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# Use of metoprolol as a relevant therapeutic agent in patients with cardiovascular disorders: A review

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## ABSTRACT

This chapter has gathered scientific evidence on metoprolol as a pharmacological tool in various cardiovascular diseases. METHODOLOGY: This is a systematic review in which scientific articles published in Pubmed databases between 2021 and 2022 were selected. The following descriptors were used: metoprolol or pharmacokinetic, pharmacodynamics, efficacy, adverse effect, combined by means of the AND operator. A total of 46 articles were found, of which 17 met the selection criteria and, therefore, are included in this study. RESULTS: Regarding the clinical use of metoprolol, it was beneficial in the treatment of arrhythmias after resection of hepatocarcinoma, in cardiac improvement in patients with permanent pacemaker, in individuals with obstructive hypertrophic cardiomyopathy, and in addition to having been cited in the increase in survival in patients with type B aortic dissection. has been shown to be beneficial in both heart failure and carotid atherosclerosis, as well as hypothalamic obesity. With regard to adverse events, patients on metoprolol were more prone to nightmares than those exposed to another beta-adrenergic antagonist drug, such as carvedilol or labetalol. In addition, when compared with another drug, it did not have an advantage over esmolol for performing CT angiography and was less effective in antihypertensive therapy of men with erectile dysfunction. Finally, with regard to new methods of detection or therapeutic intervention of the use of metoprolol, one study was successful in discovering a new way to quantify metoprolol in rat plasma, while another recent study addressed relevant considerations in personalized therapy of the drug, based on the genetic polymorphism of CYP2D6.

CONCLUSION: The present systematic review corroborates updates on the use of Metoprolol found in the current literature, contributing to the institution of personalized therapy for patients with cardiovascular disease.

**Keywords:** Clinical pharmacology, Metoprolol, Cardiovascular diseases, Therapeutic Advancement.

## 1 INTRODUCTION

Metoprolol is a drug approved by the FDA in the treatment of diseases such as: angina, heart failure, myocardial infarction, arrhythmias and hypertension; in addition to being also recommended for thyroid crisis and circumscribed choroid hemangioma (ZAMIR *et al.*, 2022). It is also a cardioselective antagonist of adrenergic receptors (as well as atenolol), which competitively blocks β-1 adrenergic receptors with minimal or no effects on β-2 adrenergic receptors (MORRIS; DUNHAM, 2022).

According to Brunton *et al.* (2018), metoprolol has low bioavailability (approximately 40%), due to its first-pass biotransformation. It is a substance metabolized in the liver, in which CYP2D6 is the main enzyme involved, and only 10% of the administered drug is recovered in the urine unchanged.

As for therapeutic use, this drug reduces myocardial oxygen consumption, improves cardiac function and reduces the burden of atrial fibrillation, while improving QT interval dispersion (YE *et al.*, 2022). In continuity, it is also an antiarrhythmic  for ventricular arrhythmias after AMI, in the prevention of paroxysmal crises of atrial fibrillation when these occur in a situation of sympathetic activation, in heart failure, where it is indicated for all patients (even asymptomatic), as it is associated with improved survival. (RITTER *et al.*, 2020). In hypertension, its use is no longer 1st line and is indicated in specific cases in which there is an association with another disease for which this drug is indispensable, or in specific cases of hypertensive crisis (such as acute aortic dissection) (BRUNTON *et al.*, 2018).

In addition to these classic applications, several studies have been developed in order to analyze the functionality of metoprolol in other cardiovascular diseases, a fact that reaffirms its relevance before the current pharmacology.

## 2 METHODOLOGY

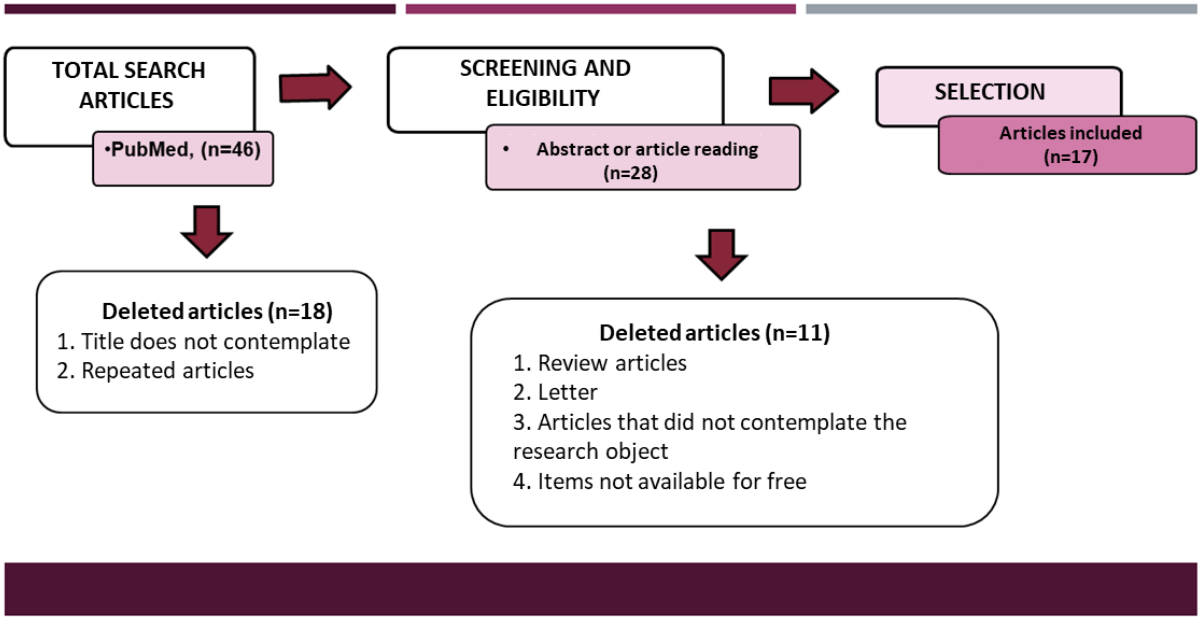
For the development of the work, a careful search of original scientific articles published in the PubMed databases was carried out, using the descriptors metoprolol or pharmacokinetic, pharmacodynamic, efficacy, adverse effect combined by means of the Boolean operator AND, according to the guidelines recommended by PRISMA.

The inclusion criteria were the original studies, which presented the descriptors in the title or abstract and written in English. Articles written in languages other than English were excluded, in

addition to those whose title or abstract/abstract did not fit the proposed theme. Comments, books, literature reviews and articles not available for free access were also excluded.

The collection of bibliographic data between 2021 and 2022 resulted in a total of 46 scientific articles. After extensive analyses, only 17 studies met all the selection criteria and were included in this study, as shown in Figure 1.

Figure 1: Diagram of recovery and selection of evidence of bibliographic research according to the guidelines of PRISMA.




Source: Own elaboration.

## 3 RESULTS

After using the inclusion and exclusion criteria, it was verified that PubMed presents 17 manuscripts that address pharmacological aspects of Metoprolol. Tables 1 and 2 show a brief description of the studies included in this study, highlighting the type of study, place of execution and the main findings. The 17 studies included in this review deal with biological assays (n=05) and clinical trials (n=12).

Thematically, the following division was found: 07 clinical studies address the clinical use of Metoprolol, and 03 of these evaluate the effects of when another drug is added to the therapeutic regimen with Metoprolol; one (01) clinical study addresses therapeutic equivalence; one (01) clinical study evaluated an adverse event of β-blockers, including Metoprolol; 02 clinical studies have shown therapeutic advantages of another β-blocker over Metoprolol; 01 clinical study and 03 biological studies analyzed pharmacological interactions of Metoprolol; and 02 biological studies presented the development of new pharmacokinetic methods of detection or therapeutic intervention of the use of Metoprolol.

Table 1 – Scientific studies of biological assays that address the pharmacokinetic aspects for metoprolol.

| Title | Country | Sample/Study Method | Findings | Reference |
|---|---|---|---|---|
| Development and validation of a LC-MS/MS method for simultaneous quantification of Ivabradine and Metoprolol in rat plasma | India | *In vitro. Validation of a* bioanalytical method LC-MS/MS that can quickly and accurately estimate the values of Ivabradine and Metoprolol, simultaneously, in the plasma of 06 Albino Wistar rats. | The accuracy was between 99.71 to 100.3% for ivabradine and 99.9 to 100.31% for metoprolol. The intra- and inter-day accuracy ranged from 0.048 to 12.68% CV for ivabradine and 0.1 and 2.66% CV for Metoprolol. The established method was accurate and adequate to determine Ivabradine and Metoprolol simultaneously in plasma samples from rats. | Eswarudu *et al*. (2022) |
| Gut microbiota and host Cyp450s co-contribute to pharmacokinetic variability in mice with non-alcoholic steatohepatitis: Effects vary from drug to drug | China | *In vivo.* 32 rats. This study aimed to analyze the effects of gut microbiota and host CYP450 on the pharmacokinetic variability of omeprazole, metoprolol, midazolam, tolbutamide, phenacetin and chlorzoxazone in rats submitted to nonalcoholic steatohepatitis (NASH). | As for Metoprolol, it was observed that: there was no significant increase in its plasma exposure when administered intragastric or intravenously in the study group; analysis of pharmacokinetic parameters showed that the gut microbiota and host CYP450 exerted minimal effects on the pharmacokinetic variability of metoprolol. | Guo *et al*. (2022) |
| Inhibitory effects of fluoxetine and duloxetine on the pharmacokinetics of metoprolol in vivo and in vitro | China | *In vivo* and *in vitro* with 18 Sprague-Dawley rats. This study aimed to compare the effects of duloxetine and fluoxetine on the metabolism of metoprolol. | *In vitro*, duloxetine showed more significant inhibitory potential when compared to fluoxetine, but major pharmacokinetic parameters revealed differences in inhibition of metoprolol metabolism, showing to be more susceptible to fluoxetine in *vivo*. | Xu *et al*. (2022) |
| Physiologically Based Pharmacokinetic Modeling to Assess the Impact of CYP2D6-Mediated Drug-Drug Interactions on Tramadol and O-Desmethyltramadol Exposures via Allosteric and Competitive Inhibition | United States | *In silico* with PBPK model developed by PK-Sim® 8.0 Software. This study aimed to compare the impact of reversible allosteric/competitive inhibition on CYP2D6 when Quinidine/Metoprolol was co-administered with Tramadol and O-desmethyltramadol. | Tramadol increases the plasma exposure of Metoprolol by 50% when co-administered. If doses are separated by 2 hours, an increase of less than 20% in the plasma exposure of Metoprolol has been predicted. | Long *et al*. (2022) |
| Physiologically based pharmacokinetic modelling to predict the pharmacokinetics of metoprolol in different CYP2D6 genotypes | South Korea | *In vitro* and *in silico* with PBPK model developed by PK-Sim® 7.4 Software. The objective of this study was to develop a model of Metoprolol related to the genetic polymorphism of CYP2D6 for use in personalized therapy. | The developed PBPK model predicts AUC, C max, Tmax and T1/2 of the different CYP2D6 genotypes for Metoprolol in individuals of various races and ages. | Lee *et al*. (2022) |

Source: Own elaboration.

Table 2: Clinical trials addressing pharmacological advances for metoprolol.

| Title | Country | Sample/Study Method | Findings | Reference |
|---|---|---|---|---|
| β-adrenoceptor antagonists and nightmares: A pharmacoepidemiological- pharmacodynamic study | France | Cross-sectional observational study of pharmacovigilance in VigiBase®, analyzing 1138 cases of nightmares reported as an adverse effect of the use of β-adrenergic antagonists. | Pindolol, Metoprolol and Alprenolol were associated with increased risk of nightmares as an adverse effect. | Garcia *et al.* (2021) |
| A randomized, cross-over trial of metoprolol succinate formulations to evaluate PK and PD end points for therapeutic equivalence | United States | This is a prospective, randomized, crossover clinical experimental analytical study with adult patients with primary hypertension to compare the therapeutic equivalence of brand-name and two generic Sustained Release Metoprolol Succinate. The final study sample was 36 patients. | The pharmacokinetic parameters AUC and Cmax, as well as the hemodynamic parameters ambulatory BP, 24-hour HR and HRV were similar between the products. Tmax of branded Metoprolol was significantly higher than that of generic 01 and significantly lower than that of generic 02. | Mosley *et al.* (2022) |
| Co-prescription of metoprolol and CYP2D6-inhibiting antidepressants before and after implementation of an optimized drug interaction database in Norway | Norway | Cross-sectional retrospective observational study of drug dispensing data retrieved from the Norwegian Prescription Database during a 1-year period prior (2007) and two 1-year periods after (2012 and 2017) the implementation of a drug interaction database, which analyzed the co-prescribing rate of metoprolol and CYP2D6 inhibitor antidepressants. | The co-prescribing rate of metoprolol with CYP2D6 inhibitors decreased by 21% 5 years after database implementation and by 40% after 10 years. Compared with atenolol/bisoprolol users, patients treated with metoprolol were significantly less likely to be prescribed a CYP2D6 inhibitor antidepressant in the two post-implementation periods. | Gedde-Dahl *et al.* (2022) |
| Dynamic Electrocardiogram under P Wave Detection Algorithm Combined with Low-Dose Betaloc in Diagnosis and Treatment of Patients with Arrhythmia after Hepatocarcinoma Resection | China | Clinical experimental analytical study to evaluate the diagnostic value of the Dynamic ECG based on the P-wave detection algorithm for arrhythmia after hepatectomy in 60 patients with primary liver cancer, and to compare the therapeutic effect of different doses of Betaloc. | The study group that used the lowest dosage of Betaloc (≤ 47.5 mg) reached the lowest values of systolic and diastolic BP, levels of pre -pro-BNP and incidence of adverse effects, as well as the highest effective rate of improvement of cardiac function. | Jiang *et al.* (2021) |
| Effects of Metoprolol Succinate Combined with Entresto on Cardiac Function Indexes and Coagulation Function in Patients with Congestive Heart Failure | China | Clinical experimental analytical study to analyze the combination of Metoprolol with Entresto (Sacubitril-Valsartan) in 120 patients with Congestive Heart Failure. | There was improvement in cardiac, hemodynamic, vascular, endothelial, oxidative and coagulation parameters. The study group obtained more significant rates of improvement, with 3.33% of side effects. | Ding *et al.* (2022) |
| Efficacy of metoprolol plus atorvastatin for carotid atherosclerosis and its influence on carotid intima-media | China | Retrospective clinical experimental analytical study to analyze the effects of combining Metoprolol with Atorvastatin in 90 | The analysis showed that the study group presented: significant reduction in carotid intima-media thickness indices, | Chen *et al.* (2022) |

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|---|---|---|---|---|
| thickness and homocysteine level | | patients with carotid atherosclerosis. | atherosclerotic plaque score, homocysteine levels, cytokines CRP and MMP-9, and coagulation factors. Lipid levels showed significant improvement only in the study group. | |
| Metoprolol Improves Myocardial Remodeling and Cardiac Function in Patients with Permanent Pacemaker Implantation | China | This is a randomized, clinical experimental analytical study with 90 patients submitted to permanent double-chamber pacemaker implantation. This study aimed to compare the effect of metoprolol on myocardial remodeling as well as on cardiac function in patients with permanent pacemakers. | Until the first week after pacemaker implantation, there was no significant difference in cardiac function between the control and study groups. 12 months after surgery, serum levels of IL-6 and TNF-α were lower in the study group, suggesting the myocardial protective properties of metoprolol. | Ye *et al.* (2022) |
| Nebivolol protects erectile functions compared to Metoprolol in hypertensive men with atherogenic, venogenic, psychogenic erectile dysfunction: A prospective, randomized, cross-over, clinical trial | Turkey | This is a clinical, prospective, randomized, crossover trial analytical study with 73 married men who maintained blood pressure above 140/90 mmHg and met the SEP and IIEF-5 tests for Erectile Dysfunction. This study aimed to compare the effects of Nebivolol and Metoprolol on cardiac and sexual functions and plasma NO levels. Of the total number of participants, 61 completed the study. | There was no difference in antihypertensive efficacy between the two drugs. Unlike Nebivolol, Metoprolol caused a significant decrease in the IIEF-5 score. After 4 weeks of treatment, baseline plasma NO levels did not change with the use of Metoprolol, but increased with Nebivolol. There was a positive correlation between plasma NO values and the IIEF-5 score used to assess sexual functions. | Gungor *et al.* (2022) |
| Prospective Clinical Trial Comparing IV Esmolol to IV Metoprolol in CT Coronary Angiography: Effect on Hemodynamic, Technical Parameters and Cost | Canada | This is a clinical, prospective and randomized experimental analytical study with 28 patients who underwent Coronary Computed Tomography Angiography. The objective of this study was to compare the use of IV Esmolol with IV Metoprolol to achieve HR of 60 bpm during the examination, analyzing hemodynamic response, image quality, radiation dose and cost. | Both Esmolol IV and Metoprolol IV reached the CF target. Esmolol IV resulted in a significantly less profound and shorter reduction in systolic BP than IV Metoprolol after the examination. There was no significant difference in HR, image acquisition, exposure window, radiation dose and image quality. The total cost of care for Esmolol IV was comparable with Metoprolol IV. | Vimala *et al.* (2022) |
| Randomized controlled trial of Tesomet for weight loss in hypothalamic obesity | Denmark | Phase 02, randomized, double-blind, placebo-controlled, clinical experimental analytical study with 21 adults with hypopituitarism and consequent hypothalamic obesity. The objective of this study was to analyze the safety and efficacy of Tesomet (0.5 mg Tesofenin | Adverse events related to the use of Tesomet were mild. There was no significant difference observed in HR and BP between the groups. Compared to placebo, Tesomet resulted in significant weight loss, an increase in the number of patients who were able to lose equal to or more than | Huynh *et al.* (2022) |

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|---|---|---|---|---|
| | | / 50 mg Metoprolol). Of the total number of participants, only 18 completed the study. | 5% of weight, and a tendency to increase abdominal waist reduction. | |
| Randomized Trial of Metoprolol in Patients With Obstructive Hypertrophic Cardiomyopathy | Denmark | Clinical experimental analytical study, monocentric, randomized, double-blind, placebo-controlled, with 29 patients with Hypertrophic Obstructive Cardiomyopathy. The objective of this study was to analyze the left ventricular outflow blood flow gradient, symptoms and exercise capacity. | The treatment with Metoprolol presented: significantly lower left ventricular outflow blood flow pressure gradient at rest, at peak exercise and post-exercise; improvement of symptomatology; no difference in exercise duration or load capacity achieved; oxygen uptake at peak exercise was comparable with placebo, with no difference observed in the METS achieved. | Dybro *et al.* (2022) |
| The Effect of Intravenous and Oral Beta-Blocker Use in Patients with Type B Thoracic Aortic Dissection | United States | Retrospective cross-sectional observational study with data extracted from Premier Healthcare between June/2009 and March/2015. The objective is to analyze the use of beta-blockers (oral or IV) in patients with type B thoracic aortic dissection. | In patients with non-traumatic thoracic aortic dissection, oral beta-blocker use was associated with significant protection against in-hospital mortality and stroke after repair. Metoprolol was the only type of intravenous beta-blocker associated with improved survival. | Nejim *et al.* (2022) |

Source: Own elaboration.

Jiang *et al*. (2021) aimed to study the diagnostic value of the Dynamic Electrocardiogram (ECG) based on the P-wave detection algorithm for arrhythmia after hepatectomy in patients with primary liver cancer, and to compare the therapeutic effect of different doses of Betaloc (Sustained Release Metoprolol Succinate). For this, the authors selected 60 patients with arrhythmia after hepatectomy for primary liver cancer, being equally divided into 04 groups: control group (no Betaloc was used), DS group (with dose equal to or less than 47.5 mg), MD group (with dose between 47.5 and 95 mg) and HD group (with dose between 142.5 and 190 mg). As results related to the use of Betoloc after diagnosis of arrhythmia by the proposed algorithm, the authors found that: systolic (SBP) and diastolic (DBP) blood pressures in the DS, MD and HD groups were significantly lower than in the control group after 02 weeks of treatment, especially for the DS group; the heart rate (HR) of the DS group after 02 weeks of treatment was significantly lower than that of the control and HD groups; the pre-pro-BNP of the DS group was notably lower than that of the other groups; the effective rate of improvement in cardiac function in the DS group was significantly higher than in the other groups; the incidence of complications in the control, DS, MD and HD groups were 34.6%, 12.4%, 20.5% and 32.5%, respectively. Therefore, it is concluded that a small dose of Betaloc is safe and effective for the treatment of arrhythmia after resection of primary hepatocarcinoma.

In addition, Metoprolol has been shown to be effective in improving myocardial remodeling and cardiac function in patients who have had a permanent pacemaker implantation. Ye *et al*. (2022) enrolled 90 patients undergoing double-chamber pacemaker implantation surgery, which were divided into two equal groups of 45 people, one of these being the control group and the other, exposed to metoprolol more previously, where in the 12-month postoperative evaluation, the cardiac function index and heart rate variability (HRV) of patients treated with metoprolol were better, and the incidence of adverse events at 12 months postoperatively also lower, which indicates an effective use of metoprolol after definitive pacemaker implantation in improving the function of the cardiac pump of patients, regulating the function of the sympathetic and vagus nerves, and reducing the risk of adverse events (including postoperative hypotension, ventricular tachycardia, and dyspnea), in addition to acting in the prevention of ventricular arrhythmias.

In addition, metoprolol has been shown to be beneficial in patients with Obstructive Hypertrophic Cardiomyopathy. Dybro *et al*. (2022) aimed to analyze the effect of Metoprolol Succinate on reducing the left ventricular outflow blood flow gradient, symptoms and exercise capacity in patients with this CVD. For this, the authors conducted a monocenter, randomized, double-blind, placebo-controlled study with 29 cases of Obstructive Hypertrophic Cardiomyopathy.

Moreover, some studies have pointed out that the best therapeutic option is the use of Metoprolol combined with another drug. For Congestive Heart Failure (CHF), Ding *et al*. (2022) aimed to analyze the combination of Metoprolol Succinate with Entresto (Sacubitril-Valsartan) in cardiac function, endothelial vascular function, oxidative stress and coagulation function. After the 14-day treatment, the authors found as results that: the efficacy rate of the study group was higher than that of the control group; left ventricular ejection fraction (EF) increased; left ventricular diameters at the end of systole and diastole decreased; levels of calcitonin gene-related peptide (CGRP) and nitric oxide (NO) increased; endothelin (ET) level decreased; levels of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) increased; malondialdehyde levels decreased; levels of partially activated prothrombin time (aPTT), prothrombin time (PT), and fibrinogen (FIB) decreased.

Also, Chen *et al*. (2022) aimed to analyze the effects of combining Metoprolol with Atorvastatin in the treatment of Carotid Atherosclerosis, more specifically Sustained Release Metoprolol Succinate at the maximum tolerated dose of 95 mg/day after gradual increase and Metoprolol and Atorvastatin, this at a dosage of 20 mg/day. The authors found that, after 24 weeks of treatment: there was a significant reduction in carotid intima-media thickness indices, atherosclerotic plaque score, homocysteine levels, and the two inflammatory cytokines detected (high-sensitivity C-Reactive Protein, or CRP; and Matrix Metalloproteinase 9, or MMP-9), for both groups, but with a reduction to lower values for the group that used Metoprolol with Atorvastatin; there was a significant improvement in blood lipid levels in the study group, with no statistically significant differences in the

control group; there was a significant improvement in coagulation factors - TT, PT, aPTT and FIB - in both groups, however, with significant differences in the post-treatment period. Of the 90 patients, 12 did not have any improvement in carotid atherosclerotic plaque and, according to the authors, the factors that affected efficacy were: advanced age (greater than or equal to 65 years), established coronary disease, established cerebral infarction, and high atherosclerotic plaque score (4 points).

### 3.1 THERAPEUTIC ADVANTAGES OVER METOPROLOL

The use of IV Esmolol was comparable with IV Metoprolol for coronary computed tomography angiography. Vimala *et al*. (2022) aimed to compare the two drugs, which are used to achieve HR of 60 beats per minute (bpm) during the examination, analyzing the hemodynamic response, image quality, radiation dose and cost. For this, they conducted β a prospective and randomized clinical study with 28 patients, of which 14 underwent the examination with Metoprolol IV and the others with Esmolol IV. The authors obtained as results that: both groups reached the HR target; Esmolol IV resulted in a significantly less profound and shorter reduction in SBP than Metoprolol IV; there was no significant difference in HR, image acquisition, exposure window, radiation dose and image quality. Although IV Esmolol is more expensive, the total cost of care was comparable with Metoprolol IV, as the post-examination observation period was reduced due to the rapid restoration of hemodynamic status.

In addition, Metoprolol has been shown to be less effective in antihypertensive therapy in men complaining of erectile dysfunction. Gungor *et al*. (2022) aimed to investigate the effects of Nebivolol and Metoprolol on the erectile functions of men with hypertension. For this, they conducted a prospective, randomized, crossover clinical study with 73 married men who maintained blood pressure above 140/90 mmHg. Those who answered negatively to the questions of the SEP (Sexual Encounter Profile) test and/or scored below 21 in the IIEF-5 (International Index of Erectile Function) score were considered to have Erectile Dysfunction (ED). Two groups of patients were made, which followed the regimen: in the 1st month, one group used Nebivolol Hydrochloride, 5 mg; and the other, Metoprolol Succinate, 50 mg, once a day; in the 2nd month, the participants did not use any β-blocker; In the 3rd month, the groups changed the β-blockers used in the 1st month of the study. Of the total, 61 patients completed the study, of which: 13 did not have ED; 27 had psychogenic ED; 10 had arteriogenic ED; and 11 had venogenic ED. The main results were: there is no difference in antihypertensive efficacy between the two drugs; unlike nebivolol, metoprolol caused a significant decrease in the IIEF-5 score of the 61 patients; in the group that did not have ED, both drugs significantly decreased the IIEF-5 score, but the decrease caused by Metoprolol was greater; after 4 weeks of treatment, baseline plasma NO levels did not change with the use of Metoprolol, but increased with Nebivolol; there is a positive

correlation between plasma NO values and the IIEF-5 score. The authors concluded that Nebivolol may be advantageous in terms of preserving sexual functions due to the increase in NO.

## 3.2 PHARMACOLOGICAL INTERACTIONS

The combination of the use of antidepressants and cardiovascular drugs is common, increasing the possibility of drug interaction. Thinking about it, Xu *et al*. (2022) aimed to compare the effects of Duloxetine and Fluoxetine on the metabolism of Metoprolol. For this, 18 Sprague-Dawley rats were randomized and equally divided into three groups: group A (received Metoprolol orally), group B (received Metoprolol and Fluoxetine orally) and group C (received Metoprolol and Duloxetine orally). Blood samples were collected and analyzed. In addition, *an in vitro* study was performed by incubating liver microsomes and CYP2D6.1 with Metoprolol and submitting them to Fluoxetine and Duloxetine. The authors obtained as results of the *in vivo* study: the administration of Fluoxetine and Duloxetine significantly increased the area on the plasma concentration-time curve and from 0 to infinity (AUC(0-infinity)) of Metoprolol; there are significant pharmacokinetic differences between Fluoxetine and Duloxetine in plasma concentration. The authors obtained as results of the *in vitro* study: Fluoxetine and Duloxetine inhibited the metabolism of Metoprolol via mixed competitive mechanism of cytochrome P450; the values of the semi-maximum inhibitory concentration (CI 50) of Fluoxetine and Duloxetine were 12.86 and 2.51 μM, respectively; the metabolism rate of Metoprolol was inhibited in 19.62% and 17.14% in CYP2D6.1 by Fluoxetine and Duloxetine, respectively. *In vitro*, duloxetine showed more significant inhibitory potential when compared to fluoxetine, but the main pharmacokinetic parameters revealed differences in the inhibition of metoprolol metabolism, showing that it is more susceptible to fluoxetine in *vivo*.

Knowing the interaction of Metoprolol with CYP2D6 inhibitor antidepressants, the frequency of its prescription also changes. Of this, Gedde-Dahl *et al*. (2022) analyzed this co-prescribing before and over a 10-year period after the implementation of an optimized drug interaction database in clinical decision support systems in Norway. Data from all individuals who received beta-blockers and antidepressants were retrospectively analyzed in the years 2007 (pre-implementation period), 2012 (post-implementation with database in the pharmacy computer system) and 2017 (post-implementation with database in pharmacies and physicians' electronic health record systems). A total of 23,341, 23,848, and 22,328 individuals received co-prescribed beta-blockers and antidepressants in 2007, 2012, and 2017, respectively, which constituted 8 to 9 percent of all persistent beta-blocker users each year. Metoprolol was the most frequently prescribed β-blocker, received by 67%, 72%, and 74% of the study population in 2007, 2012, and 2017, respectively. The proportion of metoprolol users prescribed CYP2D6 inhibitor antidepressants gradually decreased from 9.4% in 2007 to 7.4% in 2012 and 5.6% in 2017. Therefore, this study showed that the co-prescribing rate of metoprolol and potent CYP2D6-

inhibiting antidepressants was significantly reduced after the implementation of an optimized drug interaction database that provides recommendations on alternative drugs without interaction. After this implementation, the co-prescribing rate of metoprolol and potent CYP2D6 inhibitor antidepressants decreased by 21% and 40% after 5 and 10 years, respectively.

Another common combination is medications for cardiovascular disease and chronic pain, specifically opioids. Long *et al*. (2022), using a physiologically-based pharmacokinetic model (PBPK), compared the impact of allosteric inhibition caused by quinidine and reversible competitive inhibition caused by metoprolol on CYP2D6 with Tramadol and its active metabolite, O-desmethyltramadol. The authors found in this in *silico study* with simulation using PK-Sim® 8.0 software that Tramadol increases the plasma exposure of metoprolol by almost 50% when administered together. This can be significantly mitigated by separating the doses – and they cite as an example that if the doses are separated by 02 hours, an increase in the plasma exposure of Metoprolol by less than 20% has been predicted. Finally, the authors consider it necessary future studies to understand the clinical outcomes of this interaction, resulting from β2 adrenergic blockade – such as bronchoconstriction, bronchospasm and vasoconstriction.

## 4 CONCLUSION

In addition to the well-established clinical use of Metoprolol for various cardiovascular pathologies, such as heart failure and hypertension, new studies have pointed to its beneficial effects in the personalized treatment of patients, such as in the development of arrhythmias after resection of hepatocarcinoma, in the implantation of a permanent pacemaker, in patients with obstructive hypertrophic cardiomyopathy or with type B aortic dissection. it was possible to observe when the combination therapy of Metoprolol brings more benefits to patients with heart failure, carotid atherosclerosis, or hypothalamic obesity, for example. Other studies have pointed out interchangeability, adverse events, therapeutic disadvantages and pharmacological interactions that Metoprolol may present during its clinical use.

Thus, the present systematic review corroborates updates of the use of Metoprolol found in the current literature, contributing to the institution of personalized therapy for patients with cardiovascular disease.

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