Review Article

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Journal of Cardiovascular Medicine and Therapy

2019
Vol.2 No.1:3

Do Beta Adrenoceptor Blocking Agents Provide the Same Degree of Clinically Convincing Morbidity and Mortality Benefits in Patients with Chronic Heart Failure

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Received date: April 22, 2019; **Accepted date:** April 30, 2019; **Published date:** May 7, 2019

Citation: Malick MMD (2019) Do Beta Adrenoceptor Blocking Agents Provide the Same Degree of Clinically Convincing Morbidity and Mortality Benefits in Patients with Chronic Heart Failure. J Cardiovasc Med Ther Vol.2 No. 1:3.

Abstract

Chronic heart failure has been extensively characterized as a disorder arising from a complex interaction between impaired ventricular performance and neurohormonal activation. Since beta adrenoceptor blocking agents are currently considered an integral component of therapy for the management of patients with severe chronic heart failure; several well designed clinical trials have been conducted to determine the morbidity and mortality benefits of these agents. These studies however did not yield the same results in terms of morbidity and mortality benefits. Currently only Bisoprolol, Carvedilol and sustained release metoprolol succinate have clinically proven and convincing morbidity and mortality benefits.

The current list of approved medicines of the National Health Insurance Scheme (NHIS) of the republic of Ghana does not provide coverage for these live saving therapeutic agents. The objective of this review is to collate the relevant scientific evidence that will convince the authorities at the National Health Insurance Authority (NHIA) of the Republic of Ghana to include at least one of the evidence based beta adrenoceptor blocking agents in the list of approved medicines.

A thorough search on the internet was conducted using Google scholar to obtain only the clinically relevant studies associated with the benefits of beta adrenoceptor blocking agents in patients with chronic heart failure published in the English language. The phrases beta adrenoceptor blocking agents and chronic heart failure were used as search engines.

The search engine yielded several studies that met the predefined inclusion criteria. However, only the Cardiac Insufficiency BIsoprolol Studies (CIBIS-I and CIBIS-II), Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) and Metoprolol CR/XL Randomized Intervention Trial (MERIF-HF) because of the clinical relevance of their findings

Beta adrenoceptor blocking agents such as atenolol and propranolol have been used in the management of patients with chronic heart failure. However, their efficacy and optimal dose in reducing mortality have not been scientifically established

Not all beta adrenoceptor blocking agents scientifically studied provide the same degree of clinically meaningful and convincing morbidity and mortality benefits in patients with chronic heart failure.

Keywords: Chronic heart failure; Evidence-based beta adrenoceptor blocking agents; Cardiovascular mortality

Introduction

Chronic heart has been extensively characterized as a disorder arising from a complex interaction between impaired ventricular performance and neurohormonal activation [1]. Activation of the sympathetic nervous system is one of the key pathophysiological disturbances in patients with chronic heart failure [2]. Levels of circulating catecholamine's increase in patients with heart failure which is directly proportional to the severity of the disease; and those with the highest plasma levels of norepinephrine have the most unfavorable prognosis [3]. Sympathetic activation is a significant predictor of poor prognosis in patients with chronic heart failure. There is an overwhelming evidence that supports the notion that, drugs interfering with the neurohormonal activation (including sympathetic activation) in chronic heart failure not only produce symptomatic relief ; but are also capable of attenuating disease progression, with concomitant reductions in both morbidity and mortality [4].

Beta adrenoceptor blocking agents which antagonize the effects of the activated sympathetic nervous system have been shown to be beneficial in the long term in moderate to severe chronic heart failure in terms of significant improvements in both morbidity and mortality [5-7]. Several well designed clinical trials have been conducted to determine the beneficial effects of

beta adrenoceptor blocking agents on morbidity and mortality in chronic heart failure patients [8].

Objectives of the Review

To research and document the available scientific evidence that supports the use and benefits of the evidence-based beta adrenoceptor blocking agents in the management of patients with chronic heart failure.

Present the data coupled with pertinent recommendations to the relevant authorities at the National Health Insurance Authority (NHIA) of the republic of Ghana for consideration and possible inclusion into the medicines list of the NHIS (**Table 1**).

Table 1: Recommendations to the NHIA for consideration.

S. No	Recommendations
1	Since the scientific evidence supporting the use and benefits of the evidence-based beta adrenoceptor blocking agents in the management of patients with chronic heart failure is so clinically convincing; authorities at the NHIA of the Republic of Ghana should consider including at least one of these agents preferably carvedilol in the formulary of approved medications
2	Atenolol should be maintained but propranolol should be deleted permanently
3	Clinicians must be encourage to prescribe these agents with prudence keeping in mind the dosing requirements as stipulated in the current clinical practice guidelines in order to maximize therapeutic outcomes for all patients
4	Decision makers at the NHIA should also ensure that recommended formulary changes should involve all relevant stakeholders in order to allow for smooth transition and implementation
5	All experts engaged by the NHIA to clinically vet all submitted claims must keep a microscopic eye on the appropriate use of these evidence based agents in the management of patients with chronic heart failure so as to improve therapeutic outcomes

Scope of the Review

This review is focused mainly on the use and benefits of beta adrenoceptor blocking agents in the management of patients with chronic heart failure only; since the benefits of these agents in the setting of acute decompensated heart failure is still somehow of a therapeutic controversy and very much constitutes a clinical conundrum for most practicing clinicians. Emphasis is also placed only on the studies associated with carvedilol, bisoprolol and metoprolol succinate which have the most clinically convincing and meaningful morbidity and mortality benefits in patients with chronic heart failure. A metanalysis or systematic review is beyond the scope of this scientific activity.

Motivation for the Review

Despite the overwhelmingly convincing scientific evidence supporting the use and benefits of Carvedilol, Bisoprolol and sustained release Metoprolol succinate in the management of patients with heart failure; the medicines list of the National Health Insurance Scheme (NHIS) of the republic of Ghana does not provide coverage for these live saving therapeutic agents. Instead, only atenolol and propranolol are covered which do not possess the necessary scientific evidence to justify their use and benefits in the management of patients with chronic heart failure.

Hemodynamic and clinical effects of beta adrenoceptor blocking agents in chronic heart failure

Several clinical trials have demonstrated a remarkable consistency with regards to an improvement of left ventricular ejection fraction during chronic use of beta adrenoceptor blocking agents [9]. This improvement in ventricular function is due to increased systolic ventricular performance. The same studies have also shown that beta adrenoceptor blocking agents can produce both hemodynamic as well as symptomatic improvements in chronic heart failure patients (**Table 2**).

Table 2: Mechanisms through which beta adrenoceptor blocking agents elicit their beneficial effects in chronic heart failure.

S. No	Different Mechanisms
1	Reverse cardiac remodeling
2	Anti-ischemic effects
3	Metabolic benefits
4	Inhibit apoptosis
5	Improvement in systolic function
6	Improvement in diastolic function

Clinical commentary based on recommendations from current chronic heart failure clinical practice guidelines

In order to provide the best care for patients with severe chronic heart failure, clinicians must go beyond the conventional

ACE Inhibitor plus diuretic therapies. Adding one the three evidence based beta adrenoceptor blocking agents at recommended doses will further the survival rates and decrease hospitalization rates (**Table 3**).

Table 3: Summary of Clinical Trial data with beta adrenoceptor blocking agents in patients with chronic heart failure.

Trial	Year of Publication	Patient Population	No. of Patients	Beta adrenoceptor agents	Study duration	Primary Endpoints	Study Conclusions
COPERNICUS	2001	Severe HF with mean EF 19.9%	2289	Carvedilol	Mean 10.4 months	All cause mortality	Carvedilol reduced the rate of death in patients with severe HF on conventional therapy
MERIT-HF	1999	NYHA II-IV with a mean EF 28%	3991	Sustained release Metoprolol Succinate (XL)	Mean 1 year	All cause mortality, combined all cause mortality and all cause hospital admissions	Metoprolol XL significantly improved survival in patients with severe HF on conventional therapy
US CARVEDILOLSTUDY	1996	NYHA II-IV with a mean EF 23%	1094	Carvedilol	Mean 6.5 months	Death	Carvedilol reduced the risk of death in patients with symptomatic HF on conventional therapy
CIBIS	1999	NYHA III-IV with a mean EF 27.5%	2647	Bisoprolol	Mean 1.3 years	All cause mortality	Bisoprolol significantly improved survival in patients with stable symptomatic HF on conventional therapy
COMET	2003	NYHA II-IV with a mean EF 26%	3029	Carvedilol Versus IR Metoprolol tartate	Mean 58 months	All cause mortality	Carvedilol has a greater benefit on survival compared to IR Metoprolol in patients with chronic HF on conventional therapy
Conventional therapy consist of a diuretic plus an ACEI or ARB							
NYHA: New York Heart Association functional classification of chronic heart failure; IR Metoprolol: Immediate Release Metoprolol tartate; HF: Heart Failure							

Practice implications

The unavailability of the evidence-based beta adrenoceptor blocking agents on the medication formulary of the NHIS, has compelled most practicing clinicians to manage their chronic heart failure patients with beta adrenoceptor blocking agents such as atenolol and propranolol which have no scientific evidence at all to justify their use and benefits in this subset of patient population. However, a handful of clinicians with a better appreciation for the principles of evidence-based medicine will still prescribe one of these evidence-based beta adrenoceptor blocking agents, mostly carvedilol for their patients to be purchased out of pocket.

Those patients who cannot afford to purchase the evidence based beta adrenoceptor blocking agents out of pocket as well as those who are receiving therapy with the non-evidence based agents are all excellent candidates for poor prognosis and increase risk of cardiovascular morbidity and mortality.

Discussion

Meta-analysis of beta adrenoceptor blocking agents trials have shown a reduction in mortality of approximately 30-35% [10]. The beta adrenoceptor blocking agents that have been studied for chronic heart failure and have demonstrated a reduction in mortality include bisoprolol, carvedilol and sustained release metoprolol succinate (Hence these agents are routinely referred to as evidence-based beta adrenoceptor blocking agents).

It is unknown whether other beta adrenoceptor blocking agents such as atenolol and propranolol have similar beneficial effects, since not all studied beta adrenoceptor blocking agents have shown clear and clinically convincing reduction of mortality.

Carvvedilol has been shown to decrease mortality in patients with NYHA Class II-IV Heart failure [11,12]. Sustained release

metoprolol succinate has primarily been studied in patients with NYHA Class II-III with a reduction in morbidity and mortality [13]. Bisoprolol has also been studied in patients with NYHA Class II - IV Heart failure and has been shown to reduce morbidity and mortality [14,15].

The benefits of beta adrenoceptor blocking agents in patients with chronic heart failure were previously considered to be as a result of a class; meaning all these agents are equally effective at equipotent doses. However, the Carvedilol or Metoprolol European Trial (COMET) has shown that in patients with chronic heart failure; survival appears to be better with carvedililol than with immediate release metoprolol tartate [16]. Carvedilol was used at a dose of 25mg orally twice daily while immediate release metoprolol tartate was dosed at 50 mg twice daily.

Conclusion

Although therapy with beta adrenoceptor blocking agents constitute an integral part of the standard of care for the management of patients with chronic heart failure; not all these agents have proven morbidity and mortality benefits.

Beta adrenoceptor blocking agents such as atenolol and propranolol have been routinely used in the management of patients with chronic heart failure. However, their efficacy and optimal dose in reducing morbidity and mortality have not been scientifically established.

Several well designed and conducted clinical trials have demonstrated convincingly the beneficial effects of the evidenced based beta adrenoceptor blocking agents on morbidity and mortality in chronic heart failure patients. Hence these agents are duly included in several national and international clinical practice guidelines.

Based on the overwhelming cardiovascular morbidity and mortality benefits of these evidence based beta adrenoceptor blocking agents in the management of patients with chronic heart failure; most developed and developing countries have included them in their respective national drug formulary. Carvedilol is preferred over immediate release metoprolol tartate.

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