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Bisoprolo vs.Carvedilol: A Comparison of Clinical Efficacy and Tolerability in Congestive Cardiac Failure

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Abstract

BACKGROUND:

There has been no head to head comparison of the clinical outcomes between bisoprolol and carvedilol, the two beta blockers most commonly used to treat congestive heart failure in Australia. There is good evidence to support the use of either agent in the setting of CHF with significant mortality and morbidity benefits. There are some fundamental differences in the pharmacological properties, mechanisms of action and dosing regimens between the two agents. Our aim was to compare the clinical outcomes and tolerability of the two agents in the management of patients with CHF

METHODS:

Retrospective, matched, dual parallel group analysis at a community based multi-disciplinary heart failure program. Data extraction was done by chart review. Cohort of 132 patients with heart failure (NYHA functional classes II-III, aged 28-97 years) receiving bisoprolol (n=66) or carvedilol (n=66). The Main outcome measures included all-cause mortality, re-hospitalisation rates for cardiovascular reasons, change in heart rate, change in systolic blood pressure, change in diastolic blood pressure, change in left ventricular anatomy and function as measured by left ventricular ejection fraction (LVEF), left ventricular end systolic diameter (LVESD), and left ventricular end diastolic diameter (LVEDD) and change in New York Heart Association (NYHA) functional class over a period of 12 months since the initiation of therapy.

RESULTS:

Heart rate, systolic diastolic blood pressure, LVEF, LVEDD and LVESD at baseline and after 12 months were comparable in both groups. Re-hospitalisation rates for cardiovascular reasons, however, were

significantly lower in patients receiving carvedilol (1.6±0.7) vs. (2.2±1.1) (p <0.001). All-cause mortality appeared lower in the carvedilol group, 6 (9.1%) vs. 13 (19.7%), but this parameter did not reach statistical significance (p =0.083). There was a statistically significant drop in the systolic blood pressure in the carvedilol group after 12 months (132±42 mmHg) vs. (114±15 mmHg) (p<0.001).

CONCLUSIONS:

Clinical outcomes and tolerability were comparable between carvedilol and bisoprolol in the treatment of patients with CHF. However therapy with carvedilol was associated with a significantly lower rehospitalisation rate for cardiovascular reasons and a trend towards a lower mortality rate that did not reach statistical significance. These findings support the need for a prospective, randomised controlled trial comparing bisoprolol and carvedilol in the management of patients with NYHA class II-III CHF to better identify the differences in clinical outcomes and tolerability

Keywords: Congestive Cardiac Failure, Carvedilol, Bisoprolol.

Introduction

Beta blockers are very commonly used in the treatment of patients with congestive heart failure (CHF) with more than 120 million prescriptions in the United States in 2004 alone.[1] Evidence supports the efficacy of beta-blockers in reducing all-cause mortality and hospitalisation rates as well as improving New York Heart Association (NYHA) functional class in CHF.[2] Though their primary pharmacological function is to block beta adrenergic receptors, there are several important differences in the activity among the different agents within this class of drugs. Some agents exhibit relative specificity for beta-1 adrenergic receptors, whilst others are non-selective. Because of the differences in pharmacological properties of different beta blockers, it is useful to learn more about the relative efficacy and tolerability of each agent in patients with CHF.[3]

Bisoprolol is a beta-1 adrenergic receptor selective agent, with added beta-2 adrenergic receptor antagonist activity at doses higher than 20 mg. Its gastrointestinal absorption is quick and nearly complete. It has a plasma half-life of 10-12 hours.[4] It is eliminated by renal and hepatic routes with a high first-pass metabolism. It is prescribed once daily.[3] Carvedilol is a non-selective beta adrenergic receptor antagonist that blocks both beta-1 and beta-2 adrenergic receptors. It also blocks alpha-1 adrenergic receptors. In addition carvedilol has antioxidant properties that may inhibit vascular smooth muscle cell proliferation.[5,6] It has a plasma half life of 6.4 hours and eliminated by hepatic route with a high first pass metabolism. It is administered twice daily.

There is an up regulation of cardiac beta adrenergic receptor activity and an associated enhancement of sympathetic activation in CHF. Theoretically, carvedilol with its dual beta-1 and beta-2 receptors antagonist activity may cause greater reduction in heart rate, cardiac output and blood pressure[7]. This may translate into a relatively worse haemodynamic effect and intolerance compared to that of bisoprolol. Its alpha-1 receptor blockade may also contribute to a greater reduction in blood pressure compared to bisoprolol. Conversely, combined beta-1 and beta-2 blockade may be associated with better outcomes with carvedilol due to greater protection of the heart from excess sympathetic activation. Enhanced afterload reduction due to alpha-1 blockade may help better improve symptoms of CHF. Both agents have demonstrated improved morbidity and mortality outcomes compared to placebo in the pivotal randomised controlled trials in CHF[8, 9, 10]. However there has been no previous attempt at comparing the two agents head to head for morbidity and mortality in the management of heart failure patients.

Large scale randomised controlled trials in CHF have demonstrated the benefits of beta blocker therapy with carvedilol or bisoprolol in reducing all cause mortality, re-hospitalisations and cardiovascular morbidity [8,9,11,12]. Beta blockers have been observed to have similar tolerability and benefits to that of ACE inhibitors in CHF[13]. Carvedilol has non-selective beta adrenergic receptor antagonist activity together with alpha adrenergic receptor antagonist activity. In addition it also has anti oxidant properties and anti cell apoptosis properties that are believed to contribute to its clinical benefits in CHF[8]. Bisoprolol has beta-1 adrenergic specific antagonist activity. It is administered as a once daily dose, a factor that may positively impact on compliance.

Both carvedilol and bisprolol are widely used in the management of CHF in Australia. Often the decision to choose one agent over the other is determined by the clinician's personal preference and it is not based on any identified clinical criteria or comparative scientific evidence. Thus there is a need to compare these two agents to identify their relative efficacy and tolerability in the management of CHF. The aim of this study was to compare the clinical outcomes, efficacy, and tolerability of the two most commonly used beta-blockers, bisoprolol and carvedilol in the management of congestive heart failure.

Methods

This study protocol was approved by Gold Coast Health Service District Human Research Ethics Committee (EC0060).

STUDY POPULATION

We retrospectively reviewed the records 132 patients (93 males and 39 females) with heart failure (NYHA functional class II-III, aged 28-97 years, mean age 72 years) managed at the multi-disciplinary heart failure clinics in the Gold Coast Health Services District. All patients had at least one hospital admission during the previous 2 years for cardiovascular reasons, such as acute coronary syndrome, decompensated or acute heart failure, uncontrolled hypertension or cardiac syncope. Patients had been commenced on either carvedilol or bisoprolol therapy before September 2007. The selection of the agent was based on the personal preference of the treating clinician according to the clinical assessment. Patients' follow up data were collected for a period of 12 months since the initiation of therapy. 66 patients who received bisoprolol and 66 patients who received carvedilol during the relevant time period were randomly selected for the study and the analysis. The two groups were similar with respect to baseline characteristics and concomitant therapies at entry (Table 1). Inclusion and exclusion criteria for the study were as follows.

INCLUSION CRITERIA:

1. Adult patients with symptomatic congestive heart failure (NYHA functional class II–III).
2. Commencement on bisoprolol or carvedilol before September 2007 and continuation of therapy for at least 12 months.
3. Managed on conventional medical therapy during the study period (see table 1).
4. Echocardiographic confirmation of left ventricular systolic dysfunction with an ejection fraction of <50% at the initiation of study medications.
5. Haemodynamic stability at the commencement of the study medication with no symptomatic hypotension or bradycardia requiring inotropic support.

EXCLUSION CRITERIA:

1. Systemic malignancy or other serious systemic disease with a predicted life expectancy of less than one year.
2. Haemodynamically significant (critical) aortic stenosis.
3. High serum potassium > 5.0 mmol/L that can contribute to bradycardia.
4. Other co morbidities likely to cause death or serious disability within 12 months.
5. Severe anaemia (haemoglobin <6.0 g/dL) that could exacerbate heart failure.
6. Inability to walk without a personal aid since the assessment of NYHA functional class could be confounded by the disability or physical debility.

STUDY DESIGN

The study was an investigator-initiated, retrospective analysis with 2 parallel groups with comparable baseline characteristics (see table I). The patients were diagnosed with CHF according to the clinical assessment and echocardiographic findings. The aetiologies of heart failure in this study included ischaemic heart disease, cardiomyopathy, chronic hypertension and chronic regurgitant valvular disease (aortic and mitral regurgitation).

The patients were commenced on carvedilol or bisoprolol prior to September 2007, and dose increments were made according to tolerance over the following 12 months. Patients managed at the community based heart failure program upon discharge had regular follow up according to clinical requirements during the study period. Patients were also followed up in the community by the case managers and the investigators by house calls or via telephone. Patients' haemodynamic measurements were recorded during each visit. Echocardiography was performed to assess left ventricular dimensions and function. The left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) were considered as the suitable parameters for the assessment of the change in cardiac function and morphology. Patient's functionality was determined according to the NYHA functional classification.

The main therapeutic objectives in the management of CHF are to prolong life expectancy, improve functionality and prevent or reduce re-hospitalisation. Therapeutic efficacy as well as clinical tolerance of beta blocker therapy is signified by the changes in patient's heart rate and blood pressure. An objective assessment of patient's progress can be made by measuring the relevant echocardiographic parameters. The above physical and echocardiographic parameters have a direct bearing on patient's clinical status as well as prognosis. The mortality and hospital readmissions were very important factors widely used in clinical trials in the use of beta blockers in CHF patients[10,14]. Therefore, in this study, the primary endpoint was all-cause mortality at 12 months. Secondary endpoints were hospital readmission rates, haemodynamic parameters and echo parameters of left ventricular dimensions and function.

The dataset obtained from the review of medical records included the clinical diagnosis, functional class, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and results of echocardiography: at baseline and after 12 months, concomitant medications, as well as blood investigations, and relevant medical history.

After 12 months, outcomes of all-cause mortality, cardiovascular hospitalisation rates, vital signs (HR, SBP and DBP), LVEF, LVEDD, LVESD and change in NYHA functional class were recorded and compared between the two groups, following extraction of information from the patient medical records and community follow up calls.

STATISTICAL ANALYSIS

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) V16.0. Continuous data are shown as mean ± SD unless otherwise specified. Comparison of baseline variables between groups was performed with independent-sample t-tests for normally distributed continuous variables (after 12 months: LVEF, LVEDD, LVSDD, HR, DBP; baseline: HR, DBP, LVEF, LVEDD, LVSDD, NYHA class, haemoglobin), Mann-Whitney U test for non-normally distributed continuous variables (after 12 months: NYHA class, SBP; baseline: age, SBP, serum creatinine, blood glucose) and chi-square test for categorical variables (gender, aetiology, diabetes, atrial fibrillation/ flutter status, concomitant medications, history). All baseline variables were presented using appropriate descriptive summary tables. HR, SBP, DBP (after 12 months) and cardiovascular hospitalisation rates were compared between carvedilol and bisoprolol groups by independent-sample t-tests. The analysis of mortality was calculated by chi-square test. The level of statistical significance was set at a value of $p<0.05$ and all hypothesis tests reported were two-sided. The level of clinical significance was defined at a value of $p<0.10$.

Results

BASELINE CHARACTERISTICS

Compared to the bisoprolol group, participants who received carvedilol tended to have higher heart rates and lower ejection fraction, but these differences were not statistically significant (Table 1). Otherwise the two groups were well matched.

ALL-CAUSE MORTALITY

During the study period, a total of 19 deaths were recorded in the patient cohort investigated in this study. There were 6 deaths in the carvedilol group, and 13 in the bisoprolol group (p=0.083) (Table 2).

HOSPITALISATION RATES FOR CARDIOVASCULAR CAUSE

During the study period, hospitalisation rates for cardiovascular causes based on the comprehensive clinical chart analysis, recorded Diagnosis Related Group (DRG) definition as well as discharge summary and clinic letter information, for all patients were 1.9±1.0 times per patient per annum. It was less in the carvedilol group than the bisoprolol group, 1.6 (SD= 1.6±0.7) versus 2.2 (SD = 2.2±1.1) (95% CI -0.909– -0.273, $p < 0.001$) (Table 2).

COMPARISON OF NYHA FUNCTIONAL CLASS

No differences were observed in NYHA functional class between the carvedilol and bisoprolol groups either at baseline or after 12 months. At baseline, the NYHA functional class in the carvedilol group was 2.33±0.48, and was 2.39±0.49 in the bisoprolol group (p=0.473). After 12 months, the NYHA functional class in the carvedilol group was 2.26±0.45, and 2.33±0.48 in the bisoprolol group (p=0.372) (Table 2).

COMPARISON OF HR, SBP, AND DBP

Blood pressure (especially SBP) was reduced by beta-blocker therapy at 12 months (Table 2). SBP was reduced by 18 mmHg in the carvedilol group ($p<0.001$) and by 9 mmHg in the bisoprolol group ($p=0.210$). After 12 months, the averages of HR, SBP, and DBP in the carvedilol group were 73±10 beats/min, 114±15 mmHg, and 68±10 mmHg, respectively. The average of HR, SBP, and DBP in bisoprolol group were 71±12 beats/min, 121±39 mmHg, and 69±10 mmHg, respectively. These differences were not statistically significant (Table 2).

COMPARISON OF LVEF, LVEDD AND LVESD

After 12 months, ejection fractions in both groups improved relative to baseline (Table 2). There was a 9.1% increase in LVEF in the carvedilol group ($p=0.252$) and a 2.7% increase in the bisoprolol group ($p=0.389$). Mean values for LVEDD and LVESD were modestly reduced at 12 months compared with baseline in both groups. Average of LVEF, LVEDD and LVESD in the carvedilol group was 45.9±17.3%, 5.7±1.1mm and 4.5±1.3mm, respectively. The averages of LVEF, LVEDD and LVESD in bisoprolol group were 49.0±14.9%, 5.8±1.1mm and 4.3±1.2mm, respectively. These differences did not reach statistical difference (Table 2).

Discussion

This study compared two groups of patients with CHF and comparable baseline characteristics that were prescribed either carvedilol or bisoprolol together with conventional medical therapy. All patients were commenced on the starting dose according to the product description guidelines. The medication dose was up titrated at subsequent clinic visits to the maximum tolerated dose. Thus for carvedilol the dosage range varied from the starting dose of 3.125 mg twice daily to a maximum dose of 25 mg twice daily. For bisoprolol the starting dose was 1.25 mg and the maximum dose was 10 mg daily.

The results suggest a trend towards better survival with carvedilol. The primary end point of all-cause mortality, although numerically in favour of carvedilol group, did not reach statistical significance. The

secondary end point of hospital readmission rates was significantly better in the carvedilol group. The effects of carvedilol seemed to be significant on the determinants of cardiovascular re admissions rather than on the mechanism of death.

Both agents were well tolerated at the maintenance dose. Blood pressure and heart rate responses were comparable with a reduction in the measurements consistent with the anticipated haemodynamic effect with beta blockade. However there was a higher reduction in SBP in the carvedilol group and this reached statistical significance. The LVEF at baseline was lower in the carvedilol group. Overall improvement in the LVEF was greater in magnitude in the carvedilol group but this too did not reach statistical significance.

NYHA functional class improved modestly with both therapies in a comparable manner. The improvements however did not reach a statistical significance.

STUDY LIMITATIONS

The number of patients involved in this study was relatively small. The study design is a retrospective analysis. The predominant cause of CHF in the study population was ischaemic heart disease (69.7% in carvedilol group, 68.2% in bisoprolol group). This could be a bias against the accurate evaluation of outcomes in CHF due to other aetiologies.

Due to the retrospective nature of this study, one cannot be certain that some measured and unmeasured differences between the two groups may not have influenced the outcomes. These include the achieved maintenance dose of the medication, the duration of any medication interruptions, level of drug compliance, socio-economic status, and the reasons for physicians to prescribe either medication. Alternatively, the observed results may have occurred because of differences in baseline characteristics between the two groups that were not identified.

Conclusions

Compared to bisoprolol, carvedilol therapy may be associated with a further reduction in the risk of death in CHF patients who were managed on optimal conventional heart failure therapy. These results suggest that

carvedilol compared with bisoprolol may be more effective in reducing cardiovascular re admissions in patients with CHF with a trend towards a mortality benefit at one year. Haemodynamic effects of bisoprolol were comparable to that of carvedilol, except for SBP which was reduced significantly with the latter agent.

Both agents contributed to the improvement of LVEF though only modestly. Both agents demonstrate comparable tolerability and modest improvements in functional class. A randomised prospective trial is needed to compare more accurately and comprehensively the outcomes with these agents in the management of patients with CHF.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Jia Cao carried out the data collection, literature review and composed the article.

Ian Hamiltion-Craig, Laurence Howes, and John Edwards participated in its design and helped to draft the manuscript.

Jing Sun performed the statistical analysis.

Rohan Jayasinghe participated in the design and supervision of the study and obtained ethics committee approval and edited the manuscript.

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Tables

Table 1 Baseline characteristics

Characteristics	Carvedilol (n=66)	Bisoprolol (n=66)	P value
Age (yrs)	71±16	73±13	0.563
Males (%)	51(77.3%)	42(63.6%)	0.086
Heart rate (beats/min)	82±15	77±16	0.069
Systolic BP (mm Hg)	132±42	130±46	0.817
Diastolic BP (mm Hg)	74±14	73±12	0.699
NYHA functional class	2.33±0.48	2.39±0.49	0.473
AETIOLOGY OF CHF			0.705
Ischaemic heart disease	46(69.7%)	45(68.2%)	
Hypertension	2(3%)	4(6.1%)	
Cardiomyopathy	13(19.7%)	10(15.2%)	
Valvular heart disease	5(7.6%)	7(10.6%)	
LVEF (%)	39.8± 16.4	46.3± 20.5	0.097
LVEDD (mm)	6.0± 1.3	5.9± 1.4	0.581
LVESD (mm)	4.8±1.5	4.5±1.7	0.384
Diabetes	20(30.3%)	11(26.2%)	0.324
Atrial fibrillation/flutter	18(27.3%)	14(33.3%)	1.000
Haemoglobin (g/dl)	127±27	132±17	0.194
Serum creatinine (umol/l)	115±49	117±85	0.869

Blood glucose (mmol/l)	8.3±8.1	8.1±8.9	0.891
CONCOMITANT MEDICATIONS			
Diuretics	60	58	0.572
ACE inhibitors	61	56	0.170
Angiotension receptor antagonists	11	9	0.627
Digitalis	22	19	0.573
Antiarrhythmics	31	40	0.116
Nitrates	14	16	0.678
Aldosterone antagonists	9	6	0.411
Anticoagulants	24	21	0.582
Aspirin	42	37	0.375
Statins	47	38	0.102
HISTORY			
Hypertension	30	22	0.154
Myocardial infarction	8	5	0.381
Peripheral vascular disease	3	5	0.466
Cerebrovascular disease	12	15	0.517
Renal disease	10	12	0.640
Anaemia	8	6	0.572
COPD	13	9	0.350

Values are mean± SD, n (%)

New York heart association, NYHA; chronic heart failure, CHF; heart rate, HR; systolic blood pressure, SBP; diastolic blood pressure, DBP; left ventricular ejection fraction, LVEF; left ventricular end diastolic diameter,

LVEDD; left ventricular end systolic diameter, LVESD; angiotensin-converting enzyme, ACE; congestive obstructive pulmonary disease, COPD.

Table 2 Clinical differences between study groups at baseline and after 12 months

	Carvedilol (n=66)	Bisoprolol (n=66)	P value
NYHA functional class			
Baseline	2.33±0.48	2.39±0.49	0.473
After 12 months	2.26±0.45	2.33±0.48	0.372
HR (beats/min)			
Baseline	82±15	77±16	0.069
After 12 months	73±10	71±12	0.467
SBP (mm Hg)			
Baseline	132±42	130±46	0.817
After 12 months	114±15	121±39	0.192
DBP (mm Hg)			
Baseline	74±14	73±12	0.699
After 12 months	68±10	69±10	0.548
LVEF (%)			
Baseline	36.8±16.4	46.3±20.5	0.097

After 12 months	45.9±17.3	49.0±14.9	0.456
LVEDD (mm)			
Baseline	6.0±1.3	5.9±1.4	0.581
After 12 months	5.7±1.1	5.8±1.1	0.754
LVESD (mm)			
Baseline	4.8±1.5	4.5±1.7	0.384
After 12 months	4.5±1.3	4.3±1.2	0.620
Hospitalisation rates (times per patient per annum)	1.6±0.7	2.2±1.1	<0.001***
Mortality	6 (9.1%)	13 (19.7%)	0.083

Values are mean± SD, n (%)

***P<0.001

New York heart association, NYHA; heart rate, HR; systolic blood pressure, SBP; diastolic blood pressure, DBP; left ventricular ejection fraction, LVEF; left ventricular end diastolic diameter, LVEDD; left ventricular end systolic diameter, LVESD.