Beta Blockers: An overview on the current established therapeutic uses on different classes of patients for a deeper understanding on the proper utilization while prescribing a drug.

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons)

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Declaration

It is hereby declared that

1. The thesis submitted is my original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

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Ethics Statement

This study does not involve any kind of animal trial and human trial.

Abstract

Beta Blockers are one of the most prominent classes of drugs for treating various cardiovascular diseases. It has a wide array of efficacy where the drug has established itself as one of the go-to drugs by physicians for treating hypertension and other conditions. This report is an overview on what we know about Beta Blockers in general and the pharmacology (brief mechanism of action) of the drug. This overview portrays the current established therapeutic uses of the drug. The report comprises the use of beta blockers in arrhythmia, cancer prognosis, chronic heart failure, COPD, sepsis, migraine prevention, cardiomyopathy, myocardial infarction, congestive heart failure and patients undergoing coronary bypass surgery. The findings of its various uses lead report to its second part which contains the in-depth portrayal of its various trials conducted on randomized group, CKD patient groups, elderly patient groups, patient groups with cirrhosis, patients with traumatic brain injury, placebo group study, rate of mortality on beta blocker use. The report also points out the impact of selective and non-selective beta blockers on its long-term use along with potential toxicological outcomes of the drug under various conditions of administration. This report is intended to provide a more concise and medically significant information on beta blockers for aiding in the dosing pattern of the drug. The study will provide a more robust understanding for an impactful therapeutic usage of the drug on different classes of patients.

Keywords: Beta-Blockers, Sepsis, Myocardial Infarction, Pharmacology, Prescribing Pattern.

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Chapter 1

Introduction

1.1 About Beta-Blockers

Hypertension induced cardiovascular disorder is a case very much the rising factor for creating other conditions. Almost 90% of individuals having hypertension does not even know the requirement of their antihypertensive. A typical patient's blood pressure is usually from 120/80 mmHg. If the range of BP stands from 140-159/90-99 then it is termed as Stage I hypertensive. If the range is from above 160/ above 100 mmHg then it is termed as Stage II hypertensive. Hypertension induced cardiac disorders bring a wide array of problems. Let us go deeper into the world of beta blockers. In order to understand the behavior of beta blockers and why and how can it work as an established antihypertensive.

1.2 Structural Orientation of the drug

There are three kinds of Beta blockers available which includes $B_{1,}$ B_2 and B_3. All the Beta Blockers available have either selective blocking properties or might be non-selective in terms of their antagonism. Majority of the Beta blockers found are aryloxypropanolamines. The very first discovered Beta-Blocker is dichloroisoproterenol (Wilson and Gisvold, 2004).

The basic skeleton for the beta-blockers is generated from phenylethanolamine and phenoxypropanolamine where the R_1 and R_2 are substituted with mostly chlorine, methyl, nitro, methanesulfonanilide, napthyl, acetophenoxy, etc. (Laddu & Somani, 1969). Substitution with this cause variation of selectivity and use. The potency of B-adrenergic blocking is increased when the phenoxypropanol amine compounds are used. Drugs that have a certain group in the meta position have increasing blocking activity.

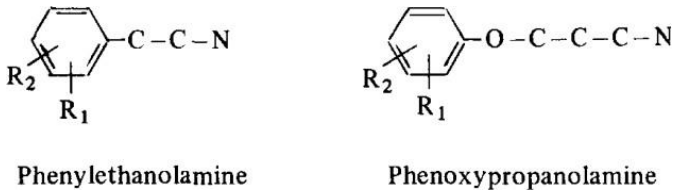


Figure 1: Basic Skeleton of Beta Blockers (Laddu & Somani, 1969)

In Dichloroisoproterenol there are 2 Cl in the 3,4 position instead of -OH. This basis has made it easier to identify that the alteration of the Cl predicts the antagonist activity as DCI is not a pure antagonist. Replacement of Cl with -OH/cyclic ring made it clear that Beta-antagonism is observe by removal of Cl. The next Beta-blocking agent to come was Pronethalol which exhibits a lesser amount of sympathomimetic activity compared to dichloroisoproterenol. From pronethalol, the very first backbone for Beta-blockers were derived which is the Propranolol as pronethalol had toxicity of inducing thymic tumor (Wilson and Gisvold, 2004). The marked $-OCH_2-$ group marked in the figure of propranolol is the benchmark parameter that has helped to figure out that it is responsible for pure antagonism.

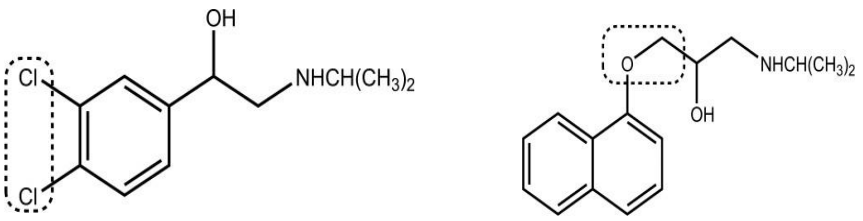


Figure 2: The first derived B-antagonists; Dichloroisoproterenol and Pronethalol (Wilson and Gisvold, 2004)

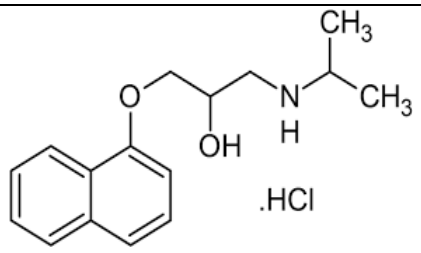
The presence of the para-substituent in the aromatic ring and absence in the meta-substituent ring makes the blocking more cardio selective in terms of antagonism (Wilson and Gisvold, 2004). Since almost all the beta blocking activity of aryloxypropanolamines are based on the R enantiomer, a few has been developed with the S enantiomer which are Levobunolol,

Timolol, Penbutolol (Wilson and Gisvold, 2004). In case of both enantiomers a presence of -OH substituent right after the marked -OCH_2- group is characteristic for increasing B1 and B2 selectivity. B1 selectivity is important as it helps functioning in treating hypertension, glaucoma, arrythmia. In brief, the presence of -OCH_2- ring is characteristic for B blocking activity. If the para group is empty without any substituent, then it is non-selective. Having a long chain substituent in the para position increases B1 selectivity. On the ortho and meta position of 1,2,4,5 presence of long substituents or even certain groups like -CH_3, -cycling ring, etc. increases selectivity. Some of the common list of Beta blockers are given below.

1.3 Brief Listing of current available Beta Blockers

This listing is provided based on their uses and specificity of their selectivity. As we know that first generation blockers are non-selective but does not show a-antagonism. In case of second-generation blockers, they are B1 selective antagonist which are most helpful for asthma patients as B2-blocking might induce bronchial asthma related issues. Lastly, third generation B-blockers are mostly B-antagonists with a_1-antagonism specifically. The name, uses and structure of the compounds are given below (Wilson and Gisvold, 2004):

Table 1: Comparison table of first-generation beta blockers. Information retrieved from (Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 2004)

First Generation Beta Blockers		
Name	Structure	Prominent Therapeutic Use
Propranolol		Hypertension, Cardiac Arrythmia, Angina Pectoris, Post myocardial Infarction, Migraine, Anxiety, Schizophrenia, Aggression

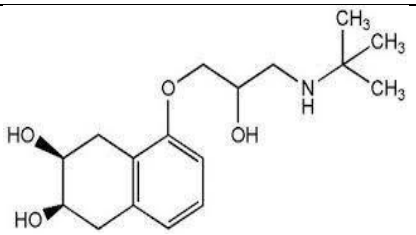
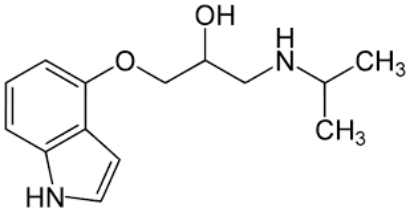
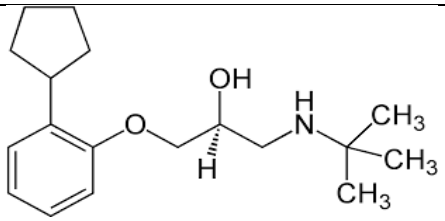
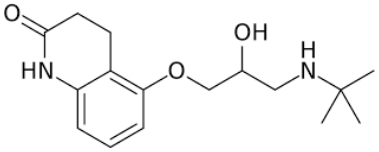
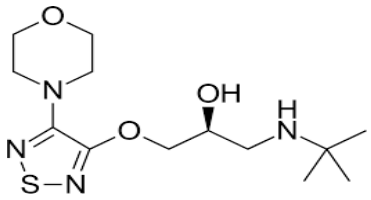
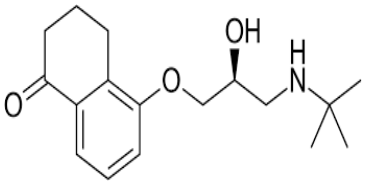
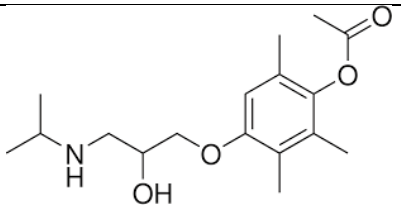
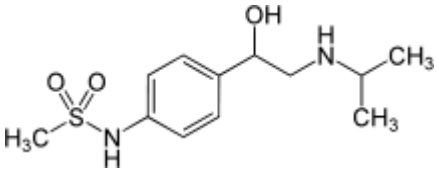
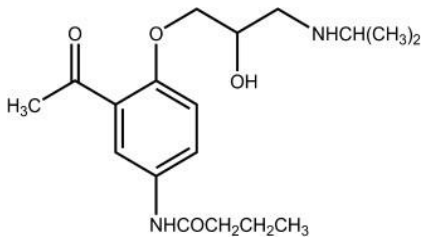
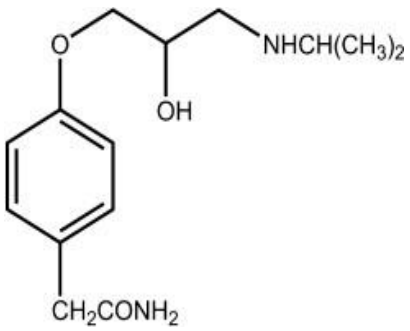
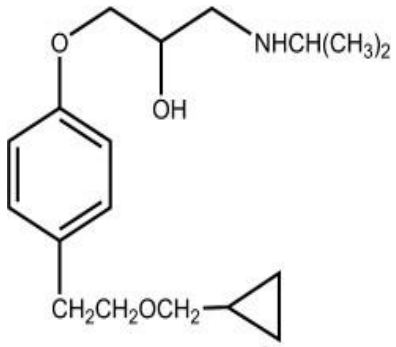
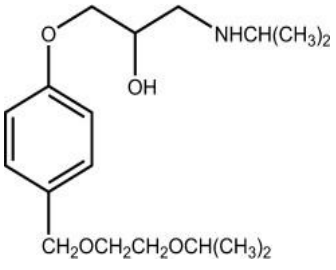
Nadolol		Hypertension, Angina Pectoris,
Pindolol		Hypertension
Penbutolol		Hypertension
Carteolol		Hypertension, Glaucoma
Timolol		Hypertension, Migraine, Glaucoma
Levobunolol		Glaucoma
Metipranolol		Glaucoma
Sotalol		Arrythmia, Atrial Fibrillation

Table 2:Comparison table of second-generation beta blockers. Information retrieved from (Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 2004)

Second Generation Beta Blockers		
Name	Structure	Prominent Therapeutic Use
Acebutolol		Hypertension
Atenolol		Hypertension, Angina Pectoris
Betaxolol		Hypertension, Glaucoma
Bisoprolol		Hypertension

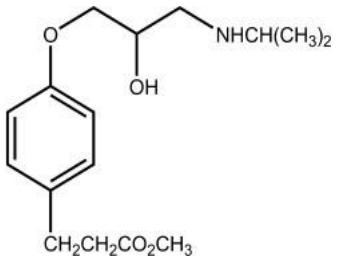
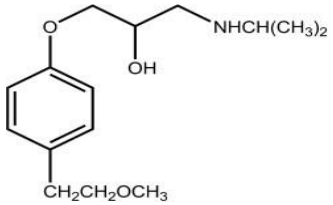
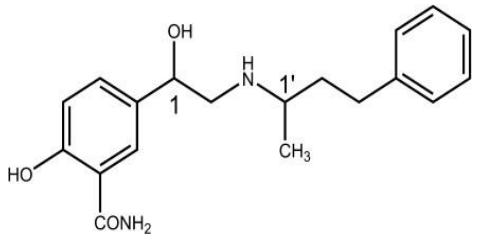
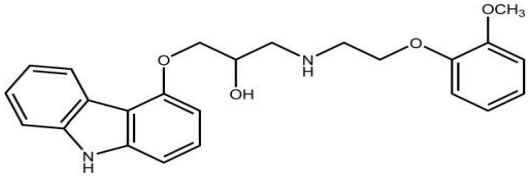
Second Generation Beta Blockers		
Name	Structure	Prominent Therapeutic Use
Esmolol		Atrial Flutter, Atrial Fibrillation, Sinus Tachycardia
Metoprolol		Hypertension, Angina Pectoris, Myocardial Infarction

Table 3:Comparison table of third-generation beta blockers. Information retrieved from (Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 2004)

Third Generation Beta Blockers		
Name	Structure	Prominent Therapeutic Use
Labetalol		Hypertension, Vasodilation, Reflex Tachycardia,
Carvedilol		Hypertension, Antioxidant, Antiproliferative, Neuroprotective, Congestive heart failure

1.4 Overview on adrenergic receptors

Before getting into the depth of beta-blockers we need to know one thing at first that is, beta blockers antagonize endogenous catecholamines which stimulates all the A1, A2, B1, B2, B3 adrenergic receptors. These catecholamines works on the CVS by bringing changes in the CNS, PNS, Heart and the Kidney (Gorre & Vandekerckhove, 2010). In case of the alpha-2 adrenoreceptors, the activation of the sympathomimetic activity is inhibited. The heart has B1 receptors of around 70% and B2 receptor of around 30%. The stimulation of B receptors is done by the cAMP pathway (Gorre & Vandekerckhove, 2010). In case of smooth muscles, we see the presence of A2 and B2 receptors. Thus, positive stimulation results to arterial vasoconstriction for A2 receptor and vasodilation for B2 receptor. The release of renin in the kidney is controlled by the B1 receptors stimulation which causes the increase in release of epinephrine. The A1 receptor and B2 receptor are also responsible in case of metabolism, pancreatic insulin release, lipolysis, bronchodilation and glyconeogenesis which will be

addressed soon. Beta blockers works by competitive antagonistic activity against these adrenergic receptors, mostly beta blockers.

1.5 Properties of Beta-Blockers

1.5.1 Effect on heart

Beta blocker works against arrythmia by increasing the length of sinus node cycle and atrioventricular refractory duration. Drugs like Sotalol show such kind of effect. Some of the other kind of effects on heart include hypokalemia and myocardial ischemia reducing effects (Gorre & Vandekerckhove, 2010). Since the heart has a higher number of B1 receptors in the heart, hence anti-hypertensives which are B1-antagonist are also called cardio selective beta-blockers. The amount of efficacy of cardio selective depends on the amount of dose. It is imperative to keep in mind that B1 selectivity reduces with the increase of dose.

The third-generation beta blockers show the effect of vasodilation, anti-oxidation and anti-inflammation. On the other hand, beta-blockers with Intrinsic Sympathomimetic Activity (ISA) are seen in partial agonists which has certain effects on the heart during rest showing negative chronotropic effect. This kind of beta-blockers reduces renin-release. B2-ISA results to vasodilation as well (Gorre & Vandekerckhove, 2010).

1.5.2 Blood Pressure Lowering Effect

Although the mechanism of it is completely not understood but beta-blockers show the reduction of blood pressure by reducing cardiac output. This reduction of cardiac output increases peripheral vascular tone to maintain blood pressure. A misunderstood mechanism but it states that the vascular resistance lowers the blood pressure after a few hours of the intake of

the drug. Another mechanism of pressure-lowering is B1 receptor mediated decrease in catecholamine release which causes lowering of blood pressure (Gorre & Vandekerckhove, 2010).

1.5.3 Comparative efficacy of Beta-blockers compared to age

The activity of a beta-blocker is based on its ISA during the time of rest, not during exercise-based state. The activity is also dependent on selectivity of B1-receptors due to peripheral vasodilation reducing action. The duration of action of the drug is also dependent for the efficacy. Now varying age shows varying response to different drugs. Among young people ISA increase is observed based on their BMI and resistance to insulin (Gorre & Vandekerckhove, 2010). In elderly people the case of cardiovascular disorder is due to increased level of catecholamines, not due to vascular resistance thus for them beta blockers are not the first options for treatment but it is preferred for them during coronary artery disease and heart failure cases.

1.5.4 Metabolic Factors due to Beta Blocker administration

Non-selective beta-blocking results to decrease of secretion and sensitivity of insulin. This also results to increase of BMI and gluconeogenesis. A study done using propranolol, metoprolol and atenolol has shown that usage of these drugs has increased the risk of new onset of diabetes by 30% (Gorre & Vandekerckhove, 2010). It is important to keep in mind that, the more the selectivity of B1 receptors, the less the metabolic effect.

Beta-blockers are also called atherogenic because it causes in reducing HDL, elevate LDL and TG. Due to beta blockage, the lipids involved in breaking down TG is inhibited and HDL is ISA dependent.

1.5.5 Objective of the Study

- Provide an overview of the different beta-blocker use
- Help physicians use the study as a minimized guideline to understand the behavior of BBL under different conditions
- Create scopes on conducting geographical based study on BBL on the existing promising scopes of its therapeutic use
- Understanding the use of beta blockers available in the market

Chapter 2

Literature Review

2.1 Beta Blocker Tolerance

A study named as 'Achieving a Maximally Tolerated Beta-Blocker Dose in Heart Failure Patients' was conducted in 2017. The study focused on calculating and figuring out the right dosing pattern of BBL along with Ivabradine to reduce HF patient hospitalization and targets on dose administration in terms of reduction of morbidity of patients with HF. Analysis suggested that the heart rate reduction or its magnitude is an important parameter to consider while considering LV function and cases of mortality (Bhatt et al., 2017). The study suggests that dose dependency is a huge factor while considering patient mortality rates. A study of Carvedilol showed that patients with 12.5mg (two times daily) were in a much riskier position than 6.5mg (two times daily) in terms of HF patient mortality despite of age. Another study on Bisoprolol has shown to increase mortality rate upon withdrawal of Bisoprolol where patients had a high dose regimen. Seeing such conflicting and uncertain outcomes, the study formulated a dosing algorithm for up-titrating Beta blockers to reduce HF mortality and hospitalization (Bhatt et al., 2017). The algorithm shows the following trend of prescribing:

If the patient has a left ventricular ejection fraction of less than 40%, then it is to be inquired if the patient has any sort of cardiogenic shock/bradycardia/heart block upon BBL administration. If no, then the patient can start taking:

Table 4:Information of dosing algorithm proposed for co-administration with Ivabradine. Retrieved from: (Bhatt et al., 2017)

Metoprolol XL: 12.5-25 mg daily initially with a target dose of 200mg in 24hours or,
Carvedilol: 6.25- 12.5 mg daily initially with a target dose of 25mg in 24hours or,
Bisoprolol: 1.25mg daily initially with a target dose of 10mg daily.

If the patient is seen to have tolerance, then this will continue and consideration of taking Ivabradine along with the beta-blocker is being made where Ivabradine has shown to reduce HF hospitalization (Bhatt et al., 2017). If intolerance is shown then an assessment is to be considered for changing the dosing of BBL to reduce HF mortality.

2.2 Arrhythmia

Another study named as ‘Antiarrhythmic mechanism of beta blocker therapy’ which was conducted in 2019. Beta-adrenergic receptors situated in the cardiovascular system upon stimulation by catecholamines causes to end up in disturbances in the rhythm of the heart leading to arrhythmia. This article focused on the use of anti-arrhythmic effect of beta-blockers in clinical settings. The article portrays that use of propranolol is significant for the fact that it reduces the risk of arrythmia by reducing the sympathetic triggers due to the presence of catecholamines in the blood (Grandi & Ripplinger, 2019). In contrast among the first-generation beta blockers, Nadolol and Timolol shows no sympathomimetic stabilization thus it is not preferred for the case of arrhythmic patients. The second and third generation beta blockers show little or no activity in terms of reducing irregular heart rhythm hence forth they are not the drug of choice for arrhythmic patients, except Carvedilol which shows membrane stability but no sort of sympathomimetic activity. The article also mentions that despite of anti-arrhythmic effect or not, Beta blockers possess a lot of therapeutic indications which makes it a certain drug class for situations like atrial fibrillation (first line therapy), reducing ventricular rate (especially atenolol, bisoprolol, metoprolol, propranolol, sotalol), treating arrhythmia in combination with Class III amiodarone. Patients with acute MI are recommended to use beta blockers like atenolol and metoprolol lacking sympathomimetic activity if they do not have cases of arrhythmia as that can pose other side effects (Grandi & Ripplinger, 2019).

2.3 Cancer Prognosis

In 2016, a study which can rather turn into a new scope for medicinal innovation was conducted under the title ‘Beta blockers and cancer prognosis – The role of immortal time bias: A systematic review and meta-analysis. This meta-analysis mentioned that BBL users had significantly higher survival rate while having specific types of cancer. But the study showed that many of the cohort studies conducted might have resulted from immortal time bias (ITB). ITB can lead to very significant change in case pharmacoepidemiologic studies by bringing various efficacy related miscalculations (Suissa, 2008). Beta blockers are known to be safe and administration of the drug reduces the sympathomimetic neurotransmitters norepinephrine and epinephrine. These neurotransmitters play an important part in terms of secondary growth of tumor cells. Thus, it helps increasing PGE2 synthesis as well (Weberpals et al., 2016). This meta-analysis secluded the chance of melanoma survival as it was out of consideration. The study gave hope on increasing concomitant use of beta-blockers to figure out if they actually gave such effect in terms of increasing cancer survival. The meta-analysis had 30 studies of which 19 studies were independent to ITB. Even though the study concluded that there were not much of conclusive evidence for the claim but it also mentioned that if studies are conducted in various populations where the introduction of beta blockers for the first time to cancer patients are recorded to eliminate the ITB, then a broader meta-analysis can be conducted to ascertain if they actually increase the chances of survival or not (Weberpals et al., 2016).

2.4 Targeted Dose Therapy

‘Beta blocker and chronic heart failure patients: prognostic impact of a dose targeted beta blocker therapy vs heart rate targeted strategy’ was published in 2018. By this time the magnitude of impact of beta blockers is by far established. But the focus on which method to follow for prescribing the drug is addressed in this paper. The research was conducted with 1669 patients having Heart Failure where all of them were taking ACE inhibitors and had a history of HF for around 6 months at least. In this research the patients were classified into 5 groups (A-D) where group A met the dose target, group B met the heart rate target, group C with no target and group D with antihypertensives except beta blockers (Corletto et al., 2018). The most administered beta blockers were carvedilol and bisoprolol for group A and metoprolol for group B and C. It was observed that the mean heart rates of group A were 73 where it was 61 for group B. It is to be mentioned that serum electrolytes and other factors like creatinine, diabetes, CKD all were under more or less similar conditions when the study was conducted. Among group A and B, it was observed that in terms of 5 years of administration, following a recommended target dose caused Carvedilol induced HF mortality of 23.7% and for a target heart rate dependent (51-69 bpm) Metoprolol based administration made the mortality of 22.7% (Corletto et al., 2018). It is to be noted that patients without any sort of beta blocker treatment had a mortality rate of 55.6%. The study concluded that targeting a dose for beta blocker therapy is beneficial but then again if the bpm of heart rate is within 50-70, then heart rate-based medication can also be provided for carvedilol, bisoprolol and metoprolol. Another study under the title ‘Heart rate is a useful marker of adherence to beta-blocker treatment in hypertension’ which was conducted in 2017. The study concluded that patients with heart rate above 75.5 beats per minute are likely to show problems in terms of adherence

to beta blockers, 62.5% of times according to the study (Kociánová et al., 2017). The only exception might be seen in Nebivolol but it is yet to be properly claimed. But all in all, heart rate above 75.5 bpm can be a marker to know when to stop beta blocker in cardiac patients.

2.5 COPD

Conducted in 2018, the review on 'Beta-Blockers in COPD: A Methodological Review of the Observational Studies' investigated on the efficacy of Beta blockers in COPD. But there lacked a proper cohesive understanding on how much or to what extent does it help. The study was conducted with 18 observational studies. The study found out a re-analysis of the TORNADO trial on bronchodilators working against COPD (Suissa & Ernst, 2018). Despite of lack of proper observational studies, there is a promising chance to further investigate the use of beta blockers for COPD.

2.6 Sepsis

‘Beta-blockers use in severe sepsis and septic shock: a systematic review’ was a study conducted in 2015 which has brought out a very prominent and promising impact of beta blocker usage in patients with sepsis. The study was done using 10 relevant clinical studies which established certain facts about Esmolol, Metoprolol and some other beta blockers as well in terms of hemodynamics and metabolism shifts which helps the septic patient greatly. The study mentioned that the clinical data found are very promising in terms of beta blockade in septic patients (Morelli et al., 2013). The beta blockers administered certainly shows cardiovascular alterations which is due to the sepsis and it helps aid patients providing a certain sort of analgesic effect as well. The study addressed certain alterations in the CVS by beta blockers which might help a septic patient, some are: modulation of MI due to sepsis, reduction of risk of myocardial ischemia, regulation of diastolic function with septic patients having heart failure. Esmolol or Metoprolol has shown improvement in decreasing the heart rate. For patients with such condition, this reduction of heart rate can help maintaining the efficiency of the CVS and consumption of oxygen as well. In case of reducing TNF-a and IL-6, it has been seen that beta blockage has modulated levels of the cytokines, especially esmolol has shown reductions of serum TNF-a (Sanfilippo et al., 2015). On the other hand, landiolol has reduced cytokine level in the lungs. Metoprolol has shown promise in reducing myocardial expression of IL-6. Although among the beta blockers present, Atenolol did not alter any sort of level of the cytokines (Sanfilippo et al., 2015).

2.7 Migraine Prognosis

Another study titled as ‘Beta Blockers for Migraine Prevention: a Review Article’ published in 2019 tried to establish the role of beta blockers in migraine prophylaxis compared to the other agents available. The study mentioned that for migraine prophylaxis the dosing pattern would differ. The top tier drugs having the most efficacy in terms of migraine is metoprolol, propranolol and timolol. Propranolol has the highest reliance and study data where the dosing from 40-160mg daily based on the requirement of the patient has proven to be effective for migraine prophylaxis, but side effects are required to be considered as it is non-selective (Danesh & Gottschalk, 2019). The drug metoprolol is amongst the ones preferred for migraine prophylaxis with a dose dependent efficacy from 50-100mg daily. The drug is very lipid soluble but has a lower affinity to 5-HT receptors. Timolol on the other hand has a better 5-HT receptor affinity which makes it a suitable candidate for migraine prophylaxis (Danesh & Gottschalk, 2019). One of the shocking outcomes is Nadolol being the second-tier beta-blocker for migraine prophylaxis. The drug is hydrophilic in nature and directly excreted from the kidney. But it can be considered as an option for patients where fewer amount of CNS side effects needs to be considered (Danesh & Gottschalk, 2019). One thing that is strictly to be considered is while administering beta blockers, patients with asthma or COPD has to be kept under close observation since the drug might enhance bronchodilation (Dickstein et al., 2008).

2.8 Cardiomyopathy

Cardiomyopathy can be classified into three types namely Acquired Cardiomyopathy, Genetic Cardiomyopathy and Mixed Cardiomyopathy (Maron et al., 2006). In 2017, an overview titled as 'Cardiomyopathy: An Overview' stated that for Hypertrophic Cardiomyopathy where the heart muscles get thickened, Beta blockers are the first line of therapy. Calcium channel blockers like verapamil can only be considered if the patient has intolerance towards beta-blockers. Patients with Stage B (at risk without any signs) and Stage C (showing symptoms of heart disease/failure) risk of heart failure due to cardiomyopathy should consider beta blockers/ACE inhibitors for their line for treatment (Brieler et al., 2017).

2.9 Myocardial Infarction

Among deaths due to heart failure, acute myocardial infarction patients stand at the top (Granger et al., n.d.)The study 'Effect of Beta-Blocker Dose on Survival After Acute Myocardial Infarction' published in 2015 ascertains an evaluated the improvement on survival after MI upon administration of beta blockers. The study consisted of 7057 candidates having AMI. The study involved metoprolol 200 mg/day, bisoprolol 10mg/day, carvedilol 50 mg/day, timolol 20mg/day, propranolol 180 mg/day. The beta-blockers were divided into 5 groups where the groups were classified based on % of target dose. The candidates were at a mean age from 63-65 years. The patients after having MI attack, 91.5% were given beta blockers where majority 67.7 % were given metoprolol and 24.3% were given carvedilol (Goldberger et al., 2015). The studies showed prominent reliance on beta blockers on reducing further reinfarction and mortality rates. Another study title as 'Post-Myocardial Infarction Heart Failure' from 2018 showed a meta-analysis of 31 random trials involving 25000 patients, where the risk of reinfarction and death was reduced by 20-25% upon administration of beta blockers ((Bahit et

al., 2018). This study involved the statistic of the CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Study) where 1959 patients were given

carvedilol at max 25mg/day which reduced the mortality rate to 12% compared to 15% which was evident in non-beta blocker patients. Another observation made in the study was the COMMIT-CCS 2 study where the co-administration of clopidogrel and metoprolol among 45,852 candidates at metoprolol up to 200mg/day was done. But the administration metoprolol has confirmed the reduction of reinfarction by 5 people. The study concluded having observations that oral beta blockers should be given within the first 24hours in patients with ST-segment myocardial infarction (STEMI) where the patient does not show signs of heart failure or low cardiac output (Bahit et al., 2018). Furthermore, another study 'Prognostic Impact of Beta Blocker Dose After Acute Myocardial Infarction' which was conducted in 2019 stated that compared to no beta blocker group, beta blockage caused reduction of risk of cardiac death. The study included 11,909 patients where 69.3% were low dose group, 13.7% were high dose group and the rest were non-beta blocker patient group. After one year of beta blocker administration (bisoprolol, carvedilol, nebivolol and metoprolol) there were significant dose dependent heart rate reduction (Hwang et al., 2019). The study also stated that the risk of cardiac death after MI upon one year of beta blocker administration reduced from 5.7% to 2.6%. Bahit et al, 2018 mentions the pattern of time dependent therapies that needs to be followed for MI:

Table 5:Efficacy of dosing anti-hypertensives at varying hours, information retrieved from Bahit et al., 2018.

Time 0-24 Hours	Initiate ACEI
Time 24 Hours to Discharge	Avoid Beta blocker for first 24 hour Re-evaluate the use of Beta blocker and concurrently keep using Aldosterone Antagonist
Time discharge to next follow up	Up-titrating ACEI and BBL to optimal dose

2. 10 Hypertension

Among many of the therapeutic effects or probable therapeutic roles, anti-hypertensive effect. Betablockers are one of the categories of antihypertensives where its efficacy has been discussed in this meta-analysis study title 'Beta blockers in hypertension: overview and meta-analysis of randomized outcome trials' which was published in 2020. The study mentioned that among all the other prevailing anti-hypertensives, beta blockers show the least pronounced activity. The analysis was conducted having 84 BP lowering trials where 67 of them has been counted, the ones where the consideration of heart failure, acute myocardial infarction has been omitted (Thomopoulos et al., 2020) . The study had found out that in one of the trials, incorporation of beta blockers shown 10/5 (systolic/diastolic) mmHg reduction in BP among patients having myocardial infarction, heart failure and coronary disease. The studies only considering hypertension studies had an elaborative table of finding where the reduction in BP ranged from 10.5-14.8/7-8.7 mmHg upon administration of beta blockers. In terms of conclusive comments, the meta-analysis stated that among the 67 considered studies, after 2.5 years upon administration the baseline BP for the patients turned out to be 136/82 mmHg where the patients had lower risk of CVS issues. In another trial of give hypertensive patients after the follow-up of 5 years, the baseline BP turned out to be 163/94 mmHg but the reduction of CVS issues reduced by 22% (Thomopoulos et al., 2020). All of this turns to one conclusive outcome which is, beta blockers are great for reducing the risk of heart failure or stroke but not that much efficient in terms of reducing BP, compared to other available anti-hypertensives.

2. 11 Congestive Heart Failure

Congestive Heart Failure is a condition under which is something that is increasing from time to time for a higher rate of survival as patients with coronary artery disease, aged are the ones who later on end up having heart failure. The study 'Optimal Use of Beta-Blockers for Congestive Heart Failure' published in 2016 mentioned that the guideline-based use of beta blockers has reduced mortality rate by 35%. Patients who have heart failure with reduction of left ventricular EF, for them beta blockers are less responsive. The study also mentioned that despite of a lower effect as an anti-hypertensive, beta blockers are often a more drug of choice instead of ACE inhibitors and aldosterone antagonists in terms of reduction of ejection fraction and ischemia. The beta blocker lowering mechanism is given in brief as a schematic diagram:

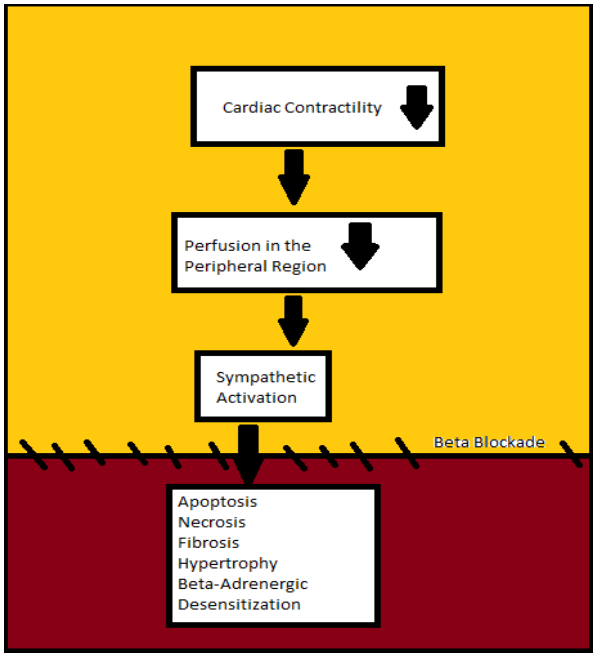


Figure 3: How Beta Blockers function

The CIBS-II study was a baseline study under the administration of Bisoprolol at 10mg/day along with ACEI for 1.3 years. The study caused the reduction of mortality risk by 34% (Lee & Baek, 2016). The MERIT-HF study conducted with 3,991 subjects were given 200mg/day of metoprolol succinate which reduced instances of sudden cardiac death and risk of mortality by 34% as well (Lee & Baek, 2016). The COPERNICUS study conducted had patients who had

low EF of less that 25%. They were given Carvedilol along with ACE inhibitors, digitalis and spironolactone. This co-administration of the drugs reduced the risk of mortality by 35%. The study mentioned the guidelines for beta blockers use given by the American Heart Foundation. The guidelines are:

Table 6:American Health Association Guidelines on Beta Blocker administration for patients with acute heart failure. Information retrieved from (Lee & Baek, 2016)

Continuation during AHF hospitalization	Continue until hemodynamics are constant without contraindications
Temporary discontinuation during AHF	Consider using in patients after recent increase of beta-blocker concentration or with low cardiac output
Administration after return of AHF again	Start administration right after admission
Timing of restarting	After the dose is optimized, start beta blockers by stopping diuretics, vasodilators and inotropic agents.
Caution after starting	Start at low dose and keep caution of patients who needed inotropes

The guidelines for patients with AHF are that, even if they are hospitalized the beta blocker should be up-titrated as far as possible before releasing the patient. Beta blockers have proven degree of efficacy against heart failure but still it is very much underused 34.2% before discharging in Japan, and 51% in Korea. The main reason is maybe physicians do not want to risk any sort of negative inotropic effects due to beta blockers (Lee & Baek, 2016).

2.12 Cirrhosis

A study named 'Non-selective beta-blocker treatment does not impact on kidney function in cirrhotic patients with varices' was done in 2017. In the study it is mentioned that the non-selective beta blockers help cirrhotic patients in many ways including: re-development of the mucosa barrier, reduction of bleeding, reduction of inflammation, reduction of translocation of bacteria. These effects are seen when hepatic venous pressure is reduced by 10% (Scheiner et al., 2017). The study also mentions that there are certain risky outcomes due to administration of non-selective beta blockers like acute kidney injury (AKI) which can increase the chances of mortality. For further clarification this study was conducted where the main parameters considered were the patients serum creatinine, incidence of AKI and glomerular filtration rate with and without non-selective beta blocker administration.

The study included 176 patients among which 93 received non-selective beta blockers and 83 did not and among them 52.3% were patients with alcoholic liver disease. The study has shown the following outcomes in terms of Creatinine, GFR, AKI:

Table 7: Comparison table of Creatinine, GFR, AKI among cirrhotic patients. Information retrieved from (Scheiner et al., 2017).

Category	Total Patients overall	Beta Blocker Patient	Non BBL Patient
Creatinine (mg/dl)	0.98 ± 0.45	0.96 ± 0.31	1.00 ± 0.58
GFR (ml/min)	81.3 ± 23.6	81.2 ± 23.5	81.3 ± 23.8
AKI (% from total candidate)	25 (14.2%)	11 (11.8%)	14 (16.9%)

The study clearly shows that there is not much significant impact of non-selective beta blockers in terms of Creatinine and GFR deterioration and the markers are even under normal physiological conditions. There was a cox regression analysis done to understand the impact

of BBL on AKI better (Scheiner et al., 2017). The results helped conclude that non-selective beta blocker was not the only factor leading to AKI. Although the positive outcomes of non-selective BBL administration is imminent, but the effect of it on cirrhotic patients lacks systematic assessments. In one study it was mentioned that non-selective beta blockers increase cardiac dysfunction which can ultimately lead to renal failure as its efficacy on reducing BP is not prominent, compared to other hypertensives which can lead to further increase of mortality rate (Krag et al., 2012).

Chapter 3

Result

Before diving into the conclusive statements, in this segment the important questions will be addressed, which involves the overall considerations while prescribing a beta blocker to any sort of patient keeping the target of therapeutic effect in mind. The table below shows a more comprehensive elaboration on when to use which drug based on our findings:

Table 8:Comprehensive guidelines on what beta blockers work best under different conditions of the patient.

Condition	Promising or established uses/ considerations to be made
Sepsis	Esmolol is a BBL for consideration for patients with sepsis. Esmolol being a cardio selective BBL. In a study of 6839 sepsis patients 73% were given cardio selective BBL where survival benefit ratio was around 0.7 and the rest was for non-selective BBL where the ratio was around 0.5. Patients receiving no BBL had increased hospitalization (Singer et al., 2017). Metoprolol and Esmolol shows reduction of risk of myocardial ischemia, control the diastolic function, reduce heart rate, keeping oxygen consumption constant (Sanfilippo et al., 2015) Landiolol also helpful in reducing lung cytokine level. Reasons to choose Esmolol: - Short acting - Ease of titration - Shorter half life - reduces patient mortality by 61%

Cirrhosis	Propranolol: reduces gastrointestinal bleeding by 96% and variceal bleeding by 74% (Dosing 20 – 180 mg/daily) Nadolol: Frees from variceal bleeding by 97% (Dosing 40-120 mg/daily) Timolol: No significant improve for GI varices. These statistics are only applicable when the patient has medium large varices. During that time BBL works on the patient, instead in end-stage cirrhosis, they reduce the survival of the patient due to decreasing of perfusion increasing mortality (Ge & Runyon, n.d.).
Hypertension For normal and renal patients	Patients having a baselines GFR of 63 ml/min where the administration of betablockers reduced mortality. The study showed that there was no reduction in GFR among patients receiving BBL (cardio selective or non-selective). There was no incidence of higher mortality with worsening renal function upon administration of BBL (Kotecha et al., 2019). The administration of BBL has shown to reduce 10/5 (systolic/diastolic) mmHg BP reduction among patients with heart failure and coronary disease where upon administration of the drug the baseline BP of the patients have been 136/82 mmHg after 2.5 years of administration with no signs of reduced renal function upon the BBL administration (Thomopoulos et al., 2020).

Myocardial Infarction	Metoprolol reduces mortality risk by 36%. Suggested beta-blockers include Metoprolol, Bisoprolol, Carvedilol Beta-blockers reduced MI mortality by 40% among 200,000 MI patients (Thaper & Kulik, 2018). Beta-blockers for MI reduced reinfarction but increased the cardiogenic shock, also chronic heart failure. Use beta blockers only when there is absence of risk of cardiogenic shock, approved by American Heart Foundation. Use of drugs at the range from: Metoprolol at 200mg/day maximum Metoprolol 200mg/day + Clopidogrel Bisoprolol 10mg/day max Carvedilol 50mg/day max Timolol 20mg/day max Propranolol 180 mg/day max (Goldberger et al., 2015)

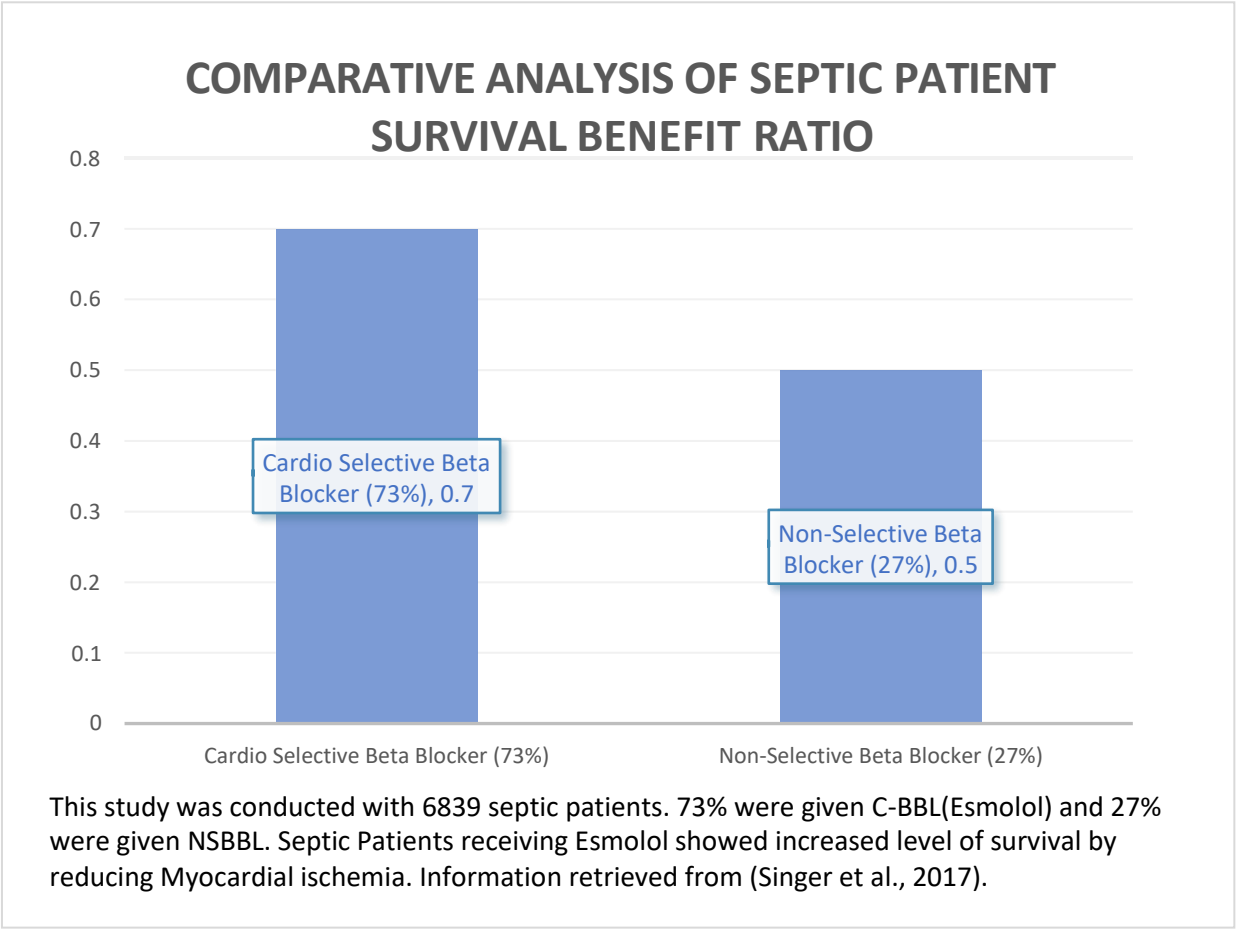


Figure 4: Comparative analysis of septic patient survival benefit ratio. Information retrieved from (Singer et al., 2017).

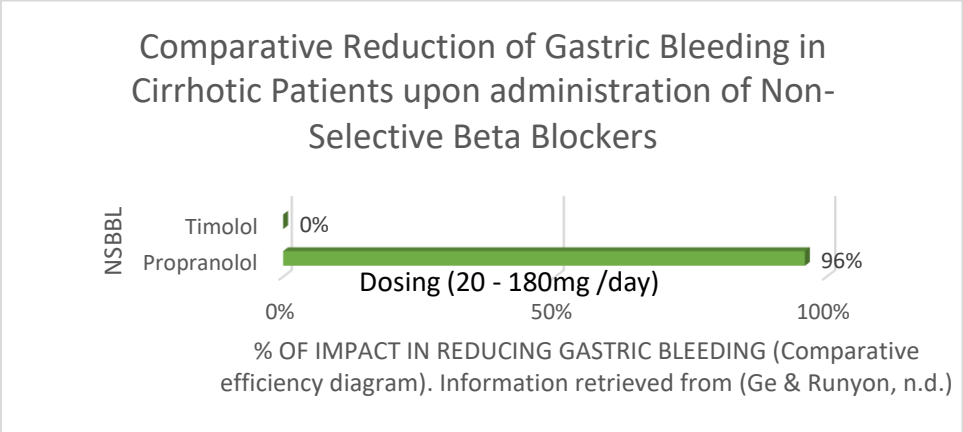


Figure 5: Graphical comparison of established non-selective beta blockers efficacious for reduction of gastric bleeding among cirrhotic patients. Information retrieved from (Ge & Runyon, n.d.)

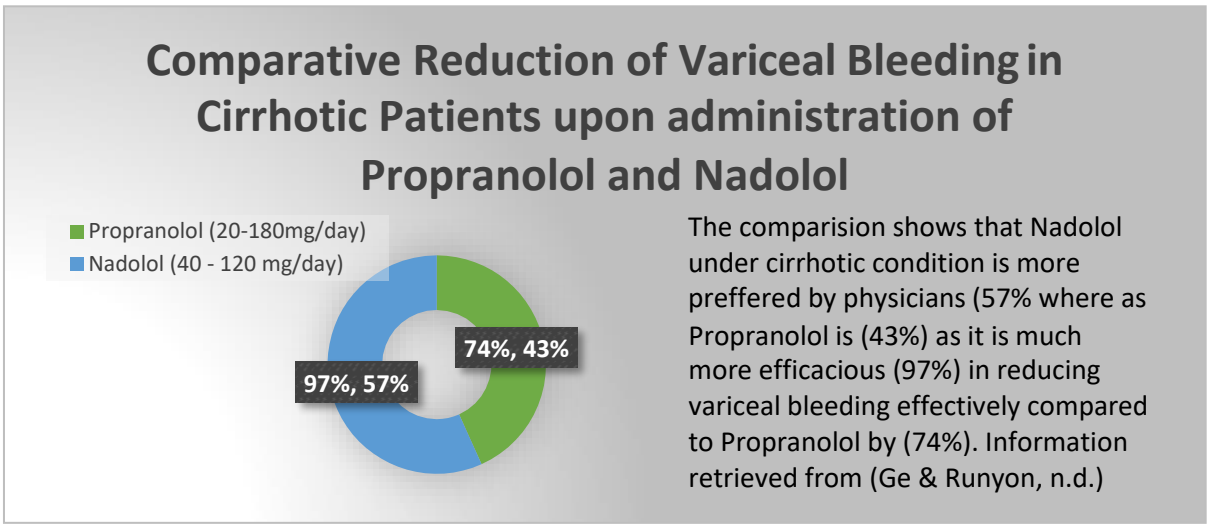


Figure 6: Comparative reduction of variceal bleeding among cirrhotic patient upon propranolol and nadolol administration. Information retrieved from (Ge & Runyon, n.d.)

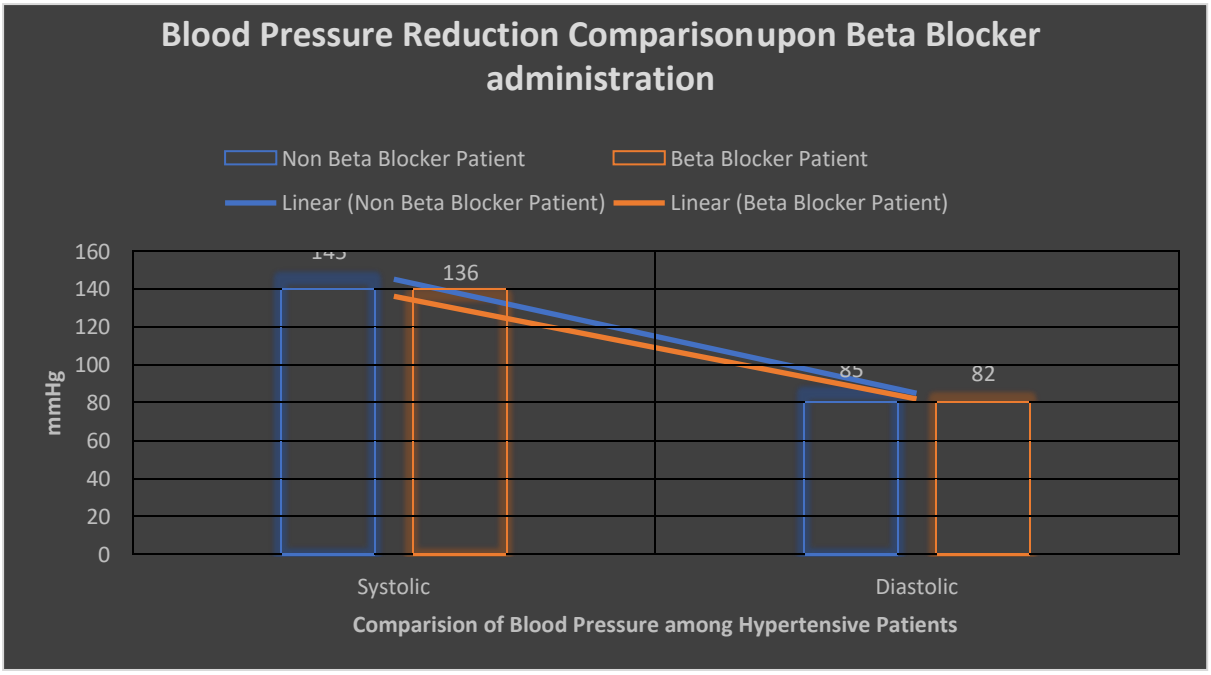


Figure 7: Blood pressure reduction comparison upon beta blocker administration. Information retrieved from (Thomopoulos et al., 2020)

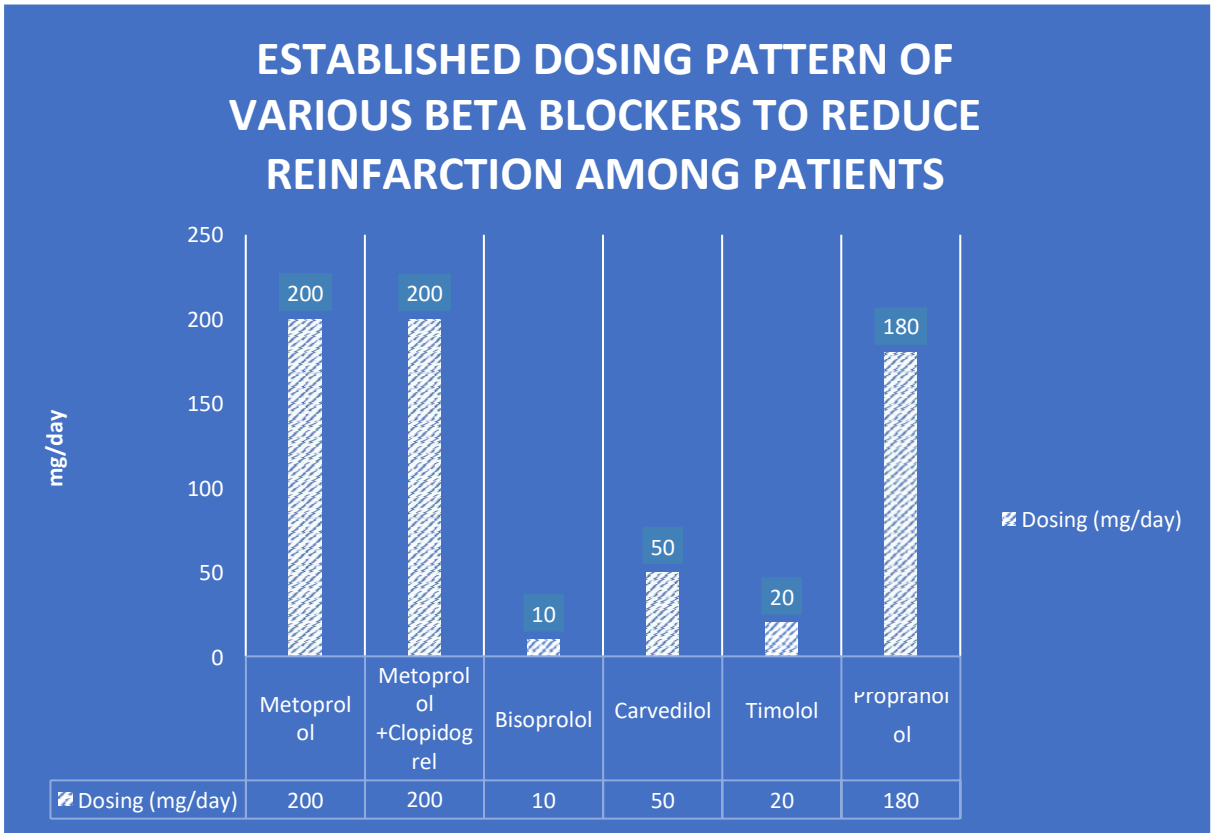


Figure 8: Established dosing for various beta blockers to reduce reinfarction among myocardial infarction patients. Information retrieved from (Goldberger et al., 2015)

Chapter 4

Discussion

Beta-blockers as we know in course of time has turned out to be a promising drug for the physicians to prescribe under different conditions. Even though beta blockers are not the first line of treatment if we consider situations like hypertension, but beta blockers have certainly established itself as a hypertensive for patients with varying complications including arrythmia, COPD, sepsis, migraine, etc. The study was intended to provide a brief overview on the various prospects of beta-blockers and its range of applications as a main line of treatment or as a supplementation to reduce the intensity of other diseases. It is safe to consider as an anti-hypertensive among renal patients. Despite of not being the most reliable anti-hypertensive, beta blockers like atenolol, bisprolol, metoprolol, sotalol, etc. can be considered as a combination drug with other anti-hypertensives to reduce arrythmia (Grandi & Ripplinger, 2019). Carvedilol has caused the HF mortality among patients 23.7% whereas without any BBL it has been seen to be 55.6% (Corletto et al., 2018). Esmolol has shown promising signs of being a drug for choice for sepsis patients to reduce variceal bleeding and GI bleeding. Pronpranolol has the highest reliance at a dose of 40-160 mg daily for the case of migraine prophylaxis (Danesh & Gottschalk, 2019). Upon beta blockers administration 20-25% reduction in risk of myocardial infarction is to be found (Bahit et al., 2018).

The study provides a more concise approach in terms of understanding which beta-blocker will be better for which category of patient. The limitations of the study will include: lack of robustness in terms of understanding the proper drug as it is an intended overview, lack of physical testing of the statistic; more of a review of existing data from different studies, lack of geographical consideration of subjects while conducting the overview. The study despite of its limitations has the promising approach to help physicians figure out which drug to prescribe

when necessary. The study's final motive is to ensure a more appropriate prescribing of beta blockers to different class of patients to ultimately enhance the cardiac health and quality of life among patients. There are many scopes and opportunities to be considered for enhancing reliance on beta-blockers in course of time. Science on beta-blockers still has its time life to unravel and re-establish new ways of beta-blockers to save patients and impact the overall patient adherence more and more in course of time.

References

Bahit, M. C., Kochar, A., & Granger, C. B. (2018). Post-Myocardial Infarction Heart Failure. In *JACC: Heart Failure* (Vol. 6, Issue 3, pp. 179–186). Elsevier Inc. https://doi.org/10.1016/j.jchf.2017.09.015

Bhatt, A. S., DeVore, A. D., DeWald, T. A., Swedberg, K., & Mentz, R. J. (2017). Achieving a Maximally Tolerated β-Blocker Dose in Heart Failure Patients: Is There Room for Improvement? In *Journal of the American College of Cardiology* (Vol. 69, Issue 20, pp. 2542–2550). Elsevier USA. https://doi.org/10.1016/j.jacc.2017.03.563

Brieler, J., Breeden, M. A., & Tucker, J. (2017). *Cardiomyopathy: An Overview* (Vol. 96). www.aafp.org/afp.

Corletto, A., Fröhlich, H., Täger, T., Hochadel, M., Zahn, R., Kilkowski, C., Winkler, R., Senges, J., Katus, H. A., & Frankenstein, L. (2018). Beta blockers and chronic heart failure patients: prognostic impact of a dose targeted beta blocker therapy vs. heart rate targeted strategy. *Clinical Research in Cardiology*, *107*(11), 1040–1049. https://doi.org/10.1007/s00392-018-1277-4

Danesh, A., & Gottschalk, P. C. H. (2019). Beta-Blockers for Migraine Prevention: a Review Article. In *Current Treatment Options in Neurology* (Vol. 21, Issue 4). Current Science Inc. https://doi.org/10.1007/s11940-019-0556-3

Dickstein, K., Cohen-Solal, A., Filippatos, G., McMurray, J. J. V., Ponikowski, P., Poole-Wilson, P. A., Strömberg, A., van Veldhuisen, D. J., Atar, D., Hoes, A. W., Keren, A., Mebazaa, A., Nieminen, M., Priori, S. G., Swedberg, K., Vahanian, A., Camm, J., de Caterina, R., Dean, V., … Zannad, F. (2008). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of

Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *European Journal of Heart Failure*, *10*(10), 933–989. https://doi.org/10.1016/j.ejheart.2008.08.005

Ge, P. S., & Runyon, B. A. (n.d.). *The changing role of beta-blocker therapy in patients with cirrhosis*.

Goldberger, J. J., Bonow, R. O., Cuffe, M., Liu, L., Rosenberg, Y., Shah, P. K., Smith, S. C., & Suba cius, H. (2015). *Effect of Beta-Blocker Dose on Survival After Acute Myocardial Infarction*.

Gorre, F., & Vandekerckhove, H. (2010). Beta-blockers: focus on mechanism of action Which beta-blocker, when and why? *Acta Cardiologica*, *65*(5), 565–570. https://doi.org/10.1080/ac.65.5.2056244

Grandi, E., & Ripplinger, C. M. (2019). Antiarrhythmic mechanisms of beta blocker therapy. In *Pharmacological Research* (Vol. 146). Academic Press. https://doi.org/10.1016/j.phrs.2019.104274

Granger, C. B., Goldberg, R. J., Dabbous, O., Pieper, K. S., Eagle, K. A., Cannon, C. P., van de Werf, F., Lvaro Avezum, ; A ´, Goodman, S. G., Flather, M. D., Keith, ;, & Fox, A. A. (n.d.). *Predictors of Hospital Mortality in the Global Registry of Acute Coronary Events*. http://archinte.jamanetwork.com/

Hwang, D., Lee, J. M., Kim, H. K., Choi, K. H., Rhee, T. M., Park, J., Park, T. K., Yang, J. H., Song, Y. bin, Choi, J. H., Hahn, J. Y., Choi, S. H., Koo, B. K., Kim, Y. J., Chae, S. C., Cho, M. C., Kim, C. J., Gwon, H. C., Jeong, M. H., & Kim, H. S. (2019). Prognostic impact of β-blocker dose after acute myocardial infarction. *Circulation Journal*, *83*(2), 410–417. https://doi.org/10.1253/circj.CJ-18-0662

Kociánová, E., Václavík, J., Tomková, J., Ondra, P., Jarkovský, J., Benešová, K., Václavík, T., Kamasová, M., & Táborský, M. (2017). Heart rate is a useful marker of adherence to beta-blocker treatment in hypertension. *Blood Pressure*, *26*(5), 311–318. https://doi.org/10.1080/08037051.2017.1346458

Kotecha, D., Gill, S. K., Flather, M. D., Holmes, J., Packer, M., Rosano, G., Böhm, M., McMurray, J. J. V., Wikstrand, J., Anker, S. D., van Veldhuisen, D. J., Manzano, L., von Lueder, T. G., Rigby, A. S., Andersson, B., Kjekshus, J., Wedel, H., Ruschitzka, F., Cleland, J. G. F., … Coats, A. J. S. (2019). Impact of Renal Impairment on Beta-Blocker Efficacy in Patients With Heart Failure. *Journal of the American College of Cardiology*, *74*(23), 2893–2904. https://doi.org/10.1016/j.jacc.2019.09.059

Krag, A., Bendtsen, F., Burroughs, A. K., & Møller, S. (2012). The cardiorenal link in advanced cirrhosis. *Medical Hypotheses*, *79*(1), 53–55. https://doi.org/10.1016/j.mehy.2012.03.032

Laddu, A. R., & Somani, P. (1969). STRUCTURE-ACTIVITY RELATIONSHIP OF THE BETA ADRENORECEPTOR BLOCKING AGENTS *. In *EUROPEAN JOURNAL OF PHARMACOLOGY* (Vol. 8).

Lee, H. Y., & Baek, S. H. (2016). Optimal use of beta-blockers for congestive heart failure. *Circulation Journal*, *80*(3), 565–571. https://doi.org/10.1253/circj.CJ-16-0101

Maron, B. J., Towbin, J. A., Thiene, G., Antzelevitch, C., Corrado, D., Arnett, D., Moss, A. J., Seidman, C. E., & Young, J. B. (2006). Contemporary definitions and classification of the cardiomyopathies: An American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention.

Circulation, *113*(14), 1807–1816. https://doi.org/10.1161/CIRCULATIONAHA.106.174287

Morelli, A., Ertmer, C., Westphal, M., Rehberg, S., Kampmeier, T., Ligges, S., Orecchioni, A., D'Egidio, A., D'Ippoliti, F., Raffone, C., Venditti, M., Guarracino, F., Girardis, M., Tritapepe, L., Pietropaoli, P., Mebazaa, A., & Singer, M. (2013). Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: A randomized clinical trial. *JAMA - Journal of the American Medical Association*, *310*(16), 1683–1691. https://doi.org/10.1001/jama.2013.278477

Sanfilippo, F., Santonocito, C., Morelli, A., & Foex, P. (2015). Beta-blocker use in severe sepsis and septic shock: A systematic review. In *Current Medical Research and Opinion* (Vol. 31, Issue 10, pp. 1817–1825). Taylor and Francis Ltd. https://doi.org/10.1185/03007995.2015.1062357

Scheiner, B., Parada-Rodriguez, D., Bucsics, T., Schwabl, P., Mandorfer, M., Pfisterer, N., Riedl, F., Sieghart, W., Ferlitsch, A., Trauner, M., Peck-Radosavljevic, M., & Reiberger, T. (2017). Non-selective beta-blocker treatment does not impact on kidney function in cirrhotic patients with varices. *Scandinavian Journal of Gastroenterology*, *52*(9), 1008–1015. https://doi.org/10.1080/00365521.2017.1329456

Singer, K. E., Collins, C. E., Flahive, J. M., Wyman, A. S., Ayturk, M. D., & Santry, H. P. (2017). Outpatient beta-blockers and survival from sepsis: Results from a national cohort of Medicare beneficiaries. *American Journal of Surgery*, *214*(4), 577–582. https://doi.org/10.1016/j.amjsurg.2017.06.007

Suissa, S. (2008). Immortal time bias in pharmacoepidemiology. In *American Journal of Epidemiology* (Vol. 167, Issue 4, pp. 492–499). https://doi.org/10.1093/aje/kwm324

Suissa, S., & Ernst, P. (2018). Beta-Blockers in COPD: A Methodological Review of the Observational Studies. In *COPD: Journal of Chronic Obstructive Pulmonary Disease* (Vol. 15, Issue 5, pp. 520–525). Taylor and Francis Ltd. https://doi.org/10.1080/15412555.2018.1554637

Thaper, A., & Kulik, A. (2018). Rationale for administering beta-blocker therapy to patients undergoing coronary artery bypass surgery: a systematic review. In *Expert Opinion on Drug Safety* (Vol. 17, Issue 8, pp. 805–813). Taylor and Francis Ltd. https://doi.org/10.1080/14740338.2018.1504019

Thomopoulos, C., Bazoukis, G., Tsioufis, C., & Mancia, G. (2020). Beta-blockers in hypertension: overview and meta-analysis of randomized outcome trials. *Journal of Hypertension*, *38*(9), 1669–1681. https://doi.org/10.1097/HJH.0000000000002523

Weberpals, J., Jansen, L., Carr, P. R., Hoffmeister, M., & Brenner, H. (2016). Beta blockers and cancer prognosis - The role of immortal time bias: A systematic review and meta-analysis. In *Cancer Treatment Reviews* (Vol. 47, pp. 1–11). W.B. Saunders Ltd. https://doi.org/10.1016/j.ctrv.2016.04.004

Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry). (2004).