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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 6-Month Period

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ABSTRACT

OBJECTIVES This study sought to characterize patients attending a community heart failure (HF) clinic and identified those who were eligible for optimization of beta-blockers (BB) or ivabradine.

BACKGROUND Among patients with HF due to left ventricular systolic dysfunction in sinus rhythm, those with higher resting heart rate have a worse prognosis. Reducing sinus rate to 50 to 60 beats/min might improve outcomes.

METHODS A total of 1,000 consecutively scheduled HF clinic follow-up appointments over a 6-month period were reviewed. Demographic, clinical, and echocardiographic data were collected for patients who attended (824 unique patients; 555 men). Mean age was 74 ± 11 years, median N-terminal pro-B-type natriuretic peptide levels were 1,002 ng/l (interquartile range: 367 to 2,151 ng/l), and the mean left ventricular ejection fraction (LVEF) was 44 ± 11%. A total of 202 (25%), 252 (31%), and 370 (45%) patients had LVEFs of ≤35%, 36% to 49%, and ≥50%, respectively. Of patients with LVEF ≤35%, 142 (70%) were in sinus rhythm.

RESULTS At 70 clinic visits, 58 patients with LVEFs of ≤35% were in sinus rhythm and had heart rates ≥70 beats/min. Of these, 13 patients had their BB dose increased, 20 were potentially eligible for, but did not have, BB uptitration, 15 were already taking target doses of BBs, and 10 patients were reported to be intolerant of higher doses. Thus, 25 patients were potentially eligible for ivabradine according to European Society of Cardiology guidelines; this number dropped to 14 when the United Kingdom National Institute for Health and Care Excellence guidelines were applied.

CONCLUSIONS Among patients with LVEFs of ≤35%, most are treated with BBs and have a heart rate at rest of <70 beats/min; 12% of these patients might be eligible for ivabradine. (J Am Coll Cardiol HF 2015;3:224–30) © 2015 by the American College of Cardiology Foundation.

A high heart rate at rest 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 BBs 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 the BB dose achieved (11,12).

Ivabradine is now recommended by the European Society of Cardiology (ESC) to reduce the risk of HF hospitalization (13,14) in patients with left ventricular ejection fractions (LVEF) of ≤35% who are in sinus rhythm, but who do not tolerate BBs or who have a heart rate at rest of ≥70 beats/min despite the maximally tolerated BB dose. Ivabradine, which is a specific inhibitor of the I_f current in the sinus node,

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lowers heart rate only in patients in sinus rhythm, and, unlike BBs, does not reduce blood pressure or directly affect myocardial systolic or diastolic function (15).

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

METHODS

Between January and July 2013, 1,000 consecutively scheduled HF clinic follow-up appointments were reviewed, and demographic, clinical and echocardiographic data were collected for patients who attended the clinic. Inclusion by using appointments rather than by patients who attended the clinic guaranteed that the series was truly consecutive without exceptions. The clinic accepts referrals from primary and secondary care physicians from Kingston-upon-Hull, United Kingdom, and the surrounding communities (population approximately 550,000) and offers long-term follow-up to patients with HF regardless of LVEF. Patients are reviewed by specialist HF physicians (trainees and consultants) and/or nurses. Importantly, new referrals were not included in this analysis because many patients would not yet have had attempts to optimize treatment. The study was approved by the local ethics committee, and all participants 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 were diagnosed with HF (diagnosed at baseline by signs and symptoms of HF in the presence of echocardiographic evidence of a structural abnormality or N-terminal pro-B-type natriuretic peptide [NT-proBNP] level >125 ng/l, according to ESC guidelines [13]), and underwent a standardized protocol at each visit that included clinical history, medications and examination, 12-lead electrocardiography (ECG), and blood tests, including a biochemical profile, full blood count, and measurement of NT-proBNP levels. Twelve-lead ECGs were obtained after at least 5-min rest in the supine position using a GE MAC 5000 machine (GE, Milwaukee, Wisconsin). Heart rate obtained from the ECG was used for analysis. Echocardiography was performed 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 LVEFs to describe patient characteristics: 1) HeFrEF (LVEF ≤35%); 2) intermediate LVEF (36% to 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 United Kingdom National Institute for Health and Care Excellence (NICE) guidelines. NICE guidelines are more stringent and require a LVEF of <35% and a heart rate of >75 beats/min as criteria for ivabradine treatment (16).

STATISTICAL ANALYSIS. Patient characteristics were expressed as mean ± SD for normally distributed variables or medians with interquartile ranges for skewed data. Normality was tested using Q-Q plots. Differences between groups were compared using the independent Student *t* test or Mann-Whitney U test (for non-normally distributed variables) for continuous variables and the chi-square test for categorical variables. Statistical analysis was performed using Microsoft Excel (Microsoft, Redmond, Washington) and SPSS software (version 18.0, IBM, Armonk, New York).

RESULTS

PATIENT CHARACTERISTICS. Patients failed to attend the clinic for only 41 of the 1,000 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 level >250 ng/l, and 94% were treated with (any dose of) BBs. 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 beats/min.

For patients with a LVEF between 36% and 49% (n = 252; 31%), 67% of those in sinus rhythm had an NT-proBNP level >250 ng/l; prescription rates for BBs and ivabradine were similar to the HeFrEF group. Of 8 patients in this LVEF group on ivabradine, 2 had a LVEF of ≤35% at the initial HF clinic visit (7 with a baseline LVEF ≤40%). Of 26 patients with a biventricular pacing device, 11 had a LVEF of ≤35% at baseline.

ABBREVIATIONS AND ACRONYMS

BB = beta-blocker

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 = ischemic heart disease

LVEF = left ventricular ejection fraction

MI = myocardial infarction

NICE = National Institute for Health and Care Excellence

NT-proBNP = N-terminal pro-B-type natriuretic peptide

TABLE 1 Baseline Characteristics of Patients, Overall and According to Subgroups of LVEF

Variable	Overall (N = 824)	HeFrEF (LVEF ≤35%) (n = 202, 25%)	36% ≤ LVEF <50% (Intermediate LVEF) (n = 252, 31%)	HeFnEF (LVEF ≥50%) (n = 370, 45%)	Missing Values
Age, yrs	74 ± 11	73 ± 10	73 ± 10	76 ± 11	0
Sex	555 (67%)	159 (79%)	185 (73%)	211 (57%)	0
IHD	455 (55%)	140 (69%)	157 (62%)	158 (43%)	0
NYHA functional class					
I	228 (28%)	58 (29%)	78 (31%)	92 (25%)	0
II	423 (51%)	99 (49%)	122 (48%)	202 (55%)	0
III	172 (21%)	44 (22%)	52 (21%)	76 (21%)	0
IV	1 (0.1%)	1 (1%)	0	0	0
BMI, kg/m^2	29 (25–33)	27 (24–31)	29 (25–33)	29 (25–34)	22
HR, beats/min	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, mm Hg	133 ± 24	126 ± 23	131 ± 24	139 ± 24	17
Hypertension, SBP >140 mm Hg	272 (34%)	47 (24%)	73 (29%)	152 (43%)	17
LVEF, %	44 ± 11	29 ± 5	41 ± 4	54 ± 5	0
NT-proBNP, ng/l	1,002 (367–2,151)	1,349 (551–2,945)	929 (339–1,997)	920 (321–1,874)	59
NT-proBNP if in SR	569 (246–1,519)	1008 (412–2,573)	607 (249–1,319)	399 (202–990)	37
NT-proBNP if not inSR	1667 (1,047–2,984)	2008 (1,181–3,405)	1618 (971–2,705)	1557 (1,091–2,880)	22
eGFR, ml/min	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

Values are mean ± SD, n (%), or median (interquartile range).

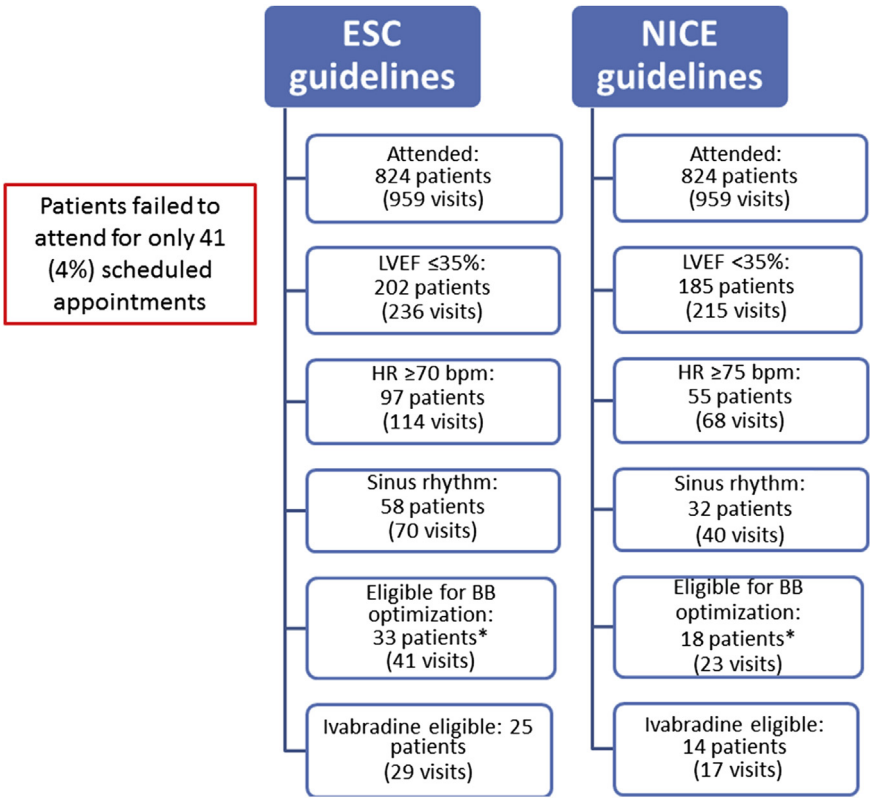
ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation/flutter; ARB = angiotensin receptor blocker; BB = beta-blocker; BMI = body mass index; BiV = biventricular; eGFR = estimated glomerular filtration rate; HeFnEF = heart failure with normal ejection fraction; HeFrEF = heart failure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

In the subgroup of patients with HeFnEF (n = 370; 45%), 63% of those in sinus rhythm had an NT-proBNP level >250 ng/l, and 78% and 2% were treated with BBs and ivabradine, respectively. Compared with patients with HeFrEF, there were more women in this group, fewer patients with ischemic heart disease (IHD), and body mass index and blood pressure were higher. Of the 7 patients treated with ivabradine, 1 had a LVEF ≤35%, and another had a LVEF of 36% to 49% at the initial clinic visit. The indication in the other 5 patients was for angina rather than HF (17). Of the 13 patients with a biventricular pacing device, 6 had a LVEF ≤35% at baseline.

ELIGIBILITY FOR BETA-BLOCKER OPTIMIZATION OR IVABRADINE. ESC guidelines. At 70 clinic visits, 58 patients had LVEFs ≤35%, sinus rhythm, and a heart rate ≥70 beats/min. 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 uptitration. 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 with patients in whom the dose was increased (Table 2).

At 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 in 15 patients (14 patients did not start ivabradine, and it was not increased in 1 patient) (Figure 3). Patients with a missed

FIGURE 1 Flowchart of Scheduled Clinic Visits (n = 1,000) With a Graphic Presentation of the Process to Identify Patients Eligible for Treatment With Ivabradine, According to ESC and NICE Guidelines



BB = beta-blocker; bpm = beats per minute; ESC = European Society of Cardiology; HR = heart rate; LVEF = left ventricular ejection fraction; NICE = National Institute for Health and Care Excellence. *Patients on target dose or with known intolerance were not included.

indication for ivabradine had a lower heart rate, and were more likely to be treated with BBs and mineralocorticoid receptor antagonists compared with patients in whom treatment was started or intensified (Table 2).

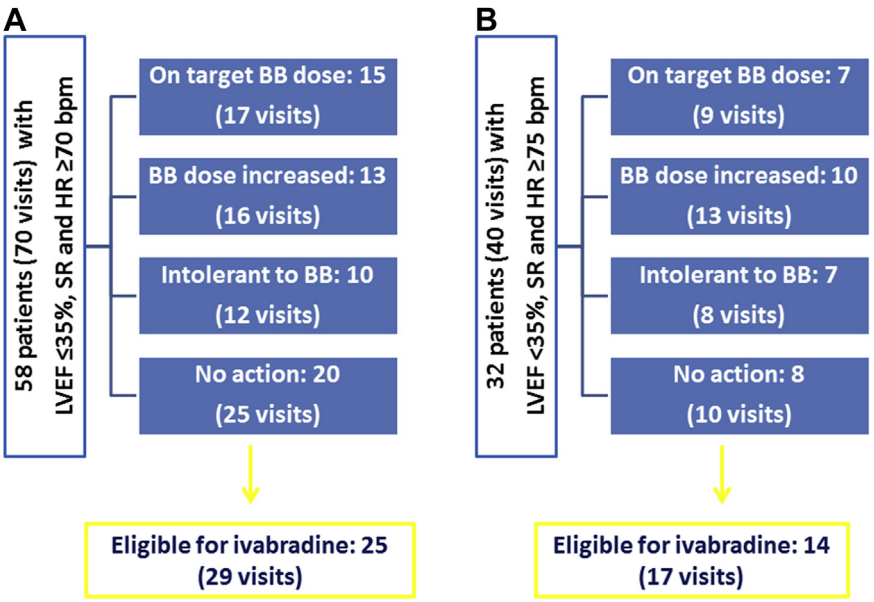
NICE guidelines. At 40 clinic visits, 32 patients had LVEFs <35%, sinus rhythm, and a heart rate ≥75 beats/min. Of these, 18 patients were eligible for BB optimization (Figure 1). However, the indication for BB uptitration was missed in 8 patients (Figure 2). Fourteen patients were receiving maximally tolerated BB doses or were BB intolerant, and were suitable for treatment with ivabradine. Two patients were already taking ivabradine, and in 1 of them, the dose was increased. In 4 patients, treatment was started at the clinic visit, and the indication to start treatment was missed in 8 patients (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 the first ever study 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 6 months. The study showed a remarkably low default rate, a diverse nature of patients, and importantly, that many patients had persistently depressed LVEF and elevated NT-proBNP levels despite a high standard of conventional treatment. We found that few patients with LVEFs ≤35% in sinus rhythm required optimization of BBs (9% to 16%; NICE vs. ESC guidelines) and/or treatment with ivabradine (7% to 12%; NICE vs. 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 uptitrate BBs and insufficient awareness of heart rate as a therapeutic target in HF

FIGURE 2 Distribution of Patients Eligible for BB Optimization, According to ESC and NICE Guidelines



(A) ESC guidelines; **(B)** NICE guidelines. SR = sinus rhythm; other abbreviations as in Figure 1.

might explain this deficiency. Presumably, in a clinic with a less systematic approach to care, fewer patients would receive optimal doses of BB; there would be more opportunities to intervene, but no greater proportion of patients should require treatment with ivabradine.

Patients with IHD were more likely to have their BB dose uptitrated. By 1988, more than 50 randomized

TABLE 2 Patients Eligible for BB Optimization or Ivabradine Treatment, as Identified by ESC Guidelines, With Baseline Characteristics According to Missed Versus Not Missed Indication

	Suitable for BB Optimization (n = 33)			Suitable for Ivabradine (n = 25)		
Variables	Missed (n = 20)	Not Missed (n = 13)	p Value	Missed (n = 15)	Not Missed (n = 10)	p Value
Age, yrs	72 ± 12	72 ± 10	0.96	68 ± 12	72 ± 13	0.40
Sex	12 (60%)	11 (85%)	0.13	10 (67%)	7 (70%)	0.86
BMI, kg/m^2	25 (22-30)	29 (24-34)	0.05	28 (25-31)	29 (26-31)	0.68
NYHA functional class III/IV	6 (30%)	2 (15%)	0.34	5 (33%)	3 (30%)	0.86
SBP, mm Hg	128 ± 20	139 ± 25	0.18	123 ± 22	123 ± 24	0.99
HR, beat/min	77 ± 7	82 ± 10	0.07	76 ± 4	86 ± 15	0.03
LVEF, %	30 ± 4	29 ± 5	0.62	27 ± 7	28 ± 7	0.66
NT-proBNP, ng/l	1,635 (541-3,970)	1,297 (603-3,236)	0.63	1,374 (712-2,156)	2,303 (1,163-5,750)	0.29
eGFR, ml/min	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

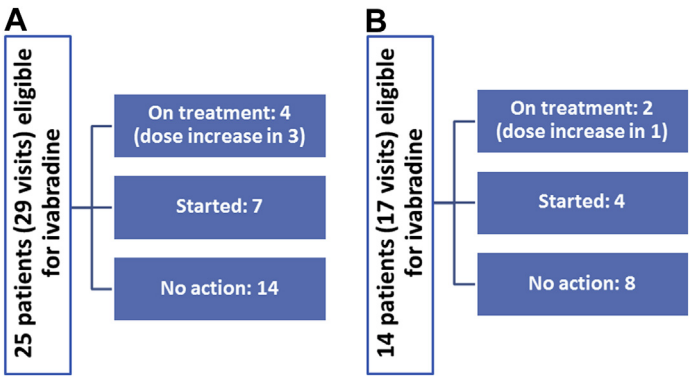
Values are mean ± SD, n (%), or median (interquartile range). p Values represent differences between missed and not missed groups.
ESC = European Society of Cardiology; other abbreviations as in Table 1.

controlled trials had investigated the use of BBs in post-myocardial infarction patients and supported the beneficial effects on short- and long-term outcomes (18). In contrast, the first definitive trials of the efficacy of BBs for patients with HFrEF were not published until 1999 (7–9). While for HF, BBs 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 the BB dose in patients with IHD in our study cohort.

One of our criteria to assess eligibility for BB uptitration or ivabradine was a heart rate that was persistently above >70 to 75 beats/min. Some studies have suggested that the beneficial effects on outcome of key HF medicines are dose-related, and have therefore advocated titrating BBs to a target dose (20–23). However, in clinical practice, only 18% to 26% of patients with HF and left ventricular systolic dysfunction reach the dose of BB targeted in trials and guidelines (20–22). Uptitration 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 underprescription of BBs (23). Importantly, subanalyses from 2 major randomized controlled trials with metoprolol and bisoprolol showed no superiority of high versus moderate-to-low-dose BBs after adjusting for the effects 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 (hemoglobin A_{1c}), 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).

STUDY LIMITATIONS. This was 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 might not be applicable to cardiology practice elsewhere. However, we suspect that the proportion of patients eligible for ivabradine would not be markedly greater than what we observed, but we would welcome verification from other sources using a similar approach. Heart rate was taken from the 12-lead ECG, as was done in the clinical trials. Ambulatory ECG monitoring would give a more comprehensive assessment of heart rate control throughout the night and day, but it has not been used to guide treatment recommendations so far.

FIGURE 3 Distribution of Patients Eligible for Ivabradine, According to ESC and NICE Guidelines



(A) ESC guidelines; **(B)** NICE guidelines. Abbreviations as in Figure 1.

CONCLUSIONS

Among patients with LVEF ≤35% attending a specialist HF clinic, most are treated with a BB at a dose that maintains heart rate at <70 beats/min, and only (at most) 16% and 12%, respectively, require BB uptitration 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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KEY WORDS beta-blocker, heart failure, heart rate, ivabradine