

# Zbrinjavanje hitnih stanja vezanih uz arterijsku hipertenziju u izvanbolničkoj hitnoj medicinskoj službi

## Management of emergency medical conditions related to arterial hypertension in the prehospital setting

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**RECEIVED:**  
**March 15, 2023**

**UPDATED:**  
**May 16, 2023**

**ACCEPTED:**  
**June 2, 2023**



**SAŽETAK:** Arterijska je hipertenzija najčešći uzrok kardiovaskularnih bolesti kao i smrtnosti. Znatno pridonosi učestalosti ostalih kroničnih bolesti, od kojih su najučestalije infarkt miokarda i moždani udar. Arterijska hipertenzija, bilo ona kronična neregulirana, a posebno u slučaju hipertenzivne hitnoće ili emergencije, kompleksno je stanje koje je potrebno odgovarajuće procijeniti i zbrinuti. Hipertenzivne emergencije nisu učestale u populaciji, ali su ozbiljna hitna stanja koja u kratkom vremenu, ako se odgovarajuće ne zbrinu, uzrokuju ireverzibilno oštećenje i gubitak funkcije ciljnih organa. Promptno i učinkovito postupanje u izvanbolničkoj hitnoj medicinskoj službi znatno doprinosi kvaliteti cjelokupnoga zdravstvenog sustava.

**SUMMARY:** Arterial hypertension is the most common cause of cardiovascular diseases and mortality. It significantly contributes to the incidence of other chronic diseases, the most frequent being myocardial infarction and stroke. Arterial hypertension, whether chronically uncontrolled or especially in case of hypertensive emergency, represents a complex state that must be adequately assessed and managed. Hypertensive emergencies are not common in the general population, but represent a serious health emergency that can rapidly lead to irreversible damage and loss of function of target organs if not treated adequately. Prompt and effective treatment in prehospital emergency care significantly contributes to the overall quality of the healthcare system.

**KLJUČNE RIJEČI:** arterijska hipertenzija, izvanbolnička hitna medicinska služba.

**KEYWORDS:** arterial hypertension, prehospital emergency services.

**CITATION:** *Cardiol Croat.* 2023;18(7-8):225-38. | <https://doi.org/10.15836/ccar2023.225>

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**TO CITE THIS ARTICLE:** Delalić Đ, Simić A, Neseek Adam V, Prkačin I. Management of emergency medical conditions related to arterial hypertension in the prehospital setting. *Cardiol Croat.* 2023;18(7-8):225-38. | <https://doi.org/10.15836/ccar2023.225>

**TO LINK TO THIS ARTICLE:** <https://doi.org/10.15836/ccar2023.225>

P ojedinačne se smjernice i konsenzusi razlikuju u stupnjevanju vrijednosti arterijskoga tlaka iznad granične vrijednosti te podjelama na priehipertenziju i „pravu” arterijsku hipertenziju (AH)<sup>1-3</sup>. Definicije, dijagnostički kriteriji i stupnjevanje AH-a prikazane u ovome preglednom članku sukladne su smjericama Europskoga kardiološkog društva i Europskoga društva za hipertenziju (engl. ESC/ESH, prema *European Society of Cardiology / European Society of Hypertension*)<sup>1</sup>. Prema preporukama ESC/ESH-a, povišene vrijednosti arterijskoga tlaka (AT) u svih bolesnika starijih od 16 godina stupnjuju se kako je navedeno u **tablici 1**. Navedene se vrijednosti AT-a odnose na one izmjerene u liječničkoj ordinaciji standardnim mjerenjem.

I ndividual guidelines and consensuses differ with regard to grading arterial pressure values above the normal range and with regard to classification into pre-hypertension and “true” arterial hypertension (AH)<sup>1-3</sup>. The definitions, diagnostic criteria, and grading for AH described in this review are based on the guidelines of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)<sup>1</sup>. According to the ESC/ESH guidelines, elevated blood pressure values in all patients above the age of 16 are graded as described in **Table 1**. These blood pressure (BP) values refer to standard in-office measurements performed in a doctor’s office.

**TABLE 1. Grading of hypertension according to blood pressure values and the current Guidelines for the Management of Arterial Hypertension<sup>1</sup>.**

Grade of hypertension	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)
Optimal blood pressure	<120	and	<80
Normal blood pressure	120-129	and/or	80-84
"Pre-hypertension/high normal" blood pressure	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and/or	<90

## Anamneza i heteroanamnestički podatci na mjestu intervencije

Timovi izvanbolničke hitne medicinske pomoći često su prvi medicinski djelatnici koji dolaze u kontakt s bolesnikom koji ima povišene vrijednosti AT-a. Navedene vrijednosti bolesnik najčešće mjeri „kućnim“ sfigmomanometrom, u većini slučajeva automatiziranim. Vrijednosti AT-a izmjerene takvim uređajem minimalno se razlikuju od onih izmjerenih u liječničkoj ordinaciji, iako postoji znanstveni konsenzus unutar hipertenzioške struke temeljen na postojećim istraživanjima koja pokazuju da kućna mjerenja prikazuju vrijednosti AT-a niže za otprilike 5 mmHg od onih mjerenih u liječničkoj ordinaciji<sup>4</sup>. Stoga i sama hipertenzioška društva granicu za prvi stupanj AH-a (ako se dijagnosticira na temelju vrijednosti izmjerenih kod kuće) spušta na vrijednosti ≥135/85 mmHg umjesto ≥140/90<sup>1</sup>. Pri dolaska na mjesto intervencije, ako je bolesnik asimptomatski (a ima povišen AT), potrebno je provjeriti uzima li antihipertenzivne lijekove koji su mu propisani, u kojoj dozi i učestalosti te preklapa li se njegov način uzimanja s onim propisanim u medicinskoj dokumentaciji. Uputno je provjeriti zabilježene vrijednosti AT-a na digitalnom bolesnikovu mjeracu tlaka (ako uređaj podržava takvu funkciju i ako postoji) te provjeriti vodi li bolesnik dnevnik AT-a radi procjene izmjerenih vrijednosti i vremenskog odmaka od početka hipertenzivne epizode. Potrebno je izmjeriti AT bolesnika. Iako ne postoji velik broj istraživanja koja uspoređuju valjanost mjerenja AT-a u izvanbolničkim uvjetima s bolničkim mjerenjem, objavljene studije pokazuju relativno male razlike između AT-a koje je izmjerio bolničar u izvanbolničkim u usporedbi s mjerenjima u bolničkim uvjetima: prosjek varijacije u sistoličkom tlaku kreće se od -3,8 do -4,6 mmHg, a u dijastoličkom od +0,42 do -3,6 mmHg<sup>5</sup>.

Pri mjerenju AT-a treba obratiti pažnju na ispravnu tehniku mjerenja, pazeći na sljedeće<sup>6</sup>:

- bolesnik nije konzumirao kofein ili nikotin minimalno 30 minuta prije mjerenja
- bolesnik bi prije mjerenja trebao sjediti uspravno barem 5 minuta, neprekriženih nogu

## Anamnesis and heteroanamnesis during a prehospital intervention

Emergency medical teams are often the first medical professionals coming into contact with patients who have elevated BP values. These values are usually measured by the patient using an at-home sphygmomanometer, in most cases an automatic one. BP values measured by such a device differ only minimally from those measured in-office, although scientific consensus among hypertension experts based on current studies indicates that measurements at home show BP values approximately 5 mmHg lower than those measured in a doctor's office<sup>4</sup>. Thus, hypertension guidelines have lowered the value for the classification of the first grade of AH (if it is diagnosed based on values measured at home) to ≥135/85 mmHg instead of ≥140/90<sup>1</sup>. When arriving at an intervention, if the patient is asymptomatic (but has elevated BP), it is necessary to ascertain whether the patient is taking the antihypertensive medication prescribed to them and at which doses and frequency, as well as whether their mode of intake matches the prescription in the medical documentation. It is recommended to assess the measurement values stored on the patient's digital pressure measurement device (if the device supports this function) and to check whether the patient is leading a BP journal in order to assess the measured values and the time since the start of the hypertensive episode. The patient's BP value should be measured. Although there are few studies comparing the validity of measuring BP values outside the hospital in comparison with in-hospital measurements, published studies found relatively small differences in BP measured by medical personnel outside the hospital in comparison with hospital conditions: the average variation in systolic BP is between -3.8 to -4.6 mmHg, and the average variation in diastolic BP ranges from +0.42 to -3.6 mmHg<sup>5</sup>.

When measuring BP values, correct measurement techniques should be adhered to, while making sure of the following<sup>6</sup>:

- That the patient has not consumed caffeine or nicotine for at least 30 minutes before the measurement.
- The patient should be seated in an upright position for at least 5 minutes before the measurement, without crossing their legs.

- duljina orukvice trebala bi iznositi 80 % opsega nadlaktice, a širina 40 % opsega nadlaktice
- bolesnik ne bi trebao govoriti tijekom mjerenja AT-a
- ruka bi trebala biti naslonjena na čvrstu podlogu otprilike na razini srca
- treba ukloniti usku odjeću na bolesnikovoj nadlaktici prije mjerenja.

Bitno je uzeti anamnezu/heteroanamnezu i obaviti klinički pregled kako bi se postavila sumnja na moguće sekundarne uzroke AH-a i razlučiti akutno nastalu od neprepoznate kronične AH.

U sljedećim su tablicama kratko navedene najvažnije preporuke. **Tablica 2** prikazuje najvažnija anamnestička pitanja te moguće uzroke, odnosno etiologiju koja se njima želi ispitati. **Tablica 3** opisuje dijelove kliničkog pregleda važne za procjenu bolesnika s hipertenzijom, a **tablica 4** navodi najčešće uzroke sekundarne hipertenzije te stavke iz anamneze i statusa povezane s njima.

- The cuff length should be 80% of the circumference of the upper arm, and the width should be 40% of the upper arm.
- The patient should not speak during BP measurement.
- The hand should be resting on a firm surface, approximately at the level of the heart.
- Tight clothing should be removed from the patient's upper arm before commencing the measurement.

It is important to perform anamnesis/heteroanamnesis and a clinical examination in order to establish suspicion of possible secondary causes of AH and differentiate newly-developed acute AH from undiagnosed chronic AH.

The following tables provide a brief overview of the most important recommendations. **Table 2** shows the most important questions related to the patient's medical history and the potential causes, i.e., the etiology, that they are used to assess. **Table 3** describes the parts of the clinical examination that are important for assessing a patient with hypertension. **Table 4** lists the most common causes of secondary hypertension and related items in the anamnesis and patient status.

**TABLE 2. Personal medical history questions useful for establishing the differential diagnosis of hypertension etiology.**

Question	Suspected etiology
Has a physician ever told you/Do you know that you have high blood pressure?	Open type question – a certain number of patients do not consider themselves as having arterial hypertension although they are taking or have been taking antihypertensive medications.
Do you have chest pain?	Myocardial infarction. Aortic dissection.
Do you have shortness of breath/difficulty breathing?	Myocardial infarction. Aortic dissection. Pulmonary edema. Heart failure.
Are you taking any medications or plant-based substances? Are you taking any supplements/drugs of abuse?	Neuroleptic malignant syndrome. Serotonin syndrome. Cocaine abuse. Tetrahydrocannabinol abuse.
Have you recently stopped taking medications/plant-based substances/drugs of abuse/alcoholic beverages?	Delirium tremens. Withdrawal syndromes. Rebound effect (with abrupt termination of beta blocker therapy).
Do you feel weakness in your arms or legs/confusion/dizziness/tingling/nausea? Are you having difficulties talking?	Cerebrovascular incident. Transient ischemic attack. Intracranial hemorrhage.
Do you snore while sleeping? Do you wake up during the night? Do you feel tired during the day?	Obstructive sleep apnea syndrome.
Have you ever had high blood pressure that did not decrease with your usual blood pressure medications?	Resistant renovascular hypertension. Hyperaldosteronism. Hyperthyroidism.
Has your physician recently changed your blood pressure medications or their dose?	Lowering of the dose of current antihypertensive medication or recent change of antihypertensive medication that could explain the sudden increase in blood pressure.
Which blood pressure medications do you take? How often?	Survey of the patient's medication-taking habits and whether they match with the prescribed therapeutic regime.
Do you urinate regularly? When was the last time you urinated? How much urine did you pass?	Chronic kidney disease. Acute kidney injury.

**TABLE 3. Clinical examination findings and their correlated etiologies.**

Clinical examination finding	Correlated etiology
Precordial murmur. Assymetrical extremity pulses. Changes in the neurologic status.	Aortic dissection
Jugular vein distension. Rhales on pulmonary auscultation. Pretibial and perimalleolar edema.	Heart failure
Palpable, pulsating abdominal mass. Auscultatory murmur over the abdomen	Abdominal aortic aneurysm
Extremity hyper/hypo-reflexia. Palpable enlarged thyroid gland.	Hypo/hyperthyroidism
Hemorrhage, papillary edema on fundoscopy.	Hypertensive retinopathy

**TABLE 4. Secondary causes of hypertension and their correlated personal medical history and clinical examination findings, along with the indicated diagnostic workup.**

Personal medical history/clinical examination finding	Etiology	Further diagnostic workup indicated in hospital unit
Murmur over the thoracic aorta (auscultated between the shoulder blades) Barely palpable or nonpalpable femoral artery pulses >20 mmHg difference in systolic BP between the upper and lower extremities	Coarctation of the aorta	Transthoracic echocardiography Multislice computed tomography of the aorta
Renal artery murmur (auscultated paraumbilically) Increased serum creatinine concentration and/or proteinuria on urine dipstick test	Renal artery stenosis	Renal artery Doppler ultrasonography Multislice computed tomography of the renal arteries
Bradycardia/Tachycardia Dysmenorrhea/Amenorrhea Sudden weight loss or weight gain	Functional disorders of the thyroid gland	Laboratory workup: measurement of serum thyroid stimulating hormone, free serum triiodothyronine, free serum thyroxine, anti-thyroid peroxidase antibodies
Hypokalemia Hypernatremia	Primary hyperaldosteronism	Laboratory workup: measurement of serum renin, aldosterone, aldosterone/renin ratio Multislice computed tomography of the adrenal glands
Snoring during sleep Apneic episodes and sudden waking from sleep Fatigue during daytime	Obstructive sleep apnea syndrome	Polysomnography, drug induced sleep endoscopy
Pallor/Headache/Syncope Tachycardia Paroxysmal BP surges	Pheochromocytoma	Laboratory workup: measurement of metanephrine/nor-metanephrine and adrenaline/noradrenaline in a 24h urine sample
Abdominal obesity "Buffalo hump" "Moon facies" Hyperglycemia Red abdominal striations	Cushing's disease/Insulin resistance	Laboratory workup: measurement of cortisol in a 24h urine sample Dexamethasone suppression test Measurement of serum insulin concentration and insulin resistance index

## Uloga 12-kanalnog elektrokardiograma u hitnim stanjima

Elektrokardiografija (EKG) je esencijalna pretraga u obradbi AH-a. Lako je ponovljiva, neinvazivna te dostupna u kući bolesnika ili u kolima izvanbolničke hitne medicinske službe, pa je stoga nužno obaviti 12-kanalni EKG pri prvom kontaktu s bolesnikom te ga ponoviti kada za to postoji indikacija. Pri obradi hipertenzivnog bolesnika, EKG ima najvažniju ulogu u otkrivanju akutnoga koronarnog sindroma, bilo da je riječ o okluzivnom infarktu miokarda (OMI, prema engl. *occlusion myocardial infarction*) bilo o neokluzivnom infarktu miokarda (NOMI, prema engl. *non-occlusion myocardial infarction*). Prema preporukama *American College of Cardiology* za obradbu akutne boli u prsištu u hitnoj službi iz 2022. godine, pri očitavanju EKG-a posebnu pozornost treba obratiti na nalaze koji upućuju na OMI jedne od koronarnih arterija ili njihovih grana<sup>7</sup>. Među takve nalaze ehokardiograma ubraja se elevacija ST-segmenta u kongruentnim odvodima te ekvivalenti poput posteriornog infarkta miokarda sa ST-elevacijom (STEMI), blok lijeve grane ili *ventricular paced* ritam s pozitivnim Sgarbossa ili modificiranim Sgarbossa kriterijima, De Winterov znak te hiperakutni T-valovi<sup>7</sup>. Detaljniji se opisi navedenih nalaza nalaze u **tablici 5**.

U slučaju kliničke sumnje, a kada na nalazu EKG-a postoji SIQ3T3 uzorak, treba razmišljati o plućnoj emboliji uz sve ostale dijagnostičke elemente. Prospektivna istraživanja koja su proučavala nalaze EKG-a pokazala su da četvrtina bolesnika s plućnom embolijom nema SIQ3T3 uzorak, odnosno patološki nalaz EKG-a<sup>8</sup>. Analiza 212 EKG zapisa pokazala je da se SIQ3T3 uzorak pojavljuje jednakom učestalošću u bolesnika koji imaju plućnu emboliju i u onih koji je nemaju te je identificirala tahikardiju (osjetljivost 62,5 %, specifičnost 77,5 %) i novonastali blok desne grane (osjetljivost 93,3 %, specifičnost 100 %) kao nalaze EKG-a statistički značajno povezane s dijagnozom plućne embolije<sup>9</sup>.

## Terapijski pristup

Terapijski pristup AH-u u ovom će se članku podijeliti na pristup hipertenzivnoj emergenciji ili krizi, koja se definira kao povišena vrijednost AT-a koja uzrokuje akutno oštećenje ciljnih organa te zahtijeva trenutačno snižavanje kako bi se očuvala funkcija zahvaćenih organa i organskih sustava, te asimptomatskoj nereguliranoj AH<sup>2</sup>. Razlog ovoj podjeli jest činjenica da, iako je relativno rijetka pojava, hipertenzivna je emergencija hitno stanje koje, ako se ne liječi odgovarajuće i pravodobno, uzrokuje trajne posljedice u izrazito kratkom razdoblju. Asimptomatska neregulirana AH (ranije poznata kao „hipertenzivna urgencija“) posljedica je kroničnih degenerativnih promjena mikrovaskulature i makrovaskulature koje nastaju tijekom nekoliko mjeseci/godina te, iako je neovisan čimbenik rizika za niz bolesti, nije hitno stanje koje će kroz nekoliko sati uzrokovati ireverzibilna oštećenja ciljnih organa<sup>10</sup>. Izbor medikamentnog liječenja te ciljevi znatno se razlikuju između opisanih patofizioloških entiteta pa ih je potrebno obraditi zasebno.

### TERAPIJSKI PRISTUP ASIMPTOMATSKOJ NEREGULIRANOJ ARTERIJSKOJ HIPERTENZIJI

U 6 – 8 % bolesnika s izmjerenim povišenim vrijednostima AT-a prilikom prvog kontakta u hitnoj službi, pri otpustu kući

## The role of the 12-lead electrocardiogram in emergencies

Electrocardiography (ECG) is an essential examination for AH. It is easily repeatable, non-invasive, and available in the patient's home or the emergency services vehicle, and it is thus necessary to perform a 12-lead ECG during the first contact with the patient, repeating the examination when indicated. During the examination of a hypertensive patient, ECG has the most important role in discovering acute coronary syndrome, whether occlusion myocardial infarction (OMI) or non-occlusion myocardial infarction (NOMI). According to the 2022 recommendations of the American College of Cardiology for the treatment of acute chest pain in emergency services, physicians interpreting the ECG should pay special attention to findings that indicate OMI of one of the coronary arteries or their branches<sup>7</sup>. Such ECG findings include ST-segment elevation in the relevant leads or equivalents such as posterior myocardial infarction with ST-elevation (STEMI), left branch block, or ventricular paced rhythm with positive or modified Sgarbossa criteria, de Winter sign, and hyperacute T-waves<sup>7</sup>. More detailed descriptions of these findings are presented in **Table 5**.

In case of clinical suspicion, when the SIQ3T3 sign is present on the ECG, pulmonary embolism should be considered along with all the other diagnostic elements. Prospective studies that examined ECG findings showed that a quarter of patients with pulmonary embolism did not have the SIQ3T3 sign, i.e., no pathological ECG findings<sup>8</sup>. Analysis of 212 ECG results showed that the SIQ3T3 sign was equally prevalent in patients with and without pulmonary embolism, and identified tachycardia (sensitivity 62.5%, specificity 77.5%) and newly-developed right branch block (sensitivity 93.3%, specificity 100.00%) as ECG findings that were statistically significantly associated with the diagnosis of pulmonary embolism<sup>9</sup>.

## Treatment approach

This review divides the treatment approaches to AH into approaches for hypertensive emergency or crisis, which is defined as elevated BP values leading to acute damage to target organs and requiring immediate reduction in order to preserve the function of affected organs and organ systems, and approaches for asymptomatic uncontrolled AH<sup>2</sup>. The reason for this division is the fact that, although relatively rare, hypertensive emergency represents an emergency state which, if not treated in an adequate and timely manner, leads to permanent consequences in a very short period of time. Asymptomatic uncontrolled AH (previously known as "hypertensive urgency") is the consequence of degenerative changes of the micro- and macro-vasculature that develop over several months or years that, although an independent risk factor for numerous diseases, does not represent a state of medical emergency that will lead to irreversible target organ damage within several hours<sup>10</sup>. The choice of medication treatment and its goals differ significantly for these two pathophysiological entities and must therefore be addressed individually.

### TREATMENT APPROACH FOR ASYMPTOMATIC UNCONTROLLED ARTERIAL HYPERTENSION

Approximately 6-8% of patients with elevated BP values measured at first contact with emergency services are diag-

**TABLE 5. Electrocardiography findings correlated with myocardial ischemia (adapted from the 2022 American College of Cardiology guidelines on the evaluation of chest pain in the emergency department).**

Finding	Criteria
<b>ST-Elevation Myocardial Infarction equivalents</b>	
Posterior STEMI	Horizontal ST-segment depression in V1-V3 Dominant R-wave (R/S ratio >1) in V2 Upright T waves in anterior leads Prominent and broad R-wave (>30 ms) Confirmation by ST-segment elevation of $\leq 0.5$ mm in at least 1 of leads V7-V9
de Winter Sign	Tall, prominent, symmetrical T waves arising from upsloping ST-segment depression >1 mm at the J-point in the precordial leads 0.5-1 mm ST-segment elevation may be seen in lead aVR
Hyperacute T-waves	Broad, asymmetric, peaked T waves may be seen early in ST-elevation myocardial infarction Serial electrocardiograms over very short intervals are useful to assess for progression to ST-Elevation Myocardial Infarction
Left bundle branch block or ventricular paced rhythm with Smith-modified Sgarbossa Criteria	Positive if any of the following are present: Concordant ST-segment elevation of 1 mm in leads with a positive QRS complex Concordant ST-segment depression of 1 mm in V1-V3 ST-segment elevation at the J-point, relative to the QRS onset, is at least 1 mm and has an amplitude of at least 25% of the preceding S-wave
Left bundle branch block or ventricular paced rhythm with Sgarbossa Criteria	A total score $\geq 3$ points is required: Concordant ST-segment elevation $\geq 1$ mm in leads with a positive QRS complex (5 points) Concordant ST-segment depression $\geq 1$ mm in leads V1-V3 (3 points) Discordant ST-segment elevation $\geq 5$ mm in leads with a negative QRS complex (2 points) If there is discordant ST-segment elevation $\geq 5$ mm, consider ST/S ratio <-0.25
<b>Findings consistent with acute or subacute myocardial ischemia</b>	
Wellens syndrome	Biphasic or deeply inverted and symmetric T waves in leads V2 and V3 (may extend to V6) Recent angina Absence of Q waves
ST-segment depression	Horizontal or downsloping ST-segment depression $\geq 0.5$ mm at the J-point in 2 or more contiguous leads is suggestive of myocardial ischemia
Inverted T-waves	May be seen in ischemia (subacute) or infarction (may be fixed and associated with Q waves) in continuous leads
ST-segment elevation in lead aVR	ST-segment elevation in aVR $\leq 1$ mm Multi-lead ST-segment depression in leads I, II, V4, and/or V4-V6 Absence of contiguous ST-segment elevation in other leads

dijagnosticira se AH i propiše se preporuka za antihipertenzivne lijekove<sup>11,12</sup>. Iako je u oko 75 % bolesnika s povišenim tlakom nalaz povišene vrijednosti AT-a nepovezan s razlogom dolaska, postoje istraživanja koja pokazuju da bolesnici

nosed with AH at hospital discharge, with a prescription for antihypertensive medication<sup>11,12</sup>. Although elevated BP values are not related to the reason for admission in approximately 75% of patients, some studies have shown that patients with

sa znatno povišenim vrijednostima (stadij 3. hipertenzije) u hitnoj službi imaju neprepoznatu kroničnu AH te da se takav nalaz ne može pripisati isključivo boli ili tjeskobi<sup>13,14</sup>.

Pri donošenju odluke o započinjanju peroralnoga antihipertenzivnog liječenja u izvanbolničkoj hitnoj službi u bolesnika s asimptomatskom nereguliranom AH, liječnik treba razmotriti nekoliko važnih čimbenika. Prije svega, treba imati na umu potencijalni rizik od pojave ijtrogene hipotenzije u starijih od 80 godina, fragilnih i/ili u onih opterećenih komorbiditetima. Valja razmotriti i korist od kratkoročnoga sniženja povišene vrijednosti AT-a uporabom peroralnih antihipertenziva u odsutnosti drugih simptoma. Također treba prikupiti informacije o lokalnoj dostupnosti liječnika obiteljske medicine te vjerojatnost da će daljnja ambulantna obradba AH-a biti provedena. Istraživanja koja su proučavala vrijednosti AT-a izmjerene uzastopnim mjerenjima u izvanbolničkoj hitnoj službi pokazale su prosječan pad dijastoličkoga tlaka za 11,6 mmHg u drugome uzastopnom mjerenju s 20 minuta razmaka od prvog. U bolesnika s urednim vrijednostima AT-a u prvome mjerenju, drugo se mjerenje razlikovalo za samo 3,7 mmHg<sup>15</sup>. Stoga odluka o započinjanju peroralnog liječenja antihipertenzivnim lijekovima ovisi o prosudbi liječnika nakon razmatranja čimbenika vezanih uz svakoga pojedinačnog bolesnika, a radi jednostavnosti postupanja smjernice ESH u slučaju izmjerenog 2. i 3. stadija AH-a preporučaju uvesti fiksnu antihipertenzivnu terapiju<sup>1</sup>. Iako ne zahtijevaju hitno i trenutačno zbrinjavanje, bolesnici s asimptomatskom nereguliranom AH i dalje su ranjiva skupina kojoj je potrebno praćenje i obradba liječnika primarne zdravstvene zaštite. U retrospektivnoj analizi koju su proveli Frei *i sur*, u 2,7 % bolesnika koji su se javili u hitnu službu zbog povišenog AT-a razvio se neželjeni događaj unutar 7 dana od otpusta iz hitne službe (75 % neželjenih događaja činilo je popuštanje srca, a 25 % akutnu bubrežnu ozljedu)<sup>16</sup>. Važno je naglasiti važnost savjetovanja uz preporuku plana obrade i liječenja koju daje bolesnikov liječnik obiteljske medicine unutar 7 dana, te pružanja uputa vezanih uz indikacije za kontaktiranje hitne službe ili javljanje u nju.

Ako je potrebno započeti antihipertenzivno liječenje, preporučuje se primjena fiksnih oralnih antihipertenziva za većinu bolesnika. U bolesnika mlađih od 65 godina s novoutvrđenom AH stadija 2. i 3. preporuka je koristiti se kombiniranom peroralnom antihipertenzivnom terapijom, a, prema Smjernicama ESH/ESC-a iz 2018., preporučuje se primijeniti inhibitor angiotenzin konvertirajućeg enzima (ACEI)/antagonist kalcija tbl. 1 puta peroralno ako bolesnik nema edeme, a, ako ih ima, preporučuje se kombinacija ACEI-a s diuretikom u jednoj tableti. Ostale fiksne kombinacije lijekova u jednoj tableti koje sadržavaju angiotenzin receptor blokator i blokator kalcijevih kanala ili druge tiazidne diuretike ili beta-blokator (u slučaju tahikardije / fibrilacije atrijske / stanja nakon infarkta miokarda) propisuju se ovisno o pridruženim stanjima. U starijih/fragilnih bolesnika preporuka je započeti s monoterapijom<sup>1</sup>. Najčešće se primjenjuje peroralno antagonist kalcija (amlodipin à 5 mg tbl. 1 puta) ili ACEI (ramipril à 5 mg tbl.). Korisnom se u izvanbolničkim uvjetima pokazala i primjena anksiolitika<sup>17</sup>.

## TERAPIJSKI PRISTUP HIPERTENZIVNOJ EMERGENCIJI

**Tablica 6** sadržava popis najčešćih uzroka vezanih uz hipertenzivnu emergenciju, tj. akutno nastalo hipertenzivno stanje

significantly elevated values (grade 3 hypertension) in emergency departments had undiagnosed chronic AH, and that such findings cannot be ascribed solely to pain or anxiety<sup>13,14</sup>.

When making a decision on commencing peroral antihypertensive treatment in a prehospital emergency setting for patients with asymptomatic uncontrolled AH, physicians must consider several important factors. Above all, they must consider the potential risk of the development of iatrogenic hypotension in patients above the age 80, fragile patients, and/or patients with comorbidities. They should also consider the benefits of short-term reduction of elevated BP values using peroral antihypertensive medication in the absence of other symptoms. Additionally, they should obtain information on the local availability of general practice physicians and the likelihood that further clinical treatment of AH will be performed. Studies that examined BP values from consecutive measurements in prehospital emergency interventions showed an average decrease of diastolic pressure of 11.6 mmHg in the second consecutive measurement that took place 20 minutes after the first. In patients with normal BP values at first measurement, the second measurement differed by only 3.5 mmHg<sup>15</sup>. Thus, the decision to commence peroral treatment with antihypertensive medication depends on the physician's assessment after considering factors tied to each individual patient, and the ESH guidelines recommend fixed antihypertensive therapy for AH grades 1 and 2 in order to simplify decisionmaking<sup>1</sup>. Although they do not require emergency and immediate treatment, patients with asymptomatic and uncontrolled AH are still a vulnerable group that requires monitoring and treatment by primary healthcare physicians. A retrospective analysis conducted by Frei *et al.* found that 2.7% of patients presenting to emergency services due to elevated BP developed an adverse event within 7 days after being discharged from emergency services (75% of adverse events were heart failure, 25% were acute kidney damage)<sup>16</sup>. It is crucial to emphasize the importance of consulting the patient's family physician and recommending a treatment plan within 7 days, as well as providing instructions with regard to indications for contacting or presenting to emergency services.

If antihypertensive treatment should be commenced, the application of fixed oral antihypertensives is recommended in most patients. Combined peroral antihypertensive therapy is recommended in patients younger than 65 with newly-diagnosed AH grades 2 and 3, and the ESH/ESC Guidelines from 2018 recommend the application of a single-pill angiotensin-converting enzyme inhibitor (ACEI)/calcium antagonist  $\times$ 1 perorally if the patient is edema-free, whereas a single-pill combination of an ACEI and diuretic is recommended for patients with edema. Other single-pill fixed combinations containing angiotensin receptor blockers, calcium channel blockers, or other thiazide diuretics or beta blockers (in case of tachycardia/atrial fibrillation/post-myocardial infarction) are prescribed depending on comorbid states and conditions. Starting with monotherapy is recommended in older/fragile patients<sup>1</sup>. This usually consists of peroral application of a calcium antagonist (amlodipine 5 mg  $\times$ 1) or ACEI (ramipril 5 mg). The application of anxiolytics has also been shown to be beneficial in out-of-hospital settings<sup>17</sup>.

## TREATMENT APPROACH IN HYPERTENSIVE EMERGENCY

**Table 6** contains a list of the most common causes related to hypertensive emergency, which is a newly-developed

koje zahtijeva promptno i odgovarajuće liječenje povišenog AT-a. Definicija hipertenzivne emergencije za potrebe ovog članka proširena je na stanja koja se prikazuju s kliničkom slikom akutnog oštećenja ciljnog organa uz izmjeren AT najčešće viši od 180/120 mmHg, uzimajući u obzir ograničene mogućnosti laboratorijske i slikovne obradbe u izvanvanbolničkoj hitnoj medicinskoj službi (HMS).

acute hypertensive state that requires prompt and appropriate treatment for elevated BP. For the purpose of these recommendations, the definition of hypertensive emergency has been extended to states that present with a clinical picture of target organ damage, with BP values usually above 180/120 mmHg, given the limited capacity for laboratory and imaging examinations in prehospital emergency services.

**TABLE 6. The most common etiologies leading to hypertensive emergencies.**

Myocardial infarction
Pulmonary edema
Preeclampsia
Cerebrovascular incident
Hyperthyroidism
Aortic dissection
Sympathomimetic intoxication (i.e., cocaine)
Malignant hypertension with acute kidney injury

### Terapijski pristup hipertenzivnoj emergenciji – terapijski ciljevi

Osim definiranja hipertenzivne emergencije, nužno je odrediti terapijske ciljeve prije započinjanja medikamentne intervencije. Preporučuje se praćenje vrijednosti srednjega arterijskog tlaka (MAP, prema engl. *mean arterial pressure*) pri određivanju početnih i ciljnih vrijednosti arterijskoga tlaka (AT) u hipertenzivnoj emergenciji<sup>18</sup>. MAP se računa prema formuli:  $[2 \times (\text{diastolički tlak}) + \text{sistolički tlak}] / 3$ . Ciljne su vrijednosti MAP-a između 70 i 100 mmHg. Ako se AT mjeri poluautomatiziranim oscilometrijskom orukvicom kakav se nalazi na većini digitalnih tlakomjera i monitora, stvarna izmjerena vrijednost jest MAP, dok su sistolički i dijastolički tlak aproksimirani formulama i algoritmima specifičnima za određenog proizvođača uređaja<sup>19</sup>. MAP pozitivno korelira sa stupnjem oštećenja ciljnih organa, najboljim pokazateljem ozbiljnosti hipertenzivne emergencije<sup>20</sup>. Ako je moguće, preporučuje se izmjeriti vrijednosti AT-a na objema rukama preko više mjerenja kako bi se što preciznije odredile početne vrijednosti MAP-a.

Pri formiranju terapijskoga plana potrebno je uzeti u obzir bolesnikovu anamnezu, tj. je li riječ o osobi s kroničnom, već postojećom AH (gdje je poželjno snizivati vrijednosti AT-a sporije i manjim intenzitetom) ili o prethodno normotenzivnoj osobi s naglo nastalom AH (gdje je moguće sniziti vrijednosti AT-a brže i većim intenzitetom).

Ako anamnestički podatci nisu dostupni, razuman je cilj sniziti MAP za otprilike 20 % unutar prva 2 sata, a zatim smanjiti MAP na 125 mmHg kroz 2 – 6 sati, ovisno o etiologiji i pridruženim stanjima bolesnika<sup>3,21</sup>.

### Treatment approach for hypertensive emergencies – treatment goals

In addition to defining hypertensive emergency, it is necessary to determine treatment goals before starting medication therapy. It is recommended to monitor mean arterial pressure (MAP) values when determining the baseline and target BP values in hypertensive emergencies<sup>18</sup>. MAP is calculated using the formula:  $[2 \times (\text{diastolic pressure}) + \text{systolic pressure}] / 3$ . Target MAP values are between 70-100 mmHg. If BP is measured using a semiautomated cuff-oscillometric device as found on most digital blood pressure devices and monitors, the displayed value is the MAP, while systolic and diastolic pressure are approximated using formulas and algorithms specific to individual manufacturers<sup>19</sup>. MAP has a positive correlation with the level of target organ damage, the best indicator of the severity of hypertensive emergency<sup>20</sup>. If possible, BP should be measured in both arms over several measurements in order to obtain the most precise possible baseline MAP value.

When forming the treatment plan, the patient's medical history must be considered, i.e., whether they are a person with chronic, preexisting AH (in which case BP reduction should be performed at a slower pace and intensity) or a previously normotensive person with suddenly-developing AH (in which case BP reduction can be performed at a higher pace and intensity).

If medical history data are not available, a reasonable goal is to reduce MAP by approximately 20% within the first 2 hours, followed by reducing MAP to 125 mmHg over the course of 2-6 hours, depending on the etiology and patient comorbidities<sup>3,21</sup>.



Prije započinjanja antihipertenzivnog liječenja poželjno je liječiti druge potencijalne uzroke povišenog AT-a u svrhu optimizacije kontrole AH-a te prevencije iatrogene hipotenzije. Primjeri su takvih uzroka navedeni u **tablici 7**.

Before starting antihypertensive treatment, it is recommended to treat other potential causes of elevated BP in order to optimize AH control and prevent iatrogenic hypotension. Examples of such causes are presented in **Table 7**.

**TABLE 7. The most common reversible secondary causes of an increase in blood pressure.**

Cause of increased blood pressure	Therapy
Pain	Analgesic agents
Volume overload	Diuretic agents
Agitation/Acute psychosis	Antipsychotic agents
Obstructive uropathy/Urinary retention	Urinary catheter placement

Izbor lijeka za zbrinjavanje pojedinog bolesnika i stanja odluka je liječnika koji zbrinjava bolesnika te stoga smatramo neuputnim pružati konkretne algoritme za zbrinjavanje pojedinih situacija. Hitni bolesnici sa simptomima i znakovima koji upućuju na hipertenzivnu emergenciju često su kompleksni te su odluke o načinu njihova zbrinjavanja multifaktorske. U nastavku ovog teksta opisana su farmakokinetička i farmakodinamska svojstva lijekova koji su se u praksi i literaturi pokazali najučinkovitijima za akutno snizivanje povišenih vrijednosti arterijskoga tlaka. Dostupnost opisanih lijekova varira ovisno o ustanovi.

## 1. INTRAVENSKI LIJEKOVI

Intraveniski se lijekovi mogu podijeliti u tri skupine, prema vremenskom trajanju djelovanja.

### a) Kratkodjelujući lijekovi

- trajanje djelovanja manje od 30 minuta – primjenjuju se u kontinuiranoj infuziji
- kratko djelovanje omogućuje titraciju

### b) Srednje dugodjelujući lijekovi

- trajanje djelovanja od 30 minuta do 2 sata – primjenjuju se u kontinuiranoj infuziji
- titracija moguća, ali nije učinkovita kao kod kratkodjelujućih lijekova

### c) Dugodjelujući lijekovi

- trajanje djelovanja dulje od 2 sata – primjenjuju se u bolusu
- titracija otežana zbog dugoga djelovanja.

U **tablici 8** navedeni su intraveniski lijekovi koji se najčešće primjenjuju u slučaju hipertenzivne emergencije. U literaturi se podacima navode nikardipin, klevidipin, labetalol, nitroglicerol, esmolol i urapidil<sup>22-27</sup>. U Republici Hrvatskoj dostupni su svi, osim nikardipina i klevidipina.

## 2. SUBLINGVALNI LIJEKOVI

Primjena nitroglicerina postoji i u sublingvalnoj formulaciji, a apliciraju se u obliku spreja prema indikaciji<sup>28</sup>. Jedan potisak

Choosing the best medication to treat individual patients and conditions is the decision of the treating physician, and we thus consider it inadvisable to provide specific algorithms for treatment in individual situations. Emergency patients with symptoms and signs that indicate hypertensive emergency often represent complex cases, and decisions on their treatment are multifactorial. The remainder of this text describes the pharmacokinetic and pharmacodynamic characteristics of medications that clinical practice and the literature have identified as most effective for acute reduction of elevated arterial pressure values. The availability of the medications described below varies between medical institutions.

## 1. INTRAVENOUS MEDICATIONS

Intravenous medications can be divided into three groups based on the duration of their effect:

### a) Short-acting medications

- Duration of action lower than 30 minutes – applied in continuous infusion
- Short-acting effect allows titration

### b) Intermediate-acting medication

- Duration of action between 30 minutes to 2 hours – applied in continuous infusion
- Titration possible, but not as effective as in short-acting medications

### c) Long-acting medications

- Duration of action longer than 2 hours – bolus application
- Titration is more difficult due to long duration of action

**Table 8** presents the intravenous medications most commonly applied in hypertensive emergencies. Literature data lists nicardipine, clevidipine, labetalol, nitroglycerine, esmolol, and urapidil<sup>22-27</sup>. All of these are available in the Republic of Croatia, except for nicardipine and clevidipine

## 2) SUBLINGUAL MEDICATIONS

Nitroglycerine can also be applied in a sublingual formulation, and it can also be applied as a spray when indicated<sup>28</sup>. One spray dose contains 400 mcg or 0.4 mg of nitroglycerine. In-

TABLE 8. Intravenous medications for blood pressure regulation in hypertensive emergency.

Name	Onset of action/ Duration of action	Contraindications	Dose	Comments
Labetalol	Onset of action: 5-10 min Duration of action: 3-6 h	Bradycardia, Atrioventricular block, Sick sinus syndrome, Cardiogenic pulmonary edema, Asthma exacerbation, Acute sympathomimetic intoxication	Applied in boluses. First bolus 20 mg, followed by a 40 mg bolus, then an 80 mg bolus up to 3 times maximum. Obligatory spacing between boluses: 15 minutes. Scheme: 20 mg - 40 mg - 80 mg-80 mg - 80mg  Maximum allowed cumulative dose: 300mg Once the desired BP is achieved, apply 10-20 mg boluses according to MAP, not more often than every 10 minutes.	May cause bradycardia, hyperkalemia
Nitroglycerin	Onset of action 2 min Duration of action: 5-10 min	Use of phosphodiesterase 5 inhibitors within 48 hours (sildenafil, vardenafil, tadalafil). Suspected increased intracranial pressure.	Applied as an infusion: 50-300 mcg/min, titrate according to MAP	Medication of choice in acute cardiogenic pulmonary edema. Coronary venodilator, indicated in acute myocardial infarction (inferior/right sided myocardial infarction are relative contraindications)
Esmolol	Onset of action: 1-2 min Duration of action: 10-30 min	Bradycardia, Atrioventricular block, Sick sinus syndrome, Cardiogenic pulmonary edema, Asthma exacerbation, Acute sympathomimetic intoxication	Loading bolus 0.5 mg/kg, then a 50 mcg/kg/min infusion. If BP remains uncontrolled: repeat bolus 0.5 mg/kg, followed by a 50 mcg/kg/min infusion. Titrate infusion to MAP (max infusion rate 200 mcg/kg/min)	May cause bradycardia, hyperkalemia
Urapidil	Onset of action 5 min Duration of action: 3 h	Aortic outflow tract stenosis. Arterio-venous shunt.	Starting dose: 25mg bolus. If BP remains uncontrolled: repeat 25 mg bolus after 10 minutes. In case of persistently elevated BP: 50 mg bolus 10 minutes after the second bolus, followed by an infusion: 5-40 mg/h	Most common medication for the management of hypertensive emergency in Croatia

spreja sadržava 400 mcg ili 0,4 mg nitroglicerina. Indikacije za primjenu sublingvalnog nitroglicerina u kontekstu hipertenzivne emergencije slične su onima za primjenu intravenske formulacije – akutni kardiogeni plućni edem, akutni infarkt miokarda (sumnja na infarkt donje stijenke ili desne klijetke relativna je kontraindikacija za primjenu). Apsolutne su kontraindikacije primjena inhibitora fosfodiesteraze 5 u razdoblju od 48 sati prije hipertenzivne epizode te sumnja na povišen intrakranijalni tlak. Najčešće su nuspojave glavobolja te eritem lica posljedično vazodilaciji. Važno je napomenuti da, s obzirom na činjenicu da sublingvalni način primjene otežava procjenu isporučene doze, bolesnika nakon primjene treba staviti u sjedeći položaj zbog rizika od naglo nastale hipotenzije. Iako se sublingvalna formulacija nitroglicerina standardno ne primjenjuje za hipertenzivne emergencije, primjeri iz literature pokazuju da je takva primjena moguća i djelotvorna. U istraživanju Prasanne *i sur* autori su primjenjivali jednu dozu (0,4 mg) sublingvalnog nitroglicerina bolesnicima s hipertenzivnom krizom te pratili vrijednosti MAP-a – nakon 10 minuta postignuta je prosječna redukcija MAP-a za 16,3 %<sup>29</sup>. Hirschl *i sur* objavili su radove u kojima se proučavala primjena sublingvalnog nitroglicerina u doza od 0,8 mg svakih 10 minuta do kumulativne doze 3,2 mg u bolesnika s hipertenzivnom emergencijom te zaključili da je

indikacije za primjenu sublingvalnog nitroglicerina u kontekstu hipertenzivne emergencije slične su onima za primjenu intravenske formulacije – akutni kardiogeni plućni edem, akutni infarkt miokarda (sumnja na infarkt donje stijenke ili desne klijetke relativna je kontraindikacija za primjenu). Apsolutne su kontraindikacije primjena inhibitora fosfodiesteraze 5 u razdoblju od 48 sati prije hipertenzivne epizode te sumnja na povišen intrakranijalni tlak. Najčešće su nuspojave glavobolja te eritem lica posljedično vazodilaciji. Važno je napomenuti da, s obzirom na činjenicu da sublingvalni način primjene otežava procjenu isporučene doze, bolesnika nakon primjene treba staviti u sjedeći položaj zbog rizika od naglo nastale hipotenzije. Iako se sublingvalna formulacija nitroglicerina standardno ne primjenjuje za hipertenzivne emergencije, primjeri iz literature pokazuju da je takva primjena moguća i djelotvorna. U istraživanju Prasanne *et al.*, the authors administered one dose (0.4 mg) of sublingual nitroglycerine to patients with a hypertensive crisis and monitored the MAP values – after 10 minutes, an average MAP reduction of 16.3% was achieved<sup>29</sup>. Hirschl *et al.* published studies that examined the application of sublingual nitroglycerine in doses of 0.8 mg every 10 minutes up to a cumulative dose of 3.2 mg in patients with hypertensive emergency and concluded

takav način zbrinjavanja jednako učinkovit kao i intravenski enalapril, no manje učinkovit od intravenskog urapidila<sup>30,31</sup>.

### 3. PERORALNI LIJEKOVI

S obzirom na dugo vrijeme do početka djelovanja većine peroralnih antihipertenzivnih lijekova te potrebu za brzim i učinkovitim snizivanjem vrijednosti AT-a u bolesnika s hipertenzivnom emergencijom, peroralni antihipertenzivi imaju ograničenu ulogu u izvanbolničkoj HMS. Prelazak na peroralnu terapiju u načelu se ne preporučuje sve dok se vrijednosti AT-a nisu stabilizirale uz intravensku primjenu lijeka. Kod peroralne primjene lijeka treba uzeti u obzir spor početak i dugo trajanje djelovanja, zbog čega može doći do akumulacije lijeka u organizmu i iatrogene hipotenzije, no na temelju istraživanja sigurno i učinkovito se mogu peroralno primijeniti labetalol, losartan i izosorbid dinitrat<sup>32-34</sup> (Tablica 9). O tome treba razmišljati i u slučaju vremenskih ili drugih nepogoda koje onemogućuju transport prema bolničkoj skrbi u izvanbolničkim uvjetima zbrinjavanja bolesnika na otocima, kod insuficijentnoga venskog pristupa (najčešće onkološki bolesnici i bolesnici s kroničnom bubrežnom bolesti) ili ograničene mogućnosti osealne primjene lijekova (amputirani udovi).

### Učinkovitost pojedinih intravenskih antihipertenzivnih lijekova

U nastavku donosimo kratak pregled vezan uz dva najčešće primjenjivana intravenska antihipertenzivna lijeka navedena u tablici 8 te njihovu učinkovitost i sigurnost u različitim kliničkim stanjima.

Labetalol je kao antihipertenziv ispitivan u više prospektivnih istraživanja te se pokazao kao učinkovit izbor koji djeluje brzo: istraživanja navode udio bolesnika s uspješnim smanjenjem vrijednosti AT-a na ciljne vrijednosti od 76 % nakon 30 minuta te 96 – 100 % nakon 60 minuta<sup>35-37</sup>. U usporedbama s drugim antihipertenzivima, labetalol se pokazao učinkovitim od intravenskog nitroglicerina<sup>36</sup>, jednako učinkovitim kao

that this form of treatment was equally effective as intravenous enalapril, but less effective than intravenous urapidil<sup>30,31</sup>.

### 3) ORAL MEDICATIONS

Due to the long onset of action for most oral antihypertensive medications and the need for rapid and effective reduction of BP values in patients with hypertensive emergency, peroral antihypertensives have a limited role in prehospital emergency services. Switching to peroral therapy is generally not recommended until BP values have stabilized after intravenous application of medication. The slow onset and long duration of action in peroral application of medication should be considered, as it can lead to accumulation of the drug in the body and consequent iatrogenic hypotension, but studies have demonstrated that the peroral application of labetalol, losartan, and isosorbide dinitrate is safe and effective<sup>32-34</sup> (Table 9). The slow onset of action of peroral medications should also be considered in case of inclement weather or other conditions preventing the transport of patients to hospital care when treating patients on islands, in case of an insufficient venous approach (most common in oncological patients and patients with chronic kidney insufficiency), or limited capacity for osseous application of the medication (amputated limbs).

### The effectiveness of different antihypertensive medications

In the section below, we present a short overview of the two most commonly used intravenous antihypertensive medications listed in Table 8 and their effectiveness and safety in various clinical conditions.

Labetalol was assessed as a antihypertensive in numerous prospective studies and was shown to be an effective, fast-acting choice: the studies report the ratios of patients with BP successfully reduced to target values was 76% after 30 minutes and 96-100% after 60 minutes<sup>35-37</sup>. In comparisons with other antihypertensives, labetalol was shown to be more

TABLE 9. Peroral medications for blood pressure regulation when transport of the patient to hospital care is not possible.

Name	Onset of action/ Duration of action	Contraindications	Dose	Comments
Labetalol	Onset of action: 2 h Duration of action: 10 h	Bradycardia, Atrioventricular block, Sick sinus syndrome, Cardiogenic pulmonary edema, Asthma exacerbation, Acute sympathomimetic intoxication	1 200 mg oral tablet every 12 h. In case of suboptimal effect, another 200 mg oral tablet can be applied 2-4 h following the first. Maximum allowed dose: 1000 mg orally every 12 h	May cause bradycardia, hyperkalemia. In stable patients, following successful BP control with intravenous labetalol and stable BP values, treatment can be continued with peroral labetalol
Losartan	Onset of action: 4-6 h Duration of action: 24 h	Hyperkalemia, Acute kidney injury, Previously reported cough or angioedema with angiotensin converting enzyme inhibitors or angiotensin receptor blockers	One 50 mg oral tablet once daily. Maximum allowed dose: 100 mg daily	Efficacy differs between patients, depending on the renin/angiotensin/aldosterone system activity level of individual patients
Isosorbide dinitrate	Onset of action: 1-2 h Duration of action: 8 h	Increased intracranial pressure. Obstructive hypertrophic cardiomyopathy	One 20 mg oral tablet every 8 h. Maximum allowed dose: One 40 mg oral tablet every 8 hours	May cause reflex tachycardia

intravenski esmolol<sup>38</sup> te manje učinkovitim od intravenskog nifedipina<sup>35</sup> i peroralnog nifedipina<sup>37</sup>.

Urapidil je antagonist alfa-1 adrenergičkih receptora koji se rabi za zbrinjavanje hipertenzivnih emergencija. U izvanbolničkim se uvjetima pokazao kao učinkovit antihipertenzivni lijek, koji već nakon 5 minuta statistički signifikantno snizuje vrijednosti AT-a bez znatnih neželjenih štetnih učinaka<sup>39</sup>. U bolničkim se uvjetima urapidil također pokazao kao učinkovit i pouzdan, brzodjelujući lijek te superioran oralnom kaptoprilu u snizivanju vrijednosti AT-a do ciljnih<sup>40</sup>. Metaanaliza koja je usporedila urapidil s nitroglicerinom pri zbrinjavanju hipertenzivnoga akutnoga popuštanja srca pokazala je da urapidil ima povoljniji sigurnosni profil te jednaku učinkovitost kao nitroglicerina u zbrinjavanju hipertenzivne emergencije, odnosno hipertenzivne krize<sup>41</sup>. Stoga bolesnike s hipertenzivnom emergencijom treba liječiti intravenskom primjenom gore navedenih lijekova, te, ako nije moguće izračunati MAP, cilj je postizanje sniženja AT-a za 25 % s obzirom na početnu vrijednost unutar standarda od jednog sata. Cilj liječenja bolesnika s kroničnom nereguliranom hipertenzijom (pojam koji se prije rabio bio je hipertenzivna urgencija) jest postupno sniženje AT-a do 20 % u usporedbi s početnom vrijednošću tlaka, a provodi se peroralnom primjenom antihipertenzivne terapije<sup>42</sup>.

## Diskusija

U uvjetima izvanbolničke HMS važnu ulogu u procjeni i dijagnozi hitnih stanja povezanih s hipertenzijom imaju anamneza te klinički pregled bolesnika<sup>43</sup>. Raos *i sur* u izvanbolničkim su uvjetima dokazali znatno sniženje sistoličkoga tlaka ako se uz antihipertenzivnu terapiju ordinirao i benzodiazepin. Postignuto je sniženje AT-a za  $19,5 \pm 7,1$  % u skupini bolesnika s kroničnom nereguliranom hipertenzijom (pojam koji se prije nazivao hipertenzivnom urgencijom) kojima je ordiniran benzodiazepam u odnosu prema kontrolnoj skupini (sniženje AT-a za  $10,1 \pm 7$  %) koja je primala antihipertenzivni lijek bez benzodiazepina<sup>44</sup>. Stoga u uvjetima izvanbolničkog zbrinjavanja treba razmotriti dodatni anksiolitički učinak koji je vrlo povoljan. Treba naglasiti važnost ambulantnog praćenja i daljnje dijagnostičke obradbe bolesnika s kroničnom nereguliranom arterijskom hipertenzijom (koja je i najčešći uzrok dolaska tima HMP-a) kroz primarnu i sekundarnu zdravstvenu zaštitu s preporukom daljnje obradbe i isključenja sekundarnih potencijalno izlječivih uzroka AH-a te osobito naglasiti važnost preporuke praćenja i kontrole u hipertenzioškim ambulantama<sup>42,44</sup>.

U slučaju hipertenzivne emergencije dijastolički tlak ne bi trebao biti manji od 100 do 110 mmHg kako bi se spriječilo daljnje oštećenje ciljnih organa zbog hipoperfuzije. Pretjerano sniženje AT-a može upućivati na cerebralnu, koronarnu ili bubrežnu ishemiju i to je potrebno izbjegavati. Iznimke od navedenoga jesu bolesnici s disekcijom aorte, feokromocitomskom krizom i teškom preeklampsijom, kao i dio bolesnika sa spontanom intracerebralnim krvarenjem koji zahtijevaju akutno sniženje tlaka<sup>42</sup>.

Pravilno zbrinjavanje hipertenzije, bilo u izvanbolničkoj bilo u bolničkoj hitnoći ključno je zbog prevencije oštećenja ciljnih organa, odnosno prevencije moždano-kardiorenovaskularnog remodeliranja i preuranjenog fibroziranja ciljnih organa kao što su mozak, srce, bubrezi te vaskularni sustav.

effective than intravenous nitroglycerine<sup>36</sup>, as effective as intravenous esmolol<sup>38</sup>, and less effective than intravenous nicardipine<sup>35</sup> and peroral nifedipine<sup>37</sup>.

Urapidil is an alpha-1 adrenergic receptor antagonist used for treating hypertensive emergencies. In prehospital conditions, it has been shown to be an effective antihypertensive medication that statistically significantly reduced BP values after as little as 5 minutes, without significant unwanted adverse effects<sup>39</sup>. In hospital conditions, urapidil was also shown to be an effective, reliable, and fast-acting medication that was superior to oral captopril in achieving target BP values<sup>40</sup>. A metaanalysis comparing urapidil with nitroglycerine for the treatment of hypertensive acute heart failure showed that urapidil had a better safety profile and equal effectiveness as nitroglycerine in the treatment of hypertensive emergency and hypertensive crisis<sup>41</sup>. Therefore, patients with hypertensive emergency should be treated the intravenous application of the medications described above, and, if MAP cannot be calculated, the goal is to achieve a 25% reduction in BP in comparison with baseline values within a one-hour standard. The treatment goal for patients with chronic uncontrolled hypertension (the previously employed term was "hypertensive urgency") is the gradual reduction of BP to 20% in comparison with initial values, which is achieved through the application of peroral antihypertensive therapy<sup>42</sup>.

## Discussion

In prehospital emergency medical conditions, anamnesis and clinical examination of the patient have a significant role in the assessment and diagnosis of emergency states associated with hypertension<sup>43</sup>. Raos *et al.* demonstrated a significant reduction in systolic pressure in prehospital conditions if benzodiazepine was prescribed alongside antihypertensive therapy. A reduction of BP of  $19.5 \pm 7.1\%$  was achieved in the group of patients with chronic uncontrolled hypertension (previously called hypertensive urgency) who were prescribed benzodiazepine in comparison with the control group (BP reduced by  $10.1 \pm 7.0\%$ ) taking an antihypertensive medication without benzodiazepine<sup>44</sup>. Its beneficial added anxiolytic effect should therefore be considered in prehospital treatment. The importance of clinical follow-up and further diagnostic examinations should be emphasized in patients with chronic uncontrolled arterial hypertension (which is also the most common reason for the arrival of an emergency medicine team) throughout primary and secondary healthcare, with a recommendation for further examination and treatment and exclusion of potentially curable secondary sources of AH, with special emphasis on the importance of recommending follow-up and control in hypertensiology clinics<sup>42,44</sup>.

In case of hypertensive emergency, diastolic pressure should not be lower than 100 to 110 mmHg, in order to prevent further target organ damage due to hypoperfusion. Excessive BP reduction can indicate cerebral, coronary, or renal ischemia and must be avoided. Exceptions comprise patients with aortic dissection, pheochromocytoma crisis, and severe preeclampsia, as well as some patients with spontaneous intracerebral bleeding that require acute pressure reduction<sup>42</sup>.

Proper management of hypertension, whether in prehospital or hospital emergency treatment, is crucial for the prevention of target organ damage as well as the prevention of cerebral, cardiac, renal, and vascular remodeling and untimely fibrosis of target organs such as the brain, heart, kidneys, and the vascular system.

## Zaključak

Djelatnici hitne medicinske službe, kao svojevrsna „sigurnosna mreža“ u zdravstvenom sustavu, imaju bitnu ulogu u informiranju bolesnika o važnosti daljnje ambulantne obrade u slučaju kronične neregulirane hipertenzije.

Nužno je poznavati etiologiju vezanu uz hitna stanja u vezi s hipertenzijom, odnosno hipertenzivnom emergencijom te farmakokinetičkim i farmakodinamskim svojstvima lijekova koji su dostupni pojedinom liječniku u HMS-u kako bi se bolesniku pružila najbolja moguća skrb u kontekstu postojećih mogućnosti i opcija sa svrhom ujednačenog postupanja i povezivanja sustava izvanbolničke i bolničke hitne službe.

## Conclusion

Emergency service providers, as a form of a “safety net” for the healthcare systems, have an important role in informing patients on the importance of subsequent clinical treatment for chronic uncontrolled hypertension.

Knowledge of the etiology of emergency states related to hypertension and hypertensive emergency, as well as the pharmacokinetic and pharmacodynamic characteristics of medications available to physicians in emergency medical services, is crucial in order to provide patients with the best possible care in the context of available options, with the goal of achieving coordinated treatment and communication across prehospital and in-hospital emergency services.

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