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REVIEW ARTICLE

Clinical pharmacokinetics of nebivolol: a systematic review

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ABSTRACT

Nebivolol is a beta-1 receptor blocker used to treat hypertension, heart failure, erectile dysfunction, vascular disease, and diabetes mellitus. This review investigated the data regarding pharmacokinetic (PK) parameters, drug-drug interactions, dextrorotatory (D), and levorotatory (L) stereoisomers of nebivolol. The articles related to the PK of nebivolol were retrieved by searching the five databases; Google Scholar, PubMed, Cochrane Library, ScienceDirect, and EBSCO. A total of 20 studies comprising plasma concentration-time profile data following the nebivolol's oral and intravenous (IV) administration were included. The area under the concentration-time curve from zero to infinity ($AUC_{0-\infty}$) was 15 times greater in poor metabolizers (PMs) than in extensive metabolizers (EMs). In hypertensive patients, L–nebivolol expressed a higher maximum plasma concentration (C_{max}) than D–nebivolol, i.e. 2.5 ng/ml vs 1.2 ng/ml. The $AUC_{0-\infty}$ of nebivolol was 3-fold greater in chronic kidney disease (CKD). The clearance (CL) was increased in obese than in controls from 51.6 ± 11.6 L/h to 71.6 ± 17.4 L/h when 0.5 mg/ml IV solution was infused. Nebivolol showed higher C_{max}, $AUC_{0-\infty}$ and half-life ($t_{1/2}$) when co-administered with bupropion, duloxetine, fluvoxamine, paroxetine, lansoprazole, and fluoxetine. This concise review of nebivolol would be advantageous in assessing all PK parameters, which may be crucial for clinicians to avoid drug-drug interactions, prevent adverse drug events and optimize the dosage regimen in diseased patients diagnosed with hypertension and cardiovascular disorders.

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Nebivolol; beta-blockers; PK parameters; systematic review; D and L enantiomers; CYP2D6 genotype; hypertension

1. Introduction

Nebivolol is a third-generation, long-acting, cardioselective β_1-adrenoreceptor antagonist, approved by the United States Food and Drug Administration (FDA) in December 2007 for the treatment of hypertension (Wojciechowski and Papademetriou 2008; Fongemie and Felix-Getzik 2015). It is effective in diabetes mellitus, erectile dysfunction, vascular disease, and angina pectoris, along with its off-label use in heart failure (Cheng 2009; Priyadarshni and Curry 2022). Nebivolol is highly selective for the β_1 receptor blockade, promoting vasodilation through endothelium-dependent nitric oxide (NO) stimulation (Toblli et al. 2012). Nebivolol differs from other β-blockers due to its unusual vasodilatory activity by L-arginine–NO pathway (Gray and Ndefo 2008). Nebivolol is a racemate of dextrorotatory (D) and levorotatory (L) enantiomers, among which D–nebivolol involves in β_1-receptor blocking activity, whereas L–nebivolol exhibits vasodilator properties (Marketou et al. 2017). It is mainly administered through the extravascular route (Priyadarshni and Curry 2022).

Nebivolol is a Biopharmaceutics Classification System (BCS) class II drug having low solubility and high permeability (Baratam et al. 2016). It is absorbed quickly with the absolute oral bioavailability (F) of 12% and 96% in extensive (EMs) and poor metabolizers (PMs), respectively (Marques et al. 2022). The protein binding of nebivolol is 98%, mainly with albumin, and its peak plasma concentration is achieved after 1.5–4 h (Sahana et al. 2011; Fongemie and Felix-Getzik 2015). Its average volume of distribution (V_d) is 10 L/kg (Kumar Saini et al. 2018), and its terminal half-life ($t_{1/2}$) is 31.9 h in PMs and 10.3 h in EMs (Mangrella et al. 1998). It is metabolized by Cytochrome P450 (CYP) 2D6 and CYP3A4 in the liver following the N-dealkylation, hydroxylation, oxidation,

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and glucuronidation (Sule and Frishman 2006). The elimination of nebivolol follows specific metabolic routes, such as urinary and biliary, with a clearance (CL/F) of 16.3–657.4 L/h for EMs and PMs (Sule and Frishman 2006).

Nebivolol is monoisotopic with a chemical formula of $C_{22}H_{25}F_2NO_4$, and its water solubility is 0.091 g/100 ml (Nebivolol hydrochloride 2023). It is a highly lipophilic drug having an octanol/water distribution coefficient (log P) of 4.03 at the negative log of hydrogen ion concentration (pH) of 11.8 (McNeely and Goa 1999). The basic dissociation constant (pKa) of nebivolol is 8.22 (Nebivolol hydrochloride 2023).

Nebivolol belongs to the pregnancy category C drug (no human data on safety or toxicity in pregnancy) (Sullo et al. 2015). It can cross the blood-brain barrier (BBB), due to which the central nervous system (CNS) side effects (depression, insomnia, and nightmare) arise (Nasima Olawi et al. 2019). Nebivolol has a greater affinity for β_1 receptors in chronic obstructive pulmonary disease (COPD) and asthma patients resulting in better tolerance (Münzel and Gori 2009). The commonly reported adverse effects of nebivolol are headache, fatigue, dizziness, rhinitis, insomnia, asthenia, hyperuricemia, paresthesias, and weakness (Priyadarshni and Curry 2022). The contraindications of nebivolol include patients with severe bradycardia, higher than 1st-degree AV nodal block, decompensated heart failure, cardiogenic shock, severe hepatic disease, and sick sinus syndrome (Münzel and Gori 2009; Priyadarshni and Curry 2022). The drugs that induce or inhibit the CYP2D6 enzyme affect nebivolol's pharmacokinetics (PK) (Cheng 2009). In severe renal disease, dose reduction may require because of the lower CL/F. There is a need to monitor the drug dosage due to the poor metabolism in moderate liver impairment (Hilas and Ezzo 2009).

This systematic review intends to illustrate the thorough details of nebivolol by using PK data from different studies, which includes oral and IV routes in healthy and diseased participants. It represents many aspects concerning the clinical responses of nebivolol, drug-drug interaction, drug-disease interaction, and the effects of other physiologic parameters in PK model development. However, a few review articles have already been published, but their focus was on the pharmacology of nebivolol (Marketou et al. 2017; Seleme et al. 2021), and till now, no systematic review provides PK data on nebivolol. Therefore, this study aims to systematically collect, compile and inspect all PK human data of nebivolol which may be favorable for dose adjustments in special and diseased populations.

2. Materials and methods

2.1. Study protocol and method of screening

This systematic review was conducted utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al. 2009) and the Cochrane Handbook Guidelines (Higgins et al. 2022). An extensive literature search was performed from different databases (Google Scholar, PubMed, EBSCO, Science Direct, and Cochrane Library) up to August 29, 2022. All studies concentrating on the PK of nebivolol were screened out. The search was carried out with the help of selected keywords, medical subject heading (MeSH) and indexing phrases. The search terms used are specified in Figure 1.

2.3. Eligibility

Original research articles reported in English containing PK parameters or plasma concentration-time graphs in healthy and diseased human populations after oral and IV administration were included. There were no restrictions placed on the age, gender and year of publications.

2.4. Study selection

All articles from the database search were transferred into the EndNote program, and the duplicates were removed by selecting the 'remove duplicate' option. The articles were then screened out based on titles, abstracts, animal studies, inaccessibility, and full-text analysis. Lastly, the pertinent studies meeting the inclusion-exclusion criteria were selected for the review. The details are specified in Supplementary Table S1.

2.5. Data extraction

The relevant data extracted from the selected articles contained the author's name, references, study size, population, age, dose, dosage form, frequency, key objective, and initial outcome. Moreover, the retrieving data of the PK parameters was comprised of the maximum time to reach the maximum plasma concentration (T_{max}), maximum plasma concentration (C_{max}), the area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$), CL/F, and $t_{1/2}$. The units of the C_{max}, $AUC_{0-\infty}$, T_{max}, CL/F, and $t_{1/2}$ were converted to the most frequent units for homogeneity, providing consistent data for the comparisons of results. Two independent assessors estimated the eligibility criteria and the extraction of data.

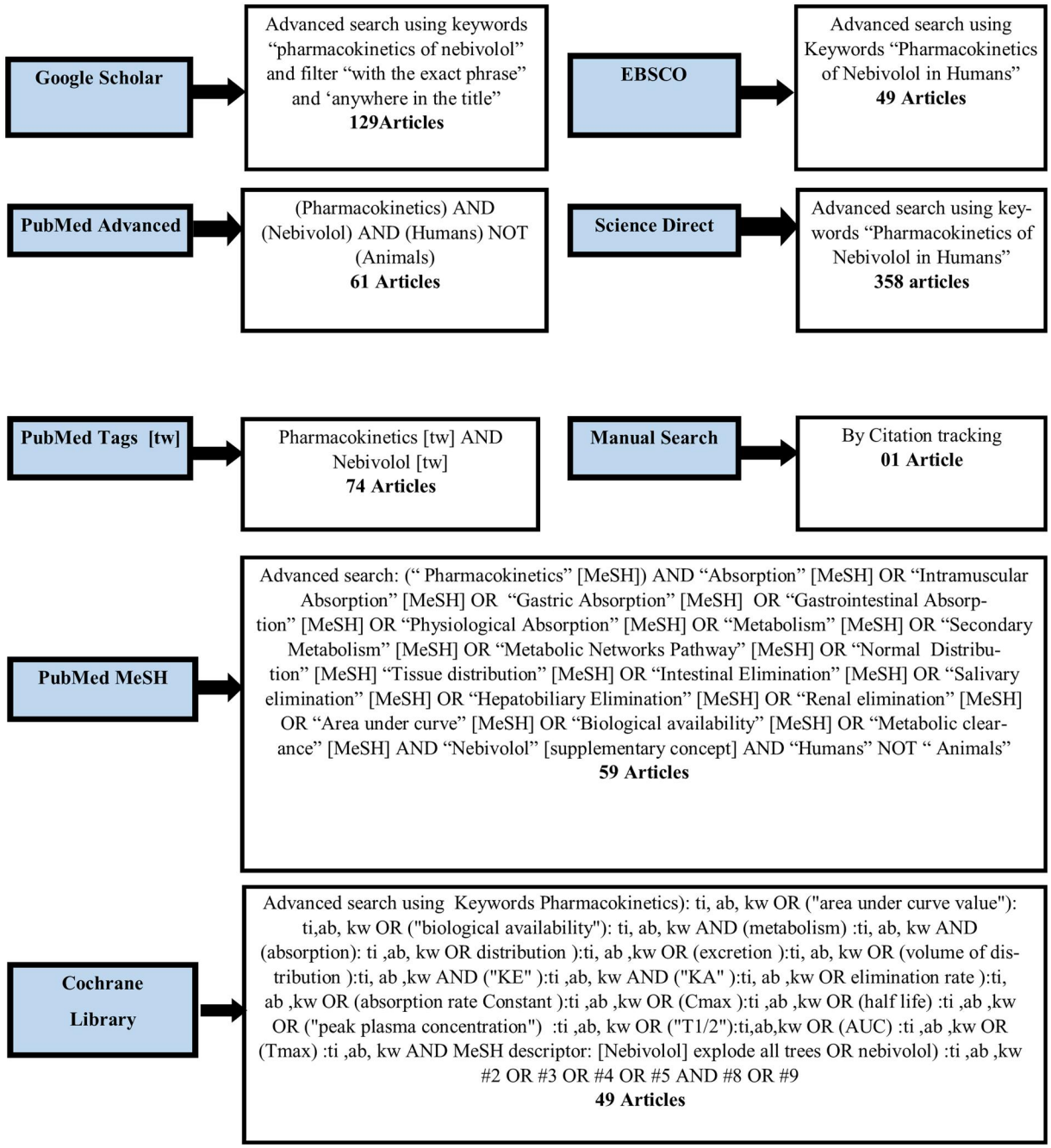

Figure 1. Method of screening.

2.6. Pharmacokinetic analysis

Non-compartmental analysis (NCA) was applied to find the PK parameters from one study of nebivolol. The parameters of each plasma concentration-time plot were extracted through the Snipping Tool, the GetData Graph Digitizer, and the add-in program of Microsoft Excel, i.e. PK-solver.

2.7. Quality and risk assessment

The quality of all the relevant articles was assessed by using the Jadad scoring (Rubin et al. 2009), the Critical Appraisal Scale Programme (CASP) (Long et al. 2020), and the critical Appraisal Clinical Pharmacokinetic (CACPK) tool (Soliman et al. 2022). Jadad scoring was a 5-point scale in which >4 scores showed high quality, 3–4 demonstrated moderate quality, and <3 indicated low quality. The CASP tool had 11 questions in which articles scored >6, 4–6, and <4 depicted high, moderate, and low quality, respectively (Long et al. 2020). The CACPK tool consisted of 21 questions, and the high, moderate, and low-quality studies scored >16, between 12 and 13, and <11, respectively.

Moreover, the risk of bias assessment was carried out using the Cochrane Collaboration Tool (CCT) (Higgins et al. 2011), which included a low, unclear, or high risk of bias for each question. In this tool, articles scored $>$ 4 showed low risk (LR), 3–4 scoring articles were at moderate risk, and studies with $a < 3$ score displayed high risk (HR). The details of these tools are illustrated in Supplementary Tables S2, S3, S4, and S5, respectively.

3. Results

3.1. Findings of database search

The primary screening process from different databases resulted in 780 articles, and then 144 duplicates were removed. Out of 636 articles, 20 were incorporated in this systematic review. The details of the inclusion and exclusion criteria are mentioned in the flow chart in Figure 2.

3.2. Characteristics of relevant studies

The study characteristics of all the relevant articles are the author's name, study size, population, age, dose, dosage form, frequency, key objective, and initial outcome, which are discussed in Table 1.

3.3. Results of quality assessment and risk of bias

A total of 20 related studies were evaluated by Jadad scoring, CASP tool, CACPK tool, and CCT to check the quality and biases. According to the Jadad scoring, only 01 study was of moderate quality, and all others showed low quality. In the CASP tool scoring, all articles were high quality because they scored $>$ 6. According to the CACPK tool, 5, 13, and 2 studies revealed high, moderate, and low quality, respectively. In the results of CCT, 9 were low, 9 were moderate, and 2 were at high risk. The results of all these critical appraisal tools are specified in the supplementary Tables S2, S3, S4, and S5, respectively.

3.4. Healthy population

3.4.1. Oral studies of nebivolol in healthy subjects

Out of 20 studies, six were reported in a healthy population. In one clinical study, the $AUC_{0-\infty}$ was recorded to be 27.2 ± 3.4 ng. h/ml and 29.4 ± 3.8 ng. h/ml for nebivolol's reference and test products, respectively (Selvan et al. 2007). One of the studies reported a C_{max} of 5.24 ± 0.48 ng/ml in PMs, whereas 1.66 ± 0.86 ng/ml in EMs after administering 5 mg nebivolol (Briciu et al. 2015). The T_{max} in the bioequivalent test and reference formulations of nebivolol was depicted as 1.47 ± 0.71 h and 1.36 ± 0.84 h correspondingly (Vespasiano et al. 2017). The C_{max} for the four genotypes of CYP2D6*10 were found to be 3.01 ± 1.73 ng/ml, 2.09 ± 0.99 ng/ml, 2.68 ± 1.23 ng/ml, and 2.63 ± 1.49 ng/ml, respectively (Luo et al. 2015). The CL/F was 28% lower in the CYP2D6*1/*10 heterozygote, and 44% decreased in the CYP2D6*10/*10 subjects, respectively (Guo et al. 2020). The other reported PK parameters T_{max}, C_{max}, $AUC_{0-\infty}$, CL/F, and $t_{1/2}$, are mentioned in Table 2.

3.5. Diseased populations

3.5.1. Hypertensive patients

In one clinical study, the C_{max} was 7.3 ng/ml and 9.1 ng/ml for D–nebivolol + hydroxylated metabolites (HM). At the same time, for L–nebivolol + HM, these were 13.1 ng/ml and 19.0 ng/ml after 1st dose and 4 weeks of treatment correspondingly (Himmelmann et al. 1996). When 5 mg dose was administered to the elderly hypertensive patients, the $AUC_{0-\infty}$ was observed to be 5.4 ng. h/ml and 10.1 ng. h/ml for D- and L- nebivolol, respectively (Vieira et al. 2017). The CL/F was reported to be 1304.4 L/h and 531.8 L/h for D and L enantiomer, respectively, after a 10 mg dose of treatment in hypertensive patients (Table 3) (Neves et al. 2013).

3.5.2. Chronic kidney disease (CKD) and hemodialysis patients

The $AUC_{0-\infty}$ in the CKD patients was recorded as 7.30 ng. h/ml and 9.94 ng. h/ml for D- and L–nebivolol, respectively. Meanwhile, the $AUC_{0-\infty}$ was found to be 4.95 ng. h/ml and 6.41 ng. h/ml in the hemodialysis treatment subjects, similar to the control subjects, such as 4.15 ng. h/ml and 6.83 ng. h/ml, for D- and L- isomers, respectively (Table 3) (Neves et al. 2016).

3.6. Intravenous (IV) infusion study of nebivolol

The IV infusion study reported the CL of 76.1 L/h, 64.5 L/h, and 67.0 L/h in the obese subjects in comparison with the control subjects, i.e. 51.6 L/h, 48.6 L/h, and 48.4 L/h for D-L–nebivolol, D–nebivolol, and L–nebivolol respectively after administration of 0.5 mg/ml IV dose (Cheymol et al. 1997). The other PK parameters are shown in Table 4.

3.7. Drug-drug interaction studies of nebivolol

One of the studies reported no significant effect of ranitidine on the PK of nebivolol; however, the C_{max} was increased from 1.48 ± 0.45 ng/ml to 1.82 ± 0.55 ng/

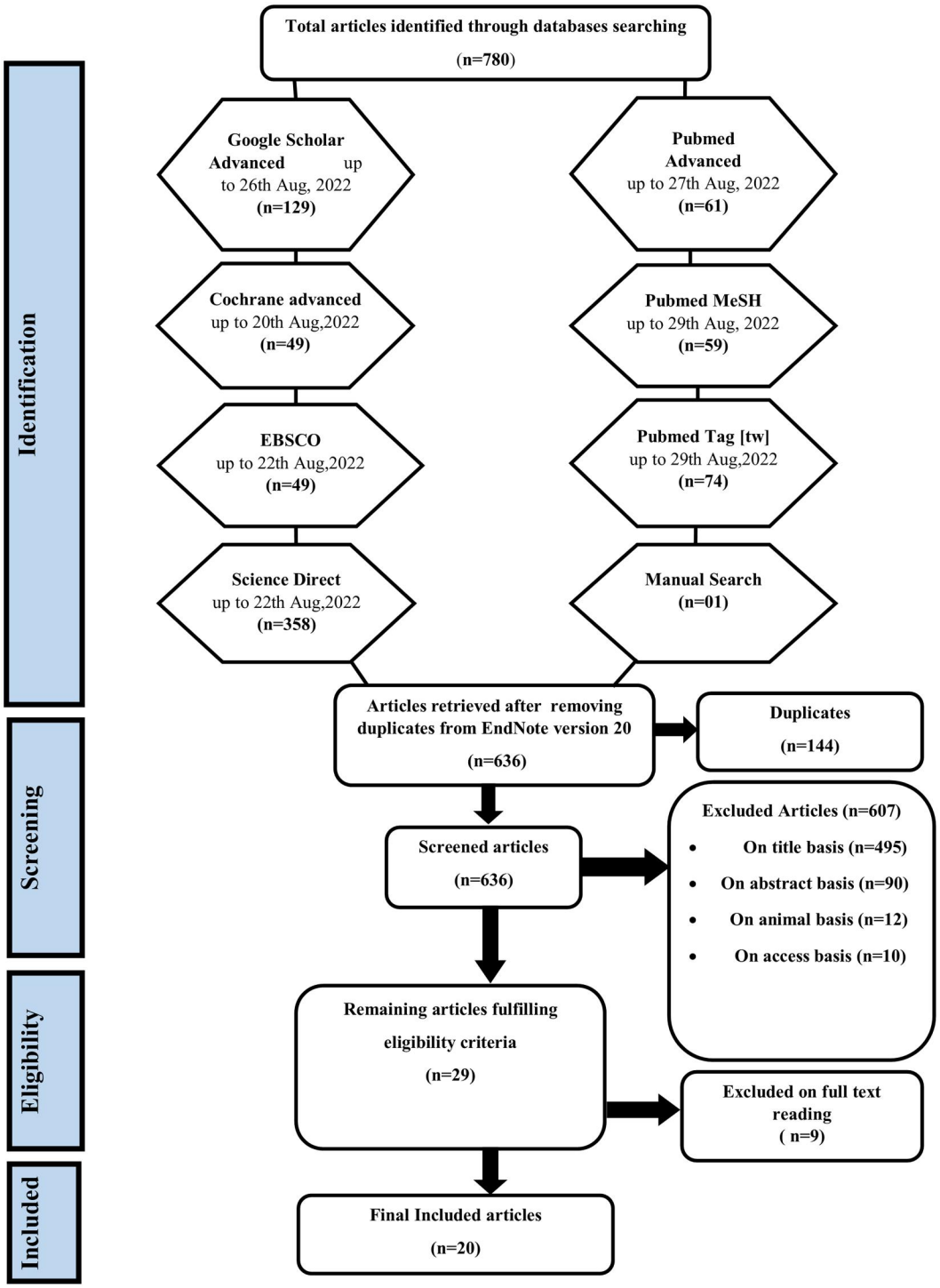

Figure 2. Flow chart of PRISMA.

ml when co-administered with cimetidine (Kamali et al. 1997). The $AUC_{0-\infty}$ was increased due to the combined usage of nebivolol with cefixime and lansoprazole (Bollam et al. 2013; Venkateswarlu et al. 2013). The C_{max} was increased from 1.78 ± 1.17 ng/ml to 4.24 ± 1.67 ng/ml for nebivolol after the co-administration with multiple dose paroxetine (Briciu et al. 2014). The T_{max} was recorded to be 1.81 ± 1.19 h vs 1.72 ± 1.00 h for nebivolol when it was taken with fluvoxamine (Gheldiu et al. 2017). When nebivolol was given with bupropion, the C_{max} was reported to be 1.67 ± 0.69 ng/ml vs 3.80 ± 1.70 ng/ml (Gheldiu et al. 2016). There was a remarkable decrease of 43–45% in the C_{max} at steady state ($C_{max,ss}$) for the four analytes of nebivolol when co-administered with valsartan (Chen et al. 2015). The C_{max} of nebivolol after co-treatment with multiple

Table 1. Characteristics of relevant studies

Sr. No.	References	Study size	Gender	Population	Age (years)	Dose (mg)	Drugs	Dosage form	Frequency	Key objective	Initial outcome
1	(Himmelmann et al. 1996)	15	12 M/ 3 F	Essential Hypertension	50 ± 7.7	5	Nebivolol	Tab	OD	PK	PK Parameters
						N/R	Placebo	N/R	4 weeks[a]		
2	(Kamali et al. 1997)	12	12 M	Healthy	19–23	5	Nebivolol	Tab	Single oral	PK	PK Parameters
						150	Ranitidine		BID		
						400	Cimetidine				
						N/R	Placebo	N/R			
3	(Cheymol et al. 1997)	9	4 M/5 F	Control healthy	32 (9)	0.5[b]	Nebivolol	INF	Single IV solution infused at 1.81 ml min^{-1}	PK	PK Parameters
		9	4 M/5 F	Obese	31 (9)	0.5[b]	Nebivolol				
4	(Selvan et al. 2007)	12	N/R	Healthy	21–27	5	Nebivolol	Tab	Ref: Single oral	PK	PK Parameters
						5	Nebivolol		Test: Single oral		
5	(Lindamood et al. 2011)	13	11 M/2 F	Healthy	19–45	10	Nebivolol	Tab	OD	PK	PK Parameters
						25	Hydrochlorothiazide	Cap			
		10	N/R	Healthy	20–52	10	Nebivolol	Tab			
						20	Fluoxetine	Cap			
		12[c]	7 M/8 F	Healthy	20–43	40	Furosemide	Tab			
		3[d]				10	Nebivolol				
6	(Neves et al. 2013)	1	N/R	Systemic Arterial Hypertension	31	10	Nebivolol	Tab	Single oral	PK	PK Parameters
7	(Venkateswarlu et al. 2013)	8	N/R	Hypertension	N/R	5	Nebivolol	Tab	Group 1: Single oral	PK	PK Parameters
						20 + 200	Nebivolol + Cefixime		Group 2: Single oral		
8	(Bollam et al. 2013)	8	N/R	Hypertension	N/R	5	Nebivolol	Tab	Group 1: Single oral	PK	PK Parameters
						20 + 30	Nebivolol + Lansoprazole	Tab/Cap	Group 2: Single oral		
9	(Briciu et al. 2014)	23	16 M/7 F	Healthy	18–55	5	Nebivolol	Tab	Period 1 (Ref) on day 1: Single oral	PK	PK Parameters
						40	Paroxetine		Initial loading dose with 12h intervals for 2 days		
						5 + 20	Nebivolol + Paroxetine		Period 2 (test) on day 8 : Single oral		
10	(Briciu et al. 2014)	23	M/F	Healthy	20–35	5	Nebivolol	Tab	Period 1 (Ref): Single oral	PK	PK Parameters
						60	Duloxetine		For 2 days between two periods: 2 equal doses 12 hours apart		
						5 + 30	Nebivolol + Duloxetine		Period 2 (Test): Single oral		
11	(Luo et al. 2015)	12[c]	N/R	Healthy	N/R	30	Dextromethorphan [f]	Tab	Day 1: Single oral	PK	PK Parameters
		12[e]				10	Nebivolol		Day 2: Single oral		
12	(Chen et al. 2015)	30	15 M/15 F	Healthy	18–45	20	Nebivolol	Tab	Treatment A: OD	PK	PK Parameters
						320	Valsartan		Treatment B: OD		
						20 + 320	Nebivolol + Valsartan		Treatment C: OD		
13	(Briciu et al. 2015)	40[c]	M/F	Healthy	18–55	5	Nebivolol	Tab	Single oral	PK	PK Parameters
		3[d]									
14	(Gheldiu A-M et al. 2016)	20	N/R	Healthy	N/R	5	Nebivolol	Tab	Single oral	PK	PK Parameters
15	(Gheldiu et al. 2016)	18	10 M/8 F	Healthy	18–55	5	Nebivolol	Tab	Period 1 (Ref): Single oral	PK	PK Parameters
						150	Bupropion		For 3days pretreatment regimen: Single oral		

(*continued*)

Table 1. Continued.

Sr. No.	References	Study size	Gender	Population	Age (years)	Dose (mg)	Drugs	Dosage form	Frequency	Key objective	Initial outcome
						300	Bupropion		For 4days pretreatment regimen: Single oral		
						5 + 300	Nebivolol + Bupropion		Period 2 (Test): Combination		
16	(Neves et al. 2016)	13 & 9	12 M/10 F	Control group: healthy & systemic arterial hypertension	18–65	5	Nebivolol	Tab	A single oral dose of 2 Tab	PK	PK Parameters
		11	5 M/6 F	CKD group with stages 3 & 4		5	Nebivolol				
		10	5 M/5 F	Stage 5 CKD undergoing Haemodialysis group		5	Nebivolol				
17	(Vespasiano et al. 2017)	48	23 M/25 F	Healthy	19–53	5 + 12.5	Nebivolol + Hydrochlorothiazide	Tab	Test: Single oral	PK	PK Parameters
						5 + 25	Nebivolol + Hydrochlorothiazide		Ref: Single oral		
18	(Gheldiu et al. 2017)	18[c]	10 M/8 F	Healthy	18–55	5	Nebivolol	Tab	Period 1 (Ref) for day 1: Single oral	PK	PK Parameters
						50	Fluvoxamine		Pretreatment for days 2,3,4: Single daily dose		
						100	Fluvoxamine		Pretreatment for Days 5, 6, 7: single daily dose		
						5 + 100	Nebivolol + Fluvoxamine		Period 2 (Test) for day 8: Single oral		
19	(Vieira et al. 2017)	11[c]	6 M/5 F	Arterial Hypertension	69 (65–74)	5	Nebivolol	Tab	After 8 h fast, a single oral dose of 2 Tab	PK	PK Parameters
20	(Guo et al. 2020)	28	14 M/14 F	Healthy	18–55	5	Nebivolol	Tab	Single oral	PK	PK Parameters

PK: Pharmacokinetics, M: Male, F: Female, N/R: Not Reported, OD: Once daily, Tab: Tablet, Cap: Capsule, BID: Twice a day, Ref: Reference, CKD: Chronic kidney disease, &: and, INF: infusion, IV: Intravenous, [a]: 4 weeks duration followed by 4 week washout period, [b]: mg/ml, [c]: Extensive metabolizers (EMs), [d]: Poor metabolizers (PMs), [e]: Intermediate metabolizers (IMs), [f]: Probe drug for CYP2D6 phenotyping.

Table 2. Oral studies of nebivolol in healthy subjects

Sr. No.	References	Administered drugs	Dose (mg)	Plasma pharmacokinetic Parameters a				
				Tmax (h)	Cmax (ng/ml)	AUC(0–∞) (ng. h/ml)	CL/F (L/h)	$t_{1/2}$ (hr)
1	(Selvan et al. 2007)	Nebivolol: Ref.	5	2.1 ± 0.3	4.1 ± 0.3	27.2 ± 3.4	N/R	12.2 ± 3.0
		Nebivolol: Test		1.9 ± 0.3	4.6 ± 0.3	29.4 ± 3.8		12.8 ± 2.3
2	(Briciu et al. 2015)	PMs: Nebivolol	5	N/R	5.24 ± 0.48[b]	139.22 ± 20.80[b]	N/R	N/R
		PMs: 4-OH-Nebivolol			0.43 ± 0.06[b]	13.54 ± 1.33[b]		
		EMs: Nebivolol			1.66 ± 0.86[b]	9.19 ± 8.91[b]		
		EMs: 4-OH- Nebivolol			0.63 ± 0.22[b]	9.34 ± 7.98[b]		
3	(Luo et al. 2015)	Nebivolol & CYP2D6*1/*10 genotype	10	1.0 ± 0.3	3.01 ± 1.73	19.10 ± 12.31	781.2 ± 562.7	12.38 ± 6.56[c]
		Nebivolol & CYP2D6*1/*10 genotype		1.6 ± 1.3	2.09 ± 0.99	15.27 ± 12.34	900.4 ± 403.3	11.26 ± 3.60[c]
		Nebivolol & CYP2D6*10/*10 genotype		1.7 ± 1.0	2.68 ± 1.23	25.62 ± 18.79	681.8 ± 583.7	13.12 ± 6.25[c]
		Nebivolol & CYP2D6*5 carriers		1.3 ± 0.9	2.63 ± 1.49	17.50 ± 11.91	830.9 ± 485.4	11.91 ± 5.34[c]
4	(Gheldiu A-M et al. 2016)	Nebivolol (M1)	5	0.84	2.25	11.01	454.00	5.60
		Nebivolol metabolite (M1)		1.96	0.72	11.73	425.91	16.13
		Nebivolol (M6)		0.97	2.23	10.49	476.19	3.39
		Nebivolol metabolite (M6)		1.96	0.71	12.74	392.43	18.84
5	(Vespasiano et al. 2017)	Test: (Nebivolol + Hydrochlorothiazide)	5 + 12.5	1.47 ± 0.71	4.08 ± 2.27	29.28 ± 49.02	N/R	13.26 ± 7.18
		Ref: (Nebivolol)	5	1.36 ± 0.84	3.92 ± 1.70	23.69 ± 19.75		11.52 ± 3.02
6	(Guo et al. 2020)	Nebivolol & CYP2D6*1/*1 genotype	5	0.86 ± 0.18	1.56 ± 0.21	8.35 ± 1.16	609.25 ± 85.99	13.09 ± 4.81
		Nebivolol & CYP2D6*1/*10 genotype		1.04 ± 0.32	1.93 ± 0.39	12.54 ± 3.90	438.46 ± 156.66	11.43 ± 1.55
		Nebivolol & CYP2D6*10/*10 genotype		1.20 ± 0.35	2.03 ± 0.44	16.96 ± 6.14	338.94 ± 147.78	11.23 ± 2.61
		Nebivolol & CYP2D6*5 carriers		0.89 ± 0.19	3.15 ± 0.80	13.17 ± 3.26	398.07 ± 111.21	13.69 ± 3.01

C_{max}: Maximum plasma concentration, T_{max}: Time to reach the C_{max}, $AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from zero to infinity, CL/F: Oral Clearance, $t_{1/2}$: half-life, Ref: Reference, N/R: Not reported, PMs: Poor metabolizers, EMs: Extensive metabolizers, 4–OH: Hydroxylated active metabolite, M1: Model 1, M6: Model 6, [a]: Data is displayed as Mean ± Standard Deviation, [b]: Median values, [c]: Terminal half-life.

doses of duloxetine was found to be 1.78 ± 1.17 ng/ml vs 1.95 ± 1.19 ng/ml (Briciu et al. 2014). The concomitant administration of nebivolol with fluoxetine decreased the CL/F from 787 L/h to 143 L/h, whereas the co-administration of hydrochlorothiazide (HCTZ) and furosemide did not alter the PK of nebivolol (Lindamood et al. 2011). The remaining values are presented in Table 5.

4. Discussion

This systematic review focused on collecting and interpreting all the published articles on the PK of nebivolol in healthy and diseased participants. Among the 20 included studies, six studies were in the healthy population, four were in the diseased (CKD, hypertension), one was in the subjects having obesity, and nine were related to drug-drug interactions. The PK parameters (T_{max}, C_{max}, $AUC_{0-\infty}$ and $t_{1/2}$) were almost the same between the reference and test products after orally administered 5 mg nebivolol, suggesting that both types of products may be given (Selvan et al. 2007).

Nebivolol is extensively metabolized by CYP2D6, having two main phenotypes, i.e. EMs, which show the regular activity of enzymes, and PMs, which are considered autosomal recessive traits. There are also two less-known phenotypes of CYP2D6: ultrarapid metabolizers (UMs) and intermediate metabolizers (IMs). The PMs show a prolonged biotransformation rate and accumulate the substrates of specific drugs. Nebivolol had three times higher C_{max} in the PMs because of the high exposure and the slow metabolism, so a low dose of the drug is required to prevent the side effects in the PMs (Briciu et al. 2015). The *10/*10 homozygotes were considered as IMs while the *1/*1 homozygotes, *1/*10 heterozygotes and the CYP2D6*1 carriers were EMs. Furthermore, these CYP2D6*10 genotypes expressed no effect on the PK of nebivolol, notably among EMs and IMs, due to the absence of a gene-dose effect (Luo et al. 2015).

The CL/F was decreased notably in CYP2D6*10/*10 and CYP2D6*5 subjects, and this change in the PK of nebivolol occurred due to the administration of dextromethorphan which was metabolized extensively through CYP2D6 (Guo et al. 2020). The PK parameters of the test and reference formulations of nebivolol were almost the same as they were bioequivalent; however, the $t_{1/2}$ value of the test product increased for one participant recommending that the drug metabolism is influenced by any unknown external factor (Vespasiano et al. 2017).

Table 3. Studies of nebivolol in diseased population

Sr. No.	References	Administered drugs	Dose (mg)	Plasma pharmacokinetic parameters [a]				
				T_{max} (h)	C_{max} (ng/ml)	$AUC_{(0-\infty)}$ (ng. h/ml)	CL/F (L/h)	$t_{1/2}$ (h)
1	(Himmelmann et al. 1996)	D–Nebivolol + HM: 1st dose	5	2.5 (1.6)	7.3 (2.5)	N/R	N/R	N/R
		D–Nebivolol + HM: 4 weeks		2.4 (1.2)	9.1 (2.4)			
		L–Nebivolol + HM: 1st dose		2.6 (1.4)	13.1 (4.2)			
		L–Nebivolol + HM: 4 weeks		3.1 (2.6)	19.0 (3.7)			
2	(Neves et al. 2013)	D–Nebivolol	10	0.4	1.2	4.7	1304.4	13.8
		L–Nebivolol		0.2	2.5	9.4	531.8	14.5
3	(Neves et al. 2016)	D–Nebivolol: Control	10	1.03 (0.43 – 2.14)[b]	0.69 (45)[c]	4.15 (41)[c]	16.84 (41)[d]	13.19 (47)[c]
		D–Nebivolol: CKD		0.98 (0.61 – 3.34)[b]	1.34 (54)[c]	7.30 (51)[c]	9.77 (51)[d]	11.57 (30)[c]
		D–Nebivolol: Haemodialysis		1.13 (0.40 – 1.86)[b]	0.80 (44)[c]	4.95 (36)[c]	15.86 (33)[d]	16.10 (31)[c]
		L–Nebivolol: Control		1.01 (0.18 – 2.10)[b]	1.31 (47)[c]	6.83 (39)[c]	10.24 (47)[d]	13.79 (35)[c]
		L–Nebivolol: CKD		1.04 (0.68 – 2.80)[b]	1.98 (47)[c]	9.94 (44)[c]	7.18 (32)[d]	12.43 (35)[c]
		L–Nebivolol: Haemodialysis		1.15 (0.27 – 1.54)[b]	1.38 (39)[c]	6.41 (35)[c]	12.45 (35)[d]	12.87 (27)[c]
4	(Vieira et al. 2017)	L–Nebivolol	10	0.8 (0.6 – 1.2)[e]	2.5 (1.8 – 3.2)[e]	10.3 (8.6 – 12.0)[e]	515.7 (423.2 – 608.4)[e]	14.2 (12.0 –16.3)[e]
		D–Nebivolol		0.9 (0.6 – 1.1)[e]	1.3 (1.0 – 1.5)[e]	5.4 (4.5 – 6.4)[e]	979.8 (786.0 –1173.7)[e]	12.7 (11.6 – 13.8)[e]
		L-glucuronide		1.7 (1.3 – 2.1)[e]	9.1 (7.0 – 11.1)[e]	71.5 (58.1 – 85)[e]	N/R	9.5 (8.3 – 10.8)[e]
		D-glucuronide		1.8 (1.4 – 2.2)[e]	58.6 (43.3 – 73.8)[e]	393.6 (236.8 – 550.3)[e]		9.5 (7.5 – 11.6)[e]

C_{max}: Maximum plasma concentration, T_{max}: Time to reach the C_{max}, $AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from zero to infinity, CL/F: Oral clearance, $t_{1/2}$: Terminal elimination half-life, N/R: Not reported, HM: Hydroxylated metabolites, CKD: Chronic kidney disease, [a]: Data is given as Mean (Standard Deviation), [b]: Median (range), [c]: Mean (coefficient of variation), [d]: L/h/kg & Mean (coefficient of variation), [e]: Mean (95% confidence interval).

Table 4. Intravenous infusion study of nebivolol

		Plasma pharmacokinetic Parameters[a]						
Sr. No.	Reference	Administered drugs	Dose (mg/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC (ng.h/ml)	CL (L/h)	$t_{1/2}$ (hr)
1	(Cheymol et al. 1997)	D–L–Nebivolol: Controls	0.5 IV solution	N/R	N/R	92.2 (22.4)	51.6 (11.6)	10.3 (2.4)
		D–L–Nebivolol: Obese				69.2 (23.4)	71.6 (17.4)	10.0 (2.6)
		D–Nebivolol: Controls (U)				47.8 (8.6)	48.6 (8.4)	9.7 (2.3)
		D–Nebivolol: Controls (U + M)				123.3 (27.3)	N/R	15.6 (4.7)
		D–Nebivolol: Obese (U)				38.3 (13.1)	64.5 (14.9)	9.3 (2.1)
		D–Nebivolol: Obese (U + M)				100.2 (38.9)	N/R	13.9 (6.3)
		L–Nebivolol: Controls (U)				48.0 (7.7)	48.4 (8.7)	12.1 (2.7)
		L–Nebivolol: Controls (U + M)				147.4 (42.0)	N/R	17.1 (7.9)
		L–Nebivolol: Obese (U)				36.7 (11.9)	67.0 (14.5)	11.3 (3.0)
		L–Nebivolol: Obese (U + M)				110.9 (28.7)	N/R	15.9 (8.1)

C_{max}: Maximum plasma concentration, T_{max}: Time to reach the C_{max}, AUC: Area under the plasma concentration-time curve, CL: Clearance, $t_{1/2}$: Half-life, U: Unchanged drug, U + M: Unchanged drug + hydroxylated metabolites, N/R: Not reported, IV: Intravenous, [a]: Values are expressed as Mean (Standard Deviation).

In the hypertensive patients, C_{max} was doubled from 1st dose to the last dose after 4 weeks of treatment for D– and L– isomers due to the prolonged elimination $t_{1/2,}$ suggesting that the dose must be monitored in the elderly hypertensive patients (Himmelmann et al. 1996).

The remarkable changes in the PK parameters were observed in some studies, which may be due to the stereoselective characteristics of nebivolol (Neves et al. 2013; Vieira et al. 2017). In CKD, $AUC_{0-\infty}$ enhanced with the disease progression as a result of the accumulation of the uremic toxins, which reduced the activity of CYP3A4, whereas, in the hemodialysis treatment, the CYP3A4 action improved as those toxins were removed, so it indicated the same $AUC_{0-\infty}$ values in comparison with the healthy participants (Neves et al. 2016). The CL values of nebivolol were raised markedly in obese subjects due to the metabolism through conjugation or oxidation, which may suggest dose monitoring (Cheymol et al. 1997).

Drug-drug interactions (DDI) can cause interference in achieving the goals of the treatment and sometimes can be lethal. Ranitidine did not affect the PK of nebivolol, but cimetidine inhibited the metabolism and urine excretion of nebivolol; as a result, C_{max} was enhanced. It suggested that close monitoring may require when nebivolol is administered in combination with cimetidine (Kamali et al. 1997). The $AUC_{0-\infty}$ values were higher due to co-administration with cefixime and lansoprazole because they increased the exposure to nebivolol (Bollam et al. 2013; Venkateswarlu et al. 2013). Paroxetine increased the C_{max} of nebivolol because the former is the potent inhibitor of CYP2D6 (Briciu et al. 2014).

The frequent doses of fluvoxamine and duloxetine affected the PK of nebivolol because they had the comparable capability to inhibit the CYP2D6, so low doses for a short duration of action could be given to avoid these interactions (Briciu et al. 2014; Gheldiu et al. 2017). The C_{max} of nebivolol was found to be increased with the co-administration of bupropion, which may suggest the monitoring of the dosing regimen (Gheldiu et al. 2016). The $C_{max,ss}$ of nebivolol was decreased when co-administered with valsartan, and this change was associated with the slight dose response between the drugs (Chen et al. 2015). No DDI of nebivolol with HCTZ and furosemide was found, which indicated that there might be no need for dose adjustment. When nebivolol was taken concomitantly with fluoxetine (a strong inhibitor of CYP2D6), different side effects such as headache, nausea, faintness, vomiting, and diarrhea were reported. It may suggest that the nebivolol dose must be adjusted according to the requirement of patients (Lindamood et al. 2011).

The strength of this study is that it reviews all the published articles up to August 29, 2022. In this review, 20 studies were obtained from five different databases, due to which chances of missing data were reduced, so the accuracy and rationality of the results were increased. Limitations of this review are that only one IV study is available, there is a lack of data related to the effect of CYP2D6 genotypes and no equal gender proportions, so this could have influenced the results to a certain degree.

5. Conclusion

This review reveals all the human data of nebivolol regarding its PK parameters, dosage form characteristics, and drug-drug interactions in healthy and diseased participants. The C_{max}, T_{max}, and $AUC_{0-\infty}$ is greater in poor metabolizers than in extensive metabolizers. The CYP2D6 phenotypes do not affect the PK of nebivolol, whereas the $AUC_{0-\infty}$ notably increases in CKD patients. This comprehensive review compiles all the PK parameters which could be helpful in the development of PK models. Additionally, it will be convenient for practitioners to predict the dose and eliminate the drug-drug interactions in hypertension, cardiac failure, and renal

Table 5. Drug-drug interaction studies of nebivolol

Sr. No.	References	Administered drugs	Plasma pharmacokinetic parameters [a] Dose (mg)	T_{max} (h)	C_{max} (ng/ml)	$AUC_{(0-\infty)}$ (ng. h/ml)	CL/F (L/h)	$t_{1/2}$ (h)
1	(Kamali et al. 1997)	Nebivolol + Placebo	5	1[b]	1.48 ± 0.45	7.76 ± 3.07	N/R	11.2 ± 7.8
		Nebivolol + Ranitidine	5 + 150	1[b]	1.50 ± 0.54	8.27 ± 3.55		11.9 ± 8.0
		Nebivolol + Cimetidine	5 + 400	1[b]	1.82 ± 0.55	11.50 ± 5.40		10.3 ± 4.1
		D–Nebivolol + OHM + Placebo	5	3.9[b]	6.04 ± 1.13	73.0 ± 18.0		14.0 ± 4.3
		D–Nebivolol + OHM + Ranitidine	5 + 150	3[b]	6.22 ± 1.35	71.3 ± 23.5		16.6 ± 7.0
		D–Nebivolol + OHM + Cimetidine	5 + 400	4[b]	7.28 ± 2.05	91.5 ± 25.7		19.0 ± 7.8
		L–Nebivolol + OHM + Placebo	5	3[b]	10.5 ± 2.5	101 ± 32		17.8 ± 8.6
		L–Nebivolol + OHM + Ranitidine	5 + 150	3.9[b]	10.2 ± 2.3	117 ± 31		16.6 ± 9.9
		L–Nebivolol + OHM + Cimetidine	5 + 400	4.0[b]	12.7 ± 3.8	123 ± 38		15.4 ± 8.9
2	(Lindamood et al. 2011)	D,L–Nebivolol	10	1.5 (1.0 – 14.0)[b]	9.7 (149)[c]	N/R	585 (86)[c]	16.3 (24)[c]
		Nebivolol + Hydrochlorothiazide	10 + 25	2.0 (1.0–14.0)[b]	11.4 (147)[c]		523 (85)[c]	16.1 (54)[c]
		EMs: Nebivolol	10	1.0 (0.5–2.00)[b]	2.5 (39)[c]	15 (33)[c]	757 (30)[c]	10.6 (17)[c]
		EMs: Nebivolol + Furosemide	10 + 40	1.0 (1.0–2.5)[b]	2.4 (25)[c]	14 (28)[c]	746 (25)[c]	12.3 (46)[c]
		PMs: Nebivolol	10	4.0 (4.0–8.0)[b]	37.9 (11)[c]	729 (12)[c]	14 (12)[c]	32.6 (25)[c]
		PMs: Nebivolol + Furosemide	10 + 40	6.0 (4.0–8.0)[b]	43.3 (16)[c]	797 (18)[c]	13 (17)[c]	34.9 (9)[c]
		Nebivolol	10	1.0 (1.0–2.00)[b]	2.3 (26)[c]	14 (32)[c]	787 (31)[c]	12.5 (22)[c]
		Nebivolol + Fluoxetine	10 + 20	2.5 (1.0–4.00) [b]	5.5 (34)[c]	92 (63)[c]	143 (54)[c]	17.5 (48)[c]
3	(Bollam et al. 2013)	Nebivolol	5	1.50 ± 0.00	3.09 ± 0.37	24.42 ± 5.08	N/R	6.60 ± 1.17
		Nebivolol + Lansoprazole	20 + 30	1.5 ± 0.00	6.37 ± 0.89	43.36 ± 10.61		11.92 ± 7.09
4	(Venkateswarlu et al. 2013)	Nebivolol	5	1.50 ± 0.00	3.09 ± 0.37	24.42 ± 5.08	N/R	6.60 ± 1.17
		Nebivolol + Cefixime	20 + 200	6.00 ± 0.00	2.98 ± 0.47	45.30 ± 6.70		7.00 ± 0.72
5	(Briciu et al. 2014)	Nebivolol	5	1.37 ± 0.88	1.78 ± 1.17	17.26 ± 43.06	N/R	6.65 ± 8.55
		Nebivolol + Paroxetine	5 + 20	3.96 ± 1.76	4.24 ± 1.67	106.20 ± 65.56		19.03 ± 10.31
		4-OH-Nebivolol	5	3.11 ± 1.76	0.58 ± 0.21	13.03 ± 11.29		16.93 ± 15.44
		4-OH-Nebivolol + Paroxetine	5 + 20–40	7.33 ± 7.84	0.79 ± 0.24	74.56 ± 88.77		72.61 ± 91.38
6	(Briciu et al. 2014)	Nebivolol	5	1.37 ± 0.88	1.78 ± 1.17	17.26 ± 43.06	N/R	6.65 ± 8.55
		Nebivolol + Duloxetine	5 + 30–60	1.46 ± 0.85	1.95 ± 1.19	20.57 ± 47.59		7.45 ± 6.61
		OH-Nebivolol	5	3.11 ± 1.76	0.58 ± 0.21	13.03 ± 11.29		16.93 ± 15.44
		OH-Nebivolol + Duloxetine	5 + 30–60	2.87 ± 1.35	0.83 ± 0.29	18.60 ± 12.76		25.50 ± 21.04
7	(Chen et al. 2015)	D–Nebivolol	20	1.32 ± 0.67[d]	2.75 ± 1.55[e]	N/R	1241.63 ± 749.77	6.88 ± 2.61
		D–Nebivolol + Valsartan	20 + 320	2.11 ± 1.57[d]	1.50 ± 0.96[e]		1539.72 ± 932.83	7.85 ± 3.12
		L–Nebivolol	20	1.25 ± 0.65[d]	5.29 ± 2.06[e]		435.53 ± 180.93	12.66 ± 1.91
		L–Nebivolol + Valsartan	20 + 320	1.96 ± 1.37[d]	3.03 ± 1.17[e]		515.08 ± 212.04	12.95 ± 1.90
		D–L–Nebivolol	20	1.32 ± 0.67[d]	8.02 ± 3.47[e]		635.31 ± 300.25	11.03 ± 2.12
		D–L–Nebivolol + Valsartan	20 + 320	1.96 ± 1.37[d]	4.50 ± 1.96[e]		760.56 ± 357.26	11.14 ± 2.14
		Nebivolol glucuronides	20	1.96 ± 0.51[d]	68.34 ± 44.68[e]		N/R	6.73 ± 2.66
		Nebivolol glucuronides + Valsartan	20 + 320	2.93 ± 1.15[d]	40.85 ± 31.41[e]			8.76 ± 3.31
		Valsartan	320	2.81 ± 1.20[d]	5550.4 ± 2016.6[e]		8.7 ± 3.2	22.44 ± 14.35
		Nebivolol + Valsartan	20 + 320	2.58 ± 1.10[d]	5038.5 ± 2305.3[e]		10.6 ± 5.4	19.48 ± 11.43
8	(Gheldiu et al. 2016)	Nebivolol	5	1.81 ± 1.19	1.67 ± 0.69	12.10 ± 11.02	N/R	7.05 ± 3.69
		Nebivolol + Bupropion	5 + 150–300	3.47 ± 1.75	3.80 ± 1.70	87.29 ± 57.49		17.32 ± 4.83
		4-OH-Nebivolol	5	3.00 ± 1.65	0.68 ± 0.22	17.61 ± 20.06		19.51 ± 19.85
		4-OH-Nebivolol + Bupropion	5 + 150–300	3.94 ± 0.92	1.13 ± 0.38	70.43 ± 32.32		57.68 ± 20.85
9	(Gheldiu et al. 2017)	Nebivolol	5	1.81 ± 1.19	1.67 ± 0.69	12.1 ± 11.0	N/R	7.05 ± 3.69
		Nebivolol + Fluvoxamine	5 + 50–100	1.72 ± 1.00	2.20 ± 0.97	19.3 ± 19.5		9.15 ± 6.74
		4-OH-Nebivolol	5	3.00 ± 1.65	0.68 ± 0.22	17.6 ± 20.1		19.5 ± 19.8
		4-OH-Nebivolol + Fluvoxamine	5 + 50–100	2.42 ± 1.13	0.96 ± 0.29	25.5 ± 29.9		25.9 ± 26.4

C_{max}: Maximum plasma concentration, T_{max}: Time to reach the C_{max}, $AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from zero to infinity, CL/F: Oral Clearance, $t_{1/2}$: half-life, N/R: Not reported, 4–OH: Hydroxylated active metabolite, OHM: hydroxylated metabolites, EMs: Extensive metabolizers, PMs: Poor metabolizers, [a]: Data is presented as mean ± Standard Deviation (SD), [b]: Median values, [c]: Mean (% Coefficient of variance), [d]: Values of time of maximum plasma drug concentration after the dose at steady state ($T_{max,ss}$), [e]: Values of maximum plasma drug concentration at steady state ($C_{max,ss}$)

impairment. Furthermore, it will be beneficial in the amendment of future clinical trials.

Availability of data

All the data supporting the results used for this publication is presented in the main article or in the Supplementary Information.

Disclosure statement

The authors declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

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References

Baratam SR, Ramanamma C, Chowdary K. 2016. Development of self emulsifying drug delivery system of nebivolol for the improvement of solubility and dissolution. 5.

Bollam V, Dodle J, Anisetti R. 2013. Effect of lansoprazole on pharmacokinetics of nebivolol in hypertensive patients. Ann Biol Res. 4(10):6–10.

Briciu C, Neag M, Muntean D, Bocsan C, Buzoianu A, Antonescu O, Gheldiu AM, Achim M, Popa A, Vlase L. 2015. Phenotypic differences in nebivolol metabolism and bioavailability in healthy volunteers. Clujul Med. 88(2):208–213. doi: 10.15386/cjmed-395.

Briciu C, Neag M, Muntean D, Vlase L, Bocsan C, Buzoianu A, Gheldiu A, Achim M, Popa A. 2014. A pharmacokinetic drug interaction study between nebivolol and duloxetine. Exp Clin Cardiol. 20(1):1374–1379.

Briciu C, Neag M, Muntean D, Vlase L, Bocsan C, Buzoianu A, Gheldiu AM, Achim M, Popa A. 2014. A pharmacokinetic drug interaction study between nebivolol and paroxetine in healthy volunteers. J Clin Pharm Ther. 39(5):535–540. doi: 10.1111/jcpt.12180.

Chen CL, Desai-Krieger D, Ortiz S, Kerolous M, Wright HM, Ghahramani P. 2015. A Single-Center, Open-Label, 3-Way Crossover Trial to Determine the Pharmacokinetic and Pharmacodynamic Interaction Between Nebivolol and Valsartan in Healthy Volunteers at Steady State. Am J Ther. 22(5):e130-140–e140. doi: 10.1097/MJT.0000000000000247.

Cheng JWM. 2009. Nebivolol: a third-generation β-blocker for hypertension. Clin Ther. 31(3):447–462. doi: 10.1016/j.clinthera.2009.03.007.

Cheymol G, Woestenborghs R, Snoeck E, Ianucci R, Le Moing JP, Naditch L, Levron JC, Poirier JM. 1997. Pharmacokinetic study and cardiovascular monitoring of nebivolol in normal and obese subjects. Eur J Clin Pharmacol. 51(6):493–498. doi: 10.1007/s002280050237.

Fongemie J, Felix-Getzik E. 2015. A Review of Nebivolol Pharmacology and Clinical Evidence. Drugs. 75(12):1349–1371. doi: 10.1007/s40265-015-0435-5.

Gheldiu AM, Popa A, Neag M, Muntean D, Bocsan C, Buzoianu A, Vlase L, Tomuta I, Briciu C. 2016. Assessment of a Potential Pharmacokinetic Interaction between Nebivolol and Bupropion in Healthy Volunteers. Pharmacology. 98(3-4):190–198. doi: 10.1159/000447266.

Gheldiu AM, Vlase L, Popa A, Briciu C, Muntean D, Bocsan C, Buzoianu A, Achim M, Tomuta I, Todor I, et al. 2017. Investigation of a Potential Pharmacokinetic Interaction Between Nebivolol and Fluvoxamine in Healthy Volunteers. J Pharm Pharm Sci. 20:68–80. doi: 10.18433/J3B61H.

Gray CL, Ndefo UA. 2008. Nebivolol: a new antihypertensive agent. Am J Health Syst Pharm. 65(12):1125–1133. doi: 10.2146/ajhp070459.

Guo L, Wang S, Wan Z, Ni S, Xu B, Zhao X, Liu L. 2020. Influence of CYP2D6*5 and *10 polymorphism on the pharmacokinetics of nebivolol in healthy Chinese subjects. J Clin Pharm Ther. 45(4):632–637. doi: 10.1111/jcpt.13155.

Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JAC. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 343(oct18 2):d5928–d5928. doi: 10.1136/bmj.d5928.

Higgins JPT, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). 2022. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022; [accessed April 4, 2023]. www.training.cochrane.org/handbook. Chichester, UK: John Wiley & Sons, Ltd.

Hilas O, Ezzo D. 2009. Nebivolol (bystolic), a novel Beta blocker for hypertension. P t. 34(4):188–192.

Himmelmann A, Hedner T, Snoeck E, Lundgren B, Hedner J. 1996. Haemodynamic effects and pharmacokinetics of oral d- and l-nebivolol in hypertensive patients. Eur J Clin Pharmacol. 51(3-4):259–264. doi: 10.1007/s002280050194.

Kamali F, Howes A, Thomas SH, Ford GA, Snoeck E. 1997. A pharmacokinetic and pharmacodynamic interaction study between nebivolol and the H2-receptor antagonists cimetidine and ranitidine. Br J Clin Pharmacol. 43(2):201–204. doi: 10.1046/j.1365-2125.1997.54212.x.

Kumar Saini A, Wal P, Verma M, Chandra S, Singh A, Yadav S, Bansode H, Nischaya K, Saraswat N. 2018. Nebivolol: an Appealing, Awaited and Nitric Oxide Potentiator Drug for the Treatment of Heart Failure. JYP. 10(2):149–154. doi: 10.5530/jyp.2018.10.34.

Lindamood C, Ortiz S, Shaw A, Rackley R, Gorski JC. 2011. Effects of commonly administered agents and genetics on nebivolol pharmacokinetics: drug-drug interaction studies. J Clin Pharmacol. 51(4):575–585. doi: 10.1177/0091270010370846.

Long HA, French DP, Brooks JM. 2020. Optimising the value of the critical appraisal skills programme (CASP) tool for quality appraisal in qualitative evidence synthesis. Res Methods Med Health Sci. 1(1):31–42. doi: 10.1177/2632084320947559.

Luo X, Lei Y, He L, Liu W, Li M, Ran L, Yu M, Guo X, Yu P, Liu Z, et al. 2015. No influence of CYP2D6*10 genotype and phenotype on the pharmacokinetics of nebivolol in

healthy Chinese subjects. J Clin Pharm Ther. 40(5):561–565. doi: 10.1111/jcpt.12310.

Mangrella M, Rossi F, Fici F, Rossi F. 1998. Pharmacology of nebivolol. Pharmacol Res. 38(6):419–431. doi: 10.1006/phrs.1998.0387.

Marketou M, Gupta Y, Jain S, Vardas P. 2017. Differential metabolic effects of beta-blockers: an updated systematic review of nebivolol. Curr Hypertens Rep. 19(3):22. doi: 10.1007/s11906-017-0716-3.

Marques L, Costa B, Vale N. 2022. New data for nebivolol after in silico PK study: focus on young patients and dosage regimen. Pharmaceutics. 14(9):1911. doi: 10.3390/pharmaceutics14091911.

McNeely W, Goa KL. 1999. Nebivolol in the management of essential hypertension. Drugs. 57(4):633–651. doi: 10.2165/00003495-199957040-00011.

Moher D, Liberati A, Tetzlaff J, Altman DG. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 151(4):264–269, W64. doi: 10.7326/0003-4819-151-4-200908180-00135.

Münzel T, Gori T. 2009. Nebivolol. J Am Coll Cardiol. 54(16):1491–1499. doi: 10.1016/j.jacc.2009.05.066.

Olawi N, Krüger M, Grimm D, Infanger M, Wehland M. 2019. Nebivolol in the treatment of arterial hypertension. Basic Clin Pharmacol Toxicol. 125(3):189–201. doi: 10.1111/bcpt.13248.

Nebivolol hydrochloride. 2023. PubChem. [Internet]. Bethesda (MD): national Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 9933004; [accessed 2023 Mar. 30]. https://pubchem.ncbi.nlm.nih.gov/compound/Nebivolol-hydrochloride.

Neves DV, Lanchote VL, Moysés Neto M, Cardeal da Costa JA, Vieira CP, Coelho EB. 2016. Influence of chronic kidney disease and haemodialysis treatment on pharmacokinetics of nebivolol enantiomers. Br J Clin Pharmacol. 82(1):83–91. doi: 10.1111/bcp.12917.

Neves DV, Vieira CP, Coelho EB, Marques MP, Lanchote VL. 2013. Stereoselective analysis of nebivolol isomers in human plasma by high-performance liquid chromatography-tandem mass spectrometry: application in pharmacokinetics. J Chromatogr B Analyt Technol Biomed Life Sci. 940:47–52. doi: 10.1016/j.jchromb.2013.09.031.

Priyadarshni S, Curry BH. 2022. Nebivolol. StatPearls Publishing, Treasure Island (FL); [updated 2022; accessed]. https://www.ncbi.nlm.nih.gov/books/NBK551582.

Rubin K, Sullivan D, Sadhasivam S. 2009. Are peripheral and neuraxial blocks with ultrasound guidance more effective and safe in children? Paediatr Anaesth. 19(2):92–96. doi: 10.1111/j.1460-9592.2008.02918.x.

Sahana G, Sarala N, Kumar T. 2011. Nebivolol-pharmacological aspects. Int J Biol Med Res. 2(2):577–580.

Seleme VB, Marques GL, Mendes AEM, Rotta I, Pereira M, Júnior EL, da Cunha CLP. 2021. Nebivolol for the Treatment of Essential Systemic Arterial Hypertension: a Systematic Review and Meta-Analysis. Am J Cardiovasc Drugs. 21(2):165–180. doi: 10.1007/s40256-020-00422-0.

Selvan PS, Gowda KV, Mandal U, Solomon WD, Pal TK. 2007. Simultaneous determination of fixed dose combination of nebivolol and valsartan in human plasma by liquid chromatographic-tandem mass spectrometry and its application to pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci. 858(1-2):143–150. doi: 10.1016/j.jchromb.2007.08.016.

Soliman ABE, Pawluk SA, Wilby KJ, Rachid O. 2022. The use of a modified Delphi technique to develop a critical appraisal tool for clinical pharmacokinetic studies. Int J Clin Pharm. 44(4):894–903. doi: 10.1007/s11096-022-01390-y.

Sule SS, Frishman W. 2006. Nebivolol: new therapy update. Cardiol Rev. 14(5):259–264. doi: 10.1097/01.crd.0000223651.03023.8e.

Sullo MG, Perri D, Sibilio M, Rafaniello C, Fucile A, Rossi F, Capuano A. 2015. Hypoglycemia, polycythemia and hyponatremia in a newborn exposed to nebivolol during pregnancy. J Pharmacol Pharmacother. 6(1):45–48. doi: 10.4103/0976-500X.149148.

Toblli JE, DiGennaro F, Giani JF, Dominici FP. 2012. Nebivolol: impact on cardiac and endothelial function and clinical utility. Vasc Health Risk Manag. 8:151–160. doi: 10.2147/VHRM.S20669.

Venkateswarlu B, Jayaprakash D, Anisetti R, Narsaiah N, Reddy MR. 2013. Effect of cefixime on pharmacokinetics of nebivolol in hypertensive patients. Int J Pharm Sci Res. 4(11):4362.

Vespasiano CF, Laurito TL, Iwamoto RD, Moreno RA, Mendes GD, De Nucci G. 2017. Bioequivalence study between a fixed-dose single-pill formulation of nebivolol plus hydrochlorothiazide and separate formulations in healthy subjects using high-performance liquid chromatography coupled to tandem mass spectrometry. Biomed Chromatogr. 31(5). doi: 10.1002/bmc.3884.

Vieira CP, Neves DV, Cesarino EJ, Rocha A, Poirier S, Lanchote VL. 2017. An indirect stereoselective analysis of nebivolol glucuronides in plasma by LC-MS/MS: Application to clinical pharmacokinetics. J Pharm Biomed Anal. 144:25–30. doi: 10.1016/j.jpba.2017.01.054.

Wojciechowski D, Papademetriou V. 2008. Beta-blockers in the management of hypertension: focus on nebivolol. Expert Rev Cardiovasc Ther. 6(4):471–479. doi: 10.1586/14779072.6.4.471.