Original Paper

Evening -Versus Morning- Dosing Drug Therapy for Chronic Kidney Disease Patients with Hypertension: A Systematic Review

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Key Words

Chronic kidney disease • Hypertension • Chronotherapy

Abstract

Background/Aims: There is a strong correlation between non-dipping status and cardiovascular events in chronic kidney disease (CKD) patients. Our study is designed to identify the effect of evening administration of antihypertensive drugs to hypertensive CKD patients. **Methods:** A comprehensive search of Medline, Embase, the Chinese Biomedical Literature Database, Wanfang Data, Chinese National Knowledge Infrastructure, and the Cochrane Central Register of Controlled Trials was performed in July 2014. Concurrent controlled or crossover trials (including randomized and non-randomized experimental trials) designed to evaluate the effects of evening- versus morning-dosing hypertensive drug regimens on clinical outcomes in CKD patients with hypertension were included. All statistical analyses were performed using the RevMan software, which is available free from the Cochrane Collaboration. **Results:** Seven trials involving 1277 patients were identified, and the randomized controlled trials (RCTs) and non-randomized controlled trials (non-RCTs) were classified into two groups. Taking at least one blood pressure-lowering medication at bedtime was not shown to reduce total death ($P=0.056$) or cardiovascular death ($P=0.059$) but was shown to reduce total events ($P<0.001$) and major cardiovascular events ($P<0.001$) in both RCTs and non-RCTs. Compared with a morning dosing regimen, taking antihypertensive drug in the evening significantly lowered nighttime systolic blood pressure (SBP) ($P<0.0001$) and diastolic blood pressure ($P<0.05$) in patients in the RCTs but did not affect blood pressure in patients in the non-RCTs ($P<0.05$). There is limited evidence from one non-RCT that taking an antihypertensive drug (benazepril 10 mg) in the evening did not increase adverse events ($P=0.72$) or withdrawals due to adverse

events ($P=0.64$). **Conclusions:** A regimen of antihypertensive drugs in the evening should be considered for CKD patients with hypertension to lower nighttime blood pressure and help prevent total events and cardiovascular mortality. More studies are needed to verify the results of this study.

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Introduction

Chronic kidney disease (CKD) is a common chronic progressive disease with high prevalence, mortality, and health costs that has increasingly drawn attention as a major public health issue. Hypertension is a major risk factor for the progression of CKD, and it has been significantly associated with the causes and consequences of CKD. In the healthy body, the blood pressure falls 10-20% during the night. Patients with a nocturnal fall $<10\%$ are defined as non-dippers, and those with a paradoxical rise during the night are defined as reverse dippers. Numerous studies [1-6] suggest that non-dipping status or nocturnal hypertension was frequent in patients with CKD and was associated with target organ damage and increased cardiovascular disease (CVD) risk. The aim of antihypertensive therapy is not only to lower blood pressure, but also to restore the circadian rhythm. Chronotherapy aims to support normal rhythms or modify the timing of therapy to achieve maximal efficacy and minimal adverse effects [7]. However, studies of chronotherapy in CKD patients are limited and controversial. Therefore, the objective of this paper is to perform a systematic review of published evidence on the value of evening dosing drug therapy for CKD patients with hypertension.

Materials and Methods

Literature Search

We conducted a systematic review of the available literature in accordance with the QUORUM guidelines for the conduct of meta-analyses of intervention studies [8]. A systematic literature search of Medline (1950-), Embase (1974-), the Chinese Biomedical Literature Database (CBLD, 1978-), Wanfang Data (1964-), National Knowledge Infrastructure (CNKI, 1950-) and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed in July 2014 by professional document retrieval personnel from the Xiang-Ya Medical Library of Central South University using 'chronotherapy', 'bedtime', 'evening time', 'sleep time', 'night time', 'hypertension', 'high blood pressure', 'renal', 'kidney', and 'controlled clinical trial' as the search terms. Reference lists of relevant meta-analyses and reviews were identified. There was no language restriction. All potentially relevant studies were examined in full.

Selection Criteria

Concurrent controlled trials (including randomized and non-randomized experimental trials) with at least 4 weeks' treatment duration and crossover trials whose designs were restricted to 2 interventions and 2 treatment periods were included in our study. Only adult patients (≥ 18 years of age) who satisfied the diagnosis criteria of CKD and hypertension (systolic or diastolic blood pressure ≥ 140 or ≥ 90 mmHg, respectively) were eligible. CKD was defined according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) criteria as follows: (1) kidney damage (structural or functional abnormalities of the kidney, including pathological abnormalities, abnormalities in the composition of the blood or urine, or abnormalities in imaging tests with or without decreased GFR) ≥ 3 months or (2) a GRF < 60 ml/min/1.73 m² for ≥ 3 months with or without kidney damage. Patients with white coat phenomenon and alternating shift workers were excluded. Intervention was defined as ≥ 1 antihypertensive drug administered in the evening (from 5:00 p.m. to 12:00 midnight), including once-daily or twice-daily drug regimens. The control group was matched to the intervention group by drug and dose but with a once-daily morning regimen (5:00 a.m. to 12:00 noon). Antihypertensive drugs were restricted to the following six classes: angiotensin-converting

enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), beta-blockers, diuretics, angiotensin II receptor 'blockers (ARBs), and alpha-blockers.

Quality Assessment

The methodological quality and risk of bias were examined carefully in accordance with the standards of the Cochrane Collaboration [9]. The items were as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases, such as the funding resources. All items were classified as "low risk", "high risk", or "unclear risk". Moreover, the intention-to-treat analysis (ITT) principle was used to evaluate the integrity of the outcome data. The GRADE system [10] was used to grade the quality of evidence and the strength of the recommendations. This system evaluates five main domains for each outcome: limitations of the study design and execution; inconsistency, indirectness, and imprecision of results; and publication bias.

Data Extraction

Two reviewers extracted data from the included studies based on methods (allocation, blinding, follow-up duration), participants (country, randomized number, age, gender, ethnicity, inclusion criteria, exclusion criteria), interventions (grouping, dosages and types of drugs, intervention duration) and outcomes (primary outcomes such as all-cause mortality, CVD mortality and CVD morbidity, and secondary outcomes, such as serious adverse events, overall adverse effects, withdrawals from treatment due to adverse effects, change from baseline in 24-hour/morning/evening mean SBP and DBP by ambulatory BP monitoring). If there were discrepancies, all authors reached a consensus by discussion. All of the obtained data were examined carefully for accuracy. Correspondence with the authors of the included studies was initiated as necessary.

Statistical analysis

All included studies were grouped according to the intervention regimen. The data from each included trial were analyzed using Review Manager (RevMan, Version 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The quantitative analysis was based on intention-to-treat principles as much as possible. Relative risks were calculated for dichotomous clinical outcomes. Blood pressure reductions were calculated before data pooling and then combined using generic inverse variance. Subgroup analyses were performed by grouping the trials into RCTs or non-RCTs. Mild, moderate, and severe heterogeneity were defined by I^2 values of 25%, 50%, and 75%, respectively. If heterogeneity was detected for the outcomes, a random effects model was used. The fail-safe number (N_{fs} 0.05) was used to assess the presence of publication bias [11]. $P \leq 0.05$ was considered statistically significant.

Results

Flow of included studies

A total of 2833 studies were identified by searching Medline, Embase, the CBLD, Wang Fang Data, CNKI, and the Cochrane Central Register of Controlled Trials. After removing duplicate studies, 1791 abstracts were screened. Thirteen relevant full-text articles were assessed for eligibility, of which 7 trials fulfilled the inclusion criteria (Figure 1).

Study characteristics

Three RCTs and four non-RCTs, which provided data on 1277 patients, were included in the systematic review. Six trials [12-17] had a parallel design, and one [18] had a crossover design. The numbers of participants were 16, 60, 70, 80, 661, 60 and 330. The average age of the patients ranged from 36 to 59 years. No trials reported ethnicity. The largest study was conducted in Spain [13], one was conducted in Italy [18], and the remainder of the studies was conducted in China [12, 14-17]. Therefore, it is likely the majority of participants were Caucasian or Asian. Five trials [14-18] administered a once-daily dose of a antihypertensive drug at night or in the morning, and two trials [12, 13] administered ≥ 1 BP-lowering

medication at bedtime or all BP-lowering medications upon waking. The antihypertensive drugs, dosages and dosing times (once-daily or twice-daily drug regimens) among the trials were different, representing substantial heterogeneity. Two trials [12, 13] reported all-cause mortality and cardiovascular outcomes. Five trials [13, 14, 16-18] reported the changes in ambulatory blood pressure from baseline to endpoint. The data for SBP, DBP, and standard error were obtained from tables. One trial [15] reported adverse events (Tables 1-2).

Six trials [19-24] examining the antihypertensive chronotherapy of CKD patients were excluded; the reasons for exclusion are reported in Table 3.

Risk of bias in included studies

Four trials [12, 15-17] were non-randomized, two trials [13, 14] used adequate randomization methods, and one trial [18] did not report random sequence generation. However, no trial reported concealment of allocation. Only one trial [18] was a double-blinded study. One trial [13] was an open-label, blinded-endpoint study. One trial [15] had missing data, which did not influence the results of adverse events. Therefore, none of the studies had incomplete outcome data, selective reporting or other biases. Figures 2 and 3 represent the overall risks of bias detected in the 7 included trials. No heterogeneity was found in this meta-analysis of RCTs, and significant heterogeneity was observed in the meta-analysis of non-RCTs.

All-cause mortality, cardiovascular mortality, and cardiovascular morbidity outcomes.

One RCT [13] and one non-RCT [12] reported data on all-cause mortality and cardiovascular mortality and morbidity. The results of the RCT [13] showed that taking at least one BP-lowering medication at bedtime did not reduce total death ($P=0.056$) or cardiovascular death ($P=0.059$). However, these patients had a significantly lower hazard risk (HR) for total events than those who took all of their medications in the morning (0.31, 95% CI 0.21 to 0.46; $P<0.001$). Bedtime treatment significantly reduced the HRs

Fig. 1. Flowchart for eligible studies.

Table 1. Baseline characteristics of included studies. HTN: hypertension; UAE: urinary albumin excretion; Ccr: Creatinine clearance (ml/min) using Cockcroft-Gault equation; eGFR, estimated GFR (ml/min/1.73 m²) using the MDRD equation; SCR: Serum creatinine; NR: not reported; ABPM: ambulatory blood pressure monitoring; CBPM: clinical blood pressure monitoring. *Data are presented as the mean±SD; # The percentage of urinary albumin excretion≥300 mg/24-hour urine

Design	Portaluppi 1995	Hermida 2011	Wang 2013	Gao 2008	Li 2010	Xiao 2010	Shen 2014
	Randomized cross-over, double-blind study	Randomized parallel, open-label, blinded-endpoint study	Randomized parallel, open-label study	Non-randomized parallel, open-label study	Non-randomized parallel, open-label study	Non-randomized parallel, open-label study	Non-randomized parallel, open-label study
Evening dosing treatment	5 mg isradipine in the evening plus matched placebo in the morning, n=8	≥1 antihypertensive drugs in the evening, n=329	Single daily valsartan (80–320 mg/d) in the evening, n=30	Hyzaar (losartan potassium 50 mg and hydrochlorothiazide 12.5 mg) in the evening (7:00 p.m.), n=30	Benazepril 10 mg in the evening (5:00–7:00 p.m.), n=35	Irbesartan 150 mg in the evening (7:00 p.m.), n=40	≥1 antihypertensive drugs in the evening, n=164
Morning dosing treatment	5 mg isradipine SRO in the morning plus matched placebo in the evening, n=8	All antihypertensive drugs in the morning, n=332	Single daily valsartan (80–320 mg/d) in the morning, n=30	Hyzaar (losartan potassium 50 mg and hydrochlorothiazide 12.5 mg) in the morning (7:00 a.m.), n=30	Benazepril 10 mg in the morning (5:00–7:00 a.m.), n=35	Irbesartan 150 mg in the morning (7:00 a.m.), n=40	All antihypertensive drugs in the morning, n=166
Duration	4 weeks	A median follow-up of 5.4 years; ABPM every 3 months to 1 year	15 months; CBMP every 1 month and ABPM every 3 months	8 weeks	6 months	8 weeks	24–26 months
Outcome	Blood pressure and heart rate data	Total death, CVD morbidity and mortality, blood pressure data (ABPM and clinic BP)	Blood pressure, proteinuria, SCR, urinary sodium excretion, blood lipids, glucose, ultrasonography	Blood pressure difference, nighttime blood pressure decrease rate	Adverse drug events, clinical blood pressure data; renal function	Ambulatory Blood pressure data, nighttime blood pressure decrease rate	Total death, CVD morbidity and mortality
Inclusion Criteria	CKD with HTN, without hemodialysis	≥18 years; CKD with HTN (eGFR<60 ml/min/1.73 m ² or UAE≥30 mg/24-hour urine or both)	18–65 years; CKD with HTN (eGFR<90 but >30 ml/min/1.73 m ² or 24-hour proteinuria >0.5 but <2.0 g or both)	Mild to moderate CKD with HTN, non-dippers	≥18 years of age, CKD with HTN (Scr133–265 μmol/l), clear consciousness without history of mental illness	Mild to moderate CKD with HTN, non-dippers	≥18 years of age, CKD with HTN (eGFR<60 ml/min/1.73m ² , UAE≥30 mg/24-hour urine or both, in at least two occasions≥3 months apart)
No. Of patients	16	661	60	60	70; 5 persons withdrew due to the drug adverse events	80	330
Men, n (%)	10 (62.5%)	396 (59.9%)	36 (60.0%)	37 (61.7%)	35 (53.9%)	51 (63.8%)	197 (59.7%)
Age, years*	56.6	59.2	36	43.2	43.9	40.1	58.5
BMI (Kg/ m ²)*	NR	30.75	23.5	NR	23.2	NR	30.8
Renal function	Ccr 26.4	eGFR 66.2	eGFR 75	NR	Ccr 38.4	NR	eGFR 62
Proteinuria	NR	96 (14.5%)#	1.05g*	NR	2.04g*	NR	48 (14.5%)#
Diabetes, n (%)	0	220 (33.3%)	4 (6.7%)	0	16 (24.6%)	NR	109 (33.0%)

Table 2. Raw outcomes of included studies. NR: not reported. *Data are presented as the mean±SD. # Data are blood pressure differences

		Portaluppi 1995	Hermida 2011	Wang 2013	Gao 2008	Li 2010	Xiao 2010	Shen 2014
No. of patients	Evening	8	329	30	30	35	40	164
	Morning	8	332	30	30	35	40	166
No. of total deaths	Evening	NR	7	NR	NR	NR	NR	7
	Morning	NR	14	NR	NR	NR	NR	13
No. of cardiovascular deaths	Evening	NR	2	NR	NR	NR	NR	2
	Morning	NR	7	NR	NR	NR	NR	7
No. of cardiovascular events	Evening	NR	13	NR	NR	NR	NR	10
	Morning	NR	51	NR	NR	NR	NR	32
24 h or 48 h ambulatory SBP (mmHg)	Evening Before*	161.2±14.8	129±16	134.6±16.0	15±4#	NR	147.5±11.4	NR
	After*	145.6±16.1	112±9	125.4±15.0		NR	124.7±13.8	NR
	Morning Before*	162.1±15.8	126±18	134.9±18.5	14±4#	NR	145.4±12.3	NR
24 h or 48 h ambulatory DBP (mmHg)	After*	146.9±16.1	113±12	126.5±17.8		NR	126.3±11.8	NR
	Evening Before*	96.4±9.3	79±11	79.4±11.7	12±3#	NR	94.4±5.1	NR
	After*	87.4±8.8	70±6	73.1±11.1		NR	82.3±7.6	NR
Daytime ambulatory SBP (mmHg)	Morning Before*	98.0±8.1	77±8	77.4±12.4	11±3#	NR	92.6±7.9	NR
	After*	87.5±8.1	68±7	71.1±11.4		NR	84.1±6.6	NR
	Evening Before*	160.9±14.6	130±16	137.4±16.2	13±5#	NR	158.1±13.7	NR
Daytime ambulatory DBP (mmHg)	After*	149.3±16.6	118±11	129.3±15.2		NR	136.8±7.4	NR
	Morning Before*	162.1±15.7	128±19	137.7±18.4	16±6#	NR	156.6±11.4	NR
	After*	149.2±15.8	116±13	128.3±17.7		NR	126.3±8.5	NR
Nighttime ambulatory SBP (mmHg)	Evening Before*	97.9±9.8	80±11	82.5±12.6	10±3#	NR	97.6±9.3	NR
	After*	90.7±10.2	73±7	76.8±11.9		NR	87.4±10.1	NR
	Morning Before*	99.0±8.6	79±9	80.3±13.0	12±4#	NR	98.3±8.1	NR
Nighttime ambulatory DBP (mmHg)	After*	90.0±8.6	71±6	73.4±11.8		NR	81.4±7.8	NR
	Evening Before*	161.8±16.4	124±16	128.7±18.5	15±5#	NR	138.8±12.0	NR
	After*	138.1±16.2	102±7	116.7±16.8		NR	116.3±10.8	NR
No. of drug adverse events	Morning Before*	162.3±16.8	121±17	129.0±20.8	12±4#	NR	137.9±9.8	NR
	After*	142.1±18.4	107±11	122.6±21.3		NR	128.8±7.9	NR
	Evening Before*	95.4±8.9	75±13	73.0±11.3	13±4#	NR	87.3±8.9	NR
No. of withdrawals due to drug adverse events	After*	80.8±7.3	63±6	65.2±10.5		NR	73.5±7.8	NR
	Morning Before*	96.0±7.6	76±13	71.2±12.3	10±4#	NR	86.5±7.6	NR
	After*	82.2±8.7	63±5	66.3±12.0		NR	82.5±6.7	NR
No. of drug adverse events	Evening	NR	NR	NR	NR	4	NR	NR
	Morning	NR	NR	NR	NR	5	NR	NR
No. of withdrawals due to drug adverse events	Evening	NR	NR	NR	NR	2	NR	NR
	Morning	NR	NR	NR	NR	3	NR	NR

Table 3. Characteristics of excluded studies

Study	Reason for exclusion
Minutolo 2007[21]	Self-control design
Wouden 2009[23]	Intervention (evening (4 mg) or twice-daily dosing (2 mg) of trandolapril) did not meet inclusion criteria.
He 2009[24]	Self-control design
Hermida 2012[20]	Study is present in abstract form using data from 'Hermida 2011'.
Crespo 2013[19]	Cross-sectional design
Rahman 2013[22]	Three-way crossover design

for myocardial infarction ($P=0.005$), angina pectoris ($P<0.001$), coronary revascularization ($P=0.004$), and heart failure ($P<0.001$). Similarly, the results of the non-RCT [12] revealed that taking at least one BP-lowering medication at bedtime did not

Fig. 2. Risk of bias graph according to recommendations from the Cochrane Collaboration.

reduce death from all causes ($P=0.18$) or cardiovascular mortality ($P=0.12$). However, these patients had a significantly lower HR for cardiovascular morbidity than those who took all of their medications in the morning (0.32, 95% CI 0.16 to 0.62; $P<0.001$).

Blood pressure outcomes

The analysis of the mean difference in 24-hour blood pressure from the RCTs showed that evening dosing regimen reduced 24-hour SBP by 0.81 mmHg (95% CI -1.60 to 3.22, $P=0.51$) and increased 24-hour DBP by 0.05 mmHg (95% CI -1.56 to 1.67, $P=0.95$). There was no statistically significant difference between the dosing regimens in reducing daytime SBP (95% CI -1.25 to 3.60, $P=0.34$) or daytime DBP (95% CI -0.51 to 2.90, $P=0.17$). The analysis of the mean difference in nighttime blood pressure found that evening dosing lowered the nighttime SBP by 5.88 mmHg (95% CI -8.59 to -3.16, $P<0.0001$) and nighttime DBP by 2.49 mmHg (95% CI -4.14 to -0.84, $P=0.003$). Heterogeneity was not observed ($I^2=0\%$).

The analysis of the mean difference in blood pressure from the non-RCTs showed that the evening dosing regimen reduced 24-hour SBP by 1.33 mmHg (95% CI -3.22 to 10.57, $P=0.17$), 24-hour DBP by 1.94 mmHg (95% CI -4.39 to 0.51, $P=0.12$), nighttime SBP by 8.01 mmHg (95% CI -18.20 to 2.17, $P=0.12$), and nighttime DBP by 6.25 mmHg (95% CI -12.91 to 0.40, $P=0.07$). Similarly to the RCTs, there was no statistically significant difference between the dosing regimens in reducing daytime SBP (95% CI -0.19 to 11.49, $P=0.06$) or daytime DBP (95% CI -0.54 to 8.58, $P=0.08$) (Figures 4-9). Significant heterogeneity was observed among the trials ($I^2=0\%$, 55%, 77%, 78%, 94%, and 91%).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gao 2008	+	+	+	+	+	+	?
Hermida RC 2011	+	?	+	+	+	+	+
Li 2010	+	+	+	+	+	+	?
Portaluppi 1995	?	?	+	+	+	+	?
Shen 2014	+	+	+	?	+	+	?
Wang 2013	+	+	+	+	+	+	?
Xiao 2010	+	+	+	+	+	+	?

Fig. 3. Risk of bias summary according to recommendations from the Cochrane Collaboration.

Fig. 4. Forest plot of comparison: Evening versus morning dosing regimen: 24-hour systolic ambulatory blood pressure.

Fig. 5. Forest plot of comparison: Evening versus morning dosing regimen: 24-hour diastolic ambulatory blood pressure.

Fig. 6. Forest plot of comparison: Evening versus morning dosing regimen: daytime systolic ambulatory blood pressure.

Fig. 7. Forest plot of comparison: Evening versus morning dosing regimen: daytime diastolic ambulatory blood pressure.

Drug-related Adverse Events

Only one trial [15] reported adverse events and withdrawals due to adverse events. Taking an ACEI (benazepril 10 mg) in the evening did not increase adverse events ($P=0.72$) or withdrawals due to adverse events ($P=0.64$).

Fig. 8. Forest plot of comparison: Evening versus morning dosing regimen: nighttime systolic ambulatory blood pressure.

Fig. 9. Forest plot of comparison: Evening versus morning dosing regimen: nighttime diastolic ambulatory blood pressure.

Discussion

Chronic kidney disease (CKD) is a worldwide public health problem that affects millions of people from all racial and ethnic groups. In well-developed countries, approximately 7% of adults who are older than 30 years suffer from CKD [25]. In China, the morbidity of CKD is approximately 10.8%, and its prevalence is estimated to be 119.5 million [26]. In Africa, for example, the prevalence of CKD in Senegal is 22%, while that in Congo is as high as 36% [27]. Hypertension is a major risk factor for the progression of CKD and has been strongly associated with the causes and consequences of CKD. Hypertension is present in 36% to 84.1% of patients with CKD and contributes to progression toward end-stage renal disease (ESRD) and cardiovascular events [28].

Circadian variation is commonly seen in healthy people; aberration in these biological rhythms is an early sign of disease. With the widespread use of ambulatory blood pressure monitoring, nocturnal blood pressure has received increasing attention. In the healthy body, the blood pressure falls 10-20% during the night. Patients with a nocturnal fall <10% are defined as non-dippers, and those with a paradoxical rise during the night are defined as reverse dippers. Non-dipping status or nocturnal hypertension was frequent in patients with CKD, even in early renal damage patients [29]. In the African American Study of Kidney Disease and Hypertension (a cross-sectional 24 h ABPM study of 617 patients with CKD [eGFR20-65 ml/1.73 m²]), 80.7% (498/617) of participants had a non-dipping or reverse

dipping profile [30]. In addition, nocturnal hypertension could lead to the misdiagnosis of hypertension, as 70% patients with controlled clinical blood pressure were shown to have masked hypertension [30]. A multicenter prospective observational study [31] that included 10,271 participants showed that the prevalence of non-dippers was significantly higher in populations with CKD than in those without CKD (60.6% vs. 43.2%; $P < 0.001$). And among the uncontrolled hypertensive patients with CKD, 90.7% had nocturnal hypertension. What's more, with the deterioration of renal function, the proportion of patients with non-dipping status significantly increased across the progressive stages of the disease.

Non-dipping status or nocturnal hypertension was associated with target organ damage and increased cardiovascular disease (CVD) risk [4, 31-40]. Nighttime systolic blood pressure ≥ 125 mmHg may increase the incidence of cardiovascular events (HR = 2.52, 95% CI 1.77-9.02) and end-stage renal disease (HR = 1.87, 95% CI 1.41-4.57) [1]. In a trial conducted by Drawz et al., the authors retrospectively studied 1085 subjects over a median follow-up period of 4.3 years. In total, 266 subjects died, 22 developed ESRD, 99 had a 50% decline in GFR, and 136 developed MI. Moreover, the results showed that the adjusted hazard ratios associated with a 10 mmHg increase in nighttime systolic BP were 1.04 (95% CI, 0.93 to 1.16) for death, 1.31 (0.95 to 1.80) for ESRD, 1.26 (1.08 to 1.47) for a 50% decline in GFR, 1.07 (0.92 to 1.23) for MI, and 1.12 (1.03 to 1.23) for a composite of death, ESRD, or a 50% decline in GFR [32]. After the follow-up period (median 10.7 years) for 8711 individuals, the results revealed that isolated nocturnal hypertension (normal clinic blood pressure but nocturnal hypertension) was an independent risk factor for all cause mortality and cardiovascular events [41]. After a mean follow-up of 5.6 years, one study revealed a 17% reduction in cardiovascular risk for every 5-mmHg decrease in the mean systolic blood pressure during sleep ($P < 0.001$). The reduction was independent of changes in any other ambulatory blood pressure parameter [37, 42]. In summary, nighttime blood pressure is a highly significant predictor of cardiovascular events and a novel therapeutic target that requires accurate evaluation by ABPM.

Although the mechanisms by which this effect take place are still speculative [43], this finding has led to a speculation that antihypertensive medication targeted for nighttime blood pressure control, in addition to the medication that provides 24-hour BP control, would result in a significant reduction of cardiovascular events in CKD patients with hypertension. In other words, antihypertensive medication is considered to lower BP consistently as well as reduce inappropriate elevation of blood pressure that may cause an additional cardiovascular risk. Six main classes of antihypertensive drugs (ACEIs, CCBs, β -blockers, diuretics, ARBs, and α -blockers) have been used worldwide. These drugs are traditionally administered once daily in the morning based on the results of many clinical trials showing advantages from morning dosing in reducing the risk of cardiovascular diseases. Moreover, this approach improves patients' adherence to the long-term treatment [44]. However, conventional long-acting antihypertensive medications or sustained-release tablet drugs have been administered without considering the circadian rhythm of blood pressure.

Chronotherapy is defined as a type of purposeful treatment that enhances the effectiveness and tolerance of a drug by choosing the optimal dosing time [7]. Although this approach has been used for several diseases, such as hypertension, osteoporosis, dyslipidemia, and malignant diseases, it is still a new concept for many physicians. Most of the published studies have focused on the effect of evening dosing on essential hypertensive patients rather than CKD patients. In primary hypertension, there have been multiple studies demonstrating the efficacy of chronotherapy [45-48]. Chronotherapy also may be important for CKD patients.

However, studies about chronotherapy in CKD patients are limited and controversial. Among the excluded trials, the results of a three-way randomized crossover trial [22]

Table 4. GRADE Analysis: Evening versus morning dosing regimen, outcome for CKD patients with hypertension. *The basis for the assumed risk: 1) Several included trials were non-randomized; 2) It's a non-RCT; 3) Publication of evidence is limited to two trials; 4) N_{fs} 0.05 values calculated by the fail-safe method were small; 5) Publication of evidence is limited to one trial; 6) Two studies consistently show evidence of RR < 0.5. #GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of the effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate.

Clinical outcome	Participants (studies); follow-up	Risk of bias*	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding would change the effect	Dose response grade	Overall quality of evidence#
Total death; Cardiovascular mortality	991 (2 studies); 0.5-8.4 years	Very serious ¹	NO	NO	NO	Strongly suspected ³	NO	NO	NO	++-;
Cardiovascular morbidity	991 (2 studies); 0.5-8.4 years	Very serious ¹	NO	NO	NO	Strongly suspected ³	Large ⁶	NO	NO	++-; Low
Ambulatory blood pressure	877 (5 studies); 1 month-1 year	Very serious ¹	NO	NO	NO	Strongly suspected ⁴	NO	NO	NO	++-;
Drug adverse events	70 (1 study); 6 months	Very serious ²	NO	NO	NO	Strongly suspected ⁵	NO	NO	NO	++-; Very low

showed that, taking drugs in the evening did not significantly reduce nocturnal hypertension compared to morning dosing of antihypertensive medications. The results of cross-sectional study [19] evaluated 2659 patients revealed that the prevalence of non-dipping was significantly higher when all hypertension medications were ingested upon awakening (68.3%) than when ≥ 1 of them was ingested at bedtime (54.2%; $P < 0.001$ between groups), and even further attenuated (47.9%) when all of them were ingested at bedtime ($P < 0.001$). In an uncontrolled 8-week study [21], Minutolo et al. demonstrated that with administration of antihypertensive medications at night, the night/day ratio of mean ambulatory blood pressure decreased in 93.7% of patients, with normal circadian rhythm restored in 87.5%. Moreover, proteinuria also was reduced with evening administration of antihypertensive drugs.

We therefore presented a comprehensive review and performed a meta-analysis of antihypertensive chronotherapy in CKD patients. Only three RCTs and four non-RCTs were eligible for this systematic review. Our results from RCTs have shown that evening dosing could significantly lower nighttime blood pressure and could provide 24 h and daytime blood pressure control similar to that provided by morning dosing. Given the high risks of bias and limited sample sizes, it is reasonable to suggest that evening dosing does not influence ambulatory blood pressure compared with morning dosing for patients in non-RCTs. Limited evidence from two eligible studies [12, 13] showed that taking ≥ 1 out of six types of traditional antihypertensive drugs in the evening could reduce cardiovascular morbidity. One study reported that an evening dosing regimen did not increase the incidence of adverse effects or withdrawals due to adverse effects compared to morning dosing.

However, the fail-safe numbers were small (the N_{fs} 0.05 values for 24 h systolic/diastolic blood pressure, daytime systolic/diastolic blood pressure, and

nighttime systolic/diastolic blood pressure for RCTs and non-RCTs were 3, 6, 6, 4, 9, 2, 4, 1, 6, and 5, respectively). One to nine additional studies showing no effect for the relationship between evening and morning dosing regimens would be required to change these results. The fail-safe numbers of nighttime systolic/diastolic blood pressure for the non-RCTs were acceptable (N_{fs} 0.05 values of 20 and 21).

The GRADE analysis of the quality of the included studies showed the strength of evidence for total death, cardiovascular death, change in ambulatory blood pressure, and drug-related adverse events was 'very low' owing due to the presence of potential bias and publication bias. Moreover, due to the large effect, the strength of the evidence for cardiovascular morbidity was 'low' (Table 4).

The present analysis has several limitations. Due to the limited number of included studies, this review is not able to determine the effects of blood pressure lowering for specific drug classes or for different stages of CKD. In addition, the results do not show any differences in cardiovascular events caused by different drug classes or drug combinations.

Conclusions

Regimens of antihypertensive drug in the evening should be considered for CKD patients with hypertension to lower their nighttime blood pressure and to prevent total events and cardiovascular mortality. More double-blinded randomized controlled trials for CKD patients (including the patients with end-stage renal disease) are needed to evaluate the administration time-related effects of different antihypertensive drug classes given as mono-therapies on mortality and cardiovascular morbidity, with long-term follow-up data for at least 3-5 years.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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References

- 1 Minutolo R, Agarwal R, Borrelli S: Prognostic role of ambulatory blood pressure measurement in patients with nondialysis chronic kidney disease. *Arch Intern Med* 2011;171:1090-1098.
- 2 Torffvit O: The effect of achieving a systolic blood pressure of 140 mmHg. A prospective study of ambulatory measurements in type 2 diabetic patients with nephropathy. *J Diab Complications* 2012;26:540-545.

- 3 Hermida RC, Smolensky MH, Ayala DE: 2013 ambulatory blood pressure monitoring recommendations for the diagnosis of adult hypertension, assessment of cardiovascular and other hypertension-associated risk, and attainment of therapeutic goals. *Chronobiol Int* 2013;30:355-410.
- 4 Agarwal R, Andersen MJ: Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. *Kidney Int* 2006;69:1175-1180.
- 5 Gabbaï FB, Rahman M, Hu B: Relationship between ambulatory BP and clinical outcomes in patients with hypertensive CKD. *Clin J Am Soc Nephrol* 2012;7:1770-1776.
- 6 Ivanovic BA, Tadic MV, Celic VP: To dip or not to dip? The unique relationship between different blood pressure patterns and cardiac function and structure. *J Hum Hypertens* 2013;2013:62-70.
- 7 Fujimura A: Chronotherapy--present and future. *Nihon Rinsho* 2013;71:2097-2101.
- 8 Moher D, Cook DJ, Eastwood S: Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Quality of Reporting of Meta-analyses*. *Lancet* 1999;354:1896-1900.
- 9 Green S: Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.
- 10 Brozek J, Oxman AD, Schünemann HJ: GRADEpro (computer program) version 3.2 for windows. 2012.
- 11 Mai JZ, Li H, Fang JQ, Liu XQ, Rao XX: Estimation of fail-safe number in meta-analysis. *J Evidence Based Med* 2006;6:297-303.
- 12 Shen Y, Lu X: Clinical study of taking medicine at bedtime for CKD patients to reduce cardiovascular events. *Mod Instrum Med Treatment* 2014;20: 89-91.
- 13 Hermida RC, Ayala DE, Mojon A, Fernandez JR: Bedtime dosing of antihypertensive medications reduces cardiovascular risk in CKD. *J Am Soc Nephrol* 2011;22:2313-2321.
- 14 Wang C, Zhang J, Liu X: Effect of valsartan with bedtime dosing on chronic kidney disease patients with nondipping blood pressure pattern. *J Clin Hypertens (Greenwich)* 2013;15:48-54.
- 15 Li X: Clinical Observation of Benazepril with suitalbe time on the progression of chronic renal failure. Hubei University of Chinese Medicine, Wuhan, Hubei, China, 2010.
- 16 Xiao X, Hu W: Effect of Irbesartan with different time on blood pressure in patients with renal hypertension. *Med J West China* 2010;22: 2212-213.
- 17 Gao Y, Yang S, Yan H, Wang R: Effect of losartan potassium/hydrochlorothiazide therapy with different time on blood pressure in patients with renal hypertension. *Clin Focus* 2008;23:810-811.
- 18 Portaluppi F, Vergnani L, Manfredini R: Time-dependent effect of isradipine on the nocturnal hypertension in chronic renal failure. *Am J Hypertens* 1995;8:719-726.
- 19 Crespo JJ, Pineiro L, Otero A, Castineira C, Rios MT, Regueiro A, Mojon A, Lorenzo S, Ayala DE, Hermida RC: Administration-time-dependent effects of hypertension treatment on ambulatory blood pressure in patients with chronic kidney disease. *Chronobiol Int* 2013;30:159-175.
- 20 Hermida RC, Ayala DE, Mojon A, Fernández JR: Use of ≥ 1 antihypertensive drug at bedtime reduced CV events more than use of all drugs in the morning in CKD. *J Am Soc Nephrol* 2011;22:2313-21.
- 21 Minutolo R, Gabbaï FB, Borrelli S, Scigliano R, Trucillo P, Baldanza D, Laurino S, Mascia S, Conte G, De Nicola L: Changing the timing of antihypertensive therapy to reduce nocturnal blood pressure in CKD: An 8-week uncontrolled trial. *Am J Kidney Dis* 2007;50:908-917.
- 22 Rahman M, Greene T, Phillips RA, Agodoa LY, Bakris GL, Charleston J, Contreras G, Gabbaï F, Hiremath L, Jamerson K, Kendrick C, Kusek JW, Lash JP, Lea J, Miller ER, 3rd, Rostand S, Toto R, Wang X, Wright JT, Jr., Appel LJ: A trial of 2 strategies to reduce nocturnal blood pressure in blacks with chronic kidney disease. *Hypertension* 2013;61:82-88.
- 23 Wouden EA, Vogt L, Henning RH, Navis GJ, Zeeuw D, Hemmelder MH: Changing the trandolapril dosage regimen does not affect the proteinuria-lowering effect of ace inhibition in non-diabetic renal disease; Wetenschappelijk Platform 2009;3:156-159.
- 24 He Z: Analysis of Chronotherapy in elderly hypertension of early renal damage. *Chin Commun Doctors* 2009;11:12.
- 25 Braun LA, Sood V, Hogue S: High burden and unmet patient needs in chronic kidney disease. *Int J Nephrol Renovasc Dis* 2012;5:151-163.
- 26 Zhang L, Wang F, Wang L: Prevalence of chronic kidney disease in china: A cross-sectional survey. *Lancet* 2012;379:815-822.
- 27 Sumaili EK, Cohen EP, Zinga CV: High prevalence of undiagnosed chronic kidney disease among at-risk population in kinshasa, the democratic republic of Congo. *BMC Nephrology* 2009;10:18.

- 28 Tedla FM, Brar A, Browne R: Hypertension in chronic kidney disease: Navigating the evidence. *Int J Hypertens* 2011;2011:132405.
- 29 Kuang Z: Early Risk Assessment and Differences of Curative Effect in Hypertensive Patients with Renal Damage. Central South University, Changsha, Hunan, China, 2014.
- 30 Pogue V, Rahman M, Lipkowitz M: Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. *Hypertension* 2009;53:20-27.
- 31 Mojón A, Ayala DE, Piñeiro L: Comparison of ambulatory blood pressure parameters of hypertensive patients with and without chronic kidney disease. *Chronobiol Int* 2013;30:145-158.
- 32 Drawz PE, Rosenthal N, Babineau DC: Nighttime hospital blood pressure-a predictor of death, ESRD, and decline in GFR. *Ren Fail* 2010;32:1036-1043.
- 33 Agarwal R: Ambulatory blood pressure and cardiovascular events in chronic kidney disease. *Semin Nephrol* 2007;27:538-543.
- 34 Agarwal R: Ambulatory blood pressure monitoring trumps estimated glomerular filtration rate in predicting cardiovascular risk in low-risk populations. *Hypertension* 2013;61:14-15.
- 35 Agarwal R, Andersen MJ: Blood pressure recordings within and outside the clinic and cardiovascular events in chronic kidney disease. *Am J Nephrol* 2006;26:503-510.
- 36 Cha RH, Kim S, Ae Yoon S, Ryu DR, Eun Oh J, Han SY, Young Lee E, Ki Kim D, Kim YS: Association between blood pressure and target organ damage in patients with chronic kidney disease and hypertension: results of the APRODiTe study. *Hypertens Res* 2014;37:172-178.
- 37 Hermida RC, Ayala DE, Mojon A, Fernandez JR: Decreasing sleep-time blood pressure determined by ambulatory monitoring reduces cardiovascular risk. *J Am Coll Cardiol* 2011;58:1165-1173.
- 38 Redon J: The importance of 24-hour ambulatory blood pressure monitoring in patients at risk of cardiovascular events. *High Blood Press Cardiovasc Prev* 2013;20:13-18.
- 39 Gabbai FB, Rahman M, Hu B, Appel LJ, Charleston J, Contreras G, Faulkner ML, Hiremath L, Jamerson KA, Lea JP, Lipkowitz MS, Pogue VA, Rostand SG, Smogorzewski MJ, Wright JT, Greene T, Gassman J, Wang X, Phillips RA, African American Study of Kidney D, Hypertension Study G: Relationship between ambulatory BP and clinical outcomes in patients with hypertensive CKD. *Clin J Am Soc Nephrol* 2012;7:1770-1776.
- 40 Minutolo R, Agarwal R, Borrelli S, Chiodini P, Bellizzi V, Nappi F, Cianciaruso B, Zamboli P, Conte G, Gabbai FB, De Nicola L: Prognostic role of ambulatory blood pressure measurement in patients with nondialysis chronic kidney disease. *Arch Intern Med* 2011;171:1090-1098.
- 41 Fan HQ, Li Y, Thijs L, Hansen TW, Boggia J, Kikuya M, Bjorklund-Bodegard K, Richart T, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Imai Y, Ibsen H, O'Brien E, Wang J, Staessen JA: Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. *J Hypertens* 2010;28:2036-2045.
- 42 Hermida RC, Ayala DE, Fernández RJ, Mojón A: Sleep-time blood pressure: Prognostic value and relevance as a therapeutic target for cardiovascular risk reduction. *Chronobiol Int* 2013;30:68-86.
- 43 Firsova OBD: Circadian regulation of renal function and potential role in hypertension. *Curr Opin Nephrol Hypertens* 2013;22:439-444.
- 44 Waeber B, Burnier M, Brunner HR: Compliance with antihypertensive therapy. *Clin Exp Hypertens* 1999;21:973-985.
- 45 Hermida RC, Ayala DE, Chayan L, Mojon A, Fernandez JR: Administration-time-dependent effects of olmesartan on the ambulatory blood pressure of essential hypertension patients. *Chronobiol Int* 2009;26:61-79.
- 46 Hermida RC, Ayala DE, Fontao MJ, Mojon A, Alonso I, Fernandez JR: Administration-time-dependent effects of spirapril on ambulatory blood pressure in uncomplicated essential hypertension. *Chronobiol Int* 2010;27:560-574.
- 47 Hermida RC, Calvo C, Ayala DE: Administration time-dependent effects of valsartan on ambulatory blood pressure in elderly hypertensive subjects. *Chronobiol Int* 2005;22:755-776.
- 48 Zhao P, Xu P, Wan C, Wang Z: Evening versus morning dosing regimen drug therapy for hypertension (review). *Cochrane Database Syst Rev* 2011;10:1-65.