ESC HEART FAILURE
ESC Heart Failure 2017; **4**: 499–506
Published online 19 April 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12153

ORIGINAL RESEARCH ARTICLE

Beta blocker dose and markers of sympathetic activation in heart failure patients: interrelationships and prognostic significance

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Abstract

Aims Extent of cardiac sympathetic activation can be estimated from physiological parameters, blood biomarkers, and imaging findings. This study examined the prognostic value of three markers of sympathetic activity and their relationship to beta blocker dose in heart failure patients.

Methods and results A *post hoc* analysis of 858 heart failure subjects in the ADMIRE-HF trial was performed. Variables related to sympathetic activity were plasma norepinephrine, baseline heart rate, the heart to mediastinum (H/M) ratio of ^{123}I-*m*IBG uptake, and beta blocker dose. Univariate and multivariate analyses for occurrence of mortality (all-cause and cardiac) and arrhythmic events were performed. Beta blocker dose was significantly related to age, heart rate, b-type natriuretic peptide (negatively), body mass index, body weight and plasma norepinephrine. Univariate predictors of all-cause and cardiac mortality were baseline heart rate (χ^2 = 4.5, P = 0.029 and χ^2 = 5 .2, P = 0.022, respectively), plasma norepinephrine level (χ^2 = 8.9, P = 0.0006 and χ^2 = 8.6, P = 0.003, respectively), and H/M (χ = 22.4, $P < 0.0001$ and χ^2 = 17.8, $P < 0.0001$, respectively). In multivariate analyses, carvedilol-equivalent dose (P = 0.017), plasma norepinephrine (P = 0.002), and H/M (P = 0.0001) were significant predictors of all-cause mortality. In separate analyses using multiple measurements of heart rate, mean heart rate >67 b.p.m. was associated with significantly higher cardiac mortality.

Conclusions Higher beta blocker dose was associated with lower mortality, but of the variables associated with sympathetic activity examined, cardiac ^{123}I-*m*IBG uptake was the most powerful prognostic marker in heart failure patients. Elevated heart rate was associated with greater risk for cardiac death.

Keywords ^{123}I-*m*IBG; Heart failure; Prognosis; Norepinephrine; Heart rate; Beta blocker

Received: 21 December 2015; Revised: 13 February 2017; Accepted: 17 February 2017
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Introduction

In chronic heart failure (HF), increased myocardial sympathetic activity is associated with progressive alteration in left ventricular function and increased risk of ventricular arrhythmias and sudden cardiac death.[1] Methods proposed to quantify cardiac sympathetic activity include biomarkers such as plasma norepinephrine, changes in heart rate and blood pressure with alteration in body habitus (standing and tilt-table testing) or in response to the Valsalva manœuvre,[2] and variations in electrocardiogram parameters at rest and stress.[3]

Increased neuronal release of norepinephrine is usually accompanied by decreased neuronal norepinephrine reuptake and increase in norepinephrine concentration in the sympathetic synaptic cleft with desensitization of myocardial beta-adrenoceptors. Plasma norepinephrine is a systemic prognostic marker,[4,5] but cardiac uptake of the norepinephrine analogue iodine-123–labelled *meta*-iodobenzylguanidine (^{123}I-*m*IBG) allows more direct assessment of cardiac denervation which has a greater prognostic value in HF patients.[6,7]

Heart rate is a simple and prognostic surrogate of sympathetic activity,[8,9] but its value depends on numerous factors

besides sympathetic activation. Exercise heart rate and heart rate variability are other indirect markers that reflect the balance between sympathetic and parasympathetic activities,[10] but they are not routinely measured.

There is increasing appreciation of the importance of heart rate control in improving HF patient prognosis, with such control most often achieved through use of beta blockers. Target beta blocker doses are usually based on results of randomized, controlled trials[11,12] rather than any marker of sympathetic drive, but studies and registries have shown these doses are not always used in clinical practice.[13,14] While there may be a dose-response relationship between beta blocker dose and hard outcomes,[15] a recent meta-analysis showed that outcome in HF was more related to heart rate achieved with beta blockers than with the achieved dose.[16] Clinical registries[17] and recent studies of non-beta blocker drugs (ivabradine) have shown that heart rate is associated with outcome, even after adjustment for other risk factors.[8]

The relative importance of high beta blocker dose, a lower heart rate, or a decrease in plasma norepinephrine during HF treatment is not established. The objectives of the present study were as follows:

(i) to compare HF patient characteristics regarding indices of sympathetic activity according to beta blocker doses
(ii) to assess the prognostic value of the dose of beta blocker for « hard » events (ventricular arrhythmias, cardiac death, all-cause mortality) and compare it to that of 3 indirect markers of sympathetic activity: heart rate, plasma norepinephrine and ^{123}I-*m*IBG heart/mediastinum (H/M) ratio.

Methods

This was a *post hoc* analysis of ADMIRE-HF data; main study results have been published.[18] In brief, ADMIRE-HF enrolled 985 stable (no recent hospitalization or cardiac procedures within 30 days) HF patients [New York Heart Association (NYHA) class II/III] with left ventricular ejection fraction (LVEF) $\leq$35%. Ninety-two per cent of the subjects were receiving beta blockers. Baseline evaluations included multiple measurements of resting heart rate prior to and on the day of ^{123}I-*m*IBG imaging, plasma norepinephrine from a blood sample drawn at rest during a screening visit prior to the ^{123}I-*m*IBG imaging day, and ^{123}I-*m*IBG H/M measurements.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the institutional review boards and ethics committees at each centre. All subjects signed informed consent before performance of any procedures.

The original ADMIRE-HF study design only included recording of the names of concomitant medications. For the present study, investigators were requested to review available records and provide the total daily doses of all cardiac medications included on the original study case report forms. Some investigators declined to participate in this data collection effort, and records for a small number of subjects could not be located. Dosing data for some subjects were obtained from review of case report forms and source documents submitted as part of the adjudication process in the original study.

Of the 961 subjects with efficacy data (24 subjects were removed for protocol violations or incomplete imaging data), beta blocker dosing data were submitted for 707 subjects. Data for an additional 73 subjects were obtained through records review. The analyses for these 780 subjects and the 78 who were not taking beta blockers (total of 89% of the efficacy population) provide the basis of the present report.

Beta blockers used by the 780 study subjects were as follows: carvedilol: 438, metoprolol: 211, bisoprolol: 99, atenolol: 28, nebivolol: 3; propranolol: 1. Beta blocker dosages were converted into carvedilol-equivalent doses[19] using the factors presented in *Table 1*. Analyses were then performed using dose as a continuous variable and in quartiles.

Outcome

Adjudication of events was performed as previously described.[18] All deaths were categorized as either cardiac or non-cardiac in origin. Cardiac deaths were further subcategorized as sudden (SCD) or non-sudden (because of HF progression, acute MI, etc).

During the follow-up period of 2 days to 30.4 months (median 17 months), 63 subjects experienced non-fatal arrhythmic events (sustained ventricular tachycardia, resuscitated cardiac arrest, and appropriate implantable cardioverter-defibrillator activation) and 77 died. Fifty deaths were adjudicated as cardiac, with 21 subcategorized as SCD (including one subject with a prior non-fatal arrhythmic event).

The prognostic value of four variables (baseline heart rate, plasma norepinephrine, beta blocker dose, and 4-hour ^{123}I-*m*IBG H/M ratio) was assessed in relation to the three endpoints. Analyses were performed using a single heart rate determination immediately prior to ^{123}I-*m*IBG

Table 1 Carvedilol equivalent doses of beta blockers

Drug	Conversion factor to carvedilol (x mg drug : y mg carvedilol)
Atenolol	3:1 (12.5 mg increments)
Bisoprolol	1:5 (5 mg increments)
Carvedilol	6.25 mg increments
Metoprolol tartrate	5:1 (50 mg increments)
Metoprolol succinate	4:1 (25 mg increments)
Nebivolol	1:5 (2.5 mg increments)
Propranolol	4:1 (40 mg increments)

administration and the mean value of multiple independent heart rate determinations from screening and imaging day safety evaluations. Analyses for the latter were performed with the mean heart rate treated as a continuous variable and in quartiles. Selected analyses were performed for the total study population (n = 961) and for the subpopulation with known beta blocker doses (n = 780).

Statistics

Baseline characteristics were summarized by counts and percentages for categorical variables and by means ± SD for continuous variables. Comparisons of continuous variables and quartiles of beta blocker doses were done using one-way analysis of variance. Comparisons of categorical variables were performed using χ^2 tests. The unadjusted relationships between beta blocker dose at baseline and patient characteristics and outcome endpoints were explored with Cox and linear regression models. For the three endpoints (cardiac death, all cause death, and arrhythmic events), predictive models were developed with the four variables of interest: heart rate (continuous variable), plasma norepinephrine (continuous variable, available in 744 beta blocker and 72 non-beta blocker patients), beta blocker dose (expressed as carvedilol-equivalent dose, continuous variable), and H/M ratio (continuous variable). Cox proportional hazards modelling was used to assess the relationship between outcomes and beta blocker dose as a continuous variable before and after adjustment for the variables found to be significantly associated with each endpoint. Kaplan–Meier survival analyses were performed to estimate 2-year event probabilities, with differences between groups assessed using the log-rank test.

A P value <0.05 was considered statistically significant for all comparisons. All analyses were performed using Medcalc v12.6-13.0 (Medcalc Software, Ostend, Belgium).

Results

Determinants of beta blocker dosage

Seven hundred eighty subjects had known baseline doses of beta blockers, 103 were using beta blockers of unknown dose, and 78 were not receiving beta blockers. Among subjects using beta blockers, those with unknown doses were more likely to be using aldosterone antagonists (*Table 2*). Compared with subjects with known beta blocker doses, subjects not receiving beta blockers were older and had lower body mass indexes (BMIs). All other demographic, medical history, and medication use characteristics for these two groups were not statistically different (*Table 2*). There was no significant difference in 2-year Kaplan–Meier mortality rates among subjects taking the three most commonly used beta blockers [carvedilol: 12.7%; metoprolol: 10.5%; bisoprolol: 7.3% (P = 0.27)].

Using quartiles of beta blocker doses, subjects receiving the highest doses were younger, had greater body weight and BMI, had more often HF of non-ischaemic aetiology, were less likely to have chronic obstructive pulmonary disease, had lower b-type natriuretic peptide (BNP), had more often been implanted with an implantable

Table 2 Baseline characteristics of subjects with and without beta blockers

	Mean ± SD or proportion			*P* value	
Variable or characteristic	Known beta blocker dose (n = 780)	Using beta blockers, dose unknown (n = 103)	Not using beta blocker (n = 78)	Known vs. unknown beta dose	Known vs. no beta blocker
Age	62.0 ± 12.0	61.4 ± 11.4	68.0 ± 9.2	0.68	<0.0001
Gender, male (%)	80.1	76.7	71.8	0.50	0.11
Race: white; black; other (%)	74.9; 14.2; 10.9	79.6; 15.5; 4.9	78.2; 7.7; 14.1	0.36	0.61
Body mass index (kg/m^2)	29.2 ± 6.1	29.8 ± 6.2	27.7 ± 6.2	0.35	0.039
ACE inhibitors/ARB (%)	94.0	95.2	91.0	0.79	0.43
Lipid lowering agents (%)	73.7	75.7	76.9	0.75	0.63
Aldosterone antagonist (%)	34.3	51.5	29.5	0.001	0.47
Diabetes (%)	36.0	37.9	44.9	0.79	0.15
Hypertension (%)	64.5	57.3	64.1	0.79	0.96
Smoker, current or past (%)	73.9	70.9	75.6	0.60	0.85
Dyslipidemia (%)	72.4	71.8	71.8	0.99	0.98
Heart failure: NYHA Class II, III (%)	82.7, 17.3	87.4, 12.6	83.3, 16.7	0.29	0.98
Heart failure: Ischaemic, non-ischaemic (%)	66.0, 34.0	67.0, 33.0	76.9, 23.1	0.93	0.07
LVEF (%)	27.1 ± 6.2	26.5 ± 5.6	27.3 ± 5.9	0.35	0.79
BNP (ng/L; n = 833)	267.8 ± 397.4	207.8 ± 283.0	271.4 ± 375.5	0.16	0.94
Plasma norepinephrine (pg/mL) (n = 816)	674.1 ± 373.7	622.6 ± 326.7	606.4 ± 302.5	0.21	0.14
H/M	1.44 ± 0.20	1.44 ± 0.16	1.40 ± 0.24	1.00	<0.0001

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BNP, b-type natriuretic peptide; H/M, heart to mediastinum ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

DOI: 10.1002/ehf2.12153

cardioverter-defibrillator, and were more likely to be receiving an aldosterone antagonist (*Table 3*). Although severity of HF as reflected by BNP was greater in subjects with low beta blocker doses, this difference was not seen in terms of NYHA clinical classes [mean (SD) carvedilol-equivalent dose (mg): NYHA class II: 24.9 (19.8); NYHA class III: 27.5 (19.6); $P = 0.15$].

In a regression analysis of beta blocker dose and covariates (*Table 4*), beta blocker dose was significantly related to age, baseline heart rate, BNP (negatively) and BMI, body weight, and (borderline) plasma norepinephrine.

Univariate analyses of outcome

By the univariate Cox proportional hazards method, beta blocker dose was a weak predictor of all-cause mortality ($\chi^2 = 5.2$, $P = 0.032$). Beta blocker dose was not a predictor of cardiac death or arrhythmic events.

Of the other candidate variables, all were predictors of all-cause and cardiac mortality: heart rate (single determination: $\chi^2 = 4.5$, $P = 0.029$ and $\chi^2 = 5.2$, $P = 0.022$, respectively; mean of multiple determinations: $\chi^2 = 4.1$, $P = 0.043$ and $\chi^2 = 5.3$, $P = 0.016$, respectively); plasma norepinephrine level ($\chi^2 = 8.9$, $P = 0.0006$ and $\chi^2 = 8.6$, $P = 0.003$, respectively); and H/M ($\chi^2 = 22.4$, $P < 0.0001$ and $\chi^2 = 17.8$, $P < 0.0001$, respectively).

Table 4 Regression analysis between beta blocker dose and various covariates.

Covariate	Regression coefficient of covariate to beta blocker dosage (carvedilol-equivalent)	*P* value
Age (years)	−0.301	<0.0001
BMI (kg/m^2)	0.479	<0.0001
LVEF (%)	−0.040	0.726
HR (b.p.m.) (Single determination)	−0.108	0.047
Mean HR (b.p.m.) (Multiple determinations)	−0.112	0.054
SBP (mmHg)	−0.021	0.565
Weight (kg)	0.141	<0.0001
Plasma Norepinephrine (ng/mL)	0.0002	0.923
BNP (ng/L)	−0.005	0.003
H/M	−3.58	0.308

BMI, body mass index; BNP, b-type natriuretic peptide; HR, heart rate; H/M, heart to mediastinum ratio; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Multivariate analyses

In previous ADMIRE-HF multivariate analyses for predictors of death, use of HF medications (angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta blockers, and aldosterone receptor antagonists) did not affect the final models.[18,29] To examine for interactions between HF medications and the four variables used in the present study,

Table 3 Characteristics of subjects (mean values for continuous variables) based on quartiles of beta blocker doses

	Q1	Q2	Q3	Q4	*P*
Carvedilol-equivalent dose (mg)	1.25–12	12.5–19	20–37.5	38–150	
Number of Subjects	186	187	210	197	—
Age (years)	65.0	62.7	62.0	58.5	<0.001
BMI (kg/m^2)	28.6	28.2	29.5	30.5	0.001
Female (%)	16.7	20.9	17.1	19.8	0.666
LVEF (%)	27.0	27.0	27.7	26.8	0.479
Creatinine (mg/dL)	1.21	1.18	1.20	1.20	0.906
eGFR (mL/min)	66.4	69.1	68.5	71.4	0.157
NYHA II (%)	87.6	82.4	79.0	79.7	0.113
Ischaemic aetiology (%)	78.5	61.0	64.3	55.8	<0.0001
Diabetes (%)	39.2	31.0	37.1	35.5	0.392
COPD (%)	13.4	7.0	12.9	5.6	0.013
HR (b.p.m.) (single determination)	69.0	67.8	67.6	65.8	0.109
Mean HR (bpm) (minimum of five determinations)	68.9	67.8	67.8	66.2	0.170
SBP (mmHg)	123.7	122.1	125.3	122.0	0.260
DBP (mmHg)	72.8	72.7	74.2	72.9	0.491
Weight (kg)	85.5	84.0	88.9	92.4	<0.001
Plasma norepinephrine (pg/mL)	637.3	695.1	680.9	681.9	0.492
BNP (ng/L)	335.5	291.1	243.9	209.8	0.014
(Baseline treatment)					
ACE-I/ARB (%)	91.9	94.1	96.7	93.4	0.237
ICD (baseline) (%)	11.3	13.9	17.6	29.4	<0.0001
Loop diuretic (furosemide-equivalent) dose (mg)	26.3	24.7	26.7	28.8	0.853
Aldosterone antagonist (%)	32.3	33.2	35.7	50.8	0.0003
H/M	1.44	1.46	1.46	1.43	0.219
LBBB (%)	19.4	21.4	21.0	22.8	0.855

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, b-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; H/M, heart to mediastinum ratio; HR, heart rate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; Q, quartile; SBP, systolic blood pressure.

mortality analyses were performed first without and then with inclusion of binary variables of use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers, aldosterone receptor antagonists, and diuretics.

For all-cause mortality, the baseline model included carvedilol equivalent dose, plasma norepinephrine and H/M (*Table 5*). Heart rate was not retained. In the analysis including HF medications, none of the medications was a significant prognostic variable and the hazard ratios for the significant variables were unchanged from the baseline model.

For cardiac mortality, H/M and plasma norepinephrine were significant predictors in the baseline model; carvedilol-equivalent dose was of borderline significance, and heart rate (single determination) was not significant. In the analysis including HF medications, none of the medications was a significant prognostic variable and the hazard ratios for the significant variables were unchanged from the baseline model.

For arrhythmic events, only H/M was retained as a predictor variable (single heart rate model only).

Additional analyses of heart rate

The aforementioned analyses included only the 858 subjects with known beta blocker doses (780 receiving and 80 not receiving beta blockers). To provide a more robust examination of the influence of heart rate control on occurrence of events, additional analyses were performed for the full efficacy population (n = 961) using the mean heart rate values, the mean heart rate as quartiles, and subjects categorized into three groups: (i) all heart rate determinations $<$60 b.p.m.; (ii) all heart rate determinations $\geq$70 b.p.m.; and (iii) at least one heart rate determination not meeting criteria for categories 1 or 2. There were 104 subjects in Group 1, 202 in Group 2, and 655 in Group 3.

Proportional hazards analysis using the mean heart rate, which ranged from 40.3 to 125.8 b.p.m., yielded hazard ratios of 1.019 [95% confidence interval (CI) 1.0027, 1.0354 (P = 0.023)] for all-cause mortality and 1.026 [95% CI 1.0063, 1.0454 (P = 0.010)] for cardiac mortality. Using mean heart rate quartiles (Q1: 40.3–58.9; Q2: 59.0–66.9; Q3: 67.0–74.9; Q4: 75.0–125.8), there was no significant difference in all-cause mortality (P = 0.19), but cardiac death was significantly higher for Q3 and Q4 [hazard ratios (versus Q2) 2.73 (95% CI 1.19, 6.26) and 2.42 (95% CI 1.05, 5.58), respectively]. Excluding 105 subjects with atrial fibrillation, mean heart rate range was 40.3–112.4 b.p.m. and hazard ratios were 1.024 [95% CI 1.0058, 1.0422 (P = 0.010)] for all-cause and 1.036 [95% CI 1.0142, 1.0576 (P = 0.002)] for cardiac mortality. On quartiles analyses for this subpopulation, there was again no significant difference in all-cause mortality (P = 0.25), but cardiac death was significantly higher for Q4 compared with Q1 [P = 0.033; hazard ratio 2.26 (95% CI 1.02, 5.01)].

Two-year survival for the three heart rate groups are summarized in *Table 6*. Subjects in Group 1 had the lowest all-cause and cardiac mortality.

Discussion

In ADMIRE-HF, the large majority of subjects was receiving beta blockers, consistent with HF guidelines during the enrolment period (2005–2008). We first looked at the determinants of beta blockers dose for two reasons: (i) many patients in clinical trials and registries do not receive the high doses of beta blockers recommended by evidence-based

Table 5 Significant predictor variables in multivariate proportional hazards analyses

Outcome	Predictor variable	HR	95% CI, HR	*P* value
Single heart rate determination				
All-cause death	Carvedilol-equiv dose (mg)	0.983	0.970, 0.997	0.017
	NE level (ng/mL)	1.0007	1.0002, 1.0011	0.002
	H/M	0.078	0.0201, 0.288	0.0001
Cardiac death	Carvedilol-equiv dose (mg)	0.984	0.968, 1.001	0.059
	NE level (ng/mL)	1.0007	1.0003, 1.0012	0.002
	H/M	0.044	0.008, 0.228	0.0002
Arrhythmic event	H/M	0.244	0.076, 0.780	0.018
Mean heart rate, multiple determinations				
All-cause death	Carvedilol-equiv dose (mg)	0.984	0.970, 0.998	0.024
	NE level (ng/mL)	1.0006	1.0002, 1.0010	0.003
	H/M	0.082	0.022, 0.308	0.0002
Cardiac death	Carvedilol-equiv dose (mg)	0.986	0.969, 1.002	0.089
	NE level (ng/mL)	1.0007	1.0002, 1.0011	0.004
	H/M	0.051	0.008, 0.228	0.0005
Arrhythmic event	H/M	0.330	0.097, 1.123	0.077

CI, confidence interval; H/M, heart to mediastinum ratio; HR, hazard ratio; NE, norepinephrine.
Variables tested: carvedilol-equivalent dose, norepinephrine level, baseline heart rate, and H/M ratio.

Table 6 Two-year mortality rates[d] in relation to heart rate control at baseline

Group	Number of subjects	Number on beta blockers (%)[a]	Mean heart rate (SD)	Two-year all-cause mortality (%)[b]	Two-year cardiac mortality (%)[b]
1. All HR < 60	104	101 (97)	50.8 (3.8)[c]	4.7	1.0
2. All HR ≥ 70	202	171 (85)	84.5 (9.0)[c]	17.1	13.3
3. All others	655	611 (93)	65.3 (7.4)[c]	13.4	9.1
Total	961	883 (92)	—	13.3	9.1

HR, heart rate – minimum of five determinations during screening visit and day of ^{123}I-*m*IBG imaging.
[a]χ^2 19.7 ($P = 0.0001$).
[b]Group 1 significantly lower than Groups 2 and 3 ($P < 0.05$).
[c]All inter-group differences $P < 0.0001$.
[d]Mortality rates based upon Kaplan–Meier survival analyses.

guidelines; (ii) a high beta blocker dose was expected to be associated with a better outcome, although it has never been clearly determined whether this was due to the high dose *per se*, to a greater degree of blockade or only to a segregation of patients with a better tolerance of high beta blocker dose due to better condition (higher blood pressure, younger age, dependence on the inotropic state, etc.).

Assessing the dose of beta blockade in terms of carvedilol equivalents, patients receiving high doses of beta blockers were, as expected, younger. They were also heavier: It has been shown that patients with severe HF develop cachexia, and this may explain in part this finding.[20] There was no significant difference in beta blocker dose in relation to several markers of HF severity, LVEF, NYHA class, and blood pressure, but plasma BNP was lower in patients receiving higher doses of beta blockers. There was no difference in eGFR among groups. As expected, there was a trend for patients with high doses of beta blockers to have chronic obstructive pulmonary disease less frequently. Interestingly, there was no relationship between beta blocker dose and plasma norepinephrine, ^{123}I-*m*IBG H/M, or baseline heart rate. The implication of these observations is that the achieved dose of beta blocker cannot be reliably predicted based on the severity of HF. This was also reflected by the very low level of correlation between these parameters and beta blocker dose.

The second aim of our study was to compare three different ways of assessing sympathetic activity to predict outcome.

(i) Plasma norepinephrine is a potent prognostic factor in HF,[4,5] and the increase in plasma norepinephrine is one of the reasons for the use of beta blockers in HF. However, norepinephrine spillover is a stronger predictor of outcome than plasma norepinephrine.[7] ^{123}I-*m*IBG H/M, reflecting cardiac denervation or more precisely the degree of decrease of presynaptic norepinephrine reuptake, has the advantage of assessing cardiac sympathetic activity and not overall adrenergic activity. It is also less subject to day to day variations than heart rate or plasma norepinephrine.

(ii) Although guidelines recommend moderate-to-high doses of beta blockers, many patients are not titrated to doses demonstrated to be advantageous in large, randomized, controlled clinical trials and registries. The relationship between beta blocker dose and outcome is complex. Bristow *et al*.[15] showed, in a small population, a clear correlation between beta blocker dose and increase in LVEF. The relationship with outcome was weaker; moreover, the study was only designed to assess the effect on LVEF and not on outcome. In contrast, in CIBIS, no clear dose relationship with outcome was found.[21] MERIT-HF did not find that patients with lower dose of beta blocker had poorer outcome than patients with high metoprolol dose: No dose response relationship with mortality was observed for metoprolol CR/XL in the overall cohort, but a wide variation in dose-response existed among patients.[22] In HF-ACTION, all-cause mortality did not show a dose-related benefit with beta blocker therapy when adjusted for other clinical variables, in particular when exercise capacity was added to the model.[19] In SENIORS, the effect of nebivolol vs. placebo was found only in the goups of patients receiving the highest doses (>50% maximal dose) of beta blocker.[23] There was no effect in the groups receiving less than 5 mg/day. However, SENIORS included only patients aged more than 70 years with both low and preserved LVEF. Recently, the CIBIS-ELD study[14] evaluated the tolerability of bisoprolol and carvedilol in elderly patients; only 31% of patients were able to reach target doses. Figures are poorer in registries: Data from the OPTIMIZE-HF registry showed that, in patients hospitalized for HF, the mean daily dose of beta blockers before hospital admission was one-half the recommended target dose.[24]

(iii) Recently, the SHIFT trial with ivabradine demonstrated heart rate as an important prognostic factor in HF patients with low LVEF and sinus rhythm.[9] This effect persisted after adjustment for baseline beta blocker dose.[8] A meta-analysis of the effects of beta blockers on outcome showed that achieved heart rate, not beta blocker dose, predicted outcome.[16] The present analyses using multiple independent measurements showed a 2–3% proportional increase in all-cause and cardiac mortality risk for each 1 b.p.m. increase in mean heart rate. Survival analyses confirmed that the group with

consistent heart rate <60 b.p.m. had the best 2-year outcome, while subjects with mean heart rates ≥67 b.p.m. had more than two times greater risk of cardiac death. In light of the results from SHIFT and these other analyses, the paradigm of aiming for the highest tolerated dose of beta blocker may need to be shifted to aiming for a lower heart rate. This concept clearly warrants further prospective study.

(iv) None of the studies mentioned previously assessed the prognostic value of cardiac ^{123}I-*m*IBG uptake, a measurement that has repeatedly been shown to be predictive.[18,25–29] The present study demonstrated the potential value of cardiac ^{123}I-*m*IBG uptake as a supplementary measure of sympathetic nervous system activity.

Limitations

The number of patients with known beta blocker doses was small compared with large therapeutic clinical trials. It is possible that the prognostic value of heart rate or of the dose of beta blocker might have been greater in a larger population. In addition, lack of dose data on 103 subjects (11% of the efficacy population) might have introduced bias, although the clinical characteristics of these subjects were comparable to those of the 780 subjects with known beta blocker doses. As beta blocker dosage was under individual physician control and not a prospective element of the study, the reasons individual patients did not have further uptitration of these doses is not known. All the analyses in this study were based upon baseline measurements and beta blocker doses; the potential effects of subsequent changes in patient condition, and beta blocker dose on occurrence of outcome events cannot be quantified. Multivariable analysis did not include other known potent prognostic variables in HF such as age, BNP, left ventricular ejection fraction, and diuretic dose because our aim was not to add another prognostic model in HF to the long list of existing ones, but to specifically address the question of the relative prognostic potency of various markers related to adrenergic tone. Extensive multivariable analyses of the data from ADMIRE-HF, including clinical characteristics, medical history, and medication usage, have been published.[18,29,30] In separate analyses including age (a demonstrated prognostc factor for death in ADMIRE-HF[29]) and loop diuretic dose (a significant factor for mortality prediction using the Seattle HF model[30]), H/M and norepinephrine level remained powerful prognostic factors for mortality (data not shown). Finally, the price and limited availability of ^{123}I-*m*IBG in some locations may be a barrier to use of this agent for routine clinical examinations.

Conclusions

Cardiac ^{123}I-*m*IBG uptake (4-hour H/M ratio) was superior to two other surrogates of sympathetic activity as a prognostic factor. Baseline beta blocker dose had only limited predictive capacity for subsequent outcomes. Whether HF therapy should be optimized according to beta blocker dose, to lowering heart rate, or to increasing H/M ratio can only be answered in appropriately designed prospective clinical trials.

Conflicts of interest

A.C.-S has received honoraria from GE Healthcare for speaker presentations and scientific board membership.

A.J. was an employee of GE Healthcare at the time this study was performed and owns shares in the General Electric Company.

I.P. has received honoraria from GE Healthcare for speaker presentations and scientific board membership.

Funding

ADMIRE-HF was funded entirely by GE Healthcare. No financial support was provided specifically for the present analyses or the preparation of this manuscript.

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