of ≥ 9%, between estimated and actual events, respectively) (Table 2). Thereby validating the mortality rate in our study population.

There was an overlap in late H/M ratio between the patients with and without appropriate ICD therapy (Figure 3). Appropriate ICD therapy exclusively occurred in patients with late H/M ratios between 1.40 and 2.10. Figure 4 shows Kaplan Meier curves for appropriate ICD therapy for each tertile of late H/M ratio. Multivariate Cox regression analysis showed no independent predictors for appropriate ICD therapy. In univariate Cox regression analysis decreased late H/M ratio (HR 0.134 [0.035 - 0.515], $p = 0.001$) and increased WO (HR 1.062 [1.014 - 1.112], $p = 0.010$) were associated with the occurrence of the combined endpoint. Multivariate Cox regression analysis showed that only decreased late H/M ratio remained significant as an independent predictor of the combined endpoint (Table 3).
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Table 2. Two-year events compared with number of events estimated by 2-year risk model.

<table>
<thead>
<tr>
<th></th>
<th>Appropriate ICD discharge</th>
<th>Sudden cardiac death</th>
<th>End stage HF death</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year risk &lt; 9% (n = 44)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6.8%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Estimated number of cardiac death by 2-year risk model</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-year risk ≥ 9% (n = 54)</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>7.4%</td>
<td>5.6%</td>
<td>1.9%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Estimated number of cardiac death by 2-year risk model</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Multivariate Cox regression analysis for freedom of appropriate ICD therapy and combined endpoint of first cardiac events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>$\chi^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined endpoint</td>
<td>Late H/M ratio</td>
<td>0.135 (0.035-0.517)</td>
<td>10.136</td>
</tr>
<tr>
<td>Free of appropriate ICD therapy</td>
<td>LVEF</td>
<td>1.052 (1.021-1.084)</td>
<td>17.542</td>
</tr>
<tr>
<td></td>
<td>Late H/M ratio</td>
<td>0.461 (0.281-0.757)</td>
<td></td>
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</tbody>
</table>

As there were no independent predictors for appropriate ICD therapy we performed a Cox regression analysis to look for clinical independent predictors of freedom of appropriate ICD therapy. Univariate Cox regression analysis showed that freedom of appropriate ICD therapy was associated with increased LVEF (HR 1.045 [1.015 - 1.077], $p = 0.003$), decreased early H/M ratio (HR 0.504 [0.304 - 0.836], $p = 0.006$) and decreased late H/M ratio (HR 0.533 [0.329 - 0.863], $p = 0.009$). In multivariate Cox regression analysis only LVEF and late H/M ratio remained independent predictors of freedom of appropriate ICD therapy (Table 3).

**DISCUSSION**

The present study demonstrates that in stable CHF patients with prophylactic ICD implantation late H/M ratio was the only independent predictor for the combined end-
123I-mIBG scintigraphy helpful for prophylactic ICD implantation?

Figure 3. Boxplot of late H/M ratios for patients with and without appropriate ICD therapy ($p = 0.036$). Green lines are mean values. The box plot indicates median, 25%, and 75% quartile with whiskers for both ends.

Figure 4. Kaplan Meier curves for appropriate ICD therapy with tertiles: H/M ratio < 1.40, H/M ratio 1.40 - 2.10, H/M ratio > 2.10.
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point. None of the parameters tested was able to predict appropriate ICD therapy solely. However, freedom of appropriate ICD therapy was independently predicted by lower late H/M ratio and higher LVEF.

ICD implantation has become an integral component of contemporary HF management. Although the benefits of ICD implantation have been demonstrated in several randomized clinical trials, questions have been raised if the current patient selection criteria are adequate, as it is still unclear which patients will benefit from ICD implantation. In the MADIT II population only 35% of the patients received appropriate ICD therapy during 3 years of follow-up. Moreover, in about 15% of patients with coronary artery disease, SCD is the first manifestation of underlying cardiac disease. Even though LVEF < 35% is most commonly used for risk stratification for ventricular arrhythmias, it does not adequately identify patients at risk for SCD. For example, arrhythmic deaths occur also in populations with normal LVEF, but these patients are not qualified for ICD implantation according to the current guidelines. Shah et al. have shown that cardiac $^{123}$I-mIBG imaging provides prognostic information across a broad spectrum of LVEFs.

In this contemporary study, modern ICD programming with longer detection times was used. This type of programming could explain the relative small number of ICD therapy in the current study compared to the results of the SCD-HeFT study.

In contrast to previous studies that demonstrated an increased risk of ventricular arrhythmia or appropriate ICD therapy with decreased late H/M ratio, the results of the present study showed that a decreased late H/M ratio was associated with freedom of appropriate ICD therapy (i.e. no ventricular arrhythmia). The results in the present study showed “bell-shape” curve for late H/M ratio in relation to appropriated ICD therapy (Figure 1). Patients with intermediate late H/M ratio (range 1.4 - 2.10) are more likely to have appropriate ICD therapy compared to patients with low and high late H/M ratios (Figure 4). In line with our findings Travin et al. concluded that the presumption of a monotonic increase in risk of an arrhythmic event with increasing $^{123}$I-mIBG SPECT defects may not be correct. This conclusion was based on the observation that in ischaemic CHF patients, those with intermediate defects on $^{123}$I-mIBG SPECT summed score appeared to be at the highest risk for cardiac events. Both findings of the present study and Travin et al. are new and may be useful to better identify patients who, most likely, benefit from ICD implantation.

In addition to global cardiac sympathetic hyperactivity assessed with $^{123}$I-mIBG scintigraphy there is evidence that in ischaemic HF regional innervation/perfusion mismatch with a larger defect size on $^{123}$I-mIBG SPECT than on myocardial perfusion imaging SPECT, predispose to ventricular arrhythmias. In a large prospective study in 116 CHF patients, eligible for ICD implantation for both primary and secondary prevention of SCD, $^{123}$I-mIBG SPECT was shown to be an independent predictor of appropriate ICD therapy and cardiac death. The cumulative incidence of appropriate
ICD therapy during 3 years of follow-up was significantly higher when a relatively large 123I-mIBG SPECT defect (median summed score ≥ 26) was present. Similar results have been shown in a prospective PET study using 11C-hydroxyephedrine for assessing sympathetic activity in ischaemic heart disease (n = 204), in which the innervation defect size predicted cause-specific mortality from SCD independently of LVEF and infarct volume.25

In the present study the defect size of 123I-mIBG SPECT was large (39.4 ± 15.5). However, there was no significant difference between patients with and without approprated ICD therapy. Consequently, 123I-mIBG SPECT had no additional predictive value to planar 123I-mIBG-derived parameters (i.e. late H/M ratio and 123I-mIBG WO). One of the possible explanations for these findings could be the inclusion of patients with both ischaemic and non-ischaemic HF, whereas in innervation/perfusion mismatch studies only subjects with ischaemic HF were included. However, the cause of HF (ischaemic and non-ischaemic) was not associated with appropriate ICD therapy.

For the secondary endpoint, decreased late H/M ratio was associated with increased risk for combined endpoint independent of LVEF and NYHA functional class. This outcome is in line with previous studies that demonstrated the prognostic value of 123I-mIBG scintigraphy derived parameters in CHF.26,27 In addition, a meta-analysis has shown similar results, but the majority of included studies were single centre.8 The large multicentre ADMIRE-HF reported that decreased late H/M ratio was associated with the composite endpoint of HF progression, ventricular tachyarrhythmia and death, independent of LVEF and brain natriuretic peptide (BNP).7 A predefined late H/M ratio > 1.6 was associated with an incidence of 1% cardiac death per year while the annual cardiac mortality in a cohort with late H/M level < 1.2 was almost 10 times higher (9.6%).

The majority of patients who die of ventricular arrhythmia have structural heart disease, predominately coronary artery disease. Although the exact pathophysiology of ventricular arrhythmias is still a matter of debate, it has been recognized that myocardial ischaemia and scar tissue may serve as substrate for ventricular arrhythmias. Areas with slow conduction may facilitate the development of reentrant tachycardia.28 Cardiac sympathetic hyperactivity is also an important factor in the genesis of potential lethal ventricular arrhythmias in patients with impaired LVEF. In these patients rhythm abnormalities develop in relation to enhanced automaticity, triggered automaticity, and reentrant mechanisms. These mechanisms are enhanced by release of NE. In addition non-uniform denervated myocardium in infarct zones can be hypersensitive to NE.29 Especially the border zone of infarct tissue with viable myocardial tissue is predisposed to develop reentrant circuits. This mechanism is most likely triggered by the fact that sympathetic nerve fibers are more susceptible to ischaemia than myocytes, thereby causing a disbalance between still viable but partly denervated and normal myocardium.30,31 This disbalance in myocardial sympathetic innervation may create a myocardial substrate particularly vulnerable to arrhythmia and arrhythmic
death. The results of our study, showing a higher rate of appropriated ICD therapy in ischaemic HF to non-ischaemic HF, are in line with this hypothesis (Figure 2).

Recently, the DANISH trial has shown that prophylactic ICD implantation in patients with symptomatic non-ischaemic systolic heart failure was not associated with improved survival compared with usual clinical care. However, SCD occurred less often in the ICD group compared to the control group (HR 0.50 [0.31 - 0.82], \( p = 0.005 \)). Most likely the outcome of this study will change the indications for prophylactic ICD implantation in non-ischaemic CHF patients. Some non-ischaemic CHF patients remain at an increased risk for SCD. In line with this finding, our study showed that despite optimal medical therapy patients without ischaemic heart disease still received appropriated ICD therapy. Future studies will be needed to confirm whether myocardial \(^{123}\text{I}-\text{mIBG}\) scintigraphy is helpful in specifically identifying non-ischaemic CHF patients with an increased SCD risk.

Based on the results of previous studies, it has been suggested that screening of guideline eligible CHF patients selected for ICD with myocardial \(^{123}\text{I}-\text{mIBG}\) scintigraphy may be cost effective with respect to ICD implantation with minimal impact on survival. Incorporating myocardial \(^{123}\text{I}-\text{mIBG}\) scintigraphy into the assessment of CHF patients eligible for ICD implantation was associated with a 21% reduction in ICD utilization. Consequently, the number needed to screen to prevent 1 ICD implantation is 5. Screening with \(^{123}\text{I}-\text{mIBG}\) imaging will reduce the costs per patient with minimal losses of 0.001 and 0.040 life-years, respectively, over 2 and 10 years.

**Study limitations**

Although the current study clearly demonstrated that \(^{123}\text{I}-\text{mIBG}\) assessed cardiac sympathetic activity was predictive for the overall prognosis and appropriate ICD therapy, some limitations need to be considered. Most importantly, the relatively small event rate of appropriate ICD therapy may have resulted in a limited statistical power. Therefore, the results should be regarded as hypothesis-generating. In addition, the aetiology of HF in the enrolled patient population was heterogeneous including ischaemic and non-ischaemic HF. Therefore, additional studies are needed to establish the specific role of \(^{123}\text{I}-\text{mIBG}\) imaging in specific subpopulations. Furthermore, \(^{123}\text{I}-\text{mIBG}\) SPECT imaging in patients with severe LV dysfunction is frequently hampered by reduced myocardial tracer uptake, resulting in poor-quality tomographic images.

In conclusion, planar myocardial \(^{123}\text{I}-\text{mIBG}\) scintigraphy derived late H/M ratio and LVEF were associated with freedom of appropriate ICD discharge. In addition there was a significant association between late H/M ratio and the combined endpoint. Therefore, \(^{123}\text{I}-\text{mIBG}\) scintigraphy appears to be able to optimize the selection of CHF subjects who might benefit from an ICD implantation and therefore helps to constrain the HF related costs.
123I-mIBG scintigraphy helpful for prophylactic ICD implantation?

APPENDIX

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I-123-mIBG scintigraphy helpful for prophylactic ICD implantation?


Chapter 10


123I-mIBG scintigraphy helpful for prophylactic ICD implantation?

