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

Xing Liu a  Xinyao Liu a  Wei Huang a  Sunnar Leo a  Ying Li b  Meilin Liu c  Hong Yuan a,b

a Department of Cardiology, the Third Xiang-Ya Hospital, Central South University; b Center of Clinical Pharmacology, Central South University, Changsha, Hunan; c Department of Gerontology, the First Hospital of Beijing University, Beijing, China

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
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.

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

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 GFR <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 to 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 I² values of 25%, 50%, and 75%, respectively. If heterogeneity was detected for the outcomes, a random effects model was used. The fail-safe number (Nfs 0.05) was used to assess the presence of publication bias [11]. P ≤ 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 an 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.
**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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evening dosing treatment</strong></td>
<td>Randomized crossover, double-blind study</td>
<td>Randomized parallel, open-label, blinded-endpoint study</td>
<td>Single daily valsartan (80-320 mg/d) in the evening, n=329</td>
<td>Non-randomized parallel, open-label study</td>
<td>Non-randomized parallel, open-label study</td>
<td>Non-randomized parallel, open-label study</td>
<td>Non-randomized parallel, open-label study</td>
</tr>
<tr>
<td>5 mg isradipine in the evening plus matched placebo in the morning, n=8</td>
<td>15 months; CBPM every 1 month and ABPM every 3 months</td>
<td>8 weeks</td>
<td>Blood pressure, proteinuria, SCR, urinary sodium excretion, blood lipids, glucose, ultrasonography</td>
<td>Blood pressure difference, nighttime blood pressure decrease rate</td>
<td>Adverse drug events, clinical blood pressure data; renal function</td>
<td>Ambulatory Blood pressure data, nighttime blood pressure decrease rate</td>
<td>Total death, CVD morbidity and mortality</td>
</tr>
<tr>
<td><strong>Morning dosing treatment</strong></td>
<td>5 mg isradipine SR in the morning plus matched placebo in the evening, n=332</td>
<td>Single daily valsartan (80-320 mg/d) in the morning, n=30</td>
<td>Hyaar (losartan potassium 50 mg and hydrochlorothiazide 12.5 mg) in the evening (7:00 p.m.), n=30</td>
<td>Hyaar (losartan potassium 50 mg and hydrochlorothiazide 12.5 mg) in the morning (7:00 a.m.), n=30</td>
<td>Benazepril 10 mg in the evening (5:00-7:00 p.m.), n=35</td>
<td>Irbesartan 150 mg in the evening (7:00 p.m.), n=40</td>
<td>All antihypertensive drugs in the morning, n=166</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>4 weeks</td>
<td>A median follow-up of 5.4 years; ABPM every 3 months to 1 year</td>
<td>15 months; CBPM every 1 month and ABPM every 3 months</td>
<td>Blood pressure, proteinuria, SCR, urinary sodium excretion, blood lipids, glucose, ultrasonography</td>
<td>Blood pressure difference, nighttime blood pressure decrease rate</td>
<td>Adverse drug events, clinical blood pressure data; renal function</td>
<td>Ambulatory Blood pressure data, nighttime blood pressure decrease rate</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Blood pressure and heart rate data</td>
<td>Blood pressure, proteinuria, SCR, urinary sodium excretion, blood lipids, glucose, ultrasonography</td>
<td>Blood pressure, proteinuria, SCR, urinary sodium excretion, blood lipids, glucose, ultrasonography</td>
<td>Blood pressure difference, nighttime blood pressure decrease rate</td>
<td>Adverse drug events, clinical blood pressure data; renal function</td>
<td>Ambulatory Blood pressure data, nighttime blood pressure decrease rate</td>
<td>Total death, CVD morbidity and mortality</td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td>CKD with HTN, without hemodialysis</td>
<td>CKD with HTN (eGFR&lt;60 ml/min/1.73 m² or UAE&gt;30 mg/24 hour urine or both)</td>
<td>CKD with HTN (eGFR&lt;90 but &gt;30 ml/min/1.73 m² or 24-hour proteinuria &gt;0.5 but &lt;2.0 g or both)</td>
<td>Mild to moderate CKD with HTN, non-dippers</td>
<td>Mild to moderate CKD with HTN, non-dippers</td>
<td>Mild to moderate CKD with HTN, non-dippers</td>
<td>Mild to moderate CKD with HTN, non-dippers</td>
</tr>
<tr>
<td>No. Of patients</td>
<td>16 (62.5%)</td>
<td>661</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>80</td>
<td>330</td>
</tr>
<tr>
<td><strong>Men, n (%)</strong></td>
<td>10 (62.5%)</td>
<td>36 (60.0%)</td>
<td>36 (61.7%)</td>
<td>35 (53.9%)</td>
<td>43.9</td>
<td>35 (63.8%)</td>
<td>197 (59.7%)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>56.6</td>
<td>59.2</td>
<td>56.3</td>
<td>53.9</td>
<td>40.1</td>
<td>30.8</td>
<td>30.8</td>
</tr>
<tr>
<td><strong>BMI (Kg/ m²)</strong></td>
<td>NR</td>
<td>36.75</td>
<td>23.5</td>
<td>23.2</td>
<td>23.2</td>
<td>23.4</td>
<td>23.4</td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td>Creatinine 26.4</td>
<td>eGFR 66.2</td>
<td>eGFR 75</td>
<td>Creatinine 38.4</td>
<td>2.0mg/dL</td>
<td>Creatinine 62</td>
<td>eGFR 62</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>NR</td>
<td>96 (14.5%)</td>
<td>1.05%</td>
<td>NR</td>
<td>2.0%</td>
<td>48 (14.5%)</td>
<td>48 (14.5%)</td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>0</td>
<td>220 (33.3%)</td>
<td>4 (6.7%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Liu/Liu/Huang/Sunnar/Li/Liu/Yuan: Chronotherapy for CKD with Hypertensive Patients

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minutolo 2007[21]</td>
<td>Self-control design</td>
</tr>
<tr>
<td>Wouden 2009[23]</td>
<td>Intervention (evening [4 mg] or twice-daily dosing [2 mg] of trandolapril) did not meet inclusion criteria.</td>
</tr>
<tr>
<td>Ho 2009[24]</td>
<td>Self-control design</td>
</tr>
<tr>
<td>Crespo 2013[19]</td>
<td>Cross-sectional design</td>
</tr>
<tr>
<td>Rahman 2013[22]</td>
<td>Three-way crossover design</td>
</tr>
</tbody>
</table>

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

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
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 \( (0.32, 95\% \text{ CI } 0.16 \text{ to } 0.62; P < 0.001) \).

**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 \( (95\% \text{ CI } -1.60 \text{ to } 3.22, P = 0.51) \) and increased 24-hour DBP by 0.05 mmHg \( (95\% \text{ CI } -1.56 \text{ to } 1.67, P = 0.95) \). There was no statistically significant difference between the dosing regimens in reducing daytime SBP \( (95\% \text{ CI } -1.25 \text{ to } 3.60, P = 0.34) \) or daytime DBP \( (95\% \text{ CI } -0.51 \text{ to } 2.90, P = 0.17) \). The analysis of the mean difference in nighttime blood pressure found that evening dosing lowered the nighttime SBP by 5.88 mmHg \( (95\% \text{ CI } -8.59 \text{ to } -3.16, P < 0.0001) \) and nighttime DBP by 2.49 mmHg \( (95\% \text{ CI } -4.14 \text{ to } -0.84, P = 0.003) \). 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 \( (95\% \text{ CI } -3.22 \text{ to } 10.57, P = 0.17) \), 24-hour DBP by 1.94 mmHg \( (95\% \text{ CI } -4.39 \text{ to } 0.51, P = 0.12) \), nighttime SBP by 8.01 mmHg \( (95\% \text{ CI } -18.20 \text{ to } 2.17, P = 0.12) \), and nighttime DBP by 6.25 mmHg \( (95\% \text{ CI } -12.91 \text{ to } 0.40, P = 0.07) \). Similarly to the RCTs, there was no statistically significant difference between the dosing regimens in reducing daytime SBP \( (95\% \text{ CI } -0.19 \text{ to } 11.49, P = 0.06) \) or daytime DBP \( (95\% \text{ CI } -0.54 \text{ to } 8.58, P = 0.08) \) (Figures 4-9). Significant heterogeneity was observed among the trials \( (I^2 = 0\%, 55\%, 77\%, 78\%, 94\%, \text{ and } 91\%) \).
### 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 ($P=0.64$).
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 [eGFR ≥ 20–65 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]
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%; \( P < 0.001 \)) and even further attenuated (47.9%) when all of them were ingested at bedtime. 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 56.8% of patients, while proteinuria also was reduced with evening administration of antihypertensive drugs.

We therefore presented a comprehensive review and performed a meta-analysis of antihypertensive chronic therapy 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 to morning dosing for patients in non-RCTs. Limited evidence from two eligible studies [12, 13] showed that taking \( \geq 1 \) out of six types of traditional antihypertensive medications did not increase the incidence of adverse events or withdrawals due to adverse effects compared to morning dosing. However, the fail-safe numbers were small (the \( N_{fs} \) values for 24 h systolic/diastolic blood pressure, daytime systolic/diastolic blood pressure, and ambulatory blood pressure were 28, 25, and 26, respectively). The results from RCTs have shown that evening dosing could provide 24 h and daytime blood pressure control similar to that provided by morning dosing. Furthermore, proteinuria also was reduced with evening administration of antihypertensive drugs. 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) \( N_{fs} \) 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.
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 (Nfs 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.

Acknowledgments

We wish to thank the Cochrane-style Systematic Review/Meta-analysis Training Course and Xia Jun, a Cochrane Systematic Review author from the University of Nottingham, who gave useful suggestions.

The Study was supported by the National Science and Technology Major Projects (No. 2012ZX09303014001), the National Key Technology R&D Program (No. 2012BAI37B05), and the Project of Technology Department of Hunan Province (No. 2013TZ2014, No. 2011SK3240).

References


Liu/Liu/Huang/Sunnar/Li/Liu/Yuan: Chronotherapy for CKD with Hypertensive Patients


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.


10 Brozek J, Oxman AD, Schünemann HJ: GRADEpro (computer program) version 3.2 for windows. 2012.


15 Li X: Clinical Observation of Benazepril with suitable time on the progression of chronic renal failure. Hubei University of Chinese Medicine, Wuhan, Hubei, China, 2010.


