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Beta-blocker use and risk of symptomatic bradyarrhythmias: a hospital-based case-control study

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Abstract

Objective   To investigate the risk factors of symptomatic bradyarrhythmias in relation to β-blockers use. **Methods**   A hospital-based case-control study [228 patients: 108 with symptomatic bradyarrhythmias (cases) and 120 controls] was conducted in Sultanah Aminah Hospital, Malaysia between January 2011 and January 2014. **Results**   The mean age was 61.1 ± 13.3 years with a majority of men (68.9%). Cases were likely than control to be older, hypertensive, lower body mass index and concomitant use of rate-controlling drugs (such as digoxin, verapamil, diltiazem, ivabradine or amiodarone). Significantly higher level of serum potassium, urea, creatinine and lower level of estimated glomerular filtration rate (eGFR) were observed among cases as compared to controls. On univariate analysis among patients on β-blockers, older age (crude OR: 1.07; 95% CI: 1.03–1.11, $P = 0.000$), hypertension (crude OR: 5.6; 95% CI: 1.51–20.72, $P = 0.010$), lower sodium (crude OR: 0.04; 95% CI: 0.81–0.99, $P = 0.036$), higher potassium (crude OR: 2.36; 95% CI: 1.31–4.26, $P = 0.004$) and higher urea (crude OR: 1.23; 95% CI: 1.11–1.38, $P = 0.000$) were associated with increased risk of symptomatic bradyarrhythmias; eGFR was inversely and significantly associated with symptomatic bradyarrhythmias in both 'β-blockers' (crude OR: 0.97; 95% CI: 0.96–0.98, $P = 0.000$) and 'non-β-blockers' (crude OR: 0.99; 95% CI: 0.97–0.99, $P = 0.023$) arms. However, eGFR was not significantly associated with symptomatic bradyarrhythmias in the final model of both 'β-blockers' (adjusted OR: 0.98; 95% CI: 0.96–0.98, $P = 0.103$) and 'non-β-blockers' (adjusted OR: 0.99; 95% CI: 0.97–1.01, $P = 0.328$) arms. Importantly, older age was a significant predictor of symptomatic bradyarrhythmias in the 'β-blockers' as compared to the 'non-β-blockers' arms (adjusted OR: 1.09; 95% CI: 1.03–1.15, $P = 0.003$ *vs.* adjusted OR: 1.03; 95% CI: 0.98–1.09, $P = 0.232$, respectively). **Conclusion**   Older age was a significant predictor of symptomatic bradyarrhythmias in patients on β-blockers than those without β-blockers.

1   Introduction

Since the introduction of β-blockers into clinical practice for more than 40 years ago, it has had a major impact on the treatment of cardiovascular and non-cardiovascular diseases. The emergence of overwhelming evidence supports the use of β-blockers particularly in treating heart failure and ischemic heart disease (IHD) as recommended by the Clinical Practice Guidelines (CPG).[1–3] Overall, the benefit gained from the use of β-blockers outweighs the potential side effect. Metoprolol, bisoprolol, carvedilol and nebivolol have been proven in reducing morbidity and mortality in heart failure,[4–7] and reported to be well tolerated in these clinical trials.[1,5,6,8–11] Most of the available information on the incidence of bradycardia caused by β-blockers comes from heart failure randomized controlled trials (RCTs). A review article on different types of β-blockers in heart failure trials found that the incidence of bradycardia was higher among patients on β-blockers (0.4%–12%) as compared to placebo (0–5%).[12] Importantly, in these RCTs, asymptomatic bradycardia during β-blocker therapy is not a reason for its discontinuation. However, the number of patients not

tolerating a minimal β-blocker dose in clinical practice could be higher than suggested by the withdrawal rate of 0.6%–0.9% in heart failure RCTs.[13] For instance, a baseline heart rate (HR) of less than 68 beats/min was an exclusion criterion in heart failure trials of carvedilol, metoprolol and bisoprolol.[6,10,14] RCTs usually recruit highly motivated willing volunteers. They are perhaps less likely to experience or report spontaneous events as potentially drug-related. Therefore, the figures of the adverse events reported may not be representative of clinical reality.

A number of studies had reported adverse drug reaction (ADR) associated with β-blockers as a cause for hospitalization.[15–17] A retrospective cohort of older veterans found that the prevalence of most common unplanned hospitalization caused by ADR were bradycardia secondary to β-blockers and digoxin.[18] Moreover, another study showed that cardiac iatrogenic complications were an important factor for intensive cardiac care unit admissions, and 91% of these events were bradyarrhythmias related to anti-arrhythmic agents such as β-blockers.[19] Understandably, the side effects of bradycardia and hypotension can arise in any patient if the dosage of β-blocker is too high or escalated too rapidly. However, there are limited studies to examine the predisposing risk factors associated with the occurrence of bradyarrhythmia in patients on usual adult dose and long term use of β-blockers. Predicting which patients may develop bradyarrhythmias after the initiation of β-blockers would be advantageous in the management of patients requiring β-blockers. Identification of the risk factors helps physicians to anticipate and avoid the potential serious ADR. Therefore, the aim of the study is to investigate the hospitalized patients diagnosed with symptomatic bradyarrhythmias and its potential risk factors in relation to the use of β-blockers as compared to patient not on β-blockers.

2 Methods

2.1 Study design

This study was a single centre, case-control study conducted in Sultanah Aminah Hospital, a 989-bed tertiary care-hospital with cardiology discipline at the southern region of peninsular Malaysia, with an average admission of 80,000 patients annually. In this hospital-based study, we prospectively identified patients admitted to cardiology unit between January 2011 and January 2014 with a primary diagnosis of symptomatic bradyarrhythmias. Bradycardia is defined as a ventricular rate of less than 60 beats per minute. For the purposes of this study, symptomatic bradyarrhythmias is defined as bradycardia (reversible or non-reversible)

with serious clinical manifestations (dizziness, dyspnea, syncope or fatigue) or hemodynamic instability that required hospitalization or cardiac pacemaker.[20] The recruitment is still on-going at the time of writing. Sample size was calculated using Power and Sample Size Calculation software version 3.1.2 for an unmatched case-control study. In our cohort, the probability of exposure (presence of β-blocker use) among controls (absence of β-blocker use) is 0.5 based on the absence of odds ratio (OR) from prior studies. If the true unadjusted OR for disease (symptomatic bradyarrhythmias) in exposed subject (presence of β-blocker use) relative to unexposed subject (absence of β-blocker use) is 3.3, we will need to study at least 50 case patients and at least 50 control patients to be able to reject null hypothesis that this OR equals 1 with probability (power) 0.8. The type 1 error probability associated with this test of this null hypothesis is 0.05.

2.2 Cases

Patients 18 years and above with symptomatic bradyarrhythmias requiring hospitalization were classified as cases. Eligible cases were patients with a confirmed diagnosis of bradyarrhythmias based on a documented standard 12-lead electrocardiography (ECG) on admission at a paper speed of 25 mm/s and an amplification of 10 mm/mV. The cases were divided into two categories according to the presence or absence of β-blockers use. The ECG diagnosis of bradyarrhythmias include sinus bradycardia, first degree heart block, second degree atrioventricular (AV) block such as Mobitz type I AV block (Wenckebach block) and Mobitz type II AV block, third-degree AV block, sick sinus syndrome and others (left bundle branch block, atrial fibrillation with bradycardia). The final ECG diagnosis of every patient was evaluated by two cardiologists. The types of β-blockers used in our cohort include cardioselective β-blockers (atenolol, metoprolol and bisoprolol) and unselective β-blockers (carvedilol).

2.3 Controls

Eligible controls were patients with normal HR and ECG. Similar to cases, the controls were divided into two categories according to the presence or absence of β-blocker use from the same hospital identified from daily admissions. For each case, we enrolled a control during the same period of admission. In summary, patients were divided into four categories according to the presence or absence of symptomatic bradyarrhythmias and presence or absence of β-blocker use as shown in Table 1.

Collaboration was sought with cardiologists, general

Table 1. Two hundred twenty eight admissions of symptomatic bradyarrhythmias and controls in relation to the use of β-blockers at Sultanah Aminah hospital, January 2011 to January 2014.

	Bradyarrhythmias*	Controls
(+) β blocker	(*n* = 57)	(*n* = 59)
(–) β blocker	(*n* = 51)	(*n* = 61)

*Symptomatic bradyarrhythmias (reversible or non-reversible) requiring hospitalization. (+): presence of β blocker use, (–): absence of β blocker use.

physicians, pharmacists and nurses. They were actively involved in the identification of eligible patients, ECG diagnosis and review of patient's medications. The distribution of potential risk factors and protective factors was compared between cases and controls. Data such as demographic characteristics [age, gender, ethnicity, height, weight, body mass index (BMI)], co-morbidities [cigarette smoking, diabetes mellitus (DM), hypertension, obstructive airway disease, prior heart failure, prior cerebro-vascular accident (CVA)], admission vital signs (HR, systolic blood pressure and diastolic blood pressure), ECG diagnosis, laboratory results on admission (fasting blood glucose, serum potassium, sodium, urea, creatinine, alanine aminotransferase and total cholesterol), type and dosage of β-blockers, concurrent use of rate-controlling drugs (i.e., digoxin, verapamil, diltiazem, amiodarone or ivabradine) and outcomes of bradyarrhythmias (reversibility, pacemaker implantation and in-hospital death) were extracted from the patients' records. In order to minimize selection bias, we checked every patient's identity and reference number to avoid the same patient being included twice. Only the data on first admission was being recorded. Kidney function was assessed using estimated glomerular filtration rate (eGFR), calculated on serum creatinine measurement at presentation by using the four-variable abbreviated Modification of Diet in Renal Disease (MDRD) Study equation.[21]

For the selection of patients on β-blockers, we chose patients on regular dose of β-blocker of more than one month in order to allow a sufficient period of exposure to β-blocker and based on the recommendation that the dose of β-blockers should be titrated over a period of four weeks.[3] The use of β-blocker was described according to the type of commonly prescribed β-blockers (i.e., atenolol, metoprolol, bisoprolol, carvedilol) and its total daily dose. We excluded patients with incomplete information on the demographic characteristics, laboratory results, ECG diagnosis and type or dosage of β-blockers. Patients on starting dose or titration dose of β-blockers were excluded from the analysis. In addition, bradyarrhythmias caused by acute myocardial infarction and hypothyroidism were excluded from our study.

All patients diagnosed with symptomatic bradyarrhythmias were admitted to the coronary care unit. If patients remained hemodynamically stable and the rhythm abnormalities resolved after elimination of precipitating factors or discontinuation of the offending drugs, no further intervention was needed. For patients with symptomatic bradyarrhythmias with hemodynamic instability, a temporary pacemaker either inserted intravenously (invasive) or transcutaneously by external pacemakers (non-invasive) were required. At the same setting, patients were investigated for reversible causative factors such as drugs effect, ischemia and electrolyte disturbances prior to the consideration of permanent cardiac pacemaker. If β-blocker was identified as the offending medicine, the drug will be temporarily or permanently discontinued at the discretion of the attending physician. Indications for permanent cardiac pacemaker implantation was based on patients' symptoms and irreversibility of bradyarrhythmias in accordance with CPG.[22] This study was approved by the ethics committee [National Medical Research Register (NMRR)] [Medical Research Ethics Comittee approval code: NMRR-14-1803-21444 (IIR)]. Written consent was waived by ethics committee.

2.4 Statistical analysis

We assessed differences between the baseline characteristics, vital signs at presentation, laboratory results and use of β-blockers of cases and controls. Numerical data was recorded as mean ± SD for normally distributed data, and median and interquartile range for non-normally distributed data. Categorical data was expressed as frequencies and percentages. A Chi square test was used to assess differences between categorical variables; independent *t*-test (parametric analysis) or Mann-Whitney *U* test (non-parametric analysis) was used to test differences between numerical variables. We performed a univariate analysis to examine the association between case-control status and the potential risk factor on symptomatic bradyarrhythmias using binary logistic analysis. The strength of associations between case-control status and potential risk factors was analyzed using OR and 95% confidence interval (CI). Variables significant in the univariable analysis were tested for collinearity using the Chi square test for independence. A multivariable logistic regression was then constructed using the 'enter method' to identify potential risk factors for symptomatic bradyarrhythmias; interactions were also tested for explanatory variables. Those explanatory variables significantly associated with case/control status in the univariable analysis ($P < 0.1$ or crude OR > 1.5) were fitted into the multivariable logistic regression analysis to calculate the adjusted OR, in order to identify which ones were independent risk

factors. $P < 0.1$ and crude OR >1.5 were chosen to include as many variables in the logistic model to minimize confounding. The results were reported as unadjusted (crude) and adjusted OR with 95% CI. Variables found to be significant (adjusted OR > 1 or < 1 at P value of < 0.05) was considered significant risk factor for symptomatic bradyarrhythmias. All statistical calculations were performed using the SPSS statistics software (version 20, IBM, Armonk, New York).

3 Results

Between January 2011 and January 2014, 128 patients with a diagnosis of symptomatic bradyarrthymias (cases) and 143 patients as controls were screened. We excluded 10 cases and 23 controls because of missing or incomplete information on drug dosages, demographic characteristics and laboratory results. After the exclusion, 228 patients remained for the analyses (108 cases and 120 controls). They were divided into four categories (presence or absence of symptomatic bradyarrhythmias and presence or absence of the β-blockers use) as shown in Table 1.

In our cohort, there were 116 patients on β-blockers. The main indications of β-blockers usage were hypertension (40.5%), IHD (STEMI, NSTEMI, UA and stable angina) (38.8%), congestive heart failure (CHF) (11.2%) and cardiac arrhythmias (atrial fibrillation) (9.5%). Among 108 patients diagnosed with symptomatic bradyarrhythmias, the majority were third-degree AV block (32.4%) followed by sinus bradycardia (25.0%), junctional bradycardia (14.8%), sick sinus syndrome (7.4%), Mobitz type II AV block (5.6%), 2: 1 AV block (4.6%), Mobitz type I AV block (Wenckebach block) (3.7%), first degree AV block (0.9%) and others (left bundle branch block, atrial fibrillation with bradycardia) (5.6%).

Concomitant use of rate-controlling drugs (i.e., digoxin, verapamil, diltiazem, amiodarone or ivabradine) were found in 15 patients (eight digoxin, one diltiazem, two amiodarone, and four ivabradine) in the symptomatic bradyarrhythmias arm, and five patients (one verapamil, two diltiazem, and two ivabradine) in the control arm. Digoxin was used for atrial fibrillation and CHF, diltiazem and verapamil were used mainly for hypertension, amiodarone was used for atrial fibrillation and ivabradine was used for IHD.

Table 2 shows the characteristics and risk factors of cases and controls. The mean age was 61.2 ± 13.3 years with a majority of men (69.4%). Cases were likely than control to be older (64.4 *vs.* 58.4 years respectively; $P = 0.000$), with hypertension (79% *vs.* 67%, respectively; $P = 0.042$), with

Table 2. Characteristics and risk factors of cases and controls in relation to the use of β-blockers.

Variables	Bradyarrhyth-mias* ($n = 108$)	Controls ($n = 120$)	P value
Age, yrs	64.4 ± 13.4	58.4 ± 12.5	0.000[§]
Height, cm	168.0 (158.0, 174.0)	162.5 (154.5, 168.0)	0.000[#]
Weight, kg	70.0 (59.8, 75.0)	69.0 (59.0, 79.0)	0.920[#]
BMI, kg/m^2	24.2 (22.4, 26.1)	26.1 (22.6, 29.5)	0.005[#]
Male	75 (69.4%)	81 (67.5%)	0.752
Ethnicity			
Malay	58 (53.7%)	45 (37.5%)	0.014
Non-Malay[π]	50 (46.3%)	75 (62.5%)	
Smoking status			
Yes (Current / Former)	13 (12.0%)	18 (15%)	0.515
No	95 (88.0%)	102 (85%)	
Hypertension			
Yes	85 (78.7%)	80 (66.7%)	0.042
No	23 (21.3%)	40 (33.3%)	
Diabetes mellitus			
Yes	53 (49.1%)	52 (43.3%)	0.385
No	55 (50.9%)	68 (56.7%)	
Obstructive airway disease			
Yes	4 (3.7%)	7 (5.8%)	0.454
No	104 (96.3%)	113 (94.2%)	
Prior CVA			
Yes	8 (7.4%)	4 (3.3%)	0.169
No	100 (92.6%)	116 (96.7%)	
Concomitant use of rate-controlling drugs[¶]			
Yes	15[†] (13.9%)	5[¥] (4.2%)	0.010
No	93 (86.1%)	115 (95.8%)	

Data are presented as mean $\pm$ SD, n (%) or median (IQR). *Symptomatic bradyarrhythmias (reversible or non-reversible) required hospitalization; [π]Chinese, Indian, Indigenous (Orang Asli) and other non-Malaysians; [§]independent student t test; [#]Mann Whitney u test; [¶]rate-controlling drugs (viz. digoxin, verapamil, diltiazem, amiodarone or ivabradine); [†] among 15 patients, eight patients on digoxin, one patient on diltiazem, two patients on amiodarone and four patients on ivabradine; [¥]Among five patients, one patient on verapamil, two patients on diltiazem and two patients on ivabradine.. BMI: body mass index; CVA: cerebro-vascular accident; IQR: interquartile range.

lower BMI (24.2 *vs.* 26.1 kg/m^2, respectively; $P = 0.005$) and concomitant use of rate-controlling drugs (13.9% *vs.* 4.2%, respectively; $P = 0.010$). The genders, smoking status, DM, obstructive airway disease and prior CVA were similar for cases and controls.

Table 3 shows admission vital signs, laboratory results and doses of β-blockers among cases and controls. At presentation, the mean HR (42 beats/min *vs.* 76 beats/min, respectively, $P = 0.000$) and diastolic blood pressure (69 *vs.*

Table 3. Vital signs, laboratory results and β-blockers doses of cases and controls.

Variables	Bradyarrhythmias* (n = 108)	Controls (n = 120)	P value
Vital signs			
HR, beat/min	42 (28, 60)	76 (30, 160)	0.000#
SBP , mmHg	137 ± 25	133 ± 24	0.227§
DBP mmHg	69 ± 15	78 ± 13	0.000§
LVEF, %	53 (25, 83)	55 (20, 80)	0.907#
Laboratory results			
FBG, mmol/L	6.2 (3.1, 26.9)	6.5 (4.0, 25.6)	0.360#
Potassium, mmol/L	4.1 (3.0, 6.8)	3.8 (2.5, 5.4)	0.004#
Sodium, mmol/L	140.0 (113.0, 159.0)	140.0 (132.0, 147.0)	0.162#
Urea, mmol/L	7.3 (1.7, 42.3)	5.2 (1.6, 23.0)	0.000#
Creatinine, μmol/L	110.0 (50.0, 191.0)	80.5 (40.0, 119.9)	0.000#
eGFR, mL/min per 1.73 m²	59.4 ± 32.7	80.0 ± 28.9	0.000§
ALT, u/L	26.0 (6.0, 977.0)	23.0 (6.0, 224.0)	0.407#
TC, mmol/L	4.3 ± 1.1	4.8 ± 1.3	0.024§

Data are presented as mean ± SD, or median (IQR). *Symptomatic bradyarrhythmias (reversible or non-reversible) required hospitalization; §independent student *t* test; #Mann Whitney *U* test. ALT: alanine aminotransferase; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; HR: heart rate at admission; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; TC: total cholesterol.

78 mmHg, respectively, $P = 0.000$) were lower among cases than controls. There were significant higher level of serum potassium (4.1 *vs.* 3.8 mmol/L, respectively, $P = 0.004$), urea (7.3 *vs.* 5.2 mmol/L, respectively, $P = 0.000$), creatinine (110 *vs.* 81 μmol/L, respectively, $P = 0.000$), total cholesterol (4.3 *vs.* 4.8 mmol/L, respectively, $P = 0.024$) and lower level of eGFR (59.4 *vs.* 80.0 mL/min per 1.73 m², respectively, $P = 0.000$) among cases as compared to controls. There were no significant differences with respect to fasting blood sugar and alanine aminotransferase between arms.

Table 4 illustrated that among patients on β-blockers, an equivalent dosage profiles were observed with atenolol, carvedilol and bisoprolol in cases and controls. Analyses of drug dosages and frequencies showed that the median dosages of different type of β-blockers of both arms had not exceeded the maximum dose recommended by CPG.[1–3] However, a significant higher median total daily dose of metoprolol (200 mg) was observed in cases than controls (100 mg) ($P = 0.003$). Metoprolol was the most often found β-blocker in patients with symptomatic bradyarrhythmias followed by atenolol, bisoprolol and carvedilol.

Table 5 shows univariate and Table 6 multivariate logistic regression analyses divided into presence or absence of β-blocker arms. In our logistic regression analyses, we assumed that there was a linear relationship between continuous variable (covariate) and symptomatic bradyarrhythmias (dependent variable) in univariate and multivariate calculations. In the 'presence of β-blocker' arm, Table 5 showed 'Malay versus non-Malay' (crude OR: 2.05; 95% CI: 0.96–4.38, $P = 0.064$), hypertension (crude OR: 5.6; 95% CI: 1.51–20.72, $P = 0.010$), lower sodium (crude OR: 0.04; 95% CI: 0.81–0.99, $P = 0.036$), higher potassium (crude OR: 2.36; 95% CI: 1.31–4.26, $P = 0.004$), higher urea (crude OR: 1.23; 95% CI: 1.11–1.38, $P = 0.000$) and were associated with increased risk of symptomatic bradyarrhythmias on univariate analysis. However, these variables were not statistically significant on multivariate logistic regression analysis.

On univariate analysis, a statistically significant inverse association was observed for eGFR and symptomatic bradyarrhythmias in both 'presence of β-blocker' (crude OR: 0.97; 95% CI: 0.96–0.98, $P = 0.000$) and 'absence of β-blocker' (crude OR: 0.99; 95% CI: 0.97–0.99, $P = 0.023$) arms. However, using multivariate logistic regression and

Table 4. β-blockers doses of cases and controls.

	Bradyarrhythmias* (n = 57)			Controls (n = 59)			P value#
	n	Total dose per day‡ (mg)	IQR, mg	n	Total dose per day‡, mg	IQR, mg	
Cardioselective β-blocker							
Atenolol	19	50.0	(25.0, 100.0)	7	50.0	(50.0, 100.0)	0.894#
Metoprolol	26	200.0	(50.0, 400.0)	23	100.0	(50.0, 200.0)	0.003#
Bisoprolol	9	2.5	(1.25, 5.0)	20	2.5	(1.25, 5.0)	0.980#
Unselective β-blocker							
Carvedilol	3	12.5	(6.25, 25.0)	9	9.4	(6.25, 50.0)	0.745#

*Symptomatic bradyarrhythmias (reversible or non-reversible) required hospitalization; ‡Median and #Mann Whitney *U* test compared the daily total dosages of β-blockers between cases and controls. IQR: interquartile range.

Table 5. Univariate logistic regression analyses divided into presence or absence of β-blocker arms.

Variables	Presence of β-blocker			Absence of β-blocker		
	Crude OR	(95% CI)	*P* value	Crude OR	(95% CI)	*P* value
Age	1.07	(1.03–1.11)	0.000	1.02	(0.99–1.05)	0.158
Male	1.67	(0.76–3.63)	0.207	0.71	(0.32–1.58)	0.399
Malay versus non–Malay[π]	2.05	(0.96–4.38)	0.064	1.95	(0.92–4.16)	0.083
BMI, kg/m^2	1.00	(0.92–1.09)	0.949	0.81	(0.71–0.92)	0.001
Cigarette smoking (current/former)	0.71	(0.21–2.40)	0.586	0.85	(0.31–2.29)	0.742
Hypertension	5.60	(1.51–20.72)	0.010	1.15	(0.54–2.46)	0.715
Diabetes mellitus	1.87	(0.89–3.91)	0.098	0.84	(0.40–1.77)	0.641
Obstructive airway disease	2.11	(0.19–23.92)	0.547	0.37	(0.07–17.3)	0.175
Prior CVA	1.58	(0.26–9.85)	0.622	3.21	(0.60–17.3)	0.175
Concomitant use of rate–controlling drugs[¶]	2.25	(0.63–7.92)	0.209	9.55	(1.13–80.41)	0.038
LVEF	1.02	(0.98–1.06)	0.307	0.99	(0.95–1.03)	0.557
FBS	0.99	(0.90–1.11)	0.970	0.99	(0.91–1.07)	0.766
Sodium	0.04	(0.81–0.99)	0.036	1.00	(0.92–1.09)	0.985
Potassium,	2.36	(1.31–4.26)	0.004	0.03	(0.97–3.31)	0.063
Urea	1.23	(1.11–1.38)	0.000	1.09	(0.99–1.20)	0.062
eGFR	0.97	(0.96–0.98)	0.000	0.99	(0.97–0.99)	0.023
ALT	1.01	(0.99–1.02)	0.181	1.00	(0.99–1.01)	0.267
TC	0.76	(0.52–1.09)	0.138	0.65	(0.40–1.07)	0.090

[π] Other ethnicity such as Chinese, Indian, Indigenous (Orang Asli) and non-Malaysians; [¶] rate-controlling drugs (viz. digoxin, verapamil, diltiazem, amiodarone or ivabradine). ALT: alanine aminotransferase; BMI: body mass index; CVA: cerebro-vascular accident; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; LVEF: left ventricular ejection fraction; TC: total cholesterol; OR: odds ratio.

Table 6. Multivariate logistic regression analyses divided into presence or absence of β-blocker arms.

Covariate	Presence of β-blocker			Absence of β-blocker		
	Adjusted OR	(95% CI)	*P* value	Adjusted OR	(95% CI)	*P* value
Age	1.09	(1.03–1.15)	0.003	1.03	(0.98–1.09)	0.232
Male	1.92	(0.64–5.71)	0.243	0.74	(0.23–2.41)	0.618
Hypertension	4.44	(0.80–24.67)	0.088	0.62	(0.15–2.56)	0.624
Diabetes mellitus	1.21	(0.43–3.33)	0.718	0.93	(0.31–2.79)	0.891
BMI, kg/m^2	1.05	(0.93–1.17)	0.442	0.82	(0.70–0.95)	0.009
Malay versus non-Malay[π]	2.99	(0.94–9.49)	0.063	3.04	(0.87–10.62)	0.082
Concomitant use of rate-controlling drugs[¶]	1.25	(0.29–9.58)	0.824	6.15	(0.42–90.76)	0.186
Sodium, mmol/L	0.93	(0.81–1.07)	0.287	1.04	(0.93–1.16)	0.515
Potassium, mmol/L	1.64	(0.75–3.58)	0.212	1.02	(0.91–1.14)	0.711
eGFR, mL/min per 1.73m^2	0.98	(0.96–1.00)	0.103	0.99	(0.97–1.01)	0.328

[π] Other ethnicity such as Chinese, Indian, Indigenous (Orang Asli) and non-Malaysians; [¶] rate-controlling drugs (viz. digoxin, verapamil, diltiazem, amiodarone or ivabradine). BMI: body mass index; eGFR: estimated glomerular filtration rate.

controlling for other variables, eGFR was not statistically significant associated with symptomatic bradyarrhythmias in the final model of both 'presence of β-blockers' (adjusted OR: 0.98; 95% CI: 0.96–0.98, *P* = 0.103) and 'absence of β-blockers' (adjusted OR: 0.99; 95% CI: 0.97–1.01, *P* = 0.328). Variables such as urea and creatinine had multi-collinearity with the eGFR were not included in the final logistic regression model.

Age was statistically significant as a predictor of symp-

tomatic bradyarrhythmias in patients 'on β-blockers' as compared to patients 'not on β-blockers' in univariate analysis (crude OR: 1.07; 95% CI: 1.03–1.11, *P* = 0.000 *vs.* crude OR: 1.02; 95% CI: 0.99–1.05, *P* = 0.158, respectively) and multivariate analyses (adjusted OR: 1.09; 95% CI: 1.03–1.15, *P* = 0.003 *vs.* adjusted OR: 1.03; 95% CI: 0.98–1.09, *P* = 0.232, respectively).

In the 'absence of β-blocker', concomitant use of rate-controlling drugs (crude OR: 9.55; 95% CI: 1.13–80.41, *P* =

0.038) was associated with increased risk of symptomatic bradyarrhythmias on univariate analysis. However, after controlling for other variables, 'concomitant use of rate-controlling drugs' was numerically higher but not statistically significant in association with symptomatic bradyarrhythmias regardless of presence (adjusted OR: 1.25, 95% CI: 0.29–9.58, P = 0.824) or absence (adjusted OR: 6.15, 95% CI: 0.42–90.8, P = 0.186) of β-blockers. In addition, a statistically significant inverse association was observed for BMI and symptomatic bradyarrhythmias on univariate (crude OR: 0.81; 95% CI: 0.71–0.92, P = 0.001) and multivariate analysis (adjusted OR: 0.82; 95% CI: 0.70–0.95, P = 0.009) in the "absence of β-blocker arm".

Table 7 shows the outcomes of symptomatic bradyarrhythmias in relation to different types of β-blockers. Meto-

prolol and atenolol were most frequently used β-blocker observed in our study in association with bradyarrhythmias. The majority of symptomatic bradyarrhythmias were reversible following cessation of β-blockers or other causative factors such as rate-control drugs.

Among the cohorts, we performed subgroup exploratory analysis on the symptomatic bradyarrhythmias arm (cases) to look into the ECG diagnoses and reversibility of bradyarrhythmias as shown in Figure 1. Of the 108 cases presenting with symptomatic bradyarrhythmias, 69 patients (63.9%) with symptomatic bradyarrhythmias have shown reversibility that required no further intervention, and 39 (36.1%) were irreversible that subsequetly required permanent pacemakers. Of the 57 patients on β-blocker and symptomatic bradyarrhythmias, 30 (52.6%) patient's ECG nor-

Table 7. Outcome of 57 patients with symptomatic bradyarrhythmias on β-blockers.

	Number of patient on different types of β-blockers								Total
	Atenolol		Metoprolol		Bisoprolol		Carvedilol		
	R	IR	R	IR	R	IR	R	IR	
Sinus bradycardia	8	0	7	0	4	0	2	0	21
Junctional bradycardia	5	0	4	2	1	0	0	0	12
Third degree AV block	2	1	1	5	2	0	0	1	12
Sick sinus syndrome	0	0	1	0	1	0	0	0	2
Mobitz type 1 AV block	1	0	0	0	0	0	0	0	1
Mobitz type 2 AV block	1	0	0	1	0	0	0	0	2
2: 1 AV block	1	0	0	0	0	0	0	0	1
First degree heart block	0	0	1	0	0	0	0	0	1
Others	0	0	3	1	1	0	0	0	5
Total	18	1	17	9	9	0	2	1	57

R (reversible): symptomatic bradyarrhythmias reversed to normal heart rate (> 60 beats/min) after cessation of β-blockers or rate-controlling drugs. IR (irreversible): symptomatic bradyarrhythmias persisted and required permanent pacemaker implantation; Others: Left bundle branch block with atrial fibrillation, 3:1 AV block, atrial flutter with junctional escape beats.
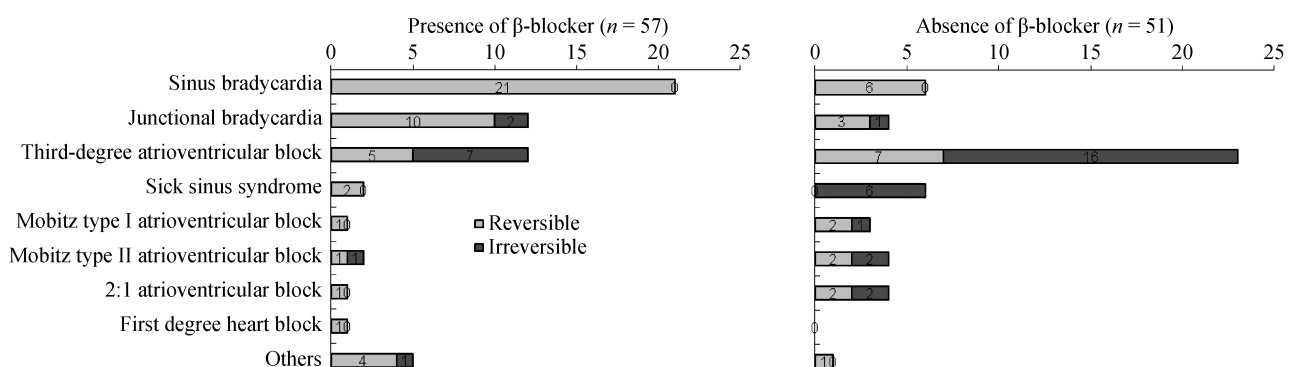
Figure 1. Outcomes of 108 patients with symptomatic bradyarrhythmias (cases) divided according to ECG diagnoses and the 'presence' or 'absence' of β-blocker use. Reversible: symptomatic bradyarrhythmias reversed to normal heart rate (> 60 beats/min) after cessation of β-blockers or rate-controlling drugs. Irreversible: symptomatic bradyarrhythmias persisted and required permanent pacemaker implantation. Others: Left bundle branch block with atrial fibrillation, 3: 1 atrioventricular block, atrial flutter with junctional escape beats.

malized following discontinuation of β-blockers or removal of the causative factors, 16 (28.1%) required temporary pacemaker but subsequently normalized and 11 (19.3%) were irreversible required permanent pacemaker implantation. Our exploratory analysis suggests that the most common reversible electrocardiographic pattern observed in patients on β-blockers was sinus bradycardia. Serious complications (in-hospital death) due to symptomatic bradyarrhythmias were not encountered in our cohort. There was one in-hospital death due to septicaemic shock in the bradyarrhythmias arm and the cause of death was not related to bradyarrhythmias.

4 Discussion

We conducted a literature search using Pubmed, Cochrane library, Ovid MEDLINE, Scopus and Google Scholar (until March 2016) did not return any studies related to the predictors of bradyarrhythmias in patients on β-blockers. Our study is unique that we identified hospitalized patients diagnosed with symptomatic bradyarrhythmias in relation to the presence and absence of β-blockers, which enables us to identify the potential risk factors in a selected cohort. Our preliminary results showed that older age was statistically significant as a predictor of symptomatic bradyarrhythmias in patients on β-blockers than those without β-blockers by univariate and multivariate regression analyses. In our cohort, the mean age of patients with symptomatic bradyarrhythmias belonged to the older age group (64.4 ± 13.4 years). Although we could not identify a cut-off point (knot) of age to predict symptomatic bradyarrhythmias in our statistic analysis, we think that our finding would be relevant in clinical setting. Nevertheless, our study population was small and restricted to hospitalized patients. Therefore, it is impossible to ascertain whether β-blockers was underused in an elderly community population with indication for β-blocker, or whether it is appropriately used and more carefully titrated among these elderly patients.

Aging is associated with electrical and structural changes of the myocardium; the response to catecholamines is also reduced and the baroreceptor reflex activity is blunted. These aspects conceivably affect the response to antiarrhythmic drugs such as β-blockers. Furthermore, age-related changes in pharmacokinetics and pharmacodynamics make the elderly vulnerable to the development of ADR.[23,24] Previous cross sectional and retrospective studies shown that the use of β-blockers have been associated with ADR in older patients. A retrospective study of ADR-related hospitalizations of older veterans showed that bradycardia secondary to beta-blockers and digoxin was the most common

cause of preventable hospitalization.[18] Another study found that serious ADR were developed by 4% of hospitalized patients taking cardiovascular drugs. Those at highest risk were older, were receiving multiple drug therapy and had higher urea levels. Warfarin and beta-blockers were the drugs causing the largest number of adverse effects.[15] In a cross sectional study of ADR-related hospitalization, found that the elderly and the poor are most affected by ADR. The study found that β-blockers consisted of 7.9% of the major therapeutic classes implicated in ADR.[16] Nevertheless, the common belief of β-blockers intolerance in the older population was not supported by RCTs. The evidence from RCTs indicates that β-blockers can be used safely and successfully in most elderly patients with CHF.[5,12,25] Further evidence comes from the SENIORS trial which was specifically designed to investigate the effects of beta- blockade (Nebivolol) in elderly CHF patients (mean age 76 years).[7] Bradycardia was reported as an adverse event in 118/1067 (11%) patients in β-blockers arm versus 28/1061 (2.6%) patients in placebo arm. However, β-blockers discontinuation rate due to intolerance was only 2.2% as compared to placebo (0.8%). It is sensible to anticipate the pharmacological differences between younger and older patients. With increasing age, renal function (or more precisely GFR) declines steadily which affect the clearance of renally metabolized medications.[24] Thus, additional dosage adjustment is necessary in the elderly especially if the drug elimination is via kidney. In addition, drug-disease interactions or drug-drug interaction may occur because of polypharmacy in older population.[24] As a result, this may unmask the underlying intrinsic disease of the sinus node or AV node causing pacemaking dysfunction that manifest as bradycardia that warrant further studies.

We found an inverse association between eGFR and symptomatic bradyarrhythmias in patients with and without β-blockers in univariate analysis. However, eGFR was not a predictor of symptomatic bradyarrhythmias on multivariate analysis regardless of presence or absence of β-blockers. In other words, lower eGFR was identified as a risk factor (or, higher eGFR was identified as a protective factor) of symptomatic bradyarrhythmias on univariate analysis. A possible explanation is the alteration of pharmacokinetics and pharmacodynamics of β-blockers in renal insufficiency. It is important to know that lipophilic β-blockers such as metoprolol and propranolol are metabolized in the liver whereas hydrophilic β-blockers such as atenolol are almost exclusively eliminated in the kidneys.[26] For this reason, the half life of hydrophilic β-blockers is significantly prolonged due to unfavorable excretion in renal insufficiency. Dose has to be adjusted according to renal function in the case of at-

enolol, sotalol and acebutolol.[27] Drugs like bisoprolol, betaxolol and pindolol have both hepatic and renal clearance. Another possible explanation for symptomatic bradyarrhythmias is the metabolic and electrolyte disturbance in renal insufficiency. Our study also showed that higher urea, potassium and lower sodium were significantly associated with symptomatic bradyarrhythmias in patients with β-blockers versus those without β-blockers on univariate analysis. It has been reported that electrolyte abnormalities such as hyperkalemia and hypercalcemia[29] could responsible for heart block in chronic renal failure.[28]

A recent meta-analysis by Badve et al. included six placebo-controlled heart failure trials of patients with CKD stages 3 to 5 (eGFR $\leq$ 60 mL/min per 1.73 m^2) demonstrated that β-blockers (carvedilol, metoprolol, bisoprolol, nebivolol and acebutolol) reduce mortality. However, the benefit of β-blockers came at a price of increased risk of bradycardia [risk ratio (RR): 4.92, 95% CI: 3.20–7.55].[30] Similarly, other studies on the use of β-blockers in patients with renal insufficiency demonstrated marginally significant increase in bradycardia[31] and higher rate of discontinuation due to adverse event such as hypotension and bradycardia.[32]

Regardless of presence or absence β-blockers, our study showed that 'concomitant use of rate-controlling drugs' has numerically higher adjusted OR but not statistically significant in association with symptomatic bradyarrhythmias estimated by multivariate regression analyses. It has been shown that β-blockers and concomitant use of other drugs such as non-dihydropyridine calcium channel antagonists (diltiazem and verapamil) were the cause of acquired complete AV block causing bradycardia in clinical practice.[33] A study by David et al aimed to determine the prognosis of drug induced-AV block found that AV block is commonly "related to drugs" but rarely "caused by drugs". Only 15% of patients who had second or third degree AV block during therapy with β-blockers, verapamil, or diltiazem was "truly caused by drugs".[34] A study by Lee, et al.[35] found that β-blockers were the most common drugs associated with drug-related bradycardia (DRB). In this study, drug discontinuation was followed by resolution of bradycardia in 60% of patients. In 23% of the cases, bradycardia persisted despite drug withdrawal, and warrant permanent pacemaker implantation. The results of our analysis showed that the majority (52.6%) of symptomatic bradyarrhythmias on β-blockers were reversible without the need of permanent pacemaker. Our study suggests that sinus bradycardia and junctional bradycardia were the most common reversible electrocardiographic pattern in association with β-blockers. Similar ECG diagnosis was reported in the above mentioned DRB study that sinus bradycardia and sinus bradycardia

with junctional escape beats were most frequently observed.[35] Notably, our study did not report any in-hospital death as a result of symptomatic bradyarrhythmias. The contributing factors towards the irreversibility of bradyarrhythmias were beyond the scope of our study. We were intrigued by the finding of higher BMI as a risk factor of symptomatic bradyarrhythmias in the multivarate analysis. This finding should be interpreted with caution because it may be related to differences in the patients who were enrolled, or it may simply represent the play of chance in statistical analyses that needs further study.

It is well-established that the survival benefit of β-blockers outweighs the side-effects risk as proven by observational, prospective and RCTs and its use is highly recommended by the CPG especially in treating heart failure and IHD.[5,6,9,10] These results should alleviate concerns in prescribing β-blockers particularly in patients with heart failure where the absolute survival benefits of β-blockers are most pronounced.[11,25] However, medication could be a double-edge sword. The result of our study does not intend to refute the benefit of β-blockers but has its clinical importance. The ability to predict potential bradyarrhythmias occurrence may be beneficial and may warrant managing patients on β-blockers more cautiously. Meanwhile, careful evaluation and constant monitoring are necessary when prescribing β-blockers to prevent ADR. ADR is an important cause of preventable morbidity with serious economic implications. Hence, special attention should be given to their prevention.[15,18,19,25] Guidelines and experts recommend that β-blockers should be prescribed at low initial doses and gradually titrated every two weeks to research validated targets or the maximally tolerated dose.[1,2,36] Patients should be instructed about the most common adverse effects (bradyarrhythmias, hypotension or worsening heart failure) which can arise in any patient if the dosage of β-blocker is too high or escalated too rapidly.

4.1 Limitation

Unlike RCTs, the authors recognize the limitation inherent in this retrospective observational study, and without RCTs we can never rule out unidentified confounders. We had difficulty in selecting suitable cases and our definition of symptomatic bradyarrhythmias was not stringent. It is because bradyarrhythmias vary in their types and nature and it is therefore difficult to decide which cases should be included. We dealt with this by recruiting all types of bradyarrhythmias with or without β-blockers use. Similar for controls, we recruited patients of similar risk profiles with the presence or absence of β-blockers use. Despite our effort to minimize sampling bias, we cannot be sure that controls

in our study ideally represent the source population to which the cases belong.

This study was constrained by small number of cases because the diagnosis of symptomatic bradyarrhythmias was rare. The small sample size was reflected in wide confidence intervals. Our focus on subjects in a single center (Johor Bahru) limits the extrapolation of the findings to entire population. However, because there is no other identical study on this topic as yet, our preliminary result may provide a basis for future study.

We recruited patients on different types of the β-blockers with comparable maximum daily dose of β-blockers in cases and controls. However, the type of β-blockers was self-reported and subjected to recall bias. The usage of different brands of generic and original beta blockers in our cohort may account for the differences in the active drugs among groups, and may potentially affect the outcomes.

Furthermore, we draw generalized conclusion with regards to the outcomes of all types of bradyarrhythmias in association with the use of different β-blockers. Other types of β-blockers such as nevibolol, sotalol, esmolol, pindolol and nadolol were not commonly prescribed in our practice and were not included in the analyses. The outcome results could be different if we include different type of β-blockers with different pharmacokinetic and pharmacodynamic properties. Obviously, further multicenter study with larger cohorts for the identification of cases, and lesser probability of referral bias to a single center is required to confirm the validity of these findings.

4.2 Strength

The main strength of this study is the design of a hospital-based case-control study that allowed us to identify risk factors of symptomatic bradyarrhythmias in association with the use of β-blockers. Unlike restricted populations in randomized control trials which tend to exclude high risk patients such as elderly and CKD patients. We believe our study is complementary to the existing RCTs and provided useful adjunctive information on the usage of β-blockers.

4.3 Conclusions

Our preliminary results showed that older age was statistically significant as a predictor of symptomatic bradyarrhythmias in patients on β-blockers than those without β-blockers. Majority of patients with symptomatic bradyarrhythmias on β-blockers were reversible without the need of permanent pacemaker implantation. The results should be intepreted with caution because of the small sample size and larger studies are required to confirm or refute these findings.

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