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Chronotherapy of cardiac and vascular disease: timing medications to circadian rhythms to optimize treatment effects and outcomes

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Circadian rhythms impact cardiac and vascular pathophysiology, resulting in 24-hour patterning of symptoms and life-threatening/ending events (*chronopathology*), plus kinetics and dynamics of medications (*chronopharmacology*), resulting in administration-time differences in efficacy and safety. Scheduling medications according to circadian rhythm determinants (*chronotherapy*) can improve treatment effects, for example, before dinner/bedtime ingestion of cholesterol-lowering medications and acetylsalicylic acid, respectively, exerts enhanced control of hypercholesterolemia and after-awakening peak of platelet aggregation; bedtime ingestion of conventional hypertension medications optimizes normalization of sleep-time blood pressure (BP) — strongest independent BP marker of cardiovascular disease (CVD) risk — and most effectively prevents (*chronoprevention*) CVD morbidity and mortality. Exploration of chronotherapeutic strategies to improve management of cardiac arrhythmias and vascular pathophysiology is still awaited.

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Introduction

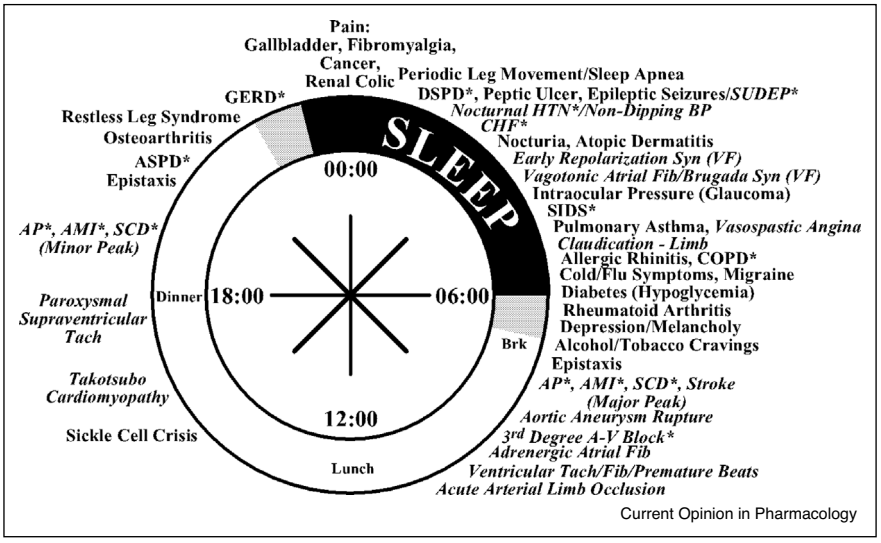
This article addresses the *chronotherapy* — timing medications to biological rhythms to optimize effect(s) and safety — of cardiac and vascular diseases. Given the limited length of this review, we authors can only introduce basic concepts and illustrative examples of current applications to stimulate future advances.

The research and practice of chronotherapuetics are not time-of-day but *biological time* based [1•,2••], and appreciation of this conceptual difference is of fundamental importance to patient care. Biological processes are not static, that is, homeostatic, as assumed by many pharmaceutical and medical scientists and practitioners. Rather, they are organized as endogenous biological rhythms of various period (τ) domains of oscillation — ultradian ($\tau < 20$ hours, e.g. sleep stage cycles), circadian ($\tau \sim 24$ hours, focus of this article), and infradian ($\tau > 28$ hours, e.g. menstrual and seasonal cycles), and characterized additionally by their amplitude — difference between peak and trough values, peak time, and level around which rhythmicity manifests [3].

Many *in vitro* and *in vivo* investigations have elucidated the cellular and molecular mechanisms of mammalian circadian timekeeping, particularly circadian rhythms (CR), which have been most studied for their relevance to medicine and pharmacology. CR derive from a master endogenous biological clock — suprachiasmatic nucleus (SCN) — within the hypothalamus that coordinates subservient endogenous peripheral biological clocks of cells, tissue, organs, and systems through modulation of constitutional clock genes (e.g. *Bmal1*, *CLOCK*, *per*^{1}, *per*^{2}, *Per*^{3}, *Cyr*^{1}, *Cyr*^{2}). The products of these clock genes cyclically activate and suppress numerous non-clock genes giving rise to circadian rhythms of biochemical pathways and most physiological, neural, endocrine, and other processes and functions, which collectively constitute the so-called circadian time structure (CTS) [4–8].

Entrainment to 24.0 hours of the period and staging — time of peak and trough — of most endogenous CR occurs mainly through the sensing of cyclic environmental time cues, the 24-hour light/dark cycle being primary [1•,8,9]. Light cues sensed by non-cone/non-rod intrinsically photosensitive melanopsin-containing retinal ganglion cells (ipRGCs) are conveyed via the retinohypothalamic neural tract to the SCN [8,9], which through neural pathways controls synthesis and release of pineal gland-derived hormone melatonin [9]. Melatonin is thus rhythmically inhibited and enabled, respectively, by the

Figure 1



Time relative to the 24-hour sleep/wake cycle of occurrence or exacerbation of chronic medical conditions and manifestation of life-threatening and life-ending events; medical conditions shown in italic font denote cardiac and vascular morbidity and mortality. *AMI = acute myocardial infarct; AP = angina pectoris; ASPD/DSPD = Advanced/Delayed Sleep Phase Disorder; A-V = atrial-ventricular; BP = blood pressure; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; Fib = fibrillation; GERD = gastroesophageal reflux disorder; HTN = hypertension; SCD = sudden cardiac death; SIDS = Sudden Infant Death Syndrome; SUDEP = Sudden Unexpected Death in Epilepsy; Syn = syndrome; Tach = tachycardia; VF = ventricular fibrillation.

light and dark cycle; accordingly, in humans melatonin circulates only during nighttime as the biochemical messenger of environmental darkness [8,9]. Phasing of the diverse CR that comprise the CTS is flexible and accommodative, although not immediately, to alteration of the light/dark cycle, for example, associated with seasonal difference in photoperiod duration, transmeridian travel, and night and rotating shift work [10,11]. Phasing of CR is additionally influenced by one's chronotype — genetic or life-stage-dependent preference for sleep and wake timings [12,13]. 'Morning' types routinely arise from sleep early in the morning and retire to sleep early at night, while 'evening types routinely rise late in the day (even afternoon) and retire to sleep late at night (often after midnight). Most humans are 'neither' types; although, seniors tend to be 'morning' types and adolescents and young adults tend to be 'evening' types.

The content of this introductory section emphasizes two critical points of relevance to the practice of clinical chronobiology and chronotherapeutics: (i) time-of-day is not indicative of biological time, and (ii) representative biomarkers of the CTS, the most convent ones being the bed and awakening times of the 24-hour sleep-wake cycle, enable synchronization of pharmacotherapy to CR to optimize effects and outcomes.

24-hour patterning of cardiac and vascular morbidity and mortality

One of the two major justifications for chronotherapeutics is 24-hour patterning of symptoms of medical conditions and risk for life-threatening or ending events due to CR in their pathophsiology (*chronopathology*) [14,15]. Figure 1 depicts, relative to the 24-hour sleep/wake cycle, occurrence, exacerbation, and death, of common medical conditions, including cardiac and vascular ones. Angina pectoris (AP), acute myocardial infarct (AMI), sudden cardiac death (SCD), cerebral and ischemic stroke, 3rd degree heart block, adrenergic atrial fibrillation, atrial premature beats, ventricular tachycardiac and premature beats, acute arterial limb occlusion, and aortic aneurysm dissection are most prevalent early in the wake span. Manifestation of takotsubo cardiomyopathy is most common early afternoon. Paroxysmal supraventricular tachycardia and secondary minor peaks in AP, AMI, SCD, and stroke happen late afternoon/early evening. Exacerbation of congestive heart failure (CHF), early repolarization syndrome, vagotonic atrial fibrillation, vasospastic (Prinzmetal variant) angina, Brugada Syndrome, limb claudication, and epilepsy-induced sudden unexpected cardiac death are most frequent during sleep [14,15].

Chronopharamacogy of cardiac and vascular medications

The second major justification for chronotherapeutics is the circadian *chronopharmacology* of medications — *chronopharmacokinetics* (administration-time differences, relative to staging of CR, in absorption, distribution, metabolism, and elimination of drugs) and/or *chronoesthesy* (CR-dependent disparity in drug concentration-effect relationship) that results in meaningful differences in efficacy

Table 1

Recommended administration time of medications per prescribing package inset (PPI) or clinical research used to manage cardiac and vascular conditions and outcome risks

Medication	Route/Timing	Medical Information
Glyceroltrinitrate	P.O./qam	Prinzmetal Angina: ↓*risk for morning event on exertion* [21]
Nitroglycerin	Patch/qhs	AP*:* ↓*risk for morning cardiac ischemic* [21]
β-blocker	P.O./Unspecified	AP, MI & SCD: ↓*risk for morning cardiac ischemic* [21]
XL-Propranolol‡	P.O./qpm, qhs	HTN: ↓morning BP/AP: ↓morning cardiac ischemic [23]
COER-Verapamil‡	P.O./qpm, qhs	HTN: ↓morning BP/AP: ↓morning cardiac ischemic [23]
CODAS-Verapamil‡	P.O./qpm, qhs	HTN: ↓morning BP/AP: ↓morning cardiac ischemic [23]
GRLA-Diltiazem‡	P.O./qpm, qhs	HTN: ↓morning BP/AP: ↓morning cardiac ischemic [23]
Acetylsalicylic Acid	P.O./qpm, qhs	Platelet aggregation: ↓morning peak of (↓blood coagulation) [22]
Fluvastatin	P.O./qpm	Dyslipidemia (PPI) [20]
Lovastatin	P.O./qpm	Dyslipidemia (PPI) [20]
Pravastatin	P.O./qpm	Dyslipidemia (PPI) [20]
Simvastatin	P.O./qpm	Dyslipidemia (PPI) [20]
Ezetimibe+Simvastatin	P.O./qhs	Dyslipidemia (PPI)
Lovastatin/Niacin	P.O./qhs	Dyslipidemia (PPI)
Niacin-XL	P.O./qhs	Dyslipidemia: (PPI)
Niacin+Simvastatin	P.O./qhs	Dyslipidemia: (PPI)
Chlorthalidone	P.O./qam	HTN: ↓BP - pragmatic ingestion time (PPI)
Indapamide	P.O./qam	HTN: ↓BP - pragmatic ingestion time (PPI)
Terazosin	P.O./qhs	HTN: ↓BP/BPH: ↓nocturia - pragmatic ingestion time (PPI)
Doxazosin Mesylate	P.O./qam	HTN: ↓BP - ingestion time, unspecified rationale (PPI)
Acetazolamide	P.O./qam	HTN: ↓BP/CHF: ↓pulmonary edema - pragmatic ingestion time (PPI)
Furosemide	P.O./qam (08/14h)	HTN: ↓BP/CHF: ↓pulmonary edema - pragmatic ingestion time (PPI)
Methyclothiazide	P.O./qam	HTN: ↓BP/CHF: ↓pulmonary edema - pragmatic ingestion time (PPI)

AP = angina pectoris; BHP = benign prostatic hyperplasia; BP = blood pressure; COER-Verapamil = controlled-onset, extended release verapamil; CODAS-Verapamil = chronotherapeutic oral drug absorption system verapamil; CHF = congestive heart failure; GRLA-Diltiazem = graded-release, long-acting diltiazem; MI = myocardial infarction; P.O. = oral ingestion; qam = every morning; qhs = every night at bedtime; qpm = every evening; qpm, qhs = either late evening or before bedtime; qam (08/14h) = every morning, but in high dose b.i.d. (= twice daily) at 08:00 and 14:00h; SCD = sudden cardiac death; XL-Propranolol = controlled onset extended-release propranolol; PPI: per prescription package insert information; entries in italic font indicate recommended time of drug administration based on post-approval marketing investigation. All entries derived from https://www.pdr.net/browse-by-drug-name, except for glyceroltrinitrate, β-blocker, and nitroglycerin [21], acetylsalicylic acid [22] and some statin medications [20]. Reference [23] provides details of the respective bedtime ingested controlled-onset, extended release medications. ‡ No longer marketed as a chronotherapy in USA.

(*chronoefficacy*) and safety (*chronotoxicology*) [16,17,18•,19]. Most pharmaceutical companies have ignored the science and concepts of chronopharmacology and chronotherapy and opportunities they present. In fact, our examination of the prescribing information of some 3200 medications legally approved for marketing in the USA revealed < 1% of them list a preferred time for administration, mostly for pragmatic reasons, for example, avoidance of compromised daytime vigilance or nighttime sleep, aversion of light-drug interactions, and advantageous posture [https://www.pdr.net/browse-by-drug-name]. Prescribing information of cardiac and vascular medications, with but few exceptions, does not designate preferred time of use; thus, recommendations for their optimal timing derive from post-approval trials primarily conducted without pharmaceutical industry involvement and financing.

Table 1 summarizes recommended/preferred times of medications commonly prescribed to manage cardiac and vascular conditions of elevated CVD risk. They include: Firstly, evening ingestion of cholesterol-lowering agents ([20], https://www.pdr.net/browse-by-drug-name); secondly, morning glyceroltrinitrate therapy to protect at this time against greatest risk for effort-induced angina of variant (Prinzmetal) patients [21]; thirdly, dosing schedules of β-adrenoceptor antagonists to ensure enhanced concentration to protect against highest risk for myocardial ischemic, AP, MI, and SCD, that is, after awakening from sleep [21]; fourthly, evening ingestion of low-dose acetylsalicylic acid to attenuate prominent morning peak of platelet aggregation [22]; fifthly, bedtime ingestion of special medications — controlled-onset, delayed-release drug delivery systems — designed to attenuate elevated morning risk for

Table 2

Differences in effects of six classes of BP-lowering medications and their combinations quantified by changes from baseline awake and asleep SBP/DBP means (mmHg) and sleep-time relative SBP/DBP decline (%) when ingested by hypertensive patients upon awakening versus at bedtime

Medication	Reduction in Awake SBP/DBP Mean		Reduction in Asleep SBP/DBP Mean		Sleep-time Relative SBP/DBP Decline	
Dose (No. Subjects)	Awakening R_x	Bedtime R_x	Awakening R_x	Bedtime R_x	Awakening R_x	Bedtime R_x
ACEI						
5 mg Ramipril (N=115)	-10.1/-6.9	-10.5/-9.0	-4.5/-4.1	-13.5/-11.5 *	-3.3/-1.8	3.4/4.9 *
6 mg Spirapril (N=165)	-9.9/-8.0	-8.5/-5.7	-5.7/-4.6	-12.8/-8.6 *	-2.5/-2.7	4.1/4.5 *
ARB						
160 mg Valsartin (N=559)	-13.4/-9.4	-14.1/-10.5	-12.4/-8.9	-18.4/-12.6 *	0.3/1.0	4.5/4.8 *
20-40 mg Olmesartan (N=203)	-14.8/-10.9	-14.5/-10.4	-11.6/-8.3	-16.4/-12.0 *	-1.1/-0.8	3.0/4.4 *
80 mg Telmisartan (N=215)	-11.7/-8.8	-11.3/-8.2	-8.3/-6.4	-13.8/-9.7 *	-1.6/-1.0	3.1/3.9 *
CCB						
5 mg Amlodipine (N=194)	-10.2/-7.7	-11.8/-7.2	-9.6/-5.5	-11.2/-6.7	0.1/-1.6	0.2/0.7 ‡
30 mg Nifedipine GITS (N=238)	-9.4/-6.3	-12.8/-7.7 ‡	-7.5/-5.1	-12.8/-7.8 *	-0.7/-0.2	1.0/1.5 ‡
α-Blocker						
4 mg Doxazosin GITS (N=91)	-3.5/-3.4	-5.6/-4.7	0.3/-0.8	-6.1/-5.7 †	-2.6/-2.6	0.5/1.7 ‡
β-Blocker						
5 mg Nebivolol (N=173)	-14.7/-12.4	-13.4/-10.9	-7.9/-7.4	-10.2/-8.1	-3.6/-3.0	-1.2/-1.4 ‡
Diuretic						
5 mg Torasemide (N=113)	-7.3/-3.7	-15.6/-9.9 *	-4.3/-2.5	-12.5/-8.0 *	-1.6/-0.7	-1.3/-0.2
Combination R_x						
160/5 mg Valsartan/Amlodipine (N=203)	-18.3/-14.5	-22.6/-12.7	-14.4/-10.1	-28.1/-14.7 *	-1.3/-2.1	5.5/5.2 *
160/12.5 mg Valsartan/ Hyperchlorothiazide (N=204)	-17.4/-11.5	-16.7/-11.4	-16.0/-12.0	-20.1/-13.6 ‡	0.5/2.4	3.9/4.7 *

Studies conducted by authors utilizing a prospective, randomized, open label, blinded endpoint (PROBE) design entailing in total 2473 Grade 1 or 2 essential hypertension participants adhering to a routine of daytime activity and nighttime sleep. Participants evaluated before and after timed treatment by simultaneous 48-hour ABPM and wrist actigraphy to accurately derive awake and asleep SBP/DBP means and sleep-time relative BP decline (([awake BP mean − asleep BP mean]/awake BP mean) × 100), that is, percent decline in mean BP during nighttime sleep relative to mean BP during daytime activity. Awakening R_x = entire dose of medication routinely ingested upon morning arising from nighttime sleep; Bedtime R_x = entire dose of medication routinely ingested at bedtime. Statistical significance of comparison between treatment-time effects on BP: * $P < 0.001$; † $P < 0.01$; ‡ $P < 0.05$. Table modified and updated from Hermida *et al.* [25] and Smolensky *et al.* [23].

cardiac ischemic and AP [23,24]; and finally, upon-awakening ingestion of diuretics assumingly for pragmatic reason (avoidance of nocturia) to attenuate daytime blood pressure (BP) and/or manage pulmonary edema of congestive heart failure [https://www.pdr.net/browse-by-drug-name].

Table 2 displays our findings of the substantial bedtime versus upon-waking difference in the efficacy of six classes of widely prescribed conventional hypertension medications and their combinations [23,25]. Their ingestion before-bedtime, versus upon awakening as usual, drastically better reduces the sleep-time BP means plus normalizes the high-CVD risk non-dipper circadian BP pattern, results consistent with >100 earlier published trials [2••,26•].

Features of the BP 24-hour rhythm most prognostic of CVD risk

Daytime clinical BP measurements, for nearly a century, have been the clinical basis for differentiating normotension from hypertension, evaluating efficacy of BP-lowering treatment, and estimating CVD risk. This antiquated method, so strongly entrenched in medicine, lacks credibility today given the robust perspective attained from around-the-clock ambulatory BP monitoring (ABPM) that elucidates the entire 24-hour BP pattern and its features that derive from: Firstly, wake/rest cycle-associated behavioral changes, for example, posture, stress, activity, and fluid and food consumptions; secondly, environmental 24-hour cycles of temperature, humidity, noise, etc.; and finally, autonomic nervous system (ANS) plus neuroendocrine, endothelial, vasoactive peptide, opioid factors, and hemodynamic high-amplitude CR [27]. Usually higher wake-time BP arises from behavioral and environmental influences, but more substantially from CR of sympathetic tone, which peaks early during diurnal activity, and renin-angiotensin-aldosterone system (RAAS), which peaks mid-to-late sleep. Usually low sleep-time BP derives from withdrawal of behavioral and environmental influences, but more so from CR-regulated attenuated sympathetic and elevated vagal tone, increased atrial natriuretic and calcitonin gene-related vasoactive peptide concentration, and decreased RAAS activity [27].

Table 3

Expert Opinion Summary

- Most cardiac and vascular pathologies Exhibit 24-hour patterning in manifestation and exacerbation of symptoms and life-threatening and life-ending events.
- Few cardiac and vascular medications have been trialed for circadian rhythm-dependencies of effectiveness and safety.
- 48-hour ambulatory blood pressure monitoring studies conducted in the primary care setting indicate the true definition of arterial hypertension is elevated asleep systolic blood pressure mean and/or non-dipping blood pressure 24-hour patterning.
- Normalization of asleep systolic blood pressure and non-dipper blood pressure 24-hour patterning is best achieved by bedtime ingestion of single and combinations hypertension medications (i.e. bedtime hypertension chronotherapy) that target deterministic circadian rhythm phenomena.
- Bedtime hypertension chronotherapy — routine ingestion of full daily dose of ≥1 blood pressure-lowering medication before retiring to sleep — versus routine ingestion upon-awakening of full daily dose of all blood pressure-lowering medications — substantially better reduces cardiac and vascular pathology and morbid and mortal cardiovascular disease events.
- Exploration of the advantage of a chronotherapeutic approach to improve management of cardiac arrhythmias and ischemia, vascular dysfunction, and other cardiovascular pathology awaits exploration.

The circadian staging of endogenous BP-controlling mechanisms produces the BP 24-hour pattern and its prominent features, expressed, not in terms of imprecise time-of-day criteria, that is, *daytime/diurnal and nighttime/nocturnal BP means*, but biomarkers more indicative of circadian time, that is, actual *wake-time and sleep-time systolic BP (SBP) and diastolic BP (DBP) means* and *sleep-time relative BP decline* (*BP dipping, percent reduction in mean SBP during nighttime sleep relative to mean SBP during wake-time activity*) [2••]. Normal dipping is conventionally defined as sleep-time relative SBP decline ≥10% and non-dipping <10%. However, preferred categorization is: extreme-dippers (decline ≥20%), dippers (decline ≥10%), non-dippers (decline <10%), and risers (decline <0%, asleep SBP mean > awake SBP mean) [28]. The dipper pattern is assumed the norm and most prevalent; but, in actuality non-dipper and riser patterns, which are of high CVD risk, are extensive, 65–81% in senior, type 2 diabetic, chronic kidney disease (CKD), and resistant hypertensive patients [29–33], thus constituting a worthy target of BP-lowering therapy.

Proper definition of hypertension required for its successful treatment and CVD prevention

ABPM-based outcome investigations verify the critical importance of sleep-time SBP in determining risk for CVD morbidity and mortality [34••,35–37]. This is illustrated by findings of two-large scale outcomes trials of ≥5.6 median year duration, that is, the MAPEC study [38] and Hygia Project [39], involving in total ~23 000 primary care patients assessed as usual clinical practice at least annually, both by daytime office BP and 48-hour ABPM (48-hour, than 24-hour, ABPM because findings are much more representative [40]). Statistical models incorporating daytime office BP values and all ABPM-derivable BP variables substantiate the *SBP sleep-time mean and SBP sleep-time relative decline* jointly most accurately predict future CVD, for example, MI, AP, CHF, lower-extremity acute arterial occlusion, retinal artery thrombotic occlusion, hemorrhagic and ischemic stroke, and transient cerebrovascular ischemia [34••]. On the basis of this and other convincing evidence [35,36], we have proposed these two ABPM-derived variables as the modern, 21st century, definition of true arterial hypertension as replacement of the antiquated 20th century one founded on limited-in-number daytime office BP measures [2••]. Accordingly, we hypothesized a hypertension treatment strategy that simultaneously enhances reduction of sleep-time SBP and normalizes SBP sleep-time relative decline, as opposed to the traditional one that aims to diminish daytime BP, better attenuates CVD risk [38,39,41••].

Chronoprevention: cardiac and vascular disease aversion achieved by bedtime hypertension chronotherapy

The multicenter primary care-based Hygia Chronotherapy Trial tested the hypothesis hypertension therapy that targets normalization of sleep-time SBP better prevents CVD morbidity and mortality (*chronoprevention)* than does normalization of daytime office SBP or DBP [39,42]. Some 19 084 ABPM-diagnosed hypertensive patients (age 60.5 ± 13.7 years) were randomized in equal number to ingest the complete daily dose of ≥1 prescribed conventional long-acting hypertension medications at bedtime — bedtime hypertension chronotherapy (n = 9552) — or all of them upon awakening (n = 9532). At least annually during the 6.3-year median follow-up patients underwent 48-hour ABPM. In total, 1752 participants experienced the primary CVD outcome variable: combined CVD death, MI, coronary revascularization, CHF, and stroke. Bedtime hypertension chronotherapy versus upon-waking therapy substantially better reduced the hazard ratio — adjusted for influential characteristics of age, sex, type 2 diabetes, CKD, smoking, HDL cholesterol, asleep SBP mean, sleep-time relative SBP decline, and previous CVD event — of the primary outcome variable [0.55 (95% CI 0.50–0.61), P < 0.001], plus each component (always $P < 0.001$): CVD death [0.44 (0.34–0.56)], MI [0.66 (0.52–0.84)], coronary revascularization [0.60 (0.47–0.75)], CHF [0.58 (0.49–0.70)], and stroke [0.51 (0.41–0.63)] [41••]. Bedtime hypertensive chronotherapy, especially when entailing an angiotensin converting enzyme inhibitor or angiotensin receptor blocker [43], normalized to greater extent sleep-time

SBP and sleep-time relative BP decline and markedly better averted major CVD events, findings consistent with other such outcome trials less rigorously designed and conducted [44]. Thus, ingestion of BP-lowering medication at the optimal circadian time enhances prevention, that is, *chronoprevention*, of CVD [39,42,44]; moreover, it greatly reduces medical care expenditures [45•], and it also better averts development of new onset type 2 diabetes plus development and progression of CKD [26•,46,47]. Remarkably, these beneficial effects of bedtime hypertension chronotherapy were associated with only relatively small enhancement of SBP and DBP reduction relative to that achieved by upon-wakening treatment. This suggests the markedly diminished vulnerability to cardiac and vascular pathology accomplished by bedtime chronotherapy results not only from better attenuation of sleep-time SBP and DBP levels but from better suppression of the RAAS, whose CR under the upon-arising treatment scheme would be expressed at greater peak level during sleep and therefore more actively induce cardiac, endothelial, and other tissue remodeling, pathology, and injury [26•,27,41••] (Table 3).

Conclusions

This review conveys current knowledge of CR of cardiac and vascular disease symptoms and risk for life-threatening/ending events and the circadian chronopharmacology and chronotherapy of medications used in their management and prevention. Our own findings, plus those of >100 publications [26•,50••], document evening/before bedtime, in comparison to morning/upon-awakening, ingestion of anti-hypertensive medications significantly better improves control of elevated BP [26•]. The 48-hour ABPM-based MAPEC Study and Hygia Project suggest a new definition of true arterial hypertension — the joint variables of elevated sleep-time SBP mean and abnormal BP dipper patterning [2••]. The large outcomes Hygia Chronotherapy Trial gives validity to this novel definition by finding ingestion of hypertension medications at bedtime to specifically target BP-controlling mechanisms at the circadian stage responsible for abnormal sleep-time SBP and abnormal dipping — in comparison to their ingestion upon awakening to reduce hypertension defined by elevated daytime office or ambulatory BP — markedly better prevents CVD mortality and morbidity [41••]. These results require verification, including for racial groups besides European Caucasians. Findings of some ABPM-based investigations differ from those reported herein, causing opinion leaders to question the relevance of the hypertension chronotherapy strategy. Disparities in outcomes between studies conducted by us and others result largely from inadequate knowledge of chronobiology and chronopharmacology leading to deficiencies in their design and conduct [26•,48] — most egregiously revealed by reliance on: Firstly, 24-hour, rather than 48-hour ABPM, secondly, external clock hour, rather than actual biological time, to designate treatment schedule, and finally, reporting of non-representative daytime and nighttime, rather than biologically meaningful wake-time and sleep-time, BP means [26•] — therefore resulting in controversy. The science of medical chronobiology and chronopharmacology/chronotherapeutics is founded on *internal biological time* — not external time — and that *must* be respected in practice to achieve favorable results of chronotherapeutic strategies [1•,16,17,23,26•]. The concept and application of chronotherapeutics is not new to clinical medicine. Medications prescribed to promote sleep are taken before bedtime and ones prescribed to promote wakefulness are taken upon arising from sleep. Furthermore, chronotherapeutic strategies are of proven value in the management of various medical conditions, for example, arthritis, duodenal ulcer, gastroesophageal reflux disease, and pulmonary asthma [24,49]. Bedtime hypertension chronotherapy shows significant promise of significantly reducing CVD risk in a safe and very cost-effective way [45•,50], and as advocated by the US Heart, Lung and Blood Institute workshop report [51], exploration of circadian mechanisms of SCD and atrial and ventricular arrhythmias plus chronotherapeutic strategies to improve patient management is encouraged.

Conflict of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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Substantiation the modern 21st century diagnosis of true arterial hypertension should be elevated sleep-time systolic blood pressure mean and non-dipper or riser blood pressure 24-hour pattern as derived from around-the-clock ambulatory blood monitoring, rather than the traditional limited number of daytime office blood pressure measures, that enable markedly improved reduction of cardiovascular disease risk by targeting its control by an appropriate hypertension chronotherapy strategy.

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