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A Novel Pleiotropic Effect of Beta-Blockers: Useful or Not?

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ABSTRACT
β-adrenergic blockers or β-blockers (BBs) have been the antihypertensive treatment for the past 50 years. Several studies were developed to further explore the therapeutic effects of BB, ranging from use in liver cirrhosis with esophageal varices to involvement in cancer treatment. The Autonomic nervous system (ANS) dysfunction has been shown to cause several of these diseases. Immune suppression, cardiovascular dysfunction, hypertension, and even worse prognosis in cancer patients are due to chronic activation of the sympathetic nervous system (SNS). Based on its mechanism of action, the use of BB drugs has different therapeutic targets, and each has different advantages and side effects. Since the discovery of a new third-generation BB drug that has a complete combination of action, several diseases have hopes of being treated with this agent. Improving survival, hospital discharge, and quality of life affecting patients is the goal of the new therapeutic approach.

Keywords: β-blockers, antihypertensive, cardiovascular, esophageal varices, cancer

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INTRODUCTION
The involvement of the autonomic nervous system (ANS) has a considerable influence on the pathophysiology of cardiovascular disease (CVD) [1]. Activation of the sympathetic nervous system (SNS) is a short term compensatory response to hemodynamic changes resulting from abnormal cardiac function. This is also influenced by withdrawal activity by the Parasympathetic Nervous System (PNS). An imbalance of SNS and PNS activities in the long term will cause anatomic abnormalities and cardiac function. Myocardial remodeling is a sign of anatomical abnormalities that have an impact on cardiac dysfunction that often occurs in heart failure (HF) [2]. The etiology of HF varies, but the presence of autonomic dysfunction is characteristic of this disease. A worsening ANS imbalance can lead to a high risk of death. Therefore one of the medical approaches to improve the prognosis of chronic HF patients is to modulate the PNS and weaken SNS activation through blockade of the β-adrenergic system [3]. Treatment of hypertension with BB has been used in clinical practice for the past 3 decades, but now new indications have been found from several studies conducted. It is known that BB can affect the immune system in the body, even being considered as a cancer treatment [4]. Based on this, we are interested in reviewing the pleiotropic and new therapeutic effects of BB use both as a short-term and long-term treatment.

PHARMACOLOGY OF β-BLOCKER
β-blockers are one of the most widely used antihypertensives in clinical practice because of their benefits in the treatment of HF or acute myocardial infarction [5]. This agent binds to the cardiac β-adrenergic receptors, thereby blocking the binding of endogenous catecholamines adrenaline and noradrenaline causing a decrease in the force contractile and heart rate [6]. Beta-blockers (BB) are competitive antagonists at adrenergic receptors, where drug selectivity can be distinguished according to the receptors [7]. β-adrenoceptors are divided into 3 identified subtypes, β1, β2, and β3. Meanwhile, β1- and β2 adrenoceptors are the strongest physiological mechanisms for increasing acute cardiac performance [8]. β1-receptors are mainly expressed in the heart and induce positive chronotropic, dromotropic, bathmotropic, and inotropic effects [9,10]. Meanwhile β2-receptors are mainly expressed in various types of smooth muscle cells located in blood vessels, skeletal muscle cells, and hollow visceral organs, such as bronchi or uterus which cause relaxation [11,12] . β3-receptors are expressed in several tissues such as adipose tissue, heart, ANS, pancreas, colon, uterus, bladder, and gut [13]. Moreover, these receptor differences include the presence of intrinsic sympathomimetic activity (ISA), lipid solubility that affects penetration into the central nervous system (CNS), as an inverse agonist, capacity to induce vasodilation, and pharmacokinetic profile. β-blockers have 3 generations that have been developed and applied in clinical practice [14,15]. The first generation includes non-selective subtypes, for example propranolol which has the same affinity for β1 and β2-receptors. The second generation includes drugs that have an affinity for β1 rather than β2 (selective), such as atenolol, bisoprolol, and metoprolol. The third generation contains selective and non-selective β1 subtypes which have additional properties of α-1 receptor antagonists or the ability to induce the production of nitric oxide (NO) which causes vasodilation [16].

Several therapeutic effect of BB have been identified including decreased cardiac output (CO) and inhibition of renin release, thereby reducing myocardial workload and oxygen demand to reduce symptoms of angina and the risk of acute coronary syndrome (ACS) [17,18]. The mechanism of action of BB against norepinephrine and epinephrine at beta receptors is to prevent the cyclic adenosine monophosphate (cAMP) accumulation, protein kinase A (PKA) activation, and subsequent changes in intracellular calcium that mediate adrenergic responses [18]. BB which is more lipophilic is usually associated with central nervous

system (CNS) side effects because it is able to cross the blood-brain barrier and is well absorbed from the intestine but undergoes extensive first pass metabolism in the liver. Meanwhile, hydrophilic BB (eg atenolol) is not fully absorbed from the intestine and does not undergo hepatic metabolism, has a longer half-life than lipophilic BB agents [19,20]. Meanwhile, BB agents with instrinsic sympathomimetic activity (ISA) may be less prone to cause bradycardia [19]. Although the use of BB has been considered to be the primary safe therapy for CVD, it is also used in the treatment of migraine [21], glaucoma [22], hyperthyroidism [23], hepatic cirrhosis [24], chronic obstructive pulmonary disease (COPD) [25,26], sepsis [27,28], and currently considered cancer [29].

β-BLOCKER AND CANCER

β-adrenergic receptors can be detected in cancer cells and immune cells by influencing the proliferation process and multiple signaling pathways involved in cancer invasion, cancer-related inflammation, angiogenesis, and lymphangiogenesis [30]. Deviated β2 expression is associated with oncogenic properties in breast cancer and increased metastases to axillary lymph nodes. This process is mediated by β2 via activation of the cAMP-calcium feed-forward loop and accumulation of mineral invadopods that increase breast cancer cell invasion. Meanwhile, β1 has been shown to be associated with increased lipolysis in cachexia cancer and β3 mutations contribute to breast cancer-related obesity [31]. Some evidence suggests that β-adrenergic receptor signaling can induce SSS activation and increase circulating catecholamine levels by the adrenal glands and locally from the term postganglionic sympathetic nerve fibers [32]. Activation of adrenergic receptors can regulate cancer-related signaling pathways including in the tumor microenvironment such as endothelial cells and macrophages which can lead to the development and spread of cancer metastases [33]. In addition, activation of tumor beta adrenergic receptors is reported to increase the production of several factors that promote metastasis such as vascular endothelial growth factor (VEGF), matrix metalloproteinase 2 (MMP-2), MMP-9, IL-6, and IL-8 [34].

Therefore, blockade of β-adrenergic receptor signaling is expected to provide a protective role in cancer patients by changing the tumor microenvironment, preventing cancer development and metastasis through decreasing tumor cell viability and inhibiting the formation of vascular remodeling. [35,36]. The use of BB has also been reported to modulate the immune response and regulation of cytokines involved in cancer development [37]. This is evidenced by the use of propranolol which can reduce mitogen-activated protein kinase (MAPK), 70-kDa heat shock protein (HSP70), iNOS activity, increases IL-10 and activates receptor activator of nuclear factor-κB ligand (RANKL). The MAPK pathway associated with cell proliferation, growth, transport, death, and many vital factors is very important in human tumors, while HSP70 is upregulated across a wide variety of cancers and is involved in tumor growth, invasion, migration and resistance to anti-cancer therapy, and RANKL which are frequently detected in the tumor microenvironment and participate in every step of cancer development [38–40].

Natural Killer cell (NK) is known to play an important role in innate immunity, killing virus-infected cells and tumors. At the cellular level, activation of β-adrenoceptors can decrease the cytotoxicity of NK cells against MADB106 mammary adenocarcinoma cells accompanied by pulmonary metastases in vitro, while at the systemic level activation of local β-adrenoceptors can reduce the number of NK cells in the lungs [41]. Other evidence shows the results of in vitro studies on SK-BR-3 cells with 24-hour propranolol exposure that show decreased phosphorylation of multiple mitogenic active protein kinase (MAPK) and cAMP responsive element binding protein (CREB), as well as increased phosphorylation of protein kinase B (PKB), glycogen synthase kinase 3 (GSK3) and p53. In addition to breast cancer, propranolol can also inhibit damage due to catecholamine stimulation of adrenoceptors in people with pancreatic cancer [42].

β-BLOCKER AND MIGRAINE

In the general population the prevalence of migraine cases is estimated to be 16% and more in women than men (ratio 3:1). Some people have episodic migraines and receive prophylactic therapy, but only 3% -13% of patients are reported to be free from post-control symptoms [43,44] . Migraine is a neurovascular disorder that is common in about 10-15% of the general population [43]. This neurovascular disorder is associated with a neurogenic inflammatory process characterized by the release of potent vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP) [45]. substance P (SP) [46], and neurokinin A [47]. Meanwhile, migraine headaches that are preceded by an aura phase of about 20% -30% may be triggered directly by cortical spreading depression (CSD), a slow depolarization wave that spreads throughout the cortex [48,49]. The involvement of CSD causes complex molecular changes in upregulation of cortical genes involved in inflammatory processing such as cyclooxygenase-2, TNF-a, IL-1b, or matrix metalloproteinase (MMP). CSD waves have also been reported to induce activation of trigeminovascular pathways derived from meningeal nociceptors [48,50].

β-blockers are widely used as prophylactic therapy for migraines and effective in reducing the frequency of attacks by 50% [49]. Abortive and prophylactic treatment for migraine may be needed in patients with acute symptoms. Prophylactic therapy can reduce the frequency, duration, or severity of attacks [51]. Inhibition of adrenoceptor β1 such as propranolol is reported to be able to modulate negative trigeminovascular nociception in thalamocortical neurons in migraine. Abnormalities in sensory processing of the thalamus and cortical can cause some migraine cardinal symptoms such as photophobia and phonophobia so this thalamic neuron may be able to be targeted as a preventive in migraine [52]. Whereas the activation of MMP causes an increase in blood brain barrier permeability and activation of trigeminal nerve afferents. These neurons act to supply sensory innervation to large blood vessels in the cerebrovascular and meningen systems. Migraine headaches may occur as a result of a cascade; pannexin-1 megachannels open, which activates caspase-1 and triggers the release of proinflammatory agents thereby activating the astrocytic NF-κB and finally transduction of the inflammatory response to the sensory trigeminal nerves that innerviate pial vasculature [53]**.** In addition, propranolol also inhibits the release of nitric oxide (NO) by blocking inducible Nitric Oxide Synthase (iNOS) which has the potential to reduce the regulation of activation of trigeminovascular complexes [54,55].

BB drugs such as metoprolol and propranolol are known to have a better therapeutic response because they can cross the blood-brain barrier (BBB), very lipophilic, and modify nerve stimulation. β1 receptor antagonists can modulate the processing of cortical information expressed as changes in visual evoked potentials (VEP) mediated

through adrenaline and noradrenaline, contingent negative variation (CNV), and auditory evoked potentials (AEP), which are usually abnormal in migraine patients. The use of metoprolol and propranolol has been proven to be able to normalize high CNV and decrease VEP amplitude, which shows that BB has a significant effect on visual system stimulation in migraine patients [49].

Furthermore, the ventrobasal complex is innervated by noradrenergic fibers which are mostly found in the ipsilateral coeruleus locus. Noradrenaline is found in the thalamus and its release is triggered by the activation of the locus coeruleus neurons. Adrenergic receptors α and β are found in somatosensory thalamus. β receptors are found in ventrobasal complexes, especially the receptor subtype β1 [52]**.** Recent findings suggest that propranolol can interfere with the process of chronic sensitization in the rostral ventromedial medulla (RVM) and locus ceruleus (LC) [56]. Propranolol and timolol have a high affinity to serotonergic system by blocking 5-HT2C and 5-HT2B receptors because 5-HT (serotonin) receptors which have a significant role in migraine pathophysiology [57].

β-BLOCKER AND COPD

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease, which is characterized by progressive limitation of air flow and is associated with an abnormal lung inflammatory response to harmful particles or gases [58,59]. The systemic inflammatory process in COPD involves several cells including macrophages, epithelial cells, dendritic cells, neutrophils, eosinophils, and T lymphocytes and B lymphocytes. These cells release many inflammatory mediators that play a role in the pathophysiology of COPD such as lipids, cytokines, chemokines, and growth factors [60]. The β-agonist drug class is a treatment that is often used in chronic obstructive pulmonary disease (COPD) where the use of this drug also has the potential for cardiovascular side effects in obstructive pulmonary disease patients. Therefore it is recommended the use of β- agonists must be careful in patients with pulmonary disease or severe cardiovascular disease and who use BB [61]. β2-adrenoceptor stimulation in the lungs can cause bronchodilation and has been recommended as a short-term treatment and long-term maintenance therapy for patients with asthma bronchial and chronic obstruction pulmonary disease (COPD) or better known as COPD [62]. According to *The Global Initiative for Chronic Obstructive Lung Disease* (GOLD) and *The European Society of Cardiology* (ESC) Guidelines, BB has been recommended as a treatment for HF with reduced ejection fraction (HFrEF) accompanied by COPD. In this case, the BB that must be chosen is a selective β1 blocker (eg bisoprolol, metoprolol, or nebivolol) while non-selective is not recommended [63,64]. The use of BB (β-1 selective) can be considered in several ways: First, reducing the risk of COPD exacerbations and heart disease by reducing the influence of adrenergic and inflammatory effects. Second, during COPD exacerbations, there is an increase in catecholamines in circulation, which will increase the risk of myocardial ischemia, tachycardia, worsening HF, and hypertension including increasing the risk of stroke. All cardiovascular risks involving endogenous exacerbations can be corrected by BB administration. Third, the administration of a β-agonist (salbutamol) in patients with COPD exacerbations causes tachycardia. Salbutamol is a bad selective ligand and causes β1-adrenoceptor activation in the heart. This shows that the administration of β2-agonists has been shown to increase the risk of CVD, therefore BB administration is needed to prevent cardiovascular risk induced by β2-agonists [51,54] [62,65].

Propranolol can inhibit G protein-dependent signaling and reduce MAPK activation through β-dependent signaling, which results in reduced MUC5AC expression and mucosal hypersecretion induced by cigarette smoke. Chronic administration of β-inverse agonists such as propranolol to animal models of obstructive respiratory disease and clinical trials shows decreased lung infiltrates, increased respiratory smooth muscle response to β-agonists, restores β2-adrenergic receptor (β2-AR) expression, decreased norepinephrine in serum, decreased cytokines (TNF-α, IL-8), and decreased mucus production and eosinophilic inflammation. Meanwhile, acute administration of β2-AR inverse agonists such as nadolol or carvedilol does not affect the airway response, but after 28 days of treatment, the inverse agonist can significantly reduce the airway response to antigens [66].

According to a cohort study that the risk of COPD patients is reduced in the group receiving BB among patients with comorbidities such as HF, coronary artery disease (CAD), ischemic heart disease, hypertension, cardiac arrhythmias, and pulmonary circulation disease (pulmonary embolism and cor pulmonale) [67]. This is also supported by a prospective COPDGene cohort study proving that BB has an acceptable safety profile in patients with GOLD II to IV criteria, including severe COPD that uses oxygen at home, and shows a decrease in exacerbations in the population [68]. Based on this analysis, several meta-analyses from cohort trials mention the use of BB, especially selective β1 including metoprolol, bisoprolol, and nebivolol can be considered in reducing COPD exacerbations with clear heart disease (eg. HFrEF or post-MI), but use BB combined with other drugs (ex. CCB or vasodilator drugs) need to be monitored because they can cause adverse effects [69].

β-BLOCKER AND HEPATIC CIRRHOSIS

In hepatic cirrhosis, splanchnic vasodilation occurs accompanied by increased blood flow to the splanchnic organs and portal system. This causes systemic vasodilation and will subsequently trigger plasma volume expansion and increase CO. If this hyperkinetic circulation continues to increase blood flow to the splanchnic organs, then an increase in portal pressure occurs [70]. As a result of splanchnic vasdilatation causes a progressive decrease in circulating volume thereby triggering activation of the neurohumoral system (SNS, renin-angiotensin-aldosterone system [RAAS], and arginine vasopressin [AVP] system). If the body cannot compensate to compensate for the vasodilation, it will lead to refractory ascites, hyponatremia, and even hepatorenal syndrome (HRS) [71]**.**

NSBB is a treatment that is often used for portal hypertension in hepatic cirrhosis. According to some RCTs, it has been proven that non selective BB (NSBB) can prevent initial variceal bleeding and subsequent rebleeding. Other evidence reports that NSBB prevents liver decompensation in patients with compensated cirrhosis. Therefore, the introduction of a new NSBB, carvedilol, has a better therapeutic effect than the previous NSBB [72]. Carvedilol has an intrinsic anti-α1 adrenergic activity that causes intrahepatic vasodilation so that it can reduce portal pressure [71]**.** Carvedilol is reported to be more effective in decreasing hepatic venous pressure gradient (HVPG) than propranolol or nadolol [73]. Moreover, carvedilol tends not to cause hypotension but reduces portal pressure significantly beyond propranolol. This

explains that carvedilol has been better tolerated than propranolol [70]. In addition, carvedilol has a cytoprotective, antioxidant effect by scavenging and suppressing reactive oxygen species (ROS), anti-inflammatory, anti-fibrotic effect, increase insulin sensitivity and improve mitochondrial function [74,75]. NSBB has been reported to reduce intestinal permeability and LPS-binding protein (LBP-dissolved protein acute phase response) and IL-6 which were found to be high related to the risk of varicose bleeding [75].

The β-adrenergic blocker has an effect on decreasing hepatic venous pressure gradient (HVPG) in patients with clinically significant portal hypertension (CSPH), in which patients with splanchnic vasodilation and hyperdynamic circulation occur. This explains the use of NSBB might be able to prevent the development of varicose veins in CSPH patients. NSBB mechanically acts by lowering the heart rate (HR) and inhibits splenic vasodilatation, thus the hemodynamic effect of NSBB depends on the severity of the hyperdynamic condition. This shows that the use of NSBB has advantages in splanchnic hemodynamics and vice versa disadvantages in systemic hemodynamics [76]. The use of NSBB in hepatic cirrhosis is proven to effectively reduce portal pressure which has an impact on reducing the risk of bleeding and reebleeding of varicose veins. Based on Baveno IV and *The American Association for the Study of Liver Diseases* (AASLD) *Guidelines* recommend NSBB as primary and secondary prophylaxis (combination with endoscopic band ligation (EBL)) bleeding varicose veins in patients with cirrhosis accompanied by esophageal varices [76]. However, not all NSBBs have the same mechanism, because the presence of additional anti-α1-adrenergic activity in carvedilol is more effective in reducing portal pressure, but can cause a clear decrease in systemic arterial pressure [76]. Carvedilol has also been shown to prevent rebleeding (secondary prophylaxis) of varicose veins in cirrhosis than other NSBBs [77]. Overall, carvedilol is a treatment of portal hypertension in cirrhosis patients with safe and good efficacy of esophageal varices [78].

Another beneficial effect of NSBB through reduced portal hypertension and its sympatholytic action can increase intestinal congestion and edema by normalizing intestinal transit so as to prevent bacterial translocation. In animal models of portal hypertension, propranolol can increase intestinal motility and reduce the overgrowth of enteric bacterial flora, migration of microbiota into the systemic circulation and the development of spontaneous bacterial peritonitis (SBP). This is supported by a meta-analysis study showing the protective effect of NSBB on the development of SBP [74]. Meanwhile, current guidelines recommend NSBB or EBL as an equivalent therapy for primary prophylaxis, but there is new evidence reporting that NSBB use in compensated cirrhosis patients accompanied by CSPH can prevent the first decompensation, ie ascites [79].

β-BLOCKER AND HYPERTHYROIDISM

Hyperthyroidism is a metabolic disorder in which the thyroid gland produces too much thyroid hormone. This situation can be controlled by administering drugs, but some people fall into worsening conditions such as thyroid storm and thyrotoxicosis [80]. Thyroid storm is a life-threatening condition that requires prompt diagnosis and prompt treatment. This situation has manifestations of decompensation in various organs including loss of consciousness, high fever, HF, diarrhea, and jaundice [81]. Whereas thyrotoxicosis refers to the clinical state that is produced by the activity of thyroid hormone that is too high in the tissue and is generally caused by inappropriate levels of tissue thyroid hormone. While hyperthyroidism is included in the form of thyrotoxicosis due to improper synthesis and secretion of thyroid hormone [82]. As a result, there is an increased risk of atrial fibrillation, embolic events, coronary events, and heart failure, especially in elderly patients and in those with underlying heart disease [83]. In overcoming such conditions it is important especially to deal with cardiac dysfunction which if not treated immediately will continue to worsen [84]. The most common medication given to thyrotoxicosis patients to improve symptoms is non-cardioselective BB [82]. The advantage of using BB is necessary because the cardiac manifestations of hyperthyroidism are caused by an increase in the action of catecholamines. In the thyrotoxicosis condition there is an increase in tissue sensitivity to catecholamines and an increase in the number of β1-adrenergic receptors and protein binding protein guanosine triphosphate. This supports the fact that the administration of NSBB in hyperthyroid patients is especially useful for managing heart problems [85].

NSBB such as propranolol (20-40 mg every 6 hours) or who work longer hours (eg atenolol/bisoprolol) can control adrenergic symptoms such as palpitations and tremors, especially during the initial stages before antithyroid drugs. High doses of propranolol (40 mg qid) can inhibit peripheral T4 to T3 conversion by inhibiting the enzymatic activity of Dio1 (iodothyronine deiodinases). Specifically, thyroid hormone activation is mediated by the conversion of Dio1 and Dio2 from T4 to T3 [86,87]. Whereas cardioselective BB with high cardioprotective effects and good prevention of atrial fibrillation are alternative options, especially for patients with asthma. The use of NSBB is needed to control hyperthyroidism especially before thyroidectomy therapy [86]. NSBB (eg. propranolol) is a standard treatment in thyroid storm and thyrotoxicosis to ward off hyperadrenergic states that can trigger a cardiovascular collapse in pre-existing cardiac dysfunction [88]. Meanwhile, tachycardia and atrial fibrillation that occur in thyroid storm are also recommended to get intravenous β1-selective BB (landiolol, esmolol) or oral (bisoprolol) as treatment [81].

β-BLOCKER AND SEPSIS

Sepsis is a complex condition characterized by simultaneous activation of inflammation and coagulation in response to microbes. Sepsis has manifestations as a systemic inflammatory response syndrome or symptoms of sepsis through the release of proinflammatory cytokines, procoagulants, and adhesion molecules from damaged immune cells and/or endothelium. At present, sepsis is a severe multisystem disease with a high mortality rate [89]. In general, first-line management for sepsis is a combination of alpha and beta-agonist, generally noradrenaline and dobutamine. However, there are several potential mechanisms underlying the protective effect of BB during sepsis, both cardiac and non-cardiac [90].

High levels of endogenous and exogenous catecholamines are most likely due to excessive sympathetic stimulation in sepsis, despite adequate fluid resuscitation. This causes diastolic dysfunction, the dominant phenotype in myocardial dysfunction associated with sepsis so that BB can be indicated in this condition. BBs such as esmolol are reported to reduce HR which allows better diastolic filling and weakens the toxic effects of catecholamine. It is

characterized by inflammation, oxidative stress and abnormal intracellular calcium trafficking that can cause apoptosis and even necrosis [90]. Increased catecholamine levels in sepsis cause catecholamine-induced cardiomyopathy and cardiac damage due to excess calcium, which causes cardiomyocyte necrosis. Sepsis also causes a decrease in myocardial beta-adrenergic receptor density and transduction of the disturbed b-adrenergic stimulant signal. Therefore, prevention of further cardiomyocyte damage due to excessive SSS stimulation is the key to managing sepsis [91].

In septic shock, BB can stabilize circulation and increase myocardial damage. BB has a role in suppressing catecholamine storms, controlling ventricular velocity and reducing mortality in acute myocardial infarction (AMI) patients and chronic heart failure. Propranolol has been reported to reduce ventricular progress by 15% in children with severe burns, inhibit heart stress caused by burns, reduce heart work, and have no significant effect on MAP. Esmolol has been widely used as a study in critical patients, because of its high selectivity to β1 receptor and its short and fast acting characteristics. A study also showed that β1-blockers do not increase oxygen consumption in septic patients and do not affect blood flow in the liver and lower extremities or peripheral vascular resistance therefore tissue perfusion can be maintained. The beneficial effect of BB in sepsis patients is supported by a systematic review and meta-analysis that esmolol is safe and effective in improving 28-day mortality and controlling the ventricular rate in sepsis patients after fluid resuscitation and does not have a significant adverse effect on tissue perfusion [92].

β-BLOCKER AND GLAUCOMA

Glaucoma is one of the main causes of irreversible blindness. The most common type of glaucoma is primary open-angle glaucoma. Increased intraocular pressure (IOP) is often associated with primary open-angle glaucoma due to chronic progressive resistance to drainage of aqueous humor through the trabecular meshwork in the anterior chamber. Increased IOP is a major risk factor in the onset and development of glaucoma and is the only risk factor that can be modified. Common topical teratments used to reduce IOP include selective or non-selective BB [93].

The mechanism of action of BB for the treatment of glaucoma by reducing IOP through the production of suppressed aqueous humor. In general, it is believed that the mechanism is based on interactions with the β2-adrenergic receptor in the ciliary epithelium because β-receptors are found in the ciliary eye and are mostly β2 subtypes. BB acts to induce vasoconstriction in the ciliary arteries so that it can reduce the production of aqueous humor. BB can reach the posterior eye segment after topical application can cause vasoconstriction and negatively affect ocular blood flow. BB is available as a solution for the eyes such as timolol, betaxolol, carteolol, levobunolol, and metipranolol [94]. There is evidence that shows the use of topical BB as glaucoma therapy for patients with respiratory and cardiovascular complications leading to adverse outcomes [93]. The first BB available for eye solution is timolol. Previously timolol was often used as a treatment for glaucoma. But now the use of timolol has decreased since the presence of a new agent namely prostaglandin analogs because of its ability to reduce IOP better and minimal side effects than BB [95,96].

CONCLUSION

Several studies have shown the efficacy of BB for several diseases with or without other comorbidities, which is evidenced by the significant decrease in mortality and morbidity in some cases, especially CVD. Its use, known as antihypertension, has been widely debated because of the findings of several BB drugs and their pleiotropic effects. However, the presence of hypertension induced by SNS hyperactivation, proves that BB placement is very plausible as a first line treatment. After more than 50 years of its discovery, new findings have emerged that show a protective effect outside the cardiovascular system, especially in the field of oncology. In a retrospective clinical study, the clinical benefits of using BB as a cancer therapy have long been suspected, but this is still debated given there is no explanation that explains the optimal use of BB as adjuvant therapy or regarding its clinical justification. This new concept will continue to be carried out research and evaluation to improve the prognosis of cancer patients.

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Table 1. Pleiotropic Effects of Beta-Blockers

Disease	BB Recommendation	Mechanism of Action	References
Vascular System			
Cancer	Propranolol	▪ Anti-apoptotic ▪ Anti-proliferative ▪ Anti-angiogenesis	[4,23,27] [30,33]
Hepatic cirrhosis is accompanied by: ▪ First bleeding variceal ▪ Variceal rebleeding	Carvedilol Propranolol	▪ Vasculoprotective ▪ Cytoprotective ▪ Antioxidant effect ▪ Anti-inflammatory ▪ Anti-fibrotic effect	[58,59,60] [61,62,63]
Glaucoma	Timolol Betaxolol Carteolol Levobunolol Metirapranolol	▪ Vasculoprotective ▪ Suppress aqueous humor production	94
Neurogenic System			
Migraine with aura (*classic migraine*)	Propranolol Metoprolol Timolol	▪ Neuroprotective ▪ Vasculoprotective	[4,40,43]
Cardiac System			
▪ COPD with HFrEF ▪ COPD with post-MI	Bisoprolol Metoprolol Nebivolol	▪ Cardioprotective ▪ Vasculoprotective ▪ Anti-inflammatory effects ▪ Antioxidant ▪ Anti-arrythmic	[4,57,83]
Sepsis	Esmolol Propranolol	Cardioprotective	[76,78]
Endocrine System			
▪ Hyperthyroidism ▪ Thyrotoxicosis ▪ Thyroid storm	Propranolol	▪ Anti-hyperthyroid ▪ Anti-apoptotic ▪ Anti-arrhythmic	[70,72] [84,85]

BB: Beta-blocker; COPD: Chronic obstructive pulmonary disease; HfrEF: Heart failure with reduced ejection fraction; MI: Myocardial infarction