Valomindo – metabolički neutralna kombinacija sartana i diuretika

Valomindo – a metabolically neutral combination of a sartan and a diuretic

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SAŽETAK: Arterijska hipertenzija jedan je od vodećih uzroka kardiovaskularnog (KV) morbiditeta i mortaliteta u svijetu, uz znatan broj bolesnika u kojih ciljne vrijednosti arterijskoga tlaka (AT) ostaju nepostignute. Kombinacija valsartana i indapamida suvremeni je terapijski pristup koji sjedinjuje prednosti inhibicije renin-angiotenzinskog sustava i antihipertenzivnog djelovanja tiazidima sličnog diuretika s povoljnim metaboličkim profilom. Valsartan se ističe učinkovitošću, podnošljivošću i povoljnim učincima na bubrežnu i KV funkciju, dok indapamid nadmašuje hidroklorotiazid u kontroli AT-a, remodelaciji lijeve klijetke te KV ishodima. Fiksna kombinacija ovih lijekova, posebno u slow release formulaciji i uz moguće i večernje doziranje, dodatno pridonosi adherenciji bolesnika i optimalnoj kontroli hipertenzije, čime se smanjuje ukupan KV rizik. Europske smjernice za liječenje hipertenzije preporučuju ovakve kombinacije lijekova zbog njihove učinkovitosti i sigurnosnog profila, čime se omogućuje individualizirani pristup liječenju hipertenzije.

SUMMARY: Arterial hypertension is one of the leading causes of cardiovascular (CV) morbidity and mortality worldwide, with a significant proportion of patients failing to achieve target blood pressure (BP) values. The combination of valsartan and indapamide represents a modern therapeutic approach, combining the benefits of renin-angiotensin system inhibition with the antihypertensive effects of a thiazide-like diuretic that has a favorable metabolic profile. Valsartan is distinguished by its efficacy, tolerability, and beneficial effects on renal and CV function, while indapamide surpasses hydrochlorothiazide in BP control, left ventricular remodeling, and CV outcomes. The fixed combination of these drugs, particularly in a slow-release formulation and with the possibility of evening dosing, further enhances patient adherence and optimal hypertension management, thereby reducing overall CV risk. European hypertension treatment guidelines recommend such drug combinations due to their effectiveness and safety profile, enabling a personalized approach to hypertension management.

KLJUČNE RIJEČI: arterijska hipertenzija, valsartan, indapamid, kardiovaskularni ishodi.

KEYWORDS: arterial hypertensio, valsartan, indapamide, cardiovascular outcomes.

CITATION: Cardiol Croat. 2025;20(1-2):49-53. | https://doi.org/10.15836/ccar2025.49

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TO CITE THIS ARTICLE: Lovrić D. Valomindo – a metabolically neutral combination of a sartan and a diuretic. Cardiol Croat. 2025;20(1-2):49-53.| https://doi.org/10.15836/ccar2025.49

TO LINK TO THIS ARTICLE: https://doi.org/10.15836/ccar2025.49

RECEIVED:
January 17, 2025

UPDATED:
January 24, 2025

ACCEPTED:
February 13, 2025

Uvod

Arterijska hipertenzija pogađa oko 1,28 milijardi ljudi diljem svijeta, a očekuje se porast na 1,5 milijardi do 2025. godine, posebno u zemljama s niskim i srednjim prihodima, u kojima žive dvije trećine hipertenzivnih bolesnika[1,2]. U Africi je prevalencija najviša i dostiže 46 %, dok je u Europi oko 37,5 %, a u Hrvatskoj svaki treći odrasli ima povišenu vrijednost arterijskoga tlaka (AT)[2,3].

Ovakvo stanje odgovorno je za 10,8 milijuna smrti godišnje i ostaje glavni uzrok kardiovaskularnih (KV) bolesti, uključujući akutni infarkt miokarda i moždani udar[3]. Globalno opterećenje

Introduction

Arterial hypertension affects around 1.28 billion of people worldwide, and this number is expected to grow to 1.5 billion by 2025, especially in low-income and medium-income countries, where two-thirds of hypertensive patients reside[1,2]. The prevalence is highest in Africa, reaching 46%, while in Europe it is approximately 37.5%, and in Croatia, one in three adults has high blood pressure (BP)[2,3].

This condition accounts for 10.8 million deaths annually and remains the leading cause of cardiovascular (CV) diseases, including acute myocardial infarction (AMI) and stroke[3]. The global

hipertenzijom povezano je s urbanizacijom, nezdravim načinom života i starenjem populacije[3].

Jedan od ključnih problema u upravljanju hipertenzijom jest slaba adherencija terapiji. Istraživanja pokazuju da čak 53 % bolesnika s rezistentnom hipertenzijom nije adherentno terapiji, a 30 % bolesnika nikada ne uzima propisane lijekove[4]. Ovi podatci naglašavaju važnost jednostavnih terapijskih pristupa, poput fiksnih kombinacija, koje povećavaju suradljivost i kontrolu AT-a[4].

Mehanizam djelovanja i učinci valsartana

Valsartan je lijek iz skupine blokatora receptora angiotenzina II koji selektivno inhibira djelovanje angiotenzina II na AT1 receptore. Kao nepeptidni antagonist, valsartan sprječava vazokonstrikcijske i aldosteronske učinke angiotenzina II, što rezultira smanjenjem sistemskoga vaskularnog otpora, snizivanjem vrijednosti AT-a te pružanjem zaštite ciljnih organa, uključujući srce, bubrege i krvne žile. Ova molekula omogućuje bolju kontrolu hipertenzije bez inhibicije enzima konvertaze angiotenzina (ACE), čime se izbjegavaju nuspojave poput kašlja i angioedema, koje su česte kod ACE inhibitora[5].

Farmakološki profil valsartana ističe se visokom selektivnošću za AT1 receptore, dok omogućuje da angiotenzin II zadrži učinak na AT2 receptore, što potencijalno pruža dodatne koristi poput vazodilatacije i regeneracije tkiva[5]. Njegovo dugotrajno djelovanje omogućuje učinkovitu kontrolu AT-a tijekom 24 sata, uz primjenu jednom na dan. Posebno je bitan učinak valsartana na jutarnji porast AT-a, koji je povezan s povećanim rizikom od infarkta miokarda i moždanog udara. Istraživanje Hermida *i sur.* pokazalo je da primjena valsartana u večernjim satima ne samo da učinkovito kontrolira AT tijekom dana nego znatno povećava omjer dnevno-noćnog pada tlaka, što dodatno smanjuje KV rizik[6].

Osim u snizivanju AT-a, valsartan pokazuje jedinstvena svojstva u smanjenju vaskularne inflamacije. Istraživanje *Val-MARC* otkrilo je znatno smanjenje razine visokoosjetljivog C-reaktivnog proteina u bolesnika liječenih visokim dozama valsartana, neovisno o njegovom učinku na AT, što dokazuje potencijal valsartana da inhibira vaskularnu upalu, a time i dodatno pridonosi smanjenju KV rizika[7].

Valsartan, osim KV zaštite, ima dokazane učinke na bubrežnu funkciju, osobito u smanjenju mikroalbuminurije. Istraživanje objavljeno 2002. godine u časopisu *Circulation* pokazalo je da valsartan znatno smanjuje izlučivanje albumina u urinu u hipertenzivnih bolesnika s dijabetesom, čime pridonosi usporivanju progresije bubrežne bolesti[8]. Slično istraživanje objavljeno 2007. godine istaknulo je superiornost valsartana u usporedbi s amlodipinom u smanjenju mikroalbuminurije u bolesnika s dijabetičkom nefropatijom, uz zadržavanje slične razine kontrole AT-a[9].

Istraživanja pokazuju da valsartan ima i povoljan učinak na neurokognitivne funkcije. Fogari *i sur.* pokazali su 2004. godine da valsartan poboljšava neurokognitivne sposobnosti u hipertenzivnih bolesnika, uključujući pažnju, pamćenje i brzinu procesuiranja informacija. Ovo je dodatna prednost u usporedbi s antihipertenzivnim lijekovima poput beta-blokatora, koji mogu nepovoljno utjecati na kognitivne funkcije[10].

Sigurnosni profil valsartana također je vrlo povoljan. U metaanalizi Bangalore *i sur.* iz 2016. godine, koja je uključivala 254 301 ispitanika, pokazano je da blokatori receptora angi-

burden of hypertension is associated with urbanization, unhealthy lifestyle and aging population[3].

One of the main challenges in managing hypertension is poor therapeutic adherence. Research shows that up to 53% of patients with resistant hypertension are non-adherent to treatment, and 30% of patients never take the prescribed medications[4]. This data highlights the value of simple therapeutic approaches, such as fixed combinations, which increase compliance and BP control[4].

Mechanism of action and effects of the valsartan

Valsartan is a drug belonging to the class of angiotensin II receptor blockers that selectively inhibits the action of angiotensin II on AT1 receptors. As a non-peptide antagonist, valsartan prevents the vasoconstrictive and aldosterone effects of angiotensin II, resulting in decreased systemic vascular resistance, lower BP, and target organ protection, including the heart, kidneys, and blood vessels. This molecule enables better hypertension control without inhibiting the angiotensin-converting enzyme (ACE), thereby avoiding adverse effects such as cough and angioedema, which are frequently associated with ACE inhibitors[5].

The pharmacological profile of valsartan has a distinctively high selectivity for AT1 receptors, while enabling angiotensin II to maintain its effect on AT2 receptors, which potentially provides additional benefits, such as vasodilation and tissue regeneration[5]. Its prolonged activity enables efficient 24-hour BP control with once-daily administration. The effect of valsartan on the morning BP surge is particularly important, since it is associated with an increased risk of AMI and stroke. A study conducted by Hermida *et al.* demonstrated that taking valsartan in the evening not only effectively controls BP during the day but also significantly increases the ratio of day-to-night BP dipping, further reducing CV risk[6].

Besides lowering BP, valsartan also demonstrates unique properties of decreasing vascular inflammation. The Val-MARC study found a significant decrease in the levels of high-sensitivity C-reactive protein in patients treated with high doses of valsartan, regardless of its effect on BP, demonstrating the potential of valsartan in inhibiting vascular inflammation, thereby further contributing to CV risk reduction[7].

In addition to CV protection, valsartan has proven effects on kidney function, especially in decreasing microalbuminuria. A study published in 2002 in Circulation showed that valsartan significantly reduces the urinary excretion of albumin in hypertensive patients with diabetes, thereby contributing to slowing kidney disease progression[8]. A similar randomized study published in 2007 highlighted the superiority of valsartan over amlodipine in decreasing microalbuminuria in patients with diabetic nephropathy, while maintaining similar levels of BP control[9].

Moreover, research also shows valsartan's beneficial effects on neurocognitive functions. A randomized study from 2004 conducted by Fogari *et al.* showed that valsartan improves neurocognitive abilities in hypertensive patients, including attention, memory and the speed of information processing. This is an additional advantage compared to antihypertensive agents such as beta-blockers, that may have unfavorable effects on cognitive functions[10].

Valsartan also has a very favorable safety profile. Studies such as the meta-analysis by Bangalore *et al.* from 2016, which included 254,301 patients, show that angiotensin II receptor blockers are equally effective as ACE inhibitors in controlling

otenzina II imaju jednaku učinkovitost kao ACE inhibitori u kontroli AT-a, ali uz mnogo manju učestalost nuspojava[11]. Nadalje, zaključci analize Messerli *i sur.* iz 2018. godine navode da, s obzirom na jednaku učinkovitost, ali manju učestalost nuspojava s blokatorima receptora angiotenzina II, trenutačno postoji malo, ako uopće ima ikakvih razloga za primjenu ACE inhibitora u liječenju hipertenzije[12].

Valsartan se uporabljuje ne samo za liječenje hipertenzije nego i za liječenje zatajivanja srca, prevenciju bubrežnih oštećenja te u postinfarktnim stanjima. Njegova svestranost i dokazana učinkovitost potvrđeni su u više od 60 velikih kliničkih istraživanja koja su uključivala više od 100 000 ispitanika, poput istraživanja *VALIANT, MARVAL* i *VALUE*[13]. Ta opsežna istraživanja svrstavaju valsartan među najistraživanije lijekove iz skupine blokatora receptora angiotenzina II na tržištu, s čvrstim znanstvenim dokazima koji podržavaju njegovu uporabu u svakodnevnoj kliničkoj praksi.

Indapamid – ni približno još samo jedan tiazidski diuretik

Indapamid je tiazidima sličan diuretik koji se ističe snažnim antihipertenzivnim djelovanjem i dodatnim koristima koje nadilaze učinke tradicionalnih diuretika poput hidroklorotiazida (HCTZ). Ovaj se lijek primjenjuje prije svega za liječenje hipertenzije, ali njegova metabolička neutralnost i učinci na vaskularnu funkciju čine ga osobito pogodnim za dugotrajnu terapiju, osobito u bolesnika s povećanim rizikom od metaboličkih poremećaja[13].

Indapamid djeluje inhibirajući reapsorpciju natrija i klorida u distalnom dijelu nefrona, čime potiče diurezu i smanjuje volumen plazme, što dovodi do snizivanja AT-a. Međutim, učinci indapamida nisu ograničeni samo na diurezu. Njegov učinak na vaskularni sustav uključuje relaksaciju glatkih mišića krvnih žila preko povećane dostupnosti dušikova oksida (NO) i smanjenja oksidativnoga stresa, što poboljšava vaskularnu funkciju i smanjuje arterijsku krutost. Ovakvi su učinci ključni za dugoročnu kontrolu hipertenzije i smanjenje KV rizika[14,15].

Farmakološka su istraživanja upozorila na važnost *slow release* (SR) formulacije indapamida, koja omogućuje stabilnu razinu lijeka u plazmi tijekom 24 sata. Ovo dugotrajno otpuštanje pridonosi ravnomjernom snizivanju AT-a tijekom dana i noći, uz smanjenu pojavu nuspojava poput naglog pada AT-a ili dehidracije. Sassard *i sur.* istaknuli su 2005. godine da SR formulacija indapamida ne samo da produljuje njegovo djelovanje nego dodatno povećava podnošljivost lijeka, što ga čini pogodnim za svakodnevnu uporabu u hipertenzivnih bolesnika[15].

Osim toga, dokazi sugeriraju da vrijeme primjene lijeka može dodatno utjecati na njegovu učinkovitost. Istraživanje Huangfu *i sur.* iz 2015. godine upozorilo je na to da večernje doziranje antihipertenzivnih lijekova, uključujući kombiniranu terapiju indapamidom, rezultira znatnim smanjenjem vrijednosti noćnoga tlaka, uz bolju kontrolu dnevno-noćnog pada AT-a. Ovakva strategija doziranja može dodatno smanjiti KV rizik, osobito u bolesnika s nedovoljno kontroliranim AT-om tijekom noći[16].

Klinička istraživanja potvrđuju superiornost indapamida u usporedbi HCTZ-om. Prema metaanalizi Rousha *i sur.*, indapamid je pokazao mnogo bolju učinkovitost u smanjenju sistoličkoga tlaka u usporedbi s HCTZ-om, s prosječnom redukcijom većom za 54 %. Ovakva razlika naglašava superiornost indapamida u postizanju optimalne kontrole AT-a, što ga čini preferiranim izborom u antihipertenzivnoj terapiji[17].

BP but have a significantly lower incidence of adverse effects.[11] Furthermore, the conclusions of the analysis by Messerli *et al.* from 2018 state that, considering the equal effectiveness and lower frequency of adverse effects with angiotensin II receptor blockers, there are currently few, if any, reasons to use ACE inhibitors in hypertension treatment[12].

In addition to hypertension treatment, valsartan is also used for heart failure treatment, kidney damage prevention and in post-myocardial infarction conditions. Its versatility and proven effectiveness have been confirmed in over 60 large-scale clinical trials with over 100,000 patients, such as VALIANT, MARVAL, and VALUE[13]. These comprehensive research studies make valsartan one of the most well-researched drugs in the class of angiotensin II receptor blockers on the market, with robust scientific evidence supporting its use in everyday clinical practice.

Indapamide – far more than just another thiazide diuretic

Indapamide is a thiazide-like diuretic distinguished by its strong antihypertensive activity and additional benefits that go beyond the effects of the traditional diuretics such as hydrochlorothiazide (HCTZ). This drug is used primarily to treat hypertension, but its metabolic neutrality and its effects on vascular function make it particularly suitable for long-term therapy, especially in patients under increased risk of metabolic disorders[13].

Indapamide works by inhibiting sodium and chloride reabsorption in the distal part of nephrons, encouraging diuresis and reducing plasma volume, which then leads to BP decrease. However, the effects of indapamide are not limited to diuresis. Its effect on the vascular system includes the relaxation of smooth muscles in blood vessels through increased availability of nitrogen oxide (NO) and reduction of oxidative stress, which in turn improves vascular function and reduces arterial stiffness. These effects are crucial for the long-term control of hypertension and CV risk reduction[14,15].

Pharmacological studies have indicated the importance of the slow-release (SR) formulation of indapamide, which provides stable 24-hour plasma levels of the drug. This prolonged release contributes to steady BP lowering during both daytime and nighttime, with reduced occurrence of adverse effects such as sudden drops in BP or dehydration. In their literature overview from 2005, Sassard *et al.* emphasize that the SR formulation of indapamide not only prolongs its action but also additionally increases the tolerability of the drug, making it suitable for daily use in hypertensive patients[15].

In addition, evidence suggests that the timing of drug administration can have an additional impact on its effectiveness. A research study by Huangfu *et al.* from 2015 indicated that evening dosing of antihypertensive drugs, including combination therapy with indapamide, results in a significant decrease in nocturnal BP, with better control over day-to-night BP dipping. This dosing strategy can additionally reduce CV risk, especially in patients with inadequately controlled BP at night[16].

Clinical trials confirm indapamide's superiority versus HCTZ. According to a meta-analysis conducted by Roush *et al.*, indapamide demonstrated significantly better efficacy in reducing systolic pressure compared to HCTZ, with a 54% higher average reduction. This difference highlights the supe-

Indapamid ima dokazano povoljan utjecaj na remodelaciju miokarda. Istraživanje LIVE (engl. *Left Ventricular Hypertrophy Indapamide Versus Enalapril*) pokazalo je da je indapamid bio učinkovitiji od ACE inhibitora enalaprila u redukciji hipertrofije lijeve klijetke u bolesnika s hipertenzijom. Ovo je posebno važno jer su ACE inhibitori poznati po svojemu povoljnom učinku na remodelaciju miokarda. Ovakvi rezultati dodatno potvrđuju jedinstvenu ulogu indapamida u KV zaštiti, osobito u bolesnika s hipertrofijom lijeve klijetke[18].

Za razliku od HCTZ-a, indapamid ima dokazano povoljan utjecaj na KV ishode. Istraživanje *HYVET* (engl. *Hypertension in the Very Elderly Trial*) upozorilo je na znatno smanjenje KV smrtnosti i incidencije moždanog udara u starijih bolesnika s hipertenzijom koji su liječeni indapamidom. Ovakvi rezultati dodatno potvrđuju ulogu indapamida kao lijeka koji ne samo da snizuje AT već pruža i širu KV zaštitu[19]. S obzirom na sve navedeno, stručne analize objavljene literature, a i stručne smjernice, uključujući Europske smjernice za liječenje hipertenzije, daju jasnu prednost indapamidu u odnosu prema HCTZ-u[20,21].

Zaključak

Kombinacija valsartana i indapamida iznimno je potentna i racionalna opcija u liječenju arterijske hipertenzije, koja obuhvaća ključne mehanizme u regulaciji AT-a te pruža dodatne koristi za KV i bubrežno zdravlje.

Valsartan je dokazano učinkovit antihipertenziv koji nudi sve prednosti inhibicije renin-angiotenzinskog sustava usporedive s ACE inhibitorima, ali uz bolju podnošljivost i mnogo manji rizik od nuspojava poput kašlja i angioedema. U praksi nema jasnog razloga zašto bi se ACE inhibitori i dalje preferirali u liječenju hipertenzije, osobito s obzirom na veću zastupljenost sartana na tržištima u Europi u usporedbi s Hrvatskom. U bolesnika sklonih kašlju, uključujući pušače, osobe s astmom, alergijama ili gastroezofagealnom refluksnom bolesti, valsartan bi trebao biti lijek izbora.

Indapamid, kao tiazidima sličan diuretik, nadmašuje HCTZ u antihipertenzivnoj učinkovitosti, sigurnosnom profilu i farmakokinetskim svojstvima. Osim toga što snizuje AT, indapamid ima povoljan učinak na remodelaciju lijeve klijetke, što je osobito bitno u bolesnika s hipertenzijom i hipertrofijom lijeve klijetke. Formulacija s postupnim otpuštanjem indapamida omogućuje dugotrajnu stabilnu koncentraciju lijeka u plazmi uz primjenu jednom na dan, čime se dodatno povećava suradljivost bolesnika.

Primjena kombinacije valsartana i indapamida u večernjem doziranju posebno je korisna u bolesnika s poremećenom dnevno-noćnom varijabilnošću AT-a, jer može pomoći u uspostavljanju normalne krivulje noćnog pada tlaka i smanjenju KV rizika.

Europske smjernice ističu važnost započinjanja antihipertenzivnog liječenja kombinacijom dvaju lijekova, a posebnu pažnju posvećuju suradljivosti bolesnika. S obzirom na to da je adherencija glavni izazov u kontroli AT-a, preporučuje se primjena fiksnih kombinacija lijekova s manjim rizikom od nuspojava, poput valsartana i indapamida. Ta kombinacija pruža optimalnu kontrolu AT-a uz minimalan rizik, čime se povećava vjerojatnost postizanja ciljeva liječenja i dugoročne zaštite bolesnika, te idealno odgovara suvremenim zahtjevima personalizirane medicine, s naglaskom na učinkovitost, sigurnost i prihvaćanje liječenja.

riority of indapamide in achieving optimal BP control, making it a preferred choice in antihypertensive therapy[17].

Indapamide has a proven favorable effect on myocardial remodeling. The LIVE study (Left Ventricular Hypertrophy Indapamide Versus Enalapril) demonstrated that indapamide was more effective than the ACE inhibitor enalapril in reducing left ventricular hypertrophy in hypertensive patients. This is particularly significant because ACE inhibitors are known for their beneficial effects on myocardial remodeling. These results further confirm the unique role of indapamide in CV protection, especially in patients with left ventricular hypertrophy[18].

Unlike HCTZ, indapamide has a proven favorable impact on CV outcomes. The HYVET study (Hypertension in the Very Elderly Trial) demonstrated a significant reduction in CV mortality and stroke incidence in elderly patients with hypertension treated with indapamide. These results additionally confirm the role of indapamide as s drug that not only lowers BP but also provides broader CV protection[19]. Considering all of the above, both expert analyses of the published literature and professional guidelines, including the European hypertension treatment guidelines, clearly prefer indapamide over HCTZ[20,21].

Conclusion

The combination of valsartan and indapamide represents an exceptionally potent and rational option in arterial hypertension treatment, encompassing key mechanisms of BP regulation and providing additional benefits for CV and renal health.

Valsartan is a proven effective antihypertensive drug that offers all the advantages of renin-angiotensin system inhibition comparable to ACE inhibitors, but with better tolerability and significantly lower risk of adverse effects such as cough and angioedema. In practice, there is no clear reason to continue giving preference to ACE inhibitors in hypertension treatment, especially considering the larger presence of sartans in European markets compared to Croatia. In patients prone to cough, including smokers, people with asthma, allergies or gastroesophageal reflux disease, valsartan could be the drug of choice.

Indapamide, as a thiazide-like diuretic, surpasses HCTZ in its antihypertensive effectiveness, safety profile, and pharmacokinetic properties. In addition to lowering BP, indapamide has a favorable effect on left ventricular remodeling, which is especially significant in hypertensive patients with left ventricular hypertrophy. The formulation of indapamide with gradual release enables long-lasting stable plasma concentrations of the drug with once-daily dosage, further improving patient compliance.

The combination of valsartan and indapamide administered in the evening is particularly useful in patients with impaired day-to-night variability BP (non-dippers), because it can help establish a normal curve of nocturnal BP drop and reduce CV risk.

The European guidelines emphasize the importance of starting antihypertensive treatment with a dual combination, with s special focus on patient compliance. Considering that adherence is the main challenge in BP control, it is recommended to use fixed combinations of drugs with a lower risk of adverse effects, such as valsartan and indapamide. This combination provides optimal BP control with minimal risk, increasing the probability of achieving treatment goals and long-lasting patient protection, while also being ideally aligned with the modern requirements of personalized medicine, with a focus on effectiveness, safety, and patient acceptance of therapy.

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