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Effect of angiotensin receptor-neprilysin inhibitor treatment on erectile dysfunction in heart failure with a reduced ejection fraction

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ABSTRACT

Objective: Erectile dysfunction (ED) is a common condition in patients with heart failure (HF), which impairs quality of life. Our study aimed to compare those patients, who received traditional treatment with a diagnosis of HF and those who received angiotensin receptor-neprilysin inhibitor (ARNI) treatment in addition to the current treatment, in terms of ED at the end of 6 months.

Patients and Methods: The study was planned as a single-center, prospective study. The study included 200 patients with heart failure. The patients' demographic, clinical, and echocardiographic characteristics were recorded, and an international ED scoring questionnaire was applied. The participants in the study were divided into two groups: those who received ARNI treatment and those who did not. After 6 months, the ED questionnaire was applied to the patients again and the groups were compared.

Results: The median age of the patients was 53 (years). The median ejection fraction (EF) value was calculated to be 30% and no significant difference was found between the groups (p: 0.122). It was found that N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels measured at the end of the 6th month were significantly lower in patients who had received ARNI treatment than in those who had not (respectively, 245 pg/ml, 200 pg/ml; p: 0.003). In the analysis performed to detect the presence of ED, it was discovered that the ED score change was significantly higher in the group that had received 6 months of ARNI treatment (p: 0.031) compared to that in the group that had not (p: 0.031). When the ED sub-parameters were compared in terms of the 6-month change rate, it was found that the ARNI group had a significant increase in terms of ED and sexual satisfaction scores, but no significant difference was found in the other parameters (p: 0.001, p: 0.029).

Conclusion: Erectile dysfunction is more common in patients with heart failure compared to the rest of society and impairs quality of life. In our study, it was determined that ED complaints decreased significantly in HF patients, who had received ARNI treatment for 6 months than in patients who had not.

Keywords: Erectile dysfunction, Heart failure, Angiotensin receptor-neprilysin inhibitor

1. INTRODUCTION

Heart failure (HF) is a complicated disease that develops due to structural or functional problems of the heart. Its prevalence varies between 1-2% in society and its incidence is increasing [1]. In everyday life, HF appears a difficult disease, and HF patients' quality of life and comfort is low.

Erectile dysfunction (ED) is one of the reasons for the reduction in quality of life in patients with HF. ED is defined as the inability to achieve a sufficient level of penile erection for sexual performance [2]. Its incidence in the general population ranges from 19 to 52% [3-5]. Several studies have found a strong link between ED and cardiovascular disease [6,7]. The frequency of ED in HF patients is more common when compared to that in those who are healthy within the general population. In publications, the frequency of ED in patients with HF has been reported at rates ranging from 30-80% [8,9]. Endothelial dysfunction, atherosclerosis, decreased effort capacity, additional drugs used, and psychological effects are prominent causes of ED in HF patients [10-14].

Heart failure treatment is constantly updated with the addition of new drugs to the treatment regimen. When real-world data from

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these drugs with different mechanisms of action were examined, it was discovered that there may be positive pleiotropic effects in the target effect structure. Angiotensin receptor-neprilysin inhibitor (ARNI) is a molecule that has recently been used in HF treatment. It improves the quality of life while decreasing hospitalization. This drug, which acts as a neprilysin inhibitor, has been shown to have numerous pleiotropic effects in patients with HF. In our study, the possible pleiotropic effect on ED was investigated in HF patients receiving ARNI treatment.

2. PATIENTS and METHODS

The study included 200 patients with a HF diagnosis, who applied to the cardiology unit of the Training and Research Hospital. Male patients over the age of 18, who were newly diagnosed with HF and for whom HF treatment was initiated in accordance with current guidelines, taking into account the patients' blood pressure and pulse rate, etc., basal kidney and liver functions, and concomitant diseases, and who agreed to fill out the ED-related questionnaire, were included. Patients under the age of 18, who had had a heart transplant, or a left ventricular assist device implanted, as well as those who were unable to receive conventional and/or ARNI treatment due to chronic renal failure (CRF), drug allergy, drug intolerance, or other reasons, were excluded from the study.

In addition to recording age, sex, height, and weight, questions were asked about patients' smoking habits, comorbidities, (diabetes mellitus (DM), coronary artery disease (CAD), hyperlipidemia (HL), CRF, hypertension (HF), atrial fibrillation (AF)), and HF etiologies. Among the biochemical markers, creatine, glomerular filtration rate (GFR), and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) values were examined.

Using echocardiography (ECHO), ejection fraction (EF), end-diastolic diameter (EDD), end-systolic diameter (ESD), right ventricular basal diameter, tricuspid annular plane systolic excursion (TAPSE), and systolic pulmonary artery pressure (SPAB) were measured, with insufficiencies and stenosis of the heart valves included in the assessment.

In our study, the patients completed The International Index of Erectile Function Questionnaire (IIEF) on the day they were included in the study before the initiation of the medication after diagnosis and 6 months after the initiation of the medication. IIEF is a widely used, multi-dimensional self-report instrument for the evaluation of male sexual function. It is has been recommended as a primary endpoint for clinical trials of erectile dysfunction (ED) and for diagnostic evaluation of ED severity. In this questionnaire developed by Rosen et al., patients' erectile function, orgasmic function, sexual desire, sexual satisfaction and general satisfaction are analyzed [15]. In many studies of ED, classification has been made based on the IIEF questionnaire score [16]. It has been linguistically validated in 32 languages and used as a primary endpoint in more than 50 clinical trials [15]. This questionnaire is ranked from 1 to 5 on the Likert scale (1: very low or not at all/ very dissatisfied, 5: very high/ very satisfied). 5 has the most positive results, and 1 shows the weakest answer, and each field is added up to reach the scores. High scores support a better quality of erectile functions. The questionnaire's question number 1-5 and 15 were evaluated in terms of erectile functions. Patients with scores of 0 to 10 were considered to have severe ED, those with 11-16 were considered to have moderate ED, those with 17-21 were considered to have mild to moderate ED, those with 22-25 were considered to have mild ED, and those with 26-30 were considered to have no ED. Answers to questions 6, 7 and 8 were evaluated for sexual satisfaction, answers to questions 9 and 10 for orgasmic function, answers to questions 11 and 12 for sexual desire and questions 13 and 14 for general satisfaction. Patients completed the questionnaire alone and in a calm environment.

The participants of this study provided written informed consent of the utilization of their medical records. All subjects gave informed consent, the study complied with the Declaration of Helsinki, and the trial was approved by the institutional local ethics committee (The protocol code: HNEAH-KAEK 2022/KK 16.).

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) 25.0 program was used for data analysis in the study. It was planned to give descriptive data on the sociodemographic information of the participants as N and %, and data on continuous variables as Mean±SD and Median (min-max).

When the study data were analyzed in terms of normality assumptions, Kolmogorov-Smirnov values were determined as $p<0.05$. Therefore, Spearman correlation analysis, one of the nonparametric tests, was performed to determine the relationship between erectile function total and subscale scores and body mass index (BMI), age, GFR, and EF variables. In addition, the nonparametric Mann-Whitney U test and Kruskal-Wallis H test were used to determine whether there was a significant difference between various categorical variables and the 0^{th} and 6^{th}-month erectile function total and subscale scores. If there was a significant difference between the groups, the posthoc test was used to answer the following question: Among which groups was the significance? Performing the Games-Howell posthoc test was planned because the variance was not homogeneously distributed, and the number of samples was not equal (Sparks, 1963). Finally, Fisher's exact test was used to compare categorical variables. A value of $p<0.05$ was considered statistically significant.

3. RESULTS

The median age of the patients, who participated in the study, was 53 (years). Median height was 174 cm and median weight was 80 kg, and no significant difference was found between the groups (p: 0.431, p: 0.303, respectively). The mean BMI was found to be 26.2 in the BMI analysis, while the BMI of the patients, who did not receive ARNI, was significantly lower than that of the patients who did receive ARNI (p: 0.017) (Table I).

Table I. Demographic and clinical parameters of patients

Parameters	Total	Group without ARNI	Group with ARNI	p
	Median (Q1/Q3)	Median (Q1/Q3)	Median (Q1/Q3)	
Age (year)	53 (47 / 57.5)	51.5 (47 / 57)	54 (48 / 58.5)	0.108 [u]
Height (cm)	174 (170 / 178)	173.5 (170 / 177.5)	175 (169.5 / 178.5)	0.491 [u]
Weight (kg)	80 (74 / 89)	80 (75 / 90)	79 (73 / 87.5)	0.303 [u]
BMI (kg/m2)	26.27 (24.91 / 28.95)	27.67 (25.01 / 29.36)	25.83 (24.69 / 27.75)	**0.017** [u]
	n (%)	n (%)	n (%)	
CAD	82 (41)	38 (38)	44 (44)	0.472 [c]
CRF	155 (77.5)	81 (81)	74 (74)	0.310 [c]
DM	116 (58)	61 (61)	55 (55)	0.474 [c]
AF	165 (82.5)	80 (80)	85 (85)	0.457 [c]
HT	94 (47)	50 (50)	44 (44)	0.479 [c]
HL	112 (56)	55 (55)	57 (57)	0.887 [c]
IHF Etiology	118 (59)	62 (62)	56 (56)	0.472 [c]

[u] *Mann Whitney U test (Monte Carlo),* [c] *Pearson Chi-Square Test (Monte Carlo), Q1: 1st Quartile, Q3: 3rd Quartile*

BMI: body mass index, CAD: Coronary artery disease, CRF: Chronic renal failure, DM: Diabetes mellitus, AF: Atrial Fibrillation, HT: Hypertension, HL: Hyperlipidemia, IHF: Ischemic heart failure

Coronary artery disease was found in 41% of the patients (n: 82), CRF in 22.5% of the patients (n: 45), DM in 58% (n: 116), AF in 82.5% (n: 165), HT in 47% (n: 94), HL in 56% (n: 112) and ischemic HF etiology in 59% (n: 118). In terms of chronic diseases, no significant difference was found between the groups (Table I). The patients' median creatinine value was 1.01 mg/dl, and the median GFR value was 86 ml/min. Between the groups, no significant difference was found regarding these parameters (p: 0.221, and p: 0290, respectively) (Table II). While the mean NT-pro-BNP value in the non-ARNI group was 750 pg/ml, the initial NT-pro-BNP value in the ARNI group was 670 pg/ml. No significant difference was found between the groups in terms of baseline values (p: 0.051) (Table IV).

When the patients' ECHO parameters were examined, the median EF value was discovered to be 30%, with no significant difference between the groups (p: 0.122). When the patients were examined in terms of EDD and ESD, the median values were 64 mm and 53 mm, respectively, and no difference was observed between the groups (p: 0.520, p: 0174, respectively). In terms of valve pathologies, right-heart size and functions, no statistically significant difference was found between the groups of patients (Table II).

Sixty-three (63%) of patients, who did not receive ARNI had ED, while 66 (66%) of patients, who were initially scheduled to receive ARNI treatment, had ED. After 6 months, one patient in the non-ARNI group developed novel ED, while 2 patients recovered. The changes were not statistically significant (p: 0.999). In the ARNI group, 6 patients recovered after 6 months, while no change was observed in terms of ED in the other patients. The rate of change in patients, who recovered from ED after 6 months compared to the initial ED status, was statistically significant in the ARNI treatment group (p: 0.031) (Table III and IV). When the patients' NT-pro-BNP levels were compared after 6 months of treatment, those who received ARNI had significantly lower levels than those who did not. After 6 months, no statistically significant difference was found in the groups' NT-pro-BNP change rates (respectively, p: 0.03, p: 0.800) (Table IV).

Table II. Echocardiographic and biochemical parameters of patients

Parameters	Total (n=200) n (%)	Group without ARNI (n=100) n (%)	Group with ARNI (n=100) n (%)	p
GFR				0.155 [ff]
Severely decreased	2 (1)	1 (1)	1 (1)	
Moderately to severely	8 (4)	6 (6)	2 (2)	
Mildly to moderate decreased	35 (17.5)	12 (12)	23 (23)	
Mildly decreased	69 (34.5)	34 (34)	35 (35)	
Normal	86 (43)	47 (47)	39 (39)	
Mitral				0.168 [ff]
Normal valve	15 (7.5)	8 (8)	7 (7)	
Mild MR	80 (40)	39 (39)	41 (41)	
Moderate MR	61 (30.5)	37 (37)	24 (24)	
Severe MR	41 (20.5)	15 (15)	26 (26)	
MVR	3 (1.5)	1 (1)	2 (2)	
Aorta				0.401 [ff]
Normal valve	139 (69.5)	73 (73)	66 (66)	
Mild AR	42 (21)	21 (21)	21 (21)	
Moderete AR	13 (6.5)	4 (4)	9 (9)	
Severe AS	2 (1)	0 (0)	2 (2)	
AVR	4 (2)	2 (2)	2 (2)	
Tricuspid				0.399 [c]
Normal valve	39 (19.5)	22 (22)	17 (17)	
Mild TR	115 (57.5)	60 (60)	55 (55)	
Moderate TR	34 (17)	13 (13)	21 (21)	
Severe TR	12 (6)	5 (5)	7 (7)	
Right Heart Dilatation	72 (36)	36 (36)	36 (36)	0.999 [c]
Left Heart Dilatation	172 (86)	85 (85)	87 (87)	0.839 [c]
TAPSE (>16)	141 (70.5)	69 (69)	72 (72)	0.757 [c]
RVS (>9)	140 (70)	70 (70)	70 (70)	0.999 [c]
	mean(SD.)	mean(SD.)	mean(SD.)	
Tapse (mm)	19.05 (4.55)	19.05 (4.64)	19.06 (4.49)	0.987 [t]
	Median (Q1/Q3)	Median (Q1/Q3)	Median (Q1/Q3)	
EDD (mm)	64 (58.5 / 69)	64 (58 / 69)	64 (60 / 69)	0.520 [u]
ESD (mm)	53 (47 / 60)	53 (46 / 59.5)	54.5 (49.5 / 60)	0.174 [u]
Creatinine (mg/dl)	1.01 (0.9 / 1.22)	1 (0.89 / 1.17)	1.015 (0.94 / 1.26)	0.221 [u]
RV Diameter (mm)	38 (34 / 43)	38 (34.5 / 43)	38 (34 / 42.5)	0.885 [u]
SPAB (mmhg)	28 (20 / 40)	25.5 (20 / 35)	30 (20 / 41)	0.302 [u]
GFR (ml/dk)	86 (67 / 99)	87 (72 / 100)	86 (59 / 96)	0.290 [u]
LVEF (%)	30 (25 / 35)	30 (25 / 35)	30 (25 / 32.5)	0.122 [u]

[u] *Mann Whitney U test (Monte Carlo),* [t] *Independent samples t test (Boostrap),* [c] *Pearson Chi-Square Test (Monte Carlo),*

[ff] *Fisher Freeman Halton test (Monte Carlo), Q1: 1st Quartile, Q3: 3rd Quartile, SD.: Standard Deviation*

GFR: Glomerular filtration rate, AS: Aortic stenosis, AR: aortic regurgitation, MR: mitral regurgitation, TAPSE: tricuspid annulus plane systolic excursion,RVS: Right ventricle systolic excursion velocity, LVEF: Left ventricle ejection fraction, EDD: End-diastolic diameter, ESD: End-systolic diameter, SPAB: Systolic pulmonary artery pressure

Table III. *Erectile function analysis of patients*

Variables	Without ARNI Group (n=100) n (%)	With ARNI Group (n=100) n (%)	p
Erectile Function Presence			
0. months	63 (63)	66 (66)	0.768 [c]
6. months	62 (62)	60 (60)	0.885 [c]
Changes			0.434 [ff]
Negative Change rates (absent → presence)	1 (1)	0 (0)	
No Change (absent → absent)	36 (36)	34 (34)	
Positive Change rates (presence → absent)	2 (2)	6 (6)	
No Change (presence → presence)	61 (61)	60 (60)	
p value for 0. vs. 6. month	0.999 [m]	**0.031** [m]	

[c] *Pearson Chi-Square Test (Monte Carlo),* [ff] *Fisher Freeman Halton test(Monte Carlo),*

[m] *McNemar test (Monte Carlo)*

Table IV. *Analysis of patients' erectile function sub-parameters*

	Group without ARNI (n=100) Median (Q1/ Q3)	Group with ARNI (n=100) Median (Q1/ Q3)	p
Erectile Function Level			
0. months	2 (0 / 3)	1 (0 / 3)	0.819 [u]
6. months	1 (0 / 2)	1 (0 / 2)	0.220 [u]
Change rates (0-6 months)	0 (0 / 0)	-0.5 (-1 / 0)	**0.001** [u]
p value for 0. vs. 6. month	**0.002** [w]	**<0.001** [w]	
Erectile Function Score			
0. months	21 (16 / 26)	22 (16 / 26)	0.600 [u]
6. months	22 (17 / 26)	25 (21 / 27)	**0.018** [u]
Change rates (0-6 months)	1 (0 / 1)	2 (0 / 4)	**<0.001** [u]
p value for 0. vs. 6. month	**<0.001** [w]	**<0.001** [w]	
Sexual Desire Score			
0. months	6 (5 / 7)	6 (4 / 7)	0.855 [u]
6. months	7 (6 / 8)	7 (6 / 8)	0.379 [u]
Change rates (0-6 months)	1 (0 / 2)	1 (0 / 1)	0.220 [u]
p value for 0. vs. 6. month	**<0.001** [w]	**<0.001** [w]	
Orgasmic Function Score			
0. months	6.5 (5 / 8)	6 (4 / 7)	**0.046** [u]
6. months	7 (6 / 9)	7 (6 / 8)	0.076 [u]
Change rates (0-6 months)	1 (0 / 1)	1 (0 / 1)	0.892 [u]
p value for 0. vs. 6. month	**<0.001** [w]	**<0.001** [w]	
Sexual Satisfaction Score			
0. months	9 (7 / 11)	8 (6 / 10)	**0.031** [u]
6. months	11 (9 / 12)	10 (9 / 12)	0.598 [u]
Change rates (0-6 months)	1 (0 / 3)	2 (1 / 3)	**0.029** [u]
p value for 0. vs. 6. month	**<0.001** [w]	**<0.001** [w]	
General Satisfaction score			
0. months	6 (5 / 7)	6 (4 / 7)	0.165 [u]
6. months	7 (6 / 8)	7 (6 / 8)	0.431 [u]
Change rates (0-6 months)	0 (0 / 1)	1 (0 / 1)	0.423 [u]
p value for 0. vs. 6. month	**<0.001** [w]	**<0.001** [w]	
NYHA functional class score			
0. months	3 (3 / 4)	3 (3 / 3)	0.904 [u]
6. months	2 (2 / 2)	2 (2 / 2)	0.999 [u]
Change rates (0-6 months)	-1 (-2 / – 1)	-1 (-1.5 / – 1)	0.791 [u]
p value for 0. vs. 6. month	**<0.001** [w]	**<0.001** [w]	
NT-Pro-BNP(pg/ml)			
0. months	750 (590 / 890)	670 (480 / 800)	0.051 [u]
6. months	245 (200 / 340)	200 (112 / 255)	**0.003** [u]
Change rates (0-6 months)	-420 (-570 / – 245.5)	-430 (-580 / – 230)	0.800 [u]
p value for 0. vs. 6. month	**<0.001** [w]	**<0.001** [w]	

[u] *Mann Whitney U test(Monte Carlo),* [w] *Wilcoxon signed-rank test(Monte Carlo), Q1: 1st Quartile, Q3: 3rd Quartile*

When the score change rates for the ED sub-parameters were compared between the groups after 6 months of treatment, a significant difference in the ED and sexual satisfaction scores in the ARNI group was found, and recovery was observed (p: 0.001, p: 0.029). No statistically significant difference was found in post-treatment change rates in other parameters. When the groups were compared in terms of ED parameters at the baseline and after 6 months, a significant improvement was observed in all parameters (Table IV).

4. DISCUSSION

In our study, patients with heart failure diagnosis who received ARNI treatment for 6 months had significantly lower ED complaints than patients who did not, and their NT-pro-BNP levels also decreased significantly.

Heart failure is a cardiovascular disease, whose rates of occurrence have increased in recent years. New agents are being developed to improve life quality and lower mortality in HF patients. In addition to their basic effects, these drugs have a positive pleiotropic effect on the daily lives of HF patients by increasing the mediators. ARNI is one of the new agents used in HF treatment with an angiotensin-neprilysin inhibitor effect. The PARADIGM-HF study found that using ARNI in patients with HF diagnosis reduced symptoms of failure and slowed HF progression compared to results recorded in enalapril treatment [17]. In the PARADIGM-HF study, it was found that NT-pro-BNP levels decreased significantly in ARNI areas after treatment. Similarly, in our study, it was observed that NT-pro-BNP levels decreased statistically significantly in the group receiving ARNI treatment after 6 months. Ceyhun et al., investigated the relationship between ED and NT-pro-BNP in patients with chronic HF. In this study, an increase in NT-pro-BNP associated with an increase in ED severity was found [16]. Similarly, in our

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study, ED was observed more frequently in the non-ARNI group that had a high NT-pro-BNP level compared to the ARNI group that had received ARNI for 6 months and had a low NT-pro-BNP level. It was thought that this increase caused endothelial healing by increasing the possible NO bioavailability of ARNI treatment or in a way that has not been determined yet.

Angiotensin receptor-neprilysin inhibitor includes valsartan, an angiotensin receptor blocker, and sacubitril, a neprilysin inhibitor. Neutral endopeptidase neprilysin reduces many endogenous vasoactive peptides such as a natriuretic peptide, bradykinin, and adrenomedullin [18,19]. Vasoconstriction, neurohormonal overstimulation and inappropriate remodeling are prevented by the double effect of the angiotensin receptor blocking effect and neprilysin inhibitor provided by sacubitril thanks to valsartan, which is present in the molecule [20,21]. According to some published studies, ARNI treatment caused partial left ventricular EF elevation in all mildly reduced EF HF patients, regardless of etiology [22]. In the study of Canale et al., it was shown that ARNI treatment caused recovery of the chemotherapy-related advanced mild EF in 4 patients, with a possible antioxidant mechanism [23]. In our study, after 6 months of ARNI treatment, no significant positive change was observed in EF values according to the initial measurements.

Nitric oxide is one of the most important molecules involved in the healing of the vascular barrier and vasodilation. It was reported that ARNI treatment particularly increased NO bioavailability and more favorable results were obtained in vascular functions in HF than valsartan alone. It is thought that the increase in NO bioavailability contributes positively to the treatment of diseases caused by underlying endothelial problems [24]. In the study of Mario et al., it was stated that in vitro ARNI treatment in rats could improve the endothelial barrier, increasing the contractility of the detrusor muscles and thus helping the recovery of EF [25]. After this study, ARNI treatment continued to be examined in terms of increased sexual function, and in the study of Zhuang et al., it was found that ARNI administration increased sexual function in female hypertensive rats. They discovered that in addition to this increase in sexual function, there was an improvement in clitoral and vaginal fibrosis. They determined that the molecule's effect on the PTEN/PI3K/AKT pathway was effective at the biochemical level [26]. In our study, it was observed that in HF patients with frequent ED complaints, patients who had received ARNI treatment had a significant increase in their ED score (ED recovery) at the end of 6 months compared to that in non-ARNI patients. Since there was no significant difference between the groups in the comparison of EF, chronic diseases, and age, and there was no change in the doses of other drugs used in the process, it was thought that a positive and significant effect in terms of ED was achieved with ARNI treatment. This is consistent with other studies that show ARNI treatment improves sexual functions. A recent study called PARADOR aimed to show the difference between ARNI and enalapril treatment in the recovery of ED in patients with low EF HF [27]. Results of randomized controlled and double-blind studies with an active-control group are awaited. Recovery of ED with ARNI treatment is important in terms of increasing the quality of life in patients with HF.

Limitation

Our study's limitations are the small number of samples and the lack of comparison of other medications used between groups.

Conclusion

It has been determined that new drugs used in HF have many pleiotropic effects apart from the target effect. In our study, it was found that there was a statistically significant decrease in ED complaints in patients with HF, who had received 6 months of ARNI treatment, compared to that those who had not.

Compliance with Ethical Standards

Ethical Approval: This study was approved by the Haydarpasa Numune Training and Research Hospital Clinical Research Ethics Committee (approval number: HNEAH-KAEK 2022/KK 16.)). The study adhered to the principles of the Helsinki Declaration.

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Authors' Contributions: S S, B G and OY: Contributed to the conception, design, and acquisition of data or analysis and interpretation of data, E K: Analysis and interpretation of data about erectile dysfunction. All authors approved the final manuscript.

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