

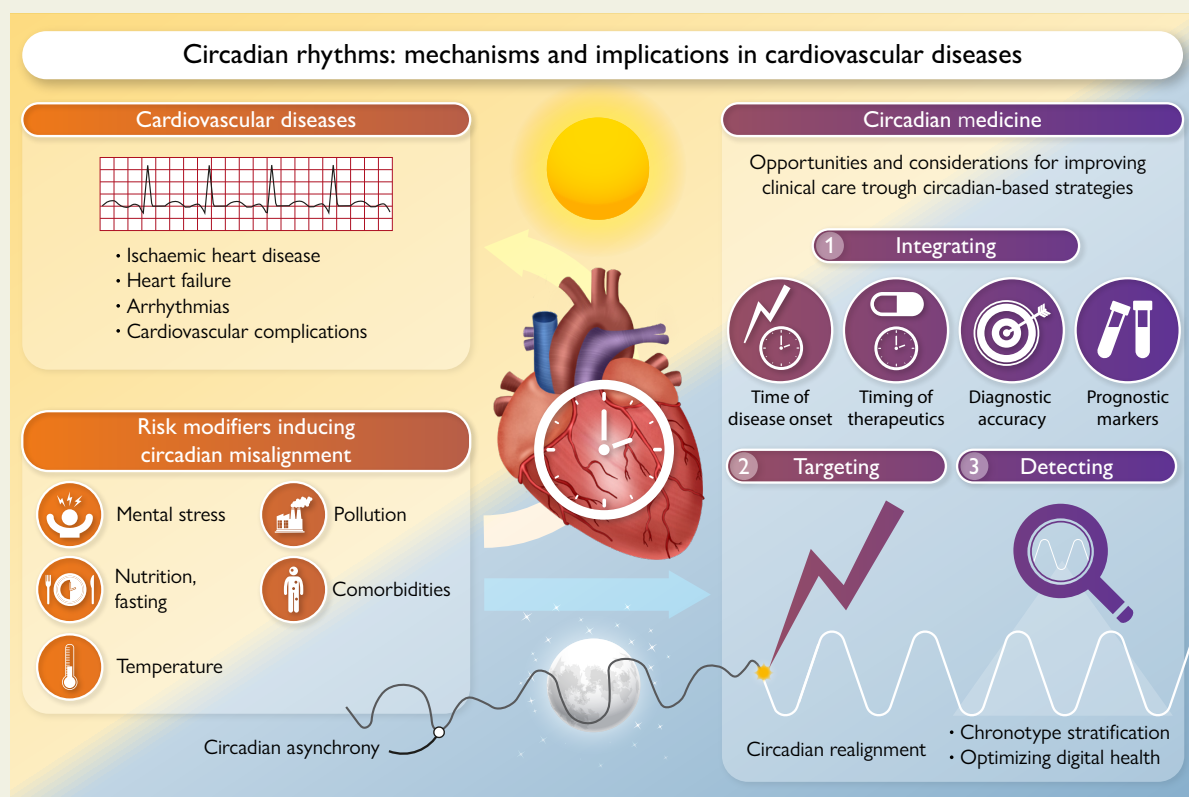
Circadian rhythms in cardiovascular disease

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Graphical Abstract



Circadian rhythms have an impact on cardiac disease, several environmental and behavioural factors can induce circadian misalignment. Several opportunities can be considered to integrate circadian-based strategies, and to target and detect circadian rhythm variation.

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Abstract

Circadian rhythms, controlled by the suprachiasmatic nucleus and peripheral clocks, regulate 24-h cycles in biological processes such as the cardiovascular system. Circadian rhythms influence autonomic balance, with parasympathetic dominance during sleep supporting cardiac recovery and sympathetic activation during the day supporting circulatory demand. Congruent with systemic and cellular circadian rhythmicity, 24-h patterns arise in the pathophysiology of cardiovascular diseases, including ischaemic heart disease, heart failure, and arrhythmias.

Daily variations influence the timing and outcome of myocardial infarction, with studies reporting patterns in infarct size depending on the time of onset. Similar daily patterns are observed in cardio- and cerebrovascular complications. In heart failure, circadian rhythms are dampened but remain intact, suggesting the potential for incorporating timing in diagnostics and therapies. Sudden cardiac death follows a distinct pattern, with a higher incidence in the morning. Atrial fibrillation onset, on the other hand, occurs more frequently at night.

Risk factors and modifiers, such as physiological, psychological, lifestyle, and environmental factors and comorbidities interact with circadian rhythms, thereby impacting cellular pathomechanisms and development of cardiovascular health and disease. Chronotherapy, which aligns treatments with circadian rhythms, has demonstrated potential for improving the efficacy of cardiovascular therapies. This review examines the influence of circadian rhythms on cardiovascular health in the context of specific cardiac diseases and risk factors, and it highlights the therapeutic opportunities informed by circadian patterns.

Keywords Circadian Rhythms • Cardiovascular Disease • Chronotherapy • Chronomodulation • Heart Failure • ischaemic Heart Disease • Myocardial Infarction • Epidemiology • Incidence

Introduction

Circadian rhythms are endogenously driven 24 h cycles in biological processes that enable organisms to anticipate and adapt to the natural day-night light cycle. Circadian rhythms (Box 1) are governed by a hierarchical system of biological clocks, with the suprachiasmatic nucleus (SCN) in the hypothalamus serving as the central pacemaker. The SCN synchronises peripheral clocks present in virtually all nucleated cells, including those in cardiovascular tissues, through neural, humoral, and behavioural signals such as sleep, food intake, and physical activity.^{1,2}

Daily patterns	Recurring physiological or behavioural changes that follow a roughly 24-h cycle, such as sleep-wake cycles, hormone release, and body temperature fluctuations.
Chronotype	An individual's natural preference for sleep and activity timing, ranging from morning types to evening types, influenced by genetic and environmental factors.

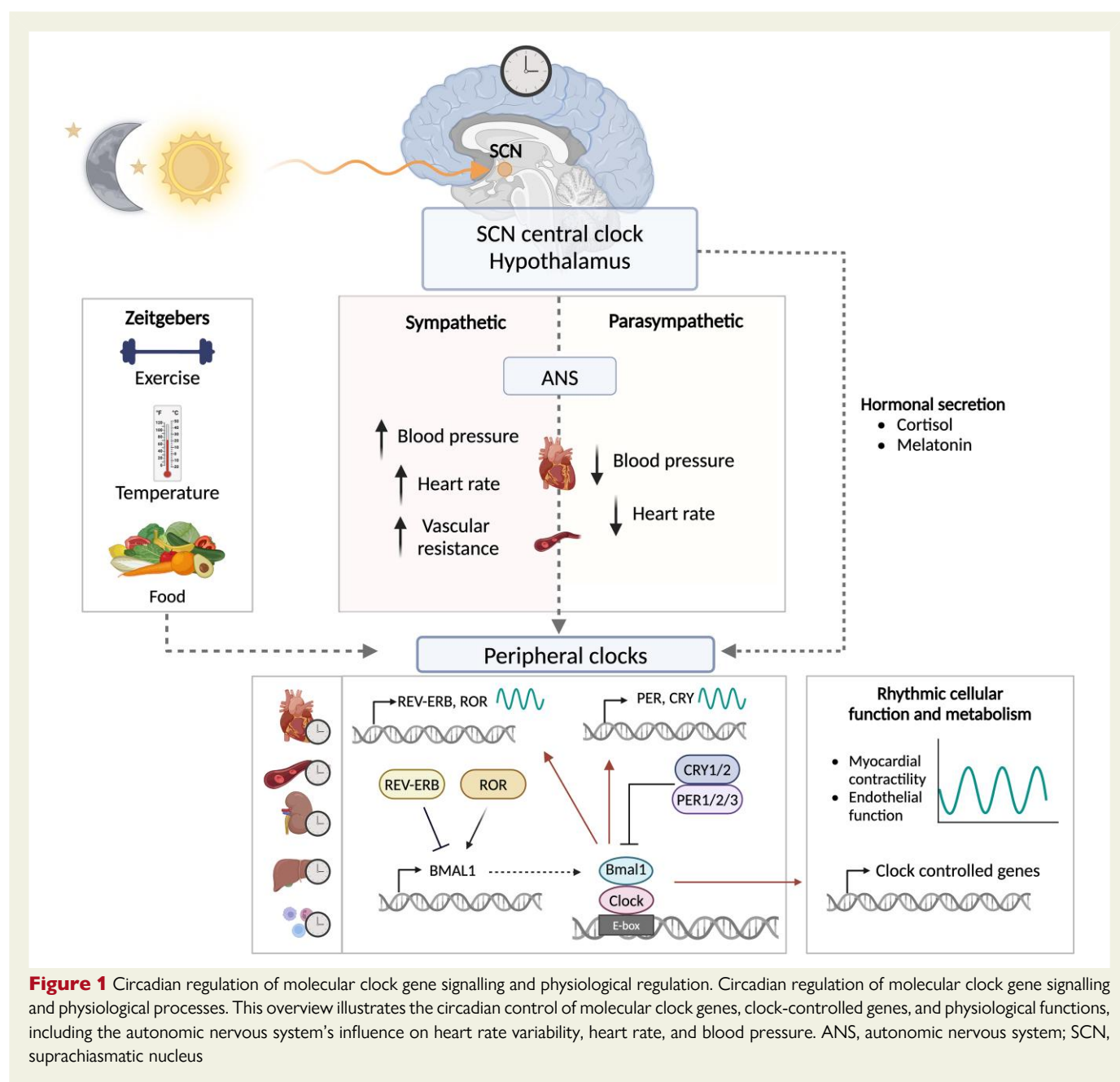
Box 1 Overview of terminology

Term	Definition
Circadian rhythm	An approximately 24-h cycle in biological processes, regulated by internal clocks and influenced by external factors such as light and temperature.
Circadian clock	The internal biological mechanism that regulates circadian rhythms, primarily controlled by the suprachiasmatic nucleus (SCN) in the brain, which synchronizes physiological and behavioural processes.
Peripheral clock	Clocks present in tissues and organs outside the SCN, which help regulate local physiological functions and can be influenced by external cues like food intake and physical activity.
Diurnal rhythm	Patterns in behaviour or physiology that occur during the daytime and are influenced by external environmental factors, such as light and temperature, rather than solely by internal biological clocks.

At the molecular level, circadian rhythms are generated by a molecular clock, which consists of multiple core clock proteins including circadian locomotor output cycles kaput (CLOCK), brain and muscle ARNT-Like 1, cryptochrome 1/2 (CRY1/2), period 1/2/3 (PER1/2/3), retinoic acid receptor orphan receptor $\alpha/\beta/\gamma$ (ROR $\alpha/\beta/\gamma$), and nuclear receptor 1D1/2 (REV-ERB α/β)(Figure 1).³ The core clock machinery regulates rhythmic fluctuations in clock-controlled genes expression via transcriptional–translational feedback loops.³ The oscillation in expression of those genes induces a 24 h cycle in processes including myocardial contractility, cell metabolism, and endothelial function.^{1,2} Both the sympathetic and parasympathetic nerve systems directly and indirectly affect circadian clock function,^{4,5} linking sleep to circadian clock function as a mediating factor.

Sleep plays an important role in maintaining 24 h rhythms and cardiovascular homeostasis. During sleep, the parasympathetic system dominance lowers heart rate (HR) and blood pressure (BP), while reduction in sympathetic tone decreases vascular resistance, collectively supporting cardiac recovery. The sympathetic system becomes more active during the day, increasing HR and BP. These fluctuations are linked with daily patterns in disease onset.⁶

The early morning transition from sleep to awake increases sympathetic activity, coinciding with an increased risk of events, such as myocardial infarction (MI) (Figure 2).⁷ Circadian rhythm disruptions—such



as shift work, sleep deprivation, or irregular meal timing—impair molecular clock pathways, increasing the risk of cardiovascular diseases (CVD) such as hypertension, atherosclerosis, and arrhythmias.^{7,8}

Heart rate variability (HRV)—reflecting autonomic nervous system regulation—follows a daily pattern influenced by the SCN through its control of the parasympathetic and sympathetic branches. Additionally, peripheral circadian clocks in cardiovascular tissues, such as myocardium and blood vessels, contribute to variations in cardiovascular function. The daily variations in HRV reflect the combined actions of the SCN and peripheral clocks,¹ with sympathetic regulation further supporting circadian clocks within the cardiovascular system.

This interplay extends to therapeutic strategies. Chronotherapy, the timing of treatments to align with the body's biological rhythms, has shown promise in improving the effectiveness of medications such

as antihypertensives and anticoagulation.^{9–11} Understanding the mechanisms by which circadian rhythms regulate cardiovascular (patho)physiology offers an opportunity to refine prevention and treatment strategies.

This review summarizes the interplay between circadian biology and cardiovascular function in the context of cardiac diseases, highlighting clinical implications, diurnal variations in disease onset, and the modulation of the circadian interactome by internal and external risk factors. We discuss how disrupted rhythms increase cardiovascular risk and their potential clinical and research recommendations as outlined in [Table 1](#).

Methods

The methods for this narrative review are described in the supplemental material (see [Supplementary data online, Methods](#) and [Table S1](#)).

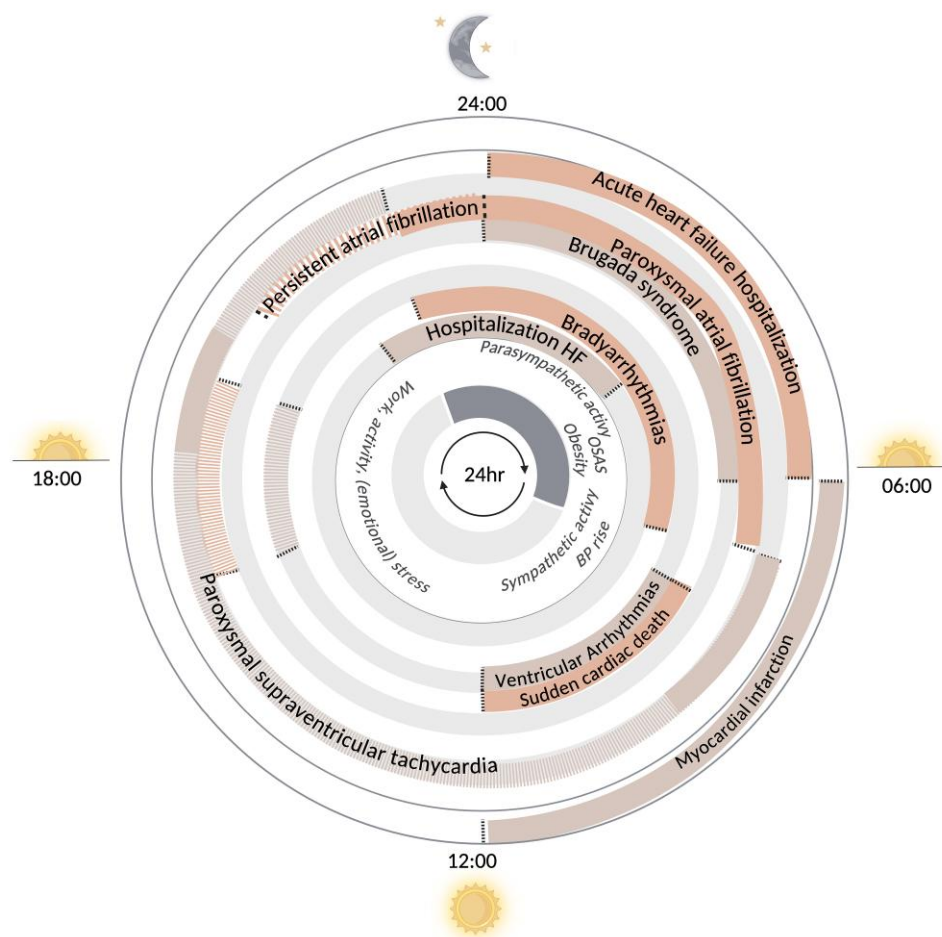


Figure 2 Incidence peaks of cardiovascular diseases during a 24-h period. A circular visualization summarizing the incidence peaks of various cardiovascular diseases. Timepoints corresponding to incidence peaks for several cardiovascular diseases are illustrated, with supporting literature provided in [Supplementary data online, Tables S2–S4](#). Dashed lines represent second-highest peak of incidence. BP, blood pressure; HF, heart failure; hr, hour; OSAS, obstructive sleep apnoea

Results

Circadian influences on ischaemic heart disease

Daily patterns and myocardial infarction risk

Myocardial infarctions (MIs) occur more frequently in the morning ([Figure 2](#)), a pattern reflecting 24 h rhythms in cardiovascular functions, such as BP and coagulation. These rhythms influence platelet aggregation, which increases in the morning, alongside higher BP, leading to a higher risk of thromboembolic events. Studies found that the incidence of MI is three times higher in the morning compared to late evening.^{12–14} Moreover, ST segment elevation myocardial infarction (STEMI) was ~10% more common in the morning than in the afternoon or night.¹⁵ Myocardial infarction with non-obstructive coronary arteries follows a similar 24 h pattern to MI with obstructive coronary arteries, with higher incidence in the morning.¹⁶ The time-of-day variations in MI incidence are outlined in [Supplementary data online, Table S2](#). Daylight saving time transitions have been linked to a rise in MI incidence, particularly at the onset of daylight saving time in spring especially during the week after transition, with an increase in non-STEMI cases.¹⁷ The week after the

autumn shift shows no significant increase or decrease in MI incidence.^{17,18} Sleep quality and duration are affected and MI incidence is increased for 3 weeks after the time reset, with a more pronounced difference in women,¹⁸ a subsequent meta-analysis supported these findings.¹⁹ However, sleep may not be the only determinant for the observed higher cardiovascular risk, as the general environmental condition, gender and individual preference in circadian rhythms (chronotype) may play a role. Evening chronotypes, for example, are more prone to sleep-related issues, unhealthy lifestyle habits, and metabolic disturbances, all of which are linked to cardiovascular risk.²⁰ Additionally, women with an evening chronotype appear to be more susceptible to sleep disruption and related health consequences, which could further influence cardiovascular outcomes.²⁰ These findings highlight the importance of considering time-of-day and external triggers in the management of ischaemic heart disease (IHD).

Infarct size and prognosis

Preclinical studies in mice have shown that ischaemia during the sleep-to-wake transition results in larger infarcts and more severe outcomes.²¹ Clinical studies were initiated to validate these findings using

Table 1 Recommendations for clinical care, studies and drug development**Clinical care**

- Registration of time in intervention, drug administration, physiological and laboratory measurements
- Timing of diagnostics considering optimal predictive value
- Optimization of clinical care organization considering common time of onset of disease
- 24 h ambulatory BP and HR measurements for cardiovascular risk
- Minimize disruption of daily rhythms and sleep in clinical patients
- Minimize health hazards of clinical staff due to shift work—provide preventive programme

Future

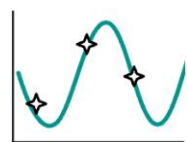
- Time-of-day-adjusted clinical reference ranges
- Biomarkers for functioning of the circadian system
- Optimizing clinical procedures considering time-of-day

Clinical studies

- Categorize sex, age, and ethnicity
- Consider the effect of cardiovascular risk factors on the circadian system (obesity, diabetes mellitus, etc.)
- Consider confounding effects of light exposure, sleeping conditions, noise, exercise, diet
- Stratify or standardize time of intervention
- Stratify or standardize time of diagnosis
- Stratify or standardize time of sample collection
- Use more than two timepoints of intervention, medication application and/or (intermediate outcome) measurement

Drug development

- Standardize circadian timing in *in vitro* and *in vivo* studies
- Study multiple time points
- Considering the influence of circadian rhythms on pharmacokinetics and dynamics
- Consider choice of animal model (diurnal, nocturnal) and translate to human rhythm if applicable
- Standardize relevant housing rhythm (e.g. light:dark schedule, temperature)
- Choose appropriate sex and age
- Align time of feeding
- Consider time of sample collection: standardize
- Consider time of intervention (e.g. drug delivery, surgery): standardize
- Use more than two timepoints for intervention and/or sampling



methods like cardiovascular magnetic resonance, echocardiography, and cardiac biomarkers such as creatine kinase and troponin-I. Biomarkers and imaging also reflect circadian differences in myocardial injury, with larger infarcts observed in the morning.²² A study analysing four randomized trials found a circadian variation in myocardial infarct size, with the largest infarcts between midnight and 06:00, suggesting that symptom onset timing impacts infarct size and potentially future treatments.²³ Another study using tissue Doppler echocardiography showed the largest infarcts and worst left ventricular function after an MI between 06:00 and noon,²⁴

a result that was confirmed by an analysis of 1031 STEMI patients revealing that both infarct size and left ventricular function were time-of-day-dependent, with the most severe effects observed during early morning hours.²⁵ The differences between these studies may reflect variations in study design, population characteristics, or definitions of time windows, but collectively current evidence suggests that infarct size is highest between midnight and noon. Several studies have explored the impact of symptom onset timing in STEMI patients on long-term prognosis. One found that late evening or early morning symptom onset increased the risk of rehospitalization for heart failure (HF) by 30%–50% after 1 year, particularly if ischaemic duration exceeded 120 min.²⁶ Another study found that night-onset STEMI was associated with higher mortality.²⁷ Additionally, patients with early morning symptom onset had larger infarct sizes and higher 30-day mortality rates.²⁸

A randomized study on aortic valve replacement surgery, where a brief ischaemic period is induced, revealed that afternoon surgeries entail less myocardial injury, possibly due to circadian patterns influencing myocardial tolerance to ischaemia.²⁹ However, not all studies confirmed a daytime dependence in elective cardiac surgery for either aortic valve replacement or coronary artery bypass grafting and clinical outcome.^{30–32} Given the substantial knowledge on the importance of the time-of-day for cardioprotective interventions, circadian regulation of central processes should be considered in future research and clinical practice.³³

Diagnostic tools

Patients with nocturnal ST segment changes, detected through dynamic electrocardiogram (ECG) monitoring in individuals undergoing coronary angiography, showed a significantly higher chance of having IHD (93%) compared to those without such changes (22%). Particularly, nightly peak-shaped ST segment changes were strongly associated with IHD.³⁴ These results might provide an opportunity for using a non-invasive 24-h diagnostic tool for IHD.

For MI diagnosis cardiac troponin-I shows no significant diurnal fluctuation between morning (23:00 to 14:00) and evening (14:00 to 23:00) presentations of MI, indicating that its diagnostic accuracy remains consistent regardless of the time of presentation.³⁵ In contrast, troponin-T exhibits a distinct pattern, with concentrations gradually declining during daytime and rising overnight, peaking in the early morning hours.^{36,37} While this pattern does not impact the diagnostic accuracy for MI, it could influence the interpretation of absolute changes in troponin levels within the first hour of presentation suggesting that interpretation in non-MI settings should be informed by time of sampling.³⁶

Clinical evidence

Unlike preclinical studies, clinical evidence on circadian biology in MI remains insufficient, as studies have been observational, focussing on time-dependent patterns (e.g. time-of-day variations in MI incidence) rather than endogenous circadian mechanisms.³⁸

Circadian influences in heart failure**Disruption of circadian biology in heart failure**

HF is a global health issue, with circadian disruption contributing to its progression. Circadian clocks regulate factors relevant in the pathophysiology of HF including HR, BP, myocardial contractility, and inflammation. Preclinical studies suggest that disruptions in these clocks contribute to declining cardiac function, impaired neurohormonal regulation, and disturbed sleep-wake cycles.^{6,39} Research highlights that time-of-day fluctuations in cardiac contractility and electrical activity

are less pronounced in HF patients, driven by altered neurohormonal rhythms and reduced ability of the heart to efficiently perform its functions, such as maintaining blood flow and oxygen delivery, particularly during the night when myocardial growth and renewal processes are more active.⁴⁰ Deviations of normal 24-h rhythmicity, indicated by elevated nocturnal HR and BP, increase the risk of arrhythmias. Sleep deprivation, which is common in HF, exacerbates HF via increased sympathetic activity and inflammation. Insomnia, obstructive sleep apnoea syndrome (OSAS), shift work, and non-dipping hypertension worsen HF, by triggering neurohormonal pathways and abnormal BP fluctuations.^{40–42} Circadian clocks also influence cardiovascular growth and remodelling, particularly during sleep when HR and BP are normally lowest. Disruptions in these mechanisms likely elevate cardiovascular risk and may worsen HF outcomes.⁴³

Diagnostic opportunities

Diagnosing disrupted 24 h patterns during HF involves detecting altered sleep patterns, electrophysiology, and neurohormonal imbalances. Recent advancements, including wearable devices, improve continuous monitoring by measuring HRV and sleep patterns in real-time. Innovative diagnostic methods further highlight the impact of time-of-day in HF diagnosis. A deep learning model integrating time, frequency, non-linear and fragmentation HRV parameters from 24-hr ECG recordings achieved high accuracy (92.6%), sensitivity (90.7%), and specificity (95.2%), particularly in diagnosing HF with preserved ejection fraction (HFpEF).⁴⁴ A colour-coded polar representation combining HRV and patient profiles showed 93% accuracy, complementing echocardiography by offering insights into 24 h patterns.⁴⁴ Time-specific ECG-based regression models used daily fluctuations to improve left ventricular ejection fraction estimation.⁴⁵ Nighttime HR patterns linked to increased HF risk in the JAMP study emphasize the need for nighttime haemodynamic assessments.⁴⁶ Furthermore, biomarker research revealed diurnal BNP and NT-proBNP variations improving acute HF diagnosis, while ambulatory BP monitoring identified non-dippers, enhancing prognostic evaluations.^{47,48} Interestingly, ambulatory invasive monitoring using CardiOMEMS revealed diurnal variation in pulmonary artery pressures with the lowest and most stable values in the morning,⁴⁹ emphasizing standardization of time of measurement.

Prognostic implications

Circadian rhythm disruption may have prognostic implications for HF patients. The central circadian clock, reflected by melatonin and cortisol levels, is dampened but intact in HF patients, emphasizing the potential opportunity of timing in clinical interventions to improve outcomes.³⁷ Persistent circadian misalignment, referring to either a blunted day-night variation or a shifted rhythm in physiological processes such as BP and HR regulation, significantly worsens prognosis.³⁹ Not being able to maintain normal circadian rhythms, as reflected by disrupted sleep, meal timing, and BP patterns, not only increases HF risk but also exacerbates the condition once it develops.^{41,43}

Wrist-based BP monitoring provides accurate nighttime BP assessment with less sleep disruption compared to upper-arm measurement, potentially improving hypertension management in these patients.⁵⁰ Furthermore, BP variability and non-dipping patterns are strong predictors of cardiovascular events in young hypertensive individuals,⁵¹ while nocturnal thoracic volume overload and abnormal circadian BP patterns—particularly the riser and non-dipper—are critical predictors of poorer outcomes in acute HF.^{52,53}

Therapeutic interventions

Therapeutic strategies, most recently sodium-glucose cotransporter 2 inhibitors have been reported to improve cardiac autonomic function, reducing daytime and nighttime HRs while enhancing parasympathetic modulation and exercise capacity, which may normalize circadian rhythm.⁵⁴ Beta-blockers enhance HRV by suppressing sympathetic activity, leading to an (indirect) increase in parasympathetic activity, particularly during high-risk morning hours, potentially supporting cardiac autonomic regulation in HFpEF patients.⁵⁵ Beta-blockers may suppress melatonin production, and while melatonin supplementation might have benefits for sleep quality in patients on beta-blockers there is limited evidence on its clinical benefits in this population.⁵⁶ Angiotensin-converting enzyme (ACE) inhibitors restore circadian BP variability, improving clinical status in congestive HF.⁵⁷ Moreover, digoxin treatment reduces sympathetic activity during sleep, modulating BP and parasympathetic function.⁵⁸ Advanced technologies, such as left ventricular assist devices and high-frequency pump monitoring, also highlight the importance of understanding 24 h rhythms in managing HF: Diurnal rhythmicity was demonstrated in pump parameters even though the technical settings are fixed, thus reflecting circadian physiology in patient-pump interaction.⁵⁹

Heart transplantation involves circadian interactions between donor and recipient, affecting graft function, immune response, and ischaemia-reperfusion injury.^{60–62} Moreover, cardiac sympathetic reinnervation is associated with improved survival rates in heart transplant patients, highlighting the beneficial influence of the autonomic nervous system.⁶³ The impact of donor heart procurement time or re-implantation timing on transplant viability, in relation to patient prognostics, is difficult to investigate due to multiple confounding factors (wakefulness/focus of the surgeon, logistics, etc.). One study found that donor hearts procured in the early morning between 04:00 and 11:00 were associated with better long-term survival rates, while nighttime surgeries were linked to worse outcomes.⁶⁰

Circadian rhythms in electrophysiology and arrhythmias

Daily rhythms are present in cardiac electrophysiology, including sinus node function, myocardial refractoriness, QT interval, QRS duration, and PR interval. These rhythms are regulated by the autonomic nervous system via the SCN, and the peripheral cardiac cell clock governing ion channel transcription and function.^{64,65}

During the night the autonomic tone shifts towards parasympathetic (vagal) dominance, facilitating relatively benign bradyarrhythmias such as sinus bradycardia and atrioventricular block with prolongation of PR, QT, and QRS intervals.⁶⁶ Conversely, the early morning hours are characterized by a surge in sympathetic activity, involving increase in circulating levels of catecholamines. This sympathetic activation, along with concurrent increases in HR, BP, and myocardial oxygen demand, are thought to increase the risk of ventricular arrhythmias (VA) by triggering abnormalities in intracellular calcium handling and action potential repolarization.⁶⁷ Another actively studied mechanism underlying the susceptibility of VA in the morning hours is the circadian clock dependent modulation of electrical activity driven by functional changes of cardiac ion channels and extrinsic autonomic receptor mediated mechanisms (reviewed by Bernardi et al.⁶⁸). Multiple ion channels subunits exhibit distinct 24-h mRNA and/or protein level oscillation, which are abolished upon disruption of the cardiomyocyte circadian clock.⁶⁸ Moreover, neurohumoral factors regulate cardiac electrophysiology by modulating ion channel expression. During the morning corticosterone peak, increased binding to the circadian clock-regulated

glucocorticoid receptor enhances the expression of ion channel subunits *Scn5a* and *Kcnh2* and corresponding ionic currents I_{Na} and I_{Kr} , along with the gap junction protein *Connexin 43*.⁶⁹ These changes alter electrophysiological properties in response to hormonal signals potentially increasing arrhythmia susceptibility in during the active phase.⁶⁹

In humans, ion channel expression also follows day-night rhythms.⁷⁰ However, it is still unknown how combination of these ion channel subunits rhythms impacts the ventricular action potential.

Daily patterns in cardiac electrophysiology are reflected by epidemiological studies, with a well-documented peak of VA incidence in the morning (07:00–12:00), mirroring sudden cardiac death patterns (Figure 2; Supplementary data online, Table S3). Variations in study populations and advances in pharmacological management have highlighted factors that attenuate this pattern, including comorbidities (chronic kidney disease, diabetes mellitus^{71,72}), beta-blockers blunting autonomic surges, and advanced HF therapies.^{73–75} Notably, ventricular tachyarrhythmias in patients with OSAS, Brugada and early repolarization syndrome often occur nocturnally.^{76–81} This is linked to elevated nocturnal sympathetic and reductions parasympathetic tone in OSAS patients.⁸²

For atrial fibrillation (AF), the interplay between autonomic inputs and time-of-day is more complex (see Supplementary data online, Table S4). A subset of patients exhibit a predominant or even exclusive nocturnal onset of AF, potentially driven by vagal tone.⁸³ This parasympathetic activity shortens the atrial effective refractory period by activation of the acetylcholine-activated outward potassium current, and promotes electrical remodelling, thereby increasing the propensity for re-entry circuits.⁸⁴ In contrast, AF episodes during the day are often triggered by adrenergic surges (physical or emotional stress), promoting arrhythmogenesis by boosting calcium dependent cardiac function via L-type calcium channels leading to early afterdepolarizations.^{85,86} However, direct sympathetic and parasympathetic nerve activity recordings in canine models have demonstrated that AF initiation is often preceded by concurrent increases in both autonomic outputs.⁸⁷ This finding suggests that autonomic co-activation may play a pivotal role, underscoring the complex and multifactorial nature of AF initiation. Additionally, sleep-related disorders, such as OSAS, exacerbate nocturnal autonomic dysregulation by introducing intermittent hypoxia and sympathetic bursts, further increasing AF susceptibility during sleep.^{86,88}

A recent literature review reported a periodicity analysis to support the hypothesis of nocturnal onset subtype of AF in more detail.⁸³ In total 2080 patients with 11 886 onsets of AF were included from 14 studies and a cosine fitting curve (R^2 .77; P = .03) with a 24 h period was plotted. Significantly more onset of AF was detected during the night (22:00–07:00) compared to the daytime (07:00–22:00). Additionally, the effect of specific sleep stages (e.g. shorter slow-wave sleep), sleep-disordered breathing, and the effect of body positions on the onset of AF were described.^{89–92} In contrast, paroxysmal supraventricular arrhythmias are most frequent during the day, conceivably driven by cell-autonomous circadian rhythmicity in addition to sympathetic drive.^{93,94}

Diagnostic, therapeutic and prognostic implications

Understanding daily variations in cardiac electrophysiology potentially has implications for diagnosis, treatment and prognosis. For instance, the QTc interval lengthens at night, and shortens with the morning autonomic surge, necessitating careful timing of ECG acquisition to avoid false-positive and false-negative diagnoses of long QT syndrome and drug induced QTc changes.⁹⁵ Moreover, the extent of QTc interval prolongation after levofloxacin administration depends on dosing time,

with the largest effect at 14:00 suggesting a time-adjusted strategy could improve safety in high-risk patients.⁹⁶ When considering prognostic implications, time-of-day was an independent determinant of the corrected QT interval, with higher mortality risk in patients showing increased (peak-to-trough amplitude >15 ms) or diminished (peak-to-trough amplitude <5 ms) QT rhythmicity, as identified in a recent cohort study of 100 644 patients.⁹⁷

Circadian rhythms in other cardio- and cerebrovascular complications

The state of the central and peripheral clocks and the control they have over the physiology of the organism (HR, BP, peak cortisol in blood) are indicative of the chronobiological patterns seen in the incidence of cardiovascular events.⁹⁸ A similar pattern exists for diverse cardiovascular complications. Rupture and dissection of aortic aneurysms are more likely to occur in the early morning,^{99–101} as well as ischaemic and haemorrhagic stroke.¹⁰² As these events represent completely different entities, similarity in chronobiological patterns is unexpected, but obviously all of them share the same circadian mechanisms.^{103,104}

Another well-known cardiovascular complication is cancer therapy related cardiac damage, a leading cause of morbidity and mortality in cancer survivors. Anti-cancer therapies, such as anthracyclines, trastuzumab, taxanes, fluoropyrimidines, and tyrosine kinase inhibitors are well-documented for their cardiotoxic potential.¹⁰⁵ While advancements in cardio-oncology have focused on mitigating these risks, the role of circadian rhythms in influencing cardiotoxicity and arrhythmogenesis is an emerging area of interest with substantial clinical implications.

The cardiomyocyte circadian clock governs numerous cellular processes, such as cardiac metabolism,¹⁰⁶ DNA repair,¹⁰⁷ cell fate,¹⁰⁸ driving the time-dependent susceptibility to anthracycline-induced cardiomyocyte death observed *in vitro*.^{109,110} Preclinical studies further substantiate a circadian pattern in anthracycline-induced myocardial injury, with a protective effect observed when anthracyclines were administered around the transition from rest to activity phase,^{111–113} hinting towards a protective effect in the morning for humans. However, randomized controlled trials assessing the impact of chronomodulated chemotherapy administration on cardiotoxicity and therapeutic efficacy are still lacking.

Modification of circadian rhythms and the interactome by risk factors and risk modifiers

Circadian interactomics describes the investigation of changes of circadian clock protein-protein interactions by various factors leading to alteration of the down-stream interactome, e.g. timekeeping of nuclear receptors and the exosome (mostly by the negative or repressive arm of the circadian clock) or of translation and transcription factors (mostly by the positive or activation arm of the circadian clock).¹¹⁴ Circadian rhythms and CVD are linked through multiple factors, with disruptions increasing the severity of cardiovascular risk factors and vice versa.^{38,115} Circadian rhythms can be disrupted at various levels, such as when clock input signals are misaligned with intrinsic molecular clocks, which can occur during jet lag or shift work.^{116,117} The present overview explores the connection between circadian rhythms and various factors affecting cardiovascular risk, including physiological modulators such as age, sex and pregnancy/lactation, comorbidities such as hypertension and metabolic disease, lifestyle factors such as smoking, alcohol intake and exercise, and environmental factors such as artificial

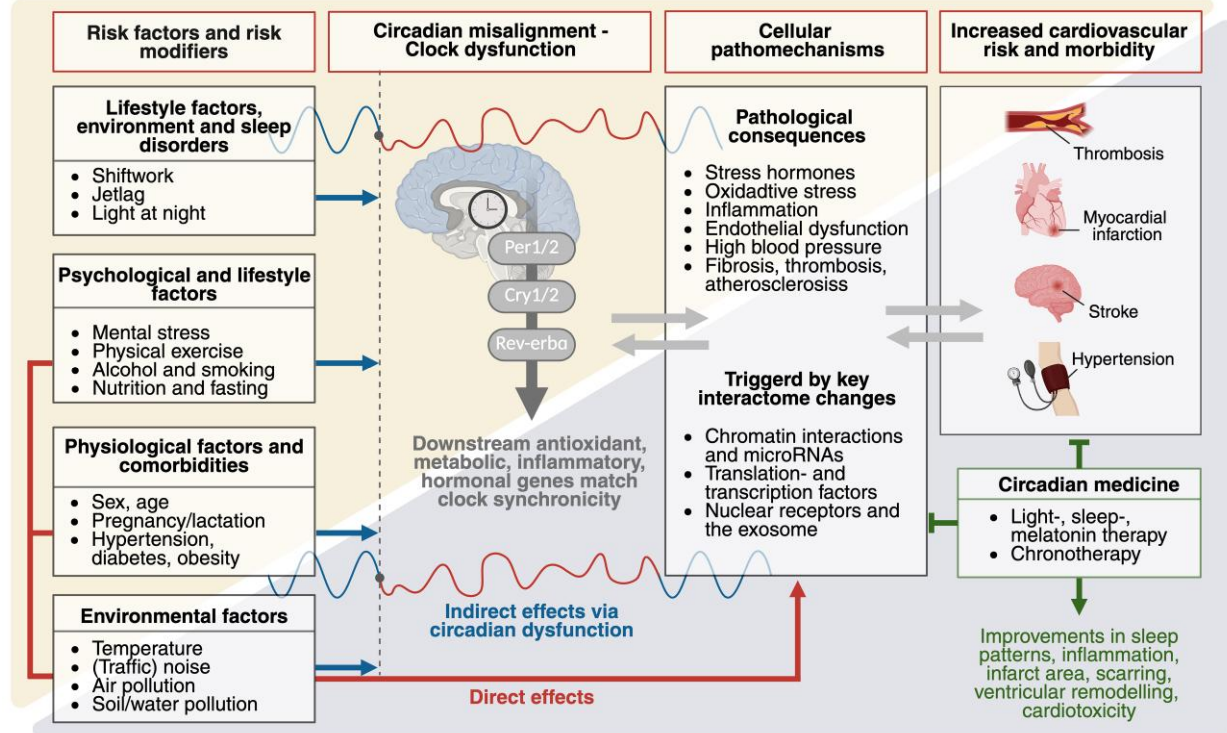


Figure 3 Overview of the circadian-cardiac interactome. An overview figure inspired by a directed acyclic graph, illustrating the key factors of the circadian-cardiac interactome. This visualization integrates the risk factors and risk modifiers influencing circadian rhythms and cardiac function. The red arrows indicate the direct influence of lifestyle, physiological, psychological and environmental factors on cardiovascular disease triggering key pathomechanisms by changes of key components of the interactome. Key pathomechanisms for cardiovascular diseases are higher levels in stress hormones, dysregulated expression of ROS producing and degrading enzymes leading to oxidative stress, activation of immune cells and increase in pro-inflammatory cytokines, exacerbated inflammation and progression of atherosclerosis, disturbed metabolism of glucose and fatty acids, impaired mitochondrial function (e.g. respiration, autophagy), dysregulated epigenetic pathways, enhanced thrombotic pathways and altered coagulation, phase shifts in blood pressure maximum and generally higher blood pressure levels, impaired vascular function, exacerbated arterial stiffness and promotion of fibrosis. The blue arrows indicate the influence of the risk factors and risk modifiers on circadian misalignment indirectly impacting cardiovascular risk. The black arrows indicate the influences between circadian misalignment, pathophysiology by interactome changes and cardiovascular disease. The latter can be beneficially influenced by chronotherapy approaches. CVD, cardiovascular disease; DAG, directed acyclic graph; SCN—suprachiasmatic nucleus;

light, temperature, air quality and noise (Figure 3).³⁸ While an association is often observed in preclinical and clinical settings, a causal relationship with most factors remains to be established.

Physiological factors and comorbidities

Circadian misalignment in healthy adults leads to sex-specific changes in energy homeostasis, independent of behavioural or environmental factors,¹¹⁸ which are also observed following central circadian clock adaptations during pregnancy and lactation.¹¹⁹ Ageing affects the period and amplitude of circadian rhythms and melatonin levels, both of which decline later in life.¹²⁰ Obesity and diabetes impact both circadian clock gene expression and function,¹²¹ and vice versa circadian rhythm disruption promotes metabolic disorders.¹²² CVD risk is also modulated by sex and age¹²³ and cardiometabolic comorbidities,¹²⁴ suggesting potential pathogenic contributions by circadian dysregulation. Inflammation and circadian rhythms are closely linked, with immune cell activity and pro-inflammatory cytokine levels showing 24 h fluctuations regulated by clock genes to maintain immune balance and tissue

homeostasis. Chronic sleep deprivation and circadian disruption can amplify inflammation, increasing pro-inflammatory cytokines (IL-1 β , IL-6, and tumour necrosis factor- α) and disrupting immune regulation, which are key contributors to CVD.^{125–127}

Psychological and lifestyle factors

Depressive disorders are often associated with disrupted clock gene expression, resulting in depressive-prone features in rodent models.¹²⁸ Mental stressors cause dysregulation of circadian rhythm through oxidative stress.¹²⁹ Physical performance is influenced by circadian clock proteins, while inactivity or exercise can affect the circadian system.¹³⁰ While exercise is a protective intervention in HF,¹³¹ benefits are also dependent on both time of the day and an individual's chronotype.¹³² Although exercise is generally regarded as highly protective, morningness persons may benefit more when exercising in the morning, whereas eveningness persons benefit from early or late exercise. Chronic alcohol consumption may disrupt molecular clocks and contribute to human alcohol-induced liver disease¹³³ and addiction. Smoking alters

gene expression of central and peripheral clock genes¹³⁴ affecting sleep and circadian rhythms.¹³⁵ Intermittent fasting improves health in part through benefits to circadian rhythm, and was found to decrease all-cause mortality and the risk of non-fatal MI.^{136,137} Nutrition and nutraceuticals can help reset peripheral circadian clocks.¹³⁸ Shift work, jetlag and other sleep disorders disrupt the circadian clock system, which is associated with increased ischaemic heart damage upon MI.^{139,140} Thus, both well-accepted cardiovascular risk factors (depression and other mental disease,¹⁴¹ alcohol, smoking, unhealthy diet,¹⁴² and shift-work) and protective factors (physical exercise, healthy diet and intermittent fasting) provide their effects at least in part via the circadian clock.

Environmental factors

Temperature oscillations, as small as 1°C, can alter the expression of circadian genes, affecting amplitude and phase.¹⁴³ The circadian period length remains constant due to temperature compensation.¹⁴⁴ Auditory function and sound stimuli, especially during the night, can also influence circadian rhythms through sleep deprivation, stress reactions (e.g. higher adrenaline and cortisol levels affect sleep) and oxidative stress (via redox modifications of clock core components and related phase/amplitude shifts).¹⁴⁵ Light is a significant environmental signal that influences circadian rhythms, with detrimental effects of artificial light at night on sleep, stress hormones and oxidative stress,¹⁴⁶ and seasonal changes affecting chronotype.¹⁴⁷ Chemical pollutants, such as air pollution and heavy metals or pesticides can significantly alter circadian rhythms mostly by oxidative stress-dependent processes or direct interaction of the toxins with thiol-based enzymatic activity,^{148,149} affecting sleep-wake patterns and increasing CVD risk by causing oxidative stress.¹⁵⁰ Extreme temperatures increase cardiovascular mortality¹⁵¹ and are a leading cause of death.¹⁴² Furthermore, transportation noise,¹⁵² air pollution,¹⁴² and toxic chemical in soil/water¹⁵² are leading risk factors for CVD or mortality.

Chronomodulation of cardiovascular medicine

Chronotherapy considers the effect of circadian clock-driven rhythms in pharmacokinetic and pharmacodynamic processes, to minimize adverse effects and optimize treatment efficacy.¹⁵³ Moreover, it includes the circadian variation in disease pathophysiology influencing symptom intensity and time-at-risk as seen in MI, VA, and HF. Many cardiovascular drugs are prescribed at specific times as recommended by pharmaceutical companies, but the rationale is rarely disclosed. For example, short-acting statins are prescribed at bedtime to match cholesterol synthesis, whereas long-acting statins, with >24 h half-lives, do not necessitate circadian considerations. This principle extends to other drug classes, yet long-acting drugs may also be optimized through chronotherapy strategies depending on their pharmacodynamic profile.¹⁵⁴

Hypertension management exemplifies the importance of circadian considerations in clinical practice. Disrupted BP rhythmicity, especially high morning surge and the absence of a nocturnal BP dip, are associated with increased risks for cardiovascular events, atrial stiffness and chronic kidney disease.^{155–157} Chronomodulated antihypertensive therapy aims at more precisely mitigating these risk factors, and has been studied in clinical trials. Initially the MAPEC study (2010)¹⁵⁸ and HYGIA trial (2019)¹⁵⁹ demonstrated significant reductions in major cardiac events (61% and 45%, respectively) with bedtime antihypertensive therapy. However, recent evidence provides a more nuanced perspective. A Cochrane systematic review and meta-analysis reported modest reductions in 24 h systolic (−1.34 mmHg, 95% confidence interval [CI]: −2.38

to −.30) and diastolic (−1.01 mmHg, 95% CI: −1.75 to −.27) BP and the morning surge following bedtime antihypertensives administration, but found no conclusive protective effect on cardiovascular outcomes.¹⁶⁰ Similarly, no significant benefit or harm associated with bedtime use of one antihypertensive medicine was found in the BedMed trial, despite a substantial difference in nocturnal systolic BP.^{161,162} Overall, these studies suggest that administering antihypertensives upon waking or at bedtime is equally effective in primary care populations. However, important limitations include the short study duration (<6 months), lack of assessment of left ventricular hypertrophy, and absence of specific analysis for non-dipping hypertensive patients, despite previous evidence of benefit.¹⁵⁸ Bedtime administration may still be considered for patients with specific risk factors comorbidities (e.g. IHD, non-dipping hypertension) or patient characteristics. For example, bedtime doses of long-acting diltiazem were associated with significantly greater reduction of mean systolic and diastolic BP in patients with moderate-to-severe essential hypertension,⁹ and an increased exercise tolerance in patients with angina pectoris¹⁶³ compared to the morning dose. Moreover, accounting for endogenous circadian rhythms has shown potential for stratification and personalized tailoring of antihypertensive therapy to mitigate the risk of adverse cardiovascular events in a recent proof-of-concept study.¹⁶⁴

Optimizing the timing of drug administration in cardiovascular therapy may offer benefits beyond BP control, potentially influencing cardiac remodelling. Circadian angiotensin expression suggests ACE inhibitor efficacy depends on dosing time. In a murine pressure-overload HF model, captopril administration during the rest period reduced cardiac remodelling and improved cardiac function without affecting BP.¹⁶⁵

Diurnal coagulation and fibrinolysis fluctuations, resulting in hypercoagulability and hypofibrinolytic conditions during the morning hours, together with increased platelet activity, suggest an optimal anticoagulant timing.¹⁶⁶ Evening rivaroxaban enhanced morning anticoagulation,¹⁰ while evening low-dose aspirin better suppressed the COX-1 platelet activity peak upon waking.^{166,167} A clinical trial confirmed bedtime low-dose aspirin more effectively reduced morning platelet activity, particularly in women, correlating with improved outcomes in high-risk pregnancies.^{168,169}

Incorporation of circadian medicine in clinical care and research

Circadian medicine encompasses multiple facets, including the timing of treatment and diagnosis (exploiting), integrating patients' circadian characteristics (detecting), and synchronizing or/and modifying the circadian system (targeting).¹⁷⁰ However, a lack of awareness among medical professionals limits the integration of circadian strategies into routine patient care. Here, we provide a summary of opportunities and considerations for integration of circadian medicine in cardiovascular research.

Routinely monitored patient variables, such as core body temperature, HR, and BP, exhibit robust 24 h rhythms in healthy individuals.¹⁷¹ Interpreting these parameters with reference to the time of measurement is already common use. Additionally, since circadian rhythms in these variables are markers of health, assessing the degree of circadian disruption may offer valuable insights for diagnosing disease or determining prognosis. For example, evaluating the peak-to-trough excursions of physiological parameters in intensive care unit patients has shown that deviations of the circadian rhythm are associated with longer length of stay and higher in-hospital mortality.¹⁷² Similarly, a non-dipping BP phenotype revealed by 24 h measurements has been linked to worse disease outcomes, as discussed in section 3.¹⁵⁷

The circadian variation of physiological processes is not limited to vital signs but extends to circulating factors in clinical laboratory measurements. For instance, cardiac biomarkers such as troponin-T,¹⁷³ NT-proBNP⁴⁷ and soluble ST2¹⁷⁴ display circadian variation in plasma levels. Establishing time-dependent reference ranges for such biomarkers could help prevent both false-negative and false-positive results leading to under- and overdiagnosis, and in research settings would increase sensitivity for treatment effects.

To further assess the value of integrating circadian medicine into clinical routines, it is essential to determine the impact of timing on drug administration and interventional therapies (e.g. surgical procedures²⁹) with respect to efficacy, safety, and healthcare costs. However, most studies conducted to date have significant limitations: (i) they are often small, single-centre studies, reducing reproducibility; (ii) they typically compare only two time points, whereas at least three are required to clearly demonstrate peak/trough variation; and (iii) they fail to account for individual circadian phase as a potential confounder (e.g. seasonal variability, working hours/shift work, transmeridian travel, and chronotype including food intake and exercise). Investigating individual variability and identification of healthy people at risk is increasingly feasible with the widespread use of wearable devices, which provide extensive data on total activity, timing of physical activity, posture, HR (and variability), sleep quality, and body temperature. Additionally, recent advancements in digital circadian assessment tools, such as TimeTeller,^{175,176} enable accurate determination of individual circadian rhythms and their strength. Integrating these circadian metrics, with the established chronotype assessment tools (e.g. questionnaire), into clinical care represents a significant opportunity to enhance patient management and optimize the efficiency of clinical studies.

Conclusions

In conclusion, circadian rhythms play a crucial role in cardiovascular health, influencing autonomic balance, cardiac function, and CVD progression. Disruptions increase the risk of IHD, HF, and arrhythmias, highlighting their role in CVD pathophysiology. By aligning interventions with the natural circadian cycle, it may be possible to enhance the efficacy of cardiovascular treatments, reduce side effects, and potentially improve long-term outcomes. Multiple factors related to the circadian clock can be considered to enhance quality or efficiency of clinical care, future clinical studies, and drug development.

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Figures 1, 2, and 3 are created in BioRender. Kelters, I. (2025).

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

No data were generated or analysed for or in support of this paper.

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References

- Dierickx P, Van Laake LW, Geijsen N. Circadian clocks: from stem cells to tissue homeostasis and regeneration. *EMBO Rep* 2018;**19**:18–28. <https://doi.org/10.15252/embr.201745130>
- Crnko S, Du Pré BC, Sluijter JPG, Van Laake LW. Circadian rhythms and the molecular clock in cardiovascular biology and disease. *Nat Rev Cardiol* 2019;**16**:437–47. <https://doi.org/10.1038/s41569-019-0167-4>
- Patke A, Young MW, Axelrod S. Molecular mechanisms and physiological importance of circadian rhythms. *Nat Rev Mol Cell Biol* 2020;**21**:67–84. <https://doi.org/10.1038/s41580-019-0179-2>
- de Juan A, Ince LM, Pick R, Chen C-S, Molica F, Zuchtriegel G, et al. Artery-associated sympathetic innervation drives rhythmic vascular inflammation of arteries and veins. *Circulation* 2019;**140**:1100–14. <https://doi.org/10.1161/CIRCULATIONAHA.119.040232>
- Hayter EA, Wehrens SMT, Van Dongen HPA, Stangherlin A, Gaddameedhi S, Crooks E, et al. Distinct circadian mechanisms govern cardiac rhythms and susceptibility to arrhythmia. *Nat Commun* 2021;**12**:2472. <https://doi.org/10.1038/s41467-021-22788-8>
- Eckle T, Bertazzo J, Khatua TN, Fatemi Tabatabaei SR, Moori Bakhtiari N, Walker LA, et al. Circadian influences on myocardial ischemia-reperfusion injury and heart failure. *Circ Res* 2024;**134**:675–94. <https://doi.org/10.1161/CIRCRESAHA.123.323522>
- Reutrakul S, Knutson KL. Consequences of circadian disruption on cardiometabolic health. *Sleep Med Clin* 2015;**10**:455–68. <https://doi.org/10.1016/j.jsmc.2015.07.005>
- Janoski JR, Aiello I, Lundberg CW, Finkelstein CV. Circadian clock gene polymorphisms implicated in human pathologies. *Trends Genet* 2024;**40**:834–52. <https://doi.org/10.1016/j.tig.2024.05.006>
- Glasser SP, Neutel JM, Gana TJ, Albert KS. Efficacy and safety of a once daily graded-release diltiazem formulation in essential hypertension. *Am J Hypertens* 2003;**16**:51–8. [https://doi.org/10.1016/s0895-7061\(02\)03153-9](https://doi.org/10.1016/s0895-7061(02)03153-9)
- Brunner-Ziegler S, Jilma B, Schörogenhofer C, Winkler F, Jilma-Stohlawetz P, Koppensteiner R, et al. Comparison between the impact of morning and evening doses of rivaroxaban on the circadian endogenous coagulation rhythm in healthy subjects. *J Thromb Haemost* 2016;**14**:316–23. <https://doi.org/10.1111/jth.13213>
- Krasińska B, Paluszkievicz L, Miciak-Lawicka E, Krasiński M, Rzymyski P, Tykarski A, et al. The effect of acetylsalicylic acid dosed at bedtime on the anti-aggregation effect in patients with coronary heart disease and arterial hypertension: a randomized, controlled trial. *Cardiol J* 2020;**26**:727–35. <https://doi.org/10.5603/CJ.a2018.0142>
- Guerci AD, Ross RS. TIMI II and the role of angioplasty in acute myocardial infarction. *N Engl J Med* 1989;**320**:663–5. <https://doi.org/10.1056/NEJM198903093201009>
- Willich SN, Linderer T, Wegscheider K, Leizorovicz A, Alamercury I, Schröder R. Increased morning incidence of myocardial infarction in the ISAM Study: absence with prior beta-adrenergic blockade. ISAM Study Group. *Circulation* 1989;**80**:853–8. <https://doi.org/10.1161/01.CIR.80.4.853>
- Mogabgab O, Giugliano RP, Sabatine MS, Cannon CP, Mohanavelu S, Wiviott SD, et al. Circadian variation in patient characteristics and outcomes in ST-segment elevation myocardial infarction. *Chronobiol Int* 2012;**29**:1390–6. <https://doi.org/10.3109/07420528.2012.728658>
- Mogabgab O, Wiviott SD, Antman EM, Foody JM, Wang TY, Sabatine MS, et al. Relation between time of symptom onset of ST-segment elevation myocardial infarction and patient baseline characteristics: from the national cardiovascular data registry. *Clin Cardiol* 2013;**36**:222–7. <https://doi.org/10.1002/clc.12101>
- Nordenskjöld AM, Eggers KM, Jernberg T, Mohammad MA, Erlinge D, Lindahl B. Circadian onset and prognosis of myocardial infarction with non-obstructive coronary arteries (MINOCA). *PLoS One* 2019;**14**:e0216073. <https://doi.org/10.1371/journal.pone.0216073>
- Jiddou MR, Pica M, Boura J, Qu L, Franklin BA. Incidence of myocardial infarction with shifts to and from daylight savings time. *Am J Cardiol* 2013;**111**:631–5. <https://doi.org/10.1016/j.amjcard.2012.11.010>
- Janszky I, Ahnve S, Ljung R, Mukamal KJ, Gautam S, Wallentin L, et al. Daylight saving time shifts and incidence of acute myocardial infarction—Swedish Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA). *Sleep Med* 2012;**13**:237–42. <https://doi.org/10.1016/j.sleep.2011.07.019>

19. Manfredini R, Fabbian F, Cappadona R, De Giorgi A, Bravi F, Carradori T, et al. Daylight saving time and acute myocardial infarction: a meta-analysis. *J Clin Med* 2019;**8**:404. <https://doi.org/10.3390/jcm8030404> 8 >
20. Manfredini R, Fabbian F, Cappadona R, Modesti PA. Daylight saving time, circadian rhythms, and cardiovascular health. *Intern Emerg Med* 2018;**13**:641–6. <https://doi.org/10.1007/s11739-018-1900-4>
21. Durgan DJ, Pulinilkunnil T, Villegas-Montoya C, Garvey ME, Frangogiannis NG, Michael LH, et al. Short communication: ischemia/reperfusion tolerance is time-of-day-dependent. *Circ Res* 2010;**106**:546–50. <https://doi.org/10.1161/CIRCRESAHA.109.209346>
22. Suárez-Barrientos A, López-Romero P, Vivas D, Castro-Ferreira F, Núñez-Gil I, Franco E, et al. Circadian variations of infarct size in acute myocardial infarction. *Heart* 2011;**97**:970–6. <https://doi.org/10.1136/hrt.2010.212621>
23. Bulluck H, Nicholas J, Crimi G, White SK, Ludman AJ, Pica S, et al. Circadian variation in acute myocardial infarct size assessed by cardiovascular magnetic resonance in reperfusion STEMI patients. *Int J Cardiol* 2017;**230**:149–54. <https://doi.org/10.1016/j.ijcard.2016.12.030>
24. Ari H, Sonmez O, Koc F, Demir K, Alihanoglu Y, Ozdemir K, et al. Circadian rhythm of infarct size and left ventricular function evaluated with tissue Doppler echocardiography in ST elevation myocardial infarction. *Heart Lung Circ* 2016;**25**:250–6. <https://doi.org/10.1016/j.hlc.2015.06.833>
25. Reiter R, Swingen C, Moore L, Henry TD, Traverse JH. Circadian dependence of infarct size and left ventricular function after ST elevation myocardial infarction. *Circ Res* 2012;**110**:105–10. <https://doi.org/10.1161/CIRCRESAHA.111.254284>
26. Paradies V, Zheng H, Chan MHH, Chan MYY, Foo DC, Lee CW, et al. Impact of time of onset of symptom of ST-segment elevation myocardial infarction on 1-year rehospitalization for heart failure and mortality. *Am Heart J* 2020;**224**:1–9. <https://doi.org/10.1016/j.ahj.2020.03.011>
27. Peng H, Sun Z, Di B, Ding X, Chen H, Li H. Contemporary impact of circadian symptom-onset patterns of acute ST-segment elevation myocardial infarction on long-term outcomes after primary percutaneous coronary intervention. *Ann Med* 2021;**53**:247–56. <https://doi.org/10.1080/07853890.2020.1863457>
28. Fournier S, Eeckhout E, Mangiacapra F, Trana C, Lauriers N, Beggah AT, et al. Circadian variations of ischemic burden among patients with myocardial infarction undergoing primary percutaneous coronary intervention. *Am Heart J* 2012;**163**:208–13. <https://doi.org/10.1016/j.ahj.2011.11.006>
29. Montaigne D, Marechal X, Modine T, Coisne A, Mouton S, Fayad G, et al. Daytime variation of perioperative myocardial injury in cardiac surgery and its prevention by Rev-Erba antagonism: a single-centre propensity-matched cohort study and a randomised study. *The Lancet* 2018;**391**:59–69. [https://doi.org/10.1016/S0140-6736\(17\)32132-3](https://doi.org/10.1016/S0140-6736(17)32132-3)
30. Götte J, Zittermann A, Deutsch MA, Schramm R, Bleiziffer S, Hata M, et al. Daytime variation in aortic valve surgery and clinical outcome: a propensity score-matched analysis. *Ann Thorac Surg* 2020;**110**:558–66. <https://doi.org/10.1016/j.athoracsurg.2019.11.026>
31. Nemeth S, Schnell S, Argenziano M, Ning Y, Kurlansky P. Daytime variation does not impact outcome of cardiac surgery: results from a diverse, multi-institutional cardiac surgery network. *J Thorac Cardiovasc Surg* 2021;**162**:56–67.e44. <https://doi.org/10.1016/j.jtcvs.2019.11.131>
32. Kenney PS, Nielsen PH, Modrau IS. Daytime-dependent cardioprotection in cardiac surgery: a large propensity-matched cohort study. *Ann Thorac Surg* 2020;**110**:1629–36. <https://doi.org/10.1016/j.athoracsurg.2020.03.030>
33. Young ME. Cardiac surgery in the morning or not in the morning: “when?” is the question. *Lancet Reg Health Eur* 2021;**7**:100143. <https://doi.org/10.1016/j.lanepe.2021.100143>
34. Yang B, Jia Z. Diagnostic value of nocturnal trend changes in a dynamic electrocardiogram for coronary heart disease. *BMC Cardiovasc Disord* 2024;**24**:561. <https://doi.org/10.1186/s12872-024-04213-2>
35. Wildi K, Singeisen H, Twerenbold R, Badertscher P, Wussler D, Klinkenberg LJJ, et al. Circadian rhythm of cardiac troponin I and its clinical impact on the diagnostic accuracy for acute myocardial infarction. *Int J Cardiol* 2018;**270**:14–20. <https://doi.org/10.1016/j.ijcard.2018.05.136>
36. Klinkenberg LJJ, Wildi K, van der Linden N, Kouw IVK, Niens M, Twerenbold R, et al. Diurnal rhythm of cardiac troponin: consequences for the diagnosis of acute myocardial infarction. *Clin Chem* 2016;**62**:1602–11. <https://doi.org/10.1373/clinchem.2016.257485>
37. Crnko S, Printezzi MI, Zwetsloot P-PM, Leiteris L, Lumley AI, Zhang L, et al. The circadian clock remains intact, but with dampened hormonal output in heart failure. *eBioMedicine* 2023;**91**:104556. <https://doi.org/10.1016/j.ebiom.2023.104556>
38. Lecour S, Du Pré BC, Bøtker HE, Brundel BJM, Daiber A, Davidson SM, et al. Circadian rhythms in ischaemic heart disease: key aspects for preclinical and translational research: position paper of the ESC working group on cellular biology of the heart. *Cardiovasc Res* 2022;**118**:2566–81. <https://doi.org/10.1093/cvr/cvab293>
39. El Jamal N, Lordan R, Teegarden SL, Grosser T, FitzGerald G. The circadian biology of heart failure. *Circ Res* 2023;**132**:223–37. <https://doi.org/10.1161/CIRCRESAHA.122.321369>
40. Sole MJ, Martino TA. Diurnal physiology: core principles with application to the pathogenesis, diagnosis, prevention, and treatment of myocardial hypertrophy and failure. *J Appl Physiol* 2009;**107**:1318–27. <https://doi.org/10.1152/japplphysiol.00426.2009>
41. Gentile F, Emdin M, Passino C, Montuoro S, Tognini P, Floras JS, et al. The chronobiology of human heart failure: clinical implications and therapeutic opportunities. *Heart Fail Rev* 2025;**30**:103–16. <https://doi.org/10.1007/s10741-024-10447-1>
42. Laugsand LE, Strand LB, Platou C, Vatten LJ, Janszky I. Insomnia and the risk of incident heart failure: a population study. *Eur Heart J* 2014;**35**:1382–93. <https://doi.org/10.1093/eurheartj/ehu019>
43. Jia H, Cui H, Zhao Z, Mo H, Zhang N, Zhang Y, et al. Abnormal circadian rhythms exacerbate dilated cardiomyopathy by reducing the ventricular mechanical strength. *Cardiovasc Res* 2024;**120**:2261–77. <https://doi.org/10.1093/cvr/cvae212>
44. Alkhodari M, Hadjileontiadis LJ, Jelinek HF, Khandoker AH. Heart failure assessment using multiparameter polar representations and deep learning. 2023 45th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), Sydney, Australia, 2023, 1–4. <https://doi.org/10.1109/EMBC40787.2023.10341132>
45. Younis SMA, Hadjileontiadis LJ, Shehhi AMA, Stefanini C, Alkhodari M, Soulaïdopoulos S, et al. Investigating automated regression models for estimating left ventricular ejection fraction levels in heart failure patients using circadian ECG features. *PLoS One* 2023;**18**:e0295653. <https://doi.org/10.1371/journal.pone.0295653>
46. Kario K, Hoshida S, Mizuno H, Kabutoya T, Nishizawa M, Yoshida T, et al. Nighttime hemodynamic phenotype. A novel risk factor for cardiovascular disease, especially heart failure: the practitioner-based nationwide JAMP study. *Clin Res Cardiol* 2023;**112**:98–110. <https://doi.org/10.1007/s00392-022-02051-w>
47. Breidhardt T, van Doorn WPTM, van der Linden N, Diebold M, Wussler D, Danier I, et al. Diurnal variations in natriuretic peptide levels: clinical implications for the diagnosis of acute heart failure. *Circ Heart Fail* 2022;**15**:e009165. <https://doi.org/10.1161/CIRCHEARTFAILURE.121.009165>
48. Mallion J-M, Neuder Y, Ormezzano O, Rochette GB, Salvat M, Baguet JP. Study of nycthemeral variations in blood pressure in patients with heart failure. *Blood Press Monit* 2008;**13**:163. <https://doi.org/10.1097/MBP.0b013e3282f216f8>
49. Crnko S, Brugs JJ, Veenis JF, de Jonge N, Slijter JG, Oerlemans MIF, et al. Morning pulmonary artery pressure measurements by CardioMEMS are most stable and recommended for pressure trends monitoring. *Neth Heart J* 2021;**29**:409–14. <https://doi.org/10.1007/s12471-021-01590-7>
50. Nakagawa N. Impact of wrist-measured nocturnal hypertension on cardiovascular prognosis: study design and baseline characteristics of the WISDOM-Night study. *Hypertens Res* 2025;**48**:824–6. <https://doi.org/10.1038/s41440-024-01978-z>
51. Palatini P, Reboli G, Saladini F, Angeli F, Mos L, Rattazzi M, et al. Dipping pattern and short-term blood pressure variability are stronger predictors of cardiovascular events than average 24-h blood pressure in young hypertensive subjects. *Eur J Prev Cardiol* 2022;**29**:1377–86. <https://doi.org/10.1093/eurjpc/zwac020>
52. Chang H-C, Huang C-J, Cheng H-M, Yu W-C, Chiang C-E, Sung S-H, et al. Nocturnal thoracic volume overload and post-discharge outcomes in patients hospitalized for acute heart failure. *ESC Heart Fail* 2020;**7**:2807–17. <https://doi.org/10.1002/ehf2.12881>
53. Komori T, Eguchi K, Saito T, Hoshida S, Kario K. Riser pattern is a novel predictor of adverse events in heart failure patients with preserved ejection fraction. *Circ J* 2017;**81**:220–6. <https://doi.org/10.1253/circj.CJ-16-0740>
54. Dogan NB, Yasar HY, Kilicaslan B. Cardioprotective effects of sodium-glucose cotransporter 2 inhibitors and their possible association with normalization of the circadian index of heart rhythm. *Tex Heart Inst J* 2023;**50**:e238196. <https://doi.org/10.14503/THIJ-23-8196>
55. Saleem S, Khandoker AH, Alkhodari M, Hadjileontiadis LJ, Jelinek HF. Investigating the effects of beta-blockers on circadian heart rhythm using heart rate variability in ischemic heart disease with preserved ejection fraction. *Sci Rep* 2023;**13**:5828. <https://doi.org/10.1038/s41598-023-32963-0>
56. Scheer FAJL, Morris CJ, Garcia JJ, Smales C, Kelly EE, Marks J, et al. Repeated melatonin supplementation improves sleep in hypertensive patients treated with beta-blockers: a randomized controlled trial. *Sleep* 2012;**35**:1395–402. <https://doi.org/10.5665/sleep.2122>
57. Giles TD, Roffidal L, Quiroz A, Sander G, Tresznewsky O. Circadian variation in blood pressure and heart rate in nonhypertensive congestive heart failure. *J Cardiovasc Pharmacol* 1996;**28**:733–40. <https://doi.org/10.1097/00005344-199612000-00001>
58. Grossmann M. Effects of cardiac glycosides on 24-h ambulatory blood pressure in healthy volunteers and patients with heart failure. *Eur J Clin Invest* 2001;**31**:26–30. <https://doi.org/10.1046/j.1365-2362.2001.03105.2026.x>
59. Numan L, Wösten M, Moazeni M, Aarts E, Van der Kaaij NP, Fresiello L, et al. Circadian rhythms in pump parameters of patients on contemporary left ventricular assist device support. *Artif Organs* 2023;**47**:1893–7. <https://doi.org/10.1111/aor.14628>
60. Gouchou DA, Ganapathi AM, Cui EY, Henn MC, Yim WY, Geng B, et al. Is time scheduling important? An analysis of donor heart heart cross-clamp times during heart transplantation. *Transplant Direct* 2024;**10**:e1588. <https://doi.org/10.1097/TXD.0000000000001588>
61. Smolensky MH, Bergman SA Jr, Barnard CN, Beck W, Kraft IA. Circadian rhythmic characteristics of innervated and non-innervated cardiac tissue of single and double-heart transplanted patients. *Cardiovasc Dis* 1976;**3**:150–68. PMID: 15216162.
62. Patlin BH, Mok H, Arra M, Haspel JA. Circadian rhythms in solid organ transplantation. *J Heart Lung Transplant* 2024;**43**:849–57. <https://doi.org/10.1016/j.healun.2024.01.017>
63. Weiner OJF, Das M, Clayton RH, McComb JM, Murray A, Parry G, et al. Sympathetic reinnervation in cardiac transplant recipients: prevalence, time course, and association

- with long-term survival. *J Heart Lung Transplant* 2025;**44**:204–12. <https://doi.org/10.1016/j.healun.2024.10.009>
64. Schröder EA, Burgess DE, Zhang X, Lefta M, Smith JL, Patwardhan A, et al. The cardiomyocyte molecular clock regulates the circadian expression of *Kcnh2* and contributes to ventricular repolarization. *Heart Rhythm* 2015;**12**:1306–14. <https://doi.org/10.1016/j.hrthm.2015.02.019>
 65. D'Souza A, Wang Y, Anderson C, Bucchi A, Baruscotti M, Olieslagers S, et al. A circadian clock in the sinus node mediates day-night rhythms in *Hcn4* and heart rate. *Heart Rhythm* 2021;**18**:801–10. <https://doi.org/10.1016/j.hrthm.2020.11.026>
 66. Brodsky M, Wu D, Denes P, Kanakis C, Rosen KM. Arrhythmias documented by 24 h continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. *Am J Cardiol* 1977;**39**:390–5. [https://doi.org/10.1016/s0002-9149\(77\)80094-5](https://doi.org/10.1016/s0002-9149(77)80094-5)
 67. Gardner RT, Ripplinger CM, Myles RC, Habecker BA. Molecular mechanisms of sympathetic remodeling and arrhythmias. *Circ Arrhythm Electrophysiol* 2016;**9**:e001359. <https://doi.org/10.1161/CIRCEP.115.001359>
 68. Bernardi J, Aromolaran KA, Zhu H, Aromolaran AS. Circadian mechanisms: cardiac ion channel remodeling and arrhythmias. *Front Physiol* 2021;**11**:611860. <https://doi.org/10.3389/fphys.2020.611860>
 69. Tikhomirov R, Oakley RH, Anderson C, Xiang Y, Al-Othman S, Smith M, et al. Cardiac GR mediates the diurnal rhythm in ventricular arrhythmia susceptibility. *Circ Res* 2024;**134**:1306–26. <https://doi.org/10.1161/CIRCRESAHA.123.323464>
 70. McTiernan CF, Lemster BH, Bedi KC, Margulies KB, Moravec CS, Hsieh PN, et al. Circadian pattern of ion channel gene expression in failing human hearts. *Circ Arrhythm Electrophysiol* 2021;**14**:e009254. <https://doi.org/10.1161/CIRCEP.120.009254>
 71. Liu S-H, Lo L-W, Tsai T-Y, Cheng W-H, Lin Y-J, Chang S-L, et al. Circadian rhythm dynamics on multiscale entropy identifies autonomic dysfunction associated with risk of ventricular arrhythmias and near syncope in chronic kidney disease. *J Cardiol* 2020;**76**:542–8. <https://doi.org/10.1016/j.jcc.2020.05.017>
 72. Cheng C, Jiang J, Chen K, Hua W, Su Y, Xu W, et al. Device-evaluated autonomic nervous function for predicting ventricular arrhythmias and all-cause mortality in patients who underwent cardiac resynchronization therapy-defibrillator. *Front Physiol* 2023;**14**:1090038. <https://doi.org/10.3389/fphys.2023.1090038>
 73. Peters RW, Muller JE, Goldstein S, Byington R, Friedman LM. Propranolol and the morning increase in the frequency of sudden cardiac death (BHAT Study). *Am J Cardiol* 1989;**63**:1518–20. [https://doi.org/10.1016/0002-9149\(89\)90019-2](https://doi.org/10.1016/0002-9149(89)90019-2)
 74. Behrens S, Ehlers C, Brüggemann T, Ziss W, Dissmann R, Galecka M, et al. Modification of the circadian pattern of ventricular tachyarrhythmias by beta-blocker therapy. *Clin Cardiol* 1997;**20**:253–7. <https://doi.org/10.1002/clc.4960200313>
 75. Ni Y-M, Rusinaru C, Reinier K, Uy-Evanado A, Chugh H, Stecker EC, et al. Unexpected shift in circadian and septadian variation of sudden cardiac arrest: the Oregon sudden unexpected death study. *Heart rhythm* 2019;**16**:411–5. <https://doi.org/10.1016/j.hrthm.2018.08.034>
 76. Matsuo K, Kurita T, Inagaki M, Kakishita M, Aihara N, Shimizu W, et al. The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. *Eur Heart J* 1999;**20**:465–70. <https://doi.org/10.1053/euhj.1998.1332>
 77. Kim S-H, Nam G-B, Baek S, Choi H-O, Kim KH, Choi K-J, et al. Circadian and seasonal variations of ventricular tachyarrhythmias in patients with early repolarization syndrome and Brugada syndrome: analysis of patients with implantable cardioverter defibrillator. *J Cardiovasc Electrophysiol* 2012;**23**:757–63. <https://doi.org/10.1111/j.1540-8167.2011.02287.x>
 78. Aizawa Y, Takatsuki S, Kaneko Y, Noda T, Katsumata Y, Nishiyama T, et al. Comparison of circadian, weekly, and seasonal variations of electrical storms and single events of ventricular fibrillation in patients with Brugada syndrome. *Int J Cardiol Heart Vasc* 2016;**11**:104–10. <https://doi.org/10.1016/j.ijcha.2016.05.008>
 79. Kumagai N, Ogawa M, Zhang B, Koyoshi R, Morii J, Yasuda T, et al. Paradoxical nocturnal elevation of sympathetic tone and spontaneous ventricular fibrillation in Brugada syndrome. *J Cardiol* 2016;**67**:229–35. <https://doi.org/10.1016/j.jcc.2015.11.002>
 80. Tokuyama T, Nakano Y, Awazu A, Uchimura-Makita Y, Fujiwara M, Watanabe Y, et al. Deterioration of the circadian variation of heart rate variability in Brugada syndrome may contribute to the pathogenesis of ventricular fibrillation. *J Cardiol* 2014;**64**:133–8. <https://doi.org/10.1016/j.jcc.2013.12.001>
 81. Zeidan-Shwiri T, Aronson D, Atalla K, Blich M, Suleiman M, Marai I, et al. Circadian pattern of life-threatening ventricular arrhythmia in patients with sleep-disordered breathing and implantable cardioverter-defibrillators. *Heart Rhythm* 2011;**8**:657–62. <https://doi.org/10.1016/j.hrthm.2010.12.030>
 82. Dissanayake HU, Bin YS, Ucak S, de Chazal P, Sutherland K, Cistulli PA. Association between autonomic function and obstructive sleep apnea: a systematic review. *Sleep Med Rev* 2021;**57**:101470. <https://doi.org/10.1016/j.smrv.2021.101470>
 83. van den Broek JLP, Gottlieb LA, Vermeer JR, Overeem S, Dekker LRC. When the clock strikes A-fib. *JACC Clin Electrophysiol* 2024;**10**:1916–28. <https://doi.org/10.1016/j.jacep.2024.05.035>
 84. Kharbanda RK, van der Does WFB, van Staveren LN, Taverne YJH, Bogers AJJC, de Groot NMS. Vagus nerve stimulation and atrial fibrillation: revealing the paradox. *Neuromodulation* 2022;**25**:356–65. <https://doi.org/10.1016/j.neurom.2022.01.008>
 85. Voigt N, Heijman J, Wang Q, Chiang DY, Li N, Karck M, et al. Cellular and molecular mechanisms of atrial arrhythmogenesis in patients with paroxysmal atrial fibrillation. *Circulation* 2014;**129**:145–56. <https://doi.org/10.1161/CIRCULATIONAHA.113.006641>
 86. Chen P-S, Chen LS, Fishbein MC, Lin S-F, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. *Circ Res* 2014;**114**:1500–15. <https://doi.org/10.1161/CIRCRESAHA.114.303772>
 87. Choi E-K, Shen MJ, Han S, Kim D, Hwang S, Sayfo S, et al. Intrinsic cardiac nerve activity and paroxysmal atrial tachyarrhythmia in ambulatory dogs. *Circulation* 2010;**121**:2615–23. <https://doi.org/10.1161/CIRCULATIONAHA.109.919829>
 88. Guo Y, Zhang H, Chen Y; mFA investigators. Population screening for atrial fibrillation in subjects with sleep apnea. *Eur Heart J* 2021;**42**:ehab724.0454. <https://doi.org/10.1093/eurheartj/ehab724.0454>
 89. Kwon Y, Gharib SA, Biggs ML, Jacobs DR Jr, Alonso A, Duprez D, et al. Association of sleep characteristics with atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Thorax* 2015;**70**:873–9. <https://doi.org/10.1136/thoraxjnl-2014-206655>
 90. Linz D, Brooks AG, Elliott AD, Nalliah CJ, Hendriks JML, Middeldorp ME, et al. Variability of sleep apnea severity and risk of atrial fibrillation: the VARIO-SA-AF study. *JACC Clin Electrophysiol* 2019;**5**:692–701. <https://doi.org/10.1016/j.jacep.2019.03.005>
 91. Gottlieb LA, Lubberding A, Larsen AP, Thomsen MB. Circadian rhythm in QT interval is preserved in mice deficient of potassium channel interacting protein 2. *Chronobiol Int* 2017;**34**:45–56. <https://doi.org/10.1080/07420528.2016.1225074>
 92. van den Broek JJ, Heydari S, Zhan Z, van 't Veer M, Sammal J, Overeem S, et al. Can body position be arrhythmogenic? *Sleep Med* 2023;**105**:21–4. <https://doi.org/10.1016/j.sleep.2023.03.004>
 93. Watanabe M, Nakagawa M, Nobe S, Ohie T, Takahashi N, Hara M, et al. Circadian variation of short-lasting asymptomatic paroxysmal supraventricular tachycardia. *J Electrocardiol* 2002;**35**:135–8. <https://doi.org/10.1054/jelc.2002.31820>
 94. Li P, Kim JK. Circadian regulation of sinoatrial nodal cell pacemaking function: dissecting the roles of autonomic control, body temperature, and local circadian rhythmicity. *PLoS Comput Biol* 2024;**20**:e1011907. <https://doi.org/10.1371/journal.pcbi.1011907>
 95. Cuomo A, Libri C, Barillà G, Cattolico M, Carmellini P, Fagiolini A. QTc interval diurnal variations in patients treated with psychotropic medications: implications for the evaluation of drug induced QTc changes. *Int Rev Psychiatry* 2022;**34**:689–92. <https://doi.org/10.1080/09540261.2022.2135985>
 96. Kervezee L, Gotta V, Stevens J, Birkhoff W, Kamerling I, Danhof M, et al. Levofloxacin-induced QTc prolongation depends on the time of drug administration. *CPT Pharmacometrics Syst Pharmacol* 2016;**5**:466–74. <https://doi.org/10.1002/psp4.12085>
 97. Leur Rvd, Pré Bd, Printezi MI, Hassink RJ, Doeveendans PA, Es Rv, et al. Altered circadian rhythmicity of the QT interval predicts mortality in a large real-world academic hospital population. *Heliyon* 2025;**11**:e41308. <https://doi.org/10.1016/j.heliyon.2024.e41308>
 98. Takeda N, Maemura K. Circadian clock and cardiovascular disease. *J Cardiol* 2011;**57**:249–56. <https://doi.org/10.1016/j.jcc.2011.02.006>
 99. Manfredini R, Boari B, Gallerani M, Salmi R, Bossone E, Distanto A, et al. Chronobiology of rupture and dissection of aortic aneurysms. *J Vasc Surg* 2004;**40**:382–8. <https://doi.org/10.1016/j.jvs.2004.04.019>
 100. Vitale J, Manfredini R, Gallerani M, Mumoli N, Eagle KA, Ageno W, et al. Chronobiology of acute aortic rupture or dissection: a systematic review and a meta-analysis of the literature. *Chronobiol Int* 2015;**32**:385–94. <https://doi.org/10.3109/07420528.2014.983604>
 101. Mehta RH, Manfredini R, Hassan F, Sechtem U, Bossone E, Oh JK, et al. Chronobiological patterns of acute aortic dissection. *Circulation* 2002;**106**:1110–5. <https://doi.org/10.1161/01.cir.0000027568.39540.4b>
 102. Manfredini R, Boari B, Smolensky MH, Salmi R, la Cecilia O, Maria Malagoni A, et al. Circadian variation in stroke onset: identical temporal pattern in ischemic and hemorrhagic events. *Chronobiol Int* 2005;**22**:417–53. <https://doi.org/10.1081/CBI-200062927>
 103. Smolensky MH, Portaluppi F, Manfredini R, Hermida RC, Tiseo R, Sackett-Lundeen LL, et al. Diurnal and twenty-four hour patterning of human diseases: cardiac, vascular, and respiratory diseases, conditions, and syndromes. *Sleep Med Rev* 2015;**21**:3–11. <https://doi.org/10.1016/j.smrv.2014.07.001>
 104. Manfredini R, Fabbian F, Manfredini F, Salmi R, Gallerani M, Bossone E. Chronobiology in aortic diseases—“is this really a random phenomenon?”. *Prog Cardiovasc Dis* 2013;**56**:116–24. <https://doi.org/10.1016/j.pcad.2013.04.001>
 105. Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. *Nat Rev Cardiol* 2020;**17**:474–502. <https://doi.org/10.1038/s41569-020-0348-1>
 106. Lal H, Verma SK, Wang Y, Xie M, Young ME. Circadian rhythms in cardiovascular metabolism. *Circ Res* 2024;**134**:635–58. <https://doi.org/10.1161/CIRCRESAHA.123.323520>
 107. Shafi AA, McNair CM, McCann JJ, Alshalal M, Shostak A, Severson TM, et al. The circadian cryptochrome, CRY1, is a pro-tumorigenic factor that rhythmically modulates DNA repair. *Nat Commun* 2021;**12**:401. <https://doi.org/10.1038/s41467-020-20513-5>
 108. Rabinovich-Nikitin I, Lieberman B, Martino TA, Kirshenbaum LA. Circadian-regulated cell death in cardiovascular diseases. *Circulation* 2019;**139**:965–80. <https://doi.org/10.1161/CIRCULATIONAHA.118.036550>
 109. Dierickx P, Vermunt MW, Muraro MJ, Creighton MP, Doeveendans PA, van Oudenaarden A, et al. Circadian networks in human embryonic stem cell-derived cardiomyocytes. *EMBO Rep* 2017;**18**:1199–212. <https://doi.org/10.15252/embr.201743897>

110. du Pré BC, Dierickx P, Crnko S, Doevendans PA, Vos MA, Geijsen N, et al. Neonatal rat cardiomyocytes as an in vitro model for circadian rhythms in the heart. *J Mol Cell Cardiol* 2017;**112**:58–63. <https://doi.org/10.1016/j.jmcc.2017.08.009>
111. Levi F, Mechkouri M, Roulon A, Bailleul F, Lemaigre G, Reinberg A, et al. Circadian rhythm in tolerance of mice for the new anthracycline analog 4'-O-tetrahydropyranyl-adriamycin (THP). *Eur J Cancer Clin Oncol* 1985;**21**:1245–51. [https://doi.org/10.1016/0277-5379\(85\)90022-7](https://doi.org/10.1016/0277-5379(85)90022-7)
112. Yang N, Ma H, Jiang Z, Niu L, Zhang X, Liu Y, et al. Dosing depending on SIRT3 activity attenuates doxorubicin-induced cardiotoxicity via elevated tolerance against mitochondrial dysfunction and oxidative stress. *Biochem Biophys Res Commun* 2019;**517**: 111–7. <https://doi.org/10.1016/j.bbrc.2019.07.029>
113. To H, Ohdo S, Shin M, Uchimaru H, Yukawa E, Higuchi S, et al. Dosing time dependency of doxorubicin-induced cardiotoxicity and bone marrow toxicity in rats. *J Pharm Pharmacol* 2003;**55**:803–10. <https://doi.org/10.1211/002235703765951410>
114. Mosier AE, Hurley JM. Circadian interatomicity: how research into protein-protein interactions beyond the core clock has influenced the model of circadian timekeeping. *J Biol Rhythms* 2021;**36**:315–28. <https://doi.org/10.1177/07487304211014622>
115. Morris CJ, Purvis TE, Hu K, Scheer FAJL. Circadian misalignment increases cardiovascular disease risk factors in humans. *Proc Natl Acad Sci U S A* 2016;**113**:E1402–11. <https://doi.org/10.1073/pnas.1516953113>
116. Pandi-Perumal SR, Trakht I, Spence DW, Srivivasan V, Dagan Y, Cardinali DP. The roles of melatonin and light in the pathophysiology and treatment of circadian rhythm sleep disorders. *Nat Clin Pract Neurol* 2008;**4**:436–48. <https://doi.org/10.1038/ncpneu0847>
117. Kerkhof GA. Shift work and sleep disorder comorbidity tend to go hand in hand. *Chronobiol Int* 2018;**35**:219–28. <https://doi.org/10.1080/07420528.2017.1392552>
118. Qian J, Morris CJ, Caputo R, Wang W, Garaulet M, Scheer FAJL. Sex differences in the circadian misalignment effects on energy regulation. *Proc Natl Acad Sci U S A* 2019;**116**: 23806–12. <https://doi.org/10.1073/pnas.1914003116>
119. Wharfe MD, Mark PJ, Wyrwoll CS, Smith JT, Yap C, Clarke MW, et al. Pregnancy-induced adaptations of the central circadian clock and maternal glucocorticoids. *J Endocrinol* 2016;**228**:135–47. <https://doi.org/10.1530/JOE-15-0405>
120. Karasek M. Melatonin, human aging, and age-related diseases. *Exp Gerontol* 2004;**39**: 1723–9. <https://doi.org/10.1016/j.exger.2004.04.012>
121. Engin A. Misalignment of circadian rhythms in diet-induced obesity. *Adv Exp Med Biol* 2024;**1460**:27–71. https://doi.org/10.1007/978-3-031-63657-8_2
122. Han H, Dou J, Hou Q, Wang H. Role of circadian rhythm and impact of circadian rhythm disturbance on the metabolism and disease. *J Cardiovasc Pharmacol* 2022;**79**: 254–63. <https://doi.org/10.1097/FJC.0000000000001178>
123. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease. *Circulation* 1999;**99**:1165–72. <https://doi.org/10.1161/01.CIR.99.9.1165>
124. Andreadou I, Daiber A, Baxter GF, Brizzi MF, Di Lisa F, Kaludercic N, et al. Influence of cardiometabolic comorbidities on myocardial function, infarction, and cardioprotection: role of cardiac redox signaling. *Free Radic Biol Med* 2021;**166**:33–52. <https://doi.org/10.1016/j.freeradbiomed.2021.02.012>
125. McAlpine CS, Swirski FK. Circadian influence on metabolism and inflammation in atherosclerosis. *Circ Res* 2016;**119**:131–41. <https://doi.org/10.1161/CIRCRESAHA.116.308034>
126. Wang C, Lutes LK, Barnoud C, Scheiermann C. The circadian immune system. *Sci Immunol* 2022;**7**:eabm2465. <https://doi.org/10.1126/sciimmunol.abm2465>
127. Young MJ, Heanue S, Kanki M, Moneghetti KJ. Circadian disruption and its impact on the cardiovascular system. *Trends Endocrinol Metab* 2024. <https://doi.org/10.1016/j.tem.2024.11.010>
128. Li JZ, Bunney BG, Meng F, Hagenauer MH, Walsh DM, Vawter MP, et al. Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *Proc Natl Acad Sci U S A* 2013;**110**:9950–5. <https://doi.org/10.1073/pnas.1305814110>
129. Xia N, Li H. Loneliness, social isolation, and cardiovascular health. *Antioxid Redox Signal* 2018;**28**:837–51. <https://doi.org/10.1089/ars.2017.7312>
130. Lee K, Hong K-S, Park J, Park W. Readjustment of circadian clocks by exercise intervention is a potential therapeutic target for sleep disorders: a narrative review. *Phys Act Nutr* 2024;**28**:35–42. <https://doi.org/10.20463/pan.2024.0014>
131. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev* 2019;**1**: CD003331. <https://doi.org/10.1002/14651858.CD003331.pub5>
132. Thomas JM, Kern PA, Bush HM, McQuerry KJ, Black VVS, Clasey JL, et al. Circadian rhythm phase shifts caused by timed exercise vary with chronotype. *JCI Insight* 2020;**5**:e134270. <https://doi.org/10.1172/jci.insight.134270>
133. Bailey SM. Emerging role of circadian clock disruption in alcohol-induced liver disease. *Am J Physiol Gastrointest Liver Physiol* 2018;**315**:G364–73. <https://doi.org/10.1152/ajpgi.00010.2018>
134. Hwang J-VW, Sundar IK, Yao H, Sellix MT, Rahman I. Circadian clock function is disrupted by environmental tobacco/cigarette smoke, leading to lung inflammation and injury via a SIRT1-BMAL1 pathway. *FASEB J* 2014;**28**:176–94. <https://doi.org/10.1096/fj.13-232629>
135. Gibson M, Munafo MR, Taylor AE, Treur JL. Evidence for genetic correlations and bidirectional, causal effects between smoking and sleep behaviors. *Nicotine Tob Res* 2018;**21**:731–8. <https://doi.org/10.1093/ntr/nty230>
136. Chang Y, Du T, Zhuang X, Ma G. Time-restricted eating improves health because of energy deficit and circadian rhythm: a systematic review and meta-analysis. *iScience* 2024;**27**:109000. <https://doi.org/10.1016/j.isci.2024.109000>
137. Karam G, Agarwal A, Sadeghirad B, Jalink M, Hitchcock CL, Ge L, et al. Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk: systematic review and network meta-analysis. *The BMJ* 2023;**380**:e072003. <https://doi.org/10.1136/bmj-2022-072003>
138. Torres-Fuentes C, Suárez M, Aragón G, Mulero M, Ávila-Román J, Arola-Arnal A, et al. Cardioprotective properties of phenolic compounds: a role for biological rhythms. *Mol Nutr Food Res* 2022;**66**:2100990. <https://doi.org/10.1002/mnfr.202100990>
139. Zhao Y, Lu X, Wan F, Gao L, Lin N, He J, et al. Disruption of circadian rhythms by shift work exacerbates reperfusion injury in myocardial infarction. *J Am Coll Cardiol* 2022;**79**: 2097–115. <https://doi.org/10.1016/j.jacc.2022.03.370>
140. Cappadona R, De Giorgi A, Boari B, Tiseo R, Lopez-Soto PJ, Fabbian F, et al. Nurses, sleep disturbances, desynchronization of circadian rhythms, and performance: a dangerous liaison? A narrative mini-review. *Eur Rev Med Pharmacol Sci* 2021;**25**: 6924–33. https://doi.org/10.26355/eurrev_202111_27241
141. Nemeroff CB, Goldschmidt-Clermont PJ. Heartache and heartbreak—the link between depression and cardiovascular disease. *Nat Rev Cardiol* 2012;**9**:526–39. <https://doi.org/10.1038/nrcardio.2012.91>
142. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;**396**:1223–49. [https://doi.org/10.1016/S0140-6736\(20\)30752-2](https://doi.org/10.1016/S0140-6736(20)30752-2)
143. Rensing L, Ruoff P. Temperature effect on entrainment, phase shifting, and amplitude of circadian clocks and its molecular bases. *Chronobiol Int* 2002;**19**:807–64. <https://doi.org/10.1081/CBI-120014569>
144. Kidd PB, Young MV, Siggia ED. Temperature compensation and temperature sensation in the circadian clock. *Proc Natl Acad Sci U S A* 2015;**112**:E6284–92. <https://doi.org/10.1073/pnas.1511215112>
145. Münzel T, Kröller-Schön S, Oelze M, Gori T, Schmidt FP, Steven S, et al. Adverse cardiovascular effects of traffic noise with a focus on nighttime noise and the new WHO noise guidelines. *Annu Rev Public Health* 2020;**41**:309–28. <https://doi.org/10.1146/annurev-publhealth-081519-062400>
146. Chepesiuk R. Missing the dark: health effects of light pollution. *Environ Health Perspect* 2009;**117**:A20–7. <https://doi.org/10.1289/ehp.117-a20>
147. Shawa N, Rae DE, Roden LC. Impact of seasons on an individual's chronotype: current perspectives. *Nat Sci Sleep* 2018;**10**:345–54. <https://doi.org/10.2147/NSS.S158596>
148. Haberzettl P. Circadian toxicity of environmental pollution. Inhalation of polluted air to give a precedent. *Curr Opin Physiol* 2018;**5**:16–24. <https://doi.org/10.1016/j.cophys.2018.05.002>
149. Li H, Kilgallen AB, Münzel T, Wolf E, Lecour S, Schulz R, et al. Influence of mental stress and environmental toxins on circadian clocks: implications for redox regulation of the heart and cardioprotection. *Br J Pharmacol* 2020;**177**:5393–412. <https://doi.org/10.1111/bph.14949>
150. Daiber A, Frenis K, Kuntic M, Li H, Wolf E, Kilgallen AB, et al. Redox regulatory changes of circadian rhythm by the environmental risk factors traffic noise and air pollution. *Antioxid Redox Signal* 2022;**37**:679–703. <https://doi.org/10.1089/ars.2021.0272>
151. Alahmad B, Khraishah H, Royé D, Vicedo-Cabrera AM, Guo Y, Papatheodorou SI, et al. Associations between extreme temperatures and cardiovascular cause-specific mortality: results from 27 countries. *Circulation* 2023;**147**:35–46. <https://doi.org/10.1161/CIRCULATIONAHA.122.061832>
152. Münzel T, Molitor M, Kuntic M, Hahad O, Rösli M, Engelmann N, et al. Transportation noise pollution and cardiovascular health. *Circ Res* 2024;**134**:1113–35. <https://doi.org/10.1161/CIRCRESAHA.123.323584>
153. Dallmann R, Brown SA, Gachon F. Chronopharmacology: new insights and therapeutic implications. *Annu Rev Pharmacol Toxicol* 2014;**54**:339–61. <https://doi.org/10.1146/annurev-pharmtox-011613-135923>
154. Awad K, Serban M-C, Penson P, Mikhailidis DP, Toth PP, Jones SR, et al. Effects of morning vs evening statin administration on lipid profile: a systematic review and meta-analysis. *J Clin Lipidol* 2017;**11**:972–85.e9. <https://doi.org/10.1016/j.jacl.2017.06.001>
155. Motiejunaite J, Alencar De Pinho N, Arnoult F, Vrtovsnik F, Tabibzadeh N, Flamant M, et al. Association between nocturnal blood pressure dipping and chronic kidney disease. *Eur Heart J* 2022;**43**:ehac544.2191. <https://doi.org/10.1093/eurheartj/ehac544.2191>
156. Liu J, Su X, Nie Y, Zeng Z, Chen H; NARRAS investigators. Nocturnal blood pressure rather than night-to-day blood pressure ratio is related to arterial stiffening in untreated young and middle-aged adults with non-dipper hypertension. *The Journal of Clinical Hypertension* 2022;**24**:1044–50. <https://doi.org/10.1111/jch.14546>
157. Staplin N, de la Sierra A, Ruilope LM, Emberson JR, Vinyoles E, Gorostidi M, et al. Relationship between clinic and ambulatory blood pressure and mortality: an observational cohort study in 59 124 patients. *The Lancet* 2023;**401**:2041–50. [https://doi.org/10.1016/S0140-6736\(23\)00733-X](https://doi.org/10.1016/S0140-6736(23)00733-X)

158. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. *Chronobiol Int* 2010;**27**:1629–51. <https://doi.org/10.3109/07420528.2010.510230>
159. Hermida RC, Crespo JJ, Domínguez-Sardiña M, Otero A, Moyá A, Ríos MT, et al. Bedtime hypertension treatment improves cardiovascular risk reduction: the hygia chronotherapy trial. *Eur Heart J* 2020;**41**:4565–76. <https://doi.org/10.1093/eurheartj/ehz754>
160. Wu C, Zhao P, Xu P, Wan C, Singh S, Varthya SB, et al. Evening versus morning dosing regimen drug therapy for hypertension. *Cochrane Database Syst Rev* 2024;**2**: CD004184. <https://doi.org/10.1002/14651858.CD004184.pub3>
161. ESC Press Office. Evening vs. Morning Dosing of Blood Pressure Medication: No Differences Seen, 2024.
162. Garrison S. BedMed & BedMed-Frail: Does the Timing of Blood Pressure Medication Really Matter? Presented at European Society of Cardiology (ESC) Congress 2024 in London, United Kingdom, 2024.
163. Claas SA, Glasser SP. Long-acting diltiazem HCl for the chronotherapeutic treatment of hypertension and chronic stable angina pectoris. *Expert Opin Pharmacother* 2005;**6**: 765–76. <https://doi.org/10.1517/14656566.6.5.765>
164. Pigazzani F, Dyar KA, Morant SV, Vetter C, Rogers A, Flynn RWV, et al. Effect of timed dosing of usual antihypertensives according to patient chronotype on cardiovascular outcomes: the Chronotype sub-study cohort of the Treatment in Morning versus Evening (TIME) study. *EClinicalMedicine* 2024;**72**:102633. <https://doi.org/10.1016/j.eclinm.2024.102633>
165. Martino TA, Tata N, Simpson JA, Vanderlaan R, Dawood F, Kabir MG, et al. The primary benefits of angiotensin-converting enzyme inhibition on cardiac remodeling occur during sleep time in murine pressure overload hypertrophy. *J Am Coll Cardiol* 2011;**57**:2020–8. <https://doi.org/10.1016/j.jacc.2010.11.022>
166. Scheer FAJL, Michelson AD, Frelinger AL 3rd, Evoniuk H, Kelly EE, McCarthy M, et al. The human endogenous circadian system causes greatest platelet activation during the biological morning independent of behaviors. *PLoS One* 2011;**6**:e24549. <https://doi.org/10.1371/journal.pone.0024549>
167. Bonten TN, Saris A, Oostrom Mv, Snoep JD, Rosendaal FR, Zwaginga JJ, et al. Effect of aspirin intake at bedtime versus on awakening on circadian rhythm of platelet reactivity. *Thromb Haemost* 2014;**112**:1209–18. <https://doi.org/10.1160/th14-05-0453>
168. Krasnińska B, Paluszkiwicz L, Miciak-Ławicka E, Krasinski M, Rzymiski P, Tykarski A, et al. The impact of acetylsalicylic acid dosed at bedtime on circadian rhythms of blood pressure in the high-risk group of cardiovascular patients—a randomized, controlled trial. *Eur J Clin Pharmacol* 2021;**77**:35–43. <https://doi.org/10.1007/s00228-020-02997-8>
169. Ayala DE, Uceda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. *Chronobiol Int* 2013;**30**:260–79. <https://doi.org/10.3109/07420528.2012.717455>
170. Kramer A, Lange T, Spies C, Finger A-M, Berg D, Oster H. Foundations of circadian medicine. *PLoS Biol* 2022;**20**:e3001567. <https://doi.org/10.1371/journal.pbio.3001567>
171. Kanabrocki EL, Sothorn RB, Scheving LE, Vesely DL, Tsai TH, Shelstad J, et al. Reference values for circadian rhythms of 98 variables in clinically healthy men in the fifth decade of life. *Chronobiol Int* 1990;**7**:445–61. <https://doi.org/10.3109/07420529009059156>
172. Beyer SE, Salgado C, Garção I, Celi LA, Vieira S. Circadian rhythm in critically ill patients: insights from the eICU database. *Cardiovasc Digit Health J* 2021;**2**:118–25. <https://doi.org/10.1016/j.cvdhj.2021.01.004>
173. Klinkenberg LJJ, van Dijk J-VV, Tan FES, van LLJC, van D-VMP, Meex SJR. Circulating cardiac troponin T exhibits a diurnal rhythm. *J Am Coll Cardiol* 2014;**63**:1788–95. <https://doi.org/10.1016/j.jacc.2014.01.040>
174. Crnko S, Printezi MI, Jansen TPJ, Leiteris L, van der Meer MG, Schutte H, et al. Prognostic biomarker soluble ST2 exhibits diurnal variation in chronic heart failure patients. *ESC Heart Fail* 2020;**7**:1224–33. <https://doi.org/10.1002/ehf2.12673>
175. Vlachou D, Veretennikova M, Usselman L, Vasilyev V, Ott S, Bjarnason GA, et al. TimeTeller: a tool to probe the circadian clock as a multigene dynamical system. *PLoS Comput Biol* 2024;**20**:e1011779. <https://doi.org/10.1371/journal.pcbi.1011779>
176. Dose B, Yalçın M, Dries SPM, Relógio A. TimeTeller for timing health: the potential of circadian medicine to improve performance, prevent disease and optimize treatment. *Front Digit Health* 2023;**5**:1157654. <https://doi.org/10.3389/fdgh.2023.1157654>