Healthy Blue

Medical Policy

Subject:	Myocardial Sympathetic Innervation Imaging with or without Single-Photon Emission Computed Tomography (SPECT)		
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Description/Scope

This document addresses use of the radiopharmaceutical tracer ^{123}iodine meta-iodobenzylguanidine (also known as ^{123}I-MIBG or MIBG, or AdreView™) for cardiac imaging to assist with identification of individuals at increased risk of short-term mortality associated with heart failure (HF). MIBG has been proposed as a prognostic marker in individuals with HF. The tracer agent can be used with or without single-photon emission computed tomography (SPECT) imaging.

Note: This document addresses **cardiac imaging** with ^{123}iodine meta-iodobenzylguanidine, (also known as ^{123}I-MIBG or MIBG), and *does not address oncologic indications* for use of this radiotracer.

Position Statement

Investigational and Not Medically Necessary:

Myocardial sympathetic innervation imaging with ^{123}iodine meta-iodobenzylguanidine (MIBG) is considered **investigational and not medically necessary** for all indications, including the evaluation of heart failure.

Rationale

The United States Food and Drug Administration (FDA) approval of a commercially available injectable MIBG agent, AdreView (GE Healthcare), was based on two studies published in a single article by Jacobson and colleagues (2010). The studies were known as the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure trial (ADMIRE-HF). The study found that the addition of the MIBG score to a known prognostic index, the Seattle Heart Failure Model (SHFM), resulted in improved predictive accuracy and that a low MIBG heart-to-mediastinum (H/M) ratio was associated with a substantially higher 2-year mortality rate. The analysis presented the combined primary efficacy results of the two studies, which included individuals with NYHA functional class II or III HF and an LVEF of 35% or lower. These clinical parameters were then specified by the FDA as the appropriate criteria for use of the AdreView in individuals with HF who were additionally treated with optimum pharmacotherapy. Major exclusion criteria were serum creatinine levels above 3.0 mg/dL, the presence of a functioning ventricular pacemaker or cardiac revascularization (history) and a history of myocardial infarction (MI) or implantable cardioverter-defibrillator (ICD) implantation within the past 30 days.

Trial participants received an injection of MIBG (AdreView) and then underwent planar and single-photon emission computer 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. The primary analysis evaluated the association between the time to first cardiac event occurrence and the late H/M ratio, categorized as < 1.6 or ≥ 1.6. The authors also evaluated the association between the 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: (1) HF progression (that is, an increase of 1 or more in NYHA functional class); (2) a potentially life-threatening arrhythmic event (that is, spontaneous ventricular tachyarrhythmia for more than 30 seconds, resuscitated cardiac arrest, or appropriate discharge of an ICD); or (3) cardiac death.

A total of 985 subjects underwent MIBG imaging and 961 subjects (98%) were available for analysis. There were 760 (79%) subjects with an H/M ratio of less than 1.60 and 201 subjects (21%) with an H/M ratio of at least 1.60. Study subjects were then followed for a median of 17 months (range 2 days to 30 months). Cardiac events occurred in 237 of 961 subjects (25%). The mean late H/M ratio was 1.39 (standard deviation [SD], 0.18) in the group with any of the study's cardiac events and 1.46 (SD, 0.21) in the group without events. The study results indicated that the risk of cardiac events was significantly lower in those with an H/M ratio of at least 1.6, as compared to those with an H/M ratio of less than 1.6 (hazard ratio [HR], 0.40; 97.5% confidence interval [CI], 0.25 to 0.64; p<0.001). In addition, there was a statistically significant association between the cardiac event rate and the H/M ratio as a continuous variable, with lower event rates seen for subjects with higher H/M ratios (HR, 0.22; 95% CI, 0.10 to 0.47; p<0.001). The estimated 2-year all-cause mortality was 16.1% for subjects with H/M ratios less than 1.60 and 3.0% for those with H/M ratios of at least 1.60 (p<0.001). The authors also compared the H/M ratios to other prognostic markers. In a multivariate model including the H/M ratio, b-type natriuretic peptide (BNP), LVEF, and NYHA functional class, all four markers were independently associated with the time to cardiac events.

An extension study, known as ADMIRE-HFX (Narula, 2015) included 964 individuals from the ADMIRE-HF study who were followed for a median of 24 months. In a Cox proportional hazards analysis, H/M was a significant additional predictor of all-cause mortality, after adjusting for demographic variables (p<0.001). H/M remained a significant predictor of all-cause mortality when LVEF and LVEF and plasma BNP were added to the model (p=0.016).

In 2012, Ketchum and colleagues published an analysis incorporating MIBG imaging findings into the SHFM, using survival data from the trial subjects included in the ADMIRE-HF primary efficacy analysis. The late H/M ratio from MIBG imaging was divided into 5 categories: less than 1.2, 1.2-1.39, 1.40-1.59, 1.6-1.79 and ≥ 1.8. In a Cox proportional hazards model, SHFM and H/M ratios were both independent predictors of overall survival. There was an 82.1% increase in risk for one SD change in the SHFM (p<0.001) and a 60.3% increase in risk for one SD change in the late H/M ratio (p<0.001). For the outcome of cardiac mortality, each SD increase in SHFM was associated with an 86.1% increase in risk (p<0.001), and each SD increase in the late H/M ratio was associated with a 57.9% increase in risk (p=0.002). In an area under the curve (AUC) analysis, the addition of H/M ratio to the SHFM significantly improved the prediction of all-cause mortality compared to the SHFM alone. When the H/M ratio was added to the SHFM, the AUC increased by 0.039 (p=0.026) for 1-year mortality and the AUC increased by 0.028 (p<0.05) for 2-year mortality.

A number of other cohort studies have been published (Doi, 2012; Jain, 2014; Marshall, 2012). Nakata and colleagues (2013) pooled data from six multicenter cohort studies, with a total of 1322 individuals, examining MIBG imaging to determine prognosis in HF. Individuals were followed for a mean of 78 months. A Cox proportional hazard analysis found that cardiac MIBG uptake was a significant predictor of all-cause mortality, along with age, NYHA functional class and LVEF.

In 2011, a working group of the National Heart, Lung, and Blood Institute (NHLBI) published a report on the translation of cardiovascular molecular imaging. Regarding cardiac MIBG imaging, the report cited the ADMIRE-HF trial and stated that additional clinical trials are needed to determine the efficacy of HF management strategies with MIBG, compared to usual care without MIBG imaging (Buxton, 2011).

In 2015, the American Society of Nuclear Cardiology (ASNC) published a joint policy statement with the Society of Nuclear Medicine and Molecular Imaging (SNMMI) with specific MIBG recommendations as follows:

> For patients with NYHA class II or III heart failure with LVEF ≤ 35% to help stratify risk and to promote more informed clinical decision-making when the result of ^{123}I-mIBG study is likely to influence the decision regarding ICD implant.

However, there is no quality of evidence rating provided and the studies cited in support of the specific recommendation do not address MIBG imaging and the potential clinical impact on decision-making and net health outcomes.

In 2021 Agostini and colleagues published 5-year follow-up data from 964 subjects who participated in the ADMIRE-HF study and were still alive at the 2-year follow-up. Mean follow-up was 62.7 months. Subjects were stratified according to the heart/mediastinum (H/M) ratio on planar ^{123}I-MIBG scintigraphic images obtained at baseline in ADMIRE-HF (< 1.60 vs. ≥ 1.60). The all-cause mortality data indicated significantly lower number of deaths in the low H/M group vs. the high H/M group (30.9% vs. 39.4; HR, 0.45, p<0.0001). Kaplan-Meier analysis indicated a significantly higher 5-year survival rate in the high H/M group (82.9% vs. 56.7%, p<0.0001). A total of 137 (41%) of the 334 reported all-cause deaths were due to cardiac-related causes. Similar to the all-cause data, the cardiac-specific death data indicated a significantly lower rate of cardiac deaths in the high H/M group (4.5% vs. 16.8%; HR, 0.22, p<0.0001). A Kaplan-Meier analysis of time to cardiac death found that 5-year survival was significantly higher in the high H/M group (96.4% vs. 84.2%; p<0.0001). Overall, there were 182 subjects (18.9%) who had either sudden cardiac death or a potentially fatal arrhythmia aborted by intervention. Such events were reported to be significantly less common in the high H/M group (10.9% vs. 21.1%; HR, 0.42, p=0.0002). The proportion of subjects without sudden cardiac death or a potentially fatal arrhythmia aborted by intervention at 5 years was higher in the high H/M group (92.7% vs 78.8%, p=0.0004). In the 5-year study period, 417 subjects (43.4%) died or required a potentially life-saving intervention, with the risk of this outcome found to be lower for the subjects with high H/M (HR, 0.46, p<0.0001). As with previous reports of the ADHERE-HF study, this retrospective data indicates that the use of myocardial sympathetic innervation imaging with MIBG may be useful in identifying individuals at high risk of cardiac-related mortality and morbidity, however the limitations of this type of study still apply. Additional issues related to loss to follow-up, a predominately male subject pool, missing data from all subjects, also impair the application of these findings to the general population.

Although studies have found associations between cardiac MIBG imaging findings and mortality in individuals with heart failure, there is a lack of evidence that prospective use of MIBG imaging improves health outcomes. Studies are needed that compare clinical outcomes in individuals managed using MIBG imaging to HF management without MIBG imaging.

Background/Overview

An estimated 6.5 million adults in the United States have heart failure (HF), which is the main cause of death of approximately 1 in 8 deaths (CDC, 2020). An early mechanism to compensate for the decreased myocardial function seen in HF is activation of the sympathetic nervous system. This increase in sympathetic activity initially helps compensate for HF by increasing the heart rate and myocardial contractility in order to maintain blood pressure and organ perfusion. Over time, additional strain is placed 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 diminishes, clinical symptoms of HF develop. Additionally, heightened sympathetic activity increases the presentation of potentially fatal ventricular arrhythmias.

Overactive sympathetic innervation associated with HF involves increased neuronal release of norepinephrine (NE), which is 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 post-synaptic beta-1, beta-2 and alpha-receptors, enhances adenyl cyclase activity and brings about the desired cardiac stimulatory effects. NE is then taken back into the presynaptic space for storage or catabolic disposal that terminates the synaptic response by the uptake-1 pathway. The increased release of NE is usually accompanied by decreased NE reuptake, which increases circulating NE levels.

Guanethidine (an antihypertensive drug) is a false neurotransmitter that is an analogue of NE; it is also taken up by the uptake-1 pathway. ^{123}Iodine meta-iodobenzylguanidine (known as ^{123}I-MIBG or MIBG) is guanethidine that has been chemically modified and labeled with radioactive iodine. MIBG moves into the synaptic cleft and is taken up and stored in the presynaptic nerve space similar to NE. However, unlike NE, MIBG is not catabolized and concentrates in myocardial sympathetic nerve endings. This concentrated MIBG can be imaged with a conventional gamma camera (Chirumamilla, 2011). MIBG myocardial imaging is conducted by an injection of MIBG and planar images are then acquired 15 minutes (early image) and 4 hours (late image) after injection. Optional SPECT imaging can be performed following the early and late planar images. MIBG uptake is semi-quantified by determining the average count per pixel in regions of interest (ROI) drawn over the heart and the upper mediastinum in the planar anterior view. The concentration of MIBG over several hours after injection of the agent is a reflection of sympathetic neuronal activity, which may correlate with HF severity. MIBG activity has also been suggested for potential use in guiding treatment decisions or in the monitoring of HF treatment effectiveness.

AdreView™ (lobenguane I^{123} injection, GE Healthcare, General Electric Company, Medi-Physics, Inc., Arlington Heights, IL), is a commercially available MIBG product. This diagnostic injectable agent was originally approved for intravenous use by the U.S. Food and Drug Administration (FDA) in 2008. According to the FDA, AdreView as a radiopharmaceutical agent for gamma-scintigraphy is indicated for:

- Use in the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests;
- Scintigraphic assessment of sympathetic innervation of the myocardium by measurement of the heart-to-mediastinum (H/M) ratio of radioactivity uptake in individuals with New York Heart Association (NYHA) class II or class III HF and left ventricular ejection fraction (LVEF) less than or equal to 35%. “Among these patients, AdreView may be used to help identify patients with lower one and two year mortality risks, as indicated by an H/M ratio ≥ 1.6” (FDA, 2020).

It was noted that, while the H/M ratio can purportedly be used as either a dichotomous or continuous variable, the FDA-approved indication is a dichotomous variable with a cutoff in H/M ratio of 1.6. A ratio less than 1.6 indicates higher risk for cardiac events and early mortality associated with HF, and a ratio of 1.6 or greater indicates lower risk.

According to the FDA prescribing information (2020):

Limitations of Use:
In patients with congestive heart failure, AdreView utility has not been established for:

- selecting a therapeutic intervention or for monitoring the response to therapy;
- using the H/M ratio to identify a patient with a high risk for death.

Contraindications:
Known hypersensitivity to iobenguane or iobenguane sulfate.

Warnings and Precautions:
Hypersensitivity reactions have followed AdreView administration. Have anaphylactic and hypersensitivity treatment measures available prior to AdreView administration.

- Drugs which block norepinephrine uptake or deplete norepinephrine stores may decrease AdreView uptake. When medically feasible, stop these drugs before AdreView administration and monitor patients for withdrawal signs and symptoms.
- AdreView contains benzyl alcohol (10.3 mg/mL) which may cause serious reactions in premature or low birth-weight infants.
- Patients with severe renal impairment may have increased radiation exposure and decreased quality of AdreView images.
- Failure to block thyroid iodine uptake may result in iodine 123 accumulation in the thyroid.

Definitions

Heart failure (HF), also referred to as Congestive Heart Failure (CHF): A condition in which the heart no longer adequately functions as a pump. As blood flow out of the heart slows, blood returning to the heart through the veins backs up, causing congestion in the lungs and other organs.

Heart-to-mediastinum (H/M) ratio: This refers to a cardiac measure which is calculated by taking the average count per pixel in the myocardium divided by the average count per pixel in the mediastinum. The H/M ratio is proposed as an independent predictor of risk for cardiac events and early mortality associated with HF.

^{123}Iodine meta-iodobenzylguanidine (known as ^{123}I-MIBG or MIBG) Imaging: This radiopharmaceutical imaging agent (known by the branded name, AdreView) is used with standard or SPECT scanning to measure the heart-to-mediastinum (H/M) ratio, in order to predict risk for cardiac events and death associated with HF.

Myocardial sympathetic innervation imaging: This technology involves use of the AdreView (MIBG) tracer injectable with scintigraphic scanning, in order to image the myocardium and measure myocardial sympathetic innervations. This imaging technique can determine certain cardiac variables, including the H/M ratio, which is proposed as a prognostic marker of HF symptom progression and risk for cardiac arrhythmias and death, associated with HF.

New York Heart Association (NYHA) Definitions:
The NYHA classification of HF is a 4-tier system that categorizes subjects based on subjective impression of the degree of functional compromise; the four NYHA functional classes are as follows:

- Class I - patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain; symptoms only occur on severe exertion.
- Class II - patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity (e.g., moderate physical exertion such as carrying shopping bags up several flights of stairs) results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III - patients with cardiac disease resulting in marked limitation of physical activity; they are comfortable at rest; less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
- Class IV - patients with cardiac disease resulting in inability to carry on any physical activity without discomfort; symptoms of heart failure or the anginal syndrome may be present even at rest; if any physical activity is undertaken, discomfort is increased.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:

CPT

0331T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment;
0332T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment; with tomographic SPECT

HCPCS

A9582	Iodine I-123 iobenguane, diagnostic, per study dose, up to 15 millicuries [AdreView; when specified for use in myocardial imaging]

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. Agostini D, Ananthasubramaniam K, Chandna H, et al; ADMIRE-HF investigators. Prognostic usefulness of planar ^{123}I-MIBG scintigraphic images of myocardial sympathetic innervation in congestive heart failure: follow-up data from ADMIRE-HF. J Nucl Cardiol. 2021; 28(4):1490-1503.
2. Al Badarin FJ, Wimmer AP, Kennedy KF, et al. The utility of ADMIRE-HF risk score in predicting serious arrhythmic events in heart failure patients: incremental prognostic benefit of cardiac 123I-mIBG scintigraphy. J Nucl Cardiol. 2014; 21(4):756-762.
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4. Doi T, Nakata T, Hashimoto A, et al. Synergistic prognostic values of cardiac sympathetic innervation with left ventricular hypertrophy and left atrial size in heart failure patients without reduced left ventricular ejection fraction: a cohort study. BMJ Open. 2012; 2(6).
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6. Jain KK, Hauptman PJ, Spertus JA, et al. Incremental utility of iodine-123 meta-iodobenzylguanidine imaging beyond established heart failure risk models. J Card Fail. 2014; 20(8):577-583.
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8. Marshall A, Cheetham A, George RS, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts ventricular arrhythmia in heart failure patients receiving an implantable cardioverter-defibrillator for primary prevention. Heart. 2012; 98(18):1359-1365.
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11. Treglia G, Stefanelli A, Bruno I, et al. Clinical usefulness of myocardial innervation imaging using Iodine-123-meta-iodobenzylguanidine scintigraphy in evaluating the effectiveness of pharmacological treatments in patients with heart failure: an overview. Eur Rev Med Pharmacol Sci. 2013; 17(1):56-68.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Buxton DB, Antman M, Danthi N, et al. Report of the National Heart, Lung, and Blood Institute (NHLBI) Working Group on the Translation of Cardiovascular Molecular Imaging. Circulation. 2011; 123(19):2157-2163.
2. Centers for Disease Control and Prevention (CDC). Heart Failure. Last reviewed January 5, 2023. Available at: https://www.cdc.gov/heartdisease/heart_failure.htm. Accessed August 7, 2023.
3. Sciammarella MG, Gerson M, Buxton AE, et al. ASNC/SNMMI Model Coverage Policy: Myocardial sympathetic innervation imaging: Iodine-123 meta-iodobenzylguanidine ((123)I-mIBG). J Nucl Cardiol. 2015; 22(4):804-811.
4. U.S. Food and Drug Administration (FDA). Center for Drug Evaluation and Research. AdreView (Iobenguane I ^{123} Injection). NDA: 3279800. Prescribing Information 2020. Available at: https://www.gehealthcare.com/-/jssmedia/47738ec8ef514611a7f0f4ed340756e4.pdf?la=en-us. Accessed on August 7, 2023.

Websites for Additional Information

1. National Heart, Lung and Blood Institute. What is heart failure? Available at: https://www.nhlbi.nih.gov/health-topics/heart-failure. Accessed on August 7, 2023.

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AdreView
Heart Failure, Congestive Heart Failure (CHF)
^{123}iodine meta-iodobenzylguanidine
lobenguane I ^{123} injection
MIBG, ^{123}I-MIBG
Sympathetic Innervation Imaging, Myocardial

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised Rationale and References sections
Reviewed	08/11/2022	MPTAC review. Updated Description, Rationale and References sections
Reviewed	08/12/2021	MPTAC review. Description/Scope, Rationale, Background/Overview, References, and Websites for Additional Information were updated.
Reviewed	08/13/2020	MPTAC review. Rationale, Background/Overview and References sections were updated.
Reviewed	08/22/2019	MPTAC review. References were updated.
Reviewed	09/13/2018	MPTAC review. References were updated.
Reviewed	11/02/2017	MPTAC review. The document header wording was updated from "Current Effective Date" to "Publish Date." References were updated.
Reviewed	11/03/2016	MPTAC review. References were updated.
Reviewed	11/05/2015	MPTAC review. References were updated. Removed ICD-9 codes from Coding section.
Reviewed	11/13/2014	MPTAC review. The Rationale, Background, and References sections were updated.
New	11/14/2013	MPTAC review. Initial document development.