Cardiac sympathetic nervous system imaging with ^{123}I-meta-iodobenzylguanidine: Perspectives from Japan and Europe

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Cardiac sympathetic nervous system dysfunction is closely associated with risk of serious cardiac events in patients with heart failure (HF), including HF progression, pump-failure death, and sudden cardiac death by lethal ventricular arrhythmia. For cardiac sympathetic nervous system imaging, ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) was approved by the Japanese Ministry of Health, Labour and Welfare in 1992 and has therefore been widely used since in clinical settings. ^{123}I-MIBG was also later approved by the Food and Drug Administration (FDA) in the United States of America (USA) and it was expected to achieve broad acceptance. In Europe, ^{123}I-MIBG is currently used only for clinical research. This review article is based on a joint symposium of the Japanese Society of Nuclear Cardiology (JSNC) and the American Society of Nuclear Cardiology (ASNC), which was held in the annual meeting of JSNC in July 2016. JSNC members and a member of ASNC discussed the standardization of ^{123}I-MIBG parameters, and clinical aspects of ^{123}I-MIBG with a view to further promoting ^{123}I-MIBG imaging in Asia, the USA, Europe, and the rest of the world.

Key Words: Arrhythmia • guidelines • heart failure • ^{123}I-MIBG • sympathetic nervous system

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INTRODUCTION

The Japanese Society of Nuclear Cardiology (JSNC) is seeking to increase international collaboration with the American Society of Nuclear Cardiology (ASNC).[1,2] As part of their initial scientific collaboration, ASNC and JSNC are planning to review ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) studies and to promote utilization of cardiac ^{123}I-MIBG imaging around the world. In the USA, the Food and Drug Administration (FDA) approved ^{123}I-MIBG for clinical use on March 22, 2013. In contrast, the Japanese Ministry of Health, Labour and Welfare approved ^{123}I-MIBG for clinical use and began reimbursement as early as 1993.[3] Since then, the Japanese nuclear cardiology community has developed ^{123}I-MIBG imaging and has conducted a number of clinical studies.[4] The guidelines of the Japanese Circulation Society (JSC) also include indications for the clinical use of ^{123}I-MIBG; heart failure (HF) is a major indication for clinical use.[5] Outside Japan and USA, ^{123}I-MIBG has also been already widely available for many years in countries such as in Brazil.[6,7] This review article summarizes this first ASNC/JSNC joint session, at which experts from JSNC and ASNC discussed the current status and future directions of ^{123}I-MIBG imaging. In particular, standardization of imaging technology, European and Japanese perspectives, and clinical applications related to HF treatments are discussed in this review.

STANDARDIZED PROCEDURES FOR ^{123}I-MIBG IMAGING

Need for Standardization

^{123}I-MIBG is currently available in clinical practice in Japan and the USA, but in Europe it is available for research purposes only. In both clinical and research settings, semi-quantitative parameters of ^{123}I-MIBG play an important role. Given the use of ^{123}I-MIBG by more and more countries, standardizing data acquisitions and processing has become essential. An index of heart-to-mediastinum ratio (HMR) is a simple method of quantification that has been very widely used.[5,8,9] However, simplicity does not necessarily mean reliability. There are issues of reproducibility among hospitals, where preferences for data acquisition and processing methods vary considerably. Some factors that are inconsistent among institutions and that therefore affect the comparability of results include a specific activity and an administered dose of ^{123}I-MIBG, image acquisition protocols, region of interest (ROI) settings for image processing, and corrections for camera-collimator differences.[10,11] While cardiac mortality risk models were created, including one based on HMR obtained using ^{123}I-MIBG imaging,[12,13] a fluctuating HMR influenced the final prediction of cardiac mortality, which could seriously impact patient management. Whereas minor differences in institutional preferences might be acceptable, diagnostic instability and differences in assessments of therapeutic effects and prognosis should be minimized before ^{123}I-MIBG can be universally applied.

Administration of ^{123}I-MIBG and Data Acquisition

The amount of ^{123}I-MIBG (MyoMIBG, FUJIFILM RI Pharma; AdreView, GE Healthcare) administered for clinical studies is 111, 185, and 370 MBq in Japan, Europe, and USA, respectively. Early and late images were acquired at 15-30 minutes and 3-4 hours, respectively, after tracer administration. A defect scoring method similar to myocardial perfusion imaging (MPI) can be used.[14,15] The Japanese Society of Nuclear Medicine working group created normal early/late, 180°/360° and gender-specific databases that can be applied to any software and are applicable for clinical and research purposes.[16]

Heart-to-Mediastinum Ratio: Regions of Interest Setting and Stability

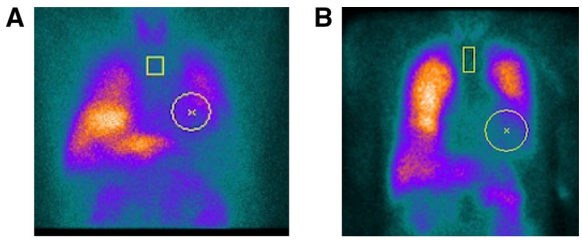
Although the HMR is a simple average count ratio between the heart and mediastinum, the location, size, and shape of the regions of interest (ROIs) may impact data accuracy, as noted in the recommendations of the European Association of Nuclear Medicine Cardiovascular Committee[8] and the ASNC.[9] In this regard, some Japanese centers use the semiautomatic *smartMIBG* software to minimize data variablity.[17] The HMR remains relatively stable for three or four hours after ^{123}I-MIBG administration, when late images can be acquired. A washout rate (WR) can also be calculated using the following equation:

$$\mathrm{WR}(\%) = [(\mathrm{H_{early}} - \mathrm{M_{early}}) - (\mathrm{H_{late}} - \mathrm{M_{late}})/(0.5^{(t/13)}]/(\mathrm{H_{early}} - \mathrm{M_{early}}) \times 100,$$

where H_{early} and H_{late} are early and late heart counts, M_{early} and M_{late} are early and late mediastinal counts, and t is the time (hours) between early and late imaging.[8,18]

Calibration Phantom to Overcome Camera-Collimator Differences

Differences among collimators, particularly low-energy (LE) and medium-energy (ME) types, cause



	Europe (A)	Japan (B)
Collimator	LEHR	LME
Original HMR	1.44	1.64
Standardized HMR	1.70	1.68

Figure 1. The effects of HMR standardization in ^{123}I-MIBG imaging from Europe and Japan **a** European study: In a 55-year-old male patient with HF (Courtesy of Dr. Janos Mester, Hamburg University), original HMR of 1.44 using low-energy high-resolution collimator (LEHR) is interpreted as 1.70 if medium-energy (ME) collimator is used. **b** Japanese study: A 71-year-old male patient with HF in Japan (Kanazawa University) shows HMR of 1.64 with low-medium-energy (LME) collimator, which can be standardized to 1.68. Lower normal limit of standardized HMR is 2.2 for both early and late ^{123}I-MIBG images.

variations in HMR measurements.[10] A cross-calibration phantom was therefore designed to calibrate HMR measured in various hospitals.[11] We proposed unifying HMRs to the medium-energy general-purpose (MEGP) type of collimator with an average conversion coefficient (CC) of 0.88. Any institutional HMR (HMR_i) can be standardized to an MEGP-collimator condition (HMR_{std}) using the formula: $HMR_{std} = 0.88/CC_i \times (HMR_i - 1) + 1$, where CC_i is the conversion coefficient of an institutional camera-collimator system. Figure 1 shows the effect of standardization using two ^{123}I-MIBG images with a low-energy high-resolution (LEHR) collimator from Europe and low-medium-energy (LME) collimator from Japan.

Application of Standardized HMR in Literature

Normal values and thresholds for predicting cardiac events significantly differ among several ^{123}I-MIBG studies at various institutions (Table 1).[4,19] The HMR in Japanese prognostic studies is slightly higher than from studies performed in Europe and the USA.[20] Although patient background differs among Japanese studies and European studies according to baseline patient characteristics, differences in collimators might also have had impacts on those differences. One factor is that Japanese vendors have attempted to optimize collimator design for the high-energy photons emitted by ^{123}I-radiopharmaceuticals that are popular in cardiac and brain studies in Japan. European studies have also used a higher threshold in some studies.[19,21]

Standardization of HMR in International Studies

There have also been attempts to standardize the HMR in Europe. The first results, representing the calibration phantom method and subsequent study, were presented at the Annual Congress of EANM meeting in 2016.[22] Based on 210 phantom experiments in 27 European institutions, the study successfully demonstrated that the standardization as performed in Japan could be successfully applied under European camera and collimator conditions. Moreover, since the multivariate mortality risk model directly used HMR in the calculation formula,[12] appropriate conversion of HMR according to collimator condition can be used (Figure 2). In a more practical way, standardized HMR is essential to obtain consistent results that directly influence risk stratification in HF patients. In order to create large databases that include results for Europe, the USA, and Asian countries, standardized ^{123}I-MIBG HMR could be effectively used for international data compilation.

European Perspective on ^{123}I-MIBG and Possible Clinical Applications

Several European studies have contributed to making cardiac ^{123}I-MIBG scintigraphy a recognized risk stratification technique for HF and prognosis,[19,21,23] while some single-center studies regarding the role of cardiac ^{123}I-MIBG in patients with non-ischemic cardiomyopathy, exercise training following cardiac resynchronization therapy (CRT), and treatment of atrial fibrillation by pulmonary vein isolation with or without renal denervation are recruiting patients (Clinical Trials NCT01940081, NCT02413151, NCT02115100). In Europe, the clinical use of cardiac ^{123}I-MIBG scintigraphy in HF patients is limited, and it is currently used mainly in research settings due largely to a lack of clinical guidelines for its use, despite FDA approval in 2013.[21,24-28] Presumably, after this approval, growth in the clinical use of ^{123}I-MIBG scintigraphy failed to rise significantly given that the impact of cardiac sympathetic innervation, as assessed by ^{123}I-MIBG, on treatment decisions to improve health outcomes was and still is unknown. Consequently, the timeline for implementation in current European guidelines will depend on the results of studies like ADMIRE-ICD, which is evaluating the efficacy of ^{123}I-MIBG imaging to appropriately guide the decision of whether or not to implant an implantable cardioverter defibrillator (ICD) in patients with NYHA class II and III HF with a left

Table 1. HMR and cardiac events in multicenter studies in Japan and Europe

Study	Authors	Year	Number of patients	HMR	Outcome	Collimators
Japanese pooled database	Nakata et al[13]	2013	1322	1.68	All-cause death, cardiac death	LEHR, LEGP
ADMIRE-HF (Europe and USA)	Jacobson et al[23]	2010	961	1.6	Cardiac death	LEHR
Multicenter study (Europe and USA)	Verschure et al[21]	2014	636	-	Heart failure progression, cardiac deaths, potentially fatal arrhythmia	Variable
	Agostini et al[19]	2008	290	1.75	Cardiac deaths, potentially fatal arrhythmia, heart transplant	LEHR, LEGP, ME

ventricular ejection fraction (LVEF) between 30% and 35% (ClinicalTrials.gov NCT02656329). In addition, standardization and validation of this imaging technique in Europe are also needed.[29] In the meantime, clinical research with ^{123}I-MIBG imaging is growing, and the number of potential clinical indications beyond HF is promising.[28]

Japanese Perspectives on ^{123}I-MIBG: Therapeutic Applications and Risk Stratification of ^{123}I-MIBG in HF

Since the official approval of ^{123}I-MIBG in Japan in 1992[2,4,30] a number of Japanese studies have demonstrated therapeutic evaluations and prognostic values of cardiac ^{123}I-MIBG, in combination with clinical information, in patients with HF and/or lethal arrhythmias.[13,30-38]

The prognostic values of cardiac sympathetic innervation assessed by cardiac neuroimaging have been established by recent multicenter studies,[4,13] facilitating better risk stratification through the use of this imaging technique in HF patients. Cardiac sympathetic innervation evaluated by HMR through the use of ^{123}I-MIBG has independent and incremental prognostic efficacies in patients with HF when the following clinical predictors of cardiac outcomes are available. These include prior myocardial infarction, NYHA functional class, LVEF, plasma B-type natriuretic peptide (BNP), HF etiology, and non-cardiac conditions such as diabetes mellitus, anemia, and kidney dysfunction. Cardiac ^{123}I-MIBG imaging can also help identify patients at increased or low risk of sudden cardiac death or lethal ventricular arrhythmias.[34-37] The Japanese multiple cohort provided 1-year, 2-year, and 5-year cardiac mortalities based on an individual numerical HMR value[12,13] (Figure 3). In addition, the cardiac mortality risk model could be widely applied to patients with HF (Figure 4).

Evaluation of Pharmacological Treatment

^{123}I-MIBG imaging has been applied to evaluate pharmacological effects in HF, such as beta-blocking agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockades, and aldosterone antagonists.[4,33] In patients with HF who may respond well to these medications, cardiac ^{123}I-MIBG activity increases along with improvement in several parameters such as NYHA functional class, plasma BNP level, and/or LVEF. However, major outcome studies in HF have revealed non-negligible numbers of patients who do not respond to these drugs, as may be indicated by the limited prognostic improvement using the drugs. In 166 Japanese HF patients with reduced LVEF, the contemporary drug treatment using combined neurohormonal inhibitors significantly reduced a 5-year cardiac mortality rate from 36% to 12% when cardiac ^{123}I-MIBG uptake was preserved with an HMR of 1.53 or more. In contrast, the 5-year mortality rate decreased from 53% to 37% when cardiac ^{123}I-MIBG activity (HMR) was less than 1.53 during a 43-month interval.[33] This indicates that patients with higher cardiac ^{123}I-MIBG activity (HMR) have greater survival benefits from the HF medications. Thus, cardiac mortality and a risk-reduction rate according to drug treatment may depend on the level of cardiac MIBG uptake activity.

Cardiac Devices for Lethal Arrhythmia

ICD and CRT contribute to the improvement in cardiac outcomes, cardiac function, and quality of life in

Thresholds of late HMR

Collimator	Severely reduced	Moderately reduced	Borderline normal	High normal
LEHR	< 1.37	1.37 - 1.63	1.64 - 1.91	≥ 1.92
LE (pooled database)	< 1.40	1.40 - 1.69	1.70 - 1.99	≥ 2.00
LEGP	< 1.43	1.43 - 1.75	1.76 - 2.07	≥ 2.08
ELEGP	< 1.50	1.50 - 1.87	1.88 - 2.24	≥ 2.25
LME	< 1.56	1.56 - 1.97	1.98 - 2.39	≥ 2.40
MEGP	< 1.59	1.59 - 2.02	2.03 - 2.46	≥ 2.47
MELP	< 1.63	1.63 - 2.10	2.11 - 2.57	≥ 2.58

Two-year risk of cardiac mortality

LVEF (%)	Two-year risk (%)			
NYHA I - II, Age < 65y				
< 35%	9	6	3	2
35% - 50%	7	4	3	1
> 50%	5	3	2	1
NYHA I - II, Age ≥ 65y				
< 35%	13	8	5	2
35% - 50%	11	7	4	2
> 50%	8	5	3	1
NYHA III - IV, Age < 65y				
< 35%	28	19	12	6
35% - 50%	23	15	10	5
> 50%	18	11	7	3
NYHA III - IV, Age ≥ 65y				
< 35%	37	26	18	9
35% - 50%	32	21	14	7
> 50%	25	16	10	5

%/y
>10
3-10
1-3
<1

Figure 2. Two-year cardiac mortality risk model using late HMR, NYHA functional class, LVEF, and age as variables. Threshold HMRs for various collimators are shown in the *upper panel*. Five-year mortality chart is presented elsewhere.[20].

patients with HF and/or lethal arrhythmias. Aside from device-related problems, there is a sub-population of patients who do not derive prognostic benefits from device therapy. On the other hand, some high-risk patients who do not meet current indication criteria for ICD/CRT may not receive ICD/CRT treatment. Thus, it is important to establish better diagnostic parameters to predict the therapeutic effects of these device treatments. Such approaches can differentiate responders from non-responders and can clarify low risk or high risk for more appropriate and cost-effective use of the devices. Cardiac ^{123}I-MIBG imaging is likely to be useful for precisely selecting ICD or CRT candidates who can benefit from the device therapy.[36-38] Impaired cardiac ^{123}I-MIBG uptake can be a significant predictor of sudden cardiac death and lethal arrhythmic risks, both of which can be ablated by an appropriate ICD shock. Preserved cardiac ^{123}I-MIBG uptake activity can be a significant predictor of positive response to CRT, leading to functional improvement and reverse left ventricular remodeling. Conversely, impaired cardiac ^{123}I-MIBG uptake can be a predictor of ineffectiveness or low effectiveness of CRT. Therefore, altered cardiac sympathetic innervation assessed by ^{123}I-MIBG is a

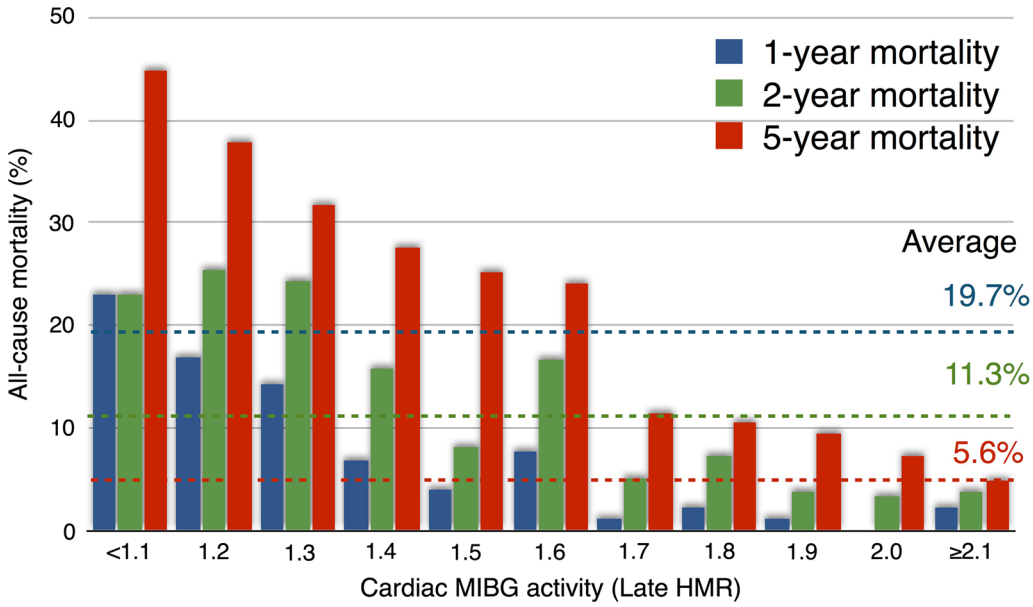


Figure 3. The correlation between all-cause mortality and cardiac MIBG uptake (HMR). The *dotted lines* indicate averages of 1-year, 2-year, and 5-year mortality rates. Reduced HMR correlated with increasing mortality.

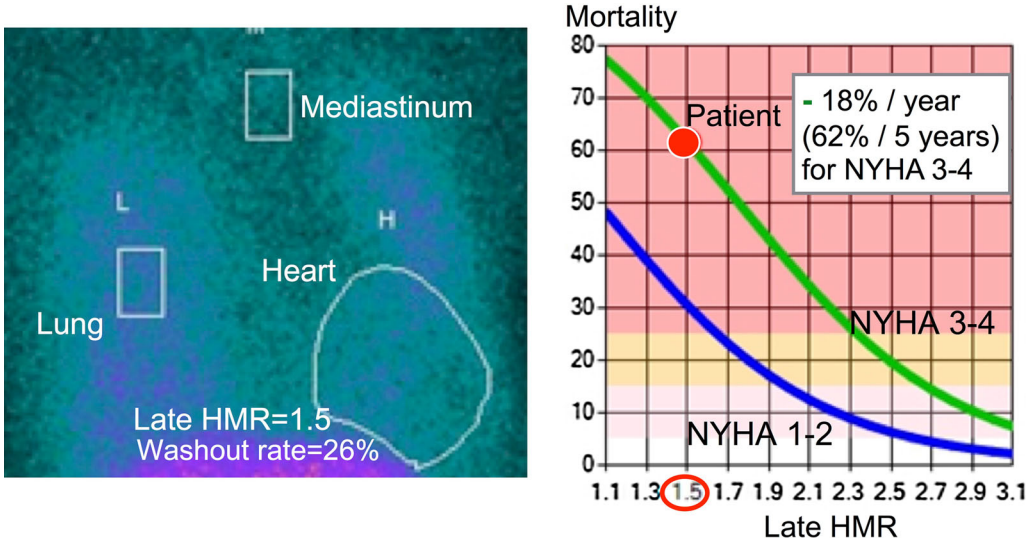


Figure 4. Cardiac ^{123}I-labeled meta-iodobenzylguanidine imaging (*left panel*) in a 77-year-old male patient with heart failure, who had been predicted to have a 1-year mortality rate of 18% (*right panel*) calculated by a computerized risk model. The model includes NYHA functional class 3, left ventricular ejection fraction (21%) and late heart-to-mediastinum ratio (HMR) of MIBG activity (1.5). This patient died due to pump failure 9 months later.

promising biomarker for predicting clinical response to device treatment.

Therapeutic Guidance of ^{123}I-MIBG

The therapeutic implications of cardiac ^{123}I-MIBG imaging, however, remain to be established. The use of cardiac sympathetic innervation impairment should be investigated with regard to selecting an appropriate drug regimen and predicting therapeutic response. As shown in the case study in Figure 5, a cardiac MIBG risk model was developed using the Japanese multiple-cohort database.[12,13] This risk model can calculate an individual cardiac mortality rate using a numerical HMR value

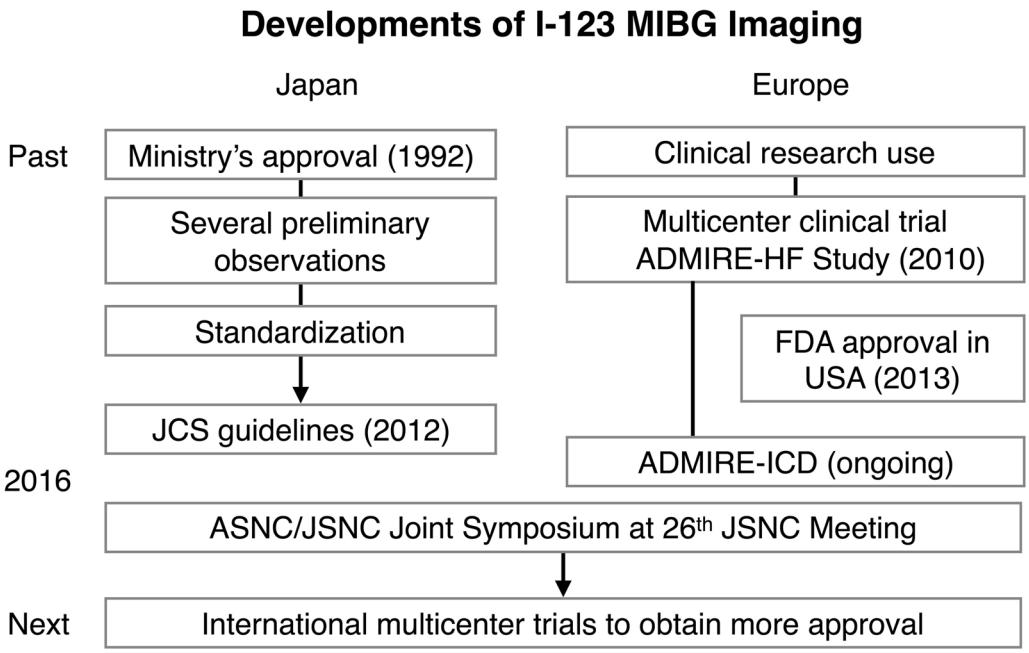


Figure 5. Past achievements and future directions for cardiac ^{123}I-labeled meta-iodobenzylguanidine (MIBG) imaging from Japanese and European perspectives.

in combination with clinical information. The cardiac ^{123}I-MIBG risk model, however, should be validated widely to establish risk-based and cost-effective HF management as the next step.

Next Steps for ^{123}I-MIBG Imaging

As mentioned in this article, Japanese research groups have extensively shown the clinical usefulness of ^{123}I-MIBG.[4,39,40] The Japanese pooled database on HF, which includes data from as long ago as the 1990s, revealed the long-term prognostic value of ^{123}I-MIBG imaging with a large population.[13] Although a multicenter study[23] and a meta-analysis using pooled databases[18] have also been conducted in Europe and North-America, well-designed multicenter studies have been limited. In particular, we need more internationally acceptable multicenter ^{123}I-MIBG trials to establish the clinical roles of ^{123}I-MIBG, which will contribute to an international guideline on heart failure and the approval of ^{123}I-MIBG by the health ministry of many countries. During our discussion at the ASNC/JSNC joint session, we noted the importance of conducting international multicenter trials with a large sample size using a standardized technique. Data from such trials would help to confirm the usefulness of ^{123}I-MIBG imaging and could hasten the approval process in several countries besides Japan, the USA, and some European countries. The ADMIRE-ICD study mentioned earlier is a good example.

CONCLUSIONS

The first ASNC/JSNC joint session at the 26th annual scientific meeting of JSNC revealed the importance of ^{123}I-MIBG in the development of sympathetic nervous system imaging. We hope this joint session will lead to further inspiration and collaboration between the two societies and help promote the clinical usefulness of cardiac ^{123}I-MIBG imaging for patients.

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