Original Article

Assessment of Tolerability of β- blockade therapy in Patient with Left Ventricular Systolic Dysfunction Heart Failure

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Abstract

Back ground: Little data exist to demonstrate the tolerability of β-blocker therapy in an unselected community heart failure population already treated with the clinical trial or higher dose ACEI or ARB.

Methods and results: 141 patients who had left ventricular systolic failure on standard therapy were recruited in our study. Patients were assigned to receive either Carvedilol or Bisoprolol.

Conclusion: This prospective observational study showed that β-blocker therapy is well tolerated and can be safely titrated in an out-patient setting.

Keywords: Carvedilol, Bisoprolol.

Heart failure, a complex clinical syndrome that develops as a consequence of cardiac disease is an increasingly common condition. The prevalence of heart failure in a recent community based study was 3.9% in people aged over 55 years old[1]. The prevalence increased with age to between 11-13% in those over 75 years old. Based on such figures, one would expect prevalence in Ireland of approximately 80.000 people. Heart failure remains a lethal condition. The most recent figures (which admittedly do not reflect recent advances) suggest a five year survival rates of less than 40% from the time of diagnosis[2]. It is a condition which represents the number one public health problem in cardiovascular medicine and this is reflected in public spending. In 1991 the US spending on heart failure represented 4.8% of the total Medicare budget[3].

The frequency of hospitalization accounts for much of the economic burden in the condition. It is a condition that is associated with readmission rates of 20%-40% especially within three month of discharge[4].

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Many advances have been made in the treatment of heart failure over the last ten years.

Aims

To assess and compare tolerability of a conventional β-blocker (Bisoprolol) with Carvedilol (which has an additional α blocking activity) in an unselected group of patients with LV systolic dysfunction on maximal medical treatment with RAAS modifying therapy (either ACEI or ARB) attending a specialist heart failure clinic.

Method

This prospective observational study recruited patients referred from either the heart failure service or from cardiology OPD at St- Vincent's university hospital Dublin, Ireland from October 2004 to September 2005.

Each patient was initially screened by the investigator following admission or referral including review their echocardiography study. The heart failure service reviews all patients admitted through Accident and Emergency with a diagnosis of heart failure.

Initially Carvedilol was added to the patients' drug therapy as Bisoprolol tablets 1.25mg were not available at that time.

Subsequent to Bisoprolol 1.25mg becoming available on the market patients were alternately assigned to either Bisoprolol or Carvedilol. Seventy-nine patients received Carvedilol and 62 received Bisoprolol.

The dose of β-blocker was up-titrated at two weeks intervals according to the current consensus recommendations (table1). Prior to this the investigator examined all patients to ensure suitability for up–titrations.

Table 1:

titration	Bisoprolol	Carvedilol
Step1	1.25 mg OD	3.125 mg BD
Step2	2.5 mg OD	6.25 mg BD
Step3	3.75 mg OD	12.5 mg BD
Step4	5 mg OD	25 mg BD
Step5	7.5 mg OD	50 mg BD
Step6	10 mg OD	

During each visit the patients had their blood pressure and pulse monitored every 30 minutes for two hours after the dose was up-titrated.

The target dose of Bisoprolol was > 5 mg once daily. The target dose of Carvedilol was 25mg twice daily and the maximum dose 50mg twice a day for those weighing more than 85kg.

Population

One hundred and forty one patients with left ventricular systolic dysfunction heart failure had β-blockers added to their standard therapy.

Inclusion criteria

Signs and symptoms of heart failure with echocardiographic and Doppler evidence of left ventricular systolic dysfunction (ejection farction less than 45 %)

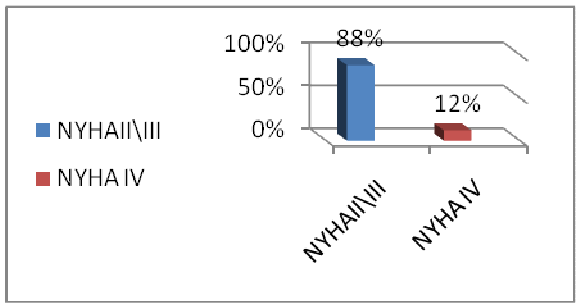
Exclusion criteria

Patients excluded were those with history of asthma confirmed by significant reversible obstructive airways disease on pulmonary test , and those with high degree of AV block (2nd and 3rd Degree Heart Block) , sinus nodal disease and chronotropic incompetence , unless paced .

Patient characteristics

The demographic and baseline characteristics of the total patient population are presented in Table 2 and 3.

All patients were on maximally tolerated ACE inhibitor or ARB before initiation of β-blocker therapy (fig2) Approximately 51% of patients were on target dose ACE inhibitor / ARB (perindopril ≥4 mg , ramipril ≥ 5 mg bd , innovace ≥ 10 mg bd , lisinopril ≥ 20 mg od , losartan ≥ 50 mg od , candesartan ≥ 8 mg od) . All were on loop diuretics , 37.6% were on digoxin , 38.3% were on nitrates and 6.4% were on spironolactone at initiation of β-blocker titration (all p = NS for C versus TD , where C is the group of patients who tolerate small dose of β-blocker therapy or are deemed intolerant and TD is the group who achieve target dose). 12 % of the patients in this study had started β-blocker therapy during admission with heart failure (NYHAIV) fig (1).



Fig(1): shows The symptomatic Classification of Heart Failure during initiation b-blocker therapy.

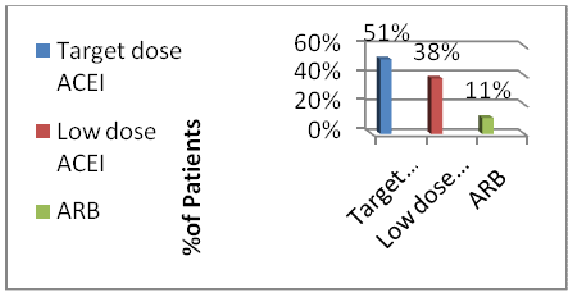


Fig (2): Shows the percentage of patients on different doses of ACE inhibitors and ARB.

Table 2 : Demographic characteristics between Bisoprolol and Carvedilol group.

Characteristic	Total Population	Bisoprolol	Carvedilol	P (BVC)
N	141	62	79	
Age± SD (years)	67.98±11.43	68.53±12.03	67.54±10.99	P=0.60
Male (n): female (n)	98:43	44 : 18	54:25	p=0.738
ACE/ARB:Neither: ACE:ARB:Both	3:122:12:4	1:56:2:3	2:66:10:1	p=0.051
Target dose ACEi/ARB,yes (n): no (n): neither	74:64:3	35:26:1	38:29:2	p=0.431
Nitrate , yes (n):no(n)	54:87	29:33	25 :54	p=0.067
Loop diuretic dose ***±SD(mg)	50.25± 28.39	52.36(34.1)	48.44(22.48)	p=0468
Digoxin,yes (n):no(n)	53:88	21:41	32:47	p=0.419
Aldactone, yes (n): no(n)	9:132	4:58	5:74	p=0.693
Mean SBP/DBP before titration± SD(mmHg)(between groups)	127/74±20/13	125/74±22/13	127/74±19/13	p=0.516 p=0.989
Mean SBP before titration ±SD	121/70±21/13	121/71±21/12	121/70±21/13	p=0.67
SBP after titration ±SD(mmHg) (within groups)				p=0.028
DBP before titration±SD/DBP	74±13:70±13	74±13:71±12	74±13:70±13	p=0.001
After titration ±SD(mmHg)(within Groups)				p=0.005
Mean urea pre titration (SD) (between groups)	8.24±3.64	8.04(3.7)	8.32 (3.6)	p=0.666
Mean urea post titration (SD) (between groups)	8.55±4.03	8.34(4.0)	8.63 (4.0)	p=0.667
Mean urea pre (SD):mean urea	8.19(3.6):8.5	8.04(3.7)	8.32(3.6)	p=0.221
Post titration (SD) (within groups)	(4.0)	8.34 (4.0)	8.62 (4.0)	p=0.370
Sinus rhythm, yes (n) :no(n)	47:94	17:45	30:49	p=0.187

Follow up

Duration of follow up was one year, with the investigator reviewing all patients at three and six months post completion of β-blocker titration.

Statistical Analysis

Age , loop diuretic dose , mean systolic and diastolic blood pressure both before and after titration , mean urea pre and post titration were all compared using the Student t-Test with a $p< 0.05$ demonstrating a significant difference .

Proportion of male to females in the study population of ACE inhibitor to ARB dose, whether nitrates, digoxin , spironolactone were administered or not , whether patients were in sinus rhythm , hypertensive or had underlying ischemia were all compared using Chi-squared test . Significance was attributed to p value < 0.05.

Although the sample population is small (n= 141), the group was very representative of a typical heart failure population, given the fact that patients form hospital admissions, GP referrals etc were included in the study. Allied to this is the fact that the only exclusion criteria were patients in whom beta-block would be contra-indicated, and those with high degree AV block.

Table 3: Baseline characteristics of total population and patient group who achieved target dose β-blocker therapy (TD) or not (C).

Characteristic	Total Population	C Group	TD Group	P (TD V C)
N	141	47	94	
Age± SD (years)	67.98±11.43	72.81±10.05	65.56±11.36	P=0.00
Male (n): female (n)	98:43	26 : 21	72:22	p=0.01
ACE/ARB:Neither(n): ACE(n) ARB(n):Both (n)	3:122:12:4	2:38:5:2	1:84:7:2	p=0.521
Target dose ACEi/ARB,yes (n):no (n): neither(n)	74:64:3	25:20:2	49:44:1	p=0.752
B-Blocker type ,BS(n):CV(n)	62:79	27:20	35:59	p=0.023
Nitrate, yes(n): no(n)	54:87	21:26	33:61	p=0.270
Loop diuretic dose ***±SD(mg)	50.25± 28.39	47.62±28.27	51.69±28.54	p=0.457
Digoxin,yes (n):no(n)	53:88	15:32	38:56	p=0.325
Aldactone, yes (n): no(n)	9:132	2:45	7:87	p=0.465
SBP/DBP before titration ±SD	127/74±20/13	123/70±21/12**	128/75±19/13**	p=0.128 P=0.020
SBP/DBP after titration ±SD	121/70±21/13	118/69±23/13	123/71±20/13	p=0.270 P=0. 335
Mean urea pre titration(SD)	8.24±3.64	9.61±4.54	7.48±2.8	p=0.001
Mean urea post titration(SD)	8.55±4.03	10.52±5.17	7.53±2.88	p=0.001
Sinus rhythm, yes (n) :no(n)	47:94	15:32	32:62	p=0.801
Ischaemia, yes (n):no(n)	99:42	37:10	62:32	p=0.118
Hypertension ,yes (n) : no(n)	30:111	11:36	19:75	p=0.662
Titration duration in days (SD)	60.47±68.07	43.15±75.5	69.23±62.61	p=0.032

Results

β-blockers titration was carried out in 141 consecutive patients with left ventricular systolic dysfunction. Ninety-four (67%) achieved target dose (TD) β-blocker therapy. Of the remaining 47 patient, 24 achieved low dose β-blocker therapy and 23 were deemed intolerant (Table 2, 3).

Age and gender differences were noted between the groups with a higher proportion of males in the C group. The mean urea values were significantly higher in patients in the C before and titration. There is no statistically significant drop in systolic blood pressure (SBP) between the groups before or after titration but there were significant drops in it SBP within the groups before and after titration. However, diastolic blood pressure (DBP) levels were significantly higher pre-titration for the TD group and dropped significantly during titration to the level of the C group. The DBP levels did not drop in the C group after titration.

Dosage and Tolerability

118 patients (83.7%) tolerated β-blocker during one years of follow up (Fig 3).

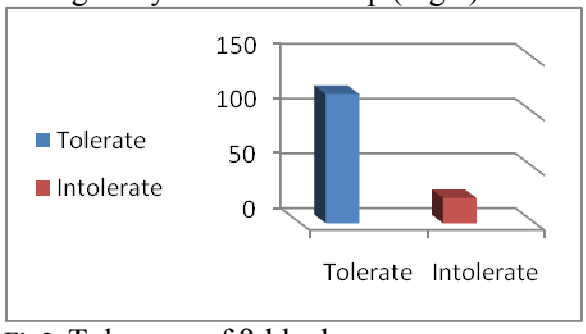


Fig3: Tolerance of β-blocker

Table 4: type of beta blocker * tolerability of blockers cross tabulation

Type of beta blocker		tolerability of beta blockers		
		tolerate	don't tol	Total
Bis	Count	49	13	62
	%within Type of BB	79.0 %	21.0 %	100.0 %
	%within Tolerability	41.5 %	56.5 %	44.0 %
	% of Total	34.8 %	9.2 %	44.0 %
Car	Count	69	10	79
	%within Type of BB	87.3 %	12.7 %	100.0 %
	%within Tolerability	58.5 %	43.5 %	56.0 %
	% of Total	48.9 %	7.1 %	56.0 %
Total	Count	118	23	141
	%within Type of BB	83.7 %	16.3 %	100.0 %
	%within Tolerability	100.0 %	100.0 %	100.0 %
	% of Total	83.7 %	16.3 %	100.0 %

74.7% of patients tolerated target dose of Carvedilol. 12.7% tolerated small doses of Carvedilol (≤ 6.25 mg twice daily). This makes total tolerability of Carvedilol 87.4%. However only 56.5% tolerated target dose of Bisoprolol and 22.6% tolerated low doses of Bisoprolol (≤ 2.5 mg once daily) making the total tolerability of Bisoprolol 79.1% (Fig 4. Table 4).

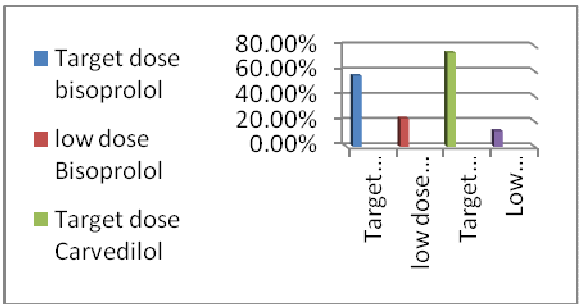


Fig (4): Shows tolerability of different doses of carvedilol and bisoprolol:

16.3% of patient (n-23) were unable to tolerate β-blocker therapy, (n-10) in Carvedilol group and(n-13) in Bisoprolol group (Table 5).

Five of the patients were intolerant to β-blocker because of worsening heart failure (n=5), objectively confirmed by weight gain and chest x-ray, and subjectively by exacerbation of symptoms (dyspnoea, fluid retention and quality of life questionnaire).

Seven of the patients were deemed intolerant because of symptomatic hypotension confirmed by blood pressure monitor for four hours. (Systolic blood pressure less than 90 mmHg).

Six patients declined to continue β-blocker titration. Five patients were intolerant of β-blocker because of syncope, bradycardia less than40, as per ECG, worsening respiratory status, Reynaud's phenomenon, pemphigus (each 1 patient).

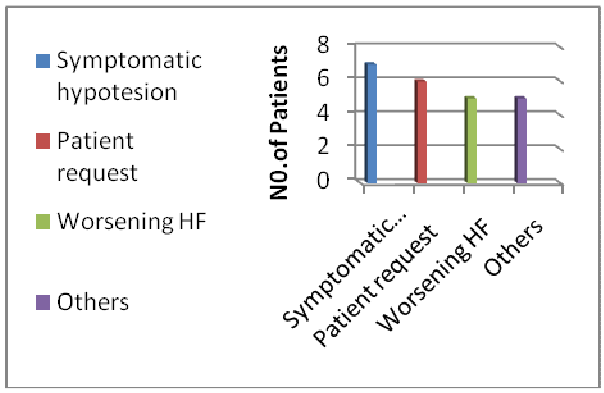


Fig (5): Shows reasons for β -blockers intolerability.

Table 5 (below). Shows adverse event rates compared to USCP and CIBIS II

	USCP		CIBS II		Present study	
Event	Placebo	Carvedilol	Placebo	Bisoprolol	Carvedilol	Bisoprolol
Worsening heart failure	21	16	23	18	2	3
dizziness	20	33	10	13	1	0
Bradycardia	1	9	5	15	0	1
Hypotension	23	25	7	11	3	4

16.3% of patient who did not tolerate the β-blocker, crossed over to the other one.

There was a small percentage, which were able to tolerate the alternative.

23.3% required adjustment of concomitant medication to achieve β-blocker titration. 51% developed systolic blood pressure of less than 90 during up-titration. 87% of those were asymptomatic (fig5, table5)

Discussion

There is considerable data from the meta–analyses of many small trials and from CIBISII showed the beneficial role of β-blocker therapy in heart failure[5-7] .The modern era of large randomised controlled trials involving β-blockers really started with the US Carvedilol Heart Failure Study, in which a very substantial reduction in mortality and morbidity was shown with Carvedilol. Another study with Carvedilol was the smaller Australia- New Zealand Heart Failure Research Group Trial of around 300 patients following myocardial infarction[8]. This showed a reduction in a composite end point of hospitalizations but focused on one aspect –the effect on left ventricular function—which suggested that it was improved by Carvedilol. This effect has now become an important future of β-blocker treatment. The Copernicus Trial showed the safety and efficacy of β-blocker therapy in sever heart failure. The follow-up of our study was one year which was equal to MERIT HF, was shorter than CIBIS II and longer than COPERNICUS and USCP. The mean LVEF of 29.4%, is comparable to those on CIBIS II, MERIT-HF and is higher than those in Copernicus and USCP. A mean age of 67 years make this study's population older compared to the previous mentioned trial. The number of male patients was double the number of female. This is consistent with previous trials (female gender under-represented). It seems quite clear from the totality of the data presented that β-blockers substantially reduce mortality and morbidity in patients with NYHA class II-IV CHF caused by left ventricular systolic of all causes[9-11] . These large trials are supported by meta-analyses of smaller studies [12,13].

The findings from this study were consistent with previous trials, which showed large populations tolerating high dose Carvedilol better than Bisoprolol, but at a low dose the tolerability is comparable (Fig.4).

Clinical trials have shown that the maximum dose of β-blockers was determined not by their clinical response but by a pre specified target dose. Although target doses were successfully achieved by many patients and produced significant clinical benefits, most trials did not evaluate whether lower doses would be effective, lower doses were prescribed only if target dose was not tolerated. Only one trial (with Carvedilol) has compared the clinical effects of different doses of β-blockers. Although high dose of Carvedilol (25 mg twice daily) appeared to be more effective than low doses (6.25 mg twice daily) in that study; low doses were associated with significant improvement in ejection fraction, and significant decrease in the risk of death or hospitalization[14]. Therefore, an effort should be made to achieve target doses, low doses β-blockers should be maintained if high doses are not tolerated. Nevertheless, the α blocking vasodilatory activity of Carvedilol may make early upward dose titration of this drug better tolerated than β-adrenergic antagonism without vasodilatory activity. It

was observed that patient on Carvedilol tended to have more dizziness (13-15%), most probably due to its α-blocker effect.
12% of our patients had started β-blockers therapy during admission with heart failure (NYHA Class IV) and they tolerated this well.

In a setting of worsening heart failure during β-blockers therapy, β-blockers dose should not be up titrated further and if necessary can be decreased gradually. Abrupt withdrawal of treatment with β-blockers can lead to dramatic clinical deterioration and should be avoided.

The ideal β-blockers choice in chronic heart failure.

β-blockers achieve most of these effects by blocking the deleterious effect of chronic over exposure of the heart to noradrenaline which cause cardiac hypertrophy, ischaemia and myocyte damage. When selecting β-blockers, no clear consensus exists as yet on which of the pharmacological activities of β-adrenergic antagonists are necessary or desirable in treatment of heart failure, however, it is probably advisable to choose a β1 selective drug because that improves tolerability. It would also seem prudent to select one that is lipophilic, this particular point is debatable. However, it is noteworthy that most existing data linking β-blockers with reductions in sudden death are for more or less lipophilic drugs – propranolol , Timolol , Metoprolol , bisoprolol- . Nadolol , atenolol ,and sotalol , which are not lipophilic , have not had the same impact on sudden death post myocardial infarction . This is not to suggest that the latter drugs do not act via β-blockers, or that they do not reduce blood pressure and infarct rates. They simply have not had the same impact on sudden death as the lipophilic β-blockers. β-blockers- like Carvedilol- which are β1,2 and α blockers can interfere with the adverse effect of sympathetic activation through several noradrenergic mechanisms which is important in severe heart failure , they also have anti-oxidant and anti-endothelin properties . However, β-blockers with significant ISA properties are shown to have excess mortality in patients taking active drug and the trial was terminated early (xamaterol in severe heart failure study) [15].
Both Carvedilol and Metoprolol are highly lipophilic compounds and are metabolized and cleared by the liver. In the setting of hepatic congestion, dosage reduction may be required. Bisoprolol is less lipophilic and exhibits both hepatic and renal clearance. There does not appear to be any significant interaction with other cardiac drugs.

Conclusion

This prospective observational study showed high tolerability levels (83.7%) in an unselected community based heart failure population. Carvedilol is better tolerated than Bisoprolol at high dose, partly due to α blocking vasodilatory effect, which reduces after load and offsets to some degree the early negative inotropic effect of β-blockers and potentially improve tolerability and early upward dose titration. However at low doses the tolerability of Carvedilol and Bisoprolol were comparable.

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