Original Article

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Differences in sex and age response to single pill combination based antihypertensive therapy reflecting in blood pressure and arterial stiffness

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Objective: There are noticeable sex differences in the treatment response to antihypertensives, with limited data on the response to single pill combinations. The aim of the PRECIOUS trial was to assess the treatment response to perindopril/amlodipine and perindopril/amlodipine/indapamide dual and triple single-pill combination in men and women.

Methods: Four hundred and forty adults with essential hypertension were assessed in the 16-week interventional, open-label, prospective, international, multicentre trial. Based on the previous antihypertensive therapy, patients were assigned to either perindopril/amlodipine 4/5 mg or perindopril/amlodipine/indapamide 4/5/1.25 mg, with the initial dose up-titrated in 4-week intervals in case of uncontrolled blood pressure. An additional analysis was performed for sex- and age-related differences on the blood pressure response and arterial stiffness in men and women aged 35–74 years.

Results: Women achieved better overall blood pressure control in all age groups, except for the 35–44 age group. Women presented higher average 24 h aortic augmentation indexes than men, but had more pronounced decreasing trends. The pulse wave velocity was only age-dependent, with reductions slightly greater in women. Both the aortic augmentation index and pulse wave velocity were significantly decreased in all groups compared to baseline.

Conclusions: The results of the PRECIOUS trial contribute significant data to the expanding body of evidence on sex differences in hypertension, including the aspect of age-related changes during the life course of women. The differences between same-aged men and women tend to be smaller with advancing age, but with a greater treatment response in women in all age groups for all observed blood pressure parameters and arterial stiffness.

Trial registration: ClinicalTrials.gov identifier NCT03738761

Keywords: Aix, arterial stiffness, BP control, hypertension, men, perindopril-based single-pill combinations, pulse wave velocity, sex differences, women

Abbreviations: FAS, full analyses set; LOCF, last observation carried forward; P/A, perindopril/amlodipine; P/A/I, perindopril/amlodipine/indapamide; SAS, safety analyses set; V, visit

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in both sexes, with CVD death accounting for 36% in men and 43% in women [1]. Since hypertension (HT) is the most important modifiable risk factor for CVD [2] it is of public interest to improve its control. However, important sex differences exist, ranging from blood pressure (BP) values over the life course, pathophysiologic mechanisms regulating BP and response to antihypertensives, to hypertension-mediated organ damage (HMOD) and related cardiovascular (CV) complications [3,4].

Sex differences in BP values are present from an early age and change across the life course. Generally, healthy young women have a lower BP than same-aged men, which is likely due to oestrogen cardioprotective and vasodilating effects [3–5]. Men continue having higher BP values until the age of 55–60. After menopause, women experience a

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more pronounced BP increase, their BP values surpass those of men and remain higher until the end of life. Hence, the prevalence of hypertension (HT) is lower in younger women, but sharply increases around menopause, resulting in higher rates in women aged 60 or more [4–6]. CV risk is known to increase at lower BP levels in women, with risk of CV events in women beginning at around 10 mmHg lower brachial systolic BP (SBP) [3,5].

Hypertension is a major determinant of vascular ageing [7], with documented sex differences in vascular structure and function. Women have smaller arterial diameters and increased arterial stiffness, even after adjusting for body size [8]. Over the life course, arterial stiffness increases in both sexes, with women experiencing more rapid increase post menopause [9]. Indicators of arterial stiffness are the aortic augmentation index (Aix) and carotid-femoral pulse wave velocity (PWV), but PWV is not influenced by heart rate and is therefore considered the gold standard [10–13]. AIx is higher in women at all ages, while PWV does not differ by sex [3]. A PWV >10 m/s represents a significant alteration of the aortic function [13]. Arterial stiffness is generally less modifiable by antihypertensive therapy in women [3]. It is noteworthy that patients who achieve significant reduction of both BP and PWV experience fewer CV events than those that only achieve BP control [7].

Prescription of antihypertensives has shown that women are more often prescribed diuretics and men more often angiotensin converting-enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs) [14–16]. Such a difference is probably attributable to adverse effects: women are more likely to develop cough from the treatment with ACEIs and peripheral oedema with CCBs [17], while men more often experience gout with diuretics. Overall, women report adverse effects more often [3,4,18,19], even if they are taking fewer antihypertensives [20]. There are noticeable sex differences in the response to antihypertensive drug classes, with women reported to have enhanced BP reduction with beta blockers (BBs) and CCBs [3]. Single-pill combinations (SPCs) have been suggested as the preferred drug treatment regimen already in previous 2018 ESC/ESH Guidelines for the management of HT [13], reinforced also by 2023 ESH guidelines [20]. The data about the sex response to SPC treatment is, however, limited.

The aim of the PRECIOUS trial (Fixed-Dose Combination of **P**e**R**indopril/Amlodipin**E** and Fixed-Dose **C**omb**I**nati**O**n of Perindopril/Amlodipine/Indapamide – Contrib**U**tion to Management in Newly Diagno**S**ed and Uncontrolled Hypertensive Patients) was to assess the treatment response to perindopril/amlodipine and perindopril/amlodipine/indapamide dual and triple SPC in men and women by evaluating a conventional measure of treatment efficacy such as BP control, and to investigate the impact of these combination therapies on PWV and Aix, thereby providing valuable insights into the vascular function and CV risk beyond conventional measurements.

MATERIALS AND METHODS

Study design

PRECIOUS was an interventional, open-label, prospective, international (conducted in Armenia, Croatia, Hungary, Poland, the Russian Federation, Serbia and Slovenia), multicentre trial (ClinicalTrials.gov identifier NCT03738761) that began in February 2018 and concluded in September 2019. It was designed to assess the efficacy and safety of perindopril-based dual and triple SPC therapies. It was approved by the Independent Ethics Committees and the National Regulatory Authorities of the participating countries and conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

All patients who provided a written consent for participation started with an initial screening visit 1 day prior to inclusion to verify eligibility. During the initial screening visit and inclusion visit (V1), a complete medical history, physical examination, laboratory analyses (blood count, clinical chemistry, liver function tests, lipid measurements, pregnancy test in women with childbearing potential), office BP, heart rate (HR), ambulatory blood pressure monitoring (ABPM) and electrocardiogram (ECG) were performed. Eligible patients were assigned treatment with one of the two study medications: naïve patients or patients uncontrolled on the previous monotherapy were assigned to the dual SPC arm with an initial dose of perindopril 4 mg/amlodipine 5 mg (P/A). Patients uncontrolled on the previous dual therapy with P/A or triple therapy (other than perindopril/amlodipine/indapamide) were assigned to the triple SPC arm with an initial dose of perindopril 4 mg/amlodipine 5 mg/indapamide 1.25 mg (P/A/I). Patients on the previous dual antihypertensive therapy other than P/A were allocated to either the dual SPC arm or the triple SPC arm at investigator's discretion, targeting the allocation ratio of 1 : 1. Patients started taking the study medication on the day of V1. At each follow-up visit at week 4 (V2), week 8 (V3) and week 12 (V4), patients with uncontrolled office BP[i]iAccording to the BP treatment targets from the 2013 ESH/ESC Guidelines for the management of HT, which were valid during the preparation of the trial protocol. [SBP ≥ 140 mmHg and/or diastolic BP (DBP) ≥ 90 mmHg (≥85 mmHg in patients with type 2 diabetes mellitus (DM) [21]] were up-titrated to P/A 8 mg/5 mg, 8 mg/10 mg or P/A/I 8 mg/10 mg/2.5 mg in the dual SPC arm and to P/A/I 8 mg/5 mg/2.5 mg or 8 mg/10 mg/2.5 mg in the triple SPC arm. Patients with controlled BP remained on the dose they were taking. At visits V2–V4 and the final visit at week 16 (V5), patients' office BP, HR and compliance were checked. ABPM was repeated at V5.

Of the 572 screened subjects, 471 were assigned to study treatment. For 440 patients sufficient efficacy data were provided for inclusion to the Full Analyses Set (FAS), defined as the set of all screened patients who received at least one dose of the study medication and had the baseline value and at least one postbaseline value of both, SBP and DBP. Safety was analysed in all screened patients who received at least one dose of the study medication, resulting in 461 patients included in the Safety Analyses Set (SAS).

An additional analysis was performed for sex- and age-related differences in men and women aged 35–74 years. Patients <35 years and >74 years were not included due to a small number which would not allow for relevant comparisons. Consequently, 399 patients were included in this additional analysis. Treatment design is presented in Fig. 1.

Office BP was measured with a validated automated BP-measuring device by a qualified health professional

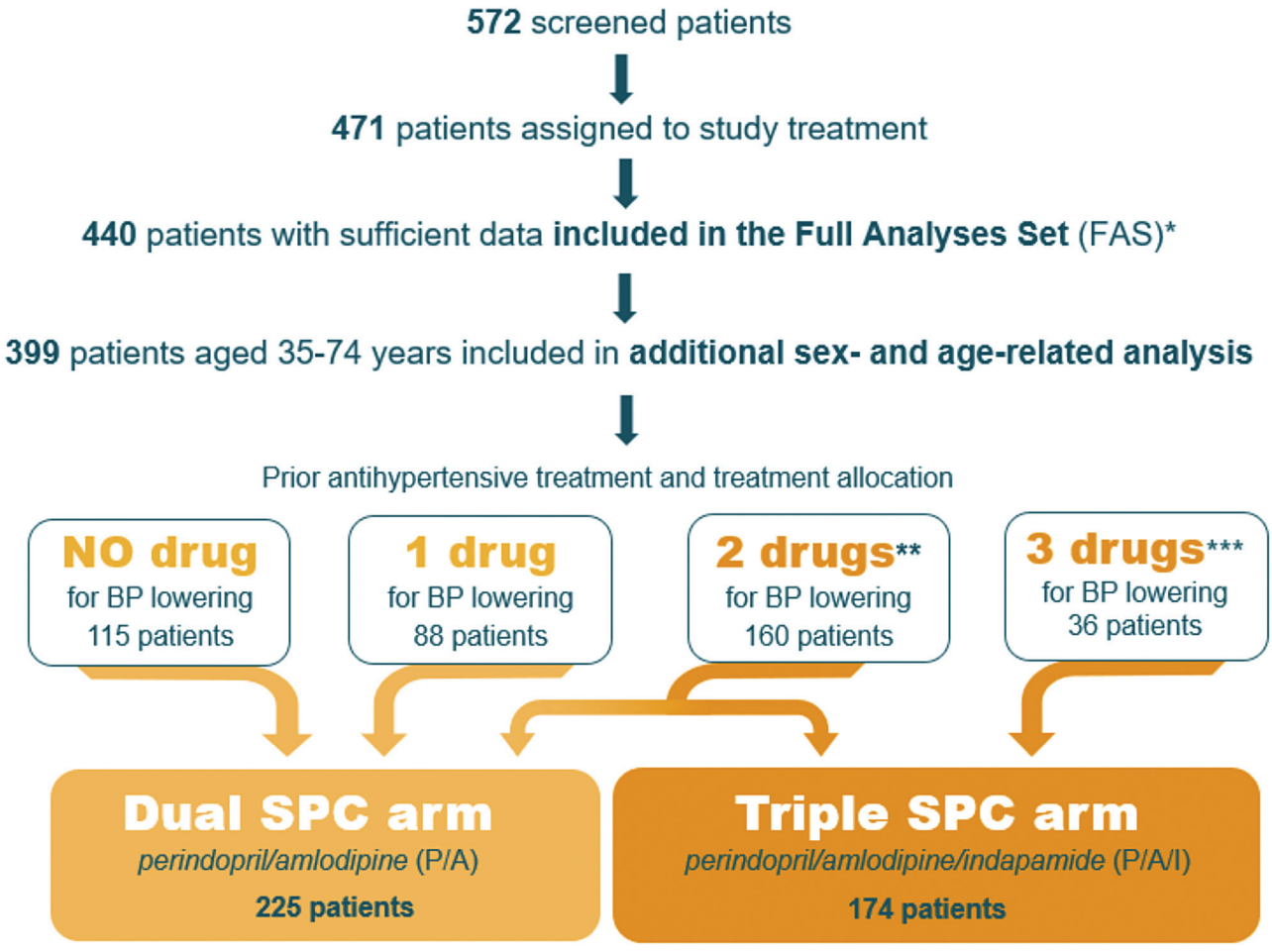

FIGURE 1 Treatment design. A, amlodipine; I, indapamide; P, perindopril. ** All 440 patients included in FAS were allocated to either the dual SPC arm or the triple SPC arm. ** Patients previously treated with two antihypertensive drugs were allocated in 1 : 1 ratio to either the dual or the triple SPC 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 drugs other than perindopril, indapamide and amlodipine.

following the guidelines' protocol. ABPM was performed with a validated automated portable BP-measuring device (Mobil-O-Graph PWA), recording brachial BP, central BP, HR, PWV and AIx. The device was worn on the nondominant arm for a 24-h period, measuring BP in a 20-min interval during the day and a 30-min interval during the night. Applicability of the Mobil-O-Graph PWA in clinical settings has been validated and confirmed in clinical studies comparing the measurement outcomes with other methods for assessing these parameters [applanation tonometry, including SphygmoCor device, magnetic resonance imaging (MRI), Doppler, invasive methods] [22–30].

The primary efficacy endpoint was the proportion of patients achieving target office BP, defined as BP <140/90 mmHg (<140/85 mmHg in patients with type 2 diabetes mellitus), at V5. The secondary efficacy endpoints included mean absolute and relative changes from the baseline in office SBP and DBP at V2–V5 and in 24 h SBP and DBP at V5, the proportion of patients reaching normal average 24 h SBP and DBP at V5, the proportion of patients reaching a reduction of central SBP below 120 mmHg at V5, the proportion of patients reaching a reduction of PWV for at least 0.5 m/s at V5. Safety outcomes, including serious adverse events (AEs), were recorded and evaluated throughout the study. Patient compliance was monitored at V2–V5 based on counting the unused trial medication vs. the days of treatment with it. Compliant patients were defined as those with compliance above 80% at each visit from V2 to V5.

Participants

Eligible participants were adults with essential arterial HT, aged 18 years or older, who were either treatment naïve and with office SBP ≥150 mmHg and/or DBP ≥95 mmHg (DBP ≥ 90 mmHg for patients with type 2 DM), or uncontrolled on the previous monotherapy, dual or triple antihypertensive therapy with SBP ≥140 mmHg and/or DBP ≥90 mmHg (DBP ≥ 85 mmHg for patients with type 2 DM).

Exclusion criteria included previous use of perindopril, indapamide and amlodipine, contraindications to any component of the dual/triple SPC; severe SBP elevation ≥200 mmHg, white-coat HT, serious concomitant medical condition, clinically significant abnormal laboratory values, concomitant treatment with aliskiren or lithium, pregnancy, breastfeeding, and childbearing potential while not using an adequate contraception.

Statistical analysis

Efficacy endpoints-related missing data were imputed by the Last Observation Carried Forward (LOCF) method, except for the proportion of patients reaching normal average 24 h-ABPM SBP and DBP and the proportion of patients reaching a reduction of PWV where the patients with missing V5 values (but available baseline values) were imputed as nonresponders. For the comparison of the distribution of numeric variables in independent groups, the unpaired t-test was employed for BMI and the Wilcoxon-Mann-Whitney exact test for all BP variables (levels and absolute differences) since some of the groups are very small and normality tests show significant departures from normality. For testing the homogeneity of proportions in independent groups, Fisher's exact test was employed. For testing the distribution of the difference of two measurements of the same parameter performed at different time points, Wilcoxon's signed-ranks test was used. Rejections of the null hypotheses were considered significant at $P < 0.05$. Microsoft Visual Basic for Applications and R 3.5.0 were used for the computational part.

RESULTS

General characteristics

The baseline characteristics of 35–74 year-old patients are presented in Table 1. Among them, 225 were treated with P/A and 174 with P/A/I. There were more men (254, 63.7%), the age groups were differently represented, with a low number of women in the youngest age group. Overall, men and women had comparable baseline characteristics in all age groups, except for baseline office DBP in the 55–64 age group and 24 h DBP in the 45–54 and 55–64 age groups. In all cases, men had significantly higher values.

In both sexes, comorbidities were present in a very similar proportion up to the age of 55. After this age, comorbidities in men rose substantially, while in women they increased around 10 years later. From 65 years on, women had more comorbidities. Men more often had diabetes and hypertriglyceridemia and women more often hypercholesterolemia, but without statistically significant differences.

Previous antihypertensive therapy

Generally, women were more commonly previously treated, except for the 35–44 age group, in which significantly more men were treated. The opposite was true for the 45–54 age group, in which significantly more women were treated. From 55 years on, no important sex difference was observed. Women started treatment after the age of 45, most often with a monotherapy or a dual combination. Contrary, men were already treated in the 35–44 age group, mostly with a dual combination (Fig. 2).

BP control

There was no important sex difference in allocation to either P/A or P/A/I. Additionally, no important differences were observed in terms of compliance, with at least 99% of patients being compliant from V2 to V5 in both treatment groups.

Irrespective of the BP parameter (office BP, 24 h BP, cBP), women achieved better overall BP control, which was significantly higher for office BP <140/90 mmHg and 24 h DBP <80 mmHg (Figure C in Appendix, Supplemental Digital Content, http://links.lww.com/HJH/C584). Women generally achieved better BP control in all age groups, except for the 35–44 age group. BP control rates were higher with office BP than with 24 h SBP in both sexes due to the lower achievement of 24 h DBP. Regarding 24 h BP, sex differences were mainly due to 24 h DBP, especially from 55 years on, where women achieved around 2-times greater DBP control (Fig. 3).

Absolute office SBP and DBP reductions were higher in women in all age groups. However, sex differences were not statistically significant. A similar picture was observed also for 24 h BP (Figure D in Appendix, Supplemental Digital Content, http://links.lww.com/HJH/C584). At V2, office BP reduction was greater in women in all age groups. The biggest sex difference was observed in the youngest age group, where women had a much greater initial BP response than same-aged men. From V2 on, the rate of BP decrease was similar among men and women (Fig. 4).

Vascular properties

Women presented higher average 24 h AIx values at baseline but had more pronounced decreasing trends. However, after 16 weeks of treatment, their Aix values still remained at higher levels than in men (Fig. 5a). In both sexes, AIx decreases at the end of the trial were significant compared to baseline.

The PWV values were only age-dependent and not sex-dependent. The PWV reductions were slightly greater in women (Fig. 5b), confirmed also by the higher proportion of women reaching a reduction of PWV for at least 0.5 m/s at the end of the trial. The sex difference was the most

TABLE 1. Baseline characteristics of 399 patients aged 35–74 years

Sex	Men	Women	Men	Women	Men	Women	Men	Women
Age	35–44	35–44	45–54	45–54	55–64	55–64	65–74	65–74
N (number)	69	15	75	44	65	53	45	33
BMI, mean (kg/m^2)	31.1 ± 4	29.8 ± 7	30.8 ± 4.5	30.4 ± 6.3	30.7 ± 4.6	31.2 ± 5.1	30.4 ± 4.6	30 ± 5.1
Office SBP, mean (mmHg)	154.1	158.8	155.1	156.3	158.4	157.0	160.6	158.4
Office DBP, mean (mmHg)	99.7	103.5	100.3	99.7	98.2	95.5	95.6	94.5
24h SBP, mean (mmHg)	144.4	142.7	143.4	141.4	144.8	146.6	147.1	148.1
24h DBP, mean (mmHg)	96.5	95.9	95.9	91.9	93	89.4	91.7	89.5
cSBP, mean (mmHg)	133.5	134.4	133.2	131.0	133.4	135.3	134.7	135.3
With comorbidity (%)	16 (23%)	4 (27%)	25 (33%)	15 (34%)	31 (48%)	18 (34%)	23 (51%)	19 (58%)

$P < 0.05$ between men and women of the same age group.

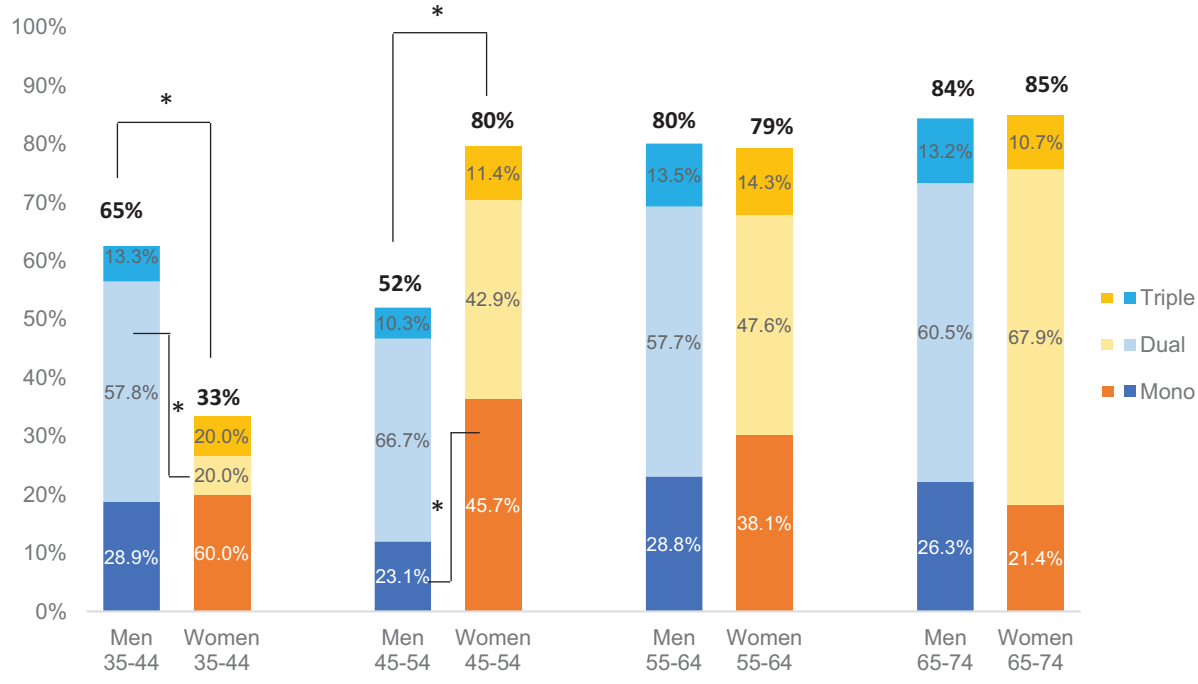

FIGURE 2 Previously treated patients by sex, age group and type of antihypertensive therapy (percentages inside the columns add up to 100%). * $P < 0.05$.

pronounced in the 65–74 age group, but did not reach statistical significance (Figure F in Appendix, Supplemental Digital Content, http://links.lww.com/HJH/C584). In both sexes, decreases of PWV values at the end of the trial were significant compared to baseline.

Safety

Out of 461 patients, 69 (15.0%) reported AEs; 45 (17.0%) patients treated with P/A, and 24 (12.2%) patients treated with P/A/I. The majority of AEs were mild (10.4%, 48) or moderate (5.6%, 26). Only 1.1% (5 patients) reported severe AEs. The most prevalent nonserious AEs in patients treated with P/A were cough (3.4%), increased blood potassium (1.9%), peripheral oedema (1.5%) and increased gamma-glutamyltransferase (1.5%). The most prevalent nonserious AEs in patients treated with P/A/I were increased gamma-glutamyltransferase (2.5%), increased alanine aminotransferase (2.5%), cough (1.5%), hypotension (1.5%) and decreased blood potassium (1.0%). Two patients had serious AEs (breast cancer and back pain), which required medical intervention; both AEs were assessed as unrelated to treatment. There were no reports of deaths in the trial.

A small proportion of patients discontinued the study due to AEs: 12 (4.5%) patients treated with P/A mostly due to cough and peripheral oedema, and 4 (2.0%) patients treated with P/A/I due to rash, urticaria and decreased blood potassium.

DISCUSSION

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- and age differences. Generally, women achieved better BP control, which was even more pronounced for DBP and could be partly attributed to significantly lower baseline office and/or 24 h DBP values in women in some age groups. Besides, SBP reduction was greater and faster in women. The reduction of arterial stiffness observed in both sexes was slightly more pronounced in women, which could be attributed to baseline value differences.

In the PRECIOUS trial, women were treated more often than men. This is in line with the results from large national population-based studies, which documented a 1 to 11% difference in favour of women [6,31–33]. However, young women are still less likely to receive CV therapies than same-aged men [8], which was observed also in the youngest age group in the PRECIOUS trial. Not only were women underrepresented (15 vs. 69 men), they were also significantly less previously treated (33% vs. 65% men). At this age, women experience reproductive years so they may tend to prioritize their reproductive health over their overall well being, leading to potential undertreatment of other health concerns, such as elevated BP. Contrary, significantly more women were treated during the menopause transition (45–54 years) (80% vs. 52% men), a period which is associated with substantial hormonal, metabolic and CV changes [34], leading to a BP increase. Here, the data from population-based studies does not show a uniform trend [32,35]. From 55 years on, women and men in the PRECIOUS trial were almost equally treated, with no statistically important sex-difference. In other studies, women at this age were slightly more often treated than same-aged men [32,35].

From 45 years on, women achieved better BP control. Again, the data from population-based studies do not show a uniform trend. The same trend was observed in Chinese men and women, aged 35–64 years [32], but not in Swedish women who achieved greater BP control rates than men regardless of age (40–60 years). Nevertheless, there are well known sex differences in pharmacokinetics as well as

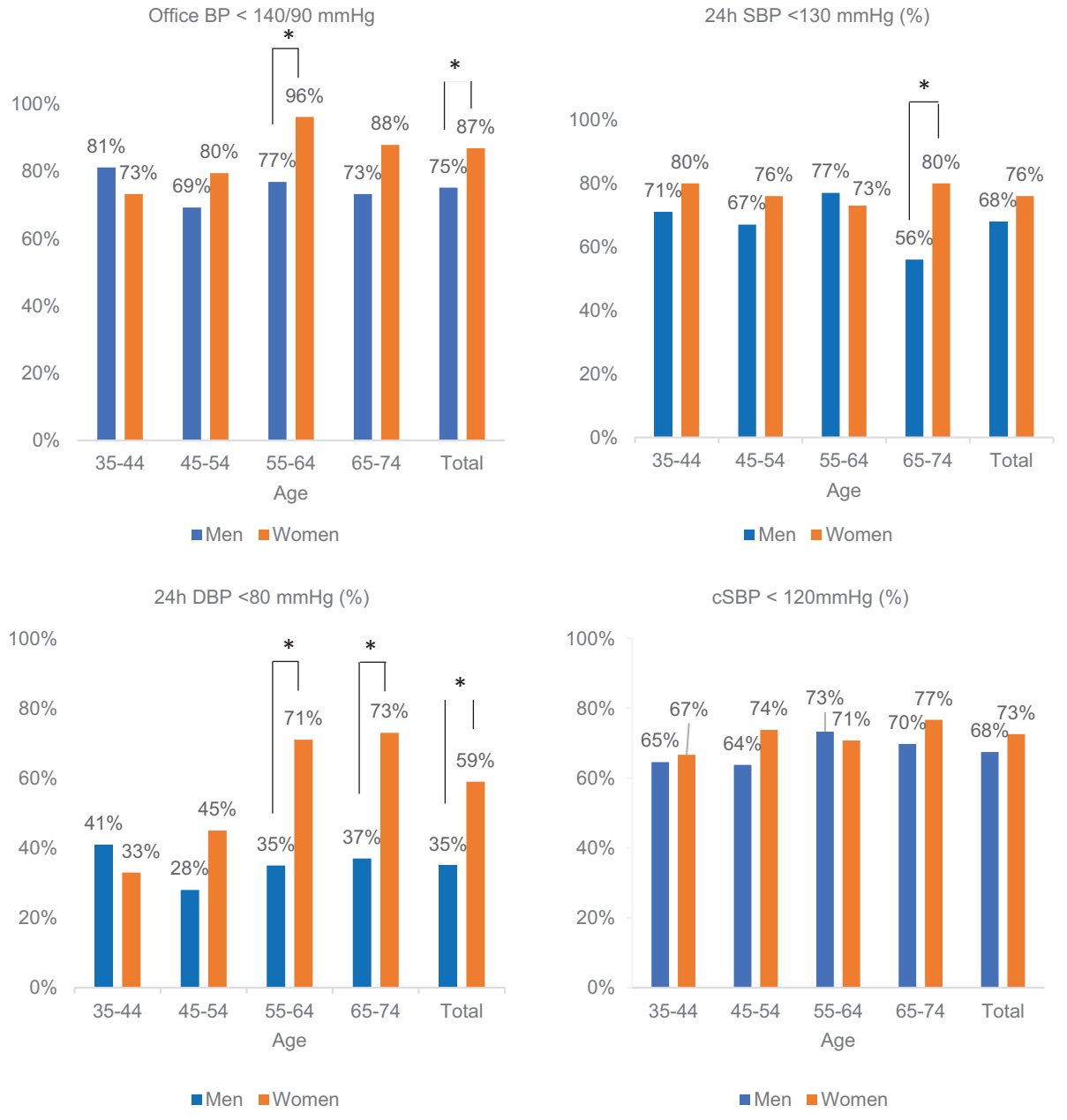

FIGURE 3 Proportion of men and women reaching BP control at visit 5, by age groups. * $P < 0.05$.

pharmacodynamics of receptor binding, postreceptor effects, and chemical interactions of drugs [2]. The IDEAL trial, which included 122 naïve hypertensive patients with a mean age of 52, showed that indapamide and perindopril reduced office SBP more in women. With indapamide, SBP reduction was 11.5 mmHg in women and 4.8 mmHg in men, while with perindopril, SBP reductions were 8.3 mmHg and 4.3 mmHg, respectively [36]. Similarly, treatment with amlodipine exhibited a greater antihypertensive effect in women [17]. In the PRECIOUS trial, overall BP reduction was greater and faster in women, especially in younger women compared to 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, with younger women exhibiting a greater β-adrenergic vasodilatation, mediated by the sympathetic nervous system [37]. However, it could also be due to the antihypertensives not being administered based on weight but as a "one size fits all" dose, meaning women were generally exposed to higher drug concentrations [38]. Despite similar BMI values in all age groups, the average sex weight differences in the PRECIOUS trial were substantial. On average, the weight of women was 11.7–18.4 kg lower than in the same-aged men, with the biggest weight difference precisely in the youngest age group. Up-titration, which was performed strictly in line with defined criteria (uncontrolled BP), showed it was greater in men in all age groups (except for age group 45–54 years, where it was similar in both sexes), meaning up-titration was not a reason for greater BP reduction in women.

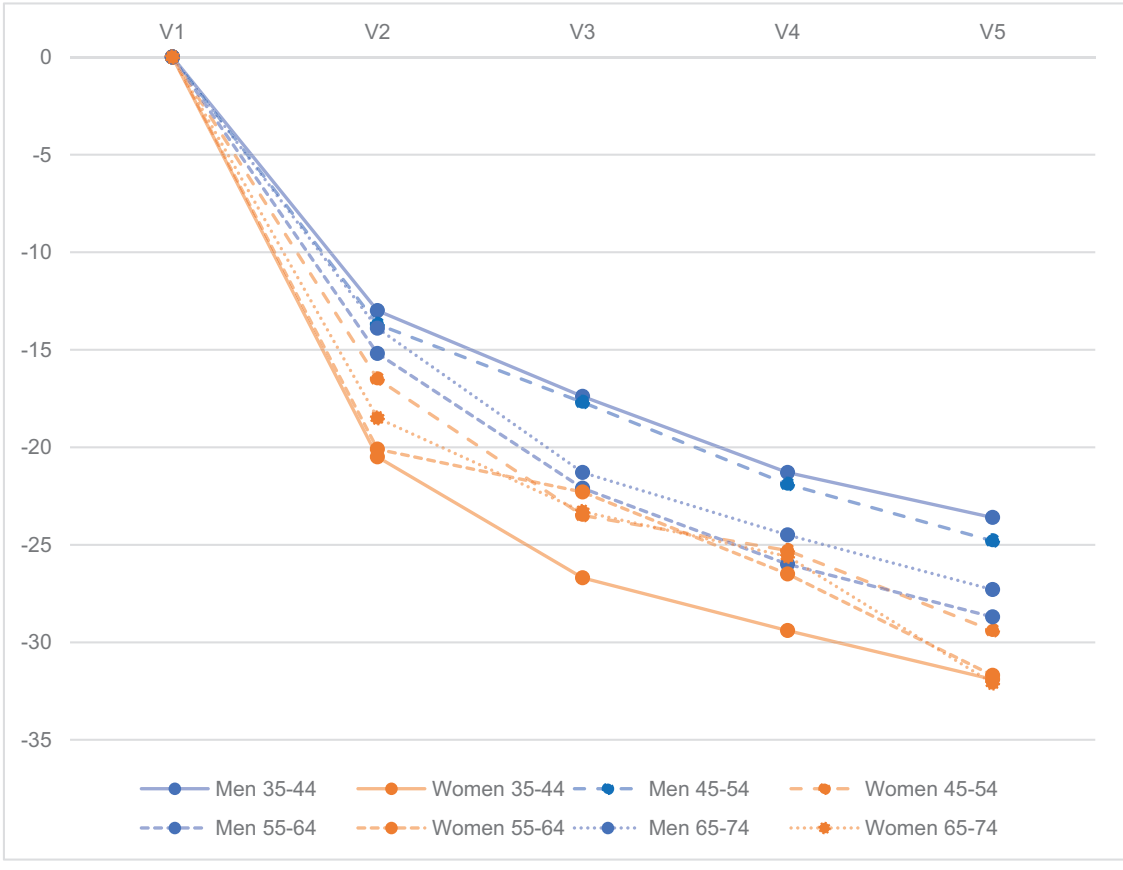

FIGURE 4 Absolute office SBP reduction from visit to visit, by sex and age groups.

As vital organs such as the brain, the heart, and the kidneys are exposed to central rather than brachial pressure, central BP is pathophysiologically more relevant. cSBP is more closely associated with HMOD than brachial SBP, and a better predictor of CV events. A recent study in 2423 untreated adults free from CVD or diabetes proposed an upper normal limit of 120 mmHg for 24-h cSBP [26]. In the PRECIOUS trial, both men and women in every age group had cSBP >130 mmHg at baseline, while at the end of the trial all age groups had their cSBP decreased to <120 mmHg. This additionally confirms the beneficial BP-lowering effect of perindopril-based SPC treatment.

Arterial stiffness increases with advancing age in both sexes, which was confirmed by both AIx and PWV [3]. Sex differences in baseline readings were similar to the findings by Costa-Hong *et al.* [39], with indexes being higher in hypertensive women in all age groups. The treatment with study drugs had a greater impact on 24-h AIx in women. While both women and men, aged 65 years or more, reached the desired PWV <10 m/s at the end of the study, we did not confirm arterial stiffness to be less modifiable by the antihypertensive therapy in women. On the contrary, women experienced a slightly greater arterial stiffness reduction, possibly due to a significant 24 h HR sex difference in age group 55–64 years.

The available data on sex differences in hypertension treatment suggest that the introduction of antihypertensives in women should be done with closer attention to AEs. Furthermore, the frequently higher drug exposure in women raises the question of the necessity of dose reduction in women [4,19]. Contrary to literature suggestions, AEs in the PRECIOUS trial, including cough and peripheral oedema, were similar in men and women. The significance of differences could not have been established due to a low number of AEs.

Strengths and limitations

The strength of the trial is its international design, with seven included countries, making the results representative for different populations.

The limitations of our trail include a low number of patients in some age groups – especially women aged 35–44 years – which could potentially affect the statistical significance of the results. A low number of women is, however, not surprising as women have been generally underrepresented in CV clinical trials (38% of all participants in 2010–2017 CV clinical trials) [8]. It is speculated that this is not so much connected to the inclusion or exclusion criteria, but rather to other factors, such as familial responsibilities and concerns about study risks [2]. The differences in BP control could be influenced by other factors, for which data was not available, such as concomitant therapy (e.g. NSAIDs, which are known to increase BP by 3/2 mmHg [40]) and the presence of psychological risk factors (e.g. depression, anxiety, cognitive impairment), which are more prevalent among women [17,41]. Neither did we collect the data regarding physical activity, occupation, parental status, menopausal status, pregnancy-related

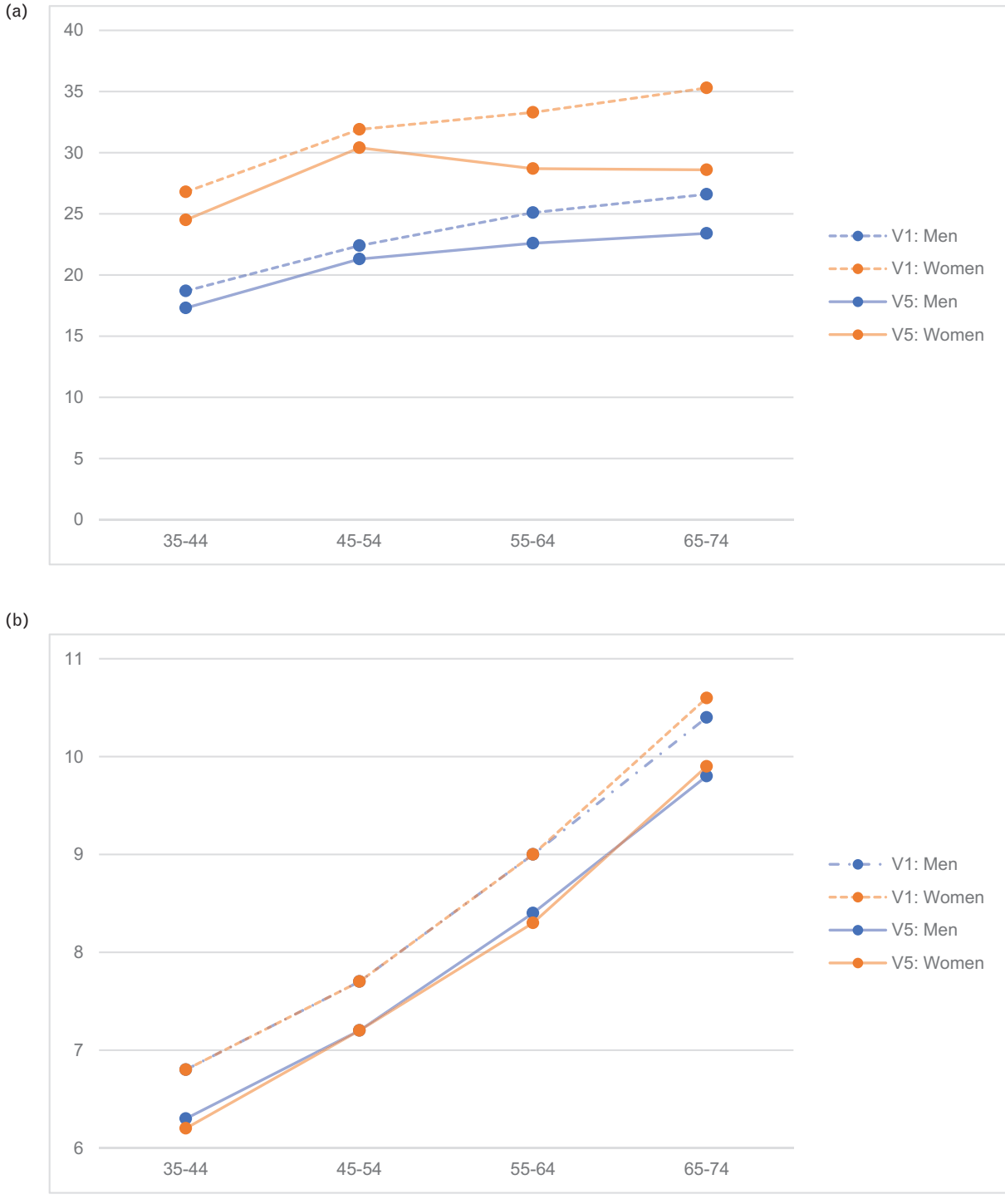

FIGURE 5 Average 24 h AIx values, by sex and age groups (a) and average 24 h PWV values, by sex and age groups (b).

complications (e.g. history of preeclampsia, gestational diabetes). The results of 24 h BP monitoring could have been affected by night-time sleep disturbances such as obstructive sleep apnoea [42] (more prevalent in men [43]), disturbances due to wearing an ABPM device [44] (may also be greater among men [45]), and a greater prevalence of white-coat hypertension in women and masked hypertension in men [46]. Another limitation is a relatively short follow-up of 16 weeks, which can be considered long enough for the assessment of BP control [13], but not vascular properties. The study also did not include HMOD measures, meaning we cannot exclude the potentially greater involvement of HMOD in men on their lower BP control.

CONCLUSION

The results of the PRECIOUS trial contribute significant data to the expanding body of evidence on sex differences in

hypertension, including the aspect of age-related changes during the life course of women. They also underscore the efficacy and safety of perindopril-based dual and triple SPCs in the treatment of men and women. Generally, treatment effects on BP and arterial stiffness were more pronounced in women, with the differences getting smaller with advancing age, thus emphasizing the importance of both sex- and age-specific considerations in hypertension management. These implications require further investigation in bigger populations and through longer time frames.

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Previous presentations: Abstracts reporting other data from this study were presented at the European Society of Hypertension (ESH), European Society of Cardiology (ESC) and International Society of Hypertension (ISH) congresses. The abstract presented at the joint ESH – ISH meeting 2021, 11–14 April, UK, was titled: Precious trial confirms safety and efficacy of guideline's single pill combination strategy. The abstract presented at ESC 2021 virtual meeting, 27–30 August 2021, was titled: Single pill combinations present a proven fast track in practice to reach the target blood pressure. The abstract presented at ESH meeting 2022, 17–20 June 2022, Greece; was titled: Effect of single pill combinations on central systolic blood pressure. The abstract presented at ISH 2022 world congress, 12–16 October 2022, Japan, was titled: Single-pill combination enables fast target BP achievement.

Conflicts of interest

This study was financially supported by Krka, d. d., Novo mesto, Slovenia with no influence on the outcome and results of study. All authors have received financial compensation for their contribution. Statistical analyses were performed by independent company.

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