Drugs (2015) 75:1349–1371
DOI 10.1007/s40265-015-0435-5

REVIEW ARTICLE

A Review of Nebivolol Pharmacology and Clinical Evidence

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Published online: 16 July 2015

Abstract Nebivolol is a highly selective β_1-adrenergic receptor antagonist with a pharmacologic profile that differs from those of other drugs in its class. In addition to cardioselectivity mediated via β_1 receptor blockade, nebivolol induces nitric oxide-mediated vasodilation by stimulating endothelial nitric oxide synthase via β_3 agonism. This vasodilatory mechanism is distinct from those of other vasodilatory β-blockers (carvedilol, labetalol), which are mediated via α-adrenergic receptor blockade. Nebivolol is approved for the treatment of hypertension in the US, and for hypertension and heart failure in Europe. While β-blockers are not recommended within the current US guidelines as first-line therapy for treatment of essential hypertension, nebivolol has shown comparable efficacy to currently recommended therapies in lowering peripheral blood pressure in adults with hypertension with a very low rate of side effects. Nebivolol also has beneficial effects on central blood pressure compared with other β-blockers. Clinical data also suggest that nebivolol may be useful in patients who have experienced erectile dysfunction while on other β-blockers. Here we review the pharmacological profile of nebivolol, the clinical evidence supporting its use in hypertension as monotherapy, add-on, and combination therapy, and the data demonstrating its positive effects on heart failure and endothelial dysfunction.

Key Points

Nebivolol is the only vasodilatory β_1-selective blocker; the vasodilatory effect is nitric oxide-mediated and activated via β_3-agonism.

Nebivolol effectively lowers blood pressure either alone or in combination with other antihypertensive drugs.

The unique pharmacological profile of nebivolol coupled with clinical evidence suggests potential utility in the treatment of hypertension and heart failure with reduced ejection fraction.

1 Introduction

Nebivolol (Bystolic®) is a third-generation, long-acting and highly selective β_1 adrenoreceptor antagonist that also exhibits nitric oxide (NO)-mediated vasodilatory effects via β_3 receptor agonism and reduces oxidative stress [1]. The β_3 receptor agonism differentiates nebivolol from traditional, non-vasodilatory β_1-blockers, such as atenolol, as well as from the vasodilatory β-blockers carvedilol and labetalol, which act via α_1 adrenergic antagonism [1]. Nebivolol does not exhibit intrinsic sympathomimetic activity or membrane-stabilizing activity. In the US, nebivolol is indicated for the treatment of hypertension, either as monotherapy or in combination with other antihypertensive agents, and has been evaluated for the treatment of chronic heart failure.

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In this article, we discuss the unique pharmacology of nebivolol and review its clinical efficacy and safety.

2 Literature Search Methodology

Discussion of safety and efficacy was limited to hypertension, heart failure (HF), and erectile dysfunction. Literature searches, conducted in the period October–December 2014, were performed using the PubMed database (without the limit in regard to date), looking for terms 'nebivolol', 'hypertension', 'blood pressure', 'heart failure', and 'erectile dysfunction' in titles and abstracts, and restricting the results to studies in humans and non-review articles in English language. Both authors examined the resulting lists of abstracts and excluded those that did not fit the scope of the article.

3 Pharmacology of Nebivolol

β-Blockers are a heterogeneous class of compounds that have evolved from first-generation, nonselective agents (e.g., propranolol) to second-generation, cardioselective β_1-blockers (e.g., atenolol, bisoprolol, metoprolol) to third-generation compounds that combine β-blockade with vasodilatory properties (e.g., carvedilol, labetalol, nebivolol) [2]. Nebivolol is highly β_1-selective at doses $\leq$10 mg per day, with approximately 320-fold greater affinity for β_1 than β_2 receptors in the cells of human myocardium [3]. While the vasodilatory properties of carvedilol and labetalol are mediated by α-adrenergic receptor blockade [4], nebivolol exerts these effects by increasing endothelium-derived NO via stimulatory effect on endothelial nitric oxide synthase (NOS), mediated through β_3 agonism [5–8].

The distinct pharmacologic profile of nebivolol is associated with a number of hemodynamically relevant effects: (1) β_1-blockade, which decreases resting and exercise heart rate, myocardial contractility, and both systolic and diastolic blood pressure; (2) NO-mediated vasodilation that results in a decrease in peripheral vascular resistance, an increase in stroke volume and ejection fraction, and maintenance of cardiac output [1]; (3) vasodilation and reduced oxidative stress that are thought to contribute to the neutral and possibly beneficial effects of nebivolol on glucose and lipid metabolism [9, 10]; and (4) reduced platelet volume and aggregation [11, 12]. These attributes suggest a potentially broad usefulness for nebivolol in the treatment of hypertension and chronic heart failure.

4 Clinical Pharmacokinetics of Nebivolol

The absolute bioavailability of nebivolol is unknown. The drug is 98 % protein bound, primarily to albumin, and reaches a peak concentration after 1.5–4 h. Nebivolol is metabolized in the liver, mainly via direct glucuronidation and secondarily through cytochrome P450 2D6 (CYP450 2D6). The active metabolites, hydroxyl and glucuronides, contribute to the β-blocking effect of nebivolol. As with other drugs metabolized via CYP450 2D6, genetic differences can impact metabolism, elimination half-life, excretion, and clinical and adverse effects of nebivolol. It should, however, be noted that data suggests that in CYP450 2D6 poor metabolizers, no dose adjustment is needed as the clinical effect and safety profiles are similar to that of extensive metabolizers [13].

The elimination half-life of nebivolol is typically 12 h, but is prolonged to 19 h in those who are poor metabolizers. Excretion of nebivolol is 35 % through urine and 44 % via feces in average metabolizers; patients who are poor metabolizers excrete 67 % of the drug in urine and 13 % in feces [13].

5 Endothelial and Hemodynamic Effects

Endothelial dysfunction caused by oxidative stress has been implicated in the development of hypertension [14]. A number of studies have demonstrated favorable endothelial effects of nebivolol versus non-vasodilatory β_1-selective blockers (atenolol, metoprolol). For example, nebivolol was shown to be superior to atenolol in improving small artery distensibility index [15], parameters of oxidative stress [16], flow-mediated dilation of the brachial artery [17, 18], and plasma concentration of asymmetric dimethyl arginine (ADMA) [18], an endogenous inhibitor of NO production that has been associated with cardiovascular risk [19]. Compared with metoprolol, nebivolol reduces plasma ADMA levels and the augmentation index (AIx) [20], a surrogate measure of arterial stiffness that is also associated with cardiovascular risk [21]. However, the AIx benefits compared with metoprolol may not extend to individuals with hypertension and diabetes mellitus who are receiving maximal tolerated doses of renin-angiotensin-aldosterone system (RAAS) blockers [22]. Of note, a 12-month randomized trial that compared the effects of nebivolol and metoprolol on a number of hemodynamic and biochemical parameters found no difference in AIx and ADMA levels between the two groups, but demonstrated that only nebivolol had a beneficial effect on oxidative stress [23] and significantly reduced central systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse

pressure (PP), and left ventricular wall thickness [24]. Whether these positive effects translate to improvement of clinical outcomes remains to be seen.

Despite the absence of data from large outcome studies with nebivolol, the vascular effects and hemodynamic profile suggest potential advantages of nebivolol compared with non-vasodilating β_1-selective and nonselective β-blockers in the treatment of hypertension. Central hemodynamic effects are important to highlight, because they are independent predictors of cardiovascular morbidity and mortality [25, 26] and because they may be a key reason why traditional β-blockers (e.g., atenolol) have been associated with smaller reductions in cardiovascular morbidity and mortality than other antihypertensive classes (e.g., calcium channel blockers) [27].

For example, studies have shown that, relative to atenolol and metoprolol succinate, nebivolol improves central hemodynamics and reduces arterial stiffness in patients with hypertension, regardless of similar reductions in peripheral DBP and SBP [24, 28–30]. In one study, 40 individuals with untreated essential hypertension were randomized to atenolol 50 mg/day or nebivolol 5 mg/day for 4 weeks; treatment with nebivolol reduced aortic PP to a significantly greater extent than atenolol (−16 vs −11 mmHg; $p = 0.04$) [29]. Though both compounds significantly reduced aortic pulse wave velocity (PWV) from baseline, only nebivolol treatment was associated with a significant reduction from baseline in AIx (from 35 to 28 %; $p < 0.05$). Furthermore, PP amplification, a hemodynamic indicator inversely associated with large artery stiffness and peripheral arterial resistance [27], was significantly increased with nebivolol treatment and significantly decreased with atenolol. Similar results were obtained in a randomized, cross-over study of 16 patients with untreated isolated systolic hypertension (ISH) [28] who received atenolol 50 mg/day, nebivolol 5 mg/day, and placebo for 5 weeks each. The significant reductions in aortic PWV compared with placebo were similar between nebivolol and atenolol, but nebivolol treatment was associated with a smaller increase in AIx compared with atenolol (6 vs 10 %; $p = 0.04$). The aortic PP after treatment with nebivolol was similar to that of placebo, but was significantly lower compared with treatment with atenolol (50 vs 54 mmHg; $p = 0.02$) [28].

A few more recent publications also provided evidence of improvement in central hemodynamics with nebivolol. For example, in a trial that randomized 45 patients with stage I hypertension to nebivolol (10 mg/day), lifestyle modifications, or the combination of nebivolol and lifestyle modifications for 12 weeks, the β-stiffness index, a blood-pressure-independent measure of arterial stiffness, decreased ($p < 0.01$), and arterial compliance increased ($p = 0.02$) [31]. Another trial randomized 138 patients with mild to moderate hypertension to atenolol (50–100 mg/day) or nebivolol (5 mg/day) for 10 weeks, with hydrochlorothiazide 25 mg/day added on if necessary to control blood pressure. After adjusting for heart rate, the mean between-group difference in AIx was 2.4 % ($p = 0.041$), with nebivolol increasing AIx to a lesser extent than atenolol [30]. Lastly, in a trial that compared nebivolol (5 mg/day) with metoprolol succinate (50–100 mg/day) in patients with mild to moderate hypertension, nebivolol reduced mean central PP from baseline significantly more than metoprolol (−6.2 vs −0.3 mmHg; $p = 0.01$), with no difference from baseline with either agent in PP amplification, PWV, or AIx [24]. The differential effects on aortic PP between nebivolol and atenolol or metoprolol succinate observed in these studies are similar in magnitude to those between the amlodipine- and atenolol-based therapies reported in the Conduit Artery Function Evaluation (CAFE) study [32], a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT; $N = 19{,}257$), which demonstrated a greater reduction in major cardiovascular events and mortality with the amlodipine-based than atenolol-based regimen, despite a similar decrease in brachial blood pressure [33]. The question of whether the more favorable effects of nebivolol on central aortic pressure versus those of non-vasodilating β-blockers translate into improved clinical outcomes would have to be tested in large primary or secondary prevention trials.

As mentioned previously, nebivolol is a β_1-selective blocker that exerts a vasodilatory effect through stimulation of endothelial NOS [1]. The contribution of vasodilation to the overall antihypertensive effect of nebivolol was recently assessed in a small, double-blind, placebo-controlled cross-over study of 20 patients with autonomic failure [34], who are devoid of adrenergic input in blood pressure control and are therefore characterized by an impaired baroreceptor function, as manifested through orthostatic hypotension and supine hypertension. In that trial, nebivolol (5 mg) but not metoprolol (50 mg) lowered night-time SBP ($p = 0.036$) and DBP ($p < 0.001$) versus placebo, effects that were driven by the subgroup of individuals who also responded to sildenafil (25 mg) [34]. This reduction in blood pressure that is independent of β_1-antagonism is consistent with the hypothesis that NO-mediated vasodilation contributes significantly to an overall antihypertensive effect of nebivolol.

While nebivolol's NO-mediated vasodilatory effects may be favorable, there is concern about the development of nitrate tolerance and the adverse endothelial effects that are associated with the continuous long-term use of organic nitrates [1]. In a small study of 16 healthy patients who were taking either nebivolol 5 mg or

placebo for 8 days, forearm blood flow was measured before and after 5 min of intravenous nitroglycerin administration (4 μg/kg body weight/min). The blood flow increase in those receiving nebivolol (96 %) was significantly greater than the increase observed in those receiving placebo (54 %; $p < 0.05$) [35]. This reduction in nitrate tolerance following nebivolol treatment remains to be confirmed in larger trials.

6 Nebivolol for the Treatment of Hypertension

Nebivolol at doses of 1.25–40 mg/day has been evaluated for the treatment of hypertension, both as monotherapy and in combination with other classes of antihypertensive agents (Table 1). It is provided in tablets of 2.5, 5, 10, and 20 mg; for most patients, it is recommended to start with a dose of 5 mg daily, which can be titrated up to 40 mg/day at 2-week intervals [13]. A lower initial dose of 2.5 mg/day is recommended in patients with moderate hepatic and/or severe renal impairment. However, nebivolol should be avoided in patients with severe hepatic impairment and has not been studied in patients who are receiving dialysis [13]. While nebivolol monotherapy is approved in the US for lowering blood pressure, recent treatment guidelines from the American Society of Hypertension and the International Society of Hypertension [36], as well as the Panel Members Appointed to the Eighth Joint National Committee (JNC 8) [37], do not recommend first-line use of β-blockers in patients with essential hypertension. The rationale provided by JNC 8 is based on results from several randomized controlled trials in which either β-blockers performed similarly to the recommended therapies of thiazide-type diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin II receptor blockers (ARBs) or firm conclusions could not be made from the evidence [37]. Additionally, the results of one trial comparing a β-blocker (atenolol) and an ARB (losartan) showed that despite similar reductions in blood pressure, losartan prevented more cardiovascular morbidity and mortality than atenolol [38]. One meta-analysis and one systematic review, which were not included as supporting evidence for recommendations in JNC 8, have also shown no benefit of β-blockers compared with other antihypertensives in reducing cardiovascular morbidity and mortality, along with an increased risk of stroke [39, 40]. It has been noted that atenolol, a non-vasodilating β_1-selective blocker, was used in the large majority of studies included in these meta-analyses, and the finding therefore may not be generalizable to third-generation, vasodilatory β-blockers such as carvedilol and nebivolol [41].

6.1 Monotherapy Data

6.1.1 Pivotal Trials

The approval of nebivolol for the treatment of hypertension in the US was based upon evidence of its efficacy in three large, randomized, placebo-controlled dose-ranging studies in adults with hypertension [42–44]. In each study, patients were randomized to 12 weeks of double-blind treatment with various fixed doses of nebivolol or placebo following a 4- to 6-week single-blind, placebo washout period. The primary efficacy parameter was change from baseline in mean trough DBP; secondary parameters included change from baseline in mean trough SBP and a response rate at endpoint, defined as the proportion of patients with mean trough DBP <90 mmHg or an absolute reduction of ≥10 mmHg from baseline. In total, over 2000 patients were included, with one trial consisting of black participants only [43]. Results from each study consistently showed significant reductions in DBP with nebivolol doses ranging from 5 to 40 mg daily and reductions in SBP at higher daily doses (10–20 mg), as well as significantly higher response rates compared with placebo. A dose-response effect in terms of both SBP and DBP reduction was observed [42–44].

6.1.2 Pooled Analyses

Post-hoc, pooled analyses from the three pivotal trials ($N = 2016$) discussed above were conducted to assess efficacy, safety, and tolerability with a greater statistical power [45], as well as to explore the effects of nebivolol on patients by age [46] and body mass index (BMI) [47]. The pooled data demonstrated a significant effect of nebivolol over placebo on both DBP and SBP for all clinically recommended dosages (5–40 mg/day), and showed that nebivolol is generally safe and well tolerated [45]. The discontinuation rate due to adverse events (AEs) among nebivolol-treated patients (all dosages) was low (2.6 %) and comparable to that observed with placebo (2.0 %). The most common AEs in patients receiving nebivolol were headache (7.1 vs 5.9 % for placebo), fatigue (3.6 vs 1.5 %), and dizziness (2.9 vs 2.0 %).

Similar efficacy results were reported in a pooled analysis of 205 placebo-treated patients and 1380 patients treated with nebivolol dosages of 5, 10, or 20 mg/day, stratified by age (22–46, 47–53, 54–62, and 63–84 years) [46]. In all age groups, each nebivolol dose significantly reduced DBP compared with placebo. All dosages of nebivolol in all age groups significantly lowered SBP versus placebo, with the exception of the oldest age group, in whom a significant effect was observed only with the 20 mg/day dosage [46]. A pooled analysis examining the

Table 1 Summary of nebivolol clinical trials in hypertension

Study	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Nebivolol pivotal trials (monotherapy)					
Saunders et al. [43]	$N = 301$ Inclusion: Blacks with stage I–II primary HTN (DBP 95–109 mmHg) Exclusion: secondary or malignant HTN, BMI >40 kg/m^2, recent MI or stroke, uncontrolled type II diabetes, BB contraindication, severe renal/hepatic disease, or clinically relevant valvular disease/arrhythmia	RCT, DB, PBO-controlled NEB: 2.5, 5, 10, 20, or 40 mg/day Randomization stratified by CYP2D6 metabolizing status, diabetes history, age, and sex Follow-up at 12 weeks	Primary: change in sitting DBP Secondary: change in sitting SBP, response rate (DBP <90 mmHg or DBP decrease ≥10 mmHg), adverse events	DBP (LS mean ± SE, mmHg) NEB: 2.5/5/10/20/40: −5.7 ± 2.1 (NS), −7.7 ± 2.1 ($p = 0.004$), −8.9 ± 2.0 ($p < 0.001$), −8.9 ± 2.1 ($p < 0.001$), −8.3 ± 2.0 ($p < 0.001$) PBO: −2.8 ± 2.1 SBP (LS mean ± SE, mmHg) NEB: −1.9 ± 3.7 (NS), −3.0 ± 3.7 (NS), −6.4 ± 3.6 ($p = 0.044$), −7.6 ± 3.7 ($p = 0.005$),−7.2 ± 3.5 ($p = 0.002$) PBO: −0.4 ± 3.8 Response rate (%) NEB: 36.7 (NS), 58.0 ($p = 0.002$), 58.8 ($p < 0.001$), 64.0 ($p < 0.001$), 56.9 ($p < 0.001$) PBO: 26.5	AEs (%) NEB (combined), 45.0 PBO, 38.8
Weiss et al. [42]	$N = 913$ Inclusion: mild–moderate primary HTN (DBP 95–109 mmHg) Exclusion: secondary or malignant HTN, BMI ≥35 kg/m^2, recent MI or stroke, HF, uncontrolled diabetes, BB contraindication or previous NEB use, severe renal/ hepatic disease, and clinically relevant valvular disease/ arrhythmia	RCT, DB, PBO-controlled NEB: 1.25, 2.5, 5, 10, 20, or 40 mg/day Follow-up at 12 weeks	Primary: change in sitting DBP Secondary: change in sitting SBP, response rate (DBP <90 mmHg or DBP decrease ≥10), adverse events NEB 40 mg/day dose was studied for safety purposes only—no efficacy hypothesis testing was done	DBP (LS mean ± SE, mmHg) NEB: 1.25/2.5/5/10/20/40: −8.0 ± 1.1 ($p < 0.001$), −8.5 ± 1.1 ($p < 0.001$), −8.4 ± 1.0 ($p < 0.001$), −9.2 ± 0.9 ($p < 0.001$), −9.8 ± 0.9 ($p < 0.001$), −11.2 ± 0.9 PBO: −2.9 ± 1.1 SBP (LS mean ± SE, mmHg) NEB: −4.4 ± 1.9 ($p = 0.002$), −6.3 ± 1.9 ($p < 0.001$), −5.9 ± 1.6 ($p < 0.001$) −7.0 ± 1.6 ($p < 0.001$), −6.5 ± 1.6 ($p < 0.001$), −9.5 ± 1.5 PBO: +2.2 ± 1.9 Response rate (%) NEB: 45.8 ($p = 0.008$), 50.0 ($p = 0.001$), 50.3 ($p < 0.001$), 53.6 ($p < 0.001$), 59.6 ($p < 0.001$), 64.5 PBO: 24.7	AEs (%) NEB (combined), 46.1 PBO, 40.7

Table 1 continued

Study	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Greathouse [44]	$N = 811$ Inclusion: stage I–II HTN (DBP 95–109 mmHg) Exclusion: not specified in the manuscript	RCT, DB, PBO-controlled NEB: 5, 10, or 20 mg/day Follow-up at 12 weeks	Primary: change in sitting DBP Secondary: change in sitting SBP, response rate (DBP <90 mmHg or DBP decrease ≥10 mmHg), adverse events	DBP (mean ± SD, mmHg) NEB: 5/10/20: −10.6 ± 7.7 ($p = 0.002$), −11.2 ± 8.1 ($p < 0.001$), −12.0 ± 8.4 ($p < 0.001$) PBO: −7.2 ± 8.2 SBP (mean ± SD, mmHg) NEB: −12.1 ± 14.1 (NS), −10.7 ± 14.8 (NS), −14.6 ± 15.4 ($p < 0.001$) PBO: −7.9 ± 12.8 Response rate (%) NEB: 66.0 ($p = 0.009$), 66.8 ($p = 0.005$), 68.9 ($p = 0.002$) PBO: 49.3	AEs (%) NEB (combined), 42.5 PBO, 36.0 Patients in NEB 20 mg reported significantly higher AE rates than those in PBO (48.4 %: $p = 0.028$)
Nebivolol monotherapy trials					
Lacourcière et al. [51]	$N = 29$ Inclusion: adults, mild to moderate HTN (DBP 95–114 mmHg) Exclusion: secondary HTN, recent CVA or MI, HF, insulin-treated diabetes, BB or ACEI contraindication, severe renal or hepatic disease, or clinically relevant valvular disease or arrhythmia	RCT, DB, cross over, active-controlled NEB: 2.5 mg/day titrated to 10 mg/day Lisinopril: 10 mg/day titrated to 40 mg/day Follow-up at 8 weeks	Change in sitting DBP and SBP	DBP (mean ± SD, mmHg) NEB: −9.1 ± 7.3 Lisinopril: −9.9 ± 8.2 SBP (mean ± SD, mmHg) NEB: −13.9 ± 12.6 Lisinopril: −17.8 ± 17.9	AEs (*N*) NEB, 6 Lisinopril, 12
Van Nueten et al. [55]	$N = 420$ Inclusion: adults with HTN, DBP >95 mmHg Exclusion: secondary or malignant HTN, bradycardia, BB contraindication, severe renal or hepatic disease, recent MI or CVA, HF, Afib, insulin-treated diabetes	RCT, DB, active-controlled NEB: 5 mg/day Nifedipine: 20 mg modified release twice daily Follow-up at 3 months	Primary: changes in trough sitting DBP Secondary: response rate (trough sitting DBP <91 mmHg or decrease ≥10 mmHg)	DBP (mean change, mmHg) NEB: −11.7 Nifedipine: −10.9 Both drugs were effective in lowering DBP from baseline ($p < 0.001$) Response rate (DBP <91 mmHg or DBP decrease ≥10 mmHg, %) NEB: 70 Nifedipine: 67 Response rate (DBP <91 mmHg, %) NEB: 54 ($p = 0.007$) Nifedipine: 42	AEs (%) NEB, 39 Nifedipine, 57

Table 1 continued

Study	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Van Nueten et al. [54]	$N = 364$ Inclusion: aged 18–71 years, mild to moderate HTN (DBP 95–115 mmHg) Exclusion: secondary or malignant HTN, bradycardia, recent MI or CVA, HF, BB contraindication, severe renal or hepatic disease, or clinically relevant valvular disease or arrhythmia	RCT, DB, PBO- and active-controlled NEB: 5 mg/day Atenolol: 50 mg/day Follow-up at 1 month	Primary: change in sitting DBP Secondary: changes in sitting SBP, response rate (sitting DBP ≤90 mmHg), adverse events	Data are estimates of mean changes from graphs DBP (mean, mmHg) NEB: −12.5, Atenolol: −12.5, PBO: −5.0 SBP (mean, mmHg) NEB: −17.5, Atenolol: −17.5, PBO: −5.0 Response rate (%) NEB: 59, Atenolol: 59, PBO: 29 ($p < 0.001$ both drugs vs PBO)	AEs (%) NEB, 28 Atenolol, 31 PBO, 25
Grassi et al. [50]	$N = 205$ Inclusion: aged 19–75 years, mild to moderate HTN (DBP 95–114 mmHg) Exclusion: secondary or malignant HTN, bradycardia, recent MI or CVA, HF, BB contraindication, severe renal/hepatic disease, or clinically relevant valvular disease or arrhythmia	RCT, DB, active-controlled NEB: 5 mg/day Atenolol: 100 mg/day HCTZ: 12.5 mg/day added to each group at week 8 if BP ≥140/90 mmHg or decrease in DBP ≤10 mmHg Follow-up at 12 weeks	Primary: change in sitting DBP and SBP Secondary: response rate (BP <140/90 mmHg or DBP reduction >10 mmHg), adverse events	DBP (mean ± SD, mmHg) NEB: −14.8 ± 7.1, Atenolol: −14.6 ± 7.9 ($p < 0.001$ change from baseline for both) SBP (mean ± SD, mmHg) NEB: −19.1 ± 12.9, Atenolol: −18.2 ± 14.0 ($p < 0.001$ change from baseline for both) Response rate (%) NEB: 47.8 Atenolol: 36.9	AEs (%) NEB, 14 Atenolol, 25 ($p < 0.001$)
Van Bortel et al. [53]	$N = 298$ Inclusion: adults with mild to moderate HTN (DBP 95–114 mmHg) Exclusion: SBP >200 mmHg, aged >70 years, uncontrolled concomitant illness, serum creatinine >1.8 mg/dL, recent MI/stroke, HF	RCT, DB, active-controlled NEB: 5 mg/day Losartan: 50 mg/day HCTZ: 12.5 mg/day added to each group at week 6 if DBP ≥90 mmHg Follow-up at 12 weeks	Changes in sitting DBP and SBP, response rate [complete responders (DBP ≤90 mmHg), partial responders (DBP >90 mmHg with decrease in DBP ≥10 mmHg)]	DBP (mean change, mmHg) NEB: −12 ($p < 0.02$ vs losartan) Losartan: −10 SBP (mean change, mmHg) NEB: −15 (NS vs losartan) Losartan: −18 Response rate (sum of partial and complete responders, %) NEB: 65.3 (NS vs losartan) Losartan: 58.3	AEs (%) NEB, 19 Losartan, 31

Table 1 continued

Study	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Punzi et al. [49]	$N = 277$ Inclusion: self-identified Hispanic, stage I–II HTN (DBP 95–114 mmHg) Exclusion: secondary/severe HTN, CAD requiring use of a BB, significant CVD, HF, uncontrolled type I or II diabetes, active liver or renal impairment	RCT, DB, PBO-controlled NEB: 5 mg/day titrated to 40 mg/day to achieve BP control Follow-up at 8 weeks	Primary: change in sitting DBP Secondary: change in sitting SBP, adverse events	48.9 % titrated to NEB 40 mg/day DBP (mean ± SD, mmHg) NEB: −11.1 ± 8.8 ($p < 0.0001$) PBO: −7.3 ± 8.9 SBP (mean ± SD, mmHg) NEB: −14.1 ± 12.7 ($p = 0.001$) PBO: −9.3 ± 13.0	AEs (%) NEB, 17.0 PBO, 22.1
Giles et al. [48]	$N = 641$ Inclusion: aged 18–54 years with stage I–II HTN (DBP 90 to <110 mmHg if on anti-HTN meds or 95 to <110 without) Exclusion: secondary/severe HTN, on >2 HTN meds, upper arm circumference >42 cm, CAD, type I or uncontrolled type II diabetes, heart block, or sick sinus syndrome	RCT, DB, PBO-controlled NEB: 5 mg/day titrated to 20 mg/day to achieve BP control Randomization stratified by BMI (<30 or ≥30 kg/m^2) Follow-up at 8 weeks	Primary: change in sitting DBP Secondary: change in sitting SBP, percent achieving treatment goal (<140/90 mmHg or <130/80 with diabetes), response rate (achieved treatment goal or decrease of ≥10 mmHg SBP or ≥8 mmHg DBP), adverse events	DBP (mean ± SD, mmHg) NEB: −11.8 ± 8.8 ($p < 0.001$) PBO: −5.5 ± 9.5 SBP (mean ± SD, mmHg) NEB: −13.7 ± 14.5 ($p < 0.001$) PBO: −5.5 ± 13.9 BP control (%) NEB: 38.3 ($p < 0.001$) PBO: 25.1 Response rate (%) NEB: 72.8 ($p < 0.001$) PBO: 47.9	AEs (%) NEB, 34.7 PBO, 32.2
Nebivolol add-on and combination trials					
Papademetriou [58]	$N = 845$ Inclusion: adults with stage I–II HTN (DBP 95–109 mmHg) who finished 1 of 3 pivotal trials Exclusion: same as 3 pivotal trials	RCT, DB, extension study NEB: 5, 10, or 20 mg/day Non-responders (DBP ≥90 mmHg) given higher NEB dose and/or thiazide or amlodipine 5 mg/day. At next follow-up could add thiazide with triamterene or amlodipine 10 mg/day Follow-up at 9 months	Primary: change in sitting DBP Secondary: change in sitting SBP, response rate (DBP decrease ≥10 mmHg or DBP ≤90 mmHg)	DBP (mean change [95% CI], mmHg) NEB monotherapy: −15.0 [−15.9 to −14.1] NEB + diuretic: −12.0 [−13.2 to −10.8] SBP (mean change [95% CI], mmHg) NEB monotherapy: −14.8 [−16.6 to −13.1] NEB + diuretic: −16.2 [−19.0 to −13.4] Response rate (%) NEB monotherapy: 74 NEB + diuretic: 65.5 Note: number of patients taking NEB + CCB too small to make meaningful comparisons	AEs (%) NEB monotherapy, 15.6 NEB + diuretic, 18.5

Table 1 continued

Study	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Neutel et al. [59]	$N = 669$ Inclusion: uncontrolled stage I–II HTN (DBP 90–109 mmHg), background treatment with 1 or 2 anti-HTN meds (ACEI, ARB, or diuretic) Exclusion: secondary/malignant HTN, bradycardia, BMI >35 kg/m^2, contraindication to BBs, uncontrolled diabetes, history of MI or cerebrovascular disease, HF, Afib or recurrent tachyarrhythmia, severe renal/hepatic disease	RCT, DB, PBO-controlled NEB: 5, 10, or 20 mg/day added to ongoing therapy PBO added to ongoing therapy Follow-up at 12 weeks	Primary: change in sitting DBP Secondary: change in sitting SBP, response rate (DBP <90 mmHg or decrease in DBP ≥10 mmHg), percent achieving treatment goal (<140/90 mmHg), adverse events	DBP (LS mean change ± SE, mmHg) NEB: 5/10/20: −6.6 ± 1.0, −6.8 ± 1.0, −7.9 ± 1.1 (all $p < 0.001$ vs PBO) PBO: −3.3 ± 1.04 SBP (LS mean change ± SE, mmHg) NEB: 5/10/20: −5.7 ± 1.7 ($p < 0.001$), −3.7 ± 1.7 ($p = 0.015$), −6.3 ± 1.7 ($p < 0.001$) PBO: −0.1 ± 1.7 Response rate (%) NEB: 53.0 ($p = 0.028$), 60.1 ($p = 0.001$), 65.1 ($p < 0.001$) PBO: 41.3 BP control (%) NEB: 43.2, 41.3, 52.7 (all $p \leq 0.029$) PBO: 29.3	AEs (%) NEB (combined doses), 40.2 PBO, 38.9
Weber et al. [60]	$N = 656$ Inclusion: untreated stage II diastolic HTN (DBP 100–110 mmHg) Exclusion: secondary HTN (SBP ≥180 mmHg or DBP ≥110 mmHg), recent stroke or MI, renal/hepatic disease, BB or ACEI contraindication	RCT, DB, PBO-controlled NEB: 5 mg/day, titrated to 20 mg/day Lisinopril: 10 mg/day, titrated to 40 mg/day NEB + lisinopril: 5/20 + 10/40 mg/day Follow-up at 6 weeks	Primary: change in sitting DBP Secondary: change in SBP, response rate (either BP <140/90 mmHg or <130/80 if diabetic), adverse events All statistical comparisons were versus combination treatment	DBP (mean ± SD, mmHg) NEB + lisinopril: −17.2 ± 10.2 NEB: −13.3 ± 8.9 ($p \leq 0.001$) Lisinopril: −12.0 ± 9.1 ($p \leq 0.001$) PBO: −8.0 ± 9.2 ($p \leq 0.001$) SBP (mean ± SD, mmHg) NEB + lisinopril: −19.2 ± 19.8 NEB: −14.4 ± 14.1 ($p < 0.05$) Lisinopril: −16.1 ± 17.2 (NS) PBO: −9.3 ± 16.4 ($p \leq 0.001$) Response rate (%) NEB + lisinopril: 33.9 NEB: 21.6 ($p = 0.003$) Lisinopril: 21.7 ($p = 0.003$) PBO: 7.5 ($p < 0.001$) Note: large PBO effect on BP compared with baseline	AEs (%) NEB + lisinopril, 30.7 NEB, 27.1 Lisinopril, 30.7 PBO, 30.5

Table 1 continued

Study	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Weiss et al. [61]	$N = 491$ Inclusion: primary HTN (SBP 170–200 mmHg untreated, 155–180 mmHg on 1 anti-HTN med, or 140–170 mmHg on 2 meds) Exclusion: secondary HTN, HF, recent MI/CVA, renal impairment, asthma/COPD, recent MI	RCT, DB, PBO-controlled 4-weeks lead-in period, background treatment initiated (lisinopril 10–20 mg/day; losartan 50–100 mg/day) NEB: 5–40 mg/day, titrated to BP goal Follow-up at 12 weeks	Primary: change in sitting SBP Secondary: change in DBP, percent achieving BP goal (<140/90 mmHg or <130/80 with diabetes), adverse events	DBP (mean ± SD, mmHg) NEB: −7.8 ± 10.1 ($p < 0.001$) PBO: −3.5 ± 10.6 SBP (mean ± SD, mmHg) NEB: −10.1 ± 16.9 (NS) PBO: −7.3 ± 15.9 BP control (%) NEB: 17.6 ($p = 0.022$) PBO: 10.3	AEs (%) NEB, 28.3 PBO, 22.3
Giles et al. [62]	$N = 4118$ Inclusion: adults with stage I–II HTN (DBP 90–109 mmHg treated, 95–109 mmHg untreated) Exclusion: secondary HTN, SBP ≥180 mmHg or DBP ≥110 mmHg, >4 anti-HTN meds, HF, poorly controlled type II diabetes, renal impairment	RCT, DB, PBO-controlled Randomized 2:2:2:2:2:2:2:1 NEB/VAL SPC: 5 and 80 mg/day, 5 and 160 mg/day, or 10 and 160 mg/day NEB: 5 or 20 mg/day VAL: 80 or 160 mg/day All doses were doubled at week 5 Follow-up at 8 weeks	Primary: change in seated DBP Secondary: change in seated SBP, adverse events	DBP (mean ± SD, mmHg) NEB/VAL SPC 20 and 320 mg/day: −15.7 ± 9.6 NEB 40: −14.4 ± 9.4 ($p = 0.03$) VAL 320: −11.2 ± 9.3 ($p < 0.001$) All other comparisons were significant favoring SPC SBP All comparisons significant favoring SPC	Similar across all treatment groups

ACEI angiotensin-converting enzyme inhibitor, *AEs* adverse events, *Afib* atrial fibrillation, *ARB* angiotensin II receptor blocker, *BB* β-blocker; *BMI* body mass index, *BP* blood pressure, *CAD* coronary artery disease, *CCB* calcium channel blocker, *COPD* chronic obstructive pulmonary disease, *CVA* cerebrovascular accident, *CVD* cardiovascular disease, *DB* double-blind, *DBP* diastolic blood pressure, *HCTZ* hydrochlorothiazide, *HF* heart failure, *HTN* hypertension, *LS* least squares, *MI* myocardial infarction, *NEB* nebivolol, *NS* not significant, *PBO* placebo, *RCT* randomized controlled trial, *SBP* systolic blood pressure, *SD* standard deviation, *SE* standard error, *SPC* single pill combination, *VAL* valsartan

effects of nebivolol treatment on patients stratified by baseline BMI [<30 kg/m^2 (non-obese) or BMI ≥30 kg/m^2 and ≤35 kg/m^2 (moderately obese)] demonstrated that nebivolol at doses ranging from 5 to 40 mg/day significantly reduced DBP and SBP versus placebo in both BMI categories [47]. Response rates at the end of treatment were significantly higher for all nebivolol dosages ≥2.5 mg/day in the non-obese group and ≥5 mg/day in the moderately obese group [47].

6.1.3 Monotherapy Trials in Special Populations

Placebo-controlled trials of nebivolol monotherapy in specific patient populations include one conducted in younger patients (age range, 18–54 years; mean age, 45.3 years) with stage 1 or stage 2 hypertension in which nebivolol significantly reduced DBP (change from baseline: −11.8 mmHg vs −5.5 mmHg; $p < 0.001$) and SBP (change form baseline: −13.7 mmHg vs −5.5 mmHg; $p < 0.001$), compared with placebo [48]. A trial conducted in self-identified Hispanics also demonstrated a significant decrease in DBP (change from baseline: −11.1 mmHg vs −7.3 mmHg; $p < 0.0001$) and SBP (−14.1 mmHg vs −9.3 mmHg; $p = 0.001$) with nebivolol treatment, compared with placebo [49]. Finally, in the pivotal trial conducted in African-Americans, nebivolol significantly reduced both DBP at all doses ≥5 mg (5 mg, $p = 0.004$; 10, 20, and 40 mg, $p < 0.001$) and SBP at all doses ≥10 mg (10 mg, $p = 0.044$; 20 mg, $p = 0.005$; 40 mg, $p = 0.002$) compared with placebo [43].

6.2 Nebivolol Versus Active Comparators

The antihypertensive efficacy of nebivolol monotherapy has been established in controlled trials with active comparators [24, 28–30, 50–54]. Two such studies compared nebivolol to the non-vasodilatory β_1-selective blocker, atenolol, in adults with mild to moderate hypertension [50, 54]. In one study, 364 patients were randomized to nebivolol 5 mg/day, atenolol 50 mg/day, or placebo. Results indicated that both active compounds were statistically superior to placebo and comparable to each other in terms of reducing DBP and SBP [54]. In another study, 205 patients were randomized to nebivolol 5 mg/day or atenolol 100 mg/day, and the diuretic hydrochlorothiazide (HCTZ; 12.5 mg/day) was added to either treatment arm after 8 weeks if BP control was not achieved (approximately 20 % in each group required concomitant HCTZ treatment) [50]. Comparable to the trial discussed previously, treatment with nebivolol and atenolol resulted in similarly significant antihypertensive effects versus baseline, with reductions in DBP and SBP of −14.8 mmHg and −19.1 mmHg for nebivolol, and −14.6 mmHg and −18.2 mmHg for atenolol ($p < 0.001$, all). Addition of HCTZ resulted in an equal additional antihypertensive effect in both groups versus monotherapy ($p < 0.03$) [50].

Nebivolol was also tested in active-controlled trials with ACEIs, ARBs, and CCBs [51–53, 55]. In an 8-week, crossover, double-blind, randomized trial, significant and comparable reductions in DBP and SBP were observed with nebivolol (2.5–10 mg/day) and lisinopril (10–40 mg/day) [51]. In a 12-week, randomized, double-blind trial, nebivolol (5 mg/day) significantly reduced DBP (−12 mmHg at 6 and 12 weeks) versus losartan (50 mg/day; −8 mmHg and −10 mmHg after 6 and 12 weeks, respectively) [53], with significantly more losartan-treated patients requiring add-on HCTZ (12.5 mg/day) treatment to achieve BP control. Similar significant reductions in SBP from baseline were observed with nebivolol and losartan. In two separate trials, the efficacy of nebivolol was comparable in lowering SBP and DBP with the dihydropyridine CCBs, sustained-release nifedipine, and amlodipine, with the exception that more patients required the addition of HCTZ to achieve BP control in the trial with amlodipine [52, 55].

6.3 Add-On and Combination Trials

Many patients with hypertension require more than a single antihypertensive agent to achieve target blood pressure [56, 57]. The efficacy of nebivolol monotherapy and in combination with other antihypertensive therapies was studied in a double-blind 9-month extension study [58] in which 845 patients from one of three 12-week studies [42–44] received nebivolol monotherapy [$N = 607$ (72 %)], nebivolol plus diuretic [$N = 206$ (24 %)], nebivolol plus amlodipine ($N = 21$ (2 %)], or nebivolol plus other antihypertensive medication [$N = 11$ (1 %)]. Significant decreases in mean DBP and SBP from baseline were observed with nebivolol monotherapy (−15.0 and −14.8 mmHg, respectively) and nebivolol plus diuretic (−12.0 and −16.2 mmHg, respectively). Overall, 74 % of patients treated with nebivolol monotherapy and 65.5 % of those treated with nebivolol plus diuretic responded to treatment (DBP ≤90 mmHg or decrease in DBP ≥10 mmHg) [58]. In a separate trial in patients with uncontrolled stage 1 or stage 2 hypertension, 12 weeks of treatment with nebivolol (5, 10 or 20 mg/day) added to ongoing antihypertensive therapy (ACEI, ARB, and/or diuretic) significantly reduced blood pressure versus placebo (placebo-subtracted least squares mean reduction range: DBP −3.3 to −4.6 mmHg, $p < 0.001$ all; SBP −3.7 to −6.2 mmHg, $p \leq 0.015$ all) and resulted in significantly more responders (range: 53.0–65.1 vs 41.3 %; $p \leq 0.028$ all) [59].

In a 6-week double-blind, placebo-controlled trial in patients with stage 2 hypertension [60], the effect of a

nebivolol/lisinopril (5–20 and 10–40 mg/day, respectively) combination on baseline-to-endpoint change in DBP (primary efficacy parameter) was significantly greater than those of placebo ($p < 0.001$), nebivolol alone (5–20 mg/day, $p = 0.001$), and lisinopril alone (10–40 mg/day, $p < 0.001$). The change from baseline in SBP with the nebivolol/lisinopril combination was also significantly reduced compared with placebo ($p < 0.001$) and nebivolol ($p < 0.05$), but not versus lisinopril monotherapy [60]. A separate 12-week trial [61] investigated nebivolol (5–40 mg/day) as add-on therapy to lisinopril (10–20 mg/day) or losartan (50–100 mg/day) in patients with untreated or uncontrolled hypertension treated with lisinopril or losartan. Nebivolol as add-on therapy significantly reduced mean DBP versus placebo (−7.8 vs −3.5 mmHg; $p < 0.001$), while the effects on SBP did not reach significance (−10.1 vs −7.3 mmHg). The authors suggested that a relatively strong placebo effect in this trial may limit data interpretation [61].

Finally, an 8-week double-blind trial compared a single-pill combination (SPC) of nebivolol and valsartan (10/160, 10/320, and 20/320 mg/day) in patients with stage 1 or stage 2 hypertension [62] with nebivolol (10 or 40 mg/day), valsartan (160 or 320 mg/day), and placebo. All comparisons for change in DBP and SBP were significant in favor of the SPCs versus their monotherapy components [62].

7 Nebivolol for the Treatment of Heart Failure (HF)

According to the 2013 American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) guidelines, the current standard treatment for HF is a combination of a RAAS inhibitor (an ACEI or an ARB) and a β-blocker [63]. β-blockers may improve the condition of patients with HF by reducing the myocardial workload (via lower heart rate) and by decreasing sudden death through reduction of arrhythmias [64]. The three β-blockers currently recommended by the ACCF/AHA guidelines—bisoprolol, carvedilol, and metoprolol succinate—were chosen based on observed reductions in mortality in multiple large-scale clinical studies [65–67]. Patients with fluid retention can also be given a loop diuretic. In the case of patients who have left ventricular ejection fraction (LVEF) of ≤35 %, an aldosterone antagonist should be considered [63].

Elevated adrenergic activity in the heart muscle after injury causes a progressive degeneration that leads to left ventricular dysfunction and reduced LVEF. It follows that an adrenergic blockade would slow this degeneration and increase survival [65], and numerous studies have shown that treatment regimens that include a β-blocker can reduce HF-related mortality [66–68]. A recent meta-analysis on β-blocker use in HF patients with reduced ejection fraction (HFrEF) showed that β-blocker treatment confers a significant mortality reduction compared with placebo or active comparator (odds ratio [95 % confidence interval (CI)]: 0.71 [0.64–0.80]; $p < 0.001$) [68]. Improvements up to 4 % were observed in LVEF, as well as reductions in sudden deaths and deaths from cardiovascular disease; these benefits occurred regardless of the treatment duration or β-blocker type [68]. However, the mechanisms of action through which β-blockers confer benefits in HF may not be limited to β-adrenergic blockade. The vasodilatory agents (nebivolol, carvedilol, labetalol) can reverse hypertension-related arterial remodeling [1, 2, 69] and arterial stiffness, both strongly associated with HF [70]. The exact role of those mechanisms, such as NO-mediated vasodilation in case of nebivolol [1, 69], would have to be examined in dedicated trials [64].

7.1 Nebivolol Studies in HF

Although nebivolol is currently not approved by the US Food and Drug Administration (FDA) for HF treatment, numerous studies suggest that it may be effective in treating patients with HF (Table 2). For example, in a randomized, double-blind study conducted in patients with uncomplicated hypertension, nebivolol (5 mg/day) preserved cardiac output while decreasing peripheral resistance [71]. Additionally, several studies conducted in patients with hypertension have shown that the hemodynamic effects of nebivolol are similar to or more favorable than those associated with the three ACCF/AHA-recommended β-blockers [70–72]. While these studies included individuals with hypertension but without HF, the observed hemodynamic effects indicate that nebivolol may have favorable effects in HF. Furthermore, results from a small-scale HF study indicate that, in patients with HFrEF, nebivolol significantly lowers heart rate and SBP and improves stroke volume [72]. Results from another study suggest that nebivolol may be beneficial over metoprolol tartrate as it does not invoke the same negative hemodynamics seen with initiation of metoprolol tartrate [increased pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP) and decreased cardiac output (CI)] [73]. In a 12-month, randomized trial ($N = 26$) in patients with HF and preserved LVEF (HFpEF), hemodynamic improvements and exercise tolerance with nebivolol were greater than those observed with atenolol [74]. Finally, in the CARNEBI (Multiparametric comparison of CARvedilol, vs NEbivolol, vs BIsoprolol in moderate heart failure) cardiopulmonary trial, 70 patients with moderate HF who were given carvedilol, nebivolol, and bisoprolol for 2 months each showed improvements on measures of lung diffusion

Table 2 Summary of nebivolol studies in heart failure

References	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Hemodynamic studies					
Brune et al. [72]	$N = 10$ Inclusion: angiographically confirmed CAD and HF (mean EF of 46 %) Exclusion: NA	Cross-over, 3-day washout trial NEB: 5 mg/day No drug Off drug Follow-up 7 days	Changes in Swan-Ganz measured PAP, PCWP, CO, MAP, HR and RAP at rest and during standardized bicycle ergometry pre- and post-intervention; AEs	No effect on work capacity, PAP, PCWP, CO or RAP Resting and exertion SBP (mmHg): 83–130 no drug, 80–121 NEB ($p < 0.05$); 103–140 off drug, 97–140 NEB ($p < 0.05$) Resting and exertion HR (bpm): 61–107 no drug, 51–75 NEB; 104–135 no drug, 85–121 NEB ($p < 0.05$) Resting and exertion stroke volume (mL): 51–108 no drug, 73–106 NEB ($p < 0.05$); 57–135 no drug, 64–163 NEB ($p < 0.05$)	No significant AEs
Hemodynamic comparison studies					
Triposkiadis et al. [73]	$N = 20$ Inclusion: LVEF ≤35 %, stable with chronic systolic ischemic/idiopathic HF NYHA III, on furosemide + ACEI Exclusion: BB treatment, hemodynamic instability, SBP <90 mmHg, HR <50 bpm, ACS or revascularization ≤3 months, mod-severe MR, other primary valve or congenital heart disease, frequent PVCs, non-sustained/sustained VT, Afib, high degree AV block, renal/hepatic failure, BB contraindications	RCT Single oral dose NEB: 5 mg Metoprolol tartrate 50 mg	Hemodynamics via PA catheter pre-intervention and hourly for 4 h post-intervention and at 6 h post-intervention; AEs	No changes in SBP, DBP, and MAP. HR decreased in both groups and was lower with metoprolol Mean RAP did not change with NEB, increased with metoprolol. PAP and PCWP did not change with NEB, increased with metoprolol PVR did not change with NEB, increased with metoprolol SVR decreased with NEB, increased with metoprolol CI did not change with NEB, decreased with metoprolol	NEB AEs (*N*): headache, 2 nausea, 2 Metoprolol AEs (*N*): nausea, 2 dyspnea, 1 headache, 1 vomiting, 1
Contini et al. [75]	$N = 61$ Inclusion: aged 18–80 years, BB treatment ≥6 months, idiopathic or ischemic dilated cardiomyopathy, previous evidence of LVEF ≤40 %, stable NYHA class I–III Exclusion: history of pulmonary embolism, primary valvular heart disease, pericardial disease, severe obstructive lung disease, primary pulmonary hypertension, occupational lung disease, asthma, severe renal failure, significant peripheral vascular disease, second-degree atrioventricular block, exercise-induced angina and/or ischemic SVT changes and/or repetitive ventricular arrhythmias, BB contraindications, inability to perform pulmonary tests	RCT, cross-over Maximal tolerated dose of carvedilol, NEB, or bisoprolol BID Follow-up at 8 weeks	Clinical conditions, quality of life, laboratory data, echocardiographic evaluation, spirometry, alveolar capillary membrane diffusion, chemoreceptor response, cardiopulmonary exercise test, response to hypoxia during constant workload exercise	No changes in clinical conditions, NYHA class and Minnesota questionnaire, renal function, hemoglobin concentration, or BNP DL_{CO} was lower on carvedilol than NEB or bisoprolol ($p < 0.0001$) With carvedilol, constant workload exercise showed in hypoxia a faster VO_2 kinetic and a lower ventilation Peripheral and central sensitivity to CO_2 was lower in carvedilol Response to hypoxia was higher with bisoprolol Ventilation efficiency (VE/VCO_2 slope) was lower with carvedilol (26.9 ± 4.1; $p < 0.001$) than with NEB (28.8 ± 4.0), or bisoprolol (29.0 ± 4.4) Peak VO_2 was lower with carvedilol (15.8 ± 3.6 mL/kg/min; $p < 0.001$), than with NEB (16.9 ± 4.1), or bisoprolol (16.9 ± 3.6)	Carvedilol AEs (*N*): drug intolerance, 1 death, 1 Bisoprolol AEs (*N*): drug intolerance, 1

Table 2 continued

References	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Systolic heart failure/HFrEF studies					
Brehm et al. [76]	$N = 12$ Inclusion: angiography prior to study, stable condition ≥4 weeks prior to study on standard therapy with ACEI, diuretics, digoxin Exclusion: NA	RCT, DB, PBO-controlled NEB: 2.5 mg/day to 5 mg/day Follow-up of 12 weeks	Bicycle ETT pre-intervention and at 12 weeks, weekly HR, BP, and Echo evaluation of left atrial diameter, end diastolic left ventricular dimensions, left ventricular systolic diameter, LVEF, and fractional shortening, and AEs	HR (bpm): 74.3 BL, 64.0 at 12 weeks with NEB ($p \leq 0.036$). SBP (mmHg) increased from 120.0 to 127.8 after 3 weeks and was 126.7 at 12 weeks (NS); a minor decrease with PBO. DBP decreased by 10 mmHg at 2 weeks ($p \leq 0.019$) and remained lower by 9 mmHg at weeks 12 ($p \leq 0.058$); no change with PBO. NYHA: all patients were class III at BL; 4 from both groups increased to class II with remaining 4 unchanged. Bicycle ETT: work capacity was constant after 12 weeks NEB; test max duration was not different between groups; maximal HR during exercise decreased from 134.7 to 112.7 bpm ($p \leq 0.004$) after 12 weeks Echo: LV end systolic diameter decreased from 56.5 to 50.2 mm after 12 weeks with NEB ($p \leq 0.019$); no change with PBO LVEF improved by 34 % after 12 weeks with NEB ($p \leq 0.01$); no acute worsening with drug up titration	No significant AEs
Uhlir et al. [82]	$N = 91$ Inclusion: aged 18–75 years, NYHA II/III due to ischemic heart disease or cardiomyopathy for ≥3 months, on diuretics and/or digoxin, reproducible exercise time of 6–20 min on 2 occasions, LVEF <40 %, competent Exclusion: resting SBP ≤100 mmHg and/or DBP ≤65 mmHg, asthma or COPD, HR <60 bpm, recurrent tachyarrhythmia, sick sinus syndrome, valvular heart disease, type I diabetes, obesity, significant renal/hepatic disease, ACEI treatment 3 months prior to trial, CCB within 1 month prior to trial, contraindications to BBs	RCT, DB, PBO-controlled 1-month single-blind PBO run-in NEB: 2.5 or 5 mg/day Follow-up 14 weeks Concomitant NTG use was permitted	Bicycle ETT, CT ratio, ECG, Echo, and blood/urine analysis at BL, weeks 4 of run-in, and weeks 8 and 14; visual analog scale, SE, and NYHA scaling at BL, weeks 4 of run-in and weeks 1, 2, 4, 8 and 14; HR and BP at BL, weeks 4 of run-in and weeks 1, 2, 4, 8, and 14; NEB level at weeks 14; AEs	ETT: BL was similar between groups and improved with NEB 2.5 mg gaining 109 s (17 % improvement; $p = 0.003$), 5 mg 61 s (8 %; $p = 0.006$), and PBO 89 s (10 %; $p = 0.037$) vs BL. No difference between groups at any point (2 pts in the PBO group were significant outliers) Echo: no change between the groups at endpoint. The 2.5-mg group did see a significant increase in EF from 30 % to 34 %, but this is within expected reader error Visual analog scale: all symptoms, except nocturnal dyspnea, improved with PBO and NEB 5 mg; the only difference between groups was on fatigue, favoring 2.5 mg over 5 mg ($p = 0.013$) and nocturnal dyspnea between the 2.5 mg and PBO group in favor of 2.5 mg ($p = 0.049$) NYHA: PBO: 19 patients in II, 10 in III at BL; at endpoint, 23 in II, 6 in III. 2.5 mg: 19 in II, 10 in III at BL; at endpoint, 1 in I, 26 in II, 1 in III. 5 mg: 27 in II, 6 in III at BL; at endpoint, 2 in I, 27 in II, 4 in III CT ratio: mean ratio decreased in NEB and PBO (2.5 mg vs PBO; $p = 0.009$ and 5 mg vs PBO; $p = 0.012$) BP and HR: no difference between groups in SBP; standing DBP was lower in NEB vs PBO (2.5 mg mean 84.4 mmHg and 5 mg 83.1 mmHg vs PBO 89.3 mmHg; $p < 0.05$ for both); HR was reduced with NEB vs PBO (2.5 mg mean 68 bpm and 5 mg 66.8 bpm vs PBO 76.3 bpm; $p < 0.01$ both)	NEB 2.5 mg AEs (*N*): HF worsening, 1 NEB 5 mg AEs (*N*): angina worsening, 1 bradycardia, 1

Table 2 continued

References	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Edes et al. [83]	$N = 259$ Inclusion: hospitalized or outpatient, aged >65 years, NYHA II–IV, stable, LVEF ≤35 %, and stable HF meds (ACEI/ARB, diuretics and/or digitalis) for ≥2 weeks Exclusion: ACS, MI ≤3 months, PTCA or CABG ≤1 month, HCM or HOCM, hemodynamically relevant congenital/valvular heart disease, treatment resistant tachyarrhythmia, bradycardia, recent BB therapy (≤4 weeks), BB contraindication	Sequential RCT, PBO-controlled NEB: 1.25 mg/day, doubled bi-weekly to highest tolerated dose, up to 10 mg/day Follow-up: 8 months	Efficacy: LVEF (primary), NYHA class change, QOL, hospitalizations, death, BP/HR, other medications, compliance Safety: AEs, ECG at rest, 24-h Holter monitor, laboratory studies	LVEF: improved by 7 % ($p = 0.027$) vs PBO (4 %); relative improvement was 36 % NEB vs 19.2 % PBO ($p = 0.008$) No difference in improvement in NYHA or QOL score All patients had at least 1 ER visit and at least 1 hospitalization; no difference in survival BP/HR: by week 40, HR was lower with NEB (76.9–67.1 bpm; $p < 0.001$) with no change with PBO. No change in BP from BL	Drug-related AEs (*N*): NEB, 40 PBO, 14 ($p < 0.001$)
Systolic heart failure/HFrEF comparison studies					
Lombardo et al. [77]	$N = 70$ Inclusion: chronic HF, LVEF ≤40 %, NYHA II–III, stable ≥4 weeks Exclusion: SBP/DBP <90 mmHg/ <60 mmHg, HR <50 bpm, CVA ≤6 months, heart or vascular surgery or MI ≤3 months, serious valvular conditions, AV conduction abnormality, malignancies, serious liver, kidney, connective tissue, respiratory or hematologic disease, allergies, intolerance to ACEI, unstable angina, diabetes, digoxin intolerance, BMI >30, exercise tolerance limited, patients on IC antiarrhythmic, CCB, α- or β-blockers/ agonists	RCT, open label NEB: 1.25–5 mg/day, based on tolerability Carvedilol ($N = 35$) 3.15–25 mg BID, based on tolerability Follow-up >6 months	NYHA, BP, ECG, symptoms, 24-h Holter monitor, Echo evaluation LVEDV, LVESV, LVEF, LAD, transmitral peak E, peak A velocities, E/A ratio, mitral and tricuspic regurgitation, LV outflow tract velocity, RV systolic pressure, ventilatory function, proBNP, 6MWT, AEs	LVEDV decreased and LVEF increased in both groups; no change from BL in these and other Echo studies Resting HR decreased in both groups No difference between groups in ventilator function. BP decreased in both groups and NYHA class decreased with carvedilol The 6MWT showed a trend towards increased time in both groups. NEB was as effective as carvedilol	No difference in AEs between groups
Marazzi et al. [78]	$N = 160$ Inclusion: CHF, LVEF <40 %, NYHA I–III, HTN, clinically stable for last 3 months Exclusion: asthma, severe COPD, severe liver or kidney disease, cardiac contraindication to or currently on BB therapy	RCT, open label NEB: 10 mg/day Carvedilol: 25 mg BID Follow-up >2 years	Primary: LVEF by echo Secondary: 6MWT, NYHA, HR and BP, AEs	LVEF increased in both groups (carvedilol 36–41 %; NEB 34–37 %, $p < 0.001$); adjusting EF changes for BL differences, there was no difference between groups Both groups had improvements in 6MWT, SBP, DBP, HR ($p < 0.001$) All other outcomes were similar between groups	AE rates were similar between groups

Table 2 continued

References	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Systolic and diastolic heart failure studies					
Flather et al. [79]	$N = 2128$ Inclusion: aged ≥70 years, LVEF <35 % within 6 months or prior hospitalization for decompensated HF in previous year Exclusion: addition to HF therapy in last 6 weeks, change in cardiovascular drugs in last 2 weeks, HF from unrepaired valvular disease, current BB use, significant hepatic or renal dysfunction, CVA within last 3 months, on waiting list for PCI or cardiac surgery, other medical conditions leading to reduced survival rate during study, and BB contraindication	RCT, DB, PBO-controlled NEB: 1.25–10 mg/day Follow-up >21 months	Primary: composite of all-cause mortality or CV hospital admission Secondary: all-cause or CV mortality or hospital admissions	Primary outcomes: 31 % NEB vs 35 % PBO group ($p = 0.039$); absolute risk reduction 4 %; NNT was 24 patients over 21 months; benefits occurred after 6 months of treatment and continued through follow-up Secondary outcomes: CV mortality or hospitalization rates were 29 % NEB vs 33 % PBO group ($p = 0.027$); all other outcomes did not differ. Note: patients with higher EF were enrolled in this study	Bradycardia (%): NEB, 11 PBO, 3
Cohen-Solal et al. [84]	$N = 2112$ Inclusion: see Flather et al. [79] Exclusion: see Flather et al. [79] Additionally: SCr ≥250 μmol/L, recent change in drug therapy, and contraindication to BB	RCT, DB, PBO-controlled NEB: 1.25–10 mg Patients stratified by eGFR tertiles Follow-up >21 months	Primary: composite of all-cause mortality or CV hospital admission Secondary: all-cause or CV mortality or hospital admissions, AEs	Primary outcomes: occurred in 29, 31, and 40 % of patients with high, mild, and low eGFR tertiles, respectively (p-value for trend <0.001) Secondary outcomes: all-cause mortality rates were 11.9, 15.6 and 23.3 per eGFR tertile ($p < 0.001$) The risk of death for patients in the lowest eGFR tertile was higher than for those in the highest eGFR tertile ($p < 0.001$) The effect of NEB on outcomes was similar between patients with varying levels of impaired renal function	AEs were similar between groups
van Veldhuisen et al. [85]	$N = 2111$ Inclusion: see Flather et al. [79] Exclusion: see Flather et al. [79] Additionally: recent changes in CV drug treatment, BB contraindications, or significant hepatic/renal dysfunction	RCT, DB, PBO-controlled NEB 1.25–10 mg Patients stratified by EF: impaired (≤35 %) or preserved (>35 %) Follow-up >21 months	Primary: composite of all-cause mortality or CV hospital admission Secondary: all-cause or CV mortality or hospital admissions	BL characteristics: patients with preserved EF had less advanced HF, higher BP, and fewer prior MIs, compared with those with impaired EF ($p < 0.001$, all) All primary and secondary outcomes were similar between groups	Not reported

Table 2 continued

References	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Dobre et al. [86]	$N = 2061$ Inclusion and exclusion: see Flather et al. [79]	RCT, DB, PBO-controlled NEB: 1.25–10 mg Patients were stratified by NEB dose tolerability: intolerable, low (1.25–2.5 mg), medium (5 mg), or high (10 mg) Follow-up >21 months	Primary: composite of all-cause mortality or CV hospital admission Secondary: all-cause or CV mortality or hospital admissions	Patient dose: intolerable 74 (7 %), low 142 (14 %), medium 127 (12 %), high 688 (67 %) BL characteristics: younger patients with higher HR and BP or lower SCr were more likely to tolerate the high dose; the high-dose group had fewer patients with a PMH which included HTN, MI, PTCA and CABG; fewer patients in this group were on aldosterone antagonists, CCBs, and antiarrhythmics Primary outcomes: the high-dose group had a reduction in the primary outcome compared with PBO; NEB intolerant patients had a higher risk of the composite end point than PBO; no benefit for low or medium dose groups After accounting for variation in baseline statistics, the medium-dose group had a similar benefit to high dose with respect to composite endpoint; similarly, low doses were associated with more secondary outcomes	Not reported
De Boer et al. [87]	$N = 2128$ (diabetes, $N = 555$; no diabetes, $N = 1573$) Inclusion and exclusion: see Flather et al. [79]	RCT, DB, PBO-controlled NEB: 1.25–10 mg Patients were stratified based on DM status Follow-up over 21 months	Primary: composite of all-cause mortality or CV hospital admissions Secondary: all-cause or CV mortality or hospital admissions	BL characteristics: patients in the DM group were younger, had greater rates of CAD, MI, HTN, hyperlipidemia and had worse renal function; HF severity (NYHA) was higher in the DM group; more DM patients were on lipid-lowering medications and aldosterone antagonists; LVEF was comparable between groups Primary outcomes: DM 40.2 % vs non-DM 30.8 % ($p < 0.001$). Composite outcome was significantly decreased in the non-DM NEB group vs PBO ($p < 0.01$); a similar decrease was not seen in the DM group Secondary outcomes: all-cause mortality was increased in the DM group ($p < 0.01$); the lesser response in the DM group to NEB was consistent for the other secondary outcomes	Glucose levels did not change in NEB patients
Mulder et al. [88]	$N = 2128$ (Afib, $N = 738$; sinus rhythm, $N = 1039$) Inclusion and exclusion: see Flather et al. [79]	RCT, DB, PBO-controlled NEB: 1.25–10 mg PBO Patients were stratified based on Afib status Follow-up >21 months	Primary: composite of all-cause mortality or CV hospital admissions Secondary: all-cause or CV mortality or hospital admissions	BL characteristics: Afib patients were older, had worse HF (NYHA), and less CAD and DM; BL HR was higher in the Afib group (83 vs 77 bpm; $p < 0.001$) Primary outcomes: Afib 38.5 % vs non-Afib 30.4 % ($p < 0.001$); no benefit was observed in the AFib group with NEB (37.1 % vs PBO 39.8 %); the non-Afib group showed benefit with NEB (28.1 % vs PBO 32.9 %; $p = 0.049$). LVEF did not affect the results HR: NEB decreased HR in both groups ($\sim$10 bpm); there was no difference between Afib and sinus groups	Not reported

Table 2 continued

References	Patient population	Design and intervention	Outcomes	Efficacy	Safety/tolerability
Diastolic heart failure/HFpEF studies					
Background: Kamp et al. [89] Results: Conraads et al. [80]	$N = 116$ Inclusion: aged ≥40 years, history of heart failure with persistent symptoms (NYHA II–III), LVEF ≥45 % and LVED diameter <3.2 cm/m^2 or LVED volume index <102 mL/m^2 by echo or nuclear study, or echo documented abnormal LV diastolic function Exclusion: inability to perform 6MWT, planned invasive cardiac procedures/cardiac surgery during the study, ACS or CVA in last 3 months, exercise-induced myocardial ischemia, concomitant disease limited exercise, BB contraindications or current use, diltiazem or verapamil, SBP <100 mmHg, breast feeding or pregnancy	RCT, DB, PBO-controlled NEB: 2.5–10 mg/day Follow-up >6 months	Primary: change from baseline in 6MWT after 6 months Secondary: symptoms, NYHA, Minnesota heart failure questionnaire, maximum exercise duration, peak oxygen consumption, slope of the minute ventilation to carbon dioxide relation, changes related to LV function (peak E/E' velocity via Doppler of transmitral inflow and mitral valve annulus septal and lateral wall, E/E' ratio), death, hospitalization, unexpected clinic visits, AEs	Primary outcomes: no difference in 6MWT with NEB vs PBO Secondary outcomes: no change/improvement in peak oxygen consumption; similar improvement in NYHA and Minnesota Living with HF Questionnaire in both groups	AEs (%): NEB, 35.1 PBO, 22.0
Nodari et al. [74]	$N = 26$ Inclusion: NYHA II-III ≥6 months, peak VO_2 ≤25 mL/kg/min by cardiopulmonary exercise testing, normal LV systolic function (EF ≥50 % and an LVED diameter <32 mm/m^2 by 2D echo, E/A <1 and/or PCWP >12 mmHg at rest or >20 mmHg at peak exercise) Exclusion: evidence of myocardial ischemia at stress or myocardial profusion testing, CAD on angiography, primary valve or congenital heart disease, resting SBP >200 mmHg or DBP >100 mmHg, Afib, concomitant diseases affecting prognosis or exercise capacity, BB contraindication or current treatment	RCT NEB: 2.5–5 mg/day Atenolol: 50–100 mg/day Follow-up >12 months	Resting and exercise hemodynamic parameters and maximal exercise capacity	Exercise capacity: both BBs improved clinical symptoms (per NYHA) NEB was associated with improvement from baseline in exercise capacity (peak VO_2, VO_2 at anaerobic threshold, and VE/VCO_2 slope); no change with atenolol. LVEF and LVED diameter did not change in either group Hemodynamics: both drugs decreased HR and BP; the decrease in HR was associated with a decrease in CI, more so with atenolol NEB showed an increase in SVI and mPAP and PCWP at rest and with peak exercise; atenolol showed an increase in SVI NEB was associated with a greater hemodynamic improvement compared with atenolol	Not reported

6MWT 6-min walk test, *ACEI* angiotensin-converting enzyme inhibitor, *ACS* acute coronary syndrome, *AE* adverse event, *Afib* atrial fibrillation, *ARB* angiotensin II receptor blocker, *AV* atrioventricular, *BB* β-blocker, *BID* twice daily, *BL* baseline, *BMI* body mass index, *BNP* brain natriurtetic peptide, *BP* blood pressure, *bpm* beats per minute, *CABG* coronary artery bypass graft, *CAD* coronary artery disease, *CCB* calcium channel blocker, *CHF* congestive heart failure, *CI* cardiac index, *CO* cardiac output, *COPD* chronic obstructive pulmonary disease, *CV* cardiovascular, *CVA* cerebrovascular accident, *DB* double-blind, *DBP* diastolic blood pressure, DL_{CO} diffusing capacity for carbon monoxide, *DM* diabetes mellitus, *ECG* electrocardiogram, *Echo* echocardiogram, *EF* ejection fraction, *eGFR* estimated glomerular filtration rate, *ER* emergency room, *ETT* exercise tolerance test, *HCM* hypertrophic cardiomyopathy, *HF* heart failure, *HFpEF* heart failure and preserved left ventricular ejection fraction, *HFrEF* heart failure and reduced ejection fraction, *HOCM* hypertrophic obstructive cardiomyopathy, *HR* heart rate, *HTN* hypertension, *IC* ischemic cardiomyopathy, *LAD* left anterior descending, *LVED* left ventricular end diastolic, *LVEDV* left ventricular end diastolic volume, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *MAP* mean arterial pressure, *MI* myocardial infarction, *mPAP* mean pulmonary arterial pressure, *MR* mitral regurgitation, *MWT* maintenance wakefulness test, *NA* not available, *NEB* nebivolol, *NNT* number needed to treat, *NS* not significant, *NTG* nitroglycerin, *NYHA* New York Heart Association, *PA* pulmonary artery, *PAP* pulmonary arterial pressure, *PBO* placebo, *PCI* percutaneous coronary intervention, *PCWP* pulmonary capillary wedge pressure, *PMH* past medical history, *PTCA* percutaneous transluminal coronary angioplasty, *PVC* premature ventricular contractions, *PVR* pulmonary vascular resistance, *QOL* quality of life, *RAP* right arterial pressure, *RCT* randomized controlled trial, *SBP* systolic blood pressure, *SCr* serum creatinine, *SD* standard deviation, *SE* standard error of the mean, *SVI* stroke volume index, *SVR* systemic vascular resistance, *SVT* supraventricular tachycardia, VCO_2, volume of carbon dioxide expired, *VE* ventilation efficiency, VO_2 volume of oxygen uptake, *VT* ventricular tachycardia

($p \leq 0.001$) and exercise performance ($p < 0.0001$) with nebivolol and bisoprolol [75].

7.1.1 HF and Reduced Ejection Fraction (HFrEF)/Systolic HF

Several studies in patients with HF suggest that nebivolol treatment may be beneficial due to the decrease in heart rate compared with placebo and a possible improvement in EF, New York Heart Association (NYHA) classification, and symptoms [72, 76–78]. Two of these studies describe an effect on LVEF similar to that of carvedilol [77, 78].

A large, randomized, placebo-controlled trial in elderly patients with a history of HF [≥70 years of age; 68 % with a history of coronary artery disease; $N = 2128$: SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure)] demonstrated a significantly lower risk of all-cause mortality or cardiovascular hospitalizations in nebivolol-treated patients versus placebo [odds ratio (95% CI): 0.86 (0.74–0.99); $p = 0.039$] [79]. However, the benefits of nebivolol in HF may be restricted to patients with HFrEF (EF < 45 %), as a 6-month, randomized (1:1) trial in patients with HFpEF (mean age 66 years; $N = 116$) failed to show a difference in exercise capacity between nebivolol- and placebo-treated patients [80]. While current data suggest a benefit in elderly patients with HFrEF, most of whom had a history of coronary heart disease, more large-scale, head-to-head, clinical outcome trials with bisoprolol, metoprolol succinate, and carvedilol are needed.

7.1.2 HF and Preserved Left Ventricular Ejection Fraction (HFpEF)/Diastolic HF

A benefit of nebivolol treatment in HFpEF is less clear than it is in patients with HFrEF. In addition to the study mentioned above, a study in which nebivolol treatment (titrated from 2.5 to 10 mg) over a 5 week period in patients with HFpEF resulted in no improvement in 6-min walk tests, peak oxygen consumption, NYHA classification, or Minnesota Living with HF questionnaire, versus placebo [80]. In contrast, two small-scale studies demonstrated a preferential hemodynamic effect with nebivolol vs atenolol and metoprolol, but clinical outcomes were not evaluated [74, 81]. At this time, the benefit of nebivolol use in patients with HFpEF is unproven and requires larger, randomized, clinical outcome trials.

8 Nebivolol and Erectile Dysfunction

The NO-mediated vasodilatory properties of nebivolol are possibly related to its benefits observed in erectile dysfunction (ED) over other β-blockers, which at worst have been associated with ED and at best have a neutral effect [90]. In a study of 44 men with hypertension treated with atenolol, metoprolol, or bisoprolol for over 6 months, switching to nebivolol treatment for 3 months resulted in an improvement in 20 out of 29 (69 %) patients who had ED, 11 of whom experienced a normalization of their erectile function [91]. In a randomized, 12-week, crossover trial of nebivolol and metoprolol in male outpatients with hypertension and no prior history of ED ($N = 48$), metoprolol was associated with a decrease in mean erectile function subscores on the international index of erectile function scale ($p < 0.05$), while nebivolol had no effect [92]. In another 12-week trial of 131 hypertensive men randomized (1:1:1) to receive nebivolol, atenolol, or atenolol and the diuretic chlorthalidone, the mean number of satisfactory sexual intercourses per month declined by 47 and 56 % in groups treated with atenolol and atenolol-chlorthalidone, respectively ($p < 0.01$, both), while it remained constant in the group treated with nebivolol [93]. Finally, a large cross-sectional observational study of men with high-risk hypertension receiving β-blocker therapy revealed that nebivolol was associated with a lower prevalence of ED compared with other agents, but this association was limited to younger patients [94, 95].

9 Pharmacoeconomics of Nebivolol Use

Nebivolol is not yet available as a generic formulation in the US, which raises the question of its cost effectiveness compared with other β-blockers. There are no prospective studies that addressed this issue, but a retrospective claims analysis suggests that switching from ≥6-month treatment with generic metoprolol to ≥6-month treatment with nebivolol, although associated with a greater cost of treatment (US$52 per month in 2011 dollars), is also associated with a 33 % reduction in all-cause hospitalizations, 60 % reduction in hospitalizations due to cardiovascular causes, 7 % reduction in monthly outpatient visits, and US$111 monthly reduction in inpatient costs (all differences: $p < 0.01$), leading to overall cost neutrality [96].

10 Limitations

The largest limitation in interpreting nebivolol trial data comes from an absence of outcomes trials in patients with hypertension, which limits our ability to assess the effect of nebivolol treatment on cardiovascular morbidity and mortality with any precision. Additionally, in the trial conducted in elderly patients with HF [79] in which a significant reduction of all-cause mortality and

cardiovascular hospitalizations was observed with nebivolol versus placebo, the minimum follow-up period of 6 months was extended to 12 months by the Steering Committee due to an unexpectedly low rate of the combined primary event, observed in a blinded analysis [79]. This extension of the observation window was interpreted by the advisory panel of the US FDA as a potential source of bias [97]. An additional limitation is that there are currently few head-to-head trials comparing nebivolol with the core β-blockers used to treat HF. Consequently, nebivolol was not granted US approval for treatment of chronic HF, despite the fact that it is used for that purpose in numerous other countries.

11 Conclusion

Nebivolol is a third-generation, long-acting and highly selective β_1 adrenoreceptor antagonist that also exhibits NO-mediated vasodilatory effects. It is currently FDA-approved for treatment of hypertension. While β-blockers are not recommended as first-line therapy for treatment of essential hypertension, nebivolol has shown comparable efficacy to ACEIs, ARBs, and CCBs in lowering SBP and DBP in adults with mild to moderate hypertension. However, β-blockers as a class have been associated with cardiovascular outcomes that are similar to or worse than currently recommended therapies. Due to its unique mechanism of action, nebivolol offers some central hemodynamic effects that differ from non-vasodilating β-blockers. Therefore, extrapolation of results from previous β-blocker trials may not be appropriate with regard to nebivolol, and large clinical outcome trials are needed to validate any difference in clinical outcomes.

While nebivolol does not currently carry an FDA approval for treatment of HF, current studies suggest that there may be clinical benefit for use in patients with HFrEF. Large comparison trials versus currently approved β-blockers are warranted. Alternatively, as with other β-blockers, data do not adequately support the routine use of nebivolol in patients with HFpEF. Nebivolol may be an appropriate alternative in patients who experience erectile dysfunction while on other β-blockers. Current research suggests that nebivolol may be a desirable treatment for specific indications, but further clinical investigation to determine its effects on cardiovascular morbidity and mortality is warranted.

Acknowledgments/Conflicts of interest J. Fongemie and E. Felix-Getzik declare no conflicts of interest. Neither author has received financial compensation from any commercial interests. Funding for manuscript development was provided by Forest Laboratories LLC, an affiliate of Actavis Inc., New York, NY, to Prescott Medical Communications Group, Chicago, IL. The authors wish to thank Lynn M. Anderson, PhD of Prescott Medical Communications Group for editorial and medical writing support.

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