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Title

Suboptimal dosing of β-blockers in chronic heart failure: a missed opportunity?

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Brief report

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Abstract

Background

The evidence base for the benefits of β-blockers in heart failure with reduced ejection fraction (HFrEF) suggests that higher doses are associated with better outcomes.

Objectives

To report the proportion of patients receiving optimised doses of β-blockers, outcomes and factors associated with sub-optimal dosing.

Methods

Prospective cohort study of 390 patients with HFrEF undergoing clinical and echocardiography assessment at baseline and at 1-year.

Results

237 (61%) patients were receiving optimised doses (≥5mg/day bisoprolol equivalent), 72 (18%) could not be up-titrated (due to heart rate <60bpm or systolic blood pressure <100mmHg) and the remaining 81 (21%) should have been. Survival was similarly reduced in those who could not and should have been receiving ≥5mg/day and patient factors did not explain the failure to attain optimised dosing.

Conclusions

Many patients with HFrEF are not receiving optimal dosing of β-blockers, and in around half there was no clear contraindication in terms of heart rate or blood pressure.

Key words: chronic heart failure, β-blockers, blood pressure, heart rate, cardiovascular nursing.

What's new?

- Many patients with HFrEF do not receive optimised doses of β-blockers and half of these 'should have' according to heart rate and blood pressure.
- Patients who 'should have' been up-titrated have worse outcomes, similar to those who 'could not' be up-titrated.
- Clinical characteristics do not explain this failure to optimise dosing, suggesting unmeasured and underexplored factors may be relevant.

Abbreviations

β-blockers – beta-adrenoceptor antagonists

HFrEF – heart failure with reduced ejection fraction

UK – United Kingdom

LVEF – left ventricular ejection fraction

COPD – chronic obstructive pulmonary disease

Introduction

Beta-adrenoceptor antagonists (β-blockers) reduce morbidity and mortality, and alongside inhibitors of the renin-angiotensin system are first line for the treatment of heart failure with reduced ejection fraction (HFrEF).[1] In clinical practice these medications are usually started at low doses, with subsequent dose titration aiming for those proven in clinical trials. However, rates of attainment of optimal dosing of β-blockers are consistently low in clinical practice, prospective observational studies[2] and in contemporary clinical trials.[3]

Failure to achieve optimal doses is likely to be multifactorial and variable within cohorts, with factors including those that could be overcome and some that are fixed. Recognised clinical factors include baseline disease severity, co-morbidity, medications side effects and cognitive dysfunction. Whilst non-clinical factors such as system failure, clinician inertia, non-adherence, health knowledge, attitude and perception are less well explored.[4]

Aims

The aims of this analysis were firstly, to report the proportion of patients receiving optimised doses of β-blockers from a real-world cohort of patients with HFrEF, divided by those who could not be up-titrated due to blood pressure or heart rate limitations and those who should have been up-titrated. Secondly, to report the outcomes of patients who were or were not receiving optimal dosing. And finally, to explore clinical and demographic factors associated with failure to attain optimal dosing.

Methods

Study design

This was a prospective cohort study in unselected ambulatory patients with HFrEF with the *a priori* aim of describing contributors to outcomes.

Setting

The study was undertaken in specialist heart failure clinics in four United Kingdom (UK) hospitals combining hospital and community care. Healthcare professionals included cardiologists specialising in heart failure, heart failure nurse specialists and a cardiac physiologist.

Participants

Between June 2006 and January 2009, consecutive patients were approached to participate, in total 628 were recruited and of these 408 underwent clinical and echocardiography assessment at the time of enrolment. Further assessment was conducted after 1-year to assess for changes in medical therapy, symptoms and left ventricular remodelling following initiation of disease modifying agents. Inclusion required signs and symptoms of chronic heart failure for at least 3 months, age ≥18 years and left ventricular ejection fraction (LVEF) ≤45% on transthoracic echocardiogram, based upon guidelines for diagnostic and therapeutic criteria in place at the time.

Variables and data sources

At the time of study recruitment patient demographics, aetiology of heart failure, past medical history and functional capacity according to New York Heart Association (NYHA) classification were recorded. At baseline and again at 1-year we measured heart rate and blood pressure, performed 2-dimension echocardiography and measured LV end-diastolic diameter and LVEF by Simpson's biplane method, and obtained venous blood samples. For the purposes of analysis doses of angiotensin converting enzyme inhibitor, β-blocker and loop diuretic were reported as equivalent doses, relative to the maximum licensed doses of ramipril, bisoprolol and furosemide, as previously published.[5] All patients were registered with the UK Office of Population Censuses and Surveys, which provided details of the time of death, with final censorship occurring in November 2018.

Definitions and outcomes

We contrasted patients who were or were not receiving optimised dosing of β-blockers at 1-year (defined as ≥5mg bisoprolol equivalent dose of β-blocker), dividing those who were not optimised according to whether they could not (due to either heart rate <60 beats/min or systolic blood pressure <100mmHg) or should have been up-titrated (absence of either of these features). We report the proportions of patients who were, could not and should have been receiving optimised dosing of β-blockers, the clinical

and demographic factors associated with failure to up-titrate dosage at 1-year and association with outcomes.

Statistics

All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corporation, Armonk, NY). After demonstrating normality of distribution, continuous variables are expressed as mean ± standard deviation. Discrete variables are presented as number and percentages in parentheses. Patients receiving optimised dosing were compared to those who were not using χ^2 for categorical variables and by Student's t-test for continuous variables. Kaplan Meier curves were used to plot survival and compared with log-rank test. Multivariate analyses used Cox proportional hazards regression and, in all analyses, statistical significance was defined as $p<0.05$.

Ethical considerations

Ethical approval was given by the Leeds West Research Ethics Committee (07/Q1205/17) and conducted in accordance with the principles outlined in the Declaration of Helsinki. All patients gave informed written consent for inclusion and long-term electronic follow-up.

Results

In total 628 patients were recruited, and of these 408 attended a follow-up visit at 1-year at Leeds Teaching Hospitals NHS Trust, 18 of which had missing data. Our final cohort consisted of 390 patients, of whom 295 (75.6%) were male with an average age of 66.4 ± 12.1 years (Table). Overall, 347 (85%) were prescribed a β-blocker (mean dose of 5.2 ± 3.7 mg/day), 237 (61%) were receiving optimised doses, 72 (18%) could not be up-titrated whilst, based upon heart rate and blood pressure data, the remaining 81 (21%) should have been up-titrated but were not (Figure 1).

During a mean follow-up of 7.6 ± 3.4 years there were a total of 242 (59.3%) deaths. We observed clear stepwise benefits in longevity with those receiving the highest doses. When adjusted for age and sex, equivalent dosing of bisoprolol received at follow-up was associated with a reduction in mortality (HR 0.95, 95% confidence interval 0.91-0.98, $p=0.004$) which persisted in multivariable analysis adjusted for

differences between groups at baseline and follow-up (HR 0.96, 95% confidence interval 0.92-1.00, *p*=0.029). Survival was lower in patients receiving suboptimal doses of β-blockers, regardless of whether they could not have been or should have been up-titrated (Figure 2).

Compared to patients receiving optimal therapy, patients who could not be up-titrated due to heart rate or blood pressure limitations were on average older, with co-morbid ischaemic heart disease or diabetes mellitus (Table). They were prescribed higher doses of loop diuretics compared to patients who were up-titrated and were less likely to be implanted with device therapy. Similarly, patients who were not up-titrated but could have been, were older and more often had ischaemic heat disease compared to those who were. The prevalence of chronic obstructive pulmonary disease (COPD) was around four times higher than in patients who were up-titrated, with more renal impairment.

On the other hand, aside from older age, the 81 patients who should have been up-titrated had evidence of less severe heart failure at baseline, with better symptomatic status, higher systolic blood pressure, a lower rate of diabetes mellitus and a higher rate of device implantation compared to patients who could not be up-titrated. However, the survival curves of these two groups were similar. For the majority of patients who were not up-titrated but who should have been, baseline characteristics did not explain the failure to optimise therapy.

Discussion

In this analysis we have shown that despite closely integrated hospital and community care multi-disciplinary follow up programmes, in a real-world cohort of patients with HFrEF, ~40% were not receiving optimal doses of β-blockers 1-year following their first attendance. Furthermore, in around half of these there were no objective contraindications and despite similar or less severe heart failure by conventional measures at baseline, these patients were at higher risk of adverse outcomes. Baseline characteristics did not explain failure to optimise doses of β-blockers for the majority suggesting that unmeasured or underexplored patient factors might be relevant to the effort to optimise therapies for patients with HFrEF.

Treatment guidelines recommending the use of β-blockers in HFrEF[1] can draw upon data from multiple randomised controlled trials demonstrating improvements in outcomes.[6] The strongest benefits to patients in terms of LV remodelling, reducing hospitalisations and extending longevity are observed in those receiving evidence-based doses,[7,8] contrasting the less clear-cut advantages for those receiving higher doses of inhibitors of the renin-angiotensin system.[9-11] In our study, not all patients received a β-blocker and the dosing was lower than is recommended, however it was broadly in line with other contemporary registry studies, and we were able to distinguish those who 'should have' or 'could not' have been up-titrated.[12-14] Optimal treatment of HFrEF includes pharmacological and device therapies with considerable cost implications, yet our data show that inexpensive and proven therapies are poorly applied. In our cohort, baseline patient factors failed to explain sub-optimal dosing for the majority of patients where heart rate and blood pressure were not limitations.

Patients with HFrEF who have co-morbidities are at increased risk of adverse outcomes, including sudden cardiac death and derive additional protective from disease modifying agents.[15] Despite this, patients with co-morbidities, especially COPD are often prescribed lower doses of β-blockers, despite evidence that these medications are effective and can be safely administered.[16]

Non-targeted strategies to optimise medication doses such as additional nurse support or education can be effective, but have considerable cost implications.[17] However, targeted intervention, applied early in the care pathway could improve the uptake of higher doses which could have significant benefits to patients with minimal additional cost. Delivering targeted intervention requires identifying those at risk of sub-optimal dosing, that have the potential to be up-titrated. We were unable to explain why the majority of patients were not up-titrated. This failure to optimise therapy in the setting of closely integrated hospital and community care services raises the possibility that unmeasured and largely underexplored patients-related factors such as attitude, perceptions, beliefs and knowledge might be relevant. The presence of mild cognitive dysfunction is also a common finding in patients with heart failure[18] which increases vulnerability to intentional or unintentional non-adherence.[19]

Knowledge about heart failure can be a key determinant of health behaviour. Multidisciplinary heart failure clinics often include education as an intervention and although education alongside more intensive follow-up can lead to changes in self-care behaviour, they have a variable effect on hospitalisation and healthcare utilisation.[20-22] There are currently no studies of education programmes that have undertaken a prior assessment of patient's knowledge or perception of their condition and therefore none provide individualised education tailored to the patient-specific deficiencies of knowledge, possibly because the tools most commonly used do not allow for this level of reliability. Additionally, no studies have explored the improvement in knowledge of heart failure following an education intervention.[23,24] Untargeted strategies to optimise medication doses are therefore costly with uncertain benefit.

Targeting requires information on who, when and what. Specifically, for an educational intervention to have the greatest possible change of success, perhaps we need to identify early following diagnosis which patients is unlikely to achieve or maintain optimising treatment at 1-year despite being suitable. We also need to know when the best time to provide an education intervention or additional community support is optimal. Although it is logical to provide this early on, patients might be more receptive once they have come to terms with a new diagnosis. We need to establish which aspects of knowledge are missing in an individual. And finally, we also need to understand the influence of early cognitive dysfunction on knowledge and learned behaviour in this setting.

<u>Limitations</u>

This was a carefully characterised cohort of patients with long-term electronic follow-up. The exclusion of patients with LVEF >45% means our findings are not generalisable to those with preserved ejection fraction. Although the mechanism of action of β-blockers extend beyond heart rate and blood pressure, these are the barriers to up-titration nurses and physicians are most likely to encounter in clinical practice. The present analysis did not explore the impact of socio-economic status, however we have previously shown that much of the attributable risk of hospitalisation and mortality from socioeconomic status relates to non-cardiovascular events.[25]

Conclusions

Despite carefully integrated hospital and community care, ~40% of patients with HFrEF did not receive optimal dosing of β-blockers and in around 20% this was not due to bradycardia or hypotension. These patients had worse outcomes, regardless of whether they should have been or could not be up-titrated. For the majority of these patients, we were unable to explain the reasons for suboptimal dosing suggesting that gaining an awareness of potentially under-explored patient factors such as disease knowledge and cognition could help healthcare professional identify those at highest risk, with targeted education and community support to facilitate better up-take of β-blockers.

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Figures

Figure 1

Study flow chart.

Figure 2

Kaplan-Meier plot of all-cause mortality divided by those who were, could not and should have been receiving optimised dosing.

Table

Title: Clinical features at baseline of patients who could not, should have and were up-titrated to ≥5mg bisoprolol equivalent dose at 1-year.

p<0.05*, <0.01**, <0.001*** compared to ≥5mg bisoprolol.

	All patients (n=390)	≥5mg bisoprolol 'Were' (n=237)	<5mg bisoprolol 'Could not' (n=72)	<5mg bisoprolol 'Should have' (n=81)
Demographics				
Age (years)	66.4 ± 12.1	64.3 ± 12.4	69.6 ± 10.7	69.7 ± 11.2*
Male sex [n(%)]	295 (75.6)	178 (75.1)	58 (80.6)	59 (72.8)
Medical history				
Ischaemic aetiology [n(%)]	245 (62.8)	134 (56.5)	54 (75.0)**	57 (70.4)*
Diabetes mellitus [n(%)]	94 (24.1)	46 (19.4)	27 (37.5)**	21 (25.9)
COPD [n(%)]	38 (9.7)	13 (5.5)	8 (11.1)	17 (21.0)***
Pacemaker/defibrillator [n(%)]	138 (35.4)	90 (38.0)	17 (23.6)*	31 (38.3)
Observations				
HR (bpm)	72.5 ± 17.9	72.8 ± 18.1	68.6 ± 18.4	75.1 ± 16.8
SBP (mmHg)	121.7 ± 22.3	121.7 ± 21.9	113.1 ± 21.3	128.7 ± 22.8
NYHA Class				
I [n(%)]	82 (21.0)	60 (25.3)	8 (11.1)	14 (17.3)
II [n(%)]	172 (44.1)	103 (43.5)	33 (45.8)	36 (44.4)
III [n(%)]	129 (33.1)	71 (30.0)	29 (40.3)	29 (35.8)
IV [n(%)]	7 (1.8)	3 (1.3)	2 (2.8)	2 (2.5)
Medications				
Ramipril equivalent dose (mg/day)	5.1 ± 3.5	5.2 ± 3.6	4.9 ± 3.6	4.6 ± 3.4
Bisoprolol equivalent dose (mg/day)	3.4 ± 3.0	4.5 ± 3.0	1.9 ± 2.1***	1.6 ± 2.0***
Furosemide equivalent dose (mg/day)	54.1 ± 49.5	51.9 ± 45.8	63.6 ± 66.1**	52.3 ± 43.2
Laboratory investigations				
Haemoglobin (g/dL)	13.9 ± 1.8	14.1 ± 1.9	13.4 ± 1.6	13.7 ± 1.8
Creatinine (μmol/L)	132.0 ± 67.6	126.7 ± 50.0	134.8 ± 51.5	144.9 ± 110.8*
Albumin (g/dL)	42.9 ± 3.2	43.2 ± 3.1	42.4 ± 3.1	42.5 ± 3.1
Electrocardiogram				
PR interval (ms)	175.6 ± 37.2	174.3 ± 31.1	171.4 ± 32.6	184.3 ± 53.0**
QRS duration (ms)	122.1 ± 30.1	123.7 ± 31.5	114.9 ± 25.6**	124.0 ± 29.4
Echocardiography				
Baseline LVEF (%)	30.8 ± 9.2	30.2 ± 9.0	31.9 ± 9.3	31.2 ± 9.3
Baseline LVEDd (mm)	59.1 ± 9.2	60.0 ± 9.2	56.9 ± 8.8	58.4 ± 8.9

COPD; chronic obstructive pulmonary disease, HR; heart rate, SBP; systolic blood pressure, NYHA; New York Heart Association, LVEF; left ventricular ejection fraction, LVEDd; left ventricular end-diastolic diameter.