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RESEARCH ARTICLE

Optimal Time to Administer Once-Daily Oral Cardiovascular Agents: Evidence Based on Randomized Clinical Trials in the Last Ten Years

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Abstract

Background: Sporadic studies have investigated the influence of administration time (morning versus evening) on the efficacy and safety of once-daily medications. It is necessary to let clinicians know the developments during the last ten years.

Methods: Focusing on chronotherapeutic topic, a literature search on randomized controlled trials (RCTs) of oral once-daily cardiovascular agents was conducted using PubMed, Cochrane Library, Scopus and Web of Science from Jan 01, 2008 to Sept 30, 2018.

Results: Forty-seven RCTs investigated cardiovascular agents. Thirty-five RCTs showed the advantages of evening or bedtime dosing, only one RCT showed the superiority of morning dosing (perindopril for patients with obstructive sleep apnoea and hypertension), and 11 RCTs showed no relationship between dosing time and therapeutic outcomes. Two RCTs reported the difference in occurrence of actual side effects following morning versus evening administration (significantly lower incidence of edema following bedtime dosing of nifedipine rather than morning dosing, significantly lower rate of CKD event following bedtime dosing of ≥ 1 hypertension medications rather than therapy with all medications upon awakening). Rivaroxaban and amlodipine were cases of exhibiting chronopharmacokinetic feature. Factors determining whether to exhibit administration time-dependent effects may include disease characteristics, gender, drug combination, treatment course, types of medications, dose, pharmaceutical dosage forms, and outcome measures.

Conclusion: Chronotherapy intervention may be considered to improve medication therapy management before attempting to increase dose or add more drugs. Clinicians should educate patients about optimal administration time to take oral once-daily medications. More RCTs are needed to explore the possibility of optimal dosing time because relevant descriptions are unavailable in prescribing information for many once-daily oral cardiovascular medications.

Keywords

Cardiovascular disease, Chronotherapy, Diurnal variation, Dosage and administration, Efficacy, Medication safety, Randomized controlled trials

Introduction

Chronotherapy, an emerging concept in the field of therapeutics, involves the drug administration in coordination with the body's circadian rhythms to maximize efficacy and reduce side effects [1]. Information provision to consumers and health professionals about the optimal time to take medications usually lags behind emerging evidence. We have presented a review on the optimal time to take oral once-daily medications in clinical practice by retrieving literature by the end of 2007 [2]. During the last ten years, sporadic studies have cropped up to investigate the influence of administration time on the efficacy and safety of once-daily medications. These studies have enriched international

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community knowledge about chronotherapeutics.

Randomized controlled trials (RCTs) are considered to provide the most reliable evidence on the effectiveness of interventions because the processes used during the conduct of an RCT can minimize the risk of confounding factors affecting the results [3]. Meanwhile, cardiovascular disease (CVD) is the leading cause of death globally, and it is important to appropriately arrange optimal time of cardiovascular drugs' administration. We present an update narrative review to summarize the findings derived from the RCTs investigating whether better therapeutic outcomes could be achieved by optimal timing of once-daily cardiovascular agents.

Methods

Search strategy

The relevant literature was identified by searching PubMed, Cochrane Library, Scopus and Web of Science from Jan 01, 2008 to Sept 30, 2018. For PubMed, the query was title containing "chronotherapy" or "chronotherapeutic" or "chrono" or "circadian" or "diurnal variation" or "administration time" or "dosing time" or "dose timing" or "time of administration" or "treatment time" or "time-dependent" or "bedtime and morning" or "evening and morning", with a filter of "language: English; article type: Randomized controlled trials". For Cochrane Library, the query was record title containing "chronotherapy" or "chronotherapeutic" or "bedtime and morning" or "evening and morning", with a filter of "publication type: randomized controlled trials" and "language: English". For Scopus, the query was article title containing "chronotherapy" or "chronotherapeutic" or "administration time" or "evening and morning" or "bedtime and morning" or "time of administration", and "article title, abstract, keywords: Randomized", with a filter of "language: English; publication type: article". For Web of Science, the query was article title containing "chronotherapy" or "chronotherapeutic" or "evening and morning" or "bedtime and morning", and topic containing "randomized clinical trial", with a filter of "language: English"; "document type: Article". The number of articles identified in PubMed, Cochrane Library, Scopus and Web of Science was 268, 122, 170 and 264, respectively. After eliminating duplicate documents, two hundred sixty-eight articles were further screened.

Selection criteria

Inclusion criteria included chronotherapeutic studies of oral once-daily medications. Exclusion criteria were articles actually irrelevant to the chronotherapeutic topics on cardiovascular drugs, conference abstracts and other non-original articles. After reviewing the summary of each article, 221 articles were directly excluded because of actually irrelevant topics (n = 199), conference abstracts (n = 10), grand rounds (n = 1), comment (n = 1), and studies not involving cardiovascular medications (n = 10). Forty-seven papers were finally chosen according to the inclusion/exclusion criteria. The full text of each include article was critically reviewed, and valuable information was summarized by data interpretation.

Results and Discussion

Antihypertensive medications

Angiotensin-converting enzyme inhibitors (ACEIs): Prescribing information for both perindopril and ramipril recommend morning administration. However, literature revealed different chronotherapeutic requirements for the two drugs. Serinel, et al. evaluated the efficacy of chronotherapy for stage 1-2 hypertension in patients with obstructive sleep apnoea (OSA) receiving evening or morning perindopril for 6 weeks. There was no difference between perindopril dosing times in terms of the extent of sleep systolic blood pressure (SBP) reduction, however, morning dosing reduced more wake SBP than evening dosing and could be preferable in patients with OSA and hypertension [4].

Hermida, et al. investigated the administration time-dependent effects of ramipril 5 mg once daily as a monotherapy after 6 weeks of treatment either on awakening or at bedtime on ambulatory BP in 115 untreated hypertensive patients. The BP reduction during diurnal activity was comparable between two treatment times. However, compared to morning administration of ramipril, bedtime administration was significantly more efficient in reducing asleep BP, significantly higher awake/asleep BP ratio toward a more dipping pattern and greater proportion of patients with controlled ambulatory BP (43% versus 65%, $P = 0.019$) [5].

Angiotensin-receptor blockers (ARBs):

Candesartan: Candesartan prescribing information does not specify the specific once-daily administration time. Eguchi, et al. observed that bedtime dosing of candesartan 4 mg/day or 8 mg/day was superior to morning dosing in improving baroreflex sensitivity and the measure of renal target organ damage [i.e., urinary albumin/creatinine ratio (UACR)] [6]. Kario, et al. studied the impact of the dosing time of candesartan titrated by self-measured home BP on cardiorenal damage in hypertensive patients. In total patients, the bedtime-dosing group experienced more markedly reduced UACR compared to the awakening-dosing group (-45.7% versus -34.5%, $P = 0.02$). However, when patients were stratified into three subgroups by the morning and evening SBPs difference [i.e., morning hypertension group (morning and evening difference at least 15 mmHg), morning-evening hypertension group (0 mmHg ≤ morning and evening difference < 15 mmHg), and evening hypertension group (morning and evening difference < 0 mmHg)], only morning hypertension group exhibited significant difference in the UACR reduction

between two dosing groups (-50.6% versus -31.3%, *P* = 0.02) and thus this subgroup may benefit from the chronotherapeutic strategy of ARB. For the other subgroups, the administration time may be adjusted to the patient's needs without any significant change in the *in-vivo* performance [7]. This case indicates that disease characteristics may be an important factor in implement the chronotherapeutic strategy.

Olmesartan: Olmesartan prescribing information does not specify the specific once-daily administration time. Mori, et al. observed that olmesartan once daily could effectively reduce morning home and office BP, SV1+RV5 and renoprotective parameters in 218 patients with primary hypertension regardless of dosing time [8]. However, Tofé Povedano, et al. confirmed the chronotherpeutic effect of olmesartan 40 mg once daily at wake up or bedtime for 8 weeks on 24-h BP and albuminuria in 40 type 2 diabetic patients with newly diagnosed hypertension. Bedtime dosing could significantly reduce night SBP (*P* = 0.007) and increase the number of dippers compared with morning dosing, without inter-group difference in 24-h BP control and urinary albumin excretion [9]. Hermida, et al. observed an administration-time-dependent effect of olmesartan 20 mg once daily as a monotherapy either upon awakening or at bedtime for 3 months on the efficacy in 123 grade 1-2 hypertensive patients. The 24 h BP reduction was similar for both treatment times, whereas bedtime dosing of olmesartan, rather than morning dosing, could significantly better achieve nocturnal BP regulation, and improve the awake/asleep BP ratio toward a greater dipper pattern [10].

Valsartan: Valsartan prescribing information does not specify the specific once-daily administration time. Ushijima, et al. observed that a dipper BP pattern could be obtained after switching from morning to evening dosing of valsartan for 4 months in hypertensive patients with a non-dipper BP pattern during morning treatment with valsartan 40-160 mg [11]. However, two RCTs did not support the superiority of evening valsartan dosing to morning dosing. Zappe, et al. confirmed no benefit of valsartan 320 mg administered at wake up or bedtime for 26 weeks on night-time BP, early morning BP and morning BP surge in patients with grade 1-2 hypertension and at least one additional cardiovascular risk factor [12]. Suzuki, et al. observed that administration time had no significant influence on the BP-lowering efficacy and reduction of UACR

Table 1: Morning versus evening administration of once-daily oral cardiovascular drugs.

Medications	Optimal dosing time			References
	Favoring evening dosing	Favoring morning dosing	Indifferent dosing time	
Perindopril		√		[4]
Ramipril	√			[5]
Candesartan	√			[6,7]
Olmesartan			√	[8]
	√			[9,10]
Valsartan	√			[11]
			√	[12,13]
Nebivolol	√			[14]
Nifedipine gastrointestinal therapeutic system	√			[15,16]
Amlodipine	√			[17]
Diuretics (thiazides, torasemide)[a]	√			[19,20]
Valsartan/hydrochlorothiazide	√			[21]
Indapamide/losartan	√			[22]
Amlodipine/hydrochlorothiazide	√			[23]
Amlodipine/valsartan			√	[24,25]
	√			[26]
Amlodipine/olmesartan			√	[27]
	√			[28]
Amlodipine/telmisartan	√			[29]
Amlodipine/fosinopril	√			[30]
Miscellaneous combination of antihypertensives	√ (Ingesting ≥ 1 antihypertensives)			[31-39]
Cardiovascular polypills (aspirin, simvastatin, lisinopril, hydrochlorothiazide)	√			[40]
Simvastatin immediate-release	√			[41]
Controlled-release simvastatin			√	[42,43]
Ezetimibe/simvastatin			√	[44]
Rivaroxaban	√			[45]
Aspirin	√			[46-48,51]
			√	[49,50]

Notes: [a]Morning dosing could still be used for patients with troublesome night-time diuresis with poor quality sleep; √: Given.

following valsartan 160 mg once daily administration for 4 weeks and then force-titrated to 320 mg for 8 weeks in 34 hypertensive patients with diabetic nephropathy [13].

Besides switching to evening dosing of valsartan without changing its dose, switching to either morning or evening dosing of olmesartan may also be a choice to obtain a dipper BP pattern in non-dipper hypertensive patients on valsartan treatment at morning. The percent reduction in SBP during night-time compared to SBP during waking hours significantly increased at 4 months after changing the treatment regimen in each group as follows: 2.4 ± 6.3% to 10.5 ± 3.8% in the valsartan-evening group ($P < 0.01$), 4.3 ± 4.0% to 10.1 ± 6.4% in the olmesartan-morning group ($P < 0.05$) and 1.2 ± 5.0% to 6.4 ± 10.4% in the olmesartan-evening group ($P < 0.05$) [11]. Olmesartan has a terminal half-life of 12-18 h and its prolonged duration of action might have contributed to equivalent lowering of BP irrespective of administration time.

Nebivolol: Nebivolol is a third-generation lipophilic β1-selective blocker with direct vasodilator properties with a half-life of 10-30 h. Nebivolol prescribing information does not specify the specific once-daily administration time. Acelajado, et al. tested whether dosing time of nebivolol 5 mg/day (force-titrated to 10 mg/day after 1 week) could alter the effects of nebivolol on the morning BP surge and nocturnal dipping in 42 nondiabetic hypertensive patients. Both dosed nebivolol significantly lowered daytime, nighttime, and 24-h BP after 3 weeks of treatment. However, only evening dosing of nebivolol significantly reduced prewaking SBP by 8.64 ± 26.46 mmHg and thus may offer a therapeutic advantage over morning dosing [14]. Further studies are needed to clarify the impact of morning versus evening dosing of nebivolol on cardiovascular outcomes.

Nifedipine gastrointestinal therapeutic system (GITS): Prescribing information for nifedipine GITS does not specify the specific once-daily administration time. Hermida, et al. investigated the administration-time dependent antihypertensive effects of nifedipine GITS (30 mg/day) for 8 weeks in 238 patients with previously untreated essential hypertension. Compared to morning treatment, bedtime treatment resulted in significantly greater extent of BP reduction for the entire 24 h ($P < 0.001$), and higher proportion of patients with controlled ambulatory BP (28% versus 43%, $P = 0.019$). Bedtime dosing, rather than morning doing, significantly reduced the morning BP surge ($P < 0.001$) and increased toward a more dipping pattern ($P = 0.026$) [15]. Another study by Hermida, et al. confirmed that bedtime dosing could increase efficacy of nifedipine GITS (30 mg/day) on ambulatory BP in 180 untreated essential hypertensive patients ($P < 0.012$) and reduce the prevalence of nondipping from 51% to 35% ($P = 0.025$) compared to morning dosing. Interestingly, bedtime dosing of nifedipine GITS, rather than morning dosing, could significantly reduce the incidence of edema from 13% to 1% ($P < 0.001$) and morning BP surge ($P < 0.001$) [16].

Amlodipine: Khodadoustan, et al. investigated the chronopharmacokinetics and chronopharmacodynamics of amlodipine following a single oral dose in hypertensive/normotensive subjects. Time to reach the peak plasma concentration (T_{max}) was shorter and peak plasma concentration (C_{max}) was greater after evening dosing than morning dosing in both hypertensive and normotensive subjects while SBP and heart rate were significantly reduced after evening dosing in hypertensive patients. This RCT indicates amlodipine administered at night may offer highly efficacious means to control BP without the need to increase either the dose or number of medications [17]. However, Qiu, et al. revealed that morning administered amlodipine had a better effect on the circadian BP (i.e., less 24-h diastolic BP load, and greater percentage of nocturnal BP fall) compared with evening administration of amlodipine in mild-to-moderate essential hypertension [18].

Diuretics: Both morning and night-time dosing of thiazides after 12 weeks of monotherapy could achieve BP control in Nigerian Africans whereas only patients who received night dosing experienced significant changes in left ventricular anatomic and functional indices [19]. Prescribing information for torasemide does not specify the specific once-daily dosing time, however, Hermida, et al. confirmed an administration-time-dependent effect on efficacy of torasemide in 113 grade 1-2 hypertensive patients randomly receiving torasemide (5 mg/day) as a monotherapy either upon awakening or at bedtime. The efficacy of torasemide was significantly greater with bedtime dosing as compared with morning dosing, i.e., greater reduction in the 24 h mean SBP and diastolic BP (DBP) ($P < 0.001$) and higher percentage of patients with controlled ambulatory BP after treatment (64% versus 23%; $P < 0.001$), while safety and tolerability were similar between the two groups [20].

For some patients, the benefit of bedtime chrono-therapy of diuretics may be countered by the potential for troublesome night-time diuresis with poor quality sleep and diuretics could still be used in the morning and any add-on drug could be given in the evening.

Combination therapy:

Valsartan/Hydrochlorothiazide: Prescribing information for the fixed formulation of valsartan/hydrochlorothiazide does not specify the specific once-daily dosing time. Compared to morning dosing, bedtime dosing resulted in better reduced asleep SBP, greater proportion of subjects with properly controlled ambulatory BP (55% versus 40%, $P = 0.037$), and significantly reduced proportion of subjects with a baseline non-dipper BP profile (59% versus 23%, $P < 0.001$) [21].

Indapamide/losartan: Prescribing information for

indapamide specifies morning as the once-daily dosing time while specific dosing time is not noted for losartan. In Huangfu, et al. study [22], patients with grade 2-3 essential hypertension were randomly divided into 4 groups: Taking indapamide and losartan together in the morning or in the evening 2 to 4 h before sleep, indapamide in the morning and losartan in the evening, losartan in the morning and indapamide in the evening. All dosing groups exhibited statistically significant reductions from baseline of daytime, nighttime and 24 h mean SBP/DBP, but only the night taken-together combination could significantly reduce morning BP surge.

Amlodipine/Hydrochlorothiazide: Both morning and bedtime dosing of fixed amlodipine/hydrochlorothiazide (5 mg/25 mg) combination could significantly reduce the 24-h mean SBP and DBP in 80 hypertensive patients. However, the bedtime group experienced more reduction in the morning BP surge, lower nocturnal and 24 h mean BP, and greater proportion of patients switching from non-dippers to dippers [23].

Amlodipine/Valsartan: Prescribing information for the fixed formulation of amlodipine and valsartan tablets does not describe the specific once-daily dosing time. Asmar, et al. described equivalent effects of morning and evening dosing with amlodipine/valsartan (5 mg/160 mg) on SBP and DBP (mean 24 h, daytime, night-time, and 24-30 h) in patients with essential hypertension uncontrolled by amlodipine 5 mg/day for 8 weeks [24]. Fujiwara, et al. confirmed the noninferiority of morning dosing to bedtime dosing of amlodipine/valsartan therapy (5 mg/80 mg) in Japanese hypertensive patients for 16 weeks in terms of reducing nocturnal brachial and central BP [25]. However, Hermida, et al. suggested that amlodipine/valsartan combination therapy (5 mg/160 mg) should be preferably administered at bedtime because it could achieve the highest reduction of the 48-h mean of SBP and DBP after 12 weeks of treatment, and significantly increase the sleep-time relative BP decline towards a more normal dipper pattern and the proportion of subjects with controlled BP as compared to any other dosing schemes (both drugs on awakening, valsartan on awakening and amlodipine at bedtime, valsartan at bedtime and amlodipine on awakening) [26].

Amlodipine/Olmesartan: Prescribing information for the fixed formulation of amlodipine and olmesartan medoxomil does not specify the specific once-daily dosing time. Rozza, et al. confirmed equivalent efficacy in 24 h BP control following combination therapy in 12 untreated or poorly controlled hypertensive patients under four dosing schemes (i.e., a fixed combination of amlodipine + olmesartan ingested at 8.00 a.m. or 8.00 p.m., respectively; amlodipine 8.00 a.m. and olmesartan 8 p.m.; olmesartan 8.00 a.m. and amlodipine 8.00 p.m.) [27]. However, compared to morning administration, bedtime administration resulted in significantly reduced morning BP surge (32.3 ± 14.2 mmHg versus 24.2 ± 13.5 mmHg, $P < 0.001$), improved nocturnal BP in nondipper without reducing nocturnal BP in dipper, and lower UACR (75.3 ± 26.4 mg/g versus 42.5 ± 59.9 mg/g, $P = 0.044$) when morning BP surge, nocturnal BP pattern and cardiovascular-renal data were analyzed in essential hypertensive patients receiving amlodipine-olmesartan combination therapy [28]. It indicates that in addition to the primary end point, the secondary end point is also important when investigating the administration-time-dependent effects of once-daily medications.

Amlodipine/Telmisartan: Prescribing information for the fixed formulation of amlodipine and telmisartan tablets does not specify the specific once-daily dosing time. Kario, et al. investigated the differences in the effect of amlodipine/telmisartan combination tablets (5 mg/40 mg) taken in the morning or at bedtime for 12 weeks on BP levels in 81 hypertensive patients with paroxysmal atrial fibrillation. The antihypertensive effects were similar regardless of the dosing timing; however, the N-terminal pro-brain natriuretic peptide (NT-ProBNP), high-sensitivity troponin T (hsTnT) and UACR levels were significantly decreased only in the bedtime administration group [29]. A larger RCT is needed to demonstrate whether bedtime dosing of a telmisartan/amlodipine combination would maximize the risk-lowering effect against atrial fibrillation recurrence in hypertensive patients with paroxysmal atrial fibrillation.

Amlodipine/Fosinopril: Meng, et al. compared the effects of a combination therapy with amlodipine and fosinopril administered concomitantly or at different times on BP and circadian BP pattern in 40 patients with grade 1-2 essential hypertension and uncontrolled BP after amlodipine or fosinopril monotherapy. Both groups experienced a reduction of 24-h mean SBP and DBP; however, compared with patients receiving two agents concomitantly in the morning, patients receiving amlodipine and fosinopril in the morning and at bedtime showed a significant reduction in mean nocturnal SBP and DBP, and significant increase in the diurnal/nocturnal BP ratios of SBP and DBP) [30].

Miscellaneous combination: Crespo, et al. revealed that hypertensive patients with chronic kidney disease (CKD) ingesting ≥ 1 medications at bedtime (n = 1213) had significantly lower variables [i.e., total cholesterol, low-density lipoprotein cholesterol (LDL-C), asleep SBP and DBP] and less prevalence of non-dipping (68.3% versus 54.2%; $P < 0.001$) than those ingesting all medications upon awakening (n = 1446). Patients taking all medications at bedtime had the lowest fasting glucose, serum creatinine, uric acid and proportion of non-dipping (47.9%) ($P < 0.001$), and they showed a significantly greater prevalence of properly controlled ambulatory BP ($P < 0.001$) obtained by a significantly lower number of antihypertensives ($P < 0.001$) compared with patients

receiving all antihypertensives upon awakening. The prevalence of a riser BP pattern, an abnormal BP rhythm associated with highest CVD risk, was much greater (21.5%) among patients ingesting all medications upon awakening, compared with those taking some (15.7%) or all medications at bedtime (10.6%; $P < 0.001$) [31].

Hermida, et al. evaluated the effect of changing the dosing time on the circadian pattern of BP in 250 resistant hypertensive patients receiving 3 antihypertensives [the first drug: a diuretic; the second drug: either an ACEI or an ARB; the third drug: either a dihydropyridine calcium channel blocker or an α-blocker. The ambulatory BP reduction was statistically significant ($P < 0.001$) in patients taking 1 drug at bedtime and this reduction was greater in the nocturnal than in the diurnal mean of BP, resulting in the proportion of dippers increased from 16% to 57% in these patients after 12 weeks of intervention ($P < 0.001$) [32].

Okeahialam, et al. compared the benefits with night-time chronotherapy after 12 weeks of treatment with morning intake of antihypertensives in African hypertensive patients [33]. The mean changes in DBP, mean arterial pressure (MAP), left ventricular posterior diameter (LVPWD) and left ventricular mass (LVM) were statistically significant greater in the night-time group, suggesting that night-time intake should be encouraged and in patients requiring two or more antihypertensives one should be taken at night.

Hermida, et al. revealed that patients ingesting ≥ 1 antihypertensives at bedtime in resistant hypertension patients had significantly lower prevalence of the non-dipping (80.5% versus 54.4%, $P < 0.001$) and the riser BP pattern (31.0% versus 17.6%, $P < 0.001$), i.e., lower prevalence of CVD risk markers compared to those ingesting all of them upon awakening [34].

Ayala, et al. showed that patients with resistant hypertension taking ≥ 1 antihypertensives at bedtime showed a significantly lower adjusted hazard ratio (HR) of total CVD events than those taking all drugs upon awakening after a median follow-up of 5.4 years (HR = 0.38; $P < 0.001$). The difference between groups in the adjusted HR of major CVD events (a composite of CVD death, myocardial infarction, ischemic stroke, and hemorrhagic stroke) was also statistically significant (HR = 0.35; $P = 0.002$).

Compared to morning dosing, bedtime dosing showed significantly lower sleep-time SBP/DBP mean values ($P < 0.001$) and higher prevalence of controlled ambulatory BP (61% versus 46%; $P < 0.001$) [35].

Hermida, et al. observed that bedtime chronotherapy with ≥ 1 antihypertensives rather than awakening treatment with all drugs more effectively improved BP control, better decreased the prevalence of non-dipping, and significantly reduced relative risk of total CVD events (HR = 0.39; $P < 0.001$) and major CVD events (HR = 0.33; number of events: 55 versus 18; $P < 0.001$) after a median follow-up of 5.6 years in 2156 hypertensive patients [36].

Hermida, et al. also investigated whether therapy with the total daily dose of ≥ 1 hypertension medications at bedtime could exert greater reduction in the risk of new-onset diabetes than therapy with all medications upon awakening during a 5.9-year median follow-up. The adjusted HR of new-onset diabetes was fully equivalent across all classes of drugs when taken in the morning, whereas only patients ingesting an ARB (HR = 0.39; $P < 0.001$), ACEI (HR = 0.31, $P = 0.015$) or β-blocker (HR = 0.35, $P = 0.021$) at bedtime had significantly lower HR of new-onset diabetes than patients ingesting dihydropyridine calcium-channel blockers, α-blockers or diuretics also at bedtime [37].

Hermida, et al. confirmed that drug classes of antihypertensives were associated with the differential administration-time-dependent effects on CVD risk. Among patients randomized to ingest ≥ 1 medications at bedtime, ARBs were associated with significantly lower HR of CVD events than ingestion of any other class of medication (ACEI, diuretic, dihydropyridine calcium-channel blockers, α-blocker doxazosin GITS, and β-blocker) also at bedtime ($P < 0.017$). The HR of CVD events was significantly higher in patients not taking an ARB, independent on whether they were taking all medications upon awakening (HR: 3.72; $P < 0.001$) or ≥ 1 of them at bedtime (HR: 2.04; $P = 0.005$) [38].

Hermida, et al. investigated whether therapy with the entire daily dose of ≥ 1 hypertension medications at bedtime exerts a greater reduction in the risk of incident CKD than therapy with all medications upon awakening in 2078 hypertensive patients without CKD during a 5.9-year median follow-up. Bedtime treatment achieved significantly lower asleep BP mean, greater sleep-time relative BP decline, and a significantly lower rate of CKD event (8.3 versus 27.1%, $P < 0.001$) compared with morning dosing group [39].

Cardiovascular polypills

Evening administration of the cardiovascular polypill (aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg and hydrochlorothiazide 12.5 mg) in patients with CVD was more effective in lowering LDL-C compared to morning administration, without statistically significantly different ambulatory BP levels [40].

Statins

The statin class of cholesterol-lowering drugs have been used for decades to successfully lower plasma cholesterol concentrations and cardiovascular risk. Prescribing information for simvastatin specifies bedtime as the optimal once-daily dosing time. Tharavanij, et al. compared the lipid-lowering efficacy and the inflammatory marker high-sensitivity C-reactive protein (hsCRP)

level between morning and evening dosing of 10 mg simvastatin in 52 hyperlipidemia patients for the total course of 12 weeks. Total lipid profiles at 12 weeks were not statistically different between two groups; however, only evening simvastatin administration significantly decreased hsCRP level ($P = 0.03$) [41].

Interestingly, this RCT indicated that treatment course might affect the chrotherapeutic effect of simvastatin on LDL-C levels. Baseline LDL levels were similar in both groups, the evening simvastatin group had significantly less LDL-C than the morning group at 4 weeks (112 ± 26.1 mg/dL versus 136.3 ± 32 mg/dL, $P = 0.001$) and 8 weeks after treatment (109.7 ± 28 mg/dL versus 129.5 ± 27 mg/dL, $P = 0.006$). However, the difference in LDL-C after 12th week between two groups was insignificant.

Kim, et al. compared the efficacy and tolerability of morning and evening doses of 20 mg controlled-release simvastatin in 132 Korean patients with hypercholesterolemia. After 8 weeks of the treatment, the two groups did not differ in achievement rates of the target goal of LDL-C and the mean change of lipid parameters [42]. Yi, et al. compared the safety of morning administration of controlled-release simvastatin 20 mg with that of evening administration of immediate-release simvastatin 20 mg in 122 patients with CKD and dyslipidemia. After 8 weeks, the treatment outcomes with respect to LDL-C, total cholesterol, triglyceride, high density lipoprotein cholesterol (HDL-C) and adverse effects of the 2 treatments showed no significant inter-group difference [43]. Simvastatin and its active metabolites have short half-lives (< 5 h) whereas controlled-release simvastatin has an extended elimination half-life (13.09 h). Pharmaceutical dosage forms may explain controlled-release simvastatin's indifference to the LDL-C lowering efficacy related to dosing time and the finding of favoring evening administration of immediate-release simvastatin. Morning administration of controlled-release simvastatin may provide the flexibility of drug administration and help improve the medication compliance among some patients.

Yoon, et al. observed that the well-known chronotherapeutic requirement on evening administration of monotherapy of simvastatin immediate release could be abolished by simvastatin/ezetimibe combination therapy [44]. Morning administration of ezetimibe/simvastatin 10 mg/20 mg once daily for 6 weeks was found to be noninferior to evening administration in patients with primary hypercholesterolemia in terms of the percentage reduction of the LDL-C level and other lipid parameters from baseline, the percentage of change in hs-CRP and the frequency of adverse events. The underlying mechanism may be associated with long half-life (22 h) of ezetimibe and its pharmacologically active ezetimibe-glucuronide.

Rivaroxaban

Rivaroxaban is a selective direct inhibitor of activated coagulation factor X (FXa) authorized for administration on a once-daily basis. For reduction in risk of stroke in nonvalvular atrial fibrillation, rivaroxaban is taken once daily with the evening meal; for other indications, the 15 mg and 20 mg once daily formulation should be taken with food, while the 10 mg once daily tablet can be taken with or without food. Brunner-Ziegler, et al. observed higher rivaroxaban concentrations 12 h after drug administration of 10 mg rivaroxaban (53.3 ng/mL versus 23.3 ng/mL; $P < 0.01$) and longer lasting suppression effect (24 h instead of 12 h relative to the "no drug" baseline values) following evening administration of 10 mg rivaroxaban in sixteen healthy volunteers compare to morning intake [45]. This pharmacokinetic and pharmacodynamic changes could better match the morning hypofibrinolysis and might further improve the efficacy and safety of rivaroxaban treatment.

Aspirin

Prescribing information for aspirin does not describe the specific once daily dosing time. van Diemen, et al. assessed the effects of morning versus evening administration of aspirin on platelet activity 12 and 24 h in outpatients with stable CVD taking aspirin once daily. The attenuation of aspirin's inhibitory action was most apparent in the morning regimen, indicating that patients might benefit from evening intake [46]. Bonten, et al. examined the effect of bedtime aspirin 100 mg intake compared with intake on awakening on 24-h ambulatory BP measurement and morning platelet reactivity in 290 patients using aspirin for CVD prevention. Aspirin intake at bedtime did not reduce BP compared with intake on awakening; however, it reduced morning platelet reactivity during the high risk morning hours [47]. Snoep, et al. showed that bedtime administration of 100 mg aspirin could significantly diminish 24-h plasma renin activity and excretion of cortisol, dopamine, and norepinephrine in 24-h urine compared with administration on awakening in 16 grade 1 hypertensive subjects. Decreased activity of these pressor systems may provide a biologically plausible explanation for the BP-lowering effect of aspirin night dosing, rather than morning dosing [48].

However, Dimitrov, et al. observed that mean 24-h, diurnal and nocturnal SBP or DBP were not statistically different between two dosing regimens of aspirin for 1 month in 75 treated hypertensive patients routinely taking aspirin for cardiovascular prevention and a mean of 2.8 antihypertensive drugs [49]. Ruiz Arzalluz, et al. also confirmed that both bedtime administration and morning administration of aspirin (100 mg) did not modify the 24-h ambulatory BP in hypertensive patients in secondary cardiovascular prevention [50].

Interestingly, Ayala, et al. observed sex differences in the administration-time-dependent influence of aspirin 100 mg daily for 3 months on BP in untreated mild hypertensive patients [51]. Ambulatory BP was

unchanged in the males and slightly but significantly elevated in the females ($P < 0.023$) following aspirin morning dosing compared to bedtime dosing, however, bedtime dosing significantly reduced BP and to a larger extent in women than men. Therefore, this timed administration of low-dose aspirin may provide a cost-effective approach for BP control and potential added cardiovascular protection in hypertensive women.

Factors determining whether to exhibit administration-time-dependent effects

Once-daily medications were divided into three categories, i.e., medications favoring evening or bedtime dosing, medications favoring morning dosing and medications irrespective of dosing time. Table 1 listed the optimal time to administer once-daily oral cardiovascular drugs. Forty-seven RCTs investigated cardiovascular agents. Thirty-five RCTs showed the advantages of evening or bedtime dosing, only one RCT showed the superiority of morning dosing (perindopril for patients with OSA and hypertension), and 11 RCTs showed no relationship between dosing time and therapeutic outcomes. One RCT reported the opposite conclusion, e.g., "evening dosing is superior to morning dosing" compared with "morning dosing is superior to evening dosing" in previous study. Two RCTs reported the difference in occurrence of actual side effects following morning versus evening administration (significantly lower incidence of edema following bedtime dosing of nifedipine rather than morning dosing, significantly lower rate of CKD event following bedtime dosing of ≥ 1 hypertension medications rather than therapy with all medications upon awakening) [16,39]. Rivaroxaban and amlodipine were cases of exhibiting chrono-pharmacokinetic feature [17,45].

Factors determining whether to exhibit administration time-dependent effects may include disease characteristics, gender, drug combination, treatment course, types of medications, dose, pharmaceutical dosage forms, and outcome measures.

- **Disease characteristics:** For example, among three subgroups by the morning and evening SBPs difference (i.e., morning hypertension group, morning-evening hypertension group, and evening hypertension group), only morning hypertension group exhibited significant difference in the UACR reduction between two dosing groups (morning versus evening) and thus this subgroup may benefit from the chronotherapeutic strategy of candesartan [7]. The differences in the characteristics of enrolled population may explain the discrepancies between studies by Dimitrov, et al. and Ayala, et al. with respect to the administration-time-dependent effects of aspirin on BP [49,51]. In the study conducted by Ayala, et al. study, recently diagnosed hypertensive patients were not receiving any antihypertensive agent and these younger patients (44.1 ± 13.2 yrs of age) did not present any comorbidity [51], whereas Dimitrov, et al. study had 33% diabetics and 65% renal failure patients [49].
- **Gender:** For example, bedtime dosing of low-dose aspirin significantly reduced BP and to a larger extent in women than men [51].
- **Drug combination:** For example, amlodipine/omesartan combination therapy lacked dosing time-dependent effects, whereas combinations (e.g., valsartan/hydrochlorothiazide, indapamide/losartan, amlodipine/hydrochlorothiazide, amlodipine/telmisartan, amlodipine/fosinopril) are preferably be taken in the evening due to more reduction in the morning BP surge, lower nocturnal and 24 h mean BP, and greater proportion of patients converting from non-dippers to dippers compared to morning dosing [21-23,27,29,30]. Unlike monotherapy of simvastatin, simvastatin/ezetimibe combination therapy did not exhibit administration-time-dependent effect on LDL-C [44]. For miscellaneous combination of antihypertensives, those taking all medications at bedtime or taking at least 1 drug at bedtime could show a chronotherapeutic benefit over those ingesting all of them upon awakening [31-39]. Hermida, et al. evaluated the administration-time-dependent effects of the number of antihypertensives on CVD risk in hypertensive patients receiving all once-daily antihypertensives upon awakening or the total daily dose of ≥ 1 of them at bedtime. There was progressive increase in the HR of total CVD events with the increase in the number of antihypertensive, when all of them were administered as a full dose upon awakening (adjusted HR: 1.75, 2.26, 3.02, and 4.18 in patients treated with 1, 2, 3, and ≥ 4 antihypertensives daily, respectively; $P < 0.001$ compared with normotensive subjects) [39].
- **Treatment course:** For example, patients receiving evening simvastatin had significantly less LDL-C than the morning group at 4 weeks and 8 weeks after treatment whereas no significant difference in LDL-C at 12 weeks after treatment was observed between two dosing groups [41]. Potucek, et al. evaluated the efficacy of morning versus evening dosing of 10 mg/kg of valsartan and 4 mg/kg of amlodipine in spontaneously hypertensive rats, and observed that only morning dosing resulted in significant BP control after short-term (1 week) treatment while both dosing groups gained similar superior results in BP control after long-term (6 weeks) treatment. This study indicated that morning administration proved to be advantageous due to earlier onset of antihypertensive action whereas the efficacy of long-term treatment was regardless of administration time [52].
- **Drug class:** For example, the extent of administration-time-dependent effects of antihypertensives

on CVD risk may depend on drug classes. Bedtime administration of ARBs exhibited significantly lower HR of CVD events than bedtime ingestion of any other class of medication (ACEI, diuretic, dihydropyridine calcium-channel blockers, doxazosin GITS, and β-blocker) [39].

- **Dose:** For example, The inconsistent chronotherapeutic effects of valsartan may be explained by the different dose used (i.e., the maximum approved daily dose 320 mg valsartan in studies by Zappe and Suzuki, et al. versus 40-160 mg valsartan once daily in Ushijima's study) [11-13].
- **Pharmaceutical dosage forms:** For example, the LDL-C lowering efficacy of controlled-release simvastatin was not related to dosing time, however, evening administration of immediate-release simvastatin is preferable [41-43].
- **Outcome measures:** Bedtime administration of amlodipine-olmesartan combination achieved equivalent efficacy in 24 h BP control in essential hypertensive patients compared with morning administration. However, bedtime dosing was superior to morning dosing if secondary end point (e.g., morning BP surge, nocturnal BP pattern and cardiovascular-renal data) were considered [27-28].

The mechanism for chronotherapeutic effect of some cardiovascular drugs

Richards, et al. provided an introduction and general overview into the role of circadian clock genes in the regulation of BP with a focus on their deregulation in the etiology of hypertension [53]. The BP circadian rhythms are controlled by the central clock in the suprachiasmatic nucleus of the hypothalamus and peripheral clocks located throughout the body, and better understanding of clock function may provide new therapeutic targets in the treatment of hypertension [54]. Potucek, et al. suggested that valsartan/amlodipine combination may serve as an independent modulator of circadian clock. They observed that mRNA levels of Bmal1 and Per2 altered in left and right ventricle, kidney and aorta predominantly in groups with evening dosing of 10 mg/kg of valsartan and 4 mg/kg of amlodipine in spontaneously hypertensive rats [52].

The pharmacokinetic phases of drugs (i.e., absorption, distribution, metabolism and excretion) may be influenced by circadian rhythms. Chronopharmacokinetics can explain individual differences in drug levels. For example, compared with morning dosing, evening dosing of amlodipine achieved shorter T_{max} and greater C_{max}. Khodadoustan, et al. hypothesis is that amlodipine is absorbed rapidly when it is given during the night time [17]. Brunner-Ziegler, et al. assumed that the higher rivaroxaban concentrations at 12 h after the evening dosing than at 12 h after the morning intake of 10 mg rivaroxaban was at least in part due to significant rhythmic variation for CYP3A activity and hepatic blood flow (i.e., enzymatic activity was higher in the morning compared to in the evening, and hepatic blood flow was greatest at 8 am) [45,55].

The difference in efficacy and/or safety between morning administration and evening administration may also involve modification of circadian rhythm of the physiological function. For example, the high-amplitude circadian rhythm of the renin-angiotensin-aldosterone system activates during nighttime sleep, which may account for that bedtime versus morning ingestion of ACEIs and ARBs better controls the asleep than awake BP [56]. Evening administration of simvastatin could better modify the normal diurnal rhythm of cholesterol biosynthesis (i.e., cholesterol synthetic rates varied from essentially zero in the morning to maximal values around midnight).

Further opportunities in research and clinical practice

Firstly, more RCTs are needed to explore the possibility of better dosing time because there are a lot of once-daily oral medicines without specific requirements in their package inserts. For example, for antiplatelet drugs, chronotherapy of low-dose aspirin rather than clopidogrel has been investigated. For oral anticoagulants, chronopharmacokinetics of rivaroxaban have been studied, however, there was no literature on the effect of administration time on pharmacokinetics and/or therapeutic outcomes of warfarin although a study protocol has been published for an RCT on the effect of medication timing on anticoagulation stability in users of warfarin [57].

Secondly, inconsistencies between studies suggest a need for more prospective RCTs with sufficient statistical power and more "smart" design of RCTs considering the factors affecting the dosing time-dependent effects. Multivariate linear regression analysis identified an independent correlation between age and percentage of nocturnal systolic BP drop ($P < 0.001$) [58], therefore the aged patients with such diurnal change may more likely experience the benefit of bedtime administration of antihypertensives.

Thirdly, it is necessary to further investigate the mechanism for chronotherapeutic effect of some cardiovascular drugs. Circadian clock genes related studies should be encouraged.

Fourthly, Hermida, et al. proposed that chronotherapy could be a cost-effective strategy for individualizing and optimizing the treatment of hypertension through normalization of the 24-h BP level and profile and for potentially reducing the risk of CVD [59]. However, pharmacoeconomic evaluation of such chronotherapy is currently unavailable.

Last but not the least, relative ethical issue might be

raised when physicians are applying the chronotherapeutic strategy. According to prescribing information, some antihypertensive drugs are suggested to be ingested in the morning whereas there are no clear requirements of dosing time for most antihypertensive medications. If physicians know the principle of chronotherapy that is believed to be beneficial to patients with hypertension, and propose patients take medication at bedtime, the paternalistic model of physician-patient relationship may consequently formed. If the patients take the chronotherapeutic advice from physicians and experience unexpected side effects and/or lower efficacy during the following treatment, moral issue about whether or not to suggest off-label use for patients would be considered.

Conclusion

This review summarized the influence of administration time (morning versus evening) on the efficacy and safety of once-daily cardiovascular agents based on RCTs in the last ten years. Chronotherapy intervention should be considered to improve medication therapy management before any attempt is made to increase the dose or add more drugs. Clinicians have an important role to play in educating patients about optimal administration time to ingest oral once-daily medications, and they also should remember patient preference and adherence and the factors affecting chronotherapeutic effects when translating the new developments of chronotherapy into the practice. More RCTs are needed to explore the possibility of optimal dosing time because relevant descriptions are unavailable in prescribing information for many once-daily oral cardiovascular drugs.

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Disclosure

The authors report no conflicts of interest in this work.

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