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Version for repository: Accepted for publication in J Nucl Med 2015;56:11S-19S
http://www.ncbi.nlm.nih.gov/pubmed/26033897
http://jnm.snmjournals.org/content/56/Supplement_4/11S.abstract

Cardiac ^{123}I-MIBG Imaging for Clinical Decision Making: 22-year Experience in Japan

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Short Running title: Cardiac ^{123}I-MIBG imaging for clinical decision-making

Abstract

Cardiac neuroimaging with ^{123}I-metaiodobenzyl guanidine (MIBG) has been officially used in clinical practice in Japan since 1992. The nuclear cardiology guidelines of the Japanese Circulation Society revised in 2010 recommend cardiac ^{123}I-MIBG imaging for the management of heart failure (HF) patients, particularly for the assessment of HF severity and prognosis of HF patients. Consensus in North American and European countries regarding incorporation into clinical practice, however, has not been established yet. This article summarizes 22 years of clinical applications in Japan of ^{123}I-MIBG imaging in the field of cardiology, which are reflected in cardiology guidelines, including recent methodological advances. A standardized cardiac ^{123}I-MIBG parameter, heart-to-mediastinum ratio (HMR), is the basis for clinical decision-making and enables common use of parameters beyond differences in institutions and studies. A number of clinical studies unanimously demonstrated its potent independent roles for prognosis evaluation and risk stratification irrespective of HF etiologies. An HMR of less than 1.6 -1.8 and an accelerated washout rate are recognized as high-risk indicators of pump-failure death, sudden cardiac death and fatal arrhythmias, and have independent and incremental prognostic values together with known clinical variables such as left ventricular ejection fraction and brain-type natriuretic peptide. Another possible use of this imaging technique has been strongly suggested for selecting therapeutic strategy, such as pharmacological and non-pharmacological treatments, using an implantable cardioverter defibrillator and/or cardiac resynchronization device; however, this possibility remains to be investigated. Recent multiple-cohort database analyses definitively demonstrated that patients at a low risk for lethal events who are defined by ^{123}I-MIBG HMR >2.0 have a good long-term prognosis. Future investigations of cardiac ^{123}I-MIBG imaging will contribute to better risk stratification of low and high-risk populations, to the establishment of cost-effective use of this imaging technique for the management of HF patients, and to world-wide acceptance of this imaging technique in clinical cardiology practice

Key Words :
^{123}I-metaiodobenzylguanidine (MIBG), scintigraphic technique, heart failure, risk stratification, prognosis

Multicenter studies using ^{123}I-metaiodobenzylguanidine (MIBG) in North America, Europe and Japan recently demonstrated the prognostic efficacies of this neuroimaging technique (*1-3*). Japan has 22 years of experience in ^{123}I-MIBG imaging in clinical cardiology practice. A number of single-center studies have clarified the clinical implications of cardiac ^{123}I-MIBG imaging, which can depict noradrenaline uptake and release processes. In 1980, ^{131}I-MIBG imaging first started as adrenal medullary imaging. In 1987, Daiichi Radioisotope Laboratory (Fujifilm RI Pharma, Co. Ltd, Tokyo, Japan, at present) performed a clinical trial of ^{123}I-MIBG (MyoMIBG™) for imaging of the heart, after which the Japanese Ministry of Welfare (Ministry of Health, Labour and Welfare at present) approved the clinical use of ^{123}I-MIBG in cardiology practice in 1992. Thereafter, Japan had a robust clinical experience dealing with heart diseases during these two decades, including ischemic heart disease, arrhythmia, idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy and cardiomyopathies secondary to diabetes, renal failure and other metabolic disorders. A majority of cardiac MIBG imaging, however, has been performed most effectively for chronic heart failure (HF), and their achievements are summarized in the Japanese Circulation Society's Guidelines: Guidelines for Clinical Use of Cardiac Nuclear Medicine (2010, English digest version 2012) (*4*).

In the 1990's, ^{123}I-MIBG imaging was applied to neurological indications such as Lewy-body diseases, which includes Parkinson disease, dementia with Lewy bodies and pure autonomic failure. Since then, MIBG imaging has contributed to effective identification of Lewy body involvement in the heart. Neurological experiences in the past decade and incorporation into the Japanese neurological guidelines have facilitated the clinical use of ^{123}I-MIBG in this field (*5*), resulting in official approval by Japanese social health insurance. In 1993, ^{131}I-MIBG was approved in the field of oncology, and the clinical indications of ^{123}I-MIBG included neuroblastoma and pheochromocytoma at present.

This review surveys a history of cardiac ^{123}I-MIBG imaging, recent advances in standardization of this imaging technique, and major achievements in cardiology. Lastly we discuss the possible efficacies and future directions for clinical decision-making in the management of HF.

Number of MIBG studies in Japan

The utility of ^{123}I-MIBG since 2000 is summarized in the Report of the Nationwide Survey "The Present State of Nuclear Medicine Practice by Japan Radioisotope Association". The number of myocardial perfusion imaging with single-photon emission computed tomography (SPECT) was about 300,000 studies per year, while approximately 40,000 studies were performed for ^{123}I-MIBG. According to data from another report (Reports on Survey of the Adverse Reaction to Radiopharmaceuticals (2002-2012), http://www.jsnm.org/system/files/k-51-1-01.pdf) the annual number of ^{123}I-MIBG studies was 33,000 for heart and 4,000 for oncology, and the increase in ^{123}I-MIBG studies was +12% from 2011 to 2012 (Figure 1). The use of ^{123}I-MIBG in HF is estimated to be approximately 10,000 studies per year. At a multi-modality era, the use of myocardial perfusion SPECT has slightly decreased in recent years in Japan, but it is noteworthy that the use of MIBG imaging has been gradually increasing.

Clinical use of ^{123}I-MIBG leading to Japanese nuclear cardiology guidelines

In the field of cardiology, the utility of MIBG was applied to ischemic heart disease, and high sensitivities for the detection of myocardial ischemia were reported. After early success of coronary revascularization in patients with acute coronary syndrome, salvaged myocardium could be visualized as denervated but viable tissue in an area at risk by MIBG SPECT (*6,7*). Cardiac ^{123}I-MIBG imaging was also used for the identification of repeated ischemia due to coronary artery spasm (*8,9*). The applications of cardiac ^{123}I-MIBG imaging are possibly useful for the detection of undetermined, unstable or recurrent ischemia without a stress test. The low image quality and nonspecific abnormality of the inferior wall (a low specificity) on cardiac ^{123}I-MIBG SPECT imaging, however, limits the application of this imaging technique for coronary artery disease. Stress myocardial perfusion imaging and myocardial fatty acid metabolism imaging with ^{123}I-beta methyl iodophenyl pentadecanoic acid are more widely preferred for detecting myocardial ischemia or ischemia-related myocardial injury in Japan, based on the Japanese Circulation Society guidelines of nuclear imaging.

Cardiac ^{123}I-MIBG imaging plays a unique and pivotal position in clinical heart failure practice. While ischemic HF is the most common etiology of HF in western countries, in Japan non-ischemic HF is more common (*2*). Non-ischemic dilated cardiomyopathy has been one of the important applications of cardiac ^{123}I-MIBG imaging since the 1990s in Japan, although it is also important in North America and Europe (*10-12*). Regardless of HF etiology, reduced cardiac ^{123}I-MIBG activity quantified as heart-to-mediastinum ratio (HMR) has been shown consistently to indicate poor cardiac survival. As discussed later, cardiac ^{123}I-MIBG imaging can evaluate pharmacological effects of inhibitors of the beta-adrenoceptor function and renin-angiotensin-aldosterone system, showing good efficacies of these drugs parallel to the improvement in HMR and ^{123}I-MIBG washout rate (WR) in responders. Hypertrophied myocardium has reduced ^{123}I-MIBG activity relative to perfusion tracer uptake together with increased ^{123}I-MIBG clearance in patients with hypertrophic cardiomyopathy (*13*). A diabetic heart is also likely to have impaired ^{123}I-MIBG activity (low HMR and ^{123}I-MIBG defect) in association with disease progression (*14*). Table 1 summarizes major investigations that prospectively followed up chronic HF patients for more than 2 years with an endpoint of cardiac death *(15-25).*

Table 2 shows pooled or multicenter analysis in Japan, North America and Europe. Based on the clinical applications of ^{123}I-MIBG and literature from Europe, North America and Japan, the Japanese Circulation Society published the Guidelines for Clinical Use of

Cardiac Nuclear Medicine in 2005 and revised them in 2010 by reviewing recent achievements (Table 3) (*4*).

Recommended protocols in Japan

Acquisition protocol

An ^{123}I-MIBG scan is performed 15-30 minutes (early) and 3-4 hours (late) after the tracer injection. A commonly used dose of ^{123}I-MIBG in Japan is 111 MBq, less than the recommended dose (111-370 MBq) in the USA and Europe (*26*). A planar image is obtained from an anterior view for 3 to 10 minutes using an energy window centered on 159 keV and a window width of 20% or 15%. When possible, tomographic data are subsequently acquired for the differential diagnosis and detection of localization of ^{123}I-MIBG defects in coronary artery disease and neurodegenerative disorder such as Lewy-body related diseases (*5*). Cardiac ^{123}I-MIBG activity is affected by the imaging condition, particularly a collimator type; HMR obtained by a medium-energy (ME) collimator is greater than that by a low-energy (LE) one.

Parameters from ^{123}I-MIBG study

HMR is the most widely used ^{123}I-MIBG parameter for the measurement of whole myocardial activity. A cardiac region of interest (ROI) is set manually over the heart without overlapping lung and liver activities, and with a rectangular mediastinal ROI as a background (*26*). The reproducibility of HMR is good as long as it is used in the same institution (*27*), although variability is observed depending on selections of ROI size and location and operator's experience. Recently, software (smartMIBG, Fujifilm RI Pharma, Co. Ltd, Japan) has become available for semiautomatic ROI settings and calculations of HMR and WR (*28*). The software algorithm uses a circular heart ROI and a mediastinal ROI with a 10% width of the body and a 30% height of the mediastinum. HMR is calculated as an average heart count per pixel divided by an average mediastinal count per pixel. Washout rate (WR) is also calculated for evaluating sympathetic tone or drive as follows:

$WR=[((H_{early}-M_{early})-(H_{late}-M_{late})*k)]/-(H_{early}-M_{early})$ x100 (%),

where H_{early} and H_{late} are average heart counts and M_{early} and M_{late} are average mediastinal counts at early and late scans, respectively. The coefficient k is a time-decay correction factor of $[0.5\^(t/13)]^{-1}$ for time t (h), and if the interval between the scans is 3 hours, k is 1.17. Ideally the tracer kinetic (WR) can be estimated precisely by using both background and physical-decay corrections. These corrections, however, are not necessarily performed routinely, and WR in the previous literature should be carefully interpreted in this context. Although no background subtraction may be used for less variability (*27*), our recommendation is to use background subtraction for consistency among various studies other than HF.

Regional vs. global, Planar vs. SEPCT

SPECT imaging can assess regional ^{123}I-MIBG defects, which indicate viable but denervated, or injured myocardial tissue. The Japanese Society of Nuclear Medicine (JSNM) working group database is the first ^{123}I-MIBG SPECT database created for 180-degree and 360-degree rotations in each gender (Figure 2) (*29*). However, there are several limitations in SPECT imaging. First, even in near-normal subjects, an inferior wall activity is often decreased, probably because of physiological change brought on by aging. Second, when cardiac ^{123}I-MIBG activity is globally and markedly reduced as often seen in advanced heart failure, reconstruction of SPECT image and regional assessment using a scoring system are difficult to achieve. Third, in a highly dilated heart, non-specific inferior wall defects are observed probably because of attenuation artifacts. Finally, inferior wall defects are also observed in diabetic hearts. Thus, while regional assessment of ^{123}I-MIBG distribution with a high-image quality is useful for the detection of localized denervation, it seems to be supplementary to the global assessment of ^{123}I-MIBG activity in HF.

Normal values and standardization

Normal values

Standardization of HMR and WR is necessary for setting a normal value and optimal threshold for risk-stratification. In a survey using 12 sources from literature from Japan from1994 to 2007, the means of early and late HMRs in the normal (control) groups ranged from 1.88 to 2.87 and from 1.84-2.49, respectively (references in supplementary file). In the normal JSNM databases, early and late HMRs are 2.39±0.21 and 2.49±0.25 for the LE collimator, and 2.76±0.31 and 3.01±0.35 for the ME collimator, respectively (*29*). Similarly, in 11 studies in Europe and the United States, late HMR ranged from 1.77 to 2.50 (references in supplementary file). Figure 2 shows mean normal HMR obtained with each collimator and standardized HMR from JSNM working group databases (n=62).

Standardization of HMR for prognostic evaluation

There are large variations in HMR value depending on a scinticamera, collimator, administration dose and specific activity of ^{123}I-MIBG, and imaging protocol. In particular, high-energy photons in ^{123}I, particularly the 529 keV photon (1.4%), result in numerical differences between measurements from LE- and ME-collimated images. Therefore, a dichotomous manner of risk-assessment (low- versus high-risk) using a HMR threshold may be questionable (*30*). However, it is critical and possible to standardize ^{123}I-MIBG parameters (HMR and WR) for the clinical application in the management of HF. Figure 3 shows one of the promising processes for appropriate utilization of ^{123}I-MIBG parameters, i. e. HMR, in the clinical decision-making in chronic HF patients. We proposed a calibration-phantom method to cross calibrate HMRs among institutions (*31,32*). Because HMRs between two camera-acquisition conditions have an approximately linear relation, a conversion formula between two systems can be determined using the cross-calibration phantom designed for the planar imaging. Using this calibration method, the conversion coefficient from an institutional HMR to the mathematically calculated reference value was measured in 225 experiments in 84 hospitals. The measured HMR was successfully converted to standardized HMR among institutions. Our proposal was to use the standardized HMR comparable to that obtained with the ME-type collimator, which is most fitted for ^{123}I-tracer currently available for heart and brain studies. The standardization of HMR significantly improved risk classification based on HMR either with LE or ME collimators (*32*). HMRs published in several works of literature also can be changed to specific conditions. Provided that the ADMIRE-HF study showed the HMR threshold was 1.6 using the LEHR collimator (*1*), the threshold can be converted to 2.0 for the institution in which the ME general-purpose collimator is used. Figure 4 demonstrates the results of data conversion and incorporation of standardized HMR into the mortality risk model (*2,33*). Thus, this method enables calibration of data obtained by any kind of HMR, either by ME or LE collimators, contributing to universal application and comparison of HMR in the decision-making for selecting a therapeutic strategy.

Incremental clinical benefits of cardiac ^{123}I-MIBG imaging in the HF

A number of works of literature have demonstrated independent and incremental prognostic values of cardiac ^{123}I-MIBG imaging in chronic HF patients in combination with clinical information, such as a history of myocardial infarction, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), plasma brain natriuretic peptide (BNP) level and co-existing non-cardiac conditions as diabetes mellitus, impaired kidney function and anemia (*2,10,15,19,20,25,34-36*). The prognostic value is also shown irrespective of etiologies (ischemic or non-ischemic) of HF and LVEF (Figure 5) (*35*). Cardiac ^{123}I-MIBG imaging can help cardiologists risk-stratify patients, select therapeutic strategy and predict long-term survival in chronic HF patients more precisely. Recent results from the multicenter studies (*1-3*) strengthened the previous findings demonstrating that cardiac ^{123}I-MIBG imaging can risk-stratify (low-risk versus high-risk for lethal events) patients with HF and predict the probability of long-term survival with pharmacological or non-pharmacological treatments.

Pharmacological treatment and cardiac ^{123}I-MIBG imaging

Because of the definitive mortality improvement, beta-blockers and renin-angiotensin-aldosterone system inhibitors are widely accepted in patients with asymptomatic and symptomatic chronic HF. Risk reduction rates for cardiac mortality by these medications, however, are still limited, that is roughly 20% to 30%. In real-world practice, some chronic HF patients do not necessarily meet entry criteria used in major drug-interventional HF studies or often have co-existing or unexpected non-cardiac diseases affecting clinical outcomes. Some chronic HF patients cannot sufficiently benefit from these drug treatments as non-responders or due to intolerance or adverse effects to these drugs, and physician's preference sometimes results in under-use or under-dose of these drugs. It is, therefore, highly desirable to establish a method to appropriately identify patients who sufficiently respond and tolerate contemporary drug therapy beyond physician's preference or experience. Although only a few studies have been conducted (*11,37-46*), cardiac 1^{123}I-MIBG imaging can monitor effects of drug treatment using beta-blocking agents, renin-angiotensin-aldosterone inhibitors or their combinations by correlating an increase in cardiac ^{123}I-MIBG activity (HMR) and a decrease in ^{123}I-MIBG WR with the improvement in NYHA functional class, LVEF or exercise tolerance.

Despite the data, It is more crucial to predict therapeutic efficacy and outcome improvement before the initiation of drug intervention. Patients with preserved cardiac HMR of 1.8 or more are shown to be tolerant to a metoprolol titration dose and the findings were more likely to be related to subsequent improvement in cardiac function during a 3-month interval together with a reduction in plasma noradrenaline concentration (*39*). In 167 chronic HF patients (*45*), treatment with ACE inhibitors and/or beta-blockers significantly reduced cardiac death prevalence and a 5-year cardiac mortality rate compared to that without these drugs (15% vs 37% and 21% vs 42%, $p<0.05$, respectively), and a risk reduction rate at 5 years in patients with HMR of 1.53 or more was significantly greater than that in those with HMR of less than 1.53 under the contemporary drug treatment (67% vs 32%, respectively; $p<0.05$). Thus, current optimal drug treatment can improve a survival rate, but the efficacy on clinical outcomes is likely to depend on cardiac ^{123}I-MIBG activity, strongly suggesting that cardiac ^{123}I-MIBG activity cannot only estimate drug effects but also predict cardiac risk improvement by appropriate drug treatment.

Needs for a new risk-stratification method in device treatment

There are inherent limitations in contemporary drug treatment, that is, some patients are originally non-responders or cease to respond to the contemporary drug therapy during a clinical course. Non-pharmacological device treatment has evolved to definitively improve symptoms, the quality life and outcomes for such patients with refractory HF. An implantable cardioverter defibrillator (ICD) can ablate lethal ventricular tachyarrhythmias and reduce sudden cardiac death (SCD) risk. Cardiac resynchronization therapy (CRT) using biventricular pacemakers can effectively reduce recurrent hospitalization and mortality risk in patients with prominent left bundle branch block and advanced systolic HF refractory to optimal drug treatment. CRT combined with ICD (CRTD) can reduce all-cause mortality, cardiac death and recurrence of symptomatic aggravation and hospitalization in patients with advanced HF in NYHA class 3-4 and severe intra-ventricular dyssynchrony (*47*). In addition to the secondary prevention of SCD or lethal arrhythmic events, the most accepted ICD indication for primary prevention of SCD is based on chronic HF presenting with prior myocardial infarction, NYHA class 2-3 and LVEF of 35% or less.

As introduced in major guidelines, continuous growth of the patient number and a robust amount of evidence relating to the efficacies of device therapy have facilitated prophylactic use of ICD, CRT and CRTD in other developed countries as well as in Japan. It is known, however, that a large percentage of ICD devices are unlikely to deliver appropriate therapy during their lifetime, and nearly one third of patients ineligible for an ICD (LVEF > 35%) die of SCD. Likewise, clinical efficacies of CRT are limited in patients who have mild to moderate chronic HF (NYHA class 1-2), do not have a prolonged QRS duration of greater than 120 msec, or do not have reduced LVEF. Some patients cannot respond adequately to or might be ineligible (at a really low risk) for the device treatment even when patients meet currently available standard indication criteria. Conversely, even when the patients are outside the indication criteria, some patients might die of SCD (consequently at high risk) and are eligible for the treatment. Besides device-related problems, the increasing need for medical resources, which are becoming limited, heightens the need to establish more appropriate identification - beyond that provided by conventional clinical markers - of patients who have chronic HF and are most likely or unlikely to benefit from device treatment in a cost-effective fashion (*48-51*).

Cardiac ^{123}I-MIBG imaging in device treatment

The Department of Japanese Government Social Insurance officially approved ICD use in 1996, CRT in 2004, then CRTD in 2006. Thereafter, several small but important studies (*22,52-58*) have shown that excess activation of cardiac sympathetic nerve function and impaired cardiac sympathetic innervation assessed by cardiac ^{123}I-MIBG imaging are associated with arrhythmogenecity leading to lethal ventricular arrhythmias, ICD shock against lethal arrhythmic events and SCD independently of clinical, electrophysiological and LVEF (*59*). In addition to the assessment of BNP, LVEF and myocardial viability, cardiac ^{123}I-MIBG activity is used for the prognosis assessment and selection of therapeutic strategy in our institutes (*56,57*). The incremental prognostic values of this imaging technique are also supported by larger studies (*60,61*) and by the positron emission tomography (PET) study using ^{11}C-meta-hydroxyephedrine (HED) (*62*). Cardiac ^{123}I-MIBG imaging has additive values to clinical information assessed by Seattle Heart Failure Model in high-risk candidates for ICD, CRT or CRTD (*61*); and arrhythmic death or appropriate ICD discharge for lethal ventricular arrhythmias correlates with amounts of denervated myocardium (*62*). In response to CRT, cardiac ^{123}I-MIBG activity improves together with symptomatic and functional improvement, and baseline cardiac ^{123}I-MIBG activity correlates with CRT effects (*63-66*). More recently, cardiac ^{123}I-MIBG activity is shown to be closely associated with mechanical dyssynchrony assessed by a speckle-tracking strain technique and ^{123}I-MIBG HMR of 1.6 is likely to be a cut-off value for predicting response to CRT and long-term outcomes in combination with dyssynchrony in Japanese patients (*67*). Thus, cardiac ^{123}I-MIBG imaging enables cardiologists to help identify patients who are most susceptible to lethal arrhythmias and event risks and who can actually benefit most from the device therapy by overcoming the limitations of current device therapy criteria, a majority of which consist of surrogate markers of lethal events such as symptoms (NYHA class), clinical backgrounds, LVEF and QRS prolongation (intra-ventricular electrical dyssynchrony).

Cardiac ^{123}I-MIBG imaging in heart transplantation

Heart transplantation for patients with terminal HF improves survival rates at 1- and 5 years, up to nearly 90% and 70%, respectively. Because of a limited number of heart donors, however, the precise indication, the order of priority and appropriate timing of operation are crucial clinical issues. Historically, due to delayed national consensus on this treatment and due to few donors, Japan has much less experience with heart transplantation per se compared to other counties and, therefore, has no significant clinical data using cardiac ^{123}I-MIBG imaging on this treatment. Nevertheless, cardiac ^{123}I-MIBG imaging possibly contributes to improvement in determination of the necessity of heart transplantation and expected survival interval than other standard parameters (*3,12,68,69*) in an era when advance device therapy combined with optimal drug treatment and cardiac ^{123}I-MIBG imaging are available. Cardiac ^{123}I-MIBG imaging may be also useful for the assessment of re-innervation in transplanted hearts. Cardiac neuroimaging using ^{11}C-HED or ^{123}I-MIBG identifies ventricular sympathetic reinnervation (*70-72*), which slowly develops from the cardiac base several months after surgery and is observed in 40% of heart-transplanted patients one year after the operation (*73*). Although clinical implications and mechanisms of the cardiac reinnervation process are not necessarily revealed, restoration of cardiac sympathetic innervation is likely to increase exercise capacity by improving blunted physiologic response of heart rate and contractile function to exercise in patients with heart transplantation (*73*). Assessment of the cardiac reinnervation process by cardiac ^{123}I-MIBG imaging may be useful for the management of patients with heart transplantation in an outpatient care unit, by determining the appropriate exercise prescription, evaluating the exercise training effect and, hopefully, predicting improvement in long-term survival.

Identification of low-risk patients with HF

Cost-effective treatment is generally a risk-based selection of therapeutic strategy. Precise identification of patients at low risk for lethal outcomes can contribute to appropriate use of medical resources by minimizing diagnostic examinations, selecting a low-cost but effective treatment appropriately and restraining from over-use of high-cost intervention in patients who are not so likely to benefit from a high-cost, invasive treatment. Previous investigations show that the cut-off value for differentiating high- from low-risk patients is likely from around 1.60 to 1.75 (*1-3,15*). Furthermore, the recent multicenter results from more than 600 to 1,300 chronic HF patients (*1-3*) definitively demonstrated the ability of cardiac ^{123}I-MIBG imaging for the identification of low-risk patients who can survive over several years independently of conventional prognostic markers (Figure 6). In the Japanese study (*2,33*), annual all-cause mortality was less than 2% in patients with HMR≥2.0, and a mortality rate at 5 years was nearly 8% in patients with HMR≥2.0 and 10% to 15% in patients with HMR between 1.7 and 2.0. Likewise, a mortality rate at 5 years was less than 3% in patients with HMR≥1.76 and nearly 15% in patients with HMR between 1.33 and 1.75 in the European study (*3*). What is noted here is that HMR cut-off values are different among the studies (*1-3*). As discussed above, this is because of the differences in patient backgrounds and, more importantly, because of technical differences in cardiac ^{123}I-MIBG imaging (*32*). Nevertheless, cardiac ^{123}I-MIBG activity quantified as HMR correlates consistently with a survival rate during a 5-year period or more over a wide range of HMR from less than 1.1 to 2.1 or more (*2*). Thus, these findings and recent advances in standardization of cardiac ^{123}I-MIBG imaging presented in this article can facilitate clinical use of the quantitative ^{123}I-MIBG parameter (HMR) for defining a low-risk probability of lethal events over 5 years (*33*), for the differentiating high- and low-risk patients and for anticipating a survival time in each chronic HF patient.

Limitations and future direction of cardiac ^{123}I-MIBG imaging

A growing body of evidence of cardiac ^{123}I-MIBG imaging demonstrates great potential in helping select patients who are most eligible for advanced contemporary treatment rather than for treatment through conventional methods. Further investigations, however, are needed to strengthen prior findings and reassurance for precise risk-stratification and decision-making on the selection of non-pharmacological device treatment, including the prediction of responsiveness to the treatment. The increasing number of chronic HF patients will limit medical costs and application of device/heart transplantation treatment in patients at a lower risk or who are less likely to sufficiently benefit from the treatment in the future. More experience in cardiac ^{123}I-MIBG imaging is needed to improve negative and positive predictive values for better differentiation of low-risk and high-risk patients, which will contribute to effective use of medical resources. Unlike in Japan, the utility of this imaging technique is still less obvious in other countries for recommendation into international guidelines, yet there are still insufficient data relating to cost-effectiveness and limited availability in cardiology practice. Future large-scale prospective multicenter studies would establish a practical and cost-effective utilization of cardiac ^{123}I-MIBG imaging in combination with clinical information in chronic HF patients to help clinicians optimize patient care (Table 4).

Acknowledgement

This work was partly supported by the working group activity of the Japanese Society of Nuclear Medicine and by Grants-in-Aid for Scientific Research in Japan (P. I. Kenichi Nakajima). The authors would like to thank Arnold Jacobson, MD, for his comments on this manuscript, and Mr. Ronald G. Belisle for his editorial assistance.

Conflict of Interest

KN has collaborative research works with FUJIFILM RI Pharma, Co. Ltd Japan, which supplies ^{123}I-MIBG in Japan.

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Figures

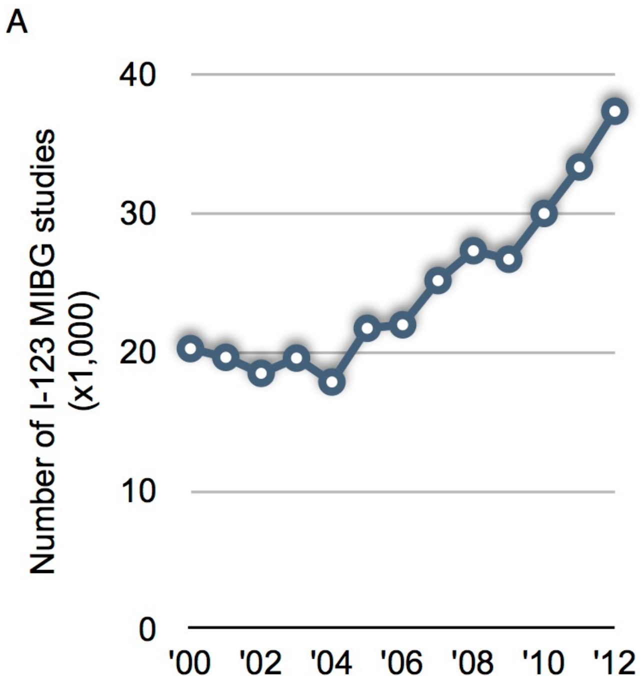

Figure 1
The number of ^{123}I-MIBG studies performed since 2000 (A) and its breakdown in 2012 (B) in Japan.

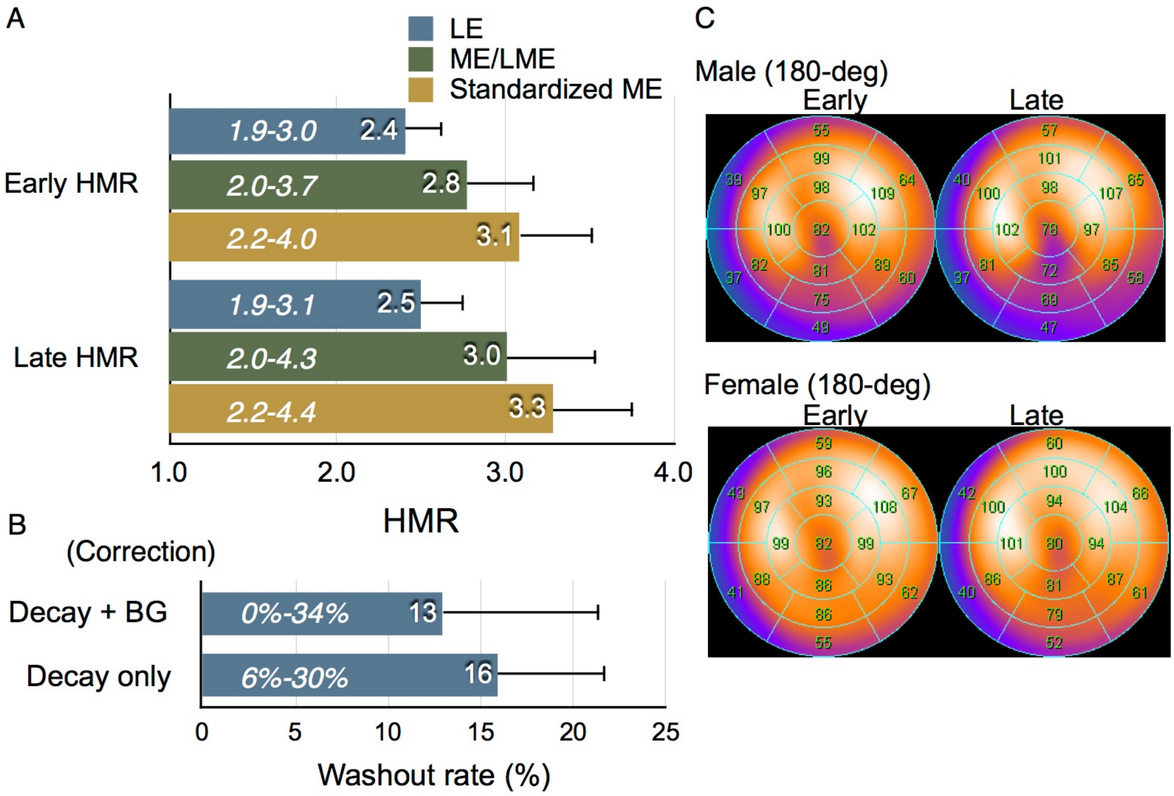

Figure 2
Normal values of HMR (A), washout rate (B) and polar maps (C) based on JSNM working group databases. Italic numbers in bars indicate normal ranges.

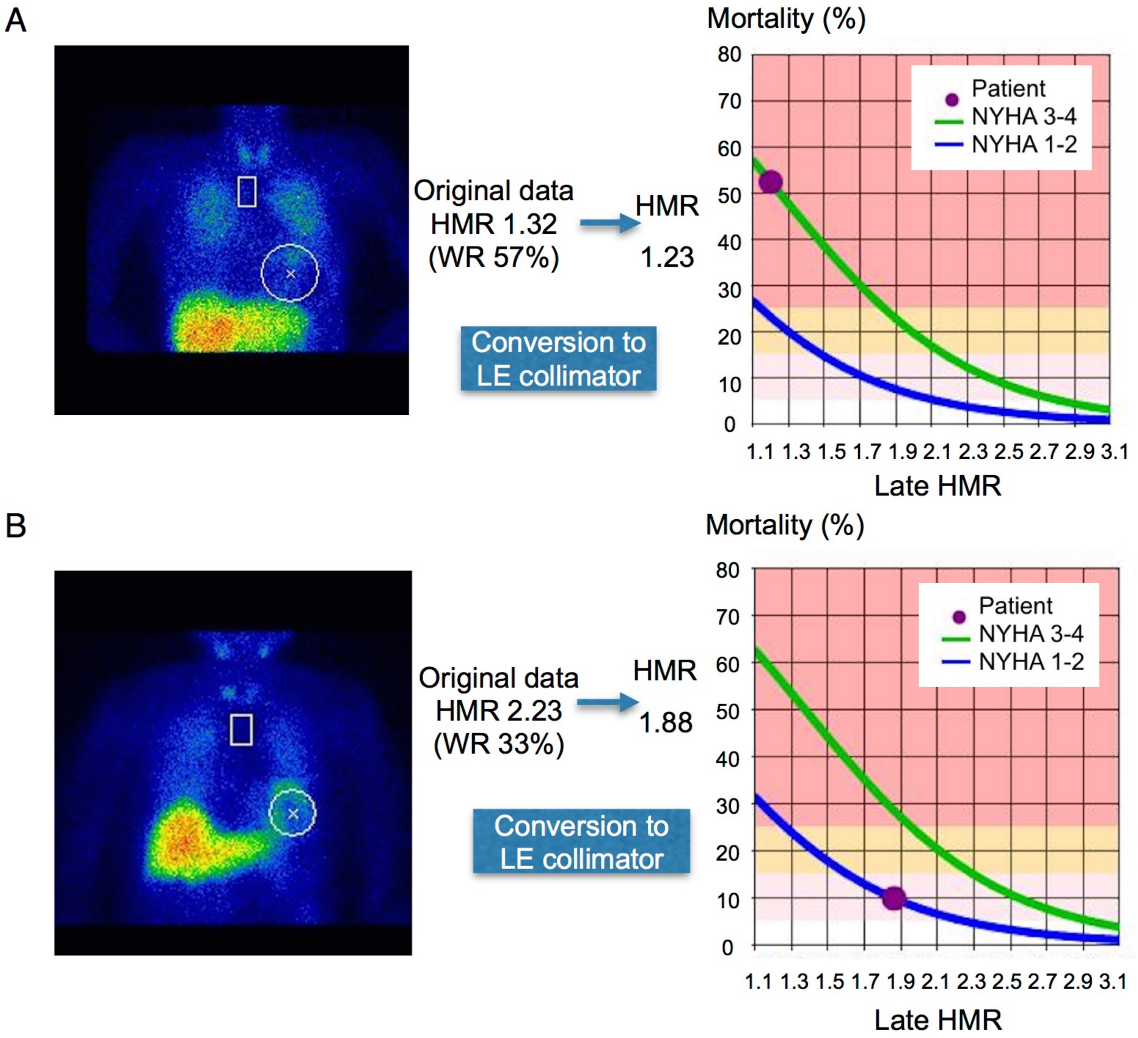

Figure 3

Standardization of cardiac ^{123}I-MIBG activity quantified as heart-to-mediastinum ratio (HMR) by converting data obtained using a low-medium-energy (LME) collimator to those using a low-energy high-resolution (LEHR) collimator. A: a 32-year old male with 22% of left ventricular ejection fraction (LVEF) and NYHA class III. The HMR was converted from 1.36 in a LME collimator to 1.23 in a LEHR collimator and a 5-year mortality rate was re-estimated to be more than 50% (10%/year). B: an 86-year old woman with LVEF 51% of and NYHA class II. Her HMR was converted from 2.33 to 1.88 and a 5-year mortality rate was re-calculated to be 10% (2%/year).

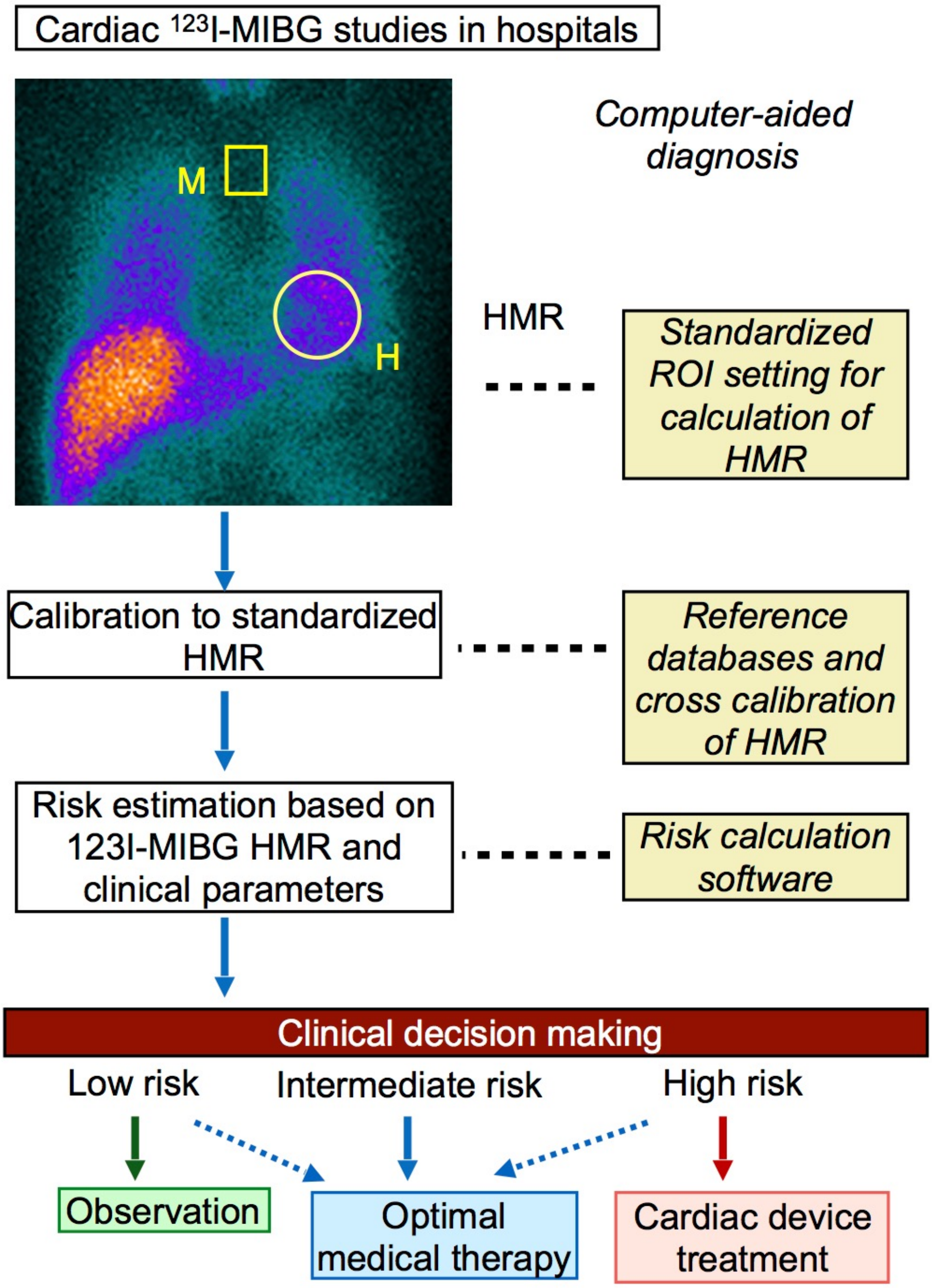

Figure 4
Standardization process of cardiac ^{123}I-MIBG data for the calculation of heart (H)-to-mediastinum (M) ratio (HMR), risk-stratification and risk-based decision making in the management of chronic HF.

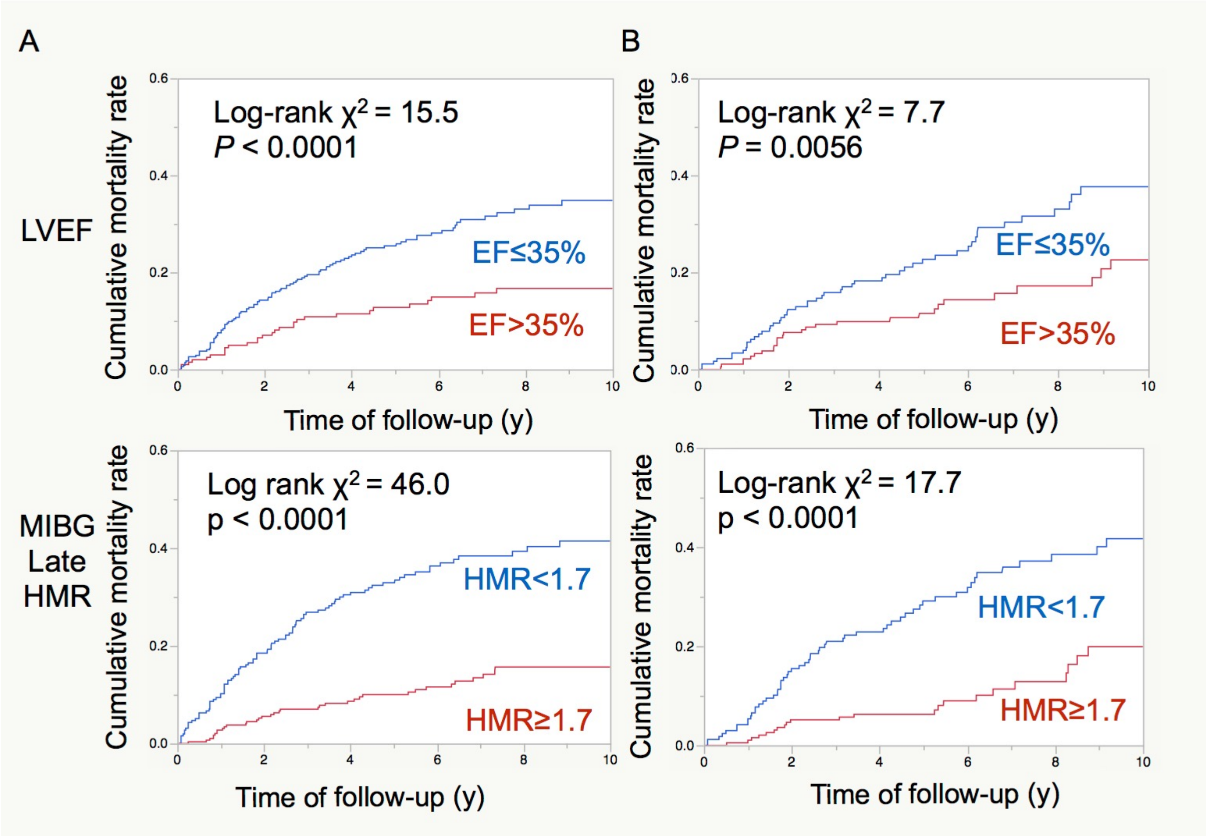

Figure 5
Cumulative mortality curves comparing patients with idiopathic dilated cardiomyopathy (A) or coronary artery disease (B) when cutoff-values of HMR 1.70 and LVEF 35% were used in Japanese pooled database (*2*).

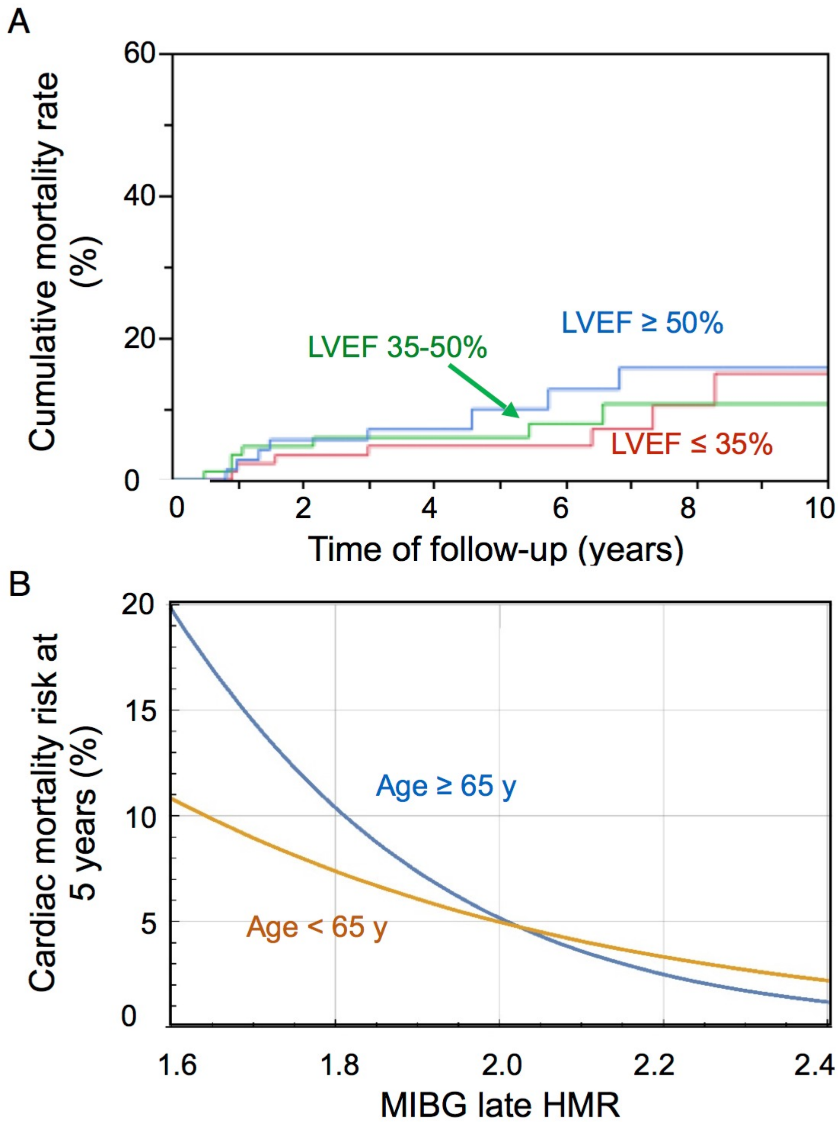

Figure 6

Low risk of mortality in subjects with HMR >2.0. All-cause mortality curves for 10 years in Japanese pooled databases (n=1322) (*2*), indicating a low probability of lethal events independently of left ventricular ejection fraction (LVEF) when ^{123}I-MIBG heart-to-mediastinum ratio (HMR) is more than 2.0 (A). Cardiac mortality curves at 5 years estimated by the logistic model of ^{123}I-MIBG HMR (n=933) (*33*), indicating a low probability of lethal events independently of age-difference when ^{123}I-MIBG HMR is more than 2.0 (B).

Table 1. 123I-MIBG prognostic study in Japan with an endpoint of death

Author [Ref]	Year	No. of patients (male)	Subjects included	Follow-up (mean or median)	MIBG HMR threshold	WR threshold	Multi-variate analysis	Endpoint	Cardiac events	CD rate
Nakata [15]	1998	414 (271)	Consecutive	22 months	1.74		HMR, nitrate, LVEF	Death	ACD 53, CD 37	8.9%
Imamura [16]	2001	171 (125)	cardiomyopathy (DCM n=96) with LVEF<40%	27 months		63%	MIBG WR, BNP	CD, Progressive HF	CD 11, SCD 5	6.4%
Ogita [17]	2001	79 (64)	Choric HF with LVEF<40%	31 months		27%	MIBG WR	Death, Progressive HF	ACD 23, CD 13	16.5%
Matsui [18]	2002	85 (59)	DCM with LVEF<45%, repeat MIBG measurement	24 months	1.89, Change in HMR after treatment		BNP, Change of HMR	CD, Progressive HF	CD 12/74	16.2%
Nakata [19]	2003	205 (145)	LVEF<50%	35 months	1.74	38%	HMR, diabetes, nitrate, NYHA class	CD	CD 38, 11 SCD	18.5%
Kyuma [20]	2004	158 (110)	Choric HF	16 months	1.74		BNP	CD	CD 17, SCD 2	10.8%
Arimoto [21]	2007	104 (67)	Early stage HF	12.5 months	1.73		H-FABP, HMR	CD	CD 8, SCD 3	7.7%
Tamaki [22]	2009	106 (81)	Choric HF with LVEF<40%	65 months		27%	MIBG WR, EF	SCD	ACD 38, CD 30, SCD 18	28.3%
Katoh [23]	2010	117 (64)	HFPEF, LVEF≥50%	34.2 months		26.5 %	MIBG WR	CD, readmission due to HF	ACD 42 (CD 3)	2.6%
Momose [24]	2011	86 (57)	DCM	110 months	1.45	50%	HMR, LVEF	Death	ACD 26, CD 7, SCD 2	8.1%
Doi [25]	2012	468 (340)	Choric HF with LVEF<50%	60.5 months	1.57		NYHA class, HMR, hemoglobin, eGFR, dyslipidemia, nitrate	CD	CD 89	19.0%

ACD, all-cause death; CD, cardiac death; SCD, sudden cardiac death; HF, heart failure; FABP, Heart-type fatty acid binding protein; DCM, dilated cardiomyopathy; HFPEF, heart failure with preserved ejection fraction

Table 2. Pooled or multicenter analysis in Japan, North America and Europe

Author [Ref]	Year	No. of patients (male)	Subjects included	Follow-up (mean or median)	MIBG HMR threshold	WR threshold	Multivariate analysis	Endpoint	Cardiac events	CD rate
Nakata [2]	2013	1322 (942)	6 cohort studies, pooled data	77.6 months	1.68	43%	NYHA class, age, MIBG HMR, LVEF	Death	ACD 326 CD 263	24.7 %
Jacobson [1]	2010	961 (770)	NYHA II-III with LVEF≤35 %	17 months	1.60		HMR, LVEF, NYHA class, BNP	Death, Progressive HF, life-threatening arrhythmia	ACD 81, CD 53, arrhythmia 64	5.5%
Vershure [3]	2014	636 (499)	8 studies for meta-analysis + 35 subjects	36.9 months	-		HMR, LVEF, (age for ACD)	Death, life-threatening arrhythmia, heart transplant	ACD 83, CD 67, arrhythmia 33, heart transplant 56	10.5 %

ACD, all-cause death; CD, cardiac death; SCD, sudden cardiac death; HF, heart failure; FABP, Heart-type fatty acid binding protein; DCM, dilated cardiomyopathy; HFPEF, heart failure with preserved ejection fraction

Table 3. Recommendations for ^{123}I-MIBG sympathetic imaging in the Japanese Circulation Society's Guidelines: Japanese Circulation Society Joint Working Group - Guidelines for Clinical Use of Cardiac Nuclear Medicine (*4*).

Indications	Classification of recommendation	Level of Evidence
Assessment of severity and prognosis of heart failure	I	B
Assessment of treatment effects of heart failure	IIa	C
Arrhythmogenic disease	IIb	C

Class I, Conditions for which there is evidence and/or general agreement that a given test is useful and effective; Class II, Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness of a test; IIa, Weight of evidence/opinion is in favor of usefulness; IIb, Weight of evidence/opinion is less established based on evidence or opinion; Level B, Verified by ≥2 multicenter randomized intervention trials on <400 patients, well-designed comparative studies, or large-scale cohort studies; Level C, Consensus opinion of specialists

Table 4. Current tentative clinical use of cardiac ^{123}I-MIBG imaging in heart failure (HF)

Purpose	Utility
Severity	Evaluation of severity of HF
Risk	Risk-stratification of HF: high-risk and low-risk assessment
	Risk assessment of ventricular tachyarrhythmias and lethal arrhythmic events
Therapy	Evaluation of therapeutic effects of pharmacological and non-pharmacological treatment
	Prediction of therapeutic response
Prognosis	Prediction of long-term survival

Supplement for normal values of 123I-MIBG studies

Cardiac 123I-MIBG Imaging for Clinical Decision Making: 22-year Experience in Japan
Kenichi Nakajima, Tomoaki Nakata
J Nucl Med 2015 56:11S-19S

Heart-to-mediastinum ratios in the control groups in the literature of Japan (1-12) and in Europe and USA (13-23) are listed.

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