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Prescribing Patterns to Optimize Heart Rate: Analysis of 1,000 Consecutive Outpatient Appointments to a Single Heart Failure Clinic over a Six Month Period

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Brief title: Heart rate reduction in heart failure

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Abstract

Aims: To characterize patients attending a community heart failure (HF) clinic and to identify the proportion eligible for optimization of beta blockers (BB) or ivabradine.

Methods: 1000 consecutively scheduled HF clinic follow-up appointments over a 6 month period were reviewed. Demographic, clinical and echocardiographic data were collected in patients who attended (824 'unique' patients, 555 men). Mean age was 74±11 years, median N-terminal pro B-type natriuretic peptide 1002 (interquartile range (IQR) 367-2151) ng/L and mean left ventricular ejection fraction (LVEF) 44±11%. Respectively 202 (25%), 252 (31%) and 370 (45%) patients had LVEF ≤35%, 36-49% and ≥50%. Of patients with LVEF ≤35%, 142 (70%) were in sinus rhythm.

Results: On 70 clinic visits, 58 patients with LVEF ≤35% were in sinus rhythm and had a heart rate ≥70 bpm. Of these, BB dose was increased in 13 patients, 20 were potentially eligible for, but did not have, BB up-titration, 15 were already taking target doses of BB and 10 patients were reported to be intolerant of higher doses. Thus 25 patients were potentially eligible for ivabradine by European Society of Cardiology (ESC) guidelines; this number dropped to 14 when UK National Institute for Health and Care Excellence (NICE) guidelines were applied.

Conclusion: Among patients with LVEF ≤35%, most are treated with BB and have a resting heart rate <70 bpm; 12% may be eligible for ivabradine.

Keywords: heart failure, heart rate, beta blocker, ivabradine

Condensed Abstract: The aim of the present study was to characterize patients attending a community heart failure clinic and to identify the proportion eligible for optimization of beta blockers or ivabradine. Thousand consecutive follow-up appointments were reviewed and demographic, clinical and echocardiographic data were collected in patients who attended. Mean age was 74 years, median N-terminal pro B-type natriuretic peptide 1002 ng/L and mean LVEF 44%. Respectively 25%, 31% and 45% patients had LVEF ≤35%, 36-49% and ≥50%. Most patients with HFrEF are treated with BB and have a resting heart rate <70 bpm; 12% may be eligible for ivabradine.

Abbreviations

ACE-I/ARB: angiotensin converting enzyme inhibitors or angiotensin receptor blockers

AF: atrial fibrillation or flutter

BB: beta blocker

BMI: body mass index

bpm: beats per minute

ECG: electrocardiogram

ESC: European Society of Cardiology

HeFrEF: heart failure with reduced ejection fraction

HeFnEF: heart failure with normal ejection fraction

HF: heart failure

IHD: ischaemic heart disease

IQR: interquartile range

LVEF: left ventricular ejection fraction

MI: myocardial infarction

MRA: mineralocorticoid receptor antagonists

NICE: National Institute for Health and Care Excellence

NTproBNP: N-terminal pro B-type natriuretic peptide

SD: standard deviation

Introduction

A high resting heart rate is associated with increased mortality in the general population (1), and in patients with hypertension (2), diabetes (3), stable coronary artery disease (4) and heart failure (HF) (5,6). In patients with heart failure and a reduced ejection fraction (HeFrEF) who are in sinus rhythm, beta-blockers (BB) improve outcomes substantially (7-10). Although the prognostic benefits of BB may not be due entirely to heart rate reduction, several meta-analyses have shown a stronger relationship between the effect on survival and heart rate rather than BB dose achieved (11,12).

In patients with left ventricular ejection fraction ≤ 35% in sinus rhythm who do not tolerate BB or who have a resting heart rate ≥70 bpm despite maximally tolerated BB dose, ivabradine is now recommended by the European Society of Cardiology (ESC) to reduce the risk of HF hospitalization (13,14). Ivabradine , a specific inhibitor of the I_f current in the sinus node, lowers heart rate only in patients in sinus rhythm and, unlike BB, does not reduce blood pressure or directly affect myocardial systolic or diastolic function (15).

The aim of the present study was to characterize consecutive patients attending a community HF clinic and to identify the proportion eligible for optimization of BB or treatment with ivabradine.

Methods

Between January and July 2013, 1000 consecutively scheduled HF clinic follow-up appointments were reviewed and demographic, clinical and echocardiographic data were collected for patients who attended. Inclusion by using appointments rather than by patients that attended guarantees that the series is truly consecutive without exceptions. The clinic accepts referrals from primary and secondary care physicians from Kingston-upon-Hull and the surrounding communities (population about 550,000) and offers long term follow-up to patients with HF regardless of left ventricular ejection fraction (LVEF). Patients are reviewed by specialist HF physicians (trainees and consultants) and/or nurses. Importantly, new

referrals were not included in this analysis as many patients would not yet have had attempts to optimize treatment. The study was approved by the local ethics committee and all subjects gave written informed consent for data collection and analysis. The protocol, data-collection period and data to be collected were all pre-specified. No attempt was made to conceal the conduct of the audit from clinic staff.

All patients had been diagnosed with HF (diagnosed at baseline by signs and symptoms of HF in the presence of echocardiographic evidence of structural abnormality or N-terminal pro B-type natriuretic peptide (NTproBNP) >125 ng/l, according to European Society of Cardiology (ESC) guidelines (13)) and underwent a standardized protocol at each visit including: clinical history, medications and examination, 12-lead electrocardiogram (ECG), and blood tests, including a biochemical profile, full blood count and NTproBNP. Twelve-lead ECGs were obtained after at least 5 min rest in the supine position using a GE MAC 5000 machine (Milwaukee, WI, USA). Heart rate obtained from the ECG was used for analysis. Echocardiograms were done routinely at the first visit and repeated at the second visit and periodically thereafter. The most recent echocardiogram was used to classify patients.

The study cohort was divided into 3 groups according to LVEF to describe patient characteristics: (1) HeFrEF (LVEF ≤35%), (2) intermediate LVEF (LVEF 36-49%) and (3) heart failure with normal ejection fraction (HeFnEF; LVEF ≥ 50%).

To assess eligibility for BB optimization or treatment with ivabradine, we compared ESC and UK National Institute for Health and Care Excellence (NICE) guidelines. NICE guidelines are more stringent and require LVEF <35% and a heart rate >75 bpm as criteria for ivabradine treatment (16).

Statistical analysis

Patient characteristics are expressed as means ± standard deviations (SD) for normally distributed variables or medians with interquartile ranges (IQR) for skewed data. Normality was tested using Q-Q plots. Differences between groups were compared using the independent Student's t-test or Mann-Whitney U-test (for variables not normally distributed) for continuous variables, and the Chi square test for categorical variables. Statistical analysis was performed using Microsoft Excel and SPSS software (18.0, SPSS Inc. Chicago IL, USA).

Results

Patient characteristics

Patients failed to attend on only 41 of the 1000 scheduled appointments. In no case was failure to attend due to death. For the remaining 959 appointments, there were 824 'unique' patients (555 men). Baseline characteristics are shown in Table 1.

Of patients with HeFrEF (n=202, 25%), 80% of those in sinus rhythm had an NT-proBNP >250ng/L and 94% were treated with (any dose of) BB. One-third of patients received at least the maximum guideline-recommended BB dose and 60% received ≥50%. Only 4% were taking ivabradine. Mean heart rate for patients in sinus rhythm was 68 ± 12 bpm.

For patients with an LVEF between 36-49% (n=252, 31%), 67% of those in sinus rhythm had an NT-proBNP >250ng/L; prescription rates for BB and ivabradine were similar to the HeFrEF group. Of 8 patients in this LVEF group on ivabradine, two had had an LVEF ≤35% at the initial HF clinic visit (7 with a baseline LVEF ≤ 40%). Of 26 patients with a biventricular pacing device, 11 had had an LVEF ≤35% at baseline.

In the subgroup of patients with HeFnEF (n=370, 45%), 63% of those in sinus rhythm had an NT-proBNP >250ng/L and 78% and 2% were treated with BB and ivabradine, respectively. Compared to patients with HeFrEF, there were more women, fewer patients with ischaemic heart disease (IHD), and body mass index (BMI) and blood pressure were higher.

Of the seven patients treated with ivabradine, one had had an LVEF ≤35% and another an LVEF 36-49% at the initial clinic visit. The indication in the other five patients was for angina rather than HF (17). Of 13 patients with a biventricular pacing device, six had had an LVEF ≤35% at baseline.

Eligibility for BB optimization or ivabradine

ESC guidelines. On 70 clinic visits, 58 patients had LVEF ≤35%, sinus rhythm and a heart rate ≥70 bpm. Of these, 33 patients were not taking the maximum BB dose and were not known to be intolerant of higher doses (Figure 1). These patients were therefore considered to be suitable for BB up-titration. However, 20 patients did not receive appropriate advice ('missed indication;' Figure 2). Patients with a missed indication for BB optimization were less likely to have IHD compared to patients in whom the dose was increased (Table 2).

On 29 of these 70 visits, 25 patients were receiving maximally tolerated BB doses or were BB intolerant, and were thus eligible for ivabradine. In 10 patients, treatment with ivabradine was started or intensified at the clinic visit, but the therapeutic opportunity was missed for fifteen patients (fourteen patients did not start ivabradine and it was not increased in one; Figure 3). Patients with a missed indication for ivabradine had a lower heart rate, and were more likely to be treated with BB and mineralocorticoid receptor antagonists (MRA) compared to patients in whom treatment was started or intensified (Table 2).

NICE guidelines. On 40 clinic visits, 32 patients had LVEF <35%, sinus rhythm and a heart rate ≥75 bpm. Of these, eighteen patients were eligible for BB optimization (Figure 1). However, in eight patients the indication for BB up-titration was missed (Figure 2). Fourteen patients were receiving maximally tolerated BB dose or were BB intolerant, and were suitable for treatment with ivabradine. Two patients were already taking ivabradine and in one of them the dose was increased; in four patients, treatment was started at the clinic visit and in eight patients, the indication to start treatment was missed (Figure 3).

All patients with a 'missed' prescribing opportunity were subsequently contacted to rectify the omission.

Discussion

As far as we are aware, this is, surprisingly, the first ever report of consecutive follow-up clinic appointments to a HF clinic. Data were collected on 1,000 scheduled patient appointments from a single specialist clinic within just 6 months. It shows a remarkably low default rate, the diverse nature of patients and importantly that many patients have persistently depressed LVEF and elevated NT-proBNP despite a high standard of conventional treatment. We found that rather few patients with LVEF ≤35% in sinus rhythm required optimization of BB (9-16%; NICE versus ESC guidelines) and/or treatment with ivabradine (7-12%; NICE versus ESC guidelines) to achieve heart rate control. However, in more than half of patients in whom further heart rate reduction was indicated, the indication to adjust treatment was missed. Reluctance to up-titrate BB and insufficient awareness of heart rate as a therapeutic target in HF might explain this deficiency. Presumably, in a clinic with a less systematic approach to care, fewer patients would be receiving optimal doses of BB and there would be more opportunities to intervene but no greater proportion should require treatment with ivabradine.

Patients with IHD were more likely to have their BB dose up-titrated. By 1988, more than 50 randomized controlled trials had investigated the use of BB in post-myocardial infarction (MI) patients and supported the beneficial effects on short- and long-term outcomes (18). On the other hand, the first definitive trials of the efficacy of BB for patients with HFrEF were not published until 1999 (7-9). While for HF, BB are mainly used for prognostic reasons, they can improve symptoms of angina in patients with coronary artery disease (19). These reasons could have contributed to the greater likelihood of optimizing BB dose in patients with IHD in our study cohort.

One of our criteria to assess eligibility for BB up-titration or ivabradine was a heart rate persistently above 70-75bpm. Some studies have suggested that the beneficial effects on outcome of key HF medicines are dose-related, and have therefore advocated titrating BB to a target dose (20-23). However, in clinical practice, only 18-26% of patients with HF and left ventricular systolic dysfunction reach the dose of BB targeted in trials and guidelines (20-22). Up-titration is often limited by bradycardia and side effects such as fatigue, hypotension and dizziness (20-22). Age >70 years and female sex are also associated with under-prescription of BB (23). Importantly, sub-analyses from two major randomized controlled trials with metoprolol and bisoprolol showed no superiority of high vs. moderate-to low dose BB after adjusting for the effect on heart rate (24,25). Achieving a physiological response to a treatment might be more important than achieving a target pharmacological dose (26). Selecting the dose of a treatment based on a biomarker response is widely practiced for hypertension (blood pressure), renal disease (potassium and creatinine), diabetes (haemoglobin A1c) and dyslipidemia (lipid profile) (27). Similarly, the best dose of a BB might be the one that lowers heart rate into the optimal range rather than a target dose (28).

Limitations

This is an observational study of a single specialist HF clinic serving a local community in the United Kingdom. Almost all patients were of European origin and investigation and treatment is offered to patients free of charge. Therefore, our results may not be applicable to cardiology practice elsewhere. However, we suspect that the proportion of patients eligible for ivabradine will not be markedly greater than we observed but would welcome verification from other sources using a similar approach. Heart rate was taken from the 12-lead ECG, as it was in the clinical trials. Ambulatory ECG monitoring would give a more comprehensive assessment of heart rate control throughout the night and day but has not been used to guide treatment recommendations so far.

Conclusion

Among patients with LVEF ≤35% attending a specialist HF clinic, most are treated with a BB at a dose that maintains heart rate <70 bpm, and only (at most) 16 and 12% respectively require BB up-titration or treatment with ivabradine. However, the opportunity to intervene to optimize treatment is still often missed, even in an expert clinic. Education and audit should increase awareness among physicians about the importance of managing heart rate in patients with left ventricular systolic dysfunction and sinus rhythm.

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Legends to tables and figures

Table 1: Baseline characteristics of patients, overall and according to subgroups of left ventricular ejection fraction (LVEF). Values are expressed as percentages for categorical variables, and mean ± standard deviation (SD) or median ± interquartile range (IQR) for continuous variables.

Table 2: Patients eligible for beta blocker (BB) optimization or ivabradine treatment, as identified by ESC (European Society of Cardiology) guidelines, with baseline characteristics according to 'missed' versus 'not missed' indication. Values are expressed as percentages, mean ± standard deviation (SD), or median with interquartile range (IQR). P-values represent differences between 'missed' and 'not missed' groups.

Figure 1: Flowchart of scheduled clinic visits (n=1000) with a graphical presentation of the process to identify patients eligible for treatment with ivabradine, according to ESC (European Society of Cardiology) and UK NICE (National Institute for Health and Care Excellence) guidelines.

LVEF: left ventricular ejection fraction; HR: heart rate; BB: beta blocker.

(* Patients on target dose or with known intolerance were not included)

Figure 2: Distribution of patients eligible for BB optimization, according to ESC (A) and NICE guidelines (B).

LVEF: left ventricular ejection fraction; BB: beta blocker; SR: sinus rhythm; HR: heart rate.

Figure 3: Distribution of patients eligible for ivabradine, according to ESC (A) and NICE guidelines (B).

Variable	Overall	HeFrEF (LVEF≤35%)	36%≤LVEF<50% (intermediate LVEF)	HeFnEF (LVEF≥50%)	Missing values
Number of patients	824	202 (25%)	252 (31%)	370 (45%)	0
Age (years, mean ± SD)	74 ± 11	73 ± 10	73 ± 10	76 ± 11	0
Sex (male)	555 (67%)	159 (79%)	185 (73%)	211 (57%)	0
IHD	455 (55%)	140 (69%)	157 (62%)	158 (43%)	0
NYHA					
Class I	228 (28%)	58 (29%)	78 (31%)	92 (25%)	0
Class II	423 (51%)	99 (49%)	122 (48%)	202 (55%)	0
Class III	172 (21%)	44 (22%)	52 (21%)	76 (21%)	0
Class IV	1 (0.1%)	1 (1%)	0	0	0
BMI (kg/m^2, IQR)	29 (25-33)	27 (24-31)	29 (25-33)	29 (25-34)	22
HR (bpm, mean ± SD)	71 ± 13	70 ± 12	71 ± 14	71 ± 14	16
Sinus rhythm	517 (63%)	142 (70%)	171 (68%)	204 (55%)	0
HR if SR	68 ± 12	68 ± 12	68 ± 12	69 ± 13	11
AF	307 (37%)	60 (30%)	81 (32%)	166 (45%)	0
HR if AF	75 ± 14	74 ± 12	76 ± 15	75 ± 15	5
SBP (mmHg, mean ±SD)	133 ± 24	126 ± 23	131 ± 24	139 ± 24	17
Hypertension (SBP > 140 mmHg)	272 (34%)	47 (24%)	73 (29%)	152 (43%)	17
LVEF (%, mean ± SD)	44 ± 11	29 ± 5	41 ± 4	54 ± 5	0
NTproBNP (ng/L, IQR)	1002 (367-2151)	1349 (551-2945)	929 (339-1997)	920 (321-1874)	59
NTproBNP if in SR	569 (246-1519)	1008 (412-2573)	607 (249-1319)	399 (202-990)	37
NTproBNP if not SR	1667 (1047-2984)	2008 (1181-3405)	1618 (971-2705)	1557 (1091-2880)	22
eGFR (ml/min, IQR)	52 (37-71)	51 (36-66)	54 (37-71)	53 (37-72)	41
BiV pacing	92 (11%)	53 (27%)	26 (10%)	13 (4%)	4

Loop diuretic	609 (74%)	167 (83%)	174 (69%)	268 (73%)	1
BB	701 (85%)	189 (94%)	226 (90%)	286 (78%)	2
>=100% of guideline BB dose	187 (23%)	64 (32%)	61 (24%)	62 (17%)	2
>=50% of guideline BB dose	413 (50%)	122 (60%)	129 (51%)	162 (44%)	2
ACE-I/ARB	698 (85%)	186 (92%)	227 (90%)	285 (77%)	1
MRA	385 (47%)	131 (65%)	136 (54%)	118 (32%)	1
Ivabradine	23 (3%)	8 (4%)	8(3%)	7 (2%)	0

Table 1. Baseline characteristics of patients, overall and according to subgroups of left ventricular ejection fraction (LVEF). Values are expressed as percentages for categorical variables, and mean ± standard deviation (SD) or median ± interquartile range (IQR) for continuous variables.

HeFrEF: heart failure with reduced ejection fraction; HeFnEF: heart failure with normal ejection fraction; LVEF: left ventricular ejection fraction; BMI: body mass index; NYHA: New York Association Class; SBP: systolic blood pressure; HR: heart rate; NTproBNP: N-terminal pro B-type natriuretic peptide; eGFR: estimated glomerular filtration rate; SR: sinus rhythm; AF: atrial fibrillation/flutter; BiV: biventricular; IHD: ischemic heart disease; BB: beta blocker; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist

Variables	Suitable for BB optimization (n=33)			Suitable for ivabradine (n=25)		
	Missed	Not missed	P-value	Missed	Not missed	P-value
Number	20	13		15	10	
Age (years, mean ± SD)	72 ± 12	72 ± 10	0.96	68 ± 12	72 ± 13	0.40
Sex (male)	12 (60%)	11 (85%)	0.13	10 (67%)	7 (70%)	0.86
BMI (kg/m^2, IQR)	25 (22-30)	29 (24-34)	0.05	28 (25-31)	29 (26-31)	0.68
NYHA class III/IV	6 (30%)	2 (15%)	0.34	5 (33%)	3 (30%)	0.86
SBP (mmHg, mean ±SD)	128 ± 20	139 ± 25	0.18	123 ± 22	123 ± 24	0.99
HR (bpm, mean ± SD)	77 ± 7	82 ± 10	0.07	76 ±4	86 ± 15	0.03
LVEF (%, mean ± SD)	30 ± 4	29 ± 5	0.62	27 ± 7	28 ± 7	0.66
NTproBNP (ng/L, IQR)	1635 (541-3970)	1297 (603-3236)	0.63	1374 (712-2156)	2303 (1163-5750)	0.29
eGFR (ml/min, IQR)	48 (30-73)	51 (28-63)	0.87	51 (40-71)	35 (21-48)	0.08
Sinus rhythm	20 (100%)	13 (100%)	N/a	15 (100%)	10 (100%)	N/a
BiV pacing	5 (25%)	2 (15%)	0.51	3 (20%)	4 (40%)	0.28
IHD	13 (65%)	12 (92%)	0.03	11 (73%)	8 (80%)	0.71
ACE-I/ARB	20 (100%)	12 (92%)	0.21	13 (87%)	10 (100%)	0.23
BB	19 (95%)	13 (100%)	0.41	14 (93%)	6 (60%)	0.04
BB >=50%	9 (45%)	6 (46%)	0.95	10 (67%)	5 (50%)	0.41
MRA	11 (55%)	11 (85%)	0.08	12 (80%)	4 (40%)	0.04

Table 2 – Patients eligible for beta blocker (BB) optimization or ivabradine treatment, as identified by ESC (European Society of Cardiology) guidelines, with baseline characteristics according to 'missed' versus 'not missed' indication. Values are expressed as percentages, mean ± standard deviation (SD), or median with interquartile range (IQR). P-values represent differences between 'missed' and 'not missed' groups.

BB: beta-blockers; BMI: body mass index; NYHA class: New York Heart Association class; SBP: systolic blood pressure; HR: heart rate; LVEF: left ventricular ejection fraction; NTproBNP: N-Terminal pro B-type Natriuretic Peptide; eGFR: estimated glomerular filtration rate; BiV: biventricular; IHD: ischaemic heart disease; ACE: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; N/a: not applicable.