

# Blood pressure control and use of antihypertensive medication across ranges of renal function in patients with type 2 diabetes and hypertension: a cross-sectional study

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## Abstract

Blood pressure (BP) control is critical for slowing the progression of chronic kidney disease (CKD) and reducing risk for cardiovascular events. Little is known about BP control and utilization patterns of antihypertensive drugs among patients with diabetes with different degrees of renal function in our population. The purpose of the study was to assess the BP control and use of antihypertensive drugs across different ranges of estimated glomerular filtration rate (eGFR) in a sample of patients with diabetes and arterial hypertension.

The study group consisted of 458 subjects with type 2 diabetes and arterial hypertension selected from an electronic database available at a single diabetes center in Romania and for which a minimum set of data including BP measurements, serum creatinine and medication for BP control was available.

BP targets (<140/85 mmHg) were achieved by 27.7% of patients, while 34.7% and 47.2% achieved systolic and diastolic BP targets, respectively. Mean pulse pressure values gradually increased across eGFR categories from 56.6 (15.8) to 66.9 (22.9) mmHg ( $p=0.030$ ). Mean number of antihypertensive drugs was 2.3 (1.3) in the overall group, and increased from 2.0 (1.3) in highest to 3.4 (1.4) in lowest eGFR category ( $p<0.0001$ ). The most commonly used antihypertensive medication were ACE inhibitors (74% of patients in the overall study group).

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Rates of BP control was unsatisfactory, those with lower glomerular filtration rates having the poorest results despite use of higher number of drugs. More complex regimens are needed to avoid unfavorable cardiovascular and renal outcomes.

**Keywords:** diabetes, antihypertensive drugs, glomerular filtration rate, renin angiotensine aldosteron system.

## Introduction

Type 2 diabetes (T2DM) and hypertension are two common conditions that affect a large number of individuals worldwide. The International Diabetes Federation (IDF) reports that diabetes afflicts 382 million people nowadays and the number is expected to climb to 592 million by 2035 [1]. Over 60% of patients with T2DM have hypertension [2] and this association results in four-fold increased cardiovascular risk and death from complications [3, 4]. Chronic kidney disease (CKD) can be found in up to 23-25% of patients with diabetes [5] and their association significantly increases rates of myocardial infarction and all-cause mortality compared to either of them alone [6].

Blood pressure (BP) control is critical for slowing the progression of CKD and reducing risk for cardiovascular events in patients with diabetes, hypertension and/or CKD [7]. Current European guidelines on hypertension recommend a BP target of <140/85 mmHg for patients with diabetes and hypertension irrespective of presence or absence of CKD, except nephropathy with overt proteinuria when a lower SBP of <130 mmHg may be considered if tolerated by the patient [8]. This new targets replaced the previous recommendations of a BP target < 130/80 mmHg for all patients with diabetes [9]. A renin angiotensin aldosterone system (RAAS) blocker, either angiotensin converting enzyme-inhibitors (ACE-I) or angiotensin receptor blockers (ARB), is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or microalbuminuria [8, 9].

The Improving Global Outcomes (KDIGO) Blood Pressure Work Group [7] recommends a BP goal of  $\leq 140/90$  mmHg in patients with diabetes and CKD with urine albumin excretion <30 mg per 24 hours (or equivalent) and a BP goal of  $\leq 130/80$  mmHg when urine albumin excretion is >30 mg per 24 hours. The use of an ARB or ACE-I is suggested in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours, while the same is recommended if urine albumin excretion is >300 mg per 24 hours [7].

Little is known about BP control and utilization patterns of antihypertensive drugs among patients with diabetes with different degrees of renal function in our population. Some preliminary data showed that patients with diabetes and hypertension and a glomerular filtration rate (GFR) <60 mL/min/1.73 m<sup>2</sup> have a

significantly poorer degree of systolic blood pressure control compared to those with a GFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>, despite using a greater number of antihypertensive drug classes [10]. The purpose of the present study, therefore, was to assess the BP control and utilization patterns of antihypertensive drugs across different ranges of glomerular filtration rate in a sample of patients with diabetes and arterial hypertension.

## Material and methods

### Data source

This cross-sectional retrospective study utilizes data from an electronic database available at a single diabetes center in Romania which included electronic health data for patients with diabetes attending the diabetes center in the period of 2012–2013. The database contained patient information including demographic data, type and duration of diabetes, diabetes treatment, vital signs measurements, laboratory results, medication use and diagnosis of concomitant illnesses. For this study, patients aged 18 years or older, with a concomitant diagnosis of type 2 diabetes according to World Health Organization criteria [11] and of arterial hypertension, and who had a minimum set of data including serum creatinine, values of systolic and diastolic blood pressure, and treatment for hypertension were eligible for inclusion. Exclusion criteria were missing data on age, sex, type of diabetes, presence of arterial hypertension, serum creatinine, blood pressure measurements, lack of data on antihypertensive medication, eGFR <15 ml/min/1.73 m<sup>2</sup>, or on dialysis.

### Variables

Glomerular filtration rate (eGFR) was estimated using online available CKD-EPI calculator (<http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr>). Patients were separated into the following categories according to eGFR:  $\geq 90$ , 60-89, 30-59, and 15-29 ml/min/1.73 m<sup>2</sup>.

Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald formula if serum triglycerides were <400 mg/dl.

Body mass index (BMI) was calculated as weight (kg)/ [height (m)]<sup>2</sup>.

A BP threshold of <140/85 mmHg was used in this study according to 2013 ESH/ESC Guidelines for the management of arterial hypertension [8]. Blood pressure control was categorized according to systolic BP (SBP),

diastolic BP (DBP) and both systolic and diastolic BP. Pulse pressure was calculated as the difference between systolic and diastolic BP. A second BP threshold of <130/80 mmHg was used according to previous guidelines [9].

Antihypertensive medications were classified as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics (all types) and other antihypertensive agents. Number of drug classes was calculated for each study subject.

Patients were classified according to their antidiabetic treatment as insulin users and non-insulin users.

**Statistical analysis**

Statistical analysis was performed using SPSS-PC 19 (SPSS Inc., Chicago, IL, USA). Data were considered to be normally distributed if the ratio of skewness to its standard deviation did not exceed the value of 2. Data were expressed as a mean (SD) for continuous variables or percentage for categorical variables. Analysis of variance (ANOVA) test (for continuous variables) and Chi-square tests (for categorical variables) were used to compare subjects across eGFR categories. The level of significance was set at 0.05, and all tests were performed two-sided.

The research was conducted in accordance with the guidelines in The Declaration of Helsinki and the study

protocol was approved by the Iuliu Hatieganu University of Medicine and Pharmacy Ethics Committee.

**Results**

The study group consisted of 458 subjects with type 2 diabetes and arterial hypertension, 260 (56.6%) men, with a mean age of 61.7 (9.8) years, a diabetes duration of 9.7 (7.5) years, and 43.7% using insulin for diabetes control. A summary of the patient demographic and clinical characteristics, in the overall study group and by category of renal function is presented in Table 1. The largest proportion of patients fell in the category of eGFR 60–89 ml/min/1.73 m<sup>2</sup>, followed by those with an eGFR of 30–59 ml/min/1.73 m<sup>2</sup>, while the group having an eGFR of 15–29 ml/min/1.73 m<sup>2</sup> had a very small number of patients. Demographic and clinical characteristics varied by eGFR category, patients with lower GFR being more likely to be older, female, with a longer duration of diabetes, and more insulin use. Levels of total and HDL cholesterol were significantly different across eGFR category, with lowest values in the category of 15–29 ml/min/1.73m<sup>2</sup>. Glucose control, BMI, waist circumference, serum triglycerides and HDL cholesterol were similar across eGFR categories.

**Table 1.** Demographic and clinical characteristics of study group, stratified by eGFR categories

Characteristic	Overall	eGFR ≥90 ml/min/1.73 m <sup>2</sup>	eGFR 60-89 ml/min/1.73 m <sup>2</sup>	eGFR 30-59 ml/min/1.73 m <sup>2</sup>	eGFR 15-29 ml/min/1.73 m <sup>2</sup>	P value
Number (% from total)	458	83 (18.1)	225 (49.1)	137 (29.9)	13 (2.8)	
Age, mean (SD)	61.7 (9.8)	55.2 (7.3)	61.3 (9.8)	65.7 (9.1)	68.5 (8.0)	<0.0001
Gender (%)						
Male	56.6	64.5	57.7	45.3	61.5	0.001
Female	43.4	35.5	42.3	54.7	39.5	
BMI, mean (SD)	31.1 (5.9)	31.2 (6.5)	30.9 (5.9)	31.1 (5.2)	32.1 (9.1)	NS
Waist, mean (SD)	110.8 (16.7)	111.3 (16.7)	111.4 (16.2)	107.7 (17.1)	110.8 (22.3)	NS
Diabetes duration, mean (SD)	9.7 (7.5)	7.9 (6.2)	9.1 (7.4)	11.1 (8.0)	15.9 (7.0)	<0.0001
Insulin users (%)	43.7	35	37.5	62.5	100	0.014
HbA1c, mean (SD)	7.3 (1.5)	7.7 (1.4)	7.1 (1.6)	7.6 (1.5)	7.7 (0.6)	NS
Total cholesterol, mean (SD)	192.5 (52.2)	196.1 (54.9)	186.6 (45.5)	202.1 (59.7)	173.3 (45.9)	0.022
HDL cholesterol, mean (SD)	40.6 (12.6)	43.2 (13.1)	40.2 (11.8)	40.1 (13.7)	36.8 (5.3)	NS
Serum triglycerides, mean (SD)	191.6 (105.4)	177.0 (87.7)	187.2 (109.8)	206.0 (106.9)	212.2 (105.0)	NS
LDL cholesterol, mean (SD)	115.7 (46.2)	118.6 (45.2)	110.8 (38.2)	123.5 (56.9)	98.5 (39.1)	0.046
Serum creatinine, mean (SD)	1.09 (0.3)	0.80 (0.1)	0.98 (0.2)	1.33 (0.3)	2.3 (0.4)	<0.0001
eGFR, mean (SD)	69.8 (20.1)	98.6 (8.5)	74.3 (7.9)	49.3 (7.9)	25.9 (2.3)	<0.0001

Continuous data is presented as mean (SD) and categorical data as percentage (%). SD, standard deviation; eGFR, estimated glomerular filtration rate; BMI, body mass index; HbA1c, glycated hemoglobin A1c; HDL, high density lipoproteins; LDL, low density lipoproteins.

**Table 2.** Blood pressure control and antihypertensive therapy stratified by eGFR categories

	Overall N=458	eGFR ≥90 ml/min/1.73 m <sup>2</sup> N=83	eGFR 60-89 ml/min/1.73 m <sup>2</sup> N=225	eGFR 30-59 ml/min/1.73 m <sup>2</sup> N=137	eGFR 15-29 ml/min/1.73 m <sup>2</sup> N=13	P value
Mean BP						
Systolic	145.1 (22.5)	142.7 (20.9)	143.5 (21.2)	148.9 (24.1)	149.6 (31.3)	NS
Diastolic	85.2 (13.1)	86.1 (12.3)	84.3 (12.2)	86.4 (14.6)	82.7 (14.8)	NS
Pulse pressure	60.0 (17.0)	56.6 (15.8)	59.2 (16.3)	62.5 (18.0)	66.9 (22.9)	0.030
BP control <140/85 mmHg						
Systolic and diastolic						
Systolic only	127 (27.7%)	26 (31.3%)	66 (29.3%)	32 (23.4%)	3 (23.1%)	NS
Diastolic only	159 (34.7%)	33 (39.8%)	84 (37.3%)	39 (28.5%)	2 (23.1%)	NS
	216 (47.2%)	36 (43.4%)	106 (47.1%)	68 (49.6%)	6 (46.2%)	NS
BP control <130/80 mmHg						
Systolic and diastolic						
Systolic only	49 (10.7%)	6 (7.2%)	30 (13.3%)	12 (8.8%)	1 (7.7%)	NS
Diastolic only	88 (19.2%)	15 (18.2%)	49 (21.8%)	22 (16.1%)	2 (15.4%)	NS
	92 (20.1%)	13 (15.7%)	49 (21.8%)	28 (20.4%)	2 (15.4%)	NS
Treatment						
Not treated	26 (5.7%)	3 (3.6%)	18 (8%)	5 (3.6%)	0 (0%)	NS
Treated	432 (94.3%)	80 (92.3%)	207 (92%)	132 (96.7%)	13 (100%)	
Number of antihypertensive drugs†	2.3 (1.3)	2.0 (1.3)	2.2 (1.2)	2.5 (1.3)	3.4 (1.4)	<0.0001
Type of antihypertensive therapy						
ACE inhibitors	339 (74.0%)	65 (78.3%)	162 (72%)	101 (73.7%)	11 (84.6%)	NS
ARBs	75 (16.4%)	11 (13.3%)	26 (11.6%)	35 (25.5%)	3 (23.1%)	0.004
CCBs	154 (33.6%)	22 (26.5%)	70 (31.1%)	55 (40.1%)	7 (53.8%)	NS
Beta-blockers	195 (42.6%)	32 (38.6%)	97 (43.1%)	59 (43.1%)	7 (53.8%)	NS
Diuretics	221 (48.3%)	23 (27.7%)	111 (49.3%)	75 (54.7%)	12 (92.3%)	<0.0001
Others	47 (10.3%)	9 (10.8%)	18 (8.0%)	16 (11.7%)	4 (30.8%)	NS

Data in table is presented as number of patient (%); †number of antihypertensive drugs is presented as mean (SD) eGFR, estimated glomerular filtration rate; BP, blood pressure; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers.

### Blood pressure control

The overall study group had a mean SBP of 145.1 (22.5) mmHg, mean DBP of 85.2 (13.1) mmHg, and a mean pulse pressure of 60.0 (17.0) mmHg. Both systolic and diastolic BP targets (<140/85 mmHg) were achieved by 27.7% of patients, while 34.7% and 47.2% achieved systolic and diastolic BP targets, respectively. When BP targets were set at <130/80 mmHg, the percentage of patients achieving targets was much lower: 10.7%, 19.2% and 20.1%, respectively. Parameters reflecting BP control are presented in Table 2.

Across eGFR categories, mean levels of systolic BP gradually increased and proportion of patients achieving both SBP and DBP targets <140/85 mmHg, as well as SBP targets, gradually decreased from an eGFR of ≥90 ml/min/1.73m<sup>2</sup> to the category of 15-29 ml/min/1.73m<sup>2</sup>, but statistical significance was not reached (p=NS for all). Mean DBP values and proportion achieving DBP targets only did not differ across eGFR categories. Mean pulse pressure values significantly and gradually increased across eGFR categories from 56.6 (15.8) to 66.9 (22.9) mmHg (p=0.030).

### Antihypertensive therapies

Use of antihypertensive therapies, overall and by eGFR categories, is presented in Table 2. In the overall study group, 5.7% of patients had no antihypertensive medication, despite carrying the diagnosis of hypertension, with a non statistically significant distribution of untreated hypertension across eGFR categories. Still, none of the 13 patients with an eGFR of 15–29 ml/min/1.73m<sup>2</sup> was untreated.

Mean number of antihypertensive drug classes was 2.3 (1.3) in the overall group, and increased from 2.0 (1.3) in highest to 3.4 (1.4) in lowest eGFR category (p<0.0001). The most commonly used antihypertensive medication was the class of ACE inhibitors, with 74% of patients in the overall study group using this medication. No statistical difference across eGFR categories was seen regarding use of ACE inhibitors. Angiotensin receptor blockers were used by 16.4% of patients from the study group, with a significant increase in use of ARBs in patients with lower eGFR levels (from 13.3 to 23.1%, p=0.004). The same pattern was demonstrated for diuretics, which for were used by 48.3% of study subjects

and gradually increased from 27.7 to 92.3% across eGFR categories ( $p < 0.0001$ ). Beta-blockers and calcium channel blockers were used by 42.6 and 33.6% in the overall study group, with no statistical difference among eGFR categories although an increased use from highest to lowest category was seen for both drugs. Other antihypertensive drugs were used by 10.3% of patients, with a nearly threefold increase in the category of 15–29 ml/min/1.73m<sup>2</sup> as compared with all other categories.

The percentage of patients using 0, 1, 2, and  $\geq 3$  antihypertensive medication across eGFR categories is presented in Figure 1. As expected, the percentage of patients using  $\geq 3$  antihypertensive medication steadily increased from 21.7 in the first to 69.2% in the last category ( $p = 0.004$ ).

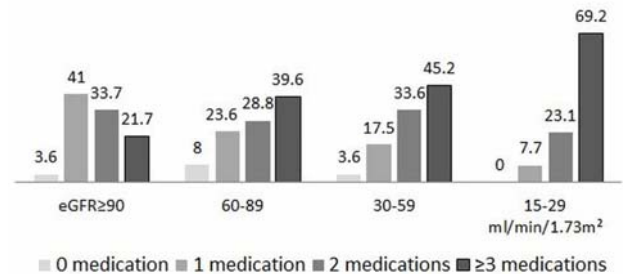
Mean number of medication in patients who achieved versus those who did not achieved BP targets were compared between eGFR categories (Figure 2). In the first two subgroups, patients who achieved BP control had significantly lower number of medications than those who did not achieved BP control (1.3 (0.7) versus 2.2 (1.4),  $p = 0.003$  and 1.8 (1.0) versus 2.3 (1.3),  $p = 0.002$  respectively) while in the last two groups the difference was not statistically significant.

**Discussion**

Achievement of BP targets in patients with diabetes is of crucial importance as numerous studies demonstrated that blood pressure control can prevent micro and macrovascular diabetes complications [12–16]. Despite this, BP control in patients with diabetes was found to be unsatisfactory in different populations. In a representative sample from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) in the United States [17], only 40% of the 998 patients with self-reported diabetes included in the study had a BP < 130/80 mmHg.

The OPTIMISE (OPtimal Type 2 diabetes Management Including benchmarking and Standard treatment) trial, a multicenter trial in six European countries, prospectively assess the effect of benchmarking on the quality of primary care in patients with type 2 diabetes, using major modifiable vascular risk factors as critical quality. The overall percentage of patients who achieved targets of SBP (< 130 mmHg and < 125 mmHg for patients with proteinuria) at baseline was 27.3% [18]. Two national subsets of results from this trial have been reported. In the Greece OPTIMISE trial, 27% achieved the same BP targets at baseline; the mean levels of SBP and DBP were  $138 \pm 17$  and  $80 \pm 9$  mmHg respectively [19]. In Luxembourg [20], it was reported that in the benchmarking group, more patients achieved target for SBP (40.2% vs. 20%). In our group, mean BP values were found to be higher and percentage of patients reaching BP targets lower than those reported in other groups of patients with diabetes, with only 10% having

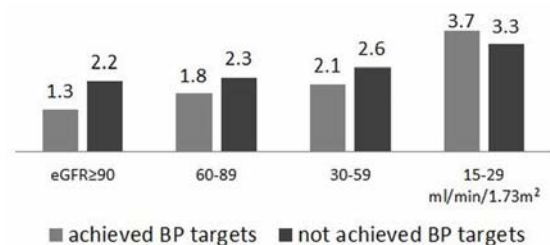
BP values < 130/80 mmHg, and 19.2% with SBP < 130 mmHg. However, it is worth to note than in the NHANES samples only more than half of patients reported to have hypertension and in OPTIMISE trial nearly 80% had a diagnosis of hypertension, while in our study all patients had concomitant hypertension.



**Figure 1.** The percentage of patients using 0, 1, 2 and  $\geq 3$  antihypertensive medication across eGFR categories. Data is presented as percentage within each category;  $p = 0.004$  for difference between groups eGFR, estimated glomerular filtration rate  $06 \times 50$  mm ( $300 \times 300$  DPI).

When newer targets < 140/85 mmHg were examined, the percentage of controlled BP in our group increased to 27.7 and 34.2% for both systolic and diastolic and systolic only. This difference can be explained, at least in part, by less accurate BP measurements but we can also note that significant number of patients have BP values between 140/85 and 130/80 mmHg.

The relationship between BP control, treatment factors, and status of renal function is still to be understood. In CKD patients, some studies have demonstrated a higher degree of BP control with increasing CKD stage [21, 22], while others showed that BP goal attainment decreased between CKD Stage 1 and 4, despite high levels of antihypertensive treatment [23, 24]. In the study of Unni S *et al.* [24] which included a cohort of patients with CKD, the overall proportion of individuals achieving BP control < 130/80 mmHg was 24.3%. Mean systolic BP increased with CKD stage, with Stage 4 CKD patients having the highest mean



**Figure 2.** Number of medication in patients who achieved vs. those who did not achieved BP targets across eGFR categories. Data is presented as mean number of medication;  $p = 0.003$  in the category eGFR  $\geq 90$  ml/min/1.73 m<sup>2</sup>,  $p = 0.002$  in the category eGFR 60-89 ml/min/1.73 m<sup>2</sup>,  $p = NS$  for categories eGFR 30-59 and 15-29 ml/min/1.73 m<sup>2</sup> eGFR, estimated glomerular filtration rate; BP, blood pressure  $110 \times 50$  mm ( $300 \times 300$  DPI).

systolic BP (136.4 mmHg) versus. Stages 1 and 2 (132.2 mmHg), and Stage 3 (132.9 mmHg). Pulse pressure increased with increasing CKD stage. The same increase in mean SBP and pulse pressure from higher to lower GFR categories was seen in our group of patients with diabetes, despite the progressive increase in number of antihypertensive medication from 2.0 (1.3) in highest to 3.4 (1.4) in lowest eGFR category. This data suggest that BP control is more difficult to be reached and need of medication to reach goals is higher when renal function is more severely impaired, and that this is true in patients with CKD as well as in patients with diabetes. Interestingly, we observed that within the first two eGFR categories, patients who attain BP goals had lower number of drugs than those who did not attain goals.

The preferred drug classes in both CKD and diabetes are ACE-I and ARBs, as recommended by all clinical guidelines. In a sample of 3999 participants with CKD selected from National Health and Nutrition Examination Survey [23], the use of beta-blockers was highest (28.98% of the utilization), followed by diuretics (24.68%). ACE inhibitors were used nearly in the same proportion as diuretics (23.80%), followed by calcium channel blockers (12.70%) while ARBs represented only 9.83% of the total utilization. The proportion of use of ACE inhibitors and diuretics differed significantly according to stage of CKD with a significantly higher proportion of participants with stage III using these two drug classes, while all other classes had a similar use across CKD stages. In another cohort study of 115,608 patients with CKD in the United States [24], the utilization patterns of antihypertensive drugs was quite different; 69% of patients were treated with ACE-I/ARBs and 36.6% with diuretics, the use of both drugs decreasing across stages of CKD while other antihypertensive drugs were used in 77% of patients with increased use in more severe CKD stages.

In a smaller study which included patients with type 2 diabetes and microalbuminuria, it was shown that the subgroup with  $eGFR < 60 \text{ ml/min/1.73 m}^2$  had lower systolic and diastolic office BP values (140.5 versus 142.1 and 74.9 versus 77.4 mmHg) and higher SBP variability than those with preserved eGFR. Patients with low eGFR used more antihypertensive drugs (2.0 versus 1.3) and more RAAS blockade drugs (0.93 versus 0.63).

Our results demonstrated that ACEI-I were the most used drugs in patients with diabetes (74% in the overall group) with a non-significant difference among eGFR categories, while ARBs were used in smaller proportions (16.4% in the overall group) but with a significantly increased use from higher to lower eGFR categories. Diuretics were the second most used drug class (48.3%) with a significant increase throughout GFR categories. Beta-blockers, calcium channel blockers and other antihypertensive agents, in this order, were used in smaller proportions, with a non-significant difference

among eGFR categories. This data suggest that the use of RAAS blockade drugs in our patients with diabetes follows the recommendations from guidelines, with 90% of patients being treated with either an ACE-I or an ARB. Less general preference for ARBs can be explained by a relative higher cost and less experience with this newer class when compared with ACE-I, still an increased use in lower GFR categories was observed. No data was available on the use of a specific ACE-I or ARB in our group.

The same preference for ARB's in patients with reduced eGFR was seen in CLARIFY study [26], which included over 22,000 patients with stable coronary artery disease, while angiotensin-converting enzyme inhibitor use was inversely related to declining eGFR.

There are data demonstrating that utilization patterns of drugs changes over time, indicating that continuous efforts are made to improve quality of care. In a report from a nephrology center [27], it was shown that the average number of antihypertensive drugs per patient with CKD increased significantly from  $1.74 \pm 0.9$  in 1996, to  $2.08 \pm 1.01$  (2011),  $2.5 \pm 1.19$  (2006) and  $2.65 \pm 1.18$  (2011), while the BP control rate showed significant improvement in the second, third and final surveys, *i.e.* 9%, 12%, 14% and 24%. The percentage of patients receiving diuretics, beta-blockers and drugs inhibiting renin-angiotensin-aldosterone also increased significantly in subsequent years.

Improvements in rates of BP control were also demonstrated in individuals with hypertension from our country, which were included in the two SEPHAR cross-sectional national surveys conducted on a representative sample for the Romanian adult population [28]. The results showed that 59.15% of hypertensive individuals are under current treatment with a control rate of 25% and that in 7-year period between the two surveys, there has been an increase by 52% in treatment of hypertension, leading to almost doubling of the hypertension control rate.

Our results showing a low rate of BP control, mainly due to SBP and poorer rate of control in more severe stages of renal dysfunction draws the attention to the need of a more aggressive strategy in antihypertensive management of patient with diabetes. This is particularly true because it was shown that the cumulative number of risk factors for atherosclerosis increased from 3.1 to 6.8 in the later stages of eGFR in patients with type 2 diabetes, placing these patients to a very high cardiovascular risk when diabetes and low eGRF are associated [29].

### Limitations of the study

The main limitations of our study is the lack of consistent data on albumin excretion rate, which was not systematically measured in the patients included in the database and could not be analyzed, and the availability of a single measurement of serum creatinine

which may have either over or underestimate the renal function measured as eGFR. The small number of patients with an eGFR of 15–29 ml/min/1.73 m<sup>2</sup> could have influenced the statistical significance of the reported results.

## Conclusions

Rates of blood pressure control was unsatisfactory in our group of patients with diabetes and hypertension and those with lower glomerular filtration rates had the poorest results despite use of higher number of antihypertensive drugs. Over 90% of patients were treated with either an ACE-I or ARB, the later class being increasingly used in more severe stages of renal dysfunction. More complex regimens of antihypertensive medication are needed to improve BP control and to avoid unfavorable cardiovascular and renal outcomes.

## Conflict of interest

The authors confirm that there are no conflicts of interest.

## References

- International Diabetes Federation 2013. IDF Diabetes Atlas. Sixth Edition. Available at [www.idf.org/diabetesatlas](http://www.idf.org/diabetesatlas)
- Nilsson PM, Cederholm J, Zethelius BR, Eliasson BR, Eeg-Olofsson K, Gudbj Rnsdottir S. Trends in blood pressure control in patients with type 2 diabetes: data from the Swedish National Diabetes Register (NDR). *Blood Press.* 2011;20(6):348-54. doi: 10.3109/08037051.2011.587288.
- Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care.* 1993;16(2):434-44. doi:10.2337/diacare.16.2.434.
- Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med.* 1998;339(4):229-234. doi: 10.1056/NEJM199807233390404.
- Tonelli M, Muntner P, Lloyd A, Manns B, Klarenbach S, Pannu N, James M, Hemmelgarn B; Alberta Kidney Disease Network. Impact of age on the association between CKD and the risk of future coronary events. *Am J Kidney Dis.* 2014;64(3):375-82. doi: 10.1053/j.ajkd.2014.03.013.
- Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, James MT, Hemmelgarn BR; Alberta Kidney Disease Network. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet.* 2012;380(9844):807-14. doi: 10.1016/S0140-6736(12)60572-8.
- Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Inter Suppl.* 2012; 2: 337-414. doi:10.1038/kisup.2012.54.
- Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, *et al.* 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) *Eur Heart J.* 2013;34(28):2159–2219. doi: 10.1093/eurheartj/eht151.
- Mancia G, De BG, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al.* 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *Eur Heart J.* 2007;28(12):1462–1536. doi: 10.1093/eurheartj/ehm236.
- Cozma IR, Rotariu MI, Roman G, Bala C. The impact of renal dysfunction upon blood pressure control in patients with diabetes mellitus and arterial hypertension. Congress of Romanian Society of Hypertension. Abstracts book 2014:43-44
- World Health Organization. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: Report of a WHO/IDF Consultation. Geneva, Switzerland, 2006
- Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355(9200):253-59. doi: 10.1016/S0140-6736(99)12323-7
- ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet.* 2007;370(9590):829-40. doi: 10.1016/S0140-6736(07)61303-8.
- Tuomilehto J, Rastenyte D, Birkenhager WH, *et al.* Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med.* 1999;340(9):677-84. doi: 10.1056/NEJM199903043400902.
- UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J.* 1998;317(7160):703-13. doi: 10.1136/bmj.317.7160.703.
- The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med.* 2010;362(17):1575-85. doi: 10.1056/NEJMoa1001286.
- Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association Clinical Practice Recommendations Among US Adults With Diabetes, 1999–2002 The National Health and Nutrition Examination Survey. *Diabetes Care.* 2006; 29(3):531-37. doi: 10.2337/diacare.29.03.06.dc05-1254.
- Hermans MP, Brotons C, Elisaf M, Michel G, Muls E, Nobels F; (for the OPTIMISE (OPTimal Type 2 Diabetes Management Including benchmarking and Standard treatment) International Steering Committee). Optimal type 2 diabetes mellitus management: the randomised controlled OPTIMISE benchmarking study: baseline

- results from six European countries. *Eur J Prev Cardiol.* 2013;20(6):1095-105. doi: 10.1177/2047487312449414.
19. Kostapanos MS, Tsimihodimos V, Elisaf MS, Tzouveleakis E, Nikas N. Rationale, design and baseline patient characteristics of the optimal type 2 diabetes management including benchmarking and standard treatment study in Greece. *World J Diabetes.* 2014;5(1):76-83. doi: 10.4239/wjd.v5.i1.76.
  20. Michel G; OPTIMISE. The OPTIMISE study (Optimal Type 2 Diabetes Management Including Benchmarking and Standard Treatment]. Results for Luxembourg. *Bull Soc Sci Med Grand Duché Luxemb.* 2012;(1):43-9 [Abstract from pubmed]
  21. Sarafidis PA, Li S, Chen SC, Collins AJ, Brown WW, Klag MJ, Bakris GL. Hypertension awareness, treatment, and control in chronic kidney disease. *Am J Med.* 2008; 121(4):332–40. doi: 10.1016/j.amjmed.2007.11.025.
  22. Ravera M, Noberasco G, Weiss U, Re M, Gallina AM, Filippi A, Cannavo R, Ravera G, Cricelli C, Deferrari G. CKD awareness and blood pressure control in the primary care hypertensive population. *Am J Kidney Dis.* 2011; 57(1):71–7. doi: 10.1053/j.ajkd.2010.08.022.
  23. Kuznik A, Mardekian J, Tarasenko L. Evaluation of cardiovascular disease burden and therapeutic goal attainment in US adults with chronic kidney disease: an analysis of national health and nutritional examination survey data, 2001–2010. *BMC Nephrol.* 2013; 14:132. doi: 10.1186/1471-2369-14-132.
  24. Unni S, White K, Goodman M, Ye X, Mavros P, Bash LD, Brixner D. Hypertension Control and Antihypertensive Therapy in Patients With Chronic Kidney Disease. *Am J Hypertens.* 2014. doi:10.1093/ajh/hpu215.
  25. Nishimura MI, Kato Y, Tanaka T, Todo R, Tone A, Yamada K, Ootani S, Kawabe Y, Yoshizumi H, Hoshiyama Y. Significance of estimating the glomerular filtration rate for the management of hypertension in type 2 diabetes with microalbuminuria. *Hypertens Res.* 2013;36(8):705-10. doi: 10.1038/hr.2013.22.
  26. Kalra PR, García-Moll X, Zamorano J, Kalra PA, Fox KM, Ford I, Ferrari R, Tardif JC, Tendera M, Greenlaw N, Steg PG; CLARIFY Investigators. Impact of chronic kidney disease on use of evidence-based therapy in stable coronary artery disease: a prospective analysis of 22,272 patients. *PLoS One.* 2014;9(7):e102335. doi: 10.1371/journal.pone.0102335.
  27. Tylicki L1, Jakubowska A, Lizakowski S, Zakrzewska A, Weber E, Świetlik D, Rutkowski B. Treatment of hypertension in chronic kidney disease patients under specialized care: One-center cross-sectional analyses. *Blood Press.* 2014. doi:10.3109/08037051.2014.986931.
  28. Dorobantu M, Darabont R, Ghiorghe S, Arsenescu-Georgescu C, Macarie C, Mitu F, Lighezan D, Musetescu R, Pop C, Ardeleanu E, Craiu E, Tautu OF. Hypertension prevalence and control in Romania at a seven-year interval. Comparison of SEPHAR I and II surveys. *J Hypertens.* 2014;32(1):39-47. doi: 10.1097/01.hjh.0000434937.62412.24.
  29. Ito H, Antoku S, Furusho M, Shinozaki M, Abe M, Mifune M, Togane M, Ito K, Sanaka T. The Prevalence of the Risk Factors for Atherosclerosis among Type 2 Diabetic Patients Is Greater in the Progressive Stages of Chronic Kidney Disease. *Nephron Extra.* 2013;3(1):66-72. doi: 10.1159/000353592.