SOCIETÀ ITALIANA DI FARMACOLOGIA

MODELLO PER INVIO RELAZIONE DI METÀ E FINE PERIODO

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TIPOLOGIA DI BORSA RICEVUTA: Borsa di ricerca SIF per soggiorno all'estero

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TITOLO DELLA RELAZIONE: Investigation of the impact on survival of the new discovered pharmacodynamics mechanism of carvedilol in patients with heart failure co-treated with beta-blocker/digoxin: a Nationwide Register-Based Retrospective Cohort Study.

RELAZIONE:

1. Introduction

At toxic doses cardiac glycosides produce calcium overload of the sarcoplasmic reticulum, which results in spontaneous release of calcium, thereby generating a depolarizing inward current mediated by sodium–calcium exchanger (which is electrogenic, exchanging three Na+ ions for one Ca2+ ion) [1]. These events are known as delayed after-depolarization, and they underlie so-called triggered arrhythmias seen in heart failure [2,3]. To date, the potential clinical benefit of carvedilol has never been compared with metoprolol (another beta-blocker commonly used in the treatment of heart failure) in patients at risk of developing cardiomyocytes calcium overload during the treatment with digoxin [4,5]. In light of this, we hypothesized that carvedilol due to its ancillary proprieties could exert an excess in the benefit of preventing fatal arrhythmia caused by calcium overload compared to metoprolol in the treatment of heart failure. Given the absence of evidence supporting this topic, we decided to perform a nationwide register-based

retrospective cohort study to compare the survival rate of these drugs during digoxin co-exposure phases in patients with heart failure.

2. Methods

Data sources

Information about the drug exposure, hospitalization diagnoses, and death were collected from four Danish registries: Danish National Patient Registry [6], Danish Registry of Medicinal Product Statistics [7], Danish Civil Registration System [8], and the National Causes of Death Registry [9]. All information were linked to an individual level through a personal identification number given to each Danish citizen at birth or immigration. The possibility to link different health administrative and socio-demographic information provides the opportunity to follow a patient with heart failure through the entire disease course making possible the risk assessment of clinical outcomes during different drug/comorbidity exposure phases.

Study population

All patients with a hospitalization diagnosis of heart failure from January 1, 1995 to December 31, 2012 were identified from the Danish National Patient Registry. We defined a patient as having heart failure according to the 10th revision of the International Classification of Diseases (ICD) system codes I110, I42, I50, and J819. The index date for each patient was identified by the first date of heart failure diagnosis. The study population was followed from the index date to death or censoring date on December 31, 2012.

Exposure

Claimed prescriptions of carvedilol, or metoprolol were identified according to the anatomical therapeutic chemical (ATC) classification codes (C07AG02, C07AB02, and C07AB07). The same procedure was performed with digoxin (ATC code C01AA05). Ongoing exposure was calculated by dividing the number of tablets dispensed by the estimated average dosage. If only one prescription was registered for an individual, a standard dosage defined as the minimal recommended dosage was used to estimate the daily dose. We defined exposure as the point at which patients had medication available and defined

discontinuation as the point at which patients had no more medication available. Patients were allowed to be in only one of beta-blocker groups at the time but the switch among groups was allowed according to claimed prescriptions.

Statistical analysis

Baseline characteristics were compared among patients treated with carvedilol, or metoprolol, at the time of the first heart failure diagnosis. For the comparison was used t-test or ANOVA for continuous variables and chi-square or Fisher exact test for categorical variables. To assess differences in survival among patients treated with beta-blockers during the phase of exposure and not exposure to digoxin, a time-dependent multivariable Cox regression model including an interaction term with digoxin was used. The study outcomes were all-causes and cardiovascular mortality. The model was adjusted for age, comorbidities (Table 1), and calendar year. Data management was performed using SAS statistical software (version 9.4, SAS Institute Inc., Cary, North Carolina) and data analysis was performed using R (version 3.2.2, R Development Core Team). All analyses used a statistically significance level of $p<0.05$ (2-sided).

Compliance with ethical standards

In Denmark, register-based retrospective studies do not require ethical approval. The study was approved by the Danish Data Protection Agency. Patient records/information were anonymized and de-identified prior to the analysis.

3. Preliminary results

At the baseline, the most frequently used beta-blocker was metoprolol, while users of carvedilol were younger and more often men with a similar prevalence of comorbidity compared to users of metoprolol. Preliminary results revealed in both un-adjusted and adjusted analyses, a statistically significant increase in the risk of all-causes mortality during the exposure to metoprolol compared to carvedilol in patients with heart failure. This effect was higher during the phases of co-exposure with digoxin as evidenced by a statistically significant interaction term ($p<0.001$). As for all-causes mortality, also for cardiovascular

mortality was observed an excess in the risk during the co-exposure phases metoprolol/digoxin versus carvedilol/digoxin, which was even higher than those observed during the non co-exposure phase to aforementioned pharmacological combinations.

References

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Table 1. Diagnoses used for defining comorbidities.

Comorbidity		
Alcohol abuse	Defined from diagnosis and adverse alcohol consumption reported during hospitalization	*ICD10*[a]: E244, E52, F10, G312, G621, G721, I426, K292, K70, K860, L278A, O354, T51, Z714, Z721
Cancer	Defined from diagnosis	*ICD10*[a]: C00-97 *ICD8*[b]: 109-140
Acute kidney disease	Defined from diagnosis	*ICD10*[a]: N17, N19, R34
History of blooding	Defined from diagnosis	*ICD10*[a]: I60, I61, N02, R31, R04, D50, D62, K250, K252, K254, K260, K262, K264, K270, K272, K280, K2921, K920, K922, S064-66, J942
Chronic kidney disease	Defined from diagnosis	*ICD10*[a]: E102, E112, E132, E142, I120, M3215, M300, M313, M319, N02-N08, N11-N12, N14, N158-N160, N162-N164, N168, N18-N19, N26, Q612-Q613, Q615, Q619,
Chronic obstructive pulmonary disease	Defined from treatment and diagnosis	Bronchial dilating medication for inhalation (ATC[c] code R03) and/or an admission for a chronic obstructive pulmonary disorder (J42-44)
Diabetes mellitus	Defined from treatment	*Treatment*: Glucose-lowering medication
Hypertension	Defined from combination treatment with a least two classes of antihypertensive drugs. This definition of hypertension has a positive predictive value of 80.0% and a specificity of 94.7%.	*Treatment*: Adrenergic α-antagonist, non-loop-diuretics, vasodilators, beta-blockers, calcium channel blockers, and renin-angiotensin system inhibitors.
Liver disease	Defined from diagnoses of liver cancer, chronic liver disease, liver surgery, cirrhosis, and hepatitis	*ICD10*[a]: B15-B19, C22, D684C, I982B, K70-K77, Z944
Myocardial infarction	Defined from diagnosis	*ICD10*[a]: I21, I22
Peripheral arterial disease	Defined from diagnosis	*ICD10*[a]: I700, I702, I709
Syncope	Defined from diagnoses	*ICD10*[a]: R55

Stroke	Defined from diagnoses	*ICD10*[a]: G458, G459, I63, I64 *ICD8*[b]: 433-438
Atrial fibrillation	Defined from diagnoses	*ICD10*[a]: I48 *ICD8*[b]: 42793-42794
Ventricular arrhythmia	Defined from diagnoses	*ICD10*[a]: I47, I493

[a]ICD10: 10th revision of the International Classification of Diseases system

[b]ICD8: 8th revision of the International Classification of Diseases system

[c]ATC: Anatomical Therapeutic Classification