# Kontrola arterijske hipertenzije u muškaraca i žena: uloga liječenja fiksnim kombinacijama lijekova na bazi perindoprila u jednoj tableti

# Hypertension Control in Men and Women: The Role of Perindopril-based Single-pill Combination Treatment

**Jana Brguljan-Hitij[1]*, Zbigniew Gaciong[2], Dragan Simić[3], Peter Vajer[4], Parounak Zelveian[5], Irina E. Chazova[6], Bojan Jelaković[7] on behalf of PRECIOUS trial investigators**

[1]University Medical Centre Ljubljana, Medical University Ljubljana, Ljubljana, Slovenia
[2]University Clinical Center of the Medical University of Warsaw, Warsaw, Poland
[3]Clinical Center of Serbia and University of Belgrade, Faculty of Medicine, Belgrade, Serbia
[4]Semmelweis University Budapest, Budapest, Hungary
[5]Center of Preventive Cardiology, Research Institute of Cardiology, Yerevan, Armenia
[6]Federal State Budgetary Institution National Research Medical Center for Cardiology of the Ministry of Health, Moscow, Russian Federation
[7]University Hospital Centre Zagreb, Zagreb, Croatia

**RECEIVED:**
**April 23, 2025**
**UPDATED:**
**July 14, 2025**
**ACCEPTED:**
**August 4, 2025**

**SAŽETAK:** Kontrola arterijskoga tlaka (AT) primarni je klinički cilj zbrinjavanja bolesnika s arterijskom hipertenzijom (AH). U Hrvatskoj samo 20 % bolesnika s AH-om uspijeva postići kontrolu AT-a, pri čemu postoji nejednakost između muškaraca (15 %) i žena (25 %). Ovom je problemu posvećena pozornost u nedavnim raspravama i istraživanjima, u kojima je fokus bio na razlikama u kontroli AT-a s obzirom na spol. Ispitivanje PRECIOUS dizajnirano je radi procjene odgovora hipertenzivnih muškaraca i žena na liječenje dvojnim i trojnim fiksnim kombinacijama u jednoj tableti: perindopril i amlodipin, odnosno perindopril, indapamid i amlodipin. Rezultati upućuju na to da početak antihipertenzivnog liječenja u bolesnika s novodijagnosticiranom AH-om ili intenzifikacija liječenja u nekontroliranih bolesnika (dvojnim ili trojnim) fiksnim kombinacijama na bazi perindoprila dovodi do učinkovitog smanjenja AT-a i u muškaraca i u žena, uz veće apsolutno smanjenje u žena. Nakon 16 tjedana 75 % muškaraca i 87 % žena postiglo je kontrolu AT-a mjerenim u ordinaciji. Ispitivanje je također pokazalo znatna smanjenja u 24-satnom AT-u i centralnome sistoličkom tlaku. Ukupno 68 % muškaraca te 76 % žena postiglo je ciljni 24-satni sistolički tlak, dok je 68 % muškaraca i 73 % žena postiglo kontrolu centralnoga sistoličkog tlaka. Neovisno o parametru, žene su postigle bolju kontrolu AT-a nego muškarci. Ova saznanja upućuju na djelotvornost i sigurnost fiksnih kombinacija na bazi perindoprila u obaju spolova, uz primjetne razlike u odgovoru AT-a na terapiju.

**SUMMARY:** Blood pressure (BP) control is a primary clinical objective in managing patients with hypertension. In Croatia, only 20% of patients with hypertension achieve BP control, with a disparity between men (15%) and women (25%). To address this issue, recent discussions and investigations have focused on sex-related differences in BP control. The PRECIOUS trial was designed to evaluate the treatment response to dual and triple single-pill combinations (SPCs) of perindopril/amlodipine and perindopril/amlodipine/indapamide in men and women with hypertension. The results indicate that initiating antihypertensive treatment in newly-diagnosed patients or intensifying treatment in uncontrolled patients with perindopril-based SPCs (dual and triple) leads to effective BP reduction in both men and women, with higher absolute reduction in women. After 16 weeks, 75% of men and 87% of women achieved office BP control. The trial also demonstrated significant reductions in 24-hour BP and central systolic BP (cSBP). A total of 68% of men and 76% of women achieved the target 24-hour systolic BP, while 68% of men and 73% of women attained cSBP control. Regardless of the examined parameter, women achieved better BP control than men. The findings highlight the efficacy and safety of perindopril-based SPCs in both sexes, with notable sex differences in BP response.

**KLJUČNE RIJEČI:** kardiovaskularne bolesti, arterijska hipertenzija, arterijski tlak, fiksna kombinacija, perindopril.

**KEYWORDS:** cardiovascular diseases, arterial hypertension, blood pressure single-pill combination, perindopril.

**CITATION:** Cardiol Croat. 2025;20(7-8):204-9. | https://doi.org/10.15836/ccar2025.204

***ADDRESS FOR CORRESPONDENCE**: Jana Brguljan Hitij, University Medical Centre Ljubljana, Department of Hypertension, Medical University Ljubljana, Vodnikova 62, Ljubljana 1000, Slovenia. / Phone: +38615225462 / E-mail: jana.brguljan-hitij@guest.arnes.si

**ORCID:** Jana Brguljan-Hitij, https://orcid.org/0000-0002-9484-7274 • Zbigniew Gaciong, https://orcid.org/0000-0002-6666-3734 Dragan Simić, https://orcid.org/0000-0003-4031-3573 • Peter Vajer, https://orcid.org/0000-0002-3393-135X Parounak Zelveian, https://orcid.org/0000-0002-6513-6772 • Irina E. Chazova, https://orcid.org/0000-0002-9822-4357 Bojan Jelaković, https://orcid.org/0000-0002-2546-4632

**TO CITE THIS ARTICLE:** Brguljan-Hitij J, Gaciong Z, Simić D, Vajer P, Zelveian P, Chazova IE, et al. Hypertension Control in Men and Women: The Role of Perindopril-based Single-pill Combination Treatment. Cardiol Croat. 2025;20(7-8):204-9.| https://doi.org/10.15836/ccar2025.204

**TO LINK TO THIS ARTICLE:** https://doi.org/10.15836/ccar2025.204

## Uvod

Kardiovaskularne bolesti (KVB) glavni su uzrok smrti općenito, a danas to čak u većoj mjeri vri-

## Introduction

Cardiovascular diseases (CVDs) are the predominant cause of death globally, and are today at an

jedi u žena u usporedbi s muškarcima[1]. Hrvatska slijedi sličan obrazac, tako da su KVB-i već desetljećima vodeći uzrok smrtnosti. Prema podatcima objavljenima 2021. godine, 23 184 osobe u Hrvatskoj umrle su od KVB-a, što čini 37 % svih umrlih. Analiza s obzirom na spolu pokazuje da je to uzrok smrti u 41,8 % žena i 32 % muškaraca.[2]

Unatoč tomu što je arterijska hipertenzija (AH) značajan promjenjiv čimbenik rizika koji pridonosi ovakvom visokom opterećenju KVB-om[3] u Hrvatskoj, gotovo polovica (48 %) odraslih osoba u dobi između 30 i 79 godina ima AH, pri čemu je prevalencija viša među muškarcima (51 %) nego među ženama (45 %). Među oboljelima 75 % njih ima dijagnozu AH-a, no samo 54 % prima terapiju. Učinkovita kontrola arterijskoga tlaka (AT) postiže se samo u 20 % bolesnika s AH-om.[4]

Sa svrhom poboljšanja trenutačne situacije s kontrolom AT-a, u posljednje se vrijeme temeljito raspravlja i istražuje o razlikama s obzirom na spol.[5] Obje skupine europskih smjernica za zbrinjavanje AH-a (Smjernice Europskoga društva za hipertenziju iz 2023. za zbrinjavanje arterijske hipertenzije i Smjernice Europskoga kardiološkog društva iz 2024. za zbrinjavanje povišenoga arterijskog tlaka i hipertenzije) govore o razlikama s obzirom na spol u nizu aspekata, od epidemiologije i patofiziologije do oštećenja organa posredovanog hipertenzijom (HMOD), antihipertenzivnog liječenja, ciljnih vrijednosti AT-a te kardiovaskularnih (KV) ishoda.[6,7]

Međutim, zbog manjka podataka specifičnih za spol, smjernice preporučuju primjenu kombinacijske terapije u većine bolesnika s hipertenzijom, i u muškaraca i u žena. Preferirani oblik u bilo kojem koraku liječenja jest fiksna kombinacija lijekova u jednoj tableti jer ona bolesnicima omogućuje da ostanu na jednostavnom režimu liječenja, cijelo vrijeme sa samo jednom tabletom, čime se povećava vjerojatnost adherencije za terapiju i napretka k boljoj kontroli AT-a.[6] Očekuje se da će takav pristup bitno povećati kontrolu nad AT-om s trenutačno niskih razina u Hrvatskoj (15 % u muškaraca te 25 % u žena)[4] na približno 60 % s terapijom dvojnom kombinacijom te čak 90 % s trojnom kombinacijom u jednoj tableti.[6]

Zasad se zna da postoje važne razlike između spolova, u rasponu od interakcije AT-a s KV rizicima i komorbiditetima, patofiziološkog mehanizma koji regulira AT, razvoja AT-a tijekom života, razvoja AH, HMOD-a koje se odnosi na srce i arterije, utjecaja incidentnih KVB-a te razlika u učinku antihipertenzivnog liječenja.[5] Osim navedenog, poznate su i razlike s obzirom na spol u propisivanju različitih skupina antihipertenziva, pri čemu se ženama češće propisuju diuretici, a muškarcima inhibitori angiotenzin-konvertaze (ACEi) i blokatori kalcijevih kanala (CCB-i).[5,8,9] Općenito govoreći, broj antihipertenziva koji se propisuje za oba spola je sličan (2 u žena i 2,1 u muškaraca).[9]

## Rezultati kliničkog ispitivanja s fiksnim kombinacijama lijekova u jednoj tableti (kliničko ispitivanje PRECIOUS)

Kliničko ispitivanje PRECIOUS dizajnirano je tako da ispituje odgovor na liječenje u muškaraca i žena liječenih dvojnim i trojnim fiksnim kombinacijama lijekova u jednoj tableti (perindopril/amlodipin i perindopril/indapamid/amlodipin), pri čemu je ispitivana konvencionalna mjera djelotvornosti liječenja, kao što je kontrola nad AT-om.[10]

Ovo 16 tjedana dugo intervencijsko, otvoreno, prospektivno, multicentrično kliničko ispitivanje uključivalo je 440 odraslih ljudi s esencijalnom AH-om. Provodilo se u sedam zemalja, uključujući Hrvatsku, iz koje su bila uključena 53 bo-

even higher level in women in comparison with men[1]. Croatia follows a similar pattern, with CVDs being the leading cause of mortality for decades. According to published data for 2021, 23 184 people in Croatia died from CVDs, which accounts for 37% of all deaths. Analysis by sex shows that CVDs were the cause of death in 41.8% of women and in 32.0% of men.[2]

Despite hypertension being a significant modifiable risk factor contributing to this high CVD burden[3] in Croatia, nearly half (48%) of adults aged 30 to 79 years have hypertension, with the prevalence being higher among men (51%) than women (45%). Among those affected, 75% have been diagnosed with arterial hypertension (AH), yet only 54% were receiving treatment. Effective blood pressure (BP) control was achieved only in 20% of patients with hypertension.[4]

Sex-related differences have recently been more thoroughly discussed and investigated, with the goal of improving the current situation of BP control.[5] Both European guidelines for the management of AH (the 2023 ESH Guidelines for the management of arterial hypertension and the 2024 ESC Guidelines for the management of elevated blood pressure and hypertension) discuss sex differences across a range of aspects, from epidemiology and pathophysiology to hypertension-mediated organ damage (HMOD), antihypertensive treatment, target BP values, and cardiovascular (CV) outcomes.[6,7]

However, due to lack of sex-specific data, the guidelines recommend the use of combination therapy in most patients with hypertension, both men and women. Single-pill combinations (SPCs) are the preferred form of therapy at all treatment steps, as this enables patients to remain on a simple treatment regimen with a single pill throughout the treatment, thus increasing the likelihood of adherence to therapy and progressing to better BP control.[6] Such an approach is expected to markedly increase BP control from the current low levels in Croatia (15% in men and 25% in women)[4] to approximately 60% with the use of dual combination therapy and even 90% with triple combination therapy.[6]

Currently, it is known that important sex differences exist, ranging from the interaction of BP with CV risks and comorbidities, the pathophysiological mechanism regulating BP, development of BP over the course of a patient's life, development of AH, HMOD in the heart and the arteries, impact on incident CVDs, and differences in the effect of antihypertensive treatment.[5] In addition to the above, there are known sex differences in prescription of different classes of antihypertensives, with women more often being prescribed diuretics and men more often receiving angiotensin converting-enzyme inhibitors (ACEi) and calcium channel blockers (CCBs).[5,8,9] In general, both sexes are prescribed a comparable number of antihypertensives (2 in women and 2.1 in men).[9]

## Clinical Trial Results With Single-Pill Combinations (Precious Clinical Trial)

The PRECIOUS clinical trial was designed to assess the treatment response in men and women to perindopril/amlodipine and perindopril/amlodipine/indapamide dual and triple SPCs by evaluating a conventional measure of treatment efficacy such as BP control.[10]

This 16-week interventional, open-label, prospective, international, multicenter clinical trial assessed 440 adults with essential hypertension. It was conducted in seven countries,

lesnika. Klinički rezultati nisu procjenjivani zasebno za svaku zemlju.[11,12] Analiza razlika s obzirom na spol i dob provedena je za 399 bolesnika: 254 muškarca i 145 žena u dobi od 35 do 74 godine. Isključeni su bolesnici mlađi od 35 te stariji od 74 godine jer njihov broj nije bio dovoljan za usporedbu.[10]

Pri uključenju, prethodno neliječeni bolesnici ili bolesnici čiji AT nije bio kontroliran na prethodnoj monoterapiji ili dvojnoj terapiji koja nije uključivala perindopril ni amlodipin svrstani su u skupinu koja je primala dvojnu fiksnu kombinaciju s početnom dozom od 4/5 mg perindoprila/amlodipina (P/A). Bolesnici čiji AT nije bio kontroliran na prethodnoj dvojnoj ili trojnoj terapiji svrstani su u skupinu koja je primala trojnu fiksnu kombinaciju s početnom dozom od 4/5/1,25 mg perindoprila/indapamida/amlodipina (P/I/A) **(slika 1)**. Ako nije postignuta kontrola AT-a mjerenog u ordinaciji, početna je doza titrirana u intervalima od 4 tjedna na 8/5 mg, 8/10 mg P/A ili 8/2,5/10 mg P/I/A u skupini na dvojnoj fiksnoj kombinaciji, odnosno na 8/2,5/5 mg ili 8/2,5/10 mg P/A/I u skupini na trojnoj fiksnoj kombinaciji. Ordinacijski AT mjerili su kvalificirani zdravstveni djelatnici validiranim automatiziranim tlakomjerom, u skladu s protokolom u Smjernicama ESH-a. Dvadesetčetirisatno mjerenje AT-a (ABPM) provedeno je na početku i na kraju kliničkog ispitivanja (Mobilograph PWA).

Za samo 4 tjedna zabilježeno je znatno smanjenje AT-a mjerenog u ordinaciji (–16,1/–10,1 mmHg) u odnosu prema srednjoj početnoj vrijednosti.[11] Do kraja ispitivanja (nakon 16 tjedana) srednja vrijednost AT-a mjerenog u ordinaciji smanjila se u skupini na dvojnoj fiksnoj kombinaciji sa 156,3 ± 10,9/98,6 ± 8 mmHg na 128,4 ± 9,4/81,7 ± 7,2 mmHg, a u skupini na trojnoj fiksnoj kombinaciji sa 157,9 ± 12,6/97,5 ± 9,5 mmHg na 127,7 ± 11,4/80,3 ± 7,5 mmHg (za 16 tjedana) **(slika 2)**.[12] Apsolutna smanjenja sistoličkog tlaka (ST) mjerenog u ordinaciji i smanjenja dijastoličkoga tlaka (DT) bila su veća u žena u svim dobnim skupinama. Međutim, razlike između spolova nisu bile statistički značajne.[10] Udio bolesnika koji su postizali kontrolu nad AT-om rastao je pri svakom posjetu.[11] Na kraju ispitivanja (nakon 16 tjedana) 75 % muškaraca i 87 % žena postiglo je

including Croatia, from which 53 patients were recruited. The clinical results were not evaluated separately for each country.[11,12] Analysis of sex- and age-related differences was conducted for 399 patients: 254 men and 145 women aged 35-74 years. Patients under 35 and over 74 were excluded due to insufficient numbers for comparison.[10]

At inclusion, naïve or patients uncontrolled on previous mono or dual therapy other than perindopril and amlodipine were assigned to the dual SPC arm with an initial dose of 4/5 mg perindopril/amlodipine (P/A). Patients uncontrolled on previous dual or triple therapy were assigned to the triple SPC arm with an initial dose of 4/5/1.25 mg perindopril/amlodipine/indapamide (P/A/I) (**Figure 1**). If office BP control was not achieved, the initial dose was up-titrated in 4-week intervals to 8/5 mg, 8/10 mg P/A, or 8/10/2.5 mg P/A/I in the dual SPC arm and to 8/5/2.5 mg or 8/10/2.5 mg P/A/I in the triple SPC arm. Office BP was measured with a validated automated BP-measuring device by qualified health professionals following the ESH guidelines protocol. Ambulatory blood pressure measurement (ABPM) was performed at baseline and at the end of the trial (Mobilograph PWA).

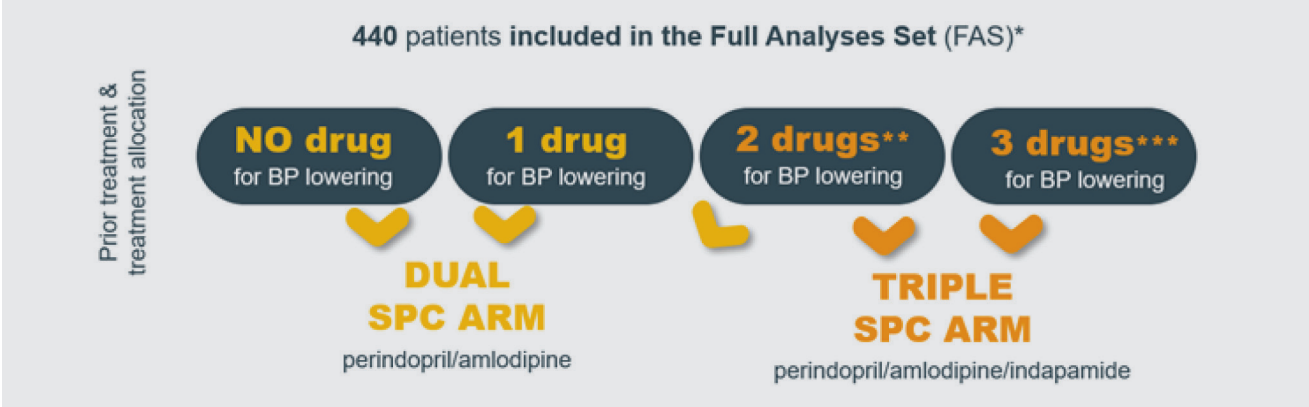


**FIGURE 1. Study treatment design.**
***All 440 patients included in full analysis set (FAS) were allocated to either the dual single-pill combination (SPC) arm or the triple SPC arm.**
****Patients previously treated with two antihypertensive medications were allocated at a 1 : 1 : 1 ratio to either the dual or the triple SPC arm, with the exception of patients previously treated with perindopril and amlodipine who were allocated to the triple SPC arm.**
*****Patients previously treated with three antihypertensive medications other than perindopril, indapamide, and amlodipine.**

After only 4 weeks, a significant decrease in office BP was observed (-16.1/-10.1 mmHg) from the mean baseline.[11] By the end of the study (after 16 weeks), mean office BP in the dual SPC arm decreased from 156.3±10.9/98.6±8 mmHg to 128.4±9.4/81.7±7.2 mmHg, and decreased in the triple SPC arm from 157.9±12.6/97.5±9.5 mmHg to 127.7±11.4/80.3±7.5 mmHg (in 16 weeks) (**Figure 2**).[12] Absolute office systolic blood pressure (SBP) and diastolic blood pressure (DBP) reductions were higher in women in all age groups. However, sex differences were not statistically significant.[10] The proportion of patients reaching BP control increased with each visit.[11] At the end of the trial (after 16 weeks) 75% of men and 87% of women achieved office BP control with the SPC treatment strategy (**Figure 3**).[10]

After 16 weeks, an average 24 h SBP decrease was observed in the dual SPC arm, from 142.9±9.6 mmHg to 125.0±9.8 mmHg,


**FIGURE 2. Blood pressure reductions after 16 weeks (visit 2) in the dual and triple single-pill combination (SPC) arms.**
**SPB (systolic blood pressure), cSBP (central systolic blood pressure)**

kontrolu AT-a mjerenog u ordinaciji slijedeći strategiju liječenja fiksnom kombinacijom **(slika 3)**.[10]

Za 16 tjedana zabilježeno je prosječno smanjenje vrijednosti 24-satnog ST-a u skupini na dvojnoj fiksnoj kombinaciji sa 142,9 ± 9,6 mmHg na 125,0 ± 9,8 mmHg, a u skupini na trojnoj fiksnoj kombinaciji sa 147,3 ± 11,8 mmHg na 124,3 ± 10,2 **(slika 2)**.[12] Slično kao i s AT-om mjerenim u ordinaciji, apsolutno smanjenje 24-satnog AT-a bilo je veće u žena, no razlike između spolova nisu bile statistički značajne. Ukupno 68 % muškaraca i 76 % žena postiglo je ciljne vrijednosti 24-satnog

whereas a decreased was observed in the triple SPC arm from 147.3.9±11.8 mmHg to 124.3±10.2 (**Figure 2**).[12] Similarly to office BP, the absolute reductions in 24 h BP were higher in women, but the sex differences were not statistically significant. In total, 68% of men and 76% of women achieved target 24 h SBP. BP control rates were higher for office BP than for 24 h SBP in both sexes, due to the lower rate of success for 24 h DBP (**Figure 3**).[10]

The PRECIOUS clinical trial also reported results on central systolic blood pressure (cSBP), a relevant prognostic risk fac-

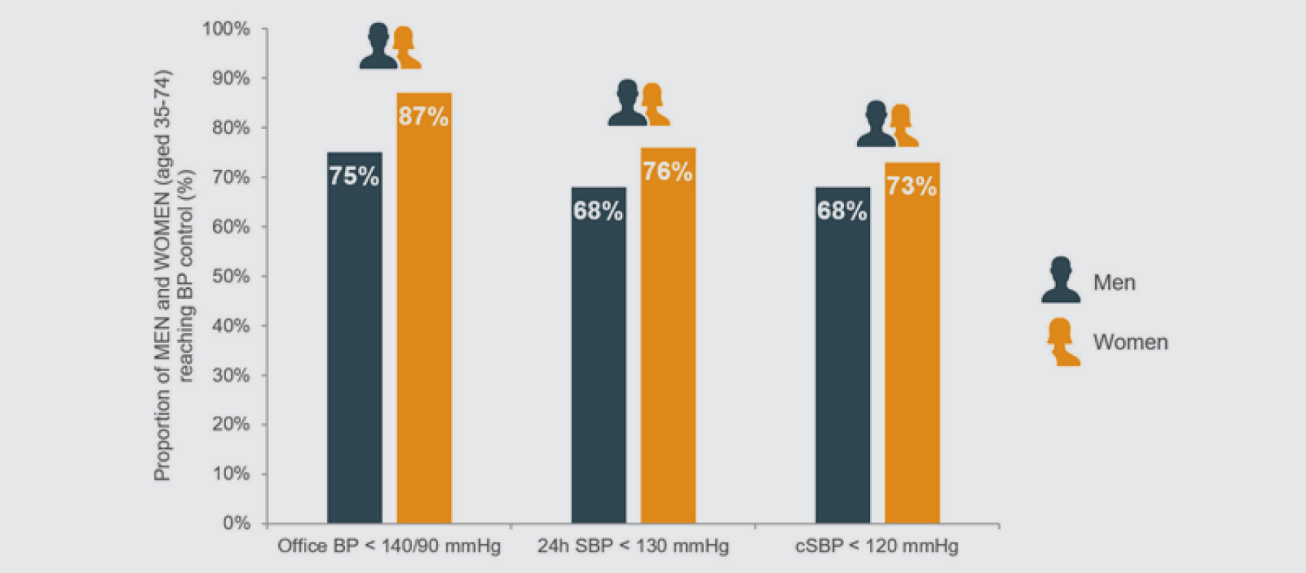


**FIGURE 3. Proportion of men and women achieving blood pressure (BP) control in 16 weeks.**
**cSBP (central systolic blood pressure)**

ST-a. Stope kontrole AT-a bile su više za AT mjeren u ordinaciji nego za 24-satni ST za oba spola zbog slabijeg postizanja 24-satnog DT-a **(slika 3)**.[10]

Kliničko ispitivanje PRECIOUS također je dalo rezultate i za centralni sistolički tlak (cST), važan prognostički čimbenik rizika, za koji nedostaju podatci o kontroli s pomoću fiksnih kombinacija. Za 16 tjedana prosječni cST smanjio se sa 132,1 ± 9,4 mmHg na 115,4 ± 8,9 mmHg za dvojnu fiksnu kombinaciju te sa 135,8 ± 11,1 mmHg na 114,7 ± 9,8 mmHg u skupini na trojnoj fiksnoj kombinaciji. Sva smanjenja AT-a bila su statistički značajna (p < 0,001) **(slika 2)**.[12] Smanjenje vrijednosti cST-a na manje od 120 mmHg postignuto je u 68 % muškaraca te u 73 % žena **(slika 3)**.[10]

## Rasprava

Kontrola AT-a ostaje glavni klinički cilj zbrinjavanja bolesnika s AH-om.[6] Unatoč različitim dostupnim strategijama liječenja, trenutačno manje od četvrtine bolesnika u Hrvatskoj koji se liječe od AH-a uspijeva postići adekvatnu kontrolu AT-a.[2] Učinkovito zbrinjavanje AT-a ključno je za smanjenje rizika od KV događaja i za poboljšanje sveukupnog KV zdravlja u muškaraca i žena.[6]

Rezultati ispitivanja PRECIOUS pokazuju da strategije liječenja na bazi perindoprila – dvojna fiksna kombinacija (perindopril/amlodipin) i trojna fiksna kombinacija (perindopril/amlodipin/indapamid) – rezultiraju učinkovitim smanjenjem AT-a mjerenog u ordinaciji, što dovodi do visokih stopa postizanja ciljnih razina AT-a mjerenog u ordinaciji u muškaraca i žena nakon četiri mjeseca liječenja.

Još jedan važan fokus u ispitivanju PRECIOUS bila je procjena djelotvornosti ispitivanih lijekova u snizivanju 24-satnog AT-a. Dvadesetčetirisatno mjerenje AT-a vrijedan je dodatak rezultatima mjerenja AT-a u ordinaciji kako bi se ispitala djelotvornost strategija za antihipertenzivno liječenje.[6] U ispitivanju PRECIOUS nakon četiri mjeseca aktivnog liječenja zabilježena su statistički značajna i klinički značajna smanjenja 24-satnog AT-a, što je dovelo do visokih stopa kontrole 24-satnog ST-a u obaju spolova.

Povoljne ishode postizanja ciljnih razina i smanjenja vrijednosti AT-a mjerenog u ordinaciji te 24-satnog AT-a dodatno su potkrijepila klinički znatna smanjenja 24-satnog cST-a zabilježena u ovom ispitivanju. Ispitivanja su pokazala da je u bolesnika s AH-om centralni tlak patofiziološki bitniji nego brahijalni tlak jer je cSKT jače povezan s oštećenjem organa posredovanim hipertenzijom i bolji je prediktor KV događaja. Međutim, i dalje nedostaju važni podatci o ishodima povezanima sa životom. Antihipertenzivni lijekovi pokazuju različite učinke na centralni i brahijalni tlak.[13] Ispitivanje PRECIOUS pokazalo je da je cST statistički značajno smanjen na <120 mmHg. Visok postotak bolesnika postiže kontrolu cST-a, što potvrđuje koristi od liječenja fiksnim kombinacijama na bazi perindoprila za snizivanje AT-a.

Sveukupno smanjenje AT-a bilo je veće i brže u žena, a posebice u mlađih žena u usporedbi s muškarcima iste dobi. Razlog tomu mogao bi biti to što u žena različiti fiziološki mehanizmi imaju brži odgovor na odabrane antihipertenzive ili na regulaciju AT-a.[14] Neovisno o vrsti izmjerenog tlaka (AT mjeren u ordinaciji, 24-satni AT, centralni tlak), žene su postizale bolju sveukupnu kontrolu AT-a. Slično tomu, ispitivanje IDEAL, koje je uključivalo 122 prethodno neliječena bo-

tor, for which data about control with SPC were lacking. After 16 weeks, the average cSBP decreased from 132.1±9.4 mmHg to 115.4±8.9 mmHg in the dual SPC arm and from 135.8±11.1 mmHg to 114.7±9.8 mmHg in the triple SPC arm. All BP reductions were statistically significant (p < 0.001) (**Figure 2**).[12] A reduction of cSBP below 120 mmHg was achieved by 68% of men and 73% of women (**Figure 3**).[10]

## Discussion

BP control remains the main clinical goal in the management of patients with hypertension.[6] Currently, despite various available treatment strategies, fewer than ¼ of patients treated for hypertension in Croatia achieve adequate BP control.[2] Effective BP management is essential for reducing the risk of cardiovascular events and improving overall CV health in both men and women.[6]

The results of the PRECIOUS trial demonstrate that the perindopril-based treatment strategies – dual SPC (perindopril/amlodipine) and triple SPC (perindopril/amlodipine/indapamide) – result in effective reduction of office BP, leading to high rates of office BP target achievement in men and women after four months of treatment.

Another important focus of the PRECIOUS trial was the assessment of the efficacy of the studied medications in lowering 24 h BP. ABPM constitutes a valuable supplement to office BP results in the assessment of the efficacy of antihypertensive treatments strategies.[6] In the PRECIOUS trial, statistically significant as well as clinically meaningful reductions in 24 h BP were observed after four months of active treatment, leading to high rates of 24 h SBP control in both sexes.

Favorable outcomes in office BP and 24 h BP target achievement and reductions were further supported by the clinically significant decrease in 24 h cSBP observed in this trial. Previous studies have demonstrated that central BP in patients with hypertension is pathophysiologically more relevant than brachial BP, as cSBP is more strongly associated with HMOD and is a better predictor of CV events. However, relevant data on life outcomes are still missing. Antihypertensive drugs exhibit differential effects on central and brachial BP.[13] The PRECIOUS trial demonstrated that cSBP statistically significantly decreased to <120 mmHg. A high percentage of patients achieved cSBP control, confirming the BP-lowering benefits of perindopril-based SPC treatment.

Overall BP reduction was greater and faster in women, especially in younger women compared with same-aged men. This could be due to a better response in women to the selected antihypertensives or to the regulation of BP by different physiological mechanisms.[14] Irrespective of the BP parameter examined (office BP, 24 h BP, cSBP), women achieved better overall BP control. Similarly, the IDEAL trial, which included 122 naïve patients with hypertension, demonstrated that indapamide and perindopril led to a greater reduction of office SBP in women.[15] Additionally, treatment with amlodipine was associated with a stronger antihypertensive effect in women.[16]

## Conclusion

The results of the PRECIOUS trial showed that treatment with perindopril-based dual and triple SPCs was effective and safe in both sexes, with important sex differences. The trial contrib-

lesnika s AH-om, pokazalo je da su indapamid i perindopril u žena doveli do većeg smanjenja AT-a mjerenog u ordinaciji.[15] Usto, liječenje amlodipinom bilo je povezano sa snažnijim antihipertenzivnim učinkom u žena.[16]

## Zaključak

Rezultati ispitivanja PRECIOUS pokazali su da je liječenje dvojnim i trojnim fiksnim kombinacijama na bazi perindoprila bilo učinkovito i sigurno za oba spola, no s važnim razlikama između spolova. Spomenuto ispitivanje dodalo je važne podatke sve većem tijelu dokaza o razlikama između spolova koje postoje kod hipertenzije.

uted significant data to the expanding body of evidence on sex differences in hypertension.

## LITERATURE


1. WHO. Cardiovascular diseases (CVDs). [cited 2025 Feb 21]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2. Kralj V, Grahovac I. Epidemiology of cardiovascular diseases in Croatia. Cardiol Croat. 2022;17(9-10):333. https://doi.org/10.15836/ccar2022.333
3. Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. Hypertension. 2020 Feb;75(2):285-292. https://doi.org/10.1161/HYPERTENSIONAHA.119.14240
4. WHO. Hypertension Croatia 2023 country profile [internet]. [cited 2025 Feb 21]. Available from: https://www.who.int/publications/m/item/hypertension-hrv-2023-country-profile
5. Gerdts E, Sudano I, Brouwers S, Borghi C, Bruno RM, Ceconi C, et al. Sex differences in arterial hypertension. Eur Heart J. 2022 Dec 7;43(46):4777-4788. https://doi.org/10.1093/eurheartj/ehac470
6. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023 Dec 1;41(12):1874-2071. https://doi.org/10.1097/HJH.0000000000003480
7. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, et al; ESC Scientific Document Group. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024 Oct 7;45(38):3912-4018. https://doi.org/10.1093/eurheartj/ehae178
8. Cífková R, Strilchuk L. Sex differences in hypertension. Do we need a sex-specific guideline? Front Cardiovasc Med. 2022 Aug 23;9:960336. https://doi.org/10.3389/fcvm.2022.960336
9. Bager JE, Manhem K, Andersson T, Hjerpe P, Bengtsson-Boström K, Ljungman C, et al. Hypertension: sex-related differences in drug treatment, prevalence and blood pressure control in primary care. J Hum Hypertens. 2023 Aug;37(8):662-670. https://doi.org/10.1038/s41371-023-00801-5
10. Brguljan Hitij J, Gaciong Z, Simić D, Vajer P, Zelveian P, Chazova IE, et al; Precious trial investigators. Differences in sex and age response to single pill combination based antihypertensive therapy reflecting in blood pressure and arterial stiffness. J Hypertens. 2025 Mar 1;43(3):387-396. https://doi.org/10.1097/HJH.0000000000003901
11. Brguljan J, Chazova IE, Gaciong Z, Simic D, Vajer P, Zelveian, Jelakovic B. Single-pill combination enables fast target BP achievement. J Hypertens. 2023;41 Suppl 1:e394-e395. https://doi.org/10.1097/01.hjh.0000916860.25615.9f
12. Brguljan J, Chazova IE, Gaciong Z, Simic D, Vajer P, Zelveian, Jelakovic B. Effect of single pill combinations on central systolic blood pressure. J Hypertens. 2022;40 Suppl 1:e304. https://doi.org/10.1097/01.hjh.0000838696.92081.37
13. Weber T, Protogerou AD, Agharazii M, Argyris A, Aoun Bahous S, Banegas JR, et al; International Academic 24-Hour Ambulatory Aortic Blood Pressure Consortium (i24abc.org). Twenty-Four-Hour Central (Aortic) Systolic Blood Pressure: Reference Values and Dipping Patterns in Untreated Individuals. Hypertension. 2022 Jan;79(1):251-260. https://doi.org/10.1161/HYPERTENSIONAHA.121.17765
14. Briant LJ, Charkoudian N, Hart EC. Sympathetic regulation of blood pressure in normotension and hypertension: when sex matters. Exp Physiol. 2016 Feb;101(2):219-29. https://doi.org/10.1113/EP085368
15. Gueyffier F, Subtil F, Bejan-Angoulvant T, Zerbib Y, Baguet JP, Boivin JM, et al; IDEAL Trial Group. Can we identify response markers to antihypertensive drugs? First results from the IDEAL Trial. J Hum Hypertens. 2015 Jan;29(1):22-7. https://doi.org/10.1038/jhh.2014.29
16. Wenger NK, Arnold A, Bairey Merz CN, Cooper-DeHoff RM, Ferdinand KC, Fleg JL, et al. Hypertension Across a Woman's Life Cycle. J Am Coll Cardiol. 2018 Apr 24;71(16):1797-1813. https://doi.org/10.1016/j.jacc.2018.02.033