REVIEW ARTICLE: AN INSIGHT ON B-BLOCKERS USES IN DIFFERENT DISEASES: APPLYING OLD FDA-APPROVED THERAPIES AND NEW OFF-LABEL ONES AS NEW TARGETS

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ABSTRACT

Beta-adrenoceptor antagonists, or β-blockers, are drugs primarily used with FDA approval in treating cardiovascular diseases, such as heart failure (HF), atrial fibrillation (AF), hypertension, migraine, myocardial infarction, hyperthyroidism, aortic dissection, glaucoma, and essential tremors. Also, they were discovered to have other new off-labeled uses, not yet FDA-approved, against sepsis and septic shock, breast cancer, and COVID-19. Recent researches suggest that using β-blockers could adjust patients' health outcomes and mortality rates against several diseases initiated by inflammation or sympathetic system activation in intensive care units (ICU) due to their sympatholytic, anti-inflammatory, and vasodilating effects. Thus, we provide a general overview of b-blockers, as we have supervised a comprehensive analysis of diseases handled with b-blockers up to 2023; summarize the most appropriate used b-blocker, even cardioselective or non-selective ones, and investigate their effect and possible mechanisms by which b-blockers induced their action in each disease and improving patient health and mortality in ICU.

Keywords

Beta-antagonists; Cardiovascular diseases; Sepsis; Breast cancer; COVID-19

Introduction

b-blockers are drugs applied primarily to manage cardiovascular complaints and other acute and chronic conditions by acting on b-adrenergic receptors (do Vale, Ceron, Gonzaga, Simplicio, & Padovan, 2019). b-adrenergic receptors exist in three different forms and are dispersed throughout the body as follows: The b1-receptor, in the heart, controls cardiac automaticity and cardiac output as it induces renin release and increases blood pressure (do Vale et al., 2019). The second type is the b2-receptor, located at different sites in body organs, controls metabolic activity and causes relaxation in smooth muscles (do Vale et al., 2019). The third type is the b3-adrenergic receptor, located in fatty tissues and induces a breakdown of fat cells (do Vale et al., 2019). In this review, we focus on b1- and b2-receptors. Blockades of those receptors by b-blockers -FDA-approved drugs- are used for treating a broad range of heart diseases, including heart and circulating system disorders, such as cardiac arrhythmias, ventricular tachycardia, aortic dissection, myocardial infarction, atrial fibrillation, hypertension, congestive heart failure, and coronary artery disease, as well as irrelevant non-cardiac conditions including hyperthyroidism, essential tremor, migraine and glaucoma (do Vale et al., 2019; Farzam & Jan, 2023). They also handle less common ailments, including hypertrophic obstructive cardiomyopathy and long QT syndrome (do Vale et al., 2019). According to previous studies, there are some other off-labeled uses of b-blockers, not yet FDA approved, including that they have a robust anxiolytic effect and can control breast cancer, general tension, sepsis, COVID-19, and tremors associated with Parkinson's disease (Crosby, Deane, & Clarke, 2003; Steenen et al., 2016).

Since b-blockers have varying degrees of specificity against different receptors, their effects are contingent upon the exact type of inhibited receptors as well as the relevant organ system (Farzam & Jan, 2023). So, the primary mechanism of action of b-blockers is through binding to b1- and b2-receptors, more critical than b3-receptors, and inhibiting their effects. As a result, due to b1 receptor blocking, the heart's inotropic and chronotropic effects undergo inhibition, diminish arrhythmias, and drop in the heart rate. b-blockers also lessen blood pressure through several strategies, such as lowered cardiac output and renin secretion. The negative inotropic and chronotropic effects of b-blockers result in diminished oxygen demand of the heart, which helps to improve angina attacks. Furthermore, these drugs have a robust antiarrhythmic impact and extend the atrial refractory intervals (Farzam & Jan, 2023; Lechat et al., 2001).

b-blockers generally fall into two main categories; the first one is b1 selective (cardiovascular selective), which includes atenolol, betaxolol, bisoprolol, nebivolol, esmolol, metoprolol and acebutolol. The second one is non-selective b-blockers, which can act on both b1- and/or b2-receptors or even b2- and/or b3- receptors, which cause antagonizing effects through the act on both receptors, including propranolol, carvedilol, sotalol, labetalol, nadolol, penbutolol, pindolol and timolol (Gorre & Vandekerckhove, 2010; Machackova, Sanganalmath, Elimban, & Dhalla, 2011; Rehsia & Dhalla, 2010). In addition to their non-selective blocking activity for b-receptors, carvedilol and labetalol exhibit a1-receptor blockade action. This feature is beneficial from a clinical standpoint

because b-blockers that inhibit the a1-receptor have a more noticeable therapeutic impact on lowering hypertension (Weir, 2009).

Numerous clinical experiments have been performed on b-blockers to enhance and extend the lives of individuals suffering from cardiovascular and non-cardiovascular conditions (Hoedemaker et al., 2020; Jensen, 2019; Suissa & Ernst, 2018).

FDA-approved uses of b-blockers

1. b-blockers in heart failure

Heart failure (HF) is an arising clinical disorder that is developed by modifications to the left ventricular (LV) construction and function, myocardial fibrosis, reinforced systemic vascular stiffness, and the development and proliferation of myocytes. It has numerous pathways involving high filling pressures, cell dropout, inflammation, cytokine activity and oxidative stress, which result in exaggerated neurohormonal activity (neurohormonal hypothesis) (Cohn, Ferrari, & Sharpe, 2000; Mann & Bristow, 2005; Packer, 1992). Almost any form of heart disease, such as injury, infection or mutation, can result in heart remodeling and subsequent failure (Mann & Bristow, 2005). Chronic heart failure has an extraordinary economic burden with a high incidence rate of almost five million patients in the USA and about five hundred thousand new cases per year (Hunt et al., 2001), and a high incubation period in hospitals, especially in patients aged more than 65 years (Kannel, 1987; O'Connell & Bristow, 1994). Any therapeutic drugs that can limit the symptoms and progression of heart remodeling and failure can reduce morbidity, hospitalization time and mortality rate (Wild & Kukin, 2007). A lot of money is spent to discover new effective therapies to treat heart failure, including symptomatic or asymptomatic HF, myocardial infarction, failure of the left ventricle, and symptomatic or asymptomatic valvular disease (Massie & Shah, 1997).

During the 1980s, the interest in utilizing b-blockers for the treatment of HF grew and was driven by the Swedish Waagstein et al.’s study involving a small number of carefully chosen patients (Waagstein, Hjalmarson, Varnauskas, & Wallentin, 1975; Waagstein & Hjalmarson, 1976a, 1976b). Many studies have assessed the efficacy of β-blockers as the first line in treating hypertension. Some of these investigations evaluated the emergence of HF as a subsequent outcome of hypertension (Black et al., 2003; "Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH). The IPPPSH Collaborative Group," 1985; Dahlöf et al., 2002; Dahlöf et al., 2005; "Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group," 1998; Hansson et al., 2000; Hansson et al., 1999; Wilhelmsen et al., 1987). Discovering that β-blockers were effective on individuals with symptomatic HF as anti-remodeling agents, as they reduced left ventricular mass and volume ("The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial," 1999; Colucci et al., 1996; "Effect of metoprolol CR/XL in chronic

heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)," 1999; Mann & Bristow, 2005; Packer, 1992; Packer et al., 2002; Vantrimpont et al., 1997). An evaluation of the SAVE trial's post-hoc analysis demonstrated the benefits of baseline-using β-blockers on the patient's outcomes. According to the study, there was a substantial 21% and 30% decrease in the probability of developing HF and cardiovascular death, respectively (Vantrimpont et al., 1997). Colucci et al., in the REVERT trial, discovered that administration of metoprolol succinate could improve and reverse cardiac remodeling in individuals with asymptomatic left ventricular systolic failure in a dose-dependent manner and also suggested that if the use of metoprolol can delay cardiac remodeling and its failure, hence it seems to delay the onset of the symptoms and the mortality rate (Colucci et al., 2007). Several studies, including CIBIS and CIBIS II trials, found that administering b-blockers (carvedilol, bisoprolol, and bucindolol) for a short period may reduce myocardial function. On the other hand, long-term administration increases the ejection fraction and enhances the clinical state of cardiac failure patients (Anthonio et al., 1999; Bristow et al., 1994; Colucci et al., 1996; Gilbert et al., 1996; Lechat et al., 2001). Many minor observational investigations had rather constantly shown that the size of LV chamber could be decreased and systolic performance could be improved by using a variety of b-blockers, such as carvedilol, metoprolol, nebivolol, and bisoprolol, in addition to non-b-blocker bradycardic drug (ivabradine) (de Groote, Ennezat, & Mouquet, 2007; Dybro et al., 2023; Karabacak, Doğan, Tayyar, Özaydın, & Erdoğan, 2015; Rossi et al., 2023).

Finally, the most recent ACC/AHA practice guideline update, released in 2022, suggested that β-blockers can be utilized in all stable patients who suffer from recent or previous symptoms of decreased left ventricular ejection fraction and heart failure except the contraindicated ones (Heidenreich Paul et al., 2022).

2. b-blockers in atrial fibrillation

Atrial fibrillation (AF) is the most prevalent permanent arrhythmia between individuals that increases in frequency with increasing age (Feinberg, Blackshear, Laupacis, Kronmal, & Hart, 1995; Kannel, Abbott, Savage, & McNamara, 1982). In the past, it was unclear if there was an advantage for the antiarrhythmic medication in AF patients. Many findings from previous investigations in heart failure patients strengthened the importance of b-blockers usage in preventing AF. Psaty et al. showed that b-blockers administration was linked to lowering the risk of new development of AF in old adults, aged between 65 and 84 years old, by approximately 39% (Psaty et al., 1997). Also, Kühlkamp et al., in the MERIT heart failure study, discovered that administration of metoprolol CR/XL (controlled/extended release) prevents initiating new AF in heart failure patients (Kühlkamp, Bosch, Mewis, & Seipel, 2002).

Additionally, it was discovered that b-blockers could suppress AF developed following coronary artery bypass graft (CABG) operation (Kowey, Taylor, Rials, & Marinchak, 1992). It was thought that treatment with b-blockers would not be effective in establishing sinus rhythm in case of AF that is not linked with CABG operation (Lafuente-

Lafuente, Mouly, Longás-Tejero, Mahé, & Bergmann, 2006). Numerous experiments showed that b-blockers indirectly affect sinus rhythm maintenance after electrical cardioversion, ventricular ectopy, and ventricular repolarization. Several trials found that a racemic mixture of (+/-) sotalol (b-blocker and class III antiarrhythmic drug) can sustain sinus rhythm in a dose-dependent manner starting from 320 mg/day (Funck-Brentano et al., 1991; Hohnloser et al., 1995; Juul-Möller, Edvardsson, & Rehnqvist-Ahlberg, 1990). Furthermore, many small studies were conducted in the last few years comparing the effect of bisoprolol (Kaplan—Meier analysis) and atenolol to sotalol on preserving sinus rhythm following persistent AF cardioversion or paroxysmal AF, respectively, and the results indicated that both drugs are just as effective as sotalol (Plewan et al., 2001; Steeds, Birchall, Smith, & Channer, 1999).

Additionally, Kühlkamp et al., in the METAFER trial, discovered that metoprolol administration maintains the sinus rhythm following cardioversion of persistent AF and prevents the relapse into AF or flutter (Kühlkamp et al., 2000). Conversely, Kochiadakis et al. found that sotalol has a superior effect over metoprolol in controlling heart rate during daily activities in digitalized patients with chronic AF (Kochiadakis et al., 2001). Also, the β-blocker esmolol was found to manipulate the ventricular rate in AF or flutter (Platia, Michelson, Porterfield, & Das, 1989; Shettigar, Toole, & Appunn, 1993). Furthermore, β-adrenergic stimulation reduces the action potential interval and induces atrial repolarization by raising the atrial-specific ultra-rapid delayed rectifier K+ current (Ikur) amplitude (Campbell, Rasmusson, Qu, & Strauss, 1993; Z. Wang, Fermini, & Nattel, 1993). Li et al. discovered that propranolol can modulate IKur, which controls human atrial repolarization and arrhythmias (Li, Feng, Wang, Fermini, & Nattel, 1996).

Thereby, β-blocker therapy successfully preserves sinus rhythm during AF cardioversion and following CABG operation. The effect of these b-blockers may be mediated by modulating Ikur amplitude or suppressing premature atrial pulses, which can be prompted by catecholamines (Chen et al., 1999).

3. b-blockers in migraine

Migraine is a type of headache that happens in children and adults, marked by recurrent episodes of moderate to intense pulsing pain on one side of the head and may last for 72 hours. Novel evidence discovered several mechanisms of b-blockers in managing migraines with superior favorable effects and better side effects than other medicines (Danesh & Gottschalk, 2019). In 1965, propranolol was launched, and until now, it remains the most prescribed -FDA-approved- b-blocker in migraine prevention (Koehler & Tfelt-Hansen, 2008; Modi & Lowder, 2006; Quirke, 2006). Still, b-blockers had a low effect on decreasing the frequency of migraine re-occurrence (Diener et al., 1989; Jackson et al., 2015).

According to our knowledge of migraine pathophysiology, migraine is a neurogenic disease with changes in neurotransmitter levels rather than a muscular disease (Gupta,

2019). Not all b-blockers have the same lipid solubility level and availability to penetrate the blood-brain barrier (BBB). Propranolol, metoprolol, atenolol, and timolol are b-blockers with CNS penetration power (Barnes & Moshirfar, 2024; Gupta, 2019; Srinivasan, 2019). Otherwise, nadolol cannot cross CNS barrier but is still effective in reducing migraine (Gopal & Mandiga, 2024). That makes the mechanism of b-blockers in migraine prevention unclear, either by crossing BBB or having another mechanism of action away from BBB. b-blockers were found to centrally affect migraines through modification of neural excitability (Sprenger, Viana, & Tassorelli, 2018). Blocking b-receptors attenuate epinephrine and nor-epinephrine effects and inhibit sympathetic nervous system activation (Hieble, 2000). This inhibiting effect on migraineurs was approved by altered amplitudes and habituation in contingent negative variation (CNV), auditory evoked potentials (AEP), and visual evoked potentials (VEP) (Diener et al., 1989; Schoenen, Maertens de Noordhout, Timsit-Berthier, & Timsit, 1986). Numerous findings have discovered amplified VEP and CNV in migraine sufferers, indicating elevated activity of the occipital cortex and slow cerebral potential, which implies altered neuronal excitability (Maertens de Noordhout, Timsit-Berthier, Timsit, & Schoenen, 1987; Schoenen, Ambrosini, Sándor, & Maertens de Noordhout, 2003). Siniatchkin et al. and Schoenen et al. found that metoprolol and propranolol restore CNV and positively correlated with treatment response (Schoenen et al., 1986; Siniatchkin et al., 2007). Also, the reduction of evoked cortical potentials' reliance on auditory stimuli strength in migraine patients by metoprolol and bisoprolol was discovered by Sándor et al., and this reduction was linked to a better clinical outcome (Sándor, Afra, Ambrosini, & Schoenen, 2000). According to these findings, the general impact of b-blockers on cortical excitability and unusual cortical information processing in migraineurs may be linked to their positive therapeutic effects.

There are three mechanisms by which b-blockers work in migraine prevention. The first one is blocking the b1-adrenergic receptors in thalamic nociceptive neurons; as discovered by Shields et al., propranolol inhibited thalamocortical stimulation aroused by superior sagittal sinus activation (Shields & Goadsby, 2005). The second mechanism is through blocking 5-hydroxytryptamine receptors (5-HT), as discovered by Johnson et al. that propranolol and timolol, not metoprolol and nadolol, had additional inhibitory effects on 5-hydroxytryptamine receptors (5-HT2B and 5-HT2C) in CNS, as these receptors involved in cortical excitability (Johnson, Phebus, & Cohen, 1998). The last mechanism, b-blockers block b2- adrenergic receptors, leads to block reducible nitric oxide synthase and inhibit nitrous oxide production, as the stimulation of the trigeminovascular network by nitrous oxide transfer constitutes an essential factor in migraine (Ashina, Bendtsen, Jensen, & Olesen, 2000). Several studies found that metoprolol is equally effective as propranolol and less likely to cause adverse effects, so it is more effective in migraine prophylaxis (Hedman et al., 1988; Langohr, Gerber, Koletzki, Mayer, & Schroth, 1985).

All these studies prove the benefits of using b-blockers in migraine prevention even if they are not used in their optimum dose; nevertheless, when they do, they appear to have a superior effect to other drug classes. Comparing more recent data with previous results, the adverse effects of b-blockers are comparatively favorable (A. J. Barron et al., 2013).

Off-labeled uses of b-blockers

1. b-blockers in sepsis

Sepsis is a multi-organ failure that has a systemic activation for the sympathetic nervous system and exaggeration for adrenaline secretion as a response to infection or toxin, which affects heart function, including tachycardia and vasoconstriction, initiation of the inflammatory cytokine storm through increasing the nuclear translocation of the transcriptional nuclear factor (NF-κB) and therefore, boosting the levels of tumor necrosis factor-alpha (*TNF-α)* along with interleukin-6 (*IL-6*), attenuation of *IL-10* production, lowering tissue demand for oxygen, raises oxidative metabolism, and increases the risk of developing septic shock, organ damage, and death (Cao, Yu, & Chai, 2019; de Montmollin, Aboab, Mansart, & Annane, 2009; Dünser & Hasibeder, 2009; Hernández et al., 2016; Singer et al., 2016; Vincent et al., 2006; F. Wang et al., 2019). A new approach discovered that using b-blockers could improve the patient's outcome with sepsis and cardiovascular dynamics who admitted to ICU, as they might decrease the peripheral adrenergic stress and modulate cytokine profile and, therefore, suppress the deterioration arising from sympathetic overactivation and improve the patient's prognosis through increasing blood flow to the organs (vasodilating effect) (Aronow et al., 2011; Boudonas, 2010; de Montmollin et al., 2009). Also, b-blockers can change metabolism, coagulation, and immunity (Morelli, Ertmer, et al., 2013). Experimental research employing animal models of sepsis, even by cecal ligation and puncture (CLP) or lipopolysaccharide (LPS) administration, was applied to assess the effects of b-blockers on cardiovascular and other organ dysfunction and inflammation.

Kimmoun et al. discovered that esmolol improved cardiac contractility, restored mesenteric vasoreactivity and applied an anti-inflammatory impact by inhibiting NF-kB activity and raising the phosphorylation of endothelial nitric oxide synthase in both cardiac and vessel levels and upregulating vascular α1 Adrenergic receptor expression in CLP model (Kimmoun et al., 2015). Guo *et al*. also found that esmolol reduced intestinal tissue apoptosis and inflammation by inhibiting NF-κB (p65) phosphorylation in CLP model (Guo et al., 2020). Furthermore, Van Loon *et al*. showed the impact of esmolol in increasing renal blood circulation and subsequent renal perfusion by weakening the autoregulation of the kidney in LPS model (van Loon, Rongen, van der Hoeven, Veltink, & Lemson, 2019) and also improving the Ventriculo-arterial coupling ratio (VACR) by reducing the right ventricle end-systolic pressure in a single-beat pressure-volume loop estimation during endotoxic shock (van Loon, van der Hoeven, Veltink, & Lemson, 2018). Also, Carrara et al. found that esmolol improved cardiac dysautonomia induced by sepsis, provided an advantage below nor-epinephrine treatment, and enhanced vascular function by increasing peripheral vascular resistance in intraperitoneal instillation of autologous feces (Carrara, Herpain, & Ferrario, 2020; Carrara, Niccolo, Herpain, & Ferrario, 2020). Additionally, several small-sized studies discovered that esmolol bolus or infusion increases blood flow in small vessels, decreases noradrenaline requirement, and decreases heart rate by blocking b1-adrenergic receptors and increasing the survival rate of septic

patients (Balik et al., 2012; Morelli, D'Egidio, Orecchioni, Maraffa, & Romano, 2014; Morelli, Donati, et al., 2013).

Bedet et al. showed the effect of atenolol on reducing systolic blood pressure, left ventricular systolic function, and cardiac output in CLP model compared to placebo rats(Bedet et al., 2020). Moreover, Calzavacca et al. discovered that atenolol infusion exerted an anti-inflammatory mechanism by increasing the secretion of *IL-10* mediator (Calzavacca et al., 2014). Kakihana et al. discovered the improvement effect of landiolol on survival and its prevention for new-onset sepsis-related AF in adult patients (Kakihana et al., 2020). Also, Hagiwara et al. found that landiolol suppressed pro-inflammatory cytokines in serum and lung in LPS-induced systemic inflammation (Hagiwara, Iwasaka, Maeda, & Noguchi, 2009). Schmittinger et al. discovered that combining metoprolol and milrinone (phosphodiesterase-3 inhibitor) infusion can improve myocardial depression associated with sepsis (Schmittinger et al., 2008). Moreover, Ackland et al. found that pretreatment with metoprolol before CLP-induced sepsis suppressed plasma and cardiac inflammatory cytokines and improved heart function (Ackland et al., 2010). Several studies discovered that β1-blockers improved survival rates in animal models of septic shock (Bedet et al., 2020; Mori et al., 2011).

All these anti-inflammatory and antiapoptotic actions were found to be mediated through the blockade of the b1-adrenergic receptor. In contrast, blockades of the b2-receptor lead to exaggeration for inflammatory mediators and apoptosis rate (Giebelen et al., 2008; Lang, Nystrom, & Frost, 2008; Oberbeck et al., 2004; Schmitz, Wilsenack, Lendemanns, Schedlowski, & Oberbeck, 2007). All of that improved the importance of b-blockers in treating sepsis and the survival rate.

2. b-blockers in breast cancer

According to the World Health Organization (WHO), breast cancer is one of the inflammatory-related diseases and is one of the five top reasons for mortality among women globally. In preclinical experiments, adrenergic stimulation and stress promote breast cancer cell invasion, migration, and proliferation (Montoya et al., 2017; Sloan et al., 2010; Wilson, Lorimer, Tyburski, & Williams, 2015). Numerous studies revealed that β-blockers can impede various cellular processes linked to the advancement of breast cancer by blocking β-adrenergic receptor signaling. These processes include tumor cell proliferation, development for metastasis, extracellular matrix invasion, apoptosis, angiogenesis, matrix metalloprotease activation, expression of chemotactic and inflammatory cytokines, and tumor immune responses (Avraham et al., 2010; Madden, Szpunar, & Brown, 2011; Shi et al., 2011; Sloan et al., 2010).

It was discovered by Ashrafi and Szewczyk and their colleagues that b-blockers (propranolol and bisoprolol) administration had direct cytotoxic activity on breast cancer through the blockade of b-adrenergic receptors (Ashrafi, Shapouri, & Mahdavi, 2017; Szewczyk, Richter, Briese, & Richter, 2012). Three studies discovered that propranolol

administration can stimulate anti-tumor immunity by inducing lymphocyte infiltration, reducing inflammatory cytokine production and potentiating the anti-angiogenic effect of different chemotherapies, such as 5-fluorouracil and paclitaxel (Caparica et al., 2020; Jean Wrobel et al., 2016; Pasquier et al., 2011). Moreover, two distinct patient cohorts (propranolol and atenolol) were included in the Barron et al. investigation and qualified for the statistical evaluation of death related to breast cancer. The data was reported as two independent studies with the same control. This study showed that pre-administration of propranolol, not atenolol, had significant improvement in tumor stage and grade in a dose-dependent manner at diagnosis time and lower risk of mortality between breast cancer women with no effect on breast cancer recurrence (T. I. Barron, Connolly, Sharp, Bennett, & Visvanathan, 2011).

Moreover, Park et al. discovered that propranolol inhibits breast cancer growth and metastasis by downregulating Vascular endothelial growth factor (*VEGF)* and Hypoxia-induced factor-1 alpha (HIF-1a) mediators in triple-negative breast cancer cells (Park et al., 2011). Drell et al. found that atenolol partially inhibited tumor cell migration in an *in vitro* study of triple-negative breast cancer cell lines (Drell et al., 2003). Furthermore, three *in vitro* studies provided that nadolol and propranolol antagonize breast cancer cell metastasis through stimulation of natural killer cells cytotoxicity (Avraham et al., 2010; Benish et al., 2008; Melamed et al., 2005).

The controllable safety profile and low cost of β-blockers, along with their preliminary activity against breast cancer, have sparked interest in repurposing these medications to improve the therapy of breast cancer patients (Aggarwal, Verma, Aggarwal, & Gupta, 2021).

3. b-blockers in Covid-19

The coronavirus (COVID-19) pandemic, discovered in 2019, is a life-threatening infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Moubarak et al., 2021). Around half of the deaths of COVID-19 patients in ICU arise from acute respiratory distress syndrome (ARDS), which is linked to many complicated consequences that can result in respiratory failure, acute renal injury, cardiac arrhythmias, and stroke (H. M. Al-Kuraishy, Al-Gareeb, Alqarni, Cruz-Martins, & El-Saber Batiha, 2021; H. M. Al-Kuraishy, Al-Gareeb, Qusty, Alexiou, & Batiha, 2022; H. M. Al-Kuraishy, Al-Gareeb, Qusty, Cruz-Martins, & El-Saber Batiha, 2021). The signs of COVID-19 are hypoxemia, exaggeration of oxidative stress, and stimulation of the sympathetic system and, in extreme circumstances, cause sympathetic storm (SS), which is marked by repeated events of tachycardia, perspiration, hypertension, tachypnea, and hyperpyrexia (Levy, McVeigh, & Ramsay, 2011; Lugnier, Al-Kuraishy, & Rousseau, 2021). Exaggerated autoimmune reaction to SARS-CoV-2 could result in uncontrolled production of pro-inflammatory cytokines, including chemokines, tumor necrosis factor-alpha (*TNF-α*), and interleukins (*IL-6, IL-1β*, and *IL-8*), which collectively cause cytokine storm (CS), cross BBB and develop thrombosis (H. M. Al-Kuraishy, Al-Gareeb, Abdullah, Cruz-Martins, & Batiha, 2021; H. M. Al-Kuraishy, Al-Gareeb, Qusti, et al., 2021; Jin, Dai, Teng, & Wu, 2020;

Tufan, Avanoğlu Güler, & Matucci-Cerinic, 2020). Aberrant immunological hyperactivation, including infections, autoimmune responses, and malignancies, is also a feature of CS (Fajgenbaum & June, 2020). In CS, immune cells, including plasmablasts, CD4, CD8, and others, are also stimulated (H. M. Al-Kuraishy, Al-Gareeb, Alkazmi, Alexiou, & Batiha, 2021). The binding domain of the SARS-CoV-2 spike glycoprotein attaches to angiotensin-converting enzyme-2 (ACE2) receptor; the interaction between the virus and its receptor promotes cell damage in the afflicted cells. Apoptotic and inflammatory signals are released as a consequence of this interaction. The signals provoke macrophages to liberate chemokines and cytokines, prompting T-cell motivation and recruitment (Moradian et al., 2020).

Furthermore, SARS-CoV-2 spike glycoprotein can stimulate toll-like receptor 4 (TLR4) and CD147, enhancing the myeloid differentiation 88 (MyD88) pathway. MyD88 triggers NF-κB to activate pro-inflammatory cytokines production and develops CS (H. M. Al-Kuraishy, Al-Gareeb, Alzahrani, Cruz-Martins, & Batiha, 2021). The interaction between SS and CS causes the development of several organ failures and subsequently increases the death rate from COVID-19 (Perlmutter, 2021). Several anti-inflammatory and anti-adrenergic agents may reduce the link between SC and SS and attenuate the complications in seriously affected COVID-19 individuals (H. M. Al-Kuraishy, Al-Gareeb, Alblihed, et al., 2021).

β-blockers have anti-inflammatory impacts as they reduce the release of pro-inflammatory cytokines through inhibitory targeting for NF-κB, which is highly activated in COVID-19 disease (Kim et al., 2020; Zhou et al., 2016). Antagonists for α1- and β-receptors had beneficial effects on COVID-19 by reducing SS and CS (Vasanthakumar, 2020). Because of this, β-blockers lessen sympathetic activation and prevent SARS-CoV-2 from combining with the binding sites of ACE2 and CD147 receptors, which are responsible for producing pro-inflammatory cytokines (Giorgi et al., 2020; Lampert et al., 2019; Porzionato et al., 2020). So, β-blockers stopped the creation of numerous CS and SS mediators to avoid neuro-cytokine storm advancement in COVID-19 patients. It has been declared that metoprolol, propranolol, and labetalol are valuable in controlling SS by normalization of autonomic dysfunction and sympathetic activation among those suffering from thalamic damage (Ammar & Hussein, 2018; Do, Sheen, & Bromfield, 2000). Furthermore, Ammar et al. discovered that early administration of propranolol had a successful effect on attenuating SS development in traumatic brain injury (TBI) (Ammar & Hussein, 2018).

Rather than brain injuries, b-blockers can reduce lung and cardiac injury induced by the overactivation of the sympathetic system. SARS-COV-2-evoked neuroinflammation that directly activates the locus coeruleus (LC) sympathetic center in the brain, leading to CS formation and increasing local *TNF-α* and *IL-6* expression and inflammation in cardiac cells and pulmonary alveoli (Giorgi et al., 2020; Porzionato et al., 2020). Also, there is a parallel inhibition for vasodilator Angiotensin1-7 due to the activation of ACE2 receptors by COVID-19, leading to sympathetic stimulation, hypertension, inflammation, and thrombosis with the emergence of ARDS and acute lung injury (ALI) (Hayder Mutter Al-

Kuraishy et al., 2020; Heriansyah, Nur Chomsy, Febrianda, Farahiya Hadi, & Andri Wihastuti, 2020). In addition, AngII, released from the activation of ACE2 receptor, exaggerates the activity of LC sympathetic center with the development of hypertension and lung injury (Boyer, Signoret-Genest, Artola, Dallel, & Monconduit, 2017). Verbrugge et al. discovered that b-blockers reduced renin-angiotensin system (RAS) activity by preventing renin and Ang II secretion from renal juxtaglomerular cells and protecting the heart and lungs from enhanced SS and RAS (Verbrugge et al., 2013). Dakhale et al. discovered that propranolol modulated the sensitivity and activity of LC and prevented sympathetic activation in migraine sufferers (Dakhale, Sharma, Thakre, & Kalikar, 2019). Furthermore, Sweeney et al. found that propranolol strongly blocked excitatory presynaptic β2-autoreceptors to suppress catecholamine secretion (Sweeney, Griffiths, & McAuley, 2013). In conclusion, β-blockers prevent the SS progression directly or indirectly by inhibiting AngII central impact.

Additionally, β-blockers avoid ALI by modulating neutrophilia and lymphopenia and releasing pro-inflammatory cytokines (Al-Qadi & Kashyap, 2015). Moreover, Noveanu et al. discovered in a retrospective study that the long-term administration of b-blocker treatment increases protective pulmonary β2 receptors, reducing the risk of sepsis-induced ARDS and mechanical ventilation in ICU patients (Noveanu et al., 2010). Mutlu et al. also found that β-blocker medication decreased the in-hospital death rate among acute respiratory failure patients in the ICU (Mutlu & Factor, 2008). Furthermore, Tang et al. discovered that b-blockers diminish coagulopathy-related microvascular and endothelial dysfunction in COVID-19 by suppressing *VEGF* (Tang et al., 2020). Also, Ohtsuka et al. discovered that the administration of b-blockers increases the secretion of the anti-inflammatory mediator *IL-10* by inhibiting macrophage activation (Ohtsuka et al., 2001).

Furthermore, SARS-COV-2 virus can activate the nod-like receptor pyrin 3 (NLRP3) inflammasome and enhance the activation of CS (Freeman & Swartz, 2020). Gao et al. discovered another mechanism for b-blockers against COVID-19, as they found that nebivolol suppresses NLRP3 inflammasome in experimental obese rats with vascular remodeling (Gao et al., 2019). All these studies provided that β-blockers potentially benefit in managing COVID-19 progression.

Conclusion

From the highlighted systemic review for previously published meta-analysis and clinical relevance for health care teams mainly work at ICU in treating patients with different diseases, including cardiovascular, AF, migraine, sepsis, cancer, and COVID-19, we concluded the great benefits from the anti-inflammatory effect of b-blockers in managing the diseases mentioned above. Additionally, b-blockers reduce the hospitalization time and mortality rate caused by these diseases. Furthermore, we demonstrated the possible mechanisms of action for different members of b-blockers against several diseases. Moreover, there is a link between these diseases, as they all have signs of the exaggerated sympathetic system, immune response, and inflammation, regardless of the mechanism of each disease, and that proves if the use of b-blocker was

successful in one disease, it might be successful in the others. Additional trials are needed to establish the outcome of b-blockers in a broad range of diseases.

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مقالة مرجعية: نظرة ثاقبة عن استخدامات حاصرات بيتا في الأمراض المختلفة: تطبيق العلاجات القديمة المعتمده من إداره الغذاء والدواء والعلاجات الجديدة الغير مصرح بها كأهداف جديدة

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مضادات مستقبلات بيتا الأدرينالية، أو حاصرات بيتا، هي فئه من الأدوية التي تستخدم في المقام الأول بموافقه إدارة الغذاء والدواء الأمريكية في علاج أمراض القلب والأوية الدموية، مثل قصور القلب، والرجفان الأذيني، وارتفاع ضغط الدم، والصداع النصفي، واحتشاء عضلة القلب، وفرط نشاط الغدة الدرقية، وتسلخ الاورطي،والماء الزرقاء بالعين، والتشنجات الأساسية. أيضا تم اكتشاف أن لها أستخدامات اخري جديدة، ولم يتم الموافقة عليها بعد من قبل إدارة الغذاء والدواء، ضد الإنتان والصدمة الإنتانية وسرطان الثدي وكوفيد-١٩. تشير الأبحاث الحديثة إلي أن استخدام حاصرات بيتا يمكن ان يعدل النتائج الصحية للمرضي ومعدلات الوفيات ضد العديد من الامراض التي يبدأها الالتهاب أو تنشيط الجهاز السيمبثاوي في وحدات العناية المركزة بسبب آثارها المضادة علي الجهاز السمبثاوي والمضادة للالتهابات وقدرتها علي توسيع الاوعية الدموية. ومن ثم، فإننا نقدم لمحة عامة عن حاصرات بيتا و أشرفنا علي تحليل شامل للأمراض التي يتم علاجها بحاصرات بيتا حتي عام ٢٠٢٣؛ حيث تم تلخيص حاصرات بيتا الأكثر استخداما، سواء تلك الانتقائية القلبية او غير الانتقائية، والتحقق من تأثيرها ولآليات الممكنة التي من خلالها تحفز عمل حاضرات بيتا في كل مرض وتحسين صحة المرضي ومعدل الوفيات في وحدة العناية المركزية.

الكلمات المفتاحية: حاصرات بيتا ، أمراض القلب والأوعية الدموية، الأنتان، سرطان الثدي، كوفيد-١٩