EBioMedicine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Elucidation of the Strongest Predictors of Cardiovascular Events in Patients with Heart Failure

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ARTICLE INFO

Article history:
Received 26 April 2018
Received in revised form 15 May 2018
Accepted 4 June 2018
Available online xxxx

Keywords:
Heart failure
Data mining
Cardiovascular events
Combinational factors
Inotropic agents
Diuretics

ABSTRACT

Background: In previous retrospective studies, we identified the 50 most influential clinical predictors of cardiovascular outcomes in patients with heart failure (HF). The present study aimed to use the novel limitless-arity multiple-testing procedure to filter these 50 clinical factors and thus yield combinations of no more than four factors that could potentially predict the onset of cardiovascular events. A Kaplan–Meier analysis was used to investigate the importance of the combinations.
Methods: In a multi-centre observational trial, we prospectively enrolled 213 patients with HF who were hospitalized because of exacerbation, discharged according to HF treatment guidelines and observed to monitor cardiovascular events. After the observation period, we stratified patients according to whether they experienced cardiovascular events (rehospitalisation or cardiovascular death).
Findings: Among 77,562 combinations of fewer than five clinical parameters, we identified 151 combinations that could potentially explain the occurrence of cardiovascular events. Of these, 145 combinations included the use of inotropic agents, whereas the remaining 6 included the use of diuretics without bradycardia or tachycardia, suggesting that the high probability of cardiovascular events is exclusively determined by these two clinical factors. Importantly, Kaplan–Meier curves demonstrated that the use of inotropes or of diuretics without bradycardia or tachycardia were independent predictors of a markedly worse cardiovascular prognosis.
Interpretation: Patients treated with either inotropic agents or diuretics without bradycardia or tachycardia were at a higher risk of cardiovascular events. The uses of these drugs, regardless of heart rate, are the strongest clinical predictors of cardiovascular events in patients with HF.

1. Introduction

Globally, cardiovascular disease has placed a significant burden both on individual patients and national economies [1, 2]. Despite the availability of effective medical treatments, heart failure (HF) remains a major cause of increased morbidity and mortality [3–5]. Notably, hospitalisation for a pathophysiologic exacerbation of HF can increase the severity of this condition, thus activating a vicious cycle that leads to cardiovascular death. Therefore, it is very important to identify the strongest clinical predictors of cardiovascular events followed by hospitalisation among patients with HF. Comorbidity (hypertension or renal dysfunction), the presence of anaemia or cardiomegaly, age and sex have been suggested as major determinants of hospitalisation or cardiac death among patients with HF [6]. However, the interactions between these comorbidities are complex, and the strongest clinical influences on the risk of a cardiovascular event remain unclear. In previous studies, several biomarkers, including blood levels of brain natriuretic peptide (BNP) [7], C-reactive protein [8] and albumin [9], have been measured in patients with HF with the aim of determining the severity and probability of cardiovascular events. Additionally, various drugs, such as angiotensin-converting inhibitors [10], diuretics [11] and inotropic agents [12], have been administered to patients with the intent to improve the pathophysiology of HF. Still, it remains difficult to determine the most important clinical predictors of cardiovascular events and to apply this knowledge to patients with HF in a clinical setting.

The existing limitations can be partially attributed to the use of different hypotheses and the lack of comprehensive or systematic investigations among the various studies. Accordingly, it is important to use a

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https://doi.org/10.1016/j.ebiom.2018.06.001

comprehensive method to determine the most essential parameters or combinations of parameters predictive of cardiovascular events in a cohort of patients with HF. As the combination of clinical parameters A + B + C may have synergistic effects on cardiovascular events even if A, B or C alone has no effect, the ability of every combination of clinical parameters to predict the occurrence of cardiovascular events should be tested. To overcome the difficulties associated with such testing in patients with HF, we have implemented recent, novel advances in statistical testing that will allow us to analyse all significant combinations of clinical parameters without any limits via the limitless-arity multiple testing procedure (LAMP) [13].

In this study, we evaluated the effects of combinations of clinical parameters on the incidence of cardiovascular events among patients with HF. First, we narrowed down all the combinations to those that could best explain the occurrence of the cardiovascular events. Second, we identified two combinations of clinical parameters, the use of inotropes or the use of diuretics without bradycardia or tachycardia, which correlated with the highest probability of cardiovascular event incidence among patients with HF.

2. Methods

2.1. Ethics Statement

This study was approved by the National Cerebral and Cardiovascular Centre Research Ethics Committee, which waived the requirement to obtain informed consent from the 167 subjects according to the Japanese Clinical Research Guideline because of the retrospective observational design. Instead, we made a public announcement on both the Internet homepage of our institution and the bulletin boards in our outpatient and inpatient clinics to comply with the Japanese Clinical Research Guideline and a request of the Ethics Committee.

For the analysis, we created a specified database of anonymised data in the Department of HF at our institution and analysed the anonymous data. Additionally, we obtained written informed consent from the 213 subjects included in the prospective observational study after receiving approval from the Research Ethics Committees at the National Cerebral and Cardiovascular Centre, Hokkaido University and Kyushu University.

2.2. Protocols for the First and Second Screenings

We filtered the clinical parameters to identify those most important with regard to the incidence of cardiovascular events in patients with HF. Initially, we obtained data of 402 clinical parameters in 151 patients with acute decompensated heart failure (ADHF) and used these data to derive an equation with which to determine the probability of cardiovascular events (hospitalisation or death due to HF) [14]. In this step, we narrowed the list to 251 clinical parameters. Next, after data cleaning, we added 16 patients to the cohort from the previous study to yield a total of 167 patients with ADHF who were admitted between November 2007 and October 2009 and followed to monitor the incidence of cardiovascular events until December 2014. HF diagnoses were confirmed by an expert team of cardiologists using the Framingham criteria. Finally, we selected the 50 most influential candidates from among the 251 parameters identified in previous studies (Table 1) [14, 15].

In the present study, we generated a new cohort of HF patients who received contemporary treatment in the context of a multi-centre trial and prospectively evaluated the combination that could best predict cardiovascular outcomes. For this purpose, we enrolled 213 patients with ADHF who were admitted to three different hospitals in Japan—National Cerebral and Cardiovascular Centre ($n = 114$), Hokkaido University ($n = 80$) and Kyushu University ($n = 19$)—between May 2013 and March 2015 and followed these patients until the end of April 2016. All patients underwent a careful history-taking process, physical examinations, laboratory testing, chest X-rays, electrocardiograms and complete Doppler echocardiographic studies. An expert team of cardiologists in charge of the HF department determined the timing of patient discharge, which was recommended when the patient presented with a stable blood pressure and improved renal function due to an optimal treatment according to international guidelines, as well as none of the following: signs of decompensation such as a New York Heart Association functional class <3, rales and galloping rhythm. Rehospitalisation of HF patients was defined as hospitalisation of an enrolled patient for decompensated HF, and cardiovascular death was defined as death attributed to a worsening of HF. The primary endpoint was a cardiovascular

Table 1
The clinical parameters in patients with heart failure, and the differences in the clinical parameters with or without cardiovascular events.

Clinical factors	
Age, (years)	72 (60–79)
Gender, male/female	98/69
NYHA class (II/III/IV) at admission	52/54/61
Heart rate at admission (beats/min)	81 (69–104)
Leg edema	91 (54)
Etiology of HF	
Cardiomyopathy	56 (34)
Hypertensive heart disease	25 (15)
Ischemic heart disease	16 (10)
Valvular heart disease	47 (28)
Comorbidity	
Hypertension	81 (49)
Hyperlipidemia	47 (28)
Chronic Af	67 (40)
Cerebrovascular disease	31 (19)
Obstructive pulmonary disease	10 (6)
CRT	35 (20)
ICD	35 (20)
Pacemaker	14 (8)
Number of family members in the same household	1 (1, 2)
Albumin at admission, (g/dl)	3.7 (3.4–4.0)
CRP at admission, (mg/dl)	0.3 (0.1–0.9)
WBC at admission, (/μl)	6500 (5000–8850)
AST at discharge, (U/l)	25.0 (20.5–21.5)
BUN at discharge, (mg/dl)	21.0 (16–30.8)
Uric acid at discharge, (mg/dl)	7.0 (5.7–8.4)
CRP at discharge, (mg/dl)	0.18 (0.04–0.53)
BNP at discharge, (pg/ml)	191 (102–413)
%FS at admission, (%)	19 (11–29)
LVDs at admission, (mm)	48 (36–57)
%FS at discharge, (%)	20 (13−31)
IVST at discharge, (mm)	9 (8–11)
AR grade (≥II) at discharge	21 (13)
MR grade (≥II) at discharge	48 (29)
TR grade (≥II) at discharge	43 (26)
Oral medications at discharge	
ACE inhibitor	80 (48)
Anti-allergic	12 (7)
Anti-inflammatory drug	5 (3)
Antiplatelet	45 (27)
Antithyroid drug	2 (1)
Beta-blockers	109 (65)
Bronchodilator	7 (4)
Choleretic drug	10 (6)
Digitalis	48 (29)
Diuretics	151 (90)
Inotropic agent	22 (13)
Intestinal disease drug	4 (2)
Lipid-lowering drug	37 (22)
Proton pump inhibitor	60 (36)
Purgative	49 (29)
Sedative-hypnotic (benzodiazepin)	36 (22)
Vitamins	14 (8)

Data are given as the Median (interquartile range) or n (%). ACE inhibitor, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; Af, atrial fibrillation; AR, aortic regurgitation; BNP, B-type natriuretic peptide; BUN, Blood urea nitrogen; CRT, cardiac resynchronization therapy; CRP, C-reactive protein; FS, fractional shortening; ICD, Implantable Cardioverter Defibrillator; VST, interventricular septum thickness; LVDs, Left ventricular end-systolic dimension MR, mitral regurgitation; NYHA, New York Heart Association; TR, tricuspid regurgitation.