International Journal of Cardiology 167 (2013) 2695–2699

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Discontinuation of beta-blockers in cardiovascular disease: UK primary care cohort study ☆

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ARTICLE INFO

Article history:
Received 3 January 2012
Received in revised form 1 June 2012
Accepted 24 June 2012
Available online 26 July 2012

Keywords:
Beta-blockers
Heart failure
Myocardial infarction
Angina
Persistence

ABSTRACT

Aims: The present study aims to investigate patterns of beta-blocker usage in a national primary care cohort.
Methods and results: This is a retrospective cohort study utilising the UK General Practice Research Database from 2004 to 2008. Inclusion criteria were (i) a first diagnosis of chronic heart failure (CHF), myocardial infarction (MI) or angina, and (ii) first-ever prescription of beta-blocker on or after 1st April 2004. Outcome measures were discontinuation of beta-blockers over time, initiation dosages, titration patterns, incidence of adverse events (AEs) and associated prescribing actions.
A total of 12,493 patients (68.0% male; mean age 58.0 ± SD 17.6 years) were included. Of these, 27% had discontinued beta-blockers within 1 year of initiation, increasing to 39% by 2 years and 50% by 3 years. Persistence appeared to be greater in the MI cohort compared with angina or CHF cohorts. Beta-blocker dose at initiation averaged approximately 33% of guideline recommended target, rising to 40% in those who continued with therapy. Dyspnoea, fatigue and dizziness were the most common incident AEs at 98, 53 and 49 per 1000 patient years, with little difference between indications.
Conclusion: A quarter of patients with cardiovascular disease who are commenced on a beta-blocker are no longer taking the drug by one year. This rises to 50% by three years, a finding that is consistent irrespective of whether the prescription is for prognostic (CHF or post MI) or symptomatic (angina) benefit. There is an urgent need to understand and address the prescribing difficulties of beta-blockers in these at-risk patients.

1. Introduction

Beta-blockers are among the most widely prescribed of all drug classes [1] with strong evidence supporting the use of beta-blockers following acute myocardial infarction (MI) [2] and in treatment of chronic heart failure (CHF) [3,4] and stable ischaemic heart disease (IHD) [5] that are translated to clinical practice guidelines [6–10]. However, there is emerging evidence that there may be under-treatment with beta-blockers in these cardiovascular conditions. Under-treatment may be related to lack of initiation, under-dosing, failure to up-titrate to target doses and early discontinuation. Although registry data suggest that usage of beta-blockers in cardiovascular diseases has increased in recent years, there are reports suggesting that they remain under-prescribed [11,12]. Data from the OPTIMIZE-HF Registry and other studies show that doses of beta-blockers prescribed for CHF in clinical practice are substantially less than those recommended in major guidelines with little up-titration [13,14]. Poor persistence with beta-blockers has also been reported [15–17] and is associated with poor outcome [16,18]. Importantly, under-treatment with recommended therapy in cardiovascular diseases has been reported to be associated with worsened outcome [11,15,16,18,19]. However, most of these prescribing data come from small cohorts and registries, which may be biased as they often come from selected tertiary centres.

The General Practice Research Database (GPRD) is both the most used and most validated computerised database of anonymised medical records of patients within primary care [20]. It offers a unique

☆ Funding: This work was supported by Servier Laboratories Ltd (UK) who provided funding for the initial GPRD analysis. All of the analysis was carried out independently by staff at the GPRD and interpretation was carried out by all authors. Writing of the manuscript and critical review for important intellectual content were carried out by all authors.

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doi:10.1016/j.ijcard.2012.06.116

opportunity to evaluate unselected patients in a 'real world' setting. Using this dataset we sought to determine across a spectrum of patients with cardiovascular disease (CHF, prior MI, angina) who had received a first ever prescription for beta-blocker how many patients stopped taking the beta-blockers prematurely. To document prescribing patterns we also evaluated the dose of beta-blocker initiated, patterns of titration, the incidence of adverse events associated with beta-blockers and any subsequent prescribing actions taken.

2. Methods

This was a retrospective cohort study utilising data from the UK GPRD which collects anonymised demographic, clinical and prescribing data from medical records taken from almost 600 primary care practices. It consists of approximately 4.8 million active research quality patients and is a generalisable UK wide dataset representing approximately 8% of the UK population [20]. This study was approved by the GPRD Independent Scientific Advisory Committee. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.1. Study population

The study population consisted of all patients, aged 18 or over, within the GPRD on or after 1st April 2004 until 2008, with a first diagnosis of CHF, MI or angina. We selected only those patients with a first ever prescription for a beta-blocker on or after this diagnosis in order to meet the study objectives, including determination of early discontinuation, and initiation doses and titration over time. Inclusion and exclusion criteria were defined according to Read codes used for diagnosis in UK primary care. Patients were followed from their first prescription of a beta-blocker (index date) until the date of censoring (the earliest date of death, transfer out of the practice, or the last collection date for the practice).

2.2. Prescribing data

The principal indication for beta-blocker use (CHF, MI or angina) was recorded. Discontinuation, dosing regimens, titration patterns, adverse events and any resulting treatment alterations were evaluated.

2.2.1. Persistence and discontinuation

Persistence was evaluated according to age, gender, indication (CHF, MI and angina) and beta-blocker. Acceptable persistence was defined as a repeat prescription within 3 months of the end of the previous prescription, as previously described [15]. The end of a period of prescribing was defined as the earliest discontinuation of drug, switch to another beta-blocker or censor date. A drug was considered discontinued if 90 days had passed since the expected duration end and no other beta-blocker was prescribed.

2.2.2. Doses

The mean initiating and follow-up daily beta-blocker doses were determined and described as a proportion of recommended target dose in clinical practice guidelines (for example target dose of bisoprolol 10 mg od) [8,21,22]. The proportion of patients reaching target doses 12 months after treatment initiation was also determined.

Dose titration was categorised as 1 of 5 pre-determined dose titration patterns: 1) stable dose over time, 2) up-titration over time with no final decrease in dose, 3) down-titration over time with no preceding dose increase, 4) up-titration followed by dose reduction, and 5) dose reduction followed by up-titration.

2.2.3. Adverse events

Adverse events (AEs) were defined as clinical or referral reports of effects occurring between treatment initiation and the end of a period of continuous use (Table 3). The proportion of patients with a down-titration, discontinuation or switch of beta-blocker within 3 months of each AE was recorded and stratified according to gender, indication and beta-blocker.

2.3. Statistical analysis

All data were analysed by the GPRD using the Stata statistical package (Stata®10), College Station, TX, USA. Inclusion and exclusion criteria for the three different cohorts (CHF, MI and angina) were defined according to OXMIS/Read codes used for diagnosis in UK primary care (Appendix A). Data collected for the GPRD have been analysed in numerous publications, which have consistently shown validity in respect to diagnostic coding [23–25]. The current study predominantly uses simple descriptive statistics with 95% confidence intervals and mean estimates with standard deviations as appropriate. The study was designed to describe patterns of beta-blocker prescribing across three cardiovascular disease entities. It was not designed to make statistical comparisons between these groups or adjust for other co-variables.

3. Results

From a total of 41,969 patients with first ever diagnosis of CHF, MI or angina on or after 1st April 2004, 12,493 (30%) receiving a first ever prescription for a beta-blocker were included in the study. Of the remaining 29,476 patients (70%) excluded from the study, 12,370 (29%) were already on a beta-blocker, 5862 (14%) were recorded as asthmatic, 469 (1%) were recorded as having a contraindication to beta-blockers, 19 refused beta-blockers, 58 had previously failed to tolerate beta-blockers and in 10,698 (25%) there was no clear reason recorded for lack of beta-blocker therapy.

Baseline characteristics at the treatment index date are detailed in Table 1. The mean age of the study population was 58.0 ± 17.6 (SD) years and 68.0% of the population were male. The most frequently prescribed beta-blocker at baseline was bisoprolol (46% patients), followed by atenolol (39%) and metoprolol (10%). Less frequently prescribed beta-blockers included carvedilol (3%), sotalol and propranolol (1%). Patients taking beta-blockers for CHF or following MI were more likely to be taking bisoprolol (67.9% and 47.6%, respectively), whereas patients with angina were more likely to be taking atenolol (49%).

3.1. Persistence and discontinuation

Overall, 27% (CI 0.26–0.28) of patients had discontinued treatment by 1 year, rising to 39% (CI 0.38–0.40) by 2 years and 50% (CI 0.49–0.51) by 3 years after initiation of beta-blockers. Discontinuation

Table 1
Baseline characteristics for 12,943 patients with a first diagnosis of angina, MI or CHF receiving a first prescription of beta-blocker on or after the diagnosis.

Characteristic	Female N = 4001 (32%)	Male N = 8492 (68%)	Total cohort N = 12,493 (%)
Age			
18–49 years	297 (7.4%)	1203 (14.2%)	1500 (12.0%)
50–59 years	572 (14.3%)	2159 (25.4%)	2731 (21.9%)
60–69 years	977 (24.4%)	2493 (29.4%)	3470 (27.8%)
70–79 years	1188 (29.7%)	1803 (21.2%)	2991 (23.9%)
80+ years	967 (24.2%)	834 (9.8%)	1801 (14.4%)
Mean age (SD)	63.3 (16.2)	55.6 (17.8)	58.0 (17.6)
Smoking status			
Smoker	671 (16.8%)	1834 (21.6%)	2505 (20.1%)
Ex smoker	1292 (32.3%)	3935 (46.3%)	5227 (41.8%)
Non smoker	1885 (47.1%)	2511 (29.6%)	4396 (35.2%)
Unknown	153 (3.8%)	212 (2.5%)	365 (2.9%)
Comorbidities			
Asthma	399 (10.0%)	625 (7.4%)	1024 (8.2%)
COPD	153 (3.8%)	308 (3.6%)	461 (3.7%)
Cerebrovascular disease	291 (7.3%)	509 (6.0%)	800 (6.4%)
Diabetes mellitus	536 (13.4%)	1168 (13.8%)	1704 (13.6%)
Hypertension	1443 (36.1%)	2328 (27.4%)	3771 (30.2%)
PVD	202 (5.0%)	401 (4.7%)	603 (4.8%)
Other cardiovascular drug use			
Anti-platelets	3262 (81.5%)	7216 (85.0%)	10,478 (83.9%)
Statins	3031 (75.8%)	7107 (83.7%)	10,138 (81.1%)
ACE inhibitors	2108 (52.7%)	5367 (63.2%)	7475 (59.8%)
ARB	361 (9.0%)	509 (6.0%)	870 (7.0%)
Nitrates	1679 (42.0%)	3339 (39.3%)	5018 (40.2%)
Calcium channel blockers	684 (17.1%)	1159 (13.6%)	1843 (14.8%)
Other anti-anginals	170 (4.2%)	275 (3.2%)	445 (3.6%)
Indication for beta-blocker prescription			
Heart failure	601 (15.0%)	916 (10.8%)	1517 (12.1%)
Myocardial infarction	1445 (36.1%)	3771 (44.4%)	5216 (41.8%)
Angina	1955 (48.9%)	3805 (44.8%)	5760 (46.1%)

ARB = angiotensin receptor blocker; SD = standard deviation; BMI = Body Mass Index; ACE = Angiotensin converting enzyme; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PVD = peripheral vascular disease.