

Italian Audit on Therapy of Hypertension in Chronic Kidney Disease: The TABLE-CKD Study

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A large body of evidence supports the validity of decreasing blood pressure to target levels in patients with essential hypertension to prevent cardiovascular disease. This issue becomes even more critical in chronic kidney disease because of the remarkably greater risk for cardiovascular fatal and nonfatal events. Indeed, renal patients should maintain blood pressure levels less than those suggested for the general population. Paradoxically, management of hypertension in this high-risk patient population is far from optimal and certainly worse with respect to essential hypertension. The Target Blood Pressure Levels in Chronic Kidney Disease (TABLE-CKD) study, performed in Italian patients with mild to advanced chronic kidney disease regularly followed-up by nephrologists, has shown that the prevalence of patients at target blood pressure is less than 20%. The assessment of antihypertensive strategy in these patients, however, suggests that there is room for improvement; in particular, a more aggressive treatment of volume expansion may ameliorate hypertension control in this population characterized by a high salt sensitivity of blood pressure.

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It is well established that the burden of cardiovascular (CV) risk is considerable across the entire spectrum of chronic kidney disease (CKD) stages.^{1,2} A recent observational prospective study in a large community-based population has shown that, at an estimated glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m², a graded and strong association between GFR decrease and risk for CV fatal and nonfatal events becomes evident, with the risk reaching a value approximately 5 to 6 times greater in patients with predialytic CKD as compared with patients with normal renal function.³

Similarly, a recent large trial that evaluated the relationship between renal dysfunction and CV outcome after myocardial infarction found that each reduction of estimated GFR by 10 units below 81 mL/min/1.73 m² is coupled with a 10% increment in the risk for death and nonfatal CV events.⁴ Finally, other recent studies in patients with CKD of various origin and degree have shown that over 5 to 6 years of follow-up evaluation, the prevalence of CV events or death is 2 to 20 times greater than that of renal events, such as doubling of serum creatinine level or initiation of a replacement therapy.⁴⁻⁷ Indeed, the high mortality of CKD patients provides a reasonable explanation to the “paradox of missing dialysis patients,” that is, the major disproportion between the size of the nondialytic and dialytic CKD population, with a ratio of about 50:1, currently observed in the United States.⁸

In this scenario, maintenance of low blood pressure (BP) values likely becomes an essential intervention in CKD patients because they have more frequent, severe, and longer exposure to hypertension than patients without renal disease.^{1,2} Moreover, in CKD the BP levels strictly correlate with

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left ventricular growth,⁹ that is, a potent independent predictor of CV mortality/morbidity.¹⁰ On the other hand, a more intensive antihypertensive treatment in moderate CKD prevents the development of CV events during the predialytic phase,^{11,12} and, as suggested by a retrospective study,¹³ ameliorates survival in the subsequent dialytic stage. Overall, these data indicate that hypertension plays a role in determining the CV risk for CKD patients that certainly is not inferior, but probably is greater, as compared with the general population in whom it accounts for a population-attributable risk for myocardial infarction of 18%.¹⁴

BP Targets in CKD

More than 6 years ago, the National Kidney Foundation (NKF) and the Joint National Committee (JNC VI) recommended maintenance of BP values at less than 130/85 mm Hg in nonproteinuric CKD patients and less than 125/75 mm Hg in the presence of proteinuria greater than 1 g/d.^{15,16} These recommendations have been emphasized further in the seventh report of JNC that identifies the value of less than 130/80 mm Hg as the BP target in patients with CKD, regardless of the degree of proteinuria.¹⁷ Similarly, the latest version of the European guidelines for the management of hypertension have stated that in CKD patients it is advisable to reduce BP intensively to the lowest tolerated level.¹⁸

The necessity of low BP values in CKD is derived mainly from the evidence of better CV protection by means of optimal BP control in the general population, and especially in high-risk patients.^{17,19} Furthermore, interventional trials aimed at the nephroprotective effects of tight BP control have shown that intensive hypertension control is practicable in CKD patients.²⁰⁻²⁴ Nevertheless, prospective studies are required to quantify the impact of entity of BP control on the degree of CV protection in the CKD population.

Despite the critical role of antihypertensive treatment, management of hypertension persistently has been unsatisfactory in CKD patients, with most of them showing BP levels higher than the proposed target values.^{2,23,25-27} In particular, in the 1988 to 1994 National Health and Nutrition Examination Survey (which was the previous largest survey on this issue performed in almost 500 CKD patients from a total population of 17,000 patients), only 11% of CKD hypertensive patients had their BP levels reduced to less than 130/85 mm Hg.²⁸ In all these previous studies, however, information not only was outdated, but also generally was limited to the entity of BP control with no data provided on antihypertensive treatment.

Target BP Levels in CKD (TABLE-CKD) Study

We performed a comprehensive audit, the TABLE-CKD study, on hypertension management in a large sample of Italian patients regularly followed-up by outpatient nephrology specialist clinics. The aims were to verify the adherence

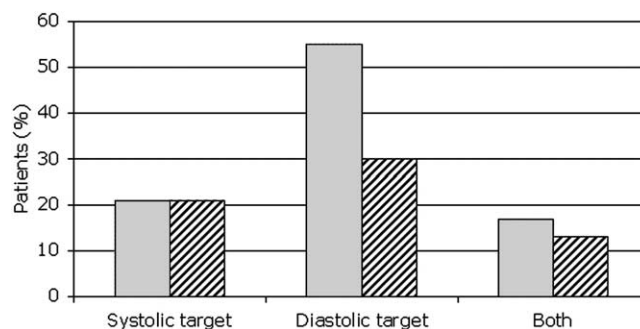


Figure 1 Percentage of patients with systolic and diastolic blood pressure values at goal. Values were considered at goal if less than 130/85 mm Hg in nonproteinuric patients and less than 125/75 mm Hg in the presence of proteinuria greater than 1 g/d (▨), or if less than 130/80 mm Hg, regardless of the degree of proteinuria (▩).

to proposed BP targets for CKD patients in the real world of clinical practice and to identify barriers to implementation of guidelines on BP control. The survey has been performed in 19 Nephrology Units situated in Italian universities or community hospitals. The sample of studied patients was derived from the population of nondialyzed and nontransplanted CKD patients with a GFR estimated by the Cockcroft-Gault equation (eGFR) to be 70 mL/min/1.73 m² or less who regularly received outpatient care in the involved nephrology clinics. To best analyze the management of hypertension by nephrologists, we excluded patients with follow-up evaluation in the nephrology clinic of less than 6 months. Patients with identified or suspected acute renal failure also were excluded. Therefore, we selected 713 patients for the study. Data were collected from September 2002 to March 2003. For a patient's BP to be considered at goal, the BP had to be less than the targets indicated by the NKF and JNC VI and published before the beginning of the study,^{15,16} that is, less than 130/85 mm Hg in nonproteinuric patients and less than 125/75 mm Hg in the presence of proteinuria greater than 1 g/d. Patients therefore were divided into 2 groups, reaching the target (Target group, n = 119) and not reaching the target (No Target group, n = 594) on the basis of both the systolic BP (SBP) and diastolic BP (DBP) values at the study visit.

On average, BP was 116 ± 9/71 ± 7 mm Hg in the Target group and 143 ± 15/83 ± 9 mm Hg in the No Target group ($P < .0001$). Most patients showed BP values above the levels recommended by guidelines at the time of the study (Fig 1). Specifically, only 17% of patients had both SBP and DBP at target, with the systolic goal being reached less frequently with respect to the diastolic target. Adequacy of antihypertensive intervention was even worse (13%) when considering the targets more recently proposed by JNC 7, that is, less than 130/80 mm Hg independently from the degree of proteinuria (Fig 1). Furthermore, only 40% of patients had their BP reduced to less than 140/90 mm Hg, that is, the treatment goal for individuals with hypertension and no compelling indications.

The main clinical and laboratory differences between the Target and No Target patients are shown in Table 1. Patients not reaching the BP target were characterized by a larger

Table 1 Main Clinical and Laboratory Characteristics of Target and No Target Patients

	Target (n = 119)	No Target (n = 594)	P
Age (y)	61 ± 14	67 ± 13	<.0001
Male sex (%)	61	57	.300
eGFR (mL/min/1.73 m ²)	35 ± 15	32 ± 15	.020
Proteinuria >1.0 g/d (%)	13	27	<.002
Urinary sodium excretion (mmol/d)	149 ± 57	152 ± 57	.532
FE _{Na} (%)	2.6 ± 2.1	2.7 ± 1.9	.479
Actual smoker (%)	16	10	.070
Diabetic patients (%)	9.0	21.0	.005
Follow-up period at the nephrology center (mo)	64 ± 60	60 ± 51	.540
Cardiovascular morbidities			
Left ventricular hypertrophy (%)	38	51	
Coronary artery disease (%)	16	24	
Stroke (%)	4.0	8.0	
Congestive heart failure (%)	3.0	4.3	
Peripheral vasculopathy (%)	10	15	

The values are mean ± SD.

prevalence of advanced age, diabetes mellitus, significant proteinuria, and CV morbidities. On the contrary, no difference was detected in the urinary sodium excretion ($U_{Na}V$) that showed a daily salt intake of approximately 9.0 g, with only 18% of patients in either group eating less than 6 g NaCl/d. Consequently, no significant difference was observed in the fractional excretion of sodium (FE_{Na}), which was greater than 1% in nearly all patients.

The evaluation of antihypertensive therapy disclosed further differences between the 2 groups. As expected, the number of prescribed antihypertensive agents per patient was significantly greater in the No Target group (2.2 ± 1.0 versus 1.8 ± 1.0 , $P < .01$), with 28% of these hypertensive patients taking any or 1 drug, 37% taking 2 drugs, and 35% taking 3 or more drugs, whereas Target patients were treated with 1 to 2 drugs in most (71%) cases. Figure 2 shows the distribution of classes of antihypertensive drugs. Agents counteracting the activity of the renin-angiotensin system were the most prescribed drugs (80% in the Target group and 74% in the No Target group, $P = .05$), with a significantly greater prevalence of converting enzyme inhibitors (CEI). Only a minority of patients received combined treatment with CEI and angiotensin II receptor blockers (8% in the Target group and 4% in

the No Target group, $P = .03$). The second most frequently used agent was the calcium channel blocker; a calcium channel blocker was given to a greater percentage of patients in the No Target group. Surprisingly, loop diuretics were given only to a minority of patients; furthermore, the daily dose of oral furosemide, the loop diuretic given in 99% of cases, was generally low, being 55 ± 59 mg in the No Target group and 61 ± 61 mg in the Target group. Interestingly, furosemide was given at a dose of 25 mg/d or less in 50% of the No Target patients.

When dividing the whole group of 713 patients in quartiles of estimated GFR, we observed a significant reduction of the percentage of patients at target from the highest to the lowest quartile (from 23% to 14%, $P = .03$). We therefore evaluated whether the level of renal function influences hypertension management in the No Target group. The analysis revealed a slight increase of SBP (+5 mm Hg, on average), but not DBP, with worsening of renal function. This occurred despite an increasing number of antihypertensive agents. Specifically, although prescription of CEI, angiotensin II receptor blockers, and β -blockers did not change significantly, a greater fraction of patients was treated with a calcium channel blocker and other vasodilating agents. Similarly, the prescription of loop diuretics was more frequent in the lowest eGFR quartiles. The dose of furosemide increased with eGFR decrease (38 ± 50 , 43 ± 46 , 56 ± 50 , and 71 ± 73 mg/d from the highest to the lowest quartile, $P < .0001$); however, a substantial number of patients still was kept at a dose of 25 mg/d or less even in the lowest quartiles (39% in the first quartile, 49% in the second quartile).

As shown by the changes of $U_{Na}V$ values, only a minor restriction of salt intake became evident with eGFR decrease (Fig 3). Consequently, FE_{Na} values increased proportionally. Of note, diuretic treatment did not influence either $U_{Na}V$ or FE_{Na} values; in fact, neither parameter differed between patients taking diuretics and those not taking diuretics in the 4 eGFR quartiles.

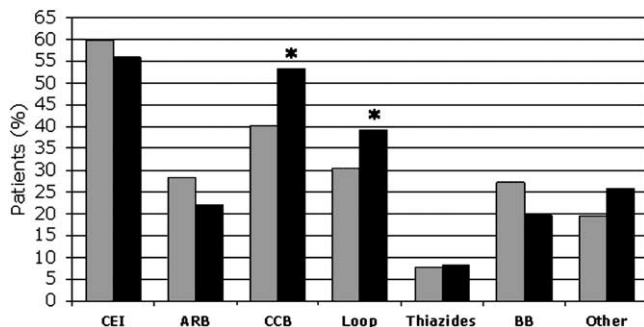


Figure 2 Distribution of classes of antihypertensive drugs in patients reaching (▨) and not reaching (■) BP targets. * $P < .05$ versus the Target group.

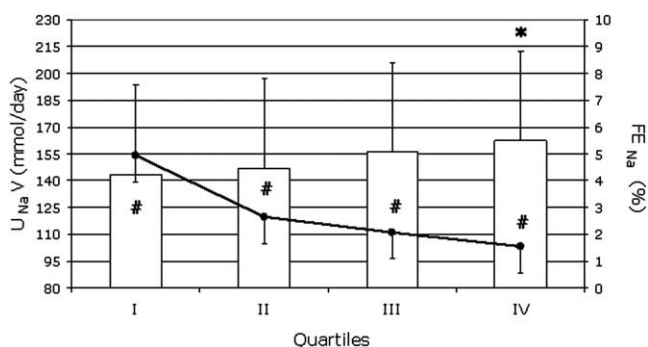


Figure 3 Urinary sodium excretion (bars) and fractional sodium excretion (line) from the first to the fourth quartile of estimated GFR in the 594 patients not reaching the BP target. Partition values were 19.8, 29.9, and 40.8 mL/min. * $P < .05$ versus first quartile, # $P < .05$ versus others.

The Lesson of TABLE-CKD Study: A Call for Action

The TABLE survey shows that, in a large CKD population, more than 5 years after the publication of the JNC VI/NKF guidelines, treatment of hypertension still is inadequate. We found that 83% of patients have BP values greater than the target specifically recommended in patients with CKD, most patients do not even reach the generic 140/90 mm Hg goal indicated for patients without renal damage. The BP target was not achieved in most patients because of the high SBP values. Similarly, studies in the general population have shown a particular willingness of physicians to tolerate a higher SBP in their patients.²⁹ These findings contrast with the increased recognition of the importance of systolic hypertension as an independent predictor of CV events and GFR decrease in patients with CKD,^{11,22,30} as in the general population.¹⁷

The observation of a scarce implementation into clinical practice of the NKF/JNC VI guidelines becomes even more remarkable if one considers that these data have been collected in patients who were followed-up regularly, for approximately 5 years, by nephrology specialist clinics. The exclusion of patients with follow-up evaluation in the nephrology clinic for less than 6 months, moreover, allows a limitation of the biases in data interpretation related to the changes of antihypertensive therapy and the concomitant variation of blood pressure and renal function, that generally are larger in the initial few months of intervention.

An additional important difference to the early studies on hypertension management in patients with CKD,^{23,25-28} this survey provides comprehensive information on patients not reaching the BP target. With respect to patients at target, the No Target group basically was characterized by clustering of major risk factors for worse renal and CV outcome such as older age, higher proteinuria level, and greater prevalence of diabetes mellitus and CV morbidities. Therefore, BP values were higher in the CKD patients who, carrying the highest risk for CKD progression and CV disease, likely would gain the greatest benefit from strict BP control.^{1,2,10,15,19}

Although the possibility that patients were not compliant to the prescribed therapy can be ruled out plausibly because of the prolonged follow-up period and the large size of the No Target group, the observational nature of this study does not allow clarification as whether the poor BP control can be ascribed to undertreatment of hypertension (ie, an attitude of nephrologists toward therapeutic inertia) or to an intrinsic resistance to antihypertensive therapy. Nevertheless, the evaluation of the therapy prescribed can shed some light on this critical issue. We found that, although 1 to 2 antihypertensive medications were sufficient to normalize BP levels in most Target patients, BP control was inadequate in the No Target group despite the prescription of at least 2 drugs in more than 70% of cases, with more than one third of patients taking 3 drugs or more. Therefore, these findings suggest that at least a substantial fraction of hypertensive patients from the No Target group somehow were resistant to the antihypertensive intervention. According to this view, the recommendation of expert panels to prescribe in CKD patients at least 2 antihypertensive agents to reach the lower BP goals probably underestimates the magnitude of the problem;¹⁷ indeed, in the trials showing optimal BP control in patients with CKD, the number of antihypertensive agents was 3.5 on average.^{21,22,24,30}

We can reasonably hypothesize that resistance was related to the persistence of extracellular volume (ECV) expansion. It is well established, in fact, that the impairment of renal function causes salt retention;^{2,31-33} the resulting ECV expansion restores the external salt balance by reducing tubular sodium reabsorption, which is shown by concomitant increase of FE_{Na} levels above the normal value of 1%, but at the expense of a steady increase in total body sodium and BP levels.^{2,33-35} As support to this hypothesis, we found high FE_{Na} values in the No Target patients that indicated the presence of a significant increment of the ECV compartment; this likely occurred because dietary salt intake in these patients was well above the recommended intake of 6 g NaCl/d.^{17,18} Interestingly, previous studies by our group and others have shown that efficacious salt restriction per se normalizes FE_{Na} values and effectively decreases BP levels in patients with moderate to advanced CKD.^{33,34} On the other hand, the pharmacologic treatment of salt retention also was deficient. In most of the No Target patients, furosemide was given at doses indicated for patients with normal renal function that, however, certainly are inadequate in the presence of reduced GFR. Indeed, most patients received furosemide at a low dose (≤ 25 mg/d), despite a mean eGFR value of approximately 30 mL/min. Conversely, under these conditions, the maintenance doses of furosemide should be at least doubled to attain efficacious natriuresis and consequent correction of volume expansion and hypertension.^{2,31,35}

The hypothesized role of volume expansion is supported further by the analysis of hypertension management in the 4 quartiles of eGFR in the No Target patients. From the highest to the lowest quartile, in fact, SBP levels significantly increased despite a larger use of antihypertensive medications. Worsening of SBP control was associated with a marked increase of FE_{Na} , showing a greater expansion of ECV in the

lowest quartiles. This likely was dependent on restriction of salt intake inadequate to the degree of renal impairment. Similarly, the loop diuretic dose still was inappropriately low (ie, 50-70 mg/d on average) even in the predialytic stages of CKD in which doses 10-fold higher are recommended.^{2,35}

Of note, also the Target group was characterized by high levels of $U_{Na}V$ and FE_{Na} ; nevertheless, these patients constantly showed, as compared with the No Target group, lower BP values despite a minor number of drugs. It is possible to hypothesize that in these patients hypertension is less salt sensitive because of less prevalence of the main determinants of salt sensitivity, such as old age and diabetes.³⁶

In conclusion, the TABLE survey shows that nowadays implementation into clinical practice of the recommendations of expert panels on strict BP control in patients with CKD remains unacceptably low even in patients who are followed-up regularly for a prolonged period in tertiary care centers, and especially in the presence of major risk factors for worse cardiovascular and renal outcome. However, there is much room for improvement. Specifically, the TABLE data suggest that the main barrier to implementation of guidelines is the insufficient treatment of extracellular volume expansion in patients characterized by a greater prevalence of the main factors increasing salt sensitivity of hypertension. A more aggressive treatment mainly based on adequate dietary salt restriction and proper prescription of diuretic agents therefore may ameliorate hypertension control in this high-risk population

Appendix

The Target Blood Pressure Levels in Chronic Kidney Disease Study Group

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