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Original Paper

Patients with Hypertensive Nephropathy and Chronic Kidney Disease Might Not Benefit from Strict Blood Pressure Control

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Key Words
Hypertensive nephropathy • Chronic kidney disease • Renoprotection

Abstract
Background/Aims: In patients with chronic kidney disease (CKD) strict blood pressure (BP) control is reno-protective. However, renal benefits from BP control might depend also on the etiology of CKD. We investigated if maintenance of BP at target is equally effective in subjects with hypertensive nephropathy (HN+) and in those with other nephropathies (HN-). ***Methods:*** We evaluated 148 patients with CKD (stages 3-5) in two visits at least 12 months apart. BP was measured both as office BP and 24h ambulatory blood pressure (ABP). Glomerular filtration rate (eGFR) was estimated with CKD-EPI formula. The slope of eGFR variation (ΔeGFR) was calculated as: (eGFR1-eGFR0)/months of follow up. ***Results:*** Cohort characteristics were: HN- (n=82) and HN+ (n=66), age (71±9 vs 74±9 years; p=0.09); prevalence of diabetes (57 vs 43%; p=0.19); average follow up (19±7 vs 21±9 months; p=0.3). HN- and HN+ did not differ regarding both baseline eGFR (34±18 vs 35±14 ml/min; p=0.97) and ΔeGFR (0.00±0.53 vs -0.06±0.35 ml/min/month, p=0.52). The proportion of patients with BP at target at both visits was similar in HN- and HN+ (office BP: HN- 18% and HN+ 27%; p=0.21; ABP: HN- 42% and HN+ 43; p=0.96). In patients with office BP at target at both visits HN- showed a significant improvement of ΔeGFR respect to HN+ (HN-: 0.240 ± 0.395 and HN+: -0.140±0.313 ml/min/month; p=0.026). In patients with office BP not at target HN- and HN+ did not show any difference in ΔeGFR (HN- 0.00±0.47; HN+ -0.030±0.420 ml/min/month; p=0.66). ABP was not associated with differences in ΔeGFR either if it was at target (HN- 0.104±0.383 and HN+ 0.00±0.476 ml/min/month; p=0.42) or not (HN- -0.057±0.503 and HN+ -0.092±0.325 ml/min/month; p=0.87). ***Conclusion:*** In patients with CKD and HN+ maintenance of BP targets recommended by current guidelines is less reno-protective than it is in HN-.

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Introduction

Hypertension is one of the principal risk factors linked to the development of chronic kidney disease (CKD) [1-3] and it is also causally related to the progression of CKD towards end stage renal disease (ESRD) [4].

Current guidelines of the European Society of Hypertension (ESH) suggest keeping a strict blood pressure (BP) control among individuals with CKD in order to slow the decline of renal function [5]. However, although renal benefits from a strict BP control are well established in patients with clinical proteinuria [6-8], those evidences are not equally consistent in subjects with non-proteinuric kidney diseases [7-11]. Those discrepancies may indicate that the beneficial effects of strict blood pressure control are not uniformly distributed among patients with CKD of different etiologies.

Patients with hypertensive nephropathy are affected by extended renal microvascular atherosclerotic damage as well as by a progressive loss of autoregulation of glomerular perfusion [12]. Therefore, the hypothesis is that, when systemic BP values are maintained too low, these patients might develop persistent renal hypoperfusion and incur in a faster decline of renal function.

We evaluated whether the maintenance of office BP at the targets indicated by the ESH guidelines has the same impact on the variation of estimated glomerular filtration rate (eGFR) in CKD patients with hypertensive nephropathy (HN+) and in those affected by other nephropathies (HN-).

Materials and Methods

Population and clinical setting

We performed a retrospective analysis of a cohort of 148 prevalent hypertensive patients with CKD stages 3-5 (eGFR 60-10 ml/min) participating to an observational study that was concluded in 2016 (Proteinuria On Vascular End-points, PROVE study). We selected all patients that underwent two 24h ambulatory blood pressure monitoring (24h-ABPM) measurements (at least 12 months apart) between January 2012 and January 2016. At each visit, we registered anthropometrics, therapy and clinical records. Blood and 24h urinary samples were collected after an overnight fasting. The severity of comorbidities was classified using Charlson comorbidity index [13–16].

Office BP was measured using a manual sphygmomanometer (Heine, GAMMA XXL LF) with an appropriate size mid-harm cuff. BP was assessed in patients maintaining the sitting position, after 5 minutes of rest. Each measurement was obtained as the mean of three office determinations taken one minute apart by a trained physician.

Ambulatory blood pressure (ABP) was measured in the 24 hours following the outpatient visit using a Spacelabs 90207 device. ABP was assessed every 15 minutes during day-time (7-23) and every 30’ during night-time (23-7) as recommended by the 2013 ESH guidelines [5].

eGFR was determined by CKD-EPI creatinine formula [17–19]. Since creatinine was not standardized with isotope dilution mass spectrometry, we used the modified formula that has been previously validated by Skali and co-authors [18]. During the time of observation, all patients were followed up by the same team of nephrologists that were free to modify the anti-hypertensive and diuretic treatment in accordance to the clinical needs, with the aim of obtaining optimal BP targets [5].

To be included in the observational cohort, all patients underwent renal ultrasonography and echo-color Doppler examination of both kidneys and renal arteries at baseline, in order to exclude subjects with clinically relevant renal artery stenosis, ADPKD and obstructive nephropathies. Etiologies of HN- where: 34% chronic glomerulonephritis, 66% undetermined diseases. In order to be enrolled in our study, all patients had to be in a stable clinical condition for at least 6 months. Furthermore, they had to be followed for at least 12 months in our out-patients’ clinic before the starting visit. The target visits of the study were programmed at least 3 months after the clinical recovery from any hospitalization and at least 1 month after the last variation of antihypertensive and/or diuretic therapy. We excluded subjects <18 years of

age, those unable or unwilling to co-operate, those with active immunosuppressive therapies, those with advanced hepatic cirrhosis and ascites, those with heart failure NYHA 3 and 4 as well as those with diabetic nephropathy. Diabetic patients were included only in the absence of diabetic retinopathy and if the diagnosis of diabetes occurred at least 5 years after the diagnosis of CKD.

Hypertensive nephropathy was defined as a presumptive diagnosis that was clinically characterized in accordance to the following criteria: 1) development of renal dysfunction only after more than 10 years from the diagnosis of hypertension; 2) negative urinalysis except for 24 h proteinuria that however had to be <1 gr/24h at all determinations (at least 3) in the 12 months before study enrollment; 3) exclusion of patients with a documented diagnosis of a different renal disease.

Clinical end-points

BP pressure targets were defined according to 2013 ESH guidelines recommendations [5]. Office BP was considered at target when systolic blood pressure (SBP) was <140 mmHg and diastolic blood pressure (DBP) was <90 mmHg for all patients, SBP <130 mmHg and DBP<90 mmHg for patients with overt proteinuria, SBP <140 mmHg and diastolic blood pressure (DPB) < 85 mmHg for diabetic patients. Overt proteinuria was defined as > 1gr/24h in accordance to MDRD study [7]. Due to the lack of specific indications for CKD patients, ABP was considered at target for mean 24-hour values of SBP <130 mmHg and DBP <80 mmHg as for the general population [5]. The slope of eGFR variation (ΔeGFR) was defined as: (eGFR at visit 1 - eGFR at visit 0)/months of follow up.

All patients had to sign an informed consent that was previously approved by the Ethical Committee of Our Institution (Proteinuria On Vascular End-points – PROVE Study, doc 347/2010).

Primary end-point. We evaluated whether ΔeGFR was different in HN+ and HN- patients. This analysis was performed separately in those subjects that maintained office BP at target at both visits (visit 0 and visit 1) and in those that were not at target in at least one visit.

Secondary end-point. We evaluated whether ΔeGFR was different in HN+ and HN- patients. This analysis was performed separately in those subjects that maintained ABP at target at both visits (visit 0 and visit 1) and in those that were not at target in at least one visit.

Statistical analysis

All data are expressed as mean ± SD or median ±IQR as appropriated. The comparison of parametric variables between HN+ and HN- was done using Student's t-test, while comparison of proportions among groups was performed using the chi-squared (χ^2) test. Mann-Whitney "U" test was used to compare ΔeGFR in HN+ and HN- according to the sub-groups that where analyzed.

P<0.05 was considered statistically significant in all analyses. All statistical analyses were performed using Statview for Windows, SAS Institute Inc. (version 5.0.1, Cary, NC).

Results

Patients characteristics

Patients' main features are summarized in Table 1. The two groups were comparable for number of patients (HN-: n=82; HN+: n=66) and did not show any relevant difference regarding their overall characteristics. The average age was: 71±9 and 74±9 for HN- and HN+ respectively, p=0.09. Both groups had a high prevalence of diabetes (57% in HN- and 43% in HN+, p=0.19) and cardiovascular comorbidities (31% both in HN- and HN+, p=0.99). Charlson index evidenced a high burden of comorbidities that, however, was not different in the

Table 1. Clinical characteristics of HN- and HN+ at baseline. BMI: body mass index; CV: cardiovascular

Clinical history and anthropometrics	HN-	HN+	p
Number of subjects	82	66	
Age (years)	71±9	74±9	0.09
Males/females (%)	67/33	71/29	0.63
BMI (Kg/m2)	27.0±4.2	27.5±4.1	0.47
Diabetes (%)	57	43	0.19
Previous CV events (%)	31	31	0.99
Charlson comorbidity index	6.2±2.0	6.1±3.3	0.64
Duration of follow up (months)	19.1±7.2	20.7±9.7	0.3
Number of visits during follow up	8 (6-14)	8 (5-15)	0.34
Hypoproteic diet (%)	54	66	0.2

two groups (6.2±2.0 in HN- and 6.1±3.3 in HN+, p=0.64). The duration of follow up was comparable in the HN- and HN+ (19.1±7.2 and 20.7±9.7 respectively; p=0.3). Moreover, the median number of visits between baseline and follow up was equivalent in the two groups 8 (6-14) and 8 (5-15) in HN- and HN+; p=0.34).

Biochemical and urinary parameters are summarized in Table 2. The two groups did not differ in basal eGFR (34±18 in HN- and 35±14 in HN+; p=0.97) as well as in ΔeGFR (0.00±0.53 in HN- and -0.06±0.35 in HN+; p=0.52), while 24h proteinuria at baseline was significantly higher in HN- (788±998 mg/24h in HN- vs 312±355mg/24h in HN+; p=0.0003). Fasting glycaemia, HbA1c, uric acid and 24h urinary sodium excretion did not differ in the two groups.

Blood pressure measurement and control

Office BP was similar in HN- and HN+ at both baseline and follow up visits (Table 3). Both groups showed a comparable proportion of patients with office BP at target at baseline (32% vs 37% in HN- and HN+; p=0.78) and at the follow up visit (39% vs 41% in HN- and HN+; p=0.51). Only a small proportion of patients maintained office BP at target at both visits, and was not statistically different between the two groups (18% and 27% in HN- and HN+; p=0.21).

Likely, also mean ABP values (24-hour, day-time and night-time) were comparable in both groups at baseline and follow up visits (Table 4). The proportion of patients that had ABP at target was similar in the two groups at baseline (45% vs 48% in HN- and HN+; p=0.84) and at follow up (48% vs 49% in HN- vs HN+, p=0.69). Forty-two percent of HN- and 43% of HN+ (p=0.96) maintained mean ABP at target at both visits.

The two groups of patients were approximately under the same number of anti-hypertensive drug classes at both visits (at baseline: HN- 2.6±1.4 and HN+ 2.6±1.1, p=0.96; at follow up: HN- 2.8±1.4 and HN+ 2.7±1.0, p=0.48; Table 5). Also, the proportion of subjects that maintained, withdrew or introduced a RAAS-inhibiting treatment during the study was comparable in HN- and HN+ (Table 5). Since changes in RAAS-inhibiting treatment that have occurred during the period of observation might have influenced the ΔeGFR independently of BP control, we evaluated this aspect separately. However, we observed an increase in ΔeGFR only in HN+ patients who have suspended RAAS-inhibiting treatment (Fig. 1).

Table 2. Biochemical and urinary parameters of HN- and HN+ at baseline. eGFR: estimated glomerular filtration rate calculated with CKD EPI formula. HbA1c: glycosylate hemoglobin

Biochemical and urinary parameters	HN- n=82	HN+ n=66	p
ΔeGFR (ml/min)	34±18	35±14	0.97
ΔeGFR (ml/min/month)	0.00±0.53	-0.06±0.35	0.52
Proteinuria 24 h (mg/24h)	788±998	312±355	0.0003
Urinary Na excretion (mEq/24h)	155±73	150±63	0.7
Glycemia (mg/dl)	116±35	114±35	0.67
HbA1c (mmol/mol)	55±13	52±17	0.54
uric acid (mg/dl)	6.2±1.7	6.1±1.4	0.88
Plasma Na (mEq/L)	142±3	142±2	0.3
Plasma K (mEq/L)	4.7±0.5	4.6±0.5	0.75
Hemoglobin (g/dl)	12.8±1.5	13.4±1.7	0.12

Table 3. Office blood pressure in HN+ and HN-. SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; BP: blood pressure

Office Blood pressure	Baseline		Follow up	
	HN-	HN+	HN-	HN+
SBP, mmHg	142±20	140±20	138±16	137±17
DBP, mmHg	81±9	81±11	79±12	78±12
PP, mmHg	62±18	59±19	59±18	59±20
SBP at target, %	38	48	43	51
DBP at target, %	72	78	79	80
BP at target, %	32	37	39	41
BP at target at both visits, %	-	-	18	27

Table 4. Ambulatory blood pressure (ABP) in HN- and HN+. **p<0.05 baseline vs follow up. SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure

ABP	Baseline		Follow up	
	HN-	HN+	HN-	HN+
24h SBP, mmHg	132±13	132±15	132±11	131±12
24h DBP, mmHg	72±8	71±8	72±9	71±8
Day SBP, mmHg	134±12	125±15	134±11	134±11
Day DBP, mmHg	74±8	74±9	74±9	74±8
Night SBP, mmHg	128±17	126±16	129±16	124±22
Night DBP, mmHg	67±9	66±9	68±10	66±10
Dippers, %	27	29	15**	27
24h BP at target, %	45	48	48	49
24h SBP at target, %	49	54	48	56
24h DBP at target, %	84	86	87	86
24 h BP at target at both visits, %	-	-	42	43

Impact of BP targets maintenance on ΔeGFR

We evaluated ΔeGFR between baseline and follow up in HN- and HN+ individuals who maintained or did not maintain office and/or ambulatory BP at target at both visits (Fig. 2, 3).

We observed a remarkable difference between HN- and HN+ regarding the impact of office BP control on ΔeGFR (Fig. 2). In particular, in those patients who maintained office BP at target at both visits, HN- showed a significant increase of ΔeGFR respect to HN+ (HN-: 0.240 ± 0.395 and HN+: -0.140±0.313 ml/min/month; p=0.026; Fig. 2). In patients with office BP not at target, HN- and HN+ did not show any difference in ΔeGFR (HN- 0.00±0.47; HN+ -0.030±0.420 ml/min/month; p=0.66).

Differently, the maintenance of ABP targets did not show any significant impact on ΔeGFR either in HN- or in HN+ (Fig. 3). In those patients who maintained ABP at target, ΔeGFR was 0.104±0.383 and 0.00±0.476 ml/min/month in HN- and HN+ respectively (p=0.42). In those patients who did not maintain ABP at target ΔeGFR was -0.057±0.503 and -0.092±0.325 ml/min/month in HN- and HN+ respectively (p=0.87).

Discussion

We observed that in a cohort of patients affected by CKD (stages 3b-5) the maintenance of BP targets over time has an impact on the decline of renal function that varies according to the etiology of the renal disease. In particular, we observed that, among those patients who maintained office BP at target, HN- showed an improvement of ΔeGFR while HN+ tended to develop a faster decline of renal function.

Conversely, the results regarding the effects of ABP on ΔeGFR did not show a clear impact of ABP targets in either HN- or HN+.

In order to exclude possible confounding factors, we compared the two sub-groups of patients for the variables that may have influenced our results. It emerged that HN- and HN+

Table 5. Anti-hypertensive drugs in HN- and HN+ at baseline and at follow up. RAAS: Renin-angiotensin-aldosterone system

Anti-hypertensive drugs	Baseline		Follow up	
	HN-	HN+	HN-	HN+
Number of anti-hypertensive drugs	2.6±1.4	2.6±1.1	2.8±1.4	2.7±1.0
RAAS inhibitors, %	61	73	56	60
Maintenance of RAAS inhibitors, %	-	-	52	60
RAAS inhibitors withdrawal, %	-	-	9	13
RAAS inhibitors new prescription, %	-	-	4	0
Diuretics, %	50	50	56	55
Maintenance of diuretics, %	-	-	39	45
Diuretics withdrawal, %	-	-	10	5
Diuretics new prescription, %	-	-	17	10

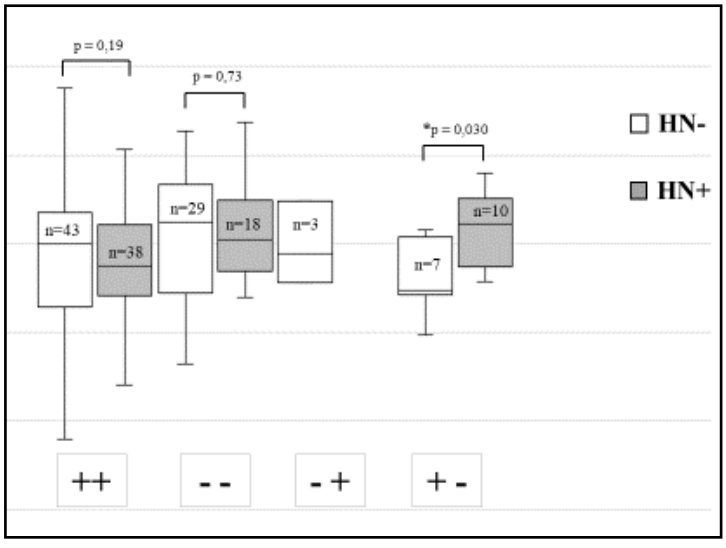

Fig. 1. Comparison of ΔeGFR between HN- and HN+ that maintained, introduced or withdrew RAAS- inhibiting treatment. HN-: other nephropathies; HN+: hypertensive nephropathy. Regarding RAAS-inhibition: ++ maintained RAAS-inhibiting treatment at baseline and follow up; -- where not on RAAS-inhibiting treatment at both baseline and follow up: -+ introduced new RAAS-inhibiting treatment between baseline and follow up; +- withdrew RAAS-inhibiting treatment between baseline and follow up.

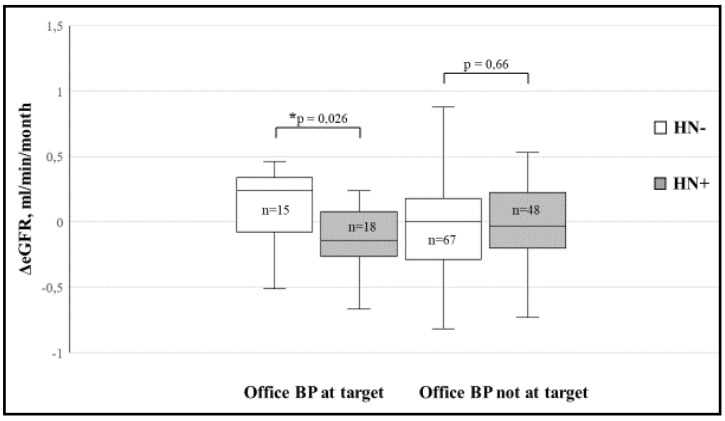

Fig. 2. Comparison of ΔeGFR between HN- and HN+ that maintained office BP at target or not. HN-: other nephropathies; HN+: hypertensive nephropathy.

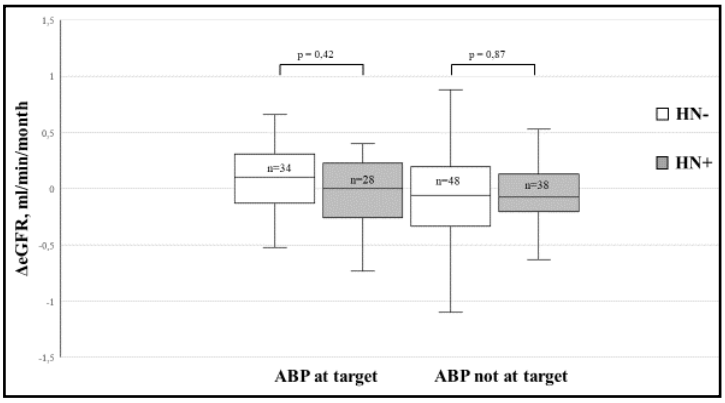

Fig. 3. Comparison of ΔeGFR between HN- and HN+ that maintained ambulatory BP (ABP) at target or not. HN-: other nephropathies; HN+: hypertensive nephropathy.

patients were well matched for mean office and ambulatory BP values as well as for the other clinical and biochemical risk factors that may have influenced ΔeGFR. Since RAAS-inhibitors bear a specific renoprotective effect that might be independent of BP control, we compared the variation of renal function in those patients that changed or maintained a RAAS-inhibiting treatment during the follow up. However, the only significant result was a slight increase of ΔeGFR in HN+ individuals that dropped RAAS-inhibitors between baseline and follow up (Fig. 1).

Overall our results suggest that HN+ CKD patients do not benefit from the maintenance of lower office BP targets as HN- do. Although the design of our study does not allow to provide any specific pathophysiological mechanism that could explain our results, we can anyway make some speculations on that. In particular, our data seem to support the hypothesis that systemic BP is differently transmitted to intrarenal microcirculation in HN+ and HN-. This may depend on the fact that in subjects with chronic hypertension small renal arteries (including afferent arterioles) incur in a number of functional and anatomical alterations (hyaline arteriosclerosis, myointimal hyperplasia) that compromise the physiological autoregulation of blood flow to the renal glomeruli. With the progression of HN, intra-glomerular pressure depends on renal perfusion pressure, thus the GFR is directly correlated with systemic BP [20]. Furthermore, since HN is associated with an atherosclerotic damage of small renal vessels (in particular interlobular and pre-glomerular arterioles), the normalization of systemic BP may induce renal hypoperfusion and ischemia. Conversely, in proteinuric nephropathies, that represent almost the totality of HN- in our study, the reduction of intra-glomerular pressure results in a reduction of proteinuria that confers a better renal prognosis. Therefore, whether this hypothesis was correct, our results may be explained by the fact that when systemic BP is maintained at lower targets, HN+ develop chronic renal ischemia while HN- benefit from a higher reduction of proteinuria. This hypothesis would be consistent also with previous observations. In fact the results

of three large clinical trials indicate that the benefits of a stricter BP control in terms of preservation of renal function are much greater in proteinuric patients [10, 11, 21].

This hypothesis might also explain why the withdrawal of RAAS-inhibiting agents was associated with a relative improvement of ΔGFR in HN+ patients respect to HN-. RAAS contributes to regulate intra-glomerular pressure and filtration fraction by constricting or dilating the efferent glomerular arteriole in function of renal perfusion pressure. In conditions characterized by renal hypoperfusion, GFR is principally maintained by an increase in filtration fraction due to RAAS-mediated vasoconstriction of the efferent arteriole [20]. Consequently, in conditions of renal hypoperfusion or ischemia, inhibition of RAAS induces a reduction of GFR [20]. Therefore, whether it was true that HN is characterized by an impaired glomerular auto-regulation and by renal parenchymal hypoperfusion, it is possible that in HN+ the preservation of GFR is mainly dependent on RAAS activity and that the withdrawal of RAAS-inhibition might induce an increase of GFR.

Hypertensive nephropathy is currently one of the leading causes of CKD and it is also associated with a significant increase of cardiovascular risk [22]. From previous trials conducted in hypertensive patients with [23] or without diabetes [24], it emerged that those that were randomized to maintain lower BP values incurred more frequently in episodes of acute kidney injury. However, the clinical significance of acute reductions in renal function in patients treated to lower BP is still debated. In fact, in patients with diabetic nephropathy, an acute decrease of eGFR was associated to a slower decline of renal function in the long term [25]. On the contrary, in hypertensive CKD patients without diabetes Ku and colleagues demonstrated that an acute reduction of eGFR >20% was associated to an increased risk of end stage renal disease [26]. In the SPRINT study those patients that were treated to reach lower BP targets developed an excess of acute renal events [27]. These data were recently confirmed by two secondary analyses of the SPRINT that evidenced a detrimental impact of lower BP targets on renal function in both CKD [28] and not CKD patients [29]. Although the BP target assigned to the intensive BP treatment harm of the SPRINT is much lower than those evaluated in our study we believe there are still some comparisons that can be done. In fact, according to the inclusion criteria, it is plausible that the vast majority of CKD patients included in the SPRINT were actually affected by HN. The detrimental effect of BP reduction on eGFR that was reported in the SPRINT study was not limited to those patients that were randomized to lower BP values, but they were rather proportional to the variation of BP form baseline independently of BP target. Thus, the results of the SPRINT seem to support the hypothesis of renal hypoperfusion as a plausible cause of renal dysfunction.

In our study, we observed inconsistent results regarding the impact of office and ambulatory BP on ΔeGFR. In fact, despite ABP was maintained at target or not, we did not find and difference of ΔeGFR between HN- and HN+.

Although we cannot exclude that our study was underpowered to detect an impact of ABP on ΔeGFR, there is also a growing amount of evidence suggesting that office and ambulatory BP may have a different impact on renal and CV events in CKD patients [30, 31]. This discrepancy of results might also depend on the fact that in CKD individuals office and ambulatory BP are scarcely correlated [32]. Furthermore, we found that among patients that maintained office or ambulatory BP at target at both visits, 20% was affected by white coat hypertension and 11% by masked hypertension. We believe that also these discrepancies of classification might contribute to explain the different results that we observed for office and ambulatory BP.

Our study presents several potential drawbacks that could have influenced our results. First of all, the definition of HN that we adopted was only presumptive since it was not confirmed by a diagnostic biopsy. Therefore, HN+ group may present some etiological heterogeneity, hence the possibility that different pathophysiological mechanisms might underlie the kidney disease in this group cannot be completely excluded. However, we have also to acknowledge that, as it was previously done in larger studies [10], the diagnosis of HN is usually based on clinical features as: risk factors, renal echography, onset features

and time course of the renal disease. Furthermore, in patients with advanced CKD the risk/benefits balance of a renal biopsy is utmost uncertain. Thereof, we preferred to define HN by applying a selection protocol that was based upon stringent clinical criteria that should have reasonably excluded renal diseases of other than HN (see method section for details).

Another possible source of bias may derive from the retrospective design of our study. However, we believe that this might be considered also as a point of strength. We evaluated in our analysis only patients characterized by a stable clinical condition in whom ΔeGFR was the principal endpoint, in fact we excluded all patients that dropped during the follow up because of death or ESRD. Furthermore, our analysis depicts a realistic picture of the outpatients setting, where only a minority of individuals maintains an adequate BP control [33].

Conclusion

Our study represents a proof of the concept that in hypertensive CKD patients BP targets could vary according to the etiology of renal disease. In particular, our results suggest that HN+ may represent a distinct phenotype of renal damage where a stricter BP control may even induce a faster decline of eGFR.

Disclosure Statement

The authors of this manuscript declare no financial support and no conflict of interest.

References

1 Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J: Blood Pressure and End-Stage Renal Disease in Men. N Engl J Med 1996;334:13–18.
2 Iseki K, Iseki C, Ikemiya Y, Fukiyama K: Risk of developing end-stage renal disease in a cohort of mass screening. Kidney Int 1996;49:800–805.
3 Haroun MK, Jaar BG, Hoffman SC, Comstock GW, Klag MJ, Coresh J: Risk factors for chronic kidney disease: a prospective study of 23, 534 men and women in Washington County, Maryland. J Am Soc Nephrol 2003;14:2934–2941.
4 Rao M V., Qiu Y, Wang C, Bakris G: Hypertension and CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES), 1999-2004. Am J Kidney Dis 2008;51:S30–S37.
5 Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, et al.: 2013 ESH/ESC Guidelines for the management of arterial hypertension. J Hypertens 2013;31:1281–1357.
6 Remuzzi G: Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet 1996;349:1857–1863.
7 Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G: The Effects of Dietary Protein Restriction and Blood-Pressure Control on the Progression of Chronic Renal Disease. N Engl J Med 1994;330:877–884.
8 Wright, Jr JT, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG, African American Study of Kidney Disease and Hypertension Study Group: Effect of Blood Pressure Lowering and Antihypertensive Drug Class on Progression of Hypertensive Kidney Disease: results From the AASK Trial. JAMA 2002;288:2421.

9 Peterson JC, Adler S, Burkart JM, Greene T, Hebert LA, Hunsicker LG, King AJ, Klahr S, Massry SG, Seifter JL: Blood Pressure Control, Proteinuria, and the Progression of Renal Disease. Ann Intern Med 1995;123:754–762.

10 Appel LJ, Wright JT, Greene T, Agodoa LY, Astor BC, Bakris GL, Cleveland WH, Charleston J, Contreras G, Faulkner ML, Gabbai FB, Gassman JJ, Hebert LA, Jamerson KA, Kopple JD, Kusek JW, Lash JP, Lea JP, Lewis JB, Lipkowitz MS, et al.: Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med 2010;363:918–929.

11 Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, Levey AS: The Effect of a Lower Target Blood Pressure on the Progression of Kidney Disease: Long-Term Follow-up of the Modification of Diet in Renal Disease Study. Ann Intern Med 2005;142:342–351.

12 Bidani AK, Polichnowski AJ, Loutzenhiser R, Griffin KA: Renal microvascular dysfunction, hypertension and CKD progression 2012; DOI:10.1097/MNH.0b013e32835b36c1.

13 Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.

14 Jassal SV, Schaubel DE, Fenton SSA: Baseline Comorbidity in Kidney Transplant Recipients: A Comparison of Comorbidity Indices. Am J Kidney Dis 2005;46:136–142.

15 Rattanasompattikul M, Feroze U, Molnar MZ, Dukkipati R, Kovesdy CP, Nissenson AR, Norris KC, Kopple JD, Kalantar-Zadeh K: Charlson comorbidity score is a strong predictor of mortality in hemodialysis patients. Int Urol Nephrol 2012;44:1813–1823.

16 Hemmelgarn BR, Manns BJ, Quan H, Ghali WA: Adapting the Charlson Comorbidity Index for use in patients with ESRD. Am J Kidney Dis 2003;42:125–132.

17 Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, Polkinghorne KR, Shankar A, Smith DH, Tonelli M, Warnock DG, Wen CP, Coresh J, Gansevoort RT, Hemmelgarn BR, Levey AS: Comparison of Risk Prediction Using the CKD-EPI Equation and the MDRD Study Equation for Estimated Glomerular Filtration Rate. JAMA 2012;307:1941–1951.

18 Skali H, Uno H, Levey AS, Inker LA, Pfeffer MA, Solomon SD: Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation. Am Heart J 2011;162:548–554.

19 Korhonen PE, Kivelä SL, Aarnio PT, Kautiainen H, Järvenpää S, Kantola IM: Estimating glomerular filtration rate in hypertensive subjects: Comparison of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study equations. Ann Med 2012;44:487–493.

20 Palmer BF: Renal Dysfunction Complicating the Treatment of Hypertension. N Engl J Med 2002;347:1256–1261.

21 Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, Lesti M, Perticucci E, Chakarski IN, Leonardis D, Garini G, Sessa A, Basile C, Alpa M, Scanziani R, Sorba G, Zoccali C, Remuzzi G, REIN-2 Study Group: Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. Lancet 2005;365:939–946.

22 De Nicola L, Provenzano M, Chiodini P, Borrelli S, Garofalo C, Pacilio M, Liberti ME, Sagliocca A, Conte G, Minutolo R: Independent Role of Underlying Kidney Disease on Renal Prognosis of Patients with Chronic Kidney Disease under Nephrology Care. PLoS One 2015;10:e0127071.

23 ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F: Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. N Engl J Med 2010;362:1575–1585.

24 ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C: Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. N Engl J Med 2008;358:1547–1559.

25 Holtkamp FA, de Zeeuw D, Thomas MC, Cooper ME, de Graeff PA, Hillege HJL, Parving HH, Brenner BM, Shahinfar S, Lambers Heerspink HJ: An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. Kidney Int 2011;80:282–287.

26 Ku E, Bakris G, Johansen KL, Lin F, Sarnak MJ, Campese VM, Jamerson K, Gassman JJ, Smogorzewski M, Hsu CY: Acute Declines in Renal Function during Intensive BP Lowering: Implications for Future ESRD Risk. J Am Soc Nephrol 2017;28:2794–2801.

27 SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT: A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;373:2103–2116.

28 Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, Cushman WC, Hawfield AT, Johnson KC, Lewis CE, Oparil S, Rocco MV, Sink KM, Whelton PK, Wright JT Jr, Basile J, Beddhu S, Bhatt U, Chang TI, Chertow GM, et al.: Effects of Intensive BP Control in CKD. J Am Soc Nephrol 2017;28:2812–2823.

29 Magriço R, Bigotte Vieira M, Viegas Dias C, Leitão L, Neves JS: BP Reduction, Kidney Function Decline, and Cardiovascular Events in Patients without CKD. Clin J Am Soc Nephrol 2018;13:73–80.

30 Minutolo R, Gabbai FB, Agarwal R, Chiodini P, Borrelli S, Bellizzi V, Nappi F, Stanzione G, De Nicola L: Assessment of Achieved Clinic and Ambulatory Blood Pressure Recordings and Outcomes During Treatment in Hypertensive Patients With CKD: A Multicenter Prospective Cohort Study. Am J Kidney Dis 2014;64:744–752.

31 Wang C, Zhang J, Li Y, Ma X, Ye Z, Peng H, Lou T: Masked hypertension, rather than white-coat hypertension, has a prognostic role in patients with non-dialysis chronic kidney disease. Int J Cardiol 2017;230:33–39.

32 Gorostidi M, Sarafidis PA, de la Sierra A, Segura J, de la Cruz JJ, Banegas JR, Ruilope LM; Spanish ABPM Registry Investigators: Differences Between Office and 24-Hour Blood Pressure Control in Hypertensive Patients With CKD: A 5, 693-Patient Cross-sectional Analysis From Spain. Am J Kidney Dis 2013;62:285–294.

33 Georgianos PI, Champidou E, Liakopoulos V, Balaskas EV, Zebekakis PE: Home blood pressure–guided antihypertensive therapy in chronic kidney disease: more data are needed. J Am Soc Hypertens 2018; DOI:10.1016/j.jash.2018.02.002.