Effect of sacubutril/valsartan and dapagliflozin on athletic performance; Can the popular cardiac medications of recent years be used as doping agents?

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Abstract

Studies conducted in recent years have demonstrated the positive effects of sacubitril/valsartan and dapagliflozin on cardiac prognosis and performance. These drugs can potentially be abused as doping agents by professional athletes. In our study, we evaluated the effects of sacubitril/valsartan and dapagliflozin on athletic performance. In the study, the swimming performances of three groups of rats were evaluated by dividing them into control, sacubitril/valsartan and dapagliflozin groups. Additionally, echocardiography, weight and rotarod data were evaluated during follow-up. In the comparison of sacubitril/valsartan and control groups, a statistical difference was seen in the 13th, 19th and 20th swimming sessions, and when the total and average swimming times were compared, the p values were 0.115 and 0.015. In the comparison of dapagliflozin and control groups, a statistical difference was observed starting from the 10th swimming session, and when the total and average swimming times were compared, the p values were <0.001 and <0.001. In triple analysis, a statistical difference was seen from the 9th swimming session until the end of the experiment. Furthermore, a statistical difference was observed in rotarod results for sacubitril/valsartan and dapagliflozin compared to baseline. (p value <0.001 and 0.011 respectively) Our study showed a limited positive effect of sacubitril/valsartan on athletic performance. The impact of dapagliflozin on athletic performance was shown to be particularly significant.

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Keywords: dapagliflozin, sacubutril/valsartan, athletic performance, sports cardiology, doping agents, performance enhancing

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Abstract

Studies conducted in recent years have demonstrated the positive effects of sacubitril/valsartan and dapagliflozin on cardiac prognosis and performance. These drugs can potentially be abused as doping agents by professional athletes. In our study, we evaluated the effects of sacubitril/valsartan and dapagliflozin on athletic performance. In the study, the swimming performances of three groups of rats were evaluated by dividing them into control, sacubitril/valsartan and dapagliflozin groups. Additionally, echocardiography, weight and rotarod data were evaluated during follow-up. In the comparison of sacubitril/valsartan and control groups, a statistical difference was seen in the 13th, 19th and 20th swimming sessions, and when the total and average swimming times were compared, the p values were 0.115 and 0.015. In the comparison of dapagliflozin and control groups, a statistical difference was observed starting from the 10th swimming session, and when the total and average swimming times were compared, the p values were <0.001 and <0.001. In triple analysis, a statistical difference was seen from the 9th swimming session until the end of the experiment. Furthermore, a statistical difference was observed in rotarod results for sacubitril/valsartan and dapagliflozin compared to baseline. (p value <0.001 and 0.011 respectively) Our study showed a limited positive effect of sacubitril/valsartan on athletic performance. The impact of dapagliflozin on athletic performance was shown to be particularly significant.

Keywords: dapagliflozin, sacubitril/valsartan, athletic performance, sports cardiology, doping agents, performance enhancing

Key points:

- Dapagliflozin and sacubitril/valsartan are cardiac medications that have an effect on athletic performance.
- The athletic performance effect of sacubitril/valsartan is limited, but this effect is more pronounced with dapagliflozin.
- These medications, which have become very popular among cardiac medication options in recent years, can be abused as doping agents.

Introduction

Athlete's heart is a definition used for the physiological adaptation of the heart to repetitive exercise. Different physiological adaptation mechanisms may develop depending on the content of the exercise performed [1]. Elite athletes aim to improve their cardiac fitness at an optimal level through training for the best athletic performance. Training is a structured procedure in which athletes are subjected to consistent and recurrent exercise stimuli in order to induce adaptations that align with a desired function. These functions may include delaying the onset of tiredness, enhancing power output, improving motor coordination, or minimizing the

likelihood of injury. The boundaries of athletic performance have been a topic of speculation and discussion for a significant period of time. Nevertheless, there appears to be a noticeable plateau in sports performance in recent years, indicating that the potential for further enhancement of individuals' physical capabilities may be limited [2]. Therefore, doping substances are becoming a suspicious factor among elite athletes. Due to the extensive range chemicals and the continual emergence of novel designer pharmaceuticals on the market, the World Anti-Doping Agency (WADA) annually revises its list of substances and methodologies that are forbidden in the realm of sports. One of the most fundamental elements of sports performance is undoubtedly cardiac function. This raises serious doubts about the use of some heart medications as doping agents. The addition of trimetazidine to WADA's Prohibited List as a doping substance in 2014 can be considered the beginning of this era [3,4]. The combination of sacubitril and valsartan, as well as dapagliflozin, which effectively improves cardiac performance and has a positive prognostic effect on heart failure, has been particularly notable in recent years in the existing literature [5,6]. These may potentially be abused as doping substances in elite athletes. Therefore, in our study, we aimed to observe the effects of these drugs on athletic performance.

Methods

A swimming experiment was designed in rat to objectively observe exercise capacity. The Sprague-Dawley male rat were obtained from the Animal Center of Health Science University. Based on the findings of the G power 3.1 analysis, it was determined that a minimum of six rat per group would be necessary to achieve the desired experimental power. Consequently, the study was designed to include a total of 24 animals, following the appropriate ethical procedures by seeking approval from the animal experiments ethics committee.

The subjects were accommodated in a controlled environment with a 12-hour light and dark cycle, at a temperature of 25 °C, and a relative air humidity of 40%. They were provided with ad libitum access to water and feed, and were allowed unrestricted activity within a laboratory animal room for a minimum duration of one week. Then, 3-month-old rat were randomly divided into three groups. The Rota-Rod test was employed to measure the motor coordination and antifatigue ability of rat at the beginning of the study. The Rota-Rod test consists of a cylindrical rod with a diameter of 3 cm, which has been partitioned into five tracks each with a width of 6 cm. Additionally, the apparatus includes an infrared detector and a computer. The Rota-Rod test comprises a rotating rod with a diameter of 3 cm (this rod was divided into 5 tracks with a width of 6 cm), an infrared detector, and a computer. In the test, rat were positioned on the horizontally oriented, rotating rod. It was ensured that there were no differences between groups.

In the first group, 60 mg/kg/1ml dose of sacubitril/valsartan was administered every day by oral gavage. In the second group, 1,5mg/kg/1ml dose of dapagliflozin was administered every day by oral gavage. The third group was the control group. The researchers who administered the drug and the researchers who performed the swim test were different people. The researcher who performed the swim test was unaware of the groups' information.

Initially, before the experiment, each group had swimming training in the water tank for three days. Each mouse was placed in a different water tank. The water tank was designed with a size of 40x40 cm and a height of 50 cm. The swimming tank was maintained at a temperature of 28oC throughout the swimming process. The endurance of each mouse was assessed by measuring the swimming time from the start of the activity until exhaustion, which was determined by observing uncoordinated movements and the inability to resurface within a period of 7 seconds. The maximum swimming seconds of each mouse were recorded daily. In addition, echocardiography (ECHO) and heart rate measurements were performed in each mouse at the beginning of the experiment, on the 15th day and at the end of the experiment.

Statistical analysis

The research analysis was conducted utilizing the Statistical Package for Social Science (SPSS) version 27.0 program. Continuous variables are given with median (minimum-maximum) values. Kruskal Wallis test was used to determine differences between groups. Mann-Whitney U test was used and bonferroni correction was applied in post hoc intergroup pairwise analyses. Friedman test was applied to determine intragroup

differences. Wilcoxon test was applied and bonferroni correction was applied in post hoc intragroup pairwise comparison. The significance level for statistical analyzes was set as $p<0.05$. determined.

Results

A total of 24 rat, divided into 3 groups of 8 rat each, were observed throughout the duration of the experiment. Table 1 shows the baseline ECHO parameters of the three groups. There is no difference between the groups when comparing echo parameters at baseline. Table 2 shows the echo parameters of the control group on days 0, 15 and 30, table 3 shows the dapagliflozin and table 4 shows the sacubitril/valsartan group.

When comparing baseline data, there was no significant difference observed in the performance of rotarods and their corresponding weights. Table 5 shows the change in the rat's weight over the course of the experiment, and Table 6 shows the results from the rotarod follow-ups.

Table 7 shows the median swimming times of each group during the swimming sessions throughout the experiment. Starting from the 9th swimming session, there was a noticeable difference in the swimming times between the groups. Figure 1 displays the average swimming performance of the three groups. Table 8 shows the comparison of sacubitril/valsartan with the control group, and table 9 shows the comparison of dapagliflozin with the control group.

Discussion

Instances of doping, as well as other forms of cheating, have been documented throughout the history of sports. The utilization of performance-enhancing drugs in sports is an obvious crisis. The utilization of substances in professional sports and competitions has significantly damaged the reputation of numerous athletes worldwide, while also posing a threat to their health. [7] The pharmaceutical industry has had significant expansion in the past decade, in tandem with advancements in technology. This growth has resulted in key advancements, particularly in the field of cardiac medications. The recently introduced cardiac medications may enhance sports performance and therefore may be abused as a form of doping. Therefore, our study aimed at examining the impact of dapagliflozin and sacubitril/valsartan, known for their significant symptomatic alleviation and favorable prognosis, particularly in heart failure, on sports performance. Both drugs have proved the ability to improve athletic performance, The impact on improving athletic performance was significantly more prominent for dapagliflozin.

The effect of exercise on the heart can be observed more quickly in rat. [8] The change seen in the echo data of the control group regarding the left ventricle is compatible with the development of an athlete's heart. This demonstrates the methodological reliability of the experiment. In both medical approaches, there was a significant increase in antegrade flow of the pulmonary artery, compared to baseline. This may be related to an increase in right ventricular functions. Another notable feature is the increase of ejection fraction (EF) observed in the sacubitril/valsartan group. The increase in EF with sacubitril/valsartan use can also be seen in heart failure patients. [9] The effect of dapagliflozin on athletic performance was assessed independently from its impact on EF.

There was a decrease in the weight of the rat in all three groups due to intense exercise throughout the experiment. But there was no significant difference between the groups in this decrease. The decrease in weight is related to both the direct effect of physical activity on energy expenditure and the increase in metabolic rate during the resting period. [10] The rat were not under any calorie restriction. They had unrestricted access to food. If the experimental period was extended, a plateau in their weight could be observed. [11]

We observed an increase in rotarod results compared to baseline data in both medication groups. There was no significant difference compared to the control group. The adaptation of rat should not be ignored. However, while there is a statistical difference in the medication groups, although there is an increase in the control group, it is not statistically significant. These results may be the beginning of more comprehensive studies. Because the positive effect of dapagliflozin and sacubitril/valsartan on the rotarod may provide an advantage in skill sports (golf, table tennis, shooting, curling, bowling etc.). [12]

The primary objective of our investigation was to reveal the improvement in athletic performance. After similar results were obtained during the first 9 swimming sessions of exercise, we observed a significant difference in the athletic performance of rat with both medications. This effect of sacubitril/valsartan was generally observed parallel to the control group and slightly better. Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor, enhances the natriuretic peptide system by suppressing the neprilysin enzyme and inhibits the renin-angiotensin-aldosterone system by inhibiting the angiotensin II receptor. Evidence demonstrates that it improves mortality and reduces hospitalization rates in individuals with heart failure caused by impaired left ventricular systolic performance. [13] Also sacubitril/valsartan augments the effects of bradykinin, substance P, and adrenomedullin, which are other hormones that may contribute to the cardiac efficacy of the medication. [14] The positive effect of sacubitril/valsartan on athletic performance may be related to increased cardiac efficiency and slightly improved left ventricular function. However, this effect was observed to be limited and there was a relative increase in athletic performance.

The effect of dapagliflozin was observed remarkably. Sodium-glucose cotransporter-2 (SGLT) inhibitors reduce the risk of hospitalization for heart failure in patients with either preserved or reduced ejection fraction. However, the specific hemodynamic processes responsible for these advantages are not yet fully understood. [15] A research conducted on rat has demonstrated that dapagliflozin has a vasodilatory impact on the thoracic aorta, which is dependent on the voltage of potassium channels. [16] This demonstrated a direct effect on vascular cells for both acute and chronic treatment. [17] Therefore, it is reasonable to observe that the improvement in performance begins during the initial periods and thereafter advances throughout time. Another possible mechanism of action may be related to its positive microvascular and endothelial activity. [18] SGLT-2 inhibitors, currently the only option in preserved EF heart failure, may have as yet undisclosed abilities regarding possible cellular myocardial efficiency. However, our study showed that dapagliflozin has an obvious doping effect on athletic performance. Future studies on the mechanism of action may reveal the reasons for this effect more clearly.

Conclusion

The development of studies in cardiac treatment provides novel and efficacious alternatives. The heart, which is the center of high-level athletic performance, and its related medications can be abused as doping agents. Our study showed a limited positive effect of sacubitril/valsartan on athletic performance. The impact of dapagliflozin on athletic performance was shown to be particularly significant.

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Figure legend: Improvement of median swimming times of the groups during the experiment

Table 1: Comparison of baseline echocardiography parameters

Echo parameters	**Control**	**Dapagliflozin**	**Sacubitril / valsartan**	**P value***
Heart rate (beat/min)	245 (223-261)	243 (225-255)	244 (213-262)	0.996
IVSD (mm)	1,9 (1,8-2)	1,9 (1,7-2)	1,9 (1,8-2)	0.980
IVSS (mm)	2,7 (2,6-2,8)	2,7 (2,4-2,8)	2,7 (2,6-2,8)	0.899
LVDD (mm)	7,4 (7,1-8,3)	8 (6,6-8,1)	7,55 (7,1-8,2)	0.648
LVSD (mm)	5,2 (4,5-6,1)	5,6 (4,1-6)	5,3 (4,6-5,9)	0.723
LVPWD (mm)	1,9 (1,8-2)	1,9 (1,7-2)	1,9 (1,8-2)	0.495
LVPWS (mm)	2,7 (2,5-2,7)	2,6 (2,6-2,8)	2,7 (2,6-2,8)	0.350
AoS (mm)	3,6 (3,5-3,7)	3,6 (3,4-3,9)	3,55 (3,4-3,7)	0.560
AoD (mm)	3,2 (3,1-3,3)	3,1 (3,1-3,4)	3,1 (3-3,3)	0.577
Aortic strain (%)	12,9 (12,12-16,12)	13,8 (9,6-16,1)	12,7 (9,6-16,6)	0.940
AV Vmax (m/sn)	1,29 (1,1-1,54)	1,43 (1,14-1,56)	1,39 (1,14-2)	0.467
PV Vmax (m/sn)	0,77 (0,63-0,91)	0,74 (0,58-0,91)	0,73 (0,6-1)	0.828
EF (%)	69 (60-74)	67 (56-79)	64 (59-72)	0.828
F shortening (%)	32,9 (26,5-36,6)	30,8 (24-40,5)	29,3 (25,9-35,2)	0.828
EDV (mL)	0,468 (0,374-0,598)	0,53 (0,30-0,55)	0,45 (0,37-0,57)	0.648
ESV (mL)	0,147 (0,095-0,237)	0,18 (0,07-0,22)	0,15 (0,11-0,21)	0.723

Echo parameters	**Control**	**Dapagliflozin**	**Sacubitril / valsartan**	**P value***
Cardiac output (mL/min)	80 (65-88)	82,7 (51,8-95)	71 (62-85)	0.471
LV mass (g)	1,94 (1,87-1,97)	1,93 (1,84-1,97)	1,94 (1,89-1,99)	0.607

*Kruskal Wallis test

AoD;aortic diastole, AoS;aortic systole, AV; aortic valve, EDV; end diastolic volume, ESV; end systolic volume, EF; ejection fraction, F; fractional, IVSD; inter ventricular septum diastolic, IVSS; inter ventricular septum systolic, LV; left ventricle, LVDD; left ventricle diastolic diameter, LVSD; left ventricle systolic diameter, LVPWD; left ventricle posterior wall diastolic, LWPWS: left ventricle posterior wall systolic, PV; pulmonary valve

Table 2: Follow-up of echocardiography parameters of the control group

Echo parameters	**Day 0**	**Day 15**	**Day 30**	**P value***
Heart rate (beat/min)	245 (223-261)	231 (208-254)	238,5 (221-266)	**0,010**
IVSD (mm)	1,9 (1,8-2)	1,9 (1,8-2)	1,95 (1,8-2)	**0,022**
IVSS (mm)	2,7 (2,6-2,8)	2,7 (2,7-2,9)	2,75 (2,7-3)	**0,006**
LVSD (mm)	7,4 (7,1-8,3)	7,45 (7,0-8,2)	7,4 (6,9-8,1)	**0,003**
LVSD (mm)	5,2 (4,5-6,1)	5,1 (4,5-6)	5,05 (4,4-6,1)	**0,034**
LVPWD (mm)	1,9 (1,8-2,0)	1,9 (1,8-2,0)	2 (1,8-2,1)	0,280
LVPWS (mm)	2,7 (2,5-2,7)	2,7 (2,5-2,8)	2,7 (2,6-2,7)	0,646
AoS (mm)	3,6 (3,5-3,7)	3,65 (3,4-3,7)	3,7 (3,5-3,9)	0,059
AoD (mm)	3,2 (3,1-3,3)	3,1 (3-3,2)	3,1 (3,1-3,3)	0,401
Aortic strain (%)	12,9 (12,12-16,12)	15,62 (9,67-23,3)	17,15 (12,5-22,58)	0,179
AV Vmax (m/sn)	1,29 (1,1-1,54)	1,41 (1,18-1,52)	1,49 (1,18-1,83)	0,115
PV Vmax (m/sn)	0,77 (0,63-0,91)	0,80 (0,69-1,05)	0,88 (0,73-1,14)	0,250
EF	69 (60,74)	70 (60,74)	68 (57,74)	0,325
F shortening	32,9 (26,5-36,6)	33,1 (26,8-36,4)	32 (24,6-36,2)	0,325
EDV	0,468 (0,374-0,598)	0,432 (0,359-0,577)	0,424 (0,343-0,556)	**0,003**
ESV	0,147 (0,095-0,237)	0,138 (0,095-0,226)	0,134 (0,089-0,237)	**0,034**
Cardiac output (mL/min)	80 (65-88)	70 (60-78)	69 (58,82)	**0,010**
LV mass (g)	1,94 (1,87-1,97)	1,96 (1,89-1,99)	1,96 (1,92-2,02)	**0,024**

*Friedman Test

AoD;aortic diastole, AoS;aortic systole, AV; aortic valve, EDV; end diastolic volume, ESV; end systolic volume, EF; ejection fraction, F; fractional, IVSD; inter ventricular septum diastolic, IVSS; inter ventricular septum systolic, LV; left ventricle, LVDD; left ventricle diastolic diameter, LVSD; left ventricle systolic diameter, LVPWD; left ventricle posterior wall diastolic, LWPWS: left ventricle posterior wall systolic, PV; pulmonary valve

Table 3: Follow-up of echocardiography parameters of the dapagliflozin group

Echo parameters	**Day 0**	**Day 15**	**Day 30**	**P value***
Heart rate (beat/min)	243 (225-255)	221 (184-253)	240 (210-282)	0,197
IVSD (mm)	1,9 (1,7-2)	1,8 (1,8-1,9)	1,85 (1,7-2)	0,368
IVSS (mm)	2,7 (2,4-2,8)	2,75 (2,2-2,9)	2,75 (2,4-2,9)	0,268

Echo parameters	**Day 0**	**Day 15**	**Day 30**	**P value***
LVSD (mm)	8 (6,6-8,1)	7,85 (6,7-8,0)	7,9 (7,2-8,3)	0,191
LVSD (mm)	5,6 (4,1-6)	5,45 (3,8-5,8)	5,5 (4-6,1)	**0,042**
LVPWD (mm)	1,9 (1,7-2)	1,9 (1,8-2)	1,95 (1,9-2,1)	**0,012**
LVPWS (mm)	2,6 (2,6-2,8)	2,7 (2,6-2,8)	2,7 (2,3-2,9)	0,229
AoS (mm)	3,6 (3,4-3,9)	3,55 (3,4-4)	3,6 (3,5-3,8)	0,882
AoD (mm)	3,1 (3,1-3,4)	3,1 (2,9-3,4)	3,1 (3-3,3)	0,891
Aortic strain (%)	13,8 (9,6-16,1)	13,1 (12,1-20,6)	15,6 (9,1-20)	0,748
AV Vmax (m/sn)	1,43 (1,14-1,56)	1,38 (1,19-1,68)	1,54 (1,37-1,99)	0,417
PV Vmax (m/sn)	0,74 (0,58-0,91)	0,92 (0,74-1,25)	0,89 (0,77-1,04)	**0,05**
EF	67 (56-79)	66 (61-81)	69 (58-82)	0,648
F shortening	30,8 (24-40,5)	30,5 (27,5-43,3)	30,8 (25,3-44,4)	0,648
EDV	0,53 (0,30-0,55)	0,50 (0,31-0,53)	0,51 (0,39-0,59)	0,191
ESV	0,18 (0,07-0,22)	0,16 (0,06-0,20)	0,17 (0,07-0,23)	**0,042**
Cardiac output (mL/min)	82,7 (51,8-95)	72 (52,7-91)	79 (65-94)	0,197
LV mass (g)	1,93 (1,84-1,97)	1,96 (1,82-1,99)	1,93 (1,84-2,02)	0,119

*Friedman Testi

AoD;aortic diastole, AoS;aortic systole, AV; aortic valve, EDV; end diastolic volume, ESV; end systolic volume, EF; ejection fraction, F; fractional, IVSD; inter ventricular septum diastolic, IVSS; inter ventricular septum systolic, LV; left ventricle, LVDD; left ventricle diastolic diameter, LVSD; left ventricle systolic diameter, LVPWD; left ventricle posterior wall diastolic, LWPWS: left ventricle posterior wall systolic, PV; pulmonary valve

Table 4: Follow-up of echocardiography parameters of the sacubitril/valsartan group

Echo parameters	**Day 0**	**Day 15**	**Day 30**	**P value***
Heart rate (beat/min)	244 (213-262)	230 (184-266)	232 (219-252)	0,325
IVSD (mm)	1,9 (1,8-2)	1,9 (1,8-2,1)	1,9 (1,8-1,9)	0,202
IVSS (mm)	2,7 (2,6-2,8)	2,6 (2,4-2,9)	2,7 (2,6-2,8)	0,878
LVSD (mm)	7,55 (7,1-8,2)	7,55 (7,2-8,2)	7,55 (7,3-8,4)	0,779
LVSD (mm)	5,3 (4,6-5,9)	5,3 (4,6-5,7)	4,6 (4-5,5)	0,061
LVPWD (mm)	1,9 (1,8-2)	1,9 (1,8-2)	1,9 (1,7-2)	0,186
LVPWS (mm)	2,7 (2,6-2,8)	2,75 (2,6-2,8)	2,7 (2,6-2,8)	0,417
AoS (mm)	3,55 (3,4-3,7)	3,5 (3,3-3,7)	3,55 (3,4-3,9)	**0,013**
AoD (mm)	3,1 (3-3,3)	3,05 (2,9-3,2)	3,1 (2,9-3,2)	0,167
Aortic strain (%)	12,7 (9,6-16,6)	12,9 (10-20,6)	15,8 (9,6-25,8)	0,227
AV Vmax (m/sn)	1,39 (1,14-2)	1,49 (1,34-1,61)	1,67 (1,52-2,23)	**0,030**
PV Vmax (m/sn)	0,73 (0,6-1)	0,8 (0,66-1,25)	1,09 (0,89-1,72)	**0,010**
EF	64 (59-72)	67 (60-75)	74 (69-83)	**0,002**
F shortening	29,3 (25,9-35,2)	31,3 (26,6-37,8)	36,9 (32,9-45,2)	**0,002**
EDV	0,45 (0,37-0,57)	0,45 (0,39-0,57)	0,45 (0,41-0,62)	0,779
ESV	0,15 (0,11-0,21)	0,16 (0,11-0,19)	0,11(0,7-0,17)	0,061
Cardiac output (mL/min)	71 (62-85)	75 (52-101)	80 (66-111)	**0,034**
LV mass (g)	1,94 (1,89-1,99)	1,93 (1,84-2,02)	1,96 (1,92-1,97)	0,891

*Friedman Testi

AoD;aortic diastole, AoS;aortic systole, AV; aortic valve, EDV; end diastolic volume, ESV; end systolic

volume, EF; ejection fraction, F; fractional, IVSD; inter ventricular septum diastolic, IVSS; inter ventricular septum systolic, LV; left ventricle, LVDD; left ventricle diastolic diameter, LVSD; left ventricle systolic diameter, LVPWD; left ventricle posterior wall diastolic, LWPWS: left ventricle posterior wall systolic, PV; pulmonary valve

Table 5: Follow-up data of the weights of the groups and comparison between groups

Group	**Day 0**	**Day 15**	**Day 30**	**P value****
Control	430 (370,450)	405 (350,430)	385 (330,400)	**0.002**
Dapaglifozin	420(390,470)	380 (360,430)	361 (344,407)	**<0.001**
Sacubitril/Valsartan	435 (380,460)	397 (340,435)	377 (319,410)	**<0.001**
P value*	0.996	0.889	0.826	

*Kruskal Wallis

**Friedman

Table 6: Rotarod follow-up data of the groups and comparison between groups

Gruop	**Day 0**	**Day 15**	**Day 30**	**P value****
Control	31 (14,131)	67,5 (27,129)	67,5 (38,131)	0.115
Dapaglifozin	43,5 (17,103)	60 (41,132)	88 (38,148)	**0.011**
Sacubitril/Valsartan	45 (30,70)	74 (58,103)	89 (75,157)	**<0.001**
P value*	0.750	0.652	0.278	

* Kruskal Wallis

**Friedman

Table 7: Comparison of swimming times of groups

Swimming session (Second) Median (Min-Max)	**Control group**	**Dapagliflozin group**	**Sacubitril/Valsartan group**	**P value***
1.	188 (165,297)	203 (171,293)	203 (182,244)	0,671
2.	339 (290,510)	345 (270,590)	394 (288,420)	0,655
3.	728 (688,910)	808 (654,950)	767 (555,954)	0,777
4.	1154 (966,1245)	1180 (945,1365)	1194 (765,1362)	0,760
5.	1269 (1100,1330)	1402 (1189,1490)	1370 (1143,1613)	0,072
6.	1532 (1214,1974)	1722 (1600,1910)	1827 (1464,2026)	0,165
7.	1680 (1430,2050)	1906 (1653,2170)	1764 (1385,2184)	0,68
8.	1746 (1480,2496)	2170 (1790,2450)	1866 (1685,2252)	0,52
9.	1889 (1478,2210)	2144 (1986,2387)	2044 (1800,2387)	**0,003**
10.	1955 (1551,3455)	2724 (2625,2939)	2085 (1686,2533)	**0,009**
11.	2110 (1810,2280)	2407 (2190,3001)	2238 (2022,2464)	**<0,001**
12.	2261 (2054,2320)	2787 (2620,3160)	2354 (2104,2773)	**<0,001**
13.	2103 (2037,2276)	3055 (3004, 3274)	2350 (2247,2656)	**<0,001**
14.	2304 (2060,2474)	3037 (2798,3345)	2677 (2136,2950)	**<0,001**
15.	2299 (2100,2382)	2630 (2229,3141)	2435 (2110,2187)	**0,039**

Swimming session (Second) Median (Min-Max)	**Control group**	**Dapagliflozin group**	**Sacubitril/Valsartan group**	**P value***
16.	2314 (2245,2405)	2710 (2340,3312)	2407 (2135,2173)	**0,011**
17.	2371 (2214,2472)	3006 (2360,3140)	2480 (2179,2895)	**0,046**
18.	2372 (2256,2492)	3372 (2480,4130)	2397 (2284,2980)	**0,001**
19.	2343 (2272,2424)	3500 (2630,4003)	2470 (2320,29559	**<0,001**
20.	2382 (2300,2467)	3580 (2914,4212)	2591 (2457,3002)	**<0,001**
Total time	35654 (32315,38332)	45406 (39839,49157)	38105 (34423,42696)	**<0,001**
Median	1782 (1615,1916)	2270 (1991,2457)	1905 (1721,2134)	**<0,001**

*Kruskal Wallis

Table 8: Comparison of swimming times of the control group and sacubitril/valsartan group

Swimming session (Second) Median (Min-Max)	**Control group**	**Sacubitril/Valsartan Group**	**P value***
1.	188 (165,297)	203 (182,244)	0.431
2.	339 (290,510)	394 (288,420)	0.528
3.	728 (688,910)	767 (555,954)	0.344
4.	1154 (966,1245)	1194 (765,1362)	0.462
5.	1269 (1100,1330)	1370 (1143,1613)	0.115
6.	1532 (1214,1974)	1827 (1464,2026)	0.172
7.	1680 (1430,2050)	1764 (1385,2184)	0.600
8.	1746 (1480,2496)	1866 (1685,2252)	0.248
9.	1889 (1478,2210)	2044 (1800,2387)	0.141
10.	1955 (1551,3455)	2085 (1686,2533)	0.401
11.	2110 (1810,2280)	2238 (2022,2464)	0.115
12.	2261 (2054,2320)	2354 (2104,2773)	0.172
13.	2103 (2037,2276)	2350 (2247,2656)	**0.002**
14.	2304 (2060,2474)	2677 (2136,2950)	0.46
15.	2299 (2100,2382)	2435 (2110,2187)	0.093
16.	2314 (2245,2405)	2407 (2135,2173)	0.462
17.	2371 (2214,2472)	2480 (2179,2895)	0.401
18.	2372 (2256,2492)	2397 (2284,2980)	0.462
19.	2343 (2272,2424)	2470 (2320,29559	**0.009**
20.	2382 (2300,2467)	2591 (2457,3002)	**0.002**
Total time	35654 (32315,38332)	38105 (34423,42696)	0.115
Median	1782 (1615,1916)	1905 (1721,2134)	0.115

*Mann-Whitney U testi

Table 9: Comparison of swimming times of the control group and dapagliflozin group

Swimming session (Second) Median (Min-Max)	Control group	Dapagliflozin group	P value*
1.	188 (165,297)	203 (171,293)	0.462
2.	339 (290,510)	345 (270,590)	0.916
3.	728 (688,910)	808 (654,950)	0.793
4.	1154 (966,1245)	1180 (945,1365)	0.636
5.	1269 (1100,1330)	1402 (1189,1490)	0.027
6.	1532 (1214,1974)	1722 (1600,1910)	0.059
7.	1680 (1430,2050)	1906 (1653,2170)	0.027
8.	1746 (1480,2496)	2170 (1790,2450)	0.046
9.	1889 (1478,2210)	2144 (1986,2387)	0.021
10.	1955 (1551,3455)	2724 (2625,2939)	**0.012**
11.	2110 (1810,2280)	2407 (2190,3001)	**0.003**
12.	2261 (2054,2320)	2787 (2620,3160)	**<0.001**
13.	2103 (2037,2276)	3055 (3004, 3274)	**<0.001**
14.	2304 (2060,2474)	3037 (2798,3345)	**<0.001**
15.	2299 (2100,2382)	2630 (2229,3141)	0.027
16.	2314 (2245,2405)	2710 (2340,3312)	**0.003**
17.	2371 (2214,2472)	3006 (2360,3140)	0.027
18.	2372 (2256,2492)	3372 (2480,4130)	**0.001**
19.	2343 (2272,2424)	3500 (2630,4003)	**<0.001**
20.	2382 (2300,2467)	3580 (2914,4212)	**<0.001**
Total time Median	35654 (32315,38332) 1782 (1615,1916)	45406 (39839,49157) 2270 (1991,2457)	**<0.001** **<0.001**

*Mann-Whitney U testi