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Optimal Timing of ACE Inhibitor and ARB Dosing: Morning versus Evening Administration in Hypertension Management

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Abstract: ***Hypertension affects 1.4 billion people globally. Blood pressure typically dips during sleep, following a circadian rhythm. There is ongoing debate about the best time to take RAAS inhibitors. If these drugs lose their effect while a patient sleeps, it may disrupt this natural dip, raising the risk of heart problems. The aim of this focused narrative review is to assess whether it is optimal for blood pressure control and reduction of cardiovascular events to take RAAS blockers (ACE inhibitors and ARBs) at night or during the day. Randomized controlled trials and chronotherapy studies evaluating the effect of dosage time on blood pressure and cardiovascular outcomes are among the assessed evidence. Particularly when evaluated using ambulatory blood pressure monitoring, smaller RAAS-specific trials show better nighttime blood pressure management and restoration of nocturnal dipping with evening dosage. Larger pragmatic trials and a number of ARB-specific studies, however, show no discernible variation in 24-hour blood pressure or cardiovascular outcomes based on dose timing. Heterogeneous medication regimens, inconsistent use of ambulatory monitoring, and low power to identify cardiovascular endpoints in RAAS-specific trials all contribute to inconsistent and limited overall results.***

Keywords: hypertension, ACE inhibitors, ARBs, medication timing, blood pressure

1. Introduction

Hypertension remains one of the leading modifiable risk factors for cardiovascular morbidity and mortality worldwide, and is the leading modifiable risk factor for strokes (1). Despite the widely available therapies for antihypertension, rates of blood pressure control remain suboptimal. With 1.4 billion sufferers of hypertension worldwide, only 1 in 5 have it under control (2). This spurs the question: Should we implement different strategies in controlling hypertension? One of these strategies is chronotherapy, means giving medication in alignment with biological circadian rhythms. Clarifying the optimal timing of ACE inhibitor and ARB administration could help clinicians maximize blood pressure control and reduce patient risk.

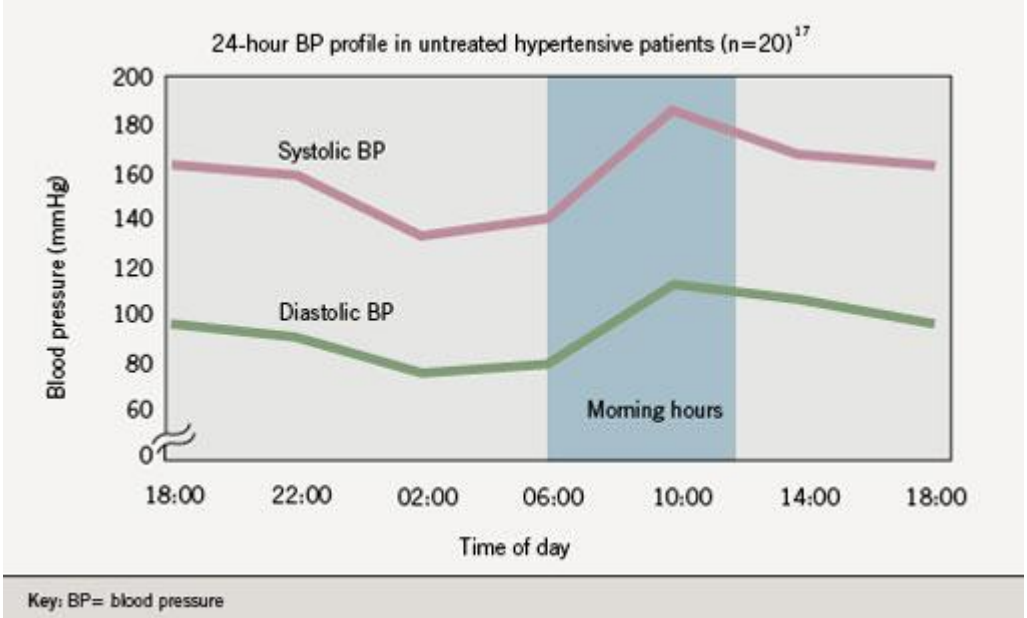

Figure 1 (3)

Blood pressure shows a circadian pattern, with a peak in the morning, a steady decline during the day and a physiological decline during sleep - often referred to as nocturnal 'dipping'. However, attenuation of nocturnal blood pressure dipping has been associated with higher risk of cardiovascular events (4) which consequently has sparked interest into whether or not the timing of anti hypertensive medication could influence nocturnal blood pressure.

The renin-angiotensin-aldosterone-system (RAAS), is a central regulator of blood pressure, and has also been shown to demonstrate circadian variation similar to the circadian variation of blood pressure.

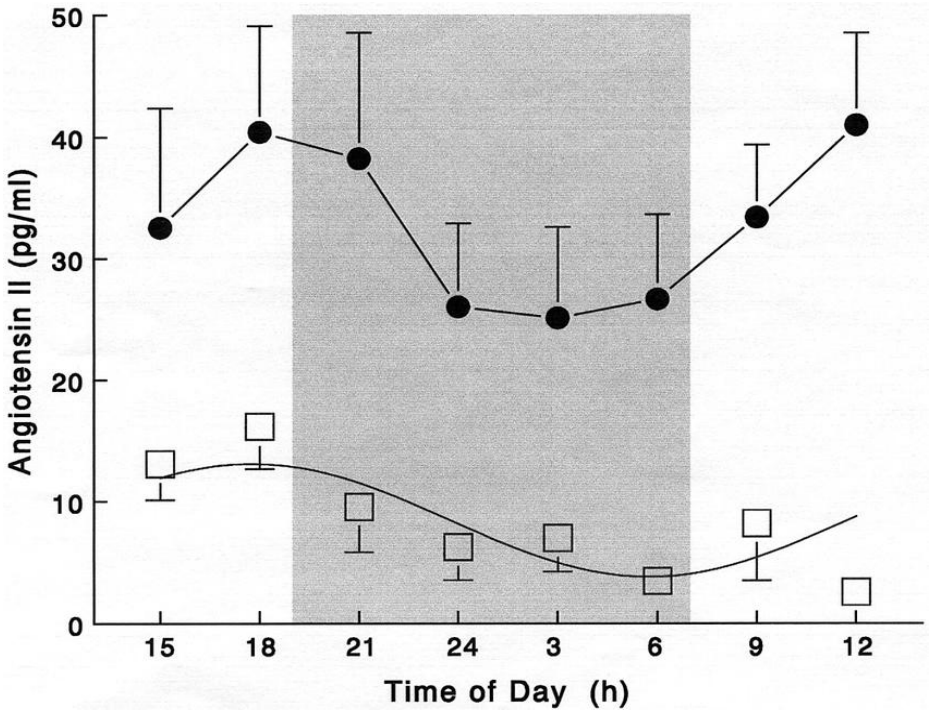

Figure 2 (5)

As seen here, there is nocturnal dipping of the levels of Angiotensin II, which is a hormone that raises blood pressure via increased sodium and water retention, as well as vasoconstriction. Because blood pressure and the RAAS system follow a circadian rhythm, giving RAAS-blocking agents in the evening may help suppress nocturnal blood pressure and restore normal dipping. Despite widespread use of ACE inhibitors and ARBs amongst a large variety of demographics, there is still uncertainty as to whether the timing of administration meaningfully influences blood pressure control. Furthermore, variations in patient characteristics, pharmacokinetic properties of the drug properties, drug half-life all influence the interpretation of the existing evidence base.

This focused narrative review aims to critically examine the available evidence regarding whether or not ACEi/ARBs should be taken in the day or evening. By integrating circadian physiology, pharmacokinetic considerations and findings from key clinical studies this review shall seek to provide clarification on the clinical implications of RAAS inhibitor chronotherapy, and to assess whether current evidence supports modification of drug administration time in hypertensive patients.

Circadian Regulation of Blood Pressure and the RAAS System

In normotensive individuals, there is a nocturnal 10-20% dip in blood pressure due to a decrease in sympathetic nervous system activity, reduction in cardiac output and a decrease in total peripheral resistance (6). As previously established this is referred to as dipping, and in many hypertensive individuals this normal physiological phenomenon may be lost, and these patients are referred to as ‘non dippers’. In hypertensive patients, there is dysregulation of the interactions between autonomic nervous system activity, vascular reactivity, renal sodium handling, and hormonal signalling. Disruption of these mechanisms may exacerbate nocturnal blood pressure elevation, diminishing the blood pressure lowering effects of antihypertensive regimens.

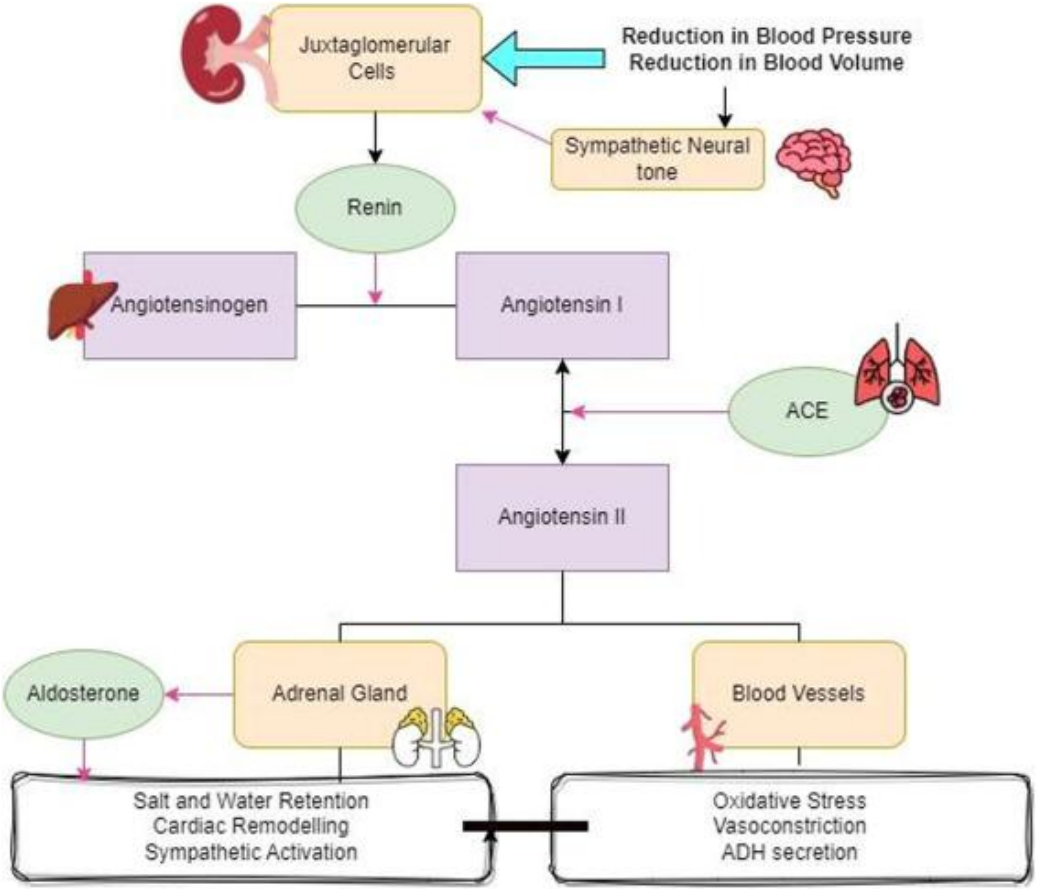

Figure 3 (7)

The diagram shows how Angiotensin II and Aldosterone affect blood vessels and kidney sodium handling. Angiotensin II raises sympathetic activity and causes blood vessels to narrow. Aldosterone helps the kidneys keep more sodium. At night, these effects may become more important because the body clears more sodium during the day than at night.

Furthermore, vasculature contributes to circadian blood pressure regulation. It has been demonstrated that endothelial function, arterial stiffness and baroreceptor sensitivity vary based on the time of day. RAAS activation has been proven to cause increased arterial stiffness and endothelial dysfunction, which suggests that RAAS blockers may have different effects depending on when they are taken. (8)

In addition to neurohormonal control, the blood vessels themselves play a role in regulation of blood pressure. At night, there is increased sensitivity of the baroreceptor reflex. This means that administering a RAAS blocker at night may yield greater effects on reducing blood pressure when compared to the morning, due to a lower response from the vasculature. (9)

As a whole, the different effects of RAAS blockers on the vasculature, kidneys, and hormonal systems have differing physiological effects that may be influenced by the time of day at which they are taken. The clinical relevance of the time-sensitive effects will ultimately depend on the pharmacokinetics of the individual drug as well as the individual characteristics of the patient.

Pharmacokinetic and Pharmacodynamic Considerations of RAAS inhibitors

Aside from the timing of administration of RAAS inhibitors, we also need to take into account pharmacokinetics and pharmacodynamics.

Active ingredient	*Dosage (mg)*	$T_{1/2}$ *(h)*	T_{max} *(h)*	*Duration (h)*
Valsartan	40–320	9	2–4	24
Losartan	50–100	6–9	3–4	24
Candesartan	4–32	9	3–4	36
Telmisartan	40–80	24	3–4	48
Irbesartan	150–300	11–15	2	24
Ramipril	1.25–20	13–17	3–6	18–24
Captopril	6.25–150	<2	1	Dose related
Perindopril	4–8	20–30	3–4	24
Lisinopril	2.5–40	12	4–6	24
Fosinopril	10–40	12	2–6	24

T_{max}: time to peak therapeutic effect.
$T_{1/2}$: time of elimination half-life.

Figure 4 (10)

ACEi exhibit a wide range of half lives and this is important for consideration when the medication should be taken. For example, Captopril has a half life of 2 hours and requires multiple daily doses whereas longer acting agents such as lisinopril and ramipril are taken once daily due to their longer half-lives. This is significant because by morning dosing a shorter acting ACEi, the effects may be diminished by night time, limiting nocturnal blood pressure control. On the other hand, longer acting ACE inhibitors maintain therapeutic concentration over 24 hours, so dosing time may not affect their efficacy. ARBs share a similar issue, whereby there are relatively short acting agents such as losartan, and longer acting agents such as telmisartan and valsartan which demonstrate sustained blood pressure control over a 24 hour period. This also means that any benefits from evening dosing are more probable to be applicable to the shorter acting drugs.

Pharmacodynamically speaking, RAAS blockers lower blood pressure by decreasing sympathetic activity, salt retention, and vasoconstriction. The timing of delivery in relation to circadian changes in vascular tone, renal salt processing, and hormonal activity may affect how strong these effects are. Therefore, by coordinating peak pharmacological action with times of higher RAAS-mediated effect, evening dosing has been hypothesised to improve suppression of nocturnal blood pressure.

Even so, each patient may respond differently to these drugs.. Factors such as baseline nocturnal blood pressure trends, renal function, and any other antihypertensive therapies alongside RAAS blockers play a role in the body's response. As well as that, enhancing nocturnal blood pressure reduction may be detrimental in certain patients, as this may cause nocturnal hypotension. (11) Therefore, we should focus holistically on the patient and take into account the previously mentioned factors, rather than attempting to draw one classwide conclusion.

Evidence Supporting Evening Dosing

A randomised study of ramipril compared the effects of evening versus morning dosing on blood pressure. Patients who took ramipril in the evening demonstrated lower nighttime blood pressure, improved dipping patterns, and an increased proportion of controlled ambulatory blood pressure. This study is directly relevant, as it evaluates the same ACE inhibitor, compares morning and evening administration, and uses ambulatory blood pressure monitoring, which is essential for assessing nocturnal BP. While supportive of the hypothesis that ACE inhibitors may be more effective at night, the study is not definitive due to its small sample size (n=115), absence of follow-up, and lack of cardiovascular outcome data. Consequently, it remains unclear whether the observed improvements in nocturnal blood pressure translate into meaningful reductions in long-term cardiovascular risk. (12)

Similarly, the OMAN trial assessed hypertensive patients on an olmesartan-based regimen using ambulatory blood pressure monitoring. Patients receiving medication at bedtime showed significantly greater nocturnal systolic and diastolic blood pressure reductions compared with morning dosing. Importantly, these benefits were achieved without compromising daytime blood pressure control or increasing adverse events. However, interpretation requires caution: the trial was not powered to evaluate cardiovascular outcomes, the use of combination medication limits attribution of effects to ARB timing alone, and higher-risk groups- including patients with established cardiovascular disease, chronic kidney disease, or advanced diabetes - were excluded, limiting generalisability. Despite these limitations, under controlled conditions, the OMAN trial provides moderate-quality evidence that RAAS-based therapy administered at night can positively influence nocturnal blood pressure patterns. (13)

The MAPEC study, a larger prospective investigation, was the first to assess whether antihypertensive medication timing influences cardiovascular outcomes and ambulatory blood pressure patterns. Compared with traditional morning dosing, administering at least one medication at bedtime significantly improved nocturnal blood pressure control and was associated with a lower risk of total and major cardiovascular events in 2,156 hypertensive adults followed for a median of 5.6 years. Despite these encouraging findings, limitations exist: the flexible medication regimens complicate attribution of effects to dosing time alone, the open-label design introduces potential performance and detection bias, and the study population was drawn from Spanish specialty clinics, limiting generalisability. Moreover, the cardiovascular benefits reported have not been consistently replicated in independent trials, and concerns regarding selection bias,

attrition, and small absolute event numbers suggest caution in interpreting the results. These factors highlight the need for larger, multicenter trials with standardised regimens to validate potential advantages of bedtime RAAS inhibitor administration. (14)

The Hygia Chronotherapy Trial also investigated night versus daytime dosing of antihypertensives, reporting significant reductions in cardiovascular events and improved nocturnal blood pressure control with bedtime administration. However, the magnitude of benefit exceeded what is typically expected from blood pressure lowering alone, raising questions about plausibility. Methodological limitations, including open-label design, lack of independent replication, and limited transparency, as well as inconsistent verification of findings by later large-scale RCTs, indicate that the Hygia results should be interpreted cautiously and not used in isolation to guide clinical practice. In both MAPEC and Hygia, the reported cardiovascular risk reductions appear disproportionate to the degree of blood pressure lowering, suggesting potential residual confounding or overestimation of treatment effects. (15)

Overall, evidence indicates that evening dosing of ACE inhibitors and ARBs can improve nocturnal blood pressure control, with studies consistently using ambulatory blood pressure monitoring to assess 24-hour efficacy and mitigate the white-coat effect. Nonetheless, RAAS-specific trials remain small and underpowered for clinical endpoints, and larger trials like MAPEC and Hygia included multiple antihypertensive classes, not solely RAAS inhibitors. To provide definitive guidance for clinicians, more robust evidence from larger, controlled trials focusing on RAAS blockers is required.

2. Evidence Supporting Morning Dosing / No Difference

No high-quality RCTs demonstrate a clear benefit of taking RAAS blockers in the morning. Some studies suggest that timing may not affect outcomes for antihypertensives more generally.

The TIME trial directly challenges prior chronotherapy claims. In this pragmatic RCT of over 21,000 hypertensive patients, evening dosing was not associated with reduced major cardiovascular events compared with morning dosing. Subgroup analyses of patients on ACE inhibitors or ARBs similarly showed no benefit from bedtime administration. The trial's large sample size, long follow-up, and use of hard clinical endpoints support the conclusion that evening RAAS inhibitor dosing does not confer additional cardiovascular protection, although ambulatory blood pressure monitoring was not performed, limiting conclusions about nocturnal dipping. Further, most participants had well-controlled baseline blood pressure, so small changes from timing alone may have minimal impact. The open-label design and heterogeneity of medications also complicate RAAS-specific interpretation. (16)

The BedMed trial, involving 3,357 hypertensive adults, similarly found no significant differences in major cardiovascular events or all-cause mortality between morning and evening dosing groups. Secondary safety outcomes were comparable, and while the trial was robust in size, it did not include ambulatory blood pressure monitoring, preventing assessment of nocturnal effects. Collectively, these pragmatic trials suggest that routine bedtime dosing of antihypertensives, including RAAS inhibitors, does not provide additional cardiovascular benefit in general hypertensive populations. (17)

Finally, a 26-week, multicentre, double-blind trial of valsartan administered in the morning versus evening also found comparable reductions in 24-hour, daytime, and nighttime blood pressure. While ambulatory monitoring was employed, the study's short duration, focus on a single RAAS agent, low-risk population, and reliance on blood pressure rather than cardiovascular outcomes limit interpretation. Nevertheless, these findings support a neutral effect of dosing time for ARBs with sustained 24-hour activity, though possible timing effects in higher-risk patients or with other RAAS inhibitors cannot be excluded. (18)

3. Clinical Implications

Currently, there is not enough evidence to make a recommendation for all patients with hypertension on the best time of day to take ACEi or ARBs. Although many smaller clinical and mechanistic studies suggest that taking these medications in the evening may help patients achieve better nocturnal blood pressure control and restore a more normal physiological dip during the night, the benefits observed in smaller studies have not consistently been seen in terms of lower rates of cardiovascular events in larger pragmatic clinical trials.

From a clinical care standpoint, this means that there should not be a "one size fits all" approach for the timing of administration of RAAS inhibitors. Healthcare providers should consider patient-specific factors when recommending a specific dosing timetable, for example blood pressure patterns throughout the day, other disease conditions (comorbidities), tolerability of medication, as well as patient adherence to the prescribed treatment regimen. Therefore, for example, patients who have documented evidence of nocturnal hypertension or non-dipping on ambulatory monitoring may theoretically benefit from receiving their RAAS inhibitors in the evening while patients whose blood pressure is well controlled with once-daily RAAS blockade are unlikely to gain a significant benefit from changing their dosing times.

Key studies such as TIME and BedMed show that changing the timing of medication does not improve heart outcomes for most people with high blood pressure. These results are especially pertinent to clinical practice because they indicate that rather than concentrating solely on dosing time, clinicians should prioritise achieving overall blood pressure control and medication adherence. Furthermore, indiscriminate bedtime dosing is discouraged due to concerns about nocturnal hypotension, especially in older adults or those at risk of falls.

In general, clinicians should refrain from strict chronotherapy recommendations and instead take a patient-centered approach, saving evening dosing for specific individuals

where nocturnal blood pressure abnormalities have been clearly demonstrated and potential risks have been taken into consideration, until more robust RAAS-specific evidence is available.

4. Future Directions and Research Gaps

Overall, there is not one sole study which perfectly encapsulates the question as to whether or not ACEi/ARBs should be taken during the day or at night. There are still significant gaps in the evidence base solely regarding administration time of RAAS blockers. Whilst there has been some promising studies regarding the effects of nighttime dosing, the studies still have their own shortcomings, whether it be a small sample size or unreproducible results.

To design a perfect study to assess this question, we need to observe the effects of nighttime dosing on a number of RAAS blockers, to assess variation between drugs with varying half lives. Furthermore, the studies should focus solely on RAAS blockers. A common downfall amongst the evidence base was the use of multiple medications, which makes it hard to isolate the effects of taking RAAS inhibitors at night as other antihypertensives act on different pathways hence chronotherapy may influence their efficacy less. Moreover, future studies should solely use ambulatory blood pressure monitoring. As established earlier, we need to assess dipping patterns as well as blood pressure over a 24 hour time period. Many of these studies did not use ambulatory blood pressure monitoring, meaning there may have been discrepancies in the data. As well as that, many of these trials focused solely on individuals without any major co-morbidities and who had well controlled blood pressure already. Future studies should aim to include patients with conditions such as: diabetes mellitus, chronic kidney disease, resistant hypertension, and existing cardiovascular conditions. This is because these patients are the individuals who are more likely to reap the benefits of well implemented chronotherapy, so the effects on them should be studied the most.

Finally, greater emphasis should be placed on standardisation and transparency of trial design, including fixed dosing regimens, consistent outcome definitions, and independent replication of findings. Until such data are available, recommendations regarding the optimal timing of RAAS inhibitor administration should remain cautious and individualised, rather than universally applied.

5. Conclusions

At the time being, there is not enough evidence to substantiate widespread change of dosing time of RAAS blockers. For the time being, the most optimal solution is likely to allow the patient to take their medications at a time convenient for them, to keep adherence high as this is more significant than administration time.

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