ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Angiotensin receptor neprilysin inhibitor for patients with heart failure and reduced ejection fraction: Real-world experience from Turkey (ARNi-TR)

Azalmış ejeksiyon fraksiyonu olan kalp yetersizliği hastalarında anjiyotensin reseptörü neprilysin inhibitörü: Türkiye'den gerçek dünya deneyimi (ARNi-TR)

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ABSTRACT

Objective: Heart failure (HF) is a growing public health problem with high morbidity and mortality. Recently, angiotensin receptor neprilysin inhibitor (ARNi) has emerged as a promising treatment for HF with reduced ejection fraction (HFrEF). Here, we shared our experience with the use of ARNi in HFrEF from multiple centers in Turkey.

Methods: The ARNi-TR is a multicenter, noninterventional, retrospective, observational study. Overall, 779 patients with HF from 22 centers in Turkey who were prescribed

ÖZET

Amaç: Kalp yetersizliği (KY), yüksek morbidite ve mortalite ile birlikte büyüyen bir halk sağlığı sorunudur. Son zamanlarda, anjiyotensin-reseptör neprilisin-inhibitörü (ARNi), düşük ejeksiyon-fraksiyonlu KY (DEFKY) tedavisi için bir umut olarak ortaya çıkmıştır. Bu çalışmada, Türkiye'deki birçok merkezden DEFKY'de ARNi kullanımı ile ilgili deneyimimizi paylaşmayı amaçladık.

Yöntemler: ARNi-TR, çok merkezli, girişimsel olmayan, retrospektif, gözlemsel bir çalışmadır. Türkiye'nin çeşitli coğrafi

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sacubitril/valsartan were examined. Initial clinical status, biochemical and echocardiographic parameters, and New York Heart Association functional class (NYHA-FC) values were compared with follow-up values after 1 year of ARNi use. In addition, the effect of ARNi on number of annual hospitalizations was investigated, and the patients were divided into 2 groups, depending on whether ARNi was initiated at hospitalization or under outpatient clinic control.

Results: N-terminal pro-brain natriuretic peptide (NT-proBNP), left-ventricle ejection fraction (LV-EF), and NYHA-FC values improved significantly in both groups (all parameters, p<0.001) within 1-year follow-up. In both groups, a decrease in hemoglobin A1c (HbA1c) values was observed in ARNi use (p<0.001), and a decrease in daily diuretic doses and hospitalizations owing to HF were observed after ARNi use (all comparisons, p<0.001). Hypotension (16.9%) was the most common side effect in patients using ARNi.

Conclusion: The ARNi-TR study offers comprehensive real-life data for patients using ARNi in Turkey. The use of ARNi has shown significant improvements in FC, NT-proBNP, HbA1c levels, and LV-EF. Likewise, reductions in the number of annual hospitalizations and daily furosemide doses for HF were seen in this study.

bölgelerindeki 22 merkezde, sakubitril/valsartan verilen 779 KY hastası incelendi. Başlangıç klinik durumları, biyokimyasal ve ekokardiyografik parametreler ve New York Kalp Cemiyeti fonksiyonel sınıf (NYHA-FS) değerleri 1 yıllık ARNi kullanımından sonraki takip değerleri ile karşılaştırıldı. ARNi'nin yıllık hastanede yatış sayısına etkisi de araştırıldı. Hastalar ayrıca ARNi'nin hastanede veya poliklinik kontrolünde başlanmasına bağlı olarak iki grupta analiz edildi.

Bulgular: 1 yıllık takip süresi boyunca, serum N-terminal pro-beyin natriüretik peptid (NT-proBNP), sol-ventrikül ejeksiyon-fraksiyonu (SV-EF) ve NYHA-FS değerleri her iki grupta da anlamlı düzeldi (tüm parametrelerde, p<0.001). Ayrıca ARNi tedavisi ile iki grupta da hemoglobin A1c (HbA1c) değerlerinde hafif bir düşüş gözlendi (p<0.001). Her iki grupta da ARNi kullanımından sonra günlük diüretik dozlarında ve KY'ye bağlı hastaneye yatışlarda azalma gözlendi (tüm karşılaştırmalarda, p<0.001).Tüm hastalarda ARNi'ye bağlı en sık görülen yan etki hipotansiyondu (%16.9).

Sonuç: ARNi-TR çalışması, Türkiye'de ARNi kullanan hastalar için kapsamlı gerçek hayat verileri sunmaktadır. ARNi kullanımı ile FS, NT-proBNP, HbA1c seviyeleri ve SV-EF'de önemli iyileşmeler olmuştur. Benzer şekilde, bu çalışmada KY için yıllık hastaneye yatış sayısında ve günlük furosemid dozlarında önemli düşüşler görülmüştür.

Chronic heart failure (HF) with reduced ejection fraction (HFrEF) represents a major public health problem and is associated with high morbidity and mortality. HF is a global epidemic that affects at least 26 million people worldwide, and its prevalence is increasing.[1] The absolute prevalence of HF in Turkey is 2.9% in the HAPPY trial. According to this study, more than 2 million people are living with HF in Turkey.[2] The number of people diagnosed with HF is increasing and projected to rise up 46% by 2030, resulting in more than 8 million people aged >18 years with HF, according to the American Heart Association's 2017 Heart Disease and Stroke Statistics Update.[3,4] Despite significant advances in treatments and prevention, mortality and morbidity are still high, and quality of life is poor.

Compared with enalapril, sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor (ARNi), has been shown to reduce cardiovascular death and hospitalization owing to HF in the PARADIGM-HF (Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial.[5] However, little is known about its safety and effectiveness in real-world practice, especially in sicker and more fragile patients.

Sacubitril/valsartan has been approved for use for HFrEF but has not been reimbursed for clinical use in Turkey. However, it has been used in patients with HFrEF in Turkey since April 2017. In this retrospective observational study, we aimed to present the experience regarding the use of sacubitril/valsartan for the treatment of HFrEF from various centers in Turkey.

METHODS

In this study, a total of 779 patients with HF from 22 centers in various geographical regions of Turkey who were prescribed sacubitril/valsartan were screened retrospectively. Patients who have used ARNi for the last 1 year for HFrEF were included in this study. Left-ventricle ejection fraction (LV-EF) of >40% and inability to access multiple data were

Abbreviations:

ARB	*Angiotensin receptor blocker*
ARNi	*Angiotensin receptor neprilysin inhibitor*
BB	*Beta-blockers*
BP	*Blood pressure*
eGFR	*Estimated glomerular filtration rate*
FC	*Functional class*
EF	*Ejection fraction*
HbA1c	*Hemoglobin A1c*
HF	*Heart failure*
HFrEF	*HF with reduced ejection fraction*
IQR	*Interquartile range*
LV-EF	*Left-ventricle ejection fraction*
MRA	*Mineralocorticoid receptor antagonists*
NT-proBNP	*N-terminal pro-brain natriuretic peptide*
NYHA-FC	*New York Heart Association functional class*
RAAS	*Renin-angiotensin-aldosterone system*
TTE	*Transthoracic echocardiogram*

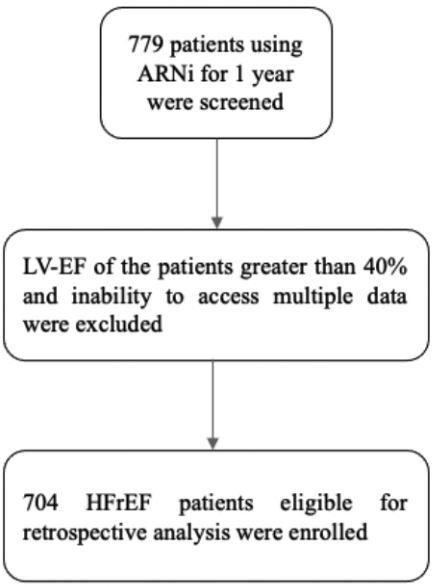

Figure 1. Flow chart of the study.
ARNi: angiotensin receptor neprilysin inhibitor; LV-EF: left-ventricle ejection fraction; HFrEF: heart failure with reduced ejection fraction.

determined as exclusion criteria. Consequently, a total of 75 patients were excluded because they met the exclusion criteria (n=69) or they did not fulfill the inclusion criteria (n=6). Overall, 704 patients (median age, 65.5 years [interquartile range (IQR), 57.8-74.0]) eligible for retrospective analysis were enrolled, including 506 (71.9%) male and 198 (28.1%) female subjects (Figure 1). Ethics committee of Fırat University School of Medicine approved the study, and we obtained informed consent from all patients.

After 1 year of ARNi use, serum biochemical parameters, including creatinine, estimated glomerular filtration rate (eGFR), serum potassium, hemoglobin A1c (HbA1c), N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, and functional class (FC) determined by the New York Heart Association (NYHA), and annual number of hospitalizations for HF were examined in detail during the follow-up period, retrospectively. The presence of chronic diseases, such as hypertension, diabetes mellitus, and hyperlipidemia, were determined according to whether the patients had received medical treatment for the relevant disorders before. Similarly, smoking status was determined from medical records or phone calls. It was thought that patients with a history of acute coronary syndrome or coronary artery disease determined by angiography had an etiology of ischemic HF. To determine the side effects of ARNi, the patients' medical records were reviewed and responses from phone calls were recorded.

All data were sent online as an Excel file to a cardiologist and biostatistics specialist blinded to the patients' clinical status. eGFR was calculated according to the Modification of Diet in Renal Disease formula. In this study, a systolic blood pressure (BP) of <100 mmHg was considered as hypotension. Consequently, BP values measured during office, home, or hospital visit were retrospectively analyzed.

Statistical analysis

The data were analyzed with the SPSS version 22.0 (IBM Corp.; Armonk, NY, USA). The normal distribution of variables was verified with the Kolmogorov-Smirnov test. Normally distributed data were presented as mean±standard deviation, and non-normally distributed data were presented as median with an interquartile range. The categorical variables were expressed as percentages. Spearman's rho correlation was used when 1 or both of the variables were not normally distributed. Comparisons between before and after sacubitril/valsartan treatment were done with the *Wilcoxon* signed-rank test. An χ^2 test was used to investigate whether distributions of categorical variables differed within groups. All analyses were stratified by baseline and first year follow-up. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 704 patients (male, 71.9%; median age, 65.5 [IQR, 57.8-74.0]) with a diagnosis of HFrEF from 22 centers in Turkey were enrolled in this study. Baseline characteristics, comorbidities, current drug use, and cardiac device used are summarized in Table 1. The etiology of most patients was detected as ischemic cardiomyopathy (71.4%). Most of the patients who started ARNi were NYHA-FCs III (55.8%) and II (25.9%) at initiation of treatment. The researchers reported that all participants who started ARNi were ambulatory patients with HF at baseline. In the initial evaluation, 41.4% of the patients were found to have type 2 diabetes mellitus. Consequently, most patients started ARNi treatment in the outpatient setting (65.1%). Additionally, 39.2% of patients had a history of cardiac devices (implantable cardioverter defibrillator/cardiac resynchronization therapy). The baseline eGFR of 182 patients (outpatient, 87; inpa-

Table 1. The baseline characteristics of patients in comparison with reference clinical studies (ARNi initiation: outpatient, A, and inpatient, B)

A	ARNi-TR (outpatient) (n=458)	PARADIGM-HF (n=4187)
Characteristic		
Age (y)	64.1±12.4	63.8±11.5
Female (%)	28.8	21.0
Systolic blood pressure (mmHg)	121.5±16.7	122.0±15.0
Heart rate (bpm)	75.8±13.6	72.0±12.0
BMI (kg/m^2)	27.1±4.2	28.1±5.5
Serum creatinine (mg/dL)	1.07 (0.90-1.32)	1.13±0.30
eGFR (mL/min/1.73 m^2)	77.00 (63.00-88.00)	N/A
Clinical features of HF		
Functional class (NYHA II-III) (%)	81.1	94.7
Ischemic etiology (%)	71.8	59.9
HF diagnosis time (y)	5.4±3.5	N/A
Annual hospitalizations for HF (n)	1.9±1.8	N/A
LV-EF (%)	28.4±6.2	29.6±6.1
NT-proBNP (pg/mL) (outpatient, 244; inpatient, 124)	1455.5 (463.00-3213.25)	1631.0 (885.00-3154.00)
Medical history (%)		
Hypertension	62.7	70.9
Diabetes mellitus	42.7	34.7
Stroke	6.1	8.5
Hyperlipidemia	44.4	N/A
Smoking	28.2	N/A
Atrial fibrillation	27.2	36.2
Medical treatment status (%)		
Beta blocker	85.2	93.1
Previous ACEi	52.4	78.0
Previous ARB	25.1	22.2
MRA	71.3	54.2
Digital	26.7	29.2
Ivabradine	25.6	N/A
Furosemide	90.8	80.3
Antiplatelet	82.4	N/A
NOAC	36.8	N/A
Warfarin	0.9	N/A
Device (ICD/CRT)	37.1	21.9

Table 1. The baseline characteristics of patients in comparison with reference clinical studies (ARNi initiation: outpatient, A, and inpatient, B) (Continue)

B	ARNi-TR (inpatient) (n=246)	PIONEER-HF (n=440)	TRANSITION (predischarge initiation) (n=495)
Characteristic			
Age (y)	65.9±12.8	61.0 (51.0-71.0)	66.7 (mean)
Female (%)	26.8	25.7	25.1
Systolic blood pressure (mmHg)	118.7±16.0	118.0 (110.0-133.0)	124.0±13.8
Heart rate (bpm)	77.3±15.1	81.0 (72.0-92.0)	73.8±13.6
BMI (kg/m^2)	27.5±5.8	30.5 (25.9-37.1)	27.9 (17.6-58.8)
Serum creatinine (mg/dL)	0.91 (0.80-1.10)	1.28 (1.07-1.51)	N/A
eGFR (mL/min per 1.73 m^2)	65.0 (53.7-82.0)	58.4 (47.5-71.5)	61.6±20.5
Clinical features of HF			
Functional class (NYHA I-II) (%)	14.7	33.6	64.6
Ischemic etiology (%)	70.6	N/A	44.0
HF diagnosis time (y)	5.2±3.5	N/A	N/A
Annual hospitalizations for HF (n)	2.9±2.6	N/A	N/A
LV-EF (%)	28.0±7.0	24.0 (18.0-30.0)	28.6±7.5
NT-proBNP (pg/mL) (outpatient, 244; inpatient, 124)	2075.5 (893.50-4690.25)	4821.0 (3109.00-8767.00)	1902.0 (945.0-3847.0)
Medical history (%)			
Hypertension	60.8	N/A	75.2
Diabetes mellitus	38.8	N/A	45.7
Stroke	9.0	N/A	10.3
Hyperlipidemia	55.6	N/A	N/A
Smoking	19.9	N/A	N/A
Atrial fibrillation	28.0	N/A	49.1
Medical treatment status (%)			
Beta blocker	86.7	59.5	43.0
Previous ACEi	42.7	N/A	50.5
Previous ARB	22.8	N/A	24.8
MRA	76.6	10.9	34.1
Digital	20.3	9.3	12.7
Ivabradine	28.3	N/A	N/A
Furosemide	90.5	59.5	48.1
Antiplatelet	92.6	N/A	N/A
NOAC	31.3	N/A	N/A
Warfarin	0.8	N/A	N/A
Device (ICD/CRT) (%)	43.1	N/A	22.4

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blockers; ARNi: angiotensin receptor neprilysin inhibitor; BMI: body mass index; BPM, beats per minute; CRT: cardiac resynchronization therapy; EF: left-ventricle ejection fraction; eGFR: estimated glomerular filtration rate; HF: heart failure; ICD: implantable cardioverter defibrillator; LV-EF: left-ventricle ejection fraction; MRA: mineralocorticoid receptor antagonists; N/A: not available; NOAC: new oral anticoagulant; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association.

Table 2. Changes seen after 1 year of ARNi use (ARNi initiation: outpatient, A, and inpatient, B)

A (outpatient) (n=458)			
Follow-up	Baseline	First year	
ARNi dosage (twice a daily) (%)			
Cessation	-	4.4	
50 mg	78.9	26.2	
100 mg	20.8	43.2	
200 mg	0.2	26.2	
			p
Potassium (mmol/L)	4.20 (3.90-4.60)	4.40 (4.10-4.70)	<0.001
Creatinine (mg/dL)	0.91 (0.80-1.10)	0.96 (0.82-1.20)	<0.001
eGFR (mL/min per 1.73 m^2)	77.00 (63.00-88.00)	77.00 (58.80-88.00)	0.029
NT-proBNP (pg/mL) (n=120)	1164.00 (399.90-2311.30)	472.50 (246.00-1382.70)	<0.001
HbA1C (%) (n=228)	6.80 (5.70-7.80)	6.60 (5.50-7.50)	<0.001
Ejection fraction (%)	28.4±6.2	30.7±7.3	<0.001
Number of annual hospitalizations	1.9±1.8	0.5±0.8	<0.001
Functional class (NYHA) (%)			
I	0.4	15.1	<0.001
II	31.9	63.7	
III	57.8	20.1	
IV	9.8	1.1	
Dose of furosemide use (mg)	40.00 (20.00-40.00)	20.00 (0.00-40.00)	<0.001
B (inpatient) (n=246)			
Follow-up	Baseline	First year	
ARNi dosage (twice a daily) (%)			
Cessation	-	3.2	
50 mg	73.9	29.7	
100 mg	25.7	41.5	
200 mg	0.4	25.6	
			p
Potassium (mmol/L)	4.3 (3.9-4.6)	4.5 (4.2-4.8)	<0.001
Creatinine (mg/dL)	1.07 (0.9-1.3)	1.10 (0.8-1.3)	0.302
eGFR (mL/min per 1.73 m^2)	65.0 (53.7-82.0)	60.0 (51.0-79.0)	0.006
NT-proBNP (pg/mL) (n=88)	1928.5 (893.5-4594.5)	852.0 (437.0-1881.7)	<0.001
hbA1C (%) (n=81)	6.9 (5.9-8.0)	6.8 (5.7-8.2)	0.008
Ejection fraction (%)	28.0±7.0	31.0±7.7	<0.001
Number of annual hospitalizations	2.9±2.6	1.2±1.6	<0.001
Functional class (NYHA) (%)			
I	0	14.0	<0.001
II	14.7	58.0	
III	52.2	25.1	
IV	33.1	2.9	
Dose of furosemide use (mg)	40.0 (40.0-80.0)	40.0 (10.0-40.0)	<0.001

ARNi: angiotensin receptor neprilysin inhibitor; eGFR: estimated glomerular filtration rate; HbA1C: hemoglobin A1c; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PARADIGM-HF: Prospective Comparison of ARN with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure.

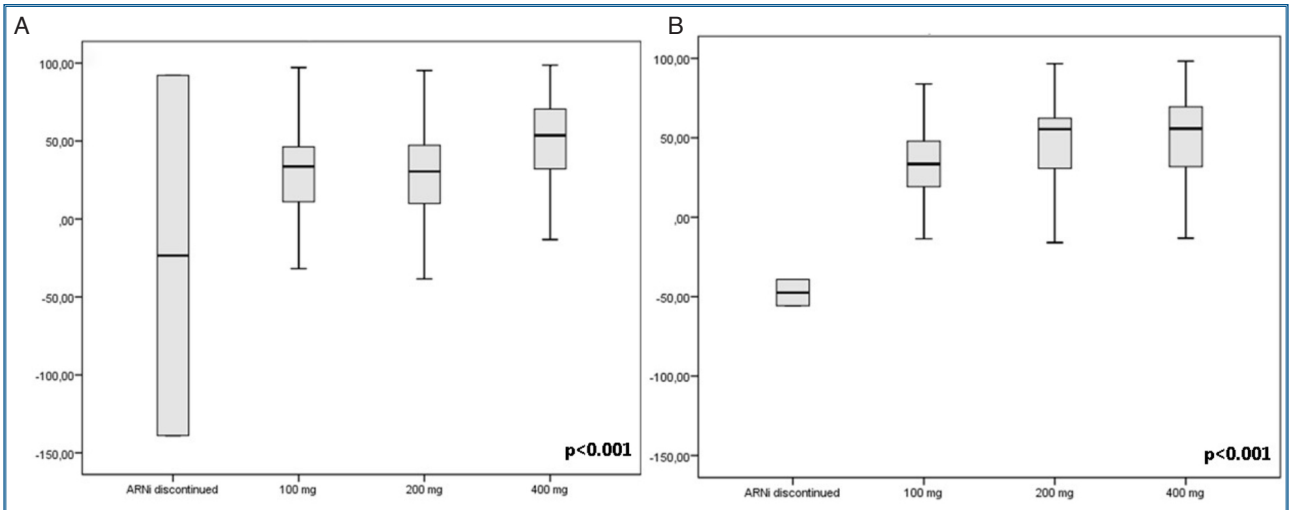

Figure 2. The percentage change in NT-proBNP values after 1 year of ARNi use (A: outpatient, B: inpatient).
NT-proBNP: N-terminal pro-brain natriuretic peptide; ARNi: angiotensin receptor neprilysin inhibitor.

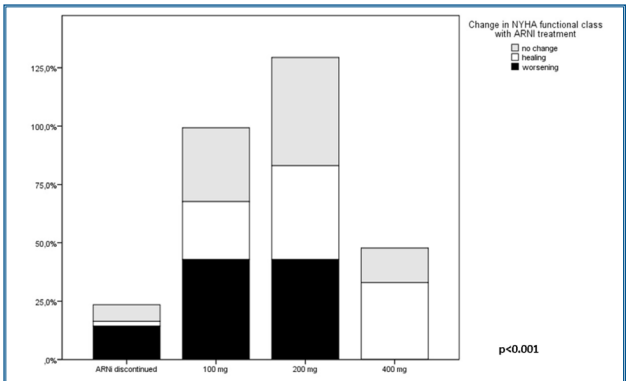

Figure 3. Change in NYHA-FC after 1 year of ARNi use.
NYHA-FC: New York Heart Association functional class; ARNi: angiotensin receptor neprilysin inhibitor.

tient, 95) using ARNi were between 30 and 60 mL/min per 1.73 m^2. The changes in patients' biochemistry parameters, LV-EF values, annual hospital stays, functional capacities, diuretic doses, and ARNi doses over time are summarized in Table 2. The rates of reaching the target dosage of 200 mg twice a day (b.i.d.) were 25.6% and 26.2%, respectively, in patients who were initiated ARNi before discharge and at outpatient clinic controls.

In 1-year follow-up, serum NT-proBNP, HbA1c levels, and LV-EF significantly improved with rare side effects that necessitate discontinuation of ARNi treatment (p<0.001 in all parameters). Furthermore, significant reductions in the number of annual hospitalizations and daily furosemide usage doses for HF were noted. Hypotension was the most common side effect (total, 16.9%; symptomatic, 2.3%). There was a statistically significant mild increase in serum potassium and creatinine levels and a decrease in eGFR. However, hyperkalemia of >6 mmol/L was observed in 5 patients (0.7%). eGFR of <30 mL/min per 1.73 m^2 of body surface area (n=10 [1.4%]) or a decrease in eGFR of >50% (n=5 [0.7%]) between enrollment and follow-up were seen in 2.1% of patients. Overall, 185 patients (26.3%) were ACEi/angiotensin receptor blocker (ARB) naïve. The incidence of hypotension in ACEi/ARB-naive patients tended to be higher than those who used these drugs previously (36 [19.5%] vs 83 [16%], respectively; p=0.304). Compared with the basal values, at the end of the first year, a statistically significant decrease in eGFR (p<0.001) and an increase in serum potassium (p<0.001) were observed in ACEi/ARB-naive patients, whereas only an increase in serum potassium was significant in other patients (p<0.001). Angioedema-like clinical status was not reported in any patient. Symptomatic hypotension (n=16 [2.3%]) and economic issues (n=25 [3.6%]) were the main reasons for discontinuation of the drug, whereas impaired renal function (n=10 [1.4%]) and hyperkalemia (n=5 [0.7%]) were the less common reasons. The box plot graph of the percentage change in NT-proBNP values after 1 year of ARNi use is shown in Figure 2 (p<0.001). Additionally, stacked bar graph of the change in NYHA-FC at the end of the first year according to ARNi use is shown in Figure 3 (p<0.001). In the follow-up peri-

od, FC was observed as NYHA classes III to IV in 39.5% of those whose ARNi was discontinued; these rates were found to be 34.2%, 23.1%, and 9.6% in patients who reached 50 mg, 100 mg, and 200 mg (2×1 b.i.d.), respectively.

DISCUSSION

Here, the rates of initiation of ARNi in patients with HF with NYHA-FC II to III were lower than the rates stated in the PARADIGM-HF trial (81.1% vs 94.7%). Moreover, in the PARADIGM-HF trial, ARNi was started predominantly in patients with FC II (71.6%) and at least FC IV (0.8%),[5] whereas these values showed an increase toward patients with FC III (56.2%) and FC IV (18.9%) in the ARNi-TR study. According to these results, we can say that researchers who participated in our study have started ARNi to more advanced patients with HF. This may be owing to the fact that ARNi has no reimbursement for clinical use in the Turkey Social Security Institution. In Turkey, physicians might face difficulties concerning the reimbursement of a drug prescribed for HF in the asymptomatic phase. Therefore, many patients who need to start ARNi in the early stages of HF cannot take the drug because of economic reasons. In the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HFs, ARNi was recommended to further reduce the risk of hospitalization because HF and death in patients with FC II to IV and in patients with HFrEF who remained symptomatic despite optimal treatment with ACEis, beta-blockers (BB), and mineralocorticoid receptor antagonists (MRA) instead of ACEi (class I, level of evidence B).[6] Almost three-quarters of patients analyzed in our study were initially prescribed an ARNi dosage of 50 mg b.i.d. This situation can be explained by the fact that physicians tend to start with a low dose as side effects, such as hypotension, are more common in high doses of ARNi. Additionally, in this study, the initiation of ARNi in more serious patients with high risk of developing side effects may be the reason why physicians start with low-dose medications. In the PARADIGM-HF trial, a dosage of 200 mg b.i.d. has been reported to reduce hospitalizations because of HF and death from any cause.[5] Similarly, in our study, although the rate of reaching target dosage, which was 200 mg b.i.d., increased, NYHA-FC III to IV patient ratios decreased. However, the rate of reaching the target dosage of 200 mg b.i.d. was found to be very far from the literature. This may be owing to the fact that physicians who do not have enough experience in ARNi use are cautious about developing side effects. Similarly, it has been reported that physicians tend to start ARNi with the lowest dose in Germany (2/3 rate). Simultaneously, 2/3 of all these patients were reported to remain at their initial dose at 6 months.[7]

In accordance with the literature, statistically significant improvements were observed in NYHA-FC,[5,8,9] serum NT-proBNP levels,[5] and LV-EF,[9,10] determined by transthoracic echocardiogram (TTE) after using ARNi, without the frequent side effects that would require discontinuation of the drug. In the PROVE-HF study, the positive effects of sacubitril/valsartan on cardiac remodeling have been demonstrated, and compared with baseline, statistically significant increases of 5.2% and 9.4% in ejection fraction (EF) values were reported at 6th and 12th months, respectively.[11] Furthermore, there was a slightly significant increase in EF but not as much as in the PROVE-HF study. Nevertheless, the maximum target dosage of 97/103 mg b.i.d. was achieved in 65% of patients in the PROVE-HF study, whereas the maximum target dose was achieved in only 27% of the study population in ARNi-TR study. This is probably the reason why the increase in EF is not as prominent as it was observed in the PROVE-HF study.

In accordance with the literature, annual hospitalization rates because of HF decreased in our study.[5,10] Likewise, decreased levels in HbA1c were reported, showing a slight improvement in the glycemic state after ARNi use. This was similar to a decrease in HbA1c levels in patients with diabetes mellitus reported by Seferovic et al.[12] in the post-hoc analysis of the PARADIGM-HF trial. Neprilysin, also called neutral endopeptidase, degrades several vasoactive peptides, such as atrial natriuretic peptide and brain natriuretic peptide. Sacubitril (neprilysin inhibitor) inhibits the breakdown of natriuretic peptides resulting in varied effects, including increased diuresis, natriuresis, and vasodilation. ARNi acts by enhancing the natriuretic peptide system via inhibition of neprilysin and by inhibiting the renin-angiotensin-aldosterone system (RAAS) via AT1 receptor blockade, thereby producing more effective neurohormonal regulation than can be achieved with

RAAS inhibition alone.[13] Consistent with the literature, the diuretic dose reduction was reported after the use of ARNi in Turkey. Therefore, the reduced furosemide doses in patients treated with sacubitril/valsartan in this study may potentially be secondary to the natriuretic effects of sacubitril or the presumed improvement in hemodynamics that may occur with ARNi.

After the stabilization of acute HF, ARNi was safely initiated in the predischarge stage in approximately one-third of patients in our study. Likewise, the TRANSITION study demonstrated that sacubitril/valsartan can be initiated early and safely in several patients with HFrEF who have been stabilized after hospitalization because of a decompensated acute HF episode.[14]

The most frequently reported adverse event in our study was hypotension (total, 16.9%; symptomatic, 2.3%). Symptomatic hypotension was reported as 14% in the PARADIGM-HF trial.[5] This problem is important for patients who are thought to start ARNi but have low BP. A slower titration and accurate follow-up can also make the drug tolerable for more "frail" patients, allowing them to achieve the expected benefit of treatment. According to the titration trial and prospectus information of ARNi, it is recommended to avoid using the drug if systolic BP is <100 mmHg.[15] In patients with systolic BP of 100 to 110 mmHg, use of low starting dose and careful monitoring are recommended.[5,15] Reducing or discontinuing the doses of BP-lowering drugs used in concomitant patients in the hypotension limit may benefit ARNi tolerance.[16] Additionally, a statistically significant increase in serum potassium and creatinine levels and a decrease in eGFR have been reported in the ARNi-TR study at levels not requiring discontinuation of treatment. However, hyperkalemia of more than 6 mmol/L has been reported in 0.7% of patients after ARNi use. This was much less than PARADIGM-HF data (4.3%).[5] In our study, a decline in renal function was observed in a few patients similar to the PARADIGM-HF trial (2.1% vs 2.2%).[5] Likewise, compared with enalapril in the study of Damman et al.,[17] ARNi resulted in a slower decrease in eGFR and improvement of cardiovascular outcomes even in patients with chronic kidney disease. Angioedema-like clinical condition reported as a rare complication with a prevalence rate of 0.4% in the PARADIGM-HF trial was not reported in our study. Although symptomatic hypotension (2.3%) and economic reasons (3.6%) were the main factors for discontinuation of ARNi, severe renal dysfunction (1.4%) and hyperkalemia (0.7%) have rarely been reported among the causes of cessation.

According to all these results, we can state that similar to the literature, with the use of ARNi in HFrEF, patients had improvements in NYHA-FC, LV-EF, NT-proBNP, and HbA1c levels and had lower hospitalization rates. These conditions occurred with a low side effect profile that would not require drug cessation. However, we can say that the use of ARNi should increase in FC II patients who can benefit more from the drug in line with the guidelines and literature suggestions, with the increased experience of using ARNi. Furthermore, failure to reach the target dosage of 200 mg b.i.d. in ARNi use in Turkey can be overcome by being more willing and cautious about increasing the dose every 2 to 4 weeks in appropriate cases.

Higher treatment persistence and compliance were associated with improved patient outcomes in HF.[18] Choosing the right patient is crucial in starting the drug and benefiting the patients. Data have suggested that compliance and continuity rates were also higher in those with a starting dosage >50 mg b.i.d. In the literature, <75 years of age, male gender, less comorbidity, 100 mg 2×1 b.i.d. initial dosage, previous ACEi, ARB, BB, MRA, new oral anticoagulants, lipid-lowering drugs, and oral diuretic use were reported in the 12th month in relation to lower drug discontinuation.[7] In the PARADIGM-HF trial, although ACEi was prescribed to patients before the study (run-in period),[5] it is known that among the real-world cohorts, 43.9% of patients did not receive ACEi/ARB before taking sacubitril/valsartan.[19] In particular, patients who have previously used ACEi/ARB have reported a higher rate of drug compliance and attendance.[19] In our study, there was more history of cardiac device implantation (39.2% vs 21.9%) compared with the PARADIGM-HF trial.[5] This may be because of the fact that our patients are mostly followed up in well-equipped tertiary care centers.

In conclusion, in accordance with the literature, according to real-life data of our study, ARNi is effective and safe in NYHA-FC II to IV adult patients with HFrEF and no history of chronic kidney disease (eGFR<30

mL/min per 1.73 m^2). In this regard, Turkey's ARNi experience is also increasing. Large-scale prospective randomized studies are needed in these issues.

Limitations

The retrospective design of this study was our main limitation. For this reason, some data (NT-proBNP, HbA1c levels, and mortality data of all patients) could not be accessed. Another limitation was that biochemical methods and TTE devices and techniques used in 22 centers were different. In addition, a 1-year follow-up is short in assessing mortality for HF and can underestimate real-life data. Another limitation was that the antidiabetic therapies used by the patients were not examined.

Conclusion

This retrospective, multicenter study is important because of the real-life consequences regarding the ARNi use in patients with HFrEF in Turkey. There were significant improvements in the important prognostic factors, such as NYHA-FC, serum NT-proBNP, and HbA1c levels; however, there was a significant rise in LV-EF without significant side effects that necessitate discontinuation of the ARNi. Additionally, significant reductions in the number of annual hospitalizations and daily diuretic doses for HF were determined in this study. In light of these results, we can say that the use of ARNi is effective and safe in patients with HFrEF in the Turkish population. The demonstration of the beneficial effects after using the ARNi in Turkey suggests that it could be used more commonly in patients with HFrEF.

The visual summary of the article can be seen in the Appendix 1.

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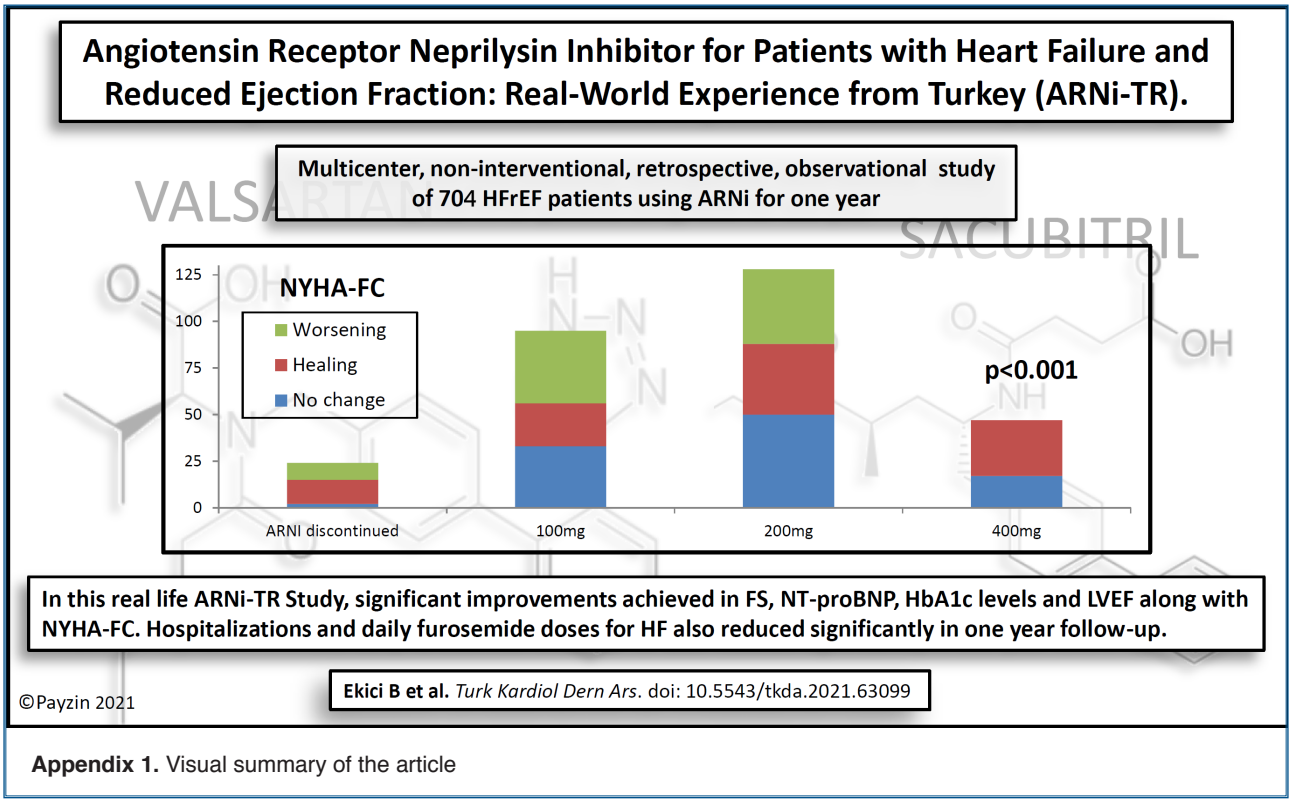
Keywords: Angiotensin receptor neprilysin inhibitor; heart failure with reduced ejection fraction; sacubitril/valsartan; real-world

Anahtar Kelimeler: Anjiyotensin-reseptör neprilisin-inhibitörü; azalmış ejeksiyon fraksiyonu olan kalp yetersizliği; sacubitril/valsartan; gerçek yaşam



Appendix 1. Visual summary of the article