NESANICA KAO FAKTOR RIZIKA KOD KARDIOLOŠKIH BOLESNIKA I TERAPIJSKI PRISTUP

PREGLEDNI RAD

REVIEW ARTICLE

INSOMNIA AS A RISK FACTOR IN CARDIAC PATIENTS AND THE TREATMENT APPROACH

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SAŽETAK

Uvod/Cilj: Nesanica je čest poremećaj spavanja koji prevazilazi subjektivni osećaj neispavanosti i predstavlja stanje perzistentne fiziološke hiperbudnosti sa značajnim uticajem na kardiovaskularno zdravlje. Cilj ovog preglednog rada bio je da prikaže patofiziološke mehanizme povezanosti nesanice i kardiovaskularnih bolesti, kao i da uporedi kliničke aspekte primene benzodiazepina i Z-hipnotika u lečenju nesanice kod kardioloških bolesnika.

Metode: Korišćenjem deskriptivno-komparativne metode analizirani su dostupni pregledni radovi, meta-analize, kohortne i opservacione studije koje su ispitivale odnos nesanice, kardiovaskularnih ishoda i farmakološkog lečenja, sa posebnim fokusom na razlike između primene benzodiazepina i Z-hipnotika u pogledu efikasnosti i bezbednosti kod kardioloških bolesnika.

Rezultati: Analizirani podaci ukazuju na to da nesanica, putem autonomne, neuroendokrine, inflamatorne i metaboličke disregulacije, doprinosi razvoju arterijske hipertenzije, atrijalne fibrilacije i srčane slabosti, pri čemu se najveći rizik beleži kod fenotipa nesanice sa objektivno kratkim trajanjem sna. Noviji longitudinalni podaci dodatno ukazuju na to da perzistentni simptomi nesanice nose veće kardiovaskularno opterećenje. U terapijskom kontekstu, benzodiazepini su kod kardioloških bolesnika povezani sa većom učestalošću nepovoljnih događaja, uključujući rehospitalizacije zbog srčane slabosti, iznenadni srčani zastoj i kardiovaskularni mortalitet, dok dostupni podaci za Z-hipnotike ukazuju na povoljniji ili neutralniji profil.

Zaključak: Nesanica predstavlja klinički značajan, ali često zanemaren faktor kardiovaskularnog rizika. Kod kardioloških bolesnika, njeno prepoznavanje i lečenje treba da budu sastavni deo sveobuhvatnog kliničkog pristupa, uz prednost nefarmakoloških mera i pažljivo odabranu farmakoterapiju. Kada je farmakološko lečenje nesanice neophodno, Z-hipnotici se mogu razmatrati kao povoljnija alternativa benzodiazepinima, pri čemu se zopiklon posebno izdvaja zbog svojih farmakoloških i kliničkih karakteristika.

Ključne reči: poremećaji spavanja, kardiovaskularne bolesti, benzodiazepini, z-hipnotici

ABSTRACT

Introduction/Objective: Insomnia is a common sleep disorder that extends beyond the subjective feeling of poor sleep and represents a state of persistent physiological hyperarousal with important cardiovascular consequences. This review aimed to summarize the pathophysiological links between insomnia and cardiovascular disease and to compare the clinical implications of benzodiazepines and Z-hypnotics in the treatment of insomnia in cardiac patients.

Methods: Using a descriptive-comparative approach, we analyzed review articles, meta-analyses, cohort studies, and observational studies addressing the relationship between insomnia, cardiovascular outcomes, and pharmacological treatment, with particular focus on differences between benzodiazepines and Z-hypnotics in cardiac patients.

Results: The available evidence indicates that insomnia, through autonomic, neuroendocrine, inflammatory, and metabolic dysregulation, contributes to the development of hypertension, atrial fibrillation, and heart failure, with the greatest risk observed in insomnia with objectively short sleep duration. Longitudinal studies further suggest that persistent insomnia symptoms are associated with greater cardiovascular burden. In therapeutic terms, benzodiazepines in cardiac patients are associated with higher rates of adverse events, including heart failure rehospitalization, sudden cardiac arrest, and cardiovascular mortality, whereas available data on Z-hypnotics suggest a more favorable or neutral profile.

Conclusion: Insomnia is a clinically important yet often overlooked cardiovascular risk factor. In cardiac patients, its recognition and treatment should be part of a comprehensive clinical approach, prioritizing non-pharmacological measures and carefully selected pharmacotherapy. When drug treatment is necessary, Z-hypnotics may be considered a more favorable alternative to benzodiazepines, with zopiclone standing out because of its pharmacological and clinical characteristics.

Keywords: sleep-wake disorders, cardiovascular diseases, benzodiazepines, Z-hypnotics

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UVOD

Spavanje je visoko organizovano ponašanje koje se karakteriše relativnim odvajanjem od spoljašnjeg sveta i smanjenjem reagovanja na različite draži. U pitanju je fiziološko besvesno stanje koje nastaje u samom mozgu i doprinosi poboljšanju njegovih integrativnih funkcija kao što su učenje, pamćenje i asocijativno mišljenje. S druge strane, premalo spavanja (nesanica) dvostruko povećava rizik od nastanka malignih ili sistemskih bolesti, doprinosi pojavi degenerativne demencije, remeti regulaciju šećera u krvi, predstavlja nezavisni faktor rizika za pojavu kardiovaskularnih bolesti i psihijatrijskih poremećaja [1].

Kada smo budni a kada spavamo

Dva najbitnija činioca koja određuju kada smo budni a kada spavamo su cirkadijalni ritam i homeostatski nagon za spavanjem. Cirkadijalni ritam (ili unutrašnji časovnik) šalje mozgu i ostalim organima signale kada treba da budemo budni, dok se homeostatski nagon za spavanjem povećava tokom budnosti, a smanjuje tokom spavanja [2].

Spavanje je organizovano u dve faze koje se smenjuju u cikličnim intervalima, sporotalasno spavanje (NREM) i spavanje sa brzim pokretima očiju (REM) (Slika 1). Kod ljudi, NREM spavanje se javlja kao posledica slabljenja mehanizama održavanja budnosti i aktivacije inhibitornog uticaja na aktivacioni sistem moždanog stabla [3]. REM san predstavlja aktivan oblik spavanja i karakteriše ga niskovoltirana iregularna i brza aktivnost (paradoksalno spavanje) povezana sa atonijom poprečnih mišića.

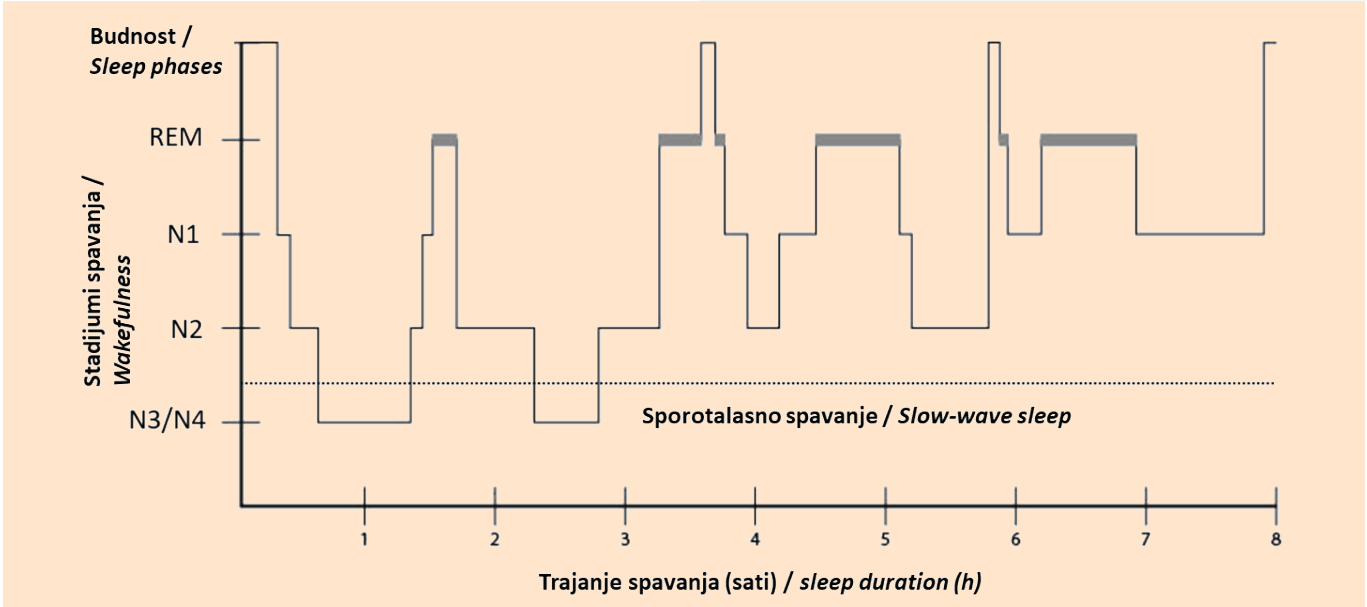
INTRODUCTION

Sleep is a highly organized behavior characterized by relative isolation from the external environment and reduced responsiveness to various stimuli. It is a physiological state of unconsciousness that originates within the brain itself and contributes to the improvement of its integrative functions, including learning, memory, and associative thinking. On the other hand, insufficient sleep (insomnia) is associated with a twofold increased risk of developing malignant or systemic diseases, contributes to the onset of degenerative dementia, disrupts blood glucose regulation, and constitutes an independent risk factor for the development of cardiovascular diseases and psychiatric disorders [1].

Wakefulness and sleep

The two principal factors determining the timing of wakefulness and sleep are the circadian rhythm and the homeostatic sleep drive. The circadian rhythm (or internal biological clock) sends signals to the brain and other organs indicating when we should be awake, whereas the homeostatic drive to sleep increases during wakefulness and decreases during sleep [2].

Sleep is organized into two phases that alternate at cyclical intervals: slow-wave sleep (NREM) and rapid eye movement (REM) sleep (Figure 1). In humans, NREM sleep occurs as a result of the weakening of the mechanisms responsible for maintaining wakefulness, accompanied by the activation of inhibitory influences on the brainstem arousal system [3]. REM sleep represents an active state of sleep and is characterized by



Slika 1. Grafički prikaz (hipnogram) strukture spavanja baziran na polisomografskom zapisu, tokom 8 sati noćnog spavanja (N1, N2 – površni stadijumi spavanja, N3/N4 – dublji stadijumi spavanja, REM – spavanje sa brzim pokretima očiju). *Autorski modifikovana slika iz reference 3*

Figure 1. Graphical representation of sleep structure based on a polysomnographic recording over five nocturnal cycles, each lasting approximately 90 minutes on average (N1, N2 light sleep stages, N3/N4 deep sleep stages, REM – rapid eye movement sleep). *Image from reference 3 modified by the author.*

no-prugastih mišića i brzim pokretima očiju. Smatra se da se većina snova dešava tokom ove faze spavanja [4].

NREM–REM ciklus se obično ponavlja četiri do šest puta tokom tipične noći spavanja. Ujutru se obično budimo iz REM faze [5].

Funkcija spavanja

Iako ne postoji široko rasprostranjena saglasnost o tome zašto je san važan, jasno je da lišavanje sna (ili hronično nedovoljno spavanje) dovodi do povećane pospanosti i smanjenog funkcionisanja [6]. Danas je poznato nekoliko hipoteza o funkciji sna, na prvom mestu u očuvanju metaboličke energije i kognicije. U sporotalasnom spavanju uklanja se adenozin iz mozga putem aktivacije glimfatičkog sistema. Sporotalasno spavanje je takođe zaduženo za uklanjanje bespotrebnih konekcija i informacija, a sa druge strane ima ulogu u konsolidaciji novoupamćenog materijala [7,8]. U REM fazi se učvršćuju proceduralna, perceptualna i emocionalna memorija. Novoupamćeni materijal se inkorporira u već poznate sadržaje i dobija se sasvim nov kvalitet u formi iskustvenog pamćenja i asocijativnog mišljenja [9].

Spavanje je posebno važno za restoraciju fiziološke kontrole kardiovaskularnog sistema, naročito posle fizičkog napora. U sporotalasnom spavanju se stabilizuje simpatička aktivnost na nivou opuštene budnosti, pojačava parasimpatička aktivnost i povećava varijabilnost srčanog rada (HRV) čime se omogućava veća adaptibilnost srca na različite nivoe rada. Posledice su smanjenje krvnog pritiska, srčane frekvence i perifernog vaskularnog otpora što sve zajedno smanjuje opterećenje srčanog rada i indukuje autonomnu stabilnost. U REM spavanju dolazi do faznog pojačanja simpatičke aktivnosti (skokovi krvnog pritiska), dok se smanjuju parasimpatička aktivnost i HRV (postoji opasnost od pojave srčanih aritmija) [10].

Da li dovoljno spavamo?

Nesanica (insomnia), može se slobodno reći, danas predstavlja najčešći poremećaj spavanja i verovatno najčešću bolest savremenog sveta [11]. Više od 30% celokupne populacije je iskusilo neki oblik nesanice. Prema trajanju ona može biti intermitentna (povremena), kratkotrajna ili hronična (bar 3 dana nedeljno, duže od 6 meseci). Oko 6–11% osoba ima dijagnozu hronične nesanice (od toga 59% imaju nesanicu i posle 5 godina). Prevalencija nesanice se povećava sa starenjem, češća je kod žena i kod bolesnika sa neurološkim komorbiditetima, psihijatrijskim bolestima, hroničnim somatskim oboljenjima ili različitim egzogenim činiocima. Ipak, kod oko 50% ljudi sa hroničnom nesanicom, u pitanju je primarna bolest (psihofiziološka nesanica) [12]. Kod njih je nesanica, na prvom mestu, posledica poremećaja aktivnosti centara u mozgu koji su odgo-

low-voltage, irregular, and rapid brain activity (paradoxical sleep), accompanied by atonia of the striated muscles and rapid eye movements. Most dreaming is thought to occur during this stage of sleep [4].

The NREM–REM cycle typically repeats four to six times during a normal night of sleep. In the morning, awakening most commonly occurs from the REM phase [5].

Function of sleep

Although there is no broad consensus regarding the importance of sleep, it is clear that sleep deprivation (chronically insufficient sleep) leads to increased sleepiness and impaired functioning [6]. Several hypotheses have been proposed regarding the function of sleep, with particular emphasis on the preservation of metabolic energy and the cognitive function. During slow-wave sleep, adenosine is cleared from the brain through activation of the glymphatic system. Slow-wave sleep also contributes to the elimination of unnecessary neural connections and information, while playing an important role in the consolidation of newly acquired memories [7,8]. During the REM phase, procedural, perceptual, and emotional memories are consolidated. Newly acquired information is integrated with previously established knowledge, resulting in a qualitatively new form of experiential memory and associative thinking [9].

Sleep is particularly important for the restoration of physiological control of cardiovascular system, especially following physical exertion. During slow-wave sleep, sympathetic activity is stabilized at levels comparable to those observed during relaxed wakefulness, while parasympathetic activity is enhanced and heart rate variability (HRV) increases. These changes facilitate greater adaptability of the heart to different levels of workload. Consequently, blood pressure, heart rate, and peripheral vascular resistance decrease, collectively reducing cardiac workload and promoting autonomic stability. During REM sleep, there is a phasic increase in sympathetic activity (transient increases in blood pressure), while parasympathetic activity and HRV decrease (there is a risk of cardiac arrhythmias) [10].

Do we sleep enough?

Insomnia can reasonably be considered the most common sleep disorder today and, arguably, one of the most prevalent diseases in the modern world [11]. More than 30% of the general population has experienced some form of insomnia. Depending on its duration, insomnia may be classified as intermittent (occasional), short-term, or chronic (occurring at least three days per week for more than six months). Approximately 6–11% of the population meets the criteria for chronic insomnia, of

vorni za promociju budnosti (prednji hipotalamus koji aktivira retikularnu formaciju) i centara koji promovišu spavanje (ventrolateralna preoptička jedra) i inhibiraju delove mozga odgovorne za budnost. Sistem za kontrolu budnosti (orexin) ne smanjuje svoju aktivnost što onemogućava ovim pacijentima da započnu spavanje. Dodatni doprinoseći faktori su poremećaj cirkadijalnog ritma i emocionalni (stresogeni) faktori koji mogu narušiti homeostazu spavanja. Tako dolazimo da zaključka da je hronična nesanica rezultat konstelacije (sinergizma) genetskih (epigenetskih), faktora okruženja i neurokognitivih/bihevioralnih uticaja na delove mozga odgovornih za smenu budnosti i spavanja [13].

Pacijenti sa hroničnom insomnijom imaju narušen kvalitet života i mnoge zdravstvene posledice u oblasti mentalnog zdravlja (veći rizik od anksioznosti, depresije i suicidalnosti), somatskog zdravlja (hipertenzija, gojaznost, infarkt miokarda, DM tip 2), narušenu radnu sposobnost, veći rizik od saobraćajnih nezgoda i povreda na radu, itd [14].

U daljem tekstu, posebno će biti prikazan negativan uticaj nesanice na funkciju autonomnog, posebno kradiovaskularnog sistema i posledice koje takvo stanje može imati.

Negativan uticaj nesanice na autonomni i neuroendokrini sistem

Nesanica ne predstavlja isključivo subjektivni poremećaj sna, već se definiše kao stanje perzistentne fiziološke hiperbudnosti [15,16]. Karakteriše se pojačanom aktivnošću centralnog nervnog sistema, hipotalamo-hipofizno-adrenalne (HHA) osovine, simpatoadrenalnog sistema i proinflamatornih signalnih puteva [17,18]. Naime, nesanica se definiše kao stabilan obrazac povišene pobuđenosti tokom čitavog 24-časovnog ciklusa, sa posledičnim porastom lučenja kortizola i kateholamina, poremećajem autonomne ravnoteže sa dominacijom simpatičkog nad parasimpatičkim tonusom [16–18]. Na ovaj način se u toku noći narušava period neurovegetativnog smirivanja i hemodinamskog rasterećenja, dok se produžava trajanje biološkog stresa, što predstavlja jednu od glavnih spona između nesanice i razvoja kardiovaskularnih bolesti [15,16] .

Jedan od najvažnijih patofizioloških mehanizama ove povezanosti jeste disfunkcija autonomnog nervnog sistema. U fiziološkim uslovima, tokom sna, naročito u dubljim stadijumima NREM faza, dolazi do smanjenja simpatičke aktivnosti i relativne dominacije parasimpatičkog tonusa, te posledičnog usporenja srčane frekvence, smanjenja perifernog vaskularnog otpora i arterijskog krvnog pritiska [16,18]. Ovaj period „kardiovaskularne restauracije" u toku sna ima zaštitnu ulogu za srce i krvne sudove, jer omogućava privremeno smanjenje hemodinamskog opterećenja [17,18]. Nasuprot tome, kod

whom 59% continue to experience insomnia five years later. The prevalence of insomnia increases with age and is higher among women and patients with neurological comorbidities, psychiatric disorders, chronic somatic diseases, or various exogenous factors. However, in approximately 50% of individuals with chronic insomnia, the condition is considered a primary disorder, referred to as psychophysiological insomnia [12]. In these individuals, insomnia is primarily a consequence of disturbances in the activity of brain centers responsible for promoting wakefulness (the anterior hypothalamus which activates the reticular formation), and centers that promote sleep (the ventrolateral preoptic nuclei) which inhibit brain regions responsible for wakefulness. The wakefulness-promoting system (orexin) fails to adequately reduce its activity, making it difficult for these patients to initiate sleep. Additional contributing factors include circadian rhythm disturbances and emotional (stress-related) factors that may disrupt sleep homeostasis. Thus, chronic insomnia can be understood as the result of a constellation, or synergy, of genetic (epigenetic) and environmental factors, together with neurocognitive and behavioral influences on the brain regions responsible for the transition between wakefulness and sleep [13].

Patients with chronic insomnia experience impaired quality of life and a range of adverse health consequences affecting mental health (an increased risk of anxiety, depression, and suicidality), somatic health (hypertension, obesity, myocardial infarction, and type 2 diabetes mellitus), impaired work performance, and an increased risk of traffic accidents and occupational injuries, among other adverse outcomes [14].

The following section will specifically examine the negative impact of insomnia on autonomic function, particularly cardiovascular function, as well as the potential consequences of these disturbances.

The negative impact of insomnia on the autonomic and neuroendocrine systems

Insomnia is not exclusively a subjective sleep disorder; rather, it is defined as a state of persistent physiological hypervigilance [15,16]. It is characterized by increased activity of the central nervous system, the hypothalamic–pituitary–adrenal (HPA) axis, the sympathoadrenal system, and pro-inflammatory signaling pathways [17,18]. Namely, insomnia is defined as a stable pattern of heightened arousal throughout the entire 24-hour cycle, resulting in increased secretion of cortisol and catecholamines and a disruption of autonomic balance, characterized by a predominance of sympathetic over parasympathetic tone [16–18]. In this way, the period of neurovegetative relaxation and hemodynamic relief that normally occurs during the night is disrupted,

osoba sa insomnijom, fragmentacijom sna ili generalno skraćenim trajanjem sna, ovaj fiziološki period oporavka biva narušen ili čak izostaje u potpunosti [16,19]. Kumulativno, takve promene povećavaju ukupno 24-časovno opterećenje srca i krvnih sudova, te značajno doprinose razvoju arterijske hipertenzije [20–24].

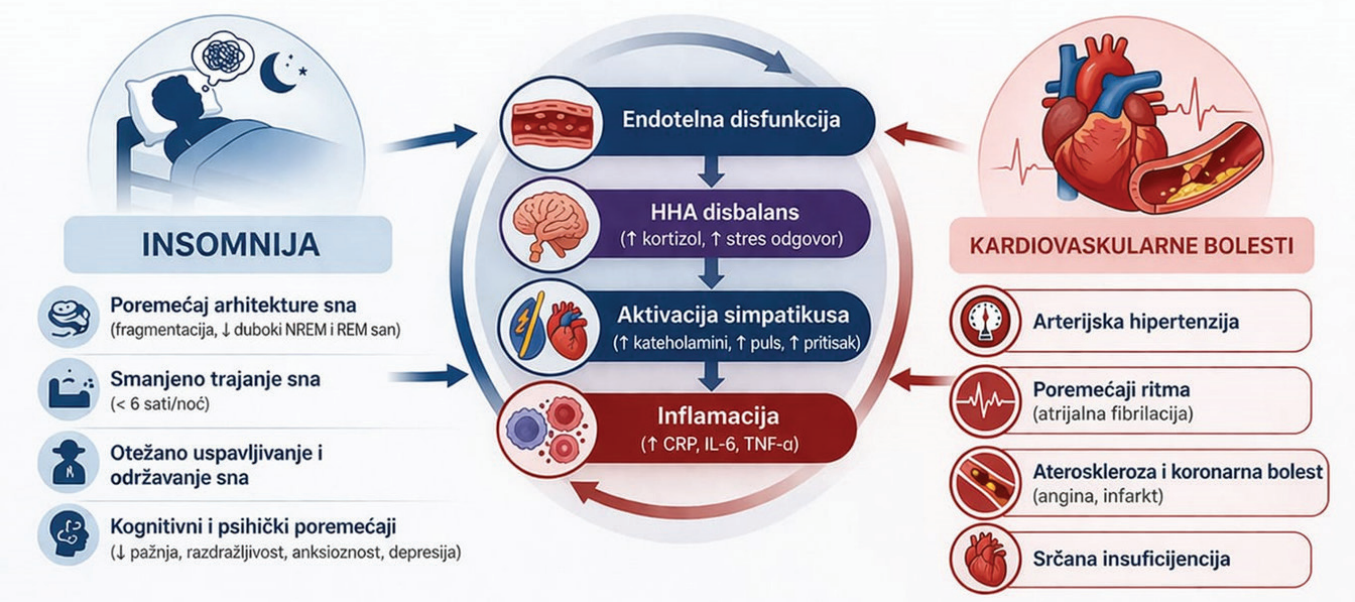
Hronična nesanica je u korelaciji sa neuroendokrinom disfunkcijom, pojačanim lučenjem kortikotropin-oslobađajućeg hormona, adrenokortikotropnog hormona i kortizola, čime se narušava normalni cirkadijalni obrazac neuroendokrine sekrecije [17,18]. Povišene noćne i jutarnje vrednosti kortizola doprinose perzistenciji budnosti, i uz povišen simpatički tonus, stvaraju niz štetnih kardiometaboličkih efekata [17,18]. Hronično narušen san praćen je povišenim koncentracijama proinflamatornih citokina, C-reaktivnog proteina i drugih medijatora sistemske inflamacije, pri čemu inflamatorni medijatori dodatno remete arhitekturu sna, stvarajući začarani krug u kome inflamacija pogoršava nesanicu, a nesanica dalje pojačava inflamatorni odgovor [15,17,18] (Slika 2).

Povećani simpatički tonus i neuroendokrina aktivacija doprinose endotelnoj disfunkciji, oksidativnom stresu, proinflamatornoj aktivnosti i poremećaju metaboličke homeostaze, uključujući insulinsku rezistenciju i poremećaj metabolizma glukoze i lipida [17,18,25,26]. Na nivou krvnih sudova, kombinacija simpatičke prenadraženosti, povišenog kortizola i inflamacije smanjuje biodostupnost azot-monoksida, povećava vaskularnu reaktivnost i arterijsku rigidnost, čime se stvaraju uslovi za razvoj hipertenzije, ateroskleroze i progresivnog vaskularnog remodelovanja [17,18]. Razvoj nesanice kod bolesnika sa već postojećim kardiovaskularnim oboljenjima, bilo da je u pitanju arterijska hipertenzija, koronarna bolest ili srčana insuficijencija, upravo može doprineti progresiji osnovne bolesti i nepovoljnijim kliničkim ishodima [27,28].

while the duration of biological stress is prolonged, representing one of the principal links between insomnia and the development of cardiovascular disease [15,16].

One of the most important pathophysiological mechanisms underlying this association is dysfunction of the autonomic nervous system. Under physiological conditions, sleep, particularly during the deeper stages of NREM sleep, is characterized by a reduction in sympathetic activity and a relative predominance of parasympathetic tone, accompanied by a consequent slowing of the heart rate, a reduction in peripheral vascular resistance, and a decrease in arterial blood pressure [16,18]. This period of "cardiovascular restoration" during sleep plays a protective role for the heart and blood vessels by enabling a temporary reduction in hemodynamic load [17,18]. In contrast, in individuals with insomnia characterized by sleep fragmentation or a generally shortened sleep duration, this physiological recovery period is impaired or may be entirely absent [16,19]. Cumulatively, these changes increase the total 24-hour workload imposed on the heart and blood vessels and significantly contribute to the development of arterial hypertension [20–24].

Chronic insomnia is associated with neuroendocrine dysfunction and increased secretion of corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol, thereby disrupting the normal circadian pattern of neuroendocrine secretion [17,18]. Elevated nocturnal and morning cortisol levels contribute to the persistence of wakefulness and, together with increased sympathetic tone, give rise to a range of adverse cardiometabolic effects [17,18]. Chronically disrupted sleep is accompanied by elevated concentrations of pro-inflammatory cytokines, C-reactive protein, and other mediators of systemic inflammation,



Slika 2. Patofiziološka povezanost nesanice i kardiovaskularnih bolesti

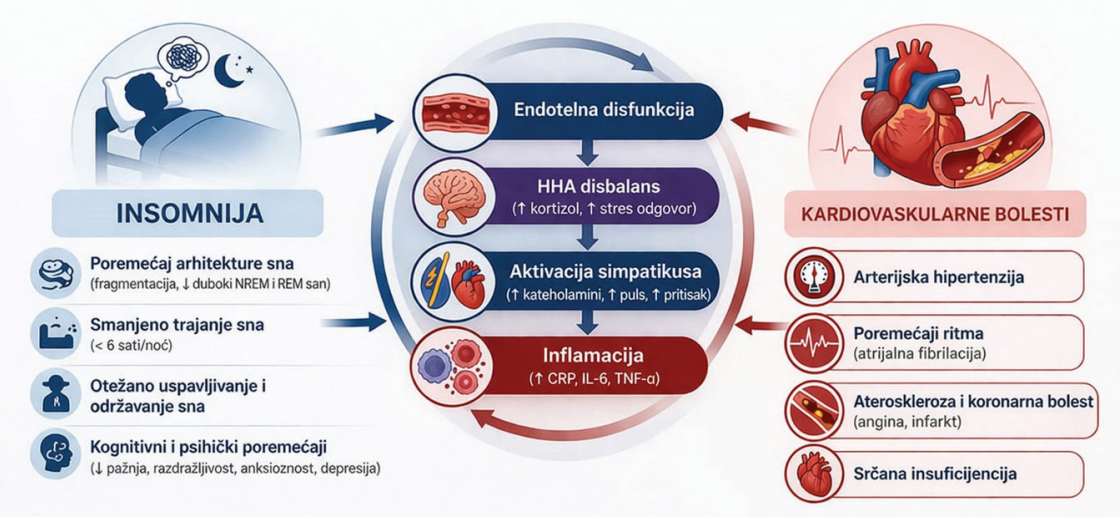


Figure 2. Pathophysiological relationship between insomnia and cardiovascular diseases

Pored hipertenzije i aterosklerotske bolesti, nesanica može doprineti i aritmogenezi [29,30]. Poremećaji sna povećavaju električnu nestabilnost miokarda kroz kombinaciju autonomne labilnosti, inflamacije, oksidativnog stresa i dugoročnog strukturnog remodelovanja [17,26] (Tabela 1).

Nesanica i kardiovaskularne bolesti

Sve je više podataka koji ukazuju da nesanica može predstavljati faktor rizika za razvoj kardiovaskularnih oboljenja, kao i doprineti nepovoljnijim ishodima i smanjenim kvalitetom života kod već obolelih bolesnika [15,28,31,32]. Najkonzistentniji i klinički najrelevantniji podaci o povezanosti nesanice i kardiovaskularnih bolesti odnose se na arterijsku hipertenziju [16,20–22]. Brojne prospektivne kohortne studije, sistematski pregledi i meta-analize pokazali su da nesanica nije povezana samo sa prolaznim porastom vrednosti krvnog pritiska, već i sa većim rizikom za razvoj incidentne hipertenzije i drugih kardiovaskularnih ishoda [20,22,31]. Posebno se izdvaja fenotip nesani-

while these inflammatory mediators further disrupt sleep architecture, thereby creating a vicious cycle in which inflammation exacerbates insomnia, and insomnia, in turn, further amplifies the inflammatory response [15,17,18] (Figure 2).

Increased sympathetic tone and neuroendocrine activation contribute to endothelial dysfunction, oxidative stress, pro-inflammatory activity, and disruption of metabolic homeostasis, including insulin resistance and disturbances in glucose and lipid metabolism [17,18,25,26]. At the vascular level, the combination of sympathetic overstimulation, elevated cortisol levels, and inflammation reduces the bioavailability of nitric oxide, increases vascular reactivity and arterial stiffness, and thereby creates conditions conducive to the development of hypertension, atherosclerosis, and progressive vascular remodeling [17,18]. The development of insomnia in patients with pre-existing cardiovascular disease, including arterial hypertension, coronary artery disease, or heart failure, may contribute to

Tabela 1. Patofiziologija povezanosti nesanice i kardiovaskularnih bolesti

Table 1. Pathophysiology of the relationship between insomnia and cardiovascular diseases

Autori / *Authors*	Časopis / *Journal*	Godina / *Year*	Broj ispitanika / *Participants (n)*	Tip studije / *Study type*	Primarni cilj rada / *Primary study objective*	Zaključak rada / *Conclusion*
Fernández-Mendoza i sar. / Fernández-Mendoza et al.	*Hypertension*	2012	~1741	Prospektivna kohorta / Prospective cohort	Incidentna HTA / Incidental HTN	Kratko trajanje sna ↑ HTA rizik / Short sleep duration ↑ HTN risk
Laugsand i sar. / Laugsand et al.	*Eur Heart J*	2014	~54000	Prospektivna kohorta / Prospective cohort	Incidentna HF / Incident HF	Nesanica povezana sa HF / Insomnia associated with HF
Liu i sar. / Liu et al.	*Int J Hypertens*	2022	>200000	Meta-analiza / Meta-analysis	Insomija i HTA / Insomnia and HTN	Dvosmerna povezanost / Bidirectional connectivity
Berger i sar. / Berger et al..	*J Am Heart Assoc*	2022	~2000+	Kohortna / Cohort	Arhitektura sna / Sleep architecture	Fragmentacija sna ↑ HTA / Sleep fragmentation ↑ HTN
Dai i sar. / Dai et a.	*Sleep Med Rev*	2024	Meta-analiza	Meta-analiza / Meta-analysis	Nesanica + kratak san / Insomnia + short sleep	↑ HTA rizik / ↑ HTN risk

HTA – hipertenzija, HF – srčana slabost

HTN – hypertension, HF – heart failure

ce sa objektivno kratkim trajanjem sna koji je povezan sa značajno većim rizikom od razvoja hipertenzije u odnosu na subjektivno loš san bez objektivnog skraćenja sna [21]. U prilog tome govore i nalazi sistematskih pregleda koji pokazuju da su hipertenzija i nepovoljna arhitektura sna usko povezane, naročito kroz veću fragmentaciju sna i redukciju dubljih stadijuma NREM spavanja, što dodatno naglašava značaj objektivnih parametara sna u stratifikaciji rizika [19]. Nadalje, noviji longitudinalni podaci ukazuju na to da sa porastom broja simptoma nesanice raste i rizik od incidentnih kardiovaskularnih događaja, dok perzistentni ili progresivno nepovoljan tok simptoma nosi dodatno kardiovaskularno opterećenje [32].

Značaj zdravih obrazaca spavanja u kardiovaskularnoj prevenciji potvrđen je i u savremenim velikim kohortnim studijama [33–35]. Yan i saradnici su pokazali da je kod osoba sa prehipertenzijom pridržavanje zdravog obrasca spavanja povezano sa značajno manjim rizikom od razvoja novonastale arterijske hipertenzije i kardiovaskularnih bolesti, pri čemu je uočen i jasan gradijent smanjenja rizika sa porastom skora zdravog spavanja [33]. Slično tome, Nambiema i saradnici su u velikim evropskim prospektivnim kohortama pokazali da su viši skor zdravog spavanja, ali i njegovo poboljšanje tokom vremena, povezani sa manjim rizikom od koronarne bolesti i moždanog udara [34]. Ovi nalazi zajedno ukazuju na to da zdravlje sna ne predstavlja samo pokazatelj, već i potencijalno modifikabilnu komponentu kardiovaskularnog rizika, zbog čega procena i optimizacija spavanja mogu imati značajno mesto u strategijama primarne prevencije kardiovaskularnih bolesti [33–35].

Pored arterijske hipertenzije, sve je više podataka koji govore u prilog tome da poremećaji sna predstavljaju dodatni faktor rizika u nastanku i održavanju poremećaja ritma po tipu atrijalne fibrilacije. Samim tim, narušena arhitektura spavanja, učestala noćna buđenja, duža latencija uspavljivanja, kao i kraće trajanje spavanja povezani su sa većim rizikom za nastanak atrijalne fibrilacije [29,30].

Srčana slabost predstavlja poseban entitet u okviru povezanosti nesanice i kardiovaskularnih bolesti, jer odražava kumulativne posledice dugotrajnog hemodinamskog, neurohumoralnog i metaboličkog opterećenja. U velikoj norveškoj populacionoj kohorti pokazana je jasna povezanost između broja simptoma nesanice i rizika od incidentne srčane slabosti. Ovi podaci ukazuju na to da teža i kompleksnija simptomatologija nesanice može implicirati veće kardiovaskularno opterećenje, posredstvom hronične simpatičke aktivacije, poremećaja HHA osovine i perzistentne inflamacije, iako opservaciona priroda dostupnih studija i dalje zahteva oprez u tumačenju uzročnosti [15,28].

Metabolički sindrom predstavlja važan klinički domen u kojem se prepliću nesanica i rizik od razvoja kardiovaskularnih oboljenja, s obzirom na to da postoje

progression of the underlying disease and result in less favorable clinical outcomes [27,28].

In addition to hypertension and atherosclerotic disease, insomnia may also contribute to arrhythmogenesis [29,30]. Sleep disturbances increase myocardial electrical instability through a combination of autonomic lability, inflammation, oxidative stress, and long-term structural remodeling [17,26] (Table 1).

Insomnia and cardiovascular diseases

There is increasing evidence that insomnia may represent a risk factor for the development of cardiovascular diseases, as well as contribute to less favorable clinical outcomes and reduced quality of life in patients who already have cardiovascular disease [15,28,31,32]. The most consistent and clinically relevant evidence regarding the association between insomnia and cardiovascular diseases concerns arterial hypertension [16,20–22]. Numerous prospective cohort studies, systematic reviews, and meta-analyses have demonstrated that insomnia is associated not only with transient increases in blood pressure but also with an increased risk of incident hypertension and other cardiovascular outcomes [20,22,31]. In particular, the insomnia phenotype characterized by objectively short sleep duration has been highlighted as being associated with a significantly higher risk of developing hypertension compared with subjectively poor sleep without objectively shortened sleep duration [21]. Supporting this association, systematic reviews have demonstrated that hypertension and unfavorable sleep architecture are closely related, particularly through greater sleep fragmentation and a reduction in the deeper stages of NREM sleep, further emphasizing the importance of objective sleep parameters in risk stratification [19]. Furthermore, recent longitudinal data indicate that an increase in the number of insomnia symptoms is associated with a corresponding increase in the risk of incident cardiovascular events, while a persistent or progressively worsening course of symptoms imposes an additional cardiovascular burden [32].

The importance of healthy sleep patterns in cardiovascular prevention has also been confirmed in recent large-scale cohort studies [33–35]. Yan et al. demonstrated that, among individuals with prehypertension, adherence to a healthy sleep pattern was associated with a significantly lower risk of developing new-onset arterial hypertension and cardiovascular disease, with a clear gradient of risk reduction with increasing healthy sleep scores [33]. Similarly, Nambiema et al. demonstrated in large European prospective cohorts that a higher healthy sleep score, as well as improvement in the score over time, was associated with a lower risk of coronary

dokazi koji ukazuju na to da poremećaji sna mogu doprineti insulinskoj rezistenciji, poremećenoj glikoregulaciji, promenama telesne mase i razvoju dislipidemije [18,25] (Tabela 2).

Kako lečiti nesanicu?

S obzirom na to da nesanica može imati bidirekcioni odnos sa mnogim psihijatrijskim i somatskim komorbiditetima, prvi korak je upravo dijagnostikovanje ovih bolesti i njihovo lečenje. Uz to, svakom pacijentu treba predočiti važne elemente adekvatne higijene spavanja: a) odlazak na spavanje uvek u isto vreme; b) izbegavanje popodnevnog spavanja („popodnevna dremka"); c) neuzimanje kofeinskih napitaka 5–6 sati pre odlaska u krevet; d) tuširanje toplom vodom pre odlaska na spavanje; e) nekorišćenje mobilnog telefona (plavo svetlo) po leganju u krevet; f) privremeno ustajanje pola sata ranije od uobičajnog („da se mozak zaželi spavanja") [36].

Kognitivno-bihevioralna terapija predstavlja najvažniji postupak u lečenju hronične nesanice (CBT-I). Ona se sastoji od nekoliko elemenata: i) kontrole stimulusa (leći tek kada se oseti pospanost, ako pacijent ne zaspi za 15–20 min treba da ustane, pređe u drugu prostoriju i radi nešto opuštajuće...); ii) restrikcije vremena provedenog u krevetu (ne kraće od 5 sati, sa postepenim produžavanjem za 15–20 min nedeljno); iii) izbegavanja nerealnih očekivanja u cilju smanjenja anksioznosti; iv) sprovođenja tehnika relaksacije (vežbe opuštanja, meditacija, itd) [37].

Ipak, kod mnogih pacijenata koji se žale na nesanicu, farmakoterapija u vidu primene hipnosedativnih lekova predstavlja najrasprostranjeniji vid lečenja uprkos činjenici da nijedan lek na tržištu koji se koristi u tu svrhu, ne

heart disease and stroke [34]. Together, these findings indicate that sleep health is not only an indicator of cardiovascular risk but also a potentially modifiable component of such risk, suggesting that sleep assessment and optimization may have an important role in primary prevention strategies for cardiovascular disease [33–35].

In addition to arterial hypertension, increasing evidence supports the notion that sleep disorders represent an additional risk factor for the development and persistence of cardiac rhythm disorders of the type of atrial fibrillation. Accordingly, disturbed sleep architecture, frequent nocturnal awakenings, prolonged sleep onset latency, and shorter sleep duration are associated with an increased risk of atrial fibrillation [29,30].

Heart failure represents a distinct entity within the association between insomnia and cardiovascular diseases, as it reflects the cumulative consequences of long-term hemodynamic, neurohumoral, and metabolic burden. A clear association between the number of insomnia symptoms and the risk of incident heart failure has been demonstrated in a large Norwegian population-based cohort. These findings suggest that more severe and complex insomnia symptomatology may be associated with a greater cardiovascular burden through chronic sympathetic activation, disruption of the HPA axis, and persistent inflammation, although the observational nature of the available studies warrants caution in interpreting causality [15,28].

Metabolic syndrome represents an important clinical domain in which insomnia and the risk of developing cardiovascular disease are closely intertwined, given evidence that sleep disturbances may contrib-

Tabela 2. Nesanica i kardiovaskularne bolesti

Table 2. Insomnia and cardiovascular disease

Autori / *Authors*	Časopis / *Journal*	Godina / *Year*	Broj ispitanika / *Participants (n)*	Tip studije / *Study type*	Primarni cilj rada / *Primary study objective*	Zaključak rada / *Conclusion*
Laugsand i sar. / Laugsand et al.	*Eur Heart J*	2014	~54000	Prospektivna kohorta / Prospective cohort	Incidentna HF / Incident HF	Doza-odgovor veza sa HF / Dose-response relationship with HF
Hu i sar. / Hu et al.	*Front Psychiatry*	2021	>1,000,000	Meta-analiza / Meta-analysis	Kardiovaskularni događaji / Cardsiovascular events	Nesanica ↑ rizik KVB / Insomnia ↑ CVD risk
Liu i sar. / Liu et al.	*Int J Hypertens*	2022	>200000	Meta-analiza / Meta-analysis	Hipertenzija / Hypertension	Dvosmerna povezanost / Bidirectional connectivity
Nambiema i sar. / Nambiema et al.	*Eur Heart J*	2023	~380000	Prospektivna kohorta / Prospective cohort	KVB / CVD	Bolji skor sna ↓ KVB rizik / Better sleep score ↓ CVD risk
Zhong i sar. / Zhong et al.	*Sleep Med*	2023	~50000	Prospektivna kohorta / Prospective cohort	KVB / CVD	Zdrav obrazac sna protektivan / A healthy sleep pattern is protective
Yan i sar. / Yan et al.	*Prev Med Rep*	2025	~300000	Kohortna / Cohort	HTA/KVB / HTN/CVD	Zdrav san ↓ incidence KVB / Healthy sleep ↓ CVD incidence
Huang i sar. / Huang et al.	*Heart*	2026	~10000+	Longitudinalna kohorta / Longitudinal cohort	Incidentna KVB / Incident CVD	Trajektorije nesanice prediktuju KVB / Insomnia trajectories are predictive of CVD

KVB – kardiovaskularni, HTA – hipertenzija, HF – srčana slabost, DM2 – dijabetes melitus tip 2, KVB – kardiovaskularne bolesti

KVB – kardiovaskularni, HTN – hypertension, HF – heart failure, DM2 – Type 2 diabetes

izaziva u potpunosti prirodan san. U našoj kliničkoj praksi najčešće prepisivani lekovi u tu svrhu pripadaju benzodijazepinskim anksioliticima (diazepam, lorazepam, bromazepam, klonazepam) i/ili sedativnim antidepresivima (trazodon, mirtazapin) (Slika 3). Nezavisno od efikasnosti ovih lekova, problemi koje oni izazivaju (tolerancija, zavisnost, apsitnencijalni sindrom, *rebound* nesanica), naročito u slučaju hronične primene, prevazilaze korist u lečenju nesanice. Ovo se posebno odnosi na bolesnike sa hroničnim kardiovaskularnim bolestima [38].

Benzodiazepini i kardiovaskularni ishodi kod bolesnika sa kardiovaskularnim bolestima

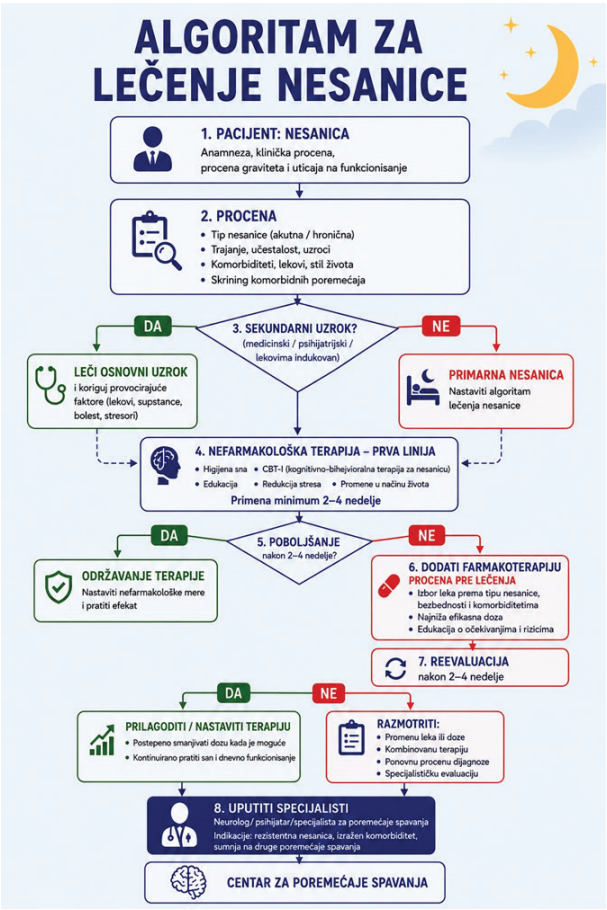
Rezultati novijih studija sugerišu da primena benzodiazepina kod bolesnika sa srčanom insuficijencijom može biti povezana sa višom stopom morbiditeta, mortaliteta i lošijim kvalitetom života. U velikoj kohorti bolesnika sa srčanom insuficijencijom i redukovanom ejekcionom frakcijom, benzodiazepini su bili udruženi sa većim rizikom kompozitnog ishoda kardiovaskularne smrti i ponavljanih hospitalizacija zbog srčane slabosti, i istovremeno sa većim rizikom nefatalnog moždanog udara i nefatalnog infarkta miokarda [39]. Ovakve nalaze podržava i studija sprovedena kod bolesnika hospitalizovanih zbog srčane slabosti i lečenih

ute to insulin resistance, impaired glycemic regulation, changes in body weight, and the development of dyslipidemia [18,25] (Table 2).

How to treat insomnia?

Given the bidirectional relationship between insomnia and many psychiatric and somatic comorbidities, the first step is to identify and appropriately treat these underlying conditions. In addition, the key principles of good sleep hygiene should be explained to each patient: a) maintaining a consistent bedtime; b) avoiding daytime sleep (”afternoon naps”); c) avoiding caffeinated beverages for 5–6 hours before bedtime; d) taking a warm shower before going to bed; e) avoiding the use of mobile phones (blue light) after going to bed; and f) temporarily waking approximately half an hour earlier than usual (”to make the brain long for sleep”) [36].

Cognitive-behavioral therapy for insomnia (CBT-I) is the most important therapeutic approach in the treatment of chronic insomnia. It consists of several components: i) stimulus control (going to bed only when drowsiness is felt; if the patient does not fall asleep within 15–20 minutes, they should get up, move to another room, and engage in a relaxing activity); ii) restriction of time spent in bed (not less than 5 hours, with a gradual



Slika 3. Algoritam lečenja nesanice

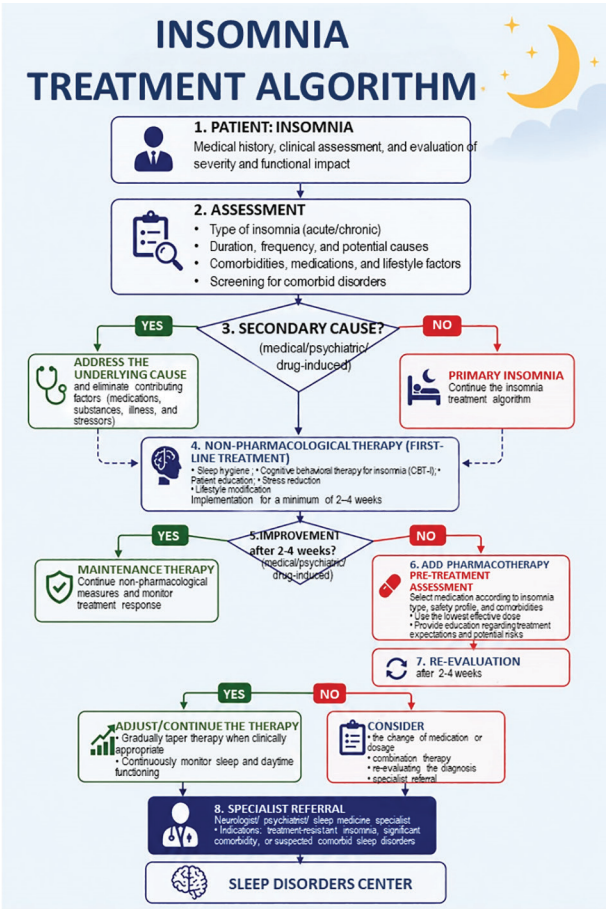


Figure 3. Algorithm for the treatment of insomnia

zbog nesanice, u kojoj su benzodiazepini, u poređenju sa Z-lekovima, bili nezavisno povezani sa većim rizikom od rehospitalizacije zbog srčane slabosti, zbog čega su autori sugerisali da bi nebenzodiazepinski hipnotici mogli imati povoljniji profil u ovoj populaciji [40].

U velikoj retrospektivnoj kohortnoj studiji iz Kine, koja je uključila približno 74.000 pacijenata sa novodijagnostikovanom kardiovaskularnom bolešću kao primarnim razlogom hospitalizacije, analizirana je povezanost započinjanja terapije benzodiazepinima sa kasnijim kardiovaskularnim ishodima. Pokazano je da je njihova primena povezana sa približno dvostruko većim rizikom od iznenadnog srčanog zastoja tokom 12 meseci praćenja, uz jasno izražen doza–odgovor odnos [41]. Hipoteza o različitim uticajima pojedinih hipnotika na kardiovaskularne ishode potvrđena je i u opservacionoj studiji koju su sproveli Xie i saradnici 2025. godine. Dobijeni rezultati ukazali su na to da je primena benzodiazepina bila statistički značajno povezana sa većim rizikom od koronarne bolesti, srčane slabosti i kardiovaskularnog mortaliteta. Nasuprot tome, autori nisu našli čvrste dokaze za to da je primena Z-lekova u opštoj populaciji bolesnika sa insomnijom povezana sa nepovoljnim kardiovaskularnim ishodima [42].

Meta-analiza koja je obuhvatila više od 2,3 miliona ispitanika pokazala je da je primena anksiolitika i hipnotika povezana sa 43% većim rizikom od ukupnog mortaliteta, pri čemu je za benzodiazepine rizik bio još izraženiji [43]. U skladu s tim, rezultati dve velike kohortne studije iz Francuske i Ujedinjenog Kraljevstva pokazali su značajno, mada umereno, povećanje jednogodišnjeg ukupnog mortaliteta kod novih korisnika benzodiazepina, čak i nakon prilagođavanja za brojne kliničke faktore i psihijatrijske komorbiditete [44]. Rezultati kohortne studije sa preko 1.320.000 učesnika potvrdili su da je primena benzodiazepina povezana sa većim rizikom od mortaliteta [45].

Većina dostupnih studija, iako retrospektivnih opservacionih, ukazuje na povezanost primene benzodiazepina sa nepovoljnijim kardiovaskularnim ishodima, uključujući veći rizik od kardiovaskularnih događaja, rehospitalizacija zbog srčane insuficijencije i mortaliteta u pojedinim populacijama bolesnika (Tabela 3). Zbog toga, primena ovih lekova u cilju lečenja nesanice zahteva strogu individualizaciju i primenu u najmanjoj mogućoj dozi ne duže od dve nedelje.

Z-lekovi (zopiklon)

Sa pojavom nebenzodijazepinskih agonista benzodiazepinskih receptora (NBBRA), mnogi od potencijalnih problema su prevaziđeni uz postizanje zadovoljavajuće efikasnosti. Ovi lekovi (zaleplon, zolpidem, zopiklon – Z lekovi) imaju selektivnije dejtvo na GABA receptore vezu-

increase of 15–20 minutes per week); iii) avoidance of unrealistic expectations in order to reduce anxiety; and iv) implementation of relaxation techniques, including relaxation exercises, meditation, etc.[37].

However, for many patients who complain of insomnia, pharmacotherapy with hypnosedative drugs remains the most common form of treatment, despite the fact that no currently available medication used for this purpose can completely reproduce natural sleep. In our clinical practice, the most frequently prescribed drugs for this purpose include benzodiazepine anxiolytics (diazepam, lorazepam, bromazepam, and clonazepam) and/or sedative antidepressants (trazodone and mirtazapine) (Figure 3). Regardless of their effectiveness, the adverse consequences associated with these drugs, including tolerance, dependence, withdrawal syndrome, and rebound insomnia, particularly with chronic use, may outweigh their benefits in the treatment of insomnia. This is especially relevant in patients with chronic cardiovascular diseases [38].

Benzodiazepines and cardiovascular outcomes in patients with cardiovascular disease

The results of recent studies suggest that benzodiazepine use in patients with heart failure may be associated with higher morbidity and mortality rates, as well as poorer quality of life. In a large cohort of patients with heart failure with reduced ejection fraction, benzodiazepine use was associated with a higher risk of the composite outcome of cardiovascular death and recurrent hospitalizations for heart failure, as well as with a higher risk of nonfatal stroke and nonfatal myocardial infarction [39]. These findings are supported by a study conducted in patients hospitalized for heart failure who were receiving treatment for insomnia, in which benzodiazepines, compared with Z-drugs, were independently associated with a higher risk of rehospitalization for heart failure. Consequently, the authors suggested that non-benzodiazepine hypnotics may have a more favorable safety profile in this population [40].

In a large retrospective cohort study from China, which included approximately 74,000 patients with newly diagnosed cardiovascular disease as the primary reason for hospitalization, the association between initiation of benzodiazepine therapy and subsequent cardiovascular outcomes was analyzed. The study demonstrated that benzodiazepine use was associated with approximately twice the risk of sudden cardiac arrest during the 12-month follow-up period, with a clear dose–response relationship [41]. The hypothesis that different hypnotic agents may have differential effects on cardiovascular outcomes was also supported by an observational study conducted by Xie et al.

Tabela 3. Povezanost upotrebe benzodiazepina i kardiovaskularnih događaja kod pacijenata sa kardiovskularnim bolestima

Table 3. Association between benzodiazepine use and cardiovascular events in patients with cardiovascular diseases

Autori / *Authors*	Časopis / *Journal*	Godina / *Year*	Broj ispitanika / *Participants (n)*	Tip studije / *Study type*	Primarni cilj rada / *Primary study objective*	Zaključak rada / *Conclusion*
Lan i sar. / *Lan et al.*	*PLoS One*	2015	~1,300,000	Prospektivna kohorta / *Retrospective cohortt*	Mortalitet /*Mortality*	Zolpidem niži rizik u poređenju sa BZD / *Zolpidem associated with lower risk than BZD*
Palmaro i sar. / *Palmaroet al.*	*Eur Neuropsychopharmacol*	2015	~200,000	Kohortna / *Cohort*	Mortalitet /*Mortality*	BZD ↑ mortalitet / *BZD ↑ mortality*
Parsaik i sar. / *Parsaik et al.*	*Aust N Z J Psychiatry*	2016	>2,300,000	Meta-analiza / *Meta-analysis*	Mortalitet /*Mortality*	Hipnotici ↑ mortalitet (BZD najviše) / *Hypnotics ↑ mortality (highest with BZD)*
Sato i sar. / *Sato et al.*	*J Am Heart Assoc*	2020	~1,000	Kohortna / *Cohort*	HF rehospitalizacija / *HF rehospitalization*	BZD lošiji od Z-lekova / *BZD worse than Z-drugs*
Chuang i sar. / *Chuang et al.*	*Acta Cardiol Sin*	2022	~6,000	Kohortna / *Cohort*	*CVD mortality + HF hospitalizations*	BZD ↑ loši ishodi / *BZD ↑ poor outcomes*
Mo i sar. / *Mo et al.*	*Sci Prog*	2024	~74,000	Prospektivna kohorta / *Retrospective cohortt*	*Sudden cardiac arrest*	BZD ~2x ↑ rizik / *BZD ⟶ ~2-fold higher risk*
Xie i sar. / *Xie et al.*	*Eur J Prev Cardiol*	2025	>100,000	Kohortna / *Cohort*	*CVD + mortality*	BZD ↑ KVB; Z-lekovi neutralniji / *BZD ↑ CVD; Z-drugs are more neutral*

KVB – kardiovaskularne bolesti, HF – srčana slabost, KVB – kardiovaskularni, BZD – benzodiazepini, CBT-I – kognitivno bihejvioralna terapija

CVD – cardiovascular disease, HF – heart failure, CV – cardiovascular, BZD – benzodiazepines, CBT-I – cognitive-behavioral therapy

jući se isključivo za alfa1 podjedinicu (selektivni antagonisti GABA receptora). Pored dobre podnošljivosti, svi imaju dobru efikasnost, visok stepen bioraspoloživosti i nastupanje dejstva unutar 15–20 min od oralne upotrebe [46].

Među ovim lekovima, posebno se izdvaja zopiklon po sledećim farmakološkim osobinama: i) ima duže poluvreme eliminacije u odnosu na zolpidem (5 vs. 2,6 sati) čime je ukupno vreme spavanja produženo, a broj buđenja tokom noći smanjen; ii) nema potencijal za razvoj tolerancije čak ni kod hronične upotrebe; iii) pojava *rebound* nesanice je izuzetno retka. Prema polisomnografskim nalazima zopiklon takođe poboljšava strukturu spavanja i približava je spavanju kod zdravih kontrola. On povećava udeo sporotalasne faze spavanja u ukupnom spavanju, bez uticaja na REM fazu. Na ovaj način, zopiklon kod bolesnika sa nesanicom povećava restorativnu ulogu spavanja uz efikasnije uklanjanje adenozina, konsolidaciju memorije i stabilizaciju vegetativnog nervnog sistema [47,48].

ZAKLJUČAK

Savremeni pristup lečenju hronične nesanice zasniva se na razumevanju da ovaj poremećaj predstavlja trajno stanje poremećene regulacije sna koje zahteva dugoročnu terapijsku strategiju, a ne isključivo simptomatsko ublažavanje tegoba, posebno u osetljivim podgrupama bolesnika kakvi su kardiovaskularni. Dostupni podaci podržavaju oprez pri primeni benzodiazepina kod kardioloških bolesnika, dok se izbor Z-lekova, uključujući zopiklon, mora tumačiti u kontekstu ograničenog broja direktnih uporednih studija i individualnog kliničkog

in 2025. The results indicated that benzodiazepine use was statistically significantly associated with a higher risk of coronary artery disease, heart failure, and cardiovascular mortality. In contrast, the authors found no strong evidence that the use of Z-drugs in the general population of patients with insomnia was associated with adverse cardiovascular outcomes [42].

A meta-analysis including more than 2.3 million subjects showed that the use of anxiolytics and hypnotics was associated with a 43% higher risk of all-cause mortality, with benzodiazepines being associated with an even greater risk [43]. Similarly, the results of two large cohort studies from France and the United Kingdom demonstrated a significant, albeit moderate, increase in 1-year all-cause mortality among new benzodiazepine users, even after adjustment for numerous clinical factors and psychiatric comorbidities [44]. The results of a cohort study involving more than 1,320,000 participants further confirmed that benzodiazepine use is associated with a higher risk of mortality [45].

Most of the available studies, although retrospective and observational in design, indicate an association between benzodiazepine use and less favorable cardiovascular outcomes, including a higher risk of cardiovascular events, rehospitalization due to heart failure, and mortality in certain patient populations (Table 3). Therefore, the use of these drugs for the treatment of insomnia requires strict individualization and administration at the lowest possible dose for no longer than two weeks.

profila bolesnika. Nasuprot tome, kognitivno-bihevioralna terapija za nesanicu (CBT-I) predstavlja terapiju prvog izbora zbog dokazane dugoročne efikasnosti, održivosti terapijskog efekta i odsustva rizika od zavisnosti.

Najkraće rečeno, budući razvoj lečenja hronične nesanice usmeren je ka individualizovanom pristupu koji integriše nefarmakološke intervencije sa selektivnom primenom farmakoterapije kod odgovarajućih bolesnika.

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Z-drugs (zopiclone)

With the advent of non-benzodiazepine benzodiazepine receptor agonists (NBBRAs), many of the potential limitations associated with conventional benzodiazepines have been addressed while maintaining satisfactory efficacy. These drugs (zaleplon, zolpidem, and zopiclone, collectively referred to as Z-drugs) exert a more selective effect on GABA receptors by preferentially binding to the α1 subunit. In addition to good tolerability, they demonstrate good efficacy, a high degree of bioavailability, and a rapid onset of action, typically within 15–20 minutes of oral administration [46].

Among these drugs, zopiclone is distinguished by the following pharmacological properties: i) it has a longer half-life than zolpidem (5 vs. 2.6 hours), which increases total sleep time and reduces the number of nocturnal awakenings; ii) it has no significant potential for the development of tolerance, even with chronic use; and iii) the occurrence of rebound insomnia is extremely rare. According to polysomnographic findings, zopiclone also improves sleep architecture and brings it closer to that observed in healthy controls. It increases the proportion of slow-wave sleep in total sleep time without affecting the REM phase. In this way, zopiclone may enhance the restorative function of sleep in patients with insomnia by promoting more efficient clearance of adenosine, memory consolidation, and stabilization of autonomic nervous system function [47,48].

CONCLUSION

The modern approach to the treatment of chronic insomnia is based on the understanding that this disorder represents a persistent state of disrupted sleep regulation requiring a long-term therapeutic strategy rather than merely symptomatic relief, particularly in vulnerable subgroups of patients, such as those with cardiovascular disease. Available data support caution in the use of benzodiazepines in cardiac patients, while the use of Z-drugs, including zopiclone, should be considered in the context of the limited number of direct comparative studies and the individual clinical profile of each patient. In contrast, cognitive-behavioral therapy for insomnia (CBT-I) is considered the treatment of first choice because of its demonstrated long-term efficacy, sustained therapeutic effects, and absence of a risk of dependence.

In short, the future development of chronic insomnia treatment is directed toward an individualized approach that integrates non-pharmacological interventions with the selective use of pharmacotherapy in appropriate patients.

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