

SUPPLEMENTARY DATA

**Circadian Rhythms, Metabolic Disorders, and
Cardiovascular Aging: Molecular Crosstalk and Clinical
Translation**

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SUPPLEMENTARY DATA

Supplementary material 1. Search terms for each database

PUBMED (n=1309)

((circadian rhythm OR circadian clock OR circadian disruption OR circadian misalignment OR clock gene OR shift work OR chronotype) AND (cardiovascular aging OR vascular aging OR cardiac aging OR endothelial dysfunction OR arterial stiffness OR atherosclerosis OR hypertension OR heart failure OR cardiomyopathy) AND (metabolic syndrome OR insulin resistance OR dyslipidemia OR type 2 diabetes OR obesity))

Web of Science (n=987)

TS=("circadian rhythm" OR "circadian disruption" OR "circadian misalignment" OR "circadian clock" OR "clock gene" OR "circadian dysregulation" OR "sleep disturbance" OR "sleep deprivation" OR "shift work" OR "light at night" OR melatonin OR chronotype) AND ("vascular aging" OR "cardiovascular aging" OR "endothelial dysfunction" OR "arterial stiffness" OR atherosclerosis OR hypertension OR "heart failure" OR "cardiac hypertrophy" OR "diastolic dysfunction" OR "vascular senescence" OR "endothelial senescence") AND ("insulin resistance" OR dyslipidemia OR obesity OR "type 2 diabetes" OR "metabolic syndrome" OR "glucose intolerance" OR hyperglycemia OR hyperlipidemia OR "fatty liver" OR "adipose tissue dysfunction"))

EMBASE (n=433)

(circadian rhythm OR circadian disruption) AND (cardiovascular aging OR vascular aging OR cardiac aging) AND (metabolic disorder OR insulin resistance OR dyslipidemia) AND (2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py OR 2024:py OR 2025:py OR 2026:py)

Supplementary Table 1. Key human studies for each intervention domain.

PMID	Title	Population	Intervention Details	Study Duration	Primary Endpoint(s)	Secondary Endpoint(s)	Main Limitations	Intervention Domain
41980852	Chronotype-aligned exercise timing in middle-aged adults at cardiometabolic risk: a randomised controlled trial	Adults with cardiometabolic risk (45-65 years)	Morning vs. evening exercise stratified by chronotype (MEQ score)	12 weeks	24-hour ambulatory blood pressure	Heart rate variability; sleep quality; lipids; fasting glucose	Small sample size; chronotype self-reported; lack of long-term follow-up	Exercise timing
41766266	Effect of Morning versus Bedtime Telmisartan on Ambulatory Blood Pressure and Exercise Response in Diabetic Hypertensive	Diabetic hypertensive patients	Morning vs. bedtime telmisartan (crossover)	8 weeks per phase	24-hour ambulatory blood pressure	Exercise blood pressure response; heart rate	Single center; no washout in crossover; chronotype not assessed	Chronotherapy

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Patients: A
Randomised
Cross-over Trial

41674 465	Sleep-Aligned Extended Overnight Fasting Improves Nighttime and Daytime Cardiometabolic Function	Healthy middle-aged adults	Sleep-aligned extended overnight fasting (≥ 13 hours)	6 weeks	Nocturnal cardiometabolic function	Daytime cardiometabolic function; continuous glucose metrics; ambulatory blood pressure	Small sample size; unblinded ; dietary adherence self- reported	Time- restricted eating
41092 452	Effects of Prednisolone Administration on Clock Gene Expression and Indices of Circadian Rhythms in Healthy Human Males	Healthy males	Prednisolone administration (acute/7-day) to assess clock gene expression	Acute + 7 days	Clock gene expression changes	Melatonin and cortisol rhythms	Male- only; small sample; prednisolone not a cardiovascular drug	Other
40760 617	Night-shift work and its association with metabolic syndrome	Night shift workers	Observational study of shift work and metabolic syndrome	Cross- sectional	Metabolic syndrome prevalence	Blood pressure; glucose; lipids	Cross- sectional cannot infer causation; shift patterns not standardized	Sleep optimization
40632 538	Morning vs Bedtime Dosing and Nocturnal Blood Pressure Reduction in Patients With Hypertension: The OMAN Randomized Clinical Trial	Hypertensive patients (OMAN RCT)	Morning vs. bedtime antihypertensive dosing	12 weeks	Nocturnal blood pressure dip	24-hour BP; BP control rate; adverse events	Short follow- up; no cardiovascular outcomes ; single center	Chronotherapy
40419 564	Differential benefits of 12- week morning vs. evening aerobic exercise on sleep and cardiometabolic health: a randomized controlled trial	Sedentary healthy adults	Morning vs. evening aerobic exercise	12 weeks	Sleep quality (PSQI)	Cardiorespiratory fitness; lipids; fasting glucose; blood pressure	Healthy population limits generalizability; no chronotype stratification	Exercise timing

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40250 088	Early time-restricted eating with energy restriction has a better effect on body fat mass, diastolic blood pressure, metabolic age and fasting glucose compared to late time-restricted eating with energy restriction and/or energy restriction alone: A 3-month randomized clinical trial	Overweight/obese adults	Early TRE vs. late TRE vs. calorie restriction alone	12 weeks	Body fat mass	Diastolic blood pressure; metabolic age; fasting glucose; lipids	Unblinded; self-reported adherence; small sample	Time-restricted eating
39689 295	The effects of morning versus evening high-intensity interval exercise on the magnitude of the morning blood pressure surge	Healthy adults	Morning vs. evening high-intensity interval training (single session)	Acute (post-exercise)	Morning blood pressure surge magnitude	24-hour blood pressure profile	Acute effect only; small sample size	Exercise timing
39394 513	Concept, study design, and baseline nighttime blood pressure control status of the WISDOM-Night Study using a wrist-type oscillometric home blood pressure monitoring device	Hypertensive patients	WISDOM-Night study protocol (wrist-type home BP monitoring)	Protocol only (no intervention)	Nocturnal BP control assessment	Device feasibility; adherence	Protocol paper; no intervention effect data	Chronotherapy
38050 268	Effect of Liuzijue exercise in different periods on circadian rhythm of blood pressure in patients with essential hypertension: A randomized trial	Essential hypertension patients	Liuzijue exercise at different times of day	12 weeks	Blood pressure circadian rhythm	Blood pressure level	Small sample; Liuzijue non-standard aerobic exercise	Exercise timing
38038 716	Effects of aerobic exercise on ambulatory blood pressure responses to acute partial sleep deprivation: impact of chronotype and sleep quality	Healthy adults	Partial sleep deprivation plus morning/evening exercise (stratified by chronotype)	Acute crossover	Ambulatory BP response to sleep deprivation	Heart rate; heart rate variability	Acute model; small sample size	Sleep optimization + Exercise timing

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38029 806	Effect of oral melatonin treatment on insulin resistance and diurnal blood pressure variability in night shift workers. A double-blind, randomized, placebo-controlled study	Night shift workers	Melatonin vs. placebo (double-blind RCT)	12 weeks	Insulin resistance (HOMA-IR)	Diurnal blood pressure variability; lipids	Melatonin not a light intervention; individual shift schedules varied	Light therapy/melatonin
37796 235	Impact of timing of antihypertensive treatment on mortality: an observational study from the Spanish Ambulatory Blood Pressure Monitoring Registry	Hypertensive patients (Spanish ABPM registry)	Morning vs. bedtime antihypertensive (observational)	Median 4.7 years	All-cause mortality	Cardiovascular mortality	Observational design; residual confounding; non-randomized	Chronotherapy
36806 380	Significant Correlates of Nocturnal Hypertension in Patients With Hypertension Who Are Treated With Antihypertensive Drugs	Hypertensive patients on treatment	Analysis of factors associated with nocturnal hypertension	Cross-sectional	Correlates of nocturnal hypertension	Age; drug regimen; office BP	Cross-sectional; no intervention	Chronotherapy
36639 984	Effect of administration of low-dose irbesartan and hydrochlorothiazide combined with levamlodipine at different times on the circadian rhythm of blood pressure and the levels of MMPs and TIMPs in non-dipper patients with grade 1 and 2 hypertension	Grade 1-2 hypertension (non-dipper)"	Combination therapy at different times (low-dose irbesartan/HCTZ + levamlodipine)	8 weeks	BP circadian rhythm	MMPs and TIMPs levels	Small sample; short follow-up	Chronotherapy
33806 529	Melatonin Supplementation for Six Weeks Had No Effect on Arterial Stiffness and Mitochondrial DNA in Women Aged 55 Years and Older with Insomnia: A Double-Blind	Females ≥ 55 yrs with insomnia	Melatonin vs. placebo	6 weeks	Arterial stiffness (PWV); mitochondrial DNA copy number	Blood pressure; sleep quality	Female-only; negative result; melatonin not a behavioral intervention	Sleep optimization

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Randomized Controlled Study								
33185 112	Morning sympathetic activity after evening binge alcohol consumption	Healthy adults	Evening binge alcohol and next-morning sympathetic activity	Acute (single dose)	Morning muscle sympathetic nerve activity	Blood pressure; heart rate	Acute experiment; small sample	Other
33136 653	Effects of ambulatory blood pressure monitoring on sleep in healthy, normotensive men and women	Healthy adults	Effect of ambulatory BP monitoring on sleep	24-48 hours	Impact of ABPM on sleep quality	Subjective sleep quality	Non-interventional; device-related	Other
32959 110	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	High cardiovascular risk patients	Bedtime vs. morning aspirin	12 weeks	BP circadian rhythm	Platelet function	Moderate sample; no cardiovascular outcomes	Chronotherapy
32701 144	Comparison of 3 Devices for 24-Hour Ambulatory Blood Pressure Monitoring in a Nonclinical Environment Through a Randomized Trial	Community-dwelling adults	Comparison of 3 ambulatory BP monitoring devices	24 hours	Agreement between devices	Subject preference	Non-interventional; device comparison only	Other
31813 824	Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients with Metabolic Syndrome	Metabolic syndrome patients	10-hour TRE	12 weeks	Body weight; blood pressure; atherogenic lipids	Glucose; sleep; dietary logs	Open-label; no control group; small sample	Time-restricted eating
31641 769	Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial	Hypertensive patients (Hygia Chronotherapy Trial)	Bedtime vs. morning dosing of all antihypertensive drugs	Median 6.3 years	Composite cardiovascular outcome (CV death; MI; revascularization; HF; stroke)	All-cause mortality; BP level; dipping conversion	Open-label; retraction controversy; differential adherence	Chronotherapy

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31087 602	Light affects heart rate's 24-h rhythmicity in intensive care unit patients: an observational study	ICU patients	Observational study of light exposure and heart rate rhythmicity	24-72 hours	24-hour heart rate rhythmicity	Association between light intensity and heart rate	Observational; multiple confounders (critical illness; drugs)	Light therapy
29845 615	Metabolic syndrome and actigraphy measures of sleep and circadian rhythms in bipolar disorders during remission	Bipolar disorder patients in remission	Actigraphy-assessed sleep/circadian rhythms and metabolic syndrome	Cross-sectional	Association of metabolic syndrome with actigraphy parameters	Not specified	Cross-sectional; specific psychiatric population	Sleep optimization
28222 574	Separate aftereffects of morning and evening exercise on ambulatory blood pressure in prehypertensive men	Prehypertensive males	Morning vs. evening exercise aftereffects	Single session + 24 hours	Ambulatory blood pressure	Autonomic function	Acute effect study; male-only	Exercise timing
27920 083	Nocturnal antihypertensive treatment in patients with type 1 diabetes with autonomic neuropathy and non-dipping: a randomised, placebo-controlled, double-blind cross-over trial	Type 1 diabetes + autonomic neuropathy + hypertension	Bedtime vs. placebo antihypertensive (double-blind crossover)	8 weeks per phase	Nocturnal BP dip	24-hour BP; urinary albumin	Small sample (n=20); highly specific population	Chronotherapy
27465 471	A Cushing's syndrome patient's severe insomnia and morning blood pressure surge both improved after her left adrenal tumor resection	Cushing's syndrome patient	Left adrenal tumor resection	Post-surgery follow-up	Severe insomnia and morning BP surge improvement	BP rhythm	Case report; not generalizable	Other
26875 906	Effect of bedtime dosing of barnidipine hydrochloride in non-dipper hypertensive patients with obstructive sleep apnoea not treated with continuous positive airway pressure	OSA + non-dipper hypertension (not on CPAP)	Bedtime barnidipine	12 weeks	Nocturnal BP dip	24-hour blood pressure	Small sample (n=18); OSA as confounder	Chronotherapy

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25691 622	Time-dependent effects of aspirin on blood pressure and morning platelet reactivity: a randomized cross-over trial	Healthy adults	Morning vs. bedtime aspirin (crossover RCT)	3 months per phase	Morning platelet reactivity	24-hour blood pressure	Healthy population; no cardiovascular outcomes; crossover design	Chronotherapy
25531 829	The effects of kidney transplantation on sleep, melatonin, circadian rhythm and quality of life in kidney transplant recipients and living donors	Kidney transplant recipients vs. living donors	Effect of kidney transplantation on sleep/melatonin/circadian rhythm	6 months post-transplant	Sleep quality; melatonin rhythm	Quality of life	Observational design; moderate sample size	Sleep optimization
25259 747	Targeting nocturnal hypertension in type 2 diabetes mellitus	Type 2 diabetes with hypertension	Bedtime vs. morning antihypertensive (crossover RCT)	8 weeks per phase	Nocturnal blood pressure	24-hour BP; urinary albumin excretion	Small sample (n=28); short follow-up	Chronotherapy
24393 346	The effect of continuous nursing intervention guided by chronotherapeutics on ambulatory blood pressure of older hypertensive patients in the community	Community-dwelling elderly hypertensive patients	Chronotherapy-guided continuous nursing intervention	12 weeks	Ambulatory blood pressure	Medication adherence	Confounded by nursing intervention; not drug chronotherapy alone	Chronotherapy
23850 195	Reproducibility of blood pressure dipping: relation to day-to-day variability in sleep quality	Prehypertensive/stage 1 hypertensive adults	Reproducibility of BP dipping and sleep quality relationship	3 sessions of 48-hour monitoring	Day-to-day variability in BP dipping	Association between sleep quality and BP	Observational; moderate sample size	Sleep optimization
23282 124	Effect of valsartan with bedtime dosing on chronic kidney disease patients with nondipping blood pressure pattern	CKD + non-dipper hypertension	Bedtime vs. morning valsartan	8 weeks	Nocturnal BP dip	24-hour BP; renal function	Small sample (n=42); short follow-up	Chronotherapy
23098 160	Treatment-time regimen of hypertension medications significantly affects ambulatory blood pressure and clinical characteristics of patients with resistant hypertension	Resistant hypertension	Bedtime vs. morning antihypertensive dosing	12 weeks	Ambulatory blood pressure	BP dipping conversion	Open-label; part of Hygia series	Chronotherapy

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23004 922	Chronotherapy with low-dose aspirin for prevention of complications in pregnancy	Pregnant women at high risk of complications	Low-dose aspirin chronotherapy (bedtime vs. morning)	Entire pregnancy	Gestational hypertension; preeclampsia	Preterm birth; fetal growth restriction	Obstetric-specific population; moderate sample	Chronotherapy
21884 956	Decreasing sleep-time blood pressure determined by ambulatory monitoring reduces cardiovascular risk	Hypertensive patients	Association of sleep-time BP reduction with cardiovascular risk	Median 5.6 years	Cardiovascular events	Sleep-time BP as risk predictor	Observational; non-interventional	Chronotherapy
21823 969	Chronotherapy with valsartan/hydrochlorothiazide combination in essential hypertension: improved sleep-time blood pressure control with bedtime dosing	Essential hypertension	Valsartan/HCTZ combination: bedtime vs. morning dosing	12 weeks	Sleep-time BP control	24-hour BP; dipping pattern	Open-label; short follow-up	Chronotherapy
21223 530	Intraocular pressure and ocular hemodynamics in patients with primary open-angle glaucoma treated with the combination of morning dosing of bimatoprost and dorzolamide hydrochloride	Primary open-angle glaucoma	Morning dosing of bimatoprost + dorzolamide	3 months	Intraocular pressure; ocular hemodynamics	Not specified	Non-cardiovascular; specific ophthalmology population	Other
20854 139	Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study	Hypertensive patients (MAPEC study)	Bedtime vs. morning antihypertensive	Median 5.6 years	Cardiovascular events	BP control; dipping conversion	Open-label; data integrity concerns	Chronotherapy
20666 269	Effects of combination therapy with amlodipine and fosinopril administered at different times on blood pressure and circadian blood pressure pattern in patients with essential hypertension	Essential hypertension	Combination amlodipine+fosinopril at different times	8 weeks	BP circadian rhythm	BP reduction magnitude	Small sample (n=46); short follow-up	Chronotherapy

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20653 455	Chronotherapy with valsartan/amlodipine fixed combination: improved blood pressure control of essential hypertension with bedtime dosing	Essential hypertension	Valsartan/amlodipine fixed combination: bedtime vs. morning	12 weeks	Sleep-time BP control	24-hour BP; dipping pattern	Open-label; short follow-up	Chronotherapy
19695 030	24-hour and nighttime blood pressures in type 2 diabetic hypertensive patients following morning or evening administration of olmesartan	Type 2 diabetes with hypertension	Morning vs. bedtime olmesartan	12 weeks	24-hour and nighttime BP	Dipping pattern	Open-label; small sample (n=48)	Chronotherapy
19142 758	Administration-time-dependent effects of olmesartan on the ambulatory blood pressure of essential hypertension patients	Essential hypertension	Time-dependent effects of olmesartan	12 weeks	Ambulatory blood pressure	BP dipping	Open-label; short follow-up	Chronotherapy
18600 215	Chronotherapy with nifedipine GITS in hypertensive patients: improved efficacy and safety with bedtime dosing	Hypertensive patients	Nifedipine GITS: bedtime vs. morning dosing	12 weeks	Ambulatory blood pressure	Safety; dipping conversion	Open-label; short follow-up	Chronotherapy
17968 001	Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension	Resistant hypertension	Bedtime vs. morning antihypertensive	12 weeks	Ambulatory BP; dipping reversal	BP control rate	Open-label; small sample (n=32)	Chronotherapy
17701 685	Ambulatory blood pressure monitoring in the prediction of cardiovascular events and effects of chronotherapy: rationale and design of the MAPEC study	Hypertensive patients	MAPEC study protocol description	Not applicable	Study design description	Not applicable	Protocol paper; no interventional data	Other
17635 851	Comparison of the efficacy of morning versus evening administration of telmisartan in	Essential hypertension	Telmisartan: morning vs. bedtime	12 weeks	Ambulatory BP; dipping pattern	BP reduction magnitude	Open-label; short follow-up	Chronotherapy

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	essential hypertension							
17612 946	Dose- and administration time-dependent effects of nifedipine gits on ambulatory blood pressure in hypertensive subjects	Hypertensive patients	Nifedipine GITS dose- and time-dependent effects	12 weeks	Ambulatory blood pressure	Dose-time effects	Open-label; crossover limitations	Chronotherapy
17364 587	Comparison of the efficacy of morning versus evening administration of olmesartan in uncomplicated essential hypertension	Uncomplicated essential hypertension	Olmesartan: morning vs. bedtime	12 weeks	Ambulatory blood pressure	Dipping pattern	Open-label; short follow-up	Chronotherapy
16679 712	Exposure to bright light modifies HRV responses to mental tasks during nocturnal sleep deprivation	Healthy adults	Bright light exposure during nocturnal sleep deprivation	Acute experiment	HRV response to mental tasks	Not specified	Acute experiment; nocturnal sleep deprivation not real-world	Light therapy
16311 912	The effect of time of day and exercise on platelet functions and platelet-neutrophil aggregates in healthy male subjects	Healthy males	Exercise at different times of day on platelet function	Single session	Platelet function; platelet-neutrophil aggregates	Not specified	Acute effect; small sample (n=12)	Exercise timing
16147 905	Administration time-dependent effects of valsartan on ambulatory blood pressure in elderly hypertensive subjects	Elderly hypertensive patients	Valsartan: bedtime vs. morning dosing	12 weeks	Ambulatory blood pressure	Safety; dipping pattern	Open-label; short follow-up	Chronotherapy
14732 734	Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension	Male essential hypertension (untreated)"	Nighttime oral melatonin vs. placebo	3 weeks	Sleep-time blood pressure	24-hour BP; heart rate	Male-only; short follow-up	Light therapy/melatonin
14668 570	Effect of morning and bedtime dosing with cilnidipine on blood pressure, heart rate, and sympathetic nervous activity in essential	Essential hypertension	Cilnidipine: morning vs. bedtime (crossover)	4 weeks per phase	BP; heart rate; sympathetic activity	Plasma norepinephrine	Small sample (n=17); short crossover	Chronotherapy

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	hypertensive patients								
14618095	Differential effects of morning or evening dosing of amlodipine on circadian blood pressure and heart rate	Hypertensive patients	Amlodipine: morning vs. evening (crossover)	8 weeks per phase	24-hour BP and heart rate rhythm	BP variability	Small sample (n=22); crossover design	Chronotherapy	
14564895	The effects of bright light and nighttime melatonin administration on cardiac activity	Healthy adults	Bright light and evening melatonin on cardiac activity	Acute experiment	Heart rate; core temperature	HRV	Acute laboratory experiment; small sample	Light therapy + melatonin	
11774859	Impact of circadian amplitude and chronotherapy: relevance to prevention and treatment of stroke	Hypertensive /stroke patients	Chronotherapy and stroke prevention (review with some original data)	Not specified	BP circadian rhythm	Not specified	Primarily a review; limited original data	Chronotherapy	
10523347	Ambulatory physical activity as a determinant of diurnal blood pressure variation	Hypertensive patients	Association of daytime physical activity with ABPM variability	24-hour monitoring	Daytime activity and BP dipping pattern	Nocturnal BP fall	Observational; cross-sectional	Exercise timing	
10480474	Differential effects of morning and evening dosing of nisoldipine ER on circadian blood pressure and heart rate	Hypertensive patients	Nisoldipine ER: morning vs. bedtime (crossover)	8 weeks per phase	Ambulatory BP and heart rate	BP variability	Crossover with insufficient washout	Chronotherapy	
1818788	Chronotherapy in coronary heart disease: comparison of two nitrate treatments	Coronary heart disease patients	Comparison of two nitrate chronotherapies	Not clearly stated	Angina frequency	ECG changes	Old study; methodological reporting insufficient	Chronotherapy	

The above table summarizes the population, intervention details, study duration, primary/secondary endpoints, and main limitations for each major intervention domain (time-restricted eating, exercise timing, sleep optimization, chronotherapy, light therapy and other). MEQ morningness-eveningness questionnaire; RCT randomized controlled trial; PSQI Pittsburgh sleep quality index; TRE time-restricted eating; WISDOM worldwide innovative strategy for diagnosis and treatment of hypertension; BP blood pressure; HOMA-IR homeostasis model assessment-insulin resistance; HCTZ hydrochlorothiazide; PWV pulse wave velocity; ABPM ambulatory blood pressure monitoring; CV cardiovascular; MI myocardial infarction; CPAP continuous positive airway pressure; OSA obstructive sleep apnea; CKD chronic kidney disease; GITS gastrointestinal therapeutic system; HRV heart rate variability; ECG Electrocardiogram.

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Supplementary Table 2. Evidence grading criteria based on ESC 2024 classification system.

Evidence Level	Criteria for Therapeutic/ Prevention Studies	Criteria for Diagnostic/ Prognostic Studies
A	Conclusive evidence from at least two high-quality RCTs or one high-quality RCT plus consistent evidence from other study types	Conclusive evidence of adequate diagnostic ability from at least two high-quality studies with external validation
B	Suggestive evidence from one high-quality RCT or at least two moderate-quality RCTs	Suggestive evidence from one high-quality or at least two moderate-quality studies
C	Preliminary evidence not classified as A or B, including evidence from less than two moderate-quality RCTs, observational studies, or expert consensus	Evidence from derivation study of at least moderate quality but low/no external validation, or low-quality derivation study, or expert consensus

Adapted from ESC Clinical Practice Guidelines 2024 Revision. RCT randomized controlled trial; ESC European Society of Cardiology.