Assessing arrhythmic risk with ^{123}I-*m*IBG and analogous tracers: Image interpretation from a different viewpoint

Mark I. Travin, MD, FASNC[a,b]

[a] Division of Nuclear Medicine, Department of Radiology, Montefiore Medical Center, Bronx, NY
[b] Division of Nuclear Medicine, Department of Radiology, Albert Einstein College of Medicine, Bronx, NY

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In patients with chronic heart failure (HF), the most catastrophic outcome is sudden cardiac death (SCD), particularly in a patient who is otherwise doing relatively well. SCD accounts for up to 50% of HF deaths.[1] While there are a variety of etiologies, it is most often a ventricular tachycardia progressing to ventricular fibrillation (VT/VF). Numerous large prospective multicenter studies have demonstrated improved patient survival with primary preventive use of an implantable cardioverter defibrillator (ICD) that in guidelines has been assigned a Class IA indication for ''primary prevention of SCD to reduce total mortality in selected patients with nonischemic [dilated cardiomyopathy] or ischemic heart disease at least 40 days post-MI with [a left ventricular rejection fraction] (LVEF) of 35% or less and NYHA class II or III symptoms on [guideline directed medical therapy], who have a reasonable expectation of meaningful survival for more than 1 year.''[2] Yet, in spite of such a strong recommendation, it is widely acknowledged that basing primary prevention ICD use on a LVEF threshold, particularly 35%, is not well supported by clinical experience,[3] or when findings of the randomized studies upon which guidelines are based are examined more closely.[4] With current practice, >80% of primary prevention patients do not use their ICD over a duration of as long as 8 years, with the device costing as high as $235,000 per year of life saved, and with a significant potential for serious device complications.[5] It is clear that a better approach to selecting HF patients for primary prevention ICD implantation is needed.

NECESSITY OF PATIENT TESTING BASED ON UNDERLYING ARRHYTHMIC MECHANISMS

It should be self-evident that a more effective way of determining arrhythmic risk would be to use testing methods that examine the basic underlying causes of arrhythmias. Such methods need, in some way, to identify myocardial substrate abnormalities predisposing to electrical conduction heterogeneity, which in the setting of a deleterious trigger and modulating factors can produce dangerous arrhythmias.[5,6] Techniques that assess cardiac autonomic systemic hormonal control or direct cardiac innervation that, if impaired in some way, has been shown to help produce an abnormal myocardial electrical conduction substrate, may produce an arrhythmic trigger and can modulate arrhythmias by either propagating or quenching them, should be effective tools for arrhythmic risk stratification.[5]

While measurements of serum neurohumoral markers, such as catecholamine levels, are commonly used to risk stratify HF patients, they tend to be nonspecific for arrhythmic risk, and therefore much recent work has focused on direct cardiac adrenergic innervation imaging using the norepinephrine (NE) single-photon emission computed tomographic (SPECT) radionuclide analog, iodine-123 *meta*-iodobenzylguanidine (^{123}I-*m*IBG). Since its development approximately 35 years ago, ^{123}I-*m*IBG was recognized as visualizing the ''wiring'' of the heart,

Reprint requests: Mark I. Travin, MD, FASNC, Division of Nuclear Medicine, Department of Radiology, Montefiore Medical Center, 111 E. 210th Street, Bronx, NY 10467-2490; *mtravin@attglobal.net*
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with potential for identifying patients with autonomic neuropathies who have partial denervation predisposing to arrhythmias and SCD.[7] Early basic and clinical work demonstrated the potential of ^{123}I-*m*IBG imaging to evaluate arrhythmic risk. In dogs, Zipes and colleagues[8] showed that artificially created sympathetic efferent denervation produces an exaggerated shortening of the effective refractory period (ERP) during NE or isoproterenol infusions, which increases vulnerability to stimulation-induced ventricular fibrillation, termed ''denervation supersensitivity.'' Visualization of a focal ^{123}I-*m*IBG defect, which was present even in the absence of a ^{201}Tl perfusion, increased arrhythmogenicity for a period of up to 3 weeks after reinnervation. In several small (<30 patient) human studies, post-MI regional ^{123}I-*m*IBG defects were found to predispose to ventricular tachyarrhythmias.[9,10]

As a key, relatively large (90 patient) prognostic study by Merlet et al[11] found global cardiac ^{123}I-*m*IBG uptake, as measured by the heart-to-mediastinum ratio (HMR), to strongly and independently risk stratify advanced HF patients in terms of overall survival, the predominant focus shifted to planar techniques. Numerous studies thereafter showed that HMR and the global tracer washout rate (WO or WR) between initial and delayed (~4 hour) planar images robustly risk stratified advanced HF patients in terms of cardiac and overall survival, as well as various secondary HF-associated events.[12] The most important investigation to date has been the prospective, rigorously performed 961-patient ''AdreView Myocardial Imaging for Risk Evaluation in Heart Failure'' (ADMIRE-HF) study, which demonstrated that an HMR <1.6 increased the occurrence of cardiac events, independent of commonly used prognostic variables such as LVEF and B-type natriuretic peptide (BNP).[13] Of course, a patient who survives does not have an arrhythmic SCD, and as ADMIRE-HF recruited patients before ICD guidelines were established, for extended periods many patients did not have ICDs to prevent this outcome. In an early analysis of such patients without an ICD, for those with an HMR ≥1.6, there was only one arrhythmic death (at HMR = 1.6), as depicted in Figure 1.[14]. A later, more rigorous analysis of 777 patients who did not initially have ICDs showed that HMR added incremental prognostic value and enhanced risk reclassification (for survival), with HMR identifying the number of lives saved by ICD use per 100 treated.[15] For all patients (ICD and no ICD) in ADMIRE-HF, combined ''arrhythmic'' events (self-limited ventricular tachycardia, resuscitated cardiac arrest, appropriate ICD discharges) were more common in subjects with HMR <1.60 (10.4%) than in those with HMR ≥1.6 (3.5%, $P < 0.01$).

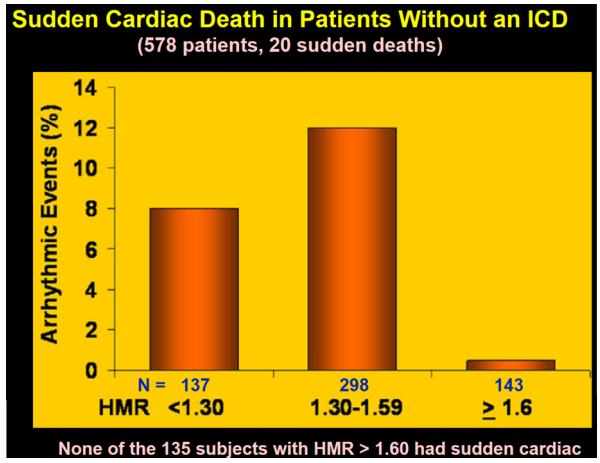

Figure 1. Arrhythmic events vs heart-to-mediastinum ratio (HMR) in patients without an implantable cardioverter-defibrillator (ICD). In patients with HMR ≥1.6, there was only one arrhythmic death, in a patient with HMR value of 1.6. Reprinted from Seminars in Nuclear Medicine, Vol. 41, Chirumamilla A, Travin MI. Cardiac applications of ^{123}I-*m*IBG imaging.; pp. 374-87, 2011, with permission from Elsevier.

Interestingly, Figure 1 illustrates that patients with the highest arrhythmic risk, i.e., those for whom an ICD would be most beneficial, may not be those with the lowest HMR, but rather those with an intermediate HMR. In accordance with this concept, a recent report by Verschure et al from a cohort of 135 stable HF patients from 13 European institutions, enrolled in an ICD implantation primary prevention trial, found that the highest occurrence of SCD or appropriate ICD therapy was in patients with HMR being between 1.4 and 2.1, as opposed to those with HMR <1.4 or >2.1.[16] While part of the explanation may be a higher rate of pump failure deaths in patients with the lower HMRs, this observation likely also indicates that an intermediate HMR represents an increased substrate heterogeneity that predisposes to electrical instability.

TOMOGRAPHIC IMAGING AS A POTENTIALLY BETTER TOOL FOR ASSESSING SUBSTRATE ELECTRICAL HETEROGENEITY

Of course, one would expect tomographic imaging to be better than planar imaging for assessing such heterogeneity. In accordance with the notion of global adrenergic imaging perhaps being too blunt a tool for arrhythmic risk stratification, in reviewing data from over 600 patients, Verschure et al noted that while HMR effectively risk stratified in terms of cardiac mortality, all-cause mortality, and the need for transplant, it did not independently stratify arrhythmic events (ArEs).[17] Thus,

the finer tool of tomographic identification of focal adrenergic abnormalities should be a better approach. In a prospective study of 116 patients receiving an ICD, Boogers et al[18] found that a dysinnervation defect score above a particular threshold increased the likelihood of an appropriate discharge. However, a more recent subanalysis from ADMIRE-HF that undertook rigorous interpretation of tomographic images from patients with ischemic HF showed that although the occurrence of ArEs was significantly related to the dysinnervation defect score, the hazard ratio was <1 because arrhythmic risk was the highest in patients with intermediate defect scores as shown in Figure 2.[19] While further investigation is required to confirm and establish this concept, such findings suggest that methods used in perfusion imaging to risk stratify patients, i.e., interpreting defects that are larger and more severe as increasing risk, may not apply when using nonperfusion tracers for the characterization of pathology that is not coronary disease. A different paradigm, i.e., interpreting nuclear cardiac images from a different viewpoint, appears to be required.

POTENTIAL FOR DETERMINING ARRHYTHMIC RISK BY ASSESSMENT OF TRACER WASHOUT HETEROGENEITY

Another widely reported aspect of ^{123}I-*m*IBG image interpretation has been assessing dynamic changes over time by deriving washout (WO) measurements between early and delayed images. Henderson et al[20] first

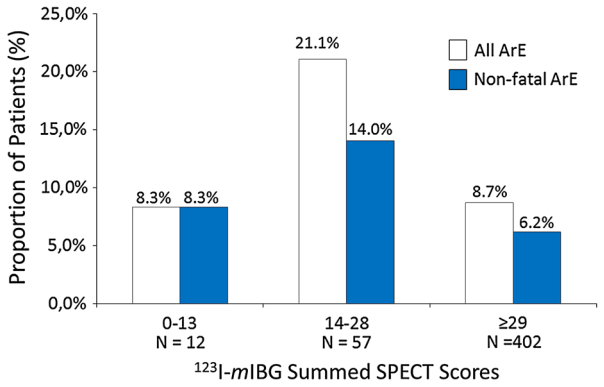

Figure 2. Proportion of arrhythmic events (ArEs) and nonfatal arrhythmic events in relation to low, intermediate, and, high 17-segment ^{123}I-*m*IBG scores. *Note* Nonfatal ArEs include only spontaneous sustained (>30 seconds) ventricular tachycardia, resuscitated cardiac arrest, and appropriate ICD activation. From Travin MI, Henzlova MJ, van Eck-Smit BLF, Jain J, Carrió I, Folks RD, Garcia EV, Jacobson AF, Verberne HJ. Assessment of ^{123}I-*m*IBG and ^{99m}Tc-tetrofosmin single-photon emission computed tomographic images for the prediction of arrhythmic events in patients with ischemic heart failure. J Nucl Cardiol; 2016; 24: 377-91, with permission of Springer.

described the presence of significantly higher ^{123}I-*m*IBG washout in patients with cardiomyopathy compared with healthy volunteers. Later work showed high WO to be associated with worsened survival[21] with potential ability to predict SCD better than many sophisticated electrocardiographic variables.[22]

The factors contributing to WO values are complex and multifactorial, involving uptake of tracer into the neuron, storage in vesicles, and transport in extraneuronal tissues,[20] as well as competition for pre-synaptic uptake receptors from circulating catecholamines[23] and augmented spillover from an accelerated sympathetic drive.[24] Various ways to derive WO rate have been described. Unfortunately, global WO measurements from planar imaging can be corrupted by overlying lung tracer uptake, and assessment of tomographic images is often impaired by extremely low counts in advanced HF.

Considering these concepts, in this issue of the journal, Yamamoto et al[25] present their findings from an investigation, in 73 patients who have HF with reduced ejection fraction, of the relationship between the regional variation of WO on SPECT ^{123}I-*m*IBG imaging, meant to reflect potential electrical heterogeneity of myocardial substrate, and the occurrence of SCD. Although patients in their report are derived from a study performed between 1995 and 1999 for another primary purpose, i.e., investigation of the HF-treatment efficacy of various medications, patients did undergo ^{123}I-*m*IBG imaging and were followed up over a mean of 7.5 years for occurrence of SCD that was defined as a ''witnessed cardiac arrest or death within 1 hour after the onset of acute symptoms or unexpected or unwitnessed death in a patient known to have been well within 24 hours,'' or development of sustained VT lasting ≥30 seconds on a series of periodic Holter monitors. It should be noted that the lack of proof that the deaths were arrhythmic in origin, and the fact that the patient did not necessarily have death from the VT episodes as observed on Holter monitors, does limit study conclusions.

For the characterization of SPECT regional WO abnormality, the authors used a calculated WO range defined as the difference between the maximum and the minimum WO values among 17 segments in their polar plot analyses, and the presence of ''abnormal regional'' WO defined as a segment having a value >2 standard deviations higher than a mean segment WO value derived from 15 ''control'' patients without HF. For 20.5% of the patients (N = 15) who subsequently had SCD (as defined by the authors), there was a higher WO range, and a significantly more frequent abnormal regional WO presence, as well as higher global WO, and lower delayed HMR on planar images. Survival

analysis showed that the presence of both an abnormally high global WO and an abnormal regional WO was associated with an overall death rate 6-fold higher than that for either alone. Multivariate analysis showed that abnormal regional and abnormal global WO values were significant and independent predictors of SCD, with both together being associated with a significantly higher ArE rate than that for none or either variable alone. On the contrary, conventional HF parameters, including serum creatinine, sodium, or NE, and especially LVEF, did not predict SCD.

Although there are significant limitations to this study, including a low number of patients, limited heterogeneity analytic techniques, issues related to SCD characterization, with study findings therefore being far from ready to be used for guidance of ICD management, the authors have made a commendable effort to advance the technique of using cardiac adrenergic imaging to improve arrhythmic risk stratification in HF patients. Their findings further support the contention that interpretation of adrenergic images for arrhythmic risk must be approached from a viewpoint different from what has conventionally been the case for perfusion imaging. Results of this study should encourage further development of algorithms to assess regional tomographic image heterogeneity, both for tracer uptake and washout, perhaps similar to the type of analyses done for gated SPECT phase analysis,[26] or maybe using a more complex technique such as fractal analysis.[27] In addition, imaging techniques that provide better resolution, such as a SPECT imaging with solid state cameras, or positron emission tomographic (PET) imaging with tracers such as ^{11}C-hydroxyephedrine (^{11}C-HED) that can better differentiate between innervated and denervated myocardium, promise better arrhythmic risk stratification.[28]

IMPORTANCE OF CLINICAL CONTEXT

When using image findings to predict events and management patients, it is of utmost importance to incorporate clinical data. Recently, Levy et al showed the potential for clinical parameters from the Seattle Proportional Risk Model to effectively predict occurrence of SCD, and thus better help determine the benefit of an ICD.[1] Another recent study showed that ICD use may not improve survival in most patients with nonischemic cardiomyopathies,[29] in which case ^{123}I-*m*IBG imaging may not be helpful at all, or conversely, that it may be a good way to identify a subset of such patients who would benefit. Thus, clinical context has to be considered when choosing the imaging technique (planar vs tomographic, SPECT vs PET) and interpreting the meaning of test findings for predicting arrhythmic risk, with more investigational data needed in this regard.

In addition, the likelihood of a particular adverse outcome varies with time.[30] Risk varies at different stages of a disease process, something that must be considered when using image findings to guide patient management. As a patient's clinical situation changes, especially if there is ischemic coronary disease, image findings may only apply for a limited period of time, after which repeat testing to update risk stratification may be necessary.

FINAL THOUGHTS

One cannot assume that techniques that have customarily been used to interpret myocardial perfusion imaging and guide management apply to other forms of radionuclide imaging. In particular, predicting arrhythmic risk with adrenergic imaging must consider underlying mechanisms, and thus one must view and interpret the images with this in mind.

Disclosure

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References

1. Levy WC, Li Y, Reed SD, Zile MR, Shadman R, Dardas T, for the HF-ACTION Investigators, et al. Does the implantable cardioverter-defibrillator benefit vary with the estimate proportional risk of sudden death in heart failure patients? JACC Clin Electrophysiol 2017;3:291–8. doi:10.1016/j.jacep.2016.09.006.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240–327.
3. Buxton AE, Lee KL, Hafley GE, Pires LA, Fisher JD, Gold MR, et al. Limitations of ejection fraction for prediction of sudden death risk in patients with coronary artery disease: Lessons from the MUSTT study. J Am Coll Cardiol 2007;50:1150–7.
4. Myerburg RJ. Implantable cardioverter-defibrillators after myocardial infarction. N Engl J Med 2008;359:2245–53.
5. Travin MI, Feng DL, Taub CC. Novel imaging approaches for predicting arrhythmic risk. Circ Cardiovasc Imaging 2015;8:e003019. doi:10.1161/CIRCIMAGING.115.003019.
6. Tomaselli GF, Zipes DP. What causes sudden death in heart failure? Circ Res 2004;95:754–63.
7. Raffel DM, Wieland DM. Development of mIBG as a cardiac innervation imaging agent. J Am Coll Cardiol Img 2010;3:111–6.
8. Minardo JD, Tuli MM, Mock BH, Weiner RE, Pride HP, Wellmann HN, Zipes DP. Scintigraphic and electrophysiologic evidence of canine myocardial sympathetic denervation and reinnervation produced by myocardial infarction or phenol application. Circulation 1988;78:1008–19.

9. Stanton MS, Tuli MM, Radtke NL, Heger JJ, Miles WM, Mock BH, Burt RW, Wellman HN, Zipes DP. Regional sympathetic denervation after MI in humans detected noninvasively using I-123-MIBG. J Am Coll Cardiol 1989;14:1519–26.
10. McGhie AI, Corbett JR, Akers MS, Kulkarni P, Sills MN, Kremers M, Buja M, Durant-Reville M, Parkey RW, Willerson JT. Regional cardiac adrenergic function using I-123 MIBG SPECT imaging after acute myocardial infarction. Am J Cardiol 1991;67:236–42.
11. Merlet P, Valette H, Dubois-Randé J, Moyse D, Duboc D, Dove P, Bourguignon MH, Benvenuti C, Duval AM, Agostini D, Loisance D, Castaigne A, Syrota A. Prognostic value of cardiac metaiodobenzylguanidine in patients with heart failure. J Nucl Med 1992;33:471–7.
12. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial 123I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: A systematic review. Eur Heart J 2008;29:1147–59.
13. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, on behalf of the ADMIRE_HF Investigators, 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;55:2212–21.
14. Chirumamilla A, Travin MI. Cardiac applications of ^{123}I-*m*IBG imaging. Semin Nucl Med 2011;41:374–87.
15. Hachamovitch R, Nutter B, Menon V, Cerqueira MD. Predicting risk versus predicting potential survival benefit using ^{123}I-*m*IBG imaging in patients with systolic dysfunction eligible for implantable cardiac defibrillator implantation. Analysis of data from the prospective ADMIRE-HF study. Circ Cardiovasc Imaging 2015;8:e003110. doi:10.1161/CIRCIMAGING.114.003110.
16. Verschure DO, de Groot JR, Mizrael S, Gheysens O, Nakajima K, van Eck-Smit BLF Cardiac ^{123}I-*m*IBG scintigraphy predicts freedom of appropriate ICD therapy in stable CHF patients. Eur Heart J Cardiovasc Imaging 2017;18:i49-i51, p.236. doi:10.1093/ehjci/jex079. Published: 09 May 2017. (https://academic.oup.com/ehjcimaging/article/18/suppl_1/i49/3806226/Moderated-Posters-session-Neurohumoral-imaging, accessed 6/11/17).
17. Verschure DO, Veltman CE, Manrique A, Somsen GA, Koutelou M, Katsikis 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;15:996–1003.
18. Boogers MJ, Borleffs CJ, Henneman MM, van Bommel RJ, van Ramshorst J, Boersma E, et al. Cardiac sympathetic denervation assessed with 123-Iodine metaiodobenzylguanidine imaging predicts ventricular arrhythmias in implantable cardioverter-defibrillator patients. J Am Coll Cardiol 2010;55:2769–77.
19. Travin MI, Henzlova MJ, van Eck-Smit BLF, Jain J, Carrió I, Folks RD, et al. Assessment of ^{123}I-*m*IBG and ^{99m}Tc-tetrofosmin single-photon emission computed tomographic images for the prediction of arrhythmic events in patients with ischemic heart failure. J Nucl Cardiol 2017;24:377–91.
20. Henderson EB, Kahn JK, Corbett JR, Jansen DE, Pippin JJ, Kulkarni P, et al. Abnormal I-123 metaiodobenzylguanidine myocardial washout and distribution may reflect myocardial adrenergic derangement in patients with congestive cardiomyopathy. Circulation 1988;78:1192–9.
21. Ogita H, Shimonagata T, Fukunami M, Kumagai K, Yamada T, Asano Y, et al. Prognostic significance of cardiac 123I metaiodobenzylguanidine imaging for mortality and morbidity in patients with chronic heart failure: A prospective study. Heart 2001;86:656–60.
22. Tamaki S, Yamada T, Okuyama Y, Morita T, Sanada S, Tsukamoto Y, et al. Cardiac iodine-123 Metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: Results from a comparative study with signal-averaged electrocardiogram, heart rate variability, and QT dispersion. J Am Coll Cardiol 2009;53:426–35.
23. Chen GP, Tabibiazar R, Branch KR, Link JM, Caldwell JH. Cardiac receptor physiology and imaging: An update. J Nucl Cardiol 2005;12:714–30.
24. Wakabayashi T, Nakata T, Hashimoto A, Yuda S, Tsuchihashi K, Travin MI, et al. Assessment of underlying etiology and cardiac sympathetic innervation to identify patients at high risk of cardiac events. J Nucl Med 2001;42:1757–67.
25. Yamamoto H, Yamada T, Tamaki S, Morita T, Furukuwa Y, Iwasaki Y, et al. Prediction of sudden cardiac death in patients with chronic heart failure by regional washout rate in cardiac MIBG SPECT imaging. J Nucl Cardiol 2017;12:1–9.
26. Chen J, Garcia EV, Bax JJ, Iskandrian AE, Borges-Neto S, Soman P. SPECT myocardial perfusion imaging for the assessment of left ventricular mechanical dyssynchrony. J Nucl Cardiol 2011;18:685–94.
27. Lopes R, Betrouni N. Fractal and multifractal analysis: A review. Med Image Anal 2009;13:634–49.
28. Fallavollita JA, Heavey BM, Luisi AJ Jr, Michalek SM, Baldwa S, Mashtare TL, et al. Regional myocardial sympathetic denervation predicts the risk of sudden cardiac arrest in ischemic cardiomyopathy. J Am Coll Cardiol 2014;63:141–9.
29. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, for the DANISH Investigators, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221–30.
30. Nakajima K, Nakata T, Matsuo S, Jacobson AF. Creating of mortality risk charts using ^{123}I meta-iodobenzylguanidine heart-to-mediastinum ratio in patients with heart failure: 2- and 5-year risk models. Eur Heart J CV Imaging 2016. doi:10.1093/ehjci/jev322.