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ORIGINAL ARTICLE

The Influence of Optimal Blood Pressure Control on the Progression of Chronic Kidney Disease

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Abstract

Background/Aim: Chronic kidney disease (CKD) has seen a rapid increase worldwide in recent decades, now recognised as a global health issue of the 21st century. Optimal, continuous control of hypertension represents a crucial part of treatment capable of slowing the progression of CKD. The aim of this study was to demonstrate that optimal regulation blood pressure control in patients with essential and secondary hypertension, along with CKD, slows the progression of CKD.
Methods: The research was conducted at the University Clinical Centre of the Republic of Srpska, Banja Luka, Internal Clinic Nephrology Department. A retrospective-prospective study was blind for patients and lasted for 24 months. It included 97 patients, aged 18 and above, of both genders, hypertensive, in the 3rd or 4th stage of CKD (creatinine clearance of 15-59 mL/min). Assess the outcome of CKD, a "complex (undesirable) clinical outcome" was taken - one of three fundamental clinically undesirable events: double increase in serum creatinine values at the end of 24 months, onset of terminal renal insufficiency, or patient death.
Patients were classified into three groups: I group - 30 patients with essential hypertension and CKD with optimally regulated blood pressure; II group - 32 patients with secondary hypertension and CKD with optimally regulated blood pressure; III control group - 35 patients with hypertension of various causes and CKD who did not achieve target blood pressure values. Blood pressure control was measured from month 0 to month 24 - once a month. Laboratory tests were taken every 3 months (red blood cells, haemoglobin, glycaemia, cholesterol, urea, creatinine, uric acid, sodium, potassium in serum and urine).
Results: There was a highly statistically significant difference in glomerular filtration rate in the first group compared to the third group and in the second group compared to the third group. No statistically significant difference in glomerular filtration rate between the first and second groups was observed, where good blood pressure regulation was achieved.
Conclusion: Optimal blood pressure control in the examined groups, regardless of the cause of CKD, was responsible for slowing the progression of CKD compared to the group with unregulated blood pressure.

Key words: Blood pressure; Hypertension; Chronic kidney disease.

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Introduction

Chronic kidney disease (CKD), which has seen a rapid increase globally in recent decades (in terms of both incidence and prevalence), is now recognised as a global health (and economic)

problem of the 21st century. The term "chronic kidney disease" was introduced by the American Kidney Foundation's working group in 2002 and published practical clinical guidelines.[1] According to these guidelines, adopted worldwide by the Kidney Disease Improving Global Outcomes (KDIGO) conference in 2004, CKD is defined as a structural or functional abnormality of the kidneys leading to impaired kidney function lasting more than 3 months, with or without a decrease in glomerular filtration rate (GFR).[2]

The stages of CKD (stages CKD 2-5 were previously CKD stages 1-4) are classified as follows:

1st stage: Normal GFR with laboratory or radiological signs of kidney damage lasting more than 3 months (eg pathological proteinuria lasting more than 3 months without a decrease in GFR);
2nd stage: (formerly Stage 1 CKD): GFR from 60 to 89 mL/min;
3rd stage: GFR from 30 to 59 mL/min;
4th stage: GFR from 15 to 29 mL/min;
5th stage: GFR less than 15 mL/min (end-stage renal disease - ESRD).

The prevalence of CKD in the United States and most European countries is steadily increasing. The overall prevalence of CKD in the USA from stages 1-5 increased from around 9.6 % to 13 % between 1999 and 2004.[3] In recent years, the prevalence of CKD in the USA has stabilised around 15 %.[4] The global prevalence is estimated at 13.4 %, with a slightly higher overall prevalence for European countries at around 18 %.[5, 6] Moreover, the prevalence of ESRD - the total number of ESRD patients per million population - is continually rising and varies significantly worldwide, ranging from the highest at 2240 patients/million in the USA in 2019 to 80/million in some underdeveloped African countries.

According to the data from the Renal Registry of Bosnia and Herzegovina, the prevalence of ESRD increased from 426/million patients in 2004 to 651/million in 2009[7] and reached 748/million in 2019.[8] The percentage of patients on haemodialysis (HD) or peritoneal dialysis (PD) was 86 %, with only 14 % being transplanted. In comparison, the percentage of transplanted patients in Norway was approximately 65 %[5] and in Croatia in 2018, it was 30 %.[9] The treatment of ESRD patients (HD, PD or transplantation), constituting only 0.1 % of the population, costs up to 2 % of the healthcare budget in European countries.[10] In our context, this percentage is even less favourable due to the significantly lower percentage of transplants - around 5 %.

Arterial hypertension is both a cause and a consequence of CKD, with high blood pressure being a key pathogenic factor influencing the deterioration of renal function.[11] The incidence of hypertension as a cause of ESRD is continually rising worldwide[5, 6] and in Bosnia and Herzegovina, it increased from 7.1 % in 2009 to 13 % in 2019.[8]

Optimal (strict) and continuous control of hypertension, a significant influence to the development of renal impairment, is a crucial part of treatment that can slow the progression of all stages of CKD.[12] Under normal conditions, renal blood flow varies very little when the mean arterial pressure is between 80 and 160 mm Hg. If the mean arterial pressure exceeds 160 mm Hg or if the autoregulatory mechanism is impaired due to kidney disease, diabetes, high daily protein intake, a linear relationship between elevated systemic blood pressure and glomerular capillary pressure can be expected.[13]

A meta-analysis of 11 studies by Jafar and colleagues showed that achieving a systolic blood pressure between 110 and 129 mm Hg in non-diabetics with proteinuria greater than 1 g/day can reduce the risk of progression of CKD.[14] European hypertension guidelines from 2018 recommend further lowering of systolic and diastolic blood pressure (systolic below 130 and diastolic below 80 mm Hg if tolerated) in patients with diabetes and CKD. Recent studies also emphasise the importance of strict hypertension control and regulation in non-dipping patients.[15, 16] These references are considered when determining target blood pressure values for patients.[14, 15]

In a meta-analysis by Bakris and colleagues involving nine large clinical studies in diabetics and non-diabetics with CKD, a linear correlation was demonstrated between the achieved blood pressure level and the progression of renal failure.[17] The Okinawa General Health Maintenance Association study showed that women with very poor blood pressure control (Stage 4 hypertension) also have a significantly increased risk of terminal renal failure.[18]

Aim of this study was to analyse whether optimal regulation of blood pressure in patients

with essential hypertension and CKD and with secondary hypertension (diabetic nephropathy, glomerular diseases, chronic pyelonephritis) and CKD have a favourable effect on slowing down the progression of CKD. Study also aimed to determine whether there is a difference in the degree of progression of CKD between the first two groups (where optimal blood pressure regulation was achieved) and the third control group, where it was not achieved optimal regulation of blood pressure in patients with CKD.

Methods

The study was conducted at the University Clinical Centre Banja Luka, Clinic for Internal Diseases, Nephrology Department and Nephrology Outpatient Clinic of the Internal Clinic of the Clinical Centre, Banja Luka, The Republic of Srpska, Bosnia and Herzegovina. The study was retrospective-prospective, blinded for patients and lasted for two years. It included patients, aged 18 and above, of both genders, with CKD in stages 3 or 4 (initial creatinine clearance of 30-60 mL/min, or 15-30 mL/min). Patients at the time of enrolment were hypertensive, having elevated blood pressure (140/90 mm Hg or higher) or were under antihypertensive therapy.

Criteria for inclusion in the study: patients older than 18 years, with CKD with a creatinine clearance level of 15-60 mL/min at the start of the test and presence of hypertension with blood pressure higher than 140/90 mm Hg or being on antihypertensive therapy. Written consent for participation in the study was signed. Criteria for exclusion from the study: ESRD requiring HD or kidney transplantation; occurrence of another serious health disorder (myocardial infarction, stroke, cancer); non-cooperation of the patient. The criterion for not being included in the study was: patients with hypertension and CKD who had a degree of renal insufficiency with a creatinine clearance of less than 15 mL/min or more than 60 mL/min.

The primary measure to assess the outcome of CKD in patients was the "complex (undesirable) clinical outcome," according to similar assessments in other studies that followed the clinical outcome of CKD. It involved one of the three fundamental clinically undesirable events: double increase in serum creatinine values at the end of 24 months (or double decrease in creatinine clearance); onset of ESRD; patient death. The follow-up period was 24 months. The target blood pressure was 130/80 mm Hg for non-diabetics, 120/80 mm Hg for diabetics with CKD and non-diabetics with CKD with proteinuria exceeding 1 g/day.

Patients were classified into three groups:

I group: 30 patients with essential hypertension and CKD who had optimally regulated blood pressure (below 130/80 mm Hg);
II group: 32 patients with secondary hypertension (diabetic nephropathy, glomerular diseases, chronic pyelonephritis, polycystic kidney disease) and CKD who also had optimally regulated blood pressure;
III control group: 35 patients with hypertension of various causes and CKD who did not achieve target blood pressure values for various reasons - uncontrolled hypertension.

Monitoring parameters were: blood pressure control with recording of the given therapy was performed from 0 to 24 months - once a month (first, highest and lowest measured values were not considered); laboratory control tests were performed every 3 months (red blood cells, haemoglobin, glycaemia, cholesterol, triglycerides, urea, creatinine, uric acid, sodium, potassium in serum and urine).

Blood pressure (systolic and diastolic) was measured using a mercury sphygmomanometer, auscultatory method, in outpatient conditions in the morning and expressed in mm Hg. The mean arterial pressure was calculated using the formula: MAP = DP + (SP-DP)/3; where MAP = mean arterial pressure; DP = diastolic pressure; SP = systolic pressure. Biochemical analyses were conducted in the Central Laboratory of the Clinical Centre. Serum creatinine (sCr) was determined by spectrophotometric method, Jaffe's reagent. Creatinine clearance was calculated using the formula: ClCr mL/min = V x uCr/sCr, where V = volume of urine excreted in a unit of time for 24 h in litres, uCr in mmol/L (creatinine in urine), sCr (serum creatinine) in μmol/L. Proteins in 24-hour urine were determined using the turbidimetric method. Biochemical analyses were performed on venous blood samples in the morning on an empty stomach.

Statistical analysis

Testing the mean values of individual research parameters involved two types of comparisons: within each group (sample) and between groups. Descriptive statistics measures of research variables, such as the mean, mode, median, standard deviation (SD) and coefficient of variation, were provided to represent the research sample. Correlation analysis was conducted to determine the interdependence of research parameters. The t-test for differences within groups and the t-test for small samples between groups were used for comparing mean values of research parameters. To determine the strength and extent of the association between arterial blood pressure and creatinine clearance in subjects during all months of monitoring these parameters, the Pearson correlation coefficient was used. X^2 test was used to evaluate the risk of a greater than 50 % decline in creatinine clearance.

Results

The age of patients at the start of patient monitoring ranged from 27 to 82 years (mean: 59.69 years) and the follow-up period was 24 months.

Dynamics of mean values of research parameters by groups over the monitoring months

There was a statistically highly significant difference ($p < 0.01$) in blood pressure at the end of the observed period between Groups I and III and Groups II and III (ie between the two examined groups where blood pressure is optimally regulated and the control group where good regulation was not achieved). There was no statistically significant difference in blood pressure levels during the 24-month follow-up between the research groups (Group I and Group II) at the end of the study ($p > 0.05$). This indicates a maintained stable level of blood pressure in the first two groups (Figure 1).

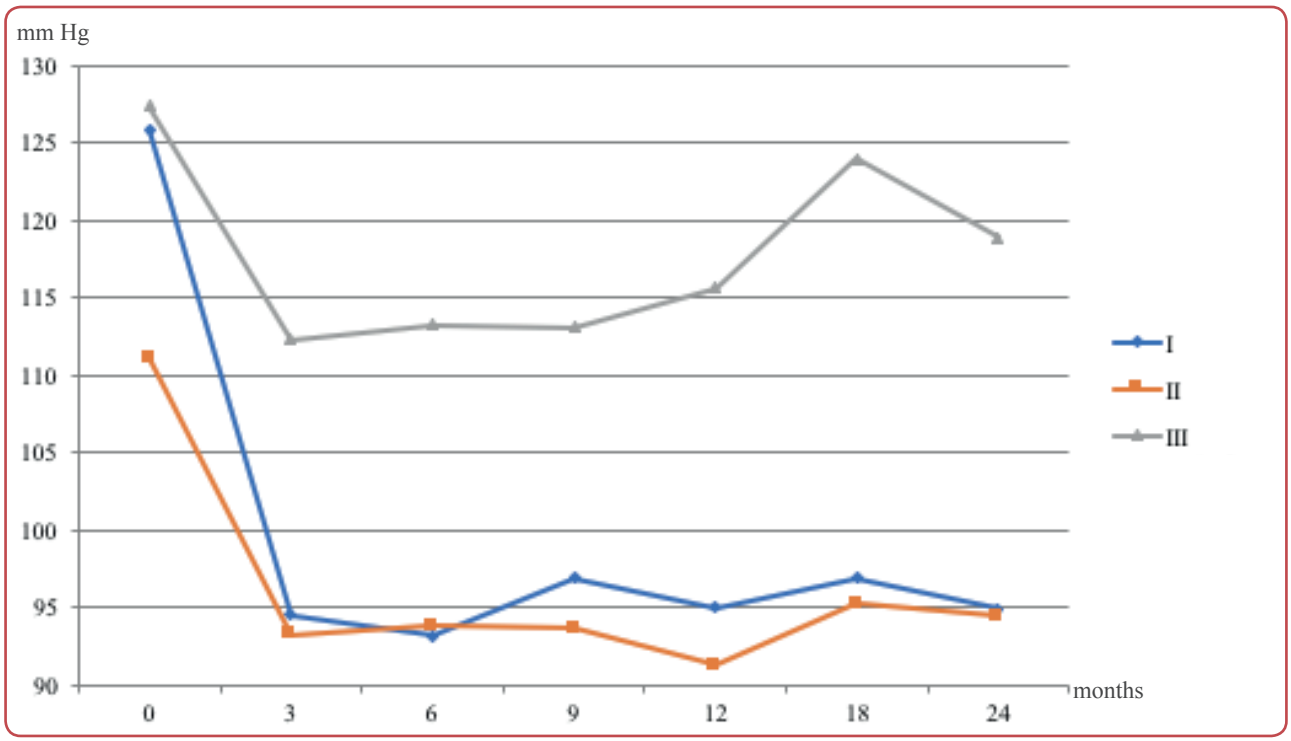

Figure 1: Mean values of mean arterial blood pressure in patients by research groups over the observed period

I group: 30 patients with essential hypertension and chronic kidney disease (CKD) with optimally regulated blood pressure (< 130/80 mm Hg); II group: 32 patients with secondary hypertension and CKD with optimally regulated blood pressure; III control group: 35 patients with hypertension of various causes and CKD who did not achieve target blood pressure values.

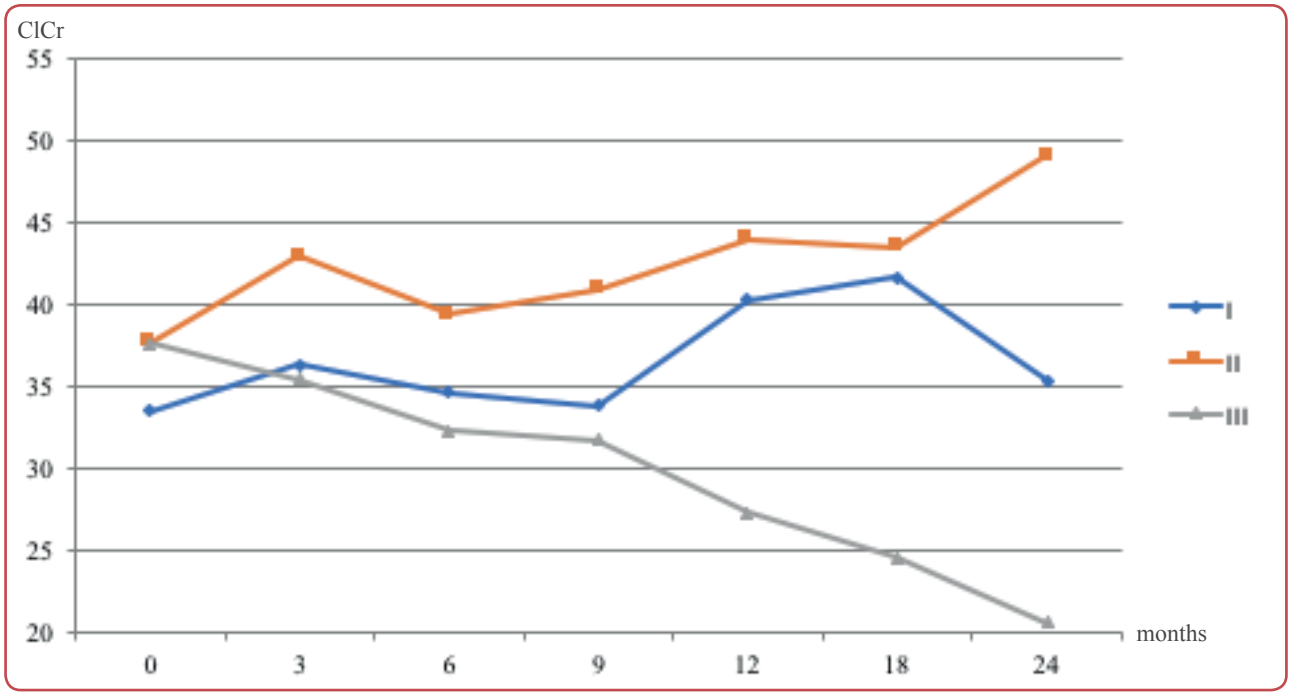

Figure 2: Mean values of creatinine clearance (ClCr) (mL/min) in patients by research groups over the observed period
I group: 30 patients with essential hypertension and chronic kidney disease (CKD) with optimally regulated blood pressure (< 130/80 mm Hg);
II group: 32 patients with secondary hypertension and CKD with optimally regulated blood pressure;
III control group: 35 patients with hypertension of various causes and CKD who did not achieve target blood pressure values;

Analysing the creatinine clearance over the observed period, the curve obtained for Group III best demonstrated a continuous decline in creatinine clearance until the end of 24 months, while values in Groups I and II remain stable and show no significant changes. Creatinine clearance did not change significantly in the first two groups. This implies that the type of disease did not affect creatinine clearance when blood pressure was well regulated. There was a statistically significant difference ($p < 0.01$) between the research groups and the control group (I-III and II-III) regarding the movement of creatinine clearance values at the end of the study compared to the beginning (Figure 2). In the first group, as well as in the second group, a statistically significant slowing of the progression of CKD compared to the group with unregulated blood pressure was observed.

As there was a highly significant difference between Groups I and III and Groups II and III at the end of 24 months in blood pressure levels, at the same time as there was a highly statistically significant difference between Groups I and III and Groups II and III at the end of 24 months in creatinine clearance levels, it can concluded that optimal blood pressure regulation was responsible for stable creatinine clearance values in Groups I and II compared to Group III.

Identical results for changes in creatinine clearance in groups with optimal blood pressure regulation compared to the group with poor blood pressure regulation at the end of 24 months were obtained for urea and creatinine values in the serum as well (stable values in groups with optimal blood pressure regulation and an increase or worsening of CKD in the group with poor regulation).

Results of correlation analysis

The average value of arterial blood pressure and the average value of creatinine clearance for each month (0, 3rd, 6th, 9th, 12th, 15th, 18th, 21st and 24th month) and strength and extent of the association between them was analysed by Pearson's correlation coefficient (Table 1).

A statistically significant correlation of these two parameters was identified in 12th, 15th, 21st and the 24th month (for a significance level of 0.05 in the 12th and 21st months and for a significance level of 0.01 in the 15th and 21st months). The strength of the correlation through the Pearson coefficient at start of the study and the 6th

Table 1: Results of correlation analysis between mean arterial pressure values and creatine clearance by month

Period	r	p-value	r^2
At the start of the study	-0.046	0.653	0.002
3rd month	-0.103	0.402	0.011
6th month	0.130	0.355	0.017
9th month	-0.225	0.137	0.051
12th month	-0.309	0.015*	0.096
15th month	-0.585	0.002**	0.343
18th month	-0.131	0.309	0.017
21st month	-0.379	0.047*	0.144
24th month	-0.290	0.005**	0.084

**correlation statistically significant for the significance level of 0.05; **correlation statistically significant for the significance level of 0.01; Pearson correlation was used; r: correlation coefficient;*

month was very weak, for the 9th, 12th, 21st and 24th months was weak and for the 15th and 18th months was of medium strength. The association between the values of these two indicators in most cases was negative (with the exception of the 6th month), which in practice means that with an increase in blood pressure, the value of creatinine clearance decreases and *vice versa*.

Unfavourable clinical outcome

In Group 1 the risk of worsening creatinine clearance by over 50 % over two years was 3.3 %. One patient in this group experienced this outcome. In Group 2 the risk was 3.1 % and one patient in this group required HD. In Group 3 the risk for worsening creatinine clearance by 50 % or the need for HD was as high as 40 %. Fourteen patients in this group experienced this outcome, with six requiring HD. Additionally, two patients in Group 3 died before starting HD (Table 2).

Table 2: Risk of worsening creatinine clearance (worsening by 50 % or more) or the occurrence of end stage renal disease by groups

Group	Unfavourable clinical outcome (N)	Overall (N)	Risk (probability)
I	1	30	0.033
II	1	32	0.031
III	14	35	0.400
Total	**16**	**97**	**0.164**

I group: 30 patients with essential hypertension and chronic kidney disease (CKD) with optimally regulated blood pressure (< 130/80 mm Hg); II group: 32 patients with secondary hypertension and CKD with optimally regulated blood pressure; III control group: 35 patients with hypertension of various causes and CKD who did not achieve target blood pressure values.

Regarding diabetic vs non-diabetic patients, no significant difference was found in the progression of CKD between diabetics and non-diabetics in all observed patients. However, in Group 3 with poor regulation, 81.8 % of diabetics developed the unfavourable clinical outcome compared to only 20.8 % of non-diabetics.

Discussion

Previous extensive studies that investigated the influence of optimal (strict) blood pressure control (when blood pressure is 130/80 mm Hg or lower, as in this study) compared to routine blood pressure control (blood pressure below 140/90 mm Hg) on the progression of CKD include the MDRD study, Escape study, AASK, REIN 2 and the study by Appel et al.[19-23] All studies followed patients with stage 2-4 or 3 and 4 of CKD. The MDRD, REIN 2 and AASK studies lasted for 4 years, the Escape study for 5 years and the study by Appel et al for 8.8 years. The participants monitored were non-diabetic patients, with the study by Appel et al and AASK specifically focusing on African Americans, where hypertension is a primary cause of CKD.

The MDRD, Escape study and the study by Appel et al showed a statistically significant advantage of additional blood pressure reduction.[19, 20, 23] The MDRD study demonstrated this advantage only in patients with proteinuria greater than 1 g/day. However, studies like REIN-2 and AASK did not statistically show the benefit of additional blood pressure reduction.[21, 22] Given the ongoing controversies about the significance and role of hypertension in the progression of CKD, the goal of this study was set to determine whether persistent therapy and maintenance of blood pressure within agreed lower limits could significantly influence the preservation of kidney function, measured as GFR and delay the progression to ESRD.

These set goals were monitored in 97 patients with stage 3 or 4 CKD under strict control, achieving therapeutic target values of blood pressure and observing the further dynamics of GFR over 24 months. All participants were divided into three groups: I, II and III. Groups I and II had CKD and optimal blood pressure control, while Group III (control) had CKD and poorly regulated blood pressure. Comparison was made of the dynamics and fluctuations in blood pressure between groups I and II, showing no statistically significant difference between them ($p > 0.05$).

However, the differences in blood pressure levels between groups I and III were highly statistically significant ($p < 0.01$), as well as between groups II and III ($p < 0.01$). This indicates that the blood pressure values in group III, throughout the entire study, are statistically significantly higher than those in participants of groups I and II.

Simultaneous monitoring of changes in the strength of GFR, or the degree of kidney damage, by determining creatinine clearance at identical intervals, showed that mean creatinine clearance values for groups with strictly controlled pressure (I and II) did not show statistically significant changes ($p > 0.05$) during the observed period from 0 to 24 months. However, creatinine clearance values in group III with uncontrolled pressure decreased during the monitoring period and this was highly significant ($p < 0.01$). This means that poor blood pressure regulation in group III led to a deterioration of kidney function (statistically highly significant), while strict blood pressure regulation in groups I and II maintains stable kidney function for the observed period of 24 months. The absence of a difference in creatinine clearance values between groups with optimal regulated blood pressure during this study indicates that optimal blood pressure regulation has a favourable impact on preserving, if not improving, GFR regardless of the underlying cause of CKD for the 24-month period.

In presented groups with optimal blood pressure regulation, there was even a slight improvement in GFR at the end of the study period (which was not statistically significant), while other studies reported a certain decline in GFR in groups with patients who achieved strict blood pressure regulation and those who did not. This could be explained by the shorter duration of this study compared to the other mentioned studies. Presented study has demonstrated the advantage of optimal blood pressure regulation in slowing the progression of CKD, aligning with the findings of the MDRD, ESCAPE and Appel studies.[19, 20, 23]

Conclusion

In patients with stage 3 or 4 of CKD, optimal blood pressure regulation and its continuous maintenance over 24 months play a significant role in preventing the progression of CKD, regardless of the cause of CKD.

Ethics

The study protocol was approved by the Ethical Committee of University Clinical Centre of the Republic of Srpska, No 01-19-61-2/24, dated 14 February 2024. Written informed consent was obtained from patients prior to their participation in the study and for publishing of the anonymised data. The study was organised and implemented based on the adherence to the Ethical Principles for Medical Research Involving Human subjects (The Declaration of Helsinki, 8th Revision, 2013).

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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Validation: MG
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Investigation: MG, SPP, AM
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Visualisation: MG
Supervision: MG
Project administration: MG

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