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ARTICLE 1

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DIFFERENT BETA-BLOCKERS USED IN THE TREATMENT OF CARDIOVASCULAR DISEASES AND ARTERIAL HYPERTENSION: A COMPREHENSIVE REVIEW

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Abstract: This study reviews different literature addressing the topic of beta-blockers available for the treatment of cardiovascular diseases (CVDs) and hypertension (HTN). CVDs are the leading cause of global mortality, and HTN is one of the main risk factors. Blood pressure control is essential to prevent serious complications, such as myocardial infarction and stroke. Among the drugs used, beta-blockers play a crucial role. Beta-blockers are divided into selective and non-selective. Selective beta-blockers, such as metoprolol, primarily target beta-1 receptors, while non-selective beta-blockers, such as propranolol, bind to beta-1, beta-2, and, in some cases, alpha receptors. Metoprolol is available in two formulations: succinate (extended release) and tartrate (immediate release), with the choice depending on the patient's needs. In addition to metoprolol, other common beta-blockers include carvedilol, bisoprolol, atenolol, nebivolol, and propranolol. Each has specific characteristics that influence its clinical indication. For example, carvedilol is a non-selective beta-blocker that also blocks alpha-1 receptors, offering additional vasodilator effects. Beta-blockers have several physicochemical, pharmacokinetic, and pharmacodynamic characteristics that influence their efficacy and safety profile. Physicochemical characteristics include water and lipid solubility, which affect drug absorption and distribution. Pharmacokinetic properties involve the absorption, distribution, metabolism, and excretion of beta-blockers. Pharmacodynamic characteristics refer to the mechanism of action of beta-blockers, which block β-adrenergic receptors, reducing heart rate and myocardial contraction force. Chemically, beta-blockers have structures that allow them to interact with β-adrenergic receptors. The technical data sheet for each beta-blocker provides detailed information on its composition, pharmaceutical form, therapeutic indications, dosage, and administration. The proper use of these drugs, combined with lifestyle changes, contributes to reducing cardiovascular mortality and improving the quality of life of hypertensive patients. Beta-blockers exert their pharmacological action through antagonism of β-adrenergic receptors in the myocardium, resulting in a cascade of physiological effects that modulate cardiovascular function. The binding of beta-blockers to β1 receptors attenuates the heart's response to adrenergic stimuli, reducing heart rate and myocardial contraction force. This decrease in cardiac output, together with the possible reduction in renin release by the kidneys, contributes to the effectiveness of beta-blockers in controlling blood pressure. In addition, the reduction in myocardial oxygen demand makes these drugs useful in the treatment of angina pectoris. The modulation of heart rate justifies their use in various arrhythmias. In summary, the literature review on the different beta-blockers available highlights the importance of these drugs in the treatment of CVD and AH. The choice of the appropriate beta-blocker depends on the individual needs of patients and adherence to treatment. The combined use of these drugs with lifestyle changes is essential for effective blood pressure control and prevention of serious complications.

Keywords: Cardiovascular diseases, Hypertension, Metoprolol, Beta-blockers, Blood pressure

INTRODUCTION

This study aims to review the literature on the different beta-blockers available on the market that are used in the treatment of hypertension (HT). Cardiovascular diseases (CVDs) are the leading cause of global mortality, and HT stands out as one of the main risk factors. Blood pressure control is essential to prevent serious complications such as myocardial infarction and stroke. Among the drugs used, beta-blockers play a crucial role [1-3].

Beta blockers are divided into two main categories: selective and non-selective. Selective beta blockers, such as metoprolol, primarily target beta-1 receptors, which influence heart rate and the heart's effort to pump blood. Non-selective beta blockers, such as propranolol, bind to beta-1, beta-2, and, in some cases, alpha receptors, influencing blood vessels throughout the body [4, 5].

Metoprolol, a drug widely known in clinical medicine, is available in two formulations: succinate and tartrate. Metoprolol succinate is based on prolonged release, which allows for once-daily dosing, making it the preferred choice in many cases. Metoprolol tartrate, on the other hand, has immediate release and requires multiple doses throughout the day. The choice between formulations depends on the patient's needs and adherence to treatment [6].

In addition to metoprolol, other common beta-blockers include carvedilol, bisoprolol, atenolol, nebivolol, and propranolol. Each of these drugs has specific characteristics that influence its clinical indication. For example, carvedilol is a non-selective beta--blocker that also blocks alpha-1 receptors, offering additional vasodilator effects[7-11].

Beta-blockers have several physicochemical, pharmacokinetic, and pharmacodynamic characteristics that influence their efficacy and safety profile. Physicochemical characteristics include water and lipid solubility, which affect the absorption and distribution of drugs in the body. Pharmacokinetic properties involve the absorption, distribution, metabolism, and excretion of beta-blockers. For example, metoprolol is metabolized mainly by the liver and excreted by the kidneys. Pharmacodynamic characteristics refer to the mechanism of action of beta-blockers, which block β-adrenergic receptors, reducing heart rate and myocardial contraction force [12-14].

Chemically, beta-blockers have structures that allow them to interact with β-adrenergic receptors. For example, propranolol has an aromatic ring that facilitates its binding to receptors. The technical data sheet for each beta-blocker provides detailed information on its composition, pharmaceutical form, therapeutic indications, dosage, and administration[15, 16].

The proper use of these drugs, combined with lifestyle changes, contributes to reducing cardiovascular mortality and improving the quality of life of hypertensive patients. Beta-blockers exert their pharmacological action through antagonism of β-adrenergic receptors in the myocardium, resulting in a cascade of physiological effects that modulate cardiovascular function. Specifically, the binding of beta-blockers to β1 receptors attenuates the heart's response to adrenergic stimuli, reducing heart rate (negative chronotropism) and myocardial contraction force (negative inotropism). This decrease in cardiac output, together with the possible reduction in renin release by the kidneys, contributes to the eff fficaciousness

of beta-blockers in controlling blood pressure. In addition, the reduction in myocardial oxygen demand makes these drugs useful in the treatment of angina pectoris. Heart rate modulation, in turn, justifies their use in various arrhythmias.

It can be concluded that the literature review confirms the importance of the different beta-blockers available on the market for the treatment of hypertension. The choice of the appropriate beta-blocker, such as metoprolol in its succinate and tartrate formulations, should be individualized, taking into account the specific needs of each patient to maximize therapeutic efficacy and treatment adherence. In addition to metoprolol, other beta-blockers such as carvedilol, bisoprolol, atenolol, nebivolol, and propranolol offer varied therapeutic options, each with specific characteristics that influence their clinical indication. The combined use of these drugs with lifestyle changes is essential for effective blood pressure control and prevention of serious complications [17].

ATENOLOL

Atenolol, a drug in the aryl ethanolamine class, was launched in 1976 as an alternative to propranolol. Its development aimed to reduce side effects affecting the central nervous system, since atenolol has a lower ability to dissolve in fats (liposolubility), which limits its passage through the blood-brain barrier. This drug demonstrates a selective affinity for β1 adrenergic receptors[18, 19].

With a molecular weight of approximately 266 g/mol, atenolol has well-defined physicochemical properties. Its melting point is between 152 and 155 °C, and it has a low octanol-water partition coefficient (LogP) of 0.16, which reinforces its low liposolubility. In terms of solubility, atenolol is highly soluble in water (above 100 mg/mL), partially soluble in ethanol, and practically insoluble in chloroform[20].

The solubility of atenolol in water facilitates its renal excretion, as it is mainly eliminated unchanged through the kidneys. This characteristic is important for its pharmacokinetic profile, especially in patients with renal disorders. In addition, the low fat solubility of atenolol prevents its significant passage through the blood-brain barrier, reducing side effects on the central nervous system. Therefore, the partition coefficient of atenolol is crucial for understanding its efficacy and safety in the treatment of cardiovascular conditions[21].

Atenolol is a beta-blocker whose chemical structure is described by the IUPAC name: (RS)-2-[4-[2-hydroxy-3-(1-methylethylamino)propoxy]phenyl]acetamide. Its molecule is composed of several important functional groups, including a secondary amine group, a hydroxyl group, and an ether group. The secondary amine group, present in the side chain, is responsible for the interaction of atenolol with beta-adrenergic receptors, blocking the action of neurotransmitters such as epinephrine [21].

The structure of atenolol also includes a hydroxyl group attached to a tertiary carbon, which contributes to its water solubility and its ability to form hydrogen bonds. In addition, the ether group connects the side chain to the benzene ring, providing stability to the molecule and facilitating its interaction with receptors in the heart. The benzene ring, in turn, is crucial for the pharmacological activity of atenolol, allowing it to bind effectively to beta-1 adrenergic receptors [21].

In summary, the molecular structure of atenolol, with its specific functional groups, is designed to selectively block beta-1 receptors in the heart, reducing heart rate and blood pressure. This selectivity is essential to minimize side effects in other body systems, making atenolol an effective and safe option for the treatment of cardiovascular conditions[21] :

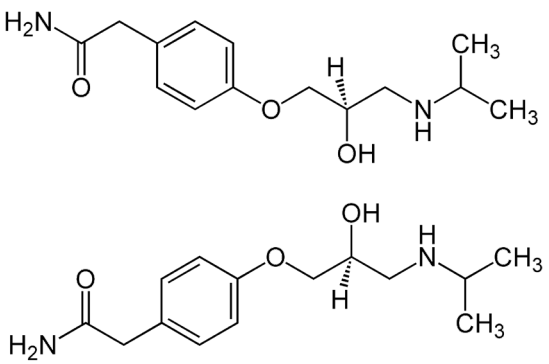

Figure 1: Atenolol molecule

Source: Own archive

The metabolism of atenolol in the body is minimal, as it is not significantly processed by cytochrome P450 enzymes in the liver. The main route of elimination is renal, with urinary excretion ranging from 85% to 100% of the administered dose in unchanged form. A small portion, less than 5%, is eliminated in the feces[22, 23].

Traces of oxidative derivatives have been identified as metabolites, but these are not clinically significant. From a pharmacokinetic point of view, atenolol has a plasma half-life ranging from 6 to 7 hours, and its *clearance*, predominantly renal, is between 100 and 150 mL/min. The drug is administered orally and is available in tablets with concentrations of 25, 50, and 100 mg [24, 25].

It is important to note that concomitant administration of atenolol with calcium channel blockers, such as verapamil or diltiazem, is contraindicated due to the risk of potentiating bradycardia (decreased heart rate). Its administration with verapamil or diltiazem should be avoided due to the risk of marked bradycardia[25].

METOPROLOL SUCCINATE

Metoprolol succinate, a sustained-release formulation of the selective β1 beta-blocker metoprolol, represents an advance in cardiovascular therapy since its development in the 1960s by Astra AB, now AstraZeneca, currently based in Sweden, with the aim of creating a β1-selective agent[26, 27].

Chemically, metoprolol succinate has a molecular weight of 652.8 g/mol and has well-defined physicochemical properties. The melting point of metoprolol base is between 120 and 123 °C. The drug is highly soluble in water (>100 mg/mL), soluble in ethanol and chloroform, and has an octanol-water partition coefficient (LogP) of approximately 1.8[28, 29].

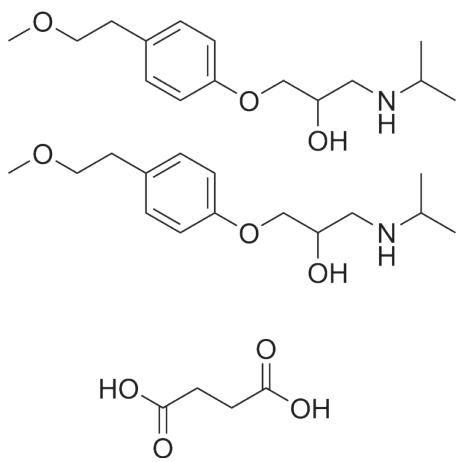

Figure 2: Metoprolol molecule next to the succinate molecule

Source: Own archive

Administered exclusively orally in extended-release tablets in various dosages, metoprolol succinate undergoes significant first-pass hepatic metabolism, mainly by the CYP2D6 subunit of cytochrome P450, resulting in a bioavailability of about 50%. Its plasma half-life ranges from 3 to 7 hours, with a total *clearance* of approximately 1 L/min, predominantly hepatic[30-32]

Excretion is mainly renal, with approximately 80% of the dose eliminated in the urine as inactive metabolites and less than 10% as unchanged drug, while less than 5% is excreted in the feces. The main metabolites identified are α-hydroxymethoprolol and α-methoxymethyl-3-[4-(2-hydroxy-3-isopropylamino)propoxy]benzoic acid, both with reduced beta-blocking activity [33].

Pharmacodynamically, metoprolol succinate acts by selectively blocking β1-adrenergic receptors in the heart, reducing heart rate and myocardial contraction force. This results in a decrease in the heart's oxygen demand, making it effective in treating angina pectoris and reducing blood pressure. In addition, metoprolol improves left ventricular function and increases survival in patients with chronic heart failure [34, 35].

The pharmacokinetics of metoprolol succinate are little affected by decreased liver function. However, in patients with severe liver cirrhosis and portacaval shunting, bioavailability may increase and total clearance may be reduced. The drug is released in a controlled manner, ensuring a prolonged effect for more than 24 hours [27, 34, 35].

Metoprolol succinate is also used in the prophylaxis of migraine, due to its ability to reduce neuronal excitability and the release of pain-related neurotransmitters. Administration should be adjusted individually, considering the clinical response and tolerance of the patient [36, 37].

METOPROLOL TARTARATE

Metoprolol tartrate, developed in the 1960s by researchers at Astra AB, now AstraZeneca, based in Sweden as a selective β1 beta-blocker, has a molecular weight of 327.83 g/mol and a melting point for the metoprolol base of around 120-123 °C. With an octanol-water partition coefficient (LogP) of approximately 1.7, it demonstrates moderate fat solubility and is highly soluble in water (>100 mg/mL), ethanol, and chloroform[38, 39].

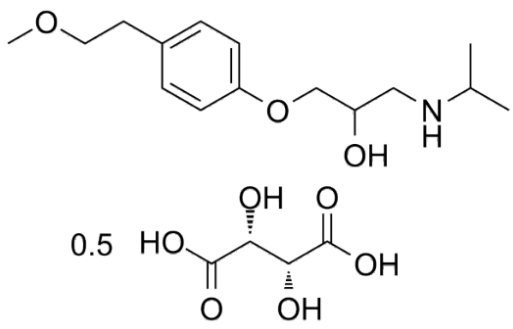

Figure 3: Metoprolol molecule next to tartrate

Source: Own archive

Administered mainly orally in immediate-release tablets, and occasionally intravenously, metoprolol tartrate has a plasma half-life of 3 to 7 hours and a total *clearance* of about 1 L/min, with extensive hepatic metabolism by the CYP2D6 subunit of cytochrome P450. Excretion is predominantly renal, with approximately 95% of the dose eliminated in the urine as metabolites and less than 10% as unchanged drug, while fecal excretion is less than 5%[40, 41].

The main metabolites include α-hydroxymetoprolol and α-methoxymethyl-3-[4-(2-hydroxy-3-isopropylamino)pro-

poxy]benzoic acid, both of which have less pharmacological activity than metoprolol. Metoprolol tartrate is mainly available in oral tablets of various dosages and, in some formulations, for injection[40-42].

Pharmacodynamically, metoprolol tartrate acts by selectively blocking β1-adrenergic receptors in the heart, reducing heart rate and myocardial contraction force. results in a decrease in the heart's oxygen demand, making it effective in treating angina pectoris and reducing blood pressure. In addition, metoprolol improves left ventricular function and increases survival in patients with chronic heart failure [43-45].

The pharmacokinetics of metoprolol tartrate are little affected by decreased liver function. However, in patients with severe liver cirrhosis and portacaval shunting, bioavailability may increase and total clearance may be reduced. The drug is released in a controlled manner, ensuring a prolonged effect for more than 24 hours [46-48].

Metoprolol tartrate is also used in the prophylaxis of migraine, due to its ability to reduce neuronal excitability and the release of pain-related neurotransmitters. Administration should be adjusted individually, considering the clinical response and tolerance of the patient[49-51].

In addition, metoprolol tartrate is indicated for the treatment of hypertension, cardiac arrhythmias, and maintenance after myocardial infarction. The recommended dose for hypertension ranges from 100 to 200 mg daily, which can be divided into morning and evening doses. For angina pectoris, the recommended dose is 100 to 200 mg daily, also in divided doses[26].

Finally, it is important to note that metoprolol tartrate should be used with caution in patients with congestive heart failure, bronchospasm, and renal or hepatic dysfunction. Abrupt discontinuation of treatment may cause adverse effects, such as exacerbation of angina and cardiac arrhythmias [52, 53].

BISOPROLOL

Bisoprolol, a selective β1 beta-blocker patented in 1976 and approved for medical use in 1986, was developed with the aim of providing effective treatment for cardiovascular diseases, exhibiting broad selectivity for β1 adrenergic receptors[54, 55].

Chemically, bisoprolol has a molecular weight of 325.4 g/mol (for the base) and a melting point between 100-103 °C, with a boiling point of approximately 445 °C. Its octanol-water partition coefficient (LogP) ranges from 1.9 to 2.3, indicating moderate fat solubility. Bisoprolol is highly soluble in water, with approximately 10 mg/mL for the hemifumarate, the commonly used form, ethanol, chloroform, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF) [56, 57].

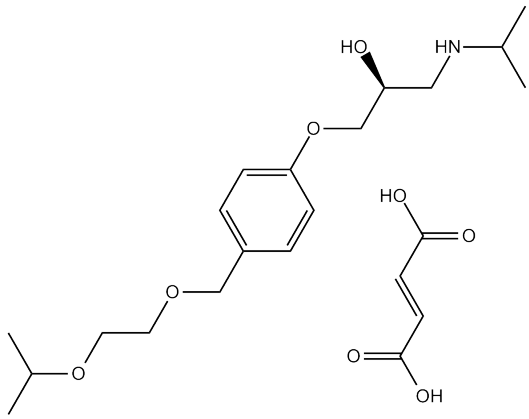

Figure 4: Bisoprolol molecule

Source: Own archive

Administered orally, mainly in tablets containing bisoprolol fumarate in dosages of 1.25 mg, 2.5 mg, 5 mg, and 10 mg, bisoprolol has a long plasma half-life of 9 to 12 hours, allowing once-daily administration. Its clearance is approximately 15 L/h, with about 50% of the dose metabolized in the liver by oxidative pathways involving mainly CYP3A4 and, to a lesser extent, CYP2D6, generating inactive metabolites. Excretion is balanced between the renal and non-renal (hepatic) routes, with approximately 50% of the dose excreted unchanged in the urine, together with inactive metabolites, while less than 2% is eliminated in the feces[58, 59].

Pharmacodynamically, bisoprolol acts by selectively blocking β1-adrenergic receptors in the heart, reducing heart rate and myocardial contraction force. results in a decrease in the heart's oxygen demand, making it effective in treating angina pectoris and reducing blood pressure. In addition, bisoprolol improves left ventricular function and increases survival in patients with chronic heart failure [60, 61].

Bisoprolol is indicated for the treatment of hypertension, angina pectoris, and stable chronic heart failure with reduced left ventricular systolic function. In patients with heart failure, bisoprolol is often used in combination with ACE inhibitors, diuretics, and, optionally, cardiac glycosides. The recommended starting dose for hypertension and angina is 5 mg once daily, which may be increased to 10 mg or even 20 mg, depending on the clinical response and medical evaluation[62, 63].

The pharmacokinetics of bisoprolol are linear and independent of age. Absorption is almost complete (>90%) from the gastrointestinal tract, and due to the reduced first-pass effect (approximately 10%), it has high bioavailability. Bisoprolol reaches its maximum effect 3-4 hours after oral administration, and the maximum antihypertensive effect is usually achieved after 2 weeks of treatment[64-66].

In addition to its main indications, bisoprolol can also be used in migraine prophylaxis due to its ability to reduce neuronal excitability and the release of pain-related neurotransmitters. Administration should be adjusted individually, considering the patient's clinical response and tolerance[67-69].

Finally, it is important to note that bisoprolol should be used with caution in patients with congestive heart failure, bronchospasm, and renal or hepatic dysfunction. Abrupt discontinuation of treatment may cause adverse effects, such as exacerbation of angina and cardiac arrhythmias.[70, 71].

ESMOLOL

Esmolol, an ultra-short-acting selective β1 beta-blocker developed by *DuPont Pharmaceuticals* and approved in 1986, is distinguished by its rapid onset and termination of action, which is crucial in acute situations. It has a molecular weight of 266.36 g/mol (for the base), with esmolol hydrochloride having a melting point of approximately 167-173 °C [58, 72, 73].

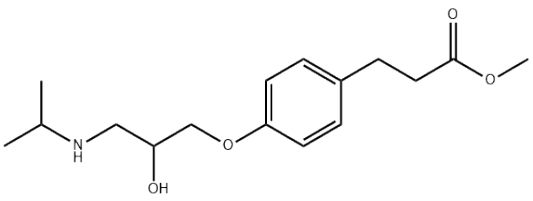

Figure 5: Esmolol molecule

Source: Own archive

Its low octanol-water partition coefficient (LogP) of approximately 0.42 indicates high hydrophilicity. Esmolol is highly soluble in water (>100 mg/mL) and is formulated exclusively for intravenous administration as a solution for injection or infusion. Its plasma half-life is extremely short, around 9 minutes, with a very high clearance of approximately 22.9 L/h/kg, due to rapid metabolism by plasma esterases into an inactive acid metabolite[74, 75].

Excretion is mainly renal, with the inactive metabolite being eliminated in the urine and less than 10% of esmolol excreted unchanged, i.e., fecal excretion is minimal. The main metabolite is methyl ester acid, which is pharmacologically inactive. Esmolol is available in solutions for intravenous injection with common concentrations of 10 mg/mL and 20 mg/mL and is not available in oral formulations [76, 77].

Pharmacodynamically, esmolol acts by selectively blocking β1-adrenergic receptors in the heart, reducing heart rate and myocardial contraction force. This results in a decrease in the heart's oxygen demand, making it effective in the treatment of supraventricular tachycardias and intraoperative hypertension. In addition, esmolol is used to control heart rate in patients with atrial fibrillation or atrial flutter [78-80]..

The pharmacokinetics of esmolol are characterized by rapid distribution and elimination. The distribution half-life is approximately 2 minutes, while the elimination half-life is approximately 9 minutes. The acid metabolite has an elimination half-life of approximately 3.7 hours. Esmolol binds to human plasma proteins by approximately 55%, while the acid metabolite binds by 10%[79, 81-83].

Esmolol is particularly useful in emergency situations due to its rapid onset and short duration of action. It is often used during surgery to help regulate blood pressure and heart rate. Intravenous administration allows for precise and rapid control of the pharmacological effects, making it ideal for use in hospital settings[84-86].

In addition to its main indications, esmolol can also be used to treat noncompensatory sinus tachycardia and intraoperative and postoperative tachycardia. The recommended initial dose ranges from 500 mcg/kg administered as a bolus, followed by a continuous infusion of 50 to 200 mcg/kg/min, adjusted according to clinical response[87-89].

Finally, it is important to note that esmolol should be used with caution in patients with congestive heart failure, bronchospasm, and renal or hepatic dysfunction. Abrupt discontinuation of treatment may cause adverse effects, such as exacerbation of angina and cardiac arrhythmias[90-92].

NEBIVOLOL

Nebivolol is a selective beta-blocker for **β1** receptors with vasodilator properties mediated by the release of nitric oxide. It was developed by Janssen Pharmaceutica and approved for use in 1997. This drug has a molecular weight of 367.89 g/mol (for the base) and a melting point for the hydrochloride between 224-227 °C. With an octanol-water partition coefficient (LogP) ranging from 3.3 to 3.7, it has moderate to high fat solubility. Its solubility in water is slightly soluble (approximately 0.1 to 1 mg/mL for the hydrochloride), being soluble in ethanol, chloroform, and propylene glycol[93-96].

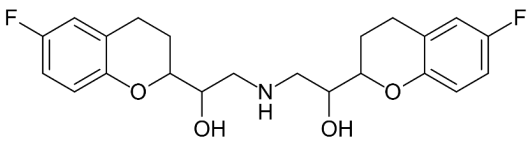

Figure 6: Nebivolol molecule

Source: Own archive

Administered orally in tablets in dosages of 2.5 mg, 5 mg, 10 mg, and 20 mg, nebivolol exhibits a highly variable plasma half-life (10 to 50 hours) due to CYP2D6 polymorphism, with extensive hepatic metabolism mainly by CYP2D6 and, to a lesser extent, by CYP3A4, generating active and inactive metabolites. Excretion occurs mainly via the renal (approximately 38% as metabolites, less than 5% unchanged) and fecal (approximately 44% as metabolites) routes[10, 97-100].

Pharmacodynamically, nebivolol acts by selectively blocking β1-adrenergic receptors in the heart, reducing heart rate and myocardial contraction force. In addition, it promotes vasodilation through the release of nitric oxide, which contributes to lowering blood pressure. This dual mechanism of action makes nebivolol effective in the treatment of hypertension and chronic heart failure[101-103].

Nebivolol is indicated for the treatment of essential hypertension and stable, mild to moderate chronic heart failure, in combination with standard therapies in elderly patients over 70 years of age. The recommended starting dose for hypertension is 5 mg once daily, which may be increased to 10 mg or up to 20 mg, depending on clinical response and medical evaluation. For heart failure, the starting dose is 1.25 mg once daily, which may be gradually adjusted to a maximum dose of 10 ml[104-106].

The pharmacokinetics of nebivolol are linear and independent of age. Both enantiomers of nebivolol are rapidly absorbed after oral administration, reaching peak plasma concentrations within 0.5 to 2 hours after ingestion. The absorption of nebivolol is not affected by food, allowing the drug to be administered with or without meals. In plasma, nebivolol enantiomers are predominantly bound to albumin, with plasma protein binding of 98.1% for SRRR-nebivolol and 97.9% for RSSS-nebivolol[10, 107, 108].

In addition to its main indications, nebivolol can also be used in the prophylaxis of migraine, due to its ability to reduce neuronal excitability and the release of pain-related neurotransmitters. Administration should be adjusted individually, considering the clinical response and tolerance of the patient[109-111].

Finally, it is important to note that nebivolol should be used with caution in patients with congestive heart failure, bronchospasm, and renal or hepatic dysfunction. Abrupt discontinuation of treatment may cause adverse effects, such as exacerbation of angina and cardiac arrhythmias[112-115].

NADOLOL

Nadolol, a long-acting non-selective beta-blocker developed by *Squibb* (now *Bristol-Myers Squibb*) and approved in 1978, is characterized by its long duration of action, allowing once-daily administration. This drug has a molecular weight of 309.40 g/mol and a melting point between 126-132 °C. Its low octanol-water partition coefficient (LogP) of approximately 0.17 indicates high hydrophilicity and low fat solubility. It is soluble in water (approximately 10 mg/mL) and slightly soluble in ethanol, being practically insoluble in chloroform and[93, 116-119].

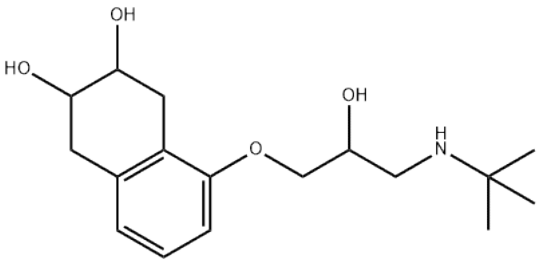

Figure 7: Nadolol molecule

Source: Own archive

Administered orally in tablets of 20 mg, 40 mg, and 80 mg, nadolol has a long plasma half-life of 14 to 24 hours and a low clearance of approximately 0.3 L/h/kg due to its minimal hepatic metabolism, as it is not significantly metabolized by cytochrome P450 enzymes. Excretion is predominantly renal, with 70-80% of the dose eliminated unchanged in the urine, while 20-30% is excreted in the feces, mainly as unabsorbed drug. Minimal amounts of metabolites have been identified, with no significant clinical relevance[120-122].

Pharmacodynamically, nadolol acts by blocking β1 and β2-adrenergic receptors, reducing heart rate and myocardial contraction force. This results in a decrease in the heart's oxygen demand, making it effective in treating angina pectoris and reducing blood pressure. In addition, nadolol is used in the treatment of cardiac arrhythmias and in the prophylaxis of migraine[123-125].

Nadolol is indicated for the treatment of hypertension, angina pectoris, and cardiac arrhythmias. The recommended starting dose for hypertension is 40 mg once daily, which can be gradually increased to a maximum of 240 mg per day, depending on clinical response and medical evaluation. For angina pectoris, the initial dose is 40 mg once daily, which may be adjusted up to 160 mg per day[121, 123, 126, 127].

The pharmacokinetics of nadolol are linear and independent of age. Absorption is rapid and almost complete after oral administration, with a bioavailability of approximately 30-50% due to the first-pass effect. Nadolol reaches maximum plasma concentrations 3 to 4 hours after administration. Plasma protein binding is low, about 30%, which facilitates its distribution in tissues[120, 128, 129].

In addition to its main indications, nadolol can also be used to prevent esophageal varices in patients with liver cirrhosis and portal hypertension. Administration should be adjusted individually, considering the patient's clinical response and tolerance[130-132].

Finally, it is important to note that nadolol should be used with caution in patients with congestive heart failure, bronchospasm, and renal or hepatic dysfunction. Abrupt discontinuation of treatment may cause adverse effects, such as exacerbation of angina and cardiac arrhythmias[133-135].

TIMOLOL

Timolol, a non-selective beta-blocker developed by *Merck & Co*. and approved in 1974, initially for ophthalmic use and later in oral formulations, has a molecular weight of 317.4 g/mol (for maleate) and a melting point of maleate around 202-204 °C. With an octanol-water partition coefficient (LogP) ranging from 0.2 to 0.6, it has low to moderate fat solubility, being soluble in water (approximately 200 mg/mL for the maleate) and ethanol, and slightly soluble in chloroform and ethanol [93, 136-138].

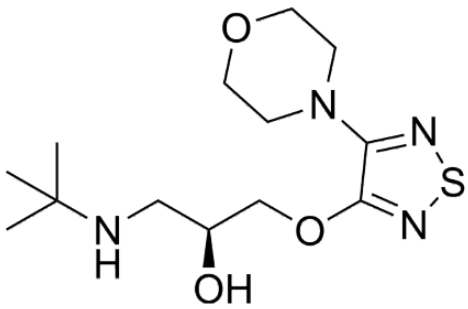

Figure 8: Timolol molecule

Source: Own archive

Administered orally in tablets (5 mg, 10 mg, and 20 mg) and ophthalmically as a solution (eye drops), timolol has a plasma half-life of 3 to 4 hours after oral administration and a clearance of approximately 0.4 L/h/kg, undergoing extensive hepatic metabolism mainly by CYP2D6 and also by CYP3A42. Excretion is mainly renal, with 60-80% of the oral dose eliminated in the urine as inactive metabolites and about 20% as unchanged drug; a small percentage is excreted in the feces. Several metabolites have been identified, some with some beta-blocking activity[139-141].

Pharmacodynamically, timolol acts by blocking β1 and β2-adrenergic receptors, reducing heart rate and myocardial contraction force. This results in a decrease in the heart's oxygen demand, making it effective in the treatment of hypertension, angina pectoris, and cardiac arrhythmias. In addition, timolol is widely used in the treatment of open-angle glaucoma and ocular hypertension, reducing intraocular pressure[142-145].

Timolol is indicated for the treatment of hypertension, angina pectoris, cardiac arrhythmias, and open-angle glaucoma. The recommended starting dose for hypertension is 10 mg twice daily, which may be gradually increased to a maximum of 60 mg per day, depending on clinical response and medical evaluation. For angina pectoris, the starting dose is 10 mg twice daily, which may be adjusted up to 40 mg per day[140, 146-148].

The pharmacokinetics of timolol are linear and independent of age. Absorption is rapid and almost complete after oral administration, with a bioavailability of approximately 60% due to the first-pass effect. Timolol reaches maximum plasma concentrations within 1 to 2 hours after administration. Plasma protein binding is low, about 10%, which facilitates its distribution in tissues[145, 149, 150].

In addition to its main indications, timolol can also be used to prevent esophageal varices in patients with liver cirrhosis and portal hypertension. Administration should be adjusted individually, considering the patient's clinical response and tolerance[151-154].

Finally, it is important to note that timolol should be used with caution in patients with congestive heart failure, bronchospasm, and renal or hepatic dysfunction. Abrupt discontinuation of treatment may cause adverse effects, such as exacerbation of angina and cardiac arrhythmias[155, 156].

SOTALOL

Sotalol, a non-selective β-adrenergic receptor blocking agent with Class III antiarrhythmic properties, developed by Mead Johnson (now Bristol-Myers Squibb) and approved in 1974, has a molecular weight of 272.34 g/mol (for the base), with the hydrochloride having a melting point of approximately 205-207 °C with decomposition. Its low octanol-water partition coefficient (LogP) of about -0.24 indicates high hydrophilicity. It is very soluble in water (>100 mg/mL for the hydrochloride) and soluble

in ethanol, being practically insoluble in chloroform and[72, 74, 157-159].

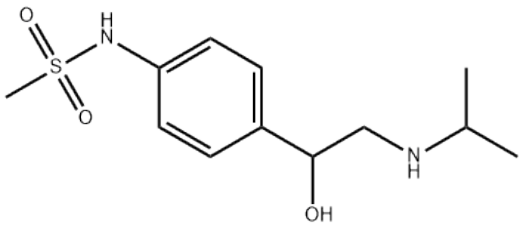

Figure 9: Sotalol molecule

Source: Own archive

Administered mainly orally in tablets in dosages of 40 mg, 80 mg, 120 mg, and 160 mg, and also available in injectable formulations for intravenous use, sotalol has a plasma half-life of approximately 12 hours and a predominantly renal clearance of about 120 mL/min, undergoing no significant hepatic metabolism. Excretion is mainly renal, with 80-90% of the dose eliminated unchanged in the urine, and a small portion (10-20%) excreted in the feces, mainly as unabsorbed drug. Minimal amounts of metabolites have been identified, with no significant clinical relevance[160, 161].

Pharmacodynamically, sotalol acts by blocking β1 and β2-adrenergic receptors, reducing heart rate and myocardial contraction force. In addition, it has Class III antiarrhythmic properties, prolonging the duration of the cardiac action potential and the refractory period, which helps prevent arrhythmias. This dual mechanism of action makes sotalol effective in the treatment of various ventricular and supraventricular arrhythmias[162-164].

Sotalol is indicated for the treatment of severe ventricular tachyarrhythmias, symptomatic non-sustained ventricular tachyarrhythmias, symptomatic premature ventricular contractions, prophylaxis of paroxysmal atrial tachycardia, paroxysmal atrial fibrillation, paroxysmal reentrant atrioventricular node tachycardia, paroxysmal atrioventricular reentrant tachycardia via accessory pathways, and paroxysmal supraventricular tachycardia after cardiac surgery. It is also used to maintain normal sinus rhythm after conversion of atrial fibrillation or flutter [162, 165-167].

The pharmacokinetics of sotalol are linear and independent of age. Absorption is rapid and almost complete after oral administration, with a bioavailability of approximately 90-100%. Sotalol reaches maximum plasma concentrations within 2 to 4 hours after administration. Plasma protein binding is low, approximately 0-10%, which facilitates its distribution in tissues[159, 168, 169].

In addition to its main indications, sotalol can also be used to prevent arrhythmias caused by excess circulating catecholamines and those due to increased sensitivity to catecholamines. Administration should be adjusted individually, considering the patient's clinical response and tolerance[165, 170, 171].

Finally, it is important to note that sotalol should be used with caution in patients with congestive heart failure, bronchospasm, and renal or hepatic dysfunction. Abrupt discontinuation of treatment may cause adverse effects, such as exacerbation of angina and cardiac arrhythmias[165, 172].

CARVEDILOL

Carvedilol, a non-selective β- and α1-adrenergic receptor blocker with antioxidant properties, was patented in 1978 and approved in the US in 1995. This drug has a molecular weight of 406.48 g/mol and a melting point of 114-115 °C. It has high liposolubility (LogP 3.3-3.6), being practically insoluble in water, but soluble

in DMSO, chloromethane, and methanol, and slightly soluble in ethanol and isopropanol[116, 173-175]

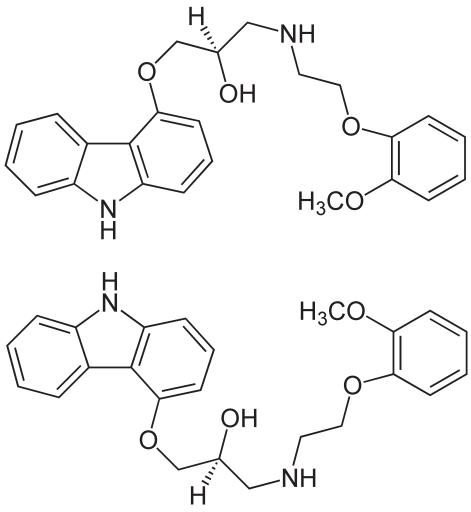

Figure 10: Carvedilol molecule

Source: Own archive

Administered orally in tablets (3.125 mg, 6.25 mg, 12.5 mg, 25 mg) and extended-release capsules (10 mg, 20 mg, 40 mg, 80 mg), carvedilol has a plasma half-life of 6 to 10 hours and a clearance of 500-700 mL/min, undergoing extensive hepatic metabolism by the CYP2D6 and CYP2C92 enzymes. Excretion is predominantly biliary and fecal, with less than 2% of the dose unchanged in urine and about 16% of metabolites in urine, with most metabolites excreted in feces. Several metabolites are formed, some with beta-blocking activity[176-180].

Pharmacodynamically, carvedilol acts by blocking β1, β2, and α1-adrenergic receptors, reducing heart rate and myocardial contraction force, and promoting peripheral vasodilation. This results in a decrease in peripheral vascular resistance and oxygen demand by the heart, making it effective in the treatment of hypertension, angina pectoris, and congestive heart failure. The antioxidant properties of carvedilol also contribute to protection against cellular damage caused by free radicals [74, 176, 181, 182].

Carvedilol is indicated for the treatment of essential hypertension, angina pectoris, and stable, mild, moderate, and severe symptomatic congestive heart failure. The recommended starting dose for hypertension is 12.5 mg once daily, which may be gradually increased to a maximum of 50 mg per day, depending on clinical response and medical evaluation. For angina pectoris, the starting dose is 12.5 mg twice daily, which may be adjusted up to 100 mg per day. For congestive heart failure, the initial dose is 3.125 mg twice daily, which may be gradually increased to 25 mg twice daily[165, 176, 183, 184].

The pharmacokinetics of carvedilol are linear and independent of age. Absorption is rapid and almost complete after oral administration, with a bioavailability of approximately 25-35% due to the first-pass effect. Carvedilol reaches maximum plasma concentrations within 1 to 2 hours after administration. Plasma protein binding is high, around 98%, which facilitates its distribution in tissues[177, 185-188].

In addition to its main indications, carvedilol can also be used to prevent esophageal varices in patients with liver cirrhosis and portal hypertension. Administration should be adjusted individually, considering the patient's clinical response and tolerance[151, 189, 190].

Finally, it is important to note that carvedilol should be used with caution in patients with decompensated heart failure, bronchospasm, and renal or hepatic dysfunction. Abrupt discontinuation of treatment may cause adverse effects, such as

exacerbation of angina and cardiac arrhythmias[63, 191-193].

LABETALOL

Labetalol, a non-selective β- and α1-adrenergic receptor blocker developed by Allen & Hanburys (later GlaxoSmithKline) and approved in 1977, has a molecular weight of 328.4 g/mol and a melting point of approximately 190 °C for the hydrochloride. It has moderate liposolubility (LogP 0.77-1.15), being soluble in water (approximately 100 mg/mL for the hydrochloride) and ethanol, and slightly soluble in chloroform and ethanol [(155, 194-198)].

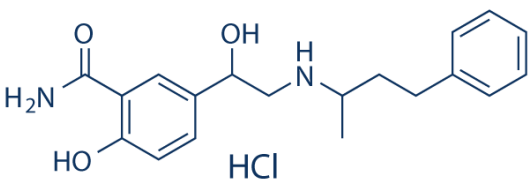

Figure 11: Labetalol molecule

Source: Own archive

Administered orally in tablets (100 mg, 200 mg, 300 mg) and intravenously as an injectable solution (5 mg/mL), labetalol has a plasma half-life of 5 to 8 hours and a high clearance of approximately 1500 mL/min². It undergoes significant first-pass hepatic metabolism by conjugation with glucuronic acid, without extensive involvement of cytochrome P450. Excretion occurs mainly via the renal (55-60% as glucuronidated metabolites, less than 5% unchanged) and fecal (20-30% as metabolites) routes. The main metabolite, labetalol glucuronide, has minimal pharmacological activity [(165, 182, 199-202)].

Pharmacodynamically, labetalol acts by blocking β1, β2, and α1-adrenergic receptors, reducing heart rate and myocardial contraction force, and promoting peripheral vasodilation. This results in a decrease in peripheral vascular resistance and oxygen demand by the heart, making it effective in the treatment of hypertension, angina pectoris, and congestive heart failure. Labetalol can also be used to achieve controlled hypotension during anesthesia[181, 203-205].

Labetalol is indicated for the treatment of severe hypertension, including severe hypertension of pregnancy, when rapid control of blood pressure is essential. The recommended starting dose for hypertension is 100 mg twice daily, which may be gradually increased to a maximum of 2400 mg per day, depending on clinical response and medical evaluation. For severe hypertension during pregnancy, the initial dose is 20 mg intravenously, which may be adjusted as necessary[200, 201, 206].

The pharmacokinetics of labetalol are linear and independent of age. Absorption is rapid and almost complete after oral administration, with a bioavailability of approximately 25% due to the first-pass effect. Labetalol reaches maximum plasma concentrations within 1 to 2 hours after administration. Plasma protein binding is high, around 50%, which facilitates its distribution in tissues[207-209].

In addition to its main indications, labetalol can also be used to prevent esophageal varices in patients with liver cirrhosis and portal hypertension. Administration should be adjusted individually, considering

the patient's clinical response and tolerance[194, 210-212].

Finally, it is important to note that labetalol should be used with caution in patients with decompensated heart failure, bronchospasm, and renal or hepatic dysfunction. Abrupt discontinuation of treatment may cause adverse effects, such as exacerbation of angina and cardiac arrhythmias[200, 213, 214].

PROPANOLOL

Propranolol, the first clinically useful beta-blocker synthesized by James Black and colleagues at ICI and launched in 1964, is a non-selective blocker of β1 and β2 adrenergic receptors. This drug has a molecular weight of 259.34 g/mol and a melting point of approximately 96 °C, as well as a boiling point of about 267 °C and high liposolubility (LogP ~3.65). Its solubility in water is slightly soluble (4 mg/mL), but increases in acidic solutions, being soluble in ethanol, chloroform, and acetone[215-218].

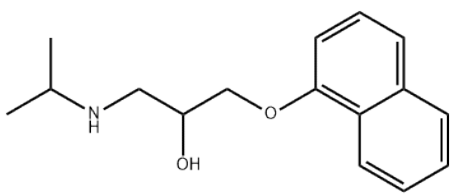

Figure 12: Propranolol molecule

Source: Own archive

Administered orally in tablets (10 mg, 40 mg, 80 mg) and extended-release capsules (60 mg, 80 mg, 120 mg, 160 mg), and also intravenously as an injectable solution (1 mg/mL), propranolol has a plasma half-life of 3 to 6 hours and a clearance of 10-20 mL/min/kg. It undergoes extensive first-pass hepatic metabolism by the enzymes CYP2D6, CYP1A2, and CYP2C19. Excretion is mainly renal as metabolites, including the active 4-hydroxypropranolol, with less than 1% excreted unchanged in the urine and a small portion in the feces [199, 219-222].

Pharmacodynamically, propranolol acts by blocking β1 and β2-adrenergic receptors, reducing heart rate and myocardial contraction force. This results in a decrease in the heart's oxygen demand, making it effective in the treatment of hypertension, angina pectoris, and cardiac arrhythmias. In addition, propranolol is widely used in the prevention of migraines and in the treatment of essential tremors[223, 224].

Propranolol is indicated for the treatment of hypertension, angina pectoris, cardiac arrhythmias, essential tremors, prevention of migraines, and anxiety. The recommended starting dose for hypertension is 40 mg twice daily, which can be gradually increased to a maximum of 320 mg per day, depending on clinical response and medical evaluation. For angina pectoris, the initial dose is 40 mg twice daily, which may be adjusted up to 240 mg per day. For migraine prevention, the initial dose is 80 mg per day, which may be increased up to 240 mg per day [165, 225, 226].

The pharmacokinetics of propranolol are linear and independent of age. Absorption is rapid and almost complete after oral administration, with a bioavailability of approximately 25-35% due to the first-pass effect. Propranolol reaches maximum plasma concentrations within 1 to 2 hours after administration. Plasma protein binding is high, around 90%, which facilitates its distribution in tissues[222, 227, 228].

In addition to its main indications, propranolol can also be used to prevent esophageal varices in patients with liver cirrho-

sis and portal hypertension. Administration should be adjusted individually, considering the patient's clinical response and tolerance[53, 229-231].

Finally, it is important to note that propranolol should be used with caution in patients with congestive heart failure, bronchospasm, and renal or hepatic dysfunction. Abrupt discontinuation of treatment can cause adverse effects, such as exacerbation of angina and cardiac arrhythmias[232, 233].

GENERAL CONSIDERATIONS

PHARMACEUTICAL CONTEXT

Pharmacotechnical tests applied to tablets, as in the case of beta-blockers, are essential to ensure their quality and efficacy in manufacturing. The average weight of the tablets is checked to ensure that each unit contains the correct amount of drug and excipients, avoiding variations that could compromise patient treatment. The drug content of the tablet is analyzed to confirm that the dosage is as specified, ensuring therapeutic efficacy. Content uniformity is another critical parameter, as it ensures that each tablet has a homogeneous distribution of atenolol, avoiding inconsistent doses[234].

In addition, the hardness and friability of the tablets are tested to assess their physical resistance during transport and handling. The disintegration resistance test checks the time required for the tablet to disintegrate in the body, influencing the release of the drug. Dissolution is analyzed to ensure that atenolol dissolves properly in the gastrointestinal tract, allowing for successful absorption. Finally, the stability of the tablet is tested to ensure that the drug maintains its efficacy and safety over time under different storage conditions. These tests are essential to ensure that the drug provides safe and effective treatment to patients without degradation of its active ingredients and excipients in the formulation[234].

The shelf stability of tablets is guaranteed by strict standards that establish specific conditions for stability testing. These tests are essential to ensure that drugs maintain their efficacy, safety, and quality over time. Accelerated stability studies simulate rapid aging of the product by exposing it to extreme temperature and humidity conditions, such as 40°C ± 2°C and 75% RH ± 5% for a period of 6 months. These tests help predict how the product will behave under normal storage conditions, allowing for adjustments to the formulation or packaging, if necessary [234].

To ensure the long-term stability of tablets in the pharmaceutical industry, studies are conducted under typical storage conditions, such as 25°C ± 2°C and 60% RH ± 5% for up to 24 months. In the case of specific climate zones, such as Brazil (zone IVb), long-term stability tests are adjusted to reflect local environmental conditions, using 30°C ± 2°C and 75% RH ± 5%, with bimonthly sampling over 24 months. These standards are essential to ensure that medicines remain safe and effective throughout their shelf life, regardless of climatic variations[234].

CONCLUSION

The literature reviewed confirms the importance of the different beta-blockers available on the market for the treatment of hypertension (HTN). Cardiovascular diseases (CVDs) are the leading cause of global mortality, and HTN stands out as one of

the main risk factors. Blood pressure control is essential to prevent serious complications, such as myocardial infarction and stroke. Among the drugs used, beta-blockers play a crucial role.

Beta-blockers are divided into two main categories: selective and non-selective. Selective beta-blockers, such as metoprolol, primarily target beta-1 receptors, which influence heart rate and the heart's effort to pump blood. Non-selective beta-blockers, such as propranolol, bind to beta-1, beta-2, and, in some cases, alpha receptors, influencing blood vessels throughout the body.

The choice of the appropriate beta-blocker, such as metoprolol in its succinate and tartrate formulations, should be individualized, taking into account the specific needs of each patient to maximize therapeutic efficacy and treatment adherence. In addition to metoprolol, other beta-blockers such as carvedilol, bisoprolol, atenolol, nebivolol, and propranolol offer varied therapeutic options, each with specific characteristics that influence their clinical indication. The combined use of these drugs with lifestyle changes is essential for effective blood pressure control and prevention of serious complications.

FUTURE PERSPECTIVES

The future outlook for beta blockers is promising, with several areas of research and development underway. Precision medicine is becoming increasingly relevant, allowing for the personalization of treatments based on patients' genetic characteristics and biomarkers. This may lead to greater efficacy of beta blockers and a reduction in side effects.

In addition, research into new beta blockers with additional properties, such as antioxidant and vasodilator effects, is progressing. These new drugs may offer additional benefits in the treatment of CVD, especially in patients with complex comorbidities.

The integration of advanced technologies, such as cardiac monitoring devices and controlled drug delivery systems, is also being explored. These advances may improve treatment adherence and allow for more precise control of blood pressure and cardiac function.

Finally, ongoing collaboration between clinical research and technology will be essential to overcoming current challenges in the treatment of hypertension and other CVDs. Innovation in gene therapies and the discovery of new biomarkers offer new hope for more targeted and effective treatments.

In summary, beta-blockers will continue to play a crucial role in the treatment of hypertension and other CVDs, with ongoing advances in research and technology promising to further improve their efficacy and safety.

REFERENCES

1. Muresan L, Cismaru G, Muresan C, Rosu R, Gusetu G, Puiu M, et al. Beta-blockers for the treatment of arrhythmias: Bisoprolol - a systematic review. Ann Pharm Fr. 2022;80(5):617-34.

2. Koldenhof T, Van Gelder IC, Crijns HJ, Rienstra M, Tieleman RG. Rate control in atrial fibrillation, calcium channel blockers versus beta-blockers. Heart. 2023;109(23):1759-64.

3. Roston TM, Chua D, Lum E, Krahn AD. Switching Between β-Blockers: An Empiric Tool for the Cardiovascular Practitioner. Can J Cardiol. 2019;35(4):539-43.

4. Zacharias AP, Jeyaraj R, Hobolth L, Bendtsen F, Gluud LL, Morgan MY. Carvedilol versus traditional, non-selective beta-blockers for adults with cirrhosis and gastroesophageal varices. Cochrane Database Syst Rev. 2018;10(10):Cd011510.

5. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2017;1(1):Cd002003.

6. Delea TE, Stanford R, Hagiwara M, Edelsberg JS, Oster G. Death and hospitalization in heart failure patients receiving carvedilol vs. metoprolol tartrate. Int J Cardiol. 2005;99(1):117-24.

7. Turco L, Reiberger T, Vitale G, La Mura V. Carvedilol as the new non-selective beta-blocker of choice in patients with cirrhosis and portal hypertension. Liver Int. 2023;43(6):1183-94.

8. Devereux G, Cotton S, Nath M, McMeekin N, Campbell K, Chaudhuri R, et al. Bisoprolol in Patients With Chronic Obstructive Pulmonary Disease at High Risk of Exacerbation: The BICS Randomized Clinical Trial. Jama. 2024;332(6):462-70.

9. Wadworth AN, Murdoch D, Brogden RN. Atenolol. A reappraisal of its pharmacological properties and therapeutic use in cardiovascular disorders. Drugs. 1991;42(3):468-510.

10. Hanif N, Zamir A, Imran I, Saeed H, Majeed A, Rehman AU, et al. Clinical pharmacokinetics of nebivolol: a systematic review. Drug Metab Rev. 2023;55(4):428-40.

11. Núñez-Villaveirán T, Sánchez M, Millán P, García-de-Lorenzo A. Systematic review of the effect of propanolol on hypermetabolism in burn injuries. Med Intensiva. 2015;39(2):101-13.

12. Al-Majed AA, Bakheit AHH, Abdel Aziz HA, Alajmi FM, AlRabiah H. Propranolol. Profiles Drug Subst Excip Relat Methodol. 2017;42:287-338.

13. Metra M, Dei Cas L, Cleland JG. Pharmacokinetic and pharmacodynamic characteristics of beta-blockers: when differences may matter. J Card Fail. 2006;12(3):177-81.

14. Ågesen FN, Weeke PE, Tfelt-Hansen P, Tfelt-Hansen J. Pharmacokinetic variability of beta-adrenergic blocking agents used in cardiology. Pharmacol Res Perspect. 2019;7(4):e00496.

15. Zielińska-Pisklak MA, Pisklak DM, Wawer I. 1H and 13C NMR characteristics of β-blockers. Magn Reson Chem. 2011;49(5):284-90.

16. Arockiaraj M, Greeni AB, Kalaam ARA, Aziz T, Alharbi M. Mathematical modeling for prediction of physicochemical characteristics of cardiovascular drugs via modified reverse degree topological indices. Eur Phys J E Soft Matter. 2024;47(8):53.

17. Ogrodowczyk M, Dettlaff K, Jelinska A. Beta-Blockers: Current State of Knowledge and Perspectives. Mini Rev Med Chem. 2016;16(1):40-54.

18. Shi M, Wargon O, Tatian A. Efficacy and safety of atenolol vs. propranolol for treatment of infantile haemangioma: a narrative review. Clin Exp Dermatol. 2025;50(2):331-8.

19. Hicke FJ, Puerta A, Dinić J, Pešić M, Padrón JM, López Ó, et al. Straightforward access to novel mitochondriotropics derived from 2-arylethanol as potent and selective antiproliferative agents. Eur J Med Chem. 2022;228:113980.

20. Schürmann W, Turner P. A membrane model of the human oral mucosa as derived from buccal absorption performance and physicochemical properties of the beta-blocking drugs atenolol and propranolol. J Pharm Pharmacol. 1978;30(3):137-47.

21. Rastogi T, Leder C, Kümmerer K. A sustainable chemistry solution to the presence of pharmaceuticals and chemicals in the aquatic environment–the example of re-designing β-blocker Atenolol. RSC Advances. 2015;5(1):27-32.

22. Kirch W, Görg KG. Clinical pharmacokinetics of atenolol--a review. Eur J Drug Metab Pharmacokinet. 1982;7(2):81-91.

23. Ivantsova E, Konig I, Souders CL, 2nd, McNabney D, Simmons DDB, Martyniuk CJ. Lipidomic, metabolomic, and behavior responses of zebrafish (Danio rerio) exposed to environmental levels of the beta blocker atenolol. Sci Total Environ. 2023;866:161272.

24. Leite FdS, Santos LMd, Bonafé WW, Chignalia AZ, Carmona MJC, Suyama MJ, et al. Influência da circulação extracorpórea sobre as concentrações plasmáticas de atenolol. Arquivos Brasileiros de Cardiologia. 2007;88:637-42.

25. Bosco F, Braz J. Beta-Bloqueadores em Anestesiologia: Aspectos Farmacológicos e Clínicos*, 51, 431–447. 2001.

26. Figueiredo Neto JAd, Mady C, Grupi C. Efeitos do tartarato de metoprolol em pacientes portadores de insuficiência cardíaca. Arquivos Brasileiros de Cardiologia. 2006;87:329-35.

27. Jou BWC. ESTIMATIVA DA ABSORÇÃO DE SUCCINATO DE METOPROLOL EM MINICOMPRIMIDOS VIA SIMULAÇÃO IN SILICO: Universidade de São Paulo; 2021.

28. Vissotto JP. Otimização de método analítico para determinação de etanol em Succinato de Metoprolol por cromatografia em fase gasosa rápida. 2023.

29. Kaiser SE. Efeito da terapia farmacológica anti-hipertensiva sobre densidade capilar e função endotelial microcirculatória. 2012.

30. de Oliveira Azevedo B, dos Santos EF, Lima GS, Pujol JT, Antunes AA, Jesus LOP. Perfil farmacoterapêutico do Zolpidem. Revista Brasileira de ciências biomédicas. 2022;3(1):E0642022-1-7.

31. de Carvalho GN, Noblat LdACB. Avaliação da Inclusão de Metoprolol Oral no Formulário Farmacoterapêutico de um Hospital Universitário. JORNAL DE ASSISTÊNCIA FARMACÊUTICA E FARMACOECONOMIA. 2016;1(1).

32. Wassel AA, Alzamel N, Alkhaldi M, Ouerfelli N, Al-Arfaj A. Physico-chemical and analytical study of Metoprolol tartrate: An antihypertensive drug. Asian J Chem. 2017;29:1351-6.

33. de Souza Santos I, Bittencourt MS. Insuficiência cardíaca. Revista de Medicina. 2008;87(4):224-31.

34. Ribeiro RM, Costa GP, Majewski JPS, dos Santos JPL, Cantanhede MG, de Melo Costa IC, et al. Novas evidências farmacológicas para o Metoprolol como ferramenta terapêutica em diferentes patologias cardiovasculares: uma revisão. Brazilian Journal of Health Review. 2023;6(3):9035-55.

35. Tangeman HJ, Patterson JH. Extended-release metoprolol succinate in chronic heart failure. Annals of Pharmacotherapy. 2003;37(5):701-10.

36. Paulitsch F, Sponchiado LdC. Manual de rotinas em cardiologia. Ed. da FURG; 2021.

37. Vargas FS. Análise de prescrições medicamentosas dispensadas no Centro de Saúde Modelo de Porto Alegre. 2013.

38. Ouerfelli N, Vrinceanu N, Mliki E, Homeida AM, Amin KA, Ogrodowczyk M, et al. Modeling of the irradiation effect on some physicochemical properties of metoprolol tartrate for safe medical uses. Scientific Reports. 2020;10(1):67.

39. Malipeddi VR, Awasthi R, Ghisleni DDM, de Souza Braga M, Kikuchi IS, de Jesus Andreoli Pinto T, et al. Preparation and characterization of metoprolol tartrate containing matrix type transdermal drug delivery system. Drug delivery and translational research. 2017;7:66-76.

40. Luch JR. Metoprolol tartrate. Analytical profiles of drug substances. 12: Elsevier; 1983. p. 325-56.

41. Talbert RL. Pharmacokinetics and pharmacodynamics of beta blockers in heart failure. Heart failure reviews. 2004;9:131-7.

42. Brogden R, Heel R, Speight T, Avery G. Metoprolol: a review of its pharmacological properties and therapeutic efficacy in hypertension and angina pectoris. Drugs. 1977;14:321-48.

43. Jordö L, Attman P, Aurell M, Johansson L, Johnsson G, Regårdh C-G. Pharmacokinetic and pharmacodynamic properties of metoprolol in patients with impaired renal function. Clinical pharmacokinetics. 1980;5:169-80.

44. Luzier AB, Killian A, Wilton JH, Wilson MF, Forrest A, Kazierad DJ. Gender-related effects on metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers. Clinical Pharmacology & Therapeutics. 1999;66(6):594-601.

45. Bauman JL, Talbert RL. Pharmacodynamics ofβ-Blockers in Heart Failure: Lessons from the Carvedilol Or Metoprolol European Trial. Journal of cardiovascular pharmacology and therapeutics. 2004;9(2):117-28.

46. Sandberg A, Blomqvist I, Jonsson U, Lundborg P. Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol: a comparison with conventional tablets. European journal of clinical pharmacology. 1988;33:S9-S14.

47. Höcht C, Di Verniero C, Opezzo JA, Bramuglia GF, Taira CA. Pharmacokinetic-pharmacodynamic (PK-PD) modeling of cardiovascular effects of metoprolol in spontaneously hypertensive rats: a microdialysis study. Naunyn-Schmiedeberg's archives of pharmacology. 2006;373:310-8.

48. Oosterhuis B, Jonkman J, Kerkhof F. Pharmacokinetic and pharmacodynamic comparison of a new controlled-release formulation of metoprolol with a traditional slow-release formulation. European Journal of Clinical Pharmacology. 1988;33:S15-S8.

49. Tfelt-Hansen P, Ågesen FN, Pavbro A, Tfelt-Hansen J. Pharmacokinetic variability of drugs used for prophylactic treatment of migraine. CNS drugs. 2017;31:389-403.

50. Jackson JL, Kuriyama A, Kuwatsuka Y, Nickoloff S, Storch D, Jackson W, et al. Beta-blockers for the prevention of headache in adults, a systematic review and meta-analysis. PloS one. 2019;14(3):e0212785.

51. Whyte CA, Tepper SJ. Adverse effects of medications commonly used in the treatment of migraine. Expert review of neurotherapeutics. 2009;9(9):1379-91.

52. ULC MP, Etobicoke O. PrMetoprolol Tartrate Injection, USP. 2014.

53. Bodke V, Waghmare K, Pandav S, Kumbhar R, Patil T, Ranaware M, et al. A REVIEW ON METOPROLOL-ANTIHYPERTENSIVE β-BLOCKER WITH ADVERSE DRUG REACTION STUDY.

54. Swedberg K. History of beta blockers in congestive heart failure. Heart. 1998;79(Suppl 2):S29.

55. Proclemer A, Gradnik R, Savonitto S, Feruglio G. Electrophysiological effects of bisoprolol. European Heart Journal. 1987;8(suppl_M):81-5.

56. Bakheit AH, Ali R, Alshahrani AD, El-Azab AS. Bisoprolol: A comprehensive profile. Profiles of Drug Substances, Excipients and Related Methodology. 46: Elsevier; 2021. p. 51-89.

57. Verma M, Pandey S, Gidwani B, Pandey RK, Shukla SS. Bisoprolol Fumarate: An Exploration on its Properties and Analytical Methods. Palestinian Medical and Pharmaceutical Journal. 2024;9(4):6.

58. Lancaster SG, Sorkin EM. Bisoprolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and angina pectoris. Drugs. 1988;36:256-85.

59. Hayes P, Jenkins D, Vavianos P, Dagap K, Johnston A, Ioannides C, et al. Single oral dose pharmacokinetics of bisoprolol 10 mg in liver disease. European Heart Journal. 1987;8(suppl_M):23-9.

60. Kirch W, Rose I, Demers H, Leopold G, Pabst J, Ohnhaus E. Pharmacokinetics of bisoprolol during repeated oral administration to healthy volunteers and patients with kidney or liver disease. Clinical pharmacokinetics. 1987;13:110-7.

61. Leopold G, Pabst J, Ungethüm W, Bühring KU. Basic pharmacokinetics of bisoprolol, a new highly beta1-selective adrenoceptor antagonist. The Journal of Clinical Pharmacology. 1986;26(8):616-21.

62. Foch C, Allignol A, Hohenberger T, Boutmy E, Schaefer S, Hostalek U. Effectiveness of bisoprolol versus other β-blockers and other antihypertensive classes: a cohort study in the Clinical Practice Research Datalink. Journal of Comparative Effectiveness Research. 2022;11(6):423-36.

63. Quaye E. Beta Blockers in Heart Failure Management: Unlocking their Potential.

64. Alkreathy HM, Alsayyid KME, Alaama JY, Al Ghalayini K, Karim S, Esmat A, et al. Bisoprolol responses (PK/PD) in hypertensive patients: a cytochrome P450 (CYP) 2D6 targeted polymorphism study. Saudi Journal of Biological Sciences. 2020;27(10):2727-32.

65. Yin H, Jin Z, Li R, Li D, Wang L, Dong R. Bioequivalence of China-and Germany--manufactured bisoprolol (Concor®) tablets in fasted and fed healthy Chinese participants: a randomized, open-label, two-way, crossover study. Frontiers in Pharmacology. 2025;16:1527623.

66. Sukmawan YP, Nofianti T, Pebiansyah A. Comparison of carvedilol vs. bisoprolol for heart failure with reduced ejection fraction (HFrEF): A systematic review and meta-analysis from the Asian population. Pharmacia. 2025;72:1-8.

67. Bourke JP, Bryant A, Landon G, Burn A, Spinty S, Quinlivan R, et al. Preventing Cardiomyopathy in Duchenne Muscular Dystrophy: Long-Term Follow-Up of Patients in the Randomised, Placebo-Controlled Drug-Trial of Perindopril and Bisoprolol. European Journal of Neurology. 2025;32(3):e70097.

68. Ahmed YM, El-Shoura EA, Kozman MR, Abdel-Wahab BA, Abdel-Sattar AR. Combined bisoprolol and trimetazidine ameliorate arsenic trioxide-induced acute myocardial injury in rats: targeting PI3K/GSK-3β/Nrf2/HO-1 and NF-κB/iNOS signaling pathways, inflammatory mediators and apoptosis. Immunopharmacology and Immunotoxicology. 2025;47(1):68-84.

69. Ionel D, Riggins N. Antidepressants, Antihypertensives & others. Migraine Pain Management: Elsevier; 2025. p. 307-17.

70. Sampson M. Antiarrhythmic drugs. Part 3: rate-control drugs. British Journal of Cardiac Nursing. 2019;14(11):1-11.

71. Hassen M, Ebsa TK, Muhammed OS, Solomon T, Demessie MB, Wendie TF, et al. Patterns of beta-blocker use and dose optimization among ambulatory heart failure patients with reduced ejection fraction (HFrEF) attending public hospitals in Northeast Ethiopia: a multi-center cross-sectional study. BMC Cardiovascular Disorders. 2025;25(1):43.

72. Kayani M, Sangeetha GK, Sarangi S, Leela Sarmada G, Sharma S, Adedara VO, et al. Pharmacogenomics and its Role in Cardiovascular Diseases: A Narrative Literature Review. Current Cardiology Reviews. 2025.

73. Erhardt PW. Case Study:"Esmolol Stat"[1]. Analogue-based Drug Discovery. 2006:233-46.

74. Vashistha VK, Kumar A. Stereochemical facets of clinical β-blockers: An overview. Chirality. 2020;32(5):722-35.

75. COMENIANAE AFPU. BASIC PHYSICOCHEMICAL CHARACTERIZATION OF NEW POTENTIAL ULTRASHORT ACTING β1-ADRENOCEPTOR BLOCKERS.

76. Achari R, Drissel D, Matier W, Hulse J. Metabolism and urinary excretion of esmolol in humans. The Journal of Clinical Pharmacology. 1986;26(1):44-7.

77. Wiest D. Esmolol: a review of its therapeutic efficacy and pharmacokinetic characteristics. Clinical pharmacokinetics. 1995;28(3):190-202.

78. Benfield P, Sorkin EM. Esmolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs. 1987;33:392-412.

79. Wiest DB, Haney JS. Clinical pharmacokinetics and therapeutic efficacy of esmolol. Clinical pharmacokinetics. 2012;51:347-56.

80. Cuneo BF, Zales VR, Blahunka PC, Benson DW. Pharmacodynamics and pharmacokinetics of esmolol, a short-acting β-blocking agent, in children. Pediatric cardiology. 1994;15:296-301.

81. Sum CY, Yacobi A, Kartzinel R, Stampfli H, Davis CS, Lai CM. Kinetics of esmolol, an ultra-short-acting beta blocker, and of its major metabolite. Clinical Pharmacology & Therapeutics. 1983;34(4):427-34.

82. Volz-Zang C, Eckrich B, Jahn P, Schneidrowski B, Schulte B, Palm D. Esmolol, an ultrashort-acting, selective β 1-adrenoceptor antagonist: pharmacodynamic and pharmacokinetic properties. European journal of clinical pharmacology. 1994;46:399-404.

83. Wiest DB, Trippel MDL, Gillette PC, Garner SS. Pharmacokinetics of esmolol in children. Clinical Pharmacology & Therapeutics. 1991;49(6):618-23.

84. Frakes MA. Esmolol: A unique drug with ED applications (CE). Journal of Emergency Nursing. 2001;27(1):47-51.

85. Sung RJ, Blanski L, Kirshenbaum J, MacCosbe P, Turlapaty P, Laddu AR. Clinical experience with esmolol, a short-acting beta-adrenergic blocker in cardiac arrhythmias and myocardial ischemia. The Journal of Clinical Pharmacology. 1986;26(S1):A15-A26.

86. Heliste M, Pettilä V, Berger D, Jakob SM, Wilkman E. Beta-blocker treatment in the critically ill: a systematic review and meta-analysis. Annals of medicine. 2022;54(1):1994-2010.

87. Garnock-Jones KP. Esmolol: a review of its use in the short-term treatment of tachyarrhythmias and the short-term control of tachycardia and hypertension. Drugs. 2012;72(1):109-32.

88. Gray RJ, Bateman TM, Czer LS, Conklin CM, Matloff JM. Esmolol: a new ultrashort-acting beta-adrenergic blocking agent for rapid control of heart rate in postoperative supraventricular tachyarrhythmias. Journal of the American College of Cardiology. 1985;5(6):1451-6.

89. Byrd RC, Sung RJ, Marks J, Parmley WW. Safety and efficacy of esmolol (ASL-8052: an ultrashort-acting beta-adrenergic blocking agent) for control of ventricular rate in supraventricular tachycardias. Journal of the American College of Cardiology. 1984;3(2):394-9.

90. Carroll R, Matfin G. Endocrine and metabolic emergencies: thyroid storm. Therapeutic advances in endocrinology and metabolism. 2010;1(3):139-45.

91. Baysal B, Şimşek A. A Case Series of Neonatal Supraventricular Tachycardia: A Review of Different Management and Clinical Outcomes. Clinical Research. 2020;30(2):117-21.

92. Rogowski S, Lesslie VW, Ebersberger U. Drugs in Cardiac CT. CT of the Heart. 2019:103-7.

93. Țieranu EN. The history of beta blockers. Journal of Humanities, Culture and Social Sciences. 2017;3(01):113-7.

94. Mason RP, Kalinowski L, Jacob RF, Jacoby AM, Malinski T. Nebivolol reduces nitroxidative stress and restores nitric oxide bioavailability in endothelium of black Americans. Circulation. 2005;112(24):3795-801.

95. Prey S, Haberstroh G, Vergier B, Taïeb A, Wassef M, Ezzedine K, et al. Successful treatment of intravascular papillary endothelial hyperplasia (IPEH) by the beta-adrenergic antagonist nebivolol. British Journal of Dermatology. 2012;166(5):1147-9.

96. Tuchalski G, Emmerling F, Gröger K, Hänsicke A, Nagel T, Reck G. X-ray investigations of nebivolol and its isomers. Journal of molecular structure. 2006;800(1-3):28-44.

97. Sacco G, Evangelista S, Criscuoli M, Goso C, Bigioni M, Binaschi M, et al. Involvement of nitric oxide in both central and peripheral haemodynamic effect of D/L-nebivolol and its enantiomers in rats. European journal of pharmacology. 2005;511(2-3):167-74.

98. Mane P, Bushetti S, Keshavshetti G. Development and In vitro evaluation of mucoadhesive buccal films of nebivolol. Indian Journal of Pharmaceutical Sciences. 2014;76(2):166.

99. Briciu C, Neag M, Muntean D, Bocsan C, Buzoianu A, Antonescu O, et al. Phenotypic differences in nebivolol metabolism and bioavailability in healthy volunteers. Clujul Medical. 2015;88(2):208.

100. Hanif N, Zamir A, Imran I, Saeed H, Majeed A, Rehman Au, et al. Clinical pharmacokinetics of nebivolol: a systematic review. Drug Metabolism Reviews. 2023;55(4):428-40.

101. Cheymol G, Woestenborghs R, Snoeck E, Ianucci R, Moing J-PL, Naditch L, et al. Pharmacokinetic study and cardiovascular monitoring of nebivolol in normal and obese subjects. European journal of clinical pharmacology. 1997;51:493-8.

102. Fongemie J, Felix-Getzik E. A review of nebivolol pharmacology and clinical evidence. Drugs. 2015;75(12):1349-71.

103. Zanchetti A. Clinical pharmacodynamics of nebivolol: new evidence of nitric oxide-mediated vasodilating activity and peculiar haemodynamic properties in hypertensive patients. Blood pressure. 2004;13(sup1):17-32.

104. de Boer RA, Voors AA, van Veldhuisen DJ. Nebivolol: third-generation β-blockade. Expert opinion on pharmacotherapy. 2007;8(10):1539-50.

105. Rosei EA, Rizzoni D. Metabolic profile of nebivolol, a β-adrenoceptor antagonist with unique characteristics. Drugs. 2007;67:1097-107.

106. Priyadarshni S, Curry BH. Nebivolol. StatPearls [Internet]: StatPearls Publishing; 2024.

107. Van Peer A, Snoeck E, Woestenborghs R, Van de Velde V, Mannens G, Meuldermans W, et al. Clinical pharmacokinetics of nebivolol: a review. Drug Investigation. 1991;3:25-30.

108. Olawi N, Krüger M, Grimm D, Infanger M, Wehland M. Nebivolol in the treatment of arterial hypertension. Basic & Clinical Pharmacology & Toxicology. 2019;125(3):189-201.

109. Schellenberg R, Lichtenthal A, Wöhling H, Graf C, Brixius K. Nebivolol and Metoprolol for Treating Migraine: An Advance on β-Blocker Treatment? Headache: The Journal of Head and Face Pain. 2008;48(1):118-25.

110. Erdil N, Kaynak M, Dönmez K, Disli OM, Battaloglu B. Nebivolol in preventing atrial fibrillation following coronary surgery in patients over 60 years of age. Brazilian Journal of Cardiovascular Surgery. 2014;29:581-7.

111. Görenek B, Çalık AN, Kepez A, Öz A, Özmen Ç, Sinan ÜY, et al. Antiarrhythmic Properties of Beta Blockers: Focus on Nebivolol. Int J Cardiovasc Acad. 2024;10(2):22-30.

112. Naidu KCB, Kumar NS, Banerjee P, Reddy BVS. A review on the origin of nanofibers/nanorods structures and applications. J Mater Sci Mater Med. 2021;32(6):68.

113. Manrique C, Whaley-Connell A, Sowers JR. Nebivolol in obese and non-obese hypertensive patients. The Journal of Clinical Hypertension. 2009;11(6):309-15.

114. Zylberman M. ASMA EN SITUACIONES ESPECIALES. REVISTA ARGENTINA DE MEDICINA. 2022;10(Supl. I):25-9.

115. Su J, editor The Heart Failure Treatment of β-Blockers. Proceedings of the 2020 7th International Conference on Biomedical and Bioinformatics Engineering; 2020.

116. Frishman WH. A historical perspective on the development of β-adrenergic blockers. The Journal of Clinical Hypertension. 2007;9:19-27.

117. Oliver E, Mayor Jr F, D'Ocon P. Beta-blockers: historical perspective and mechanisms of action. Revista Española de Cardiología (English Edition). 2019;72(10):853-62.

118. Jack D. Is there a relationship between the physical properties and cardioselectivity of beta-adrenoceptor antagonists? British Journal of Clinical Pharmacology. 1981;11(4):402.

119. Kovács K, Tegze A, Bezsenyi A, Wojnárovits L. Hydroxyl radical induced degradation of the ß-blocker Nadolol and comparison with Propranolol. Journal of Environmental Chemical Engineering. 2023;11(4):110330.

120. Kalsoom S, Zamir A, Rehman AU, Ashraf W, Imran I, Saeed H, et al. Clinical pharmacokinetics of nadolol: A systematic review. Journal of Clinical Pharmacy and Therapeutics. 2022;47(10):1506-16.

121. Jackson EA, Cardoni AA, Blanford MF. Nadolol (Corgard®;—Squibb). Drug Intelligence & Clinical Pharmacy. 1980;14(12):825-30.

122. Dreyfuss J, Shaw JM, Ross JJ. Absorption of the β-adrenergic-blocking agent, nadolol, by mice, rats, hamsters, rabbits, dogs, monkeys, and man: An unusual species difference. Xenobiotica. 1978;8(8):503-8.

123. Heel R, Brogden R, Pakes G, Speight T, Avery G. Nadolol: a review of its pharmacological properties and therapeutic efficacy in hypertension and angina pectoris. Drugs. 1980;20:1-23.

124. Misaka S, Miyazaki N, Yatabe MS, Ono T, Shikama Y, Fukushima T, et al. Pharmacokinetic and pharmacodynamic interaction of nadolol with itraconazole, rifampicin and grapefruit juice in healthy volunteers. The Journal of Clinical Pharmacology. 2013;53(7):738-45.

125. Abe O, Ono T, Sato H, Müller F, Ogata H, Miura I, et al. Role of (−)-epigallocatechin gallate in the pharmacokinetic interaction between nadolol and green tea in healthy volunteers. European Journal of Clinical Pharmacology. 2018;74:775-83.

126. Coumel P, Escoubet B, Attuel P. Beta-blocking therapy in atrial and ventricular tachyarrhythmias: experience with nadolol. American Heart Journal. 1984;108(4):1098-108.

127. Sudilovsky A, Elkind A, Ryan Sr R, Saper J, Stern M, Meyer J. Comparative efficacy of nadolol and propranolol in the management of migraine. Headache: The Journal of Head and Face Pain. 1987;27(8):421-6.

128. Miyazaki N, Misaka S, Ogata H, Fukushima T, Kimura J. Effects of itraconazole, dexamethasone and naringin on the pharmacokinetics of nadolol in rats. Drug Metabolism and Pharmacokinetics. 2013;28(4):356-61.

129. Mehvar R, Brocks DR. Stereospecific pharmacokinetics and pharmacodynamics of beta-adrenergic blockers in humans. 2001.

130. Idéo G, Bellati G, Fesce E, Grimoldi D. Nadolol can prevent the first gastrointestinal bleeding in cirrhotics: a prospective, randomized study. Hepatology. 1988;8(1):6-9.

131. Gatta A, Sacerdoti D, Merkel C, Milani L, Battaglia G, Zuin R. Effects of nadolol treatment on renal and hepatic hemodynamics and function in cirrhotic patients with portal hypertension. American Heart Journal. 1984;108(4):1167-72.

132. Bosch J, Navasa M, Garcia-Pagan J, DeLacy A, Rodes J. Portal hypertension. Medical Clinics of North America. 1989;73(4):931-53.

133. INC AP. Anti-anginal and Antihypertensive Agent. 2015.

134. DiBianco R, Morganroth J, Freitag JA, Ronan Jr JA, Lindgren KM, Donohue DJ, et al. Effects of nadolol on the spontaneous and exercise-provoked heart rate of patients with chronic atrial fibrillation receiving stable dosages of digoxin. American Heart Journal. 1984;108(4):1121-7.

135. Hawkins NM, Petrie MC, MacDonald MR, Jhund PS, Fabbri LM, Wikstrand J, et al. Heart failure and chronic obstructive pulmonary disease: the quandary of beta-blockers and beta-agonists. Journal of the American College of Cardiology. 2011;57(21):2127-38.

136. Realini T. A history of glaucoma pharmacology. Optometry and Vision Science. 2011;88(1):36-8.

137. Heel R, Brogden R, Speight T, Avery G. Timolol: a review of its therapeutic efficacy in the topical treatment of glaucoma. Drugs. 1979;17:38-55.

138. Lyle RE, Budhiraja A, Mehta A, Dahle SE, Isseroff RR. The use of Timolol for wound healing—A review. Current Dermatology Reports. 2024;13(1):8-27.

139. Tan AY, LeVatte TL, Archibald ML, Tremblay F, Kelly ME, Chauhan BC. Timolol concentrations in rat ocular tissues and plasma after topical and intraperitoneal dosing. Journal of Glaucoma. 2002;11(2):134-42.

140. Yordi SF, Pandiri S, Gratton SM. Beta blocker (timolol) eye drops. Migraine Pain Management: Elsevier; 2025. p. 279-87.

141. Sadiq S, Vernon S. Sublingual timolol--an alternative to topical medication in glaucoma? British journal of ophthalmology. 1996;80(6):532-5.

142. Lewis R, Lennard M, Jackson P, Tucker G, Ramsay L, Woods H. Timolol and atenolol: relationships between oxidation phenotype, pharmacokinetics and pharmacodynamics. British journal of clinical pharmacology. 1985;19(3):329-33.

143. Aggarwal D, Kaur IP. Improved pharmacodynamics of timolol maleate from a mucoadhesive niosomal ophthalmic drug delivery system. International journal of pharmaceutics. 2005;290(1-2):155-9.

144. Storgaard L, Tran TL, Freiberg JC, Hauser AS, Kolko M. Glaucoma clinical research: trends in treatment strategies and drug development. Frontiers in medicine. 2021;8:733080.

145. Nezhad NM, Kamali H, Sarchahi AA, Jalalifar S, Amani A, Oroojalian F. Investigating the efficacy of liquid crystal nano cubosomes containing dorzolamide and timolol for drug delivery to the cornea. Journal of Drug Delivery Science and Technology. 2025;106:106724.

146. Xia M, Ding K, Ji Y, Liu W, Liu Y, Zeng Q, et al. The timing and safety of topical timolol treatment for superficial infantile hemangioma: a retrospective cohort study. European Journal of Pediatrics. 2025;184(2):151.

147. Rolle T, Curto D, Alovisi C, Franzone M, Brogliatti B, Grignolo FM. Timogel® vs timolol 0.5% ophthalmic solution: efficacy, safety, and acceptance. European journal of ophthalmology. 2012;22(1):28-33.

148. Tuleski GL, Pscheidt MJGR, Dos Santos JP, Sousa MG. Timolol 0.5% ophthalmic solution influences cardiac function in healthy cats. Journal of Feline Medicine and Surgery. 2022;24(6):e57-e69.

149. del Amo EM. Pharmacokinetic models: Indispensable tools for ophthalmic drug development. ONdrugDelivery. 2022;2022:59-63.

150. Khan MS, Murthy A, Ahmed T. Advancements in Ocular Modelling and Simulations: Key Considerations and Case Studies. AAPS PharmSciTech. 2024;26(1):14.

151. Porada M, Bułdak Ł. From Pathophysiology to Practice: Evolving Pharmacological Therapies, Clinical Complications, and Pharmacogenetic Considerations in Portal Hypertension. Metabolites. 2025;15(2):72.

152. Villanueva C, Tripathi D, Rodrigues SG, Torres F, Ripoll C, Bosch J, editors. β-Blockers to Prevent Decompensation of Cirrhosis in Compensated Patients With Clinically Significant Portal Hypertension. Portal Hypertension VII: Proceedings of the 7th Baveno Consensus Workshop: Personalized Care in Portal Hypertension; 2022: Springer.

153. Jachs M, Reiberger T. Non-selective Beta Blockers in Liver Cirrhosis. Pharmacotherapy for Liver Cirrhosis and Its Complications: Springer; 2022. p. 127-40.

154. Dillon A, Tripathi D. Portal Hypertension: Varices. Liver Disease in Clinical Practice: Springer; 2016. p. 41-56.

155. Hofmann J. Mind Maps in Medical Pharmacology-E-Book: Mind Maps in Medical Pharmacology-E-Book: Elsevier Health Sciences; 2023.

156. Neagoe A-M, Rexhaj E, Grossman E, Messerli FH. Beta blockers and calcium channel blockers. Cardiovascular Hemodynamics: An Introductory Guide. 2019:73-88.

157. Yellepeddi VK, Ismail M, Bunch TJ, Deering TF, Holubkov R, Kennedy R, et al. Population Pharmacokinetics and Pharmacodynamics of Sotalol Following Expedited Intravenous Loading in Patients With Atrial Arrhythmias. CPT: Pharmacometrics & Systems Pharmacology. 2025.

158. Lambarki LZ, Jhilal F, Slimani L, El Hajji R, Bakkali F, Iskandar S, et al. Comparison of approaches for assessing detection and quantitation limits in bioanalytical methods using HPLC for sotalol in plasma. Scientific Reports. 2025;15(1):5472.

159. Sharma G, Sharma A. Recent Insights on Drug Delivery System in Hypertension: From Bench to Market. Current Hypertension Reviews. 2023;19(2):93-105.

160. LaBreck ME, Chopra N, Robinson A, Billakanty SR, Fu EY, Nemer DM, et al. Home sotalol initiation for the management of atrial and ventricular arrhythmias using remote electrocardiographic monitoring. Clinical Electrophysiology. 2025;11(2):386-96.

161. Delpón E, Caballero R, Tamargo J. Class III Antiarrhythmic Drugs. Antiarrhythmic Drugs: Springer; 2025. p. 133-72.

162. Borowicz-Reutt KK, Banach M, Rudkowska M, Stachniuk A. Sotalol does not interfere with the antielectroshock action of selected second-generation antiepileptic drugs in mice. Pharmacological Reports. 2021;73:516-24.

163. Caballero R, Delpón E, Tamargo J. Drug Interactions of Antiarrhythmic Drugs. Antiarrhythmic Drugs: Springer; 2025. p. 311-41.

164. Sus I, Ivanescu A, Dobreanu D. Antiarrhythmic Drugs in Children. Antiarrhythmic Drugs: Springer; 2025. p. 475-90.

165. Buzea CA, Dan AR. Beta-blockers as antiarrhythmic agents. Antiarrhythmic Drugs: Springer; 2025. p. 93-132.

166. Gasperetti A, Targetti M, Olivotto I. Anti-arrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: the importance of optimal beta-blocker dose titration. International Journal of Cardiology. 2021;338:150-1.

167. Mubarik A, Kerndt CC, Patel P, Cassagnol M. Sotalol. StatPearls [Internet]: StatPearls Publishing; 2024.

168. Blokhina SV, Sharapova AV, Ol'khovich MV. Solid-liquid equilibrium and distribution in pharmaceutically relevant media of cardiovascular sotalol hydrochloride. The Journal of Chemical Thermodynamics. 2025;200:107362.

169. Yagnala N, Moreland-Head L, Zieminski JJ, Mara K, Macielak S. Assessment of dofetilide or sotalol tolerability in the elderly. Journal of Cardiovascular Pharmacology and Therapeutics. 2024;29:10742484231224536.

170. Remme CA, Heijman J, Gomez AM, Zaza A, Odening KE. 25 years of basic and translational science in EP Europace: novel insights into arrhythmia mechanisms and therapeutic strategies. Europace. 2023;25(8):euad210.

171. Giacché M, Tacchetti MC, Agabiti-Rosei C, Torlone F, Bandera F, Izzi C, et al. Pheochromocytoma–Paraganglioma Syndrome: A Multiform Disease with Different Genotype and Phenotype Features. Biomedicines. 2024;12(10):2385.

172. Sulashvili N, Nimangre RR. MANIFESTATION OF SOME ASPECTS OF CARDIOVASCULAR DISEASES, IMPLICATIONS, PHARMACOTHERAPEUTIC STRATEGIES, EFFECTS, IMPACTS AND POTENTIAL HAZARDS IN GENERAL. Junior Researchers. 2025;3(1):1-27.

173. Song Y, Woo AY-H, Zhang Y, Xiao R. Cardiac β-adrenoceptor signaling: the new insight on an old target in the therapy of cardiovascular disease. International Journal of Drug Discovery and Pharmacology. 2022:3-.

174. Frishman WH. Carvedilol. New England Journal of Medicine. 1998;339(24):1759-65.

175. Maggi L, Urru C, Friuli V, Ferrara C, Conti DM, Bruni G, et al. Synthesis and Characterization of Carvedilol-Etched Halloysite Nanotubes Composites with Enhanced Drug Solubility and Dissolution Rate. Molecules. 2023;28(8):3405.

176. Carnovale C, Gringeri M, Battini V, Mosini G, Invernizzi E, Mazhar F, et al. Beta-blocker-associated hypoglycaemia: New insights from a real-world pharmacovigilance study. British Journal of Clinical Pharmacology. 2021;87(8):3320-31.

177. Sardar PK, Yeung S, Tow R, Luga J, Huang M, Shahid A, et al. Oral delivery of the non-β-blocking R-carvedilol enantiomer for skin cancer chemoprevention in SKH-1 mice. AAPS Open. 2025;11(1):1.

178. Yadav N, Kushwaha N, Kushwaha SK, Yadav P. Role of Conventional and Novel Classes of Diuretics in Various Diseases. Current Drug Therapy. 2025;20(2):135-48.

179. Embaby MA, El Maghraby GM, Osman MA, Sultan AA. Investigation of the effect of concurrently administered carvedilol, atorvastatin and bile salts on intestinal absorption of linagliptin. Journal of Pharmacy and Pharmacology. 2023;75(5):635-44.

180. Lai JC-T, Dai J, Liang LY, Wong GL-H, Wong VW-S, Yip TC-F. Pharmacological Treatment of Ascites: Challenges and Controversies. Pharmaceuticals. 2025;18(3):339.

181. Del Mauro JS, Prince PD, Allo MA, Plantamura YS, Moretton MA, Gonzalez GE, et al. Effects of third-generation β-blockers, atenolol or amlodipine on blood pressure variability and target organ damage in spontaneously hypertensive rats. Journal of Hypertension. 2020;38(3):536-45.

182. Fravel MA, Ernst M. Drug interactions with antihypertensives. Current hypertension reports. 2021;23:1-8.

183. Jung W, Hubbard RA, Smith AM, Ko K, Huang A, Wang J, et al. Risk-guided cardioprotection with carvedilol in patients with breast cancer (CCT guide): a phase 1 randomized clinical trial. Breast Cancer Research and Treatment. 2025:1-13.

184. Dimza M, Aranda JM. Heart Failure Guideline Directed Medical Therapy: Which One and When? Cardiovascular Innovations and Applications. 2023;8(1):936.

185. Santander Plantamura YA, Allo M, Riedel J, Fuentes P, Riesco AS, Bernabeu E, et al. Development of a new micellar formulation of carvedilol and curcumin to enhance blood pressure reduction in a spontaneously hypertensive rat model. Naunyn-Schmiedeberg's Archives of Pharmacology. 2024:1-13.

186. Elbakry AM, Marzouk MA, Khalil R, Zahran A, ElArini S. Design and Evaluation of Carvedilol Ethosomes using Box-Behnken Design. International Journal for Holistic Research. 2024:1-12.

187. Kumar A, Sinha-Ray S. A review on biopolymer-based fibers via electrospinning and solution blowing and their applications. Fibers. 2018;6(3):45.

188. Sinha S, Lee S, our Team M. Are there any foods I should avoid while taking carvedilol?

189. Brown Jr RS, Brown KA, Flamm S, Bejarano RE, Rahimi RS, Singal AK, et al. Screening and management of portal hypertension and varices in cirrhosis: Expert perspectives. Hepatology Communications. 2025;9(4):e0682.

190. Diaz-Soto MP, Garcia-Tsao G. Management of varices and variceal hemorrhage in liver cirrhosis: a recent update. Therapeutic advances in gastroenterology. 2022;15:17562848221101712.

191. Premkumar M, Rangegowda D, Vyas T, Khumuckham JS, Shasthry SM, Thomas SS, et al. Carvedilol combined with ivabradine improves left ventricular diastolic dysfunction, clinical progression, and survival in cirrhosis. Journal of Clinical Gastroenterology. 2020;54(6):561-8.

192. Sartiani L, Cerbai E. AAD in Patients with Comorbidities. Antiarrhythmic Drugs: Springer; 2025. p. 409-38.

193. Easa J, Easa N, Chappell J, Warriner D. Understanding the pharmacology of heart failure. Journal of Prescribing Practice. 2021;3(10):404-10.

194. Umaid Rauf M, Cross J. Management of High Blood Pressure. Primer on Nephrology: Springer; 2022. p. 335-51.

195. Bansal N, Kathuria D, Babu AM, Dhiman S, Lakhanpal S, Prasad KN, et al. A perspective on small molecules targeting the renin–angiotensin–aldosterone system and their utility in cardiovascular diseases: exploring the structural insights for rational drug discovery and development. RSC Medicinal Chemistry. 2025.

196. Peters JU. Molecular Properties and Structural Motifs Related to Pharmacological Promiscuity. Polypharmacology: Strategies for Multi-Target Drug Discovery. 2025:49-59.

197. Yang Z, Zhao J. Effectiveness of placental blood perfusion monitoring of nitroglycerin and labetalol in treatment of women with pregnancy-induced hypertension. African Journal of Reproductive Health. 2025;29(2):61-8.

198. Ali S, Ahmad Z, Mahmood A, Khan MI, Siddique W, Latif R, et al. Enhanced Transdermal Drug Delivery of Labetalol via Nanoparticle-Loaded Dissolvable Microneedle Patches. BioNanoScience. 2025;15(1):181.

199. Silva MC, Costa Filho RC, Estato V. Strategic Use of Intravenous Medications to Protect Target Organs in Hypertensive Emergencies. International Journal of Cardiovascular Sciences. 2025;38:e20240117.

200. Piotrkowicz E, Skrzypczyk P, Prejbisz A, Dobrowolski P, Gawlak M, Kosiński P. Safety and Risks of Antihypertensive Medications During Breastfeeding: A Review of Current Guidelines. 2025.

201. Conti-Ramsden F, de Marvao A, Chappell LC. Pharmacotherapeutic options for the treatment of hypertension in pregnancy. Expert opinion on pharmacotherapy. 2024;25(13):1739-58.

202. Lazo OLE, White PF, Yumul R, Yumul F, Kariger RK, Kaplan M, et al. Labetalol as an alternative to esmolol and fentanyl for maintaining hemodynamic stability during laparoscopic surgery: Comparative effects on recovery profiles and a literature review. Journal of Surgery and Research. 2020;3(4):444-56.

203. Kumari P, Sharma S, Kumar R, Singh H, Singh N, Kumar P, et al. An overview on global and Indian Scenario of hypertension with clinical agents for their potential pharmacological mechanism. Research Journal of Pharmacology and Pharmacodynamics. 2024;16(1):35-41.

204. Popova K. The Management of Critical Illness in Obstetric Patients. The Pharmacist's Expanded Role in Critical Care Medicine: A Comprehensive Guide for Practitioners and Trainees. 2025:987-1022.

205. Dodeja P, Chaphekar N, Caritis SN, Venkataramanan R. Optimizing drug therapy during pregnancy: a spotlight on population pharmacokinetic modeling. Expert Opinion on Drug Metabolism & Toxicology. 2025;21(2):143-60.

206. Bostock B. Medication for hypertension management. Journal of Prescribing Practice. 2023;5(11):466-72.

207. H Alghamdi R. Enhancing Chemical Adherence Testing through Pharmacokinetics and Pharmacogenetics Insights and Mass Spectrometry Advancements: University of Leicester; 2024.

208. Hazra PK, Mehta A, Desai B, Pandey U, Mehta KD, Bajpai S, et al. Long-acting nifedipine in the management of essential hypertension: a review for cardiologists. American Journal of Cardiovascular Disease. 2024;14(6):396.

209. Tsvirenko S, Rossokha Z. O. Skavinska1, L. Fishchuk1, V. Pokhylko2, Yu. Cherniavska2, O. Yevseienkova3.

210. Greenlees C, Delles C. RAAS inhibitors in pregnancy, breastfeeding and women of childbearing potential: a review of national and international clinical practice guidelines. Journal of Human Hypertension. 2025:1-5.

211. Bokuda K, Ichihara A. Preeclampsia up to date—What's going on? Hypertension Research. 2023;46(8):1900-7.

212. Sánchez R, Coca A, de Salazar DIM, Alcocer L, Aristizabal D, Barbosa E, et al. 2024 Latin American Society of Hypertension guidelines on the management of arterial hypertension and related comorbidities in Latin America. Journal of Hypertension. 2025;43(1):1-34.

213. Lakshmanan M. Antihypertensive Agents. Introduction to Basics of Pharmacology and Toxicology: Volume 2: Essentials of Systemic Pharmacology: From Principles to Practice. 2021:411-9.

214. Ojha U, Ruddaraju S, Sabapathy N, Ravindran V, Worapongsatitaya P, Haq J, et al. Current and emerging classes of pharmacological agents for the management of hypertension. American Journal of Cardiovascular Drugs. 2022:1-15.

215. Karunarathna I, Jayawardana A. Propranolol therapeutic uses and toxicity management. Retrieved from ResearchGate: https:// www. researchgate. net/publication …; 2024.

216. Li H, Zhang Z, Yang S, Zhu G. Systematic review and meta-analysis of propranolol in the prevention and treatment of post-traumatic stress disorder. Frontiers in Pharmacology. 2025;16:1545493.

217. Lacassia C, Cutrignelli A, la Forgia FM, Fontana S, Lopalco A, Denora N, et al. Evaluation of Five Ready-to-Use Bases for the Topical Administration of Propranolol Hydrochloride to Treat Infantile Hemangioma. Pharmaceutics. 2025;17(1):83.

218. Szeleszczuk Ł, Bethanis K, Christoforides E, Pisklak DM. Combining X-ray and NMR crystallography to explore the structural disorder in racemic propranolol hydrochloride. CrystEngComm. 2025;27(3):433-46.

219. Moghimipour E, Khazali M, Makhmal-Zadeh BS, Abedini Baghbadorani M, Zangeneh A, Sohrabi S, et al. Development of propranolol loaded SLN for transdermal delivery: in-vitro characterization and skin deposition studies. Therapeutic Delivery. 2025:1-11.

220. Kaur D, Gupta A, Singh N, Dhakate SR. Anti-emetic drug delivery for cancer patients through electrospun composite nanofibers transdermal patch: in vitro study. Advanced Materials Letters. 2015;6(1):33-9.

221. Wilson JF. Propranolol. Drugs Eicosanoids: Second Messengers November 1995: Springer; 1995. p. 1604-5.

222. Lee C-M, Jung E-H, Cho C-K, Oh K-Y, Shin H-B, Lim C-W, et al. Physiologically Based Pharmacokinetic Modeling of Propranolol in Relation to CYP2D6 Genotypes. The FASEB Journal. 2020;34(S1):1-.

223. Karunarathna I, Dius S, Ranwala R, Bandara S, Godage S, Rodrigo P, et al. Propranolol: Mechanisms, Efficacy, and Safety Considerations.

224. Tsai M, Case M, Ardayfio P, Hochstetler H, Wilbraham D. Effects of lasmiditan on cardiovascular parameters and pharmacokinetics in healthy subjects receiving oral doses of propranolol. Clinical pharmacology in drug development. 2020;9(5):629-38.

225. Isoardi KZ, Chiew AL, Do C, Humphreys M, Mustafa A, Roberts MS, et al. A prospective study of acute propranolol overdose defining dose thresholds of severe toxicity (ATOM–9). Clinical Toxicology. 2025;63(1):1-9.

226. Nakafero G, Grainge MJ, Valdes AM, Townsend NP, Mallen C, Zhang W, et al. Propranolol reduces risk of knee or hip replacement due to osteoarthritis: A propensity score matched cohort study-using data from the Clinical Practice Research Datalink. NIHR Open Research. 2023;3:51.

227. Ren L, Xu X, Liu X, Ning H, Ding Q, Yang M, et al. Recent Advances in Propranolol Hydrochloride Formulations for the Treatment of Infantile Hemangiomas. Drug Design, Development and Therapy. 2025:1163-83.

228. Zhao M, Wang Y, Chen M, Wu B. Introduction to Pharmacokinetics. Circadian Pharmacokinetics. 2020:23-40.

229. Tchivileva IE, Hadgraft H, Lim PF, Di Giosia M, Ribeiro-Dasilva M, Campbell JH, et al. Efficacy and safety of propranolol for treatment of temporomandibular disorder pain: a randomized, placebo-controlled clinical trial. Pain. 2020;161(8):1755-67.