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P.M. Dosing Outcomes of ACE Inhibitors or Angiotensin II Receptor Blockers in Hypertension Versus P.M. Dosing in Hypertension with Comorbidities

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by

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Abstract

The purpose of this research is to compare p.m. dosing outcomes of angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs) in those with hypertension and hypertension with chronic kidney disease and diabetes. In this review, three databases were utilized including PubMed, ClinicalKey, and DynaMed with a time frame of 15 years. Studies chosen for review were peer reviewed, and included randomized control trials, systematic reviews, meta-analyses, and a preclinical animal trial. There were several studies excluded because they did not focus on ACE inhibitors or ARBs, or they did not focus on the disease processes intended for research in this project. Other studies that included dosing ACE inhibitors or ARBs at night and in the morning per participant were also excluded because this project focuses on the effects of using one methodology verses the other. Therefore 17 articles met the final criteria. The research shows evidence of reduced blood pressures throughout the night and into the next day, decreased proteinuria, and decreased cardiovascular events when dosing ACE inhibitors or ARBs at night, or dosing at least one antihypertensive medication at night. This research shows beneficial evidence and no documented adverse patient reactions when dosing ACE inhibitors or ARBs at night. However, further research needs to be conducted with larger patient populations to make official recommendations in those with hypertension and hypertension with diabetes or chronic kidney disease.

Keywords: chronotherapy in hypertension, chronotherapy in hypertension with CKD, chronotherapy in diabetes, chronotherapy of ACE inhibitors, chronotherapy of angiotensin II receptor blockers.

Introduction

As more discoveries are being made about the intricate details of what occurs during the sleep cycle that is part of our circadian rhythm, chronotherapy research is being done that specifically targets the mechanisms that take place during that time, allowing medications to be more effective and beneficial. In patients with hypertension and hypertension with other comorbidities, such as diabetes and chronic kidney disease (CKD), dosing angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs) at night may prevent blood pressure from spiking during the early morning hours that could initiate myocardial infarctions, strokes, increase kidney damage, and the risk for further diabetic complications. The purpose of this study is to compare p.m. dosing of ACE inhibitors or ARBs in those with hypertension versus those with hypertension with diabetes or CKD, to determine any beneficial outcomes in that dosing schedule.

Statement of the Problem

According to the Center of Disease Control and Prevention (2017), nearly half a million deaths in the United States included hypertension as a primary source or contributing cause. Only about one in four adults with hypertension have it under control and about nearly half of adults in the United States have hypertension (systolic blood pressure greater than or equal to 130 mm Hg or diastolic blood pressure greater than or equal to 80 mm Hg) or are taking medication for hypertension. The American Diabetes Association (2018) states that, “Nearly one in three American adults have high blood pressure and two of the three people with diabetes report having high blood pressure”. According to the National Kidney Foundation (2010), high blood pressure is a leading cause of CKD and high blood pressure can also be a complication of CKD. Hypertension, diabetes, and CKD can be causes and effects of one another, it is important

as medical providers to be educated on the best possible treatment and prevention strategy for patients with hypertension and hypertension with comorbidities, due to their increasing prevalence.

Research Question

In patients taking ACE inhibitors or angiotensin II receptor blockers, what are the outcomes of p.m. dosing in hypertension versus p.m. dosing in hypertension with comorbidities?

Methods

A literature review was conducted searching the following electronic databases: PubMed, ClinicalKey, and DynaMed. Keywords and phrases were used to define a set of the literature discussing p.m. dosing of ACE inhibitors or ARBs in patients with hypertension and hypertension with comorbidities. The literature was searched by chronotherapy of the disease states and then specifically by pharmacotherapy. The search revealed a total of 543 studies. Several studies were excluded because they did not focus on ACE inhibitors or ARBs, or they did not focus on the disease processes intended for research in this project. Other studies that included dosing ACE inhibitors or ARBs at night and in the morning per participant were also excluded because this project focuses on the effects of using one methodology verses the other. Seventeen articles met the final criteria, and a time frame of 15 years was used to allow more data to be explored.

Keywords: chronotherapy in hypertension, chronotherapy in hypertension with CKD, chronotherapy in diabetes, chronotherapy of ACE inhibitors, chronotherapy of angiotensin II receptor blockers.

Review of the Literature

A review of the literature shows many studies researching effects and outcomes of chronotherapy by aligning it with the mechanisms of the circadian rhythm to provide the most efficacious treatment in those with hypertension and hypertension with comorbidities such as diabetes or CKD. Since this research is still developing, guidelines have not been set as a result from the studies because organizations want further data on the subject. It has been shown that dosing ACE inhibitors or ARBs at night have maintained lower blood pressure throughout the night and into the following day, which prevents the morning spike in blood pressure that may cause strokes and myocardial infarctions. Themes were designed to evaluate the research by chronotherapy and circadian rhythm, effects of p.m. dosing of angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs) in those with hypertension, effects of p.m. dosing of ACE inhibitors or ARBs in those with hypertension with chronic kidney disease, and effects of p.m. dosing of ACE inhibitors or ARBs in those with hypertension with diabetes.

Chronotherapy and Circadian Rhythm

Understanding the mechanisms and physiology that occurs throughout the circadian rhythm is important to understand before tailoring chronotherapy to certain disease processes.

Bowles, Thosar, Herzig, and Shea (2018) provided information on the potential benefits of utilizing chronotherapy in concert with the physiologic processes that occur throughout the 24-hour circadian rhythm. Sleep-wake cycles, rest-activity cycles, fasting-feeding cycles, daily fluctuations of gastric pH, gastric emptying, gastrointestinal transit time, organ blood flow, liver enzyme activity, and renal function are some of physiologic processes to remember while considering chronotherapy. Hypertension, chronic kidney disease, and diabetes are a few of the

chronic conditions that may show benefits in those taking their antihypertensive medications at night before bed. The benefit of dosing antihypertensive medications at night is to reduce cardiovascular complications in those with a non-dipping pattern (<10% drop in average nocturnal vs. daytime blood pressure) and a reverse dipping pattern (average nighttime blood pressure greater than daytime blood pressure). Non-dipping blood pressure patterns can result in increased left atrial systolic volume, left ventricular wall thickness, and lower right atrial ejection fraction. Reverse dipping blood pressure patterns can result in severe renal dysfunction, cardiovascular injuries, carotid plaque formation, and lacunar infarctions.

Methods included an extensive review of meta-analyses and systematic reviews using Google Scholar, PubMed, and Scopus. Publications used were limited from January 2013 to December 2017. Abstracts of articles were scanned for relevance and categorized based on primary hypertension (n = 14 studies), hypertension with a specific comorbid condition (n = 13 studies), meta-analysis or systematic review (n = 5 studies), or chronopharmacology (n = 4 studies). Tables were provided for a summary of each study.

The results concluded that taking at least one antihypertensive medication at night would improve regulation of nocturnal blood pressure to prevent increased cardiovascular related complications. There were no reports within the studies of nocturnal hypotension, non-compliance, or complaints of additional adverse effects with an evening dosing regimen, therefore, it would be advantageous for a patient to adhere to this dosing schedule.

Further in-depth studies could be done to research the intricate details of the physiologic processes that occur during the sleep cycle to personalize medication appropriately by taking into consideration of the last meal intake, sleep patterns, or endogenous circadian rhythms.

Before discussing chronotherapy, it is important to assess how blood pressure is best monitored. Hermida et al. (2017) emphasized the importance of ambulatory blood pressure monitoring (ABPM) when documenting consecutive blood pressures while someone is asleep or awake. A systematic review was performed to evaluate the recently completed research regarding chronotherapy. This review analyzed studies completed from 1992-2017. The authors excluded trials and studies that did not reflect 24-hour or longer patient ambulatory blood pressure monitoring assessment and those that did not report therapeutic effects of different medication timings upon both the awake and the asleep systolic blood pressure and diastolic blood pressure means.

The results of this review indicated that ABPM readings are more accurate than office blood pressure measurements (OBPM) when evaluating the physiologic events that occur during the day when people are awake and during the night when people are asleep. According to Hermida et al. (2017), “Various independent prospective studies demonstrate CVD events are better predicted by the ABPM- derived asleep than either the awake or 24-hour blood pressure means or conventional daytime OBPM” (p. 760). Ambulatory monitoring is speculated to be the most accurate as it removes the outliers of possible white-coat hypertension with an office visit, masked hypertension, and inconsistencies of methods between staff members when taking blood pressures.

The readings provided by ABPM will determine if a patient is a dipper (normal decrease in blood pressure while sleeping), or a non-dipper. This information is beneficial to healthcare providers as it allows them to determine if their patient is a non-dipper and thus is at higher risk for cardiovascular disease (CVD), myocardial infarctions, stroke, kidney damage, or diabetes. By

evaluating these blood pressures, it can be decided if dosing antihypertensive medications in the evening will be more proactive in preventing the diseases listed above.

Normal circadian physiological processes, such as gastric pH, gastric motility, biliary function glomerular filtration, hepatic enzyme activity, and organ blood flow, play a part in the pharmacokinetics and pharmacodynamics in metabolism of antihypertensive medications. Hermida et al. (2017) also evaluated the most common mistakes in other studies when evaluating the efficacy of dosing antihypertensive medications at night and suggested outside factors that need to be considered before applying quality statistical data to the theory, such as the time of day a patient is taking their medications. Patients will want a set hour of the day to take their medication every day, but in reality, the medication should be taken around the human biological clock of when physiological changes are happening during the sleep cycle and the awake cycle. Another common mistake that occurs within studies is strictly using OBPM during the day to assess participant qualifications for future studies without doing the complete 24- hour ambulatory method.

Rabinovich-Nikitin, Lieberman, Martino, and Kirshenbaum (2019) conducted a systematic review of journal articles that also evaluated different meta-analysis studies on the effects of circadian regulated cell death in cardiovascular diseases. Heart rate, blood pressure, endothelial cell function, platelet aggregation, and thrombus formation are some of the physiological processes that are regulated by the circadian rhythm. In the early morning, these processes become enhanced to prepare for awakening, which can generate myocardial infarctions, arrhythmias, stroke, heart failure, and sudden cardiac death. It has been found that many genes regulating cellular homeostasis are controlled by the circadian rhythm, which

explains why having a consistent awake and sleep cycle is important to prevent increased cell death that could possibly lead to cardiovascular diseases, myocardial infarctions, or strokes.

The results of this review indicate that those with a non-dipping blood pressure pattern during sleeping hours may have increased risk for developing left ventricular hypertrophy, heart failure, myocardial infarction, and stroke compared to those with a normal dipping pattern when asleep. Interestingly enough, it was noted in six different meta-analyses that during spring daylight savings time there was an increase in the amount of myocardial infarctions occurring during the early morning hours which could be due sleep deprivation, altered diurnal patterns of sympathetic activity, hormonal changes, or production of inflammatory cytokines. It is important to note that there were no p values, confidence intervals, or number of participants listed when mentioning the six different meta-analyses.

The relevance of the circadian rhythm is demonstrated especially in those who do shiftwork (day shift vs night shift) and those who experience jet lag after flying. One study followed nightshift mill employees for >15 years, which revealed prevalent ischemic heart disease compared to those who worked consistent day shifts, because of the constant disruption in the normal circadian rhythm and physiological processes that occur during that time frame. This study excluded age or smoking history of the employees.

The theory of chronotherapy is studied to potentially maximize benefits of medications based on liver and kidney function during certain times of the day. Since pharmacokinetics and pharmacodynamics are different for certain medications, when considering chronotherapy, one should consider the rate at which the medication will be metabolized and excreted based off the patient’s circadian rhythm- which could increase the efficacy of antihypertensive medications if given properly in concordance with the biological clock.

Subsequent studies showed that there was an increase in autophagy vacuoles within the tissue of the heart during late-night hours when studied in rats, which reiterates the importance of a normal circadian rhythm for tissue restoration. According to Rabinovich-Nikitin et al. (2019), "Future studies will address the complex interplay between homeostatic processes such as autophagy, programmed cell death, and circadian rhythms in the diseased heart. This will lead to innovative approaches to benefit treatment and outcomes for patients with CVD" (p. 979). This area of research is gradually progressing, which implies that experts do not have complete details mapped out of the exact physiological processes that occur during the night and daytime hours in order for chronotherapy to be targeted specifically at a certain system.

Smolensky, Hermida, and Portaluppi (2017) published a systematic review about the endogenous mechanisms that take place during the circadian rhythm and how they can affect blood pressure. Because the articles above go into detail about many of these processes already, the focus of this information will involve the renin-angiotensin-aldosterone system's (RAAS) circadian rhythmicity.

The results indicated that components of the RAAS system such as, prorenin, plasma renin activity (PRA), serum angiotensin-converting enzyme (ACE) activity, plasma angiotensin II (ANG II), and aldosterone, are major contributors to the variation of daytime and late evening blood pressures of those that are normotensive and have uncomplicated hypertension. The RAAS system typically becomes activated during the middle to late night hours of the sleep cycle. PRA responds to external stimuli, so patients that are active throughout the day will have higher levels of PRA during the awake cycle versus the sleep cycle. Plasma aldosterone, which is regulated by adrenocorticotropic hormone (ACTH), is at its highest level in the middle to late night hours during the sleep cycle. During the awake cycle, the RAAS system will also control aldosterone

levels alongside of ACTH. Three studies (two from Italy and one from Japan) were completed with a participant group of normotensive and uncomplicated hypertensive patients that were under controlled mealtime and wake/sleep routines. The Italian studies indicated a late afternoon peak of ACE and the Japanese study indicated late night into early morning hour peak of ACE. Explanations as to why these two studies found variable information may be due to external causes such as the variation of foods and liquids participants were consuming, varying stressors, or amount of activity in a day. A theory as to why ACE levels were peaked in the late afternoon of the Italian studies may be due to maximum ANG II activity during the late night into the early morning, which leads to consumption of ACE and decreases those levels at that time.

Vitamin D plays an important role in the regulation the RAAS system as well. A study performed on animals showed that administration of vitamin D3 decreased renin expression. In a study conducted on mice, when the vitamin D receptor was blocked, levels of plasma renin and ANG II increased causing hypertension and organ damage. In humans, low levels of vitamin D caused elevated levels of PRA and ANG II, which was reversed when supplementation of vitamin D was administered.

This information is beneficial by providing insight into the 24-hour variation of the RAAS system to determine if dosing ACE inhibitors or angiotensin II receptor blockers (ARBs) at night would be of significance based on the levels of ACE and ANG II. Statistical data was not noted to support the validity of the information provided. The authors cited many articles which upon further review may elaborate on statistical significance and associated p-values.

Effects of P.M. Dosing of ACE Inhibitors or ARBs in Those with Hypertension

De Giorgi et al. (2013) conducted a systematic review to compare the efficacy of antihypertensive mediations, that are most commonly used by internists, when they are dosed in

the morning versus in the evening. For purposes of this literature review, ACE inhibitors and ARBs will be evaluated to determine their efficacy when dosed in the evening for participants with hypertension.

In a table provided within this study, it classifies ACE inhibitors and ARBs into one group of antihypertensives showing that ramipril, enalapril, zofenopril, benazepril, perindopril, olmesartan, valsartan, and telmisartan all had better blood pressure lowering effects when dosed in the evening compared to the morning dose. Each medication listed had a separate study done to determine if their blood pressure lowering effects was more efficacious when dosed in the morning versus the evening. Ramipril, olmesartan, telmisartan, and valsartan were evaluated by way of individual randomized trials with 115 participants, 123 participants, 215 participants, and 90 participants, respectively. Enalapril, zofenapril, and perindopril were evaluated by way of individual cross over trials with 8 participants, 33 participants, and 20 participants, respectively. Benazepril was a single-blind, crossover trial with 10 participants. According to DeGiorgi et al. (2013), “Evening doses of ramipril, enalapril, zofenopril, benzepril, and perindopril induces a higher nighttime blood pressure dip, followed by a slower increase during the day”. When the ARBs were dosed in the evening, they showed physiological normalization of blood pressure when compared to the morning dose. This review indicated that in hypertensive patients who are taking one antihypertensive medication or multiple antihypertensive medications, ACE inhibitors and ARBs should be taken in the evening to have the best blood pressure control.

Hermida et al. (2017) conducted a systematic review to evaluate the benefits of ambulatory blood pressure and how it can be more of an effective predictor in diagnosing cardiovascular disease by having the advantage to monitor blood pressures at night while a

person is asleep. It also analyzes chronotherapy effects of ACE inhibitor monotherapy and ARB monotherapy in those with hypertension, which will be the focus in this literature review.

This review included effects of calcium channel blocker monotherapies, doxazosin, carvedilol, nebivolol, loop-diuretic torasemide, and fixed combination hypertension therapies, but were excluded because it did not fall within the scope of this literature review. It separated the effects of certain antihypertensive medications based on disease states such as hypertension, resistant hypertension, chronic kidney disease, diabetes, and non-dipper hypertension. Untreated hypertension was the only disease state analyzed in this theme. There were three different ACE inhibitors explored- ramipril, spirapril, and zofenopril and two different ARBs- valsartan and telmisartan. Ramipril had 115 untreated hypertensive patients who were randomized and instructed to take 5 mg before bed or upon awakening and were monitored with ABPM 48 hours before administration and 6 weeks after. Spirapril had 165 untreated hypertensive patients who were randomized and instructed to take 6 mg before bed or upon awakening for 12 weeks. Zofenopril had 33 untreated hypertensive patients who were instructed to take 30 mg before bedtime or upon awakening for 1 month. Valsartan had 90 hypertensive patients that were randomized into bedtime or awakening administration of 160 mg for 12 weeks. Telmisartan had 215 patients with grade 1-2 hypertension who were randomized for bedtime or awakening administration of 80 mg for 12 weeks.

The results of this systematic review concluded with bedtime administration of ACE inhibitors or ARBs did not significantly impact the daytime blood pressures as it did the nighttime blood pressures when compared to awakening administration. Ramipril, spirapril, zofenopril, valsartan, and telmisartan, all demonstrated significant reduction in the asleep blood pressure ($p < 0.001$) when dosed at bedtime. Ramipril, spirapril, valsartan, and telmisartan had

reduction in the overall 24-hour blood pressure when dosed at bedtime or upon awakening ($p < 0.05$). It is interesting to note, when analyzing the 24-hour graphs of the systolic blood pressure variations between awakening and bedtime administration, much of the time, the bedtime administration consistently kept the systolic blood pressure below the awakening administration.

The authors provided beneficial information depicting the hours that the medications were the most effective and showed the differing hours of effectiveness between awakening administration and bedtime administration.

Hermida et al. (2011) conducted a systematic review to compare morning administration versus evening administration of ACE inhibitors and ARBs in those with essential hypertension to evaluate which regimen normalizes the 24-hour blood pressure profile more effectively to prevent injury of target tissues, cardiac and cerebrovascular events.

Captopril-hydrochlorothiazide results were excluded in this review because diuretics are not included in the formulated PICO question. There was a heterogenous approach to this review as some trials evaluated fixed timed administration (a.m. or p.m.) or awake versus bedtime administration.

Various ACE inhibitors and ARBs were evaluated individually by way of single-blinded crossover studies or randomized cross over studies that included anywhere from eight to 215 participants. The time frame in which a.m. versus p.m. dosing of these medications were evaluated varied from 4 weeks to 12 weeks. Participants in these studies were diagnosed with essential hypertension.

It was shown that ACE inhibitors and ARBs are very effective in reducing the nighttime blood pressure and that they are able to effectively convert those who were non-dippers to dippers. Initially, it was hypothesized that successful asleep blood pressure reduction with

bedtime administration was due to medication levels peaking at the corresponding time of RAAS activation, which prevents a damaging blood pressure surge in the early morning hours. However, this hypothesis became invalid and further research needs to be conducted with larger participant pools, longer evaluation times, and appropriate follow-up for participants to make a definitive conclusion.

Hermida and Ayala (2009) conducted a randomized, open-label, parallel-group, blinded end point multicenter clinical trial on 115 participants with untreated, uncomplicated essential hypertension to receive a ramipril (5 mg/d) dose in the morning upon awakening or at night before bed. The purpose of this study was to determine which dosing regimen has the most impactful reducing effects on ambulatory blood pressure.

Ambulatory blood pressures were obtained every 20 minutes from 7:00 a.m.-11:00 p.m. and every 30 minutes during the night for 48 consecutive hours and then were measured again after 6 weeks of treatment. Patients wore an actigraph to monitor physical activity during ambulatory blood pressure monitoring.

Results indicated that administering ramipril before bed better regulated the asleep blood pressure ($p < 0.001$) when compared to morning administration, and decreased the amount of patients that were considered non-dippers when compared to morning administration ($p = 0.026$). The participants had an overall decreased 24-hour blood pressure mean ($p < 0.001$) when comparing both regimens. The awake blood pressure mean did not significantly differ between morning administration versus bedtime administration.

Hermida, Calvo, Ayala, and Lopez (2005) conducted a 3-month randomized, open-label, blinded endpoint trial on 200 patients with grade 1-2 essential hypertension that were previously untreated and did not display proteinuria. The patients were dosed with valsartan (160 mg/day)

upon awakening or before bed to determine the effects on blood pressure, albumin in the urine, and levels of plasma fibrinogen.

Exclusion criteria of participants included shift-workers, heavy drinkers (>80 g/day), smokers (>20 cigarettes/day), heavy exercisers, severe arterial hypertension, diabetes, proteinuria (urinary albumin excretion>300 mg/24 hours), and other cardiovascular diseases. Inclusion criteria consisted of untreated grade 1-2 hypertensive participants. Blood and urine samples were obtained consistently throughout the patient population. Ambulatory blood pressure monitoring was obtained every 20 minutes from 7:00 a.m.-11:00 p.m. and every 30 minutes during the night for 48 consecutive hours. This study utilized actigraphy to monitor physical activity in 1-minute intervals.

Results of this study revealed when valsartan was dosed upon awakening, there was significant reduction in the 24-hour mean blood pressure ($p < 0.001$). After treatment, those dosed in the morning, had 57.8% controlled diurnal blood pressure and 45.1% controlled nocturnal blood pressure. When valsartan was dosed at bedtime, there was significant reduction in the 24-hour mean blood pressure ($p < 0.001$). After treatment, those dosed in the evening, had 74.5% controlled diurnal blood pressure and 61.2% controlled nocturnal blood pressure. When valsartan was dosed at night, there was a significant increase in the diurnal/nocturnal ratio of systolic blood pressure ($p < 0.001$) versus morning administration. Urinary albumin excretion reduction was found to be correlated with an increase in the diurnal/nocturnal systolic blood pressure ratio ($p < 0.001$), but it was not correlated with the overall 24-hour blood pressure mean decrease. Data suggests increased reduction in nocturnal blood pressure with bedtime dosing reduces urinary albumin excretion. Plasma fibrinogen levels were decreased in those patients

taking valsartan before bed ($p = 0.046$), which may reduce the risk of myocardial infarctions, strokes, or kidney disease.

Martino et al. (2011) conducted a pre-clinical research study on murine animals with surgery induced transverse aortic constriction (TAC) to induce pressure overload. This was to determine if there are any cardioprotective effects when administering captopril in the morning versus administering at night.

This study was conducted for pre-clinical research and was performed on murine animals. A total of 40 mice were used and divided into groups labeled TAC captopril sleep time, TAC captopril wake time, TAC placebo, and Sham-operated control- 10 in each group. They controlled the mice's biological clock by providing them with 12 hours of light and 12 hours of darkness. At 8-10 weeks, TAC was applied to the descending aorta. Captopril was utilized in this pre-clinical research trial because of its short half-life to prevent overlap of daytime and nighttime effects. This study lasted 9 weeks, 1 week was allowed for recovery and the other 8 weeks were for the administration of captopril. Captopril was administered to 10 mice in the morning and 10 separate mice in the evening. Echocardiography, radiotelemetry, histological analyses, and mRNA measurements were also utilized in these subjects.

Results of this pre-clinical trial revealed that the TAC placebo mice group ($n = 10$) had significant cardiac hypertrophy ($p < 0.005$). The TAC captopril sleep time group showed reduced heart weight and heart-weight-to-body-weight ratios ($p < 0.005$) when compared with the placebo group. Upon echocardiography, TAC mice with sleep time administration of captopril had reduced left ventricular end systolic dimension and left ventricular end-diastolic dimension ($p < 0.05$) when compared to TAC mice with awake administration of captopril. Upon histological analysis, the sham mice revealed increased myocyte size after TAC procedure ($p <$

0.005) and showed TAC mice that were dosed with captopril in the evening had decreased hypertrophy ($p < 0.005$) when compared to TAC placebo mice. TAC increased wall-to-lumen ratio of arterial vessels when compared to Sham mice ($p < 0.05$). In TAC mice with awake administration of captopril, myocyte hypertrophy and wall-to-lumen area ratio were not reduced ($p > 0.05$). TAC mice presented with higher blood pressure when compared to sham mice. After captopril administration to the TAC sleep time mice, significant reduction in blood pressure was the greatest after 2 hours of administration and then slowly began to rise due to the short half-life of captopril. These results indicated that dosing captopril at night could possibly reduce cardiovascular remodeling and interfere with the peak of the RAAS system to also control blood pressure. Although, reducing blood pressure alone is not the only intervention needed to reduce cardiovascular remodeling.

This study provided compelling information on the potential cardioprotective effects of dosing ACE inhibitors at night. This study was homogeneous and had a very regulated schedule of day light versus darkness hours, properly controlled administration of captopril, and a logical approach to the groups that were tested. They provided many methodologies to prove cardiac remodeling changes or no changes. Since this study was performed on mice, no definitive recommendations can be made for humans based on this data.

Ushijima et al. (2015) conducted a 4-month multicenter, open-label, parallel, randomized controlled trial on 94 participants to study valsartan dosed in the evening and olmesartan dosed in the morning and evening on participants that are considered to have a non-dipping pattern at night to evaluate blood pressure regulation, eGFR, and serum creatinine.

Since this study was conducted in Japan, they elaborated on their criteria of hypertension, which was systolic blood pressure greater than or equal to 140 and diastolic blood pressure

greater than or equal to 90. Twenty-four-hour ambulatory blood pressure was obtained from participants for baseline evaluation and after the 4-month study was completed. Blood pressure measurements were taken every 30 minutes from 6:00 a.m. - 10:00 p.m. and every 60 minutes from 10 p.m. - 6 a.m. Fifty-two patients were considered dippers and 40 patients were considered non-dippers. The dippers (n = 52) were their own group dosed with valsartan in the morning (80 mg/day). The non-dippers (n = 40) were separated into three different groups: valsartan evening administration (n = 12) (80 mg/day), olmesartan morning administration (n = 13) (20 mg/day), and olmesartan evening administration (n = 15) (20 mg/day).

Results of this study indicated that the four different groups did not significantly differ in awake systolic blood pressure or mean 24-hour blood pressure. Patients being dosed with valsartan in the evening ($p < 0.01$), olmesartan in the morning ($p < 0.05$), and olmesartan in the evening ($p < 0.05$) had a greater percent reduction in systolic blood pressure during the night when compared with systolic blood pressure during the morning. Sixty-four percent of patients converted to a dipping pattern when dosed with valsartan in the evening. Forty-six percent of patients converted to a dipping pattern when dosed with olmesartan in the morning. Forty-two percent of patients converted to a dipping pattern when dosed with olmesartan in the evening. Serum creatinine did not show any changes after 4 months with both valsartan groups but did show significant mild reduction with olmesartan dosed in the morning ($p = 0.02$) and olmesartan dosed in the evening ($p = 0.04$). Estimated glomerular filtration rate (eGFR) did not reveal any changes after 4 months with both valsartan groups and olmesartan being dosed in the evening but showed mild significant increase with olmesartan being dosed in the morning.

Valuable information was provided to determine which drug was more successful in converting non-dippers to a dipping pattern and evaluating the effects on serum creatinine and

eGFR. A limitation worth mentioning was that there was no non-dipper group who continued to take valsartan in the morning throughout the trial which would have provided consistency when evaluating the effectiveness of valsartan between morning and evening administration.

Effects of P.M. Dosing of ACE Inhibitors or ARBs in Those with Hypertension and CKD

Hermida, Ayala, Mojon, and Fernandez (2011) conducted a randomized controlled, open-label trial on 661 patients with CKD to take at least one antihypertensive mediation at night or to take all antihypertensive medications upon awakening to determine any beneficial cardiovascular or renal outcomes of that regimen.

ACE inhibitors, ARBs, calcium channel blockers, alpha blockers, beta blockers, and diuretics were the antihypertensives evaluated in this trial. Follow-up consisted of 48-hour ABPM, actigraph wrist activity monitoring annually, and review of records annually to assess any CVD morbidity and mortality. A median follow-up of 5.4-years was conducted, but it did not state the percentage of patients they followed up with.

Results of this trial showed that eGFR was unchanged in those with bedtime dosing of antihypertensives ($p = 0.551$). Albumin showed decreased values from baseline in those that were administering at least one hypertensive at bedtime ($p = 0.018$). Although, decreased albumin excretion did not correlate to predicting increased survival ($p = 0.172$). Night-time systolic blood pressure was significantly reduced in those taking one antihypertensive at bedtime when compared to taking all antihypertensives upon awakening ($p < 0.001$). Interestingly, patients who were taking one antihypertensive upon bedtime, showed significantly lower amounts of cardiovascular events when compared to the awakening group ($p < 0.001$).

Strengths and benefits of this study showed promising results in reducing albumin in the urine, reducing asleep blood pressure, and reducing cardiovascular events by administering at

least one antihypertensive medication at bedtime. Since non-dipper sleeping patterns in those diagnosed with CKD is prevalent and can cause decreased kidney function, it is important to note the reduction in the asleep blood pressure when administering one antihypertensive medication at night. This study had intricate inclusion and exclusion criteria to draw an appropriate conclusion and had a median of 5.4-year follow-up with patients.

It would have been beneficial if this study would have provided statistical data and separated each class of antihypertensives to show how they benefit blood pressure, albumin present in the urine, and amount of cardiovascular events determined from follow-up to aid in making medical decisions for successful patient outcomes. Further studies need to be conducted with larger sample sizes and to analyze how each class of antihypertensives will affect those that are diagnosed with hypertension and CKD. ACE inhibitors and ARBs were not evaluated separately in this study, which is a limitation to this theme.

Minutolo et al. (2007) conducted an 8-week uncontrolled pilot trial on 32 participants by switching those on antihypertensive medications to at least 1 before bedtime in patients with chronic kidney disease to determine if it decreases nocturnal blood pressure and proteinuria.

Methods utilized in this trial had enrollment criteria that patients had to meet, which included CKD (no dialysis and no kidney transplant) with eGFR less than 90 mL/min/1.73^2 and a non-dipper pattern with a night-day (N/D) ratio mean ambulatory blood pressure greater than 0.9. Exclusion criteria for the potential participants included ambulatory daytime blood pressure of 135/85 or greater, absence of antihypertensive pharmacological therapy, steroid therapy, and atrial fibrillation. All classes of antihypertensive drugs were included in this trial. Before and after the 8-week trial patients were evaluated by body weight, office BP and ABP recordings,

and laboratory tests. Ambulatory blood pressure was monitored every 15 minutes from 7:00 a.m. - 11:00 p.m. and every 30 minutes from 11:00 p.m. - 7:00 a.m.

The results of this trial discovered blood pressure lowering effects of the participants that shifted one antihypertensive medication to the nighttime dose ($p < 0.001$). With at least one antihypertensive medication switch to nighttime administration, proteinuria significantly decreased ($p < 0.001$). No change was detected in eGFR between the initial evaluation and after the trial. Twelve patients shifted ACE inhibitors, seven patients shifted ARBs, and the remaining patients shifted calcium channel blockers, beta blockers, or alpha blockers. There was no decrease in nocturnal blood pressure in those taking medications inhibiting the renin-angiotensin-system (systolic $p = 0.5$ and diastolic $p = 0.2$), which is contrary to other studies that have found nighttime administration to be successful at reducing nocturnal blood pressure.

This study was not excluded to monotherapy only, some patients were on two or three antihypertensive medications and they only had to switch one to nighttime administration. Some of the participants had underlying diabetes, previous cardiovascular events, and left ventricular hypertrophy which doesn't necessarily fit the theme, but it was useful to see that there is promise for further studies to prevent the amount of protein that is excreted into the urine in those with CKD. It would have been beneficial to see these antihypertensive medications analyzed separately to determine how they affect reduction of proteinuria instead of grouping the data as "antihypertensives".

Wang et al. (2013) conducted a two-year pilot study in the Division of Nephrology, Third Hospital of Sun Yat-Sen University on 60 patients with a non-dipping blood pressure pattern and 30 patients with a dipping blood pressure pattern that were previously diagnosed with chronic

kidney disease (CKD). The purpose of this study was to determine if administration of valsartan at bedtime or upon awakening was more successful for kidney and cardioprotective effects.

Methods utilized in this study consisted of patients being separated into 3 different groups: dippers, and the non-dippers which were then separated into an awakening administration group and a bedtime administration group. Patient inclusions of this trial consisted of CKD presence, 18-65 age range, estimated GFR < 90 mL/min/1.73 m^2 but > 30 mL/min/1.73 m^2, 24-hour proteinuria > 0.5 g but < 2.0. Blood pressure measurements were recorded every 15 mins from 7:00 a.m. - 10:00 p.m. and every 30 mins from 10:00 p.m. - 7:00 a.m. Left ventricular volumes, mass, systolic function, and diastolic function were obtained by 2-dimensional echocardiography. High resolution B-mode ultrasonography was used to measure carotid intima-media thickness. 24-hour urine samples within a 7-day period were obtained to measure urinary protein, creatinine, and sodium excretion. Separate urine samples were collected from 7:00 a.m. – 10:00 p.m. and 10:00 p.m. - 7:00 a.m. to analyze any proteinuria or sodium excretion. Follow-up consisted of patients having blood pressure measurements once a month, 24-hour ABPM were scheduled once every 3 months, and ultrasonography was performed every 6 months.

Results of this pilot study revealed that the non-dipper group experienced elevated nighttime blood pressure, increased ratio of bedtime/awakening proteinuria, left ventricular mass index, carotid intima-media thickness, and increased frequency of plaque when compared to the dipper group ($p < 0.05$), there were no differences shown in the non-dipper bedtime group or non-dipper awakening group ($p > 0.05$). The dipper group showed decreased deterioration of eGFR than the non-dipper groups with valsartan administration ($p < 0.05$). Both non-dipper groups displayed lower proteinuria when dosed with valsartan upon awakening and at bedtime (p

< 0.05), but the changes of proteinuria in non-dipping patients receiving the bedtime dose were higher than in patients receiving the awakening dose ($p < 0.05$). When valsartan was administered at night, the ratio of bedtime/awakening urine sodium excretion was significantly decreased when compared to the group of awakening non-dippers ($p < 0.05$). 24-hour sodium excretion did not differ between the dipper and non-dipper groups. When comparing the awakening dose of non-dippers and the dipper group, administration of valsartan for one-year decreased changes in left ventricular mass index for the dipper group. When comparing the awakening and bedtime dose of the non-dippers, the bedtime dose decreased changes in the left ventricular mass index for the bedtime group ($p <0.05$). There was no difference in left ventricular ejection fraction or carotid-intima-media thickness between the three groups. After reviewing these results, promising information shows that bedtime dosing with valsartan at night, for those who have chronic kidney disease and are considered “non-dippers”, could achieve successful cardiac and kidney protection with that type of regimen. All three groups were evaluated the exact same way with blood pressure monitoring, ultrasonography, urine collection, and follow-up.

Since this was a pilot study, further research on this topic is required before making patient recommendations. It would have been interesting to see the dippers being split into a bedtime and awakening dosing schedule to determine any significant changes in cardiac or renal protective effects for that population. Larger population sizes or the use of different ARBs/ACE inhibitors with this type of study design would be beneficial to those that prescribe those classes of medications.

Effects of P.M. Dosing of ACE Inhibitors or ARBs in Those with Hypertension and Diabetes

Hermida, Ayala, Mojon, and Ferandez (2011) conducted a randomized, open-label, blinded end point trial on 448 hypertensive patients with type 2 diabetes to determine if switching one antihypertensive administration to bedtime, instead of taking all antihypertensives in the morning, would affect blood pressure control and cardiovascular disease risk.

Participants were randomized into two different groups: the first group was to take all antihypertensive medications in the morning upon awakening and the second group was to take at least 1 antihypertensive medication before going to bed. Blood samples were obtained in a scheduled fashion. Ambulatory blood pressure monitoring was obtained and measured every 20 minutes between 7:00 a.m.-10:00 p.m., and every 30 minutes throughout the night for 48 consecutive hours. All patients wore an actigraph to monitor physical activity. Follow-up was conducted on patients at least annually for a median of 5.4 years. Antihypertensive medications used in this study included: ARBs, ACE inhibitors, calcium channel blockers, alpha blockers, beta blockers, and a diuretic.

Results of this study discovered that the participant group administering at least 1 antihypertensive medication before bed had significant reduction in mean asleep blood pressure ($p < 0.001$) compared to the group administering all their antihypertensive medications in the morning. Blood pressure during the day did not differ between the two treatment groups, however, the bedtime administration group showed significantly reduced overall blood pressure ($p <0.001$, 70.8% versus 54.7%). Patients taking one antihypertensive medication at night had an overall decrease in cardiovascular disease events ($p = 0.038$) compared to the awakening regimen.

The authors reported 91 cardiovascular disease events that were recorded during the follow-up period which included deaths, myocardial infarctions, angina pectoris, coronary revascularizations, cerebrovascular events, heart failure, aortoiliac occlusive disease, and thrombotic occlusions of the retinal artery.

A limitation to this study is that they did not provide individual statistics on how the different antihypertensives affected patients. It would be interesting to read a study done on different classes of antihypertensives arranged in this study design to determine cardiovascular disease outcomes in those with type 2 diabetes and hypertension or with chronic kidney disease as an additional comorbidity

Rossen et al. (2014) organized a 16-week randomized control, open-label, crossover study on 41 patients with type 2 diabetes and nocturnal hypertension. The participants were placed into groups: the first group was to take all antihypertensive medications in the morning and the second group was to take at least 1 antihypertensive medication at night before bed. Each participant group would be in one dosing group for 8 weeks and would switch to the opposite group for the next 8 weeks.

Blood pressures were obtained by ambulatory blood pressure monitoring and were scheduled to measure every 20 minutes day and night. Blood and urine samples were obtained during scheduled days to analyze results from baseline to the end of the trial. Cardiovascular autonomic neuropathy, compliance, and tolerability of medications were also evaluated. Antihypertensives used in this study included: ACE inhibitors, ARBs, beta blockers, calcium channel blockers, thiazides, spironolactone, indapamide, and moxonidine.

Results of this study showed significant reduction of nighttime systolic blood pressure ($p < 0.001$) , diastolic blood pressure ($p < 0.001$), pulse pressure ($p < 0.001$), mean arterial pressure

($p < 0.001$), and overall 24-hour blood pressures (systolic $p = 0.014$, diastolic $p = 0.047$, pulse $p = 0.023$, mean arterial $p = 0.022$) when dosing one antihypertensive medication at night in those with type 2 diabetes and nocturnal hypertension compared to dosing all antihypertensive medications in the morning upon awakening. C-reactive protein was significantly reduced upon bedtime administration ($p = 0.017$), and fibrinogen levels were unaffected by bedtime administration ($p = 0.153$). Urinary creatinine was reduced ($p < 0.001$) and urinary sodium/creatinine was increased ($p < 0.001$) with bedtime administration of an antihypertensive, which correlates with increased nocturnal natriuresis. Urine osmolality was decreased ($p = 0.031$) and urine potassium/creatinine were increased ($p = 0.013$) with bedtime administration. There was no significant reduction in urinary albumin/creatinine upon bedtime administration of an antihypertensive medication. This study exhibited promising results for type 2 diabetic patients with reducing nocturnal hypertension to prevent further organ damage.

The authors did not list the specific medications used at night or in the morning, which is a limitation to this theme and this trial for interpretation and future application purposes.

Tofe Povedano & Garcia De La Villa (2009) conducted a 16-week small randomized controlled trial using a cross-over design on 40 participants that were diagnosed with type 2 diabetes and hypertension. This study was done to compare 40 mg of olmesartan dosed in the morning upon awakening and at night before going to bed to evaluate the effects of blood pressure and albumin excretion rate.

Methods utilized during this trial started with inclusion criteria of type 2 diabetes patients that were between the ages of 18-75 years, body mass index between 20- 40 kg/m^2, systolic blood pressure > 130 mm Hg, diastolic BP > 80 mm Hg, and no pharmacologic agents used to treat hypertension in the past 6 months. Those who met the criteria for participation were

randomly assigned to receive olmesartan upon awakening (7:00 a.m. - 9:00 a.m.) or at bedtime (10:00 p.m. – 12:00 a.m.). After 8 weeks, patients on the morning administration regimen switched to the nighttime regimen and vice versa for another round of 8 weeks.

Results revealed that upon administration of olmesartan, it provided significant blood pressure reduction in both the morning and evening groups. Nighttime blood pressure was significantly reduced with nighttime administration versus the morning administration ($p = 0.007$). Daytime values remained the same when comparing the nighttime regimen and the morning regimen. Morning administration failed to significantly impact nighttime blood pressure fall when comparing it to the baseline blood pressure measurement ($p = 0.0501$). Sixty-eight percent of the participant population were considered dippers. Morning administration of olmesartan increased the dipper population percentage to 74, and nocturnal administration increased the percentage to 82 ($p = 0.012$). Morning and nocturnal administration of olmesartan both decreased the amount of albumin excreted, however there was no significant difference in one regimen versus the other ($p = 0.669$).

Strengths and benefits of this trial showed patients who are diagnosed with type 2 diabetes and hypertension need proactive measures taken due to potential renal damage and cardiovascular events. Dosing olmesartan showed effective reduction of blood pressure and albumin excretion. Dosing olmesartan at night revealed better blood pressure control during the night, which is important to take into consideration, since type 2 diabetic patients are more prone in transitioning to a non-dipper status. It would be intriguing to see any differences in long term effects between morning and evening administration regarding albumin excretion, renal function, and cardiovascular events in those diagnosed with type 2 diabetes and hypertension.

Discussion

In patients taking ACE inhibitors or angiotensin II receptor blockers, what are the outcomes of p.m. dosing in hypertension versus p.m. dosing in hypertension with comorbidities?

To obtain fluent understanding of the information provided above, individual medications will be discussed together from different references to analyze their effectiveness and beneficial outcomes as a whole.

The circadian rhythm is important to understand when determining how to effectively optimize antihypertensive medication use. Hypertension, diabetes, and chronic kidney disease are a few of the prevalent diseases that can cause an alteration in the nocturnal blood pressures known as non-dipping and reverse dipping patterns. A non-dipping pattern is defined as <10% drop in average nocturnal blood pressure when compared to daytime blood pressure and reverse dipping is defined as having increased blood pressure while asleep when compared to daytime hours. According to Bowels et al. (2018), experiencing a consistent non-dipping pattern may lead to increased left atrial systolic volume, left ventricular wall thickness, and lower right atrial ejection fraction, and having a reverse dipping pattern can result in severe renal dysfunction, cardiovascular injuries, carotid plaque formation and lacunar infarctions. Rabinovich-Nikitin et al. (2019) explains how heart rate, blood pressure, endothelial cell function, platelet aggregation and thrombus formation are regulated by the circadian rhythm, therefore, as these processes become enhanced before awakening, it may lead to myocardial infarctions, arrhythmias, stroke, heart failure, and sudden heart attack in the early morning hours. Keeping the blood pressure and heart rate controlled while the awakening mechanisms take place may lead to decreased cardiovascular and cerebrovascular events. The focus on dosing ACE inhibitors or ARBs at night

can promote successful conversions of non-dipper and reverse dipping patterns to normal dipping patterns by regulating the levels of ACE and ANG II at night and into the following day.

Ramipril had a study conducted on 115 participants to compare awakening and bedtime administration for patients with untreated uncomplicated hypertension. Hermida and Ayala (2009), dosed participants with 5 mg/d before bed which resulted in blood pressure control throughout the night and decreased the amount of patients that were considered non-dippers when compared with morning administration.

A study on Valsartan was performed on 200 participants dosed with 160 mg/d to compare awakening and bedtime administration, which revealed significant reduction in the 24-hour mean blood pressure, 74.5% controlled diurnal blood pressure, 61.2% controlled nocturnal blood pressure, and a significant increase in diurnal/nocturnal ratio of systolic blood pressure, which is associated with reduced urinary albumin excretion and decreased plasma fibrinogen levels. In an additional study conducted by Ushijima et al. (2015), 64% of 12 participants converted to a dipping pattern when dosed with 80 mg of valsartan in the evening. Wang et al. (2013), performed a 2-year pilot study on 60 patients with a non-dipping blood pressure pattern and 30 patients with a dipping blood pressure that were previously diagnosed with chronic kidney disease. The non-dippers were split into an awakening administration group and a bedtime administration group. Both groups displayed decreased proteinuria, but proteinuria was decreased more significantly in those receiving the bedtime dose when compared to those receiving the awakening dose ($p < 0.05$). In the bedtime dosing group, the ratio of bedtime/awakening urine sodium excretion was significantly decreased when compared to the group of awakening administration non-dippers ($p < 0.05$). The bedtime dose decreased changes

in the left ventricular mass index for the non-dippers ($p < 0.05$) after one year of valsartan administration.

In a study conducted by Ushijima et al. (2015), 42% of 15 participants converted to a dipping pattern when dosed with 20 mg of olmesartan in the evening. Serum creatinine was also mildly reduced with olmesartan dosed in the evening. Tofe et al. (2009), conducted a study on 40 participants with type 2 diabetes and hypertension by dosing 40 mg of olmesartan upon awakening and at night before bed. Night-time blood pressure was significantly reduced, and 82% of the participants became dippers. Morning administration and evening administration both reduced albumin excretion, however, there was no significant difference in the amount of albumin excreted between regimens.

In those with hypertension and chronic kidney disease, a study was performed by Hermida et al. (2011) with 661 participants, which revealed eGFR was unchanged in those with bedtime dosing of antihypertensives. Albumin values decreased from baseline with bedtime administration of antihypertensives. Night-time systolic blood pressure was significantly reduced, and lower amounts of cardiovascular events were documented with bedtime administration of antihypertensives. Hermida et al. (2011), conducted a study on 448 hypertensive patients with type 2 diabetes which revealed a significant mean reduction in asleep blood pressure and reduced overall blood pressure ($p <0.001$) in those dosed with at least 1 antihypertensive medication before bed when compared to the group administering all their antihypertensive medications in the morning. Participants in the bedtime administration group showed an overall decrease in cardiovascular disease events when compared to the awakening regimen. Rossen et al. (2014), organized a study on 41 patients with type 2 diabetes and nocturnal hypertension. The group who took at least 1 antihypertensive medication at night

showed noteworthy reduction of nighttime systolic blood pressure, diastolic blood pressure, mean arterial pressure, overall 24-hour blood pressures, and decreased C-reactive protein when compared with taking all antihypertensives in the morning. Urinary creatinine was reduced, urinary sodium/creatinine was increased, urine osmolality was decreased, and urine potassium/creatinine were increased with bedtime administration.

Overall, a majority of these studies showed beneficial effects of dosing ACE inhibitors or ARBs before bed to decrease blood pressure throughout the night, especially in those who are considered non-dippers, to prevent consequences of constant elevated blood pressure. More studies need to be conducted with larger patient populations and longer time frames of acquiring data on participants to make future official recommendations on dosing antihypertensive medications at night. Limitations in this literature review included lack of documented ethnic or gender diversity, no specific section of methods listed in some of the studies, criteria for hypertension was not listed in a selected few, and not all provided the exact dosages of medications that participants were given to correlate effective dosages.

Application to Clinical Practice

Hypertension, diabetes, and chronic kidney disease will be commonly encountered within clinical practice. Therefore, discussing treatment regimens with your patients to determine which plan suites them best is important to prevent further progression of the diseases listed above. This review will help medical providers weigh the advantages and disadvantages of dosing ACE inhibitors or ARBs at night in those with hypertension and those with hypertension plus diabetes or chronic kidney disease to enhance the efficacy and benefits of the prescribed medications to prevent complications.

My research has shown benefits of dosing ACE inhibitors or ARBs at night in order to decrease blood pressure throughout the night and into the next day to avoid constant elevation and early morning spikes in blood pressure that may initiate cardiac events, cerebrovascular events, or further kidney damage. Ramipril, valsartan, and olmesartan were the only drugs in my literature review that had studies performed independently from other classes of antihypertensives. No adverse patient events or complications stemmed from these trials.

Tailoring chronotherapy to the physiologic mechanisms that take place during the circadian rhythm is requiring further research involving gastric pH, gastric motility, biliary function, glomerular filtration, hepatic enzyme activity, and organ blood flow to determine the most effective time to dose antihypertensive medications in order to improve beneficial outcomes.

The advantages of utilizing chronotherapy when dosing ACE inhibitors or ARBs is the possibility of not adding another medication to a patient's already long list of prescriptions, not having to increase the financial burden to those having to take another medication, and slowing the progression of chronic disease states. One disadvantage to the theory of dosing ACE inhibitors or ARBs at night is the potential for non-compliance with the evening dose if patients are already taking medications in the morning.

Further research needs to be done with larger patient populations to make official recommendations on dosing ACE inhibitors or ARBs at night before bed in those with hypertension and hypertension plus diabetes or chronic kidney disease. However, because there were no documented patient adverse events or complications that arose from these trials, it would be worth trying this type of intervention on patients who are willing to be compliant with the dosing regimen.

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