Comparative effectiveness between bisoprolol and metoprolol succinate among patients with heart failure

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Introduction
With firm evidence of reduction of morbidity and mortality\(^1\), \(\beta\)-blockers are one of the cornerstones of therapy in patients with heart failure (HF). The major HF-guidelines do not recommend any of the approved \(\beta\)-blockers over the other, thus implying equal efficacy. Similarly, no significant differences between different \(\beta\)-blockers were found in a recent network meta-analysis of HF-trials\(^2\), suggesting a general class effect. Nonetheless, there are pharmacologic differences between \(\beta\)-blockers (for example, \(\beta\)-receptor selectivity, vasodilator activity, and bioavailability), which raises the possibility that differences in clinical effectiveness may exist. Indeed, randomized trials of xamoterol and bucindolol\(^{34}\) did not demonstrate significant survival benefits in patients with HF which argues against the concept of a general class effect.

There is a paucity of head to head randomized trials comparing mortality between different \(\beta\)-blockers in HF and only a few observational comparative effectiveness studies of evidence-based \(\beta\)-blockers (metoprolol succinate, bisoprolol, and carvedilol) have been performed. Published observational studies have typically been based on hospitalised patients alone and have not included information about HF severity (as assessed by left ventricular ejection fraction [LVEF] and New York Heart Association [NYHA] classification\(^5\)). In a recent\(^6\) study of a well-defined cohort of Danish patients with HF, no significant difference in all cause mortality between the two most commonly used agents in Denmark, carvedilol and metoprolol succinate, was observed. In contrast to carvedilol that has \(\beta_1\), \(\beta_2\), and \(\alpha_1\) receptor–blocking properties, metoprolol and bisoprolol are highly specific \(\beta_1\) receptor selective. Differences that could be in favour of patients with asthma and low blood pressure since they do not possess any vasodilating or bronchoconstructive properties. Hence these pharmacological similarities the two agents are often used interchangeably and clinicians lack the data to guide the decision on which specific drug to choose.

Study cause
To investigate the comparative effectiveness between Bisoprolol and Metoprolol succinate in patients with HF.

scientific method
Primary and secondary outcome is all cause- and cardiovascular mortality. In subgroup analyses we stratified patients by sex, age, NYHA class, LVEF, and history of ischemic heart disease.
Methods

A national registry based cohort study of patients with HF was conducted. All adults from 50 to 84 years of age with first time diagnosis of HF with reduced LVEF (≤40%) that received bisoprolol or metoprolol succinate were eligible for inclusion. Patients were followed for up to 3 years. Primary outcome was all cause mortality and secondary outcome was cardiovascular mortality. All cause mortality was analysed using Cox regression with adjustment for propensity score. Patients were identified from the danish HF registry, a database where hospitals and clinics that care for inpatients and outpatients with HF are recommended to participate. The study was approved by the Danish Data Protection Agency and the Danish HF Registry. Databases used for this study were; the Central Person Register, Statistics Denmark, the National Patient Register, the National Prescription Registry, and the Cause of Death Register.

Cohort

Between 2003 and 2012, all patients between 50 to 84 years of age were qualified for enrollment if they had an incident diagnosis of HF with reduced LVEF ≤40%. Every patient who was prescribed and filled a prescription for bisoprolol or metoprolol succinate within 60 days of HF diagnosis was eligible for inclusion. If a second prescription for the same drug was filled within 120 days following the first one, patients were included in the study cohort. Patients that filled prescriptions for multiple beta-blockers on the same date or had not been residing in Denmark for at least 2 years were excluded.

Propensity Score

A propensity score to account for potential confounders was estimated using logistic regression. As predictors for bisoprolol treatment several different variables were included; HF characteristics, socioeconomic characteristics, co-morbidities, other medication, health care utilization, and lifestyle
Multiple imputations (Markov chain Monte Carlo method) were used to handle missing data\textsuperscript{12}; all analyses were conducted using 5 imputed data sets.

**Statistical Analyses**

Patients were observed for up to 3 years and were censored if switching to another β-blocker during the study period or emigrated. In the secondary analysis for cardiovascular mortality, other cause death was used as an additional censoring criterion. Data on causes of death were available through 2011 and the analysis of cardiovascular mortality was truncated accordingly. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) with 95\% confidence intervals (CIs), adjusted for propensity scores categorized in quintiles. The adjusted absolute risk difference per 100 person-years of bisoprolol use was estimated as (adjusted hazard ratio [aHR] – 1) × crude rate among metoprolol users. In subgroup analyses we stratified patients by sex, age, NYHA class, LVEF, and history of ischemic heart disease. In the primary analysis, patients using bisoprolol or metoprolol succinate before HF diagnosis, as well as those who initiated treatment after diagnosis were included. We performed 4 sensitivity analyses; in the first one we implemented the new-user design\textsuperscript{13}. New users were defined as patients who initiated treatment after HF diagnosis and had no prior use of a study drug during the previous 2 years. Second, given the possible importance of β-blocker dosage\textsuperscript{14}, we performed an analysis restricted to patients who reached the target daily dose\textsuperscript{15}, (10 mg for bisoprolol and 200 mg for metoprolol) in which patients were observed from the day they reached the target dose. Third, we implemented an alternative time-updated definition of drug exposure. We assumed that a prescription generated 3 months of drug use and patients were classified as ongoing users as long as prescriptions were re-filled (with each new prescription generating 3 months of use). If treatment was paused or discontinued, events during that period were defined as occurring off treatment and did not contribute to the analysis. Patients who resumed their medication and later filled a prescription were again defined as being on-treatment. By using the most similar estimated propensity score we also performed a frequency match (1:1) between bisoprolol and metoprolol users, using the greedy 5→1 digit matching algorithm\textsuperscript{16}. All statistical analyses were performed using SAS software, version 9.3.

**Ethical consideration**

Retrospective register studies in Denmark do not require ethical approval.
Time frame

The study was conducted within the Department of Epidemiology Research, Statens Serum Institut, Copenhagen, during the winter 2014. All together, 8 weeks was set aside for the research project.

Significance of the study

Bisoprolol and metoprolol succinate are often used interchangeably and clinicians lack the data to guide the decision on which specific drug to choose. This study aim to shed a light on eventual differences between the two agents and to hopefully facilitate the choice in treatment of patients with HF.


3 Xamterol in severe Heart failure study group. Xameterol in severe heart failure. Lancet 1990;336(8713):698


15 McMurray JJ, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology—developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012; 33(14):1787-1847.