Exploration of a Better Beta Blocker in The Management of Heart Failure

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ABSTRACT

Supervision of patients with heart failure has been altered dramatically throughout the past decade. A fundamental change in the approach to treating heart failure caused by systolic dysfunction is in headway. Beta blockers have made an appearance as an important intervention to improve the clinical consequence of heart failure patients. In spite of initial perception about their safety, they are the most widely studied class of agents in the treatment of heart failure. The beta blockers in Heart Failure Collaborative group (BB-HF) was manifested to attain and scrutinized individual patient data from the major randomized controlled trial of beta blockers in heart failure. We have conceded 13 large randomized trials of beta blockers in heart failure and endeavor to analyze the data. All these trials have enrolled 20427 patients in total. Our prime objectives include acquiring a comprehensive estimate of efficacy for all cause mortality and cardiovascular hospitalization.

Keywords: heart failure, beta blockers, left ventricular ejection fraction, all-cause mortality

INTRODUCTION:

Heart failure (HF) is a common and widespread condition concerning high morbidity and mortality rates, making it a chief health problem particularly among the elderly.[1-3]An annual estimation of health care cost related to heart failure is $39.2 billion in the United States and £625 million in the UK which is increasing along with its incidence and prevalence.[4-5] Beta-blockers showed negative impacts on myocardial contractility and were contraindicated in HF patients.[6] With more knowledge about the pathophysiology of HF, the hypothesis developed that beta blockers may reduce inappropriate sympathetic drive, alleviate heart rate and allow a better cardiac filling.

The efficacy and safety of beta blockers in HF patients have been examined in a series of clinical trials. According, to the result beta-blockers are a key treatment of heart failure.[6]

This paper provides a chronological framework of the controlled trials of beta-blockers in heart failure. Our main objective is to provide information to clinicians and physicians to help them decide which beta-blocker is better suitable for different group of patients. This paper will also be of great help to researchers as they will be able to deduce how many studies have been done regarding this case including the results and limitations.

PHARMACODYNAMICS AND PHARMACOKINETICS:

Beta blockers produce their effects through competitive inhibition on the effects of catecholamines, which activate the adrenergic receptor.[7] Carvedilol, laetelol and bucindolol are alpha-1 adrenergic receptor antagonists and this activity are important in heart failure. Though nebivolol doesn't show alpha-1 adrenergic receptor antagonism, but it's vasodilating property and antioxidant property can play a great role in heart failure.[8] The beta blockers can be subdivided according to their cardioselectivity, their intrinsic sympathomimetic activity, their vasodilatory property and hydrophobicity or lipophilicity.[9] Beta blockers that are lipophilic in nature, e.g. metoprolol, bucindolol, carvedilol etc. are rapidly absorbed in GIT when they are administered orally. They are extensively metabolized by the liver and they have short half life. The higher the lipophilicity of the beta blockers, the more their membrane stabilizing property will increase and the more they can cross the blood brain barrier(BBB).[10] Beta blockers with intermediate lipophilicity have higher bioavailability(90%). Many beta blockers are metabolized by the liver through CYP2D6 enzyme. Others CYP isoenzymes e.g. CYP1A2, CYP2C9 etc. can contribute also but to a lesser extent.

In a controlled clinical trial two different forms of metoprolol were used and in the COMET study it was found that metoprolol tartrate arm had reduced efficacy compared to carvedilol. As a result an idea was risen that this pharmacological difference occurred due to the different degree of β-blockade by metoprolol and carvedilol and this result might occur due to the insufficient dose of metoprolol (Poole-Wilson et al., 2003).[11]

Table 1: Pharmacological Properties of Common β –blockers[12-16]

Beta blockers	Property	β_1 selectivity (less/more)	Degree of ISA (none/some)	Vasodilatory (yes/no)	α – AR blockade	Membrane stabilizing activity	Bioavailability (%)	Half life (hrs)
Non-selective β -blockers								
Propranolol	Lipophilic	0	0	No	0	++	25	3-5
Nadolol	Hydrophilic	0	0	No	0	0	35	10-20
Timolol	Hydrophilic	0	0	No	0	0	50	3-5
Pindolol	Hydrophilic	0	++	No	0	±	75	3-4
Labetalol	Hydrophilic	0	+	Yes	+	±	20	4-6
Carvedilol	Lipophilic	0	0	Yes	+	0	30	7-10
β_1 –selective								
Metoprolol	Lipophilic	++	0	No	0	±	40	3-4
Atenolol	Hydrophilic	++	0	No	0	0	50	5-8
Esomolol	Hydrophilic	++	0	No	0	0		0.13
Acebutolol	Lipophilic	+	0	No	0	+	40	8-12
Bisoprolol	Lipophilic	++	0	No	0	0	90	9-12
Nebivolol	Lipophilic	++	0	Yes	0	0	12-96	10-30

** 0 indicates no activity , + & ++ indicate relative activity , ± indicates activity can be opposed

CLINICAL TRIALS:

Many trials have already been conducted on CHF patients using beta blockers. Questions are raised which of the beta blockers are better to use on CHF patient. These protocols are important in understanding the effect of beta blockers in patient with Congestive Heart Failure. A variety of beta blockers were used in these studies.

Table 2: Chronological order of thirteen randomized trial on CHF patient.

Trial	Year
CIBIS-I[19]	1994
US Carvedilol HF study[17]	1996
ANZ[18]	1997
MERIT-HF trial[21]	1999
CIBIS-II[20]	1999
BEST[23]	1999
COPERNICUS[22]	2001
COMET[24]	2003
CIBIS-III[25]	2005
Marazzi et al.[26]	2007
SENIORS[27]	2009
CARNEBI[29]	2013
J-DHF study[28]	2013

One of the prominent controlled clinical trials (**US Carvedilol HF study**) have shown that beta blockers can give symptomatic and hemodynamic improvement in CHF. In a double blinded, placebo controlled trial, they had taken 1094 patients with CHF (Left Ventricular Ejection Fraction ≤ 0.35). The aim of this trial to observe the occurrence of death or hospitalization for cardiovascular reason. All causes of mortality were reduced by 65% due to carvedilol compared with placebo (95% confidence interval; $p < 0.001$). Carvedilol reduces the risk or death as well as the risk of hospitalization for Cardiovascular causes in patients with heart failure who are receiving treatment with digoxin, diuretics, and angiotensin converting enzyme (ACE) inhibitor.[17]

In another study of Australia / New Zealand (**ANZ**) Heart Failure Research Collaborative Group has shown that use of beta blockers improves Left Ventricular Ejection Fraction (LVEF). It was a double blind, placebo controlled, randomized trial of carvedilol versus placebo. LVEF had increased by 5.3% ($p<0.0001$) after 12 months and significant reduction in end-diastolic and end-systolic heart dimensions by 1.7 mm ($p=0.06$) and 3.2 mm ($p=0.001$) respectively. Death or hospital admission reduction in this trial is 26% ($p=0.02$).[18]

In another randomized trial of **C**ardiac **I**nsufficiency **BI**soprolol **S**tudy (**CIBIS**) with 641 heart failure patients, bisoprolol had shown improvement in HF due to idiopathic dilated cardiomyopathy. However, in this trial no benefit was proven for survival.

The age of the patients was between 18 to 75 (EF<40%) and patients were in NYHA functional class III (95%) or IV at inclusion. All of them were given diuretics as well as ACE Inhibitors. After 1.9 years mean follow up, it is found that no significant difference is observed in the sudden death rate between the bisoprolol and placebo. However, observed improvement is seen in the functional states of the patients. Markedly less patients of the bisoprolol group required hospitalization for cardiac decompensation (90 on placebo Vs 61 Bisoprolol; $P<0.001$). Moreover, many patients were improved by at least one functional class by the end of the trial. (48 on placebo Vs 68 on bisoprolol; $p=0.04$) Overall, reduction in mortality was 67 deaths in placebo Vs 53 on bisoprolol. However, using bisoprolol shows extremely insignificant improvement in survival.[19]

Again, another double blind randomized placebo controlled trial **(CIBIS II)** conducted in Europe 2647 symptomatic patients with NYHA class III and Iv (LVEF≤35%). Patients also given background therapy of diuretics and ACE inhibitors. Mean follow up period was only 1.3 years. This study was terminated quickly because bisoprolol showed significant improvement in the mortality. All cause mortality was lower for bisoprolol group (11.8%) Vs placebo (17.3%). Death with (HR: 0.66;95% CI: 0.54-0.81;$p=0.0001$) fewer sudden death in patients of bisoprolol group than that of placebo [(3.6% Vs 6.3%)] (HR: 0.5;95%CI: 0.39-0.80;$p=0.0011$). This trial confirms the benefits for survival in stable heart patients. However, safety and efficacy have not been established yet for severe NYHA class IV patients.[20]

Before **MERIT-HF trial**, the role of beta blockers was unclear. MERIT-HF (i.e. **Metoprolol CR/XL Randomized Intervention Trials in congestive Heart Failure**) was one of the large double blinded blind randomized controlled study enrolling 3991 symptomatic HF patients of age between 40 to 80. Mean follow up time was around one year (EF≤40%). This trial showed that there was a reduction in mortality was 34% composed to placebo. Along with that sudden death was also lower for metoprolol CR/XL group than in the placebo (79 Vs 132, 0.59 [0.45-0.78]; $p=0.0002$) and death from worsening heart failure (30 Vs 58; 0.51 [0.33-0.79]; $p=0.0023$). This trial was also stopped quickly because metoprolol CR/XL was well tolerated using it once daily had shown to improve survival.[21]

The **Carvedilol prospective randomized cumulative survival** (**COPERNICUS**) trial was used to investigate the influence of carvedilol on the survival of patient with severe HF. The trial had enrolled 2289 patients in NYHA class III or IV (LVEF≤25%). After, 27% fewer days spent in hospital and 40% less days the 10.4 months of follow up, carvedilol showed a 34% reduction in mortality spent in for HF patients. Less serious adverse event was found with carvedilol and the benefit of carvedilol appeared during the up-titration period.[22]

After all these studies, it was certain that few beta blockers reduce morbidity and mortality significantly in patients with wild chronic HF. However, the effect of **B**eta blockers **E**valuation of **S**urvival **T**rial (**BEST2001**) was conducted with 2708 patients and those in NYHA class IV HF. Mean follow up period was 2 years. However, the trial was terminated early it was unsuccessful to show any improvement in mortality (23% bucindolol and 25% placebo). On the other hand, in this trial, cardiac mortality and re-hospitalization benefits were observed in bucindolol group. Digoxin was also given to all patients as background therapy. Exploration of this reduced effect of bucindolol in HF patient said that the existence of many different polymorphism of the β1 adrenergic receptor group and variants of the pre-functional adrenergic receptor may influence the clinical response of bucindolol.[23]

COMET 2003 remains the greatest and most well designed face to face trial of beta blockers. It was mainly built upon data from MERIT-HF (1999) and COPERNICUS(2001) trial which shows survival benefit of metoprolol and carvedilol respectively.

COMET trial recruited 3029 patients with chronic HF, systolic dysfunction and who are on background treatment with diuretics and ACE Inhibitors. The results show a 17% reduction in all cause mortality as

carvedilol compared with metoprolol tartarate. However, limitations in this trial were using metoprolol tartrate instead of scent. Moreover, possible metoprolol tartarate (200mg q.d) was underdosed compared to metoprolol succinate in MERIT-HF (100mg q.D). Thus the optimal use of metoprolol tartarate was not done in COMET trial.[24]

A randomized trial called the **C**ardiac **I**nsufficiency **B**isoprolol **S**tudy (**CIBIS**)-**III** was carried out with 1010 of a mean age of 72 years, with mild to moderate CHF (NYHA class II or III) and LV ejection fraction ≤35%. The main aim of this study was to observe if a beta blocker was as safe and effective for initial therapy compare to the ACE inhibitor. Mean follow up period was 1.22 years. There was a non-significant 12% reduction in the number of deaths when bisoprolol was used as initial treatment with 65 deaths in bisoprolol first group and 73 deaths in enalapril first group (HR0.88;95%CI:0.63to 1.22). Also 151 patients were hospitalized in the bisoprolol group compared to 157 patients in the enalapril first group (HR0.95;95%CI 0.76 to1.19). This study indicates that it might be safe and efficacious to use bisoprolol as an initial therapy for CHF compound to enalapril, although non-inferiority of using bisoprolol first was not proven.[25]

Head to head trial among the beta blockers had also been conducted in small scales. **Marazzi et al**. compared the effect on LVEF of nebivolol(10 mg/day) versus carvedilol(25 mg/b.i.d) on 160 patients with CHF (LVEF < 40% and NYHA class I-III). After a follow up for more than 2 years they found that LVEF increased in both groups (Carvedilol 36–41 %; nebivolol 34-37%, p<0.001). Results show that nebivolol is as effective as carvedilol in patients with symptomatic chronic heart failure and reduced LV systolic function.[26]

Another beta blocker, nebivolol with vasodilating properties had shown effectiveness in treating elderly HF patients(age>70years). This trial recruited 2128 patients with a history of heart failure with past 12 months (LVEF≤35%). Mean follow up month was 21months. Results shown that nebivolol had a 14 % relative risk reduction in all cause mortality or cardiovascular hospital admission. (95% CI: 0.74-0.99;p=0.039). **SENIORS** is the also first major study of beta blockers elderly HF that has shown benefit with nebivolol.[27]

After all these trials, it was not still clear about the therapeutic efficacy for HF with reserved ejection fraction. The Japanese Diastolic Heart Failure Study **(J-DHF 2013**) was designed to know the effects of carvedilol in HFPEF patients.[28]

Recently another study named **CARNEBI** (Multi-parametric comparison of **CAR**vedilol Vs **NE**bivolol Vs **BI**soprolol in moderate HF). This trial enrolled 70 patients with moderate HF. After 2 month benefit was seen with bisoprolol and nebivolol in exercise performance (p<0.0001) and lung diffusion (p≤0.001). In case of low DLCO (Diffusing capacity of the lungs for carbon monoxide), or likely exposure to hypoxia either hypobaric (high altitude) or normobaric (respiratory comorbidities or frequent acute lung edema episodes), Bisoprolol or Nebivolol seems to be preferable to Carvedilol. On the other hand, carvedilol gave better ventilation efficacy during exercise.[29]

Table 3: Some clinical trials and their results

Clinical trials	Drug that was used	Sample Size	Age (Years)	State of Patient	Mean Follow Up Time	Outcomes
CIBIS-I[19]	Bisoprolol vs Placebo	641	18-75	Patients with HF	1.9 Years	Bisoprolol had shown improvement in HF and reduce the rate of hospitalization but in this trial no benefit was proven for survival
US carvedilol HF study[17]	Carvedilol, Placebo	1094	More than 64	Patients with CHF	1 Year	Mortality risk was reduced by 65% and the combined risk of hospitalization and death was reduced by 38%
ANZ[18]	Carvedilol vs placebo	415	67 (Approx.)	Patients with HF	19 Months	LVEF had increased by 5.3% and Death or hospital admission reduction in this trial is 26%
MERIT-HF trial[21]	Metoprolol, Placebo	3991	40-80	Sympto-matic HF patients	1 Year (Approx.)	Metoprolol significantly reduced all cause mortality by

						34%
CIBIS-II[20]	Bisoprolol vs Placebo	2647	More than 60	Sympto-matic HF patients	1.3 Years	All cause mortality was lower for bisoprolol group (11.8%) Vs placebo (17.3%). This trial confirms the benefits for survival in stable heart patients.
BEST[23]	Bucindolol vs Plavebo	2708	More than 60	Wild chronic HF patients	2 Years	This trial was unsuccessful to show any improvement in mortality (23% bucindolol and 25% placebo) but re-hospitalization benefits was observed with bucindolol group
COPERNICUS[22]	Carvedilol vs placebo	2289	More than 64 years	Patients with severe HF	10.4 Months	Carvedilol showed a 34% reduction in mortality and less serious adverse event was found with carvedilol
COMET[24]	Carvedilol vs Metoprolol	3029	61 Years (Approx.)	Patients with chronic HF	4.83 Years	Results showed 17% reduction in all cause mortality as carvedilol compared with metoprolol tartarate.
CIBIS-III[25]	Bisoprolol vs Enalapril	1010	72 years	Patients with mild to moderate CHF and LVEF ≤35%	1.22 years	It might be safe and efficacious to use bisoprolol as an initial therapy for CHF patient prior to enalapril
Marazzi et al.[26]	Nebivolol vs Carvedilol	160	More than 50 Years	Patients with CHF	More than 2 years	Results showed that nebivolol is as effective as carvedilol in patients with symptomatic chronic heart failure and reduced LV systolic function.
SENIORS[27]	Nebivolol vs Placebo	2128	More than 70 years	Patients with HF	1.9 Years	Result showed that nebivolol had 14% relative risk reduction for all cause mortality
CARNEBI[29]	Carvedilol vs Nebivolol vs Bisoprolol	70	55-65 Years	Patients with moderate HF	2 Months	In low DLCO, hypoxia nebivolol and bisoprolol are preferred over carvedilol. Carvedilol gave better ventilation efficacy
J-DHF study[28]	Carvedilol vs placebo	245	40-55 Years	Patients with HF	3.2 Years	Carvedilol did not improve prognosis of HFPEF patients

DISCUSSION:

CIBIS trial showed that hypotension is the main symptoms in elderly patient that result withdrawing of the treatment or to give low doses of bisoprolol. It would be possible to reach the target dose of 10 mg/day without any trouble if the bisoprolol was well tolerated by the patients.[30] Therefore, the information about the tolerance is very important to know, especially while treating elderly patients, COPD patient, severe renal failure patient etc. CIBIS II trial was quickly terminated because of significant benefit in mortality. Still another question arises whether bisoprolol is safe for long term therapy for CHF patients. The answer to this question is still unknown. Overall, bisoprolol is well tolerated except few side effects which cause permanent withdrawal of the treatment. Additionally, in the CIBIS III trial, no placebo group was found which makes the result open to discussion how much successful a beta blocker was as an intial treatment for heart failure.

A non-selective beta blocker carvedilol have shown to improve LVEF in chronic stable heart failure patient in the ANZ study 1997. However, mortality reduction due to carvedilol group composed with placebo group was non-significant. On the other hand, reductions of hospitalization were higher for carvedilol group. Through regulatory authorities, some countries already accepted this treatment.[31]

Another drug name bucindolol shows transparent survival benefit in CHF patients in BEST trial.[23] However, it still stands in contrast to other studies because of not offering a convincing illustration of beta blocker effectiveness.The reason for this still remains unknown. Few reviewers claim that difference in the population examined (African Americans) might lead to different results. Even now bucindolol might get the FDA green light if a proper trial can be performed with it.

In the Merit HF study, metoprolol succinate is found to be safe and effective when it is prescribed in low dose at first and carefully increased. In this study, metoprolol succinate proved useful mainly for patients with stable mild to moderate HF. Still further research is required to find out why on small dose patients respond with a significant HR reduction and mortality risk.[32]

In another study of carvedilol (COPERNICUS 2001) it is not clear whether this beta blocker can be used in class IV patient or not. As during COPERNICUS study, the NYHA functional class was not assessed. This study was abruptly stopped due to high significant mortality benefit.

Later carvedilol seem to be effective in reduction in mortality in COMET trial. However, limitation to this study is that they used metoprolol tartarate instead of metoprolol succinate which found significant clinical benefit in Merit HF study. Underdosing of metoprolol tartarate (100mg q.d compared with 200mg q.d in Merit HF) might be the reason for which made carvedilol superior to metoprolol. Still the answer to this question is debatable. Therefore, clinicians must consider convenient dosing while prescribing beta blocker is necessary.

Another large trial performed on elderly patients in SENIOR trial with nebivolol, another beta blocker. Benefits of nebivolol can only be found if the proper maintenance of dose can be achieved. Moreover, the results for nebivolol is very important for patient with preserved EF because yet no treatment has shown benefit in this group. However, ACE inhibitors and ARB have also shown positive data.[33] This is the only study done with elderly patients found. More clinical trials on elderly patients could reflect better understanding for their treatment.

Later in another trial (JD-HF2013) was conducted to find the efficacy of beta blocker in the treatment of heart failure with reserved ejection fraction (HFPEF). Carvedilol did not show any benefit in the HFPEF treatment as there were many limitations to this study. Firstly, the sample is very small. Secondly, the study was not a community based study. Thirdly, the control group of this secondary analysis study involves HFPEF patients without carvedilol and with the administration of low-dose carvedilol. However, further investigation with large populations and standard doses of beta blocker may exert a greater benefit in outcomes in HFPEF patients with advanced rather than mild diastolic dysfunction.[34]

CONCLUSION:

Most of the studies were followed up less than 2 years. Many of them were abruptly stopped due to significant benefit. Hence it is not sure whether the long term effect of beta blocker will maintain this benefit or not. Moreover, further investigation with proper dosing of beta blocker might find new effective treatment for elderly patients, HFPEF patients, COPD patients, etc. No head to head trial was found among different beta blockers to find the better beta blocker for CHF patients. This review article tried to figure out which beta blocker is better for what kind of patients. In addition to this, it will help clinicians to understand the importance of convenient dosing. Also, many researchers can find where new research will be helpful to solve the controversy of using beta blockers in HF patients. According to 2013 **A**merican **C**ollege **C**ardiology **F**oundation (**ACCF)** and **A**merican **H**eart **A**ssociation guidelines, three beta blockers were approved for HF are bisoprolol, carvedilol and metoprolol succinate.[35] Nebivolol is still not chosen by US FDA for HF treatment, although studies suggest that it could be effective for HF.

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