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Pharmacological intervention in hypertension using beta-blockers: Real-world evidence for long-term effectiveness

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ABSTRACT

The study objective was to compare the long-term incidence and risk of mortality and cardiovascular outcomes in patients with hypertension initiating bisoprolol, other β-blockers or other antihypertensive therapies. Cohort analysis using UK Clinical Practice Research Datalink (CPRD). Adult patients with first diagnosis of hypertension recorded between 2000 and 2014, with ≥365 days of registration to first event and initiating monotherapies of bisoprolol, other β-blockers or drugs other than β-blockers within 6 months of diagnosis were included. Incidence rates (IR) for each treatment cohort were compared using adjusted hazard ratio (HR) and 95% confidence intervals (CI) obtained from Cox regression analyses. Of 100,066 patients included, 539 were prescribed bisoprolol, 3701 other β-blockers, and 95,826 drugs other than β-blockers. Patients receiving bisoprolol had significantly increased survival from 2 up to <15 years (HR for <15 years 0.34; 95% CI 0.18–0.67) versus other β-blockers, and from 5 to <15 years (HR for <15 years 0.52; 95% CI 0.27–1.00) versus drugs other than β-blockers. Over time, the risk of arrhythmia was higher in the bisoprolol cohort versus other β-blockers, and risks of arrhythmia and angina were higher versus drugs other than β-blockers. No differences in the risk of embolism, stroke, and myocardial infarction (MI) were found between cohorts. Over time, mortality and cardiovascular outcome IRs decreased in each cohort. In conclusion, bisoprolol showed sustained benefit on survival, evident from 2 years after treatment initiation versus other β-blockers, and from 5 years versus drugs other than β-blockers, providing long-term evidence supporting the use of bisoprolol in patients with hypertension in primary care.

1. Introduction

The use of β-blockers is well-characterised for the treatment of hypertension and they have been used in clinical practice for many years [1,2]. Guidelines differ in their recommendations regarding the use of β-blockers in patients with hypertension. β-blockers are recommended by the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) guidelines as a preferred treatment option for patients with hypertension and previous myocardial infarction (MI), angina pectoris, heart failure (HF), and atrial fibrillation (AF) [3]. The current National Institute for Health and Care Excellence (NICE) guidance, however, does not recommend β-blockers as a first line therapy for hypertension [4,5].

The discrepancies in the recommendations arise from evidence that β-blockers may be inferior to some other classes of antihypertensive drugs in terms of total mortality, cardiovascular outcomes, and stroke [5–7]. In contrast, a large meta-analysis of 147 randomised trials of antihypertensive drugs reported that β-blockers are effective in reducing chronic heart disease (CHD) events, in particular in patients with CHD and a recent history of MI [8]. The evidence described by NICE includes a systematic review that concluded that lowering blood pressure (BP) contributed to almost all of the reduced risk of stroke, and over half of the risk for CHD events [5,9]. NICE also describe a pooled analysis in which patients receiving β-blockers had a significantly reduced risk of stroke (19%), while risk of death and MI were non-significantly reduced (6% and 8%, respectively) compared with placebo [5].

Bisoprolol is a long-acting β_1-receptor selective blocker. The high selectivity of bisoprolol for β_1 receptors limits undesired β_2 receptor inhibition [10]. While a number of studies have evidenced the efficacy and tolerability of bisoprolol for patients with hyper-

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tension [11–14], real-world evidence is more limited. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that β-blockers can reduce cardiovascular mortality in young and middle-aged, overweight or obese hypertensive patients with type 2 diabetes [15–17]. After an 8–9 year follow-up period, patients with tight BP control had significantly better outcomes in terms of cardiovascular, diabetes, and mortality endpoints [16]. In those originally randomized to the β-blocker, there was also a 23% reduction in death from any cause compared with those randomized to ACE-inhibitor treatment among patients followed for up to 20 years [18].

Given the substantial impact of hypertension on patients and healthcare resources [19], a greater understanding of the comparative long-term, real-world benefits of β-blockers, and specifically bisoprolol, in hypertension is warranted. The aims of this population-based cohort study were to compare the incidence and risk for mortality and cardiovascular outcomes in patients with hypertension treated with monotherapies of bisoprolol, other β-blockers or other antihypertensive therapies, and to evaluate whether bisoprolol treatment improved these outcomes compared with other β-blockers or other antihypertensive drugs in patients followed for up to 15 years.

2. Material and methods

2.1. Data source

The UK Clinical Practice Research Datalink (CPRD) database is an ongoing primary care database of anonymised medical records from general practitioners [20,21]. The CPRD includes 800 practices in the UK, and over 5 million active patients (alive, currently registered) [22]. The database covers approximately 8.5% of the population in the UK and is considered representative of the general population, with similar distribution in terms of age, gender and ethnicity [23,24]. The recorded information on diagnosis and drug exposure has proven high quality in validation studies [25,26]. The study was reviewed and approved by the Independent Scientific Advisory Committee (ISAC) for the Medicines and Healthcare products Regulatory Agency (MHRA) database research. Patients' records were anonymized and de-identified prior to analysis.

2.2. Study population

The study population was comprised of all patients in the CPRD during years 2000–2014 with a READ Code for hypertension. Patients were included if they had a first-time diagnosis of hypertension during the study period and were ≥18 years of age at index date. The index date for each case was defined as the first diagnosis of hypertension. The baseline period was defined as any time ≥1 year before the index date. To increase the capture of only incident cases and to ensure a sufficient history of medication exposure, all patients were required to have an active history in the database for at least one year prior to the index date. Included patients had a recorded prescription of bisoprolol, other β-blockers, or drugs other than β-blockers, defined by the gemscript classification codes, within 6 months of the first disease diagnosis. Patients were excluded if they had no recorded treatment after the first diagnosis of hypertension, received β-blocker treatment before the index date (bisoprolol or other β-blockers), received combination drugs from any of the treatment cohorts within 6 months of the index date.

Each patient was followed from first recorded hypertension event until the earliest date of one of the following was reached (whichever came first): patient death, last data collection date in the CRPD, or treatment cohort switch.

2.3. Exposures

Patients were categorised into three cohorts according to initial treatment recorded within 6 months of the index date. The bisoprolol cohort included bisoprolol fumarate as monotherapy. The other β-blocker cohort included individual use of any other β-blocker except bisoprolol (acebutolol hydrochloride, atenolol, carteolol hydrochloride, carvedilol, celiprolol hydrochloride, esmolol hydrochloride, isoprenaline hydrochloride, labetalol hydrochloride, metoprolol, metoprolol tartrate, nadolol, nebivolol hydrochloride, oxprenolol hydrochloride, penbutolol, pindolol, practolol, propranolol hydrochloride, sotalol hydrochloride, and timolol maleate). In the drugs other than β-blockers cohort, monotherapy treatment with CCBs, ACE-Is, diuretics, alpha-blockers, aldosterone receptor antagonists, and digitalis were included.

The duration of exposure was calculated from the time between the first prescription after the index date and the last prescription recorded in CPRD. Treatment discontinuation was defined as a gap of ≥90 days after last prescription was due to expire for patients who did not switch treatment groups.

2.4. Covariates

The study variables reported for the treatment cohorts included: age in years at index date; gender; body mass index (BMI; kg/m^2), heart rate (/min), systolic blood pressure (SBP; mmHg), and diastolic blood pressure (DBP; mmHg) at most recent recorded value prior to index date. The presence of comorbidities pre-index was assessed including MI, chronic heart failure (CHF), asthma, chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), diabetes, peripheral vascular disease, AF, interstitial pulmonary disease, erectile dysfunction, and dyslipidaemia. The presence of comedications pre-index was assessed including NSAID, statins, and anti-platelets agents. Adherence to treatment was calculated from the amount of medication supplied and the refill interval [27]. The result was reported as a proportion, with a cut-off of 80% or above defined as being adherent.

2.5. Outcomes definition

The primary outcome for this study was total mortality and was indicated by date of death by any cause in CPRD. Secondary outcomes were identified using READ codes (available upon request) and included non-fatal MI, non-fatal stroke, non-fatal arrhythmia, embolism event and angina episodes.

2.6. Data analysis

Descriptive statistics of baseline and treatment characteristics were performed according to treatment cohort. To illustrate the effect over time, the analysis of the outcomes was performed using cumulative follow-up times, categorized as <1 year; <2 years, <5 years, <10 years, <15 years. Patients surviving beyond the thresholds were artificially right censored. Crude incident rates (IR) for each treatment cohort were calculated as the number of each outcome per 1000 person-years (PY) with corresponding 95% confidence intervals (CI) for each reporting interval. Cox proportional hazard models were conducted to estimate the crude and adjusted hazard ratio (HR) by age and sex of each outcome in relation to treatment cohort (bisoprolol versus other β-blockers; and bisoprolol versus drugs other than β-blockers). HR were presented with corresponding 95% CI. The survival probability of all-cause mortality was estimated using the Kaplan-Meier esti-

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