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The Safety and Tolerability of Nebivolol in Hypertensive Patients with Coronary Artery Disease and Left Ventricular Ejection Fraction ≥40%: A Population-Based Cohort Study (Nebivolol-TR Study)

Nebivololün Hipertansiyon ve Koroner Arter Hastalığı Olup Sol Ventrikül Ejeksiyon Fraksiyonu ≥%40 Olan Hastalarda Güvenilirlik ve Tolere Edilebilirliği: Popülasyon Bazlı Bir Kohort Çalışması (Nebivolol-TR Çalışması)

ABSTRACT

Background: This study aimed to assess the safety and tolerability of nebivolol in hypertensive patients with coronary artery disease and left ventricular ejection fraction ≥40% in a Turkish cohort.

Methods: A total of 1015 hypertensive patients and coronary artery disease with left ventricular ejection fraction ≥40% were analyzed from 29 different centers in Turkey. Primary outcomes were the mean change in blood pressure and heart rate. Secondary outcomes were to assess the rate of reaching targeted blood pressure (<130/80 mmHg) and heart rate (<60 bpm) and the changes in the clinical symptoms (angina and dyspnea). Adverse clinical events and clinical outcomes including cardiovascular mortality, cardiovascular hospital admissions, or acute cardiac event were recorded.

Results: The mean age of the study population was 60.3 ± 11.5 years (male: 54.2%). During a mean follow-up of 6 months, the mean change in blood pressure was −11.2 ± 23.5/−5.1 ± 13.5 mmHg, and the resting heart rate was −12.1 ± 3.5 bpm. Target blood pressure and heart rate were achieved in 76.5% and 37.7% of patients. Angina and functional classifications were improved by at least 1 or more categories in 31% and 23.2% of patients. No serious adverse events related to nebivolol were reported. The most common cardiovascular side effect was symptomatic hypotension (4.2%). The discontinuation rate was 1.7%. Cardiovascular hospital admission rate was 5% and hospitalization due to heart failure was 1.9% during 6 months' follow-up. Cardiovascular mortality rate was 0.1%.

Conclusion: Nebivolol was well tolerated and safe for achieving blood pressure and heart rate control in hypertensive patients with coronary artery disease and heart failure with preserved or mildly reduced ejection fraction.

Keywords: Coronary artery disease, heart failure, hypertension, nebivolol, preserved ejection fraction, safety, tolerability

ÖZET

Amaç: Hipertansiyon ve koroner arter hastalığı olup sol ventrikül ejeksiyon fraksiyonu ≥%40 olan hastalarda nebivolol'ün güvenirlik ve tolere edilebilirliğini bir Türk kohortu üzerinde araştırmak.

Yöntemler: Türkiye'deki 29 farklı markezden toplamda 1015 hipertansiyon ve koroner arter hastalığı olup sol ventrikül ejeksiyon fraksiyonu ≥%40 olan hasta çalışmaya dahil edildi. Çalışmanın birincil sonlanım noktaları kan basıncı ve kalp hızındaki ortalama değişim miktarıydı. İkincil sonlanım noktaları ise hedef kan basınvı (<130/80 mmHg) ve kalp hızına (<60 atım/dk) ulaşma oranını, klinik bulgulardaki (angina, dispne) değişimi değerlendirmekti. Klinik yan etkiler ve kardiyovasküler mortalite, hastaneye yatış, akut kardiyak olayları içeren klinik sonuçlar kaydedildi.

Bulgular: Çalışma popülasyonunun ortalama yaşı 60,3 ± 11,5'di (Erkek: %54,2). Ortalama 6 aylık takip sonunda kan basıncı ve kalp hızında ortalama değişiklik −11,2 ± 23,5/−5,1 ± 13,5 mmHg ve −12,1 ± 3,5 atım/dk'ydi. Hedef kan basıncı ve kalp hızına hastaların %76,5 ve

ORIGINAL ARTICLE
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Cihan Altın, M.D.[1]
Kaan Okyay, M.D.[2]
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Hayati Eren, M.D.[4]
Lütfi Bekar, M.D.[5]
Yasemin Doğan, M.D.[6]
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Mehmet Mustafa Yılmaz, M.D.[5]
Mustafa Agah Tekindal, M.D.[30]
Mehdi Zoghi, M.D.[22]

[1]*Department of Cardiology, Başkent University Faculty of Medicine, İzmir, Turkey*
[2]*Department of Cardiology, Başkent University Faculty of Medicine, Ankara, Turkey*
[3]*Department of Cardiology, Silopi State Hospital, Şırnak, Turkey*

%37,7'sinde ulaşıldı. Angina ve fonksiyonel sınıflamada açısından en az 1 sınıf iyileşen hasta sırasıyla %31 ve %23,2'ydi. Nebivolol ile ilişkili ciddi bir yan etki bildirilmedi. En sık görülen kardiyovasküler yan etki semptomatik hipotansiyondu (%4,2). İlacı bırakma oranı %1,7'ydi. 6 aylık takip içinde kardiyovasküler nedenli hastaneye başvuru oranı %5 iken kalp yetersizliği nedenli hastaneye yatış oranı %1,9'du. Kardiyovasküler mortalite oranı %0,1'di.

Sonuç: Nebivolol hipertansiyon ve koroner arter hastalığı olup sol ventrikül ejeksiyon fraksiyonu korunmuş veya hafif azalmış olan hastalarda kan basıncı ve nabız kontrolü sağlamak için iyi tolere edilmiştir ve güvenlidir.

Anahtar Kelimeler: Hipertansiyon, güvenilirlik, kalp yetersizliği, koroner arter hastalığı, korunmuş ejeksiyon fraksiyonu, nebivolol, tolere edilebilirlik

Beta-blockers (BB) are heterogeneous group of drugs, widely used for many cardiovascular conditions. Nebivolol is a new-generation β1-selective blocker having vasodilator properties associated with nitric oxide pathway activation that leads to reduction in peripheral vascular resistance.[1] Previously 2.5-40 mg/day doses of nebivolol were preferred to be safe and effective to control blood pressure (BP).[2] As known, BB are not initial therapy for essential hypertension (HT) due to unfavorable results of previous randomized controlled trials (RCT).[2] However, RCT about nebivolol are currently lacking. The favorable effects of nebivolol on central BP have been previously demonstrated.[1,2] In addition, nebivolol has neutral or beneficial metabolic effects, unlike other BBs. Therefore, nebivolol may be a suitable option to control BP even in patients with impaired glucose and lipid metabolism or metabolic syndrome (Mets).[1,2]

Coronary artery disease (CAD), heart failure (HF), and HT constitute main global health problems.[2-4] Several large RCT and meta-analyses have shown that BB reduce hospital admissions in the case of worsening HF and mortality in hypertensive patients with CAD and reduced left ventricular ejection fraction (LVEF). Patients with LVEF >40% were excluded in these previous trials.[2-4] Until to date, there is no prospective, observational study available in hypertensive patients with CAD and LVEF ≥40%. Therefore, we aimed to assess the safety and tolerability of nebivolol in hypertensive patients with CAD and echocardiographic LVEF greater than 40% in a prospective, multicenter, observational study.

Methods

Researchers from all over Turkey including university, private, state, and training and research hospitals' cardiology clinics enrolled consecutive hypertensive patients (aged ≥18 years) with CAD and LVEF ≥40% who had been under nebivolol treatment for 3 months between January 15, 2020, and December 1, 2020. Participants were followed up for additional 3 months. Timeline of Nebivolol-TR study was given in Figure 1. Nebivolol-TR was an observational study so drug management was left to the local investigator. Therefore; the indication, initiation, and posology of nebivolol, modification, maintenance, or discontinuation of the therapy, management of the related adverse events were entirely accepted as the responsibility of the local investigator. Exclusion criteria were contraindication or intolerance to BB, patients with an LVEF <40%, and lacking informed consent. Baseline cardiovascular medications were recorded. Initiation or major dose change of other cardiovascular medications which may affect

ABBREVIATIONS

BB	Beta-blocker
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
ESC	European Society of Cardiology
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HR	Heart rate
HT	Hypertension
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
RCT	Randomized controlled trial

[4]*Department of Cardiology, Elbistan State Hospital, Kahramanmaraş, Turkey*
[5]*Department of Cardiology, Hitit University Faculty of Medicine, Çorum, Turkey*
[6]*Department of Cardiology, Kayseri City Hospital, Kayseri, Turkey*
[7]*Department of Cardiology, Balıkesir City Hospital, Balıkesir, Turkey*
[8]*Department of Cardiology, Akhisar State Hospital, Manisa, Turkey*
[9]*Department of Cardiology, Düzce Atatürk State Hospital, Düzce, Turkey*
[10]*Department of Cardiology, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey*
[11]*Department of Cardiology, Kartal Koşuyolu Training and Research Hospital, İstanbul, Turkey*
[12]*Department of Cardiology, Ankara City Hospital, Ankara, Turkey*
[13]*Department of Cardiology, Mehmet Akif İnan Training and Research Hospital, Şanlıurfa, Turkey*
[14]*Department of Cardiology, Yedikule Training and Research Hospital, İstanbul, Turkey*
[15]*Department of Cardiology, Başkent University Faculty of Medicine, Alanya, Turkey*
[16]*Department of Cardiology, Samsun Training and Research Hospital, Samsun, Turkey*
[17]*Department of Cardiology, Bahçelievler State Hospital, İstanbul, Turkey*
[18]*Department of Cardiology Ağrı State Hospital, Ağrı, Turkey*
[19]*Department of Cardiology, İstanbul University Cerrahpaşa Institution of Cardiology, İstanbul, Turkey*
[20]*Department of Cardiology, Osmangazi University Faculty of Medicine, Eskişehir, Turkey*
[21]*Department of Cardiology, İstanbul Training and Research Hospital, İstanbul, Turkey*
[22]*Department of Cardiology, Ege University Faculty of Medicine, İzmir, Turkey*
[23]*Department of Cardiology Malazgirt State Hospital, Muş, Turkey*
[24]*Department of Cardiology Kelkit State Hospital, Gümüşhane, Turkey*
[25]*Department of Cardiology, Harran University Faculty of Medicine, Şanlıurfa, Turkey*
[26]*Department of Cardiology, Isparta City Hospital, Isparta, Turkey*
[27]*Department of Cardiology, Kurtalan State Hospital, Siirt, Turkey*
[28]*Department of Cardiology Gazi Yaşargil State Hospital, Diyarbakır, Turkey*
[29]*Department of Cardiology, Cizre State Hospital, Şırnak, Turkey*
[30]*Department of Biostatistic, Katip Çelebi University Faculty of Medicine, İzmir, Turkey*

Corresponding author:
Cihan Altın
✉ drcihanaltin@hotmail.com

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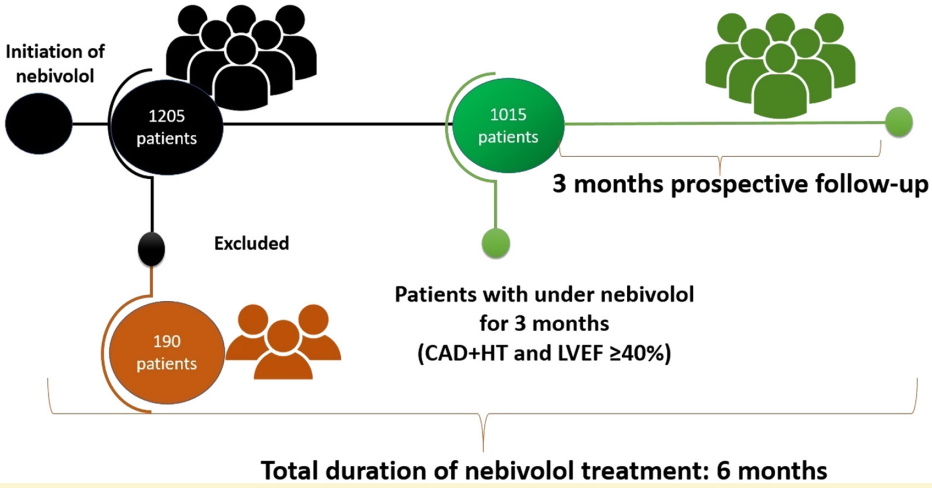

Figure 1. Timeline of nebivolol-TR study.

the result of the present study was another exclusion criterion. All patients underwent standard 2-dimensional and Doppler echocardiography conforming to current guideline recommendations and echocardiographic LVEF was calculated by modified Simpson's method.[5]

Patients having CAD were described as if one of the following was present: typical angina pectoris with typical abnormalities on electrocardiogram and echocardiogram, detection of ischemia by using non-invasive stress tests, history of myocardial infarction, or coronary revascularization of detection of coronary artery stenosis more than 50% on coronary angiography.

According to the latest European Society of Cardiology (ESC) Heart Failure Guideline,[4] patients with symptoms and signs of HF and LVEF between 40% and 49% are considered to have HF with mildly reduced ejection fraction (HFmrEF). Heart failure with preserved ejection fraction (HFpEF) was described as the presence of symptoms and/or signs of HF with objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of left ventricular diastolic dysfunction/raised LV filling pressures, including raised elevated natriuretic peptides, and with LVEF ≥50%.

H_2FPEF score comprised the following: Body mass index (BMI) >30 kg/m^2, atrial fibrillation, age >60 years, treatment with ≥2 antihypertensives, left ventricular filling pressure estimated using Doppler E/e' ratio >9, and echocardiographic pulmonary artery systolic pressure >35 mm (Table 1). A score ≥5 suggests definitive HFpEF; however, ≤1 point implies diagnostic unlikely and 2-4 points are in gray zone for diagnosis of HFpEF.[6-9] We calculated H_2FPEF score for the diagnosis of HFpEF in our study population.

Stages in the development and progression of HF according to this guideline[4] were given as respectively;

- *Stage A:* Patients at risk for HF (HT, CAD, diabetes, obesity)
- *Stage B:* Patients having one of the following evidence: structural heart disease; abnormal cardiac function, elevated natriuretic peptide, or cardiac troponin levels without having symptoms or signs.

Table 1. Parameters and Calculation of H_2FPEF Score

H_2FPEF Score	Clinical Variables	Values	Points
H	**H**eavy	BMI > 30 kg/m^2	**2**
H	**H**ypertensive	Treatment with ≥2 antihypertensives	**1**
F	Atrial fibrillation	Paroxysmal or persistent	**3**
P	**P**ulmonary hypertension	PAP >35 mm Hg	**1**
E	**E**lder	Age > 60 years	**1**
F	**F**illing pressure	Doppler E/e' ratio >9	**1**
			(0-9)

BMI, body mass index; PAP, pulmonary artery systolic pressure; E, early diastolic mitral inflow velocity; e', early diastolic mitral annular velocity.

- *Stage C:* Patients with symptoms and/or signs of HF caused by structural and/or functional cardiac abnormality.
- *Stage D:* Severe symptoms and/or signs of HF even at rest, recurrent hospitalizations despite optimal medical therapy.

Anginal symptoms were assessed by using Canadian Cardiovascular Society Angina Classification and functional capacity by using New York Heart Association (NYHA) Functional Classification.

Patients with diabetes were described according to criteria in 2019 ESC guideline on diabetes, pre-diabetes, and cardiovascular diseases[10] and hyperlipidemia was described according to criteria in 2019 ESC guideline for the management of dyslipidemias.[11]

Primary outcomes of the study were to find out the mean change in BP and heart rate (HR) of patients in the sixth month. Secondary outcomes were to assess the rate of reaching targeted BP (<130/80 mmHg) and HR (<60 bpm) and the changes in the symptoms (angina and dyspnea) and biochemical parameters at the sixth month. For tolerability, the rates of adverse clinical events and clinic outcomes including cardiovascular mortality or cardiovascular hospital admissions or acute cardiac event were recorded.

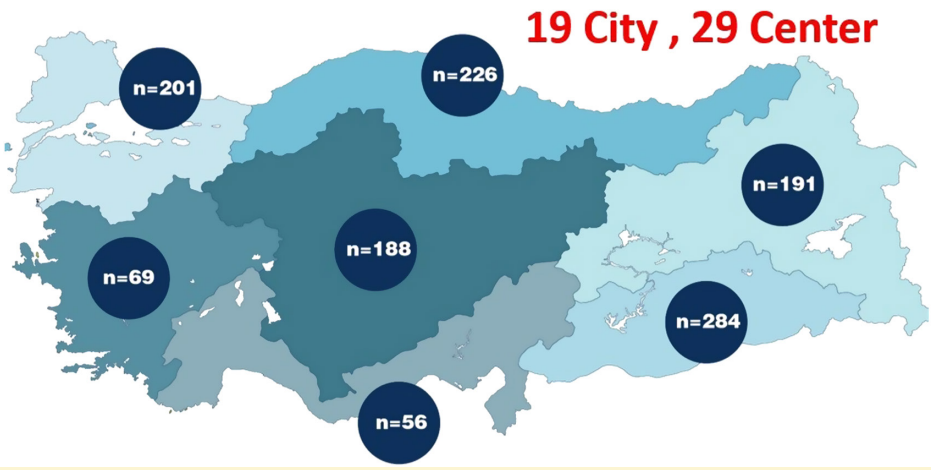

Figure 2. Distribution of our study population according to the geographic regions of Turkey.

This study was approved by Baskent University Institutional Review Board (Project No: 19/342) and supported by our Baskent University Research Fund. Written informed consent was obtained from all study participants.

Statistical Analysis

The Statistical Package for the Social Sciences version 25 (IBM Corp., Armonk, NY, USA) is used to analyze the data. The study provided descriptive statistics for categorical and continuous variables. The homogeneity of variance, which is one of the prerequisites of the parametric test, was also examined using Levene's test. "Shapiro–Wilk" and "Student's *t*-test" are used if parametric test requirements are met. If not, then the Mann–Whitney *U* "Pairing *t*-test" is used to assess the differences between the 2 groups, when the difference between the 2 dependent groups meets the parametric test requirements. When the parametric test requirements were not met with the above-mentioned analysis methods, the relationship between categorical variables was analyzed using the "Wilcoxon test", Fisher exact test and chi-square test. If the expected frequency is less than 20%, evaluation is made as follows: $P < .05$ was considered statistically significant to include these frequencies in the analysis.

Results

Of the 1205 enrolled patients from 29 different centers in Turkey, 1015 patients with complete 6 months follow-up were included for analysis. Distribution of our study population according to the different geographic regions of Turkey is given in Figure 2. Baseline characteristics of the study population were given in Table 2. The mean age of the study population was 60.2 ± 11.6 years and 54.2% of them are male. The most common comorbidities were hyperlipidemia and diabetes mellitus. The mean systolic and diastolic BP and resting HR at baseline were 135.5 ± 21.1/80.1 ± 10.9 mmHg and 77.8 ± 13.9 bpm, respectively. Baseline echocardiographic parameters are summarized in Table 3. The mean LVEF of study population was 57.1 ± 6.5%. The rate of patients with mildly reduced LVEF (40%-49%) was 20.4%. The mean H_2FPEF score for patient with LVEF ≥50% was 6.1 ± 1.4.As primary outcomes, during follow-up of 6 months, the mean change in systolic/diastolic BP was −11.2 ± 23.5/−5.1 ± 13.5 mmHg and resting HR was −12.1 ± 3.5 bpm. The rate of reaching targeted BP and HR as given in methods was 76.5% and 37.7%, respectively. The mean maintenance dose of nebivolol was 7.6 ± 3.3 mg per day at 6 months. There were no significant differences in certain biochemical parameters including creatinine, electrolytes, glucose, and lipid parameters as seen in Table 4.

Significant improvements in symptoms including angina and dyspnea were observed at a 6-month follow-up. Canadian Cardiovascular Society Angina and NHYA Functional Classification were improved in at least 1or more categories in 315 (31%) and 235 (23.2%) patients. Improvements in symptoms including angina and dyspnea in patients with LVEF ≥50% were similar to the study population as seen in Table 5.

No serious adverse events considered causally related to nebivolol were reported. The rates of clinical adverse events and clinical outcomes including cardiovascular mortality or cardiovascular hospital admissions or acute cardiac events are given in Table 6. The most common cardiovascular side effect was symptomatic hypotension (4.2%). The discontinuation rate due to adverse events was 1.7%. The most common reasons for discontinuation were erectile dysfunction (9 patients) followed by allergic reaction (4 patients), bronchospasm (2 patients), conduction disorder (1 patient), and tachyarrhythmia (1 patient). There were no adverse events associated with nebivolol withdrawal including rebound hypertension. Total cardiovascular hospital admission rate was 5% and hospitalization due to HF was 1.9% during 6 months. Total cardiovascular mortality rate was 0.1%.

Discussion

Nebivolol was safe and effective in reducing BP and HR in hypertensive patients with CAD and LVEF ≥40%. In previous RCT including renin–angiotensin system blockers or/and BB, patients with LVEF ≥40% were typically excluded.[3,4] A recently published meta-analysis (284 unique RCT and 1 617 523 patient-years of follow-up) showed that BB significantly reduced mortality in patients with sinus rhythm in patients with LVEF<40%, regardless of age, gender, or achieved HR. However, these findings were non-significant in patients with LVEF ≥40%.[12] Although several large RCT and meta-analyses[3,4] showed that BB reduce the

Table 2. Baseline Characteristics of the Study Population

Baseline Characteristics	
Age (year)	60.2 ± 11.6
Body mass index (kg/m^2)	31.3 ± 3.9
Sex (male, %)	54.2
Systolic blood pressure (mmHg)	135.5 ± 21.1
Diastolic blood pressure (mmHg)	80.1 ± 10.9
Heart rate (beat/min)	77.8 ± 13.9
LVEF (%)	57.1 ± 6.5
Patients with HFmrEF (%)	20.4
H_2FPEF score of patient with HFpEF	6.1 ± 1.4
Comorbidities	
Hyperlipidemia (%)	38.1
Diabetes mellitus (%)	31.5
Ischemic stroke (%)	7.9
Chronic kidney disease (%)	5.8
Chronic lung disease (%)	10.5
Asthma (%)	7.4
Psychiatric disorder (%)	11.4
Malignancy (%)	4
Peripheral artery disease (%)	5
Atrial fibrillation (%)	8.2
Concomitant medications	
ACEİ (%)	34.6
Angiotensin II receptor blockers (%)	27.3
Mineralocorticoid antagonists (%)	7.7
Acetylsalicylic acid (%)	68.3
Statin (%)	42.9
Calcium channel blockers (%)	23.3
Clopidogrel (%)	20.7
Ticagrelor (%)	3.3
Thiazide (%)	35.7
Loop diuretic (%)	11.3
Ivabradine (%)	2.8
Digitalis (%)	1.9
α blocker therapy (%)	5
Oral antidiabetics (%)	24.2
Insulin (%)	9.3
Warfarin (%)	2.7
NOAC (%)	6.5
Pacemaker (%)	0.5
Implantable cardioverter defibrillator (%)	0.3

HFmrEF, heart failure with mildly reduced ejection fraction (40%-49%); HFpEF, heart failure with preserved ejection fraction (≥50%); LVEF, left ventricular ejection fraction; NOAC, non-vitamin K antagonist oral anticoagulants.

Table 3. Baseline Certain Echocardiographic Parameters of Our Study Group

Parameters	**Mean Value**
Left atrium (cm)	3.4 ± 0.5
Right atrium (cm)	3.2 ± 0.4
Left ventricular end systolic diameter (cm)	3.0 ± 0.3
Left ventricular end diastolic diameter (cm)	4.6 ± 0.4
Septum (cm)	1.2 ± 0.1
Posterior wall (cm)	1.1 ± 0.1
E/A ratio	0.8 ± 0.2
Doppler E/e' ratio	12.2 ± 2.0
Pulmonary artery systolic pressure (mmHg)	31.6 ± 8.9
Left ventricular ejection fraction (%)	57.1 ± 6.5

E, early diastolic mitral inflow velocity; e', early diastolic mitral annular velocity

mortality and hospitalization in hypertensive CAD patients with LVEF <40%; however, there is little information on the group of patients with LVEF ≥40%. Our study is the first study investigating the safety and tolerability of nebivolol in these patients in a prospective, multicenter, observational manner.

Most of the patients in our study group were in stage A (patients at risk for HF) and stage B (patients having structural heart disease without symptoms or signs) according to ESC heart failure guideline.[4] Our results suggest that nebivolol seems to be effective for improving cardiovascular symptoms including angina and dyspnea with a reasonable safety profile and adverse clinical event rates in patients with HF patients in stages A and B.

Table 4. Changes in Blood Pressure, Heart Rate, and Biochemical Parameters After 6 Months of Nebivolol Therapy

	Baseline	**6. months**	***P***
Systolic blood pressure (mmHg)	135.5 ± 21.1	124.4 ± 13.1	<.001 ¥
Diastolic blood pressure (mmHg)	80.1 ± 10.9	75.0 ± 8.9	<.001 ¥
Heart Rate (beat/min)	77.5 ± 13.7	65.2 ± 9.4	<.001 ¥
e-GFR	86.3 ± 20.7	86.7 ± 28.8	.852 ¤
Sodium (mEq/L)	139.6 ± 3.2	139.2 ± 3.3	.102 ¥
Potassium (mEq/L)	4.3 ± 0.5	4.5 ± 0.4	.227 ¥
Hemoglobin (g/dL)	13.0 ± 1.3	12.8 ± 1.3	.311 ¥
ALT (U/L)	29.6 ± 16.0	29.5 ± 15.9	.072 ¥
LDL-C (mg/dL)	114.6 ± 34.7	113.9 ± 34.4	.071 ¤
Fasting plasma glucose (mg/dL)	122.6 ± 56.8	118.4 ± 46.9	.133 ¤
HbA1c (%)	6.4 ± 1.4	6.1 ± 1.3	.06 ¥
Nebivolol dosage (mg)	5.5 ± 1.6	7.6 ± 3.3	<.001 ¥

ALT, alanine transaminase; e-GFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol.
*To compare continuous variables before and after the treatment; ¥Paired sample t-test was used or ¤Wilcoxon test was used for variables that were not distributed normally.

Table 5. Frequency of Angina and Dyspnea Reported at Baseline and 6 Months Follow-Up of the Study Population

	Baseline, n (%)	6. months, n (%)	*P*
Study population (LVEF >40%)	n=1015 (%)	n=1015 (%)	
***LVEF≥50 subgroup**	n= 870 (%)	n= 870 (%)	
Angina (Canadian Cardiovascular Society Angina classification)			
None	651 (64.1%)[a]	834 (82.2%)[a]	<.001
***LVEF≥50 subgroup**	548 (63%)[a]	725 (83.3%)[a]	<.001
Class I	219 (21.6%)	150 (14.8%)[a]	<.001
***LVEF≥50 subgroup**	184 (21.1%)[a]	122 (14%)[a]	<.001
Class II	109 (10.7)[a]	24 (2.4%)[a]	<.001
***LVEF≥50 subgroup**	102 (11.7%)[a]	16 (1.8%)[a]	<.001
Class III	33 (3.3%)[a]	6 (0.6%)[a]	< .001
***LVEF≥50 subgroup**	33 (3.8%)[a]	6 (0.7%)[a]	-<0.001
Class IV	3 (0.3%)[a]	1 (0.1%)[a]	**.317**
***LVEF≥50 subgroup**	3 (0.3%)[a]	1 (0.1%)[a]	**.561**
Dyspnea (New York Heart Association (NYHA) functional capacity)			
Class I	751 (74.0%)[a]	863 (85.1%)[a]	<.001
***LVEF≥50 subgroup**	648 (74.5%)[a]	741 (85.2%)[a]	<.001
Class II	240 (23.6%)[a]	136 (13.4%)[a]	<.001
***LVEF≥50 subgroup**	200 (23%)[a]	113 (13%)[a]	<.001
Class III	23 (2.3%)[a]	14 (1.4%)[a]	**.136**
***LVEF≥50 subgroup**	21 (2.4%)[a]	14 (1.6%)[a]	**.230**
Class IV	**1 (0.1%)**[a]	**2 (0.2%)**[a]	**.854**
***LVEF≥50 subgroup**	**1 (0.1%)**[a]	**2 (0.2%)**[a]	**.998**

*Categorical data were analyzed using Fischer's exact test and the chi-square test. In cases in which the expected counts for inclusion were not met in less than 20% of the cells, the "Monte Carlo Simulation Method" was used and the values were determined; [a]No significant differences between study population and subgroup of patient with LVEF ≥ 50 ($P > .05$)

Table 6. Adverse Clinical Events and Clinical Outcomes During 6 Months' Treatment of Nebivolol

Adverse Clinical Events	N	%
Fatigue–dizziness	163	16.1
Gastrointestinal symptoms	45	4.4
Symptomatic hypotension	43	4.2
Tachyarrhythmia	25	2.5
Erectile dysfunction	23	2.3
Depression	15	1.5
Conduction disorder	13	1.3
Bronchospasm	7	0.7
Allergic reaction	4	0.4
Discontinuation	17	1.7
Clinical outcomes	N	%
Hospitalization (any cause)	52	5.1
Hospitalization (cardiovascular)	51	5.0
Acute coronary syndrome	23	2.3
Hospitalization (heart failure)	19	1.9
Stroke	4	0.3
Death (any cause)	1	0.1
Cardiovascular death	1	0.1

Unfortunately, we do not have long-term follow-up data. If we have, favorable effect on the development and progression of HF may be shown. Further studies are required to support our results.

Making a firm diagnosis of HFpEF remains a challenge. Elevated natriuretic peptides support but do not exclude a diagnosis of HFpEF. We calculated H_2FPEF score as previously described for the diagnosis of HFpEF.[6-9] Approximately 80% of study population's LVEF was ≥50% and their mean H_2FPEF score was 6.1 ± 1.4.

SENIORS[13] study aimed to assess the effects of nebivolol in patients ≥70 years and showed a significant effect in risk reduction on mortality and morbidity in patients with HF regardless of the initial LVEF. The subgroup analysis of SENIORS study[13] has suggested that the effect of nebivolol was similar in patients with preserved (approximately one-third of the patients had LVEF >35%) and impaired EF. The beneficial effects of nebivolol in risk reduction become more prominent in patients taking 6 or more months of treatment.

Nebivolol-TR included hypertensive patients with CAD and LVEF ≥40% and showed that nebivolol seems to be effective for improving cardiovascular symptoms with a reasonable safety profile and adverse clinical event rates in this study group.

Despite different design and study population, Nebivolol-TR and SENIORS study support each other in terms of favorable effects of nebivolol in patients with LVEF ≥40%. Although these results did not adequately support the use of BB in HFpEF patients, BB are recommended for HFmrEF with class IIb, level C by 2021 ESC heart failure guideline.[4]

The SENIORS study[13] also suggested that nebivolol was well-tolerated with an adverse event incidence similar to that observed with placebo. Despite different patient characteristics, the rates of common adverse effects of nebivolol in SENIORS study were similar to adverse effects in our study (Table 7). No serious adverse events considered causally related to nebivolol were reported. According to summary of product, it is known that gastrointestinal adverse events including constipation, diarrhea, nausea, dyspepsia, flatulence, and vomiting are common (1%-10%) in patients under nebivolol treatment as seen in our study group (4.4%). The most common cardiovascular side effect in our study population was symptomatic hypotension (4.2%) which is also known as one of the common side effect of nebivolol. There were no significant differences in biochemical parameters during follow-up including creatinine, electrolytes, glucose, and lipid parameters. The rate of discontinuation related to adverse events was 1.7% which is similar to SENIORS study.[13] No adverse

Table 7. The Comparison Between Side Effects of SENIORS Study with Nebivolol-TR

Side Effect	Nebivolol (SENIORS Study)	Placebo (SENIORS Study)	Nebivolol-TR
Dizziness	15.6	13.4	16.1*
Fatigue	6.7	5.8	
Hypotension	7.7	7.2	4.2
Atrial fibrillation	7.3	7. 0	2.5†
Nasopharyngitis	4.0	3.2	4.4§
Unstable angina	2.9	4.2	2.3¥
Discontinue	1.7	0.4	1.7

*Fatigue–Dizziness; †Tachyarrhythmia; ¥Acute coronary syndrome; §Gastrointestinal intolerance.

events were associated with BB withdrawal including rebound hypertension. Phase IV randomized trials[14] showed that nebivolol withdrawal resulted in minimal increase in mean BP and was not associated with rebound hypertension as not seen in our study.

Nebivolol is a β1-selective blocker that leads to reduction in peripheral vascular resistance associated with nitric oxide pathway activation. We showed efficacy and safety of nebivolol in hypertensive patients with CAD and LVEF ≥40%. The effect of nebivolol on hypertension has been extensively investigated.[15,16] However, exact mechanisms of nebivolol such patients with CAD and LVEF ≥40% are not known. It may be associated with reduction in ventricular wall stress or neurohormonal stimulation and acute coronary events.[15] It is estimated that the vasodilatory properties of nebivolol provided better tolerability compared to other classes of BB.[15-17] In addition, nebivolol has favorable effects on nitric oxide release which may play a key role in the treatment of patients with CAD and LVEF ≥40%. Detailed investigations are needed to clarify this point in further studies.

In conclusion, nebivolol seems to be effective for achieving BP and HR control and improving cardiovascular symptoms with a reasonable safety profile and adverse clinical event rates in hypertensive patients with CAD and LVEF ≥40%. We suggest nebiovol may be a preferable option for symptomatic therapy in patients with EF ≥40%. Further large RCT are needed to support our results.

There are several limitations; with an open-label study design, Nebivolol-TR was sensitive to selection bias. Nebivolol-TR was a single-arm and observational study. Unfortunately, direct comparison with the other BB or placebo was not possible. This is major limitation of the present study. In addition, the study had not any clinical event committee. So, the clinical outcome adjudications and submissions were conducted by researchers. As seen in any observational study, the managements of patients were also entirely the responsibility of the clinician. In addition, our study results could not be adopted to the global population with different ethnicities. Patients were enrolled from 29 different centers including state hospitals from different geographic regions of Turkey. Nebivolol-TR was not funded by industry. Due to lack of facility, we could not measure natriuretic peptides in most of patients. This is another important limitation of our study. Unfortunately, we do not have long-term follow-up data. Nevertheless, mid-to-long-term clinical follow-up could render our study results more robust. Further studies are required to support our results. Visual summary of the article can be seen in Figure 3.

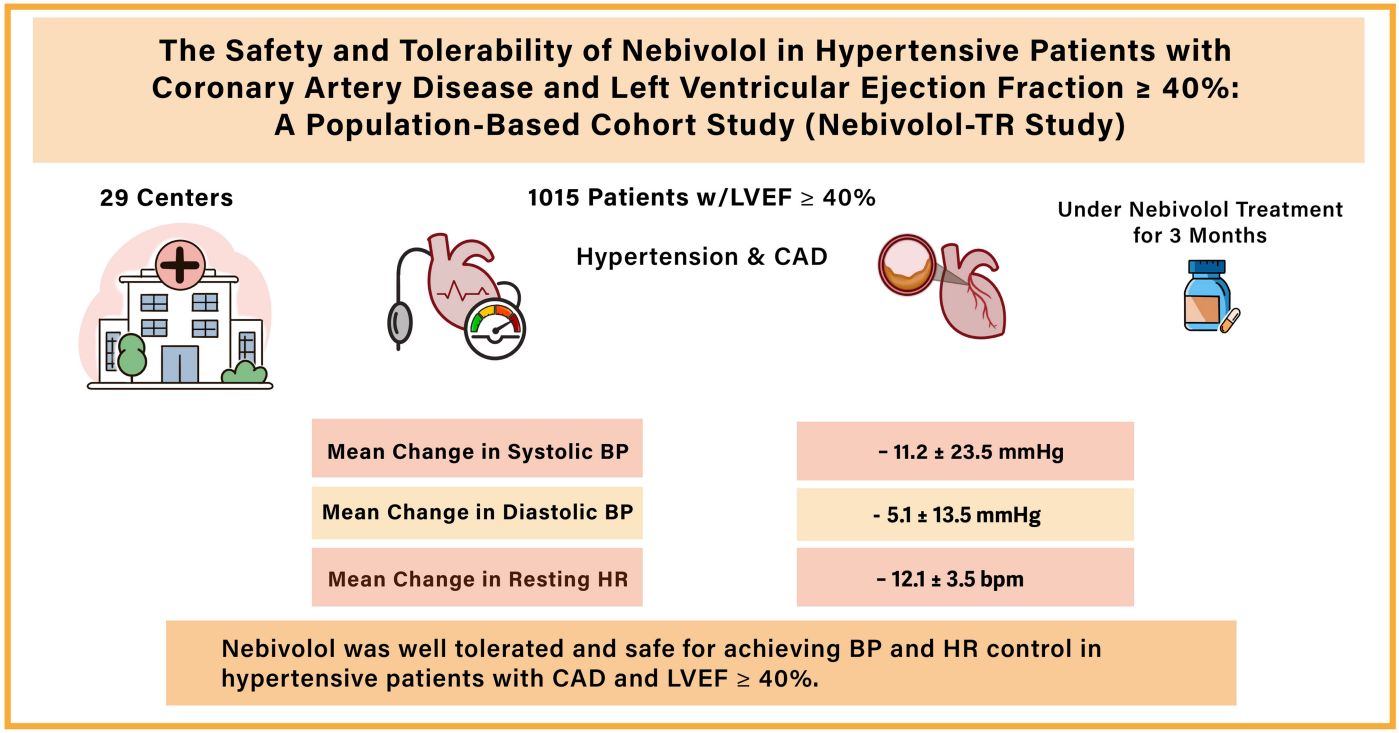

Figure 3. A visual summary of the article.

Ethics Committee Approval: This study was approved by Baskent University Institutional Review Board (Project No: 19/342).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.A., K.O., M.K., L.B., Y.D., T.G., M.Z.; Design – C.A., K.O., M.Z.; Supervision – M.Z., U.K., M.Y., Ü.Y.S., S.G., A.Ö.; Funding – C.A., K.O.; Materials – C.A., K.O., M.Z.; Data Collection and/or Processing – C.A., K.O., M.K., H.E., L.B., Y.D., G.A., T.G., H.H., V.O.T., S.Ç., Ö.Ç.K., Y.Ç., F.B., A.Ç., U.K., M.Y., S.Ç., F.E., Ü.Y.S., T.U., S.G., A.Ö., A.C., Ö.Ç., E.İ.Y., Z.T., M.B.T., M.Y., B.Ö., Ö.Ö., Ö.B., M.M.Y., M.A.T., M.Z.; Analysis and/or Interpretation – C.A., Ü.Y.S., M.Z. ; Literature Review – C.A., Y.D., V.O.T., U.K., M.K., T.G., Ö.Ç.; Writing – C.A., K.O., M.Z.; Critical Review – M.Z., T.G., M.K.

Declaration of Interests: The authors declare that they have no competing interest.

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