Impact of adjunctive tolvaptan on sympathetic activity in acute heart failure with preserved ejection fraction

Shunsuke Tamaki*, Takahisa Yamada, Takashi Morita, Yoshio Furukawa, Masato Kawasaki, Atsushi Kikuchi, Tsutomu Kawai, Masahiro Seo, Makoto Abe, Jun Nakamura, Kyoko Yamamoto, Kiyomi Kayama, Masatsugu Kawahira, Kazuya Tanabe, Kunpei Ueda, Takanari Kimura, Daisuke Sakamoto, Yuto Tamura, Takeshi Fujita and Masatake Fukunami

Division of Cardiology, Osaka General Medical Center, Osaka, Japan

Abstract

Aims   Acute decompensated heart failure (ADHF) is generally treated by decongestion using diuretic therapy. However, the use of loop diuretics is associated with increased cardiac sympathetic nerve activity (CSNA). We aimed to evaluate the effect of adjunctive tolvaptan therapy on CSNA in ADHF patients with preserved left ventricular ejection fraction (LVEF).
Methods and results   We enrolled 51 consecutive ADHF patients with LVEF ≥45%. Patients were randomly assigned to receive either tolvaptan add-on (*n* = 25) or conventional diuretic therapy (*n* = 26). Cardiac iodine-123 metaiodobenzylguanidine (MIBG) imaging was performed after stabilisation of heart failure symptoms, and the cardiac MIBG heart-to-mediastinum ratio (HMR) and washout rate (WR) were calculated. There were no significant differences in the body weight change and total urine volume during 2 days after randomisation or in the HMR on delayed image (HMR(d)) and WR between the tolvaptan and conventional groups. After stratification based on the median change in body weight, the patients with higher weight reduction had a significantly lower HMR(d) (*P* = 0.0128) and tended to have a higher WR (*P* = 0.0786) in the conventional group, whereas the cardiac MIBG imaging results were not influenced by body weight reduction in the tolvaptan group.
Conclusions   Adjunctive tolvaptan therapy may provide rapid decongestion without a harmful effect on CSNA in ADHF patients with preserved LVEF.

Background

The mainstay of treatment for acute decompensated heart failure (ADHF) is decongestion by diuretic therapy mainly with loop diuretics,[1] although their use is associated with increased cardiac sympathetic nerve activity (CSNA).[2] On the other hand, tolvaptan, a selective oral vasopressin V2 receptor antagonist that induces aquaresis,[3] has been shown to provide decongestion without adversely affecting neurohumoral systems.[4]

Cardiac iodine-123 (^{123}I) metaiodobenzylguanidine (MIBG) imaging is the most widely used method to evaluate CSNA. The heart-to-mediastinum ratio (HMR) represents the distribution of neurons and function of the uptake-1 pathway, while the washout rate (WR) reflects the retention of norepinephrine by sympathetic neurons.[5] These parameters in cardiac MIBG imaging provide prognostic information in patients with heart failure (HF).[5,6]

Patients with HF with preserved left ventricular ejection fraction (LVEF) represent an increasing proportion of

hospitalisations for ADHF.[7] In patients with HF with preserved LVEF (HFpEF), increased CSNA has been shown to be associated with reduced functional capacity,[8] diastolic dysfunction,[9] and poor clinical outcomes.[10] However, the effect of tolvaptan therapy on CSNA in ADHF patients with preserved LVEF is unknown.

Aims

We sought to investigate whether the effect of decongestion by adjunctive tolvaptan therapy on CSNA would differ from that of conventional diuretic therapy in ADHF patients with preserved LVEF using cardiac MIBG imaging.

Methods

Study patients and protocol

This is a substudy of our prospective, single-centre, randomised, open-label study to evaluate the efficacy of tolvaptan add-on therapy compared with conventional diuretic therapy in ADHF patients with HFpEF.[11] This study conforms to the Declaration of Helsinki and was approved by the institutional ethics committee. All patients gave written informed consent.

A total of 51 consecutive ADHF patients with LVEF ≥45%,[12] who were admitted to our hospital and met the eligibility criteria, were enrolled. ADHF was defined as a gradual or rapid change in the signs and symptoms of HF sufficient to warrant hospitalisation.[13] HF was diagnosed according to the Framingham criteria.[14] The details of the inclusion and exclusion criteria have been described previously.[11]

Eligible patients were enrolled within 6 h of admission. Enrolled patients were randomly assigned in a 1:1 ratio to receive either tolvaptan add-on therapy (TLV(+)) or conventional diuretic therapy (TLV(−)) according to a computer-generated block randomisation table (four per block). Tolvaptan was started at an initial dose of 7.5 mg/day, and the maximum dose was set at 15.0 mg/day. The choice of therapy including the up-titration or down-titration of tolvaptan was left at the discretion of each primary physician. The total furosemide-equivalent dose of loop diuretics was calculated according to previous reports.[11]

Data collection

Transthoracic echocardiography was performed according to standard techniques using a commercially available machine as previously reported.[15] Body weight and daily total urine output were measured every day. Blood sampling was

performed at baseline and 6, 12, 24, and 48 h after randomisation. The serum sodium level was also measured. The occurrence of hypernatraemia was defined as previously reported.[16] Cardiac MIBG imaging was performed after the stabilisation of HF symptoms (14.7 ± 5.7 days after admission). No patient was taking drugs known to interfere with MIBG uptake on the day of cardiac MIBG imaging. All patients underwent myocardial imaging with ^{123}I-MIBG (MyoMIBG-I 123 Injection; FUJIFILM Toyama Chemical, Tokyo, Japan) using a conventional rotating gamma camera (BrightView; Philips, Amsterdam, The Netherlands) equipped with a low-energy type cardiac high-resolution collimator. Patients were placed in the supine position. A 111 MBq dose of ^{123}I-MIBG was injected intravenously at rest after an overnight fast. Initial and delayed image acquisitions were performed in the anterior chest view 20 and 200 min after isotope injection. All images were reviewed by two independent observers who were blinded to the clinical data. As previously reported,[17] HMR(e) and HMR(d) were determined from the counts/pixel in a visually drawn region of interest over the entire left ventricular myocardium divided by the counts/pixel in a 7 × 7 pixel region of interest placed in the upper mediastinum. The cardiac WR of MIBG was calculated from the initial and delayed images with the correction for radioactive decay of ^{123}I and background subtraction.

Endpoints

The primary endpoint was the difference in the results of cardiac MIBG imaging. Secondary endpoints included changes in body weight and total urine volume during 2 days after randomisation and the total furosemide-equivalent dose of loop diuretics used within 48 h of randomisation.

Statistical analysis

Data are presented as the mean ± standard deviation. The Student's *t*-test and Fisher's exact test were used to compare differences in continuous and discrete variables, respectively. Correlations between variables were determined by Pearson's correlation coefficient. A *P* value < 0.05 was considered significant. Statistical analysis was performed with a standard statistical program package (MedCalc Statistical Software version 19, MedCalc Software bvba, Ostend, Belgium).

Results

A total of 51 patients were included in this study. There were no significant differences in the baseline characteristics of the two groups (*Table 1*). Within 48 h of randomisation, the total

Table 1 Baseline characteristics of the study patients with and without tolvaptan

Characteristic	All (n = 51)	TLV(+) group (n = 25)	TLV(−) group (n = 26)	P value
Age (years)	76 ± 9	78 ± 7	75 ± 10	0.2444
Male sex (%)	43	44	42	0.9999
NYHA class IV (%)	82	88	77	0.4654
Body weight (kg)	58.3 ± 13.8	56.5 ± 12.2	60.1 ± 15.1	0.3622
Body mass index (kg/m^2)	24.0 ± 4.2	23.1 ± 3.5	24.9 ± 4.7	0.1428
Atrial fibrillation (%)	37	44	31	0.3929
Hypertension (%)	94	92	96	0.6098
Coronary artery disease (%)	31	32	31	0.9999
Diabetes mellitus (%)	53	44	62	0.2668
COPD (%)	4	4	4	0.9999
Prior HF hospitalisation (%)	24	28	19	0.5230
Oral medications				
Loop diuretics (%)	55	56	54	0.9999
Spironolactone (%)	16	16	15	0.9999
ACE inhibitor/ARB (%)	45	40	50	0.5771
β-blocker (%)	57	60	54	0.7793
Intravenous agents				
Vasodilators (%)	75	72	77	0.7554
Carperitide (%)	14	8	19	0.4189
NPPV (%)	20	20	19	0.9999
Heart rate (beats/min)	86 ± 22	85 ± 22	88 ± 23	0.7039
Systolic blood pressure (mmHg)	133 ± 20	130 ± 20	136 ± 19	0.3501
Diastolic blood pressure (mmHg)	64 ± 13	65 ± 11	64 ± 15	0.6552
Echocardiography				
LVEDD (mm)	48 ± 7	47 ± 6	50 ± 8	0.1069
LVEF (%)	62 ± 9	63 ± 10	60 ± 8	0.2639
LAD (mm)	44 ± 8	45 ± 6	43 ± 9	0.3687
E/e'	15.1 ± 6.0	15.8 ± 6.0	14.3 ± 6.0	0.4192
Haemoglobin (g/dL)	10.8 ± 1.9	10.8 ± 1.8	10.8 ± 2.0	0.8711
Sodium (mEq/L)	139 ± 4	138 ± 4	139 ± 3	0.5256
Potassium (mEq/L)	4.0 ± 0.6	4.0 ± 0.7	3.9 ± 0.6	0.8302
Creatinine (mg/dL)	1.39 ± 1.27	1.36 ± 1.33	1.42 ± 1.24	0.8733
BUN (mg/dL)	27.5 ± 15.6	28.0 ± 15.7	27.2 ± 15.8	0.8559
eGFR (mL/min/1.73 m^2)	47.3 ± 21.3	48.6 ± 23.2	46.2 ± 19.8	0.6897
BNP (pg/mL)	692 ± 568	687 ± 546	696 ± 599	0.9534

ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; E/e', a ratio of the peak transmitral velocity during early diastole to the peak mitral valve annular velocity during early diastole; eGFR, estimated glomerular filtration rate; HF, heart failure; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NPPV, non-invasive positive pressure ventilation; NYHA, New York Heart Association; TLV, tolvaptan.
Data are presented as the mean value ± SD or percentage of patients.

dose of tolvaptan in the TLV(+) group was 27.6 ± 7.7 mg. The total furosemide-equivalent dose of loop diuretics used in the TLV(+) group was 18.0 ± 27.7 mg, which was significantly lower than that in the TLV(−) group (118.5 ± 56.0 mg, $P < 0.0001$).

There was no significant difference in the change in body weight (−2.9 ± 1.7 kg vs. −3.2 ± 1.8 kg, $P = 0.5769$) and total urine volume (4199 ± 1550 mL vs. 4019 ± 1422 mL, $P = 0.6704$) during 2 days after randomisation between the TLV(+) and TLV(−) groups. The change in serum sodium level between baseline and 6 (1.7 ± 1.7 mEq/L vs. 0.3 ± 1.6 mEq/L, $P = 0.0040$), 12 (2.3 ± 1.8 mEq/L vs. 0.8 ± 1.8 mEq/L, $P = 0.0037$), 24 (2.5 ± 3.2 mEq/L vs. 0.7 ± 2.5 mEq/L, $P = 0.0287$), and 48 h (1.8 ± 3.3 mEq/L vs. −0.4 ± 3.1 mEq/L, $P = 0.0167$) after randomisation was significantly higher in the TLV(+) group than in the TLV(−) group. Although one patient in the TLV(+) group developed hypernatraemia 12 h after randomisation, the serum sodium level returned to normal 48 h after randomisation with no sequelae.

There was no significant difference in the HMR(e) (2.05 ± 0.41 vs. 1.97 ± 0.40, $P = 0.4929$), HMR(d) (1.77 ± 0.33 vs. 1.79 ± 0.37, $P = 0.8937$), and WR (36.1 ± 12.4% vs. 31.7 ± 14.6%, $P = 0.2517$) between the TLV(+) and TLV(−) groups. However, when the patients were stratified based on the median change in body weight during 2 days after randomisation (−2.5 kg in TLV(+) group and −3.0 kg in TLV(−) group), those with higher body weight reduction had a significantly lower HMR(e) and HMR(d) and tended to have a higher WR in the TLV(−) group. In contrast, the cardiac MIBG imaging results were not influenced by the extent of weight reduction in the TLV(+) group (*Figure 1*). Moreover, there was an inverse correlation between HMR(d) and the total furosemide-equivalent dose of loop diuretics used in the TLV(−) group ($r = −0.415$, $P = 0.0352$) but not in the TLV(+) group. There was no significant difference in the total furosemide-equivalent dose of loop diuretics between the patients with higher body weight reduction and those with lower body weight reduction in both the TLV(+)

Figure 1 Results of cardiac metaiodobenzylguanidine imaging in the tolvaptan and conventional groups. Patients were stratified according to the median change in body weight during 2 days after randomisation. HMR(d), the heart-to-mediastinum ratio on delayed images; HMR(e), the heart-to-mediastinum ratio on early images; TLV, tolvaptan; WR, washout rate of cardiac metaiodobenzylguanidine
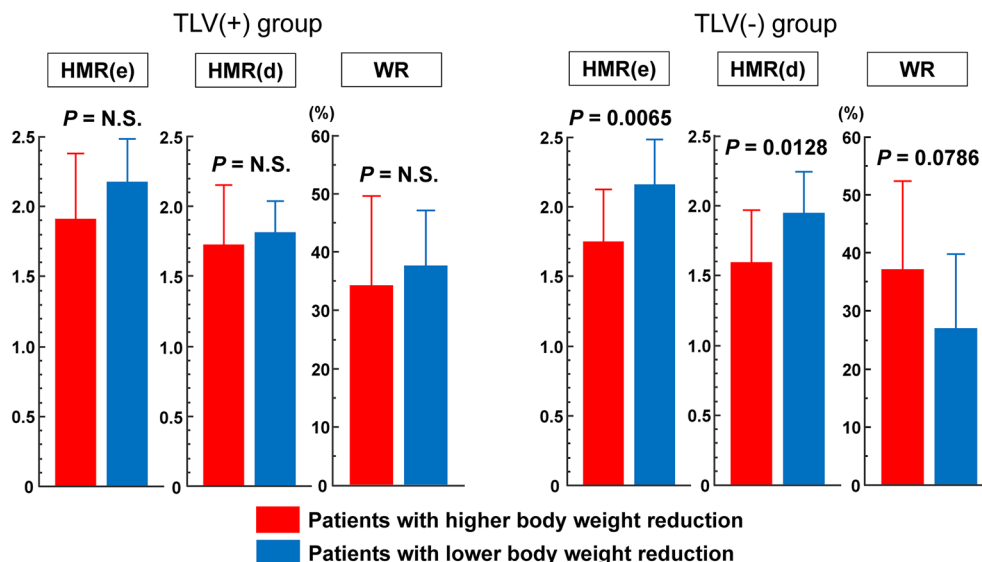
(21.3 ± 33.1 mg vs. 15.0 ± 22.5 mg, P = 0.5777) and the TLV(−) (122.9 ± 71.8 mg vs. 114.9 ± 40.4 mg, P = 0.7245) groups.

Conclusions

To the best of our knowledge, this is the first study to compare the effect of adjunctive tolvaptan therapy and conventional diuretic therapy on CSNA in ADHF patients with preserved LVEF using cardiac MIBG imaging. Our study demonstrated that rapid decongestion was associated with increased CSNA in ADHF patients receiving conventional diuretic therapy but not in those receiving tolvaptan add-on therapy.

Because residual congestion at discharge is associated with poor clinical outcomes, aggressive decongestive therapy during hospitalisation is thought to be important in ADHF patients.[18] However, controversy exists as to whether rapid decongestion in the early phase of ADHF admission is associated with better clinical outcomes.[19,20] Increased CSNA is associated with poor prognosis in HF patients[21] and even in patients with HFpEF.[10] Our results suggest that, in ADHF patients with preserved LVEF, rapid decongestion by conventional diuretic therapy might not be necessarily associated with better prognosis because of increased CSNA.

Unlike loop diuretics, tolvaptan has been shown to provide decongestion without adversely affecting neurohumoral systems.[4] Our study further demonstrated that the extent of decongestion in the early phase of adjunctive tolvaptan therapy had no significant effect on CSNA in ADHF patients

with preserved LVEF. Although the exact mechanism remains unknown, intravascular volume depletion caused by loop diuretics and rapid volume removal might have synergistically resulted in increased CSNA in the TLV(−) group, while in the TLV(+) group, a reduction in the use of loop diuretics and the aquaretic effect of tolvaptan might have prevented further intravascular volume depletion which can induce reflective CSNA. The direct effect of tolvaptan therapy on CSNA is likely to be small, as there was no significant difference in the results of cardiac MIBG imaging between the two groups. However, our results imply that tolvaptan add-on therapy might be a potential therapeutic option for rapid decongestion without a harmful effect on CSNA in ADHF patients with preserved LVEF.

Our study has several limitations. This was a single-centre, open-label study with a small sample size. Subgroups according to body weight change were not prospectively defined. Further studies to validate our findings are needed.

Conflict of interest

All authors declare that they have no relevant conflict of interest.

Funding

References

1. Peacock WF, Costanzo MR, De Marco T, Lopatin M, Wynne J, Mills RM, Emerman CL, Committee ASA, Investigators. Impact of intravenous loop diuretics on outcomes of patients hospitalized with acute decompensated heart failure: insights from the AD-HERE registry. *Cardiology* 2009; **113**: 12–19.
2. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med* 1985; **103**: 1–6.
3. Fukunami M, Matsuzaki M, Hori M, Izumi T, Tolvaptan I. Efficacy and safety of tolvaptan in heart failure patients with sustained volume overload despite the use of conventional diuretics: a phase III open-label study. *Cardiovasc Drugs Ther* 2011; **25**: S47–S56.
4. Costello-Boerrigter LC, Smith WB, Boerrigter G, Ouyang J, Zimmer CA, Orlandi C, Burnett JC Jr. Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. *Am J Physiol Renal Physiol* 2006; **290**: F273–F278.
5. van der Veen BJ, Al Younis I, de Roos A, Stokkel MP. Assessment of global cardiac I-123 MIBG uptake and washout using volumetric quantification of SPECT acquisitions. *J Nucl Cardiol* 2012; **19**: 752–762.
6. Nakajima K, Nakata T, Matsuo S, Jacobson AF. Creation of mortality risk charts using 123I meta-iodobenzylguanidine heart-to-mediastinum ratio in patients with heart failure: 2- and 5-year risk models. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 1138–1145.
7. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC, Get With the Guidelines Scientific Advisory C, Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation* 2012; **126**: 65–75.
8. Messias LR, Messias AC, de Miranda SM, Wiefels CC, Ferreira AG, Santos LM, Teixeira JA, Marostica E, Mesquita CT. Abnormal adrenergic activation is the major determinant of reduced functional capacity in heart failure with preserved ejection fraction. *Int J Cardiol* 2016; **203**: 900–902.
9. Aikawa T, Naya M, Obara M, Manabe O, Tomiyama Y, Magota K, Yamada S, Katoh C, Tamaki N, Tsutsui H. Impaired myocardial sympathetic innervation is associated with diastolic dysfunction in heart failure with preserved ejection fraction: (11)C-hydroxyephedrine PET study. *J Nucl Med* 2017; **58**: 784–790.
10. Katoh S, Shishido T, Kutsuzawa D, Arimoto T, Netsu S, Funayama A, Ishino M, Niizeki T, Nishiyama S, Takahashi H, Miyashita T, Miyamoto T, Nitobe J, Watanabe T, Kubota I. Iodine-123-metaiodobenzylguanidine imaging can predict future cardiac events in heart failure patients with preserved ejection fraction. *Ann Nucl Med* 2010; **24**: 679–686.
11. Tamaki S, Sato Y, Yamada T, Morita T, Furukawa Y, Iwasaki Y, Kawasaki M, Kikuchi A, Kondo T, Ozaki T, Seo M, Ikeda I, Fukuhara E, Abe M, Nakamura J, Fukunami M. Tolvaptan reduces the risk of worsening renal function in patients with acute decompensated heart failure and preserved left ventricular ejection fraction—prospective randomized controlled study. *Circ J* 2017; **81**: 740–747.
12. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM, Investigators T. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; **370**: 1383–1392.
13. Gheorghiade M, Zannad F, Sopko G, Klein L, Pina IL, Konstam MA, Massie BM, Roland E, Targum S, Collins SP, Filippatos G, Tavazzi L, International Working Group on Acute Heart Failure S. Acute heart failure syndromes: current state and framework for future research. *Circulation* 2005; **112**: 3958–3968.
14. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971; **285**: 1441–1446.
15. Tamaki S, Mano T, Sakata Y, Ohtani T, Takeda Y, Kamimura D, Omori Y, Tsukamoto Y, Ikeya Y, Kawai M, Kumanogoh A, Hagihara K, Ishii R, Higashimori M, Kaneko M, Hasuwa H, Miwa T, Yamamoto K, Komuro I. Interleukin-16 promotes cardiac fibrosis and myocardial stiffening in heart failure with preserved ejection fraction. *PLoS ONE* 2013; **8**: e68893.
16. Kinugawa K, Sato N, Inomata T, Yasuda M, Shibasaki Y, Shimakawa T. Novel risk score efficiently prevents tolvaptan-induced hypernatremic events in patients with heart failure. *Circ J* 2018; **82**: 1344–1350.
17. Ogita H, Shimonagata T, Fukunami M, Kumagai K, Yamada T, Asano Y, Hirata A, Asai M, Kusuoka H, Hori M, Hoki N. Prognostic significance of cardiac (123)I metaiodobenzylguanidine imaging for mortality and morbidity in patients with chronic heart failure: a prospective study. *Heart* 2001; **86**: 656–660.
18. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC Jr, Grinfeld L, Udelson JE, Zannad F, Gheorghiade M, Investigators ET. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013; **34**: 835–843.
19. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S, Okumura T, Kida K, Mizuno A, Oishi S, Inuzuka Y, Akiyama E, Matsukawa R, Kato K, Suzuki S, Naruke T, Yoshioka K, Miyoshi T, Baba Y, Yamamoto M, Murai K, Mizutani K, Yoshida K, Kitai T. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017; **69**: 3042–3051.
20. Park JJ, Kim SH, Oh IY, Choi DJ, Park HA, Cho HJ, Lee HY, Cho JY, Kim KH, Son JW, Yoo BS, Oh J, Kang SM, Baek SH, Lee GY, Choi JO, Jeon ES, Lee SE, Kim JJ, Lee JH, Cho MC, Jang SY, Chae SC, Oh BH. The effect of door-to-diuretic time on clinical outcomes in patients with acute heart failure. *JACC Heart Fail* 2018; **6**: 286–294.
21. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, Agostini D, Weiland F, Chandna H, Narula J, Investigators A-H. 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**: 2212–2221.