For what endpoint does myocardial $^{123}$I-MIBG scintigraphy have the greatest prognostic value in patients with chronic heart failure? Results of a pooled individual patient data meta-analysis

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Aims
The purpose of this study was to determine the most appropriate prognostic endpoint for myocardial $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy in patients with chronic heart failure (CHF) based on aggregate results from multiple studies published in the past decade.

Methods and results
Original individual late (3–5 h) heart/mediastinum (H/M) ratio data of 636 CHF patients were retrieved from six studies from Europe and the USA. All-cause mortality, cardiac mortality, arrhythmic events, and heart transplantation were investigated to determine which provided the strongest prognostic significance for the MIBG imaging data. The majority of patients was male (78%), had a decreased left ventricular ejection fraction (31.1 $\pm$ 12.5%), and a mean late H/M of 1.67 $\pm$ 0.47. During follow-up (mean 36.9 $\pm$ 20.1 months), there were 83 deaths, 67 cardiac deaths, 33 arrhythmic events, and 56 heart transplants. In univariate regression analysis, late H/M was a significant predictor of all event categories, but lowest hazard ratios (HRs) were for the composite endpoint of any event (HR = 0.30, 95% CI 0.19–0.46), all-cause (HR = 0.29, 95% CI 0.16–0.53), and cardiac mortality (HR = 0.28, 95% CI 0.14–0.55). In multivariate analysis, late H/M was an independent predictor for all event categories, except for arrhythmias.

Conclusions
This pooled individual patient data meta-analysis showed that, in CHF patients, the late H/M ratio is not only useful as a dichotomous predictor of events (high vs. low risk), but also has prognostic implication over the full range of the outcome value for all event categories except arrhythmias.

Keywords
Cardiac sympathetic nerve function • Heart failure • Metaiodobenzylguanidine • Pooled analysis • Prognosis

Introduction
Despite the numerous single-centre studies demonstrating the prognostic value of myocardial $^{123}$I-metaiodobenzylguanidine (MIBG) imaging in chronic heart failure (CHF) patients, clinical use of this procedure remains limited.$^{1-4}$ One potential reason for the limited clinical impact of many publications is that the different ways in which increased risk was characterized could not be directly related to patient management considerations. In addition, most of the studies analysed the results using a dichotomous division of
patients into low and high cardiac uptake groups, without adequate standardization of the thresholds chosen for division of the populations.5 Cardiac uptake of MIBG was only rarely analysed as a continuous quantitative variable, making it difficult to assess the full scope of the prognostic potential of MIBG.6,7 In addition, there was a lack of consistency in defining the population in whom MIBG should be used and the endpoints most likely to influence therapeutic decisions.

The purpose of this study was to examine the relative performance of cardiac MIBG imaging results as a prognostic marker for different endpoints in order to determine the endpoint for which this imaging had the greatest power. The basis for this new analysis was the aggregate results from individual patient data from multiple studies published in the past decade.

Methods

Study selection

Eligibility criteria

Published studies were eligible if survival was analysed in patients with heart failure stratified by the late heart to mediastinal (H/M) ratio as a parameter of MIBG myocardial uptake. The primary outcomes of interest were all-cause mortality, cardiac death, non-fatal arrhythmic events [i.e. sustained ventricular tachycardia, resuscitated cardiac arrest, and implantable cardioverter defibrillator (ICD) activations], cardiac transplantation, and a composite endpoint of any of the listed events.

Search strategy

A computer-assisted search was performed on the medical databases MEDLINE (January 2000 to January 2012), PubMed (January 2000 to January 2012), EMBASE (January 2000 to January 2012), the Cochrane Controlled Trial Register, and the Cochrane Database of Systematic Reviews (from their inception to January 2012). We used the following previously described highly sensitive search and adapted strategy:5


The publications were restricted to those originating from Europe or the USA without any language restrictions. In addition, data from the ADMIRE-HF trial were not accessible for the current analysis.5

Selection procedure

All publications matching the eligibility criteria were retrieved. In the case of overlapping and duplicated datasets, care was taken to include only the most recent or most complete dataset. The primary responsible authors of the selected articles were contacted to determine whether the data used in the original publications still existed, and whether they were willing and able to share individual subject results for the combined pooled meta-analysis.

Definition of endpoints

All-cause mortality data were extracted from the long-term survival information collected as part of the original published research. The time to death was defined as the number of days from the date of MIBG administration until the date of death. For reasons of consistency, the follow-up was truncated at 60 months. Cardiac death was a component of the endpoint of all-cause mortality. Based on information collected during the course of the original studies, all reported deaths were categorized as either cardiac, non-cardiac, or unknown. Cardiac mortality included sudden cardiac death, deaths as a result of progressive heart failure or acute myocardial infarction, and other deaths for which complications involving the heart were a central factor. All other deaths were categorized as non-cardiac if a primary cause such as malignancy or infection was known or unknown if there was no information concerning the circumstances of the death.

Arrhythmic events included any of the following documented occurrences: resuscitated cardiac arrest, appropriate ICD discharge (antitachycardia pacing or defibrillation), sustained ventricular tachycardia of >30 s duration and a heart rate >100 bpm. The rhythm must also have been poorly tolerated (associated with hypotension and collapse) and/or have required an intervention (intravenous medications, antitachycardia pacing, and direct current shock) to terminate. Cardiac transplantation performed for any indication was recorded.

Statistical analysis

Cox’s proportional hazard regression analysis was used to investigate the relationship between several possible patient-related explanatory variables [age, gender, late H/M, left ventricular ejection fraction (LVEF), aetiology of CHF, and baseline New York Heart Association (NYHA) functional class] and the different endpoints: all-cause mortality, cardiac death, arrhythmic events, cardiac transplantation, and the composite endpoint. In the case of multiple events, only the first event was used for analysis. Each individual parameter was entered in the Cox’s proportional hazard regression analysis, based on forward likelihood ratio, if P < 0.05 and removed from the analysis, if P > 0.10. The χ² test, Cox’s proportional hazard regression coefficient (coefficient B), and exponent (exponent B) were used to describe the model and relative contribution of the parameters to the model. Exponent B can, therefore, be considered to be the predicted change in hazard for a unit change in the predictor, i.e. hazard ratio (HR). A P-value of <0.05 was considered statistically significant. All statistical analyses were performed with the SPSS software (SPSS for Windows, version 20.0; SPSS, Inc., Chicago, IL, USA).

Results

Study selection

Full reports or abstracts from 129 references of papers yielded eight studies that fulfilled the inclusion criteria of our pooled individual patient data meta-analysis. The primary responsible authors of these eight studies were contacted and six agreed to share their individual patient data, all but one of the datasets were generated in Europe.5–14 The individual data of 601 subjects could be retrieved from local databases and aggregated into one database. Compared with the total number of subjects mentioned in the original publications, 35 additional subjects could be added to the aggregated database. As part of an ongoing registry of CHF patients undergoing MIBG, these subjects all came from one centre and were added to the local database after the original publication.11 These 35 additional subjects were not included in any other previous publication. In addition, further follow-up data collected after the original publication were submitted for subjects in one previous aggregated study.10 Therefore, 636 subjects were eligible for the aggregated analysis. Figure 1 shows the progress through the selection of studies eligible for the pooled individual patient data meta-analysis.

Datasets

The types of data available for all patients were: demographics, medical history, medication usage, CHF aetiology, LVEF, late H/M,
and follow-up data. The majority of datasets was lacking complete information on other parameters (e.g. biochemistry and renal function data), thus requiring exclusion of these variables from the multivariate analyses.

All eligible studies reported that, to block uptake of free $^{123}$I by the thyroid gland, patients were pre-treated with either a form of saturated solution of potassium iodide or perchlorate prior to the injection of MIBG. In all eligible studies, patients were intravenously
injected with $\sim 185$ MBq (5 mCi) of MIBG. Anterior planar images of the chest were acquired in almost all eligible studies at $\sim 3–4$ h ('late') post-injection of MIBG. In all studies, the myocardial region of interest (ROI) was drawn manually. A square or rectangular mediastinal ROI was drawn in the upper mediastinum where the size of the mediastinal ROI changed with matrix size. All eligible studies reported that the H/M ratio was calculated as the ratio of the counts/pixel in the two ROIs.

**Baseline subject characteristics**

The majority of the 636 subjects (599 from Europe and 37 from the USA) was male, had non-ischaemic CHF and a decreased LVEF, and was on beta-blockers, aldosterone antagonists, and either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (Table 1).

**Follow-up and events**

During follow-up, truncated at 60 months (mean 36.9 ± 20.1 months with a range of 1–60 months), 159 patients had 172 events: 83 deaths, 33 arrhythmic events, and 56 cardiac transplantations. The majority of subjects experienced one event and only 13 subjects had a second event. All these 13 subjects eventually died: six subjects had a cardiac transplantation prior to death and the remaining seven subjects had arrhythmias prior to death.

**123I-MIBG parameters**

In all the subjects, the late H/M ratio was available. The mean late H/M with a range of 1–60 months), 159 patients had 172 events: 83 deaths, 33 arrhythmic events, and 56 cardiac transplantations. The majority of subjects experienced one event and only 13 subjects had a second event. All these 13 subjects eventually died: six subjects had a cardiac transplantation prior to death and the remaining seven subjects had arrhythmias prior to death.

**Table 1 Patient characteristics (N = 636)**

| Age (years) | 56 ± 12 | range: 21–87 |
| Female/male | 137/499 | 22 vs. 78% |
| BMI (kg/m²) | 27.1 ± 4.8 | range: 16–45.8 |
| LVEF (%)   | 31.1 ± 12.3 | range: 7–47 |
| NYHA class |          |          |
| I          | 33       | 5.2%     |
| II         | 300      | 47.2%    |
| III        | 278      | 43.7%    |
| IV         | 25       | 3.9%     |
| Medical history |          |          |
| Ischaemic vs. non-ischaemic | 264/372 | 42 vs. 58% |
| Hypertension | 143       |          |
| Diabetes Mellitus | 84       |          |
| Medication |          |          |
| ACE-I/ARB  | 519      |          |
| Beta-blockers | 420      |          |
| Amiodarone | 102      |          |
| Aldosterone antagonist | 128     |          |

**Discussion**

This study demonstrates the independent prognostic value of increased cardiac sympathetic activity as assessed by the late H/M ratio as a measure of MIBG myocardial uptake when used as a continuous parameter by aggregating individual data of patients with HF from multiple single-centre cohort studies. While the late H/M ratio can be effectively used as a dichotomous or categorical predictor of events (high vs. low risk), the present results confirm that the risk of events is continuously associated with the late H/M, with prognostic implication over the full range of this parameter.

In heart failure, abnormal activity of the sympathetic nervous system has been shown to be of pathophysiological importance. Increased neuronal release of norepinephrine (NE) in response to a deterioration of cardiac function is accompanied by decreased presynaptic NE reuptake due to down-regulation of the cardiac NE transporter. If prolonged, this leads to a reactive desensitization.
of the myocardial beta-adrenergic receptors in the synaptic cleft, further exacerbating ventricular dysfunction.\textsuperscript{17,18}

MIBG is a radiolabelled NE analogue that allows for the visualization and quantification of myocardial sympathetic innervation. MIBG shares the same uptake, storage, and release mechanisms as NE, but is not metabolized. The quantified myocardial MIBG parameters have proved to be of prognostic value in CHF. The meta-analyses of Verberne et al.\textsuperscript{5} and Kuwabara et al.\textsuperscript{19} showed that HF patients with abnormal myocardial MIBG parameters have a significantly worse prognosis compared with those with relatively preserved myocardial MIBG parameters (i.e. late H/M and MIBG myocardial washout). The ADMIRE-HF trial demonstrated for the first time in a large prospective study that the late H/M ratio, especially in concert with LVEF and B-type natriuretic peptide (BNP), was a strong independent predictor of prognosis in HF patients.\textsuperscript{6} The recent publication by Nakata et al.\textsuperscript{7} confirmed, by pooled analyses

Figure 2: Kaplan–Meier (K–M) survival curves classified by quintiles of late H/M. The K–M survival curve for the combined endpoint without any relation to the late H/M shows an overall cumulative increase of events over time (A). When the K–M survival curves for the combined event are plotted in relation to the late H/M (expressed in quintiles), there is a clear association showing that with lower late H/M the risk of events increase (B). This holds also true for all-cause mortality (C) and cardiac mortality (D) and to lesser extent for arrhythmias (E) and cardiac transplantation (F).
of independent cohort studies from Japan, the long-term prognostic value of cardiac MIBG uptake in patients with CHF independently of other markers, such as NYHA functional class, BNP, and LVEF. However, only in the most recent studies have MIBG parameters been analysed consistently as continuous variables. In the majority of earlier studies, cardiac uptake of MIBG was either dichotomized to differentiate high-risk from low-risk populations (ADMIRE-HF) or subdivided into more pre-specified risk groups (i.e. low, intermediate, and high risks). These categorizations made it difficult to assess the full scope of the prognostic potential of MIBG. The results of...
this study using the late H/M as a continuous parameter give further support to the prognostic role of cardiac MIBG in patients with CHF. The two available meta-analyses on the prognostic role of MIBG in CHF were based on published aggregate imaging and outcome results. However, this study, like the recent study by Nakata et al., involved collection of the individual data records for individual patients with CHF. This enabled detailed analyses of the full combined population and the merged data from the participating sites provided consistent evidence of efficacy for cardiac MIBG imaging equivalent to that typically obtained from a multicentre prospective trial. The less robust performance of the planar late H/M for prediction of arrhythmic events than for cardiac or all-cause death has been observed in other studies. There are several possible explanations for this finding. The relationship between occurrence of arrhythmic events and late H/M as a measure of global cardiac innervation status is non-linear (highest incidence in patients with modest reduction in uptake) and as a result reduces the effectiveness of the Cox proportional hazard regression analysis. This non-linear relationship was also observed in the present dataset, with the highest incidence of arrhythmic events in patients with a late H/M of 1.40–1.59 (15/147; 10.2%). The use of planar rather than SPECT quantitation of innervation status also likely contributes to the poorer performance of the imaging results, given previous demonstrations of the relationship between regional MIBG defect extent and susceptibility to occurrence of arrhythmic events. The use of tomographic techniques to better predict arrhythmic events is further corroborated by the publication of Fallavollita et al., focusing on regional abnormalities using PET. So, while cardiac MIBG imaging has potential for improving assessment of arrhythmic risk in CHF patients, realizing this potential will require greater use of SPECT with appropriate methods for relative or preferably absolute uptake quantification. As aetiology of heart failure (i.e. ischaemic vs. non-ischaemic) was not an independent predictor in the multivariate analyses for any of the outcome events, this already suggested that in time the events and possible explanatory variables were relatively more or less equally divided over both groups. In addition, the number of patients and their outcome events in the two subgroups (i.e. ischaemic and non-ischaemic) was not sufficient to support meaningful multivariate analyses for the individual event categories. One factor that has constrained acceptance of cardiac MIBG imaging as a clinical patient management tool in heart failure has been the variability of technical aspects of the procedure. Although most publications have included the late H/M as the measure of myocardial uptake, the methods used to obtain this parameter have varied. For example, variation in collimator selection and the impact of administered activity, acquisition time, and duration have been shown to influence the final results. With the publication of the proposal for standardization of MIBG cardiac sympathetic imaging by the European Association of Nuclear Medicine (EANM), these variations will hopefully be limited in the future.

However, as the majority of studies included in the present analysis was performed before the publication of this standardization proposal, the impact of variation in outcome related to the aforementioned parameters cannot be assessed. The lack of consensus on how to extrapolate the available MIBG data into clinical practice is reflected in the absence of MIBG in the majority of the current guidelines regarding heart failure except in Japan. The Japanese Circulation Society guidelines for nuclear cardiology list the use of MIBG for the evaluation of severity and prognosis of heart failure as Class I recommendation (general agreement of effectiveness and usefulness) based on level B evidence (verified by two or more multicentre randomized intervention trials on fewer than 400 patients, well-designed comparative studies, or large-scale cohort studies). As the amount of high-quality data continues to accumulate, it is likely that MIBG imaging will eventually be incorporated into both Europe and the USA HF guidelines. However, the prerequisite for this is that future studies need to be of high quality and with sufficient numbers of patients to allow for adequate and statistically reliable analyses.

Limitations
The two most limiting factors of this study are that data from Japan were excluded, and that ADMIRE-HF data were not available. The exclusion of data from Japan was primarily related to the difference in the numerical range of the published H/M results, compared with data from Europe or the USA. Published late H/M values in control subjects from Japan are higher compared with similar data from Europe and the USA (2.42 ± 0.30 vs. 1.93 ± 0.16). These differences cannot be explained by differences in baseline characteristics of the control subjects, but are probably related to variations in technique, especially variation in types of collimators. While the exclusion of Japanese data may have limited the statistical power of this study, the results of this study are nevertheless similar to those of Nakata et al. With regard to ADMIRE-HF, even if these data had been available, their addition would likely have skewed the aggregate results towards shorter follow-up, given the median 17 months in that study compared with 37 months in the present analyses.

In contrast to the ADMIRE-HF study and the Nakata publication, this study had no access to BNP and/or N-terminal prohormone BNP (NT-proBNP) data. We can therefore not exclude the possible prognostic role BNP or NT-proBNP might have played in our analyses. However, in both the recent Nakata publication and in the ADMIRE publication, late H/M remained significant in analyses including BNP.

Conclusion
This meta-analysis, using the individual data of 636 CHF patients predominantly from Europe, showed the intermediate to long-term (i.e. 5 years) prognostic value of cardiac sympathetic activity as assessed with cardiac MIBG-derived late H/M. The continuous numeric late H/M has prognostic implication over the full numeric range of the parameter, with greatest strength as a predictor of mortality. In the present retrospective analyses, the weakest performance of the planar H/M was for prediction of arrhythmias. In the future, use of the late H/M by cardiologists for individual patient-risk assessment or choice of therapeutic interventions will depend on improvements in the technical consistency of clinical MIBG examinations, and prospective generation of data documenting a positive effect of this procedure in clinically relevant situations.

Conflict of interest: A.F.J. is employed by GE Healthcare.
References


