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## Comparison of the Clinical Result of Diverse $\beta$ -Blockers in Heart Failure Patients: A Systematic Review

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### ABSTRACT

**Background:** Starting from the mid-late 90s,  $\beta$ -blockers have ended up as the therapy of choice for heart failure (HF).  $\beta$ -blockers act with important and reliable beneficial effects on survival and reduction of the manifestations of patients with heart failure (HF). In a placebo-controlled study conducted at that time,  $\beta$ -blockers have been recognized as necessary treatment in patients who are slowly but steadily. However, today there are many options for  $\beta$ -blockers.

**Objective:** To provide a logical basis for the use of  $\beta$ -blockers for patients with heart failure and determine the most effective  $\beta$ -blockers.

**Methods:** The authors made statistical associations, and calculated the different levels and risks that can distribute different blockers in heart failure patients. Studies were identified from Scopus, ScienceDirect, PubMed, and Google Scholar databases and then analyzed using Prism Chart 2020.

**Results:** Carvedilol is a superior drug class against cardiac remodeling and consequent heart failure compared to other specific  $\beta$ -blockers. Some of its advantages include combining comprehensive blocking of all 3 adrenergic receptors, anti-apoptotic and anti-endothelin effects.

**Conclusions:** Carvedilol is said to be the most effective heart drug to date, although many other side effects have been discovered. There needs to be a breakthrough in halal medicine for halal medicinal diseases when used by the Muslim community, which is relatively safer and more comfortable to use.

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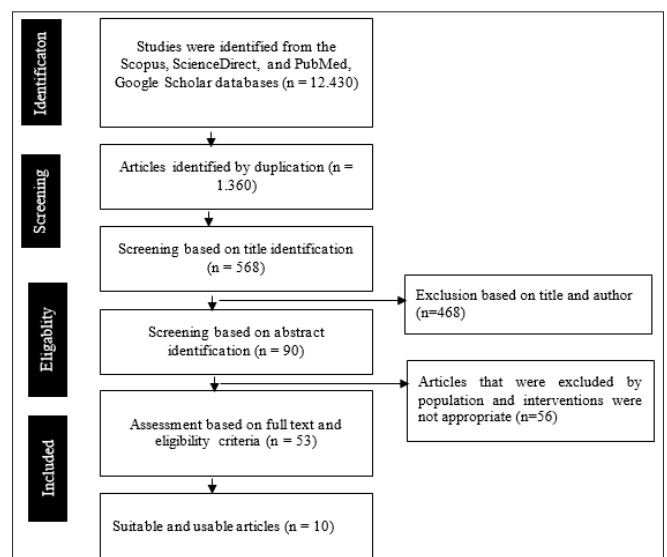
### Introduction

Recently,  $\beta$ -blockers have become one of the fastest growing options in the treatment of heart failure. It is because of their important and stable impact on survival and symptomatic reduction of heart failure (HF) in the extensive placebo-controlled studies conducted at that time;  $\beta$ -blockers have been recognized as mandatory treatment in patients with slowly stable, direct, and chronic HF. [1-4]. In addition, in patients with LV damage and/or heart failure immediately after intense local myocardial necrosis, carvedilol also resulted in improved survival compared with placebo treatment [5, 6]. As a result, carvedilol, bisoprolol, metoprolol succinate, and nebivolol have been recognized for the treatment of continuous HF (NYHA II-IV) with either ischemic or non-ischemic concomitant use, which is used in the universal rule for the treatment of HF. [7,8]. Such a rule, however, does not address an important address for doctors: "which beta blocker to use"? Are they all basically viable and equally enduring, or maybe one is more preferable for  $\beta$ -blockers as the treatment of continuous heart failure?

### Method

All English-language articles from extensive randomized controlled clinical trials surveying the mortality benefit of beta-blockers in patients with heart failure are recognized to supply a logical method of reasoning for the utilization of beta-blockers in

heart failure. The authors analyzed all reports from 2003 - 2022. Fundamental science studies were examined to provide a diagram of the physiological part of beta-blockers potential in heart failure. Finally, clinical guidelines for the treatment of patients with heart failure were evaluated to decide on current recommendations for the use of beta blockers in this disease.



**Diagram 1:** Literature Search Using Prism Chart 2020

**Result**

After searching the journals based on the inclusion and exclusion criteria that the author made. Furthermore, a journal study was carried out, and 10 research articles were obtained which were included in this systematic review (Table 1).

**Discussion**

**Mechanism Action of  $\beta$ -Blocker Drugs**

$\beta$ -blockers decrease adrenergic system activity through the blockade of adrenergic receptor subtypes, particularly  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$ .  $\beta_1$  receptors are basically inside the heart and many of the valuable impacts of blockade consolidate bradycardia and made strides in diastolic coronary filling time, lessened oxygen necessities, and a diminishment of renin, all invaluable in heart failure and myocardial ischemia [6-12].  $\beta_2$  receptors are for the foremost portion found within the smooth muscle of blood vessels and the bronchial tree and prompting leads to broadening.  $\beta_3$  receptors are found in adipocytes and the heart, and bar by nonselective masters might contribute to their weight-increase and metabolic impacts [13].  $\beta$ -blocker specificity implies to the drugs' more noticeable affection for  $\beta_1$  receptors over  $\beta_2$  at regular sedate levels, and so specificity for cardiac impacts, and nonspecific administrators that additionally piece  $\beta_2$  receptors reduce antihypertensive movement [14].

**Table 1: Comparison of the Clinical Result of Diverse  $\beta$ -Blockers in Heart Failure Patients**

Author	Origin	Method	Period	Result	Outcome
Keating GM, Jarvis B.	Adis International Limited, Mairangi Bay, New Zealand	Combined analysis of studies in the US Carvedilol Heart Failure Trials Program	2003	Carvedilol was for the most part well endured in patients with CHF. Unfavorable occasions related with the alpha- and beta-blocking impacts of the sedate happened more commonly with carvedilol than with fake treatment, though fake treatment beneficiaries were more likely to involvement compounding heart failure. In conclusion, carvedilol squares beta(1)-, beta(2) - and alpha(1)-adrenoceptors and features a special pharmacological profile.	In conclusion, carvedilol squares beta (1)-, beta (2) - and alpha (1)-adrenoceptors and features a special pharmacological profile. It is thought that extra properties of carvedilol (e.g. antioxidant and antiproliferative impacts) contribute to its useful impacts in CHF. Carvedilol moves forward ventricular work and decreases mortality and dreariness in patients with mellow to extreme CHF, and ought to be considered a standard treatment choice in this setting. Regulating carvedilol in expansion to ordinary treatment diminishes mortality and constricts myocardial renovating in patients with cleared out ventricular brokenness taking after intense MI. Additionally, mortality was altogether lower with carvedilol than with metoprolol
James E Udelson	Tufts University School of Medicine, Boston, Massachusetts, USA	Literature review	2004	Cleared-out ventricular (LV) remodeling has an imperative part in the movement of cardiovascular disease. An understanding of the method of LV remodeling has driven more prominent information on the pathophysiology of heart failure. Sedate treatments that moderate or turn around the remodeling preparation appear to have favorable normal history impacts in short-term and long-term treatment. Angiotensin-converting protein (Pro) inhibitors have been related to a noteworthy lessening in mortality, and the impact of beta-blockers on the remodeling preparation has presently been considered over much of the range of seriousness in patients with heart failure.	Beta-Blockade appears to include favorable and free impacts on the post-myocardial localized necrosis remodeling preparation over and over those of Pro inhibitors. A combination of both drugs shows the most noteworthy lessening in mortality (i.e., the foremost favorable turnaround remodeling). Contrasts in their impact on remodeling have been as of late appeared among the beta-blockers.

Michel Komajda	Institut de Cardiologie, France	Double-blind randomized trials	2004	There was no gather-related contrast in unfavorable occasions amid up-titration. Withdrawal rates were 31, 30, and 30%, and genuine unfavorable occasions were 28, 29, and 34% within the combination, carvedilol, and enalapril arms. Mortality was comparable in all bunches (all-cause N=14, 14, and 14; cardiovascular N=9, 13, and 14). All-cause and cardiovascular hospitalizations happened in 26, 27, and 32%, and in 12, 16, and 22% within the combination, carvedilol and enalapril arms, individually.	The security profile was comparable in all treatment arms. In differentiate to common recognition, there was no distinction in tolerability between the ACE-I and carvedilol. This result is indeed more surprising as the tall prestudy utilizes ACE-I (65%) might have presented an inclination by selecting ACE-I tolerant patients, who were as it was exchanged from their previous ACE-I to enalapril.
Britt Kveiborg et al	Bispebjerg University Hospital, Copenhagen, Denmark	Double-blind randomized matter	2007	Beta-blockers have appeared to make strides in survival in patients with constant heart failure. The impact of diverse eras of beta blockers has been talked about. Both metoprolol and carvedilol have illustrated advantageous impacts in placebo-controlled trials. Within The Carvedilol Or Metoprolol European Trial (COMET) two beta-blockers were compared in a double-blind randomized matter. Typically, the primary coordinate comparison between metoprolol and carvedilol of long-term impact on survival in patients with incessant heart failure.	The all-cause mortality was significantly diminished with the support of carvedilol. The measurements and definition of metoprolol used in this trial have caused talk about, and it has been addressed whether a comparative beta1-blockade is obtained within the two mediation bunches. At this time there is an uncertain wrangle about as to whether carvedilol may be a predominant beta-blocker or whether contrasts in beta1-blockade clarified the comes about of COMET.
Robert Neil Doughty	Auckland Hospital Support Building, Park Road, Auckland, New Zealand	Control Trial	2007	Carvedilol may be a beta-adrenergic adversary with vasodilatory properties (alpha1-antagonism), which has been broadly assessed within the treatment of patients with heart failure. In patients with constant heart failure, carvedilol moves forward left-ventricular (LV) launch division over 6 to 12 months of treatment and weakens LV rebuilding. Large-scale randomized, fake treatment controlled trials including more than 4000 patients with constant heart failure have illustrated that carvedilol moves forward survival and decreases hospitalizations.	Comparative thinks about metoprolol in patients with heart failure have recommended that carvedilol may be related to a more prominent survival advantage even though contrasts within the arrangement of metoprolol have cleared out vulnerability in this zone. Carvedilol features a tall security profile and the clinical benefits show up kept up over a wide extent of patients with comorbidities such as diabetes and renal failure.
LucPoirierB Pharm et al	Clinique d'hypertension et département de pharmacie, Canada	Literature Review	2014	It remains that $\beta$ -blocking specialist with their abilities to piece the $\beta$ 1-adrenergic receptor are the drugs of choice strongly or constant cardiac ischemia's patients. They are part of patients's treatment with heart failure in expansion with a renin-angiotensin-aldosterone framework inhibition-based treatment.	This audit will center on the heterogeneity of the pharmacologic characteristics of $\beta$ -blockers, and we are going examine the metabolic and hemodynamic contrasts inside the $\beta$ -blocker lesson and attempt to evaluate the potential suggestions of these contrasts for ideal determination in hypertension.

Rasmus Bølling	Aalborg University, Denmark.	Cohort Study	2014	High-dose carvedilol was associated with a lower likelihood of all-cause hospitalization (HR 0.842, 0.774-0.915) than high-dose metoprolol, whereas high-dose bisoprolol had a lower risk than high-dose metoprolol (HR 0.948, 0.850 -1.057).	Patients with heart failure that receiving high-dose carvedilol ( $\geq 50$ mg daily) seem to have a lower risk of death and hospitalization from all causes, compared with other beta-blockers.
Daniele Masarone	Monaldi Hospital, Naples, Italy;	Literature Review	2021	$\beta$ -Blockers are one of the four disease-modifying medicate sorts that have the most noteworthy effect on the long-term forecast of patients with HFrEF; subsequently, all universal rules prescribe the utilize of $\beta$ -blockers as a first-line treatment for patients with HFrEF. Be that as it may, to date, they are underused, primarily since of the misinterpretation that hypotension and bradycardia may compound the hemodynamic status of patients with HFrEF as a result of the nearness of comorbidities dishonestly accepted to be supreme contraindications to their utilize.	It is trusted that the down to earth approach examined in this audit will permit for a appropriate dissemination of information approximately the right utilize of $\beta$ -blockers and the drug-disease intelligent to attain their expanded utilize and titration, as well as for the choice of a particular operator with a see to an appropriately custom-made approach for HFrEF patients.
Yodo Tamaki	Kyoto University, Japan	Study Population	2021	Among 3817 patients without ACS included, 1512 patients gotten beta-blockers on affirmation for the ADHF inpatient record, while 2305 patients did not. The empowering comes about were that patients who gotten beta-blockers had less bronchial asthma or dementia than those who did not get beta-blockers at affirmation.	HF patients accepting beta-blocker treatment at the time of certification were related with essentially lower in-hospital mortality rates than patients with strongly decompensated heart failure.
Stefania Polalio	University of Naples, Italy	Literature Review	2021	The point of this think about was to analyze open prove on the utilize of $\beta$ -blockers in HFrEF patients with the foremost common comorbidities.	$\beta$ -blockers are disease-modifying drugs that have important effects in the long-term therapy of patients with HFrEF. These drugs are first-line drugs in close proximity to left ventricular dysfunction which must be titrated to the largest sustained dose in order for us to experience their full prognostic benefit. Beta-blockers are still underutilized in patients with HFrEF because they are affected by complex comorbidities, including contraindications.

## Pharmacological Effect of $\beta$ -Blocker Drugs

**Table 2: The Pharmacological Effect of  $\beta$ -Blocker Drugs**

	Bisoprolol	Bucindolol	Carvedilol	Metoprolol	Nebivolol	Acebutolol	Atenolol	Labetolol	Pindolol	Nadolol	Sotalol	Timolol
Anti-oxidant effect			+		+							
Anti-apoptotic			+		+							
Inhibit endothelin			+									
Intrinsic sympathomimetic activity		+				+			+			
$\alpha$ 1 blockade		+	+									
$\beta$ 1 blockade	+	+	+	+	+	+	+	+	+	+	+	+
$\beta$ 2 blockade		+	+			+	+	+				

The  $\beta$ -blockers recognized for HF treatment differentiate astonishingly (Table 2). Metoprolol and bisoprolol are  $\beta$ -1-specific administrators. Nebivolol to boot a  $\beta$ -1 particular calm but has additional vasodilating properties, conceivably related to endothelial nitric oxide generation. In separate, carvedilol pieces not because it were the  $\beta$ -1 receptor, but additionally the  $\beta$ -2 and alpha-1 adrenoceptors. In development, carvedilol has anti-oxidative and anti-endothelin properties. The address rises whether the assorted adrenergic blocking works out of these  $\beta$ -blockers are germane to their valuable affect on HF. One basic heading to answer that addresses without the necessity for colossal controlled think almost concerns their individual adjusting affect on cardiac remodeling [9].

### Result

Carvedilol is as favored beta-blocker in cardiac remodeling and heart failure. Carvedilol secures more better against cardiac remodeling and following heart failure than more particular beta-adrenergic blockers. The disputes for this consolidate its comprehensive blocking of all 3 adrenergic receptors, as appeared over, and its anti-oxidant, anti-apoptotic, and anti-endothelin impacts. Compared to metoprolol succinate, carvedilol at estimations that drove to comparable heart rate diminishments started through and through more essential changes of cardiac work in mutts with pacing-induced heart failure and extended renal, hepatic, and skeletal muscle circulatory system [15-18]. In extension, it moved forward myocardial glucose take-up (giving more better essentialness conservation) compared to metoprolol and antagonized the response to exogenous norepinephrine to a more conspicuous degree than metoprolol succinate [19-23].

In heart failure patients, carvedilol applies a more powerful anti-adrenergic impact than metoprolol amid push [24, 25]. This may mostly clarify the way better anti-remodeling properties of carvedilol were watched in most thinks about which compared it to beta-1 specific blocking operators such as metoprolol. Sanderson et al watched a more prominent diminish in LV volumes with carvedilol than with metoprolol in heart failure patients [26]. Metra and colleagues detailed an altogether more noteworthy increment in LV discharge division after 1-year treatment with carvedilol compared to metoprolol [27]. In differentiation, Kukin et al found comparable enhancements in LV discharge division [28]. Be that as it may, this was a little considered over a shorter period. At last, in a meta-analysis counting all accessible controlled trials, Packer and colleagues too found an altogether more noteworthy increment in LV discharge division with carvedilol than with metoprolol [29].

Suggestions for further research are cohort studies of sufficient duration to compare the long-term effects of carvedilol on morbidity and survival compared to selective beta-1 blockade. Because current studies are not available to demonstrate sufficient size or sufficient duration to allow comparison of the long-term effects of carvedilol.

### Conclusion

$\beta$ -Blockers have for the most part illustrated littler diminishments in cardiovascular occasions, compared with other antihypertensive classes, in spite of comparable decreases in blood weight. This may be due to the incapability of conventional  $\beta$ -blockers, such as atenolol, in lessening central aortic weight, a solid, autonomous indicator of the cardiovascular result. Be that as it may, the  $\beta$ -blocker course is heterogeneous, and a few more up-to-date  $\beta$ -blockers, which display vasodilatory impacts autonomous of  $\beta$ -blockade, give advantageous impacts on blood vessel solidness and endothelial brokenness, which may lead to decreases in central aortic weight and enhancements in clinical results. For case, the vasodilating  $\beta$ -blocker nebivolol appeared to progress lower arm bloodstream and blood vessel solidness and, in an expansive clinical consider, to altogether decrease horribleness and mortality, autonomous of cleared out ventricular launch division, among patients with unremitting heart failure.

There is adequate proof from pre-clinical and clinical ponders that carvedilol has more articulated anti-remodeling impacts in heart failure than specific  $\beta$ -blocking operators have, more particularly the  $\beta$ -1 particular blocking drugs metoprolol and bisoprolol. The noteworthy distinction inadequacy is due to a combination of components, counting the comprehensive bar of all 3 adrenergic receptors by carvedilol, and its anti-oxidative, anti-apoptotic and anti-endothelin effects. As a result, carvedilol was driven to a noteworthy and clinically significant change in survival, superior well-being, less unused onset diabetes, and essentially fewer vascular occasions counting MI and stroke. Taken together, these come about clearly indicate that carvedilol is the favored  $\beta$ -blocker in the treatment of incessant heart failure.

But, because this drug is not halal drug so that still there are some adverse effects reported. The most common adverse effect associated with carvedilol is related to undesired, excessive hypotension secondary to its vasodilating properties. These include dizziness, lightheadedness, fatigue, and headaches. Other adverse effects are related to the beta-blocking properties, including dyspnea, bronchospasm, bradycardia, malaise, and asthenia. Additional symptoms of diarrhea, weight gain, headache, depression, impotence, and renal insufficiency also

have correlations with carvedilol administration [30-40].

### Suggestion

Consuming halal is a command of Allah for Muslim. According to the Q.S. Al-Baqarah verses 168 and 172. Using halal products is not only in food, but halal has now developed in medical science, which is commonly called halal pharmacy. Halal can be interpreted as things that are permissible and can be done because they are free or not bound by the provisions that prohibit them. The things that determine halal are halal in substance, halal in processing it, halal in storage, halal in presentation or transportation, and halal way of obtaining it. In Indonesia, because the majority of the population is Muslim, there should be a halal substitute medicine that is correct for HF sufferers.

“Indeed, Allah has not made healing for you in what he has forbidden.” (Narrated by Bukhari). Therefore, the authors hope that halal drugs will be developed to reduce the adverse effects of illicit drugs on the body and soul of heart failure patients.

There are many medicines that Allah (SWT) has described as a cure for all diseases, such as black cumin. In addition, honey, bidara leaves, grapes, figs and other fruits also have a good effect on the physical and mental health of heart failure patients.

In addition to good treatment, Rasulullah also ordered us to give charity. Because charity can prolong life. Rasulullah SAW said, “Alms to the poor only gets the reward of charity, while alms to relatives contains two virtues, namely charity and connecting kinship ties.” (HR Tirmidhi, Abu Dawud, Nasa’i, and Ibn Majah)

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