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Myocardial Sympathetic Innervation Imaging in Individuals With Heart Failure

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Coverage

Myocardial sympathetic innervation imaging with iodine 123 meta-iodobenzylguanidine **is considered experimental, investigational and/or unproven** for use in individuals with heart failure.

Policy Guidelines

None.

Description

In individuals with heart failure, activation of the sympathetic nervous system is an early response to compensate for decreased myocardial function. The concentration of iodine 123 meta-iodobenzylguanidine over several hours after the injection of the agent is a potential marker of sympathetic neuronal activity. Iodine 123 meta-iodobenzylguanidine activity is

proposed as a prognostic marker in individuals with heart failure to aid in the identification of individuals at risk of 1- and 2-year mortality. The marker could also be used to guide treatment decisions or to monitor the effectiveness of heart failure treatments.

Heart Failure

An estimated 6.7 million adults in the U.S. have heart failure. In 2022, heart failure was mentioned on 457,212 death certificates in the U.S. (1) According to data in the 2022 Heart and Stroke Statistics Update, 1 in 6 patients with heart failure and reduced ejection fraction developed worsening disease within 18 months of diagnosis and these individuals were more likely to be Black, >80 years of age, and have increased comorbidity burden. (2) Black individuals also have the highest risk of developing heart failure in the future, followed by Hispanic, White, and Chinese American individuals, reflecting disparities in the incidence of hypertension, diabetes, and socioeconomic status among these populations. Black individuals also have the highest proportion of incident heart failure not preceded by myocardial infarction (75%). Underlying causes of heart failure include coronary artery disease, hypertension, valvular disorders, and primary cardiomyopathies. These conditions reduce myocardial pump function and decrease left ventricular ejection fraction (LVEF). An early mechanism to compensate for this decreased myocardial function is activation of the sympathetic nervous system. The increased sympathetic activity initially helps compensate for heart failure by increasing heart rate and myocardial contractility to maintain blood pressure and organ perfusion. However, over time, this places additional strain on the myocardium, increasing coronary perfusion requirements, which can lead to worsening of ischemic heart disease and/or myocardial damage. As the ability of the heart to compensate for reduced myocardial function diminishes, clinical symptoms of heart failure develop. Another detrimental effect of heightened sympathetic activity is an increased susceptibility to potentially fatal ventricular arrhythmias.

Overactive sympathetic innervation associated with heart failure involves increased neuronal release of norepinephrine (NE), the main neurotransmitter of the cardiac sympathetic nervous system. In response to sympathetic stimulation, vesicles containing NE are released into the neuronal synaptic cleft. The released NE binds to postsynaptic β_1, β_2, and α receptors, enhances adenyl cyclase activity, and brings about the desired cardiac stimulatory effects. Norepinephrine is then taken back into the presynaptic space for storage or catabolic disposal, terminating the synaptic response by the uptake-1 pathway. The increased release of NE is usually accompanied by decreased NE reuptake, thereby further increasing circulating NE levels.

Diagnostic Imaging

Guanethidine is a false neurotransmitter that is an analogue of NE; it is also taken up by the uptake-1 pathway. Iodine 123 meta-iodobenzylguanidine (^{123}I-MIBG or MIBG) is chemically-modified guanethidine labeled with radioactive iodine. Iodine 123 MIBG moves into the synaptic cleft and then is taken up and stored in the presynaptic nerve space in a manner similar to NE. However, unlike NE, MIBG is not catabolized and thus concentrates in myocardial sympathetic nerve endings. This concentrated MIBG can be imaged with a conventional gamma

camera. (3) The concentration of MIBG over several hours after injection is thus a reflection of sympathetic neuronal activity, which in turn may correlate with the severity of heart failure.

Iodine 123 meta-iodobenzylguanidine myocardial imaging has been in use in Europe and Japan, and standardized procedures for imaging have been proposed by European organizations. (4) Administration of MIBG is recommended by slow (1 to 2 minute) injection. Planar images of the thorax are acquired 15 minutes (early image) and 4 hours (late image) after injection. In addition, optional single photon emission computed tomography (SPECT) can be performed following the early and late planar images. Iodine 123 meta-iodobenzylguanidine uptake is semi-quantified by determining the average count per pixel in regions of interest drawn over the heart and the upper mediastinum in the planar anterior view. There is no single universally used myocardial MIBG index. The most commonly used myocardial MIBG indices are the early heart to mediastinum (H/M) ratio, late H/M ratio, and the myocardial MIBG washout rate. The H/M ratio is calculated by taking the average count per pixel in the myocardium divided by the average count per pixel in the mediastinum. The myocardial washout rate is expressed as the rate of decrease in myocardial counts over time between early and late imaging (normalized to mediastinal activity).

Iodine 123 meta-iodobenzylguanidine activity is proposed as a prognostic marker in patients with heart failure, to be used in conjunction with established markers or prognostic models to identify heart failure patients at increased risk of short-term mortality. Iodine 123 meta-iodobenzylguanidine activity could also be used to guide treatment decisions or to monitor the effectiveness of heart failure treatments.

Regulatory Status

In 2008, AdreView® (Iobenguane I 123) Injection (GE Healthcare) was approved via the U.S. Food and Drug Administration (FDA) new drug application process (22-290) for the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests. (5)

The FDA (2013) approved a supplemental new drug application (22-290/S-001) for AdreView and expanded the labeled indication to include scintigraphic assessment of sympathetic innervation of the myocardium by measurement of the H/M ratio of radioactivity uptake in patients with New York Heart Association (NYHA) class II or class III heart failure and LVEF less than 35%. (6)

Rationale

Medical policies assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

The U.S. Food and Drug Administration (FDA) approved indication for the scintigraphic imaging agent iodine 123 meta-iodobenzylguanidine (MIBG) in individuals with heart failure is to measure the heart to mediastinum (H/M) ratio, which can be used to predict the risk of 1- and 2-year mortality. While the H/M ratio can be used as a dichotomous or a continuous variable, the FDA approved indication is a dichotomous variable with an H/M cutoff of 1.6. A ratio of less than 1.6 indicates higher risk, and a ratio of 1.6 or greater indicates a lower risk. (7) Thus, evaluation of this technology involves first searching for evidence that an H/M ratio of at least 1.6 is statistically associated with mortality in individuals with heart failure.

Myocardial Sympathetic Innervation Imaging in Heart Failure

Clinical Context and Test Purpose

The purpose of prognostic imaging using MIBG in individuals with heart failure is to risk-stratify them to determine the appropriate next steps.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with heart failure.

Interventions

The test being considered is MIBG for prognosis.

Comparators

The following practice is currently being used to make decisions about managing individuals with heart failure: management with standard heart failure prognostic markers.

Outcomes

The general outcomes of interest are overall survival, disease-specific survival, functional outcomes, health status measures, quality of life, hospitalizations, and medication use. Outcomes of interest for heart failure are overall survival (i.e., cardiac death), heart failure progression, and arrhythmic events. Adverse outcomes for MIBG injection are infrequent, typically a short-term spike in blood pressure and side effects of radiation.

Given 1-year mortality rates from heart failure, follow-up monitoring will be necessary for the short term for those at high risk of heart failure and over the long term for those at low risk.

Study Selection Criteria

For the evaluation of clinical validity of MIBG, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard (describe the reference standard);
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

The first step in evaluating MIBG is assessing its prognostic accuracy, specifically, whether an H/M ratio of less than 1.6 is associated with a higher risk of heart failure mortality.

Systematic Reviews

Verschure et al. (2014) published the results of an individual patient data meta-analysis to assess which heart failure-related endpoint had the strongest association with MIBG results. (8) The meta-analysis included 636 patients with congestive heart failure from 6 studies from the U.S. and Europe. Inclusion criteria were studies reporting survival in patients with heart failure stratified by the H/M ratio, which yielded 8 studies, 6 of which were willing to share individual patient data. Over a mean follow-up of 36.9 months, 159 patients had 172 events: 83 deaths (67 of which were cardiac), 33 arrhythmic events, and 56 cardiac transplantations. In univariate analysis, the H/M ratio was significantly associated with all cardiac-related outcomes, but the lowest hazard ratios (HR) were associated with the composite endpoint of any event (HR, 0.30; 95% confidence interval [CI], 0.19 to 0.46), all-cause mortality (HR, 0.29; 95% CI, 0.16 to 0.53), and cardiac mortality (HR, 0.28; 95% CI, 0.14 to 0.55).

A systematic review by Verberne et al. (2008) selected studies that reported survival in patients with heart failure stratified by MIBG myocardial parameters (early H/M, late H/M, and/or myocardial washout). (9) Eighteen studies met the eligibility criteria. Thirteen studies were prospective, and all but 1 had at least 3 months of follow-up. Sample sizes ranged from 37 to 205 patients; 5 studies included more than 100 patients. Patient populations varied across studies. Some studies included the whole heart failure spectrum (i.e., New York Heart Association [NYHA] functional status class I through IV) and others focused on a narrower range of functional status. Fourteen studies included patients with depressed left ventricular ejection fraction (LVEF; <40%). Acquisition of early H/M ratio was performed at 15 to 20 minutes in 9 studies and ranged from 30 to 60 minutes in the other 6 studies. Seventeen studies acquired late H/M ratio at 240 minutes after injection. Reviewers evaluated methodologic quality using a tool they developed to rate each study; the scoring range was 0 to 9. The median quality score of the included studies was 6; 2 studies scored 9.

In reviewers' initial calculations, the pooled HR for death and late H/M ratio and for a cardiac event and late H/M ratio showed significant heterogeneity among studies and therefore pooled results were not presented for the entire body of studies. Reviewers eliminated statistical heterogeneity by selecting the highest quality studies (i.e., top fifth in terms of quality score, n=3 studies). When findings from these 3 highest quality studies were pooled, there was a statistically significant effect of MIBG on cardiac events (HR, 1.98; 95% CI, 1.57 to 2.50). However, when findings from the 2 highest-quality studies reporting the outcome of cardiac death were pooled, there was no statistically significant effect of MIBG on this outcome (HR, 1.82; 95% CI, 0.80 to 4.12). Reviewers did not pool findings on the prognostic value of early H/M or myocardial washout due to failure to identify a subset of studies without heterogeneity.

Prospective Studies

ADMIRE-HF Study

Jacobson et al. (2010) published data from 2 prospective, multicenter, industry-sponsored studies, together known as the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study. (10) This study was the primary evidence used by the FDA to grant approval for AdreView. The analysis presented the combined primary efficacy results of the 2 studies. The study included patients with NYHA functional class II or III heart failure and LVEF of 35% or lower, which are the clinical parameters specified by the FDA documents as the appropriate criteria for use of AdreView in heart failure patients. In addition, patients had to be treated with optimum pharmacotherapy. Major exclusion criteria were serum creatinine above 3.0 mg/dL, functioning ventricular pacemaker and cardiac revascularization, myocardial infarction, or implantable cardioverter-defibrillator implantation within the past 30 days.

Patients received an injection of MIBG and then underwent planar and single photon emission computed tomography (SPECT) imaging of the thorax at 15 minutes after injection (early) and at 3 hours and 50 minutes after injection (late). The H/M ratio, on a scale from 0 to 4, was determined from both the early and late images. Patients then received standard clinical care and were followed for 2 years. The primary analysis evaluated the association between time to first cardiac event occurrence and the late H/M ratio categorized as under 1.6 or 1.6 and higher. The authors also evaluated the association between time to first cardiac event occurrence and late H/M ratio as a continuous variable. The composite outcome of cardiac events was defined as the occurrence of either 1) heart failure progression (i.e., increase of ≥1 NYHA functional class); 2) potentially life-threatening arrhythmic event (i.e., spontaneous ventricular tachyarrhythmia for >30 seconds, resuscitated cardiac arrest, or appropriate discharge of implantable cardiac defibrillator); or 3) cardiac death.

A total of 985 patients underwent MIBG imaging (435 in the first study, 532 in the second study) and 961 (98%) patients were available for analysis. There were 760 (79%) patients with an H/M ratio less than 1.6 and 201 (21%) patients with an H/M ratio of at least 1.6. Patients were followed for a median of 17 months (range, 2 days to 30 months). Cardiac events occurred in 237 (25%) of 961 patients. The mean late H/M ratio (standard deviation [SD]) was 1.39 (0.18) in the group of patients with events and 1.46 (0.21) in the group of patients without events. The risk of cardiac events was significantly lower for patients who had an H/M at least 1.6

compared with those who had an H/M ratio less than 1.6 (HR, 0.40; 97.5% CI, 0.25 to 0.64; p<.001). In addition, there was a statistically significant association between the cardiac event rate and H/M ratio as a continuous variable, with lower event rates in patients with higher H/M ratios (HR, 0.22; 95% CI, 0.10 to 0.47; p<.001). The estimate of 2-year all-cause mortality was 16.1% for patients with an H/M less than 1.6 and 3.0% for patients with an H/M ratio at least 1.6 (p<.001). The authors also compared H/M ratios with other prognostic markers. In a multivariate model including the H/M ratio, b-type natriuretic peptide, LVEF, and NYHA functional class, all 4 markers were independently associated with time to cardiac events.

Ketchum et al. (2012) published an analysis incorporating MIBG imaging findings into the Seattle Heart Failure Model (SHFM) using survival data from the 961 patients included in the primary efficacy analysis of the ADMIRE-HF study. (11) The late H/M ratio from MIBG imaging was divided into 5 categories: less than 1.2, 1.2 to 1.39, 1.40 to 1.59, 1.6 to 1.79, and at least 1.8. (Note that this differs from the dichotomous late H/M variable used in the main ADMIRE-HF analysis.) In a Cox proportional hazards model, SHFM and H/M were both independent predictors of overall survival. There was an 82.1% increase in risk for each 1 SD change in the SHFM (p<.001) and a 60.3% increase in risk for each 1 SD change in the late H/M ratio (p<.001). For the outcome of cardiac mortality, each SD increase in SHFM was associated with an 86.1% increase in risk (p<.001), and each SD increase in the late H/M ratio was associated with a 57.9% increase in risk (p=.002). In an area under the curve analysis, the addition of H/M to the SHFM significantly improved the prediction of all-cause mortality compared with the SHFM alone. When H/M was added to the SHFM, the area under the curve increased by 0.039 (p=.026) for 1-year mortality, and the area under the curve increased by 0.028 (p<.05) for 2-year mortality.

Al Badarin et al. (2014) conducted another subgroup analysis of the ADMIRE-HF study to evaluate whether the addition of MIBG scintigraphy to conventional markers of arrhythmic risk had an incremental predictive value for arrhythmic events in patients with heart failure. (12) This analysis included 778 patients from ADMIRE-HF with an LVEF less than 35% and NYHA class II or III heart failure symptoms who did not have an implantable cardioverter-defibrillator at the time of enrollment. Of these, 6.9% experienced the primary endpoint of an arrhythmic event, which was a composite of sudden cardiac death, appropriate implantable cardioverter-defibrillator therapy, resuscitated cardiac arrest, or sustained ventricular tachycardia. An H/M ratio of less than 1.6 was significantly associated with risk of arrhythmic events (HR, 3.48; 95% CI, 1.52 to 8; p=.02). Other predictors of arrhythmic events were LVEF less than 25% and systolic blood pressure less than 120 mm Hg. The authors derived a risk score, incorporating the H/M ratio, systolic blood pressure, and LVEF. Risk scores ranged from -3 to 20, with higher scores associated with an increased risk of arrhythmic events. Stratified by tertiles, patients with low (<4), intermediate (4 to 15), and high (>15) risk scores had significantly different arrhythmic event rates (2%, 10%, 16%, respectively; p<.001). The integrated discrimination improvement by adding MIBG imaging, systolic blood pressure, and LVEF results to the risk model was 0.45 (absolute integrated discrimination improvement, 0.01; 95% CI, 0.001 to 0.014), which demonstrated a 45% improvement in discriminatory ability with the addition of MIBG results.

Jain et al. (2014) evaluated the incremental predictive value of adding MIBG imaging to 4 published heart failure risk models using data from ADMIRE-HF. (13) The 4 risk models varied by predictor variables and the patient populations from which the models were derived. In the ADMIRE-HF population, the 4 models had modest discrimination for identifying patients at risk of experiencing the composite primary endpoint of heart failure progression necessitating hospital admission, life-threatening arrhythmia, or cardiac death (C statistic range, 0.611 to 0.652). When the H/M ratio was added to the risk prediction models, the integrated discrimination improvement had an absolute improvement of 2.1% to 3.0% in each model, representing a relative improvement in predictive utility ranging from 33% to 59%.

Narula et al. (2015) reported on the ADMIRE-HF extension study (ADMIRE-HFX), which extended the follow-up to a median of 24 months and focused specifically on the predictive value of MIBG imaging for mortality prediction. (14) The primary endpoint for this extension study was all-cause mortality, which was analyzed using 2 coprimary analysis methods, proportional hazards, and logistic regression. In both the multivariate Cox proportional hazards analysis and the multivariate logistic regression analysis with receiver operating characteristic curve comparisons, the H/M ratio was a significant additional predictor for all-cause mortality (HR, 0.08; p<.001; odds ratio, 0.07; 95% CI, 0.20 to 0.238, respectively).

Agostini et al. (2021) continued to evaluate the value of MIBG imaging for predicting mortality, cardiac death, and arrhythmic events in the ADMIRE-HF study at a median follow-up of 62.7 months. (15) Results revealed that all-cause mortality (38.4% vs. 20.9%) and cardiac mortality (16.8% vs. 4.5%) were significantly increased for those patients with a H/M ratio < 1.6 versus those with a ratio ≥ 1.6 (p<.05 for both comparisons). Patients with preserved sympathetic innervation of the myocardium (H/M ≥ 1.6) also had a significantly lower risk of 5-year mortality (17.1% vs. 34.3%; p<.0001), 5-year cardiac mortality (4.6% vs. 15.8%; p<.0001), and sudden cardiac death or potentially life-threatening arrhythmias (10.9% vs. 21.1%; p=.0002). A trend toward a higher mortality for subjects with H/M < 1.6 was seen reaching significance for patients with a LVEF of 25 to ≤35% only.

Other Prospective Studies

For patients with heart failure without reduced LVEF (i.e., LVEF of at least 50%), several prospective studies have found that MIBG is an independent predictor of cardiac outcomes. (16-20) For example, Nakata et al. (2013) published the results of a pooled patient-level analysis of 6 prospective heart failure studies from Japan in which cardiac MIBG imaging was used. (21) The 6 studies initially included 1360 patients, but 38 patients were excluded (32 due to loss to follow-up, 6 due to follow-up <1 year) for the present analysis. The H/M ratio and the washout rate of MIBG activity were the primary cardiac sympathetic innervation markers. In a multivariate Cox proportional hazards model, the late H/M ratio was significantly associated with the primary outcome of all-cause mortality (p<.001). The addition of the H/M ratio to a model of cardiac risk based on clinical information led to a net reclassification improvement of 0.175 (p<.001).

A prospective single-center study by Doi et al. (2012) evaluated the prognostic value of MIBG activity assessment in 178 heart failure patients without reduced LVEF. (17) Eligibility for the trial included symptomatic heart failure and LVEF more than 50%. Mean LVEF in the sample was 64.5%. Cardiac planar and tomographic MIBG images were obtained 15 to 30 minutes (early) and 4 hours (late) after the agent was injected. Iodine 123 meta-iodobenzylguanidine activity was quantified as the H/M ratio by an experienced technician blinded to clinical data. Patients were followed for a mean of 80 months (minimum, 3 months). The primary endpoints were cardiac events consisting of death, sudden cardiac death, pump failure, or rehospitalization due to the progression of heart failure. During follow-up, cardiac events were documented in 34 (19%) of 178 patients. Events included 7 deaths due to pump failure, 2 sudden deaths, and 25 readmissions due to heart failure progression. There were significantly lower early and late MIBG levels in patients who experienced cardiac events compared with those without events. This study evaluated MIBG activity as a continuous variable; it did not use a cutoff (e.g., an H/M ratio of at least 1.6), as was used to indicate decreased risk in the ADMIRE-HF study. (10) The mean early H/M ratio level was 1.86 in the group with cardiac events and 2.00 in the group without cardiac events. The mean late H/M ratio was 1.64 in the group with, and 1.89 in the group without, cardiac events. In a multivariate analysis, use of diuretics, late atrial diameter, and late H/M ratio were all independent predictors of cardiac events.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

As noted, numerous prospective studies have indicated that MIBG imaging is associated as a prognostic marker with heart failure mortality. No studies were identified that evaluated the impact of cardiac sympathetic innervation assessed by MIBG on treatment decisions for heart failure or that evaluated whether managing heart failure patients with this test (vs. managing patients without the test) leads to patient management decisions that improve health outcomes.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A systematic review by Treglia et al. (2013) included 33 studies, primarily performed in Europe and Japan, that compared MIBG imaging results in patients with heart failure before and after receiving medication treatment. (22) Reviewers provided brief descriptions of the findings of individual studies; they did not pool study results. Studies addressed different classes of

medications (e.g., β-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers) and different MIBG parameters used. Reviewers did not report the number of studies with statistically significant findings but described a number of studies that found significant associations between medication treatment and changes in 1 or more MIBG parameters. They also described some studies that found significant associations between changes in 1 or more MIBG parameters and cardiac outcomes in patients receiving medication treatment. However, none of the studies used MIBG imaging results to guide medication treatment choices or compared management strategies that did and did not include MIBG imaging.

Management changes that might be made as a result of MIBG myocardial imaging are uncertain. It is possible that medication therapy could be intensified based on MIBG scanning that indicated a poor prognosis. However, the evidence is lacking that such a management change would result in improved outcomes. It is also possible that medications that block sympathetic overactivity (e.g., β-blockers or angiotensin-converting enzyme inhibitors) could be adjusted to achieve an optimal H/M ratio. It is also not known whether such medication adjustments made as a result of MIBG imaging would lead to improvements in health outcomes.

Section Summary: Myocardial Sympathetic Innervation Imaging in Heart Failure

The available evidence has demonstrated that MIBG imaging is a predictor of future cardiac events and mortality in patients with heart failure. Numerous prospective studies have evaluated this question and a systematic review that pooled the highest quality studies estimated that cardiac events were approximately 2 times more frequent for patients with a lower MIBG ratio than for those with a higher ratio. The primary study on which the FDA approval was based reported that a low MIBG ratio was associated with a substantially higher mortality rate at 2 years. Data from this same study reported that the addition of the MIBG score to a known prognostic index (the SHFM) resulted in improved predictive accuracy. The evidence does not support a finding that MIBG imaging can be used to direct management in patients with heart failure. Numerous studies have correlated medication changes with changes in MIBG imaging. However, these studies do not provide evidence on the type of management changes that might follow from MIBG imaging. Further studies are needed to determine the impact of MIBG imaging on health outcomes.

Summary of Evidence

For individuals with heart failure who receive imaging with iodine 123 meta-iodobenzylguanidine (MIBG) for prognosis, the evidence includes numerous studies that MIBG cardiac imaging findings predict outcomes in individuals with heart failure. Relevant outcomes are overall survival, disease-specific survival, functional outcomes, health status measures, quality of life, hospitalizations, and medication use. While the available studies vary in their patient inclusion criteria and methods for analyzing MIBG parameters, the highest quality studies have demonstrated a significant association between MIBG imaging results and adverse cardiac events, including cardiac death. Moreover, MIBG findings have been shown to improve the ability of the Seattle Heart Failure Model (SHFM) and other risk models to predict mortality. However, there is no direct published evidence on the clinical utility of MIBG (i.e., whether

findings of the test would lead to patient management changes that improve health outcomes) and no chain of evidence can be constructed to support clinical utility. Management changes made as a result of MIBG imaging are uncertain, and it is not possible to determine whether management changes based on MIBG results lead to improved health outcomes compared with management without MIBG imaging. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (2011) published a report on the translation of cardiovascular molecular imaging. (23) In regard to heart imaging with iodine 123 meta-iodobenzylguanidine (MIBG), the report cited the ADMIRE-HF trial, (10) and stated that additional clinical trials would be needed to determine the efficacy of heart failure management strategies using MIBG compared with usual care without MIBG imaging.

American College of Cardiology Foundation et al.

The American Heart Association, American College of Cardiology, and Heart Failure Society of America published joint guidelines on the management of heart failure in 2022. (24) These guidelines did not address the use of MIBG imaging in heart failure management.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in August 2024 did not identify any studies that might influence this medical policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	0331T, 0332T
HCPCS Codes	A9582, A9590

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
11/15/2025	Reviewed. No changes.
01/01/2025	Document updated with literature review. Coverage unchanged. No new references added; some updated and others removed. Title changed from: Myocardial Sympathetic Innervation Imaging in Patients With Heart Failure.
12/01/2023	Reviewed. No changes.
01/15/2023	Document updated with literature review. Coverage unchanged. References 2, 16, and 26 added; others removed.
02/01/2022	Reviewed. No changes.
03/01/2021	Document updated with literature review. Coverage unchanged. No references added or removed.
07/15/2020	Reviewed. No changes.
03/01/019	Document updated with literature review. Coverage unchanged. References 4, 5 and 24 added.
03/15/2018	Reviewed. No changes.
07/15/2017	Document updated with literature review. The following was changed in coverage: Myocardial sympathetic innervation imaging with iodine 123 meta-iodobenzylguanidine is considered experimental, investigational and/or unproven for patients with heart failure.
09/15/2016	Reviewed. No changes.
09/01/2015	Document updated with literature review. Coverage unchanged. Title changed from Myocardial Sympathetic Innervation Imaging.
12/15/2014	Reviewed. No changes.
07/01/2013	New medical document. Myocardial sympathetic innervation imaging is considered experimental, investigational and unproven, including but not limited to patients with heart failure or left ventricular ejection fraction.