Clinical Review Criteria
I MIBG Imaging for Heart Failure

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Criteria
For Medicare Members

<table>
<thead>
<tr>
<th>Source</th>
<th>Policy</th>
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<tbody>
<tr>
<td>CMS Coverage Manuals</td>
<td>None</td>
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<td>National Coverage Determinations (NCD)</td>
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<td>Local Coverage Determinations (LCD)</td>
<td>Non-Covered Services (L35008).</td>
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For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, KPWA will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Heart failure (HF) is a complex clinical syndrome responsible for high morbidity and mortality in the world. The prognosis of HF remains poor and its burden on mortality, reduced quality of life, and healthcare cost is increasing across the world. The goals of HF treatment are to improve symptoms, slow the progression of the disease, and prolong survival (Martins da Silva 2013, Perrone-Filardi 2011, Nakou 2013, Jain 2014).

Treatment options for HF include medications, devices, and nonpharmacological interventions. Drug therapy for chronic heart failure including B-adrenergic blockade, vasodilators, angiotensin converting enzyme (ACE) inhibitors, mineralocorticoid receptor antagonists, and diuretics can relieve symptoms and/or improve survival. Devices as cardiac resynchronization therapy may improve outcomes in some patients with NYHA class II-IV heart failure, and implantable cardioverter defibrillators (ICDs) can reduce the risk of sudden cardiac death in patients with HF and reduced left ventricular ejection fraction (LVEF). However, these devices are not beneficial to all patients, are costly, and have potential significant complications. It is thus essential to identify the patients who are more likely to benefit from intensive therapies, and those among whom devices such as ICD are not indicated (Nakou 2013, Gupta 2014, Nakajima 2014).

Heart failure is characterized by sympathetic nerve hyperactivity (up to 50 times more active than normal), which serves as a compensatory mechanism for the cardiac dysfunction associated with HF. The increased sympathetic response is initially favorable to maintain the systemic hemodynamics and peripheral circulation. However, long-lasting and excess stimulation of sympathetic nerve function leads to deleterious consequences including myocardial remodeling, reduced LVEF, and electrical instability which increase the likelihood of arrhythmia and sudden cardiac death (SCD) (Martins da Silva 2013, Jacobson 2010, Nakata 2013, Treglia 2013).
Researchers found that persistent stimulation of sympathetic nerve function in failing hearts impairs the efficiency of reuptake, turnover, and storage of norepinephrine (NE) at presynaptic nerve endings, resulting in spill-over and deficiency in NE stores leading to a decline in the myocardial sympathetic innervation. On this pathophysiological basis, it was suggested that the assessment of the degree of sympathetic activation of the heart can potentially be an indicator of the severity of the disease process and provide an insight to the prognosis of a patient with HF. This has led to the development of radiotracers for single-photon computed tomography (SPECT) and positron emission tomography (PET) (Martins da Silva 2013, Nakata 2013, Gupta 2014).

Guanethidine is a false neurotransmitter that is taken up by the uptake pathway for NE into presynaptic terminal. Chemical modification and labeling with radioactive iodine produce metaiodobenzylguanidine (123I-MIBG), an analog of NE that permits the visualization of adrenergic innervation in vivo. After depolarization MIBG is released into the synaptic cleft similar to NE, but unlike NE it is not metabolized by monoamine oxidase (MAO) or catechol-o-methyl-transferase (COMT), leading to higher cytoplasmic concentration that permits scintigraphic imaging in early and delayed phases (Treglia 2013, Gupta 2014).

The conventional protocol for scintigraphic myocardial imaging involves the injection of 123I-MIBG intravenously at rest after which early (from 10-30 minutes after administration) and delayed (3-4 hours after administration) images are obtained. The planar images with anterior view are adequate for evaluating cardiac sympathetic function. Tomographic images (SPECT) are often acquired to evaluate the regional myocardial uptake pattern. The most common semi-quantitative indices used for interpreting the images are the heart to mediastinum ratio (H/M) and washout rate (WR) obtained from the anterior planar images. Regions of interest are set in the heart (H: target region) and the mediastinum (M: background region) to obtain a mean count at each region. H/M ratio is calculated, and the degree of accumulation evaluated based on the resulting ratio. The WR is an index that indicates the rate at which MIBG is washed out between the early and delayed images through comparison with the cardiac count in the early image. This may reflect turnover of catecholamines attributable to the sympathetic drives and measures the ability of the myocardium to retain. MIBG normal values for these are derived from control patients and may differ between institutions (Treglia 2013).

Medical Technology Assessment Committee (MTAC)

I 123I-MIBG Imaging for Heart Failure

10/20/2014: MTAC REVIEW

Evidence Conclusion: AdreView Myocardial imaging for Risk Evaluation in Heart Failure (ADMIRE-HF, Evidence table 1), was the pivotal study that led to the recent FDA approval of 123I-MIBG use in HF patients was a large, observational, multicenter study that evaluated the prognostic value of 123I-MIBG in HF patients. 961 participants with NYHA class II/III HF and LVEF <35% underwent 123I-MIBG myocardial perfusion imaging and were followed for a maximum of 2 years to assess the primary composite endpoint of HF progression necessitating hospital admission, life-threatening arrhythmic event, and cardiac death. During a median of 17 months of follow-up (range 2 days-30.4 months), 237 first cardiac events were observed. The analysis of the results suggests that H/M ratio <1.6 was most discriminative for identifying patients at higher risk of the composite endpoint and each of its components. Patients with H/M >1.60 had a significantly lower risk of cardiac events (HR 0.40; 95% CI, 0.25-0.64), lower rate of HF progression, lower rate of arrhythmic events, and higher 2-year survival rates. The incidence of cardiac death was <1% per year in patients with H/M >1.6 and 9.6% per year among those with H/M <1.6. The results also showed that late H/M ratio provided additional information to that of plasma BNP and LVEF for identifying patients at greater risk of cardiac events. The other parameters of the 123I-MIBG imaging (early H/M and washout rate (WR) were also associated with risk for cardiac events, but late H/M ratio was the only one with independent prognostic value. A subsequent retrospective analysis of the ADMIRE-HF (Shah 2012) suggests that 123I MIBG has prognostic value across the spectrum of LVEFs. Verschure D et al, 2014 (Evidence table 2) conducted a meta-analysis of individual patient data from 6 studies incorporating 636 chronic HF patients (599 from Europe and 37 from the USA) to determine the most appropriate prognostic endpoint for 123I-MIBG scintigraphy in patients with chronic heart failure. The primary outcomes were all-cause mortality, cardiac mortality, arrhythmic events, heart transplantation, and a composite outcome of all listed events. Overall, the results of the pooled analysis indicate that late H/M was an independent predictor for all outcomes studies except for arrhythmias. The lower late H/M is associated with higher risk. LVEF was also found to be an independent predictor for these events. The analysis did not examine whether MIBG has an incremental prognostic value over other independent variables. The etiology of HF i.e. ischemic vs. non-ischemic was not an independent predictor in the multivariate analysis for any of the outcome events. The meta-analysis had the advantage of including patient data from longitudinal studies, however, the authors did not evaluate the quality of the studies included, did not test for homogeneity or publication bias, or do a sensitivity analysis. The analysis did not include the Japanese studies or the ADMIRE-HF study. In addition, there were variations between the studies.
Nakata T, Nakajima K. and colleagues (2013, Evidence table 3) pooled data from six prospective cohort studies conducted in Japan from 1990 to 2009. The studies enrolled a total 1,322 patients with chronic HF, the mean follow-up duration was 78 months, and the five-year outcomes were available for 933 patients. The five-year cardiac deaths were determined by the original study investigators. Multivariate analysis was performed using the variables age, gender, early H/M, late H/M, MIBG washout rate, NYHA functional class, LVEF, history of diabetes, hypertension, dyslipidemia, atrial fibrillation, sustained ventricular tachycardia, and medications used. BNP data was available for only 512 patients. The results of the analysis indicate that survival rates decreased with decreasing H/M independent of other markers as NYHA class, BNP, and LVEF. All-cause mortality progressively decreased with increasing H/M ratio. Based on the ROC curve, a late H/M ratio threshold of 1.68 identified patients at a significantly higher mortality. This analysis only included data from studies conducted in Japan, and the H/M values as well as the results may not be generalized to other geographic areas using other methodologies or in populations with different characteristics. Pooled results of two earlier meta-analyses (Verberne H et al, 2008 et al and Kuwabara Y et al, 2011) also suggest that HF patients with reduced late H/M ratio or increased 123I-MIBG washout rate (WR) have a higher incidence of cardiac events compared to those with normal or relatively preserved uptake and washout rates. Incremental value of myocardial sympathetic innervation imaging with 123I-MIBG in heart failure patients Jain K and colleagues (2014) used data from ADMIRE-HF to assess the performance of four HF risk models (EFFECT, CARE-HF, MADIT-II and PACE) for predicting the composite clinical endpoint of cardiac death, progressive HF, or life-threatening arrhythmia. They then quantified the incremental prognostic utility of H/M ratio 123I-MIBG imaging when added to each of the individual models. The results of the analysis suggest that H/M ratio >1.6 was consistent with the other models in identifying patient at lower risk of cardiac events, and that the addition of H/M to EFFECT, CARE-HF, MADIT-II and PACE models improved their discrimination by 33%, 59%, 49% and 37% respectively. These results, however, have to be interpreted with caution as it was derived from post-hoc evaluation of risk factors in ADMIRE-HF study. It may be limited to the characteristics of the participants included as well as the limitations of the observational study design.

Ketchum E, et al (2012) also used survival data from 961 NYHA II-III subjects in the ADMIRE-HF trial to investigate the incremental value of MIBG cardiac imaging when added to the Seattle Heart Failure Model (SHFM) for prediction of all-cause mortality. The results of the analysis showed that the addition of H/M to the SHFM in a Cox model significantly improved risk prediction (P<0.0001), with a greater utility in higher risk SHFM patients. The net reclassification improvement (NRI) was 22.7% (P<0.001), with 14.9% of subjects who died reclassified into a higher risk category than suggested by SHFM score alone (P=0.01) and 7.9% of subjects who survived reclassified into a lower risk category (P<0.0001). The 1-year area under the receiver-operator curve showed significant improvement for the combined model with H/M compared to the SHFM alone. Nakajima K, Nakata T, and colleagues (2014) used the same database (created By Nakata et al, 2013) to create a model for predicting fatal cardiac events by adding information from MIBG imaging. Nakata et al’s pooled analysis included data for 1,322 chronic HF patients enrolled in cohort studies performed in Japan from 1990 to 2009. Prediction models were created with single and multiple variables to calculate cardiac mortality. Net reclassification improvement (NRI) analysis was based on prediction models with and without H/M ratio. The five-year risk levels were defined as low (<5%, corresponding to 1% mortality /year), intermediate (5-25%) and high (>25% corresponding to 5% mortality /year). For 5 years 205/933 patients (22%) died of a cardiac event. A multivariate analysis showed that age, gender, NYHA functional class (highest OR and X2 values), LVEF, and late MIBG H/M were significant predictors for 5-year cardiac mortality. The calculated ROC AUC (area under receiver operator curve) was 0.749 with the first 4 variables, and 0.780 after the addition of H/M (p=0.0015 for difference). The authors performed NRI analysis by the combination of age, gender, NYHA functional class and LVEF (model 1) and with the addition of late H/M (model 2). Patients who died with cardiac events were classified into the 3 risk levels according to the 2 models. The results indicate that classification was improved in 23 patients and made worse among 13 in model 2 vs. model 1. The net gain in classification was 4.9% (p=0.096). Of those who did not die of a cardiac event 38 were classified upwards and 103 downward with a net gain in classification of -9.0% (p=0.0001). This indicates that the addition of H/M is significantly improved the identification of patients at lower risk of cardiac death, i.e. it is more useful for reclassifying patients downwards to lower risk groups. This latter finding is contradictory to that observed in ADMIRE-HF study and the Ketchum and colleagues’ analysis where MIBG was more effective in reclassifying patients upwards. The authors explained that this might be due to the differences between the Japanese trials and the ADMIRE-HF (USA and Europe) study. Participants in the Japanese trials were overall healthier as regards their NYHA functional class, LVEF level, higher prevalence of non-ischemic HF, and lower overall mortality. The mean H/M values were 1.71 in ADMIRE-HF, and 1.44 in the Japanese trials, which as the authors explained may be related to the technical differences between the imaging equipment in Japan vs. gamma cameras in the US and Europe. The study had its limitations as data were compiled from a number of studies conducted as early as 1990, with some variations in the population included, medication used, and MIBG imaging techniques. Its results need to be validated in prospective large studies.
Clinical Utility of myocardial sympathetic innervation imaging with 123I-MIBG in heart failure patients. There are no published randomized controlled trials to date that directly evaluated the benefit of 123I-MIBG imaging as an aid to clinical management of HF patients. A number of published studies evaluated the use of MIBG scintigraphy in monitoring improvement in sympathetic activity in HF patients treated with vasodilators and beta-blockers. Treatment decisions and selection therapy were not based on the results of MIBG imaging and thus may not be the right study design to evaluate the effect of the test on the management decisions and/or patient outcomes.

Conclusion: There is fair evidence from a number of observational studies and pooled analyses that 123I imaging of patients with heart failure and low LVEF may have an independent predictive value for estimating their risk of fatal cardiac events. There is some evidence from three analyses that H/M may have an additive (incremental) value to other risk models used for predicting cardiac mortality in patients with HF and low LVEF. There is insufficient evidence, to date, to determine that 123I-MIBG imaging of patients with heart failure and low LVEF impacts the management plan and/or improves patient outcomes. The review of the technology conducted Blue Cross Blue Shield Association, Kaiser Permanente. TEC program in April 2014 came to similar conclusions that there is evidence that myocardial MIBG innervation imaging provides prognostic information for cardiac events, and that there is a lack of evidence that the prognostic information will lead to improved health outcomes.

**Articles:** The literature search revealed over 200 articles on 123I-MIBG sympathetic imaging, many of which were unrelated to the current review. There were a number of published studies that examined the prognostic value of 123I-MIBG imaging of patients with HF. The studies include the pivotal ADMIRE-HF study that led to the FDA approval of using 123I-MIBG sympathetic imaging for patients with HF. The results of many of these published studies were pooled in four systematic reviews (Verberne et al, 2008, Kuwabara et al, 2011 [Japanese studies only], Nakata et al. 2013, and Verschure et al 2014 [European and USA studies]). Two subanalyses from the ADMIRE-HF study examined the ability of 123I MIBG in predicting the arrhythmic events and hospitalization in subpopulations were recently published (Sood et al 2013, and Parker et al, 2014). The search also identified the recent assessment of 123I-MIBG sympathetic imaging by Blue Cross Blue Shield Association, Kaiser Permanente. Technology Evaluation Center (TEC) Assessment Program. The literature search did not identify any trial that evaluated the clinical utility of the 123I-MIBG sympathetic imaging in heart failure patients, i.e. the impact of the test results on the management of patients. Treglia and colleagues 2013, reviewed studies that used the 123I MIBG to evaluate the effectiveness of different pharmaceutical agents in patients with HF. These studies did not actually examine the clinical utility of the test as the title of the review implies, as the management of the patients or selection of pharmaceutical agents were not based on the test results. The most recent pooled analyses (published after the TEC review) as well as the ADMIRE-HF study were selected for critical appraisal. Jacobson AF, Senior R, Cerqueira MD, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol. 2010;55 (20): 2212-2221. See Evidence Table 1. Verschure DO, Veltman CE, Manrique A, et al. For what endpoint does myocardial 123 I-MIBG scintigraphy have the greatest prognostic value in patients with chronic heart failure? Results of a pooled individual patient data meta-analysis. Eur Heart J Cardiovasc Imaging. 2014 Sep;15 (9): 996-1003. See Evidence Table 2. Nakata T, Nakajima K, Yamashina S, et al. A pooled analysis of multicenter cohort studies of (123) I-mIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. JACC Cardiovasc Imaging. 2013;6 (7):772-784. See Evidence Table 3.

The use of I MIBG Imaging for Heart Failure does not meet the Kaiser Permanente Medical Technology Assessment Criteria.